P-219 Real-life experience with chemotherapy plus biologics in first-line treatment of right-sided, RAS wild-type, metastatic colon cancer: A multicenter Onco-Colon Turkey study

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Background: Prognosis of metastatic right-sided colon cancer (mrCC) is poor compared to left-sided counterparts. There is ambigous data for the first-line treatment choice of anti-EGFR or anti-VEGF monoclonal antibody (mAb) in RAS type mrCC. Our aim was to study the real-life experience (onco-colon registry Turkey) of doublet chemotherapy backbone plus antiEGFR or antiVEGF mAbs in RAS wild-type mrCC.

Methods: Data of mrCC patients treated with a first-line regimen between 2016 and 2019 from 28 centers were recorded. Treatment regimens were as follows: FOLFOX (XELOX), FOLFIRI plus panitumumab (6 mg/kg on d1), cetuximab (500 mg/m2 on d1, iv) or bevacizumab (5 mg/kg on d1, iv) every 2 weeks.

Results: There were 210 (19.7%) right-sided of 1065 metastatic colorectal cancer (mCRC) patients treated with first-line FOLFOX/FOLFIRI plus panitimumab/cetuximab or bevacizumab regimens. Four patients treated with triplet chemotherapy backbone (5-fluorouracil, oxaliplatin and irinotecan) were excluded from the analysis. The median age was 62 (26-84). Thirty-five percent of patients were female. BRAF mutation and MSI-h status rates were 9,1% and 20%. The proportion of patients receiving treatment including panitumumab, cetuximab and bevacizumab was 19%, 27% and 54%, respectively. The median follow-up time was 18,7 months(mo's) (2-73). Overall response rate was 46.8% (CR: 5.2%). Median treatment cycles was 6 (1 to 30) and 26,2% of the patients were given maintenance treatment with a median of 6 cycles (1 to 27). Second-line treatment was given to 56,2% of patients. Median PFS was 9,8 months (95% CI; 8,8- 10,8) and OS was 24,6 months (95% CI; 20,1-29,2). Response type was the only statistically significant parameter in multivariate cox regression analysis for progression free survival (p: 0.000). Complete and partial responders had longer PFS durations (21.2 and 11.2 mo's) compared to stable and progressive disease (9.9 and 3.3 mo's) patients (p:0.000). PFS in anti-EGFR treated group was numerically longer with oxaliplatin compared to the irinotecan treated group (11.7 vs 8.7 mo's; p:0.093), but PFS duration was similar in bevacizumab and oxaliplatin or irinotecan treated patients (9.9. vs 9.7 mo's). Metastatectomy rate was higher in anti-EGFR treated group (9.8% vs 17.2%). Biologic treatment and chemotherapy backbone and response type were statistically significant parameters in multivariate cox regression analysis for overall survival (OS, $p < 0.05$). Patients treated with panitimumab (32.8 mo's) and cetuximab (28.7 mo's) lived longer compared to bevacizumab (21.7 mo's; p:0.047). Patients treated with oxaliplatin (26 mo's) had longer survival than irinotecan (18.8) based chemotherapy backbone (p:0.045). ORR was similar in anti-VEGF and anti-EGFR mAb treated patients (44.2% and 44.3%). OS was longer with oxaliplatin (anti-EGFR vs anti-VEGF; 32.8 vs 22.8 mo's) compared to irinotecan (anti-EGFR vs anti-VEGF; 18.8 vs 19.3 mo's) based regimens.

Conclusions: Anti-EGFR and oxaliplatin based treatment regimens and treatment responders were positive prognostic factors for OS in RAS wild-type mrCC patients.

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P-220 Linc01088 promotes the progression and tumor immune escape in colorectal cancer by sponging multiple microRNAs

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Background: LincRNA, a newly discovered long non-coding RNA, is epigenetically regulated and plays an important role in a variety of pathological and physiological processes, including cancer progression. Long intergenic non-protein coding RNA 1088 (Linc01088), located in chromosome 4q21.21, is a recently identified LincRNA. Its biological function in colorectal cancer (CRC) progression and immune escape are still unclear.

Methods: Here, to elucidate the function of Linc01088, 36 paired CRC and paracancerous tissues were collected under approval. Linc01088 expression was determined using fluorescence in situ hybridization and qPCR analysis. Protein expression was evaluated by Western blotting analysis. CCK-8 assay, colony formation assay and transwell migration and invasion assays were performed to detect cell viability, proliferative, migratory, and invasive capabilities. The interaction between microRNAs and Linc01088 was confirmed using RNA immunoprecipitation (RIP) assay. Besides, xenograft tumor mouse models were utilized to unveil the in vivo function of Linc01088. Biological activity of Linc01088 was also evaluated using the human intestinal organoid culture.

Results: Our findings confirmed that Linc01088 was significantly upregulated in colorectal cancer tissues and CRC cell lines (HCT116, LoVo, CaCo2, SW480) compared to the adjacent normal tissues and human colonic epithelial cells CCD-841CoN. High Linc01088 expression was associated with poor prognosis in patients with CRC. Linc01088 was mainly located in the cytoplasm. Further in vitro experiments confirmed that silencing of Linc01088 inhibited the proliferation, migration, invasion, and immune escape of colorectal cancer cells in comparison to the controls. Mechanistically, RIP experiments demonstrated that Linc01088 directly bound a series of miRNAs (has-miR-149-5p, has-miR-4778-5p, has-miR-548b-5p, has-miR-548c-5p, has-miR-548d-5p, has-miR-548i, has-miR-548w, has-miR-548y, has-miR-590-3p), of which miR-548b-5p and miR-548c-5p significantly upregulated the expression levels of targeted downstream genes (BRDW1, G3BP1 and PD-L1). Furthermore, Linc01088 knockdown in colorectal cancer cells contributed to the upregulation of the corresponding miRNAs and the downregulation of the downstream gene expressions, affecting CRC cell phenotypes. In mouse xenograft models, our results further revealed that Linc01088 knockdown significantly suppressed tumor growth, lung metastasis and immune escape. Notably, by culturing human colorectal cancer organoids in ex vivo (n=2), data indicated that Linc01088 knockdown significantly reduced the growth of CRC organoids compared with the control group.

Conclusions: Taken together, these data suggest that Linc01088 directly targets intracellular miRNAs (miR-548b-5p and miR-548c-5p), promoting the expression levels of target genes (BRDW1, G3BP1 and PD-L1), thereby facilitating colorectal cancer development and immune escape. This may provide new insights into the development of potential targets for colorectal cancer diagnosis and treatment.

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P-221 Repurposing disulfiram as treatment for metastatic colorectal cancer: An investigator-initiated clinical phase II trial

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Background: Fundamental problems in the current treatment of patients with metastatic colorectal cancer (mCRC) are a lack of new effective drugs and a high percentage of patients with mCRC receiving chemotherapy that do not benefit from the treatment due to inherited or acquired drug resistance. We present a repurposing strategy by introducing the drug disulfiram to patients with mCRC and irinotecan-resistant disease. Bartek et al. (Nature 2017) describe in detail the molecular mechanisms of disulfiram plus copper effects on cancer cells. They show that the molecular target of disulfiram's anticancer effects is inhibition of NPL4, which is essential for turnover of proteins in cells. Besides blocking the enzyme acetaldehyde dehydrogenase, disulfiram targets drug efflux-pumps, induces production of reactive oxygen species, activates the JNK and p38 MAPK signaling pathways, inhibit NFkB and inhibits the proteasome activity. All of these effects are well-known anti-cancer drug effects. Furthermore, disulfiram-mediated NFkB inhibition is known to enhance the cytotoxic anti-cancer effect of 5-FU and irinotecan in colorectal cancer cells, which further