Clinical Response to Avapritinib by RECIST and Choi Criteria in ≥4th Line and PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST)

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Disclosures

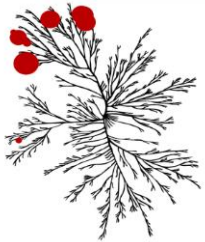
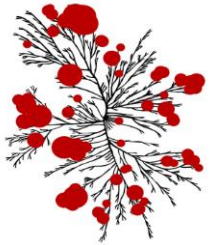
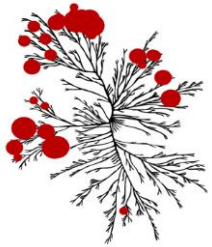
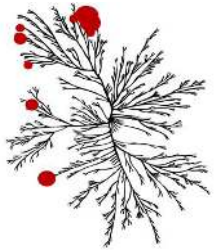
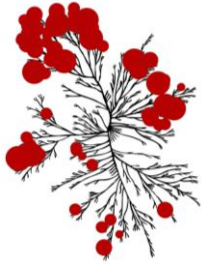
- Avapritinib is an investigational agent discovered and currently in development by Blueprint Medicines and has not been approved by the U.S. Food and Drug Administration or any other health authority for use in the U.S. or any other jurisdiction for any indication
- Data are based on a cutoff date of November 16, 2018
- Dr. Robin Jones is an investigator for Blueprint Medicines' ongoing clinical studies in unresectable gastrointestinal stromal tumors
- Dr. Robin Jones has the following disclosures:
  - Consultant: Blueprint Medicines, Lilly, Immune Design, Merck Serono, Adaptimmune, Daiichi Sankyo, Eisai, Morphotek, TRACON Pharma, Immodulon Therapeutics, Deciphera, PharmaMar, Clinigen Group, and Epizyme, UpToDate
  - Research funding: GlaxoSmithKline, MSD
- Disclosures for all authors are reported at the end of this presentation

Background

- The standard of care for metastatic GIST post-imatinib involves sequential use of multi-targeted tyrosine kinase inhibitors[1–4]
- No effective therapy is currently approved for GIST after failure of imatinib, sunitinib, and regorafenib[1–7]
- Avapritinib is an investigational precision therapy designed to be a highly selective and potent inhibitor of KIT and PDGFRA mutant kinases[8]
- Radiologic assessment of GIST can be challenging, especially when measurement of tumor size is used alone, as is done with mRECIST 1.1, the standard criteria used to assess response in oncology clinical trials[9]
- Choi criteria, which utilizes both unidimensional tumor measurements as well as change in tumor density, can be used to assess clinical activity[10]

[1]Sutent® [package insert]. Pfizer Laboratories; 2017; [2]Stivarga® [package insert]. Bayer HealthCare Pharmaceuticals Inc; 2017; [3]Demetri GD, et al. *Lancet* 2006;368:1329–38; [4]Demetri GD, et al. *Lancet* 2013;381:295–302; [5]Nishida T, et al. *Gastric Cancer* 2016;19:3–14; [6]Serrano C, George S. *Ther Adv Med Onc* 2014;6:115 – 27; [7]Cassier PA, et al. *Clin Cancer Res* 2012;18:4458–64; [8]Evans EK, et al. *Sci Transl Med* 2017;9. pii: eaao1690; [9]Choi H, et al. *AJR Am J Roentgenol* 2004;183:1619–28; [10]Choi H, et al. *J Clin Oncol.* 2007;25:1753–1759. GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha.

Avapritinib is a selective KIT/PDGFRA inhibitor

	Selective therapies	Multi-targeted kinase therapies	
Approved for GIST	 Imatinib	 Sunitinib	 Regorafenib
Investigational for GIST	 Avapritinib	 Ripretinib	

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

NAVIGATOR (NCT02508532) is an open-label, dose escalation/dose expansion study of avapritinib

Safety population
N=204
Avapritinib 300/400 mg orally once daily

Key eligibility:
- Advanced GIST following at least 2 prior lines of TKI therapy
- Mutation in *KIT* or *PDGFRA*[b]

Pivotal analyses
Populations with no approved therapy

PDGFRA Exon 18 GIST	4L+ GIST[a]
n=43	n=121
Response evaluable n=43	Response evaluable n=111

Avapritinib once daily at the RP2D of 300 mg or MTD of 400 mg

Key objectives: Overall response rate, duration of response, and safety

[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.

Most common AEs occurring in ≥20% of the 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

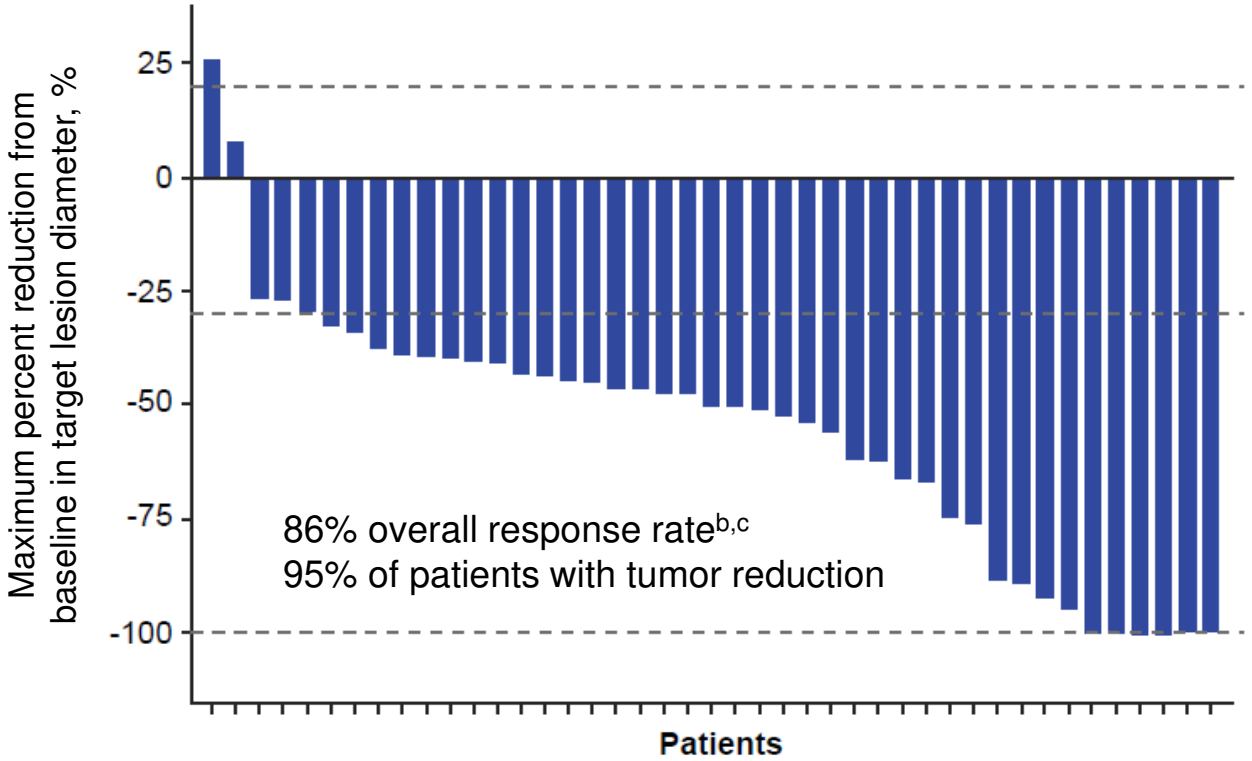
[a]Cognitive effects include pooled terms of memory impairment (29%), cognitive disorder (11%), confusional state (7%), and encephalopathy (1%). Blueprint Medicines considered all cognitive effect AEs as treatment-related in this analysis. [b]All grade AEs occurring in ≥20% of patients. [c]Grade ≥3 AEs 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.

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.

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.

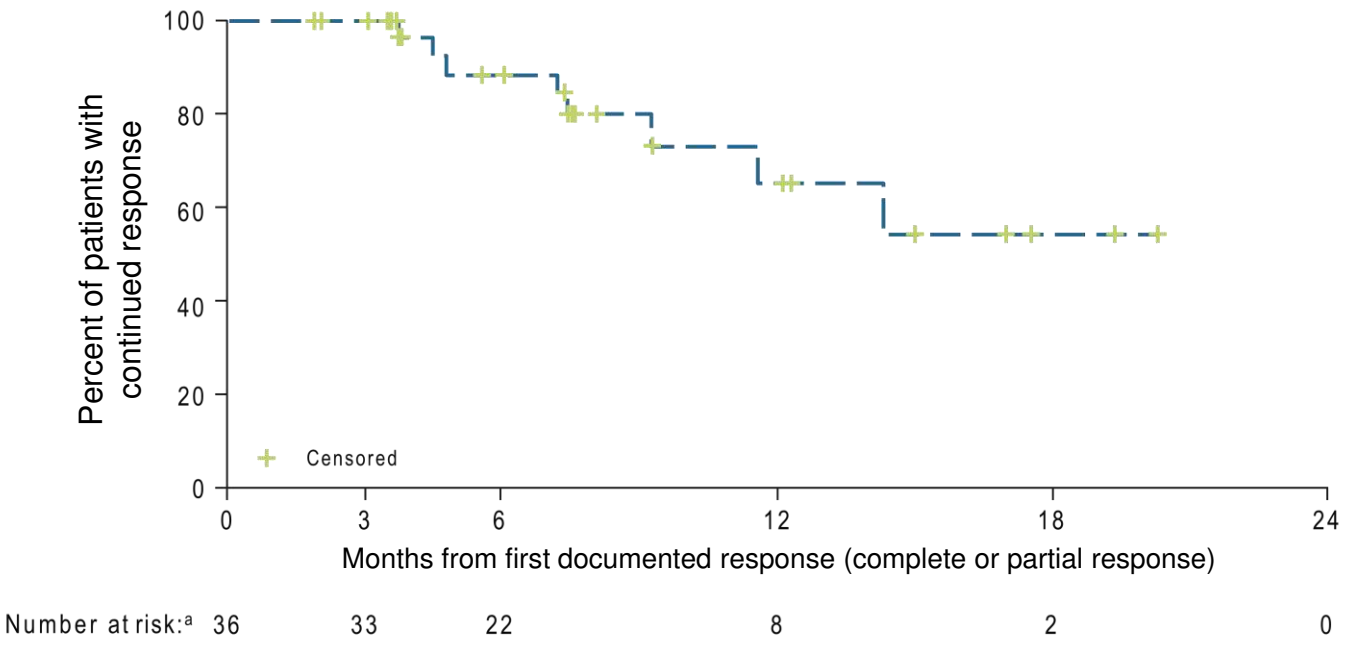
Overall response rate in response-evaluable patients[a]
PDGFRA Exon 18 GIST – avapritinib starting dose 300/400 mg QD (central radiology)

Response (central radiology review), % (n)	mRECIST (n=43)	Choi criteria (n=43)
Overall response rate[b] [95% CI]	86% (37)[d] [72.1–94.7]	95% (41) [84.2–99.4]
Clinical benefit rate[c] [95% CI]	95% (41) [84.2–99.4]	95% (41) [84.2–99.4]
Complete response	7% (3)	7% (3)
Partial response	79% (34)[d]	88% (38)
Stable disease	12% (5)	2% (1)
Progressive disease	2% (1)	2% (1)

Best response by line of therapy, % (n) (mRECIST)	First line (n=5)	≥2nd line (n=38)
Complete response	40% (2)	3% (1)
Partial response	60% (3)	82% (31)[d]
Stable disease	0	13% (5)

[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 mRECIST 1.1 in patients treated with avapritinib starting dose 300/400 mg once daily. [c]Proportion with complete response, partial response, or stable disease lasting ≥16 weeks from first dose. [d]1 response pending confirmation. CI, confidence interval; QD, once daily.

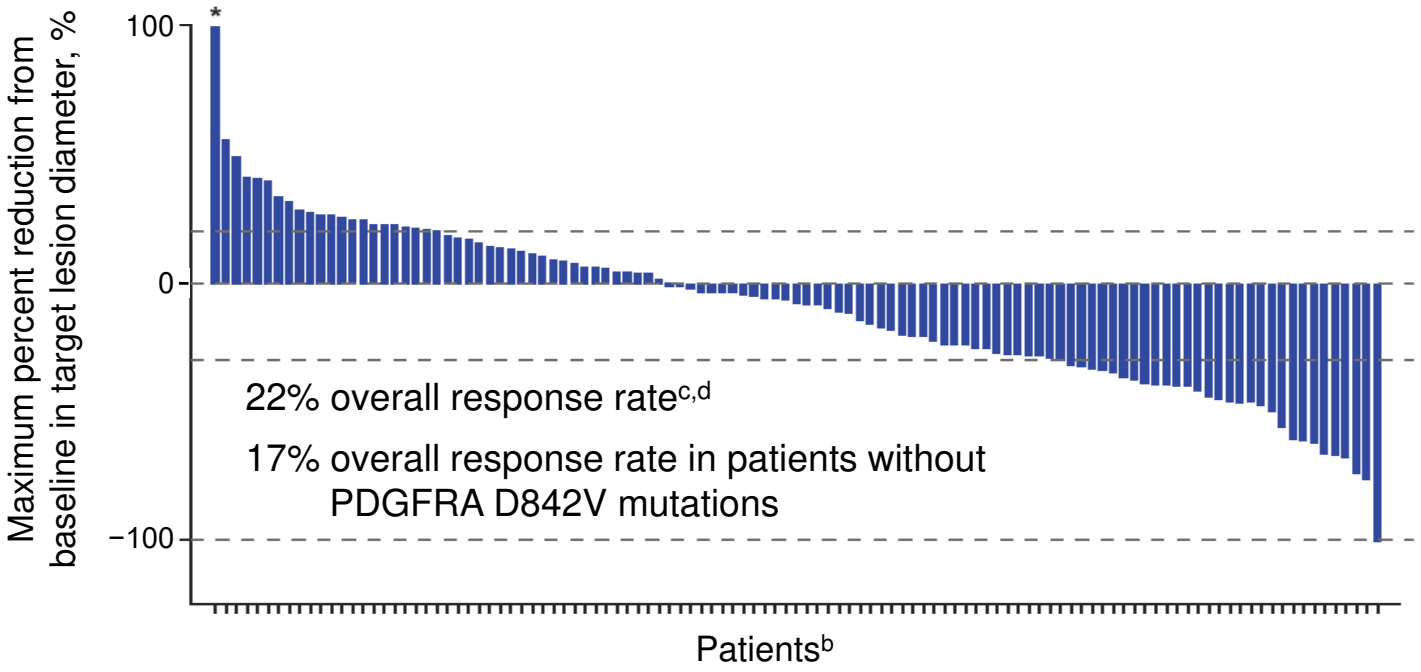
Duration of response
PDGFRA Exon 18 GIST – avapritinib starting dose 300/400 mg QD



- 78% (28/36) of responding PDGFRA exon 18 patients did not have disease progression as of 16 November 2018 (data cutoff), median DOR not reached
- PFS at 12 months was 74% (95% CI, 57.7-90.2), median PFS not reached
- OS at 12 months was 90% (95% CI, 80.0-99.3), median OS not reached

[a]Patients with a confirmed response. CI, confidence interval; DOR, duration of response; OS, overall survival; PFS, progression-free survival; QD, once daily.

Antitumor activity in response-evaluable patients[a]
4L+ treatment – avapritinib starting dose 300/400 mg QD (central radiology)



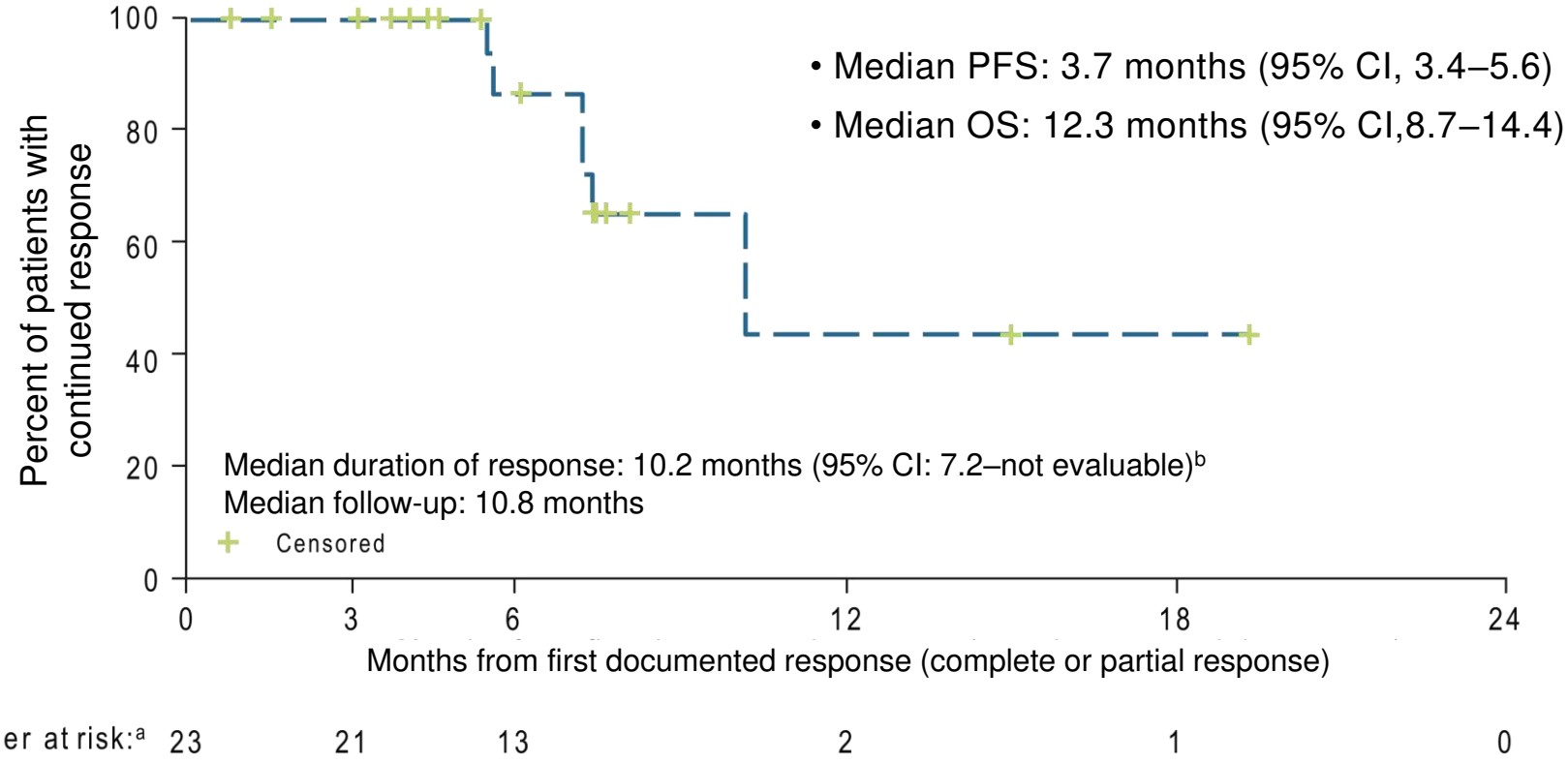
*One patient had an outlier value of >200% increase in target lesion diameter. [a]Response-evaluable patients were comprised of patients who had ≥1 target lesion assessed at baseline by central radiology review and had ≥1 post-baseline disease assessment by central radiology. [b]Two patients who had best response assessment are not included in the plot because they did not have measurable target lesions at baseline and thus, no percent change could be calculated. [c]1 partial response pending confirmation. [d]Includes 8 patients with PDGFRA D842V mutations; duration of response remains unchanged when these patients were removed from analysis. QD, once daily.

Overall response rate in response-evaluable patients[a]
4L+ treatment – avapritinib starting dose 300/400 mg QD (central radiology)

Response, % (n)	mRECIST (n=111)	Choi criteria (n=111)
Overall response rate,[b] [95% CI]	22% (24)[d,e] [14.4–30.4]	38% (42)[e] [28.8–47.5]
Clinical benefit rate,[c] [95% CI]	41% (46)[e] [32.2–51.2]	41% (46)[e] [32.2–51.2]
Complete response	1% (1)	1% (1)
Partial response	21% (23)[d]	37% (41)
Stable disease	47% (52)	29% (32)
Progressive disease	32% (35)	33% (37)

[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 mRECIST 1.1 in patients treated with avapritinib starting dose 300/400 mg once daily. [c]Proportion with complete response, partial response, or stable disease lasting ≥16 weeks from first dose. [d]1 response pending confirmation. [e]Includes 8 patients with PDGFRA D842V mutations. CI, confidence interval.

Duration of response
4L+ treatment – avapritinib starting dose 300/400 mg QD



[a]Patients with a confirmed response. [b]Duration of response is unchanged without the inclusion of patients with PDGFRA D842V mutations.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; QD, once daily.

Conclusions

- Avapritinib showed important clinical activity in patients with advanced GIST who have no approved therapies
  - Among patients with PDGFRA exon 18 mutated GIST, 86% of patients responded, with 78% in response at data cutoff
  - In patients treated in the 4L+ setting, 22% of patients responded and responses were durable
  - Response rate as assessed by Choi may represent a complimentary measure of clinical benefit when used in conjunction with mRECIST
- Avapritinib was generally well tolerated
  - Most AEs were grade 1 or grade 2, predictable, and manageable
- Based on antitumor activity and safety, avapritinib 300 mg QD is the recommended dose for patients with unresectable or metastatic GIST
- Data from the NAVIGATOR study led to evaluation of avapritinib in the phase 3 VOYAGER study vs regorafenib (NCT03465722), which has completed target enrollment

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Declaration of interests (1 of 3)

- MH owns stock in MolecularMD; has received honoraria from Novartis; has served in advisory or consultancy roles for MolecularMD, Novartis, Blueprint Medicines, and Deciphera; and has provided expert testimony for Novartis. He has a patent “Activating Mutations of PDGFRA”. His institution receives royalties for a patent “Treatment of Gastrointestinal Stromal Tumors”licensed by Novartis.
- RLJ has served in advisory or consultancy roles for Blueprint Medicines, Lilly, Immune Design, Merck Serono, Adaptimmune, Daiichi Sankyo, Eisai, Morphotek, TRACON Pharma, Immodulon Therapeutics, Deciphera, PharmaMar, Clinigen Group, Epizyme, and UpToDate; and has received institutional research funding from GlaxoSmithKline and MSD.
- MvM reports a leadership position with NCCN (chair of the Soft Tissue Sarcoma panel); has served in advisory or consultancy roles for Blueprint Medicines, Deciphera, Arog, and Exelexis; and has received research funding from Blueprint Medicines, Deciphera, Arog, and Novartis.
- SB has received honoraria from Novartis, Pfizer, Bayer, PharmaMar, and GlaxoSmithKline; has served in advisory or consultancy roles for Blueprint Medicines, Bayer, Lilly, Deciphera, Exelixis, Janssen-Cilag, Plexxikon, and Nanobiotix; has received institutional research funding from Blueprint Medicines, Novartis, and Incyte; and has received travel and accommodation funding from PharmaMar.
- Y-KK has served in advisory or consultancy roles for Lilly/ImClone, Taiho Pharmaceutical, Roche/Genentech, Merck Serono, DAW HWA Pharmaceutical, Bristol-Myers Squibb, Astellas Pharma, and LSK BioPharma; and has received research funding from LSK BioPharma and DAE HWA Pharmaceutical.
- PS has served in an advisory or consultancy role for Exelixis (honoraria provided to PS) as well as Plexxikon, Eisai, Loxo Oncology, Lilly, Blueprint Medicines, Ellipses Pharma, Deciphera, Merck, SERVIER, Genmab, Adaptimmune, Intellisphere, and Transgene (honoraria provided to institution); and he has received institutional research funding from Blueprint Medicines, Boehringer Ingelheim, CoBioRes NV, Eisai, Lilly, Excelixis, G1 Therapeutics, Novartis, PharmaMar, and Plexxikon.

Declaration of interests (2 of 3)

- FE has served in advisory or consultancy roles for Merck Serono, Roche, Eisai, and Ipsen; and has received travel and accommodation funding from Pfizer.
- OM owns stock in Transgene; has received honoraria from Roche; has served in advisory or consultancy roles for AstraZeneca, Amgen, Bayer, Lilly, GlaxoSmithKline, Novartis, Pfizer, Roche, SERVIER, and Vifor Pharma; has served on speakers' bureaus for Lilly and Roche; and has received travel and accommodation funding from Roche, Pfizer, and PharmaMar.
- PAC has received honoraria from Novartis, Roche/Genentech, Blueprint Medicines, and Amgen; has received institutional research funding from Novartis, Roche/Genentech, Lilly, Blueprint Medicines, Bayer, AstraZeneca, Celgene, Plexxikon, Abbvie, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme, Taiho Pharmaceutical, Toray Industries, Transgene, Loxo Oncology, GlaxoSmithKline, Innate Pharma, and Janssen; and has received travel and accommodation funding from Roche, Amgen, Novartis, Bristol-Myers Squibb, and Merck Sharp & Dohme.
- CS has received honoraria from Bayer; has served in advisory or consultancy roles for Deciphera and Blueprint Medicines; has received research funding from Deciphera, Bayer, and Pfizer; and has received travel and accommodation funding from Novartis, Lilly, PharmaMar, Pfizer, and Bayer.
- WDT has served in leadership roles at and owns stock in Certis Oncology Solutions and Atropos; has served in advisory or consultancy roles for EMD Serono, Janssen, Lilly, Daiichi Sankyo, Novartis, Eisai, Immune Design, Blueprint Medicines, Loxo Oncology, Agios, GlaxoSmithKline, and Nanocell Therapy; has received research funding from Novartis, Lilly, Plexxikon, Daiichi Sankyo, TRACON Pharma, Blueprint Medicines, Immune Design, BioAtla, and Deciphera; and reports a patent/royalty/other intellectual property for companion diagnostics for CDK4 inhibitors - 14/854,329.
- JT has received honoraria from GlaxoSmithKline and has served in advisory or consultancy roles for Novartis, Lilly, and Janssen.

Declaration of interests (3 of 3)

- PR has received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Lilly, and Pfizer; has served in advisory or consultancy roles for Novartis, Blueprint Medicines, Bristol-Myers Squibb, Pierre Fabre, Merck Sharp & Dohme, and Amgen; has served on speakers' bureaus for Pfizer, Novartis, and Lilly; has received research funding from Novartis, Roche, and Bristol-Myers Squibb; and has received travel and accommodation funding from Orphan Europe and Pierre Fabre.
- SP has served as a paid consultant to Novarits, Daiichi Sankyo, Immune design, and Epizyme; had received research support from Blueprint Medicines, Bavarian Nordic, Janssen, and Eisai
- SPC has received honoraria from Amgen, Roche, GlaxoSmithKline, Threshold Pharmaceuticals, CytRx Corporation, Ignyta, Immune Design, TRACON Pharma, Karyopharm Therapeutics, SARC: Sarcoma Alliance for Research though Collaboration, and Janssen; has served in advisory or consultancy roles for Amgen, Roche, GlaxoSmithKline, Threshold Pharmaceuticals, CytRx Corporation, Ignyta, Immune Design, TRACON Pharma, Karyopharm Therapeutics, SARC: Sarcoma Alliance for Research though Collaboration, and Janssen; has served on speakers' bureaus for Amgen, Roche, GlaxoSmithKline, Threshold Pharmaceuticals, CytRx Corporation, Ignyta, Immune Design, TRACON Pharma, Karyopharm Therapeutics, SARC: Sarcoma Alliance for Research though Collaboration, and Janssen; and has received research funding from Amgen, Roche, GlaxoSmithKline, Threshold Pharmaceuticals, CytRx Corporation, Ignyta, Immune Design, TRACON Pharma, Karyopharm Therapeutics, SARC: Sarcoma Alliance for Research though Collaboration, and Janssen.
- EM has no financial relationships to disclose
- TZ and MR are employees and equity holders of Blueprint Medicines.
- SG owns stock in Abbott Laboratories and Allergan; has served in advisory or consultancy roles for Blueprint Medicines, Deciphera, Bayer, Eli Lilly, Exelixis, Daiichi Sankyo, UpToDate, Research to Practice, and MORE Health; has received institutional research funding from Pfizer, Novartis, Bayer, ARIAD, Blueprint Medicines, and Deciphera; receives royalties from UpToDate; has provided expert testimony for Bayer; and also reports a relationship with Research to Practice.