Editorial Commentary

An effective drug combination for the first-line treatment of advanced gastrointestinal stromal tumor

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Imatinib, an inhibitor of a few tyrosine kinases including KIT and platelet-derived growth factor receptor alpha (PDGFRα), has been the standard agent for the first-line treatment of patients with advanced gastrointestinal stromal tumor (GIST) since the year 2001 (1). About 75% of GISTs harbor a mutation in the *KIT* proto-oncogene (encodes the KIT protein), and 10–15% in *PDGFRA* (encodes the platelet-derived growth factor receptor-alpha protein). Most patients with advanced GIST respond to imatinib, and the standard imatinib dose, 400 mg taken once daily orally, is generally well tolerated. Common imatinib adverse effects include macrocytic anemia, periorbital edema, watery eyes, diarrhea, and muscle cramps, but these are usually mild (grade 1 or 2) in severity when present, and most GIST patients have a good quality of life while on imatinib. Besides overtly metastatic GIST, imatinib is now the standard therapy also in the adjuvant setting for patients who have a high risk of GIST recurring despite macroscopically complete surgery (2,3). In a randomized study, 3 years of adjuvant imatinib reduced the risk of death of patients with high-risk GIST about 50% compared to 1 year of imatinib during a median follow-up of 10 years (4).

Responses to imatinib are often durable. Approximately 50% of patients with advanced GIST respond to imatinib for about 2 years, and about 10% continue to respond for 10 years or longer (5). Most advanced GISTs eventually become refractory to imatinib due to emergence of *KIT* mutations that lead to kinase conformational changes that reduce imatinib binding, causing drug resistance and GIST progression.

Some GISTs have primary resistance to imatinib, so all patients with advanced GIST cannot be expected to respond to imatinib. The most common mutations in GIST, *KIT* exon 11 mutations, are generally sensitive to imatinib and are associated with the longest progression-free survival (PFS) times, whereas *KIT* exon 9 mutations are less sensitive (6). GISTs that lack *KIT* and *PDGFRA* mutations (about 10% of GISTs) are unlikely to respond (7). The *PDGFRA* exon 18 D842V mutation, which is infrequent in patients with advanced GIST, is insensitive to imatinib, but sensitive to avapritinib (8). For these reasons, sequencing of at least *KIT* and *PDGFRA* genes is considered standard practice when planning the treatment for GIST patients. Sunitinib, regorafenib, and ripretinib have been approved for use as the second-line, third-line, and fourth-line agent after imatinib failure, respectively, but responses to these agents are usually shorter than to first-line imatinib (9).

Besides imatinib, several other tyrosine kinase inhibitors (TKIs) and alteration of 2 TKIs have been evaluated as first-line treatments of advanced GIST in phase 1/2 trials (9), but the evaluation only rarely led to a randomized phase 3 trial. Nilotinib, a generally well tolerated TKI, was compared to imatinib in a phase 3 trial (ENESTg1) as a first-line agent, but trial accrual was terminated early due to crossing of the futility boundary. In the final analysis of the ENESTg1 trial PFS was longer in the imatinib group than in the nilotinib

arm (2-year PFS 59% and 52%, respectively) (10). Thus far, immunotherapy has yielded only modest results in GIST and is currently not considered standard (11).

A rational combination of 2 targeted agents could be another approach for improving survival outcomes of patients with advanced GIST, but few combinations have been investigated. With this background the recent report from Chi *et al.* is of particular interest (12). The authors evaluated the combination of imatinib plus binimetinib, an ATP-uncompetitive, allosteric, selective MAPK/ERK kinase (MEK) inhibitor, as the first-line treatment of advanced GIST in a phase 1b/2 trial (NCT01991379). The rationale for evaluating this combination is sound. The MEK is a part of the mitogen-activated protein kinase (MAPK) signaling pathway, a key pathway involved in cell proliferation and survival. MAPK signaling downstream of activated KIT prolongs stability of the ETS variant transcription factor 1 (ETV1) protein, a master transcriptional regulator in GIST (13). In some GIST xenograft mouse models, dual targeting with imatinib and binimetinib synergistically inhibited tumor growth (14).

The primary endpoint in the phase 2 part of the study by Chi *et al.* (12) was the best objective response rate [complete response (CR) plus partial response (PR)]. Imatinib was administered orally at the standard dose of 400 mg/day, but the binimetinib dose used, 30 mg twice daily orally, was a lower dose than the phase 2 dose of 45 mg b.i.d. the authors recommended based on the findings in part 1b of the same study (NCT01991379) (15), and smaller than the recommended dose in combination with encorafenib for advanced melanoma (also 45 mg b.i.d.) (16). The phase 2 part of the study was designed to detect a 20% improvement in the objective response rate achieved with single-agent imatinib in the first-line treatment of advanced GIST in randomized trials (5,17-20). A response rate of 45% or lower was considered unacceptable, and a rate 65% or over acceptable.

Of the 50 patients enrolled to the phase 2 part of the Chi *et al.* study, 42 (84%) were considered evaluable for response to imatinib plus binimetinib. Twenty-nine (69%; 95% confidence interval, 53% to 82%) out of the 42 patients had confirmed objective response. Since the response rate exceeded the threshold of 65%, the study was considered to have met its primary endpoint. Median PFS was 29.9 months, and median overall survival was not reached. Treatment toxicity was regarded manageable. The authors concluded that the combination of imatinib and binimetinib warrants further study in a direct comparison with imatinib as the first-line treatment of advanced GIST.

Chi *et al.* evaluated efficacy of imatinib plus binimetinib also in the phase 1b part of the trial (15). In the phase 1b part, 9 GIST patients were treated in a binimetinib dose escalation cohort and 14 in a dose expansion cohort. Unlike in the phase 2 part of the study, the patients treated in the phase 1b part had been extensively treated with TKIs for advanced GIST prior to study enrollment. The prior therapies included imatinib (all 23 patients), sunitinib (19 patients), and regorafenib (11 patients). The binimetinib dose was either 30 mg twice daily or 45 mg twice daily. Only 1 (5%) out of the 22 evaluable patients responded, the single responding patient had succinate dehydrogenase (SDH)-deficient *KIT*/*PDGFRA*-wild type GIST. None of the 13 patients with *KIT*-mutant GIST responded, and they had a short median time on treatment suggesting low activity of imatinib plus binimetinib in a patient population with *KIT*-mutated GIST that has progressed on imatinib.

At the first glance, a response rate of 69% to imatinib plus binimetinib and median PFS of 29.9 months seem favorable efficacy results compared to those obtained in prior randomized trials where patients with advanced GIST were treated with imatinib alone (*Table 1*). Yet, comparisons with historical series need to be made with caution, since several factors might bias the efficacy assessments. Most of the randomized reference trials were analyzed according to the intention-to-treat principle, whereas 8 (16%) out of the 50 patients enrolled to the Chi *et al.* study were excluded from the analysis for evaluability reasons. GIST mutation analysis was usually not available for a substantial proportion of the patients who participated in the randomized comparator trials, but the slightly lower proportions of the most sensitive *KIT* exon 11-mutated GISTs and higher proportions of GISTs with the less sensitive *KIT* exon 9-mutated GISTs or GISTs with no *KIT*/*PDGFRA* mutation in the randomized comparator series might have lowered the response rates in these series compared to the Chi *et al.* study patient population (*Table 1*). None of the GISTs in the Chi *et al.* series harbored the imatinib insensitive *PDGFRA* D842V mutation. All patients were not evaluable for response rate in the randomized trials, and after omission of the unevaluable patients the response rates improve slightly.

Prior adjuvant imatinib was allowed in the Chi *et al.* study, which may further complicate the efficacy comparisons with GIST patient series that date back to the era when adjuvant therapy was not used in the treatment of GIST patients. Tumor bulk at the time of initiation of

Table 1 Five trials evaluating imatinib as the first line treatment of advanced GIST

Trial	Phase	Accrual	Patients, N	Patients excluded, N	*KIT* exon 11 mutation	ORR	ORR[†]	Median PFS
Adjuvant imatinib era								
Chi *et al.* (12)	Phase 2	2014–2020	42	8/50	79%	69%	69%	29.9 mo[‡]
ENESTg1 (10)	Phase 3	2009–2011	320	3	75%	52%	56%	29.7 mo[‡]
Pre-adjuvant imatinib era								
B2222 (17,18)	Phase 2	2000–2001	147	0	67%	68%	71%	20 mo[‡], 26 mo[§]
EORTC/Intergroup (5)	Phase 3	2001–2002	943	0	60%	52%	56%	20 mo[‡], 24 mo[¶]
S0033 (19,20)	Phase 3	2000–2001	746	52	71%	53%	61%[s]	18 mo[‡], 20 mo[¶]

[†], ORR omitting patients unevaluable for response; [‡], imatinib dose 400 mg/day; [§], imatinib dose 600 mg/day; [¶], imatinib dose 800 mg/day; [s], includes 54 patients with unconfirmed response. GIST, gastrointestinal stromal tumor; ORR, objective response rate; PFS, progression-free survival.

upfront imatinib treatment may influence the response rate, the rate of emergence of drug resistance mutations, and PFS. When the tumor bulk is large, resistance mutations may arise more rapidly by chance, simply because the number of cancer cells is greater. Not surprisingly, GIST patients who had a large tumor burden at baseline screening imaging examinations had shorter survival than those with a smaller tumor burden (17). GIST patients who have been treated with adjuvant imatinib tend to be asymptomatic and have a small tumor burden at the time of GIST recurrence, because patients are usually followed up during and after adjuvant imatinib with longitudinal imagining, usually with computed tomography (CT) of the abdomen and the pelvis. Besides contributing to a low volume of disease at the time or detection of GIST recurrence, longitudinal imaging also allows detection of GIST recurrence earlier during the natural course of the disease compared to patients who have symptomatic GIST recurrence, thus resulting in a lead time bias. On the other hand, one could speculate that adjuvant imatinib might reduce efficacy of imatinib in the treatment of GIST that recurs after adjuvant therapy, but some recent evidence suggests that this may not be the case (4). Taken together, due to confounding factors and potential biases, it is difficult to judge whether the efficacy results achieved with the imatinib plus binimetinib combination are superior to those that can be achieved with imatinib alone.

Besides the MAPK pathway, KIT signals also via the phosphatidyl-inositol-3-kinase (PI3K)-AKT pathway and via the signal transducer and activator of transcription 3 (STAT3) (21). Some preclinical findings suggest that pharmacological inhibition of PI3K reduces GIST cell line proliferation more than MEK inhibition (22). Hence, specific inhibition of the MAPK pathway with MEK-inhibitors might not be as helpful in the treatment of GIST as MEK-inhibition is in the treatment of *BRAF*-mutated melanoma. Binimetinib was approved by the Food and Drug Administration (FDA) of the U.S. in 2018 in combination with encorafenib, a BRAF inhibitor, for the treatment of *BRAF* V600E or V600K mutation-positive advanced melanoma, and combination treatment with a BRAF inhibitor and a MEK inhibitor is now standard of care for treating patients with *BRAF* V600-mutant advanced melanoma (23). Constitutively active *BRAF* V600 mutations activate the MAPK signaling pathway driving melanoma cell proliferation, which could be a fundamentally different scenario from GIST *KIT* mutations that signal also via other pathways.

Treatment tolerability is of great importance when treating GIST patients who often stay on TKI treatment for a few years. Both imatinib and binimetinib may be associated with edema when administered as single agents, imatinib in about a third of the patients (10) and binimetinib in about 45% of the patients (24). Thirty-four (79%) out of the 43 evaluable patients treated with the combination of imatinib plus binimetinib in the phase 2 part of the trial had peripheral edema, and weight gain of the trunk was recorded in 9 (21%) patients, but edema was considered grade 3 or 4 in only 1 (2%) patient. Skin rash is relatively infrequent with single-agent imatinib (about 15% of the patients) (10), whereas 32 (74%) of the patients treated with the combination had acneiform skin rash and 21 (49%) maculopapular rash. Diarrhea was the most frequently

recorded gastrointestinal side effect (26 patients, 61%; grade 3 or 4 in 1 patient), which frequency also appears higher than with single-agent imatinib (about 30%) (10). Cardiac ejection fraction decrease, blurred vision, anemia, and elevation of blood creatinine phosphokinase (CPK) occurred in 3 (7%), 9 (21%), 38 (88%), and 43 (100%) of the patients treated with the combination, respectively. These observations suggest that the combination of imatinib and binimetinib is associated with more adverse events than imatinib alone despite the relatively low dose of binimetinib administered, but a randomized comparison with imatinib is needed for making more reliable conclusions about treatment safety and quality of life.

In sum, the combination of imatinib and binimetinib had substantial efficacy in the upfront treatment of patients with advanced GIST and manageable toxicity, but it is not clear how the efficacy of this combination compares with imatinib alone, because the efficacy comparisons with historical series are mudded with differences between the series and potential biases. A randomized trial comparing binimetinib plus imatinib to imatinib alone is needed to provide a firm answer, and the efficacy improvement with the combination, if any, will need to be balanced with toxicity and financial constraints. Meanwhile, imatinib remains the standard first-line agent for patients with advanced GIST except for infrequent exceptions, such as patients with *PDGFRA* D842V mutation, patients who have no *KIT* or *PDGFRA* mutation, and those with *NTRK* gene-fusion positive GIST (3,8,25).

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Footnote

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