PUBLICATIONS

Chiritescu G, Dumon K, Macarulla Mercadé T, Lang I, Santos Vivas C, Papai Z, Janssens J, Hendrickx K, Pracht M, Van Den Eynde M, Taïeb J, Moons V, Geboes K, Van Laethem JL, Greil R, Cervantes A, Vergauwe P, Ferrante M, Vanderstraeten E, Van Cutsem E. (2018). A two-arm phase II study of FOLFIRI in combination with standard or escalating dose of cetuximab as first line treatment for metastatic colorectal cancer: Everest 2 final results. Annals of Oncology, Volume 29, Issue suppl_5, 1 June 2018. Oral presentation O-015, ESMO GI congress, Barcelona, Spain, 2018.

Abstract:
Introduction: Adding cetuximab to first-line FOLFIRI improves clinical and surgical outcomes in RAS wild-type metastatic colorectal (mCRC) patients. Skin-toxicity secondary to cetuximab has been reported to be related to the activity of the cetuximab-based regimens. Methods: In an academic multinational phase II study, chemo-naïve patients with unresectable mCRC received standard FOLFIRI (irinotecan 180mg/m2, leucovorin 400mg/m2, 5-FU 400mg/m2 bolus, 5-FU 2400mg/m2 infusion every 2 weeks) with cetuximab (250mg/m2 weekly after loading with 400mg/m2). If no cetuximab-related skin toxicity occurred by day (D)22 or 36 respectively, cetuximab was escalated to 350, then to 500mg/m2. Patients were tested K-Ras (codons 12, 13) wild-type to participate. Progression-free survival (PFS) rate at 9 months in the dose escalation group was the primary endpoint. Overall survival (OS), response rates (RR) and safety were secondary endpoints. Molecular exploratory analyses on tumour tissues and blood from consenting patients and pharmacokinetic evaluations were foreseen per protocol. The study was terminated early for low accrual in the escalation group. Results: One hundred eight patients with median age 60 were included in five countries between Jan-2011 and Mar-2014; 90 (83%) had left-sided mCRC. Seven patients were discontinued before arm allocation. Eight were assigned to dose escalation on D22, and three escalated further on D36 based on the “no skin toxicity” criterion. Average dose exposure was 94% of the planned doses for cetuximab and 85-90% for all other drugs. Overall RR was 67% (95% CI_57-75) with 14 (13%) patients in complete response. Following tumour shrinkage, surgery with curative intent was performed in 19 (18%) patients with median disease-free interval of 9 months (range 1-57). PFS rates at 9 months and median PFS times will be reported at the meeting. Median OS of all patients was 30 months (95%CI_25-36) with 77% and 57% alive at one and two years. Standard and dose escalation schedules were generally well tolerated. Most serious adverse events (SAE) were due to mCRC, 12/76 were deemed related to study treatment (diarrhea, infection or hematological modifications). Six deaths unrelated to treatment were recorded during study treatment. Skin reactions during the first three weeks of treatment occurred at much higher rates than foreseen (over 90% instead of 30% estimated historically) leading to very low assignment to the escalation arm. Post study analyses showed K-Ras mutated tumours in 9 patients for other codons than initially tested, NRAS mutations in 3 patients and BRAF mutations in 4; 4 other patients presented ERBB2 amplification. Conclusion: The Everest 2 study could not demonstrate that dose escalation of cetuximab in patients without early skin toxicity is a feasible strategy because most patients had skin reactions in the first three weeks. FOLFIRI in combination with cetuximab had an acceptable safety profile with good RR influenced by RAS mutation status. Secondary resections could be performed in a relatively high number of patients with initially unresectable disease. Patient selection by tumour molecular characteristics is needed for maximal benefit. Translational studies are ongoing. Conducted with financial support and medication from Merck BV, Belgium, affiliate of Merck KGaA, Darmstadt, Germany. Trial registration: EudraCT 2009-009992-36; NCT01251536.