INTERVIEW

Robert C Doebele, MD, PhD

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Tracks 1-11

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the mechanisms of resistance to EGFR and ALK inhibitors?

DR DOEBELE: ALK-positive disease is an exciting area that follows on the heels of successes we've had with targeted therapies for EGFR mutation-positive lung cancer. I actually consider them analogous situations, even though the rates of incidence of each mutation are different.

The analogies continue even with drug resistance, which is an area that I'm highly involved with and interested in. We observe kinase domain mutations and evidence of bypass signaling as mechanisms of drug resistance. This is going to be a key area — these subsets of lung cancer may be our best hope for turning this type of disease into a chronic illness because we do see such great responses with agents that target these mutations. We simply need a better understanding of the biology of these cancers so that we can either prevent or at least significantly delay drug resistance.

The easiest mechanism of resistance to understand is a kinase domain mutation, which is a secondary mutation that's selected out during treatment with these targeted therapies. These inhibit or prevent adequate drug binding so that the abnormal protein, whether it's ALK or EGFR, is able to signal despite the presence of the drug.

The rate of ALK kinase domain mutations is probably only about 25%, a little lower than what we observe in EGFR-mutant disease, with which T790M mutations are probably in the range of 50% to 60%. The other difference between the 2 disease entities is that there's a greater diversity of resistance mutations too, and that makes our job a bit more difficult in terms of pinpointing a mechanism of resistance.

Another mechanism of resistance is bypass signaling, by which the cancer cell turns to another kinase to drive cellular proliferation and metastasis. That type of resistance mechanism might require dual therapy with different targeted agents, whereas kinase mutations might respond more favorably to a more potent inhibitor.

Track 4

DR LOVE: Is pemetrexed more effective than other agents for patients with ALK-positive NSCLC whose disease has progressed on crizotinib?

DR DOEBELE: Some data indicate that pemetrexed may be particularly useful in patients with ALK-positive lung cancer. Our group had demonstrated that patients with ALK-positive lung cancer have a longer PFS on pemetrexed-based therapy compared to patients with EGFR- or KRAS-mutant or pan-wild-type disease (Camidge 2011).

2.1

PROFILE 1007: Results of a Phase III Study of Crizotinib versus Standard Second-Line Chemotherapy for Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer

Response	Crizotinib (n = 172)	Pemetrexed (n = 99)	Docetaxel (n = 72)
Overall response rate	66%	29%	7%
Median progression-free survival (PFS)	7.7 mo	4.2 mo	2.6 mo

	Crizotinib (n = 172)		Chemotherapy (n = 171)	
Adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Vision disorder	60%	0%	9%	0%
Diarrhea	60%	0%	19%	1%
Nausea	55%	1%	37%	1%
Vomiting	47%	1%	18%	0%
Edema	31%	0%	16%	0%
Fatigue	27%	2%	33%	4%
Dysgeusia	26%	0%	9%	0%
Dyspnea	13%	4%	19%	3%

Median PFS: Crizotinib versus pemetrexed or docetaxel, $p < 0.001$

Differences in response rate between crizotinib and pemetrexed or docetaxel were significant ($p < 0.001$).

Shaw AT et al. *N Engl J Med* 2013;368(25):2385-94.

In the PROFILE 1007 trial patients were randomly assigned to crizotinib or standard second-line chemotherapy with docetaxel or pemetrexed. The study demonstrated superiority of crizotinib compared to single-agent chemotherapies in response rate and PFS. However, the objective response rate was about 30% for patients with ALK-positive disease receiving single-agent pemetrexed (Shaw 2013; [2.1]). This is higher than the overall response rate of 12.8% with pemetrexed as second-line therapy in unselected patients with lung adenocarcinoma (Scagliotti 2009). Pemetrexed is well tolerated and can be administered for many cycles.

DR LOVE: Should we consider clinical trials with second-generation ALK inhibitors rather than chemotherapy for patients with ALK-positive lung cancer?

DR DOEBELE: If a clinical trial with a second-generation ALK inhibitor is available, I believe it's reasonable. These agents appear promising, with response rates that are higher than those with chemotherapy. However, a clinical trial may not be available for some patients. I prepare these patients for the inevitability that we will have to consider standard platinum-based chemotherapy a year or two down the road.

Tracks 6, 11

DR LOVE: What is known about the incidence of brain metastases and the effects of targeted therapies on brain metastases in patients with EGFR-mutant or ALK-positive NSCLC?

DR DOEBELE: When you consider brain metastases, you must think about incidence at diagnosis versus lifetime incidence. We investigated patterns of metastatic spread in subsets of NSCLC characterized by driver oncogenes like ALK and EGFR. Approximately 30% of patients had brain metastases at the time of diagnosis, and no molecular cohort of patients exhibited a predisposition to develop brain metastases (Doebele 2012). Because patients with EGFR mutations or ALK gene rearrangements are living longer, their lifetime incidence of brain metastasis is higher.

One of the common sites of disease progression for patients who are receiving a targeted therapy is the central nervous system (CNS). CNS penetration of these agents is unpredictable, and the effective dose of drugs is lower than for other tissues in the body. All of the new next-generation inhibitors have shown some anecdotal data reporting responses in the CNS. The questions are how long the responses will last and whether those drugs have a problem with CNS penetration after long-term use.

For patients with small, asymptomatic brain metastases, it is reasonable to start therapy with crizotinib or an EGFR tyrosine kinase inhibitor (TKI). If the disease does not respond, some form of stereotactic radiosurgery might be a good approach to ablate metastatic disease while continuing the targeted therapy.

DR LOVE: What do we know about using high-dose pulses of EGFR TKIs for patients with advanced EGFR-mutant NSCLC and brain metastases?

DR DOEBELE: An article by Grommes and colleagues reported that a pulse dose of 1,500 mg of erlotinib administered once weekly resulted in a reasonable response in the CNS (Grommes 2011; [2.2]). I have administered pulse-dose erlotinib at 1,500 mg a week for a patient who had been receiving standard-dose erlotinib and had experienced problems with rash and diarrhea. This patient did not experience any rash during pulse-dose treatment, suggesting that pulsatile dosing may not cause the same toxicity.

2.2

Pulsatile High-Dose Weekly Erlotinib for Central Nervous System (CNS) Metastases from EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

Response	N = 9
Best CNS response	
Partial response	67%
Stable disease	11%
Progressive disease	22%
Median time to CNS progression	2.7 mo
Median overall survival	12 mo

- Treatment was well tolerated.
- Major toxicities included rash, fatigue, diarrhea, nausea, hair thinning and asymptomatic intratumoral CNS hemorrhage.
- No Grade ≥3 toxicities were observed.

Conclusion: These results suggest that pulsatile erlotinib at approximately 1,500 mg per week is safe and has activity in patients with CNS disease from EGFR-mutant NSCLC even when systemic resistance has developed and been confirmed. Poor penetration of erlotinib when administered at standard low doses daily may explain in part the failure to achieve control of CNS metastases, rather than acquired resistance mutations such as T790M.

Grommes C et al. *Neuro-Oncology* 2011;13(12):1364-9.

Ongoing studies are exploring even higher doses — up to 2,000 mg of erlotinib. Another study of intermittent, high-dose afatinib to obtain better penetration of the drug for patients with EGFR-mutant NSCLC is also under way (NCT01647711).

Track 8

DR LOVE: Would you discuss your recent editorial "Time to shift the burden of proof for oncogene-positive cancer" (Doebele 2013)?

DR DOEBELE: The incidence of lung cancer driven by oncogenes is low. For example, the ROS1 fusion occurs in 1% to 2% of patients with NSCLC. The question going forward is whether our current model for drug development will benefit patients with oncogene-driven cancer.

I believe we now have enough data to set a reasonably high bar for success so that we can obtain rapid approval of targeted therapies. We know that second-line chemotherapy for NSCLC typically produces response rates of 10% to 15% and a PFS of 3 to 4 months. Do we need randomized Phase III trials of targeted therapies versus chemotherapy if we see response rates of 50% to 60% and PFS of greater than 3 to 4 months with oncogene-targeted therapies? We need to think about new ways to bring targeted therapies to patients faster. As we recognize the heterogeneity of lung cancer and the success of targeted therapies, alternate approaches to approval should be considered. ■

SELECT PUBLICATIONS

Camidge DR et al. **Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on pemetrexed.** *J Thorac Oncol* 2011;6(4):774-80.

Doebele R. **Targeted therapies: Time to shift the burden of proof for oncogene-positive cancer?** *Nat Rev Clin Oncol* 2013;10(9):492-3.

Doebele R et al. **Oncogene status predicts patterns of metastatic spread in treatment-naïve non-small cell lung cancer.** *Cancer* 2012;118(18):4502-11.