Editorial

Personalized medicine in immuno-oncology: a novel prognostic index in non-small cell lung cancer

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Immune checkpoint inhibitors have revolutionized the treatment of selected cancers with meaningful survival improvement in melanoma (1), renal cell carcinoma (2), and non-small cell lung cancer (NSCLC) (3-5). Despite these advances, a substantial proportion of patients do not benefit from treatment. Therefore, the validation of biomarkers both prognostic (to help identify those patients at higher risk for poor disease related outcomes independent of treatment) and predictive (to assess likelihood of response to therapy) remains a critical part of current research (See *Figure 1*).

In their recent article, Mezquita and colleagues (6) validated a prognostic index for immune checkpoint inhibitor response in NSCLC named the Lung Immune Prognostic Index (LIPI). The authors performed a retrospective analysis of 466 patients with advanced NSCLC treated with programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors, splitting their cohort into a 161 patients derivation cohort with internal validation using bootstrapping as well as a 305 patients validation cohort using multivariable survival analysis adjusted for pre-treatment clinical variables. Results showed that the following variables were associated independently with overall survival (OS): high lactate dehydrogenase (LDH) (HR 2.51, 95% CI: 1.32–4.76) and baseline derived neutrophil-to-lymphocyte ratio (dNLR) greater than 3 (HR 2.22, 95% CI: 1.23–4.01). These two variables were incorporated into the LIPI score which comprised of three distinct risk groups defined by number of factors presents; good risk (0 factors), intermediate risk (1 factor), and poor risk (2 factors). The LIPI risk score was able to differentiate risk with median OS of 34, 10, and 3 months in the three groups respectively. The LIPI groups were also associated with differential progression free survival (PFS); (P=0.001) and disease control rate (DCR); (P=0.004). Of interest, the LIPI score was not able differentiate outcomes in a control cohort of 162 NSCLC patients treated with chemotherapy suggesting that its use is specific to NSCLC patients treated with PD-1/PD-L1 inhibitors.

The key elements of LIPI namely LDH (7,8) and dNLR (9) have been demonstrated to be prognostic variables for cancer related outcomes in prior studies. A prior systematic review and meta-analysis has established that elevated neutrophil-to-lymphocyte ratio (NLR) is associated with adverse OS, adverse PFS, and adverse disease free survival (DFS) in multiple tumor types (N=40,559 patients) including NSCLC (N=1,591 patients) (10). The use of dNLR (neutrophils/total white blood cells-neutrophils) in a registry study of 27,031 patients was found to have similar prognostic value as NLR (9) and is often easier to compute from clinical trial data which may not

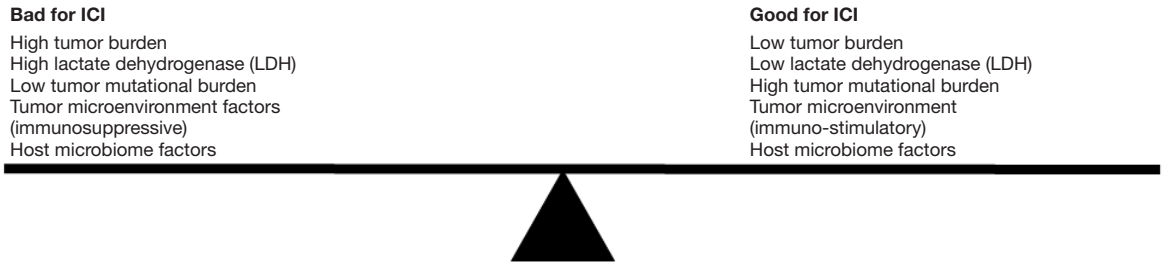

Figure 1 Balance of factors that impact response to immune checkpoint inhibitors (ICI).

collect data on lymphocyte counts systematically.

The use of immunotherapy in lung cancer, in particular PD-1/PD-L1 checkpoint inhibitors, has become a standard of care. In previously treated metastatic NSCLC, improved survival relative to chemotherapy has been observed with atezolizumab (11), nivolumab (3,4) and pembrolizumab (5). In untreated NSCLC with positive PD-L1 expression (defined as PD-L1 staining ≥50% using Dako™ 223C assay) improvements in both PFS and OS relative to chemotherapy have also been observed (12). It is important to note that NSCLC with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements may not benefit from immune checkpoint blockade as well as wildtype variants. A meta-analysis (13) comparing checkpoint inhibitors to docetaxel in previously treated NSCLC showed no OS benefit in the EGFR cohort (N=186). Additionally in a small retrospective cohort (14) of adenocarcinoma patients (N=28) harboring ALK rearrangement there were no responses observed with checkpoint inhibitor therapy.

While the above data are promising, overall response rates to immunotherapy in NSCLC remain low. Even amongst those with positive PD-L1 expression, response rates are only around 30% (5) and substantially lower than response rates seen for EGFR or ALK inhibitors (15) in sensitive populations. The need for more robust biomarkers in NSCLC is therefore of upmost importance. High PD-L1 expression seems to increase the benefit from Pembrolizumab in untreated NSCLC (12); however, this biomarker has limitations such as intratumor and inter-assay variability (16). Additionally, PD-L1 status has been shown to vary over the course of the natural history of NSCLC (17). Furthermore, as a predictive biomarker, PD-L1 positivity does not always guarantee that the tumor microenvironment has sufficient effector T cells to produce a response to PD-1/PD-L1 therapy (18). The use of other biomarkers in conjunction with PD-L1 expression such as tumor mutational burden (TMB) has been reported (19). In one biomarker analysis of a randomized trial (20), high TMB measured using whole exome sequencing was associated with improved PFS and increased objective response rates with nivolumab. However, no data were presented for the chemotherapy group meaning that the value of TMB as a predictor of benefit from nivolumab (rather than just a prognostic marker) remains uncertain.

In light of the aforementioned difficulties, the development of the LIPI as a clinical prognostic tool for NSCLC is of significant interest. The LIPI includes readily available and inexpensive biomarkers which are prognostic in NSCLC patients treated with immune checkpoint inhibitors. Additionally, the LIPI appears to have been validated robustly both internally and externally. However, there still are some limitations to the development of LIPI. First, the index uses somewhat arbitrary cutoffs for continuous variables (dNLR >3 and LDH > upper limit of normal). With respect to dNLR, the authors chose a cut-point of greater than 3 from a study with immune checkpoint inhibitors in metastatic melanoma (21). This cut-off might not be applicable in cancers with different pathogenesis and tumor micro-environment. Published data from a large registry trial of multiple cancer histologies does suggest that the optimal cut-off for dNLR based on predictive and discriminatory accuracy is 2 (9). Second, as reported by the authors, the lack of central radiology review in the validation and chemotherapy cohorts does introduce potential for bias in outcome results such as PFS and DCR. Third, the conclusion derived by the authors that pre-treatment LIPI could be used as a tool when selecting immune checkpoint inhibitors needs further prospective validation, preferably in a randomized trial. The

implications of using a prognostic biomarker in a predictive fashion could result in potentially denying some patients a beneficial therapy.

In conclusion, we congratulate Mezquita and colleagues on this important and clinically meaningful study that strives to give greater clarity on prognosis of patients with NSCLC. Additional validation of the LIPI as a predictive marker is warranted using data from a randomized trial of immune checkpoint inhibitors versus chemotherapy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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