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BITS AND BYTES

Pembrolizumab as the first-line monotherapy for non-small-cell lung cancer with a low programmed death ligand 1 threshold

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Abstract

Pembrolizumab monotherapy has been demonstrated as a first-line therapy for non-small-cell lung cancer (NSCLC) patients with a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) of ≥50%; however, the clinical efficacy is limited by the unreasonable threshold of the TPS. A recent study published by Mok et al. (Lancet 393:1819–1830, 2019) showed that pembrolizumab monotherapy could also be extended as an effective first-line therapeutic strategy for NSCLC patients with low TPS. However, this needs to be further evaluated in detail after considering the following issues. In Mok's report, the survival curves were much lower in a pembrolizumab-treated group in the first 6 months of treatment compared with a chemotherapy group. These contradictory findings might have been due to anecdotal occurrences of rapid progression, especially hyperprogressive disease.

Keywords Pembrolizumab · NSCLC · PD-L1 · TPS · Hyperprogressive disease

Patients with non-small-cell lung cancer (NSCLC) have unique tumor molecular profiles and very poor survival outcomes. Thus, understanding the most relevant molecular mechanisms for NSCLC pathology could promote the discovery of potential drug targets and more effective therapeutic strategies (Herbst et al. 2018). To date, the clinical treatment for NSCLC patients has become increasingly personalized, driven by targeted therapy based on defined biomarkers, especially treatments targeting programmed death 1 (PD-1) or its ligand PD-L1 (Antonia et al. 2019). It was widely accepted that the PD-1/PD-L1 signaling pathway plays important inhibitory roles in adoptive immunity, impairing the anti-tumor immune responses of lung cancers, especially NSCLC populations (Kordbacheh et al. 2018). Thus, drugs that block PD-1/PD-L1 signaling would offer a promising novel approach in NSCLC.

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At present, antibodies that target PD-1 or PD-L1 have been identified as a mainstay of first-line treatment for patients with newly diagnosed and metastatic NSCLC (Zuazo et al. 2017). Previously, as the therapeutic molecular target for NSCLC patients, PD-L1 expression was selected with a tumor proportion score (TPS) cut-off of ≥50% (Arbour and Riely 2019). However, Mok et al. (2019) recently identified the PD-L1 antibody, pembrolizumab, as a first-line monotherapy for locally advanced and metastatic NSCLC patients with a PD-L1 TPS ≥ 1%. Compared with the chemotherapy group, the overall survival in the pembrolizumab group was significantly longer in these low TPS populations. These findings can generally affect the clinical practice of NSCLC management.

However, some key issues should be addressed. Inconsistent with the conclusion from Mok et al. (2019), Peters et al. (2019) reported that NSCLC patients with a PD-L1 TPS < 50% could achieve the best overall outcomes from a combination of chemotherapy and pembrolizumab. Thus, to establish who should receive pembrolizumab monotherapy or chemotherapy plus pembrolizumab should be a routine clinical question of interest. More importantly, no satisfactory explanation for crossed survival curves was proposed by the authors. In the first 6 months of treatment, the survival curves were much lower in the pembrolizumab-treated group than in the chemotherapy group. This might have been due to hyperprogressive disease (Ferrara et al. 2018), a paradoxical

condition accelerating tumor growth following PD-L1 blockade. A better understanding of the molecular mechanisms underlying hyperprogressive disease is very important for designing pembrolizumab monotherapy that would be more suitable for individualized NSCLC patients. Of note, the risk of hyperprogression should be fully considered in drug response assessment involving immunotherapies targeting PD-L1 for lung cancers. Some novel tumor response assessment methods, such as ctDNA liquid biopsies (Champiat et al. 2018), appear to be appropriate for the detection of patients with hyperprogressive disease.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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