INTERVIEW

Nasser H Hanna, MD

Dr Hanna is Associate Professor of Medicine at the Indiana University Medical Center School of Medicine in Indianapolis, Indiana.

Tracks 1-13

Select Excerpts from the Interview

Track 5

DR LOVE: The IPASS paradigm of using an EGFR tyrosine kinase inhibitor (TKI) up front in EGFR mutation-positive, advanced non-small cell lung cancer (NSCLC) is now well established. What about patients with wild-type tumors?

DR HANNA: Obviously erlotinib is not the preferred first-line therapy for these patients, but I believe it's reasonable to administer erlotinib to them as second-, third- and sometimes fourth-line therapy. If you evaluate the IPASS

data, those patients who were never smokers with EGFR wild-type adenocarcinoma had a significant early drop-off in terms of response if they received the EGFR inhibitor gefitinib (Mok 2009; [1.1]) instead of chemotherapy. Some patients who received gefitinib experienced rapid disease progression, and unfortunately, a significant number of patients died. These data support the use of chemotherapy rather than an EGFR inhibitor for never smokers with EGFR wild-type disease.

For a patient with an EGFR mutation, the preponderance of the data supports administering an EGFR inhibitor in the first-line setting. But we don't see a rapid drop-off in progression-free survival or overall survival in the first three months if we administer chemotherapy to those patients. So I don't believe you're wrong to administer chemotherapy in the front line for these patients, but a drug like erlotinib is preferred in this setting.

1.1

IPASS: A Phase III Randomized Trial of Gefitinib versus Carboplatin/Paclitaxel as First-Line Therapy for Clinically Selected (Asian, Nonsmokers or Former Light Smokers, Adenocarcinoma) Patients with Advanced Non-Small Cell Lung Cancer

Progression-free survival (events)	Gefitinib	Carboplatin + paclitaxel	Hazard ratio* (95% CI)	*p*-value
Intent-to-treat population (n = 609; 608)	74.4%	81.7%	0.74 (0.65-0.85)	<0.001
EGFR mutation-positive (n = 132; 129)	73.5%	86.0%	0.48 (0.36-0.64)	<0.001
EGFR mutation-negative (n = 91; 85)	96.7%	82.4%	2.85 (2.05-3.98)	<0.001

* Hazard ratio < 1.0 favors gefitinib; CI = confidence interval

Conclusions:
"The presence of an EGFR mutation was a robust predictor of improved progression-free survival with gefitinib, as compared with carboplatin-paclitaxel, and of the benefit of gefitinib with respect to the objective response rate, indicating that patients in whom an EGFR mutation has been identified will benefit most from first-line therapy with gefitinib.

Whenever possible, EGFR-mutation status should be determined before the initial treatment of pulmonary adenocarcinoma."

Mok TS et al. *N Engl J Med* 2009;361(10):947-57.

Track 10

DR LOVE: Would you discuss the clinical data we have with crizotinib, the small-molecule inhibitor that targets the EML4-ALK fusion oncogene?

DR HANNA: Many advances in cancer treatment have taken decades to develop, but the EML4-ALK mutation story in lung cancer has developed rapidly. Phase II results presented in the plenary session at ASCO 2010

reported that nearly 60 percent of patients with ALK rearrangements had an objective response to crizotinib (Kwak 2010; [1.2]).

Activation of a worldwide, Phase III study occurred a few months afterward. Other protocols are now under way in the first- and second-line settings. Another study is evaluating crizotinib as a single agent for patients who

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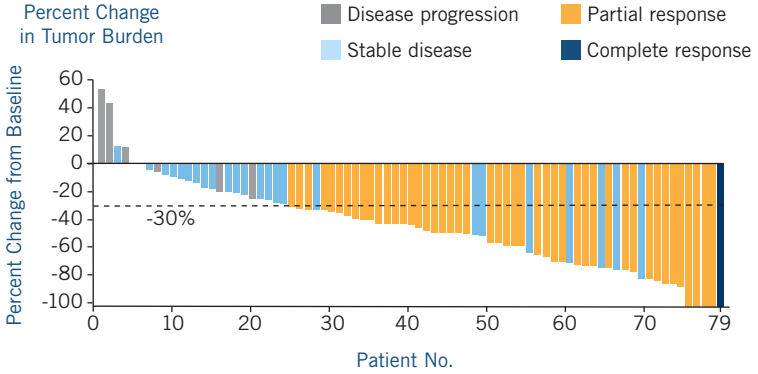
Tumor Response to Crizotinib in Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer



Overall response rate: 57%; stable disease: 33%; median progression-free survival: Not yet reached

Kwak EL et al. *N Engl J Med* 2010;363(18):1693-703.

1.3

Ongoing Studies of Crizotinib for Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer

Protocol	Phase	N	Treatment/ randomization	Eligibility
NCT00932451	II	400	• Crizotinib	• EML4-ALK-positive • Progressive disease on pemetrexed or docetaxel from previous Phase III trial (A8081007) • >1 prior chemotherapy
NCT00932893	III	318	• Crizotinib • Pemetrexed or docetaxel	• EML4-ALK-positive • 1 prior platinum-based regimen
NCT01154140	III	334	• Crizotinib • Pemetrexed/cisplatin or pemetrexed/carboplatin	• EML4-ALK-positive • Metastatic nonsquamous cell lung carcinoma • No prior treatment

www.clinicaltrials.gov. Accessed February 2011.

experienced disease progression while receiving chemotherapy on a prior second-line study or for patients who never entered any of the trials because of eligibility issues (1.3).

Crizotinib is clearly active in patients with ALK mutations. I expect that even though this mutation only occurs in three to four percent of patients, it is such an exciting field that physicians and patients are highly motivated to gain access to these studies. Hopefully, within six months to a year we'll have data, and if they remain positive, I expect rapid approval.

Track 13

DR LOVE: What is your take on the Phase II trial data presented at ASCO 2010 of erlotinib alone or in combination with the oral c-MET inhibitor ARQ 197 for patients with previously treated, EGFR inhibitor-naïve advanced NSCLC?

DR HANNA: This was one of the more interesting trials presented at ASCO 2010. ARQ 197 combined with erlotinib seemed to have better efficacy compared to erlotinib alone in patients with advanced NSCLC (Schiller 2010; [1.4]).

c-MET amplification is observed in approximately one third of patients who have acquired resistance to drugs such as erlotinib, so it is logical to combine a drug that inhibits c-MET with a drug that inhibits EGFR.

We and others will be participating in a Phase III trial of ARQ 197, which is probably at the forefront of newer classes of drugs that are furthest along in development. ■

1.4

Efficacy of the Oral c-MET Inhibitor ARQ 197 (A) in Combination with Erlotinib (E) for Patients with Previously Treated, EGFR Inhibitor-Naïve Advanced Non-Small Cell Lung Cancer

	E + A (n = 84)	E + placebo (n = 83)	Hazard ratio	*p*-value
Median progression-free survival	16.1 weeks	9.7 weeks	0.68	<0.05

Schiller JH et al. *Proc ASCO* 2010;**Abstract LBA7502**.

SELECT PUBLICATIONS

Kwak EL et al. **Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer.** *N Engl J Med* 2010;363(18):1693-703.

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

Schiller JH et al. **Results from ARQ 197-209: A global randomized placebo-controlled phase II clinical trial of erlotinib plus ARQ 197 versus erlotinib plus placebo in previously treated EGFR inhibitor-naive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract LBA7502**.