The landmark paper published in 1996 experimentally demonstrated for the first time the idea that one of the immune system checkpoints, Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), could be targeted with a monoclonal antibody to enhance anti-tumor immunity, which eventually led to treatment of cancer in mouse model (1). This was a discovery that granted the authors the 2018 Nobel prize in Medicine. Fifteen years after the publication of the paper, the first monoclonal antibody targeting human CTLA-4 (ipilimumab), was approved to treat melanoma (2). Other immune checkpoints were subsequently studied as potential therapeutic targets, including programmed death receptor ligand 1 (PD-L1) (3). Figure 1 depicts the various cell receptors position and their effect on T-Cells. Various trials demonstrated the effectiveness of inhibitors of programmed death receptor 1 (PD-1) and its ligand (PD-L1) as treatment options for squamous and non-squamous non-small cell lung cancer (NSCLC) (4-14). A complete list of immune checkpoint inhibitors either FDA approved or still under clinical trials are shown in Table 1. Not all PD-1/L1 inhibitors have the same efficacy in first line therapy for NSCLC, even after combination with chemotherapy. We believe that the reason of the different clinical performance among these agents is related to study design.

In a recent multicenter randomized double-blinded Phase 3 clinical trial, Paz-Ares et al. (15) reported on 559 patients with untreated metastatic, squamous NSCLC who receive either pembrolizumab (PD-1 inhibitor) plus chemotherapy (N=278) or chemotherapy plus placebo (N=281). A significantly better overall survival and progression-free survival were seen in the pembrolizumab-chemotherapy group compared to the chemotherapy-placebo group, with a HR for death of 0.64 (95% CI, 0.49 to 0.85; P<0.001) and HR for disease progression of disease or death of 0.56 (95% CI, 0.45 to 0.7; P<0.001). The difference in median overall survival and progression free survival between the two arms was 4.6 and 1.6 months respectively, both in favor of pembrolizumab. The benefit was observed in all PD-L1 proportion score subgroups in the progression-free survival and in all subgroups of the overall survival, with the exception of PD-L1 ≥50% that was associated with a trend toward better survival in pembrolizumab group but did not reach statistical significance (HR 0.64, 95% CI, 0.37 to 1.10). Other randomized clinical trials (RCTs) (6,11,14) have investigated the association between PD-L1 tumor proportion score and treatment activity. Immunotherapy combination improved outcomes compared to placebo combination regardless of the PD-L1 expression score (6,11,14,15). The role of this biomarker is still not completely defined in many studies (6,11,14,15) but recently Paz-Ares and colleagues reported a relationship between higher PD-L1 expression and longer progression-free survival (11). Among our unpublished ongoing meta-analysis on NSCLC, we found HR for progression free survival of 0.63 (95% CI, 0.47 to 0.84) among those with PD-L1 expression of 50% or more favoring pembrolizumab monotherapy over chemotherapy but no difference among those less than 50%.
Table 1 List of immune checkpoint inhibitors either FDA approved or still under clinical trials

<table>
<thead>
<tr>
<th>Target</th>
<th>Name</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Yes</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Atezolizumab</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>No. Phase III trials ongoing</td>
</tr>
<tr>
<td>CTLA</td>
<td>Ipilimumab</td>
<td>No. Phase III trials ongoing</td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td>No. Phase III trials ongoing</td>
</tr>
</tbody>
</table>

Another point that warrants discussion is the number of adverse events that occurred during the study period. Adverse events of grade 3 or higher that occurred more frequently in the chemotherapy-pembrolizumab group than in the chemotherapy-placebo group included pneumonitis, reported in the literature as an uncommon but potentially life-threatening complication. Therefore, a recent meta-analysis has investigated the occurrence of pneumonitis as an adverse event in PD-1 and PD-L1 inhibitors. The study reported a higher incidence of pneumonitis with the use of PD-1 inhibitors compared with PD-L1 inhibitors. However, high grade pneumonitis occurrence was statistically insignificant upon comparing immunotherapy to chemotherapy (16).

Finally, a cost-effective analysis should be considered when approaching new treatments. A literature review of the recently published papers analyzing this issue (17-25) did not provide uniform results. The minimum and maximal incremental cost-effectiveness ratio (ICER) were $36,493 and $194,372 respectively per quality-adjusted life-years (QALY) (19,20). Some authors found a cost-effectiveness in all PD-L1 tumor proportion scores (23-25), other only in some subgroups (17,21,22), and others only minimal or no cost-effectiveness (18-20). No definitive conclusion can therefore be drawn, until further analyses are performed.

Paz-Ares and colleagues (15) should be congratulated for their trial which is one of the largest series analyzing pembrolizumab as a treatment option for NSCLC. Other PD1/PD-L1 inhibitors have been investigated, like nivolumab (4,7,10,13) and atezolizumab (9,12), but couldn’t reach a significant survival benefit, as monotherapy or in combination with chemotherapy, for NSCLC as with pembrolizumab.
Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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2. FDA Approves YERVOYTM (ipilimumab) for the Treatment of Patients with Newly Diagnosed or Previously-Treated Unresectable or Metastatic Melanoma, the Deadliest Form of Skin Cancer. (accessed January 8, 2020). Available online: https://news.bms.com/press-release/rd-news/fda-approves-yervoy-ipilimumab-treatment-patients-newly-diagnosed-or-previousl