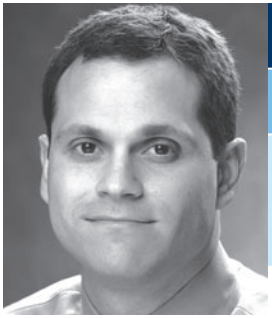

INTERVIEW

David R Spigel, MD

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Tracks 1-15

Track 1 Final results from the OAM4558g trial

Track 2 MetMAb-associated edema

Track 3 Rationale for targeting the MET pathway in patients with EGFR activating mutations and acquired resistance to erlotinib

Track 4 Phase III trial of MetMAb and erlotinib for patients with MET diagnostic-positive NSCLC who have received chemotherapy for advanced disease

Track 5 Analysis of patients with MET amplification by FISH on the OAM4558g trial

Track 6 MET inhibitor-associated side effects

Track 7 Results of a Phase III trial of amrubicin versus topotecan as second-line treatment for small cell lung cancer

Track 8 **Case discussion:** A 37-year-old man and nonsmoker with ALK, EGFR and K-ras wild-type adenocarcinoma of the lung experiences disease progression while receiving CP

Track 9 Treatment approach for EGFR wild-type metastatic adenocarcinoma of the lung

Track 10 Updated survival results of a Phase III study comparing carboplatin/nanoparticle albumin-bound (*nab*) paclitaxel to carboplatin/paclitaxel as first-line therapy for advanced NSCLC

Track 11 **Case discussion:** A 63-year-old woman and nonsmoker with resected T2N1 Stage IIA NSCLC and an L858R EGFR activating mutation

Track 12 TREAT: A randomized Phase II trial on the refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin/pemetrexed versus cisplatin/vinorelbine

Track 13 Initial results and future role of immunotherapy in the treatment of lung cancer

Track 14 Perspective on the role of the irreversible EGFR tyrosine kinase inhibitor (TKI) afatinib for patients with newly diagnosed NSCLC and those with acquired resistance to erlotinib or gefitinib

Track 15 Phase II study of erlotinib/tivantinib versus erlotinib alone for previously treated NSCLC

Select Excerpts from the Interview

Tracks 1-2, 4-5

DR LOVE: Would you discuss the results you presented at ASCO 2011 evaluating MetMAb in combination with erlotinib for advanced NSCLC?

DR SPIGEL: We presented data from the Phase II OAM4558g trial, which evaluated MetMAb/erlotinib versus erlotinib/placebo. No advantage was observed with MetMAb/erlotinib compared to placebo/erlotinib for PFS or OS in the overall patient population, but a PFS advantage was evident for patients with MET diagnostic-positive disease treated with MetMAb/erlotinib. In the MET diagnostic-negative subgroup, the opposite was true — patients who received MetMAb/erlotinib experienced decreased PFS and OS (Spigel 2011; [2.1]).

No excess toxicity was observed with MetMAb except for edema. Peripheral edema was largely low grade and reversible, but a few patients experienced serious generalized edema, which appears to be a class effect. The other toxicities observed were what we'd expect with erlotinib — rash, diarrhea and fatigue. We did not witness any imbalances based on MetMAb exposure.

DR LOVE: Any indication as to why the MET diagnostic-negative group fared worse?

DR SPIGEL: We don't understand it. It's not simply that patients don't benefit — the suggestion is harm to the patients. If we know erlotinib offers so much benefit in the diagnostic-negative subgroup and worse outcomes are observed with the addition of MetMAb, the obvious connection is that MetMAb interferes with erlotinib's activity.

Crosstalk occurs among the MET pathway, hepatocyte growth factor signaling and the EGFR pathway, so it may have something to do with dependence on the pathway. Overall, it was felt that it was not a safe design for a Phase III study for these patients. However, I believe MetMAb and other agents

2.1

OAM4558g: A Phase II Trial of Erlotinib (E) with or without MetMAb in Advanced Non-Small Cell Lung Cancer

	Patients with positive c-MET immunohistochemistry			
	E + MetMAb	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**.

targeting this pathway should continue to be explored in solid tumors, and we shouldn't discount them for patients with MET-negative tumors until the studies have been completed.

DR LOVE: Would you expect erlotinib/MetMAb to be effective in EGFR mutation-positive disease, EGFR mutation-negative disease or both?

DR SPIGEL: We don't know yet. A prospective randomized Phase III study is in development that will focus on patients with MET diagnostic-positive disease, so patients will be selected up front for MET positivity. EGFR mutations are a source of continued debate, but it's unlikely that they will confound the data because of their low prevalence in the Western population.

Track 9

DR LOVE: How do you generally approach EGFR wild-type metastatic adenocarcinoma in terms of chemotherapy and maintenance therapy?

DR SPIGEL: Outside of a trial, when the results come back negative for EGFR and ALK, you turn to standard chemotherapy. I've been impressed with carboplatin/pemetrexed, not because of its efficacy but because I believe it's easier to administer than carboplatin/paclitaxel.

We participated in the PointBreak trial — jokingly referred to as "Sandler versus Patel" — as it evaluated the ECOG-E4599 regimen of carboplatin/paclitaxel/bevacizumab followed by bevacizumab versus carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab. We await those results to see if it makes sense to administer bevacizumab.

I discuss bevacizumab with all patients, and for some I administer it with pemetrexed and carboplatin. The question is, what do I do after 4 cycles? Do I stop and administer pemetrexed and bevacizumab, stop and administer pemetrexed alone, stop and administer bevacizumab alone or stop altogether?

I've done each of those based on patient preference and how they're faring overall. It's a big commitment to stay on pemetrexed and bevacizumab every 3 weeks indefinitely, but that may be where we're headed.

Track 10

DR LOVE: What are your thoughts on nanoparticle albumin-bound (*nab*) paclitaxel and the data presented this year at ASCO by Mark Socinski?

DR SPIGEL: I've been surprised by not only how easy *nab* paclitaxel is to administer but also by the amount of disease control. Dr Socinski presented results of a randomized Phase III study first presented last year, including updated survival data (2.2).

An advantage was observed in favor of *nab* paclitaxel in terms of response rate, although no advantage was evident for survival. Signals were observed

in subset analyses of patients with squamous cell carcinoma and in the elderly, and this agent probably offers the same activity as any second- or third-line monotherapy. It's well tolerated, patients can stay on it and it's a quick infusion.

2.2

Efficacy of Carboplatin/*Nab* Paclitaxel versus Carboplatin/Paclitaxel as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

Response rate by histologic subtype[1]	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
All patients (n = 531; 521)	25%	33%	1.31	0.005
Squamous (n = 221; 228)	24%	41%	—	<0.001
Nonsquamous (n = 310; 292)	25%	26%	—	0.808
Survival by histologic subtype and age[2]	**Carboplatin/ paclitaxel**	**Carboplatin/ *nab* paclitaxel**	**Hazard ratio**	***p*-value**
Median PFS — all patients (n = 531, 521)	5.8 mo	6.3 mo	0.902	0.214
Squamous (n = 221, 229)	5.7 mo	5.6 mo	0.865	0.245
Nonsquamous (n = 310, 292)	6.5 mo	6.9 mo	0.933	0.532
Median OS — all patients (n = 531, 521)	11.2 mo	12.1 mo	0.922	0.271
Age ≥70 years (n = 82, 74)	10.4 mo	19.9 mo	0.583	0.009

* Response ratio >1 favors *nab* paclitaxel

PFS = progression-free survival; OS = overall survival

[1] Socinski MA et al. *Proc ASCO* 2010;**Abstract LBA7511**.
[2] Socinski MA et al. *Proc ASCO* 2011;**Abstract 7551**.

Track 12

DR LOVE: Would you comment on the TREAT study of adjuvant cisplatin/vinorelbine versus cisplatin/pemetrexed for early-stage NSCLC?

DR SPIGEL: This is the first adjuvant data set to compare the so-called standard — cisplatin/vinorelbine — to what might be considered our most modern regimen, cisplatin/pemetrexed (Kreuter 2011; [2.3]). I was impressed that cisplatin/pemetrexed showed activity and safety, but I typically administer carboplatin/paclitaxel in this setting. I've considered pemetrexed and carboplatin, but I've only used it for about 5 patients.

Track 15

DR LOVE: What is known about the combination of erlotinib and tivantinib (ARQ 197) in previously treated NSCLC?

2.3

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
Proportion of patients receiving planned cumulative dose	74.6%	20.0%	<0.0001
Grade 3 or 4 hematologic toxicity	10.5%	76.5%	<0.0001

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

DR SPIGEL: ARQ 197 is an oral small-molecule inhibitor of MET. We recently saw the updated results from a randomized Phase II study of ARQ 197 in combination with erlotinib or placebo for patients with refractory disease (Sequist 2011). The initial intent-to-treat analysis didn't report a benefit, but an adjusted analysis favored ARQ 197 and erlotinib in terms of PFS.

A preplanned subset analysis evaluating patients with nonsquamous tumors showed that the advantage was even larger in that setting, which was true for PFS and OS. An unusual advantage was also observed in patients with K-ras mutations. That led to a randomized global Phase III study in which patients with nonsquamous tumors are randomly assigned to ARQ 197/erlotinib or erlotinib/placebo. The primary endpoint is OS, and total planned enrollment is nearly 1,000. ■

SELECT PUBLICATIONS

Adjei AA et al. **Early clinical development of ARQ 197, a selective, non-ATP-competitive inhibitor targeting MET tyrosine kinase for the treatment of advanced cancers.** *Oncologist* 2011;16(6):788-99.

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**.

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.

Socinski MA et al. **Survival results of a randomized, phase III trial of *nab*-paclitaxel and carboplatin compared with Cremophor-based paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer.** *Proc ASCO* 2011;**Abstract 7551**.

Socinski MA et al. **Results of a randomized, phase III trial of *nab*-paclitaxel (*nab*-P) and carboplatin (C) compared with Cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract LBA7511**.

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**.

Surati M et al. **Role of MetMAb (OA-5D5) in c-MET active lung malignancies.** *Expert Opin Biol Ther* 2011;11(12):1655-62.