Research Update for Soft Tissue Sarcomas

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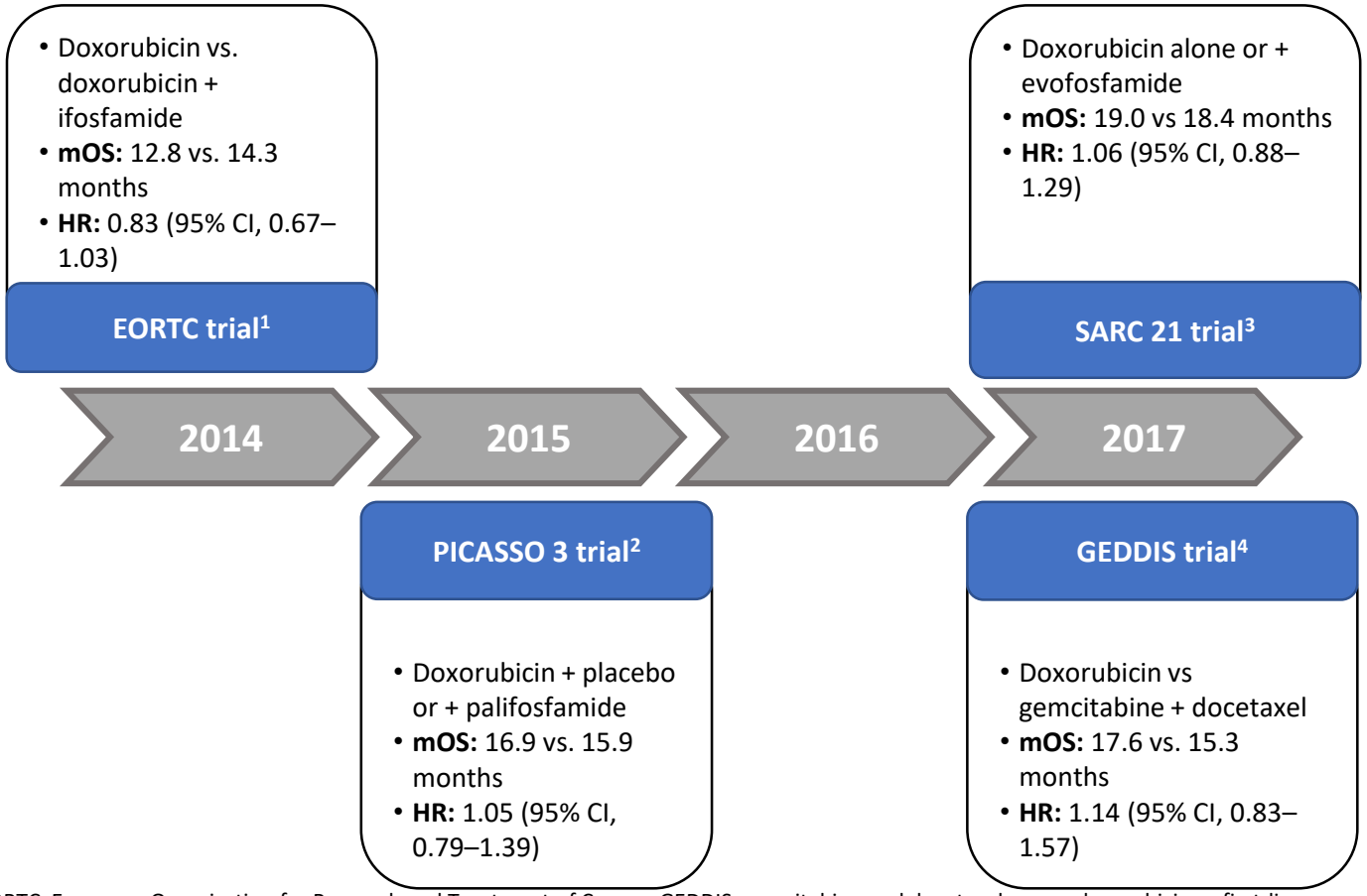
Institute of Cancer Research

Disclosures

- Receipt of grants/research support:
  - MSD
  - GSK

- Receipt of consultation fees:
  - Adaptimmune
  - Athenex
  - Bayer
  - Boehringer Ingelheim
  - Blueprint
  - Clinigen
  - Eisai
  - Epizyme
  - Daichii
  - Deciphera
  - Immunedesign
  - Lilly
  - Merck
  - Pharmamar
  - Springworks
  - Tracon
  - Upto Date

Anthracyclines: First-line Trials



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.

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

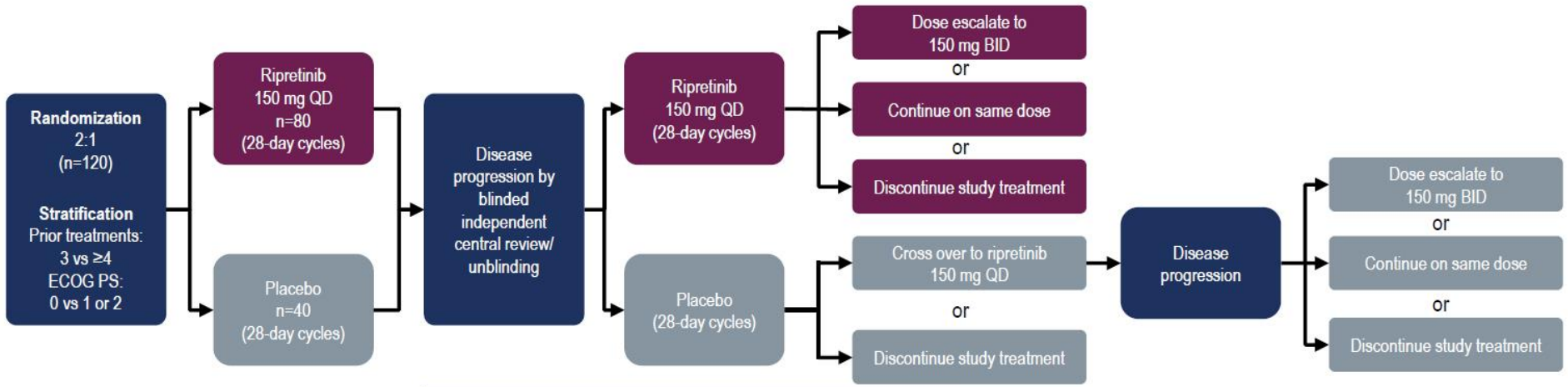
2nd-line and beyond

- Ifosfamide
- Gemcitabine/ docetaxel
- Gemcitabine/ DTIC
- Pazopanib
- Trabectedin
- Eribulin

Ripretinib

INVICTUS: Randomized Phase 3 Study Design

Evaluated ripretinib as ≥4th line therapy in patients with advanced GIST



Primary endpoint

PFS

(per modified RECIST based on **B**linded **I**ndependent **C**entral **R**eview [BICR])

Select Secondary endpoints

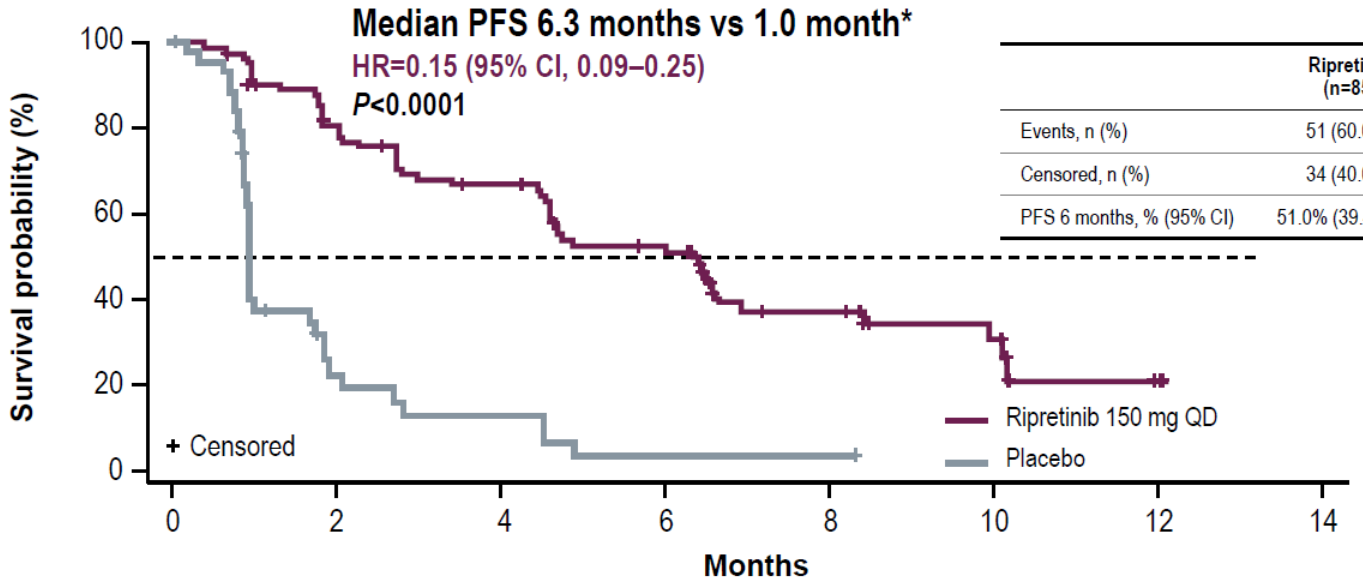
- **Objective response rate (ORR)** assessed by BICR (Key endpoint)
- **Overall survival (OS)**

Data cutoff
May 31, 2019

BARCELONA 2019 ESMO congress

Blay JY et al. Lancet Oncol 2020

85% Risk Reduction of Disease Progression or Death With Ripretinib Compared With Placebo



	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	51 (60.0%)	37 (84.1%)
Censored, n (%)	34 (40.0%)	7 (15.9%)
PFS 6 months, % (95% CI)	51.0% (39.4–61.4)	3.2% (0.2–13.8)

Number of patients at risk:

Ripretinib 150 mg QD	85	64	52	37	18	8	1	0
Placebo	44	7	4	1	1	0		

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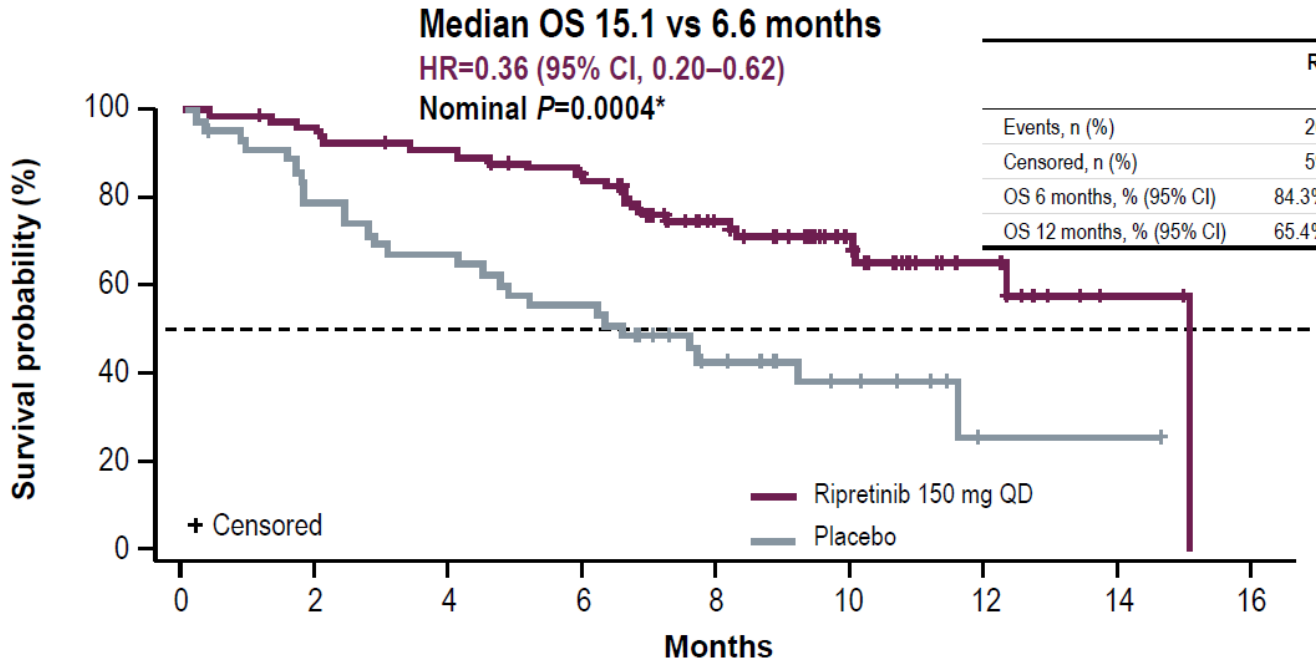
*Double-blind period.

Blay JY et al. Lancet Oncol 2020

OS Benefit: 64% Risk Reduction of Death Compared With Placebo



	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	26 (30.6%)	26 (59.1%)
Censored, n (%)	59 (69.4%)	18 (40.9%)
OS 6 months, % (95% CI)	84.3% (74.5–90.6)	55.9% (39.9–69.2)
OS 12 months, % (95% CI)	65.4% (51.6–76.1)	25.9% (7.2–49.9)

Number of patients at risk:									
Ripretinib 150 mg QD	85	81	76	67	42	24	10	2	0
Placebo	44	34	29	24	14	8	1	1	0

BARCELONA 2019 ESMO congress

*Due to hierarchal testing procedures of the end points, the OS end point could not be formally tested because the ORR was not statistically significant.

Blay JY et al. Lancet Oncol 2020

TEAEs in >10% of Patients

Preferred Term	Ripretinib any grade (n=85)	Placebo any grade (n=43)*
Any TEAE or grade 3/4 TEAE**	**84 (98.8%)**	**42 (97.7%)**
Alopecia	44 (51.8%)	2 (4.7%)
Fatigue	36 (42.4%)	10 (23.3%)
Nausea	33 (38.8%)	5 (11.6%)
Abdominal pain	31 (36.5%)	13 (30.2%)
Constipation	29 (34.1%)	8 (18.6%)
Myalgia	27 (31.8%)	5 (11.6%)
Diarrhea	24 (28.2%)	6 (14%)
Decreased appetite	23 (27.1%)	9 (20.9%)
Palmar-plantar erythrodysesthesia syndrome	18 (21.2%)	0
Vomiting	18 (21.2%)	3 (7%)
Headache	16 (18.8%)	2 (4.7%)
Weight decreased	16 (18.8%)	5 (11.6%)

Preferred Term	Ripretinib any grade (n=85)	Placebo any grade (n=43)*
Arthralgia	15 (17.6%)	2 (4.7%)
Blood bilirubin increased	14 (16.5%)	0 (0%)
Edema peripheral	14 (16.5%)	3 (7%)
Muscle spasms	13 (15.3%)	2 (4.7%)
Anemia	12 (14.1%)	8 (18.6%)
Hypertension	12 (14.1%)	2 (4.7%)
Asthenia	11 (12.9%)	6 (14%)
Dry skin	11 (12.9%)	3 (7%)
Dyspnea	11 (12.9%)	0
Hypophosphatemia	9 (10.6%)	0
Lipase increased	9 (10.6%)	0
Pruritus	9 (10.6%)	2 (4.7%)
Stomatitis	9 (10.6%)	0

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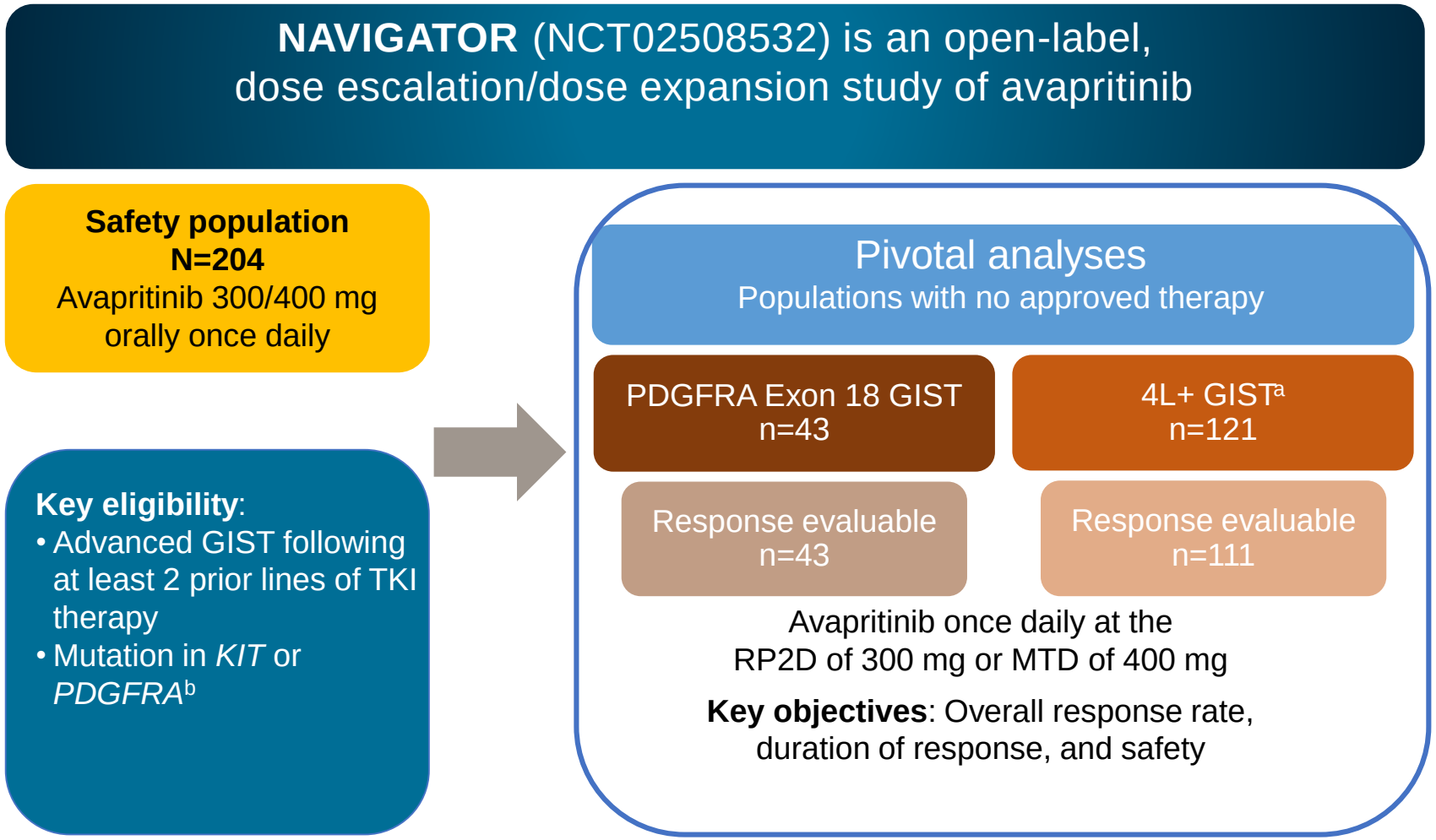
*44 patients were randomized to placebo, but 1 did not receive treatment.
**Regardless of causality

Blay JY et al. Lancet Oncol 2020

Avapritinib

Analysis of avapritinib starting dose 300/400 mg QD in ≥4th line (4L+) and PDGFRA exon 18 mutated GIST



[a]Enrollment criteria specified that patients were required to have received only ≥2 prior lines of TKI therapy (ie, analysis population of 3L+), observed enrollment reflected a more heavily pretreated population (ie, 4L+). [b]Mutational analysis was performed locally and confirmed centrally. 3L, 3rd line; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

Heinrich M et al. Lancet Oncol 2020

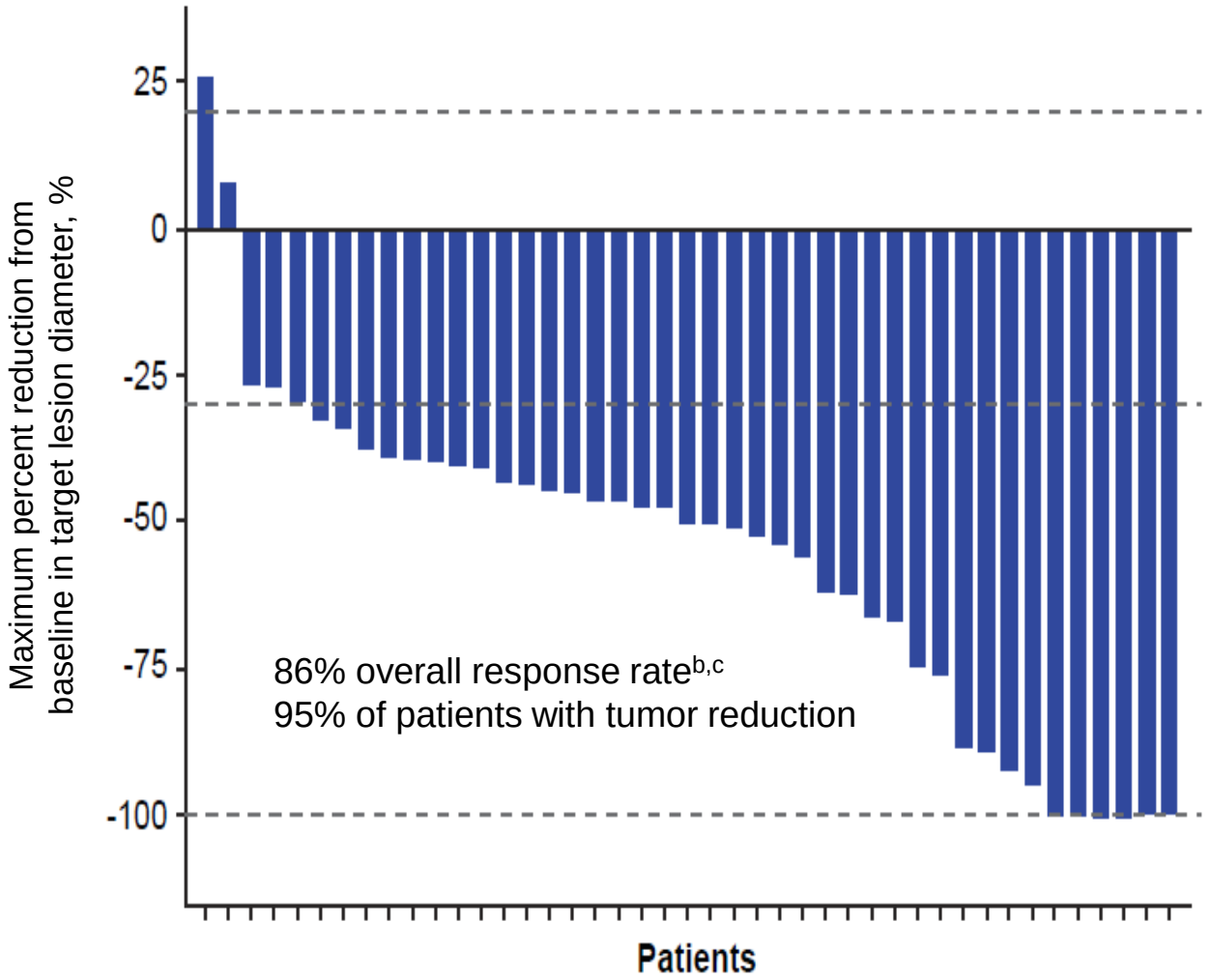
Demographics and baseline characteristics
Avapritinib starting dose 300/400 mg QD

Characteristic	PDGFRA exon 18 (n=43)	4L+ (n=121)
Age, median years (min–max)	64 (29–90)	59 (33–80)
GIST mutational subtype, n (%)		
KIT	0	110 (91)
PDGFRA D842V	38 (88.4)	8 (7)
PDGFRA exon 18 non-D842V[a]	5 (11.6)	3 (2)
No. prior lines of TKIs, median (range)	1 (0–5)	4 (3–11)
n (%)	0: 5 (12)	3: 40 (33)
	1: 19 (44)	4: 35 (29)
	≥2: 19 (44)	≥5: 46 (38)
Metastatic disease, n (%)	42 (98)	119 (98)
Largest target lesion, n (%)		
≤5 cm	20 (47)	40 (33)
>5 to ≤10 cm	14 (33)	57 (47)
>10 cm	9 (21)	22 (18)

[a]*PDGFRA* exon 18 non-D842V mutations including D842Y, DI 842-845V, I843_D846del, D842-H845, and DI 842-843V. QD, once daily.

Heinrich M et al. Lancet Oncol 2020

Antitumor activity in response-evaluable patients[a]
PDGFRA exon 18 GIST – avapritinib starting dose 300/400 mg QD (central radiology)



[a]Response-evaluable patients were comprised of patients who had ≥1 target lesion assessed at baseline by central radiology review and had ≥1 post-baseline disease assessment by central radiology. [b]Proportion of response-evaluable patients with a confirmed best response of complete response or partial response, confirmed by central radiology and assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST 1.1) in patients treated with avapritinib starting dose 300/400 mg QD. [c]1 partial response pending confirmation. QD, once daily.

Heinrich M et al. Lancet Oncol 2020

Most common AEs occurring in ≥20% of safety population Avapritinib starting dose 300/400 mg QD

n (%)	Safety Population (N=204)			
	All AEs		Treatment-related AEs	
	All Grades[b]	Grade ≥3[c]	All Grades[b]	Grade ≥3[c]
Nausea	131 (64)	5 (3)	121 (59)	-
Fatigue	113 (55)	15 (7)	96 (47)	13 (6)
Anemia	102 (50)	58 (28)	74 (36)	33 (16)
Cognitive effects[a]	84 (41)	8 (4)	84 (41)	8 (4)
Periorbital edema	83 (41)	-	82 (40)	-
Vomiting	78 (38)	4 (2)	65 (32)	-
Decreased appetite	77 (38)	6 (3)	58 (28)	-
Diarrhea	76 (37)	10 (5)	65 (32)	6 (3)
Increased lacrimation	67 (33)	-	62 (30)	-
Peripheral edema	63 (31)	-	55 (27)	-
Face edema	50 (25)	-	49 (24)	-
Constipation	46 (23)	-	-	-
Dizziness	45 (22)	-	-	-
Hair color changes	43 (21)	-	42 (21)	-
Blood bilirubin increased	43 (21)	9 (4)	-	8 (4)
Abdominal pain	41 (20)	11 (5)	-	-

- Most AEs were grade 1–2, with a higher incidence of commonly reported AEs in the 400 mg vs 300 mg QD dose group
- No treatment-related grade 5 AEs reported
- Most patients were able to remain on treatment with dose modifications when needed; relative dose intensity was 86% at 300 mg QD and 73% at 400 mg QD
- 8.3% of patients discontinued avapritinib for treatment-related toxicity
  - 2.0% discontinued treatment for cognitive effects

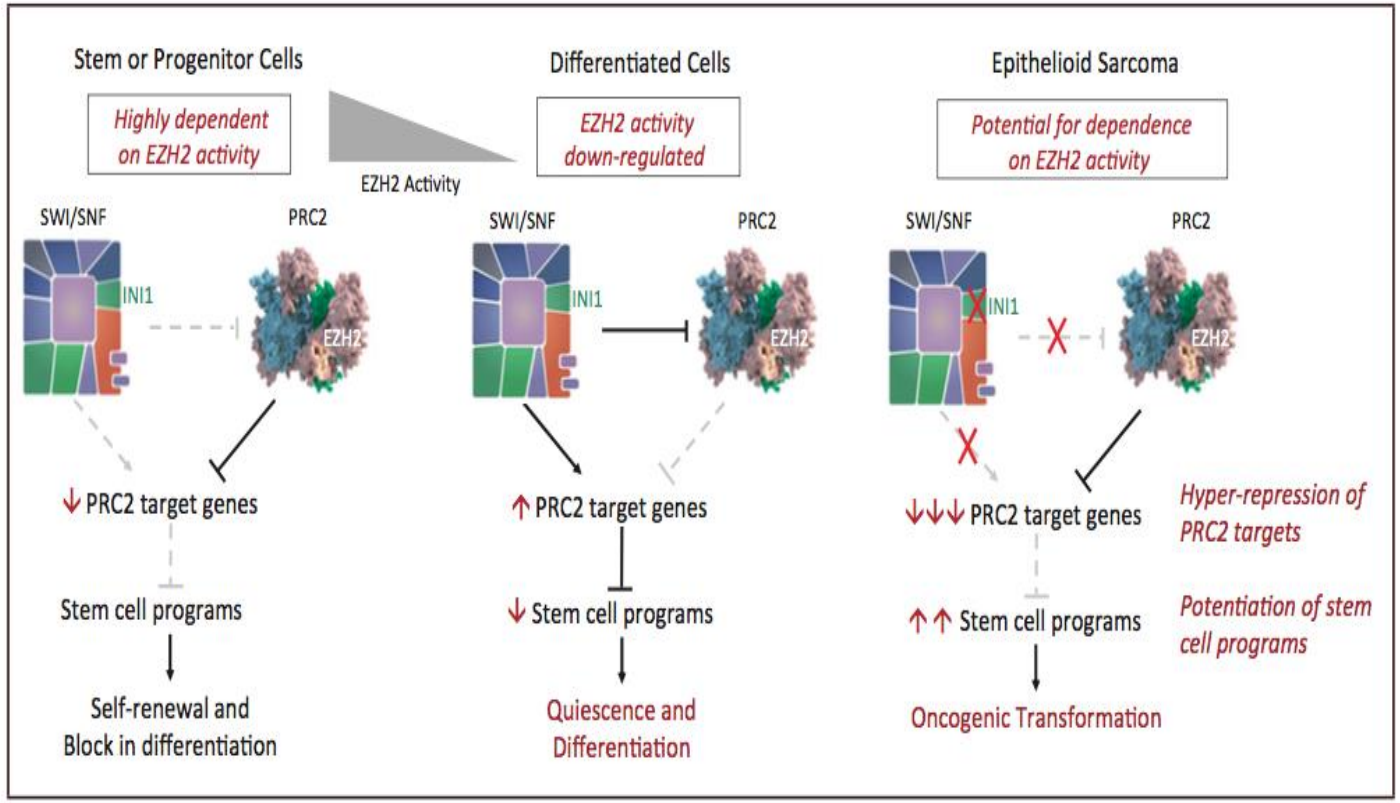
[a]Cognitive effects include pooled terms of memory impairment (29%), cognitive disorder (11%), confusional state (7%), and encephalopathy (1%). Blueprint Medicines considered all cognitive effect AEs as treatment-related in this analysis. [b]All grade AEs occurring in ≥20% of patients. [c]Grade ≥3 AEs occurring in ≥2% of patients. Note: 3 events of intracranial hemorrhage occurred; 2 were grade 3, 1 was grade 1.
AE, adverse event; QD, once daily.

Heinrich M et al. Lancet Oncol 2020

EZH2 inhibitors in Epithelioid Sarcoma

- Loss of INI1 creates oncogenic dependency on EZH2

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

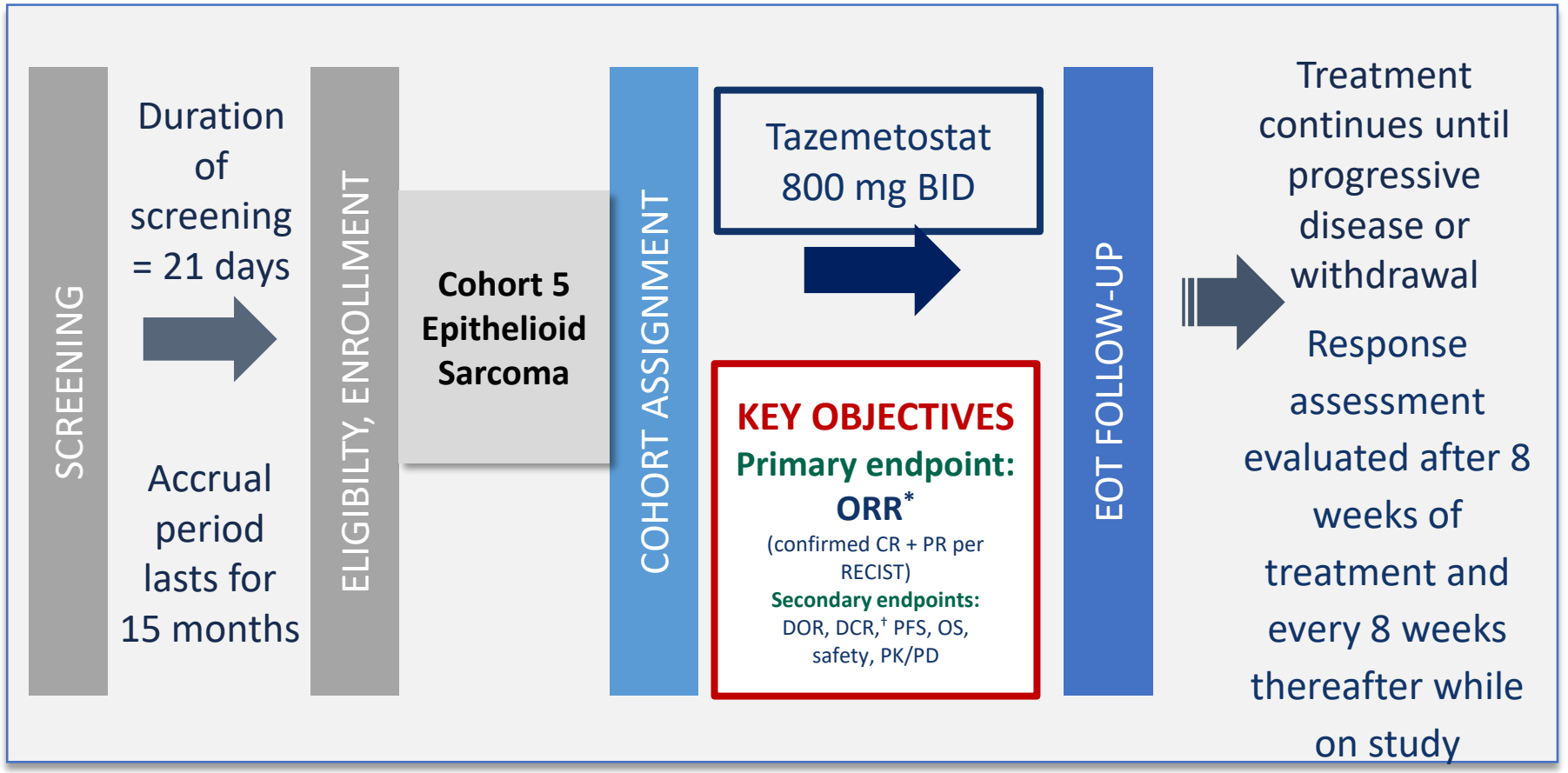


Patient Selection: INI1 loss in Sarcomas

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

Tazemetostat: Phase 2, open-label, Multi-Center Trial



* Objective response: RECIST 1.1 – confirmed complete response or partial response at week 24. † Disease control: RECIST 1.1 – confirmed complete. BID, twice daily dosing; CR, complete response; DCR, disease control response; DOR, duration of response; EOT, end of trial; ES, epithelioid sarcoma; ORR, objective response rate; OS, overall response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response

Stacchiotti S et al. ASCO 2019

Tazemetostat: Baseline Demographics: 62 PATIENTS

Characteristic	Patients (N=62*)
Age (years), mean (SD)	37 (15.1)
Male/female, n (%)	39 (63)/23 (37)
Subtype,† n (%)	
Proximal	27 (44)
Distal	31 (50)
Missing	4 (6)
Stage at diagnosis,¶ n (%)	
I	2 (3)
II	7 (11)
≥III	44 (71)

Characteristic	Patients (N=62*)
Evidence of progression at baseline, Yes/No, n (%)	59 (95)/3 (5)
Lines of prior anticancer therapy, n (%)	
Median (range)	1 (0–9)
0	24 (39)
1–3+	38 (61)
ECOG Status, n (%)	
0	36 (58)
1	21 (34)
2	5 (8)

* All adult patients were INI1 negative; † There were 3 (5%) patients with unknown subtype which reflected data not included by investigator; ¶ There were 9 patients without staging at diagnosis. ECOG, Eastern Cooperative Oncology Group.

Stacchiotti S et al. ASCO 2019

Tazemetostat: Primary Endpoint: RECIST ORR

Endpoint Category (RECIST), n (%)	Treatment-Naive (n=24)	Prior 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)
SD	15 (63)	20 (53)	35 (56)
PD*	2 (8)	11 (29)	13 (21)

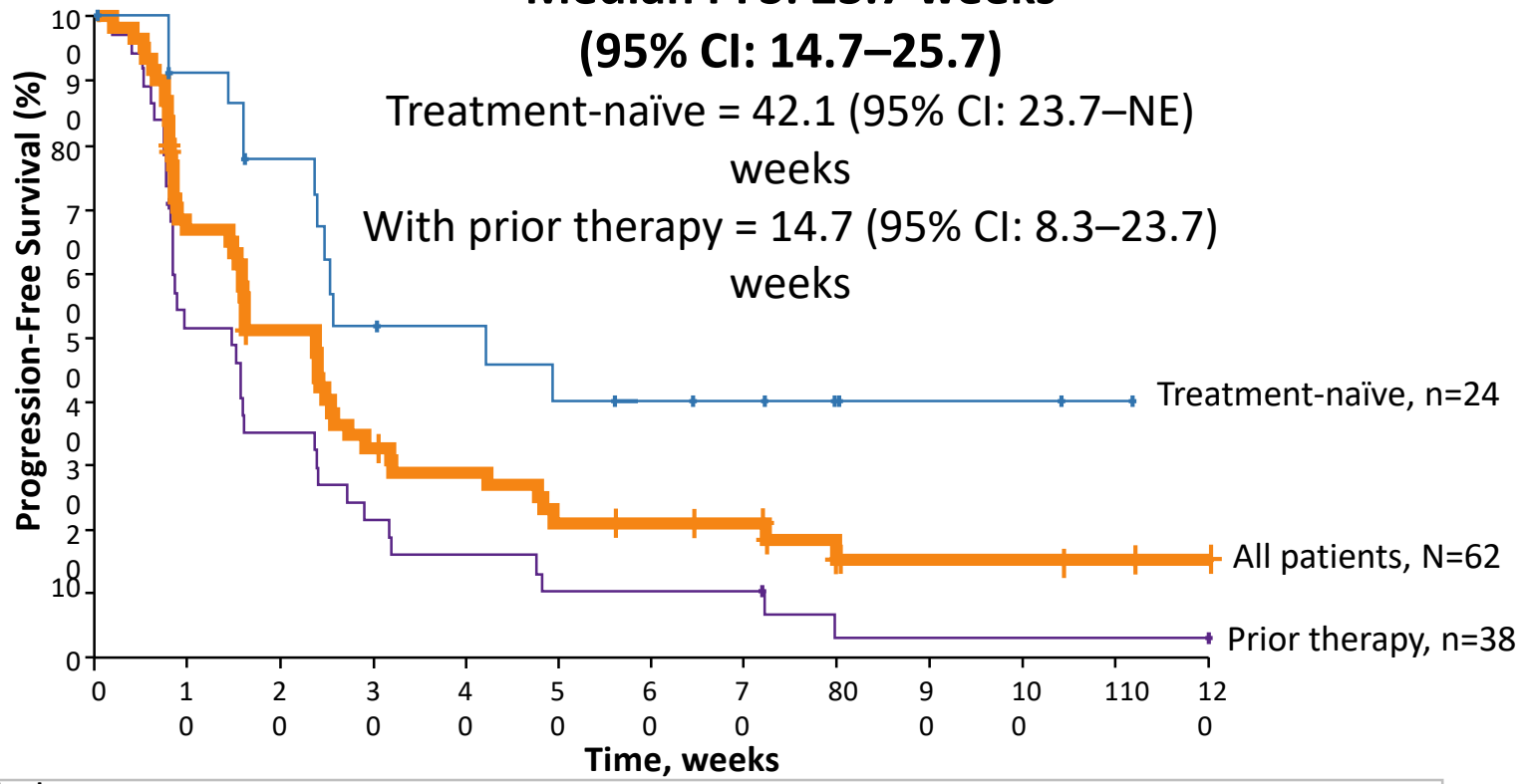
*Objective response: RECIST 1.1 – confirmed complete response or partial response at week 24.
CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

Stacchiotti S et al. ASCO 2019

Tazemetostat: Progression-free Survival

Median follow-up: 59.9 weeks

Median PFS: 23.7 weeks
(95% CI: 14.7–25.7)
Treatment-naïve = 42.1 (95% CI: 23.7–NE) weeks
With prior therapy = 14.7 (95% CI: 8.3–23.7) weeks



Patients at Risk:													
Treatment-naive:	24	20	15	10	9	7	6	5	3	2	2	1	0
Prior therapy:	38	19	13	8	6	4	4	4	1	1	1	1	1
All patients:	62	39	28	18	15	11	10	9	4	3	3	2	1

CI, confidence interval; NE, not estimable; PFS, progression-free survival.
+ censored

Stacchiotti S et al. ASCO 2019

Tazemetostat: Frequently Occurring Adverse Events

Category, n (%)	All TEAEs (N=62)		Treatment-related AEs (N=62)	
	Any Grade *	Grade ≥3 †	Any Grade *	Grade ≥3 †
NON-HEMATOLOGIC AEs				
Fatigue	24 (39)	1 (2)	17 (27)	1 (2)
Nausea	22 (35)	0	17 (27)	0
Cancer pain	20 (32)	3 (5)	3 (5)	0
Decreased appetite	16 (26)	3 (5)	10 (16)	1 (2)
Vomiting	15 (24)	0	10 (16)	0
Constipation	13 (21)	0	5 (8)	0
Headache	11 (18)	0	4 (6)	0
Cough	11 (18)	0	0	0
Diarrhea	10 (16)	0	8 (13)	0
Weight decreased	10 (16)	4 (6)	4 (6)	2 (3)
Dyspnea	8 (13)	4 (6)	0	0
Pleural effusion	7 (11)	4 (6)	0	0
HEMATOLOGIC AEs				
Anemia	10 (16)	8 (13)	6 (10)	4 (6)
Thrombocytopenia	2 (3)	0	0	0
Lymphopenia	1 (2)	0	1 (2)	0
Neutropenia	0	0	0	0

* All grades TEAEs reported as occurring in ≥10% of patients; † Grade ≥3 TEAEs reported in ≥5% patients; ¶ Data not shown.
AE, adverse event; ES, epithelioid sarcoma; TEAE, treatment-emergent adverse event

- Only 1 patient discontinued due to an AE
- There were no treatment-related deaths
- Safety profile was consistent between ES and all cohorts (ES and non-ES patients)¶

Stacchiotti S et al. ASCO 2019

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

- Rare – occur in diverse range of tumors

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

Trk Receptor Signaling

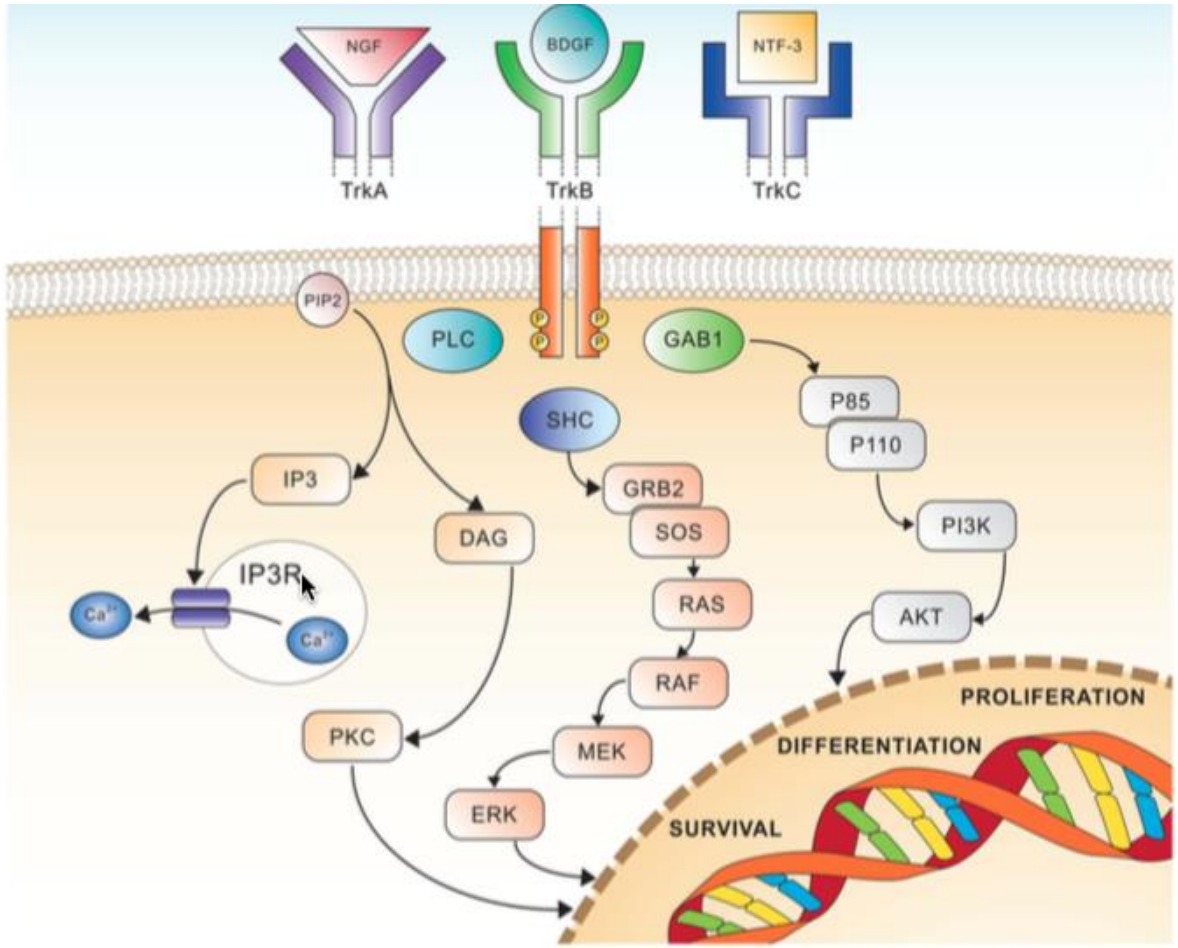


Figure 1 Schematic view of Trk receptors signalling, showing the three major pathways involved in cell differentiation and survival. AKT, v-akt murine thymoma viral oncogene homologue; BDGF, brain-derived growth factor; DAG, diacyl-glycerol; ERK extracellular signal-regulated kinase; GAB1, GRB2-associated-binding 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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

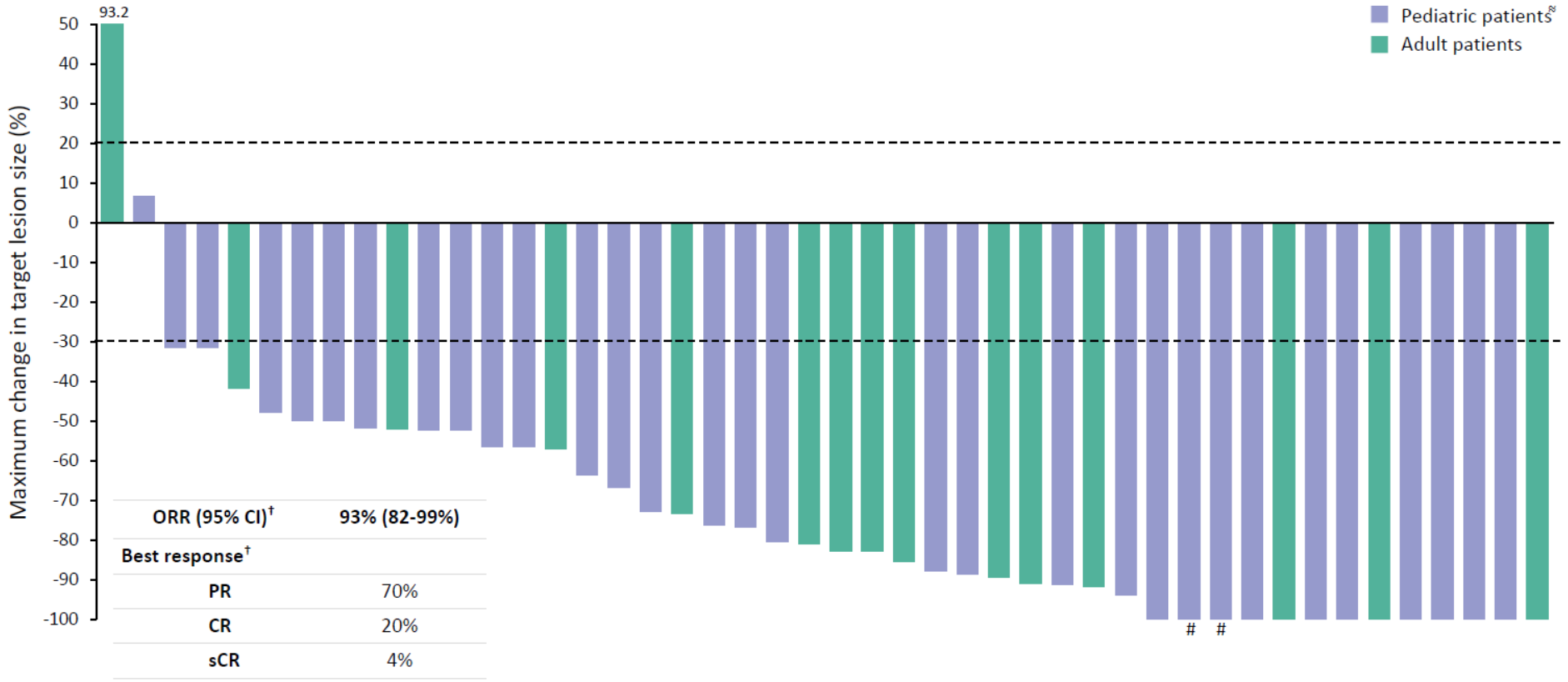
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

Robert C Doebele, Alexander Drilon*, Luis Paz-Ares, Salvatore Siena, Alice T Shaw, Anna F Farago, Collin M Blakely, Takashi Seto, Byung Chul Cho, Diego Tosi, Benjamin Besse, Sant P Chawla, Lyudmila Bazhenova, John C Krauss, Young Kwang Chae, Minal Barve, Ignacio Garrido-Laguna, Stephen V Liu, Paul Conkling, Thomas John, Marwan Fakih, Darren Sigal, Herbert H Loong, Gary L Buchschacher Jr, Pilar Garrido, Jorge Nieva, Conor Steuer, Tobias R Overbeck, Daniel W Bowles, Elizabeth Fox, Todd Riehl, Edna Chow-Maneval, Brian Simmons, Na Cui, Ann Johnson, Susan Eng, Timothy R Wilson, George D Demetri, on behalf of the trial investigators*

Larotrectinib in *TRK* fusion sarcomas

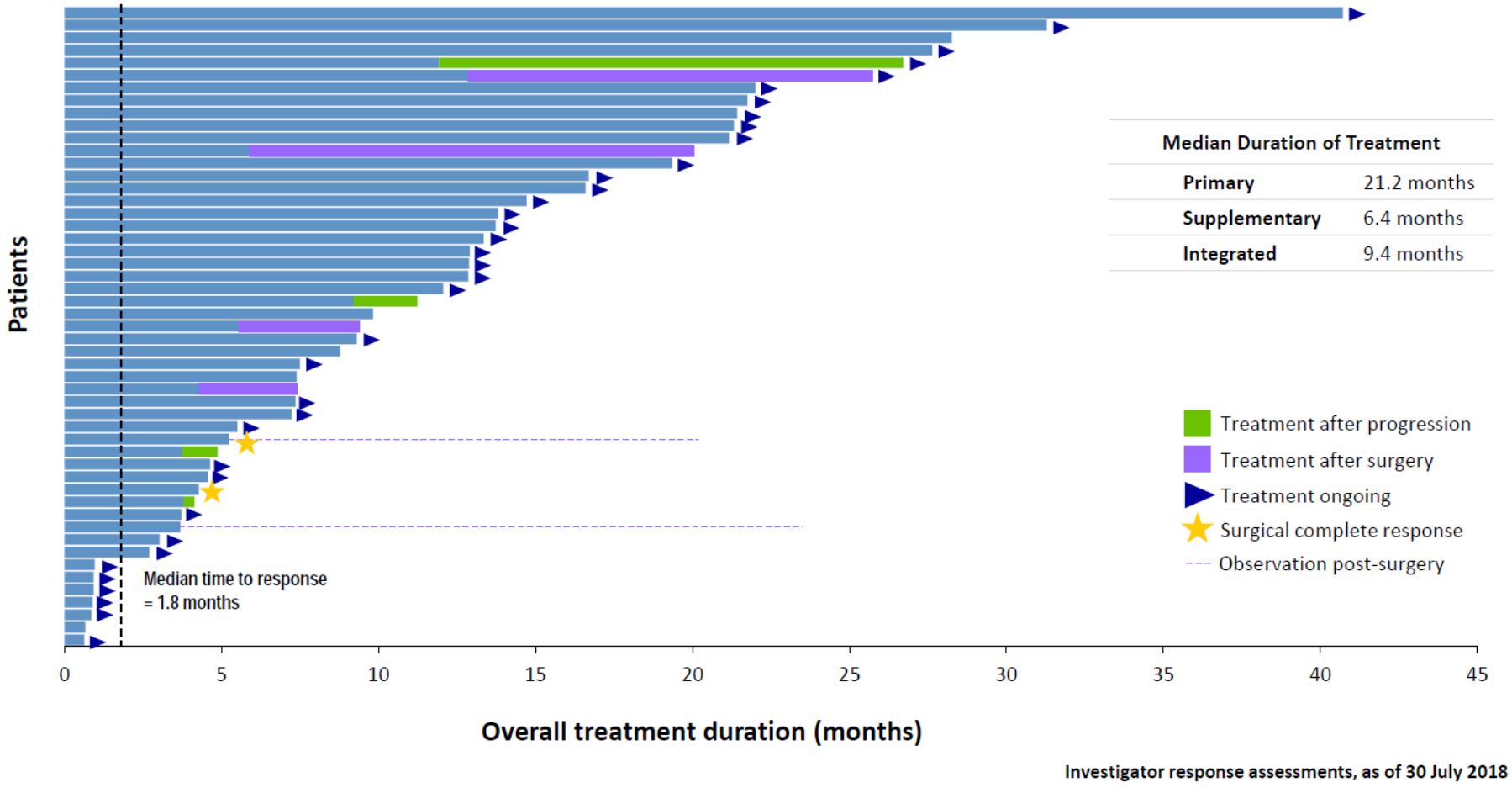


[†]n=46 patients; includes 3 unconfirmed PRs pending confirmation; does not include 5 patients continuing on study and awaiting initial response assessment.
[≈]Age <21 years. [#]sCR. CR, complete response; ORR, objective response; PR, partial response; sCR, surgical complete response

Investigator response assessments, as of 30 July 2018

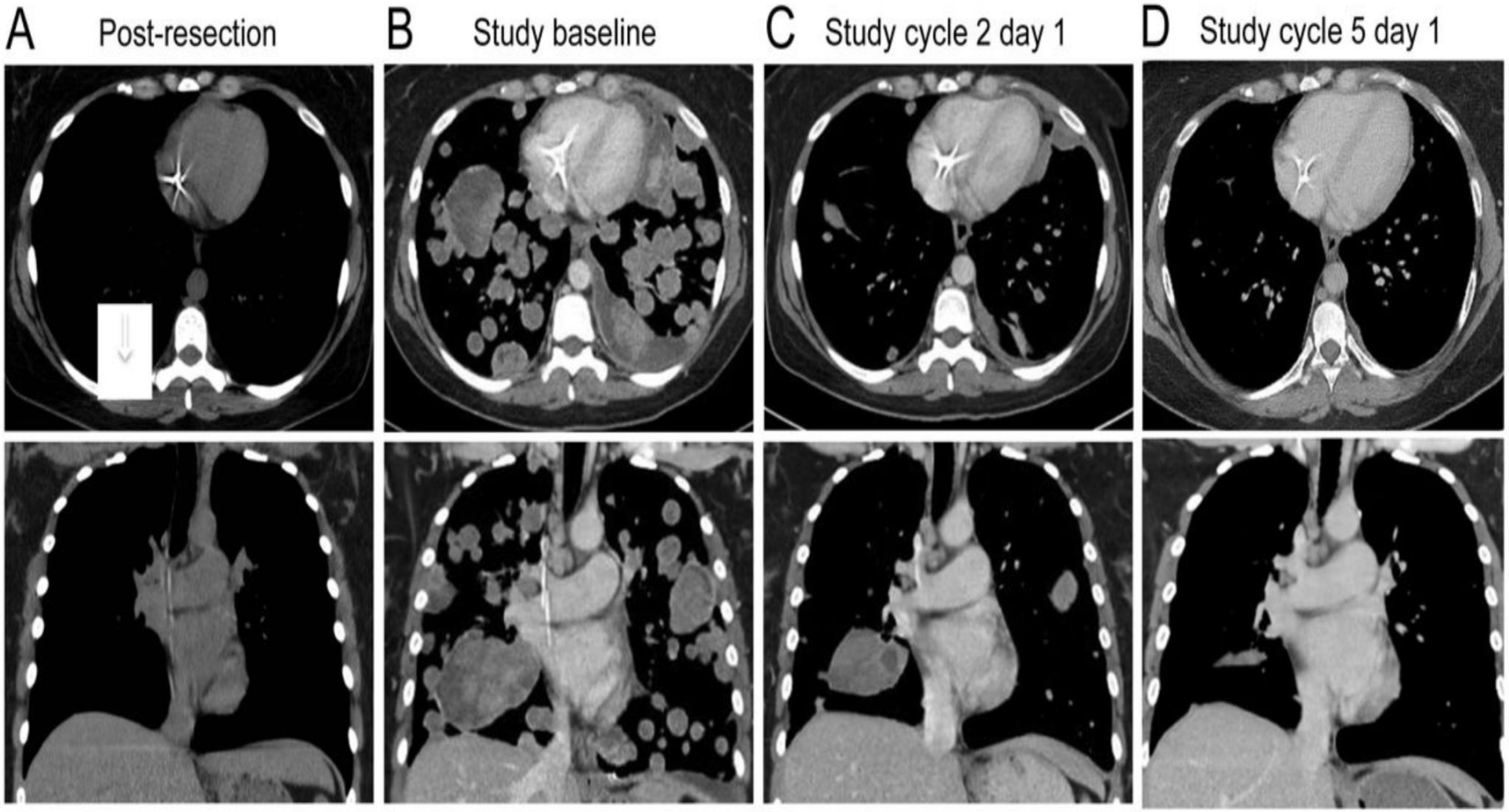
Federman N et al. CTOS 2018

Larotrectinib: Duration of treatment



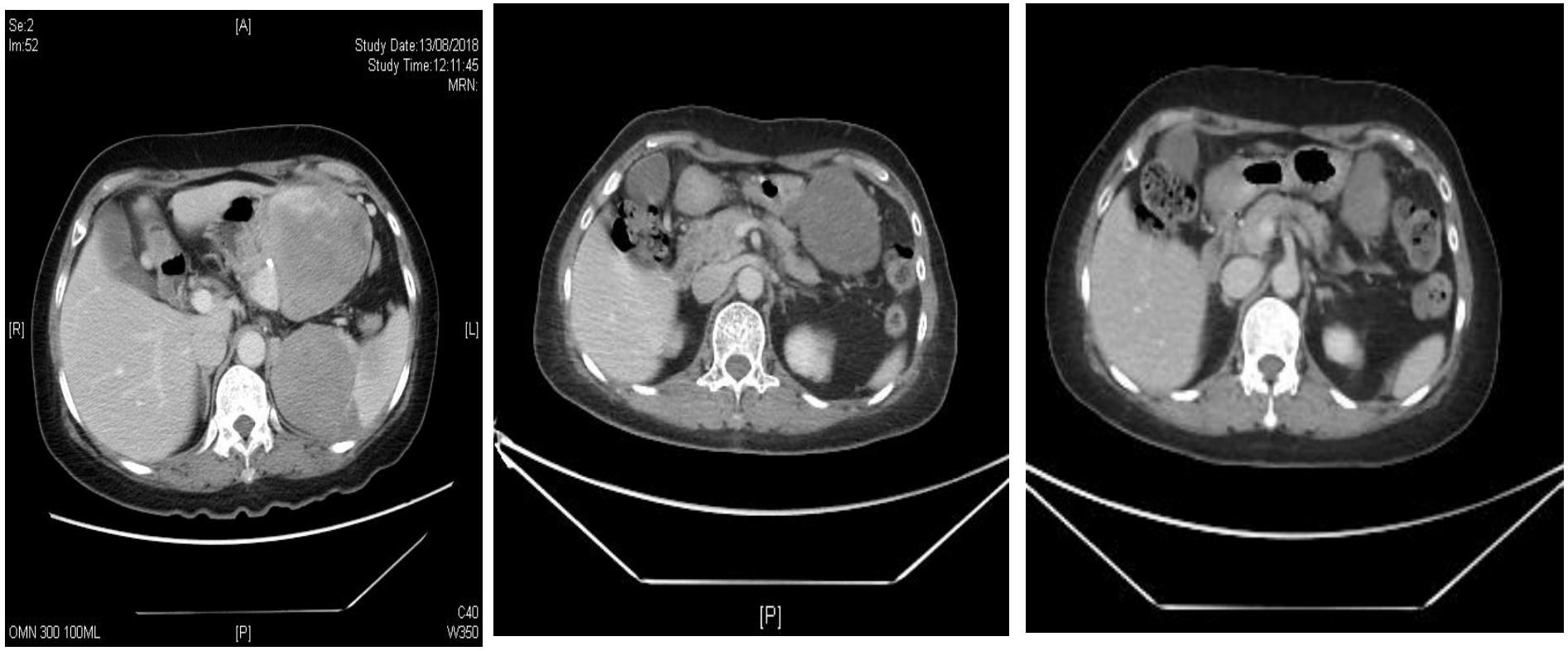
Federman N et al. CTOS 2018

Response in sarcoma with *LMNA-NTRK1* fusion



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

Figure 1: Radiological response in a patient with a high grade sarcoma with histiocytic differentiation (ETV6:NTRK3 exon 14) treated with entrectinib (clinical trial)



Baseline

~ 3 months after treatment

Nadir achieved at ~6 months after treatment

Alveolar Soft Part Sarcoma (ASPS)

Phase II Axitinib + Pembrolizumab

Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial

Breelyn A Wilky, Matteo M Trucco, Ty K Subhawong, Vaia Florou, Wungki Park, Deukwoo Kwon, Eric D Wieder, Despina Kolonias, Andrew E Rosenberg, Darcy A Kerr, Efrosyni Sfakianaki, Mark Foley, Jaime R Merchan, Krishna V Komanduri, Jonathan C Trent

Wilky BA et al. Lancet Oncol 2019

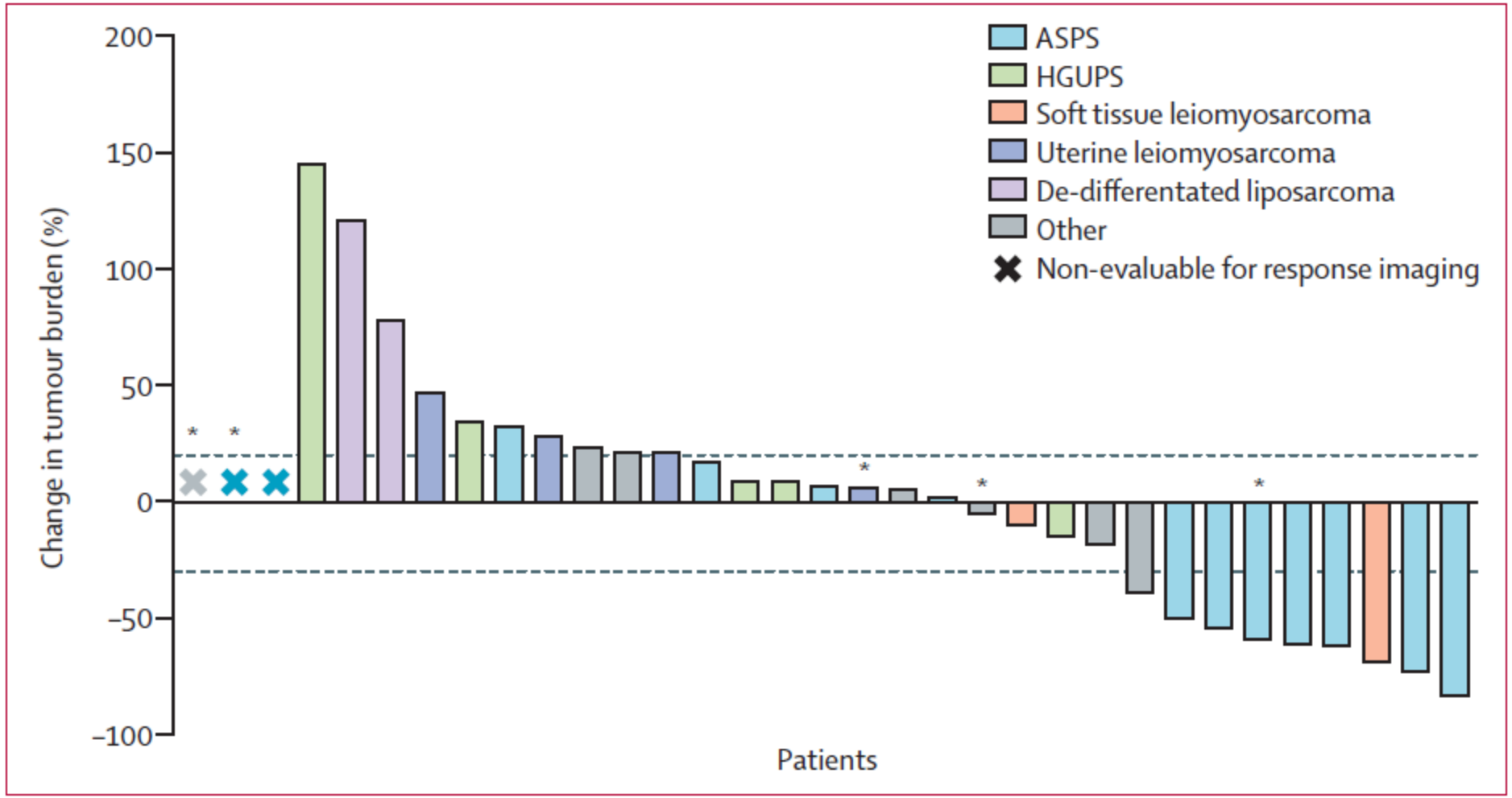


Figure 3: **Change from baseline in tumour burden**

Each bar represents one patient (n=30). Three patients were removed from the study before radiographic imaging assessments; two for clinical progression, and one for toxicity. Dashed lines indicate RECIST criteria for progressive disease (+20%) or partial response (−30%). ASPS=alveolar soft part sarcoma. HGUPS=high-grade undifferentiated pleomorphic sarcoma. RECIST=response evaluation criteria in solid tumors. *These patients met criteria for progression due to non-target lesion progression, emergence of new lesions, or clinical deterioration; bars represent best change in dimension of target lesions.

Wilky BA et al. Lancet Oncol 2019

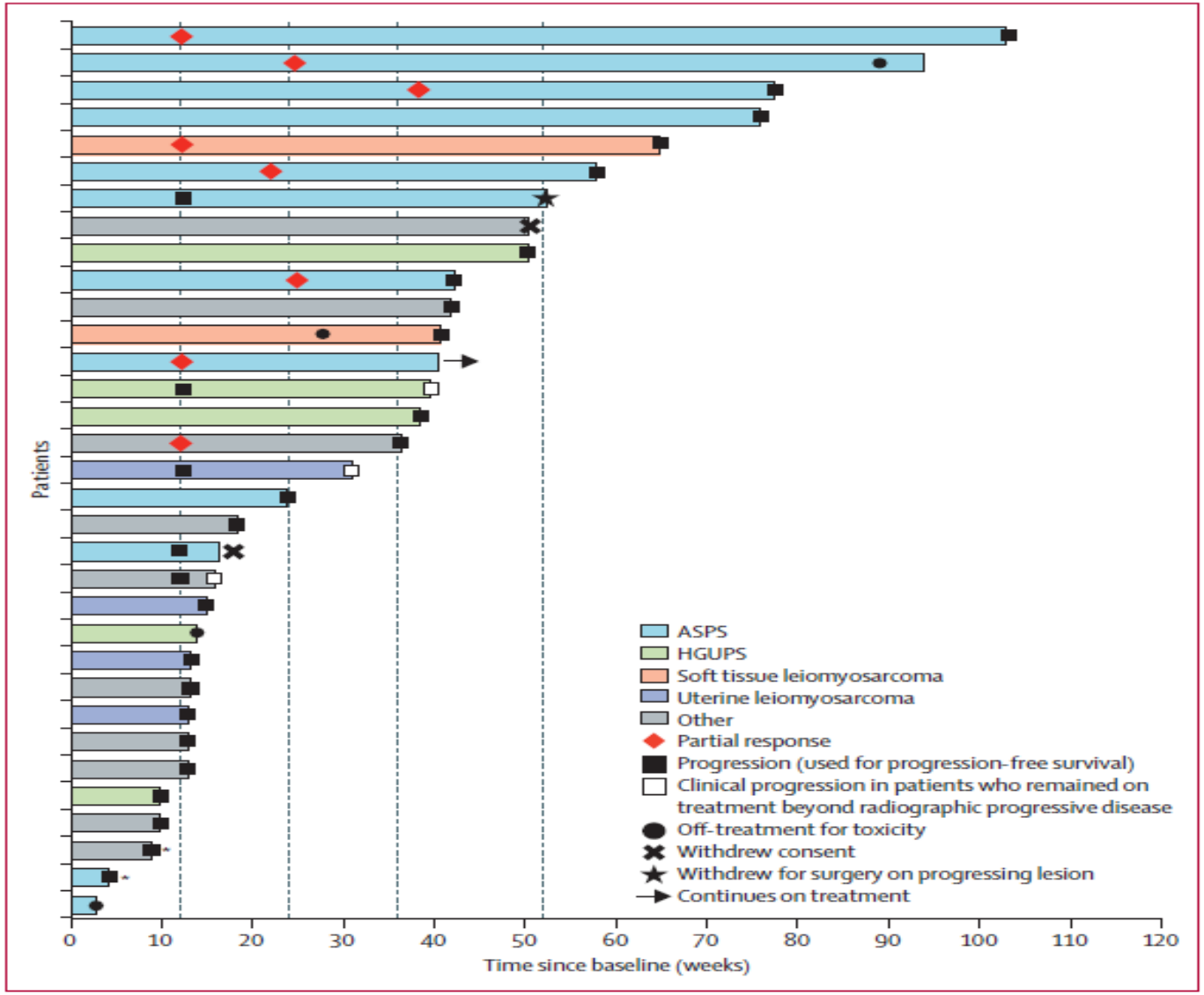


Figure 4: **Duration of responses**
Each bar represents one patient on study (n=33) and dashed lines indicate 12, 24, 36, and 52 weeks. Black boxes are the timepoint at which radiographic progression occurred that was used in analysis. Three patients continued on therapy after radiographic progression due to clinical benefit or changes in tumour appearance suggestive of necrosis. Patients without partial response or progression noted achieved stable disease during interim scans. *Did not have radiographic confirmation of progression. ASPS=alveolar soft part sarcoma. HGUPS=high-grade undifferentiated pleomorphic sarcoma.

Wilky BA et al. Lancet Oncol 2019

Phase II Axitinib + Pembrolizumab

- 32 evaluable for response
- Partial response: 8 (25%, 95%CI 12.1-43.8)
  - ASPS: 6/ 11
  - Epithelioid sarcoma: 1 patient
  - Soft tissue leiomyosarcoma: 1 patient
- Stable disease: 9 (28%)
- Clinical benefit rate: 17 (53%, 95%CI 35-70.5)

Wilky BA et al. Lancet Oncol 2019

	Grade 1 or 2	Grade 3	Grade 4
Fatigue	26 (79%)	..	..
Oral mucositis	22 (67%)	1 (3%)	..
Hypothyroidism or hyperthyroidism	21 (64%)	..	..
Nausea or vomiting	20 (61%)	2 (6%)	..
Nasopharyngeal congestion	18 (55%)	..	..
Diarrhoea	18 (55%)	1 (3%)	..
Elevated ALT, AST, or AP	17 (51%)	..	1 (3%)
Abdominal pain or dyspepsia	16 (48%)	1 (3%)	..
Tumour pain	15 (45%)	..	..
Arthralgia or myalgia	15 (45%)	..	..
Palmar-plantar erythrodysesthesia syndrome	15 (45%)	..	..
Hypertension	11 (33%)	5 (15%)	..
Anorexia or weight loss	12 (36%)	..	..
Cough	11 (33%)	..	..
Rash or pruritis or dry skin	9 (27%)	..	..
Constipation	9 (27%)	..	..
Mucositis rectal or vaginal inflammation	6 (18%)	..	..
Creatinine or BUN increased	6 (18%)	..	..
Haemoglobin increased	5 (15%)	..	..
Headache	5 (15%)	..	..
Haemoptysis	2 (6%)	1 (3%)	..
Hypertriglyceridemia or hyperlipidaemia	2 (6%)	..	1 (3%)
Pneumothorax	..	1 (3%)	..
Seizures*	..	2 (6%)	..
Autoimmune toxic effects	4 (12%)	5 (15%)	..
Hyperglycaemia	4 (12%)	1 (3%)	..
Autoimmune hepatitis	..	1 (3%)	..
Autoimmune colitis	..	1 (3%)	..
Autoimmune arthritis	..	2 (6%)	..

Data are n (%). Grade 1 and 2 events are reported here if they occurred in over 10% of patients. All grade 3 and 4 and autoimmune adverse events are shown. No treatment-related deaths occurred. Nasopharyngeal congestion includes nasal congestion, rhinorrhea, ear pain, or hoarseness. ALT=alanine aminotransferase. AST=aspartate aminotransferase. AP=alkaline phosphatase. BUN=blood urea nitrogen. *Two patients with alveolar soft part sarcoma and brain metastases previously treated with radiation therapy had seizures on therapy.

Table 2: **Treatment-related adverse events**

ASPS: Randomized Phase 2

Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial

Ian Judson, James P Morden*, Lucy Kilburn, Michael Leahy, Charlotte Benson, Vivek Bhadri, Quentin Campbell-Hewson, Ricardo Cubedo, Adam Dangoor, Lisa Fox, Ivo Hennig, Katy Jarman, Warren Joubert, Sarah Kernaghan, Antonio López Pousa, Catriona McNeil, Beatrice Seddon, Claire Snowdon, Martin Tattersall, Christy Toms, Javier Martinez Trufero, Judith M Bliss

Judson I et al. Lancet Oncol 2019

Randomized trial ASPS

- Median % change in sum of target marker lesion diameters for the evaluable population:
  - Cediranib: −8·3% (IQR −26·5 to 5·9) versus
  - Placebo: 13·4% (IQR 1·1 to 21·3), one-sided p=0·0010

- Most common grade 3 adverse events on (blinded) cediranib:
  - Hypertension (6 [19%] of 31)
  - Diarrhoea (2 [6%])

- 15 serious adverse reactions in 12 patients;
  - 12 of these reactions occurred on open-label cediranib

Judson I et al. Lancet Oncol 2019

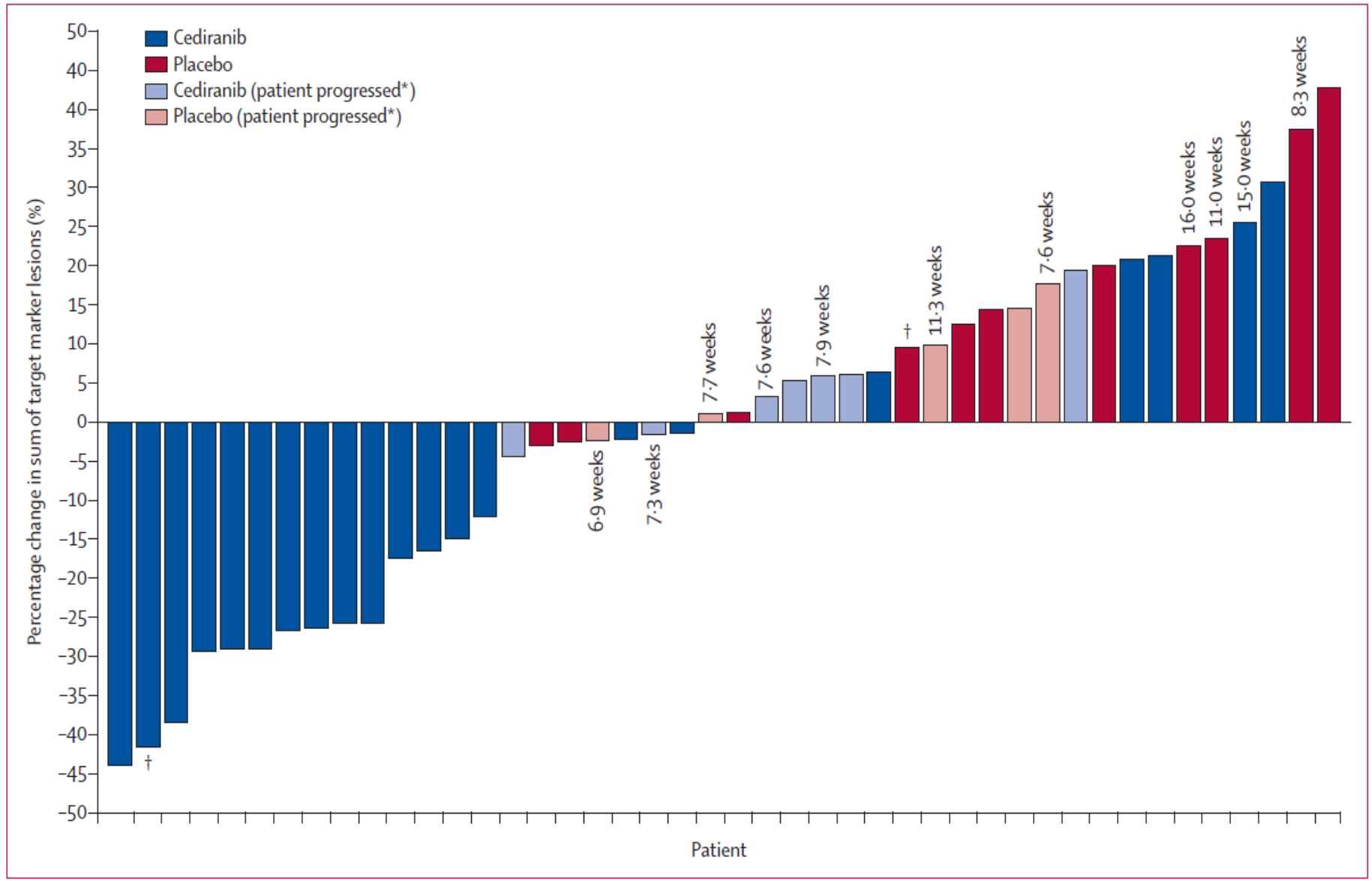


***Figure 2*: Percentage change in sum of target marker lesions from baseline to week 24 (or progression if sooner) in all evaluable participants (n=44)**
Each bar represents one patient. Where the number of weeks is given, it indicates the timepoint at which progression occurred for those who did not reach the 24 week assessment. *Patients who progressed had either progression of non-target lesions or appearance of new lesions despite a less than 20% decrease in the sum of target marker lesions. †Patient received cediranib before trial entry.

Judson I et al. Lancet Oncol 2019

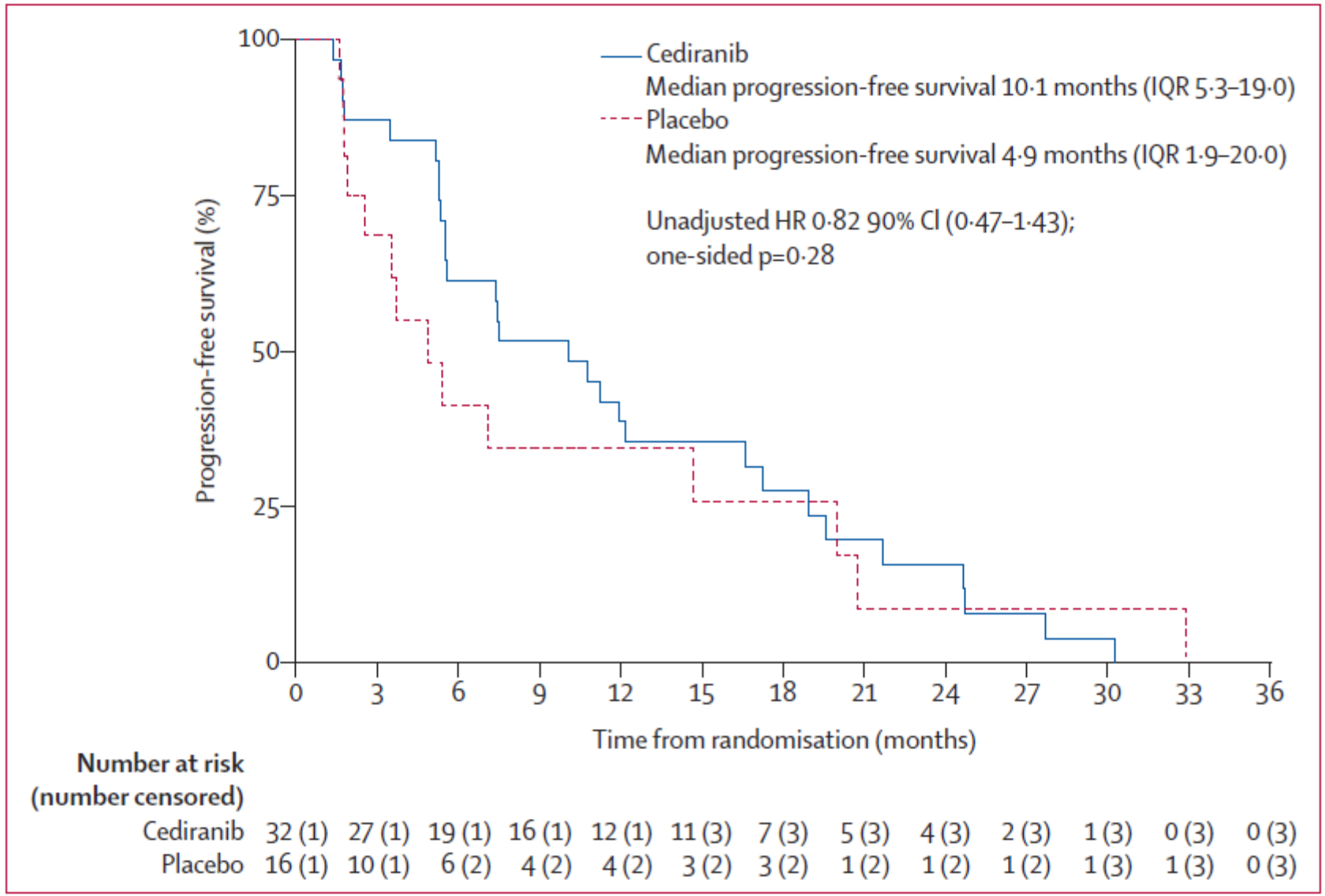


Figure 3: **Progression-free survival**
HR=hazard ratio.

Judson I et al. Lancet Oncol 2019

Inflammatory Myofibroblastic Tumor

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%]

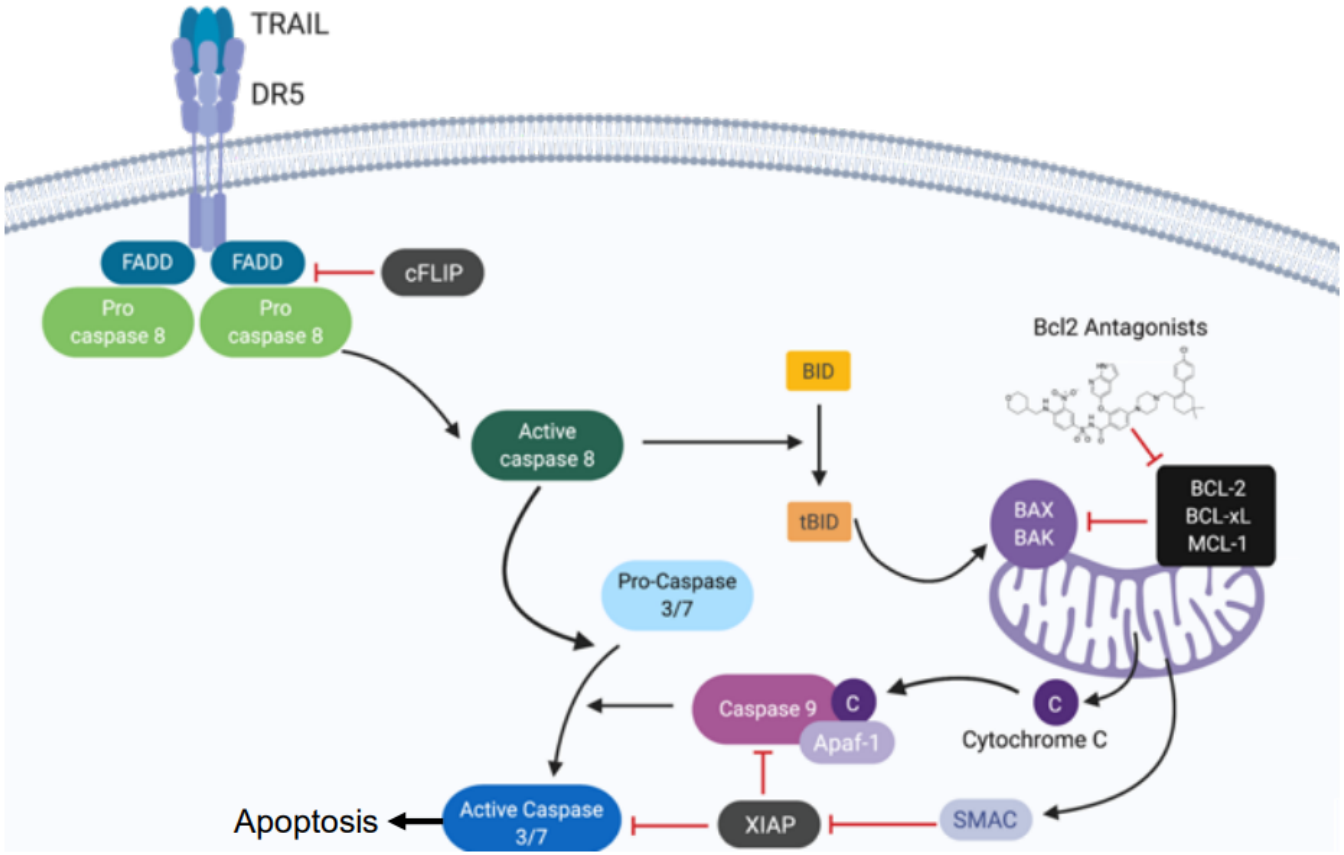
- 8 serious adverse events in 5 patients
  - Pneumonia
  - Fever of unknown cause
  - Heart attack with increased creatinine and possible sepsis
  - Abdominal abscess with acute renal insufficiency
  - QT prolongation

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

Chondrosarcoma

Death receptor 5 (DR5) apoptosis pathway

- Death receptor 5 (DR5) is a receptor for the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)
- DR5 activation naturally eliminates damaged or neoplastic cells
- Normal cells are less sensitive to DR5-mediated apoptosis
- Higher order clustering of DR5 receptors is optimal for signaling



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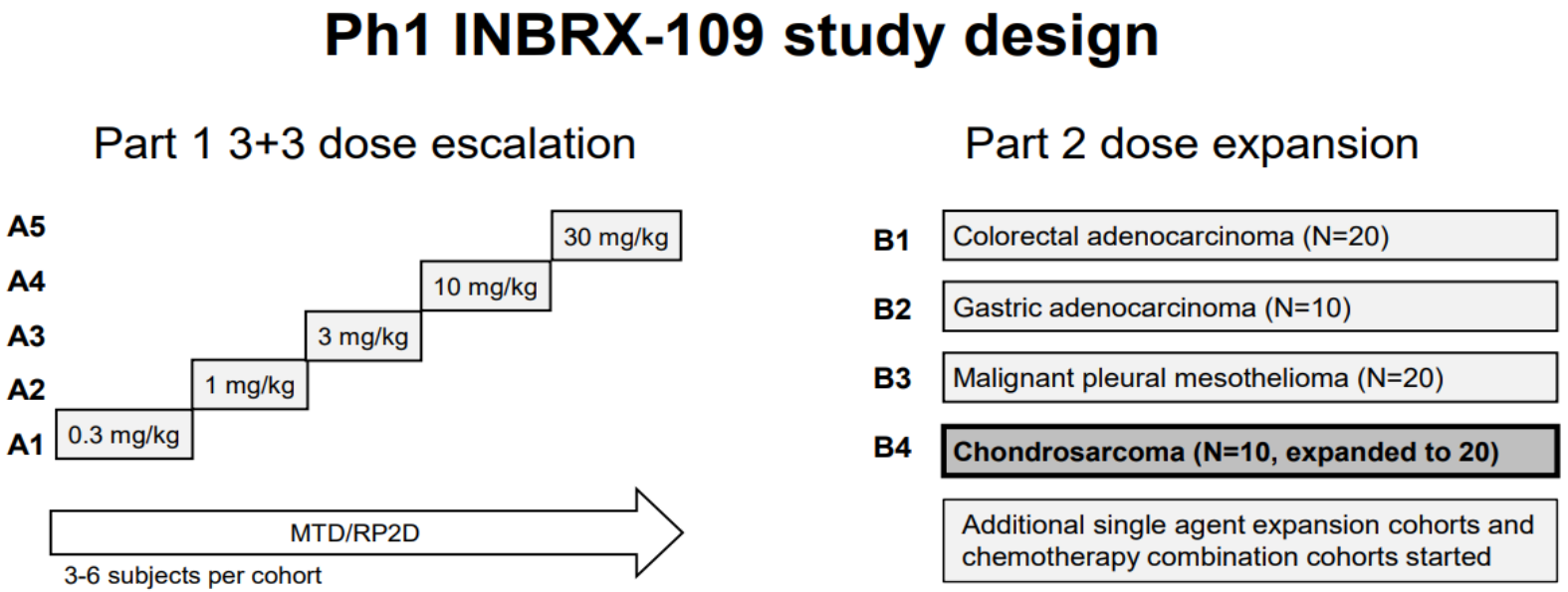
INBRX-109: Tetravalent DR5 Agonist Antibody



- First in human Phase 1 trial, NCT03715933
- Administration of INBRX-109 IV (60 min infusion) q21d without premedication
- DLT assessment window 21 days
- Primary objective: Safety and tolerability
- Exploratory objective: Assessment of anti-tumor activity by RECISTv1.1
- Study ongoing

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Chondrosarcoma patient demographics and disease characteristics

	Age Gender Race	Diagnosis	Histology	Grade	Prior lines of systemic therapy	Progression six months prior to study	ECOG PS	Metastatic
1	56 M W	26-Oct-2018	Conventional chondrosarcoma	Gr2	1	Yes	1	Yes
2	65 M O	01-Feb-2018	Conventional chondrosarcoma	Gr2	1	Yes	1	Yes
3	65 M W	11-Aug-2017	Conventional chondrosarcoma	Gr2	2	Yes	1	Yes
4	86 M W	10-Mar-2005	Conventional chondrosarcoma	Gr3 (Gr2B)	1	Yes	0	Yes
5	81 M W	17-May-2018	Conventional chondrosarcoma	Gr2 (Gr1B)	0	Yes	1	Yes
6	57 F W	01-Jul-2019	Conventional chondrosarcoma	Gr3	0	Yes	1	Yes
7	30 M W	08-May-2008	Conventional chondrosarcoma	Gr2	1	Yes	1	Unresectable
8	29 M W	06-Mar-2019	Conventional chondrosarcoma	Gr3	0	Unk	1	Yes
9	55 M W	23-May-2014	Conventional chondrosarcoma	Gr3	4	Yes	1	Yes
10	49 M Asian	10-Oct-2018	Conventional chondrosarcoma	Gr2	4	Yes	1	Yes
11	42 F AA	12-Oct-2012	Conventional chondrosarcoma	Gr3	2	Unk	1	Yes
12	57 M Asian	25-Jul-2019	Conventional chondrosarcoma	Gr2/3	0	Unk	1	Yes
	Median 56.5 Range 29-86 10:2 M:F			(MDACC Grading)	Median 1 Range 0-4			

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Most common adverse events (≥ 4) attributed to INBRX-109

- Data based on 76 subjects in all parts of the Ph1 INBRX-109 study
- Part 1 dose escalation: Maximum tolerated dose not reached, one dose limiting toxicity
- Overall INBRX-109 was well tolerated, in particular, in the majority of patients (~ 90%) no drug related liver-related adverse events were observed
- Few serious adverse events attributed to study drug
- One death possibly attributed to study drug, acute hepatic failure in patient with mesothelioma (N=1/76,1.3%)

Relationship to INBRX-109	**Very Likely/Certain**			**Probable**		**Possible**			**Sum**
Preferred Term	**Gr3**	**Gr2**	**Gr1**	**Gr2**	**Gr1**	**Gr3**	**Gr2**	**Gr1**	**All**
Fatigue	0	0	0	1	2	0	3	8	14
Aspartate aminotransferase (AST) increased	1	1	3	0	1	1	0	3	10
Alanine aminotransferase (ALT) increased	1	2	2	0	1	1	0	3	10
Nausea	0	0	1	0	3	1	1	1	7
Pyrexia	0	1	1	1	0	0	0	2	5
Diarrhea	0	0	0	2	1	0	0	1	4

Data cut off 02-Aug-2020

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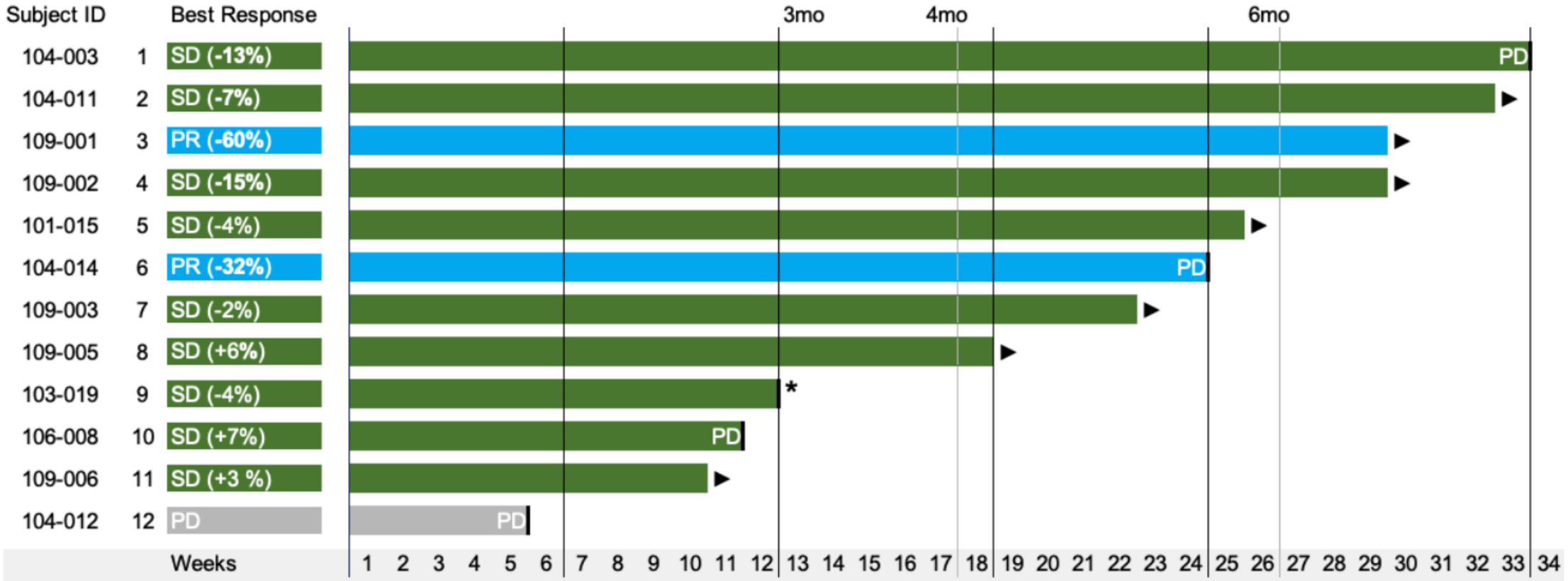
Time on treatment with INBRX-109 in chondrosarcoma patients



Data cut point 17-Oct-2020, study ongoing
RECISTv1.1 tumor assessments per Investigators, not confirmed by central radiology review yet
PR = Partial Response, **SD** = Stable Disease, **PD** = Progressive Disease
*Off-study per subject request
▶ Subject continuing on INBRX-109

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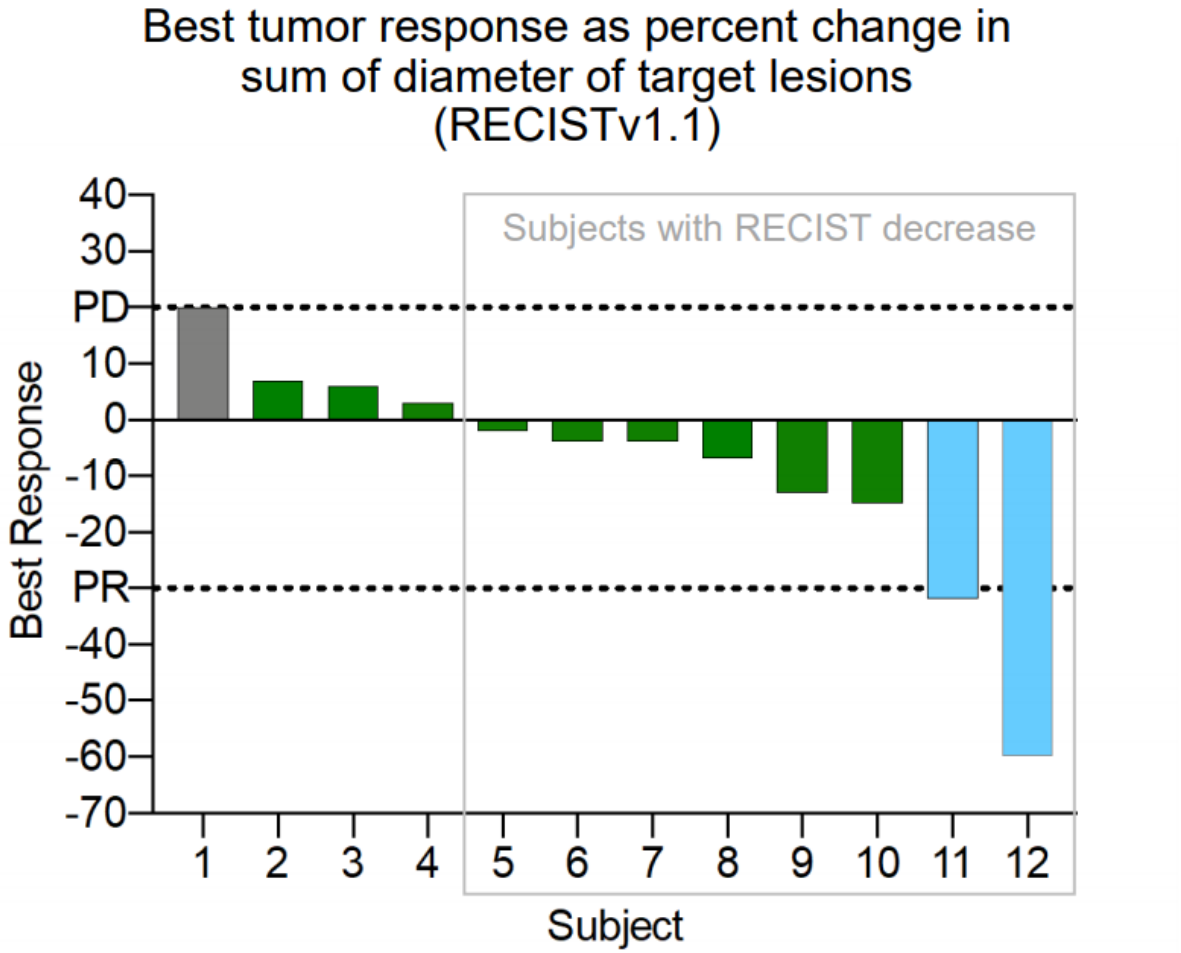
Summary of anti-cancer activity of INBRX-109 in chondrosarcoma

Summary of activity

	INBRX-109
MOA	DR5 Agonist
Number of subjects	12
Partial response	17% (N=2/12)
Stable disease	75% (N=9/12)
Disease control rate (DCR)	92% (N=11/12)
RECIST decrease	67% (N=8/12)
DCR > 4 months	67% (N=8/12)*
DCR > 6 months	33% (N=4/12)*

**study ongoing*



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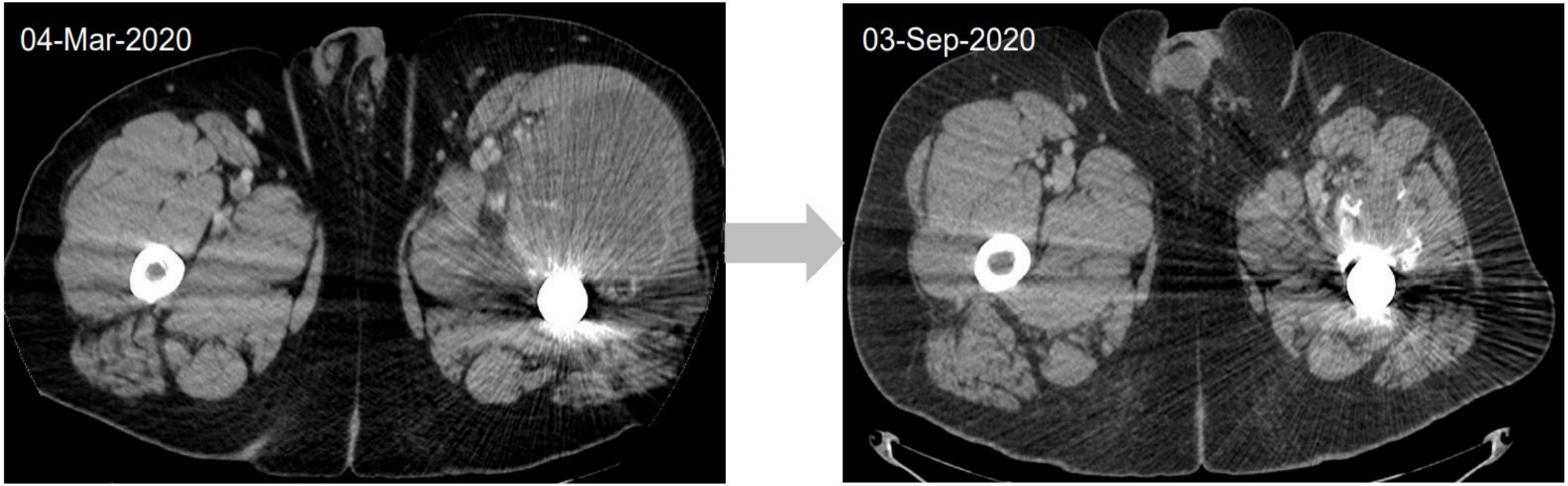
Example of partial response in chondrosarcoma patient treated with INBRX-109

- 29 year old male, white (109-001), with conventional chondrosarcoma, histologic Grade 3, diagnosed Mar-2019, metastatic to lung in Jan-2020
- Started INBRX-109 on 25-Mar-2020, achieved durable partial response with 60% decrease in target lesions (RECISTv1.1)*



*patient ongoing on study > 6 months

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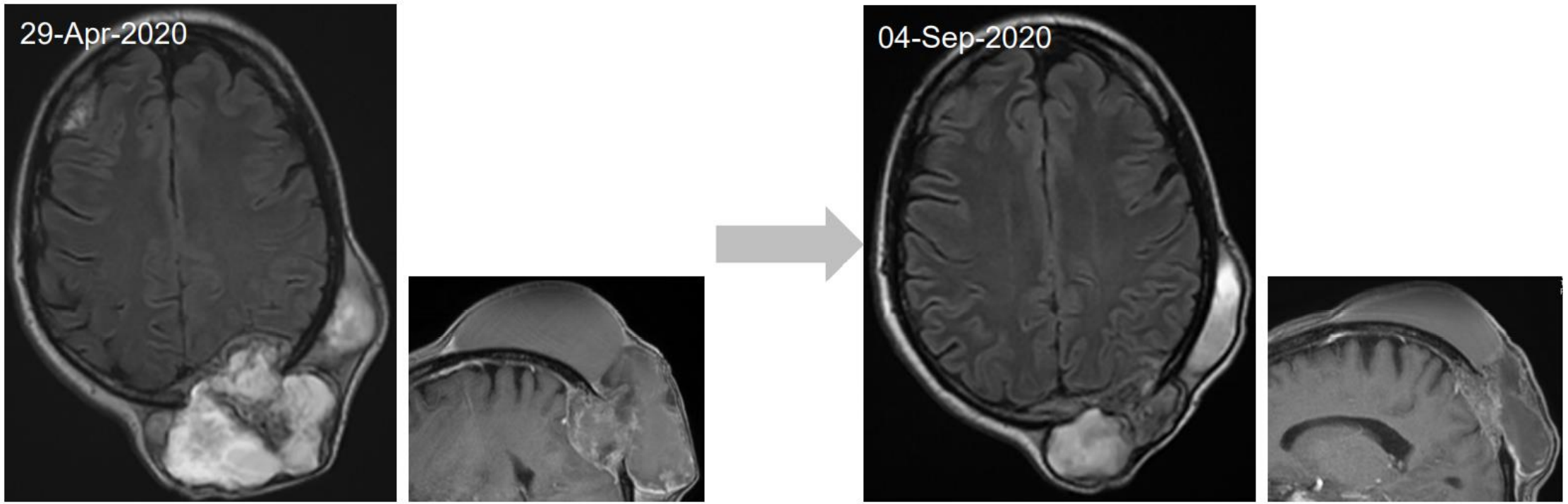
Example of durable stable disease in chondrosarcoma patient

- 55 year old male, white (109-002), with conventional chondrosarcoma, histologic Grade 3, diagnosed May-2014, metastatic to brain Jul-2016
- Prior therapies: TGFβ inhibitor, pazopanib, nivolumab, pazopanib & nivolumab
- Started INBRX-109 on 24-Mar-2020, achieved durable stable disease with 15% decrease in target lesions (RECISTv1.1)*



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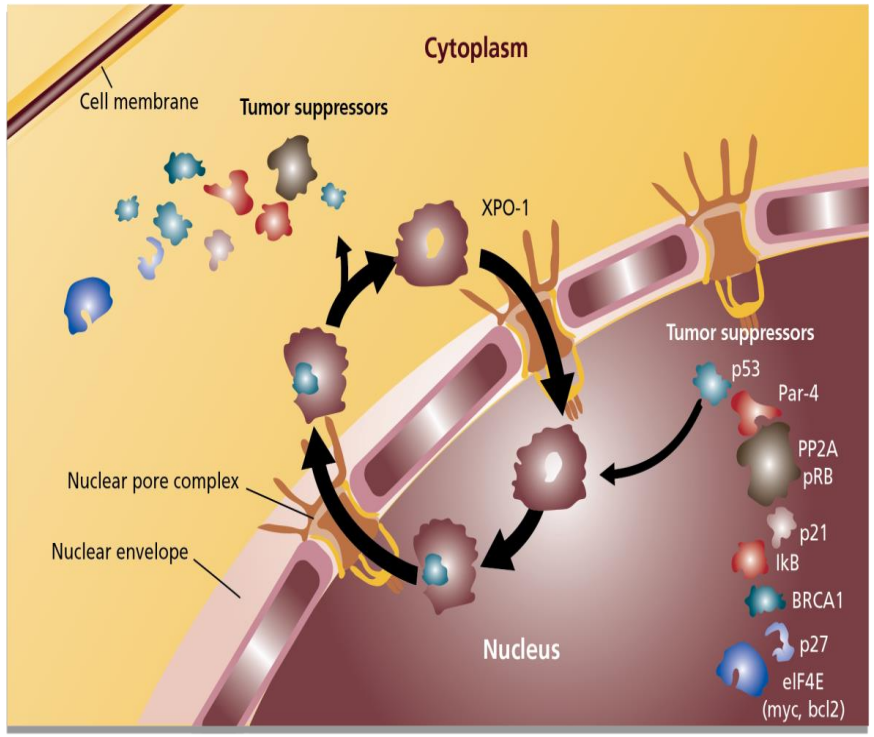
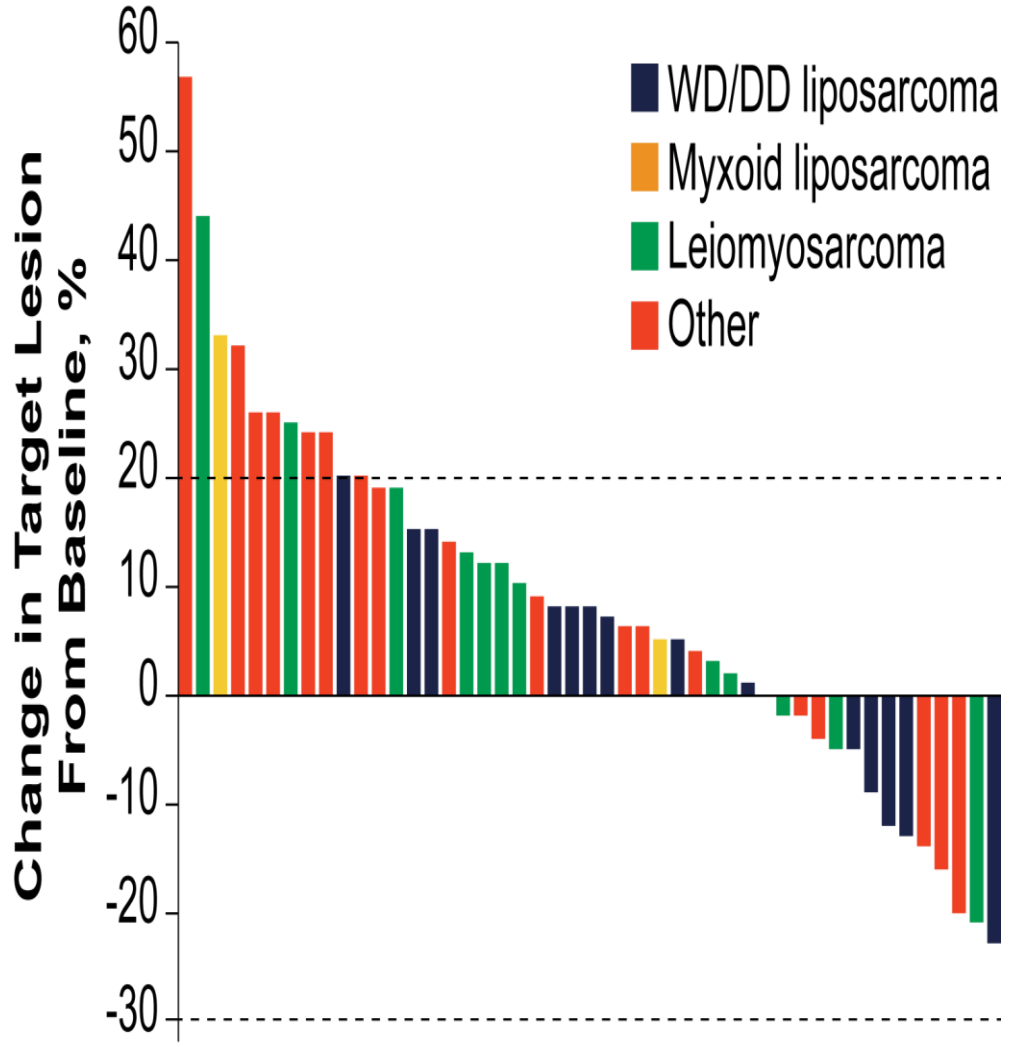
Well-/ dedifferentiated Liposarcomas

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



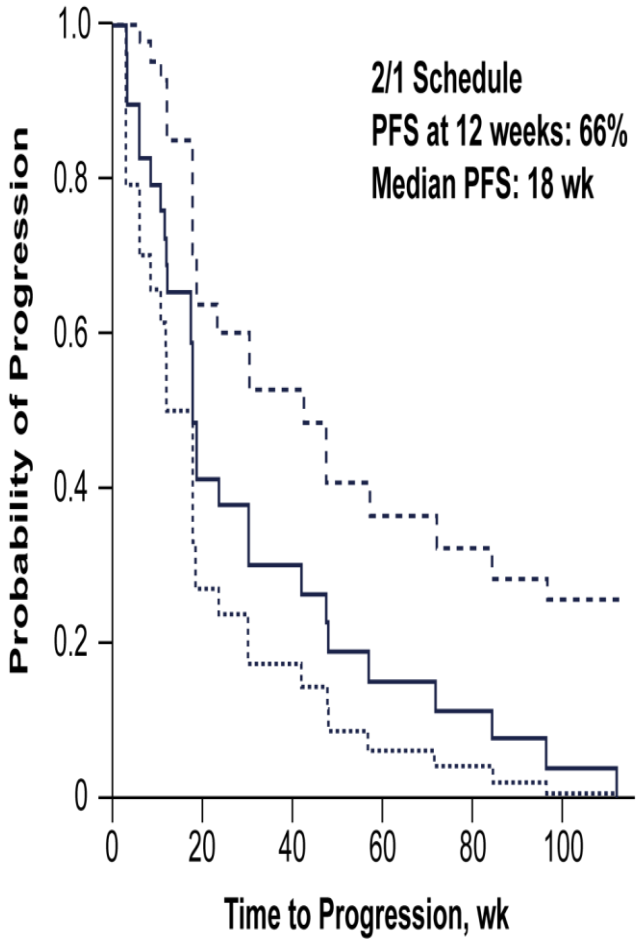
Selinexor: Change in Tumor Size



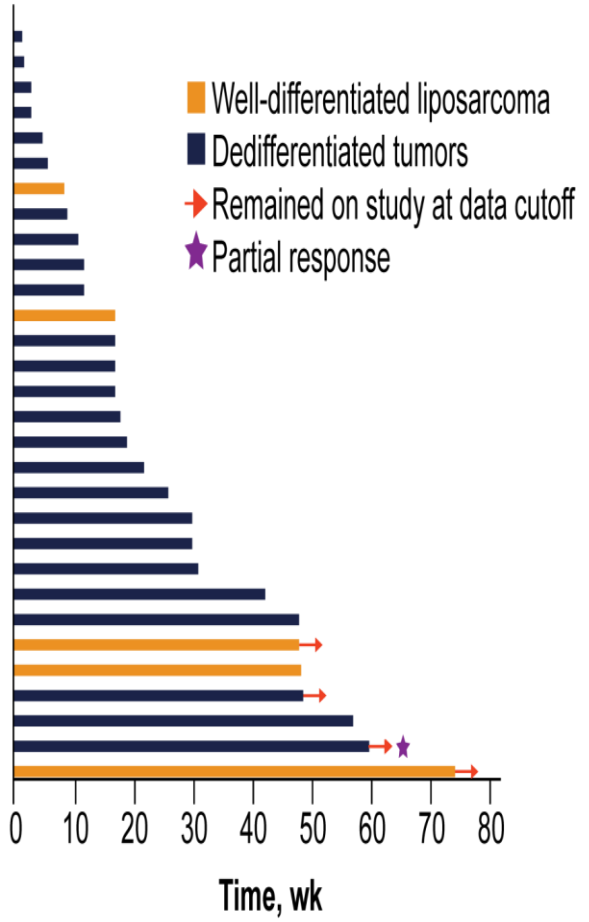
Gounder MM et al. *J Clin Oncol* 34; 3166-3174: 2016

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).

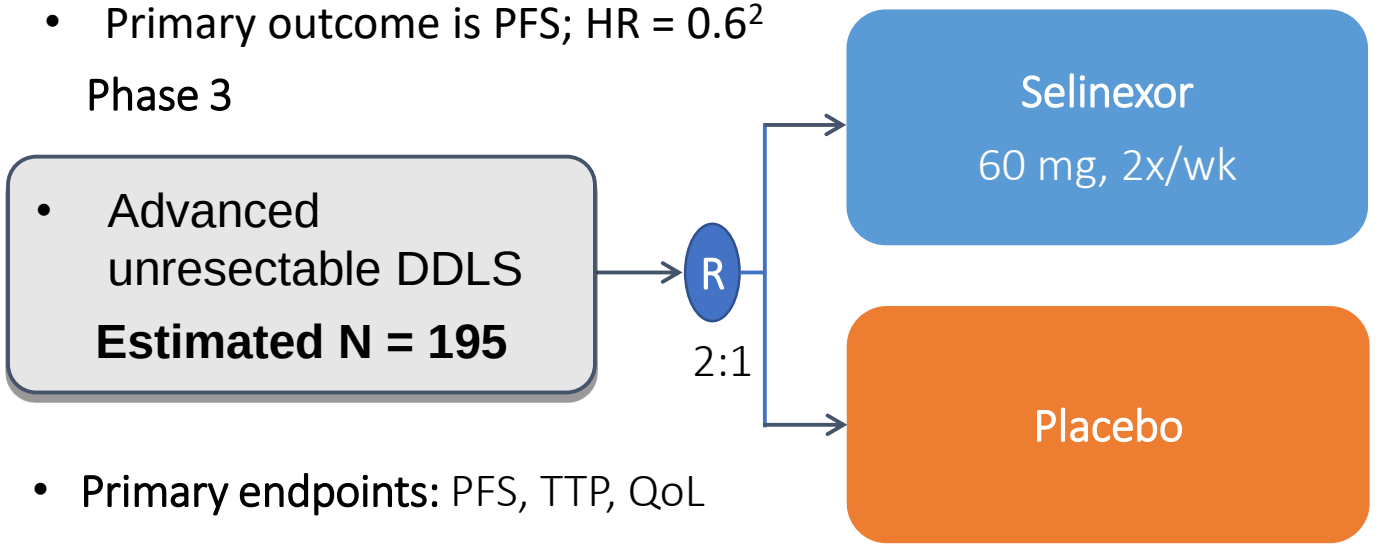
†Indicates a significant difference between 30 mg/m^2 and 50 mg/m^2 for dizziness (P = .01).

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

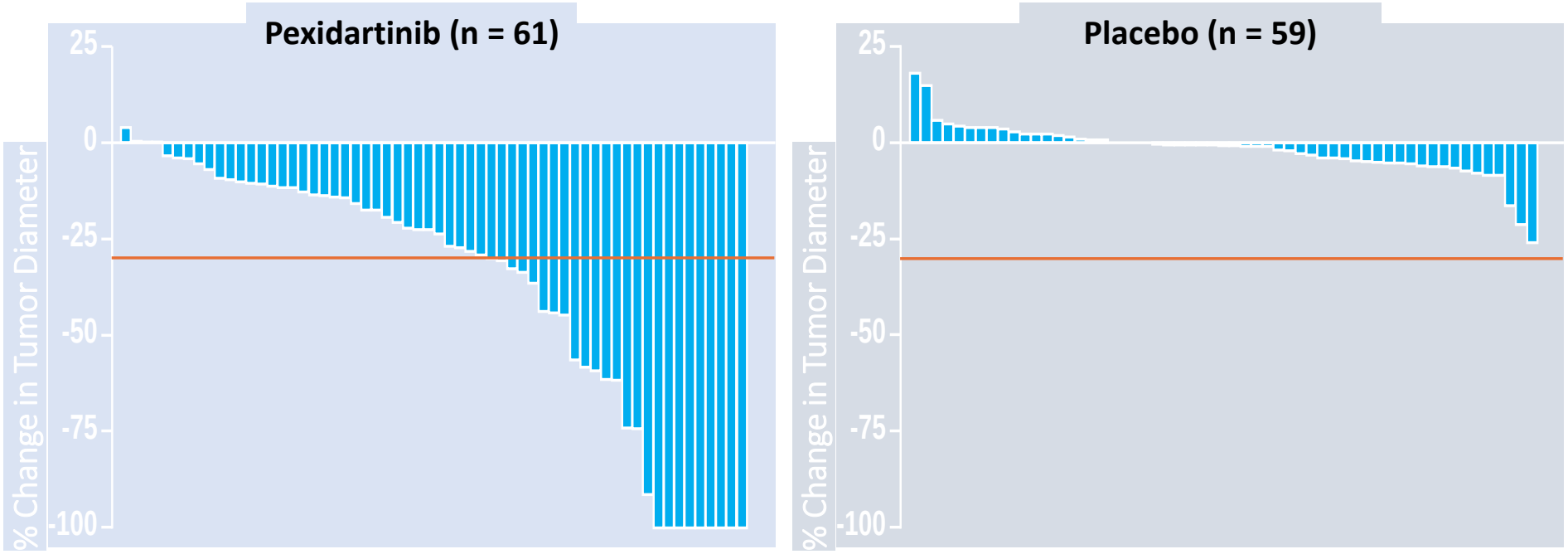
Tenosynovial giant cell tumor

Phase 3 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 and function on active study drug

Tap WD et al. Lancet 394; 478-487: 2019

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]

Tap WD et al. Lancet 394; 478-487: 2019

Desmoid Tumor

Phase 3: Sorafenib vs Placebo, double blind, randomized trial with crossover

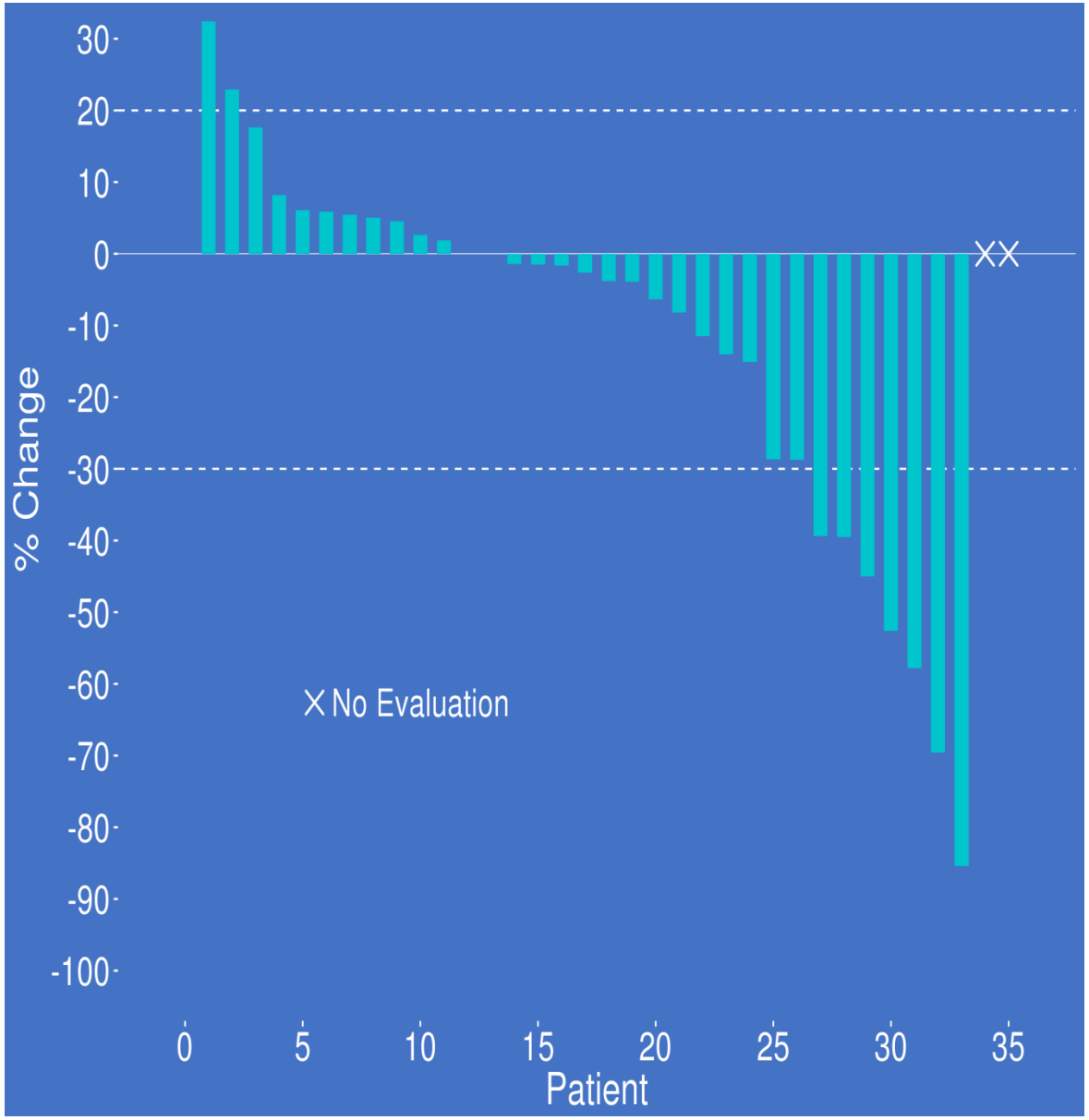
- Unresectable or unacceptable surgical morbidity
- Progressive disease (10% by RECIST 1.1 within 6 months)
- Symptomatic disease – Brief Pain Inventory score ≥ 3 and considering addition or increase in narcotics

- 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

Objective Response – RECIST 1.1 – Placebo (N = 35)



ORR: CR/PR: 20% 95% CI 8 – 38%

Median time to response:

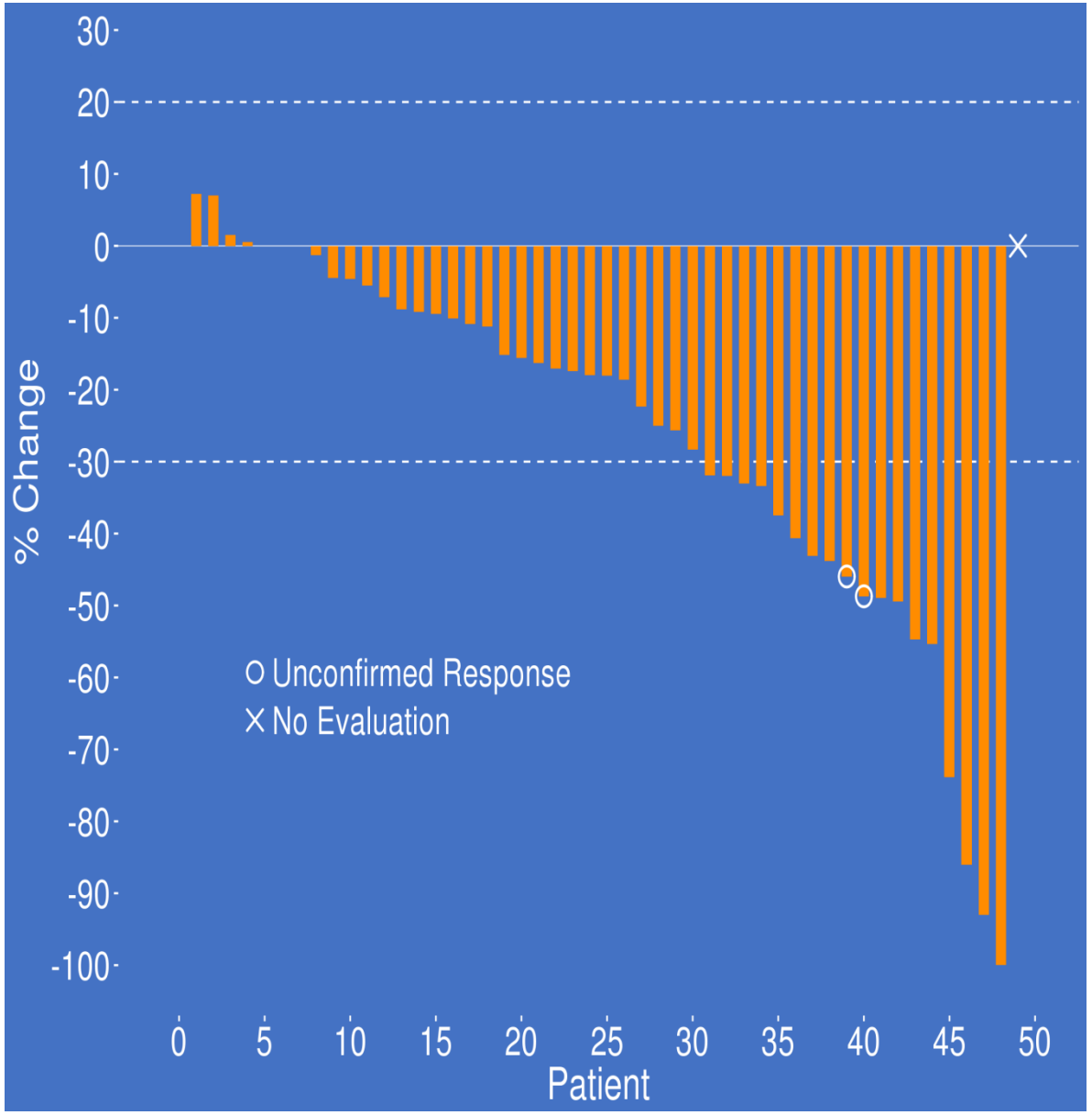
13.3 months, IQR (11.2 – 31.1)

Average best % change: -12% (-85%, +32%)

All patients with PR continue to respond

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

Objective Response – RECIST 1.1 – Sorafenib (N = 49)



ORR: CR/PR: 33%
95% CI 20 – 48%

Median time to response:

9.6 months, IQR (6.6 – 16.7)

Average best % change: -26% (-100, +7%)

All patients with CR/PR continue to respond

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

original reports

Telemedicine During the COVID-19 Pandemic: Impact on Care for Rare Cancers

Alannah Smrke, MD[1]; Eugenie Younger, MD[1]; Roger Wilson, CBE[2]; Olga Husson, PhD[3]; Sheima Farag, MD[1]; Eve Merry, MBBS, MD[1]; Aislinn Macklin-Doherty, MBChB, MD[1,3]; Elena Cojocaru, MD[1]; Amani Arthur, MBChB, MD[1,3]; Charlotte Benson, MBChB, MD[1]; Aisha B. Miah, MBBS, MD, PhD[1,3]; Shane Zaidi, MD, PhD[1]; Spyridon Gennatas, MBChB, MD, PhD[1]; and Robin L. Jones, MD[1,3]

Telemedicine: Delivery of health services using communication technology

The Study

- Key Objectives:
- What is the impact of rapid enforced telemedicine use during the COVID-19 pandemic on
  - Patients
  - Clinicians
  - Health systems ?

- Patients were offered a telemedicine appointment prior to their scheduled OP appointment
- Except for: Symptomatic patients + known symptomatic or radiologic PD
- Retrospective data collected (23/03-24/04/20)
- Average travel times & distance from patient address - RMH were calculated using Google Maps

Smrke A et al. JCO Glob Oncol 6; 1046-1051: 2020

What we did

- Patients with a clinic appointment were invited to consent to participate in an anonymous patient experience survey

- Clinicians in the sarcoma unit were provided an anonymous electronic survey via e-mail

Smrke A et al. JCO Glob Oncol 6; 1046-1051: 2020

Findings - Patients

- 283/ 379 planned face-to-face appointments were converted to telemedicine = 75%
- Patients lived on average 1.5 hours from RMH
- Patient satisfaction (n = 108) with telemedicine was high (mean, 9/10)
- Only 48% (n = 52/108) would not want to hear bad news using telemedicine
- 80% desired some telemedicine as part of their future care, citing reduced cost and travel time

Smrke A et al. JCO Glob Oncol 6; 1046-1051: 2020

Findings - Clinicians

- Found telemedicine efficient, with no associated increased workload, compared with face-to-face appointments
- Indicated lack of physical examination did not often affect care provision when using telemedicine
- Most (n = 17; 94%) believed telemedicine use was practice changing

Smrke A et al. JCO Glob Oncol 6; 1046-1051: 2020

Conclusion

- Half of telemedicine appointments were performed by a clinician who had never met the patient
- More than one-third (n = 7; 39%) desired nurse presence with patient for all telemedicine appointments
- There was no difference in reported change in workload
- Telemedicine can revolutionize delivery of cancer care
- Particularly for patients with rare cancers who often live far away from expert centres

Smrke A et al. JCO Glob Oncol 6; 1046-1051: 2020

cancers

MDPI

Article

Health-Related Quality of Life and Experiences of Sarcoma Patients during the COVID-19 Pandemic

Eugenie Younger [1], Alannah Smrke [1], Emma Lidington [1], Sheima Farag [1], Katrina Ingley [2], Neha Chopra [2], Alessandra Maleddu [2], Yolanda Augustin [1], Eve Merry [1], Roger Wilson [3], Charlotte Benson [1], Aisha Miah [1,4], Shane Zaidi [1], Anne McTiernan [2], Sandra J. Strauss [2], Palma Dileo [2], Spyridon Gennatas [1], Olga Husson [4,†] and Robin L. Jones [1,4,*,†]

Why QOL?

- The pandemic has had a negative impact on mental health and wellbeing in the general population
- What about in patients with cancer?
- Sarcomas are rare and variable
- Impact of the pandemic:
  - Care experiences
  - Worry
  - Health-related quality of life (HRQoL)

Younger E et al. Cancers 12(8); 2288: 2020

The Study

- Cross-sectional survey assessing the experiences of sarcoma patients
  - Royal Marsden NHS Foundation Trust (RMH) and
  - University College London Hospitals NHS Foundation Trust (UCLH, London Sarcoma Service)

- >16 years with a diagnosis of sarcoma (STSs, bone sarcomas and GIST)

- Planned OPA 23 March - 23 May 2020 Med or Clin Onc

Younger E et al. Cancers 12(8); 2288: 2020

Highlights

- 350 patients, median age 58, 55% F, 82% Caucasian

- Care modifications
  - Telemedicine (74%)
  - Postponement of appointments (34%), scans (34%) or treatment (10%)
  - 72% felt the quality of care was not affected (72%)
  - Social life (87%) and emotional wellbeing (41%) were affected

- 85 patients (24%) were lonely

- 150 patients (33%) were low resilient copers

Younger E et al. Cancers 12(8); 2288: 2020

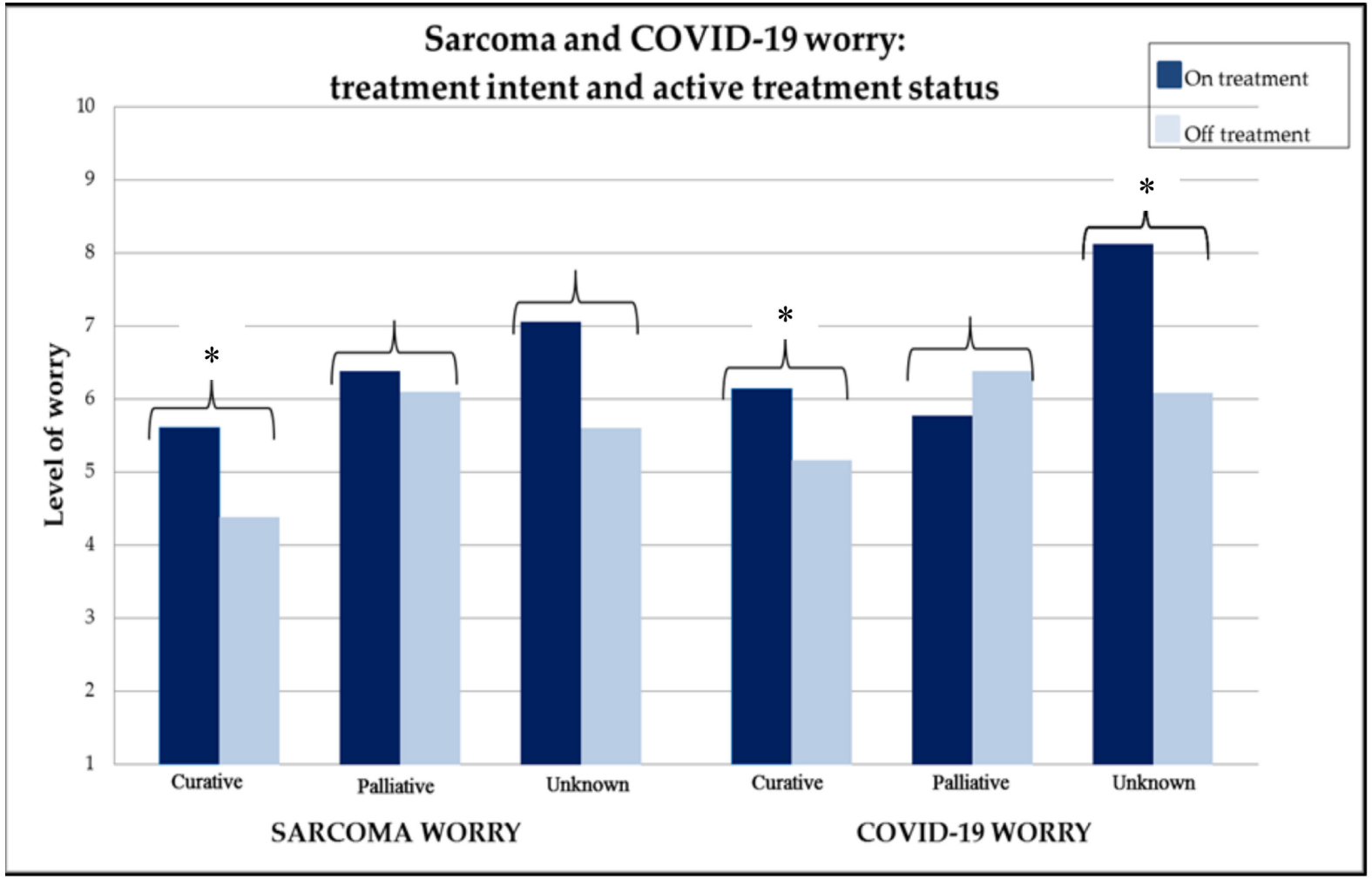


Figure 1. Sarcoma and COVID-19 worry according to treatment intent and active treatment status.
* $p < 0.05$.

Satisfaction with telemedicine

- Telephone appointment mean score 8.7/10
- Video appointment mean score 7.4/10
- F2F appointment mean score 8.4/10
- 74% of patients would like some telemedicine in the future
  - Money, time, convenience
- 22% would like only F2F
  - Treatment intent, low resilient coping score

Younger E et al. Cancers 12(8); 2288: 2020

Some final points

- 22% did not know their treatment intent
  - Higher COVID-19 worry and insomnia
  - More likely to want F2F appointments
- Telemedicine is here to stay beyond the pandemic
- Longer term consequences of telemedicine or postponement of care is not know
- Extra psychological support
  - Needed?
  - Feasible

Younger E et al. Cancers 12(8); 2288: 2020

What next?

- We need to carry on delivering the best possible care to our patients
- This is not always as straightforward as it may sound
- Treatment intent Vs QOL
- We will learn a lot from this
  - Psychological/ emotional impact
  - Telemedicine has many advantages
  - Crucial to know what patients think

Younger E et al. Cancers 12(8); 2288: 2020

Conclusions

- More systemic therapy options for advanced disease
- We need
  - Better understanding of underlying biology
  - Incorporation of putative biomarkers into clinical trial design
- Number of promising agents in clinical trials

Sarcoma Unit The Royal Marsden/ Institute of Cancer Research

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

- **Pathology**
- Khin Thway
- Magnus Hallin

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

- **Oncology**
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- Steph Elston
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- **Institute of Cancer Research**
- Paul Huang + Huang Lab
- Chris Wilding
- Eugenie Younger
- Amani Arthur

- Janet Shipley + Shipley Lab