TPS3642 **Poster Session**

A phase II study of encorafenib and cetuximab (EC) beyond progression in combination with FOLFIRI in *BRAF* V600E-mutated metastatic colorectal cancer (mCRC).

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Background: *BRAF* V600E mutation occurs in approximately 10% of metastatic colorectal cancers (mCRC) and confers poor prognosis. While the combination of encorafenib and cetuximab (EC) has demonstrated improved outcomes in previously treated *BRAF* V600E-mutated mCRC patients (pts), the duration of response remains suboptimal with median progression-free survival (mPFS) of 4.3 months (m). Approximately half of pts (45%) receive subsequent treatment after EC progression, predominantly with chemotherapy (ChT). Data from the safety lead-in (SLI) of the BREAKWATER trial, assessing EC in combination with ChT doublet in the first-line setting, demonstrated manageable safety profile and promising early efficacy signals for EC in combination with FOLFIRI, despite pharmacokinetic interaction. **Methods:** ECLYPse (NCT06640166; EU CT Number 2023-508615-24-00) is a multicenter, single-arm, phase II study evaluating EC continuation beyond progression in combination with FOLFIRI in pts with *BRAF* V600E-mutated mCRC who progressed on second-line EC. Key eligibility criteria include: histologically confirmed colorectal adenocarcinoma, *BRAF* V600E mutation, documented disease progression on EC in second-line setting, benefit to previous treatment with EC (best response: complete response, partial response or stable disease lasting for at least 3 months), measurable disease according to RECIST 1.1 criteria, ECOG PS $\leq$1, and availability of archival tumor tissue. Patients receive encorafenib 300 mg daily, cetuximab 500mg/m2 iv every 2 weeks, and standard FOLFIRI regimen. The primary endpoint is 6-month PFS rate. Secondary endpoints include PFS, overall survival, duration of response, objective response rate, disease control rate, and safety. Translational analyses include comprehensive genomic profiling on archival tissue and serial ctDNA analysis. Tumor assessment with contrast-enhanced CT scan of thorax, abdomen and pelvis is performed every 8 weeks. Using a single-stage design with one-sided α = 0.05 and 80% power, 25 patients will be enrolled to detect an improvement in 6-month PFS rate from 10% (null hypothesis) to 30% (alternative hypothesis). If at least 7 pts will be alive and not progressing at 6 months, the treatment will be considered sufficiently active to warrant further investigation. The study is currently enrolling at multiple sites in Italy. Clinical trial information: NCT06640166. Research Sponsor: Pierre Fabre.