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 multidisciplinarity 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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CENTRAL NERVOUS SYSTEM MALIGNANCIES

Dacomitinib monotherapy shows activity in patients with recurrent glioblastoma and EGFR amplification with and without EGFRvIII mutation: GEINO-11

Juan Manuel Sepúlveda, 12 de Octubre Universitary Hospital, Madrid, Spain, presenting findings on behalf of the Spanish Group for Research in Neurooncology (GEINO) from a multicentre, 2-stage, open-label, phase II trial evaluating the efficacy and safety of dacomitinib in adult patients with recurrent glioblastoma. The study enrolled patients with tumours having EGFR gene amplification, with or without EGFRvIII mutation, since EGFR amplification is reported in approximately 50% of glioblastoma cases; furthermore, about 50% cases with amplification are associated with deletion of the extracellular ligand-binding domain, the constitutively active mutant protein EGFRvIII. Dacomitinib is a second-generation, oral, irreversible, pan-HER tyrosine kinase inhibitor (TKI), that has shown activity to EGFRvIII, and also in preclinical models of lung cancer that were resistant to erlotinib and gefitinib. Dacomitinib has been recently reported to inhibit tumour growth in glioblastoma cell lines having EGFR amplification.

Patients were enrolled following first disease recurrence and stratified into cohort A comprising 30 patients with EGFR gene amplification, but no EGFRvIII mutations, or cohort B comprising 19 patients with EGFR amplification plus the EGFRvIII mutation. All patients received dacomitinib at 45mg daily until disease progression, unacceptable toxicity or study end. The primary endpoint was progression-free survival (PFS) at six months (PFS-6m) according to RANO criteria. Response was MRI assessed by investigators and confirmed by an independent radiologist.

A planned interim analysis revealed that an insufficient number of cohort B patients remained progression-free at 6 months; therefore, cohort B recruitment was terminated. Overall, 6-month PFS was 11% and 13% in cohort A versus 6.3% months in cohort B. No significant difference in PFS was observed between cohorts: Overall median PFS was 2.3 months; median PFS was 2.3 months in cohort A and 1.8 months in cohort B. At 12 months, 4 patients were progression-free and 2 patients remained progression-free at 24 months. Median overall survival (OS) was 7.3 months; median OS was 7.8 months in cohort A versus 6 months in cohort B. In cohort A, one (2%) complete and one (2%) partial response were observed. The patient achieving complete response is still on treatment and shows no radiological evidence of disease after 24 months. The partial

response reported in one patient was of 12-month duration. Stable disease was achieved by 13 (26.6%) patients, 9 patients in cohort A and 4 patients in cohort B.

Diarrhea and rash were the most common adverse events (AEs); 19 (38.7%) patients experienced grade 3/4 drug-related AEs. The authors concluded that dacomitinib had limited single-agent activity in patients with recurrent glioblastoma with EGFR amplification, with or without EGFRvIII mutation but, since ongoing responses were achieved by a number of patients, biomarker assessment could be used to identify selected patients that are likely to benefit from dacomitinib. NCT01520870. Sepúlveda et al. Abstract 2902.

Practice point and future research opportunities

Recurrent glioblastoma has a very poor prognosis with an unmet need for new treatment options and EGFR is an attractive therapeutic target. EGFR is amplified at high rates in glioblastoma and the activation of EGFR and tumour proliferation, survival, angiogenesis, and invasion have been linked. Single-agent dacomitinib has shown activity in this setting, albeit limited, but may show greater clinical benefit in biomarker-selected patients or in combination.

EGFR amplification detected by FISH shows strongest association to radiographic response following ABT-414 treatment in patients with glioblastoma

Martin J. Van den Bent, Erasmus University Medical Centre, Rotterdam, The Netherlands presented findings from an analysis of biomarkers in glioblastoma. Noting that glioblastoma involves aberrant EGFR signalling, the investigators analysed patient samples to characterise the EGFR status. Patients with glioblastoma were treated with 3 different regimens of ABT-414, an EGFR-targeted antibody conjugated to the toxic antimicrotubule agent monomethylauristatin F, in in an open-label, 3-arm, phase I study.

To determine biomarkers for ABT-414-based therapy, they measured EGFR and EGFRvIII expression using reverse transcription-polymerase chain reaction (RT-PCR), EGFR gene amplification was detected with fluorescence in situ hybridisation (FISH), and the total EGFR protein expression was analysed by immunohistochemistry (IHC). Tumour tissue from 89 patients was used to determine which marker most strongly associated with patient outcomes. IHC and RT-PCR confirmed expression of EGFR mRNA and protein was found to be correlated in glioblastoma tissue samples; the Spearman correlation was −0.86 ($p = 0.0026$). A strong association between

EGFR gene amplification and mRNA overexpression was observed and EGFRvIII mRNA was detected almost exclusively in cases with EGFR amplification.

EGFR amplification detected by FISH seems to be the strongest marker for patient outcome. EGFR amplification has been confirmed in 23 of 29 glioblastoma patient samples tested. Furthermore, EGFR gene amplification was detected in all 6 of 6 patients showing a confirmed objective radiographic response according to the Response Assessment in Neuro-Oncology criteria compared with 5 of 6 patient samples showing total EGFR mRNA overexpression and with EGFRvIII expression, which was detected in 4 of 6 patients. NCT01800695. Van Den Bent *et al.* Abstract 2903.

Practice point and future research opportunities

This analysis used several assays to characterise the EGFR status of glioblastoma samples from patients treated with ABT-414 in an ongoing phase I trial and found that EGFR amplification detected by FISH most strongly associated with objective radiographic responses, followed by EGFR mRNA overexpression, and by EGFRvIII expression. The assays developed may be useful in patient selection to identify those most likely to respond to ABT-414.

Analysis finds no survival advantage from valproic acid in newly patients with diagnosed glioblastoma

Valproic acid is an anti-epilepsy drug that is known to be an inhibitor of multiple enzymes and is often used as needed to control the epileptic seizures that are often seen in patients with newly diagnosed glioblastoma. Recent reports have suggested improved outcome when valproic acid was added to temozolomide, leading Michael Weller, University Hospital, Zurich, Switzerland and colleagues to conduct a combined analysis of survival between the use of anti-epileptic drugs from the inception of temozolomide chemotherapy and radiotherapy. The database included a pooled patient cohort of 1869 patients participating in one of 4 recent randomised clinical trials in newly diagnosed glioblastoma: AVAGlio (NCT00943826), RTOG-0825 (NCT00884741), CENTRIC (NCT00689221) and CORE (NCT00813943). The analysis compared progression-free (PFS) and overall survival (OS) between cohorts receiving chemoradiotherapy plus sole valproic acid, or with valproic acid plus another enzyme-inducing anti-epileptic drug or versus a non-enzyme inducing anti-epileptic drug and with no anti-epileptic drug. The investigators used Cox regression models stratified by trial and adjusted baseline prognostic factors, including O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status.

No significant improvement in PFS or OS was observed in any of the compared treatment groups over chemoradiotherapy; the comparison between valproic acid included at the beginning of chemoradiotherapy with patients receiving no anti-epileptic drug regarding PFS was HR 0.92 (p = 0.41) and OS was HR 1.00 (p = 0.95). The comparison in PFS between added valproic acid and an enzyme inducing anti-epilepsy drug was HR 0.95 (p = 0.62) and OS was HR 1.02 (p = 0.93). Finally, PFS for valproic acid compared with a non-enzyme inducing anti-epilepsy drug was HR 1.02 (p = 0.92) and OS was HR 1.06 (p = 0.67). The analyses were also done for levetiracetam and showed similar findings. Weller *et al.* Abstract 26LBA.

Practice point and future research opportunities

This pooled analysis did not confirm the previous report of an association between valproic acid or levetiracetam with improved overall or progression-free survival, thus challenging the need for a phase III trial evaluating an anti-epilepsy drug add-on to the standard of care in newly diagnosed glioblastoma.

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AFFILIATION AND DISCLOSURE

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Disclosure

No conflicts of interest to disclose.

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