Editorial

Combination immuno-oncology therapy with pembrolizumab, an anti-PD-1 monoclonal antibody targeting immune evasion, and standard chemotherapy for patients with the squamous and non-squamous subtypes of non-small cell lung cancer

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Immuno-oncology drugs that inhibit immunosuppressive receptors (CTLA4, LAG3, PD-1, TIGIT and TIM3) or activate immunostimulatory receptors (4-1BB, GITR, ICOS and OX40) are emerging as promising therapeutics for cancer patients (1-3). PD-1 (CD279 or PDCD1), consisting of the extracellular N-terminal loop and immunoglobulin variable (IgV) domain, a single transmembrane domain and intracellular ITIM and ITSM motifs, is a representative target of immuno-oncology therapy (4-6). PD-L1 and PD-L2 ligands on tumor cells or tissue macrophages bind to the PD-1 receptor on T cells to induce the phosphorylation of ITIM (Y223) and ITSM (Y248) motifs of PD-1 and the subsequent repression of PI3K and PLCγ1 signaling cascades (*Figure 1*). Because ligand-dependent PD-1 signaling activation leads to immune evasion through the suppression of anti-tumor immunity in the tumor microenvironment, anti-PD-1 monoclonal antibodies (mAbs) [camrelizumab/SHR-1210 (7), cemiplimab/REGN2810 (8), MEDI0680/AMP-514 (9), nivolumab (10), pembrolizumab (11), sintilimab/IBI308 (12) and tislelizumab/BGB-A317 (13)] and anti-PD-L1 mAbs [atezolizumab (14), avelumab (15), BMS-936559 (16) and durvalumab (17)] have been developed as investigational drugs targeting immune evasion, also known as immune checkpoint blockers.

Among these anti-PD-1 mAbs, nivolumab and pembrolizumab have been approved by the US Food and Drug Administration (FDA) for the treatment of cancer patients: nivolumab for classical Hodgkin lymphoma, colorectal cancer, hepatocellular carcinoma, head and neck squamous cell carcinoma (HNSCC), melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma and urothelial carcinoma; whereas pembrolizumab for a relatively wider range of cancers, including cervical cancer, gastric cancer, HNSCC, Hodgkin lymphoma, melanoma, NSCLC, primary mediastinal large B-cell lymphoma, urothelial carcinoma and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers (https://www.cancer.gov/about-cancer/treatment/drugs). Nivolumab interacting with the N-terminal loop of PD-1 (6) failed to show benefits in a phase 3 clinical trial (CheckMate 026) for the treatment of stage IV NSCLC patients with PD-L1 tumor expression ≥1% (10). In contrast, pembrolizumab interacting with the PD-L1-binding IgV domain of PD-1 (5) successfully showed benefits in a phase 3 clinical trial (KEYNOTE-024) for the treatment of advanced NSCLC patients with PD-L1 tumor expression ≥50% (11). Although nivolumab and pembrolizumab exert anti-tumor effects through a common mechanism of the PD-1 signaling blockade, there are some functional divergences between nivolumab and pembrolizumab (*Figure 1*).

Lung cancers are classified into small cell lung cancer (SCLC), lung adenocarcinoma, lung squamous cell carcinoma (SCC) and other subtypes. Lung cancers other than SCLC have been traditionally categorized as NSCLC because of their relative unresponsiveness to combination chemotherapy; however, recent progress in genomic sequencing technology revealed subtype-specific

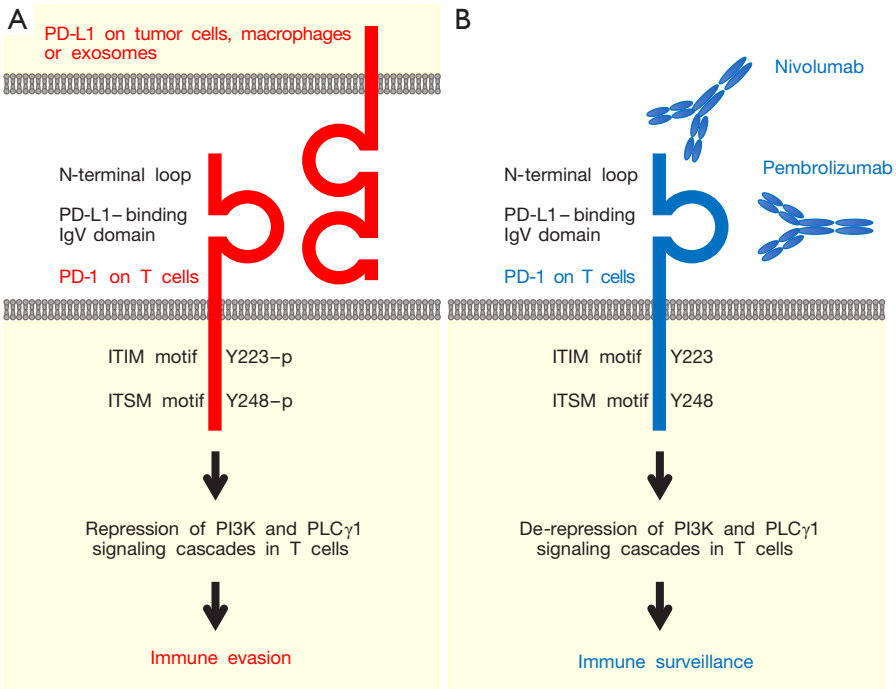

Figure 1 PD-1 signaling and functional divergences of anti-PD-1 monoclonal antibodies (mAbs). (A) In the presence of the PD-L1 ligand on tumor cells, macrophages or exosomes, the PD-1 receptor on T cells is activated to induce immune evasion through the repression of PI3K and PLCγ1 signaling cascades; (B) in the presence of antagonistic anti-PD-1 mAb, the PD-1 receptor is inactivated to restore anti-tumor immunity through de-repression of the PI3K and PLCγ1 signaling cascades in T cells. Pembrolizumab interacting with the ligand-binding IgV domain of PD-1 showed benefits as a first-line monotherapy for advanced non-small cell lung cancer (NSCLC) patients with PD-L1 tumor expression ≥50%, whereas nivolumab interacting with the N-terminal loop of PD-1 did not show benefits as a first-line monotherapy for stage IV NSCLC patients with PD-L1 tumor expression ≥1%. Pembrolizumab is approved for the treatment of a relatively wider range of cancer patients, including NSCLC, cervical cancer, gastric cancer, head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma, melanoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers.

genetic alterations in lung cancers. Gene amplification of the *FGFR1* gene preferentially occurs in lung SCC and SCLC, whereas driver mutations in the *ALK*, *EGFR*, *HER2*, *NTRK1*, *RET* and *ROS1* genes preferentially occur in lung adenocarcinoma (18-20). The standard therapy for patients with advanced lung SCC is platinum-based combination chemotherapy because FGFR inhibitors are not yet approved for the treatment of cancer patients, whereas initial therapy for advanced lung adenocarcinoma patients with the driver mutations mentioned above are receptor tyrosine kinase (RTK)-targeted therapies (20-22). Due to the distinct genomic landscapes of and therapeutic options for lung SCC and lung adenocarcinoma, NSCLC are further divided into squamous NSCLC and non-squamous NSCLC.

Pembrolizumab is a representative immuno-oncology drug for NSCLC patients (23-26). The phase 3 clinical trial KEYNOTE-024 demonstrated the superiority of pembrolizumab monotherapy over platinum-based standard chemotherapy as the first-line treatment for PD-L1-positive NSCLC patients without *EGFR* or *ALK* driver mutations (11). Both the pembrolizumab monotherapy group and platinum-based chemotherapy group included approximately 20% squamous NSCLC and 80% non-squamous NSCLC patients and showed almost similar safety profiles. The median progression-free survival (PFS) of the pembrolizumab monotherapy group and chemotherapy group was 10.3 and 6.0 months, respectively (hazard ratio, 0.50; 95% confidence interval, 0.37–0.68; P<0.001). In addition, the overall response rate (ORR) of

the pembrolizumab monotherapy group and chemotherapy group was 44.8% and 27.8%, respectively. Pembrolizumab established its role as the first-line therapy for NSCLC patients based on the results of the KEYNOTE-024 clinical trial (11). However because the benefits of pembrolizumab monotherapy are limited to approximately 15% of NSCLC patients irrespective of the PD-L1 status, it was conceived that a combination strategy using pembrolizumab and platinum-based standard chemotherapy might enhance the benefits of pembrolizumab treatment for NSCLC patients.

Recently, Dr. Paz-Ares and colleagues reported the promising results of a phase 3 clinical trial of combination immune-oncology therapy with pembrolizumab and standard chemotherapy for the first-line treatment of patients with metastatic squamous NSCLC (KEYNOTE-407, NCT02775435) (27). The incidence of grade ≥3 adverse events for the chemotherapy (carboplatin and paclitaxel/nab-paclitaxel) plus pembrolizumab group and chemotherapy alone group was 69.8% and 68.2%, respectively, whereas the ORR of chemotherapy plus pembrolizumab group and chemotherapy alone group were 58.4% and 35.0%, respectively (P=0.0004), and the median PFS of the chemotherapy plus pembrolizumab group and chemotherapy alone group was 6.4 months and 4.8 months, respectively (hazard ratio, 0.56; 95% confidence interval, 0.45–0.70; P<0.0001). In contrast, Dr. Gandhi and colleagues reported the promising results of a phase 3 clinical trial of combination immune-oncology therapy with pembrolizumab and standard chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC without *EGFR* or *ALK* driver mutations (KEYNOTE-189, NCT02578680) (28). The incidence of grade ≥3 adverse events for the chemotherapy (pemetrexed and a platinum-based drug) plus pembrolizumab group and chemotherapy alone group was 67.2% and 65.8%, respectively, whereas the median PFS of the chemotherapy plus pembrolizumab group and chemotherapy alone group was 8.8 and 4.9 months, respectively (hazard ratio, 0.52; 95% confidence interval, 0.43–0.64; P<0.001). Together, these facts clearly indicate that combination with standard chemotherapy significantly enhances the benefits of pembrolizumab for squamous as well as non-squamous NSCLC patients. Synergy between pembrolizumab and chemotherapy is a hot issue in the field of clinical oncology (29).

Combination with therapeutics targeting the tumor microenvironment is another strategy to enhance the benefits of immune checkpoint blockers for cancer patients (*Figure 2*). Aberrant VEGF signaling in the tumor microenvironment leads to a leaky and hypoxic condition that promotes the survival of cancer stem cells, the epithelial-to-mesenchymal transition of tumor cells, and immune evasion through the recruitment of myeloid-derived suppressor cells (MDSCs) and regulatory T (T_{reg}) cells and the functional suppression of $CD8^+$ T cells and natural killer (NK) cells (30-33). Anti-VEGF mAb (bevacizumab), anti-VEGFR2 mAb (ramucirumab) and VEGFR inhibitors (axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib and sunitinib) are VEGF signaling targeted therapeutics (34-37) that are approved by the US FDA for the treatment of cancer patients, whereas apatinib (38) is a small-molecule VEGFR2 inhibitor that is approved by the Chinese FDA for the treatment of gastric cancer patients. Synergistic effects of immune checkpoint blockers and VEGF signaling blockers (*Figure 2*) have been investigated in the following clinical trials for the treatment of cancer patients: pembrolizumab plus apatinib (NCT03407976); pembrolizumab plus axitinib (NCT02853331); pembrolizumab plus bevacizumab (NCT02681549); pembrolizumab plus cabozantinib (NCT03149822); pembrolizumab plus lenvatinib (NCT02501096); pembrolizumab plus pazopanib (NCT02014636); pembrolizumab plus ramucirumab (NCT02443324); pembrolizumab plus regorafenib (NCT03347292); pembrolizumab plus sorafenib (NCT03211416) and pembrolizumab plus sunitinib (NCT03463460). Among these clinical trials, pembrolizumab-based combination therapies with bevacizumab or lenvatinib are in progress for the treatment of NSCLC patients.

The exploration and establishment of predictive biomarkers for patient selection are also necessary to enhance the benefits of immuno-oncology therapies. The immunohistochemistry-based detection of PD-L1 protein upregulation on tumor cells or tumor-associated macrophages (11) (Reck *et al*., 2016), reverse phase protein array (RPPA)-based detection of exosomal PD-L1 protein upregulation after immuno-oncology therapy (39), $CD14^+CD16^-HLA\text{-}DR^{high}$ monocytes in peripheral blood mononuclear cells (40), mismatch-repair deficiency (41) and higher tumor mutational burden (42) are biomarkers to predict responders to PD-1 signaling blockade therapy. In contrast, loss-of-function alterations in the *JAK1/2* and *beta-2-microglobulin (B2M)* genes (43) and loss of neoantigens (44) are detected in cases with resistance to the immune checkpoint blockers. Among these predictive biomarkers to stratify or monitor cancer patients, liquid biopsy tests

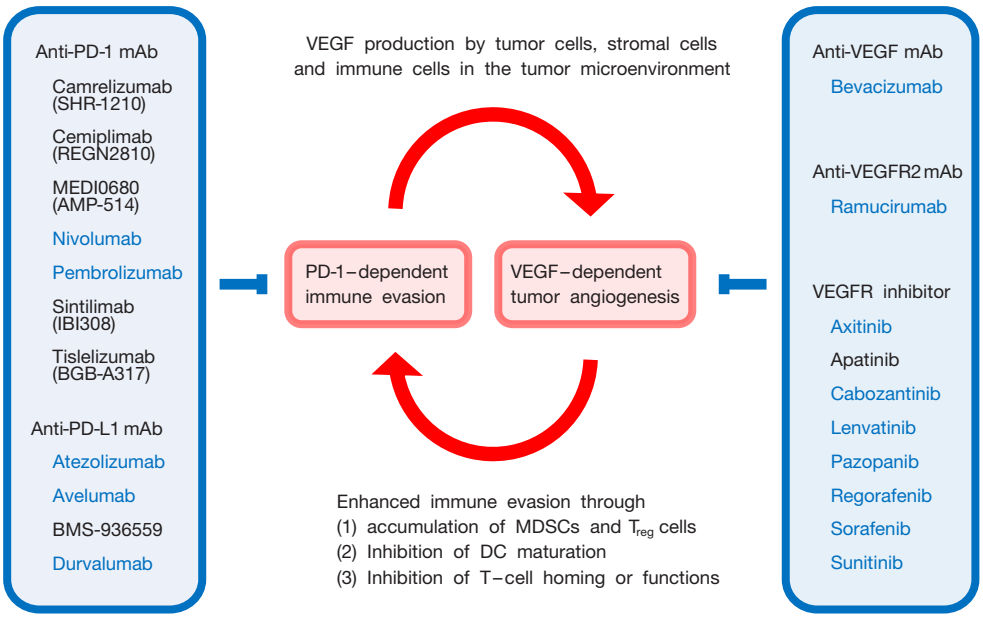

Figure 2 Synergistic anti-tumor effects of PD-1 signaling blockade therapy and VEGF signaling blockade therapy. VEGF is produced by tumor cells, stromal cells and immune cells in the tumor microenvironment with PD-1-dependent immune evasion. VEGF signaling activation induces tumor angiogenesis, and promotes immune evasion through the accumulation of myeloid-derived suppressor cells (MDSCs) and regulatory T (T_{reg}) cells in the tumor microenvironment, the inhibition of dendritic cell (DC) maturation, and the inhibition of T-cell homing or functions. Among anti-PD1 mAbs (camrelizumab, cemiplimab, MEDI0680, nivolumab, pembrolizumab, sintilimab and tislelizumab) and anti-PD-L1 mAbs (atezolizumab, avelumab, BMS-936559 and durvalumab) that have been developed as investigational immuno-oncology drugs, atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab, shown in blue, are approved by the US Food and Drug Administration (FDA) for the treatment of cancer patients. Anti-VEGF mAb (bevacizumab), anti-VEGFR2 mAb (ramucirumab) and small-molecule VEGFR inhibitors (axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib and sunitinib), shown in blue, are approved by the US FDA for the treatment of cancer patients, and another VEGFR inhibitor (apatinib) was approved by the Chinese FDA for the treatment of gastric cancer patients. The synergistic effects of immune checkpoint blockers and VEGF signaling blockers have been investigated in clinical trials for the treatment of cancer patients, such as NCT02014636, NCT02443324, NCT02501096, NCT02681549, NCT02853331, NCT03149822, NCT03211416, NCT03347292, NCT03407976 and NCT03463460.

detecting exosomal PD-L1 protein and $CD14^{+}CD16^{-}HLA\text{-}DR^{high}$ monocytes are both promising technologies that might drastically improve the benefit-cost ratio of PD-1 blockade therapy.

In conclusion, the combinatorial optimization of immune checkpoint blockers, VEGF signaling blockers and cytotoxic chemotherapies as well as the development of biomarkers for the positive and negative selection of patients are necessary for the beneficial maximization of immuno-oncology drugs for the treatment of NSCLC patients and other types of cancer patients.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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