Clinical Efficacy Comparison of Avapritinib With Other Tyrosine Kinase Inhibitors (TKIs) in Gastrointestinal Stromal Tumors (GIST) With *PDGFRA* D842V Mutation: A Retrospective Analysis of Clinical Trial and Real-World Data

#1630P

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Background

- Over 85% of gastrointestinal stromal tumors (GIST) are driven by oncogenic mutations of the genes encoding KIT or platelet-derived growth factor receptor A (PDGFRA) receptor tyrosine kinases[1,2]
- The most common *PDGFRA* mutation is the exon 18 D842V mutation located in the kinase activation loop[2,3]
- Avapritinib is a selective, potent inhibitor of PDGFRA D842V- and KIT D816V-mutant kinases and is currently approved in the US for the treatment of adults with unresectable or metastatic GIST that harbor a *PDGFRA* exon 18 mutation[2,4]
- Other approved tyrosine kinase inhibitors (TKIs) lack activity against PDGFRA D842V-mutant kinase, and without effective treatments available for patients with unresectable/metastatic *PDGFRA* D842V-driven GIST, prognosis is poor with a median progression-free survival (PFS) of 2–10 months and median overall survival (OS) of ~9–15 months[5–7]
- The objective of this retrospective, indirect analysis was to compare efficacy outcomes in patients with PDGFRA D842V-mutant GIST treated with avapritinib in the NAVIGATOR study with patients treated with other TKIs in a retrospective natural history study (Study 1002)

Study design and methods

- Patients with unresectable/metastatic GIST harboring a *PDGFRA* D842V mutation were enrolled in the NAVIGATOR trial or retrospectively selected for Study 1002 based on their treatment history (Figures 1 and 2)
  - In Study 1002, patient demographic and clinical data following each line of therapy were gathered retrospectively from patients between January 1, 2000 and July 1, 2016

Figure 1: NAVIGATOR and Study 1002 analysis

NAVIGATOR (NCT02508532)
Phase I, open-label, non-randomized study evaluating avapritinib in patients with unresectable/metastatic GIST

Key eligibility criteria:
- Age ≥18 years
- Histologically/cytologically confirmed diagnosis of unresectable GIST
- Unresectable GIST that had progressed following imatinib and at least 1 other TKI[a] or had a D842V mutation in the *PDGFRA* gene

Treatment: Avapritinib

Study 1002
Retrospective, observational study evaluated the response and survival of patients with unresectable/metastatic PDGFRA D842V-mutant GIST treated with TKI[a]

Key eligibility criteria:
- Age ≥18 years
- Confirmed diagnosis of GIST
- Patients treated with a commercially available or investigational TKI for unresectable GIST
- Patients who received prior TKI therapy only in an adjuvant setting or treated with avapritinib were excluded

Treatment: First TKI prescribed for unresectable/metastatic GIST

Primary endpoint: OS
Secondary endpoint: PFS (RECIST v1.1)[b]
OS and PFS were measured from the start of treatment to the date of death event (or censoring data)

- **In NAVIGATOR: RP2D was 300 mg and MTD was 400 mg**
- **Data cut-off date for this indirect analysis was March 9, 2020**

[a]Includes sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase inhibitor agent. [b]PFS was assessed by modified RECIST v1.1 (NAVIGATOR) and RECIST v1.1 in (Study 1002); MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; RP2D, recommended phase 2 dose.

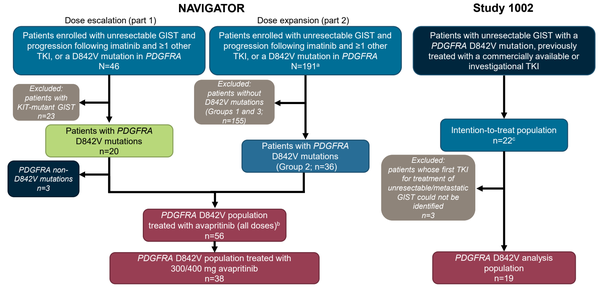
Statistical analysis

- Inverse probability of treatment weighting (IPTW)-adjusted Kaplan–Meier (KM) survival functions were estimated for patients treated with avapritinib (NAVIGATOR) and other TKIs (Study 1002) using calculated propensity score (PS) weighting
  - PS was used to adjust for imbalances in the characteristics of patients
- Log-rank and Cox regression-based tests were used to compare unadjusted and adjusted KM survival curves, respectively

Results

- Patient characteristics were balanced between NAVIGATOR (both *PDGFRA* D842V patients treated with avapritinib any dose (n=56) and the subgroup of patients treated with 300/400 mg (n=38) and Study 1002 (n=19) for sex, tumor anatomical location, proportion of patients with metastatic disease, and duration of disease (Table 1)

Figure 2: Patient disposition



[a]Enrollment at the data cut-off of November 16, 2018. [b]The D842V population included all patients with *PDGFRA* D842V mutations from part 1 and part 2. [c]All patients were treated with an approved treatment for GIST or investigational TKI, with initial treatment administered between Jan 1, 2000 and July 1, 2016.

Table 1: Analysis of patient-related confounding factors

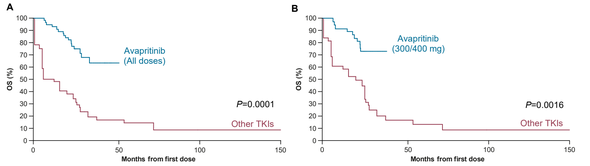
	NAVIGATOR		Study 1002	*P*-value	
	All doses n=56	300/400 mg n=38	n=19	NAVIGATOR All doses vs Study 1002	NAVIGATOR 300/400 mg vs Study 1002
Sex					
Male	39 (69.6)	25 (65.8)	12 (63.2)	0.601	0.844
Female	17 (30.4)	13 (34.2)	7 (36.8)		
Age[a]					
<60 years	18 (32.1)	13 (34.2)	11 (57.9)	0.046*	0.088
≥60 years	38 (67.9)	25 (65.8)	8 (42.1)		
Race[b]					
White	39 (78.0)	25 (71.4)	18 (94.7)	0.101	0.042*
Non-white	11 (22.0)	10 (28.6)	1 (5.3)		
Anatomical site[c]					
Gastric (stomach)	46 (82.1)	29 (76.3)	15 (79.0)	0.757	0.823
Small bowel or rectal (any other organ)	10 (17.9)	9 (23.7)	4 (21.0)		
Metastatic disease[a]					
No	2 (3.6)	1 (2.6)	1 (5.3)	0.745	0.611
Yes	54 (96.4)	37 (97.4)	18 (94.7)		
Duration of disease[d]					
<3 years	32 (57.1)	21 (55.3)	13 (68.4)	0.386	0.340
≥3 years	24 (42.9)	17 (44.7)	6 (31.6)		
Number of TKIs treatment lines[e]					
1	11 (19.6)	5 (13.2)	3 (15.8)	0.124	0.040*
2	23 (41.1)	20 (52.6)	3 (15.8)		
3	9 (16.1)	6 (15.8)	4 (21.0)		
4+	13 (23.2)	7 (18.4)	9 (47.4)		

Not all available baseline and demographic characteristics could be used due to differences in the timing of the measure (i.e., screening in NAVIGATOR vs diagnosis in Study 1002). [a]Estimated at the start of reference treatment. [b]Data was missing for 6 patients across the NAVIGATOR population and 3 from the 300/400 mg subgroup. [c]Recorded at the primary diagnosis. [d]Estimated from the date of diagnosis to the date of start of reference treatment. [e]The number of TKIs was counted from the first TKI for treatment of unresectable/metastatic disease and included avapritinib for the NAVIGATOR population.
*P-value statistically significant (≤0.05); comparison of patient characteristics in NAVIGATOR vs Study 1002.

Overall survival

- Median OS was not reached in NAVIGATOR (both adjusted and unadjusted analyses) and in Study 1002 median OS was 12.6 months (adjusted analysis) and 26.4 months (unadjusted analysis (Figures 3 and 4)
- Adjusted and unadjusted OS rates were higher in the overall *PDGFRA* D842V NAVIGATOR population (all avapritinib doses) and in the avapritinib 300/400 mg cohort vs Study 1002 at all time-point landmarks through 36 months (Figures 3C, 3D, 4C and 4D)
- Adjusted analysis demonstrated the difference between the survival curves in NAVIGATOR (both all doses and 300/400 mg patient cohorts) vs Study 1002 was statistically significant (Figures 3A and 3B)

Figure 3: Adjusted overall survival



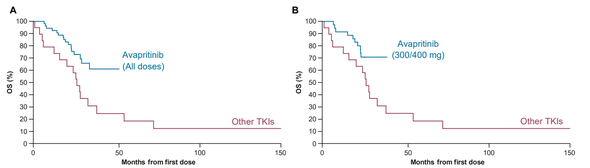
C

Months	Adjusted OS rate (%) NAVIGATOR All doses	Study 1002
6	100	56
12	93	50
18	89	41
24	77	38
36	63	19
48	63	17
60	–	14

D

Months	Adjusted OS rate (%) NAVIGATOR 300/400 mg	Study 1002
6	100	68
12	91	61
18	89	52
24	73	49
36	73	20
48	–	17
60	–	13

Figure 4: Unadjusted overall survival



C

Months	Unadjusted OS rate (%) NAVIGATOR All doses	Study 1002
6	100	84
12	92	79
18	89	68
24	75	63
36	61	31
48	61	25
60	–	18

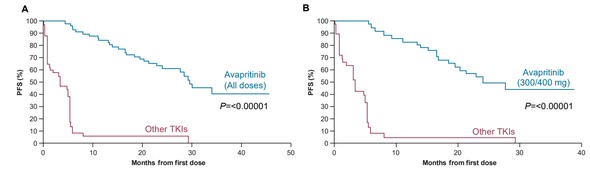
D

Months	Unadjusted OS rate (%) NAVIGATOR 300/400 mg	Study 1002
6	100	84
12	91	79
18	89	68
24	71	63
36	71	31
48	–	25
60	–	18

Progression-free survival

- Median PFS was 29.5 months (adjusted) and 29.2 months (unadjusted) in NAVIGATOR (all doses) compared with 3.4 months in Study 1002 (adjusted and unadjusted) (Figures 5 and 6)
- In the 300/400 mg cohorts in NAVIGATOR, adjusted median PFS was 24.0 months (Figure 5B)
- Adjusted and unadjusted PFS rates were higher in the overall *PDGFRA* D842V NAVIGATOR population (all avapritinib doses) and in the 300/400 mg cohort vs Study 1002 at all time-point landmarks through 24 months (Figure 5C, 5D, 6C and 6D)
- The adjusted analysis showed the difference between NAVIGATOR (both all doses and the 300/400 mg cohorts) vs Study 1002 was statistically significant (Figures 5A and 5B)

Figure 5: Adjusted progression-free survival



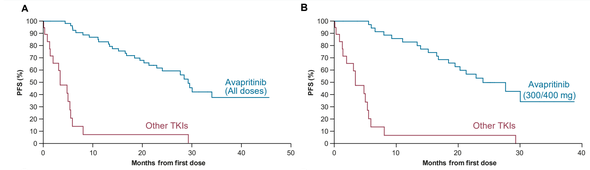
C

Months	Adjusted PFS rate (%) NAVIGATOR All doses	Study 1002
6	93	9
12	84	6
18	72	6
24	63	6
36	41	–

D

Months	Adjusted PFS rate (%) NAVIGATOR 300/400 mg	Study 1002
6	94	8
12	83	5
18	68	5
24	54	5
36	44	–

Figure 6: Unadjusted progression-free survival



C

Months	Unadjusted PFS rate (%) NAVIGATOR All doses	Study 1002
6	92	14
12	83	7
18	72	7
24	62	7
36	37	–

D

Months	Unadjusted PFS rate (%) NAVIGATOR 300/400 mg	Study 1002
6	94	14
12	83	7
18	69	7
24	53	7
36	34	–

Conclusions

- In this retrospective, indirect analysis, patients with GIST harboring a *PDGFRA* D842V mutation treated with avapritinib in NAVIGATOR had more durable survival outcomes than those treated with other TKIs in a natural history study
- This analysis was limited by differences between populations in age, race, and number of prior lines of therapy, and limited sample sizes necessitated IPTW adjustments rather than PS matching
- The data support the previously reported results in the NAVIGATOR trial in which avapritinib demonstrated unprecedented clinical activity in the PDGFRA D842V-mutant population
- These results underscore the importance of testing patients for *PDGFRA* and *KIT* mutations at initial diagnosis, to ensure the most suitable treatment plan is provided

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