

ORIGINAL RESEARCH

## Benefit of pazopanib in advanced gastrointestinal stromal tumours: results from a phase II trial (SSG XXI, PAGIST)

M. Eriksson<sup>1\*</sup>, P. Reichardt<sup>2</sup>, H. Joensuu<sup>3</sup>, A. Krarup-Hansen<sup>4</sup>, O. Hagberg<sup>5</sup>, P. Hohenberger<sup>6</sup>, H. Hagberg<sup>7</sup>, L. Hansson<sup>8</sup>, T. Foukakis<sup>9</sup>, K. Pulkkanen<sup>10</sup>, S. Bauer<sup>11</sup>, D. Goplen<sup>12</sup>, P. Blach Rossen<sup>13</sup> & K. Sundby Hall<sup>14</sup>

<sup>1</sup>Department of Oncology, Skane University Hospital and Lund University, Lund, Sweden; <sup>2</sup>Sarcoma Center Berlin-Brandenburg and Helios Clinic Berlin-Buch, Berlin, Germany; <sup>3</sup>Department of Oncology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; <sup>4</sup>Department of Oncology, Herlev Hospital, Copenhagen, Denmark; <sup>5</sup>Institution of Translation Medicine, Lund University, Malmö, Sweden; <sup>6</sup>Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Center, Mannheim, Germany; <sup>7</sup>Department of Oncology, Uppsala Academic Hospital, Uppsala; <sup>8</sup>Department of Oncology, Sahlgrenska University Hospital, Gothenburg; <sup>9</sup>Breast Cancer, Endocrine Tumours and Sarcoma Section, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden; <sup>10</sup>Department of Oncology, Kuopio University Hospital, Kuopio, Finland; <sup>11</sup>Department of Medical Oncology, Sarcoma Center, West German Cancer Center, University of Duisburg-Essen, Essen, Germany; <sup>12</sup>Department of Oncology, Haukeland University Hospital, Bergen, Norway; <sup>13</sup>Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; <sup>14</sup>Department of Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway



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**Background:** Patients with advanced gastrointestinal stromal tumours (GISTs) resistant to the tyrosine kinase inhibitors imatinib and sunitinib may be treated with regorafenib, which resulted in a median progression-free survival (PFS) of 4.8 months in the GRID trial. Also, pazopanib, another tyrosine kinase inhibitor, has been studied in a randomized, placebo-controlled trial (PAZOGIST) in the third line, which showed a PFS of 45.2% 4 months after study entry, but patients intolerant to sunitinib were also included. We designed another trial evaluating pazopanib, enrolling only patients with progression on both imatinib and sunitinib.

**Patients and methods:** Since all eligible patients had progressive disease, we preferred a non-randomized, phase II multicentre trial so that all patients could receive a potentially active drug. Patients had a progressive metastatic or locally advanced GIST and were  $\geq 18$  years of age, with a performance status of 0-2, and sufficient organ functions. The primary endpoint was disease control rate (defined as complete remission + partial remission + stable disease) at 12 weeks on pazopanib. A Simon's two-stage analysis was used with an interim analysis 12 weeks after enrollment of the first 22 patients, and if passed, there was a full enrolment of 72 patients. GIST mutational analysis was done, and most patients had pazopanib plasma concentration measured after 12 weeks.

**Results:** Seventy-two patients were enrolled. The disease control rate after 12 weeks was 44%, and the median PFS was 19.6 weeks (95% confidence interval 12.6-23.4 weeks). Pazopanib-related toxicity was moderate and manageable. No statistically significant differences were found related to mutations. Plasma concentrations of pazopanib had a formal but weak correlation with outcome.

**Conclusion:** Pazopanib given in the third line to patients with GIST progressing on both imatinib and sunitinib was beneficial for about half of the patients. The PAGIST trial confirms the results from the PAZOGIST trial, and the median PFS achieved seems comparable to the PFS achieved with regorafenib in the third-line setting.

**Key words:** GIST, pazopanib, tyrosine kinase inhibitor, third-line treatment, phase II trial

### INTRODUCTION

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract, and one of the most common types of soft tissue sarcomas. Before

the millennium shift, there was no effective treatment of metastatic or locally advanced non-operable GIST, and the prognosis was poor.

Tyrosine kinase inhibitors (TKIs) have been established as an effective treatment of the majority of GIST patients for almost 20 years.<sup>1,2</sup> Imatinib is approved for both advanced non-operable disease and for adjuvant use in high-risk patients.<sup>3</sup> It is also used frequently in the preoperative setting to facilitate surgery. Sunitinib is approved for advanced GIST when the disease progresses on imatinib or when the patient does not tolerate that drug,<sup>4</sup> and regorafenib is approved in the third line.<sup>5</sup>

\*Correspondence to: Associated Prof. Mikael Eriksson, Department of Oncology, Skane University Hospital, Getingevägen 4, SE-221 85 Lund, Sweden. Tel: +46-46177507

E-mail: [mikael.eriksson@med.lu.se](mailto:mikael.eriksson@med.lu.se) (M. Eriksson).

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Pazopanib is a TKI approved for the treatment of renal cancer and non-GIST soft tissue sarcoma.<sup>6,7</sup> The spectrum of target kinases resembles those for sunitinib and regorafenib, including the receptor tyrosine kinases KIT, PDGFRA, and VEGF 1-3. However, pazopanib does have less burdensome skin and mucosal toxicity as shown in clinical practice. The similarity between these TKIs makes it relevant to investigate the effect of pazopanib in advanced GIST. In advanced GIST, TKIs are often used in more than three lines, if available. All TKIs are different and any new TKI may be beneficial for a GIST patient.

The PAZOGIST trial on pazopanib, which included patients after imatinib and sunitinib failure, showed a progression-free survival (PFS) of 45.2% after 4 months from the date of randomization, but some of them may have had a more indolent course since not only patients with progressing disease, but also patients who were intolerant to sunitinib were included.<sup>8</sup>

In most studies on advanced GIST in the third-line setting or beyond, patient eligibility has not only been progressive disease during an earlier TKI treatment, but also encompassed non-tolerance for the on-going drug. Tolerance is, however, a relative conception. Side-effects may often be ameliorated with symptom-relieving drugs or by reduction of the dose, and even markedly reduced doses have often been shown to be effective enough to control the disease. Patients who terminated the previous treatment due to intolerance may not have resistant disease. We wanted to specifically investigate whether patients progressing on both imatinib and sunitinib at their highest tolerable doses could benefit from treatment with pazopanib. Patients who had also been treated with nilotinib, earlier evaluated for GIST, were also eligible provided that they had progressed during all three mentioned TKIs. Most of these patients had participated in a first-line trial compared with imatinib.

A GIST in progression leads to a very poor PFS without treatment, and thus also on placebo, shown in all placebo-controlled trials in advanced GIST so far. We therefore decided to investigate pazopanib in a phase II single-arm trial.

## PATIENTS AND METHODS

A non-comparative, single-arm phase II trial was carried out at selected sites in five countries (Sweden, Germany, Norway, Finland and Denmark).

The trial (SSG XXI, PAGIST) was sponsored by the Scandinavian Sarcoma Group (SSG), and it was approved by the Institutional Review Boards/Ethical Boards in the participating countries. All patients signed a written informed consent form.

This trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) website with an identifier NCT01524848, and had a European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2011-004404-37.

### Eligibility criteria

Eligible patients had locally advanced or metastatic histologically and/or genetically proven GIST, as confirmed by a

specialized sarcoma pathologist, and had measurable disease according to the RECIST.<sup>9</sup> Patients were required to have a history of progressive disease according to the RECIST 1.1 criteria after both imatinib and sunitinib treatment, and also on nilotinib if this drug had been used. No other TKIs were allowed as earlier treatments. Age was required to be at least 18 years at the time of the diagnosis of GIST, and the World Health Organization (WHO) performance status (PS) at inclusion 0-2. All side-effects from earlier TKI treatments must have been subsided to Grade 1 or 0. Sufficient organ functions of the bone marrow, liver, kidneys and heart were mandatory, and no serious comorbidities as specified in the study protocol were allowed. Pregnant or lactating women were not eligible. For further details, see the complete SSG XXI protocol which is available on the SSG website.<sup>10</sup>

### Treatment and assessments

Eligible patients started on pazopanib (Votrient®) at 800 mg daily, between meals, with strict criteria for dose reductions in case of toxicity. The treatment was continued until any of the following events occurred: progressive disease according to RECIST 1.1, unacceptable toxicity defined as grade 3-4 adverse events occurring at the dose level of 400 mg, intercurrent conditions contraindicating further pazopanib, or patient's preference.

Within 14 days before treatment start, a computed tomography (CT) scan of the thorax, abdomen, and pelvic region was carried out, and CT of the abdomen/pelvic region (and thorax only if involved at baseline) was repeated at treatment week 12 and thereafter every 8 weeks as long as the treatment continued, or earlier if clinically indicated.

At baseline, a physical examination including blood pressure and assessment of PS was carried out, comprehensive laboratory testing was done, and electrocardiography was also included. All these examinations were repeated at weeks 4, 8, 12 and every 8 weeks thereafter during the whole treatment period. At baseline, a pregnancy test was also done for women with childbearing potential.

Left ventricular ejection fraction was assessed by echocardiography or multigated acquisition (MUGA) scintigraphy at baseline, at week 12 and every 16 weeks thereafter.

Follow-up was done until 30 days after the end of treatment of all patients. Thus, the trial ended 30 days after the end of treatment of the last patient since overall survival was not an endpoint to be followed.

One blood sampling for plasma concentration of pazopanib was done at week 12 on treatment, and the measurement was carried out at the PPD Laboratories, Madison, WI, USA.

For further details, see the complete SSG XXI protocol which is available on the SSG website.<sup>10</sup>

### Study endpoints

The primary endpoint was defined as disease control rate (DCR) at 12 weeks after treatment start according to RECIST

Table 1. Patient characteristics	
Sex	
Male	47
Female	25
Median age (years)	64.2
Progression on	
Imatinib	72/72
Sunitinib	72/72
Nilotinib	11/11
WHO performance status	
0	45
1	25
2	2
GIST mutations	
<i>KIT</i> exon 11	31
<i>KIT</i> exon 9	13
<i>KIT</i> exon 13	2
<i>KIT</i> exon 17	1
<i>PDGFRA</i>	0
Non- <i>KIT</i> , non- <i>PDGFRA</i>	11
Not evaluable	14

GIST, gastrointestinal stromal tumour; WHO, World Health Organization.

version 1.1.<sup>9</sup> DCR was defined as complete remission + partial remission (PR) + stable disease (SD).

Secondary endpoints encompassed PFS, overall response rate (ORR), DCR in relation to mutational status, DCR in relation to plasma concentration at week 12, and toxicity measured with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.<sup>11</sup>

### Statistics

For the primary endpoint, DCR, Simon's two-stage analysis was used.<sup>12</sup> The study tested the null hypothesis  $H_0: P \leq 20\%$  against the complementary hypothesis  $H_1: P > 20\%$ , where  $P$  is the probability of clinical benefit. The type I error probability should be  $<5\%$ . If the true value of  $P$  is  $35\%$ , the type II probability should be  $<20\%$ . An interim analysis was carried out after 22 patients, and the condition to proceed was that  $>5$  patients experienced clinical benefit. The total number of patients needed was 72, and  $H_0$  should be rejected if  $>19$  patients had clinical benefit.

ORR was calculated. Kaplan–Meier estimates of PFS were produced together with 95% confidence interval (CI). DCR was calculated separately within each mutational status group.

Plasma concentration of pazopanib at week 12 was correlated with DCR using a linear model adjusting for age.

### RESULTS

In total, 72 patients were enrolled between 15 March 2012 and 1 October 2014, and their characteristics are shown in Table 1. The male/female ratio was 47/25, and median age 64.2 years. All 72 patients had demonstrated progression on imatinib, and after that also on sunitinib. Furthermore, 11 of the patients had also used nilotinib with progression in all cases. A total of 45 patients had a WHO PS 0, 25 had PS 1, and 2 patients had PS 2. *KIT* exon 11 was the dominating site for primary mutation ( $n = 31$ ), followed by exon 9 ( $n = 13$ ), no detected mutation ( $n = 11$ ), exon 13 ( $n = 2$ ), and

exon 17 ( $n = 1$ ). The primary mutation was not available for 14 patients. No patients had a known mutation in the *PDGFRA* gene.

Two patients died before week 12 of treatment, and five further patients were not assessable at week 12; three of them did not show up for a visit after report of disease progression, one did not come because of some intercurrent disease, and one wished to end study participation. The DCR after 12 weeks was 32/72 (44%), with 2 PRs and 30 SD. The median PFS was 19.6 weeks (95% CI 12.6–23.4 weeks) (Figure 1). No statistically significant differences were found related to *KIT* exon 9 or 11 mutations (Figure 2).

Research samples for measurement of plasma pazopanib concentration at week 12 were obtained from 54/72 (75%) patients. The concentration had a significant positive correlation with disease control, when a linear model adjusting for age was applied ( $R = 6.758$ , 95% CI 0.216–13.300,  $P = 0.0432$ ) (Figure 3). Hence, there is evidence that plasma concentration may have an impact on disease control, which has also earlier been indicated for imatinib.<sup>13</sup> Removing one single observation, however, makes the relation non-significant ( $R = 4.991$ , 95% CI 1.048–11.029,  $P = 0.1032$ ), which still makes the finding somewhat provisional.

The toxicity was moderate and manageable, with no toxic deaths. The most common adverse events of grade 3–4 were hypertension in 28%, and diarrhoea and fatigue in 8% each (Table 2). A large number of different low-grade (1–2) toxicities occurred (not shown). Notably, however, there were no patients experiencing grade 3–4 hand-foot syndrome; 14 grade 1 and 3 grade 2.

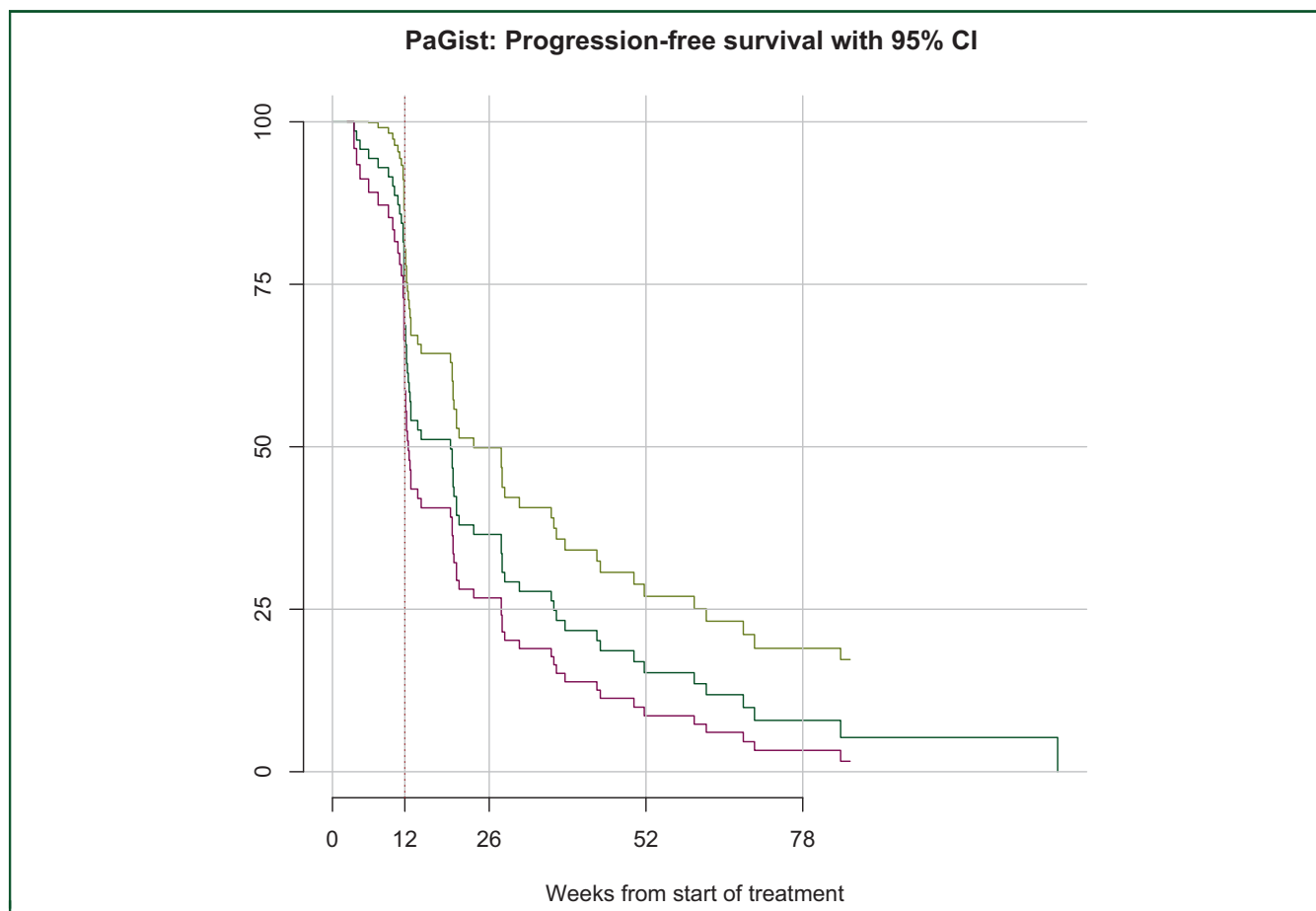
### DISCUSSION

With 72 patients with advanced GIST enrolled for third-line or fourth-line pazopanib treatment, to our knowledge, this trial had the highest number of GIST patients treated with this drug to date.

The trial shows a DCR according to RECIST 1.1 at 12 weeks of 44% in patients with truly progressive disease at the time of enrolment, which demonstrates that pazopanib may be a good treatment alternative in the third line. The median PFS of 19.6 weeks is quite similar to the result in the GRID trial with regorafenib, described as 4.8 months.<sup>5</sup> The toxicity seems to be favourable compared with regorafenib in the GRID trial (e.g. grade 3–4 hand-foot skin reactions in 0% for the present trial and 20% in the GRID trial). Hypertension grade 3–4 was slightly more common for pazopanib in PAGIST (28%) than for regorafenib in GRID (23%).

All mutation analyses were carried out at highly experienced laboratories. There was no difference with respect to outcome based on primary mutation. This is not surprising, since the progression of advanced GIST in later treatment lines is driven by secondary mutations in *KIT*.

The plasma concentration of pazopanib was measured at week 12 and gave an indication that lower concentrations may give a worse disease control, but there is clear



**Figure 1. Progression-free survival.**  
CI, confidence interval.

uncertainty since removing one single observation makes the correlation non-significant.

The single-arm design of this trial was motivated by the fact that patients with a progressive GIST, which was a main eligibility criterion for the study, have an extremely poor PFS without any TKI at all. Thus, the placebo arm in the pivotal trial for the use of sunitinib in second line in GIST had a median PFS of only 1.5 months, despite enrolling patients with imatinib intolerance only.<sup>4</sup> The RIGHT trial comparing imatinib rechallenge with placebo, with so called best supportive care (BSC) in both arms, in patients with progression or intolerance on second-line sunitinib, showed a median PFS for the placebo arm of 0.9 months only.<sup>14</sup> The GRID trial on regorafenib also demonstrated a median PFS of 0.9 months for the placebo arm.<sup>5</sup> In the PAZOGIST trial, 15% in the BSC arm showed no progression after 4 months, but the trial allowed patients with intolerance for imatinib and/or sunitinib to be enrolled, which may include patients with a rather indolent course.<sup>8</sup> Even recently, the new TKI ripretinib was approved in the USA based on a placebo-controlled trial with a PFS for the placebo arm of 1.0 month.<sup>15</sup> Some of these placebo-controlled trials have a cross-over design for patients in the placebo arm, but in all studies, there are patients obviously too poor to benefit

from this possibility. Bearing this in mind, further trials in advanced GIST, controlled by placebo or BSC, must be discouraged as ethically doubtful.

Furthermore, in most trials in advanced GIST, eligibility has included intolerance for last TKI as an acceptable alternative to progressive disease. However, intolerance is seldom clearly defined. Since it is well known that the disease in many patients on TKIs for advanced GIST may be controlled by reduced doses in case of intolerance on full dose, there is an obvious risk that patients may be switched to a less active TKI based on intolerance before step-wise dose reduction to an acceptable dose has been carried out (e.g. from imatinib to sunitinib). Furthermore, when eligibility in a trial includes intolerance, it may be tempting to enrol patients with moderate toxicity. For this reason, the present PAGIST trial claimed progressive disease on the highest tolerable dose of all the used TKIs, whereas intolerance only was not enough. Thus, the trial tested pazopanib in patients truly refractory to earlier lines of treatment.

In summary, this phase II trial on pazopanib as third-line treatment in advanced and truly progressive GIST demonstrates a meaningful activity in the same order as regorafenib, and with a favourable tolerance.

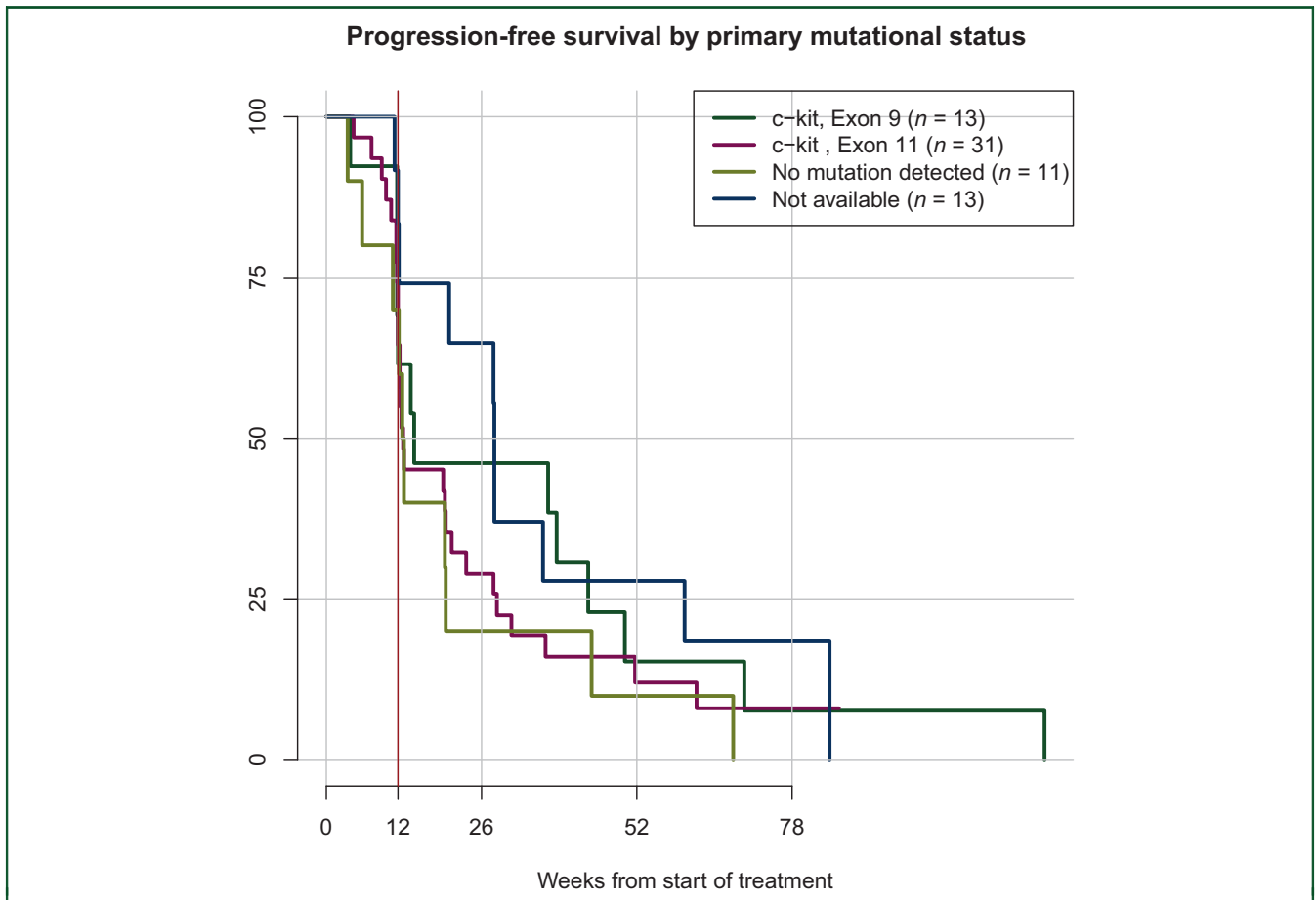


Figure 2. Progression-free survival (PFS) in relation to primary mutational status.

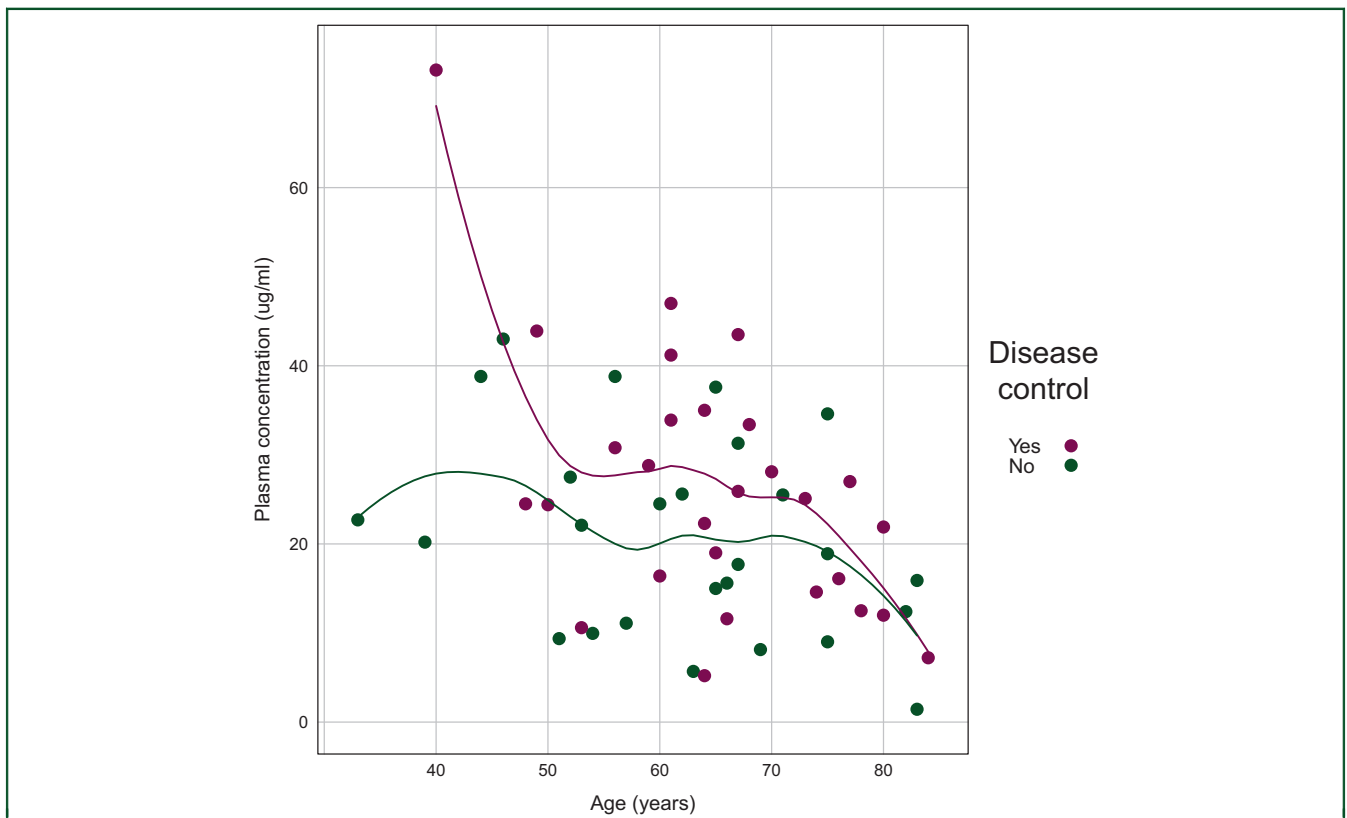


Figure 3. Plasma concentration of pazopanib 12 weeks after treatment start correlated with disease control when applying a linear model adjusting for age.

**Table 2. Grade 3 or 4 adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**

	N (%)
Hypertension	20 (28.2)
Diarrhoea	8 (11.3)
Fatigue	8 (11.3)
Anorexia	5 (7.0)
Abdominal pain	4 (5.6)
Proteinuria	3 (4.2)
Alkaline phosphatase increase	2 (2.8)
Nausea	2 (2.8)
Bilirubin increase	1 (1.4)
Abdominal distension	1 (1.4)
Neutropenia	1 (1.4)

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## DISCLOSURE

ME is a consultant for Blueprint Medicines and has participated in advisory boards for Clinigen and Bayer. He is a trial physician in the Scandinavian Sarcoma Group, which receives trial support from Novartis. PR reports advisory roles for Bayer, Clinigen, Roche, Merck Sharp & Dohme, Deciphera, PharmaMar, MundibioPharma, and Blueprint, and speaker's honoraria from Lilly and PharmaMar. HJ reports being Chair of the Scientific Advisory Boards for Maud Kuistila Foundation, Neutron Therapeutics, and Orion Pharma. He also reports a full-time or part-time employment at Orion Pharma until 31 August 2020. He owns stocks/shares in Orion Pharma and Sartar Therapeutics. SB reports personal fees from Deciphera, Lilly, Daichii-Sankyo, Plexikon, Exelixis, Bayer, PharmaMar, Roche, and GlaxoSmithKline. He reports grants and personal fees from Blueprint Medicines and Novartis. He reports grants from Incyte, and other support from Pfizer. All other authors have declared no conflicts of interest.

## REFERENCES

- Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med*. 2001;344:1052-1056.
- Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347:472-480.
- Joensuu H, Eriksson M, Sundby Hall K, et al. Survival outcomes associated with 3 years vs 1 year of adjuvant imatinib for patients with high-risk gastrointestinal stromal tumors. An analysis of a randomized clinical trial after 10-year follow-up. *JAMA Oncol*. 2020;6(8):1241-1246.
- Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368:1329-1338.
- Demetri GD, Reichardt P, Kang Y-K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:295-302.
- Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068.
- van der Graaf WTA, Blay J-Y, Chawla SP, et al. Pazopanib for soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379:1879-1886.
- Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care vs best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multi-centre, open-label phase 2 trial. *Lancet*. 2016;17:632-641.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guidelines (version 1.1). *Eur J Cancer*. 2009;45:228-247.
- Scandinavian Sarcoma Group Homepage. Available at <http://www.ssg-org.net>. Accessed July 11, 2021.
- Common Terminology Criteria for Adverse Events, v 4.0. May 28, 2009. US Department of Health and Human Services. National Cancer Institute.
- Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clin Trials*. 1989;10:1-10.
- Demetri GD, Wang Y, Wehrle E, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol*. 2009;27:3141-3147.
- Kang Y-K, Ryu M-H, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised placebo-controlled phase 3 trial. *Lancet Oncol*. 2013;14(12):1175-1182.
- Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2020;21:923-934.