

SWOG study shows significant long-term overall survival for advanced gastrointestinal stromal tumor patients with imatinib treatment

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Comment on: Heinrich MC, Rankin C, Blanke CD, *et al.* Correlation of Long-term Results of Imatinib in Advanced Gastrointestinal Stromal Tumors With Next-Generation Sequencing Results: Analysis of Phase 3 SWOG Intergroup Trial S0033. *JAMA Oncol* 2017;3:944-52.

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract with an annual incidence rate of 7 to 10 per one million people (1,2). Over the past two decades, the molecular classification and clinical treatment of GISTs has emerged as a paradigm for precision medicine, as it highlights the importance of matching patient-specific molecular aberrations to molecular targeted therapies for subgroups of patients (3,4). The vast majority of GISTs are driven by constitutively activated mutant isoforms of the KIT (CD117; 75–85%) or platelet-derived growth factor receptor α (PDGFRA; 5–15%) tyrosine kinases (5–7), resulting in oncogenic signaling. Less frequent pathogenic aberrations are described including (I) *KRAS* or *BRAF* mutations; (II) loss of succinate dehydrogenase (SDH) complex iron sulfur subunit B protein expression due to mutations or epigenetic deregulation; and (III) the association to the autosomal dominant disorder neurofibromatosis type 1 (NF1) (8–12). Complete surgical resection remains the gold standard and cornerstone of treatment for primary localized tumors. Historically, radio-/chemotherapy has not been effective as cytotoxic treatment for patients with metastatic or unresectable disease and prognosis was poor with survival generally measured in weeks to a few months (13). Molecular targeted therapy in form of specific and highly effective tyrosine kinase inhibitors (TKIs) has revolutionized the patient-specific options

of clinical management for GISTs (14). However, the emergence of TKI-resistant GISTs has raised critical treatment challenges. Since 2001, several clinical trials conducted in GISTs confirmed the breakthrough benefit and clinical efficacy of imatinib mesylate (drug marketed as Glivec/Gleevec), an orally administered multiple TKI (15–18). High response rates and lasting disease control are dependent on the *KIT* and *PDGFRA* genotype. The US Food and Drug Administration (FDA) has first granted imatinib mesylate accelerated approval in 2002 for use in advanced or metastatic CD117-positive GIST. In 2012, full FDA approval was received as an adjuvant treatment following surgical removal of CD117-positive GIST in adult patients.

In a recent study published in *JAMA Oncology* (19), a follow-up on long-term treatment outcomes of 695 randomized CD117-positive GIST patients originally enrolled in the phase III clinical trial S0033, was reported by Dr. Michael Heinrich (MD of Knight Cancer Institute, Oregon Health and Science University) and cooperative SWOG (formerly the Southwest Oncology Group) affiliates from the National Clinical Trials Network. Based on the initial study results published in 2008 (20,21), SWOG supported imatinib mesylate as the highly effective standard-of-care therapy for patients with advanced and/or metastatic GIST. To assess the long-term survival rates of GIST patients who were not surgically

curable, post-protocol data was collected after closure of S0033. In addition, the SWOG research team performed next-generation sequencing to re-analyze DNA from GIST tissue samples deposited in a biospecimen bank for the S0033 study. Analysis of the 695 eligible GIST patients treated with imatinib mesylate at two dosage levels (400 vs. 800 mg daily doses) showed that (I) 189 patients survived 8 years or longer, with a 10-year estimate of overall survival of 23%, or nearly one-fourth of GIST patients with advanced disease and (II) survival rates were significantly higher for GIST patients harboring a *KIT* exon 11 mutation compared to *PDGFRA*-mutated GIST or GIST lacking *KIT*/*PDGFRA* mutations (*KIT*/*PDGFRA* WT GIST). Resequencing of 20 cases which originally had been classified as *KIT*/*PDGFRA* WT GIST using Sanger sequencing in well-established *KIT* and *PDGFRA* gene hot spots revealed that when using deep sequencing NGS technology (also including, e.g., *SDH* and *NF* genes), 85% (17/20) harbored a pathogenic mutation either of the *SDH* complex (n=12; found to be localized in subunits A, B, or C) or in the neurofibromin 1 gene (n=2). Moreover, three cases carried *KIT* mutations (*KIT* exons 9, 11, 13 one each) which were missed in the original less sensitive Sanger sequencing-based approach. Overall, the authors estimate that 97.5% of GIST can be assigned to a pathogenic genotype, supporting the hypothesis that most GISTs harbor identifiable pathogenic mutations.

In summary, Heinrich *et al.* report that a significant subset of patients with advanced and/or metastatic GIST experience long-term overall survival (≥ 10 years) benefit from front-line imatinib mesylate treatment. In a multivariate analysis, *KIT* exon 11 genotype was the single best predictor of favorable clinical response without significant differences between different mutational subtypes in exon 11. Although the amount of available information about status and post-protocol therapies and the number of available tumor samples from long-survivors was low, this SWOG study provides clinical guidance for GISTs harboring the most common *KIT*/*PDGFRA* mutations. Furthermore, the usage of more sensitive deep sequencing NGS technology is strongly encouraged, even though beneficial management of patients harboring less frequent genotypic GIST subtypes (e.g., *SDH* deficient) remains challenging.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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