Soft Tissue Sarcomas: Update on New Agents and Ongoing Clinical Trials

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Disclosures

- Receipt of grants/research support:
  - MSD

- Receipt of honoraria and consultation fees:
  - Adaptimmune
  - Blueprint
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  - Eisai
  - Epizyme
  - Daichii
  - Deciphera
  - Immunedesign
  - Lilly
  - Merck
  - Pharmamar
  - Tracon

Plan

- Olaratumab

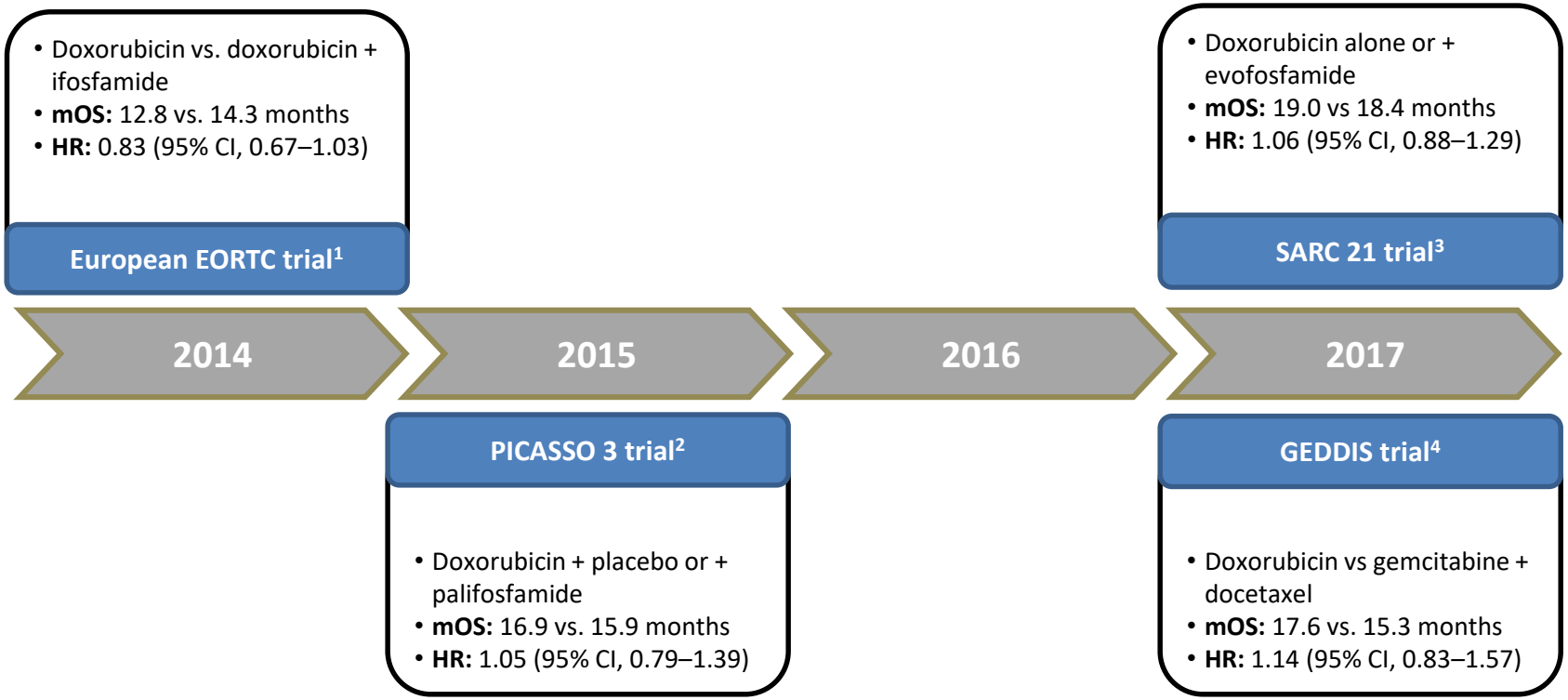
- Tyrosine kinase inhibitors
  - Anlotinib + regorafenib
  - (Alveolar soft part sarcoma, ASPS)
- Immunotherapy
  - ASPS
- NTRK inhibitors

- Subtype specific trials
  - GIST, DFSP, IMT
  - Angiosarcoma
  - Liposarcoma
  - Epithelioid sarcoma
  - Chondrosarcoma, PVNS, Desmoid tumor

- Conclusion

Olaratumab

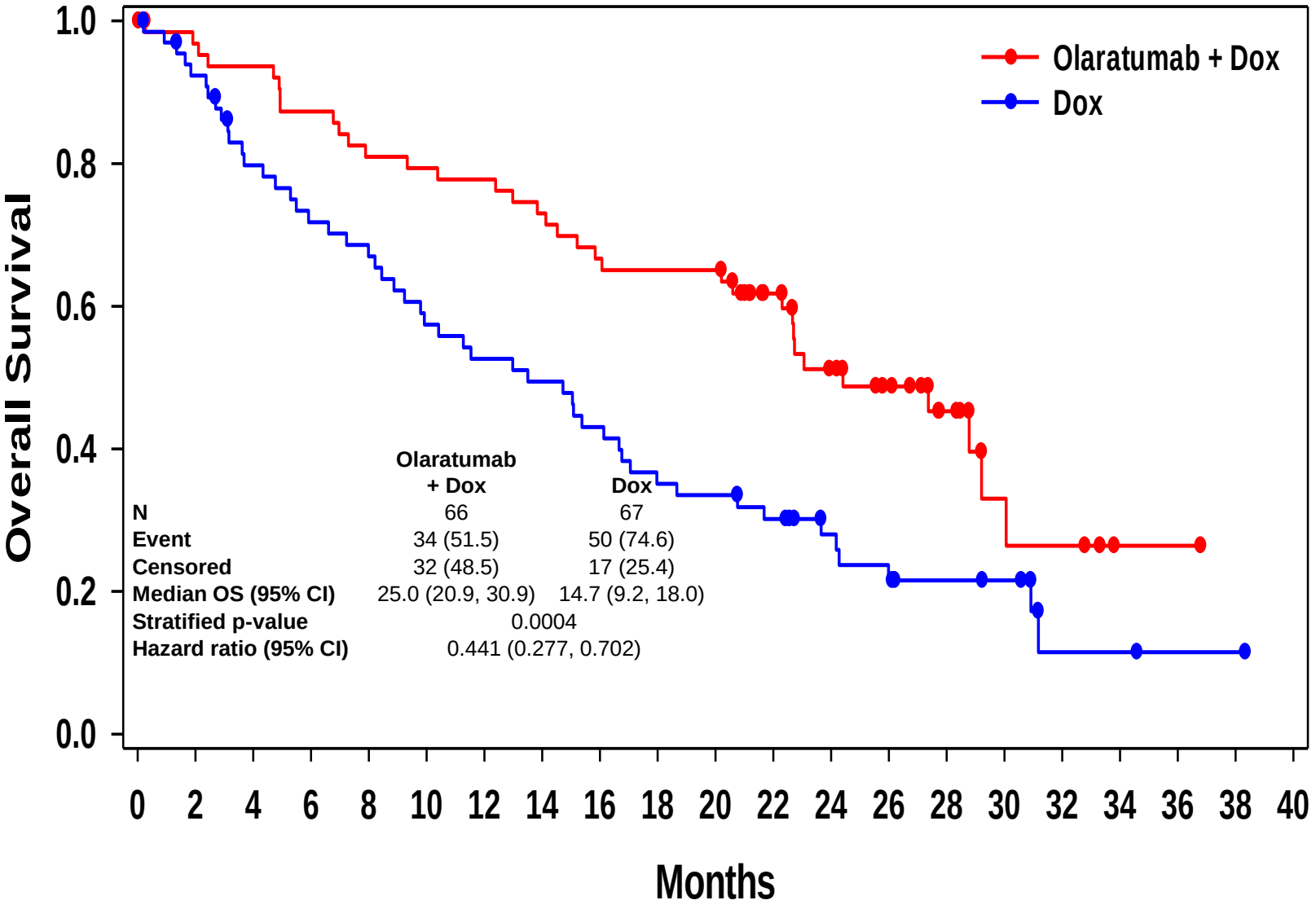
Anthracyclines in advanced Soft Tissue Sarcomas



CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GEDDIS, gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas; HR, hazard ratio; mOS, median overall survival; PICASSO, palifosfamide-tris with doxorubicin for soft tissue sarcoma; SARC, Sarcoma Alliance for Research Through Collaboration; STS, soft tissue sarcoma.

1. Judson I, et al. *Lancet Oncol*. 2014;15;415–23; 2. Ryan CW, et al. *J Clin Oncol*. 2016;34:3898–905; 3. Tap WD, et al. *Lancet Oncol*. 2017;18:1089–103; 4. Seddon B, et al. *Lancet Oncol*. 2017;18:1397–1410.

Phase 2: Olaratumab Overall Survival



Tap W et al. Lancet 388(10043); 488-497: 2016

PRESS RELEASE ARCHIVES

Lilly Reports Results of Phase 3 Soft Tissue Sarcoma Study of LARTRUVO®

- Study did not meet the primary endpoints of overall survival (OS) in the full study population or in the leiomyosarcoma (LMS) sub-population; there was no difference in survival between the study arms for either population.
- There were no new safety signals identified and the safety profile was comparable between treatment arms.

Jan 18, 2019
6:45am

INDIANAPOLIS, Jan. 18, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today reported that the results of ANNOUNCE, the Phase 3 study of LARTRUVO® (olaratumab), in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma (STS), did not confirm the clinical benefit of LARTRUVO in combination with doxorubicin as compared to doxorubicin, a standard of care treatment. Specifically, the study did not meet the primary endpoints of overall survival (OS) in the full study population or in the leiomyosarcoma (LMS) sub-population; there was no difference in survival between the study arms for either population. LARTRUVO was well tolerated; there were no new safety signals identified and the safety profile was comparable between treatment arms. Lilly plans to present the ANNOUNCE data at an upcoming medical conference and will publish the results in a medical journal.

LARTRUVO in combination with doxorubicin previously showed an OS benefit in STS in a 133-patient, U.S.-only, randomized Phase 2 trial, which led to accelerated approval by the U.S. Food and Drug Administration and conditional marketing authorization by the European Medicines Agency. Continued approval is contingent upon verification of clinical benefit in a confirmatory trial. As ANNOUNCE did not confirm clinical benefit, Lilly is working with global regulators to determine the appropriate next steps for LARTRUVO. While these discussions are ongoing, patients who are currently receiving LARTRUVO may, in consultation with their physician, continue their course of therapy if they are receiving clinical benefit. For patients who have not previously received LARTRUVO, the results of the Phase 3 trial do not support initiating treatment with LARTRUVO in patients with STS, outside of participation in a clinical trial. At this time, Lilly is suspending promotion of LARTRUVO.

"Lilly was surprised and disappointed that LARTRUVO did not improve survival for patients with advanced soft tissue sarcoma in this study," said Anne White, president, Lilly Oncology. "Lilly is committed to helping people

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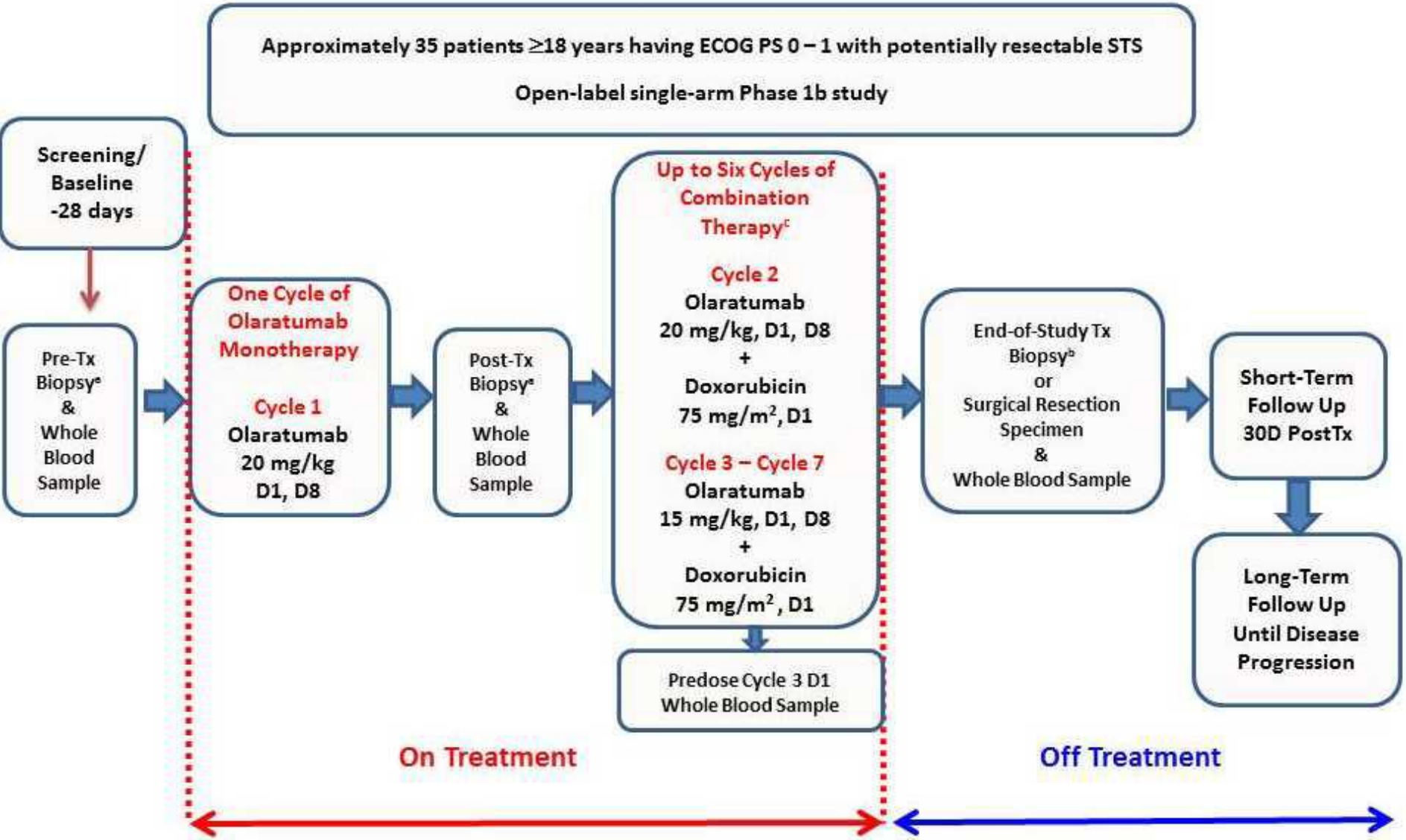
SEARCH NEWS

Olaratumab

- Promising Phase 2 data
- Mechanism of action
  - Incorporation of putative biomarker into trial design
- Heterogeneity
  - Between and within subtype: Leiomyosarcoma
  - Entry criteria: disease bulk
  - “Response rate” and “PFS”

Olaratumab: Biomarker Trial



Metastatic Soft Tissue Sarcomas

- Median overall survival 12 - 20 months
- Limited treatment options
- Increasing range of therapies
  - Gemcitabine and docetaxel
  - Pazopanib
    - Not active in liposarcomas
  - Trabectedin
    - Leiomyosarcomas + liposarcomas
  - Eribulin
    - Liposarcomas
  - Dacarbazine
- Improved survival over time
  - More systemic therapy options
  - Improved palliative care
  - Better confirmation of diagnosis
  - Multi-disciplinary care

Ryan CW et al. JCO 34; 3898–3905: 2016
Tap WD et al. Lancet Oncol 18; 1089–1103: 2017

Different drugs for different diseases

• Localized	
– Osteosarcoma	MAP
– Ewing	VDC/ IE
– Rhabdomyosarcoma	VAC
– GIST	Imatinib
• Metastatic	
– Dermato fibrosarcoma protuberans	Imatinib
– Giant cell tumor of bone	Denosumab
– Alveolar soft part sarcoma	Cediranib/ sunitinib
– Inflammatory myofibroblastic tumor	ALK inhibitors
– PEComas	mTOR inhibitors
– Endometrial stromal sarcoma	Aromatase inhibitors
– Chordoma	Imatinib/ mTOR Inhibitors
– Ewing/ Rhabdomyosarcoma	Cyclo/ topotecan
– Ewing/ Rhabdomyosarcoma	Irinotecan/ temozolamide
– Solitary fibrous tumor	Anti angiogenic agents

Noujaim J et al. Int J Surg Pathol 24(1); 5-15: 2016

Tyrosine Kinase Inhibitors

Abstract 11503

Anlotinib for metastasis soft tissue sarcoma : A randomized, double-blind, placebo controlled and multi-centered clinical trial (ALTER0203)

Yihebali Chi[1], Yang Yao[2], Zhiwei Fang[3],Shusen Wang[4], Gang Huang[5], Qiqing Cai[6], Guanning Shang[7], Guowen Wang[8], Guofan Qu[9], Qiong Wu[10], Yu Jiang[11], Jianmin Song[12], Jing Chen[13], Xia Zhu[14], Zhengdong Cai[15], Chunmei Bai[16], Yongkui Lu[17], Zhihua Yu[18], Jingnan Shen[19], Jianqiang Cai[1] , *

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* Corresponding author

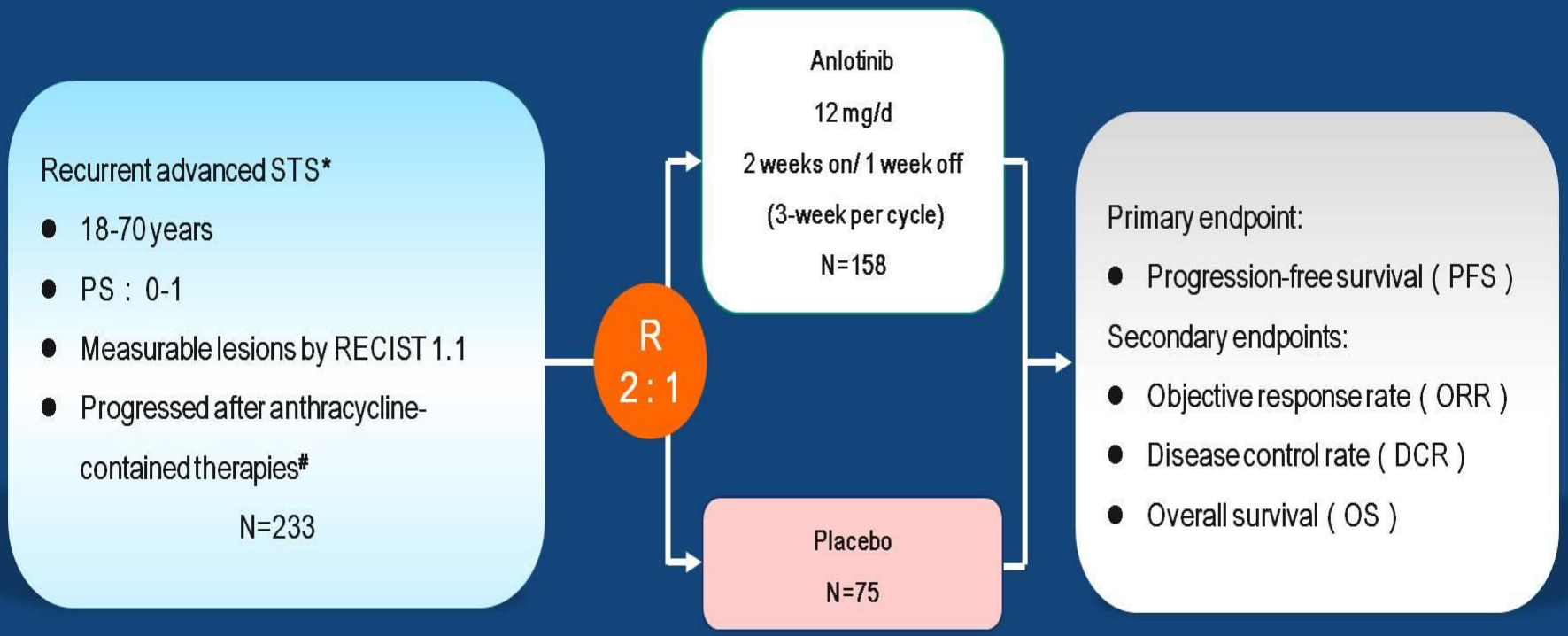
ClinicalTrials.gov Identifier: NCT02449343

Anlotinib in Soft Tissue Sarcomas

- Anlotinib inhibits multiple receptor tyrosine kinases
  - VEGFR
  - FGFR
  - PDGFR
  - C-Kit
- No current FDA approved indication
- No current approved TKI in STS in China

Chi Y et al. ASCO 2018

Study design



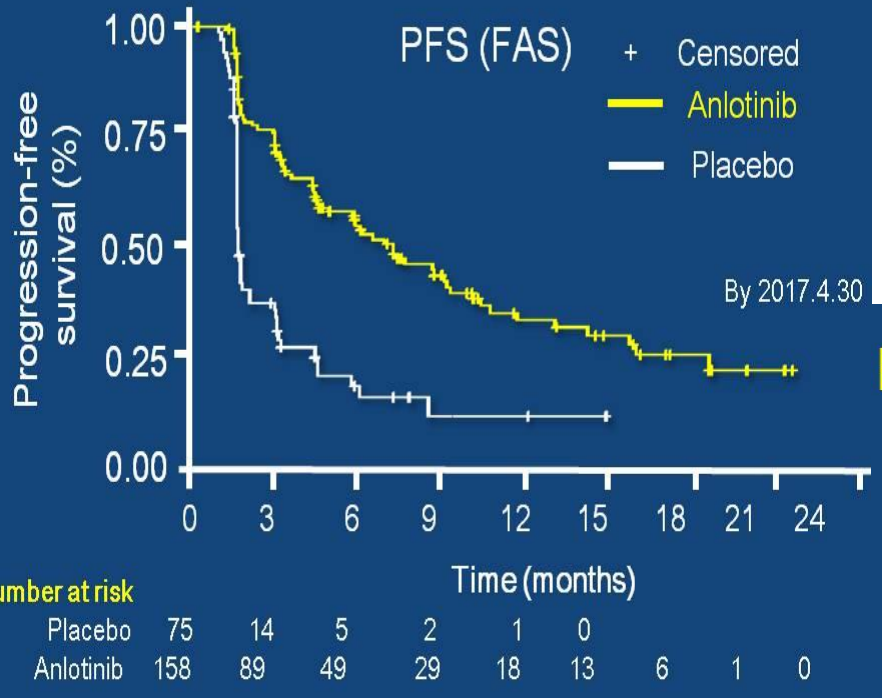
*STS included: Undifferentiated pleomorphic sarcoma (UPS), Liposarcoma(LPS), Leiomyosarcoma (LMS), Synovial sarcoma (SS) , Alveolar soft part sarcoma (ASPS) , Fibrosarcoma (FS), Clear cell sarcoma (CCS), Epithelioid sarcoma (ES) and other sarcomas.

Excluded: Rhabdomyosarcoma (RMS), Chondrosarcoma (CS), Osteosarcoma (OS), Ewing's sarcoma, Primitive neurotodermal tumour (PNET), Dermatofibrosarcoma protuberans (DFSP) and GIST.

#Not required for ASPS and CCS.

Chi Y et al. ASCO 2018

Primary endpoint : PFS

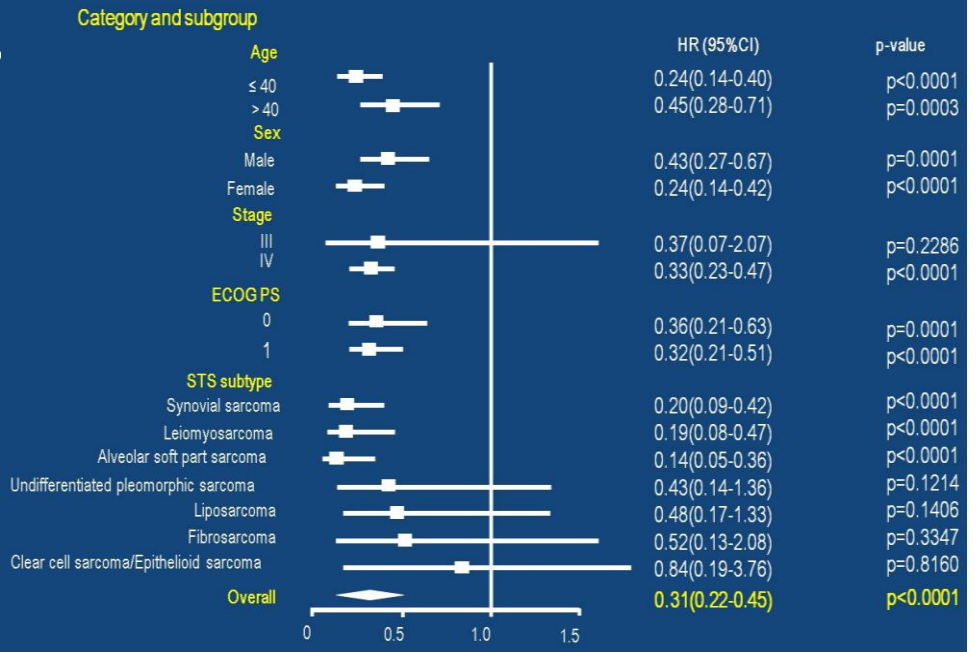


Number at risk

Placebo	75	14	5	2	1	0			
Anlotinib	158	89	49	29	18	13	6	1	0

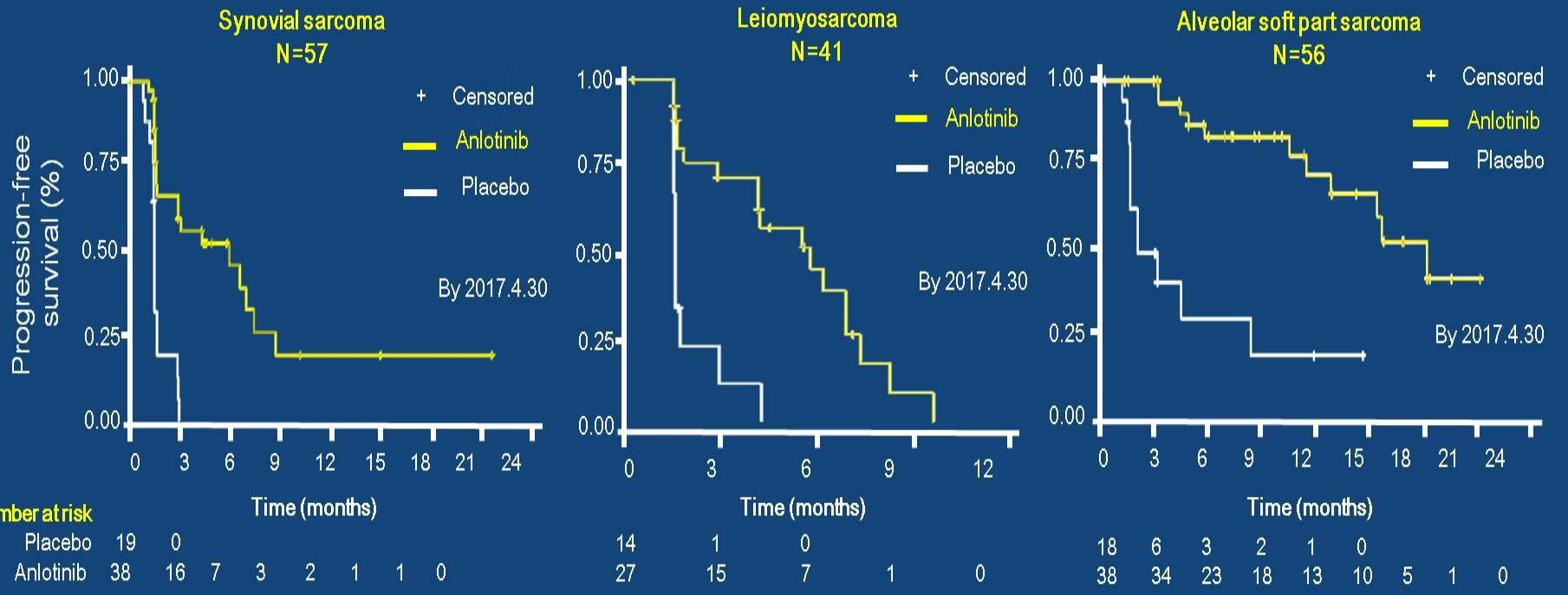
	mPFS (months)	p-value
Anlotinib	6.27 (95%CI : 4.30-8.40)	p< 0.0001, HR = 0.33
Placebo	1.47 (95%CI : 1.43-1.57)	

PFS Forest Plot



Chi Y et al. ASCO 2018

PFS subgroup analysis



	mPFS (months)	p-value
Anlotinib	5.73 (95%CI : 1.77-9.70)	p< 0.0001
Placebo	1.43 (95%CI : 1.39-1.47)	

	mPFS (months)	p-value
Anlotinib	5.83 (95%CI : 2.85-8.81)	p< 0.0001
Placebo	1.43 (95%CI : 1.41-1.45)	

	mPFS (months)	p-value
Anlotinib	18.23 (95%CI : 13.97-22.49)	p< 0.0001
Placebo	3.00 (95%CI : 1.19-4.81)	

Alveolar Soft Part Sarcoma: HR 0.14 (0.05 - 0.36)

Chi Y et al. ASCO 2018

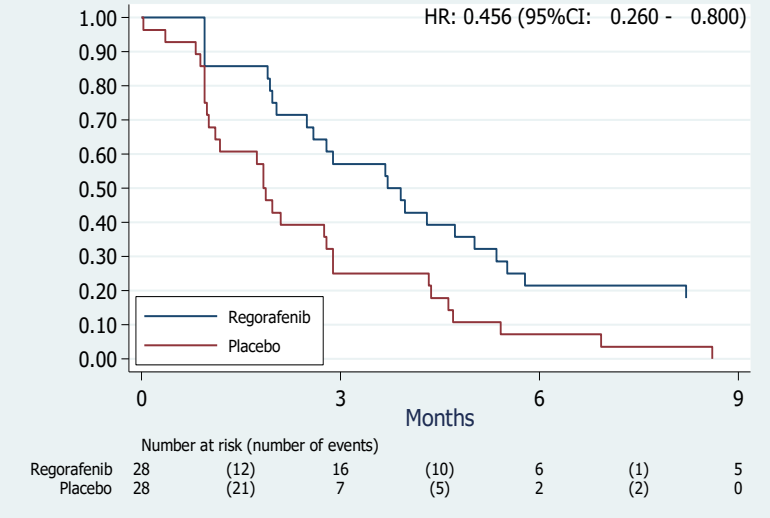
Regorafenib

- REGOSARC
- SARC
  - Cohorts
- Osteosarcoma
  - Regorafenib
  - Cabozantinib

Leiomyosarcoma

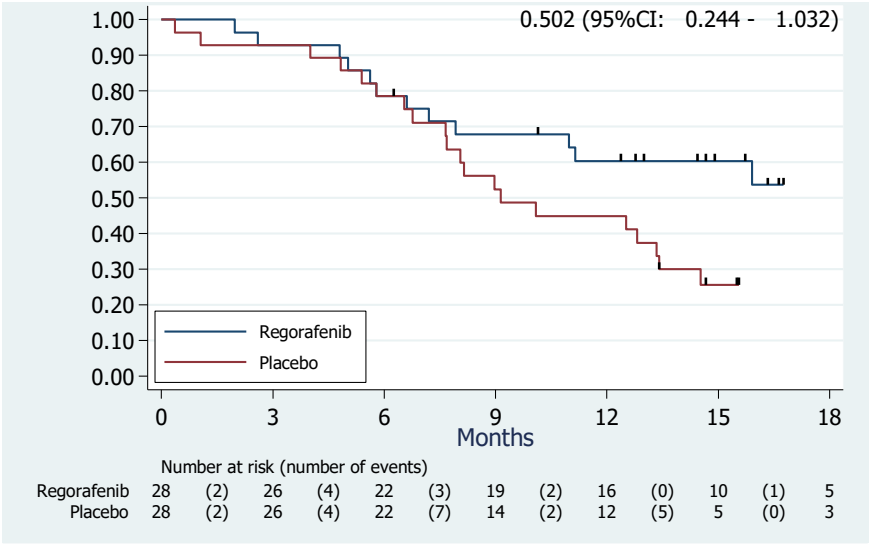
Progression-free survival

Regorafenib **3.7 (2.5-5.0)**
Versus
Placebo **1.8 (1.0-2.8)**
HR = 0.46 [0.26-0.80] **P=0.005**



Overall survival

Regorafenib **21.0 (7.2-NR)**
Versus
Placebo **9.1 (7.7-13.4)**
HR=0.50 [0.24-1.03]
P=0.06



Nicolas PENEL et al. ASCO 2016

Synovial Sarcoma

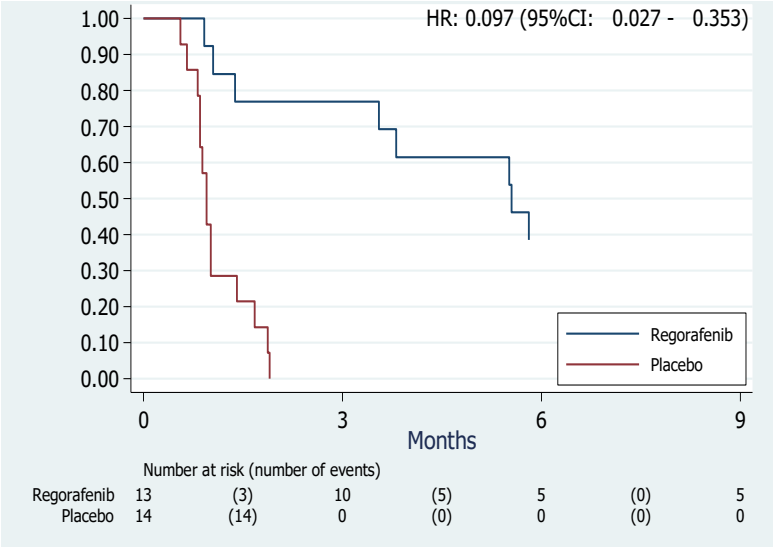
Progression-free survival

Regorafenib **5.6 (1.4-11.6)**

Versus

Placebo **1.0 (0.8-1.4)**

HR= 0.09 [0.02-0.35] **p<0.00001**



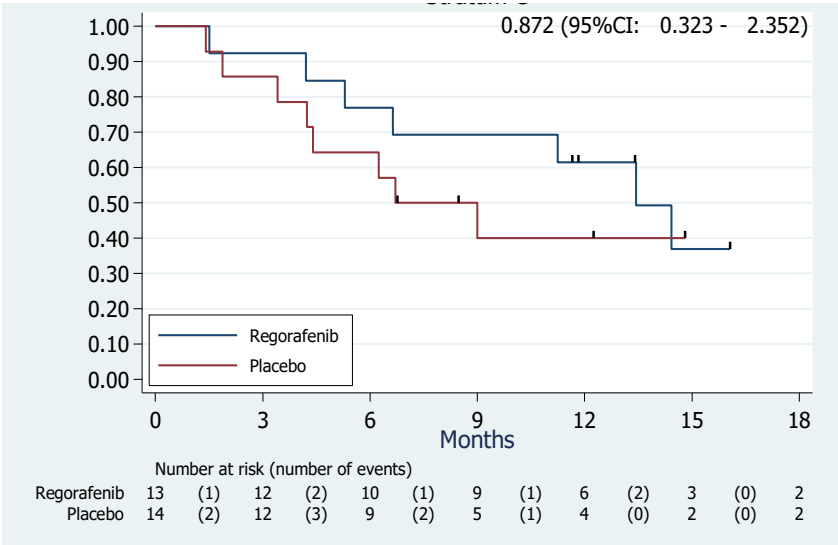
Overall survival

Regorafenib **13.4 (5.3-NR)**

Versus

Placebo **6.7 (2.2-NR)**

HR= 0.87 [0.32-2.35] **P=0.790**



Nicolas PENEL et al. ASCO 2016

Liposarcoma

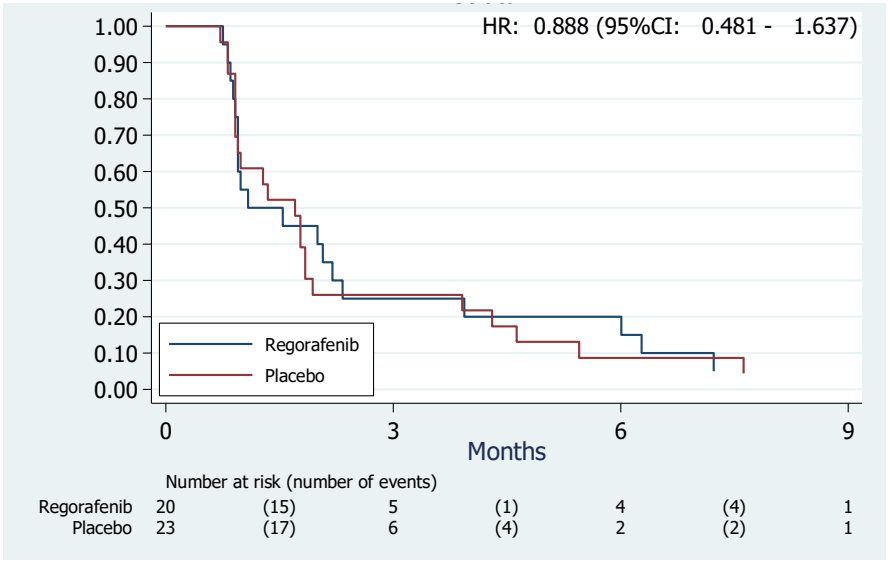
Progression-free survival

Regorafenib **1.1 (0.9-2.3)**

Versus

Placebo **1.7 (0.9-1.8)**

HR = 1.13 [0.48-1.63] **P=0.700**



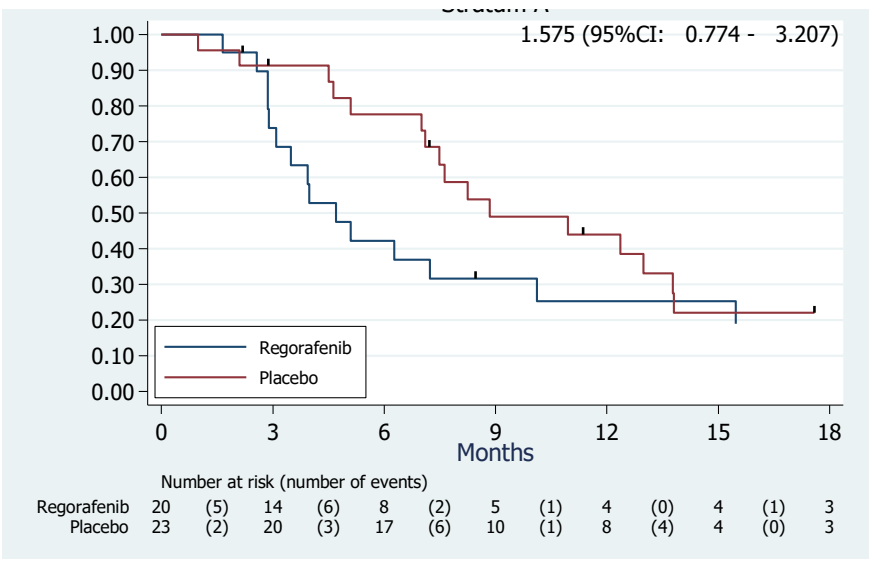
Overall survival

Regorafenib **4.7 (2.9-10.1)**

Versus

Placebo **8.8 (7.0-13.8)**

HR = 1.57 [0.77-3.20] **P=0.210**

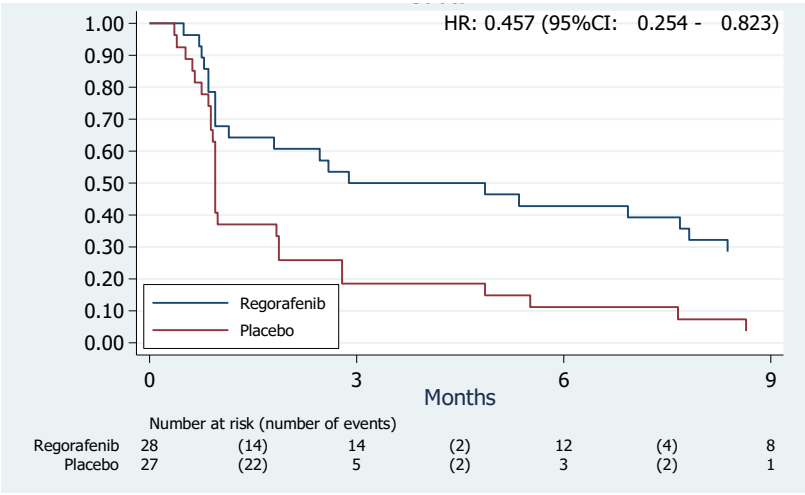


Nicolas PENEL et al. ASCO 2016

Other Sarcomas

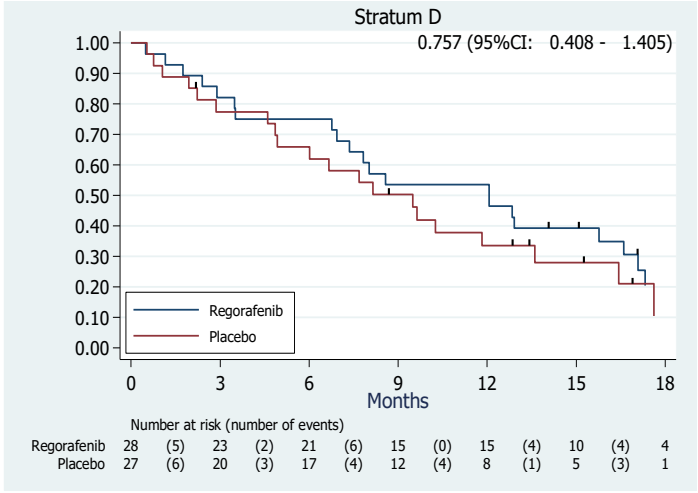
Progression-free survival

Regorafenib **2.9 (1.0-7.8)**
Versus
Placebo **1.0 (0.9-1.9)**
HR = 0.45 [0.26-0.80] **P=0.006**



Overall survival

Regorafenib **12.1 (6.9-16.6)**
Versus
Placebo **9.5 (4.7-16.6)**
HR = 0.50 [0.24-1.03] **P=0.380**



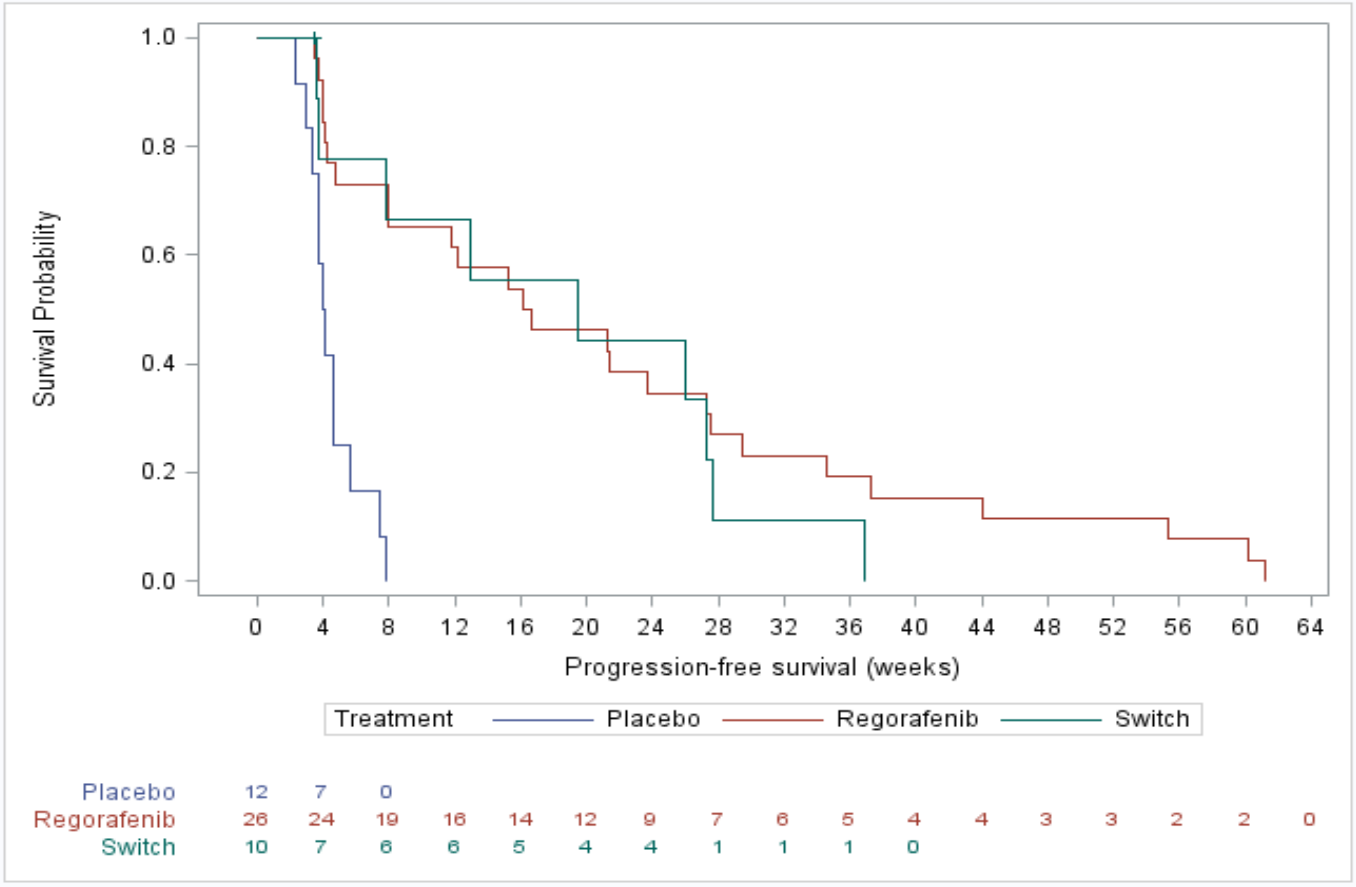
Nicolas PENEL et al. ASCO 2016

Regorafenib in Osteosarcoma

- Main inclusion criteria:
- Progressive disease at study entry within prior 3 months
- Prior treatment required: at least 1, but no more than 2 prior (combination) chemo regimen for metastatic disease
- Age ≥ 10 years
- ECOG PS < 2 (Karnofsky ≥ 60%)

Duffaud F et al. 2018

Regorafenib in Osteosarcoma



10/12 patients on Placebo arm crossed over

	Placebo	Rego	Rego post switch
Median PFS	4.1 (3;5.7)	16.4 (8;27.3)	19.4 (3.5;27.7)
PFS rate at 12 weeks	/	62 (40-77)	66 (28-88)
PFS rate at 24 weeks	/	35 (17-52)	44 (14-72)

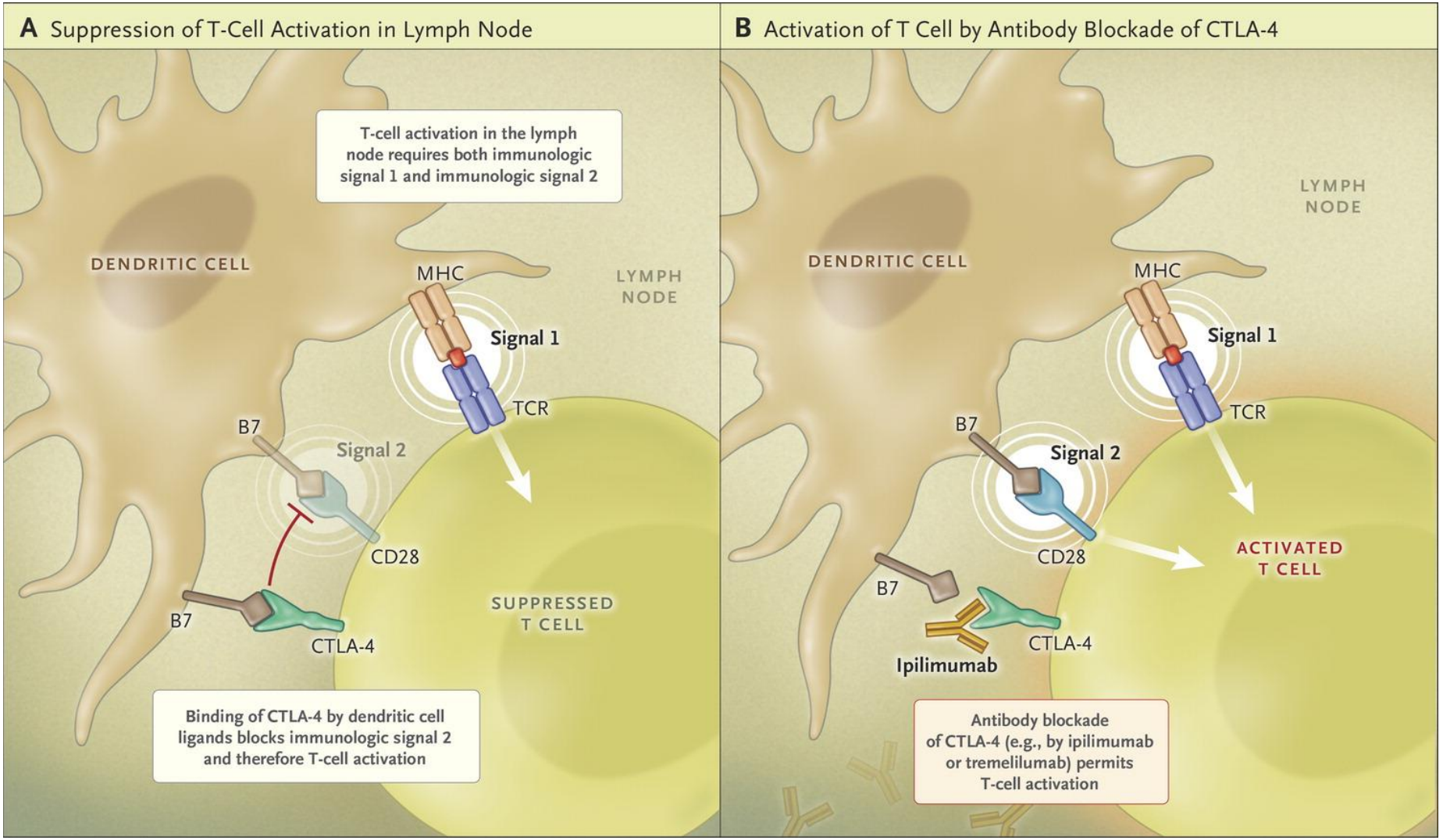
Duffaud F et al. 2018

Checkpoint Inhibitors

T cell activation lymph node

- 2 immunological signals
  - **1st:** Interaction T cell receptor with
    - Peptide Ag presented by the APC (Ag binding groove of MHC)
  - **2nd:** Interaction T cell surface molecules (CD28) with ligands on APC (B7)
- Binding B7 to CTLA-4 block T cell activation
- Ab blockade CTLA-4:
  - De-repress signaling by CD28

T-cell activation in the lymph node

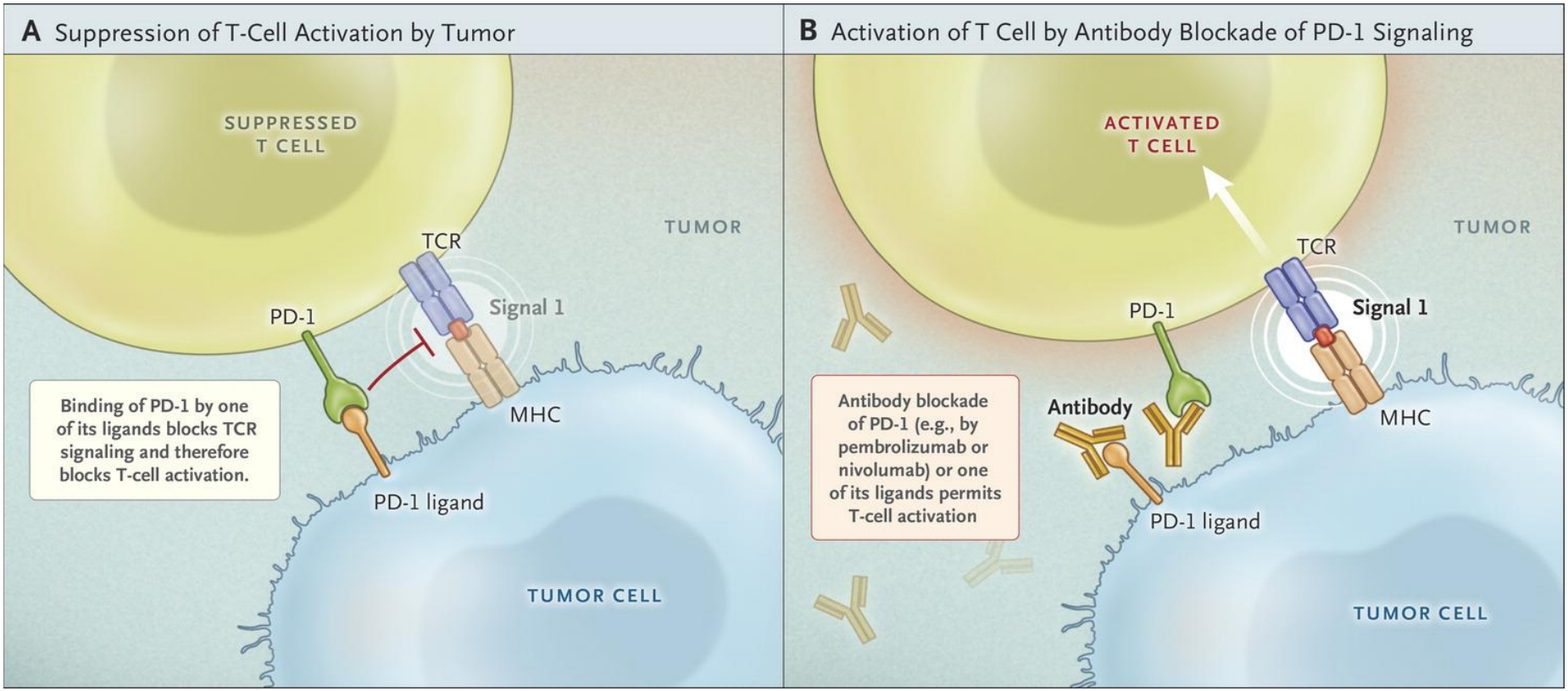


Ribas A. N Engl J Med 373; 1490-1492: 2015

T cell activation tumour microenvironment

- Long-term Ag exposure
  - Programmed death 1 (PD1) inhibitor receptor expressed by T cells
  - Suppress effect of T cell receptor on T cell activation
- Blockade PD-1 or ligand de-repress TCR signaling = T cell activation

T-cell activation in tumour



Ribas A. N Engl J Med 373; 1490-1492: 2015

PD-L1 and PD-1 Expression

- PD-L1 expression:
  - Liposarcoma: n=13 (48%)
  - Leimoyosarcoma: n=11 (58%)
  - Pleomorphic sarcoma: n=16 (80%)
  - Synovial sarcoma: n=7 (47%)

- PD-1 expression
  - Liposarcomas: n=24 (89%)
  - Leiomyosarcomas: n=16 (84%)
  - Pleomorphic sarcomas: n=18 (90%)
  - Synovial sarcomas: n=15 (100%)

- Undifferentiated pleomorphic sarcomas:
- Older patients
- Higher grade tumors
  - Associated with higher expression levels
    - PD-L1
    - PD-1 expressing infiltrates

Pollack S et al. Cancer 123; 3291-3304: 2017

SARC 28 Trial: Pembrolizumab

- Soft tissue sarcomas:
  - Median PFS: 18 weeks (95%CI: 8-21)
  - Median OS: 49 weeks (95%CI: 34-73)

  - 12 week PFS: 55% (95%CI: 40-70)

- Undifferentiated pleomorphic sarcoma:
  - Median PFS: 30 weeks (95%CI: 8-68)

- Bone Sarcomas:
  - Median PFS: 8 weeks (95%CI: 7-9)
  - Median OS: 52 weeks (95%CI: 40-72)

Tawbi HA et al. Lancet Oncol 18; 1493-1501: 2017

Phase 2: Axitinib + Pembrolizumab

- Primary endpoint
  - Progression-free rate at 12 weeks: 48% (14/29)

- Best response

  PR 5/29 (17%)

  SD 9/29 (31%)

  <u>For ASPS</u>

  PR 4/9 (44%)

  SD 3/9 (33%)

CBR 78%

Wilky B et al. CTOS 2017

Phase 2: Axitinib + Pembrolizumab

- ASPS
- Early responses
- Continued to respond out to 40 weeks or beyond

- Median duration of response 29.3 weeks

- Prolonged responses seen in ASPS + non-uterine LMS

- Median PFS not reached for ASPS

- Median OS not reached

- For pre-treated + naïve progressing ASPS
- 12 week PFS: 78%
- ORR: 44%
- (exceeds previously reported data cediranib + axitinib single agent)

Wilky B et al. CTOS 2017

Immunotherapy in Sarcomas

- Limited success so far….
  - Heterogeneity
  - Further evaluation in ASPS, pleomorphic, angiosarcoma
- Other cancers
  - Not all PD1 expressing tumors respond
    - Limitations of immunohistochemistry/ scoring criteria
  - High mutational burden ≠ response/ benefit
- Adoptive T cell therapy
  - Responses not durable
  - Infrastructure + Cost
- Combination trials: other agents, radiation

NTRK inhibitors

NTRK tumors

- Tropomyosin receptor kinase (Trk)
  - 3 trans-membrane proteins (Trk A, B + C receptors)
  - Encoded by the *NTRK1*, *2* + *3* genes
  - Expressed human neuronal tissue
  - Essential role nervous system activation neurotrophins

- Oncogenic *Trk* gene fusions
  - Induce cell proliferation
  - Engage downstream signaling pathways

- Mutations rare – occur in diverse range of tumors

Doebele RC et al. Cancer Discov 5(10); 1049-1057: 2015

Trk Receptor Signaling

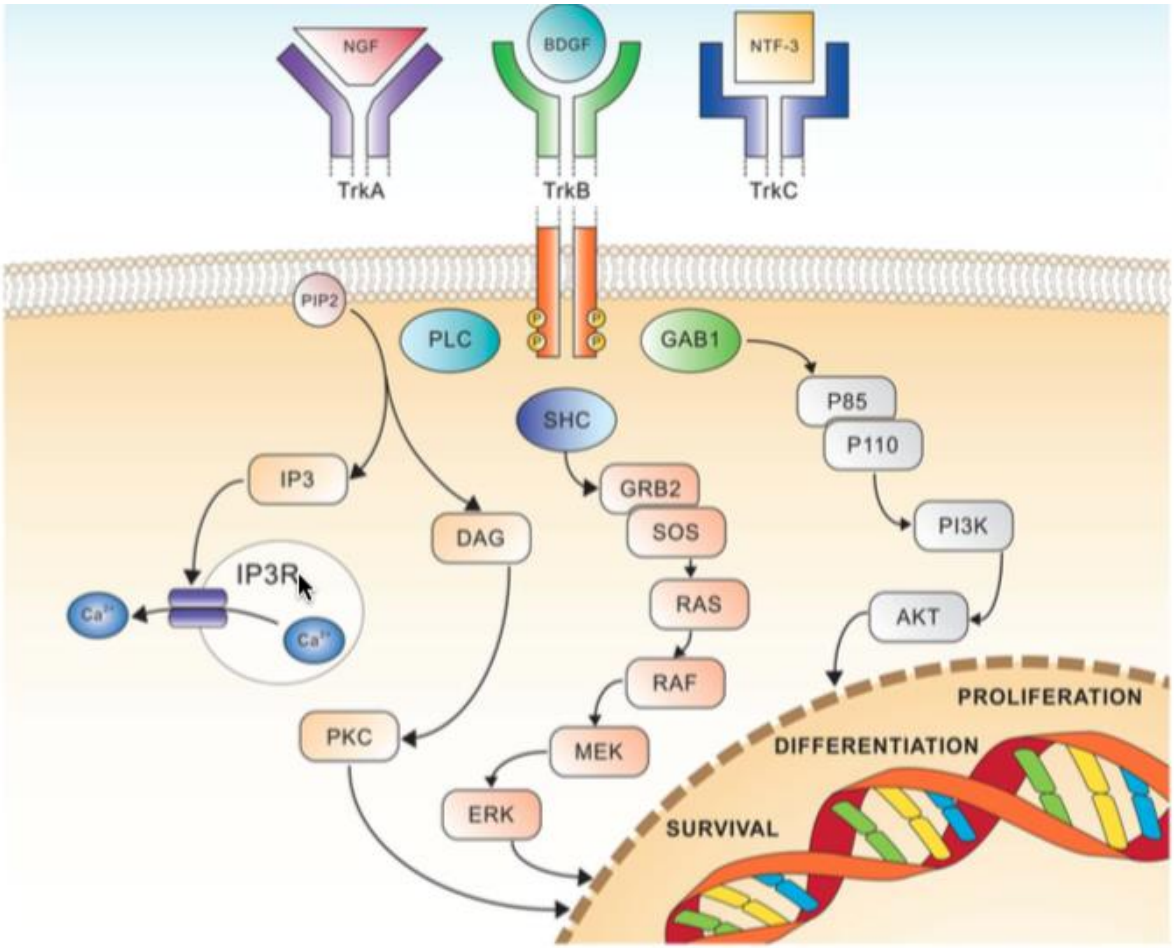
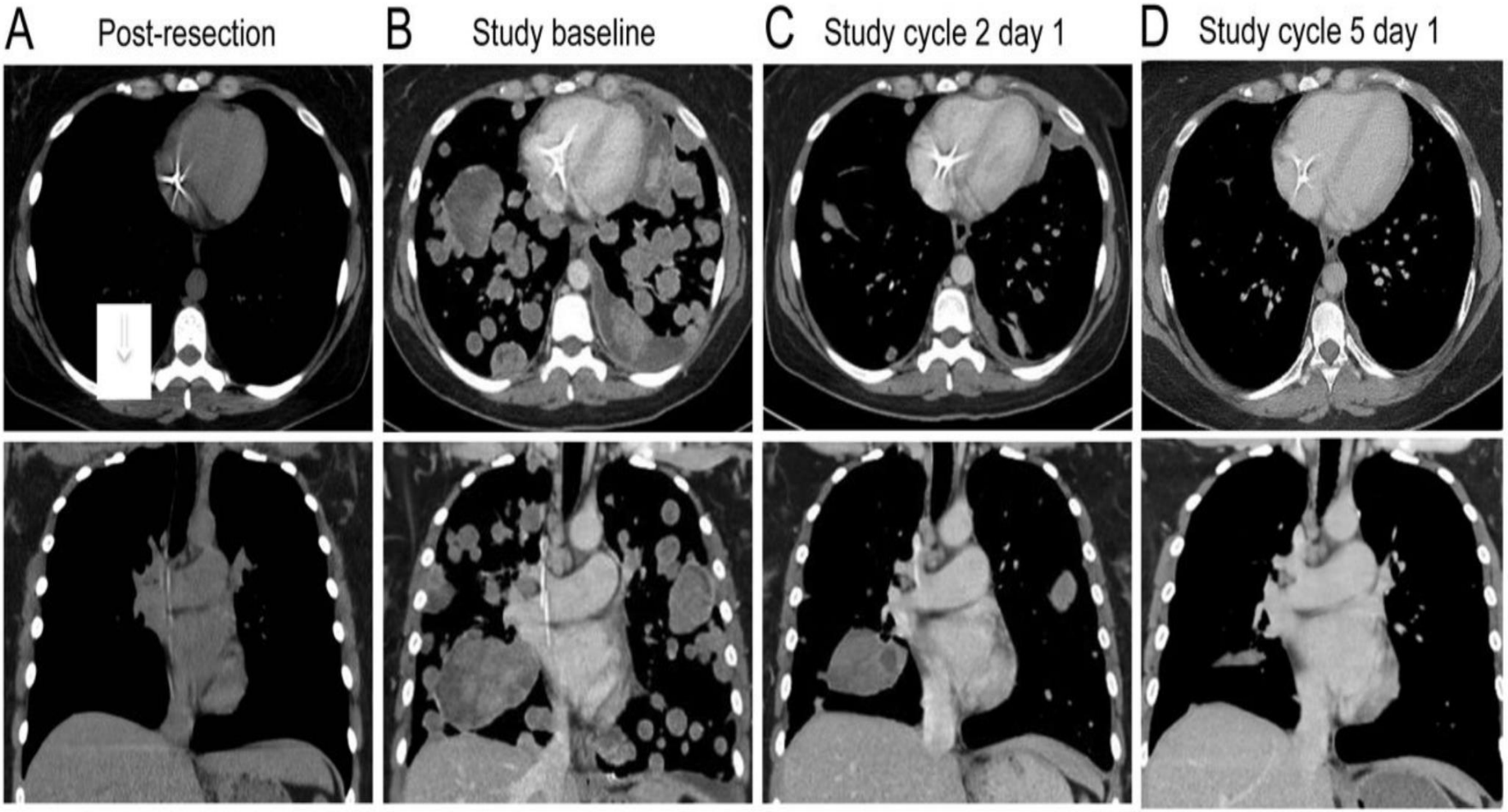


Figure 1 Schematic view of Trk receptors signalling, showing the three major pathways involved in cell differentiation and survival. AKT, v-akt murine thymoma viral oncogene homologue; BDGF, brain-derived growth factor; DAG, diacyl-glycerol; ERK extracellular signal-regulated kinase; GAB1, GRB2-associated-binding protein 1; GRB2, growth factor receptor-bound protein 2; IP3, inositol trisphosphate; MEK, mitogen-activated protein kinase; NGF, nerve growth factor; NTF-3, neurotrophin 3; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma kinase; SHC, Src homology 2 domain containing.

Response in sarcoma with *LMNA-NTRK1* fusion



Doebele RC et al. Cancer Discov 5(10); 1049-1057: 2015

Subtype Specific Data

GIST

- Blu-285
  - Phase I data
    - *PDGFRa* D842V mutation
  - Phase III
    - 3rd line
      - Blu-285 versus regorafenib
- Crenolanib
- DCC-2618
  - Phase I data
  - Phase III
    - 4th line
      - DCC-2618 versus placebo
    - 2nd line
      - DCC-2618 versus sunitinib

Dermatofibrosarcoma protuberans (DFSP)

Dermatofibrosarcoma protuberans (DFSP)

- <5% probability of metastases
- Specific rearrangement
  - chromosome 17 and 22
  - t(17;22)(q22;q13)
- Collagen type I A1 chain (*COL1A1*) gene
- To *PDGFB* gene
- Up-regulation of *COL1A1- PDGFB* fusion

- Imatinib, Phase II trials
  - PR: 11 (45.9%)
  - SD: 6 (25.0%)
  - PD: 4 (16.6%)
- 3 (12.5%) not evaluable
- Median time to progression:
  - 1.7 years
  - Range, 0.65 year – not reached

McArthur et al JCO 23; 866-873: 2005
Rutkowski P et al, JCO 28; 1772-1779: 2010

Adverse events from imatinib in DFSP

Table 4. Adverse Events From Imatinib Reported in Patients With DFSP

Adverse Event	EORTC (n = 16)						SWOG (n = 8)						Total (N = 24)					
	Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia	4	25.0	2	12.5	1	6.3	2	25.0	0	0	0	0	6	25.0	2	8.3	1	4.2
Neutropenia	2	12.5	1	6.3	2	12.5	0	0	0	0	2	25.0	2	8.3	1	4.2	4	16.7
Thrombocytopenia	1	6.3	0	0	1*	6.3	0	0	0	0	0	0	1	4.2	0	0	1*	4.2
Anemia	11	68.8	4	25.0	0	0	1	12.	0	0	1	12.5	12	50.0	4	16.7	1	4.2
Bilirubin	4	25.0	1	6.3	1	6.3	0	0	0	0	0	0	4	16.7	1	4.2	1	4.2
AST increase	4	25.0	1	6.3	1*	6.3	2	25.0	0	0	0	0	6	25.0	1	4.2	1*	4.2
Arterial hypertension	1	6.3	1	6.3	0	0	0	0	0	0	0	0	1	4.2	1	4.2	0	0
Fatigue	3	18.8	2	12.5	2	12.5	5	62.5	0	0	2	25.0	8	33.3	2	8.3	4	16.7
Rash	4	25.0	1	6.3	1	6.3	3	37.5	0	0	0	0	7	29.2	1	4.2	1	4.2
Anorexia	2	12.5	0	0	0	0	2	25.0	0	0	0	0	4	16.7	0	0	0	0
Diarrhea	3	18.8	3	18.8	0	0	1	12.5	0	0	1	12.5	4	16.7	3	12.5	1	4.2
Nausea	3	18.8	2	12.5	1	6.3	4	50.0	0	0	0	0	7	29.2	2	8.3	1	4.2
Vomiting	1	6.3	0	0	2	12.5	1	12.5	0	0	0	0	2	8.3	0	0	2	8.3
Head and neck edema	6	37.5	0	0	0	0	5	62.5	0	0	0	0	11	45.8	0	0	0	0
Limbs/trunk/visceral edema	6	37.54	1	6.3	1	6.3	5	62.5	0	0	0	0	11	45.8	1	4.2	1	4.2
Pain	3	18.8	0	0	0	0	0	0	0	0	1	12.5	3	12.5	0	0	1	4.2

Abbreviations: DFSP, dermatofibrosarcoma protuberans; EORTC, European Organisation for Research and Treatment of Cancer; SWOG, Southwest Oncology Group.

*Grade 4; two toxic grade 4 events were noted in one patient with pre-existing liver disturbances and alcohol abuse history—thrombocytopenia and AST level increase.

Rutkowski P et al, JCO 28; 1772-1779: 2010

Inflammatory Myofibroblastic Tumor (IMT)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

SUMMARY

Inflammatory myofibroblastic tumor (IMT) is a distinctive mesenchymal neoplasm characterized by a spindle-cell proliferation with an inflammatory infiltrate. Approximately half of IMTs carry rearrangements of the anaplastic lymphoma kinase (*ALK*) locus on chromosome 2p23, causing aberrant ALK expression. We report a sustained partial response to the ALK inhibitor crizotinib (PF-02341066, Pfizer) in a patient with *ALK*-translocated IMT, as compared with no observed activity in another patient without the *ALK* translocation. These results support the dependence of *ALK*-rearranged tumors on ALK-mediated signaling and suggest a therapeutic strategy for genomically identified patients with the aggressive form of this soft-tissue tumor. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.)

From the Dana–Farber Cancer Institute (J.E.B., M.C., N.R., P.A.J., G.D.D., G.I.S.); the Ludwig Center at Dana–Farber/Harvard Cancer Center (J.E.B., G.D.D.); Harvard Medical School (J.E.B., J.L.H., M.C., S.J.R., E.L.K., J.W.C., P.A.J., G.D.D., G.I.S.); Brigham and Women's Hospital (J.L.H., P.D.C., S.J.R.); and Massachusetts General Hospital (E.L.K., J.W.C.) — all in Boston; Memorial Sloan-Kettering Cancer Center, New York (D.R.D., C.R.A., S.C.J., M.L., R.G.M.); and Pfizer Global Research and Development, La Jolla, CA (K.D.W., J.G.C.). Address reprint requests

EORTC Phase II Crizotinib trial

- N=20 Inflammatory myofibroblastic tumor: advanced disease
- Response rate:
  - 6/ 12 ALK-positive (50%, 95%CI: 21·1-78·9)
  - 1/ 7 ALK-negative (14%, 95%CI: 0·0-57·9)

- Most common treatment-related adverse events
  - Nausea 11 [55%]
  - Fatigue 9 [45%]
  - Blurred vision 9 [45%]
  - Vomiting 7 [35%]
  - Diarrhoea 7 [35%]

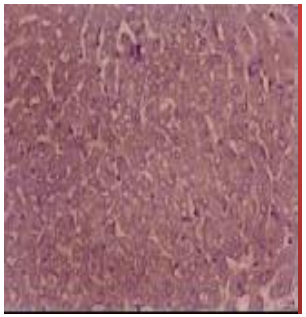
- 8 serious adverse events in 5 patients
  - Pneumonia
  - Fever of unknown cause
  - Heart attack with increased creatinine and possible sepsis
  - Abdominal abscess with acute renal insufficiency
  - QT prolongation

Schöffski P et al. Lancet Respir Med 6(6); 431-441: 2018

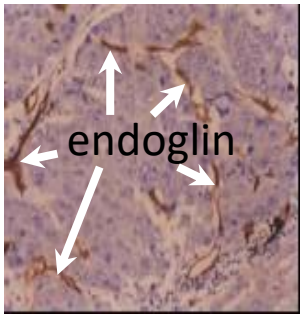
Angiosarcomas

Endoglin: Essential Endothelial Cell Target

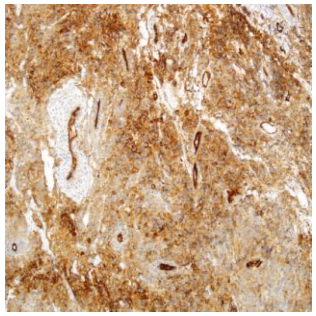
- Endoglin: expressed on endothelial cells and is essential for angiogenesis
  - Selectively expressed on proliferating vessels in cancer and AMD
  - Up-regulated following VEGF inhibition
  - Unfavorable prognostic marker
- Attenuated endoglin expression causes Osler-Weber-Rendu syndrome
  - Associated with improved cancer survival (31% reduced risk of death)
- Persistent expression on tumor vessels results in progression despite VEGF inhibition
  - Knockdown of endoglin resensitizes tumors to VEGF inhibition
- Targeting VEGF + endoglin concurrently improves antitumor effects
- Endoglin also expressed directly on angiosarcoma tumor cells in addition to tumor vasculature



Normal Human Liver



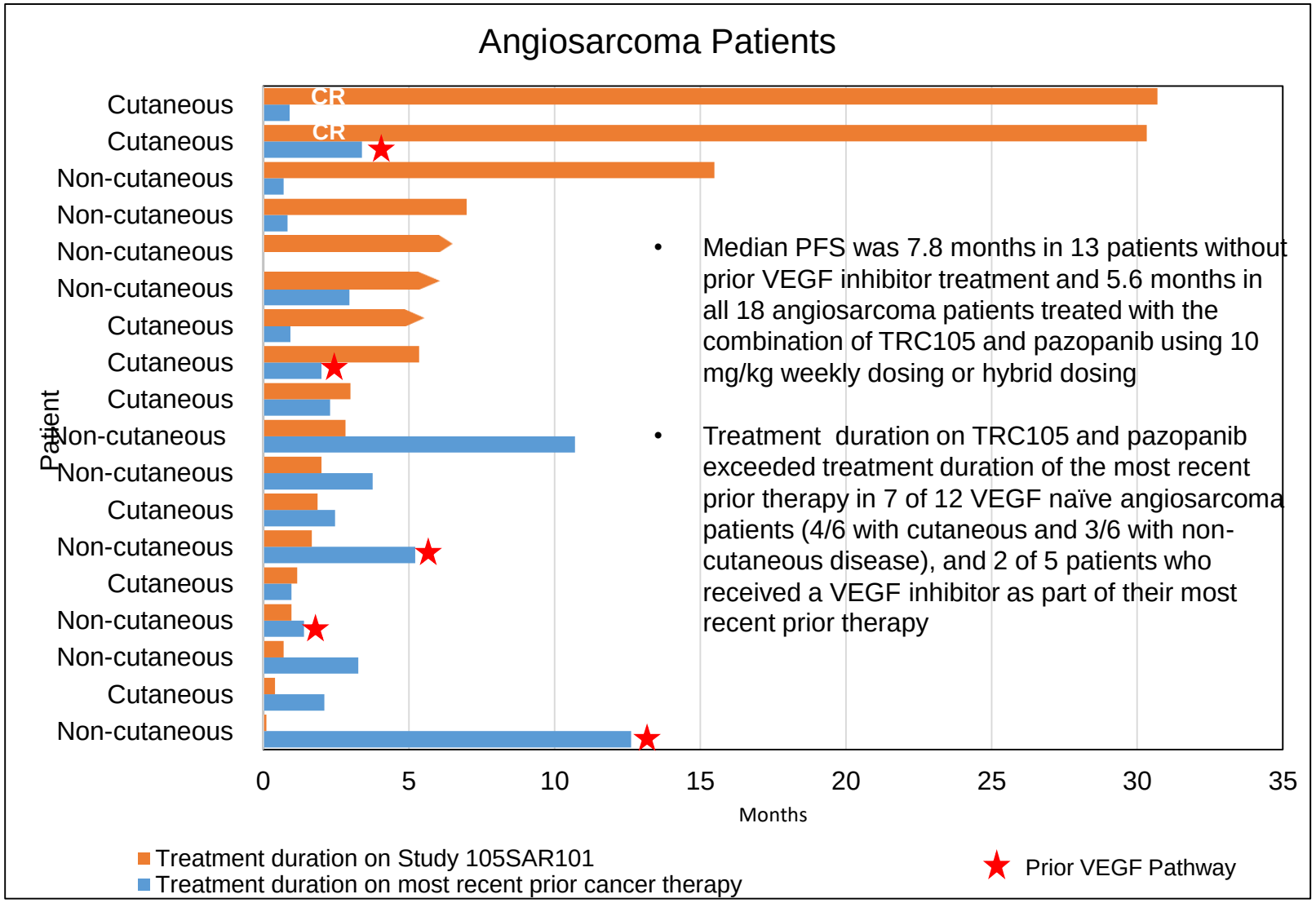
Human Liver Cancer



Angiosarcoma

Jones RL et al. ASCO 2017

TRC 105: Efficacy in Patients with Angiosarcomas



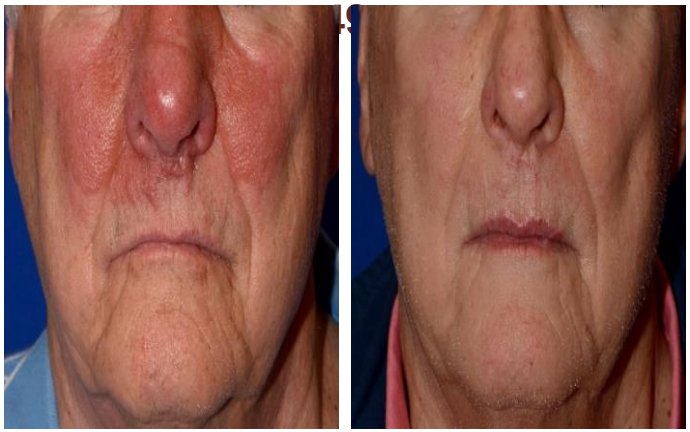
*Treatment duration is calculated from date of first dose to date of last dose

Jones RL et al. ASCO 2017

TRC105 with Pazopanib Produced Durable Complete Responses in STS Patients

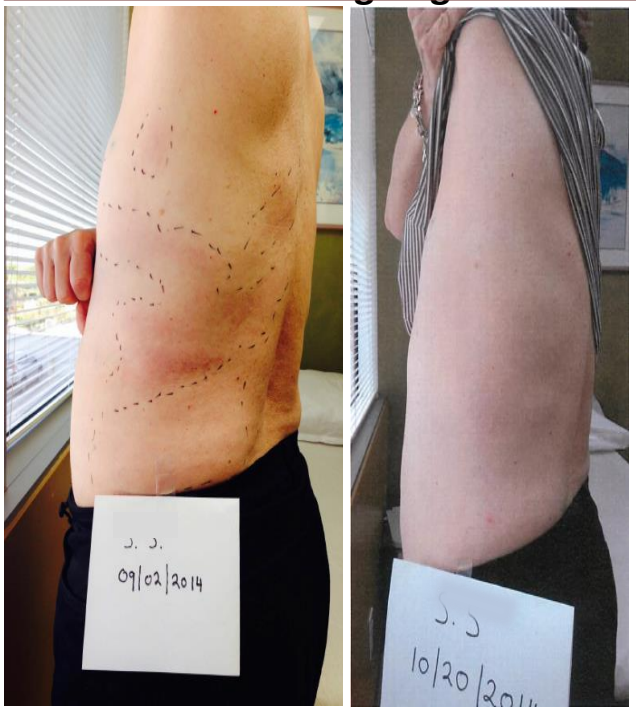
- Two complete responses (CRs) in angiosarcoma patients ongoing at Week 49 and Week 80

CR from Patient Ongoing Week



Day 0 Day 37

CR from Patient Ongoing Week 80

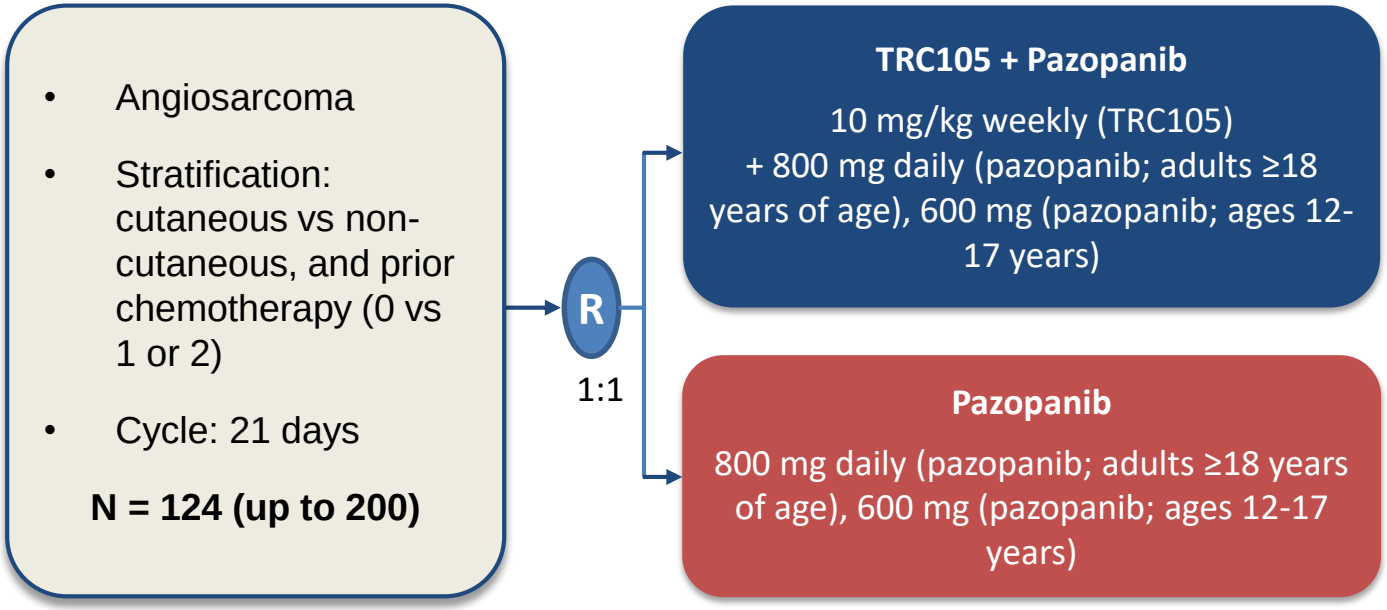


Day 0 Day 48

- Durable CR observed in an undifferentiated pleomorphic sarcoma patient ongoing at Week 56

Jones RL et al. ASCO 2017

TAPPAS: TRC105 + Pazopanib vs Pazopanib in Angiosarcomas



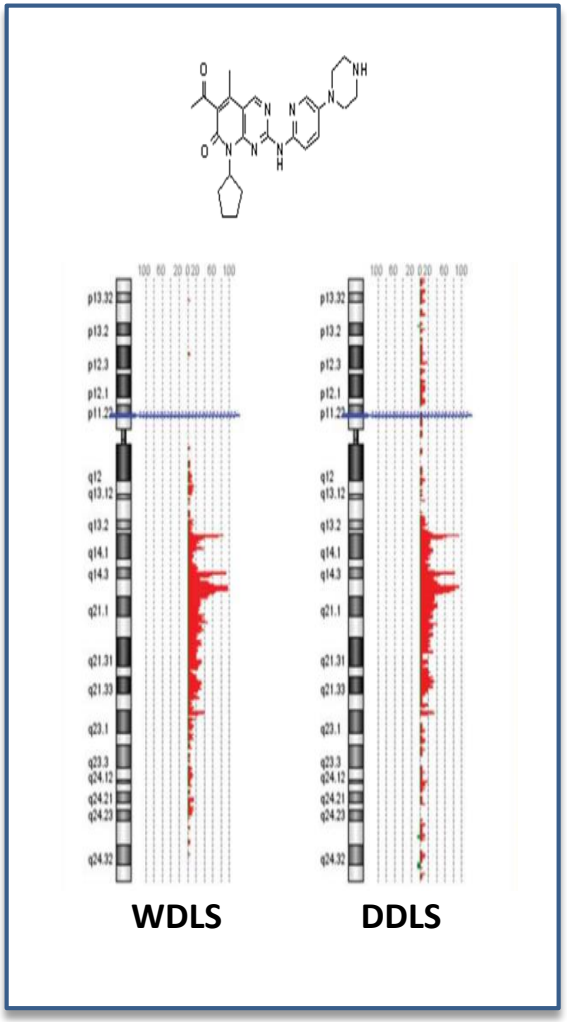
TRC105 is an anti-endoglin antibody

Jones RL et al. ASCO 2017

Liposarcomas

Phase 2 Trial of Palbociclib

- Single arm, phase 2, N = 29
  - 200 mg palbociclib per day for 14 days; 7 days off
- Eligibility:
  - WDLS/DDLS, *CDK4* amplification, and RB expression
  - ≥1 prior systemic therapy
- Median PFS: 18 weeks
- 1 partial response
- Grade 3/ 4 AEs:
  - Anemia (17%), Thrombocytopenia (30%)
  - Neutropenia (50%), febrile neutropenia (3%)



Dickson MA et al. *J Clin Oncol* 31; 2024-2028: 2013

Phase II Trial Palbociclib: Adverse Events

Table 2. Incidence of Grade 2 to 4 Adverse Events Possibly, Probably, or Definitely Related to Treatment

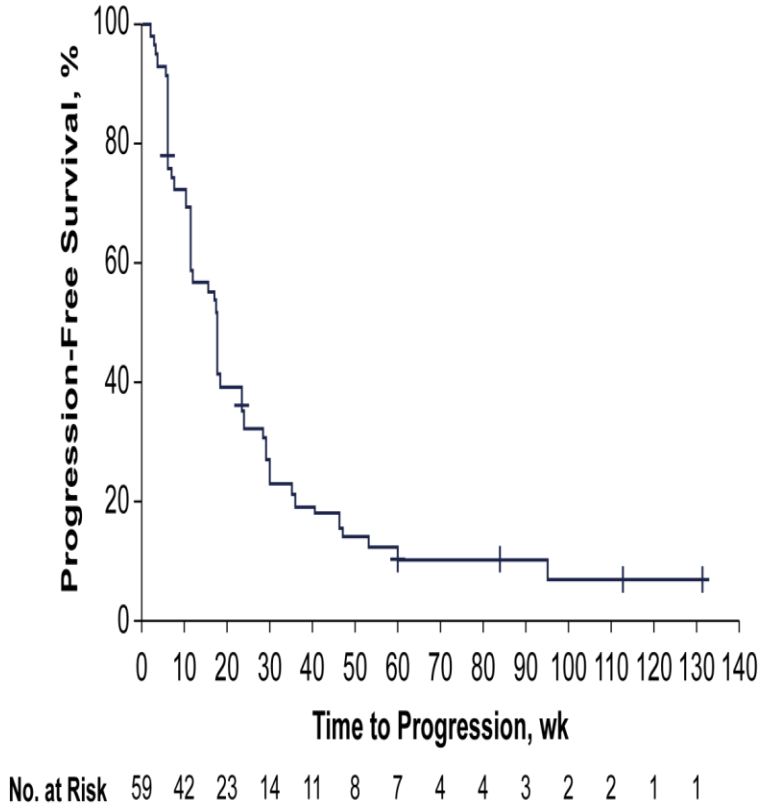
Toxicity	Grade 2	Grade 3	Grade 4	Total
Hematologic				
Anemia	6	5		11
WBC decreased	13	13	1	27
Platelet count decreased	2	5	4	11
Lymphocyte count decreased	4	6	2	12
Neutrophil count decreased	13	13	2	28
Febrile neutropenia		1		1
Nonhematologic				
Anorexia	1			1
Constipation		1		1
Diarrhea	1			1
Dry skin	1			1
Epistaxis	1			1
Fatigue	1	2		3
Hematuria		1		1
Upper respiratory infection		1		1

Dickson MA et al. *J Clin Oncol* 31; 2024-2028: 2013

Palbociclib: Progression-Free Survival

- Phase 2, N = 60
  - Advanced WDLS/DDLS
- Palbociclib 125 mg/day in a 4-week cycle
  - 3 weeks on, 1 week off
- Primary endpoint: PFS
  - Median PFS: 17.9 weeks
  - 2 sided 95%CI; 11.9-24 weeks
- 1 complete response

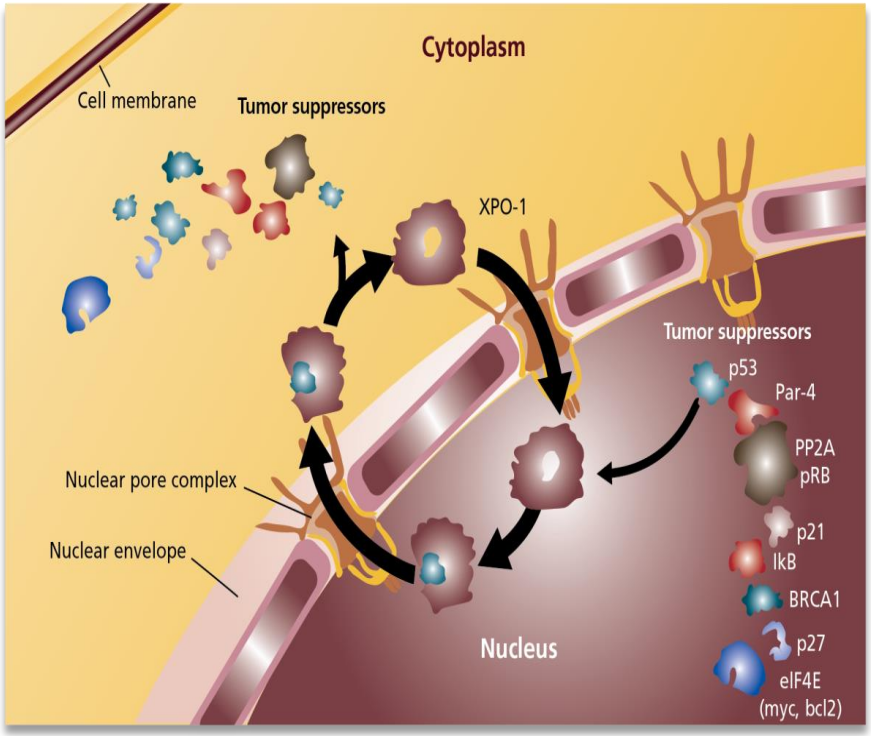
Median PFS: 17.9 weeks



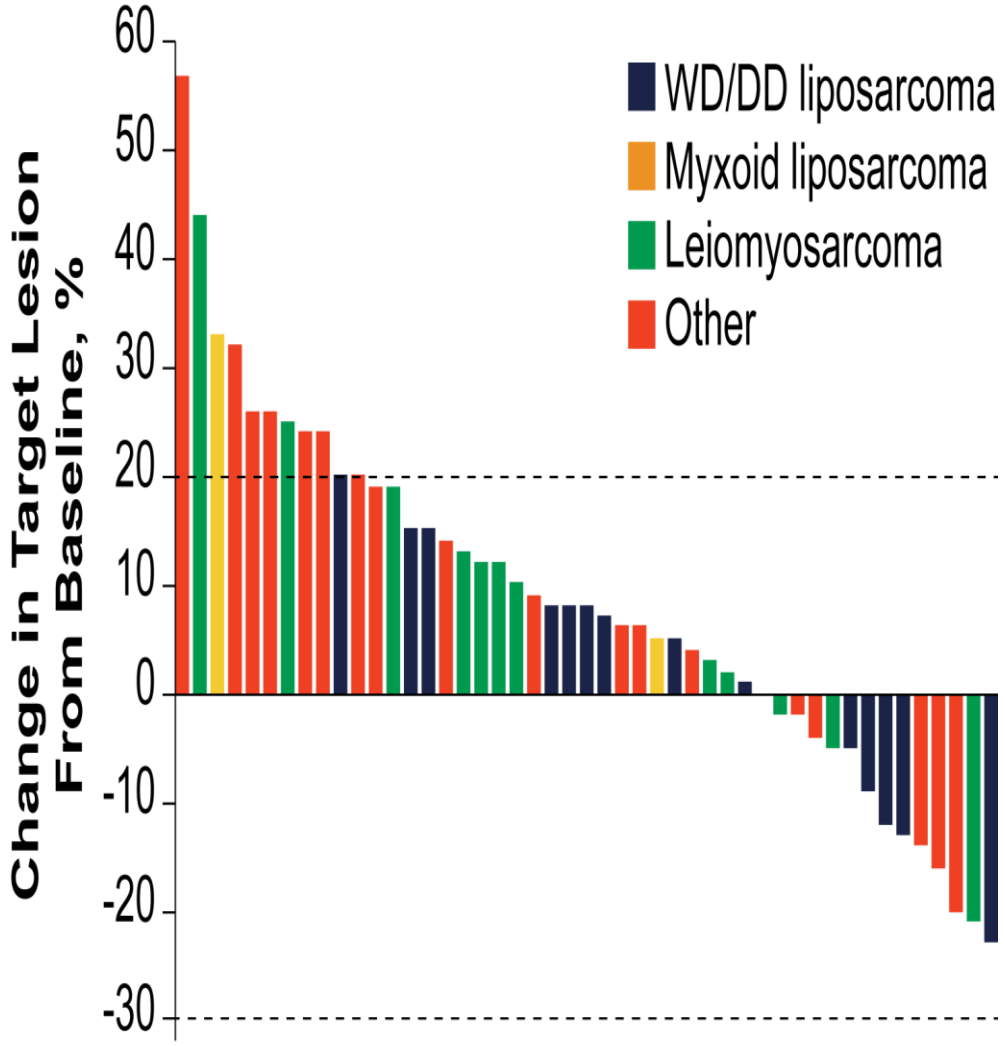
Dickson MA et al. *JAMA Oncol 2; 937-940: 2016*

Selective Inhibition of Nuclear Export (SINE)

- Selinexor: oral inhibitor of XPO-1 (nuclear exportin protein 1)
- Phase 2/3 study initiated based on early clinical activity in a phase 1b trial



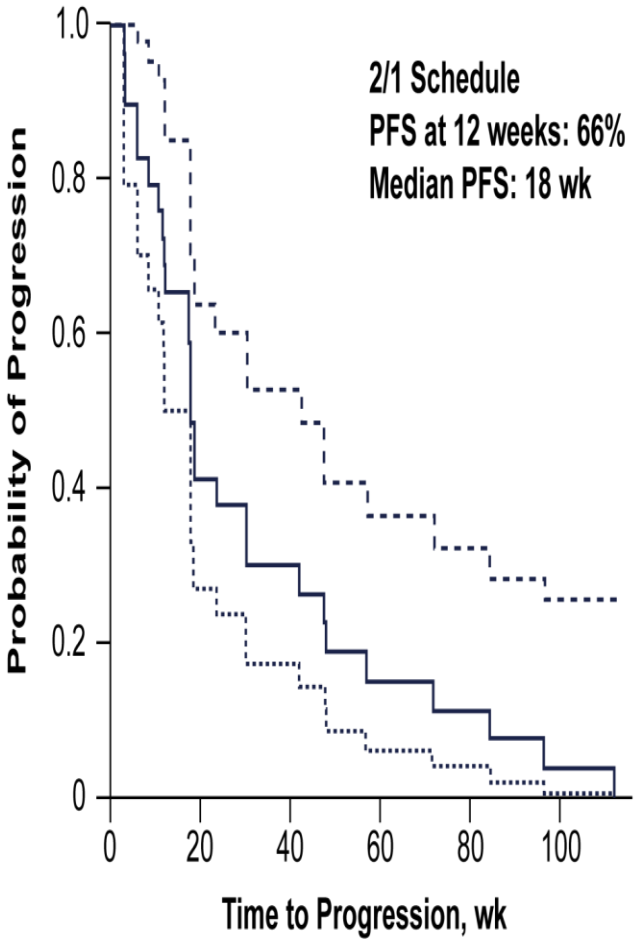
Selinexor: Change in Tumor Size



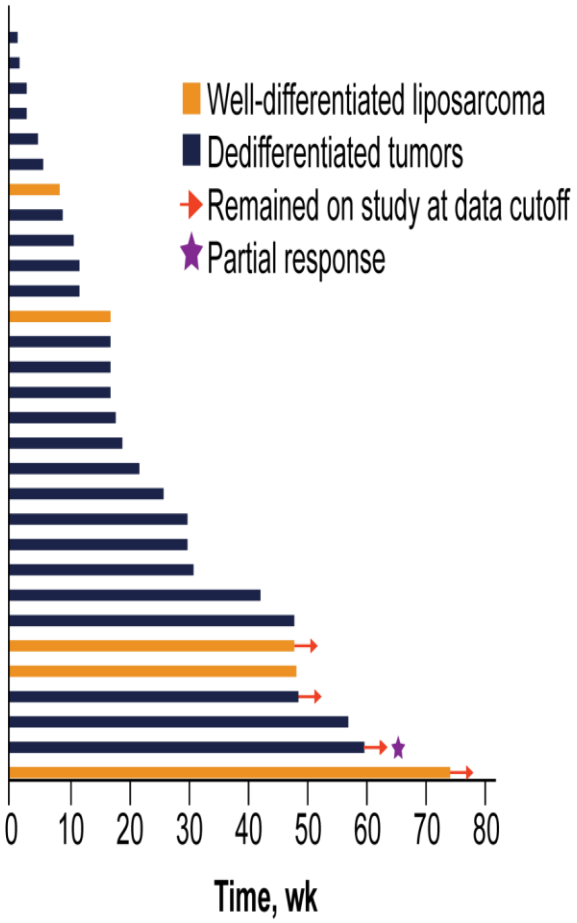
Gounder MM et al. *J Clin Oncol* 34; 3166-3174: 2016

Selinexor: PFS and Time on Study

Progression-Free Survival



Time on Study



Gounder MM et al. *J Clin Oncol* 34; 3166-3174: 2016

Selinexor: Toxicity

Table 2. Summary of Toxicities

AE	No. (%)														
	Selinexor 30 mg/m^2 (n = 19)					Selinexor 50 mg/m^2 (n = 17)					Selinexor 60 mg (n = 18)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
GI															
Nausea*	11 (57.9)	3 (15.8)			14 (73.7)	8 (47.1)	7 (41.2)	1 (5.9)		16 (94.1)	7 (38.9)	4 (22.2)			11 (61.1)
Dysgeusia	8 (42.1)				8 (42.1)	4 (23.5)	4 (23.5)			8 (47.1)	3 (16.7)				3 (16.7)
Vomiting*	8 (42.1)		1 (5.3)		9 (47.4)	7 (41.2)	4 (23.5)	1 (5.9)		12 (70.6)	4 (22.2)	2 (11.1)			6 (33.3)
Anorexia*	6 (31.6)	2 (10.5)			8 (42.1)	3 (17.6)	6 (35.3)	1 (5.9)		10 (58.8)	1 (5.6)	3 (16.7)			4 (22.2)
Diarrhea	6 (31.6)	1 (5.3)	1 (5.3)		8 (42.1)	3 (17.6)	1 (5.9)			4 (23.5)	1 (5.6)	1 (5.6)	1 (5.6)		3 (16.7)
Constitutional															
Fatigue	6 (31.6)	8 (42.1)	1 (5.3)		15 (78.9)	2 (11.8)	7 (41.2)	5 (29.4)		14 (82.4)	4 (22.2)	5 (27.8)	1 (5.6)		10 (55.6)
Weight loss	1 (5.3)	2 (10.5)			3 (15.8)	5 (29.4)	1 (5.9)			6 (35.3)	2 (11.1)	2 (11.1)			4 (22.2)
Blood															
Platelet count decreased	5 (26.3)	3 (15.8)	1 (5.3)	1 (5.3)	10 (52.6)	3 (17.6)	3 (17.6)	2 (11.8)		8 (47.1)	4 (22.2)	3 (16.7)	1 (5.6)		8 (44.4)
Anemia		5 (26.3)	1 (5.3)		6 (31.6)	4 (23.5)	3 (17.6)	3 (17.6)		10 (58.8)	4 (22.2)	3 (16.7)		1 (5.6)	8 (44.4)
WBC decreased	2 (10.5)	4 (21.1)	2 (10.5)		8 (42.1)	1 (5.9)	4 (23.5)	1 (5.9)		6 (35.3)	1 (5.6)	3 (16.7)	1 (5.6)		5 (27.8)
Neutrophil count decreased		4 (21.1)	2 (10.5)		6 (31.6)	2 (11.8)	2 (11.8)	1 (5.9)		5 (29.4)		1 (5.6)			1 (5.6)
Lymphocyte count decreased			4 (21.1)		4 (21.1)		1 (5.9)			1 (5.9)			1 (5.6)		1 (5.6)
Metabolic															
Hyponatremia	4 (21.1)		2 (10.5)		6 (31.6)	5 (29.4)		1 (5.9)		6 (35.3)	8 (44.4)				8 (44.4)
Hypoalbuminemia	3 (15.8)	2 (10.5)			5 (26.3)	1 (5.9)				1 (5.9)	2 (11.1)	1 (5.6)			3 (16.7)
ALT increased	3 (15.8)				3 (15.8)	1 (5.9)				1 (5.9)	1 (5.6)		1 (5.6)		2 (11.1)
Other															
Blurred vision	3 (15.8)				3 (15.8)	8 (47.1)				8 (47.1)	2 (11.1)	1 (5.6)			3 (16.7)
Dizziness*†	1 (5.3)	1 (5.3)			2 (10.5)	7 (41.2)	2 (11.8)			9 (52.9)	1 (5.6)				1 (5.6)

NOTE. Treatment-related adverse events (AEs) occurring in at least 10% of the patient population (as a total sum of all grades) by selinexor dose (30 mg/m^2, 50 mg/m^2, or 60-mg flat dose). Grade 3 AEs occurring in fewer than 10% included: central autonomic dysfunction (n = 1), cataract (n = 1), urinary tract infection (n = 1), lipase increased (n = 2), serum amylase increased (n = 1), dehydration (n = 1), hypokalemia (n = 1), hypophosphatemia (n = 1), hematuria (n = 1), and maculopapular rash (n = 1). There were no unlisted grade 4 AEs related to selinexor treatment.

*Indicates a significant difference between 60 mg and 50 mg/m^2 for nausea (P = .03), vomiting (P = .04), and anorexia (P = .04).

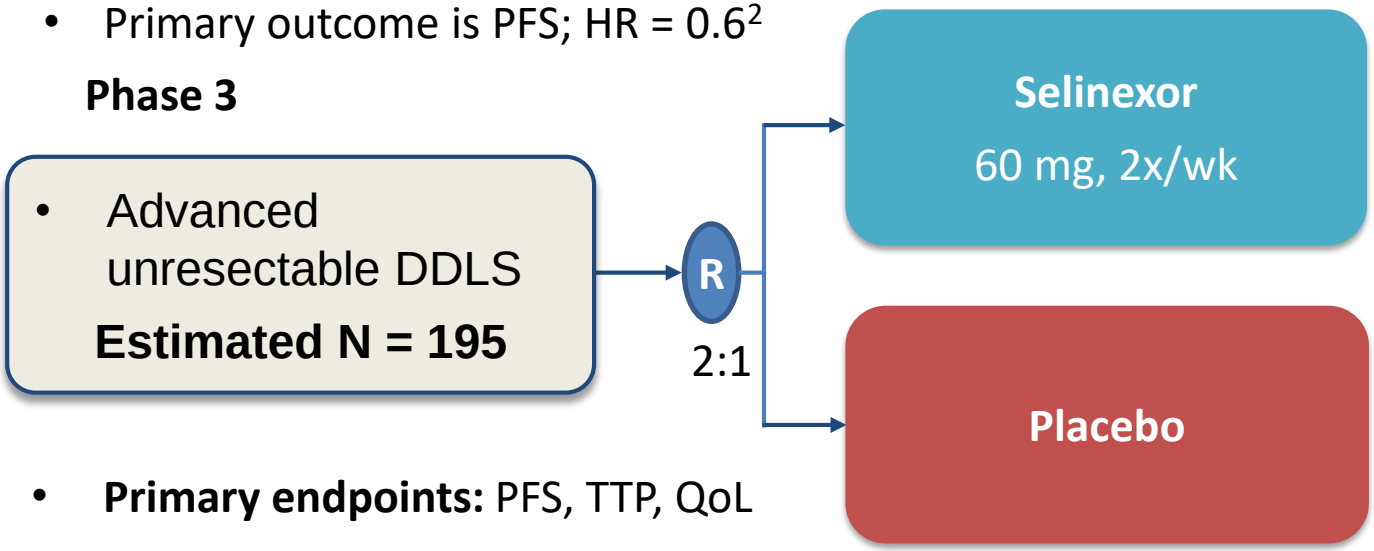
†Indicates a significant difference between 30 mg/m^2 and 50 mg/m^2 for dizziness (P = .01).

Gounder MM et al. *J Clin Oncol* 34; 3166-3174: 2016

Phase 2/3 Trial (SEAL): **SE**linexor in **A**dvanced **L**iposarcoma

- **Phase 2:** 57 patients randomized 1:1 to selinexor or placebo
- Phase 2 PFS data will inform adjustment of phase 3 sample size
- Primary outcome is PFS; HR = 0.6[2]

Phase 3

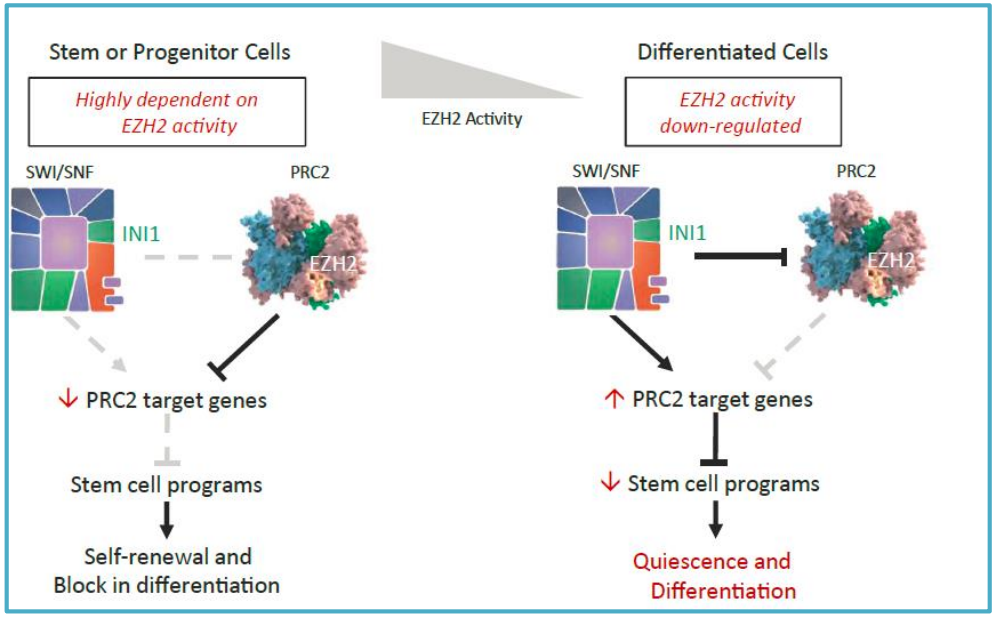


- **Primary endpoints:** PFS, TTP, QoL

https://www.clinicaltrials.gov/ct2/show/NCT02606461

EZH2 inhibitors in Epithelioid Sarcoma

INI1/ BAF47/ SMARCB1/ hSNF5



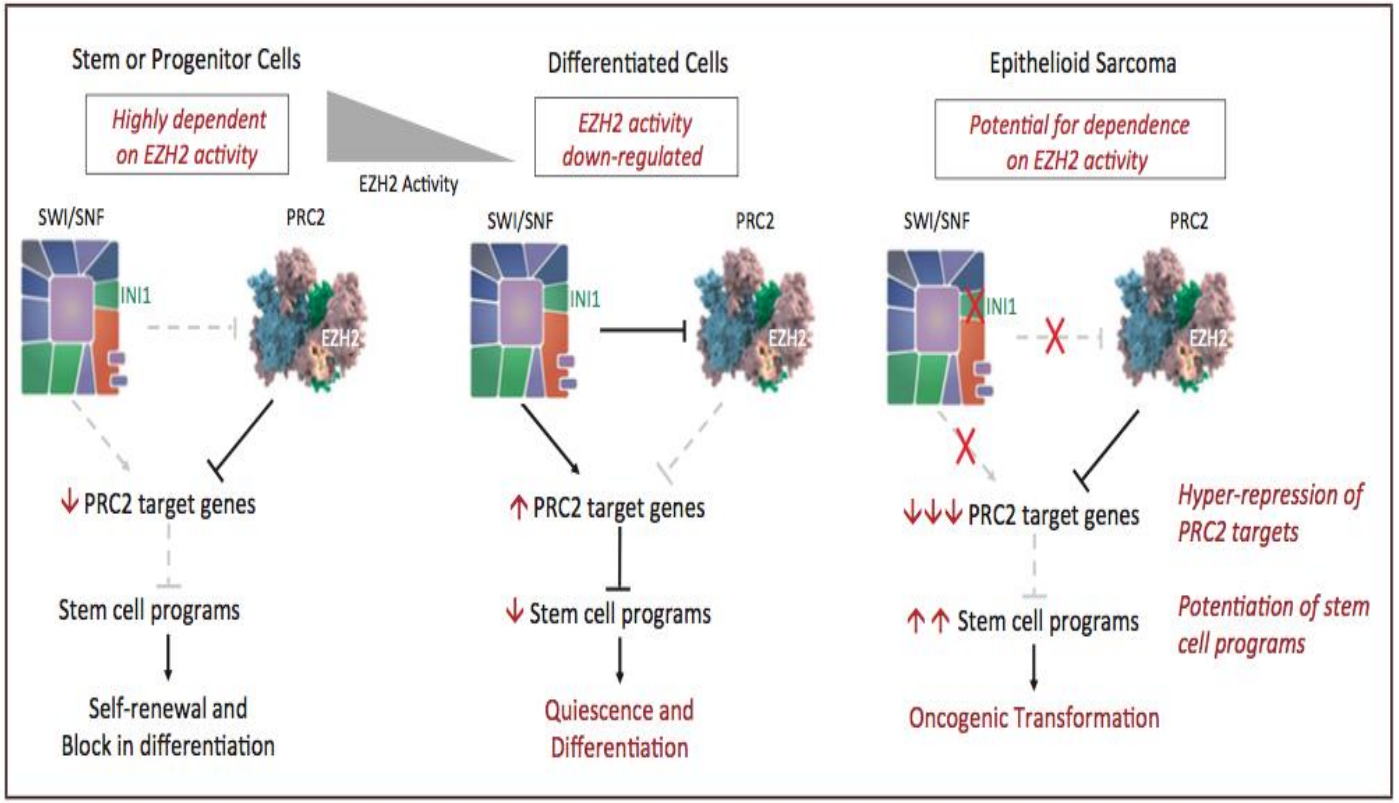
- Tumor suppressor
- Loss of *Integrase Interactor 1*, *INI1 (BAF47/ SMARCB1/ hSNF5*) gene causes
  - Extremely aggressive rhabdoid tumors
- Re-expression *INI1* in rhabdoid tumors cells
  - Stops their proliferation
- Eviction of INI1 (BAF47/ SMARCB1/ hSNF5*)* from the BAF [SWI/ SNF] complex
  - Plays an important role in synovial sarcoma tumorigenesis
  - Allows EZH2 (epigenetic modifier) to become an oncogenic driver in tumor cells
- INI1 loss characteristic of epithelioid sarcoma

PRC2, polycomb repressive complex 2

Kadoch C, Crabtree GR. Cancer Cell 153(1); 71-85: 2013

- EZH2: Catalytic subunit PRC2 + responsible for methylation activity PRC2
  - Enzyme histone methylation
  - Chromatin remodeling
  - Transcriptional repression

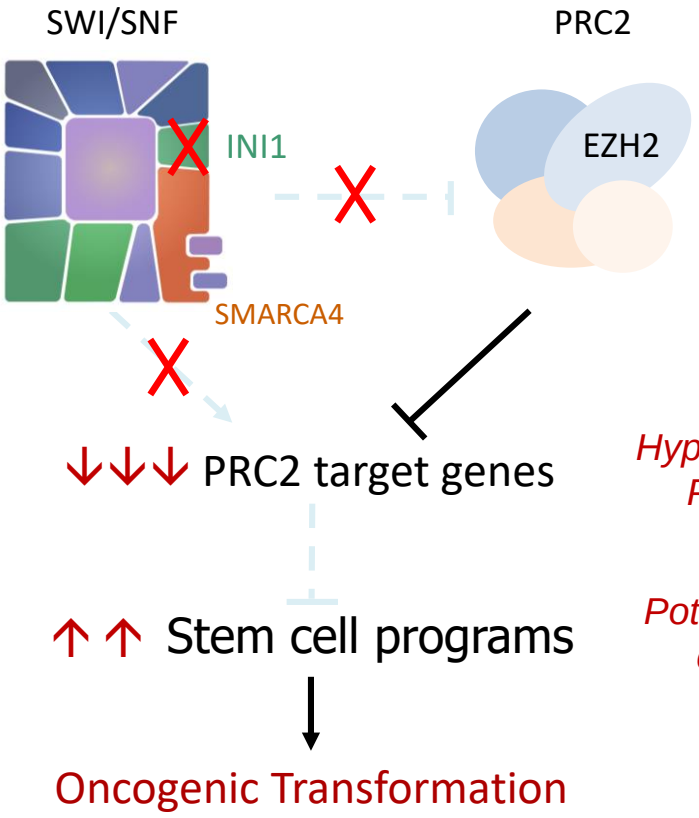
Figure 1: Loss of INI1 impairs SWI/SNF function, causing aberrant PRC2 activity and a dependence on EZH2 activity



INI1 Loss Creates an Oncogenic Dependency on EZH2 in Tumors

Stem or Progenitor Cells

Highly dependent on EZH2 activity



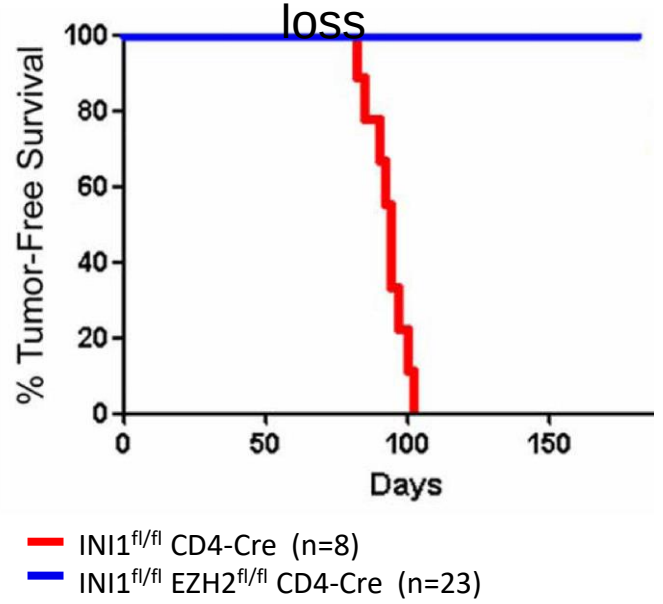
Hyper-repression of PRC2 targets

Potentiation of stem cell programs

<u>INI1-negative tumors, e.g.:</u>

Malignant rhabdoid tumor (MRT)
Epithelioid sarcoma

EZH2 knockout reverses oncogenesis induced by INI1 loss



Adapted from Wilson 2010

Patient Selection: INI1 loss in Sarcomas

Subtype	INI1 loss
Epithelioid Sarcoma	90%
Epithelioid MPNST	50 - 67%
Myoepithelial Carcinoma	10 - 40%
Extraskeletal Myxoid Chondrosarcoma	17%
Poorly Differentiated Chordoma	Limited data

Adapted from Hollmann TJ, Hornick JL. Am J Surg Pathol 35; 47-63: 2011

Epithelioid Sarcoma

- 1961: Lakowski “aponeurotic sarcoma”
- 1970: Enzinger: 62 cases
  - Distinct subtype
  - Confused with chronic inflammatory process, necrotizing granuloma, squamous cell carcinoma
- Can occur at any age
  - Peak incidence young adults
  - Frequently males
- Characterized by INI1 loss
- Etiology remains unknown
- Up to 27% associated with previous trauma
  - Originating in scar tissue

- Classic variant
  - Most commonly upper extremities
  - Adolescents + young adults
  - Male predominance (2:1)
  - Superficial, slowly growing painless, firm nodule
  - Repeated local recurrences
    - Successive lesions arising more proximally
- Proximal variant
  - Proximal limbs/ limb girdles/ midline of trunk
  - Slightly older adults
  - Slight male predominance
  - Deep, infiltrating soft-tissue masses with hemorrhage + necrosis
  - More aggressive clinical course

Thway K et al. Adv Anat Pathol 23; 41-29: 2016
Noujaim J et al. Front Oncol 5; 1-11: 2015

Phase II EZH2 inhibitor

Table 2: Patient demographics and baseline disease characteristics

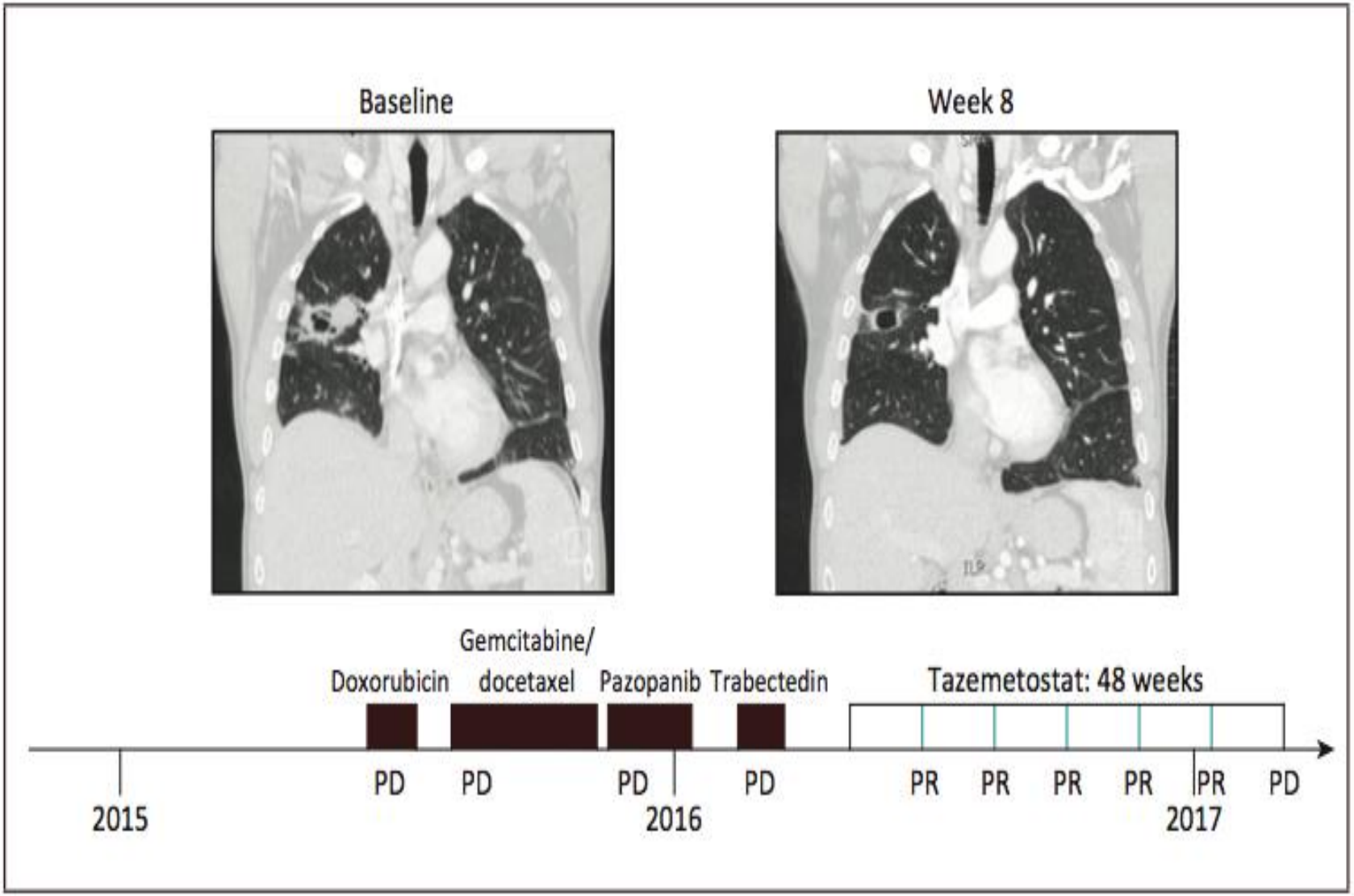
Characteristic	Epithelioid sarcoma (n=31)
Median age, years (range)	33 (19–79)
Sex (male/female), n	21/10
Number of lines of prior anti-cancer therapy, n (%)	
0	9 (29)
1	5 (16)
2	7 (23)
3	2 (6)
4	4 (13)
≥5	4 (13)
Median	2
Primary tumor location, n (%)	
Distal	15 (48)
Proximal	16 (52)
Metastatic disease at study entry, n (%)	27 (87)

Table 3: Objective response and disease control rate in patients with ES–preliminary assessment

Response	Epithelioid Sarcoma (n=31)
Best overall response, n (%)	
Complete response	0 (0)
Partial response (confirmed)	4 (13)
Stable disease	18 (58)
Ongoing study drug	6 (19)
Progressive disease	7 (23)
Not evaluable/unknown	2 (6)
ORR, n (%)	4 (13)
DCR, n (%)	10 (32)
Objective response (confirmed)	4 (13)
Stable disease ≥32 weeks	6 (32)
Median PFS (mos)	5.7

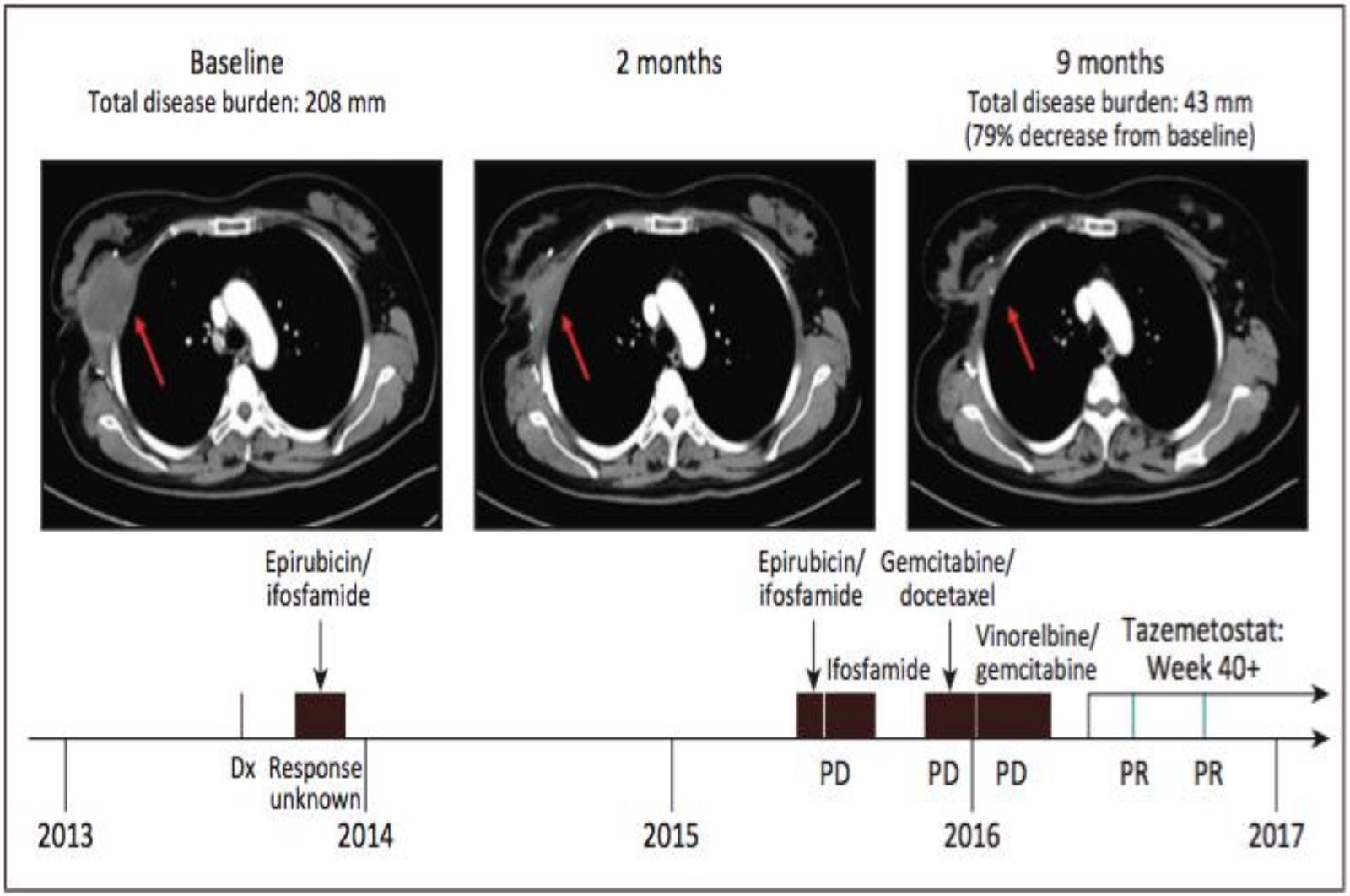
Gounder MM et al. ASCO 2017. Abstract 11058

Proximal-type Epithelioid Sarcoma: EZH2 Inhibitor



Gounder MM et al. ASCO 2017. Abstract 11058

Classic-type Epithelioid Sarcoma



Gounder MM et al. ASCO 2017. Abstract 11058

Chondrosarcomas

IDH1 and IDH2

- IDH (isocitrate dehydrogenase)
  - Essential enzyme
  - Catalyzes oxidative decarboxylation of isocitrate
  - Producing α-ketoglutarate (α-KG) + CO_2
    - Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$) + NAD^+ as cofactors
    - α-KG intermediate in tricarboxylic acid (TCA) cycle

- 3 distinct isoforms

- *IDH1/ IDH2*
  - Mutations are mutually exclusive
  - Glioma, AML, cholangiocarcinoma, chondrosarcoma (>50%)
  - Mutated enzymes lose ability to convert isocitrate to α-KG
  - Gain novel function consisting of
    - NADPH-dependent reduction of α-KG to
    - Oncometabolite D-2HG (2 Hydroxyglutarate)

Dang L et al. Nature 462; 739-744: 2009
Ward PS et al. Cancer Cell 17; 225-234: 2010
Losman + Kaelin. Genes Dev 27; 836-852: 2013

IDH1 + 2 in Chondrosarcomas

- Chemo-resistant
  - NO effective systemic therapy
- Clear unmet need
- Biological rationale for IDH 1 + 2 inhibitors
- Early phase clinical trial participation
  - Preferred option to chemotherapy

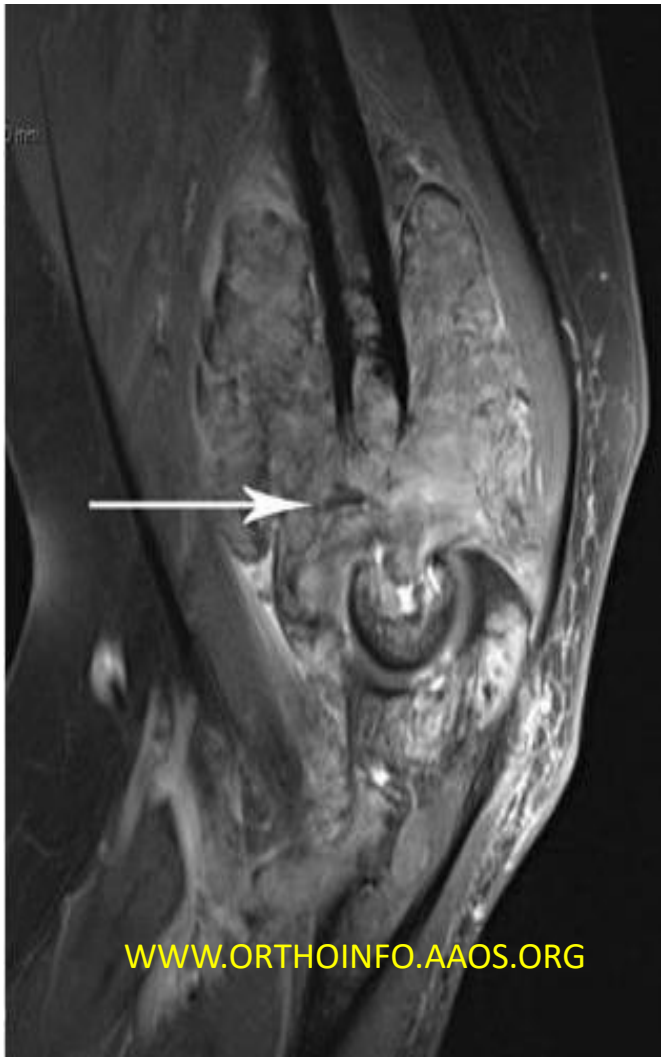
- AG-120 Phase I trial
  - N=21 chondrosarcoma
    - N=12 dose escalation
    - N=9 dose expansion
- Stable disease:
  - N=11 (55%)
- 3-month progression-free rate:
  - 58%
- Reduction of plasma + tumor 2-HG

Tap W et al. CTOS, Lisbon, Nov 2016

Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis)

Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis)

- Benign, though often highly morbid inflammatory neoplasm arising in joints
- Driven primarily by a small proportion of cells harboring a *COL6A3-CSF1* translocation leading to excessive CSF1 expression
- NO current approved systemic therapy



West et al. PNAS 2006
Tap WD et al. ASCO 2018

Randomized, Double-Blind, Phase 3 Study Design

PATIENTS

- **Histologically confirmed, advanced, symptomatic TGCT**
- **Surgical resection associated with potential for worsening of functional limitation or severe morbidity**
- **Measurable disease ≥ 2 cm by RECIST v1.1**

STRATIFICATION

- **US vs non-US sites**
- **Upper vs lower extremity**

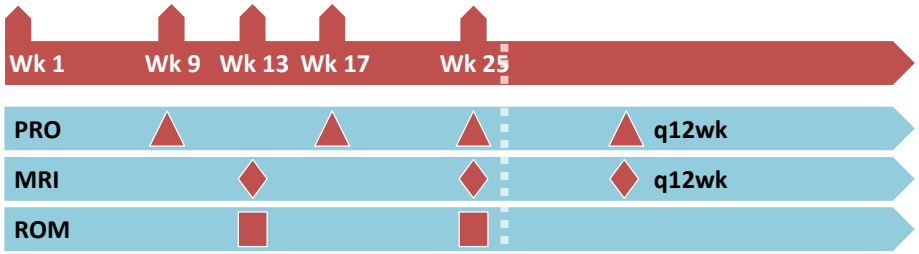
RANDOMIZED 1:1

Placebo-controlled & blinded (24 wk) | Open-label extension (25 wk+)

Pexidartinib
1000 mg/d split bid (2 wk), then
800 mg/d split bid (22 wk)

Placebo
(matching placebo)

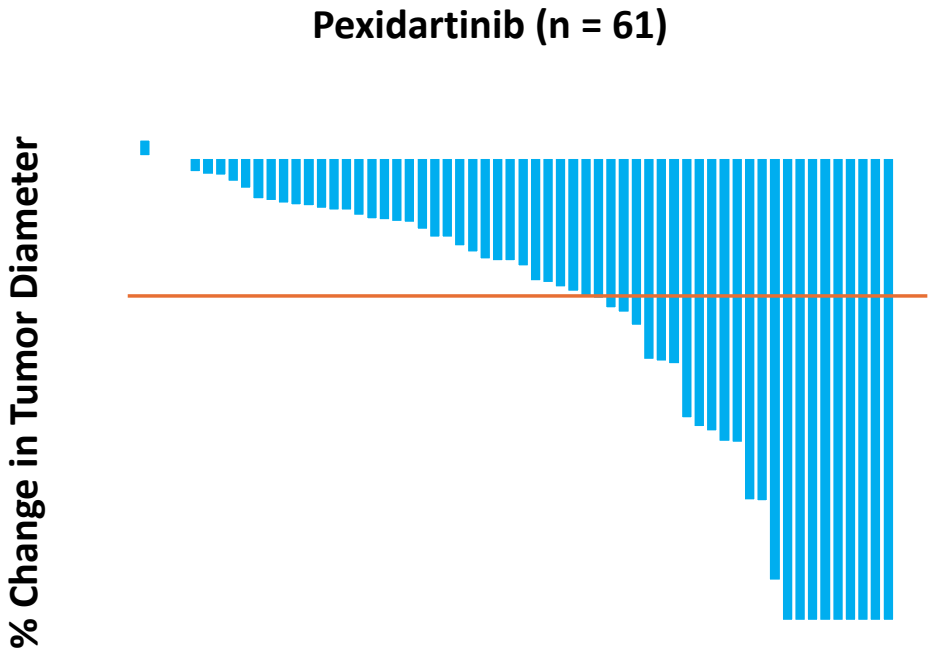
Pexidartinib
Current dose

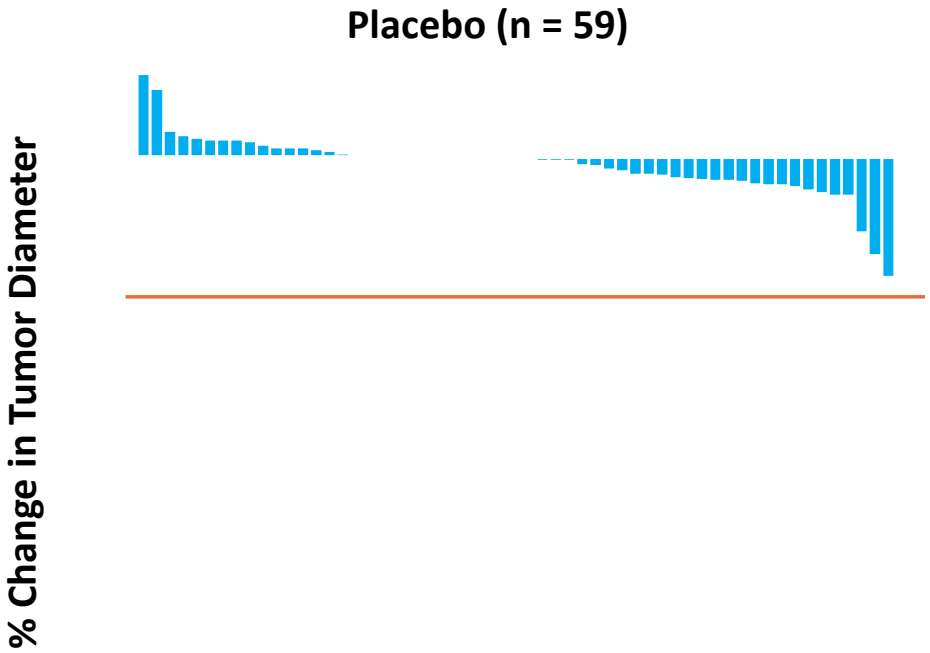


ClinicalTrials.gov Identifier: NCT02371369

Tap WD et al. ASCO 2018

Primary Endpoint: Tumor Response by RECIST v1.1*
Week 25 Response (Blinded, Central MRI Review; ITT Population)





Treatment, n (%)	Complete	Partial	Stable Disease	Progressive Disease	Not Evaluable	Overall Response Rate [95% CI]
Pexidartinib n = 61	9 (15)	15 (25)	24 (39)	1 (2)	12 (20)	24 (39) [28.1, 51.9] $P < 0.0001$
Placebo n = 59	0	0	46 (78)	1 (2)	12 (20)	0 [0, 6.1]

*Baseline mean sum of the longest tumor diameters was 10.1 and 10.6 cm for pexidartinib and placebo, respectively.

Tap WD et al. ASCO 2018

Pexidartinib in Tenosynovial Giant Cell Tumor

- Significantly improved ORR over placebo
  - RECIST: 39% vs 0%, $P < 0.0001$
  - TVS: 56% vs 0%, $P < 0.0001$
- Generally well tolerated
  - Serious, nonfatal liver toxicity with increased bilirubin in 4% of patients
  - Majority of other AEs < grade 3
- Improved patient symptoms + function on active trial drug

Tap WD et al. ASCO 2018

Desmoid Tumour

Alliance A091105: Sorafenib vs Placebo Phase III, double blind, randomized trial with crossover

- Unresectable or unacceptable surgical morbidity
- Progressive disease (10% by RECIST 1.1 within 6 months)
- Symptomatic disease – Brief Pain Inventory score ≥ 3 and considering addition or increase in narcotics

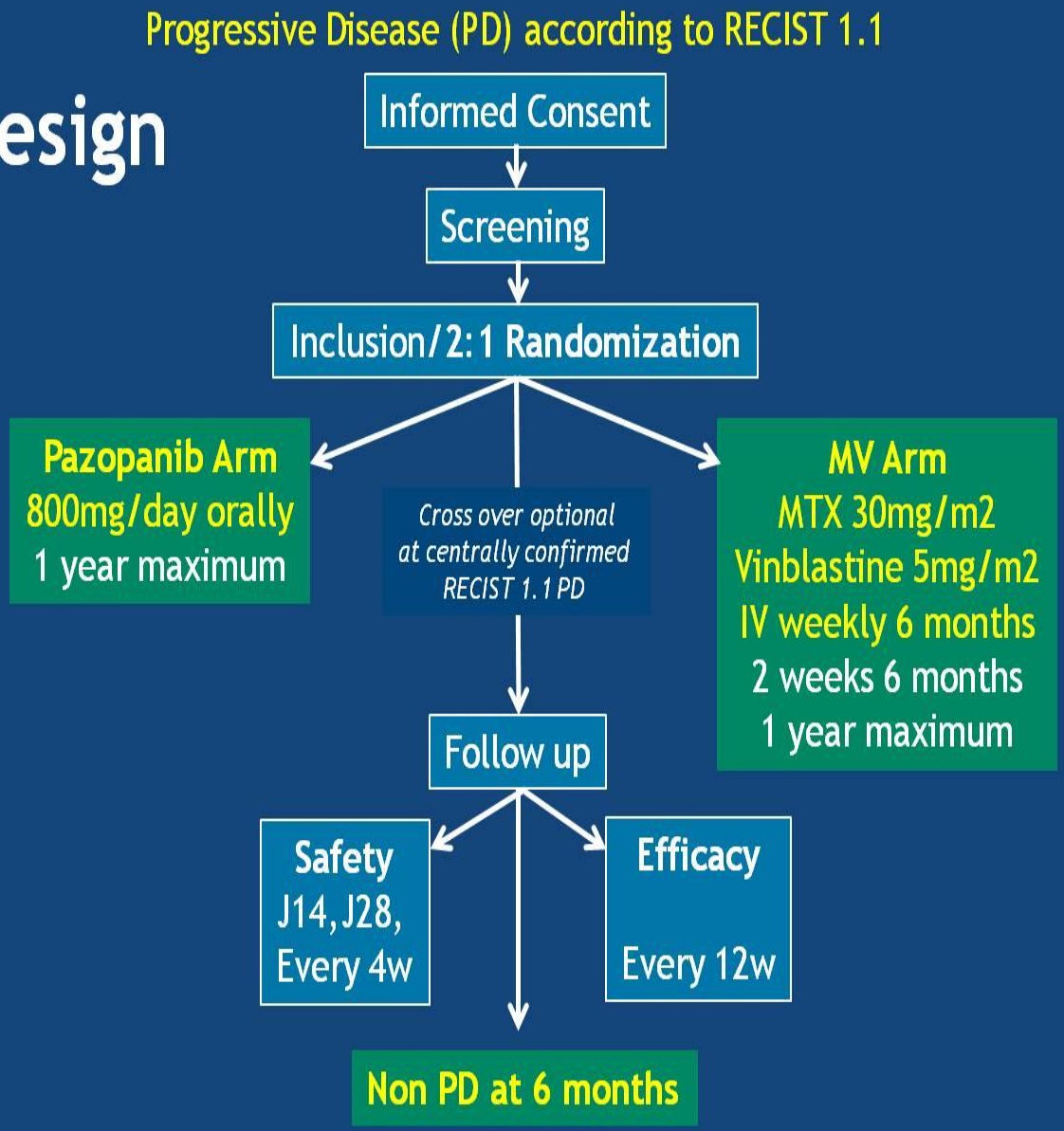
- Response rate:
  - Sorafenib (n=49): 33% (95%CI, 20-48%)
  - Placebo (n=35): 20% (95%CI, 8-38%)

- Median PFS:
  - Sorafenib: not reached
  - Placebo: 11.3 months (95%CI: 5.7 – not reached)
- HR 0.14 (95%CI, 0.06-0.33), p<0.0001

Gounder M et al. NEJM 379(25); 2417-2428: 2018

Methods - Study Design

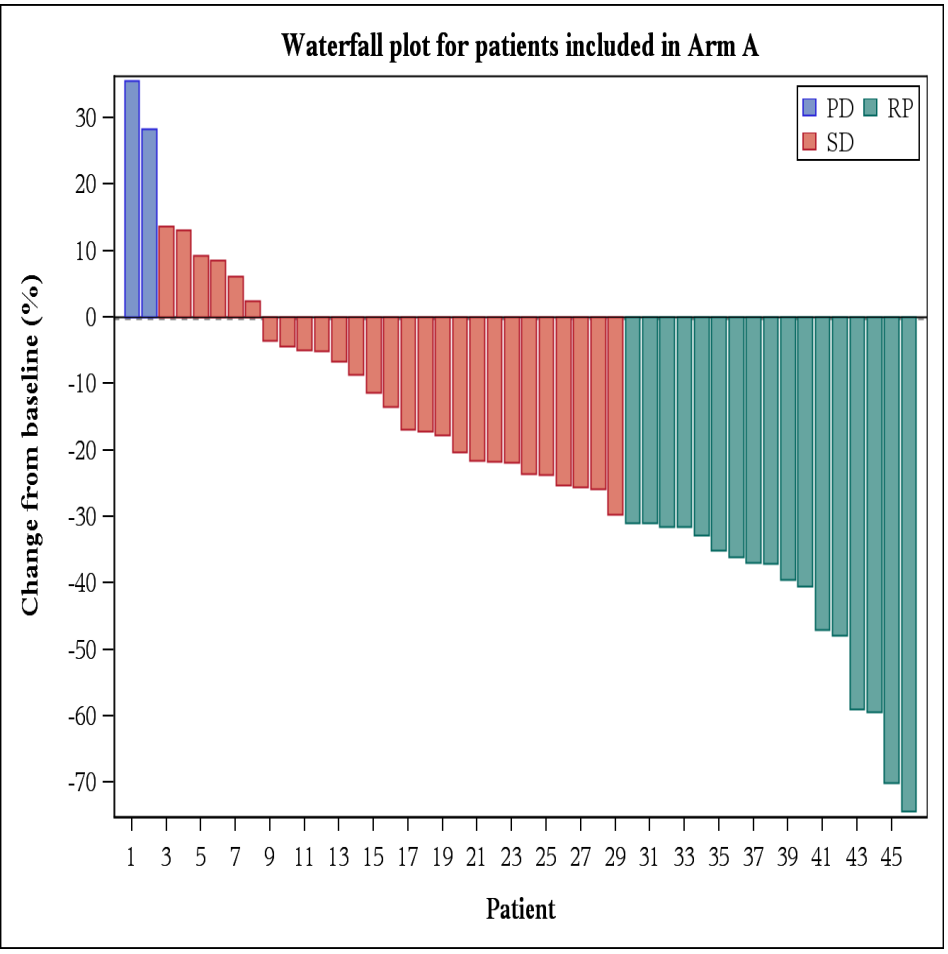
- DESMOPAZ is a multicenter non-comparative randomized phase 2 clinical trial
- Required RECIST progression within 6 months of study entry



Toulmonde M et al. ASCO 2018

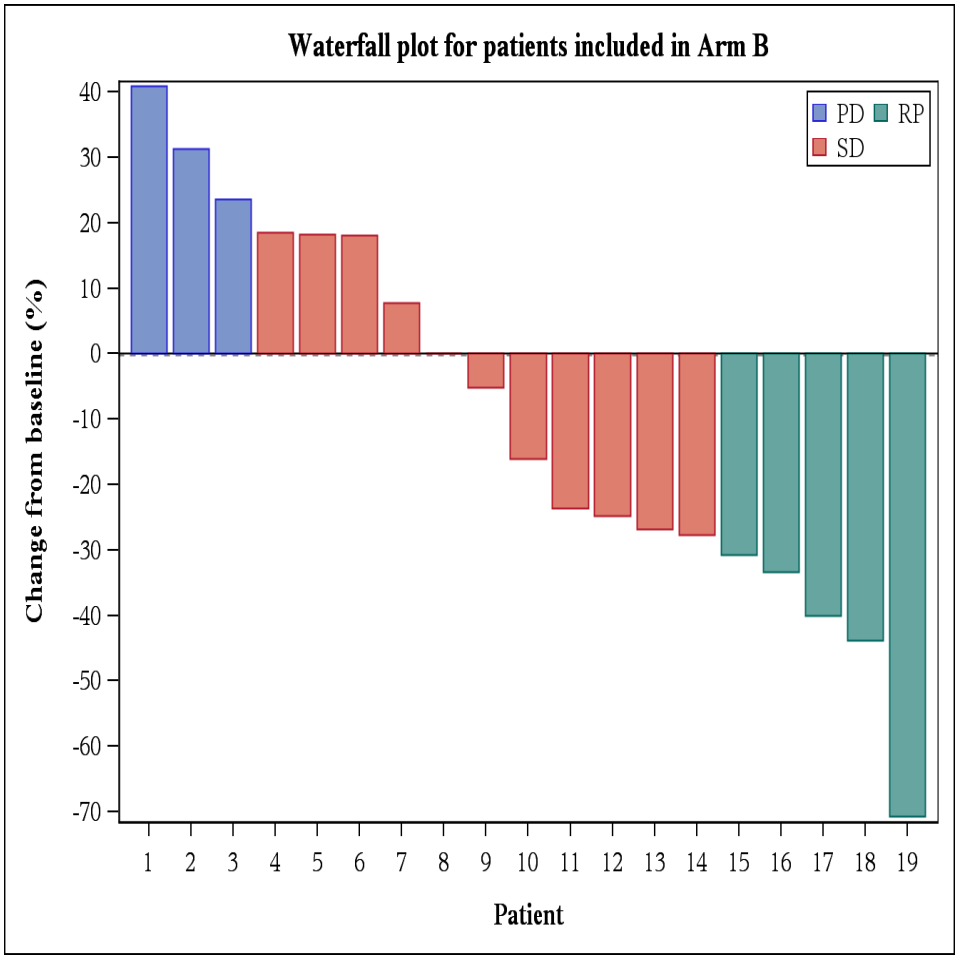
Pazopanib Arm

PR = 37% (95%CI: 23.2-52.5%)



Methotrexate + Vinblastine Arm

PR = 25% (95%CI: 8.6-44%)



Toulmonde M et al. ASCO 2018

Conclusion

- Phase 3 olaratumab trial
  - Not all sarcomas are the same……..
- Number promising agents in development
  - Subtype specific
  - Molecular rationale
- Phase III trials in
  - GIST
    - Blu-285
    - DCC-2618
  - Angiosarcoma
  - Liposarcoma
- Phase II single agent activity
  - Crizotinib
  - EZH2 inhibitor
- Randomized data in Desmoid tumors + Tenosynovial giant cell tumor
  - Optimal incorporation in management

Sarcoma Unit Royal Marsden/ Institute of Cancer Research

- **Surgery**
- Andrew Hayes
- Dirk Strauss
- Myles Smith
- Simon Jordan (Royal Brompton)
- Sofina Begum (Royal Brompton)

- **Pathology**
- Khin Thway
- Silvia Bague

- **Radiology**
- Christina Messiou
- Eleanor Moskovic
- Nicos Fotiadis

- **Oncology**
- Charlotte Benson
- Julia Chisholm
- Ian Judson
- Aisha Miah
- Shane Zaidi
- Spyros Gennates

- **Palliative Care**
- Julia Riley

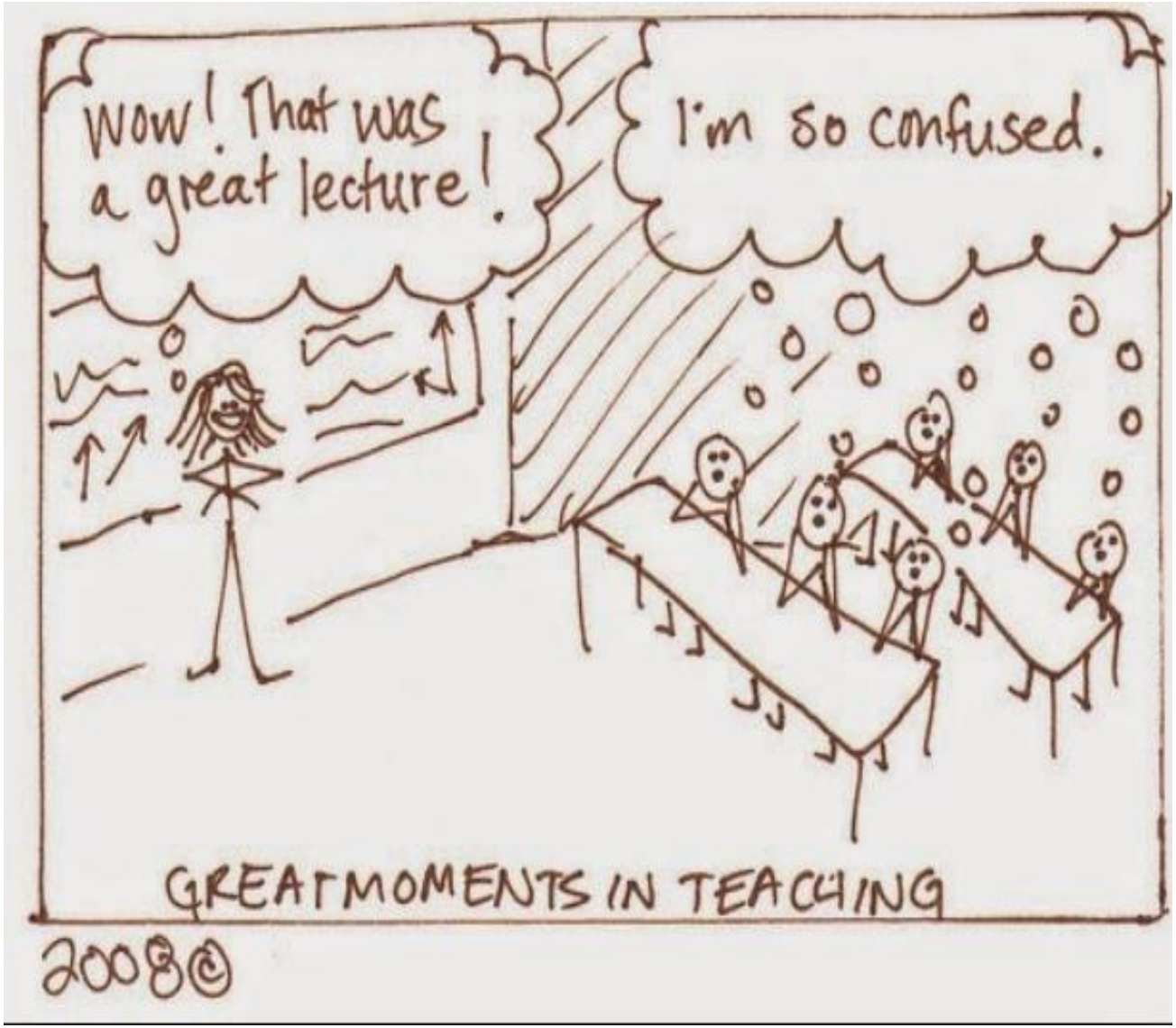
- **Specialist Nurses and Physiotherapy**
- Alison Dunlop
- Elaine Stephens
- Angela Teague
- Kelly Mckibbin
- Lucy Dean

- **Clinical Trials Team**
- Liz Barquin
- Diego Bottero
- Steve Edmunds
- Alice Burridge
- Galina Petrikova
- Steph Elston
- Bodil Engelman and Flo Chamberlain

- **Institute of Cancer Research**
- Paul Huang + Huang Lab
- Alex Lee
- Chris Wilding
- Janet Shipley + Shipley Lab
- Eugenie Younger

- And all the patients + families
- Sarcoma UK + GIST Support UK

Thank you!



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