

PD-1 targeted Immunotherapy as first-line therapy for advanced non-small-cell lung cancer patients

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The better understanding of interactions between tumor and immune system (e.g., tumor-associated upregulation of PD-L1 to induce checkpoint for cytotoxic lymphocytes; *Figure 1A*) gave rise to the development of immune modulating therapies. To overcome T-cell tolerance and to boost cellular immune response, the application of monoclonal antibodies targeting CTLA-4 (4) or the PD-1/PD-L1 axis enlarged our therapeutic options for advanced cancer patients. With regard to this type of immunotherapy, non-small cell lung cancer (NSCLC) proved to be a suitable entity. The approval of immune checkpoint inhibitors [i.e., Nivolumab (5,6), Pembrolizumab (7-9) and Atezolizumab (10)] enriched our therapeutic armamentarium for advanced NSCLC patients (11).

Basically, there are two molecular pathways with impact on tumor cell survival. On the one hand, concomitant engagement of both the T-cell receptor (TCR) and the PD-1 receptor regulate T cellular differentiation (*Figure 1B*) (3). On the other hand the binding of PD-1 to PD-L1 impairs i.a. Fas-mediated apoptotic mechanisms (*Figure 1C*) (2). However, PD-L1 activity is not stable. Besides tumor heterogeneity it depends on other factors such as EGFR-mutational status (12), JAK2 gene amplification (13) or following tyrosine kinase inhibitor (TKI) therapies (14).

At present, there are two PD-1 inhibiting antibodies approved for NSCLC therapy: Nivolumab and Pembrolizumab. The design of the underlying studies pivotal for approval differs in terms of methodology.

Whereas Nivolumab was tested as a 2nd line treatment in squamous (5) and non-squamous (6) NSCLC patients (against prior standard of care: docetaxel chemotherapy), the KEYNOTE-001 trial focused on the response rates of Pembrolizumab in correlation with PD-L1 expression in NSCLC tumor tissues (7). Similar to the pivotal studies for Nivolumab, Pembrolizumab was compared to docetaxel chemotherapy as second line treatment in a phase II/III-study (8). Only patients with a PD-L1 expression level of at least 50% in the investigated tumor cells were included in this study (8).

Against the background of the reported favorable therapeutic results (8), Reck *et al.* investigated Pembrolizumab as 1st line treatment for untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells. With focus on progression-free survival (as primary end point), overall survival, response rate, and safety (as secondary end points), Pembrolizumab (tested in n=154 patients with a PD-L1 expression) was compared to standard chemotherapy (n=151 patients) (9).

In the comparative analysis, Pembrolizumab was associated with increased progression free survival (PFS) [hazard ratio (HR) for disease progression or death =0.50; P<0.001], overall survival (OS) (HR for death =0.6; P=0.005) and improved response rates (44.8% *vs.* 27.8%). Moreover, less adverse events were observed for the Pembrolizumab treatment. With regard to the immune-mediated specific side effects, hypothyroidism (9.1%), hyperthyroidism

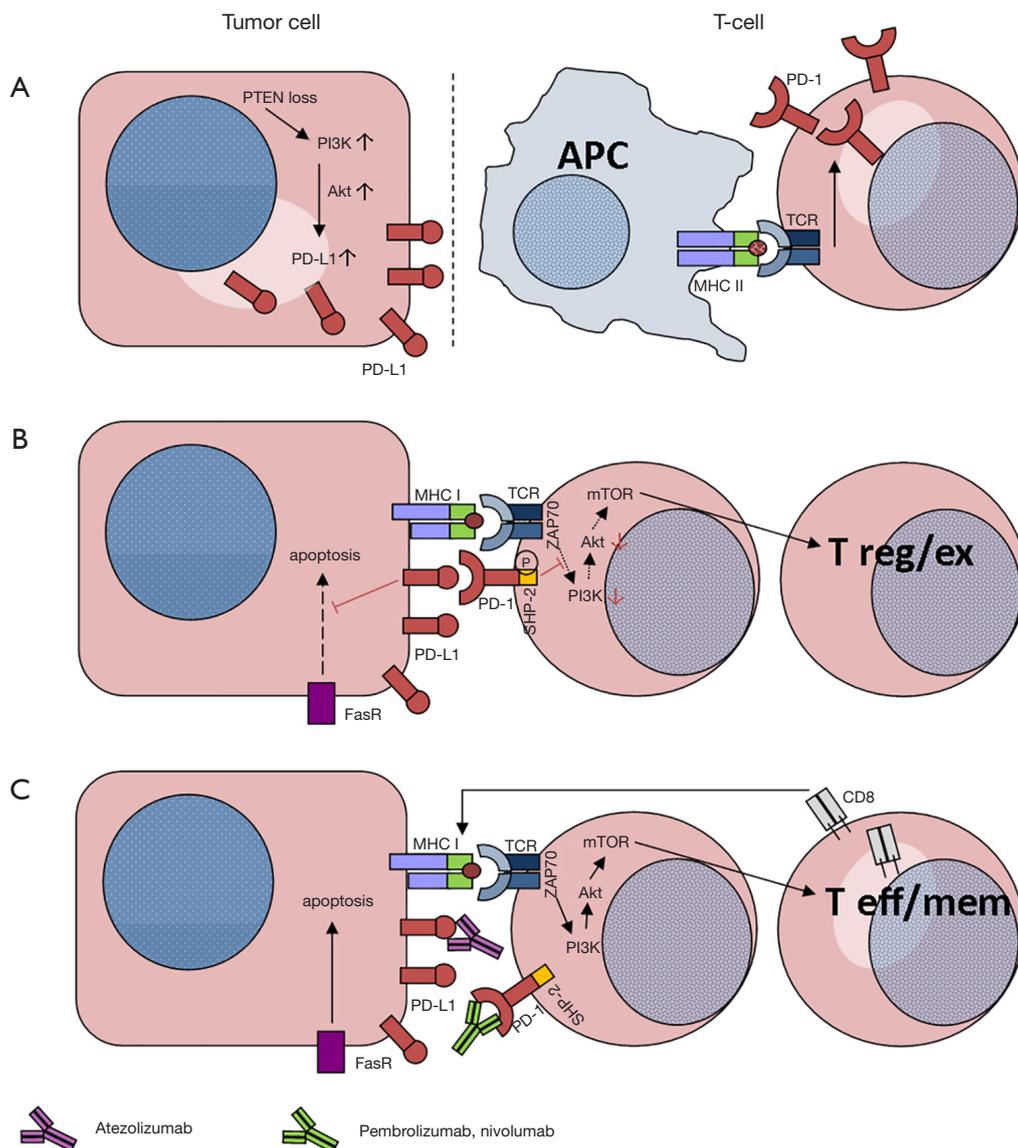


Figure 1 PD-1:PD-L1 mechanisms between T-cells and tumor cells. (A) Loss of phosphatase and tensin homolog (PTEN) in tumor cells induces the Phosphoinositol-3-kinase (PI3K)—Akt pathway with consecutive overexpression of PD-L1 (1); (B) once PD-L1 binds to PD-1, the resulting inhibition influences tumor surveillance such as Fas-mediated apoptosis (2). By co-activation of PD-1 concomitant to TCR in T-cells, the phosphorylation of the SHP-2 domain results in a down-regulation of the PI3K-Akt pathway. This step alters the mTOR complex, which regulates T cellular differentiation (3); (C) upon immune checkpoint inhibition, either with PD-L1-mAb (Atezolizumab) or PD-1-mAbs (Pembrolizumab and Nivolumab), T-cell differentiation is switched to CD8+ T effector (T *eff*) or T memory (T *mem*) cells, inducing apoptosis by completing the major histocompatibility complex (MHC) of the tumor cells (3).

(7.8%) and pneumonitis (5.8%) were observed in the Pembrolizumab cohort. Other side effects, e.g., nausea, vomiting, fatigue, and constipation were seen more often following platinum based doublet chemotherapies (9).

Due to the confirmed favorable benefit-to-risk profile

of PD-1 inhibition, this therapeutic option now becomes relevance for 1st line NSCLC treatment. With regard to future therapeutic implications, the combined application of immunotherapy and chemotherapy have already been investigated in two phase I/II-trials (15,16). Whether there

are beneficial effects for both neoadjuvant and adjuvant immune checkpoint inhibition, requires further investigation.

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Footnote

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

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