warranted to confirm these findings and to establish if sKIT can be used as a general surrogate marker of clinical outcomes in GIST pts treated with SU or other therapies.

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KIT mutations and sunitinib resistance in gastrointestinal stromal tumors (GISTs)

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Background: Sunitinib malate (SUTENT®; SU) is an oral, multitargeted inhibitor that is now standard treatment for imatinib (IM)-resistant or -intolerant GIST. Although clinical efficacy and safety of SU were demonstrated in a double-blind, placebo-controlled, phase III trial, it is unclear if the activity of SU in this setting is due to inhibition of KIT and/or PDGFRA in tumor cells, inhibition of VEGFRs and PDGFRs in endothelial cells and pericytes, respectively, or a combination of antitumor and antiangiogenic effects. This study examines the molecular mechanisms of SU resistance in vitro and in patient-derived tumors.
Materials and Methods: The in-vitro effects of IM or SU on cells with KIT exon 11 mutations, either alone or in combination with known IM-resistant secondary mutations, were studied by transiently transfecting CHO cells with mutant KIT cDNA constructs and treating them with various concentrations of SU or IM. IC_{50}'s for SU and IM were determined by sequentially probing immunoblots for phospho-KIT or total KIT. Samples of tumor DNA from pts undergoing salvage surgery after SU treatment failure were also analyzed and genotyped for primary and secondary mutations.
Results: KIT exon 11 mutations commonly associated with GIST (eg, V560D) were found to be approximately 2–5-fold more sensitive to SU than IM. Secondary mutations involving the ATP binding pocket (V654A or T670I), that confer high-level resistance to IM, did not substantially alter SU potency. Mutations involving the KIT activation loop (exon 17, codons 816, 820, 822, and 823) however, were resistant to both SU and IM. Nine progressing lesions obtained during surgical resection of two GIST pts with clinical progression on SU contained substitutions in exon-17 codons 816, 820, and 822. A novel mutation, L783V, was identified and was found to be associated with tumor progression. In contrast, two non-progressing tumors from these two pts both contained a V654A secondary mutation.
Conclusions: The IM-resistant KIT mutation V654A was found to be highly sensitive to SU. By contrast, mutations in the KIT activation loop were resistant to SU. Novel KIT kinase mutations not previously associated with IM resistance, such as L783V, may also contribute to clinical SU resistance. Data from the ex vivo analysis corroborates the in vitro results. These findings suggest that the antiangiogenic effects of SU may be insufficient to inhibit GIST progression when the primary oncogenic kinase remains active.

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Early progression in patients with high-risk soft tissue sarcomas (STS): A phase III randomized prospective trial (EORTC/ESHO intergroup trial) of neoadjuvant chemotherapy with or without regional hyperthermia (RHT)

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Background: A randomized phase III trial of neoadjuvant chemotherapy combined with or without RHT for pts with locally advanced high grade STS was recently completed (Issels, ASCO 2007). By interim analysis the overall risk of early progression (PD) during the 3-months duration of neoadjuvant chemotherapy with or without RHT was 15% (Lindner, ASCO 2005, abstract 9020). We now analyzed the risk of early PD for both treatment arms including subgroup analysis for pts with not operated primary (S1) or recurrent (S2) STS and for pts after R1/R2 resection of primary or recurrent STS (S3).
Methods: From 7/97−11/06 341 pts (S1 = 161; S2 = 37; S3 = 143) with STS > 5 cm, grade II/III, deep and extracompartmental have been randomized to receive initially 4 cycles of systemic chemotherapy (etoposide 250 mg/m^2; ifosfamide 6 g/m2; adriamycin 50 mg/m^2) alone (EIA) or systemic chemotherapy combined with RHT (EIA + RHT). Early PD was defined as local and/or distant relapse or any kind of death after 3 and 6 months, respectively. By intention to treat analysis the risk of early PD was assessed for all randomized 341 pts after a median follow up time of 25.5 mths.
Results: The local progression free survival (LPFS) for EIA+RHT vs. EIA alone after 3 mths was 94.6% vs. 86.0% (Diff. = 8.6%, CI95 = 2.3−14.9%, p = 0.008) and after 6 mths 91.4% vs. 77.8% (Diff. = 13.6%, CI95 = 5.9−21.3%, p < 0.001). The disease free survival (DFS) for the EIA+RHT vs. EIA alone after 3 mths was 94.0% vs. 83.1% (Diff. = 10.9%, CI95 = 4.1−17.6%, p = 0.002) and after 6 mths 87.7% vs. 73.8% (Diff. = 13.9%, CI95 = 5.5−22.3%, p = 0.001). For the S1/S2 subgroup the LPFS for EIA+RHT vs. EIA alone after 3 mths was 90.5% vs. 81.0% (Diff. = 9.5%) and after 6 mths 85.0% vs. 73.4% (Diff. = 11.4%). For the S3 subgroup the LPFS for EIA+RHT vs. EIA alone after 3 mths was 100% vs. 92.8% (Diff. = 7.2%) and after 6 mths 100% vs. 83.8% (Diff. = 16.2%).
Conclusions: Compared to chemotherapy alone, the risk of early PD for all pts is significantly lower for the hyperthermia combined chemotherapy regimen irrespective of time point of surgery.
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7505 ORAL

Personalized therapy with trabectedin (Yondelis®) in advanced pre-treated sarcomas

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Trabectedin (T) is a marine derived DNA binder and transcription interacting agent with positive therapeutic impact in patients (pts) with advanced pre-treated soft-tissue sarcoma. In experimental models its antiproliferative effects are maximized by an intact Transcription Coupled Nucleotide Excision (TC-NER) DNA Repair and by a deficient Homologous Recombination Repair (HRR).
In order to seek for a molecular signature for sensitivity/resistance to T we have characterized using qRT-PCR the mRNA expression levels of BRCA1, ERCC1 and XPD in paraffin embedded tumor samples from 181 pts treated with T. The studied pt cohort had a RECIST response rate RR= 13%, a 6-month Progression Free Survival PFS6= 31.6%, and a median survival OS= 11.5 months (mo) similar to that reported in other sarcoma series. The median values for mRNA expression of each gene have been used as cut-off to separate high vs low expression pt.
Pts with low levels of BRCA1 expression have a statistically significantly better outcome than those whose tumors have high expression levels; RR 15% vs 9% (p < 0.001), tumor control (CR+PR+MR+SD >6 months), 46% vs 19% (p < 0.001), PFS6 rate 41% vs 15% (p = 0.001), median PFS 4.2 vs 1.8 mo (p = 0.0002) and median OS 15.4 vs 6.8 mo (p < 0.001). In contrast to other DNA interacting agents, high levels of mRNA expression of ERCC1 and XPD lack a detrimental effect on patients' outcome rather than a non statistically significant trend for superior response, tumor control and survival in favour of patients bearing a functional TC-NER signature. Furthermore the combination of the efficiency patterns of HRR and TC-NER defines signatures correlated with extreme sensitivity/resistance to T.

	Low BRCA1 + High ERCC1+XPD	High BRCA1 + Low ERCC1+XPD	P value
CR+PR	15%	0%	0.025
CR+PR+SD >6 mo	68%	0%	0.006
PFS6 rate	69%	0%	0.005
Median PFS (mo)	7.1	1.4	0.004
Median survival (mo)	20.4	5.8	0.026