# Clinical efficacy of avapritinib in gastrointestinal stromal tumors (GISTs) with different *KIT* genotypes: post hoc analysis of the phase 1 NAVIGATOR and phase 1/2 CS3007-101 trials

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Abstract #11523

## BACKGROUND

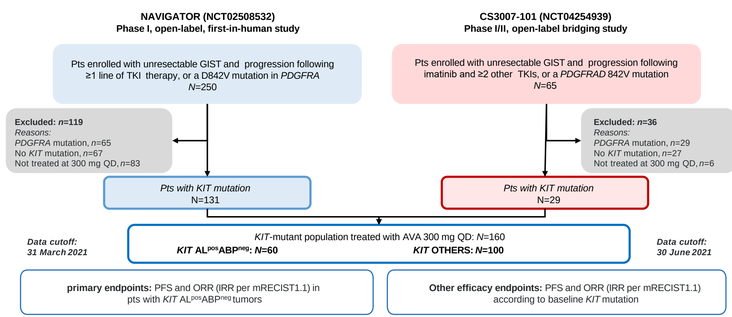
- Tyrosine kinase inhibitors targeting KIT/PDGFRA are the standard of care for patients with unresectable/metastatic GISTs. However, the efficacy of approved tyrosine kinase inhibitors (TKIs) for GISTs is modest and varies according to genotypes in the second- and later-line settings.[1,2] A tumor-genotype-based treatment paradigm is needed.
- Avapritinib (AVA) is a highly selective KIT/PDGFRA inhibitor approved to treat patients (pts) with *PDGFRA18*-mutant GISTs that has also demonstrated preclinical activity against *KIT* activation loop (AL) and *KIT exon 9* (*KIT* 9) mutations.[1,3]
- A post hoc efficacy analysis of AVA in pts with non-*PDGFRA*-mutant GISTs enrolled in the phase 1 NAVIGATOR (NCT02508532) and phase 1/2 China bridging (NCT04254939; CS3007-101) trials[4,5] was conducted.

## METHODS

### Study design and patients

- Pts with *KIT* mutations treated with 300 mg QD AVA from either trial were included in the analysis. Tumor tissue and/or plasma (circulating tumor DNA) were analyzed at baseline to identify tumor *KIT* mutations.
- Pts were divided into two groups: those with *KIT* AL (exon 17 or 18) mutations without *KIT* ATP binding pocket (ABP; exon 13 or 14) mutations (*KIT* AL$^{pos}$ABP$^{neg}$) versus all other *KIT* mutations (*KIT* OTHERS) (**Figure 1**).
- Progression-free survival (PFS) and objective response rate (ORR) were compared using Cox and logistic regression, respectively; adjustment by inverse probability weighting of baseline characteristics (IPW$_{BL}$) was conducted.

**Figure 1. Pt population for the post-hoc analysis of AVA in *KIT*-mutant GIST**




GIST, gastrointestinal stromal tumor; IRR, independent radiology review; *KIT* AL$^{pos}$ABP$^{neg}$, activation-loop positive, ATP binding pocket negative; mRECIST1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; PFS, progression-free survival; pts, patients; QD, once daily.

## RESULTS

### Patient population

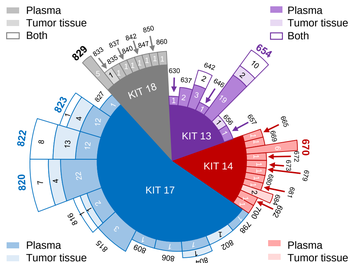
- The pts were predominantly male (63.8%) and White (56.9%) with heavily treated (61.3% with ≥3 prior TKIs) metastatic disease (96.9%) (**Table 1**).
- *KIT*-AL mutations occurred more frequently than *KIT*-ABP mutations (**Table 1**, **Figure 2**).
- Median follow-up duration was 22.0 months (range, 0.5–39.0 months).

**Table 1. Pt demographic and baseline characteristics**

| n (%) unless stated otherwise | All patients (*N*=160) |
|---|---|
| Age (years), median (range) | 58 (33–80) |
| Sex, male | 102 (63.8%) |
| Ethnicity | |
| White | 91 (56.9) |
| Asian | 45 (28.1) |
| Other | 24 (15.0) |
| Tumor size (longest diameter), cm | |
| ≤5 | 59 (36.9) |
| >5 to 10 | 71 (44.4) |
| >10 | 26 (16.3) |
| Missing | 4 (2.5) |
| Metastatic disease, yes | 155 (96.9) |
| Location of KIT mutation | |
| ECD exon 9 | 43 (26.9) |
| JMD exon 11 | 111 (69.4) |
| AL exon 17/18 | 74 (46.3) |
| ABP exon 13/14 | 34 (21.3) |
| AL$^{pos}$ABP$^{neg}$ | 60 (37.5) |
| ≥3 prior TKIs | 98 (61.3) |

AL, activation loop; AL$^{pos}$ABP$^{neg}$, activation-loop positive, ATP binding pocket negative; ABP, ATP binding pocket; ECD, extracellular domain; JMD, juxtamembrane domain.

**Figure 2. Distribution of *KIT* AL and ABP mutations**




Label number outside the sector diagram represents the affected codon in KIT; Label number in the sector represents the number of patients with corresponding mutations detected. ABP, ATP binding pocket; AL, activation loop; TISSUE, tumor tissue

### Antitumor response

- The unadjusted ORR was significantly higher in the *KIT* AL$^{pos}$ABP$^{neg}$ group than in the *KIT* OTHERS group (26.7% [16/60] vs 12.0% [12/100]; P=0.0185); the disease control rate was also higher (**Table 2. Figure 3**); findings were consistent following IPW$_{BL}$ adjustment (ORR, 31.4% vs 12.1%; P=0.0047).
- Pts receiving AVA in the 2L setting (38.5%) achieved numerically higher ORRs compared with those receiving other lines (**Table 2**).
- ORRs were numerically higher for Chinese pts (36.4%) than for non-Chinese pts (24.5%) in the ≥2L setting (P=0.4244) (**Table 2**).
- Meaningful antitumor activity was seen in pts with *KIT*-9-mutant GIST in the fourth- and later-line (≥4L) settings (**Table 2**).

**Table 2. Tumor response data**

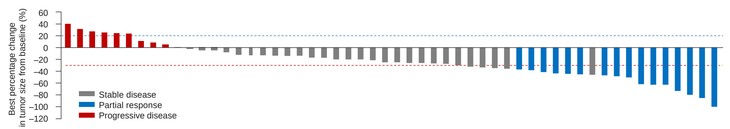
| Data are n (%) unless stated otherwise | *KIT* groups: unadjusted | | *KIT* groups IPW$_{BL}$-adjusted | | Efficacy in *KIT* AL$^{pos}$ABP$^{neg}$ by therapy line | | | | *KIT* AL$^{pos}$ABP$^{neg}$ (≥2L) | | *KIT* 9 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AL$^{pos}$ABP$^{neg}$ | OTHERS | AL$^{pos}$ABP$^{neg}$ | OTHERS | 2L | 3L | 4L | >4L | Chinese | Non-Chinese | 4L | >4L |
| | *N*=60 | *N*=100 | *N*=58 | *N*=95 | *n*=13 | *n*=9 | *n*=15 | *n*=23 | *n*=11[b] | *n*=49[c] | *n*=14 | *n*=19 |
| ORR (%) | **26.7** | **12.0** | **31.4** | **12.1** | **38.5** | **22.2** | **20.0** | **26.1** | **36.4** | **24.5** | **14.3** | **15.8** |
| Partial response | 16 (26.7) | 12 (12.0) | 31.4 | 12.1 | 5 (38.5) | 2 (22.2) | 3 (20.0) | 6 (26.1) | 4 (36.4) | 12 (24.5) | 2 (14.3) | 3 (15.8) |
| Stable disease | 30 (50.0) | 43 (43.0) | 47.2 | 43.6 | 6 (46.2) | 6 (66.7) | 9 (60.0) | 9 (39.1) | 6 (54.5) | 24 (49.0) | 9 (64.3) | 10 (52.6) |
| Progressive disease | 10 (16.7) | 40 (40.0) | 15.8 | 40.5 | 2 (15.4) | 1 (11.1) | 3 (20.0) | 4 (17.4) | 0 | 10 (20.4) | 3 (21.4) | 6 (31.6) |
| Not available/unknown | 4 (6.7) | 5 (5.0) | 5.7 | 3.8 | 0 | 0 | 0 | 4 (17.4) | 1 (9.1) | 3 (6.1) | 0 | 0 |
| Odds ratio (95%CI), % | 2.67 (1.16–6.12) | | 3.31 (1.44–7.58) | | – | – | – | – | 1.76 (0.44–7.08) | | – | – |
| *P* value | 0.0185 | | 0.0047 | | – | – | – | – | 0.4244 | | – | – |
| Disease control rate, n (%) | 79.7 | 55.0 | 78.6 | 55.7 | 84.6 | 88.9 | 80.0 | 65.2 | 90.9 | 73.5 | 78.6 | 68.4 |

≥2L, second line and beyond; 2L, second line; 3L, third line; 4L, fourth line; >4L, beyond fourth line; AL$^{pos}$ABP$^{neg}$, activation-loop positive, ATP binding pocket negative; IPW$_{BL}$, inverse probability weighting of baseline characteristics; ORR, objective response rate.

## CONCLUSIONS

- AVA demonstrated greater antitumor activity in pts with GIST harboring *KIT* AL$^{pos}$ABP$^{neg}$ mutations than in pts with other *KIT* mutations.
- AVA is a promising 2L treatment option for pts with *KIT* AL$^{pos}$ABP$^{neg}$-mutant GISTs and has potential as a later-line therapy (≥ 4L) for pts with *KIT* 9 mutations.
- AVA may confer meaningful clinical benefit in pts with GIST and specific types of *KIT* mutation, especially *KIT*-AL or *KIT* 9 mutations.

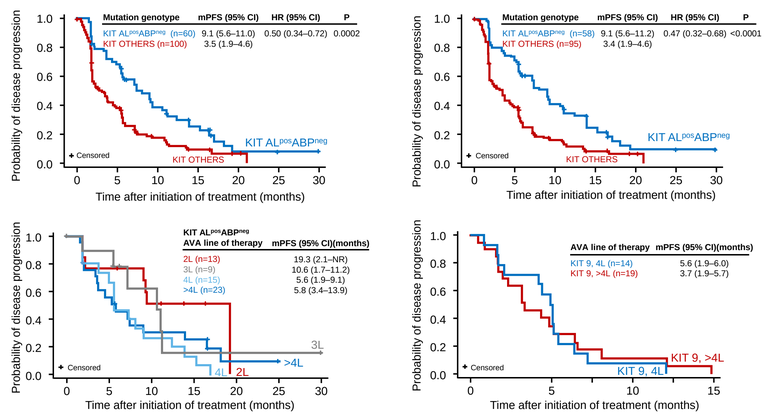
**Figure 3. Best percentage change from baseline in tumor size: *KIT* AL$^{pos}$ABP$^{neg}$ group**




### Progression-free survival

- Both unadjusted and IPW$_{BL}$-adjusted median PFS were significantly higher in the *KIT* AL$^{pos}$ABP$^{neg}$ group versus *KIT* OTHERS (**Figure 4A,B**).
- A PFS benefit with AVA was observed in *KIT* AL$^{pos}$ABP$^{neg}$ pts in the second-line setting over later lines (**Figure 4C**).
- There was also clinically meaningful PFS benefit with AVA in pts with a *KIT* 9 mutation in both the fourth-line (4L) and ≥4L settings (**Figure 4D**); median PFS was 7.2 months in *KIT* AL$^{pos}$ABP$^{neg}$ pts harboring a *KIT* 9 mutation (*n*=8) in the 4L and ≥4L settings.

**Figure 4. Kaplan–Meier estimates of PFS assessed by IRR per mRECIST (A) unadjusted and (B) after IPW$_{BL}$ adjustment, and by line of therapy (C) and in 4L and ≥4L pts with *KIT*-9-mutant disease (D)**




2L, second line; 3L, third line; 4L, fourth line; >4L, beyond fourth line; AL$^{pos}$ABP$^{neg}$, activation-loop positive, ATP binding pocket negative; AVA, avapritinib; CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival.

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**Acknowledgements:**

This study was funded by (Suzhou) CStone Pharmaceuticals. We thank all study participants and their families, and the investigators and study teams at each study site. We also thank Jacqueline Kolston PhD (Parexel Int) provided medical writing support under the direction of the authors, which was funded by Cstone.

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Poster presented at: American Society of Clinial Oncology (ASCO) – 2 to 6 June 2023