INTERVIEW

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Tracks 1-11

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: The results of the Phase III RADIANT trial of 2 years of adjuvant erlotinib versus placebo in patients with EGFR-positive non-small cell lung cancer (NSCLC) were reported at ASCO 2014. No survival benefit was reported overall with erlotinib, but in a previously unspecified subset of 161 patients with activating EGFR mutations, disease-free survival increased from 28.5 to 46.4 months (Kelly 2014; [1.1]). What are your thoughts on this study?

DR NEAL: When the RADIANT trial was developed, it wasn't known if EGFR mutations were important predictors of response for patients receiving erlotinib. RADIANT was designed to enroll patients with EGFR-positive NSCLC as determined by either immunohistochemistry (IHC) or FISH analysis. Now that we know a lot more about EGFR tyrosine kinase inhibitors (TKIs), these enrollment criteria may

1.1

RADIANT: Results of a Phase III Trial of Adjuvant Erlotinib versus Placebo After Complete Tumor Resection with or without Adjuvant Chemotherapy in EGFR-Positive Stage IB to IIIA Non-Small Cell Lung Cancer (NSCLC)

All patients	**Erlotinib** (n = 623)	**Placebo** (n = 350)	Hazard ratio	*p*-value
Median disease-free survival	50.5 mo	48.2 mo	0.90	0.3235
Median overall survival	Not reached	Not reached	1.13	0.3350
Patients with EGFR-mutant NSCLC	**Erlotinib** (n = 102)	**Placebo** (n = 59)	Hazard ratio	*p*-value
Median disease-free survival	46.4 mo	28.5 mo	0.61	0.0391
Median overall survival	Not reached	Not reached	1.09	0.8153
Adverse events (AEs) in patients with EGFR-mutant NSCLC	**Erlotinib** (n = 100)		**Placebo** (n = 59)	
AEs leading to treatment termination				
Any	30%		5.1%	
Drug related	25%		0%	
AEs leading to dose alteration				
Interruption	22%		6.8%	
Reduction	22%		1.7%	
Interruption and reduction	34%		1.7%	
Grade ≥3 rash	19%		0%	
Grade ≥3 diarrhea	5%		0%	

Kelly K et al. *Proc ASCO* 2014;**Abstract 7501**.

have little to do with responsiveness to erlotinib. EGFR amplification by FISH seems to correlate somewhat with the presence of EGFR mutations. IHC positivity occurs across many lung cancers, and I don't believe it's particularly predictive of response to EGFR TKIs. In the RADIANT trial, an improvement in 2-year disease-free survival with erlotinib was observed in the subset of patients who had EGFR mutations.

DR LOVE: Would you also discuss the updated results of the Phase II single-arm SELECT trial of adjuvant erlotinib in resected early-stage EGFR-mutant NSCLC (Pennell 2014)?

DR NEAL: The results for all 100 patients on the SELECT trial were presented at ASCO 2014. We observed a 2-year disease-free survival of 89% across multiple disease stages. A 2-year disease-free survival of 89% is impressive in lung cancer, regardless of the subset. These results are consistent with the results of the RADIANT EGFR-mutant subgroup analysis.

Track 6

DR LOVE: What is the current status of the third-generation EGFR inhibitors in lung cancer?

DR NEAL: Studies of 3 of these inhibitors, CO-1686, AZD-9291 and HM61713, were presented at ASCO 2014. These agents belong to a slightly different class than erlotinib and afatinib in that they have minimal activity against wild-type EGFR.

They induce minimal rash and diarrhea but exhibit specific activity against sensitizing EGFR mutations such as exon 19 deletion and L858R. They are active against disease with acquired resistance to TKIs in the form of the T790M mutations, which occur in approximately 50% of NSCLC with acquired resistance.

We don't know whether one of these agents is better than the others. Each has a different side-effect profile. CO-1686 is associated with hyperglycemia, and AZD-9291 was associated with a low incidence of interstitial lung disease. HM61713, which was used at a much lower dose, demonstrated a lower response rate of approximately 30% in patients with T790M EGFR mutations, but we have not yet seen its effects at the maximum tolerated dose (Kim 2014). For AZD-9291 (Janne 2014) or CO-1686 (Sequist 2014), the response rate was more than 60%. I believe these agents may be more tolerable for longer periods in the adjuvant setting. They hold promise in the first-line treatment of advanced EGFR-mutant NSCLC.

Track 8

DR LOVE: What is your view on the utility of the VeriStrat proteomic assay and the results of the Phase III PROSE trial (Gregorc 2014; [1.2])?

DR NEAL: The prospective PROSE study investigated the role of an EGFR TKI in all patients, not just those with EGFR mutations. The VeriStrat assay is a mass spectrometry-based serum marker assay that categorizes patients with active cancer into a poor or good prognostic group.

It's currently impossible to predict who will respond to EGFR TKI therapy from the tumor tissue. For example, it is not known whether a man who is an active smoker with squamous cell disease will respond to erlotinib therapy, even though it is FDA approved as second- and third-line therapy for that patient. As a result, the VeriStrat assay is trying to tease out those for whom erlotinib should be used.

The PROSE study indicated that patients in the VeriStrat good group seemed to perform better with erlotinib than the VeriStrat poor patient subset. I believe that the overall enthusiasm for using erlotinib in the second-, third- or fourth-line setting has diminished considerably since its initial introduction in 2004. Erlotinib is still perfectly appropriate in the second- and probably the third-, fourth- and fifth-line setting, regardless of what the VeriStrat assay shows. Once a patient has received chemotherapy several times up to the fourth line, I believe a TKI is a reasonable next option. My personal practice hasn't been to order the VeriStrat assay, although it seems to be prognostically useful.

1.2

Phase III PROSE Trial: Predictive Value of the VeriStrat Proteomic Signature in Non-Small Cell Lung Cancer Treated with Second-Line Erlotinib or Chemotherapy

Median overall survival	Erlotinib	Chemotherapy	Hazard ratio	*p*-value
All patients (n = 134, 129)	7.7 mo	9.0 mo	1.22	0.148
VeriStrat good (n = 96, 88)	11.0 mo	10.9 mo	1.06	0.714
VeriStrat poor (n = 38, 41)	3.0 mo	6.4 mo	1.72	0.022

Gregorc V et al. *Lancet Oncol* 2014;15(7):713-21.

Track 10

DR LOVE: What are your thoughts on the results of the trial of erlotinib with or without bevacizumab for patients with nonsquamous NSCLC with activating EGFR mutations (Kato 2014; [1.3])?

DR NEAL: The progression-free survival (PFS) with erlotinib was 9.7 months, but in combination with bevacizumab it was 16 months. A similar trial is ongoing in the United States (NCT01562028). It's possible that the angiogenic signal from EGFR-mutant lung cancer is rather monotone and may be VEGF driven. Perhaps those are the patients who should receive bevacizumab, possibly with erlotinib. Extrapolating from these results, maybe these patients should receive bevacizumab whenever they receive chemotherapy, whether in the second line or beyond. This would be more in line with standard treatment. ■

1.3

Randomized Trial of Erlotinib (ERL) and Bevacizumab (Bev) versus ERL Alone as First-Line Therapy for Advanced EGFR Mutation-Positive Nonsquamous Non-Small Cell Lung Cancer

All patients	Bev/ERL (n = 75)	ERL (n = 77)	Hazard ratio	*p*-value
Median PFS	16.0 mo	9.7 mo	0.54	0.0015
Objective response rate	69%	64%	NR	0.4951
Disease control rate	99%	88%	NR	0.0177
PFS by EGFR mutation type	**Bev/ERL**	**ERL**	**Hazard ratio**	***p*-value**
Exon 19 deletion (n = 40, 40)	18.0 mo	10.3 mo	0.41	NR
Exon 21 L858R (n = 35, 37)	13.9 mo	7.1 mo	0.67	NR
	Bev/ERL (n = 75)		**ERL** (n = 77)	
Select adverse events	All grades	Grade ≥3	All grades	Grade ≥3
Rash	99%	25%	99%	20%
Hypertension	76%	60%	13%	10%
Proteinuria	52%	8%	4%	0%
Hemorrhagic events	72%	3%	29%	0%

PFS = progression-free survival; NR = not reported

Kato T et al. *Proc ASCO* 2014;**Abstract 8005**.

SELECT PUBLICATIONS

Janne PA et al. **Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014;**Abstract 8009**.

Kim DW et al. **Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs).** *Proc ASCO* 2014;**Abstract 8011**.

Pennell NA et al. **SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC.** *Proc ASCO* 2014;**Abstract 7514**.

Sequist LV et al. **First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M).** *Proc ASCO* 2014;**Abstract 8010**.