ESMO 2014 Congress Scientific Meeting Report – Sarcoma Extract

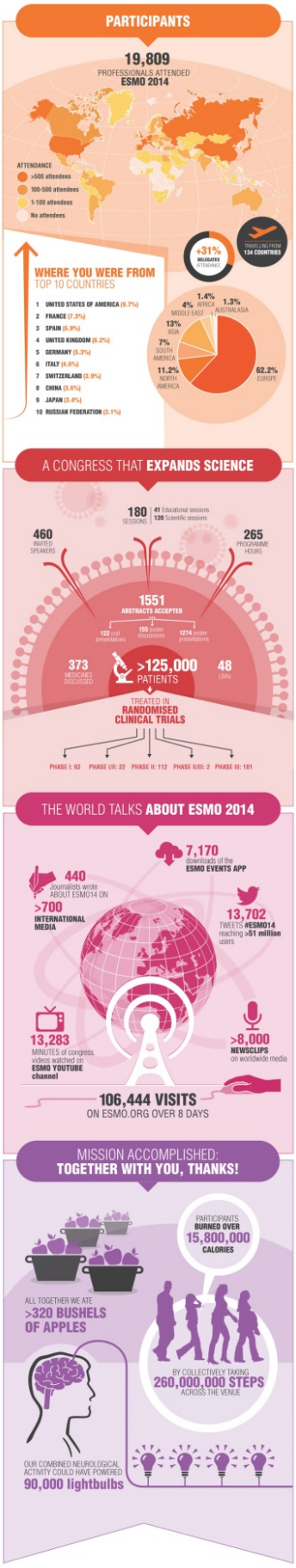
26-30 September 2014

Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. 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 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



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Sarcoma

Pazopanib improves PFS in phase II study in patients with advanced GIST

The results of PAZOGIST, a randomised phase II study of pazopanib plus best supportive care vs. best supportive care alone in patients with unresectable metastatic and/or locally-advanced gastrointestinal stromal tumours (GIST), who are resistant or experienced toxicity to previous treatments with standard doses of imatinib and sunitinib, show an improvement in PFS in favour of the pazopanib arm. The study was presented by Prof. Jean-Yves Blay of the University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France.

GIST is the most common mesenchymal neoplasm of the GI tract. In unresectable and metastatic or locally-advanced disease, imatinib followed by sunitinib, then regorafenib represent the standard treatments in first-, second- and third-line treatments, respectively.

Pazopanib is an active treatment in soft tissue sarcomas, but it has never been evaluated in a randomised setting in advanced GIST.

In this open-label, multicentre phase II study, eligible adult patients with adequate organ functions were randomly assigned 1:1 to receive pazopanib plus best supportive care or best supportive care alone. Randomisation was stratified by number of prior drugs (2 vs. ≥ 3). Switch to pazopanib was allowed for patients from the best supportive care arm with a progressive disease.

The primary endpoint was PFS. It was planned to include 80 patients to detect an improvement in the 4 month PFS rate from 15% in the best supportive care arm alone to 45% in the pazopanib plus best supportive care with 5% two-sided α error and 80% power. Secondary objectives included OS, ORR at 4 months, best response rate and tolerance.

It was required that patients have GIST diagnosis documented histologically, measurable disease according to RECIST criteria, ECOG PS ≤ 2, adequate organ functions, and absence of known contraindication to pazopanib administration.

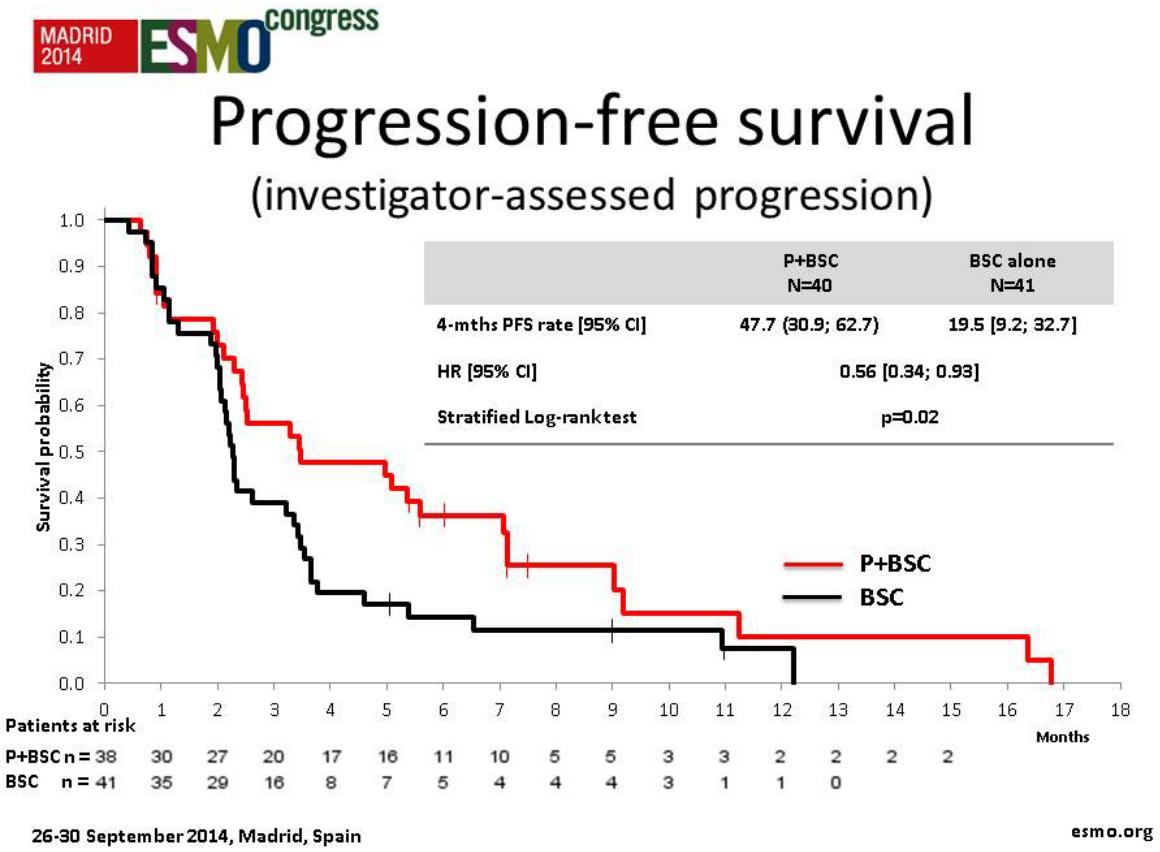
For data analysis, 42 PFS events were needed, and 80 randomised patients were planned. An interim analysis with a futility stopping rule was planned after a 4 month follow-up of 27 randomised patients.

At the interim analysis in September 2012, based on both efficacy and safety results, the IDMC recommended that study enrollment should be pursued until the targeted sample size.

From April 2011 to December 2013, 81 patients were randomised: 40 to the pazopanib plus best supportive care and 41 to the best supportive care alone arm.

Median age was 65 years in the pazopanib plus best supportive care arm and 59 years in the best supportive care arm. The location of the primary in the pazopanib plus best supportive care vs. best supportive care arms were small intestine (35.9% vs. 43.6%), stomach (30.8% vs. 30.8%), colon/rectum (7.7% vs. 5.1%), mesentery (2.6% vs. 2.6%), oesophagus (0% vs. 2.6%) and other (23.1% vs. 15.4%). Regarding disease status at inclusion, there were 30.8% vs. 53.8% of patients with locally-advanced disease in the pazopanib plus best supportive care vs. best supportive care arms, respectively.

The ITT analysis based on investigator-assessed progression showed a significant improvement in PFS with 4 month PFS rate of 47.7% for pazopanib plus best supportive care vs. 19.5% for best supportive care (HR 0.56, stratified log-rank p = 0.02).



Caption: Investigator-assessed PFS. © Jean-Yves Blay.

Following progression assessed by investigators, 36 of 41 patients allocated to the best supportive care arm received pazopanib. Median duration from inclusion to switch was 2.2 months and median PFS from date of switch 3.6 months.

The best ORR assessed by central review showed PR in 0% vs. 2.4%, SD in 84.2% vs. 70.7% and progressive disease in 15.8% vs. 26.8% of patients in the pazopanib plus best supportive care and best supportive care arms.

At least one serious adverse event was experienced by 52.5% of patients receiving pazopanib plus best supportive care vs. 14.6% of patients receiving best supportive care alone. In the pazopanib plus best supportive care arm, the most frequent serious adverse events were GI disorders (17.5%), deterioration of global health status (15%) and pulmonary embolism (12.5%).

Prof. Blay concluded that pazopanib deserves further evaluation in this population of patients. When combined with best supportive care, it improves PFS in patients with advanced GIST resistant to imatinib and sunitinib. The 4 month PFS rate was 50% in the pazopanib arm. Toxicity was consistent with that reported with pazopanib in other indications. The OS data will be available at beginning of 2015.

Prof. Stefan Sleijfer of the Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, who discussed the study results, said that the introduction of imatinib in advanced GIST led to a RR higher than 50%, median OS of 5 years (before imatinib it was 9 months)

and >10% benefits for more than 10 years from first-line imatinib, results that made this cancer a chronic disease. Despite the great success of imatinib, the vast majority of patients develop resistance. Subsequent treatment options based on randomised phase III studies are sunitinib in second-line with a RR of 7% and median PFS of 6-7 months, and regorafenib in third-line with a RR of 5% and median PFS of 4-5 months. Pazopanib is active in non-adipocytic soft tissue sarcoma and targets VEGFR1-3, PDGFRa, and c-KIT.

Prof. Sleijfer further said that based on the results of the PAZOGIST phase II study, a further study of pazopanib is needed. An appropriate design for a subsequent study would be a phase III trial of pazopanib vs. regorafenib in GIST patients failing to imatinib and sunitinib.

He also said that imatinib-treated GIST has transformed from a homogeneous disease with one major tumour driver to a heterogeneous disease with multiple drivers differing in tyrosine kinase inhibition sensitivity. It is unlikely that one drug will induce prolonged SD in majority of patients after imatinib failure, as illustrated by short PFS and low response rate from KIT-targeting agents after failure to imatinib.

New treatment approaches would be combination treatments that are difficult due to toxicity, inhibition of KIT-signaling downstream from KIT, KIT degradation, and individualised treatment based on mutational profile of dominant clone.

For future treatment in GIST after imatinib failure it would be important to identify drugs based on the molecular characteristics of the dominant clone, to monitor molecular evolution of tumour cells during treatment, and to adjust treatment if necessary. The requirements would be to know which KIT mutations causing imatinib resistance respond to other targeting TKIs (sunitinib, regorafenib, pazopanib, sorafenib, nilotinib, masitinib), tools to assess the mutational profile of the dominant clone (ctDNA, molecular imaging), and randomised study in imatinib resistant GIST of traditional treatment (sunitinib followed by regorafenib) vs. treatment based on mutational profiles.

Prof. Sleijfer concluded by stating that it is obvious to the sarcoma community that, in order to address these challenges, global collaboration is needed.

GlaxoSmithKline provided the study drug and research funding for this investigator-sponsored study.

Reference

LBA45: A randomized multicentre phase II study of pazopanib plus best supportive care (BSC) vs BSC alone in metastatic gastroIntestinal stromal tumors (GIST) resistant to imatinib and sunitinib

Phase II study of imatinib in RECIST progressive desmoid tumours not amenable to surgical resection or accompanied by unacceptable function loss

Prof. Bernd Kasper of the University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany presented results from a study conducted by the German Interdisciplinary Sarcoma Group (GISG). With a 65% progression arrest rate at 6 months after start of treatment, imatinib exceeded the primary study endpoint encouraging further investigation in this histology. Follow-up will continue until the end of the two years treatment duration.

Desmoid tumours are rare monoclonal, fibroblastic proliferations characterised by a variable and often unpredictable clinical course. Surgery is the therapeutic mainstay for progressing patients, except if mutilating and associated with considerable function loss. For advanced disease different treatment approaches have been investigated and promising results could be demonstrated using imatinib.

This phase II trial was initiated with imatinib to induce tumour progression arrest in desmoid tumour patients not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss. Major eligibility criteria were histologically confirmed desmoid tumour showing progressive disease according to RECIST v1.0 within 6 months. Patients were treated with imatinib daily over two years.

Primary endpoint was the non-progression rate after 6 months of treatment. Eleven out of 37 evaluable patients were needed to achieve a positive study result. Accrual started in July 2010 in five GISG centers and was finalised in September 2013.

The final analysis for the primary endpoint showed that 24 out of 37 evaluable patients were progression-free at 6 months of imatinib treatment and reached the primary endpoint. Response assessment after 6 months revealed 1 PR (3%) and 23 SDs (62%). Out of the 13 patients counted as non-successors, 10 patients had documented disease progression (27%). One patient terminated due to toxicity and there were two study withdrawals.

Prof. Stefan Sleijfer of the Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, who discussed the study results, said that several small studies explored imatinib in desmoids. However, the biological rationale is not that strong, the response rate between 6 and 16%, and PFS data difficult to put into perspective due to indolent growth of the disease. Imatinib is highly likely to induce growth arrest in progressive desmoids. It might have a role in selected patients, but there is a strong need for predictive markers. In this study, translational research considered therapy monitoring using FDG PET to determine early whether patients benefit from imatinib therapy or not, and analysis of mutations in the beta-catenin gene CTNNB1 and correlation with PFS. The results are pending.

The study was funded by Novartis Pharma GmbH.

Reference

1412O: Phase II study evaluating imatinib to induce progression arrest in RECIST progressive desmoid tumors not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss - a study of the German Interdisciplinary Sarcoma Group (GISG)

Outcome of first-line treatment of elderly advanced soft tissue sarcoma patients

Prof. Winette Van der Graaf of the Radboud University Medical Centre Nijmegen, Nijmegen, The Netherlands reported that outcome of elderly patients with advanced soft tissue sarcoma is slightly worse and new strategies are urgently needed in this setting. The results from the pooled analysis of 11 EORTC Soft Tissue and Bone Sarcoma Group trials can be used as benchmark for developing new trials in this age group.

Half of patients diagnosed with soft tissue sarcoma are older than 65 years, yet little data is available about survival of elderly patients with metastatic disease receiving standard chemotherapy.

The researchers evaluated patients who had an indication for systemic treatment because of locally unresectable or metastatic disease. The EORTC database contains information on 2636 patients who did not receive prior chemotherapy and who were treated with doxorubicin, epirubicin, ifosfamide or a combination of doxorubicin and ifosfamide in the context of 11 clinical trials in advanced soft-tissue sarcoma. Of these, 274 patients were older than 65 years. The endpoints of interest for this analysis were OS, PFS and RR.

Median age of elderly patients was 68 years, with a maximum of 80 years. Almost half (49%) had PS 1, 12% had PS of 2 or more; 27% had histological grade 3. The most frequently reported histology was leiomyosarcoma (39%). For 48% of patients disease involved the primary site of origin, 47% had lung metastases, 19% liver metastases, 8% bone metastases and 26% had other metastases.

In total 91 (33%) patients were treated with doxorubicin, 43 (16%) with epirubicin, 26 (9%) with ifosfamide and 114 (42%) with doxorubicin-ifosfamide. Median OS of elderly patients was 9.8 months for doxorubicin, 9.9 months for epirubicin, 9.7 months for ifosfamide, 12 months for doxorubicin-ifosfamide. Median PFS was 2.8 months for doxorubicin, 3.8 months for epirubicin, 2.2 months for ifosfamide and 5.2 months for doxorubicin-ifosfamide. In total 42 (15.4%) patients achieved a response to treatment (CR or PR).

In comparison, median OS of the 2363 patients aged less than 65 (median age 49 years) was 11.5 months for doxorubicin, 11.2 months for epirubicin, 11.1 months for ifosfamide and 13.2 months for doxorubicin-ifosfamide, respectively. Median PFS was 3.5 months for doxorubicin, 2.9 months for epirubicin, 2.8 months for ifosfamide and 6.2 months for doxorubicin-ifosfamide, respectively.

Dr Thomas Brodowicz of the Medical University Vienna, Austria, who discussed the study results, said that it seems that elderly patients are less likely to be treated with adjuvant anthracyclines/ifosphamide. He said that open questions are if this regimen is appropriate as first-line in metastatic disease in elderly and if > 65 years is really considered elderly. Studies in elderly patients with soft-tissue sarcomas are needed with less toxic drug(s) even in first line.

All authors in this study have declared no conflicts of interest.

Reference

1415O: Outcome of first-line treatment of elderly advanced soft tissue sarcoma (STS) patients: a pooled analysis of eleven EORTC Soft Tissue and Bone Sarcoma Group trials

RELATED INFORMATION

Click here to access the Conference abstracts.

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Save the date

European Cancer Congress 2015 (ECC 2015), Vienna, Austria, 25-29 September 2015.

Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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