

O – 027 **BEACON CRC study safety lead-in: Assessment of the BRAF inhibitor encorafenib + MEK inhibitor binimetinib + anti-epidermal growth factor receptor antibody cetuximab for BRAFV600E metastatic colorectal cancer**

E Van Cutsem¹, P Cuyle², S Huijberts³, J Schellens⁴, E Elez⁵, R Yaeger⁶, M Fakih⁷, C Montagut⁸, M Peeters⁹, J Desai¹⁰, T Yoshino¹¹, F Ciardiello¹², H Wasan¹³, K Maharry¹⁴, J Christy-Bittel¹⁴, A Gollerkeri¹⁴, S Kopetz¹⁵, A Grothey¹⁶, J Tabernero¹⁷

¹University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, ²Imelda Ziekenhuis, Bonheiden, Belgium, ³Netherlands Cancer Institute, Amsterdam, Netherlands, ⁴The Netherlands Cancer Institute, Amsterdam, Netherlands, ⁵Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, ⁶Memorial Sloan-Kettering Cancer Center, New York, New York, USA, ⁷City of Hope, Duarte, California, USA, ⁸Department of Medical Oncology, Hospital Universitari del Mar, Barcelona, Spain, ⁹Department of Oncology, Antwerp University Hospital, Edegem, Belgium, ¹⁰Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Walter and Eliza Hall Institute, Parkville, Australia, ¹¹National Cancer Center Hospital East, Kashiwa, Japan, ¹²University of Campania, Naples, Italy, ¹³Hammersmith Hospital, Department of Cancer Medicine, London, UK, ¹⁴Array BioPharma Inc., Boulder, Colorado, USA, ¹⁵UT MD Anderson Cancer Center, Houston, Texas, USA, ¹⁶Mayo Clinic, Rochester, Minnesota, USA, ¹⁷Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain

Introduction: The BRAFV600E mutation, which occurs in 10%–15% of patients with metastatic colorectal cancer (mCRC), confers a poor prognosis. After failure of first-line approaches, standard therapies in such patients provide limited benefits, with objective response rates (ORRs) <10%, progression-free survival (PFS) of ~2 months, and overall survival (OS) of 4–6 months. BEACON CRC (NCT02928224) is an ongoing phase 3 trial with a primary endpoint of OS for the BRAF inhibitor encorafenib (ENCO) + MEK inhibitor binimetinib (BINI) + anti-epidermal growth factor receptor (EGFR) antibody cetuximab (CETUX) vs control arm (irinotecan/CETUX or FOLFIRI/CETUX) in patients with BRAFV600E mCRC with disease progression after 1–2 previous regimens. To assess the safety and efficacy of the ENCO + BINI + CETUX triplet, a safety lead-in (SLI) was conducted in the BEACON CRC trial.

Methods: Patients received ENCO 300 mg QD + BINI 45 mg BID + CETUX 400 mg/m² (initial dose) then 250 mg/m² QW. Assessments included efficacy (ORR, duration of response, time to response, PFS, ORR, and OS), safety, tolerability, and changes in tumor markers CEA and CA19-9 (evaluated by central laboratory based on blood samples collected on cycle 1 day 1 and day 1 of subsequent cycles, and at end of treatment). Current data reflect patient study drug exposure of up to 11.9 (median: 7.8) months. Updated safety and efficacy from the SLI, including the first analysis of OS, will be presented at the meeting.

Results: Of 30 patients receiving the triplet combination, BRAFV600E mutation was detected in 29. Among these, confirmed ORR (complete response [CR] + partial response) occurred in 14/29 (48%) patients, including CR in 3/29 patients. Responses were ongoing in 6/14 responding patients (43%) at the time of data cutoff; the remaining 15 patients achieved a best response of stable disease (SD; 9 patients [60%] had prolonged SD ≥ 6 months). Preliminary estimated median PFS was 8.0 months (95% CI, 5.6–8.5) and similar in patients who had 1 vs 2 previous regimens (7.6 vs 8.1 months, respectively). Among the 30 treated patients, grade 3/4 AEs (in ≥ 10%) were fatigue (13%), urinary tract infection (10%), increased aspartate aminotransferase (AST; 10%), and increased blood creatine phosphokinase (10%); of these, all were grade 3 except for grade 4 AST in 1 patient. Grade 3/4 skin-related AE (grade 3 rash) occurred in 1 patient (3%).

Conclusion: The ENCO + BINI + CETUX triplet combination was well tolerated, with AEs consistent with known toxicities of BRAF, MEK, and EGFR inhibitors. Efficacy outcomes showed substantial improvements over historical data in patients with BRAFV600E mCRC, with PFS exceeding OS achieved with current standards of care. The phase 3 portion of the BEACON CRC trial has been initiated, with enrollment ongoing.