INTERVIEW

David E Gerber, MD

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Tracks 1-13

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you review existing clinical trial data on the use of EGFR inhibitors for patients with surgically excised EGFR-mutant non-small cell lung cancer (NSCLC)?

DR GERBER: We've known about the efficacy of erlotinib in EGFR-mutant lung cancer for a long time, yet we don't know its role in the postoperative or adjuvant setting. The NCIC CTG BR19 study of adjuvant gefitinib or placebo had a target accrual of 1,242 patients with resected Stage IB to Stage IIIA lung cancer (Goss 2013). This study was stopped early because a concomitant Phase III trial of gefitinib failed to show a survival benefit. So only 503 patients were enrolled. Fewer than 20 patients had EGFR-mutant NSCLC. Gefitinib showed no benefit and possibly had a harmful effect,

but the number of patients with EGFR-mutant NSCLC was small and the confidence intervals were wide.

Clearly BR19 doesn't answer the question. We're awaiting the results of the double-blind Phase III RADIANT trial, which recently completed enrollment of about 1,000 patients (NCT00373425). The study used a 2:1 randomization to erlotinib or placebo after complete tumor resection with or without adjuvant chemotherapy for patients with Stage IB to IIIA NSCLC who have EGFR-mutant tumors.

DR LOVE: What is the rationale for and the design of the ongoing ALCHEMIST trial?

DR GERBER: The ALCHEMIST trial is a huge effort sponsored by the National Cancer Institute (NCI). It is evaluating the role of targeted therapy in molecularly defined subsets of patients with NSCLC after surgery, after postoperative chemotherapy (if indicated) and after postoperative radiation therapy (if indicated).

It's attempting to enroll patients and collect data from about 8,000 resected nonsquamous NSCLC cases. The effort is not limited to the NCI or NCI-designated cancer centers. We're hoping to secure widespread community participation to answer questions that we've had now for the better part of a decade.

Tissue samples from patients who have undergone surgery will be sent for central testing. For patients harboring EGFR mutations or ALK rearrangements, specific adjuvant trials are available (1.1). The Alliance group has a study of adjuvant erlotinib in EGFR mutation-positive NSCLC with a target accrual of 430 patients, and the ECOG trial of adjuvant crizotinib in ALK-positive NSCLC has a target accrual of 378 patients. For these 2 studies, the primary endpoint is overall survival (OS).

1.1

Phase II-III ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial for Patients with Nonsquamous Non-Small Cell Lung Cancer

Trial category (ID)	ALCHEMIST — Screen component (A151216)	ALCHEMIST — ALK (ECOG-E4512)	ALCHEMIST — EGFR (A081105)
Target	Registry/intervention with biopsy at recurrence	ALK-positive	EGFR mutant
Prevalence	All comers	Approximately 5%	Approximately 10%
Target accrual (n)	6,000 to 8,000	378 (5% ineligible)	430 (5% ineligible)
Primary endpoint	N/A	Overall survival	Overall survival
Statistical power	N/A	80%	85%
1-sided α	N/A	0.025	0.05
Hazard ratio	N/A	0.67	0.67

Doroshow JH. Genomic Clinical Trials: NCI Initiatives. National Cancer Advisory Board Meeting 2013. Available at: **deainfo.nci.nih.gov/advisory/ncab/164_1213/Doroshow.pdf**.

Track 7

DR LOVE: What is your experience with the next-generation ALK inhibitor ceritinib (LDK378) in advanced NSCLC?

DR GERBER: A substantial number of patients with disease progression on crizotinib respond to the second-generation ALK inhibitors. I have fairly extensive experience with ceritinib on clinical trials (Shaw 2014; [1.2]).

I saw a patient in her mid-70s with ALK-positive NSCLC who had disease control for only about 4 months on crizotinib. When we discontinued her crizotinib, she was immediately enrolled on a trial of ceritinib and has experienced ongoing disease control for about 10 months.

The starting oral dose is 750 mg daily. At this dose, many patients experience diarrhea, nausea and in the long term develop transaminitis but typically do not experience a dramatic change in bilirubin levels. In my experience, the transaminitis is reversible. I tend to dose reduce from 750 mg to 600 mg daily. All of my patients have been able to tolerate that lower dose and have ongoing disease control for months thereafter.

Editors note: On April 29, 2014, the US Food and Drug Administration granted accelerated approval to ceritinib for the treatment of ALK-positive, metastatic NSCLC in patients who experience disease progression on or who are intolerant to crizotinib.

1.2

Phase I Trial of Ceritinib (LDK378) in Patients with Advanced ALK-Rearranged Non-Small Cell Lung Cancer

≥400 mg/day of ceritinib	All patients (n = 114)	Crizotinib pretreated (n = 80)	Crizotinib naïve (n = 34)
ORR	66 (58%)	45 (56%)	21 (62%)
Complete response	1 (1%)	1 (1%)	0 (0%)
Partial response	65 (57%)	44 (55%)	21 (62%)
Median PFS	7.0 months	6.9 months	10.4 months
750 mg/day of ceritinib*	**All patients (n = 78)**	**Crizotinib pretreated (n = 50)**	**Crizotinib naïve (n = 28)**
ORR	46 (59%)	28 (56%)	18 (64%)
Complete response	0 (0%)	0 (0%)	0 (0%)
Partial response	46 (59%)	28 (56%)	18 (64%)
Stable disease	14 (18%)	8 (16%)	6 (21%)
Progressive disease	8 (10%)	8 (16%)	0 (0%)
Unknown response	10 (13%)	6 (12%)	4 (14%)
Select Grade 3/4 adverse events	**All patients (n = 130)**	**400 mg/d (n = 14)**	**750 mg/d* (n = 81)**
Elevated ALT	27 (21%)	1 (7%)	19 (23%)
Elevated AST	14 (11%)	1 (7%)	10 (12%)
Diarrhea	9 (7%)	1 (7%)	6 (7%)
Elevated lipase level	9 (7%)	0 (0%)	8 (10%)
Nausea	7 (5%)	0 (0%)	6 (7%)
Fatigue	6 (5%)	0 (0%)	5 (6%)
Hypophosphatemia	4 (3%)	1 (7%)	2 (2%)

ORR = overall response rate; PFS = progression-free survival

* Established maximum tolerated dose

Shaw AT et al. *N Engl J Med* 2014;370(13):1189–97.

Tracks 12-13

DR LOVE: Would you discuss some of the clinical trial data evaluating maintenance therapy in advanced NSCLC?

DR GERBER: One key study was the PARAMOUNT trial in which patients received 4 cycles of induction cisplatin/pemetrexed (Paz-Ares 2013). Patients without progressive disease (PD) or intolerable toxicity were randomly assigned to maintenance pemetrexed or placebo. The study was notable for a clinically meaningful improvement in PFS and OS with maintenance pemetrexed. Patients on both arms of the study fared well. Only patients without PD after induction were randomly assigned to pemetrexed or placebo.

This explains why the results are different from those of the PointBreak trial (Patel 2013). Even though 72% of the patients assigned to placebo went on to receive therapy after disease progression, only 4% received pemetrexed. We know that pemetrexed is an effective, well-tolerated and convenient agent. An important question is whether a role exists for pemetrexed for a patient who has received platinum/pemetrexed and experienced disease control for several months before developing PD.

DR LOVE: How do you generally treat pan-wild-type nonsquamous lung cancer in the front-line setting?

DR GERBER: For a bevacizumab-eligible patient, no data favor one treatment over another. For patients with pan-wild-type NSCLC, I usually administer 6 cycles of induction carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance therapy, consistent with the ECOG-E4599 trial. Carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab is also effective and well tolerated.

From the PointBreak study, we learned that OS is not different between the 2 regimens (Patel 2013). The response rate and severity of toxicities also did not differ significantly. With carboplatin/paclitaxel as the backbone, more alopecia and neuropathy will occur. With a pemetrexed backbone, more myelosuppression will occur. The use of up-front carboplatin/paclitaxel/bevacizumab reserves pemetrexed for use after PD if the patient has received maintenance bevacizumab. For a bevacizumab-ineligible patient with nonsquamous NSCLC, I would use a platinum/pemetrexed combination as first-line therapy. ■

SELECT PUBLICATIONS

Goss GD et al. **Gefitinib versus placebo in completely resected non-small-cell lung cancer: Results of the NCIC CTG BR19 study.** *J Clin Oncol* 2013;31(27):3320-6.

Patel JD et al. **PointBreak: A randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(34):4349-57.

Paz-Ares LG et al. **PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(23):2895-902.

Shaw AT et al. **Ceritinib in ALK-rearranged non-small-cell lung cancer.** *N Engl J Med* 2014;370(13):1189-97.

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