

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)	Study 1002
Phase I, open-label, non-randomized study evaluating avapritinib in patients with unresectable/metastatic GIST	Retrospective, observational study evaluated the response and survival of patients with unresectable/metastatic <i>PDGFRA</i> D842V-mutant GIST treated with TKI ^a
Key eligibility criteria:	Key eligibility criteria:
<ul style="list-style-type: none"> 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 <i>PDGFRA</i> gene 	<ul style="list-style-type: none"> 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: Avapritinib	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

^aIncludes sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase inhibitor agent. ^bPFS 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.

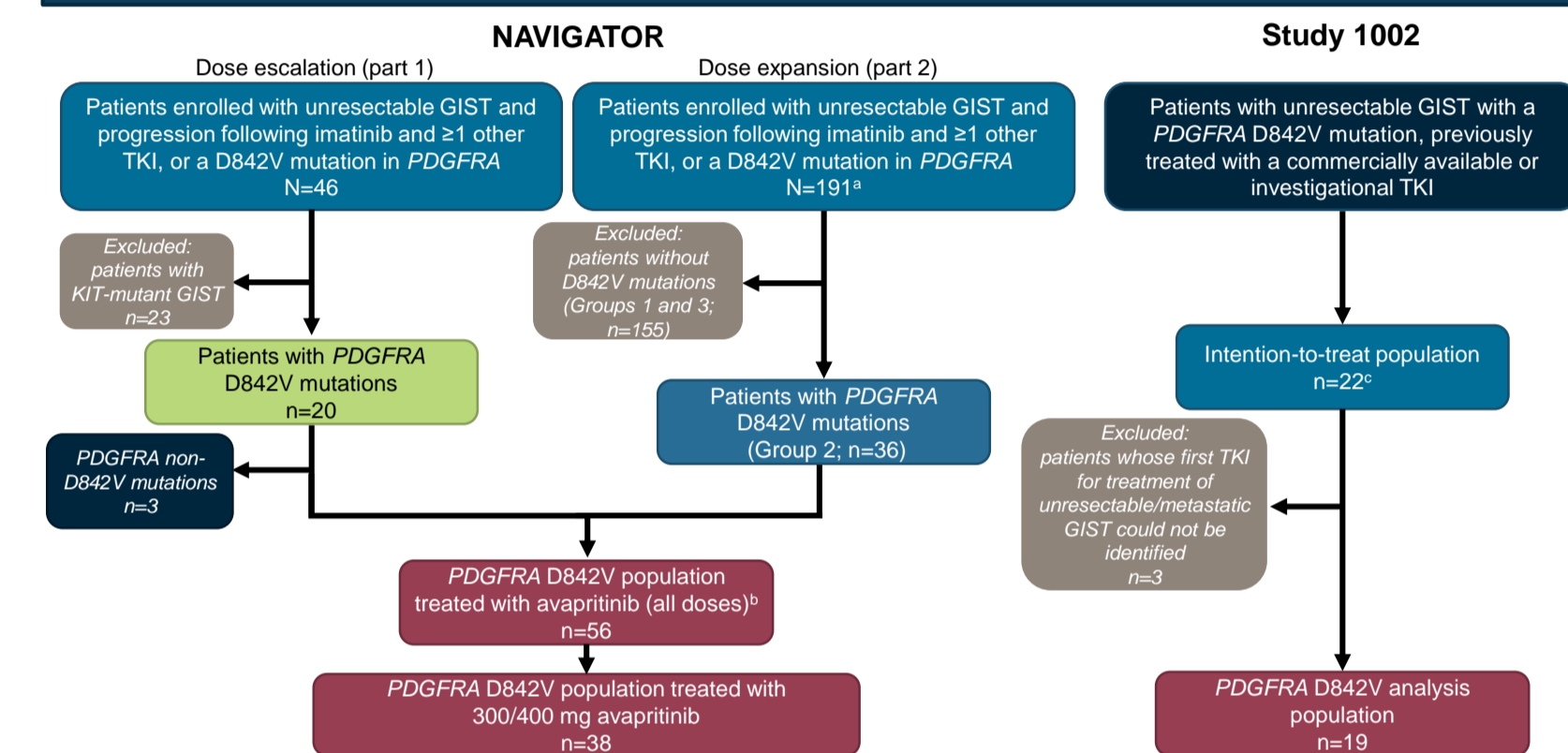
Statistical analysis

- 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



^aEnrollment at the data cut-off of November 16, 2018. ^bThe D842V population included all patients with *PDGFRA* D842V mutations from part 1 and part 2. ^cAll 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			P-value	NAVIGATOR vs Study 1002	
	All doses n=56	300/400 mg n=38	Study 1002 n=19		All doses	300/400 mg
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^d						
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). ^aEstimated at the start of reference treatment. ^bData was missing for 6 patients across the NAVIGATOR population and 3 from the 300/400 mg subgroup. ^cRecorded at the primary diagnosis. ^dEstimated from the date of diagnosis to the date of start of reference treatment. ^eThe 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

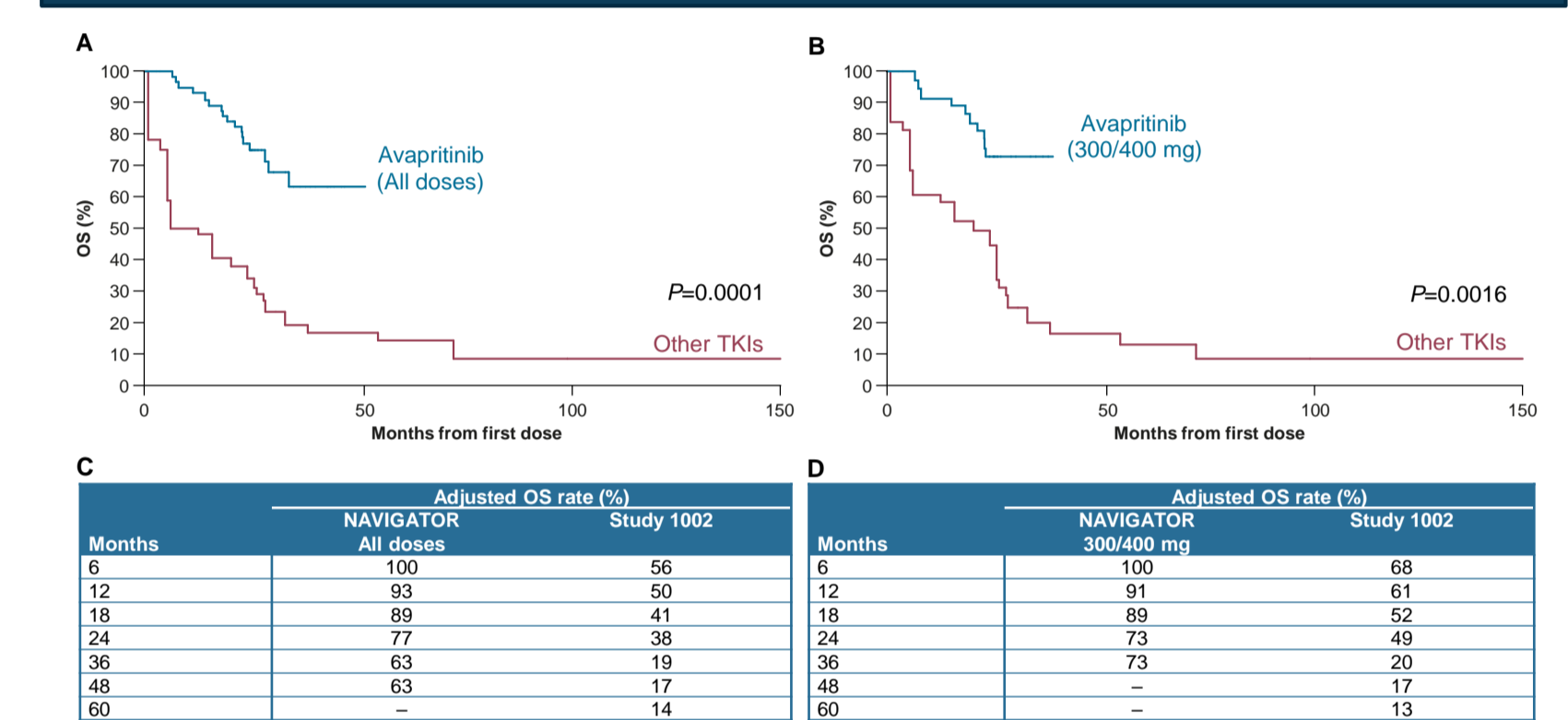
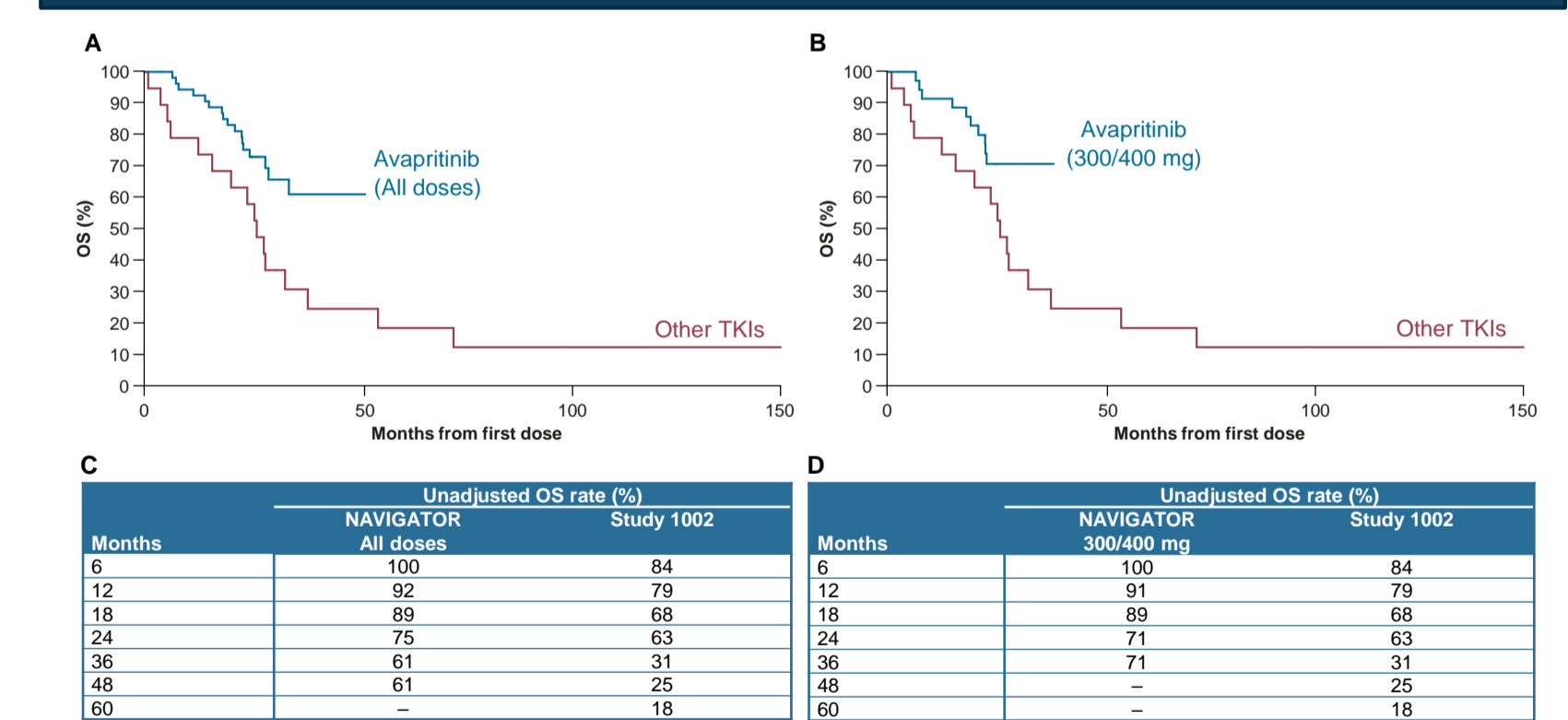


Figure 4: Unadjusted overall survival



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

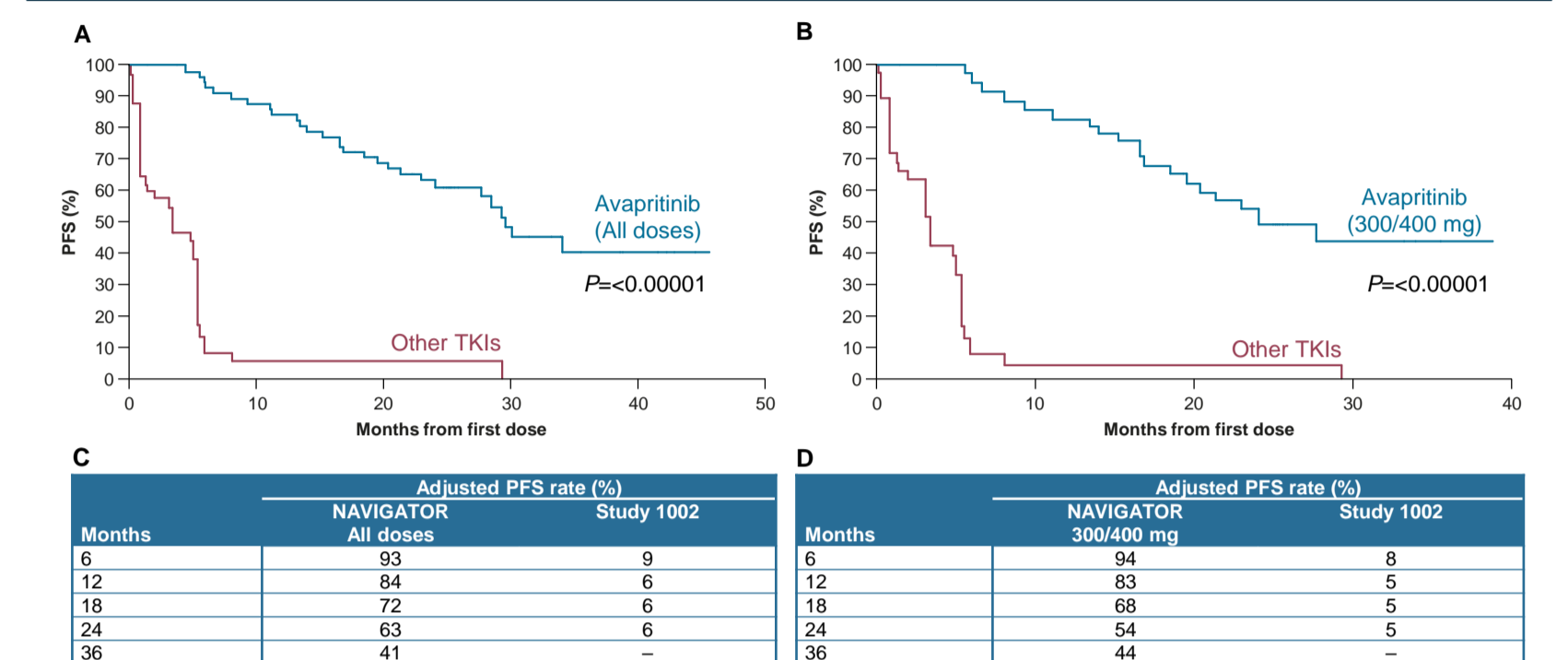
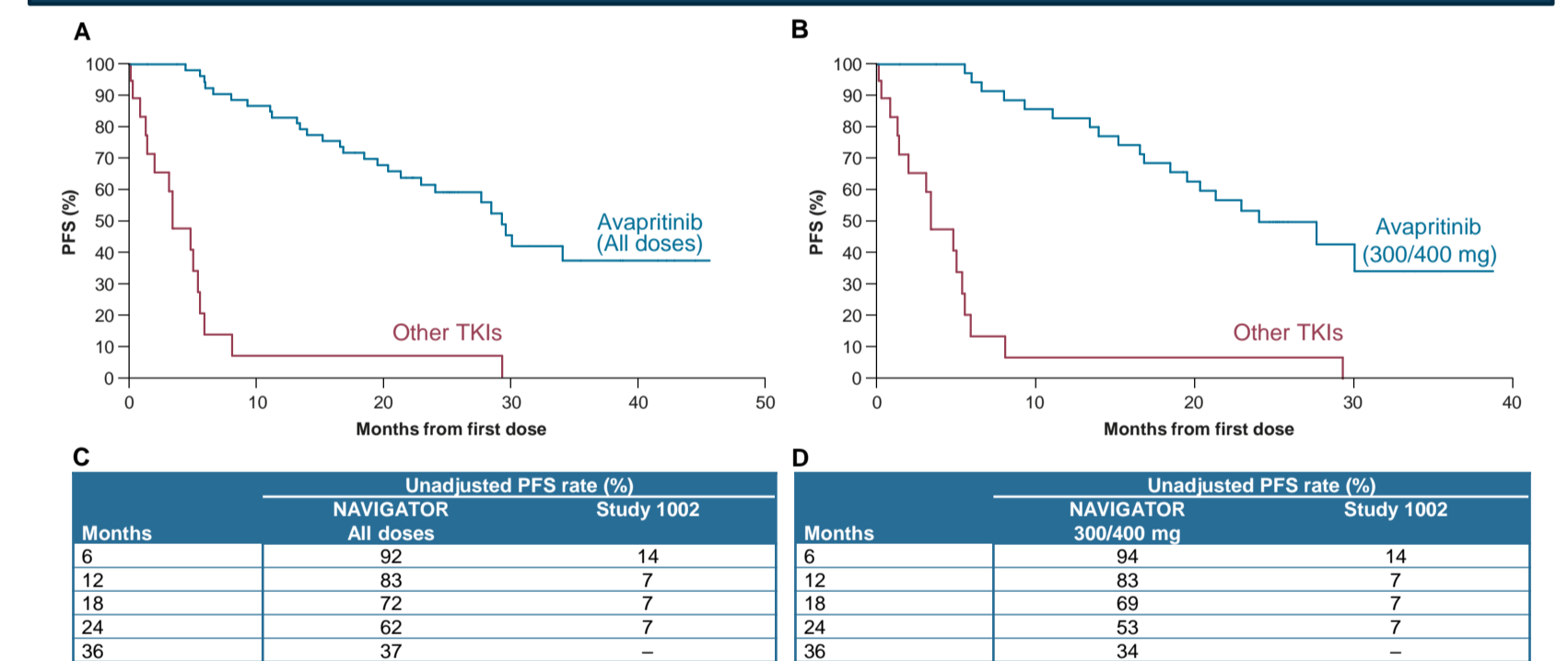


Figure 6: Unadjusted progression-free survival



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

References

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