

Programmed death ligand-1 inhibitors potentially carry a lower risk of pneumonitis compared with programmed death-1 inhibitors in patients with non-small cell lung cancer

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Cancer cells are attacked by innate and acquired immune mechanisms; however, they can escape from immune surveillance via various mechanisms. Immunotherapies involving monoclonal antibodies against programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1); i.e., checkpoint inhibitors, have been developed to inhibit the PD-1 pathway and cause T-cells to attack cancer cells. These treatments are used against various malignancies, including advanced non-small cell lung cancer (NSCLC) (1-4). The PD-1 inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitor atezolizumab have been demonstrated to be superior to docetaxel; i.e., they resulted in improved survival and lower toxicity, as a salvage treatment for advanced NSCLC (1,2,4,5). The PD-L1 inhibitor durvalumab has been reported to be effective against stage III NSCLC when used after chemoradiotherapy (6). As these drugs are associated with serious and potentially fatal immune-related adverse events (irAE) (7-9), patients treated with immune checkpoint inhibitors must be monitored carefully. The recent development of checkpoint inhibitors has increased the number of treatment options for various types of cancer, and clinicians can have difficulty choosing the optimal agent.

Pillai *et al.* conducted a meta-analysis comparing the toxicities of the PD-1 and PD-L1 inhibitors used to treat advanced NSCLC (10). The analysis included 23 studies, 3,284 patients that were treated with PD-1 inhibitors

(nivolumab or pembrolizumab), and 2,460 patients that were treated with PD-L1 inhibitors (atezolizumab, durvalumab, or avelumab). There was no significant difference in the overall incidence of adverse events or the response rate between the groups. However, PD-L1 inhibitor treatment resulted in a significantly lower incidence of pneumonitis (2%) compared with PD-1 inhibitor treatment (4%) (P=0.01). The frequencies of irAE and hypothyroidism tended to decrease under PD-L1 inhibitor treatment (P=0.07). Although some of the trials of PD-L1 inhibitor treatment were carried out during an earlier phase, the abovementioned findings should help to guide future general practice and clinical trials to a certain extent.

The PD-1 pathway mainly contains two ligands, PD-L1 and PD-L2. PD-L1 is constitutively present on both hematopoietic and non-hematopoietic cells and is regulated by external stimuli. In cancer cells, the PD-1/PD-L1 system inhibits the proliferation of T lymphocytes, cytokine release, and cytotoxicity, which leads to the exhaustion and apoptosis of tumor-specific T cells and provides cancer cells with the opportunity to avoid immune responses (11). PD-L2 is a second PD-1 ligand. It is inducibly expressed on the surfaces of macrophages, dendritic cells, mast cells, and certain B cell populations (12,13). PD-L2 is suggested to regulate asthmatic responses through an interferon-gamma-

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dependent, but PD-1-independent, mechanism (14), and a lack of PD-L2 induces significant increases in transforming growth factor- β and interleukin-1 α levels in the lungs, which can result in chronic airway hyperreactivity (15). PD-1 inhibitors can inhibit PD-L2-mediated immune reactions, whereas PD-L1 inhibitors do not. It is speculated that monoclonal antibodies against PD-L1 still allow PD-1 to interact with PD-L2, which results in lower rates of pneumonitis being observed during PD-L1 inhibitor treatment than during PD-1 inhibitor treatment.

Recently, the PD-L1 inhibitor durvalumab was introduced as a post-chemoradiotherapy treatment for stage III NSCLC (6), and further PD-1 inhibitors are also in development (16,17). If PD-L1 inhibitors carry a lower risk of pneumonitis, they could become more important for combination with radiotherapy as a treatment for stage III NSCLC. In a study about the PD-L1 inhibitor durvalumab, the cases of 475 patients were evaluated, and 16 patients (3.4%) experienced grade 3/4 pneumonitis or radiation pneumonitis (6). In another study, the PD-1 inhibitor pembrolizumab was evaluated in 93 patients, and 5 patients (5.4%) experienced grade 3/4 pneumonitis (17). Thus, it seems that the PD-L1 inhibitor carried a slightly lower risk of pneumonitis; however, the latter study was not a full publication, and there is little data available about this issue.

PD-L1 inhibitors potentially carry a lower risk of pneumonitis and have advantage for clinical use compared with PD-1 inhibitors in various situation.

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Footnote

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