Table: 503P

	Left side + Rectum wild type	Left side + Rectum mutant	Right side mutant
	New alterations at first progression		
UPTR	N: 4 BRAF amp, CDK12 D643fs, FGFR1 amp, PIK3CA amp.	N: 1 RB1 R621H	N: 2 APC L292FS, TP53 P177L
NO UPTR	N: 7 APC R405,CDKN2A H83Y, PIK3CA E545K, TP53 R273H, APC splice site SNV, NOTCH1 V1721fs, PTEN P2045	N: 11 APC L749fs, KRASG12D, NOTCH1 S1708, TP53 S240G, TP53 V274G, TP53 E336FS, EFGR amp, MAP2K1 K57N, NRASG12V, TP53 E336, TP53 E271V	N: 13 APC R1450, EGFR amp, HNF1A R203H, PIK3CA E545K, STK11 P281L, TP53 R175H, TP53 R273C, BRAF amp, FGFR1 amp, PIK3CA E542K, PTEN F257S, TP53 C275W, TP53 R273H

Methods: We retrospectively analyzed the mutational landscape (excluding Variants of Unknown Significance) in 64 consecutive patients with synchronous mCRC who underwent a comprehensive genomic profiling with the Guardant360 74 gene panel at baseline and at first tumor progression according to UPTR in the context of tumour location and RAS status. The Variant Allele Fraction (VAF%) and the total number of new alterations at first progression were evaluated.

Results: 1- The total number of new alterations at first progression was higher in all subgroups for the non UPTR patients (Table):

The median number of metastatic sites at baseline was the same between both subgroups although more irresectable metastatic sites were found in the non UPTR subgroup 2- For Left side + rectum locations either wild-type or mutant, the median VAF% was higher at baseline and at first progression in patients without UPTR as compared with UPTR. This was not the case in the right-side mutant subgroup: Left side + Rectum WT median VAF%: Baseline: no UPTR vs UPTR: 51.1% vs 22.5%. At first progression: 23.3% vs 9.0%. Left side + Rectum mutant median VAF%: Baseline: no UPTR vs UPTR: 90.5% vs 49.0%. At first progression: 68.7% vs 64.9% Right side mutant median VAF%: Baseline: no UPTR vs UPTR: 58.4% vs 107.9%. At first progression: 39.76% vs 67.3%

Conclusions: Clearly higher number of new molecular alterations at first tumoral progression were detected in patients with synchronous mCRC and no UPTR as compared with those patients with UPTR. Next-Generation Sequencing platforms may be of great value to clarify different outcomes of mCRC patients and to further validate our findings in larger prospective studies.

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504P Prognostic factors of patients with AFP-positive colorectal cancer: A case-control study

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Background: α-Fetoprotein-positive colorectal cancer (AFPP-CRC) is a rare type of colorectal cancer (CRC), and there have been no comprehensive investigations on prognostic factors of AFPP-CRC. The aim of this study was to elucidate the prognostic factors of AFPP-CRC.

Methods: During the years of 2010 to 2020, 127 CRC patients with preoperative elevated serum AFP level were collected, after excluding the diagnosis of hepatitis, hepatocirrhosis and hepatocarcinoma. The AFPP-CRC group control was matched by 1:2 to the AFPN(α-Fetoprotein-negative)-CRC group after propensity score matching (PSM) analysis. Prognostic factors were investigated using univariate and multivariate Cox regression model. Kaplan-Meier curves were performed among the prognostic factors as well.

Results: After PSM analysis, these two groups were balanced for age, sex, and tumor stage. After adjusting for other confounding factors, AFP positivity and tumor stage were shown to be associated with poorer overall survival (OS) and disease-free survival (DFS). The median of OS was 26.4 months versus 30.3 months when comparing AFPP-CRC group versus AFPN-CRC group. The median of disease-free survival was 23.3 months in the AFPP-CRC group, as compared to 26.0 months in the AFPN-CRC group. Among AFPP-CRC patients, those who also had a worse prognosis were characterized by elevated serum CEA level ($P<0.001$), liver metastasis($P<0.001$), nerve infiltration($P=0.009$), peritoneal metastasis($P=0.02$), poorer stage($P<0.001$) and microsatellite stability ($P=0.007$).

Conclusions: We found higher serum AFP level before surgery was associated with worse OS in patients with CRC, even adjusting for tumor stage. Besides, AFPP-CRC with microsatellite stability might had a worse prognosis.

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505TiP REGINA: A phase II trial of neoadjuvant regorafenib (rego) in combination with nivolumab (nivo) and short-course radiotherapy (SCRT) in intermediate-risk, stage II-III rectal cancer (RC)

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Background: Despite recent improvements, management of locally advanced rectal cancer (LARC) remains challenging, and many patients (pts) still experience recurrence. In preclinical models, combining Rego with an anti-PD-1 inhibitor led to superior tumour growth suppression as compared with either treatment alone. In a phase I clinical trial, remarkable results were reported for the combination of Rego and Nivo in advanced MSS colorectal cancer. This synergistic effect is thought to be secondary to the anti-angiogenic effects of Rego and its potential to reduce TAMs, promote M1 macrophage conversion, and downregulate expression of immunosuppressive factors. Building on these data, we designed a trial of Rego-Nivo with standard SCRT in the neoadjuvant setting of RC.

Trial design: REGINA is an academic, multicentre, single-arm, phase II trial sponsored by Institut Jules Bordet. Eligible patients are treated according to the following plan: induction phase (Nivo 240 mg IV D1&15, and Rego 80 mg PO D1-14), SCRT (D22-26), consolidation phase (Nivo 240 mg IV D29,43&57, and Rego 80 mg PO D29-49), and surgery (7-8 weeks after SCRT). Key eligibility criteria include age $\geq$18 years, ECOG PS $\leq$1, adenocarcinomas below the peritoneal reflection, intermediate-risk, stage II-III tumour (ie, cT3/T4aNany or cT1-2N+, no involvement/threatening of the mesorectal fascia, no involvement of lateral pelvic lymph nodes). The primary endpoint is pathological complete response (pCR). Secondary endpoints include, among others, toxicity, compliance to treatment, pTRG, event-free survival, and overall survival. The study follows a Simon's two-stage design (null hypothesis pCR=12%, alternative hypothesis pCR=24%; α=5%, β=20%) with a maximum of 60 pts to be enrolled. A safety interim analysis is planned after the first 6 pts have completed treatment. Serial collection of tumour, blood, and stool samples is mandatory at pre-specified time points for exploratory correlative biomarker analyses. The trial is planned to be run at 8-10 centres across Belgium. Study recruitment started in Q1 2021 and is anticipated to complete in Q3 2023. Clinical trial information: NCT04503694.

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