



Advances in the Treatment of Soft Tissue and Bone Sarcomas

*16th Annual California
Cancer Consortium*

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Overview

Soft Tissue Sarcoma

- New Roles for Pazopanib
- TVEC and Pembrolizumab
- Tazemetostat

Bone Sarcoma

- Regorafenib

Other

- Entrectenib
- Avapritinib/Ripretinib
- Pexidartinib

ARST1321 Trial

Pazopanib Added to AIM Neoadjuvant Chemotherapy

- COG and NRG Open Label Phase II, compared AIM vs AIM + Pazopanib
- 81 patients enrolled, 1:1 randomization

	Pazopanib group	Control group	p value
Pathological response*			
≥90%	14 (58%)	4 (22%)	0.020†
<90%	10 (42%)	14 (78%)	..
Institutional radiographical response following induction‡			
Complete response	0 (0%)	2 (8%)	0.45
Partial response	14 (52%)	12 (50%)	..
Stable disease	12 (44%)	8 (33%)	..
Progressive disease	1 (4%)	2 (8%)	..
Not evaluated	15	15	..

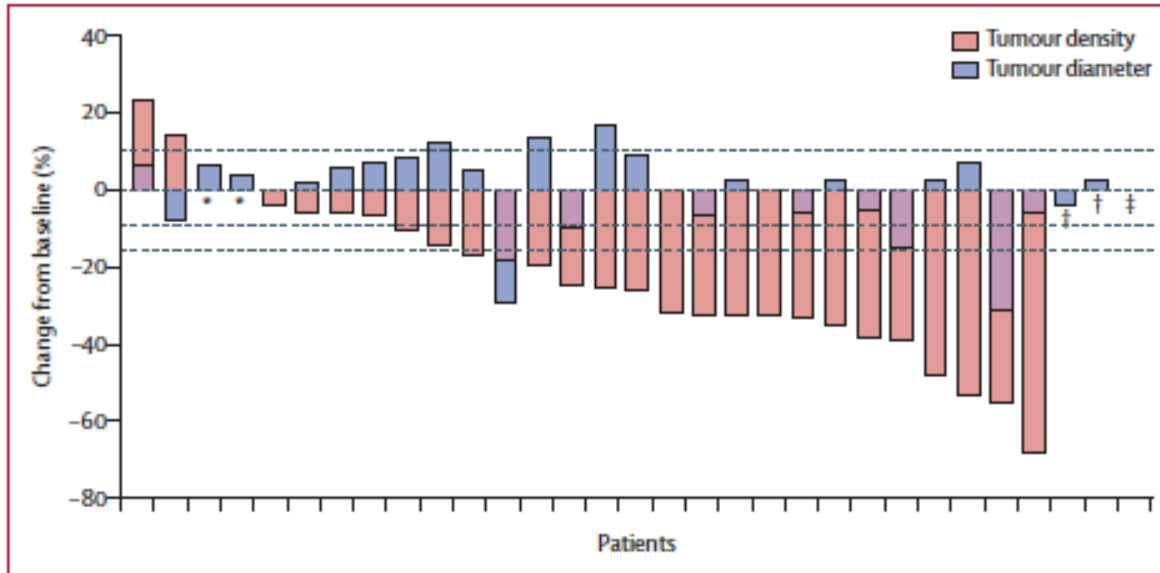
Data are n (%). *24 evaluable patients in the pazopanib group and 18 evaluable patients in the control group.
†One-sided with a 0.081 level of significance for the second interim monitoring. ‡27 evaluable patients in the pazopanib group and 24 evaluable patients in the control group.

Weiss et al. Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial. *Lancet Oncology*. 2020.

Multicenter Phase II Trials

Pazopanib and Solitary Fibrous Tumor (SFT)

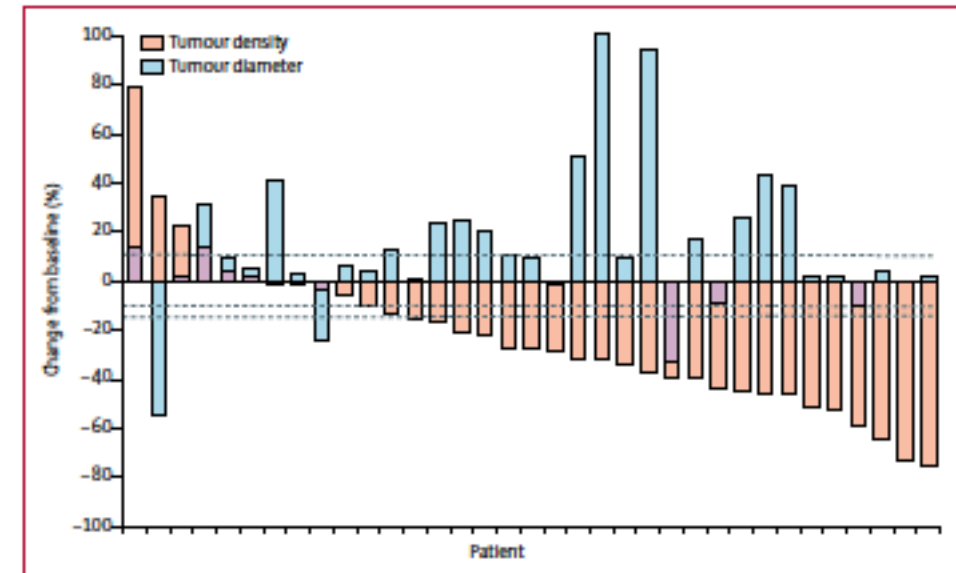
Typical SFT



- 364 patients evaluated
- 18 months of follow up
- **58% PR, 39% SD, 3% PD**

Martin-Broto et al. Pazopanib for treatment of typical solitary fibrous tumours: a multicenter, single-arm, phase 2 trial. *Lancet Oncology* 21(3): 2020

Advanced and Dedifferentiated



- 36 patients evaluated
 - 34 advanced, 2 with dedifferentiated
- 27 months of follow up
- **51% PR, 26% SD, 23% PD**

Martin-Broto et al. Pazopanib for treatment of advanced malignant and dedifferentiated solitary fibrous tumour: a multicenter, single-arm, phase 2 trial. *Lancet Oncology* 20(1): 2019.

Single Institution Phase II Trial

TVEC and Pembrolizumab in STS

- Open lab, single-institution phase 2 trial
- 20 patients with metastatic STS
 - Leiomyosarcoma
 - Angiosarcoma
 - UPS
- Median 3 lines of prior therapy

Table 2. Objective Response Rate per RECIST, Version 1.1, and Immune-Related RECIST Criteria

Variable	RECIST v1.1 (n = 20)	Immune-Related RECIST (n = 20)
Objective response, No. (%)		
Best overall response	7 (35)	7 (35)
Complete response	0	0
Partial response	7 (35)	7 (35)
Stable disease	7 (35)	5 (25)
Progressive disease	6 (30)	8 (40)
Best objective response rate, No. (%)		
At 24 wk	6 (30)	6 (30)
Disease control rate, No. (%)		
	14 (70)	12 (60)
Duration of response		
Patients with response, No. (%)	7 (35)	7 (35)
Duration of response, median (range), wk	56.1 (49.4-87)	56.1 (49.4-87)

Abbreviation: RECIST, Response Evaluation Criteria In Solid Tumors.

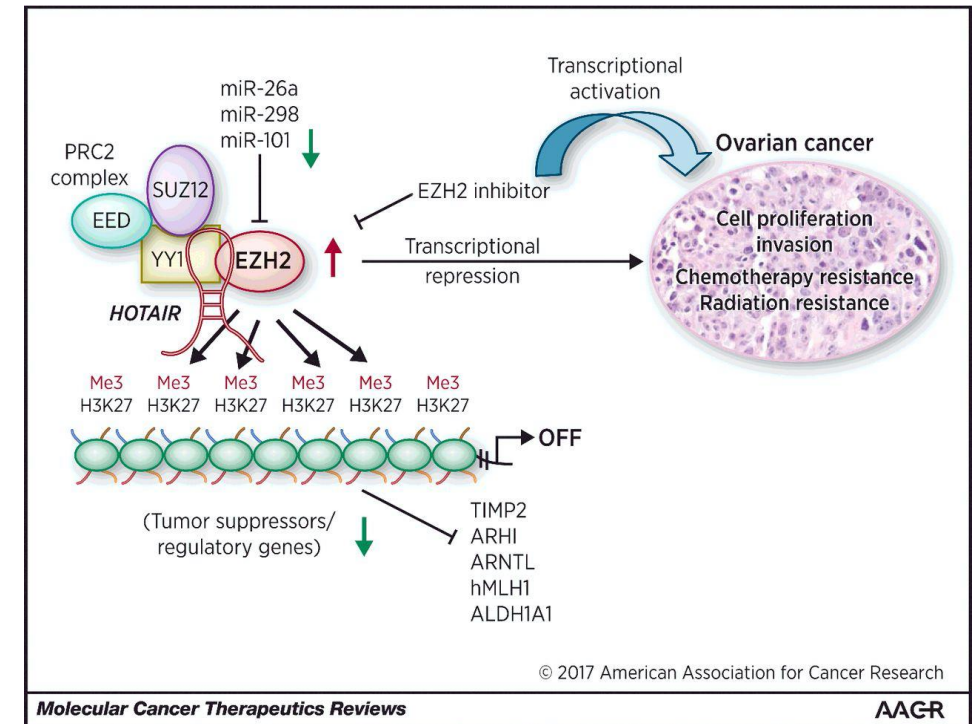
Kelly et al. Objective response rate among patients with locally advanced or metastatic sarcoma treated with talimogene laherparepvec in combination with pembrolizumab. A phase 2 clinical trial. JAMA oncology 6(3): 2020.

EZH-202 (Cohort 5)

Tazemetostat in Epithelioid Sarcoma

- FDA Accelerated Approval: January 2020
- Phase II, multicenter, open-label, single arm study
- Metastatic or locally advanced
- Epithelioid sarcoma with INI-1 loss

**62 patients, ORR 15%, 1.6% CR, 13% PR,
67% of responses were >6 months**

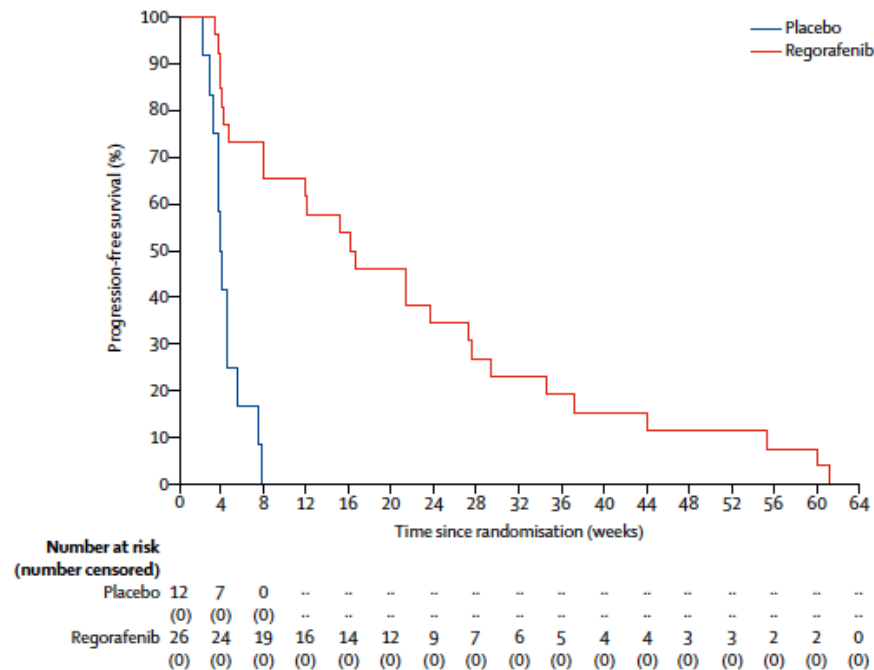


Jones et al. Histone methyltransferase EZH2: A Therapeutic Target for Ovarian Cancer. *Molecular Cancer Therapeutics* 17(3): 2018.

REGOBONE Trial

Regoarafenib in Metastatic Osteosarcoma

- Randomized, placebo-controlled, Phase II Trial
- 38 patients evaluated, crossover was allowed
- 65% in the regorafenib were non-progressive at 8 weeks



	Regorafenib group (n=26)	Placebo group (n=12)
Non-progressive disease at 8 weeks	17 (65%; 95% CI 47-)*	0
Response at 8 weeks		
Complete response	0	0
Partial response	2 (8%)	0
Stable disease	15 (58%)	0
Progressive disease	9 (35%)	12 (100%)
Median progression-free survival, weeks	16.4 (95% CI 8.0-27.3)	4.1 (95% CI 3.0-5.7)
Progression-free survival at 12 weeks	62% (95% CI 40-77)	0
Progression-free survival at 24 weeks	35% (95% CI 17-52)	0

Data are n (%) unless otherwise specified. *One-sided 95% CI (due to the Fleming design).

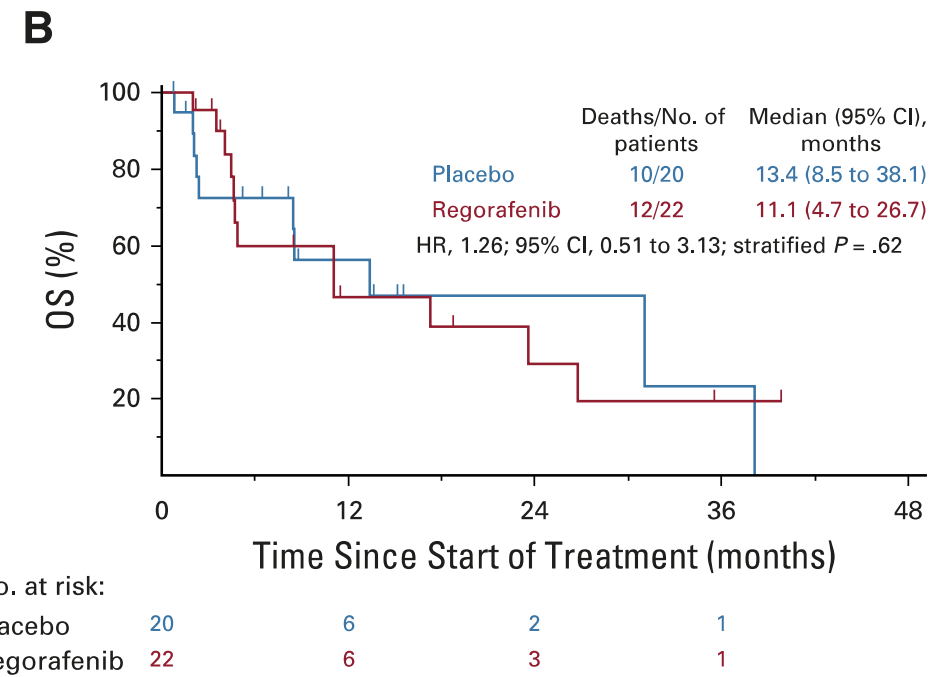
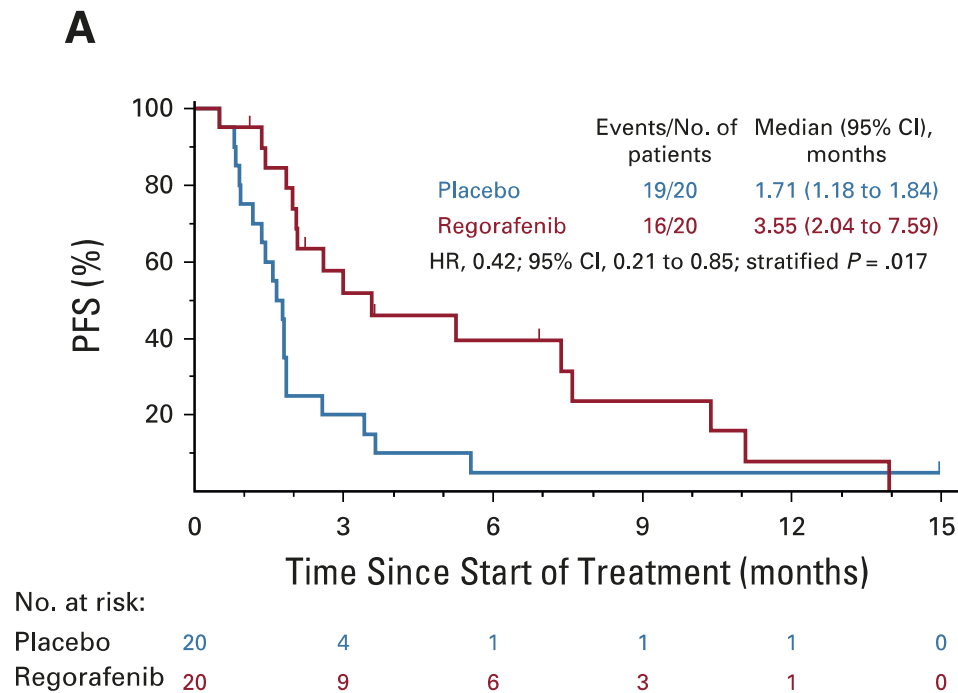
Table 2: Efficacy outcomes

Duffaud et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomized, double-blind, placebo-controlled, phase 2 study. The Lancet 20(1): 120-133. 2019.

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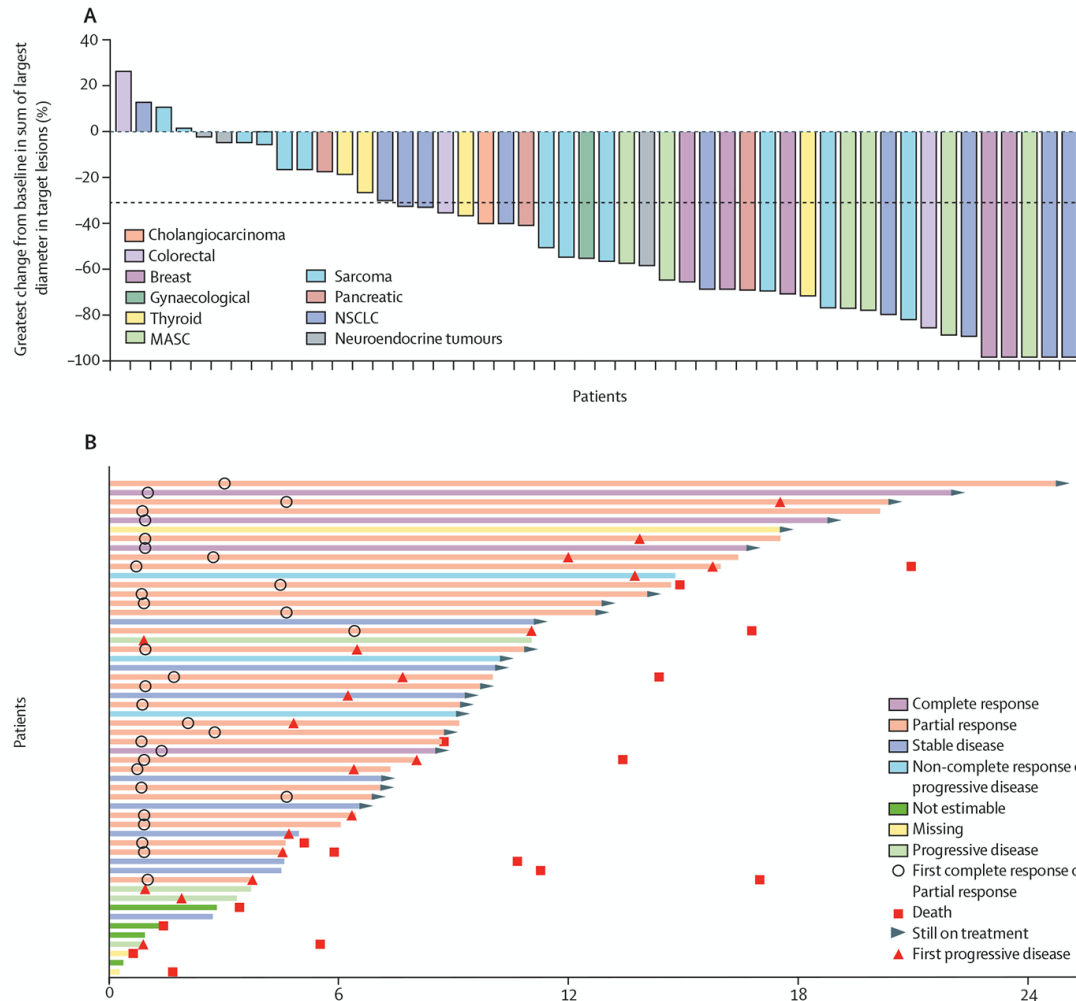
Regorafenib in Metastatic Osteosarcoma

- Phase II, multicenter, randomized, placebo controlled
- 42 patients, 12 centers
- Placebo controlled, crossover allowed



ALKA 372-001, STARTRK-1, STARTRK-2 Trials

Entrectenib for NTRK Fusions, Regardless of Histology

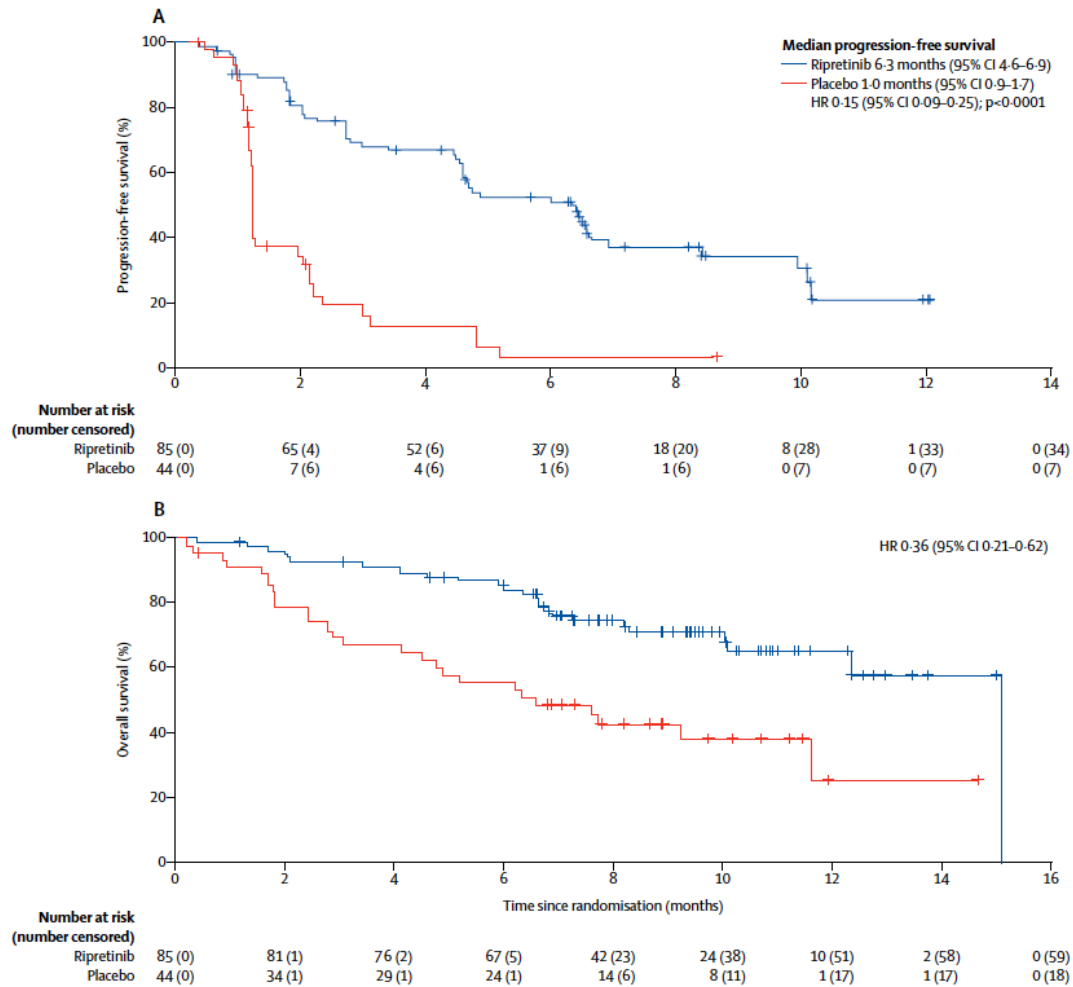


- Treated regardless of tumor type or gene rearrangement, 54 patients
- 10 tumor types, 19 histologies
 - **13 sarcoma patients**
- 12.9month follow up
- **7% CR, 50% PR**

Doebele et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncology* 21 (2): 271-282. 2020.

INVICTUS Trial

Ripretinib as a Fourth Line Agent in GIST



	Ripretinib group (n=85)	Placebo group (n=44)	p value
Confirmed objective response	8 (9%; 4–18)	0 (0%; 0–8)	0.0504
Complete response	0 (0%; 0–4)	0 (0%; 0–8)	..
Partial response	8 (9%; 4–18)	0 (0%; 0–8)	..
Stable disease (6 weeks)	56 (66%; 55–76)	9 (20%; 10–35)	..
Stable disease (12 weeks)	40 (47%; 36–58)	2 (5%; 1–16)	..
Progressive disease	16 (19%; 11–29)	28 (64%; 48–78)	..
Not evaluable	4 (5%)	3 (7%)	..
No response assessment	1 (1%)	4 (9%)	..

Data are n (%; 95% CI) or n (%). * Assessed by blinded independent central review.

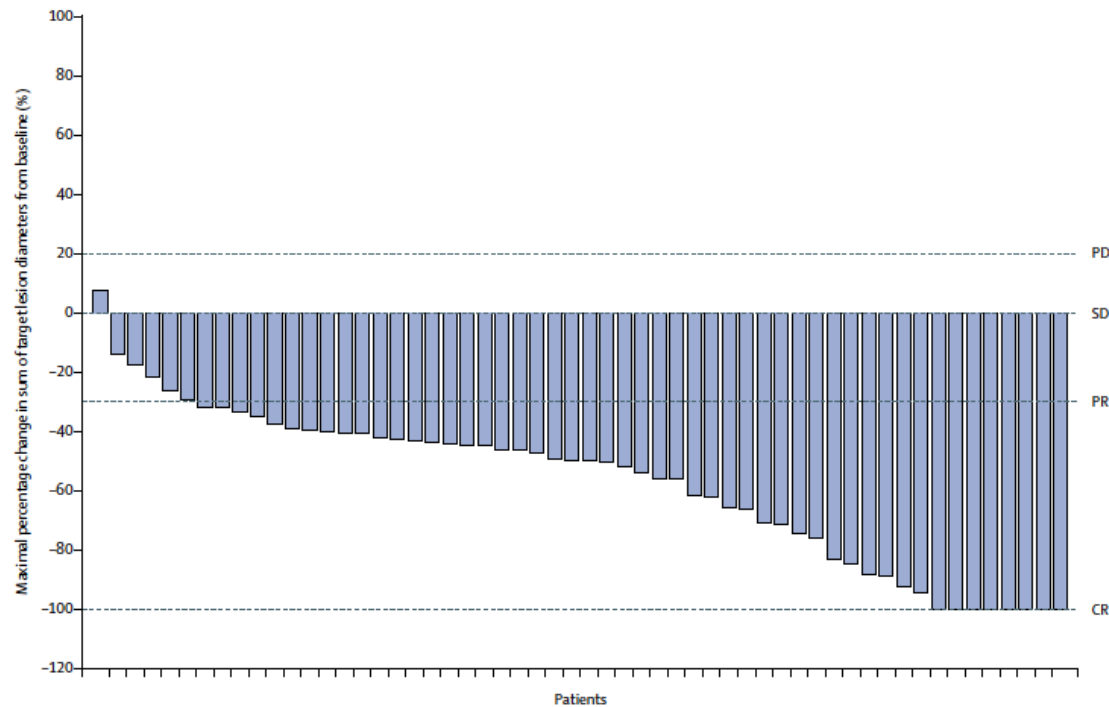
Table 2: Objective response rate*

Blay et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomized placebo-controlled, phase 3 trial. *Lancet Oncology* 21:923-34. 2020.

NAVIGATOR Trial

Avapritinib for PDGFR D842V Mutated GIST

- Multicenter Open-label, phase I trial
- 46 patients in dose escalation, 191 in dose expansion



	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

D842V=Asp842Val. mRECIST=Response Evaluation Criteria in Solid Tumors modified for patients with gastrointestinal stromal tumour. *Data cutoff on Nov 16, 2018.

Table 3: Best confirmed response by central assessment per mRECIST (version 1.1) in patients with PDGFRA D842V-mutant gastrointestinal stromal tumour*

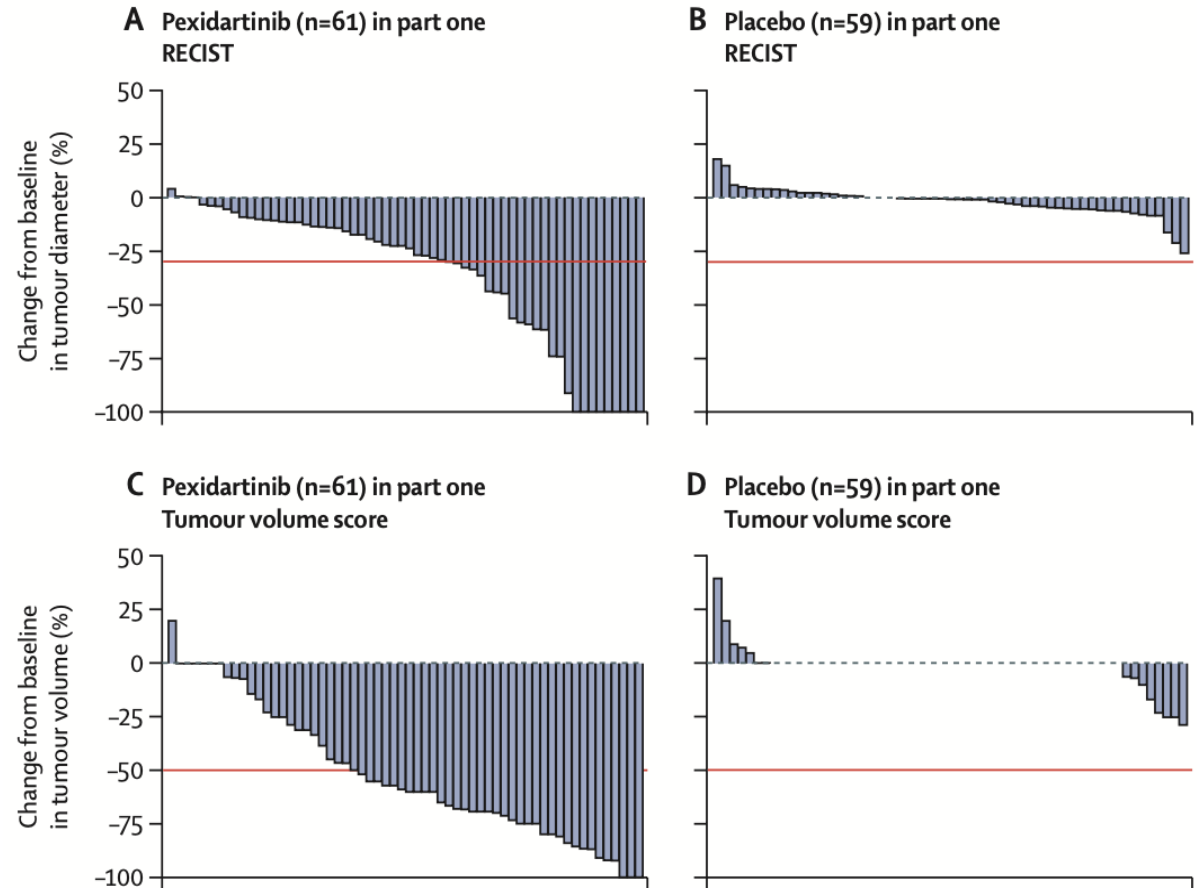
Heirrich et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicenter, open-label, phase 1 trial. *Lancet Oncology* 21(7): 935-946. 2020.

ENLIVEN Trial

Pexidartinib in PVNS/TGCT

Phase III, placebo-controlled trial

- PVNS/TGCT, diffuse type
- 120 patients, evaluated at week 25
- Overall Response Rate **39% vs 0%**



Updates in Sarcoma

- Pazopanib can be considered in the neoadjuvant setting for localized STS those that are fit for AIM chemotherapy
- Pazopanib can be used for treatment of either Extraskeletal Myxoid Chondrosarcoma, typical or advanced Solitary Fibrous Tumor, not dedifferentiated
- Tazemetostat is approved for INI-1 deficient Epithelioid Sarcoma
- Regorafenib has efficacy in Metastatic or Unresectable Osteosarcoma
- Entrectinib is approved with NTRK fusion tumors
- Avapritinib and Ripritinib are now approved for GIST
- Pexidartinib is approved and available for PVNS/TGCT