Editorial Commentary

Dawn of immunotherapy treatment for gastrointestinal stromal tumors

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Comment on: Singh AS, Hecht JR, Rosen L, *et al.* A Randomized Phase II Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Patients with Advanced Gastrointestinal Stromal Tumors. Clin Cancer Res 2022;28:84-94.

Received: 03 March 2022; Accepted: 09 May 2022; Published online: 30 April 2023.

doi: 10.21037/gist-22-4

View this article at: https://dx.doi.org/10.21037/gist-22-4

Gastrointestinal stromal tumors (GIST) are characterized by pathogenic activating mutations in tyrosine kinases, or less commonly by loss of succinate dehydrogenase (SDH) complex activity through epigenetic silencing or loss of function mutation in one of the SDH subunits (1). A large majority of GIST contain activating mutations in *KIT* or platelet-derived growth factor receptor-alpha (*PDGFRA)* which are generally mutually exclusive. Very rarely, loss of neurofibromin-1, activation of RAS, translocation of neurotrophic receptor tyrosine kinase (*NTRK)* or cryptic genomic changes lead to development of GIST. A recent study suggests that spindle cell neoplasms of the gastrointestinal tract harboring translocations involving *NTRK* are distinct from GIST, and these malignancies respond to treatment with inhibitors of NTRK activity (2). The development of orally bioavailable small molecule inhibitors of KIT and PDGFRA substantively changed the treatment and survival of patients with locally advanced or metastatic GIST extending medial survival from less than 2 to more than 4 years with about 25% of patients surviving more than 10 years after the start of imatinib (3-5). However, secondary mutations in *KIT* or *PDGFRA* leading to resistance to kinase inhibition develop in many patients, and a minority have mutations in GIST that render primary resistance to imatinib. Once resistance to imatinib develops, the tumor progression-free interval generally is much shorter than with initial imatinib therapy (6-8). Moreover, SDH-deficient GISTs are resistant to treatment with imatinib although a minority may respond to treatment with sunitinib or other vascular growth factor receptor inhibitors. Few formal trials of non-tyrosine kinase inhibitor (TKIs) chemotherapy in treatment of advanced GIST have been conducted, but data collected prior to widespread incorporation of TKIs into the treatment of GIST suggests that GIST is resistant to conventional chemotherapy such as DNA-damaging agents (9,10). Thus, there is strong interest in developing alternative treatments for GIST in combination with TKIs in sensitive tumors, or in place of TKIs in resistant tumors.

Much has been written about preclinical studies and biomarker analyses that suggests a role for immunotherapy in management of GIST (11-13). However, we are in the dawn of immunotherapy for GIST, and much needs to be learned to translate our understanding of GIST immunobiology into standard clinical care. A pilot study of imatinib combined with interferon-α2b in patients with imatinib-naïve GIST showed objective partial response in all patients treated (N=8); however, to my knowledge, a larger trial to confirm the high response rate has not been conducted (14). A pilot trial of low-dose metronomic oral cyclophosphamide combined with pembrolizumab in 10 patients with GIST produced no objective responses (although 1 patient had minor reduction in GIST) and a median PFS of 1.4 months (15). The hypothesis that immunostimulatory effects of metronomic cyclophosphamide would prime the environment for

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response of GIST treated with an immune checkpoint inhibitor was not supported by the study results, and patients did not appear to benefit from the treatment. The authors found an immunoinhibitory environment in GIST samples from patients that were examined for exploratory analyses which may have contributed to lack of activity of pembrolizumab. In a phase 1 study of dasatinib combined with ipilimumab in which 20 patients with GIST enrolled, there were no objective tumor responses per RECIST but 7 of 13 evaluable had partial response per Choi criteria (16). The median PFS was a short 2.8 months. A conclusion by the authors was that the combination produced results similar to treatment with dasatinib alone. Thus, there was no additional benefit from use of ipilimumab. A different approach to stimulating immune response in GIST was explored by administration of activated allogeneic dendritic cells directly into tumors. Ilixadencel is a monocyte-derived dendritic cell product that may stimulate host immunity through secretion of chemokines and activation of NK cells. In a pilot phase I trial, 6 patients with GIST progressing on treatment with second-line or later TKI were given two injections of ilixadencel into GIST tumor to evaluate safety and preliminary efficacy (17). Tyrosine kinase inhibitors were continued during the study. Four patients had metastatic GIST and 2 had unresectable, locally advanced disease. In 4 of the patients, progressive disease was the best response with enlargement of injected and non-injected target lesions; however, 2 patients had reduction in the size of injected and non-injected lesions meeting definition of partial response per Choi criteria and stable disease for 9 or more months per RECIST. The 2 patients with partial response received a dendritic cell product manufactured by BioNTech, Germany which was administered directly after thawing, whereas the 4 with disease progression received product manufactured at Cancer Center Karolinska, Sweden that was washed and resuspended with human serum albumin prior to administration. The additional manipulation of cells may have had a detrimental effect on immune activation and needs further study. Although the treatment was not associated with significant adverse effects, the study was terminated early due to slow accrual. This dendritic cell immune treatment is likely to be more effective in management of patients with locally advanced GIST or progression of disease isolated in a single metastasis than in patients with widespread progression of disease unless robust, sustained, systemic immunity to GIST can be achieved. Further study of ilixadencel would benefit from trial design that evaluates activity in patients with progression of a single GIST lesion accessible for percutaneous administration of the cell product separately from patients with wide-spread progression of metastatic GIST.

The results of a randomized phase II trial of nivolumab or nivolumab combined with ipilimumab in patients with advanced GIST previously treated with imatinib were recently reported by Singh *et al.* in *Clinical Cancer Research* (18). Randomization to treatment arms was stratified by the number (1 *vs.* >1) of prior therapies received; however, only 4 of the enrolled and treated patients had received only 1 line of prior therapy. Although the primary endpoint of objective response rate >15% was not met in either arm, one patient treated with nivolumab and ipilimumab experienced complete remission of disease that had been previously treated with imatinib, regorafenib, sorafenib and sunitinib (although exposure to VEGFR inhibitors was very limited because of adverse allergic reactions to the drugs). Eight patients (including the patient with complete remission) had prolonged control of GIST for more than 24 weeks. The GIST originated in the small intestine in 5 (63%) of the patients with prolonged stable disease. The 6-month PFS rate was 26% in patients (N=19) treated with nivolumab and 19% in patients (N=16) treated with nivolumab and ipilimumab; whereas, the median PFS was 8.3 weeks in the nivolumab arm and 11.7 weeks in the nivolumab + ipilimumab arm. Because tumor response was assessed every 8 weeks, the median PFS results indicate many of patients did not benefit from treatment with immune checkpoint inhibitors having evidence of disease progression on the first radiologic evaluation to assess tumor response. This finding is consistent with patients treated with placebo in randomized, blinded, placebo-controlled trials in advanced GIST, although in the placebo-controlled trials, imaging was performed after 4–6 weeks of treatment (6-8). Pseudoprogression and hyperprogression of cancer has been reported following treatment with immune checkpoint blocking antibodies (19). Pseudoprogression from immune cell infiltration is followed by tumor response. Hyperprogression is associated with early patient death. Singh *et al.* stated a separate study of GIST response comparing RECIST1.1, immune-related RECIST and Choi criteria is being conducted. This analysis may shed light on whether pseudoprogression occurs in GIST treated with immune checkpoint inhibitors.

The trial by Singh *et al.* was conducted prior to commercial availability of ripretinib which is a tyrosine kinase inhibitor that affects the activation domain in KIT and PDGFRA. A phase III trial of ripretinib demonstrated

a median PFS of 6.3 months in a 4th-line treatment setting and is available for clinical use (6). Additionally, in an open-label phase II trial of cabozantinib in patients with advanced GIST previously treated with imatinib and sunitinib, the objective response rate was 14% and median progression-free survival duration was 5.5 months (20). The results of the phase 3 ripretinib and phase 2 cabozantinib trials suggests these TKIs are more active than nivolumab in GIST after treatment with imatinib and sunitinib. Treatment with nivolumab or nivolumab + ipilimumab was associated with significant adverse events including grade 3–4 type 1 diabetes mellitus requiring treatment with insulin, diarrhea, rash, fatigue, and weakness; therefore, the potential benefit of treatment with immune checkpoint inhibitors in patients with advanced GIST should be sufficiently high to justify exposing patients to potential risks from immunotherapy.

The investigators of the randomized phase II study of nivolumab versus nivolumab and ipilimumab are to be commended for providing detailed information on patient and tumor characteristics, in particular on the patients with prolonged stable disease. Unfortunately, patient characteristics and GIST genotypes, with exception of GIST location, do not illuminate potential biomarkers that may be used for selection of patients likely to benefit from the treatment. Prolonged stable disease was not seen in patients with a gastric GIST. Prolonged stable disease was seen in GIST with mutations in *KIT* exon 9, exon 11, exons 11 & 13, exons 11 & 17 and in one patient with "wild-type" GIST indicating that tumor control with nivolumab does not associate with GIST genotype. Patients with secondary mutations in *KIT* exon 13 and 17 were also shown to benefit from treatment with ripretinib, thus development of secondary *KIT* mutations is not an indication for nivolumab over ripretinib after treatment with imatinib and sunitinib (21). Pre-treatment and post-treatment tumor biopsies along with blood samples during treatment were collected in the nivolumab study for biomarker analysis. The authors report that analyses of these samples is ongoing, and this research may identify tissue or blood markers that associate with prolonged stable GIST on treatment with nivolumab with or without ipilimumab.

We now have a palette of TKIs with which to treat patients with advanced GIST, but primary and secondary resistance remain critical problems adversely affecting patient survival. And patients with SDH-deficient GIST lack a good standard treatment for advanced disease that cannot be managed with surgery. With focused efforts from the community of GIST researchers, we may be able to identify and validate markers that will predict tumor control and response to immune checkpoint inhibitors and novel immunotherapy agents that will not only lead to a greater likelihood of GIST response but to durable remissions and cures. Although we are in the dawn of immunotherapy in management of patients with advanced GIST, the day ahead appears bright.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gastrointestinal Stromal Tumor*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://gist.amegroups.com/article/view/10.21037/gist-22-4/coif). SMS is a Site PI for multi-site BluePrint Medicine sponsored clinical trial of avapritinib in patients with advanced, previously treated GIST and is committee member of the NCCN soft tissue sarcoma treatment guidelines which includes GIST. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/gist-22-4
Cite this article as: Schuetze SM. Dawn of immunotherapy treatment for gastrointestinal stromal tumors. Gastrointest Stromal Tumor 2023;6:1.