Avapritinib vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST): Efficacy and Safety Data From Phase 3 VOYAGER Study

Abstract 3461883

Yoon-Koo Kang[1], Suzanne George[2], Robin L. Jones[3], Piotr Rutkowski[4], Lin Shen[5], Olivier Mir[6], Shreyaskumar Patel[7], Yongjian Zhou[8], Margaret von Mehren[9], Peter Hohenberger[10], Victor Villalobos[11], Mehdi Brahmi[12], William D. Tap[13], Jonathan Trent[14], Maria A. Pantaleo[15], Patrick Schöffski[16], Kevin He[17], Paggy Hew[17], Kate Newberry[17], Maria Roche[17], Michael Heinrich[18], Sebastian Bauer[19]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Sarcoma Center, Dana Farber Cancer Institute, Boston, MA, USA; [3]Royal Marsden Hospital and Institute of Cancer Research, London, UK; [4]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [5]Peking University Cancer Hospital and Institute, Beijing, China; [6]Institut Gustave Roussy, Villejuif, France; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Fujian Medical University Union Hospital, Fuzhou, China; [9]Fox Chase Cancer Center, Philadelphia, PA, USA; [10]Medical Faculty Mannheim (UMM), University of Heidelberg, Mannheim, Germany; [11]University of Colorado Denver – Anschutz Medical Campus, Aurora, CO, USA; [12]Centre Léon Bérard, Lyon, France; [13]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [14]University of Miami-Sylvester Comprehensive Cancer Center, Miami, FL, USA; [15]University of Bologna, Bologna, Italy; [16]University Hospitals Leuven, Leuven, Belgium; [17]Blueprint Medicines Corporation, Cambridge, MA, USA; [18]Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR, USA; [19]Sarcoma Center, West German Cancer Center, DKTK-Partner-Site, University of Duisburg, Essen, Germany

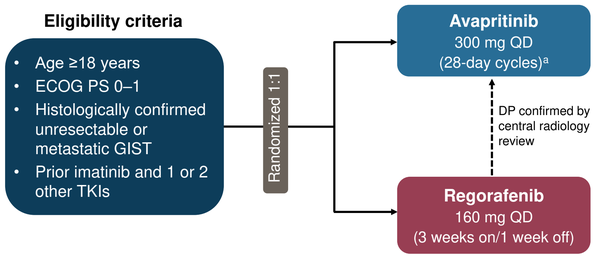
Background

- Over 85% of patients with gastrointestinal stromal tumors (GIST) have tumors which harbor activating mutations in the *KIT* receptor or platelet-derived growth factor receptor A (*PDGFRA*) tyrosine kinase proto-oncogenes[1,2]
- Despite FDA approved second-, third- and fourth-line tyrosine kinase inhibitors (TKIs), prognosis is poor for patients who tumors progress following first-line imatinib or who are resistant to TKIs[3–6]
- Avapritinib demonstrated clinical activity in patients whose tumors harbor active *KIT* and *PDGFRA* mutations in a Phase 1 study (NAVIGATOR)[7] and is currently approved in the United States for the treatment of adults with unresectable or metastatic GIST harboring a *PDGFRA* exon 18 mutation, including D842V[8,9] and in the European Union to treat adults with unresectable or metastatic GIST harboring the D842V mutation[10]
- The objective of the open-label, randomized Phase 3 VOYAGER study (NCT03465722) was to assess avapritinib versus regorafenib in patients with heavily pretreated locally advanced unresectable or metastatic GIST

Study design and methods

- VOYAGER study design is shown in **Figure 1**
- Crossover from regorafenib to avapritinib was allowed for patients who experienced centrally confirmed disease progression (**Figure 1**)

Figure 1: VOYAGER Study Design (NCT03465722)



Primary endpoint: PFS (modified RECIST v1.1)
Secondary endpoints: ORR (modified RECIST v1.1), OS, DOR, safety

- **Data cut-off date for these analyses was March 9, 2020**

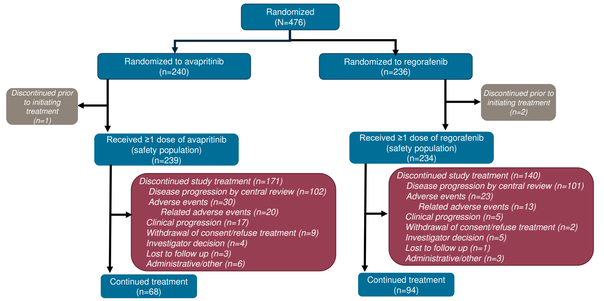
DOR, duration of response; DP, disease progression; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumors; ORR, overall response rate; OS, overall survival; PFS, progression-free survival, RECIST v1.1, response evaluation criteria in solid tumors v1.1; TKI, tyrosine kinase inhibitor. [a]Continuous 28-day cycles.

Statistical analysis

- Kaplan–Meier (KM) estimates were used to assess PFS and OS. Cox regression model was used to assess hazard ratio (HR) and 95% confidence interval (CI)
- ORR was estimated with a stratified Cochran-Mantel-Haenszel test, and 95% CI was estimated with the Clopper-Pearson method. KM estimates were used to descriptively summarize DOR. DCR was estimated for the intent-to-treat (ITT) population using the Clopper-Pearson method

Results

Figure 2: CONSORT diagram



- A total of 476 patients were enrolled in the study between March 26, 2018 and November 15, 2019, of whom 240 patients received avapritinib and 236 patients received regorafenib (**Figure 2**)
- The majority had KIT mutations based on local testing, and 3% had PDGFRA D842V mutations (**Table 1**)

Table 1: Demographics and baseline characteristics

	Patients, n (%)		
	Avapritinib (n=240)	Regorafenib (n=236)	Total (n=476)
Sex			
Male	162 (68)	156 (66)	318 (67)
Female	78 (33)	80 (34)	158 (33)
Age			
<65 years	143 (60)	144 (61)	287 (60)
≥65 years	97 (40)	92 (39)	189 (40)
Race[a]			
White	139 (58)	143 (61)	282 (59)
Non-white	85 (35)	81 (34)	166 (35)
ECOG PS			
0	125 (52)	103 (44)	228 (48)
1	108 (45)	131 (56)	239 (50)
2	7 (3)	2 (1)	9 (2)
Metastatic disease	238 (99)	231 (98)	469 (99)
Prior treatment			
Imatinib	240 (100)	236 (100)	476 (100)
Sunitinib	227 (95)	225 (95)	452 (95)
Mutation status			
KIT V654A or T760I	33 (14)	34 (14)	67 (14)
KIT exon 17 not V654A or T760I	49 (20)	60 (25)	109 (23)
PDGFRA exon 18	11 (5)	7 (3)	18 (4)
PDGFRA D842V	7 (3)	6 (3)	13 (3)
PDGFRA exon 18 not D842V	4 (2)	1 (<1)	5 (1)
Other[b]	147 (61)	135 (57)	282 (59)

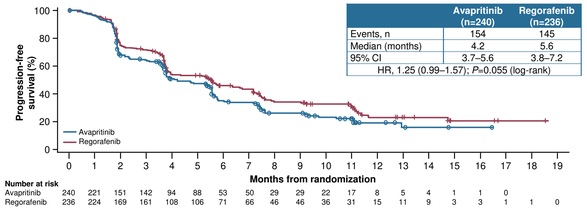
ECOG PS, Eastern Cooperative Oncology Group performance status; KIT, KIT proto-oncogene receptor tyrosine kinase; PDGFRA, platelet-derived growth factor receptor alpha. [a]Data was missing for 16 and 12 patients in the avapritinib and regorafenib groups, respectively; [b]Other includes any mutations other than *KIT* Exon 17 or *PDGFRA* Exon 18.

Efficacy

Progression-free survival

- The primary endpoint for this study was not met, as there was no significant difference in median PFS between avapritinib and regorafenib (HR 1.25 [95% CI 0.99–1.57]; median PFS 4.2 versus 5.6 months; *P*=0.055 (**Figure 3**)

Figure 3: Progression-free survival



	Avapritinib (n=240)	Regorafenib (n=236)
Events, n	154	145
Median (months)	4.2	5.6
95% CI	3.7–5.6	3.8–7.2
HR, 1.25 (0.99–1.57); *P*=0.055 (log-rank)		

Overall survival

- At the cut-off date, OS data were immature with a median follow-up of 8.5 months for avapritinib and 9.6 months for regorafenib. At 12 months, KM OS estimates were similar for avapritinib (68%) and regorafenib (67%)

Response rates

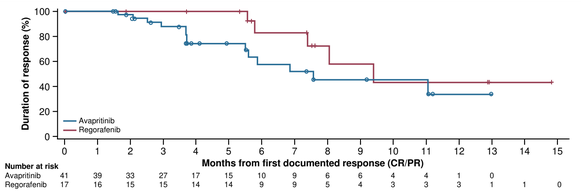
- In the ITT population, ORR was higher for avapritinib (17%; 95% CI 13–23; all partial response [PR]) compared with regorafenib (7%; 95% CI 4–11; all PR; *P*<0.001; **Table 2**)
- In patients without D842V mutations (n=230 vs n=233), ORR was higher for avapritinib (16%; 95% CI 12–22; all PR) compared with regorafenib (7%; 95% CI 4–12; all PR; *P*=0.003)

Table 2: ORR in the ITT population

Best response	Avapritinib (n=240)	Regorafenib (n=236)
ORR, % (95% CI)	17 (13–23)	7 (4–11)
CR, n (%)	0	0
PR, n (%)	41 (17)	17 (7)
SD, n (%)	113 (47)	159 (67)
PD, n (%)	67 (28)	49 (21)
NE, n (%)	1 (<1)	0
Unknown, n (%)	18 (8)	11 (5)
DCR[a], % (95% CI)	42 (35–48)	46 (40–53)

CR, complete response; NE, non-evaluable.

Figure 4: Duration of response



Duration of response

- The median DOR was 7.6 months (95% CI 5.6–not reached [NR]) for avapritinib and 9.4 months (95% CI 7.4–NR) for regorafenib (**Figure 4**)

Safety

- In the safety population, incidence of any-grade treatment-related adverse events (TRAEs) was similar between patients receiving avapritinib (92%) and patients receiving regorafenib (96%), with 55% and 58% reporting Grade ≥3 TRAES, respectively (**Table 3**)
- Serious adverse events (SAEs; requiring hospitalization) occurred in 41% and 36% of patients treated with avapritinib or regorafenib, respectively. Treatment-related SAEs occurred in 20% of patients treated with avapritinib and 15% of patients treated with regorafenib

Table 3: TRAEs occurring in ≥15% of patients in either treatment group

	Avapritinib (n=239)		Regorafenib (n=234)	
Adverse event	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
TRAEs occurring in ≥15% of patients in either arm				
Any TRAE, n (%)	221 (92)	132 (55)	225 (96)	135 (58)
Anemia	96 (40)	50 (21)	28 (12)	6 (3)
Nausea	94 (39)	2 (1)	34 (15)	1 (<1)
Fatigue	84 (35)	9 (4)	80 (34)	12 (5)
Increased blood bilirubin	66 (28)	12 (5)	40 (17)	7 (3)
Periorbital edema	66 (28)	3 (1)	0	0
Face edema	65 (27)	6 (3)	1 (<1)	0
Cognitive effects[a]	62 (26)	3 (1)	9 (4)	4 (2)
Diarrhea	50 (21)	4 (2)	81 (35)	16 (7)
Peripheral edema	45 (19)	1 (<1)	5 (2)	0
Vomiting	44 (18)	0	24 (10)	3 (1)
Decreased appetite	42 (18)	2 (1)	58 (25)	5 (2)
Increased lacrimation	42 (18)	0	0	0
Decreased white blood cell count	38 (16)	10 (4)	6 (3)	2 (1)
Decreased weight	13 (5)	0	37 (16)	0
Hypertension	12 (5)	4 (2)	54 (23)	28 (12)
Dysphonia	7 (3)	0	65 (28)	2 (1)
Stomatitis	6 (3)	0	37 (16)	2 (1)
Palmar-plantar erythrodysesthesia syndrome	2 (1)	0	138 (59)	38 (16)
Intracranial bleeding[b]	3 (1)	2 (1)	0	0

[a]Cognitive effects comprised pooled terms of cognitive disorder, memory impairment, confusional state, and encephalopathy. [b]Included as adverse event of special interest, intracranial bleeding comprised pooled terms of intracranial hemorrhage, subdural hematoma, and cerebral hemorrhage.

Conclusions

- The primary endpoint for this study was not met, as there was no significant difference in median PFS between avapritinib and regorafenib (HR 1.25; *P*=0.055)
- ORR was higher with avapritinib versus regorafenib both in the overall population (17% versus 7%; *P*<0.001) and in patients without D842V mutations (16% versus 7%; *P*=0.003)
- Overall, the frequency of AEs with avapritinib and regorafenib were similar, but differed in their specific safety profiles
  - Cognitive effects were reported in 26% (Grade ≥3, 1%) of patients with avapritinib and 4% (Grade ≥3, 2%) of patients with regorafenib; incidence with avapritinib was lower than in the NAVIGATOR trial (41%)[7]
  - Avapritinib's AE profile lacked some typical AEs associated with regorafenib, including stomatitis, hypertension, and palmar-plantar erythrodysesthesia, while the rate of some AEs including anemia, nausea, and edema were higher with avapritinib
- The well-known heterogeneity of TKI resistance mutations observed in late-line GIST[11] may have contributed to the outcome of this study; circulating tumor DNA collected throughout this study will be analyzed to evaluate this further

References

1. Hirota S *et al. Gastroenterology.* 2003;125:660–667; 2. Schaefer IM *et al. Adv Anat Pathol.* 2017;24:259–267; 3. Demetri GD *et al. N Engl J Med.* 2002;347:472–480; 4. Demetri GD *et al. Lancet Oncol.* 2006;368:1329–1338; 5. Demetri GD *et al. Lancet.* 2013;381:295–302; 6. Blay JY *et al. Lancet Oncol.* 2020;21:923–934; 7. Heinrich MC *et al. Poster B26.* Presented at ASCO Gastrointestinal Cancers Symposium, Jan 23–25 2020, San Francisco CA; 8. Blueprint Medicines Corporation. AYVAKIT™ (avapritinib). Prescribing information. 2020. Available from: https://www.blueprintmedicines.com/uspi/AYVAKIT.pdf. Accessed September 10, 2020; 9. Heinrich MC *et al. Lancet Oncol.* 2020;21:935–946; 10. Blueprint Medicines Corporation. AYVAKIT® (avapritinib) Summary of Product Characteristics. 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf. Accessed October 2, 2020; 11. Liegl B *et al. J Pathol.* 2008;216:64–74

Acknowledgements

The authors would like to thank the patients, their families, and all investigators involved in this study. Medical writing support was provided by Jennifer Brewins, PhD, and editorial support was provided by Sinead Stewart, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA according to Good Publication Practice guidelines.

Disclosures

Study sponsored by Blueprint Medicines Corporation. YKK reports receiving personal fees from ALX Oncology, Zymeworks, Amgen, Novartis, Macrogenics, Daehwa, Surface Oncology, BMS. Full disclosures for all other authors available on request by email to corresponding author (see below).

Corresponding author: ykkang@amc.seoul.kr