Lernen Sie zwei neue GIST-Therapien besser kennen:

- **Gegen Exon 18 - D842V: BLU-285 - Avapritinib (Ayvakit®)**
- **GIST 4.-Linie: DCC-2618 - Ripretinib (Qinlock®)**

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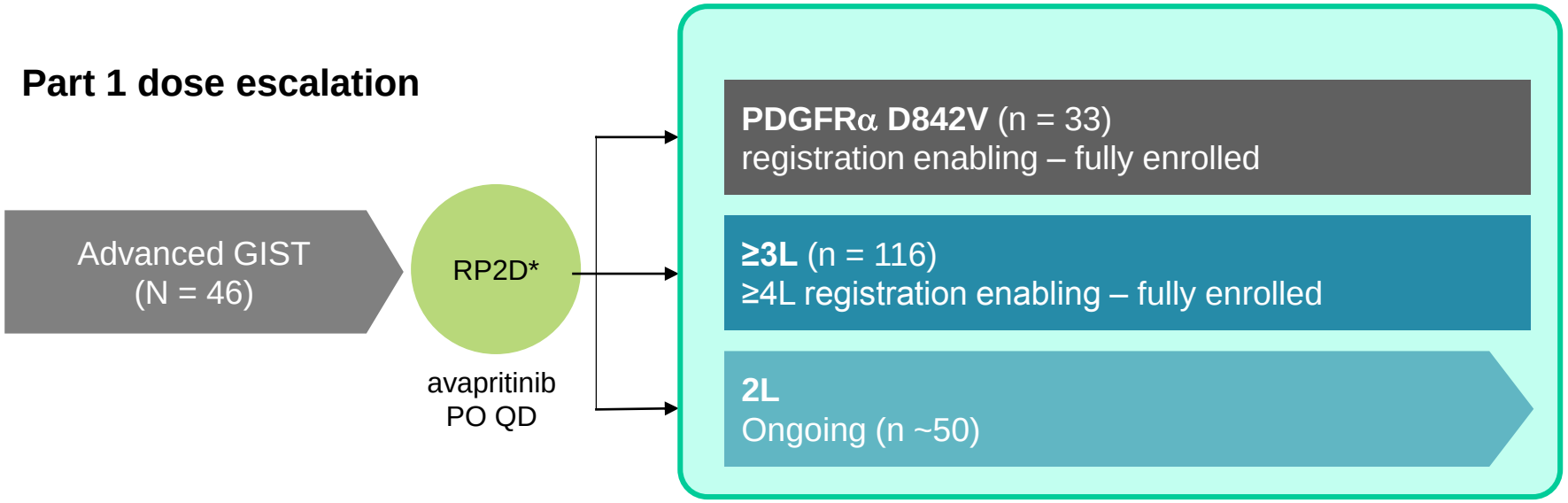
DKG KREBSGESELLSCHAFT | Zertifiziertes Sarkomzentrum

BLU-285 - Avapritinib (Ayvakit®)

NAVIGATOR Phase 1 Studiendesign



KEY OBJECTIVES

- Determine MTD/RP2D, safety, PK and clinical activity by line of therapy and mutational status
- ORR/DOR per central radiology assessment (mRECIST 1.1) for planned NDA and MAA regulatory filings

RP2D, recommended Phase 2 dose; PO, orally; QD, once daily; MTD, maximum tolerated dose; PK, pharmacokinetics; DOR, duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NDA, New Drug Application; MAA, Marketing Authorization Application.
*MTD 400 mg; RP2D 300 mg.

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

*Contributed equally

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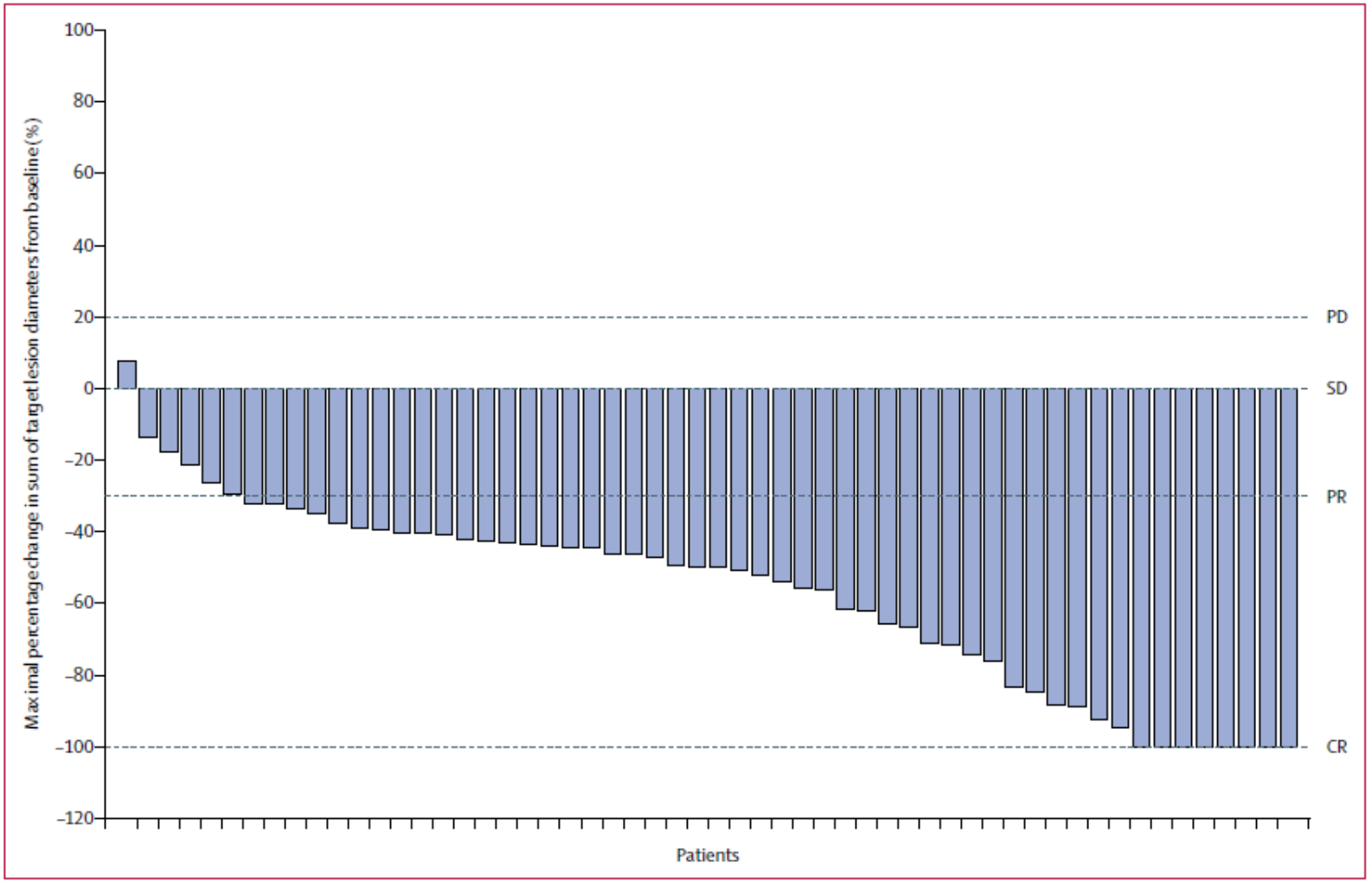


Figure 2: **Maximal percentage change in sum of target lesion diameters from baseline in patients with PDGFRA D842V-mutant gastrointestinal stromal tumours**

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.

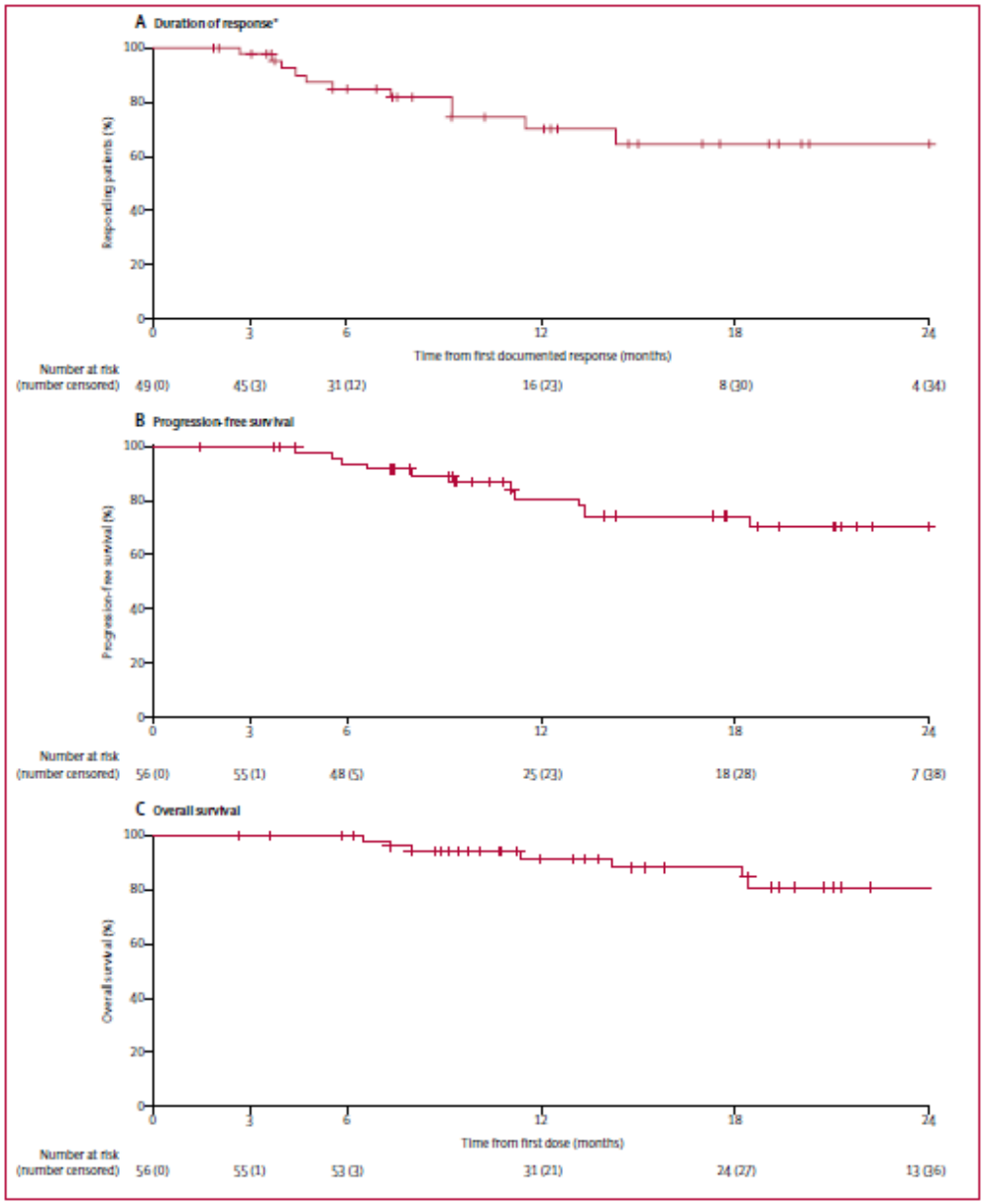
Heinrich et al., Lancet Oncol 2020

	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

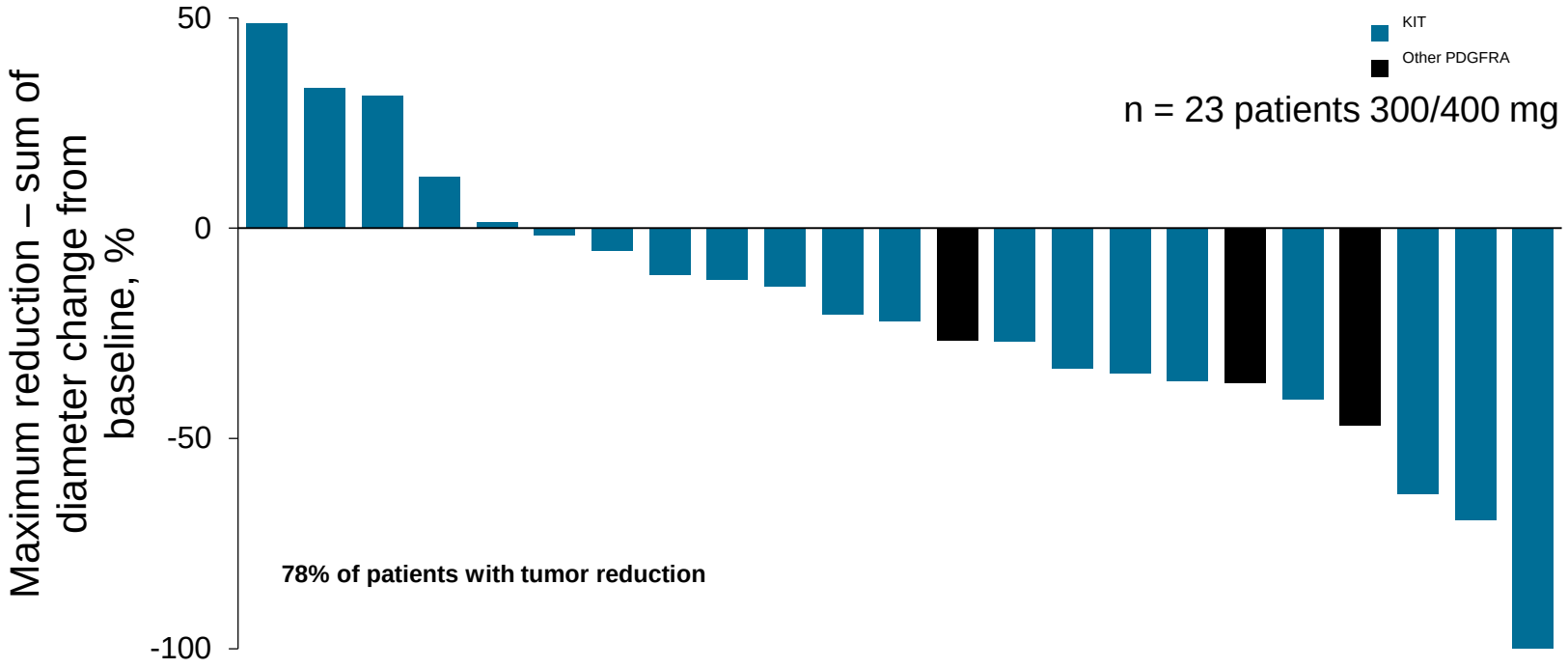
Headache	3 (10%)	0	0	0	4 (13%)	0	0	0
Hyperbilirubinaemia	3 (10%)	1 (3%)	0	0	2 (6%)	1 (3%)	0	0
Dry mouth	4 (13%)	0	0	0	2 (6%)	0	0	0
Pleural effusion	2 (7%)	1 (3%)	0	0	3 (9%)	1 (3%)	0	0
Cognitive disorder	1 (3%)	1 (3%)	0	0	4 (13%)	0	0	0
Dry skin	2 (7%)	0	0	0	3 (9%)	0	0	0
Hypomagnesaemia	2 (7%)	1 (3%)	0	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†

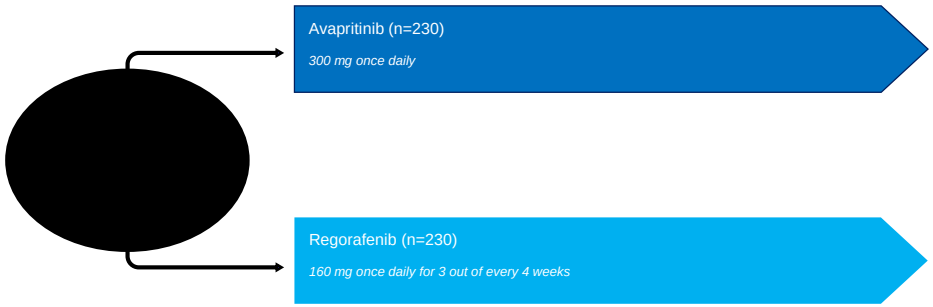
Heinrich et al., Lancet Oncol 2020

Best response by central radiology in 3L/4L regorafenib-naïve GIST



Phase 3 VOYAGER trial now enrolling patients with 3L and 4L GIST

VOYAGER GIST



Primary end point: progression-free survival[1]

Design1

- Open-label, randomized, phase 3 clinical trial
- Patients are randomized to receive either avapritinib or regorafenib
- Patients assigned to receive regorafenib may cross over to receive avapritinib following confirmed disease progression
- Key secondary end points include QoL measures

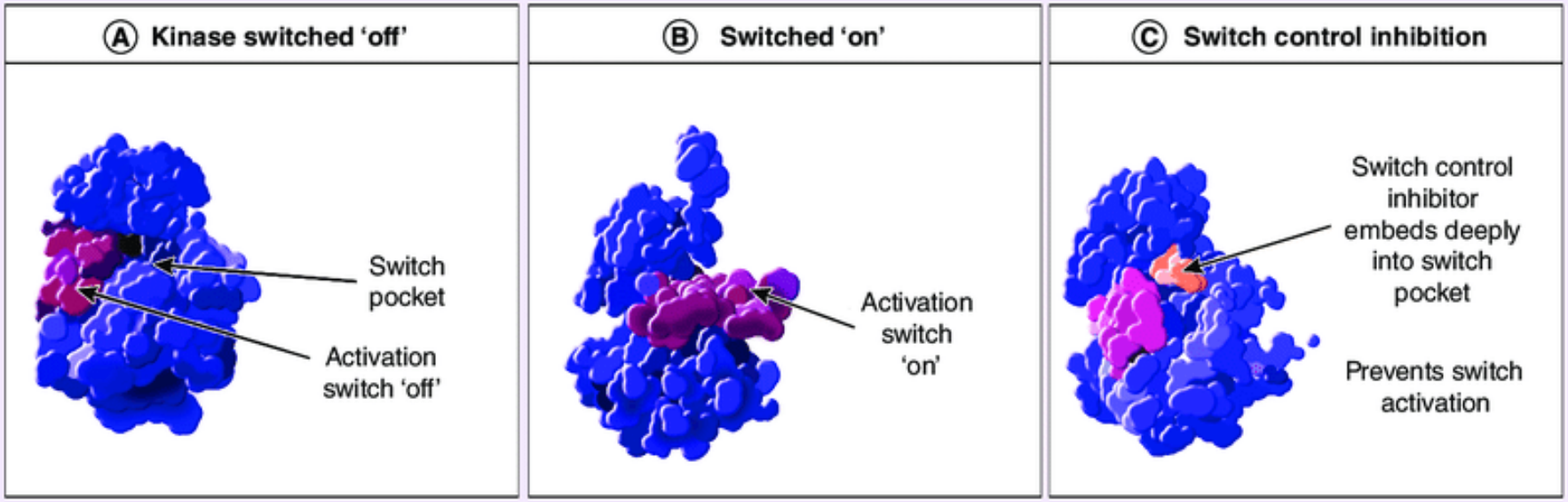
Eligibility1

- Aged 18 years or older
- Metastatic and/or unresectable GIST
- Have received imatinib and 1 or 2 other kinase inhibitors (regorafenib naïve).

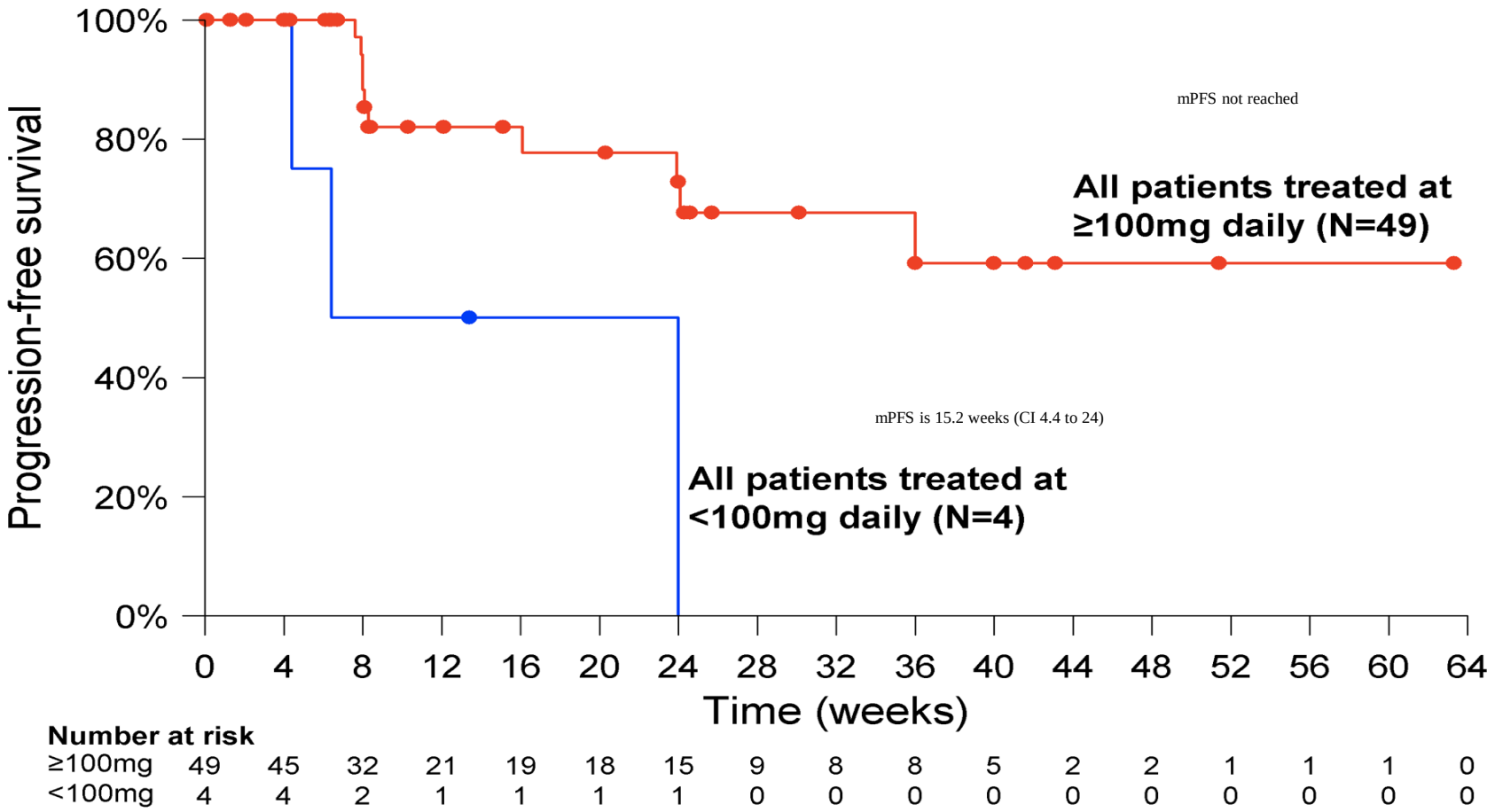
More information

- Website: www.VoyagerTrial.com
- Email: studydirector@blueprintmedicines.com

DCC-2618 - Ripretinib (Qinlock®)


A Kinase switched 'off'
Switch pocket
Activation switch 'off'
B Switched 'on'
Activation switch 'on'
C Switch control inhibition
Switch control inhibitor embeds deeply into switch pocket
Prevents switch activation

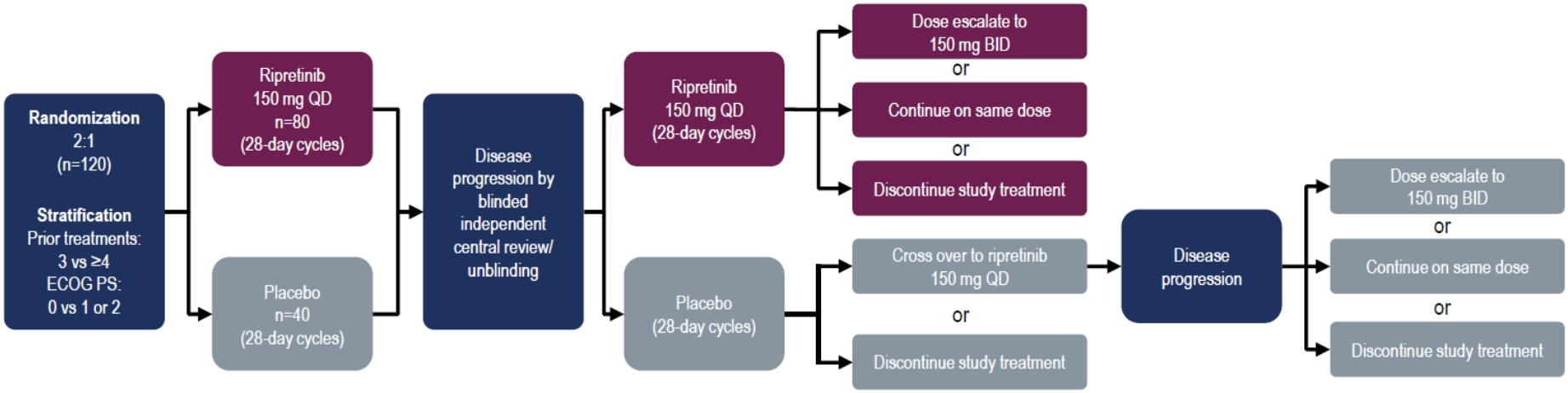
Repritinib (DCC-2618): Progression-free survival in heavily pretreated GIST



Janku F et al., ESMO 2017

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

Articles

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

Jean-Yves Blay, César Serrano, Michael C Heinrich, John Zalcberg, Sebastian Bauer, Hans Gelderblom, Patrick Schöffski, Robin L Jones, Steven Attia, Gina D'Amato, Ping Chi, Peter Reichardt, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Suzanne George, Margaret von Mehren

Summary

Background Resistance to approved inhibitors of *KIT* proto-oncogene, receptor tyrosine kinase (*KIT*), and platelet-derived growth factor receptor α (PDGFRA) is a clinical challenge for patients with advanced gastrointestinal stromal tumours. We compared the efficacy and safety of ripretinib, a switch-control tyrosine kinase inhibitor active against a broad spectrum of *KIT* and *PDGFRA* mutations, with placebo in patients with previously treated, advanced gastrointestinal stromal tumours.

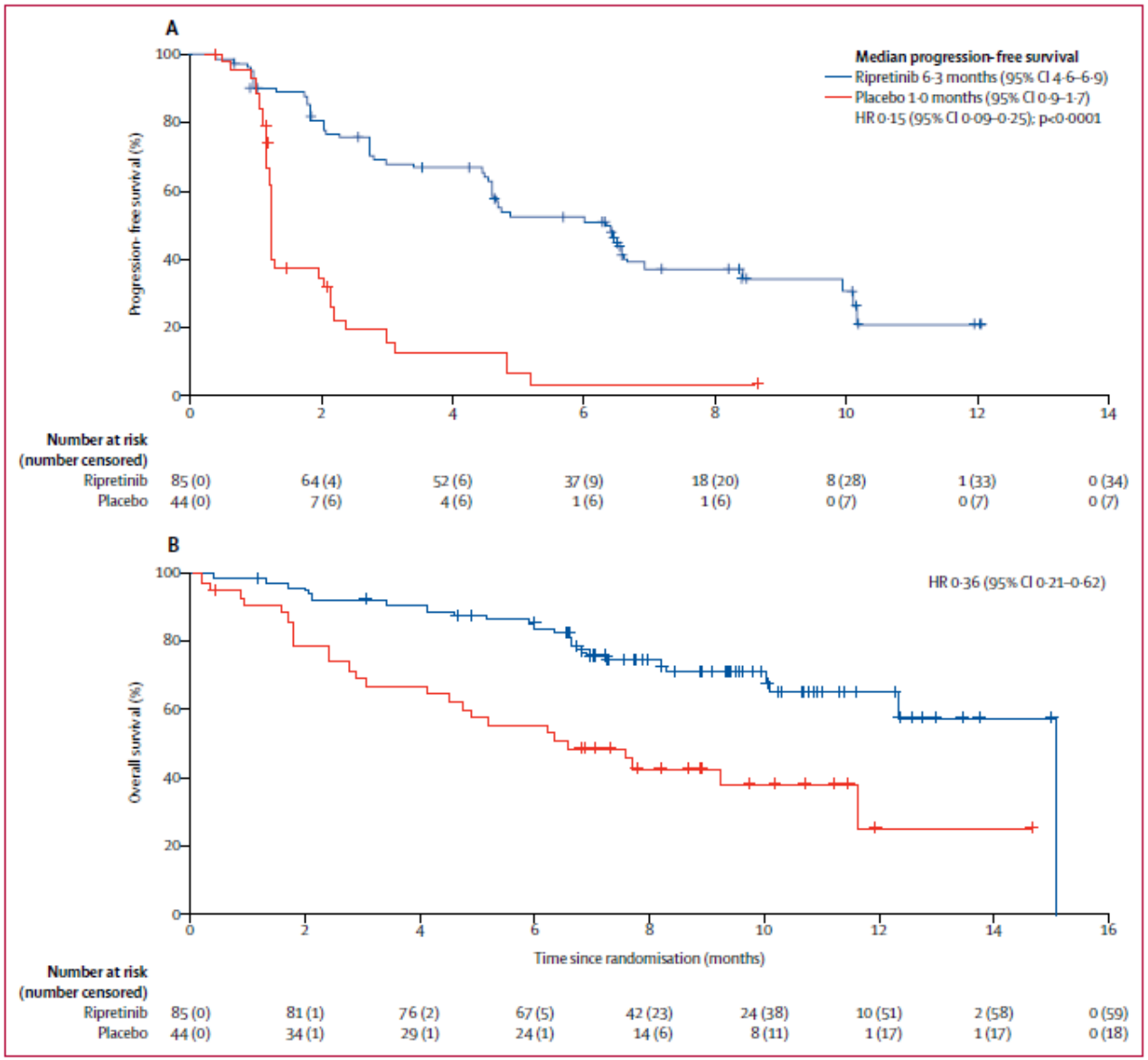
Lancet Oncol 2020
Published Online June 5, 2020
https://doi.org/10.1016/S1470-2045(20)30168-6
See Online/Comment

	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 (95%; 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.

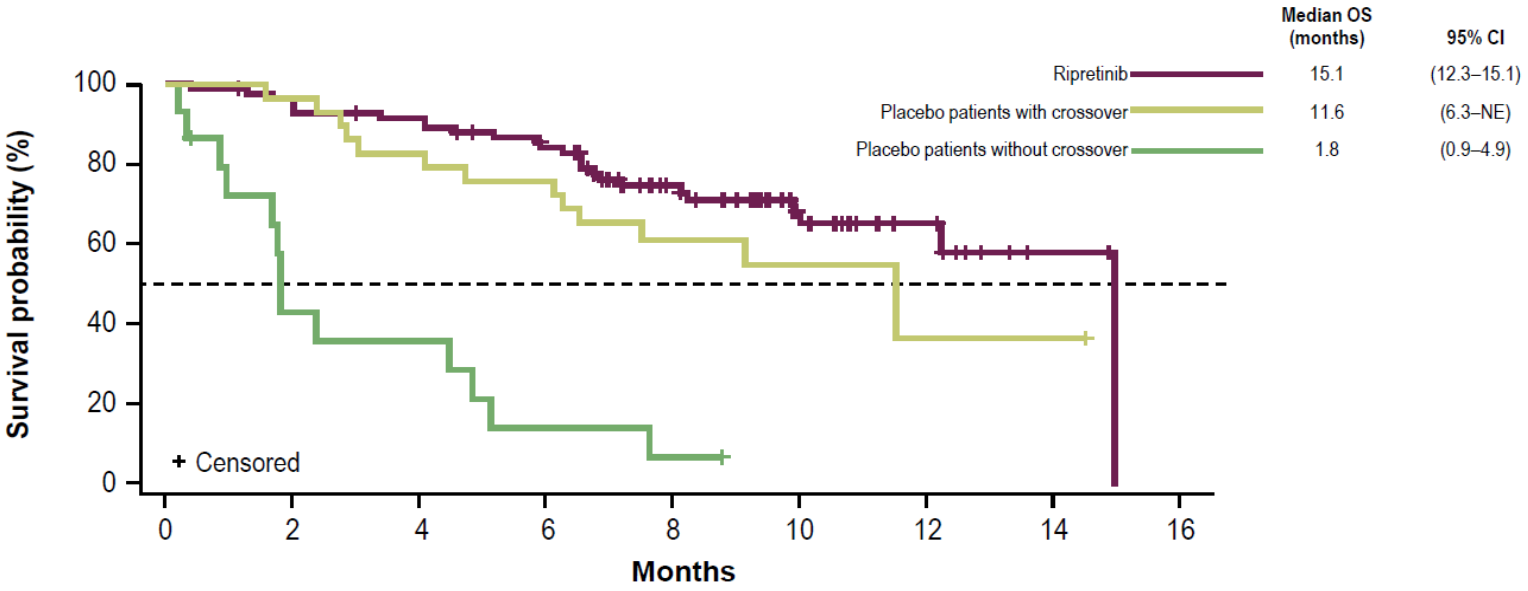
Table 2: Objective response rate*

Blay et al., Lancet Oncol 2020



Blay et al., Lancet Oncol 2020

Crossover Provided OS Benefit



Number of patients at risk:									
Ripretinib	85	81	76	67	42	24	10	2	0
Placebo patients with crossover	29	28	24	22	13	8	1	1	0
Placebo patients without crossover	15	6	5	2	1	0			

	Ripretinib group (n=85)				Placebo group (n=43)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Alopecia	42 (49%)†	..	..	..	1 (2%)	..	..	..
Myalgia	23 (27%)	1 (1%)	..	..	4 (9%)	0	..	..
Nausea	21 (25%)	1 (1%)	..	..	1 (2%)	0	..	..
Fatigue	20 (24%)	2 (2%)	..	..	6 (14%)	1 (2%)	..	..
Palmar–plantar erythrodysesthesia syndrome	18 (21%)	0	..	..	0	0	..	..
Diarrhoea	17 (20%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Constipation	13 (15%)	0	0	0	3 (7%)	0	0	0
Decreased appetite	12 (14%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Weight loss	13 (15%)	0	..	..	3 (7%)	0	..	..
Blood bilirubin increased	12 (14%)	0	0	..	0	0	0	..
Arthralgia	10 (12%)	0	..	..	0	0	..	..
Muscle spasms	10 (12%)	0	..	..	2 (5%)	0	..	..
Hypertension	4 (5%)	3 (4%)	0	0	1 (2%)	0	0	0
Lipase increase	4 (5%)	4 (5%)	0	..	0	0	0	..
Pain in extremity	5 (6%)	1 (1%)	..	..	1 (2%)	0	..	..
Hypophosphataemia	3 (4%)	2 (2%)	0	0	0	0	0	0
Anaemia	2 (2%)	0	1 (1%)	0	1 (2%)	2 (5%)	1 (2%)	0
Blood triglycerides increase	1 (1%)	1 (1%)	0	0	0	0	0	0

Blay et al., Lancet Oncol 2020

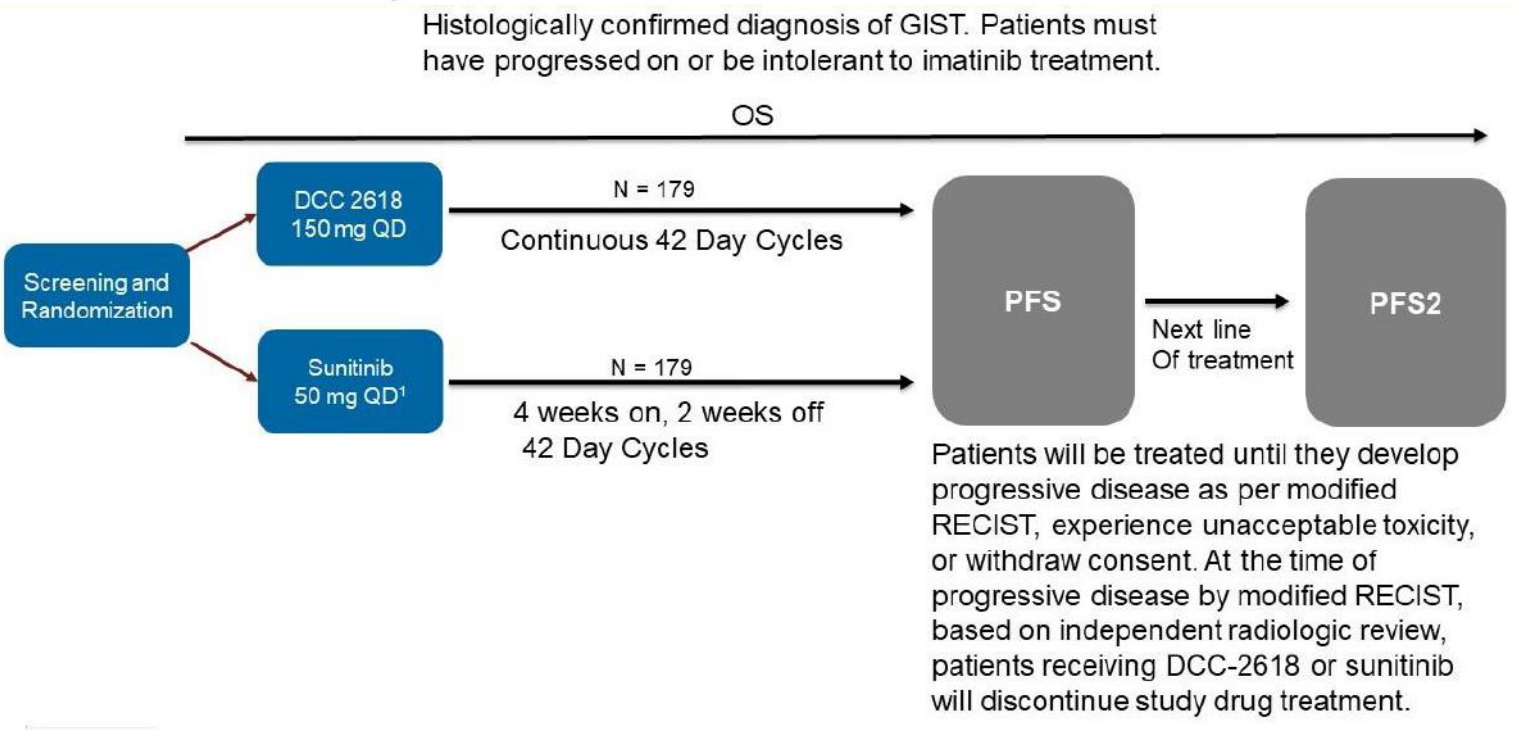
Dermatosis	1 (1%)	1 (1%)	0	0	0	0	0	0
Dehydration	1 (1%)	0	0	0	0	1 (2%)	0	0
Gastroesophageal reflux disease	1 (1%)	1 (1%)	..	..	0	0	..	..
Hyperkalaemia	0	1 (1%)	0	0	0	1 (2%)	0	0
Hypokalaemia	0	1 (1%)	0	0	0	0	0	0
Anal abscess	0	1 (1%)	0	0	0	0	0	0
Ascites	0	1 (1%)	0	0	0	0	0	0
Cardiac failure	0	1 (1%)	0	0	0	0	0	0
Death, reason unknown	..	..	..	1 (1%)	..	..	..	0
Fecaloma	0	1 (1%)	0	0	0	0	0	0
Skin infection	0	1 (1%)	0	0	0	0	0	0
Syncope	..	1 (1%)	..	..	..	0	..	..
Upper gastrointestinal haemorrhage	0	1 (1%)	0	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	1 (2%)	0	0
Pulmonary oedema	0	0	0	0	0	0	1 (2%)	0
Septic shock	..	..	0	0	..	..	0	1 (2%)

Data are n (%). Treatment-related treatment-emergent adverse events are listed that occurred in ≥10% of patients in either treatment group or were reported as grade 3, 4, or 5 in either treatment group are shown. .. indicates that no data were captured per adverse event grade ratings specified by Common Terminology Criteria for Adverse Events version 4.03. *44 patients were randomly assigned to receive placebo, but one patient did not receive treatment. †24 (63%) of 38 women who were given ripretinib had alopecia.

Table 3: **Treatment-related treatment-emergent adverse events**

Blay et al., Lancet Oncol 2020

Phase 3 INTRIGUE trial now enrolling patients with 2L GIST



[1]Sunitinib dose modifications are allowed per approved package insert or institutional guidelines. Every effort should be made to continue patients on the initial regimen throughout the first cycle, unless toxicity mandates dose modification. PK-guided dosing is not allowed.

Herzlichen Dank für Ihre Aufmerksamkeit!