Sarcoma

Oral presentations (Thu, 27 Sep, 09.00−11.00)
Sarcoma

7500 ORAL

Impact of independent review on efficacy outcomes in a randomised multicenter trial of trabectedin given by two dosing regimens in patients (pts) with progressing leiomyosarcomas or liposarcomas (L-sarcomas)

G.D. Demetri[1], S. Schuetze[2], A. Le Cesne[3], S. Chawla[4], P.G. Casali[5], J. Gomez[6], A. Nieto[6], Y. Elsayed[7], M.A. Izquierdo[6], J.Y. Blay[8]. *[1]Ludwig Center at Dana-Farber/Harvard, Oncology, Boston, USA; [2]University of Michigan, Oncology, Ann Arbor, USA; [3]Institut Gustave Roussy, Oncology, Villejuif, France; [4]Century City Hospital, Oncology, Los Angeles, USA; [5]Istituto Nazionale Tumori, Oncology, Milano, Italy; [6]PharmaMar, Clinical, Madrid, Spain; [7]Johnson & Johnson, Oncology, Raritan, USA; [8]On behalf of Yondelis Sarcoma Study Group; Center Leon Berard, Clinical, Lyon, France*

Background: The efficacy of 2 trabectedin (T) IV regimes: 1.5 mg/m^2 24h q3 wk (q3wk 24h) or 0.58 mg/m^2 3h weekly for 3 of 4 wk (qwk 3h) was studied in an international trial of pts with L-sarcoma progressing despite prior therapy with at least anthracyclines and ifosfamide. Primary endpoint, time to progression (TTP), was assessed by study investigators (IA) and also by independent review (IR) which was the primary study analysis. Pts were restaged symmetrically every 8 wks in both arms.
Methods: To assess the impact of IR on TTP in this trial, a comprehensive comparison of IR vs IA assessments was conducted. IR was performed by an independent team using a predefined charter blinded to study arm: two radiologists independently evaluated images; if any discrepancy was noted, a 3rd radiologist adjudicated. Then a medical oncologist reviewed all assessments with predefined relevant clinical data to provide a final TTP date (event or censored) for each pt.
Results: 270 pts were randomised. In the protocol-specified primary analysis, TTP was significantly better for the q3wk 24h regime by both IA and IR. The reduction in the risk of progression was more profound per IA [HR: 0.668; p = 0.005] vs IR [HR: 0.734; p = 0.030]. There were slightly fewer TTP events per IR (206; 24% censored) vs IA (216; 20% censored). Overall the IR-IA concordance (event/censored) was 85%. TTP length (regardless of event/censored) was judged identical by IA and IR in 60% of pts, shorter per IR in 25% and longer per IR in 15% of pts. Full concordance (event/censored and TTP length) was reached in 53% of pts. Common discrepancies were: shorter TTP (event) by IR in 19%, longer TTP (censored) by IR in 10%; other discrepancies accounted for $\leqslant$5% each. TTP curves were superimposable in the qwk 3h arm despite IA-IR discrepancies. However, in the more efficacious q3wk 24h arm, TTP per IR was non significantly shorter than TTP per IA. Similar findings were seen for PFS.
Conclusions: Overall consistent TTP outcomes were observed with both T regimes between IA and IR. IR resulted in fewer TTP events and a slightly less profound reduction in risk of progression. The impact of IR on TTP reduction was only evident in the more efficacious q3wk 24h regime but did not result in loss of statistical significance for the benefit in TTP associated with T q3wk 24h. IR adds methodological strength and should be performed in large-scale clinical trials of sarcomas when TTP or PFS is the primary endpoint.

7501 ORAL

Continuous daily dosing (CDD) study of sunitinib malate (SU) in patients (pts) with advanced GIST compares favorably with intermittent dosing

J.Y. Blay[1], S. George[2], P.G. Casali[3], A. Le Cesne[4], J.A. Morgan[2], J. Pokela[2], M.T. Quigley[2], V. Tassell[5], C.M. Baum[5], G.D. Demetri[6]. *[1]Centre Léon Bérard, Medical Oncology, Lyon, France; [2]Dana-Farber Cancer Institute, Medical Oncology, Boston, USA; [3]Instituto Nazionale Tumori, Cancer Medicine, Milan, Italy; [4]Institut Gustave-Roussy, Medicine, Villejuif, France; [5]Pfizer, Research and Development, La Jolla, USA; [6]Dana-Farber Cancer Institute, Medical Oncology/Solid Tumor Oncology, Boston, USA*

Background: SU is an oral, multitargeted tyrosine kinase inhibitor of KIT, PDGFRs, VEGFRs, RET, CSF-1R, and FLT3, approved multinationally for the treatment of imatinib-resistant/-intolerant GIST. SU safety and efficacy has been demonstrated in a phase III trial using a regimen of 50 mg/d delivered in 6 wk cycles (4 wks on, followed by 2 wks off treatment; 4/2 schedule). This study evaluates the safety and efficacy of CDD of SU (37.5 mg) in pts with GIST after failure of imatinib.
Materials and Methods: 61 pts with imatinib-resistant/-intolerant GIST were randomized to receive SU 37.5 mg once daily either in the morning (AM) or evening (PM) in this open-label, multicenter, phase II trial. The primary endpoint was clinical benefit rate (CBR), defined as percentage of patients with CR, PR, or SD $\geqslant$ 24 weeks per RECIST. Secondary endpoints included ORR, PFS, safety/tolerability measures and PK parameters. Investigator-assessed efficacy and safety data obtained from this study and the earlier phase III trial were compared informally.
Results: 60 of the 61 randomized pts received treatment with SU on the CDD schedule (30 pts per arm). After a median follow-up of 43 weeks (range: 4–66+), 17 pts remain on study, 11 pts have completed, and 33 have discontinued. AEs necessitated dose reduction to 25 mg in 9 pts. The most common non-hematologic AEs of any cause were diarrhea (42%), asthenia (38%), and fatigue (35%). Grade 3 AEs were asthenia (15%), fatigue (8%), and diarrhea (12%); grade 4 abdominal pain was reported in 5% of patients. Grade 3/4 hematologic AEs included neutropenia (13%), anemia (15%), and thrombocytopenia (3%). Toxicities were comparable between AM and PM dosing, and the AE profile from this trial was similar to that seen in the phase III trial. Preliminary PK data indicated no unexpected accumulation with CDD. To date, the median PFS is 34 weeks (CI: 25.1–40.2) with an overall CBR of 31%, including 11% of patients with PRs. Efficacy results from the phase III trial were comparable (PFS: 28 weeks [CI: 14–34]; CBR: 25%; PR: 7%; N = 207).
Conclusions: In pts with imatinib-resistant/-intolerant GIST, administration of SU at 37.5 mg CDD results in a similar safety/tolerability and efficacy profile as when administered at 50 mg/d on the 4/2 schedule, and appears to be a safe and effective alternative dosing strategy in pts with imatinib-resistant/-intolerant GIST.

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Assessment of plasma levels of soluble KIT (sKIT) as a potential surrogate marker for TTP in patients (pts) with advanced gastrointestinal stromal tumor (GIST) treated with sunitinib

P. Schoffski[1], X. Huang[2], G.D. Demetri[3], P.G. Casali[4], C.R. Garrett[5], M. Blackstein[6], M.H. Shah[7], J. Verweij[8], C.M. Baum[2], S.E. DePrimo[2]. *[1]U.Z. Gasthuisberg, Clinical Oncology, Leuven, Belgium; [2]Pfizer, Global Research and Development, La Jolla, USA; [3]Ludwig Center at Dana-Farber/Harvard Cancer Center, Medical Oncology/Solid Tumor Oncology, Boston, USA; [4]Instituto Nazionale Tumori, Cancer Medicine, Milan, Italy; [5]H. Lee Moffitt Cancer Center & Research Institute, Drug Discovery Gastrointestinal Tumor Experimental Therapeutics, Tampa, USA; [6]Mount Sinai Hospital and the University of Toronto, Clinical Oncology, Toronto, Canada; [7]Ohio State University Comprehensive Cancer Center, Hematology/Oncology, Columbus, USA; [8]Erasmus University Medical Center, Medical Oncology, Rotterdam, The Netherlands*

Background: A previous analysis from a phase I/II GIST trial suggested that a decline in plasma levels of sKIT may correlate with measures of clinical benefit in pts treated with sunitinib malate (SUTENT®; SU). SU is an oral multitargeted tyrosine kinase inhibitor of KIT, PDGFRs, VEGFRs, RET, CSF-1R, and FLT3, approved multinationally for the treatment of imatinib-resistant or -intolerant GIST and advanced renal cell carcinoma. In this study, using samples from of a previously reported phase III trial, changes in plasma levels of sKIT were evaluated as a potential surrogate marker for TTP in GIST pts treated with SU.
Materials and Methods: Pts in the original phase III trial were randomized in a 2:1 ratio to receive SU 50 mg (n = 207) or placebo (n = 105) daily in 6-wk cycles (4 wks on and 2 wks off treatment). The primary endpoint was TTP using RECIST. Samples for sKIT measurement were taken predose on days 1, 14, and 28 (cycle 1), and days 1 and 28 (cycles 2 and 3). Plasma sKIT levels were analyzed with performance-validated ELISA. Prentice Criteria, Cox models, and the Proportion of Treatment Effect (PTE) were used to analyze the results (PTE = 1 is a perfect surrogate).
Results: After 4 wks (cycle 1 day 28) of treatment, 215 pts (SU 138, placebo 77) had matched pairs of baseline and on-study plasma samples for sKIT. At this timepoint, SU treatment was associated with a significant decrease in sKIT levels (P < 0.0001). Decreases in sKIT levels were also found to be a significant predictor of longer TTP, compared with increases in sKIT levels (HR = 0.53; 95% CI, 0.37–0.75; P = 0.0003). The relationships between SU treatment and sKIT levels, and lowered sKIT levels and longer TTP, continued throughout the sampling period, including off-treatment periods. By the end of cycle 2 (161 pts [SU 121, placebo 40]), changes in sKIT levels replaced initial treatment group as a stronger indicator of TTP (PTE = 0.62; HR = 0.51; 95% CI, 0.38–0.69; P < 0.0001), which continued through to the beginning of cycle 3 day 1 (143 pts [SU 102, placebo 41]; PTE = 0.64; HR = 0.42; 95% CI, 0.29–0.60; P < 0.0001).
Conclusions: These preliminary results suggest that, after two cycles of SU treatment, circulating levels of sKIT appear to function as a surrogate marker for TTP in pts with imatinib-resistant GIST. Further studies are

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)

J.A. Fletcher[1], C.L. Corless[2], B. Liegl[1], C.D. Fletcher[1], C.P. Raut[3], R. Donsky[1], M.M. Bertagnolli[4], A. Harlow[5], G.D. Demetri[6], M.C. Heinrich[7]. *[1]Brigham and Women's Hospital, Pathology, Boston, USA; [2]OHSU Cancer Institute, Pathology, Portland, USA; [3]Brigham and Women's Hospital, Surgical Oncology, Boston, USA; [4]Brigham and Women's Hospital, Medical Oncology, Boston, USA; [5]OHSU Cancer Institute, Hematology/Medical Oncology, Portland, USA; [6]Ludwig Center at Dana-Farber/Harvard, Medical Oncology/Solid Tumor Oncology, Boston, USA; [7]OHSU Cancer Institute and Portland VAMC, Hematology/Medical Oncology, Portland, USA*

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)

L. Lindner[1], O. Mella[2], M. Kuhlencordt[3], P. Reichardt[4], P. Hohenberger[5], S. Abdel-Rahman[1], M. Schmidt[6], J. Verweij[7], J. Blay[8], R. Issels[9]. *[1]Klinikum Grosshadern, Medical Department III, Munich, Germany; [2]Haukeland Hospital, Department of Radiotherapy, Bergen, Norway; [3]Interne Klinik Dr. Argirov, Department of Internal Medicine, Berg, Germany; [4]Charite-Campus Virchow, Department of Internal Medicine, Berlin, Germany; [5]Universitätsklinikum Mannheim, Department of Surgery, Mannheim, Germany; [6]Klinikum Grosshadern, Institute of Medical Informatics Biostatistics and Epidemiology, Munich, Germany; [7]Erasmus University Medical Center, Department Medical Oncology, Rotterdam, The Netherlands; [8]INSDETM Centre Léon Bérard, Department Medical Oncology, Lyon, Georgia; [9]GSF – Nat. Res. Center for Environment and Health, Department of Molecular Immunology, Munich, Germany*

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

J. Jimeno[1], P. Schöffski[2], P. Casali[3], F. Grosso[3], I. Judson[4], M. Scurr[4], J.Y. Blay[5], R. Maki[6], A. LeCesne[7], R. Rosell[8]. *[1]PharmaMar, R&D, Madrid, Spain; [2]UZ Gasthuisberg, Medical Oncology, Leuven, Belgium; [3]Nazionale Tumori, Medical Oncology, Milan, Italy; [4]Royal Marsden Hospital, Medical Oncology, London, United Kingdom; [5]Centre Leon Berard, Medical Oncology, Lyon, France; [6]Memorial Sloan Kettering Cancer Center, Medical Oncology, New York, USA; [7]Institut Gustave Roussy, Medical Oncology, Paris, France; [8]Hospital Germans Trias i Pujol, Medical Oncology, Barcelona, Spain*

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