INTERVIEW

Geoffrey R Oxnard, MD

Dr Oxnard is Assistant Professor of Medicine at Harvard Medical School and Medical Oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-13

Select Excerpts from the Interview

Track 2

DR LOVE: Can you review current efforts to target RET- and BRAF-mutant tumors?

DR OXNARD: All of the RET TKIs are "dirty" because they target multiple kinases. Vandetanib, sunitinib and sorafenib are well studied in lung cancer and effective in subsets of patients. However, they are associated with toxicities.

The use of BRAF inhibitors is an option, but these agents cause serious cutaneous toxicities. We've seen responses that are not as durable compared to those with crizotinib or erlotinib. The question is, for a relatively heavy smoker with adenocarcinoma,

is it worthwhile to hunt for the V600E mutation that's present in about 1% of NSCLC cases? If the V600E mutation is present, I believe it is appropriate to integrate a BRAF inhibitor into second- or third-line care as available drugs start to wane in efficacy. The NCCN guidelines state that one can consider vemurafenib or dabrafenib in V600E-mutant NSCLC. The more targetable V600E BRAF mutation is more common in nonsmokers, whereas the less targetable non-V600E mutations are more enriched in smokers, especially in patients with squamous cell cancer.

Track 5

DR LOVE: Would you talk about the activity of afatinib in patients with uncommon EGFR mutation-positive or wild-type NSCLC?

DR OXNARD: We don't know if afatinib is more effective than erlotinib or gefitinib for these patients, but if I'm going to administer a first-line EGFR inhibitor for a patient who prefers such an approach to chemotherapy, perhaps I will reach for afatinib. It has more potency against wild type and potentially more potency against uncommon EGFR mutations.

Afatinib is active against wild-type EGFR and against HER2, based on preclinical models suggesting it has broader effects that likely lead to some of its toxicity. Erlotinib is dosed in such a way that it has some of that wild-type activity. Gefitinib is administered at a lower dose with less of that wild-type activity. We are trying to piece together the preclinical and clinical data to make these decisions, and based on the broader activity of afatinib against a couple of targets, I believe it's reasonable to use it in these rare populations for whom you want the agent with the most "punch."

However, the overall picture is somewhat murky, and if the patient's not a "gambler," I believe the standard of care for first-line therapy with these rare mutations is chemotherapy, saving the TKI as a maintenance or second-line therapy.

Track 9

DR LOVE: What are your thoughts on the combination of afatinib/cetuximab in EGFR-mutant NSCLC with acquired resistance to TKI therapy?

DR OXNARD: To date, the most potent EGFR-directed regimen is the combination of afatinib with cetuximab, which results in a good response rate of approximately 30% and an impressive waterfall plot (Janjigian 2012).

Compared to erlotinib, afatinib may cause increased toxicity for some patients. Cetuximab has its own toxicity profile, wherein more rash may mean more drug effect. When afatinib is added to cetuximab, more significant toxic effects are observed. Afatinib/cetuximab can be administered if a response is needed. The important question is whether such a combination will produce better results than the more familiar carboplatin/pemetrexed regimen, which elicits reliable effects.

If a patient receiving afatinib has become comfortable with the side effects, an intuitive next step would be to add cetuximab and see if that helps to regain a response. Switching a patient who's been receiving erlotinib to afatinib/cetuximab may pose a bigger challenge in terms of toxicity. Although it's a reasonable approach with a compelling rationale, it needs to be studied.

Track 11

DR LOVE: A recent press release suggested promising preliminary results from the Phase III REVEL trial of second-line ramucirumab in advanced NSCLC (4.1). What are your thoughts on the role of anti-VEGF therapy in NSCLC?

DR OXNARD: Ramucirumab is a novel VEGF inhibitor, and bevacizumab is approved for use in lung, colon and renal cell cancer. We have multiple VEGF antagonists in renal cell cancer and colon cancer. Studies have demonstrated that bevacizumab prolongs survival in cervical cancer, and ramucirumab prolongs survival in gastric cancer. The data with ramucirumab highlight the importance of continuing to target the VEGF pathway and to integrate anti-VEGF therapy with chemotherapy, although currently no biomarker exists to select patients for benefit.

The magnitude of benefit from anti-VEGF therapy is small compared to the huge responses observed with erlotinib or crizotinib in the right group of selected patients. I hope that we will be able to identify patients who will benefit from anti-VEGF agents in such a way that the benefits are dramatic rather than marginal like the responses currently being observed. Because of the increasing repertoire of anti-VEGF agents, making a choice is confusing, and it's unclear how to integrate one's choice into patient care.

4.1

REVEL: A Phase III Trial Evaluating Ramucirumab or Placebo in Combination with Docetaxel as Second-Line Therapy for Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Protocol ID: NCT01168973

Accrual: 1,242 (Closed)

Eligibility

- Disease progression during or after 1 prior first-line platinum-based chemotherapy with or without maintenance therapy
- ECOG PS 0-1

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- Docetaxel + ramucirumab
- Docetaxel + placebo

Primary endpoint: Overall survival (OS)

Key secondary endpoints: Progression-free survival (PFS), objective response rate

Press Release (2/19/14): REVEL showed statistically significant improvements in the primary endpoint of OS and secondary PFS endpoint in the ramucirumab/docetaxel arm compared to the control arm of placebo/docetaxel. Data will be presented at an upcoming scientific meeting and submitted to regulatory authorities in 2014.

www.clinicaltrials.gov, May 2014.

Track 12

DR LOVE: Currently, what first-line therapy do you generally recommend for your patients with metastatic squamous cell lung cancer?

DR OXNARD: The approved regimen for squamous cell lung cancer is cisplatin/gemcitabine. For a young and fit patient, that is what I'd administer. For a patient who is ineligible for cisplatin, a fairly common scenario in squamous cell lung cancer, I would likely administer carboplatin/paclitaxel. Notably, this combination is not FDA

approved, so it's an off-label use. *Nab* paclitaxel was recently approved based on a Phase III trial in which it demonstrated a better response rate than carboplatin/solvent-based paclitaxel (Socinski 2012).

Although carboplatin/solvent-based paclitaxel is conveniently administered every 3 weeks, carboplatin/*nab* paclitaxel is a weekly regimen. These regimens have different toxicity profiles (Socinski 2013; [4.2]). Solvent-based paclitaxel requires steroid therapy, whereas *nab* paclitaxel requires none.

This is a conversation that I have with my patients. *Nab* paclitaxel is becoming more widely used because it confers a greater chance of response, does not require steroids and is easier on the kidneys. Each regimen has different rules, and I make my decision based on what the patient needs. ■

4.2

Analysis of Efficacy and Safety of Weekly *Nab* Paclitaxel in Combination with Carboplatin (*nab*-P/C) as First-Line Therapy for Patients with Advanced Squamous Cell Non-Small Cell Lung Cancer

Outcome	*nab*-P/C (n = 229)	sb-P/C (n = 221)	Response rate ratio (RRR) or hazard ratio (HR)	*p*-value
ORR	94 (41%)	54 (24%)	RRR 1.680	<0.001
Median PFS	5.6 months	5.7 months	HR 0.865	0.245
Median OS	10.7 months	9.5 months	HR 0.890	0.284
Hematologic adverse events	***nab*-P/C** (n = 222)		**sb-P/C** (n = 214)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	20%	6%	4%	<1%*
Neutropenia	32%	11%	34%	17%
Thrombocytopenia	18%	4%	4%	3%*
Nonhematologic adverse events	***nab*-P/C** (n = 226)		**sb-P/C** (n = 218)	
	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	4%	0%	6%	0%
Sensory neuropathy	3%	0%†	11%	<1%
Alopecia	<1%	0%	0%	0%
Febrile neutropenia	<1%	0%	0%	<1%

sb-P/C = solvent-based paclitaxel with carboplatin; ORR = overall response rate; PFS = progression-free survival; OS = overall survival

* $p < 0.05$ in favor of sb-P/C, combined Grade 3/4 adverse events

† $p < 0.05$ in favor of *nab*-P/C, combined Grade 3/4 adverse events

Socinski MA et al. *Ann Oncol* 2013;24(9):2390–6.

SELECT PUBLICATIONS

Janjigian YY 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**.

Lazzari C et al. **PROSE: Randomized proteomic stratified phase III study of second-line erlotinib versus chemotherapy in patients with inoperable non-small cell lung cancer.** *Proc ASCO* 2013;**Abstract LBA8005**.

Socinski MA et al. **Weekly *nab*-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial.** *J Clin Oncol* 2012;30(17):2055–62.