Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial

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Summary

Background Targeting of KIT and PDGFRA with imatinib revolutionised treatment in gastrointestinal stromal tumour; however, PDGFRA Asp842Val (D842V)-mutated gastrointestinal stromal tumour is highly resistant to tyrosine kinase inhibitors. We aimed to assess the safety, tolerability, and antitumour activity of avapritinib, a novel KIT and PDGFRA inhibitor that potently inhibits PDGFRA D842V, in patients with advanced gastrointestinal stromal tumours, including patients with KIT and PDGFRA D842V-mutant gastrointestinal stromal tumours (NAVIGATOR).

Methods NAVIGATOR is a two-part, open-label, dose-escalation and dose-expansion, phase 1 study done at 17 sites across nine countries (Belgium, France, Germany, Poland, Netherlands, South Korea, Spain, the UK, and the USA). Patients aged 18 years or older, with an Eastern Cooperative Oncology Group performance status of 2 or less, and with adequate end-organ function were eligible to participate. The dose-escalation part of the study included patients with unresectable gastrointestinal stromal tumours. The dose-expansion part of the study included patients with an unresectable PDGFRA D842V-mutant gastrointestinal stromal tumour regardless of previous therapy or gastrointestinal stromal tumour with other mutations that either progressed on imatinib and one or more tyrosine kinase inhibitor, or only received imatinib previously. On the basis of enrolment trends, ongoing review of study data, and evolving knowledge regarding the gastrointestinal stromal tumour treatment paradigm, it was decided by the sponsor's medical director together with the investigators that patients with *PDGFRA* D842V mutations would be analysed separately; the results from this group of patients is reported in this Article. Oral avapritinib was administered once daily in the dose-escalation part (starting dose of 30 mg, with increasing dose levels once daily in continuous 28-day cycles until the maximum tolerated dose or recommended phase 2 dose was determined; in the dose-expansion part, the starting dose was the maximum tolerated dose from the dose-escalation part). Primary endpoints were maximum tolerated dose, recommended phase 2 dose, and safety in the dose-escalation part, and overall response and safety in the dose-expansion part. Safety was assessed in all patients from the dose-escalation part and all patients with PDGFRA D842V-mutant gastrointestinal stromal tumour in the dose-expansion part, and activity was assessed in all patients with PDGFRA D842V-mutant gastrointestinal stromal tumour who received avapritinib and who had at least one target lesion and at least one post-baseline disease assessment by central radiology. This study is registered with ClinicalTrials.gov, NCT02508532.

Findings Between Oct 26, 2015, and Nov 16, 2018 (data cutoff), 46 patients were enrolled in the dose-escalation part, including 20 patients with a PDGFRA D842V-mutant gastrointestinal stromal tumour, and 36 patients with a PDGFRA D842V-mutant gastrointestinal stromal tumour were enrolled in the dose-expansion part. At data cutoff (Nov 16, 2018), 38 (46%) of 82 patients in the safety population (median follow-up of 19·1 months [IQR 9·2–25·5]) and 37 (66%) of the 56 patients in the *PDGFRA* D842V population (median follow-up of 15·9 months [IQR 9·2–24·9]) remained on treatment. The maximum tolerated dose was 400 mg, and the recommended phase 2 dose was 300 mg. In the safety population (patients with PDGFRA D842V-mutant gastrointestinal stromal tumour from the dose-escalation and dose-expansion parts, all doses), treatment-related grade 3–4 events occurred in 47 (57%) of 82 patients, the most common being anaemia (14 [17%]); there were no treatment-related deaths. In the PDGFRA D842V-mutant population, 49 (88%; 95% CI 76–95) of 56 patients had an overall response, with five (9%) complete responses and 44 (79%) partial responses. No dose-limiting toxicities were observed at doses of 30–400 mg per day. At 600 mg, two patients had dose-limiting toxicities (grade 2 hypertension, dermatitis acneiform, and memory impairment in patient 1, and grade 2 hyperbilirubinaemia in patient 2).

Interpretation Avapritinib has a manageable safety profile and has preliminary antitumour activity in patients with advanced PDGFRA D842V-mutant gastrointestinal stromal tumours.

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Research in context

Evidence before this study

We searched PubMed for studies published in English between Jan 1, 2015, and Dec 31, 2019, investigating tyrosine kinase inhibitor treatment of gastrointestinal stromal tumours with *PDGFRA* Asp842Val (D842V) mutations. Search terms included "GIST" plus "PDGFRA" plus "D842V" plus "treatment" plus ["tyrosine kinase inhibitor" or "imatinib"] plus ["outcome" or "safety" or "efficacy"] plus ["investigation" or "study"]. Out of six entries returned from PubMed, we identified four investigations reporting treatment outcomes in patients with PDGFRA D842V-mutated gastrointestinal stromal tumours; two of the articles reported on in-vitro and cytogenetic analyses and were therefore not relevant. All four articles reported on retrospective investigations of imatinib treatment in patients with PDGFRA-mutated gastrointestinal stromal tumours. Subgroups of patients with PDGRFA D842V-mutated gastrointestinal stromal tumours with treatment-related data included five to 31 patients. Overall response rates were 0–12%, and other efficacy measures were reported as notably worse in patients with D842V *PDGFRA* mutations than in those with non-D842V *PDGFRA* mutations. Investigators concluded that imatinib has little efficacy in gastrointestinal stromal tumours with D842V mutations, although investigators from one study noted that in the absence of better treatment options imatinib should not be universally withheld given the (albeit limited) possibility of some response. One study also reported results in six patients with D842V mutations treated with sunitinib, none of whom had an objective response.

Added value of this study

To our knowledge, the NAVIGATOR trial is the first prospective study to investigate treatment of D842V-mutated gastrointestinal stromal tumours with avapritinib. Our data show that avapritinib is clinically active in patients with D842V-mutated gastrointestinal stromal tumours. Most adverse events associated with avapritinib were grade 1–2; these adverse events were generally proportional to dose and exposure. Although cognitive effects are a concern, these effects were manageable for most patients through dose modifications, including dose interruptions with or without dose reductions; two (2%) of 82 patients discontinued treatment because of intracranial bleeding. Overall, we found that avapritinib had clinical activity and a manageable safety profile in patients with advanced, *PDGFRA* D842V-driven gastrointestinal stromal tumours.

Implications of all the available evidence

Gastrointestinal stromal tumours are a molecularly heterogeneous disease driven by various oncogenic primary and secondary KIT and PDGFRA mutants. Findings from our study suggest that avapritinib has preliminary antitumour activity in the unique subset of gastrointestinal stromal tumours harbouring the *PDGFRA* D842V mutation, a subset that has been refractory to all currently approved tyrosine kinase inhibitors. Avapritinib might have the potential to improve the outcome of these patients with advanced PDGFRA D842V-mutated gastrointestinal stromal tumours.

Introduction

Oncogenic mutations in the genes encoding receptor tyrosine kinases KIT and PDGFRA are the driver mutations in more than 85% of gastrointestinal stromal tumours, the most common sarcoma of the gastrointestinal tract.[1,2] Targeting of KIT or PDGFRA with imatinib revolutionised treatment for patients with metastatic or unresectable gastrointestinal stromal tumours, changing a uniformly fatal cancer to a manageable disease with durable responses and improved overall survival.[3] However, imatinib and other approved agents do not target PDGFRA Asp842Val (D842V), which is the primary driver mutation in 5–6% of gastrointestinal stromal tumours.[4–7] Patients with advanced D842V-mutant gastrointestinal stromal tumours have a poor prognosis, similar to that of all patients with gastrointestinal stromal tumours in the pre-imatinib era, because approved agents provide essentially no objective responses, and median progression-free survival and overall survival are only 3–5 months and approximately 15 months, respectively.[8–10]

The D842V mutation occurs in the region of the gene encoding the PDGFRA activation loop (exon 18) and shifts the kinase into the active conformation, which drives oncogenic signalling and renders the kinase largely resistant to imatinib and other type 2 tyrosine kinase inhibitors that preferentially bind to the inactive conformation.[11,12] Avapritinib (also known as BLU-285) was designed to potently and selectively target the active conformation of KIT and PDGFRA via a type 1 inhibition mechanism.[12,13] In preclinical studies, avapritinib demonstrated notable selectivity within the kinome for KIT and PDGFRA, potent biochemical activity against KIT and PDGFRA, including PDGFRA D842V (half maximal inhibitory concentration [IC_{50}]=0·2 nM), and in-vivo efficacy against gastrointestinal stromal tumour xenografts that were resistant to imatinib.[13]

We aimed to evaluate the safety, tolerability, and antitumour activity of avapritinib in patients with advanced gastrointestinal stromal tumours, including patients with KIT and PDGFRA D842V-mutant gastrointestinal stromal tumours.

Methods

Study design and participants

NAVIGATOR is a two-part, open-label, dose-escalation and dose-expansion, phase 1 study done at 17 sites across nine countries (Belgium, France, Germany, Poland, Netherlands, South Korea, Spain, the UK, and the USA; appendix p 1). Dose escalation followed a 3+3 design for

See Online for appendix

determination of the maximum tolerated dose (defined as the highest dose with no more than one dose-limiting toxicity in six patients) or the recommended phase 2 dose (observations related to pharmacokinetics, pharmacodynamics, and any cumulative toxicity after multiple cycles were included in the rationale supporting the dose to use during dose expansion set below the maximum tolerated dose). Three patients were initially enrolled per dose-escalation cohort, and three additional patients were enrolled if the cohort required expansion because of dose-limiting toxicities. Additional accrual was allowed to doses previously determined to be tolerable (enrichment cohorts). Dose expansion included three prespecified groups. The original study design included two groups: patients who progressed following imatinib plus one or more other approved tyrosine kinase inhibitor and no known *PDGFRA* D842V mutation (group 1), and patients with PDGFRA D842V-mutant gastrointestinal stromal tumours regardless of previous therapy (group 2). On the basis of encouraging initial activity and favourable tolerability, a third expansion group was added: patients without D842V mutations who had received only previous imatinib (group 3). All protocol modifications, including those increasing the number of patients and cohorts in the expansion part, are described and justified in the trial protocol version dated Feb 28, 2018.

Patients who were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 2 or less, and had adequate end-organ function were eligible to participate. The dose-escalation part of the trial was open to patients with histologically or cytologically confirmed refractory solid tumours or unresectable gastrointestinal stromal tumour; however, only patients with gastrointestinal stromal tumours were enrolled. The dose-expansion part included patients who had unresectable gastrointestinal stromal tumours with one or more measurable target lesions per modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST 1.1; for patients with gastrointestinal stromal tumour) in addition to the inclusion criteria specific to each prespecified group: patients with disease progression following imatinib plus one or more other kinase inhibitors and no known D842V mutation (group 1); patients with PDGFRA D842V-mutant gastrointestinal stromal tumours (mutation identified by local or central assessment on an archival tissue sample, a new tumour biopsy, or circulating tumour DNA obtained before avapritinib treatment) regardless of previous therapy (group 2); and patients who had received only imatinib and no known D842V mutation (group 3). A full list of inclusion and exclusion criteria are in the protocol. The statistical analysis plan prespecified selected analyses based on the line of tyrosine kinase inhibitor therapy and gastrointestinal stromal tumour mutation types. On the basis of enrolment trends, ongoing review of study data, and evolving knowledge regarding the gastrointestinal stromal tumour treatment paradigm, it was decided by the sponsor's medical director in combination with the investigators that patients with *PDGFRA* D842V mutations (group 2) would be analysed separately, and therefore this Article focuses on the safety and antitumour activity of avapritinib in this population.

The study was done in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the International Conference on Harmonisation Good Clinical Practice and applicable regulatory requirements. The institutional review board or independent ethics committee of each study centre approved the study. All patients provided written, informed consent. The study protocol in included in the appendix.

Procedures

In the dose-escalation part, the first cohort of patients received a starting dose of oral avapritinib 30 mg once daily; increasing dose levels once daily in continuous 28-day cycles occurred until determination of the maximum tolerated dose or the recommended phase 2 dose. To minimise the number of patients treated at potentially inactive doses, intrapatient dose escalation was permitted after a patient had completed at least two cycles of treatment without having grade 3 or worse toxicity. The patient's dose could then be escalated to a dose that had been reviewed at a dose-escalation meeting and did not exceed the maximum tolerated dose. Dose escalation was not permitted after dose reduction due to an adverse event.

In the dose-expansion part, the maximum tolerated dose (400 mg) from the dose-escalation part was used as the starting dose; however, this dose was subsequently reduced to 300 mg, which was identified as the recommended phase 2 dose. For each individual patient dose interruption, reductions and treatment discontinuation decisions were made considering the dose-modification guidelines for avapritinib-related toxicity (appendix p 5), which determined treatment interruption for any grade 3 or 4 toxicity until it was resolved to grade 2 or better; treatment would then resume at a dose generally reduced by 100 mg from the dose (300 or 200 mg) received at time of the event or restarted at 100 mg. Patients were anticipated to receive at least one 28-day cycle of oral daily avapritinib during the dose-expansion part of the study; no maximum treatment duration was set. Treatment could continue until precluded by toxicity, non-compliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study.

Formalin-fixed, paraffin-embedded tumour samples from archival tissue, or a new tumour biopsy, were used for *PDGFRA* mutation testing. All patients with PDGFRA D842V-mutant gastrointestinal stromal tumours were enrolled on the basis of local available mutation testing. On study, *PDGFRA* mutation status was determined centrally in plasma with the OncoBEAMPDGFRA assay (Sysmex Hamburg, Hamburg, Germany) for dose escalation to evaluate pharmacodynamics and to explore

the mechanism of resistance. In the dose-expansion part, the PGDx PlasmaSELECT-R next-generation sequencing panel (Personal Genome Diagnostics, Baltimore, MD, USA) was used. Mutational *PDGFRA* D842V status in patients included in the efficacy analysis was also assessed using a modified version of the CancerSELECT125 assay (Personal Genome Diagnostics) as part of the exploratory analysis.

Adverse events were evaluated at each follow-up visit (days –3, –2, –1, and days 1, 8, 15, and 22 in cycle 1, and days 1 and 15 in cycle 2 in the dose-escalation part; days 1, 2, and 15 in cycle 1 and day 1 in cycle 2 in the dose-expansion part; and day 1 of cycle 3 and all subsequent cycles until cycle 13 in both dose-escalation and dose-expansion parts) from the start of study drug administration up to 30 days after the final dose, and were graded according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). Clinical laboratory investigations for haematology, coagulation, and serum chemistry parameters were done at screening, baseline (day –3 of the pharmacokinetics lead-in stage in the dose-escalation part or day 1 of cycle 1 in the dose-expansion part), cycle 1 (day 8 in the dose-escalation and dose-expansion parts; day 15 in the dose-escalation part; and day 22 in the dose-escalation and dose-expansion parts), cycle 2 (days 1 and 15 in the dose-escalation and dose-expansion parts), cycle 3 and onward cycles (day 1 in the dose-escalation and dose-expansion parts), and 14 days after the last dose of treatment. Urinalysis was done at screening, baseline (day 3 in the dose-escalation part or day 1 of cycle 1 in the dose-expansion part) and 14 days after the last dose of treatment. All patients underwent tumour imaging for response assessment via CT or MRI at screening, on day 1 of cycle 3, every two cycles up to and including cycle 13, and then every 3 months until progression or discontinuation. Target and non-target lesions were assessed per mRECIST 1.1 (appendix p 3)[14] for gastrointestinal stromal tumours by independent, blinded, central radiographic review (BioTelemetry, Rockville, MD, USA). In the dose-escalation part, serial blood samples were collected pre-dose and at multiple timepoints through cycle 4; pharmacokinetic parameters were calculated from the plasma concentration–time data using standard non-compartmental methods. For day 15 of cycle 1, the area under the plasma concentration–time curve over the dosing interval (τ=24 h) at steady state ($AUC_{0-\tau,ss}$) was calculated using a population pharmacokinetic model-derived avapritinib concentration at pre-dose, and at 0·5 h, 1 h, 2 h, 4 h, 8 h, and 24 h after the previous dose. Detailed methods and plasma sample collection times are presented in the appendix (p 7).

Outcomes

The primary endpoints in the dose-escalation part were determination of the maximum tolerated dose and recommended phase 2 dose of avapritinib as well as evaluation of safety. The primary endpoints in the dose-expansion part were evaluation of the overall response rate (defined as the proportion of patients with a partial or complete response by central radiology review per mRECIST 1.1), and the overall safety profile of avapritinib. Pharmacokinetics, the clinical benefit rate, duration of response, and progression-free survival per mRECIST 1.1 were secondary endpoints, and overall survival was a prespecified exploratory endpoint, all of which are reported here. Clinical benefit rate was defined as the proportion of patients with a confirmed complete or partial response of any duration or stable disease for at least 16 weeks from the start of treatment. Duration of response was defined as the time from first documented response (complete or partial) to the date of first documented disease progression or death due to any cause, whichever occurred first. Progression-free survival was defined as the time from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurred first. Overall survival was defined as the time from start of treatment to the date of death; patients who died before or on the data cutoff date were considered to have had an event, otherwise they were censored at the last date known alive. Additional secondary endpoints, which will be reported elsewhere as they have not been analysed yet, include response rate by Choi criteria, progression-free survival on last previous anticancer therapy, assessment of additional cancer-relevant mutations (baseline and end of treatment), and changes from baseline of their mutant allele fraction in peripheral blood.

Statistical analysis

The dose-determining population, defined as all patients who completed cycle 1 of treatment and received at least 75% of their prescribed doses or experienced a dose-limiting toxicity in cycle 1 in the dose-escalation part, was used to determine the maximum tolerated dose. The maximum tolerated dose was defined as the highest dose level with no more than one dose-limiting toxicity in six patients. The safety population included all patients from the dose-escalation part and all patients with PDGFRA D842V-mutant gastrointestinal stromal tumours in the dose-expansion part. We summarise safety results using descriptive statistics. Reporting of safety results by dose level was prespecified in the statistical analysis plan.

The D842V population included all patients with PDGFRA D842V-mutant gastrointestinal stromal tumours who received avapritinib in either the dose-escalation or dose-expansion part. We evaluated antitumour activity in patients from the D842V population who had at least one target lesion and at least one post-baseline disease assessment by central radiology.

In the dose-expansion part, for the primary endpoint of overall response rate, a sample size of 31 patients allowed testing the null hypothesis of an overall response rate of

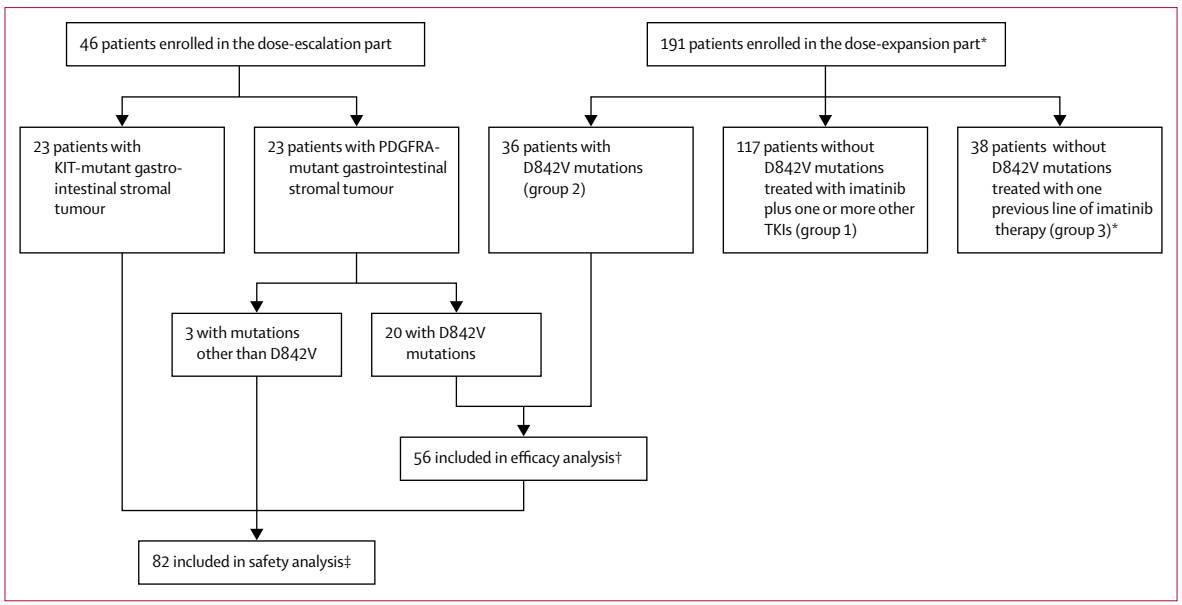

Figure 1: **Patient disposition**
D842V=Asp842Val. TKI=tyrosine kinase inhibitor. *Enrolment at the data cutoff of Nov 16, 2018. At the data cutoff, enrolment in group 3 was ongoing. †The D842V population included all patients with *PDGFRA* D842V mutations from the dose-escalation and dose-expansion parts. All patients in the D842V population received at least one dose of study medication and met criteria for inclusion in the response-evaluable population (patients with at least one target lesion and at least one post-baseline disease assessment by central radiology). ‡The safety population included all patients in the dose-escalation part and patients with D842V mutations in the dose-expansion part.

10% or less versus the alternative hypothesis of an overall response rate of 35% or more with 90% power, assuming a two-sided type I error rate of 0·05; we calculated estimates and 95% CIs based on the exact binomial distribution. We used Kaplan-Meier methods to estimate duration of response, progression-free survival, and overall survival; 95% CIs are provided. We also calculated estimated duration of response, progression-free survival, and overall survival rates at certain timepoints (duration of response: 12 months; progression-free survival: 3, 6, and 12 months; and overall survival: 6, 12, and 24 months). Efficacy results were summarised by daily starting dose and/or subpopulations according to the prespecification in the statistical analysis plan. Efficacy results for patients with KIT-mutant gastrointestinal stromal tumours will be reported separately. All statistical analyses were done with SAS (version 9.3 or higher).

This study is registered with ClinicalTrials.gov, NCT02508532.

Role of the funding source

The study was designed by the funder together with the study investigators. The funder collected, analysed, and interpreted the data in conjunction with the authors. The authors wrote the first draft of the manuscript with editorial support from a medical writer paid for by the funder. Bioanalysis of plasma samples was done by Frontage Laboratories (Exton, PA, USA), and pharmacokinetic parameters were calculated by Model Answers (Brisbane, Australia) under the paid supervision of the funder. MCH, TZ, MR, and BBW had access to all of the raw data; each investigator had access to the raw data of all patients they enrolled and any other data requested. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Oct 26, 2015, and Jan 9, 2017, 46 patients were enrolled in the dose-escalation part, including 25 patients in the dose-escalation cohorts and 21 patients in the enrichment cohorts (appendix pp 8, 18). On the basis of early observations of activity, enrolment to the enrichment cohorts was restricted to patients with PDGFRA D842V-mutant gastrointestinal stromal tumours. At the data cutoff date of Nov 16, 2018, the dose-escalation part included 20 patients with *PDGFRA* D842V mutations, 23 patients with a *KIT* mutation, and three patients with non-D842V *PDGFRA* mutations (figure 1).

36 patients with PDGFRA D842V-mutant gastrointestinal stromal tumours were enrolled in the dose-expansion part between Feb 15, 2017, and April 10, 2018. Altogether, the safety population included 82 patients and the D842V population 56 patients, all of whom were evaluable for response and are included in the efficacy analysis in this study (figure 1).

In the safety population, the median age was 62 years (IQR 54–68), 49 (60%) of 82 patients were men, and 62 (76%) were white (table 1); 80 (98%) patients had

	Safety population (n=82)
Age, years	62 (54–68)
Sex	
Men	49 (60%)
Women	33 (40%)
Race	
Asian	6 (7%)
Black or African American	5 (6%)
White	62 (76%)
Unknown or other	9 (11%)
Primary mutation status	
PDGFRA exon 18 D842V	56 (68%)
PDGFRA exon 18 non-D842V	2 (<1%)
PDGFRA exon 14	1 (<1%)
KIT	23 (28%)
ECOG performance status	
0	33 (40%)
1	46 (56%)
2	3 (4%)
Metastatic disease	80 (98%)
Primary tumour site of gastrointestinal stromal tumour	
Stomach	54 (66%)
Small intestine*	16 (20%)
Large intestine†	2 (2%)
Omentum	2 (2%)
Peritoneum	5 (6%)
Oesophagus	1 (1%)
Other	2 (2%)
Largest target lesion size	
≤5 cm	35 (43%)
>5 to ≤10 cm	26 (32%)
>10 cm	20 (24%)
No target lesion	1 (<1%)
Number of previous tyrosine kinase inhibitors	
0	11 (13%)
1	22 (27%)
2	13 (16%)
3	10 (12%)
4	9 (11%)
≥5	17 (21%)

Data are median (IQR) or n (%). Proportions might not add to 100% as a result of rounding. ECOG=Eastern Cooperative Oncology Group. *Small intestine, duodenum, jejunum, or ileum. †Colon and rectum.

Table 1: **Baseline characteristics**

metastatic disease with at least one target lesion of more than 5 cm (46 [56%] patients) and were treated with at least one previous tyrosine kinase inhibitor (71 [87%] patients). Baseline characteristics of the safety and D842V populations were generally similar, except for mutational status and median number of previous tyrosine kinase inhibitors (two *vs* one; appendix p 9).

Median follow-up for the 82 patients in the safety population was 19·1 months (IQR 9·2–25·5). The 46 patients enrolled in the dose-escalation part received avapritinib doses of 30–600 mg once daily. 44 patients met the criteria to be included in the dose-determining population; two patients were excluded because they did not receive at least 75% of their prescribed doses. No cycle 1 dose-limiting toxicities were observed at doses of 30–400 mg per day (appendix p 18). At 600 mg, two patients had cycle 1 dose-limiting toxicities (grade 2 hypertension, dermatitis acneiform, and memory impairment in patient 1, and grade 2 hyperbilirubinaemia in patient 2). Both patients had temporary dose interruptions and resumed dosing at 400 mg. Avapritinib 400 mg was considered the maximum tolerated dose and chosen as the starting dose for dose expansion. The dose-expansion part starting dose was subsequently reduced to 300 mg after joint investigator and sponsor review of available safety, pharmacokinetic (full pharmacokinetic results are included in the appendix pp 11–14, 19), pharmacodynamic, and clinical activity data (pharmacodynamic and clinical activity data are not available yet and will be published elsewhere). Emerging data during early expansion suggested a higher incidence of grade 3 cognitive adverse events and further dose reductions with the 400 mg starting dose after multiple cycles of treatment. On the basis of these factors, and data suggesting a similar preliminary antitumour activity, 300 mg was considered the recommended phase 2 dose and used as the starting dose for the remainder of the study.

Most treatment-related adverse events were grade 1–2 (table 2). At the 300 mg dose, the most common treatment-related grade 1–2 events were nausea (22 [69%] of 32 patients), diarrhoea (13 [41%]), decreased appetite (12 [38%]), and fatigue (12 [38%]), and at the 400 mg dose the most common treatment-related grade 1–2 events were nausea (12 [71%] of 17 patients), vomiting (eight [47%]), fatigue (eight [47%]), and periorbital oedema (eight [47%]). Across doses, treatment-related grade 3–4 events occurred in 47 (57%) of 82 patients, the most common being anaemia (14 [17%]). Drug-related serious adverse events (any grade) occurred in 21 (26%) of 82 patients, of which the majority were grade 3; the most common (any grade) were anaemia and pleural effusion (three [4%] patients each) and diarrhoea and vertigo (two [2%] patients each).

Two categories were determined as adverse events of special interest: cognitive effects and intracranial bleeding (appendix p 15). Cognitive effects (any cause) occurred in 33 (40%) of 82 patients and included memory impairment (25 [30%]), cognitive disorder (eight [10%]), confusional state (seven [9%]), and encephalopathy (two [2%]). Cognitive effects were primarily grade 1 (19 [23%]) and resulted in treatment discontinuation in two (2%) patients. Intracranial bleeding occurred in two (2%) patients. Both events were grade 3, non-fatal, considered possibly related to the study drug, and improved or resolved following treatment discontinuation. The study drug was not restarted in either patient. A total of 69 (84%) of 82 patients

	<300 mg (n=30)				300 mg (n=32)				400 mg (n=17)				600 mg (n=3)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any related adverse event	16 (53%)	12 (40%)	2 (7%)	0	11 (34%)	19 (59%)	2 (6%)	0	8 (47%)	8 (47%)	1 (6%)	0	0	3 (100%)	0	0
Nausea	13 (43%)	1 (3%)	0	0	22 (69%)	0	0	0	12 (71%)	0	0	0	3 (100%)	0	0	0
Fatigue	18 (60%)	1 (3%)	0	0	12 (38%)	1 (3%)	0	0	8 (47%)	3 (18%)	0	0	2 (67%)	0	0	0
Diarrhoea	11 (37%)	1 (3%)	0	0	13 (41%)	2 (6%)	0	0	6 (35%)	1 (6%)	0	0	2 (67%)	0	0	0
Periorbital oedema	15 (50%)	0	0	0	11 (34%)	1 (3%)	0	0	8 (47%)	0	0	0	1 (33%)	0	0	0
Anaemia	6 (20%)	5 (17%)	0	0	11 (34%)	7 (22%)	0	0	4 (24%)	1 (6%)	0	0	0	1 (33%)	0	0
Decreased appetite	6 (20%)	1 (3%)	0	0	12 (38%)	0	0	0	5 (29%)	0	0	0	3 (100%)	0	0	0
Vomiting	10 (33%)	1 (3%)	0	0	5 (16%)	0	0	0	8 (47%)	0	0	0	2 (67%)	0	0	0
Memory impairment	7 (23%)	0	0	0	10 (31%)	0	0	0	7 (41%)	0	0	0	1 (33%)	0	0	0
Hair colour changes	11 (37%)	0	0	0	8 (25%)	0	0	0	5 (29%)	0	0	0	0	0	0	0
Increased lacrimation	9 (30%)	0	0	0	7 (22%)	0	0	0	7 (41%)	0	0	0	1 (33%)	0	0	0
Peripheral oedema	10 (33%)	0	0	0	10 (31%)	0	0	0	4 (24%)	0	0	0	0	0	0	0
Blood bilirubin increased	3 (10%)	0	0	0	7 (22%)	1 (3%)	0	0	5 (29%)	1 (6%)	0	0	2 (67%)	0	0	0
Face oedema	3 (10%)	0	0	0	11 (34%)	0	0	0	3 (18%)	0	0	0	2 (67%)	0	0	0
Dysgeusia	5 (17%)	0	0	0	7 (22%)	0	0	0	2 (12%)	0	0	0	2 (67%)	0	0	0
Hypophosphataemia	3 (10%)	1 (3%)	1 (3%)	0	3 (9%)	1 (3%)	0	0	4 (24%)	2 (12%)	0	0	0	1 (33%)	0	0
Neutropenia	2 (7%)	1 (3%)	0	0	6 (19%)	3 (9%)	0	0	1 (6%)	1 (6%)	0	0	0	1 (33%)	0	0
Dizziness	2 (7%)	0	0	0	6 (19%)	0	0	0	5 (29%)	0	0	0	1 (33%)	0	0	0
Dyspepsia	6 (20%)	0	0	0	4 (13%)	0	0	0	2 (12%)	0	0	0	1 (33%)	0	0	0
Alopecia	4 (13%)	0	0	0	4 (13%)	0	0	0	3 (18%)	0	0	0	1 (33%)	0	0	0
Eyelid oedema	3 (10%)	0	0	0	5 (16%)	0	0	0	3 (18%)	0	0	0	0	0	0	0
Leukopenia	2 (7%)	0	0	0	3 (9%)	0	0	0	5 (29%)	0	0	0	0	1 (33%)	0	0
Headache	3 (10%)	0	0	0	4 (13%)	0	0	0	1 (6%)	0	0	0	2 (67%)	0	0	0
Hyperbilirubinaemia	3 (10%)	1 (3%)	0	0	2 (6%)	1 (3%)	0	0	1 (6%)	0	0	0	1 (33%)	1 (33%)	0	0
Dry mouth	4 (13%)	0	0	0	2 (6%)	0	0	0	2 (12%)	0	0	0	1 (33%)	0	0	0
Pleural effusion	2 (7%)	1 (3%)	0	0	3 (9%)	1 (3%)	0	0	0	1 (6%)	0	0	1 (33%)	0	0	0
Cognitive disorder	1 (3%)	1 (3%)	0	0	4 (13%)	0	0	0	0	1 (6%)	0	0	1 (33%)	0	0	0
Dry skin	2 (7%)	0	0	0	3 (9%)	0	0	0	2 (12%)	0	0	0	1 (33%)	0	0	0
Hypomagnesaemia	2 (7%)	1 (3%)	0	0	4 (13%)	0	0	0	1 (6%)	0	0	0	0	0	0	0
Rash	4 (13%)	0	0	0	1 (3%)	0	0	0	2 (12%)	0	0	0	1 (33%)	0	0	0
Decreased weight	4 (13%)	0	0	0	3 (9%)	0	0	0	0	0	0	0	1 (33%)	0	0	0
Decreased neutrophil count	0	1 (3%)	0	0	2 (6%)	2 (6%)	1 (3%)	0	0	1 (6%)	0	0	0	0	0	0
Vertigo	1 (3%)	2 (7%)	0	0	2 (6%)	0	0	0	1 (6%)	0	0	0	0	0	0	0
Lymphopenia	1 (3%)	0	0	0	0	1 (3%)	0	0	1 (6%)	1 (6%)	0	0	0	0	0	0
Hypocalcaemia	1 (3%)	1 (3%)	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0
Mental impairment	0	0	0	0	1 (3%)	1 (3%)	0	0	0	0	1 (6%)	0	0	0	0	0
Peripheral neuropathy	1 (3%)	0	0	0	1 (3%)	1 (3%)	0	0	0	0	0	0	0	0	0	0
Delirium	0	1 (3%)	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0
Psychotic disorder	0	1 (3%)	0	0	0	0	0	0	0	1 (6%)	0	0	0	0	0	0

Data are n (%). The table lists treatment-related adverse events of any grade occurring in 10% or more of all patients or grade 3–4 adverse events in 2% or more of all patients (n=82). There were no treatment-related grade 5 adverse events. *As determined by investigator. †National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Table 2: **Adverse events related to study drug* (at starting dose) by grade†**

required at least one dose reduction or treatment interruption. The median daily dose was 229 mg (range 30–478) in the 82 patients in the safety population. Relative dose intensity is shown in the appendix (p 16).

In the safety population, 44 (54%) of 82 patients discontinued treatment. The most common reasons for treatment discontinuation were disease progression (determined by an investigator; 26 [32%]) and adverse events (15 [18%]), ten (12%) of which were considered to be related to avapritinib (appendix p 17). 11 (13%) deaths were reported; causes were related to patients' general physical health (three [4%] patients), disease progression (three [4%]), cardiac failure (one [1%]), hepatic failure (one [1%]), hyperbilirubinaemia (one [1%]), metastatic neoplasm (one [1%]), and sepsis (one [1%]). There were no treatment-related deaths. As of the data cutoff, 38 (46%) of the 82 patients in the safety population remained on treatment. Of the D842V population, 19 (34%) of 56 patients discontinued treatment. Most common reasons for treatment discontinuation included disease progression (four [7%]) and adverse events (12 [21%]), eight (14%) of which were considered to be related to avapritinib.

In the D842V population, confirmed overall responses per central radiology mRECIST 1.1 assessments were seen in 49 (88%; 95% CI 76–95) of the 56 patients (five [9%] patients had a complete response, 44 [79%] had a partial response, and seven [13%] had stable disease; table 3; figure 2; appendix p 20) treated at any dose level. Clinical benefit was seen in 55 (98%; 95% CI 90–100) patients. The 12-month duration of response was 70% (95% CI 54–87; figure 3A). Progression-free survival was 100% (95% CI 100–100) at 3 months, 94% (88–100) at 6 months, and 81% (69–93) at 12 months (figure 3B). As of the data cutoff, 37 (66%) of the 56 patients in the D842V population remained on treatment with a median follow-up of 15·9 months (IQR 9·2–24·9) for the overall survival analysis. Overall survival was estimated to be

	All doses (n=56)	300 mg (n=28)
Complete response	5 (9%)	1 (4%)
Partial response	44 (79%)	25 (89%)
Overall response (partial plus complete response)	49 (88%; 95% CI 76–95)	26 (93%; 95% CI 77–99)
Stable disease	7 (13%)	2 (7%)
Clinical benefit (complete response or partial response plus stable disease lasting at least 16 weeks)	55 (98%; 95% CI 90–100)	28 (100%; 95% CI 88–100)
Progressive disease	0	0

D842V=Asp842Val. mRECIST=Response Evaluation Criteria in Solid Tumors modified for patients with gastrointestinal stromal tumour. *Data cutoff on Nov 16, 2018.

Table 3: **Best confirmed response by central assessment per mRECIST (version 1.1) in patients with PDGFRA D842V-mutant gastrointestinal stromal tumour***

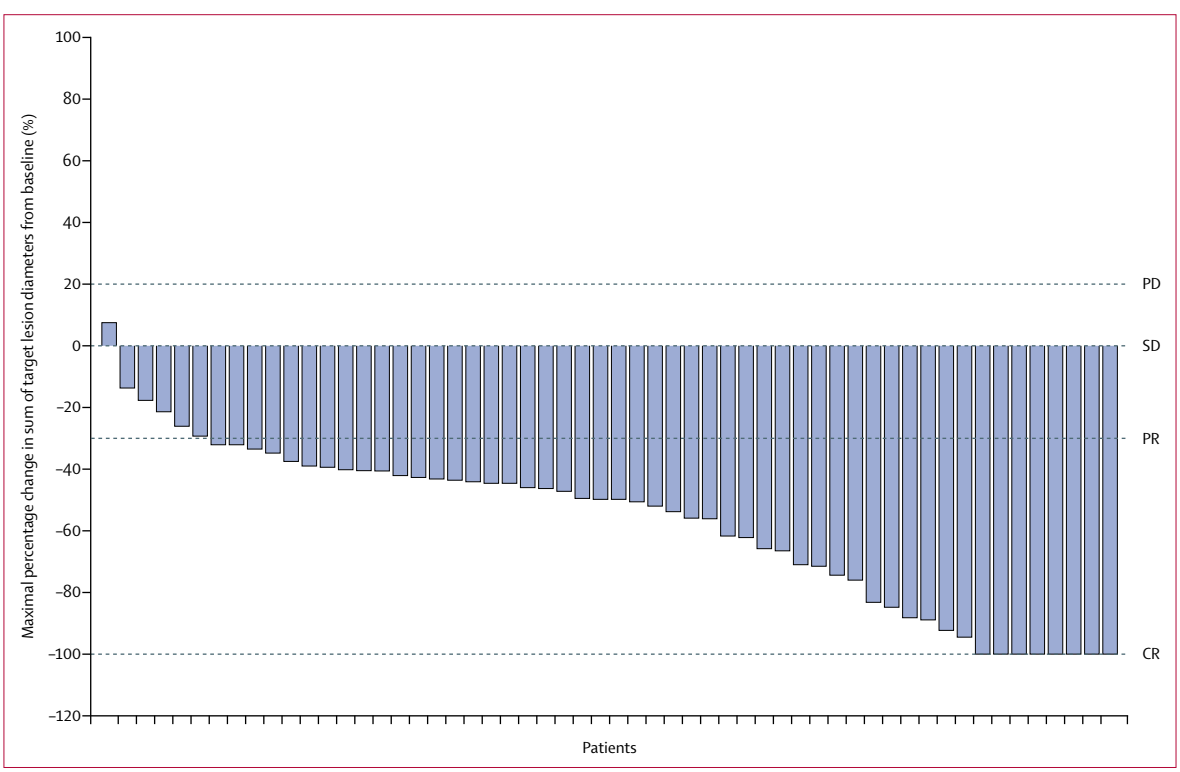

Figure 2: **Maximal percentage change in sum of target lesion diameters from baseline in patients with PDGFRA D842V-mutant gastrointestinal stromal tumours**

Horizontal dashed lines denoting complete response, partial response, stable disease, and progressive disease refer only to response in target lesions. CR=complete response. D842V=Asp842Val. PD=progressive disease. PR=partial response. SD=stable disease.

100% (95% CI 100–100) at 6 months, 91% (83–100) at 12 months, and 81% (67–94) at 24 months (figure 3C). 11 patients had progression events (ie, disease progression or death) and seven patients had died by 24 months. Data were not sufficiently mature as of the data cutoff to allow accurate estimation of median values for duration of response, progression-free survival, and overall survival. Among patients who received a 300 mg

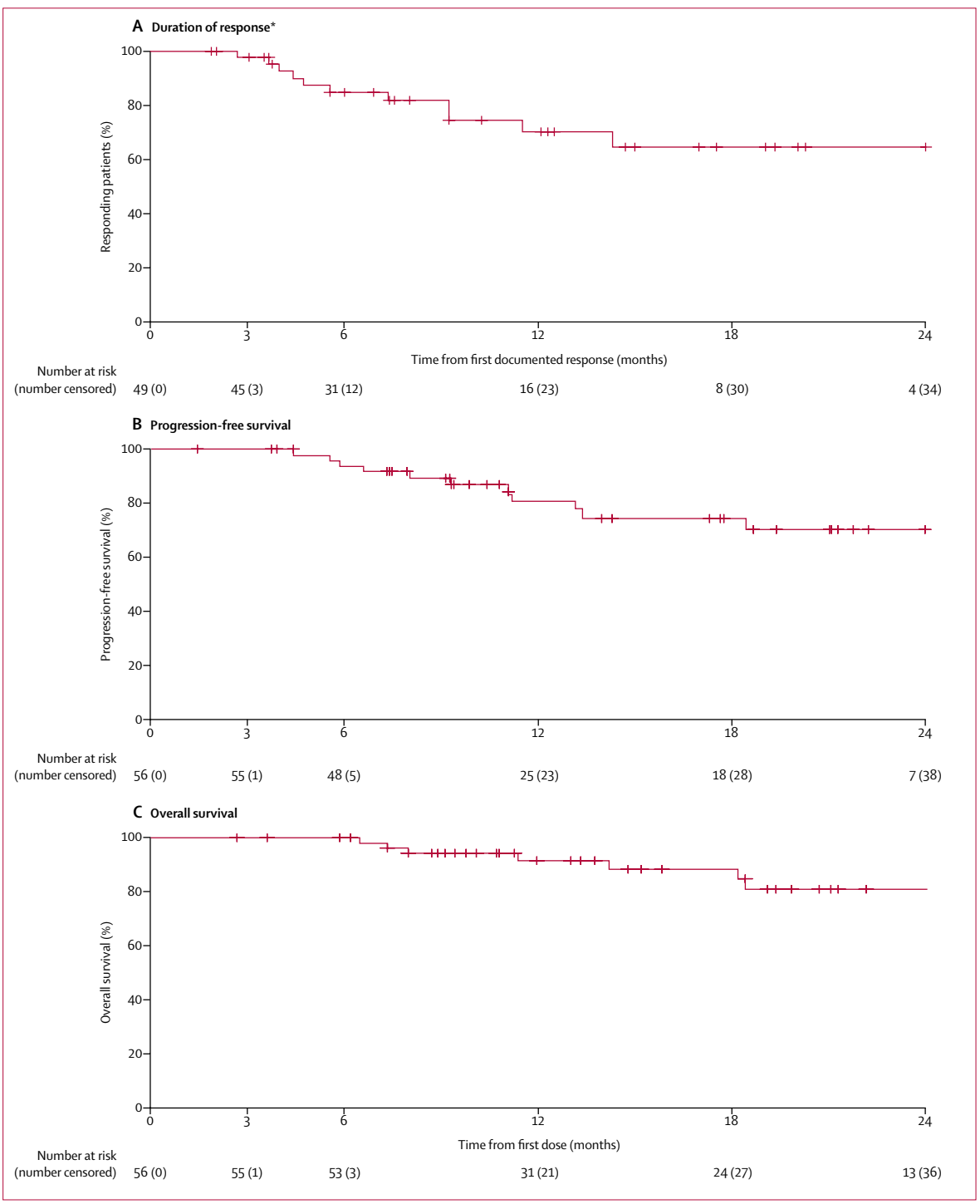

Figure 3: **Duration of response (A), progression-free survival (B), and overall survival (C) in patients with PDGFRA D842V-mutant gastrointestinal stromal tumours**

D842V=Asp842Val. *Evaluated only in patients with complete or partial response.

starting dose, 26 (overall response rate 93%; 95% CI 77–99) had an objective response (post-hoc analysis).

Discussion

Although imatinib revolutionised care for most patients with advanced gastrointestinal stromal tumours, patients with PDGFRA D842V-mutant gastrointestinal stromal tumours rarely respond to imatinib or other approved multikinase inhibitors.[4–7,15,16] Our study shows that avapritinib has clinical activity with durable responses and a manageable safety profile in patients with advanced *PDGFRA* D842V-driven gastrointestinal stromal tumours. These results suggest that PDGFRA D842V is a relevant target, and highlight that potent and selective inhibitors such as avapritinib can demonstrate clinical benefit in early clinical testing when administered to genomically defined patient populations.

Based on central radiology review, avapritinib induced tumour reductions in 55 of 56 patients with PDGFRA D842V-mutant gastrointestinal stromal tumours, with 88% achieving a partial or complete response. This finding is particularly encouraging given that 96% of patients in the D842V population had metastatic disease and 61% had target lesions of more than 5 cm. By contrast, previous experience with imatinib, sunitinib, and regorafenib (type 1 or 2 tyrosine kinase inhibitors) has demonstrated little response or disease stabilisation in D842V gastrointestinal stromal tumours.[4–9] Clinical activity in D842V gastrointestinal stromal tumours has also been reported with the investigational type 1 inhibitor crenolanib,[17] suggesting that a type 1 mechanism might be required for efficacy against *PDGFRA* D842V and other activation loop mutations. Supporting this notion, avapritinib has also been shown to have activity in advanced systemic mastocytosis, a mast cell neoplasm driven by the *KIT* D816V activation loop mutant, which is structurally homologous to the *PDGFRA* D842V mutant.[13,18]

Response to avapritinib in PDGFRA D842V-mutated gastrointestinal stromal tumours was durable, despite most patients having received previous kinase inhibitor therapy. The duration of response, progression-free survival, and overall survival observed in this study was longer than that observed previously with imatinib,[8,9] suggesting that avapritinib could potentially provide better clinical benefit in D842V-mutated gastrointestinal stromal tumours, although formal comparison in a randomised trial is needed to confirm this hypothesis. Before the use of imatinib to treat advanced gastrointestinal stromal tumours, prognosis was poor, with median overall survival expected to be 10–20 months. However, outcomes improved with the approval of imatinib, with response rates of 54% or higher, median progression-free survival of 20–24 months, and median overall survival of 50–55 months.[19–22]

Most treatment-related adverse events among the patients treated with avapritinib were grade 1 or 2 and were generally proportional to dose and exposure. Treatment-related adverse events infrequently led to treatment discontinuation and were generally manageable with standard supportive medical treatments and dose modifications. Overall, few patients discontinued treatment because of adverse events. Many of the events observed with avapritinib, including nausea, vomiting, anaemia, and oedema, are also reported with imatinib and other KIT and PDGFRA inhibitors.[14,23] By contrast, hypertension and hand-foot skin reactions—toxicities associated with multi-kinase inhibitors active against the vascular endothelial growth factor receptor[14,24]—were uncommon.

Cognitive effects with avapritinib were reported in approximately 40% of patients. Similar events have been reported with other kinase inhibitors that penetrate the CNS, such as lorlatinib[25] and larotrectinib.[26] Cognitive effects were typically grade 1 and were manageable, showing improvement or resolution with modifications including dose interruptions with or without dose reductions. The incidence and severity of cognitive effects were higher at 400 mg (used during dose escalation and early phases of expansion) than 300 mg, determining the latter to be used for the remainder of the study.

Rare intracranial bleeding events reported in two patients from the safety population occurred, but resolved or improved with treatment discontinuation. Whether KIT or PDGFRA inhibition accounts for the cognitive effects and intracranial bleeding remains to be established.[27,28]

There are several limitations in the data presented here. First, NAVIGATOR is an open-label, single-arm, phase 1 study. Besides a small sample size due to the rarity of D842V-mutant gastrointestinal stromal tumours, there was no control group to comprehensively characterise the safety features. Second, at the time of the analysis, the secondary endpoints of duration of response, progression-free survival, and overall survival were not sufficiently mature to further interpret the outcomes. Finally, because few patients had disease progression at the time of the data cutoff, PDGFRA D842V resistance mechanisms remain unknown.

A key strength of this trial was the use of a blinded, independent central radiology review for tumour measurements, thereby eliminating potential bias associated with investigator assessments. Another important aspect of the NAVIGATOR study design was inclusion of multiple preplanned molecularly defined patient groups, including patients with *PDGFRA* D842V mutations. Avapritinib has also demonstrated promising activity in patients with *PDGFRA* activation loop mutations besides D842V, as well as in patients with heavily pretreated KIT-mutant gastrointestinal stromal tumours.[29] Given the heterogeneous nature of gastrointestinal stromal tumours driven by different mutations, results from the preplanned molecularly defined groups will be analysed separately. The antitumour effect observed with avapritinib in this study is particularly important for

patients with D842V mutations, given the high unmet need for treatment options for these patients.

Gastrointestinal stromal tumours are a molecularly heterogeneous disease driven by various oncogenic primary and secondary *KIT* and *PDGFRA* mutations. Data from our study suggest that avapritinib is active and has a manageable safety profile in the subset of gastrointestinal stromal tumours harbouring the *PDGFRA* D842V mutation, a subset that has been refractory to all currently approved tyrosine kinase inhibitors.

Contributors

MCH, RLJ, MvM, PS, PAC, OM, FE, MT, EKE, TL, TZ, BBW, SB, and SG were involved in the study design. MCH, RLJ, MvM, PS, CS, Y-KK, PAC, OM, FE, WDT, PR, SPC, JT, MT, EKE, TL, TZ, MR, BBW, SB, and SG were involved in data collection and interpretation. MCH, MvM, MR, BBW, SB, and SG were involved in manuscript writing. MCH, RLJ, MvM, PS, CS, Y-KK, PAC, OM, FE, WDT, PR, SPC, JT, MT, EKE, TL, TZ, MR, BBW, SB, and SG were involved in manuscript revision. The authors vouch for the validity of the study results reported here and adherence to the protocol. All authors approved the final version and agreed with the decision to submit to publication.

Declaration of interests

MCH owns stock in MolecularMD; has received honoraria from Novartis; has served in advisory or consultancy roles for MolecularMD, Novartis, Blueprint Medicines, and Deciphera; has provided expert testimony for Novartis; has a patent Activating Mutations of *PDGFRA*; and his institution receives royalties for a patent Treatment of Gastrointestinal Stromal Tumors licensed by Novartis. RLJ has served in advisory or consultancy roles for Blueprint Medicines, Athenex, Lilly, Immune Design, Merck Serono, Adaptimmune, Daiichi Sankyo, Helsinn, Eisai, TRACON Pharmaceuticals, Deciphera, PharmaMar, Clinigen Group, Epizyme, and UpToDate; and has received institutional research funding from Merck Sharp & Dohme. MvM reports a leadership position with the US National Comprehensive Cancer Network (chair of the Soft Tissue Sarcoma panel); has served in advisory or consultancy roles for Blueprint Medicines, Deciphera, Arog, and Exelexis; and has received research funding from Blueprint Medicines, Deciphera, Arog, and Novartis. PS has served in an advisory or consultancy role for Exelixis (honoraria provided to PS) as well as Plexxikon, Eisai, Loxo Oncology, Lilly, Blueprint Medicines, Ellipses Pharma, Deciphera, Merck, SERVIER, Genmab, Adaptimmune, Intellisphere, and Transgene (honoraria provided to institution); and received institutional research funding from Blueprint Medicines, Boehringer Ingelheim, CoBioRes NV, Eisai, Lilly, Excelixis, G1 Therapeutics, Novartis, PharmaMar, and Plexxikon. CS has received honoraria from Bayer; served in advisory or consultancy roles for Deciphera and Blueprint Medicines; received research funding from Deciphera, Bayer, and Pfizer; and received travel and accommodation funding from Novartis, Lilly, PharmaMar, Pfizer, and Bayer. Y-KK has served in advisory or consultancy roles for Lilly/ImClone, Taiho Pharmaceutical, Roche/Genentech, Merck Serono, Dae Hwa Pharmaceutical, Bristol-Myers Squibb, Astellas Pharma, and LSK BioPharma; and received research funding from LSK BioPharma and Dae Hwa Pharmaceutical. 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FE has served in advisory or consultancy roles for Merck Serono, Roche, Eisai, and Ipsen; and received travel and accommodation funding from Pfizer. WDT has served in leadership roles at and owns stock in Certis Oncology Solutions and Atropos; served in advisory or consultancy roles for EMD Serono, Janssen, Lilly, Daiichi Sankyo, Novartis, Eisai, Immune Design, Blueprint Medicines, Loxo Oncology, Agios, GlaxoSmithKline, and Nanocell Therapy; received research funding from Novartis, Lilly, Plexxikon, Daiichi Sankyo, TRACON Pharma, Blueprint Medicines, Immune Design, BioAtla, and Deciphera; and reports a patent and royalty for companion diagnostics for CDK4 inhibitors (14/854,329). PR has received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Lilly, and Pfizer; served in advisory or consultancy roles for Novartis, Blueprint Medicines, Bristol-Myers Squibb, Pierre Fabre, Merck Sharp & Dohme, and Amgen; served on speakers' bureaus for Pfizer, Novartis, and Lilly; received research funding from Novartis, Roche, and Bristol-Myers Squibb; and received travel and accommodation funding from Orphan Europe and Pierre Fabre. 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SG owns stock in Abbott Laboratories and Allergan; has served in advisory or consultancy roles for Blueprint Medicines, Deciphera, Bayer, Eli Lilly, Exelixis, Daiichi Sankyo, UpToDate, Research to Practice, and MORE Health; has received institutional research funding from Pfizer, Novartis, Bayer, ARIAD, Blueprint Medicines, and Deciphera; receives royalties from UpToDate; has provided expert testimony for Bayer; and also reports a relationship with Research to Practice.

Data sharing

The anonymised derived data from this study that underlie the results reported in this Article will be made available, beginning 12 months and ending 5 years after this Article's 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.

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For **GPP3** see http://www.ismpp.org/gpp3

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