ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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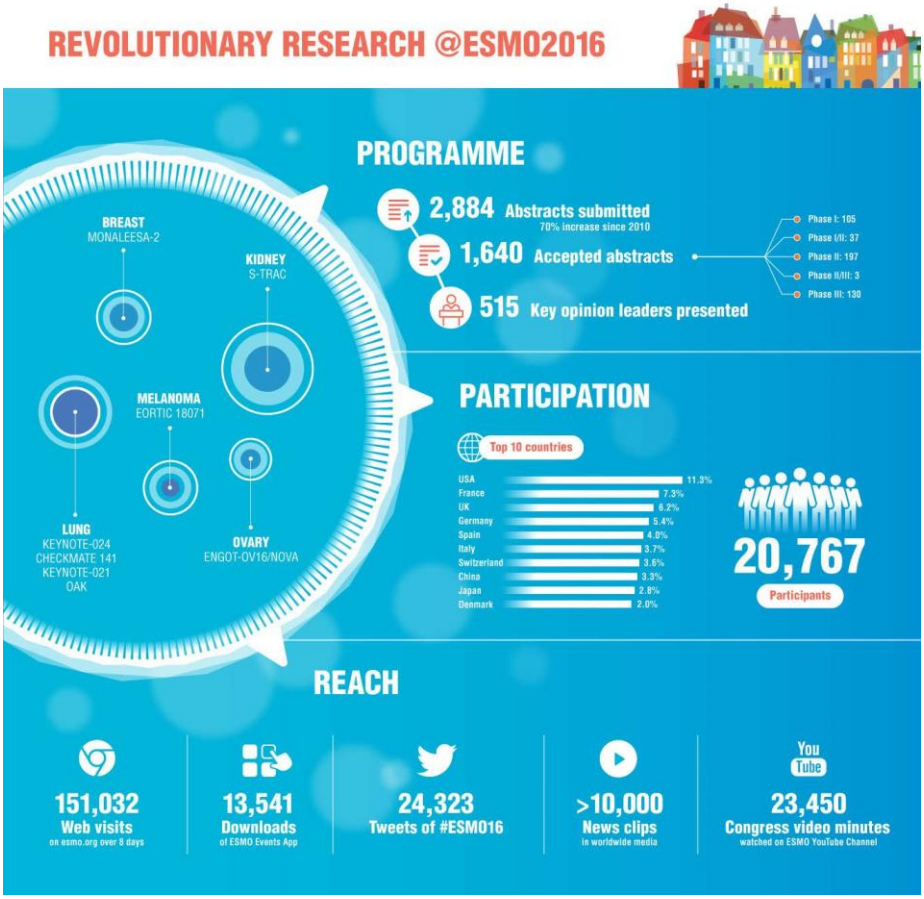
Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

SARCOMA

Neoadjuvant chemotherapy in patients with localised high-risk STS

No additional benefit was observed from chemotherapy regimens that were matched to specific histologic subtypes of sarcoma but the study did show that neoadjuvant chemotherapy with an anthracycline plus ifosfamide associates with significant survival gains in patients with localised high grade soft tissue sarcoma (STS) of the trunk or extremities. Alessandro Gronchi, Chair of the Sarcoma Surgery at the National Cancer Institute, Milan, Italy presented findings from an interim analysis on behalf of the Italian Sarcoma Group from a multi-centre study, of patients with localised high-risk STS of the trunk or extremities. The study compared neoadjuvant chemotherapy with chemotherapy regimens that were tailored to the individual histology sub-types based upon previously published data. Patients with one of the 5 sarcoma histological subtypes were randomised 1:1 to receive pre-operative treatment with either 3 cycles of epirubicin at 120 mg/m^2 plus ifosfamide at 9 g/m^2, or to receive 3 cycles of one of the following histology-based regimens:

- Trabectedin in 65 patients with high-grade myxoid liposarcoma
- Gemcitabine/docetaxel in 97 undifferentiated pleomorphic sarcoma patients
- High-dose prolonged-infusion ifosfamide in 70 patients with synovial sarcoma
- Gemcitabine/dacarbazine in 28 patients with leiomyosarcoma
- Etoposide/ifosfamide in 27 patients with malignant peripheral nerve sheath tumours

After a median follow-up of 12.3 months, patients randomised to epirubicin plus ifosfamide showed significantly higher probability of relapse-free survival (RFS) at 46 months regardless of underlying histological subtype compared to patients randomised to a histology-driven regiment; the RFS probability was 0.62 versus 0.38 ($p = 0.004$), and the probability of overall survival (OS) was 0.89 versus 0.64, ($p = 0.033$). The study was halted early.

Subgroup analysis showed that patients with high-grade myxoid liposarcoma fared as well on trabectedin as with neoadjuvant chemotherapy; this subgroup demonstrated similar progression-free survival and OS to patients receiving epirubicin plus ifosfamide. This was an important finding, since trabectedin is far less toxic than conventional chemotherapy, according to the authors who now plan to expand this subgroup to evaluate whether there is a difference between the treatments in terms of outcomes. NCT01710176; EUDRACT 2010 – 023484 – 17. Gronchi *et al.* Abstract LBA6_PR

Practice point and future research opportunities

The benefit of adjuvant chemotherapy in STS has been controversial in recent years due to contradictory study outcomes. From this study, it may be concluded that neoadjuvant anthracycline plus ifosfamide is better than the histology-driven regimens, but it remains

unresolved whether neoadjuvant chemotherapy is better in comparison to no treatment. To address this controversy, it is necessary to show that using a neo-adjuvant therapy in patients affected by localised high risk STS of the extremities or trunk wall is associated with a clear-cut OS and RFS advantage, as compared with any other strategy, including no treatment.

No additional benefit with evofosfamide in combination with doxorubicin over doxorubicin monotherapy in patients with advanced STS

The results for evofosfamide, a prodrug that is activated under hypoxic conditions commonly found in the tumour microenvironment and leads to DNA alkylation, were reported by lead author William Tap, Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA. Evofosfamide was tested in multi-national, open-label, phase III trial that randomised equally 640 patients to doxorubicin on day one or doxorubicin plus evofosfamide at 300 mg/m^2 i.v. on days 1 and 8 of a 21-day cycle. The patients had locally advanced unresectable or metastatic soft tissue sarcoma (STS), intermediate or high grade, ECOG performance status 0/1, and measurable disease by RECIST 1.1. Leiomyosarcoma was confirmed in 36% of patients, 17% had liposarcoma, and 12% of patients had undifferentiated pleomorphic sarcoma. Metastatic disease was reported for 89% of patients and 11% had locally advanced disease. The primary endpoint was overall survival (OS).

A median of 6 cycles were delivered and the docetaxel dose intensity was >90% through 6 cycles, in both arms. The 317 patients in the evofosfamide/docetaxel showed poorer outcomes than the 323 patients on docetaxel and the primary endpoint of OS was not met, (hazard ratio [HR] 1.06; 95% confidence interval [CI] 0.88, 1.29). The median OS was 18.4 months with the combination versus 19.0 months with docetaxel. Although the response rate favoured the combination, no statistically significant difference was observed in progression-free survival (PFS) between the groups. The response rate was 28.4% with evofosfamide/docetaxel versus 18.3% with docetaxel, odds ratio 1.77; 95% CI 1.20, 2.58 (p = 0.003). Median PFS was 6.3 months on evofosfamide/docetaxel versus 6.0 months on docetaxel, HR 0.85; 95% CI 0.70, 1.03 (p = 0.099).

The most common grade 3/4/5 adverse events (AEs) were anaemia (35%), neutropenia (33%) and leucopenia (18%). Febrile neutropenia occurred in 18% of patients on evofosfamide/docetaxel and 11% of patients on docetaxel. The AEs leading to death were reported in 2.6% of patients on evofosfamide plus docetaxel and for 1.0% of patients on docetaxel. The AEs led to discontinuation in 8.3% and 6.2% of patients in the respective treatment arms. NCT01440088. Tap *et al.* Abstract 1395O

Practice point and future research opportunities

The combination of evofosfamide/docetaxel did not improve OS or PFS compared to docetaxel alone. The safety profile was consistent with previous reports. Evofosfamide is still being evaluated in pancreatic cancer and soft tissue sarcoma.

PFS improved with trabectedin over BSC in patients with pretreated advanced STS

Axel Le Cesne, Department of Medicine, Institut Gustave Roussy, Villejuif, France and colleagues in the French Sarcoma Group assessed the efficacy, safety and quality of life of trabectedin versus best supportive care (BSC) as a second or later treatment line in patients with advanced soft tissue sarcoma (STS) in the phase III, multicentre T-SAR trial. The trial enrolled 103 patients with histologically proven advanced STS, including both lipo-leiomyosarcoma and non lipo-leiomyosarcoma histotypes, who progressed after at least one anthracycline-containing regimen but had received fewer than 3 previous chemotherapy lines.

The patients had ≥1 measurable baseline lesion (RECIST v.1.1) and were stratified according to lipo-leiomyosarcoma status; 60.2% of patients had lipo-leiomyosarcoma and 39.8% of patients had non lipo-leiomyosarcoma The patients had WHO performance status scores of 0 or 1, and were required to have adequate haematological and hepatic function. The investigators randomised 52 patients to trabectedin at 1.5 mg/m^2 intravenously for 24 hours for 21 days and 51 patients to best supportive care (BSC) until progressive disease (PD), unacceptable toxicity, or patient's request. Crossover to trabectedin upon PD was allowed for patients receiving BSC. The primary endpoint was progression-free survival (PFS), which was defined as time from randomisation to PD or all-cause death.

After 88 cases of PD were observed the data were evaluated for PFS. The patients receiving trabectedin demonstrated significantly prolonged PFS compared to patients receiving BSC; the median PFS was 3.12 months with trabectedin compared with 1.51 months with BSC, hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.26, 0.63 ($p < 0.0001$). The response to trabectedin was strongest in patients with lipo-leiomyosarcoma where the median PFS was 5.13 months with trabectedin versus 1.4 months with BSC, HR 0.29; 95% CI 0.15, 0.55 ($p < 0.0001$). In the non lipo-leiomyosarcoma cohort the median PFS was 1.81 versus 1.51 months with trabectedin versus BSC, respectively, HR 0.60; 95% CI 0.29, 1.26 ($p = 0.18$). 2014-003176-23. Le Cesne *et al.* Abstract 1396O

Practice point and future research opportunities

Although trabectedin has demonstrated single-agent activity in patients with pretreated advanced STS and has been approved in Europe since 2007 for this indication, trabectedin had not been compared with BSC in a randomised trial comprising patients with all sarcoma histotypes. The pre-planned analysis in this study demonstrated a significant improvement in median PFS with trabectedin over BSC in patients with pretreated advanced STS of multiple histologies, thereby meeting the primary endpoint of the study. Trabectedin had a major impact in the lipo-leiomyosarcoma STS cohort whereas in the non lipo-leiomyosarcoma STS group the median PFS was lower and similar to that seen in the BSC cohort and showed a statistically non-significant difference, suggesting that these patients could benefit more from a treatment other than trabectedin.

The NETSARC reference network of sarcoma patients shows a major impact of multidisciplinary board presentation prior to first treatment

Jean-Yves Blay, Medical Oncology, Centre Léon Bérard, in Lyon, France, presented outcomes of the 26,883 patients registered in the NETSARC multidisciplinary tumour boards (NMTB) and demonstrated how NMTB discussion enabled better care for these patients. This network of 26 reference centres for sarcoma in France was designated by the French National Cancer Institute in 2009 and includes the patient characteristics, treatment and diagnosis procedures, disease progression, and survival information for patients with sarcomas.

Soft tissue, visceral, and bone sarcomas represent 17,801 (66%), 4,625 (17%), and 4,457 (17%) patients, respectively. Individual NETSARC centres managed a median of 404 (range: 92.2 to 974) patients in 5 years.

The median follow-up of the series in this study was 26 months (range: 6 to 590 months). During this time, 13,845 women (52%) and 13,038 men (48%), with a median age of 60 years (range: 0 to 101) were treated within the NETSARC network. The most frequently diagnosed histotypes were leiomyosarcoma, gastrointestinal stromal tumour (GIST), liposarcoma, and undifferentiated pleomorphic sarcoma. At diagnosis, 11% of patients presented with metastases and 37% of patients were presented to a NMTB prior to initial treatment. At 24 months, local and metastatic relapse rates were 24% and 22%, respectively. The 24-month overall survival rate was 87%.

Investigators reviewed relapse rates in patients not reviewed and those reviewed by NMTB prior to treatment and found the local relapse rate (LRR) was significantly lower in patients discussed in NMTB prior to receiving the first treatment; LRR was 22% for non-reviewed versus 29% for reviewed patients at 24 months ($p = 0.000$); however, metastatic relapse rates did not significantly differ between these groups. Patients discussed in NMTB prior to the first treatment had significantly larger tumours of a higher grade that were more frequently deep-seated and located in the head/neck or internal trunk ($p = 0.000$ all comparisons).

In multivariate analysis, the lack of discussion in NMTB prior to initial treatment emerged as an independent unfavourable prognostic factor for relapse, (hazard ratio [HR] 1.9; 95% confidence interval [CI] 1.6, 2.2) together with age, grade, tumour size, depth and tumour location (all p values < 0.001), and lack of discussion was also associated with the highest hazard ratio along with tumour status of grade 3. Blay *et al.* Abstract 1397O

Practice point and future research opportunities

This large audit demonstrates how discussion of patients by multidisciplinary tumour boards prior to the first treatment resulted in overall better outcome for these patients that associated with a lower rate of relapse. The relapse rate was found to be higher in this large real-life series of

26,883 sarcoma patients of the NETSARC network than that previously published in the literature.

Characterisation of the tumour microenvironment reveals CD8 T-cell presence associates with improved outcome in localised osteosarcoma

Emanuela Palmerini, Muscoloskeletal Oncology, Istituto Ortopedico Rizzoli in Bologna, Italy and colleagues investigated whether immune infiltrates were associated with superior survival, and examined primary osteosarcoma tissue microarrays (TMA) to test this hypothesis. The investigators analysed biopsies from 129 patients that were prospectively treated from April, 2001 to November, 2006 and TMA from representative areas were assembled. Clinical and pathological characteristics at diagnosis, immunological characterisation including immune cell markers (CD8, CD4, CD3, FOXP3, CD20, CD68) of the tumour microenvironment (TME), PD-1 expression on TME, and PD-L1 both on tumour cells and in the TME were correlated with outcome.

Of the 129 enrolled patients, samples from 86 patients had adequate staining for all markers. The 86 patients had a median age of 16 (range: 4 to 39) years; high LDH was reported in 36 patients and high alkaline phosphatase (AP) in 18 patients. All patients underwent neoadjuvant chemotherapy and surgery, which resulted in a good pathologic response of ≥90% necrosis in 45 patients. The immunohistochemistry revealed that no patients had a tumour that expressed PD-L1but 12 patients had a TME that was positive for PD-L1. PD-1 expression was identified in the tumour and TME of 67 and 74 patients, respectively. CD8, CD3, FOXP3, CD20, and CD68 were detected in the TME of 74, 77, 28, 25, and 85 patients, respectively.

At a median follow-up of 8 years (range: 1 to 13 years), the 5-year overall survival (OS) was 74% (95% confidence interval [CI] 64, 85). Univariate analysis showed better 5-year OS associated with good responders (good 89% versus poor 57%, p = 0.0001), patients with CD8 tumoural infiltrates (CD8+ 78% versus CD8- 50%, p = 0.003), and with patients with normal AP (AP normal 85% versus AP high 44%, p = 0.04). A non-significant inferior 5-year OS was found in PD-L1 (TME) positive cases (PD-L1-positive 58% versus PD-L1 negative 77%, p = 0.14). No statistically significant difference in 5-year OS according to PD-1, FOXP3, CD68, CD20, age, gender or LDH status was observed. By multivariate analysis, good histologic response (p = 0.002) and CD8 infiltration (p = 0.02) were independently correlated with better survival. Palmerini *et al.* Abstract 1399PD

Practice point and future research opportunities

This study confirms the importance of good pathologic response, but also supports the hypothesis that CD8+ T effector cells present in the tumour microenvironment at diagnosis associates with superior survival for patients with localised osteosarcoma and further evaluation as a prognostic factor is warranted.

RELATED INFORMATION

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ESMO 2017 Congress, Madrid, Spain, 8-12 September 2017.

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

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