The Oncologist®

Gastrointestinal Cancer

Avapritinib in Patients With Advanced Gastrointestinal Stromal Tumors Following at Least Three Prior Lines of Therapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. KIT • Platelet-derived growth factor receptors • Protein-tyrosine kinases • Gastrointestinal stromal tumors • Clinical trial • Avapritinib

Abstract

Background. Most gastrointestinal stromal tumors (GIST) driven by *KIT* or platelet-derived growth factor receptor A (*PDGFRA*) mutations develop resistance to available tyrosine kinase inhibitor (TKI) treatments. NAVIGATOR is a two-part, single-arm, dose escalation and expansion study designed to evaluate safety and antineoplastic activity of avapritinib, a selective, potent inhibitor of KIT and PDGFRA, in patients with unresectable or metastatic GIST.

Materials and Methods. Eligible patients were 18 years or older with histologically or cytologically confirmed unresectable GIST and Eastern Cooperative Oncology Group performance status ≤2 and initiated avapritinib at 300 mg or 400 mg once daily. Primary endpoints were safety in patients who initiated avapritinib at 300 mg or 400 mg once daily and overall response rate (ORR) in patients in the safety population with three or more previous lines of TKI therapy.

Results. As of November 16, 2018, in the safety population (n = 204), the most common adverse events (AEs) were nausea (131 [64%]), fatigue (113 [55%]), anemia (102 [50%]), cognitive effects (84 [41%]), and periorbital edema (83 [41%]); 17 (8%) patients discontinued due to treatment-related AEs, most frequently confusion, encephalopathy, and fatigue. ORR in response-evaluable patients with GIST harboring *KIT* or non-D842V *PDGFRA* mutations and with at least three prior therapies (n = 103) was 17% (95% confidence interval [CI], 10–25). Median duration of response was 10.2 months (95% CI, 7.2–10.2), and median progression-free survival was 3.7 months (95% CI, 2.8–4.6).

Conclusion. Avapritinib has manageable toxicity with meaningful clinical activity as fourth-line or later treatment in some patients with GIST with *KIT* or *PDGFRA* mutations. ***The Oncologist*** 2021;26:e639–e649

Implications for Practice: In the NAVIGATOR trial, avapritinib, an inhibitor of KIT and platelet-derived growth factor receptor A tyrosine kinases, provided durable responses in a proportion of patients with advanced gastrointestinal stromal tumors (GIST) who had received three or more prior therapies. Avapritinib had a tolerable safety profile, with cognitive adverse events manageable with dose interruptions and modification in most cases. These findings indicate that avapritinib can elicit durable treatment responses in some patients with heavily pretreated GIST, for whom limited treatment options exist.

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Introduction

The *KIT* proto-oncogene encodes the receptor tyrosine kinase inhibitor KIT (CD117). When mutated in gastrointestinal stromal tumors (GIST), KIT becomes constitutively active, leading to a malignant phenotype [1]. The vast majority of GIST harbor activating mutations in either KIT (75%–80%) or platelet-derived growth factor receptor A (PDGFRA) receptor tyrosine kinases (5%–10%) [2–7]. Historically, chemotherapy and radiation have been ineffective in GIST [8, 9]. Inhibition of oncogenic KIT or PDGFRA with tyrosine kinase inhibitors (TKIs) is the current backbone of management of advanced GIST, with the discovery of imatinib mesylate, a selective TKI of KIT and PDGFRA, leading to substantial improvements in clinical outcomes [10–12].

Imatinib is the standard first-line treatment for unresectable or metastatic GIST [8, 13], with a subset of patients experiencing long-term survival [14]. However, nearly all patients eventually develop resistance attributed to polyclonal expansion of heterogeneous tumor clones. In *KIT*-mutant GIST, these clones typically harbor secondary mutations in KIT located in the ATP-binding pocket (exons 13 and 14) or in the activation loop (exons 17 and 18) of the kinase domain [15–18]. Sunitinib and regorafenib are approved and recommended second- and third-line treatments, respectively [8, 13], with both demonstrating improved efficacy compared with placebo [19, 20]. However, both drugs show activity against only a limited subset of resistance mutations [21–23], which may explain the low objective response rates of 5%–7% in phase III trials [19, 20]. Ripretinib was recently approved as fourth-line therapy with a median progression-free survival (PFS) of 6.3 months versus 1.0 months with placebo [24, 25].

Avapritinib (formerly BLU-285; Blueprint Medicines Corporation, Cambridge, MA, USA) is a selective, potent inhibitor of KIT and PDGFRA that shows activity against resistance mutations in the activation loop of each kinase (exons 17/18 and exon 18, respectively) in addition to other well-characterized disease-driving KIT mutants [2]. Avapritinib is the only therapy approved in the U.S. for patients with unresectable or metastatic GIST harboring a *PDGFRA* exon 18 mutation (including *PDGFRA* D842V mutations), due to the remarkable overall response rate (ORR) of 88%, in this otherwise TKI-resistant molecular subtype of GIST [26]; avapritinib is also approved in the E.U. for patients with unresectable or metastatic GIST harboring the *PDGFRA* D842V mutation [27]. Avapritinib is not approved outside of these specific indications (PDGFRA exon 18-mutant GIST in the U.S. and PDGFRA D842V-mutant GIST in the E.U.).

NAVIGATOR (ClinicalTrials.gov: NCT02508532) is a phase I study designed to evaluate the safety and antineoplastic activity of avapritinib in patients with unresectable GIST. Findings from the dose escalation portion of this study and from the subset of patients with *PDGFRA* D842V mutations have recently been reported [28]. Here we present safety and efficacy findings from prespecified analyses of patients with KIT- or PDGFRA-mutant GIST who initiated avapritinib 300 mg or 400 mg once daily in the fourth- or later-line setting.

Materials and Methods

Study Design

NAVIGATOR is a first-in-human, two-part, single-arm, multicenter, dose escalation and expansion study evaluating safety, tolerability, pharmacokinetics, and efficacy of avapritinib in adults with unresectable GIST. Methods and results from part 1 (dose escalation) have been reported previously [28]. In part 2 (dose expansion), patients were enrolled into three prespecified groups based on prior therapy (supplemental online Methods and supplemental Fig. 1); here we report on patients with KIT- or PDGFRA-mutant GIST who had received three or more lines of prior therapy; data are presented for patients regardless of tumor genotype as well as excluding patients with tumors harboring *PDGFRA* D842V mutations.

The protocol was approved by the institutional review board or independent ethics committee of each study center. The study was conducted in accordance with the International Conference on Harmonization/Good Clinical Practice Guidelines, the ethical principles of the Declaration of Helsinki, and applicable national and local regulatory requirements. All patients provided written informed consent.

Patients

Eligible patients were ≥ 18 years with histologically or cytologically confirmed unresectable GIST (parts 1 and 2) or other advanced solid tumor (part 1 only), an Eastern Cooperative Oncology Group performance status ≤2, and adequate organ function. In addition to the inclusion criteria specific to each prespecified group, patients in part 2 were also required to have one or more measurable target lesion(s) in accordance with response evaluation criteria in solid tumors (RECIST) version 1.1 modified for patients with GIST (mRECIST v1.1) [19]. Mutational status was determined by local testing and centrally confirmed using circulating tumor DNA (part 1: OncoBEAM PDGFRA assay, Sysmex Inostics GmbH, Hamburg, Germany; part 2: Plasma*SELECT*-R next-generation sequencing panel and CancerSELECT 125 assay, Personal Genome Diagnostics, Baltimore, MD) as well as archival or new tumor biopsy samples (MolecularMD Corporation, Portland, OR, USA). Lines of therapy were reported by the investigator; each line was counted separately following progression or relapse. Full eligibility criteria are described in the supplemental online Methods.

Procedures

In dose escalation (part 1), avapritinib 400 mg once daily was identified as the maximum tolerated dose and selected as the starting dose for part 2. Preliminary safety data from part 2 suggested a higher incidence of adverse events (AEs) and dose modifications after multiple treatment cycles at 400 mg once daily, whereas preliminary antitumor findings appeared similar between 400 mg and 300 mg once-daily doses. Therefore, the starting dose was reduced to 300 mg avapritinib once daily, and this was considered the recommended phase II dose (RP2D) for the remainder of the

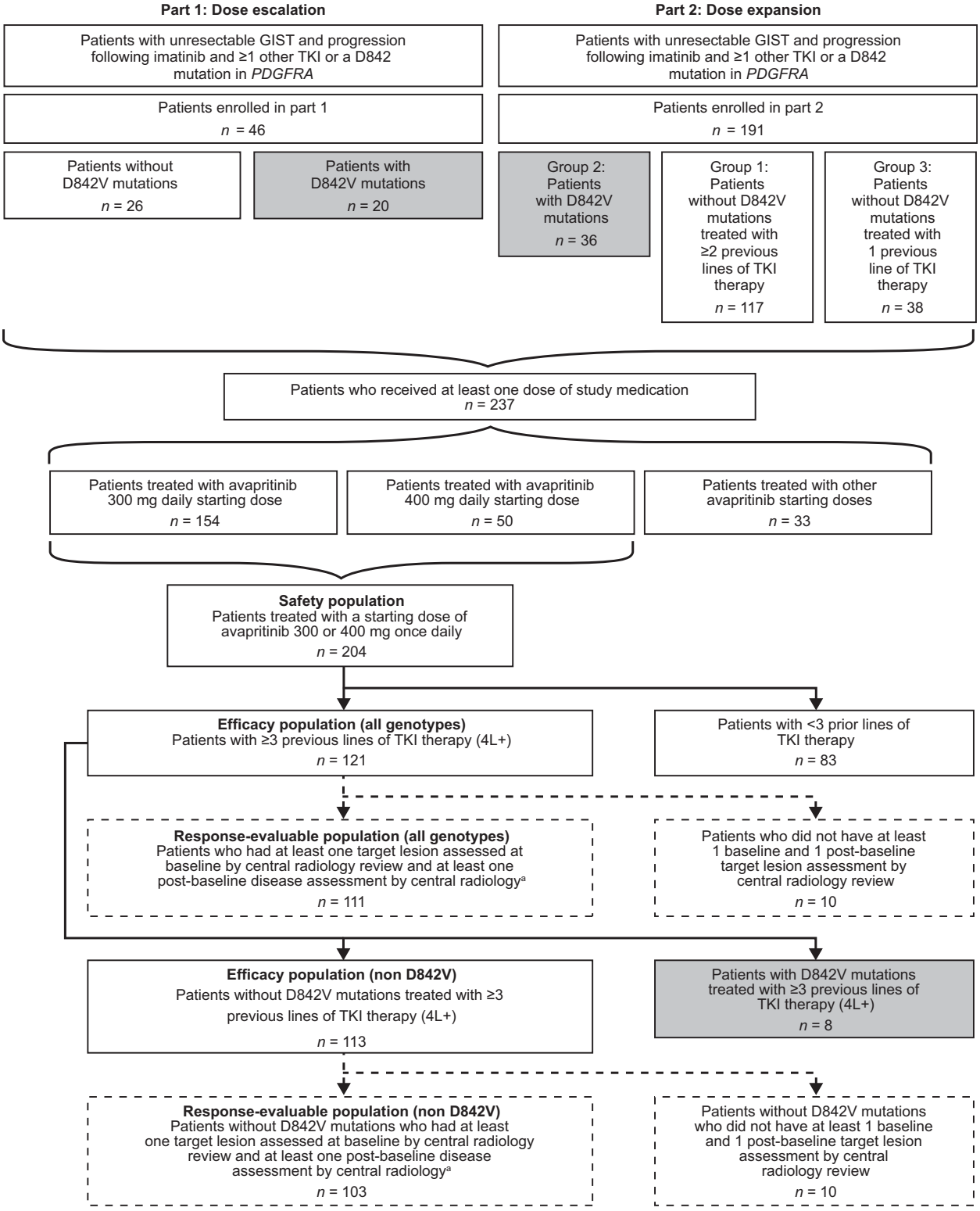


Figure 1. Patient disposition. [a]Central radiology assessment by mRECISTv 1.1. Efficacy of avapritinib specifically in patients with PDGFRA D842V-mutant GIST (shaded boxes) has been previously reported upon [28].
Abbreviations: 4L+, ≥3 prior lines of TKI treatment; GIST, gastrointestinal stromal tumor; mRECIST v1.1, Response Evaluation Criteria in Solid Tumors modified for patients with GIST; PDGFRA, platelet-derived growth factor receptor A; TKI, tyrosine kinase inhibitor.

study. Avapritinib was administered in continuous 28-day cycles, and patients continued treatment until unacceptable toxicity, progressive disease, death, noncompliance, withdrawal of consent, or physician decision. Patients initiating at 300 mg could escalate to 400 mg after completing two or more treatment cycles with no grade ≥3 toxicities. Procedures for dose modifications are described in supplemental online Table 1.

Table 1. Baseline demographics and disease characteristics (efficacy population, *n* = 121)

Characteristics	Avapritinib starting dose		
	300 mg (*n* = 84)	**400 mg (*n* = 37)**	**300/400 mg (*n* = 121)**
Median age (min–max)	61 (33–80)	58 (35–74)	59 (33–80)
Sex, *n* (%)			
Male	49 (58)	21 (57)	70 (58)
Female	35 (42)	16 (43)	51 (42)
Race, *n* (%)			
White	57 (68)	29 (78)	86 (71)
Asian	14 (17)	0	14 (12)
Black/African American	3 (4)	1 (3)	4 (3)
Other[a]	4 (5)	1 (3)	5 (4)
Unknown	6 (7)	6 (16)	12 (10)
GIST mutational subtype, *n* (%)			
KIT	75 (89)	35 (95)	110 (91)
PDGFRA D842V	6 (7)	2 (5)	8 (7)
PDGFRA exon 18 non-D842V	3 (4)	0	3 (2)
ECOG PS, *n* (%)			
0	25 (30)	14 (38)	39 (32)
1	56 (67)	22 (59)	78 (64)
2	3 (4)	1 (3)	4 (3)
Metastatic disease, *n* (%)	82 (98)	37 (100)	119 (98)
Largest target lesion (central radiology review), *n* (%), cm			
≤5	30 (36)	10 (27)	40 (33)
>5–10	36 (43)	21 (57)	57 (47)
>10	16 (19)	6 (16)	22 (18)
Unknown	2 (2)	0	2 (2)
Prior lines of TKIs, *n* (%)			
Median (min–max)	4 (3–11)	4 (3–9)	4 (3–11)
3	32 (38)	8 (22)	40 (33)
4	19 (23)	16 (43)	35 (28)
≥5	33 (39)	13 (35)	46 (38)
Prior sunitinib	83 (89)	36 (97)	119 (98)
Prior regorafenib	70 (83)	33 (89)	103 (85)
Prior surgical resection, *n* (%)	75 (89)	32 (86)	107 (88)

The efficacy population includes all patients treated with a starting dose of avapritinib 300 mg or 400 mg, and who had ≥3 prior lines of therapy.
[a]Includes patients with a race identified as American Indian, Alaska Native, or other.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor.

Response evaluation by computed tomography or magnetic resonance imaging scanning was performed at screening, every two cycles through cycle 13, and then every 12 weeks until progression or discontinuation. Target and non-target lesions were identified and assessed according to mRECIST v1.1 [19] by central radiology review (BioTelemetry, Inc., Rockville, MD, USA).

Adverse events were evaluated at each visit from the start of study drug administration up to 30 days after the final dose and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Two categories of AEs of special interest (AESI), cognitive effects and intracranial bleeding, were identified. Cognitive effects were defined as the NCI CTCAE preferred terms of memory impairment, cognitive disorder, confusional state, or encephalopathy. Intracranial bleeding was defined as the terms cerebral hemorrhage, intracranial hemorrhage, or subdural hematoma.

Outcomes and Statistical Analysis

Primary endpoints of part 2 were ORR by central radiology assessment per mRECIST v1.1 and the overall safety profile of avapritinib. Complete responses (CRs) and partial responses (PRs) had to be confirmed at a subsequent assessment without intervening progression. Secondary efficacy endpoints included duration of response (DOR), PFS, clinical benefit rate (CBR; defined as patients with CRs and PRs or stable disease [SD] lasting ≥16 weeks, all

Table 2. Summary of adverse events (safety population, *n* = 204)

	Avapritinib starting dose					
	300 mg (*n* = 154)		400 mg (*n* = 50)		300/400 mg (*n* = 204)	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
AE	153 (99)	106 (69)	49 (98)	41 (82)	202 (99)	147 (72)
Treatment-related AE	151 (98)	78 (51)	47 (94)	27 (54)	198 (97)	105 (51)
Serious AE	79 (51)	67 (43.5)	27 (54)	25 (50)	106 (52)	92 (45)
Serious treatment-related AE	34 (22)		8 (16)		42 (21)	
AE of special interest						
Cognitive effects	60 (39)	4 (2.6)	24 (48)	4 (8)	84 (41)	8 (4)
Intracranial bleeding	2 (1)	1 (<1)	0	0	2 (<1)	1 (<1)
AE leading to study discontinuation	31 (20)		11 (22)		42 (21)	
AE leading to dose modification						
Dose interruption	102 (66)		34 (68)		136 (67)	
Dose reduction	66 (43)		33 (66)		99 (49)	
On-study deaths[a]	16 (10)[b]		8 (16)[c]		24 (12)	
Treatment-related deaths	0		0		0	

Safety population includes all patients treated with a starting dose of avapritinib 300 mg or 400 mg once daily.
[a]Includes deaths that occurred on or after the date of first dose and up to and including the date of last dose +30 days.
[b]Cause of death was disease progression (*n* = 8), general physical health deterioration (*n* = 4), sepsis (*n* = 2), tumor hemorrhage (*n* = 1), and cardiac failure (*n* = 1), all identified as not related to avapritinib.
[c]Cause of death was disease progression (*n* = 4), general physical health deterioration (*n* = 1), sepsis (*n* = 1), tumor hemorrhage (*n* = 1), and respiratory failure (*n* = 1), all identified as not related to avapritinib.
Abbreviation: AE, adverse event.

evaluated according to central radiology assessment per mRECIST v1.1), and response rate according to Choi criteria [29]. Overall survival (OS) was evaluated as an exploratory endpoint.

Because patients who initiated avapritinib at doses of 300 mg or 400 mg per day showed similar response rates (see results section below), data for these patients were pooled and presented collectively as avapritinib 300/400 mg. Most patients who started at 400 mg had dose reductions to 300 mg, further supporting the pooled analysis of the 300-mg and 400-mg starting dose groups. Safety is reported for patients who received a starting dose of 300 or 400 mg in either part 1 or part 2. The efficacy population included patients from parts 1 or 2 who received a starting dose of avapritinib 300/400 mg and had received three or more previous lines of TKI therapy, regardless of mutational status. Although the inclusion criteria for dose expansion group 1 only specified treatment with at least two prior lines of TKI therapy (supplemental online Methods), observed enrollment reflected a more heavily pretreated patient population. Therefore, based on initial enrollment trends, evolving knowledge regarding the GIST treatment paradigm, and the high unmet need, analyses were conducted in patients treated in the fourth- or later-line setting who had *KIT* or *PDGFRA* mutations. Overall response rate was evaluated in the efficacy population and in the response-evaluable population, which included patients in the efficacy population who had ≥1 target lesion assessed at baseline by central radiology and had ≥1 post-baseline disease assessment by central radiology. Efficacy outcomes are also presented removing the eight patients with *PDGFRA* D842V mutations whose data are reported separately [28]. A summary of patients for whom efficacy and safety data have been previously reported is included in supplementary material.

Results

Patients

Between October 12, 2015, and January 9, 2017, 46 patients were enrolled in the dose escalation part, and between February 15, 2017, and November 16, 2018, 191 patients were enrolled in the three dose expansion groups (Fig. 1). The safety population (*n* = 204) included 154 patients who received a starting dose of avapritinib 300 mg and 50 patients who received a starting dose of avapritinib 400 mg. The efficacy population (all genotypes) included 121 patients who received a starting dose of avapritinib 300/400 mg and were treated with three or more previous lines of TKI therapy, and the response-evaluable population included 111 patients (76 and 35 patients with starting doses of 300 mg and 400 mg, respectively); of these, 8 patients had tumors harboring *PDGFRA* D842V mutations (six with starting dose 300 mg, two with starting dose 400 mg). At the data cutoff (November 16, 2018), median follow-up in the efficacy population was 10.8 months (11.0 months in the *KIT*/non-D842V *PDGFRA* mutation efficacy population), and 25 of 121 patients (21%) remained on treatment, including 18 of 113 (16%) patients without *PDGFRA* D842V mutations and 17 of 110 (15%) patients with *KIT* mutations.

In the safety population, median age was 62 years (range, 29–90), 124 of 204 (61%) were male, and 146 of 204 (72%) were white (supplemental online Table 2). Baseline characteristics were generally similar between the

Table 3. Most common adverse events (safety population, *n* = 204)

	All adverse events, *n* (%)		Treatment-related adverse events, *n* (%)	
AEs	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Nausea	131 (64)	5 (2)	121 (59)	3 (1)
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)	1 (<1)	82 (40)	1 (<1)
Vomiting	78 (38)	4 (2)	65 (32)	2 (<1)
Decreased appetite	77 (38)	6 (3)	58 (28)	1 (<1)
Diarrhea	76 (37)	10 (5)	65 (32)	6 (3)
Increased lacrimation	67 (33)	0	62 (30)	0
Peripheral edema	63 (31)	2 (<1)	55 (27)	2 (<1)
Face edema	50 (24)	1 (<1)	49 (24)	1 (<1)
Constipation	46 (23)	3 (1)	13 (6)	0
Dizziness	45 (22)	1 (<1)	29 (14)	1 (<1)
Hair color changes	43 (21)	1 (1)	42 (21)	1 (<1)
Blood bilirubin increased	43 (21)	9 (4)	38 (19)	8 (4)
Abdominal pain	41 (20)	11 (5)	13 (6)	1 (<1)
Headache	34 (17)	1 (<1)	18 (9)	1 (<1)
Dyspnea	34 (17)	5 (2)	13 (6)	1 (<1)
Dyspepsia	32 (16)	0	21 (10)	0
Hypokalemia	32 (16)	6 (3)	11 (5)	2 (<1)
Dysgeusia	31 (15)	0	31 (15)	0
Hypophosphatemia	28 (14)	9 (4)	24 (12)	7 (3)
Aspartate aminotransferase increased	28 (14)	1 (<1)	19 (9)	0
Pyrexia	28 (14)	1 (<1)	4 (2)	1 (<1)
Alopecia	27 (13)	0	23 (11)	0
Insomnia	26 (13)	0	9 (4)	0
Decreased weight	26 (13)	2 (<1)	16 (8)	1 (<1)
Rash	26 (13)	1 (<1)	21 (10)	1 (<1)
Pleural effusion	24 (12)	4 (2)	16 (8)	2 (<1)
Hypomagnesemia	22 (11)	1 (<1)	10 (5)	1 (<1)
Cough	19 (9)	0	1 (<1)	0
Neutropenia	18 (9)	4 (2)	18 (9)	4 (2)
Hypertension	17 (8)	6 (3)	3 (1)	1 (<1)
Asthenia	16 (8)	4 (2)	9 (4)	2 (<1)
Ascites	16 (8)	4 (2)	5 (2)	1 (<1)
Disease progression	12 (6)	12 (6)	0	0
Neutrophil count decreased	11 (5)	7 (3)	11 (5)	7 (3)
Lymphopenia	11 (5)	4 (2)	10 (5)	4 (2)
Hyponatremia	9 (4)	6 (3)	5 (2)	2 (<1)
General physical health deterioration	6 (3)	6 (3)	1 (<1)	1 (<1)
Sepsis	6 (3)	6 (3)	0	0

Table shows number of patients with each event. All-grade AEs in ≥10% of patients and/or grade ≥3 AEs in ≥2% of patients are listed.
Safety population includes all patients treated with a starting dose of avapritinib 300 mg or 400 mg once daily.
[a]Cognitive effects are pooled terms of memory impairment (all-grade, *n* = 60, 29.4%; grade ≥3, *n* = 1, <1%), cognitive disorder (22, 10.8%; 2, <1%), confusional state (15, 7.4%; 4, 2.0%), and encephalopathy (3, 1.5%; 2, <1%). Some patients experienced multiple cognitive effects. All cognitive effect AEs were considered treatment-related in this analysis.
Abbreviation: AE, adverse event.

A

	Efficacy population			Response-evaluable population		
	Avapritinib starting dose			Avapritinib starting dose		
Best overall response, *n* (%)[a]	300 mg (*n* = 78)	400 mg (*n* = 35)	300/400 mg (*n* = 113)	300 mg (*n* = 70)	400 mg (*n* = 33)	300/400 mg (*n* = 103)
Complete response	0	0	0	0	0	0
Partial response	12 (15)	5 (14)	17 (15)	12 (17)	5 (15)	17 (17)
Stable disease	34 (44)	18 (51)	52 (46)	33 (47)	18 (55)	51 (50)
Progressive disease	26 (33)	10 (29)	36 (32)	25 (36)	10 (30)	35 (34)
ORR, % (95% CI)[b]	15 (8–25)	14 (5–30)	15 (9–23)	17 (9–28)	15 (5–32)	17 (10–25)
CBR, % (95% CI)[c]	35 (24–46)	34 (19–52)	35 (26–44)	39 (27–51)	36 (20–55)	38 (29–48)

B

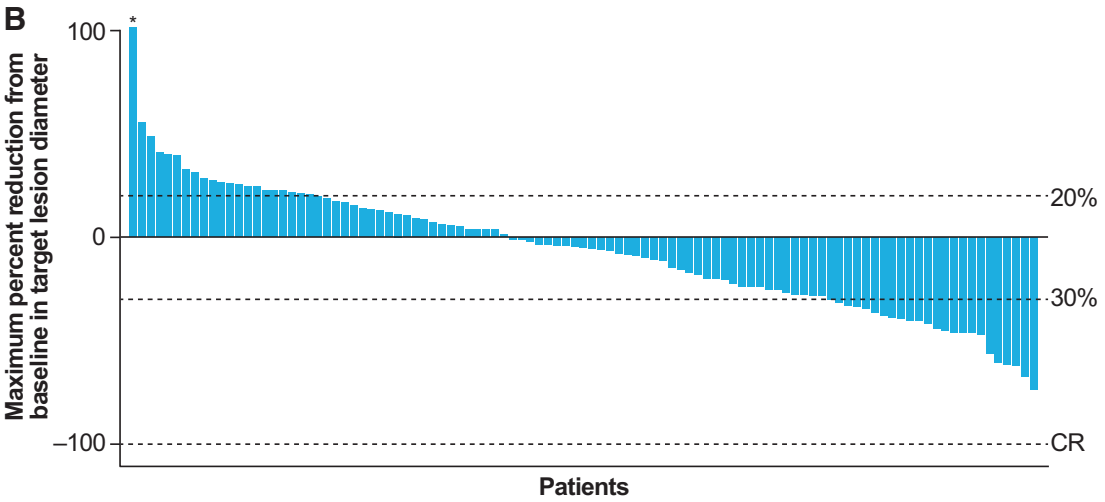


Figure 2. Best overall response. **(A):** Best overall response. **(B):** Waterfall plot of maximum percent change in sum of target lesion diameters.

[a]Best overall response according to RECIST v1.1 modified for patients with GIST, with response confirmed by central radiological assessment. Efficacy population included all patients with gastrointestinal stromal tumors harboring *KIT* or non-D842V *PDGFRA* mutations who received a starting dose of avapritinib 300 mg or 400 mg once daily, with ≥3 prior lines of treatment. Response-evaluable population includes all patients from the efficacy population who had at least one baseline and one postbaseline radiographic assessment. Ten patients were not included in the response-evaluable population because of missing postbaseline assessments.

[b]Includes patients with complete and partial responses.

[c]Includes patients with complete and partial responses or stable disease ≥4 months. *One patient had an outlier value for percent change from baseline of >200% increase in target lesion diameter.

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, overall response rate.

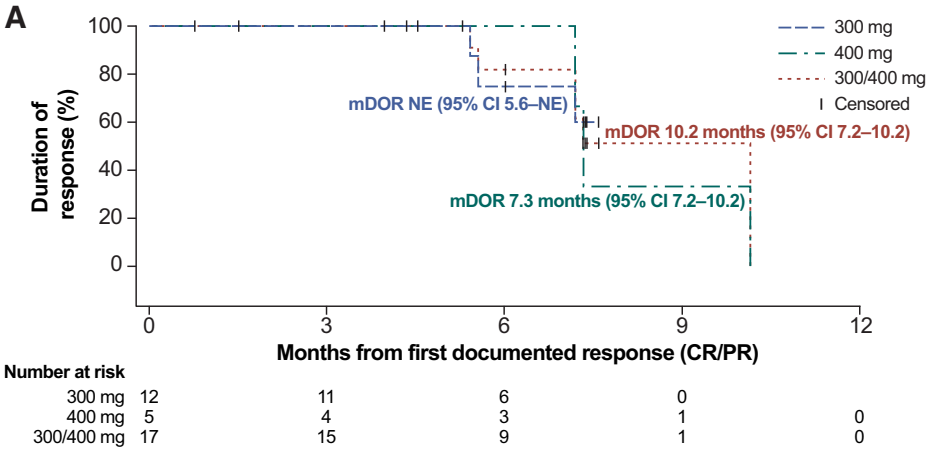
safety and efficacy populations (Table 1), although median number of previous TKIs was higher in the efficacy population compared with the safety population (4 vs. 3, respectively); in the efficacy population, the majority of patients had tumors with *KIT* mutations (110/121 [91%]), eight (7%) had *PDGFRA* D842V mutations, and three (2%) had *PDGFRA* exon 18 non-D842V mutations.

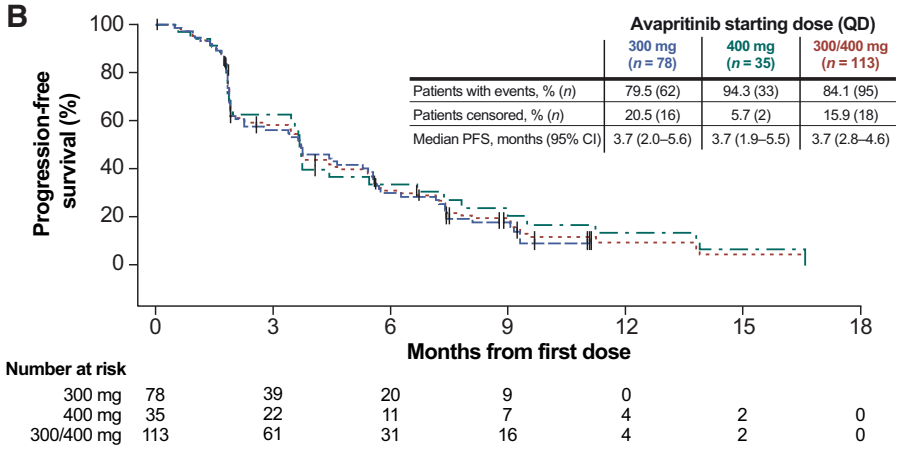
Safety

In the safety population, median treatment duration (range) was 23.6 weeks (0.1–107.1). Median dose intensity (range) was 258 mg per day (74–372) and 290 (64–400) in the 300-mg and 400-mg starting dose groups, respectively. A total of 101 of 204 patients (50%) required at least one dose reduction because due to of an AE (supplemental online Table 3; starting dose of 300 mg, *n* = 68 [44%]; starting dose 400 mg, *n* = 33 [66%]). A total of 134 (66%) patients had at least one dose interruption (starting dose 300 mg, *n* = 100 [65%]; starting dose 400 mg, *n* = 34 [68%]), of whom 83 (41%) had two or more dose interruptions (*n* = 57 [37%] and *n* = 26 [52%], respectively).

Almost all patients experienced one or more AE during the study (202/204 [99%]); 147 patients (72%) experienced a grade ≥3 AE, and 105 (51%) experienced a treatment-related grade ≥3 AE (Table 2). The most common all-grade AEs were nausea (131 [64%]), fatigue (113 [55%]), anemia (102 [50%]), cognitive effects (84 [41%]), and periorbital edema (83 [41%]); in general, the majority of specific AEs were grade 1–2 (Table 3) and were clinically manageable. There was a numerically higher incidence of AEs in the 400-mg starting dose group compared with the 300-mg group. The most common grade ≥3 treatment-related AEs were anemia (33 [16%]) and fatigue (13 [6%]).

Of the patients who had an AESI classified as cognitive effects, 58 (69%) experienced a grade 1 event, 18 (21%) a grade 2 event, and eight (10%) a grade 3 event (Table 2). Cognitive effects were primarily due to memory impairment, which occurred in 60 patients (29%; supplemental online Table 4). Intracranial bleeding occurred in two patients (1%) from the safety population (one grade 1, one grade 3). One additional patient from the dose escalation part experienced intracranial bleeding. The starting dose for this patient was 90 mg once daily, and the patient had been escalated to 200 mg at the time of the event; therefore, the patient was not included in the safety analysis of patients who initiated at 300/400 mg once daily.





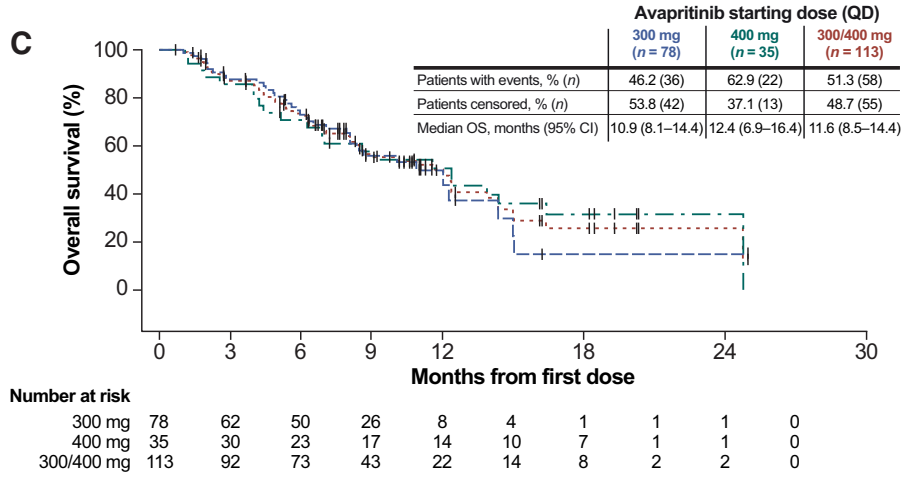


Figure 3. Efficacy of avapritinib.
Evaluated in the efficacy population of all patients with gastrointestinal stromal tumors harboring *KIT* or non-D842V *PDGFRA* mutations treated with a starting dose of avapritinib 300 mg or 400 mg once daily and who had three or more prior lines of therapy. DOR evaluated in patients with a CR or PR (*n* = 17).
Abbreviations: CI, confidence interval; CR, complete response; mDOR, median duration of response; NE, not evaluable; OS, overall survival; PFS, progression-free survival; PR, partial response; QD, once daily.

Twenty-four deaths were reported, which included 12 patients with disease progression and 12 with death due to AEs unrelated to study treatment (general health deterioration, *n* = 5; sepsis, *n* = 3, tumor hemorrhage, *n* = 2; cardiac failure, *n* = 1; respiratory failure, *n* = 1). There were no treatment-related deaths.

A total of 138 (68%) patients discontinued treatment, the majority because of disease progression (91 [45%]) or AEs (33 [16%]); 17 patients (8.3%) discontinued because of treatment-related AEs. The most common treatment-related AEs leading to treatment discontinuation were confusional state (*n* = 2 [1%]), encephalopathy (*n* = 2 [1%]), and fatigue (*n* = 2 [1%]; supplemental online Table 5). Four patients (2%) discontinued treatment because of cognitive effects (confusional state [*n* = 2]; encephalopathy [*n* = 2]), and one patient discontinued because of intracranial bleeding.

Efficacy

In the response-evaluable population of patients with advanced GIST and *KIT* or non-D842V *PDGFRA* mutations treated with avapritinib following three or more prior therapies (*n* = 103), centrally confirmed responses were observed in 17 patients (all PRs); ORR was 17% (95% confidence interval [CI], 10–25; Fig. 2), and median DOR was 10.2 months (95% CI, 7.2–10.2; Fig. 3); 51 patients (50%) had SD. Twenty-two patients had SD ≥4 months; CBR (defined as patients with objective response or SD lasting ≥16 weeks) was 38% (95% CI, 29–48). Radiographic tumor reductions were observed in 58% of patients (*n* = 60/103) with GIST harboring *KIT* or non-D842V *PDGFRA* mutations who initiated 300/400 mg avapritinib (Fig. 2). The ORR was 17% (12/70; 95% CI, 9–28) in patients treated with a 300-mg starting dose and 15% (5/33; 95% CI, 5–32) with a 400-mg starting dose. These data support both the pooled analysis of efficacy across patients who received starting doses of avapritinib 300/400 mg and our selection of 300 mg as the RP2D. Best overall responses and ORRs in the *KIT*/non-D842V *PDGFRA* mutation efficacy population are also shown in Figure 2A, and those for the efficacy and response-evaluable populations including patients with *PDGFRA* D842V mutations are shown in supplemental online Figure 2; KM analysis of duration of response including patients with *PDGFRA* D842V mutations is shown in supplemental online Figure 3A.

Response evaluation according to Choi criteria in the *KIT*/non-D842V *PDGFRA* mutation efficacy population (*n* = 113) revealed 35 patients (31%) with PR; the Choi ORR was 31% (95% CI, 23–40; supplemental online Table 6) and the Choi CBR was 35% (95% CI, 26–44).

For patients in the efficacy population without *PDGFRA* D842V mutations, median PFS was 3.7 months (95% CI, 2.8–4.6), and Kaplan-Meier–estimated PFS rates at 6 and 12 months were 31% (95% CI, 22–40) and 10% (95% CI, 3–17), respectively (Fig. 3B). Median OS was 11.6 months (95% CI, 8.5–14.4; Fig. 3C), with median follow-up of 11.0 months (95% CI, 9.9–12.6). PFS and OS analyses in the efficacy population including patients with *PDGFRA* D842V mutations (median follow-up for OS 10.8 months; 95% CI, 9.9–11.8) are shown in supplemental Figure 3B and C.

Discussion

In this study, avapritinib was generally well tolerated and had meaningful antitumor activity in heavily pretreated patients with advanced GIST harboring *KIT* or *PDGFRA* mutations, showing an ORR of 17%, a CBR of 38%, a median DOR of 10.2 months, and a median PFS of 3.7 months in this population of patients with GIST (excluding patients with *PDGFRA* D842V mutations) treated with at least three prior TKIs.

In the fourth- or later-line setting, treatment options for patients with advanced GIST are limited with the recently approved therapy of ripretinib as the only option [24]. Resumption of imatinib has been evaluated after two or more lines of TKI therapy (imatinib and sunitinib), with PFS of 1.8 months, and only a small benefit was reported over placebo in patients who had received a third-line TKI [30]. For the approved second- and third-line treatments, studies of sunitinib and regorafenib, respectively, reported ORRs of 5%–18% with an additional 58%–73% of patients experiencing SD of any duration, median PFS was 4.8–13.2 months, and median OS was 16.6–25.0 months; the CBR with third-line regorafenib was 76% [19, 20, 31, 32]. Finally, in a recently published phase III study, ripretinib as fourth-line or later treatment showed an ORR of 9% and PFS of 6.3 months [25]. In the present study, the ORR of 17%, CBR of 38%, and median PFS of 3.7 months show the activity of avapritinib in this heavily pretreated population (median, 4 prior therapies), with DOR of 10.2 months, suggesting there is a subpopulation of patients with GIST who experience significant benefit from avapritinib in the fourth-line setting and beyond. It should be noted that, as ripretinib was not approved at the time of the conduct of this study, we could not specifically address the benefit of avapritinib in patients who have previously progressed on ripretinib. In the previously reported *PDGFRA* D842V-mutant population, avapritinib demonstrated unprecedented clinical activity and durable responses. The centrally confirmed ORR was 88% (49/56 patients, 95% CI, 76–95), the estimated 12-month DOR rate was 70%, and median PFS was not reached [28].

The safety analysis of once-daily avapritinib 300/400 mg revealed that most AEs were low grade (1–2), albeit with a higher incidence of AEs with the 400-mg starting dose. Frequently observed AEs with avapritinib, including fatigue, gastrointestinal events, fluid retention, and anemia were generally consistent with those observed with other KIT kinase inhibitors in GIST [10–12, 19, 20]. Cognitive effects, defined as a composite of four CTCAE preferred terms (memory impairment, cognitive disorder, confusional state, encephalopathy), were reported in 41% of patients and were considered an AESI. Events were grade 1 (69%) or grade 2 (21%) in the large majority of patients, were manageable with dose modifications, and led to treatment discontinuation in only four patients (2%); notably, the overall incidence of cognitive effects was numerically lower in patients who initiated at 300 mg versus 400 mg (39% vs. 48%). Cognitive effects have not typically been reported as AEs for other TKIs, although they are known to be associated with the anaplastic lymphoma kinase inhibitor lorlatinib [33] and the tropomyosin receptor kinase inhibitors larotrectinib and entrectinib [34, 35]. Patients should be closely monitored for cognitive effects after initiating treatment and treatment interrupted at the first sign of cognitive impairment; detailed guidance on management of cognitive effects with avapritinib is provided in a separate

publication [36]. In addition, intracranial bleeding was observed in <1% of patients in this population.

Conclusion

The current results demonstrate that avapritinib is tolerable and has moderate clinical activity in fourth- and later-line treatment of patients with GIST harboring primary *KIT* or *PDGFRA* mutations with or without D842V mutations. Based on its overall safety profile and antitumor activity in the present study, avapritinib 300 mg once daily has been set as the recommended starting dose. A notable proportion of patients with advanced GIST in the fourth line or later and a *KIT* or non-D842V *PDGFRA* mutation experience significant reduction in tumor burden which is durable as reflected in the ORR of 17% and median duration of response of approximately 10 months, thus highlighting the clinical activity of avapritinib in a subset of patients with heavily pretreated GIST.

Acknowledgments

The authors would like to thank the patients, caregivers, and clinical research staff who assisted in patient care and data collection. Medical writing support was provided by Jeremy Kennard, Ph.D., and editorial support by Michelle Seddon, both of Paragon, Knutsford, U.K., supported by Blueprint Medicines Corporation. Blueprint Medicines Corporation follows all current policies established by the International Committee of Medical Journal Editors and Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M15-0288).

The NAVIGATOR study (NCT02508532) was funded by Blueprint Medicines Corporation, Cambridge, MA. Dr. Heinrich received salary support from a Department of Veterans Affairs Merit Review Grant (I01 BX000338). Dr. Trent received salary support from NIH/National Cancer Institute Cancer Center Support Grant P30CA240139.

The anonymized derived data from this study that underlie the results reported in this article will be made available, beginning 12 months and ending 5 years following this article publication, to any investigators who sign a data access agreement and provide a methodologically sound proposal to medinfo@blueprintmedicines.com. The trial protocol will also be made available as will a data fields dictionary.

The study was designed by the sponsor together with the study investigators. The sponsor collected the data and performed the analyses in conjunction with the authors. The authors wrote the first draft of the manuscript with editorial support from a sponsor-funded medical writer. All authors reviewed and provided input to the manuscript, and the corresponding author had final responsibility for the decision to submit for publication.

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Patrick Schöffski: Merck Sharpe & Dohme, Ipsen (RF); Deciphera, Blueprint Medicines, Exelixis, Plexxikon, Eisai, Loxo, Eli Lilly & Co, Ellipses Pharma, Merck, Servier, Genmab, Adaptimmune, Intellisphere, Transgene (Other/Personal fees); **Olivier Mir:** Bristol-Myers Squibb, Eli Lilly & Co, Ipsen, Janssen, Lundbeck, Merck Sharpe & Dohme, Roche, Servier, Vifor Pharma (Other/Personal fees); **Phillipe A. Cassier:** Novartis (RF), Blueprint, Amgen, Bristol-Myers Squibb, Roche/Genentech, Abbvie, Bayer, Merck Serono, GlaxoSmithKline, Janssen, Eli Lilly & Co., Bristol-Myers Squibb, Roche/Genentech, Merck Sharpe & Dohme, Novartis (Other/Personal fees); **Cesar Serrano:** Deciphera Pharmaceuticals, Bayer AG, Pfizer, Inc (RF), Deciphera Pharmaceuticals, Blueprint Medicines (C/A), Bayer AG, Blueprint Medicines (Other: lecture fees), Pharmamar, Pfizer, Bayer AG, Novartis, Eli Lilly & Co (Other: travel fees); **William D. Tap:** Atropos Therapeutics, Daiichi Sankyo (OI), Daiichi Sankyo (C/A), Patent for Companion Diagnostic for CDK4 inhibitors (14/854,329) pending to institution (IP), Certis Oncology Solutions, Atropos Therapeutics (SAB), X, Eli Lilly & Co, EMD Serono, Eisai, Janssen, Immune Design, Daiichi Sankyo, Blueprint, Loxo, GlaxoSmithKline, Agios Pharmaceuticals, NanoCarrier, Deciphera (Other/Personal fees); **Jonathan Trent:** iBlueprint Medicines, Deciphera Pharmaceuticals, Daiichi-Sankyo, Epizyme, Agios (C/A); **Piotr Rutkowski:** Novartis, Bristol-Myers Squibb, Merck Sharpe & Dohme, Roche, Pierre Fabre, Pfizer, Blueprint Medicines Corporation, Pfizer (Other/Personal fees); **Shreyaskumar Patel:** Immune Design, Bayer, Epizyme, Novartis, Daiichi Sankyo, Dova Pharmaceuticals, Deciphera Pharmaceuticals (C/A), Blueprint Medicines (RF-institution); **Sant P. Chawla:** Amgen, Roche, Threshold Pharmaceuticals, GlaxoSmithKline, CytRx Corporation, Ignyta, Immune Design, Tracon Pharma, SARC, Karyopharm Therapeutics, Jansen (RF); **Eval Meiri:** Amgen (C/A), Bayer (SAB); **Michael Gordon:** Medimmune, Merck, Bristol-Myers Squibb, Amgen, Tesaro, Beigene, Abbvie, Aeglea, Arcus, Astex, BluePrint, Calithera, CellDex, Corcept, Clovis, Eli Lilly & Co, Endocyte, Five Prime, Genocea, Neon, Plexxicon, Revolution Medicine, Seattle Genetics, Serono, SynDevRx, Tolero, Roche/Genentech, Syndax, FujiFilm, Veru, Medelis, Caremission, ImaginAB, Agenus, Imaging Endpoints, Tracon, Deciphera, Salarius, Daiichi, RedHill Biopharma, (Other/Personal fees); **Teresa Zhou:** Blueprint Medicines (E); **Maria Roche:** Blueprint Medicines (E, OI), Epizyme (Other); **Michael C. Heinrich:** Patent "Treatment of Gastrointestinal Stromal Tumors" licensed to Novartis, Patent "Activating Mutations of PDGFRA" issued (IP), Blueprint Medicines, Deciphera Pharmaceuticals (RF), MolecularMD, Novartis, Blueprint Medicines, Deciphera Pharmaceuticals (Other/Personal fees); **Margaret von Mehren:** Blueprint, Arog Pharmaceuticals, Deciphera Pharmaceuticals (Other). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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