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

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BACKGROUND

- The current standard of care for metastatic GIST post-imatinib involves sequential use of multikinase inhibitors, which are associated with low ORR and off-target effects. As secondary resistance mutations accumulate, multikinase inhibitors do not substantially address the underlying molecular basis of the disease and have limited efficacy[1-4]
- Currently, no therapies are approved and available for relapsed GIST after failure of imatinib, sunitinib, and regorafenib. 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 received breakthrough therapy designation from the FDA for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation

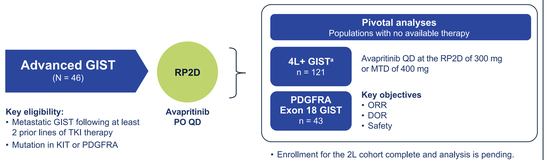
OBJECTIVE

- 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+

METHODS

- NAVIGATOR is an open-label, dose escalation/dose expansion phase 1 study of avapritinib

Study design and objectives.



[a]While enrollment criteria in the study protocol specified that patients in expansion group 1 were required to have received only at least 2 prior lines of TKI therapy, equating to an analysis population of 3L+, the observed enrollment reflected a population more heavily pretreated.

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 Corporation
- Most AEs were grade 1 or 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
  - 2.0% discontinued treatment for cognitive effects

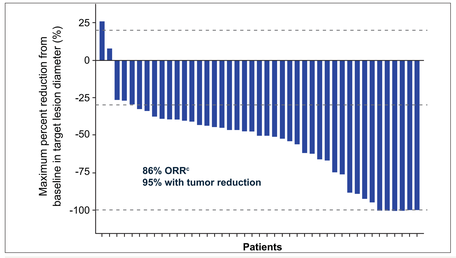
Most Common AEs Occurring in ≥ 15% of Patients % (n)	300/400 mg QD Starting Dose (N = 204)			
	All AEs		Treatment-related AEs	
	All Grades[b]	Grade ≥3[c]	All Grades[b]	Grade ≥3[c]
Nausea	64.2 (131)	2.5 (5)	59.3 (121)	-
Fatigue	55.4 (113)	7.4 (15)	47.1 (96)	6.4 (13)
Anemia	50.0 (102)	28.4 (58)	36.3 (74)	16.2 (33)
Cognitive effects[a]	41.2 (84)	3.9 (8)	41.2 (84)	3.9 (8)
Periorbital edema	40.7 (83)	-	40.2 (82)	-
Vomiting	38.2 (78)	2.0 (4)	31.9 (65)	-
Decreased appetite	37.7 (77)	2.9 (6)	28.4 (58)	-
Diarrhea	37.3 (76)	4.9 (10)	31.9 (65)	2.9 (6)
Increased lacrimation	32.8 (67)	-	30.4 (62)	-
Peripheral edema	30.9 (63)	-	27.0 (55)	-
Face edema	24.5 (50)	-	24.0 (49)	-
Constipation	22.5 (46)	-	-	-
Dizziness	22.1 (45)	-	-	-
Hair color changes	21.1 (43)	-	20.6 (42)	-
Blood bilirubin increased	21.1 (43)	4.4 (9)	18.6 (38)	3.9 (8)
Abdominal pain	20.1 (41)	5.4 (11)	-	-
Headache	16.7 (34)	-	-	-
Dyspnea	16.7 (34)	2.5 (5)	-	-
Dyspepsia	15.7 (32)	-	-	-
Hypokalemia	15.7 (32)	2.9 (6)	-	-
Dysgeusia	15.2 (31)	-	15.2 (31)	-

[a]Cognitive effects include pooled terms of memory impairment (29.4%), cognitive disorder (10.8%), confusional state (7.4%), and encephalopathy (1.5%). Blueprint Medicines considered all cognitive effect AEs as treatment-related in this analysis.
Note: 3 events of intracranial hemorrhage occurred, 2 were grade 3, 1 was grade 1. [b]All grade AEs occuring in ≥15% of patients.
[c]Grade ≥3 AEs occuring in ≥2% of patients.

Characteristic	PDGFRA Exon 18 (n = 43)	4L+ (n = 121)
Age, median (min–max)	64 (29–90)	59 (33–80)
Sex, % (n)		
Male	67.4 (29)	57.9 (70)
Race, % (n)		
White	67.4 (29)	71.1 (86)
GIST mutational subtype, % (n)		
KIT	0	90.9 (110)
PDGFRA D842V	88.4 (38)	6.6 (8)
PDGFRA Exon 18 non-D842V[a]	11.6 (5)	2.5 (3)
Number of prior lines of TKIs, median (range)	1 (0–5)	4 (3–11)
Metastatic disease, % (n)	97.7 (42)	98.3 (119)
Largest target lesion (central radiology review), % (n)		
≤5 cm	46.5 (20)	33.1 (40)
>5 to ≤10 cm	32.6 (14)	47.1 (57)
>10 cm	20.9 (9)	18.2 (22)
Prior surgical resection, % (n)		
Yes	86.0 (37)	88.4 (107)
ECOG PS, % (n)		
0	32.6 (14)	32.2 (39)
1	60.5 (26)	64.5 (78)
2	7.0 (3)	3.3 (4)

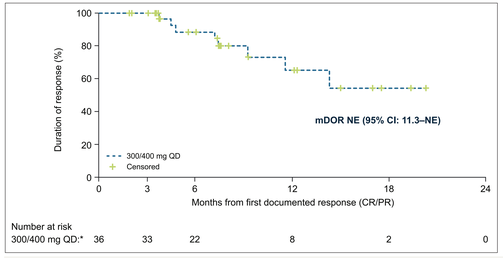
[a]PDGFRA Exon 18 non-D842V mutations including D842Y, DI 842-845V, I843_D846del, I843_D846del, and D842-H845.

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



Best Response,[b] n	PDGFRA Exon 18 n=43
CR	3
PR[b]	34 (1 pending)
SD	5
PD	1
ORR (CR+PR),[c] % (95% CI)	86.0 (72.1–94.7)
CBR,[d] % (95% CI)	95.3 (84.2–99.4)
DOR,[e] months (95% CI)	NE (11.5–NE)
PFS, months (95% CI)	NE (13.4–NE)

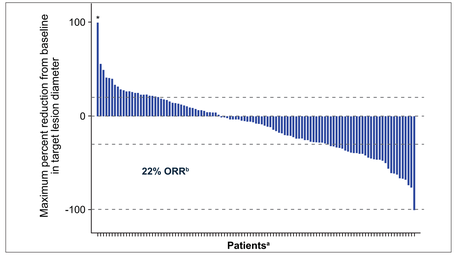
[a]Assessed by mRECIST 1.1. Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable at 300/400 mg QD.[b]1 response pending confirmation. [c]ORR defined as the proportion of patients with a confirmed best response of CR or PR. [d]CBR defined as CR/PR+SD lasting ≥16 weeks from first dose. [e]DOR defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever came first.



[*]Patients with confirmed response.

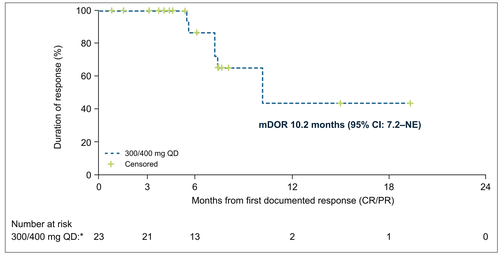
- 78% (28/36) of PDGFRA Exon 18 patients were still in response as of the November 16, 2018, data cutoff
- Median follow-up was 10.9 months

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



Best Response,[c] n	4L+ n=111
CR	1
PR (confirmed)	23 (1 pending)
SD	52
PD	35
ORR (CR+PR), % (95% CI)	22 (14.4–30.4)
CBR, % (95% CI)	41 (32.2–51.2)
DOR, months (95% CI)	10.2 (7.2–NE)
PFS, months (95% CI)	3.7 (3.4–5.6)

[a]One patient had an outlier value for percent change from baseline of >200% increase in target lesion diameter.
[b]Two patients who had best response assessment are not included in the waterfall plot because they did not have measurable target lesions at baseline and thus, no percent change could be calculated. [c]There were 8 patients with PDGFRA D842V mutations and when these patients were removed from analysis, the ORR is 17% and DOR remains unchanged. [d]Assessed by mRECIST 1.1. Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable at 300/400 mg QD.



[*]Patients with confirmed response.

- Median follow-up was 10.8 months across all 4L+ patients

Best confirmed response: PDGFRA Exon 18 by line of therapy.

Best response, % (n)	300/400 mg QD Starting Dose		
	1L n = 5	2L+ n = 38	Total n = 43
CR	40.0 (2)	2.6 (1)	7.0 (3)
PR	60.0 (3)	78.9 (30)	76.7 (33)
SD	0	15.8 (6)	14.0 (6)
PD	0	2.6 (1)	2.3 (1)

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

CONCLUSIONS

- Pivotal data analyses from the NAVIGATOR trial demonstrate important clinical activity and favorable tolerability in advanced Exon 18 mutant PDGFRA and 4L+ GIST, highlighting the potential of avapritinib to change the treatment paradigm for patients with advanced GIST
  - Avapritinib shows remarkable activity in both D842V, a previously undruggable target, and other Exon 18 mutant PDGFRA GIST
  - In the fourth line setting, patients with advanced GIST have no effective therapies; avapritinib has activity with durable responses, and response rates exceeding that reported with other kinase inhibitors
  - The safety profile of avapritinib is predictable and manageable, thus allowing for prolonged treatment in patients benefiting from avapritinib
  - Based on its overall safety profile and antitumor activity, 300 mg QD is the recommended dose for patients with unresectable or metastatic GIST
- These data support evaluating avapritinib in earlier lines of therapy; plan to initiate COMPASS-2L trial in 2H 2019 and the VOYAGER-3L trial is ongoing

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Abbreviations

1L, 1st treatment line; 2L, 2nd treatment line; 3L, 3rd treatment line; 4L, 4th treatment line; AE, adverse event; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FDA, Federal Drug Administration; GIST, gastrointestinal stromal tumor; KIT, KIT receptor tyrosine kinase; mDOR, median duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PDGFR, platelet-derived growth factor receptor; PO, orally; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose; SD, stable disease; TKI, tyrosine kinase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.

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