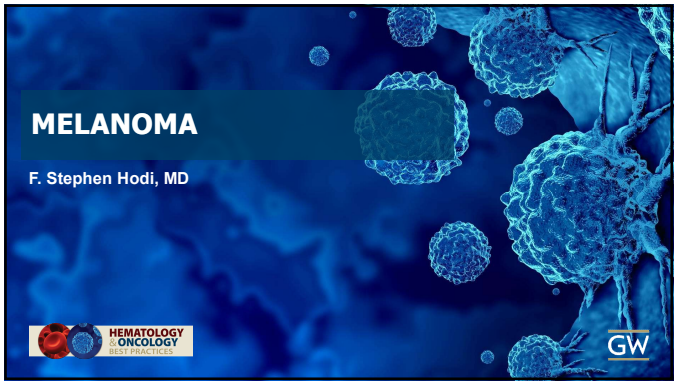

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Advisory Committee/Board Member: Bristol-Myers Squibb, Merck
- Consultant: Sanofi, EMD Serono, Genentech and Novartis

Resolution

- Reviewed by peers and found to be unbiased.

Off-Label Usage

- Nivolumab, Ipilimumab, Pembrolizumab

Epidemiology

- Incidence in US rising faster than any other cancer
- Approximately 60,000 new cases in US; 8,000 deaths
- Incidence varies by region
  - US: 15/100,000
  - New South Wales Australia: 1 in 20

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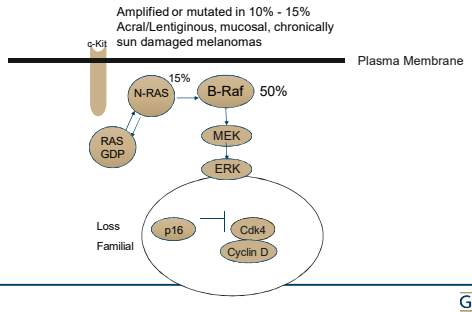
Melanoma Risk Factors

- Outdoor leisure (RR 1-2)
- History of sunburn (RR 1.5-3)
- Intense intermittent sun (RR 2-3)
- Fair skin (RR 2-5), blonde or red hair (RR 1.5-5)
- Family History: 8-12%
- Five or more painful sunburns (RR 2-6)
- Sun Exposure
  - Degree and Intensity
  - Ultraviolet Radiation, especially UV-B (290-320 nm)

Molecular Changes



Clinical Features of Cutaneous Melanoma

A. Asymmetry
B. Border
C. Color
D. Diameter

Any changing lesion

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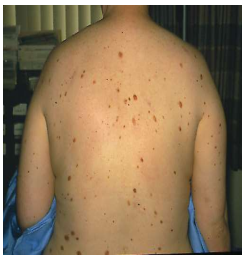
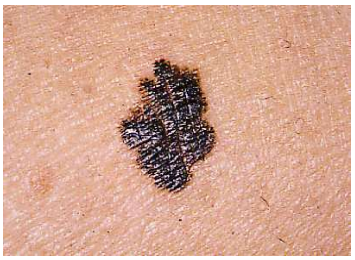
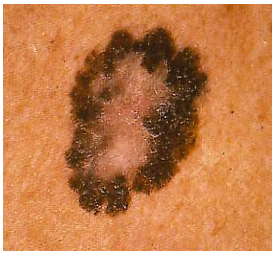
Dyplastic Nevus Syndrome



Superficial Spreading Melanoma



Spontaneous Regression in Primary Melanoma



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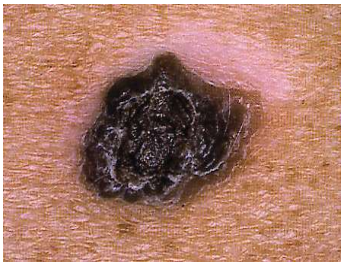
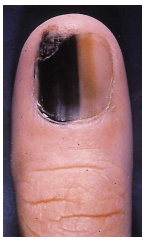
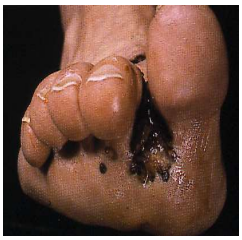
Nodular Melanoma

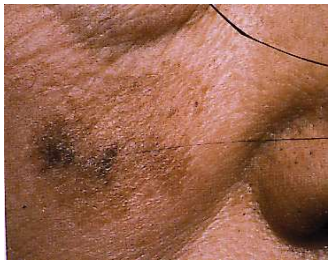


Acral Melanoma





Lentigo Maligna Melanoma



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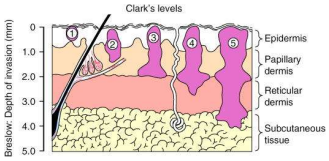
Prognostic Features

- Thickness (mm)
- Ulceration
- Mitoses (per mm^2)
- Anatomic location
- Histologic subtype
- LVI
- Microsatellites



Sabiston Textbook of Surgery, 17th ed., 2004 Saunders

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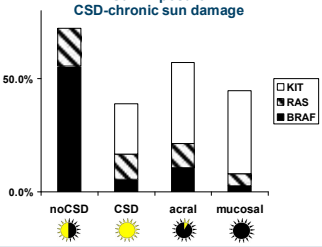
MAP/PI3: Genetic Variations
Correlation with Causative Factor



Curtin et al, *JCO*, 2006

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Melanoma Surgical Margins

- In situ: 0.5 cm
- Primary <1.0 mm: 1 cm
- Primary >1.0 mm: 2 cm
- Anatomy must be taken into consideration for surgical margins, e.g. face
- Randomized trials have not shown a benefit for larger surgical procedures

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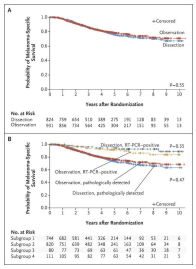
Sentinel Lymph Node Sampling

- Indication: Melanoma > 1mm or melanoma < 1 mm with ulceration or Clark's level IV or V (20% will have positive SLN)
- No evidence that SLN improves survival
- Important prognostic indicator
- Requires surgical expertise for accurate results (sensitivity and specificity)
- Recommendation for completion lymphadenectomy has changed

Morton et al NEJM, 2006

Completion Lymph Node Dissection Does Not Improve Survival in Patients with Positive Sentinel Lymph Node



the NEW ENGLAND JOURNAL of MEDICINE

Faries MB et al. *N Engl J Med* 2017;376:2211-2222.

AJCC 8th Edition T Categories

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS/MITOSES
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

T Category	Thickness	Ulceration Status
TX (Primary tumor thickness cannot be assessed)		
T0 (No evidence of primary tumor)		
Tis (Melanoma *in situ*)		
T1	**≤1.0 mm**	**Unknown or unspecified**
T1a	<0.8 mm	Without ulceration
T1b	<0.8	With ulceration
T1b	≥0.8–1.0 mm	With or without ulceration
T2	**>1.0–2.0 mm**	**Unknown or unspecified**
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	**>2.0–4.0 mm**	**Unknown or unspecified**
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0	With ulceration
T4	**>4.0 mm**	**Unknown or unspecified**
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual. 8th Ed. 2017.

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AJCC 8th Edition N Categories

N Category	Number of tumor-involved regional lymph node(s)	Presence of in-transit, satellite and/or microsatellite metastases
N0	No regional metastases detected	None
N1		
N1a	1 clinically occult (i.e., detected by SLN biopsy)	None
N1b	1 clinically detected	None
N1c	No regional lymph node disease	Yes
N2		
N2a	2-3 clinically occult (i.e., detected by SLN biopsy)	None
N2b	2-3, at least 1 of which clinically detected	None
N2c	1 clinically occult or clinically detected	Yes
N3		
N3a	4 or more clinically occult (i.e., detected by SLN biopsy)	None
N3b	4 or more, at least 1 of which clinically detected, or presence of any number of matted nodes	None
N3c	2 or more clinically occult or clinically detected	Yes

Microsatellites, Satellite Metastases, and In-transit
Metastases are now part of each N category

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual. 8th Ed. 2017.

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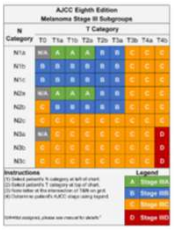
AJCC 8th Edition Clinical and Pathological Stage Groups

When T is…	And N is…	And M is…	Then the clinical stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

When T is…	And N is…	And M is…	Then the pathological stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a–N2b	M0	IIIB
T1a–T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a–N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV



Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual. 8th Ed. 2017.

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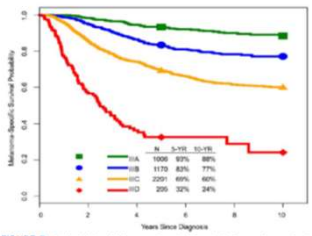

FIGURE 7. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage III Subgroups From the Eighth Edition International Melanoma Database.

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual. 8th Ed. 2017.

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M Category: Important Changes

- New fourth M category M1d: Distant metastasis to CNS
  - Poorest prognosis
  - Poor response to novel therapies
  - Exclusion from clinical trials
- Serum LDH levels are now part of each M category
  - Suffix (0) if normal
  - Suffix (1) if elevated
  - No suffix implies unknown

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual. 8th Ed. 2017.

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Staging work-up

Stage I/II

- CXR
  - Additional imaging if specific signs/symptoms
- CBC with diff, hepatic panel, LDH
- Full skin exam

Stage III/IV

- CT C/A/P or PET/CT whole body
  - Additional imaging if specific signs/symptoms
- Brain MRI with and without gadolinium
- CBC with diff, hepatic panel, LDH
- Full skin exam

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Stage IV Melanoma

- Median Survival: 11 months
  - Wide Range: Dependent upon site(s) of disease, LDH
- Treatments:
  - Chemotherapy
  - Cytokines
  - Biochemotherapy
  - Vaccines/Immunotherapy
  - Targeted Small Molecules
  - Combinations

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Single Agent Chemotherapy

- Dacarbazine (DTIC): approved single agent
  - RR 8-25%
  - CRs 2%
  - 31% durable
  - Temozolomide
- Nitrosoureas: BCNU, CCNU RR 12-17%
- Taxanes: RR15-20%
- Platinum compounds: RR 20%

Combinations with Chemotherapy does not improve OS

Regimen	RR	CR	Median Survival
DTIC	9.9%	0%	6.3 months
Dartmouth (CVD/Tam)	16.8%	0%	7.7 mos
P value		0.13	0.52

Chemotherapy vs. Biochemotherapy

- Three randomized studies presented at ASCO 2003
- Varying chemo/biochemo doses and regimens
- Biochemotherapy better RR, more toxicity, no statistically significant difference in survival

Chapman et al., *JCO* 1999

IL-2 in Melanoma

- 374 patients at NCI Surgery Branch
- 15.5% response rate (58/374)
- 5.1% CR, 10.4% PR
- Skin only metastases RR 53.6% (15/28)
- Skin and lymph node RR 32.5% (26/80)
- All other sites of disease RR 9.2% (32/348)
- Patient selection likely influences RR
- TIL therapy

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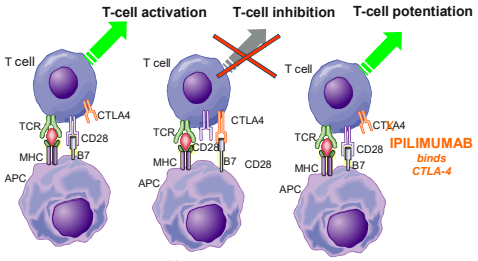
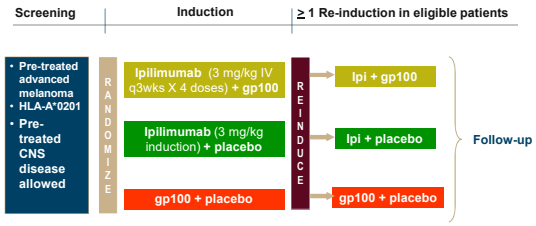
Ipilimumab: Mechanism of Action



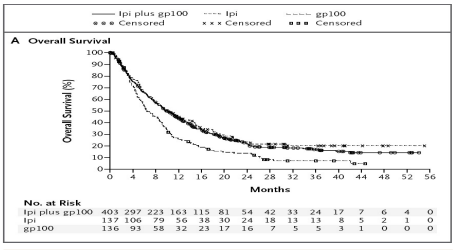
Phase II: 20-30% durable disease control

Wolchok et al. Ann NY Acad Sci 2013

MDX010-20: Study Design



Hodi NEJM 2010



Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

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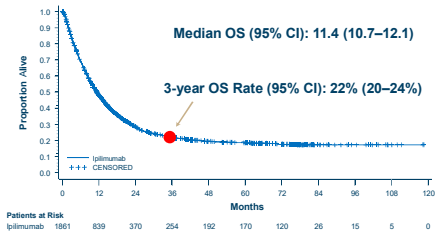
Primary Analysis of Pooled OS Data: 1861 Patients



ECCO 2013

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Ipilimumab

- FDA approved 2011
- Indication- stage IV melanoma or unresectable stage III melanoma.
- Approved dose- 3 mg/kg IV over 90 minutes q 3 weeks for a total a 4 doses
- Silent regarding maintenance, NCCN guidelines
- Reinduction; approximately 35% response

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Ipilimumab Assessment of response

- Conventional response criteria may not adequately assess the effect of immunotherapy
- Anti-tumor responses may be delayed and scans may show progression before response (immune mediated response criteria)

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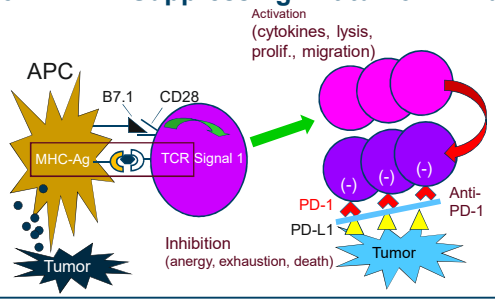
Role of PD-1 in Suppressing Antitumor Immunity



Keir ME et al. Annu Rev immunol 2008; Pardoll DM, Nat Rev Cancer 2012

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Nivolumab–Related Adverse Events

Drug-Related Adverse Event	All Grades		Grades 3-4	
	Tot Pop*	MEL	Tot Pop	MEL†
	No. (%) of Patients, All Doses			
Any adverse event	207 (70)	82 (79)	41 (14)	21 (20)
Fatigue	72 (24)	30 (29)	5 (2)	2 (2)
Rash	36 (12)	21 (20)	—	—
Diarrhea	33 (11)	18 (17)	3 (1)	2 (2)
Pruritus	28 (9)	15 (14)	1 (0.3)	—
Nausea	24 (8)	9 (9)	1 (0.3)	1 (1)
Appetite ↓	24 (8)	7 (7)	—	—
Hemoglobin ↓	19 (6)	7 (7)	1 (0.3)	1 (1)
Pyrexia	16 (5)	5 (5)	—	—

*AEs occurring in ≥5% of the total population.
†Common grade 3-4 AEs also included lymphopenia (3 pts) and abdominal pain and lipase increased (2 each). An additional 27 grade 3-4-related AEs were observed and one or more occurred in a single patient.

Topalian et al. *NEJM* 2012

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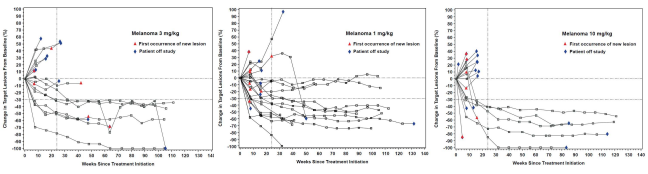
Changes in Target Lesions Over Time in Melanoma Patients



Topalian et al. *NEJM* 2012

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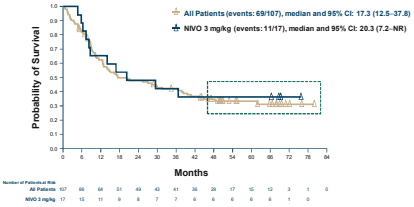
Nivolumab Overall Survival at 5 Years of Follow-up



Hodi AACR 2016

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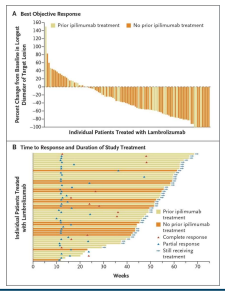
Antitumor Activity of Pembrolizumab



Hamid O et al. *N Engl J Med* 2013. DOI: 10.1056/NEJMoa1305133

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Immunotherapy: Toxicity = irAE

- Occur in approximately 60% of patients
- Grade 3/4 in approximately 10-15% of patients
- Any organ system can be involved
  - **Gastrointestinal** – enterocolitis, abdominal pain, diarrhea, bowel perforation (e.g. CTLA-4)
  - **Pulmonary** – pneumonitis (e.g. PD-1)
  - **Endocrinopathy**-thyroid (TSH before cycle), pituitary, adrenal insufficiency
  - **Hepatitis**-elevated AST or ALT or bililrubin
  - **Dermatitis**-rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - **Neurologic**-neuropathy, Guillain–Barré
  - Other- ocular manifestations

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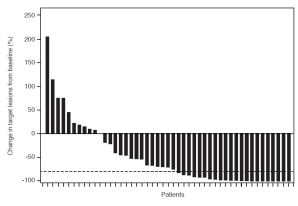
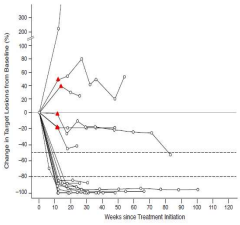
Checkpoint Blockade
Treatment of immune adverse reactions

- Rule out infections or other etiologies
- Corticosteroids-
  - High grade: IV methylprednisolone
  - PO
  - Steroids tapered slowly over one month
  - Rarely need infliximab (mycophenylate liver inflammation)

Ipilimumab + Nivolumab Best Responses in All Evaluable Patients





Wolchok et al. *NEJM* 2013

Treatment-Related Select Adverse Events Occurring in ≥1 Patient

Select Adverse Event	Concurrent Regimen All Cohorts (n=53)		Sequenced Regimen All Cohorts (n=33)	
Number of Patients (%)	All Gr	Gr 3-4	All Gr	Gr 3-4
Pulmonary	3 (6)	1 (2)	1 (3)	0
Renal	3 (6)	3 (6)	0	0
Endocrinopathies	7 (13)	1 (2)	3 (9)	2 (6)
Uveitis	3 (6)	2 (4)	0	0
Skin	37 (70)	2 (4)	8 (24)	0
Gastrointestinal	20 (38)	5 (9)	3 (9)	0
Hepatic	12 (23)	8 (15)	1 (3)	0
Infusion reaction	1 (2)	0	0	0
Lipase	10 (19)	7 (13)	4 (12)	2 (6)
Amylase	8 (15)	3 (6)	1 (3)	1 (3)

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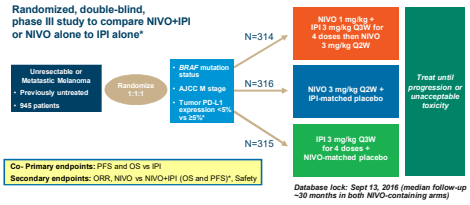
CA209-067: Study Design

CA209-067: Study Design

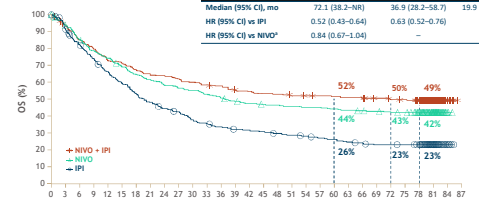


*The study was not powered for a comparison between NIVO and NIVO+IPI

GW 43

Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.43–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO*	0.84 (0.67–1.04)	–	–



*Descriptive analysis.

Wolchok et al. ASCO 2021

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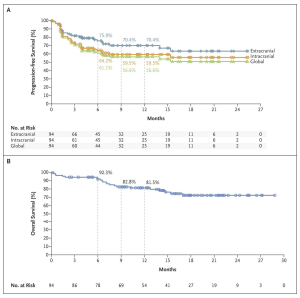
Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Table 2. Response to Treatment.

Variable	Intracranial (N = 94)	Extracranial (n = 94)	Global (N = 94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥8 mo	2 (2)	6 (6)	5 (5)
Progressive disease	51 (55)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)



Steroid dependence limits efficacy

Tawbi et al. NEJM 2018

GW

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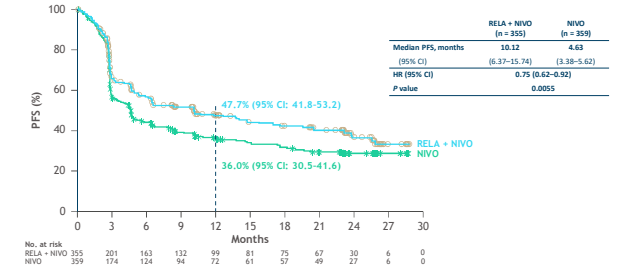
RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO: LAG3



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37–15.74)	(3.38–5.62)
HR (95% CI)	0.75 (0.62–0.92)	
P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

Lipson et al. ASCO 2021

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Conclusions

- Blockade of the PD-1 pathway represents basis for immune therapy for patients with melanoma
- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes will be further explored
- Pembrolizumab, Nivolumab, Nivolumab plus Ipilimumab approved
- NCCN recommendation PD-1 first line
- Combinations continue to be developed

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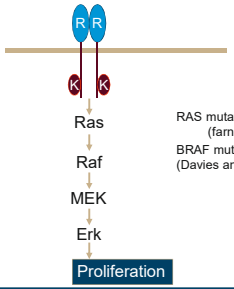
Downstream signaling events: The MAPK pathway



RAS mutations: 15% cancers, 90% pancreatic (farnesyl transferase inhibitors)

BRAF mutations: 66% malignant melanomas (Davies and Futreal, Nature 2002)

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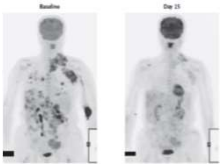
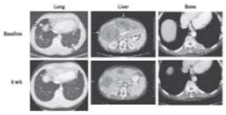
Vemurafenib: V600E BRAF Specific

FDG-PET



Computed Tomography



Flaherty et al NEJM 2010

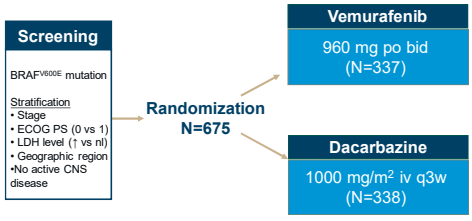
GW 49

Vemurafenib

- ORR of 53%
- OS at 6 months 77% (95% CI: 70, 85)
  12 months 58% (95% CI: 49, 67)
- Median duration of response 6.7 months
- 960 mg BID is manageable, with most AEs being reversible with dose modification or interruption

GW 50

Phase III BRIM3 Study design



Chapman et al. 2011

GW 51

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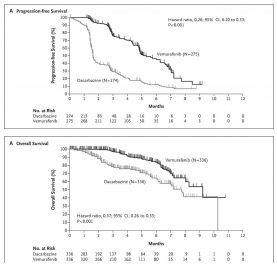
Melanoma Progression-Free Survival and Overall Survival



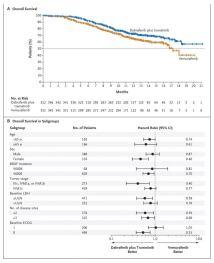
Chapman PB et al. N Engl J Med 2011;364:2507-2516.

Selective B-Raf Inhibitors in Patients with Metastatic Melanoma: Safety

Side effects:

Rash, arthritis, diarrhea, squamous cell skin cancer, pancreatitis keratoacanthoma, photosensitivity, LFTs, prolonged QTc. Visual changes.

BRAFi + MEKi: Overall Survival Improved Dabrafenib (BRAFi) + Trametinib (MEKi)



- Increased incidence of pyrexia
- Decreased incidence of skin manifestations of BRAFi

Robert C et al. *N Engl J Med* 2015;372:30-39.

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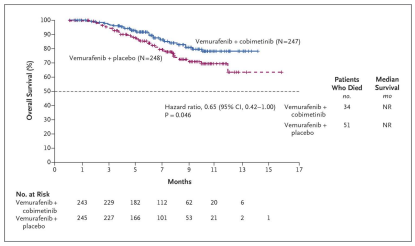
Vemurafenib (BRAFi) + Cobimetinib (MEKi) Improves Survival



Larkin J et al. *N Engl J Med* 2014;371:1867-1876.

The NEW ENGLAND JOURNAL of MEDICINE

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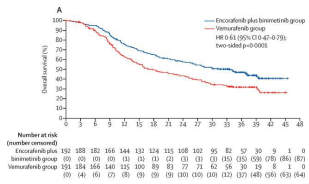
Encorafenib plus Binimetinib versus Vemurafenib (COLUMBUS):



Check CPK

Dummer et al. *Lancet Oncology* 2018

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Targeting BRAF Mutant Melanoma

- Selective BRAF inhibitors are a breakthrough for melanoma.
- Benefit seen in all subgroups and baseline characteristics
- Combination of BRAF and MEK inhibition improves survival
- Pyrexia and less skin toxicity with BRAFi + MEKi combination
- Not indicated for wild type BRAF
- Side effects: rash, arthritis, diarrhea, squamous cell skin cancer, keratoacanthoma, photosensitivity, LFTs, prolonged QTc

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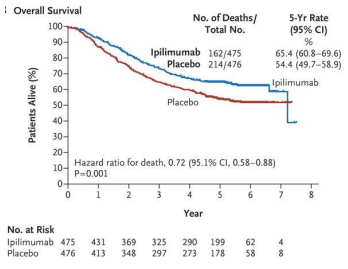
Does the benefit of immune and targeted therapies in the metastatic setting offer benefit for adjuvant patients?

Adjuvant Therapy

- High risk patients: thick primary melanomas > 4mm or node positive disease; 25-75% chance of dying from melanoma
- Multiple chemotherapy trials
  - Overall not improve survival
- Multiple biologics investigated
  - Interferon

Overall Survival



Eggermont et al NEJM 2016

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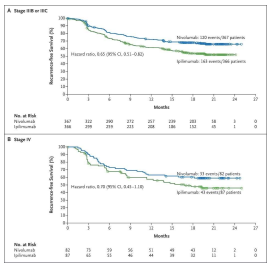
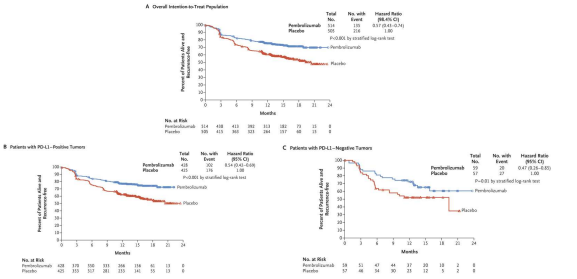
Nivolumab vs. Ipilimumab
Recurrence-free Survival, According to Disease Stage



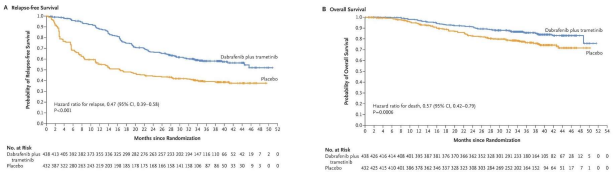
Weber J et al. *N Engl J Med* 2017. DOI: 10.1056/NEJMoa1709030

Pembrolizumab vs Placebo



Eggermont et al. NEJM 2018

Dabrafenib plus Trametinib
Relapse-free Survival and Overall Survival.



Long GV et al. *N Engl J Med* 2017. DOI: 10.1056/NEJMoa1708539

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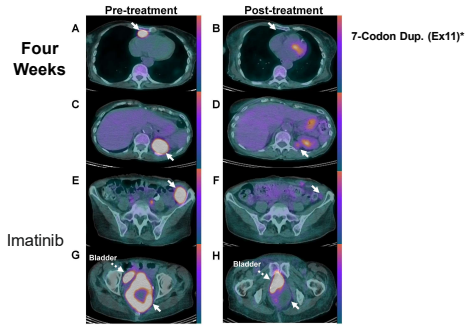
Treatment options for patients with Stage III melanoma

- Observation
- IFN
- Participation in a clinical trial
- Nivolumab, Pembrolizumab
- Dabrafenib plus Trametinib

Mucosal and Acral Melanomas

- Clinical behavior different than cutaneous melanomas
  - Non Risk Factors for Cutaneous Melanomas
- Mucosal Melanoma
  - Vaginal, Anal, Sinus, Oropharynx
  - 400-600 Cases per year
- Acral (Non-Hair Containing Skin) Melanoma
  - Palms, Soles, and Nailbeds
  - 5% Melanomas
- 15-20% with KIT mutation and/or amplification



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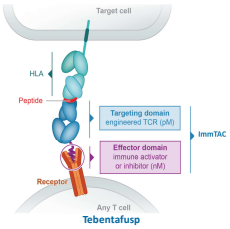
Imatinib in KIT Melanoma

- Phase II studies
- 8-12% KIT mutational rate of tumors
- Mutation +/- amplification
- RR 24%
- TTP 3 months
- PFS 9 months for patients who experience SD/PR

Ocular Melanoma

- Most common extra-cutaneous melanoma
- Most commonly involving choroid and ciliary body; conjuntival lesions are rare
- Recurrence over 5-10 years; surveillance not well defined
- Improving understanding of genetics (not BRAF)
  - In contrast to cutaneous lesions, 50% GNAQ mutations, 20% GNA11 mutations (G-coupled proteins)
- Local therapy: enucleation vs. external beam/radioactive rings
- Liver predominant organ for metastases

Tebentafusp



Tebentafusp

- Bispecific, soluble TCR therapeutic
- Affinity-enhanced TCR fused to anti-CD3
- Designed to redirect T cells to gp100+ melanocytic cells

ImmTAC, immune mobilizing T cell receptor Against Cancer; TCR, T cell receptor.

Piperno-Neumann, Hassel et al. AACR 2021

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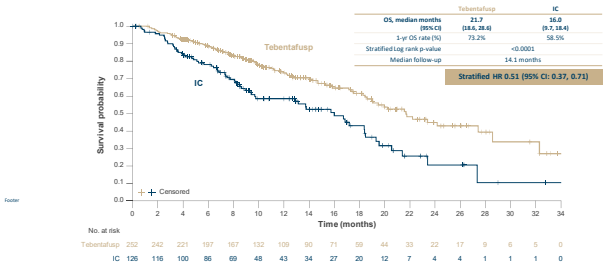
Primary endpoint: Overall survival



	Tebentafusp	IC
OS, median months (95% CI)	21.7 (18.6, 28.4)	16.0 (9.7, 18.4)
1-yr OS rate (%)	73.2%	58.5%
Stratified Log rank p-value	<0.0001	
Median follow-up	14.1 months	

Stratified HR 0.51 (95% CI: 0.37, 0.71)

Piperno-Neumann, Hassel et al. ACR 2021

Treatment for Stage IV Disease: Summary

- Immune modulation
  - CTLA-4 blockade
  - PD-1 blockade
  - Anti-CTLA-4 + anti-PD-1
- Improved genetic understanding
  - BRAFi + MEKi
  - KIT
- Combinatorial Approaches

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Thank You

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