Editorial

The big, the bad, and the exon 11: adjuvant imatinib for all gastrointestinal stromal tumors or just the ugly?

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Comment on: Joensuu H, Wardelmann E, Sihto H, *et al.* Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol 2017;3:602-9.

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Gastrointestinal stromal tumor (GIST), a type of sarcoma, is the most common mesenchymal tumor of the gastrointestinal tract. Because the majority of GIST is driven by KIT proto-oncogene receptor tyrosine kinase (*KIT*) (encodes KIT protein) (OMIM 164920) and platelet-derived growth factor receptor α (*PDGFRA*) (encodes platelet-derived growth factor receptor α) (OMIM 173490), it represents a paradigm for targeted therapy in solid tumors. An exploratory analysis of the Scandinavian Sarcoma Group (SSG) XVIII/Arbeitsgemeinschaft Internistische Onkologie (AIO) trial was recently published by Joensuu *et al.* (1). The parent trial, originally published in 2016, compared 3 years to 1 year of adjuvant imatinib (Gleevec®) in surgically resected GISTs (2). It established 3 years of adjuvant imatinib as the standard of care for high risk GIST. The authors, hoping to capitalize on lessons learned about the molecular biology of this disease, evaluated the mutation status of patients enrolled in the trial.

Other investigators have previously established the prognostic value of mutations in KIT *PDGFRA*, showing that deletions are more aggressive than point mutations (3). The authors asked: Does the duration of adjuvant imatinib have an effect on the prognostic power of various mutations?

The analysis was performed retrospectively and is thus limited. To avoid a "fishing expedition" and to maximize power of this retrospective analysis, they focused their efforts on *KIT* exon 11 mutations in comparison to all others. This was a prudent choice as *KIT* exon 11 is the most commonly involved mutation site in GIST, and codons 557 and 558 especially are associated with higher mitotic rate and poor prognosis.

The analysis focused on relapse-free survival (RFS) rather than overall survival. This was a deliberate choice since the original trial had RFS as the primary endpoint. It also increased statistical power since there were more RFS events than deaths. The authors chose a two-sided P-value to ensure that differences could be accounted for in either direction.

Unsurprisingly (4), *KIT* mutations constituted 80.4% of all samples, 12.6% were *PDGFRα*, and the remaining 7% wild type for either gene. Of the *KIT* mutated patients 54% had exon 11 deletion or insertion and 74.5% of those cases involved exon 557 and/or 558. The samples with both codon 557 and 558 deletion had the highest mitotic rate corresponding to the highest risk disease.

The comparison of exon 11 deletions or insertions to all other mutations affirmed that this group had a shorter RFS and highlighted the worst prognosis for double deletion exon 11 codons 557 and 558. This difference was observed in the 1-year imatinib group. However, when the same analysis was performed for the 3-year group no such differences were observed. The authors concluded that the

unfavorable prognosis of exon 11 deletions and insertion/deletions, including those involving codons 557 and/or 588, could be reversed by extending adjuvant imatinib from 1 year to 3 years. They further suggest that prolonged exposure to imatinib alters the molecular biology of certain GIST subtypes. The same analysis repeated for PDGFRα, exon 9, and wild-type GIST samples showed no benefit to the prolonged administration of imatinib.

We commend the authors for undertaking this analysis to shed light on who truly benefits from extended adjuvant imatinib. The price of imatinib has been decried as the poster-child for unsustainable cancer drug prices (5). Beyond the financial strain this puts on individuals, health insurers, and the safety net system this drug comes with a long list of adverse events. Current practice is to put any high risk patient on 3 years of adjuvant imatinib. This analysis suggests that we are grossly over-treating patients. Granted, we are likely excluding most *PDGFR*α tumors because of their low mitotic rate. However, it is clear that many patients are not benefiting from current practice including patients with exon 9 duplication which has reduced sensitivity to the 400 mg dose of imatinib (6).

One critique of this study is the choice to report the RFS rather than overall survival. This has been validated in colon cancer as an acceptable surrogate marker (7), but the applicability to GIST is not clear. The authors suggest that extended adjuvant imatinib changes the biology of some GISTs. This would have been better demonstrated with overall survival. The original SSG/AIO trial on which this analysis is based reported that 3-years of imatinib resulted in prolonged overall survival. The advantage of this strategy is that a statistically significant result is obtained. The disadvantage is that we are left with a correlation rather than a causation. A prospective trial is needed now to show that 3 (or more) years of adjuvant imatinib improves OS in exon 11 deletions and indels. This trial would of course be difficult to initiate and accrue given the already established standard of care.

The mutational landscape of GIST is becoming increasingly complex. We started with the simple exons 9 and 11, later adding *PDGFR*α, and exon 11 codon 557 and 558. The rest we classify as wild-type. This wild-type group constitutes 10–15% of patients and also harbors potentially actionable alterations (4). For example, *NF1* and *BRAF* mutant GIST do not respond to imatinib, but are amenable to other targeted therapies. This study used conventional sequencing of KIT exons 9, 11, 13, and 17 as well as PDGFRα exons 12 and 18. This approach covers 85–90% of all cases, but can be improved using targeted exome next generation sequencing (NGS). When future studies are designed, the addition of NGS may enhance our understanding of resistance mechanisms, co-occurring mutations, as well as expand our repertoire of therapies (8) for "wild-type" GIST. The use of serial "liquid biopsies" and circulating tumor DNA sequencing can further elucidate the evolution of GIST under pressure from adjuvant imatinib.

In conclusion, we consider this work to be a vital first step in redefining adjuvant therapy for GIST. Not all patients benefit and some may be over treated. In the age of affordable gene sequencing, there is no reason a blanket approach should be applied with adjuvant targeted therapy. This analysis calls for a new biomarker driven prospective trial with randomization to groups based on gene and mutation. If imatinib is used, then an academic or collaborative group trial using public or philanthropic dollars will be needed as it is unlikely that drug companies would sponsor the trial that potentially restricts the indication for their drug. One of the other tyrosine kinase inhibitors in the GIST space may be more interested in funding such an enterprise to move their drug to the front-line or adjuvant setting. A potential trial design is a phase III biomarker stratified design (9) that will allow sufficient power to test such a hypothesis.

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None.

Footnote

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

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