Clinical Activity of Avapritinib in ≥4th Line (4L+) and PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST)

Michael Heinrich,[1] Robin L. Jones,[2] Margaret von Mehren,[3] Sebastian Bauer,[4] Yoon-Koo Kang,[5] Patrick Schöffski,[6] Ferry Eskens,[7] Olivier Mir,[8] Philippe Cassier,[9] Cesar Serrano,[10] William D. Tap,[11] Jonathan Trent,[12] Piotr Rutkowski,[13] Shreyaskumar Patel,[14] Sant P. Chawla,[15] Eyal Meiri,[16] Teresa Zhou,[17] Maria Roche,[17] Suzanne George[18]

[1]OHSU Knight Cancer Institute, Portland, OR, USA; [2]Royal Marsden Hospital and Institute of Cancer Research, London, UK; [3]Fox Chase Cancer Center, Philadelphia, PA, USA; [4]University of Duisburg-Essen, Essen, Germany; [5]Asan Medical Centre, Seoul, South Korea; [6]University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [7]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [8]Institut Gustave Roussy, Villejuif, France; [9]Centre Léon Bérard, Lyon, France; [10]Vall d' Hebron Institute of Oncology, Barcelona, Spain; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [13]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [14]MD Anderson Cancer Center, Houston, TX, USA; [15]Sarcoma Oncology Center, Santa Monica, CA, USA; [16]Cancer Treatment Center of America, Atlanta, GA, USA; [17]Blueprint Medicines Corporation, Cambridge, MA, USA; [18]Dana Farber Cancer Institute, Boston, MA, USA

BACKGROUND

- The current standard of care for metastatic GIST post-imatinib involves sequential use of multi-targeted TKIs, which are associated with low ORR and off-target toxicities. As secondary resistance mutations accumulate, multi-targeted TKIs lose activity[1-4]
- Effective approved therapies for the treatment of GIST after failure of imatinib, sunitinib, and regorafenib are limited. Retreatment with imatinib has a 0% ORR[1–7]
- Avapritinib is an investigational precision therapy designed to be a highly selective and potent inhibitor of KIT and PDGFRA mutant kinases[1,2]
- Avapritinib has been approved by the U.S. FDA for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. Avapritinib is not approved for other indications or in other regions of the world[8]

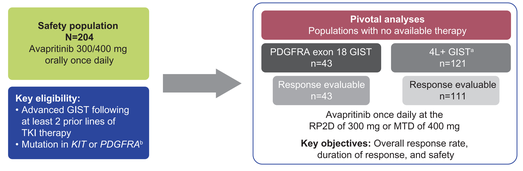
OBJECTIVE

- The objective of this analysis of the NAVIGATOR study (ClinicalTrials.gov Identifier: NCT02508532) was to determine the clinical activity of avapritinib at the RP2D (300 mg QD) and MTD (400 mg QD) in patients with GIST with mutations in PDGFRA exon 18 or in 4L+ irrespective of KIT or PDGFRA mutation

METHODS

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

Study design and objectives.



[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.

RESULTS

- Data are based on a data cut-off date of November 16, 2018. Avapritinib is an investigational agent discovered and currently in development by Blueprint Medicines
- Most AEs were grade 1–2, with a higher incidence of commonly reported AEs in the 400 mg QD dose group compared with the 300 mg QD dose group
- No treatment-related grade 5 AEs were 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 a treatment-related toxicity in the starting dose 300/400 mg QD group
  - Treatment discontinuation due to cognitive effects occurred in 2.0% of patients

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Abbreviations

3L, 3rd treatment line; 4L, 4th treatment line; AE, adverse event; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FDA, Federal Drug Administration; GIST, gastrointestinal stromal tumor; KIT, KIT receptor tyrosine kinase; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MTD, maximum tolerated dose; ORR, overall response rate; PDGFRA, platelet-derived growth factor receptor alpha; PO, orally; QD, once daily; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

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Most common AEs occurring in ≥15% of the safety population

	300/400 mg QD starting dose (N=204)			
	All AEs		Treatment-related AEs	
n (%)	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)	38 (19)	8 (4)
Abdominal pain	41 (20)	11 (5)	-	-
Headache	34 (17)	-	-	-
Dyspnea	34 (17)	5 (2)	-	-
Dyspepsia	32 (16)	-	-	-
Hypokalemia	32 (16)	6 (3)	-	-
Dysgeusia	31 (15)	-	31 (15)	-

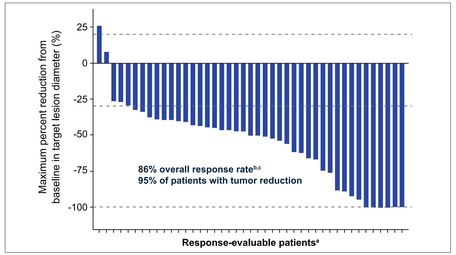
[a]Cognitive effects include pooled terms of memory impairment (29%), cognitive disorder (11%), confusional state (7%), and encephalopathy (1%). Blueprint Medicines considered all cognitive effect AEs as treatment-related in this analysis. [b]All grade AEs occuring in ≥15% of patients. [c]Grade ≥3 AEs occuring in ≥2% of patients.
Note: 3 events of intracranial hemorrhage occurred; 2 were grade 3, 1 was grade 1.

Demographics and baseline characteristics

	300/400 mg starting dose	
Characteristic	PDGFRA exon 18 (n=43)	4L+ (n=121)
Age, median years (min–max)	64 (29–90)	59 (33–80)
Sex, male, n (%)	29 (67)	70 (58)
Race, white, n (%)	29 (67)	86 (71)
GIST mutational subtype, n (%)		
KIT	0	110 (91)
PDGFRA D842V	38 (88)	8 (7)
PDGFRA exon 18 non-D842V[a]	5 (12)	3 (2)
Number of 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 (central radiology review), n (%)		
≤5 cm	20 (47)	40 (33)
>5 to ≤10 cm	14 (33)	57 (47)
>10 cm	9 (21)	22 (18)
Prior surgical resection, n (%)	37 (86)	107 (88)
ECOG performance status, n (%)		
0	14 (33)	39 (32)
1	26 (60)	78 (64)
2	3 (7)	4 (3)

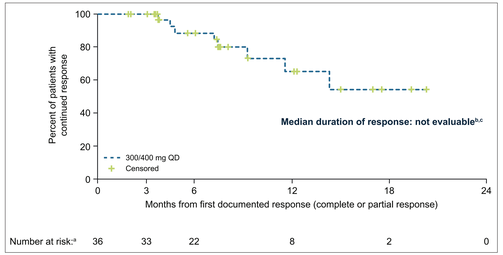
[a]PDGFRA exon 18 non-D842V mutations including D842Y, DI 842-845V, I843_D846del, D842-H845, and DI 842-843V.

Antitumor activity and duration of response: PDGFRA exon 18 GIST (avapritinib 300/400 mg QD starting dose, central radiology review)



Response (mRECIST, central radiology review), % (n)[a]	PDGFRA exon 18 n=43
Overall response rate[b] [95% CI]	86 (37)[c] [72.1–94.7]
Clinical benefit rate[d] [95% CI]	95 (41) [84.2–99.4]
Best response	
Complete response	7% (3)
Partial response	79% (34; 1 pending)
Stable disease	12% (5)
Progressive disease	2% (1)

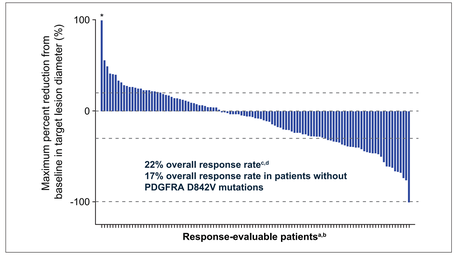
[a]Response-evaluable patients were comprised of patients who had ≥1 target lesion assessed at baseline by central radiology review and had ≥1 post-baseline disease assessment by central radiology. [b]Proportion of response-evaluable patients with a confirmed best response of complete or partial response, 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. [d]Proportion with complete response, partial response, or stable disease lasting ≥16 weeks from first dose.



[a]Patients with confirmed response. [b]Duration of response defined as the time from first documented response (complete or partial response) to the date of first documented disease progression or death due to any cause, whichever came first. [c]95% CI: 11.3 months through not evaluable.

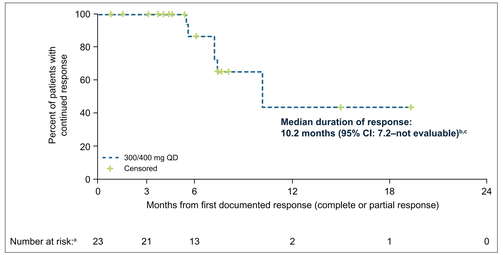
- 78% (28/36) of responding PDGFRA exon 18 patients did not have disease progression as of 16 November 2018 (data cutoff)
- Median follow-up was 10.9 months across all PDGFRA exon 18 patients
- PFS at 12 months was 74% (95% CI, 57.7–90.2), median PFS not reached

Antitumor activity and duration of response: 4L+ treatment (avapritinib 300/400 mg QD starting dose, central radiology review)



Response (mRECIST, central radiology review), % (n)[a]	4L+ n=111
Overall response rate[c] [95% CI]	22% (24)[d] [14.4–30.4]
Clinical benefit rate[e] [95% CI]	41% (46) [32.2–51.2]
Best response	
Complete response	1% (1)
Partial response	21% (23; 1 pending)
Stable disease	47% (52)
Progressive disease	32% (35)

*One patient had an outlier value for percent change from baseline 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]Proportion of response-evaluable patients with a confirmed best response of complete 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. [d]1 partial response pending confirmation. [e]Proportion of patients with complete response, partial response or stable disease lasing ≥16 weeks from first dose.



[a]Patients with confirmed response. [b]Duration of response defined as the time from first documented response (complete or partial response) to the date of first documented disease progression or death due to any cause, whichever came first. [c]Duration of response is unchanged without the inclusion of patients with PDGFRA D842V mutations.

- Median follow-up was 10.8 months across all 4L+ patients
- Median PFS was 3.7 months (95% CI, 3.4–5.6)

Best confirmed response: PDGFRA exon 18 by line of therapy

	300/400 mg QD starting dose		
Best response by line of therapy (mRECIST), % (n)	First line (n=5)	≥Second line (n=38)	Total (n=43)
Complete response	40% (2)	3% (1)	7% (3)
Partial response	60% (3)	82% (31)	79% (34)[a]
Stable disease	0	13% (5)	12% (5)
Progressive disease	0	3% (1)	2% (1)

[a]1 pending confirmation.

- Avapritinib demonstrated clinical activity in first line and subsequent lines of therapy in the PDGFRA exon 18 population

CONCLUSIONS

- Avapritinib showed important clinical activity in patients with advanced GIST who have limited 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
- 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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