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ORIGINAL REPORT

Correlation of Kinase Genotype and Clinical Outcome in the North American Intergroup Phase III Trial of Imatinib Mesylate for Treatment of Advanced Gastrointestinal Stromal Tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group

Michael C. Heinrich, Kouros Owzar, Christopher L. Corless, Donna Hollis, Ernest C. Borden, Christopher D.M. Fletcher, Christopher W. Ryan, Margaret von Mehren, Charles D. Blanke, Cathryn Rankin, Robert S. Benjamin, Vivien H. Bramwell, George D. Demetri, Monica M. Bertagnolli, and Jonathan A. Fletcher

From the Oregon Health and Science University Cancer Institute; and Portland Veterans Affairs Medical Center, Portland, OR; Cancer and Leukemia Group B Statistical Center; and Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC; Cleveland Clinic Foundation, Cleveland, OH; Dana-Farber/Harvard Cancer Center; and Departments of Surgery and of Pathology, Brigham and Women's Hospital, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Southwest Oncology Group Statistical Center, Seattle, WA; The University of Texas M. D. Anderson Cancer Center, Houston, TX; and Tom Baker Cancer Centre, Calgary, Alberta, Canada.

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Corresponding author: Michael C. Heinrich, MD, Portland VA Medical Center and Oregon Health and Science University, Division of Hematology/Oncology, 3710 SW US Veterans Hospital Road, R&D-19, Portland, OR 97239; e-mail: heinrich@ohsu.edu.

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ABSTRACT

Purpose
Imatinib mesylate is standard treatment for patients who have advanced gastrointestinal stromal tumor (GIST), but not all patients benefit equally. In previous studies, GIST genotype correlated with treatment outcome and optimal imatinib dosing.

Patients and Methods
We examined the relationship between kinase genotype and treatment outcome for 428 patients enrolled on the North American phase III study SWOG S0033/CALGB 150105 and treated with either 400 mg or 800 mg daily doses of imatinib.

Results
The presence of *KIT* exon 11–mutant genotype (n = 283) correlated with improved treatment outcome when compared with *KIT* exon 9–mutant (n = 32) and wild-type (WT; n = 67) genotypes for objective response (complete response [CR]/partial response [PR], 71.7% *v* 44.4% [*P* = .007]; and 44.6% [*P* = .0002], respectively); time to tumor progression (TTP; median 24.7 months *v* 16.7 and 12.8 months, respectively); and overall survival (OS; median 60.0 months *v* 38.4 and 49.0 months, respectively). The survival outcomes for patients with exon 9–mutant, exon 11–mutant or WT GIST were not affected by imatinib dose. However, there was evidence of improved response rates for patients with exon 9–mutant tumors treated with imatinib 800 mg versus 400 mg (CR/PR, 67% *v* 17%; *P* = .02). Patients who had CD117-negative GIST had similar TTP but inferior OS compared with patients who had CD117-positive disease, which suggests that patients who have CD117-negative GIST may benefit from imatinib treatment. In addition, we identified novel but rare mutations of the *KIT* extracellular domain (exons 8 and 9).

Conclusion
We confirmed the favorable impact of *KIT* exon 11 genotype when compared with *KIT* exon 9 and wild-type genotype for patients with advanced GIST who are treated with imatinib.

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. In 1998, Hirota et al[1] made the seminal discovery that these tumors express the KIT tyrosine kinase and commonly harbor oncogenic mutations in the *KIT* gene. Subsequently, several investigators reported in vitro evidence of antitumor activity of the small molecule KIT inhibitor imatinib mesylate (Glivec/Gleevec; Novartis Pharma AG, Basel, Switzerland) against *KIT* mutant cell lines.[2,3] These observations led to clinical testing of this agent as a medical therapy for patients who have advanced disease.[4-7]

When the early trials were underway, laboratory studies revealed significant molecular heterogeneity among GISTs. Notably, 75% to 85% of GISTs had an activating mutation of *KIT*, 5% to 7% had an activating mutation of the homologous *PDGFRA* kinase, and approximately 12% to 15% of GISTs did not have a detectable mutation of either kinase.[8-11] Correlative molecular studies in phase I to II studies revealed significant differences in

objective response, progression-free survival (ie, time to tumor progression [TTP]), and overall survival (OS) between GISTs with different kinase genotypes. Specifically, the outcomes for patients with *KIT* exon 11–mutant GIST were better than for patients with *KIT* exon 9–mutant GIST or tumors without a detectable *KIT* mutation.[7,8,12]

Prospective studies of the relationship between kinase genotype and imatinib response were incorporated into two pivotal phase III trials that were designed to compare 400 mg and 800 mg daily doses of imatinib.[13-15] In this study, we examine the correlation between kinase genotype, imatinib dose, and clinical outcomes in 397 patients with GIST from the North American phase III trial.[14] Our findings confirmed that *KIT* exon 11 mutation is a positive predictive factor for objective response, TTP, and OS. This study also provides prognostic data for other GIST genotypes, including those with *KIT* exon 9 mutation, *PDGFRA* mutation, and wild-type (WT) status.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have a histologic diagnosis of CD117-positive GIST, as determined by immunohistochemistry with the DAKO polyclonal rabbit antibody (DAKO, Carpinteria, CA), that was deemed incurable (ie, metastatic or unresectable) by expert multimodality management. Institutional review board approval was obtained at each participating center. Each participant signed an institutional review board–approved, protocol-specific informed consent in accordance with federal and institutional guidelines.[14] Whenever possible, a tumor sample was collected and sent to the Cancer and Leukemia Group B Pathology Coordinating Office for diagnostic review by a single study pathologist (C.F.), which was followed by tumor genotyping (Appendix Table A1, online only).

Treatment Arms

Patients were randomly allocated to receive either the conventional dose (400 mg once daily) or a high dose (800 mg daily, given as 400 mg twice daily) of imatinib. Patients received treatment until disease progression or unacceptable toxicity occurred. Complete details and results from this study were reported recently.[14]

RESULTS

The main clinical study enrolled 746 patients who had advanced GIST between December 15, 2000 and September 1, 2001. Median follow-up was 4.5 years for patients who remained on study at the time of this report.[14] Tumor samples were obtained from 447 consenting patients, 428 of whom (95.7%) were successfully genotyped (Table 1; Fig 1). Of the 428 samples analyzed, central pathology review was performed on all but 36 patient cases, and it confirmed 368 (93.9%) of 392 as CD117-positive GIST. Another 10 were diagnosed as CD117-negative GIST, and 14 were non-GIST sarcoma. The 14 patient cases of non-GIST sarcoma included nine patient cases of leiomyosarcoma, one patient case of monophasic synovial sarcoma, one patient case of malignant peripheral-nerve sheath tumor, one patient case of well-differentiated liposarcoma (spindle cell type), one patient case of undifferentiated sarcoma with epitheloid morphology, and one patient case of epitheloid malignancy not otherwise specified (NOS). Patient cases not centrally reviewed were categorized as CD117-positive GIST on the basis of immunohistochemical staining performed at the enrolling institution.

Similar to previous reports, mutations in *KIT* exon 11 were the most common imatinib-target mutation found among the confirmed and unconfirmed CD117-positive GISTs (71.3% of patient cases), followed by mutations in *KIT* exon 9 (8.2%), *KIT* exon 13 (1.2%), *PDGFRA* exon 18 (1.2%), and *KIT* exon 17 (approximately 1%). One of 14 tumors judged to be a non-GIST sarcoma was found to have a *PDGFRA* mutation. On the basis of our experience and the published literature, intragenic *PDGFRA* gain-of-function mutations do not occur in other human sarcomas, so this was likely a GIST with unusual immunophenotypic (CD117-negative) and morphologic features.[9,16-21] However, on the basis of central pathology review and the study protocol, this case was classified as a non-GIST sarcoma (ie, epitheloid malignancy, NOS). Notably, this tumor had epitheloid morphology and had no immunohistochemical staining for CD117, CD34, desmin, smooth muscle actin, S100, or cytokeratin.

Thirty-three patients had *KIT* exon 9 mutations, of which 31 were the usual AY502-503 internal tandem duplication that has been

Table 1. Tumor Genotype Versus Tumor Pathology Status

	Pathology Status							
	Confirmed CD117+*		Confirmed CD117−†		Confirmed Non-GIST Sarcoma†		Unconfirmed CD117+‡	
Genotype	No.	%	No.	%	No.	%	No.	%
KIT 8	1	0.3	0	0.0	0	0.0	0	0.0
KIT 9	31	8.4	0	0.0	0	0.0	2	5.6
KIT 11	269	73.1	6	60.0	0	0.0	19	52.7
KIT 13	3	0.8	0	0.0	0	0.0	2	5.6
KIT 17	4	1.1	0	0.0	0	0.0	0	0.0
PDGFRA 12	0	0.0	0	0.0	0	0.0	1	2.8
PDGFRA 18	4	1.1	2	20.0	1	7.1	1	2.8
WT	56	15.2	2	20.0	13	92.9	11	30.6
Total	368		10		14		36	

Abbreviations: GIST, gastrointestinal stromal tumor; *KIT* 8, mutation of *KIT* exon 8; WT, wild type (no mutation of *KIT* or *PDGFRA*).
*Five patients were ineligible (3, *KIT* 11; 1, *KIT* 9; 1, *PDGFRA* 18).
†All patients were otherwise eligible except for pathology review.
‡Two patients were ineligible (both with *KIT* 11 mutations).

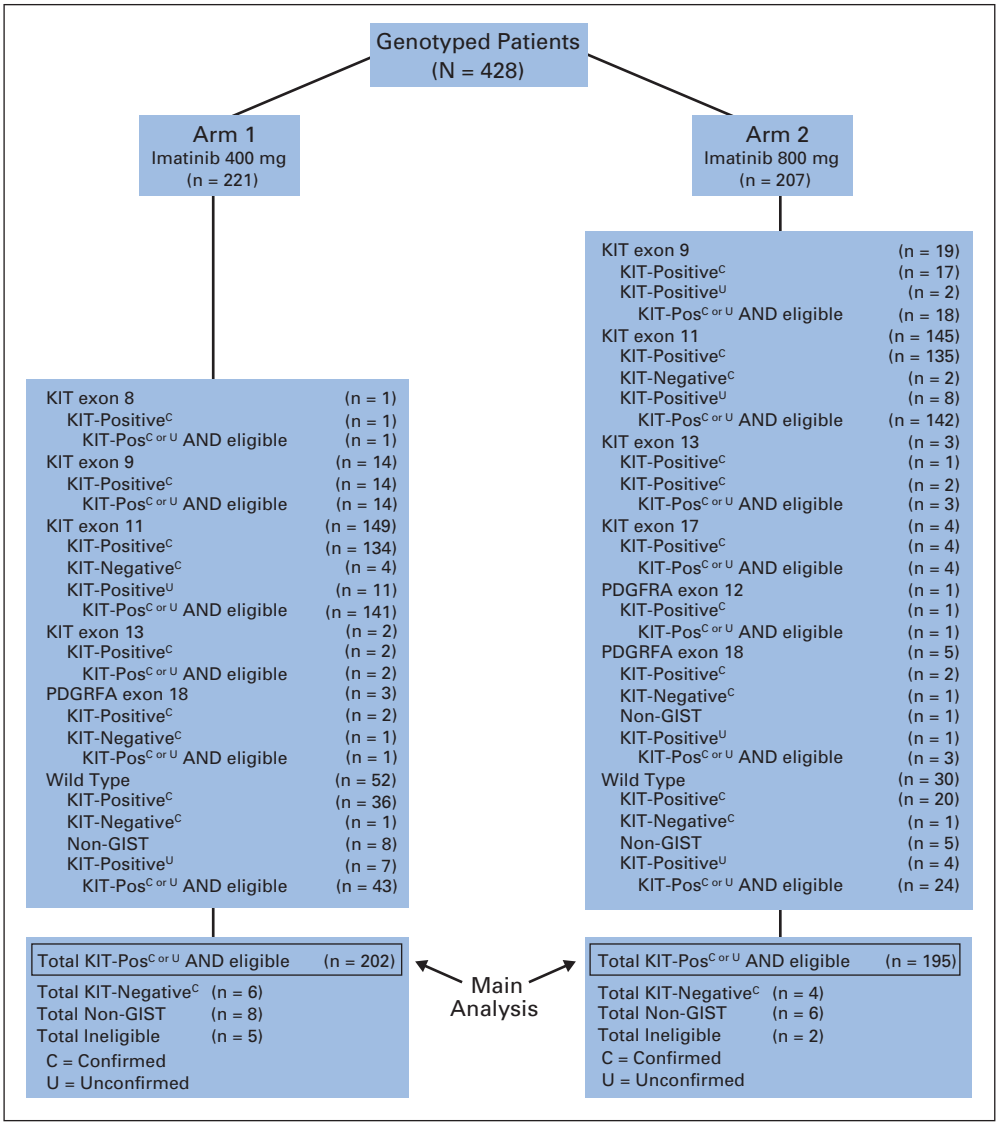

Fig 1. CONSORT diagram of Cancer and Leukemia Group B study 150105. GIST, gastrointestinal stromal tumor; Pos, positive.

reported previously.[8,22-24] However, two patients had variant exon 9 mutations. One was a tandem reduplication of codons 506 to 508 (FAF) after F508, which we have observed only once before in our series of greater than 1,500 genotyped GISTs.[8] The second was a novel homozygous deletion of codons 484 to 487 (KHNG). Imatinib response for these two variant exon 9–mutant cases was not assessed, but the TTP was 10.6 and 46.9 months for the patients with the 506 to 508 FAF tandem duplication and the deletion KHNG 484 to 487, respectively. In addition, we found one GIST with a *KIT* exon 8 deletion/substitution (TYD417-419Y). The only previous report of an exon 8 mutation in GIST was in a familial GIST kindred (deletion codon 419).[25] Germline DNA from surrounding normal tissue in our patient case was found to be WT; therefore, this patient represents the first example of a sporadic GIST with a *KIT* exon 8 mutation. The patient had an unconfirmed partial response to standard-dose imatinib (TTP, 8.1 months) and a censored OS of 59.3 months.

Eight patients had tumors with a *PDGFRA* exon 18 mutation. These mutations included the deletion/substitution IMHDS 843-847M (one patient case) and the deletion DIMH842-845 (three patient cases). As expected from in vitro data and previous clinical trials, the overall survival was more than 12 months for all four of these patients (mean 40.8 months).[8,26] There were four patients whose tumors harbored the substitution D842V, which has in vitro resistance to imatinib, including the case classified as epitheloid malignancy, NOS.[8,11,26] Three of these patients had a progression-free survival less than 2 months, while the fourth patient had not progressed as of 34 months of follow-up. The mean overall survival time was 9.7 months for these patients. A *PDGFRA* exon 12 V561D was found in the tumor from one patient, who had not progressed or died as of 31 months of follow-up.

Correlation of Tumor Genotype With Clinical Outcome (All Doses)

The primary objective of the correlative studies was to determine the effects of tumor genotype and/or imatinib dose on clinical outcome. For this analysis, we included all genotyped cases that met clinical eligibility criteria, except those that were categorized as CD117-negative or non-GIST sarcoma. The total was 397 of the 428 genotyped patients (Fig 1).

Table 2. Tumor Genotype Versus Objective Clinical Response for All CD117+ Tumors

	Genotype															
	KIT 8		*KIT* 9		*KIT* 11		WT		*KIT* 13		*KIT* 17		*PDGFRA* 12		*PDGFRA* 18	
Response	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
CR			1	3.1	18	6.4	3	4.5	0	0.0						
PR	1	100.0	11	34.4	162	57.2	22	32.8	2	40.0	1	25.0	1	100.0	1	25.0
SD			12	37.5	53	18.7	19	28.4	1	20.0	2	50.0			2	50.0
PD			3	9.4	18	6.4	12	17.9	1	20.0	1	25.0			1	25.0
NA			5	15.6	32	11.3	11	16.4	1	20.0						
Total	1		32		283		67		5		4		1		4	

NOTE. Responses were reported for both confirmed and unconfirmed tumors from eligible patients.
Abbreviations: *KIT* 8, mutation of *KIT* exon 8; WT, wild type (no mutation of *KIT* or *PDGFRA*); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessable.

The best clinical response to imatinib was classified as complete response (CR), partial response (PR), stable disease (SD), PD (progressive disease), or not assessable (NA) using RECIST criteria. After patient cases with unknown response (NA) were omitted, patients whose tumor had a *KIT* exon 11 mutation were significantly more likely to achieve a CR/PR than patients whose tumor had a *KIT* exon 9 mutation (71.7% *v* 44.4%; $P = .007$; Table 2), or WT genotype (71.7% *v* 44.6%, $P = .0002$). There was no statistically significant difference in the likelihood of achieving a CR/PR for patients with *KIT* exon 9–mutant GIST compared with WT GIST ($P = 1.00$).

TTP and OS for the entire study were reported previously.[14] There were no significant differences in TTP or OS between genotyped and nongenotyped patients (n = 299). Kaplan-Meier plots (Fig 2) demonstrated significantly longer TTP for patients whose GISTs contained a *KIT* exon 11 mutation compared with those whose GISTs had a *KIT* exon 9 mutation or no kinase mutation (ie, WT; $P = .0013$ and $P = .005$, respectively). In contrast, there was no significant difference in TTP between patients whose GIST had a *KIT* exon 9 mutation or WT genotype ($P = .46$). The median TTP was 24.7, 16.7, and 12.8 months for *KIT* exon 11–mutant, *KIT* exon 9–mutant, and WT GISTs, respectively.

OS was analyzed for these GIST subgroups: median OS was 60.0, 38.4, and 49.0 months for *KIT* exon 11–mutant, *KIT* exon 9–mutant, and WT GISTs, respectively (Fig 2). Patients whose GIST had a *KIT* exon 11–mutant kinase had a significantly longer OS than patients whose GIST had an exon 9–mutation or no kinase mutation (ie, WT; $P = .011$ and $P = .049$, respectively). In contrast, there was no significance difference in OS for patients whose GISTs had a *KIT* exon 9 mutation compared with those who had WT genotype ($P = .46$).

Correlation of Tumor Genotype and Imatinib Dose With Clinical Outcome

We examined whether there was any interaction of imatinib dose, GIST genotype, and clinical outcomes. There is borderline evidence that the degree of association between response and treatment arm depends on genotype ($P = .05$). In particular, patients with *KIT* exon–9 mutant GISTs had a significantly higher response rate when treated with IM800 compared with IM400 (CR/PR 17% *v* 67% for 400 mg and 800 mg, respectively; odds ratio [OR], 9.05; $P = .02$; Appendix Table A2, online only). In contrast, there were no differences in objective response rates for patient with *KIT* exon 11–mutant or WT GISTs treated with either dose of imatinib.

We also examined the effect of the assigned imatinib dose and genotype on TTP (Table 3; Fig 3). The differences between the treatment arms were not significant for the patients with *KIT* exon 11–mutant or WT GISTs ($P = .53$ and $P = .94$, respectively). Previously, Debiec-Rychter et al[15] reported that patients who had *KIT* exon 9–mutant GIST had a significantly increased median TTP when treated with imatinib 800 mg compared with imatinib 400 mg. However, in this study, the difference in TTP between the two treatment

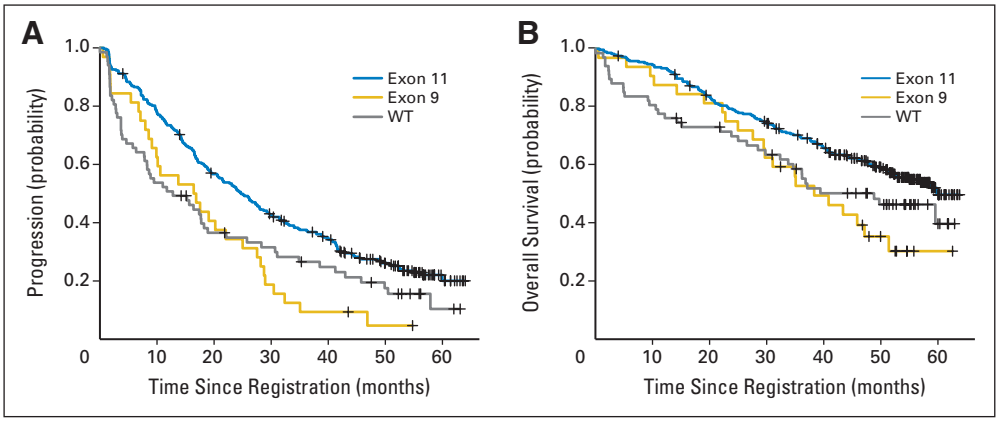

Fig 2. Correlation of gastrointestinal stromal tumor (GIST) genotype and time to progression or overall survival for patients with CD117-positive GISTs.

Table 3. Correlation of Imatinib Dose and Tumor Genotype With TTP and OS

Genotype	Treatment Arm	No. of Patients	TTP (months)	OS (months)
Exon 11	IM400	141	27.2	60.0
Exon 11	IM800	142	23.9	NR
KIT exon 9	IM400	14	9.4	38.6
KIT exon 9	IM800	18	18.0	38.4
WT	IM400	43	15.6	49.0
WT	IM800	24	9.8	39.5

Abbreviations: TTP, time to progression; OS, overall survival; IM400, imatinib 400 mg daily; IM800, imatinib 800 mg daily; NR, not reached; WT, wild type.

arms was not significant (9.4 months and 18.0 months for 400 mg and 800 mg, respectively; $P = .97$).

Similarly, the assigned imatinib dose did not affect OS for these three subgroups of patients with GISTs ($P = .99$ for exon 11, $P = .91$ for exon 9, and $P = .78$ for WT, respectively). The median OS for patients with GISTs who had *KIT* exon 11 mutations was 60 months and has not yet been reached for the 800-mg imatinib dose. The median OS for patients with GISTs who had *KIT* exon 9 mutations was 38.6 and 38.4 months for doses of 400 mg and 800 mg, respectively. The median OS for patients who had WT GISTs was 49.0 and 39.5 months for doses of 400 gm and 800 mg, respectively.

Among the 382 patients who had *KIT* exon 11 or exon 9 mutations or WT genotype, the following cofactors were identified in univariate analyses as statistically significant with respect to TTP: *KIT/PDGFRA* WT genotype, *KIT* exon 9 mutation, Zubrod performance status, absolute neutrophil count, and hemoglobin. In multivariate analysis, patients who had *KIT* exon 9 –mutant or WT genotypes had inferior TTP; hazard ratios were 2.07 ($P = .0008$) and 1.85 ($P = .0002$), respectively (Appendix Table A3, online only).

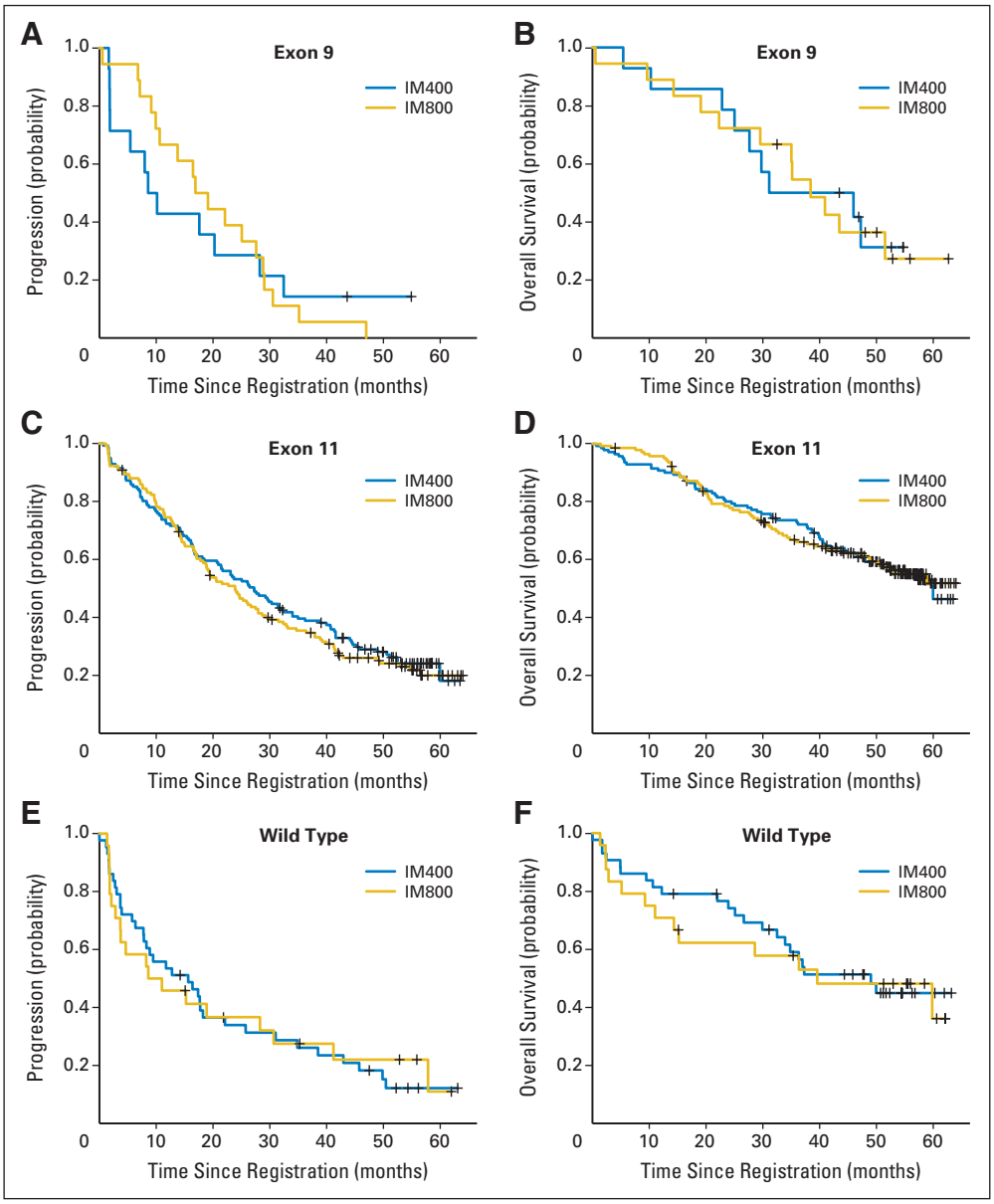

Fig 3. Correlation of tumor genotype (*KIT* exon 9–mutant, *KIT* exon 11–mutant, or wild-type tumors), imatinib dose (400 mg [IM400] *v* 800 mg [IM800]), and time to progression and overall survival for patients with CD117-positive gastrointestinal stromal tumors.

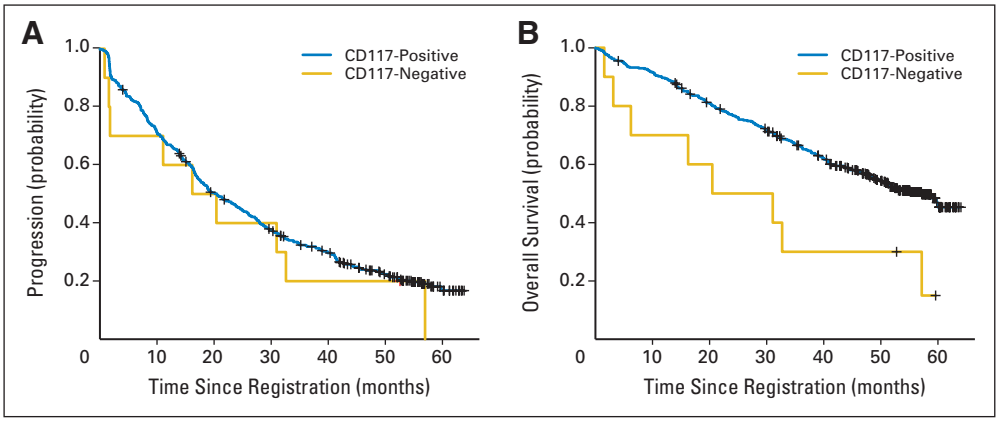

Fig 4. Comparison of time to progression and overall survival for patients with CD117-positive and CD117-negative gastrointestinal stromal tumors.

Patients who were men and who had a performance status of 2 to 3 also had shorter TTP.

In univariate analyses, *KIT* exon 9 mutation, *KIT/PDGFRA* WT genotype, age, sex, performance status, baseline hemoglobin, baseline absolute neutrophil count, and primary tumor site were significantly associated with worse OS (Appendix Table A4, online only). In multivariate analysis, *KIT* exon 9 genotype, *KIT/PDGFRA* WT genotype, male sex, increased age, performance status of 2 to 3, increased absolute neutrophil count, and lower hemoglobin were significantly associated with worse OS. Notably, the European Organisation for Research and Treatment of Cancer (EORTC) study did not find an association of male sex and worsened survival outcomes.[15,28]

CD117-Negative GISTs

To date, all phase I through III studies of imatinib for the treatment of advanced GIST have required that patients have CD117-positive tumors. At the time that these clinical studies were designed (2000 to 2001), it was widely believed that all GISTs were positive for this marker.[5,6,13,14] As a consequence, regulatory approval around the world for the use of imatinib in GIST treatment has been limited to CD117-positive tumors. It is now established that 2% to 5% of all GISTs are CD117-negative; many of these harbor a *PDGFRA* mutation.[17,18,19,21] To date, only anecdotal case reports have described clinical outcomes of patients with CD117-negative GISTs who are treated with imatinib.[27] Thirteen patient cases in our trial were confirmed on central review to be CD117-negative GISTs. Genotyping was performed on 10 of these patient cases, which represents the largest group of such tumors for which imatinib treatment outcomes are available.

Consistent with previous studies, kinase mutations were identified in eight of the 10 CD117-negative patient cases,[17,18] and *KIT* exon 11 mutations were present in six of these patient cases. The apparent absence of CD117 staining in these patient cases could reflect false-negative immunohistochemistry as a consequence of poor tumor fixation. Alternatively, the levels of KIT protein in these tumors may have been sufficient for oncogenic signal transduction but may have been less than the limit of detection by standard immunohistochemistry. Two of the CD117-negative patient cases contained *PDGFRA* exon 18 mutations (D842V and deletion IMHD842-846). Four of the six patients with *KIT* exon 11–mutant GISTs had CR (n = 1) or PR (n = 3) as the best objective response to therapy. The remaining two patients had SD or were nonassessable for response, respectively. None of the four patients with *PDGFRA*-mutant or WT CD117-negative GISTs had objective responses (PD, n = 3; NA, n = 1).

The TTP and OS of patients with CD117-negative GIST were compared with our main study population of CD117-positive tumors (Fig 4). The median TTP for CD117-negative GISTs was 18.3 months versus 20.5 months for CD-117 positive GISTs ($P = .46$). The median OS for the genotyped CD117-negative GISTs was 25.8 months versus 57.1 months for CD117-positive GISTs ($P = .01$). The median TTP and OS for the exon 11–mutant, CD117-negative GISTs were 31.9 and 44.9 months, respectively. These results are comparable to those seen for *KIT* exon 11–mutant, CD117-positive GISTs: 24.7 and 60.0 months, respectively ($P = .81$ and .42 for TTP and OS, respectively).

DISCUSSION

This prospective biomarker study of 397 patients who had genotyped CD117-positive tumors represents the largest genotyped collection of patients with GIST enrolled on a clinical study. The North American intergroup phase III trial was written in conjunction with another international phase III study (EORTC 62005) to determine the optimal imatinib dose for treating patients who have advanced GIST. Results from the EORTC trial have been published and will be compared with our current results.[13,15] The frequency and spectrum of *KIT* and *PDGFRA* mutations that were identified match well with the EORTC phase III trial and with other series. Similar to previous studies, these results confirm the favorable impact of the *KIT* exon 11 genotype on the response to imatinib therapy compared with GISTs that have *KIT* exon 9 –mutant or WT genotypes. This is evidenced by the following: superior objective CR/PR rates (71.7%, 44.4%, and 44.6% for *KIT* exon 11, *KIT* exon 9, and WT, respectively); superior TTP (median 24.7, 16.7, and 12.8 months for *KIT* exon 11, *KIT* exon 9, and WT, respectively); and superior OS (median 60.0, 38.4, and 49.0 months for *KIT* exon 11, *KIT* exon 9, and WT, respectively). There was no significant difference in OS between patients whose tumors had a *KIT* exon 9 –mutant or a WT genotype.

This study also addressed the relationship between GIST genotype, imatinib dose, and treatment outcome. Patients with *KIT* exon 9 –mutant GISTs who were treated with imatinib 800 mg had a higher objective response rate compared with patients who were treated with imatinib 400 mg. In contrast, there was no difference in objective response rates for patient with *KIT* exon 11–mutant or WT

GISTs who were treated with either dose of imatinib. However, there was no significant difference in TTP or OS between the two dose groups for any of the three largest genotype groups (ie, *KIT* exon 11–mutant, *KIT* exon 9–mutant, or WT). Multivariate analyses showed that GIST genotype significantly impacted TTP and OS. Other variables with significant impact included sex, patient age, and Zubrod performance status. Potentially, male sex might influence response to imatinib through pharmacokinetic (eg, body mass) and/or hormonal mechanisms.[28]

The EORTC study reported a significant improvement in TTP, but not OS, for patients with *KIT* exon 9–mutant GISTs who were treated with high-dose imatinib. We did not confirm this finding. However, there were 58 patients with *KIT* exon 9–mutant GISTs in the EORTC study[15] and only 32 in this study; this study is likely underpowered for detection of an impact of dose on TTP for this subgroup of patients with GISTs. In support of this hypothesis, the median TTP for patients with *KIT* exon 9–mutant GISTs who were treated with standard-dose imatinib in this study was 9.4 months compared with 18.0 months for patients who were treated with high-dose imatinib. Nine patients with *KIT* exon 9–mutant GISTs crossed over from the 400-mg to the 800-mg treatment arm at the time of progression, which potentially obscured any effect of dose on OS of patients with *KIT* exon 9–mutant GISTs. For patients with *KIT* exon 11–mutant or WT GISTs, our results agree with those of the EORTC report, which thus confirms that there is no effect of dose on objective response, TTP, and OS in these tumors.

The relatively large size of our treatment cohort allowed us to study clinical outcomes for genotyped CD117-negative patient cases. The TTP for this group was similar to that of CD117-positive patient cases, but OS was significantly shorter. Despite this, comparison of these results with historical chemotherapy outcome data[13] suggests that patients with CD117-negative GISTs, especially those with a *KIT* exon 11 mutation, may benefit from imatinib treatment.

From their inception, results from the North American and the EORTC phase III trials were intended to be integrated into a common data set for a prospectively planned combined analysis. This analysis will include the integration of clinical and molecular data; analysis of this combined data set should additionally define the relationship between genotype, imatinib dose, and clinical outcome of patients with advanced GIST who are treated with imatinib.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

Conception and design: Michael C. Heinrich, Christopher L. Corless, Ernest C. Borden, Christopher D.M. Fletcher, Christopher W. Ryan, Margaret von Mehren, Charles D. Blanke, Cathryn Rankin, Robert S. Benjamin, Vivien H. Bramwell, George D. Demetri, Monica M. Bertagnolli, Jonathan A. Fletcher
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Administrative support: Michael C. Heinrich, Donna Hollis, Ernest C. Borden, Christopher W. Ryan, Margaret von Mehren, Charles D. Blanke, Cathryn Rankin, Robert S. Benjamin, George D. Demetri, Monica M. Bertagnolli, Jonathan A. Fletcher
Provision of study materials or patients: Michael C. Heinrich, Christopher L. Corless, Ernest C. Borden, Christopher D.M. Fletcher, Christopher W. Ryan, Margaret von Mehren, Charles D. Blanke, Robert S. Benjamin, Vivien H. Bramwell, George D. Demetri, Monica M. Bertagnolli
Collection and assembly of data: Michael C. Heinrich, Kouros Owzar, Christopher L. Corless, Donna Hollis, Christopher D.M. Fletcher, Charles D. Blanke, Cathryn Rankin, Vivien H. Bramwell, George D. Demetri, Jonathan A. Fletcher
Data analysis and interpretation: Michael C. Heinrich, Kouros Owzar, Christopher L. Corless, Donna Hollis, Christopher D.M. Fletcher, Charles D. Blanke, Cathryn Rankin, George D. Demetri, Monica M. Bertagnolli, Jonathan A. Fletcher
Manuscript writing: Michael C. Heinrich, Kouros Owzar, Christopher L. Corless, Donna Hollis, Ernest C. Borden, Christopher D.M. Fletcher, Christopher W. Ryan, Margaret von Mehren, Charles D. Blanke, Robert S. Benjamin, Vivien H. Bramwell, George D. Demetri, Monica M. Bertagnolli, Jonathan A. Fletcher
Final approval of manuscript: Michael C. Heinrich, Kouros Owzar, Christopher L. Corless, Donna Hollis, Ernest C. Borden, Christopher D.M. Fletcher, Christopher W. Ryan, Margaret von Mehren, Charles D. Blanke, Cathryn Rankin, Robert S. Benjamin, Vivien H. Bramwell, George D. Demetri, Monica M. Bertagnolli, Jonathan A. Fletcher

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

