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Circulating tumor DNA (ctDNA) analyses of the phase III VOYAGER trial: KIT mutational landscape and outcomes in patients with advanced gastrointestinal stromal tumor (GIST).

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Background: The genotype of primary mutations predicts imatinib response in untreated metastatic GIST. However, the sequence of salvage treatments in metastatic GIST is based solely on the chronological order of registration trials. ctDNA sequencing offers a powerful diagnostic tool to detect resistance mutations in GIST but has not been shown to correlate with outcomes in clinical trials of pretreated patients (pts). We analyzed ctDNA samples collected at baseline in the phase III VOYAGER trial (NCT03465722) to describe the landscape of KIT alterations and its association with outcomes of pts treated with avapritinib or regorafenib. **Methods**: In VOYAGER, 476 pts with advanced KIT-mutant GIST were randomly assigned to avapritinib (240 pts) or regorafenib (236 pts) in 3rd-4th line. Baseline plasma was collected and ctDNA analyzed with the Guardant 360 (G360), 74-gene panel. KIT molecular subgroups were determined and correlated with outcomes. PDGFRA-mutant GISTs were excluded from outcomes analysis. **Results**: Baseline ctDNA analysis was performed in 386/476 pts (81%). ctDNA was detected in 333 pts (86%), with 250 and 18 pts showing at least one KIT (75%) or PDGFRA (5%) variant, respectively. KIT primary mutations were detected in 71% pts (exon 11, 56%; exon 9, 14%; exon 13, 1%) and KIT secondary mutations in 55% of pts. Activation loop (AL, exons 17 and 18) was more commonly affected (44%) than the ATP-binding pocket (ABP, exons 13 and 14; 23%). Among KIT-mutant tumors, multiple KIT mutations were commonly detected within individual tumors (mean, 2.56; range, 1-14). Notably, 17% of pts had > 3 mutations (mean, 6.07; range, 4 to 14). Median PFS and OS were shorter for patients whose ctDNA was positive for V654A or T670I (ABP hot spots) when treated with avapritinib vs. regorafenib: mPFS, 1.9 mo vs. 7.4 mo; log-rank p <.001; mOS, 8.3 mo vs. 11.7 mo; log rank p =.0651. mPFS was shorter for patients with ctDNA positive for KIT exon 17 mutation if concurrently KIT V654A/T670I was absent when treated with avapritinib, with no difference in OS: mPFS, 4.7 mo vs. 6.7 mo; log-rank p =.03; mOS, 19.2 mo vs. NR; log-rank p =.628. mPFS on avapritinib was longer when ABP mutations were absent when compared to those with ABP present (5.6 vs. 1.9 mo; log-rank p <.001). There were no differences considering AL mutations vs. no AL mutations (3.8 vs. 3.9 mo; log-rank p =.622) when treated with avapritinib. Regorafenib showed similar activity regardless of KIT mutational status and the location of KIT mutation. **Conclusions**: Hybrid capture-based plasma sequencing detects ctDNA in the majority of patients with advanced TKI-resistant GIST, including heterogeneity of KIT mutations. This study is the first to show that ctDNA sequencing correlates with outcomes in pretreated GIST. Identification of ABP (exon13/14) KIT mutations negatively correlates with avapritinib activity. Research Sponsor: Blueprint Medicines, Other Foundation.

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