Several previous reports indicated that cetuximab (Cmab) rechallenge may be efficacious in patients for whom Cmab was previously effective. On the other hand, some reports did not support this. Considering the plasticity of sensitive clone, we assumed that an anti-EGFR antibody-free interval (aEFI) and efficacy may be correlated. This current study investigates the efficacy and safety of Cmab rechallenge as a salvage chemotherapy.

### Study Design

**multicenter phase II study**

- main eligibility criteria
  - mCRC patients who have become refractory to fluoropyrimidines, L-OHP, CPT-11, Cmab and bevacizumab, and in whom previous treatment with Cmab was effective
  - in any earlier line (achieving CR, PR, or SD that persisted for 6 months)
  - AUS wild-type
  - measurable disease
  - aEFI 216 weeks between the last dose of Cmab during previous treatment and the start of Cmab rechallenge

**Protocol treatment:**
combination of weekly Cmab with biweekly CPT-11.

**Primary endpoint:** response rate (RR)

**Secondary endpoints:** progression free survival (PFS), overall survival (OS), association between the aEFI and efficacy, and safety

**Statistical considerations:** Using a single-stage binominal design, 45 patients were required; a RR of 20% was considered promising, and a RR of 5% unacceptable (one-sided α = 2.5%, β = 10%).

### E-Rechallenge-E Trial

**Liquid biopsy research**

**Methods**

Additional research of ctDNA was conducted optionally. Blood samples at baseline collected in STRECK BCT® tubes. ctDNA was extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qagen). We performed ddPCR assays on a QX200 digital PCR system (BioRad laboratories). The PCR data were quantified as copies/μL using Quantasoft™ software (BioRad laboratories).

A mutation was considered positive with more than 0.1% fractional abundance of KRAS (G12S/L) and EGFR (L858R) mutants. The uniplex ddPCR method had been validated beforehand by comparative analysis of a dilution series of synthetic copies of each indicated mutation allele.

**Results of Liquid biopsy research** (Table 4 and 5, Figure 4)

**Conclusion**

Cmab rechallenge showed some activity in the salvage setting, in patients for whom Cmab was previously effective. KRAS and BRAF screening by liquid biopsy may contribute to identify the patients with benefit from Cmab rechallenge.