O-9 5-FU/LV + cetuximab + vemurafenib as maintenance therapy for BRAF-mutant (BRAFmut) metastatic colorectal cancer: Efficacy, safety, and exploratory biomarker findings from Cohort 1 of the MODUL trial

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Background: MODUL is an adaptable, phase 2, signal-seeking trial testing novel agents as first-line maintenance therapy for metastatic colorectal cancer (mCRC). Patients with measurable, unresectable, previously untreated mCRC received up to 8 cycles of induction treatment (FOLFOX + bevacizumab) followed by randomisation to control or experimental maintenance treatment in 1 of 4 biomarker-driven cohorts. We report efficacy, safety, and exploratory biomarker findings from Cohort 1 (BRAF mut mCRC).

Methods: Control treatment was fluoropyrimidine [FP]/bevacizumab (1600−2400 mg/m 2 5-FU 46-h IV infusion d1 q2w; LV 400 mg/m 2 2-h infusion d1 q2w; or 1000 mg/m 2 bid capecitabine orally d1−14 q3w; bevacizumab 5 mg/kg 15−30-min IV infusion d1 q2w). In patients with BRAF mut mCRC, experimental treatment was 5-FU/LV (1600−2400 mg/m 2 5-FU 46-h IV infusion d1 and LV 400 mg/m 2 2-h infusion d1 q2w) + cetuximab (500 mg/m 2 IV infusion d1 q2w) + vemurafenib (960 mg bid orally). Primary efficacy endpoint: progression-free survival (PFS, surgery censored). Secondary efficacy endpoints: PFS (surgery not censored), overall survival (OS); objective response rate (ORR). Spider plots were run on plasma samples with clear acquired mutations to select on-treatment timepoints. An exploratory genomic analysis was performed on archival tissue and plasma samples (baseline and progressive disease [PD] or last timepoint available) using FoundationOne and FoundationOneLiquid, respectively, to evaluate correlations between mutations and response, innate/adaptive resistance, and resistance to cetuximab + vemurafenib.

Results: 93 patients with BRAF mut mCRC received induction treatment; 24 discontinued all drugs, including 12 with PD during induction. 60/69 patients who completed induction treatment were randomised (2:1) to maintenance treatment in Cohort 1. After a median follow-up of 16.4m, median PFS was 11.6 vs 10.0m in the control vs experimental arms (HR=0.95; 95% CI 0.50−1.82; p=0.87). Corresponding values for other secondary endpoints: median PFS (surgery not censored) 10.7 vs 10.2m (HR=0.79; 95% CI 0.44−1.41; p=0.43); median OS 21.3 vs. 24.0m (HR=0.69; 95% CI 0.34−1.38; p=0.29); ORR 25.0% vs. 50.0% (p=0.06). Exposure to experimental treatment was longer than control treatment; safety was similar to that observed in previous trials of vemurafenib-based regimens, with no new safety concerns. The exploratory genomic analysis included 49 patients (control n=15; experimental treatment n=34). MAPK pathway genes, KRAS, NRAS, BRAF, NF1 and MAP2K1 mutations in the presence of BRAF V600E were detected as drivers of acquired resistance at time of PD in a patient with stable disease during experimental treatment. Acquired alterations in MAPK pathway genes were higher in 5-FU/LV + cetuximab + vemurafenib-treated patients than in FP/bevacizumab-treated patients.

Conclusions: Due to events unrelated to Cohort 1, the MODUL study was closed to enrolment prematurely; results from the Cohort 1 efficacy analysis should therefore be considered as descriptive only. Exploratory biomarker findings revealed that selective pressure of the treatment arm leads to acquired mutations that reactivate and converge in the MAPK pathway as drivers of resistance to cetuximab + vemurafenib. Further mutation analyses need to be performed to confirm and identify other mechanisms of resistance to cetuximab + vemurafenib in patients with BRAF mut mCRC that might inform future combination strategies.

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