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CORRESPONDENCE

Novel trial designs for patients with gastrointestinal stromal tumor

The unique difficulties associated with clinical trial development in rare neoplasms can sometimes make them impractical due to their rarity and heterogeneity. In selected populations, researchers may resort to placebo-controlled randomized trials (PCRTs) as a means to streamline patient recruitment and shorten trial duration. Nevertheless, these intrinsic difficulties in clinical drug development in rare tumors still contribute to the worse survival rates compared with patients with common cancers.[1]

Gastrointestinal stromal tumor (GIST), a rare malignant neoplasm of mesenchymal origin, is characterized by gain-of-function mutations in *KIT* or *PDGFRA* receptor tyrosine kinases. After the onset of first-line imatinib resistance, all GIST trials that successfully led to drug approvals consistently used placebo as the comparator arm, considering that there was no efficient standard of care.[2] In a recent study, we undertook a pooled analysis of the five phase III PCRTs to understand the natural history of imatinib-resistant metastatic GIST in the absence of active treatment.[3] Placebos constituted the last line of treatment in all cases. Time-to-event outcomes were extracted from published Kaplan–Meier curves to reconstruct individual patient data and Cox models were used to estimate hazard ratio (HR) with 95% confidence interval (95% CI).

Outcomes in the placebo arms were consistent across the five studies. In the pooled analysis, the overall median progression-free survival (PFS) in the placebo arms was 1.2 months (range 0.9-1.5 months), while it increased to 4.2 months in patients treated with the experimental arms (HR 3.36, 95% CI 2.79-4.04, $P < 0.001$). Similarly, no relevant differences were observed in overall survival (OS) in patients treated with placebo, with a median OS of 9.8 months compared with 13.9 months in the pooled analysis of experimental arms (HR 1.67, 95% CI 1.30-2.15, $P < 0.001$).

The homogeneity of PFS observed across all placebo arms was equally consistent when explored as 3-month and 6-month PFS rates, two known surrogate endpoints (Figure 1A and B). Interestingly, and regardless of the line of treatment, 14.1% of GIST patients treated with placebo were progression free at 3 months, and only 2.9% at 6 months, clearly indicating a shared natural history after imatinib failure in patients randomized to placebo across clinical

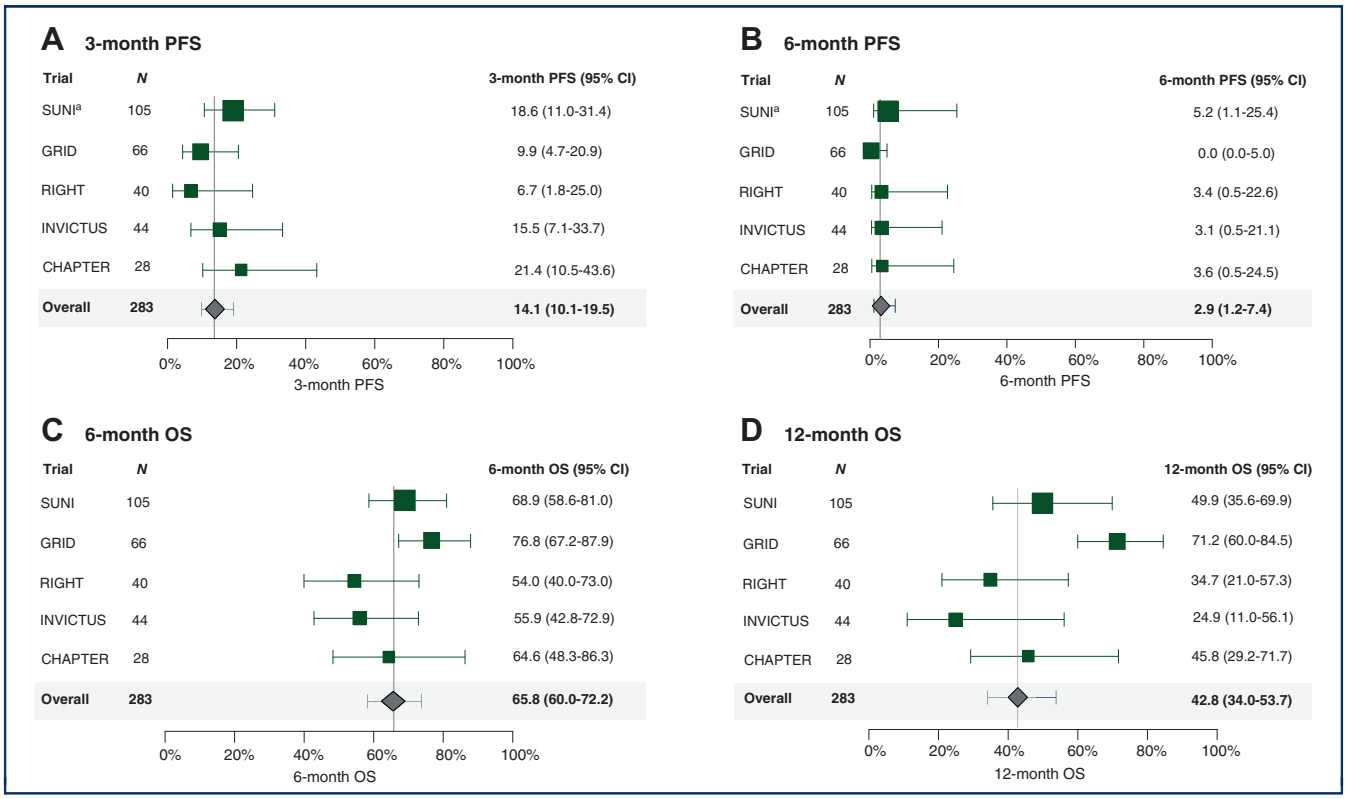

Figure 1. Forest plot with the 3- and 6-month PFS and OS estimation in the placebo arms. SUNI: sunitinib versus P. GRID: regorafenib versus P. RIGHT: imatinib versus P. INVICTUS: ripretinib versus P. CHAPTER: pimitespib versus P. (A) Three-month PFS per trial and overall. (B) Six-month PFS per trial and overall. (C) Six-month OS per trial and overall. (D) Twelve-month OS per trial and overall.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; P, placebo.
[a]Sunitinib endpoint is time to treatment failure.

trials. Although OS outcomes may be affected by data maturity and crossover designs, the decline in OS is unequivocal at 6 and 12 months, with only 42.8% of GIST patients alive after 12 months of randomization to placebo arms (Figure 1C and D). Hence, these data underscore that patients initially treated with placebo have lower OS irrespective of the type of therapy, crossover, and the line of treatment.

Together, our data evidence a consistent, rapid, and homogeneous PFS decline across all placebo arms that leads us to discourage the use of placebo arms in future trials in imatinib-resistant GIST. Instead, external control arms constitute promising tools to facilitate clinical research and drug approvals of novel therapies in GIST and other rare tumors.[4] In this sense, it is critical to build such controls using high-quality, homogenous, and updated data in well-defined molecular populations.

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