The initial treatment for metastatic squamous cell non-small cell lung cancer (NSCLC) consists of platinum-based combination chemotherapy. The most commonly used regimens are carboplatin and paclitaxel, carboplatin and protein-bound paclitaxel (nab-paclitaxel), and cisplatin and gemcitabine. In November 2015, the U.S. Food and Drug Administration (FDA) approved necitumumab, a fully human IgG1 monoclonal antibody that targets epidermal growth factor receptor (EGFR), for the first-line treatment of metastatic squamous cell NSCLC, in combination with cisplatin and gemcitabine (1). Still, the clinical utility of necitumumab is limited due to the high cost of the drug, the added toxicity when combined with cisplatin and gemcitabine and the limited clinical benefit, with a 16% reduction of the risk of death in comparison to chemotherapy alone (1). Immunotherapy has now emerged as an approach to combat, among other tumors, squamous cell NSCLC (2).

Pembrolizumab, a fully human IgG4 anti-programmed cell death-1 (PD-1) monoclonal antibody, has shown clinical efficacy in lung cancer patients, particularly those with high PD-L1 expression (3-5). Pembrolizumab is approved for the first-line therapy of squamous and non-squamous cell NSCLC patients with programmed cell death ligand-1 (PD-L1) of at least 50% tumor proportion score. The drug is also approved for the treatment of patients after progression to first-line chemotherapy, if there is at least 1% PD-L1 expression on tumor cells (6). In most trials that compare anti-PD-1/L1 antibodies with chemotherapy (5,7-12), progression-free survival (PFS) and overall survival (OS) curves are overlapping at early time points (13). One biological explanation for this could be that immunotherapy needs some time to demonstrate its effect and, patients with rapidly progressive disease, lack an effective adaptive immune response. Cytotoxic chemotherapy can delay progression and allow immunotherapy to elicit its treatment effect (13). Indeed, we saw this in the PACIFIC study, in which the anti-PD-L1 antibody durvalumab significantly prolonged the PFS of stage III NSCLC patients who had previously received chemoradiotherapy (14). Now, combination strategies with chemotherapy and immunotherapy in NSCLC are ongoing or have been completed, with evidence that they may be the way to go ahead with the treatment of this disease. In the case of non-squamous cell NSCLC, the combination of pembrolizumab with platinum-pemetrexed has been tested in a phase II (KEYNOTE-021) (15) and a phase III (KEYNOTE-189) (16) clinical trial. In May 2017, FDA approved pembrolizumab in combination with pemetrexed-carboplatin for the first-line treatment of metastatic non-squamous cell NSCLC, irrespective of PD-L1 expression based on the tumor response rate and PFS results of the KEYNOTE-021 (6). Continued approval for this indication is contingent and FDA has now granted priority review for the results of the phase III KEYNOTE-189, which confirmed a PFS and OS benefit compared to chemotherapy alone in patients with non-squamous cell NSCLC, independent of PD-L1 expression (16).
In the 2018 ASCO Annual Meeting, the results of the KEYNOTE-407 (17) followed on the heels of the KEYNOTE-189 clinical trial. A total of 559 treatment naïve patients with stage IV squamous cell NSCLC were enrolled and randomized 1:1 to receive pembrolizumab with chemotherapy (carboplatin-paclitaxel/nab-paclitaxel) or chemotherapy alone (17). PD-L1 expression was not required for the entry in the study, but before randomization, patients were stratified based on three criteria: PD-L1 expression on tumor cells (TC) or immune cells (IC). 1, TC0 and IC0; no PD-L1 expression on tumor cells (TC) or immune cells (IC). 2, TC1/2 or IC1/2; PD-L1 expression on TC or IC <5% (TC1 or IC1) or ≥5% but <50% (TC2 or IC2). 3, TC3 or IC3; PD-L1 expression on TC or IC ≥50%. *, carboplatin-paclitaxel/nab-paclitaxel; **, carboplatin-nab-paclitaxel. mo, months.

<table>
<thead>
<tr>
<th>Main endpoints</th>
<th>KEYNOTE-407, pembrolizumab + chemotherapy vs. chemotherapy*</th>
<th>IMpower131, atezolizumab + chemotherapy vs. chemotherapy**</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N Results</td>
<td>N Results</td>
</tr>
<tr>
<td>mOS</td>
<td>278 vs. 281</td>
<td>343 vs. 340</td>
</tr>
<tr>
<td>Overall</td>
<td>15.9 vs. 11.3 mo; HR =0.64 (0.49–0.85); P=0.0008</td>
<td>14.0 vs. 13.9 mo; HR =0.96 (0.78–1.18); P=0.6931</td>
</tr>
<tr>
<td>PD-L1 &lt;1% or negative1</td>
<td>95 vs. 99</td>
<td>95 vs. 99</td>
</tr>
<tr>
<td>PD-L1 1–49% or low2</td>
<td>103 vs. 104</td>
<td>103 vs. 104</td>
</tr>
<tr>
<td>PD-L1 ≥50% or high3</td>
<td>73 vs. 73</td>
<td>73 vs. 73</td>
</tr>
<tr>
<td>mPFS</td>
<td>278 vs. 281</td>
<td>343 vs. 340</td>
</tr>
<tr>
<td>Overall</td>
<td>6.4 vs. 4.8 mo; HR =0.56 (0.45–0.70); P&lt;0.0001</td>
<td>6.3 vs. 5.6 mo; HR =0.71 (0.60–0.85); P=0.0001</td>
</tr>
<tr>
<td>PD-L1 &lt;1% or negative1</td>
<td>95 vs. 99</td>
<td>160 vs. 171</td>
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<tr>
<td>PD-L1 1–49% or low2</td>
<td>103 vs. 104</td>
<td>129 vs. 121</td>
</tr>
<tr>
<td>PD-L1 ≥50% or high3</td>
<td>73 vs. 73</td>
<td>53 vs. 48</td>
</tr>
</tbody>
</table>

1, TC0 and IC0; no PD-L1 expression on tumor cells (TC) or immune cells (IC). 2, TC1/2 or IC1/2; PD-L1 expression on TC or IC <5% (TC1 or IC1) or ≥5% but <50% (TC2 or IC2). 3, TC3 or IC3; PD-L1 expression on TC or IC ≥50%. *, carboplatin-paclitaxel/nab-paclitaxel; **, carboplatin-nab-paclitaxel. mo, months.
adverse events 10.8% vs. 3.2%) (17).

In the same meeting, the interim OS results of the IMpower131 phase III clinical trial, did not look favorable for the anti-PD-L1 antibody, atezolizumab plus carboplatin-paclitaxel/nab-paclitaxel in patients with newly diagnosed stage IV squamous cell NSCLC (18). The IMpower131 has a different design from the KEYNOTE-407, with 1021 patients randomly assigned to one of three arms: atezolizumab plus carboplatin/paclitaxel (Arm A), atezolizumab plus carboplatin/nab-paclitaxel (Arm B), or carboplatin/nab-paclitaxel (Arm C) (18). In the first analysis of investigator-assessed PFS, there was a PFS benefit with the addition of atezolizumab to chemotherapy that, similar to the KEYNOTE-407, emerged across all patient subgroups evaluated, including all PD-L1 expressing subgroups (18) (Table 1). However, the IMpower131 did not show a difference in median OS between Arm B and Arm C (14.0 vs. 13.9 months). Although the median OS trended favorably for Arm B in the high PD-L1 expressing subgroup (23.6 vs. 14.1 months; HR 0.56, 95% CI: 0.32–0.99) there was an unexpected worse median OS for the low PD-L1 expressing subgroup with the addition of atezolizumab to chemotherapy (12.4 vs. 16.6 months; HR 1.34, 95% CI: 0.95–1.90) (18) (Table 1). In summary, atezolizumab combined with chemotherapy for the first-line therapy of squamous cell NSCLC reduces the risk of disease progression by 29% compared to chemotherapy alone (18), when at the same time pembrolizumab in the same setting reduces the risk of disease progression by 44% and the risk of death by 36% compared to chemotherapy alone (17).

The above results raise several thoughts and concerns. If it is a matter of chemotherapy plus immunotherapy induced immunogenic cell death that leads to immune memory and a sustained long-term response (19,20), then why do we not have similar results from the KEYNOTE-407 and IMpower131? As it was discussed during the 2018 ASCO Annual Meeting, maybe with a longer follow-up, by the time of the final analysis, a difference may emerge for the atezolizumab combination in the IMpower131 study (18). At least in breast cancer models, it has been shown that chemotherapy may have an immunotherapy countertherapeutic effect by inducing hypoxia and the expression of proteins like CD47, CD73 and PD-L1, that ultimately cause T-cell anergy and increase the intratumoral ratio of regulatory/effectort T-cells (21). In the squamous cell NSCLC subgroup of the KEYNOTE-024 trial, pembrolizumab alone reduced the risk of death by 65% compared to chemotherapy, for patients with high (≥50%) PD-L1 expression (5). In both the KEYNOTE-407 (17) and IMpower131 (18) trials, in the same group of patients, the combination of pembrolizumab or atezolizumab with chemotherapy cut that same risk by 44%. Caution should be taken, considering the recent restriction of pembrolizumab and atezolizumab by the European Medicines Agency as first-line therapy only for locally advanced or metastatic urothelial cancer patients with high PD-L1 expression (22). This is a surprise, considering that, initially, PD-L1 expression was not correlated with response for both pembrolizumab (23) and atezolizumab (24). Both drugs showed reduced survival compared to chemotherapy for treatment-naïve patients with low PD-L1 expression KEYNOTE-361 (NCT02853305) and IMvigor130 (NCT02807636) trials (22). Finally, the cost effectiveness vs. the affordability of the treatments should be also taken into account.

Acknowledgements

Funding: Work in Dr Rosell’s laboratory is partially supported by a grant from La Caixa Foundation, an Instituto de Salud Carlos III grant (RESPONSE, PIE16/00011) and a Marie Skłodowska-Curie Innovative Training Networks European Grant (ELBA No. 765492).

Footnote

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

References