Cetuximab beyond progression in RAS wild type (WT) metastatic colorectal cancer (mCRC): the CAPRI-GOIM randomized phase II study of FOLFOX versus FOLFOX plus cetuximab

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Abstracts

Introduction: Cetuximab in combination with chemotherapy (CT) is a standard treatment for mCRC with KRAS and NRAS ("all RAS") WT tumours. No data are available on the role of continuing anti-epidermal growth factor receptor (EGFR) therapy beyond progression after first line therapy with CT plus anti-EGFR monoclonal antibody. This study evaluates the efficacy of cetuximab plus CT as second line treatment for patients (pts) with mCRC who progressed after CT plus cetuximab.

Methods: In the non profit, academic CAPRI-GOIM trial (EudraCT 2009-014041-81), 340 mCRC pts with mCRC exon 2 WT tumour, as assessed by local molecular pathology laboratory, were treated in first line with FOLFIRI plus cetuximab until disease progression or unacceptable toxicity, as previously reported (Ciardiello et al, Annals of Oncology 2014). After first line therapy progression, pts were treated with FOLFOX plus cetuximab (Arm A) or FOLFOX (Arm B) in a 1:1 randomized phase II study. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), response rate and safety. Archival tissue samples from primary tumours were centrally assessed by next generation sequencing (NGS) with the Ion AmpliSeq Colon and Lung cancer panel (500 hotspot mutations in 22 genes) by using Ion Reporter™ Software, as previously reported (Ciardiello et al, Annals of Oncology 2014; Normanno et al., Annals of Oncology 2015).

Results: From February 2010 to September 2014, 153 pts (intention to treat population, ITT) were randomized (74 pts in arm A and 79 pts in arm B). Baseline patient and disease characteristics were well balanced between arms. Median PFS of the ITT population was 6.4 months for FOLFOX plus cetuximab and 4.5 months for FOLFOX (HR = 0.81; 95% CI 0.58–1.12; log-rank test, p = 0.36). NGS was performed in 117/153 (76.5%) cases. Seventy-five out of 117 pts had "all RAS" WT tumours, whereas a KRAS (exon 2, 3 or 4) or a NRAS (exon 2, 3 or 4) mutation was found in the tumour of 42 pts. KRAS exon 2 mutation were detected in approximately 15% of tumours that were originally defined as WT by local pathology assessment by Sanger sequencing or RT-PCR confirming the results that were previously reported by Ciardiello et al. (Annals of Oncology 2014). Median PFS for the "all RAS" WT population was 6.8 months for arm A and 5.5 months for arm B (HR = 0.80; 95% CI 0.50–1.29; log-rank test, p = 0.36). Median PFS in the RAS mutated population was 2.7 months for arm A and 4.1 months for arm B (HR = 1.53; 95% CI 0.79–2.96; log-rank test, p = 0.2). Furthermore, in 66 out of 117 pts, tumours had no mutation in KRAS, NRAS, BRAF, or PIK3CA genes ("quadruple WT"), whereas in 51 out of 117 pts, a mutation in at least one of these genes was found. Median PFS of the "quadruple WT" population was 6.9 months for arm A and 5.3 months for arm B (HR = 0.56; 95% CI 0.33–0.94; log-rank test, p = 0.025). Median PFS of the mutated (any mutation in KRAS, NRAS, BRAF and/or PIK3CA genes) population was 2.7 months for arm A and 4.4 months for arm B (HR = 1.79; 95% CI 0.94–3.05; log-rank test, p = 0.07).

Conclusions: This is the first study to demonstrate that in mCRC pts, whose tumours have no mutation in KRAS, NRAS, BRAF and PIK3CA genes, FOLFOX plus cetuximab therapy significantly prolong PFS as compared to FOLFOX alone, after progressing from FOLFIRI plus cetuximab first line treatment. On the contrary, a detrimental effect of the combination of FOLFOX plus cetuximab is observed in patients whose tumours are mutated for any of the KRAS, NRAS, BRAF and/or PIK3CA genes. Continuing EGFR inhibition by switching the CT backbone is a potential therapeutic strategy that could be further evaluated in a randomized phase III study in mCRC pts with an EGFR-dependent tumour.