Results: A total of 102 out of 735 mCRC patients (13,9%) were analyzed. Median age was 57.3 year and 55% were male. The outcomes were as follows: ORR 12%, DCR 39%, and mPFS 4.0 months (CI95% 3.29-5.03). Of note, 28 patients (27%) had a mPFS $>$ 6 months with rechallenge (range from 6.57 to 14.2 months) and constituted the best-responders group. Data of prognostic characteristics and molecular alterations are available for 19 of these patients. The prognostic subgroup classification was as follows: 9 patients (47.4%) PPC, 5 patients (26.3%) GPC, and 5 (26.3%) BPC. Most frequent molecular alterations were: APC (68.4%), TP53 (63%), RAS (47.4%), and PIK3CA (21%). Concomitant APC and TP53 mutations were detected in 47.4% of patients. No associations between prognostic characteristics and molecular alterations were observed.

Conclusions: This study suggests that rechallenge with oxaliplatin can achieve a clinically meaningful mPFS $>$ 6 months in 27% of patients. No enrichment in GPC and BPC was observed. APC, TP53 and RAS detected in this best-responders group are the major tumour genes which are frequently mutated in mCRC. A more extensive molecular analysis should be carried out to better characterise the patients who benefit the most from this treatment strategy.

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PD-13 Plasma RAS dynamics and efficacy of anti-EGFR rechallenge in patients with RAS/BRAF wild-type metastatic colorectal cancer: REMARRY and PURSUIT trials

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Background: Assessment of plasma RAS (pRAS) mutations in circulating-tumor DNA at 'just before' rechallenge with anti-EGFR monoclonal antibody (EGFR mAb) may predict efficacy for the rechallenge therapy in patients with RAS/BRAF V600E wild-type metastatic colorectal cancer (mCRC). However, the clinical impact of pRAS status at progression on prior EGFR mAb for the rechallenge therapy is unknown. The REMARRY trial is a prospective longitudinal study to investigate the pRAS dynamics, and PURSUIT trial is a phase II trial to investigate the efficacy of EGFR mAb rechallenge in patients with pRAS wild-type just before rechallenge therapy.

Methods: Eligibility criteria of REMARRY included RAS/BRAF V600E wild-type mCRC; ECOG PS 0-1; CR or PR during prior EGFR mAb; and progressed $\leq$ 2 months from the last administration of EGFR mAb. pRAS status by the BEAMing method (OncoBEAM RAS CRC Kit) was prospectively monitored at timepoints of progression on EGFR mAb and each subsequent therapy. Among participants of the REMARRY, patients who satisfied the following eligibility criteria were enrolled in PURSUIT; pRAS wild-type within 28 days prior to enrollment in PURSUIT; being refractory or intolerant to fluoropyrimidine, oxaliplatin, and irinotecan; and $\geq$ 4 months of EGFR mAb-free interval. Study treatment was rechallenge with panitumumab 6 mg/kg + irinotecan 150 mg/m2q2wks. Primary endpoint of PURSUIT was a confirmed objective response rate (ORR) according to RECIST v1.1. Biomarker analysis was performed for blood samples after disease progression on prior EGFR mAb, immediately prior to PURSUIT, and after disease progression in PURSUIT using plasma next generation sequencing (Guardant360). Plasma RAS, BRAF V600E, and EGFR extracellular domain mutations were defined as acquired resistances for EGFR mAb.

Results: Between May 2019 and May 2021, 183 patients were enrolled in REMARRY from 27 institutions, and 50 patients were enrolled in PURSUIT; median age, 68 years; left-sided primary, 44 patients; and prior EGFR mAb, 1st/2nd/$\geq$3rd lines in 28/6/16 patients. Confirmed ORR and disease control rate were 14% (90% CI, 7.8%—23.9%) and 80% (95% CI, 67.0%—88.8%), respectively. In addition, 4 patients showed an unconfirmed PR. Median progression-free survival (PFS) was 3.6 months (95% CI, 3.0—4.7 months). Among 31 patients with biomarker results after disease progression on prior EGFR mAb, ORR occurred in 5 of 21 patients (23.8%) with pRAS/BRAF/EGFR wild-type, whereas no responses occurred in patients whose tumors harbored any pRAS/BRAF/EGFR mutations (0/10) (p=0.092). Median PFS was 4.2 months and 2.8 months in patients without vs with pRAS/BRAF/EGFR mutations, respectively (p=0.06). In terms of pRAS/BRAF/EGFRstatus immediately prior to PURSUIT, 4 of 22 patients with wild-type responded to the study treatment (ORR, 18.2%), while one patient harboring pKRAS/EGFR co-mutations in 9 patients with any mutations also responded (ORR, 11.1%) (p=0.63). No trend in PFS was observed between the groups; median, 3.1 month and 3.3 months in patients with wild-type and those with any mutations (p=0.62).

Conclusions: Plasma RAS/BRAF/EGFR mutational status after progression on prior EGFR mAb may identify patients with RAS/BRAF V600E wild-type mCRC who could benefit from rechallenge with EGFR mAb.

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PD-14 Resectability, conversion, and resection rates with survival according to RAS and BRAF mutations in a prospective metastatic colorectal cancer study (liver-limited subgroup in the RAXO study)

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Background: RAS and BRAF mutations are associated with worse outcomes for patients with colorectal cancer (CRC) liver metastases, but little is known about their effects on resectability, conversion, and resection rates.

Methods: The prospective Finnish RAXO-study (NCT01531621) included 1086 patients with treatable metastatic CRC 2012-2018 (Osterlund TLRHE 2021, Isoniemi BJS 2021) of which 354 patients with known RAS/BRAFV600E status and liver-limited metastases at baseline were included in this secondary endpoint analysis. Resectability was assessed repeatedly at a tertiary liver centre multidisciplinary team meeting (MDT). Resectability, conversion, and resection rates with outcomes after R0/1-resection of liver only metastases were studied according to mutational status.

Results: The study included 123 RAS&BRAF wild type (wt), 209 RAS mutated type (mt) and 22 BRAFmt patients. Demographics for RAS&BRAFwt/RASmt/BRAFmt, respectively, showed significant differences in male proportion (72%/59%/46%) and location of primary (right colon 9%/30%/64%, left colon 62%/38%/23%, rectum 29%/32%/14%). RAS&BRAFwt, RASmt, and BRAFmt patients had high upfront-resectability rates of 48%, 45%, and 27% with conversion rates of 25%, 22%, and 18% (of all included), in centralized MDT assessment. Corresponding resection rates were 71%/60%/41% (OR reference/0.62 [CI95% 0.38-0.99]/0.29 [0.11-0.73]). When patient was considered upfront resectable in tertiary centre MDT, the local hospital underestimated resectability in 39%/43%/83%, respectively. When tertiary centre MDT considered a patient borderline resectable, the local assessment was never resectable in 16%/15%/0%. Reasons for not operating a technically resectable patient were progressive disease during neoadjuvant therapy (63%), comorbidities (26%), and inoperable at exploratory surgery (11%). In upfront borderline resectable liver only metastases, conversion rates were 80% (31/39) in RAS&BRAFwt, 82% (45/55) in RASmt, and 40% (4/10) in BRAFmt. In patients with left-sided primaries (colon/rectum), conversion rates were 82% (31/38) in RAS&BRAFwt, 87% (33/38) in RASmt, and 100% (3/3) in BRAFmt, and for patients with right-sided primaries they were 0% (0/1) in RAS&BRAFwt, 71% (12/17) in RASmt, and 14% (1/7) in BRAFmt. Conversion rates for borderline resectable left-sided primaries were 90% (17/19) with doublet chemotherapy + cetuximab/panitumumab, 89% (39/44) with doublet/triplet chemotherapy + bevacizumab, and 69% (11/16) with 1-2 drugs (1-2 cytotoxics +/- biologic). With right-sided colon cancers conversion rates were 0% (0/1) with cetuximab/panitumumab-based, 55% (11/20) with bevacizumab-based, and 50% (2/4) with 1-2 drugs. From the first resection for metastases, 1-year recurrence-free survival was 64%/58%/29% for R0/1-resected RAS&BRAFwt/RASmt/BRAFmt (n=197), median overall survival (mOS) was 82/73/28 months (HR reference/1.55 [0.91-2.65]/7.24 [2.38-22.00]), and 5-year OS-rates 68%/60%/0%. From the diagnosis of metastatic disease mOS for R0/R1 resected was 83/75/30 months, while patients with R2-resection or ablation had 'not reached'/37/16, and 'systemic therapy only' 27/19/19, respectively.

Conclusions: High resectability, conversion and resection rates, with excellent survival are achievable for patients with RAS&BRAFwt and RASmt CRC liver metastases, with slightly inferior rates and survival for BRAFmt. Highest conversion rates (80-90%) in borderline resectable are seen in RAS&BRAFwt and RASmt, and in left-sided primaries. Mutations and sidedness should not preclude proper repeated assessment of resectability, preferably in centralized organ-specific MDTs.

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