INTERVIEW

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Track 15 Response and tolerability of osimertinib and rociletinib (CO-1686) in advanced T790M-mutant adenocarcinoma of the lung

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Do you believe tumor angiogenesis is still a viable research target in advanced NSCLC?

DR HEYMACH: Several angiogenesis inhibitors prolong OS. Other drugs have prolonged PFS but not OS. It seems that once angiogenesis inhibitors are discontinued, tumors

are able to regrow. This has raised the question of whether to continuously administer angiogenesis inhibitors or to avoid using them in the first place.

Certain mutations appear to be much more responsive to VEGF inhibitors. When erlotinib was tested in combination with bevacizumab without respect to EGFR mutation status in the Phase III BeTa study, it seemed to prolong PFS but no benefit in OS was observed (Herbst 2011). However, in the subgroup of patients with EGFR mutations, a trend appeared in favor of the addition of bevacizumab.

A Phase II study of first-line erlotinib with or without bevacizumab for patients with advanced NSCLC and EGFR mutations demonstrated an impressive benefit with the addition of bevacizumab (Seto 2014). Although they are striking, the findings have not necessarily gained widespread attention. For my patients with lung cancer and EGFR mutations, I like to find a way to administer the combination of bevacizumab and erlotinib. If they are receiving chemotherapy, I often use bevacizumab and erlotinib in the maintenance setting, especially if chemotherapy was initiated before the EGFR status was known.

Sometimes, for my patients with progressive disease on an EGFR inhibitor, I determine if it is feasible to combine bevacizumab with erlotinib, particularly after chemotherapy. I have patients who experience disease progression after receiving erlotinib but end up achieving prolonged stable disease or response with bevacizumab/erlotinib, particularly after chemotherapy. I always try to take advantage of the heightened sensitivity of EGFR-mutant tumors to bevacizumab/erlotinib in one way or the other.

We now have to figure out how to combine anti-angiogenic agents more effectively and determine the subset of patients with the potential to achieve the most benefit.

DR LOVE: What about other anti-angiogenics, particularly the efficacy and tolerability of ramucirumab in squamous versus nonsquamous NSCLC?

DR HEYMACH: The FDA approval for ramucirumab applies to both squamous and nonsquamous cell histologies, unlike bevacizumab, which is used in the nonsquamous setting. In the Phase III REVEL trial, the benefit of ramucirumab/docetaxel was modest. It's not like the benefit that a patient with EGFR-mutant disease yields from an EGFR inhibitor.

However, although it is not enormous, the benefit is real with little additional toxicity. If you're going to administer docetaxel, you have little reason not to add ramucirumab, unless the patient has a serious cardiovascular risk factor, a recent thromboembolic event or a bleeding risk. The regimen is a reasonable option for patients with squamous cell histology, and most of these patients will receive docetaxel, although it will likely be after immunotherapy.

Track 6

DR LOVE: What is your perspective on the results of the Phase III PROCLAIM trial of pemetrexed/cisplatin and thoracic radiation therapy (TRT) versus etoposide/cisplatin/TRT followed by consolidation chemotherapy for patients with previously untreated locally advanced NSCLC?

DR HEYMACH: Two common chemotherapy regimens have been used with radiation therapy in this setting: carboplatin/paclitaxel and cisplatin/etoposide. We usually admin-

ister weekly carboplatin/paclitaxel with radiation therapy. Typically, after completion of chemoradiation therapy, we administer 2 cycles of consolidation carboplatin/paclitaxel once every 3 weeks at full doses. Cisplatin/etoposide is administered on a different schedule with TRT. For this regimen, we often administer docetaxel consolidation after.

Pemetrexed/cisplatin/TRT looks like an intriguing regimen that is arguably better tolerated than etoposide/platinum/TRT in terms of the Grade 3 or 4 hematologic toxicities, but no difference was observed in terms of OS (Senan 2015). We will have to wait to see if other parameters differ between regimens. It'll be interesting to discern whether this regimen begins to be much more widely used in the future.

Track 15

DR LOVE: What is your perspective on the efficacy of the third-generation EGFR tyrosine kinase inhibitors (TKIs) osimertinib and rociletinib in NSCLC?

DR HEYMACH: Both drugs are active specifically in patients with T790M mutations and are well tolerated (2.1, 2.2). Both are highly active in patients with EGFR TKI-refractory disease, with response rates of approximately 60% in the T790M-positive population and 20% in those with T790M mutation-negative disease. I believe both agents will have a role in the T790M-negative patient subgroup.

We now have some preclinical and clinical data documenting resistance to these agents. It involves a new mutation that we will soon be hearing more about, the C797S mutation (Oxnard 2015; Simmons 2015). Presumably, we will need a new generation of drugs able to inhibit both the T790M mutation and C797S-mutated disease.

2.1

Phase I/II AURA Trial: Efficacy and Safety of Osimertinib (AZD9291) for EGFR Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer

	Dose-escalation and expansion cohorts		
Response	**All patients** (n = 239)	**T790M-positive** (n = 127)	**T790M-negative** (n = 61)
ORR	51%	61%	21%
DCR	84%	95%	61%
Survival	n = 222	n = 138	n = 62
Median PFS	8.2 mo	9.6 mo	2.8 mo
Select AEs (Grade ≥3)	**20 mg qd** (n = 21)	**80 mg qd** (n = 90)	**160 mg qd** (n = 63)
Rash	0%	0%	3%
Diarrhea	0%	1%	2%
Nausea	5%	0%	0%
Appetite decrease	5%	1%	0%
Fatigue	5%	0%	0%

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; AEs = adverse events

Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99.

Editor's note: Subsequent to this interview, on November 13, 2015 the FDA granted accelerated approval to osimertinib for the treatment of EGFR T790M mutation-positive advanced NSCLC after disease progression on other EGFR-blocking therapy. ■

2.2

Efficacy and Safety Results from the Phase I/II Trial of Rociletinib (CO-1686) for Patients with EGFR-Mutated Non-Small Cell Lung Cancer After Failure of an EGFR Inhibitor

Outcome (any dose)	T790M-positive (n = 46)	T790M-negative (n = 17)
Objective response rate	59%	29%
Disease control rate	93%	59%
Median PFS	13.1 mo	5.6 mo
Select AEs (n = 92)*	**Any grade**	**Grade 3**
Hyperglycemia	47%	22%
Nausea	35%	2%
Fatigue	24%	4%
Diarrhea	22%	0%
Vomiting	14%	2%
QTc prolongation	12%	5%

PFS = progression-free survival; AEs = adverse events

* Therapeutic dose of rociletinib (500, 625, 750, 900 and 1,000 mg BID)

Press release (November 16, 2015): "In the company's NDA [new drug application] submission, both immature confirmed and unconfirmed response analyses were submitted. As the efficacy data have matured, the number of patients with an unconfirmed response who converted to a confirmed response was lower than expected."

Sequist LV et al. *N Engl J Med* 2015;372(18):1700-9.

SELECT PUBLICATIONS

Herbst RS et al. **Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): A double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2011;377(9780):1846-54.

Jänne PA et al. **AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.** *N Engl J Med* 2015;372(18):1689-99.

Oxnard GR et al. **Mechanisms of acquired resistance to AZD9291 in EGFR T790M positive lung cancer.** *Proc IASLC* 2015;**Abstract ORAL17.07**.

Senan S et al. **Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC).** *Proc ASCO* 2015;**Abstract 7506**.

Sequist LV et al. **Rociletinib in EGFR-mutated non-small-cell lung cancer.** *N Engl J Med* 2015;372(18):1700-9.

Seto T et al. **Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): An open-label, randomised, multicentre, phase 2 study.** *Lancet Oncol* 2014;15(11):1236-44.

Simmons AD et al. **Identification of effective drug combinations to prevent or delay resistance to the EGFR mutant selective inhibitor rociletinib (CO-1686).** *Proc IASLC* 2015;**Abstract 3010/MINI09.04**.