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.

9401 ORAL

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