

1802MO 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 tumours 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 sec. Ryan –AJCC Eight ed.).

Methods: 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. Response to pre-operative chemoradiotherapy was assessed according to TRG.

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 PD-1+ cells after therapy did not change significantly. The relative increase of lymphocytes CD8+ 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 treatment could be the use of specific immune cells (T lymphocytes) to trigger the system's immune response against disease.

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1803P The differences of TMB scores could be found in patients with different tumor types or pathological types

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Background: Tumor mutational burden (TMB) has been reported to be a predictive biomarker for immune checkpoint inhibitor (ICI). However, most studies adopted a universal TMB for a cohort of cancers. Therefore, we test whether TMB vary across cancer types. Moreover, we compared TMB in cancers of the same type while of different pathology. And we explore whether the predictive effect of TMB for ICI vary according to tumor types or whether the predictive value of TMB might be pathology-dependent even in the same tumor type.

Methods: The genomic (based on MSK-IMPACT sequencing) and survival information of enrolled patients with various types of cancer were collected. cBioPortal was adopted to analyze these data. We have compared the TMB score in a cohort of cancers. We further investigated the optimal TMB cutoff values for different tumor types and tumors of different histology within the same tumor type using the X-tile model.

Results: We found a wide range of the median TMB value in different cancer types, ranging from 4.25 Mut/Mb in renal cell carcinoma to 26.67 Mut/Mb in colorectal cancer. Despite of the same cancer type, tumors of different pathologies were found to have different median TMB. The optimal TMB cutoff value affecting survival was lowest in renal cell carcinoma, and highest in NSCLC, with others in between. For patients with NSCLC, melanoma, bladder cancer, renal cell carcinoma, head and neck cancer, esophagogastric cancer and colorectal cancer, high TMB was associated with relatively better survival. However, for glioma, high TMB is linked with relatively worse survival with ICI treatment. We demonstrated a marked difference in TMB cutoff between LUAD and LUSC. Moreover, higher TMB is linked with better prognosis with ICI in LUAD while predicts worse survival in LUSC subject to ICI. Similarly, the optimal TMB cutoff to predict survival is discrepant in tumors with different pathological types.

Conclusions: Our results reveal that TMB is cancer type and pathology specific. We recommend that tumor type and pathological type should not be neglected when distinguishing tumor mutational burden scores. Our findings allow a more robust and precise assessment rather than arbitrary judgment of TMB, which affects our decision-making regarding ICI adoption.

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1804P Baseline mutational profiles of patients (pts) with carcinoma-of-unknown-primary-origin (CUP) enrolled onto CUPISCO

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Background: NCCN guidelines consider next-generation sequencing important in guiding therapeutic decision-making in CUP. CUPISCO (NCT03498521) 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-embedded tissues using the F1CDx assay. Gene alterations (GAs) found 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%), MTAP (12%), PIK3CA (10%), MYC (8%), PBRM1 (8%), BAP1 (8%) and FGFR2 (8%). Beyond PIK3CA and FGFR2, other targetable GAs were identified in EGFR (2%), ERBB2 (6%), ALK (0.3%), ROS1 (1%), 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 in the study cohort, each 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.

Clinical trial identification: NCT03498521.

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1805P Assistance with an artificial intelligence-powered PD-L1 analyzer reduces interobserver variation in pathologic 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 of interobserver bias, variation in subjectivity on the area of interest, and intensive labor. 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 (WSI) of NSCLC stained by 22C3 pharmDx immunohistochemistry. Three independent pathologists labeled PD-L1 TPS into 3 class categories: TPS < 1%, 1-49%, or ≥ 50%, of 479 NSCLC slides. For the cases of disagreement between each pathologist and AI model, the pathologists were asked to revise TPS class in assistance with AI model which not only detects PD-L1 positivity of tumor cells, but also calculates WSI-level TPS. Finally, we compared the concordance rate of three pathologists with or without AI assistance.

Results: Without AI assistance, 3 pathologists concordantly labeled TPS in 81.4% of cases (n = 390 / 479, κ = 0.798), and the concordance rate between the consensus of pathologists and standalone AI model was 86.4% (n = 337 / 390). Afterward, pathologists revised their initial labeling with assistance of AI model for the cases of disagreement 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 = 432 / 479, κ = 0.890). Subgroup analysis showed that the concordance rates without AI assistance according to PD-L1 TPS <1%, 1-49%, and ≥50% class 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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