An Open-label, Randomized, Phase 3 Study of Avapritinib vs Regorafenib in Patients With Locally Advanced Metastatic or Unresectable Gastrointestinal Stromal Tumor (GIST)

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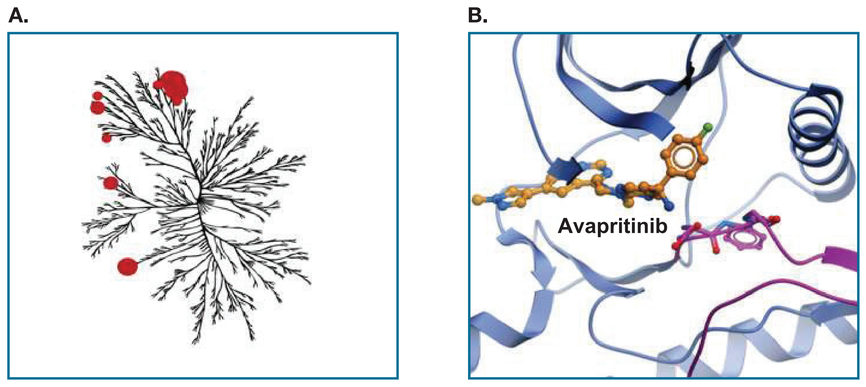
INTRODUCTION

- Oncogenic activating mutations in either KIT or platelet-derived growth factor receptor alpha (PDGFRA) mutant proteins drive greater than 85% of gastrointestinal stromal tumors (GIST)[1,2]
  - Approximately 80% of GIST harbor mutations in KIT.[1] In 5% to 6% of newly diagnosed GIST patients, an activation loop mutation in PDGFRA at amino acid 842 occurs as the primary mutation[1,2]
- The PDGFRA D842V mutation shifts the kinase into the active conformation, rendering it insensitive to all approved agents because they can bind only to the inactive conformation of the kinase[3–5]
  - With no effective treatments available, the prognosis for patients with metastatic PDGFRA D842V GIST is poor. Published data have shown a 0% response rate and median progression-free survival (PFS) of 3 to 5 months with available agents in patients with metastatic PDGFRA D842V GIST. Overall survival in these patients is approximately 15 months[4,6]
- Of the treatment options approved for imatinib-resistant GIST, each offers minimal sustained disease control, with overall median PFS of 5 to 6 months and objective response rates (ORR) of 5% to 7%[7–10]
  - Currently, no therapies are approved and available for relapsed GIST after failure of imatinib, sunitinib, and regorafenib
- Avapritinib (BLU-285) is a potent and selective inhibitor of activated KIT and PDGFRA mutant kinases that is uniquely designed to bind and inhibit the active conformation of KIT and PDGFRA mutants, including those that confer resistance to approved tyrosine kinase inhibitors (TKIs;[11] **Figure 1**)

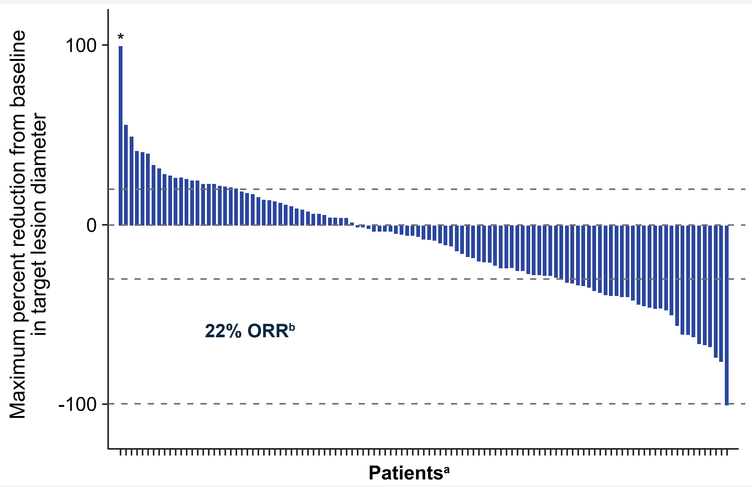
Figure 1. Avapritinib is a potent and highly selective kinase inhibitor (A) that binds to the active conformation of KIT and PDGFRA (B).



KIT, V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PDGFRA, platelet-derived growth factor receptor alpha. Binding data for compounds screened at 3 mM against 392 kinases are depicted as red circles on the kinome tree. Circle sizes represent binding potency. Reproduced with permission of Cell Signaling Technology (www.cellsignal.com). The foregoing website is maintained by Cell Signaling Technology, Inc., and Blueprint Medicines is not responsible for its content.

- In the ongoing first-in-human, phase 1 NAVIGATOR study (ClinicalTrials.gov Identifier: NCT02508532), avapritinib showed substantial clinical activity in patients with both KIT- and PDGFRA-mutant GIST that was resistant to all available therapies.[12] As of the data cutoff date of November 16, 2018:
  - Avapritinib was well tolerated, with a recommended phase 2 dose of 300 mg once daily (QD) and a maximum tolerated dose of 400 mg QD
  - When used in heavily pretreated patients (fourth line or greater [4L+]), avapritinib demonstrated radiographic responses in KIT-mutant GIST with an ORR of 22% (**Figure 2**)[13]
  - Avapritinib had strong clinical activity in PDGFRA D842–mutant GIST (median number [range] of prior kinase inhibitors: 1 [0–5]) with an ORR of 86% (**Figure 3**)[13]

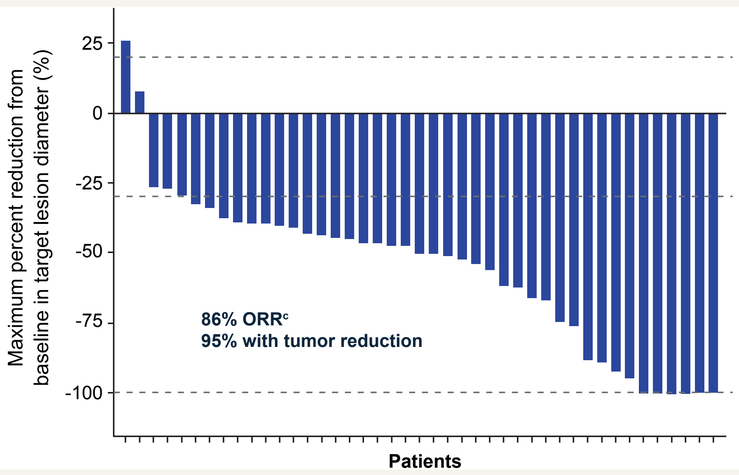
Figure 2. Antitumor activity (central radiology review): 4L+ avapritinib 300/400 mg QD starting dose.



Best Response,[c] n	4L+ n = 111
CR	1
PR	23 (1 pending)
SD	52
PD	35
ORR (CR+PR), % (95% CI)	22 (14.4–30.4)
CBR, % (95% CI)	41 (32.2–51.2)
DOR, months (95% CI)	10.2 (7.2–NE)
PFS, months (95% CI)	3.7 (3.4–5.6)

*One patient had an outlier value for percent change from baseline of >200% increase in target lesion diameter.
[a]Two patients who had best response assessment are not included in the waterfall plot because they did not have measurable target lesions at baseline and thus, no percent change could be calculated. [b]There were 8 patients with PDGFRA D842V mutations and when these patients were removed from analysis, the ORR is 17% and DOR remains unchanged. [c]Assessed by mRECIST 1.1. Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable at 300/400 mg QD. Data previously presented at the 2019 American Society of Clinical Oncology Annual Meeting, May 31–June 4, 2019, Chicago, IL. Data cutoff: November 16, 2018. CBR, clinical benefit rate; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; QD, once daily; SD, stable disease.

Figure 3. Antitumor activity (central radiology review): PDGFRA Exon 18 avapritinib 300/400 mg QD starting dose.



Best Response,[a] n	Exon 18 n = 43
CR	3
PR[b]	34 (1 pending)
SD	5
PD	1
ORR (CR+PR),[c] % (95% CI)	86.0 (72.1–94.7)
CBR,[d] % (95% CI)	95.3 (84.2–99.4)
DOR,[e] months (95% CI)	NE (11.5–NE)
PFS, months (95% CI)	NE (13.4–NE)

[a]Assessed by mRECIST 1.1. Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable at 300/400 mg QD. [b]1 response pending confirmation. [c]ORR defined as the proportion of patients with a confirmed best response of CR or PR. [d]CBR defined as CR/PR+SD lasting ≥16 weeks from first dose. [e]DOR defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever came first. Data previously presented at the 2019 American Society of Clinical Oncology Annual Meeting, May 31–June 4, 2019, Chicago, IL. Data cutoff: November 16, 2018. CBR, clinical benefit rate; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; QD, once daily; SD, stable disease.

- 68 (33%) patients had grade ≥3 treatment-related adverse events: anemia (33%), fatigue (13%), cognitive effects (8%), blood bilirubin increased (8%), and diarrhea (6%); no treatment-related grade 5 adverse events were reported[13]
- Based on these encouraging data, the phase 3 VOYAGER study was initiated to compare avapritinib and regorafenib in patients with locally advanced metastatic or unresectable GIST

Objective

- To evaluate the efficacy and safety of avapritinib versus regorafenib in patients with metastatic or locally advanced unresectable GIST previously treated with imatinib and 1 or 2 other TKIs

METHODS

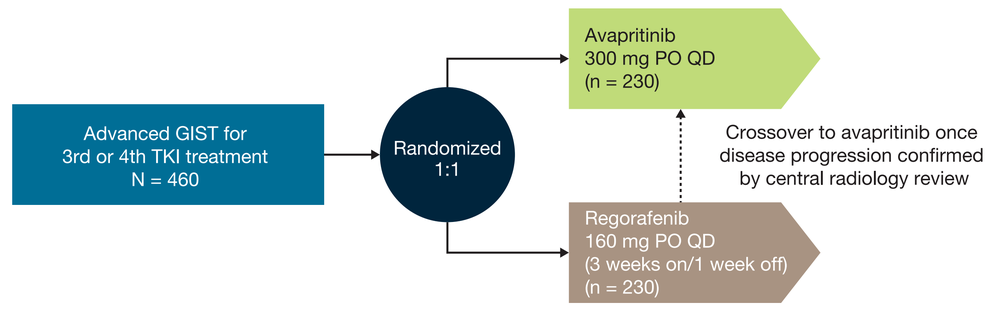
Key Eligibility Criteria

- ≥18 years of age
- Eastern Cooperative Oncology Group performance status of 0–1
- Histologically confirmed metastatic or unresectable GIST
- Prior treatment with imatinib and 1 or 2 other TKIs for the treatment of GIST (including TKIs used for adjuvant therapy) and disease progression prior to enrollment
- No prior treatment with avapritinib or regorafenib
- No patients known to be both KIT and PDGFRA wild type
- No systemic anticancer therapy, radiotherapy to major organs, or neutrophil growth factor support within 2 weeks before randomization or focal radiotherapy to areas not involving major organs within 3 days of randomization
- No arterial thrombotic or embolic events within 6 months before randomization, or venous thrombotic events within 14 days before randomization. Patients with venous thrombotic events ≥14 days before randomization were eligible if stable on, or have completed, an anticoagulation regimen
- No grade ≥3 hemorrhage or bleeding event within 4 weeks of randomization
- Pretreatment clinical laboratory values meeting the following criteria:
  - No persistent grade ≥3 proteinuria
  - Alanine aminotransferase and aspartate aminotransferase ≤3 × upper limit of normal (ULN) if no hepatic metastases (≤5 × ULN if hepatic metastases present)
  - Total bilirubin ≤1.5 × ULN except for subjects with Gilbert syndrome, in which case total bilirubin ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN
  - Estimated or measured creatinine clearance ≥40 mL/min
  - Platelet count ≥90 × 10^9/L and absolute neutrophil count ≥1.0 × 10^9/L
  - Hemoglobin ≥9 g/dL
- No concomitant medication that is a strong inhibitor or strong or moderate inducer of CYP3A4

Study Design

- VOYAGER is a phase 3, international, randomized, open-label, multicenter study comparing avapritinib with regorafenib in patients with locally advanced metastatic or unresectable GIST previously treated with imatinib and 1 or 2 other TKIs (**Figure 4**)

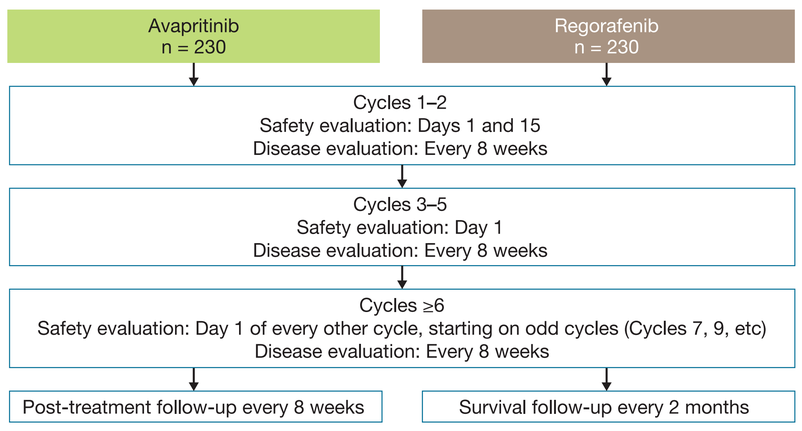
Figure 4. VOYAGER study design.



GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor; PO, orally; QD, once daily.

- Approximately 460 patients will be randomized 1:1 to receive the following:
  - Avapritinib 300 mg orally (PO) QD in continuous 28-day cycles
  - Regorafenib 160 mg PO QD (3 weeks on/1 week off)
- Patients who experience disease progression on regorafenib, as confirmed by central radiology review, will be allowed to cross over to avapritinib
- Safety evaluations will occur on Days 1 and 15 during Cycles 1 and 2, Day 1 during Cycles 3 to 5, and then Day 1 during every other cycle, starting on odd cycles (Cycle 7, Cycle 9, etc; **Figure 5**)
- Disease evaluations will occur every 8 weeks (**Figure 5**)

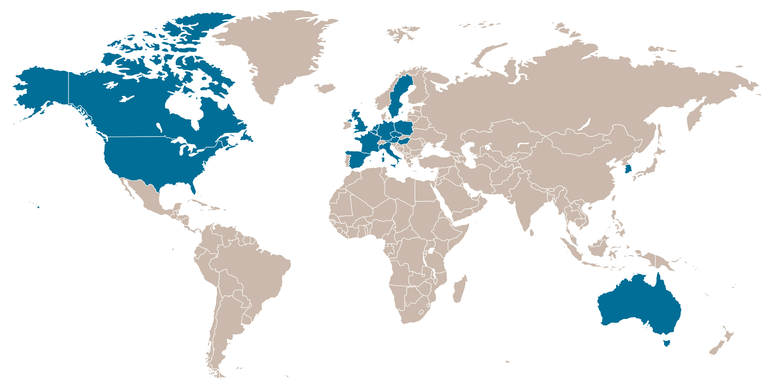
Figure 5. VOYAGER assessment schedule.



Crossover to avapritinib once disease progression confirmed by central radiology review.

- The study will include approximately 90 sites that span 17 countries (**Figure 6**)

Figure 6. VOYAGER clinical sites.



Study sites are in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, The Netherlands, Poland, Singapore, South Korea, Spain, Sweden, United Kingdom, and United States (shaded in blue).

Study Endpoints and Evaluations

- Primary
  - PFS, based on central radiological assessment by modified Response Evaluation Criteria in Solid Tumors (mRECIST, v1.1)
- Secondary
  - Response rate
  - Overall survival
  - EORTC Quality of Life Questionnaire (QLQ) Core 30 physical functioning, pain, role functioning, and appetite loss scores
  - Safety
- Exploratory
  - Correlation of baseline KIT, PDGFRA, and other cancer-relevant mutation status with antitumor activity
  - Functional Assessment of Cancer Therapy–Cognitive Function scores
  - Patients' Global Impression of Severity and Patients' Global Impression of Change questionnaire scores
  - European Quality of Life 5 Dimensions Questionnaire health utility values

Conclusions

- Data from the ongoing NAVIGATOR study will support avapritinib New Drug Application submission for 4th line GIST and PDGFRA-mutant GIST, and led to the evaluation of avapritinib in 3rd line GIST in the VOYAGER study
- VOYAGER is a phase 3, open-label, parallel-group, multicenter trial evaluating the efficacy and safety of avapritinib versus regorafenib in patients with locally advanced metastatic or unresectable GIST previously treated with imatinib and 1 or 2 other TKIs
- This study is currently enrolling patients

References

1. Heinrich MC, et al. *Science*. 2003;299(5607):708–710.
2. Hirota S, et al. *Gastroenterology*. 2003;125(3):660–667.
3. Liang L, et al. *Biochem Biophys Res Comm*. 2016;477(4):667–672.
4. Cassier PA, et al. *Clin Cancer Res*. 2012;18(16):4458–4464.
5. Heinrich MC, et al. *J Clin Oncol*. 2003;21(23):4342–4349.
6. Yoo C, et al. *Cancer Res Treat*. 2016;48(2):546–552.
7. Sutent® (sunitinib malate) capsules, for oral use [package insert]. New York, NY: Pfizer Laboratories; 2017.
8. Stivarga® (regorafenib) tablets [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2018.
9. Demetri GD, et al. *Lancet*. 2006;368(9544):1329–1338.
10. Demetri GD, et al. *Lancet*. 2013;381(9863):295–302.
11. Evans EK, et al. *Sci Transl Med*. 2017;9(414).
12. Heinrich M, et al. Presented at: 2017 American Society of Clinical Oncology Annual Meeting; June 2–6, 2017; Chicago, IL, USA.
13. Heinrich M, et al. Presented at: 2019 American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2019; Chicago, IL, USA

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