Influence of preoperative chemoradiation on tumor-infiltrating lymphocytes in locally advanced rectal cancer: The STAR-01 cohort


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Background: Preoperative chemoradiotherapy (CRT) may increase antitumor immunity through enhancing T-cell activation and tumor infiltration. These effects could possibly sensitize the tumor to immunotherapies, including checkpoint inhibitors. We explored whether preoperative CRT for locally advanced rectal cancer (LARC) induces immunologic changes and if the post-operative biological parameters are associated with tumour regression grade (TRG). Method: The multicenter randomized STAR-01 study compared a standard preoperative CRT regimen (50.4 Gy in 28 daily fractions with concomitant infused fluorouracil) at the dose of 225 mg/m2/d with the same regimen plus oxaliplatin given weekly at the dose of 60 mg/m2 in patients with LARC. Paired pre- and post-operative specimens were available for 81 patients and were analyzed by immunohistochemistry. The immunohistochemical analysis was performed with a panel of immune cells and associated factors as CD3, CD20, CD4/CD8, PD1. The pattern of tumor infiltrating lymphocytes (TILs) and related infiltrating lymphocytes (RILs) was also evaluated. Results: After therapy we observed a decreased CD4/CD8 ratio (p < 0.001) and reduced expression level of CD20 (p < 0.001). The expression level of CD3+ and PD1+ cells after therapy did not change significantly. The relative increase of lymphocytes CDB+ inside CD4/CD8 ratio evaluated on post-operative samples was significantly associated with TRG 0 (p < 0.001).

Conclusions: Our data suggest that CRT may induce an enrichment of CD8+ T lymphocytes and this translates in better response to CRT. The new frontier of best immuno-therapeutic strategy could be the use of specific immune cells (T lymphocytes) to trigger the system’s immune response against disease.

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Baseline mutational profiles of patients with carcinoma-of-primary-origin (CUP) enrolled onto CUPISCO


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Background: NCCN guidelines consider next-generation sequencing important in guiding the neoplastic decision-making in CUP. CUPISCO (CUP International Study of Comprehensive Oncology) is an ongoing, phase II randomised study of targeted therapy/cancer immunotherapy vs platinum-based chemotherapy in pts with unfavourable CUP, defined per ESMO guidelines. We present a preliminary, descriptive molecular analysis of ~50% of pts designated for enrolment.

Methods: Upon enrolment, comprehensive genomic profiling, including determination of microsatellite instability and tumour mutational burden (TMB), was performed on formalin-fixed, paraffin-embbeded tissues using the FICDX assay. Gene alterations (GA) were assessed in ~3% of pts were analysed using multiple correspondence analyses and hierarchical clustering to identify co-occurrences.

Results: Median age was 61.5 years (n = 346 [Apr 2021]; range: 22–84); median TMB was 2.5 mutations/Mb [0–63.0]. In our analysis, 30% of patients carried a potentially targetable GA. Most frequent GAs were TP53 (44%), CDKN2A (32%), KRAS (21%; 2% G12C alterations), CDKN2B (21%), ARID1A (13%), STK11 (13%), MTA3 (12%), PIK3CA (10%), MYC (8%), RB1 (8%), BAP1 (8%) and FGFR2 (8%). Beyond PIK3CA and FGFR2, other targetable GAs were identified in EGFR (2%), ERBB2 (6%), ALK (0.3%), ROS1 (3%), MET (2%), NTRK1 (1%) and BRAF (6%). The frequency of microsatellite instability and TMB-high (~16 mutations/Mb) samples was 3% and 9%, respectively. Based on hierarchical clustering of co-mutational profiles, multiple clusters were identified and characterised by specific GA co-occurrences.

Conclusions: This descriptive analysis sheds further light on the molecular landscape in pts with poor-prognosis CUP. Our analyses demonstrate that CUP cases can be clustered based on molecular profiling; further studies are needed to determine if these clusters carry clinical relevance. Our early results suggest that comprehensive genomic profiling of CUP samples identifies therapeutically relevant GAs in a significant proportion of patients and could thus guide personalised treatment of these tumours.
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Assistance with an artificial intelligence-powered PD-L1 reading of tumor proportion score in non-small cell lung cancer

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Background: Programmed death ligand 1 (PD-L1) expression is the standard biomarker in advanced non-small cell lung cancer (NSCLC). However, manual evaluation of PD-L1 tumor proportion score (TPS) by pathologists has practical limitations and inter-pathologist variation in subjective reading of this clinical actionable biomarker. This study aimed to explore whether the artificial intelligence (AI)-powered TPS analyzer could reduce the human discrepancy.

Methods: AI-powered TPS analyzer, namely Lunit SCOPE PD-L1, was developed with a total of 393,565 tumor cells annotated by board-certified pathologists for PD-L1 expression in 802 whole-slide images (WSIs). To validate the accuracy and reproducibility of the AI-powered TPS analyzer, we conducted a study comparing the concordance of PD-L1 TPS in 432 WSIs with or without AI assistance (n = 370/390, 97.3%). The TPS scores were assessed by three major research institutes: Astra Zeneca, Merck, and SanoPharma. Three independent pathologists labeled PD-L1 TPS into 3 categories: TPS <1%, 1-49%, ≥50%. The cases for the discordance between each pathologist and AI model were reviewed and classified by the authors.

Results: Without AI assistance, 3 pathologists concurrently labeled TPS in 81.4% of cases (n = 370/479, x = 0.798), and the concordance rate between the consensus of three pathologists and AI was 86.4% (n = 337/390). Afterward, pathologists revised their initial labeling with assistance of AI model for the cases of discordance between the pathologist and AI model (n = 91, 93, and 107, respectively for each pathologist). Interestingly, the overall concordance rate of three pathologists with AI assistance was increased to 90.2% (n = 418, x = 0.918). Subgroup analysis showed that the concordance rates without AI assistance according to PD-L1 TPS <1%, 1-49%, ≥50% were 67.9%, 72.2%, and 92.4%, respectively, which were increased with AI assistance to 89.6%, 86.2%, and 93.6%, respectively.

Conclusions: Assistance with AI-powered TPS analyzer substantially improved the pathologist’s consensus and could be regarded as a reference for the final labeling of TPS, especially in the subgroups of TPS <1% and 1-49%.

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