Hematologic Malignancies Syllabus

Session 1: Lymphomas, CLL, ALL, CML, Plasma Cell Disorders, and MDS

Session 2: AML, Pharmacology, and BMT

Course Organizers:

THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC

28

Pathology of Lymphomas

L. Jeffrey Medeiros, MD

August 16, 2020

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Non-Hodgkin's Lymphoma

John Leonard, MD

August 16, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

29 – Non-Hodgkin's Disease

John P. Leonard, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consulting - Gilead, Celgene, Sutro, Genentech/Roche, Bayer, ADC Therapeutics, MEI Pharma, AstraZeneca, Karyopharm, Miltenyi, Regeneron, BMS, Epizyme

Non Hodgkin lymphoma

- **Epidemiology**
- **Aggressive Lymphomas**
  - **DLBCL, PMBCL, BL, LBL, PCNSL, T cell**
- **Indolent Lymphomas**
  - **Follicular, Marginal Zone**
- **Mantle Cell Lymphoma**

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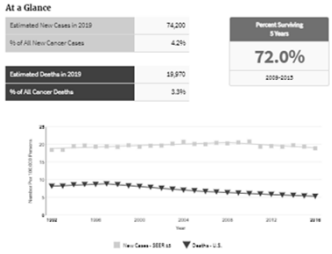
Non Hodgkin lymphoma epidemiology - SEER



https://seer.cancer.gov/statfacts/html/nhl.html

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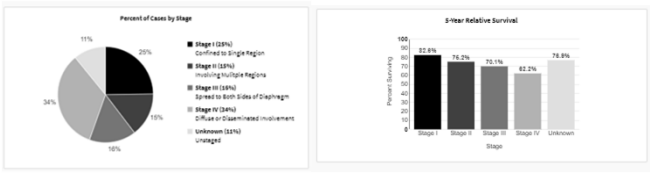
Non Hodgkin lymphoma epidemiology – SEER Stage and survival

EFS



https://seer.cancer.gov/statfacts/html/nhl.html

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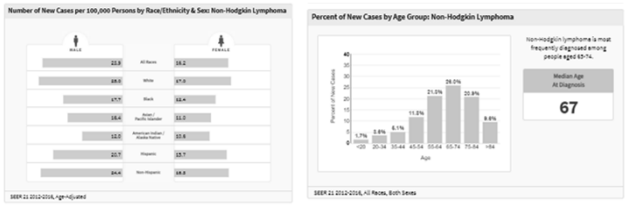
Non Hodgkin lymphoma epidemiology – SEER Sex and age

EFS



https://seer.cancer.gov/statfacts/html/hodg.html

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NHL Risk Factors

- Infectious
  - H. Pylori (Gastric MALT), EBV (Burkitt), Hep C (MZL), HTLV-1 (ATLL)
- Environmental/Occupational
  - Pesticides, herbicides, dark hair dye (old)
- Autoimmune disease – RA, Sjogrens, IBD, psoriasis
- Immunosuppression – transplant, HIV, medications
- Hereditary – first degree relatives
- Dietary – low vegetable, red meat

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WHO Lymphoma Classification 2016

100 + entities

Swerdlow et al, Blood 2016

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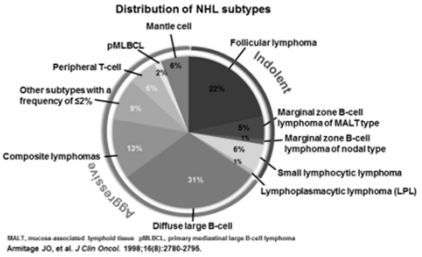
Most common NHL subtypes



MALT, mucosa associated lymphoid tissue pMLBCL, primary mediastinal large B-cell lymphoma

Armitage JO, et al. *J Clin Oncol.* 1998;16(8):2780-2795.

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NHL presenting signs and symptoms

- Painless LN enlargement
- "B symptoms" (fever, night sweats, weight loss)
- Splenomegaly
- Cytopenias or other laboratory abnormalities
- Site specific symptoms
  - Respiratory, CNS, abdominal, edema, etc

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Tissue evaluation

- Hematopathology review of slides/blocks
- FNA inadequate
- Core biopsies often inadequate (need architecture)
- Immunohistochemistry panel essential
- Cytogenetics/FISH appropriate for histology
  - Mantle cell (11:14), Double Hit (MYC, BCL2, BCL6)

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Lymphoma: Staging and Evaluation

- History and Physical
  - Fertility discussion (as relevant)
- Labs:
  - CBC
  - Chemistries, LDH, Uric Acid
  - Hepatitis B (Rituximab use)
  - Hepatitis C (some NHL)
  - HIV (when appropriate)
  - Pregnancy test (as relevant)
- Bone marrow biopsy/aspirate (subtype specific)
- Ejection fraction testing – ECHO/MUGA (if anthracycline)
- PET/CT (or CT N/C/A/P alone less common)
- MRI of brain or selected area (as appropriate)
- LP –
  - DLBCL if high risk
  - HIV, BL, Lymphoblastic, Blastic MCL, D Hit
  - Site – testicular, sinus/eye, near spinal area

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Staging of lymphomas: Lugano classification

- PET-CT standard for FDG-avid lymphomas
- CT for non-avid histologies (CLL/SLL, MZL, MF)
- Modified Ann Arbor staging for disease localization
  - Patients treated according to prognostic and risk factors
- Suffixes A and B are only required for HL
- "X" for bulky disease is no longer necessary, but record the largest tumor diameter

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Revised staging system for primary nodal lymphomas

Stage	Involvement	Extranodal Status
Limited		
Stage I	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited, contiguous extranodal involvement
Bulky stage II	II as above with "bulky" disease ≥ 7.5 cm	N/A
Advanced		
Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	N/A
Stage IV	Additional non-contiguous extranodal involvement	

Cheson et al, JCO 32: 3059-3067, 2014

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Deauville 5-Point Scale for PET Interpretation

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Moderately increased uptake compared to liver
5. Markedly increased uptake compared to liver or new areas of FDG uptake

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Revised criteria for response assessment

	PET-CT Response	CT-based response
	Complete metabolic response (CMR)	Complete radiologic response – All of the following
Nodes and extralymphatic sites	Score 1,2,3* with or w/o residual mass	Nodes/masses ≤ 1.5 cm in LDi No extralymphatic disease
Non-measured lesions	N/A	Absent
Organ involvement	N/A	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease	Normal by morphology, IHC

* Negative at interim scan; positive end of treatment

Cheson et al, JCO 32: 3059-3067, 2014

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Revised criteria for response assessment

	Partial Metabolic Response	Partial Response - All of the following
Nodes and extra-Lymphatic sites	Score 4,5 reduced from baseline with mass of any size At interim suggests responding disease At end of treatment suggests treatment failure	≥ 50% reduction in PPD of up to 6 lesions
Non-measured lesions	Not applicable	Absent/normal, regressed
Organ enlargement	Not applicable	Spleen regressed >50% from length beyond normal
New lesions	None	None
Bone marrow	Higher than normal but reduced from baseline	Not applicable

Cheson et al, JCO 32: 3059-3067, 2014

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Post therapy follow-up imaging recommendations

Organization	DLBCL	Hodgkin	F/LG
IWG/Lugano	CT-PET 6-8 wk post-tx No surveillance scans HX/PE/Labs q2-3 m x 1 yr Q 6 mo x 1 yr Then annually	Same	Q 6 mo or as indicated by clinical status, treatment regimen, and clinical judgment
ESMO	PET surveillance not recommended for routine follow-up	CT to confirm response then PRN Hx/PE/labs with ESR q 3 mo x 2 yr Q 6 mo to 5 yr Then annually No PET surveillance	Hx/PE q 3 mo x 2 yr Q 4-6 mo x 3 yr Then annual CBC, chem q 6 mo x 2 yr No routine scans
NCCN	Q 3 mo x 2 yr Q 6 mo x 3 yr No PET surveillance	Q 2-4 mo x 1-2 yr Q 3-6 mo to 5 yr Then annually No PET surveillance	If in CR – CT q 6 mo X 2 years then no more than yearly

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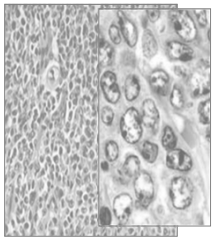
Diffuse large B-cell lymphoma (DLBCL)

- Most common NHL, peak incidence in 6th decade
- Large cells with loss of follicular architecture of node
- May present as extranodal disease (stomach, CNS, testis, skin)
- Curable in 60-75% or more of the cases
- Median survival: weeks to months if not treated
- Diagnosis
  - Typical immunophenotype: CD20+, CD45+, and CD3-,
  - FISH: eval for *bcl-2*, *bcl-6*, *c-myc* rearrangements
  - IHC for bcl-2, bcl-6, c-myc expression
  - IHC for CD10, Bcl-6, MUM1 (GCB/non-GCB)
  - Gene Expression Profile testing/Nanostring non-standard (COO)



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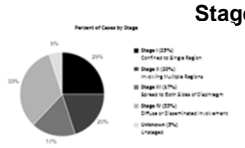
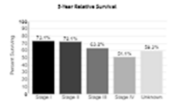
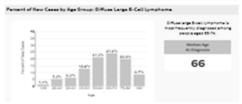
DLBCL epidemiology – SEER
Stage and survival







https://seer.cancer.gov/statfacts/html/nhl.html

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General DLBCL standard of care: R-CHOP 21

R-CHOP-21 v CHOP-21

MINT R-CHOP-like v CHOP-like

R-CHOP-14 v R-CHOP-21

Coiffier et al. Blood (2010) 116(12): 2040–2045; Pfreundschuh Lancet Oncol (2011) 11(12):1013–1022; Cunningham et al. Lancet (2013) 381 (9880):1817-1826

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When to consider treating patients with DLBCL today with something other than R-CHOP x 6?

Limited stage (?)

Testicular

Double hit subtype

Data not robust in double protein subtype

Primary mediastinal

HIV associated (DA-R-EPOCH)

CNS

Elderly (mini-R-CHOP)

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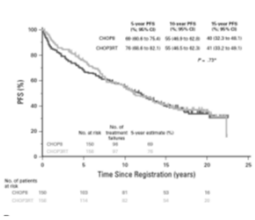
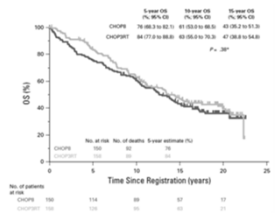
Long term F/U limited stage DLBCL

S8736 – CHOP x 3 + IFRT vs CHOP x 8





Stephens et al, JCO 2016

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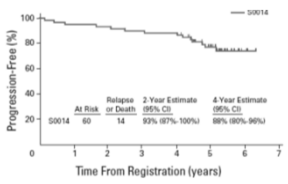
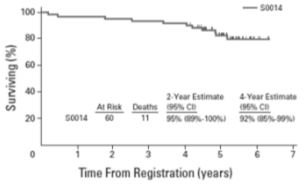
Approach to limited stage DLBCL

S0014 – R-CHOP x 3 + IFRT





Persky et al, JCO 2008

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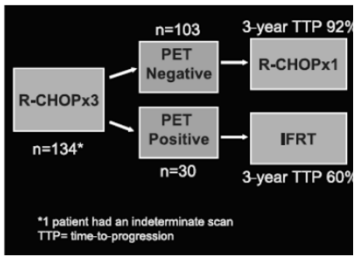
Approach to limited stage DLBCL

Is RT needed?



Sehn, Cancer Journal, 2012

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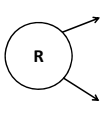
FLYER: Limited stage DLBCL

- **Front-line treatment of aggressive B-cell lymphoma**
- **18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)**



R-CHOP x 6 cycles

R-CHOP x 4 cycles + R x 2 cycles

Poeschel et al, ASH 2018

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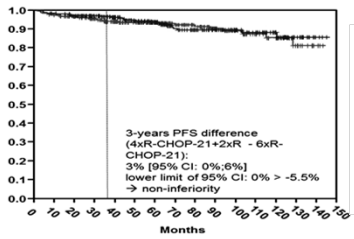
FLYER: Limited stage DLBCL



At 36 months:

6 x R-CHOP-21
94% (95% CI: 91 %; 97 %)
(n = 295)

4 x R-CHOP-21 + 2 x R
96 %, (95 % CI: 94 %; 99 %)
(n = 293)

Median follow-up: 66 months

Poeschel et al, ASH 2018

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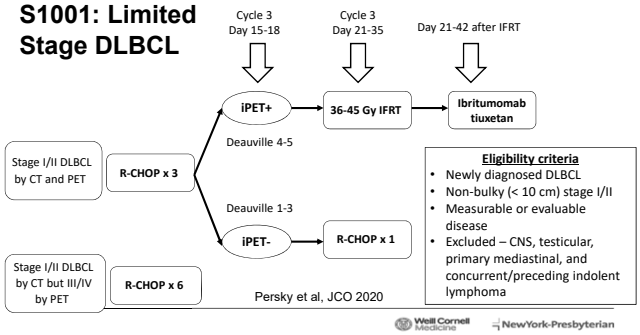
S1001: Limited Stage DLBCL



Eligibility criteria

- Newly diagnosed DLBCL
- Non-bulky (< 10 cm) stage I/II
- Measurable or evaluable disease
- Excluded – CNS, testicular, primary mediastinal, and concurrent/preceding indolent lymphoma

Persky et al, JCO 2020

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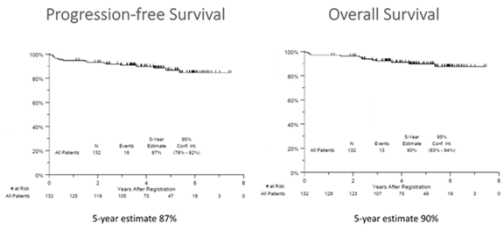
S1001: Limited stage DLBCL



Persky et al, JCO 2020

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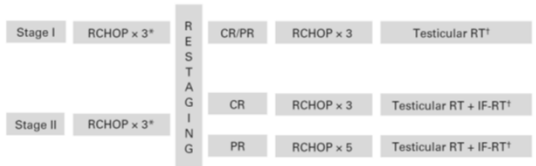
Approach to testicular DLBCL

IELSG10 – 53 patients



+ 4 doses IT MTX

Vitolo et al, JCO 2011

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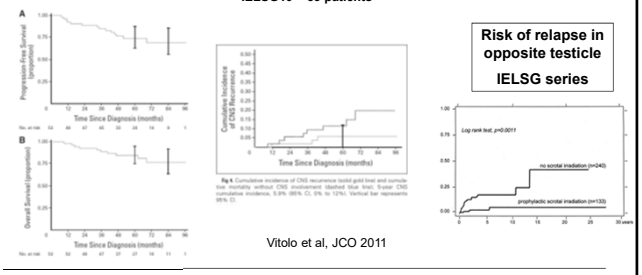
Approach to testicular DLBCL

IELSG10 – 53 patients



Vitolo et al, JCO 2011

Risk of relapse in opposite testicle

IELSG series

Treatment algorithm for DLBCL

CHOP-R (100%) (DA-R-EPOCH)

- **Cure (60-70%)**
- **Relapsed/Refractory (30-40%)**
  - **2nd line therapy**
    R-ICE, R-DICE, R-DHAP, etc
    - **Transplant eligible (20-25%)**
      - **ASCT + HDC**
        - **Cure (5%)**
        - **Relapse (15-20%)**
    - **Transplant ineligible (10-15%)**
      - **Relapse (10-15%)**

3rd line or later therapy (25-35%)

Comparison of CHOP-R and EPOCH-R

R-CHOP	DA*-R-EPOCH
Rituximab 375 mg/m² d1	Rituximab 375 mg/m² d1
Cyclophosphamide 750 mg/m2 d1	Etoposide 50 mg/m²/d CI d1-4*
Doxorubicin 50 mg/m² d1	Doxorubicin 10 mg/m²/d CI d1-4*
Vincristine 1.4 mg/m² (2 mg cap) d1	Vincristine 0.4 mg/m²/d CI d1-4
Prednisone 40 mg/m² d1-5	Cyclophosphamide 750 mg/m² d5*
	Prednisone 60 mg/m² bid d1-4
	G-CSF 5 µg/kg d6-ANC recovery
q3w × 6	q3w × 6

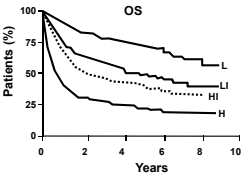
International Prognostic Index (IPI) in aggressive NHL

Prognostic factors (APLES)

- **A**ge >60 years
- **P**erformance status >1
- **L**DH >1× normal
- **E**xtranodal sites >1
- **S**tage III or IV

OR

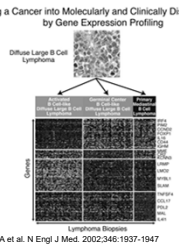
Risk Category	Factors
Low (L)	0 or 1
Low intermediate (LI)	2
High intermediate (HI)	3
High (H)	4 or 5



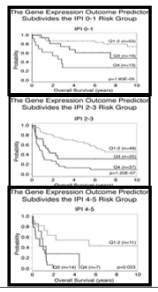
International NHL Prognostic Factors Project. *N Engl J Med.* 1993;329:987.
Armitage. *CA Cancer J Clin.* 2005;55:368.

Germinal Center vs Activated B Cell DLBCL

Dissecting a Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

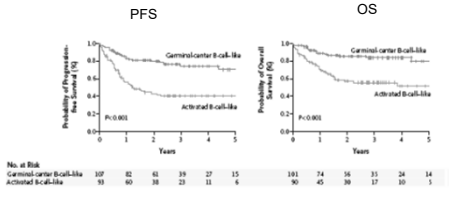


Rosenwald A et al. N Engl J Med. 2002;346:1937-1947



IHC surrogate (Hans) - CD10, bcl-6, MUM-1
GCB vs "non-GCB"

Outcome by GCB vs ABC gene signatures in DLBCL N=233 patients treated with R-CHOP



Lenz G, et al, NEJM 2008

Oncogenic mechanisms and potential therapeutic targets in GCB and ABC DLBCLs

DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	*BCL2* translocation*	BCL6
		EZH2 mutations‡	EZH2
		PTEN deletions§	PI3K/Akt
		Loss of PTEN expression	
ABC	Post-germinal centre B-cell	NF-κB activation‖	BCR
		CARD11 mutations	CBM complex
		MYD88 mutations	IRAK-4
		CD79B mutations	JAK–STAT
		A20 deletions	

Roschewski M. et al. *Nat. Rev. Clin. 2013*;11:12-23.

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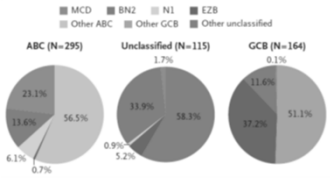
"Genetics and Pathogenesis" of DLBCL

MCD – MYD88 plus CD79B mutations
N1 – NOTCH1 mutations

ABC / unfavorable

BN2 – BCL6 fusions and NOTCH2 mutations
EZB – EZH2 mutations and BCL2 translocations

Mixed / favorable
GCB / favorable



Schmitz et al NEJM 2018

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Double hit vs Double protein DLBCL 10-25% of DLBCL

- **Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both ("triple-hit")**
  - **Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma**
  - **Cell of origin: Virtually always germinal center subtype**
  - **Outcome poor with standard therapies**
- **Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations**
  - **Cell of origin: Usually activated B cell subtype**
  - **Outcome inferior to other DLBCLs, but not as poor as DHL**

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High Grade B-cell Lymphoma – DH/TH

Genetic double hit lymphoma (DHL) predominantly observed in the GCB subset of DLBCL

Double MYC and BCL2 protein expression are observed in both the ABC and GCB subsets

DHL accounts for a small subset of the cases with double protein expression

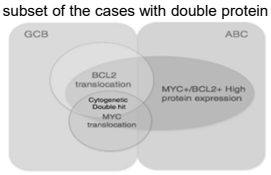

Fig. 1. Relationship among cell of origin in diffuse large B-cell lymphoma in terms of MYC/BCL2 protein expression and genetic translocations.

Campo, E. et al. Blood (2015)

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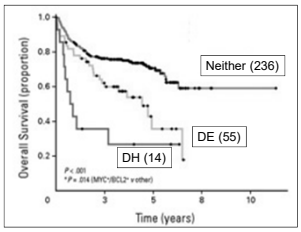
Double hit vs Double expression in DLBCL



Double expression 4x more common than Double hit

Double expression intermediate in outcome between DH and neither

Johnson et al JCO 2012; 30: 3452

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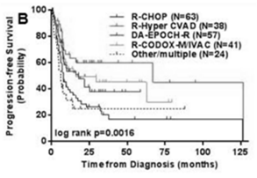
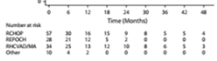
DA-EPOCH-R in double hit lymphoma





Petrich et al Blood 2014
Oki et al BJH 2014

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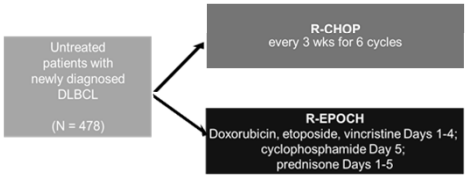
Alliance/CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL



- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling pathological diagnosis

Bartlett et al, ASH 2016 Clinical Trials.gov. NCT00118209. http://www.clinicaltrials.gov

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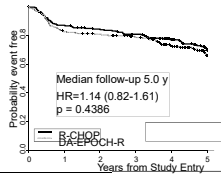
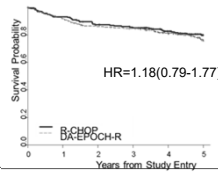
Alliance 50303: Outcomes

	R-CHOP	DA-EPOCH-R	P-value
ORR	89%	89%	0.983
CR/CRu	62%	61%	
PR	27%	27%	

Event Free Survival



Overall Survival



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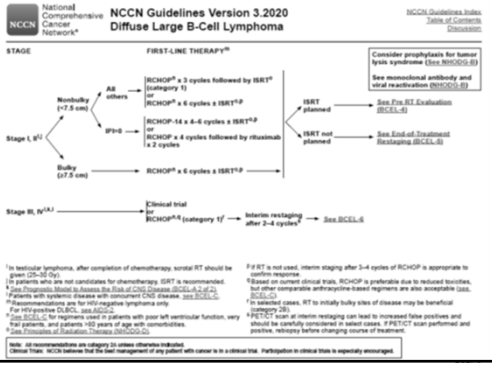
NCCN Guidelines Version 3.2020 Diffuse Large B-Cell Lymphoma



R-mini CHOP for age 80 and over

- **Rituximab 375 mg/m2 day 1**
- **Cyclophosphamide 400 mg/m2 day 1**
- **Doxorubicin 25 mg/m2 day 1**
- **Vincristine 1 mg day 1**
- **Prednisone 40 mg/m2 days 1-5**

Peyrade et al: Lancet Oncol 12: 460-68, 2011

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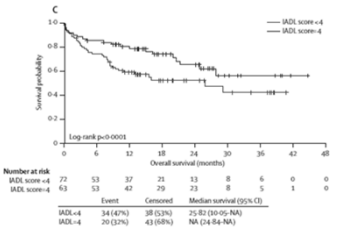
R-mini CHOP for age 80 and over



Peyrade et al: Lancet Oncol 12: 460-68, 2011

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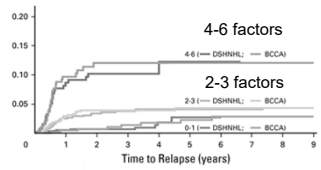
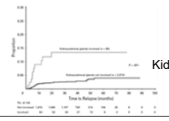
Predicting risk of CNS progression: CNS IPI

Factor	Hazard Ratio
Kidney and/or adrenal glands involved	2.8
Age > 60 years	2.5
LDH > normal	2.4
ECOG PS > 1	2.2
Stage III/IV disease	2.0
Extranodal involvement > 1	1.0





Kidney/adrenal involvement vs not

Schmitz et al., *J Clin Oncol* 34:3150-6 2016

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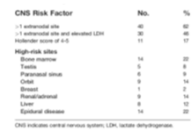
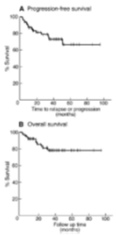
CNS prophylaxis for high risk patients
R-CHOP + d14 MTX 3.5 g/m2 x 3-4 cycles

Retrospective analysis
65 "high risk" patients
2 CNS recurrences

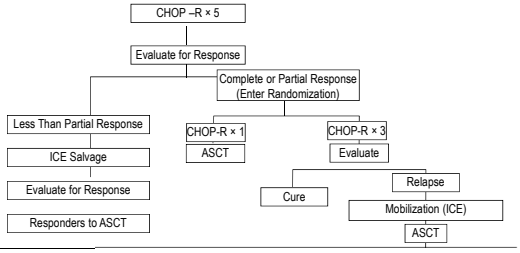




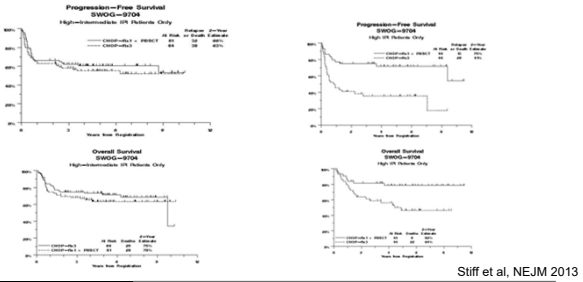
Prophylaxis options
- IT MTX
- Systemic MTX 3g/m^2 d15 of R-CHOP or after completion x 2-3 doses

Abramson et al, Cancer 2010

SWOG, ECOG, CALGB, NCIC – S9704 Early Versus Delayed High-Dose Therapy in High Intermediate/High IPI DLCL

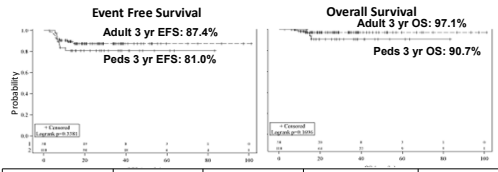


S9704: AuSCT in CR1 improves PFS but not OS (ITT)



Stiff et al, NEJM 2013

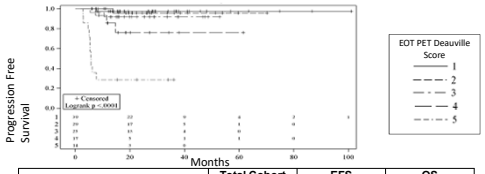
DA-R-EPOCH in PMBCL



	Total Cohort n=156	Pediatrics (age<21) n=38	Adult (age ≥ 21) n=118	P value for peds vs. adult
3 yr EFS (95% CI)	85.9 (80.3-91.5)	81.0 (68.3-93.7)	87.4 (81.2-93.6)	0.338
3 yr OS (95% CI)	95.4 (91.8-99.0)	90.7 (80.6-100.0)	97.1 (94.0-100.0)	0.170
Follow up in mo: Median (range)	22.6 (2.1-101.0)	24.0 (6.0-83.3)	22.6 (2.7-101.0)	0.780

Roth et al, BJH 2017

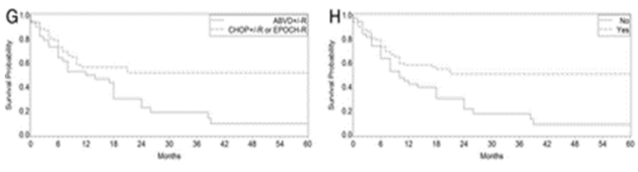
Outcome by end of therapy FDG-PET



		Total Cohort n=156	EFS	OS
Patients evaluated by PET or PET/CT at end of therapy:		149 (96.1%)		
Deauville score : number (%)	≤3	94 (75.2%)	95.4%	96.2%
	4	17 (13.6%)	75.4%	100%
	5	14 (11.2%)	28.6%	74.1%

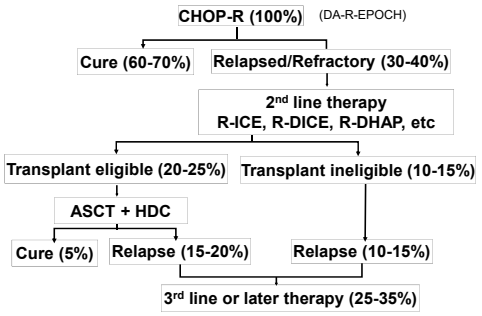
Roth et al, BJH 2017

Gray zone lymphoma (Thymic B cell derived) PFS improved with DLBCL type therapy and use of rituximab

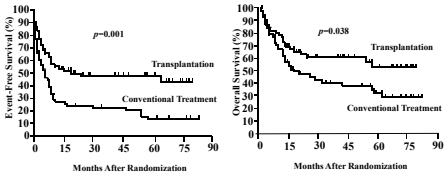


Evens et al, Am J Hematology 2015

Treatment algorithm for DLBCL



Chemosensitive relapsed DLBCL patients benefit from autologous SCT



Philip et al: *N Engl J Med*. 1995

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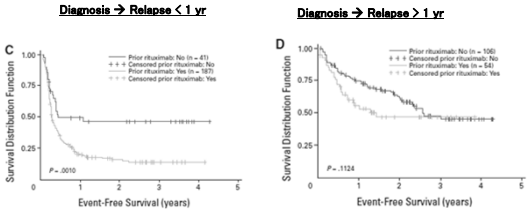
DLBCL patients with early relapse and prior rituximab are high risk



By ITT analysis (includes many patients who never underwent ASCT):
52% of randomized patients were transplanted.

[1]Gisselbrecht et al, JCO 28:4184 (2010)

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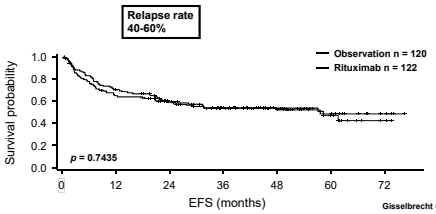
No role for maintenance rituximab after AuSCT in DLBCL



Gisselbrecht C, *et al. J Clin Oncol* 2012.

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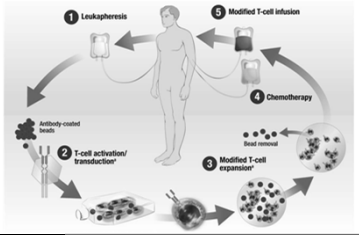
CAR-T cell therapy Approved for multiply relapsed/refractory aggressive lymphoma



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Initial clinical trial data with CAR-T cells

- Studies are small, single arm (range 100 patients)
- Time in preparing the T cells creates some biases
- Significant responses have been seen (some extending 1-2 years +) in ALL, CLL and NHL of various types with refractory disease
- Toxicity (cytokine release) involving transient mental status changes/encephalopathy and ICU stays can occur
- ORR about 60-70%, CR about 30% (tend to be more durable)
- About 1/3 non-respond, 1/3 short response, 1/3 longer response
- Cytopenias, immunoglobulin depletion occur

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Recent approvals for recurrent DLBCL

- Selinexor (inhibitor of XPO1 nuclear export protein)
  - Oral, twice weekly
  - ORR 29%, CR 13%, 38% of responders > 6 mo
  - Toxicities – cytopenias, GI (nausea), fatigue
- Tafasitamab (anti-CD19) with lenalidomide
  - Weekly x 12 doses then q 2 week with Len 25 mg
  - ORR 67%, CR 39%, median PFS 12 mo
  - Toxicities – infusion, cytopenias, infection, GI

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Burkitt lymphoma

- **Very aggressive NHL**
- **C-myc translocation, t (8;14) or t (8;22)**
- **Treatment should be intensive regimen – R-CODOX-M/R-IVAC, Hyper CVAD – High dose MTX important**
- **DA-R-EPOCH in older patients or HIV + patients**
- **Rituximab adds benefit**
- **CNS treatment or prophylaxis**
- **Tumor lysis prophylaxis important, watch cytopenias and kidney function**

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Lymphoblastic Lymphoma

- **Uncommon**
- **Usually young males with a large mediastinal mass**
- **T-cell 95%**
- **Use an ALL type regimen or Hyper CVAD with a consolidation and POMP maintenance therapy (ALL type 2-3 years)**
- **Use of Peg-asparaginase may improve results – but has toxicity (pancreatitis, thrombosis – need prophylaxis)**
- **CNS prophylaxis also necessary**

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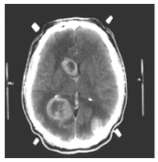
Primary CNS Lymphomas

- **Median age 60's, 1500 cases/yr, non-GCB subtype primarily**
- **HIV, immunosuppression risk factors**
- **High dose MTX-based induction (>3 g/m^2)**
- **Consolidation –**
  - **Cytarabine-based**
  - **Consideration for auto PSCT in CR1**
- **WBRT also consolidation (neurotox esp. > 60 yo) or palliation**
- **Other active agents often included –**
  - **Rituximab, temozolomide (MTR)**
  - **Ibrutinib, checkpoint inhibitors**



Grommes et al, JCO 2017

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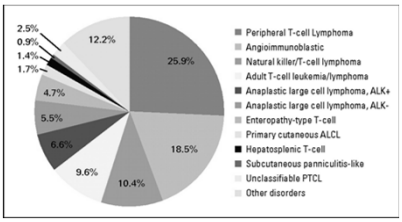
International T-cell Lymphoma Project: Distribution of 1,314 cases of PTCL by consensus diagnosis



Vose et al: J Clin Oncol; 26:4124-4130 2008

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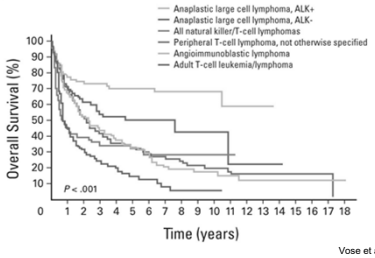
Overall survival in PTCL



Vose et al: *J Clin Oncol.* 2008;26:4124.

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Approach to PTCL

- **CHOP vs CHOEP (? Addition of etoposide of value in age <60)**
- **Unclear value of auto vs allo SCT in first remission vs observation**
- **Add/use brentuximab vedotin (Anti-CD30 ADC) if CD30+ (>10%)**
  - **Anaplastic large cell lymphoma (ALCL) is the key CD30+ subtype**
- **In relapse multiple options (HDAC inhibitors, hypomethylating agents)**
  - **HDAC inhibitors - romidepsin, vorinostat, belinostat**
  - **Antimetabolite – pralatrexate**
  - **Angioimmunoblastic (AITL) – azacitidine with activity**

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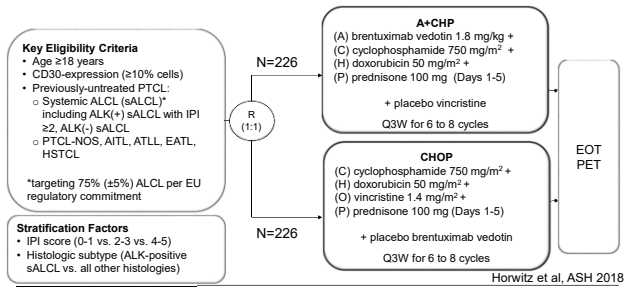
ECHELON-2 Study Design



Horwitz et al, ASH 2018

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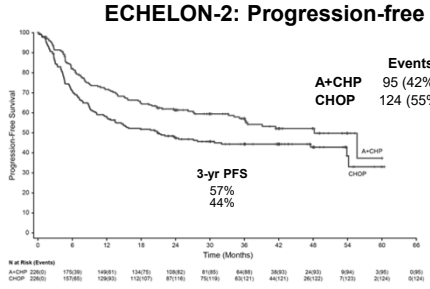
ECHELON-2: Progression-free survival



	Events	HR (95% CI)	*P*
A+CHP	95 (42%)	0.71 (0.54, 0.93)	0.011
CHOP	124 (55%)		

3-yr PFS
57%
44%

Median PFS (95% CI)
48.2 mo (35.2, NE)
20.8 mo (12.7, 47.6)

Median Follow-up
36.2 months

Horwitz et al, ASH 2018

Increased diarrhea, neuropathy

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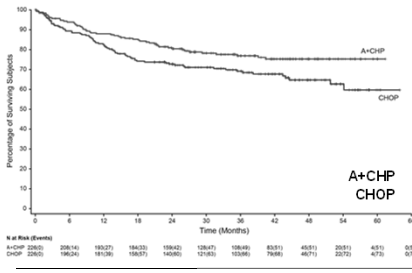
ECHELON-2 Overall Survival



75th Percentile
Not reached
17.5 mo

	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

Median Follow-up
42.1 months

Horwitz et al, ASH 2018

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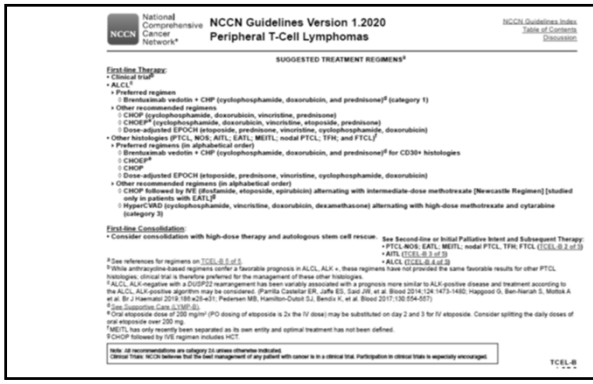

NCCN Guidelines Version 1.2020
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]

First-line Therapy:
• Clinical trial[b]
• ALCL[c]
  ▸ Preferred regimen
    ○ Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] (category 1)
  ▸ Other recommended regimens
    ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
    ○ CHOEP[e] (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
    ○ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
• Other histologies (PTCL, NOS; AITL; EATL; MEITL; nodal PTCL; TFH; and FTCL)[f]
  ▸ Preferred regimens (in alphabetical order)
    ○ Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] for CD30+ histologies
    ○ CHOEP[e]
    ○ CHOP
    ○ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
  ▸ Other recommended regimens (in alphabetical order)
    ○ CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL][g]
    ○ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

First-line Consolidation:
• Consider consolidation with high-dose therapy and autologous stem cell rescue.

See Second-line or Initial Palliative Intent and Subsequent Therapy:
• PTCL-NOS; EATL; MEITL; nodal PTCL, TFH; FTCL (TCEL-B 2 of 9)
• AITL (TCEL-B 3 of 9)
• ALCL (TCEL-B 4 of 9)

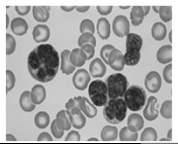
[a] See references for regimens on TCEL-B 5 of 9.
[b] While anthracycline-based regimens confer a favorable prognosis in ALCL, ALK +, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.
[c] ALCL, ALK-negative with a DUSP22 rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered. (Parrilla Castellar ER, Jaffe ES, Said JW, et al. Blood 2014;124:1473-1480; Haggood G, Ben-Neriah S, Mottok A et al. Br J Haematol 2018;180:429-431; Pedersen MB, Hamilton-Dutoit SJ, Bendix K, et al. Blood 2017;130:554-557)
[d] See Supportive Care (UNIF-6)
[e] Oral etoposide dose of 200 mg/m² (PO dosing of etoposide is 2x the IV dose) may be substituted on day 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg.
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] CHOP followed by IVE regimen includes HCT.

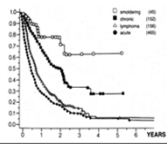
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TCEL-B

Diagnosis of ATL

- **Acute-type ATL (prototype) has characteristic findings, including flower cells in PB, hypercalcemia, lytic bone lesions, and frequent organ involvement (skin, GI-tract, lung)**
- **Peripheral T-cell phenotype (CD4+, CD8-, CD25+)**
- **Presence of antibodies to HTLV-I in serum**
- **Four clinical subtypes; acute-, lymphoma-, chronic- and smoldering types**





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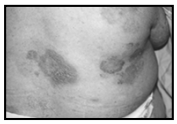
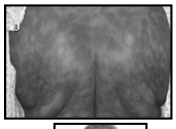
Staging of Mycosis Fungoides


T1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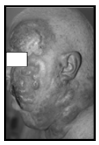
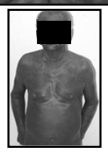

T3


T4

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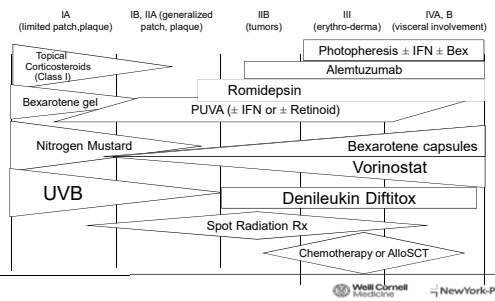
Mycosis Fungoides/Sézary Syndrome treatment approach



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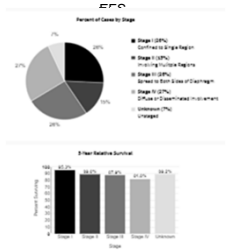
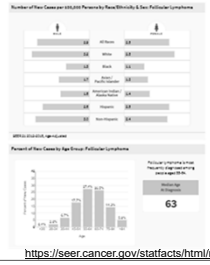
FL epidemiology – SEER Stage and survival





https://seer.cancer.gov/statfacts/html/nhl.html

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Common genetic alterations in follicular lymphoma

Pathway	Gene	Function	Frequency (%)*	Oncogenic alteration
Epigenetic and transcriptional regulation	*KMT2D*	Histone H3K4 methyltransferase	70–90	Loss of function
	CREBBP	Histone H3K27 and H3K18 acetyltransferase	50–70	Loss of function
	Histone-encoding genes	Histone linkers and core histones	20–30	Unknown
	EZH2	Histone H3K27 methyltransferase	10–30	Gain of function
	EP300	Histone H3K27 and H3K18 acetyltransferase	10–20	Loss of function
	MEF2B	Transcription factor	10–20	Gain of function
BCR signalling	*IGH* and *IGL* variable domains	Promotes N-glycosylation	~80	Gain of function
	CARD11	BCR-NF-κB signalling pathway	10–15	Gain of function
Survival	*BCL2*	Anti-apoptosis	Translocations, ~85 Mutations, ~50	Gain of function Unknown
	SOCS1, *STAT6* and *STAT3*	JAK–STAT signalling	20	Gain of function
	NOTCH1, *NOTCH2*, *NOTCH3*, *NOTCH4*, *DTX1* and *SPEN*	NOTCH pathway	18	Unknown
Immune escape	*HVEM*	Receptor	~50[a]	Loss of function
	EPHA7	Ephrin receptor	70[a]	Loss of function

Huet et al, Nat Rev Cancer. 2018;18:224-39

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How do FL patients present?

- Lymphadenopathy
- Palpable mass, edema
- Splenomegaly
- Abnormal blood counts
- Skin lesions, endoscopy findings
- Staging: Exam, labs, imaging (CT, PET), ? BM
- FL grade 1, 2, 3a (similar) vs 3b (like DLBCL)

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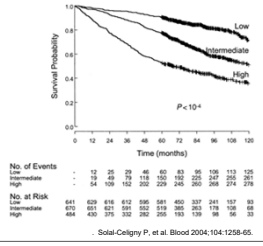
Prognostic tools for newly diagnosed FL patients Follicular Lymphoma International Prognostic Index (FLIPI) - OS

Risk factors:

Nodal sites > 4
Stage III/IV
LDH > ULN
Hgb < 12 g/dL
Age > 60 y

Low risk – 0-1
Intermediate – 2
High – 3-5



. Solal-Celigny P, et al. Blood 2004;104:1258-65.

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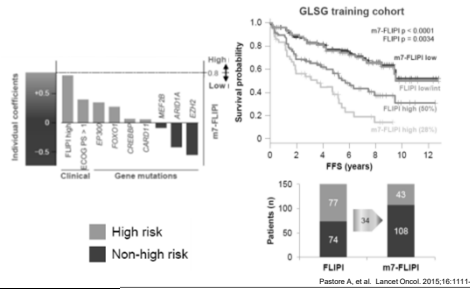
Refinements with the m7-FLIPI



Pastore A, et al. Lancet Oncol. 2015;16:1111-22.

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What follicular lymphoma patients need treatment?

GELF criteria[1]	BNLI criteria[2]
High tumour bulk defined by either • Tumour > 7 cm • 3 nodes in 3 distinct areas each > 3 cm • Symptomatic splenic enlargement • Organ compression • Ascites or pleural effusion	Rapid disease progression in the preceding 3 months
	Life-threatening organ involvement
	Renal or liver infiltration
	Bone lesions
Presence of systemic symptoms	Systemic symptoms or pruritus
Serum LDH or β2-microglobulin above normal values	Hb < 10 g/dL or WBC < 3.0 × 10⁹/L or platelet count < 100 × 10⁹/L, related to marrow involvement

1. Brice P, et al. J Clin Oncol. 1997;15:1110-7.
2. Ardeshna KM, et al. Lancet. 2003;362:516-22.

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Considerations in the choice of therapy for a FL patient at diagnosis or relapse

- Indications for therapy
- Bulk of disease
- Comorbidities
- Toxicity concerns
- Interest in and availability of clinical trials
- Risk of transformation
- Grade (typically treat FL grade 1, 2 and 3A similarly)

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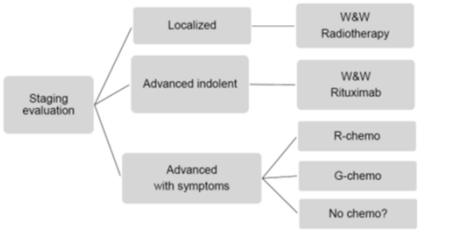
One general framework for initial therapy for FL



R = Rituximab, G = Obinutuzumab

Kahl BS, Yang DT. Blood. 2016; 127:2055-63.

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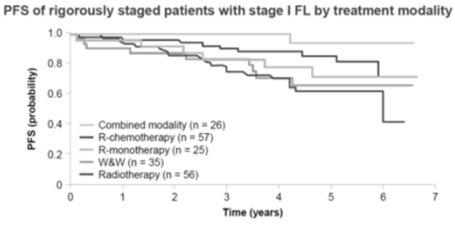
Initial approach to limited stage FL appears to affect PFS OS impact unclear, concept of "cure" is complex



Friedberg JW, et al. J Clin Oncol. 2012;30:3368-75 .

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IFRT + (R-)CVP vs IFRT alone in limited stage FL

- 150 patients, Stage I/II FL (PET not mandatory), 75% stage I
- Randomized 30 Gy IFRT alone or with 6 cycles (R-)CVP
- Median f/u 9.6 years
- 10 year PFS 59% vs 41%
- Better with R-CVP, less disease, PET staged
- Overall survival similar (87% and 95% at 10 years)

MacManus M et al, JCO 2018

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General approach to limited stage FL initial treatment

- **Watch and wait acceptable**
  - Particularly if suspicion of disease elsewhere or alternatively low chance of needing therapy soon (resected low volume disease, some older patients)
- **RT common – location/size dependent - ? "curative"**
  - **Boom-boom (2 fractions less effective than full course)**
- **Unclear value of combined modality therapy**
  - Debatable value for early vs later (if relapse) systemic treatment
- **Favorable long term outlook (OS) regardless of approach**

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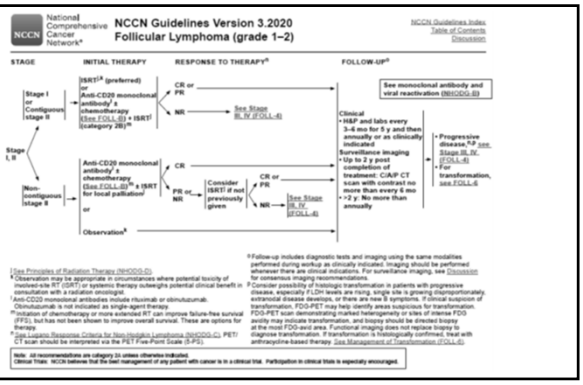
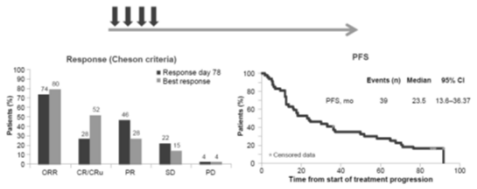


Single agent rituximab for advanced stage low tumor burden FL



Colombat P, et al. Ann Oncol. 2012;23:2380-5. .

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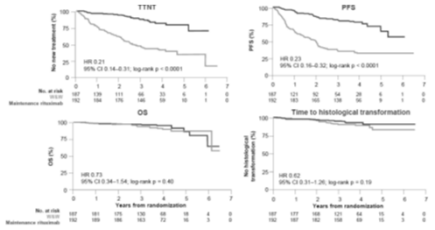
Single agent rituximab vs "watch and wait" for low tumor burden FL



Ardeshna KM, et al. Lancet Oncol. 2014;15:424-35 .

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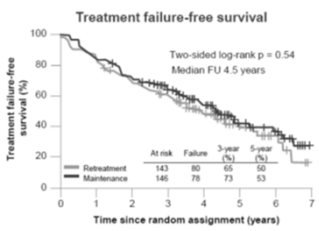
RESORT trial: Single agent rituximab x 4 then maintenance vs retreatment



Kahl BS, et al. J Clin Oncol. 2014;32:3096-102. .

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Approach to low tumor burden, advanced stage FL

- **Watch and wait acceptable**
  - Often at least for some time to allow patient to understand disease and MD to get a sense of pace over time
- **Rituximab x 4 if desires therapy/minimal symptoms/findings without maintenance**
- **Chemoimmunotherapy or other emerging combinations (lenalidomide/rituximab) if patient prefers a longer remission and prefers efficacy/toxicity tradeoffs**

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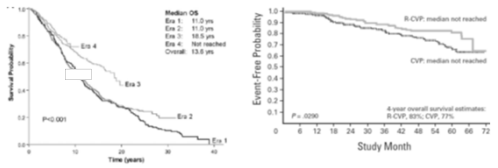
Chemoimmunotherapy for advanced stage FL

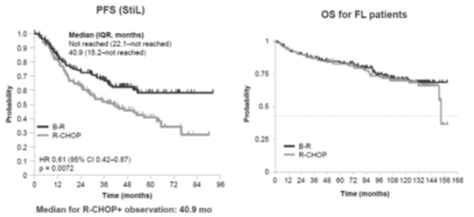
Rituximab added to CHOP, CVP improves survival



R-Bendamustine commonly administered

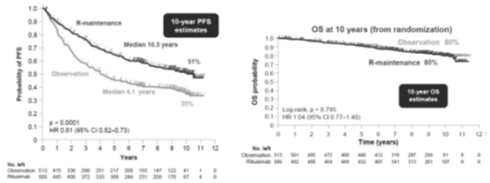
Tan, Blood 2013
Hiddemann, Blood 2005; Marcus, JCO 2008; Rummel, Lancet 2013

Bendamustine-Rituximab vs R-CHOP for advanced stage FL



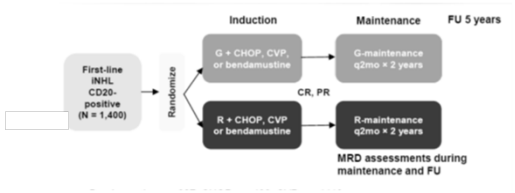
Rummel MJ, et al. Lancet. 2013;381:1203-10. and updated ASCO 2017

PRIMA: Maintenance R after R-CHOP/R-CVP improves PFS but not OS



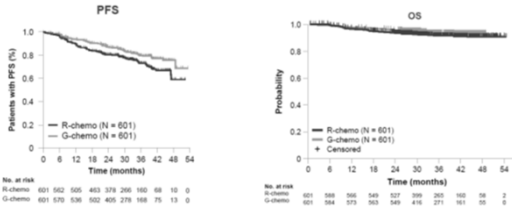
Salles G, et al, ASH 2017

GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance)



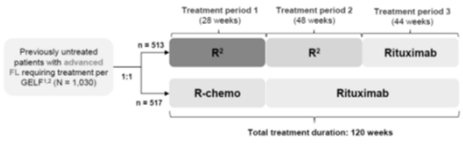
Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance) improves PFS but not OS



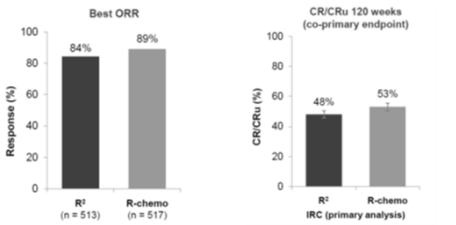
Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R



Morschhauser F, et al, NEJM 2018

RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar ORR and CR as initial therapy for FL



Morschhauser F, et al, NEJM 2018

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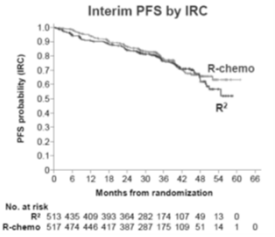
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar PFS and OS as initial therapy for FL



Morschhauser F, et al, NEJM 2018

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RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Safety comparisons

	R²	R-chemo
Grade 4 neutropenia, %	32	50
Time to grade 3/4 neutropenia, months	3.7	0.6
Febrile neutropenia, %	2	7
Range of grade ≥ 3 TEAEs, %	~ 60	~ 70
Grade 3/4 infections, %	2	4
Grade ≥ 3 rash, %	7	1

- R-chemo was associated with more febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia
- R² was associated with more frequent cutaneous reactions, tumour flare, and diarrhoea

Morschhauser F, et al, NEJM 2018

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An approach to higher tumor burden, advanced stage FL

- **Bendamustine + Rituximab induction most commonly**
  - Less toxicity, ? greater/similar efficacy to R-CHOP
  - However, if concern for occult transformation (high SUV), consider R-CHOP
- **Maintenance R use variable (PFS but not OS, unclear QOL)**
- **Lenalidomide + Rituximab of limited value (if tox profile preferred)**
- **Obinutuzumab of variable use (PFS but not OS, unclear QOL)**
  - No subcutaneous option
  - Perhaps "commits" to maintenance based on GALLIUM
  - Potentially more infection with maintenance after B-antibody

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Approach to following FL patients in remission

- Tailor followup to risk of relapse (extent of prior disease, CR vs PR, possibility of occult transformation)
- Periodic history, physical exam, labs (every 4-6 months initially, longer interval over time)
- Minimize surveillance imaging in asymptomatic patients
- Encourage "return to normalcy" as much as possible

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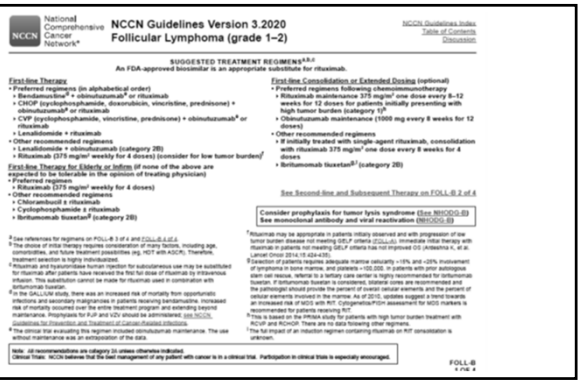

NCCN Guidelines Version 3.2020
Follicular Lymphoma (grade 1–2)

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c]
An FDA-approved biosimilar is an appropriate substitute for rituximab.

First-line Therapy
- Preferred regimens (in alphabetical order)
  - Bendamustine[d] + obinutuzumab[e] or rituximab
  - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab[e] or rituximab
  - CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab[e] or rituximab
  - Lenalidomide + rituximab
- Other recommended regimens
  - Lenalidomide + obinutuzumab (category 2B)
  - Rituximab (375 mg/m² weekly for 4 doses) (consider for low tumor burden)[f]

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Preferred regimen
  - Rituximab (375 mg/m² weekly for 4 doses)
- Other recommended regimens
  - Chlorambucil ± rituximab
  - Cyclophosphamide ± rituximab
  - Ibritumomab tiuxetan[g] (category 2B)

First-line Consolidation or Extended Dosing (optional)
- Preferred regimens following chemoimmunotherapy
  - Rituximab maintenance 375 mg/m² one dose every 8–12 weeks for 12 doses for patients initially presenting with high tumor burden (category 1)[h]
  - Obinutuzumab maintenance (1000 mg every 8 weeks for 12 doses)
- Other recommended regimens
  - If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses
  - Ibritumomab tiuxetan[g] (category 2B)

See Second-line and Subsequent Therapy on FOLL-B 2 of 4

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens on FOLL-B 3 of 4 and FOLL-B 4 of 4.
[b] The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with ASCR). Therefore, treatment selection is highly individualized.
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[d] In the GALLIUM study, there was an increased risk of mortality from opportunistic infections and secondary malignancies in patients receiving bendamustine. Increased risk of mortality occurred over the entire treatment program and extending beyond maintenance. Prophylaxis for PJP and VZV should be administered; see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[e] The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.
[f] Rituximab may be appropriate in patients initially observed and with progression of low tumor burden disease not meeting GELF criteria (FOLL-A). Immediate initial therapy with rituximab in patients not meeting GELF criteria has not improved OS (Ardeshna K, et al. Lancet Oncol 2014;15:424-435).
[g] Selection of patients requires adequate marrow cellularity (>10% and <25% involvement of lymphoma in bone marrow, and platelets >100,000). In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan. If ibritumomab tiuxetan is considered, dosimetry scans are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT. Cytogenetics/FISH assessment for MDS markers is recommended for patients receiving RIT.
[h] This is based on the PRIMA study for patients with high tumor burden treatment with RCVP and RCHOP. There are no data following other regimens.
[i] The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-B

Early relapse of FL defines high risk group needing better therapies

30

Multiple Myeloma, Plasmacytoma, MGUS

S. Vincent Rajkumar, MD

August 16, 2020

31

Hodgkin's Disease

John Leonard, MD

August 16, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

31 – Hodgkin's Disease

John P. Leonard, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consulting - Gilead, Celgene, Sutro, Genentech/Roche, Bayer, ADC Therapeutics, MEI Pharma, AstraZeneca, Karyopharm, Miltenyi, Regeneron, BMS, Epizyme

Hodgkin lymphoma

- **Epidemiology**
- **Lymphocyte Predominant vs Classical**
- **Initial therapy limited stage**
- **Initial therapy advanced stage**
- **Relapsed disease**
- **Survivorship**

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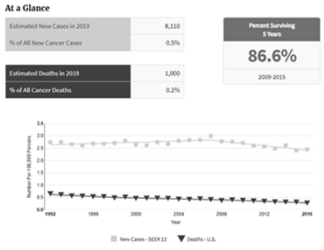
Hodgkin lymphoma epidemiology - SEER



https://seer.cancer.gov/statfacts/html/hodg.html

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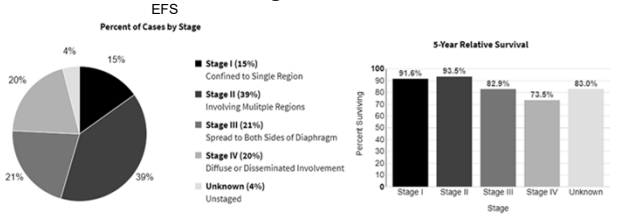
Hodgkin lymphoma epidemiology – SEER Stage and survival

EFS



https://seer.cancer.gov/statfacts/html/hodg.html

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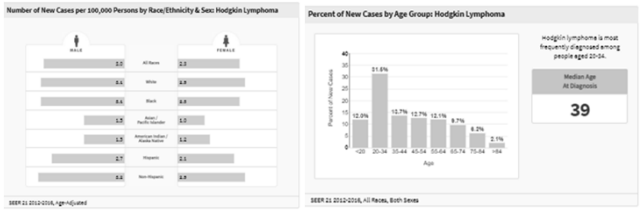
Hodgkin lymphoma epidemiology – SEER Sex and age

EFS



https://seer.cancer.gov/statfacts/html/hodg.html

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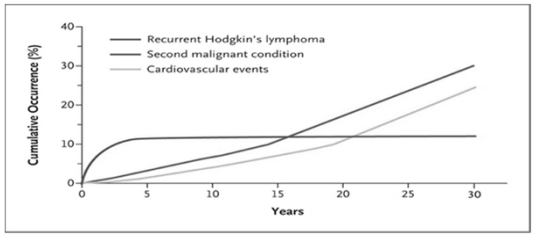
Competing risks after combined modality therapy



Minimize late effects

Maximize cure

Armitage JO. N Engl J Med 2010;363:653-662.

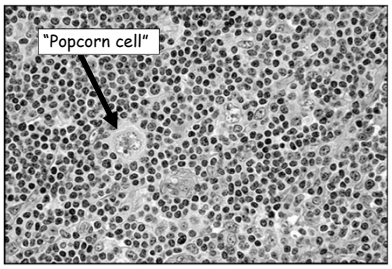
Hodgkin lymphoma

- Risk factors
  - Genetic, Epstein Barr Virus, immunosuppression
- Presenting signs and symptoms
  - Painless LN enlargement (neck, axilla, mediastinum most common)
  - "B symptoms" (fever, night sweats, weight loss)
  - Other (fatigue, pruritis, cough/SOB, alcohol pain)

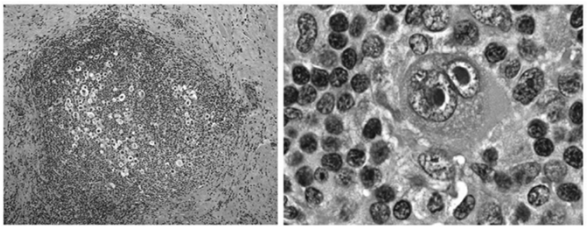
Hodgkin lymphoma – Key subtypes

- Nodular lymphocyte-predominant (NLP) – 5%
  - Pathology – "popcorn-like" cells, CD20+, CD30-, CD15-
- Classical Hodgkin lymphoma (cHL) – 95%
  - Pathology – Hodgkin Reed Sternberg cells in background of inflammatory cells, CD15+, CD30+, CD20-

Lymphocyte Predominant HL



Classical Hodgkin RS cells in background of inflammatory infiltrate in cHL



Hodgkin lymphoma - workup

- Excisional biopsy for diagnosis
- History and physical exam
- Blood tests – CBC, ESR, Chem, Liver enzymes, BHCG
- PET/CT
- Fertility
- Additional in some cases
  - PFT with DLCO (Bleo), HIV, Hepatitis B/C, Bone marrow (unlikely positive if PET neg), ECHO/MUGA

Revised staging system for nodal lymphomas

Stage	Involvement	Extranodal Status
Limited		
Stage I	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited, contiguous extranodal involvement
Bulky stage II	II as above with "bulky" disease ≥ 7.5 cm	N/A
Advanced		
Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	N/A
Stage IV	Additional non-contiguous extranodal involvement	

Cheson et al, JCO 32: 3059-3067, 2014

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Nodular LP HL and classical HL
Patient characteristics (%)

	NLPHL (n=394)	cHL (n=7904)
Age (years, median)	37	33
Male	75	56
B-Symptoms	9	40
Early favorable	63	22
Intermediate	16	39
Advanced	21	39

Nogova et al JCO 2008

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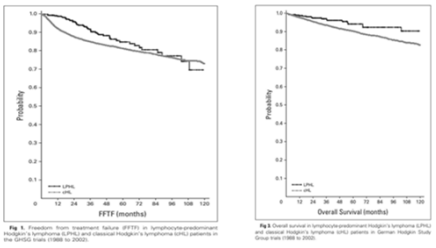
NLPHL and classical HL
FFTF and Overall Survival



Nogova et al JCO 2008

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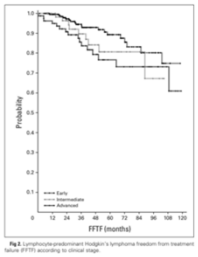
Progression-free survival of LP Hodgkin Lymphoma



Localized disease typically treated with RT

Advanced stage disease typically treated with systemic chemotherapy (ABVD or CHOP), ? addition of rituximab, or observation

Randomized comparisons lacking

Nogova et al JCO 2008

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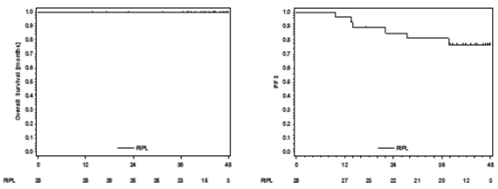
Rituximab in NLPHL
Phase II in stage IA pts (PFS and OS)



Overall survival

Progression-free survival

Eichenauer DA et al, Blood 2011: 118(16):4363-5

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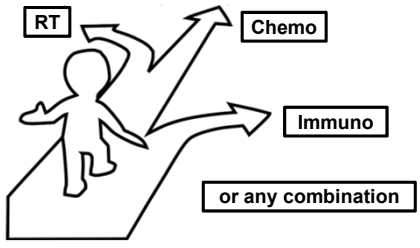
NLPHL - The early stage dilemma



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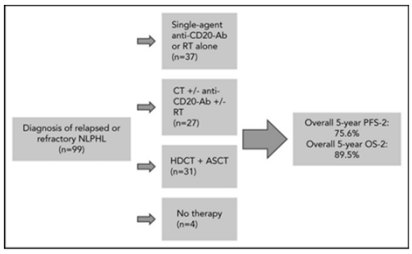
Various approaches to recurrent NLPHL



Eichenauer DA et al. Blood 2018;132:1519-1525

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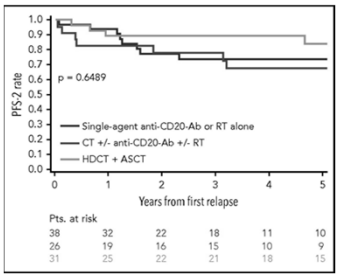
PFS-2 with various approaches to recurrent NLPHL



Eichenauer DA et al. Blood 2018;132:1519-1525

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How should we treat NLPHL?

- NLPHL (CD30$^-$CD15$^-$CD20$^+$) destinguished by immunohistology from cHL (CD30$^+$CD15$^+$CD20$^-$)
- Prognosis slightly better although more late relapses
- IF-RT primarily in stage IA NLPHL
- Advanced stage, ABVD longest history, ?Rituximab (anti-CD20)
- R-ABVD and R-BEACOPP being evaluated, observation also ok
- Anti-CD20 Moabs an option for relapsed NLPHL (and ? upfront)
- ? Use of NHL regimens (e.g. R-CHOP)
- Biopsy at relapse looking for diffuse large B cell (DLBCL) transformation

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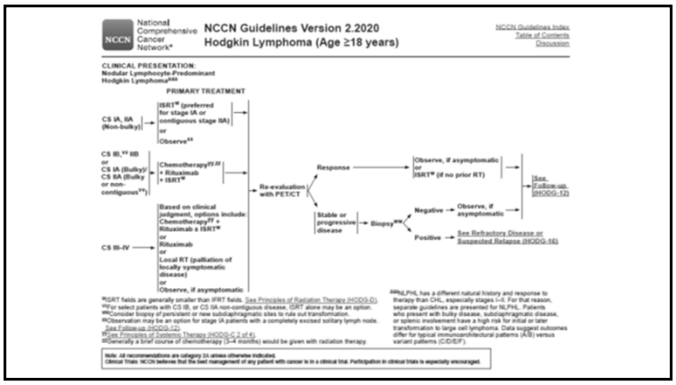

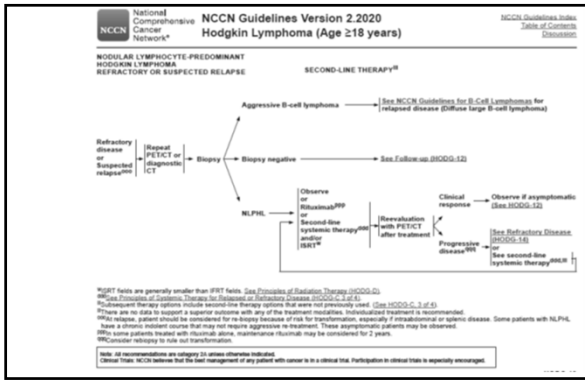

Hodgkin lymphoma (cHL): Early-stage risk groups

Early stage: favorable — **I, II (with ø RF)**

Early stage unfavorable (Intermediate) — **I, II with RF**

Advanced stages — **III, IV (IIB with bulk >10cm)**

Stage I/II risk factors a) Large mediastinal mass (LMM)
b) Extranodal involvement
c) Elevated ESR > 50
d) ≥ 3 involved lymph node areas

*****EORTC definition of risk factors differs from GHSG*****

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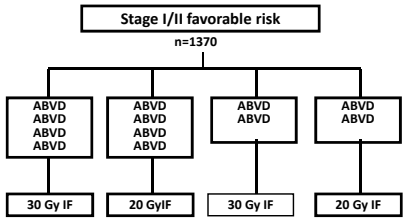
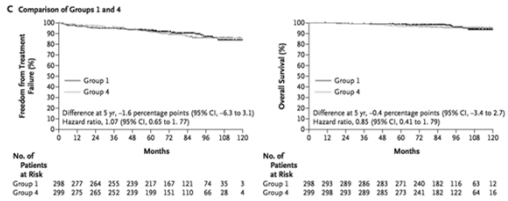
HD10 Trial GHSG



Engert A et al. N Engl J Med 2010

HD10: ABVD x 2 + 20Gy is a standard in low risk early stage cHL



HD 13 trial subsequently showed AVD inferior to ABVD in this setting

Engert A et al. N Engl J Med 2010

Radiation-free approach: HD-6

Patients with Clinical Stage I-IIA non-bulky Hodgkin's lymphoma

Standard Arm
Treatment by Strata
Favourable:STNI (35Gy)
Unfavourable*: ABVD x 2 + STNI

Experimental Arm:
Both Strata: ABVD x 2
If CR: x 2 more = 4
If PR: x 4 more = 6

*Unfavorable:
- Age > 40
- ESR > 50
- MC / LD histology
- ≥ 4 sites

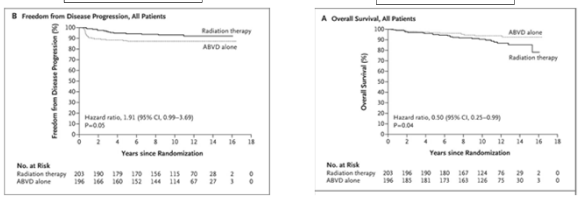
Primary Outcome:
12 yr OS

Meyer RM et al. NEJM 2012

HD-6 – pros and cons of XRT

FFDP better in RT group

OS better in ABVD group



Meyer RM et al. N Engl J Med 2012;366:399-408.

HD6 - Causes of death according to treatment/risk

Table 2. Causes of Death, According to Treatment Strategy and Risk Profile.

Cause of Death	ABVD Alone (N=196)			Radiation Therapy, with or without ABVD (N=203)		
	Total	Cohort with Favorable Risk Profile	Cohort with Unfavorable Risk Profile	Total	Cohort with Favorable Risk Profile	Cohort with Unfavorable Risk Profile
	number of patients					
Any	12	1	11	24	1	23
Hodgkin's lymphoma*	6	1	5	4	0	4
Second cancer	4	0	4	10	1	9
Cardiac event	2	0	2	2	0	2
Related to infection	0	0	0	3	0	3
Other†	0	0	0	5	0	5

* Deaths due to acute treatment-related protocol therapy or to therapy given for progressive Hodgkin's lymphoma were attributed to Hodgkin's lymphoma.
† Other causes of death included Alzheimer's disease, accidental drowning, suicide, and respiratory failure; the cause of one death was unknown.

Meyer RM et al. N Engl J Med 2012;366:399-408.

PET adapted approach – Deauville 5-Point Scale for Interim-PET Interpretation

1. No uptake
2. Uptake ≤ mediastinum

Negative scan

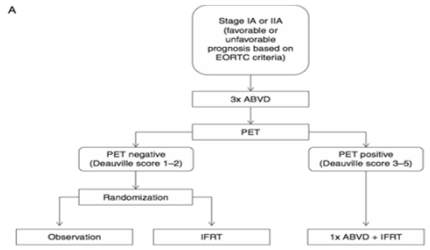
3. Uptake > mediastinum but ≤ liver

Depends on study

4. Moderately increased uptake compared to liver
5. Markedly increased uptake compared to liver or new areas of FDG uptake

Positive scan

RAPID UK PET-driven approach in early stage HL



Radford et al. N Engl J Med. 2015;372: 1598–607.

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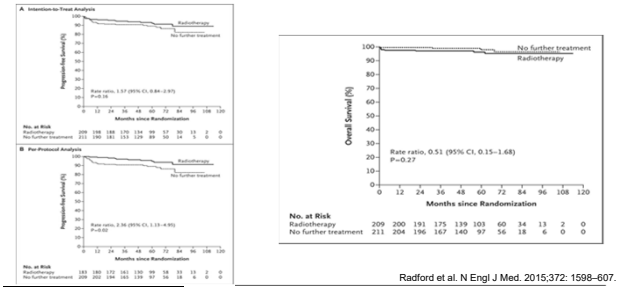
RAPID UK PET-driven approach in early stage HL – PET negative



Radford et al. N Engl J Med. 2015;372: 1598–607.

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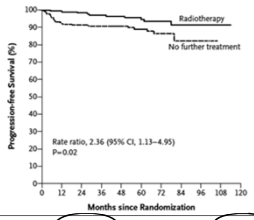
RAPID: PFS in the Per Protocol Population



ITT Population
N = 420

- **3-yr absolute risk difference: 95% CI -8.8 to 1.3 (exceeded pre-specified non-inferiority boundary)**

3-year PFS 97.1% (94.7%-99.6%) vs 90.8% (86.8%-94.7%)

Rate Ratio 2.36 in favor of IFRT, *P* = 0.02

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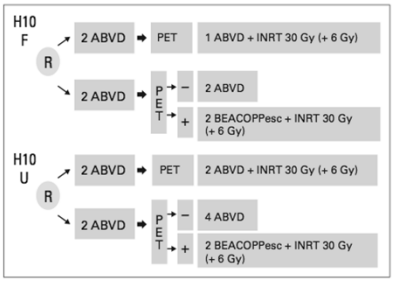
Radford J, et al. *N Engl J Med*. 2015;372(17):1598-1607.

H10: Interim PET driven strategy in early HL



Raemaekers et al. JCO. 2014

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Interim analysis H10

Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

Subset	No. of Patients	No. of Observed Events	HR	Adjusted CI*	*P*†	1-Year PFS %	1-Year PFS Adjusted CI*
Favorable					.017		
Standard	188	1	1.00			100.00	
Experimental	193	9	9.36	2.45 to 35.73		94.93	91.89 to 96.85
Unfavorable					.026		
Standard	251	7	1.00			97.28	95.17 to 98.48
Experimental	268	16	2.42	1.35 to 4.36		94.70	92.11 to 96.46

Abbreviations: HR, hazard ratio; PET, positron emission tomography; PFS, progression-free survival.
*Confidence level adjusted to significance level used in interim test: 79.6% CI for favorable group and 80.4% CI for unfavorable group.
†One-sided Wald-test *P* value of superiority test.

Chemotherapy only arms closed early

Raemaekers et al. JCO. 2014

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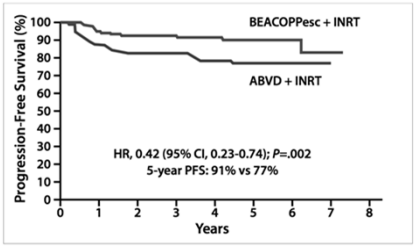
BEACOPP arm with improved PFS for PET2 positive patients



Raemaekers et al. Lugano 2015

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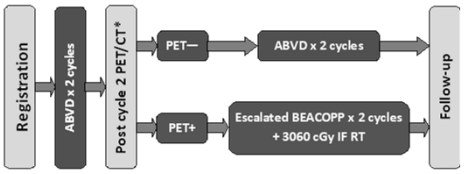
CALGB 50604 Design



*PET/CT reviewed centrally (2 reviewers, 1 adjudicator) assessed according to 5-point scale (Deauville criteria)

- Phase II trial in newly-diagnosed stages I/II non-bulky HL conducted in Intergroup (CALGB/Alliance, SWOG, ECOG)

Prophylactic G-CSF only after febrile neutropenia or neutropenia and infection with ABVD. Prophylactic G-CSF with escalated BEACOPP.

Straus et al, Blood 2018; 132:1013-1021

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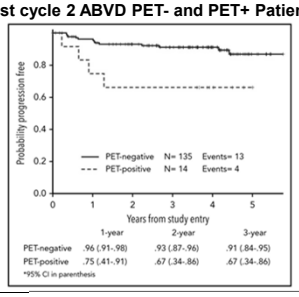
CALGB 50604 Progression Free Survival

Post cycle 2 ABVD PET- and PET+ Patients



Straus et al, Blood 2018; 132:1013-1021

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PET adapted approach – Deauville 5-Point Scale for Interim-PET Interpretation

1. No uptake 2. Uptake ≤ mediastinum	Negative scan
3. Uptake > mediastinum but ≤ liver	Depends on study
4. Moderately increased uptake compared to liver 5. Markedly increased uptake compared to liver or new areas of FDG uptake	Positive scan

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CALGB 50604: PFS according to Deauville score for PET2-

Deauville Score	N (%)	3-yr PFS
1-3	137 (91%)	92% (84%-96%)
1-2	109 (75%)	95% (87%-98%)

- PET- by scores 1-3 vs 1-2 reduces patients exposed to IF RT by 16% (9% PET+ vs 25% PET+) while maintaining PFS>90%
- RAPID trial[1] used Deauville 1-2

[1]NEJM 372: 1598-1607, 2015

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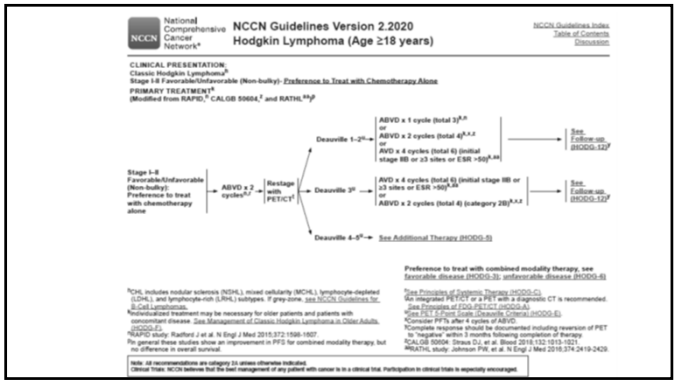
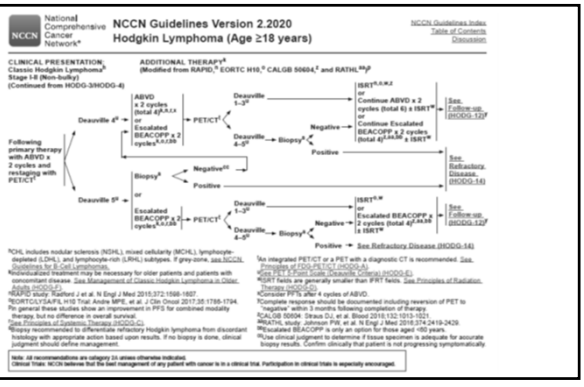

NCCN Guidelines Version 2.2020
Hodgkin Lymphoma (Age ≥18 years)


NCCN Guidelines Version 2.2020
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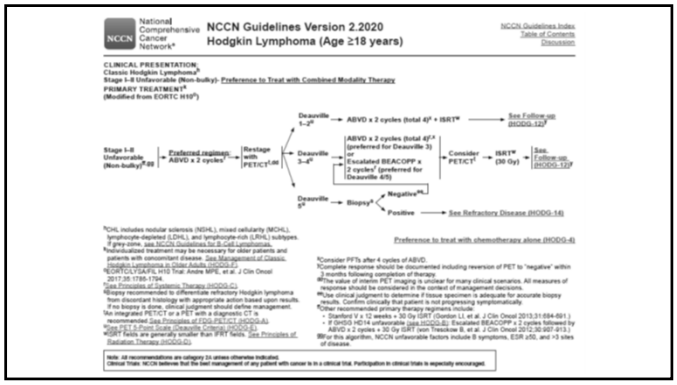
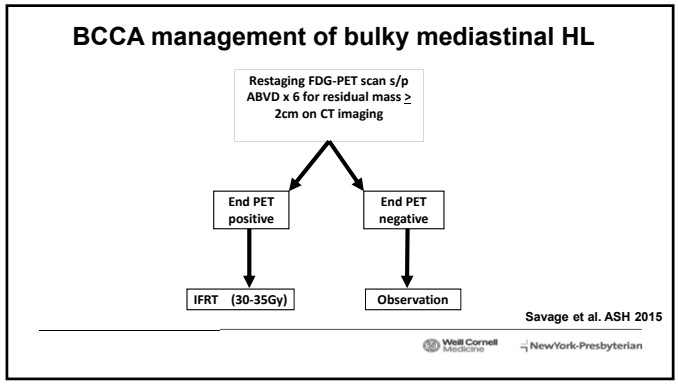
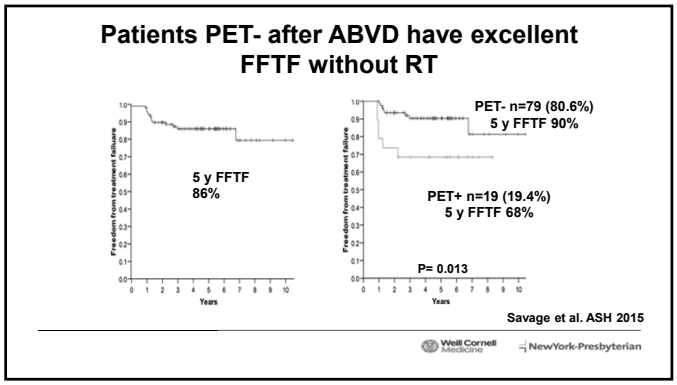
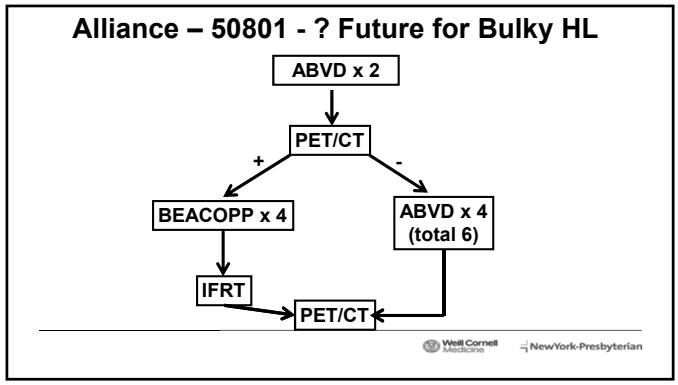
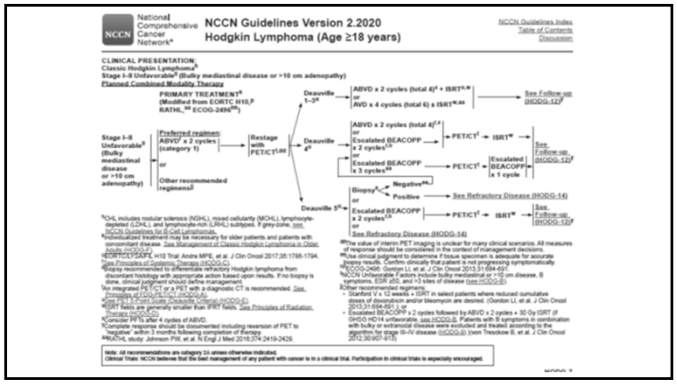
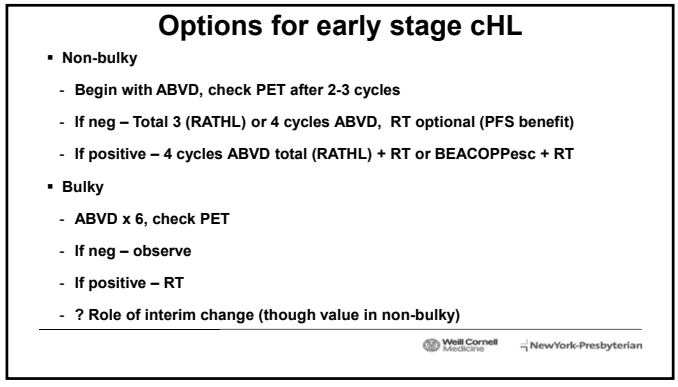






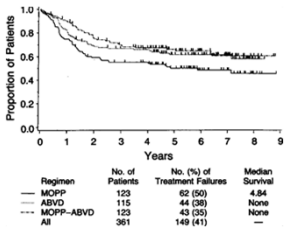






CALGB 8251 ABVD/MOPP/Hybrid in advanced stage cHL

Time to Treatment Failure



Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
MOPP	123	62 (50)	4.84
ABVD	115	44 (38)	None
MOPP–ABVD	129	43 (35)	None
All	361	149 (41)	—

Canellos et al, NEJM 1992

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International Prognostic Score (IPS) for Advanced HL

- **Albumin < 4.0 gm/dl**
- **Hemoglobin < 10.5 gm/dl**
- **Male gender**
- **Age ≥ 45 years**
- **Stage IV disease**
- **WBC > 15,000/mm^3**
- **Lymphocyte count < 600/mm^3**

Hasenclever, et al: N Engl J Med 339: 1506-1514, 1998.

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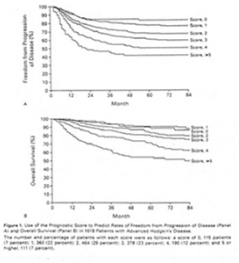
Is risk stratification via IPS useful?

Hasenclever
N=1618, validation on N=2643

IPS 5-7: 5-yr. FFP 42%, 5-yr. OS 56%



Hasenclever D, et al. *N Engl J Med.* 1998;339:1506-1514.

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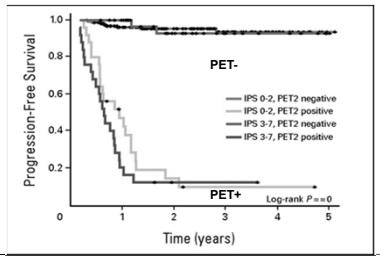
Early PET in HL

PFS by PET2 and IPS



Gallamini, J Clin Oncol. 25:3746, 2007.

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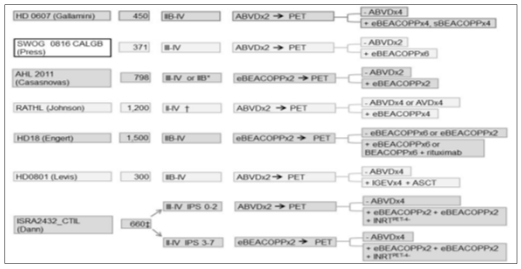
Interim PET adapted strategies in advanced HL



Press et al JCO 2016

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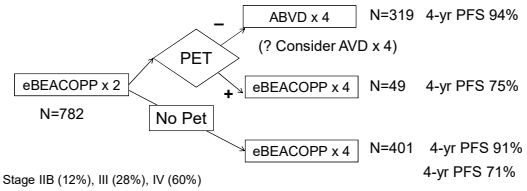
Interim PET Driven Treatment *De-Escalation*

AHL2011 LYSA Study



- High risk Stage IIB (12%), III (28%), IV (60%)
- 4-yr PFS → standard (87.4%) and PET driven (87.1%), P= 0.68

Casasnovas O et al. Blood 2015;126:577

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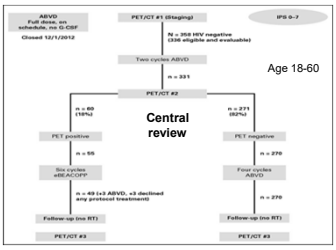
US Intergroup Trial (S0816)
Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma



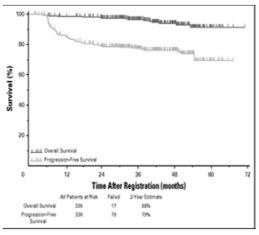
Age 18-60

Central review

	%
Median age yr	32 (18-60)
Males	%
Stage III IV	52% 48%
B symptoms	%
Bulky disease	
IPS 0-2 3-7	49% 51%

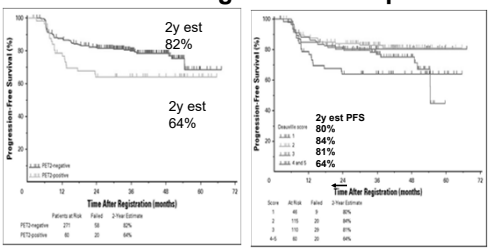
Press et al. JCO 2016

Results: US Intergroup Trial (S0816)
OS and PFS regardless of interim PET scan result or treatment arm



Press et al. JCO 2016

Results: US Intergroup Trial (S0186)
PFS according to PET-2 response

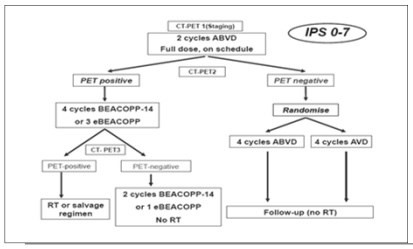


Press et al. JCO 2016

No difference in OS: 2 y estimate 98%

Advances Hodgkin Lymphoma: UK RATHL Trial
Interim PET Based Therapy Escalation

Deauville 1-3 considered negative

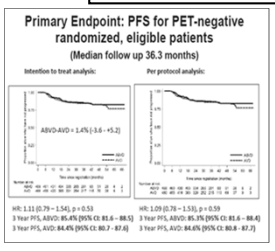


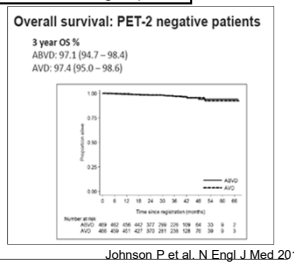
	%
Median age yr	33 (18-79)
Male gender	55%
Stage II III IV	41% 31% 28%
B symptoms	61%
Bulky disease	32%
PS 0 or 1	96%
IPS 0-1 2-3 ≥4	34% 49% 18%

Johnson P et al. N Engl J Med 2016

RATHL Results: Bleomycin can be omitted if interim PET-

AVD is non-inferior to ABVD in all sub groups



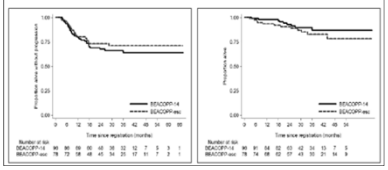


Johnson P et al. N Engl J Med 2016

Results for patients with positive PET-2

3 year PFS %
BEACOPP-14: 66.0 (55.0 – 74.9)
eBEACOPP 71.1 (59.0 – 80.2)

3 year OS %
BEACOPP-14: 89.6 (80.0 – 94.7)
eBEACOPP: 82.8 (70.5 – 90.2)



Escalated therapy for interim PET + patients has promising PFS results

Johnson P et al. N Engl J Med 2016

Summary of PET adapted strategies

- Results of escalation/de-escalation (Start with ABVD vs BEACOPP) strategies similar
- Interim PET is not a perfect test
  - Some treatment failures observed, even in PET2-negative patients (most relapses)
- Bleomycin can be safely omitted if PET scan is negative after 2 cycles of ABVD
  - PET – rate ~ 80%
- Escalation of therapy if PET-2 positive may improve outcome over historical results with ABVD
  - No control arm with continuing with ABVD, toxicity issues with BEACOPP
  - BEACOPP or IGEV salvage/ASCT

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Phase III Frontline HL (ECHELON-1)

Newly Diagnosed Stage 3-4 cHL Patients ≥18 y

R

Experimental Arm AVD + B-Vedotin x 6

Standard of Care ABVD x 6

- N= 1334
- Completed Accrual late 2015
- Primary outcome measure: "modified" PFS

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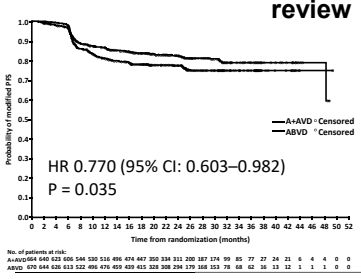
ECHELON-1: Modified PFS per independent review



Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-yr	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

Connors J. et al NEJM. 2018 378:331-44

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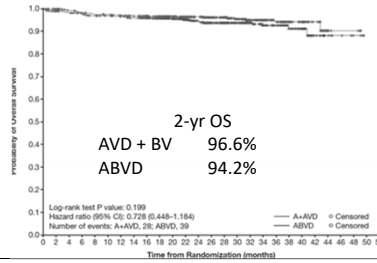
ECHELON-1: Overall Survival



Connors J. et al NEJM 2018; 378:331-344

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Adverse Events ECHELON-1

Adverse Event	A + AVD (n=664)		ABVD (n=670)	
	All	Gr ≥ 3	All	Gr ≥ 3
Any		83%		66%
Hospitalization	37%		28%	
Toxic Death		1% (n=7)		1.6% (n=11)
Pneumonitis	2%	<1%	7%	3%
F/N (no GCSF)		22%		8%
F/N (+ GCSF)		11%		7%
Peripheral neuropathy	67%	11%	43%	2%

Connors J. et al NEJM 2018; 378:331-344

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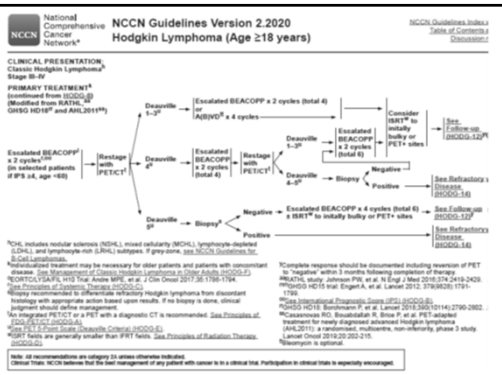

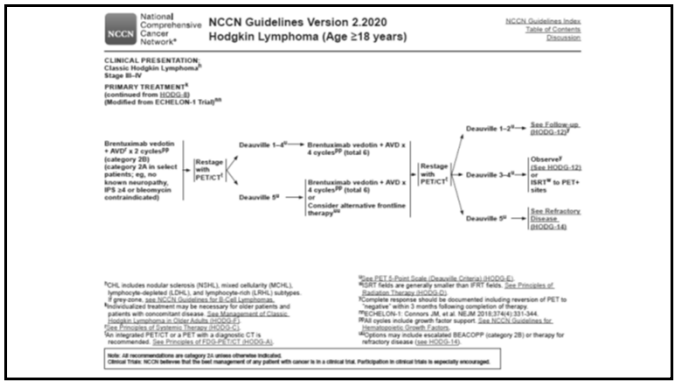

Older Patients with HL

10 - 20% of HL occurs in patients age ≥ 60

Subset Analysis of Phase III Study of ABVD and Stanford V

	Older (≥60 years)	Younger	P Value
5-yr FFS	48%	74%	0.002
5-yr OS	58%	90%	<0.0001
Tx-related mortality	9%	0.3%	<0.001

Time to progression similar for younger and older pts, but deaths without progression significantly higher in older pts.

Evens et al, Br J Haematol 2013;161:76-86

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Pulmonary toxicity in older patients

- US multicenter retrospective analysis, 92 pts ages 60-89
  - 32% incidence of bleomycin lung toxicity (BLT)
  - 25% mortality among those with BLT
- French multicenter retrospective analysis, 147 pts, ≥ 60, ABVD
  - 21% had Gr 3 -4 pulmonary toxicity
- RAPID trial, N = 602 (median age 34)
  - 6 treatment related deaths on ABVD (ages 60, 62, 70, 71, 73, 75)
  - 5/6 due to pneumonia/pneumonitis

Evens AM, Blood 2012; 119:692, Stamatoullas A, Br J Hematol 2015;170:179

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Front-line sequential BV + AVD in older patients

- Small multicenter trial, N = 48
- Elig: age ≥ 60, stage IIB – IV
- Treatment (no bleomycin)
  - BV x 2 → AVD x 6 → BV x 4
- 52% completed ALL treatment, 6 pts completed < 2 cycles AVD
- ITT - ORR 88%, CR 81%
  - Response rate after C2 BV - ORR 86%, CR 30%

Evens AM et al. Blood 2017 130:733

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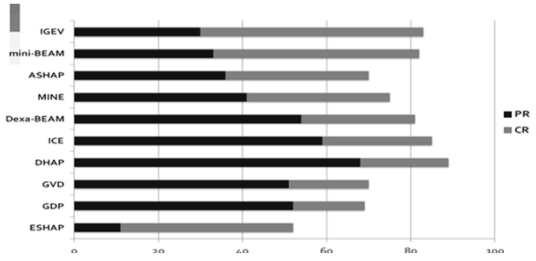
Results of pre-transplant regimens in HL



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Relapsed HL combinations for pre-ASCT

Regimen	CR rate	PFS/EFS
ICE	60%	4-yr 68%
ICE → GVD	78%	4-yr 70%
BV → ICE	76%	2-yr 80%
BV + Bendamustine	79%	1-yr 88%
BV + ICE	88%	
BV + ESHAP	70%	
BV + Nivolumab	61%	6-mo 89%

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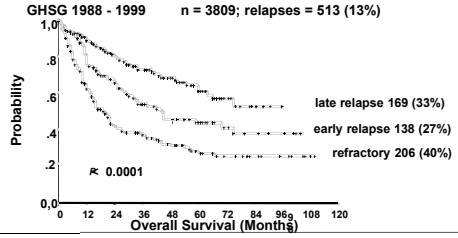
Primary progressive, early and late relapsed HL Outcome after secondary Tx (including AutoSCT)



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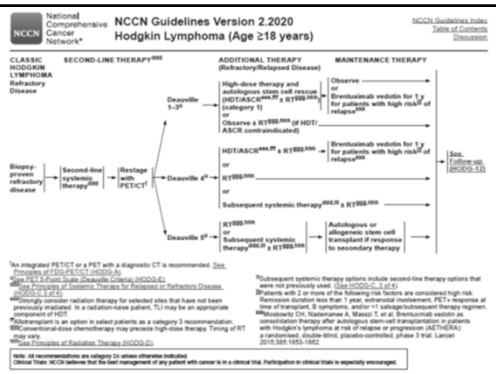
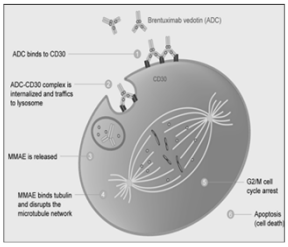


Brentuximab vedotin



- **Anti-CD30 monoclonal antibody conjugated to monomethyl auristatin (MMAE), a highly potent anti-microtubule toxin**
- **Pivotal study in relapsed/refractory cHL after auto SCT:**
  - **ORR 75%**
  - **CRR 34%**
  - **Median DOR 20.5 months**

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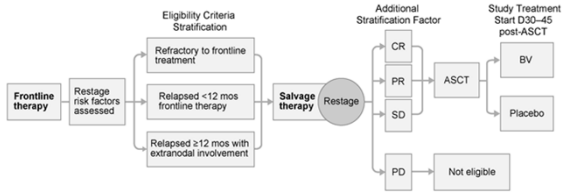
Brentuximab vedotin consolidation after AutoSCT: AETHERA Trial

- **329 patients were randomized at 78 sites in North America and Europe**
- **BV/placebo x 16 cycles every 21d**



Moskowitz et al, Lancet, 2015

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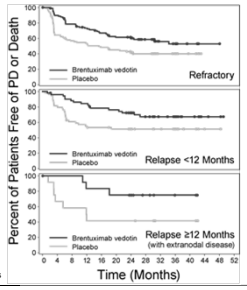
PFS* by Eligibility Criteria



N=196

N=107

No overall survival benefit

N=26

* Per investigator analysis

Moskowitz et al, Lancet, 2015

Moskowitz et al, Lancet, 2015

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Key points about brentuximab vedotin in cHL

- **Improves PFS (not OS) when incorporated (replacing Bleomycin) in ABVD as initial therapy**
  - **In A(BV)VD upfront need GCSF**
- **Studies in elderly patients and as part of second line rx**
- **Improves PFS (not OS) after AutoSCT**
- **ORR 70+% single agent in relapsed setting, 30-35% CR, some durable**
- **Principal toxicities neuropathy, cytopenias, rash**

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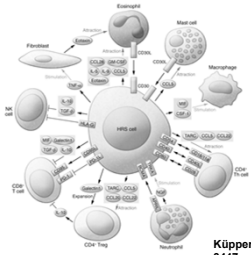
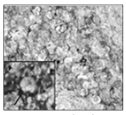
Cellular interactions in the HL microenvironment



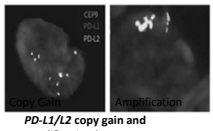
Küppers et al. J Clin Invest. 2012;122(10):3439-3447.

PD-1 and Hodgkin lymphoma

- Classical HL (cHL) is characterized pathologically by a failed immune response
- cHL frequently harbors amplification at 9p24.1 leading to overexpression of PD-L1 and PD-L2
- cHL may have a genetically driven vulnerability to PD-1 blockade



PD-L1 expression in cHL



PD-L1/L2 copy gain and amplification by FISH

Chen et al. *Clin Cancer Res.* 2013.
Ansell et al. *N Engl J Med.* 2015.

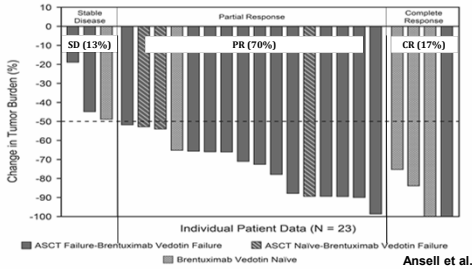
Pembrolizumab in recurrent HL: Keynote 087

	Cohort 1 Progressed after ASCT and subsequent BV therapy N = 69		Cohort 2 Failed salvage chemotherapy, ineligible for ASCT and failed BV therapy N = 81		Cohort 3 Failed ASCT and not treated with BV after transplantation N = 60	
	n (%)	95% CI†	n (%)	95% CI†	n (%)	95% CI†
ORR	**51 (73.9)**	**61.9-83.7**	**52 (64.2)**	**52.8-74.6**	**42 (70.0)**	**56.8-81.2**
Complete remission‡	15 (21.7)	12.7-33.3	20 (24.7)	15.8-35.5	12 (20.0)	10.8-32.3
Partial remission	36 (52.2)	39.8-64.4	32 (39.5)	28.8-51.0	30 (50.0)	36.8-63.2
Stable disease	11 (15.9)	8.2-26.7	10 (12.3)	6.1-21.5	10 (16.7)	8.3-28.5
Progressive disease	5 (7.2)	2.4-16.1	17 (21.0)	12.7-31.5	8 (13.3)	5.9-24.6
Unable to determine	2 (2.9)	0.4-10.1	2 (2.5)	0.3-8.6	0 (0)	–

†Based on binomial exact confidence interval method.
‡For complete remission, a residual mass was permitted for patients who were negative on PET scanning.

Moskowitz et al. ASH 2016 abstract #1107

Nivolumab in relapsed/refractory cHL

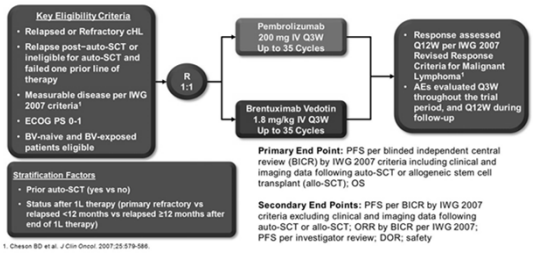


Ansell et al. NEJM. 2015

Key points about immune checkpoint inhibitors in cHL

- Active in relapsed/refractory setting, some durable (about 70% ORR), about 30% CR
- Under evaluation as part of frontline and relapsed setting
- Principal toxicities autoimmune as in other settings

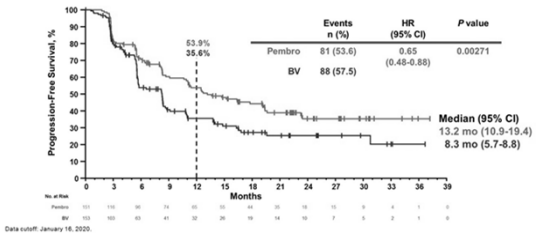
Pembrolizumab vs Brentuximab Vedotin in recurrent HL: KEYNOTE-204



1. Cheson BD et al. *J Clin Oncol.* 2007;25:579-586.

Kuruvilla J, et al. ASCO 2020 (abstr 8005).

Pembrolizumab vs Brentuximab Vedotin in recurrent HL: KEYNOTE-204



Kuruvilla J, et al. ASCO 2020 (abstr 8005).

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Surveillance and followup of cHL patients in remission

- Beyond 2 years, relapse risk lower
- Surveillance scans of little value in asymptomatic patients (avoid)
- Periodic 3-4 mo, then 6 months, then yearly visits
  - History, physical exam, labs, symptom/finding-directed imaging as needed
- Monitor for long term toxicity

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Hodgkin lymphoma: Success comes at a cost

• Secondary Malignancies	AML	← Alkylating agents
	NHL	
	Solid tumors	← Combined Therapy
• Organ damage	Lung	← Bleomycin-Radiation Therapy
	Heart	← Combined Therapy
	Thyroid	← Radiation Therapy
• Others	Sterility	← MOPP>BEACOPP>ABVD
	Fatigue	
	Psychosocial	

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AML, acute myeloid leukemia; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; MOPP: methlorethamine, vincristine, procarbazine, prednisone; NHL, non-Hodgkin leukemia

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Serious late effects

- Second Solid Cancers
  - 18,862 5-yr survivors in 13 population-based registries

Age at Diagnosis	30 year cumulative incidence of second cancer			
	♂ - HL	♂ - control	♀ - HL	♀ - control
20 yrs	10.5%	2.4%	24.3%	4.5%
30 yrs	18.3%	6.9%	26.1%	8.9%
40 yrs	27.1%	17.4%	26.7%	15.4%

  - No difference in RR in pts tx 1970-84 vs. 1985-96

Hodgson D et al. *JCO* 2007: 25:1489

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Late effects: Cardiac

- CAD/MI
- Valvular heart disease
- Stroke
- CHF
- Risk factors from treatment
  - Radiation to areas near heart/neck
  - Doxorubicin
  - Typical cardiac risk factors

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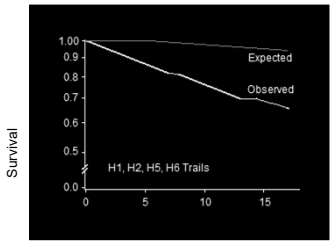
Risk of hypothyroidism after neck RT (Stanford)



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Recovery of spermatogenesis after HL therapy

Regimen	Recovery
MOPP-like	5-14%
ABVD	100%
BEACOPP	10% (variable)

Female fertility nearly unchanged after ABVD, affected by other regimens

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Survivorship care

- Monitoring for relapse
- Preventing late effects
- Diagnosing late effects
- Managing late effects
- Other health conditions
- General preventative care/wellness
- Coordinating with other providers

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Breast cancer risk associated with chest RT
Greater risk with younger patients receiving RT
Surveillance guidelines

NCCN	COG (adapted)
– Initiate 8-10y post-RT or age 40, whichever *first*	– Initiate 8y post-RT or age 25, whichever *last*
– Annual mammogram + breast MR if age ≤30 at RT	– Annual mammogram + breast MR

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Hodgkin Lymphoma (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS

Follow-up and Monitoring After 5 Years[MS,ccc]

- Interim H&P: Annually
  - Annual blood pressure, aggressive management of cardiovascular risk factors.
  - Pneumococcal, meningococcal, and Haemophilus influenzae type b revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (according to CDC recommendations).
  - Annual influenza vaccine and other vaccines as clinically indicated (see NCCN Guidelines for Survivorship).
- Cardiovascular symptoms may emerge at a young age.
  - Consider stress test/ECHO at 10-y intervals after treatment is completed.
  - Consider carotid ultrasound at 10-y intervals if neck irradiation.
- Laboratory studies:
  - CBC, platelets, chemistry profile annually
  - TSH at least annually if RT to neck
  - Biannual lipids
  - Annual fasting glucose
- Annual breast screening: Initiate 8–10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10–30 y, which is consistent with the American Cancer Society (ACS) Guidelines. Consider referral to a breast specialist.
- Perform other routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer as per the NCCN Guidelines for Detection, Prevention, and Risk Reduction and the ACS Cancer Screening Guidelines.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, and skin cancer risk.
- Treatment summary and consideration of transfer to PCP.
- Consider a referral to a survivorship clinic.
- Screening for secondary cancers as clinically indicated (See NCCN Guidelines for Survivorship).

[MS]Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation-Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-10, 2003, Bellagio, Italy. Eur J Haematol Suppl 2005;(66):68-76.
[ccc]Appropriate medical management should be instituted for any abnormalities.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Hodgkin Lymphoma

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Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Senior Associate Dean for Innovation and Initiatives
Executive Vice Chairman, Weill Department of Medicine

Weill Cornell Medicine NewYork-Presbyterian

32

Acute Lymphocytic Leukemia

Hagop Kantarjian, MD

August 16, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

32 - Acute Lymphocytic Leukemia

Hagop Kantarjian, MD

Disclosures

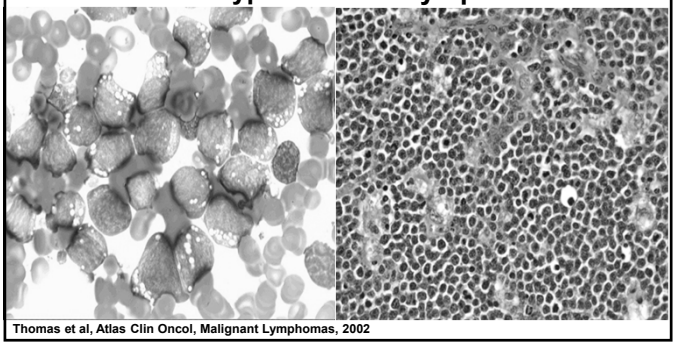
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

ALL. Diagnostic Pre requisites

- **Morphology + stains: L1, L2, L3**
- **Immunophenotype**
  - **Pre B ALL ± CALLA positive**
  - **TALL: early, thymic, mature→precursor T vs others**
  - **Burkitt**
- **Cytogenetics-molecular**
  - **Ph +**
  - **Burkitt: t (8;14), t (8;2), t (8;22)**
  - **t (4;11)**
  - **t (12;21) / *TEL-AML1/ETV6-RUNX1***
  - **Ph-like: CRLF2, JAK2, Abl translocations**

Burkitt-type leukemia/lymphoma



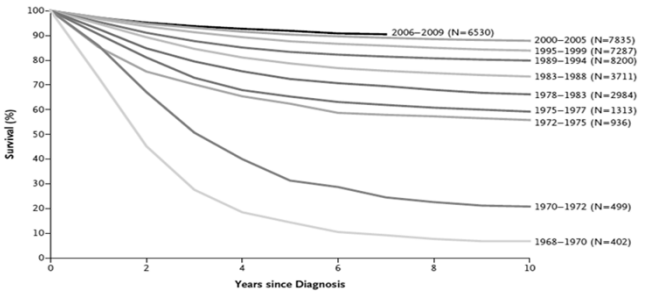
Thomas et al, Atlas Clin Oncol, Malignant Lymphomas, 2002

ALL Myeloid Markers

Study	No.	Percent Myeloid +	Worse Prognosis For CR	CRD	Survival
Sobol	76	33	+	--	+
Urbano	62	13	+	+	+
Guyotal	41	46	+	--	--
Boldt	113	28	--	--	+
Larson	214		--	--	--
MDACC	162	40	--	--	--

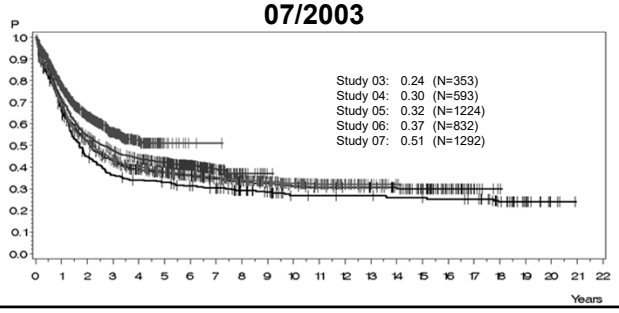
5

Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials



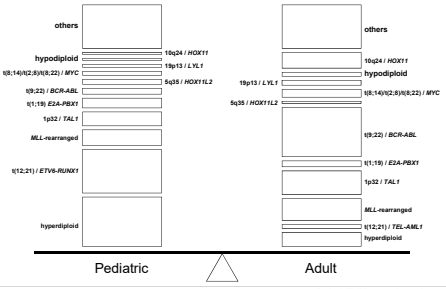
Hunger. NEJM. 2015;373(16):1541-1552

Overall Survival
Comparison of the GMALL studies 03/87 until 07/2003



Genetics in Pediatric vs. Adult ALL

Courtesy of T. Haferlach



Pui . NEJM, 350, 1535-1548, 2004

Reasons Why Pediatric ALL Does Better Than Adult ALL

Entity	Prognosis	% Pediatric	% Adult
Hyperdiploid	Favorable	25-30	5
t(12;21), *ETV6-RUNX1*	Favorable	20-25	2
Ph+ALL	Unfavorable	5	25
Ph-like ALL	Unfavorable	10	25

Key subtypes of B-cell precursor ALL

Subtype	Prevalence - pedi/adult (%)	Comment
Hyperdiploidy >50 chromosomes	20–30/5	Excellent prognosis
Hypodiploidy < 44 chromosomes	2–3	Poor prognosis, high frequency of Ras pathway and IKAROS gene family and *TP53* mutations
t(12;21)(p13;q22), *ETV6–RUNX1* fusion	15–25/2	Excellent prognosis
t(1;19)(q23;p13), *TCF3–PBX1* fusion	2–6	Excellent prognosis; association with CNS relapse
t(9;22)(q34;q11.2), *BCR–ABL1* fusion	2–4/25	Outcome improved with addition of imatinib / dasatinib to intensive chemotherapy
Ph-like ALL	10/25	Multiple cytokine receptor and kinase-activating lesions; associated with *IKZF1* alteration and very high leucocyte count
t(4;11)(q21;q23), *MLL–AF4* fusion	2-4	Common in infant ALL (especially <6 months of age); poor prognosis
t(8;14)(q24;q32), t(2;8)(q12;q24), t(2;8)(q12;q24) *MYC* rearrangement	2-5	Favorable prognosis with short-term high-dose chemotherapy
CRLF2 rearrangement (*IGH–CRLF2*; PAR1 deletion and *P2RY8–CRLF2*)	5–7	Common in Down syndrome-associated and Ph-like ALL (~50% each); associated with *IKZF1* deletion and/or mutation and *JAK1/2* mutation and poor prognosis
ERG-deregulated ALL	7	Distinct gene expression profile; majority have focal ERG deletions and favorable outcome despite *IKZF1* alterations

Adapted--Roberts,Mullighan (2015) Nat. Rev. Clin. Oncol.

2016 WHO Classification

B-lymphoblastic leukemia/lymphoma

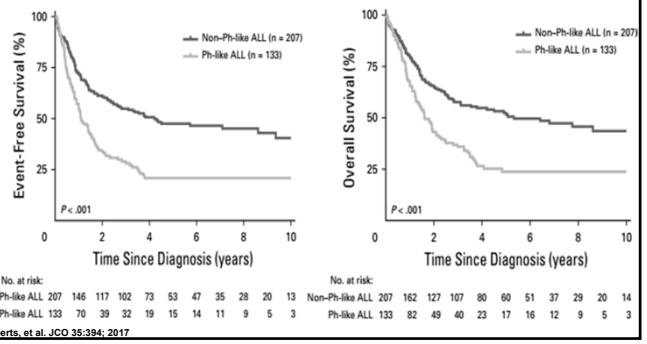
- B-lymphoblastic leukemia/lymphoma, NOS
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
- B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
- B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
- B-lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-lymphoblastic leukemia/lymphoma with hypodiploidy
- B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
- B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
- *Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like*
- *Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21*

T-lymphoblastic leukemia/lymphoma

- *Provisional entity: Early T-cell precursor lymphoblastic leukemia*

Arber. Blood 2016;127(20):2391-405

Ph-Like ALL-- Survival and EFS



Roberts, et al. JCO 35:394; 2017

Ph-like ALL. Higher MRD + Rate

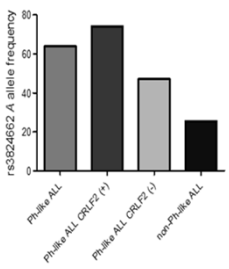
B-ALL Categories (N=155)				
	Ph-Like	Ph+	B-other	p-value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	0.57
MRD at CR				
Positive	23 (70)	15 (44)	4 (13)	<0.001
Negative	10 (30)	19 (56)	27(87)	

Jain. Blood 2017; 129:572-581

Ph-Like ALL: More Common in Hispanic Ethnicity

B-ALL Categories (N=155)					
	N	Ph-Like	Ph+	B-other	p-value
Ethnicity					
Caucasian	60	13 (22)	20 (33)	27 (45)	
Hispanic	70	38 (54)	16 (23)	16 (23)	<0.001
African-American	16	2 (12)	8 (50)	6 (38)	
Asian	7	3 (44)	2 (28)	2 (28)	
Unclassified	2	-	-	2 (100)	

GATA3 rs3824662A Variant More Common in Hispanics and inPh-like ALL

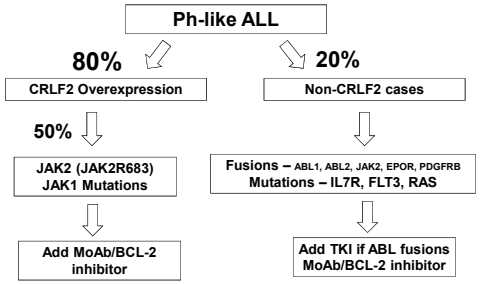


- GATA3 variant associated with Ph-like ALL (CRLF2+ ALL)
  - Children
    - OR=3.25; P=1.05 x 10^{-8}
  - Adults
    - 48% VS 4.6%; P=4.9 X 10^{-7}
- GATA3 variant more common in Hispanics
  - Allele frequency of 40% (Hispanic) VS 14% (European descent)

Jain. ASH 2017; Perez-Andreu. Nat genetics 2013

Ph-like ALL Molecular Lesions

- Ph-like 25-30% of ALL; poor prognosis



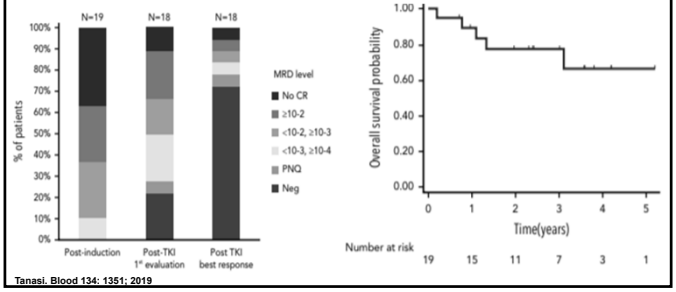
Ph-like ALL: non-CRLF2

II. Alterations activating cytokine receptor and tyrosine signaling

- Genes deregulating tyrosine kinases/receptors
  - *NUP214-ABL1, ETV6-ABL1, RANBP2-ABL1, RCSD1-ABL1*
  - *BCR-JAK2, PAX5-JAK2, STRN3-JAK2*
  - *EBF1-PDGFRB*
  - *IGH-EPOR*
- Activate signaling pathways
  - ABL1, PDGFRB fusions: Dasatinib
  - JAK2 fusions: Ruxolitinib

BCR-ABL TKIs + Chemo Rx in Ph-like ALL

- 24 pts with Ph-like ALL: NUP214-ABL1-- 6, ETV6-ABL1-- 3, others -- 9. 19 frontline; 5 relapse.All Rx with chemo Rx + TKI



Tanasi. Blood 134: 1351; 2019

Principles in Adult ALL Therapy

- **Induction:** VCR, steroids, anthracyclines
- **Maintenance:** 6MP, MTX, VCR, steroids
- **Consolidation:** CTX, ara-C, Asp, VP-16, autoSCT alloSCT
- **CNS prophylaxis:** XRT, IT chemo
- **Risk oriented therapy**

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Reasons for Recent Success in Adult ALL Rx

- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR-T therapy

ALL Personalized Therapy

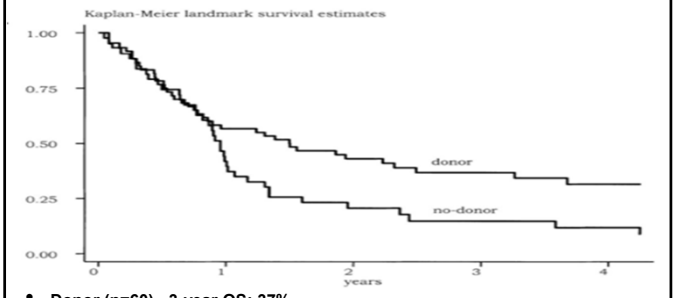
Entity	Management	% Cure/5-yr survival
Burkitt	HCVAD-R x 8; ITx16; R/O-EPOCH	80-90
Ph-positive ALL	HCVAD + TKI; TKI maintenance; allo SCT in CR1	75+
Ph-like ALL	HCVAD+TKI / MoAbs	60-70??
T-ALL (except ETP-ALL)	Lots of HD CTX, HD ara-C, Asp; nelarabine; venetoclax??	60+
CD20 – positive ALL	ALL chemo Rx+ rituximab/ofatumomab	60-70+??
AYA	Augmented BFM; HCVAD-R/O	60-70+
Older ALL>60yrs	MiniCVD-ino-blina	60?
MRD by FCM	Prognosis; need for allo SCT in CR1	--

Hyper-CVAD in ALL – Pearls and Vignettes to Optimize Rx

- Even courses : MTX 750 mg/m2; ara-C 2 g/m2. Dose adjust for older age
- Check Cr after MTX; if increase(>1.4), hold araC (avoid renal failure and cerebellar toxicity)
- VCR 2 mg flat dose (not 2 mg/m2). If constipation or neuropathy, omit VCR
- Prophylaxis : levo or vantin; posaconazole or voriconazole; Valtrex
- Hold azoles Day-1,0,+1 of VCR (avoid excess neurotoxicity)
- Switch IT Day 2 from MTX to araC in even courses (neurotoxicity with IT MTX and HD systemic MTX)

Rausch. Cancer E-pub, December 3,2019

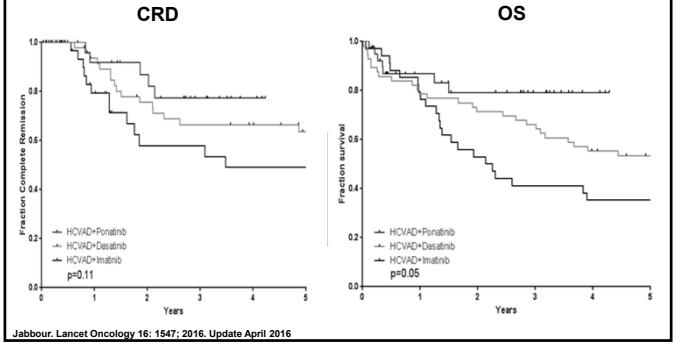
SCT for Ph+ ALL. Pre-TKI



- Donor (n=60) - 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

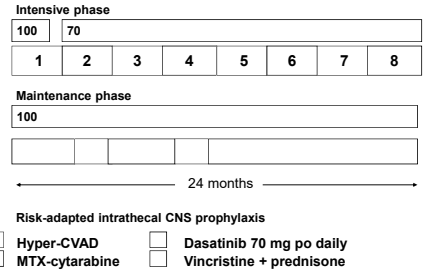
Dombret H et al *Blood* 2002

Hyper-CVAD + TKI in Ph-Positive ALL. Survival



Jabbour. Lancet Oncology 16: 1547; 2016. Update April 2016

Hyper-CVAD + Dasatinib in Ph+ ALL: Regimen



Ravandi . Blood Advances. 2016;1:250-259.

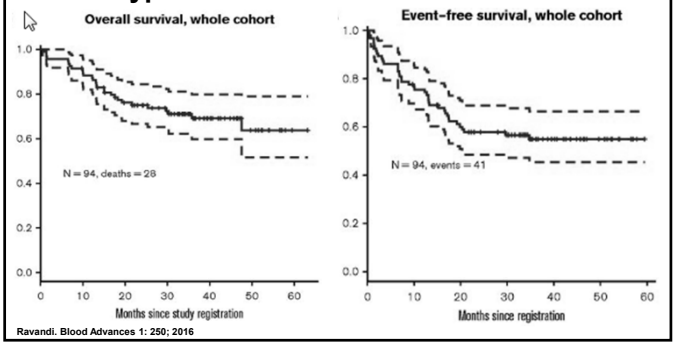
25

HyperCVAD+Dasatinib in Ph+ALL. Response

Response	N = 94 (%)
CR	81 (86)
CRi	2 (2)
No CR/CRi	10 (11)
Missing data	1 (1)

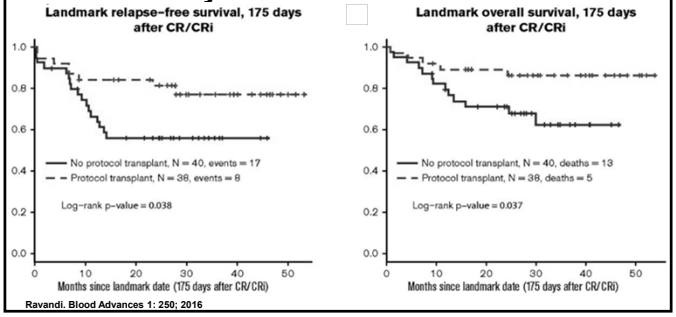
Ravandi. Blood Advances 1: 250; 2016

HyperCVAD+Dasatinib in Ph+ALL.



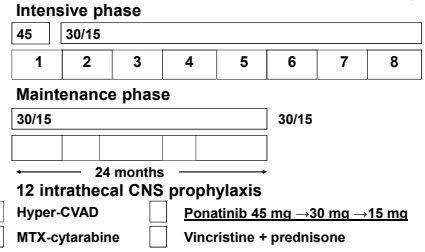
Ravandi. Blood Advances 1: 250; 2016

HyperCVAD+Dasatinib in Ph+ALL. Landmark Analysis: No ASCT vs. ASCT



Ravandi. Blood Advances 1: 250; 2016

Hyper-CVAD + Ponatinib. Design

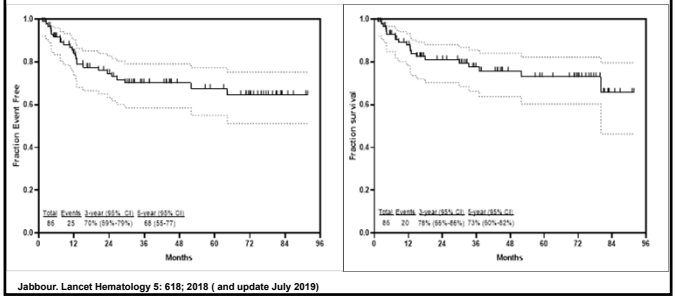


- After the emergence of vascular toxicity, protocol was amended: Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Jabbour. Lancet Onc. 16:1547;2015. Jabbour. Lancet Hematology 2018

HyperCVAD + Ponatinib in Ph-positive ALL

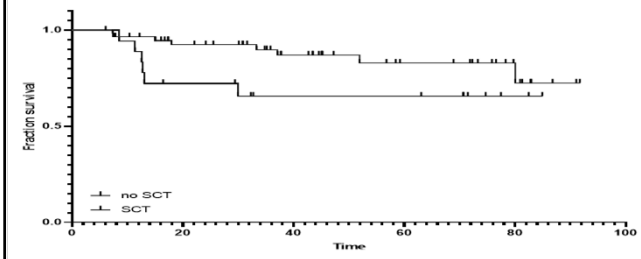
- 86 pts Rx; median age 47 yrs (39-61); median FU 43 mos(2-92)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); CMR 84%; 3/5-yr OS 78/73%,EFS 76/71%



Jabbour. Lancet Hematology 5: 618; 2018 (and update July 2019)

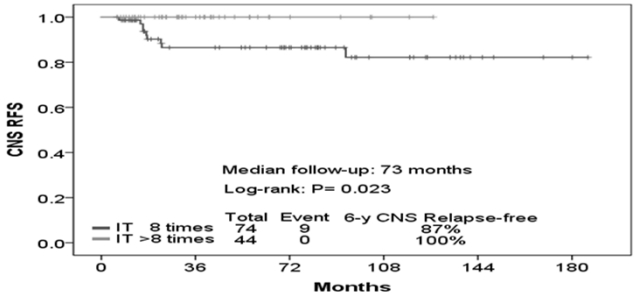
Hyper-CVAD + Ponatinib in Ph+ ALL. Landmark Analysis at 6 Months by HSCT

- 3-year OS rate was 66% for pts who underwent HSCT (n=18) and 90% for pts who did not undergo HSCT (n=57; P=0.07)



Jabbour. Lancet Hematology 5: 618; 2018 (and update July 2019)

HYPER-CVAD-Ponatinib . IT x8 vs. ITx12 in Ph+ ALL 6M Landmark: CNS Relapse-free Survival



Dasatinib vs Imatinib in Pediatric Ph-positive ALL

- 189 pts randomized to dasatinib (n=92) or imatinib (n=97)

% 4-yr	Dasatinib	Imatinib	p-value
EFS	71	49	0.007
Relapse	19	34	0.01
CNS	2.7	8.4	0.06

Shen. JAMA Oncology: 6:358;2020

NCCN Guidelines Version 5.2017 Acute Lymphoblastic Leukemia

NCCN Guidelines Index | Table of Contents | Discussion

PRINCIPLES OF SYSTEMIC THERAPY (1 of 6)

INDUCTION REGIMENS FOR Ph-POSITIVE ALL[a]

Protocols for AYA patients:
- COG AALL-0031 regimen: vincristine, prednisone (or dexamethasone), and pegaspargase, with or without daunorubicin; or prednisone (or dexamethasone) and pegaspargase with or without daunorubicin; imatinib added during consolidation blocks[1]
- EsPhALL regimen: imatinib; and a backbone of the Berlin-Frankfurt-Münster regimen[2]
- TKIs (ponatinib, imatinib, dasatinib) + hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[3–7]
- TKIs (imatinib, nilotinib) + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)[8-10]
- TKIs (imatinib, dasatinib, nilotinib)[11,12] + corticosteroids[b]
- TKIs (imatinib, dasatinib, nilotinib) + vincristine + dexamethasone[13,14,b]

Adult patients: Treatment of Older Patients (≥65 y) with ALL (ALL-D 6 of 6)
- TKIs (ponatinib, imatinib, dasatinib) + hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate, and cytarabine)[3–7]
- TKIs (imatinib, nilotinib) + multiagent chemotherapy: daunorubicin, vincristine, prednisone, and cyclophosphamide[8-10]
- TKIs (imatinib, dasatinib, nilotinib)[11,12] + corticosteroids[b]
- TKIs (imatinib, dasatinib, nilotinib) + vincristine + dexamethasone[13,14,b]

Maintenance regimens:
- Add TKIs (imatinib, dasatinib, nilotinib, ponatinib) to maintenance regimen
- Monthly vincristine/prednisone pulses (for 2–3 years). May include weekly methotrexate + daily 6-mercaptopurine (6-MP) as tolerated[c,d]

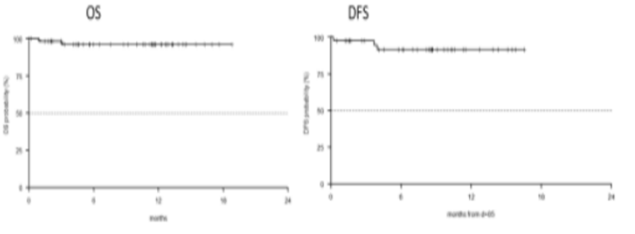
Blinatumomab and Inotuzumab in R-R Ph-positive ALL

Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
% MRD negative in CR	88	63
Median OS (mos)	7.1	8.1
% later allo SCT	44	32

Martinelli. JCO 35: 1795; 2017. Stock. Proceedings ASCO 2018

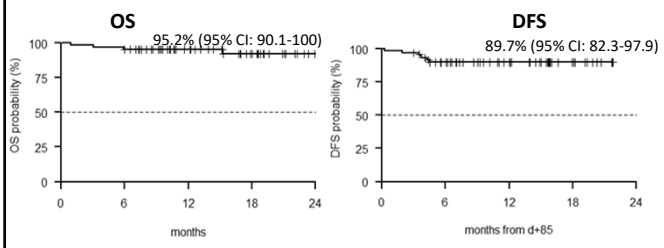
Dasatinib-blinatumomab in Ph-positive ALL

- 63 pts, median age 54 yrs (24-82)
- Dasatinib 140mg/D x 3 mos ; add blinatumomab x 2-5
- 35 post dasa-blina x 2--molecular response 19/35 (54%), 10 CMR (29%) . MRD ↑ in 11— 4 T315I;12-mos OS 96%; DFS 92%



Chiaretti. EHA; abst S1617; 2019

D-ALBA: OS and DFS



Median follow-up: 14.3 months (0.9-25)

24 patients underwent an allo-SCT

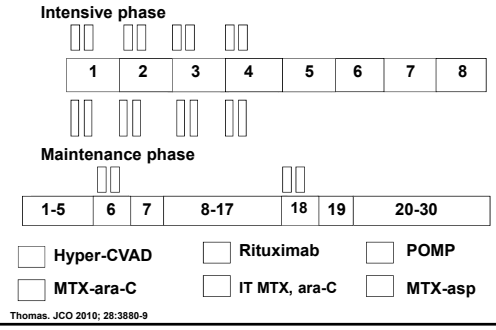
Ph-positive ALL – Current and Future Studies

- **HyperCVAD + ponatinib**
- **Mini-CVD + ponatinib (add blina or ino for MRD+ disease on other protocols)**
- **Ponatinib + blinatumomab/inotuzumab**

Mature B Cell (Burkitt) ALL

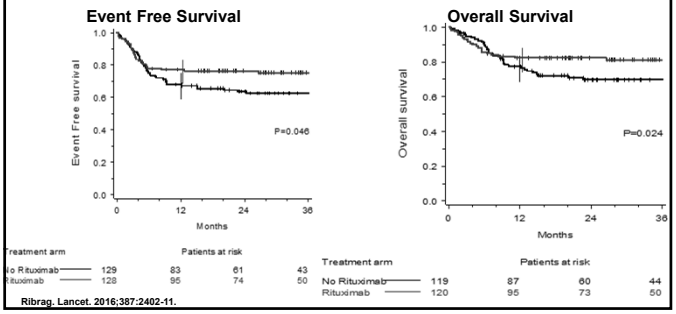
- **Median age 25-55 years**
- **1) L3 morphology; 2) T(8;14), t(8;2), t(8;22); 3)MYC – Today, if BCL2/BCL6 +, then reclassified as double-triple-hit high-risk (Burkitt-like) lymphoma and Rx with R-DA-EPOCH**
- **Tdt negative, SIg positive, clonal K/L**
- **Rapid doubling time →emergency Rx**
- **LN, hepatosplenomegaly, TLS; high LDH and U.A., renal failure**
- **CNS frequently involved; chin numbness 50%**
- **Dose intensive short-term chemo; fractionated high-dose CTX, MTX ,HD ara-C + rituximab.No maintenance**
- **Hyper-CVAD + rit; DA R-EPOCH: CR 90%, cure 60-80%--not if BM or CNS +**

Hyper-CVAD + Rituximab in Precursor B-ALL



Thomas. JCO 2010; 28:3880-9

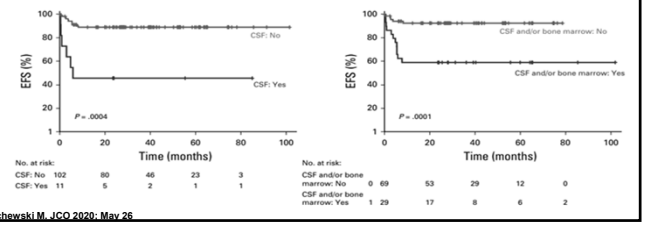
ChemoRx +/- Rituximab in Burkitt Disease--Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study



Ribrag. Lancet. 2016;387:2402-11.

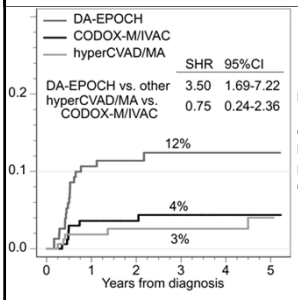
DA-EPOCH in Burkitt Lymphoma

- **113 pts median age 49 (18-86); 87% high-risk (any of Stage ≥ 3; PS ≥ 2; elevated LDH; tumor> 7 cm); 25% BM disease and 10% CNS disease**
- **5-y OS: 85% low-risk vs 87% high-risk**
- **4-y EFS with baseline CNS disease 46% vs 90%, P=0.004**
- **4-y EFS for pts with CNS and/or blood/BM involvement 67% vs 92%, P=0.0086**
- **CNS relapses: 2/81 vs 6/11 for high-risk pts without and with baseline CNS disease**



Roschewski M. JCO 2020: May 26

Risk of CNS Recurrence by First-Line Regimen



	N	CNS Recurrence at 3 Years	95% CI
DA-EPOCH	154	12.5%	7.7, 18.5
CODOX-M/IVAC	174	4.4%	1.9, 8.4
Hyper-CVAD/MA	164	2.6%	0.9, 6.1

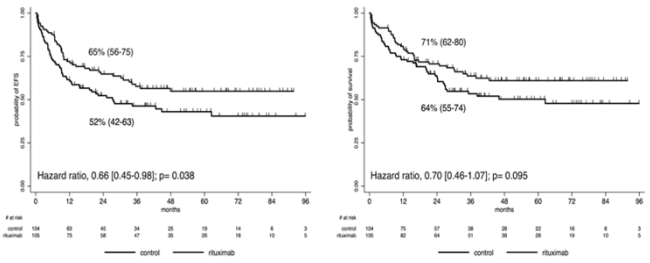
Higher risk of CNS recurrence with DA-EPOCH independent of:

HIV-positive status	(*P interaction* = .90)
Baseline CNS involvement	(*P interaction* = .70)
Poor PS	(*P interaction* = .14)

Zayac . Blood 134;2019. Abst 402 .

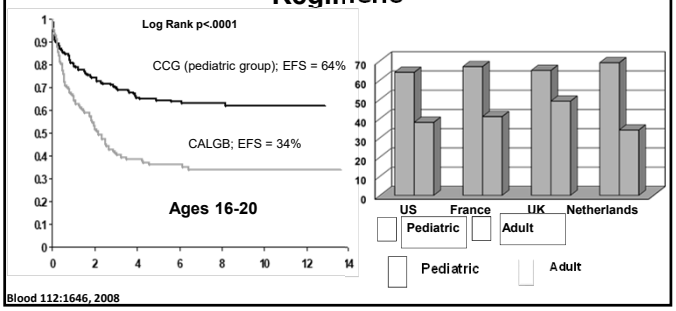
Chemo Rx +/- Rituximab: Results of the Randomized GRAALL-R 2005 in Pre B-ALL

- Median follow-up 30 months



Maury. N Engl J Med. 2016;375:1044-53

Survival in AYA ALL by Pediatric vs " Adult" Regimens



Blood 112:1646, 2008

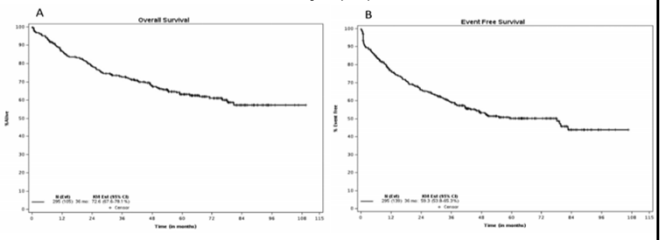
US Intergroup Study for AYA: A041501 Randomized Phase III trial, 18-39 yrs

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
Inotuzumab	VCR	VCR	Cyclo	VCR
VCR	Dex	Peg-ASP	Dex	6MP
Dex	Peg-Asp	IT-MTX	Peg-Asp	MTX
Peg-Asp	Ara-C		Ara-C	IT-MTX
IT-MTX	6MP		6-TG	
IT-AraC	IT-MTX		IT-MTX	

CD20+ Patients will Receive Rituximab with I, C, IM, DI
Maintenance therapy continues for 2 (F) – 3 (M) years

Pediatric Regimen (CALGB10403) for AYA ≤ 40 yrs

- 318 Rx; 295 evaluable. Median age 24 yr (17-39)
- CR 263/295=89%. Induction mortality 9 (3%)



- % 3/5-yr OS 73/60
  % 3/5-yr EFS 59/48

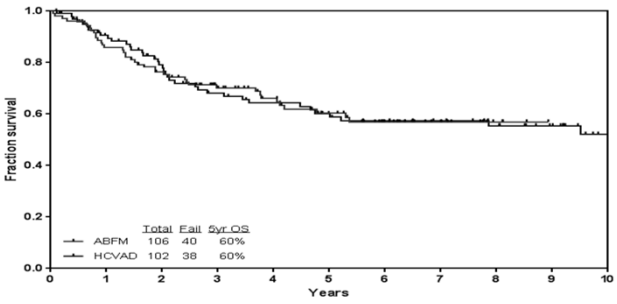
Stock Blood. 2019;133:1548

Augmented BFM and Hyper-CVAD

Response	No. (Percent)	
	ABFM (n=106)	Hyper-CVAD (n=102)
• Complete response	99 (93)	100 (98)
• Induction mortality	1 (1)	1 (1)
• Resistant disease	6 (6)	1 (1)

Rytting. Cancer 120: 3660-8; 2014 .Rytting.AJH 91: 819; 2016

Hyper-CVAD vs. ABFM.Overall Survival



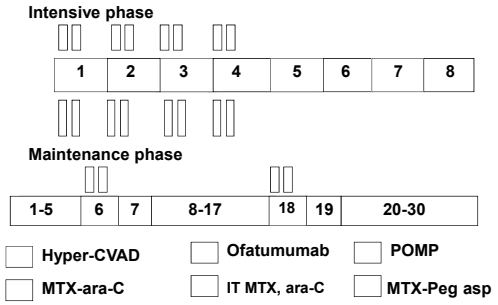
Rytting. Cancer 120: 3660-8; 2014 . Rytting. AJH 91: 819; 2016

ABFM vs HyperCVAD. Severe Toxicities

% Toxicity	ABFM (n=106)	Hyper-CVAD (n=102)	p value
Asparaginase allergy	19	N/A	NS
Hypofibrinogenemia	35	14	<0.001
Pancreatitis	11	3	0.02
↑LFTs	41	44	0.60
↑ Bili	38	18	0.001
Osteonecrosis	9	8	0.68
Thrombosis	19	12	0.16
Stroke	3	0	0.09
Induction infections	22	45	<0.001
Induction bleeding	1	5	0.09
Infections in CR first 60 days	30	60	<0.001
Bleeding in CR first 60 days	1	5	0.09
Deaths in CR	8	7	.85

Rytting. Cancer 120: 3660-8; 2014 . AJH 91: 819; 2016

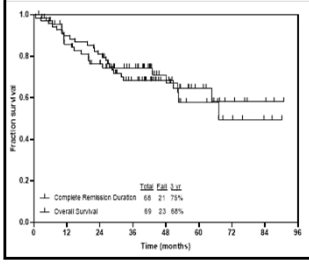
Hyper-CVAD + Ofatumumab. Design



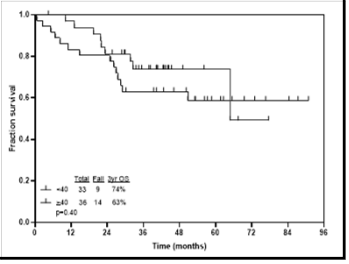
HCVAD + Ofatumumab. Outcome (N=69)

- Median follow up of 44 months (4-91)
- CR 98%, MRD negativity 93% (at CR 63%), early death 2%

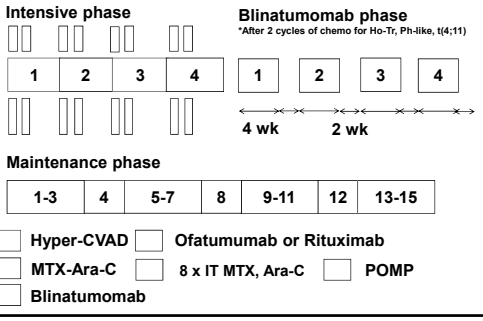
CRD and OS Overall



OS by Age



Hyper-CVAD + Blinatumomab in Frontline B-ALL Treatment schedule



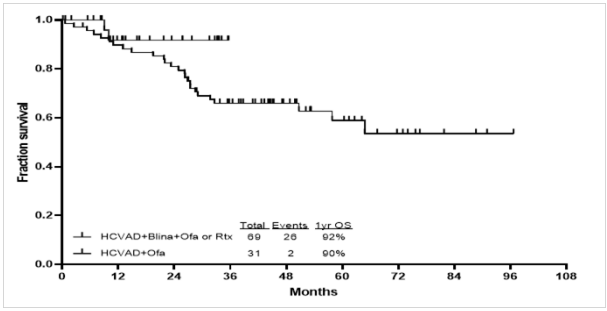
Hyper-CVAD + Blinatumomab in FL B-ALL . Response rates

Response assessment	N (%)
CR after induction	20/24 (83)
CR at any time	24/24 (100)
MRD negativity after induction	17/20 (85)
MRD negativity at any time	28/29 (97)
Early death (30-day)	0/24 (0)

* 2 are too early, 5 are CRs at start
Median time to MRD negativity : 20 days

Richard-Carpentier. Blood 134: abst 3807; 2019

R/O-Hyper-CVAD + Blina vs O-Hyper-CVAD . Survival



Richard-Carpentier. Blood 134: abst 3807; 2019

T Cell ALL

- Median age 50 yrs;CD1-CD8 positive;mediastinal involvement 50%
- Rx with ALL regimens that include CTX, ara-C, asparaginase– now nelarabine included
- Maintenance POMP x2-3 years essential (like ALL, unlike lymphoma). If not, then autologous SCT
- CNS prophylaxis needed
- ? Mediastinal XRT if bulky mediastinal disease (at time of MRD)
- CR 90%; cure 60% to 70%
- Immunophenotype important: early precursor-T ALL (CD1a-,sCD3-, MY+) worst = allo SCT

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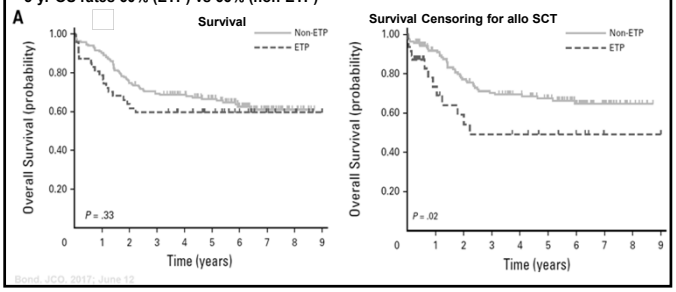
T-ALL Outcome (French GRAALL Study)

- 213 ALL (47 ETP; 22%); MRD positivity post induction ETP vs non-ETP 70% vs 20%; allo SCT in CR1 in 49% of ETP-ALL
- 5-yr OS rates 60% (ETP) vs 66% (non-ETP)



Blood JCO. 2017; June 12

CNS Prophylaxis in Adult Acute Lymphocytic Leukemia

- Regimens without cranial irradiation effective
- High dose systemic therapy for low-risk disease
- Intrathecal MTX alone or alternating with ara-C effective without need for TIT
- Early IT therapy + high dose systemic therapy effective for high risk disease
- Risk oriented approach optimal

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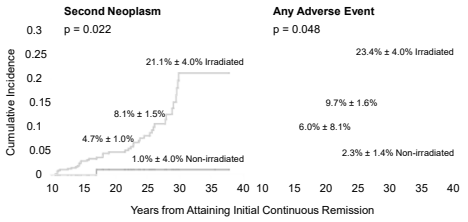
Cumulative Incidence of Adverse Events in 10-year EFS of Childhood ALL According to the Use of CNS Irradiation



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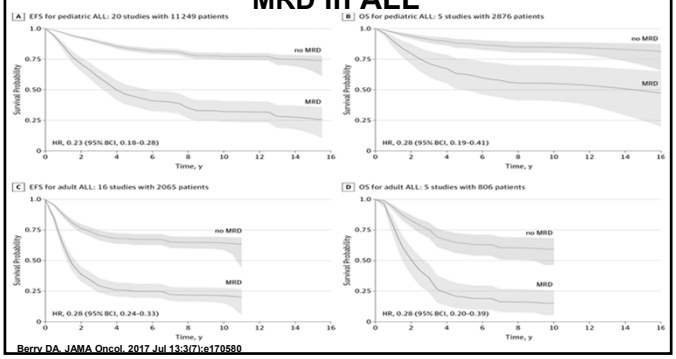
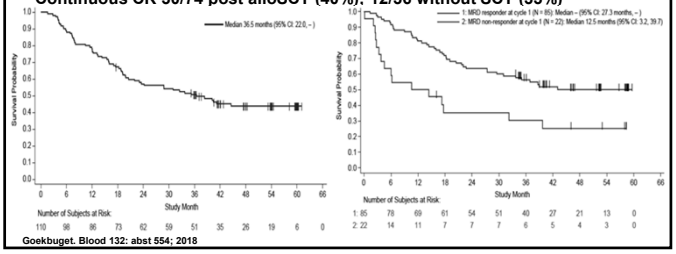
MRD in ALL



Berry DA. JAMA Oncol. 2017 Jul 13;3(7):e170580

Blinatumomab for MRD-positive ALL in CR1/CR2

- 113 pts Rx. Post blina MRD-negative 88/113=78%
- 110 evaluated (blasts <5%, MRD+). 74 received alloSCT.Median FU 53 mos
- Median OS 36.5 mos; 4-yr OS 45%; 4-yr OS if MRD- negative 52%
- Continuous CR 30/74 post alloSCT (40%); 12/36 without SCT (33%)



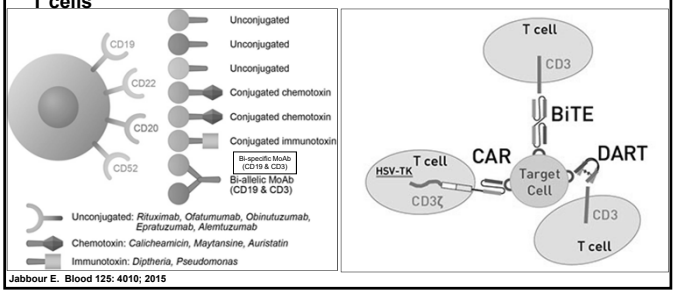
Goekbuget. Blood 132: abst 554; 2018

ALL—Next Questions. Do We Need Allo SCT ?

- ALL-MLL; t(11q23; ---)
- Precursor T ALL
- Complex CG ≥ 5 abn; near hypoploid+p53
- Others: Ph-positive ALL PCR+in CR3 mos; Ph-like ALL; ALL CR1 MRD+---may be managed with blina-ino

Immuno-oncology in ALL

- Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells



Jabbour E. Blood 125: 4010; 2015

ALL Salvage Standards of Care in 2020

- Refer for investigational therapies-- MoAb + ChemoRx; CAR-T
- Ph-positive ALL-- TKIs+ chemoRx; blinatumomab
- Pre-B ALL--
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
  - CARTs (FDA approvals 8.2017; age<26 yrs, Salvage 2+)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD

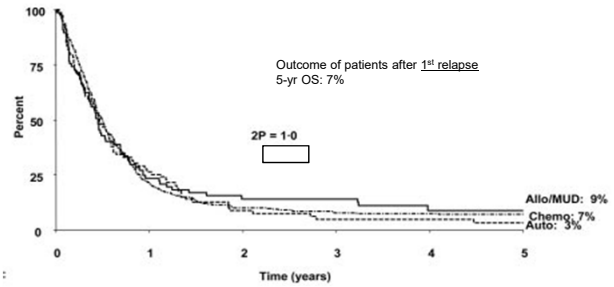
Historical Results in R/R ALL

- Poor prognosis in R-R ALL Rx with standard of care (SOC) chemotherapy

Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

Gökbuget N, et al. *Haematologica*. 2016;101:1524–33.

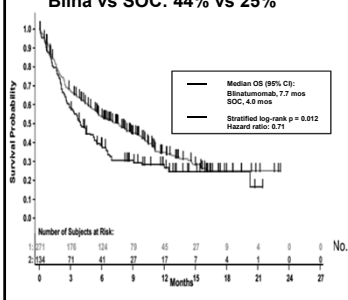
Outcome for 609 Adults with Relapsed ALL. MRC UKALL2/ECOG2993 Study



Fielding et al Blood. 2007;109:944-950

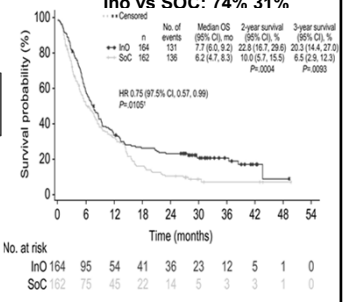
Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

- Marrow CR
  Blina vs SOC: 44% vs 25%



Kantarjian. NEJM. 376: 836-47; 2017

Ino vs SOC: 74% 31%



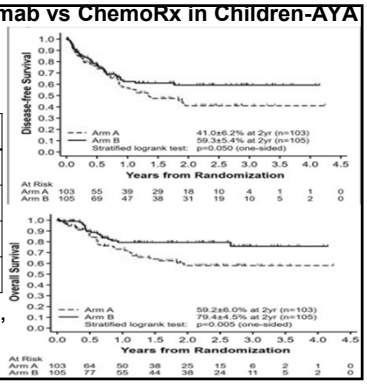
Kantarjian. NEJM. 375: 740; 2016 . Cancer. May 2019

Phase 3 Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

- 208 pts randomized 1:1 to blina (n=105) vs chemo Rx (n=103)

Parameter	Blina	Chemo	p
%2-yr DFS	59	41	.05
%2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001

- Rates of FUO, infections, sepsis, all significantly lower with blina

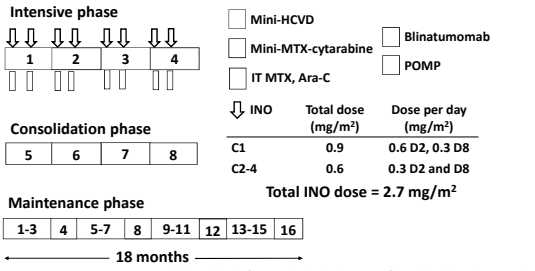


Brown. Blood 134: LBA1; 2019

MiniHCVD-INO-Blina in ALL. Design

- Dose reduced HyperCVD for 4-8 courses
  - Cyclophosphamide (150 mg/m^2 x 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 x 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m^2 C2-4 (0.3 and 0.3 on D1&8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Mini-HCVD + INO ± Blina in Older ALL: Modified Design (Pts #50+)



⇩ INO	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m^2

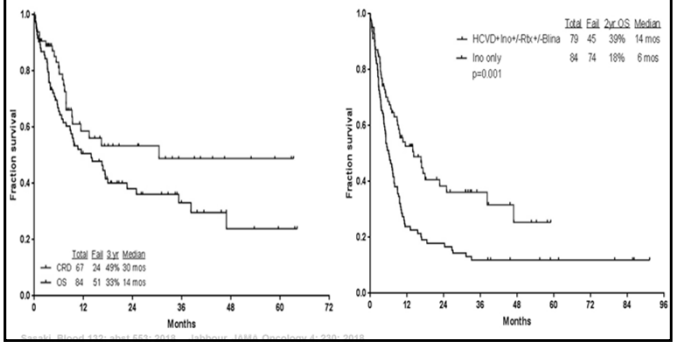
Jabbour E et al. *Cancer* 2018;124(20):4044-55; Short. Blood 132: abst 36; 2018

Mini-HCVD + INO ± Blinatumomab in R/R ALL Response by Salvage (N=89)

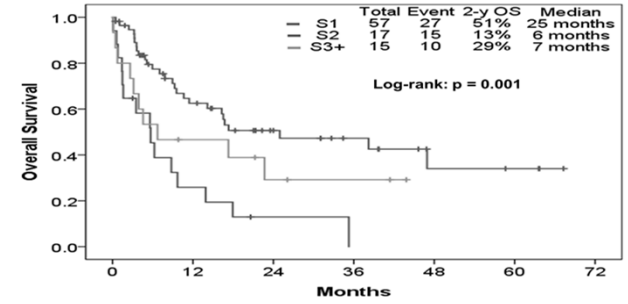
Response	N	(%)
Salvage 1	51/56	91
S1, Primary refractory	5/5	100
S1, CRD1 < 12 mos	19/23	83
S1, CRD1 ≥ 12 mos	27/28	96
Salvage 2	9/16	56
≥ Salvage 3	9/15	60
Overall	69/87	79
MRD negativity	55/67	82
Salvage 1	42/49	86
≥ Salvage 2	13/18	72
Early death	7/87	8

Sasaki. Blood 132: abst 553; 2018 Jabbour. JAMA Oncology 4: 230; 2018

Mini-HCVD+Inotuzumab/Blinatumomab in R-R ALL

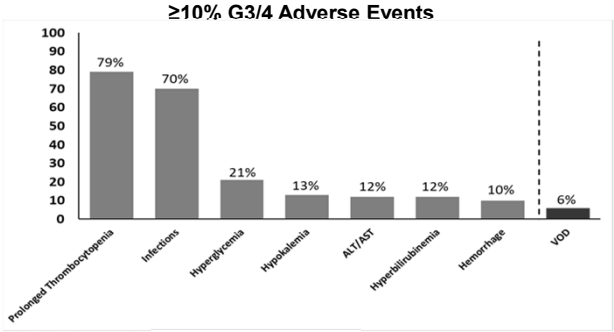


Mini-HCVD + INO ± Blinatumomab in R/R ALL
OS by Salvage Status



Sasaki. Blood 132: abst 553; 2018 Jabbour. JAMA Oncology 4: 230; 2018

Mini-HCVD + INO ± Blinatumomab in R/R ALL
≥10% G3/4 Adverse Events



Sasaki. Blood 132: abst 553; 2018 Jabbour. JAMA Oncology 4: 230; 2018

Elderly ALL. Historical Results

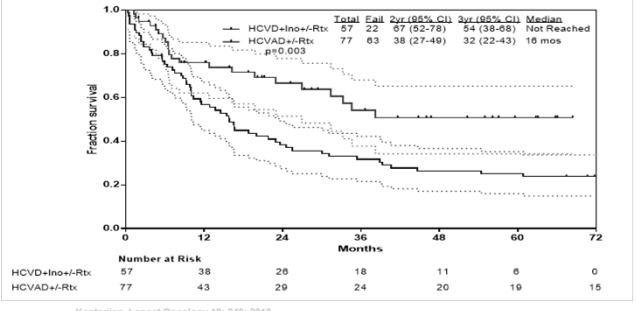
	MDACC	GMALL	SEER	Medicare
N	122	268	1675	727
Median OS (mos)	15	NA	4	10
%OS (x-yr)	20 (3)	23 (5)	13 (3)	NA

O'Brien. Cancer 113: 2097, 2008; Gökbuget. Blood. 2013;122:1336; Li S. Blood. 2016;128:3981; Geyer. Blood 2017;129:1878

Mini-HCVD + INO ± Blina in Older ALL . Response

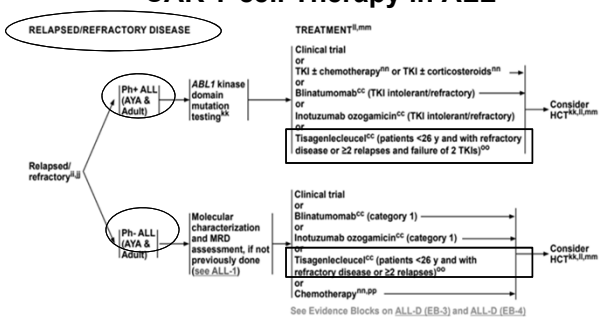
Response (N=59)	N (%)
ORR	58 (98)
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	0
Flow MRD response	**N (%)**
D21	50/62 (81)
Overall	60/63 (95)

MiniHCVD-INO vs HCVAD in ALL.



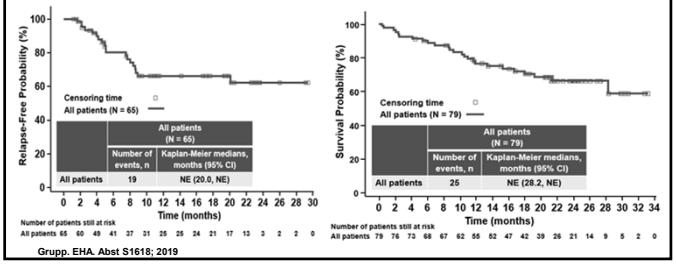
Kantarjian. Lancet Oncology 19: 240; 2018

CAR T-cell Therapy in ALL



ELIANA Trial Update

- 113 screened, 97 enrolled, 79 infused
- 3-mo CR 65/79=82%, or 65/97=67%
- 24-mos OS 66%; RFS 62%. G 3-4 CRS 49%. ICU 48%



Grupp. EHA. Abst S1618; 2019

Leukemia Questions?

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Chronic Myeloid Leukemia

Hagop Kantarjian, MD

August 16, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

33 - Chronic Myeloid Leukemia

Hagop Kantarjian, MD

Disclosures

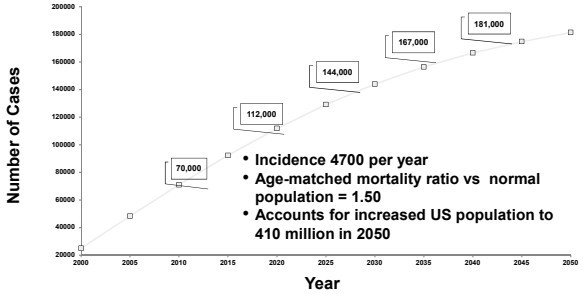
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Chronic Myeloid Leukemia

- Clonal myeloproliferative disorder of pluripotent stem cells
- ↑ proliferation, ↓apoptosis
- Hallmarks: Cytogenetic: Ph-chromosome
  Molecular: BCR/ABL
- 7% to 15% of adult leukemias
- Incidence $1.5/10^5$; prevalence $5/10^5$ ---↑annually until 2040; prevalence = 35x incidence = $50/10^5$
- 2010 statistics: 4,870 new patients, 440 deaths
- Etiology: irradiation in <5%
  unknown in 95%

CML - Increasing Prevalence Over Time



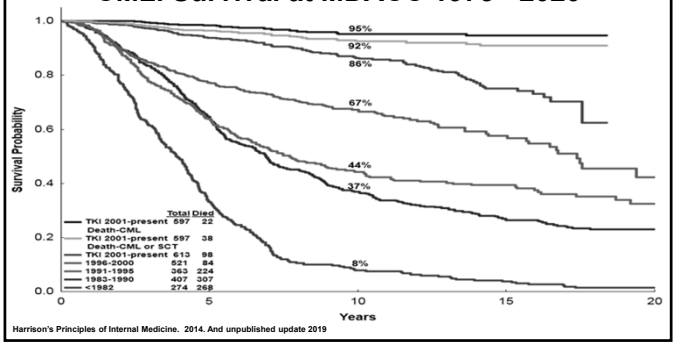
Wang. Blood 127: 2742; 2016

CML. The Past and Today

Parameter	Before 2000	Today
•Course	Fatal	Indolent
•Prognosis	Poor	Excellent
•10-yr survival	10%	84 - 90%
•Frontline Rx	Allo SCT; IFN-α	Imatinib; dasatinib; nilotinib; bosutinib
•Second line Rx	?	Bosutinib, ponatinib ; allo SCT

5

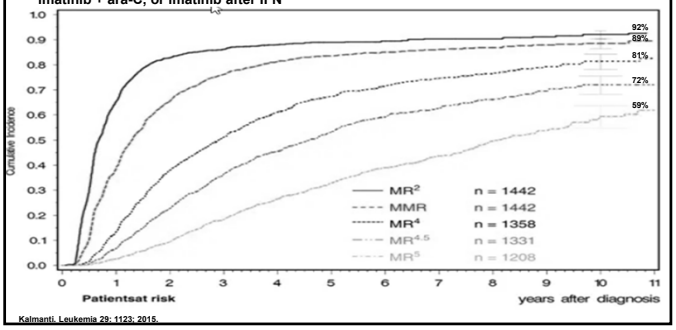
CML. Survival at MDACC 1975 - 2020



Harrison's Principles of Internal Medicine. 2014. And unpublished update 2019

Final Results CML IV–Molecular Response With Imatinib

- 1538 pts newly diagnosed CML-CP randomized to imatinib 400, imatinib 800, imatinib + IFN, imatinib + ara-C, or imatinib after IFN



Kalmanti. Leukemia 29: 1123; 2015.

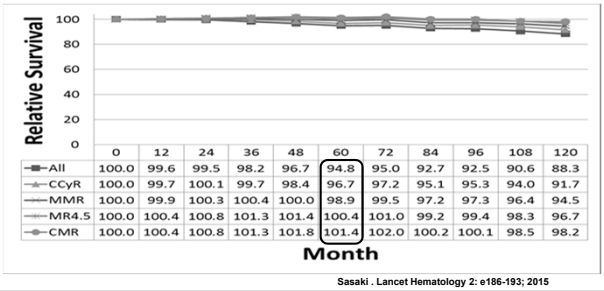
5-yr OS Survival by Response

Response	Observation Time (years)	5-year Survival (%)
CG CR	4.7	94
MMR	4.5	95
MR^4	3.8	97
$MR^{4.5}$	3.0	97

Hehlmann. JCO 32: 415; 2013

Relative Survival with TKI by Response to Therapy

- 483 pts with CML treated with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111) or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1 - 97.4]

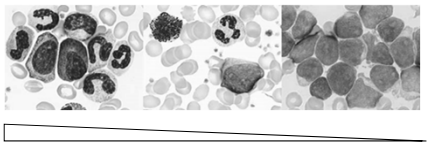


	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.6	99.5	98.2	96.7	94.8	95.0	92.7	92.5	90.6	88.3
CCyR	100.0	99.7	100.1	99.7	98.4	96.7	97.2	95.1	95.3	94.0	91.7
MMR	100.0	99.9	100.3	100.4	100.0	98.9	99.5	97.2	97.3	96.4	94.5
MR4.5	100.0	100.4	100.8	101.3	101.4	100.4	101.0	99.2	99.4	98.3	96.7
CMR	100.0	100.4	100.8	101.3	101.8	101.4	102.0	100.2	100.1	98.5	98.2

Sasaki . Lancet Hematology 2: e186-193; 2015

Natural evolution of CML

Chronic phase | Accelerated phase | Blast phase



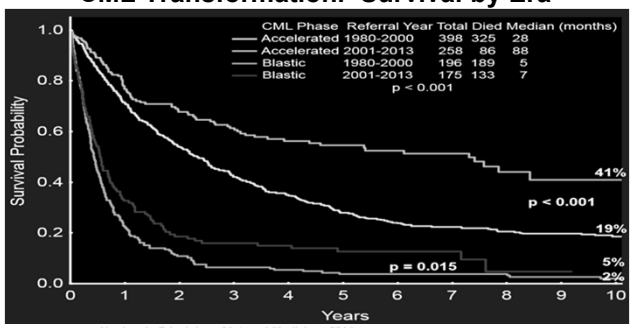
Median survival

35-65 months | 12-24 months | 3-12 months

CML Accelerated Phase Criteria

Parameter	Old Criteria	New Criteria
% Blasts	≥ 15%	? ≥ 20%
% Blasts + Pros	≥ 30%	??
% Basophils	≥ 20%	?
CG Clonal evolution	Any	Iso 17, 17p
Platelets	< $100x10^9$/L	---
BCR-ABL1 p 190	--	yes

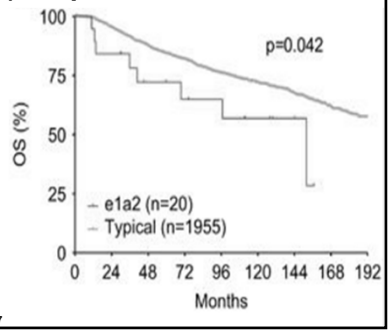
CML Transformation. Survival by Era



Harrison's Principles of Internal Medicine, 2014

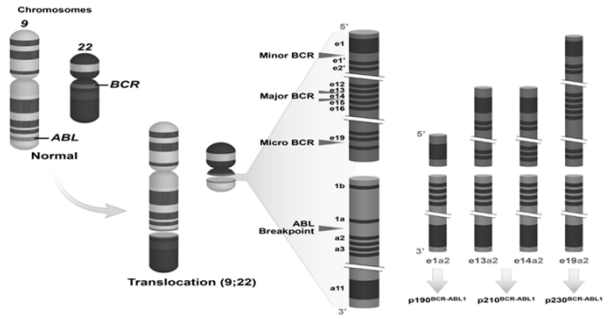
P190 (e1a2) Ph-positive CML

- 41/2307 (1.8%) have e1a2 Ph-positive CML
- CP 23, AP 2, BP 16
- P190=worse survival and ↑ BP
- MVA :
  e1a2 adverse-HR 2.09;
  p=0.002



Gong. Blood Cancer Journal 7: e583; 2017

CML Ph-Associated CG and Molecular Events



Visual Art: © 2013 The University of Texas MD Anderson Cancer Center

Clinical Relevance of Alternative BCR-ABL Transcripts

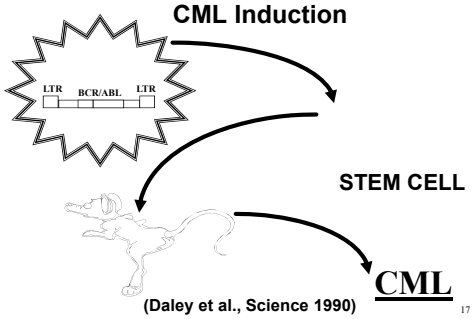
- At diagnosis:Ph+ by CG t (9;22), or FISH positive, but PCR negative → consider e13a3, e14a3 (p210), e6a2-3 (p195), or e19a2-3 (p230)
- Therefore, must do PCR at Dx. Otherwise later PCRs falsely negative=false CMR

BCR-ABL Transcripts and Messages

- BCR breakpoints: e13 (b2), e14 (b3), e1, e6, e19
- ABL breakpoints: a2, a3
- Total 10 possible transcripts/messages

Transcripts	Oncoprotein messages	Incidence	Detected by Routine PCR	Needs Alternative Assay/not Quantitative
e13 a2 (b2 a2)	p210	55%	Yes	--
e14 a2 (b3 a2)	p210	40%	Yes	--
e13 a3 (b2 a3)	p210	1%	No	Yes
e14 a3 (b3 a3)	p210	1%	No	Yes
e1 a2/a3	p190	1%	Yes	No (but not IS)
e6 a2/a3	p195	< 1%	No	Yes
e19 a2/a3	p230	< 1%	No	Yes

BCR-ABL Expression Sufficient for CML Induction



(Daley et al., Science 1990)

17

CML Presentations

- At diagnosis:
  - 85% in chronic phase
  - 5% Ph-negative
- 50% asymptomatic
- Others:
  - constitutional symptoms
  - LUQ discomfort
  - early satiety
  - → splenomegaly, hepatomegaly, purpura

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CML Workup

- Performance, splenomegaly, EMD
- CBC, plts, diff, SMA12
- BM Asp, CG
- If Ph negative → molecular (Southern, PCR)
- FISH, QPCR

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CML Presentations

Presentation	Percent
•Chronic	80-85
•Accelerated	10
•Blastic	5
•Ph-negative	5

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Do We Need Bone Marrow At Dx?

- Assess % of blasts and basos (10-15% have CML transformation at Dx)
- Confirm Ph by CG; detect clonal evolution particularly iso17/17p, 3q26.2 rearrangement
- FISH can be falsely positive
- QPCR can be falsely positive or negative

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CML. Minimal Workup

- Exam (spleen, EMD); counts (blasts, basos)
- Confirm Ph by CG -- detect clonal evolution; FISH and QPCR can be falsely + or -
- Marrow to assess % blasts and basos --10-15% have CML transformation at Dx
- FISH --baseline for later monitoring of CG response
- *BCR-ABL* transcripts -- baseline for later monitoring; detect pre Rx false negative if e13a3 or e14a3 (2-3%)
- If Ph-negative + morphologic CML→BCR-ABL molecular studies; FISH--- Ph-negative BCR-ABL positive CML

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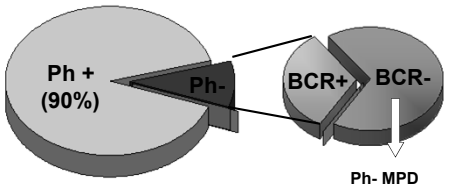
Ph+ vs. Ph-

Leukocytosis
Hypercellular BM
Splenomegaly



Ph- MPD
Atypical CML
CMML

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Poor Prognostic Factors in CML

- Older age
- Splenomegaly
- Anemia
- Thrombocytosis, thrombocytopenia
- ↑ Blasts, promyelocytes, basophils
- Marrow fibrosis
- Cytogenetic clonal evolution

Prognostic Models: Sokal, Hasford (Euro), MDACC

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Prognostic Scores in CML

- **Sokal: age, spleen, platelets, blasts**
- **Hasford: age, spleen, platelets, blasts, eosinophils, basophils**
- **EUTOS: spleen, basophils**

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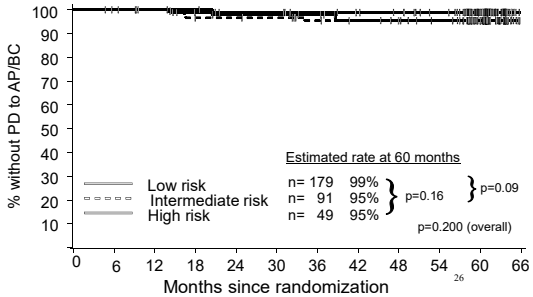
IRIS. PFS Associated With CGCR At 12 Mos, Not With Sokal Risk



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Developmental Therapeutics in CML

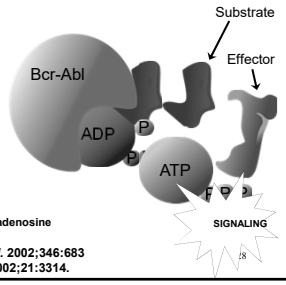
FDA Approval		
Agent	**Salvage**	**Frontline**
Interferon	**1986**	**1986**
Imatinib	**2001**	**2002**
Nilotinib	**2007**	**2010**
Dasatinib	**2006**	**2010**
Ponatinib	**2012**	
Bosutinib	**2012**	**2017**
Omacetaxine	**2012**	

Kantarjian. NEJM 346:645;2002. Kantarjian. NEJM 354:2542;2006. Talpaz. NEJM 354; 2531: 2006. Kantarjian. NEJM 362:2260:2010. Kantarjian. Lancet Oncol 12: 841; 2011. Cortes. NEJM 367: 2075; 2012. Cortes. Blood 120: 2573; 2012. Cortes. AJH e-Pub 2/2013.

Normal Bcr-Abl Signaling

The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation

This activated substrate initiates a signaling cascade culminating in cell proliferation and survival



ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Savage and Antman. *N Engl J Med.* 2002;346:683
Scheijen and Griffin. *Oncogene.* 2002;21:3314.

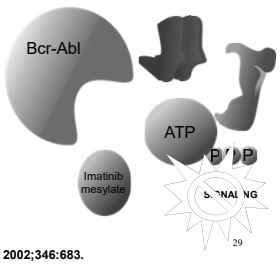
28

Imatinib Mesylate: Mechanism of Action

Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain

This prevents substrate phosphorylation and signaling

A lack of signaling inhibits proliferation and survival



Savage and Antman. N Engl J Med. 2002;346:683.

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Therapy of CML in 2019

- **Frontline**
  - **imatinib 400 mg daily**
  - **dasatinib 100 mg daily**
  - **nilotinib 300 mg BID**
  - **bosutinib 400mg daily**
- **Second / third line**
  - **nilotinib, dasatinib, bosutinib, ponatinib, omacetaxine**
  - **allogeneic SCT**
- **Other**
  - **decitabine, peg IFN**
  - **hydrea, cytarabine, combos of TKIs and with TKIs**

MDACC Sequence of Frontline and Salvage Strategies in CML

	Choice of TKI	
Frontline Rx	Dasatinib 50mg/D	Imatinib 400mg/D
Salvage for Resistance	-Ponatinib 30mg/D if no guiding mutations -if V299L, T315A, F317L/V/I/C then nilotinib 300-400 mg BID	-Dasatinib 50→100mg/D or bosutinib 300-500 mg/D -if failure then ponatinib
Salvage for toxicities	Bosutinib 300-500mg/D	Dasatinib or bosutinib

- Always adjust TKI dose if side-effects before considering change of TKI

CML. Questions

- Best frontline TKI therapy
- Generic imatinib vs Gleevec and second generation TKIs
- Endpoint of Rx: CGCR vs CMR
- Aim of Rx: survival vs Rx-free remission
- Long-term side effects; costs
- Role and timing of allo SCT
- TKIs vs allo SCT– cost considerations
- Optimal monitoring of CML
- TKI Rx discontinuation

Survival with Imatinib vs IFN + ara-C in Newly Dx CML (IRIS; 10 yr)

- 553 pts randomized to imatinib
- 10 yr survival 83.3%
- Cumulative CGCR rate 83%
- 10-Yr CGCR rate 22%
- 10-Yr MMR rate 93%
- 10-Yr MR 4.5 rate 23%
- 10 yr survival by Sokal: low 90%; intermediate 80%; high 69%
- Annual rate of transformation: 1.5%, 2.8%, 1.8%, 0.9%, 0.5%, 0%, 0%, & 0.4%

Hochhaus. NEJM 2017; 376: 917

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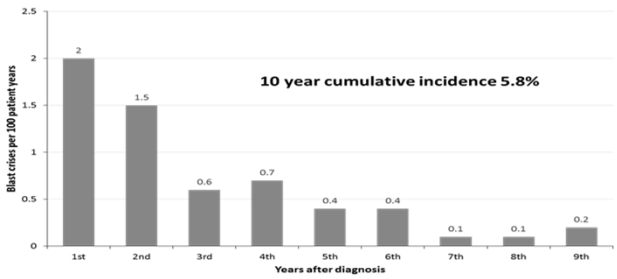
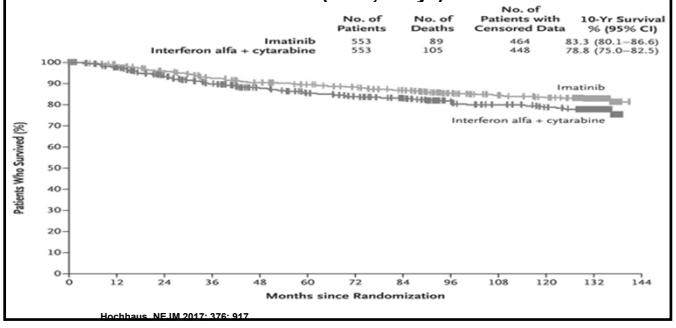
CML. Incidence of CML-BP Over Time



Hehlmann. Leukemia 2017

Survival with Imatinib vs IFN + ara-C in Newly Dx CML (IRIS; 10 yr)



Hochhaus. NEJM 2017; 376: 917

Generic vs Patent Imatinib-Chinese Experience

- 442 pts Tx with generic (n=236) or patent imatinib (n=206)

% 4-yr Outcome	Generic	Patent
CG CR	97	97
MMR	88	90
MR4	55	68
MR4.5	33	39
PFS	94	96
OS	96	98

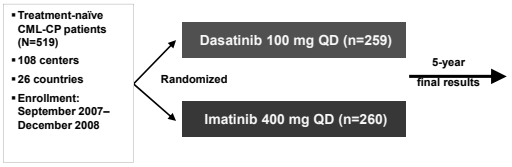
Dou. Blood 734: abst 2940; 2019

CML Frontline Therapy

- Up to 16, and 8 main studies compared new generation TKIs to imatinib frontline: ENEST-nd (nilotinib), DASISION (dasatinib), BELA (bosutinib), EPIC (ponatinib), others
- All showed higher rates of favorable early surrogate endpoints: CG CR, MMR, MR4.5, ↓ AP/BP
- Increased uncommon toxicities with newer TKIs: PAOD-MI-TIA, pancreatitis, pleural effusions; HT and pulmonary HT, ↑BS, vasospastic reactions, ↑non-CML deaths

DASISION 5-Year Final Study Results

DASISION (CA180-056) Study Design



- Database lock of 24-Mar-2014
- Primary end point: confirmed CCyR by 12 months
  - 77% dasatinib vs. 66% imatinib (*P*=0.007)[1]

Kantarjian. NEJM. 362: 2260, 2010

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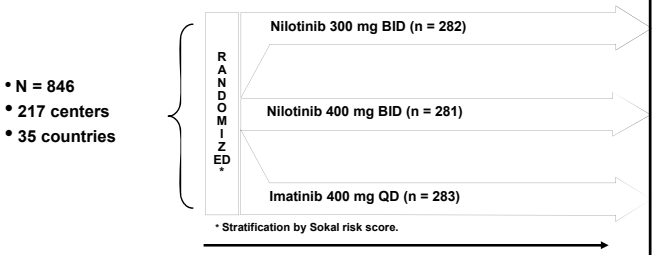
DASISION – The Final Report

- 519 pts randomized to dasatinib (n=259) or imatinib (n=260)
- Minimum follow-up 5 yrs

Outcome (%)	Dasatinib	Imatinib	P value or HR
Discontinued	39	37	
12m cCCyR	77	66	P=0.007
5y MMR	76	64	P=0.0022
5y MR4.5	42	33	P=0.025
3m <10%	84	64	
5y AP/BP	4.6	7.3	
5y OS	91	90	HR 1.01
5y PFS	85	86	HR 1.06

Cortes. JCO. 34: 2333; 2016

ENEST-nd. Study Design



Kantarjian. Lancet Oncology 12: 841; 2011

ENESTnd – The 6-Year Update

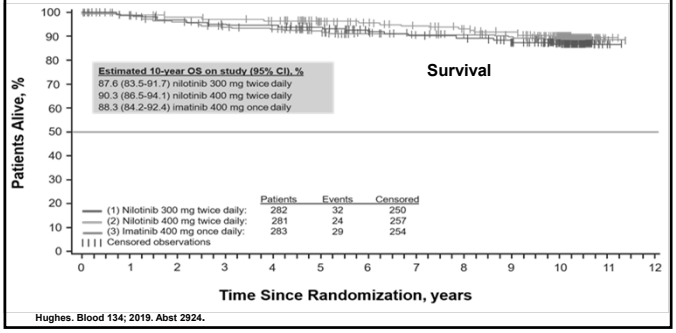
- 846 pts: nilotinib 600 (n=282), nilotinib 800 (n=281) or imatinib (n=283)
- Minimum follow-up 6 yrs

Outcome (%)	Nil 600	Nil 800	Imatinib	P value or HR
Discontinued*	40	38	50	
5y MMR*	77	77	60	P<0.0001
6y MR4.5	56	55	33	P<0.0001
3m <10%	91	89	67	
6y AP/BP	3.9	2.1	7.4	P=0.06/0.003
6y OS	92	96	92	HR 0.9/0.46

* 5-yr data from Larson et al ASCO 2014; Abstract #7073

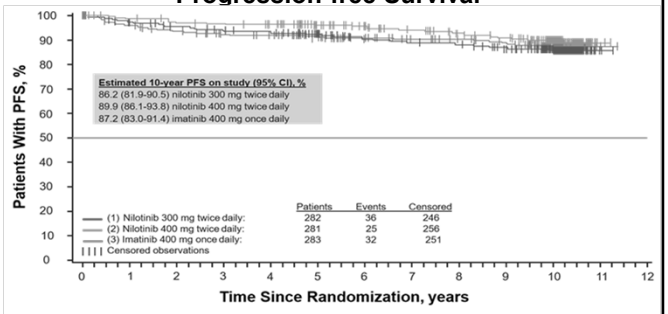
Hochhaus. Leukemia 30: 1044; 2016

Nilotinib vs Imatinib in CML(ENESTnd)--10-Yr Results Survival



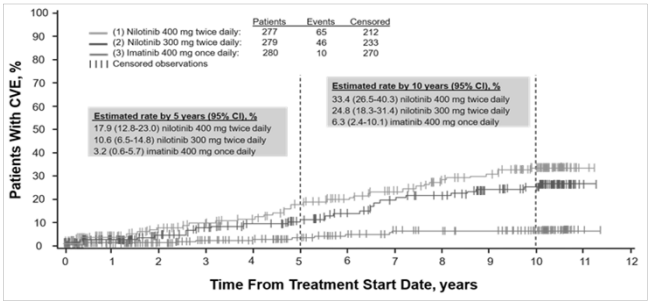
Hughes. Blood 134; 2019. Abst 2924.

Nilotinib vs Imatinib in CML(ENESTnd)--10-Yr Results Progression-free Survival



Hughes. Blood 134; 2019. Abst 2924.

Nilotinib vs Imatinib in CML(ENESTnd)--10-Yr Results Cardiovascular Events



Hughes. Blood 134; 2019. Abst 2924.

CML Therapy in 2020

- Imatinib for lower-risk Sokal and older pts (≥ 65-70 yrs); or for all CMLs until second TKIs prices lower?
- Second TKIs for high-risk Sokal
- Second TKIs for younger pts (< 50 yrs) in whom Rx DC important (?); but higher cost and toxicities

CML Monitoring

- Establish confirmed CGCR in first year (FISH; PCR)
- In CGCR
  - PCR every 3-6 mos
  - If MMR (QPCR < 0.1%), may monitor with PCR Q 6 mos
  - If QPCR ↑ by 0.5 – 1 log and/or loss of MMR (PCR> 0.1%) → monitor more frequently
- Mutations studies if resistance / need to change TKIs
- Change TKI only for loss of CGCR, not based on MMR/QPCR

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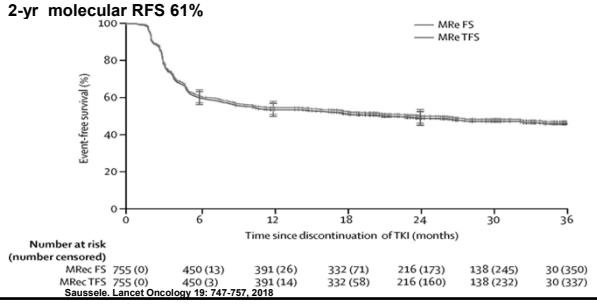
Rx Endpoints When Comparing Second TKIs to Imatinib in Frontline Rx

- Lower incidence of early transformation to AP-BP
- Survival
- Molecular cure
- Long-term safety
- Cost; cost-effectiveness = "Rx value"

TKIs Rx DC and Rx-Free Remissions in CML

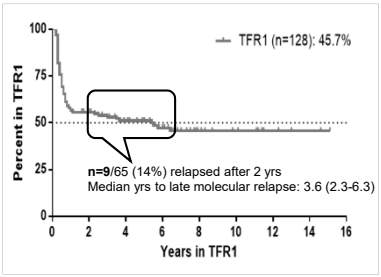
- 758 pts Rx with TKIs for >3 yrs and in Deep MR for >1 yr Relapse=loss of MMR; *BCR-ABL* transcripts [IS] >0.1%
- 2-yr molecular RFS 61%



Saussele. Lancet Oncology 19: 747-757, 2018

TFR Experience in CML (France)
Single Institution Experience Over 15 Years

- Observational study of pts who DC TKI after DMR (≥ MR4)
- N = 128 in TFR1
- Median follow-up in TFR1: 6.5 y
- Median TKI duration: 7.1 y
- TKI: imatinib 61%, 2G 11%, 2nd line 2G 28%
- MR4 100%, stable MR4 81%, stable MR4.5 67%
- MVA TFR duration: TKI duration, MR4 duration



Rousselot P, et al. ASH 2019. Abstract 27.

TKIs Rx DC in Clinical Practice--Requirements

Parameter	Yes	No
Sokal risk	low-intermediate	high
BCR-ABL transcripts	quantifiable-B2A2, B3A2 (e13a2 or e14a2)	not quantifiable
CML past Hx	chronic	AP-BP
Response to first TKI	optimal	failure
Duration of all TKIs Rx	> 8 yrs	< 3 yrs
Depth of molecular response	CMR (MR 4.5)	less than MR 4.0
Duration of molecular response	> 2-3 yrs	< 2 yrs
Monitoring availability/center-pt	ideal (q2 mo in yrs 1-2)	poor; non-compliant

Therapy of CML- General Principles I

- Patient with CML should be on daily TKIs everyday , whether in CG CR or even if 100% Ph-positive, in the course of CML-CP or in transformation (AP-BP= TKIs combinations)
- Exceptions: lower-risk CML post allo SCT; "molecular cure/ TFR"; severe cytopenias

Important Monitoring and Rx Change in CML. General Principles II

- Do not discard a TKI unless there is loss of CGCR (not MMR) at the maximum tolerated adjusted dose that does not cause grade 3-4 or chronic grade 2 (affecting QOL) toxicities
- Dose ranges
  - —imatinib 300-400mg/D (rarely 200mg/D)
  - —nilotinib 200-400mg BID (rarely 200mg/D)
  - —dasatinib 20-100mg/D
- Mutation studies only if CG or hematologic relapse

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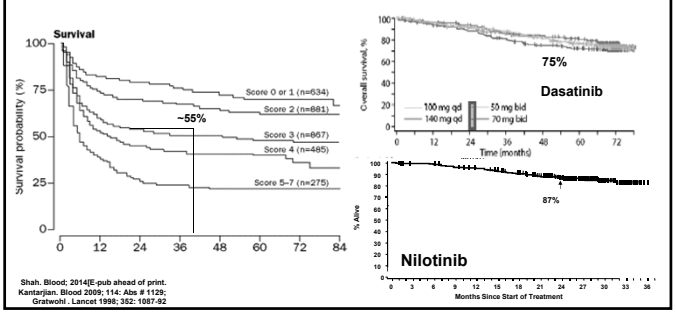
Overall Survival With TKI After Imatinib Failure or With SCT



Shah. Blood; 2014[E-pub ahead of print.
Kantarjian. Blood 2009; 114: Abs # 1129;
Gratwohl . Lancet 1998; 352: 1087-92

Timing of Allogeneic SCT

- General —Failure of multiple TKIs
- I consider allo SCT for candidate patients with resistance (not toxicity) to a second generation TKIs and no guiding mutations
- Scenario 1—Patient with resistance to imatinib → consider second generation TKIs (dasatinib if no guiding mutations) before allo SCT
- Scenario 2—Patient with resistance to dasatinib (if no mutations involving 299 or 317) → alloSCT
- Scenario 3—Patient with resistance to any TKI and T315I mutation → ponatinib → alloSCT

When Not to Consider Allo SCT Even if Multiple TKIs Failures And no CG CR

- Older pt(e.g. age 65-70+) regardless of molecular or CG status– Continue most appropriate TKI, and consider adding LD araC, AZA, omacetaxine, or even hydrea
- Scenario– 70 yr man with CG relapse (Ph 20-70%; or PCR > 1%) after second TKI and ponatinib. I would keep TKI alone or add AZA/LD araC– Pt may live their normal life with good QOL; rather than aim for allo SCT/cure at the expense of complications

Imatinib and Pregnancy

- Rare syndrome of fetal malformations (exomphalos, kidneys, bones) in 3/125
- Stop imatinib if pregnancy
- Fathered pregnancies/deliveries on TKIs →no problems
- If pregnancy / children highly desired: achieve durable CMR on TKIs then hold TKI and proceed with pregnancy / delivery under closer monitoring (e.g. FISH/QPCR every 2-3 mos)

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Pye. Blood. 111: 5505; 2008

Dasatinib and Pregnancy

- 78 women became pregnant on dasatinib; outcome available in 46
- 15 delivered normal babies (33%)
- 18(39%) had elective, and 8(17%) had spontaneous abortions
- 5(11%) had abnormal pregnancy —encephalocele, kidneys, hydrops fetalis
- 30/33 (91%) fathered infants normal
- Dasatinib may be a selective developmental toxicant

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Cortes. AJH 90: 1111; 2015

When to Look For Mutations?

- Mutation analysis in 1301 pts receiving imatinib or 2nd generation TKI (GIMEMA)

Clinical condition	% Positive
Failure	27
No CHR at 3 mo	19
No CyR at 6 mo	11
No PCyR at 12 mo	17
No CCyR at 18 mo	17
Loss CCyR	31
Loss CHR	50
Suboptimal	5
No CyR at 3 mo	7
No PCyR at 6 mo	5
No CCyR at 12 mo	8
No MMR at 18 mo	0
Loss MMR	4

Soverini. Blood 118:1208 and abst 112, 2011

CML. Mutations and Resistance

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Mutation	IC_{50}-fold increase relative to WT (W=1)				
	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
M244V	0.9	0.9	2.0	1.2	3.2
L248R	14.6	27.9	12.6	39.2	6.2
L248V	3.5	3.5	5.1	2.8	3.4
G250E	6.9	4.3	4.4	4.6	6.0
Q252H	1.4	0.8	3.1	2.6	6.1
Y253F	3.6	1.0	1.6	3.2	3.7
Y253H	8.7	0.6	2.6	36.8	2.6
E255K	6.0	9.5	5.6	6.7	8.7
E255V	17.0	5.5	3.4	19.3	12.8
D276G	2.2	0.6	1.4	2.0	2.1
E279K	3.6	1.0	1.6	2.0	3.0
E292L	0.7	1.1	1.3	1.8	2.0
V299L	1.5	8.3	8.7	1.3	0.6
T315A	1.7	6.0	36.8	2.7	0.4
T315I	17.5	45.4	75.0	39.4	3.0
T315V	12.2	29.3	738.8	57.0	2.1
F317L	2.6	2.4	4.5	2.2	0.7
F317R	2.3	33.5	114.8	2.3	4.9
F317V	0.4	11.5	21.3	0.5	2.3
M343T	1.2	1.1	0.9	0.8	0.9
M351T	1.8	0.7	0.9	0.4	1.2
F359I	6.0	2.9	3.0	8.9	2.9
F359V	2.9	0.9	1.5	5.2	4.4
L384M	1.3	0.5	2.2	2.3	2.2
H396P	2.4	0.4	1.1	2.4	1.4
H396R	3.9	0.8	1.6	3.1	5.9
F486S	8.1	2.3	3.0	1.9	2.1
L248R + F359I	11.7	39.3	13.7	96.2	17.7

Sensitive	<2-fold difference
Moderately sensitive	2.1- to 4-fold difference
Resistant	4.1- to 10-fold difference
Highly resistant	>10-fold difference

Adapted from Redaelli S et al. *Am J Hematol.* 2012;87:E125-E128.

Eiring et al. Genome Biol. 2014; 15 (9): 461.

Analysis of Mutations in CML

- If CG or hematologic relapse, mutations studies help
- No role for mutation studies pre-Rx or in imatinib responding patients
- T315I: ponatinib; allo SCT;others(DAC/AZA, ara-C, omacetaxine)
- Y253H, E255K/V, F359V/C/I : dasatinib
- V299L,T315A, F317L/V/I/C : nilotinib

Kantarjian. Blood 111:1774, 2007. Soverini. Blood 118 : 1208 ,2011

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BCR-ABL Transcripts < 10% at 6 mos Associated with Better Outcome

Response					
3 Mo	6 Mo	No.	% Survival	% PFS	% FFS
≤ 10	≤1	342	97	97	87
≤ 10	1-10	42	100	97	79
≤ 10	> 10	10	89	90	51
> 10	≤ 1	18	100	100	76
> 10	1-10	36	100	94	79
> 10	> 10	35	74	69	11

Brandford. Blood 122: abst 254; 213

Criteria for Response/Failure and Change of Rx

Time (mo)	Imatinib
3-6	Major CG; QPCR ≤ 10%
12	CG CR
Later	CG CR

- CG ≤ 35% ≈ QPCR ≤ 10%
- CGCR ≈ QPCR ≤ 1%

Important Response Categories in CML

Response	Translates into:
BCR-ABL ≤ 10% at 6 mos; CCyR later	Significantly improved survival
MMR	Modest improvement in EFS; possible longer duration CCyR; no survival benefit
CMR	Possibility of Rx discontinuation (clinical trials only)

Therapy of CML Post Frontline Failure

-

Dasatinib in CML CP After Imatinib Failure

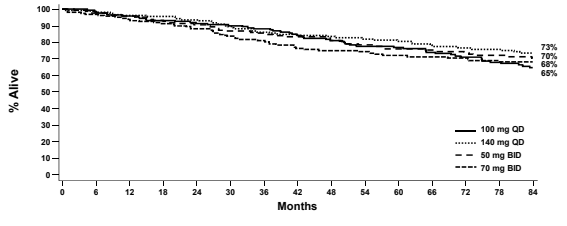
- 670 pts randomized to 4 dasatinib schedules
- 6-year follow-up

Outcome (100 mg/d)	Percent
MCyR / CCyR (within 2 yr)	63 / 50
MMR	46
IM Resistant	43
IM Intolerant	55
7-yr OS	65
7-yr PFS	42
DC Rx	78

- Reason for DC: AE 30% (related 24%, unrelated 6%), progression 21%, other 47%.
- Pleural effusion 28%, pulmonary hypertension 2%.

Shah . Am J Hematol 2016; 91: 869-74

OS by Dasatinib Dose After Imatinib Failure

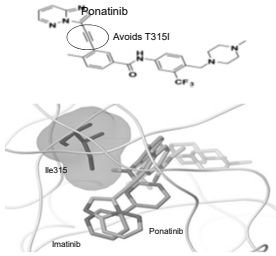


	Imatinib-resistant	Imatinib-intolerant	Overall
OS, % (95% CI)	63 (53–71)	70 (52–82)	65 (56–72)
PFS, % (95% CI)	39 (29–49)	51 (32–67)	42 (33–51)

Shah . AJM 91: 896; 2016

Ponatinib (AP24534). Pan-BCR-ABL Inhibitor

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT
- Once-daily oral activity in murine models



O'Hare T. Cancer Cell. 2009;16:401-412

5-Year Outcome with Ponatinib in CML-CP by Prior TKI

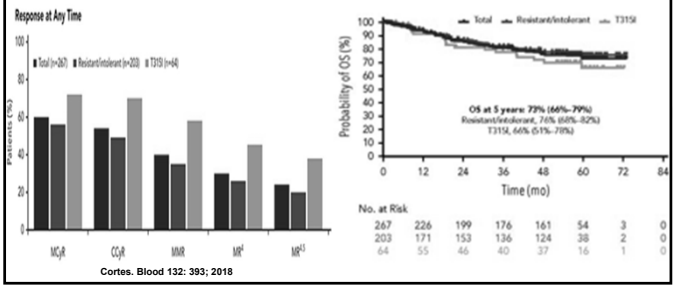
- 270 pts CML-CP Rx with ponatinib 45 mg/d post-TKI failure
- Median F/U 56.8 mo (0.1-73.1 mo)

	Percent			5-yr Probability			
	MCyR	MMR	MR4.5	MCyR	MMR	PFS	OS
1 TKI	79	58	32	75	NA	62	89
2 TKI	71	45	25	88	65	68	78
3 TKI	50	37	24	84	54	45	73
4 TKI	58	8	8	NA		NA	NA

Hochhaus A, et al. *Blood*. 2017;130(suppl): Abstract 1617.

Ponatinib in CML—CP (PACE)

- 449 pts Rx; 270 in CP
- CG major 60%, MMR 40%, 5-yr OS 73%



Cortes. Blood 132: 393; 2018

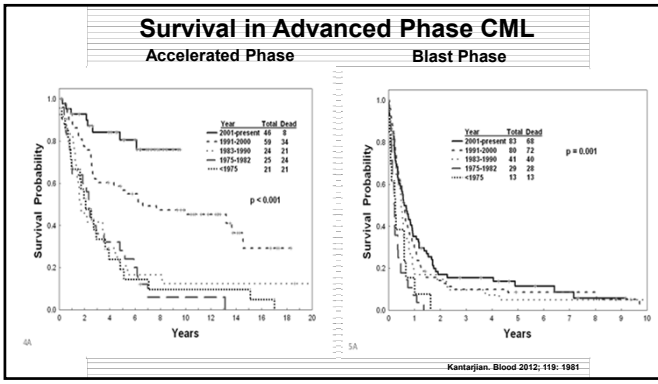
Ponatinib Toxicities of Concern in CML Therapy

- Optimal dose: 30 vs. 45 mg daily?
  - I use 30 mg daily
- Incidence of toxicities of concern
  - Pancreatitis 7%
  - Skin rashes 40%; severe 4-7%
  - Vasoocclusive disorders (cardiac, CNS, PAOD) 12%
  - Hypertension 67%; severe 20%

Therapy of CML Transformation

- Accelerated--TKI alone or combo with low intensity Rx (DAC, AZA, LD ara C, HU, etc)
- Lymphoid BP--TKI + ALL Rx (e.g. HCVAD)
- Non-lymphoid BP--TKI + AML Rx or DAC/AZA

Survival in Advanced Phase CML



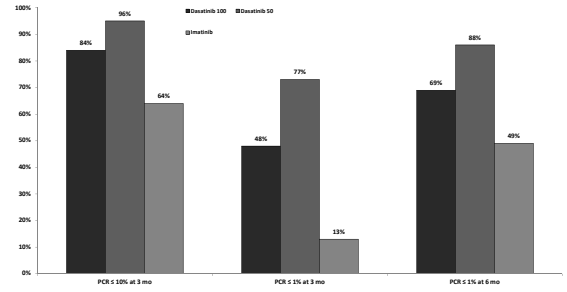
Kantarjian. Blood 2012; 119: 1981

CML-BP. MDACC Experience (1997-2016)

- 477 pts Rx: lymphoid BP 28%; TKI alone 35%, TKI + ChemoRx 48%; allo SCT 22%
- MHR 50%; CGCR 21%; MHR with TKI alone 43%; TKI + chemo 64%
- Median OS 12 mos
- MVA for OS: TKI combo, allo SCT, lymphoid BP favorable

Jain. Cancer 2017. Epub ahead of print.

Low-dose Dasatinib (50mg/D) in CML-CP. Response



Naqvi. Cancer 126: 67; 2020; 2020

CML Summary 2020

- Frontline Rx excellent (and getting better, safer and cheaper?)
- 2nd line options grossly equivalent; 3rd line ponatinib better (new ones safer?)
- Dose reductions safe in most instances
- Rx DC feasible (better to wait for long MR4.5 > 3-5 yrs = high "cure rates")
- Minimal intervention during pregnancy

Leukemia Questions?

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- Office: 713-792-7026

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Chronic Lymphocytic Leukemia

Matthew Davids, MD

August 16, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

34 - Chronic Lymphocytic Leukemia

Matthew Davids, MD, MMSC

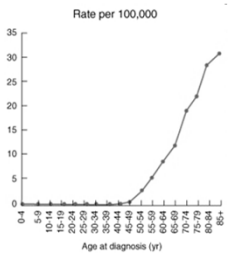
Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultancy/Advisory Committee: Janssen, Genentech, Pharmacyclics, AbbVie, TG Therapeutics, Astra-Zeneca, MEI Pharma, Verastem, Adaptive Biotechnologies, Zentalis, Ascentage Pharma, Eli Lilly, Beigene
- Research Funding: Verastem, Pharmacyclics, TG Therapeutics, Genentech, BMS, MEI Pharma, Surface Oncology, Ascentage Pharma, Novartis
- Honoraria: Research to Practice

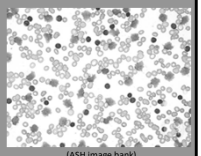
Chronic Lymphocytic Leukemia

- Most common adult leukemia of Western world
- Estimated 18,960 new cases and 4,600 deaths in 2016
- Male to female ratio is 2:1
- Median age of diagnosis is ~ 72 yrs, with only 10% of patients younger than 50 yrs of age
- Highly heterogenous clinical course, ranging from indolent to aggressive



Chronic Lymphocytic Leukemia
Clinical and Laboratory Findings

- **Variable presentation, asymptomatic or non-specific symptoms**
  - Recurrent infections in 10%
- **Signs**
  - Lymphadenopathy
  - Splenomegaly
- **Increased number of mature-appearing lymphocytes in blood**
- **Bone marrow infiltration by these lymphocytes leading to:**
  - Anemia
  - Thrombocytopenia
  - Neutropenia


(ASH image bank)

Diagnostic Workup

- At diagnosis:
  - *Flow cytometry to confirm CLL diagnosis*
  - FISH
  - IGHV gene status assessment
  - *TP53* mutational analysis
- β_2-microglobulin
- No CT scan unless symptoms are present; PET scan can be helpful if Richter's suspected
- Bone marrow biopsy and aspirate not necessary in absence of cytopenias

Diagnostic Criteria

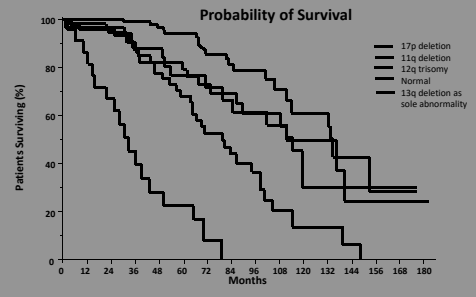
- ≥ 5,000/µL B lymphocytes in peripheral blood
- Flow cytometry → Low level of sIg, either κ- or λ-light chain expression, CD5+, CD19+, CD20+(dim), CD79b+(dim), usually CD23+
- If <5,000/µL peripheral lymphocytosis but with LAD or extranodal disease → small lymphocytic lymphoma (SLL)

Hallek, et al. *Blood*. 2018.

Chronic Lymphocytic Leukemia
Staging

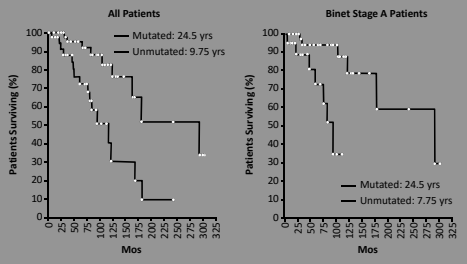
Rai Stage	Median survival (yrs)
Stage 0 Lymphocytosis only	12.5
Stage I Lymphadenopathy	8.4
Stage II Splenomegaly	5.9
Stage III Anemia	1.6
Stage IV Thrombocytopenia	1.6

Interphase Cytogenetics: **FISH**



Dohner et al. *NEJM*. 2000.

OS Is Influenced by ***IGVH*** **Gene Mutation Status**

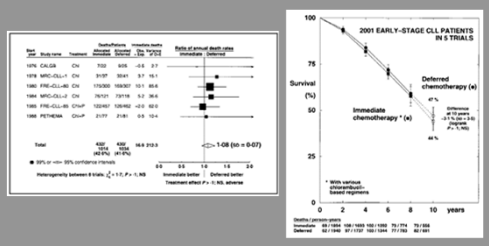


Hamblin TJ, et al. Blood. 1999;94:1848-1854.

Treatment

- No evidence that early therapy prolongs survival
- In majority of patients, a watch and wait approach is used
- High risk disease and/or lymphocytosis, alone, are not indications to treat

No survival advantage to early treatment



CLL Trialists' Group Meta-analysis, *JNCI*, 1999

Treatment

- Treat if :
  - Bone marrow failure (cytopenias)
  - Symptomatic lymphadenopathy
  - Symptomatic splenomegaly
  - Constitutional symptoms related to CLL
  - Refractory Auto-immune hemolytic anemia/ thrombocytopenia

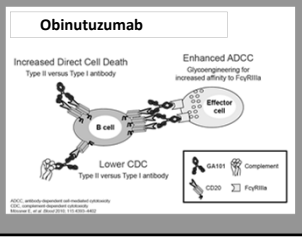
Treatment of CLL
Historical Perspective

- Before 1985: Alkylating agent monotherapy
- 1984-1990: Purine analog monotherapy
- 1990-2000: Purine analog + alkylating agent
- 2000-2013: CIT: Purine analog + mAb +/- alkylator
- 2014+: **Small molecule inhibitors**

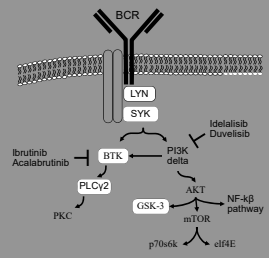
CD20 mAbs

FDA-approved CD20-targeted agents for CLL:

- Rituximab
- Ofatumumab
- Obinutuzumab



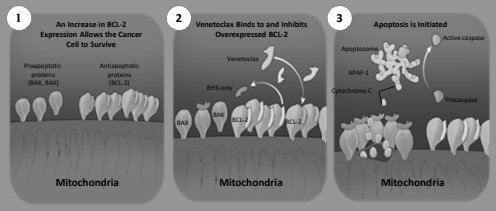
Targeting of BCR Signaling in CLL



- BCR-associated kinases are targets of 4 approved drugs in CLL
  - Btk (Bruton's tyrosine kinase) inhibitors: ibrutinib, acalabrutinib
  - PI3 kinases: isoform-selective inhibitor of PI 3-kinases,[2] idelalisib, duvelisib

Quiroga MP, et al. Blood. 2009;114:1029-1037. 2. Niedermeier M, et al. Blood. 2009;113:5549-5557.

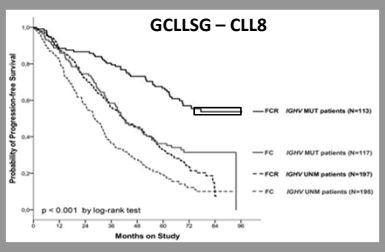
Venetoclax: Mechanism of Action



Kumar S, et al. ASCO 2015. Abstract 8576.

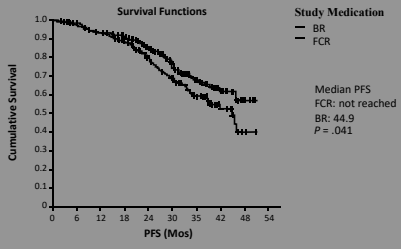
First Line Treatment

Time-limited FCR has with curative potential, but use is restricted to young patients with m*IGHV,* long term risks



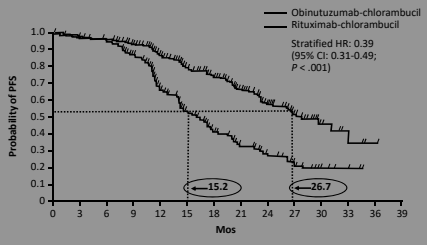
Fischer et al., *Blood*, 2016

CLL10 Study: FCR VS BR in Frontline PFS



Eichhorst B, et al. ASH 2013. Abstract 526.

CLL11 Trial: PFS Head-to-Head Comparison



Goede V, et al. N Engl J Med. 2014;370:1101-1110.

RESONATE-2: Ibrutinib vs Chlorambucil With Tx-Naive CLL/SLL

- An international, randomized phase III trial

Pts 65 yrs of age or older with treatment-naive CLL/SLL; no warfarin use; no del(17p) (N = 269)

Ibrutinib
420 mg/day until progression

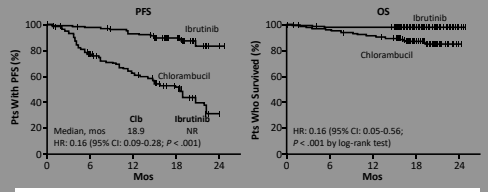
Chlorambucil
0.5 mg/kg (up to maximum of 0.8 mg/kg) on Days 1, 15 of 28-day cycle for up to 12 cycles

Crossover upon PD (n = 43)

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, EFS, rate of hematologic improvement, and safety

Burger JA, et al. N Engl J Med. 2015

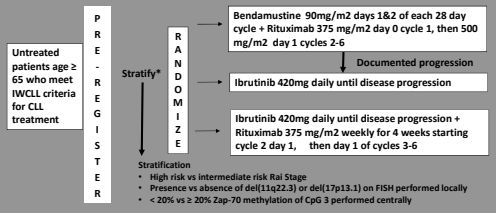
RESONATE-2: Superior Efficacy



AEs Summary	Ibrutinib	Chlorambucil
Most frequent AEs	Diarrhea, fatigue, cough and nausea	Nausea, fatigue, neutropenia, anemia, and vomiting
AEs leading to discontinuation, %	9	23

Burger JA, et al. N Engl J Med. 2015

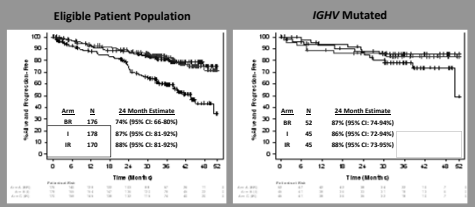
Alliance A041202 Schema



Woyach JA, et al. N Engl J Med. 2018

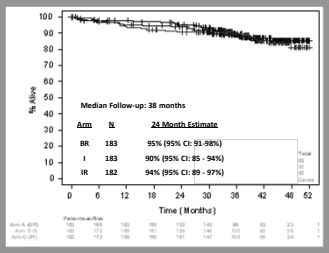
23

Alliance A041202 Primary Endpoint: Progression Free Survival



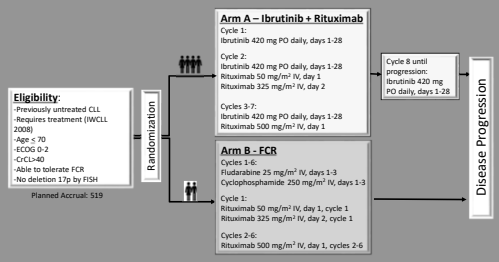
Woyach JA, et al. N Engl J Med. 2018

Overall Survival
Intention-to-Treat Patient Population



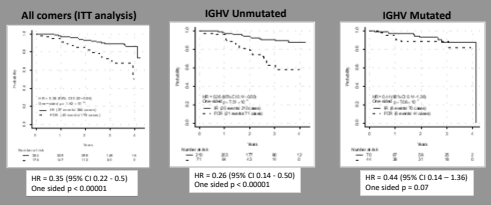
Woyach JA, et al. N Engl J Med. 2018

ECOG 1912: Study design



Shanafelt et al., ASH Annual Meeting, 2018

ECOG 1912: Progression Free Survival



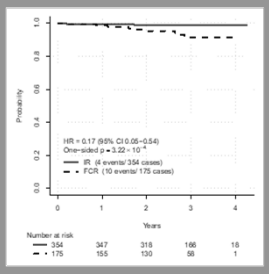
HR = 0.35 (95% CI 0.22 - 0.5)
One sided p < 0.00001

HR = 0.26 (95% CI 0.14 - 0.50)
One sided p < 0.00001

HR = 0.44 (95% CI 0.14 – 1.36)
One sided p = 0.07

Shanafelt et al., ASH Annual Meeting, 2018

ECOG 1912: Overall Survival

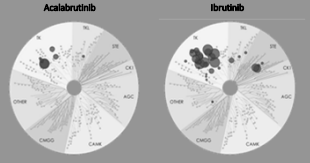


Shanafelt et al., ASH Annual Meeting, 2018

Second Generation BTKi: Acalabrutinib: Agent Overview

- Highly-selective, potent kinase inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling

Kinase selectivity profiling at 1 μM

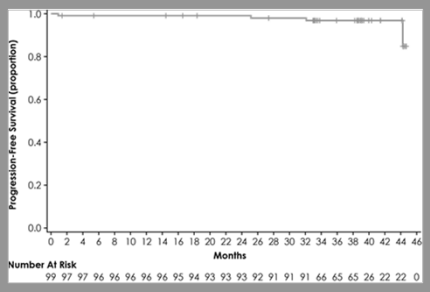


The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

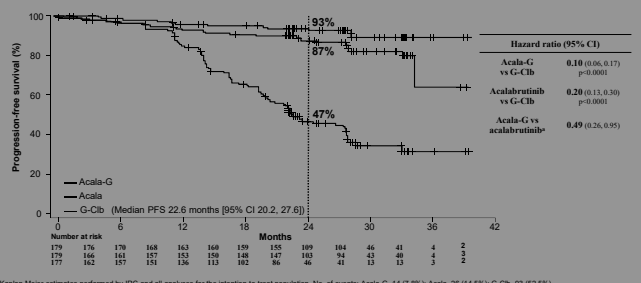
Barf T, et al. *J Pharmacol Exp Ther.*

Acalabrutinib is highly effective in frontline CLL



Byrd et al., ASH 2018, abstract 692

IRC-Assessed Progression-Free Survival
Median follow-up 28.3 months



Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)
[a]*Post hoc* analysis.
Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

Sharman et al., *ASH*, 2019

Events of Clinical Interest for Acalabrutinib

AEs, n (%)	Acala-G N=178		Acalabrutinib N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
Major bleeding[a]	5 (2.8)[b]	3 (1.7)	3 (1.7)[c]	3 (1.7)	2 (1.2)[d]	0
Infections	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancies, excluding NMSC	10 (5.6)[e]	6 (3.4)	5 (2.8)[f]	2 (1.1)	3 (1.8)[g]	2 (1.2)

There were no reported events of ventricular tachyarrhythmias
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system. [b]Includes gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, postprocedural hemorrhage, and subdural hemorrhage. [c]Includes hemarthrosis, postprocedural hematoma, and retinal hemorrhage. [d]Includes subdural hemorrhage and hemoptysis. [e]Includes non-small cell lung cancer (n=2), squamous cell carcinoma (n=2), basosquamous carcinoma, bladder transitional cell carcinoma, breast cancer, gastric cancer stage IV, metastases to bone, prostate cancer, and renal cell carcinoma (all n=1). [f]Includes prostate cancer (n=2), glioblastoma, malignant melanoma in situ, transitional cell carcinoma (all n=1). [g]Includes prostate cancer, acute myelomonocytic leukemia, and lung adenocarcinoma (all n=1)
NMSC, nonmelanoma skin cancer

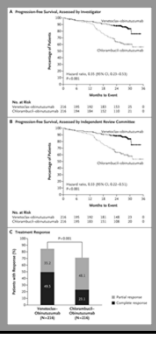
Sharman et al., *ASH*, 2019

CLL-14

7502 Effect of fixed-duration venetoclax plus obinutuzumab on progression-free survival, and rates and duration of minimal residual disease negativity in previously untreated patients with chronic lymphocytic leukemia (CLL) and comorbidities

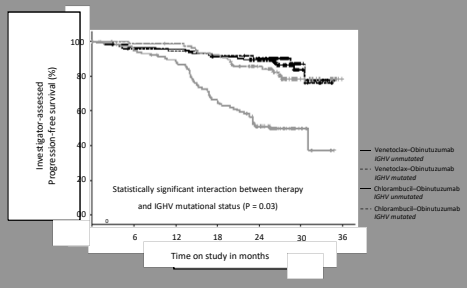
Kirsten Fischer MD, Othman Al-Sawaf MD, Jasmin Bahlo PhD, Anna-Maria Fink MD, Maneesh Tandon MD, Mark Dixon, Sandra Robrecht PhD, Simon Warburton, Kathryn Humphrey, Olga Samoylova MD, Anna Marina Liberati MD, Javier Pinilla-Ibarz MD PhD, Stephen Opat MD, Liliya Sivcheva MD, Katell Le Du MD, Laura Maria Fogliatto MD, Carsten Utoft Niemann MD PhD, Robert Weinkove MD, Sue Robinson MD, Thomas J. Kipps MD PhD, Sebastian Boettcher MD, Eugen Tausch MD, Rod Humerickhouse MD, Barbara Eichhorst MD, Clemens-Martin Wendtner MD, Anton W Langerak PhD, Karl-Anton Kreuzer MD, Valentin Goede MD, Stephan Stilgenbauer MD, Mehrdad Mobasher MD, Matthias Ritgen MD and Michael Hallek MD

CLL14: **Efficacy Data**



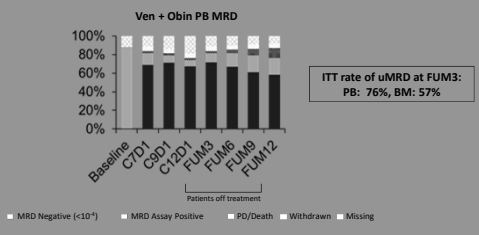
Fischer et al., N Engl J Med, 2019

CLL14: **PFS by *IGHV* Mutational Status**



Fischer et al., N Engl J Med, 2019

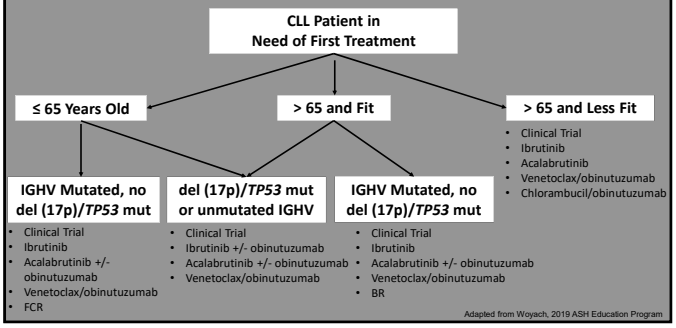
CLL14: **MRD Status**



ITT rate of uMRD at FUM3:
PB: 76%, BM: 57%

Fischer et al., N Engl J Med, 2019

Approach to frontline CLL treatment in 2020



Adapted from Woyach, 2019 ASH Education Program

Relapsed/Refractory CLL

Considerations in selecting next therapy in a R/R patients progressing after CIT

- Patients should receive a chemo free approach when available
- Should re-assess TP53 status particularly in younger patients to guide future treatment approach

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Considerations in Choosing a First NA for R/R Disease

- Ibrutinib or Venetoclax + rituximab are now both considered to be standard of care for this population
- If significant cardiac/bleeding risks and significant renal dysfunction, can consider PI3Ki as first NA

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Considerations in Choosing a Second NA for R/R Disease

- Prospective data are limited
- If BTKi has been used as the first NA:
  - Venetoclax preferred
  - Idelalisib + rituximab or duvelisib are options
- If BTKi has not been used as the first NA then BTKi preferred

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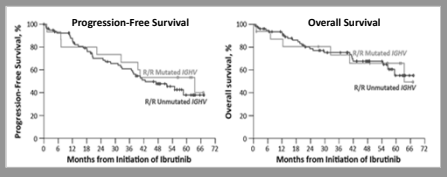
In R/R CLL, ibrutinib leads to comparable PFS/OS regardless of *IGHV* status (PCYC-1102 study)



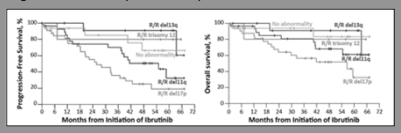
	Median PFS	5-year PFS
Mutated *IGHV* (n=16)	63 mo	53%
Unmutated *IGHV* (n=79)	43 mo	38%

	Median OS	5-year OS
Mutated *IGHV* (n=16)	63 mo	66%
Unmutated *IGHV* (n=79)	NR	55%

O'Brien et al., Blood, 2018

In R/R CLL, ibrutinib leads to durable response in most FISH subgroups

Progression-Free Survival (median 55 mo.) | Overall Survival

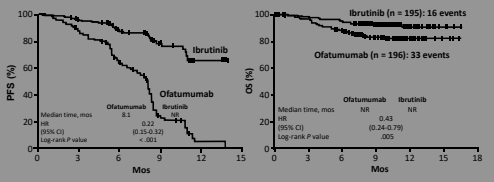


	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

O'Brien et al., Blood, 2018

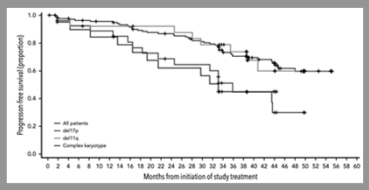
Phase III (RESONATE) Ibrutinib vs Ofatumumab: PFS and OS



- 78% reduction in risk of progression or death
- Investigator-assessed PFS HR: 0.133 (95% CI: 0.085-0.209; *P* < .0001)
- Richter's transformation was confirmed in 2 pts on each arm
- 57% reduction in the risk of death for ibrutinib arm
- 57 pts initially randomized to ofatumumab were crossed over to ibrutinib arm following IRC-confirmed PD, at the time of analysis
- OS rate at 12 mos: 90% in ibrutinib group vs 81% in ofatumumab group (censored data at time of crossover)

Byrd JC, et al. N Engl J Med. 2014;371:213-223.

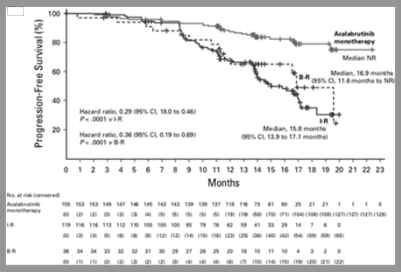
Acalabrutinib in Relapsed/Refractory CLL—Updated Phase II Results



- 17/155 patients (13%) discontinued acalabrutinib due to AEs
- Dose reductions occurred in 36 patients (27%)
  - 6 patients (4%) had a dose reduction due to an AE
- Dose withholding, defined as missing dosing for ≥7 consecutive days, occurred in 84 patients (63%)

Byrd JC, et al. *Blood*. 2020;135:1204-1213.

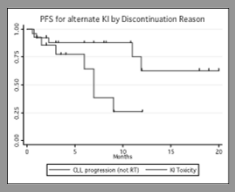
ASCEND—IRC-Assessed PFS Was Superior for Acalabrutinib vs Idela-R or B-R



Ghia P, et al. *J Clin Oncol*. 2020 May 27. [Epub ahead of print]

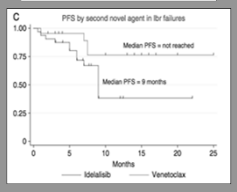
What should we do for patients coming off ibrutinib?

KI-intolerant patients can be successfully treated with an alternate KI



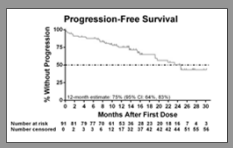
blood Mato *et al*, Blood 2016

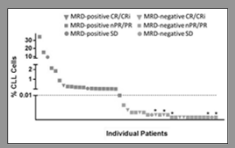
Venetoclax may be better choice for patients who progress on ibrutinib



Mato *et al*, Annals Oncology 2017 Annals of Oncology

M14-032, the first prospective study of any treatment for pts progressing on a KI, found that venetoclax is active post ibrutinib



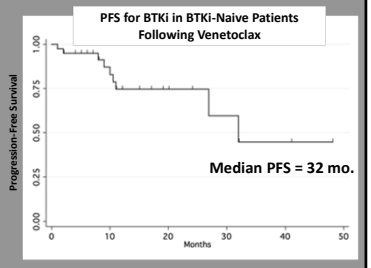


- **91 pts progressed after ibrutinib, treated with venetoclax**
- **Median 4 prior therapies (range 1-15), del(17p) in 44%**
- **Overall response rate: 65%, CR/CRi rate: 9%**
- **Peripheral Blood MRD rate at 24 weeks (n=57): 42%**
- **Median follow-up: 14 mo.**

Jones et al., Lancet Oncol, 2018

After Venetoclax, BTK Inhibition Produces High ORR and Durable Remissions in BTK Inhibitor-Naive Patients

- CLL pts who discontinued venetoclax in the first-line (4%) and R/R settings (96%)
- Median of 3 therapies prior to venetoclax
- 40% were BTKi naïve (*n* = 130)
- ORR to BTKi was 84% (*n* = 44) in BTKi-naïve patients vs 54% (*n* = 30) in BTKi-exposed patients



Mato AR, et al. *Clin Cancer Res*. 2020 Mar 20. [Epub ahead of print]

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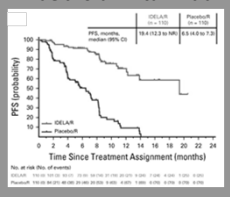
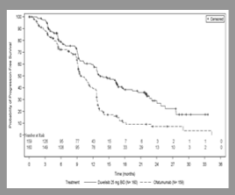
Approved PI3Ki are also efficacious, with manageable toxicity

Idelalisib + Rituximab



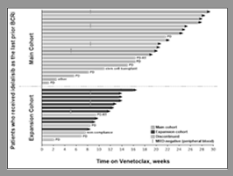
Sharman et al., J Clin Oncol, 2019

Duvelisib

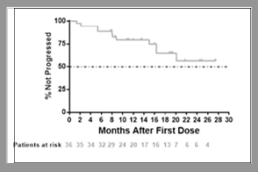


Flinn et al., *Blood*, 2018

Venetoclax is also active for patients progressing on idelalisib



- **36 pts progressed after idelalisib were treated with venetoclax**
- **Median 3 prior therapies (range 1-11)**
- **Del(17p) in 22%, unmutated *IGHV* in 88%**



- **Overall response rate: 67%**
- **Median follow-up: 14 mo.**

Coutre et al...Davids, *Blood*, 2018

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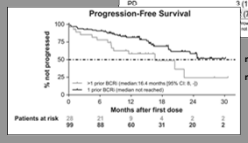
Venetoclax is active for patients progressing on >1 BCRi, though response rates and PFS are poorer

- **28 pts who progressed after >1 prior BCRi were treated with venetoclax**
- **Median 6.5 prior therapies (range 2-15)**
- **Del(17p) in 36%, unmutated *IGHV* in 70%**

	>1 prior BCRi	1 prior BCRi
n (%)	n=28	n=99
ORR	12 (43)	74 (75)
CR/CRi	1 (4)	10 (11)
nPR	0	3 (3)
PR	11 (39)	61 (61)
SD	11 (39)	17 (17)
PD	3 (11)	4 (4)
	(7)	4 (4)



median not reached

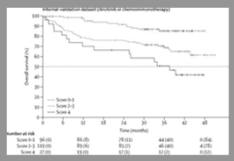
median 16.5 mo.

Wierda, et al, BJH, 2019

52

High risk CLL patients have short survival with novel agent monotherapy (n=2,475)

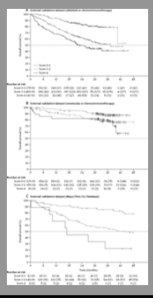
Ibrutinib



Idelalisib

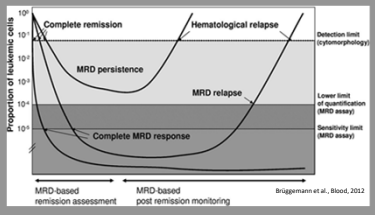
Venetoclax

Mayo Clinic External Validation



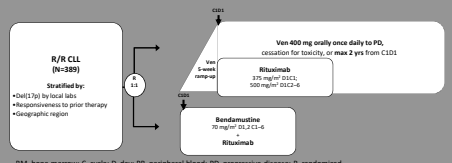
Soumerai J et al., *Lancet Haem*, 2019

MRD in CLL



- Testing with the use of 4-color flow cytometry, ASO-PCR, and now NGS (Adaptive ClonoSEQ)
- In Pts receiving chemoimmunotherapy, MRD positivity is associated with increased relapse and shorter survival
- Role of MRD assessment with continuous signaling kinase inhibitors is less relevant
- Data suggest that MRD also prognostic for time-limited venetoclax-based therapies

MURANO Study Design



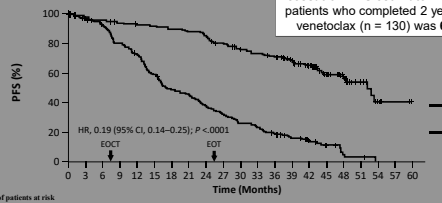
BM, bone marrow; C, cycle; D, day; PB, peripheral blood; PD, progressive disease; R, randomized

- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)
- Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed every 3 months for 3 yrs, then every 6 months thereafter, or until PD
- Primary analysis was pre-planned at 140 PFS events; this follow-up analysis was conducted 1 yr later

Seymour JF, et al. N Engl J Med 2018;378:1107–20

MURANO: PFS Benefit With Venetoclax-Rituximab vs Bendamustine-Rituximab Sustained 2 Years Post-EOT

The **24-month post-treatment cessation PFS estimate** in VenR patients who completed 2 years of venetoclax (n = 130) was **68%**



Treatment	4-yr PFS, % (95% CI)
VenR (n = 194)	57.3 (49.4–65.3)
BR (n = 195)	4.6 (0.1–9.2)

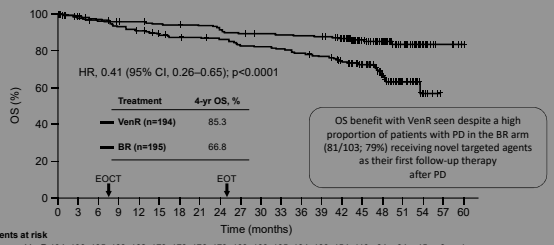
No. of patients at risk

VenR	194	190	185	179	176	174	170	167	161	150	141	134	130	118	101	55	40	14	7	2	-				
BR	195	178	165	143	129	104	85	80	66	56	45	40	32	23	14	9	3	2	-	-	-				

Median follow-up: 48 months

Abbreviations: BR, bendamustine-rituximab; EOCT, end of combination treatment; EOT, end of treatment; PFS, progression-free survival; VenR, venetoclax-rituximab.
With permission from Seymour JF, et al. *Blood.* 2019;134(suppl 1):Abstract 355. Presented at: 2019 ASH annual meeting; December 7–10, 2019; Orlando, FL.

OS benefit maintained with VenR vs BR 2 years post-EOT



OS benefit with VenR seen despite a high proportion of patients with PD in the BR arm (81/103; 79%) receiving novel targeted agents as their first follow-up therapy after PD

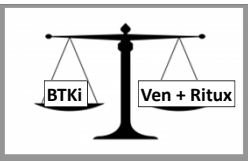
No. of patients at risk

VenR	194	190	185	183	182	179	178	176	173	168	166	165	164	163	154	110	84	34	15	6	1				
BR	195	181	175	167	162	155	152	150	147	141	140	138	134	130	116	94	58	29	7	-	-				

BR, bendamustine-rituximab; EOCT, end of combination treatment; EOT, end of treatment; OS, overall survival; PD, progressive disease/disease progression; VenR, venetoclax–rituximab

Relapsed Refractory CLL: Sequencing Decisions

No definitive data support ven vs. BTKi as first novel agent in the relapsed/refractory setting



- **Convenience (no infusions, TLS monitoring)**
- **Longterm efficacy data**
- **Phase 3 data compared to other NA (acala)**
- **More data for efficacy of ven at time of ibrutinib progression**
- **Potential for 2-year time-limited therapy**
- **No known cardiac or bleeding risks**
- **Less concern for longterm adherence**
- **Potential for cost-saving if 2-years of therapy is durable**

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What can we do for CLL patients who progress after novel agent therapy?

Allogeneic Stem Cell Transplant

- Prolonged DFS in advanced, refractory disease and in 17p-/TP53mut
- 17p-/TP53mut may lose its negative prognostic effect with AlloSCT
- Factors associated with poor outcome:
  - > 3 lines of therapies
  - Advanced clinical stage
  - Marked lymphadenopathy
  - Refractory disease at time of transplant

RIC allo-HSCT has curative potential in CLL but also serious risks

	Fred Hutchinson Cancer Center[28]	German CLL Study Group[47,48]	MD Anderson Cancer Center[49]	Dana Farber Cancer Institute[29]
Number of patients	82	90	86	76
Conditioning regimen	Flu/low-dose TBI	Flu/Cy ± ATG	Flu/Cy ± R	Flu/Bu
Donors, % (sibling/MUD)	63/37	41/59	50/50	37/63
Median follow-up, mo	60	72	37	61
Median PFS, %	39 (5 y)	38 (6 y)	36 (6 y)	43 (6 y)
Median OS, %	50 (5 y)	58 (6 y)	51 (6 y)	63 (6 y)
Early mortality, % (<100d)	<10	<3	<3	<3
NRM, %	23	23	17	16
Acute grade 3-4 GVHD, %	20	14	7	17
Severe chronic GVHD, %	53	55	56	48

ATG, antithymocyte globulin; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; MUD, matched unrelated donor; R, rituximab; TBI, total body irradiation.

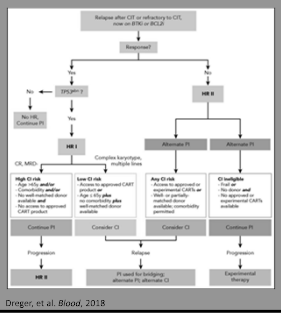
Gribben J, *Blood*, 2017

Selected Trials of CD19-Targeted CAR T-Cells in CLL

	Source	Number of Patients with CLL	Costimulatory Domain	ORR n, %	CR n, %
CAR T Alone	Kochenderfer et al. (2012 and 2015)	8	CD28	7/8 (87%)	4/8 (50%)
	Porter et al. (2014)	14	4-1BB	8/14 (58%)	4/14 (29%)
	Porter et al. (2016)	13	4-1BB	4/13 (31%)	1/13 (8%)
		17		9/17 (53%)	6/17 (35%)
	Turtle et al. (2016 and 2017)	24	4-1BB	14/19 (74%)	4/19 (21%)
CAR T + ibrutinib	Gill et al. (2018)	14	4-1BB	10/14 (71%)	6/14 (43%)
	Gauthier et al. (2018)	17	4-1BB	14/16 (88%)	NR

- Kochenderfer JN et al., *Blood*, 2012
- Kochenderfer JN et al., *J Clin Oncol*, 2015
- Porter DL et al., *Blood*, 2014
- Porter DL et al., *J Clin Oncol*, 2016
- Turtle CJ et al., *J Clin Oncol*, 2016
- Turtle CJ et al., *J Clin Oncol*, 2017
- Gill SI et al., *Blood*, 2018
- Gauthier J et al., ASH, 2018

Allogeneic Transplantation in CLL: 2018 EBMT Guidelines



Refractoriness to	TP53 abnormality present (del17p/TP53mut)	High risk Category
CIT only	yes	I – CITresistant (BTKi- and BCL2i-sensitive)
CIT + BTKi or CIT + BCL2i or BTKi + BCL2i (+/- CIT)	yes or no	II – CIT- and PI-resistant (BTKi- and/or BCL2i-refractory)

Dreger, et al. *Blood*, 2018

Conclusions

- **CLL is a highly heterogeneous disease**
- **Watch and wait for most initially**
- **Role for chemoimmunotherapy diminishing**
- **Novel agent based therapies have revolutionized the therapeutic paradigm, including continuous and time-limited regimens**
- **Cellular therapies remain an option for high risk, refractory patients**
- **Future studies will help determine the optimal treatment approach (sequential continuous vs. time-limited combinations)**

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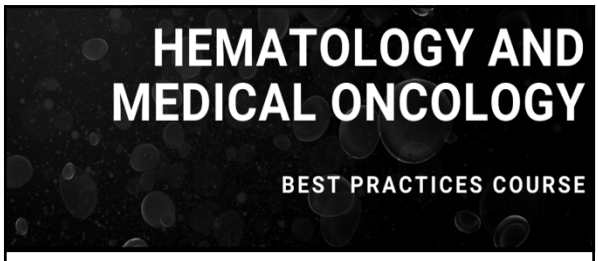
Myelodysplasia

Mikkael Sekeres, MD

August 16, 2020



35 - Myelodysplasia

Mikkael A. Sekeres, MD, MS

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- N/A

MDS | Agenda

- Patient
- Definitions and the Notion of Risk
- Ameliorating Anemia
- Tackling Thrombocytopenia
- Modifying Multilineage Dysplasia
- The Higher-risk Hurdle
- Conclusions

@MikkaelSekeres

MDS | Agenda

- **Patient**
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@MikkaelSekeres

MDS | Patient

72 yo woman with worsening fatigue:
"Feels like my legs are encased in cement."
Now uses a  to park close to the casino entrance.

PMH: HTN, CAD, smoking

@MikkaelSekeres

MDS | Patient

Laboratory Results:

WBC	**4500/uL with ANC 2100, no blasts**
Hgb	**7.8 g/dL with MCV of 102**
Platelet count	**174,000/uL**
Reticulocyte ct	**0.4%**
Epo level is	**80 mIU/ml**

A bone marrow biopsy shows hypercellularity (70%), dyserythropoiesis and 25% ring sideroblasts, and she is diagnosed with MDS-SLD-RS (2% blasts).

Cytogenetics: no growth; NGS with SF3B1 (VAF 26%)

@MikkaelSekeres

MDS | Agenda

- Patient
- **Definitions and the Notion of Risk**
- Ameliorating Anemia
- Tackling Thrombocytopenia
- Modifying Multilineage Dysplasia
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- Conclusions

@MikkaelSekeres

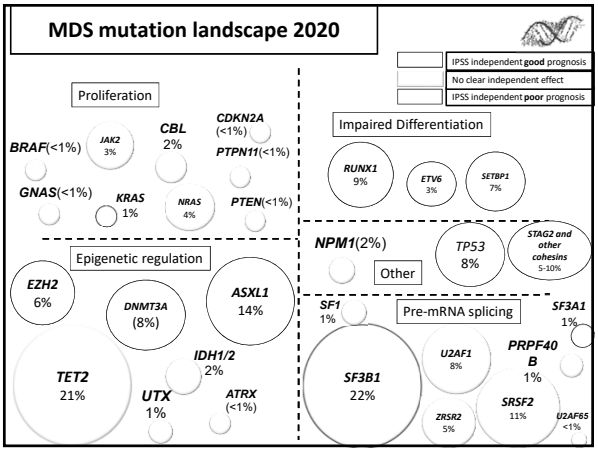
MDS | Definition

- A heterogeneous clonal hematopoietic disorder derived from an abnormal multipotent progenitor cell
- Characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis

MDS is a Cancer!!!

@MikkaelSekeres

MDS mutation landscape 2020



MDS | Epidemiology

Site	Both Sexes Rate	Both Sexes Count	Males Rate	Males Count	Females Rate	Females Count
Myelodysplastic Syndromes (MDS)						
By age						
Ages <40	0.1	438	0.1	222	0.1	216
Ages 40-49	0.7	549	0.7	280	0.7	269
Ages 50-59	2.1	1,764	2.5	1,010	1.8	754
Ages 60-69	8.2	4,868	10.5	2,920	6.2	1,948
Ages 70-79	26.9	8,579	36.4	5,154	19.3	3,425
Ages 80+	55.4	11,940	83.8	6,688	38.5	5,252
By race						
All Races	4.5	28,138	6.2	16,274	3.3	11,864
White	4.7	23,870	6.5	14,017	3.4	9,853
Black	3.6	2,206	4.7	1,129	2.9	1,077
Asian/Pacific Islander	3.0	1,632	4.0	904	2.3	728
American Indian/Alaska Native[b]	2.7	80	3.8	51	1.9	29
Hispanic[c]	3.2	2,183	4.1	1,158	2.6	1,025

Incidence Rate = 4.5/100,000 per year

SEER Cancer Statistics Review, 2012-2016.
https://seer.cancer.gov/csr/1975_2016/results_merged/sect_30_mds.

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MDS | Epidemiology

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Ages 50-59	2.1	1,764	2.5	1,010	1.8	754
Ages 60-69	8.2	4,868	10.5	2,920	6.2	1,948
Ages 70-79	26.9	8,579	36.4	5,154	19.3	3,425
Ages 80+	55.4	11,940	83.8	6,688	38.5	5,252
By race						
All Races	4.5	28,138	6.2	16,274	3.3	11,864
White	4.7	23,870	6.5	14,017	3.4	9,853
Black	3.6	2,206	4.7	1,129	2.9	1,077
Asian/Pacific Islander	3.0	1,632	4.0	904	2.3	728
American Indian/Alaska Native[b]	2.7	80	3.8	51	1.9	29
Hispanic[c]	3.2	2,183	4.1	1,158	2.6	1,025

Men > Women

SEER Cancer Statistics Review, 2012-2016.
https://seer.cancer.gov/csr/1975_2016/results_merged/sect_30_mds.

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MDS | Epidemiology

Site	Both Sexes Rate	Both Sexes Count	Males Rate	Males Count	Females Rate	Females Count
Myelodysplastic Syndromes (MDS)						
By age						
Ages <40	0.1	438	0.1	222	0.1	216
Ages 40-49	0.7	549	0.7	280	0.7	269
Ages 50-59	2.1	1,764	2.5	1,010	1.8	754
Ages 60-69	8.2	4,868	10.5	2,920	6.2	1,948
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Whites > African-Americans

SEER Cancer Statistics Review, 2012-2016.
https://seer.cancer.gov/csr/1975_2016/results_merged/sect_30_mds.

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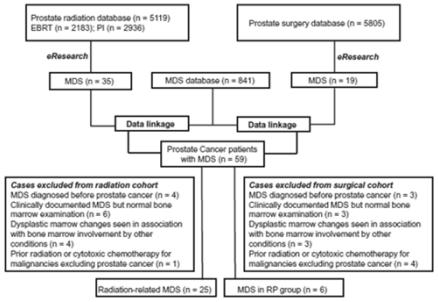
MDS | Epidemiology – Prostate CA



Mukherjee et al. J National Cancer Inst 2014;106:462

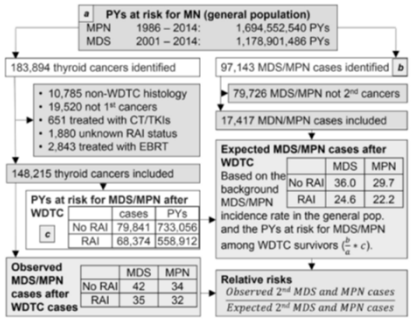
MDS | Epidemiology – Prostate CA

Age at MDS diagnosis, y	SEER 17†	Ohio ‡	Cleveland Clinic cohort				
			All	Radiation	EBRT	PI	RP
<40	0.2	0.60	0	0	0	0	0
40-49	0.8	0.62	0	0	0	0	0
50-59	2.3	1.69	0	0	0	0	0
60-69	9.4	3.21	1.79	4.66	0	6.46	0
70-79	30.4	10.26	26.42	33.81	56.99	15.22	14.09
≥80	577	10.22	38.16	38.82	32.88	51.95	35.73

Yearly incidence rate /100,000

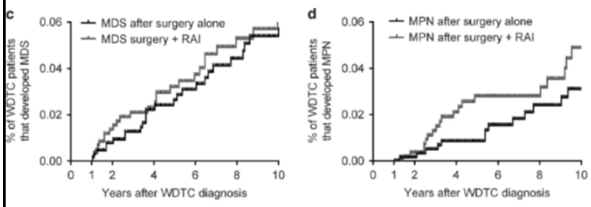
Mukherjee et al. J National Cancer Inst 2014;106:462

MDS | Epidemiology – Thyroid CA



Molenaar et al. Leukemia 2018:32;952-9. and JCO 2018;36:1831-9.

MDS | Epidemiology – Thyroid CA



RR of developing MDS for surgery + RAI = 3.9 compared to background rate (P<0.001); for MPN = 3.1 (P=0.012).

Molenaar et al. Leukemia 2018:32;952-9. and JCO 2018;36:1831-9.

MDS | WHO Classification

2008 Name	Abbrev.	2016 Name	Abbrev.
Refractory cytopenia with unilineage dysplasia	RCUD (includes RA, RN and RT)	**MDS with single lineage dysplasia**	MDS-SLD
Refractory anemia with ring sideroblasts	RARS	**MDS with ring sideroblasts**	MDS-RS
MDS w/ isolated del(5q)	Del(5q)	*unchanged*	*unchanged*
Refractory cytopenia with multilineage dysplasia	RCMD	**MDS with multilineage dysplasia**	MDS-MLD
		(with ring sideroblasts)	MDS-RS-MLD
Refractory anemia with excess blasts, type 1	RAEB-1	**MDS with excess blasts, type 1**	MDS-EB-1
Refractory anemia with excess blasts, type 2	RAEB-2	**MDS with excess blasts, type 2**	MDS-EB-2
MDS, Unclassifiable	MDS-U	*unchanged*	*unchanged*
Refractory cytopenia(s) of childhood	RCC	*unchanged*	*unchanged*

Adapted from Arber et al. Blood 2016;127:2391.

MDS | IPSS Classification

Calculation of prognostic score

Score	0	0.5	1.0	1.5	2.0
BM Blast %	< 5	5-10		11-20	21-29
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

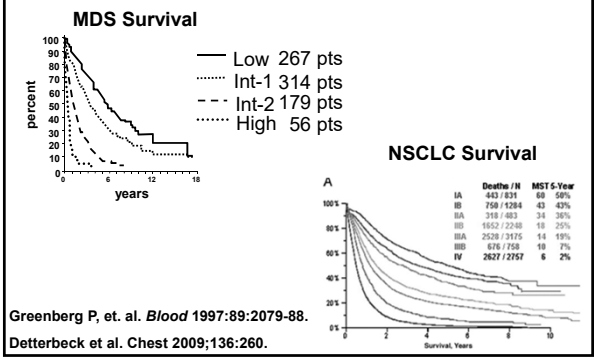
Estimation of prognosis

Lower-Risk

Overall Score	IPSS Subgroup	Median Survival (Years)
0	Low	5.7
0.5-1.0	Intermediate-1	3.5
1.5-2.0	Intermediate-2	1.2
≥2.5	High	0.4

Greenberg P, et. al. *Blood* 1997:89:2079-88.

MDS | IPSS "Staging"



Greenberg P, et. al. *Blood* 1997:89:2079-88.

Detterbeck et al. Chest 2009;136:260.

MDS | IPSS-R Cytogenetics

Prognostic subgroup	Abnormality			Overall survival		
	Single	Double	Complex	n (%)	Median (months; 95% CI) P<0.01	HR (95% CI)
Very good	del(11q) -Y	-	-	81 (2.9)	60.8 (50.3-NR)	0.5 (0.3-0.7) +
Good (ref.)	Normal del(5q) del(12p) del(20q)	inc. 5q-	-	1809 (65.7)	48.6 (44.6-54.3)	1.0 (0.8-1.3)
Intermediate	del(7q) +8 i(17q) +19 Any other Ind. clones	any other	-	529 (19.2)	26.0 (22.1-31.0)	1.6 (1.4-1.8) +
Poor	inv(3)/t(3q)/del(3q) -7	inc. -7/7q-	3 abn.	148 (5.4)	15.8 (12.0-18.0)	2.6 (2.0-3.3) +
Very poor	-	-	>3 abn.	187 (6.8)	5.9 (4.9-6.9)	4.2 (3.4-5.3) +

Schanz et al. JCO 2012;30:820-9.

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MDS | IPSS-R Classification

VARIABLE	0	0.5	1	1.5	2	3	4
Cytogenetics	V. Good		Good		Intermediate	Poor	V. Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Prognostic Risk Categories/Scores

RISK GROUP	Risk Score	Median Survival (Yrs)
Very Low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3.0
High	>4.5-6	1.6
Very High	>6	0.8

Greenberg et al. Blood 2012;120:2454-65.

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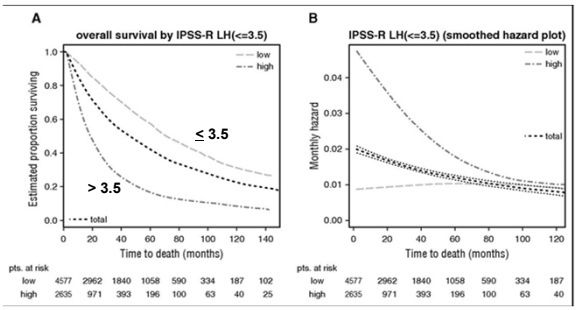
MDS | IPSS-R Classification



Pfeilstocker et al. Blood 2016;128:902.

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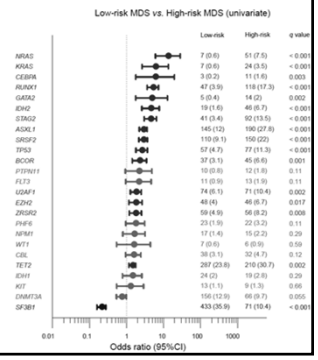
MDS | Mutation Risk

Driver genes can be classified into molecular subtypes differentially associated with disease severity



Makishima et al. Nat Genetics 2017; 49:204.

MDS | Agenda

- Patient
- Definitions and the Notion of Risk
- **Ameliorating Anemia**
- Tackling Thrombocytopenia
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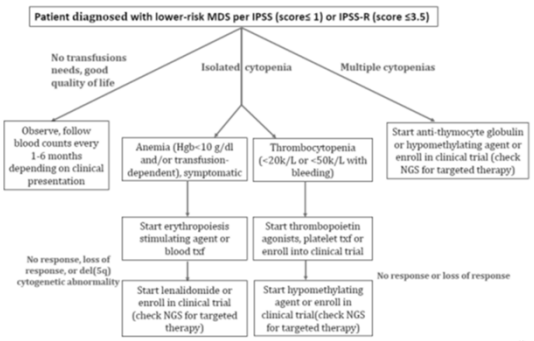
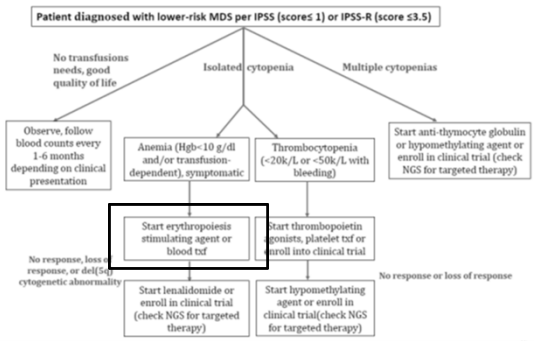
MDS | Treatment



Sekeres and Patel Hematology (ASH Educ Book) 2019.

MDS | Ameliorating Anemia



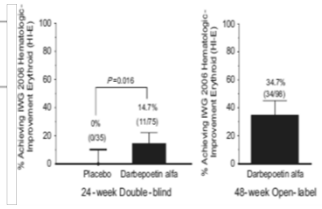
Sekeres and Patel Hematology (ASH Educ Book) 2019.

MDS | Ameliorating Anemia: ESAs

ESAs RR 15 - 40%

Table II. Response results.

	Patients (%)	Response rate
Growth factors	100	39·5
EPO	57·3	
EPO + GCSF	23·4	47·8
GMCSF	6·2	37·8
EPO + GMCSF	5·8	33·7
GCSF	3·0	47·9
IL3	3·0	17·0
IL6	1·3	38·1



N = 1587 **N = 147 (2:1)**

Golshayan et al. Br J Haem 2007;137:125.
Platzbecker et al. Leukemia 2017;31:1944.

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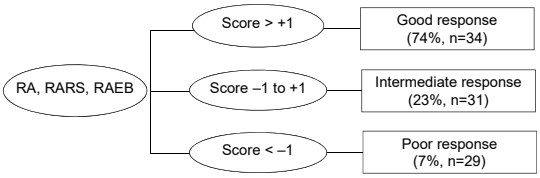
MDS | Ameliorating Anemia: ESAs



Treatment response score

s-epo	<100	+2
U/L	100–500	+1
	>500	–3
Transf	<2 units/m	+2
U RBC/m	= or >2 units/m	–2

Hellström-Lindberg E et al. *Br J Haematol*. 2003;120:1037

MDS | Patient

Treated with darbepoietin 500mcg q3w x 10 months with increase in hgb from **7.8** g/dl to **9.4** g/dl.

Hgb then slips to **7.6** g/dl.

Repeat bone marrow essentially unchanged, but cytogenetics (previously NG) show **Del (5q)**.

NGS with SF3B1, ASXL2

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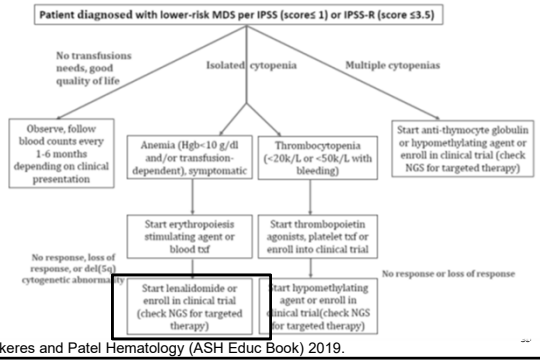
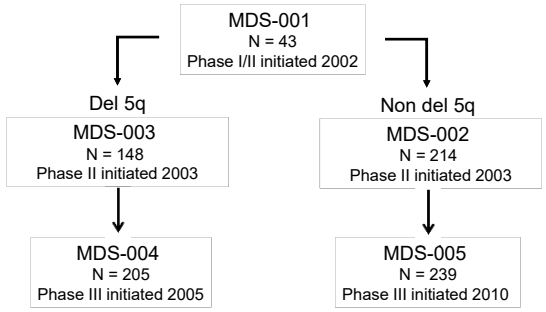
MDS | Ameliorating Anemia



Sekeres and Patel Hematology (ASH Educ Book) 2019.

MDS | Ameliorating Anemia: LEN

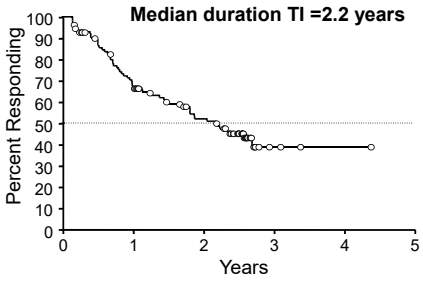


MDS | Ameliorating Anemia: LEN

	RBC-TI, n (%) [95% CI]		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
mITT population	n = 51	n = 47	n = 41
Protocol defined (≥ 26 weeks)	3 (5.9) [1.2-16.2]	20 (42.6) [28.3-57.8]*	23 (56.1) [39.7-71.5]*
IWG 2000[13] (≥ 8 weeks)	4 (7.8) [2.2-18.9]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*
IWG 2006[14] (≥ 8 weeks)	3 (5.9) [1.2-16.2]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*

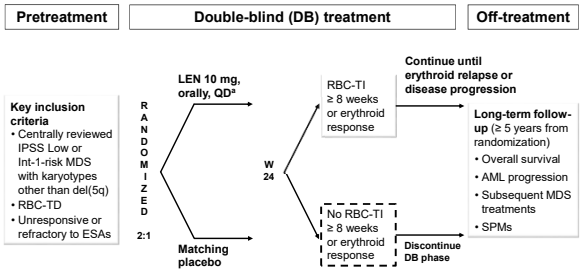
Fenaux et al. Blood 2011;118:3765-76.

MDS | Ameliorating Anemia: LEN



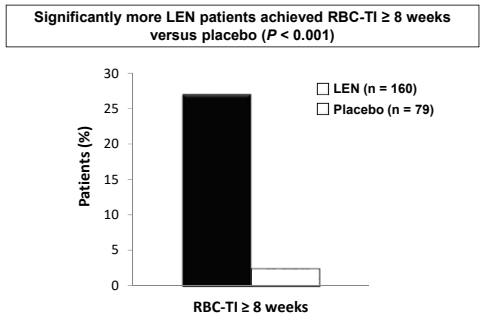
List et al. Leukemia 2014;28:1033.

MDS | Ameliorating Anemia: LEN



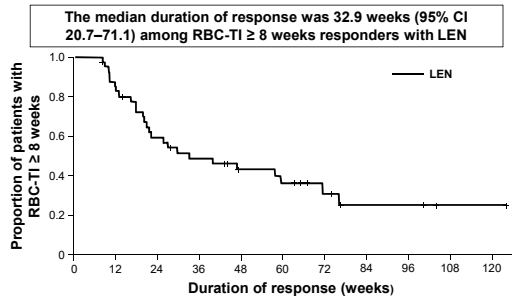
Santini et al. JCO 2016;34:2988

MDS | Ameliorating Anemia: LEN



Santini et al. JCO 2016;34:2988

MDS | Ameliorating Anemia: LEN



Santini et al. JCO 2016;34:2988

MDS | Ameliorating Anemia: LUSPAT

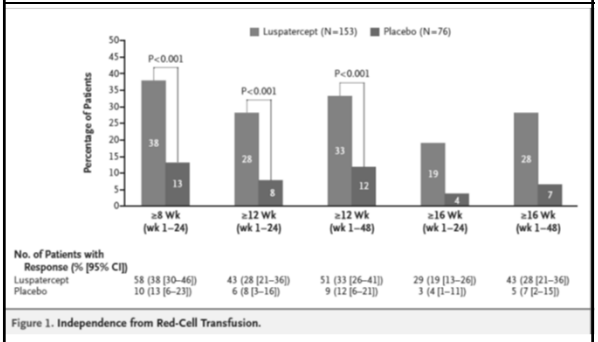


Figure 1. **Independence from Red-Cell Transfusion.**

Fenaux et al. NEJM 2020;382:140-151.

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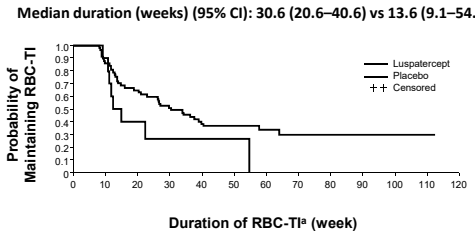
MDS | Ameliorating Anemia: LUSPAT



Fenaux et al. NEJM 2020;382:140-151.

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MDS | Patient

On LEN, Hgb improves to **11.7** g/dl x 22 months. Then, over the next few months changes in **Laboratory Results:**

WBC	**1800/uL with ANC 950, no blasts**
Hgb	**7.8 g/dL with MCV of 106**
Platelet count	**24,000/uL**

A bone marrow biopsy shows hypercellularity (80%), trilineage dyspoiesis, and she is diagnosed with MDS-MLD-RS (2% blasts).

Cytogenetics: Del (5q); NGS with SF3B1, ASXL2

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MDS | Agenda

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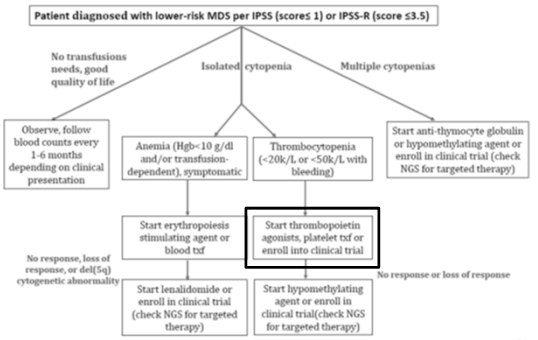
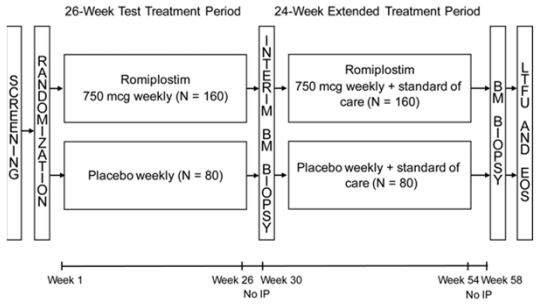
MDS | Tackling Thrombocytopenia



Sekeres and Patel Hematology (ASH Educ Book) 2019.

MDS | Tackling Thrombocytopenia



Giagounides et al. Cancer 2014;120:1838.

MDS | Tackling Thrombocytopenia

		Placebo (N = 83)	Romiplostim (N = 167)	Total (N = 250)
Male, n (%)		53 (63.9)	95 (56.9)	148 (59.2)
Age, median (Q1, Q3)		69 (61, 76)	71 (62, 77)	70 (61, 77)
WHO classes, n (%)	RA, RARS, RCMD, RCMD-RS	62 (74.7)	126 (75.5)	188 (75.2)
	RAEB-1	**9 (10.8)**	**24 (14.4)**	**33 (13.2)**
	RAEB-2	0 (0)	1 (0.6)	1 (0.4)
	MDS-U	**12 (14.5)**	**16 (9.6)**	**28 (11.2)**
IPSS status, n (%)	**Low**	**23 (27.7)**	**40 (24.0)**	**63 (25.2)**
	Int-1	**58 (69.9)**	**120 (71.9)**	**178 (71.2)**
	Int-2	0 (0)	1 (0.6)	1 (0.4)
	Missing	2 (2.4)	6 (3.6)	8 (3.2)

Giagounides et al. Cancer 2014;120:1838.

MDS | Tackling Thrombocytopenia

	Baseline platelets < 20x10⁹/L		Baseline platelets ≥ 20x10⁹/L	
	Placebo (N = 43)	Romiplostim (N = 87)	Placebo (N = 40)	Romiplostim (N = 80)
CSBE (rate/100 pt-yr)	501.2	514.9	**226.4**	**79.5**
	RR = 1.03, p = 0.827		**RR = 0.35, p<0.0001**	
PTE (rate/100 pt-yr)	**1778.6**	**1250.5**	179.8	251.8
	RR = 0.71, p<0.0001		RR = 1.38, p = 0.1479	

Giagounides et al. Cancer 2014;120:1838.

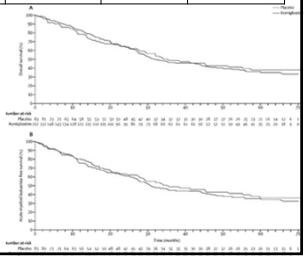
MDS | Tackling Thrombocytopenia

	Romiplostim	Placebo	HR	95% CI
Deaths	**17.9% (30)**	**20.7% (17)**	**0.86**	**0.47, 1.56**
AML	**6.0% (10)**	**4.9% (4)**	**1.20**	**0.38, 3.84**
AML-free survival	**19.6% (33)**	**23.2% (19)**	**0.85**	**0.48, 1.50**

OS

5 years of follow-up

LFS



Giagounides et al. Cancer 2014;120:1838.
Fenaux et al. BJH 2017;178:906.

MDS | Agenda

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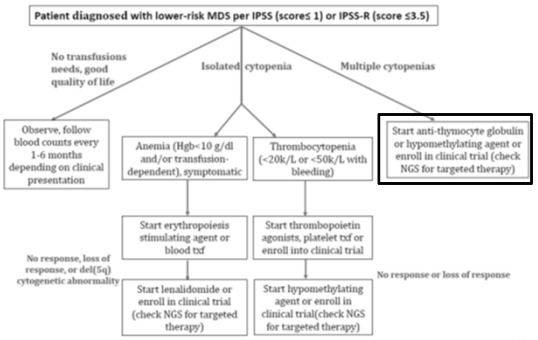
MDS | Modifying MLD



Sekeres and Patel Hematology (ASH Educ Book) 2019.

MDS | Modifying MLD: HMA

- **Regimens:**
  - **DAC 20 mg/m² IV D1-3 every 4 weeks**
  - **AZA 75 mg/m² IV/SC D1-3 every 4 weeks**
- **113 pts with LR-MDS treated and evaluable for response**
- **Median duration of follow-up = 14 months (range: 2-30 months)**
- **Randomized follow-up study NCT02269280**

Jabbour et al. for MDS CRC Blood 2017;130:1514

MDS | Modifying MLD: HMA

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Jabbour et al. for MDS CRC Blood 2017;130:1514

MDS | Modifying MLD: ATG

	N. (total)	% (95%CI)
All responses - intent to treat	9 (27)	33.3 (15-54)
HI-E[†]	7 (18)	38.9
HI-E, major	6	
HI-E, minor	1	
HI-N, major[%]	3 (10)	30.0
HI-P, major[‡]	3 (13)	23.0
No response - intent to treat	18 (27)	66.7 (46-83)

Measure	Treatment Arm: ATG+CSA (n = 45)	BSC (n = 43)	P
No treatment, No. of patients*	5	—	
Crossed over to ATG+CSA, No. of patients	—	14	
Hematologic response (CR+PR) by 3 months			
No. of patients	9	4	
%	20	9	
Hematologic response (CR+PR) by 6 months†			.016
No. of patients	13	4	
%	29	9	
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)†‡			.009
No. of patients	14	4	
%	31	9	

Komrokji et al Haematologica 2014;99:1176.
Passweg et al. JCO 2011;29:303.

MDS | Modifying MLD: ATG

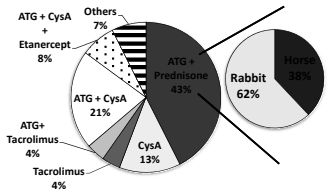
A retrospective cohort, International, multi-center, study

13 Centers: 8 USA and 5 Europe

Stahl M et al. Blood Advances 2018;2:1765.

MDS | Modifying MLD: ATG

166 patients treated with ATG



Response	%	95%CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR	48.8	39.8-57.9

Type of IST used (N=217) and responses

Stahl M et al. Blood Advances 2018;2:1765.

MDS | Patient

Treated with 3-day AZA, has improvement in Plts to 147k and Hgb to 10.4 g/dL, lasting 15 months. But then has these **Laboratory Results:**

WBC **2100/uL with ANC 450, no blasts**
Hgb **7.9 g/dL with MCV of 106**
Platelet count **21,000/uL**

A bone marrow biopsy shows hypercellularity (80%), trilineage dyspoiesis, but now with MDS-EB2 (12% blasts). Cytogenetics: Del (5q); NGS with SF3B1, ASXL2, TP53

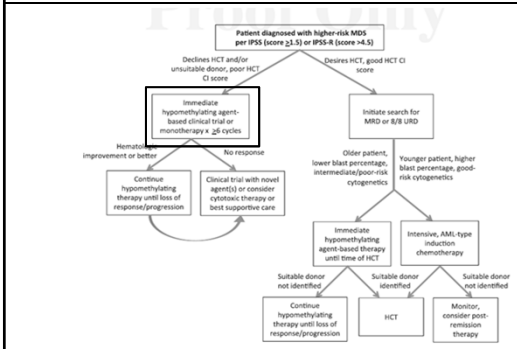
@MikkaelSekeres

MDS | Agenda

- Patient
- Definitions and the Notion of Risk
- Ameliorating Anemia
- Tackling Thrombocytopenia
- Modifying Multilineage Dysplasia
- **The Higher-risk Hurdle**
- Conclusions

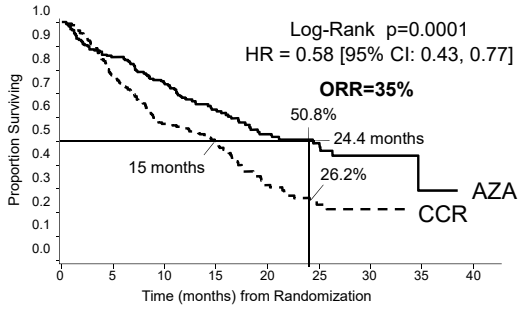
@MikkaelSekeres

Higher-risk MDS | HMA and HCT



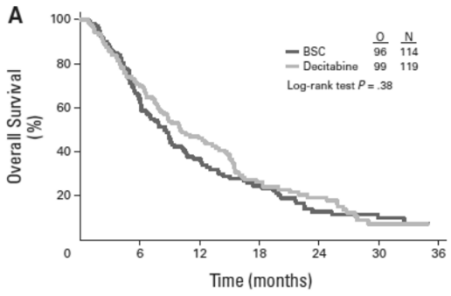
Sekeres and Cutler Blood 2014;123:829.

Higher-risk MDS | HMAs: AZA



Fenaux P, et al. Lancet Oncology 2009;10:223-232.

Higher-risk MDS | HMAs: DAC



Median OS 10.1 vs. 8.5 months

Lubbert et al. JCO 2011;29:1987.

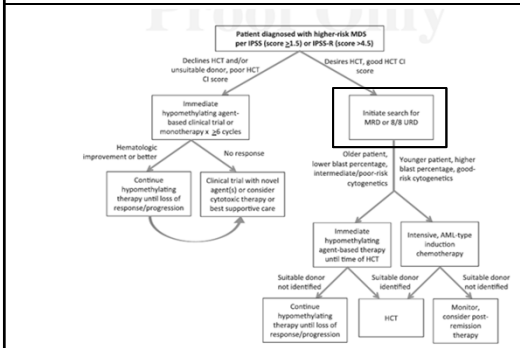
Higher-risk MDS | HMAs: DAC/CED

Oral Cedazuridine/Decitabine Phase 2 In Int-1, Int-2, High, CMML

	Phase 2 overall (N=80)	
Type of response	**n (%)**	**95% CI**
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
With HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

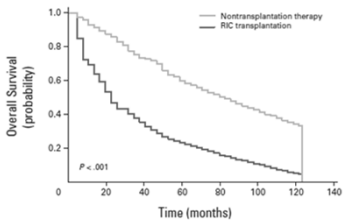
Garcia-Manero et al. Blood 2020

Higher-risk MDS | HMA and HCT



Sekeres and Cutler Blood 2014;123:829.

Lower-risk MDS | HCT

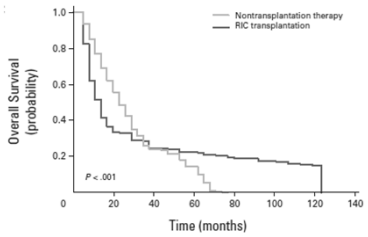


Test of Equality over Strata	
Test	**p**
Log-Rank	<.0001
Wilcoxon	<.0001
-2Log(LR)	<.0001

Low/Int-1 MDS

Koreth et al. JCO 2013;31:2662

Higher-risk MDS | HCT



Test of Equality over Strata	
Test	p
Log-Rank	<.0001
Wilcoxon	<.0001
-2Log(LR)	<.0001

Int-2/High MDS

Koreth et al. JCO 2013;31:2662

MDS | Conclusions

- **Biology** >> What we can do about it
- For Lower-risk MDS, focus on what bugs patient most:
  - **Anemia**
  - **Thrombocytopenia**
  - **Lots o' penia**
- Same for Higher-risk, and focus on Response Duration, Overall Survival.
- Goals of therapy should reflect goals of patient

@MikkaelSekeres

Thanks!!!

MDS The National Myelodysplastic Syndromes Natural History Study

Cleveland Clinic Leukemia/MDS Program

Jaroslaw Maciejewski, MD, PhD
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Renee Gagnon, BA
Rodwin Chua, BA
Olivia Kodramaz
Caitlin Swann, PharmD
Madeline Waldron, PharmD
Kelly Gaffney, PharmD
Jenna Thomas, PharmD

And Our Patients!!!

DRESNERFOUNDATION

April 2020!

36

Waldenstom's Macroglobulinemia and Amyloidosis

Morie Gertz, MD, MACP

August 16, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

36 - Waldenstom's Macroglobulinemia and Amyloidosis

Morie A. Gertz, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

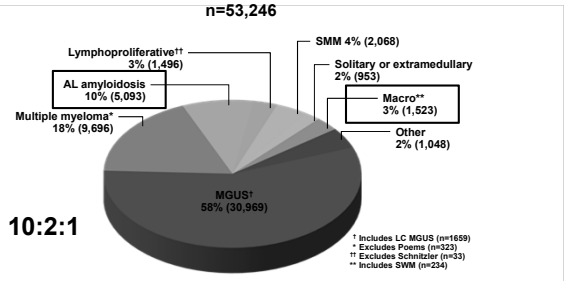
- Celgene, Neotope, Annexon, Research to Practice, Ionis, Amgen, Johnson & Johnson

Off-Label Usage

- Bendamustine AL & WM
- Bortezomib AL & WM

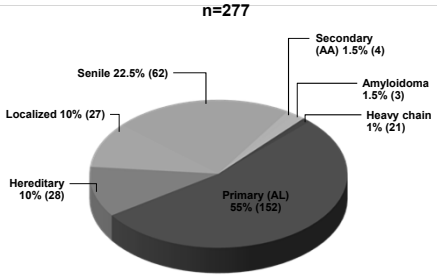
MONOCLONAL GAMMOPATHIES

MAYO CLINIC: ROCHESTER, MN
JANUARY 1, 1960 TO DECEMBER 31, 2019



AMYLOIDOSIS

MAYO CLINIC: ROCHESTER, MN, 2019

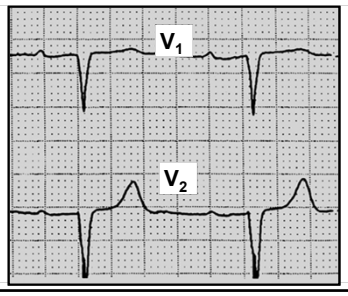


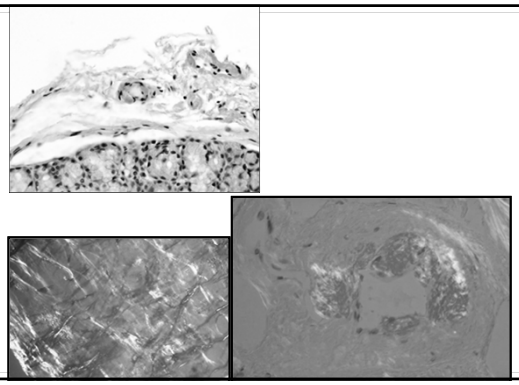
78F RICHMOND KY

- Aκ found April 2018
- Hb 16.8; M spike 13; IgA 1960; κ/λ 45.7/13.2 3.46 ratio
- Urine was not measured (mistake)
- Reassured **MGUS**
- Seen WFMC May 10 2019
- ROS: Weight loss 68 to 48 kg; numb feet; multiple syncopal episodes and diarrhea BP 94/64

Patient EKG-Normal Coronary Angio

Anterior Infarction ("Pseudoinfarct")





78 YO M **SMM**

- Oct 2016 AK 0.55g/dL marrow 5% PC no bone lesions or anemia
- Placed on randomized trial of len vs obs
- Observed 2 years stable
- Seen a Mayo rising creatinine attributed to long standing IDDM
- K FLC 46 mg/dl ratio i/u 15
- Urine 3.2 g/d

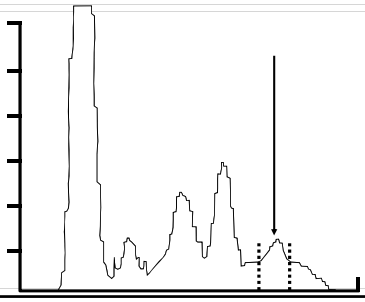
- TT 0.03; Nt pro-BNP 537
- Fat packed with amyloid

PATIENT 2

- 79 yo W M DOE 1 yr, LE edema
- Echo concentric LVH, EKG Anterior infarct
- Cath negative, normal coronaries
- Referred to Mayo for non cardiac dyspnea

SPEP

Densitometric Tracing



PATIENT 2

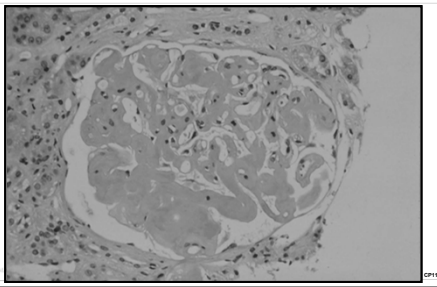
- Mayo Echo: Heart Walls & Valves Thickened Restrictive diastolic filling (stiff heart)- HFpEF
- Hypertrophy reinterpreted as infiltration
- Fat Aspirate +
- Began Protocol Chemotherapy

64 YO M WITH WALDENSTROMS

- Diagnosed in MSP with 30 % LPL and IgM of 3000
- Treated with CFZ and R
- Sought opinion for intractable edema
- Albumin 1.0 urine protein 8 g
- IgMλ
- Echo thickening with low voltage and abnormal strain
- **Renal amyloid 13.3% of biopsies nephrotic > 60years**

J Nephrol 2015 28:39-49

Renal Biopsy Demonstrating "Hyaline" Eosinophillic Amorphous Deposits



NEUROLOGY REFERRAL PATIENT 4

- 71 yo M progressive sensory motor PN
- Neurologist finds 1.1 g/dL Gλ
- Diagnosis **MGUS-Neuropathy** (CIDP like)
- Plasma Exchange- IvIg tried over 8 months
- Given azathioprine & prednisone
- Progress & referred
- Sural n biopsy + amyloid

SCREENING FAT ASPIRATE IN PATIENTS WITH PN, 1994-1999

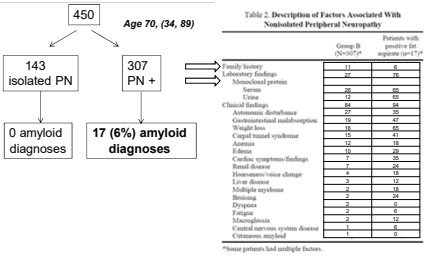
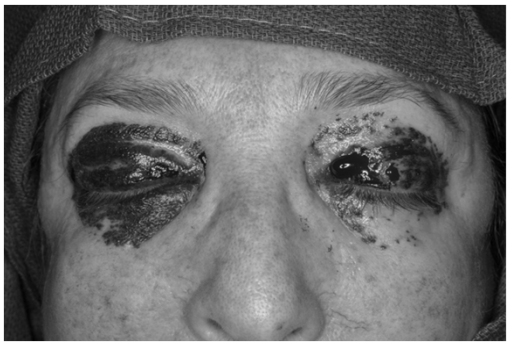


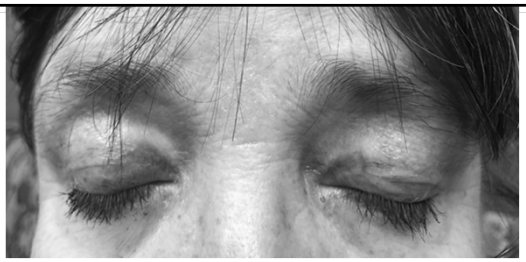
Table 2. Description of Factors Associated With Nonisolated Peripheral Neuropathy

	Group B (N=307)*	Patients with positive fat aspirate (n=17)*
Family history	11	6
Laboratory findings	27	76
Monoclonal protein		
Serum	26	65
Urine	12	65
Clinical findings	84	94
Autonomic disturbance	27	35
Gastrointestinal malabsorption	19	47
Weight loss	16	65
Carpal tunnel syndrome	15	41
Anemia	12	18
Edema	10	29
Cardiac symptoms/findings	7	35
Renal disease	7	24
Hoarseness/voice change	4	18
Liver disease	3	12
Multiple myeloma	3	18
Bruising	2	24
Dyspnea	2	6
Fatigue	2	6
Macroglossia	2	12
Central nervous system disease	1	6
Cutaneous amyloid	1	0

*Some patients had multiple factors.

Andrews et al Mayo Clinic Proceedings 2002; 77:1287-90





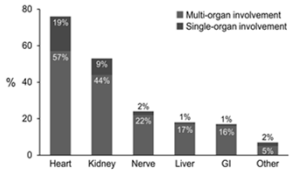
26 months post SCT sCR

CONSIDER AL IN :

- **Non-diabetic nephrotic syndrome-check for light chains**
- **Non-ischemic cardiomyopathy with an echocardiogram showing "LVH"-check for light chains**
- **Hepatomegaly or alkaline phosphatase elevation without imaging abnormality-check for light chains**
- **Peripheral neuropathy with MGUS or CIDP with autonomic features**
- **Atypical SMM/MGUS monoclonal light chains urine and modest marrow plasmacytosis**
- **At 20 years 4% of MGUS will develop AL**.

DISEASE PRESENTATION: ORGAN INVOLVEMENT

- Mayo cohort of 592 patients with mass spectrometry-verified AL type
- Period:2008-2015

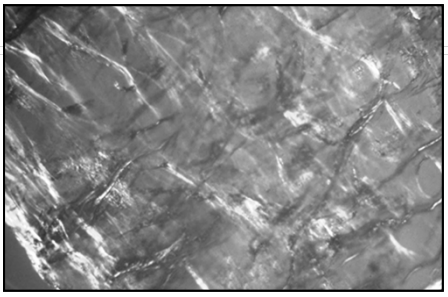


No. of involved organs:
- **Single-organ: 34%**
- **2 organs: 41%**
- **3 organs: 21%**
- **4-5 organs: 4%**

Muchtar E et al, Mayo Clinic Proceedings, 2019

SCREEN SUSPICIOUS PATIENTS

- Immunofixation serum and urine and serum-free light chain assay
- If Assay is negative
  - Its not AL amyloidosis
  - If its systemic it could be ATTRwt or inherited
  - Its localized amyloidosis and not systemic

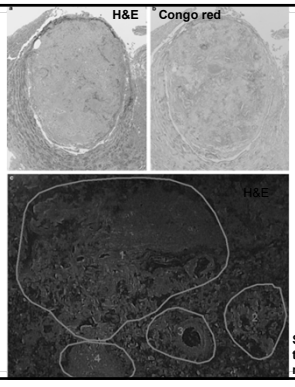


Sensitivity 75% https://www.youtube.com/watch?v=tctYTmxd9gQ

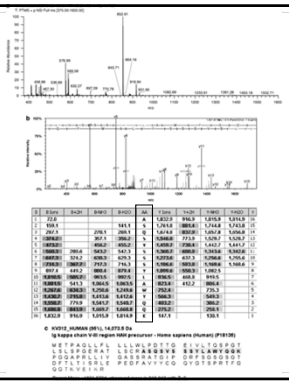
CP1106207-25

AMYLOID TYPING

- Verify that the amyloidosis is <u>light chain</u> with your pathologist
  - 3-5% of elderly patients with localized, familial, & secondary amyloidosis will have an incidental unrelated MGUS
  - 20% of ATTR wt have MGUS
- Classic sites for localized amyloidosis are bladder, gastric ulcer, colon polyp larynx & skin



Several areas are traced in the computer screen, microdissected



κ-light chain V-III

Identifies amyloid in formalin fixed tissue as immunoglobulin - AL

Now done routinely on all fat aspirates and bone marrow biopsies at Mayo

Laboratory Investigation (2008) **88,** 1024–1037

Distribution of Amyloid types

28% of amyloid biopsies Are not AL and Chemotherapy contraindicated

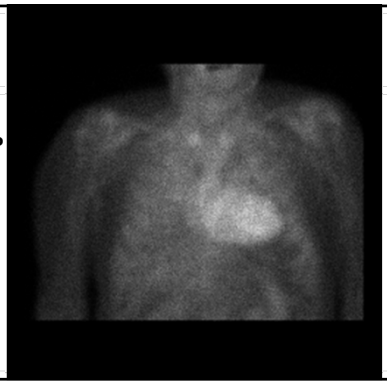
Amyloid Subtype	Number (%) of cases
AL	2553 (61.68)
ATTR	1015 (24.52)
AA	151 (3.65)
ALect2	148 (3.58)
Alns	48 (1.09)
Keratin*	36 (0.87)
AApoA1	30 (0.72)
AH	27 (0.65)
AFib	26 (0.63)
TGFB1-IP*	22 (0.53)
AApoA4	20 (0.48)
AANF	14 (0.34)
Ab2M	12 (0.29)
AGel	12 (0.29)
ASem1	12 (0.29)
APro	7 (0.17)
ALys	3 (0.07)
ACal	2 (0.05)
Enfuvirtide*	2 (0.05)
AIAPP	2 (0.05)

66-YEAR-OLD MALE, DYSPNEA ON EXERTION X 1 YEAR

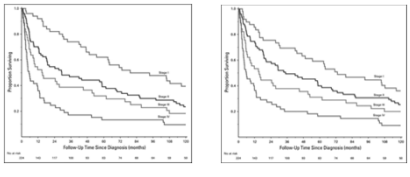
- Previously healthy, no HTN
- Bilateral carpal tunnel – 10 yrs ago
- Echo –amyloid, EF 40%
- 15 lb diuresis – much improved
- Normal serum FLC/ratio, no urine or serum monoclonal protein
- Negative fat aspirate

You recommend:
1. PYP scan

TC-PYP



MAYO 2012 MODEL SURVIVAL OUTPUT WITH TNT CONVERSION



cTnT at 0.025 mcg/L

hs-cTnT at 40 ng/L

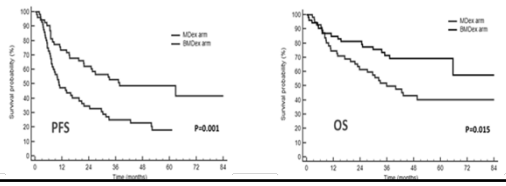
hi sensitivity TT 40; NT-proBNP<1800; dFLC<18)

Kumar S et al, J Clin Oncol. 2019;37:171-173

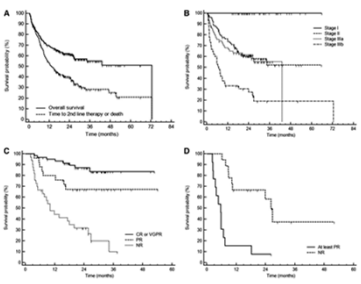
A phase III trial of BMDex vs. MDex in newly-diagnosed AL

Courtesy of Giovanni Palladini, Pavia. Mastris, et al. Manuscript in preparation

Response	MDex (56 pts)	BMDex (53 pts)	P
Overall Hem.	**32 (57%)**	**43 (81%)**	**0.005**
CR	11 (20%)	12 (23%)	0.440
VGPR	11 (20%)	22 (42%)	0.007
PR	10 (17%)	9 (17%)	0.454
Heart	10/36 (28%)	10/26 (38%)	0.195
Kidney	15/35 (43%)	16/36 (44%)	0.448



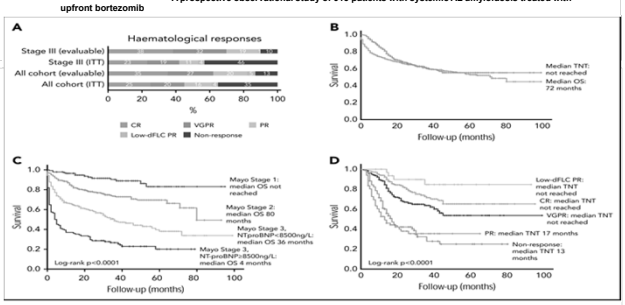
Survival of 230 patients with AL amyloidosis treated with CyBorD.



Giovanni Palladini et al. Blood 2015;126:612-615

blood

A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib



Blood, Dec 19 2019,.

American Society of Hematology

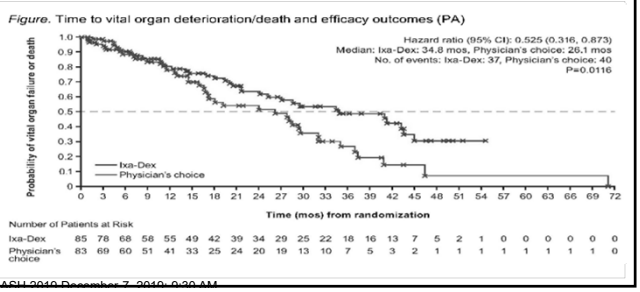
PI's other than bortezomib

- Ixazomib[1]:
  - Failed to meet its primary endpoint in phase 3 trial. No deepening of response
- Carfilzomib[2]:
  - Challenging use in AL amyloidosis: 10% cardiac toxicity in MM patients; IV infusion
  - Dose-escalating phase 1 (n=28). MTD ˜ 20/36 mg/m²
  - ORR 54%, ≥VGPR 39%
  - Cardiac toxicity 36% (VTs, decreased EF, hypoxemia…)

[1]Sanchorawala V et al., Blood. 2017;130(5):597-605
[2]Cohen AD et al, Blood. 2016;128:645-645

TRIAL OF IXAZOMIB-DEXAMETHASONE VERSUS PHYSICIAN'S CHOICE OF THERAPY IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY PRIMARY SYSTEMIC AL AMYLOIDOSIS (RRAL)

Figure. Time to vital organ deterioration/death and efficacy outcomes (PA)



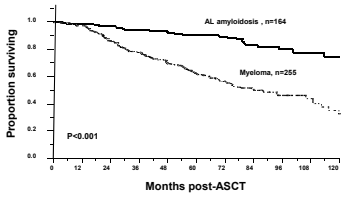
ASH 2019 December 7, 2019: 9:30 AM

TRIAL OF IXAZOMIB-DEXAMETHASONE VERSUS PHYSICIAN'S CHOICE OF THERAPY IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY PRIMARY SYSTEMIC AL AMYLOIDOSIS (RRAL)

- Treatment with ixa-Dex significantly prolonged duration of composite survival and vital organ function, PFS, and time to subsequent therapy vs physician's choice. Moreover, ixa-Dex resulted in an improved CR rate and DOR

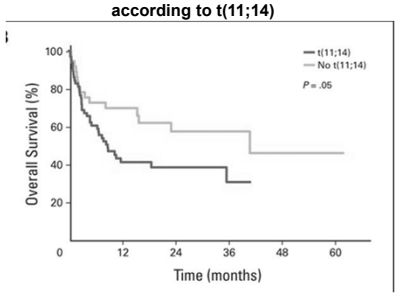
ASCT for AL versus MM
Survival* Based on Depth of Response and Diagnosis

Patients achieving CR



*Only patients receiving ASCT within 12 months of diagnosis &surviving 3 months post ASCT included.
Dispenzieri et al, Bone Marrow Transplant. 2013;48(10):1302-7..

Overall survival in the bortezomib-dexamethasone cohort according to t(11;14)



Tilmann Bochtler et al. JCO 2015;33:1371-1378

DOXY

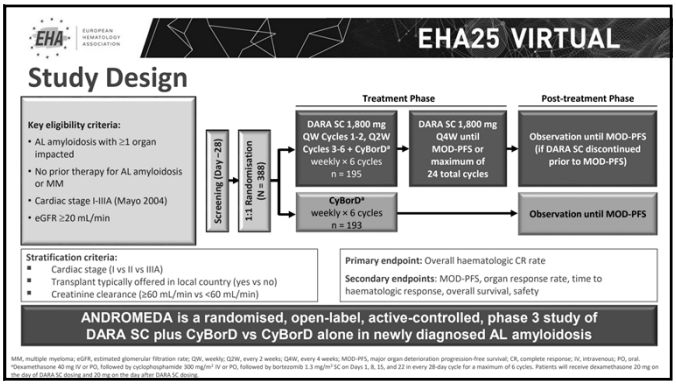
- Oral doxycycline along with meticulous supportive care can improve survival in cardiac amyloidosis.
  - The survival of stage II and IIIa cardiac AL can be markedly improved but has limited impact on advanced stage IIIb disease
- Doxycycline has additional benefit only if used in conjunction with meticulous supportive care and reaching a haematological CR/VGPR with chemotherapy
- This data supports further randomised prospective study of oral doxycycline in cardiac AL amyloidosis.

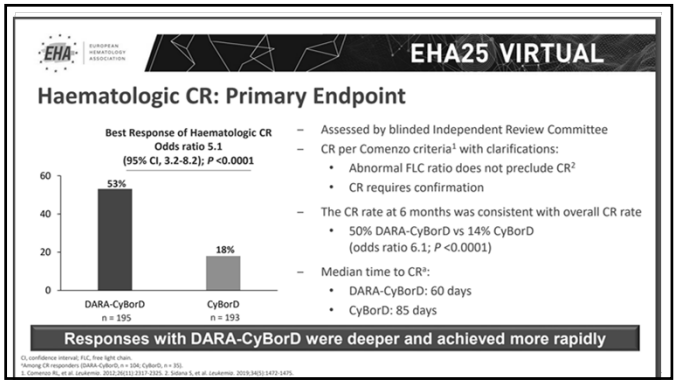
DARATUMUMAB: SUMMARY OF DATA

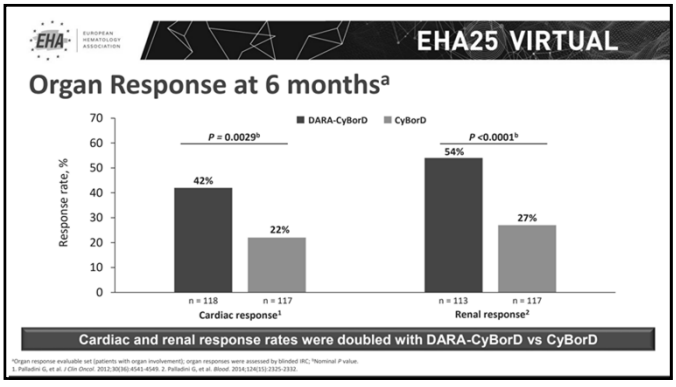
Ref	Design	Prior lines, med	N	Median time to response	ORR (%)	≥VGPR/CR (%)	Median FU
1	Retrospective	3	25	1.0 month	76%	60%/36%	NR
2	Retrospective	3	44; 50% in combination	2.2 months	83%	80%/17%	10.2 months
3	Retrospective	3	20	4 weeks	86%	86%/33%	10 months
4	Phase II	2	21	Fast	100%	84.2% at 3mo	NR
5	Phase II	3	32	1.0 month	63%	46%/17%	NR

1 Kaufman GP et al, Blood. 2017 130(7):900-902
2 Abeykoon JP et al, Leukemia. 2018
3 khouri J et al, Br J Haematol 2018
4 Sanchorawala V et al, *Blood*. 2017;130(Suppl 1):507.
5 Roussel M et al, *Blood*. 2017;130(Suppl 1):508

ORR=Overall response rate
VGPR=Very good partial response
CR-Complete response







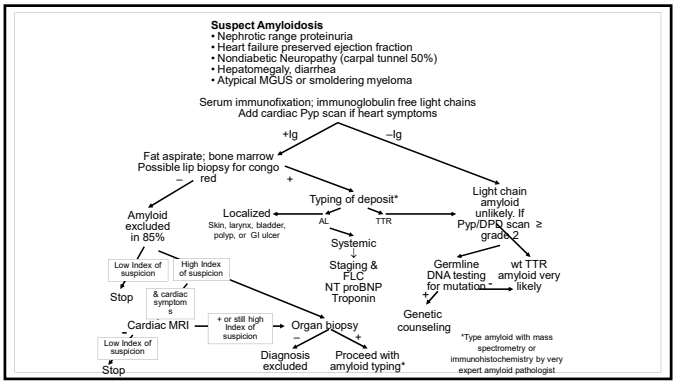
POMALIDOMIDE IN AL AMYLOIDOSIS

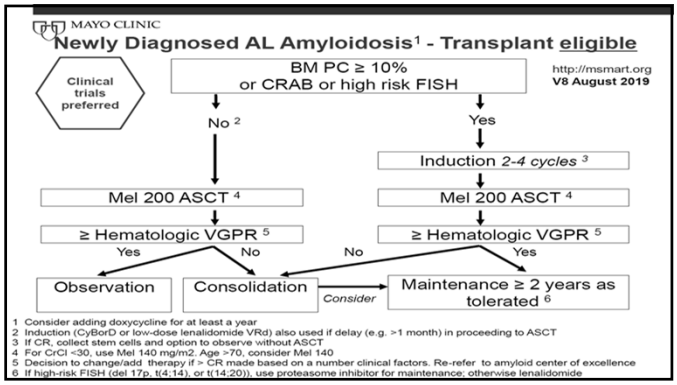
Ref	Prior lines	N	Dosing	Median time to response	ORR/ ≥ VGPR	PFS	FU
1	2 (1-8)	33	2 mg daily Dex 40 mg/W	1.9 months	48%/18%	14 months	28 months
2	2 (1-6)	27	2/3 mg/d (n=15) 4 mg/d for 21 days (n=12) Dex 20 mg/W	3 months	50%/37.5%	18 months	17 months
3	2 (1-7)	28	2 mg/d (n=3) 4 mg/d daily (n=25) Dex 20/40 mg/W	1 month	68%/29%	16 months	44 months

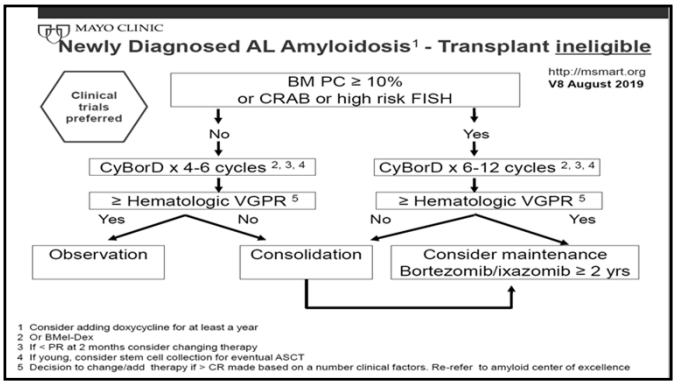
- **Dose reduction:** 48%[1], NR[2]- 32%[3]
- **Grade 3/4 toxicities:**
  - Myelosuppression 26%-45%
  - Fatigue 18%
  - Pneumonia 11%-21%
  - Renal failure 3%-7.5%
  - Arrhythmias 0-21%

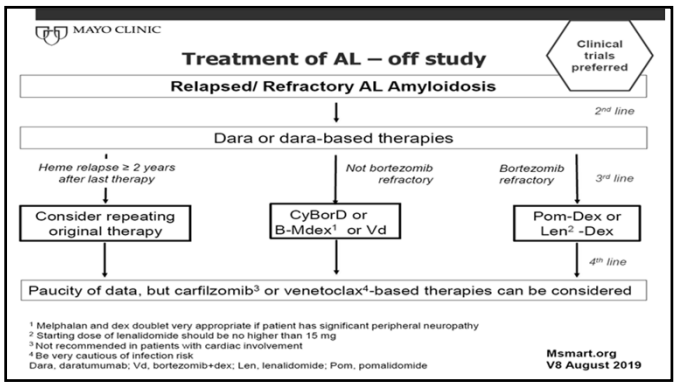
Rise in NT-proBNP was frequently seen, in most cases w/o clinical CHF

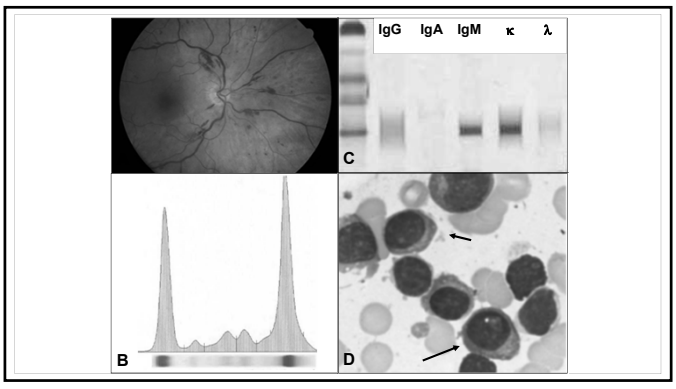
[1]Dispenzieri A et al, Blood. 2012;119(23):5397-404
[2]Sanchorawala V et al, Blood. 2016;128(8):1029-62
[3]Palladini G et al, Blood. 2017;129(13):2120-2123











MACROGLOBULINEMIA DEFINITIONS

	Monoclonal Serum IgM	Marrow Infiltration	Sx. Due to IgM Protein	Sx due to Tumor Mass
WM Symptomatic	+	+	+	+
WM Smoldering	+	+	-	-
IgM related disorder	+	-	+	-
MGUS	+	-	-	-

MYD88 IN LYMPHOMA

Table 1. Relative frequency of the MYD88 L265P mutation among different B-cell LPDs

Figures and tables index

Entity	n	MYD88 L265P
Waldenström's macroglobulinemia	117	101 (86%)
IgM MGUS	31	27 (87%)
Non-GC diffuse large cell lymphoma	48	9 (19%)
Marginal zone lymphomas	14	3 (21%)
B-CLL (16 with monoclonal component)	39	0 (0%)
Hairy cell leukemia	35	0 (0%)
Multiple myeloma (three IgM)	24	0 (0%)
IgA/IgG-MGUS	25	0 (0%)
Lymphoplasmacytic lymphoma	9	0 (0%)
Amyloidosis	6	0 (0%)
IgM-related disorder (neuropathy+IgM component)	1	0 (0%)
Healthy volunteers	38	0 (0%)

Leukemia 2013; 1722-8

ISSWM: INTERNATIONAL STAGING SYSTEM FOR WM

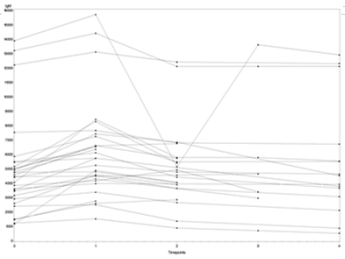
Factors Associated with Prognosis in the IWMSS

- Age >65
- Hemoglobin <11.5 gr/dL
- Platelet count <100k/ml
- B2-microglobulin >3 mg/dL
- Monoclonal IgM concentration >7 gr/dL

Risk Category	Factors	Median survival (months)
Low	0 or 1 (except age)	142.5
Intermediate	Age>65 or 2	98.6
High	>2	43.5

Morel P et al. Blood 2009;113(18):4163-4170

RITUXIMAB FLARE



Cancer. 2004 Dec 1;101(11):2593-8

BENDAMUSTINE

- 41 patients with WM, of whom 22 received bendamustine and rituximab and 19 received R-CHOP
- In both groups, the response rate was 95%
- The median PFS for R-CHOP was 36 mo Vs not reached with bendamustine and rituximab (*P*<.0001). At analysis, 4 relapses (18%) in the bendamustine and R group & 11 relapses (58%) in the R-CHOP group

Lancet. 2013 Feb 19

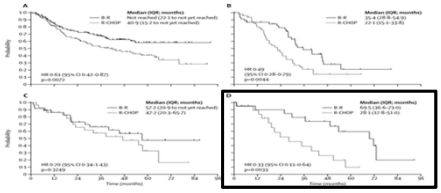


Figure 3 Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D) B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Mathias J Rummel , Norbert Niederle , Georg Maschmeyer , G Andre Banat , Ulrich von Gr?nhagen , Christoph Losem , ...

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

The Lancet null 2013 null

http://dx.doi.org/10.1016/S0140-6736(12)61763-2

RITUXIMAB MAINTENANCE IN MACROGLOBULINEMIA

- median progression-free survival for patients treated with R bendamustine 78 months
- 218 randomized to R for 2 years vs obs
- 5 year survival 78%
- 1 AML 1 MDS 0.7%
- PFS 101 versus 83 months p= 0.32; OS P =ns

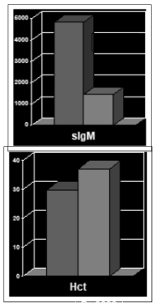
ash abstract 343; 2019 MAINTAIN trial

BORTDR RESPONSE ASSESSMENT

- N = 23
- Overall Responses
  - CR: 3 (13%)
  - nCR 2 (9%)
  - VGPR: 3 (10%)
  - PR: 11 (48%)
  - MR: 3 (13%)

83% / 91%

- Median time to response 1.4 months
- With a median follow-up of 22.8 months (range, 3.3 to 33.2 months), all patients are alive
- 18/23 patients remain free of disease progression



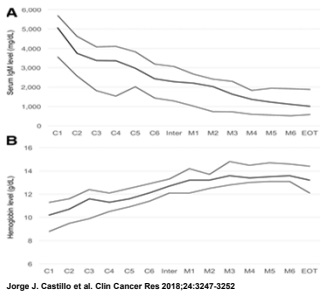
Treon SP et al. J Clin Oncol. 2009; 27(1):120-126

CARFILZOMIB RD

- CFZ 20/36 1,2,8,9
- Rd d2,9 of each cycle
- Maintenance q8 weeks x8
- N=31 1CR 10 VGPR 10PR 6MR (87%); ≥VGPR36%
- Median TTR 2.1 mos
- NO > gr1 PN; no impact MYD or CXCR4

ASH abstract 757;2013; Blood 2014 124: 503-10

Impact of ixazomib, dexamethasone, and rituximab therapy on (A) serum IgM and (B) hemoglobin levels.



Jorge J. Castillo et al. Clin Cancer Res 2018;24:3247-3252

Clinical Cancer Research

HOW ABOUT IBRUTINIB?

- 1 prior treatment
- Intended therapy consisted of 420 mg of oral ibrutinib daily for 2 years.
- median time to response of 4 weeks. Median IgM 3610 to 1340. Hb 10.5 to 12.6
- Diarrhea, bleeding, atrial fibrillation (10.6%) Am J Hematol 2016 March 19 Epub

Efficacy

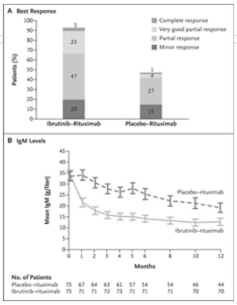
- **Response rate: 61.9% (95% CI: 48.8, 73.9)**
- **Partial response: 50.8%**
- **Very good partial response: 11.1%**
- **Median duration of response: not reached (range, 2.8+ - 18.8+ months)**

IBRUTINIB FOR NEWLY DIAGNOSED WM

- 30 patients who were newly diagnosed and received ibrutinib was recently reported. The major response rate was **80** percent with no difference between patients with wild type or mutated CXCR4.

Ibrutinib Is Highly Active As First Line Therapy in Symptomatic Waldenstrom's Macroglobulinemia
Steven P Treon, Joshua Gustine, Kirsten Meid, Toni Dubeau, Patricia Severns, Christopher Patterson, Lian Xu, Guang Yang, Xia Liu, Maria Demos, Amanda Kofides, Jiaji Chen, Manit Munshi, Nickolas Tsakmaklis, Gloria Chan, Andrew J Yee, Noopur Raje, Elizabeth O'Donnell, Zachary Hunter and Jorge J. Castillo
Blood 2017 130:2767;

Best Response Rates and a Comparison of IgM Levels.



DIMOPOULOS ET AL. N ENGL J MED 2018. DOI: 10MA .1056/NEJMOA1802917

BING NEEL SYNDROME

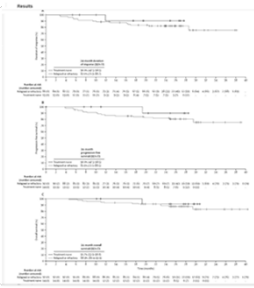
- Multiple case reports of significant benefit using ibrutinib for central nervous system macroglobulinemia.
- Ibrutinib is able to cross the blood-brain barrier
- 7 patients reported all reported improvement on magnetic resonance imaging or cerebrospinal fluid findings

ACALABRUTINIB

- 14 new diagnosis 92 R/R Median 2 prior therapies, median 6.1 years following diagnosis median time from last therapy 16 months
- NDWM RR 93%; RRWM RR 93%
- Neutropenia 16% pneumonia 7%
- Bleeding 3%
- AF 1%
- adverse events leading to discontinuation of therapy 7%
- 100 mg BID

Lancet Haematology, The, 2020-02-01, Volume 7, Issue 2, Pages e112-e121

ACALABRUTINIB



Response duration

PFS

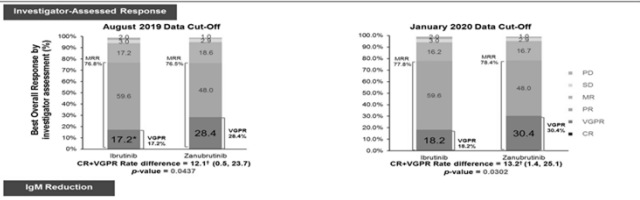
OS

Lancet Haematology, The, 2020-02-01, Volume 7, Issue 2, Pages e112-e121

Phase III Ibrutinib vs Zanubrutinib

ASPEN: Secondary Efficacy Endpoints
Assessment of Response According to Investigator and IgM Analysis

Investigator-Assessed Response



CR+VGPR Rate difference = 12.1† (0.5, 23.7) *p*-value = 0.0437

CR+VGPR Rate difference = 13.2† (1.4, 25.1) *p*-value = 0.0302

IgM Reduction

- Area-under-the-curve (AUC) for IgM reduction over time was significantly greater for zanubrutinib vs ibrutinib (p=0.037)

CR, complete response; EMD, extramedullary disease; IgM, immunoglobulin M; IRC, independent review committee; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PR, partial response; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.
*Excluded two patients with VGPR by IRC; MR (IGM present) and PR (IgM assessment by local SPEP N-protein)
†Adjusted for stratification factors and age group. *P*-value is for descriptive purpose only.

Presented By Constantine Tam at TBD

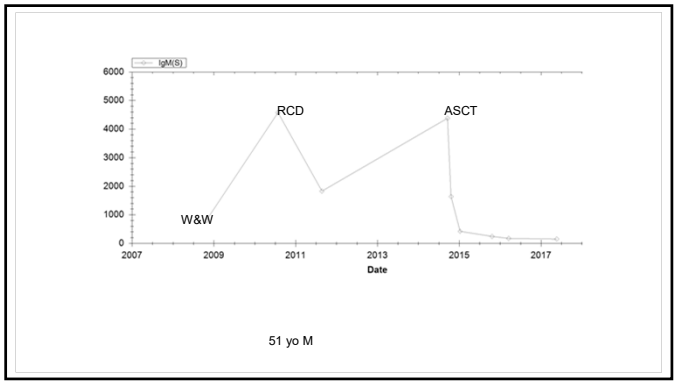
ASPEN: AE Categories of Interest (BTKi Class AEs) with additional 5 months follow-up (Data cutoff: 31 January 2020)

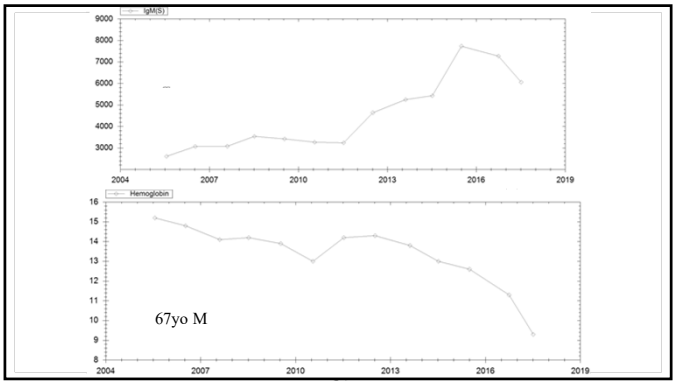
- **An additional 5 patients had discontinued ibrutinib treatment due to AEs versus 0 in the zanubrutinib arm (14.3% vs 4%)**

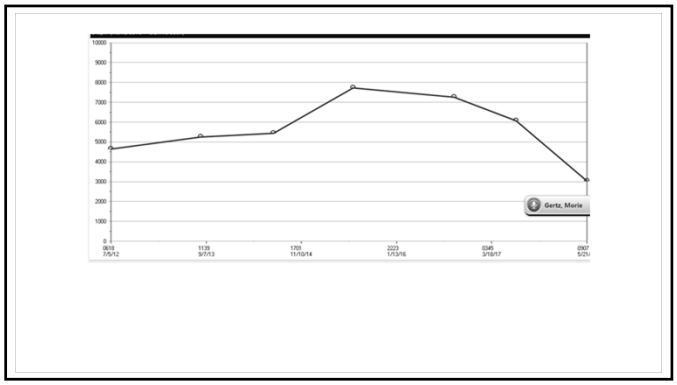
AE *Categories*, n (%) *(pooled terms)*	All Grades		Grade ≥ 3	
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)
Atrial fibrillation/ flutter†	18 (18.4)	3 (3.0)	7 (7.1)	0 (0.0)
Diarrhea (PT)	32 (32.7)	22 (21.8)	2 (2.0)	3 (3.0)
Hemorrhage	59 (60.2)	51 (50.5)	9 (9.2)	6 (5.9)
Major hemorrhage[a]	10 (10.2)	6 (5.9)	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	13 (12.9)	15 (15.3)	8 (7.9)
Neutropenia[b†]	15 (15.3)	32 (31.7)	8 (8.2)	23 (22.8)
Infection	70 (71.4)	70 (69.3)	23 (23.5)	19 (18.8)
Second Malignancy	12 (12.2)	13 (12.9)	1 (1.0)	3 (3.0)

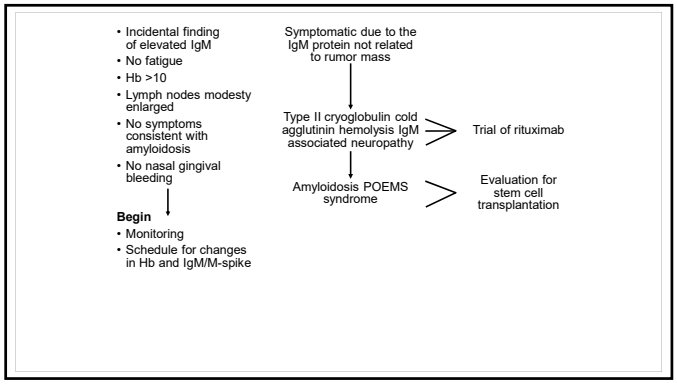
Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
† Descriptive two-sided *P*-value < 0.05.

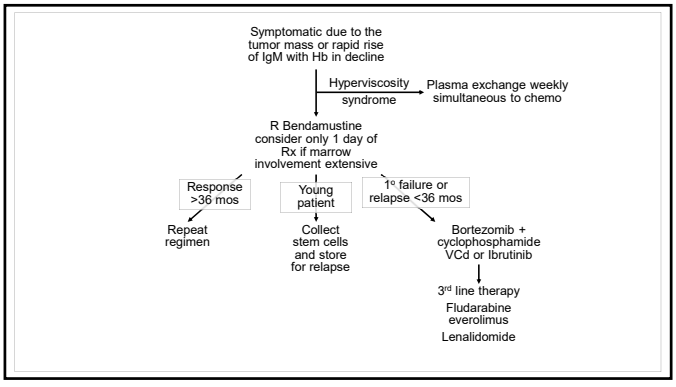
Presented By Constantine Tam at TBD











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Acute Myeloid Leukemia

Richard Stone, MD

August 17, 2020

38

Bone Marrow Transplantation

F. Marc Stewart, MD

August 17, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

38 - Bone Marrow Transplantation

F. Marc Stewart, MD

Disclosures

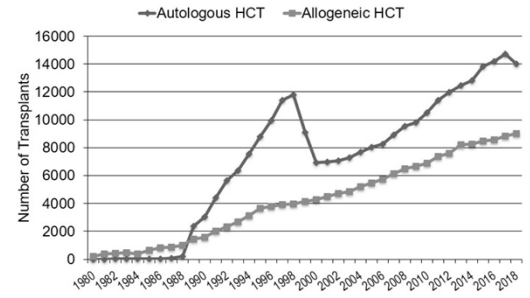
Disclosures of Financial Relationships with Relevant Commercial Interests

- Microbot Medical, Inc. (excluding diversified mutual funds)

"Following" this lecture and study thereafter

- Will discuss highlighted 'yellow' text in lecture; other text is additional information for you.
- Some extra slides for future study are included that are not discussed in lecture (see Appendix)
- Results of BMT vs. other treatment approaches left to disease-group presentations.

Annual Number of HCT Recipients in the US by Transplant Type

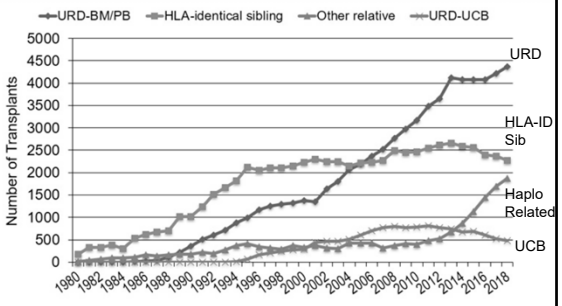


CIBMTR

CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

3

Allogeneic HCT Recipients in the US, by Donor Type



CIBMTR

CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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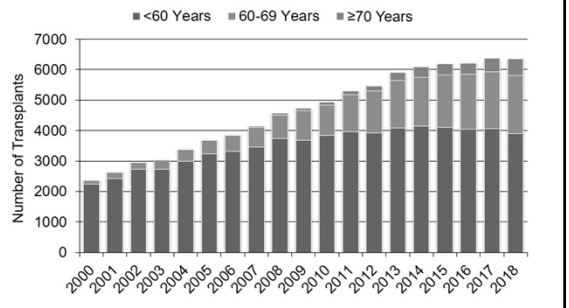
Trends in Allogeneic HCT in the US by Recipient Age^



CIBMTR

^Transplants for AML, ALL, MDS, NHL, HD, MM

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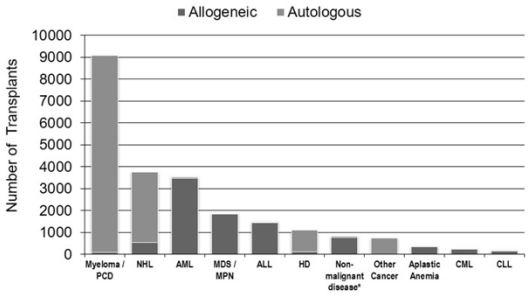
Indications for Hematopoietic Cell Transplant in the US, 2018



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*excludes aplastic anemia.

CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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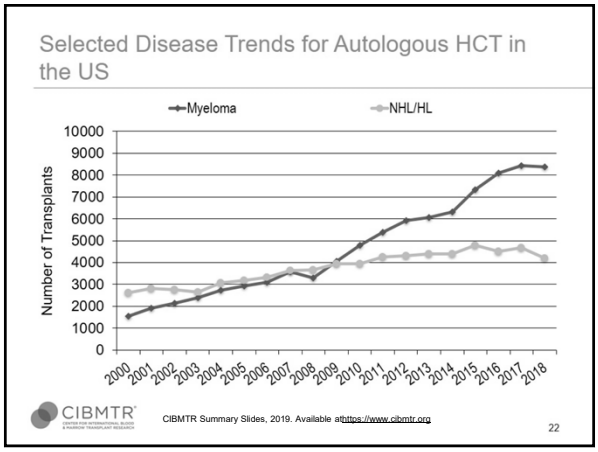
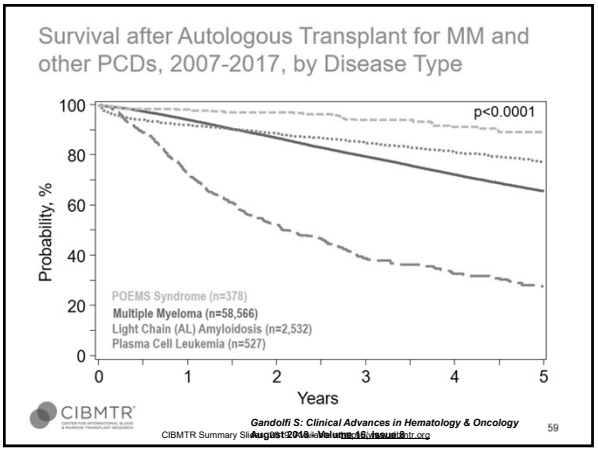
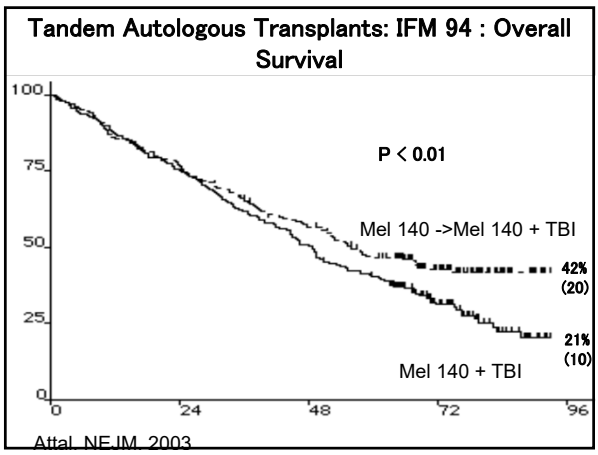
Autologous Stem Cell Transplantation

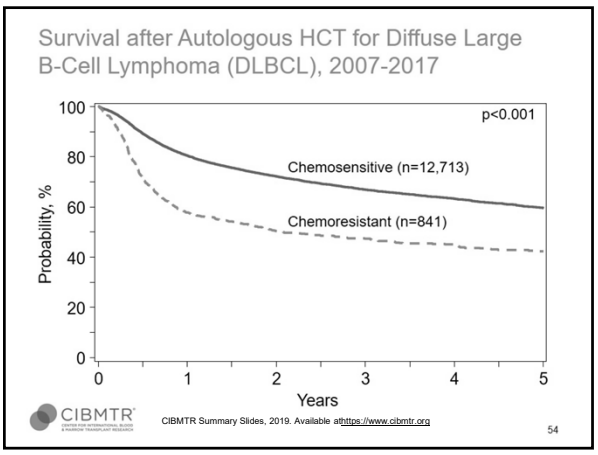
Autologous:

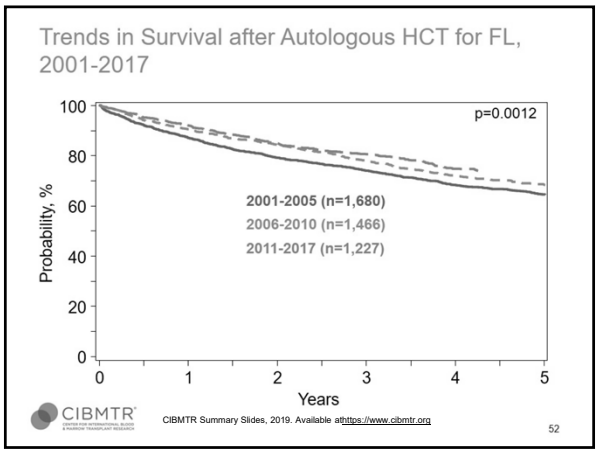
- Treat underlying disease with ablative therapy
- Results in toxicity such as BM aplasia
  - If not rescue patients with infusion of hematopoietic stem cells, they would die of infection and bleeding problems
  - Preference for tumor-free stem cell product.
  - Risk for tumor contamination.
  - CD34 selection did not change relapse rates and increased infection risks especially for CMV
  - 100 day Non-relapse mortality: less than 5%
  - Does not have GVHD issue
  - Risk for MDS/AML secondary cancers

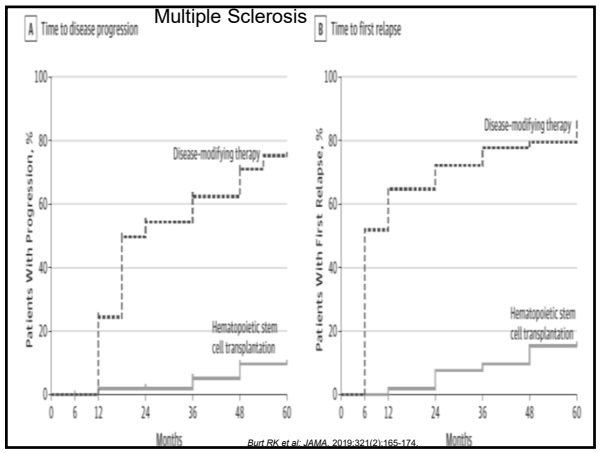


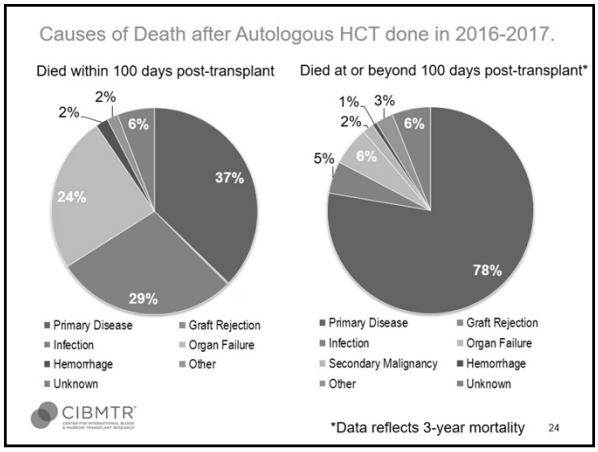






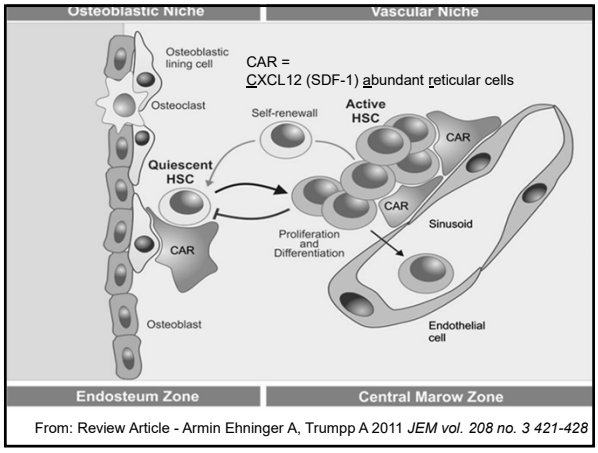




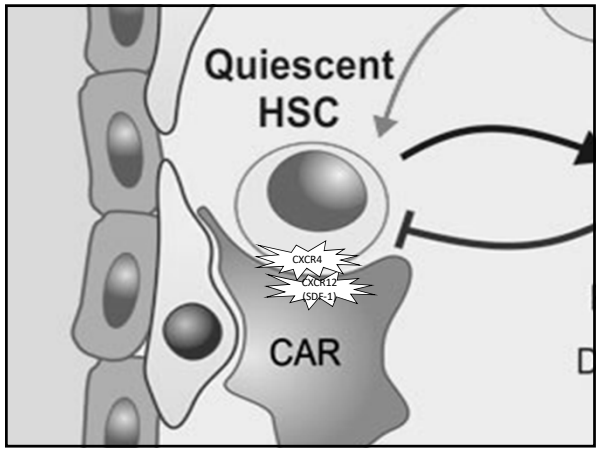


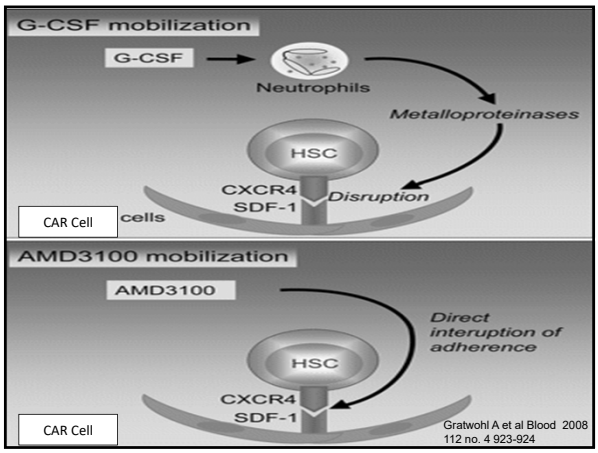
Autologous Source of Stem Cells

- Peripheral Blood Stem Cells (PBSC)
  - Rarely Bone Marrow (backup)



From: Review Article - Armin Ehninger A, Trumpp A 2011 *JEM vol. 208 no. 3 421-428*





Autologous Peripheral Blood Stem Cells (PBSC)

PBSC have replaced BM as source of hematopoietic stem cells

- Superior in speed of engraftment post-transplant
- Decreased TRM to less than 5% and decreased morbidity
- No anesthesia and hospitalization for BM harvest
- Better able to collect stem cells from patients who previously received pelvic irradiation
- Decreased tumor contamination

How To Collect Autologous PBSC

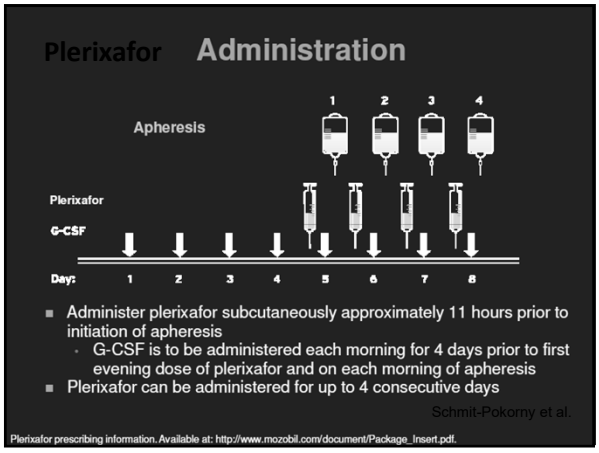
Using cytokine mobilizing agents alone

- Most commonly used: G-CSF
- GM-CSF pegylated filgrastim also used
- G-CSF plus Plerixafor (when failure to mobilize)
- Chemotherapeutic agents + cytokines
- Cyclophosphamide or Cyclophosphamide and etoposide
  - Disease-specific regimens: (eg, (R)ICE, (R)DHAP, many others)

Collection Goal of Autologous PBSC

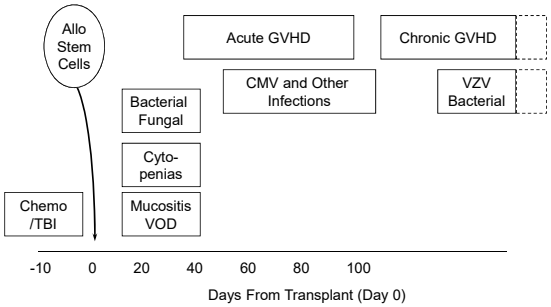
Autologous:

- Minimum: 2 x 10^6 CD34+ cells/kg
- Preference: 4-5 X 10^6 CD34+ cells/kg



Allogeneic Stem Cell Transplantation

Complications Following Allogeneic Transplantation

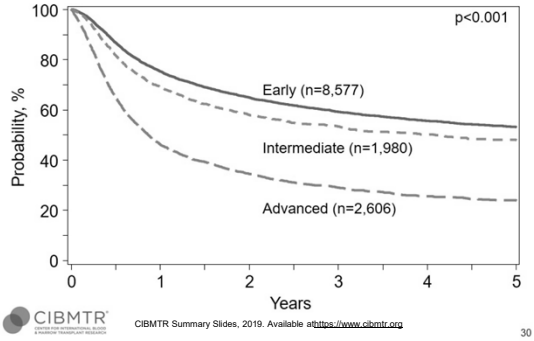


Allogeneic BMT

100 day Non-relapse mortality for myeloablative regimens: 15-35%

- Need recipient immune suppression to allow donor engraftment
- Clean normal stem cell source
- Graft versus host disease can cause morbidity and mortality
- Graft-versus-Tumor Effect
  - Tumor Relapse Is Lower after Allogeneic Donor
  - Lymphocyte infusions can induce GVT.

Survival after HLA-Matched Sibling Donor HCT for AML, 2007-2017



CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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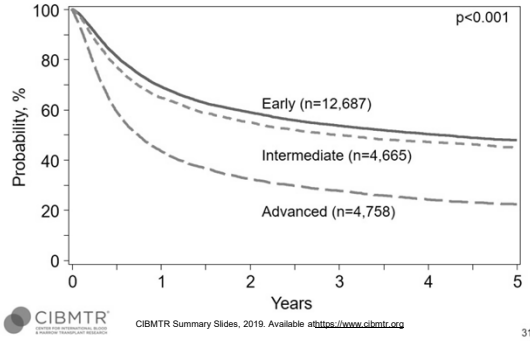
Survival after Unrelated Donor HCT for AML, 2007-2017



CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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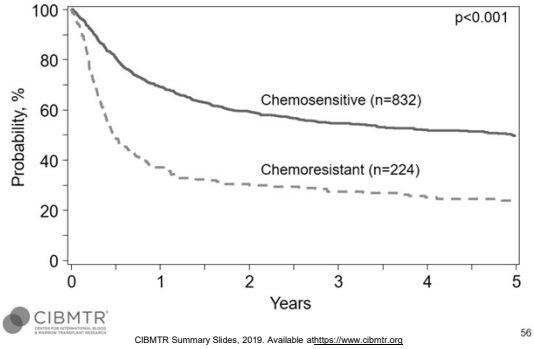
Survival after HLA-Matched Sibling HCT for Diffuse Large B-Cell Lymphoma (DLBCL), 2007-2017



CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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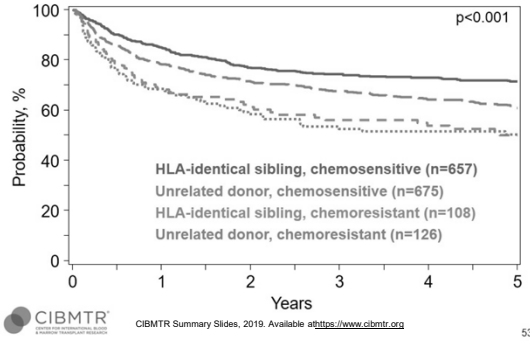
Survival after Allogeneic HCT for Follicular Lymphoma, 2007-2017



CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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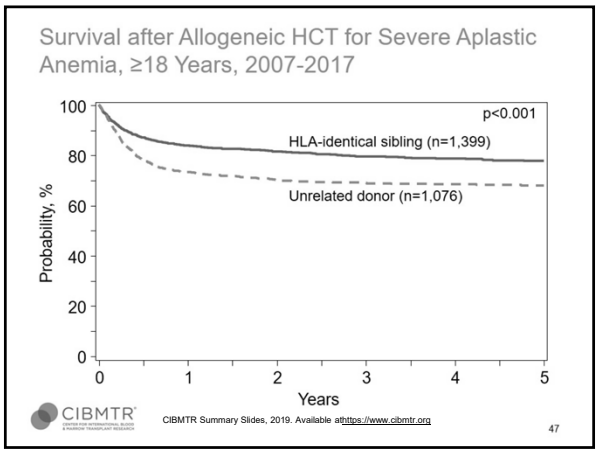
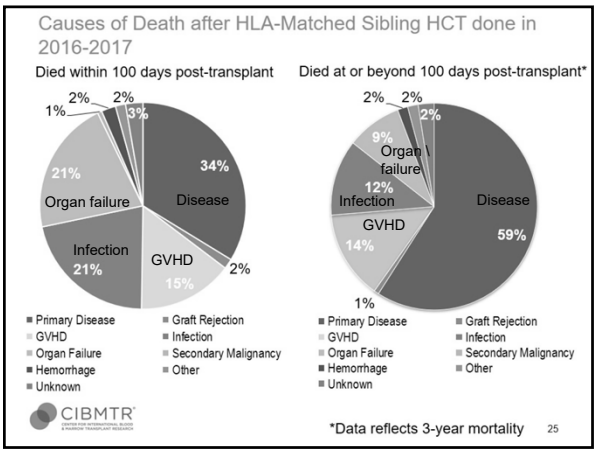
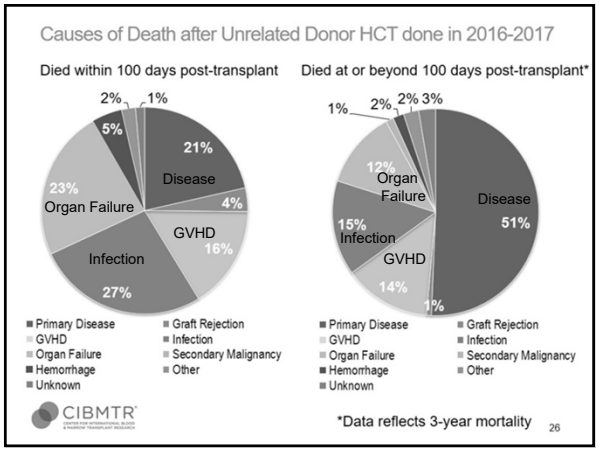
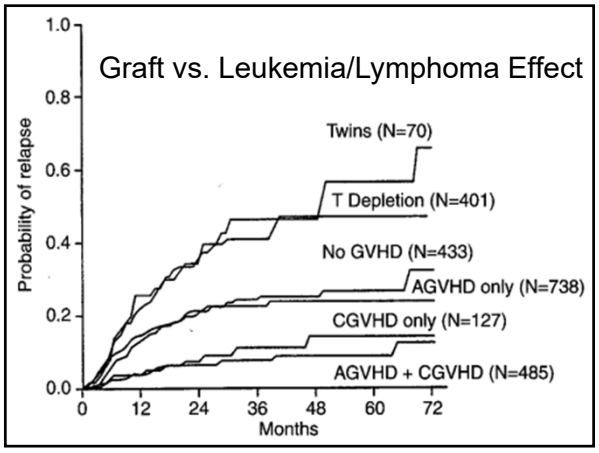






Allogeneic BMT

- Relies on tumor sensitivity to high dose therapy AND/OR graft versus tumor effect.
- Conditioning regimens
  - Ablative (defined as: total body irradiation single doses of ≥500 cGy, or fractionated doses totaling ≥800 cGy, busulfan doses of >9mg/kg, or melphalan doses of >150 mg/m^2 given either as single agents or in combination with other drugs.
  - Reduced intensity (defined as: < 500 cGy of total body irradiation as a single fraction or 800 cGy in fractionated doses, busulfan dose < 9 mg/kg, melphalan dose <140 mg/m^2, or thiotepa dose < 10 mg/kg).
  - Non-myeloablative (minimally intensive) (e.g. Flu/TBI 200-400 cGy). Lower TRM so allows elderly patient and patients with co-morbidity to be offered Allogeneic Transplant.



Initial Evaluations

Donors

- H and P, (hx of medical issues including malignancy plus hx of recreational drug use, transfusions, pregnancy, abortion, travel, vaccinations); determine caregiver support and reliability.
- Routine labs plus urine analysis, CMV PCR/Ab, hep A, hep BcAb, hep BsAg/Ab, HTLV I/II, HIV I/II, EBV, VZV, toxo, RPR, ß-HCG (females < age 55) West Nile (allo), Chagas Disease (allo), COVID screening/? cryo Chest X-ray (hx of pulmonary disease and SAT< 90%), and EKG (DM, Cardiovascular disease, Pulmonary disease, smoke >20 pack years, age: > 40 yr male and > 50 yr female);
- Ethical issues: 1 physician serves 2 persons whose medical care is interdependent

Hamadani M: Cryoreservaton of donors cells COVID Biol Blood Marrow Transplant. 2020 Apr 10 doi: 10.1016/j.bbmt.2020.04.001

Patients

- H and P (same)
- Routine Labs plus (same)
- •Restaging studies
- •BM
- •Dental Evaluation
- •RT consult if TBI or other RT
- •? Fertility preservation
- •ECG/Cardiac ejection fraction; PFTs (DLCO > 50)
- •PPD as clinically indicated
- •CXR, Sinus CT if clinically indicated
- •Other tests/regulatory standards as indicated
- •COVID Screening

O'Donnell P: Blood. 2010 Jun 17;115(24):5097-101
Ljungman P: EBMT COVID Bone Marrow Transplantation, May, 2020 https://doi.org/10.1038/s41409-020-0919-0

Primary Factors for Allogeneic Donor Selection

- Conventional practice in order of preference:
  1. HLA matched family member
  2. Then HLA matched Unrelated donor:
     - 60-70% chance of finding an 8 of 8 allele level, HLA-A, B, C, or DRB1 matched unrelated donor for Caucasian patients
     - 10% to 30% for U.S. ethnic minorities
  3. Alternative Donors (Order of preference not defined)
     - Haplo-identical
     - Cord Blood (usually double)
     - Mismatched unrelated

Anasetti C, Biol Blood Marrow Transplant 18:S161-S165, 2012

Secondary Factors forAllogeneic Donor Selection

1. Age of donor (relevant if multiple donors are available)
   a. 3% mortality for each decade increase in age of donor.

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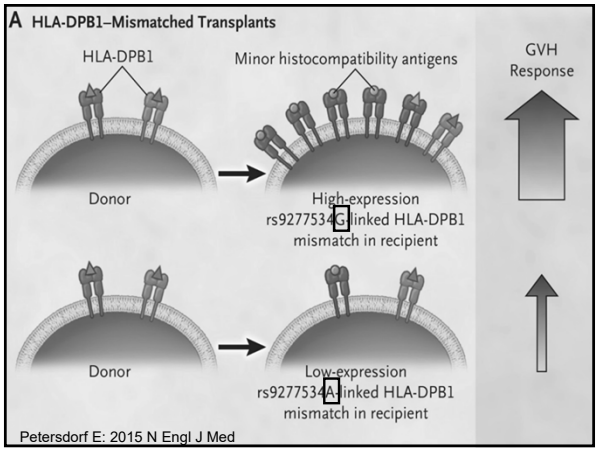
2. CMV status of recipient and donor (preferred combinations)
   a. CMV+ donor to CMV+ recipient
   b. CMV- donor to CMV- recipient

3. ABO red cell match (little effect)

Shaw BE et al: Biol Blood Marrow Transplant 24 (2018) 1049–1056
Ljungman P: Clinical Infectious Diseases 2014;59(4):473–81

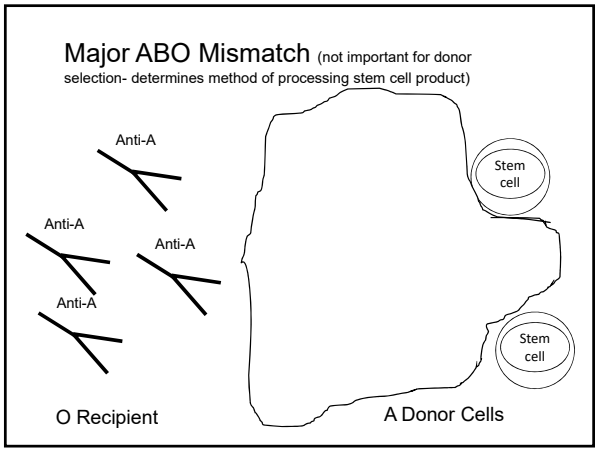


Petersdorf E: 2015 N Engl J Med

T-Cell Epitope: Effects on Immunogenicity

DPB1*	TCE group	Immunogenicity
09:01, 10:01, 17:01	1	
03:01, 14:01, 45:01	2	
01:01, 02:01, 04:01 + others	3	

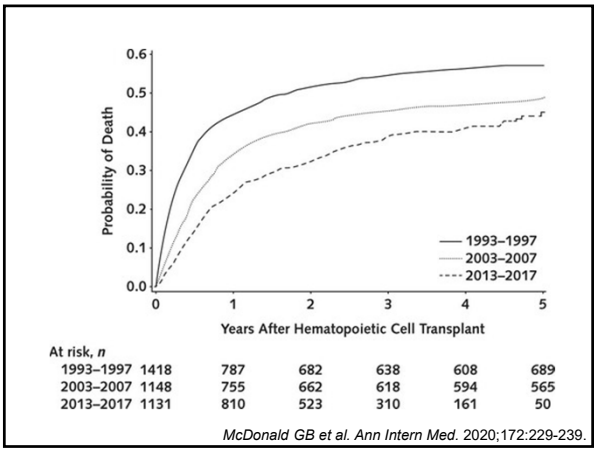
Katharina Fleischhauer Hematology Am Soc Hematol Educ Program (2019) 2019 (1): 532–538.



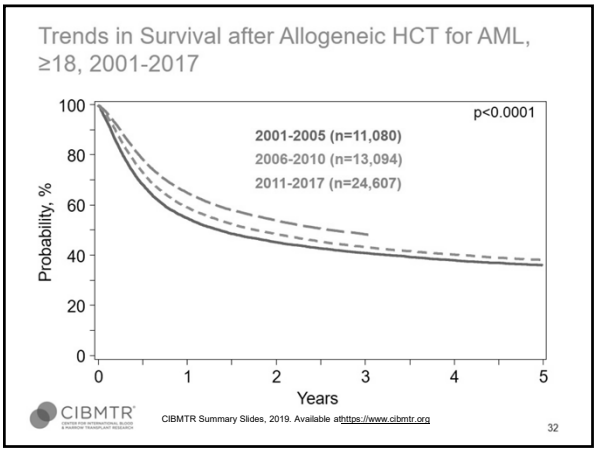
Pre-transplant Risk Scores

- **Co-morbidity Index:** CHF, diabetes, CVA, hepatic, obesity, renal, pulmonary
- **Disease Risk Index:**
  - Disease: Low, intermediate, high risk – e.g. CML, chronic phase (low), AML adverse cytogenetics (high).
  - Stage: Low: 1st PR, CR, High: induction failure, active relapse.
- **Pre-transplant Assessment of Mortality (PAM):**
  - Age, Donor Type (degree of matching), Disease Risk, Conditioning Regimen, Creatinine, ALT, FEV1, DLCO.

Elsawy, and Sorror: Up to date Tools for Risk Assessment before Allo BMT: BMT (online) June, 2016;
Thakar M, Sorror M, et al: Blood 2019 133:754-762;



McDonald GB et al. Ann Intern Med. 2020;172:229-239.



Reasons for Improvement in Allogeneic BMT Over Time

- Better HLA matching
- Better supportive care including anti-fungal and anti-viral therapy
- Less aggressive conditioning regimens i.e. targeted busulfan

Allogeneic Source of Stem Cells

- Peripheral Blood Stem Cells (PBSC)
  - Bone Marrow (haplo-identical, aplastic anemia)

Allogeneic Stem Cell Source: PBSC

- Human hematopoietic stem cells are present in the blood in small numbers so growth factor such as G-CSF needed to mobilize HSC from BM into blood.
- Higher CD34+ cell dose produces faster engraftment than marrow and UCB (reduced time to neutrophil, platelet recovery; fewer transfusions)
- More T-cells than BM; higher chronic GVHD.
- Donor side effects with G-CSF
  - Common bone pain 80%
  - Rare: Severe cardiovascular events 1 in 1500. splenic rupture 1 in 10,000 est.
  - G-CSF not proven to induce secondary hematological malignancies
  - FDA contraindicated in pregnancy – but probably safe; check pregnancy test in female donors

Allogeneic G-CSF PBSC Mobilization

- Donor receives G-CSF at a
  - Dose = 10 -16 mcg/kg subcutaneously per day,
  - Collect stem cells at 4-6 days
- Minimum allogeneic collection at some centers:
  - >5-6 CD34+ 10^6 cells/kg.

; 2001 Jan 18;344(3):175-81

Bone Marrow Vs. Peripheral Blood Stem Cells:

HLA Matched Related

- Patients with high-risk disease (AML beyond first CR1 or after first chronic phase of CML) had improved overall survival if they received PBSC compared to patients with advanced disease characteristics who received BM.

Bensinger et al: 2001
N Engl J Med 2001; 344:175-18

HLA Matched Unrelated

- Showed PBSC are associated with about same amount of Acute GVHD, faster engraftment and higher probability of keeping graft compared to marrow.
- Relapses were not less
- Chronic GVHD was higher with PBSC by a 16% difference
- Survival at 2 years was not different

Anasetti et al N Engl J Med 2012; 367:1487-1496

Bone Marrow Is Associated With Better Patient-reported Outcomes Than Peripheral Blood In Survivors 5 Years After Unrelated Donor Transplantation

- Patients randomized to receive BM vs PB.
- BM; better psychological well-being, fewer chronic GVHD symptoms, more likely to return to work.
- Survival, relapse and treatment-related mortality are similar.
- Failed to see an increase in the proportion of HCTs using BM.
- Suggests clinical results published in 2012 were not compelling enough to change management of these patients.

Lee S et al: JAMA Oncol. 2016 December 01; 2(12): 1583–1589

Alternative Donors:

- Cord blood units.
- Mismatched Unrelated Donor.
- Haplo-identical related donor.

Mismatched Unrelated BMT

- Advances:
  - High-resolution molecular typing and matching for HLA-A, -B, -C, and -DRB1 is the precise current standard.
  - Screening for donor-specific antibodies.
- Outcomes:
  - 5-year Overall Survival (based on allele match)
    - 8 of 8 (37%).
    - 7 of 8 (29%).
    - 6 of 8 (22%).

    Better outcomes in all categories with low risk disease
  - Both allele and antigen level mismatches adversely impacted survival.
  - Single mismatches at HLA-B and -C may be better tolerated than HLA-A and -DRB1.
  - Mismatch for DQB or DPB does not affect survival of these patients with malignancy.
  - Bone marrow = PBSCT

Anasetti C, Biol Blood Marrow Transplant 18:S161-S165, 2012

Umbilical Cord Blood Transplantation

Advantages

- Ease of procurement post-transplant and no donor risk.
- Availability for immediate use
- Low risk of GVHD despite HLA mismatch.
- Reduced risk of transmissible infections.
- Lower incidence of graft versus host disease (offset by mismatching).
- Extends transplant to minority populations (a unit can be found for many patients (4-6 of 6 HLA matched)

Limitations

- Limited cell dose in each unit and defects in bone marrow homing:
  - Delayed blood count recovery and engraftment
  - Higher rates of graft failure post-transplant (5-15%)
  - Delayed immune reconstitution and increased infections
  - Limit for large recipients
- Expense (2 cords, extended hospital stay)

Double Cord Blood Transplants

- In adults more frequent than single cords since 2005.
- Engraftment rate is comparable although higher Grade II acute GVHD in double cords versus single cord; chronic GVHD is equal.
- At day 21 post transplant single unit dominance can be detected in 80% (facilitator versus unit with 'engrafting potential' OR graft versus graft effects).
- Patients with mixed chimerism at 1 year more prone to GVL/GVHD.

Milano F et al. Blood 2017 130:1480-1482; Wagner: N Engl J Med 2014 Oct 30;371(18):1685-94 *Haematologica 2011;96(8):1213-1220. doi:10.3324/haematol.2010.038836*

Haploidentical Related Donor Transplants

- Strategies for GVHD prophylaxis paved the way to test this possible approach.
  - Administering cyclophosphamide after transplantation to limit mutual donor/recipient allograft reactivity
- Advantages:
  - Likely available parent, child or sibling as a potential donor
  - Additional progenitor and immune cells available for cellular therapies
- Disadvantages:
  - Need for either ex vivo or in vivo T cell depletion or aggressive immune-suppression regimens,
  - With T-cell depletion:
    - Delayed immune reconstitution
    - Increase the risk of opportunistic infections and relapse
    - With post-transplant cytoxan – less risk of above

Anasetti C, Biol Blood Marrow Transplant 18:S161-S165, 2012

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase 2 studies

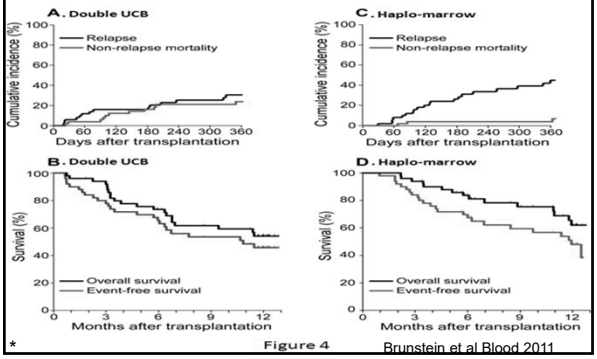


Figure 4

Brunstein et al Blood 2011

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase II studies

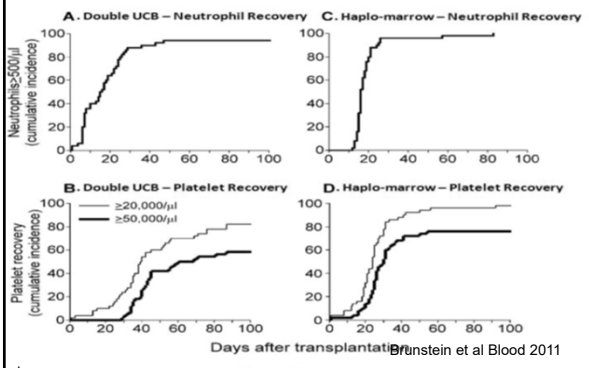


Figure 2

Brunstein et al Blood 2011

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase II studies

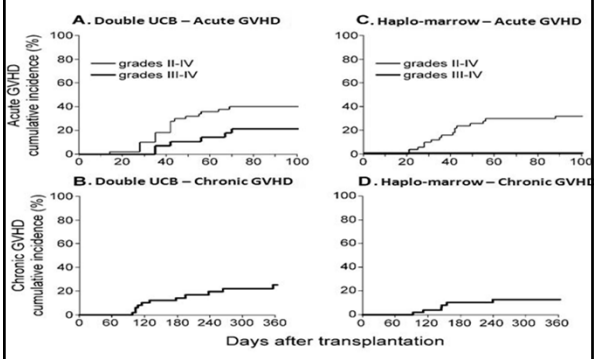


Figure 3

Regimen Considerations

Major Drugs Used in Conditioning

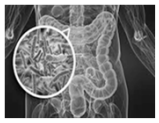
Drug	Major Toxicities	Considerations
High Dose Cyclophosphamide	Myelosuppression; SIADH, nasal stuffiness, rare cardiac necrosis, pericarditis, hemorrhagic cystitis (so need give with mesna and/or urinary irrigation)	Most frequent drug contributing to SOS; Given alone, not myeloablative; stem cell sparing.
High Dose Busulfan	Myelosuppression; Seizures (prophylaxis required); lung toxicity	Targeted dosing based on plasma levels; IV or p.o.
High Dose Melphalan	Mucositis, diarrhea; myelosuppression	
Fludarabine	Immunosuppression; autoimmune syndromes	Reduced intensity

Supportive Care

Mucositis and Nutritional Deficiency

- Risk Factors:
  - TBI Containing regimens
  - Most intense chemotherapy
  - Poor performance status
  - Prior radiation to head and neck regions.
  - Increased body surface area.
  - Methylenetetrahydrofolate reductase 677TT gene mutation (use of methotrexate for prophylaxis).
- Palifermin
  - Indicated for autologous regimens associated with TBI.
  - Reduced duration and severity; no change in relapse-free survival
  - Expense is an issue; rash, cotton mouth

TPN vs. Enteral Nutrition



- **Research:** RCTs are needed
- **Clinical Practice:**
  - Entereal Nutrition (EN) is safe.
  - Data showing potential benefit vs TPN.
  - Need to think about role of EN not just for adequate nutrient intake, but also for impact on microbiome.
- **Diet Guidelines:**
  - Traditional neutropenic diet no longer recommended.
  - Liberalizing diet will increase choice as well as pre-/probiotic food sources to feed the gut.

McMillan, Kerry et al 2020, Seattle

Ursodiol

- A large multi-center trial of prophylaxis after myeloablative allogeneic
  - Beneficial effect on the incidence of clinical jaundice, severe acute GVHD and survival.
- Decrease in the number of patients with jaundice and elevated serum alanine aminotransferase (ALT).
- Lower incidence of grade 3-4 acute GVHD
- Lower incidence of stage 2-4 liver GVHD

Ruufu T et al: Blood. 2002 Sep 15;100(6):1977-83
Gooley TA et al N Engl J Med 2010; 25: 363_

Allogeneic Graft versus Host Disease

Factors that Impact Risk of GVHD

- Donor- Host Factors
  - Related < unrelated donor
  - HLA disparity between the donor & host
    - Fully matched < 1 antigen MM < 2 antigen MM
  - Minor HLA antigen disparities
  - Differences in antigen expression (e.g. A vs. G for DP).
  - Sex mismatching and donor parity
    - Female donor into male recipient (HY antigens)
    - Multi-parous female donor
  - Age (Younger age < older age)
- Stem Cell Source
  - Bone marrow < peripheral blood
- Immune Modulation
  - T cell depletion (in vivo/ex vivo); graft engineering,
  - Serotherapy or augmented conventional agent regimens
- Tissue tolerance impaired and perturbed microbiota

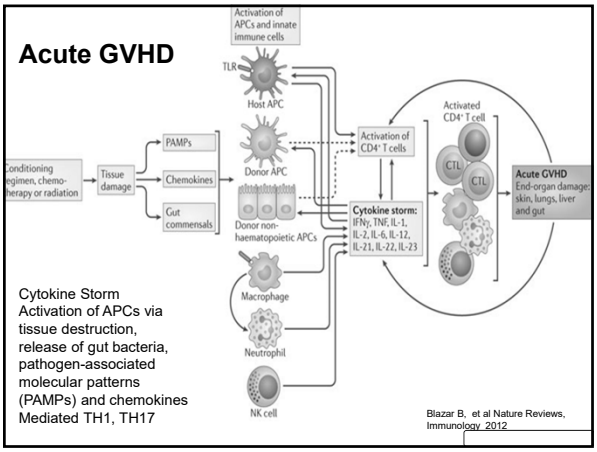
Prevention of Acute GVHD

Immunosuppressive therapy pre/post transplant
- Methotrexate, cyclosporine +/- sirolimus
- Tacrolimus, mycophenolate mofetil
- Corticosteroids (conflicting data on benefit) or antithymocyte globulin (ATG).

T-cell depletion from the donor graft (may increase relapse/rejection) unless very high intensity conditioning used.

Optimal HLA-matched

Acute GVHD



Cytokine Storm
Activation of APCs via tissue destruction, release of gut bacteria, pathogen-associated molecular patterns (PAMPs) and chemokines
Mediated TH1, TH17

Blazar B, et al Nature Reviews, Immunology 2012

Acute GVHD

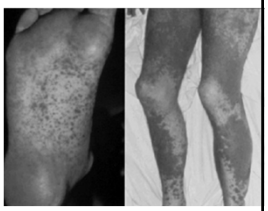
- Skin rash, diarrhea, elevated bilirubin, infections (bacteria, virus, fungus)
  - Occurs in 10 to 50 percent of patients who receive a matched related allogeneic transplant
  - Response to tx still carries 25% mortality for Grades I-II; 40-50% for Grade III, 90% for Grade IV
  - Infection is major issue
  - Severity of GVHD depends on recipient age, toxicity of the conditioning regimen, donor source, amount of mismatch and GVHD prevention measures.
- Steroids are the first line of treatment.
- Steroid-refractory acute GVHD has long-term mortality rates near 90%.

Stage*	Skin	Liver	Gut (adults)§¶	Gut (children)§
0	No evidence of GVHD	bili < 2.0 mg/dL	< 500 mL/d diarrhea	< 10 mL/kg/d diarrhea
1	< 25% body surface area involved	bili 2.0 - 3.0 mg/dL	500 - 999 mL/d diarrhea, or persistent nausea with histologic evidence	10 - 15 mL/kg/d diarrhea
2	25% - 50%	bili 3.1 - 6.0 mg/dL	1000 - 1499 mL/d diarrhea	16 - 20 mL/kg/d diarrhea
3	> 50%	bili 6.1 - 15.0 mg/dL	≥ 1500 mL/d diarrhea	21 - 25 mL/kg/d diarrhea
4	With bullous formation	bili > 15.0 mg/dL	Severe abdominal pain with/without ileus	> 26 mL/kg/d diarrhea

Grade	Skin	Liver	Gut
0	None	None	None
1	Stages 1 - 2	None	None
2	Stage 3, or	Stage 1, or	Stage 1
3		Stages 2 - 3, or	Stages 2 - 4
4*	Stage 4, or	Stage 4	

Acute GVHD: Skin

- Erythematous, maculopapular often beginning on palms and soles.
- Becomes confluent over cheeks, ears, neck, trunk;
- In severe cases, bullae and epidermal necrosis may occur.
- Main differential diagnosis: drug reaction.
- Biopsies only helpful after three weeks (drug effects and GVHD indistinguishable before then).
- Liver or GI involvement is unusual without skin involvement



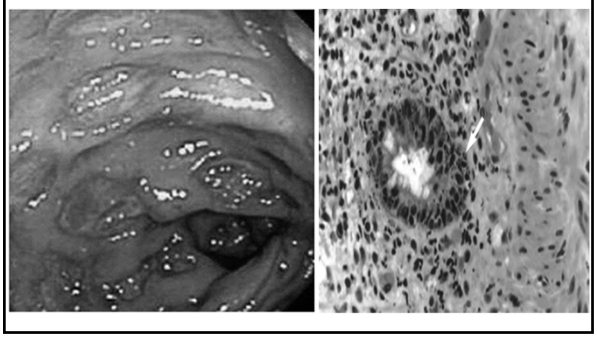
Acute GVHD: Liver

- Rising bilirubin, alk phos and AST due to three components:
  - Cytokines from GVHD process (IL-6, similar to cholestasis lenta mechanism)
  - Lymphocytic infiltration of bile ducts
  - Hepatitis from alloreactivity
- Persistence of disease and peak intensity both important prognostic factors.
- In less than 5% of current allograft recipients, acute GVHD is a fatal illness for which there is no effective therapy.
- Persistent jaundice is an independent predictor of mortality.

Acute GVHD: Gut

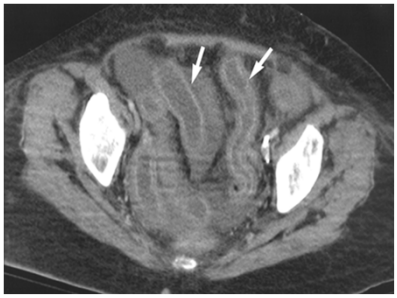
- Upper tract (stomach) GVHD not uncommon.
  - Presents with nausea, vomiting often during period of engraftment; responds to short course steroids/topical steroids.
- Diarrhea (green, water, mucoid; occasionally intestinal bleeding, crampy abdominal pain, ileus
- Biopsy for diagnosis. Differentiate from CMV enteritis, C. Difficile, other enteroviruses.
- May be difficult to treat if failure to respond to first and second line therapy.
- Patients can live with supportive care for months despite 'terminal' nature of gut GVHD.

Gut GVHD: Endoscopy and Biopsy



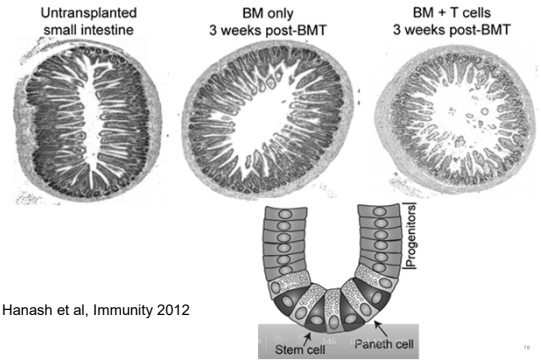
Gastrointestinal GVHD

Small bowel thickening on CT



Kalantari B N et al. AJR 2003;181:1621-1625

Intestinal Stem Cells are eliminated during GVHD



Hanash et al, Immunity 2012

Increased GVHD mortality with broad spectrum antibiotic use after allo-HCT

- Recipients who sustain more pronounced microbiota injury more likely develop severe GVHD
- Microbiota injury manifests in several ways including loss of overall biodiversity, loss of Blautia (a type of Clostridiales) and expansion *Enterococcus species*.
- Retrospective study found increased GVHD-related mortality at 5 years for Imipenem and Pip/Tazo vs untreated patients (cefeprime and aztreonam were OK)
  - Imipenem reduced the protective mucous lining (in mice)

Shono et al, Sci Trans Med 2016

Treatment of Acute GVHD

- Methylprednisolone at 2 mg/kg/day (max).
- Grade II GVHD: no disadvantage of lower-dose initial treatment at 1.0 mg/kg/day.
- Upper GI tract (anorexia, nausea, vomiting, and dyspepsia): 1 mg/kg prednisone plus topical steroids ("B and B") .
- Experience with lower-dose steroids in patients with grade III to IV GVHD is limited (being studied).
- Tapering of steroid doses should begin as soon as GVHD manifestations show major improvement.

Martin P, Carpenter P, et al. BBMT, 2012

Immunosuppressive Drugs for GVHD

- Glucocorticoids
  - Osteopenia, avascular bone necrosis, myopathy, impaired wound healing, and secondary adrenal insufficiency.
  - Viral reactivation and mold infections especially with doses >2 mg/kg/day.
- MMF (CellCept, Myfortic)
  - Mechanism of action: Non-competitive inhibitor of IMPDH, the rate limiting step for de novo purine synthesis on which lymphocytes depend.
  - Dose related cytopenia and gastrointestinal toxicity; consider risk: benefit carefully when treating gastrointestinal GVHD. Enteric-coated MMF (Myfortic) may be better tolerated.

Immunosuppressive Drugs

- **Sirolimus (Rapamune)**
  - Blocks mTOR, blocks co-stimulation via CD28.
  - Toxicity: Reversible cytopenia, hypertriglyceridemia, and nephrotoxicity (HUS/TMA) and neurotoxicity (TTP) when combined with calcineurin inhibitors.
  - Substrate for CYP3A4 and P-glycoprotein; initial 90% dose reduction in sirolimus when combining with voriconazole
  - May increase the risk for rhabdomyolysis if used with statins.
  - Dose adjustments for renal failure and increased bilirubin

ATG (anti-thymocyte globulin)

- Horse:
  - Sera from horses immunized with human thymocytes
  - Test dose required.
  - Frequent fever, chills; thrombocytopenia, leukopenia; minimal lymphocytopenia; serum sickness in 5% (less if steroids used for premedication).
- Rabbit
  - Sera from rabbits immunized with human thymocytes
  - Immunosuppression immediate and greater than horse ATG.
  - Viral infection risk high (monitor for EBV and CMV with PCR for six months).
  - No skin testing required.
  - Reactions less likely if infusion given > 6 hours.

Post-Transplant High Dose Cyclophosphamide (e.g. Day 3-4)

- Spares Stem Cells
- Reduces GVHD but no increased relapse risk.
- Reduces HLA barriers to transplant (haplo-ID)
- Reduces GVHD risk with post-transplant Anti-PD-1 therapy.

Haverkos BM: Blood Volume 130, Issue 2
July 13 2017
DOI: https://doi.org/10.4414/smw.2019.20150
Sandchez DO: 10.11.2019
Swiss Med Wkly. 2019;149:w20150

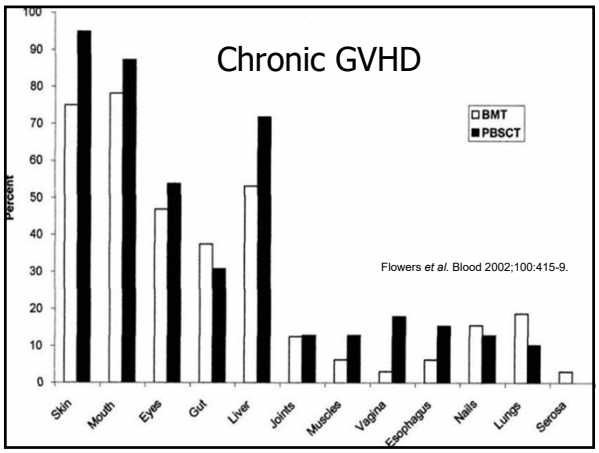
Extracorporeal Photopheresis (ECP)

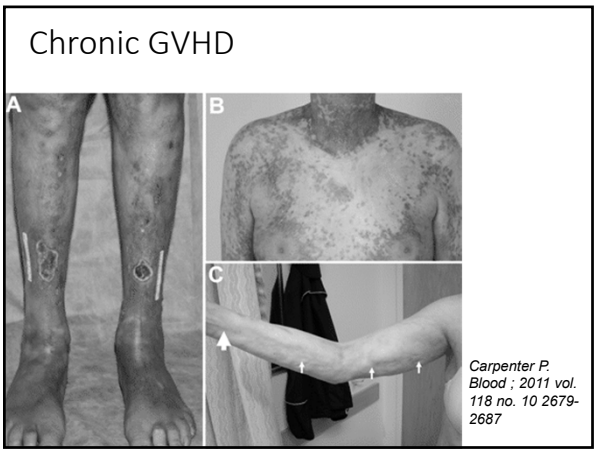
Psoralens plus UV light to ex-vivo lymphocytes.

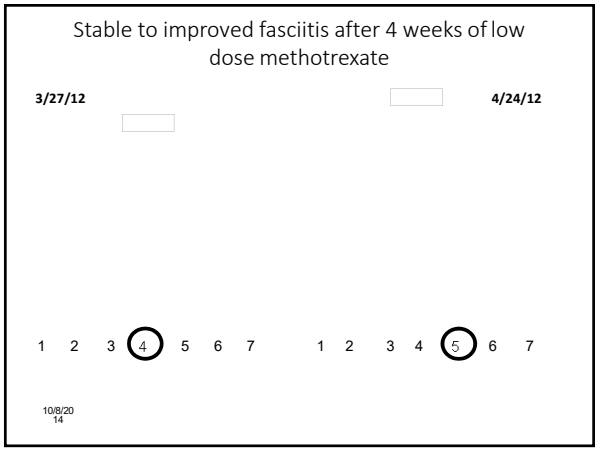
- Direct apoptosis of lymphocytes.
- Reinfusion generates tolerogenic responses by
  - interference with dendritic cell maturation.
  - modulation of cytokine production.
  - expansion of regulatory T cells.
- Advantage: no increased risk for viral reactivation.
- Used in acute and chronic GVHD but very slow response and very expensive.

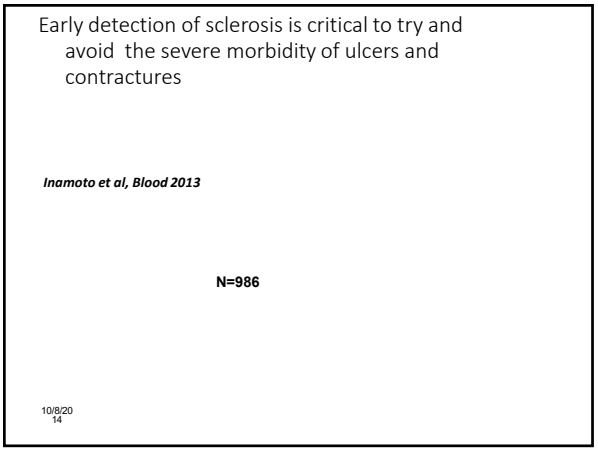
Diagnosis of Chronic GVHD

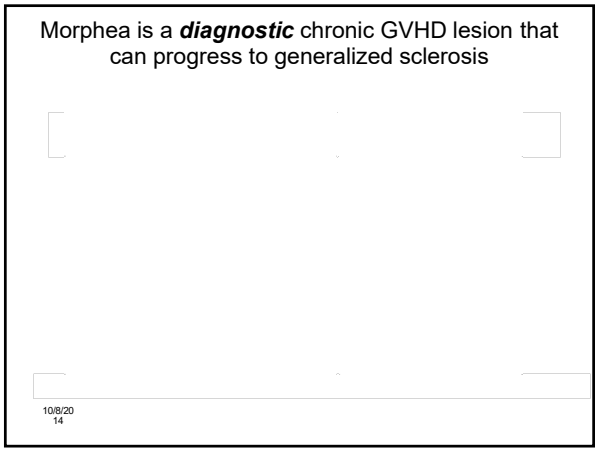
- NIH consensus Working Group standardized criteria :
  - No time limit
  - requires the presence of at least one diagnostic clinical sign of chronic GVHD (scleroderma or esophageal thickening) or the presence of at least one distinctive manifestation (keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests (e.g. Schirmer's)
  - Exclusion of other possible diagnoses to explain clinical findings e.g. infection.
- Global assessment of chronic GVHD severity has been developed to replace the historical "extensive/limited" classification.

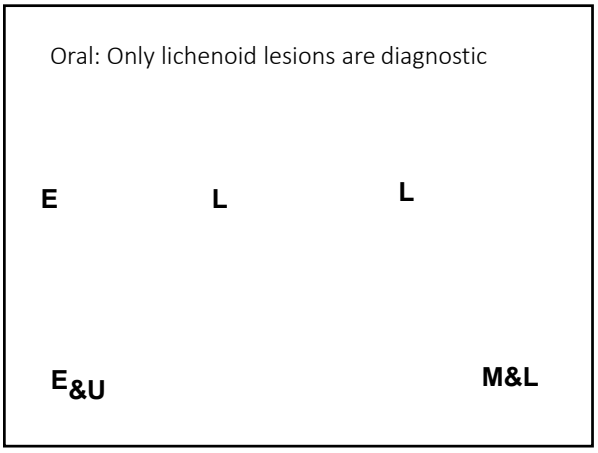












Chronic GVHD

- Characteristic clinical presentation
  - Some similarity to autoimmune diseases
  - Occurs in 30–60%
- Pathogenesis: thymic damage leading to decreased elimination of autoreactive ? TH2-type responses (autoimmune/autoantibody); decreased reg T-cells; secretion of IL-4, 5, 11: IL2, 10 leading to fibroblastic cytokines, e.g. PDGF in many organs;
- Key point: chronic GVHD is a syndrome that likely has many overlapping pathogenic mechanisms, including inflammation, humoral immunity, cell-mediated immunity, and fibrosis, with variation in the dominant driver from one patient to the next.

Blazar B, et al Nature Reviews, Immunology 2012

Treatment of Chronic GVHD

- Glucocorticoids (1mg/kg/day) followed by taper to eventually reach an alternate-day or daily regimen, with or without daily cyclosporine or tacrolimus (FK506).
- Requires at least one year of therapy.
- Approximately 80% of patients require systemic immunosuppressive for 2 years.
- 40% of them requires therapy for at least 4 years.

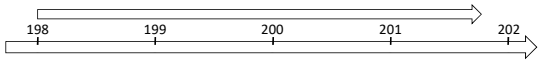
Chronic GVHD: Treatment

- Ruxolitinib and Ibrutinib are among the preferred options for chronic GVHD.
- Ibrutinib has received FDA approval for chronic GVHD based on a phase Ib/II study, but suffers from a high rate of discontinuation.
- ECP remains a viable option for chronic GVHD, particularly if it affects the skin.
- Novel therapeutic modalities target IL-2 signaling (aldesleukin, AMG 592), T-cell costimulation via CTLA4 (Abatacept) and those increasing the proportion of T-regulatory cells (Tregs) with respect to other effector T-cell populations (the Rho kinase KD-025).

Shapiro RM and Antin J: Expert Review of HematologyVolume 13, 2020 - Issue 5

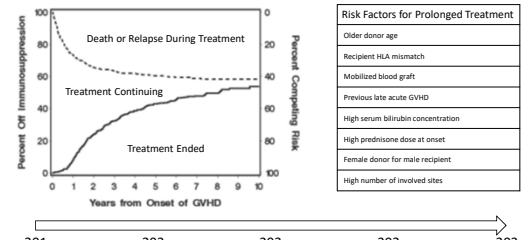
Chronic GVHD: Controlled Trials of Initial Treatment—1980 to present

First Author	Arms Compared	Double Blind	N	Results
Sullivan	Prednisone ± azathioprine	Yes	179	Decreased survival
Koc	Prednisone ± cyclosporine	No	287	Steroid-sparing?
Koc	Cyclosporine/prednisone ± thalidomide	Yes	51	Toxicity
Arora	Cyclosporine/prednisone ± thalidomide	No	54	No benefit
Martin	Calcineurin inhibitor/prednisone ± mycophenolate mofetil	Yes	151	No benefit
Gilman	Calcineurin inhibitor/prednisone ± hydroxychloroquine	No	54	No benefit
Carpenter	Sirolimus/prednisone ± calcineurin inhibitor	No	138	No benefit

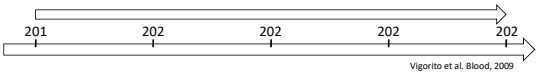


Martin, Paul 2019, Seattle

Chronic GVHD: Tolerability of Long-Term Treatment



Risk Factors for Prolonged Treatment
Older donor age
Recipient HLA mismatch
Mobilized blood graft
Previous late acute GVHD
High serum bilirubin concentration
High prednisone dose at onset
Female donor for male recipient
High number of involved sites



Vigorito et al. Blood, 2009

Martin, Paul 2019, Seattle

GVHD Overview

SKIN
red rash
LIVER
⇧AST/ALT
GI TRACT
anorexia, nausea, diarrhea

Grade I-IV

- SKIN
  - lichen planus, dyspigmentation, nail/hair dystrophy, scleroderma (morphea)
  - ORAL
  - sicca, atrophy, lichenoid changes
  - DRY EYES
  - GI TRACT
  - wasting, dysphagia
  - LUNGS
  - Bronchiolitis obliterans
  - JOINTS/FASCIA
  - contractures

Paul Carpenter Seattle

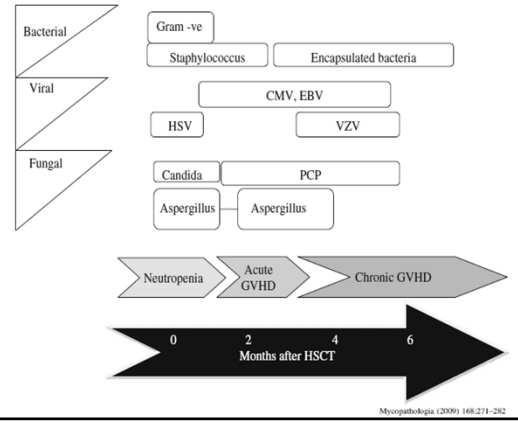
Chronic GVHD Fast Facts

- Median onset: 6 months
  - 10% happens >1 year
- Dx usually requires:
  - ≥1 ***diagnostic*** sign or
  - ≥1 ***distinctive*** feature confirmed by biopsy or other relevant tests
  - Exclude other Dx

Graft source of stem cells	Incidence	Median years on systemic GVHD therapy
Cord blood	64% (late acute) 32% (NIH chronic)	~1
Marrow	48%	~1.9
Peripheral blood	60%	~3.3

Paul CarpenterSeattle

Infectious Complications



Bacterial Infection

- Prophylaxis:
  - fluoroquinolones for gram negative – no proven survival advantage. Resistance emerging: E. coli, strep viridans, Pseudomonas
  - Most use levofloxacin (rare tendonitis)
- C difficile emergence with antibiotic usage.
- Initial Therapy for Fever/Neutropenia (NCCN Guidelines)
  - Need to work up fever and infectious signs aggressively
  - Category I: meropenem, piperacillin-tazobactam, imipenem/cilastin, cefepime
  - Category 2B: ceftazidime

Infections: 0-30 Days

- Total body irradiation and high dose chemotherapy results in more mucositis, diarrhea, bacteremia than other regimens.
- Bacteremia in 15-50% with both gram positive and gram negative organisms.
  - Staph epi- usually catheter associated.
  - Streptococcus viridans – associated with fluoroquinolone prophylaxis and mucositis.
- Clostridium difficile –associated disease at a higher frequency in this population; most common cause of infectious diarrhea (15%)
- Uncommon infections:
  - Typhlitis: enterocolitis up to 50% mortality.
  - Nocardia: pulmonary nodules, CNS infection (e.g. brain abscess, meningitis)

Infections: 0-30 Days

- Invasive fungal infections have been reported to be 10%-20%.
  - Risk factors: prolonged neutropenia > 7 days, broad-spectrum antibiotics, treatment with corticosteroids, TPN; Low CD4 T-cells
- Candida (50/50 albicans/non-albicans) and Aspergillus accounts for 80% of fungal infections.
  - Azole resistant Candida glabrata and Candida krusei more common due to fluconazole prophylaxis; Caspofungin or vori
  - Aspergillus occurs in up to 20% of BMT patients;
    - Sinusitis or lung disease through inhalation of spores,
    - Galactomannan testing (serum, BAL)
    - Treatment with Voriconazole (+/- echinocandin).
- Mucormycosis (inhalation, trauma) occurs infrequently: 80% mortality. Tx: high dose amphotericin-B, surgery.

Infections: 30-100 Days

- Viruses Other than CMV:
  - Adenovirus: 70% mortality in patients with disseminated adenovirus infection/pneumonia. May cause cystitis.
  - BK virus: hemorrhagic cystitis. ? Cidofovir.
  - Respiratory viral infections (11%)
    - Treatable: Influenza: oseltamivir, baloxavir (new); RSV: ribavirin
    - Not Treatable: Metapneumovirus, parainfluenza, rhinovirus, coronavirus, SARS-CoV-2
  - Enteroviral infections
  - HHV-6. often asymptomatic but can be associated with prolonged fever and encephalitis, pneumonia, graft failure.
- Pneumocystis carinii and toxoplasmosis: less common due to prophylaxis with TMP-SMX.

Respiratory Virus Prevention in the era of COVID

- Healthcare workers and visitors with URI symptoms should be restricted from contact with BMT recipients and candidates under-going conditioning therapy to minimize the risk for viral transmission.
- Some centers restrict all visitors to BMT units.
- Practice of distancing (six feet), masking, COVID screening donors and patients those both symptomatic and asymptomatic.
- Survey screening for healthcare workers.
- Work from home considerations.

CMV in BMT: Pre-emptive Therapy Based on CMV PCR+

- Preemptive therapy with GCV reduced CMV disease to <5% transplantation.
- CMV occurs later in non-myeloablative transplant patients
- Leukocyte reduced platelet and red blood cell components or CMV sero negative blood products (CMV 'safe') reduce the risk of CMV transmission in all patients.
- GCV used for early CMV PCR positivity in blood.
- CMV disease has significant mortality despite tx with GCV and Ig (combined therapy for CMV pneumonia only).
- GCV causes severe neutropenia and delays reconstitution of CMV-specific T cell immunity (change to foscarnet if neutropenia or failure of G-CSF to increase neutrophils)
- Recipients of non-myeloablative conditioning regimens appear to be particularly susceptible to ganciclovir-related neutropenia.

Boechk M ASH Ed, 2011

CMV in BMT: High Risk Categories

- General Risk:
  - Seropositive patients receiving steroids in first 100 days (30% risk for CMV disease unless pre-emptive therapy given)
  - Patients receiving ATG for the treatment of steroid refractory GVHD or as part of the conditioning regimen (cont weekly surveillance for six months after last ATG dose)
  - Cord blood or CD 34+ selected transplants recipients
  - Haplo identical related recipients particularly those who received ATG
- Late CMV Disease Risk (monitor weekly for 1 year):
  - CMV-seropositive recipients receiving steroids for chronic GVHD
  - Patients who were treated for CMV early after transplant.
  - Cord blood transplant recipients

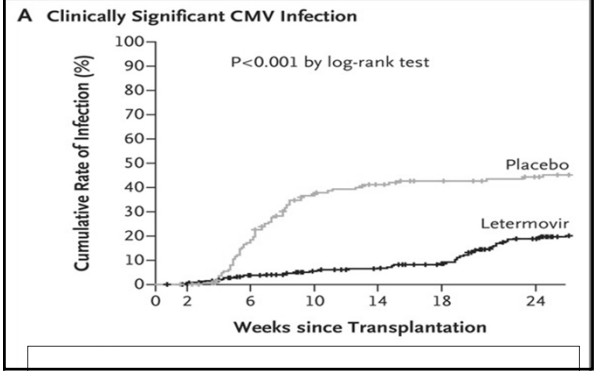
Boechk M ASH Ed, 2011

Drugs for Treatment of CMV

- Ganciclovir: a synthetic nucleoside analogue of 2'-deoxyguanosine that inhibits the replication of herpes viruses in vitro and in vivo. (add Ig for pneumonia only); neutropenia
- Valganciclovir: an oral precursor of ganciclovir, which has 10-fold greater bioavailability than oral ganciclovir.
- Foscarnet : inhibits the pyrophosphate- binding site on viral DNA polymerases at concentrations that do not affect human DNA polymerases; Major toxicity is renal and electrolyte changes (Mg, Ca, K, PO4).
- Cidofovir: suppresses CMV replication by selective inhibition of viral DNA polymerase; nephrotoxicity is the major toxicity.
- Letermovir: effective for CMV prophylaxis.

Boechk M ASH Ed, 2011

Letermovir Prophylaxis Marty et al N Engl J Med 377(25):2433–2444, 2017
Infect Drug Guy El Helou Resist Infect Drug Resist. 2019; 12: 1481–1491. 2019; 12: 1481–1491.



CMV: Caveats

- CMV infection acquired close to a planned allogeneic BMT associated with increased risk of early mortality post-BMT
- Screen Patient by PCR during the pretransplantation workup and preemptive therapy administered if CMV is detected.
- Drug resistance is rare after BMT
  - Reported with ganciclovir or valganciclovir
  - Genotypic assays are available for diagnostic analysis in reference laboratories.
  - Should be suspected when viral load increases for more than 2 weeks on drug.
- After starting preemptive therapy, viral load increases occur in approximately one-third of patients due to the underlying immunosuppression.

Boechk M ASH Ed, 2011

Infections: After Day 100

- VZV:
  - Median time 5-6 months.
  - Manifests as shingles (e.g. reactivation) more commonly than chickenpox (primary infection)
  - Risk of dissemination with chickenpox.
- Bacterial: encapsulated organisms (functional asplenia in patients with chronic GVHD).
- Fungal
- Late CMV

Boechk M ASH Ed, 2011

Long-term Prophylaxis for Bacterial, Pneumocystis carinii pneumonia (PCP) and VZV

- Bacterial:
  - Increased risk with chronic GvHD and steroid use, especially Streptococcus pneumoniae, H. influenzae, Neisseria meningitidis.
  - Decreased CD4 T-cells, decreased opsonizing antibodies.
  - TMP-SMX or PCN (if sulfa allergy)
- PCP
  - TMP-SMX for at least 6 months after the transplant or until all immunosuppressive medications have been discontinued.
  - 2 consecutive days weekly.
  - Sulfa allergy: desensitize if possible or dapsone (test for G-6PD).
  - Other alternative PCP prophylaxis regimens have been less effective e.g. inhaled pentamidine, atovaquone.
- Varicella-zoster virus
  - Seropositive or prior infection: Prophylaxis with acyclovir or valacyclovir throughout the first year after the transplant or until 6 months after systemic immunosuppressive for control of GVHD ends.

Vaccinations Post-BMT (allo or auto)

Vaccine	*Recommended for use after BMT*	*Time post-BMT to initiate vaccine*	*No. of doses*	*Improved by donor vaccination (practicable only in related-donor setting)*
Pneumococcal conjugate (PCV)	Yes	3–6 months	3–4	Yes; may be considered when the recipient is at high risk for chronic GVHD. One dose of Pneumovax if GVHD
Shingrix -zoster	Yes			
Tetanus, diphtheria, acellular pertussis	Yes	6–12 months	3	Tetanus: likely Diphtheria: likely Pertussis: unknown
Hemophilus influenzae conjugate	Yes	6–12 months	3	Yes
Meningococcal conjugate	Yes	6–12 months	2	Unknown
Inactivated polio	Yes	6–12 months	3	Unknown
Recombinant hepatitis B	Yes	6–12 months	3	Likely
Inactivated influenza	Yearly (All)	4–6 months	1–2[‡]	Unknown

Hepatic Complications

SOS (Sinusoidal Obstruction Syndrome): Clinical Presentation and Course

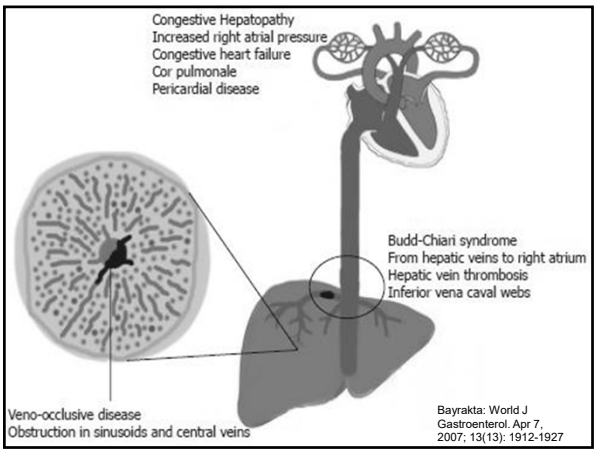
- Occurs in the first two to three weeks after transplant.
- Onset usually 3-6 days post-transplant with sudden weight gain - 2-5% body weight.
- Mild (no tx), moderate (diuretics), severe (renal cardiopulmonary, high risk of death)
- Elevated conjugated bilirubin occurs on day 6 or later usually with transaminase abnormalities.
- Complete recovery occurs in over 70% of patients supportive care only.
- Defibrotide may be helpful in severe cases.*

* Richardson, PG: Blood 2016 127:1656-1665;

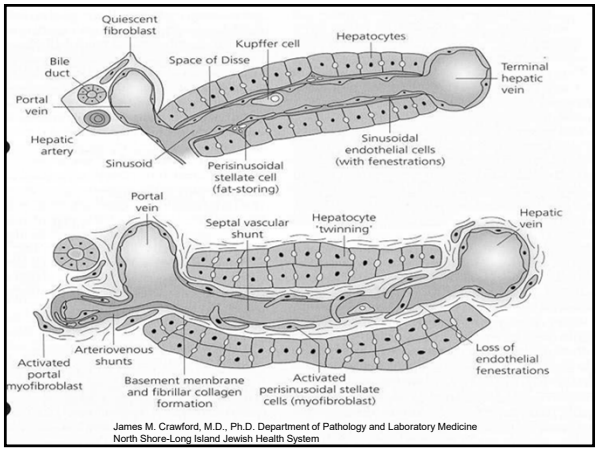
Risk Factors for SOS

- Pre-existing liver disease (hepatitis C, hepatic fibrosis, cirrhosis)
- Previous exposure to a myeloablative regimen
- Past history of SOS
- Myeloablative regimens
  - High dose total-body irradiation
  - Cyclophosphamide-containing regimens
    - Reverse order of Bu/Cy to Cy/Bu – Bu depletes liver of glutathione; Cy damages liver)
  - Myelotarg
- Cyclophosphamide after busulfan
- Fixed dose of busulfan (i.e. no monitoring of plasma levels)
- Oral rather than IV busulfan
- Performing transplant late in the course of leukemia
- Myelofibrosis with extramedullary hematopoiesis (collagen deposition)
- Sirolimus containing regimens (late SOS)

Khimani F[1], McDonald GB Bone Marrow Transplant. 2019 Jan;54(1):85-89

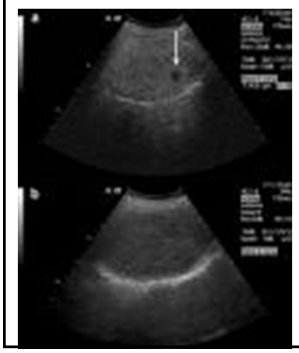


Bayrakta: World J Gastroenterol. Apr 7, 2007; 13(13): 1912-1927

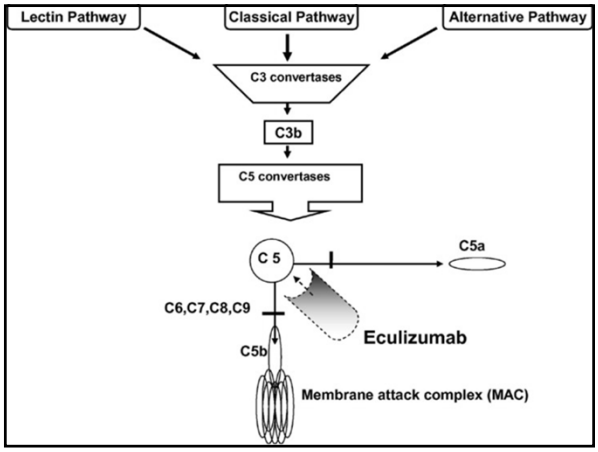


James M. Crawford, M.D., Ph.D. Department of Pathology and Laboratory Medicine
North Shore-Long Island Jewish Health System

SOS: Ultrasonography



- Findings:
  - Ascites
  - Hepatomegaly
  - Abnormal portal vein waveform
  - Hepatic artery resistance index (RI) >0.75
- Reversal of flow in portal vein
- Distinction from Budd Chiari
  - venous outflow obstruction in SOS is due to occlusion of the terminal hepatic venules and hepatic sinusoids rather than the hepatic veins and inferior vena cava.



Pulmonary/Cardiac Complications

Organ Toxicities: Cardiac

- Incidence of occult cardiac disease higher now that older patients undergo transplant.
- After high dose cyclophosphamide often in setting of pre-existing heart disease;
- Cumulative doses of doxorubicin or other anthracyclines
- After TBI/prior local irradiation
- Sudden death/arrhythmia as a consequence of amyloid heart.
- Careful fluid management is key if pre-existing abnormalities in ejection fx

Spectrum of Noninfectious Lung Complications

Early Complications

- often leads to acute respiratory failure
- Very early complications
  - Volume overload/pulmonary edema
  - Aspiration pneumonitis
  - Mucositis
- **Idiopathic Pneumonia Syndrome/ARDS**
  - **Diffuse Alveolar Hemorrhage**
  - **Organizing pneumonia**

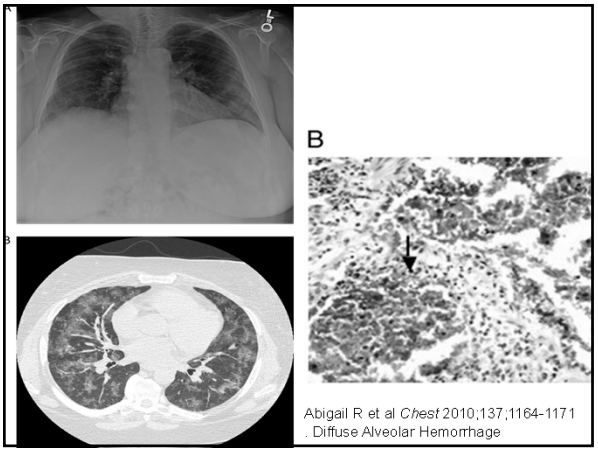
Late Complications

- **Incidence up to 20%**
- **Bronchiolitis Obliterans Syndrome (chronic GVHD)**
- Organizing pneumonia
- Other Interstitial Lung Disease
  - Pleuropulmonary fibroelastosis
- Pleural Effusions
- Pulmonary Embolism

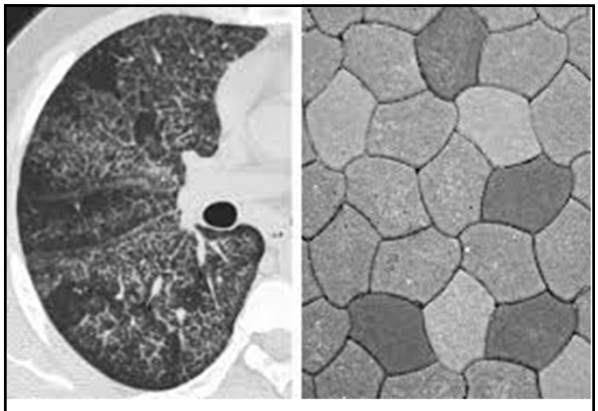
Diffuse Alveolar Hemorrhage

- Occurs in 5% of auto and allo patients; mortality > 50%;
- May be recurrent or chronic.
- Present with cough/SOB, anemia, diffuse pulmonary infiltrates, hypoxia; Hemorrhage: hemoptysis or on BAL .
- Regimen-related diffuse alveolar damage with cytokine release.
- Risk factors: older age, myeloablative conditioning regimen, total body radiation, and acute graft-vs-host disease
- Chest x-ray: patchy alveolar infiltrates which may start in a focal, unilateral pattern and become more diffuse
- CT may be helpful in guiding location for bronchoscopy.
- High dose steroids, aggressive hematological management of plt, ? Embrel; mechanical ventilation

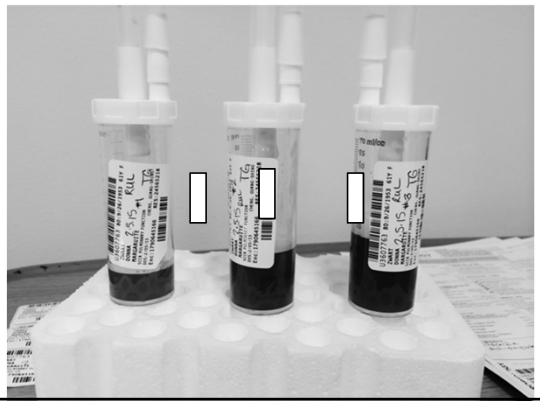
Abigail R et al *Chest* 2010;137;1164-1171
. Diffuse Alveolar Hemorrhage



Abigail R et al *Chest* 2010;137;1164-1171
. Diffuse Alveolar Hemorrhage



BAL in DAH



Long-term Complications (Adults)

Long Term Complications After BMT

- Relapse
- Sequela of GVHD
  - Immunity and infections issues
  - Ocular, skin and oral ie. Cataracts, Oral cGVHD (mucosal changes, poor dentition, xerostomia)
  - Esophageal (webs, rings, submucosal fibrosis & strictures, aperistalsis, Pill esophagitis etc.)
  - Muscle, connective tissue and skeletal ie. Osteoporosis
  - Respiratory
  - Liver
  - Chronic renal insufficiency
  - CHF and increased associated risk factors
  - Iron overload
  - Endocrine (hypothyroidism, secondary adrenal insufficiency) /gonadal (fertility) dysfunction
  - Psychiatric /integration into normal life (employment), sexual dysfunction.
  - CNS
  - Secondary cancers

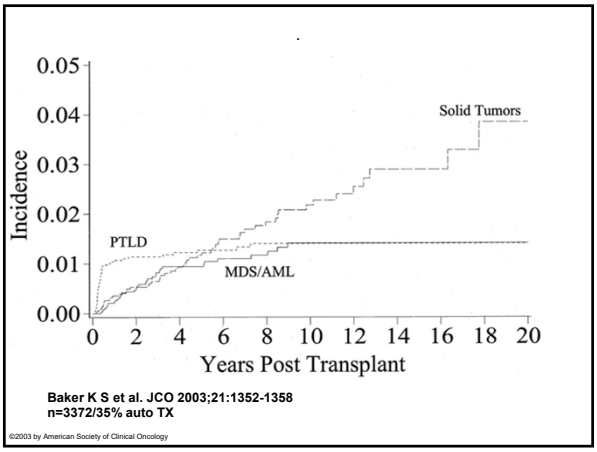
Bone Loss in Long-term Survivors

- Occurs predominantly within the first 6–12 months after autologous and allogeneic HCT.
- Recovery first occurs in the lumbar spine and is followed by a slower recovery in the femoral neck.
- Recovery slowed by steroids.
- DXA scan to determine use of anti-resorptive agents.

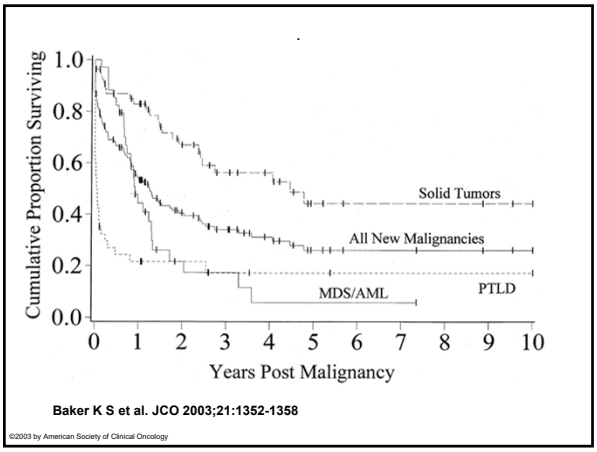
Late Mortality From Therapy Related Secondary Cancers After Autologous and Allogeneic Transplant

- After auto:
  - 12 X more likely to die of new malignancy than general population
    - Hematological cancers (68%)
    - Solid tumors (32%)
- After allo:
  - 3.6 X more likely to die of new malignancy than general population
    - Solid tumors (82%)

Bhatia S et al Blood 2007:110, 3784–3792 and Bhatia S et al Blood 2005:105, 4215–4222



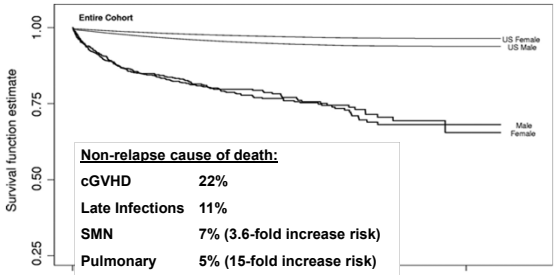
Baker K S et al. JCO 2003;21:1352-1358
n=3372/35% auto TX



Baker K S et al. JCO 2003;21:1352-1358

Late Mortality >2 yr Survivors after HCT

N=1479



Non-relapse cause of death:	
cGVHD	22%
Late Infections	11%
SMN	7% (3.6-fold increase risk)
Pulmonary	5% (15-fold increase risk)
Cardiac	3% (2.3-fold increase risk)
Other/external	11%

Bhatia, S. et al. Blood 2007;110:3784-3792

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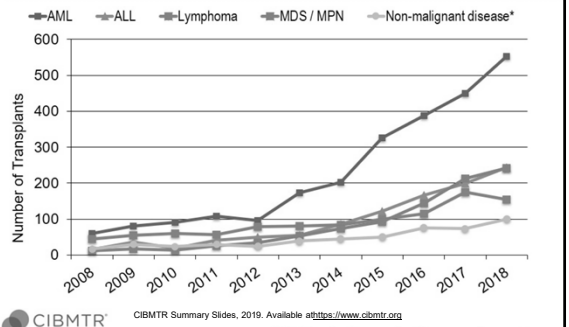
Appendix

Caveats for HLA-Matching Decisions

25% likelihood of HLA matching with a sibling

- < 1% chance of HLA matching with another relative.
- History of intermarriage in families rarely produce HLA ID cousins or combination of rare haplotype and common HLA haplotype.
- Mismatch HLA A, B and C increases risk of Graft rejection.
- Mismatch of HLA DR increase risk for GVHD.
- Single Ag mismatched related transplants
  - Unknown whether to prefer single Ag mismatched related donor versus MUD (we prefer MUD)

Haploidentical HCT Recipients in the US, by Disease



CIBMTR

CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

*Not including aplastic anemia.

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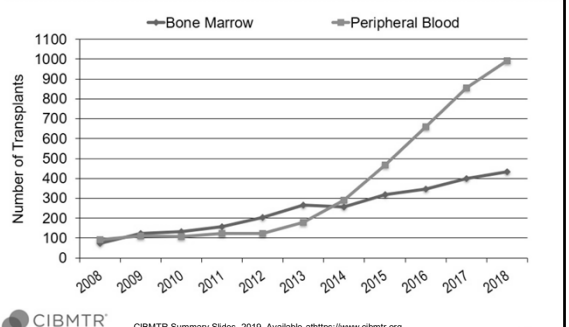
Haploidentical HCT Recipients in the US, by Graft Type



CIBMTR

CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

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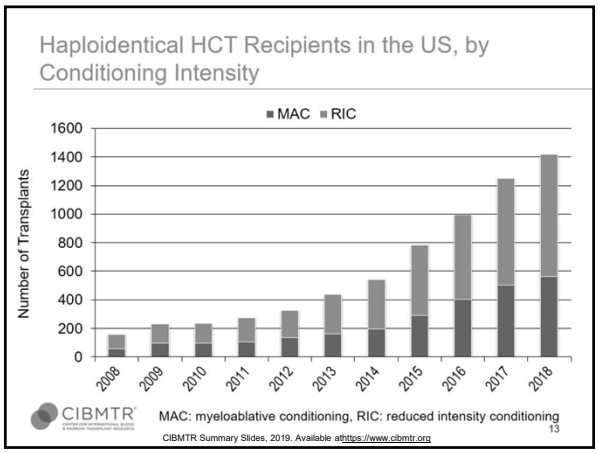
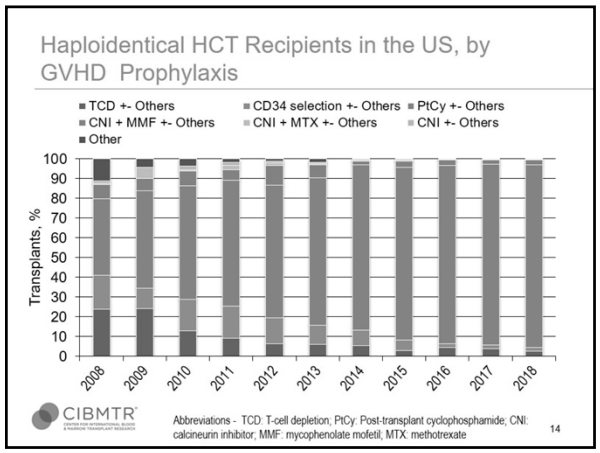
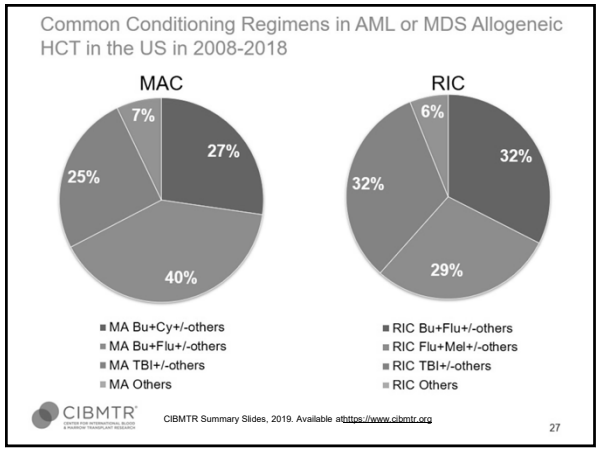




Lung Manifestations of CGVHD

- Bronchiolitis obliterans (BO) is a ***diagnostic*** feature:
  - Early BO may be asymptomatic
  - Advanced BO may lead to pneumo-thorax / mediastinum
  - Must exclude infection
- Restrictive PFT abnormalities may be related to:
  - Chest wall sclerosis
  - Myopathy from steroids or other causes
  - Cryptogenic organizing pneumonia (COP)
- COP is a **common feature *not specific to GVHD***
  - historically has usually required a lung biopsy to be sure



Transplant Preparative Regimens: Radiation

- Total-Body Irradiation
  - Dose: nonmyeloablative 200-400 cGy; Ablative 1200-1400cGy
  - Careful planning if prior involved field RT;
  - Toxicity: nausea, erythema, inflammation of parotid gland, growth failure; hypothyroidism; cataracts, infertility, MDS/leukemia; lung with diffuse alveolar hemorrhage (fractionation/shielding reduce DAH);
- Radioimmunotherapy:
  - Antibody therapy targeted to tumor and spares general organ toxicity;
  - Antibodies: ie. anti-CD45 + I^{131} (expression on leukemia cells) and anti-CD20 B1 antibody (Tositumomab) for B-cell NHL
  - Usually combined with other treatment of varying degrees
  - Research efforts to enhance targeting and eliminate non-specific binding (toxicity).

CMV in BMT- Era Before Pre-emptive Therapy

- Seropositive recipients:
  - 35-40% develop disease
- Seronegative recipients with a seropositive donor
  - 10% develop disease
- Seropositive autograft recipients
  - 5-7% develop disease
- Seronegative autograft recipients or seronegative recipients/seronegative donor
  - < 3% develop disease
- Autologous patients with CD34-selected autologous PBSC transplants
  - > 20% develop disease.
- CMV exhibits immunosuppressive effect.

Boechk M ASH Ed, 2011

Iron Overload

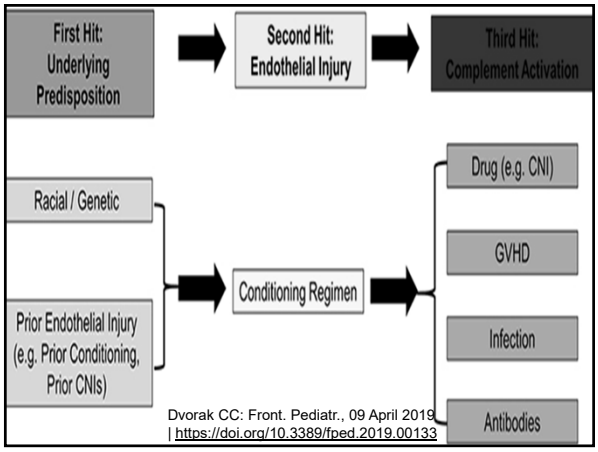
- Patients with aplastic anemia, MDS, or thalassemia may have hepatic iron overload.
- In heavy iron overload (defined by MRI), effective pre-transplant chelation therapy improves survival.
- Excess tissue iron does not appear to increase the toxicity of the conditioning regimen.
- Heavy iron overload has been associated with liver function abnormalities after transplant.

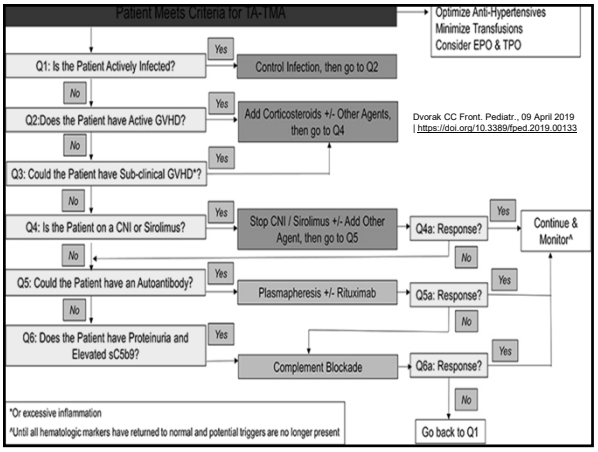
GB McDonald M.D; Hepatology, 51: 1450–1460. 2010

Viral Hepatitis in Allogeneic HCT Donors

- Transmission of B and C viruses possible from infected donors.
- Antiviral drugs will reduce viral load prior to procurement of donor cells.
- Viruses may persist in donor cells despite clearance from serum.
- All recipients of cells from hepatitis B surface antigen (HBsAg)-positive donors should receive antiviral prophylaxis.
- HBsAg-negative, anti-hepatitis B core (HBc)-positive donors are viremic in fewer than 5% of cases and can be used as donors if their serum and peripheral blood stem cells are HBV DNA-negative.
- HBcAb false + which is why rely on PCR testing
- A donor who is naturally anti-HBs-positive is the preferred donor if the recipient is HBsAg-positive or anti-HBc-positive, as adoptive transfer of immunity can effect clearance of HBV from the recipient.
- Treatment of an HCV RNA+ donor pre-transplant may decrease likelihood of transmission.
- If virus is transmitted, the acute phase of HCV infection may cause elevated liver enzymes at 2-3 months post-HCT, after recovery of T cell function.
- Severe hepatitis is rare and the outcome of HCV-infected transplant survivors over 10 years of follow-up is no different than in survivors without HCV infection.

GB McDonald M.D; Hepatology, 51: 1450–1460. 2010





Bronchiolitis Obliterans Syndrome

BOS FAST FACTS

- Affects 3-6% all allo-HCT, 14% of those with chronic GVHD
- Other risk factors:
  - Low IgG levels
  - Respiratory viral infection
  - FEV1 decline @ d100
  - Conditioning regimen
- 2 year survival ~70%; 5-year ~ 40%
- Airflow decline/obstruction is generally irreversible due to obliterative bronchiolitis lesion
- Treatment includes inhaled corticosteroids with bronchodilators, azithromycin, and montelukast, +/- prednisone
- Patients who progress may require lung transplantation

2014 NIH Diagnostic Criteria

(Requires Pulmonary Function Testing)

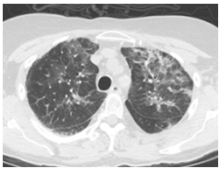
1) **Evidence of Airflow Obstruction**
   - $FEV_1/VC < 0.7$ or fifth percentile of predicted
2) **Evidence of Airflow Decline**
   - FEV_1 <75% predicted (no bronchodilator response)
   - >/= 10% decline from baseline or within 2 years
3) **Absence of respiratory tract infection**
4) **Evidence of supportive findings**
   - By high resolution chest CT: air trapping, small airway thickening, or bronchiectasis by chest CT
   - By PFTs: Elevated Residual Volume (RV) or elevated RV/TLC

- **Only 1-3 need to be met if patient has <u>chronic GVHD</u> in another organ**
- **Lung biopsy required if no other cGVHD present for purposes of clinical trial**

Other Late Noninfectious Lung Disease

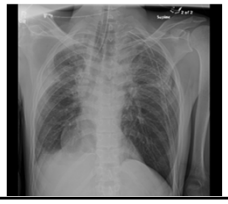
Organizing Pneumonia

- Moderate association with chronic GVHD
- May look like infectious pneumonia
- Generally responds to prednisone but a small number progress to fibrosis



Pleuropulmonary Fibroelastosis (PPFE)

- Rare fibrotic disease involving upper lung zones
- Progressive restrictive physiology
- Poor prognosis

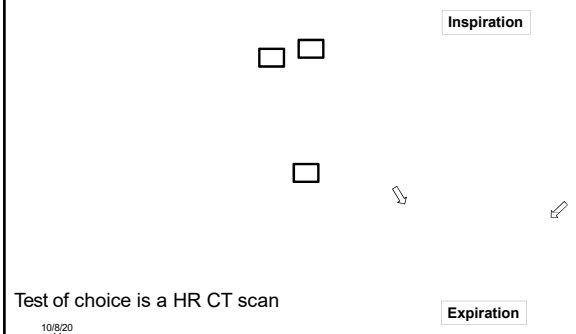


Using Azithromycin for Lung Disease in HCT: Pros and Cons

PROS
- May potentially reduce infectious exacerbations
- Broad experience in other chronic lung conditions
- Generally well tolerated

CONS
- Risk of relapse early post-HCT when used for prophylaxis
  - *Bergeron et al, JAMA 2018*
- Risk of subsequent malignancies when given long-term for BOS
  - *Cheng et al, BBMT 2020*
- Associated with arrhythmias
- May alter microbiome and reduce tumor surveillance
- No reported effect on lung function

Bronchiolitis Obliterans



Test of choice is a HR CT scan

10/8/20
14

Cryptogenic Organizing Pneumonia

10/8/20
14

Cancer Screening Recommendations: Special Considerations after HCT

	Risk Factors	Screening
Breast	Chest radiation and/or TBI (if dose ≥20Gy)	Yearly mammograms and MRI starting beginning 8 yrs after XRT or age 25 (whichever occurs last)
Lung	BU/CY conditioning and older age at HCT and history of smoking	Not determined. Consider low dose chest CT
Oral	History of cGVHD, Fanconi Anemia	Annual oral exam
Skin	Young age at HCT, XRT, aGVHD, cGVHD	Annual Skin exam
Thyroid	Young age at HCT, TBI, males, cGVHD	Annual clinical thyroid exam

Multiple Sclerosis: Randomized Controlled Trial Non-myeloablative transplant vs. conventional tx

- 110 randomized patients
- Disease progression occurred in 3 patients in the HSCT group and 34 patients in the DMT group.
- Median time to progression could not be calculated in the HSCT group because of too few events; it was 24 months (interquartile range, 18-48 months) in the DMT group (hazard ratio, 0.07; 95% CI, 0.02-0.24; $P < .001$).
- During the first year, mean EDSS scores decreased (improved) from 3.38 to 2.36 in the HSCT group and increased (worsened) from 3.31 to 3.98 in the DMT group (between-group mean difference, −1.7; 95% CI, −2.03 to −1.29; $P < .001$).
- There were no deaths and no patients who received HSCT developed nonhematopoietic grade 4 toxicities (such as myocardial infarction, sepsis, or other disabling or potential life-threatening events).

Burt RK et al: JAMA. 2019;321(2):165-174.

Additional (Challenging) Cases:

Case 1:

A 54-year-old white male in good overall clinical condition was scheduled for allogeneic BMT to treat high-risk acute myeloid leukemia in first complete remission. Since he lacked a suitable HLA-matched sibling, a URD search was initiated and the patient was typed at high resolution for HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 (to left of red bar). To further define the search immunogenicity/T cell epitope (1- high immunogenicity, 2 intermediates, 3 low immunogenicity) and SNP expression genes (A=low expressor, G=high expressor) were assessed (to the right of the red bar).
Understanding that HLA DPB1 is often mismatched in donor searches that otherwise show identity, and given the patient's clinical condition with high risk for relapse, which donor would you select?

Note the following: Donor 4 is mismatched at one of the HLA-A loci as well as both loci at HLA DP. ID = allele(s) not shown but identical with donor. Bold (**A** or **G**) connotates mismatch.

	Age	HLA A	HLA B	HLA C	HLA DRB1		HLA DQ B1	HLA DP B1	T cell epitope	SNP Proxy	HLA allele matching
Patient	60	ID	ID	ID	ID		ID	ID		A/A	
Donor 1	52	ID	ID	ID	ID		ID	ID	Permissive	A/A	12/12
Donor 2	35	ID	ID	ID	ID		ID	02:01 ID	Permissive	A/A	11/12
Donor 3	35	ID	ID	ID	ID		ID	02:01 03:01	Non-permissive	A/G	10/12
Donor 4	22	02:01 ID	ID	ID	ID		ID	14:01 09:01	Non-permissive	G/G	9/12

Select the preferred answer.

- Donor 1
- Donor 2
- Donor 3
- Donor 4
- None of the above.

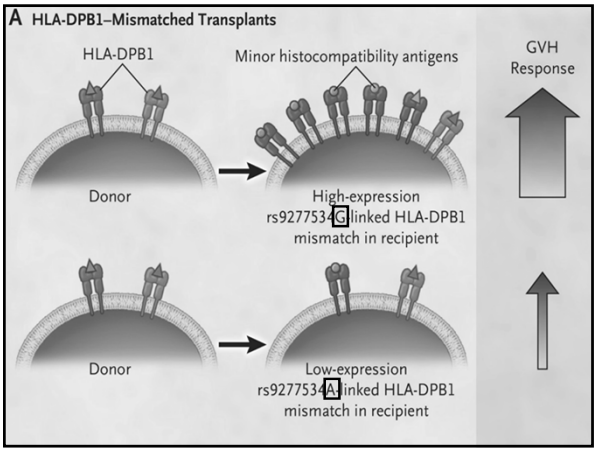
- Katharina Fleischhauer Hematology Am Soc Hematol Educ Program (2019) 2019 (1): 532–538. https://doi.org/10.1182/hematology.2019000057

This case illustrates a standard URD selection workflow for patients with several 8/8 URD donors. At the time of medical indication for an unrelated HCT, high-resolution typing of the patient is immediately performed for all 6 HLA loci (to the left of the red bar). Several well-matched URD can readily be identified for this patient of white European descent. The search focuses on donors with high-resolution 6 locus HLA typing already available to avoid the need for time-consuming complementary typing of the donors. The 8/8 URD (donors 1,2,3) are preferred over the 7/8 donor despite the younger age of the latter (donor 4), because the effect of donor age is secondary to HLA-A, -B, -C, -DRB1 matching according to NMDP guidelines. Younger donors are associated with better survival. Donor 1 is undesirable compared to other choices due to age of 52 which is nearly two decades older than the younger donors. This may result in a difference of up to 6 percent in diminished survival. The next youngest donors among the 8/8 HLA matches are donors 2 and 3 who happen to be equal in age.

The next focus is functional matching for HLA-DPB1 which is often mismatched. Given that the transplantation indication is high-risk acute myeloid leukemia, a donor with an HLA-DPB1 mismatch is preferred because HLA-DPB1 disparity has been shown to reduce the risk of relapse. To keep the risk of severe GVHD limited, the donor with functional HLA-DPB1 mismatch should be T-cell epitope (TCE) permissive and low risk (low expression according to the SNP. One can use (https://www.ebi. ac.uk/ipd/imgt/hla/dpb.html) for T-cell receptor epitope scoring (refer to tables below). The limited risk of acute GVHD potentially experienced by the patient is likely reflective of limited T-cell alloreactivity, possibly helpful to eradicate residual leukemia cells if present after conditioning. All these factors favored the long-term positive outcome for this patient if donor 2 is used. In large studies other factors such as CMV status, gender, and Red cell blood type were not associated with a discernable difference in outcome. Some studies suggest that for "CMV Matching" should be as follows: CMV+ patient should receive CMV+ donor particularly for ablative regimens while CMV- patient should receive CMV- donor if possible.

a

DPB1*	TCE group	Immunogenicity
09:01, 10:01, 17:01	1	
03:01, 14:01, 45:01	2	
01:01, 02:01, 04:01 + others	3	



Answer to above question: B

Case 2:

A 22-year-old male was referred for hematopoietic stem cell transplantation for myelodysplastic syndrome characterized by monosomy 7 (IPSS-R high risk). The patient's 24-year-old sister is reportedly healthy apart from recurrent herpes stomatitis. She is a 10 of 10 HLA allele-match to the patient. He has no other siblings. His mother is 44 years of age and has mild thrombocytopenia. His father is 51 years of age and is healthy.

- Which of the following studies is most likely to establish a diagnosis?
- a. Bone marrow aspirate of donor
- b. Cytogenetics of donor
- c. Genetic testing of blood/marrow in donor
- d. Genetic testing of cultured skin fibroblasts in patient
- e. None of the above

This patient presents with a high-risk MDS characterized by monosomy 7 at a young age (22 years-old). Additionally, his family history is notable for a mother with thrombocytopenia and a sister with recurrent herpes stomatitis. These findings suggest GATA2 deficiency. Inherited and de novo heterozygous germline mutations in the hematopoietic transcription factor, GATA2, cause this pleotropic autosomal dominant genetic disorder characterized by cellular immunodeficiency (complicated frequently by viral and disseminated nontuberculous mycobacterial infections) and a high risk for myeloid malignancy. Hematopoietic stem cell transplantation offers the only cure for MDS/AML and for reconstitution of the immune system in this syndrome. GATA2 deficiency underlies ~ 7% of pediatric and adolescent myelodysplastic syndrome patients and is particularly enriched among those whose disease is characterized by monosomy 7 (37%, all ages, 72% of adolescents).

The broad use of next-generation sequencing technologies in research and clinical care has led to recognition of an ever-expanding number of inherited hematologic malignancy predisposition syndromes. These germline predisposition syndromes are now included in The World Health Organization's Classification of Myeloid Neoplasms and Acute Leukemia. The European LeukemiaNet Guidelines on the diagnosis and management of acute myeloid leukemia[4], and The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology on MDS.

Genetic screening to evaluate for an underlying genetic cause among individuals presenting with myeloid malignancies has emerged as a very clinically relevant need. This is particularly important in the context of hematopoietic stem cell transplantation (HSCT). In addition to informing the timing and indication for HSCT, accurate distinction of these entities informs HSCT approaches. Many inherited hematologic malignancy predisposition syndromes are associated with excessive transplant regimen-related toxicities such as prolonged cytopenias, pulmonary complications, and severe mucositis, and may require specialized reduced intensity conditioning regimens for optimal outcomes. These patients may also face altered post-HSCT long-term consequences. For example, post-HSCT Fanconi anemia (FA) patients demonstrate a striking increase in the cumulative incidence of cancer and their cancers present at a younger age compared to non-transplanted FA patients. Additionally, the careful evaluation of a related stem cell donor is critical in the context of a familial genetic disease; siblings may carry the same mutation as the proband and so screening of potential sibling donors for the genetic defect may be indicated to avoid transplantation of the same genetic mutation. Transplantation using a GATA2 mutation-positive seemingly "healthy" donor has resulted in donor-derived posttransplant MDS/AML and fatal infection due to impaired immune reconstitution.

Apart from the implications of diagnosing these syndromes on transplant planning, recognition of these syndromes more broadly informs surveillance for disease-specific extra hematopoietic complications and family counseling.

In this patient, genetic testing is indicated and testing on DNA derived from a nonhematopoietic source such as cultured skin fibroblasts is recommended in order to distinguish a constitutional (i.e. germline) mutation from a somatic mutation present in the patient's MDS (i.e., cancer). Importantly, the absence of characteristic clinical features or suggestive family history does not exclude the possibility of an underlying genetic syndrome due to phenotypic heterogeneity, which reflects overlapping features between inherited syndromes and variable expressivity within a syndrome. Also, a concerning family history of an inherited disorder is not expected in patients in whom the disease-causing mutation occurred de novo. Given these complexities, single-gene testing for diagnosis may lack adequate sensitivity in the initial evaluation of such patients.

Answer: d

39

Myeloproliferative Neoplasms

Ayalew A. Tefferi, MD

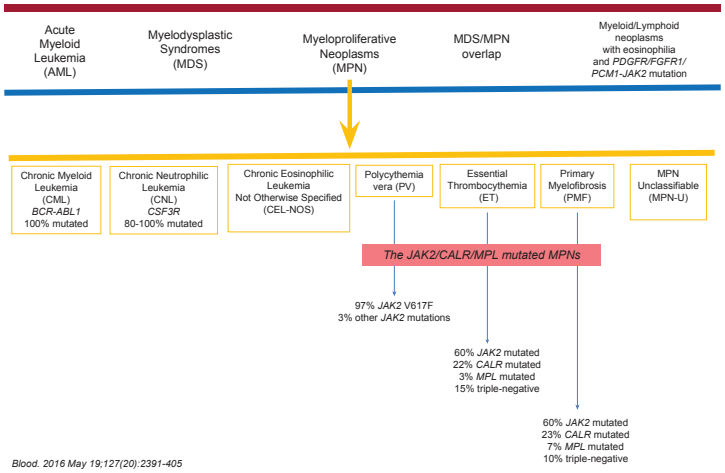
August 16, 2020

Myeloproliferative Neoplasms

Ayalew Tefferi, MD
Professor of Medicine
Mayo Clinic, Division of Hematology
Rochester, MN

I have nothing to declare

2016 WHO Classification of Myeloid Malignancies



Blood. 2016 May 19;127(20):2391-405

Objectives

- Molecular pathogenesis
- Practical diagnostic algorithms
- Genetic prognostication
- Treatment algorithms
- Overview of mastocytosis and eosinophilic disorders

Remarkable discoveries
JAK2V617F

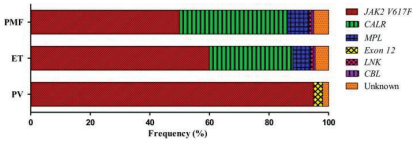
William Vainchenker

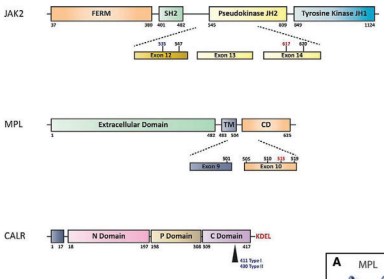
Nature 2005
NEJM 2005
Lancet 2005
Cancer Cell 2005

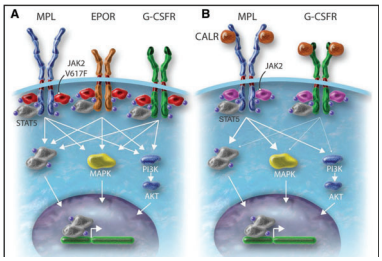
Practice-changing observations

Tiziano Barbui

NEJM 1995 (HU in high-risk ET)
NEJM 2004 (low-dose ASA in PV)
NEJM 2013 (aggressive phlebotomy in PV)







Blood 2017;129:667
J Cell Mol Med 2017;21:1660

Targeted deep sequencing

PV

	Total #	% Total
JAK2	130	98%
TET2	29	22%
ASXL1	16	12%
SH2B3	12	9%
CEBPA	8	6%
ZRSR2	6	5%
SF3B1	4	3%
CSF3R	4	3%
KIT	4	3%
SRSF2	4	3%
IDH2	3	2%
DNMT3A	3	2%
SUZ12	2	2%
SETBP1	2	2%
RUNX1	2	2%
CBL	1	1%
TP53	1	1%
FLT3	1	1%
CALR	0	0%
MPL	0	0%
EZH2	0	0%
NRAS	0	0%
NPM1	0	0%
IDH1	0	0%
U2AF1	0	0%
PTPN1	0	0%
IKZF1	0	0%

ET

	Total #	% Total
JAK2	95	52%
CALR	47	26%
TET2	30	16%
ASXL1	20	11%
DNMT3A	11	6%
SF3B1	9	5%
CEBPA	8	4%
MPL	7	4%
SH2B3	6	3%
ZRSR2	6	3%
CSF3R	5	3%
EZH2	5	3%
TP53	4	2%
SRSF2	3	2%
SETBP1	3	2%
RUNX1	3	2%
PTPN1	3	2%
KIT	3	2%
U2AF1	2	1%
CBL	2	1%
FLT3	2	1%
IDH2	1	1%
NRAS	1	1%
NPM1	0	0%
SUZ12	0	0%
IDH1	0	0%
IKZF1	0	0%

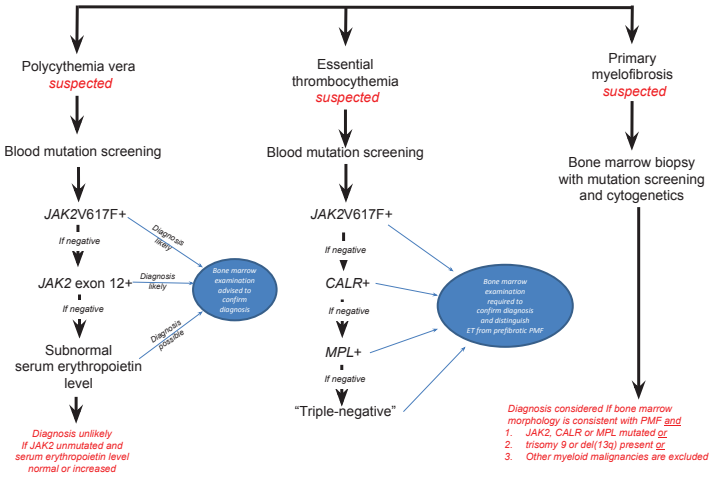
MF

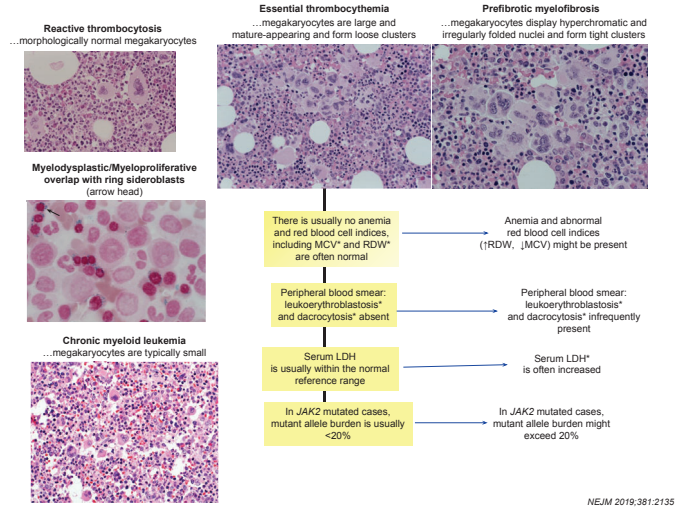
	Total #	% Total
JAK2	111	61%
ASXL1	65	36%
CALR	40	22%
TET2	33	18%
SRSF2	32	18%
U2AF1	30	16%
ZRSR2	19	10%
SF3B1	18	10%
DNMT3A	17	9%
CEBPA	16	9%
MPL	11	6%
SH2B3	11	6%
CBL	9	5%
SETBP1	8	4%
RUNX1	8	4%
CSF3R	7	4%
NRAS	7	4%
IDH2	6	3%
SUZ12	4	2%
PTPN11	3	2%
IDH1	2	1%
KIT	2	1%
TP53	2	1%
EZH2	1	1%
FLT3	0	0%
IKZF1	0	0%
NPM1	0	0%

Blood Advances 2016 1:21. Blood Advances 2016 1:105. Blood Advances 2018 2:370

Practical algorithm for diagnosis of myeloproliferative neoplasm

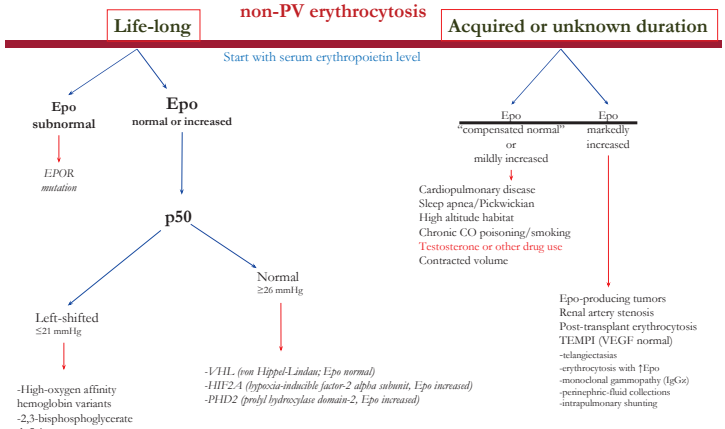
JAMA Oncology 2015



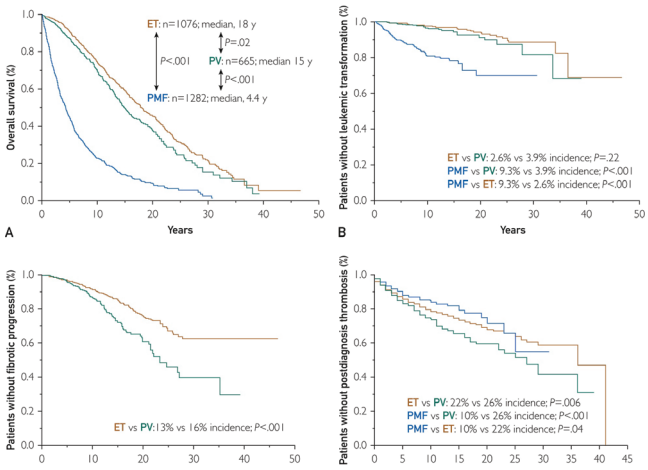


NEJM 2019;381:2135

Practical approach for non-PV erythrocytosis

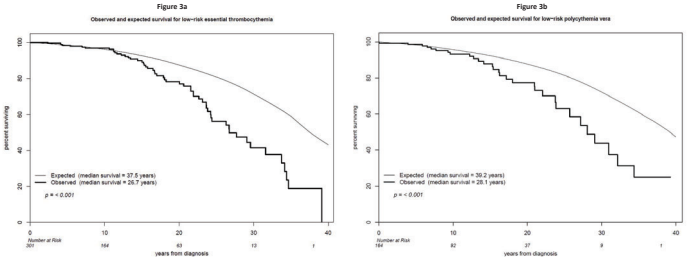


Overall (A), leukemia-free (B), myelofibrosis-free (C), and thrombosis-free (D) survival for 3,023 Mayo Clinic patients with myeloproliferative neoplasms (ET; PMF; PV) seen between 1967 and 2017. Median f/u = 20 years



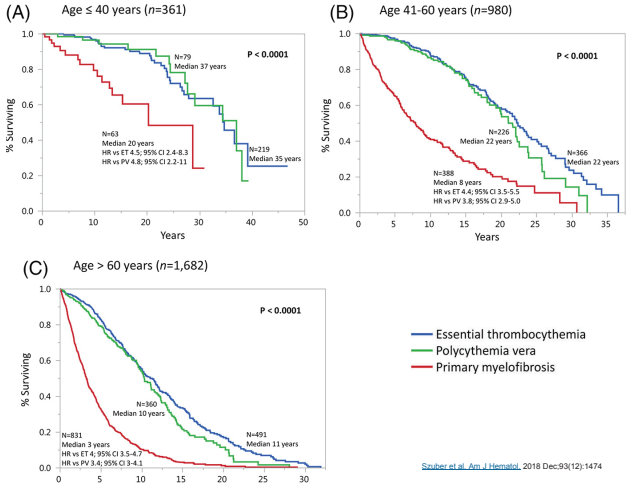
Szuber et al. Mayo Clin Proc. 2019 Apr;94(4):599-610.

Figure 3: Comparison of survival data for low risk essential thrombocythemia (figure 3a) and low risk polycythemia vera (figure 3b) with age- and sex-matched general population from Olmsted county, Minnesota, USA



Szuber et al. Mayo Clin Proc 2019 Apr;94(4):599-610.

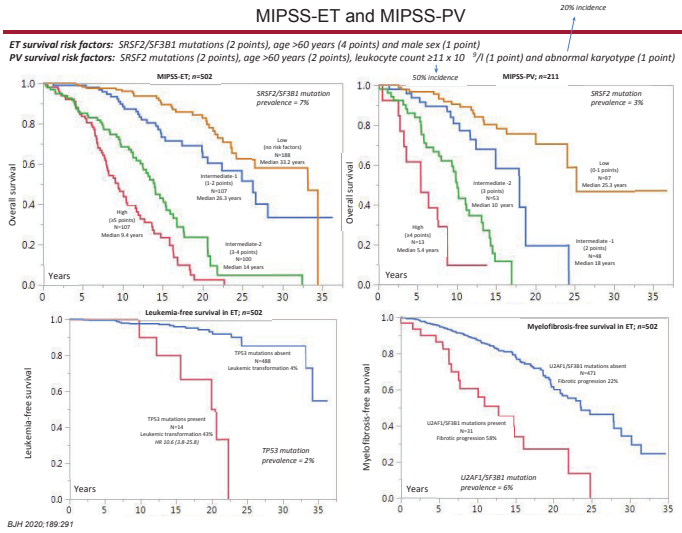
Age and survival in myeloproliferative neoplasms



Szuber et al. Am J Hematol. 2018 Dec;93(12):1474

MIPSS-ET and MIPSS-PV

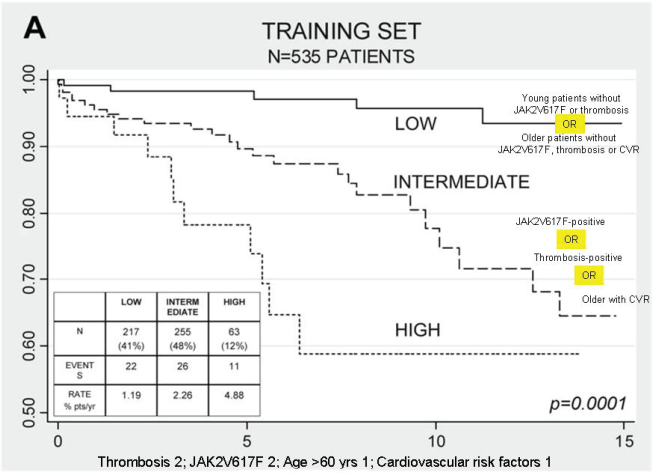
ET survival risk factors: *SRSF2/SF3B1 mutations (2 points), age >60 years (4 points) and male sex (1 point)*
PV survival risk factors: *SRSF2 mutations (2 points), age >60 years (2 points), leukocyte count ≥11 x 10 ^{9}/l (1 point) and abnormal karyotype (1 point)*



BJH 2020;189:291

Thrombosis-free survival curves.

Barbui T et al. Blood 2012;120:5128-5133

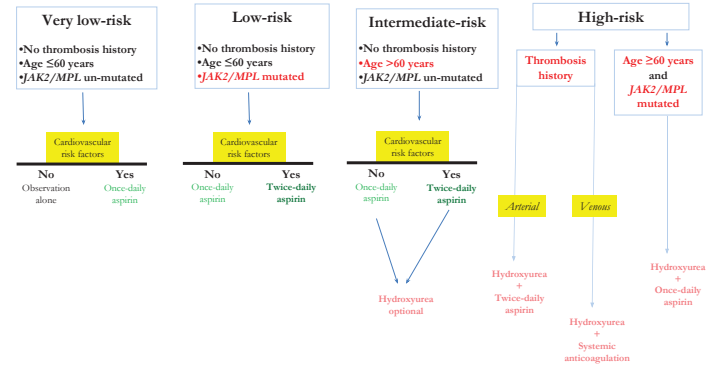


	LOW	INTERMEDIATE	HIGH
N	217 (41%)	255 (48%)	63 (12%)
EVENTS	22	26	11
RATE % pts/yr	1.19	2.26	4.88

Low risk implies a score = 0-1; intermediate risk, score = 2; and high risk, score ≥ 3

Current Treatment Algorithm in Essential Thrombocythemia

Blood Cancer J. 2018 Jan 10;8(1):2



Additional points:
-Must consider the possibility of AvWS before instituting aspirin therapy, especially in the presence of extreme thrombocytosis
-Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN- α or busulfan

Polycythemia Vera

Risk factors for survival

- Age >60 years
- Presence of SRSF2 mutations
- Leukocytosis
- Abnormal karyotype

Risk factors for thrombosis

- Age >60 years
- History of thrombosis

Current Treatment Algorithm in Polycythemia Vera

Blood Cancer J. 2018 Jan 10;8(1):3

Phlebotomy to hematocrit <45% in both male and female patients
+
Once-daily baby aspirin (81 mg)

Low-risk Disease
•No history of thrombosis
•Age ≤60 years

Consider twice-daily aspirin in the presence of:
- *Cardiovascular risk factors*
- *Hypertension*
- *Leukocytosis*
- *Persistent microvascular symptoms*

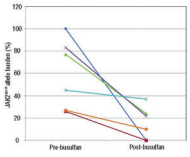
High-risk disease
•History of thrombosis
or
•Age >60 years

Hydroxyurea (500 mg BID starting dose)

- Hydroxyurea intolerant or resistant
  - Pegylated IFN-α (Age <65 years)
  - Busulfan (Age ≥65 years)
  - Ruxolitinib (If all the above fails)
- *Arterial thrombosis history* → Consider twice-daily aspirin
- *Venous thrombosis history* → Add systemic anticoagulation

Additional points in the treatment of essential thrombocythemia and polycythemia vera

1. What if you can't use hydroxyurea
   i. Interferon alpha
   (Blood 2013; CHR 76% in PV, 77% in ET; CMR 18% in PV and 17% in ET)
   i. Busulfan
   (Ann Hematol 2014; CHR in HU-refractory PV or ET was 83%; Haematologica 2013; CMR in 2 (33%) of 6 PV patients)
   i. Anagrelide
   (Not recommended because of its association with disease progression into myelofibrosis and increased thrombosis risk in ET phase-3 study; NEJM 2005)
   i. Ruxolitinib
   (Vannucchi et al. NEJM 2015; randomized study in HU-refractory PV with ruxo vs standard therapy; 59% of patients on standard therapy received HU??? 21% of ruxo treated patients achieved both hematocrit control and 35% reduction in spleen volume; 60% hematocrit control; 49% symptoms control; CHR 24%; No CMR reported)

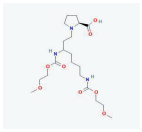


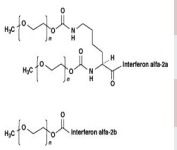
3. What about treatment during pregnancy?
   i. Low-risk…ASA only
   ii. High-risk…IFN alpha

4. What about treatment of pruritus?….paroxetine, IFN-alpha, UVB, ruxolitinib

Background: peg-interferon (eg, pegasys; peg-interferon alfa-2a) induces complete hematologic and molecular response rates of 76–95 and 18%, respectively

Blood. 2013;122:893; *Blood.* 2008;112:3065



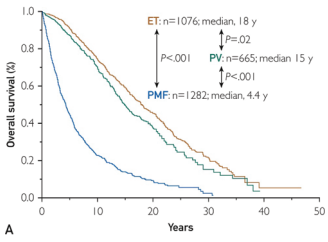


Ropeginterferon (long-acting mono-pegylated) α-2b in PV
Approved by EMA February 2019 for PV without splenomegaly

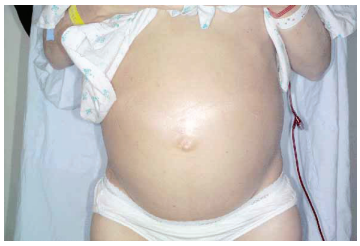
Month 48	Ropeginterferon n = 95	BAT n = 76 97% hydroxyurea	*P* value
Complete hematological response	45/94 (48%) *80% phlebotomy free*	27/76 (35.5%)	.06
Molecular response	63/94 (67%)	19/74 (25.7%)	< .0001
Complete molecular response	13/94 (14%) *Including 11 with CHR*	0%	
Incidence of thrombotic events	1.4% patient-year	1.2% patient-year	
Rate of pts with major thrombotic events	3.1%	3.1%	

Lancet Haematol. 2020 Mar;7(3):e196-e208.

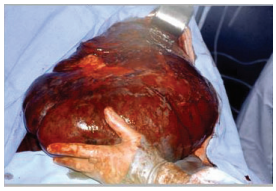
Disease complications in myelofibrosis



A



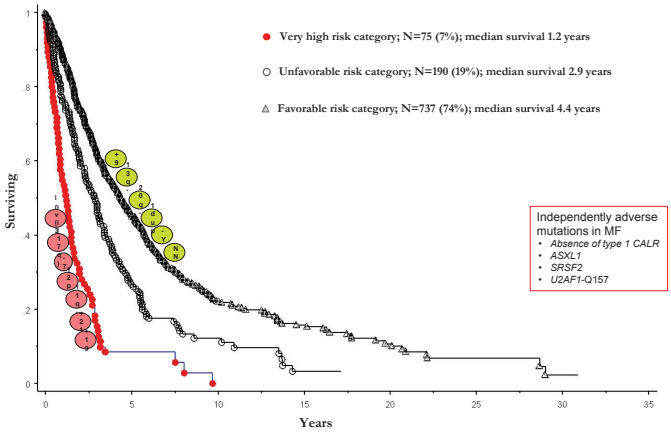
- Anemia
- Splenomegaly
- Constitutional symptoms
- Cachexia



Therapeutic options in myelofibrosis

- **Curative or with potential to improve survival**
  - ✔ Allogeneic hematopoietic cell transplant (allo-HCT)
- **Palliative**
  - ✔ Observation alone (watch-and-wait)
  - ✔ Treatment for anemia
    - Thalidomide ± prednisone
    - Androgens
    - Danazol
    - ESAs
    - Lenalidomide/pomalidomide
  - ✔ Treatment for symptomatic splenomegaly
    - Hydroxyurea
    - JAK2 inhibitors
    - Splenectomy
  - ✔ Treatment for constitutional symptoms
    - JAK2 inhibitors
  - ✔ Involved field radiotherapy for extra-medullary hematopoiesis
  - ✔ Experimental therapy

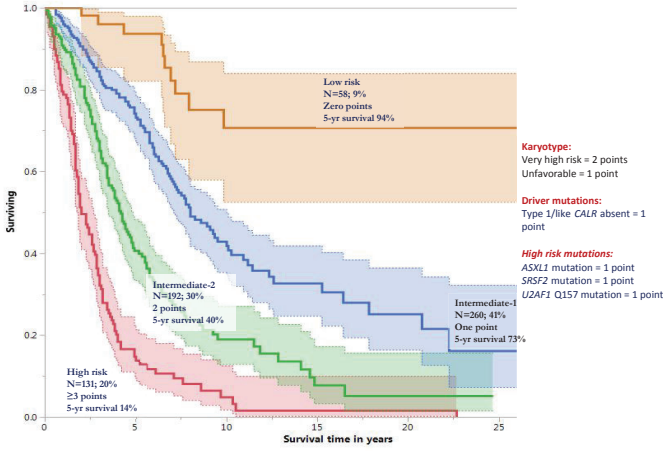
Survival of 1,002 patients with primary myelofibrosis stratified by the revised three-tiered cytogenetic risk model



Leukemia. 2018;32:1189

GIPSS

genetically-inspired prognostic scoring system-stratified survival data in 641 patients with primary myelofibrosis



Karyotype:
Very high risk = 2 points
Unfavorable = 1 point

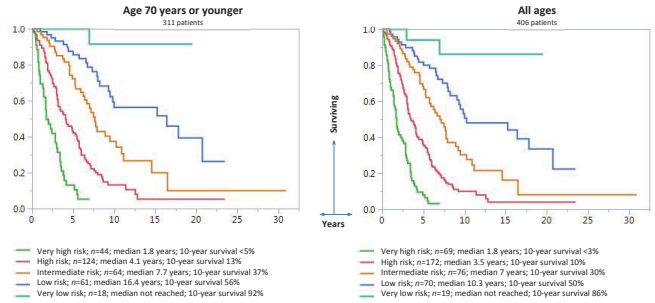
Driver mutations:
Type 1/like *CALR* absent = 1 point

High risk mutations:
ASXL1 mutation = 1 point
SRSF2 mutation = 1 point
U2AF1 Q157 mutation = 1 point

Leukemia. 2018;32:1631

Survival data on Mayo Clinic patients with primary myelofibrosis stratified by MIPSS70+ *version 2.0*

Risk categories: very high risk ≥9 points; high risk 5-8 points; intermediate risk 3-4 points; low risk 1-2 points; and very low risk zero points



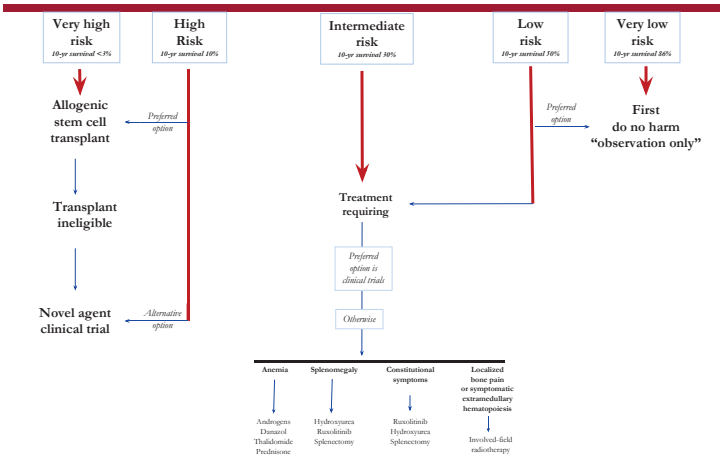
Very high risk karyotype	4 points
Unfavorable karyotype	3 points
≥2 HMR mutations	3 points
One HMR mutation	2 points
Type 1/like CALR mutation absent	2 points ✓
Constitutional symptoms	2 points ✓
Severe anemia	2 points
Moderate anemia	1 point
≥2% circulating blasts	1 point ✓

J Clin Oncol. 2018;36:1769

http://www.mipss70score.it/

Treatment Algorithm in Myelofibrosis

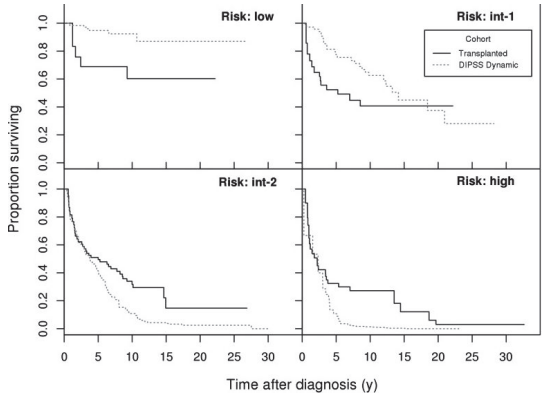
based on risk stratification according to MIPSS70+ version 2.0



Blood Cancer J. 2018 Jul 31;8(8):72.

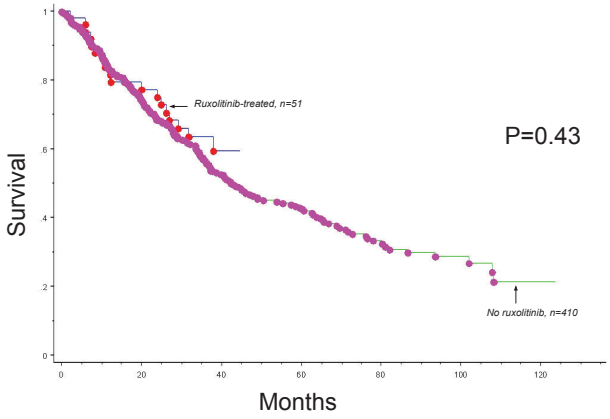
Impact of Allogeneic Stem Cell Transplantation on Survival of Patients Less Than 65 Years of Age With Primary Myelofibrosis

Stratified by DIPSS including 190 transplanted and 248 non-transplant patients



Blood. 2015 May 21;125(21):3347

Survival impact of ruxolitinib in myelofibrosis: Mayo Clinic study

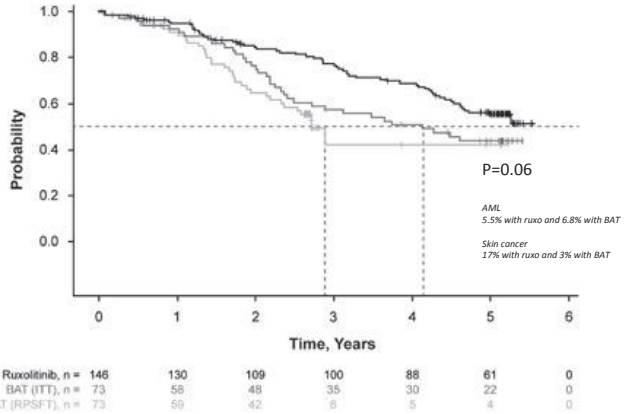


NEJM 2011:365;15

COMFORT-2 Ruxolitinib vs best available therapy (BAT) long-term follow-up

Median f/u 4.3 years

27% ruxo-randomized patients completed 5-year treatment

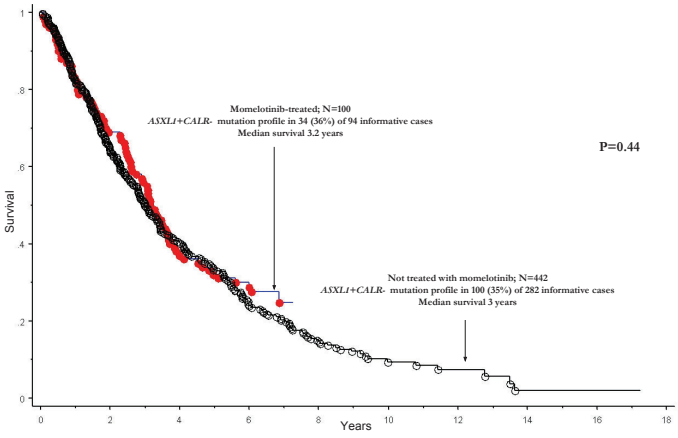


Leukemia (2016) 30, 1701

Momelotinib therapy in myelofibrosis 7-year follow-up

Comparison of survival between 100 momelotinib treated patients and 442 not receiving momelotinib

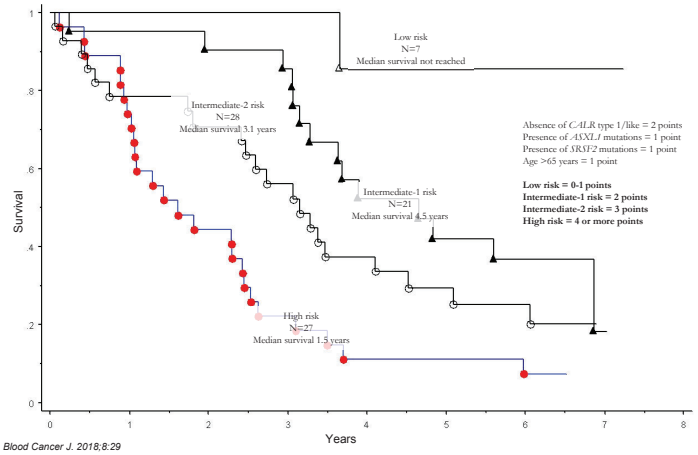
DIPSS-plus high or intermediate-2 risk disease only



Blood Cancer J. 2018;8:29

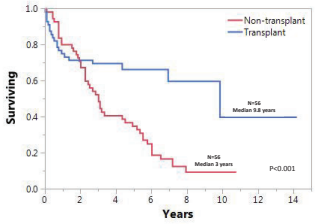
Momelotinib therapy in myelofibrosis 7-year follow-up

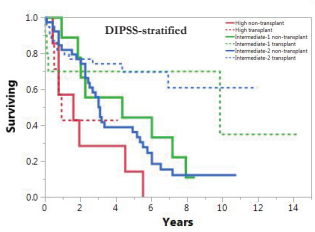
Survival of 83 molecularly-annotated patients from time of momelotinib study entry to last follow-up or death, and stratified by age and mutation profile

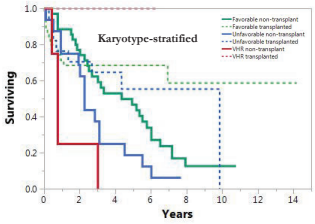


Blood Cancer J. 2018;8:29

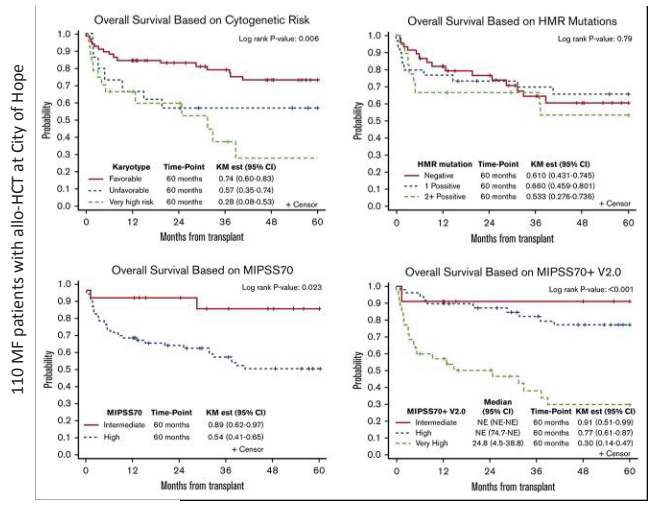
Transplant myelofibrosis (n=56) vs no transplant primary myelofibrosis (n=56), stringently matched for age, DIPSS and karyotype







Am J Hematol. 2018;93:649



Blood Adv. 2019 Jan 8; 3(1): 83–95.

Phase-3 tested JAK2 inhibitors in myelofibrosis

N Engl J Med. 2010 Sep 16;363(12):1117 (ruxolitinib phase-3)
JAMA Oncol. 2015 Aug;1(5):643 (fedratinib phase-3)
Leukemia. 2018 Apr;32(4):1035-1038 (momelotinib phase-2)
Blood. 2015 Apr 23;125(17):2649-55 (pacritinib phase-2)

2013 revised IWG-MRT response rates for 166 JAKi treated Mayo Clinic patients

	CR	PR	1-2-3 years discontinuation rates
Momelotinib (n=100)	0%	1%	31%-52%-71%
Ruxolitinib (n=51)	0%	0%	49%-71%-86%
Fedratinib (n=15)	0%	0%	20%-67%-80%

Leukemia 2014

	JAK targets	Other targets	Symp. resp.	Spleen resp.	Anemia resp.	Side effects
Ruxolitinib *FDA approved 11/16/2011*	JAK1 JAK2	TRK-B, ACK1 FAK, LCK RET	Yes	32-42% (MRI)	14%	↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections
Fedratinib (SAR302501) *FDA approved 8/16/2019*	JAK2	FLT3, RET, ACK1 JNK1	Yes	47% (MRI)	NR	↓Hgb/Plts Nausea/Diarrhea ↑LFTs/Lipase/amylase Encephalopathy
Pacritinib (SB1518) Phase-3 completed	JAK2	FLT3	Yes	37% (MRI)	NR	Diarrhea/Nausea
Momelotinib (CYT387) Phase-3 completed	JAK1 JAK2	PKD3, PKCμ CDK2, ROCK2 JNK1, TBK1 ALK-2	Yes	39% (PE)	53%	↓Plts 1st dose effect ↓BP/dizzy Neuropathy/Headache ↑LFTs/Lipase/Amylase

Ruxolitinib practice points

Indications
1. Marked splenomegaly that is symptomatic and resistant to hydroxyurea
2. Severe constitutional symptoms including pruritus, night sweats, fatigue and cachexia
3. Sometimes there is no other option, even in the presence of severe cytopenias

Short-term side effects
1. Anemia, including becoming transfusion-dependent
2. Thrombocytopenia

Long-term side effects
1. Immunosuppression
2. Opportunistic infections
3. Protracted myelosuppression

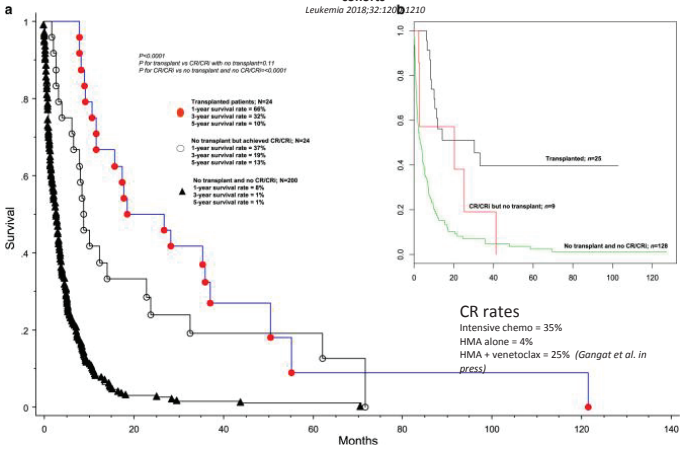
Special concerns
1. Might compromise future eligibility for clinical trials because of protracted myelosuppression
2. Effect lasts for an average of approximately one year; might be prudent to save it until HU fails
3. **BEWARE** of withdrawal symptoms that might include SIRS and overt and immediate relapse of splenomegaly/symptoms

Unresolved issues in myeloproliferative neoplasms

- Pre-transplant management of the spleen
  - No specific intervention
  - Splenectomy
  - Splenic irradiation
  - Ruxolitinib
- Palliative treatment options after ruxolitinib
  - First try to increase ruxolitinib dose
  - Splenectomy
  - Experimental therapy
  - Fedratinib (don't hold your breath)
- Management of splanchnic vein thrombosis
- Management of blast-phase disease

Blast phase myeloproliferative neoplasm: Mayo-AGIMM study of 410 patients from two separate cohorts

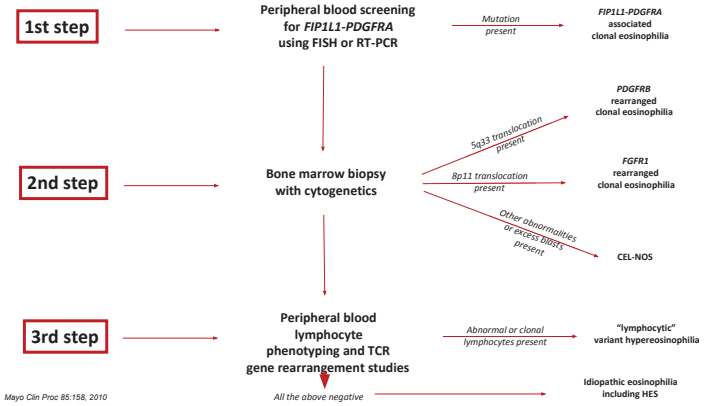
Leukemia 2018;32:1207-1210



CR rates
Intensive chemo = 35%
HMA alone = 4%
HMA + venetoclax = 25% *(Gangat et al. in press)*

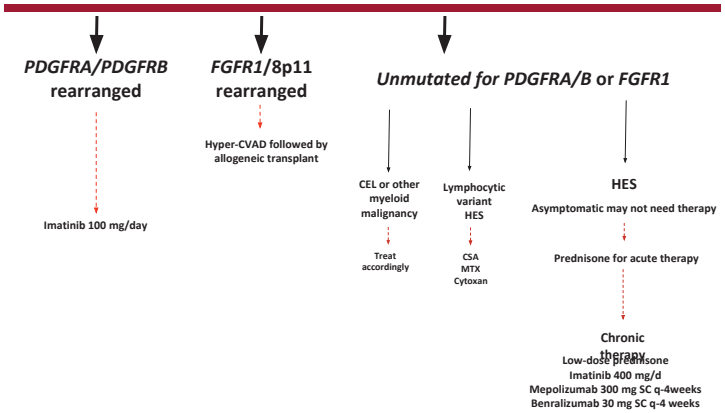
Primary eosinophilia

Diagnostic algorithm



Mayo Clin Proc 85:158, 2010

Management approach to HES or HES-like eosinophilic disorders



Hyper-eosinophilic syndrome/idiopathic eosinophilia

Prognostication

NGS revealed 11% harbored pathogenic mutation;
TET2=3, *ASXL1* =2, *KIT*=2, and *IDH2*, *JAK2*, *SF3B1 and TP53*=1 each.
15% harbored a variant of unknown significance;
TET2=8, *ASXL1*=2, *SETBP1*=2, and *CALR*, *CEBPA* and *CSF3R*=1 each.

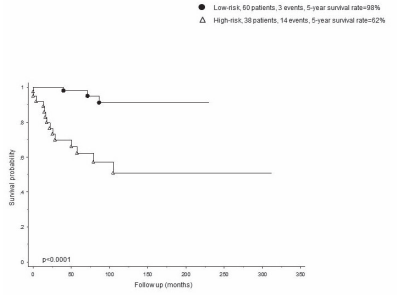
NO DIFFERENCE IN MUTATED VS NON-MUTATED IN PHENOTYPE
MUTATED PATIENTS HAD INFERIOR SURVIVAL IN UNIVARIATE ANALYSIS

98 Mayo Clinic patients with WHO-defined HES/IH (*Leukemia 2016;30:1924*)

Risk factors for survival:

Advanced age (2 points)
Hgb <10 g/dl (one point)
Cardiac involvement (one point)
Hepatosplenomegaly (3 points)

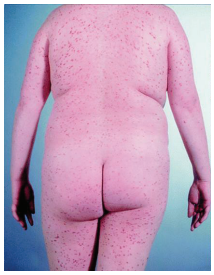
Low risk 0-1 points
High risk 2 or more points



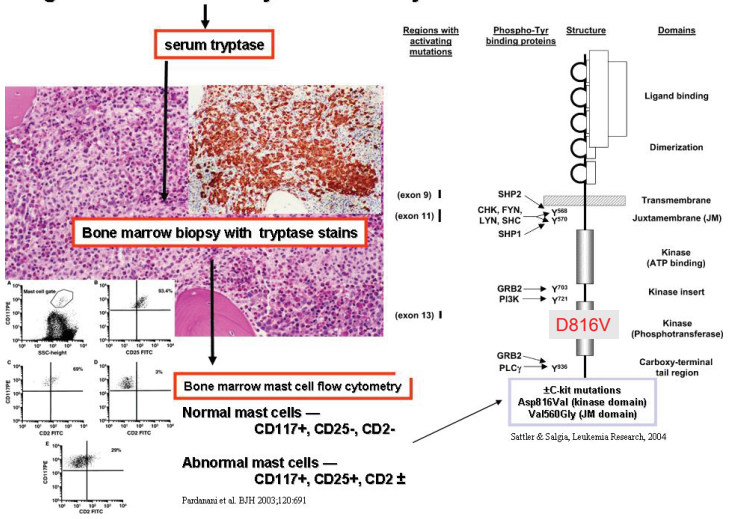
Mastocytosis

When should you suspect it?

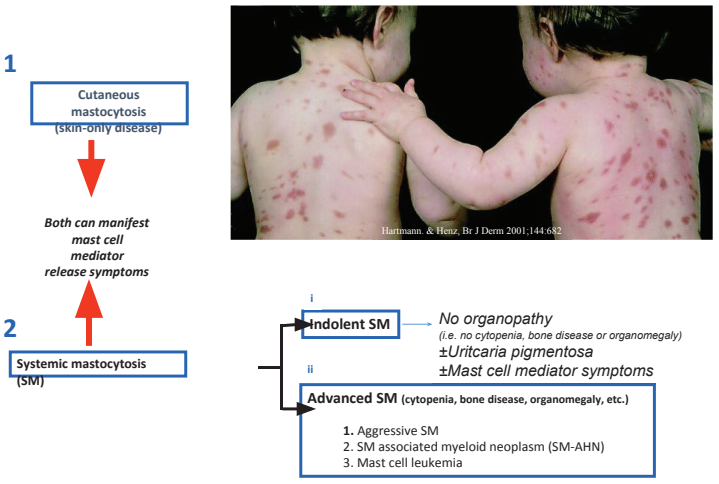
- Urticaria pigmentosa-like lesions
- Mast cell mediator symptoms
  - Anaphylactoid symptoms/dizziness
  - Diarrhea
  - Flushing/urticaria
- Osteopenia/unexplained fractures



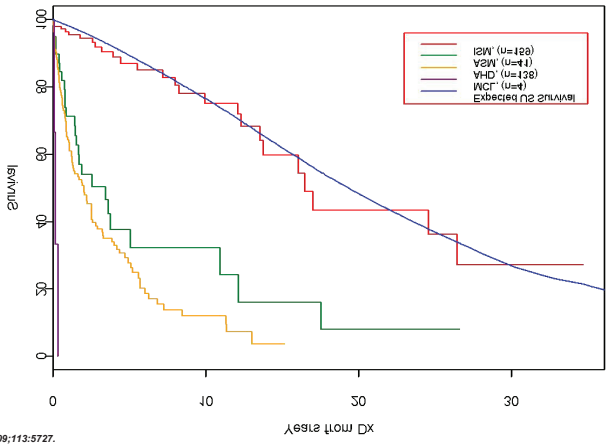
Diagnostic Evaluation in Systemic Mastocytosis



Practical classification of mast cell disease



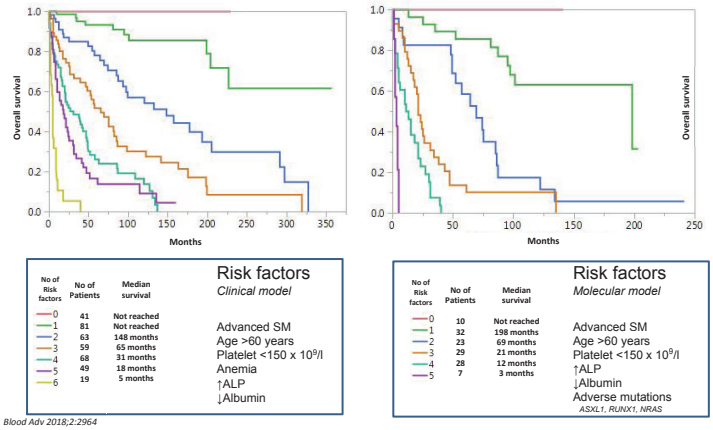
Survival for 342 systemic mastocytosis patients classified by disease type compared with the expected age and gender matched US Population's survival



Blood 2009;113:5727.

Figure 1a: A "clinical" risk model for systemic mastocytosis (N=380)

Figure 1b A "clinical-molecular" risk model for systemic mastocytosis (N=129)



Blood Adv 2018;2:2964

Systemic Mastocytosis Treatment

Indolent

H1 and H2 blockers
Leukotriene antagonist
Cromolyn
Phototherapy
Topical steroids

Cetrizine 5-10 mg QD
Fexofenadine 60 mg BID
Hydroxyzine 25 mg q 6 hours

Ranitidine 150 mg BID
Famotidine 10 mg BID
Cimetidine 400 mg BID

Montelukast 10 mg QD
Zafirlucast 20 mg BID

Sodium cromolyn 100-200 mg QID

Osteoporosis prevention
Alendronate 70 mg weekly
Risedronate 35 mg weekly
Pamidronate IV 90 mg q-4 weeks
Zolendronic acid 4 mg IV q 4 weeks

If this fails, try cladribine 5 mg/m2 2-hour infusion x 1-5 days every 4 to 12 weeks

Advanced

See next slide

Advanced Systemic Mastocytosis Treatment

Aggressive SM

Cladribine 5 mg/m2 2-hour infusion x 1-5 days every 4 to 12 weeks

OR 50%
CR 0%
MR 38%
PR 13%

Midostaurin 100 mg PO BID

OR 50%
CR 0%
MR 45%; PR 15%
Grade ¾ neutropenia 24%; thrombocytopenia 29%; anemia 41%
Nausea 79%; vomiting 66%
Diarrhea 54%; headache 23%

Mast cell leukemia

Avapritinib 300 mg PO QD

OR 77%
CR 8%
CRh 15%; PR 46%
Grade ¾ neutropenia 10%; thrombocytopenia 23%; anemia 29%
Cognitive impairment 19%; ICH 10%

Associated with another hematologic neoplasm (SM-AHN)

SM associated with lymphoid neoplasm

Symptoms attributed to SM

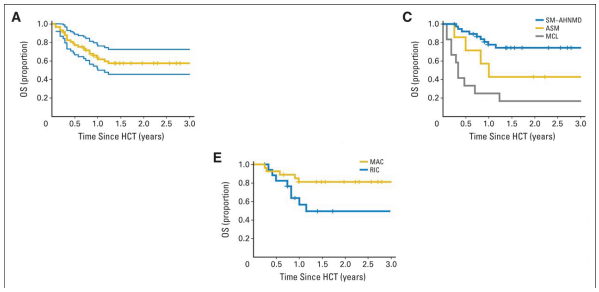
SM associated with myeloid neoplasm

Symptoms attributed to the myeloid neoplasm

Treat the myeloid neoplasm

Blood 2015;126:1009
NEJM 2016;374:2530
Blood 2020;135:1365

Allogeneic hematopoietic stem-cell transplantation (HCT) in 57 patients with advanced systemic mastocytosis (SM): 38 SM-AHNMD; 12 MCL and 7 aggressive SM



JCO 2014;32:3264

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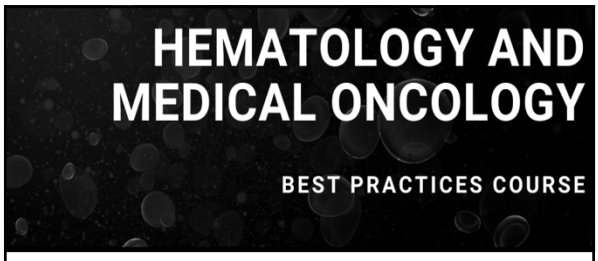
Pharmacology I

Edward Chu, MD

August 17, 2020



40 - Pharmacology I

Edward Chu, MD

Question 1

A 55-yo male with newly diagnosed stage IV colorectal cancer and widespread metastatic involvement of the liver and lungs has been started on FOLFIRI chemotherapy in combination with the anti-VEGF antibody bevacizumab. Within 4 days of receiving his first cycle of therapy, he begins to note increased oral discomfort with a number of new mouth sores, 6-7 loose stools per day, repeat CBC shows significant myelosuppression with neutropenia, and the patient's wife states that her husband's mental status appears to be markedly altered from his normal baseline.

Question 1

Which of the following enzymes is most likely altered in this patient?

a) **Dihydrofolate reductase**
b) **UDP glucuronyltransferase**
c) **Dihydropyrimidine dehydrogenase**
d) **Thymidylate synthase**
e) **Thiopurine methyltransferase**

Answer for Question 1

(C) Dihydropyrimidine dehydrogenase

This is a classic presentation of the DPD deficiency in which there is either partial or complete deficiency in dihydropyrimidine dehydrogenase (DPD). In this setting, patients present with severe toxicities in the form of myelosuppression, GI toxicity with diarrhea, mucositis, nausea/vomiting, and neurotoxicity with altered mental status, lethargy, and/or encephalopathy.

Question 2

Which one of the following statements is correct?

a) **All DPD mutations are associated with DPD deficiency**
b) **The absence of DPD mutations rules out DPD deficiency**
c) **DPD*2A is associated with inactive DPD protein and DPD deficiency**
d) **All of the above**
e) **None of the above**

Answer for Question 2

(C) DPD*2A is associated with inactive DPD protein and DPD deficiency

To date, more than 30 sequence variations in the DPD gene have been identified, with the most well-established variant being DPD*2A (c.1905+1G>A; IVS14+11G.A;rs3918290). This is a single-nucleotide variant at the intron boundary of exon 14 that results in a splicing defect, skipping of the entire exon, and a completely inactive protein. The other DPD variants that are associated with reduced DPD enzyme activity and increased 5-FU toxicity include DPD*5, DPD*6, DPD*9A, DPD*13 (c.1679T>G; I560S; rs55886062), c.2846A>T (D949V; rs67376798), c.1236G>A (E412E; rs56038477). It has now been well-established that not all DPD mutations are associated with DPD deficiency. In fact, there are some mutations that lead to increased DPD expression and activity. In up to 40% of patients who present with the class symptoms of DPD deficiency, mutations in the DPD gene have yet to be identified.

Question 3

A 49 yo white female is diagnosed with stage III colon cancer. She is diabetic and has impaired kidney function with a creatinine clearance of 35 mL/min. She has decided to be treated with the XELOX combination regimen. Which of the following statements is correct?

a) **Give full dose of capecitabine with no dose reduction**
b) **Reduce the capecitabine dose by 25%**
c) **Reduce the capecitabine dose by 30%**
d) **Reduce the capecitabine dose by 50%**
e) **Capecitabine should not be given**

Answer for Question 3

(B) Reduce the capecitabine dose by 25%

Capecitabine and capecitabine metabolites are cleared by the kidneys, and increased toxicity has been observed with capecitabine therapy in the presence of renal impairment. The capecitabine dose does not need to be dose-reduced when the creatinine clearance is >50 mL/min. The dose of capecitabine needs to be reduced by 25% when the creatinine clearance is between 30-50 mL/min. Capecitabine is contraindicated and should not be administered when the creatinine clearance is <30 mL/min.

Question 4

A patient with metastatic osteogenic sarcoma is about to start treatment with high-dose methotrexate. With respect to the extent of his disease, the patient has multiple pulmonary nodules, mediastinal lymph node, and a malignant left pleural effusion. He complains of lower back pain, unrelated to his underlying cancer, which is well-controlled on indomethacin.

Question 4

Which one of the following is the most appropriate intervention?

a) **Administer intravenous fluids with alkalinization of the urine to a pH>6**
b) **Continue with indomethacin**
c) **Leucovorin rescue should be continued even when serum MTX levels are <50 nM**
d) **Drainage of the left pleural effusion prior to initiation of methotrexate infusion**
e) **Discontinue indomethacin and begin patient on a different non-steroidal agent**

Answer for Question 4

(D) Drainage of the left pleural effusion prior to initiation of methotrexate infusion
MTX is cleared by the kidneys, and the process of renal excretion is inhibited in the presence of aspirin, non-steroidal anti-inflammatory agents, penicillins, cephalosporins, and probenecid. MTX distributes in to third-space fluid collections, such as pleural effusions and ascites, and the fluid collections should be drained prior to the start of MTX as they can cause a delay in drug clearance. In the presence of these fluid collections, patients may experience increased toxicity. Vigorous intravenous hydration with alkalinization of the urine to a pH of>7.0 is required to prevent precipitation of MTX and MTX polyglutamates in acidic urine, which can then lead to renal failure. The rationale for leucovorin (LV) rescue is to protect normal cells from methotrexate toxicity. LV should be given until the serum MTX levels are down to 50 nM, and once below that threshold level, LV resuce can be stopped.

Question 5

A patient with metastatic non-squamous non-small cell lung cancer is being treated with pemetrexed and cisplatin. Which one of the following is the most appropriate treatment option?

a) **Supplementation with folic acid and vitamin B6**
b) **Supplementation with folinic acid and vitamin B6**
c) **Supplementation with folic acid and vitamin B3**
d) **Supplementation with folic acid and vitamin B12**
e) **Supplementation with vitamin B6 and dexamethasone**

Answer for Question 5

(D) Supplementation with folic acid and vitamin B12

Patients who receive pemetrexed-based therapy should receive vitamin supplementation with folic acid (350 µg/day) and vitamin B12 (1,000 µg IM every 3 cycles) to reduce the risk and severity of toxicity while on therapy. Steroids have been shown to reduce the development of skin rash, and dexamethasone (4 mg PO bid) can be given for 3 days beginning the day before starting pemetrexed.

Question 6

A 46 yo male patient with primary CNS lymphoma is presently receiving high-dose methotrexate. He receives leucovorin rescue according to protocol, and serum MTX levels are being closely monitored. Which one of the following best describes when leucovorin rescue can be safely stopped?

a) **Serum MTX levels < 500 nM**
b) **Serum MTX levels < 100 nM**
c) **Serum MTX levels < 250 nM**
d) **Serum MTX levels < $5x10^{-8}$ M**

Answer for Question 6

(D) Serum MTX levels < $5x10^{-8}$ M (50 nM)

The rationale for leucovorin rescue is to protect normal cells from methotrexate toxicity. Leucovorin should be given until the serum MTX levels below 50 nM ($5x10^{-8}$ M), and once below that threshold level, leucovorin rescue can be stopped.

Question 7

A patient with non-Hodgkin's lymphoma is being treated with the combination of fludarabine, cyclophosphamide, and rituximab. Which one of the following statements is true?

a) **Dose modification of fludarabine is not required in the setting of renal dysfunction**
b) **Dose modification of cyclophosphamide is not required in the setting of renal dysfunction**
c) **Dose modification of fludarabine is required in the setting of liver dysfunction**
d) **Prophylaxis with bactrim to prevent Pneumocystis carinii is required**
e) **Fludarabine is active in its parent form**

Answer for Question 7

(D) Prophylaxis with bactrim to prevent Pneumocystis carinii is required

Fludarabine is a prodrug, and following administration, it is rapidly dephosphorylated to 2-fluoro-ara-adenosine. This nucleoside then enters the cells via a nucleoside-mediated process, and it is then initially phosphorylated to the monophosphate form and eventually metabolized to the fludarabine triphosphate form, which is the active cytotoxic metabolite. Both fludarabine and cyclophosphamide are renally excreted. In the presence of renal dysfunction, the doses of fludarabine and cyclophosphamide need to be modified. Dose modification of fludarabine is not required in the setting of liver dysfunction. Fludarabine therapy is associated with an increased risk of opportunistic infections, including Pneumocystis carinii, and patients should be empirically placed on bactrim prophylaxis.

Question 8

A deficiency in thiopurine methyltransferase (TPMT) results in significantly increased toxicity to which one of the following agents?

a) Methotrexate
b) Nelarabine
c) 6-Mercaptopurine
d) Fludarbine
e) Cladribine

Answer for Question 8

(C) 6-Mercaptopurine

A partial or complete deficiency of TPMT results in excessive, severe toxicity with myelosuppression, GI toxicity, and/or neurotoxicity, in response to the thiopurines, 6-mercaptopurine and 6-thioguanine. TPMT is not involved in the metabolism of other purine analogs, such as nelarabine, cladribine, and fludarabine.

Question 9

A 38 yo male with newly diagnosed metastatic colorectal cancer is started on mFOLFOX6 plus bevacizumab. There was a miscalculation in the chemotherapy orders, and he was given a 20-fold higher dose of 5-FU in the 46-hour infusion. Which of the following is the most appropriate treatment intervention?

a) Administer high-dose leucovorin
b) Administer glucarpidase
c) Immediate hemodialysis
d) Administer uridine triacetate
e) Wait for symptoms to occur and then institute appropriate supportive care measures

Answer for Question 9

(D) Administer uridine triacetate

The administration of uridine triacetate (vistonuridine), an oral prodrug form of uridine, has been shown to be a safe and effective antidote to 5-FU overdose, and this agent was recently approved by the US Food and Drug Administration. 5-FU can not be removed by hemodialysis, and it is not known whether peritoneal dialysis can be used to remove circulating 5-FU. Leucovorin and glucarpidase are two agents that have been used to prevent and/or rescue against MTX-associated toxicities but would not be able to prevent the toxicities of 5-FU.

Question 10

Which reduced folate is part of the thymidylate synthase ternary complex?

a) 5,10-methylenetetrafolate
b) 5-formyltetrahydrofolate
c) 10-formyltetrahydrofolate
d) folic acid
e) 5-methyltetrahydrofolate

Answer for Question 10

(A) 5,10-methylenetetrafolate

The thymidylate synthase (TS) ternary complex is made up of the 5-FU metabolite FdUMP, the reduced folate 5,10-methylenetetrahydrofolate, and the TS enzyme. The role of the reduced folate is to enhance the inhibitory effect of the 5-FU metabolite on inhibition of TS. When TS is bound in this ternary complex, TS enzymatic activity is optimally inhibited, leading to inhibition of thymidylate synthesis and subsequent inhibition of DNA biosynthesis. Leucovorin is 5-formyltetrahydrofolate, which is eventually metabolized within the cell to 5,10-methylenetetrahydrofolate.

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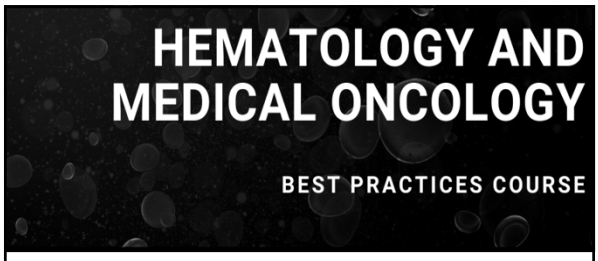
Pharmacology II

Edward Chu, MD

August 17, 2020



41 - Pharmacology II

Edward Chu, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question 1

The multidrug resistance (mdr) phenotype is a well-established mechanism of cellular drug resistance. Which one of the following statements is true regarding this resistance mechanism?

a) **Decreased drug efflux**
b) **Decreased drug influx**
c) **Enhanced drug influx**
d) **Enhanced intracellular drug accumulation**
e) **Enhanced drug efflux with reduced intracellular drug accumulation**

Answer for Question 1

(E) Enhanced drug efflux with reduced intracellular drug accumulation

The multidrug resistance (mdr) gene encodes a P-170 glycoprotein whose function is to cause efflux of drug out of the cell, which results in reduced intracellular accumulation of drug within the cell. This mechanism is a well-established mechanism for a wide range of unrelated classes of drugs, which include anthracyclines, taxanes, camptothecins, and the vinca alkaloids.

Question 2

Which of the following is true relating to oxaliplatin dosing in a patient with a creatinine clearance of 35 mL/min?

a) **No dose reduction is necessary**
b) **Reduce the oxaliplatin dose by 25%**
c) **Reduce the oxaliplatin dose by 33%**
d) **Reduce the oxaliplatin dose by 50%**
e) **Oxaliplatin should not be given**

Answer for Question 2

(A) No dose reduction is necessary

As with other platinum agents, oxaliplatin is excreted by the kidneys. However, renal dysfunction studies have shown no increase in pharmacodynamic drug-related toxicities in patients with mild or moderate renal dysfunction and CrCL down to 20 mL/min. No formal studies have been conducted to date in patients with CrCl<20 mL/min, and in this setting of severe renal dysfunction, oxaliplatin should not be administered.

Question 3

Which of the following statements about the platinum agents is correct?

a) **Cisplatin is effective for upper GI cancers, while oxaliplatin is only effective in colorectal cancer**
b) **The mechanisms of resistance to cisplatin, carboplatin, and oxaliplatin are identical**
c) **The DNA lesions associated with oxaliplatin are different than those associated with cisplatin and carboplatin**
d) **Carboplatin is less nephrotoxic, less emetogenic, and less myelosuppressive than cisplatin.**
e) **Oxaliplatin can be safely administered to patients with moderate impaired renal function (CrCl, 20-39 mL/min)**

Answer for Question 3

(E) Oxaliplatin can be safely administered to patients with moderate impaired renal function (CrCl, 20-39 mL/min)

The DNA lesions are similar for cisplatin, carboplatin, and oxaliplatin with formation of both inter- and intra-strand cross-links. With respect to safety profile, carboplatin is less nephrotoxic and less emetogenic than cisplatin, but significantly more myelosuppressive than cisplatin. The resistance mechanisms for cisplatin and carboplatin are identical. However, in the presence of mismatch repair defects where cisplatin and carboplatin resistance develops, sensitivity to oxaliplatin is maintained, which explains the efficacy of oxaliplatin in colorectal cancer and other GI cancers where mismatch repair defects have been identified. Oxaliplatin can be safely administered to patients with abnormal function with CrCl down to as low as 20 mL/min.

Question 4

A 45 yo male patient with metastatic colorectal cancer is being treated in the second-line setting with FOLFIRI plus cetuximab. One week after his initial treatment, the patient presents with a 2-day history of increasing fatigue and an absolute neutrophil count of 500/µl. What is the most likely diagnosis?

a) **DPD deficiency**
b) **FOLFIRI-associated myelosuppression**
c) **UGT1A1*28**
d) **UGT2B4**
e) **UGT2B7**

Answer for Question 4

(C) UGT1A1*28

DPD deficiency presents with severe toxicity to 5-FU with the classic triad of myelosuppression, GI toxicity, and neurotoxicity. This patient presents with isolated myelosuppression, which would be unusual for DPD deficiency. Irinotecan is metabolized by UDP glucuronyltransferase, and the process of glucuronidation leads to inactive metabolites of both irinotecan and SN-38. In patients with the UGT1A1*28 genotype, there is significant reduction in irinotecan and SN-38 glucuronidation, which then leads to increased myelosuppression and/or GI toxicity. Approximately 10% of the North American population is homozygous for this specific genotype.

Question 5

A 38 yo female with stage IV Hodgkin's lymphoma is being treated with ABVD chemotherapy. She has been treated with 4 cycles, and repeat CT scans show a nice response to therapy. Review of her serum chemistries are notable for a serum sodium of 125 mEq/L, potassium of 3.7 mEq/L, bicarbonate of 25 mEq/L, chloride of 100 mEq/L, blood urea nitrogen of 10 mg/dL, creatinine of 1.1 mg/dL, and uric acid <4 mg/dL. Which one of the following is the most appropriate cause of her hyponatremia?

a) **Dehydration**
b) **Adrenal insufficiency**
c) **Renal tubular acidosis**
d) **SIADH**
e) **Underlying kidney disease**

Answer for Question 5

(D) SIADH

SIADH presents with hyponatremia and normal potassium, chloride, BUN/creatinine levels, and reduced serum uric acid levels. Several anticancer agents are associated with SIADH, including the vinca alkaloids, cyclophosphamide, cisplatin, and melphalan. While SIADH has been observed with certain tumor types, the most common being small cell lung cancer, Hodgkin's lymphoma is not normally associated with SIADH. In patients with dehydration and underlying kidney disease, the BUN and/or creatinine levels should be elevated. With adrenal insufficiency, patients present with hyponatremia and hyperkalemia. In renal tubular acidosis, the bicarbonate levels are reduced along with an elevation in chloride levels and a reduction in potassium levels.

Question 6

Which one of the following agents acts by inhibiting microtubule function?

a) Methotrexate
b) Nelarabine
c) Estramustine
d) Topotecan
e) Mitoxantrone

Answer for Question 6

(C) Estramustine

Estramustine inhibits microtubule function and the process of microtubule assembly by binding to microtubule-associated proteins. This agent was initially developed as an alkylating agent but it has no alkylating activity. Methotrexate and nelarabine are antimetabolites, topotecan is a topo I inhibitor, and mitoxantrone is a topo II inhibitor.

Question 7

Which one of the following agents acts by inhibiting topoisomerase II?

a) Vincristine
b) Irinotecan
c) Paclitaxel
d) Epirubicin
e) TDM-1

Answer for Question 7

(D) Epirubicin

Epirubicin is an anthracycline analog that inhibits topo II. Other mechanisms include formation of oxygen free radicals resulting in single- and double-stranded DNA breaks and direct intercalation into DNA. Vincristine, paclitaxel, and TDM-1 are microtubule inhibitors and irinotecan is a topo I inhibitor.

Question 8

Bevacizumb binds to which one of the VEGF ligands?

a) VEGF-A
b) VEGF-B
c) VEGF-C
d) PlGF
e) All of the above

Answer for Question 8

(A) VEGF-A

Bevacizumab binds to only the VEGF-A ligand, of which there are 6 isoforms. In contrast, ziv-aflibercept binds to VEGF-A, VEGF-A, and PlGF. Ramucirumab binds to the VEGF-R2 receptor.

Question 9

Imatinib inhibits all of the following RTK's except?

a) **c-KIT**
b) **Bcr-Abl**
c) **Bcr-Abl T315I mutation**
d) **Platelet-derived growth factor**
e) **None of the above**

Answer for Question 9

(C) Bcr-Abl T315I mutation

Imatinib inhibits Bcr-Abl, platelet-derived growth factor (PDGF), and c-Kit. It is unable to inhibit the T315I gatekeeper mutation. Dasatinib and nilotinib are able to overcome resistance to imatinib by being active against Bcr-Abl mutations, but they are also inactive against the T315I mutant. Only pomatinib has activity against the T315I mutant.

Question 10

Which one of the following proteasome inhibitors is not altered by green tea products?

a) **Bortezomib**
b) **Carfilzomib**
c) **Ixazomib**
d) **All of the above**
e) **None of the above**

Answer for Question 10

(B) Carfilzomib

Green tea products/supplements bind to the boron moiety that is present on bortezomib and ixazomib and inactivate these proteasome inhibitors. Carfilzomib does not contain this boron moiety so green tea should not have negative effects on its clinical activity.

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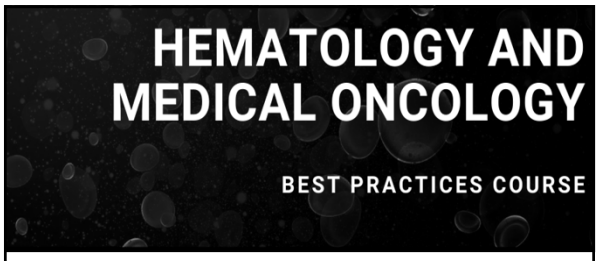
Pharmacology III

Edward Chu, MD

August 17, 2020



42 - Pharmacology III

Edward Chu, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question 1

Treatment with cetuximab is associated with which electrolyte abnormality?

a) **Hyponatremia**
b) **Hypokalemia**
c) **Hypophosphatemia**
d) **Hypomagnesemia**
e) **Hypouricemia**

Answer for Question 1

(D) Hypomagnesemia

Treatment with anti-EGFR antibodies, cetuximab and panitumumab, is associated with magnesium wasting with inappropriate urinary excretion, which then leads to hypomagnesemia. EGFR is strongly expressed in the kidney, especially in the ascending limb of the loop of Henle, where up to 70% of filtered magnesium is reabsorbed. In patients being treated with anti-EGFR antibody therapy, serum magnesium levels need to be routinely measured and repleted as necessary.

Question 2

A 48-yo female patient stage IV non-small cell lung cancer has been treated with erlotinib for the past 5 months. She now presents with progressive disease with new lesions in both lobes of the liver and new lung nodules in the right lung. A biopsy of one of the new liver lesions confirms progressive disease and molecular testing reveals the presence of the EGFR T790M mutation. Which of the following is the most appropriate treatment option?

a) **Gefinitib**
b) **Osimertinib**
c) **Afatinib**
d) **Ceritinib**
e) **Regorafenib**

Answer for Question 2

(B) Osimertinib

Osimertinib is FDA-approved for patients with EGFR T790M mutation-positive NSCLC after progression on an EGFR TKI therapy. Gefitinib and afatinib do not have activity in the presence of the T790M mutation. Ceritinib is an ALK inhibitor and would not have any activity in this setting. Regorafenib is an inhibitor of several tyrosine kinases, but has no activity against the EGFR-associated tyrosine kinase.

Question 3

Which one of the following is a true statement?

a) **Nivolumab targets the PD-L1 ligand**
b) **Pembrolizumab targets the PD-1 receptor on tumor cells**
c) **Pembrolizumab targets the PD-1 receptor on T cells**
d) **Atezolizumab targets the PD-L2 ligand**
e) **Ipilimumab targets the PD-1 receptor**

Answer for Question 3

(C) Pembrolizumab targets the PD-1 receptor on T cells

Nivolumab and pembrolizumab are antibodies that bind to the PD-1 receptor on T cells and prevents the interaction of this receptor with the PD-L1 and PD-L2 ligands, which are expressed on tumor cells.

Atezolizumab is an antibody that binds to the PD-L1 ligand and inhibits its subsequent interaction with the PD-1 receptor.

Ipilumumab is an antibody that binds to the CTLA4 receptor, which is expressed on T cells. This leads to inhibition of the interaction between CTLA4 and its target ligands, resulting in inhibition of immune escape.

Question 4

Which one of the following statements is true relating to sorafenib therapy?

a) **Drugs such as rifampin, phenytoin, and phenobarbital reduce the metabolism of sorafenib leading to increased drug levels**
b) **Drugs such as ketoconazole and other CYP3A4 inhibitors increase the metabolism of sorafenib leading to reduced drug levels**
c) **Sorafenib is an inducer of UGT1A1**
d) **Avoid Seville oranges and grapefruit products while on sorafenib therapy**
e) **The oral bioavailability of sorafenib is not affected by food.**

Answer for Question 4

(D) Avoid Seville oranges and grapefruit products while on sorafenib therapy

Sorafenib is metabolized in the liver primarily by the CYP3A4 microsomal enzymes. There are a number of important drug-drug interactions with sorafenib therapy. Drugs that inhibit CYP3A4, such as ketoconazole, may reduce the metabolism of sorafenib leading to higher drug levels and potentially increased toxicity. Drugs, such as rifampin, phenytoin, phenobarbital, and carbamazepine, increase the metabolism of sorafenib leading to reduced drug levels and potentially reduced clinical benefit. Seville oranges, grapefruit products, starfruit, and pomelos contain substances that inhibit the liver metabolism of sorafenib, which can then lead to increased drug levels and potentially increased toxicity.

Answer for Question 4

(D) Avoid Seville oranges and grapefruit products while on sorafenib therapy

Sorafenib is an inhibitor of UGT1A1, and caution must be used when sorafenib is administered with agents that are metabolized by UGT1A1, such as irinotecan.

Sorafenib is rapidly absorbed after an oral dose. The general recommendation is to take sorafenib without food at least one hour before or 2 hours after eating, as oral bioavailability is affected by food. In particular, foods with a high fat content reduce oral bioavability by as much as 30%.

Question 5

A 56 yo male patient with advanced renal cell cancer was treated with sunitinib for 5 months. He now presents with disease progression with widespread involvement of both lobes of the liver. The decision is made to now switch over to everolimus therapy and to use a daily dose of 10 mg PO. In reviewing his various laboratory results, his total serum bilirubin level is 2.5 mg/dL, serum albumin is 2.6 g/dL, prothrombin time is elevated to 18 sec, and there is no ascites. Taken together, he is determined to have moderate liver impairment (Child-Pugh Class B).

Question 5

Which one of the following statements is true?

a) **Grapefruit products can be taken while on therapy**
b) **St. John's Wort can be safely taken as there is no drug-drug interaction with everolimus**
c) **The dose of everolimus should be reduced to 5 mg daily**
d) **Oral bioavailability is not affected by food content**
e) **There is no increased risk of opportunistic infections**

Answer for Question 5

(C) The dose of everolimus should be reduced to 5 mg daily

Grapefruit products, Seville oranges, starfruit, and pomelos should be avoided as these food products can impair liver metabolism of everolimus, which then leads to increased drug levels. There is a drug-drug interaction between St. John's Wort and everolimus where St. John's Wort can increase everolimus metabolism in the liver, resulting in lower effective drug levels. Food with a high fat content reduces oral bioavailability by up to 20%. Patients are at increased risk for developing opportunistic infections, including fungal infections, while on everolimus therapy. Metabolism of everolimus occurs mainly in the liver the CYP3A4 enzymes, and elimination of drug is mainly hepatic with excretion in feces. In patients with moderate liver impairment (Child-Pugh Class B), the everolimus dose should be reduced to 5 mg daily, and in the setting of severe liver impairment (Child-Pugh Class C), everolimus therapy should not be given.

Question 6

A 65 yo female patient with metastatic HER2-positive disease is being treated with the combination of capecitabine and trastuzumab. Of note, she has a history of ischemic heart disease, but she has not had any cardiac symptoms for the past 2 years. She has been on therapy for 8 months, and is tolerating this combination regimen well with no symptoms. CT scans were just performed, and they confirm a nice response to therapy. A follow-up MUGA scan to assess her cardiac status shows a 20% reduction in the LVEF from a normal baseline. Which one of the following statements is true?

a) **Continue with current dose of trastuzumab**
b) **Reduce dose of trastuzumab by 25%**
c) **Reduce dose of trastuzumab by 50%**
d) **Withhold trastuzumab therapy and continue with capecitabine**
e) **Stop trastuzumab and capecitabine and switch to a new treatment regimen**

Answer for Question 6

(D) Withhold trastuzumab therapy and continue with capecitabine

Careful baseline assessment of cardiac function (LVEF) must be done prior to the start of trastuzumab therapy with frequent monitoring (every 2-3 months) while on therapy. Trastuzumab should be held if there is an absolute reduction in LVEF by >16% from a normal baseline value. Trastuzumab should be stopped immediately in any patient who develops clinically significant symptoms of congestive heart failure.

Question 7

Which one of the following statements is true relating to pertuzumab?

a) **Immunologic mechanisms are not involved in antitumor activity**
b) **Binds to subdomain II of the HER2-neu growth factor receptor**
c) **Main biological effect is inhibition of homodimerization of HER2**
d) **Patients with prior exposure to anthracyclines or radiation therapy to the chest are not at increased risk for developing cardiac toxicity**
e) **Infusion reactions are usually observed with prolonged therapy**

Answer for Question 7

(B) Binds to subdomain II of the HER2-neu growth factor receptor

Pertuzumab is a recombinant humanized IgG1 monoclonal antibody direct against the extracellular domain (subdomain II) of the HER2-neu growth factor receptor. It binds to a different epitope on HER2-neu receptor than trastuzumab, which binds to subdomain IV. Binding of pertuzumab to the HER2-neu receptor leads to inhibition of heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As pertuzumab is an IgG1 antibody, immunologic mechanisms may also be involved in its antitumor activity, including antibody-dependent cellular cytotoxicity. The main side effects of pertuzumab are cardiac toxicity and infusion-related reactions. Patients with a prior history of anthracycline treatment or radiotherapy to the chest and/or mediastinal region may be at increased risk of developing cardiac toxicity, which is usually manifested by a reduction in LVEF.

Question 8

Which of the following tyrosine kinases are inhibited by crizotinib?

a) c-Met
b) ALK
c) RON
d) ROS1
e) All of the above

Answer for Question 8

(E) All of the above

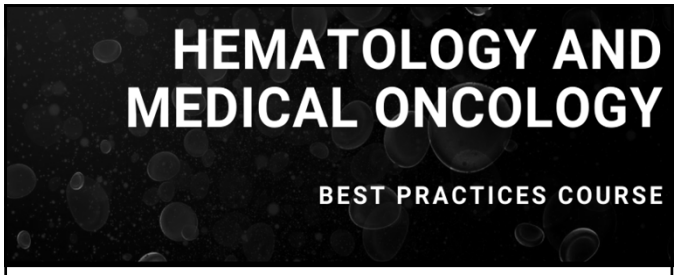
Crizotinib inhibits the tyrosine kinases associated with c-Met, ALK, RON, and ROS1. This agent is now approved in the U.S. to treat patients with metastatic non-small cell lung cancer whose tumors are ALK-positive or ROS1-positive.

43

Palliative Care

Erica Schockett, MD

August 17, 2020



43 – Palliative Care

Erica Schockett, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

ABIM Exam Blueprint

- Supportive Care, Survivorship, and Communication **11%**
- Today:
  - Discuss the role of opioids for cancer pain and related substance use disorder
  - Recognize mood disorder in the seriously ill patient
  - Describe the use of pharmacologic and non-pharmacologic therapies to relieve common symptoms in cancer patients
  - Define total pain
  - Refine serious illness communication skills
  - Distinguish palliative and hospice care

Question 1:

- A 70 yo female was admitted to the hospital with anorexia, severe abdominal pain and 30-pound weight loss over 4 months. CT revealed a large pancreatic body mass and a biopsy confirmed malignancy. She underwent a celiac plexus block with IR during her hospital stay and experienced initial relief for two weeks.
- Now the pain has returned, is aching and constant and she declines an exam due to fear of more pain. She declines any more procedures for the pain and asks for something that will work "right away". This is her first appointment with you and she is not ready to focus on treatment options until she is more comfortable. She has normal renal function and NKDA.

What is the best initial option to help control her pain?

A. Fentanyl patch 12mcg TD q72hr
B. MS Contin (extended release morphine) 15mg po bid
C. Hydrocodone-acetaminophen 5mg-325mg po q4hr prn pain
D. MSIR (morphine immediate release) 7.5mg po q4hr prn pain
E. Acetaminophen 1,000mg po q8hr ATC

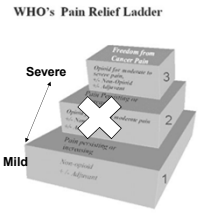
Choosing an Approach

- Pain type (visceral, somatic, neuropathic)
- Pain location (localized, regional, diffuse) – is this patient a candidate for neurolysis/targeted interventional pain technique? Radiation?
- Metabolism (drug-drug CIs, comorbid organ impairment, drug use disorder)
- Route of administration (enteral access, mental status, cytopenias)
- "Think two steps ahead" – What will my patient's needs be in two days? in two weeks?

WHO Pain Ladders

- Adults

- Children



http://www.who.int/cancer/palliative/painladder/en/

Opioids for Cancer Pain

- If moderate or severe start with mu-agonist opioid (morphine)
- Unlike drugs with mixed opioid-monoaminergic mechanisms of action (tramadol), pure mu-agonist opioids have no dose ceiling
- Avoid combination products due to dose ceilings such as with acetaminophen or ibuprofen (can schedule those separately)
- Start with an immediate release preparation to "dose find" over at least 24 hours and monitor effects before committing to a long-acting opioid regimen
- Most initial adverse effects of nausea, sedation resolve within days
- Rotate to another opioid if dose increase continues to be ineffective or adverse effects are intolerable

What is the best initial option to help control her pain?

A. Fentanyl patch 12mcg TD q72hr – avoid a long-acting regimen until you titrate to an appropriate dose, also no reason to avoid oral dosing here
B. MS Contin (extended release morphine) 15mg po bid – as above; must dose-find first with short-acting agent
C. Hydrocodone-acetaminophen 5mg-325mg po q4hr prn pain – per WHO pain ladder, severe pain requires a strong opioid
D. MSIR (morphine immediate release) 7.5mg po q4hr prn pain – correct choice
E. Acetaminophen 1,000mg po q8hr ATC – May schedule in addition if appropriate but need strong opioid

Question 2:

- Your patient returns to clinic the following week and her pain has improved from 9/10 to 3/10 which is tolerable for her. She is taking MSIR 7.5mg orally 4 – 5 times daily to achieve relief. When she wakes up having not taken morphine in 5 or 6 hours she is in intense pain which only adequately controlled after her second dose of morphine each day. Also, she has not moved her bowels in 5 days and feels bloated.

Which of the following is the best next step in the management of this patient?

A. Add docusate sodium to her regimen and have her take a long-acting morphine preparation at night before bed
B. Administer naloxegol in the office to relieve OIC (opioid induced constipation)
C. Add psyllium daily and a long acting morphine twice a day for extended pain relief
D. Start senna twice daily in addition to a long-acting morphine preparation twice a day

Opioid induced Constipation

- Affects up to 90% of patients receiving opioid therapy
- Leads no non-adherence, hospitalization, suffering
- Patients do NOT develop tolerance to this one side effect of opioids
- Delay transit time, increase reabsorption fluid in gut
- Increased hydration and physical activity may be difficult for some patients
- First line is stimulant laxatives; rectal stimulation may be required if constipation has lasted more than 3 days

Please co-prescribe opioid and stimulant laxative!

Bell RJ, Panchal SJ, Miaskowski C et al. The Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction: Results of a US and European Patient Survey (PROBE 1). Pain Medicine. 2009; 10(1):35-42.

Which of the following is the best next step in the management of this patient?

A. Add docusate sodium to her regimen and have her take a long-acting morphine preparation at night before bed – stool softener ineffective for OIC
B. Administer naloxegol in the office to relieve OIC – selective opioid receptor antagonists indicated for refractory OIC
C. Add psyllium daily and a long acting morphine twice a day for extended pain relief – psyllium can predispose to obstruction (requires 1.5 liters fluid intake daily), especially if less hydrated and less mobile
D. Start senna twice daily in addition to a long-acting morphine preparation twice a day – co-treat to help prevent OIC; also if more than 3 PRNs per day, think long-acting regimen

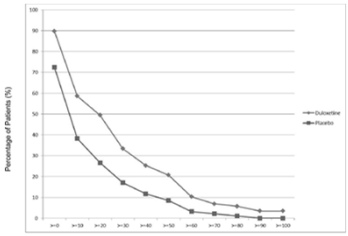
Question 3:

- A 45 yo obese female sees you for routine follow-up in breast cancer clinic. She currently has no evidence of disease and has been able to return to most of her usual activities but is discouraged by her significant limitations in her hobbies, aerobic walking and painting, due to persistent numbness and pain since chemotherapy. Even her arthritis pain is acting up since she's not exercising. She's so thankful her cancer is in remission but so frustrated about her symptoms! You order a metabolic profile with TSH, which is reassuring.

Which therapy below is most appropriate to recommend to help control her pain?

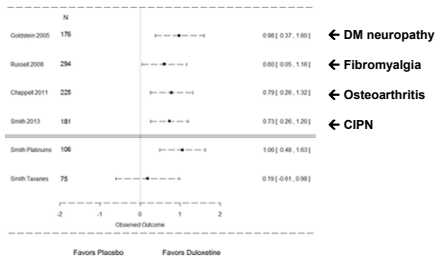
A. Weight reduction
B. Oxycodone
C. Duloxetine
D. Pregabalin
E. Naproxen sodium

Chemotherapy-induced Peripheral Neuropathy



Lavoie E, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. A randomized clinical trial. JAMA. 2013; 309(5):1359-67.

Chemotherapy-induced Peripheral Neuropathy



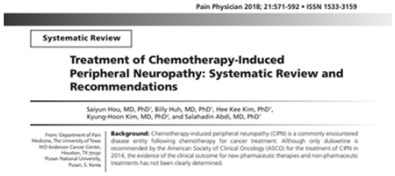
← DM neuropathy
← Fibromyalgia
← Osteoarthritis
← CIPN

Lavoie E, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. A randomized clinical trial. JAMA. 2013; 309(5):1359-67.

Which medication below is most appropriate to prescribe to help control her pain?

A. Weight reduction – not address CIPN
B. Oxycodone – may provide for immediate short-term pain relief while awaiting adjuvant agent to take effect
C. Duloxetine – proven useful for CIPN, also FDA approved for depression and MSK pain
D. Pregabalin – lacks evidence for efficacy
E. Naproxen sodium – may address some arthralgias but not other symptoms

Hou S, Hait B, Kim HK, et al. Treatment of Chemotherapy-Induced Peripheral Neuropathy: Systematic Review and Recommendation. Pain Physician. 2018 Nov; 21(6):571-592.



Question 4:

- A 65 yo gentleman with CAD s/p CABG, atrial fibrillation, HTN and now NSCLC metastatic to bone and lymph nodes only per recent imaging presents for follow-up in your clinic. When he is using the bathroom his wife confides in you that her husband's personality seems different. He's always been stoic but lately she finds him staring at old papers, only picking at his food, skipping their weekly card game and she hears him crying in the bathroom some nights.
- You interview the patient alone and he denies suicidal ideation.

What feature should prompt you to prescribe an anti-depressant?

A. Decreased appetite
B. Changes in sleep pattern since diagnosis
C. Episodes of crying and sadness
D. Feelings of hopelessness

Depression and Grief in the Terminally Ill

- Anticipatory Grief (Preparatory Grief) – natural part of dying process, may include sadness but there is mixture of good and bad days, hope is there but may shift, can still experience pleasure, social support seems to help
- Depression – Hallmarks include *worthlessness*, *guilt* (about being a burden), *hopelessness*, a poisoned sense of self
  - *Sustained* suicidal ideation
- This is NOT your classic SIGECAPS!

Block SD, for the ACP-ASIM End-of-Life Consensus Panel. Assessing and managing depression in the terminally ill patient. Annals of Intern Med. 2000; 132:209-218.

Single question screening

"Are you feeling down, depressed or hopeless <u>most</u> of the time over the last 2 weeks?"

- Up to 100% Sensitivity and specificity in studies

What feature should prompt you to prescribe an anti-depressant?

A. Decreased appetite – must focus on cognitive symptoms rather than physical symptoms in terminally ill patients
B. Changes in sleep pattern since diagnosis – same as above
C. Episodes of crying and sadness – can be present in anticipatory grief
D. Feelings of hopelessness – a hallmark of depression in the terminally ill, should be treated

What is the best medication choice for your patient?

A. Buproprion 150mg po daily
B. Methylphenidate 2.5mg po bid
C. Amitriptyline 25mg po qhs
D. Mirtazapine 7.5mg po qhs
E. Single dose ketamine

Treating depression

- Determine prognosis
- Prognosis < 4 weeks consider psychostimulant. Onset 1-2 days and safe in most patients
- Prognosis at least 4 weeks - more options. Try to treat 2 if not more symptoms with one drug!
  - If insomnia – Mirtazapine (histaminergic)
  - If neuropathic pain – SNRI such as duloxetine (CIPN)
  - If anorexia – Mirtazapine
  - If hot flashes – SNRI such as venlafaxine
- Minimize unwanted adverse effects (SSRI can increase QTc, HA, nausea, diarrhea; SNRI may increase bleeding time)
- Start low and go slow, as always

What is the best medication choice for your patient?

A. Buproprion 150mg po daily – can be weight negative and no other helpful effects for this patient
B. Methylphenidate 2.5mg po bid – may increase energy and appetite; CI for CV risk, also not a short prognosis
C. Amitriptyline 25mg po qhs – sedating but TCAs would be relatively CI for this older patient
D. Mirtazapine 7.5mg po qhs – may increase appetite (up to doses of 15mg) and aid in sleep
E. Single dose ketamine – limited evidence available but promising, not first line approach

Question 5:

- A 61-year-old male is diagnosed with metastatic cholangiocarcinoma and is started on a regimen of gemcitabine and cisplatin. He has lost 30 pounds over 2 months but remains physically active, is able to do all of his activities of daily living and is motivated to pursue treatment.
- After two cycles he informs you that despite taking the medications you provided he has intense nausea and vomiting even up to a couple of days after chemo and does not think he can continue. You reassure him that there are many more options to treat his nausea and vomiting than the dexamethasone and ondansetron he has already tried.
- For next cycle you prescribe aprepitant without good effect.

What is the next best choice to help this gentleman tolerate palliative chemotherapy?

A. Substitute palonosetron for ondansetron
B. Discontinue glucocorticoid
C. Substitute olanzapine for aprepitant
D. Add a benzodiazepine

Chemotherapy-induced Nausea and Vomiting

- Acute – minutes to hours after chemo; resolves within 24 hours
- Delayed – onset 24 hours after chemo up to 5 days
- Anticipatory – precedes chemotherapy (N > V)
- Breakthrough – despite preventive antiemetics
- Refractory – despite preventive and rescue medications
- Treatment relates to emetogenicity of the regimen

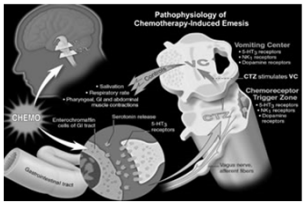
Tillman J, Pirk A, DeSimone E, et al. Chemotherapy-Induced Nausea and Vomiting. US Pharm. 2018;43(2)(Specialty&Oncology suppl):2-5.

Chemotherapy-induced Nausea and Vomiting

- Low Emetogenic – single agent therapy or even prn
- MEC – Glucocorticoids (acute and delayed CINV) + 5-HT3 receptor antagonists (acute CINV); if refractory add NK-1 receptor antagonist (aprepitant and pro-drug fosaprepitant) for acute and delayed CINV
- Refractory – Offer an alternate agent then given with prophylaxis such as olanzapine or metoclopramide

Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol. 2011;9:188-95.
Rapoport L, Jordan K, Boice J-A et al. Aprepitant fo the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemo-therapies and tumor types: a randomized, double-blind study. Support Care Cancer 2010; 18:421-31.

Chemoreceptor Trigger Zone



- Damaged enterochromaffin cells release serotonin which triggers 5-HT3 receptors on vagal and splanchnic afferent fibers
- Chemo can also directly activate medullary CTZ mediated by serotonin, dopamine and NK-1 receptors

http://pharmacologycorner.com/drugs-cinv-prophylaxis-treatment/

Olanzapine – a Swiss Army knife for CINV

- Atypical antipsychotic
- Acts at multiple receptors: dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2A, 5-HT2C, 5-HT3, 5-HT6), adrenergic (a1), histaminergic (H1), muscarinic (m1, m2, m3, m4)
- Dose 5-10mg (max 20mg) usually once nightly
- Less strongly affects QTc than other anti-emetics


The Oncologist

Symptom Management and Supportive Care | Free Access

Effectiveness of Antiemetic Regimens for Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Network Meta-Analysis

Takamichi Yokoe, Tetsu Hayashida, Aiko Nagayama, Ayako Nakashoji, Hinako Maeda, Tomoko Seki, Maiko Takahashi, Toshimi Takano, Takayuki Abe, Yuko Kitagawa

First published: 17 October 2018 | https://doi.org/10.1634/theoncologist.2018-0140

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What is the next best choice to help this gentleman tolerate palliative chemotherapy?

A. Substitute palonosetron for ondansetron – 2nd generation 5-HT3 receptor antagonists not superior
B. Discontinue glucocorticoid – can prevent acute and delayed CINV
C. Substitute olanzapine for aprepitant – effective for refractory CINV due to action on multiple receptors at CTZ
D. Add a benzodiazepine – no need to target GABA receptors as in anticipatory nausea

Question 6:

- A 42 yo female with metastatic squamous cell carcinoma of the cervix is seen in clinic for ongoing palliative chemotherapy. In previewing her chart you notice repeated calls requesting dose escalation of oxycontin and oxycodone due to never having had her pain controlled, and note two missed lab appointments.
- During the visit she notes ongoing severe pain you relate to progressive peritoneal carcinomatosis. She brings her pill bottles and you note she is using her long-acting medication as prescribed but is out of the short-acting medication. You prescribe the same dose of opioid and number of pills she has been receiving for 4 months, refer her for a therapeutic paracentesis and order a urine tox screen. She consents without issue and apologizes for missing appointments. She describes her stressful schedule caring for her 8 yo twins. Her car is on the fritz and her mother who usually helps is isolating during the pandemic. Her faith and a couple close friends give her strength to cope.
- The next week she calls, describes some initial relief after paracentesis but again requests a higher dose of opioid. A urine tox screen is positive for opioids only.

Question 6:

What is the most likely diagnosis?

A. Total pain
B. Substance use disorder
C. Tolerance
D. Pseudoaddiction
E. Narcotic diversion

During the visit she notes ongoing severe pain you relate to progressive peritoneal carcinomatosis. She brings her pill bottles and you note she is using her long-acting medication as prescribed but is out of the short-acting medication. You prescribe the same dose of opioid and number of pills she has been receiving for 4 months, refer her for a therapeutic paracentesis and order a urine tox screen. She consents without issue and apologizes for missing appointments. She describes her stressful schedule caring for her 8 yo twins. Her car is on the fritz and her mother who usually helps is isolating during the pandemic. Her faith and a couple close friends give her strength to cope.

Question 6:

What is the most likely diagnosis?

A. Total pain – suffering involving all of a person's physical, emotional, social, spiritual and practical struggles
B. Substance use disorder – disease manifested by compulsive behavior around drug acquisition and use despite harmful consequences
C. Tolerance – need to increase drug to achieve same effect
D. Pseudoaddiction – iatrogenic condition from withholding opioids, can be prevented and treated with more aggressive opioid prescribing; "drug seeking" resolves when properly treated
E. Narcotic diversion – transfer of legally prescribed controlled substance to another for illicit use

Weissman D, Haddox J. Opioid pseudoaddiction – an iatrogenic syndrome. Pain. 1989 Mar;36(3)363-6.

Question 7:

- A 72-year-old male is seen by you in the hospital for evaluation of metastatic prostate cancer. He has not seen a physician in 3 years, was previously aware of a diagnosis of "early mild prostate cancer" but told by his doctor that they would just watch and wait to see if it got worse. Now he has extensive bony disease and was hospitalized for related bony pain. You want to review with him his treatment options. When you enter the hospital room his daughter is present and they both seem frustrated before you even begin to speak. You introduce yourself and your role at which point his daughter states, "You didn't seem to care about my father three years ago. What do you have to say now? What, are you going to make more money giving him chemo now? I know how you doctors think."

Question 7:

Which is the most appropriate response?

A. I am here to help you. Please calm down so we can talk this out.
B. Let me assure you my salary is not based upon your father's treatment. I just want to do what's best for him.
C. It sounds like you are frustrated. I can tell you're doing everything possible to make sure your father receives the best care. Tell me more about what has been shared with you already.
D. Dad's cancer is worse and he needs treatment soon to help control it, even if that means chemotherapy. He could do very well with that.

Responding to Emotion: Articulating empathy using NURSE statements

NURSE statements for articulating empathy

	Example	Notes
Naming	"It sounds like you are frustrated"	In general, turn down the intensity a notch when you name the emotion
Understanding	"This helps me understand what you are thinking"	Think of this as another kind of acknowledgment but stop short of suggesting you understand everything (you don't)
Respecting	"I can see you have really been trying to follow our instructions"	Remember that praise also fits in here eg "I think you have done a great job with this"
Supporting	"I will do my best to make sure you have what you need"	Making this kind of commitment is a powerful statement
Exploring	"Could you say more about what you mean when you say that…"	Asking a focused question prevents this from seeming too obvious

Three fundamental skills

	Example	Notes
Tell me more	"Tell me more about…"	Use when you are not sure what someone is talking about (rather than jump to an assumption).
Ask-tell-ask	"What do you think about…" "Here's what the tests show" "Does that make sense…?"	Related to Assess-Knowledge-Respond in SPIKES. Think of this as one unit of information transfer
"I wish" statements	"I wish I could say that the chemo always works"	Enables you to align with the patient while acknowledging the reality of the situation

Retrieved from https://www.vitaltalk.org/guides/responding-to-emotion-respecting/

Question 7:

Which is the most appropriate response?

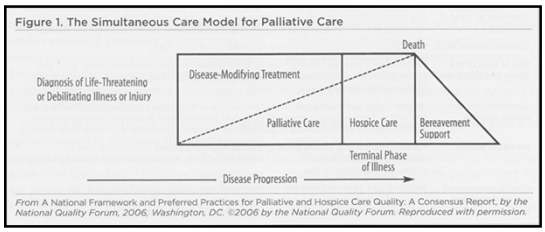
A. I am here to help you. Please calm down so we can talk this out.
B. Let me assure you my salary is not based upon your father's treatment. I just want to do what's best for him.
C. It sounds like you are frustrated. I can tell you're doing everything possible to make sure your father receives the best care. Tell me more about what has been shared with you already.
D. Dad's cancer is worse and he needs treatment soon to help control it, even if that means chemotherapy. He could do very well with that.

Question 8:

Which of the following is/are required for hospice enrollment under Medicare guidelines?

A. Two physicians must independently certify that if a patient's disease runs its natural course, death may be expected within 6 months
B. Patient must elect a DNR code status
C. Patient must no longer be able to work
D. Patient must agree to no re-hospitalization
E. All of the above

Continuum for Serious Illness Care



Integration of Palliative Care Into Standard Oncology Care: ASCO Clinical Practice Guideline Update Summary (2016)

- "Patients with advanced cancer, inpatients and outpatients, should receive dedicated palliative care services early in the disease course and concurrent with active treatment. Referring patients to interdisciplinary palliative care teams is optimal, and services may complement existing programs. Providers may refer caregivers of patients with early or advanced cancer to palliative care services."
- "For newly diagnosed patients with advanced cancer, the Expert Panel suggests early palliative care involvement within 8 weeks of diagnosis."

Ferrell BR, Temel, JS, Temin S, and Smith TJ. Integration of Palliative Care Into Standard Oncology Care: ASCO Clinical Practice Guideline Update Summary. Journal of Oncology Practice 2017 13:2, 119- 21.

Care Pathways

Palliative Care

- IDT (ideally) focused on quality of life
- Any age, any diagnosis, any stage of illness
- Concurrent with any life-prolonging and disease directed therapies
- Inpatient, outpatient, residential
- Traditional payment models

Hospice Care

- IDT focused on quality of life and relief of suffering
- Any age, any diagnosis, prognosis up to 6 months if disease follows a usual course
- Usually must forego disease related curative treatments
- Any type of home, not one place
- Medicare hospice benefit provides cost-free disease related care (DME, supplies, meds, IDT visits/support, 24/7 access)

There's [illegible]ng more we [illegible]do.

You deserve the MOST care possible.
You deserve the BEST care possible.

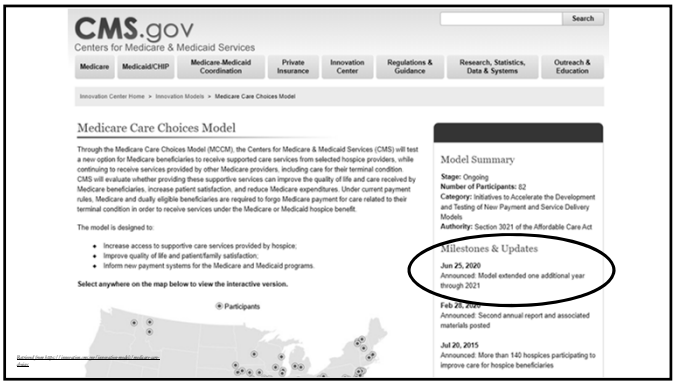
Which of the following is/are required for hospice enrollment under Medicare guidelines?

A. Two physicians must independently certify that if a patient's disease runs its natural course, death may be expected within 6 months - correct
B. Patient must elect a DNR code status – may be full code
C. Patient must no longer be able to work - as long as prognosis is appropriate may do any usual activities
D. Patient must agree to no re-hospitalization – may revoke hospice benefit at any time
E. All of the above

Saying YES – A future of more sensible care

Models of expanded care

- "Open access" – a hospice may agree to cover a non-traditional or "expanded hospice therapy" such as palliative radiation, TPN, IV antibiotics, IVF if clinically appropriate for that individual patient
- Concurrent care – the future of providing comprehensive cancer care for advanced illness. Sometimes available under private insurance plans – you need to ask – and Medicare demonstration projects underway for cancer diagnosis . . .



Communicating Prognosis in Advanced Cancer

- **Function** drives prognosis as much as it drives your therapeutic approach
- Many solid tumor cancer patients lose about 70% of function in the last 2-3 months of life
- Provide a RANGE when communicating prognosis with patients (days to weeks, weeks to months, etc.)
- *When in doubt*, or a bit tangled in the situation, take a time out and ask yourself:

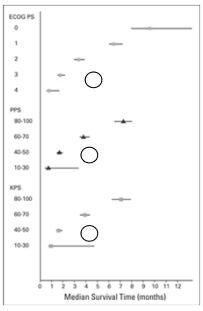


Figure 1. Graphical representation of median survival and 95% CI by performance status. ECOG PS, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky Performance Status; PPS, Palliative Performance Scale.

- Survival approximately halved for each decline in performance level
- Prognosis of two months:
  - ECOG 3
  - PPS 40-50
  - KPS 40-50
    - All signify limited self-care; mainly bed or bed/chair >50% of daytime, may have normal or reduced po intake and consciousness

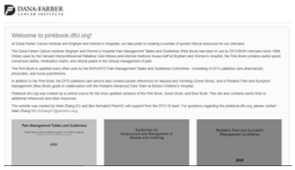
Jang RW, Caraiscos VB, Swami N, et al. Simple Prognostic Model for Patients With Advanced Cancer Based on Performance Status. JOP 2014; 10(5): e335-41.

The Surprise Question

Would I be surprised if this patient died in the next 12 months?

White, Nicola et al. "How Accurate Is the 'Surprise Question' at Identifying Patients at the End of Life? A Systematic Review and Meta-Analysis." BMC Medicine 15 (2017): 139. PMC. Web. 25 Apr. 2018.

Further Resources



2020 Updates

Thank you.
May you be safe and well.

44

Next Gen Sequencing for the Diagnosis and Treatment of Neoplastic Disorders

Skip Burris, MD

August 17, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

44 - Next Gen Sequencing for the Diagnosis and Treatment of Neoplastic Disorders

Howard "Skip" Burris, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- None
- Dr. Burris is employed by HCA Healthcare/Sarah Cannon (stock ownership).
- Sarah Cannon, the Institution that employs Dr. Burris, has been paid for consulting/advisory roles from the following companies: AstraZeneca, Celgene, FORMA Therapeutics, and Incyte. Daiichi Sankyo and Pfizer (non-compensated).
- Sarah Cannon, the Institution that employs Dr. Burris, has conducted research projects funded by the following companies: Agios, Arch, Array BioPharma, Arvinas, AstraZeneca, Bayer, BIND Therapeutics, BioAtla, BioMed Valley, Boehringer Ingelheim, Bristol-Myers Squibb, CicloMed, CytomX, eFFECTOR Therapeutics, Foundation Medicine, Lilly, Roche/Genentech, Gilead Sciences, GlaxoSmithKline, Harpoon Therapeutics, Incyte, Janssen, Jounce Therapeutics, Kymab, MacroGenics, MedImmune, Merck, Millennium/Takeda Pharmaceuticals, Mirna Therapeutics, Moderna, Novartis, Pfizer, Revolution Medicine, Seattle Genetics, Tesaro, TG Therapeutics, Verastem and Vertex Pharmaceuticals.

Why Do We Need to Profile Patients?

- For the patient/individual benefit
- For clinical research/drug development (trial accrual)
- For cancer research/benefit of all (biology, resistance)

Burning Questions

- With the new immunotherapies, do I still need to molecularly profile my patient?
- Is it worth ordering a molecular profile to search for the rare mutation?
- Is it not simpler to just order a blood based test on my patients?

Biomarker Successes of Precision Medicine

- **Breast**: hormone receptor, HER2, BRCA
- **Ph+ Leukemia**: BCR-ABL
- **Colorectal**: RAS pathway, MSI, BRAFV600E
- **Melanoma**: BRAF
- **Non-small cell lung**: EGFR, ALK, ROS, BRAF, RET, MET exon 14, PDL1
- **Thyroid**: BRAF, RET
- **Bladder**: FGFR3, FGFR2
- **Pancreas**: BRCA
- **Ovarian**: BRCA
- **Prostate**: BRCA, HRR
- **GIST**: PDGFRA exon 18 mutation
- **Cholangiocarcinoma**: FGFR2
- **Follicular Lymphoma**: EZH2
- **Tumor Agnostic**: NTRK, MSI, TMB

2020 Approvals

Two Trends, One Triage Decision

Precision Medicine

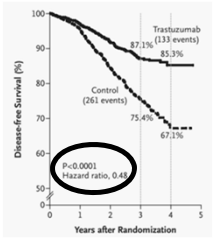
Immuno-Oncology

NGS Profiling

Actionable Genomic Alterations

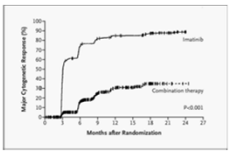
MSI and TMB

Trastuzumab: The First HER2 Targeted Therapy

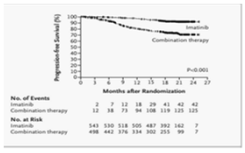


NSABP B-31/NCCTG N9831
NEJM 2005

Imatinib versus Interferon/Cytarabine in Newly Diagnosed Chronic Phase CML



Major Cytogenetic Response
85% versus 22%

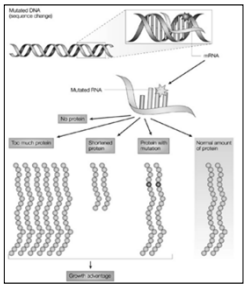


12 Month PFS 97% versus 80%
18 Month PFS 92% versus 74%

O'Brien, et al. NEJM 2003;348:994-1004.

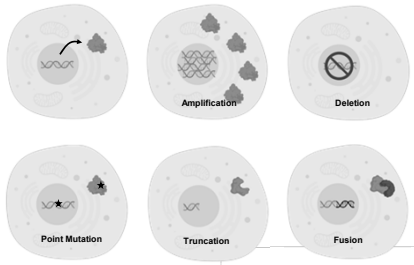
Cancer

"There is a broad consensus that cancer is, in essence, a genetic disease, and that accumulation of molecular alterations in the genome of somatic cells is the basis of cancer progression."- Vogelstein

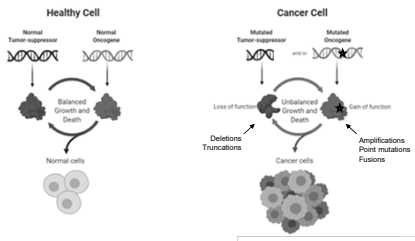


Poirier, M. 2004. Nature Reviews Cancer

Types of Genetic Alterations



The Functional Consequences



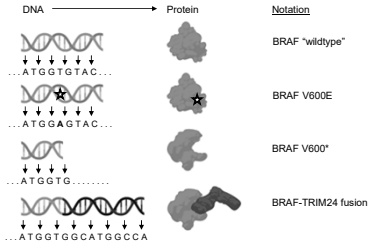
DNA Sequencing Reveals Genetic Alterations

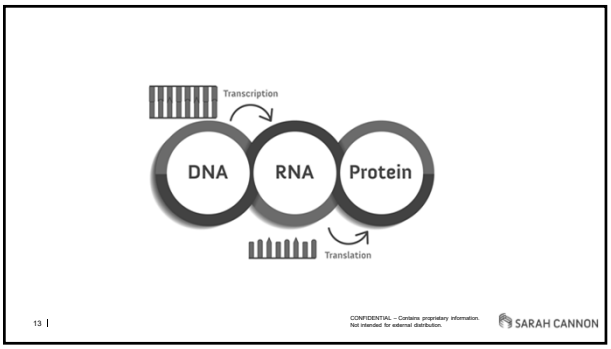
Alterations Detected by NGS:

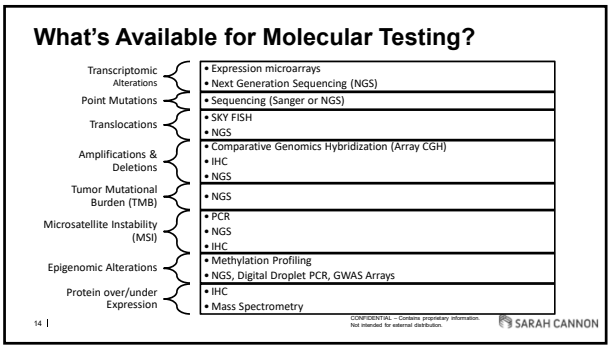
- Point mutations
- Truncations
- Fusions
- Amplifications/Deletions

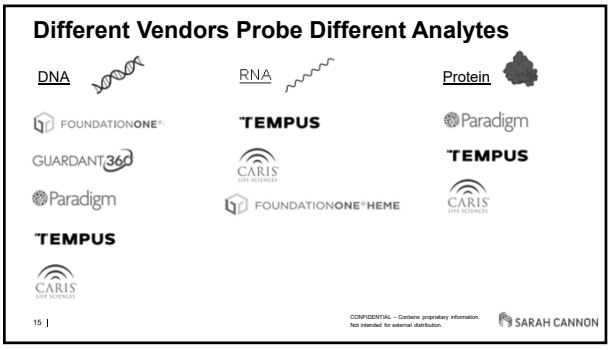
Inactionable Alterations:
***Benign* alterations do not impact protein function.**

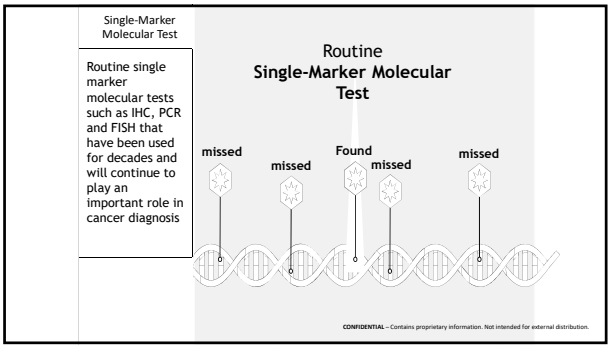
***Variants of Uncertain Significance (VUS)* have not been characterized.**

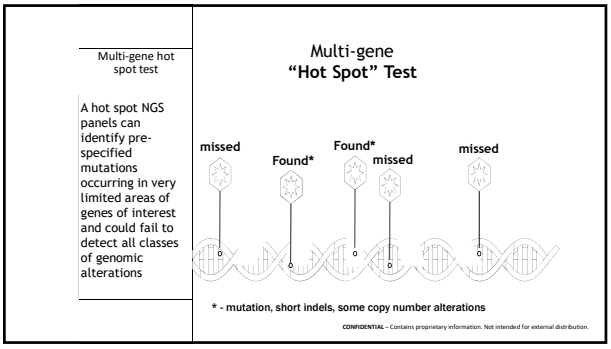


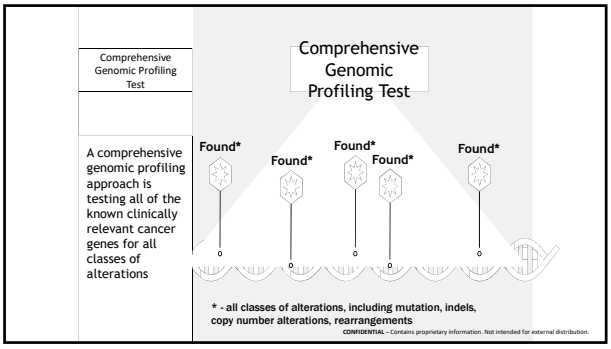








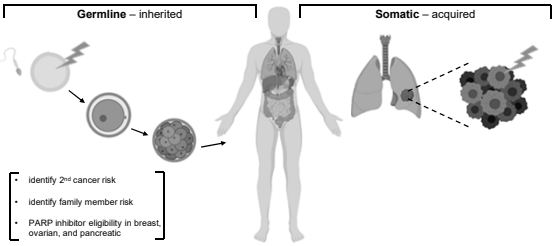




What's the Difference and Why Should We Care?

Germline – inherited

Somatic – acquired



- identify 2nd cancer risk
- identify family member risk
- PARP inhibitor eligibility in breast, ovarian, and pancreatic

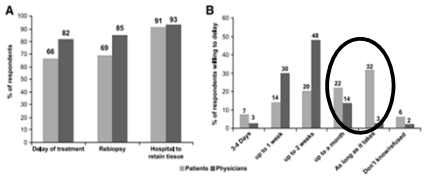
Who Tests for What?

Somatic Testing	Germline Testing	Both
FOUNDATIONONE®	MYRIAD myRisk® Hereditary Cancer	TEMPUS
GUARDANT360	INVITAE	CARIS LIFE SCIENCES
Paradigm		

Challenges of Molecular Diagnostics

- Cost
- Tissue availability
- Time
- Frequency of applicability
- Interpreting the data

Self-reported and Physician Assessed Willingness to Consider Biomarker Testing



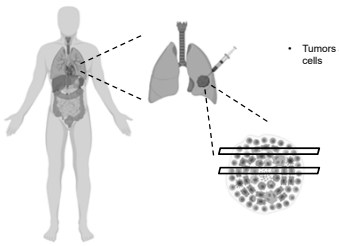
Ciardiello et al. The Oncologist 2016;21:292-300

Tissue Biopsy vs Liquid Biopsy

Tissue Biopsy
- Gold standard
- Invasive procedure
- Tissue accessibility
- Limited to biopsied tissue only
- Clinical complications
- Cost
- Time

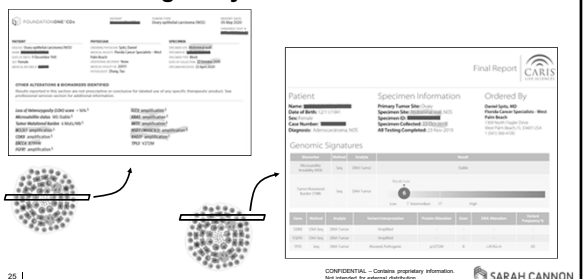
Liquid Biopsy
- Non-invasive blood test
- "Summation" tumor heterogeneity
- Potential for periodic monitoring for response or resistance
- Unable to detect gene loss (eg. *RB1*, *PTEN*, *NF1*)
- ? Cost
- ? Speed

Tumor Heterogeneity

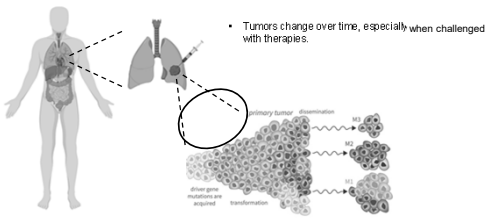


- Tumors are comprised of a **heterogeneous mix** of cells

Tumor Heterogeneity



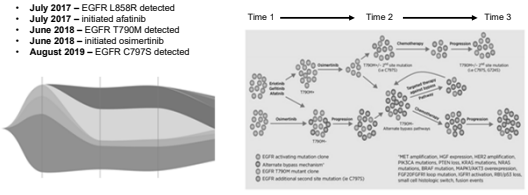
Tumor Evolution



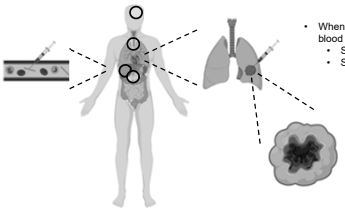
- Tumors change over time, especially when challenged with therapies.

Tumor Evolution

- **July 2017 –** EGFR L858R detected
- **July 2017 –** initiated afatinib
- **June 2018 –** EGFR T790M detected
- **June 2018 –** initiated osimertinib
- **August 2019 –** EGFR C797S detected

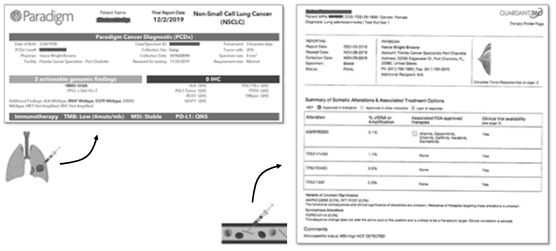


Tissue vs. Liquid Specimens

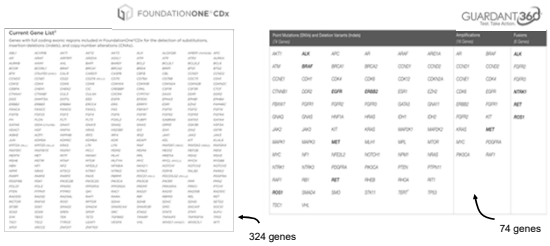


- When, how, and why a tumor "sheds" DNA into the blood stream is still not well understood.
  - Sampling subset of dying cells
  - Sampling metastatic site or other primary tumor

Tissue vs. Liquid Specimens



Different Vendors Offer Different Gene Panels



CMS.gov
Centers for Medicare & Medicaid Services

March 16, 2018

Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)

- Patients
  - Advanced cancer
  - Not previously tested for same cancer
  - Willing to have treatment
- Test
  - FDA approved as a companion in vitro diagnostic
  - FDA approved or cleared indication for the patient's cancer
  - Test report includes specific treatment options

Press release

CMS Expands Coverage of Next Generation Sequencing as a Diagnostic Tool for Patients with Breast and Ovarian Cancer

January 27, 2020

Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

- Patients
  - Ovarian or breast cancer*
  - Clinical indication for germline testing
  - Risk factor for germline cancer
  - Not previously tested with the same germline test
- Test
  - FDA approved or cleared
  - Results include specific treatment options

**MACs may determine coverage for other diagnoses*

FDA Approved Tumor Profiling Tests

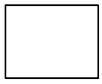
- FoundationOne CDx (Foundation Medicine)
- MSK-IMPACT (Memoral Sloan Kettering Cancer Center)
- Myriad myChoice CDx (Myriad Genetic Laboratories)
- Omics Core (NantHealth)
- PGDx elio tissue complete (Personal Genome Diagnsotics)
- Guardant 360® CDx (Guardant Health)

https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests

GUARDANT

Guardant Health Guardant360® CDx First FDA-Approved Liquid Biopsy for Comprehensive Tumor Mutation Profiling Across All Solid Cancers

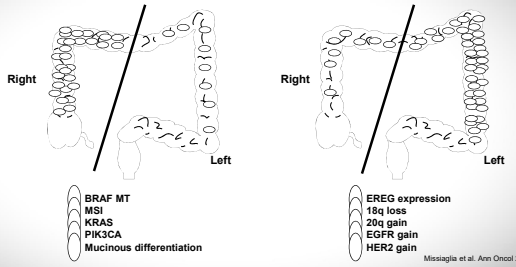
Now FDA approved, the Guardant360 CDx delivers critical genomic information to oncologists from a simple blood draw



Definition of heterogeneity: clinical relevance in colon cancer

Molecular characteristics	Tumour characteristics
RAS	Tumour location
BRAF	
HER2	
MSI status	
Gene expression	

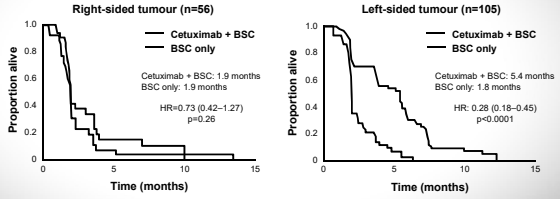
Distal and proximal colon cancers differ in terms of molecular, pathological and clinical features



Missiaglia et al. Ann Oncol 2014

NCIC CO.17 trial: effect of tumour location on PFS in KRAS WT patients

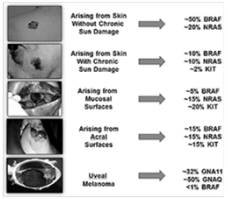
- Phase III trial of cetuximab plus best supportive care (BSC) vs BSC alone in patients with EGFR+ refractory advanced CRC



Brulé et al. Eur J Cancer 2015

Molecular Profiling of Melanoma

MUTATED GENE	FREQUENCY IN MELANOMA
BRAF	37-50%
CTNNB1	2-4%
GNA11	1.2%
GNAQ	1.3%
KIT	2-8%
MEK1	6-7%
NF1	11.9%
NRAS	13-25%



Lovly, C., W. Pao, J. Sosman. 2018. Molecular Profiling of Melanoma. *My Cancer Genome* https://www.mycancergenome.org/content/disease/melanoma/ (Updated March 16).

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SARAH CANNON

FDA Approved Targeted Therapies for Melanoma

Combination Regimen	Overall Response Rate	Progression Free Survival	Overall Survival
Dabrafenib/trametinib* (COMBI-D) (COMBI-V)	66% 64%	9.3 months 11.4 months	25.1 months Not reported
Vemurafenib/cobimetinib (CoBRIM)	70%	12.3 months	22.3 months
Encorafenib/binimetinib (COLUMBUS)	63%	14.9 months	Not reported
Vemurafenib/cobimetinib/ atezolizumab (IMspire150)	66%	15.1 months	28.8 months (not mature)

**Dabrafenib/trametinib also approved in the adjuvant setting*

Product package insert data

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SARAH CANNON

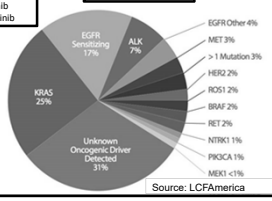
Genetic Mutations in Lung Cancer (NCCN Guidelines)

Sensitizing EGFR
Afatinib
Erlotinib
Dacomitinib
Gefitinib
Osimertinib

ALK Rearrangement
Alectinib
Brigatinib
Ceritinib
Crizotinib
Lorlatinib

MET Exon 14 Skipping
Capmatinib
Crizotinib

ROS1 Rearrangement
Ceritinib
Crizotinib
Entrectinib



BRAFV600E
Dabrafenib/trametinib
Vemurafenib

RET rearrangement
Selpercatinib
Cabozantinib
Vandetanib

NTRK1 Rearrangement
Larotrectinib
Entrectinib

Source: LCFAmerica

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SARAH CANNON

FDA grants regular approval to dabrafenib and trametinib combination for metastatic NSCLC with BRAF V600E mutation

On June 22, 2017, the U.S. Food and Drug Administration granted regular approvals to dabrafenib and trametinib (TAFINLAR® and MEKINIST®, Novartis Pharmaceuticals Inc.) administered in combination for patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.

	Dabrafenib Monotherapy Previously Treated	Dabrafenib + Trametinib Previously Treated	Dabrafenib + Trametinib Untreated
ORR	25%	38%	64%
DOR	9.6 mos	9.8 mos	10.4 mos
PFS	5.5 mos	10.2 mos	10.9 mos
OS	12.7 mos	18.2 mos	24.6 mos

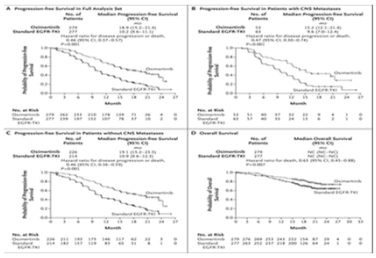
Planchard et al. J Clin Oncol 35,no. 15_suppl (May 2017) abstract 9075

Planchard et al. Lancet Oncol 2017 Oct;18 (10):1307-1316

41 |

SARAH CANNON

FLAURA: Osimertinib in Untreated *EGFR*-Mutated NSCLC



Soria et al. NEJM 2018;378:113-125.

42 |

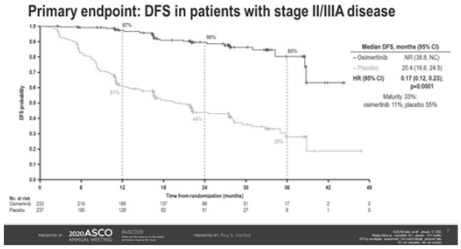
SARAH CANNON

Osimertinib as adjuvant therapy in patients with stage IB–IIIA EGFR mutation positive NSCLC after complete tumor resection: ADAURA

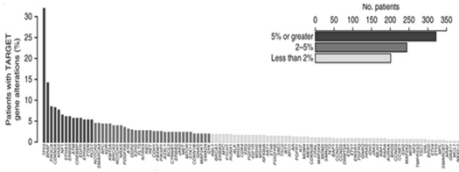
Roy S. Herbst[1], Masahiro Tsuboi[2], Thomas John[3], Christian Grohe[4], Margarita Majem[5], Jonathan W. Goldman[6], Sang-We Kim[7], Dominika Marmol[8], Yuri Rukazenkov[8], Yi-Long Wu[9]

[1] Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; [2] Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3] Department of Medical Oncology, Austin Health, Melbourne, Australia; [4] Klinik für Pneumologie - Evangelische Lungenklinik Berlin Buch, Berlin, Germany; [5] Medical Oncology Services, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [6] David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; [7] Department of Oncology, Asan Medical Center, Seoul, South Korea; [8] Oncology Research & Development, AstraZeneca, Cambridge, United Kingdom; [9] Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China

Primary endpoint: DFS in patients with stage II/IIIA disease

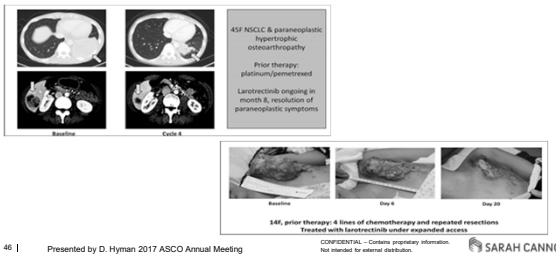


The Challenge of Precision Medicine



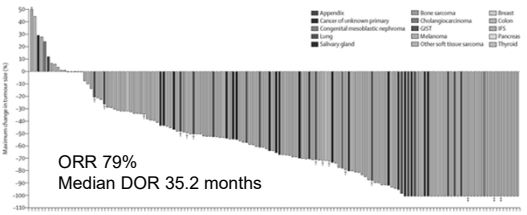
Van Allen et al. Nature Medicine 2014;20:682-688

Tumor Agnostic Approval: Larotrectinib (TRK fusion)



Presented by D. Hyman 2017 ASCO Annual Meeting

Larotrectinib (TRK fusion) Pooled Analysis



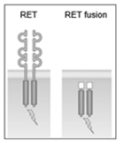
Hong et al. https://doi.org/10.1016/S1470-2045(19)30856-3

Recent Approval: Selpercatinib (RET inhibitor)

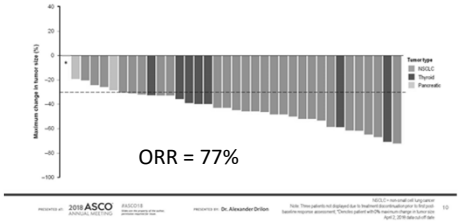
FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions

On May 8, 2020, the Food and Drug Administration granted accelerated approval to selpercatinib (RETEVMO, Eli Lilly and Company) for the following indications:

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC);
- Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).



Efficacy of LOXO-292 in *RET* fusion-positive cancers



JOURNAL OF CLINICAL ONCOLOGY | EDITORIAL

Tumor Mutation Burden: Leading Immunotherapy to the Era of Precision Medicine?

Conor E. Steuer and Suresh S. Ramalingam, *Winship Cancer Institute of Emory University, Atlanta, GA*

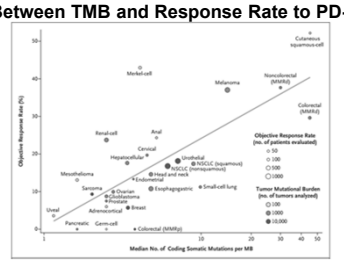
See accompanying article doi:https://doi.org/10.1200/JCO.2017.75.3384

How is TMB Measured?

- Measure of the somatic mutation rate within a tumor genome
- Reported as the number of mutations/megabase of DNA sequenced
- Sufficient area of the genome (>800,000 base pairs) must be sequenced for accuracy
- Germline mutations and particular mutations associated with cancer (*EGFR* or *ALK)* must be removed from the count to reduce bias

Foundation Medicine Website: TMB FAQs

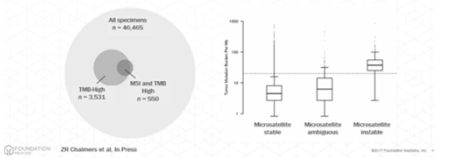
Correlation Between TMB and Response Rate to PD-1 Inhibition



Yarchoan et al. NEJM 2017;377;25:2500-2501

MSI-High specimens are a subset of high TMB specimens (n=46,465)

- The majority of MSI-H specimens (~84%) are TMB-H, but not the reverse
  - Only 14.5% of TMB-H specimens are also MSI-H



ZH Chalmers et al, In Press

P Stephens AACR 2017

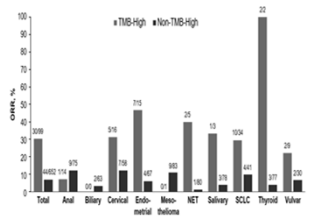
Tissue Agnostic FDA Approval---Mismatch Repair Deficiency

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Approximately 60,000 people per year (4% of all cancers)

Le et al. Science 2017 July 28;357 (6349): 409 - 413

FDA Approves Pembrolizumab for Adults and Children with TMB-H Solid Tumors



- **TMB-H ≥ 10 mut/Mb**
- **ORR: 29%**
- **DoR ≥ 12 mos: 57%**
- **DoR ≥ 24 mos: 50%**

www.fda.gov (June 16, 2020)

Marabelle et al. ESMO 2019

All patients with recurrent or metastatic disease should have their cancer molecularly profiled

- Incorporating the complete molecular profile will provide much more information and give us better insights.
- While the rare mutation can be a source of frustration, the impact of targeted therapy in these patients can be profound.
- "Basket-style" trials are a source of great learning -- future trials, biology of subtypes, areas of opportunity.
- Tumor mutation burden (TMB) will help identify patients who are likely to respond to treatment with immunotherapy.

THANK YOU

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T Cell Therapies for Cancer

Catherine Bollard, MD

August 17, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

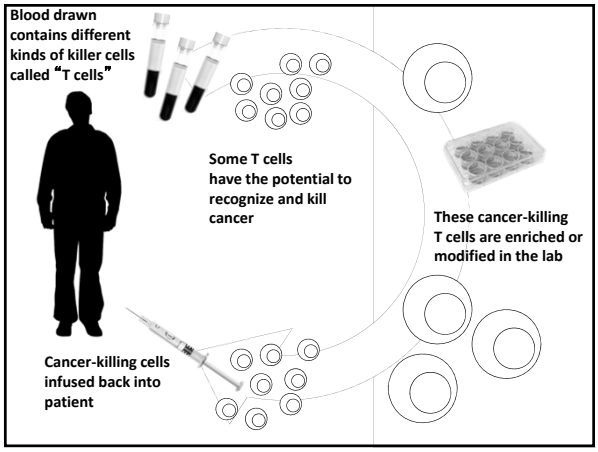
45 - T Cell Therapies for Cancer

Catherine M. Bollard, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

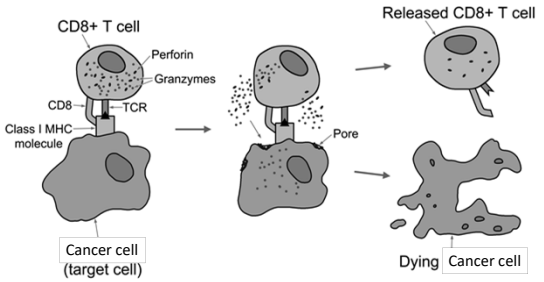
- Advisory Board: Cellectis, BMS
- Co-Founder: Mana Therapeutics and Catamaran Bio
- Board of Directors: Cabaletta Bio
- Stock/ownership: Repertoire Immune Medicines and Neximmune Therapeutics



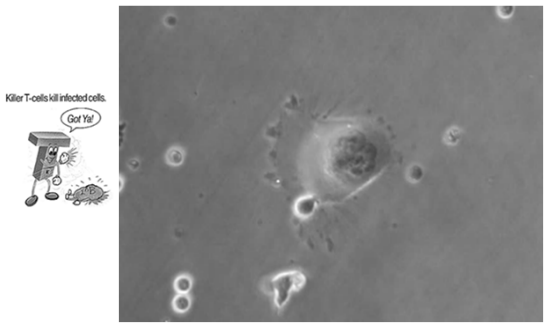
Advantages of T-cell therapies

- sequentially kill a multiplicity of target cells
- recruit additional components of the immune system
- migrate through microvascular walls, extravasate and penetrate the core of solid tumors (e.g. EBV lymphomas)

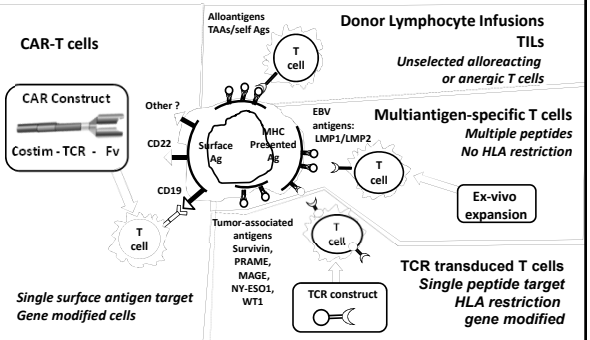
T cell mediated killing of its target cell



T cell mediated killing of its target cell

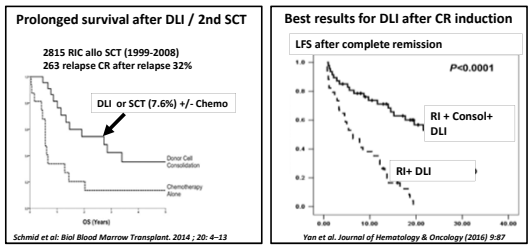


Antigen Targets and T cell effectors

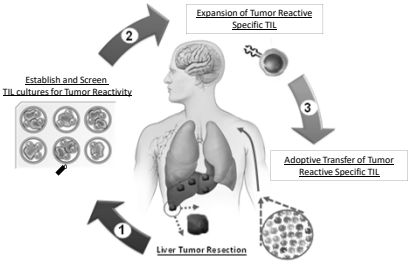


1. DLI and TILs

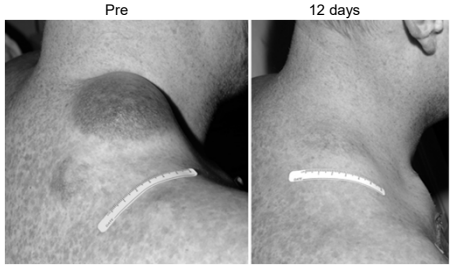
DLI FOR POST SCT RELAPSE MOST EFFECTIVE WITH CHEMOTHERAPY



Adoptive Immunotherapy for Metastatic Melanoma



Rapid Tumor Response after TIL Transfer Therapy: Cutaneous Melanoma

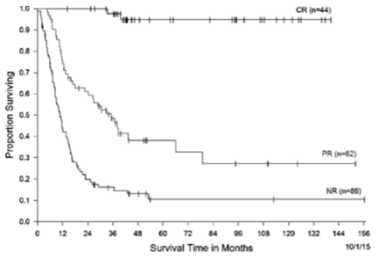


Adoptive TIL Transfer Therapy for Metastatic Cutaneous Melanoma: Surgery Branch/NIH

n	PR (%)	CR (%)	ORR (%)
194	62 (32%)	44 (23%)	106 (55%)

- *J Clin Oncol.* 2005 Apr 1;23(10):2346-57
- *J Clin Oncol.* 2008 Nov 10;26(32):5233-9
- *J Clin Oncol.* 2016 Jul 10;34(20):2389-97

Survival of Metastatic Melanoma Patients After TIL Therapy



Adoptive TIL Transfer for Additional Metastatic Solid Tumors

Cervical Cancer
3/9 responses (1 CR) - NCI

Cholangiocarcinoma
Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.
Tran et al., *Science*. 2014 May 9;344(6184):641-5.

Colorectal Cancer
T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer.
Tran et al., *N Engl J Med*. 2016 Dec 8;375(23):2255-2262.

TIL ADVANTAGES

- Evidence of efficacy
  - Documented PR and CR rates with long durations
  - Patients with prior immunotherapy
  - Patients with brain metastases
  - Patients with advanced, high bulk disease
- One treatment
  - No ancillary therapies needed after TIL and IL-2
- TIL can now be successfully prepared from > 90% of melanoma patients (NCI, Moffitt)
- Response rates reproduced at multiple sites and in multiple countries
- Opportunity for combination with checkpoint inhibitors

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TIL CHALLENGES

- Requires GMP manufacturing facility
- Special skills required for manufacture
- Production is expensive (labor, cytokines, plasticware)
- Length of time from tumor resection to treatment
  - Some patients may progress in the interim
- Preconditioning with cy/flu required → TOXICITY
- High dose IL-2 used
  - Inpatient treatment to monitor toxicities
  - Centers need to be comfortable administering high dose IL-2
  - IL-2 is expensive

JCI Insight. 2018 Oct 4; 3(19): e122467.

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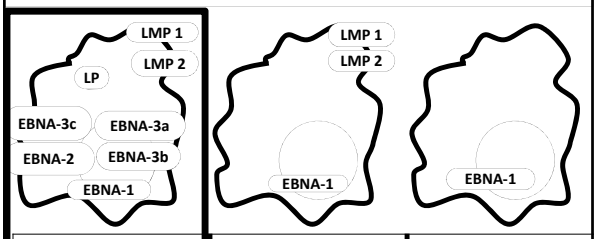
Optimizing Antigen-specific T cells

2. Targeting EBV+ Lymphomas

Types of EBV Latency



Type 3	Type 2	Type 1
Post transplant lymphoproliferative Disease Lymphoblastoid cell lines	NHL and HL Nasopharyngeal carcinoma	Burkitt's lymphoma

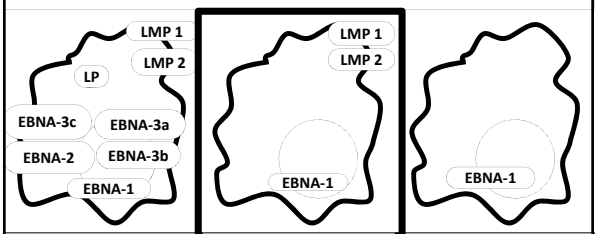
EBV-specific T cells for PTLD

- Use of EBV-CTL post HSCT is highly successful ***(Rooney and Heslop, Blood 2010 / Doubrovina and O'Reilly, Blood 2012)***
  - **155 patients**
  - **6.5% GVHD**
  - **≈91% success (durable)**
  - **14 failures -1 death from PTLD**
  - **1.2% CRS** ***Heslop and Bollard, Blood 2016***

Rationale of Immunotherapy for Lymphoma ….Beyond PTLD

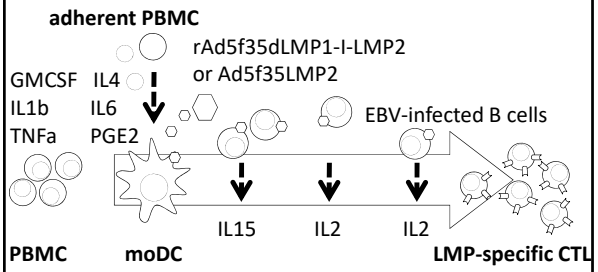
- Significant failure rate of therapy for advanced stage or recurrent disease
- Long-term side effects of chemotherapy and radiation
- EBV antigens expressed by 20-40% of lymphomas are potential targets for T cell immunotherapy

Types of EBV Latency



Type 3	Type 2	Type 1
Post transplant lymphoproliferative Disease Lymphoblastoid cell lines	NHL and HL NPC	Burkitt's lymphoma

Making LMP1 and LMP2 Immunodominant Antigens

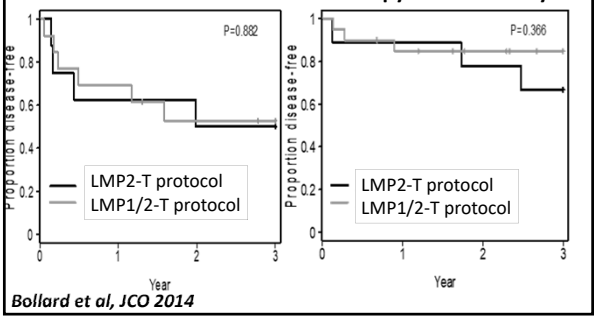


Bollard et al, JIT 2004
Straathof et al J Immunol 2005

Clinical Responses Post LMP T cells in Patients with Active Disease and Adjuvant Rx

12/21 CR - 50% Disease Free Survival at 2 Years

27/28 CR as Adjuvant Therapy 90% DFS at 2 years



Bollard et al, JCO 2014

Conclusions – LMP1/2 T Cells

- No toxicity
- Accumulation of LMP-T at disease sites
- Anti-tumor effects seen (13/21 patients PR/CR) (*Bollard et al, JCO 2014*)

Next….

→ LMP T cells post allo BMT (*McLaughlin et al, Blood 2018*)

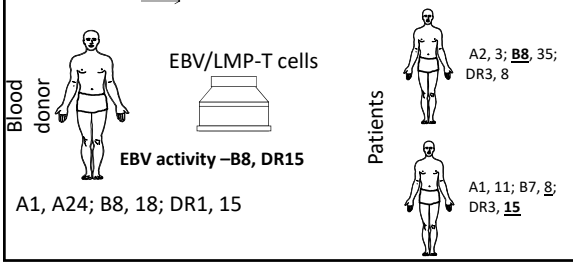
→ TGFβ resistant LMP-T (*Bollard et al, JCO 2018*)

Antigen specific T cells

3: Making T cells "Off the Shelf"

Making T cell Therapies "Off the Shelf"

Utilizing a third party EBV/LMP T cell bank can bypass the need for an available donor, and eliminates the wait for T cell production.

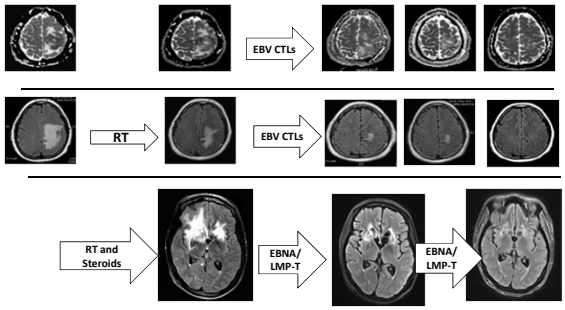


Third-Party EBV-directed T cells Support Safety

Study	Target	n	SAEs	Clinical Results
Haque, 2007	EBV post SOT / BMT	33	None	14 patients achieved CR, 3 PR (52%)
Barker, 2010; Doubrovina, 2012	EBV	5	None	4 patients achieved CR (3-5 VST doses)
Uhlin, 2010	EBV	1	None	CR (2 VST doses)
Leen, 2013	CMV, EBV, Adv	50	8 cases GvHD after VST (2 *de novo*)	74% CR/PR (69% for EBV n=9)
Tzannou, 2017	EBV, BKV, CMV, Ad, HHV6	38	2 cases *denovo* GVHD (grade I)	92% CR/PR (100% for EBV n=2).
Prockop, JCI, 2020	EBV post SOT/BMT	46	None	65% CR/PR (BMT) 54% CR/PR (SOT)

CNS Disease Successfully Treated with 3rd party EBV-directed T cells

87% CR/PR after SOT or BMT (MSKCC, BCM, CNMC)



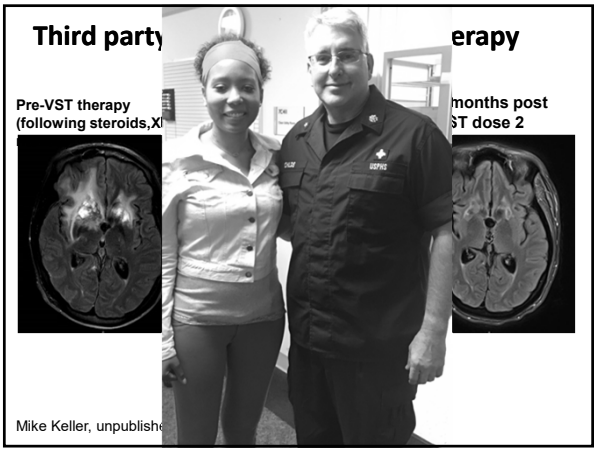
Prockop et al, JCI 2020
Bollard et al, ASHI 2017 Keller et al, ESID 2017

Pakakasama S et al, Transplantation. 2004

Third party erapy

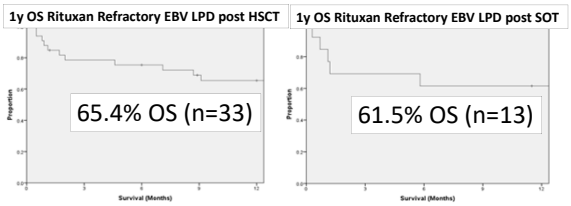
Pre-VST therapy (following steroids,X

months post ST dose 2



Mike Keller, unpublishe

Moving Third Party EBV T cells to a Multicenter Setting



No patient who achieved a CR or PR has died from EBV lymphoma

Atara Biotherapeutics licensed to develop and commercialize the MSKCC EBV cell therapy (ATA129). Prockop et al, JCI 2020

4. Antigen specific T cells - Targeting tumor associated antigens (TAA)

Targeting TAAs in Heme Malignancies– The Shortlist

Goswami et al, Leukemia 2014 Rooney et al, Imm Rev 2014	AML	CML	ALL	CLL	HL	NHL
WT1	+	+	+			
Proteinase 3	+	+				
PRAME	+	+	+		+	+
RHAMM	+	+	+	+		
Aurora A Kinase	+	+	+			
MAGE	+	+		+	+	+
MPP11				+		
HAGE	+	+				
BCR/ABL	+	+		+		
NY ESO 1		+				+
BMI-1		+		+		
Telomerase	+	+	+	+		
Fibromodulin				+		
Syntaxin				+		
SSX					+	+
Survivin	+	+	+	+	+	+

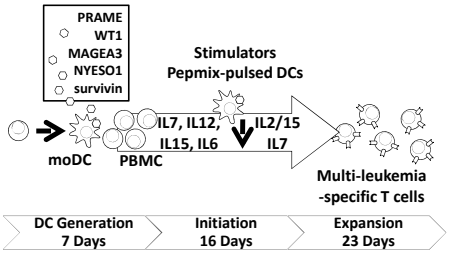
Use of Donor-derived WT-1 specific T cells for Acute Leukemia

- 11 patients infused with HLA-A*0201-restricted WT1-specific donor-derived CD8+ T cell clones.
- No attributed toxicities/GVHD.
- 2 clinical responses
- 3 patients at high risk for relapse remain in CR.
- CTLs generated in the presence of IL-21 remained detectable long-term

Studies using WT1 specific T cells generated using overlapping peptides ongoing at MSKCC
(Koehne and O'Reilly)

Chapuis and Greenberg Sci Trans Med 2013

Clinical Use of Multi TAA T cells for Cancer



Weber et al, CCR 2013, ***Weber et al, Leukemia 2013****, Gerdemann et al, Mol Ther 2012*

TAA-T for AML after allo SCT – Phase I study

TAA: WT1 NyESO PRAME Survivin Dose escalation 5 x 10^6 → 1x 10^7 → 2 x 10^7 /m²

27 enrolled

20 treated

13 HIGH RISK for relapse ADJUVANT

- 3 CR2/3
- 3 FLT3-ITD
- 3 MDS tAML
- 2 MLL-r
- 1 Ph+
- 1 DNMT3a

8 CCR
4 Relapsed

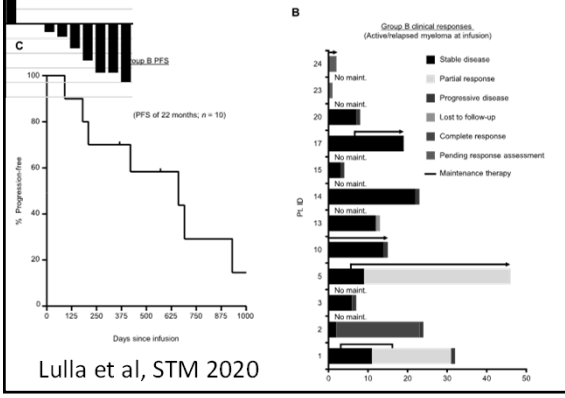
7 RELAPSE /ACTIVE DISEASE POST SCT >d30

- 5 30-70% blasts in BM
- 2 extramedullary relapse

1 CR
1 PR
4 NR
1 NE

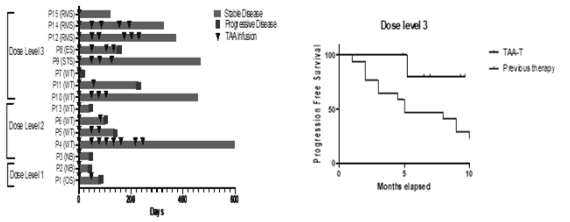
Lulla et al , TCT meeting 2019

Use of TAA-T cells in Myeloma



Lulla et al, STM 2020

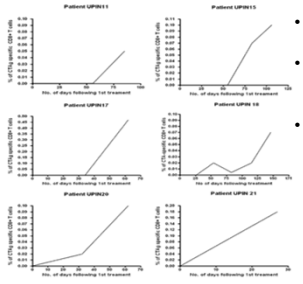
Prolonged disease stabilization in Patients with solid tumors post TAA-T



No SAEs attributable to Rx
No CRS

Hont et al JCO 2019

Increased TAA-specific T cells in patients with AML/MDS post Epigenetic Therapy- Opportunity for Combination RX



- 21 patients treated with AZA/VPA.
- CTL responses seen in 10 patients.
- 8 patients with circulating MAGE CTLs achieved a major clinical response

blood

Goodyear et al Blood 2010

Summary- Use of TAA-T as Treatment for Relapsed Cancers

- TAA-T cells can be generated from healthy donors for clinical use (> 90% success rate)
- TAA-T cells are safe for patients with relapsed hematopoietic malignancies (lymphoma, AML, myeloma) after chemotherapy/autologous BMT and post allo HSCT
- Early evidence of efficacy?

5. abTCR transduced T cells

HIGH AFFINITY WT1 TCR TRANSDUCED T CELLS TO PREVENT POST SCT RELAPSE

12 AML HLA A2 (10 proven WT1 +) RISK: 6 adverse, 4 intermediate, 2 favorable

At transplant 8 CR 4 detectable disease

Days between SCT and T cell infusion 47-175 median 100d

1-4 infusions of WT1 high affinity TCR transfected into donor EBV specific CD8+ T cells

Study group	P = 0.002	Comparative untreated group
12 AML 100% RFA at 44 mo		88 AML 54% RFS

Long-term persistence of functional WT1 TCR T cells

Chapuis et al 2019 Nature Medicine 25: 1106

Published clinical TCR-T therapy for solid tumors and Myeloma.

Target	Disease	Vector	Pretreatment	#patients	Response
MART-1	Melanoma	Retrovirus	Chemotherapy	20	30% objective antitumor response
Gp100	Melanoma	Retrovirus	Chemotherapy	16	19% objective antitumor response
CEA	Colorectal	Retrovirus	Chemotherapy	3	1 objective response
NY-ESO-1	Melanoma/ sarcoma	Retrovirus	Chemotherapy	17	2 CR; 1 PR
NY-ESO-1	MM	Lentivirus	Chemotherapy	20	80% maintained remissions post ASCT
MAGE A3	Melanoma Sarcoma Esophageal	Retrovirus	Chemo/RT/Surgery	9	4 PR (4-12+mths), 1 CR (15+mths)
MAGE-A3	Melanoma /MM	Lentivirus	CY	2	2 died of cardiac toxicities (titin)
MAGE-A4	Esophageal	Retrovirus	Surgery; radiotherapy; chemotherapy	10	7/10 tumor progression

Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. *Front Immunol*. 2019;10:2250. Published 2019 Oct 11. doi:10.3389/fimmu.2019.02250

Cancer Regression and Neurological Toxicity Following Anti-MAGE-A3 TCR Gene Therapy

Richard A. Morgan, Nachimuthu Chinnasamy,* Daniel Abate-Daga,* Alena Gros,* Paul F. Robbins,* Zhili Zheng,* Mark E. Dudley,* Steven A. Feldman,* James C. Yang,* Richard M. Sherry,* Giao Q. Phan,* Marybeth S. Hughes,* Udai S. Kammula,* Akemi D. Miller,* Crystal J. Hessman,* Ashley A. Stewart,* Nicholas P. Restifo,* Martha M. Quezado,† Meghna Alimchandani,† Avi Z. Rosenberg,† Avindra Nath,‡ Tongguang Wang,‡ Bibiana Bielekova,‡ Simone C. Wuest,‡ Nirmala Akula,§ Francis J. McMahon,§ Susanne Wilde,‖ Barbara Mosetter,‖ Dolores J. Schendel,‖¶ Carolyn M. Laurencot,* and Steven A. Rosenberg**

Case Report of a Fatal Serious Adverse Event Upon Administration of T Cells Transduced With a MART-1-specific T-cell Receptor

Joost H van den Berg[1,2], Raquel Gomez-Eerland[1], Bart van de Wiel[3], Lenie Hulshoff[4], Daan van den Broek[5], Adriaan Bins[6], Hanno L Tan[7], Jane V Harper[8], Namir J Hassan[8], Bent K Jakobsen[8], Annelies Jorritsma[1], Christian U Blank[1,6], Ton NM Schumacher[1] and John BAG Haanen[1,6]

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

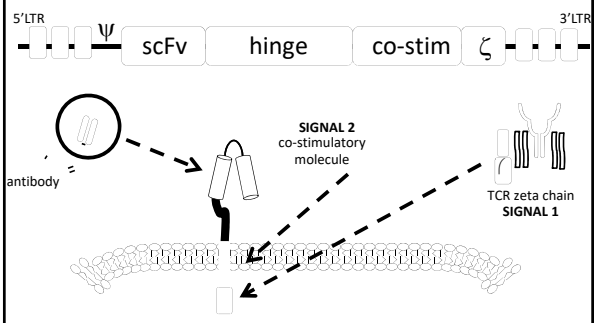
Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma

Gerald P. Linette,[1] Edward A. Stadtmauer,[2] Marcela V. Maus,[3] Aaron P. Rapoport,[3] Bruce L. Levine,[3] Lyndsey Emery,[3] Leslie Litzky,[3] Adam Bagg,[3] Beatriz M. Carreno,[1] Patrick J. Cimino,[1] Gwendolyn K. Binder-Scholl,[4] Dominic P. Smethurst,[4] Andrew B. Gerry,[4] Nick J. Pumphrey,[4] Alan D. Bennett,[4] Joanna E. Brewer,[4] Joseph Dukes,[5] Jane Harper,[5] Helen K. Tayton-Martin,[5] Bent K. Jakobsen,[5,6] Namir J. Hassan,[6] Michael Kalos,[3] and Carl H. June[1]
[1]Abramson Cancer Center and Departments of Medicine and Pathology and Immunology, Washington University School of Medicine, St. Louis, MO; [2]Abramson Cancer Center, Department of Medicine, and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [3]The Greenebaum Cancer Center, University of Maryland, Baltimore, MD; [4]Adaptimmune Ltd, Philadelphia and Abingdon, United Kingdom; and [5]Immunocore Ltd, Abingdon, United Kingdom

Chimeric Antigen Receptor (CAR) T cells

4: CD19 CAR T cells

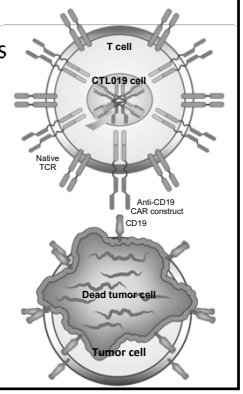
Designing a Chimeric Antigen Receptor



Redirecting the Specificity of T Cells

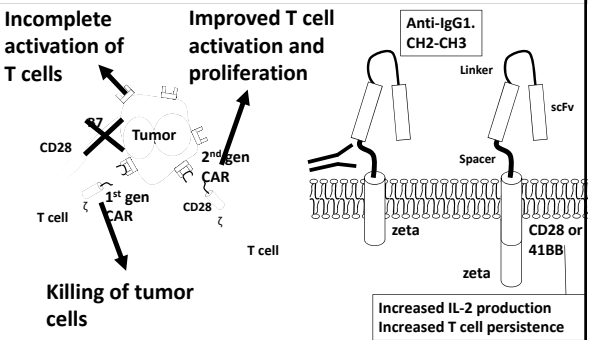
- Different transduction systems to get CARs into T cells:

→Retroviral transduction
→Lentiviral transduction
versus
→ non viral transduction (Sleeping Beauty)



Courtesy of David Porter- U Penn

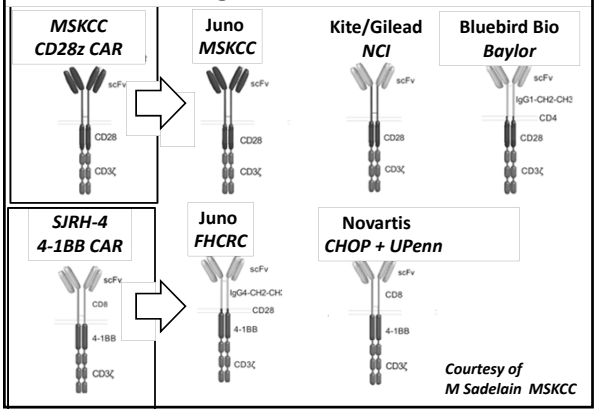
Incomplete activation of 1st generation CAR-directed T cells



Courtesy of Carlos Ramos- BCM

(Maher, Nat Biotechnol 2002 and Savoldo JCI 2011)

Original CD19 CARs



Courtesy of M Sadelain MSKCC

Multicenter CD19 CAR T-cell trials in aggressive NHL

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al. NEJM 2017	Schuster NEJM 2018	Abramson et al. ASH 2017, EHA/ASCO 2018
CAR T dose	2 x 10^6/kg	0.6-6 x 10^8 Median 3x10^8	0.5-1 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL Gr 3B
Relapsed/ Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	47%	42%
Bridging therapy	Not allowed	Allowed (93%)	Allowed
Manufacturing success	99%	94%	98%
Treated/Enrolled	101/111 (91%)	111/165 (67%)	108/140 (77%)

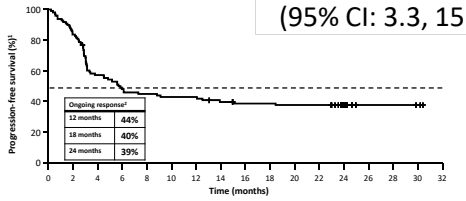
Efficacy in multicenter CD19 CAR T trials for adult DLBCL

Best response					Durability of responses			
Study/ Sponsor	Product	N	Best ORR	Best CR rate	F/U mo	Durable ORR	Durable CR rate	Ref
ZUMA1 / Kite/Gilead	CD19/ CD3ζ/ CD28	108	83%	58%	27	39%	37%	Locke et al, Lancet Oncol 2018
JULIET / Novartis	CD19/ CD3ζ/ 4-1BB	111	52%	40%	14	37%	30%	Schuster et al, NEJM 2018
TRANSCEND Celgene/ Juno	CD19/CD 3ζ/ 4-1BB	88	74%	52%	6	47%	42%	Abramson et al, ASH 2017/EHA 2018

ZUMA-1: Durable progression-free survival

Median follow-up: 27.1 months (IQR 25.7–28.8) N=101

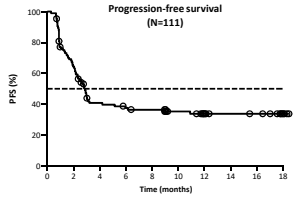
Median PFS: 5.9 months*
(95% CI: 3.3, 15.0)



1. Locke FL, *et al. Lancet Oncol* 2019; 20:31–42 (incl. suppl.).
2. Neelapu SS, *et al.* ASH 2018 (Abstract 2967; poster).

72% of patients progression free at 24 months IF CR at 3 months, 75% IF PR at 3 months[1]
Median duration of response for complete responders not reached[1]

JULIET: Durable responses also seen with tisagenlecleucel



- **Among responders, the 12-month PFS was 65%[2,3]**
- **54% (15/28) of patients who had achieved a PR converted to CR[3]**
  - **Includes two patients with CR 9–12 months after initial PR[4]**
- **CAR T cells were detectable for up to 2 years in responding patients[2]**

1. Tisagenlecleucel CHMP assessment report (Jun 2018; available at: www.ema.europa.eu).
2. 2. Schuster S, *et al. N Engl J Med* 2019; 380:45–56.
3. Schuster SS, *et al.* ASH 2018 (Abstract 1684; poster).

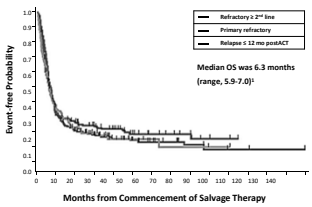
Median PFS: 2.9 months*
(95% CI: 2.2, 6.2)[1]

Are CD19 CAR T cells Better than Standard of Care?
R/R DLBCL: SCHOLAR-1 study

a patient level, pooled analysis from 2 RCTs and 2 registries

N=636 patients
- **N=178 primary refractory**
- **N=458 refractory to salvage or relapsed <1 yr after auto-SCT**

- **ORR: 26% (22,31)**
- **CR: 7% (3,15)**
- **Median OS 6.3 months**



Crump et al, Blood 2017

The Cytokine Release Syndrome and Neurotoxicity

Median time of CRS onset = 2-3 days (range 1–22 days)

Prodromal syndrome* to life-threatening manifestations.
*Flu-like syndrome with fever, fatigue, headache, arthralgia, myalgia, and malaise.

Pyrexia (fever > 38°C) is the most frequent, and usually first sign → hypoxia and mild hypotension

GIT Sx such as nausea, diarrhea and vomiting common.

Severe CRS→hemodynamic instability and organ dysfunction

<10% of patients, CNS toxicity occurs in the absence of CRS→ typically mild (grade 1).
Other 90%, CNS toxicity concurrent with CRS or following its resolution
Clinical features vary from headache, pain, memory loss, meningismus, dizziness, alterations in mental status, movement disorders, impaired speech→ seizures and encephalopathy → coma

Treatment
Cytokine Release Syndrome and Neurotoxicity

Adverse effect	Commercial CAR T	
	Tisagenlecleucel[5]	Axicabtagene ciloleucel[8]
Cytokine release syndrome (CRS) 	• Administer tocilizumab in patients with CRS that requires moderate to aggressive intervention. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper.	• Administer tocilizumab if CRS grade ≥ 2. • Administer methylprednisolone if CRS grade ≥ 3 or CRS grade 2 if no improvement within 24 hours after starting tocilizumab.
Central Nervous Toxicity (CNS) 	• No specified management in the prescribing information.	• If neurotoxicity is associated with CRS administer tocilizumab as previously described. • If neurotoxicity is grade ≥ 3 administer dexamethasone (CNS grade 3) or high dose of methylprednisolone (CNS grade 4) with the first dose of tocilizumab. • If neurotoxicity is not associated with CRS, administer dexamethasone (CNS grade 2 or 3) or high dose of methylprednisolone (CNS grade 4)

Can CAR T-cells beat alloSCT in DLBCL?

CIBMTR data - 3-5 year PFS = 20-30%
CAR T- 2 year PFS= 40%

	CAR T-cells	alloSCT
Need for a donor	No	Yes
Need to be in remission	No	Yes
NRM	<5%	20-30%
Acute toxicity (neuro)	Yes	No
Long term complications	hypogamma	GVHD Opp. infections
Sec malignancies	No?	Yes

Epperla, Hematol Oncol Stem Cell Therapy 2017;10:277-284

CD19 CARs – Remaining Issues

- Managing CRS/ MAS/Neurotoxicity
- Complex study esp in multicenter setting
- Managing Prolonged B cell depletion
- **Expense! Insurance Issues?**
- CAR attributes for potency remain unclear
- **Immunogenicity- (Turtle et al, STM 2016)**
  Hu19-CD828Z CAR T cells
  →ORR 12/16, CR 8/16 (NCI)
- **Immune escape through antigen loss**

BCMA-CAR T cells for Myeloma

B-cell maturation antigen (BCMA)-directed CAR T cells have shown promising efficacy and safety profiles in various phase I/II clinical trials.

CR rates range from <10- 30%

However, almost all treated patients continue to relapse

A BCMA-directed product for the treatment of multiple myeloma is expected to be approved shortly.

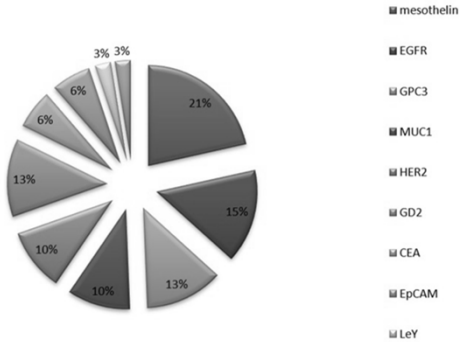
Curr Opin Oncol . 2020 Jul 27.

Published Clinical Results: CAR-T Cells in AML

CAR Target	Cytotoxicity	Results
CD123	Long term hematopoiesis High rates of CRS	Potent in vitro activity In vivo studies No clinical trials results
CD33	Lung and GI Hematopoietic toxicity	"potent but transient"
Lewis-Y Antigen	GI Toxicity High rates of CRS	Transient – all pts relapsed
NKG2D	No toxicity	No response

Other Targets Under Investigation:
CD33, CD38, CD56, CD117,CD123,CD34 or Muc1 *

Current clinical target of CAR-T therapy in solid tumor



Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. *Front Immunol*. 2019;10:2250. Published 2019 Oct 11. doi:10.3389/fimmu.2019.02250

Selected Clinical Trials - CAR T cells Solid Tumors

Trial	Tumor	Target	CAR Design	Phase	Best Response Data
Brown et al	Glioblastoma	IL-13Rα2	CD3ζ	I	*
Louis et al	Neuroblastoma	GD2	CD3ζ	I	CR, 27%; 19 patients**
Park et al	Neuroblastoma	CD171	CD3ζ	I	PD
Feng et al	Non–small cell lung cancer	EGFR	4-1BB/CD3ζ	I	PR, 18%; SD, 45%; 11 patients
Beatty et al	Mesothelioma/pancreatic cancer	Mesothelin	4-1BB/CD3ζ	I	PR, 50%; 2 patients
Junghans et al	Prostate cancer	PSA	CD3ζ	I	PR, 40%; 5 patients
Lamers et al	Renal cell carcinoma	CAIX	FcRγ	I	PD
Kershaw et al	Ovarian cancer	Folate receptor α	FcRγ	I	PD
Ahmed et al	Sarcoma	*HER2*	CD28/CD3ζ	I/II	SD, 24%; 17 patients
NCT02209376	Glioblastoma	EGFRIII	4-1BB/CD3ζ	I	N/A
NCT01454596	Malignant glioma Glioblastoma Brain cancer	EGFRIII	CD28/CD3ζ	I/II	N/A
NCT02664363	Glioblastoma	EGFRIII	†	I	N/A
NCT02208362	Glioblastoma	IL-13Rα2	4-1BB/CD3ζ	I	N/A
NCT02311621	Neuroblastoma Ganglioneuroblastoma	CD171	4-1BB/CD3ζ CD28/41BB/CD3ζ	I	N/A
NCT01822652	Neuroblastoma	GD2	CD28/OX40/CD3ζ	I	N/A
NCT01818323	Head and neck cancer	*ErbB*	CD28/CD3ζ	I	N/A
NCT02547961	Breast cancer	*HER2*	CD28/CD3ζ	I/II	N/A
NCT02349724	Lung cancer Colorectal cancer Gastric cancer Breast cancer Pancreatic cancer	CEA	†	I	N/A
NCT02414269	Malignant pleural disease Mesothelioma metastases Lung cancer Breast cancer	Mesothelin	CD28/CD3ζ	I	N/A
NCT02159716	Pancreatic cancer Ovarian cancer Mesothelioma	Mesothelin	4-1BB/CD3ζ	I	N/A
NCT01583686	Cervical cancer Pancreatic cancer Ovarian cancer Mesothelioma Lung cancer	Mesothelin	†	I/II	N/A
NCT01140373	Prostate cancer	PSMA	CD28/CD3ζ	I	N/A
NCT02498912	Ovarian cancer	Muc-16	CD28/CD3ζ	I	N/A
NCT00902044	Sarcoma	*HER2*	CD28/CD3ζ	I	N/A
NCT02107963	Sarcoma Osteosarcoma Neuroblastoma Melanoma	GD2	OX40/CD28/CD3ζ	I	N/A

*Patients underwent craniotomy before CAR therapy.
**Patients with NED before CAR therapy were not included in denominator of responders.
†Not listed on clinicaltrials.gov
Abbreviations: CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CR, complete response; EGFRIII, EGFR variant III; FcR, fragment crystallizable receptor; GD2, disialoganglioside GD2; IL-13Rα2, interleukin-13 receptor α2; MUC-16, mucin 16; N/A, not applicable; NED, no evidence of disease; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SD, stable disease.

Published in: Oladapo Yeku; Xinghuo Li; Renier J. Brentjens; *American Society of Clinical Oncology Educational Book* 37193-204, 2017.
DOI: 10.1200/EDBK_180328

CAR Therapy in the USA 2014 to present: Summary

Large trials with long follow up confirm ability of CD19-directed CAR T cells to induce CRs

Partnerships with industry and licensure now broaden applicability

But still no major "home run" beyond CD19-CAR

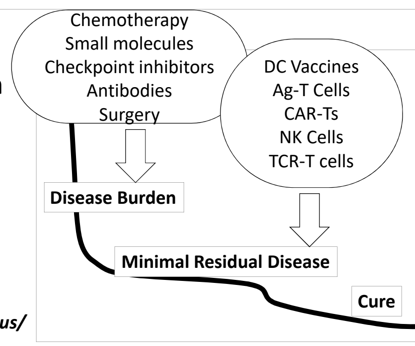
Overall Summary

- CD19 CAR-T cells highly effective in R/R - B cell NHL
- CD19-negative escape is a mechanism of relapse
- Other CAR targets are available (with advantages and disadvantages) - still in early stages of development
- Combinatorial targeting could reduce antigen-negative escape and improvement of T cell based therapies overall?

→ improve outcome with a combination approach (SCT, checkpoint blockade, vaccines, multi tumor antigen specific T cells, oncolytic viruses, nanoparticles, etc etc etc) ?

Cell Therapy for Cancer – The Vision

Potential for Combination Therapies



Sources: Autologous/ Allogeneic

Acknowledgements

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Kieron Dunleavy,
Mitch Smith, Eduardo Sotomayor
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Children's National Medical Center

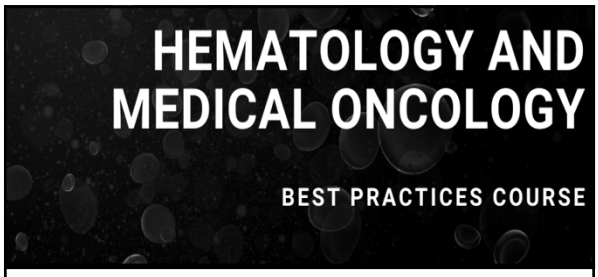
Michael T. Lotze
University of Pittsburgh
Marie José Kersten
University of Amsterdam

46

Hematologic Complications of COVID

Emiliano Muganaini, MD

August 17, 2020



46 - Hematologic Complications of COVID

Emiliano Mugnaini, MD, PhD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

OUTLINE

1. Normal coagulation homeostasis
1. Disease course & Lab results COVID-19
2. Inflammatory coagulopathy COVID-19
   - microscopic findings
3. Hematologic management COVID-19 hypercoagulability

Hypercoagulability in COVID-19

an inflammatory coagulopathy

OBJECTIVES:

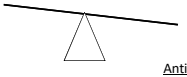
1. Review physiology of clotting
2. Understand that inflammatory markers rise during disease course
3. Recognize the high incidence of vascular events in COVID-19
4. Appreciate prominence of platelets + fibrin deposition in tissues
5. See direct viral infection resulting in endotheliitis.
6. Proactive anticoagulation management strategy may be of benefit.

1. Normal coagulation homeostasis

Human homeostatic system provides balance b/w procoagulant and anticoagulant forces.

allows for blood flow (normal) vs. clotting (prevent exsanguination following injury)

The Players:
1. platelets
2. plasma proteins (clotting factors + inhibitors)
3. vessel wall



Procoagulant forces:
- platelet adhesion
- platelet aggregation
- fibrin clot formation

Anticoagulant forces:
- inhibitory proteins
- fibrinolysis

adapted from Harrison's Principles of Internal Medicine, 20th Edition

1. Normal coagulation homeostasis

Vascular injury → platelets ADHERE to denuded vascular intimal surface.

primarily to: a) von Willebrand Factor (vWF)
(large multimeric protein present in plasma + extracellular matrix of subendothelium).

also to: b) subendothelial collagen.

PLATELET ADHESION → ACTIVATION + AGGREGATION.

Platelet glycoprotein (Gp) IIb/IIIa complex = most abundant Rc on platelet surface.
Platelet activation converts: Inactive Gp IIb/IIIa → Active Gp IIb/IIIa.

Platelets bind further vWF + fibrinogen .

FIBRINOGEN BRIDGES form b/w platelets.
Further PLATELET-PLATELET INTERACTION recruits more platelets.

Response enhanced/amplified by :
- Epinephrine (in plasma)
- Thrombin (in plasma)
- Adenosine DiPhosphate (from platelets)
- Serotonin (from platelets)

Resultant platelet plugs ANCHORS TO FIBRIN MESH.

RESULT = PLATELET THROMBUS.

adapted from Harrison's Principles of Internal Medicine, 20th Edition

1. Normal coagulation homeostasis

adapted from Harrison's Principles of Internal Medicine, 20th Edition

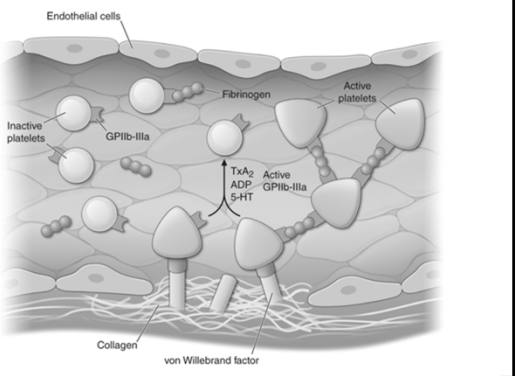


FIGURE 113-1

Platelet activation and thrombosis. Platelets circulate in an inactive form in the vasculature. Damage to the endothelium and/or external stimuli activates platelets that adhere to the exposed subendothelial von Willebrand factor and collagen. This adhesion leads to activation of the platelet, shape change, and the synthesis and release of thromboxane (TxA_2), serotonin (5-HT), and adenosine diphosphate (ADP). Platelet stimuli cause conformational change in the platelet integrin glycoprotein (GP) IIb/IIIa receptor, leading to the high-affinity binding of fibrinogen and the formation of a stable platelet thrombus.

1. Normal coagulation homeostasis Coagulation cascade

adapted from Harrison's Principles of Internal Medicine, 20th Edition

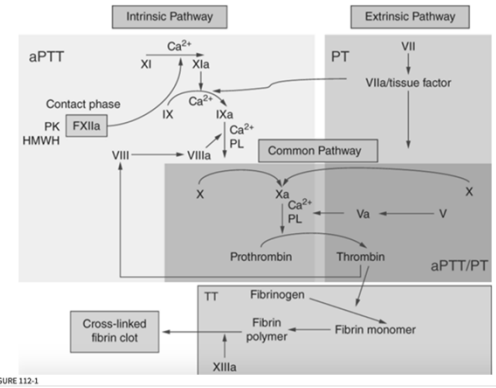


FIGURE 112-1

Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL).

1. Normal coagulation homeostasis

adapted from Harrison's Principles of Internal Medicine, 20th Edition

Coagulation cascade

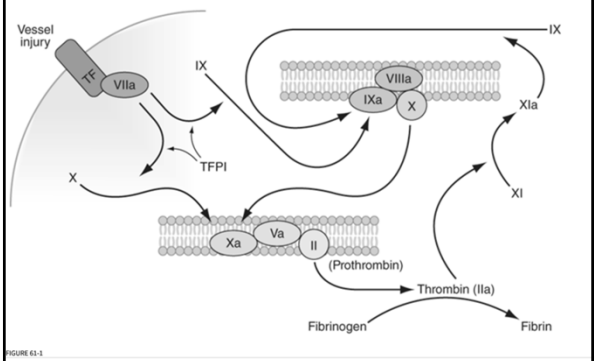


FIGURE 61-1

Coagulation is initiated by tissue factor (TF) exposure, which, with factor (F) VIIa, activates FIX and FX, which in turn, with FVIII and FV as cofactors, respectively, results in thrombin formation and subsequent conversion of fibrinogen to fibrin. Thrombin activates FXI, FVIII, and FV, amplifying the coagulation signal. Once the TF/FVIIa/FXa complex is formed, tissue factor pathway inhibitor (TFPI) inhibits the TF/FVIIa pathway, making coagulation

2. Disease course & Lab results COVID-19

SARS-CoV-2 = "Severe Acute Respiratory Virus-Coronavirus-2"

beta coronavirus 2b lineage

COVID = "Coronavirus Disease 2019"

Zhou *et al.*, Lancet, 2020

2. Disease course & Lab results COVID-19

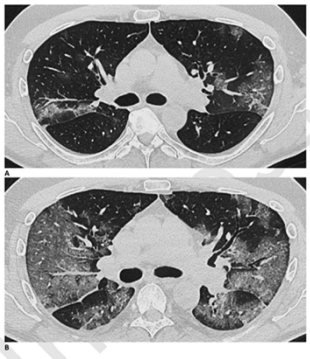


Figure 2: Chest CT images in 51-year-old male patient presenting with progressive symptoms of cough and fever, proven COVID-19. (A) Day 7 after onset of symptoms: CT demonstrates bilateral ground glass opacities (GGOs) and early vascular enlargement. (B) Day 10: Rapid progression of GGOs with vascular thickening and interstitial pulmonary edema. (Figure courtesy of Department of Radiology, Haaglanden Medical Centre, The Hague, the Netherlands.)

Oudkerk *et al.*, Radiology, 2020

2. Disease course & Lab results COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical Treatment Expert Group for Covid-19*

n = 1099

N Engl J Med 2020;382:1708-20.

n = 138

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China

Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD

JAMA. 2020;323(11):1061-1069.

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Lancet 2020; 395: 1054-62

n = 191

Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

2. Disease course & Lab results COVID-19 **poor outcome (p <0.05)*

	Guan *et al.*, NEJM	Wang *et al*, JAMA	Zhou *et al.*, Lancet
median age	47	56*	56*
M/F	58/42	54/46	62/38
co-morbidity	HTN (15%) DM (7%) CAD (3%) hep B (2%)	HTN (31%)* CAD (15%)* DM (10%)* cancer (7%)	HTN (30%)* DM (19%)* CAD (8%)* COPD (3%)
most common sxs #89% during hosp.	cough (68%) fever (44%)# fatigue (38%) sputum (34%) SOB (19%)	fever (99%) fatigue (70%) cough (59%) anorexia (40%)* myalgia (35%)	fever (94%) cough (79%) SOB (29%) fatigue (23%) sputum (23%)
ICU admit	5.0%	26%	26%
mortality	1.4%	4.3%	28%

2. Disease course & Lab results COVID-19 **poor outcome (p <0.05)*

	Guan *et al.*, NEJM	Wang *et al*, JAMA	Zhou *et al.*, Lancet
leukocytosis	6%		21%*
lymphocytopenia	83% (<1.5)		40% (<0.8)*
thrombocytopenia	36% (<150)		7% (<100)
high CRP	61%		
high d-dimer	46%		68%*
high ferritin			80%*
high LDH	41%	40%	67%*
prolong PT		58% (>13)	6%* (>16)
abnorm CXR	59%		59%
abnorm CT Chest	86%	100%	71-75%
ICU admit	5.0%	26%	26%
mortality	1.4%	4.3%	28%

2. Disease course & Lab results COVID-19

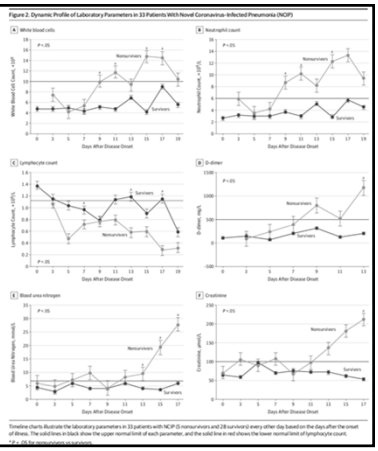


Figure 2. Dynamic Profile of Laboratory Parameters in 33 Patients With Novel Coronavirus-Infected Pneumonia (NCP)

Timeline charts illustrate the laboratory parameters in 33 patients with NCP (5 nonsurvivors and 28 survivors) every other day based on the days after the onset of illness. The solid lines in black show the upper normal limit of each parameter, and the solid line in red shows the lower normal limit of lymphocyte count.

Wang *et al.*, JAMA, 2020

2. Disease course & Lab results COVID-19

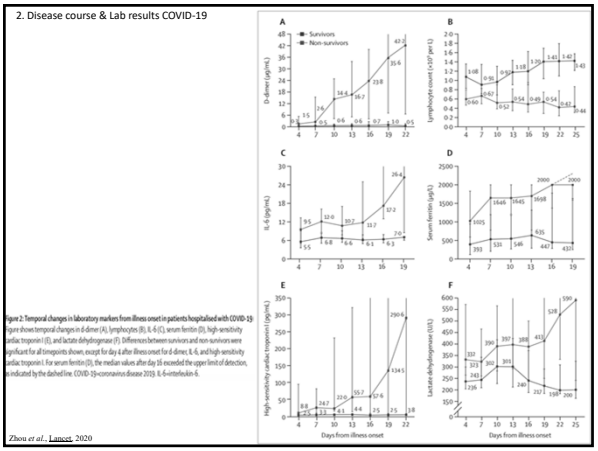


Figure 2: Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19

Figure shows temporal changes in d-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors and non-survivors were significant for all timepoints shown, except for day 4 after illness onset for d-dimer, IL-6, and high-sensitivity cardiac troponin I. For serum ferritin (D), the median values after day 16 exceeded the upper limit of detection, as indicated by the dashed line. COVID-19=coronavirus disease 2019. IL-6=interleukin-6.

Zhou *et al.*, Lancet, 2020

2. Disease course & Lab results COVID-19

COVID-19 = highly inflammatory/coagulopathic clinicopathologic state.

"age-dependent defects in T-cell and B-cell function
+
excess production of type-2 cytokines

could lead to:

a) deficiency in control of viral replication

&

b) more prolonged pro-inflammatory response,

possibly leading to poor outcome."

Zhou *et al.*, Lancet, 2020

2. Disease course & Lab results COVID-19

nature https://doi.org/10.1038/s41586-020-2588-y

Accelerated Article Preview

Longitudinal analyses reveal immunological misfiring in severe COVID-19

Carolina Lucas, Patrick Wong, Jon Klein, Tiago B. R. Castro, Julio Silva, Maria Sundaram, Mallory K. Ellingson, Tianyang Mao, Ji Eun Oh, Benjamin Israelow, Takehiro Takahashi, Maria Tokuyama, Peiwen Lu, Arvind Venkataraman, Annsea Park, Subhasis Mohanty, Haowei Wang, Anne L. Wyllie, Chantal B. F. Vogels, Rebecca Earnest, Sarah Lapidus, Isabel M. Ott, Adam J. Moore, M. Catherine Muenker, John B. Fournier, Melissa Campbell, Camila D. Odio, Arnau Casanovas-Massana, Yale IMPACT Team, Roy Herbst, Albert C. Shaw, Ruslan Medzhitov, Wade L. Schulz, Nathan D. Grubaugh, Charles Dela Cruz, Shelli Farhadian, Albert I. Ko, Saad B. Omer & Akiko Iwasaki

Received: 23 June 2020
Accepted: 21 July 2020
Published online: 27 July 2020

Science

Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications

Divij Mathew[1,2†], Josephine R. Giles[1,2,3†], Amy E. Baxter[1,2†], Derek A. Oldridge[1,2†], Allison R. Greenplate[1,2†], Jennifer E. Wu[1,2,3†], Cécile Alanio[1,2,3†], Leticia Kuri-Cervantes[1,2], M. Betina Pampena[1,2], Kurt D'Andrea[1], Sasikanth Manne[1,2], Zeyu Chen[1,2], Yinghui Jane Huang[1,2], John P. Reilly[1], Ariel R. Weisman[1], Caroline A. G. Ittner[1], Oliva Kuthuru[1,2], Jeanette Dougherty[1,2], Kito Nzingha[1,2], Nicholas Han[1,2], Justin Kim[1,2], Ajinkya Pattekar[1,2], Eileen C. Goodwin[1,2], Elizabeth M. Anderson[1,2], Madison E. Weirick[1,2], Sigrid Gouma[1,2], Claudia P. Arevalo[1,2], Marcus J. Bolton[1,2], Fang Chen[3], Simon F. Lacey[3,4,5], Holly Ramage[6], Sara Cherry[1,2], Scott E. Hensley[1,2], Sokratis A. Apostolidis[1,2,3], Alexander C. Huang[1,2,3], Laura A. Vella[1,2,3], The UPenn COVID Processing Unit†, Michael R. Betts[1,2,7], Nuala J. Meyer[1,2], E. John Wherry[1,2,3,7]

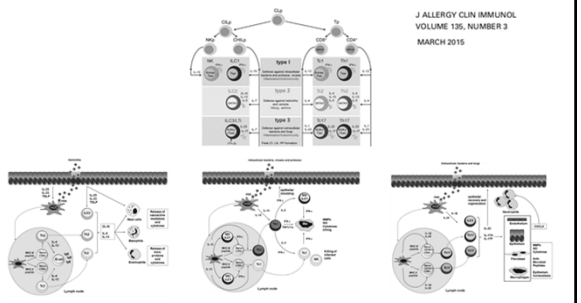
First release: 15 July 2020

2. Disease course & Lab results COVID-19

The 3 major types of innate and adaptive cell-mediated effector immunity

Francesco Annunziato, PhD,[a] Chiara Romagnani, MD, PhD,[b] and Sergio Romagnani, MD[a] *Florence, Italy, and Berlin, Germany*

J ALLERGY CLIN IMMUNOL
VOLUME 135, NUMBER 3
MARCH 2015



2. Disease course & Lab results COVID-19

J Thromb Haemost. 2020;18:844–847.
jth

BRIEF REPORT

Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang[1] | Dengju Li[2] | Xiong Wang[1] | Ziyong Sun[1]

n = 191
mortality 11%

coagulation parameters tracked from d1-d14 after admission at 3 day intervals

data from consecutive patients retrospectively analyzed.

FINDINGS:

1) abnorm coagulation results assoc w poor prognosis.

2) DIC common in deaths with COVID-19.

2. Disease course & Lab results COVID-19

1) abnorm coagulation results assoc w poor prognosis.

TABLE 1 Coagulation parameters of NCP patients on admission

Parameters	Normal range	Total (n = 183)	Survivors (n = 162)	Non-survivors (n = 21)	*P* values
Age (years)		54.1 ± 16.2	52.4 ± 15.6	64.0 ± 20.7	<.001
Sex (male/female)		98/85	82/80	16/5	.035
With underlying diseases		75 (41.0%)	63 (38.9%)	12 (57.1%)	.156
On admission					
PT (sec)	11.5-14.5	13.7 (13.1-14.6)	13.6 (13.0-14.3)	15.5 (14.4-16.3)	<.001
APTT (sec)	29.0-42.0	41.6 (36.9-44.5)	41.2 (36.9-44.0)	44.8 (40.2-51.0)	.096
Fibrinogen (g/L)	2.0-4.0	4.55 (3.66-5.17)	4.51 (3.65-5.09)	5.16 (3.74-5.69)	.149
D-dimer (μg/mL)	<0.50	0.66 (0.38-1.50)	0.61 (0.35-1.29)	2.12 (0.77-5.27)	<.001
FDP (μg/mL)	<5.0	4.0 (4.0-4.9)	4.0 (4.0-4.3)	7.6 (4.0-23.4)	<.001
AT (%)	80-120	91 (83-97)	91 (84-97)	84 (78-90)	.096

Abbreviations: APTT, activated partial thromboplastin time; AT, antithrombin activity; FDP, fibrin degradation product; NCP, novel coronavirus pneumonia; PT, prothrombin time (PT).

Tang *et al*., J Thromb Haemost, 2020

2. Disease course & Lab results COVID-19

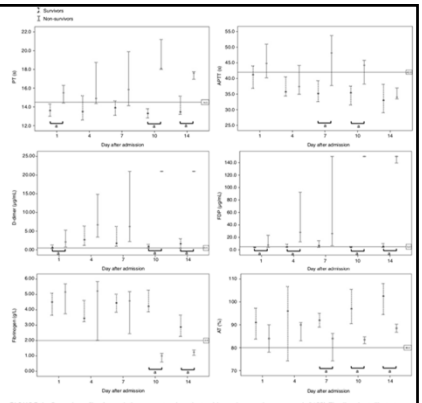


FIGURE 1 Dynamic profile of coagulation parameters in patients with novel coronavirus pneumonia (NCP). Timeline charts illustrate the changes of coagulation parameters in 183 patients with NCP (21 non-survivors and 162 survivors) after admission. The error bars show medians and 25% and 75% percentiles. The horizontal lines show the upper normal limits of prothrombin time, activated partial thromboplastin time, D-dimer and fibrin degradation product, and the lower normal limits of fibrinogen and antithrombin activity, respectively. *P < 0.05 for survivors versus non-survivors.

Tang *et al*., J Thromb Haemost, 2020

2. Disease course & Lab results COVID-19

2) DIC common in deaths with COVID-19.

TABLE 2 The grade of DIC in non-survivors with NCP (n = 21)

	Number of patients (%)
Platelet counts (×10^9/L)	
50-100 (1 point)	7 (33.3)
<50 (2 points)	5 (23.8)
D-dimer (μg/mL)	
1.0-3.0 (2 points)	3 (14.3)
>3.0 (3 points)	18 (85.7)
Fibrinogen (g/L)	
<1.0 (1 point)	6 (28.6)
Prolongation of PT (sec)	
3-6 (1 point)	5 (23.8)
>6 (2 points)	10 (47.6)
Meeting the ISTH criteria of DIC (Total points ≥5)	15 (71.4)

Note: D-dimer cutoff levels were defined according to a previous report derived from more than 1000 samples in intensive care.[7]
Abbreviations: DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; NCP, novel coronavirus pneumonia

On the contrary, only one (0.6%) survivor matched the DIC criteria during hospital stay.

Tang *et al*., J Thromb Haemost, 2020

2. Disease course & Lab results COVID-19

Articles

Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study

George Goshua, Alexander B Pine*, Matthew L Meizlish*, C-Hong Chang, Hanming Zhang, Parveen Bahel, Audrey Baluha, Noffar Bar, Robert D Bona, Adrienne J Burns, Charles S Dela Cruz, Anne Dumont, Stephanie Halene, John Hwa, Jonathan Koff, Hope Menninger, Natalia Neparidze, Christina Price, Jonathan M Siner, Christopher Tormey, Henry M Rinder, Hyung J Chun*, Alfred I Lee**

Lancet Haematol 2020
Published Online
June 30, 2020

Measured:

soluble P-selectin (a marker of endothelial cell and platelet activation),
sCD40L (a marker of platelet and T-cell activation),
soluble thrombomodulin (a marker of endothelial cell activation)

in 40 ICU and 10 non-ICU patients and in 13 non-COVID-19, non-hospitalised controls

2. Disease course & Lab results COVID-19

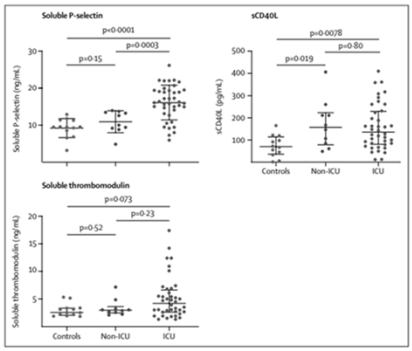


Figure 2: **Comparisons of endothelial cell and platelet activation markers in ICU patients, non-ICU patients, and controls**
Datapoints indicate individual measurements, whereas horizontal bars show mean (SD) for soluble P-selectin and median (IQR) for sCD40L and soluble thrombomodulin. ICU=intensive care unit. sCD40L=soluble CD40 ligand.

Goshua and Pine *et al*., Lancet Haematol, 2020

2. Disease course & Lab results COVID-19

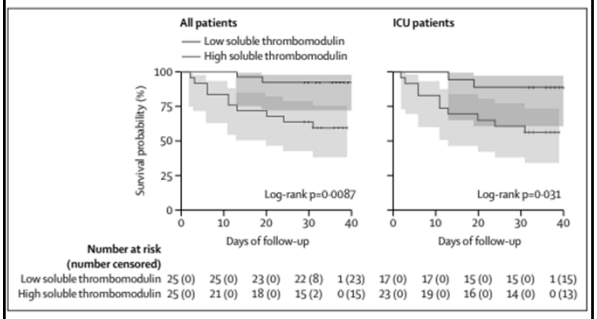


Figure 3: **Kaplan–Meier curve of survival and soluble thrombomodulin concentration**
Data are shown for patients with low soluble thrombomodulin (<3·26 ng/mL) and high soluble thrombomodulin (>3·26 ng/mL). Shaded areas represent 95% CIs. ICU=intensive care unit.

Goshua and Pine *et al*., Lancet Haematol, 2020

2. Disease course & Lab results COVID-19

BRIEF REPORT

jth

High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients

J Thromb Haemost. 2020;00:1–4.

Jean-François Llitjos[1] | Maxime Leclerc[2] | Camille Chochois[2] | Jean-Michel Monsallier[3] | Michel Ramakers[2] | Malika Auvray[2] | Karim Merouani[3]

n = 26
mortality = 12%

Retrospective study of consecutive patients 2 French ICUs.

Baseline bil LE U/S (within 1-3 days admission to ICU).
MD choice: prophylactic (31%)/therapeutic (69%) anti-coagulation.

Re-Check: 2nd bil LEs U/S after 7 days.
CT Chest/Echo if concerns persistent/worsening hypoxia.

Prophylaxis group: 8 pats → 8/8 VTE = 100% rate
Therapeutic group: 18 pats → 10/18 VTE = 56% rate.
(includes 6 PEs = 33%) p = 0.03

Combined: 26 pats → 18/26 VTE = 69% rate

3. Inflammatory coagulopathy COVID-19

Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans

Sharon E Fox, Aibek Akmatbekov, Jack L Harbert, Guang Li, J Quincy Brown, Richard S Vander Heide

Lancet Respir Med 2020
Published Online
May 27, 2020

n = 10

age 44-78.
cause of death attributed to COVID-19.

no evidence 2ndary pulm infection by micoorganisms (except one immunosuppressed patient).

report relevant cardiopulmonary findings.

cardiac findings: dilated RV
individual cell necrosis w/o lymphocytic myocarditis
no coronary artery stenosis or acute thrombi.

3. Inflammatory coagulopathy COVID-19

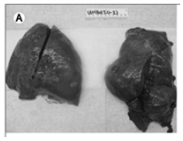
lungs heavier than normal.

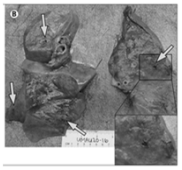
bronchi: pink froth.

serosanguinous peri-cardial + pulm effusions

parenchyma: diffusely oedematous + firm (c/w ARDS).

throughout periph parenchyma: focal regions dark haemorrhage.





after fixation, cut surfaces:

alternating areas tan-gray consolidation / patchy haemorrhage, upto 6cm.

additionally, peripheral parenchyma: small, firm thrombi.

Fox *et al*., Lancet Respir Med, 2020

3. Inflammatory coagulopathy COVID-19

Diffuse alveolar damage

Phase I: Early Exudative Phase
oedema + early hyaline membrane formation

Phase II: Proliferative Phase

Phase III: Fibrotic Phase

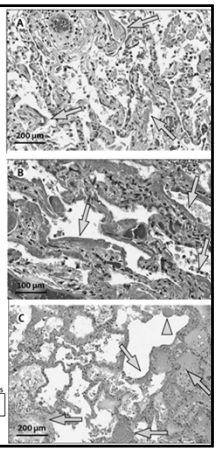
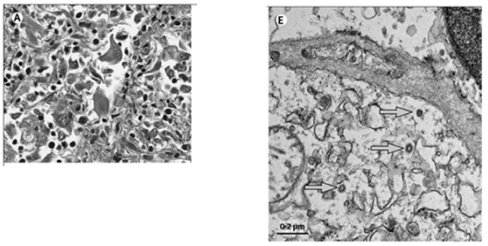


Figure 2: **Pulmonary diffuse alveolar damage**
All patients had extensive diffuse alveolar damage. (A) Green arrows indicate early hyaline membranes in a patient with 1 week of symptomatic illness and no mechanical ventilation (H&E stain). (B) Green arrows indicate extensive hyaline membranes and fibrinous exudate in a patient with 9 days of symptomatic illness, including 6 days of ventilation (H&E stain). (C) Green arrow indicates dense hyaline membranes, with organising fibrosis (green arrowhead), and fibrin thrombi present in small vessels (blue arrows), with a pauci-immune and oedematous background in a patient after 32 days of illness, including 25 days on ventilatory support. Extensive haemorrhage was also present (H&E stain).

Fox *et al*., Lancet Respir Med, 2020

3. Inflammatory coagulopathy COVID-19

Figure 4: **SARS-CoV-2 cytopathic effects**
(A) Several enlarged pneumocytes within a damaged alveolus, having enlarged nuclei, prominent nucleoli, and cytologic atypia (H&E stain).



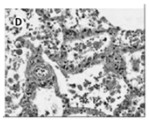
(E) Electron microscopy of the lung, showing [ ] particles suggestive of viral infection (examples highlighted by blue arrows. H&E=haematoxylin and eosin.

Fox *et al*., Lancet Respir Med, 2020

3. Inflammatory coagulopathy COVID-19

inflammatory cell infiltrates: CD4+/CD8+

located in interstitial spaces
+
around larger bronchioles or blood vessels:



alveolar capillaries notably thickened, w surrounding oedema;
some containing thrombi + platelets:

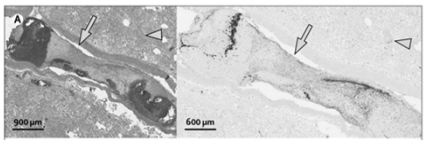


Figure 3: **Pulmonary thrombi and microangiopathy**
(A) Thrombus in a small pulmonary artery (green arrow), with small thrombus seen in adjacent pulmonary venule (green arrowhead), with H&E present on the left, and CD61 immunostain highlighting platelets within the thrombi

Fox *et al*., Lancet Respir Med, 2020

3. Inflammatory coagulopathy COVID-19

A notable finding: presence of CD61+ megakaryocytes,
possibly representing resident pulmonary megakaryocytes,
w significant nuclear hyperchromasia + atypia.

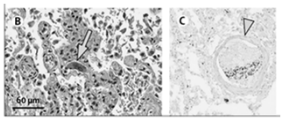


Figure 3: **Pulmonary thrombi and microangiopathy**
[ ](B) Many megakaryocytes were present within the small vessels and alveolar capillaries (green arrow).
(C) CD61 immunostain highlighting additional fibrin and platelet thrombus shown in a small vessel, with megakaryocyte stained below (green arrowhead).[ ]

These cells were located within alveolar capillaries,
and could be seen actively producing platelets.

The fibrin + platelets present within small vessels also appeared
to aggregate inflammatory cells, with entrapment of many neutrophils.

Thrombi were not grossly apparent in any other organs examined,
including kidneys, spleen, pancreas, and liver.

Fox *et al*., Lancet Respir Med, 2020

3. Inflammatory coagulopathy COVID-19

COVID-19 = highly inflammatory/coagulopathic clinicopathologic state.

"thrombotic process may involve activation of megakaryocytes,

possibly those native to the lung,

with platelet aggregation and platelet-rich clot formation,

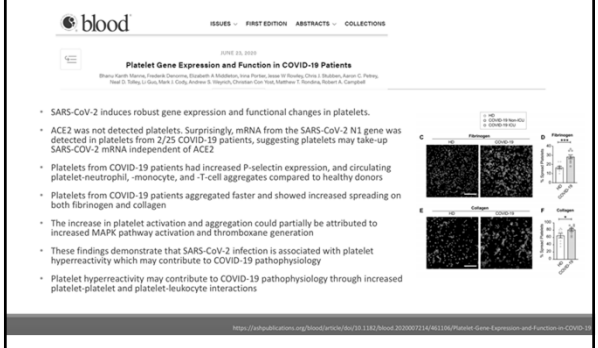
in addition of fibrin deposition…

.

Effective therapy for… patients with severe infection…
should target the thrombotic and microangiopathic effects…
and possibly a maladaptive immune response".

Fox *et al*., Lancet Respir Med, 2020

2. Disease course & Lab results COVID-19


blood ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

JUNE 23, 2020

Platelet Gene Expression and Function in COVID-19 Patients

- SARS-CoV-2 induces robust gene expression and functional changes in platelets.
- ACE2 was not detected platelets. Surprisingly, mRNA from the SARS-CoV-2 N1 gene was detected in platelets from 2/25 COVID-19 patients, suggesting platelets may take-up SARS-COV-2 mRNA independent of ACE2
- Platelets from COVID-19 patients had increased P-selectin expression, and circulating platelet-neutrophil, -monocyte, and -T-cell aggregates compared to healthy donors
- Platelets from COVID-19 patients aggregated faster and showed increased spreading on both fibrinogen and collagen
- The increase in platelet activation and aggregation could partially be attributed to increased MAPK pathway activation and thromboxane generation
- These findings demonstrate that SARS-CoV-2 infection is associated with platelet hyperreactivity which may contribute to COVID-19 pathophysiology
- Platelet hyperreactivity may contribute to COVID-19 pathophysiology through increased platelet-platelet and platelet-leukocyte interactions

https://ashpublications.org/blood/article/doi/10.1182/blood.2020007214/461106/Platelet-Gene-Expression-and-Function-in-COVID-19

3. Inflammatory coagulopathy COVID-19

Does SARS-CoV-2 directly infect endothelial cells?

Endothelial cell infection and endotheliitis in COVID-19

*Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, Mandeep R Mehra, Reto A Schuepbach, *Frank Ruschitzka, Holger Moch*

www.thelancet.com Vol 395 May 2, 2020

n = 3

SARS-CoV-2 infects the host using ACE-2 Rc,

ACE-2 Rc = expressed on lungs,heart, kidney, and intestine.

ACE-2 Rc also expressed in by endothelial cells.

Are vascular derangements caused by endothelial cell infection by the virus?

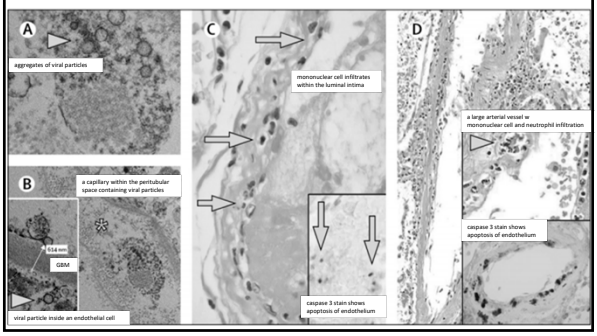
Here we demonstrate endothelial cell involvement of different organs.

3. Inflammatory coagulopathy COVID-19

Direct viral infection of endothelial cells + diffuse endothelial inflammation:

- Lungs (d)
- Heart (however, no lymphocytic myocarditis)
- Kidney (a,b)
- Small bowel (c)
- Liver

Varga *et al*., Lancet, 2020



3. Inflammatory coagulopathy COVID-19

"The vascular endothelium is an active paracrine, endocrine, and autocrine organ

that is indispensable for the regulation of vascular tone

and the maintenance of vascular homeostasis.

Endothelial dysfunction is a principal determinant of microvascular dysfunction
by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia,
inflammation with associated tissue oedema, and a
procoagualant state.

COVID-19 endotheliitis could explain the
systemic impaired microcirculatory function in different vascular beds and
their clinical sequelae in patients with COVID-19.

This hypothesis provides a rationale for therapies to stabilise the endothelium
while tackling viral replication,
particularly with anti-inflammatory anti-cytokine drugs,
ACE-I, and statins. "

Varga *et al*., Lancet, 2020

3. Inflammatory coagulopathy COVID-19

Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases

CYNTHIA MAGRO, J. JUSTIN MULVEY, DAVID BERLIN, GERARD NUOVO, STEVEN SALVATORE, JOANNA HARP, AMELIA BAXTER-STOLTZFUS, and JEFFREY LAURENCE

NEW YORK, NEW YORK; POWELL, OHIO; AND NEW YORK, NEW YORK

Translational Research
June 2020

Skin and lung tissues in severe COVID-19 resp failure (n= 5) + purpuric skin rash (n=3).

COVID-19 pneumonitis = pauci-inflammatory septal capillary injury w significant septal capillary mural + luminal fibrin deposition.

No viral cytopathic changes observed

Hallmarks of classic ARDS
(DAD w hyaline membranes, inflammation, type II pneumocyte hyperplasia)
NOT prominent.

3. Inflammatory coagulopathy COVID-19

Pulmonary findings were accompanied by significant deposits in microvasculature:

1. terminal complement components C5b-9 (MAC),
2. C4d,
3. mannose binding lectin (MBL)-associated serine protease (MASP)2

The purpuric skin lesions similar.

In addition, co-localization of COVID-19 spike glycoproteins with C4d + C5b-9.

In conclusion, at least a subset of sustained, severe COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement.

Magro *et al*., Transl Res, 2020

3. Inflammatory coagulopathy COVID-19 Magro *et al*., Transl Res, 2020

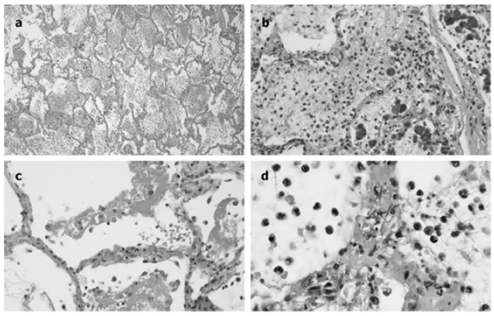


Fig 1. Microscopic features of pulmonary autopsy samples from Case 1. **A,** Significant fibrin deposition within the interalveolar septa and alveolar spaces, accompanied by marked hemorrhage and hemosiderin deposition. (Hematoxylin and eosin stain, 200×). **B,** Prominent destructive septal capillary injury is apparent, with fibrinoid necrosis of the capillaries accompanied by evidence of vascular compromise, with hemorrhage and fibrin and hemosiderin deposition within alveolar spaces. (Hematoxylin and eosin stain, 400×). **C,** Septal capillary injury is a pauci-inflammatory response. (Hematoxylin and eosin, 1000×). **D,** The septal capillary injury includes an interstitial and intra-alveolar accumulation of neutrophils. (Hematoxylin and eosin, 400×).

3. Inflammatory coagulopathy COVID-19 Magro *et al*., Transl Res, 2020

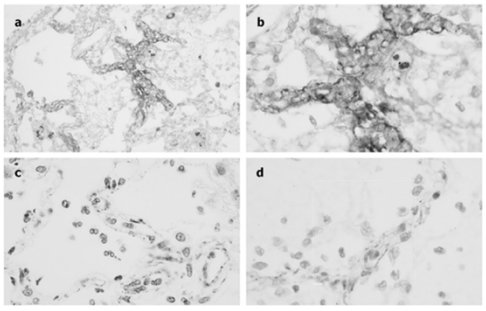


Fig 2. Immunohistochemistry analysis of pulmonary autopsy samples from Case 1. **A,** Extensive C4d deposition is seen throughout the lung parenchyma, with striking septal capillary localization. (Diaminobenzidene stain, 200×). **B,** Higher power magnification documents a clear localization of C4d within septal capillaries. (Diaminobenzidene, 1000×). **C,** A similar septal capillary distribution for C5b-9 deposition is observed, although it is less pronounced than that observed for C4d. (Diaminobenzidene, 1000×). **D,** A similar septal capillary distribution of C3d staining is observed, although it is also less pronounced than was observed for C4d. (Diaminobenzidene, 1000×).

3. Inflammatory coagulopathy COVID-19

Magro *et al.*, Transl Res. 2020

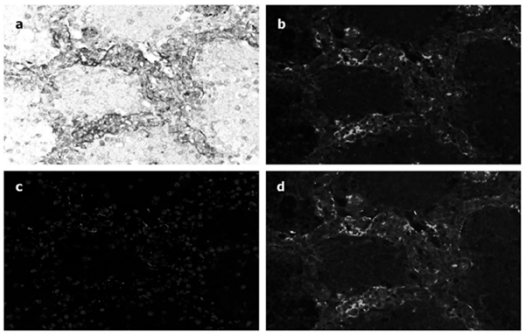
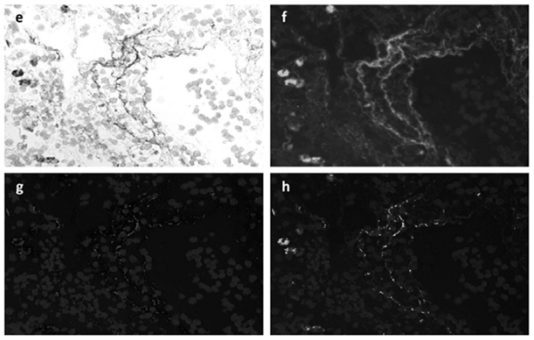


Fig 8. Demonstration of co-localization of complement components with SARS-CoV2 spike glycoprotein in the lung of Case 1. **A,** Striking deposition of C4d within the interalveolar septa of the lung was first demonstrated by DAB staining. Using NUANCE software the C4d image appears green (**B**) while the SARS-CoV2 spike protein appears red (**C**). **D,** A merged image shows a significant degree of C4d and SARS-CoV2 co-localization, as revealed by intense yellow staining.

3. Inflammatory coagulopathy COVID-19

Magro *et al.*, Transl Res. 2020



E–H, A similar pattern was observed using an anti-C5b-9 reagent whose image appears green, with a significant degree of C5b-9 and SARS-CoV2 co-localization, as revealed by intense yellow staining.

3. Inflammatory coagulopathy COVID-19

"Our histologic findings are consistent with emerging observations suggesting that COVID-19 has clinical features distinct from typical ARDS.

That is, COVID- 19-related severe respiratory distress can be manifest by relatively well-preserved lung mechanics, despite the severity of hypoxemia, characterized by high respiratory compliance, high shunt fraction, and prolonged requirement for mechanical ventilation.

The pathology in these cases might therefore be expected to differ from the diffuse alveolar damage and hyaline membrane formation which are hallmarks of typical ARDS.

Albeit preliminary pathology studies of lungs from COVID-19 cases described DAD with edema, hyaline membranes, and inflammation, followed by type II pneumocyte hyperplasia, features characteristic of typical ARDS, the pulmonary abnormalities in our patients appear largely restricted to the alveolar capillaries, that is, more of a thrombotic microvascular injury with few signs of viral cytopathic or fibroproliferative changes.

An increase in the dead space fraction might be anticipated with this type of pathology, i.e., respiratory failure accompanied by greater lung compliance and less pulmonary consolidation than is characteristic of typical ARDS."

Magro *et al.*, Transl Res. 2020

3. Inflammatory coagulopathy COVID-19

REVIEW Open Access

The unique characteristics of COVID-19 coagulopathy

Toshiaki Iba[1*], Jerrold H. Levy[2], Jean Marie Connors[3], Theodore E. Warkentin[4], Jecko Thachil[5] and Marcel Levi[6]

Critical Care

(2020) 24:360

3. Inflammatory coagulopathy COVID-19

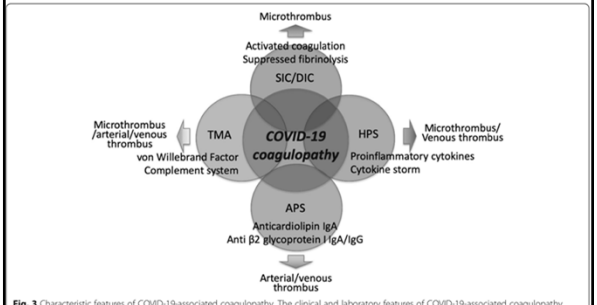
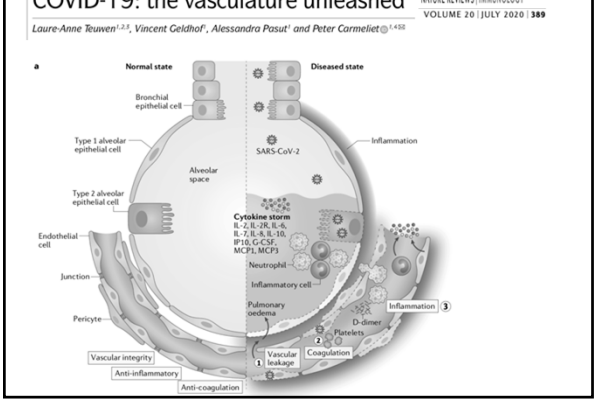


Fig. 3 Characteristic features of COVID-19-associated coagulopathy. The clinical and laboratory features of COVID-19-associated coagulopathy (CAC) partially overlap with sepsis-induced coagulopathy (SIC)/disseminated intravascular coagulation (DIC), hemophagocytic syndrome (HPS)/ hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic microangiopathy (TMA); however, it does not perfectly match with any of these other coagulopathies

Iba *et al.*, Critical Care 2020

3. Inflammatory coagulopathy COVID-19



3. Inflammatory coagulopathy COVID-19

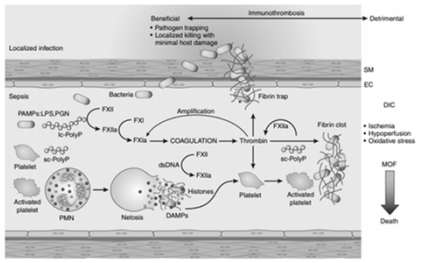


FIGURE 1 Bacteria-induced contact activation leading to immunothrombosis and DIC. The coagulation factor XII (FXII) is activated by live bacteria and bacterial wall–derived pathogen-associated molecular patterns (PAMPS), such as lipopolysaccharides (LPS) for gram-negative or peptidoglycan (PGN) for gram-positive bacteria or bacteria-produced long-chain polyphosphates (lc-PolyP). Activation of FXII leads to thrombin generation, platelet activation, and fibrin formation, which in concert trap and contain pathogens. Activated platelets promote neutrophils to release their nuclear contents to form extracellular traps (netosis) as part of the routes of pathogen clearance; NETs are also potent platelet activators and cytotoxic to the host cells. Histones and double-stranded DNA (dsDNA) act as damage-associated pattern molecules (DAMPs) that together with platelet-derived short-chain polyphosphates (sc-polyP) contribute to contact activation via direct and indirect mechanisms. Failing the redundant pathways of pathogen clearance offered by the immune and coagulation systems, immunothrombosis can result in widespread microvascular thrombosis termed disseminated intravascular coagulation (DIC) followed by consumptive coagulopathy and bleeding. Thrombosis within the microvasculature of vital organs leads to ischemia, hypoperfusion, and oxidative stress, thus impairing organ function and leading to multiple organ failure (MOF). When more than two organs fail, death is the most likely outcome

Raghunathan *et al*., Res Pract Thromb Haemost, 2019

3. Inflammatory coagulopathy COVID-19

REVIEW ARTICLE

rpth

The contact pathway and sepsis

Vikram Raghunathan MD[1] | Jevgenia Zilberman-Rudenko PhD[2] | Sven R. Olson MD[1,2] | Florea Lupu PhD[3] | Owen J. T. McCarty PhD[2] | Joseph J. Shatzel MD[1,2]

Res Pract Thromb Haemost. 2019;3:331–339.

Essentials

- The contact activation system serves as a common node linking inflammatory and coagulation cascades.
- In vitro and in vivo studies suggest that contact pathway inhibition may be a therapeutic target in sepsis.
- Contact inhibition in animal models blunts cytokine response and improves survival in bacterial sepsis.
- Further studies in humans are required to evaluate efficacy in clinical practice.

Abstract

The contact pathway factors XI (FXI) and XII (FXII) have been demonstrated to be largely dispensable for hemostasis, as their absence results in a mild to absent bleeding diathesis. A growing body of literature, however, suggests that the contact pathway contributes to the pathologic host response to certain infectious organisms that produces the often-fatal syndrome known as sepsis. The contact pathway factors serve as a central node connecting inflammation to coagulation, and may offer a potentially safe therapeutic target to mitigate the morbidity and mortality associated with sepsis. Herein, we summarize published in vivo and in vitro data that have explored the roles of the contact pathway in sepsis, and discuss potential clinical applications of novel FXI- and FXII-inhibiting drugs currently under investigation.

KEYWORDS
contact activation, factor XI, factor XII, kallikrein-kinin system, sepsis

3. Hematologic management of COVID-19 hypercoagulability

AMERICAN SOCIETY OF HEMATOLOGY — COVID-19 RESOURCES

All hospitalized patients with COVID-19 should receive pharmacological thromboprophylaxis with LMWH over unfractionated heparin to reduce contact, unless the risk of bleeding outweighs the risk of thrombosis.

Whether critically ill COVID-19 patients should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown.
Multiple randomized controlled trials are underway.

Patients hospitalized for acute medical illness are at increased risk for VTE for upto 90 days after discharge. Therefore, it is reasonable to consider extended thromboprophylaxis after discharge using a regulatory-approved regimen (betrixaban for 35-42 days or rivaroxaban for 31-29 days).

3. Hematologic management of COVID-19 hypercoagulability

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19

Letters

JACC

VOL. 76, NO. 1, 2020
JULY 7, 2020:122–9

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Anuradha Lala, MD
Adam J. Russak, MD
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Matthew A. Levin, MD
Alexander W. Charney, MD, PhD
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Zahi A. Fayad, PhD
Emilia Bagiella, PhD
Shan Zhao, MD, PhD
†Girish N. Nadkarni, MD, MPH

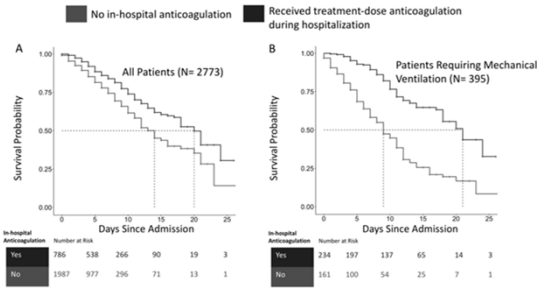
n = 2,773

Single-institution retrospective study hospitalized pats: examine effect of full-dose AC.

Compared:
ANY treatment-dose systemic AC (28% pats, median 3 days duration, any reason)
vs.
NO treatment-dose systemic AC.

3. Hematologic management of COVID-19 hypercoagulability

In-hospital mortality for patients treated with AC:
22.5% with a median survival of 21 days, compared to
22.8% and median survival of 14 days in patients who did not receive AC.



In patients who required mechanical ventilation (N=395), in-hospital **mortality was 29.1%** with a median survival of 21 days for those treated **with AC** as compared to **62.7%** with a median survival of 9 days in patients who did **not receive AC**.

Paranjpe *et al*., JACC, 2020

3. Hematologic management of COVID-19 hypercoagulability

Major bleeding defined:

1) HgB <7 g/dL and any red blood cell transfusion,
2) ≥ 2 units PRBC in 48 hrs or
3) dx code for major bleeding (intracranial hemorrhage, hematemesis, melena, peptic ulcer with hemorrhage, colon, rectal, or anal hemorrhage, hematuria, ocular hemorrhage, acute hemorrhagic gastritis).

Among those who did not receive AC,
38 (1.9%) individuals had bleeding events, compared to
24 (3%) among those who received AC (p=0.2).

Paranjpe *et al*., JACC, 2020

3. Hematologic management of COVID-19 hypercoagulability

DC VAMC Heme Interim COVID-19 Recommendations:

3) **FLOOR PATIENTS: start PROPHYLACTIC ANTICOAGULATION,**

"**INTERMEDIATE-DOSE**"

body weight	**CrCl ≥ 30 mL/min**	**CrCl < 30 mL/min**
Regular	enoxaparin 40mg sq bid	UFH 7,500 units sq tid
Obese (≥120kg or BMI ≥ 35)	enoxaparin 0.5mg/kg sq bid** (max dose 100mg sq bid)	UFH 10,000 units sq tid
Low body wt (< 60kg)	enoxaparin 30mg sq bid**	UFH 7,500 units sq tid

**Consider check anti-Xa level (send 4-6 hrs after 3-4 injections), target for VTE prophylaxis = 0.2 to < 0.5
unless: active bleeding, platelets <25K, or fibrinogen <50 mg/dL (i.e. OK to give with abnormal PT/PTT).

4) **ICU PATIENTS: start empiric FULL-DOSE THERAPEUTIC ANTICOAGULATION,**

enoxaparin 1mg/kg sq bid or heparin IV/SQ.
(for Cr Cl < 30: heparin).

unless: active bleeding, platelet <50K, or fibrinogen <100 mg/dL (i.e. OK to give with abnormal PT/PTT) or d-dimer <0.5.
for platelets 25-50K, or fibrinogen 50-100 mg/dL: consider intermediate-dose prophylaxis, as above.
for d-dimer <0.5: consider intermediate-dose prophylaxis, as above.

3. Hematologic management of COVID-19 hypercoagulability

COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection

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blood[1] 23 JULY 2020 | VOLUME 136, NUMBER 4

Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified?

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Thromb Haemost

Hypercoagulability in COVID-19

an inflammatory coagulopathy

SUMMARY:

1. Inflammatory markers rise during disease course, may culminate in DIC.
2. High incidence of vascular events in COVID-19.
3. Direct viral infection results in endotheliitis.
1. Prominence of platelets + fibrin deposition in tissues represents unique, COVID-19 associated coagulopathy (CAC).
5. Proactive anticoagulation management strategy is followed by some centers.