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.

7503 ORAL

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.

7504 ORAL

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.
Supported by Deutsche Krebshilfe und HGF VH-VI-140

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

The antitumor activity of T in pts with advanced pre-treated sarcoma is modulated by the pattern of DNA repair functionality. A personalized intervention with T based on the DNA repair signature of tumor seems to be feasible. However, prospective studies are needed to validate these retrospective findings.

7506 ORAL

Up to 6 years follow-up of patients receiving imatinib mesylate (Glivec) to treat unresectable or metastatic gastrointestinal stromal tumors (GISTs)

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Background: Imatinib mesylate (Glivec) is a selective tyrosine kinase inhibitor that targets the deregulated activity of KIT and PDGFRA, the cause of oncogenic activity in GIST. Treatment with imatinib has been well documented to induce high rates of response and disease control which translates into prolonged overall survival relative to historical controls. A phase II, randomized clinical trial of two dose levels (400 vs. 600 mg daily) of imatinib mesylate in patients (pts) with unresectable or metastatic CD117+ (KIT+) GIST was previously published (NEJM 2002;347:472−80). Herein we report the longest follow-up of imatinib therapy in any series of pts with advanced GIST.
Methods: 147 pts with unresectable or metastatic GIST were randomly assigned to treatment with imatinib at either 400 mg/d (n = 73) or 600 mg/d (n = 74) and followed continuously.
Results: At current cut-off (~5−6 years after all pts had been randomized), 28% of pts remain on imatinib study therapy. The overall response (CR+ PR) rate for all 147 pts was 68%, with an additional 15.6% achieving stable disease (SD). Median time to response was 3 months; however, time to maximal response was >12 months in 6% of responding pts. Median time to progression was 24 months for all pts, 20 months for pts who received 400 mg/d, and 26 months for pts who received 600 mg/d (P = 0.3712), and was significantly longer for pts who achieved a response (CR or PR) than for those who achieved stable disease: 33 versus 12 months, respectively (P < 0.0001). Median overall survival (OS) for all pts was 57 months with an estimated 5-year OS of 48%, which is significantly longer than historical controls showing a median OS of <2 years. There was no difference in OS by initial dose, nor by stable or better response status. In pts with CR+PR+SD, the estimated OS was 55% at 5 years (median 64 months). Finally, among pts with GISTs harboring KIT mutations, those who had exon 11 mutations had a higher overall response rate than patients with exon 9 mutations: 86% vs 48%, respectively. Exon 9 patients who received 600 mg initial dose (n = 17) had a higher response rate than those with 400 mg (n = 6): 59% vs 17%, however the number of patients is small.
Conclusion: These long-term follow-up data of up to 6 years confirm that patients with GIST benefit from imatinib therapy, even those that achieve stable disease. Updated information on predictors of OS for patients treated with imatinib will be presented.

7507 ORAL

Optical navigation-assisted surgical planning for sarcoma patients receiving pre-operative radiotherapy

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Background: Contemporary local management of soft tissue sarcoma (STS) requires greater precision in surgical and radiotherapy (RT) integration and delivery. This study examines workflow, accuracy, and precision of a novel optical navigation system for STS patients undergoing pre-operative intensity modulated RT (IMRT) intended to spare tissues from surgical and RT morbidity.
Materials and Methods: An optical tracking process relates predetermined CT data including avoidance tissues required for surgical wound closure and IMRT targets to patient anatomy. 4 fiducial marker locations on a leg phantom were manually acquired with a passive tool and related to their CT position using the least-squares solution to a rigid transformation. 10 fiducial positions were verified and simulated surgical borders outlined. 5 repetitions of the procedure quantified fiducial and target registration error (FRE/TRE). Within an ethics approved protocol, patients returned for pre-surgical consultation where their planning CT was registered to real-time anatomy using treatment positioning tattoos and immobilization. Prospective skin excision borders were reproduced using a passive tool and recorded with a marker, radio-opaque wire, and CT. Bony anatomy was used to register the reference planning and pre-surgical CT to simulate external fiducial set-up. This provided a reference frame allowing the relative position of radio-opaque wires, representing skin excision borders defined pre- and post-RT, to be quantified. In a subset of patients (N = 12), a MATLAB script located the centroid of their contours in the treatment planning system. Absolute mean, standard deviation, maximum, and minimum for 200 adjacent points on these wires were computed and defined as "distance to agreement" measurements (DTA).
Results: Analysis of the system resulted in an FRE of 0.1 mm and a TRE of 3.0 mm. DTA absolute (mean±SD), maximum, and minimum (mm) in the right-left, anterior-posterior, and superior-inferior directions, respectively are: 3.1±1.8, 7.1 and, 0.3; 6.0±2.2, 10.4, and 2.2; 6.4±2.3, 10.7, and 2.7. An efficient method (15.0 min) for multi-disciplinary interaction has been coordinated, workflow/process defined, and hardware/software constructed
Conclusions: Optical navigation facilitates surgical planning/design of sarcoma patients receiving multi-modal treatment by permitting accurate identification of highly irradiated tissues for resection and safe wound reconstruction.

Poster presentations (Tue, 25 Sep, 14:00−17:00)

Sarcoma

7508 POSTER

Clinical follow-up of desmoid tumors and the impact of APC gene mutations

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Background: Desmoid tumors are very rare mesenchymal tumors with a partially aggressive growth pattern and high relapse rates. These tumors may occur intra- or extra-abdominal, sporadically or in association with familial adenomatous polyposis (FAP). Different germline mutations of the APC gene account for desmoid tumors in FAP. The aim of our study was to evaluate the clinical phenotype and genotype-phenotype correlations in a cohort of patients with desmoid tumors.
Material and Methods: We performed a multicentric, retrospective review of 62 primary desmoid tumor cases, treated with surgical resection alone or combination with other treatments (radiation-, chemotherapy, non-steroidal anti-inflammatory drug or hormonal agents) between 1981–2006.
Results: The median follow-up time was 86.4 months. Forty-seven patients were female and 16 were male. The median age was 31.9 years. Family history of desmoid tumor was positive in one case, of colorectal cancer in 6 cases, of Crohn's disease in 3 cases. An antecedent history of trauma to the site of the tumor was elicited in approximately 16% of the cases. In one case desmoid arised from the capsule around a silicone breast implant, in an other case the tumor was multicentric. All surgical resections were macroscopically complete, but the microscopically status of the resection margin was given only in 30 out of the 62 cases. The resection margin was tumor-free in 18 cases (60%) and tumor-positive in 12 cases (40%). Thirty-five patients (56%) experienced local recurrence. Germline mutation testing for the entire coding sequence of APC gene (using multiplex heteroduplex / SSCP analysis and direct sequencing) showed that deleterious mutations in APC gene accounted for the most severe disease outcome.
Conclusions: Deleterious germline mutations in the APC gene were detected in all the FAP families tested, suggesting a strong association of these APC mutations with the development of desmoid tumors in FAP families. Supported by OTKA T046570