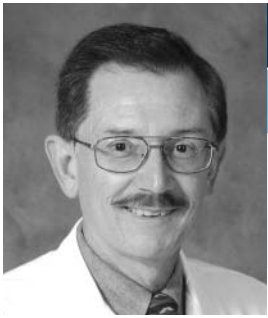

INTERVIEW

David R Gandara, MD

Dr Gandara is Professor of Medicine, Director of the Thoracic Oncology Program and Senior Advisor to the Director at UC Davis Comprehensive Cancer Center in Sacramento, California.

Tracks 1-11

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What do we know about KRAS mutations in NSCLC versus colorectal cancer (CRC)?

DR GANDARA: KRAS mutation patterns and their prevalence are different in NSCLC and CRC. In lung cancer, more KRAS mutations are associated with cigarette smoking. How KRAS mutations behave, their prognostic effects and the other proteins that associate with KRAS are also distinct. So the tumor type and the milieu of the tumor are important.

DR LOVE: Is KRAS a driver mutation in NSCLC, and what are the approaches to inhibit that pathway?

DR GANDARA: A driver mutation is important in carcinogenesis and would have prognostic significance. If a targeted therapy against the mutation were available, it would have predictive value also. I believe that KRAS is a driver mutation in lung cancer, although that is currently under debate.

We do not have a specific inhibitor of KRAS. Most therapies focus on targeting proteins further downstream in the pathway. For example, MEK inhibitors are effective against KRAS-mutated lung cancers. A study by Jänne and colleagues demonstrated a significantly better objective response and PFS for patients with KRAS-mutant advanced NSCLC treated with the MEK1/MEK2 inhibitor selumetinib in combination with docetaxel versus docetaxel alone (Jänne 2013).

We recently reported that the combination of the MEK inhibitor trametinib with docetaxel elicited approximately a 30% response in patients with both KRAS-mutant and wild-type lung cancer. The type of KRAS mutation was important. All 10 patients with the G12C mutation, the most common tobacco-related KRAS mutation, experienced tumor shrinkage. The response rate was 40%, and the disease control rate was 80% in this group of patients (Gandara 2013).

Track 7

DR LOVE: What are your thoughts about rebiopsying a tumor in recurrent NSCLC?

DR GANDARA: For a patient with oncogene-driven cancer, rebiopsy of the tumor should be performed after the first EGFR TKI fails. Will earlier rebiopsy of a tumor help to determine if resistance is emerging and suggest therapy would need to be altered? Some interesting data were presented in support of this idea, and it follows up on our own work detecting these driver mutations in plasma DNA.

Tony Mok and colleagues performed a retrospective analysis of the concordance between EGFR mutations detected in tumor specimens and those detected from plasma DNA samples from the FASTACT-2 study (Mok 2013; [3.1]). Tests revealed approximately a 90% concordance. After 3 months of erlotinib-based therapy, the blood was reanalyzed. Those patients who had cleared the mutation experienced a long PFS. The patients with persistence of the mutation quickly experienced therapy failure. This is an

3.1

Concordance of EGFR Mutation Analysis between Tumor and Plasma Samples in the FASTACT-2 Study of Intercalated Chemotherapy with Erlotinib versus Chemotherapy with Placebo for Advanced Non-Small Cell Lung Cancer

EGFR activating mutations	p-EGFR mutation-positive (plasma)	p-EGFR mutation-negative (plasma)	Total
t-EGFR mutation-positive (tumor)	69	21	90
t-EGFR mutation-negative (tumor)	5	129	134
Total	**74**	**150**	**224**

p-EGFR mutation = EGFR mutation status by plasma DNA analysis; t-EGFR mutation = EGFR mutation status by tissue DNA analysis

Study conclusions

- Concordance rate between tests on tumor and plasma samples is high (88%).
- The predictive power of EGFR mutations in plasma DNA for treatment outcome is similar to that with tumor tissue.
- EGFR mutation analysis of plasma DNA is a potential alternative method for patients with inadequate tumor tissue.

Mok T et al. *Proc ASCO* 2013;**Abstract 8021**.

example of being able to detect a plasma marker that will help to determine if therapy needs to be changed.

Tracks 9-10

DR LOVE: Would you discuss the background and rationale for the lung cancer Master Protocol initiative?

DR GANDARA: About 2 years ago, the Lung Cancer Thoracic Malignancy Steering Committee — the NCI committee for directing trials — met to discuss the issue of developing better clinical trials. One of the conclusions of that meeting was that we needed master protocols. This is a protocol that would encompass a large group of patients with a certain category of cancer, include a genomic analysis and place those patients on multiple different experimental treatment regimens depending on what was found in each patient's cancer. If we're successful in lung cancer, we will take this concept into other tumor types and globalize it. We have to show that the strategy can work and that we can efficiently screen more than 1,000 patients per year. We're starting with squamous cell lung cancer because that's an area of unmet need.

The Lung Master Protocol, or SWOG-S1400, is set to launch soon and will focus on patients with advanced squamous cell cancer. Each of the arms of the Master Protocol is a Phase II/III trial that will genomically screen patients. If an arm clears an intermediate hurdle in a comparison to a standard therapy, it proceeds to Phase III. At the end of the day, if a trial is positive for PFS, that agent and that biomarker will be FDA approved. So if we're screening more than 1,000 patients a year and we have 6 arms open at the same time and the prevalence of a genomic biomarker varies from 2% to 40%, we project a hit rate of at least 65% to 70%. This means that a physician who puts a patient through this process will have at least a 65% to 70% chance of matching that patient with a treatment. You might ask, "What about that 30% who didn't match?" We've tried to anticipate that. We have a "nonmatch arm." Our first nonmatch arm will evaluate an anti-PD-L1 agent.

The goal is to develop an infrastructure that becomes self-sustaining. Let's assume that the study agent on arm 1 is not effective and doesn't meet its interim endpoint. That arm closes and a new arm 1 is applied, or we can add arms. We're hoping that 10 years from now if this initiative is successful, we will have changed the way we do business in drug development and we will be able to get better drugs to patients faster and more cost efficiently. ■

SELECT PUBLICATIONS

Gandara D et al. **Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with docetaxel in KRAS-mutant and wild-type (WT) advanced non-small cell lung cancer (NSCLC): A phase I/Ib trial.** *Proc ASCO* 2013;**Abstract 8028**.

Jänne PA et al. **Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: A randomised, multicentre, placebo-controlled, phase 2 study.** *Lancet Oncol* 2013;14(1):38-47.

Maus MK et al. **KRAS mutations in non-small-cell lung cancer and colorectal cancer: Implications for EGFR-targeted therapies.** *Lung Cancer* 2014;83(2):163-7.

Mok T et al. **Detection of EGFR-activating mutations from plasma DNA as a potent predictor of survival outcomes in FASTACT 2: A randomized phase III study on intercalated combination of erlotinib (E) and chemotherapy (C).** *Proc ASCO* 2013;**Abstract 8021**.

O'Byrne KJ et al. **Molecular biomarkers in non-small-cell lung cancer: A retrospective analysis of data from the phase 3 FLEX study.** *Lancet Oncol* 2011;12(8):795-805.