| 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**

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**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**

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**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)**

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**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