INTERVIEW

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CD 1, Tracks 18-29 — CD 2, Tracks 1-6

CD 1

Track 18 Second opinion recommendation regarding adjuvant chemotherapy in NSCLC

Track 19 Tolerability of adjuvant cisplatin/pemetrexed versus cisplatin/vinorelbine in the randomized Phase II TREAT study

Track 20 Ongoing ECOG-E1505 Phase III trial of adjuvant chemotherapy with or without bevacizumab in Stage IB (≥4 cm) to IIIA NSCLC

Track 21 Second opinions on the treatment approach for patients with Stage III NSCLC

Track 22 **Case discussion:** A 52-year-old Asian man with a light smoking history is diagnosed with Stage IIIA mixed adenosquamous NSCLC and receives cisplatin/docetaxel in combination with bevacizumab on the ECOG-E1505 study

Track 23 EGFR and ALK testing in lung cancer

Track 24 Use of erlotinib off-protocol as a component of adjuvant therapy for EGFR-mutant, early NSCLC

Track 25 Clinical decision-making regarding adjuvant chemotherapy and radiation therapy (RT) for Stage IIIA NSCLC

Track 26 Perspective on the optimal duration of adjuvant bevacizumab in lung cancer and other solid tumors

Track 27 Continuation of bevacizumab after disease progression

Track 28 Continuation of erlotinib after disease progression in patients with EGFR-mutant advanced NSCLC

Track 29 **Case discussion:** A 57-year-old Asian woman and never smoker presents with sudden left eye visual loss and has possible leptomeningeal enhancement on brain MRI and a right lung mass with multiple pulmonary nodules biopsy proven to be EGFR, K-ras, BRAF and ALK wild-type adenocarcinoma

CD 2

Track 1 ROS1 translocation as a driver mutation in lung cancer potentially responsive to crizotinib

Track 2 PointBreak: A Phase III trial of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC

Track 3 **Case discussion:** A 55-year-old woman with a 15 pack-year smoking history presents with EGFR wild-type multifocal lung disease 1 year after completion of adjuvant chemotherapy and receives erlotinib followed by pemetrexed, gemcitabine and fourth-line cabozantinib on a clinical trial

Track 4 Cabozantinib — an oral, potent inhibitor of VEGFR2, RET and MET with single-agent activity in lung cancer

Track 5 Results of clinical trials combining MET inhibitors — tivantinib or onartuzumab — with erlotinib in advanced NSCLC

Track 6 Efficacy and side effects of the irreversible EGFR TKI afatinib in combination with cetuximab in patients with advanced NSCLC and acquired resistance to erlotinib or gefitinib

Select Excerpts from the Interview

CD 1, Tracks 18-20

DR LOVE: In which common clinical situations have you evaluated patients seeking second opinions and made significantly different recommendations from those of the initial oncologist?

DR WAKELEE: That has happened quite a bit recently with regard to adjuvant chemotherapy. I discuss the ECOG-E1505 trial with eligible patients (NCT00324805). The trial design allows for 4 different chemotherapy backbones to assess whether bevacizumab improves adjuvant chemotherapy — cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine and, for patients with nonsquamous cell histology, cisplatin/pemetrexed. We are starting to generate considerable comparative data on these different regimens in that setting (Wakelee 2011).

I find that a push is still felt for cisplatin/vinorelbine in our community. I usually treat patients with nonsquamous cell histology with cisplatin/pemetrexed, and for patients with squamous cell histology I tend to use cisplatin/gemcitabine.

The Phase II TREAT trial is the only randomized study that has evaluated cisplatin/pemetrexed in the adjuvant setting. It reported that cisplatin/pemetrexed was better tolerated than cisplatin/vinorelbine (Kreuter 2011; [2.1]). Higher doses of cisplatin/pemetrexed were administered without treatment discontinuations due to neutropenia or other complications.

2.1

TREAT: A Phase II Trial on Refinement of Early-Stage Non-Small Cell Lung Cancer Adjuvant Chemotherapy with Cisplatin/Pemetrexed (CPx) versus Cisplatin/Vinorelbine (CVb)

	CPx (n = 67)	**CVb** (n = 65)	*p*-value
Clinical feasibility rate*†	95.5%	75.4%	0.001
Delivery of absolute intended dose	74.6%	20.0%	<0.0001
Grade 3 or 4 hematologic toxicity	10.5%	76.5%	<0.0001

* No death due to cancer, toxicity or comorbidity; no nonacceptance by patients leading to premature withdrawal; no observation of dose-limiting toxicity
† Primary endpoint; secondary efficacy endpoints not yet reported — awaiting longer follow-up

Kreuter M et al. *Proc ASCO* 2011;**Abstract 7002**.

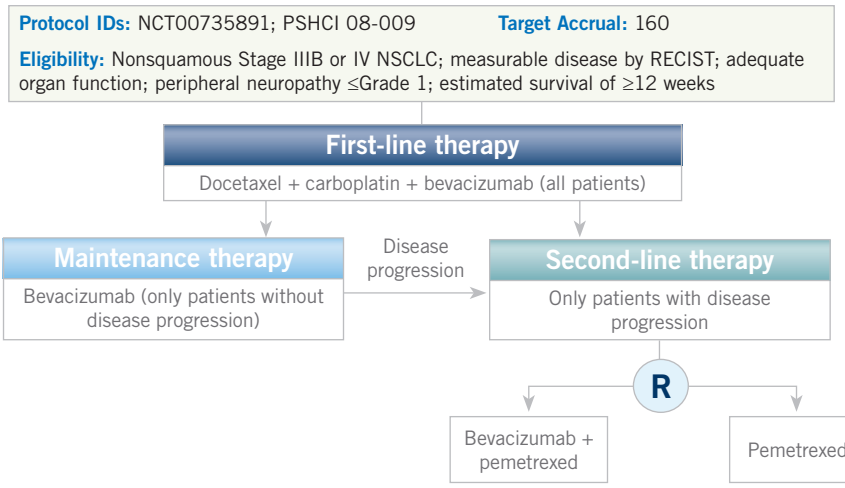
CD 1, Track 27

DR LOVE: How do you approach the patient with metastatic disease who develops slow progression after having a long response to chemotherapy/bevacizumab?

DR WAKELEE: Currently we have a trial in which patients with metastatic disease receiving bevacizumab maintenance are randomly assigned to continue with bevacizumab or not when a new agent is added to second-line therapy upon disease progression (2.2). This will provide important information about the utility of bevacizumab continuation in patients with lung cancer, but I don't currently use the continuation approach outside a trial setting.

2.2

Phase II Trial to Determine the Potential Benefit of Continued Bevacizumab Therapy After Disease Progression or Treatment Failure in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)



www.clinicaltrials.gov, May 2012.

CD 2, Track 2

DR LOVE: Would you discuss the "Patel regimen" as first-line therapy for NSCLC and the ongoing Phase III trial evaluating this regimen?

DR WAKELEE: A Phase II trial of patients who received the "Patel regimen" of 4 cycles of carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab had encouraging progression-free and overall survival (Patel 2009). The Phase III PointBreak trial is now comparing that regimen to the standard ECOG-E4599 regimen, and those results should be available soon (2.3).

CD 2, Track 5

DR LOVE: Would you talk about the new research strategy of combining MET inhibitors and erlotinib for patients with advanced NSCLC?

DR WAKELEE: In 2 randomized Phase II trials, patients with erlotinib-naïve disease received erlotinib with or without one of the MET inhibitors onartuzumab (a monoclonal antibody) or tivantinib (a TKI). Onartuzumab and tivantinib inhibit MET but by different mechanisms. A progression-free survival benefit and an overall survival advantage trend were observed in patients who received tivantinib (Sequist 2011; [2.4]). Thus a Phase III trial has been initiated (NCT01244191).

On evaluation of all patients in the intention-to-treat population treated on the Phase II trial of onartuzumab, no progression-free or overall survival advantage was seen. However, in the subgroup of patients with high MET expression, a substantial benefit occurred. Patients without high MET expression did not benefit. If anything, there

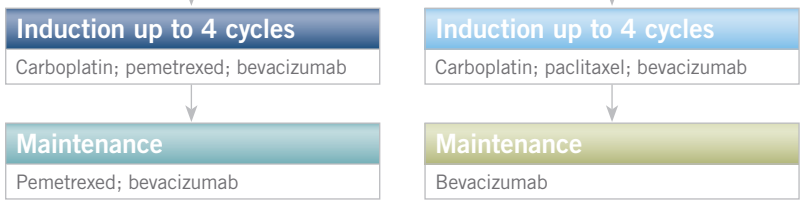
was potential harm (Spigel 2011; [2.5]). This has led to a focused Phase III trial in a subpopulation of patients with high MET expression (NCT01456325).

2.3

PointBreak: A Phase III Study of Chemotherapy/Bevacizumab Followed by Maintenance Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT00762034 **Target Accrual:** 900

Eligibility: Nonsquamous Stage IIIB or IV NSCLC; no prior treatment allowed, excluding radiation therapy to <25% of bone marrow; stable, treated brain metastasis allowed



Primary endpoint: Overall survival

www.clinicaltrials.gov, May 2012.

2.4

Phase II Trial of Erlotinib and Tivantinib (ET) versus Erlotinib and Placebo (EP) for Patients with Erlotinib-Naïve, Previously Treated Advanced Non-Small Cell Lung Cancer

Outcome	**ET** (n = 84)	**EP** (n = 83)	Hazard ratio	*p*-value
Median PFS (INV)	3.8 mo	2.3 mo	0.81	0.24
Median PFS (IRR)	3.6 mo	2.0 mo	0.74	0.09
Median OS (INV)	8.5 mo	6.9 mo	0.87	0.47

PFS = progression-free survival; INV = investigator assessment; IRR = independent central radiology review; OS = overall survival
Hazard ratio <1 favors ET.

Sequist LV et al. *J Clin Oncol* 2011;29(24):3307-15.

CD 2, Track 6

DR LOVE: What are your thoughts on new trials evaluating the use of the irreversible TKI afatinib in combination with cetuximab for patients with advanced NSCLC who experience progression on erlotinib?

DR WAKELEE: The combination of afatinib/cetuximab in patients with NSCLC and acquired EGFR resistance produced striking results (Horn 2011; [2.6]). Most patients with EGFR mutation-positive NSCLC demonstrated a good response to erlotinib for a while and then developed resistance. In this study most of the patients responded to treatment regardless of whether the disease was T790M mutation positive. ■

2.5 OAM4558g: A Phase II Trial of Erlotinib (E) with or without Onartuzumab as Second- or Third-Line Therapy for Advanced Non-Small Cell Lung Cancer

	Patients with positive c-MET immunohistochemistry			
	E + onartuzumab	E + placebo	Hazard ratio	*p*-value
Median progression-free survival	2.9 mo	1.5 mo	0.53	0.04
Median overall survival	12.6 mo	3.8 mo	0.37	0.002
	Patients with negative c-MET immunohistochemistry			
Median progression-free survival	1.4 mo	2.7 mo	1.82	0.05
Median overall survival	8.1 mo	15.3 mo	1.78	0.16

Spigel DR et al. *Proc ASCO* 2011;**Abstract 7505**.

2.6 Efficacy of Combined EGFR Targeting with Afatinib and Cetuximab by T790M Mutation Status in Patients with Advanced Non-Small Cell Lung Cancer and Resistance to an EGFR Tyrosine Kinase Inhibitor

Best response	T790M-positive (n = 35)	T790M-negative (n = 16)	T790M uninformative (n = 2)	No EGFR mutation (n = 2)
Any partial response (PR)	51%	56%	50%	—
Confirmed PR	31%	32%	50%	—
Stable disease (SD)	43%	38%	50%	100%
Clinical response (any PR + SD)	94%	94%	100%	100%
Progressive disease	6%	6%	—	—

Dose: Afatinib 40 mg PO per day, cetuximab 500 mg/m^2 IV

Horn H et al. *Proc IASLC* 2011;**Abstract O19.07**.

SELECT PUBLICATIONS

Horn L et al. **Activity and tolerability of combined EGFR targeting with afatinib (BIBW 2992) and cetuximab in T790M+ NSCLC patients.** *Proc IASLC* 2011;**Abstract O19.07**.

Janjigian YY et al. **Phase I/II trial of cetuximab and erlotinib in patients with lung adenocarcinoma and acquired resistance to erlotinib.** *Clin Cancer Res* 2011;17(8):2521-7.

Kreuter M et al. **Randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed (CPx) versus cisplatin and vinorelbine (CVb): TREAT.** *Proc ASCO* 2011;**Abstract 7002**.

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.

Sequist LV et al. **Randomized Phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non–small-cell lung cancer.** *J Clin Oncol* 2011;29(24):3307-15.

Spigel DR et al. **Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC.** *Proc ASCO* 2011;**Abstract 7505**.

Wakelee HA et al. **Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small cell lung cancer (NSCLC).** *Proc ASCO* 2011;**Abstract 7013**.