

Atezolizumab in advanced non-small cell lung cancer

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Atezolizumab (Tecentriq[®], MPDL3280A, Genentech, CA, USA) is a humanized IgG1 antagonist antibody to PD-L1 engineered to avoid antibody-dependent cell-mediated cytotoxicity of activated T cells that may express PD-L1 (1). It blocks directly the interaction between the PD-L1 and PD-1/B7.1 receptors activation complex, hence it activates the tumor-specific immune response, and induces tumor cell killing (1).

In patients with non-small cell lung cancer (NSCLC) expressing PD-L1 atezolizumab can improve the proportion of patients achieving an objective response rate (ORR) compared with historical controls, according to the results of a new study (2). In the open-label phase II BIRCH trial of 659 patients whose tumors expressed PD-L1 on $\geq 5\%$ PD-L1-expressing tumor cells (TC2) or tumor-infiltrating immune cells (IC2), using the SP142 immunohistochemistry (IHC) assay (Ventana Medical Systems, Tucson, AZ), ORR associated with atezolizumab (1200 mg IV every three weeks) were 22% among treatment-naïve patients, 19% among patients being treated in the second-line setting, and 18% among those receiving atezolizumab as third-line therapy. Higher ORR (26–31%) was observed in the TC3 ($\geq 50\%$ TC) or IC3 ($\geq 10\%$ IC) subgroups for both first-line and \geq second line, although in first-line patients it was comparable to chemotherapy. The epidermal growth factor receptor (EGFR) or KRAS mutation status had no impact on treatment responses. The efficacy

of atezolizumab could not be assessed in patients with rearranged anaplastic lymphoma kinase (ALK) due to an insufficient number of patients. An updated survival analysis at 20 months of follow-up showed that the median overall survival (OS) was highest in first-line treated patients at 23.5 months (95% CI: 18.1 months–not estimable) *vs.* 15.5 (12.3–19.3) months in the second-line cohort and 13.2 (10.3–17.5) months in the third-line cohort. Unlike the ORR, the PD-L1 status seemed to have no impact on OS. Nonetheless, the treatment with atezolizumab improved the OS relative to platinum-based chemotherapy (23.5 *vs.* 10 to 12 months) for patients who received first-line treatment and showing high PD-L1 expression (e.g., TC2/3 or IC2/3 patients and TC3 or IC3 subgroup) (2).

Similar results were reported in the POPLAR and OAK trials, in which the ORR and median PFS results underestimated the broad OS benefit seen with atezolizumab *vs.* docetaxel (3,4). In these studies, the PD-L1 was predictive for clinical efficacy such as ORR, but may be less important for OS.

Overall, results from the BIRCH study demonstrated a clinically meaningful efficacy and safety of atezolizumab in all lines of therapy.

The efficacy of atezolizumab across these studies in terms of both efficacy as well as toxicity profiles over conventional chemotherapy has made it the third PD-1/PD-L1 checkpoint inhibitor approved by the FDA for

relapsed advanced NSCLC (5).

This study confirms that a PD-L1-selected group has a favorable outcome with agents that inhibit the interaction between PD-1 and PD-L1. However, while these results add to the evidence of a subgroup benefit with PD-L1 inhibitors, it does not have the power of a randomized controlled trial as the patients are compared to historical controls (6). Further studies are needed prior to use of atezolizumab in the first-line setting.

Atezolizumab represents a step forward in the treatment of patients with relapsed advanced NSCLC. Nonetheless, the choice of the most appropriate checkpoint inhibitor in the second-line setting between the three FDA-approved for use in NSCLC—atezolizumab, nivolumab, and pembrolizumab—is still unclear (5). All three are effective in second-line setting, with pembrolizumab being approved for use in NSCLC patients with $\geq 1\%$ PD-L1 expression on tumor cells, while atezolizumab and nivolumab demonstrated clinical benefit over chemotherapy irrespective of the PD-L1 expression (7). Pembrolizumab is the only drug holding a first-line indication for single-agent treatment in NSCLC patients with $\geq 50\%$ PD-L1 expression on tumor cells (8). The OAK study demonstrated clinical benefit over conventional chemotherapy in both squamous and non-squamous NSCLC, regardless of the PD-L1 expression. However, significant improvement of ORR and OS was observed in patients showing high PD-L1 expression, confirming the SP142 assay as a reliable predictive biomarker to select patients most likely to benefit from treatment with atezolizumab (4). Additional studies are needed to define further the place of these agents in the second-line setting.

Importantly, these studies also demonstrated that only optimal patient selection is the key to successful PD-1/PD-L1 inhibition. Efforts to standardize the different PD-L1 IHC assays and to identify additional predictive biomarkers are currently in progress (9).

At present, each immune checkpoint inhibitor was approved with its own companion or complementary PD-L1 expression assay. Thus, there is growing interest in assessing the interchangeability across different IHC assays. By opposition to companion tests, complementary assays do not restrict patients from receiving treatments based on the test result. This is because the biomarker status assessed by the complementary assay was not related to therapeutic benefit in all patients. Nevertheless, the biomarker status may inform on increased therapeutic benefits in some subgroups of patients. Currently, there are

two PD-L1 complementary diagnostics, namely, the SP142 assay (Ventana) for use with atezolizumab (for bladder and NSCLC indications) and the 28-8 assay (Dako) for use with nivolumab (for melanoma and NSCLC indications) (10).

The PD-L1 SP142 IHC assay used in BIRCH, was specifically designed and validated for use with atezolizumab. Compared with the other commercial PD-L1 IHC assays (Dako 28-8, Dako 22C3 and Ventana SP263), the SP142 scoring is distinctive by the assessment of PD-L1 expression on both tumor cells and tumor-infiltrating immune cells (11-13). Recent standardization work demonstrated that the SP142 clone exhibited less overall stained tumor cells when compared to the other three IHC assays (11-13). Moreover, the SP142 assay showed the highest inter-pathologist variability, in particular when immune cells were scored (14). These results suggest, at least at this stage, that it is crucial to use the drug's companion/complementary IHC test with validated cutoff for PD-L1 positivity, in order to confidently obtain a clinical benefit specific to that particular treatment (15). Moreover, the IHC technique holds the intrinsic disadvantage of subjective interpretation, in particular when PD-L1 is expressed on both tumor cells as well as on tumor-infiltrating immune cells. Therefore, there is also growing interest in developing alternative methods for more reliable PD-L1 quantification. It is certainly possible that observer bias can lead to a shift towards the utilization of nivolumab, which does not require PD-L1 testing, and thus places extra emphasis on reducing inter-pathologist variability (15).

It would be of interest to evaluate tissue IHC assays in combination with multicolor flow cytometry to better characterize the immune tumor microenvironment by staining cells such as CD8+/CD4+ T cells, macrophages, myeloid-derived suppressor cells, natural-killers or regulatory T cells (16). These new methodologies may contribute to better biomarker assessment on clinical samples, as well as improve the predictive value of PD-L1 expression on both tumor cells and immune cells for immunotherapy.

Finally, some NSCLC patients without PD-L1 expression may still respond to checkpoint inhibitor treatment (9). Moreover, *de novo* resistance to immunotherapy has been reported in a relatively significant proportion of NSCLC patients, despite PD-L1 being expressed in tumors (9). Importantly, the intratumoral heterogeneity of PD-L1 expression may fail to appreciate the PD-L1 status in the whole tumor burden when assessed on biopsy samples (17). In addition, several blood-based assays are currently under investigation as predictive biomarkers for response to

checkpoint inhibitors (18, 19).

In conclusion, future challenges will be to identify the most effective treatment sequence including immunotherapies, to standardize the different PD-L1 IHC assays, to understand the resistance mechanisms of checkpoint inhibitors, and to identify additional biomarkers to optimize benefit of immunotherapy for NSCLC patients.

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Footnote

Conflicts of Interest: Paul Hofman is a member of different industrial scientific advisory boards (Roche, AstraZeneca, Novartis, Bristol-Myers Squibb, Pfizer, Qiagen, Janssen, Biocartis) for which he receives honorarium. Marius Ilié has no conflicts of interest to declare.

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