

2015 EUROPEAN CANCER CONGRESS

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SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European CanCer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

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EARLY DRUG DEVELOPMENT

The investigational oral pan-RAF kinase inhibitor, MLN2480, is safe and shows anti-tumour activity in patients with advanced solid tumours or melanoma

Drew Warren Rasco, South Texas Accelerated Research Therapeutics, San Antonio, USA, reported results from the first-in-human phase I study evaluating the safety of MLN2480, an investigational pan-RAF kinase inhibitor. Other primary objectives included determining the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetics (PK) and preliminary efficacy. MLN2480 targets RAF kinases, which play a key role in MAPK signalling that is often hyperactivated due to the MAPK pathway mutations commonly found in solid tumours. This study initially showed that 200 mg MLN2480 every other day (Q2D) had an acceptable safety profile and preliminary antitumour activity [Middleton et al, ENA 2014, Abstract 364]. However, weekly (QW) dosing is also being evaluated with the aim of achieving higher MLN2480 exposures and enhanced pathway inhibition.

The melanoma arm of this study enrolled patients with inoperable stage III/IV melanoma and the PK arm enrolled patients with advanced solid tumours; all patients were 18 or more years of age. Tumour biopsies were taken at screening and post-dose on days 21 or 22 of cycle 1. At the time of analysis, 52 patients in the melanoma and 20 patients in the PK arms received MLN2480 at 200 mg Q2D and 13 patients received 400 to 800 mg QW. In the QW dose escalation arm, 2 patients had grade 3 dose limiting toxicities (DLTs) during cycle 1 consisting of elevated bilirubin and maculopapular rash at the 800 mg dose; therefore, the MTD was set as 600 mg QW. In the Q2D and DX/QW dose escalation arms, 38% and 23% of patients, respectively, had grade ≥ 3 drug-related adverse events (AEs), including maculopapular rash (7%) and anaemia (8%). In all, 19% and 15% of patients in the Q2D and DX/QW arms discontinued due to AEs. The PK analysis showed that MLN2480 was rapidly absorbed with a median T_{max} of approximately 3 hours, and dose-proportional exposure with 400 to 800 mg QW dosing, with no apparent plasma accumulation after repeated QW dosing. C_{max} after day one QW dosing was similar to that at steady state for Q2D dosing over 1 cycle (equivalent doses). PD analyses are ongoing.

Decreased pERK and increased BIM expression was observed post-dose in patients in the Q2D BRAF-/NRAS-mutated melanoma arm. In the cohort of patients with melanoma and BRAF-mutation receiving MLN2480 Q2D, 6 patients achieved partial responses (PR) lasting from 1.9 to

16.4 months, and one patient achieved stable disease (SD) lasting more than 5 months. In the cohort of Q2D patients with melanoma and NRAS mutation, one patient achieved a PR lasting 1.5 months and 3 patients experienced SD lasting from 3.5 to 5.4 months. One QW patient with BRAF mutated thyroid cancer showed PR for less than one month after receiving an 800 mg dose that was reduced to 600 mg and one 400-mg QW patient with BRAF-mutated thyroid cancer showed SD lasting 9.2 months. The investigators have decided to further evaluate the weekly dosing schedule. NCT01425008. Rasco *et al.* Abstract 300.

Practice point and future research opportunities

MLN2480 showed acceptable safety and pharmacokinetic profiles at a dosing regimen of 400 to 600 mg administered weekly. PD results were consistent with the proposed mechanism of action of MLN2480. Preliminary antitumour activity was observed and the overall data support ongoing further investigation.

S 49076, a novel MET/AXL/FGFR inhibitor, demonstrates anti-tumour activity in a first-in-human phase I dose-escalation study in patients with advanced solid tumours

Analia Azaro, Vall d'Hebron University Hospital, Barcelona, Spain presented findings on behalf of an international team from the first-in-human phase I dose-escalation study of S 49076, a novel MET/AXL/FGFR inhibitor. S 49076 is an ATP-competitive tyrosine kinase inhibitor (TKI) that does not inhibit VEGFR-2, but selectively targets MET, AXL and FGFR-1/2/3 kinases that are deregulated and strongly implicated in tumour progression and metastasis. S 49076 could be expected to have efficacy in treating patients with primary cancer and metastasis and also preclinical data showed a favourable pharmacological and good safety profile. This phase I open label, dose-escalation study aimed to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics (PK), pharmacodynamics (PD) and potential efficacy of an oral formulation of S 49076 in patients with advanced solid tumours. Patients received oral capsule(s) of S 49076 once (QD) or twice (BID) daily over a continuous 21-day cycle. Plasma concentrations of S 49076 were assessed to characterise the pharmacokinetics at day one and steady state and tumour evaluation was performed once every 2 cycles. The study enrolled 79 patients that were treated at doses ranging from 15 to 900 mg QD or 7.5 to 285 mg BID. The patients' characteristics were balanced across both arms; patients were 58% male, with a median age of 60 years.

At data cut-off, 69 patients had evaluable data; 38 (55%) patients who were treated at a variety of doses achieved prolonged stable disease, with a median of duration of 17.7 weeks. Maximal

plasma concentration was reached between 2 and 6 hours, showed a mean oral bioavailability of approximately 30% and the elimination half-life was approximately 15 hours. C_{max} and exposure increased proportionally to the dose.

Similar adverse event (AE) frequency was seen for QD and BID dosing regimens at the equivalent total daily dose. Overall, 76% of the 76 patients receiving treatment had drug-related AEs. DLTs were reported for 9 patients and the most frequent drug-related adverse events occurring in more than 15% of patients included peripheral oedema in 27.8%, hypoalbuminemia in 25.3%, yellow skin pigmentation in 20.3%, dysaesthesia in 19% and asthenia, which occurred in 17.7% of patients. The majority of these events were grades 1/2 and did not lead to S 49076 discontinuation; however, 9 patients required dose reductions.

The investigators determined that the MTD was reached at 760 mg in QD arm and 285 mg in BID arm and decided to bring the once-daily administration schedule of 600 mg S 49076 forward for further development in an expansion cohort of up to 24 patients. S 49076 in combination with other therapies will be also be evaluated. Azaro et al. Abstract 301.

Practice point and future research opportunities

Based upon the promising anti-tumour activity demonstrated by S 49076 in a cohort of patients with advanced solid tumours, the general safety profile of oral treatment, which was good at the doses tested, and pharmacokinetic data suggesting no marked drug accumulation, further development is warranted.

Patients with advanced solid tumours harbouring NTRK1, NTRK2, NTRK3, ROS1, and ALK gene rearrangements show objective response to entrectinib (RXDX-101)

Entrectinib (RXDX-101) shows promise for the treatment of patients with advanced solid tumours harbouring NTRK1/2/3, ROS1, or ALK molecular alterations, according to lead investigator Salvatore Siena, Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, and Università degli Studi di Milano, Milan, Italy. Entrectinib is a potent oral small molecule inhibitor of the tyrosine kinases TrkA, TrkB, TrkC, which are encoded by the genes NTRK1, NTRK2, NTRK3, respectively, as well as ROS1, and ALK. Entrectinib demonstrated high potency, selectivity, and good tolerability in two phase I studies involving patients with advanced or metastatic solid tumours having NTRK1/2/3, ROS1, or ALK molecular alterations. These studies employed a 3+3 dose escalation schema to assess safety, pharmacokinetics (PK) and the recommended phase 2 dose (RP2D).

Doses ranging from 100 to 1600 mg/m² were given under both fasted and fed conditions either intermittently or in a continuous once-daily dosing (QD) regimen to 67 patients at 9 sites in the US and Italy. Plasma PK was assessed following a single dose and at steadystate, and anti-tumour activity was assessed by RECIST v1.1. The study enrolled patients with advanced or metastatic solid tumours and patients also having controlled asymptomatic central nervous system (CNS) disease at baseline were allowed. Exposures of entrectinib administered QD increased in a dose proportional manner and plasma half-life was estimated at 20 to 24 hours. The RP2D was determined as 600 mg QD, based upon 2 dose limiting toxicities (DLTs) that were observed at a fixed dose of 800 mg, approximately 500 mg/m² QD, which were grade 3 cognitive impairment and grade 3 fatigue. Both resolved upon dose interruption.

Clinical benefit was observed across a variety of tumour types, with 10 out of 11 (91%) patients who had not received prior ALK-or ROS1-inhibitors showing an objective response. Of these, one patient had previously shown intolerance to an ALK-inhibitor. These responses included 3 (100%) patients with tumours having a confirmed gene rearrangement in NTRK1/2/3, 2 (100%) patients with ALK and 5 of 6 (83%) patients harbouring confirmed ROS1. One patient having rearranged ROS1 achieved complete response. Responses were observed in non-small cell lung cancer (NSCLC), colorectal, and salivary gland cancers as early as cycle 1 and lasted more than 16 months, with 5 patients showing duration of response greater than six months. Of particular interest is a 46-year old male patient with NTRK1-SQSTM1-rearranged NSCLC who had received 4 prior lines of chemotherapy that achieved a partial response (PR) in both CNS and lung lesions, and a 22-year old female patient with a known activating ALK-mutated (F1245V) neuroblastoma who had received 4 prior lines of chemotherapy and who achieved a PR that lasted 8 months.

The most commonly reported adverse events (AEs) occurring in >15% of patients were fatigue/asthenia, and paresthesia which each occurred in 33% of patients, nausea in 30%, dysgeusia in 25%, myalgia in 19%, and vomiting which was reported for 18% of patients. Three other grade 3 AEs of asthenia, muscular weakness, and neutropenia occurred that resolved with dose interruption and/or reduction. A global basket study across multiple tumour types is enrolling patients as of January, 2016. Siena et al. Abstract 29LBA.

Practice point and future research opportunities

Continued clinical development of entrectinib is supported by the tolerability and early evidence of anti-tumour activity, also in the CNS, in patients with relevant molecular alterations. Entrectinib was granted orphan drug designation in December 2015 by the EMA for the treatment of neuroblastoma.

PF-06650808, an anti-Notch3 antibody drug conjugate shows promise in adult patients with advanced solid tumours

Lead investigator Lee S. Rosen, Cancer Institute Medical Group, Los Angeles, USA, reported results from phase I, dose escalation clinical trial done to assess the safety and tolerability of PF-06650808 and to establish the maximum tolerated dose (MTD), pharmacokinetics (PK), immunogenicity, and assess preliminary evidence of anti-tumour activity. PF-06650808 is an antibody drug conjugate (ADC) comprised of a humanised IgG1 antibody linked to a novel auristatin-based cytotoxic payload with a cleavable cysteine-reactive linker that targets Notch3. The Notch pathway plays an important role in the growth of several solid tumours, including breast and ovarian cancer and in melanoma. Specifically, Notch3 alterations, including gene amplification and upregulation are associated with poor patient survival.

Cohorts of 2 to 4 patients with treatment refractory solid tumours unselected for Notch3 expression are receiving escalating doses of PF-06650808 administered intravenously once every 3 weeks. The starting dose was 0.2mg/kg and a modified continual reassessment method with a dose limiting toxicity (DLT) rate of 25% is being utilized. PK profiling was performed using validated assays for determining ADC, unconjugated payload, and total antibody concentrations in serum at various time points during cycles 1 and 4. The mean age was 56.8 (range: 22 to 75) years in the 22 female and 5 male patients enrolled.

At the ECC, findings were reported from an analysis of 27 PF-06650808 treated patients. Two patients each received doses of 0.2, 0.4, 0.8, and 1.6mg/kg, while 5 patients received 2.4 mg, 6 patients each received 3.0 and 3.6 mg, and an additional 2 patients received 4.68 mg/kg. As of June 15, 2015, 89 cycles had been administered and DLTs were observed in 4 patients during the first cycle. The most common adverse events (AEs) of any grade (AE) included decreased appetite occurring in 56% of patients, nausea in 41%, fatigue in 37%, alopecia and dehydration, which each occurred in 30% of patients. Two patients receiving the highest dose (4.68mg/kg) experienced grade 4 neutropenia and one patient receiving 3.0mg/kg experienced grade 4 febrile neutropenia. Grade 3 AEs observed in 3 or more patients were abdominal pain, decreased lymphocyte count, hypophosphataemia, each occurring in 3 patients, and hyponatraemia, which was seen in 4 patients.

Putative clinical activity was seen in one patient with ER-positive breast cancer who achieved a confirmed partial response (PR) and an unconfirmed PR was reported in a patient with triple negative breast cancer. Following determination of the MTD, expansion cohorts for patients with

advanced breast tumours selected for high levels of Notch3 expression are planned. Rosen *et al.* Abstract LBA30.

Practice point and future research opportunities

PF-06650808 is a novel anti-Notch3 ADC that has demonstrated a manageable adverse event profile in patients with advanced malignancies. Research using Notch3 targeting is an innovative approach to treating solid malignancies and preliminary findings showed responses in two patients with breast cancer. Targeting Notch3 may become a future treatment approach in patients with selected solid tumours.

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Disclosure

No conflicts of interest to disclose.

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