Seltene GIST-Subtypen (verstehen) und behandeln

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BRAF Mutant Gastrointestinal Stromal Tumor: First report of regression with BRAF inhibitor dabrafenib (GSK2118436) and whole exomic sequencing for analysis of acquired resistance

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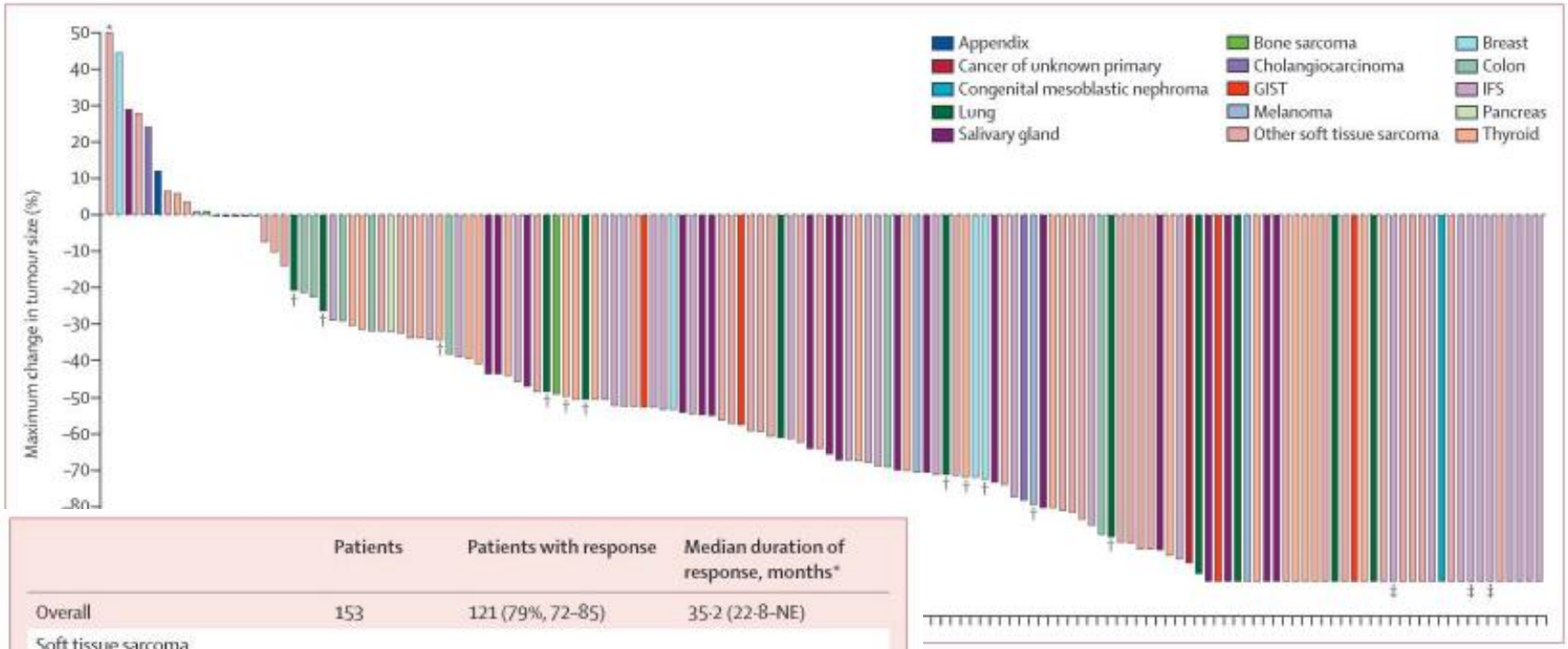
Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials

David S Hong, Steven G DuBois, Shivaani Kummar, Anna F Farago, Catherine M Albert, Kristoffer S Rohrberg, Cornelis M van Tilburg, Ramamoorthy Nagasubramanian, Jordan D Berlin, Noah Federman, Leo Mascarenhas, Birgit Geoerger, Afshin Dowlati, Alberto S Pappo, Stefan Bielack, François Doz, Ray McDermott, Jyoti D Patel, Russell J Schilder, Makoto Tahara, Stefan M Pfister, Olaf Witt, Marc Ladanyi, Erin R Rudzinski, Shivani Nanda, Barrett H Childs, Theodore W Laetsch, David M Hyman, Alexander Drilon**



	Patients	Patients with response	Median duration of response, months*
Overall	153	121 (79%, 72–85)	35·2 (22·8–NE)
Soft tissue sarcoma			
Infantile fibrosarcoma	28	27 (96%, 82–100)	NE (NE–NE)
Gastrointestinal stromal tumour	4	4 (100%, 40–100)	26·3 (7·6–26·3)
Other	36	29 (81%, 64–92)	NE (10·1–NE)

atients who were not evaluable due to insufficient time on therapy.
growth. †Patients with brain metastases. ‡Patients with a pathological complete

Hong et al., Lancet Oncol 2020

Treatment of SDH-deficient GIST

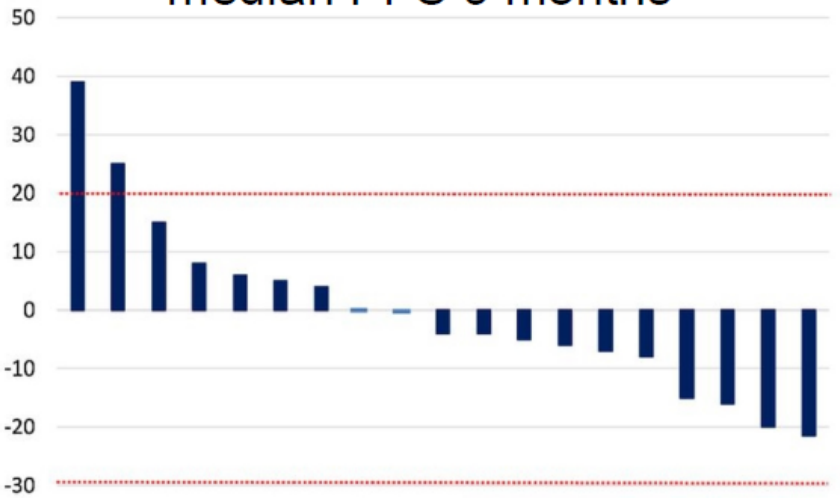
Sunitinib
7 pediatric patients
1 PR
median PFS 18 months

Janeway, Pediatr Blood Cancer 2009; 52:767

Regorafenib
6 patients
2 PR
median PFS 10 months

Ben-Ami, Ann Oncol 2016; 27:1794

Linsitinib
20 patients
0 PR
median PFS 9 months

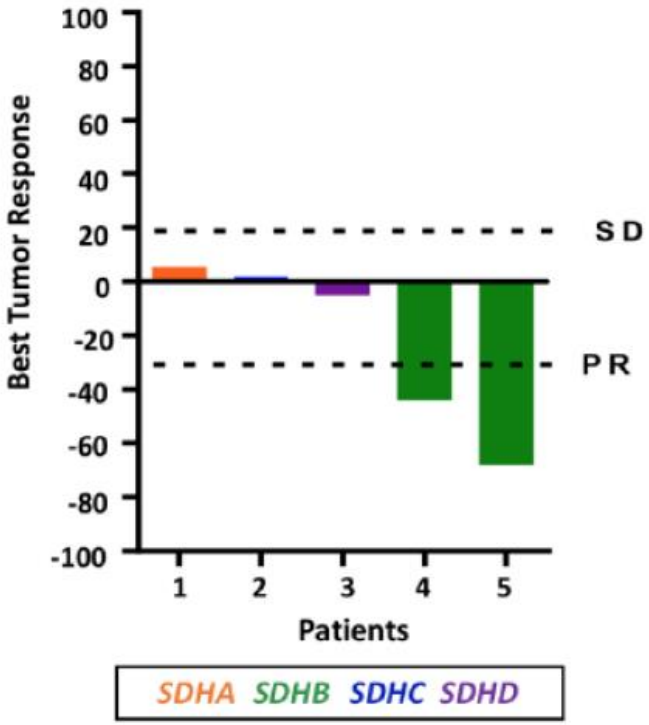


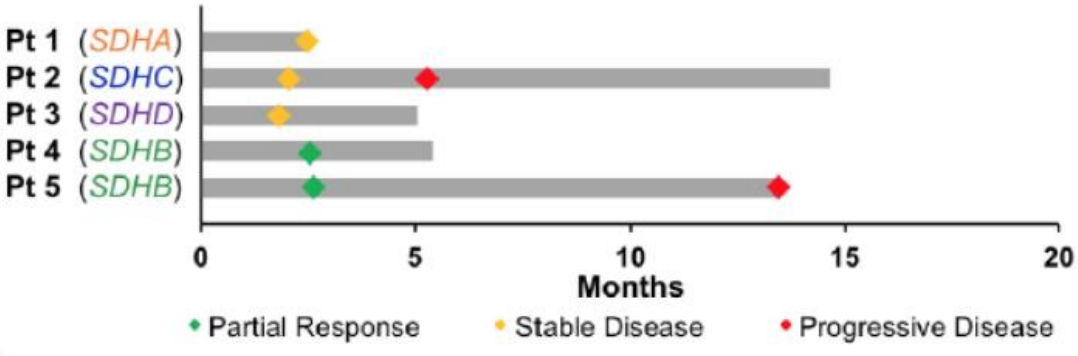
von Mehren, Clin Cancer Res 2020; 26:1837

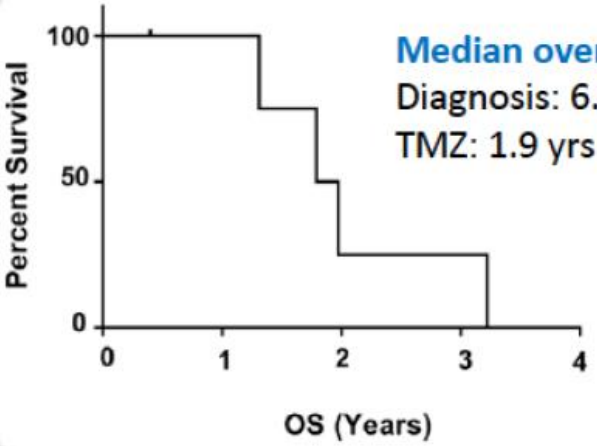
Sicklick et al., CTOS 2020

TMZ Efficacious in SDH-Deficient GIST Patients

Objective Response Rate 40%







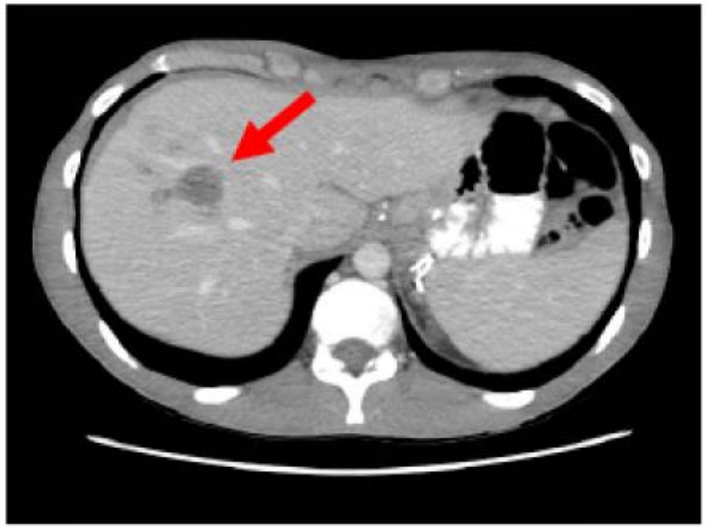
Median overall survival (OS)

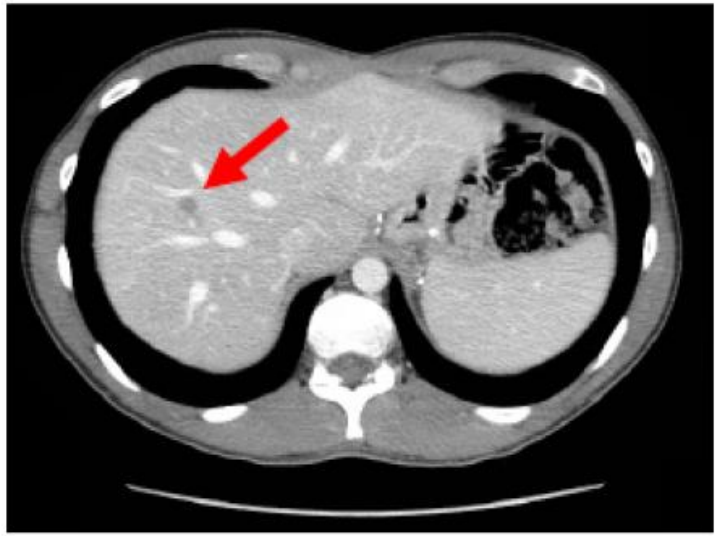
Diagnosis: 6.4 yrs (95% CI 0.9–13.6)

TMZ: 1.9 yrs (95% CI 0.07–1.2)

Sicklick et al., CTOS 2020

- 22 yo male treatment with TMZ





Sicklick et al., CTOS 2020

Articles

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

Michael C Heinrich, Robin L Jones*, Margaret von Mehren*, Patrick Schöffski, César Serrano, Yoon-Koo Kang, Philippe A Cassier, Olivier Mir, Ferry Eskens, William D Tap, Piotr Rutkowski, Sant P Chawla, Jonathan Trent, Meera Tugnait, Erica K Evans, Tamieka Lauz, Teresa Zhou, Maria Roche, Beni B Wolf, Sebastian Bauer*, Suzanne George**

Summary

Background Targeting of KIT and PDGFRA with imatinib revolutionised treatment in gastrointestinal stromal tumour; however, PDGFRA Asp842Val (D842V)-mutated gastrointestinal stromal tumour is highly resistant to tyrosine kinase inhibitors. We aimed to assess the safety, tolerability, and antitumour activity of avapritinib, a novel KIT and PDGFRA inhibitor that potently inhibits PDGFRA D842V, in patients with advanced gastrointestinal stromal tumours, including patients with KIT and PDGFRA D842V-mutant gastrointestinal stromal tumours (NAVIGATOR).

Lancet Oncol 2020; 21: 935–46

See Comment page 865

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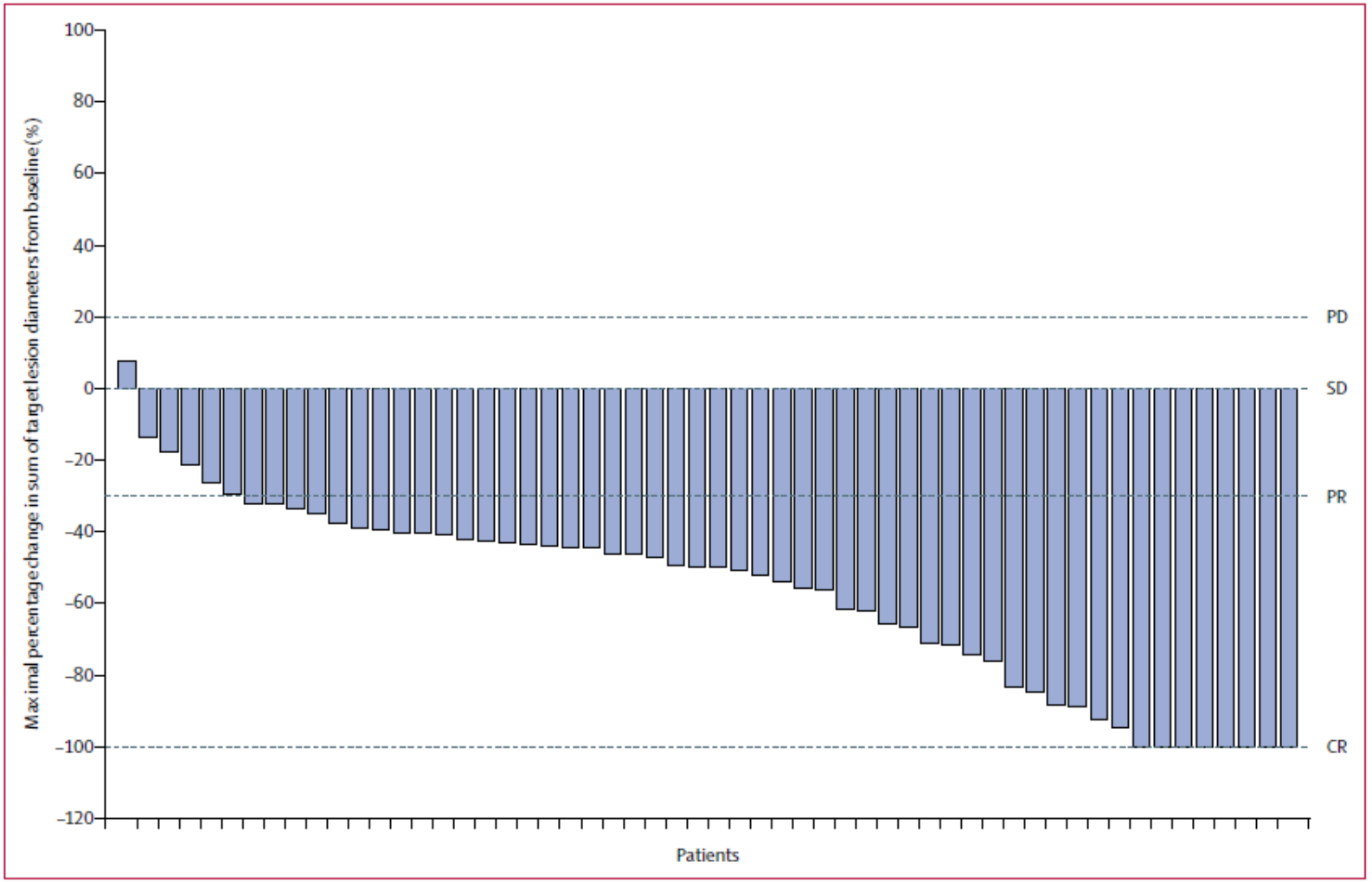


Figure 2: **Maximal percentage change in sum of target lesion diameters from baseline in patients with PDGFRA D842V-mutant gastrointestinal stromal tumours**

Horizontal dashed lines denoting complete response, partial response, stable disease, and progressive disease refer only to response in target lesions. CR=complete response. D842V=Asp842Val. PD=progressive disease. PR=partial response. SD=stable disease.

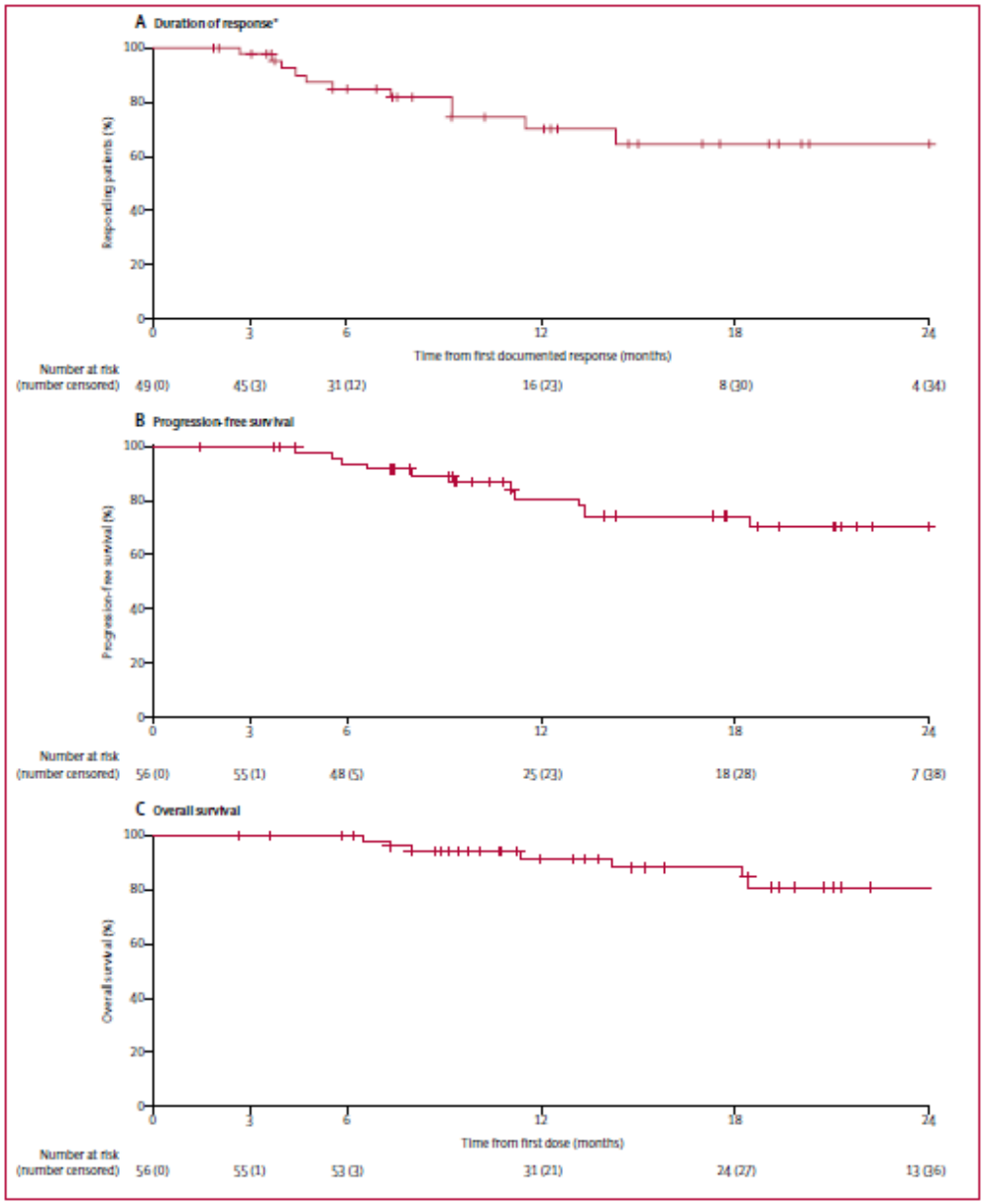
Heinrich et al., Lancet Oncol 2020

	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*

Heinrich et al., Lancet Oncol 2020



Heinrich et al., Lancet Oncol 2020

	<300 mg (n=30)				300 mg (n=32)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any related adverse event	16 (53%)	12 (40%)	2 (7%)	0	11 (34%)	19 (59%)	2 (6%)	0
Nausea	13 (43%)	1 (3%)	0	0	22 (69%)	0	0	0
Fatigue	18 (60%)	1 (3%)	0	0	12 (38%)	1 (3%)	0	0
Diarrhoea	11 (37%)	1 (3%)	0	0	13 (41%)	2 (6%)	0	0
Periorbital oedema	15 (50%)	0	0	0	11 (34%)	1 (3%)	0	0
Anaemia	6 (20%)	5 (17%)	0	0	11 (34%)	7 (22%)	0	0
Decreased appetite	6 (20%)	1 (3%)	0	0	12 (38%)	0	0	0
Vomiting	10 (33%)	1 (3%)	0	0	5 (16%)	0	0	0
Memory impairment	7 (23%)	0	0	0	10 (31%)	0	0	0
Hair colour changes	11 (37%)	0	0	0	8 (25%)	0	0	0
Increased lacrimation	9 (30%)	0	0	0	7 (22%)	0	0	0
Peripheral oedema	10 (33%)	0	0	0	10 (31%)	0	0	0
Blood bilirubin increased	3 (10%)	0	0	0	7 (22%)	1 (3%)	0	0
Face oedema	3 (10%)	0	0	0	11 (34%)	0	0	0
Dysgeusia	5 (17%)	0	0	0	7 (22%)	0	0	0
Hypophosphataemia	3 (10%)	1 (3%)	1 (3%)	0	3 (9%)	1 (3%)	0	0
Neutropenia	2 (7%)	1 (3%)	0	0	6 (19%)	3 (9%)	0	0
Dizziness	2 (7%)	0	0	0	6 (19%)	0	0	0
Dyspepsia	6 (20%)	0	0	0	4 (13%)	0	0	0
Alopecia	4 (13%)	0	0	0	4 (13%)	0	0	0
Eyelid oedema	3 (10%)	0	0	0	5 (16%)	0	0	0
Leukopenia	2 (7%)	0	0	0	3 (9%)	0	0	0

Heinrich et al., Lancet Oncol 2020

Headache	3 (10%)	0	0	0	4 (13%)	0	0	0
Hyperbilirubinaemia	3 (10%)	1 (3%)	0	0	2 (6%)	1 (3%)	0	0
Dry mouth	4 (13%)	0	0	0	2 (6%)	0	0	0
Pleural effusion	2 (7%)	1 (3%)	0	0	3 (9%)	1 (3%)	0	0
Cognitive disorder	1 (3%)	1 (3%)	0	0	4 (13%)	0	0	0
Dry skin	2 (7%)	0	0	0	3 (9%)	0	0	0
Hypomagnesaemia	2 (7%)	1 (3%)	0	0	4 (13%)	0	0	0
Rash	4 (13%)	0	0	0	1 (3%)	0	0	0
Decreased weight	4 (13%)	0	0	0	3 (9%)	0	0	0
Decreased neutrophil count	0	1 (3%)	0	0	2 (6%)	2 (6%)	1 (3%)	0
Vertigo	1 (3%)	2 (7%)	0	0	2 (6%)	0	0	0
Lymphopenia	1 (3%)	0	0	0	0	1 (3%)	0	0
Hypocalcaemia	1 (3%)	1 (3%)	0	0	0	1 (3%)	0	0
Mental impairment	0	0	0	0	1 (3%)	1 (3%)	0	0
Peripheral neuropathy	1 (3%)	0	0	0	1 (3%)	1 (3%)	0	0
Delirium	0	1 (3%)	0	0	0	1 (3%)	0	0
Psychotic disorder	0	1 (3%)	0	0	0	0	0	0

Data are n (%). The table lists treatment-related adverse events of any grade occurring in 10% or more of all patients or grade 3–4 adverse eve
determined by investigator. †National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Table 2: Adverse events related to study drug* (at starting dose) by grade†

Heinrich et al., Lancet Oncol 2020

Herzlichen Dank für Ihre Aufmerksamkeit!