INTERVIEW

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Tracks 1-14

Select Excerpts from the Interview

Track 9

DR LOVE: What are your thoughts on the recent data presented on the novel ALK inhibitor LDK378 in advanced, ALK-positive NSCLC (Shaw 2013; [3.1])?

DR PENNELL: In this trial, LDK378 was administered to patients with crizotinib-naïve disease and to patients who had experienced disease progression while receiving crizotinib. The response rate was the same in both groups, approximately 60%. The progression-free survival (PFS) was also the same in both groups, and that raises the question of sequencing. Should we be administering crizotinib first line and upon

3.1

Phase I Trial of the ALK Inhibitor LDK378 at 400 mg to 750 mg Daily in Advanced, ALK-Positive Non-Small Cell Lung Cancer

	All patients (n = 114)	CRZ pretreated (n = 79)*	CRZ naïve (n = 35)†
Overall response rate	58%	57%	60%
Complete response	1%	1%	0%
Partial response	57%	56%	60%
Median progression-free survival (PFS)‡ (≥400 mg/d) (n = 114)	8.6 mo		

The most common adverse events among all patients were nausea (73%), diarrhea (72%), vomiting (58%) and fatigue (41%).

Conclusion: LDK378 induces durable responses in the majority of patients with advanced, ALK-positive non-small cell lung cancer, including patients with crizotinib-resistant disease with and without crizotinib resistance mutations. These results suggest that more potent ALK inhibition by LDK378 represents a highly efficacious therapeutic strategy for patients with ALK-positive disease, particularly those who experience relapse on crizotinib.

CRZ = crizotinib; * 1 response unknown; † 4 responses unknown; ‡ Median PFS at 750 mg/d not reached

Shaw AT et al. *Proc ASCO* 2013;**Abstract 8010**.

disease progression switch to LDK378 to see a potentially longer PFS? We need a head-to-head first-line trial to compare the 2 agents.

Track 11

DR LOVE: Your group presented a poster at ASCO on erlotinib beyond disease progression (Halmos 2013). What is your take on erlotinib/chemotherapy versus chemotherapy alone for patients who experience disease progression after response to a TKI?

DR PENNELL: When disease progression occurs, it makes sense to maintain TKI therapy as long as possible. However, many patients have been receiving treatment for a while, and when it is general disease progression, it is necessary to change therapy. If they've never received chemotherapy, or if they have and it has been more than a year since then, switching to chemotherapy makes sense. But should we stop the erlotinib?

The trial we presented at ASCO was for patients who had received first-line chemotherapy and developed acquired resistance to erlotinib. Patients either stopped the erlotinib and moved on to second-line chemotherapy or continued the erlotinib with chemotherapy to see if the combination helped. Unfortunately, we did not find a difference in response rates or PFS between the 2 arms. Some argue that one should continue the TKI therapy because of the risk of disease flare after discontinuation of erlotinib for patients with EGFR-mutant disease and acquired resistance to erlotinib, but I ask patients to stop erlotinib the day before they start the chemotherapy.

Track 13

DR LOVE: Data were recently presented on the VeriStrat assay (Lazzari 2013). Would you discuss what was presented and what you believe is significant?

DR PENNELL: PROSE was a randomized Phase III trial for patients unselected for the presence of EGFR mutations or EGFR wild-type disease (Lazzari 2013; [3.2]). They were randomly assigned to second-line chemotherapy with docetaxel or pemetrexed or to erlotinib. All of the patients were tested up front with the VeriStrat assay, which is a proteomic profile test developed in retrospective patient samples to categorize patients into either a good- or a poor-prognosis group when receiving an EGFR TKI such as erlotinib.

Patients received erlotinib or chemotherapy, and the trial reported no significant difference in efficacy in the overall population between the arms. However, a difference was observed depending on VeriStrat status. Patients with good VeriStrat status, approximately 70% of patients, fared equally on both arms, but patients with poor VeriStrat status fared worse with the TKI. The assay was both predictive of patients who didn't benefit from erlotinib and prognostic — patients with poor VeriStrat status didn't live as long as patients with good VeriStrat status.

How can we use this in practice? I can see it being used if you are undecided about administering erlotinib versus chemotherapy and the patient feels strongly about erlotinib but is willing to receive chemotherapy. If you plan to use chemotherapy no matter what, the assay doesn't matter. If the patient isn't fit enough to receive chemotherapy, again the assay doesn't matter because you'd use erlotinib anyway. ■

3.2

Results of PROSE: A Prospective Phase III Trial of Proteomic-Stratified (VeriStrat) Second-Line Erlotinib versus Chemotherapy for Patients with Inoperable Non-Small Cell Lung Cancer

Median overall survival	Chemotherapy	Erlotinib	Hazard ratio	*p*-value
All patients (n = 129, 134)	9.0 mo	7.7 mo	1.14	0.313
VeriStrat good (n = 96, 88)	10.92 mo	10.95 mo	1.06	0.714
VeriStrat poor (n = 38, 41)	6.38 mo	2.98 mo	1.72	0.022

- Overall, patients with VeriStrat good status have better outcomes than those with VeriStrat poor status.
- VeriStrat classification is useful in guiding second-line treatment decision-making for patients with EGFR wild type or unknown EGFR status.

Lazzari C et al. *Proc ASCO* 2013;**Abstract LBA8005**.

SELECT PUBLICATIONS

Chen J et al. **LDK378: A promising anaplastic lymphoma kinase (ALK) inhibitor.** *J Med Chem* 2013;[Epub ahead of print].

Halmos B et al. **Erlotinib beyond progression study: Randomized phase II study comparing chemotherapy plus erlotinib with chemotherapy alone in EGFR tyrosine kinase inhibitor (TKI)-responsive, non-small cell lung cancer (NSCLC) that subsequently progresses.** *Proc ASCO* 2013;**Abstract 8114**.

Hashemi-Sadraei N, Pennell NA. **Advanced non-small cell lung cancer (NSCLC): Maintenance therapy for all?** *Curr Treat Options Oncol* 2012;13(4):478-90.

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

Pennell NA. **Selection of chemotherapy for patients with advanced non-small cell lung cancer.** *Cleve Clin J Med* 2012;79(Electronic Suppl 1):46-50.

Shaw AT et al. **Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC.** *Proc ASCO* 2013;**Abstract 8010**.