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LBA-3 **Integrated analysis of cell-free DNA (cfDNA) *BRAF* mutant allele fraction (MAF) and whole exome sequencing in *BRAFV600E* metastatic colorectal cancer (mCRC) treated with BRAF-antiEGFR +/- MEK inhibitors**

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Background: The combination of encorafenib and cetuximab has led to a paradigm change in *BRAFV600E* mCRC with significant improved outcomes over the standard of care. Our group previously reported that *BRAFV600E* mCRC patients treated with BRAF/EGFR+/-MEK inhibitors could be split into three different prognostic subgroups according to tumor load surrogates. Here, we integrate the analysis of *BRAFV600E* MAF in cell-free DNA (cfDNA) and whole exome sequencing data to unveil predictive/prognostic profiles.

Methods: An international, prospective, multicentric cohort included 59 *BRAFV600E* mutated mCRC patients from Vall d'Hebron and Università della Campania L. Vanvitelli, Naples that received encorafenib-cetuximab +/- binimetinib. Basal plasma samples were extracted from 40 patients and *BRAF* MAF by ddPCR was performed baseline. Moreover, samples for plasma Whole Exome Sequence (plWES) were also extracted baseline from 23 patients. All patients received BRAF/EGFR+/-MEK inhibitors. Responses were evaluated every 8 weeks. The primary endpoint is to correlate *BRAF* MAF with overall survival and overall response rate. Secondary endpoints included the identification of a WES driving signature that could predict clinical

outcomes. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.

Results: In total, 70 patients were included in the analysis. Median age was 61y (33-83), 56% female, 34% right-sided tumors, and 56% received 2 or more prior chemotherapy lines. Overall, median PFS was 5.2 months (m) (CI 95% 4.1-8.5) and median OS (mOS) was 10.3 m (CI 95% 6.5-20.2). *BRAF* MAF was >5% in 14 pts (35%), <5% in 10 pts (25%), and undetectable in 16 pts (40%) with a mOS of 4.2 m, 17.1 m (HR 0.21, p<0.001), and 17.5 m (HR 0.15, p<0.001), respectively. In the multivariate analysis the most parsimonious model included five factors: ECOG, presence of liver metastases, CEA, NLR levels, and *BRAF* MAF. We stratified patients into three risk prognostic groups based on their number of presenting risk factors. These three prognostic groups showed differentiated OS outcomes, with a median OS of 5.1 m, 8.4 m (HR 0.26, p<0.001), and 21.8 m (HR 0.05, p<0.005), respectively. Added to this, WES analysis showed a clinical benefit of targeted therapy in those tumors with a BRAF/EGFR gain as well as an enrichment of response in RNF43 mutated tumors.

Conclusions: Our preliminary data suggest that cfDNA *BRAF* MAF may constitute a significant tumor load surrogate with correlation with overall survival. cfDNA *BRAF* MAF and WES could help to identify three subgroups of patients with different prognostic and predictive features that could potentially have therapeutic implications.

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