INTERVIEW

Julie R Brahmer, MD

Dr Brahmer is Associate Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at John Hopkins in Baltimore, Maryland.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you discuss the data you reported with the monoclonal antibody anti-PD-1 in non-small cell lung cancer (NSCLC)?

DR BRAHMER: These data are exciting in that this is the first time we've observed robust responses to antibody therapy in patients with lung cancer. For 76 patients with lung cancer, the reported response rate with the anti-PD-1 antibody was 18% (Brahmer 2012a; [1.1]).

If you break this down by histology, the response rate among patients with squamous cell histology was approximately 33% and the response rate for patients with nonsquamous cell histology was approximately 11%. But it is important to realize that most of these patients' disease was heavily pretreated — this Phase I trial allowed patients to have received 2 to 5 prior therapies. The majority of the patients had received 3 or more therapies.

So the fact that we saw long-lasting responses is interesting. The progression-free survival rate for the patients who were followed for 6 months was higher than 20%. The responses are maintained with time and, in my experience, are longer than those in patients who receive chemotherapy, particularly among those with heavily pretreated disease.

DR LOVE: In the "spider plot" from your presentation, 1 patient was a year out from stopping therapy but the response continued (Brahmer 2012a; [1.2]). How many patients like that have you seen?

DR BRAHMER: In the lung cancer group a handful of patients are beyond 2 years without needing therapy. We saw more patients with melanoma and renal cell carcinoma in that situation, but they've been followed longer. On this trial patients started therapy and if they achieved a response or stable disease, they received treatment for up to 2 years. At that point if the response was maintained, therapy was stopped.

1.1

Efficacy and Tolerability of the Anti-PD-1 Antibody in Patients with Advanced Non-Small Cell Lung Cancer

Efficacy

	Dose mg/kg	Patients n	ORR n (%)	Duration of response, months	SD ≥24 wk n (%)	PFSR at 24 wk %
All evaluable patients	1-10	76	14 (18)	1.9+ to 30.8+	5 (7)	26
Dose levels evaluated	1	18	1 (6)	9.2+	1 (6)	16
	3	19	6 (32)	1.9+ to 30.8+	2 (11)	41
	10	39	7 (18)	3.7 to 14.8+	2 (5)	24

Select drug-related adverse events (AEs) occurring in ≥5% of the population

	All grades	Grades 3 and 4*
	Number (%) of patients, all doses	
Any AE	78 (64)	10 (8)
Fatigue	22 (18)	2 (2)
Rash	5 (4)	—
Diarrhea	7 (6)	1 (1)

ORR was assessed using modified RECIST v1.0. The response rate was higher for patients with squamous cell histology.
* The most common Grade 3 and 4 AEs were fatigue, pneumonitis and elevated AST (2 patients each). An additional 16 Grade 3 and 4 drug-related AEs were observed, 1 or more occurring in a single patient.
ORR = overall response rate; SD = stable disease; PFSR = progression-free survival rate

Brahmer JR et al. *Proc ASCO* 2012a;**Abstract 7509**.

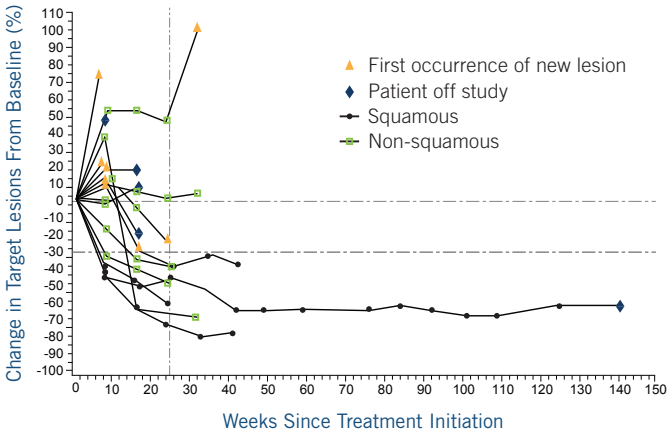
DR LOVE: Another aspect of the spider plot that caught my attention was that in at least a couple of patients the disease progressed and then responded. What are your thoughts on the issue of monitoring responses for patients receiving immune-based therapies?

DR BRAHMER: The hardest aspect for us to get used to is leaving patients on therapy while their disease is radiographically worsening. In this trial and in other immunotherapy trials we're moving toward immune-related response criteria with which clinically stable patients are allowed to remain on study while the disease is getting worse. We do observe the disease decreasing in size with time. In some patients a new lesion is found, and in other studies treatment would be discontinued but they're allowed to stay on this trial.

DR LOVE: What are the side effects observed with the anti-PD-1 antibody?

DR BRAHMER: In terms of side effects, we observed immune-related toxicities such as colitis, hepatitis, hypophysitis and thyroiditis. Probably the most worrisome was pneumonitis, and 3 patients on this study died from complications related to pneumonia. The most common toxicity was fatigue (1.1). That being said, in general the side effects are easier to tolerate than those of chemotherapy, which is in part why the anti-PD-1 antibody can be administered for so long.

1.2 **Clinical Activity of the Anti-PD-1 Antibody in Advanced Non-Small Cell Lung Cancer**



Changes from baseline in the tumor burden, measured as the sum of the longest diameters of target lesions, in patients with NSCLC who received anti-PD-1 antibody at a dose of 3.0 mg/kg.

With permission from Brahmer JR et al. *Proc ASCO* 2012a;**Abstract 7509**.

Track 8

DR LOVE: Would you discuss the LUX-Lung 3 data from ASCO on afatinib, which demonstrated superiority to cisplatin/pemetrexed as first-line therapy for patients with advanced disease harboring EGFR mutations?

DR BRAHMER: The data are tantalizing and indicate that irreversible EGFR tyrosine kinase inhibitors (TKIs) also delay disease progression for longer and outperform chemotherapy in those patients with EGFR mutations (Yang 2012; [1.3]). You can't

compare these data directly to those from similar trials with reversible TKIs, but the progression-free survival here is impressive.

1.3

LUX-Lung 3: A Phase III Trial of Afatinib versus Cisplatin/Pemetrexed (Cis/Pem) as First-Line Therapy in Advanced EGFR-Mutant Non-Small Cell Lung Cancer

Efficacy	Afatinib (n = 230)	Cis/pem (n = 115)	Hazard ratio	*p*-value
Median progression-free survival	11.1 mo	6.9 mo	0.58	0.0004
Objective response rate	56.1%	22.6%	—	<0.001

Yang JC et al. *Proc ASCO* 2012;**Abstract LBA7500**.

Track 9

DR LOVE: How do you approach patients with EGFR mutations who have good responses to erlotinib and then experience disease progression?

DR BRAHMER: I try to find a clinical trial for these patients, and in the past 6 months I've started obtaining a biopsy to ascertain if a T790 mutation has developed. We have trials for that, and other mechanisms of resistance are being discovered also, including MET amplification. A Phase I trial is combining 2 oral agents that may block these pathways.

Other trials use oral TKIs that bind to the pocket of the T790 mutation, and MET amplification, MET inhibitors or MEK inhibitors may play a role in these patients. Six months ago I wouldn't have biopsied the disease, but now I do when it's progressing in patients with previous EGFR mutations to determine whether they're developing resistance mutations.

If we don't have a clinical trial, I don't stop the erlotinib but I add chemotherapy. If patients are not tolerating erlotinib, I may stop and switch to chemotherapy, but I consider the afatinib/cetuximab data from Memorial, which initially included a long washout period (Janjigian 2011).

Many patients' disease progressed quickly, and that's part of the reason the washout period was shortened in that trial. In taking patients off the erlotinib, a rebound was observed. Maintaining the response to the EGFR TKI is important for these patients. ■

SELECT PUBLICATIONS

Brahmer JR et al. **Clinical activity and safety of anti-PD1 (BMS-936558, MDX-1106) in patients with advanced non-small-cell lung cancer (NSCLC).** *Proc ASCO* 2012a;**Abstract 7509**.

Brahmer JR et al. **Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.** *N Engl J Med* 2012b;366(26):2455-65.

Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525**.

Topalian SL et al. **Anti-PD-1 (BMS-936558, MDX-1106) in patients with advanced solid tumors: Clinical activity, safety, and a potential biomarker for response.** *Proc ASCO* 2012a;**Abstract CRA2509**.

Topalian SL et al. **Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.** *N Engl J Med* 2012b;366(26):2443-54.