EVALUATION OF LIQUID BIOPSY-BASED PLASMA COPY NUMBER BURDEN, DNA METHYLATION AND PERSONALIZED MINIMAL RESIDUAL DISEASE APPROACH FOR MONITORING MOLECULAR RESPONSE TO DIFFERENT DRUG REGIMENS IN METASTATIC COLORECTAL CANCER PATIENT
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Background Liquid biopsy (LBx) based low pass whole genome sequencing (LP-WGS) derived blood copy number burden (bCNB) with defined clinical cut-offs provides a genome-wide overview for monitoring molecular response. LBx DNA methylation analysis promises sensitivity for monitoring treatment response and possibly provides tissue of origin (TOO) insights. The potential clinical utility of the multi-faceted approaches to monitor molecular response using bCNB and DNA methylation in the metastatic colorectal cancer (mCRC) palliative treatment setting were investigated.

Methods Seventy longitudinal (baseline, on-treatment, and end of treatment (EOT)) plasma samples were collected from 14 mCRC patients treated with chemotherapy (CTx) alone or in combination with one or more targeted agents and PD-L1 blockade (figure 1). bCNB and DNA methylation were analyzed at all timepoints, respectively. bCNB is calculated based on the genome-wide copy number abnormalities, normalized by the LP-WGS profiles from healthy donors. Furthermore, a clinical applicable cut-off can be defined for molecular response monitoring. DNA methylation provides whole-genome methylation profiles using input amounts as low as 1 ng. Personalized MRD which uses patient-specific mutation and fixed panels, was utilized to generate MRD data for the 11 baselines, time points and EOT samples.

Results Using bCNB, eight patients treated with CTx in combination with different therapies such as targeted agents and PD-L1 blockade showed a consistent reduction in tumor burden compared to baseline, with post-treatment bCNB values below the cut-off of 5.2 (log2) derived from healthy donors (figure 2). DNA Methylation determined TOO, exemplified by the preliminary data detected the enrichment of SMAD4-associated hypermethylated DNA fragments in a patient with metastasis. A cut-off of 9.5 (log2) was defined based on abnormally methylated fragments, which correlated with bCNB (R²=0.83; figure 2). Additionally, indication specific tiered cut-offs for molecular responses can be defined. Tumor fraction estimates using Personalized MRD showed a correspondence with both bCNB (patient-wise correlation, Pearson r=0.87) and abnormal DNA Methylation cut-offs (patient-wise correlation, Pearson r = 0.82) for patients with matching data points, respectively.

Conclusions bCNB is a feasible approach for assessing molecular response with cut-off determination, and its low cfDNA input requirement enables clinical utilities. Preliminary data supported that DNA methylation assay detected TOO and demonstrated potential clinically applicable cut-off definitions. bCNB, DNA methylation and Personalized MRD demonstrated concordance and provided a comprehensive suite of solutions for molecular response and MRD monitoring. Collectively, the holistic LBx approaches with clinical applicable cut-off definition would possibly facilitate the selection of patient-centric tailored treatments.

Ethics Approval The study protocol was in accordance with the tenets of the Declaration of Helsinki. Commercial samples used in this study were procured from Indivumed GmbH following protocols approved by the local Institutional Review Board (IRB) committee. Informed consent forms were obtained from all the human subjects in this study.

Consent Written informed consent was obtained from the patient for publication of the abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.