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Long-term efficacy, tolerability and overall survival in patients with unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumor treated with avapritinib: NAVIGATOR phase 1 trial update

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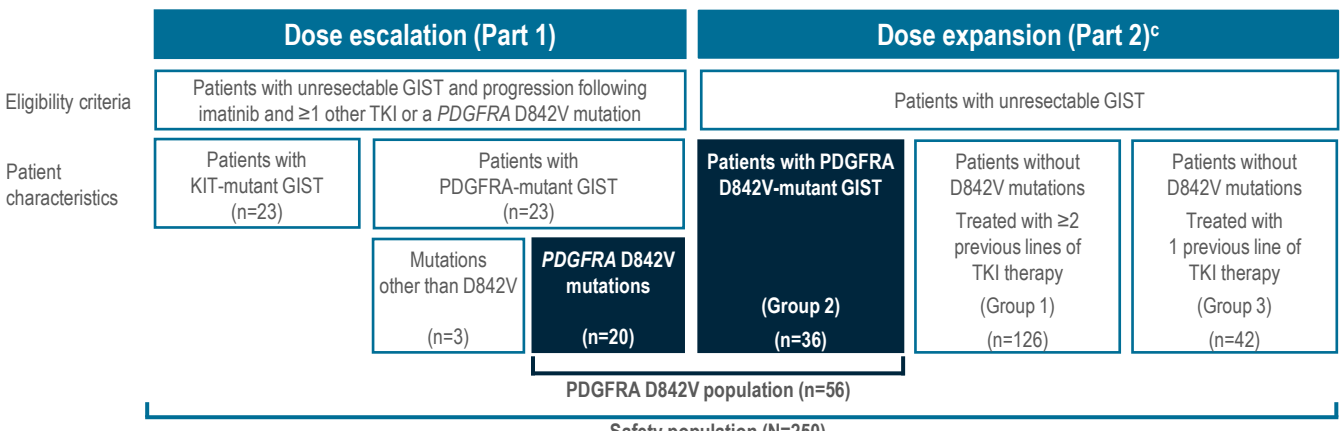
AYVAKIT™ (avapritinib) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. Avapritinib is not approved for the treatment of any other indication in the USA by the FDA or for any indication in any other jurisdiction by any other health authority.

Long-term follow-up of PDGFRA D842V-mutant GIST population from NAVIGATOR, a phase 1 study of avapritinib

- PDGFRA D842V-mutant GIST is highly resistant to all TKIs approved by the EMA for unresectable or metastatic GIST
- NAVIGATOR (NCT02508532) evaluated the safety and clinical activity of avapritinib at the RP2D[a] and MTD[b] in patients with unresectable or metastatic GIST



[a]300 mg QD. [b]400 mg QD. [c]Enrollment as of a data cut-off March 9, 2020.
EMA, European Medicines Agency; GIST, gastrointestinal stromal tumor; MTD, maximum tolerated dose; PDGFRA, platelet-derived growth factor receptor alpha; QD, once daily; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

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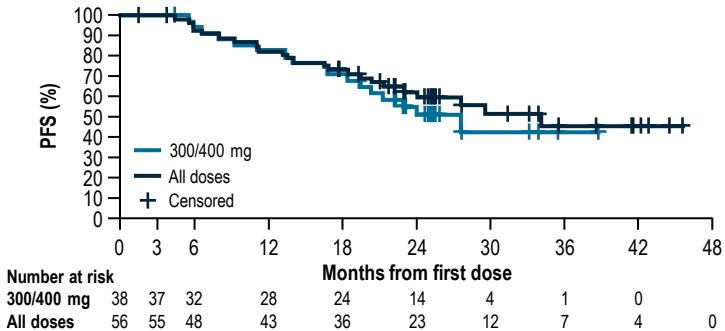
PDGFRA D842V-mutant GIST: Baseline demographics and disease characteristics

Characteristics	Avapritinib starting dose				
	<300 mg (n=17)	300 mg (n=28)	400 mg (n=10)	300/400 mg (n=38)	All doses[a] (N=56)
Median age (range), years	65 (41–77)	63 (29–90)	66 (35–70)	64 (29–90)	64 (25–90)
Male, n (%)	13 (76)	18 (64)	7 (70)	25 (66)	39 (70)
Race, n (%)					
White	13 (76)	17 (61)	8 (80)	25 (66)	39 (70)
Other[b]	4 (24)	11 (39)	2 (20)	13 (34)	17 (30)
Largest target lesion size, n (%)					
≤5 cm	5 (29)	12 (43)	4 (40)	16 (42)	21 (38)
>5 to ≤10 cm	2 (12)	9 (32)	4 (40)	13 (34)	16 (29)
>10 cm	10 (59)	7 (25)	2 (20)	9 (24)	19 (34)
Stage at screening visit (TNM), n (%)					
Stage III	1 (6)	1 (4)	0	1 (3)	2 (4)
Stage IV	9 (53)	13 (46)	6 (60)	19 (50)	29 (52)
Unknown	7 (41)	14 (50)	4 (40)	18 (47)	25 (45)

[a]Includes n=1 patient with 600 mg starting daily dose. [b]Other includes patients of Black, Asian, and other or unknown race.
TNM, tumor, node, metastasis.

PDGFRA D842V-mutant GIST: ORR and PFS

Response,[a] n (%)	Avapritinib starting dose				
	<300 mg (n=17)	300 mg (n=28)	400 mg (n=10)	300/400 mg (n=38)	All doses[b] (N=56)
ORR[c]	14 (82)	27 (96)	9 (90)	36 (95)	51 (91)
95% CI	57–96	82–100	56–100	82–99	80–97
CR	2 (12)	3 (11)	2 (20)	5 (13)	7 (13)
PR	12 (71)	24 (86)	7 (70)	31 (82)	44 (79)
SD	3 (18)	1 (4)	1 (10)	2 (5)	5 (9)



- Of the 5 TKI-naïve patients receiving avapritinib 300/400 mg, 2 achieved a CR and 3 achieved a PR
- Median DOR with avapritinib 300/400 mg was 22 months (95% CI, 14–NR), median PFS was 24 months (95% CI, 18–NR), and median OS was not reached
- At 36 months, estimated PFS and OS rates with avapritinib 300/400 mg were 34% and 71%, respectively

Enrollment as of a data cut-off March 9, 2020. Median follow-up for OS: 27.5 months. [a]mRECIST v1.1. [b]Includes n=1 patient with 600 mg starting daily dose. [c]CR or PR.
CI, confidence interval; CR, complete response; DOR, duration of response; mRECIST v.1., modified Response evaluation criteria in solid tumors version 1.1; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

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PDGFRA D842V-mutant GIST: Most common AEs and AEs of special interest

Most common AEs (any cause and grade) in ≥30% of patients, n (%)	D842V population 300/400 mg dose (n=38)	Safety population All doses (N=250)
Nausea	28 (74)	161 (64)
Anemia	26 (68)	136 (54)
Diarrhea	25 (66)	112 (45)
Fatigue	22 (58)	157 (63)
Memory impairment	18 (47)	81 (32)
Periorbital edema	17 (45)	110 (44)
Decreased appetite	15 (39)	101 (40)
Increased lacrimation	13 (34)	88 (35)
Vomiting	12 (32)	106 (42)
Peripheral edema	12 (32)	80 (32)
Abdominal pain	12 (32)	64 (26)
Increased blood bilirubin	12 (32)	54 (22)
Hypokalemia	12 (32)	48 (19)

AESI (any cause and grade), n (%)	D842V population 300/400 mg dose (n=38)	Safety population All doses (N=250)
Cognitive effects	24 (63)	115 (46)
Memory impairment	18 (47)	81 (32)
Confusional state	7 (18)	17 (7)
Cognitive disorder	5 (13)	28 (11)
Encephalopathy	1 (3)	5 (2)
Intracranial bleeding	2 (5)	7 (3)
Intracranial hemorrhage	2 (5)	3 (1)
Cerebral hemorrhage	0	1 (<1)
Subdural hematoma	0	3 (1)

- Overall, 13 (34%) patients receiving avapritinib 300/400 mg in the PDGFRA D842V population discontinued treatment due to AEs of any cause
  - 8 (21%) of patients discontinued due to treatment-related AEs
- Dose interruption and/or reduction was an effective method of improving Grade ≥2 cognitive effect AEs, in a median of 12 days[1]

Enrollment as of a data cut-off March 9, 2020. AE, adverse event; AESI, adverse event of special interest.

1. Joseph CP et al. Presented at the Connective Tissue Oncology Society Annual Meeting, November 13-16, 2019, Tokyo, Japan.

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Conclusions

- Avapritinib produced unprecedented durable clinical benefit in patients with unresectable or metastatic PDGFRA D842V-mutant GIST, a population with high unmet need as no other approved treatments target the PDGFRA oncoprotein with this mutation
- ORR for all doses was 91%, which was similar across the different avapritinib dose cohorts
  - ORR was 96% in patients receiving a 300 mg starting dose
  - All TKI-naïve patients receiving a 300/400 mg starting dose achieved CR or PR
  - At a 300/400 mg dose, median DOR was 22 months and median PFS was 24 months
- Avapritinib had a generally tolerable safety profile that was similar between the total safety population from NAVIGATOR (all doses) and patients with *PDGFRA* D842V mutations treated at a 300/400 mg dose

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