INTERVIEW

Chandra P Belani, MD

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Tracks 1-13

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What are your thoughts on maintenance treatment for patients with metastatic non-small cell lung cancer (NSCLC)?

DR BELANI: I believe maintenance therapy is a new treatment paradigm in advanced NSCLC, but some skepticism still exists regarding its role.

In our recent study, the use of maintenance pemetrexed after four cycles of platinum-based chemotherapy was associated with significant improvements in progression-free survival and overall survival compared to placebo maintenance. The preplanned subset analysis of patients with nonsquamous cell

histology revealed a provocative 5.2-month improvement in median overall survival. In this intent-to-treat analysis, significant survival advantages were observed in the entire population.

DR LOVE: How do you approach maintenance treatment for patients with EGFR mutation-positive advanced NSCLC?

DR BELANI: In the SATURN study of erlotinib as maintenance treatment for patients with advanced NSCLC, erlotinib was associated with a significant improvement in median progression-free survival and highly significant survival advantages in patients with EGFR mutations, with a *p*-value of less than 0.0001 (Cappuzzo 2010). Based on these data, patients with EGFR mutations should receive maintenance treatment with erlotinib. Otherwise, patients with

1.1

PARAMOUNT: Efficacy and Safety of Maintenance Pemetrexed (Pem) with Best Supportive Care (BSC) versus Placebo with BSC Immediately After Induction Therapy with Pem and Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer

Efficacy — Independent review*	Pem + BSC (n = 316)	Placebo + BSC (n = 156)
Median progression-free survival (PFS), from maintenance	3.9 months	2.6 months
Response rate	2.8%	0.6%
Complete response	0%	0%
Partial response	2.8%	0.6%
Stable disease	69%	59%
Select Grade 3 or 4 adverse events	**Pem (n = 359)**	**Placebo (n = 180)**
Fatigue†	4.2%	0.6%
Anemia†	4.5%	0.6%
Neutropenia†	3.6%	0%
Leukopenia	1.7%	0%
Sensory neuropathy	0.3%	0.6%
Mucositis/stomatitis	0.3%	0%
ALT (SGPT)	0.3%	0%

Conclusions

- The trial met its primary PFS endpoint with pem continuation maintenance therapy resulting in a significant benefit compared to placebo for patients with advanced nonsquamous non-small cell lung cancer.
- Pem maintenance was well tolerated.
- Mature overall survival data are pending.

* 88% of patients were independently reviewed (472/539)
† Statistically significant between arms ($p \leq 0.05$)

Paz-Ares LG et al. *Proc ASCO* 2011;**Abstract CRA7510**.

nonsquamous cell disease are good candidates for pemetrexed maintenance, and patients with a poor performance status should not receive maintenance therapy.

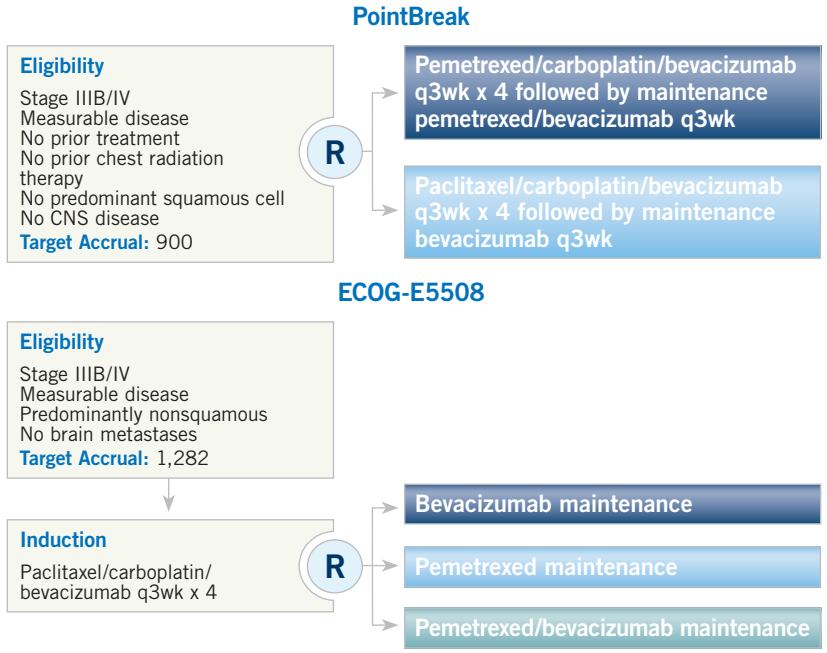
DR LOVE: How do you approach maintenance in patients with nonsquamous tumors who receive pemetrexed in the up-front setting?

DR BELANI: In clinical practice, pemetrexed is being continued into the maintenance setting, and the platinum agent is being discontinued. The PARAMOUNT trial (Paz-Ares 2011; [1.1]) is evaluating induction therapy with cisplatin/pemetrexed followed by maintenance with pemetrexed versus placebo.

The PointBreak study (Patel 2009) is evaluating the combination of carboplatin, pemetrexed and bevacizumab followed by maintenance with bevacizumab and pemetrexed compared to the investigational regimen used in the ECOG-E4599 trial — carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance (1.2). The PointBreak study is attempting to answer two different questions. One question is in the up-front setting and the other is in the maintenance setting.

1.2

Key Trials of Maintenance Therapy in Advanced Non-Small Cell Lung Cancer



CNS = central nervous system

www.clinicaltrials.gov. Identifiers NCT00762034 and NCT01107626.

Another maintenance therapy trial, ECOG-E5508, is studying the use of combination pemetrexed and bevacizumab (1.2). Patients are randomly assigned to maintenance with single-agent bevacizumab, single-agent pemetrexed or the combination of pemetrexed and bevacizumab.

DR LOVE: Outside of a research setting, how do you treat metastatic, EGFR-negative, EML4-ALK-negative adenocarcinoma?

DR BELANI: As a member of ECOG, I generally recommend either carboplatin/paclitaxel with or without bevacizumab followed by maintenance therapy with bevacizumab or the ECOG-E4599 regimen (Sandler 2006). The alternative is to administer carboplatin and pemetrexed, which I usually use without bevacizumab, and then use single-agent pemetrexed as maintenance therapy.

In North America, we substitute carboplatin for cisplatin, as the age-old controversy continues about which platinum agent is optimal.

DR LOVE: What is your approach to the treatment of metastatic squamous cell lung cancer?

DR BELANI: We tend to use carboplatin/paclitaxel or carboplatin/docetaxel. Carboplatin/gemcitabine is also available, but I don't favor it because of the associated thrombocytopenia.

Tracks 5-6

DR LOVE: What do we know about resistance to EGFR inhibitors?

DR BELANI: Sometime during treatment with reversible EGFR inhibitors, the disease eventually progresses. We are unsure whether this is attributable to MET gene amplification or the development of T790 mutation in the EGFR gene, which may be present at disease onset, but this type of disease stops responding to reversible EGFR inhibitors (Belani 2010).

For patients with EGFR mutations, the debate is whether to continue using the EGFR TKI while adding a new drug or whether an irreversible inhibitor of EGFR should be used instead.

Afatinib is an irreversible inhibitor of both EGFR — or HER1 — and HER2. A hint of activity has been seen in the Phase IIb/III clinical trial, in which afatinib was administered to patients whose disease progressed after 12 weeks or more of erlotinib or gefitinib.

Compared to placebo, a provocative and significant 2.2-month improvement in progression-free survival was observed with afatinib (Miller 2010; [1.3]), but no improvement in survival was evident because the patients on the placebo arm were crossed over to active treatment after only three to six weeks.

I believe afatinib is quite active, and the ongoing clinical trials for patients with EGFR mutations will probably show efficacy compared to combination chemotherapy in the front-line setting. ■

1.3

LUX-Lung 1: A Phase IIb/III Trial of Afatinib (BIBW 2992) with Best Supportive Care (BSC) versus Placebo and BSC for Patients with Non-Small Cell Lung Cancer Progressing on Chemotherapy and Erlotinib/Gefitinib

	Afatinib + BSC (n = 390)	Placebo + BSC (n = 195)	Hazard ratio	*p*-value
Efficacy				
Median overall survival	10.78 months	11.96 months	1.08	NS
Median progression-free survival	3.3 months	1.1 months	0.38	<0.0001
Disease control rate at eight weeks	58%	19%	—	<0.0001
Overall response rate	7.4%	0.5%	—	<0.01

NS = not significant

Miller VA et al. *Proc ESMO* 2010;**Abstract LBA1**.

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Paz-Ares LG et al. **PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC).** *Proc ASCO* 2011;**Abstract CRA7510**.

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