INTERVIEW

Nasser H Hanna, MD

Dr Hanna is Associate Professor of Medicine at Indiana University in Indianapolis, Indiana.

Tracks 1-11

Track 1 **Case discussion:** A 55-year-old woman who initially received treatment for pan-wild-type adenocarcinoma of the lung found upon rebiopsy to harbor an ALK rearrangement receives crizotinib

Track 2 Appropriate use of next-generation sequencing

Track 3 Clinical experience with the next-generation ALK inhibitor ceritinib in crizotinib-naïve and crizotinib-resistant advanced NSCLC

Track 4 Approach to choice of maintenance regimen for patients with pan-wild-type adenocarcinoma of the lung

Track 5 Overall survival advantage with the recently FDA-approved anti-PD-1 agent nivolumab as compared to docetaxel for patients with advanced squamous NSCLC with disease progression on or after platinum-based chemotherapy

Track 6 **Case discussion:** A 44-year-old woman and heavy smoker with Stage IV squamous cell carcinoma (SCC) of the lung with disease progression on carboplatin/gemcitabine experiences a dramatic response to nivolumab

Track 7 Activity of nivolumab in adenocarcinoma of the lung

Track 8 Investigation of anti-PD-1 agents as first-line therapy in lung cancer

Track 9 Potential biomarkers for anti-PD-1 benefit

Track 10 Ongoing and planned clinical trials combining anti-PD-1/anti-PD-L1-based therapy with chemotherapy and/or radiation therapy

Track 11 Pros and cons of second-line therapy options (nivolumab versus ramucirumab/docetaxel versus docetaxel alone) for SCC of the lung

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you describe the current methodology for ALK testing and whether patients can be classified as ALK wild type initially but then be found to harbor an ALK rearrangement on rebiopsy?

DR HANNA: We have 3 methods to test for ALK. You can use immunohistochemistry, but that method is not validated nor FDA approved at this point. The gold standard is FISH. A FISH score of 0 obviously indicates ALK negativity. A score of 2+ or 3+ is almost always indicative of ALK positivity. A 1+ is more than likely negative, but a few ALK-positive cases have this score. You can perform PCR, but you may miss the fusion partner, and ALK has multiple partners. EML4 is the most common partner, but others exist.

DR LOVE: How do the available NGS platforms come into play here?

DR HANNA: Several NGS platforms are available. The most commonly used is FoundationOne®. We also use the PCDx™ test. All of these testing platforms claim some advantages compared to others. The company that makes FoundationOne has suggested that more ALK abnormalities are found than with other platforms, but we do not have any head-to-head comparisons. It's interesting that one platform may be better at detecting more of these ALK changes or EGFR mutations than others. This may contribute to a possible bias of some of the results.

DR LOVE: Is it reasonable to perform NGS testing on a biopsy sample from a nonsmoker that tested negative for EGFR mutations and ALK rearrangements by FISH analysis?

DR HANNA: Yes. That approach may lead to the discovery of mutations other than ALK. I have had a number of patients for whom such an approach paid off.

Track 3

DR LOVE: What are your thoughts on the next-generation ALK inhibitors, such as ceritinib? Where are these agents headed in the management of lung cancer?

DR HANNA: Ceritinib is now FDA approved for the treatment of ALK-positive metastatic NSCLC after disease progression on or intolerance to crizotinib. I believe it will also be approved in the up-front setting as it has been tested in pretreated and crizotinib-naïve disease (Kim 2014; [2.1]). It's highly active in both settings, with response rates of more than 50% and 60%, respectively. So, logically, one could conceive that ceritinib would be a more effective ALK inhibitor than crizotinib because it is so active after disease progression on crizotinib. However, a head-to-head comparison is needed to confirm this suggestion.

Ceritinib is a much more potent ALK inhibitor than crizotinib. Although crizotinib is an extremely potent MET inhibitor, it is not nearly as good as an ALK inhibitor. Crizotinib is probably a better ROS1-targeting agent than ceritinib. These drugs have distinct nuances. It's not a one-size-fits-all situation.

It is similar to the story of EGFR inhibitors. Patients with lung cancer receive erlotinib or afatinib if they have activating EGFR mutations. Even though we tend to lump all EGFR activating mutations together, a picture appears to be emerging suggesting that exon 19 and L858R are different, and so is their responsiveness to these agents (Yang 2015).

Ceritinib can be a tough drug, however. Nausea and diarrhea are the dominant, day-to-day side effects. If you hold the drug for 2 to 3 days, the nausea goes away. I've had patients who've experienced a great deal of difficulty tolerating ceritinib, but we've been able to dose reduce and use antiemetics. Because ceritinib is highly active, patients tend to put up with the side effects when they can and continue therapy.

Tracks 5-6

DR LOVE: Perhaps the biggest change in the field of oncology in a long time is the approval of an anti-PD-1 agent in lung cancer. What are your thoughts on the role of immune checkpoint inhibitors in NSCLC?

DR HANNA: We've had advances in lung cancer research with regard to things like the role of chemotherapy in the adjuvant and metastatic settings and the addition of chemo-

2.1

Phase I ASCEND-1 Trial: Efficacy and Safety of Ceritinib in Locally Advanced or Metastatic ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Clinical outcome	All patients (n = 246)	ALKi treated (n = 163)	ALKi naïve (n = 83)
Overall response rate	58.5%	54.6%	66.3%
Complete response	1.2%	1.2%	1.2%
Partial response	57.3%	53.4%	65.1%
Stable disease	6.5%	19.6%	22.9%
Median PFS	8.21 months	6.9 months	NE
12-month PFS	39.1%	28.4%	61.3%

Select AEs (n = 255)*	All grades	Grade 3 or 4
Diarrhea	86%	6%
Decreased hemoglobin	84%	5%
Nausea	80%	4%
Increased ALT	80%	27%
Increased AST	75%	13%
Fatigue	52%	5%
Increased blood glucose	49%	13%

* All patients received the maximum tolerated dose (750 mg/d), including 9 patients with cancers other than NSCLC.

ALKi = ALK inhibitor; PFS = progression-free survival; NE = not estimable; AEs = adverse events

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

therapy to radiation therapy for patients with Stage III disease, but I believe we'd all agree that these were modest advances.

Lung cancer oncologists tend to be more on the understated side. They don't tend to proclaim these huge advances. We can all agree that agents like crizotinib and erlotinib are major advances.

But the data with the anti-PD-1 antibody nivolumab as second-line therapy for squamous NSCLC are practice changing. In my 15 years of taking care of patients with lung cancer, this is the biggest "difference maker" that I've seen yet. The early results of the randomized Phase III CheckMate 017 trial of second-line nivolumab or docetaxel in squamous NSCLC compelled the Data Safety Monitoring Committee to recommend early closure because nivolumab made such a substantial difference (Brahmer 2015; [2.2]).

The hazard ratio for overall survival was 0.59 in favor of nivolumab. We simply don't see that in lung cancer and certainly not in patients with squamous cell carcinoma. Oddly enough, the tumors that have the highest mutational load, that are the most molecularly dirty, perhaps are those in which agents like PD-1/PD-L1 inhibitors will be most active.

We've now administered nivolumab to 30 patients at our center, and so far I have been impressed with the results. Our patients tend to be older in age, with a smoking history and comorbidities. So I was fearful of toxicities such as pneumonitis, colitis, hepatitis, rash, fevers and arthralgias. Surprisingly, I have not observed any Grade 2 or Grade 3 side effects. This is not to say that nivolumab is a totally benign agent. It certainly has side effects, but the patients I have cared for so far have tolerated it remarkably well.

2.2

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

Outcome	Nivolumab (n = 135)	Docetaxel (n = 137)	Hazard ratio (HR)	*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
CR	1%	0%	—	—
PR	19%	9%	—	—
Stable disease	29%	34%	—	—
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%
Asthenia	10%	0%	14%	4%
Nausea	9%	0%	23%	2%
Diarrhea	8%	0%	20%	2%
Pneumonitis	5%	0%	0%	0%
Arthralgia	5%	0%	7%	0%
Rash	4%	0%	6%	2%
Anemia	2%	0%	22%	3%
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; CR = complete response; PR = partial response; PN = peripheral neuropathy

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

However, patients with autoimmune diseases or those with a history of pneumonitis should not receive these agents.

DR LOVE: Would you consider administering immune checkpoint inhibitors in the first-line setting?

DR HANNA: Randomized trials are ongoing with single-agent pembrolizumab (NCT02142738) or nivolumab (NCT02041533) versus chemotherapy in the up-front setting. With second-line nivolumab being much better than docetaxel, it's logical to think that it will be better than chemotherapy up front. The unanswered question is how to use it. Is it going to be better to combine it with chemotherapy? Should it be administered as a single agent before switching to or combining it with chemotherapy at disease progression? Should it be used as maintenance therapy? Although I am optimistic, we still need the data. ■

SELECT PUBLICATION

Yang JC et al. **Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials.** *Lancet Oncol* 2015;16(2):141-51.