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Editorial Comment

Adjuvant treatment of GIST with imatinib: Solid ground or still quicksand? A comment on behalf of the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, the NCRI Sarcoma Clinical Studies Group (UK), the Japanese Study Group on GIST, the French Sarcoma Group and the Spanish Sarcoma Group (GEIS)

Alessandro Gronchi^a, Ian Judson^b, Toshirou Nishida^c, Andres Poveda^d, Javier Martin^e, Peter Reichardt^f, Paolo G. Casali^g, Axel Le Cesne^h, Peter Hohenbergerⁱ, Jean-Yves Blay^{j,*}

^aSarcoma Unit, Department of Surgery, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy

^bThe Institute of Cancer Research, Royal Cancer Hospital, 123 Old Brompton Road, London SW7 3RP, UK

^cDepartment of Surgery, E1, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

^dMedical Oncology Department, Fundacion Instituto Valenciano de Oncologia, Valencia, Spain

^eSkeletal-Muscle Tumour Committee, Hospital Son Dureta, Palma de Mallorca, Spain

^fHELIOS Klinikum Bad Saarow, Pieskower Straße 33, 15526 Bad Saarow, Germany

^gAdult Sarcoma Medical Treatment Unit, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy

^hDepartment of Medicine, Institut Gustave Roussy, 94805 Villejuif Cedex, France

ⁱDivision of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Theodor Kutzer Ufer 1-3, D-68167 Mannheim, Germany

^jDepartment of Medicine, Centre Leon Berard, 28, rue Laennec, 69008 Lyon, France

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1. Introduction

Mutations of the KIT gene are the molecular hallmark of most GISTs, and were first reported more than 10 years ago.¹ Since then, GIST has become a tumour model for targeted treatment of solid tumours, imatinib becoming the standard first line treatment of these tumours in the advanced phase.^{2–5} Following the introduction of imatinib, the median survival

of advanced GIST increased from 18 months to 60 months in the most recent update of the B2222 trial, i.e. the trial with the longest follow-up so far.⁶

Because of the efficacy of imatinib treatment in the advanced setting, it was logical to investigate the role of adjuvant imatinib following resection of a primary non-metastatic GIST. Three randomised trials have been initiated to investigate the role of a 400 mg daily dose of imatinib, given for 1 year versus

* Corresponding author.

E-mail address: blay@lyon.fnclcc.fr (J.-Y. Blay).

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placebo (ACOSOG Z9001) with relapse-free survival (RFS) as the primary end-point, for 2 years versus observation alone (Inter-group GEIS/EORTC/ISG/FSG/AGITG 62024) with overall survival as the primary end-point or for 3 years versus 1 year in the SSG XVIII/AIO trial with RFS as the primary end-point.

Existing clinical practice guidelines (NCCN, ESMO) recommend the administration of imatinib for patients with metastases in the liver or the peritoneum, even if these have been completely resected. Conversely, until the reporting of the Z9001 study consensus, clinical practice guidelines recommended to include patients with resected non-metastatic disease in clinical trials of adjuvant therapy.^{3–5}

The ACOSOG Z9001 trial was presented at ASCO 2007, and demonstrated a significant improvement in RFS, but not of overall survival, in patients with tumours ≥ 3 cm in diameter.⁷ The updated results of this trial led to the recent (December 2008) FDA marketing approval of imatinib for the treatment of GIST in the adjuvant setting, without definite guidance as to the optimal duration of treatment or which patients would be most likely to benefit.⁸ Preliminary data showed a major reduction in the risk of recurrence from 17% to 2% at 1 year ($p = 0.0001$), with a hazard ratio of 0.35. In the updated report, the difference in RFS was significant for all tumour size subgroups. No significant impact was observed on overall survival, because of the limited follow-up, the limited number of relapses and the considerably improved survival of patients in metastatic phase with imatinib.^{7,8} In addition, after the study was unblinded, patients on placebo at that time were allowed to cross-over to active treatment on the advice of the IDMC; this may have an impact on the final survival benefit. The other studies have just been completed, and results have therefore not been reported. At this stage several questions remain unanswered.

2. Delay or prevention

In ACOSOG Z9001, imatinib yielded a significant reduction in relapse rate for an adjuvant study in a solid tumour. Although this result was anticipated to a certain extent, the benefit in patients with large tumours is substantial. Whether adjuvant treatment will *prevent* relapse or only *delay* it remains unclear, and yet this remains a major question. In view of the observations gathered in an advanced disease from the BFR14 trial in particular, imatinib interruption at either 1 or 3 years is followed consistently by relapse at a median of 6 months.^{9,10} Though these are the only data available so far, a complete analogy with the adjuvant setting should be taken with caution. Yet it is possible that relapse may only be delayed, and not prevented, in the adjuvant setting, and the current survival curves in Z9001 cannot exclude this possibility.

3. Overall survival

The ambition of any adjuvant treatment is both to reduce the risk of relapse and, in particular, to improve overall survival. However, given the relatively limited risk of death from GIST in the first years following the initiation of imatinib for advanced phase, it is likely that the impact of adjuvant treat-

ment on overall survival, if any, will not be apparent until 7 or 8 years following the completion of the EORTC trial. The treatment strategy we should adopt during this interim period is therefore uncertain. At present, both physicians and patients are in the difficult situation of not knowing whether survival will or will not be affected by this treatment, nor the optimal duration of the treatment.

4. Resistance to imatinib

The impact of adjuvant treatment on imatinib sensitivity at the time of relapse remains unclear. Most reassuring is the observation that response and tumour control are observed in virtually all patients who stopped imatinib in the BFR14 and subsequently re-progressed.^{9,10} However, it is also striking to note, as presented at ASCO 2008, that the duration of imatinib sensitivity is not significantly prolonged by imatinib interruption: in other words, within the BFR14 trial, for time to resistance to imatinib the clock may start ticking on the first day of imatinib administration, and is not stopped at imatinib interruption.¹⁰ Importantly, the power of the BFR14 study on the specific question of duration of imatinib sensitivity in an advanced phase is very limited, and the consequence of this observation in the adjuvant setting is presently unclear; a crucial parameter to investigate in the adjuvant trials will therefore be time to imatinib resistance in an advanced phase, following treatment of relapse after cessation of adjuvant therapy, possibly as another surrogate marker for OS. Admittedly, no treatment that has improved RFS in the adjuvant setting has ever been shown to be detrimental on OS in oncology, but the reverse does need to be proved.

5. Duration of treatment

The optimal duration of adjuvant imatinib is not known, and the only available data show the efficacy of 1-year treatment on PFS. One year of treatment may not be enough, particularly in view of the RFS curves of the ACOSOG Z9001 trial, which show a trend to come together following the end of adjuvant treatment. Although the results of the SSG/AIO trial comparing 1 versus 3 years are not yet available, it is likely that RFS will be better for the 3-year arm, since there is no reason to believe that the outcome of patients may be different in the minimal residual disease setting. However, only the SSG/AIO trial will finally provide a reliable answer to the question of duration. Of note, the EORTC 62024 trial uses a 2-year duration of treatment, and will also provide important information on this question.

6. Selection of patients

It is well known that the risk of relapse will be influenced by tumour size, mitotic count, mutation type and site and of course the quality (completeness) of surgery.^{11–13} These classifications have evolved to improve the accuracy of risk evaluation; subgroups with a $>80\%$ risk of relapse have been identified, i.e. virtually metastatic patients without evaluable disease, and conversely, patients with large tumours of the stomach with a low mitotic index have quite a good prognos-

sis.¹² In the ACOSOG study, the patients were only stratified according to tumour size, which may not be the most relevant prognostic factor in the recent studies, making it difficult to adequately select those patients for whom the adjuvant treatment could be clearly beneficial.^{14–16}

7. Dose

Should different molecular subtypes of GIST receive different adjuvant treatment? KIT exon 9 mutated tumours benefit from a 800 mg/d dose in an advanced phase, but the impact of such a dose in the adjuvant setting has not yet been explored.^{17,18} Similarly, some (and indeed not all) exon 18 PDGFRA mutations such as D842 V, which are seen in gastric GISTs, appear to be relatively indolent but are less likely to be as sensitive as GISTs with KIT mutations in the adjuvant setting, even though this needs to be formally explored, with data available at this stage only *in vitro* and in a metastatic setting.^{19,20} Other patient groups responding less to imatinib are those with wild type GIST or those affected by GIST in association with neurofibromatosis (von Recklinghausen's disease).²¹ Those cohorts account for about 15% of all GIST patients and, possibly, they may not benefit from adjuvant therapy with imatinib. Again, this question will need to be carefully addressed in the currently ongoing or completed studies.

In conclusion, imatinib mesylate has dramatically improved the survival of patients with advanced and metastatic GIST, and has induced a major reduction of the risk of relapse in the only adjuvant trial for which results are yet available. However, we do not know yet whether adjuvant imatinib prevents or merely delays relapse, whether it will improve overall survival, whether specific risk populations or molecular subtypes should or should not be offered treatment or whether adjuvant imatinib will affect the response to imatinib reintroduction in the metastatic phase (although this is likely to be known relatively soon) and, finally, we do not yet know the optimal duration of this treatment in these patients. Thus, there are many unknowns in spite of the recent FDA approval.

Today, physicians and patients are therefore put in a difficult situation of not having all the answers (on ultimate benefit in terms of OS, on prevention or delay of relapse) with which to make a meaningful and scientifically based decision. Given the uncertainties, longer follow-up and the results from additional trials are needed. Until then, should we

- (1) wait 6–7 years for the results of overall survival, but until then deny our patients the opportunity to receive a possibly life-improving treatment? or
- (2) conversely, offer imatinib to all patients thus exposing them to a treatment which delays relapses but whose consequences on secondary resistance are not yet known.

We do not know the answer as of January 2009 which means that with scientific rigor we need to obtain more information, a longer follow-up, which requires more time, and more studies, before a final conclusion can be drawn on benefit. The decision made within the Intergroup GEIS/EORTC/ISG/FSG/AGITG 62024 trial to explore a possible surrogate end-point, i.e. time to imatinib resistance, more suitable for

a molecularly targeted agent, will hopefully prove to be a methodological advance. Clearly, the adjuvant GIST experience, with so many uncertainties remaining despite three large randomised trials having been rapidly completed, strongly encourages the whole research community to rethink the methodology of clinical trials in the era of molecularly targeted therapy.

Conflict of interest statement

All authors participated to one of the adjuvant clinical trials of imatinib, partly supported by Novartis.

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