INTERVIEW

Mark G Kris, MD

Dr Kris is Chief of the Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

CD 1, Tracks 1-17

Select Excerpts from the Interview

CD 1, Tracks 2, 12-13

DR LOVE: Would you comment on EGFR mutations, EML4-ALK translocations and which patients should be tested for both?

DR KRIS: It makes sense at the diagnosis of metastatic disease to test for EGFR mutations. In the trial reported by Tony Mok in the *New England Journal of Medicine*, even if patients with adenocarcinoma had characteristics that predicted sensitivity

to erlotinib or gefitinib — women, Asians, never smokers — if they didn't have the mutation, there was a 1% chance that gefitinib would shrink the tumor (Mok 2009).

That changed how people approach patients at diagnosis and, as often as possible, patients undergo biopsies to determine whether EGFR mutations are present. If so, they receive erlotinib. If not, they receive chemotherapy. Now that we have crizotinib for patients with ALK rearrangements, it's been added to the repertoire. So at diagnosis tumors are tested for EGFR and ALK status. If you don't find either or are unable to obtain results, you administer chemotherapy. These concepts have been encoded and are standard in the NCCN guidelines.

I believe that every patient with metastatic adenocarcinoma of the lung should undergo testing, although I wouldn't recommend routine testing for patients with small cell lung cancer. I also wouldn't recommend it routinely for patients with squamous cell tumors, with a few exceptions. Never smokers with squamous cell tumors should be tested. Also, if the squamous cell diagnosis is based on a small biopsy specimen, it makes sense to test because of the possibility that it's actually adenocarcinoma. The NCCN guidelines don't say you should never test squamous cell tumors — only that you shouldn't do so routinely.

We've completed work that will be presented at ASCO indicating that roughly the same proportion of driver molecular lesions exist in squamous cell carcinoma as in adenocarcinoma. However, the mutations are different (Rekhtman 2012). We find amplification of the FGFR1 gene, a loss of PTEN and mutations in FGFR2, PI3 kinase and DDR1. If you add them up, it totals about 55%. So I believe that within the next 1 to 2 years we'll have a testing panel for squamous cell lung cancer that will differ from adenocarcinoma. The treatments directed at those targets are currently under investigation.

CD 1, Track 9

DR LOVE: How do you manage the side effects of EGFR TKIs?

DR KRIS: We are extremely fortunate to have dermatologist Dr Mario Lacouture at Memorial. He has dedicated his career to researching the optimal treatment for EGFR TKI dermatologic side effects, and not just the rashes but also the skin dryness, fingertip cracking and pruritus. It's a great resource for patients facing these toxicities. We have a whole repertoire of ways to ameliorate them, and Dr Lacouture approaches his patients in the same way — by using emollients, topical corticosteroids and antibiotics to treat secondary infections and trying to minimize the side effects.

I've also learned that you can use a much lower dose of the TKI and still obtain a good result. Dr Dan Costa from Beth Israel Deaconess in Boston reported on a series of patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) who received 25 mg of erlotinib, one sixth of the maximum tolerated dose (Yeo 2010). Basic scientific literature also indicates that mutated kinases are much more sensitive to the effects of TKIs like erlotinib and gefitinib, so you often can use a lower dose.

For patients with severe toxicities I often stop treatment until the toxicity resolves or is more tolerable, then I start back at a lower dose and try to titrate upward. In addition, I routinely start erlotinib at 100 mg per day. Among all the patients receiving erlotinib, that's the dose the majority tolerate. You can increase it if it's well tolerated or decrease even that dose if not.

CD 1, Track 16

DR LOVE: What are your thoughts on where nanoparticle albumin-bound (*nab*) paclitaxel is headed in lung cancer?

DR KRIS: The agent has distinct advantages. It doesn't have to be administered with dexamethasone, which can be difficult for many patients, particularly those with diabetes and those who are uncomfortable after receiving the high-dose steroids necessary to safely administer paclitaxel and docetaxel. It's also tremendously helpful for patients who experience hypersensitivity reactions to paclitaxel or docetaxel.

The NCCN guidelines permit you to recommend *nab* paclitaxel for patients who can't tolerate dexamethasone or have experienced hypersensitivity reactions, so our standard in those cases is to discontinue paclitaxel or docetaxel and substitute with *nab* paclitaxel. With an extra hour of infusion you can reduce the incidence of neutropenia.

With a 2-hour infusion the degree of neuropathy, which can otherwise be dose limiting, is also diminished. I've had patients receive this drug for years without neuropathy. Although preliminary, the data are compelling that a 2-hour infusion is better, and that's how we routinely administer this agent (Paik 2011; [1.1]). ■

1.1

Phase II Study of a 2-Hour versus 30-Minute Infusion of Weekly *Nab* Paclitaxel for Patients with Advanced Non-Small Cell Lung Cancer

	***Nab* paclitaxel 2-hour infusion (n = 25)**	***Nab* paclitaxel 30-minute infusion (n = 40)**
Safety		
Grade 3 or 4 neuropathy	4 (16%)	9 (23%)
Grade 3 or 4 neutropenia	3 (12%)	8 (20%)
Efficacy		
Median progression-free survival	5.3 months	5.3 months
Median overall survival	11 months	11 months

Paik PK et al. *Cancer Chemother Pharmacol* 2011;68(5):1331-7.

SELECT PUBLICATIONS

Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009;361(10):947-57.

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Non-small cell lung cancer — Version 3.2012.** Available at **www.nccn.org/professionals/physician_gls/pdf/nscl.pdf**.

Paik PK et al. **A phase 2 study of weekly albumin-bound paclitaxel (Abraxane®) given as a two-hour infusion.** *Cancer Chemother Pharmacol* 2011;68(5):1331-7.

Rekhtman N et al. **Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: Lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations.** *Clin Cancer Res* 2012;18(4):1167-76.

Yeo WL et al. **Erlotinib at a dose of 25 mg daily for non-small cell lung cancers with EGFR mutations.** *J Thorac Oncol* 2010;5(7):1048-53.