Immunotherapies for Lung Cancer

Presented by Matthew A. Gubens, MD, MS

Abstract

In 2017, immunotherapy is the standard of care for patients with non–small cell lung cancer (NSCLC) either in the first or second line depending on programmed death ligand-1 (PD-L1) and mutation status. For first-line therapy, pembrolizumab is currently the standard of care for patients whose tumors express PD-L1 >50%. All patients with NSCLC should undergo PD-L1 testing before initiating treatment on pembrolizumab. For patients not eligible in the first line, immunotherapy is the standard of care for most in the second line. Nivolumab and atezolizumab are approved in all patients as second-line therapies after platinum-based doublet failure regardless PD-L1 expression level, although pembrolizumab is approved as second-line therapy for those whose tumors express PD-L1 >1%.

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Matthew A. Gubens, MD, MS, Assistant Clinical Professor of Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, discussed the past, present, and future of immunotherapies for non–small cell lung cancer (NSCLC) at the NCCN 22nd Annual Conference.

"Immunotherapy is not a new idea. It was proposed by William B. Coley, MD, in 1893 as a treatment for cancer. Today, we have immunotherapies directed against PD-1 [programmed death], PD-L1 [programmed death ligand-1], and CTLA-4," he stated.

The first PD-1 inhibitor was approved by the FDA in 2014 for advanced melanoma in patients who had exhausted other therapies. Since then, checkpoint inhibitors have also been approved for use in NSCLC.

"Looking at somatic mutations that lead to carcinogenesis, the expectation was that treatments that are effective in melanoma could be active in lung cancer," Dr. Gubens explained.

In 2015, the first PD-1 inhibitor (nivolumab) was approved for the treatment of NSCLC. Approval was based on CheckMate 057, a phase III study that compared nivolumab versus docetaxel in nonsquamous NSCLC after failure of first-line, platinum-based therapy. The study showed improved response rates with nivolumab, longer duration of response (median, 17 vs 5.6 months with docetaxel), and improved overall survival (OS; median, 12.2 vs 9.4 months, respectively).[1]

The data suggested that PD-L1 expression could be a marker of response. However, patients whose tumors did not express PD-L1 fared similarly on docetaxel and nivolumab, thus suggesting that nonexpressers can also respond to nivolumab.

Pembrolizumab was shown to be more effective than docetaxel in a selected population of patients with PD-L1 expression of ≥1%. Markedly improved survival was observed in patients with PD-L1 expression levels of >50% who were treated with second-line pembrolizumab. Median OS for all patients was 10.4 months with 2 mg/kg of pembrolizumab and 12.7 months with 10 mg/kg of pembrolizumab versus 8.5 months for docetaxel (P=.008 and P<.0001, respectively, vs docetaxel). For PD-L1, in >50% patients, median OS was 14.9 months with 2 mg/kg of pembrolizumab and 17.3 months for 10 mg/kg of pembrolizumab versus 8.2 months for docetaxel (P=.002 and P<.0001, respectively, vs docetaxel). Duration of response was not reached in the pembrolizumab group versus 6 to 8 months for docetaxel. Grade 3 through 5 adverse events (AEs) were less common with pembrolizumab (13% for the 2 mg/kg dose; 16% for 10 mg/kg dose) versus docetaxel (35%) (Figure 1).[2] Pembrolizumab was approved as second-line treatment.

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OAK was the first phase III trial to evaluate a PD-L1 inhibitor, atezolizumab, versus docetaxel as second- or third-line therapy in unselected patients with NSCLC.[3] Atezolizumab significantly improved survival (*P*=.003), regardless of PD-L1 expression level, including in those with no expression. Atezolizumab was added to the 2017 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC as a second-line option based on this trial.

"When comparing immunotherapy checkpoint inhibitors to chemotherapy, the vast majority of patients have superior tolerability," Dr. Gubens said.

The rates of commonly reported side effects with chemotherapy are much lower with immunotherapy (eg, nausea, fatigue), and when they do occur, are typically less than grade 3. Immunotoxicity, however, is associated with checkpoint inhibitors. Most of the immune-related AEs are due to inflammation of organ systems and end in "-itis." They are relatively uncommon, but can be serious when they occur, and oncologists need to be aware of potential immunotoxicity and know how to treat it.[2]

Take-home messages for the second-line use of PD-1 inhibitors are as follows: nivolumab, pembrolizumab, and atezolizumab all have a similar magnitude of benefit compared with chemotherapy, they have similar toxicities, and are all category 1 recommendations in the 2017 NCCN Guidelines. Nivolumab is approved as second-line therapy for all patients, regardless of PD-L1 expression level; pembrolizumab is approved as second-line treatment for patients whose tumors express >1% of PD-L1; and atezolizumab is approved as second-line therapy for all patients. Nivolumab is given every 2 weeks, and pembrolizumab and atezolizumab are given every 3 weeks.

Immunotherapy is less toxic than chemotherapy, but does have toxicity. Most patients tolerate anti–PD-1 and anti–PD-L1 therapy better than chemotherapy, but virtually any organ can become inflamed while receiving immunotherapy.

For patients on a checkpoint inhibitor, oncologists should have a low threshold for ordering a chest scan to check for pneumonitis and should order

	Pembrolizumab 2 mg/kg (n=339)		Pembrolizumab 10 mg/kg (n=343)		Docetaxel (n=309)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Related to treatment*						
Any	215 (63%)	43 (13%)	226 (66%)	55 (16%)	251 (81%)	109 (35%)
Occurring in ≥10% of patients in any group						
Decreased appetite	46 (14%)	3 (1%)	33 (10%)	1 (<1%)	49 (16%)	3 (1%)
Fatigue	46 (14%)	4 (1%)	49 (14%)	6 (2%)	76 (25%)	11 (4%)
Nausea	37 (11%)	1 (<1%)	31 (9%)	2 (1%)	45 (15%)	1 (<1%)
Rash	29 (9%)	1 (<1%)	44 (13%)	1 (<1%)	14 (5%)	0 (0%)
Diarrhoea	24 (7%)	2 (1%)	22 (6%)	0 (0%)	56 (18%)	7 (2%)
Asthenia	20 (6%)	1 (<1%)	19 (6%)	2 (1%)	35 (11%)	6 (2%)
Stomatitis	13 (4%)	0 (0%)	7 (2%)	1 (<1%)	43 (14%)	3 (1%)
Anaemia	10 (3%)	3 (1%)	14 (4%)	1 (<1%)	40 (13%)	5 (2%)
Alopecia	3 (1%)	0 (0%)	2 (1%)	0 (0%)	101 (33%)	2 (1%)
Neutropenia	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	44 (14%)	38 (12%)
Of special interest occurring in ≥2 patients in the pembrolizumab groups†						
Hypothyroidism	28 (8%)	0 (0%)	28 (8%)	0 (0%)	1 (<1%)	0 (0%)
Pneumonitis‡	16 (5%)	7 (2%)	15 (4%)	7 (2%)	6 (2%)	2 (1%)
Hyperthyroidism	12 (4%)	0 (0%)	20 (6%)	1 (<1%)	3 (1%)	0 (0%)
Colitis	4 (1%)	3 (1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)
Severe skin reactions	4 (1%)	3 (1%)	7 (2%)	6 (2%)	2 (1%)	2 (1%)
Pancreatitis§	3 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adrenal insufficiency	2 (1%)	0 (0%)	3 (1%)	1 (<1%)	0 (0%)	0 (0%)
Myositis	2 (1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Thyroiditis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Autoimmune hepatitis	1 (<1%)	1 (<1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Hypophysitis	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Type 1 diabetes	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)

Superior tolerability compared to chemo

Immune-related toxicity is unique

Figure 1. Safety of PD-1 inhibitors.
Modified from Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. Lancet 2016;387:1540–1550. Reprinted with permission from Elsevier ©2016.

regular thyroid function tests to detect hypothyroidism or hyperthyroidism, and to be aware of a long list of other potential "-itises." When immunotoxicity occurs, they should consider the use of corticosteroids and other immune modulators and make use of consultants in endocrinology, rheumatology, pulmonology, and others as appropriate.

First-Line Checkpoint Inhibitor Therapy

Two first-line trials were presented at ESMO 2016: pembrolizumab versus chemotherapy in patients with PD-L1 expression levels ≥50% and nivolumab versus chemotherapy in PD-L1 expression levels of >5%. The pembrolizumab trial was positive, whereas the nivolumab trial was negative.

KEYNOTE-024 compared first-line pembrolizumab versus platinum doublet in 1,653 patients with PD-L1 expression levels of ≥50%. Patients had no activating *EGFR* mutation or *ALK* rearrangement, and crossover was allowed at disease progression. Approximately 30% (n=500) had PD-L1 expression levels of >50%. There was a clear separation of the progression-free survival curves based on PD-L1 expression in patients treated with pembrolizumab. Patients whose tumors expressed high levels of PD-L1 had significantly improved survival (*P*=.005), and the Data Monitoring and Safety Committee recommended stopping the trial; 44% of patients crossed over to pembrolizumab.[4]

"There was a clear survival benefit to using pembrolizumab in the first line in patients with PD-L1 expressions levels ≥50%. Objective response rate eclipsed that of platinum-based chemotherapy," Dr. Gubens said. "A benefit to pembrolizumab was seen across all subgroups."

By contrast, the second study showed no benefit to first-line nivolumab versus chemotherapy in patients with PD-L1 expression levels of >5% or in PD-L1 expression levels of >50%.[5]

The 2017 NCCN Guidelines[6] state that pembrolizumab is a category 1 recommendation for first-line therapy in patients whose tumors express PD-L1 at levels ≥1% with no known *EGFR*, *ALK*, or *ROS1* mutations. If patients experience disease progression on pembrolizumab, they should be treated with subsequent chemotherapy as per first-line recommendations for nonexpressers. If chemotherapy is used in the first line, then nivolumab, pembrolizumab, and atezolizumab can be used in the second-line.

The Future

Every drug company developing PD-1 and PD-L1 inhibitors also has a proprietary PD-L1 test. Three out of 4 of these tests appear to be concordant, but SP142 is discordant for patients with lung cancer and may undercall eligibility for first-line pembrolizumab. The future is moving toward more sophisticated biomarkers, Dr. Gubens said.

"There are a lot more savvy approaches being studied for biomarkers," he stated. "None of the clinicians who treat with checkpoint inhibitors think that PD-L1 is the 'be all and end all' of biomarkers. Stay tuned!"

Approximately 20% of patients will experience response to immunotherapy in second-line treatment, and approximately 40% in first-line treatment. Combinations of immunotherapy drugs, such as nivolumab and ipilimumab, and combinations of checkpoint inhibitors with chemotherapy are being studied, with robust phase III data due to be mature in the next year, with early data suggesting the combinations may well have higher response rates and durations of response.

Caveats with the combination approach include the need for steroids with some chemotherapies, which induce a general immunosuppressive state.

"These are early days. We have to think about responses differently with immunotherapy. We are beginning to understand how the immune system acts against cancer, at each step, with stimulatory and inhibitory factors, many of which are targetable. We can begin to think about using immunotherapies in rationally designed combinations," he said, looking past the current PD-1/CTLA4 combinations to novel agents going forward.

Take-home messages about the future include staying tuned for immunotherapy/chemotherapy combinations, immunotherapy/immunotherapy combinations, and earlier-stage use of immunotherapy. Clinical trials will pave the way.

"These are expensive drugs. This galvanizes us to be mindful about how we use these drugs. Optimizing them in better combinations and better patient selection may yield superior value by providing a meaningful improvement in survival," Dr. Gubens stated.

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