ESMO 2014 Congress Scientific Meeting Report – Developmental Therapeutics Extract

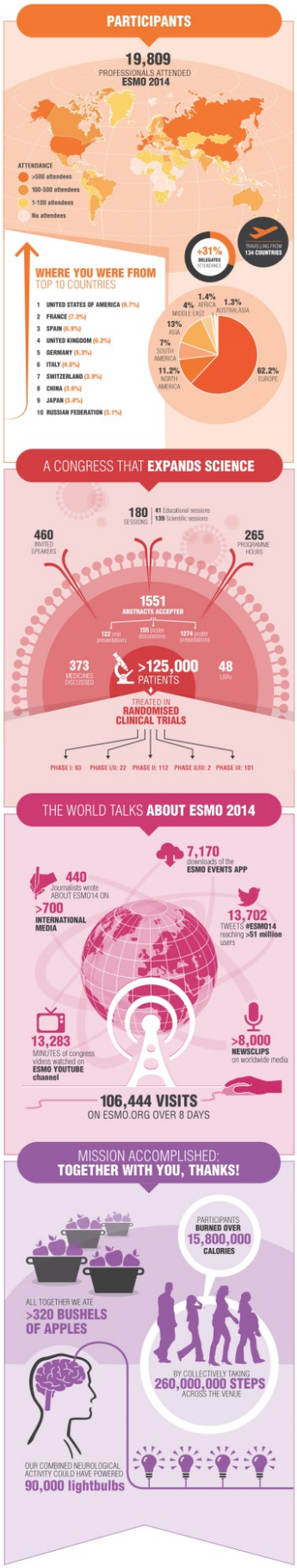
26-30 September 2014

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



Contents

Developmental Therapeutics 3
Pimasertib and SAR245409, a MEK and PI3K/mTOR inhibitors combination: A phase Ib trial with expansions in selected genotype-defined solid tumours 3
Phase Ib trial trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in combination with cetuximab or erlotinib in patients with advanced/metastatic tumours of epithelial cell origin expressing HER3 protein 4
Dose-escalation study of sonidegib (LDE225) plus buparlisib (BKM120) in patients with advanced solid tumours 5
RELATED INFORMATION 7
Save the date 7
Affiliations and Disclosure 7
Acknowledgment 7

Developmental Therapeutics

Pimasertib and SAR245409, a MEK and PI3K/mTOR inhibitors combination: A phase Ib trial with expansions in selected genotype-defined solid tumours

Dr Rebecca Heist of the Massachusetts General Hospital Cancer Center, Boston, USA reported that dual inhibition of the MAPK and PI3K pathways using a combination of pimasertib and SAR245409 given once daily is feasible. Combination therapy is generally well tolerated. Pimasertib and SAR245409 combination therapy demonstrated clinical activity in patients with solid tumours; however, the response rate was limited. Further investigations are required, including pharmacokinetic analyses, to better understand these preliminary outcomes.

In preclinical studies, simultaneous inhibition of the MAPK and PI3K/PTEN signalling pathways led to enhanced antitumour activity compared with inhibition of either pathway alone. Pimasertib (MEK1/2 inhibitor) combined with SAR245409 (PI3K and mTOR inhibitor) is being evaluated in patients with solid tumours. Initial dose-escalation investigations determined the maximum tolerated dose (MTD) for pimasertib/SAR245409 and based on this, expansion into disease-specific patient populations has occurred. Patient populations to be investigated were chosen based on activity signals from the dose-escalation phase of this study and published evidence from ongoing trials with similar combinations, scientific rationale and supportive non-clinical data, as well as unmet medical needs.

Inclusion criteria considered patients with ECOG PS 0-1. Prior MEK and/or PI3K inhibitor therapy was not allowed. Safety and efficacy were analysed using standard criteria (NCI CTCAE v4.0 and RECIST v1.1).

At the recommended phase 2 dose (RP2D), 4 disease- and genotype-specific cohorts were recruited: RAS mutated non-small cell lung cancer (NSCLC) - 24 patients, triple-negative breast cancer (TNBC, 26 patients), BRAF inhibitor resistant melanoma (15 patients) and dual KRAS and PIK3CA mutated CRC (18 patients).

The most frequent (≥20%) all grade treatment-emergent adverse events were: diarrhoea (77.1%), fatigue (54.2%), nausea (50.6%), vomiting (47.0%), dermatitis acneiform (37.3%), maculo-papular rash (30.1%), decreased appetite (30.1%), peripheral edema (25.3%), pyrexia (25.3%), stomatitis (24.1%), dizziness (24.1%), dyspnea (21.7%), skin rash (21.7%), increased creatinine phosphokinase levels (21.7%), abdominal pain (20.5%) and pruritus (20.5%). Serous retinal detachment, which is a class effect of MEK inhibitors, was reported in 34.9% of patients and all cases were resolved without serious damage to the eyesight.

Confirmed responses were observed in 2 of 18 evaluable NSCLC patients and in 1 of 13 evaluable melanoma patients.

Dr Elizabeth Eiesenhauer of the Queen’s University, Kingston, Canada, who discussed the study results, said that dual pathway inhibition in this study represents one of many combination of MEK and PI3K (mTOR) inhibitors. Tumour and biomarker in the study are defined based on relevant pathway mutations (KRAS, PIK3CA, BRAF mutations). The both drugs have limited activity in solid tumours. Approximately 80% of patients experienced > grade 3 adverse events, but they were considered tolerable. Doses of both drugs were lower than if applied as a single agent. Antitumour activity of combination is low, similar to other PI3k/mTOR combinations.

The study was sponsored by Merck KGaA and Sanofi.

Reference

443O: Pimasertib (PIM) and SAR245409 (SAR) - a MEK and PI3K/MTOR inhibitor combination: A phase Ib trial with expansions in selected genotype-defined solid tumors

Phase Ib trial trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in combination with cetuximab or erlotinib in patients with advanced/metastatic tumours of epithelial cell origin expressing HER3 protein

Dr Ulrik Lassen of the Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark reported that RG7116 combination with cetuximab or erlotinib in a phase Ib study was well tolerated, and demonstrated preliminary signs of clinical activity.

RG7116 locks HER3 in its closed, inactive conformation. It shows a strong inhibition of HER3 signalling. It is glycoengineered for enhanced immune effector recruitment and showed antitumour activity in numerous xenograft models.

Patients with ECOG PS ≤2, advanced or metastatic solid tumours of epithelial origin, and centrally confirmed HER3 protein expression were included. RG7116 plus cetuximab and RG7116 plus erlotinib combinations were evaluated in a dose escalation study with “3 + 3” design.

Twenty-seven patients were enrolled in 5 cohorts in the cetuximab arm. One dose-limiting toxicity (DLT) of grade 3 dehydration was reported in the 800 mg cohort.

Twenty-seven patients were enrolled in 4 cohorts in the erlotinib arm. One DLT was reported in the 1600 mg cohort (grade 3 diarrhoea and grade 3 hypokalaemia) and one DLT was reported in the 2000 mg cohort (grade 3 blood bilirubin increase).

No maximum tolerated dose was reached.

The most frequently reported adverse events of any grade were EGFR inhibitor related: diarrhoea (78%) and rash (59%) for the cetuximab arm and diarrhoea (82%) and decreased appetite (48%) for the erlotinib arm. In the erlotinib arm treatment-related grade 3 diarrhoea was observed more frequently at higher doses of RG7116. Overall, infusion-related reactions related to RG7116 occurred in 11% of patients. Two of these were grade 3 (4%).

The pharmacokinetic profile of RG7116 in combination with cetuximab and erlotinib was comparable to that in the monotherapy setting.

HER3 membranous protein down-regulation was observed from 400 mg onwards in on-treatment tumour and skin tissue.

In the cetuximab arm, two patients with colorectal carcinoma had confirmed partial response (PR). In the erlotinib arm, one patient with ovarian carcinoma had a confirmed PR. Metabolic PR on FDG-PET occurred in 42% of patients in the cetuximab arm and in 28% of patients in the erlotinib arm.

Dr Elizabeth Eiesenhauer of the Queen’s University, Kingston, Canada, who discussed the study results, said that in this study two drugs were investigated of different MOA affecting same target/pathway to maximise inhibition of the pathway. Their combination was studied in any epithelial solid tumour that must be HER3-positive. However, it is unclear if prior epidermal growth factor receptor (EGFR) inhibitor was allowed. RG7116 (HER3 inhibitor) is not evaluated yet in

solid tumours, while cetuximab and erlotinib were but data in HER3 selected patients are unknown. Full doses of erlotinib and cetuximab were foreseen by design. Toxicity was not limiting. Activity of combination is low. Higher response was seen when using PET, but meaning of this finding is unclear.

The study was sponsored by F. Hoffmann La-Roche.

Reference

444O: Phase Ib trial trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in combination with cetuximab or erlotinib in patients with advanced/metastatic tumors of epithelial cell origin expressing HER3 protein

Dose-escalation study of sonidegib (LDE225) plus buparlisib (BKM120) in patients with advanced solid tumours

Dr Quincy Siu-chung Chu of the University of Alberta Cross Cancer Institute, Edmonton, Canada reported that LDE225 and BKM120 combination is tolerable, with expected DLTs, consistent with phase I studies. Pharmacokinetics of each agent in combination appear similar to pharmacokinetics observed in single-agent studies. Based on these data, further study of the combination is warranted.

Aberrant hedgehog (Hh) signaling has been observed in tumours with dysregulated PI3K signalling. Sonidegib (LDE225; smoothened inhibitor that blocks Hh activity) and buparlisib (BKM120; pan class I PI3K inhibitor) show antitumour activity in phase I studies and combined, enhanced activity in xenograft models.

In this phase Ib study, the MTD and/or recommended dose for expansion (RDE), pharmacokinetic interaction, and preliminary antitumour activity of LDE225 plus BKM120 were assessed in patients with metastatic breast cancer, pancreatic adenocarcinoma, metastatic CRC, or recurrent glioblastoma.

Adult patients received different daily doses (followed by Bayesian logistic regression model) of LDE225 and BKM120. Safety, tolerability, pharmacokinetic, antitumour activity, and biomarkers PIK3CA/PTEN were assessed. The researchers reported at ESMO 2014 safety and pharmacokinetic results.

In total 46 patients (7 with metastatic breast cancer, 9 with pancreatic adenocarcinoma, 19 with mCRC, and 11 with glioblastoma) were enrolled into 5 cohorts. As of 12 December, 2013, 44 patients (95.7%) discontinued, primarily due to disease progression (29 cases) and adverse events (7 cases).

Grade 3/4 adverse events (> 5%) regardless of study drug included increased alanine and aspartate aminotransferase (21.7% each), increased blood creatine phosphokinase (17.4%), hyperglycaemia (8.7%), and increased blood alkaline phosphatase, aphasia, nausea, fatigue (6.5% each).

The team reported DLTs in each cohort; however MTD was not reached. At the RDE (LDE225 400 mg/BKM120 80 mg), no drug-drug interaction was observed, the interindividual variability of LDE225 and BKM120 pharmacokinetic (cycle 1, day 1) was approximately 67% and 30%, respectively, and trough levels over time aligned with single-agent exposure. No obvious drug-

drug interactions between sonidegib and buparlisib were observed. The pharmacokinetics of each agent in combination appear similar to those observed in single-agent studies.

Dr Elizabeth Eiesenhauer of the Queen's University, Kingston, Canada, who discussed the study results, said that a dual pathway inhibition in this study was tested in tumours associated with aberrant Hh and/or PI3K signalling. Sonidegib shows activity in basal cell cancer, but not in tumours tested. Buparlisib has limited activity in solid tumours reported to date. Approximately 74% patients had > grade 3 adverse events, but they were considered tolerable. Doses of both drugs were lower than for single agent use. Activity of combination was not reported.

The study was sponsored by Novartis.

For all three above targeted drugs combination studies, Dr Eisenhauer said that it is unlikely these combinations will have dramatic effects in randomised clinical trials.

Reference

445O: Dose-escalation study of sonidegib (LDE225) plus buparlisib (BKM120) in patients (pts) with advanced solid tumors

RELATED INFORMATION

Click here to access the Conference abstracts.

Click here to access the meeting webcast page.

Save the date

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

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office

Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank Drs Gligorov, von Minckwitz, Zhu, Kang, Lenz, Stintzing, Konecny, Krishnansu, Goss, Robert, McArthur, Weber, and Blay for giving their permission to publish images from the studies presented during the ESMO 2014 Congress in the ESMO Scientific report.