

A New Era in Lung Cancer Treatment

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Advances in immunotherapy are revolutionizing the treatment of cancer, and some of the breakthroughs are happening in the area of lung cancer. Instead of using strong drugs or radiation to attack cancer cells, immunotherapy trains the body's immune system to fight the disease.

Immunotherapy, broadly classified as anti-cancer treatments that potentiate the immune system's ability to recognize and destroy cancer cells, is now a standard of care for patients with non-small cell lung cancers (NSCLCs). Monoclonal antibodies directed against the T-cell inhibitory receptor PD-1 and its ligand PD-L1 are available from several companies and have supplanted, for many patients, chemotherapy as the superior treatment option within a given line of therapy.

Several clinical trials of anti-PD-L1/PD-1 immunotherapies showed improved survival of patients with advanced NSCLC given atezolizumab in the OAK trial, a 2-year update on nivolumab in the CheckMate 057 and 017 trials, and promising evidence for pembrolizumab in the update to the KEYNOTE-10 trial. Some investigators suggest that the clinical benefit of anti-PD-1/PD-L1 monotherapy is not expected in the population of patients without elevated PD-L1 expression. Updated findings from these clinical trials indicate large variations in the expression of PD-L1 from diseased tissue. However, multiple trials support high PD-L1 expression as an effective tumor biomarker in predicting clinical response.

Atezolizumab is a human monoclonal immunoglobulin (Ig) G1 antibody specifically targeted to PD-L1 on tumor. Based on the results of numerous clinical trials (FIR, POPLAR, BIRCH, OAK), atezolizumab is indicated for use in patients with metastatic NSCLC who experience disease progression during or following treatment with platinum-containing chemotherapy. The BIRCH trial was a single-arm, phase 2 study evaluating the efficacy and safety of atezolizumab as first-line or subsequent therapy. Atezolizumab was evaluated in 659 patients with recurrent, locally advanced, or metastatic (stage IIIB/IV) NSCLC with medium to high PD-L1 expression in diseased tissue. Patients in the study scored depending on the PD-L1 expression. Patients receiving atezolizumab as a first-line treatment continued therapy until they experienced progression of the disease or toxicity. The primary endpoint of the BIRCH study was the objective response rate (ORR), assessed by an independent review facility per RECIST v1.1 criteria. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Atezolizumab was found to be an effective monotherapy in patients with advanced NSCLC and PD-L1 overexpression. The ORR in patients treated with atezolizumab was greater with increased expression of PD-L1, with similar rates in those with or without previous chemotherapy. Of patients who received first-line atezolizumab treatment, those with the highest PD-L1 expression had a stronger overall response, as 26% of TC3-/IC3-scored patients had reduction of tumor burden compared with 19% in the lower PD-L1-expressing subgroup. This pattern was also observed in the patients treated with atezolizumab as a second-line treatment. The findings of the BIRCH trial indicate that PD-L1 may serve as a biomarker to identify patients most likely to benefit from atezolizumab monotherapy and that this biomarker can be used to determine which patients may benefit most from a combination of atezolizumab and another medicine. The POPLAR trial further assessed the value of PD-L1 expression levels on tumor and tumor-infiltrating ICs in predicting atezolizumab efficacy. The phase 2, open-label POPLAR trial evaluated the efficacy and safety of atezolizumab as a second- or third line treatment in patients with NSCLC. The trial included 287 patients in 13 countries with advanced

or metastatic NSCLC who had disease progression after platinum-based chemotherapy treatment. A key strength of POPLAR was that it enrolled patients irrespective of PD-L1 status, which was assessed on both TCs and tumor-infiltrating ICs. After a minimum follow-up of 13 months, investigators found that atezolizumab was associated with significant ($P = .04$) improvements in OS, with a rate of 12.6 months compared with 9.7 months in patients treated with docetaxel (HR, 0.73; 95% CI, 0.53-0.99). Much like the results of the BIRCH trial, POPLAR showed that OS with atezolizumab increased among patients with higher TC and IC PD-L1 expression.

Nivolumab is a humanized IgG4k monoclonal antibody that binds to the PD-1 receptor expressed on T cells. Based on the results of the CheckMate clinical trials, nivolumab is indicated for use in patients with metastatic NSCLC who experience progression during or following platinum-based chemotherapy. The phase 3 CheckMate 017 trial compared the safety and efficacy of nivolumab with docetaxel in patients with advanced SQ NSCLC who experienced progressive disease during or after treatment with platinum based chemotherapy. The primary outcome was OS in patients with SQ NSCLC treated with nivolumab and docetaxel. Results from this trial demonstrated that nivolumab significantly improved patient survival over treatment with docetaxel. The median OS was 9.2 months in patients given nivolumab compared with 6.0 months for patients receiving docetaxel. Nivolumab also was found to nearly double the rate of 1-year survival, as 42% of patients were likely to be alive following randomization after 12 months compared with 24% of patients treated with docetaxel.

In 3 KEYNOTE trials, PDL1 expression was used to identify patients who would benefit from pembrolizumab treatment. A total of 4784 patients with advanced NSCLC whose tumors were evaluable for PD-L1 expression from the KEYNOTE-001 ($n = 909$), KEYNOTE-010 ($n = 2222$), and KEYNOTE-024 ($n = 1653$) trials were evaluated.

The findings showed that 67% of patients with advanced NSCLC enrolled for pembrolizumab treatment in the KEYNOTE trials had detectable PD-L1 expression from at least 1% of TCs and 28% had high levels from at least 50% of tumors. KEYNOTE-024 trial assessed the efficacy of pembrolizumab monotherapy compared with standard of- care platinum-based chemotherapies in patients previously untreated for advanced NSCLC.

Pembrolizumab showed significantly ($P < .001$) improved PFS by approximately 4 months compared with chemotherapy, with a 10.3-month median PFS in patients treated with pembrolizumab compared with 6.0 months in patients treated with chemotherapy (HR, 0.50; 95% CI, 0.37 - 0.68). At 6 months following randomization, an estimated 62.1% of patients treated with pembrolizumab were alive and did not have progression of disease compared with 50.3% of patients treated with chemotherapy. Secondary endpoints were OS, ORR, and safety. Pembrolizumab was associated with significant ($P = .005$) reduction in the risk of death compared with chemotherapy (HR, 0.60; 95% CI, 0.41 - 0.89). An estimated 80.2% of patients treated with pembrolizumab were alive at 6 months compared with 72.4% of patients treated with chemotherapy. Based on results from the KEYNOTE-024 trial, pembrolizumab proved to be a promising first-line treatment in patients with advanced NSCLC, with superior improvements in survival and response to treatment compared with platinum-based chemotherapy.

KEYNOTE-021 study, which evaluated the efficacy and safety of pembrolizumab in combination with platinum-based doublet chemotherapy in a cohort of previously untreated patients with metastatic non-SQ NSCLC. The study showed a significantly greater objective response ($P = .0016$) in patients who received pembrolizumab plus chemotherapy (55%) compared with chemotherapy alone (29%).

However, the success of immunotherapy throws open the door for clinical trials, as researchers study the new treatment possibilities from every angle: Does a combination of two immunotherapies work better than one? Does immunotherapy work with certain mutations or specific biomarkers? Does it work better before or simultaneously with chemotherapy, rather than as a second-line option? Is it as effective in never-smokers as it is in smokers? Multiple trials are examining these questions.

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Percentage of tumor area. In this way, the subgroup of patients with NSCLC TCs expressing the highest PD-L1 level (at least 50%) are scored as TC3, and patients with PD-L1 expression from 5% to 50% are scored as TC2. Patients scored as TC1 have less than 5% PD-L1 ex-

pression, and tumors scored as TC0 have less than 1%. Tumor-infiltrating ICs with a score of IC3 have PD-L1 expression and represent at least 10% of tumor area; IC2, at least 5%; IC1, at least 1% but less than 5%; and IC0, less than 1%. As the goal of this study was to provide atezolizumab to patients with NSCLC who would have the greatest response and treatment benefits, those with PD-L1 expression scoring of TC2/3 or IC2/3 were treated with a 1200-mg intravenous (IV) dose of atezolizumab monotherapy every 3 weeks. Patients receiving atezolizumab as a first-line treatment continued therapy until they experienced progression of the disease or toxicity, whereas the drug was continued until loss of clinical benefit in patients with prior platinum-based chemotherapy. At the data cutoff on May 28, 2015, patients with TC3/IC3 PD-L1 expression had greater reduction of tumor burden compared with those with lower PD-L1 expression levels when receiving atezolizumab as first-line or subsequent therapy. The ORR in patients treated with atezolizumab was greater with increased expression of PD-L1, with similar rates in those with or without previous chemotherapy. Of patients who received first-line atezolizumab treatment, those with the highest PD-L1 expression had a stronger overall response, as 26% of TC3-/IC3-scored patients had reduction of tumor burden compared with 19% in the lower PD-L1-expressing subgroup. This pattern was also observed in the patients treated with atezolizumab as a second-line treatment: the ORR was 24% in patients with higher PD-L1 TC or IC expression levels and 17% in those with lower PD-L1 expression. In patients who had undergone 2 or more prior chemotherapy regimens, ORRs increased when stratified by PD-L1 expression: 27% in the TC3 or IC3 subgroup compared with 17% in those with lower PD-L1 expression scored as TC2/3 or IC2/3.

Patients were stratified by PD-L1 expression on ICs and TCs and scored using a highly reproducible Roche Diagnostic IHC assay. Patients with NSCLC were randomized 1:1 to receive either 1200 mg of atezolizumab (n = 144) or 75 mg/m² of docetaxel (n = 143) intravenously every 3 weeks. Atezolizumab was continued in patients until loss of clinical benefit, while patients received docetaxel until disease progression or unacceptable toxicity. The primary endpoint in the POPLAR trial was OS in both arms, and the results were stratified by varying PD-L1 expression. Investigators assessed tumors through imaging at baseline, every 6 weeks.

Of these patients, 33% were found to have the lowest amount of TCs expressing PD-L1, for a TPS less than 1%, and 38% had a TPS of 1% to 49%. The highest expression of PD-L1 was found in 28% of patients who had a TPS of at least 50%. The prevalence of PD-L1 expression was similar in patients treated with pembrolizumab as a first-line therapy and those who had disease progression with previous lines of platinum-based chemotherapy: 30% had the highest level of PD-L1 expression, 40% had PDL1 expression from 1% to 49% of diseased tumors, and 31% had less than 1% of tumors expressing PD-L1. In patients who had previous lines of chemotherapy and experienced disease progression, 27% had the highest level of PD-L1 expression, 38% had PD-L1 expression from 1% to 49% of diseased tumors, and 35% had less than 1% of tumors expressing PD-L1.

Enrolled patients had an ECOG performance score of 0 or 1, life expectancy of at least 3 months, no prior treatment regimen, and high PD-L1 expression. Of the 1653 patients screened for PD-L1 expression, 500 (32%) had a TPS of 50% or more tumors expressing PD-L1, as assessed by a specific 22C3 pharmDx IHC assay. A total of 305 patients from 16 countries met all inclusion criteria for enrollment and were randomized 1:1 to receive an IV dose of 200-mg pembrolizumab every 3 weeks for up to 35 cycles (n = 154) or investigator's choice of platinum-based chemotherapy (n = 151) for 4 to 6 cycles of either carboplatin plus pemetrexed, gemcitabine, or paclitaxel, or cisplatin plus pemetrexed or gemcitabine. Treatment continued in both arms until disease progression, treatment-related AEs of unacceptable severity, or a patient withdrew consent.

A higher ORR was observed in patients given pembrolizumab compared with chemotherapy: 44.8% of those in the pembrolizumab group had a confirmed complete or partial response based on RECIST v1.1 criteria compared with 27.8% of patients in the chemotherapy group. Median time to response was 2.2 months in both treatment groups, with 69 and 42 patients in the pembrolizumab and chemotherapy groups, respectively, having an objective response. At the time of data cutoff, responses were ongoing in the pembrolizumab group and the median DOR was 6.3 months in the chemotherapy group. Treatment-related AEs occurred in 73.4% of patients given pembrolizumab and 90.0% of patients given chemotherapy. The most common treatment-related AEs in patients given pembrolizumab were diarrhea (14.3%), fatigue (10.3%), and pyrexia (10.4%). Certain AEs also occurred at a higher incidence with chemotherapy, and

included anemia (44.0%), nausea (43.3%), and fatigue (28.7%). AEs of grade 3 to 5 severity occurred in twice as many patients in the chemotherapy group as in the pembrolizumab group, with 53.3% and 26.6% of patients affected, respectively.

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