INTERVIEW

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Tracks 1-16

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DR LOVE: Would you discuss your perspective on the rapidly emerging role of checkpoint inhibitors in the treatment of lung cancer?

DR GOLDBERG: The initial approvals of nivolumab and pembrolizumab were in melanoma, but now the PD-1 and PD-L1 inhibitors are being developed for multiple cancer types, and we're seeing astonishing Phase III data with some of these agents.

Nivolumab was recently approved for patients with squamous cell lung cancer on the basis of a trial comparing that antibody to docetaxel in the second-line setting after disease progression on a platinum-based doublet (Brahmer 2015; [3.1]). At ASCO this year we heard the results of a similar trial that enrolled patients with nonsquamous cell lung cancer, and again the data are promising with a survival benefit, but nivolumab has not yet been approved in that setting (Paz-Ares 2015; [3.2]).

Editor's note: Subsequent to this interview, on October 2, 2015, the FDA granted accelerated approval to pembrolizumab for patients with previously treated metastatic NSCLC with PD-L1 expression. On October 9, 2015, the FDA expanded approval for nivolumab to include patients with metastatic nonsquamous NSCLC and disease progression during or after platinum-based chemotherapy.

DR LOVE: What kind of response rate, duration of response and side effects have been observed with anti-PD-1 antibodies?

DR GOLDBERG: The response rates are better with nivolumab than with docetaxel, but they're still lower than many people would like, at approximately 20%. The duration of response is exciting, with many patients living several years, and this is in the setting of heavily pretreated disease.

Another astonishing feature of these agents is that many patients experience no or limited toxicity. The potential challenge is that when patients do develop toxicity, it can be in the form of side effects that we typically don't see, including endocrinopathies like thyroid dysfunction and adrenal insufficiency. I recently saw a patient who was experiencing nonspecific symptoms, was fatigued and was not eating well. It was

3.1

CheckMate 017: Efficacy and Safety Results from a Phase III Trial of Nivolumab versus Docetaxel for Patients with Advanced Squamous Non-Small Cell Lung Cancer After Disease Progression on 1 Platinum-Based Chemotherapy Regimen

Outcome	Nivolumab (n = 135)	Docetaxel (n = 137)	Hazard ratio	*p*-value
Median OS	9.2 months	6.0 months	0.59	<0.001
Median PFS	3.5 months	2.8 months	0.62	<0.001
ORR*	20%	9%	NR	0.008
Select adverse events	**Nivolumab** (n = 131)		**Docetaxel** (n = 129)	
	All grades	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Fatigue	16%	1%	33%	8%
Nausea	9%	0%	23%	2%
Diarrhea	8%	0%	20%	2%
Pneumonitis	5%	0%	0%	0%
Arthralgia	5%	0%	7%	0%
PN	1%	0%	12%	2%
Neutropenia	1%	0%	33%	30%
Febrile neutropenia	0%	0%	11%	10%

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; NR = not reported; PN = peripheral neuropathy * Odds ratio: 2.6

Brahmer J et al. *N Engl J Med* 2015;373(2):123-35.

3.2

CheckMate 057: Efficacy Results of a Phase III Trial of Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small Cell Lung Cancer

	Nivolumab (n = 292)	Docetaxel (n = 290)	Hazard ratio	*p*-value
Median OS	12.2 months	9.4 months	0.73	0.002
Median PFS	2.3 months	4.2 months	0.92	0.3932
ORR*	56 (19%)	36 (12%)	—	0.02
Complete response	4 (1%)	1 (<1%)	—	—
Partial response	52 (18%)	35 (12%)	—	—
Stable disease	74 (25%)	122 (42%)	—	—
Median time to response	2.1 months	2.6 months	—	—
Median duration of response	17.2 months	5.6 months	—	—

OS = overall survival; PFS = progression-free survival; ORR = objective response rate

* Odds ratio = 1.72

Paz-Ares L et al. *Proc ASCO* 2015;**Abstract LBA109**; Borghaei H et al. *N Engl J Med* 2015;373(17):1627-39.

a notable difference from only a few weeks before, and her cortisol level was undetectable. You need to keep this in mind because it's so different than with chemotherapy. Checking a patient's cortisol level is not something we usually consider doing.

Pneumonitis, hepatitis and colitis have been problematic in some patients. Now that we are more aware that pneumonitis is a potentially life-threatening issue, we've become aggressive in testing for it even if it's only a remote possibility and then treating it with steroids.

Colitis is less common than it is with the anti-CTLA-4 antibodies, but it's possible, especially when we start combining different immunotherapies. Any organ system can be affected by these agents. Some patients develop skin toxicities, although these are manageable with oral steroids or IV steroids in certain cases.

DR LOVE: Do you stop treatment with a PD-1 or PD-L1 inhibitor after a certain period? Have you seen patients who stopped treatment on a trial and demonstrated continued responses?

DR GOLDBERG: The first question does not have an answer yet. Some patients on trials receive treatment for 1 year and then stop, and many trials allow re-treatment at disease progression. Some trials administer treatment for 2 years and then stop, and still others use continuous treatment until disease progression or toxicity. So it's unclear how long to administer treatment off trial.

We do see patients with sustained responses. In the trials that require stopping treatment after 1 or 2 years, several patients have continued to demonstrate responses for years after. But it's too early to know the right duration of treatment. With such minimal toxicity, it's tempting to continue treatment, but then the issue of cost arises.

These drugs are expensive. Do you continue treatment forever even if someone might experience a sustained benefit without it? Hopefully, with more data we will understand what's happening after treatment is stopped and whether rechallenging after disease progression is beneficial.

DR LOVE: What do we know about anti-PD-L1 antibodies and how they compare to anti-PD-1 antibodies?

DR GOLDBERG: In many ways the mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies are similar. By inhibiting either the ligand or the receptor, you're preventing the interaction between PD-1 and PD-L1. But because the immune system is complicated, other interactions are also being inhibited by each agent, and that's where the potential differences in benefit and toxicity come into play.

We're starting to learn more about the anti-PD-L1 antibodies, such as atezolizumab, but the trials are not as far along as those with the anti-PD-1 antibodies. The data appear promising (Spira 2015; [3.3]), although it is difficult to distinguish whether one agent is better than another. They do seem to be tolerable — based on the biology of the immune system, perhaps even more tolerable than the anti-PD-1 antibodies, but it is difficult to draw conclusions from the trials. ■

3.3

POPLAR: A Randomized Phase II Study Comparing Atezolizumab (MPDL3280A) to Docetaxel for Previously Treated Advanced Non-Small Cell Lung Cancer

Outcome	Atezolizumab (n = 144)	Docetaxel (n = 143)	Hazard ratio	*p*-value
Median OS	11.4 mo	9.5 mo	0.77	0.11
TC3 or IC3 (n = 24, 23)	NR	11.1 mo	0.46	0.070
TC2/3 or IC2/3 (n = 50, 55)	13 mo	7.4 mo	0.56	0.026
TC1/2/3 or IC1/2/3 (n = 93, 102)	NR	9.1 mo	0.63	0.024
TC0 and IC0 (n = 51, 41)	9.7 mo	9.7 mo	1.12	0.70
Median PFS	2.8 mo	3.4 mo	0.98	—
ORR	15%	15%	—	—
Safety summary	**Atezolizumab** (n = 142)		**Docetaxel** (n = 135)	
Median treatment duration	3.7 mo		2.1 mo	
All-grade AEs, any cause	97%		96%	
Grade 3-4 AEs, any cause	39%		52%	
Withdrawal from treatment due to AEs	8%		22%	

OS = overall survival; TC3 or IC3 = tumor cells ≥50% or immune cells ≥10% PD-L1-positive; NR = not reached; TC2/3 or IC2/3 = TC or IC ≥5% PD-L1-positive; TC1/2/3 or IC1/2/3 = TC or IC ≥1% PD-L1-positive; TC0 and IC0 = TC and IC <1% PD-L1-positive; PFS = progression-free survival; ORR = overall response rate; AEs = adverse events

With atezolizumab, immune-related AEs included increased AST (4%), increased ALT (4%), pneumonitis (2%), colitis (1%) and hepatitis (1%).

Spira AI et al. *Proc ASCO* 2015;**Abstract 8010**.

SELECT PUBLICATIONS

Brahmer J et al. **Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer.** *N Engl J Med* 2015;373(2):123-35.

Spira AI et al. **Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR).** *Proc ASCO* 2015;**Abstract 8010**.