INTERVIEW

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Tracks 1-12

Track 1 Immune checkpoint blockade strategies — CTLA4 inhibition, anti-PD-1 and anti-PD-L1 monoclonal antibodies

Track 2 Mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies

Track 3 Anti-PD-1-associated pneumonitis and colitis

Track 4 **Case discussion:** An 85-year-old patient with EGFR and ALK wild-type, KRAS mutation-positive metastatic adenocarcinoma of the lung experiences a considerable response to nivolumab on a clinical trial before discontinuing therapy because of an allergic reaction

Track 5 Investigation of the novel ALK inhibitor X-396 in patients with advanced solid tumors

Track 6 Mechanisms of action of approved and novel ALK inhibitors in NSCLC

Track 7 **Case discussion:** A former smoker who previously received treatment 8 years ago for Stage IV adenocarcinoma of the lung and is now undergoing X-396 therapy for crizotinib-resistant disease

Track 8 Efficacy of second-generation ALK inhibitors in crizotinib-resistant, ALK-positive NSCLC with CNS metastases

Track 9 **Case discussion:** A 59-year-old former smoker who received adjuvant cisplatin/pemetrexed for Stage IIIA adenocarcinoma with an EGFR exon 19 deletion

Track 10 Tolerability of novel third-generation EGFR inhibitors

Track 11 Acquired resistance of EGFR-mutant adenocarcinoma of the lung to afatinib/cetuximab is associated with activation of mTORC1

Track 12 Dealing with stress and burnout in the practice of oncology

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What are your thoughts on the emerging data with immune checkpoint inhibitors for the treatment of lung cancer?

DR HORN: Inhibitors of immune checkpoint pathways are changing the way we think about immunotherapy in lung cancer. Ipilimumab, an antibody to CTLA4, has demonstrated promising results in combination with chemotherapy.

Phase II trials investigating the addition of ipilimumab to chemotherapy in both small cell lung cancer (SCLC) and NSCLC have demonstrated encouraging results with a phased regimen of chemotherapy followed by ipilimumab and chemotherapy (Reck 2013; Lynch 2012). Two large Phase III trials in SCLC and NSCLC evaluating this regimen of ipilimumab and chemotherapy versus chemotherapy have recently closed, and we're awaiting those results.

I believe that PD-1/PD-L1 inhibitors are some of the most exciting drugs that we have in lung cancer currently. In contrast to CTLA4 inhibitors, they have single-agent activity. So the toxicities from chemotherapy can be eliminated with these agents. The response rates of around 20% to 30% are much higher than those with chemotherapy.

Response rates are higher for patients whose tumors are positive for PD-L1 expression. Interestingly, however, responses are also observed in patients with tumors that are PD-L1-negative, so we don't yet fully understand which patients will benefit most from these drugs.

What is impressive is that when these inhibitors are effective, responses are durable. Some patients on the early Phase I trials who have finished 2 years of treatment with the anti-PD-1 inhibitors have not required re-treatment more than 18 months later. This is unheard of in lung cancer.

DR LOVE: What is the mechanism of action of PD-1/PD-L1 inhibitors?

DR HORN: The interaction of PD-1 with its ligands PD-L1/L2 prevents overactivation of T cells and dampens the immune response. PD-1/PD-L1 inhibitors work in the tumor microenvironment to block this interaction and maintain T-cell activity against tumor cells.

I believe that in terms of efficacy, the PD-1 and PD-L1 inhibitors are similar. The big difference between the PD-1 and PD-L1 inhibitors is that whereas anti-PD-1 antibodies inhibit the interaction between PD-1 and its ligands PD-L1 and PD-L2, the anti-PD-L1 antibodies do not inhibit PD-L2 expressed on lung cells. The risk of pneumonitis is lower with anti-PD-L1 antibodies compared to anti-PD1 antibodies. Cases of severe or fatal pneumonitis have not been observed with the anti-PD-L1 antibodies.

DR LOVE: Would you comment on the side effects reported with the PD-1/PD-L1 inhibitors?

DR HORN: A few cases of pneumonitis have been reported with these agents. The risk of severe pneumonitis that requires intervention and therapy is less than 5%. It is important to educate patients that pneumonitis may occur. We tell patients that if they develop coughing or shortness of breath and have difficulty breathing, they should go to the emergency room. Early administration of steroids is key to managing pneumonitis.

Colitis is the other severe toxicity associated with these agents, but it is not common. Early intervention is also important in managing colitis. A side effect that we have observed quite commonly is hypothyroidism, so we routinely monitor thyroid function.

The toxicities with PD-1/PD-L1 inhibitors are less severe than those observed with ipilimumab. Overall, the side effects associated with these agents are easier to tolerate than those with chemotherapy.

Track 5

DR LOVE: Would you discuss the recent data with the novel second-generation ALK inhibitors?

DR HORN: Crizotinib is an effective ALK inhibitor but does not have good CNS penetration. It elicits about a 70% response rate in patients who have ALK-positive lung cancer, but about half of those patients will develop disease progression in the brain.

The second-generation ALK inhibitor ceritinib was recently approved for patients with ALK-positive metastatic NSCLC that is resistant to or for those who are intolerant to crizotinib. At ASCO this year, data were presented that reported a response rate of more than 50% in patients with ALK-rearranged NSCLC. What was also impressive is that ceritinib demonstrated activity in some patients with brain metastases (Kim 2014; [3.1]).

Ceritinib is associated with a fairly high rate of gastrointestinal toxicities that can affect patient quality of life. That may be significant if we see that other second-generation inhibitors that do not have the same toxicity profiles yield similar responses.

We were excited to open a Phase I trial of X-396, another second-generation ALK inhibitor. Durable responses to X-396 were observed (Horn 2014; [3.2]). The trial has only enrolled about 35 patients so far, and not all patients have ALK-positive disease. In the expansion study we are only enrolling patients with ALK-positive NSCLC.

3.1

Phase I ASCEND-1 Trial: Ceritinib in Advanced ALK-Rearranged Non-Small Cell Lung Cancer

Efficacy	ALK inhibitor treated	ALK inhibitor naïve	Overall
All patients (n = 163, 83, 246)			
Overall response rate	54.6%	66.3%	58.5%
Complete response	1.2%	1.2%	1.2%
Partial response	53.4%	65.1%	57.3%
Patients with brain metastases at baseline (n = 98, 26, 124)			
Overall response rate	50.0%	69.2%	54.0%

Select adverse events (n = 255)	Any grade	Grade 3/4
Diarrhea	86%	6%
Nausea	80%	4%
Vomiting	60%	4%
Fatigue	52%	5%
Elevated ALT	80%	27%
Elevated AST	75%	13%

Kim D et al. *Proc ASCO* 2014;**Abstract 8003**.

Track 11

DR LOVE: You were part of a group that recently published a paper titled "Acquired resistance of EGFR mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1" (Pirrazoli 2014). Would you discuss some of the work by your colleague William Pao that led to the concept of combining afatinib and cetuximab?

DR HORN: Dr Pao previously reported that the combination of afatinib and cetuximab was superior to either agent alone in mice with L858R and T790M mutations. These data led to a large Phase Ib trial of afatinib and cetuximab for patients with EGFR-mutant NSCLC and acquired resistance to EGFR TKIs. The rate of disease control and responses in both T790M-positive and T790M-negative disease was fairly high (Janjigian 2012).

3.2

Phase I Trial of X-396, a Novel ALK Inhibitor, for Patients with Advanced Solid Tumors

Efficacy	(n = 11)*
Partial response	55%
Stable disease	18%

- Responses were observed in patients with crizotinib-naïve disease and disease resistant to crizotinib.
- Responses were observed in 2 patients with CNS metastases.

Select adverse events (n = 35)	Any grade	Grade 3/4
Nausea	31%	0%
Rash	31%	6%
Vomiting	29%	0%
Fatigue	26%	0%
Edema	17%	0%
Pruritus	11%	3%

* ALK-positive evaluable disease

Horn L et al. *Proc ASCO* 2014;**Abstract 8030**.

The recent paper demonstrating mTORC1 as a mechanism of resistance to afatinib and cetuximab came out of a collaboration with Yale. Many were interested in determining why the combination was effective in patients with T790M-negative disease. Studies have shown that HER2 amplification is one mechanism of acquired resistance to EGFR TKIs (Takezawa 2012). This may explain the efficacy of afatinib, a HER2 inhibitor, in patients with T790M-negative disease.

Two large trials are being launched through the cooperative groups. A trial coordinated by SWOG will compare afatinib to the combination of afatinib and cetuximab as first-line therapy for patients with EGFR-mutant NSCLC. A proposed trial in the second-line setting through ECOG will compare afatinib to afatinib and cetuximab in patients with EGFR-mutant NSCLC who have acquired resistance to EGFR TKIs. ■

SELECT PUBLICATIONS

Janjigian Y et al. **Activity of afatinib/cetuximab in patients (pts) with EGFR mutant non-small cell lung cancer (NSCLC) and acquired resistance (AR) to EGFR inhibitors.** *Proc ESMO* 2012;**Abstract 1227O**.

Kim D et al. **Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial.** *Proc ASCO* 2014;**Abstract 8003**.

Lynch TJ et al. **Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study.** *J Clin Oncol* 2012;30(17):2046-54.

Pirazzoli V et al. **Acquired resistance of EGFR-mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1.** *Cell Rep* 2014;7(4):999-1008.

Reck M et al. **Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase 2 trial.** *Ann Oncol* 2013;24(1):75-83.

Takezawa K et al. **HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation.** *Cancer Discov* 2012;2(10):922.