INTERVIEW

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Select Excerpts from the Interview

Track 4

DR LOVE: What is known about the clinical behavior of tumors based on the type of EGFR mutation present?

DR JOHNSON: Not all EGFR mutations respond in the same way. The most common are exon 19 deletions, which are associated with the highest response rate of about 80%. Patients with exon 19 deletions who receive EGFR TKI therapy experience a median PFS in the 15- to 18-month range. The second most common is a L858R mutation, which has response rates of approximately 60% and median PFS of about 12 months.

One EGFR mutation that's dramatically different is called an insertion mutation of exon 20, meaning several amino acids are inserted into the epidermal growth factor receptor. Tumors with this mutation are resistant to EGFR TKI therapy. So we typically don't administer erlotinib to patients with this mutation.

It's important for an oncologist in practice to know whether a mutation sensitizes a tumor to a specific inhibitor or makes it resistant. We also believe it is important for oncologists who don't work with these agents every day to have a tool that will allow them to provide additional information to the patient as to why this is the case. Perhaps the leading site for providing this information is an academic site developed by Dr William Pao at Vanderbilt. It is called My Cancer Genome. I believe it provides unbiased information and is probably the leading site we use for both defining the mutations and determining whether these mutations are sensitizing or nonsensitizing.

Track 9

DR LOVE: Would you discuss what is currently known about BRAF mutations in melanoma and lung cancer and how agents like vemurafenib might fit into the management of these patients?

DR JOHNSON: BRAF mutations are present in about half of melanoma cases. As was published last year, vemurafenib is active in melanoma and is FDA approved for patients with BRAF mutations. Vemurafenib has produced a response rate in excess of 50% with a PFS of 8 to 10 months in patients with BRAF V600-mutant advanced melanoma (Sosman 2012). It demonstrates dramatic activity, particularly because this disease historically has not been highly responsive. The majority of BRAF mutations in melanoma are at one specific amino acid location, and they typically cause the V600E mutation.

BRAF mutations occur in 2% of patients with lung cancer, with a smaller proportion being V600E mutant (Paik 2011). In our current trial of a BRAF inhibitor for patients with NSCLC with BRAF mutations, only 1 out of the 7 patients has had to discontinue therapy, and that was due to the development of an allergic reaction.

In contrast, BRAF mutations are apparently not as active in colon cancer. Even though findings were similar in lung cancer and melanoma, thus far the same is not true for colon cancer. So it appears that the tumor type makes a difference. In terms of treating all tumors based on mutation expression, that approach has been used with selumetinib (AZD-6244), a MEK inhibitor, in an attempt to control BRAF-mutant disease.

Track 10

DR LOVE: What is known about agents directed at K-ras mutations?

DR JOHNSON: We were encouraged by the results of a randomized Phase II trial of docetaxel with or without selumetinib as second-line treatment for advanced K-ras-mutant NSCLC (Jänne 2012). The addition of selumetinib to docetaxel produced dramatic benefits with 37% response rates, a longer PFS and a median overall survival of 9 months. In comparison, patients who received docetaxel in combination with placebo had a median overall survival of 5 months without responses. The hazard ratio for survival was about 0.8, which was disappointing because the lines crossed over at the end. But the response rates and the PFS were encouraging. Based on these results, a randomized Phase III trial with approximately 80 patients is being discussed.

Track 11

DR LOVE: What other novel agents for lung cancer are you excited about?

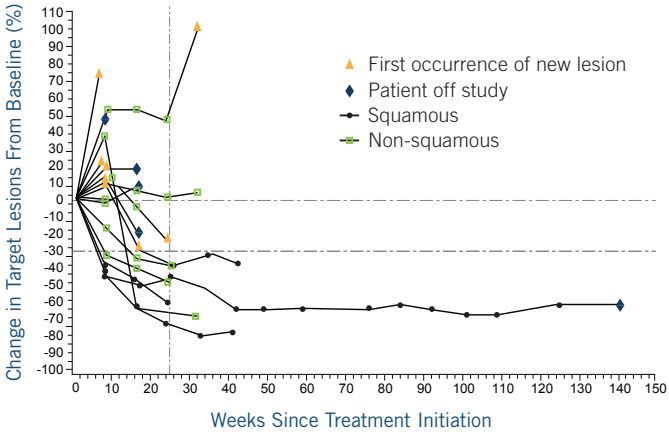
DR JOHNSON: Anti-PD-1 is a monoclonal antibody that inhibits an immune checkpoint, and we have had personal experience with it. It has demonstrated dramatic antitumor activity in melanoma, for which it was initially developed (Topalian 2012).

The recent report of 3 different dose levels — 1, 3 and 10 mg/kg — with approximately 70 patients with NSCLC showed clinical responses to 3 and 10 mg/kg in approximately 20% of the patients (Brahmer 2012). Some of these responses are encouraging (2.1), with the patients continuing therapy for years. A disproportionate share of responses were observed in patients with squamous cell carcinomas, and further trials of this agent versus chemotherapy are under consideration.

In our experience we've observed dramatic and prolonged responses in subsets of patients with NSCLC. We don't yet have a predictive biomarker to identify the patients who will benefit from such therapy, but the overall response rate in lung cancer at 3

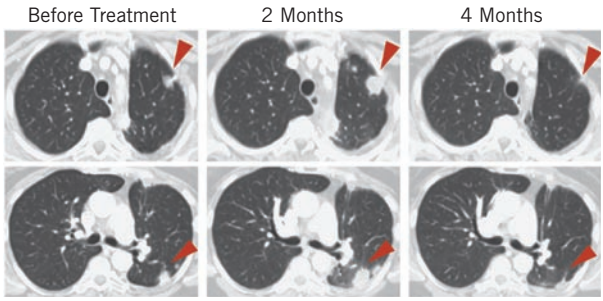
2.1 **Clinical Activity of Anti-PD-1 in Advanced Non-Small Cell Lung Cancer**

1



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.

2



Partial response in a patient with metastatic nonsquamous NSCLC who received anti-PD-1 antibody at a dose of 10.0 mg/kg. The arrows show initial progression in pulmonary lesions, followed by regression (an immune-related pattern of response).

[1] With permission from Brahmer JR et al. *Proc ASCO* 2012;**Abstract 7509**; [2] From *New England Journal of Medicine*, Topalian SL et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer, 366:2443-54. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

or 10 mg/kg appears to be approximately 20%. This would be as high or even higher than the 10% response rate observed with the conventional agents pemetrexed and docetaxel as second-line therapy.

Track 14

DR LOVE: Do you have any comments on the research strategy of using afatinib in combination with cetuximab for patients who previously received an EGFR TKI?

DR JOHNSON: One promising trial of the irreversible inhibitor afatinib in combination with cetuximab demonstrated response rates in excess of 50% (Janjigian 2011; [2.2]). This combination is believed to have the ability to inhibit the tyrosine kinase domain of EGFR and block agonist binding. The original hypothesis was that this combination would work in patients with disease harboring the T790M mutation, which is the most common mutation associated with resistance. However, antitumor activity has been observed in patients with acquired resistance as well as in other patients. So it's by far the most promising combination that we've seen in the acquired-resistance setting, and it's one that we as an institution are trying to get involved with for our patients. ■

2.2

Phase Ib Study of Afatinib and Cetuximab for Patients with Non-Small Cell Lung Cancer with Acquired Resistance to Erlotinib or Gefitinib

Best response at MTD	T790M-positive (n = 26)	T790M-negative (n = 14)	T790M unknown (n = 3)	No EGFR mutation (n = 2)
Any partial response (PR)	50%	57%	67%	—
Confirmed PR	35%	50%	67%	—
Stable disease (SD)	42%	36%	33%	100%
Clinical response (any PR + SD)	92%	93%	100%	100%
Select adverse events at MTD (n = 47)	All grades		Grade ≥3	
Rash	89%		6%	
Diarrhea	74%		6%	

MTD = maximum tolerated dose

Janjigian YY et al. *Proc ASCO* 2011;**Abstract 7525**.

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* 2012;**Abstract 7509**.

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**.

Jänne PA et al. **Phase II double-blind, randomized study of selumetinib (SEL) plus docetaxel (DOC) versus DOC plus placebo as second-line treatment for advanced KRAS mutant non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract 7503**.

Paik PK et al. **Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations.** *J Clin Oncol* 2011;29(15):2046-51.

Sosman JA et al. **Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib.** *N Engl J Med* 2012;366(8):707-14.

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