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.

712 ORAL

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

J.-L. Lee, M. Ryu, H. Chang, T. Kim, H. Kang, H. Sohn, J. Lee, Y. Kang.
Asan Medical Center, University of Ulsan College of Medicine, Division of Oncology, Department of Internal Medicine, Seoul, Korea

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.

713 ORAL

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

A. Le Cesne[1], I. Ray-Coquard[2], B. Bui[3], F. Duffaud[4], N. Deligny[5], D. Cupissol[6], J.O. Bay[7], C. Perol[8], C. Delbaldo[1], J.Y. Blay[2]. [1]*Institut Gustave Roussy, Medecine, Villejuif, France;* [2]*Centre Léon Bérard, Medecine, Lyon, France;* [3]*Institut Bergonié, Medecine, Bordeaux, France;* [4]*La Timone, Medecine, Marseille, France;* [5]*Centre Oscar Lambret, Medecine, Lille, France;* [6]*Centre Val d'Aurelle, Medecine, Montpellier, France;* [7]*Centre Jean Perrin, Medecine, Clermont-Ferrand, France;* [6]*Centre Léon Bérard, Statistique, Lyon, France*

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

714 ORAL

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

A.D. Van den Abbeele[1], Y. Melenevsky[1], D. de Vries[1], J. Manola[1], P. Dileo[1], R. Tetrault[1], C. Baum[2], R.D. Badawi[3], G. Demetri[1].
[1]*Dana-Farber Cancer Institute, Boston, USA;* [2]*Pfizer Inc., La Jolla, USA;* [3]*UC Davis Medical Center, Sacramento, USA*

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.

Comparison	Difference (mean log SUVmax)	95% Confidence	P value
Scan 0 – scan 1	0.28	0.23–0.32	<0.001
Scan 2 – scan 1	0.15	0.10–0.20	<0.001
Scan 2 – scan 3	0.14	0.02–0.25	0.02
Scan 4 – scan 3	−0.07	−0.20–0.05	0.25

Conclusions: Use of FDG-PET imaging in GIST patients resistant to or intolerant of IM indicated that a significant decrease in glucose metabolism occurs in response to sunitinib as early as 7 days following initiation of therapy, far earlier than responses detected by conventional radiography. Target inhibition with sunitinib was confirmed by rebound of FDG uptake after withdrawal of sunitinib and by re-demonstration of significant decrease in tumor metabolic activity after subsequent sunitinib dosing cycles. Thus, metabolic response correlated with treatment on and off periods.

715 ORAL

Receptor tyrosine kinase activity and apoptosis in gastrointestinal stromal tumours: a pharmacodynamic analysis of response to sunitinib malate (SU11248) therapy

D.W. Davis[1], J.V. Heymach[2], D.J. McConkey[2], J. Desai[2], S. George[2], J. Jackson[2], C.D. Bello[3], C. Baum[3], D.R. Shalinsky[3], G.D. Demetri[2].
[1]*University of Texas MD Anderson Cancer Center, Houston, USA;* [2]*Dana-Farber Cancer Institute, Boston, USA;* [3]*Pfizer Inc., La Jolla, USA*

Background: Most gastrointestinal stromal tumours (GIST) contain activating mutations in KIT and/or PDGFR. Early resistance to first-line imatinib therapy has been reported in approximately 14% of patients. Sunitinib malate, an oral multitargeted tyrosine kinase inhibitor of KIT, PDGFR, RET and VEGFR, has demonstrated antitumour and antiangiogenic activity in imatinib resistant or intolerant GIST patients. The effects of sunitinib on endothelial and tumour cells in GIST are reported.
Methods: Paired tumour biopsies, obtained from GIST patients enrolled in phase I/II trials with sunitinib (*J Clin Oncol* 2004; 22[Suppl]: Abstract 3001) were collected at baseline and after at least 11 days in the first cycle of sunitinib treatment. Response to therapy was assessed by RECIST. For each biopsy, endothelial and tumour cell apoptosis, microvessel density (MVD), and the phosphorylation of PDGFR-β and other RTKs were quantified using immunofluorescence coupled with laser scanning cytometry.
Results: Tumour biopsies were obtained from 20 patients receiving sunitinib therapy. Eight patients had clinical benefit (CB; defined as partial response [PR] or stable disease [SD] for >6 months), and 12 patients had progressive disease (PD). Overall, tumours from patients with CB displayed a 10- and 6-fold ($P < 0.05$) increase from baseline in endothelial and tumour cell apoptosis, respectively. In contrast, tumours from patients with PD had little or no change from baseline in endothelial and tumour cell apoptosis. The changes in phosphorylated PDGFR-β (p-PDGFR-β) activity in biopsies from all patients are shown in Table 1.

Table 1. Correlation of change in p-PDGFR-β activity with clinical benefit.

Clinical outcome by RECIST	No. of patients	Change in p-PDGFR-β activity
CB	8	18.2% decrease ($P = 0.006$)
PR	2	26.1% decrease ($P = 0.001$)
SD	6	13.9% decrease ($P = 0.04$)
PD (SD <6 months)	12	9.9% increase ($P = 0.06$)

Conclusions: This study demonstrates that PDGFR-β phosphorylation is significantly decreased in tumour biopsies from patients with GIST treated with sunitinib who had CB but not in those who had PD. CB is also associated with an increase in endothelial and tumour cell apoptosis. Suppression of PDGFR-β activity implicates other RTKs in addition to KIT as targets for sunitinib. Investigation of other key RTKs (e.g. VEGFR-2) is underway. We hypothesize that the multitargeted nature of sunitinib results in the inhibition of RTKs on both tumour and endothelial cells.

716 ORAL

Sunitinib malate (SU11248) prolongs progression-free and overall survival for GIST patients after failure of imatinib mesylate therapy: update of a phase III trial

G. Demetri[1], A. van Oosterom[2], C. Garrett[3], M. Blackstein[4], M. Shah[5], J. Verweij[6], G. McArthur[7], I. Judson[8], C. Baum[9], P. Casali[10].
[1]*Dana-Farber Cancer Institute, Boston, USA;* [2]*UZ Gasthuisberg, Leuven, Belgium;* [3]*H. Lee Moffitt Cancer Center, Tampa, USA;* [4]*Mount Sinai Hospital and the University of Toronto, Toronto, Canada;* [5]*Ohio State University, Columbus, USA;* [6]*Erasmus Medical Center, Rotterdam, The Netherlands;* [7]*Peter MacCallum Cancer Center, East Melbourne, Australia;* [8]*Royal Marsden Hospital, Sutton, United Kingdom;* [9]*Pfizer Inc., La Jolla, USA;* [10]*Istituto Nazionale Tumori, Milan, Italy*

Background: Sunitinib (SU) is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT, RET and FLT-3 with antiangiogenic and antitumour activities. This study assessed the efficacy and safety of SU in patients (pts) with progressive metastatic and/or unresectable GIST following failure of prior imatinib mesylate (IM) therapy due to resistance or intolerance.
Patients and methods: In this double-blind, placebo-controlled, international, multicentre, phase III trial, 312 pts with documented progression of GIST despite previous IM therapy were randomised 2:1 to receive SU ($n = 207$) or placebo ($n = 105$). SU was administered as 50 mg capsules once daily for 4 weeks, followed by a 2-week break, in repetitive 6-week cycles. Pts in the placebo arm were offered the opportunity to receive open-label SU if RECIST-defined disease progression occurred. The primary study endpoint was time to progression (TTP). Secondary endpoints included overall survival (OS), response rates, time to tumour response, duration of response, functional status and clinical benefit-related parameters (McGill Pain Questionnaire, investigator-rated changes in severity of signs and symptoms and other pt-reported outcomes) as well as tolerability and safety assessments.
Results: SU therapy resulted in a >4-fold increase in median TTP compared with placebo (HR 0.335, $P < 0.00001$) at the first planned interim analysis for efficacy. Estimated median TTP was 6.3 months with SU vs. 1.5 months with placebo. SU improved the TTP in pts with either primary or secondary resistance to IM. SU was also associated with significantly greater estimated OS (HR 0.491; $P = 0.00674$). The median OS has not yet been reached in either treatment arm. A total of 59 pts in the placebo group crossed over following disease progression to receive SU, with 10% subsequently exhibiting a partial response as assessed by investigators. SU therapy was well tolerated overall, with the most common non-haematologic adverse effects (AEs) being fatigue, diarrhoea, nausea, sore mouth and skin discolouration. AEs were generally mild to moderate (grade 1 or 2), and there were no grade 4 events during the study.
Conclusions: SU was associated with significant efficacy and acceptable tolerability in this large-scale international phase III trial of GIST pts resistant to or intolerant of IM therapy.

Oral presentations (Wed, 2 Nov, 9.15–11.15)
GI – non-colorectal cancer – advanced

717 ORAL

Gemcitabine (GEM) plus Capecitabine (CAP) versus GEM alone in locally advanced or metastatic pancreatic cancer. Aspects of quality of life in a randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG)

R. Herrmann[1], G. Bodoky[2], T. Ruhstaller[3], B. Glimelius[4], P. Saletti[5], E. Bajetta[6], J. Schüller[7], J. Bernhard[8], D. Dietrich[8], W. Scheithauer[9].
[1]*University Hospital, Basel, Switzerland;* [2]*St. Laszlo Hospital, Budapest, Hungary;* [3]*Cantonal Hospital, St. Gallen, Switzerland;* [4]*University Hospital, Uppsala, Sweden;* [5]*Oncology Institute of Southern Switzerland, Bellinzona, Switzerland;* [6]*Istituto Nazionale Tumori, Milano, Italy;* [7]*Rudolfstiftung, Vienna, Austria;* [8]*SAKK Coordinating Center, Bern, Switzerland;* [9]*University Hospital, Vienna, Austria*

Background: While GEM is widely accepted for the treatment (trt) of advanced pancreatic cancer, CAP has shown single agent activity and promising efficacy in combination with GEM in phase II studies.
Methods: Major eligibility criteria: KPS $\geqslant 60$, no previous chemotherapy. Stratification factors: locally advanced/metast. disease, absence/presence of pain, institution, KPS 60–80/90–100. Primary endpoint is overall survival (OS), secondary endpoints are quality of life, clinical benefit (CB) response, objective tumor response (RECIST criteria), duration of response, time to