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Comparison of Toxicity Profile of PD-1 versus PD-L1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Analysis of Literature

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Abstract

Background—Monoclonal antibodies against Programmed Death 1 (PD-1) and Programmed Death Ligand 1 (PD-L1) are effective therapies in NSCLC. We performed a systematic review investigating differences in the toxicities of PD-1 and PD-L1 inhibitors.

Methods—An electronic literature search was performed of public databases (MEDLINE, EMBASE) and conference proceedings for trials utilizing PD-1 inhibitors (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab, durvalumab, avelumab) in NSCLC patients. A formal systematic analysis was conducted with Comprehensive Meta-Analysis software (Version 2.2). Clinical and demographic characteristics, response, and toxicity data were compared between both groups.

Results—Twenty-three studies reported between 2013 and 2016 were eligible for analysis. The total number of patients evaluated for toxicities were 3,284 patients in the PD-1 group and 2,460 patients in the PD-L1 group. The baseline patient characteristics of the two groups were similar, although there was a trend towards increased squamous histology in the PD-L1 group (32% versus

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Formal analysis: M. Behera
Investigation: R. Pillai, M. Behera, S. Ramalingam
Resources: M. Behera
Data curation: R. Pillai, M. Behera
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Writing – review and editing: T. Owonikoko, A. Kamphorst, S. Pakkala, C. Belani, F. Khuri, R. Ahmed, S. Ramalingam
Visualization: R. Pillai
Supervision: S. Ramalingam
Project administration: R. Pillai, M. Behera, S. Ramalingam
Funding acquisition: S. Ramalingam
There was no difference in response rate between PD-1 (19%) and PD-L1 (18.6%) inhibitors, $p=0.6$. The incidence of overall adverse events (AEs) was comparable between PD-1 and PD-L1 inhibitors (64% (CI 63-66%) versus 66% (CI 65-69%), $p=0.8$). Fatigue is the most frequently reported AE with both classes. Patients treated with PD-1 inhibitors have a slightly increased rate of immune related AEs (IRAEs) (16% (CI 14-17%) versus 11% (CI 10-13%), $p=0.07$) and pneumonitis (4% (CI 3-5) versus 2% (CI 1-3), $p=0.01$) compared to patients who received PD-1 inhibitors.

**Conclusions**—In this systematic review involving 5,744 patients, the toxicity and efficacy profiles of PD-1 and PD-L1 inhibitors in NSCLC patients are similar.

**Keywords**

Immune checkpoint inhibitors; NSCLC; adverse events; immune related adverse events

**Introduction**

Immune checkpoint inhibition is an effective treatment strategy in multiple tumor types, including non-small cell lung cancer (NSCLC). The immune checkpoint Programmed Death 1 (PD-1) receptor is expressed on activated T cells and binds to its ligands PD-L1 and PD-L2 to limit T cell activation and prevent autoimmunity in peripheral tissues. Activation of the PD-1 pathway induces T cell exhaustion, which is necessary to prevent continued immune activation following successful removal of cells carrying the antigen of interest. Several tumors overexpress PD-L1 and evade detection by T cells, which leads to immune tolerance of the tumor. Overexpression of PD-L1 is also associated with more aggressive phenotypes and poor outcomes in NSCLC.

Monoclonal antibodies against PD-1 and PD-L1 have emerged as effective therapies in patients with advanced NSCLC. These agents have been shown to be tolerated well and exert anti-cancer effects even in patients who have failed multiple prior lines of therapy. The PD-1 inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitor atezolizumab are superior to docetaxel in the salvage setting with improved survival outcomes and toxicity. More recently, pembrolizumab was shown to be superior to platinum doublet chemotherapy in treatment naïve metastatic NSCLC patients with high tumoral PD-L1 expression, resulting in a major shift in treatment paradigm.

The immune checkpoint inhibitors have unique mechanism-based toxicities compared to cytotoxic chemotherapy. Inhibition of the PD-1 pathway can lead to autoimmune toxicities, some of which can be severe and even fatal reactions. Lung cancer patients are particularly more vulnerable for toxicities given the older age of the patient population and presence of co-morbid conditions. Of particular interest in NSCLC patients is the development of autoimmune pneumonitis, which led to a few treatment-related deaths in early phase studies of these agents. As clinicians have increasing number of checkpoint inhibitors to choose from in the treatment of advanced stage NSCLC patients, it will be important to understand potential differences in efficacy and toxicity profiles of these agents. There has been speculation that since monoclonal antibodies against PD-L1 still allow for the interaction of PD-1 with its other ligand PD-L2, this could lead to less blockade of the
negative inhibitory signal and result in reduced autoimmunity. Whether this can also have implications on the efficacy of the individual agents is not known. Given that it is highly unlikely for comparative clinical trials to be conducted to compare the check point inhibitors against one another, there is an urgent need to understand key differences in efficacy and toxicity between the various immune checkpoint inhibitors. In particular, comparison of PD-1 versus PD-L1 inhibitors is of immense clinical interest. Therefore, we conducted a systematic review of clinical trials to evaluate differences in toxicity profiles between PD-1 and PD-L1 inhibitors used as monotherapy in NSCLC.

Methods

Search Strategy

A comprehensive and methodical search of the literature of electronic databases (Medline, Embase, Cochrane) for studies published between 2000 and 2016 was conducted. Applicable terms, such as “PD-1, PD-L1 and NSCLC,” were used with the filters “clinical trial,” “humans,” and “all adult: 19+ years” for the MEDLINE searches. Relevant abstracts were manually searched and retrieved from the conference proceedings of annual meetings of the American Society of Clinical Oncology (ASCO) (2011-2016), the World Conference on Lung Cancer (2011-2016), and from the European Society of Medical Oncology (2011-2016).

Study Eligibility

All studies potentially meeting the eligibility criteria defined by the search strategy were independently reviewed by three of the authors (RP, MB and SSR), which was followed by a consensus meeting to determine the final list of eligible studies. All trials utilizing PD-1 inhibitors (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab, durvalumab, avelumab) as monotherapy in NSCLC patients were included in this analysis. Phase 1 trials, trials that enrolled less than 10 patients, and trials that utilized PD-1 or PD-L1 inhibitors in combination with chemotherapy, other immunotherapies, or radiation were excluded from the analysis. Studies that did not report toxicities were excluded from the analysis. For data that were both presented at a meeting and subsequently published in full form, only the data from the full publication was included. If data had been presented multiple times, then the data from the most current presentation was used, and the older data excluded. All prospective randomized, non-randomized, and single arm studies that met the inclusion criteria were included in the analysis. Retrospective studies were excluded from this analysis.

Data extraction and statistical analysis

The studies were reviewed for any available data. Standard data extraction templates were used to collect any analyzable data that were reported. The extracted data included demographics, treatment, and clinical outcomes including: overall response rate (ORR), progression free survival (PFS), overall survival (OS), and toxicities. Not all of the trials reported all outcome measures. Toxicities were extracted as the primary outcome for this analysis.
The outcome data extracted for each arm were analyzed using fixed-effect model which controls for time invariant variables and reported as weighted measures. Each study in the fixed effect analysis is weighted based on its sample size. Toxicities were extracted and reported as overall adverse events, Grade 3-5 adverse events, most common adverse events and immune related adverse events (IRAEs). IRAEs were defined as toxicities mediated by an autoimmune mechanism, defined by the authors to include pneumonitis, colitis, thyroid disorders, and inflammatory conditions reported in any organ system, such as hepatitis or nephritis. All analyses were performed using Comprehensive Meta-Analysis software (CMA Version 2.2) and SPSS statistical package (version 22.0, IBM Corp.). The comparisons between the two arms PD-1 and PD-L1 inhibitors were conducted based on weighted estimates. Two-tailed T-test with a significance level of 0.05 was used for all comparisons. Heterogeneity among studies was assessed used the $I^2$ test, which provides the percentage of variation across studies that is due to the heterogeneity. The overall AE rate was reported as pooled proportions of the percentage of patients treated with each drug that experienced AEs; there was no test of significance between the drugs.

**Results**

A total of 549 studies were retrieved and reviewed from the searches, out of which twenty-three studies met our inclusion criteria. Of these, twelve trials utilized PD-1 inhibitors and eleven trials utilized PD-L1 inhibitors. The study selection scheme is shown in Figure 1. The trials with PD-1 inhibitors and PD-L1 inhibitors that met criteria studies included in the analysis are outlined in Table 1.

A total of 5,744 patients were evaluated for toxicity, including 3,284 patients treated with PD-1 and 2,460 treated with PD-L1 inhibitors. The patient characteristics are described in Table 2. The median age of the PD-1 inhibitor treated population was 64 years and that of the PD-L1 inhibitor was 64.5 years (p=0.5). The PD-1 inhibitor treated population had a slightly higher proportion of males compared to PD-L1 (59% vs. 56%, p=0.4). The two cohorts had a similar proportion of patients with smoking history (83%, p=0.5). Although the two cohorts were comparable in baseline characteristics, trials utilizing PD-L1 enrolled a higher proportion of patients with squamous histology compared to the PD-1 trials (32% vs. 25%, p=0.6).

The objective response rate in the PD-1 inhibitor treated population (n= 3,284) was identical to the PD-L1 inhibitor group (n=2,460) (19% vs. 18.6%, p=0.17; Table 3). The progression free survival and overall survival data were only reported in few studies and were not sufficient to make a comparable analysis.

**Toxicities**

The overall incidence of adverse events were found to be similar between the PD-L1 and PD-1 inhibitor treated cohorts (Table 3), with patients treated with PD-1 inhibitors experiencing a comparable incidence of adverse events compared to PD-L1 inhibitors (64% in PD-1 (CI 63-66%) vs. 66% (65-69%) in PD-L1, p= 0.8). Grade 3-5 toxicities were observed in 13% (CI 12-14%) in the PD-1 cohort vs. 21% (CI 19-23%) in PD-L1 cohort (p= 0.15). Fatigue was the most common toxicity in both cohorts of patients (19% in PD-1 (CI
17-20%) vs. 21% (CI 19-23%) in PD-L1 cohorts, p=0.4). The overall immune related adverse events (IRAEs) had a trend towards higher incidence with PD-1 inhibitors compared to the PD-L1 (16% (CI 14-17%) vs. 11% (CI 10-13%); p=0.07; Table 3), although the rate of grade 3-5 IRAEs was equivalent in the two groups (3%, p=0.4). The most common IRAE was hypothyroidism in both groups. Although the incidence of hypothyroidism was numerically higher with PD-1 inhibitors compared to PD-L1 inhibitors, this was not significant (6.7% in PD-1 (CI 6-8%) vs. 4.2% (3-5%) in PD-L1, p=0.07). The incidence of pneumonitis was higher in PD-1 cohort vs. PD-L1 (4% (CI 3-5%) vs. 2% (1-3%), p-value=0.01). In analyzing the incidence of toxicities by type of drug, durvalumab was associated with the highest proportion of toxicities (Table 4).

Discussion

Immune checkpoint inhibition with PD-1 and PD-L1 inhibitors has become a standard of care for NSCLC patients with metastatic disease. While each drug has activity in NSCLC, it is unclear how these agents compare in terms of efficacy and toxicity. Our systematic review of 5,744 NSCLC patients treated with PD-1 and PD-L1 inhibitors sheds light on this important clinical issue and provides guidance to treating physicians and researchers. The objective response rate appears similar for PD-1 and PD-L1 inhibitors in an unselected population with advanced stage NSCLC. The toxicity profiles are also comparable between the two classes of checkpoint inhibitors with relatively minor differences. First, the overall incidence of clinically significant adverse events was low with immune checkpoint inhibition, which represents a significant improvement in therapeutic index relative to systemic chemotherapy. Fatigue was the most common AE with both PD-1 and PD-L1 inhibitors. Even among IRAEs, the differences between the two classes of agents were relatively minor. In our view, the most notable difference was observed for grades 3/4 immune-mediated pneumonitis, which was slightly higher with PD-1 inhibitors compared to PD-L1 inhibitors.

This is a large dataset and the first systematic review of toxicity profiles of immune checkpoint inhibitors in NSCLC to our knowledge. This analysis adds to the understanding of differences between PD-1 and PD-L1 inhibitors in NSCLC. A major strength of the analysis is that several of the trials included were conducted in the multi-national setting, thus representative of a heterogeneous and representative patient population from across the world. This included a phase IIIB/IV safety study, the Checkmate 153 study, which collected data on advanced NSCLC patients treated with nivolumab in community oncology practices. This study demonstrates that checkpoint inhibitor therapy with nivolumab is well tolerated even in patients with a performance status of 2 with a 53% rate of treatment related AEs and reflects a more real world practice setting. The majority of these studies enrolled patients primarily from North America and Europe; we did identify phase II data from Sakai et al that reported on the use of nivolumab in 111 patients in Japan. From this report, the efficacy and toxicity in Japanese patients appears similar to the overall population of patients analyzed. Asia is the only region that was not represented proportionally, and hence it will be important to study this issue as more trials are specifically conducted in Asia.
There are limitations to this analysis despite the comprehensive nature of our review. We selected the toxicity data by using reported treatment related adverse events (TRAEs) whenever possible. However, not all the studies had toxicity reported as TRAEs. In addition, the attribution of an AE as treatment-related could be somewhat subjective and vary between clinical trials and drugs.

Another caveat of this analysis is the availability of toxicity data. When possible we used full publications to extract toxicity data for each clinical trial. Some of the newer data were only available as presentations from conferences. In these cases, there was limited toxicity data available for extraction. This could lead to a selection bias of more toxicity reporting in the studies with more complete AE data in the full publication. It is of note that since the PD-1 inhibitors have been in clinical development longer, more of the studies for these agents were in full publication format. A higher proportion of studies for PD-L1 inhibitors were only reported in conferences and could explain some of the differences in toxicities seen between PD-1 and PD-L1 inhibitors.

The most significant finding of our analysis is the doubling in pneumonitis seen in patients treated with PD-1 inhibitors. Again, this may have been partly due to less complete AE reporting with the PD-L1 inhibitors; these drugs are in earlier phases of clinical development and also have fewer complete publications available for review. The rate of pneumonitis could have been influenced by different inclusion criteria used in each study in regards to allowing patients with prior interstitial lung diseases. We did not have access to the inclusion criteria for all of the clinical trials included in our analysis. Another potential confounding factor contributing to the difference in pneumonitis incidence could be the underreporting of pneumonitis as other toxicities, such as pneumonia, dyspnea, or interstitial lung disease.

We also acknowledge that the meta-analysis was not based on individual patient data, which would have been an ideal way to study this issue. An individual patient data meta-analysis would have been more comprehensive and would have allowed for better time-to-toxicity assessment. However, given that the trials were conducted primarily by the respective pharmaceutical companies, gaining access to primary datasets is challenging.

Our comparison of efficacy in terms of response rate is a secondary and exploratory endpoint and also has limitations. The patients included in this analysis were from clinical trials in different phases of drug development. There was also variability in regards to number of treatment lines received. Furthermore, some of the patients enrolled in these studies were selected by PD-L1 expression. There is an association between higher likelihood of response and tumor expression of PD-L1, and the heterogeneity of PD-L1 expression in these patients could have also impacted the reported ORR and toxicities.

Despite these limitations, this systematic review adds to our knowledge of the toxicity profiles and efficacy of PD-1 and PD-L1 inhibitors in NSCLC. It will be interesting to see how information changes with more frontline data and combination strategies being reported. Since these studies are among the first to evaluate this entirely new class of anticancer agents, it is likely that the steep learning curve for early recognition and management of toxicities with more clinical experience will result in an even more favorable toxicity
profile for checkpoint inhibitors in the next wave of clinical trials. Another important way to improve the risk-benefit ratio is to choose treatment based on biomarkers, which is an area of active investigation. PD-L1 expression in the tumor tissue has emerged as a valuable selection method, though it is subject to certain limitations. Presently the cost of PD-1 and PD-L1 inhibitors are also similar in the United States, and hence treatment choice will primarily be based on proven efficacy in the chosen setting and the schedule of administration.

In summary, PD-1 and PD-L1 inhibitors are both associated with comparable efficacy and toxicity in patients with advanced stage NSCLC.

Acknowledgments

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References


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Figure 1. CONSORT Diagram
Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature
Table 1
Studies with PD-1 and PD-L1 Inhibitors in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Line of Therapy</th>
<th>Number of Patients Evaluated for Safety</th>
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<tbody>
<tr>
<td>Gettinger 2015</td>
<td>Nivolumab 1, 3, or 10 mg/kg</td>
<td>Salvage</td>
<td>129</td>
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<tr>
<td>Rizvi 2015</td>
<td>Nivolumab 3 mg/kg</td>
<td>Salvage</td>
<td>117</td>
</tr>
<tr>
<td>Brahmer 2015</td>
<td>Nivolumab 3 mg/kg</td>
<td>Salvage</td>
<td>135</td>
</tr>
<tr>
<td>Borghaei 2015</td>
<td>Nivolumab 3 mg/kg</td>
<td>Salvage</td>
<td>292</td>
</tr>
<tr>
<td>Garon 2015</td>
<td>Pembrolizumab 2 or 10 mg/kg</td>
<td>Salvage</td>
<td>495</td>
</tr>
<tr>
<td>Sakai 2015</td>
<td>Nivolumab 3 mg/kg</td>
<td>Salvage</td>
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<td>Herbst 2016</td>
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<td>Herbst 2016</td>
<td>Pembrolizumab 10 mg/kg</td>
<td>Salvage</td>
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<td>Goldberg 2016</td>
<td>Pembrolizumab 10 mg/kg</td>
<td>Salvage</td>
<td>18</td>
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<td>Gettinger 2016</td>
<td>Nivolumab 3 mg/kg</td>
<td>First-line</td>
<td>52</td>
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<td>Socinski 2016</td>
<td>Nivolumab 3 mg/kg</td>
<td>First-line</td>
<td>267</td>
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<td>Reck 2016</td>
<td>Nivolumab 3 mg/kg</td>
<td>First-line</td>
<td>154</td>
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<td>Brahmer 2014</td>
<td>Durvalumab</td>
<td>Salvage</td>
<td>155</td>
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<tr>
<td>Rizvi 2015</td>
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<td>Salvage</td>
<td>228</td>
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<tr>
<td>Spigel 2013</td>
<td>Atezolizumab</td>
<td>Salvage</td>
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<tr>
<td>Horn 2015</td>
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<td>Salvage</td>
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<td>Spigel 2015</td>
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<td>Besse 2015</td>
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<td>Fehrenbacher 2016</td>
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<td>Salvage</td>
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<td>Verschaegens 2016</td>
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<td>Antonia 2016</td>
<td>Durvalumab</td>
<td>First-line</td>
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<td>Barlesi 2016</td>
<td>Atezolizumab</td>
<td>Salvage</td>
<td>609</td>
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### Table 2
Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>PD-1 Inhibitor (n=3284)</th>
<th>PD-L1 Inhibitor (n=2460)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Median age (yrs)</td>
<td>64</td>
<td>64.5</td>
<td>0.5</td>
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<tr>
<td>Males (%)</td>
<td>59</td>
<td>56</td>
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</tr>
<tr>
<td>Smokers (%)</td>
<td>83</td>
<td>83</td>
<td>0.5</td>
</tr>
<tr>
<td>Squamous histology</td>
<td>25</td>
<td>32</td>
<td>0.6</td>
</tr>
<tr>
<td>ECOG PS 0/1(%)</td>
<td>31.5/68</td>
<td>32/68</td>
<td>0.2/0.4</td>
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Table 3
Adverse Events (AEs), Immune Related Adverse Events (IRAEs), and Overall Response Rates with PD-1 versus PD-L1 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>PD-1 Inhibitors (n=3284)</th>
<th>PD-L1 Inhibitors (n=2460)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall AEs (%)</td>
<td>64</td>
<td>66</td>
<td>0.8</td>
</tr>
<tr>
<td>Grade 3-5 AEs (%)</td>
<td>13</td>
<td>21</td>
<td>0.15</td>
</tr>
<tr>
<td>Fatigue, any grade (%)</td>
<td>19</td>
<td>21</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhea, any grade (%)</td>
<td>9</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>Rash, any grade (%)</td>
<td>9</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>IRAEs (%)</td>
<td>16</td>
<td>11</td>
<td>0.07</td>
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<tr>
<td>Grade 3-5 IRAEs (%)</td>
<td>3</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypothyroidism, any grade (%)</td>
<td>6.7</td>
<td>4.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Pneumonitis, any grade (%)</td>
<td>4</td>
<td>2</td>
<td>0.01</td>
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<tr>
<td>Colitis, any grade (%)</td>
<td>1.7</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Overall Response Rate (ORR) (%)</td>
<td>19</td>
<td>18.6</td>
<td>0.17</td>
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</table>
### Table 4
Overall Adverse Event Rate by Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>AE Rate (%)</th>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>62</td>
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<tr>
<td>Pembrolizumab</td>
<td>67.5</td>
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<tr>
<td>Atezolizumab</td>
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<tr>
<td>Durvalumab</td>
<td>75</td>
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<td>Avelumab</td>
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