Editorial Commentary

Unravelling the puzzle of immunotherapeutic efficacy in lung cancer

Petros Christopoulos[1,2]^

[1]Department of Medical Oncology, Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Heidelberg, Germany; [2]Translational Lung Research Center at Heidelberg University Hospital, the German Center for Lung Research (DZL), Heidelberg, Germany

Correspondence to: Petros Christopoulos, MD, PhD. Department of Medical Oncology, Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Röntgenstr. 1, Heidelberg 691269, Germany; Translational Lung Research Center at Heidelberg University Hospital, the German Center for Lung Research (DZL), Heidelberg, Germany. Email: petros.christopoulos@med.uni-heidelberg.de.

Comment on: Lo Russo G, Prelaj A, Dolezal J, *et al.* PEOPLE (NTC03447678), a phase II trial to test pembrolizumab as first-line treatment in patients with advanced NSCLC with PD-L1 <50%: a multiomics analysis. J Immunother Cancer 2023;11:e006833. Erratum in: J Immunother Cancer 2024;12:e006833corr1.

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Higher response rates and longer survival have established programmed death cell (ligand)-1 [PD-(L)-1] inhibitors in addition to chemotherapy as the new first-line standard for non-small cell lung cancers (NSCLCs) without treatable genetic alterations (1). Nonetheless, combined chemoimmunotherapy has a relatively high rate of grade ≥3 adverse events at >60%, which makes PD-(L)1 inhibitor monotherapy a more attractive option for older and frail patients, as recently demonstrated by the IPSOS phase 3 trial in patients unfit for platinum and several retrospective analyses (2,3). The respective approval in Europe is, however, currently restricted to tumors with a high PD-L1 tumor proportion score (TPS) ≥50%, which show the greatest immunotherapeutic (IO) sensitivity (1).

The identification of further biomarkers to expand the scope and improve patient selection for IO has been extremely difficult so far. Since tumor profiling with next-generation sequencing (NGS) is already being performed at initial diagnosis (4), most previous efforts have focussed on the potential correlation of additional genetic parameters with IO benefit. However, despite promising early results in pancancer studies, the tumor mutational burden (TMB) did not show a strong enough association with clinical enpoints in phase 3 trials for formal regulatory approval (5), which is partly due to the technical challenges of panel-based TMB estimation (6). More recently, other genetic markers, like *STK11*, *KEAP1*, *KRAS/TP53* and *METΔex14/TP53* co-mutations were also linked to IO benefit in retrospective studies, but they concern relatively small patient groups without formal prospective validation (7-9).

An alternative strategy with increasing momentum is the exploration of purely immunologic, instead of genetic, biomarkers, which could theoretically capture the immunopathophysiology of each individual patient better and provide insights for the development of tailored IO strategies. With a recent study in the *Journal for Immunotherapy of Cancer*, Lo Russo *et al.* nicely demonstrate the methodological principles, power, and prospects, but also limitations of this approach (10). One first challenge arises due to the complexity and plasticity of the immune system, which necessitate multiparametric "omics" studies for adequate representation. Another issue is the continuous nature of most immunologic variables, in contrast to the binary presence or absence of genetic alterations,

^ ORCID: 0000-0002-7966-8980.

which complicates statistical analyses and requires the introduction of cut-offs with unclear biologic significance. Finally, the relatively low efficacy of monotherapy with PD-(L)1 inhibitors in NSCLC with PD-L1 TPS <50%, as exemplified by the progression-free survival (PFS) of only 2.9 months and the short overall survival (OS) of 12.1 months observed by Russo *et al.*, is an additional hurdle, because the distinction between favorable and unfavorable patient courses becomes more difficult within such a narrow range.

Despite these difficulties, Lo Russo *et al.* could identify a plethora of correlates for IO efficacy in univariate testing and furthermore construct a composite model of independent predictors (10). These were 4 blood immune cells populations, i.e., the abundance of peripheral blood natural killer cells/$CD56^{dim}CD16^{+}$ [hazard ratio (HR) 0.56, P=0.006] at baseline, as well as the abundance of non-classical $CD14^{dim}CD16^{+}$ monocytes (HR 0.52, P=0.004), eosinophils ($CD15^{+}CD16^{-}$) (HR 0.62, P=0.03) and lymphocytes (HR 0.32, P=0.001) after first radiologic evaluation, along with the tissue expression levels of 5 genes at baseline, i.e., CD244 (HR 0.74, P=0.05), PTPRC (HR 0.55, P=0.098), KLRB1 (HR 0.76, P=0.05), IRF9 (HR 3.03, P=0.08) and COMP (HR =1.22, P=0.06). While the performance of the model is currently being validated within the INT-led I3LUNG Horizon Europe project (https://cordis.europa.eu/project/id/101057695), several other points are also worth noting here. First, 2 out of the 4 significant immune cell populations have a myeloid origin and 3 out of 4 refer to innate cells, which underlines the relative importance of natural besides adaptive immunity for the efficacy of PD-(L)1 inhibitors. Similar observations were made by a recent study of miRNA in the blood on NSCLC patients, which identified a signature of 5 myeloid-derived species as reliable predictor of IO benefit outperforming tissue-based PD-L1 staining (11). Moreover, the association of gene expression results with the patient outcome is of direct practical relevance, as targeted RNA profiling with the Nanostring platform has been found suitable for integration with the routine molecular diagnostics of NSCLC patients, whose tumor RNA is anyway isolated from tissue biopsies at initial diagnosis for the sake of RNA NGS (4). One remaining point of interest here is the relationship of IO outcomes with the tissue abundance of immune cell populations, which can be calculated both in relative and absolute terms from Nanostring results and have demonstrated strong predictive potential in previous studies (12), but were not analyzed by Lo Russo *et al.* (10). As for the intestinal microbiome, the lack of independent representation in the final IO predictive model derived by the broad analysis of Lo Russo *et al.* is not surprising, since the presence of favorable bacterial taxa in stool is known to correlate strongly with immunologic parameters of the host (13).

Overall, the results by Lo Russo *et al.* add to the growing body of evidence supporting multiple immunologic parameters as potentially useful non-invasive IO biomarkers in the future. Other examples so far range from simple and readily available laboratory values, like the neutrophil-to-lymphocyte ratio (NLR) and advanced lung cancer inflammation index (ALI) (14), to more technically demanding parameters, like the proximity of tumor infiltrating $CD8^{+}$ to PD-$L1^{+}$ cancer cells (15), various serum cytokines (16), the T-cell receptor repertoire (17), miRNA signatures (18) and the course of ctDNA levels in longitudinal measurements (19). Considering the rapidly accumulating data, there is an urgent need for head-to-head comparison of promising assays to prioritize further development of novel technologies with the highest likelihood of successful clinical application and identify special patient groups that would likely require alternative approaches. Furthermore, we will need to systematically consider additional unmet biomarker needs, such as the development of predictors for immune-related adverse events (20), criteria for therapy de-escalation (21), IO biomarkers in other thoracic tumors inherently resistant to PD-(L)1 inhibitors, like $EGFR^{+}$/ALK^{+} NSCLC (22) and thymomas (23), as well as tools to guide application of emerging IO, including next-generation antibodies (24) and TCR-T cells (25). Similar biomarker-centered phase 2 studies to deepen biologic understanding of the disease and improve patient management are ongoing also for tyrosine kinase inhibitor (TKI)-treated NSCLC, for example the ABP trial for ALK^{+} tumors (NCT04318938), whose analysis can be inspired by the premium systematic work and follow the avenues of further research nicely demonstrated by Lo Russo *et al.* (10).

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