INTERVIEW

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Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: What do we currently know about predictors of response for immune checkpoint inhibitors in lung cancer, and how does PD-L1 positivity tie in with response to anti-PD-1 treatment?

DR RIZVI: Predictors of response are becoming increasingly helpful. Smoking history is emerging as somewhat of a useful predictor in that smokers seem more likely to respond (Soria 2013). The main predictor that we're trying to understand is expression of PD-L1 (Garon 2014; Horn 2013). The notion is that if you have high levels of PD-L1, that means that you have a lot of inhibition of T cells within that tumor microenvironment and that may correlate with how dependent that tumor is on PD-1 inhibition.

For clinical trials administering an immune checkpoint inhibitor as first-line treatment for lung cancer, the bar is higher because the patients are more chemo-responsive. You want to enrich for likelihood of response, and I believe that the data that have been presented were favorable in terms of response rate with anti-PD-1 agents as first-line therapy for patients with PD-L1-positive disease (Garon 2014; Gettinger 2014; [4.1]). Both pembrolizumab and nivolumab are being studied in Phase III randomized trials as first-line therapy for patients with PD-L1-positive NSCLC (4.2).

4.1

Antitumor Activity of Anti-PD-1 Agents as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

	Pembrolizumab[1] (n = 45)	Nivolumab[2] (n = 20)
Overall response rate	26%	30%
Median OS	Not reached	Not reached
6-month OS	86%	Not reported
12-month OS	Not reported	75%
Median PFS	27 weeks	Nonsquamous: 47.2 weeks Squamous: 15.1 weeks
24-week PFS	51%	60%

OS = overall survival; PFS = progression-free survival

[1] Garon EB et al. *Proc ESMO* 2014;**Abstract LBA43**; [2] Gettinger SN et al. *Proc ASCO* 2014;**Abstract 8024**.

4.2

Select Ongoing Phase III Trials of PD-1/PD-L1 Checkpoint Inhibitors in Non-Small Cell Lung Cancer (NSCLC)

Study	Target Accrual	Setting	Randomization
Checkmate 017	264 (closed)	Stage IIIB/IV squamous cell NSCLC after platinum-based chemotherapy	Nivolumab versus docetaxel
Checkmate 057	574 (closed)	Stage IIIB/IV nonsquamous cell NSCLC after platinum-based chemotherapy	Nivolumab versus docetaxel
Checkmate 026	495	Untreated Stage IV EGFR mutation-/ALK-, PD-L1+ NSCLC	Nivolumab versus investigator's choice of chemotherapy
Keynote 010	920	Previously treated PD-L1+ NSCLC	Low or high dose of pembrolizumab versus docetaxel
Keynote 024	300	Previously untreated Stage IV EGFR mutation-/ALK-, PD-L1+ NSCLC	Pembrolizumab versus platinum-based chemotherapy
Keynote 042	1,240	Previously untreated EGFR mutation-/ALK-, PD-L1+ advanced/metastatic NSCLC	Pembrolizumab versus platinum-based chemotherapy

www.clinicaltrials.gov. Accessed November 2014.

When you move to clinical trials in the second-line setting, in which response rates with chemotherapy are in the vicinity of 10%, or third-line therapy, with which activity is even lower, I believe that the requirement for PD-L1 positivity will be less, because if you have a comparable response rate or potentially even a better response rate as second- or third-line therapy, even if the disease is PD-L1-negative, there will be a lot of interest in using these agents. It's much more difficult to develop resistance to immunotherapy than with chemotherapy or targeted therapy, so we are seeing longer-term durable benefits in that subset of patients who experience a response.

Tracks 4-5

DR LOVE: Would you discuss the difference between anti-PD-1 agents and anti-PD-L1 agents and what is known about the relative efficacy and tolerability of these 2 strategies?

DR RIZVI: It's difficult to compare the agents because they are quite different. The response rates for unselected patients seem fairly comparable. Globally, the toxicities are low with all of these agents. Most patients don't feel that they're experiencing any side effects.

The most frequent toxicities include mild instances of pruritus, rash, myalgias and fatigue. We need to monitor these patients carefully for endocrine dysfunction in terms of their thyroid function test or, if patients are developing any symptoms of adrenal insufficiency, monitor their ACTH and cortisol levels. Thyroid function abnormalities are common. Adrenal insufficiency is fairly uncommon. But you have to be alert to these possibilities and introduce replacement thyroid hormone as needed. We don't see much colitis and transaminase elevation like we do with anti-CTLA-4 therapy.

The PD-L1 inhibitors might carry less risk of pneumonitis, which is something that people using these agents need to be mindful of. I have a low threshold to order a noncontrast chest CT scan for patients who develop increasing cough, shortness of breath or may be desaturating a bit on their oxygen saturation measures to ensure that we're not dealing with pneumonitis.

It's also important to note that if you observe radiologic abnormalities, they do not need to be bilateral like those we see with typical drug toxicities and bilateral inflammation. Often you may see only patchy infiltrate in the left or right lower lobe. The key is to act on those findings quickly, usually by managing with corticosteroids. We typically admit patients who are more sick or who are developing hypoxia to administer high-dose steroids.

We also allow for a longer tapering course of therapy than we would for perhaps radiation-related pneumonitis or chemotherapy-related pneumonitis, because T cells continue to be active, even without therapy, for a longer period of time. We taper treatment for these patients slowly and are alert to recrudescence of pneumonitis when the agent is stopped. By and large, we're fairly leery of re-treatment for those patients who develop pneumonitis on immunotherapy.

Track 7

DR LOVE: What are your thoughts on combining immunotherapies with other systemic agents in NSCLC?

DR RIZVI: We love that patients achieve a 15% to 20% response rate and durable responses with single-agent immune checkpoint inhibitor therapy, but we are also excited about the combination trials. Some of these include combining anti-CTLA-4 and anti-PD-1 or anti-PD-L1 agents. Trials are under way evaluating ipilimumab and nivolumab (Antonia 2014; [4.3]) in addition to tremelimumab and MEDI4736 (Pinder 2014). I consider immunotherapy similar to where we were 30 years ago with cisplatin as a backbone therapy, and with time we've been able to build on it and do better. The benefits of adding therapy may not be incremental, but hopefully they'll be bigger.

4.3

Interim Results of a Phase I Trial of Nivolumab (N) with Ipilimumab (I) as First-Line Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)*

	N 1 mg/kg + I 3 mg/kg		N 3 mg/kg + I 1 mg/kg	
	Nonsquamous (n = 15)	Squamous (n = 9)	Nonsquamous (n = 16)	Squamous (n = 9)
ORR	13%	11%	13%	33%
Stable disease	33%	22%	25%	56%

- Any-grade treatment-related adverse events (AEs) reported in 88% of patients
- Grade 3 or 4 treatment-related AEs reported in 49% of patients
- AEs led to discontinuation of treatment in 35% of patients
- Treatment-related deaths included respiratory failure (n = 1), bronchopulmonary hemorrhage (n = 1) and toxic epidermal necrolysis (n = 1).

* Patients with chemotherapy-naïve nonsquamous or squamous NSCLC (n = 49) received the 3+1 mg/kg or the 1+3 mg/kg combination dose, q3w IV for 4 cycles followed by nivolumab 3 mg/kg q2w IV until disease progression or unacceptable toxicity.

ORR = overall response rate

Antonia SJ et al. *Proc ASCO* 2014;**Abstract 8023**.

The list is growing in terms of potential combination immunotherapies and also combinations of immunotherapy with small molecules. We also presented data on the combination of erlotinib and nivolumab at ASCO 2014 and reported an approximately 20% durable response rate in patients with EGFR-mutant advanced NSCLC (Rizvi 2014).

Patients who are never smokers typically don't respond as well to checkpoint inhibitors. Patients with EGFR mutations are typically never smokers, but it's possible that the combination or possible upregulation of PD-L1 by erlotinib in acquired resistance may be a patient population in which we can use these TKIs and antibodies in combination effectively. ■

SELECT PUBLICATIONS

Antonia SJ et al. **Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results.** *Proc ASCO* 2014;**Abstract 8023**.

Garon EB et al. **Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients with advanced NSCLC.** *Proc ESMO* 2014;**Abstract LBA43**.

Gettinger SN et al. **First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status.** *Proc ASCO* 2014;**Abstract 8024**.

Horn L et al. **An analysis of the relationship of clinical activity to baseline EGFR status, PD-L1 expression and prior treatment history in patients with non-small cell lung cancer (NSCLC) following PD-L1 blockade with MPDL3280A (anti-PDL1).** *Proc WCLC* 2013;**Abstract MO18.01**.

Pinder MC et al. **A phase 1b open-label study to evaluate the safety and tolerability of MEDI4736, an anti–PD-L1 antibody, in combination with tremelimumab in subjects with advanced non–small cell lung cancer.** *Proc ASCO* 2014;**Abstract e19137**.

Rizvi NA et al. **Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014;**Abstract 8007**.

Soria JC et al. **Clinical activity, safety and biomarkers of PD-L1 blockade in non-small cell lung cancer (NSCLC): Additional analyses from a clinical study of the engineered antibody MPDL3280A (anti-PDL1).** *Proc ECC* 2013;**Abstract 3408**.