Sarcoma

Oral presentations (Thu, 24 Sep, 09:00−10:45)
Sarcoma

9400 ORAL

A phase II clinical trial of neoadjuvant trabectedin in patients with non metastatic advanced myxoid / round cell liposarcoma (MRCL)

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Background: Trabectedin (T) (ET-743, Yondelis®), a marine-derived alkaloid has demonstrated significant activity in the treatment of soft tissue sarcomas (STS) and has received EMEA approval for this indication. Myxoid /round cell liposarcoma (MRCL), a subtype that accounts for 10% of STS, displays the (12:16) (q13; p11) translocation leading to the fusion gene FUS-CHOP in 95% of all cases. Preliminary results of neoadjuvant T in advanced MRCL showed reduction in size and density of the tumor, clinical improvement, and a pathological complete response (pCR) in the resected tumor mass. A phase II multicenter study to further determine the response to T in the MRCL population is presented.
Methods: Patients (pts) with locally advanced (stage III) or locally recurrent MRCL were treated for 3−6 cycles with T (1.5 mg/m^2 q3wk) in the neoadjuvant setting. Main endpoints were: pCR rate, objective response rate by RECIST and correlation of molecular parameters from tissue samples with clinical outcomes.
Results: Twenty-nine pts with locally advanced MRCL were recruited, 23 of them evaluable. All had the translocation which causes the chimeric FUS-CHOP. Median age was 47 (23−75) and male:female ratio was 1.2;1. Nineteen pts had completed therapy and undergone curative surgery. Pathological assessment was performed in 16 pts: 2 achieved pCR, as per central pathology review, 1 pt had a very good pathological response and 7 had moderate tumor regression. Seven patients remain to be histologically evaluated. Response rate by RECIST from pts who completed therapy was: 5 partial responses (26%) and 14 disease stabilizations. Remarkably, pathological response did not entirely correlate with response by RECIST since pts with pCR still had radiological disease but no malignant component was found in the excised tumor mass (connective and reactive tissue). Three serious adverse reactions of severe rhabdomyolysis, asthenia, nausea and transaminase elevation and mucositis were reported. Most common events were liver enzyme elevation, neutropenia and thrombocytopenia. Updated results will be presented.
Conclusion: These results in terms of objective and complete pathologic responses, strongly suggest that T may have an important role in the neoadjuvant setting in pts with MRCL.

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Translocation-related sarcomas (TRS): a retrospective analysis of activity with trabectedin

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Background: Twenty-five percent of soft tissue sarcomas (STS) have specific recurrent chromosomal translocations, which result in chimeric fusion proteins that act as abnormal transcription factors. These proteins are potential targets for developing more effective therapies for STS. In a retrospective analysis, 51 patients (pts) with advanced pretreated myxoid liposarcoma (MLPS) characterised by specific translocation (t(12.16) (q13: p11)) showed an overall response rate of 51% and a median progression-free survival (PFS) of 14 months after receiving compassionate-use trabectedin (Yondelis®) (T) (Grosso F et al., Lancet Oncol 2007; 8:595−602). The current retrospective pooled analysis includes data from 8 multicentre phase II trials to further assess the efficacy of T in TRS.
Materials and Methods: Data from 81 pts with TRS were included in the analysis; these represent around 10% of all STS pts treated with T in clinical trials.
Results: 52% of pts were male and median age was 43 years (range, 17−76). All had a performance status (PS) score of 0/1 at baseline. Tumour types were synovial sarcoma (SS) (n = 45), MLPS (n = 27), alveolar soft part sarcoma (n = 4), endometrial stromal sarcoma (ESS) (n = 3) and clear cell sarcoma (n = 2). All patients but one received prior chemotherapy (median 2 lines; range, 0−4). T schedules were 24-hour infusion every 3 weeks (q3wk) (n = 43), 3-hour infusion q3wk (n = 24) and 3-hour infusion weekly (n = 14). Pts received a median of 4 T cycles (range, 1−48), with a median dose intensity of 0.40 mg/m^2/wk (range, 0.15−0.50). Discontinuations were due to disease progression (n = 53, 65%), toxicity (n = 7, 9%), death (n = 5, 6%) or other causes (n = 16, 20%). Partial responses (PR) occurred in 8 pts: 10%, (SS n = 3 (7%), MLPS n = 4 (15%), and 1 ESS) and stable disease (SD) in 40 (49%). Tumour control was achieved in 48 pts (59%). Median PFS was 4.1 months [95% confidence interval (CI): 2.8−6.1)], with 3-month and 6-month PFS rates of 57% (95% CI: 46−68%) and 40% (95% CI: 29−51%). Median overall survival was 17.4 months (95% CI: 11.1−23.2) and survival rate at 12 months was 60% (95% CI: 49−71%). All T schedules had acceptable and manageable safety profiles.
Conclusions: T showed encouraging antitumour activity in TRS that deserves to be further explored. A randomised, phase III trial is ongoing to compare T with doxorubicin-based chemotherapy as first-line therapy in pts with TRS.

9402 ORAL

Efficacy and safety of trabectedin in soft tissue sarcoma (STS) are independent of patient age

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Background: Limited data are available on the benefits of chemotherapy in older patients (pts), generally under-represented in clinical trials. Nearly half of pts with STS are ⩾65 at diagnosis, and 16% of those aged ⩾70 receive no treatment (Nijhuis PH et al. Eur J Cancer 1999, 35(12): 1705−10).
Materials and Methods: A pooled analysis of data from 5 phase II trials assessed the effects of age on the efficacy and safety of trabectedin (Yondelis®) [1.5 mg/m^2 as a 24-hour intravenous (i.v.) infusion every 3 weeks] in 350 STS pts.
Results: The younger cohort included 267 pts aged <60 years [median 48 years (19−59)] and the older cohort had 83 pts aged ⩾ 60 years [median 65 years (60−81)]. Most pts were female (61% and 54%), had liposarcoma/leiomyosarcoma (72% and 75%) and a performance status (PS) score of 0/1 (99.6% and 98.8%), respectively. Pts were pretreated with a median of 1 line each. A median of 3 trabectedin cycles was given (range 1−48 and 1−59 for younger and older pts), with median dose intensities of 0.42 mg/m^2/wk (younger cohort) and 0.40 mg/m^2/wk (older cohort). Overall, the response rate was 10% in both cohorts (complete + partial response), while stable disease occurred in 40% of younger pts and 47% of older pts. No significant differences in median progression-free survival (PFS) were observed (p = 0.44). PFS rates at 6 months were 30% [95% CI: 24−35%] in younger pts and 36% (95% CI: 26−47%) in older pts. Median overall survival (OS) was 13.0 months (95% CI: 11.3−14.9) and 14.0 months (95% CI: 9.5−23.9), respectively, and OS rates were 55% and 56% at 12 months, and 29% and 38% at 24 months. Grade 3/4 toxicities were slightly more common in older pts (fatigue 6.3% *vs.* 14.4%, neutropenia 43.6% *vs.* 60.2%, thrombocytopenia 11.3% *vs.* 20.5%, anaemia 10.1% *vs.* 19.2%) but major complications were uncommon (grade 3/4 febrile neutropenia 0.4% *vs.* 1.2%) and use of colony stimulating factors (G-CSF) was similar (12.7% *vs.* 13.3%). No major differences were found in the safety profile of a subset of 24 pts aged ⩾70 years.
Conclusions: Even in these older pts, trabectedin has an acceptable and manageable safety profile. Trabectedin appears better tolerated than agents commonly used in STS therapy (doxorubicin, ifosfamide), which are more likely to cause dose-limiting cardiac and renal toxicity in older pts. In contrast, no evidence of cumulative toxicity or end-organ dysfunction

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)

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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])

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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

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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