INTERVIEW

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Tracks 1-15

Track 1 **Case discussion:** A 45-year-old woman and never smoker with metastatic adenocarcinoma of the lung for whom a next-generation sequencing (NGS) assay identifies a RET rearrangement

Track 2 Use of NGS to identify actionable genomic alterations in patients with adenocarcinoma of the lung otherwise negative for such alterations by other genomic testing

Track 3 Identification of actionable mutations in patients with squamous cell carcinoma (SCC) of the lung

Track 4 Integration of NGS technologies into clinical practice

Track 5 Activity of pemetrexed-based systemic therapy in RET-rearranged non-small cell lung cancer (NSCLC)

Track 6 Results of a Phase II trial of cabozantinib for patients with advanced RET-rearranged NSCLC

Track 7 Perspective on the investigation of RET inhibitors approved for other solid tumors

Track 8 Cabozantinib-associated transaminitis and hypopigmentation

Track 9 **Case discussion:** An 81-year-old woman and never smoker with previously treated recurrent adenocarcinoma of the lung receives crizotinib after NGS identifies a MET exon 14 mutation

Track 10 **Case discussion:** A 57-year-old man and current smoker with BRAF V600E mutation-positive adenocarcinoma of the lung and multiple brain metastases receives dabrafenib monotherapy after postoperative whole brain radiation therapy

Track 11 Activity of dabrafenib alone and in combination with trametinib for patients with BRAF V600E mutation-positive NSCLC

Track 12 **Case discussion:** A 50-year-old woman and never smoker with previously treated metastatic adenocarcinoma of the lung is found to harbor a ROS1 rearrangement and experiences a durable partial response with crizotinib

Track 13 Response to cabozantinib in advanced ROS1-rearranged adenocarcinoma

Track 14 **Case discussion:** A 63-year-old woman and former smoker with recurrent adenocarcinoma of the lung who is found to harbor a HER2 (ERBB2 L755S) point mutation receives neratinib on a clinical trial

Track 15 Clinical experience with HER2-directed therapies for patients with HER2 mutation-positive adenocarcinoma of the lung

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you discuss your recent paper on the use of next-generation sequencing (NGS) to identify actionable genomic alterations in patients with adenocarcinoma of the lung?

DR DRILON: The premise of this paper was to determine how good NGS is as a clinical assay. We enrolled patients with lung adenocarcinoma who were never smokers or light smokers and who had tested negative for alterations in 11 genes, including EGFR, ALK and BRAF, via non-NGS methods. This was a unique population of patients chosen with the intent of trying to enrich the results for potential driver mutations. A broad, hybrid, capture-based NGS was performed on their tumor specimens.

Interestingly, in about 94% of patients who had "pan-negative" disease, a genomic alteration was identified by NGS. Findings included an EGFR mutation and several fusions, including ALK, RET and ROS1. It is difficult to explain why these mutations were not detected by non-NGS methods. NGS detected a driver mutation in 1 out of 4 of these patients for which a targeted therapy was listed in the NCCN Guidelines. We were able to administer targeted therapy to a portion of these patients, and they experienced responses.

In 39% of patients, NGS identified a genomic alteration with a targeted agent available on a clinical trial (Drilon 2015a; [1.1]). A lot of guidance must be provided to clinicians as to which genomic alterations are potentially actionable and for which alterations we might have targeted therapies that are approved or available on protocols.

DR LOVE: What is the likelihood of finding a targetable mutation in squamous cell non-small cell lung cancer (NSCLC)?

DR DRILON: We published a review in *Lancet Oncology* evaluating actionable alterations in squamous cell lung cancer, and several are recognized (Drilon 2012). About 1 out of 5 patients harbors an FGFR1 amplification. Other mutations, such as PIK3CA, PTEN and AKT, are enriched in squamous cell lung cancer. DDR2 mutations are another example, for which dasatinib has been described as a potentially useful agent.

DR LOVE: Should oncologists in general practice be using NGS for patients with metastatic lung cancer?

DR DRILON: I would definitely recommend that community oncologists use NGS as opposed to non-NGS methods. With NGS, we are able to identify many more clinically actionable genomic alterations for which targeted therapies are either approved or are in testing. Also, patients who undergo multiple non-NGS tests endure a huge biopsy load. In our study, two thirds of the patients required multiple biopsies.

Although the population chosen for the study included patients who were light/never smokers with adenocarcinoma, the results of the paper are applicable to patients with a

1.1

Next-Generation Sequencing (NGS) Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches

"One or more genomic alterations were uncovered by NGS in tumors from 94% (n = 29 of 31) of patients. Actionable genomic alterations with a targeted agent based on NCCN Guidelines were identified in 26% of patients. Comprehensive genomic profiling using this method also identified a genomic alteration with a targeted agent available on a clinical trial in an additional 39% of patients.

These findings support first-line profiling of lung adenocarcinomas using this approach as a more comprehensive and efficient strategy compared with non-NGS testing."

Drilon A et al. *Clin Cancer Res* 2015a;21(16):3631-9.

smoking history and to those with varied clinical features, including squamous cell carcinomas (SCC) and potentially other cancers of the lung, such as small cell lung cancer.

At our institution, we usually send tumor samples solely for NGS unless the patient is extremely symptomatic. NGS is wonderful in that it can capture 200 to 400 different genes, but the turnaround time is about 4 weeks. If you have a young patient who is a never smoker and you're suspicious that he or she may have an EGFR mutation or an ALK fusion, it is possible to conduct tests that have a quick turnaround time.

Tracks 5-6, 8

DR LOVE: At ASCO 2015 you presented data from a Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancer. Would you discuss the efficacy and side effects of cabozantinib in that study?

DR DRILON: The first stage of this Phase II trial has been completed. The overall response rate was approximately 40%, and the disease control rate was almost 100%. So no primary disease progression occurred. The progression-free survival (PFS) with cabozantinib was 7 months, and the median overall survival (OS) was 10 months (Drilon 2015b; [1.2]).

Even though RET is a driver mutation, we observed responses in only 40% of patients. This may be speaking to the biology of RET rearrangements. It may be that we can elicit a 60% to 80% response rate using targeted therapy for one biologic "bucket" that includes EGFR mutations and ALK fusions, whereas another bucket, which consists of BRAF mutations and RET, responds with lower efficacy to single-agent targeted therapy. The flip side is that we also may need a better targeted agent. Many patients on this trial required dose reductions during therapy. Patients receiving cabozantinib may develop transaminitis. Another interesting side effect observed with chronic daily dosing of cabozantinib is hypopigmentation of the skin and the hair. In the future, it may be possible to discover a RET-specific inhibitor without a lot of off-target effects.

DR LOVE: Would you also comment on your study investigating pemetrexed-based systemic therapy in RET-rearranged NSCLC?

1.2

Phase II Trial of Cabozantinib for Patients with Advanced RET-Rearranged Non-Small Cell Lung Cancer

Efficacy	(n = 16)	
Overall response rate	6 (38%)	
Stable disease	9 (56%)	
Median progression-free survival	7 mo	
Median overall survival	10 mo	
Select adverse events	All grades	Grade 3
ALT increase	15 (94%)	0
AST increase	12 (75%)	1 (6%)
Diarrhea	10 (63%)	0
Skin/hair hypopigmentation	7 (44%)	0

Drilon A et al. *Proc ASCO* 2015b;**Abstract 8007**.

DR DRILON: We presented data at the 2015 World Lung meeting showing that RET-rearranged lung cancer, like ALK-rearranged cancer, is sensitive to pemetrexed-based therapies (Delasos 2015). This retrospective analysis demonstrated a response rate of approximately 48% to pemetrexed-based systemic therapy in RET-rearranged lung cancer.

Track 11

DR LOVE: What are your thoughts on the efficacy of the dabrafenib/trametinib combination for BRAF V600E mutation-positive NSCLC?

DR DRILON: Data presented last year on single-agent dabrafenib in a Phase II study showed that the response rate was approximately 30%. However, we know from the melanoma experience that treatment of BRAF-mutant tumors with the combination of a BRAF and MEK inhibitor improves response rates.

At ASCO 2015, a Phase II trial demonstrated that patients with BRAF-mutant lung adenocarcinomas who received the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib experienced a response rate of approximately 60%, echoing what is observed in melanoma (Planchard 2015; [1.3]).

Two patients at our institution with BRAF V600E mutations received single-agent BRAF inhibition. After disease progression, a MEK inhibitor was added. Both of these patients again responded to the combination with several months of disease control. So it's possible that if you come in with a BRAF inhibitor at disease progression, you might be able to yield more efficacy with the addition of a MEK inhibitor. ■

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Interim Results of a Phase II Study of the BRAF Inhibitor Dabrafenib in Combination with the MEK Inhibitor Trametinib in Patients with BRAF V600E-Mutated Metastatic Non-Small Cell Lung Cancer

Efficacy	Dabrafenib + trametinib (n = 24)	
Overall response rate	15 (63%)	
Disease control rate (>12 wk)	88%	
	(n = 33)	
Select adverse events	All grades	Grade ≥3
Pyrexia	13 (39%)	1 (3%)
Diarrhea	11 (33%)	1 (3%)
Nausea	11 (33%)	0
Vomiting	11 (33%)	0
Rash	7 (21%)	1 (3%)
Asthenia	7 (21%)	0
Peripheral edema	7 (21%)	0

Planchard D et al. *Proc ASCO* 2015;**Abstract 8006**.

SELECT PUBLICATIONS

Delasos L et al. **Clinical outcomes with pemetrexed-based systemic therapy in RET-rearranged lung cancers.** *Proc IASLC* 2015;**Abstract 03.05**.

Drilon A et al. **Squamous-cell carcinomas of the lung: Emerging biology, controversies, and the promise of targeted therapy.** *Lancet Oncol* 2012;13(10):e418-26.