INTERVIEW

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Tracks 1-17

Select Excerpts from the Interview

Tracks 2-3, 5, 8-9

DR LOVE: What is your experience with the next-generation ALK inhibitor ceritinib for patients with advanced NSCLC?

DR RIELY: Ceritinib was approved last year for the treatment of ALK-positive metastatic NSCLC after disease progression on or intolerance to crizotinib. Crizotinib

and ceritinib are similar, but the binding of ceritinib to ALK is much better. I believe that this is the reason why ceritinib is more effective in the brain.

The FDA-approved dose of ceritinib is 750 mg daily, which is quite high. The number of patients who receive that dose is small. I routinely start patients who are young and fit at 600 mg and may reduce the dose to 450 mg for older patients.

Gastrointestinal problems such as nausea and diarrhea are the biggest challenge in determining the right dose of ceritinib. The other major side effect is liver function test abnormalities, which we monitor and then adjust the dose if necessary.

DR LOVE: How would you sequence crizotinib and ceritinib for patients with ALK-positive NSCLC?

DR RIELY: Treatment for ALK-positive lung cancer with crizotinib in the first-line setting results in a median PFS of approximately 11 months. If ceritinib is administered after disease progression on crizotinib, the median PFS is around 7 months. Taken together, the median PFS for crizotinib and ceritinib is about 18 months. When ceritinib is administered as first-line therapy, the median PFS is about 10 months (Kim 2014).

So switching from one to the other does not necessarily yield optimal benefits. The reason for administering crizotinib first would be more related to drug tolerability. Patients tend to find crizotinib easier to tolerate than ceritinib. However, some patients who are receiving crizotinib may experience significant edema, which can be a real problem. An early switch to ceritinib for those patients who don't tolerate crizotinib well would be reasonable.

DR LOVE: What are your thoughts about continuing crizotinib beyond disease progression for ALK-positive NSCLC?

DR RIELY: No matter which agent we choose, most patients will eventually develop progressive disease. For ALK-positive NSCLC, I believe one should try to maximize the benefit from crizotinib. If single sites of disease progression are amenable to treatments such as radiation therapy, surgery or interventional radiology procedures, they should be employed as well. This will delay the start of the next PFS clock and the switch to systemic therapy.

DR LOVE: What is known about the activity and tolerability of alectinib for ALK-rearranged NSCLC?

DR RIELY: I believe that alectinib is the next agent that will become available for patients with ALK-positive NSCLC. Alectinib, similar to ceritinib, is a more potent ALK inhibitor than crizotinib.

Alectinib began its initial development in Japan. The first trial of alectinib in patients with crizotinib-naïve, ALK-positive disease reported an objective response rate of more than 90%. This was one of the highest response rates we've seen in the treatment of NSCLC. The dose used in that study was 300 mg. A later study by our group identified the recommended Phase II dose as 600 mg, double the dose used in the Japanese study (Gadgeel 2014). My experience with alectinib is that it's relatively well tolerated.

DR LOVE: How do patients with ALK-positive NSCLC respond to chemotherapy?

DR RIELY: Chemotherapy may be slightly more effective for patients with ALK-positive disease. Data from a randomized trial of cisplatin/pemetrexed versus

crizotinib as first-line therapy showed that the combination was effective. So that would be my treatment of choice. A study randomly assigning patients to standard chemotherapy or crizotinib in the second-line setting demonstrated that PFS was much better with pemetrexed than with docetaxel (Shaw 2013).

Track 10

DR LOVE: What is your approach to the use of bevacizumab with erlotinib for patients with advanced EGFR mutation-positive NSCLC?

DR RIELY: Results from a recent study demonstrated that combining bevacizumab with erlotinib in the first-line setting significantly improves PFS in comparison to erlotinib alone. It's a relatively small data set from Japan, but it does demonstrate that the addition of bevacizumab to erlotinib is efficacious (Seto 2014; [2.1]).

In practice, patient preferences influence my choice of therapy. Patients who want to spend as little time in the doctor's office as possible may choose single-agent erlotinib. Other patients want the best response or the longest duration of response and are happy to receive erlotinib with bevacizumab or investigate clinical trial options.

2.1

Results of a Phase II Trial of Erlotinib Alone or with Bevacizumab (Bev) as First-Line Therapy for Patients with Advanced EGFR-Mutant Nonsquamous Non-Small Cell Lung Cancer

Efficacy	Erlotinib + bev (n = 75)	Erlotinib (n = 77)	Hazard ratio	*p*-value
Median PFS	16.0 mo	9.7 mo	0.54	0.0015
ORR	69%	64%	NR	0.49
DCR	99%	88%	NR	0.0177
	Erlotinib + bev (n = 75)		Erlotinib (n = 77)	
Select adverse events	All	Grade 3 or 4	All	Grade 3 or 4
Rash	99%	25%	99%	19%
Diarrhea	81%	1%	78%	1%
Hemorrhagic event	72%	3%	29%	0%
Hypertension	76%	60%	13%	10%
Proteinuria	52%	8%	4%	0%

PFS = progression-free survival; ORR = objective response rate; NR = not reported; DCR = disease control rate

Seto T et al. *Lancet Oncol* 2014;15(11):1236-44.

Tracks 14-15

DR LOVE: Ramucirumab, an antibody against VEGFR2, was recently approved for use in combination with docetaxel for patients with metastatic NSCLC with disease progression after platinum-based therapy. Would you discuss the results of the study that led to its approval and your approach in practice?

DR RIELY: A substantial amount of data now indicate that ramucirumab improves PFS, overall survival and response rate in the second-line setting in combination with

docetaxel, though the improvement is not dramatic (Garon 2014; [2.2]). The adverse effects associated with ramucirumab are modest. So it would be a reasonable option for patients who do not have EGFR or ALK mutations and for whom second-line docetaxel is being considered.

I administer ramucirumab for my patients occasionally. Because the clinical benefit is marginal, we must consider the cost, side effects and convenience of administration. As a member of the NCCN Guidelines Panel, I must consider these factors when developing treatment recommendations. In my practice I consider everything I can to help my patients live longer and maintain better control of their disease. ■

2.2

REVEL: Results of a Phase III Trial of Docetaxel (Doc) with or without Ramucirumab (Ram) as Second-Line Therapy for Patients with Stage IV Non-Small Cell Lung Cancer After Disease Progression on 1 Platinum-Based Regimen

Efficacy	Ram + doc (n = 628)	Plac + doc (n = 625)	Hazard ratio	*p*-value
Median OS	10.5 mo	9.1 mo	0.86	0.023
Median PFS	4.5 mo	3.0 mo	0.76	<0.0001
ORR	23%	14%	1.89*	<0.0001
DCR	64%	53%	1.60*	<0.0001

	Ram + doc (n = 627)		Plac + doc (n = 618)	
Select adverse events	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**
Neutropenia	55%	49%	45%	39%
Febrile neutropenia	16%	16%	10%	10%
Bleeding/hemorrhage	29%	2%	15%	2%
Hypertension	11%	6%	5%	2%
Venous thromboembolism	3%	2%	6%	3%

Plac = placebo; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; DCR = disease control rate

* Odds ratio

Garon EB et al. *Lancet* 2014;384(9944):665-73.

SELECT PUBLICATIONS

Gadgeel SM et al. **Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): Results from the dose-finding portion of a phase 1/2 study.** *Lancet Oncol* 2014;15(10):1119-28.

Garon EB et al. **Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial.** *Lancet* 2014;384(9944):665-73.

Kim DW et al. **Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial.** *Proc ASCO* 2014;**Abstract 8003**.

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.

Shaw AT et al. **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.** *N Engl J Med* 2013;368(25):2385-94.