**Introduction:** RAS mutant mCRC patients (pts) are excluded from treatment with anti-EGFR monoclonal antibodies. Nevertheless, retrospective data from large phase III trials led to hypothesize a potential benefit from cetuximab in KRAS G13D mutant pts both in first and advanced lines of treatment (De Roock JAMA 2010, Tejpar JCO 2012). In the refractory setting, KRAS G13D mutant pts achieved a superior PFS (4.0 vs 1.9 months, HR = 0.51, p = 0.004) and OS (7.6 vs 5.7 months, HR = 0.50, p = 0.005) compared to pts with other KRAS mutations. We conducted the present trial in order to prospectively confirm those findings and to evaluate the clinical relevance of single agent cetuximab in KRAS G13D mutant mCRC pts.

**Methods:** According to previous results p0 was set at 10%. Using a phase 2 Fleming single-stage design, with 90% power and alpha 0.05, and p1 set at 50%, the study required the inclusion of 12 pts. The alternative hypothesis would have been rejected if 3 or less pts would have been progression-free at 4 months after treatment start. We prospectively enrolled eligible mCRC pts to receive treatment with cetuximab monotherapy (500 mg/m² biweekly). Main selection criteria were the following: KRAS G13D mutant, measurable metastatic disease, progression after treatment with fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab or no other valid therapeutic option. RECIST 1.1 criteria were adopted.

**Results:** 12 consecutive eligible pts were enrolled. Main pts’ characteristics were the following: M/F = 6/6; median age = 74 (range 26-79); ECOG-PS 0/1-2 = 6/6; synchronous/metachronous disease = 8/4, median number of previous CT lines = 2 (range 0-5). 3 patients (25%) showed disease stabilization at 4 months after treatment start and no RECIST responses were observed. Disease control rate at 6 months was 0%. Median PFS and OS were 1.9 and 7.2 months, respectively. Grade 3 rash was observed in 2 (17%) patients and no unexpected toxicities occurred.

**Conclusion:** The hypothesis of a clinically relevant benefit with cetuximab monotherapy in KRAS G13D mutant mCRC pts was rejected. KRAS G13D mutant mCRC pts should not be treated with cetuximab and alternative strategies should be adopted.