INTERVIEW

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Tracks 1-14

Track 1 **Case discussion:** A 76-year-old man who previously received multiple lines of local and systemic therapy for a multifocal SCC of the lung experiences an excellent response to the anti-PD-1 antibody pembrolizumab (MK-3475) on a clinical trial

Track 2 Clinical experience with and dosing of nanoparticle albumin-bound (*nab*) paclitaxel for patients with SCC and elderly patients with NSCLC

Track 3 Clinical activity and tolerability of pembrolizumab in PD-L1-negative SCC

Track 4 Ongoing and future trial strategies evaluating immune checkpoint inhibitors in NSCLC

Track 5 Common side effects of anti-PD-1 and anti-PD-L1 antibodies

Track 6 Chimeric antigen receptor-directed therapy in thoracic tumors

Track 7 **Case discussion:** An 89-year-old former heavy smoker with Stage IIIA, poorly differentiated SCC of the lung

Track 8 RTOG-1306/Alliance 31101: An ongoing randomized Phase II study of erlotinib or crizotinib prior to chemoradiation therapy for Stage III NSCLC

Track 9 **Case discussion:** A 65-year-old never smoker who underwent treatment 9 years ago for metastatic adenocarcinoma presents with progressive disease and is now found to harbor an ALK rearrangement

Track 10 First-line and maintenance therapy for patients with pan-wild-type adenocarcinoma who are eligible to receive bevacizumab

Track 11 Joint analysis of elderly patients on the Phase III PointBreak and ECOG-E4599 trials: Paclitaxel/carboplatin with bevacizumab as first-line therapy for nonsquamous NSCLC

Track 12 Activity of pemetrexed as second-line therapy for patients with ALK-positive NSCLC

Track 13 Perspective on the use of the VeriStrat® assay in clinical practice

Track 14 Recently approved and novel second- and third-generation ALK inhibitors

Select Excerpts from the Interview

Tracks 2, 10

DR LOVE: What is your approach to first-line and to maintenance therapy for patients with pan-wild-type adenocarcinoma of the lung?

DR LANGER: I will typically initially administer pemetrexed/carboplatin to these patients, and I will frequently graft bevacizumab onto that regimen if the patient has no contraindications (eg, active brain metastases, antecedent hemoptysis or ongoing thromboembolic phenomena).

Some may argue against such an approach by citing the PointBreak trial results, which compared pemetrexed/carboplatin/bevacizumab to paclitaxel/carboplatin/bevacizumab and reported no obvious survival advantage (Patel 2013). I believe from a toxicity standpoint, pemetrexed/carboplatin/bevacizumab is far better tolerated. Patients develop less neuropathy and alopecia, so their sense of wellbeing is much less impaired. And remember, they're only undergoing treatment every 3 weeks.

If the patient's condition has stabilized or a response is evident after 4 to 6 cycles, I continue pemetrexed and bevacizumab as maintenance therapy if possible. I do not have overall survival (OS) data to justify that approach, but we do have PFS data from the AVAPERL trial comparing bevacizumab to pemetrexed/bevacizumab as maintenance therapy. The authors reported a 3.7-month improvement in PFS with the combination. A trend toward improved survival was also apparent, but the trial was underpowered to demonstrate a survival benefit (Barlesi 2014).

A landmark analysis of the maintenance portion of the PointBreak trial reported about a 2-month difference in OS and PFS between the pemetrexed/bevacizumab combination and the control arm of bevacizumab. Unfortunately we have not seen the *p*-values or the hazard ratios for that analysis.

If a patient is older or has compromised renal function, I will frequently administer taxanes, either weekly paclitaxel or weekly *nab* paclitaxel. Remember, pemetrexed is not reliable or necessarily safe if the creatinine clearance is below 45. There's a relative paucity of data in that situation and highly unpredictable pharmacokinetics.

DR LOVE: Do you currently use *nab* paclitaxel in any other situations, and what is your clinical experience with its dosing in NSCLC?

DR LANGER: I administer *nab* paclitaxel to patients who are aged 70 or older and to patients with squamous cell NSCLC. I generally dose it weekly in order to reduce the peripheral neuropathy that is typically observed with solvent-based paclitaxel administered every 3 weeks. In preference to an uninterrupted schedule, I administer 80 to 100 mg/m^2 weekly for 3 weeks in a row and then allow a week off. I combine the *nab* paclitaxel with carboplatin, which is dosed at AUC 6 every 4 weeks. I find this to be an extraordinarily well-tolerated regimen. Even though many of these patients experience some neuropathy, it's generally quite mild and usually reverses a little faster and more profoundly than with solvent-based paclitaxel.

Track 11

DR LOVE: Any thoughts about the recent data evaluting bevacizumab in older patients?

DR LANGER: A secondary retrospective analysis of ECOG-E4599 by Suresh Ramalingam and colleagues evaluating bevacizumab in combination with chemotherapy versus chemotherapy alone for patients older than age 70 reported a trend toward superior PFS with the combination but no obvious OS advantage. As one might expect, a lot more toxicity occurred with the combination (Ramalingam 2008).

We performed a joint analysis of the PointBreak and ECOG-E4599 trials, comparing the paclitaxel/carboplatin/bevacizumab arms of both to the control arm from E4599 of paclitaxel/carboplatin alone. Obviously caveats apply to such an analysis, but these 2 trials had virtually identical eligibility criteria, and although they weren't contemporaneous,

they weren't so many years apart as to produce major differences in outcome. In this joint analysis the hazard ratio for the survival advantage with bevacizumab persists up until the age of 75. Beyond 75, that advantage is lost (Langer 2013; [2.1]). If anything, the control group fared a little better and the heightened toxicity continued. But nevertheless, on the basis of these data, which are virtually the only data that exist for patients between 70 and 75, I'll still offer bevacizumab. I'm a lot less enthused for patients beyond age 75.

2.1

Joint Analysis of the PointBreak and ECOG-E4599 Trial Results by Patient Age: Hazard Ratios for Paclitaxel/Carboplatin/Bevacizumab versus Paclitaxel/Carboplatin as First-Line Therapy for Nonsquamous Non-Small Cell Lung Cancer

	<65 years (n = 735)	65-75 years (n = 453)	70-75 years (n = 203)	<75 years (n = 1,188)	≥75 years (n = 157)
Overall survival	0.75 $p < 0.01$	0.80 $p = 0.05$	0.68 $p = 0.03$	0.78 $p < 0.01$	1.05 $p = 0.83$
Progression-free survival	0.71 $p < 0.01$	0.62 $p < 0.01$	0.57 $p < 0.01$	0.69 $p < 0.01$	0.95 $p = 0.80$

Langer CL et al. *Proc ASCO* 2013;Abstract 8073.

Tracks 3-4

DR LOVE: What are some of the ongoing and future approaches for using immune checkpoint inhibitors in the treatment of NSCLC?

DR LANGER: A significant proportion of patients with heavily pretreated advanced NSCLC seem to derive benefit from this class of compounds. Responses often continue for well over a year on observation without maintenance treatment (Brahmer 2012). That flies in the face of our typical approach with maintenance therapy.

Studies are now investigating this class of agents up front. The multiarm Phase I CheckMate 012 trial is investigating the anti-PD-1 antibody nivolumab in combination with platinum-based doublets, bevacizumab maintenance, erlotinib and ipilimumab or as monotherapy for newly diagnosed and Stage IIIB/IV NSCLC. Tremendous interest exists in combining anti-PD-1 agents with other immunotherapies, such as CTLA-4 inhibitors (NCT01928394). However, this combination may cause more toxicity than patients with advanced NSCLC can handle because they are generally older with more comorbidities than patients with melanoma. ■

SELECT PUBLICATIONS

Barlesi F et al. **Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: Updated survival analysis of the AVAPERL (MO22089) randomized phase III trial.** *Ann Oncol* 2014;25(5):1044-52.

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

Patel JD et al. **PointBreak: A randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(34):4349-57.

Ramalingam SS et al. **Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: Analysis of Eastern Cooperative Oncology Group Trial 4599.** *J Clin Oncol* 2008;26(1):60-5.