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EDITORIAL

DNA damage response signaling as a predictive biomarker and synergistic therapeutic target for anti-PD-1/PD-L1 immunotherapy in non-small cell lung cancer

Lung cancer is the most common cancer and leading cause of cancer-related mortality worldwide. In 2015, more than 610,000 people died from lung cancer in China.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and the five-year survival rate of advanced NSCLC remains < 15%. PD-1 is an important immune checkpoint protein that mediates immunosuppression by binding to PD-L1. Compared to conventional chemotherapy, antibody-directed therapies against the PD-1/PD-L1 checkpoint have shown remarkable and persistent anti-cancer efficacy for advanced NSCLC.[2] The United States Food and Drug Administration has approved several monoclonal antibodies directed to the PD-1/PD-L1 pathway (nivolumab, pembrolizumab, atezolizumab, durvalumab) for first-line or second-line treatment of advanced NSCLC.[3] Presently, PD-1/PD-L1 inhibitors play an important role in therapeutic strategies for advanced NSCLC. In China, domestic pharmaceutical companies have made enormous efforts to develop counterpart antibodies. The China Food and Drug Administration (CFDA) has approved clinical trial applications for 16 agents: PD-1 inhibitors including JS001, SHR-1210, IBI308, BGB-A317, GLS-010, GB226, BAT1306, LZM009, HLX10, and HX008; and PD-L1 inhibitors including KN035, SHR-1316, TQB2450, KL-A167, ZKAB001, and CS1001. Moreover, at least six agents (CS1003, AK104, AK105, HLX20, MSB2311, BGB-A333) are under review by the CFDA for clinical trial approval. Numerous randomized clinical trials of PD-1/PD-L1 inhibitors both domestically and abroad are being performed in patients with advanced NSCLC to explore the efficacy, safety, and optimal regimen of these agents.

Early clinical trials with PD-1/PD-L1 inhibitors have shown durable responses and good tolerance in patients with advanced NSCLC. However, the response rate in the overall population remains only 14–20%.[4–8] Many studies have attempted to identify effective biomarkers for predicting the clinical efficacy of PD-1/PD-L1 inhibitors. PD-L1 expression was initially examined as a predictive biomarker. The results of clinical trials (CheckMate 017,[4] CheckMate 057,[5] POPLAR phase 2,[6] durvalumab phase 1b,[7] avelumab phase 1b[8]) reported that patients with PD-L1-positive NSCLC benefitted from these agents. However, the predictive ability of PD-L1 expression remains controversial. Not all patients with PD-L1-positive NSCLC benefit from PD-1/PD-L1 inhibitors. Additionally, some patients with PD-L1-low-expressing or PD-L1-negative NSCLC benefit from these agents.[9] Pembrolizumab has only been approved for patients with PD-L1-positive tumors, while nivolumab has been approved regardless of PD-L1 status. These inconsistencies have created confusion in clinical practice. Technical challenges related to the antibodies used, assay methods, scoring cutoffs, heterogeneity, and dynamic changes in PD-L1 expression contribute to this dilemma, indicating that any single assay for PD-L1 expression is not sufficient to distinguish PD-L1-low-expressing or PD-L1-negative patients who may benefit from the inhibitors.

Given the limitations of using PD-L1 expression as a definitive biomarker, other potential biomarkers for PD-1/PD-L1 inhibitors have been identified in diverse clinical trials, including oncogenic driver mutations, mismatch repair deficiency (dMMR), and tumor mutation burden (TMB). The results of the KEYNOTE-001 trial of pembrolizumab demonstrated that progression-free survival was shorter in *EGFR*-mutant patients compared to *EGFR* wild-type patients.[10] Similarly, the CheckMate 057 trial showed that *EGFR*-mutant patients were less likely to benefit from nivolumab.[5] This difference was also observed between *KRAS*-mutant and *KRAS* wild-type patients.[5] However, these findings were only observed in the PD-L1-negative subgroup, while those with high PD-L1 expression were predicted to have a higher response to pembrolizumab regardless of their mutation status.[9]

In recent years, researchers have observed that tumors generally contain large numbers of somatic mutations that induce the production of neoantigenes. The recognition of mutation-associated neoantigenes by tumor-infiltrating T cells is essential to achieve the effects of PD-1/PD-L1 inhibitors. High TMB has been shown to have a greater association with the benefits of PD-1/PD-L1 inhibitors compared to PD-L1 expression.[11] However, TMB reflects the mutational landscape requiring additional technical support, and the TMB scoring cutoffs remain disputable. dMMR results in the accumulation of somatic mutations and the appearance of multiple alleles at microsatellite loci, known as microsatellite instability (MSI). Previous studies have suggested that dMMR/MSI has a notable positive correlation with high TMB.[11] In 2017, pembrolizumab was approved for dMMR/MSI-high patients regardless of their

cancer type, indicating that dMMR/MSI-high is a universal genetic alteration in tumors. Nevertheless, in NSCLC, the frequency of dMMR/MSI-high is < 2%. Thus, studies have examined whether other genetic variants have the same role in diverse tumors and are related to the benefits of PD-1/PD-L1 checkpoint blockage immunotherapy. DNA polymerase ε (POLE) and δ (POLD1), and PMS2 were reported to be closely associated with a hypermutated phenotype and increased TMB.[11] Gong *et al.* reported that patients harboring a *POLE* mutation with microsatellite stable metastatic colorectal carcinoma largely benefited from pembrolizumab.[12] Moreover, deleterious mutations in *POLE*, *POLD1*, and *MSH2* were identified in three NSCLC responders to pembrolizumab with the highest mutation burden.[13] The involved genes (*MMR*, *POLE*, *POLD1*, *PMS2*, and *MSH2*) are all members of DNA damage response (DDR) pathways.

DNA damage response is a complex network of signaling pathways that repair DNA damage. These processes include recognition of DNA damage, transduction of damage signals, and execution of downstream DNA repair or cell death pathways. Sensor proteins such as poly (ADP-ribose) polymerase 1 (PARP1) and PARP2, effector kinases such as ataxia telangiectasia mutated (ATM) and ATM-related and Rad3-related (ATR), and downstream checkpoint proteins such as checkpoint kinases 1 (CHK1) and 2 (CHK2) are involved. DNA damage is mainly repaired by nucleotide excision repair, base excision repair, MMR, non-homologous DNA end joining, and homologous recombination (HR). It has been accepted that tumors harbor diverse DDR defects causing higher TMB and making them more dependent on the remaining pathways. dMMR/MSI has been approved as an effective biomarker for pembrolizumab treatment. We consider other high TMB-associated DDR genes (such as HR) or gene profiles are becoming an area of interest for exploring potential biomarkers. Additionally, patients with ERCC1- or PARP1-negative NSCLC appeared to be sensitive to platinum-based chemotherapy.[14] DDR alterations or HR deficiency were reported to be associated with improved clinical outcomes to platinum-based chemotherapy.[15,16] Therefore, DDR is also expected to be a promising therapeutic target for novel cancer treatments.[17,18]

However, many challenges remain in identifying predictive biomarkers and therapeutic targets suitable for Chinese patients. Among Chinese patients with NSCLC, activating *EGFR* mutations are much more common (approximately 50%),[19] indicating that the gene profiles in Chinese patients with NSCLC are obviously different from those in Western populations. Additionally, data from clinical trials of PD-1/PD-L1 inhibitors in Chinese patients with NSCLC are limited. Therefore, studies should be conducted to obtain information on these inhibitors. First, DDR profiles, particularly those of high TMB-associated variants, should be determined to identify the correlation with the efficacy of PD-1/PD-L1 inhibitors. Recently, Teo *et al.* reported that patients with DDR mutation-positive urothelial carcinoma were more likely to benefit from PD-1/PD-L1 inhibitors than patients with wild-type DDR, suggesting that DDR alterations are a potential predictive biomarker for PD-1/PD-L1 inhibitors.[20] Nevertheless, the predictive ability of DDR in NSCLC patients must be validated in prospective clinical trials. Second, it is necessary to develop effective agents targeting DDR alterations and explore rational strategies for DDR-targeted agents alone or combined with PD-1/PD-L1 inhibitors. Several inhibitors targeting DDR proteins, such as ATM, ATR, CHK1, and WEE1, have been developed as monotherapies or combination therapies in phase I/II clinical trials.[17] Moreover, nivolumab has been administered with the PARP inhibitor veliparib to treat metastatic or advanced NSCLC (http://clinicaltrials.gov identifier: NCT02944396). Therefore, we expect that combinations of PD-1/PD-L1 inhibitors and DDR-targeted agents might be applied to improve the outcomes of patients with advanced NSCLC. Third, when designing domestic clinical trials, researchers should emphasize the characteristics of Chinese populations rather than purely duplicate the design of international trials. High-quality and stratified randomized clinical trials are needed to identify potential biomarkers.

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