Disclosures

Off-Label Usage
- None

Advisory Board/ Speaker's Bureau
- BMS
- Regeneron
- Blueprint Medicine
- Deciphera
- Sanofi Genzyme

Outline

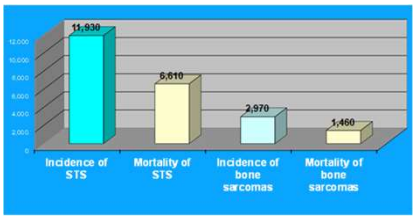
Background	• Incidence • Epidemiology • Etiology
Soft tissue sarcomas (STS)	• GIST vs non-GIST
Bone sarcomas	• Osteosarcoma • EFTS • Chondrosarcoma • Rare Tumors with FDA approved drugs

Sarcomas

- Represent <1% of all adult malignant tumors
- Heterogeneous group of mesenchymal neoplasms
- More than 50 individual histologic subtypes identified
- Categorized as either primary soft tissue sarcoma or bone sarcoma
  - Classification based on line of differentiation, biological potential and genetic/molecular features

Skubitz KM, D'Adamo DR. *Mayo Clin Proc.* 2007; 82:1409-1432
Doyle L. *Cancer* 2014;120:1763–1774 & Fletcher C. WHO classification of tumours of soft tissue and bone

Sarcoma: Incidence



- True incidence of Gastrointestinal stromal tumors (GIST) are likely underestimated as they are included under GI malignancies

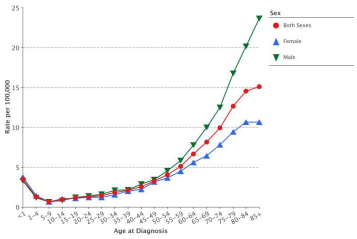
Siegel RA et al. *Cancer Statistics*, 2015. *CA Cancer J Clin* 2015; 65(1): 5-29.

Sarcomas: Epidemiology

- Slight male predominance
- No race predilection
- Age distribution for soft tissue sarcomas:
  - increases with increasing age
  - **Age > 60 y/o: > 51.7%**
- Age distribution of bone sarcomas:
  - Children and young adults: osteosarcoma and EFTs
  - Adults: chondrosarcomas

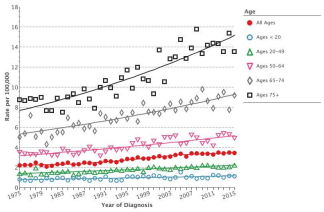
SEER Database. http://seer.cancer.gov/statfacts/html/soft.html

Soft Tissue: SEER Incidence Rates by Age at Diagnosis , 2011-2015, by sex



https://seer.cancer.gov/

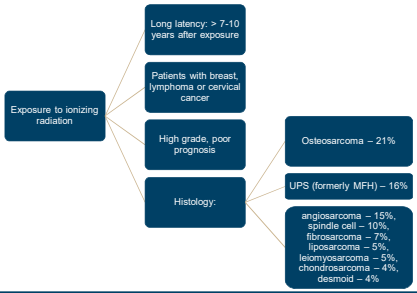
Soft Tissue: Long Term Trends in SEER Incidence Rates, 1975-2015



STSs are common in elderly patients aged ≥ 65 years, with an age-adjusted incidence of 11.3 cases per 100,000 population compared to 2.3 cases per 100,000 in those age <65 years.

https://seer.cancer.gov/

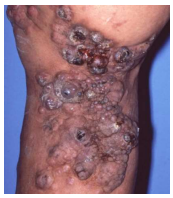
Sarcomas: Etiology- Spontaneous Vs Risk Factor



Brady MS, et. al. *Arch Surg*. 1992; 127 (12): 1379 – 85.

Sarcomas: Etiology

- Chronic lymphedema (Stewart-Treves)
  - Angiosarcoma
- Exposure to chemicals:
  - Vinyl chloride: Hepatic angiosarcoma
- Viruses
  - Human herpesvirus 8 – Kaposi's sarcoma
  - Epstein-Barr virus and leiomyosarcoma



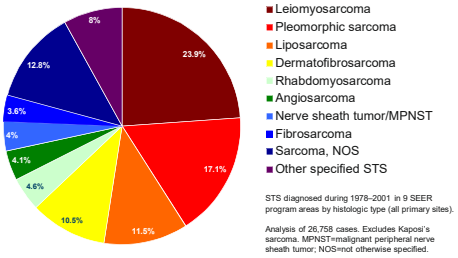
Non-GIST STS

Soft Tissue Sarcoma: Subgroups

3 most common subgroups (other than GIST):	• Undifferentiated Pleomorphic Sarcoma (UPS, formerly MFH), • Liposarcoma • Leiomyosarcoma
Other histologies:	• synovial sarcoma • angiosarcoma
Biological classification:	• Benign: usually do not recur • Intermediate, locally aggressive or rarely metastasizing • Malignant

*some slides courtesy of Dr. Maki

Epidemiology and Etiology



STS diagnosed during 1978–2001 in 9 SEER program areas by histologic type (all primary sites).

Analysis of 26,758 cases. Excludes Kaposi's sarcoma. MPNST=malignant peripheral nerve sheath tumor; NOS=not otherwise specified.

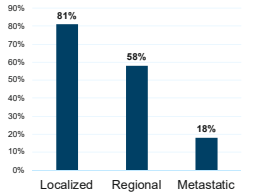
- Diagnosis
  - Core needle biopsy
- Biopsy/needle track site chosen should lie within a future en bloc resection of the tumor
- Imaging used: CT/MRI
  - PET: may be useful for prognostication, following response to treatment

Clark M. Soft tissue sarcoma. *NEJM.* 2005; 353:7: 701-711

Soft Tissue Sarcoma: Prognosis

- Prognostic factors:[1]
  - patient age
  - tumor size, histologic grade, and stage at diagnosis
- Factors with a poor prognosis:[2]
  - age >60 years
  - tumors >5 cm
  - high-grade histology
  - R1/R2 resection

5-Year Survival Rates for Soft Tissue Sarcomas[3]



1. NIH-NCI. Adult Soft Tissue Sarcoma Treatment (PDQ®)–Patient Version. Available: https://www.cancer.gov/types/soft-tissue-sarcoma/patient/adult-soft-tissue-treatment-pdq. Revised May 6, 2020. Accessed June 10, 2020. 2. NIH NCI. Adult Soft Tissue Sarcoma Treatment (PDQ®)–Health Professional Version. Available https://www.cancer.gov/types/soft-tissue-sarcoma/hp/adult-soft-tissue-treatment-pdq. Accessed June 9, 2020.
3. American Cancer Society. Survival rates for soft tissue sarcoma. https://www.cancer.org/cancer/soft tissue-sarcoma/detection-diagnosis-staging/survival-rates.html. Updated 6 March 2019. Accessed 19 March 2019.

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Sarcoma-Specific Survival by depth, grade and size

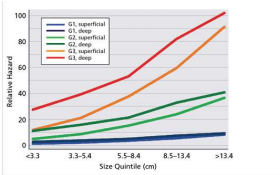


Figure 2.

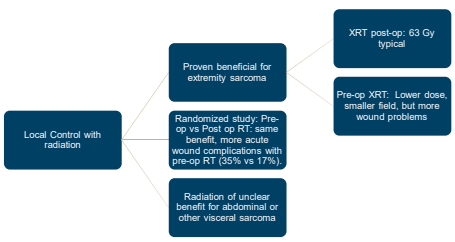
Predicted relative hazard ratios for sarcoma-specific survival for cases without nodal or distant metastasis by tumor depth and histologic grade over quintiles of tumor size. Plots are relative to superficial, low-grade tumors <3.3 cm in greatest dimension and are adjusted for interactions between tumor depth and size. Abbreviations: G1, low-grade (grade 1); G2, intermediate-grade (grade 2); G3, high-grade (grade 3).

J Natl Compr Canc Netw February 1, 2018 vol. 16 no. 2 144-152

General Principles of Therapy for Soft Tissue Sarcomas

Local control	• Surgical en bloc resection is the goal • Radiation of benefit for close surgical margins or residual disease (especially for extremity sarcomas)
Systemic control	• Chemotherapy – role for palliation in metastatic disease • Targeted therapies

Soft Tissue Sarcoma: Radiation therapy



Davis AM et al. Radiother Oncol 2005; 75: 48
O'Sullivan B et al. Lancet 2002; 359: 2235; O'Sullivan et al. ASCO 2004, abst 9007

Treatment of Soft Tissue Sarcomas

- Adjuvant Chemotherapy

The role of chemotherapy in the adjuvant setting for standard adult soft tissue sarcoma remains controversial.

There are situations when adjuvant therapy clearly is not indicated.	• no benefit for soft tissue sarcomas that arise from visceral or abdominal sites, and surgery alone remains the standard of care.
Specific subtypes of adult soft tissue sarcomas may benefit from adjuvant chemotherapy:	• synovial sarcoma • high-grade myxoid/round cell liposarcoma.

Adjuvant Chemotherapy for STS

- Meta-analysis 1997 and 2008
  - 14 trials: 1568 pts: Increased DFS, RFS, distant mets in favor of chemotherapy, not OS
    - no ifosfamide
  - 18 trials: 1953 pts: marginal efficacy in favor of chemotherapy with doxorubicin and ifosfamide with respect to local, distant, overall recurrence and OS (11% absolute risk reduction: (30 vs 41% risk of death).

Sarcoma Meta-Analysis Collaboration, *Lancet* 350:1647, 1997.; Pervaiz N et a. *Cancer* 2008; 112:573

Conclusions: Adjuvant chemotherapy for STS

- **Disease-free survival is longer** in patients who receive chemotherapy.
- **Overall survival may be improved** with chemotherapy for all STS based on studies using doxorubicin-based therapy, but if there is a benefit, it appears to be a small one. The risks and benefits of adjuvant therapy should be discussed on a case-by-case basis.

Classic Chemotherapy Drugs for Metastatic Sarcoma: Response Rates

Doxorubicin	20%
Ifosfamide	20%
Cyclophosphamide	12%
Paclitaxel	12%
Dacarbazine	10%
Pegylated doxorubicin	10%
Trabectedin	10%
Gemcitabine	8%
Eribulin	7%

Edmonson JH, et. al. *J Clin Oncol* 1993; 11:1269 – 1275.; Santoro A., et. al. *J Clin Oncol.* 1995; 13: 1537-1545.;Patel A, et. Al. *J Clin Oncol.* 1997; 15 – 2378.; van Oosterom et. al., *Eur J Cancer.* 2002; 2397 – 2406; Judson I, et. Al. *Eur J Cancer.* 2001; 37:870-77.;Demetri G, et. al. *Hematol Oncol Clin North Am.* 1995; 9 (4): 765-85.;Antman K, et. al. *Semin Surg Oncol.* 1988; 4: 53 – 58.;Skubitz KM, D'Adamo DR. Sarcoma. *Mayo Clin Proc.* 2007; 82:1409-1432, Demetri GD, et. al. *PNAS* 1999;96: 3951-56; Debrock G, et. Al. *Br J Cancer.* 2003; 89:1409-12;Schoffski P et. al. *Lancet Oncol* 2011: 12: Demetri GD et al. *JCO* 2015: 33: Abst 10503^; Schoffski P et al. *JCO* 2015: 33 Abstr LBA10502^^

Combination Therapy

Adriamycin/Olaratumab vs Adriamycin	• RR in a phase Ib/II trial: ~18% vs 12%
AIM	• ~40% RR
MAID	• ~40% RR
Gemcitabine/Docetaxel vs Gemcitabine	• RR in a phase II trial: ~18% vs 8%
Gemcitabine/DTIC vs DTIC	• RR in a phase II trial: ~12% ORR vs 4%

Elias A, et. al. *J Clin Oncol.* 1989; 7:1208 – 1216.; Antman K et. al. *J Clin Oncol.* 1993; 11: 1276 – 1285; Judson, et. al. *Lancet Oncol* 2014; Maki RG et al. *J Clin Oncol.* 2007; 25:2755; Hensley et. al. *JCO* 2002; Garcia-del-Muro, X, et. al. *JCO* 2011, Tap, William D et al. *The Lancet* , Volume 388 , Issue 10043, 488 - 497

Soft Tissue Sarcoma: NCCN Guideline Recommended Agents/Regimens

- Systemic therapy agents and regimens with activity for general STS subtypesa,b,c,* are shown below:[1]

Neoadjuvant / Adjuvant

Preferred:
- AIM (doxorubicin, ifosfamide, mesna
- Ifosfamide, epirubicin, mesna

Other recommendations:
- AD (doxorubicin + dacarbazine[†])
- Doxorubicin
- Gemcitabine + docetaxel

Useful in certain circumstances:
- Ifosfamide

1L Advanced / Metastatic

Preferred:
- Doxorubicin **or** epirubicin **or** liposomal doxorubicin
- AD **or** AIM **or** MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
- Ifosfamide, epirubicin, mesna

Other recommendations:
- Gemcitabine-based regimens

Useful in certain circumstances:
- Pazopanib[‡]
- Larotrectinib[‡,1]
- Entrectinib[‡,1]

2L+ Advanced / Metastatic

Preferred:
- Eribulin[‡a,1]
- Pazopanib[‡,¶]
- Trabectedin[‡,h,#]

Other recommendations:
- Dacarbazine
- Ifosfamide
- Temozolomide[‡]
- Vinorelbine[‡]
- Regorafenib[‡]

*Soft tissue sarcoma subtypes with non-specific histologies. Regimens appropriate for general STSd,e; see other NCCN guideline sections for histology-specific recommendations. Category 2A recommendations unless otherwise noted. See Notes for NCCN alphabetical footnotes. †If ifosfamide is not considered appropriate. ‡Patients ineligible for IV chemotherapy. §For NTRK gene-fusion sarcomas. ICategory 1 recommendation for liposarcoma, Category 2A recommendation for other subtypes. ¶For non-adipocytic sarcoma. #Category 1 for liposarcoma and leiomyosarcoma.
1L, first-line; 2L+, subsequent lines of therapy; STS, soft tissue sarcoma.
1. NCCN Guidelines. *Soft Tissue Sarcoma*. Version 2.2020–May 28, 2020.

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Overview of Targeted Therapies for Cancer

- Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumor growth and progression.
- Ideally- A primary goal of targeted therapies is to fight cancer cells with more precision and potentially fewer side effects.
- Targeted cancer agents are broadly classified as:
  - **Therapeutic monoclonal antibodies** target specific antigens found on the cell surface.
  - **Small molecules** can penetrate the cell membrane to interact with targets inside a cell.

Agent	Target(s)	FDA-approved indication(s)
Ado-trastuzumab emtansine (Kadcyla)	HER2 (ERBB2/neu)	Breast cancer (HER2+)
Afatinib (Gilotrif)	EGFR (HER1/ERBB1), HER2 (ERBB2/neu)	Non-small cell lung cancer
Aldesleukin (Proleukin)		Renal cell carcinoma Melanoma
Alectinib (Alecensa)	ALK	Non-small cell lung cancer
Avapritinib	KIT and PDGFR	GIST
Atezolizumab (Tecentriq)	PD-L1	Urothelial carcinoma Non-small cell lung cancer
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	Renal cell carcinoma
Bevacizumab (Avastin)	VEGF ligand	Cervical, Fallopian tube and Ovarian cancer Colorectal cancer Glioblastoma Non-small cell lung cancer Renal cell carcinoma
Cabozantinib (Cabometyx [tablet], Cometriq [capsule])	FLT3, KIT, MET, RET, VEGFR2	Medullary thyroid cancer Renal cell carcinoma
Ceritinib (Zykadia)	ALK	Non-small cell lung cancer
Cetuximab (Erbitux)	EGFR (HER1/ERBB1)	Colorectal cancer Squamous cell cancer of the head and neck
Cobimetinib (Cotellic)	MEK	Melanoma
Crizotinib (Xalkori)	ALK, MET, ROS1	Non-small cell lung cancer

Agent	Target(s)	FDA-approved indication(s)
Dabrafenib (Tafinlar)	BRAF	Melanoma
Denosumab (Xgeva)	RANKL	Giant cell tumor of the bone
Erlotinib (Tarceva)	EGFR (HER1/ERBB1)	Non-small cell lung cancer Pancreatic cancer
Everolimus (Afinitor)	mTOR	neuroendocrine tumor Renal cell carcinoma Breast cancer
Gefitinib (Iressa)	EGFR (HER1/ERBB1)	Non-small cell lung cancer
Imatinib (Gleevec)	KIT, PDGFR, ABL	GI stromal tumor Dermatofibrosarcoma protuberans
Ipilimumab (Yervoy)	CTLA-4	Melanoma
Lapatinib (Tykerb)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1)	Breast cancer
Lenvatinib (Lenvima)	VEGFR2	Renal cell carcinoma Thyroid cancer
Necitumumab (Portrazza)	EGFR (HER1/ERBB1)	Squamous non-small cell lung cancer

Agent	Target(s)	FDA-approved indication(s)
Nivolumab (Opdivo)	PD-1	Head and neck squamous cell carcinoma Melanoma Non-small cell lung cancer Renal cell carcinoma Urothelial carcinoma
Olaparib (Lynparza)	PARP	Ovarian cancer
Osimertinib (Tagrisso)	EGFR	Non-small cell lung cancer
Palbociclib (Ibrance)	CDK4, CDK6	Breast cancer
Panitumumab (Vectibix)	EGFR (HER1/ERBB1)	Colorectal cancer
Pazopanib (Votrient)	VEGFR, PDGFR, KIT	Renal cell carcinoma Soft tissue sarcoma
Pembrolizumab (Keytruda)	PD-1	Melanoma Non-small cell lung cancer (PD-L1+) Head and neck squamous cell carcinoma
Pertuzumab (Perjeta)	HER2 (ERBB2/neu)	Breast cancer
Pexidartinib	CSF1R	tenosynovial giant cell tumor
Ramucirumab (Cyramza)	VEGFR2	Colorectal cancer Gastric cancer or Gastroesophageal junction Non-small cell lung cancer
Regorafenib (Stivarga)	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3	Colorectal cancer Gastrointestinal stromal tumors

Agent	Target(s)	FDA-approved indication(s)
Ribociclib (Kisqali)	CDK4, CDK6	Breast cancer
Ripretinib	KIT and PDGFRα inhibitor	GIST
Sipuleucel-T (Provenge)		Prostate cancer
Sonidegib (Odomzo)	Smoothened	Basal cell carcinoma
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	Hepatocellular carcinoma Renal cell carcinoma Thyroid carcinoma
Sunitinib (Sutent)	VEGFR, PDGFR, KIT, RET	Renal Cell Carcinoma GIST Pancreatic NET
Tazemetostat	EZH2	Epithelioid Sarcoma
Temsirolimus (Torisel)	mTOR	Renal cell carcinoma
Trametinib (Mekinist)	MEK	Melanoma
Trastuzumab (Herceptin)	HER2 (ERBB2/neu)	Breast cancer Gastric cancer
Vandetanib (Caprelsa)	EGFR (HER1/ERBB1), RET, VEGFR2	Medullary thyroid cancer
Vemurafenib (Zelboraf)	BRAF	Melanoma
Vismodegib (Erivedge)	PTCH, Smoothened	Basal cell carcinoma
Ziv-aflibercept (Zaltrap)	PlGF, VEGFA/B	Colorectal cancer

Soft Tissue Sarcoma: NCCN Guideline Recommended Targeted Agents

- NCCN recommended non-chemotherapy targeted agents are described in the table below

Drug Name	Brand Name	Mechanism of Action	Recommended for:
Pazopanib[2]	Votrient®	Inhibits VEGFR, PDGFR, FGFR, c-Kit	Option for 1L advanced/metastatic disease in patients ineligible for IV chemotherapy
Larotrectinib[3]	VITRAKVI®	Inhibits TRKA, TRKB, TRKC, TNK2	Option for 1L advanced/metastatic disease
Entrectinib[4]	Rozylytrek®	Inhibits TRKA, TRKB, TRKC, ROS1, ALK, JAK2 and TNK2	Option for 1L advanced/metastatic disease
Regorafenib[5]	STIVARGA®	Inhibits c-Kit, VEGFR, PDGFR, RET, BRAF	Option for 2L+ advanced/metastatic disease
Tazemetostat[6]	Tazverik®	Inhibits EZH2, EZH2 gain-of-function mutations Y646X and A687V	Option for metastatic or locally advanced epithelioid sarcoma not eligible for complete resection
Pembrolizumab[7]	Keytruda®	Inhibits PD-L1/PD-L2 and PD-1; immunotherapy	Option for metastatic undifferentiated pleomorphic sarcoma
Palbociclib[8]	Ibrance®	Inhibits CDK-4 and 6, preventing downstream cell proliferation	Option for unresectable well-differentiated / dedifferentiated liposarcoma (WD-DDLS)

BRAF: B-raf proto-oncogene; FGFR: fibroblast growth factor receptor; KIT: hematopoietic growth factor receptor; PDGFR: platelet-derived growth factor receptor; VEGFR: vascular endothelial growth factor receptor
1. Vitrakvi® (larotrectinib) caps, oral soln. [prescribing information]. Stamford, CT: Loxo Oncology, Inc.; November 2018. 2. VOTRIENT® (pazopanib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2020. 3. VITRAKVI® (larotrectinib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. 4. Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech, Inc.; August 2019. 5. STIVARGA (regorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; February 2020. 6. Tazverik (tazemetostat) [prescribing information]. Cambridge, MA: Epizyme, Inc.; January 2020. 7. Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: MERCK & Co., Inc.; April 2020. 8. Ibrance (Palbociclib) [prescribing information]. New York, NY: Pfizer Inc; February 2019.

Pazopanib- Multi-tyrosine Kinase Inhibitor

Pazopanib is a small-molecule TKI of growth factor receptors associated with angiogenesis and tumor cell proliferation

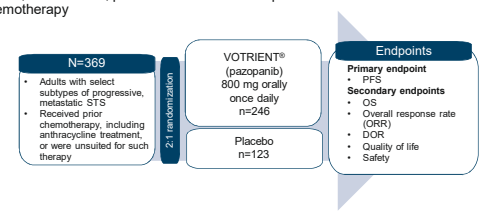
Pazopanib exhibits inhibition of:

- Vascular endothelial growth factor receptors (VEGFR-1, -2, and -3)
- Platelet-derived growth factor receptors (PDGFR-α and -β)
- Fibroblast growth factor receptors (FGFR-1 and -3)
- Stem cell factor receptor (c-Kit)
- Interleukin-2 receptor inducible T-cell kinase (Itk)
- Leukocyte-specific protein tyrosine kinase (Lck)
- Transmembrane glycoprotein receptor tyrosine kinase (c-Fms)

Sleijfer et. al., *J Clin Oncol* 2009; 3126

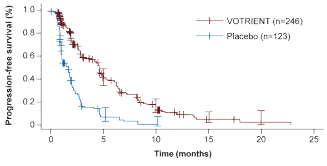
PALETTE Study
Objective and design

- **PA**zopanib exp**L**or**E**d in Sof**T**-**T**isue Sarcoma—a phas**E** 3 study (PALETTE) was a multicenter, randomized, double-blind, placebo-controlled trial in patients with metastatic STS who received prior chemotherapy



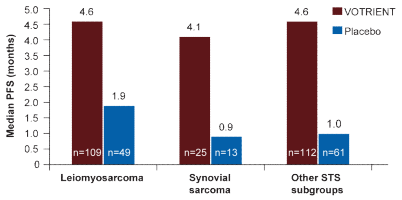
PALETTE Study
Efficacy: primary endpoint

Median PFS	pazopanib (n=246)	Placebo (n=123)
Months	4.6	1.6
Hazard ratio (95% CI)	0.35 (0.26-0.48)	
	P<0.001	



PALETTE Study
Efficacy: primary endpoint (cont'd)

- Pazopanib demonstrated PFS benefit in prespecified subgroups based on STS histology

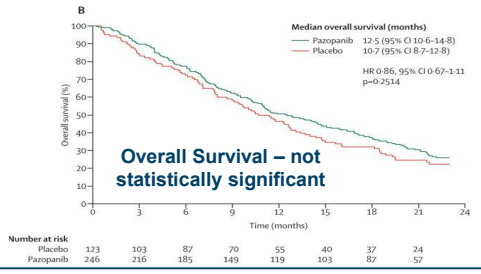


PALETTE Study
Efficacy: secondary endpoints

Endpoint	pazopanib (n=246)	Placebo (n=123)
Median OS (months)	12.6	10.7
HR (95% CI)	0.87 (0.67-1.12)	
ORR (CR+PR), % (95% CI)	4 (2.3-7.9)	0 (0.0-3.0)
Duration of response Median (months) (95% CI)	9.0 (3.9-9.2)	

CR: complete response; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PR; partial response

PALETTE (EORTC 62072)
Overall Survival

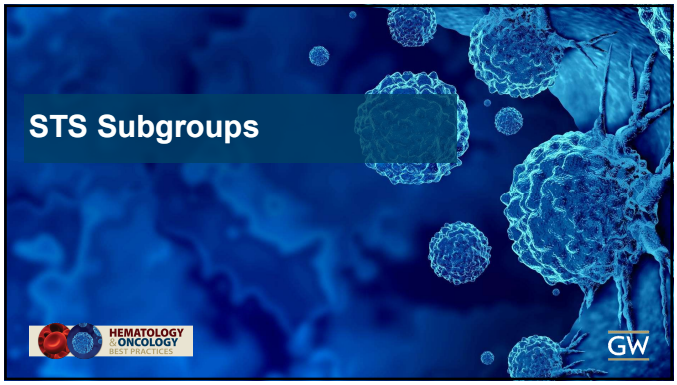


Overall Survival – not statistically significant

Van Der Graaf et. al. *Lancet* 2012; 379: 1879

Pazopanib

- On April 26, 2012, the U.S. Food and Drug Administration granted approval for pazopanib for the treatment of patients with advanced soft tissue sarcoma who have previously received chemotherapy



Liposarcomas (Adipocytic)

- Tied 2nd most common
- Subtypes (WHO 2013):
  - Atypical lipomatous tumor/Well-differentiated liposarcoma
  - Myxoid liposarcoma
  - *round-cell liposarcoma*
  - dedifferentiated liposarcoma
  - Pleomorphic liposarcoma
- Well-differentiated liposarcoma and dedifferentiated: retroperitoneum
- Myxoid and pleomorphic liposarcomas: extremities
- Myxoid, dedifferentiated and pleomorphic: more aggressive
- Well-differentiated - unlikely to metastasize, treated with surgery

Liposarcoma

Well-differentiated/ Dedifferentiated Liposarcoma	• MDM2 and CDK4 amplification • Variable clinical course and chemo sensitivity
Myxoid/ Round Cell Liposarcoma	• FUS-CHOP translocation • Some P13K mutations • Peculiar pattern of metastases • Relatively sensitive to anthracyclines, alkylators and trabectedin
Pleomorphic Liposarcoma	• Frequent p53 mutation • Aggressive clinical course

Well-Differentiated or Dedifferentiated Liposarcoma

- More than 90% of well-differentiated or dedifferentiated liposarcomas (WD/DDLS) have CDK4 amplification.
- Phase 2 Trial of Palbociclib

	2/1 schedule	3/1 schedule
Sample size	30	60
PFS at 12 weeks	66%	57%
Median PFS	18 weeks	18 weeks
Response Rate	3%	2%
Grade 3/4 Anemia	17%	22%
Grade 3/4 Neutropenia	50%	36%
Grade 3/4 Thrombocytopenia	30%	7%

Dickson et. al., *J Clin Oncol* 2013; *JAMA Oncol* 2016.

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Results of previous and current study in dedifferentiated liposarcoma

	palbociclib	palbociclib	abemaciclib
	14/21d schedule 200 mg OD	21/28d schedule 125 mg OD	Continuous 200 mg BID
Sample size	30	60	30
PFS at 12 weeks	66%	57%	76%
Median PFS	18 weeks	18 weeks	30 weeks
Response Rate	3%	2%	3%

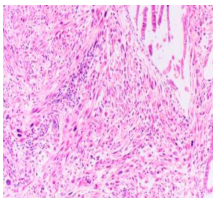
High grade Myxoid (formerly Round cell Liposarcoma)

- Myxoid/round cell with t(12;16) TLS-CHOP
  - 40% of liposarcomas
  - Younger patients (age 15-45)
  - Most chemotherapy sensitive liposarcoma subtype
    - Doxorubicin, ifosfamide
    - Trabectedin (ET-743) (Phase III)
    - Eribulin (Phase III)

Demetri GD, et. al. *PNAS* 1999;96: 3951-56; Debrock G, et. Al. *Br J Cancer.* 2003; 89:1409-12;Schoffski P et. al. *Lancet Oncol* 2011: 12: Demetri GD et al. *JCO* 2015: 33: Abst 10503*; Schoffski P et al. *JCO* 2015: 33 Abstr LBA10502**

Leiomyosarcoma

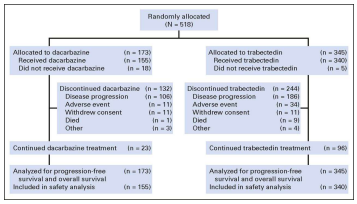
- uLMS- may represent a distinct phenotype;
- Doxorubicin, DTIC, Gemcitabine or Gemcitabine-Docetaxel combinations useful
- Trabectedin (ET-743)
- Eribulin



Maki RG et al. *J Clin Oncol.* 2007; 25:2755; Hensley ML. *Curr Opin Oncol.* 2010; 22 (4): 356 - 61.
Demetri GD et al. *JCO* 2015: 33: Abst 10503*; Schoffski P et al. *JCO* 2015: 33 Abstr LBA10502**

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

Fig 1. CONSORT diagram



Published in: George D. Demetri; Margaret von Mehren; Robin L. Jones; Martee L. Hensley; Scott M. Schuetze; Arthur Staddon; Mohammad Milhem; Anthony Elias; Kristen Ganjoo; Hussein Tawbi; Brian A. Van Tine; Alexander Spira; Andrew Dean; Nushmia Z. Khokhar; Youn Choi Park; Roland E. Knoblauch; Trilok V. Parekh; Robert G. Maki; Shreyaskumar R. Patel; *JCO* 2016, 34, 786-793. DOI: 10.1200/JCO.2015.62.4734

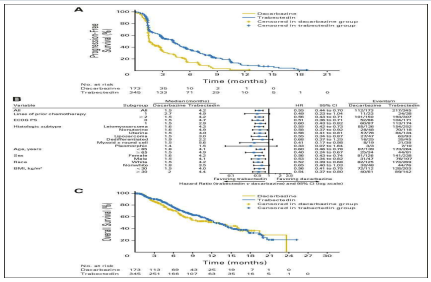
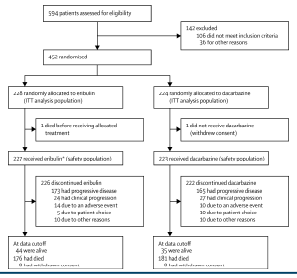


Fig 2. Kaplan-Meier estimates of progression-free survival, subgroup analyses, and overall survival at the interim analysis. (A) Progression-free survival. (B) subgroup analysis (hazard ratios [HRs] and 95% CIs) of progression-free survival, and (C) overall survival. HR was calculated as the hazard in the trabectedin treatment group divided by the hazard in the dacarbazine treatment group. BMI, body mass index.

JCO 2016, 34, 786-793
DOI: 10.1200/JCO.2015.62.4734

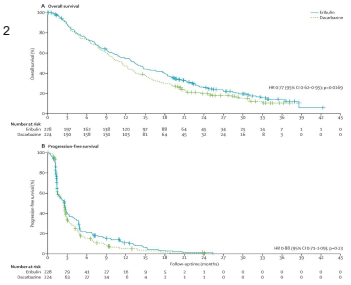
Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial



The Lancet Volume 387, Issue 10028, Pages 1629-1637 (April 2016)

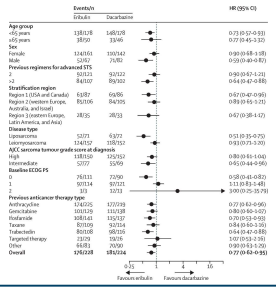
OS and PFS

Figure 2



Subgroup Analysis

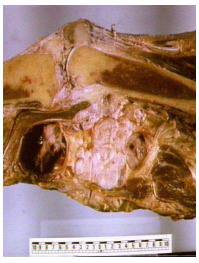
Figure 3



GW

Synovial Sarcoma

- Named for resemblance to synovium
- Considered high-grade
- 2 types: monophasic and biphasic (spindle & epithelial)
- t(X;18) SYT-SSX1 (biphasic) or SYT-SSX2 (monophasic); **>90%**
- SSX1 / biphasic better prognosis than monophasic
- Among most sensitive 'adult' sarcoma to chemotherapy especially to ifosfamide regimens

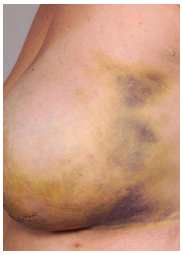


Rosen, et. al. *Cancer* 1994; 73:2506-2511. Skubitz KM, D'Adamo DR. *Mayo Clin Proc.* 2007; 82:1409-1432; slides courtesy of R. Maki

GW

Angiosarcoma

- Uncommon subtype
- Typically on scalp, face and post radiation fields
- Associated with lymphedema, vinyl chloride
- Surgery followed by radiation (scalp/face)
- Taxanes (Docetaxel, Paclitaxel) and anthracyclines (Doxil®) have been used and effective
  - Sorafenib; Bevacizumab

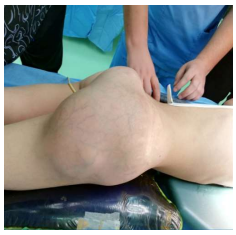


Fury MG, et. al. *Cancer J.* 2005; 11(3): 241 – 7.; Glazebrook KN, et. al. *AJR Am J Roent* 2008; 190 (2): 533-8; Maki R, et. al. *J Clin Oncol.* 2009; 27:3133.

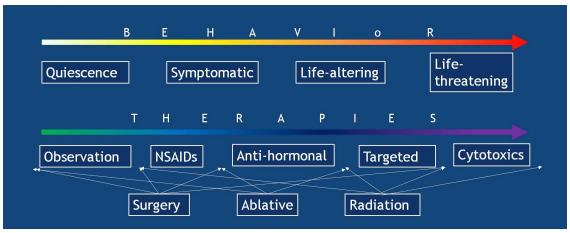
GW

Desmoid Tumors

- "Benign" but locally aggressive tumors arising from fibroblasts.
- Resembles out of control scar tissue
- Arise in any anatomical location and infiltrate the mesentery, neurovascular structures, and visceral organs.
- There is no standard of care.

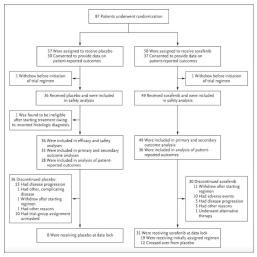


Spectrums of Desmoid



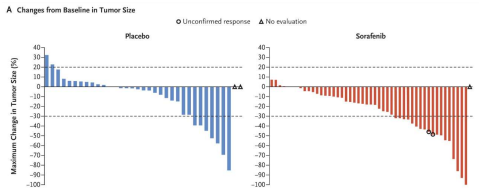
Sorafenib for Advanced and Refractory Desmoid Tumors

- Double-blinded
- Phase 3 trial
- 87 patients with progressive, symptomatic, or recurrent desmoid tumors received either sorafenib (400-mg tablet once daily) or matching placebo
- Crossover to the sorafenib group was permitted for patients in the placebo group who had disease progression
- The primary end point was investigator-assessed progression-free survival
- Rates of objective response and adverse events were also evaluated



N Engl J Med 2018; 379:2417-2428 DOI: 10.1056/NEJMoa1805052

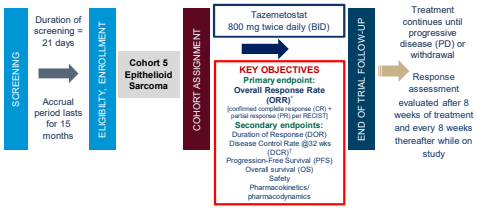
Sorafenib for Advanced and Refractory Desmoid Tumors



Among patients with progressive, refractory, or symptomatic desmoid tumors, sorafenib significantly prolonged progression-free survival and induced durable responses.

Epithelioid Sarcoma

STUDY DESIGN **PHASE 2, OPEN-LABEL, MULTI-CENTER STUDY OF TAZEMETOSTAT**



* Objective response: RECIST 1.1 confirmed complete response or partial response at week 24.
† Disease control: RECIST 1.1 confirmed complete.

Epitheliod Sarcoma

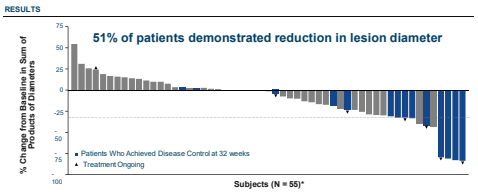
RESULTS **PRIMARY STUDY ENDPOINT: OBJECTIVE RESPONSE RATE (ORR) PER RECIST**

Endpoint Category (RECIST), n (%)	No Prior Systemic Therapy (n=24)	Prior Systemic Anticancer Therapy (n=38)	Total (N=62)
ORR [CR+PR]¶ 95% CI	6 (25%) (9.8–46.7)	3 (8%) (1.7–21.4)	9 (15%) (6.9–25.8)
CR	0	0	0
PR	6 (25%)	3 (8%)	9 (15%)
SD	15 (63%)	20 (53%)	35 (56%)
PD	2 (8%)	11 (29%)	13 (21%)
Not evaluable	1 (4%)	4 (11%)	5 (8%)

¶ ORR is the percentage of subjects achieving a confirmed CR or PR from the start of tazemetostat until PD or the start of subsequent anticancer therapy, whichever is earlier. CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors.

Best Percent Change In Sum Of Diameters Per Investigator Assessment

RESULTS



* Post-baseline sum of diameters was not calculated for 7 subjects in the Intent-to-Treat population due to a lack of complete tumor diameter measurements at any post-baseline visit. These subjects were excluded from the figure.

SUMMARY

- FIRST PROSPECTIVE STUDY CONDUCTED IN EPITHELIOID SARCOMA
- TREATMENT WITH TAZEMETOSTAT, AN INVESTIGATIONAL, FIRST-IN-CLASS ORAL EZH2 INHIBITOR, ACHIEVED
  - AN ORR BY RECIST IN 15% OF ALL PATIENTS
  - A DECREASE IN TUMOR SIZE IN 51% OF ALL PATIENTS
  - DURABLE RESPONSES. AT A MEDIAN FOLLOW-UP OF 59.9 WEEKS, THE MEDIAN DOR WAS NOT REACHED
  - A MEDIAN PFS OF 23.7 WEEKS, WITH 21.3% PATIENTS PROGRESSION-FREE AT 1 YEAR.
  - A MEDIAN OS OF 82.4 WEEKS
- TAZEMETOSTAT WAS GENERALLY WELL TOLERATED WITH NO TREATMENT-RELATED DEATHS AND <2% DEFINITIVE DISCONTINUATIONS
- TAZEMETOSTAT, WAS APPROVED 1/23/2020 FOR ACCELERATED APPROVAL FOR THE TREATMENT OF PATIENTS WITH METASTATIC OR LOCALLY ADVANCED EPITHELIOID SARCOMA NOT ELIGIBLE FOR CURATIVE SURGERY

DOR, duration of response; ES, epithelioid sarcoma; EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; ORR, objective response rate; PFS, progression-free survival; RECIST, response evaluation in solid tumors.

Gastrointestinal Stromal Tumor (GIST)

- Exact incidence is unknown, estimated annual US incidence ~ 3000 - 6000 cases/ year *
- Median age 63 - 69 y/o
- Most common mesenchymal tumor of intestinal origin
  - Originates from interstitial cells of Cajal
- Symptoms variable, median size at diagnosis: 5 cm
- Stomach is most common site (60 – 70%) -> small intestine (20 - 30%)

Von Mehren M. NCCN Task Force Report: Gastrointestinal Stomal Tumors; *NCI data

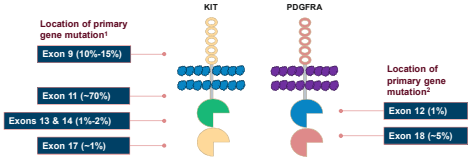
Gastrointestinal Stromal Tumor (GIST)

- Surgery - mainstay of treatment
- Poor response to chemotherapy (< 5% response to doxorubicin)
- Commonly results from activating/gain-of-function mutations in the KIT (CD117)* or PDGFRA (Platelet derived growth factor alpha)

*Hirota S et al. *Science.* 1998 Jan 23;279(5350):577-80;

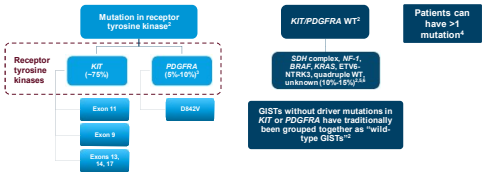
The Majority of GISTs Harbor Primary Mutations in *KIT* or *PDGFRA*[1]

While most primary mutations occur in exon 11 of *KIT* (70%), others may occur in *KIT* at exons 9, 13, 14, and 17 and in *PDGFRA* at exons 12 and 18[1]



KIT=KIT proto-oncogene receptor tyrosine kinase; PDGFRA=platelet-derived growth factor receptor a.
1. Oppelt PJ et al. *J Gastrointest Oncol.* 2017;8(3):466-473. 2. Corless CL et al. *Nat Rev Cancer.* 2011;11(12):865-878.

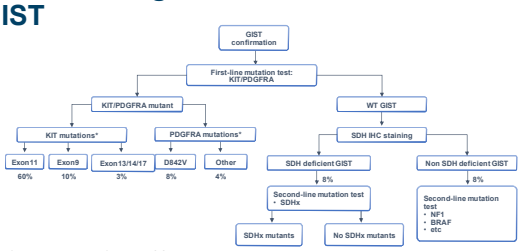
While the Majority of GISTs Have Mutations in *KIT* and *PDGFRA*, Additional Genes Have Been Found Associated With GISTs[1]



GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; NF1=neurofibromin 1; PDGFRA=platelet-derived growth factor receptor a; SDH=succinate dehydrogenase; WT=wild type.

1. Mei L et al. *Front Oncol.* 2018;8:135. 2. Oppelt PJ et al. *J Gastrointest Oncol.* 2017;8(3):466-473. 3. Lopes LF et al. *J Cell Mol Med.* 2010;14(1-2):42-50. 4. Liegl B et al. *J Pathol.* 2008;216(1):64-74. 5. Nannini M et al. *BMC Cancer.* 2014;14:685. 6. Lasota J et al. *Mod Pathol.* 2013;26(11):1488-1491.

Mutation Testing Can Reveal a Driver Mutation in GIST



*Percentages reflect primary mutations found in all GIST.
GIST=gastrointestinal stromal tumor; IHC=immunohistochemistry; KIT=KIT proto-oncogene receptor tyrosine kinase; NGS=next generation sequencing; PDGFRA=platelet-derived growth factor receptor a; SDHx=succinate dehydrogenase x; WT=wild-type.
Wang Y et al. Current Cancer Drug Targets. 2019;19(1):1-10.

Image adapted from Wang Y et al. *Curr Cancer Drug Targets.* 2019.

Phase III Trials of Imatinib in GIST

SWOG S0033/CALGB 150105

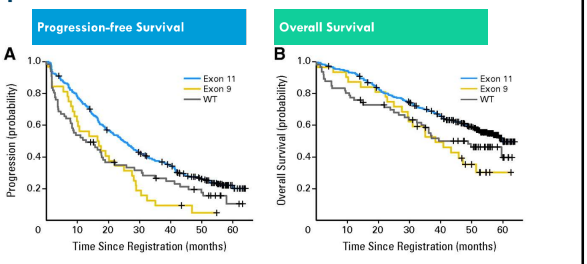
- N=746 patients
- Median PFS of 18 months on 400 mg vs 20 months on 800 mg imatinib
- Median OS was 55 and 51 months, respectively
- 22% alive at 10 years*
- After progression on 400 mg imatinib, 33% of patients who crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease

EORTC 62005

- N=946 patients
- 263 (56%) of 473 patients on imatinib once daily had progressed compared with 235 (50%) of 473 on imatinib twice daily treatment
- Responses: CR: 52 (5%); PR: 442 (47%); SD: 300 (32%), no difference between groups
- Median time to best response was 107 days

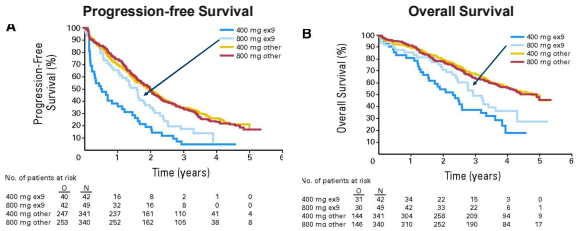
Blanke C et al. *J Clin Oncol* 2008; 26:626-32; Veerweij et. al. *Lancet* 2004; 364:1127-134;
*Demetri G et al. ASCO 2014: Abstr 10508.

KIT Exon 11 predicts better survival with metastatic GIST patients on imatinib



Heinrich MC et al. *J Clin Oncol* 2008; 21: 5360

MetaGIST Analysis: Predictive factors for the benefit of high-dose Imatinib therapy with regard to PFS and OS



Presence of *KIT* exon 9 mutation was the only significant predictive factor for the benefit of high-dose therapy

Heinrich M, et al. *JCO* Mar 1 2010: 1247-1253.

Use of Imatinib for KIT mutations

- Standard starting dose of 400 mg daily
- Increase to 800 mg can be considered as up to 30% response can be seen
- Start at 800 mg daily (may dose-escalate 4-8 wks)
  - KIT exon 9 mutations
  - Potentially delay the first occurrence of disease progression and increase objective response rate

Zalcberg JR et al. *Eur J Cancer* 2005;41:1751–1757.

Resistance to Imatinib

- **Primary resistance** - progression during the first 6 months of imatinib
  - Commonly seen with KIT exon 9, PDGFRA D842V -mutant or exon 18, or wild-type GIST
- **Secondary resistance** - >6 months of imatinib or those with an initial response who then experience progression
- Mechanisms: secondary kinase mutations
  - Newly acquired kinase mutations (ATP Binding or Activation loop)
  - Genomic amplification of target receptor
  - Drug transporters

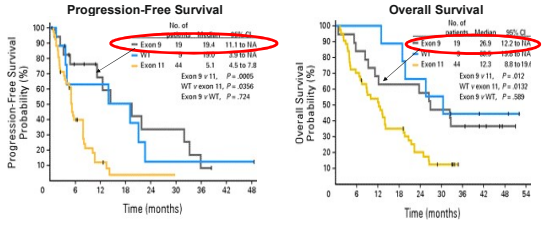
Benjamin RS et. al. *Semin Oncol* 2009;36:302–311; Antonescu CR et. al. *Clin Cancer Res* 2005;11:4182–4190.
Maleddu A. et. al. *Oncol Rep* 2009;21:1359–1366

Efficacy of Sunitinib in Imatinib-resistant or intolerant patients

Efficacy parameter	Sunitinib (n=207)	Placebo (n=105)	p Value (log-rank test)	HR	95%CI
Median TTP [weeks (months)]	27.3 (6.4)	6.4 (1.5)	<0.0001	0.33	0.23 to 0.47
Median PFS [weeks (months)]	24.1 (5.6)	6.0 (1.4)	<0.0001	0.33	0.24 to 0.47
Partial response (%)	6.8	0			
Durable stable disease(%)	17.4	1.9			
Objective response rate (%)	7	0	0.006		

Demetri et. al. *Lancet*. 2006 Oct 14;368(9544):1329-38; Younous et. al. *Curr Oncol*. 2010 17: 4

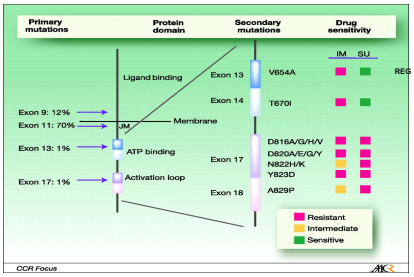
KIT Genotype and Efficacy of Sunitinib



Opposite sensitivity pattern to imatinib: *KIT* exon 9 mutation and WT better

Heinrich M C. et. al. *J Clin Oncol* 2008; 26: 5352 - 5359

Secondary KIT kinase mutations in TKI-resistant GIST

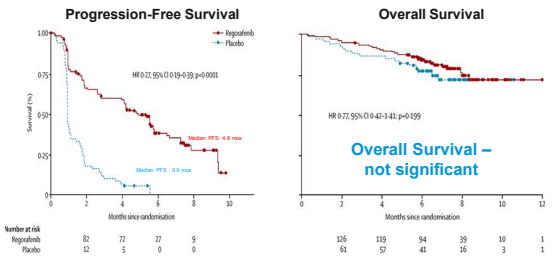


Regorafenib in the GRID Study (GIST Regorafenib in Progressive Disease)

- Oral multikinase inhibitor
- 199 patients with metastatic or unresectable GIST with disease progression while on, or intolerance to, previous imatinib and sunitinib
- 2:1 randomization on regorafenib 160 mg daily vs placebo 3 out of 4 weeks cycle
- Cross-over to regorafenib allowed upon progression (85%)
- The primary endpoint was PFS

Demetri G et al. *Lancet* 2013; 81: 295 - 302

Regorafenib



Demetri G et al. *Lancet* 2013; 81: 295 - 302

Avapritinib

- Avapritinib is a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations[1]
- Avapritinib binds directly to the active conformation of PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants[1,2]
- In in vitro assays, avapritinib was shown to be a selective KIT/PDGFRA kinase inhibitor[1,2]
- Avapritinib demonstrated potent cellular in vitro activity on PDGFRA D842V mutants associated with resistance to approved kinase inhibitors[1]

1. AYVAKIT Prescribing Information. Blueprint Medicines Corporation, Cambridge, MA. January 2020.
2. Data on file (DOF-REF-00206). Blueprint Medicines Corporation, Cambridge, MA. 2019.

Avapritinib in advanced PDGFRA D842V-mutant GIST (NAVIGATOR): a multicentre, open-label, phase 1 trial

- A multi-center, single-arm, open-label clinical trial where patients received avapritinib 300 mg or 400 mg orally once daily until disease progression or unacceptable toxicity
- **Eligibility:** Patients were required to have a confirmed diagnosis of GIST and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2

Endpoints:

- **Primary Endpoint:** Overall response rate (ORR) as defined by patients who achieved a complete response (CR) or partial response (PR)
- **Secondary Endpoint:** Duration of response (DOR)

https://doi.org/10.1016/S1470-2045(20)30269-2

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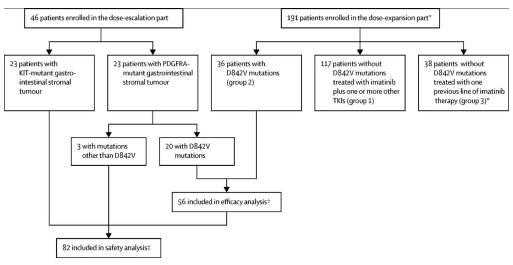
Patient disposition

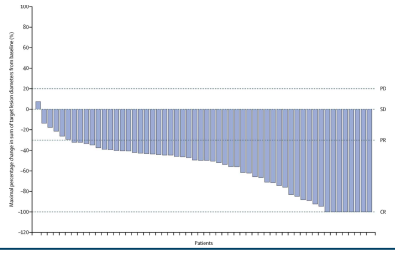


Best confirmed response by central assessment per mRECIST (version 1.1) in patients with PDGFRA D842V-mutant gastrointestinal stromal tumor

	All doses (n=56)	300 mg (n=28)
Complete response	5 (9%)	1 (4%)
Partial response	44 (79%)	25 (89%)
Overall response (partial plus complete response)	49 (88%; 95% CI 76–95)	26 (93%; 95% CI 77–99)
Stable disease	7 (13%)	2 (7%)
Clinical benefit (complete response or partial response plus stable disease lasting at least 16 weeks)	55 (98%; 95% CI 90–100)	28 (100%; 95% CI 88–100)
Progressive disease	0	0

mRECIST=Response Evaluation Criteria in Solid Tumors modified for patients with gastrointestinal stromal tumour.

Maximal percentage change in sum of target lesion diameters from baseline in patients with PDGFRA D842V-mutant GIST



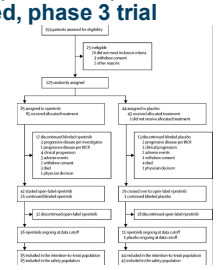
Ripretinib

Ripretinib (DCC-2618) is a switch-control TKI that broadly inhibits KIT and PDGFRA kinase signalling through a dual mechanism of action.

Specifically and durably binds to both the switch pocket and the activation loop to lock the kinase in the inactive state, preventing downstream signaling and cell proliferation.

This dual mechanism of action provides broad inhibition of *KIT* and PDGFRA kinase activity, including for wild-type *KIT* and *PDGFRA* mutations and multiple primary and secondary mutations associated with drug-resistant gastrointestinal stromal tumors.

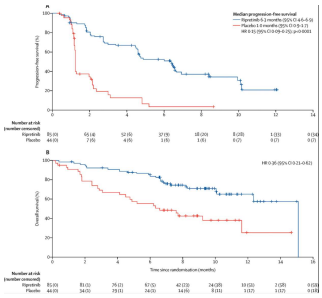
Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomized, placebo-controlled, phase 3 trial



https://doi.org/10.1016/S1470-2045(20)30168-6

A: Median PFS
B: OS

- Median overall survival was 15.1 months (95% CI 12.3–15.1) in the ripretinib group and 6.6 months (4.1–11.6) in the placebo group (HR 0.36, 95% CI 0.21–0.62



Ripretinib

Results from the INVICTUS study showed the efficacy and safety of ripretinib as fourth-line (or further-line) therapy in patients who have advanced GIST.

In May, 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received previous treatment with three or more kinase inhibitors, including imatinib.

Ripretinib is being evaluated in an ongoing phase 3 study (INTRIGUE) in second-line treatment compared with sunitinib.

GIST: Current Treatment Approaches

- Surgery remains the only curative intervention in patients with primary, localized GIST (where avoiding tumor rupture is possible, and the associated risk of injury or death is acceptable)[1,2]
- Tumors often recur or metastasize[2]
- NCCN recommended systemic agents and regimens for unresectable or metastatic GIST are shown below:*[3]

1L Therapy for Unresectable, Recurrent, or Metastatic Disease	2L Therapy for Unresectable, or Metastatic Disease (PD after Imatinib)	3L Therapy for Unresectable, or Metastatic Disease (PD after Imatinib and Sunitinib)	4L Therapy for Unresectable, or Metastatic Disease (PD after Imatinib, Sunitinib, and Regorafenib)
Preferred: • Imatinib† (category 1) • Avapritinib‡§,¶	**Preferred:** • Sunitinib (category 1)	**Preferred:** • Regorafenib (category 1)	**Preferred:** • Ripretinib **Useful Under Certain Circumstances:** • Sorafenib or Nilotinib or Dasatinib‡ or Pazopanib or Everolimus + TKIs or Avapritinib,‖

1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; GIST, gastrointestinal stromal tumor; NCCN, National Comprehensive Cancer Network; PD, progressive disease.
*Category 2A recommendations unless otherwise noted. See Notes for NCCN alphabetical footnotes. †For GIST with *PDGFRα* exon 18 mutation including *PDGFRα* D842V mutations.
‡For patients with *PDGFRα* D842V mutation.
1. The ESMO/European Sarcoma Network Working Group. *Ann Oncol.* 2014;25(Suppl 3):iii102–iii112. 2. Wang CJ, et al. *World J Gastroenterol.* 2015;21:8398-8407. 3. NCCN Guidelines. Soft Tissue Sarcoma. Version 2.2020–May 28, 2020.

Abstract #11503

AIO

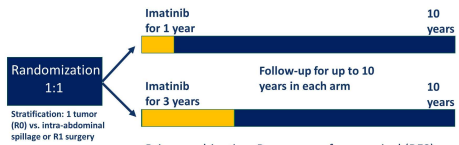
Three versus one year of adjuvant imatinib for high-risk gastrointestinal stromal tumor (GIST): Survival analysis of a randomized trial after 10 years of follow-up

Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, Annette Reichardt, Barbara Hermes, Jochen Schütte, Silke Cameron, Peter Hohenberger, Philipp J Jost, Salah-Eddin Al-Batran, Lars H Lindner, Sebastian Bauer, Eva Wardelmann, Bengt Nilsson, Raija Kallio, Panu Jaakkola, Jouni Junnila, Thor Alvegård, Peter Reichardt

Three versus one year of adjuvant imatinib for high-risk gastrointestinal stromal tumor (GIST): Survival analysis of a randomized trial after 10 years of follow-up

SSGXVIII/AIO Design and Objectives

- An open-label, multicenter, Phase III trial



- Primary objective: Recurrence-free survival (RFS)
- Secondary objectives include: Safety, overall survival

ClinicalTrials.gov identifier NCT00116935

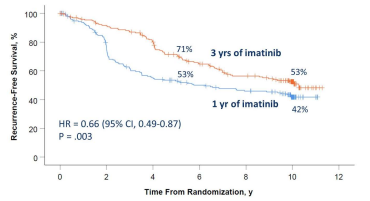
Key inclusion criteria

- Histologically confirmed KIT-positive GIST
- High risk of recurrence according to the modified Consensus Criteria[1,2]:
  - Tumor size >10 cm *or*
  - Tumor mitosis count >10/50 HPFs *or*
  - Size >5 cm and mitosis count >5/50 HPFs *or*
  - Tumor rupture spontaneously or at surgery

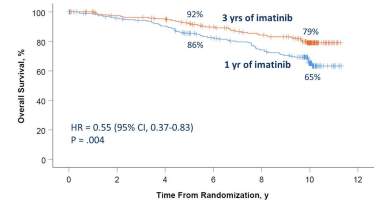
HPF = high-power field of the microscope

[1]Fletcher CD et al. Hum Pathol 2002; 33:459-65
[2]Joensuu H. Hum Pathol 2008;39:1411-9

Recurrence-free survival in the Intention-To-Treat Population



Overall Survival in the Intention-To-Treat Population



Conclusions

- Three years of adjuvant imatinib is superior in efficacy RFS and OS) as compared to 1 year of imatinib
- About 50% of deaths can be avoided during the first 10 years of follow-up after surgery with the longer adjuvant imatinib treatment

Bone Sarcomas

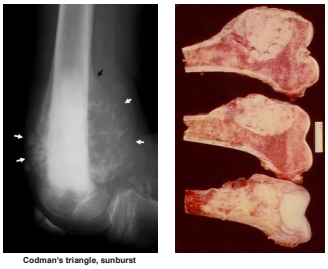
- Rare (2970 cases in the US in 2015 with 1640 deaths)
- Improvement in terms of limb-sparing procedures and survival with chemotherapy
- More common:
  - Osteosarcoma
  - Chondrosarcoma
  - Ewing Sarcoma

Osteosarcoma

- Osteosarcoma: characterized by osteoid or immature bone
- Most common primary malignant bone tumor present in children and young adults
  - Bimodal peak: adolescents and older at 60 – 80 y/o associated with Paget's disease

Bone Sarcomas - Osteosarcoma

- Most frequent in the femur, tibia and humerus (metaphysis of long bones)



Codman's triangle, sunburst

Osteosarcoma Biology

- Associated with p53, Rb deletions
- 20% will present with metastatic disease
- 80% of metastasis will be in the lungs
  - Surgery for lung mets may provide remission
- Prognostic factors:
  - Poor: increased alkaline phosphatase or LDH
  - Good histopathologic response (>90% necrosis) to neoadjuvant chemotherapy predictive of survival

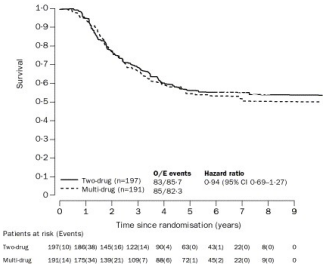
Bacci et. al. *Eur J Cancer* 2005;41:2079

Osteosarcoma: Treatment

- Surgery for local control: Wide excision
  - Radiation not often effective
- Chemotherapy is mandatory and a standard of care in the therapy of bone osteosarcoma
  - Chemotherapy effective in either neo-adjuvant or adjuvant setting
- Doxorubicin and cisplatin as neoadjuvant therapy without high dose methotrexate appears to be as useful as a more complex regimen for overall survival: standard of care for adults

Link et al. *NEJM* 1986; 314:1600.;
Goorin A et al. *J Clin Onc* 2003; 21:1574
Souhami RL et. al. *Lancet* 1997; 350: 911
Ferrari S, et. al. *JCO* 2012; 30:2112–2118

Overall Survival: Osteogenic sarcoma



Souhami et al. *Lancet* 1997; 350:911

Osteosarcoma

- Adjuvant chemotherapy shown to decrease recurrence from 80% to 30%
- Standard of care is still doxorubicin + cisplatin +/- methotrexate for adjuvant therapy

Sutow WW, et. al. *Cancer* 1975; 36: 1598 – 1602;
Link MP, et. Al. *NEJM* 1986; 314: 1600

Osteosarcoma MAP Regimen

Weeks	Agents	Dose	Days
Induction MAP (weeks 1 through 10)			
1, 6	Doxorubicin	37.5 mg/m^2 per day by continuous IV infusion or IV push	1 and 2
	Cisplatin	60 mg/m^2 per day IV over four hours	
4, 5, 9, 10	High-dose methotrexate	12 grams/m^2 IV over four hours*	1
	Leucovorin rescue	15 mg (approximately 10 mg/m^2) every six hours IV or orally for 10 doses¶	Starting 24 hours after beginning high-dose methotrexate
Surgery (week 11)			
11	Resection or amputation		
Postoperative MAP (weeks 12 through 29)			
12, 17	Doxorubicin$^\Delta$	37.5 mg/m^2 per day by continuous IV infusion or IV push	1 and 2
	Cisplatin	60 mg/m^2 per day IV over four hours	
22, 26	Doxorubicin$^\Delta$	37.5 mg/m^2 per day IV over 24 hours	
15, 16, 20, 21, 24, 25, 28, 29	High-dose methotrexate	12 grams/m^2 IV over four hours	1
	Leucovorin rescue	15 mg (approximately 10 mg/m^2) every six hours IV or orally for 10 doses	Starting 24 hours after beginning high-dose methotrexate

Bone Sarcomas - Chondrosarcoma

- Chondrosarcomas: commonly arise in benign cartilage abnormality
- 2nd most common tumor of the bone
- More common in older adults
- Typically in the pelvis, femur, knee, shoulder
- Grade, size and tumor location prognostic
- Rx: surgical resection
  - Consider palliative resection even in advanced disease
- Chemotherapy: little role*
- Unresectable: treated with RT

*Dedifferentiated: Treat like osteosarcoma; Mesenchymal: Treat like Ewing's

Bone Sarcomas – Ewing Sarcoma

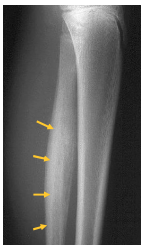
- Small, round-cell neoplasms: Ewing sarcoma, primitive neuroectodermal tumor (PNET), PNET of bone, extraosseous Ewing sarcoma
- EWS gene on chromosome 22q12 fuses with various members of the ETS family (FLI1, ERG, ETV1, ETV4, FEV)
- EWS-FLI1 fusion transcript from translocation t(11;22)(q24;q12) – 85% of Ewings sarcoma*

*PNET (removed in the WHO 2013 classification as synonym for Ewings)

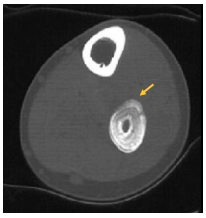
Bone Sarcomas – Ewing Sarcoma

- Adolescents and young adults
- May affect soft tissues or bone
- Most common sites are: femur, pelvis, chest wall
- Diaphysis is most frequent affected site: mottling; onion skin periosteal reaction
- Favorable prognosticators: distal site, normal LDH, no metastasis at presentation

Ewing Sarcoma (Bone)



Infiltrative changes



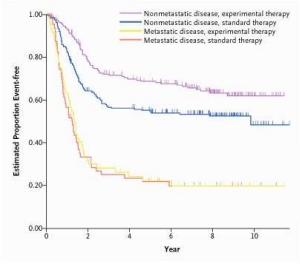
Onion-skinning

Ewing Sarcoma

- Treatment consists of systemic therapy and local control therapy
- Primary treatment – Neoadjuvant multiagent chemotherapy for 12 – 24 weeks
- Local treatment: surgical wide excision +/- pre-operative RT, definitive chemoRT
- Adjuvant chemotherapy for 28 – 49 weeks

Ewing Sarcoma Adjuvant Study (IESS-III 1988 – 1992)

- 518 pts (398 pts without metastases) randomized
- Age < 30
- VAC +/- I/E arms
- OS 72% vs 61% in favor of 5 drugs
- Standard of care for non-metastatic disease
- I/E did not improve survival when given in this fashion for metastatic disease



Grier HE et al. *NEJM* 2003; 348:694

Chemotherapy Protocol for Ewing Sarcoma

Drug	Dose	Regimen	
		VDCA	VDCA/IE
Vincristine	2 mg/m^2 (max 2 mg), day 1	Cycles 1-17	Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17
Doxorubicin	75 mg/m^2, day 1	Cycles 1-5*	Cycles 1, 3, 5, 7, 9
Cyclophosphamide plus mesna	1200 mg/m^2, day 1	Cycles 1-17	Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17
Dactinomycin	1.25 mg/m^2, day 1*	Cycles 6-17*	Cycles 11, 13, 15, 17
Ifosfamide plus mesna	1800 mg/m^2 daily, days 1-5	-	Cycles 2, 4, 6, 8, 10, 12, 14, 16
Etoposide	100 mg/m^2 daily, days 1-5	-	Cycles 2, 4, 6, 8, 10, 12, 14, 16

Courses administered every 21 days for 17 courses.
* Substitute dactinomycin for doxorubicin when cumulative doxorubicin dose is 375 mg/m^2.

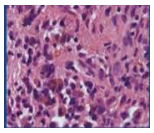
Grier H, et al. N Engl J Med 2003; 348:694.

Conclusions: Bone sarcomas

- Each bone sarcoma has a characteristic radiographic appearance
- Chemotherapy essentially mandatory for osteogenic sarcoma and Ewing sarcoma, in addition to surgery (and XRT for Ewing sarcoma) - cure rate improved
- Conventional chondrosarcomas are treated surgically as a standard of care

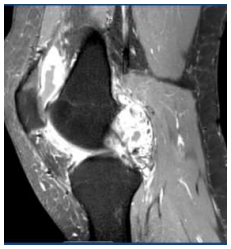
Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis)

- Vascular, proliferative, inflammatory synovium
  - Multinucleated giant cells, macrophages, and hemosiderin
- Localized or diffuse-type growth pattern
- Intra- or extra articular locations
- Translocations (1p13)/alterations involving CSF1 gene
- ↑ CSF1 expression → macrophage recruitment to tumor site → CSF1/CSF1R autocrine/ paracrine loop of neoplastic/ non-neoplastic cells



Tenosynovial Giant Cell Tumor Therapies

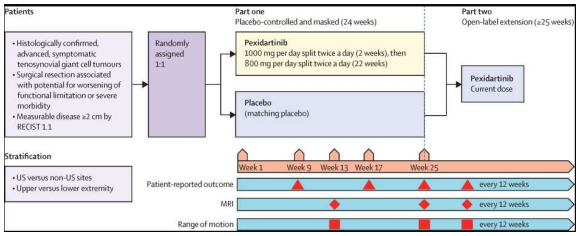
- Localized
  - Surgical- subtotal/ total resection, synovectomy to arthroplasty
  - Radiation/ radio-synovectomy
- Systemic → anti-CSF1R therapies



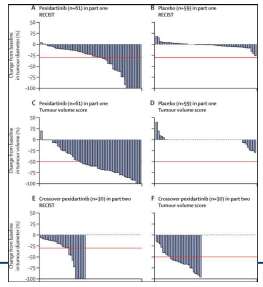
Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial

William D Tap, Hans Gelderblom, Emanuela Palmerini, Jayesh Desai, Sebastian Bauer, Jean-Yves Blay, Thierry Alcindor, Kristen Ganjoo, Javier Martín-Broto, Christopher W Ryan, David M Thomas, Charles Peterfy, John H Healey, Michiel van de Sande, Heather L Gelhorn, Dale E Shuster, Qiang Wang, Antoine Yver, Henry H Hsu, Paul S Lin, Sandra Tong-Starksen, Silvia Stacchiotti, Andrew J Wagner*, on behalf of the ENLIVEN investigators†*

Study Design



Maximum change in tumor size according to RECIST and tumor volume score



Adverse Reactions

WARNING: HEPATOTOXICITY
- **TURALIO can cause serious and potentially fatal liver injury.**
- **Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity.**
- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.**

- Serious ARs were reported in 13% leading to permanent discontinuation- the most frequent ARs included increased ALT (4.9%), increased AST (4.9%), and hepatotoxicity (3.3%)
- Dose reductions or interruptions occurred in 38% of patients 2ndary to increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%)

- On August 2, 2019, the FDA approved pexidartinib capsules for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery
- Pexidartinib is the first systemic therapy approved for patients with TGCT
- The approval was based on durable ORR
- After 25 weeks of treatment, the ORR was 38% (95% confidence interval: 27, 50), with a 15% complete response rate and a 23% partial response rate
- No patients receiving placebo had a response ($p<0.0001$)
- 22 of 23 patients who responded and had been followed for a minimum of 6 months after the initial response maintained the response for ≥6 months

Thank you and Good Luck!

Email with any questions:
magulnik@coh.org