Atezolizumab in non-small cell lung cancer: the era of precision immuno-oncology

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For patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose disease progressed after first-line platinum-based combination chemotherapy, effective treatment options are limited, especially in the absence of targetable oncogenic mutations. In the past decade, docetaxel has remained the standard second-line agent. It has a low response rate of approximately 10% and diseases tend to progress shortly after treatment (1). In recent years, there have been major breakthroughs in the use of immune checkpoint inhibitors in advanced lung cancer, demonstrating an improved survival in the relapse setting (2-4).

Immune evasion plays a pivotal role in lung cancer carcinogenesis, and is partly mediated by the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) pathway. PD-L1 is often overexpressed on lung cancer tumor cells as well as the surrounding tumor-infiltrating lymphocytes (5). Through interaction with PD-1 receptors on activated T-cells, it dampens anti-tumor immune response and facilitates evasion from cell kill. Atezolizumab, a humanized IgG1 PD-L1 immune checkpoint inhibitor, was designed to disrupt the interaction between PD-L1 and PD-1/B7-1 activation complex, hence unleashes the brake on immune system, restores tumor-specific immune response, and promotes endogenous tumor cell destruction.

In the randomized phase III OAK trial (6), published in *The Lancet*, Rittmeyer *et al*. reported an overall survival (OS) improvement of atezolizumab *vs*. docetaxel in previously treated locally advanced or metastatic NSCLC. The trial recruited 1,225 patients with stage IIIB or IV NSCLC whose diseases had progressed on one or more lines of platinum-based chemotherapy, randomized in 1:1 fashion to either atezolizumab or docetaxel. Patients were unselected for PD-L1 expression before trial entry. The primary endpoint was OS, in both the intention-to-treat (ITT) population and in subgroups with different levels of PD-L1 expression. Secondary endpoints included progression-free survival (PFS), objective response rate, duration of response, and safety. In the ITT population, median OS was significantly longer with atezolizumab [13.8 *vs*. 9.6 months; hazard ratio (HR) =0.73; 95% confidence interval (CI), 0.62–0.87; P=0.0003]. A survival benefit was observed across all levels of PD-L1 expression, including the low or undetectable subgroup. Median PFS (2.8 *vs*. 4.0 months; HR =0.95; 95% CI, 0.82–1.10; P=0.49) and objective response rate (14% *vs*. 13%) were similar between treatment groups. However, the responses in atezolizumab arm were significantly more durable compared with docetaxel (median, 16.3 *vs*. 6.2 months; HR =0.34; 95% CI, 0.21–0.55; P≤0.0001). Atezolizumab was also better tolerated than docetaxel, giving rise to less grade 3 or 4 treatment-related adverse events (15% *vs*. 43%).

OAK is the first phase III clinical trial reporting on the efficacy of an anti-PD-L1 antibody in advanced NSCLC. It further confirmed the efficacy of immune-checkpoint inhibitors in this devastating disease, with a magnitude of benefit consistent with what we saw in anti-PD1 antibodies

(*Table 1*). Despite the difference in mechanism of action, i.e., sparing the PD-L2/PD1 interaction pathway, which theoretically could help reduce immune-mediated toxicities, atezolizumab seemed to give a similar spectrum and severity of adverse events as with anti-PD1 antibodies as well. This observation might be related to the fact that the constitutive basal expression of PD-L1 is generally higher than PD-L2 (7), where blockade on PD-L1/PD1 is responsible for most observed autoimmune phenomena in cancer immunotherapies.

In the OAK trial, median OS was improved with atezolizumab regardless of PD-L1 expression levels. It was confirmed that a high PD-L1 expression was predictive of a greater clinical benefit, as shown by a median OS up to 20.5 months (20.5 *vs.* 8.9 months; HR =0.41; 95% CI, 0.27–0.64) in tumors with PD-L1 expression ≥50% on tumor cells, or ≥10% on tumor-infiltrating immune cells. Even in the 45% of patients who had low or undetectable PD-L1 expressions, there was a statistically significant median OS difference of 3.7 months between treatment arms. This demonstrated that PD-L1 expression level is useful in enriching a population who would gain more from atezolizumab, but at the same time, proved itself as an imperfect biomarker in dichotomizing patients in treatment selection. The finding of observing response in tumors with low PD-L1 expression is further complicated by the high degree of intratumoral heterogeneity in NSCLC, which renders the PD-L1 expression level detected in biopsy specimens unrepresentative of whole tumor sample (8).

Recent researches have shown that tumor mutation burden (TMB) could be used as an independent biomarker of response to immune checkpoint inhibitors (9). It was hypothesized that, with higher number of TMB, there is a corresponding increase in neo-antigens recognized by T-cells, therefore inducing body to mount a more effective anti-tumor immune response. The effect of TMB on the efficacy of atezolizumab has previously been reported (10). In a PD-L1 selected population, high TMB was predictive of an improved PFS, in association with a trend towards improved OS as well. Importantly, there was no response observed in the subgroup which both PD-L1 expression and TMB are low. This provided suggestive evidence that TMB may be used together with PD-L1 expression to help identify right patients for atezolizumab in the future.

Apart from TMB, *EGFR* mutation status may also affect treatment outcomes from PD-1/PD-L1 checkpoint inhibition. As shown in the exploratory subgroup analysis in OAK, although not statistically significant, *EGFR* mutant status was the only subgroup whose survival numerically favored docetaxel (HR =1.24, CI: 0.71–2.18). In a recent meta-analysis assessing the role of second-line immune checkpoint inhibition in *EGFR*-mutated NSCLC, comparing with docetaxel, there was no improvement in OS in this particular subgroup (HR =1.05; 95% CI, 0.70–1.55; P<0.81) (11). Whether this is an indirect reflection of a low TMB in *EGFR*-mutant tumors, or does this represent an intrinsic insensitivity to immune modulation in this subgroup, is yet to be answered by further studies.

Despite an impressive duration of response, most tumors eventually develop acquired resistance after initial response to immune checkpoint inhibition. Active researches are underway to investigate the underlying resistance mechanisms. Recent work from Anagnostou *et al*. demonstrated that acquired resistance to anti-PD-1 or anti-cytotoxic T-lymphocyte-associated antigen 4 antibodies can arise from the loss of mutations encoding for putative tumor specific antigens, via both tumor subclones elimination or chromosomal loss of truncal alterations (12). This evolving landscape of genomic changes equip tumor cells again with the ability to evade anti-tumor immune responses, and partly explained the seemingly inevitable disease progression in patients with responded tumors, and provided insights on future therapeutic strategies in tackling resistance to immune modulation.

Apart from discoveries on resistance mechanisms, ongoing researches also focus on the standardization of PD-L1 immunohistochemistry (IHC) assays. Currently, with each checkpoint inhibitor co-developed with its own companion PD-L1 expression testing system, there is a growing interest in assessing the interchangeability across various assays. The PD-L1 IHC assay used in OAK, Ventana SP142, was specifically designed and validated for atezolizumab. Compared with the other three available PD-L1 IHC assays (Dako 28-8, Dako 22C3 and Ventana SP263), the SP142 interpretive scoring is unique in that it scores not only PD-L1 expression on tumor cells, but on the surrounding tumor-infiltrating immune cells as well. Recent work from the Blueprint PD-L1 IHC Assay Comparison Project has shown that, while the other three available assays showed consistent staining equivalency, SP142 stood out and exhibited relatively fewer overall stained tumor cells (13). In addition, when comparing all four PD-L1 IHC assays using each of their own validated cutoffs, there was a positivity discordance rate up to 37%. The result suggests that, at least at this stage, if PD-L1 testing is performed as a predictive marker of efficacy for immune checkpoint inhibitors, it is crucial to adhere with the drug's companion

Table 1 Phase III randomized clinical trials on agents targeting PD-1/PD-L1 pathway in patients with advanced or metastatic NSCLC failed first-line chemotherapy

Study	Study design	Patient population	PD-L1 expression	Treatment arms	Primary endpoint	Results
Keynote 010 (2)	Phase 2/3	Previously treated NSCLC	>1%	Pembrolizumab 2 mg/kg Q3W *vs.* Pembrolizumab 10 mg/kg Q3W *vs.* docetaxel 75 mg/m^2 Q3W	OS and PFS	Pembrolizumab 2 mg/kg *vs.* docetaxel: OS: 14.9 *vs.* 8.2 months (HR =0.54; 95% CI, 0.38–0.77; P=0.0002) PFS: 3.9 *vs.* 4.0 months (HR =0.88; 95% CI, 0.74–1.05; P=0.07) Pembrolizumab 10 mg/kg *vs.* docetaxel: OS: 17.3 *vs.* 8.2 months (HR =0.50; 95% CI, 0.36–0.70; P≤0.0001) PFS: 4.0 *vs.* 4.0 months (HR =0.79; 95% CI, 0.66–0.94; P=0.004)
Checkmate 017 (3)	Phase 3	Previously treated squamous NSCLC	Unselected	Nivolumab 3 mg/kg Q2W *vs.* docetaxel 75 mg/m^2 Q3W	OS	9.2 *vs.* 6.0 months (HR =0.59; 95% CI, 0.44–0.79; P<0.001)
Checkmate 057 (4)	Phase 3	Previously treated non-squamous NSCLC	Unselected	Nivolumab 3 mg/kg Q2W *vs.* docetaxel 75 mg/m^2 Q3W	OS	12.2 *vs.* 9.4 months (HR =0.73; 96% CI, 0.59–0.89; P=0.002)
OAK (6)	Phase 3	Previously treated NSCLC	Unselected	Atezolizumab 1200 mg Q3W *vs.* docetaxel 75 mg/m^2 Q3W	OS	13.8 *vs.* 9.6 months (HR =0.73; 95% CI, 0.62–0.87; P=0.0003)

PD-1, programmed death-1; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; *vs.*, versus; OS, overall survival; PFS, progression-free survival; Q3W, every three weeks; Q2W, every two weeks; HR, hazard ratio; CI, confidence interval.

IHC assay and its respective validated PD-L1 cutoffs, in order to confidently project a calibrated clinical outcome specific to that particular inhibitor. In addition to IHC, which has inherent disadvantage of subjective interpretation, there is also a growing interest in alternative methods for PD-L1 quantification. Chargin *et al*. reported the use of non-enzymatic tissue dissociation and flow cytometry for PD-L1 testing, which enable an automated and fully quantitative assay on both biopsies and fine needle aspiration samples (14). These novel techniques may help facilitate better biomarker assessments on routine clinical samples, as well as improve the predictive value of PD-L1 expression levels on lung cancer immunotherapies.

The success of atezolizumab has made it the third FDA-approved PD-1/PD-L1 checkpoint inhibitors joining the battlefield of relapsed advanced NSCLC, demonstrating a unique advantage over conventional chemotherapy, in terms of both efficacies as well as toxicity profiles. Studies are already underway to explore the possibility of combining these active agents with cytotoxic chemotherapy as well as radiotherapy, where there is a theoretical synergistic effect from enhanced immunogenicity due to increased antigen release. Future challenges will be to homogenize various PD-L1 assays, unravel the resistance mechanisms towards immune inhibition, and to identify better biomarkers to maximize benefit of checkpoint inhibition in this exciting era of precision immuno-oncology (IO) for lung cancer.

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Footnote

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

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