PD-L1-targeting drug atezolizumab nabs approval for non-small cell lung cancer

The approval last fall by the US Food and Drug Administration (FDA) of the immune checkpoint inhibitor atezolizumab for the treatment of metastatic non–small cell lung cancer (NSCLC) marked the second approved indication for the drug in a single year. Atezolizumab, which targets the programmed cell death protein-ligand 1 (PD-L1), has a unique mechanism of action compared with other approved immune checkpoint inhibitors and had been previously approved for the treatment of patients with advanced urothelial carcinoma. The current approval was based on 2 international, randomized, open-label trials, involving more than 1,000 patients, in which atezolizumab outperformed the chemotherapeutic drug docetaxel.

The POPLAR trial[1] was a phase 2 study performed at 61 academic centers and community oncology practices across 13 countries in Europe and North America and enrolled 287 patients, while the phase 3 OAK trial[2] was carried out at 193 centers in 31 countries and enrolled 850 patients.

Eligibility criteria for the 2 studies were similar; patients were 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), and adequate hematologic and end-organ function. Patients with asymptomatic or treated central nervous system (CNS) metastases were also eligible.

Patients were excluded from both studies if they had a history of autoimmune disease, pneumonitis or chronic viral diseases, or had received previous treatment with docetaxel, CD137 agonists, anti-CTLA4, anti-PD-L1 or anti-PD-1 therapeutics.

Patients were randomized 1:1 to receive atezolizumab, administered intravenously at a fixed dose of 1,200 mg, or a 75 mg/m^2 dose of docetaxel, every 3 weeks on day 1 of each 3-week cycle. Randomization was stratified according to PD-L1 expression, number of previous chemotherapy regimens, and histology (squamous vs nonsquamous). Tumors were assessed at baseline and every 6 weeks for 36 weeks, and every 9 weeks thereafter until progression or, in patients who continued beyond progression, until discontinuation. PD-L1 expression was assessed prospectively on tumor cells and tumor-infiltrating immune cells, using the FDA-approved companion diagnostic, Ventana SP142 PD-L1 immunohistochemistry assay.

What's new, what's important

The immune checkpoint inhibitor atezolizumab targets the PD-L1 protein and has a unique mechanism of action. Its approval for metastatic non-small cell lung cancer – its second after a previous approval for advanced urothelial carcinoma – was based on findings from 2 trials that compared atezolizumab and docetaxel.

Findings in both of the studies showed significantly improved OS in the atezolizumab groups (POPLAR trial [n = 287]: median OS, 12.6 vs 9.7 months; OAK trial [n = 850]: 15.7 vs 10.3 months). The OS benefit in the POPLAR trial reached statistical significance only in patients with the highest levels of PD-L1 expression; in the OAK study, improvement was regardless of PD-L1 expression status. PFS and ORR were similar in the 2 treatment arms in both studies.

The most common adverse events included fatigue, decreased appetite, and dyspnea, cough, nausea, musculoskeletal pain, and constipation. There were fewer incidences of grade 3/4 AEs with atezolizumab compared with docetaxel and a lower rate of discontinuation. Treatment should be permanently discontinued in the event of grade 3/4 pneumonitis; AST/ALT levels of >5 times the ULN or bilirubin levels of >3 times the ULN; grade 4 diarrhea or colitis; myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome or meningoencephalitis (all grades); grade 3/4 ocular inflammatory toxicity; grade 4 or recurrent (any grade) pancreatitis; grade 3/4 infusion-related reactions; or grade 4 rash.

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The primary endpoint in both studies was overall survival (OS), which was significantly improved in the atezolizumab treatment arm. In the POPLAR trial, over a minimum follow-up of 13 months, the median OS was 12.6 months in atezolizumab-treated patients, compared with 9.7 months in docetaxel-treated patients (hazard ratio [HR], 0.73; P = .04) and in the OAK trial, over a median follow-up of 21 months, the median OS was 15.7 months and 10.3 months, respectively.

The main difference between the 2 trials was that the OS benefit in the POPLAR trial reached statistical significance only in patients with the highest levels of PD-L1 expression, whereas in the OAK study, the OS was signif-

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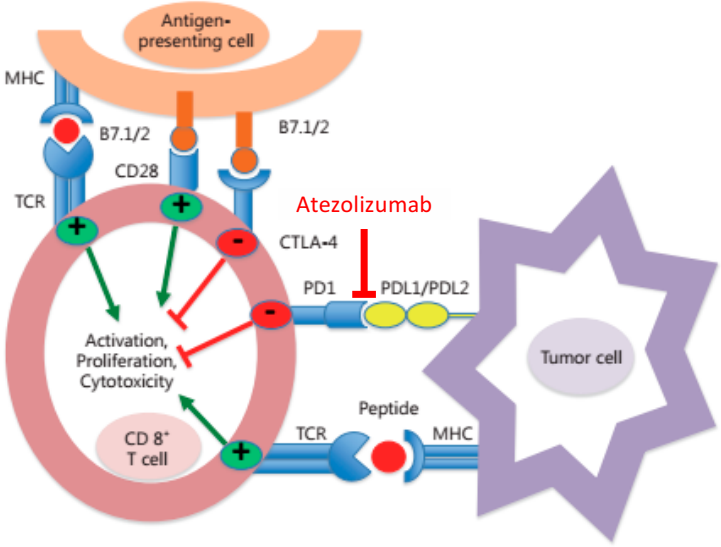
Mechanism of action: atezolizumab

Receptor and PD-L1 signaling axis are valid therapeutic targets. A hallmark of cancer is genomic instability and the resulting mutated or aberrantly expressed proteins found on the surface of cancer cells can serve as neoantigens that can trigger an immune response. However, tumors have developed numerous methods to overcome immune surveillance, central among them is their ability to suppress T-cell responses. One of the ways in which they do this is to hijack the coinhibitory signals – so-called immune checkpoints – that are vital regulators of T-cell activation. Normally these receptors serve to dampen T-cell activity to keep the immune system in check and protect healthy tissues from immune-mediated damage. Best understood are the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) receptors.

PD-1 is expressed on the surface of activated T cells and after binding by its ligands, PD-L1 and PD-L2, it inhibits downstream signaling pathways involved in T-cell activation. PD-L1 also serves as the ligand for another negative regulator of T-cell activation, the B7-1 (or CD80) receptor. PD-1 and PD-L1 have both been shown to be highly expressed on the surface of tumor cells and tumor-infiltrating T cells, fostering an immunosuppressive microenvironment.

PD-1 inhibition has already proven to be an effective treatment strategy in several different cancer types, with the approval of several different PD-1-targeting drugs. Atezolizumab is the first FDA-approved drug that targets the PD-L1 ligand. It specifically blocks the interaction between the PD-1 and B7-1 receptors and the PD-L1 ligand, preventing PD-1-mediated T-cell suppression and boosting the anti-tumor immune response, while leaving the interaction between PD-1 and the PD-L2 ligand intact. Since this pathway plays an important role in limiting autoimmunity, leaving it partially activated through the PD-L2 ligand can help to limit interruption to the normal effects of this pathway on the immune system.

Atezolizumab is also engineered to minimize its binding to Fc receptors on target cells, to prevent antibody-dependent cellular cytotoxicity. Therefore, it will merely bind to PD-L1, blocking its activity, without killing the T cell and inadvertently reducing anti-tumor immunity.



Atezolizumab is a new class of immune checkpoint inhibitor that targets the PD-L1 ligand instead of the PD-1 receptor. Specifically blocking the interaction between PD-1 and the PD-L1 ligand can release T cells from PD-1-mediated inhibition, boosting the anti-tumor immune response, while leaving its interaction with the PD-L2 ligand intact, thus maintaining the important effects of PD-L2 on immune homeostasis.

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icantly improved regardless of PD-L1 expression status, although the greatest benefit was derived in patients with higher levels of PD-L1 expression (20.5 months and 8.9 months, respectively). The OS benefit was observed across all other prespecified subgroups, except in patients with *EGFR* mutation-positivity in the OAK trial. Progression-free survival and overall response rates were similar in the 2 treatment arms in both studies.

An additional 375 patients were enrolled in the OAK trial and included in the safety analyses. In both studies, the safety profile of atezolizumab was similar to that observed in previous studies of this drug. The most commonly observed adverse events (AEs) with atezolizumab treatment were fatigue, decreased appetite, dyspnea, cough, nausea, musculoskeletal pain, and constipation. Despite longer treatment duration, there were fewer incidences of grade 3/4 AEs with atezolizumab compared with docetaxel (37% vs 54%, respectively, in the OAK trial), a lower rate of discontinuation with atezolizumab treatment, and no deaths related to the study drug. The most common grade 3/4 AEs included dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, and anemia. Clinically significant immune-related AEs included pneumonitis, hepatitis, colitis, and thyroid disease.

Atezolizumab is marketed as Tecentriq by Genentech and the prescribing information details warnings and pre-

cautions about immune-related AEs; pneumonitis, colitis, endocrinopathies (eg, thyroid disorders, adrenal insufficiency, and diabetes mellitus), and others, as well as infections, infusion-related reactions, and embryofetal toxicity.[3]

Atezolizumab treatment should be withheld for grade 2 pneumonitis; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of >3-5 times the upper limit of normal (ULN) or total bilirubin levels of >1.5 and up to 3 times the ULN; grade 2/3 diarrhea or colitis, adrenal insufficiency, hypothyroidism, or grade 3/4 hyperglycemia; grade 2 ocular inflammatory toxicity; grade 2/3 pancreatitis or grade 3/4 increases in amylase or lipase levels; grade 3/4 infection; grade 2 infusion-related reactions; and grade 3 rash. Treatment can then be resumed in patients whose AEs recover to grade 0 or 1.

Treatment should be permanently discontinued in the event of grade 3/4 pneumonitis; AST/ALT levels of >5 times the ULN or bilirubin levels of >3 times the ULN; grade 4 diarrhea or colitis; myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome or meningoencephalitis (all grades); grade 3/4 ocular inflammatory toxicity; grade 4 or recurrent (any grade) pancreatitis; grade 3/4 infusion-related reactions; or grade 4 rash. Patients should also be advised of the risk of fetal harm.

References

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