was found with trabectedin. Similar antitumour efficacy was shown in pts younger and older than 60 years in a multivariate analysis.

9403 ORAL

Eribulin mesylate (E7389) in patients with leiomyosarcoma (LMS) and other (OTH) subtypes of soft tissue sarcoma (STS): a Phase II study from the European Organisation for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group (EORTC 62052)

P. Schöffski[1], J.T. Hartmann[2], P. Hohenberger[3], A. Krarup-Hansen[4], J. Wanders[5], C. Hayward[5], D. Druyts[6], M. Van Glabbeke[7], R. Sciot[7], J.Y. Blay[8]. *[1]University Hospitals Leuven, General Medical Oncology, Leuven, Belgium; [2]Comprehensive South West German Comprehensive Cancer Center Eberhard-Karls-Universität, Oncology and Hematology, Tübingen, Germany; [3]Universitätsmedizin Mannheim, Surgical Oncology and Thoracic Surgery, Mannheim, Germany; [4]Copenhagen University Hospital, X, Herlev, Denmark; [5]EISAI Europe Ltd., London, United Kingdom; [6]EORTC Headquarters, Brussels, Belgium; [7]University Hospitals Leuven, Department of pathology, Leuven, Belgium; [8]Centre Léon Bérard, Department of Medical Oncology, Lyon, France*

Purpose: Eribulin is a synthetic analogue of halichondrin B, a substance derived from a marine sponge (Lissodendoryx sp.). Eribulin binds close to but does not overlap with the vinca domain of tubulin, inhibits tubulin polymerization and forms non-functional tubulin aggregates, resulting in inhibition of mitotic spindle assembly, induction of cell cycle arrest at the G2/M phase and tumor regression in preclinical models. EORTC 62052 assesses the efficacy and safety of eribulin mesylate in four strata of pts with different STS.
Patients and Methods: We report on the completed LMS (39 pts) and OTH (30 pts) strata of this trial. Results on adipocytic and synovial sarcoma will be reported elsewhere. Pts with intermediate or high grade STS who had received no more than two lines of previous chemotherapies (two single agents or one combination) for advanced disease, with documented progression, adequate performance status, and good organ function were eligible. Eribulin mesylate 1.4 mg/m^2 was given over 2−5 min as i.v. bolus on days 1 and 8 every three weeks until intolerance or disease progression. The primary end point was the progression-free rate at 12 weeks (PFR12wks) according to RECIST. Secondary end points included safety, response and time-related parameters. A Simon 2-stage design was applied (P1: 40%; P0: 20%; $\alpha = \beta = 0.1$) for each stratum.
Results: Grade 3−4 drug-related adverse events occurring in >1 pat were leucopenia (34% of pts), neutropenia (51%), anemia (9%), febrile neutropenia (4%), increases in ALAT (3%) and fatigue (3%). One patient died of cerebrovascular ischemia, for which a relationship with eribulin could not be ruled out. The PFR12wks was 32% (12/37 pts) in LMS and 29% (7/24 evaluable pts) in OTH. The median PFS in LMS was 3 mo (95% confidence interval 2−4), the median OS 18 (9-N) mo, with 65% of pts alive at 1 year, which compares favorably to historical controls. The median PFS in OTH was 2 (1−3) mo, the median OS 8 (5−15) mo, with 26% of pts alive at 1 year. Conclusions: Eribulin mesylate is very well tolerated in pretreated pts with defined subtypes of STS, and it deserves further study in LMS. The PFR12wks reached predefined statistical boundaries by the Simon 2-stage design in both LMS and OTH.

9404 ORAL

A Phase II study of cediranib in patients with metastatic gastrointestinal stromal tumours (GIST) and metastatic soft tissue sarcoma (STS) (including alveolar soft part sarcoma [ASPS])

K. Gardner[1], I. Judson[1], M. Leahy[2], E. Barquin[1], M. Marotti[3], B. Collins[3], H. Young[3], M. Scurr[1]. *[1]Royal Marsden Hospital, London, United Kingdom; [2]The Christie Hospital, Manchester, United Kingdom; [3]AstraZeneca, Alderley Park, Macclesfield, United Kingdom*

Background: Cediranib (RECENTIN™) is an oral highly potent VEGF signalling inhibitor of all three VEGF receptors. The primary objective of this open-label, two-centre study was to assess the antitumour activity of cediranib in patients with GIST using FDG-PET (standardized uptake value, SUV_{max}). Secondary objectives included assessments of objective tumour response (RECIST), and safety and tolerability in both GIST and STS.
Methods: Patients with histologically or cytologically confirmed GIST resistant or intolerant to imatinib, or metastatic STS refractory to standard therapies or for which no standard therapy existed, received cediranib 45 mg/day (ClinicalTrials.gov Identifier NCT00385203; AZ 2171IL/0046). The primary analysis was performed after all patients had received 16 weeks of treatment and had undergone a week 16 scan for RECIST assessment or had withdrawn from the study before week 16.
Results: Thirty-six patients were enrolled and 34 received treatment with cediranib with a mean daily dose of 36 mg (GIST: n = 24 [13 of whom had previously received sunitinib following imatinib]); STS: n = 10, including ASPS: n = 6). In the GIST patients, FDG-PET showed no significant change from baseline in mean SUV_{max} at days 8 or 29. Some partial metabolic responses were observed in individual patients (Table). Best objective response (RECIST) in the GIST patients showed a 62% stable disease (SD) rate (Table), including 10 patients with SD >16 weeks. There was some evidence of antitumour activity in patients with STS, particularly in the six patients with ASPS (PR, n = 3; SD, n = 3 [including 2 patients with SD >16 weeks]). The most common adverse events (GIST; STS) were diarrhoea (n = 18; n = 6), fatigue (n = 15; n = 7) and hypertension (n = 17; n = 3).
Conclusions: This ongoing study has provided evidence of activity with cediranib monotherapy in some patients with second- and third-line GIST as measured by FDG-PET and SD >16 weeks. In patients with metastatic ASPS, cediranib showed evidence of antitumour activity by RECIST and further investigation in this disease is warranted. The overall safety profile was consistent with previous cediranib studies.

	GIST (n = 24)	
	Day 8 (n = 22)	Day 29 (n = 20)
FDG mean % change from baseline in SUV_{max} (95% CI)	6.8%(−19.95, 33.54)	4.6% (−8.05, 17.34)
FDG tumour response, n	Day 8 (n = 24)	Day 29 (n = 24)
Partial metabolic response (PMR, SUV decrease ⩾25%)	3*	4
Stable metabolic disease (SUV increase ⩽25% or decrease <25%)	16	12
Progressive metabolic disease (SUV increase >25%)	3	4
Non-evaluable	2	4

*Including 1 unconfirmed PMR

Best overall response (RECIST), n	GIST (n = 24)	STS	
		ASPS(n = 6)	Other (n = 4)
CR	0	0	0
PR	0	3	0
SD	15	3	1
Progressive disease	5	0	1
Non-evaluable	4	0	2

9405 ORAL

Spectrum of KIT and PDGFRA mutations in primary gastrointestinal stromal tumours: Polish clinical GIST registry experience

A. Wozniak[1], P. Rutkowski[2], M. Debiec-Rychter[3], J. Siedlecki[4], W. Michej[5], C. Osuch[6], M. Matlok[7], W. Ruka[2], J. Limon[1]. *[1]Medical University of Gdansk, Department of Biology and Genetics, Gdansk, Poland; [2]Sklodowska-Curie Cancer Institute, Department of Soft-Tissue/Bone Sarcoma and Melanoma, Warsaw, Poland; [3]Catholic University of Leuven, Center for Human Genetics, Leuven, Belgium; [4]Sklodowska-Curie Cancer Institute, Department of Molecular Biology, Warsaw, Poland; [5]Sklodowska-Curie Cancer Institute, Department of Pathology, Warsaw, Poland; [6]Jagiellonian University, Dept of Surgery, Cracow, Poland; [7]Jagiellonian University, Department of Surgery, Cracow, Poland*

Background: *KIT* or *PDGFRA* gene mutations are found in 80−90% of gastrointestinal stromal tumors (GIST). The prognostic value of those mutations for the outcome in primary tumours is controversial. Objective: To assess the spectrum, frequency and prognostic significance of the *KIT* and *PDGFRA* gene mutations in Polish group of surgically treated primary GISTs.
Materials and Methods: DNA isolated from paraffin blocks from 300 patients (pts) with histologically diagnosed primary GISTs included in clinical registry database, were analyzed using denaturing high performance liquid chromatography DNA isolated from paraffin blocks from 300 patients (pts) with histologically diagnosed primary GISTs included in clinical registry database, were analyzed using denaturing high performance liquid chromatography (DHPLC) and direct sequencing for *KIT* (exons 9, 11, 13, 17) and *PDGFRA* (exons 12, 14, 18) mutations. For primary GIST risk assessment the Miettinen stratification was used.
Results: *KIT*/*PDGFRA* genes mutations were found in 82% tumours: *KIT* was mutated in 69% and *PDGFRA* in 13%/genes mutations were found in 82% tumors: was mutated in 69% and in 13% of tumors. *KIT* exon 11 and 9 mutations were found in 61.5% and 7.5% respectively. Among *KIT* exon 11 mutants the most frequent were deletions (32.7%) followed by point mutations (15.3%), duplications (8.4%) and complex rearrangements (5.1%). *KIT* exon 11 mutations were found at the similar rates in tumours with gastric and nongastric localization (53.9% vs. 46.1% respectively) while *KIT* exon 9 duplications were more often observed in nongastric GISTs (86.4%, p = 0.00036) and *PDGFRA* mutations were more frequently found in tumours originated from the stomach (86.8%; p = 0.00017). In high

risk tumors *KIT* exon 11 deletions were more frequently found than point mutations (p = 0.017). On the other hand mutations in *PDGFRA* were more often observed in very low-/low- than high risk GISTs as compared to *KIT* exon 11 (p = 0.0026). There was no statistically significant correlation between disease-free survival and the spectrum or frequency of mutations.
Conclusions: Spectrum and frequency of *KIT* and *PDGFRA* mutations in Polish GIST population are similar to the Spectrum and frequency of and mutations in Polish GIST population are similar to the previously described groups. No significance of mutations for disease outcome after surgery of primary tumors was found.

9406 ORAL

Can a surgical classification provide information on the necessity of adjunctive medical treatment for resected GIST?

U. Ronellenfitsch[1], J. Jakob[1], P. Ströbel[2], D. Pink[3], C. Krefter[1], P. Reichardt[3], E. Wardelmann[4], P. Hohenberger[1]. [1]*University Hospital Mannheim, Division of Surgical Oncology, Mannheim, Germany;* [2]*University Hospital Mannheim, Institute of Pathology, Mannheim, Germany;* [3]*Sarcoma Center Berlin-Brandenburg, Department of Internal Medicine, Bad Saarow, Germany;* [4]*University Medical Center Bonn, Department of Pathology, Bonn, Germany*

Background: Gastrointestinal stromal tumors (GIST) differ in their risk to recur or metastasize after resection of the primary. It has been tried to define criteria for the usefulness of adjunctive medical therapy. So far, most classifications draw on size, mitotic count and location and do not regard surgical aspects. We evaluate if a classification of the surgical procedure used to resect the primary proves useful in defining candidates for adjunctive treatment.
Patients and Methods: 457 pts with confirmed GIST were retrieved from a prospective database. Primary location was: oesophagus n = 9 (2%), stomach n = 199 (44%), duodenum n = 21(4%), small bowel n = 141(31%), rectum n = 31(7%), others and metastatic n = 56 (12%). Resections were classified into: enucleation (class1), limited (segmental small bowel, Billroth I; class2), standard organ removal (gastrectomy, anterior resection; class 3), and multivisceral (class 4). Median tumor size was 7.5 (range 0.5−37) cm. All tumors were classified according to Consensus (Hum Pathol 2002). Median follow-up was 31 months. Pts treated with imatinib pre- or postoperatively were excluded from the analysis of recurrence.
Results: Operations were class 1: n = 57, class 2: n = 158, class 3: n = 59, class 4: n = 96. N = 51 M1 pts did not undergo resection of the primary, and for n = 36 pts data were incomplete. R0 resection rate was 80%, R1 rate 11%, and R2 rate 9%. Pre- or intraoperative tumor rupture occurred in n = 24 pts. Tumors were classified in 4.4% as very low, 11.5% low, 19% intermediate, and 65% high risk for aggressive behaviour. 44% of pts eligible for analysis recurred. After multivisceral resection (class 4), 52/68 eligible pts (77%) developed recurrence after a median of 10 months. In groups 3, 2, and 1, the recurrence rate was 59%, 50% and 37% respectively (p < 0.01). 18/19 pts with tumor rupture suffered from recurrence.
Conclusions: For GIST, the risk of postoperative tumor recurrence increases with the extent of the surgical procedure. Patients who require multivisceral resection or have tumor rupture show a significantly adverse course with early recurrence even after R0 resection. They must be considered having metastatic disease and adjunctive medical therapy is strongly recommended regardless of tumour size or mitotic count. In other cases, a classification of the surgical procedure can provide complementary information to estimate the risk of tumor recurrence and thus the necessity for adjunctive treatment.

Poster presentations (Wed, 23 Sep, 09:00−12:00)
Sarcoma

9407 POSTER

Ewing's family (EFT) tumours: biomolecular characterization on paraffine-embedded samples

S. Del Bianco[1], A. Parafioriti[1], E. Armiraglio[1], P. Daolio[2], S. Mapelli[2]. [1]*Orthopaedic Institute Gaetano Pini, Pathology, Milan, Italy;* [2]*Orthopaedic Institute Gaetano Pini, Oncologic Orthopaedic Surgery Center, Milan, Italy*

Background: Ewing sarcoma is a malignant bone tumour characterized, in 90% of the cases, by the balanced chromosomal translocation t(11;22) which generates a chimeric oncogene that acts as a transcriptional activator. The detection of translocation can be fundamental in cases with an extraosseous or unusual location which are difficult to diagnose histologically and it is also helpful in evaluation of residual disease. We joined immunohistochemical analysis with a routine RT-PCR method which allows the detection of the more common fusion transcript EWS-FLI1 in archival paraffine-embedded tissues of EFT patients. We used a pair of primers which allowed us to discriminate between two subtypes of EWS-FLI1 transcript. We selected some samples for EWS-FLI1 typing using a Real.Time PCR assay.
Material and Methods: We analysed 54 EFT patients. RNA was extracted from paraffine-embedded sections and reverse transcribed into cDNA. On every sample we performed RT-PCR and immunohistochemistry for the marker CD99; we also selected 5 samples for Real-Time PCR analysis.
Results: Fourty-nive out of 54 samples had a RNA suitable for analysis. Thirthy-six patients had EWS-FLI1 type I fusion transcript while 6 patients EWS-FLI1 type II; in 7 samples we couldn't find any fusion transcript although their RNA was good. We tested 5 of these negative samples with Real-Time PCR and we found 2 patients who were carriers of EWS-FLI1 type I fusion transcript. CD99 resulted positive in 34 samples out of 54.
Conclusions: The detection of fusion transcripts using RT-PCR methods can be useful as a support to EFT diagnosis. Moreover the possibility to assess a Real-Time PCR assay enhances analysis sensibility and minimizes false positives risk. EFT cytogenetic characterization completes morphologic and immunophenotipic data owing a more careful classification and an identification of subgroups with different prognosis.

9408 POSTER

Synovial sarcoma: molecular characterization from paraffine-embedded samples

S. Del Bianco[1], A. Parafioriti[1], E. Armiraglio[1], P. Daolio[2], S. Mapelli[2]. [1]*Orthopaedic Institute Gaetano Pini, Pathology, Milan, Italy;* [2]*Orthopaedic Institute Gaetano Pini, Oncologic Orthopaedic Surgery Center, Milan, Italy*

Background: Synovial sarcomas are mesenchymal tumours with undefined histogenesis which represent 5−10% of soft tissues tumours; they are divided into different subtypes according to morphology and epithelial differentiation. From a molecular point of view, synovial sarcoma is characterized by t(X;18)(p11; q11) translocation which joins SYT gene with a member of SSX gene family. We developed an efficient method to detect the two main fusion transcripts SYT-SSX1 and SYT-SSX2 based on RT-PCR or Real-Time PCR applied to archival paraffine-embedded samples.
Material and Methods: This study includes 51 patients surgically treated for synovial sarcoma and analyzed with routine immunohistochemical analysis. We used alternatively nested-PCR or Real-Time PCR, with SYBR green method, to detect SYT-SSX transcripts: these techniques allowed us to discriminate between the two transcripts.
Results: In 44 subjects out of 51 we could find a specific fusion transcript and, in particular, 32 patients were carriers of SYT-SSX1 translocation. Interestingly we could find 7 patients who were carriers of both SYT-SSX1 and SYT-SSX2 transcripts. In 5 patients we didn't detect any fusion transcript. We selected 12 samples for Real-Time PCR analysis and we could quantify the reciprocal ratio between the two fusion transcripts when they were both present in the same sample.
Conclusions: The use of molecular techniques such as RT-PCR represents a sensitive and reliable tool as an aid to histopathologic diagnosis of synovial sarcoma. Moreover, Real-Time PCR enormously enhances sensibility and enables to dose single transcript quantity when both SYT-SSX1 and SYT-SSX2 are present in the same sample. This method can also be used to reclassify those cases whom diagnosis is still undefined after routine analysis.

9409 POSTER

Inhibition of Notch pathway prevents osteosarcoma growth by regulation of cell cycle

T. Setoguchi[1], M. Tanaka[1], S. Komiya[1]. [1]*Graduate School of Medical and Dental Sciences Kagoshima University, Department of Orthopaedic Surgery, Kagoshima, Japan*

Background: It was demonstrated constitutive activation of the Notch pathway in various types of malignancies. However, it remains unclear how the Notch pathway is involved in the pathogenesis of osteosarcoma. We investigated the expression of the Notch pathway molecules in osteosarcoma biopsy specimens' and examined the effect of Notch pathway inhibition.
Materials and Methods: Real-time PCR was performed with specific primers. Immunohistochemistry was performed using human osteosarcoma cell lines and human osteosarcoma samples. Cells were treated with increasing concentrations of various GSI (Notch signal inhibitor). *CBF1* siRNA was used to confirm the effect of Notch signal inhibition. Cell proliferation was quantitated using a MTT assay. Nude mice were inoculated with osteosarcoma cells. Cell cycle was analyzed by flow cytometry. The expression of the components of cell cycle machinery was analyzed by real-time PCR and western blot.