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Review

Optimizing the dose of imatinib for treatment of gastrointestinal stromal tumours: Lessons from the phase 3 trials

Shreyaskumar Patel[a,*], *John R. Zalcberg*[b]

[a]*University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA*
[b]*Peter MacCallum Cancer Centre and Department of Medicine, University of Melbourne, East Melbourne, Australia*

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ABSTRACT

Imatinib therapy for unresectable or metastatic gastrointestinal stromal tumour (GIST) is typically initiated at a dosage of 400 mg/d. Two phase 3 studies investigated whether the higher dose of 800 mg/d – administered initially or upon progression on the 400-mg dose – would improve outcomes. Both the studies confirmed the 400 mg/d starting dose for most patients. However, two groups benefited from the treatment with 800 mg/d of imatinib: patients with disease progression on standard-dose therapy, and patients whose tumour harbours an exon 9 mutation in *KIT*. Initial treatment with 800 mg/d of imatinib (400 mg BID) should be considered for patients with *KIT* exon 9–mutant GIST. In unselected patients, dose optimisation to 800 mg/d may be warranted as a first step in managing progressive disease; such patients should be closely monitored.

1. Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract, occurring principally in the stomach or small intestine, and occasionally in the colon, rectum or oesophagus.[1] GIST accounts for 2% of all gastric tumours, 14% of tumours in the small intestine and 0.1% of those in the colon.[2] The annual incidence of GIST estimated from recent population-based studies is 10–15 cases per million persons.[3–5]

Approximately 95% of GISTs express KIT (CD117) – a transmembrane tyrosine kinase.[6] Under normal circumstances, binding of its ligand (stem-cell factor) promotes KIT dimerisation, enables tyrosine kinase activity, and activates various downstream signalling pathways. Activating *KIT* gene mutations are present in the large majority of GISTs (80–86%), most commonly (66% of cases) in the juxtamembrane domain (exon 11) of *KIT*, less frequently (13%) in the extracellular domain (exon 9) and rarely (1%) in the kinase 1 domain (exon 13) or (<1%) activation loop (exon

* *Corresponding author:* Tel.: +1 713 794 4632; fax: +1 713 794 1934.
E-mail address: spatel@mdanderson.org (S. Patel).
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17).[6] These gain-of-function mutations in GISTs lead to ligand-independent constitutive activation of the KIT receptor. In the subset of GISTs without *KIT* mutations, approximately one-third have activating mutations of the platelet-derived growth factor receptor alpha gene (*PDGFRA*, encoding PDGFRα).[7] These *KIT* and *PDGFRA* mutations are mutually exclusive, but they have similar consequences, causing constitutive activation of the expressed tyrosine kinase, thereby driving intracellular pathways involved in cell proliferation and survival.[7,8]

The clinical outcome of patients with advanced GIST was historically poor because this tumour is characteristically resistant to conventional chemotherapy and radiation therapy. In a cohort of 288 patients, median survival was 1.4 years for those with metastatic GIST and 3.4 years for those with primary tumours, classified as high-risk disease according to the National Institutes of Health consensus risk stratification.[5] Since the introduction of targeted therapy with imatinib, overall survival (OS) of patients with metastatic or unresectable GIST has increased markedly, reaching a median of 4.8 years in a pivotal phase 2 study of imatinib therapy for advanced GIST with 64 months of follow-up.[9] Imatinib is a small-molecule tyrosine kinase inhibitor with a potent and specific activity against KIT and PDGFRα.[10]

Imatinib is the recommended first-line agent for treatment of unresectable or metastatic GIST and recurrent disease.[11–13] The usual recommended starting dose is 400 mg/d. However, the clinical activity of imatinib in patients with advanced GIST was initially demonstrated in phase 1 and phase 2 studies at doses ranging from 400 mg/d to 1000 mg/d.[14–17] In the phase 1 study, dose-limiting toxicities were noted at the highest dose of 1000 mg/d, the lowest effective dose was 400 mg/d and the recommended dose for phase 2 studies was 800 mg/d. Two intergroup phase 3 studies investigated whether an imatinib dose of 800 mg/d, given initially or upon disease progression on the 400 mg/d dose, would further improve outcomes in patients with unresectable or metastatic GIST.

2. Description of the phase 3 studies

The European Organisation for Research and Treatment of Cancer (EORTC)/Italian Sarcoma Group/Australasian Gastrointestinal Trials Group study 62005 was conducted at 56 study centres in Europe, Australia, New Zealand and Singapore. The North American Intergroup study S0033 was carried out at 57 sites in the United States and Canada.[18,19] These trials enrolled patients with a biopsy-proven diagnosis of unresectable or metastatic GIST and documented expression of KIT by DAKO immunohistochemical staining. Patients aged 18 years or older with World Health Organization performance status of 0–3 were eligible for the European–Australasian study, whereas those aged 15 years or older with a Zubrod performance status of 0–3 were eligible for S0033. In both studies, previous chemotherapy was allowed if it had been completed at least 4 weeks before enrolment.

The design of the two studies was similar, but the European–Australasian trial 62005 registered a larger number of patients (946 versus 746).[18,19] Patients were enrolled from February 2001 to February 2002 in study 62005 and from December 2000 to September 2001 in study S0033. Patients were stratified by disease measurability and performance status (in addition to study site in the European–Australasian trial), and then randomly assigned to receive 400 mg/d or 800 mg/d of imatinib (400 mg twice daily) (Fig. 1). Imatinib was continued until disease progression or the development of unacceptable toxicity that could not be addressed by dose reduction or appropriate symptomatic treatment. In both studies, patients assigned to imatinib 400 mg/d were offered the option of crossover to 800 mg/d at the time of disease progression.

The European–Australasian study was designed to assess progression-free survival (PFS), whereas the North American trial was designed to compare both PFS and OS between the two dose levels.[19] The two studies were powered statistically similarly, although study 62005 eventually recruited more patients than S0033 and, therefore, was slightly more sensitive than study S0033 for detecting improvements in PFS at the

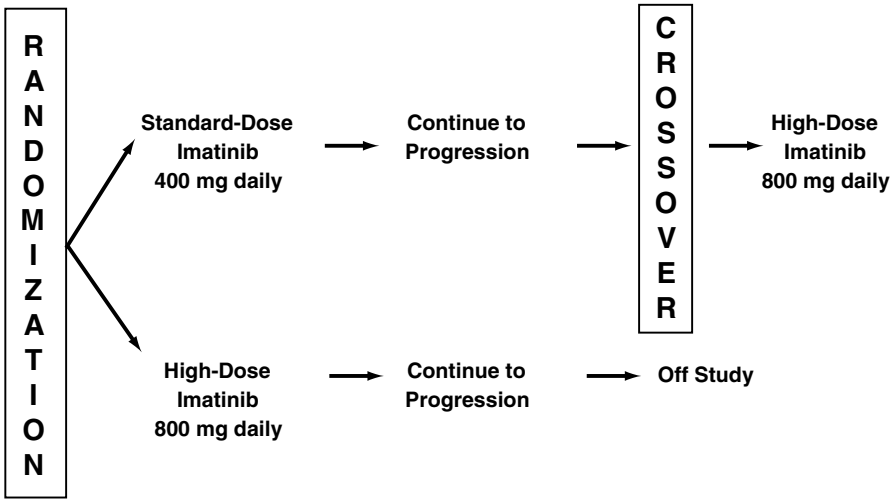

Fig. 1 – Design of the multinational, multicentre, randomized, phase 3 trials of imatinib 400 mg/d versus 800 mg/d.

Table 1 – Demographic and clinical characteristics of patients enrolled in European–Australasian Study 62005 and North American Study S0033[18,19]

Characteristic	62005		S0033	
	400 mg/d (*n* = 473)	800 mg/d (*n* = 473)	400 mg/d (*n* = 353)[a]	800 mg/d (*n* = 354)[a]
Median age, years (range)	59 (49–67)	60 (49–68)	61 (18–86)	61 (17–94)
Men, %	60	61	54	54
Performance status 0–2, %	96	96	96	96

a Eligible patients (*N* = 707); total of 746 patients were registered (400 mg/d, *n* = 376; 800 mg/d, *n* = 370).

800-mg/d dose. Response rates and toxicities were evaluated as secondary end-points in both studies, with study 62005 also considering OS as a secondary end-point. Treatment responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST).

3. Comparison of high-dose versus standard-dose imatinib

The European–Australasian study was published after a median follow-up of 760 d,[19] and the updated results have appeared in other published articles and abstracts.[20–22] To date, results of the North American study have been presented orally and in published abstracts.[18,23–25] Patients enrolled in the 2 trials were generally similar (Table 1).

3.1. *Dose reductions and toxicity*

Delays and adjustments in dosing were made in the event of severe neutropaenia or thrombocytopaenia, or grade 2 or worse non-haematologic toxicity.[19] Dose reductions were more likely in the 800-mg/d group than in the 400-mg/d group (60% versus 16% in the European–Australasian study, $P < 0.0001$; 44% versus 10% in the S0033 study, *P*-value not reported) and were usually because of non-haematologic toxicities.[19,23] Severe toxicities occurred in more patients treated with 800 mg/d than with 400 mg/d (50% versus 32% in study 62005; 57% versus 38% in study S0033, $P < 0.0001$ in both the studies).[18,19]Although the option to start at a higher dose of imatinib exists, there is no absolute proof at this time that starting at a dose of 800 mg/d in patients with a *KIT* exon 9 mutation is preferable to crossing over to a higher dose at the time of progression. However, the magnitude of the benefit in PFS despite the lack of a survival benefit suggests this is worth considering, especially if patients cannot be monitored extremely closely both clinically and by PET scan immediately after crossover.

3.2. *Response rates*

Objective response rates were independent of imatinib dose within each study and across the two studies (Table 2).[18,19] The response rates with the standard and high doses of imatinib were 50% and 54%, respectively, in the European–Australasian trial, and 48% in both the groups in the North American trial. Most patients had partial responses, although 5% in study 62005 and 3% in study S0033 had complete responses. As previously noted, responses were evaluated according to the RECIST criteria, which are suboptimal for the assessment of imatinib-treated GIST because they do not take into account the spectrum of anatomical changes (e.g. cystic degeneration, variable alterations in size) that occur in lesions responding to therapy.[26,27]As a result, RECIST-based assessments may underestimate objective responses. A subanalysis of the 62005 trial investigated whether achievement of an objective response, according to the RECIST criteria, had any predictive value for time to progression (TTP) and OS. The investigators concluded that RECIST criteria for response are optimal only for identifying imatinib-resistant GIST and are not adequate for the evaluation of imatinib efficacy.[22] An additional 32% of patients in the 62005 trial and 27% of patients in the S0033 trial achieved stable disease, a noteworthy finding because objective response and stable disease conferred a similar survival benefit in the long-term follow-up of the pivotal B2222 phase 2 trial.[28]

3.3. *Progression-free and overall survival*

In the European–Australasian trial after a median follow-up of 760 d (range 644–859) or 2.1 years, disease progression

Table 2 – Response rates in European–Australasian Study 62005 and North American Study S0033[18,19]

	62005		S0033	
	400 mg/d (*n* = 473)	800 mg/d (*n* = 473)	400 mg/d (*n* = 350)[a]	800 mg/d (*n* = 351)[a]
Complete response	24 (5%)	28 (6%)	12 (3%)	10 (3%)
Partial response	213 (45%)	229 (48%)	157 (45%)	157 (45%)
Stable disease	150 (32%)	150 (32%)	95 (27%)	91 (26%)
Progression/non-responders	61 (13%)	42 (9%)	86 (25%)	93 (26%)
Not assessable	25 (5%)	24 (5%)	NR	NR

NR, not reported.
a Number of patients for whom response and disease-control data were reported.

occurred in 56% and 50% of patients in the 400-mg and 800-mg initial-dosing groups, respectively.[19] The hazard ratio for the high dose compared with the standard dose was 0.82 (95% confidence interval [CI]: 0.69–0.98, $P = 0.026$). In the S0033 trial at a median follow-up of 768 d (range 70-1029), 527 of 746 patients (70.6%) were alive.[18] The 2-year estimates of PFS were 47% (95% CI: 42–53%) in the 400-mg group and 52% (95% CI: 47–57%) in the 800-mg group. The difference was not significant ($P = 0.13$), very likely because of the smaller sample size. Progression-free survival at approximately 2 years was essentially the same in both the studies (44% and 50% in 62005, and 47% and 52% in S0033 with imatinib 400 mg/d and 800 mg/d, respectively) (Fig. 2).[18,19] After 3 years of follow-up, however, the PFS advantage associated with the 800-mg dose in the European–Australasian trial was no longer significant.[29]

Median OS was not reached in either phase 3 study after 2 years of follow-up, thus confirming the superior efficacy of imatinib as compared with historical data for chemotherapy.[18,19] Two-year OS did not differ between the 400-mg and 800-mg groups in the European–Australasian (69% versus 74%, P-value not reported) and North American (76% versus 72%, $P = 0.87$) studies.[18,19] Taken together, the response and survival data in the phase 3 trials confirmed 400 mg once daily as the standard starting dose of imatinib for most patients with advanced GIST.

3.4. *Crossover to imatinib 800 mg/d after progression on 400 mg/d*

Patients with disease progression on the initial 400-mg daily dose of imatinib were eligible to cross over to 800-mg/d therapy in both studies. Crossover data from study 62005 were analysed after a median follow-up of 25 months.[30] A total of 133 (55%) of 241 patients crossed over to imatinib 800 mg/d within 2 months of documented disease progression. Median time on high-dose imatinib after crossover was 112 d (95% CI: 83–154 d), with 23% of patients estimated to remain on treatment for 1 year after crossover. Of the 98 patients in study S0033 included in the crossover analysis (April 2004), 24 (24%) were still receiving treatment per protocol.[18] Median time on treatment was not reported.

In general, patients who crossed over to 800 mg/d had not required a dose reduction during treatment with 400 mg/d. After crossover, the incidence of dose reductions was lower than that observed in the cohort initially assigned to receive 800 mg/d. In the European–Australasian study, 17% of patients required a dose reduction within 6 months of crossover, versus 49% during the first 6 months of initial 800-mg/d therapy.[27] In the North American study, 16% of patients with complete dosing information had a dose reduction after crossover.[23] Thus, crossover from 400 mg/d to 800 mg/d is feasible, particularly in patients able to tolerate the standard dose.

Toxicity before and after crossover to 800 mg/d was analysed in the European–Australasian trial.[30] Anaemia and fatigue were more likely to be worse after crossover ($P = 0.015$ and $P = 0.00001$, respectively), but neutropaenia was likely to be slightly less severe ($P = 0.002$). The haemoglobin level declined by about 10% during the first 8 weeks after crossover before stabilizing, which is consistent with the experience during initial 400-mg imatinib therapy. All other toxicities did not differ significantly in severity before and after crossover.

Three (2%) of the 133 patients who crossed over in the European–Australasian study had a partial response and 36 other patients (27%) had stable disease, for a clinical benefit rate of 29%.[30] The median duration of disease stabilisation in this group was 153 d (range, 37–574 d). Similarly, 5 of 77 evaluable patients (7%) had partial responses and 25 (32%) had stable disease following crossover in the North American study, for a clinical benefit rate of 39%.[18]

Median and 1-year PFS after crossover were 81 d and 18%, respectively, in the European–Australasian study (Fig. 3).[18,30] A competing risk analysis of disease progression versus death without progression showed that the treatment failure after crossover was predominantly due to disease progression rather than death (77.5% versus 4.4%). In study S0033, median PFS after crossover was 4 months and median OS was 15 months. The median OS compares favourably with a historical value of 9 months reported in the pre-imatinib era.[31]

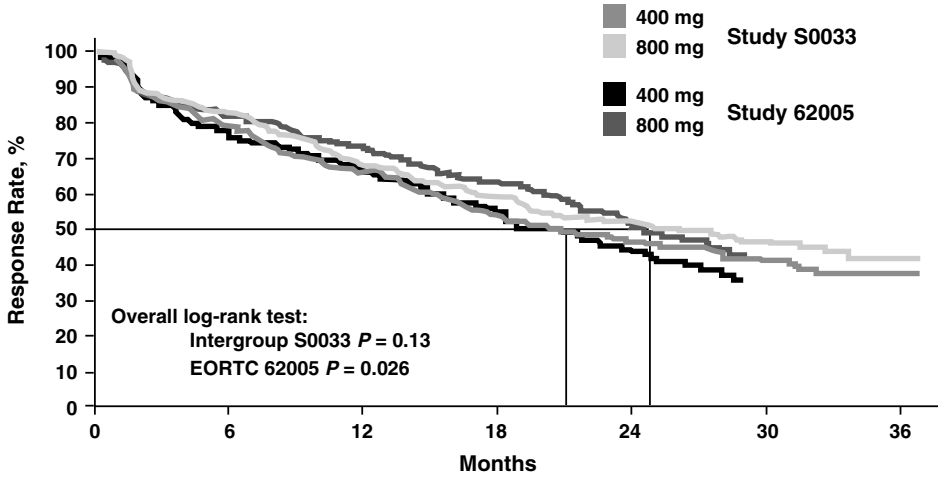

Fig. 2 – Progression-free survival (Kaplan–Meier estimates) with standard-dose (400 mg/d) and high-dose (800 mg/d) imatinib in European–Australasian study 62005 and North American study S0033.[18,19]

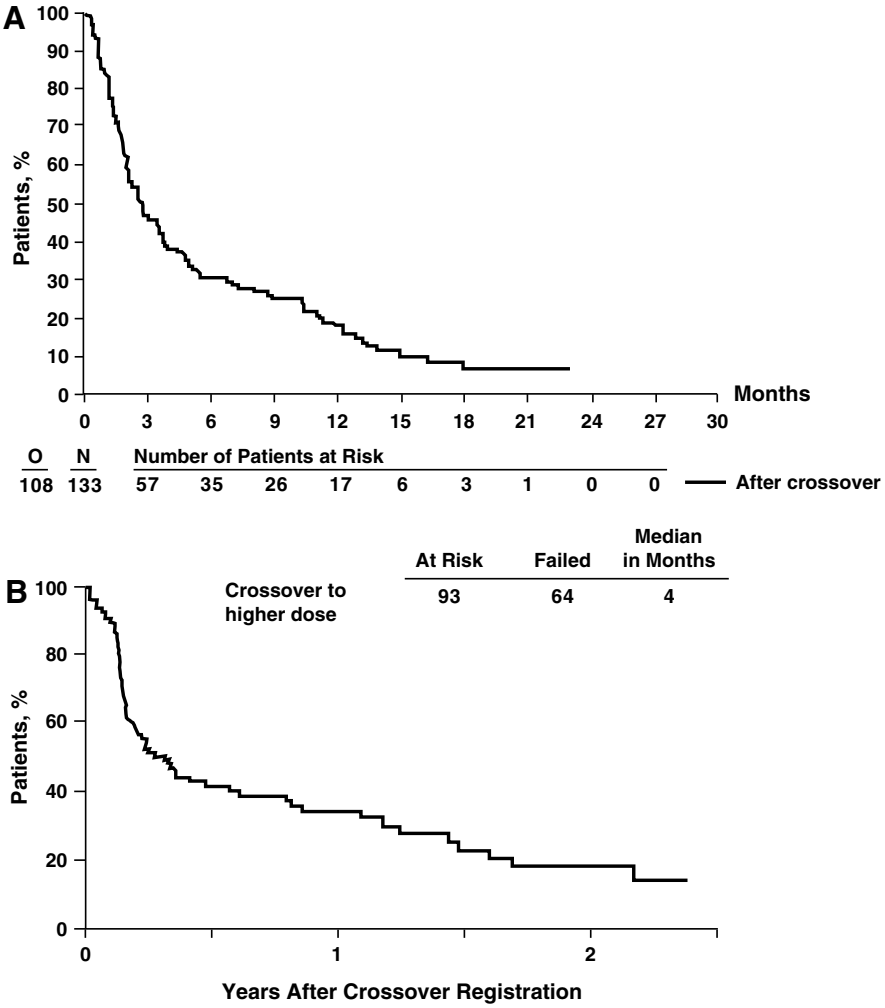

Fig. 3 – Progression-free survival after crossover from 400 mg/d to 800 mg/d in European–Australasian study 62005[27] (A) and North American study S0033 (B).[19] (A) Adapted with permission from Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer*. 2005;41:1751–1757.[30] (B) Reprinted with permission from Cathryn Rankin.[18]

Thus, crossover data from studies 62005 and S0033 show that a subset of patients – approximately 1 in 3 – with disease progression on imatinib 400 mg/d may benefit from a dosage increase to 800 mg/d. Clinical benefit after crossover to the higher dose was typically due to disease stabilisation, although some patients achieved partial responses. Some increase in toxicity was seen, but it was generally manageable, and dose reductions were not usually necessary.

4. Tumour mutational status and imatinib dose

In the European–Australasian study, pretreatment tumour specimens from 377 patients were analysed for mutations in exons 9, 11, 13, and 17 of *KIT*. Specimens with no detectable *KIT* mutation were analysed for mutations in *PDGFRA* exons 12 and 18.[32] Activating *KIT* mutations were detected in 315 of 377 tumours (83.6%), including mutations of exon 11 in 248 (65.8%), exon 9 in 58 (15.4%), exon 13 in 6 (1.6%) and exon 17 in 3 (0.8%). *PDGFRA* genotyping performed for 62 tumours without activating *KIT* mutations identified PDGFRα mutants in 10 (16.1%), usually involving point mutations or deletions in exon 18. In the North American trial, mutational status was evaluated in pretreatment specimens from 324 patients with KIT-positive GISTs.[24] KIT mutants were identified in 280 specimens (86.4%), and PDGFRα mutants in 3 (0.9%).

Clinical response to imatinib was related to tumour mutational status in both phase 3 studies. Patients with *KIT* exon 11 mutations had higher response rates than those with *KIT* exon 9 mutations or without *KIT* or *PDGFRA* mutations.[24,32] Response rates for these 3 patient subgroups were 69%, 34% and 25% in study 62005, and 67%, 40% and 39% in study S0033, respectively.

PFS was also related to tumour mutational status. After a median follow-up of 33 months in the European–Australasian study, patients with *KIT* exon 11 mutations had significantly better PFS and OS than those with *KIT* exon 9 mutations and those without detectable *KIT* or *PDGFRA* mutations.[32] Patients with exon 9 mutations had a 171% increase in the risk of progression relative to those with exon 11 mutations

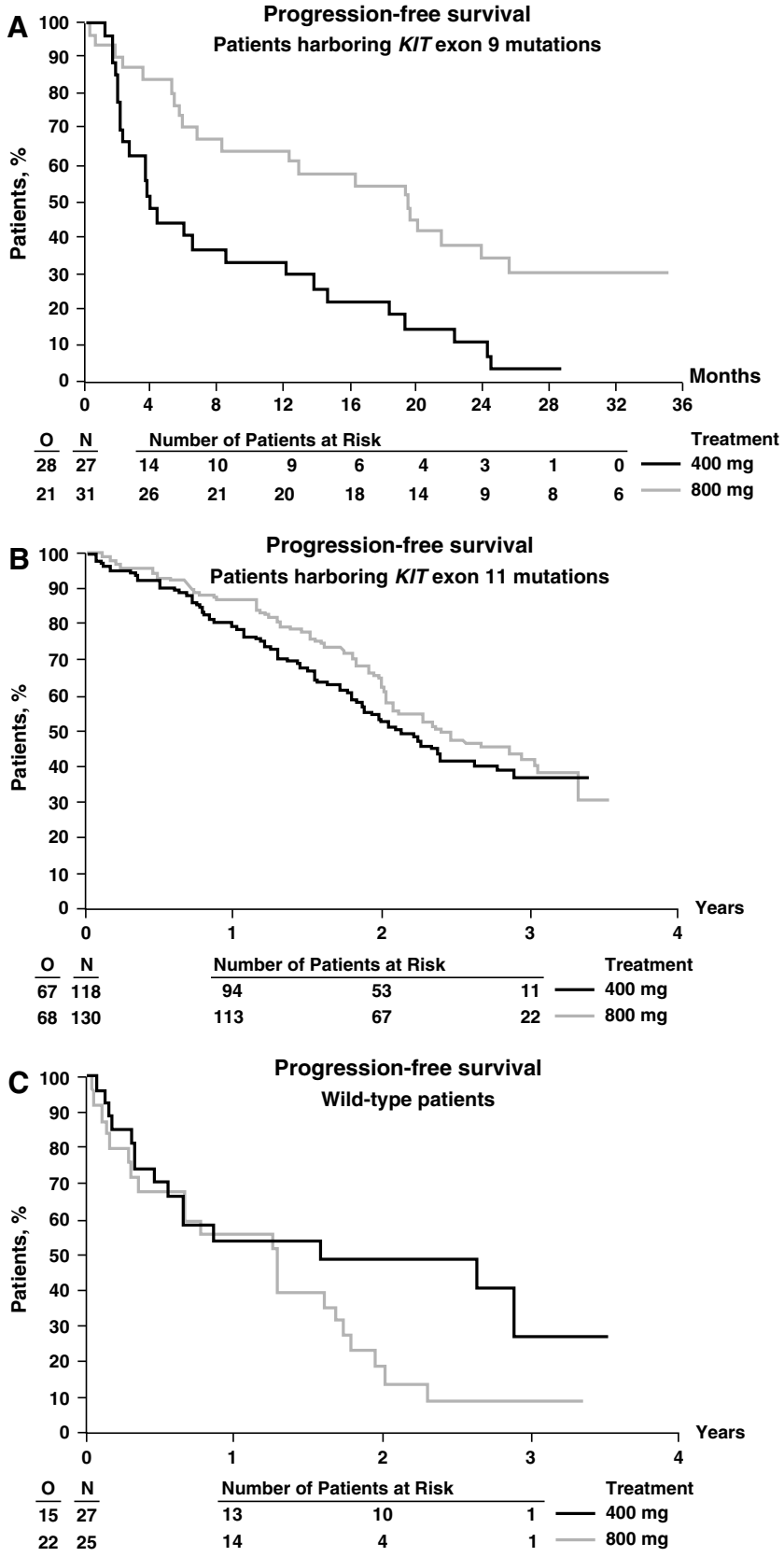

Fig. 4 – Impact of initial imatinib dose (400 mg/d versus 800 mg/d) on PFS in patients having tumours with *KIT* exon 9 mutations (A), exon 11 mutations (B), or no detectable *KIT* or *PDGFRA* mutations (C) in the European–Australasian trial 62005.[32] Adapted with permission from Debiec-Rychter M, Sciot R, Le Cesne A, et al. *KIT* mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer*. 2006;42:1093–1103.

($P < 0.0001$), and those without detectable mutations had a 108% relative risk increase ($P < 0.0001$). Similarly, in study S0033, patients with *KIT* exon 11 mutations had a significantly longer time to treatment failure than those with exon 9 mutations or without detectable kinase mutations (576, 308 and 251 d, respectively, $P = 0.007$).[24]

The impact of imatinib dose on PFS was associated with mutational status in the European–Australasian study.[32] Initial treatment with imatinib 800 mg/d resulted in significantly better PFS than 400 mg/d in patients with *KIT* exon 9 mutations (Fig. 4). The hazard ratio for the high dose relative to the standard dose was 0.39 (95% CI: 0.22–0.71, $P = 0.0013$), representing a 61% reduction in the risk of progression. In contrast, PFS was independent of initial imatinib dose in the subgroups with *KIT* exon 11 mutations ($P = 0.25$) or no detectable *KIT* or *PDGFRA* mutation ($P = 0.07$).

Survival results with respect to starting dose and mutational status were recently reported for the North American study in a meta-analysis of the phase 3 trials.[25] The meta-analysis was based on data from 1640 patients with a median follow-up time of 45 months. The significant PFS advantage observed with the 800-mg/d initial dose in patients with *KIT* exon 9 mutations in the European–Australasian study was not confirmed in the North American study. However, a significant PFS advantage was documented for the 800-mg starting dose in the pooled data set for all patients ($P = 0.041$) and for the total of 91 patients in the *KIT* exon 9–mutated subgroup ($P = 0.017$) (Table 3). Overall survival was the same for both initial doses. The results of this meta-analysis may have been influenced by population heterogeneity, as the North American trial included more women, more GISTs of bowel or stomach origin, fewer *KIT* exon 9 mutations, and patients with a lower baseline absolute neutrophil count.

The 62005 study showed that the clinical benefit of crossover from 400 to 800 mg/d of imatinib at disease progression was associated with the mutational status of the tumour. Responses to the dose increase (assessed using a growth modulation index) occurred most often in patients without detectable kinase mutations (83%) and in those with *KIT* exon 9 mutations (57%), and infrequently in patients with *KIT* exon 11 mutations (7%) (Fig. 5).[32] Thus, mutational analysis may be beneficial in predicting which patients are most likely to respond to imatinib 800 mg/d. In cases of patients with tumours with a *KIT* exon 11 mutation, close monitoring is required at the higher dose; at the first sign of progression, treatment with a next-generation tyrosine kinase inhibitor should be considered.

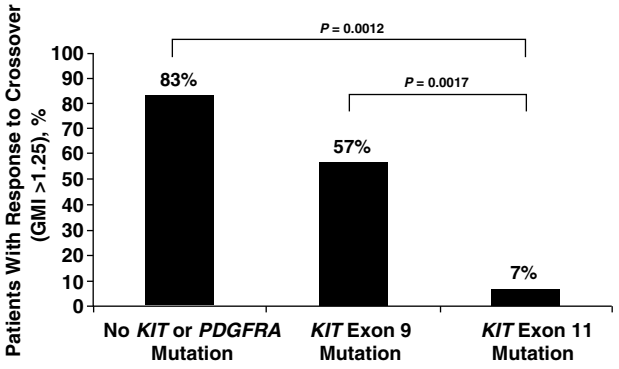

Fig. 5 – Response to crossover to imatinib 800 mg/d according to genotype in study 62005.[32] Response was assessed by a growth modulation index (GMI), defined as the ratio between time to progression after crossover and time to progression on standard-dose imatinib (400 mg/d). Patients with a GMI > 1.25 were considered to be responders.

5. Imatinib in KIT-undetectable GIST

Both phase 3 studies required immunohistochemical demonstration of KIT (CD117) positivity as a criterion for patient enrolment. On retrospective central pathology review, 14 patients in the North American trial were found to have KIT-undetectable GISTs.[33] Eight of these tumours were genotyped, with mutations in *KIT* or *PDGFRA* identified in 4 and 3

Table 3 – Survival results from a meta-analysis of European–Australasian Study 62005 and North American Study S0033

Cohort	N	Estimated median (years)		3-year estimated (%)[a]		HR	P-Value
		400 mg/d	800 mg/d	400 mg/d	800 mg/d		
PFS							
All	1640	1.58	1.95	30	34	0.89	0.041
62005	946	1.74	2.02	31	35	0.89	0.12
S0033	694	1.46	1.64	29	33	0.89	0.18
OS							
All	1640	4.08	4.05	60	61	1.00	0.97
PFS KIT Exon 9							
All	91	0.50	1.59	5	17	0.58	0.017
62005	59	0.35	1.62	0	25	0.43	0.0023
S0033	32	0.78	1.40	14	6	0.99	0.97

HR, hazard ratio; PFS, progression-free survival; OS, overall survival.
Adapted with permission from Van Glabbeke MM, Owzar K, Rankin C, Simes J, Crowley J, GIST Meta-analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of gastrointestinal stromal tumors (GIST): a meta-analysis based on 1640 patients (pts) [abstract]. *J Clin Oncol*. 2007;25 [Abstract 10004].[25]
a Kaplan–Meier method.

specimens, respectively. No difference in response rates was found between the patients with GISTs in which the KIT protein was not detected and those with KIT-positive tumours. Two-year PFS also did not differ between patients with KIT-undetectable and KIT-positive GISTs (43% versus 48%, $P = 0.41$), although 2-year OS was significantly lower for the KIT-undetectable group (57% versus 77%, $P = 0.007$).

This post hoc analysis suggests that imatinib can provide clinical benefit in patients with KIT-undetectable GISTs. Imatinib should not be withheld when the tumour location and phenotype are consistent with a GIST diagnosis but KIT is not detected. Equivocal diagnoses should be referred to an experienced GIST pathologist, and genotyping should be pursued.

6. Imatinib dose and plasma concentration

The rationale for prescribing imatinib at 800 mg/d either for initial treatment of patients with *KIT* exon 9–mutated GIST or in cases of disease progression at the standard dose in countries where this dose is readily accessible may be that higher blood and tissue concentrations may help overcome the apparent relative resistance of tumours carrying this mutation.[34] Plasma imatinib concentration was demonstrated to increase exponentially with increasing imatinib dose per square metre,[35] and imatinib exposure was found to be dose proportional for the dose range of 25–1000 mg.[34,36,37]

7. Conclusion

Imatinib is effective in more than 80% of patients with unresectable or metastatic GIST when administered at the standard starting dose of 400 mg/d. Phase 3 clinical testing identified 2 groups of patients who clearly benefited from treatment with 800 mg/d. First, approximately one-third of patients whose tumour progressed on the 400-mg initial dose had a partial response or stable disease after a dose increase to 800 mg/d. Second, patients with *KIT* exon 9 mutations experienced significantly increased PFS when treated with 800 mg/d initially, according to the evidence from the European–Australasian study and the meta-analysis of both phase 3 trials. Though initial dosing with 800 mg/d improved PFS in patients with a tumour with a *KIT* exon 9 mutation, this did not translate into better overall survival. In addition, increased toxicity and dose adjustments were associated with the 800-mg starting dose. However, 800 mg/d was generally well tolerated after crossover from 400-mg therapy. GISTs that were immunohistochemically negative for KIT also responded to imatinib.

Conflict of interest statement

S. Patel has received honoraria from Novartis and is a member of the Novartis Speaker's Bureau. J. Zalcberg has received travel support, honoraria, and clinical and research support as a member of various Novartis advisory boards. J. Zalcberg also was the principal investigator for the EORTC-Australasian Advanced GIST trial in Australia.

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