trial by the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Italian Sarcoma Group (ISG), and the Australasian Gastro-Intestinal Trials Group (AGITG). Progression-free survival (PFS) data at a median follow-up of 25 months have been published (Verweij J et al, Lancet 2004; 364: 1127). At a median follow-up of 40 months, the number of events has now allowed an overall survival (OS) analysis.
Patients and Methods: 946 pts with locally advanced and/or metastatic GIST were randomly allocated to Imatinib mesylate 400 mg or 800 mg daily. Pts progressing at 400 mg were eligible for cross-over to 800 mg. Age was 18–91 yrs, PS 0–3, M/F ratio was 61% / 39%. Mutational analysis data were available for a subset of 377 pts with suitable material.
Results: At a median follow-up of 40 months, median OS was still not reached, and OS at 3 years was = 59%. Median PFS was 22 months, and PFS at 3 years was = 33%. There was no significant difference in OS between the two arms. At a longer follow-up, the previously reported PFS advantage for the high-dose arm was not statistically significant for long-term PFS. In the subset of pts with mutational analysis, c-kit exon 9 mutation or wild type predicted a significantly worse OS, as compared to exon 11 mutations. Largest tumor diameter and granulocyte count were the most consistent predictors for OS across prognostic models, along with age, PS, initial hemoglobin and albumin level, and prior chemotherapy. None of these factors was associated to significant differences in OS in favour of the high dose arm, save for disease origin outside stomach / small bowel. A trend towards better OS for the high dose arm amongst exon 9 mutants was not statistically significant at this median follow-up, though against a strong advantage in terms of early PFS (Debiec Rychter M et al, in press).
Conclusions: Imatinib mesylate provides an obvious OS advantage to advanced GIST pts, with a median OS still not reached at 3 years, though against a PFS in the 30% range. OS was not affected by the dose level at treatment start, though the cross-over study design allowed some progressing pts to benefit from dose escalation (Zalcberg J et al, in press). Prognostic factors for OS seem to be associated to 1) mutational status, and 2) initial disease extent. The group of pts with exon 9 mutation needs to be dealt with separately.

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Clinical outcome in gastrointestinal stromal tumor patients who interrupted imatinib after achieving stable disease or better response

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Background: Imatinib has become standard therapy for patients with gastrointestinal stromal tumor (GIST) and it is usually given until progressive disease (PD) or patient intolerance. It is not known if patients with GIST controlled with imatinib will require continuous therapy, or whether imatinib could be safely discontinued in these situations. The aim of the current study is to evaluate the clinical outcome of imatinib interruption in GIST patients who achieved stable disease or better response to imatinib therapy.
Methods: From July 2001 to December 2004, we prospectively gathered clinical data from 62 consecutive patients with metastatic or unresectable GIST. Fifty-eight (93.5%) achieved stable disease or better response to imatinib therapy and 14 of them interrupted imatinib therapy because of patients will or physician's discretion and are included in this study. Median time to imatinib interruption after the onset of imatinib therapy was 11.9 months. Progression free survival (PFS) after imatinib interruption was calculated and imatinib-refractory PFS was compared between the interrupted imatinib group and continuous imatinib group.
Results: With a median FU duration of 17.9 months after imatinib interruption, nine patients (64%) had PD. Median PFS was 10.0 months (95% CI, 5.6–14.5 months). There was significant difference in PFS between the groups (P = 0.029). Median PFS was not reached in the continuous group and 21.8 months (95% CI, 17.3–26.3 months) for the interruption group. Eighty-eight percent of patients had the second disease control with the imatinib reintroduction.. There were no significant differences in imatinib-refractory PFS and overall survival (OS) between the groups (P = 0.405, P = 0.498).
Conclusion: In the patients with advanced GIST controlled with imatinib, imatinib interruption resulted in the high risk of PD within one year. However, the majority of the disease was controlled with imatinib re-challenge on PD and there were no significant differences in imatinib-refractory PFS and OS between groups. Imatinib may be interrupted, at least temporarily, in patients with GIST controlled with it when various clinical situations constrain continuous treatment.

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Interruption of Imatinib (IM) in responding patients after one year treatment does not influence overall survival of patients with advanced GIST: Updated results of the French Sarcoma Group randomized phase III BFR14 trial

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Background: IM (Gleevec/Glivec®; Novartis Pharma) the front-line treatment (Tx) for advanced GIST seems to be given continuously until disease progression (PD) or intolerance. IM interruption in responding patients (pts) was significantly associated with a poor PFS. The impact of IM re-introduction was evaluated both on response and overall survival.
Methods: This prospective multicenter BFR14 study was initiated in June 2002. After 1 year of IM 400 mg/day, 58 pts free from progression were randomly offered to continue or interrupt Tx until PD. Pts allocated to the interruption (I) arm could restart IM (same dose) in case of PD. Primary endpoint was progression-free survival (PFS); secondary endpoints were OS, quality of life (QoL), secondary response after IM re-introduction, identification of molecular determinants of response. Survival data were compared using the log-rank test.
Results: Patient characteristics were well balanced between the two arms. Current median follow-up after inclusion and randomization are 21 and 12 months respectively. 24/32 pts (75%) in arm I versus 6/26 pts (23%) in continuous (C) arm experienced PD. (P < 10−4) with a median of 6 months (95% CI, 3–9) for arm I. IM reintroduction (median: 5.7 months after randomization) allowed tumor control (OR or SD) in 19/22 evaluated pts (86%). One-year OS rates were 93% and 95% for arms I and C, respectively (P = 0.6), with no significant difference in QoL.
Conclusions: IM reintroduction in GIST patients was safe and allowed a similar tumor control rate than in front-line treatment (86%). The one year OS rates were 93% and 95% for the experimental and control arms, respectively (p = 0.6) A transient interruption of IM in elderly patients will advanced GIST and/or in patients exhibiting a grade 3–4 toxicity could be a therapeutic option. GIST mutational analysis of the 58 randomized patients is ongoing. A new randomization (same schedule) is planned after 3 years of IM in non progressive patients

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FDG-PET imaging demonstrates kinase target inhibition by sunitinib malate (SU11248) in GIST patients resistant to or intolerant of imatinib mesylate

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Background: The purpose of this study was to use FDG-PET to image tumor metabolism before and after treatment with sunitinib malate in GIST patients after failure of imatinib mesylate (IM) therapy due to resistance or intolerance, as an early indicator of clinical activity.
Materials and methods: Sunitinib is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT, RET and FLT3 with antiangiogenic and antitumor activities. 97 IM-resistant or intolerant GIST patients received 1 of 3 schedules of daily sunitinib: 25–75 mg, 2 weeks on/2 weeks off; 50 mg, 4 weeks on/2 weeks off; or 50 mg, 2 weeks on/1 week off. FDG-PET was performed on 75 of these patients at baseline (scan 0, n = 74), after 7 days on therapy (scan 1, n = 61), after the first period off therapy (scan 2, n = 51) and after subsequent cycles while on treatment (scan 3, n = 8 and scan 4, n = 28). Maximum standardized uptake value (SUVmax) was measured in the lesions with the greatest uptake (⩽5 lesions per patient) in these 75 patients. SUVmax measurements were transformed by log base 10 to improve model fit, and a linear mixed effects model was used to estimate log SUVmax at each time point. This model accounts for correlated lesions and repeated measures over time. Linear contrasts were used for pair-wise comparisons.
Results: Model-based estimates of mean log SUVmax values (±SE, n = 75 patients) for the 5 time points were: 0.91 (±0.03), 0.63 (±0.03), 0.78 (±0.03), 0.64 (±0.06) and 0.57 (±0.03). Comparisons of mean log SUVmax at different scan times are shown in the table. Mean log SUVmax was significantly lower after periods of sunitinib treatment than at baseline or at the end of the period off treatment.