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Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST) from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (ISG), and Spanish Group for Research on Sarcomas (GEIS)

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Citation

Casali, P. G., Cesne, A. le, Velasco, A. P., Kotasek, D., Rutkowski, P., Hohenberger, P., ... Blay, J. Y. (2021). Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST) from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (ISG), and Spanish Group for Research on Sarcomas (GEIS). *Annals Of Oncology*, 32(4), 533-541. doi:10.1016/j.annonc.2021.01.004

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Note: To cite this publication please use the final published version (if applicable).

ORIGINAL ARTICLE

Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST) from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (ISG), and Spanish Group for Research on Sarcomas (GEIS)[☆]

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Available online 19 January 2021

Background: In 2004, we started an intergroup randomized trial of adjuvant imatinib versus no further therapy after R0-R1 surgery in localized, high/intermediate-risk gastrointestinal stromal tumors (GIST) patients. Interim analysis results were published in 2015 upon recommendation from an independent data review committee. We report the final outcome of the study.

Patients and methods: This was a randomized, open-label, multicenter phase III trial carried out at 112 hospitals in 12 countries. Patients were randomized to 2 years of imatinib, 400 mg daily, or no further therapy after surgery. The primary endpoint was imatinib failure-free survival (IFFS), while relapse-free survival (RFS), relapse-free interval (RFI), overall survival (OS) and toxicity were secondary endpoints. Adjusting for the interim analyses, results on IFFS were assessed on a 4.3% significance level; for the other endpoints, 5% was used.

Results: Nine hundred and eight patients were randomized between January 2005 and October 2008: 454 to imatinib and 454 to observation; 835 patients were eligible. With a median follow-up of 9.1 years, 5 (10)-year IFFS was 87% (75%) in the imatinib arm versus 83% (74%) in the control arm [hazard ratio (HR) = 0.87, 95.7% confidence interval (CI) (0.65; 1.15), $P = 0.31$]; RFS was 70% versus 63% at 5 years and 63% versus 61% at 10 years, [HR = 0.71, 95% CI (0.57; 0.89), $P = 0.002$]; OS was 93% versus 92% at 5 years and 80% versus 78% at 10 years [HR = 0.88, 95% CI (0.65; 1.21), $P = 0.43$]. Among 526 patients with high-risk GIST by local pathology, 10-year IFFS and RFS were 69% versus 61%, and 48% versus 43%, respectively.

Conclusions: With 9.1 years of follow-up, a trend toward better long-term IFFS in imatinib-treated patients was observed in the high-risk subgroup. Although the difference was not statistically significant and the surrogacy value of such an endpoint is not validated, this may be seen as supporting the results reported by the Scandinavian/German trial, showing a sustained small but significant long-term OS benefit in high-risk GIST patients treated with 3 years of adjuvant imatinib.

Key words: gastrointestinal stromal tumors (GIST), imatinib, adjuvant

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[☆]Note: Presented during oral session in ESMO 2017.

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0923-7534/© 2021 Published by Elsevier Ltd on behalf of European Society for Medical Oncology.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare cancers whose treatment in the advanced phase of disease has been a model of the way targeted therapies may impact the prognosis of sensitive advanced solid cancers.^{1,2} Imatinib is able to provide a median survival in excess of 5 years in the advanced setting, with a proportion of patients becoming long-term progression-free survivors in the range of 10%.³⁻⁵ The main limiting factor is secondary resistance, with a median time to its occurrence in the range of 2 years. Thus, it was logical to conceive imatinib as an adjuvant to surgery, looking at its prognostic impact on minimal residual disease.

In 2004, the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) launched a randomized clinical trial of adjuvant imatinib in collaboration with the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, the Italian Sarcoma Group (ISG) and the Spanish Group for Research on Sarcoma (GEIS). We decided to include all GIST patients with an 'intermediate' or 'high' risk of relapse, following the consensus classification used at the time, thus only excluding patients with low-risk disease. In subsequent years, a proportion of those eligible patients would have been considered to have a low risk as well. When designing the trial, we believed that a benefit in relapse-free survival (RFS) was more than likely, and decided that a meaningful benefit would have been in place only if it resulted in an increase in the cure rate, or, at least, in a substantial delay of relapses, provided no decrease in the time to progression was to occur when re-challenging relapsing patients with imatinib. Therefore, we chose overall survival (OS) as the primary endpoint of the trial. At a planned interim analysis in March 2009, it was clear to the study Independent Data Monitoring Committee (IDMC) that keeping OS as the primary endpoint would have been incompatible with a reasonable duration of the trial. We then conceived another primary endpoint, imatinib failure-free survival (IFFS), as an estimate of the time to resistance to imatinib, pragmatically defined as a survival interval to the date of switching to an alternate tyrosine kinase inhibitor at any time during or following the adjuvant period. As per recommendations of the IDMC, the interim analysis was published in 2015 while continuing the study follow-up to the planned final analysis; this is reported in this paper.⁶

PATIENTS AND METHODS

Study design and participants

This was a randomized, open-label, multicenter phase III trial carried out at 112 hospitals in 12 countries (Australia, Belgium, Denmark, France, Germany, Italy, New Zealand, Poland, Singapore, Spain, The Netherlands, UK). Patients could be randomized if they had a histologically proven diagnosis of primary resected GIST, with positive immunostaining for KIT (CD117), with risk of relapse documented on the surgical specimen, according to the 2002 National Institutes of Health (NIH) Consensus Diagnosis of GIST,⁷ as

'high risk' (tumor size >10 cm; or mitotic rate >10/50 high-power field (HPF); or tumor size >5 cm and mitotic rate >5/50 HPF), or 'intermediate risk' (tumor size ≤5 cm and mitotic rate 6-10/50 HPF; or tumor size >5-10 cm and mitotic rate ≤5/50 HPF). Surgery had to be carried out from 2 weeks to 3 months before randomization and surgical margins had to be either R0 or R1. Eligible patients were randomized (using minimization) after surgery either to receive imatinib (400 mg/day) for 2 years or to be followed without further antitumoral therapy. Randomization was stratified by center, risk category (high versus intermediate), tumor site (gastric versus other) and resection level (R0 versus R1). Neither patients nor investigators were masked to treatment allocation.

The study was approved by the institutional review boards and/or ethics committees of each participating institution.

METHODS

In the adjuvant arm, imatinib was administered for 2 years and treatment was discontinued in case of relapse of disease, unacceptable toxicity or withdrawal from study. Dose modifications for hematological and non-hematological adverse events were foreseen in the protocol. The study protocol did not specify the treatment to be administered following relapse. However, guidelines were circulated after amending the protocol, recommending re-starting imatinib at the dose of 400 mg daily and possibly 800 mg for patients with an exon 9 *KIT*-mutated GIST, with the only logical exception of those patients who relapsed during imatinib therapy.

While on treatment, patients were followed up every week for the first month, then every 2 weeks for the second month, then monthly until the end of the sixth month of therapy, and subsequently every 3 months until treatment discontinuation. Chest X-ray and abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI) were required within 1 month before randomization and every 3 months thereafter. After the end of treatment (treated arm) and after randomization (control arm), follow-up was carried out every 3 months until 2 years after randomization, then every 4 months until 5 years had elapsed, and thereafter at least annually, at the discretion of the responsible physician.

Outcomes

Details of the historical amendments to this study have been previously provided (REF JCO 2015). After study amendment, the primary endpoint of this study was IFFS, determined from the date of randomization to the date of start of a new systemic treatment, a combination of imatinib with any new systemic treatment or death from any cause, whichever occurred first. Secondary endpoints were RFS, OS and incidence of adverse events. RFS was measured from the date of randomization to the date of relapse (local and/or distant) or death, whichever occurred first. In the absence of such events, patients were censored at the date

of last follow-up or the clinical cut-off date, whichever occurred first. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistical analysis

Improvement of IFFS was considered clinically significant if the risk of imatinib failure was decreased by 34.5% in the adjuvant treatment arm relative to the reference group, corresponding to a hazard ratio (HR) of ≤ 0.655 . To detect such a difference using a two-sided log-rank test, and allowing for one interim analysis, a total of 196 events needed to be observed ($\beta = 0.2$). An interim analysis was planned and carried out after observation of 98 events, testing both for H0 and H1. After careful review, the IDMC recommended release of the interim results (REF JCO 2015). A power family of error spending function with a boundary parameter equal to 0.2 was used. An overall alpha level of 0.05 (two-sided test) was used, with a significance level of 0.015 dedicated to the interim analysis and 0.043 remaining available for the final analysis.

All efficacy analyses were carried out according to the intent to treat (ITT) policy. These time-to-event endpoints

were estimated using the Kaplan–Meier method and compared between the treatment arms using Cox models adjusted for the stratification factors. Safety analysis included patients who had started adjuvant therapy.

East (version 6.4) was used to calculate sample size and stopping boundaries; we did all other statistical analyses with SAS (version 9.4). This trial was registered with ClinicalTrials.gov, number NCT00103168. This report is based on all data available on 12 July 2017.

RESULTS

In total, 908 patients were randomized between 8 December 2004 and 20 October 2008; 454 were in the adjuvant imatinib arm and 454 in the observation arm (see [Figure 1](#)). All patient files were reviewed by the study coordinator and the clinical research physician at the EORTC headquarters. Seventy-two (7.9%) patients did not meet the eligibility criteria: 67 had an inappropriate diagnosis, 2 were ineligible due to prior treatment, 1 had concurrent malignant disease, 1 had a prior cancer less than 5 years ago and 1 had a presentation highly suggestive of retroperitoneal sarcoma. Median age was 59 years [interquartile range

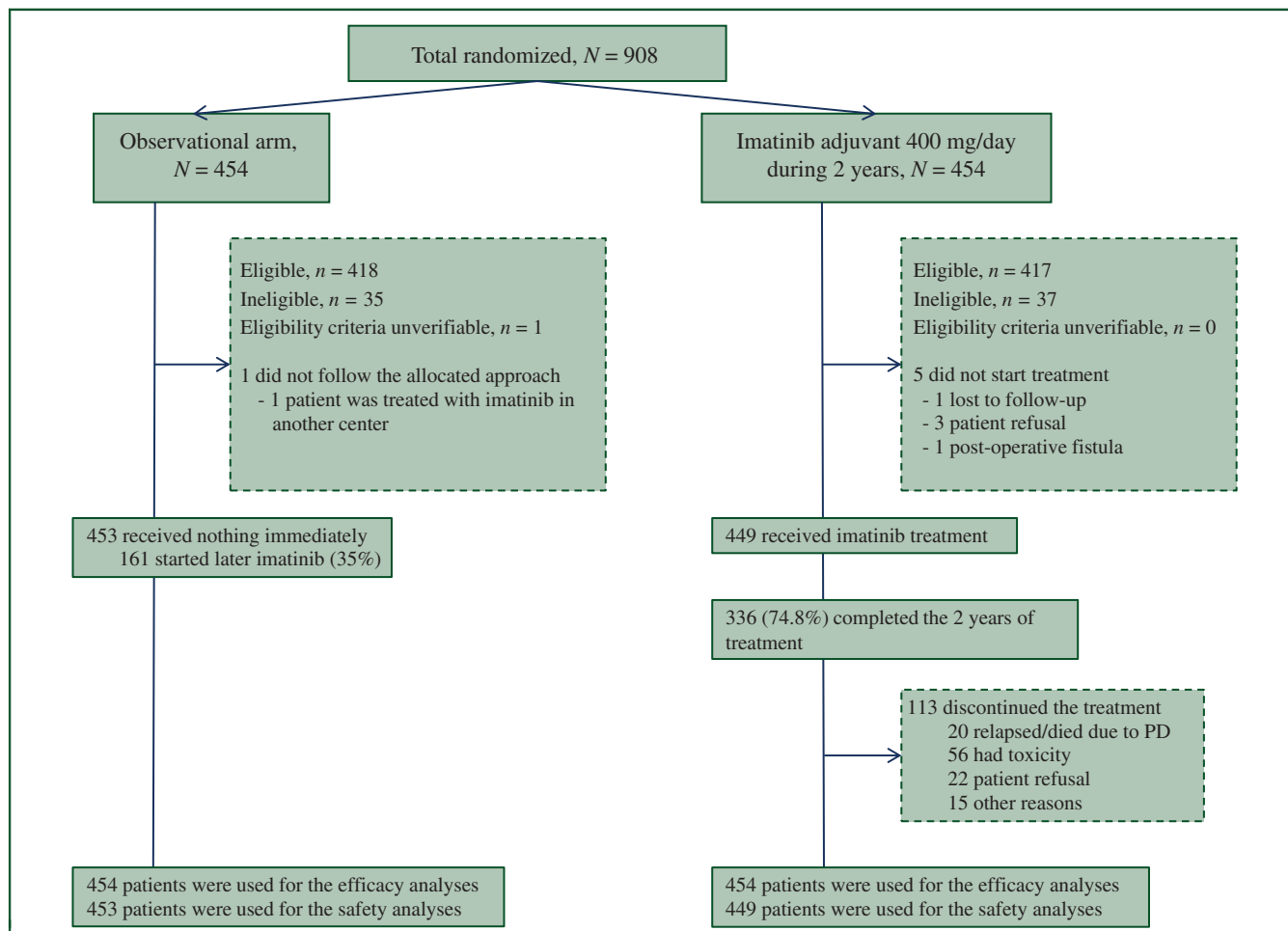


Figure 1. Consort diagram.
PD, progressive disease.

(IQR) 49–68], 51% were male, 86% had performance status (PS) 0, 55% of patients had a gastric GIST (Table 1).

Median follow-up for the final analysis was 9 years (IQR: 8–10). Figure 2A shows the IFFS curves by treatment arm. There was no significant difference between the arms [adjusted HR = 0.87, 95.7% confidence interval (CI) 0.65–1.15, $P = 0.307$]. Seven hundred and six patients remained imatinib failure free (358 versus 348), 142 patients (66 versus 76) were switched to a systemic treatment other than imatinib (including 99 patients to sunitinib, 12 to masitinib and 9 to nilotinib), and 60 patients (30 versus 30) died without starting new systemic treatment.

Relapse or death occurred in 326 patients (155 versus 171), with RFS significantly better in the adjuvant imatinib arm than in the observation arm (adjusted HR = 0.71, 95% CI 0.57–0.89, $P = 0.002$; Figure 2B). RFS rates were 70% versus 63% at 5 years and 62.5% versus 61% at 10 years. For OS, 158 patients died (75 versus 83), mostly due to progressive disease (49 versus 56). There was no OS significance difference between the treatment arms (adjusted HR = 0.88, 95% CI 0.65–1.21, $P = 0.429$; Figure 2C). In addition, survival did not differ between the two treatment arms in terms of point estimate rates (10-year survival rates 80% versus 78% in the imatinib arm versus observational arm, respectively). Sensitivity analyses with log-rank tests showed similar results (not presented here).

Two hundred ninety-nine patients received salvage imatinib on relapse (138 in the imatinib arm and 161 in the observation arm).

Figure 3 shows IFFS, RFS and OS broken down between the intermediate- and the high-risk subgroups following the criteria of the more recent Armed Forces Institute of Pathology risk classification⁷ into ruptured tumors, high-risk tumors (gastric: >5 cm and >5 mitoses; non-gastric: >10 cm or >5 mitoses) and low/intermediate-risk tumors (everything else).

Table 1. Main patient characteristics			
	Treatment arm		Total (N = 908)
	Observation (n = 454)	Imatinib adjuvant (n = 454)	
	n (%)	n (%)	n (%)
Performance status			
0	380 (83.7)	399 (87.9)	779 (85.8)
1	74 (16.3)	54 (11.9)	128 (14.1)
2	0 (0.0)	1 (0.2)	1 (0.1)
Sex			
Male	234 (51.5)	232 (51.1)	466 (51.3)
Female	220 (48.5)	222 (48.9)	442 (48.7)
Age (years)			
≤20	1 (0.2)	3 (0.7)	4 (0.4)
20–40	29 (6.4)	52 (11.5)	81 (8.9)
40–60	223 (49.1)	189 (41.6)	412 (45.4)
>60	201 (44.3)	210 (46.3)	411 (45.3)
Median	58	59	59
Range	20–89	18–86	18–89
Q1–Q3	49–68	48–67	49–68
Tumor site			
Gastric	254 (55.9)	250 (55.1)	504 (55.5)
Other	200 (44.1)	204 (44.9)	404 (44.5)

No significant differences in IFFS or OS were found in the subgroup of patients with a tumor rupture (Figure 4).

DISCUSSION

This is the final analysis of a randomized trial of adjuvant imatinib for 2 years versus observation in patients with resected localized GIST. It showed no significant difference in terms of its primary endpoint, i.e. IFFS, though a marked difference in RFS was observed, confirming available evidence that adjuvant therapy with imatinib in GIST substantially delays relapse, with a limited impact on more definitive endpoints. In fact, at a non-preplanned subgroup analysis, a trend of IFFS in favor of adjuvant therapy was observed in patients with high-risk tumors. If one assumed IFFS to be a surrogate endpoint for OS, this would be consistent with the possibility that adjuvant therapy may give some OS benefit in the long run, as observed in one of the other published trials, but the benefit would be limited.

Indeed, OS was the original primary endpoint of this trial. Given what was already known at the time the study protocol was drafted, we wrote in its rationale that ‘one may expect a striking benefit on the short-medium term in terms of RFS, but it is left to demonstrate whether this benefit may translate into a survival benefit’. Given the formidable impact of imatinib on the prognosis of GIST, we had then to give up OS as the primary endpoint of this study, but we consistently decided not to replace it with RFS. In agreement with the IDMC, we worked out IFFS as a new primary endpoint, assuming it could be the best conceivable surrogate for OS. In principle, IFFS corresponds to a survival interval to switching to an alternate tyrosine kinase inhibitor from the first used in the patient. The rationale why it could be a surrogate for OS is that the molecular landscape of GIST is so profoundly altered after secondary resistance to imatinib, with substantial molecular heterogeneity, that a limited benefit is foreseeable, at the moment, with any salvage therapy. Thus, it is logical that OS will be severely affected when secondary resistance arises. In practice, IFFS is marked by secondary resistance as its failure time, even if this occurs after imatinib has been re-established following relapse. On the contrary, the drawback of relapse as the failure time is that, after it occurs, imatinib can still be exploited, possibly for long periods of time. Then the patient could respond, and survival will be prolonged by the delay in relapse. The patient may respond less, and survival will be the same or even shorter than in patients not receiving imatinib as an adjuvant. Thus, under the only assumption that in most cases secondary resistance can be impacted to a limited extent by therapies, a first targeted therapy failure-free survival endpoint like IFFS may be a potential surrogate for OS in adjuvant trials on targeted therapies in solid cancers. However, although there is a clinical rationale supporting IFFS as a potential surrogate endpoint for OS, in the absence of data from other trials, no formal analysis of surrogacy could be carried out at the time. We believe that, if validated, such an endpoint could be of great interest for trials on the adjuvant use of molecularly targeted therapies in solid cancers. A practical limitation is

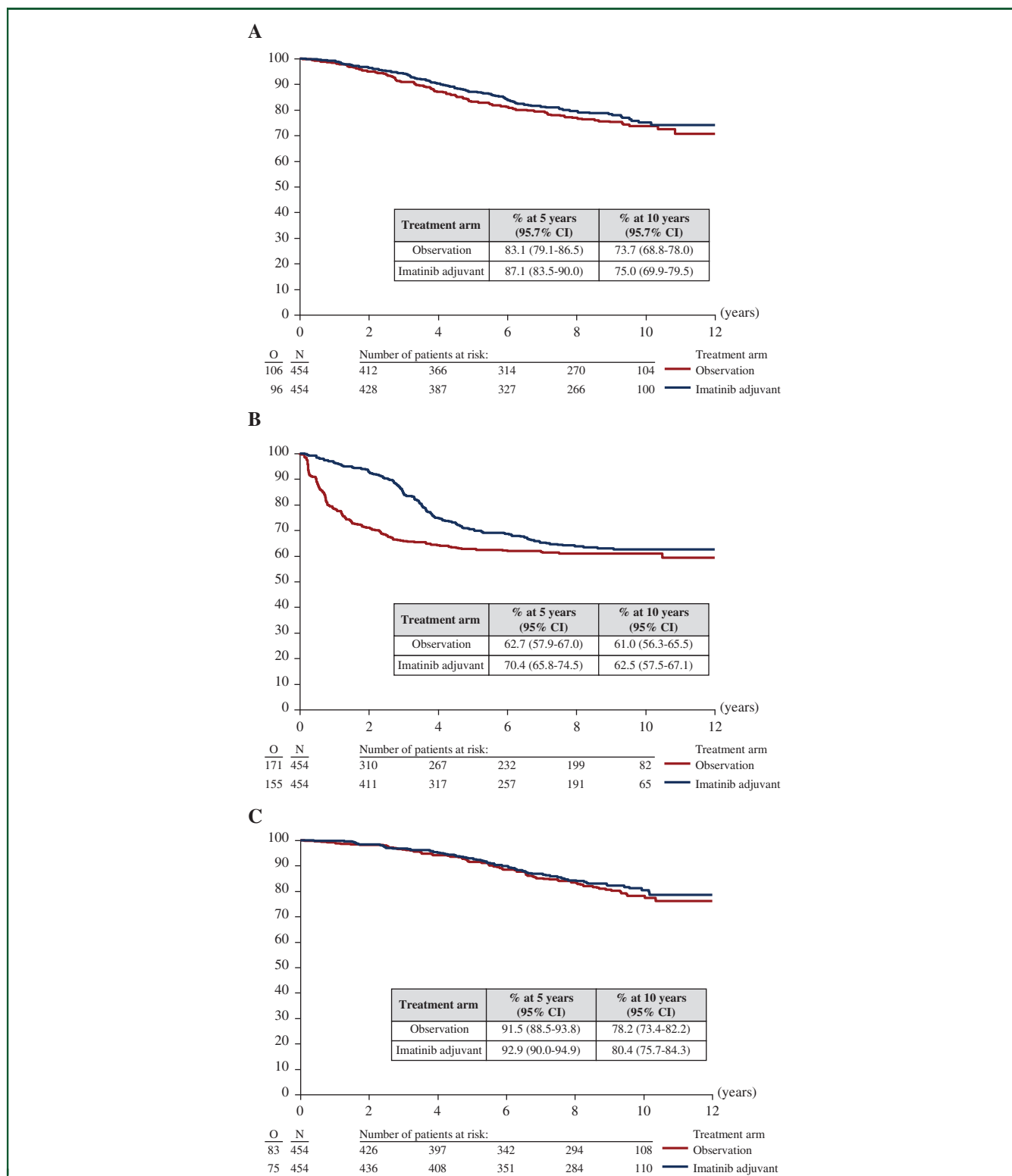


Figure 2. Imatinib monotherapy failure-free survival (A), relapse-free survival (B) and overall survival (C) by treatment arm. Adj., adjuvant; CI, confidence interval.

that the protocol should at least foresee recommendations on how to treat patients at relapse. This was not done in our study protocol and is thus a limitation of this trial. However, we later provided guidelines to participating institutions about selecting imatinib as treatment on relapse, and we

carried out sensitivity analyses on the final results, which do not seem to alter conclusions.

Therapeutically, what this and the other published trials clearly show is that up to 3 years of adjuvant imatinib do not lead to harm.^{8,9} On the contrary, a statistically

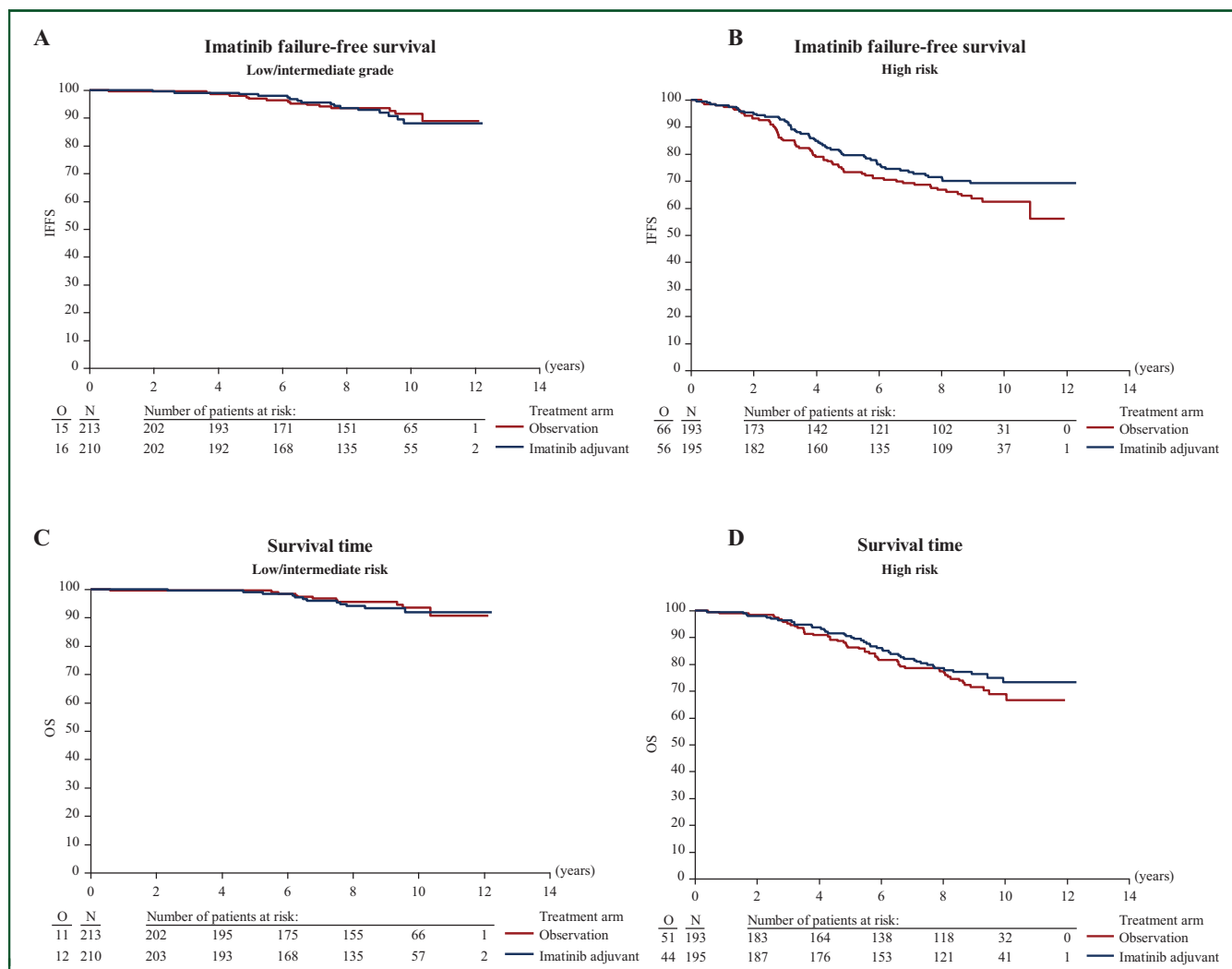


Figure 3. Imatinib monotherapy failure-free survival (A-B), and overall survival (C-D) by intermediate- (A, C) or high-risk (B, D) classification according to AFIP. AFIP, Armed Forces Institute of Pathology.

significant survival benefit was shown in the German/Scandinavian trial on 3 years versus 1 year, and the IFFS non-statistically significant trend in this trial may be regarded as being consistent with, and complementing, it, also considering that treatment duration was 2 years. Thus, an adjuvant therapy interval of 3 years is the standard today, while ongoing randomized trials are looking at the efficacy of longer intervals, i.e. 5 and 6 years, following an uncontrolled study exploring 5 years.¹⁰ Interestingly, in the face of the well-known good safety profile of imatinib, excluding relapsing patients, 21% of patients randomized to imatinib did not complete their 2-year adjuvant treatment period. This parallels what was observed in the other adjuvant trials: in the German/Scandinavian trial, 27% in the 3-year group and 13% in the 1-year group stopped their therapy earlier due to reasons other than recurrence. This should be factored in when planning trials on adjuvant therapy with oral therapies administered continuously. Clearly, even low-grade toxicities from continuous therapies may impact the patient's quality of life substantially. Unfortunately, this trial did not foresee any formal quality of life assessment. Of course, another reason for early treatment interruptions

within trials may well be the experimental intent perceived by patients.

This was a large trial that was repeatedly amended in order to preserve its statistical power on patients having a significant risk of relapse. In fact, when the study was conceived, we decided to enroll patients with an intermediate and high risk of relapse according to the 2002 NIH Consensus classification.⁷ Actually, some of these patients then turned out to carry a low risk of relapse.^{11,12} This is the reason why we broke down the analysis according to widely accepted current risk criteria, namely according to the Armed Forces Institute of Pathology classification. In practice, we singled out patients with a risk of relapse >50%, and this is the patient population in which a trend of IFFS in favor of adjuvant imatinib was seen. In fact, it is currently common practice to treat those patients with such a risk while sharing the decision with patients with a risk in the range of 30%-50%.¹³

In this trial, we included patients with both R0 and R1 resections, as well as patients who had tumor rupture (within the R1 stratum). The proportion of the latter was 11%. A panel of surgeons reviewed original surgical reports and their findings are the subject of a separate paper now

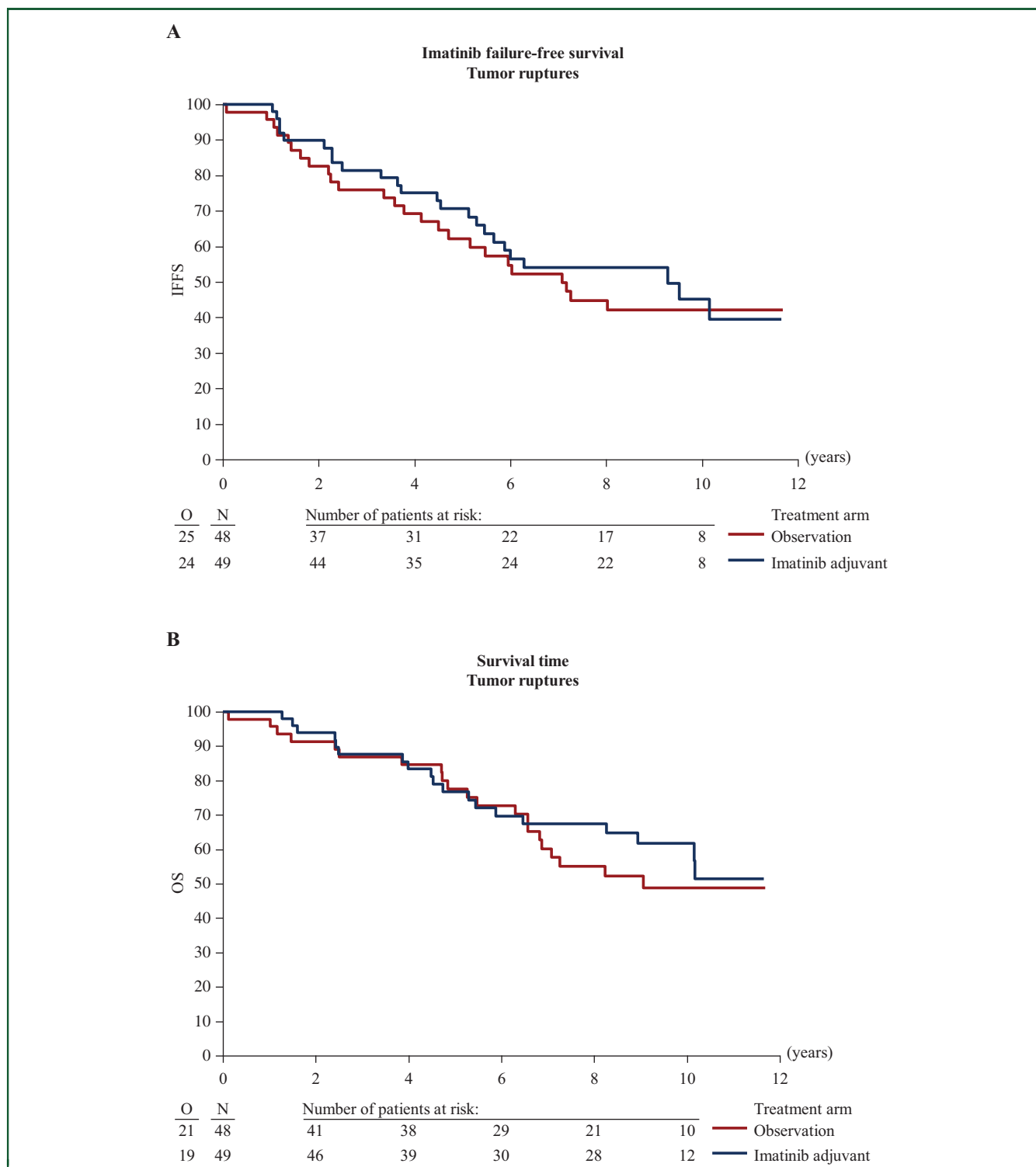


Figure 4. Imatinib failure free survival (A) and overall survival (B) for patients with tumor rupture.

published.¹⁴ This showed that presence of R1 margins was not associated with worse OS when patients with rupture were excluded. Likewise, the prognostic correlations of mutational analysis will be the subject of a distinct analysis. Indeed, at the time when this trial was conceived we could not exclude imatinib-insensitive mutations or modulate drug dosages depending on the kind of KIT mutation.

The final analysis of this trial confirms the efficacy of adjuvant therapy with imatinib in localized GIST in terms of RFS. For both OS and its potential surrogate we defined in this trial, i.e. IFFS, the study data did not show an effect in favor of adjuvant therapy overall, but a trend was observed in the high-risk group. This is consistent with the OS benefit recently reiterated in the German/Scandinavian trial and

may attenuate a mismatch between RFS and OS that undoubtedly marks the efficacy of adjuvant targeted therapy in GIST.⁹ At the moment, adjuvant therapy with imatinib for 3 years is standard treatment in GISTs with a significant risk of relapse.¹³

ACKNOWLEDGEMENTS

We thank Anne Kirkpatrick, Axelle Nzokirantevye, Christine Olungu, Monia Ouali, Martine Van Glabbeke and the other staff at EORTC headquarters who contributed to the success of the trial.

We are grateful to all the patients who took part, and their relatives, and thank the participating investigators and centers who worked on the study, in addition to those mentioned as co-authors, from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), including V. Grünwald (Medizinische Hochschule Hannover, Hannover, Germany), J. Verweij (Erasmus MC Cancer Institute, Rotterdam, The Netherlands), S. Rodenhuis (The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands), P. Schöffski (University Hospitals Leuven, KU Leuven, Leuven, Belgium), P. Ebeling (Universitaetsklinikum Essen, Essen, Germany), M. Leahy (The Christie NHS Foundation Trust, Manchester, UK), P. Reichardt (HELIOS Klinikum Berlin-Buch, Berlin, Germany), M. Schlemmer (Klinikum der Universität München, Campus Grosshadern, München, Germany); from the Australasian Gastro-Intestinal Trials Group (AGITG) with the NHMRC Clinical Trials Centre (CTC), including M. Smithers (Princess Alexandra Hospital, Brisbane, Australia) and J. Simes (NHMRC Clinical Trials Centre, Sydney, Australia), K. Wilson (NHMRC Clinical Trials Centre, Sydney, Australia); from the Italian Sarcoma Group (ISG), including G. Grignani (Fondazione del Piemonte per l'Oncologia, Institute for Cancer Research and Treatment, Candiolo, Italy), G. Biasco (Policlinico S. Orsola-Malpighi, Bologna, Italy), A. Comandone (Ospedale Gradenigo, Torino, Italy), from UNICANCER including O. Bouche (CHU de Reims, Hôpital Robert Debré, Reims, France), J. L. Raoul (Centre Eugene Marquis, Rennes, France); from the French Sarcoma Group (FSG), including E. Bompas [Institut de Cancerologie de l'Ouest (ICO), Centre Rene Gauducheau, Nantes/St. Herblain, France]; from Grupo Español de Investigación en Sarcomas (GEIS) including X. Garcia del Muro [ICO L'Hospitalet, Hospital Duran i Reynals (Institut Catala D'Oncologia), L'Hospitalet de Llobregat, Spain], A. Lopez Pousa (Hospital De La Santa Creu I Sant Pau, Barcelona, Spain); and the following pathologists for performing the central review for EORTC STBSG: C. Fisher (Royal Marsden Hospital, Chelsea, London, UK), E. Wardelmann (Gerhard Domagk Institute of Pathology, University Hospital Münster, Münster, Germany), P. C. W. Hogendoorn (Leiden University Medical Center, Leiden, The Netherlands), R. Sciot (UZ Leuven, Campus Gasthuisberg, Leuven, Belgium), S. Daugaard (University of Copenhagen, Copenhagen, Denmark); for UNICANCER, J. M. Coindre (Institut Bergonie, Bordeaux, France); for AGITG, S. Pieterse (Adelaide Pathology Partners, Adelaide, Australia);

for GEIS, A. Llombart-Bosch (Department of Pathology, University of Valencia, Valencia, Spain); and for ISG, P. Collini (Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy).

FUNDING

We are grateful to Novartis for supporting this independent EORTC study.

DISCLOSURE

In the last 3 years, PGC had honoraria for speaker, consultancy or advisory role from Bayer, Deciphera, Eisai, Eli Lilly, Pfizer. At PC's institution, PC Unit received funds from Advenchen Laboratories, Amgen Dompé, AROG Pharmaceuticals, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera, Eisai, Eli Lilly, Epizyme Inc., Glaxo, Karyopharm Pharmaceuticals, Novartis, Pfizer, PharmaMar. At EF's institution, PC Unit received funds from Advenchen Laboratories, Amgen Dompé, AROG Pharmaceuticals, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera, Eisai, Eli Lilly, Epizyme Inc., Glaxo, Karyopharm Pharmaceuticals, Novartis, Pfizer, PharmaMar. IRJ had honoraria from the Institute of Cancer Research. AI had honoraria from Epizyme, Bayer, Lilly, Roche, SpringWorks Therapeutics and non-financial support from Epizyme, Merck; AI's institution had research grants from AstraZeneca, Bayer, Chugai, MSD, BMS, Novartis, Roche. ALC had honoraria from PharmaMar, Deciphera, Lilly, Bayer. PR received honoraria from Novartis, Pfizer, MSD, BMS, Merck, Pierre Fabre, Roche, Sanofi for lectures and advisory boards. FD had honoraria from Bayer, Leo Pharma, PharmaMar, Lilly and funding for travel/for meetings from PharmaMar, Leo Pharma. DG: advisory role for Deciphera. JMB had honoraria for advisory board participation and expert testimony from PharmaMar, Eli Lilly and Company, Bayer and Eisai, and research grants from PharmaMar, Eisai, Immix Biopharma and Novartis. At JMB's institution, grants were received from PharmaMar, Eli Lilly and Company, Adaptimmune Therapeutics, AROG, Bayer, Eisai, Lixte, Karyopharm, Deciphera, GSK, Novartis, Blueprint, Nektar, Forma, Amgen and Daiichi Sankyo. EW received honoraria, research and travel grants from Nanobiotix, Milestone/Menarini, New Oncology, Lilly, Novartis Oncology, Roche and Bayer. J-YB had honoraria and research support from Novartis, Bayer and Deciphera. All other authors have declared no conflicts of interest.

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