INTERVIEW

Paul K Paik, MD

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Tracks 1-15

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What is known about the biology of squamous cell carcinoma (SCC) of the lung, particularly in relation to genetic mutations?

DR PAIK: SCC is distinct from adenocarcinoma at a biologic level. Genotype data generated by the Cancer Genome Atlas and other centers demonstrate that EGFR mutations, ALK rearrangements, ROS1 fusions and RET fusions don't occur in SCC. KRAS mutations are also uncommon, probably occurring at a frequency of 1% to 2% (Rekhtman 2012).

We have found, though, that FGFR1 amplification and PI3 kinase pathway changes are fairly common in SCC. These 2 alterations alone are probably present in approximately 50% of SCC.

DR LOVE: Would you explain the Lung Cancer Master Protocol (Lung-MAP) in SCC and discuss your thoughts on it?

DR PAIK: This initiative being spearheaded by SWOG is a multicenter clinical trial protocol providing patients with SCC access to logical and rational trials in order to validate potential therapeutic targets (2.1). Every patient will be centrally genotyped. Based on their genotype, patients will be enrolled on trials evaluating agents targeted against their specific genetic alterations. Patients who test negative for the specific mutations will be enrolled on a trial investigating an agent targeted against the PD-1/PD-L1 axis. All the trials are randomized against docetaxel as the standard second-line therapy. These trials are not set in stone and will be adaptable depending on future results.

2.1

Lung-MAP Trial: S1400 Phase II/III Biomarker-Driven Master Protocol for Second-Line Therapy of Squamous Cell Lung Cancer

Trial Identifier: NCT02154490 **Estimated Enrollment:** 10,000 (Open)

Patients with pathologically confirmed, recurrent Stage IIIB to IV squamous cell non-small cell lung cancer will have their tumors analyzed for various genetic mutations. Clinical trial assignment will be based on the results of these tests.

Positive test result	Trial assignment
PI3KCA gene mutation	GDC-0032 versus docetaxel
CCND1, CCND2, CCND3 or CDK4/6 gene amplification	Palbociclib versus docetaxel
FGFR gene amplification, mutation or fusion	AZD4547 versus docetaxel
High protein levels of c-MET	Rilotumumab + erlotinib versus erlotinib
None of the above mutations	MEDI4736 versus docetaxel

Primary objectives: Progression-free survival by RECIST 1.1 (Phase II); overall survival (Phase III)

www.clinicaltrials.gov. Accessed August 2014.

Track 5

DR LOVE: What are your thoughts on the results of the Phase III SQUIRE trial, which were recently presented at ASCO 2014?

DR PAIK: The SQUIRE trial randomly assigned patients with Stage IV SCC to first-line cisplatin/gemcitabine with or without the EGFR antibody necitumumab. The primary endpoint of overall survival (OS) was met, with the addition of necitumumab leading to an improvement from 9.9 months to 11.5 months (Thatcher 2014; [2.2]). However, PFS and response rates were not consistent with the OS result and would suggest that the therapy, at least while patients were receiving it, was not better than placebo and that the benefit was manifested later in terms of survival. Based on the modest survival benefit with necitumumab, the questions arise, is this clinically meaningful and should we support its approval?

The dermatologic toxicity is similar to that observed with cetuximab, so whether we will observe an increase in toxicity is another issue. If necitumumab is approved, the toxicity and the modest survival benefit must be discussed with the patient.

2.2

SQUIRE: A Phase III Trial of First-Line Gemcitabine/Cisplatin (Gem/Cis) with or without Necitumumab for Stage IV Squamous Cell Non-Small Cell Lung Cancer

	Gem/cis + necitumumab (n = 545)	Gem/cis (n = 548)	Hazard ratio	*p*-value
Median OS	11.5 mo	9.9 mo	0.84	0.012
Median PFS	5.7 mo	5.5 mo	0.85	0.020
ORR	31.2%	28.8%	—	0.400

Select Grade ≥3 adverse events	Gem/cis + necitumumab (n = 538)	Gem/cis (n = 541)
Neutropenia	24.3%	27.5%
Thrombocytopenia	10.2%	10.7%
Hypomagnesemia	9.3%	1.1%
Skin rash	7.1%	0.4%
Venous thromboembolic events*	5.0%	2.6%

OS = overall survival; PFS = progression-free survival; ORR = overall response rate
* Fatal events, n (%): Gem/cis + necitumumab = 1 (0.2%); gem/cis = 1 (0.2%)

Thatcher N et al. *Proc ASCO* 2014;**Abstract 8008**.

Track 7

DR LOVE: Would you comment on your current algorithm for first- and second-line treatment of SCC and where, if at all, nanoparticle albumin-bound (*nab*) paclitaxel fits in?

DR PAIK: At my institution, the de facto standard in the first-line setting is platinum and gemcitabine. However, I'm not dogmatic about the selection of first-line therapy because we don't have head-to-head data comparing platinum/gemcitabine to other doublets. My second-line treatment choice is a taxane.

The subset analysis of the randomized Phase III trial of carboplatin and *nab* paclitaxel versus carboplatin and paclitaxel demonstrated that patients with SCC seemed to benefit in terms of response rate and PFS with *nab* paclitaxel (Socinski 2012). Based on these results, I may consider carboplatin/*nab* paclitaxel in the first-line setting for patients with SCC who are symptomatic and need a tumor response. Use of *nab* paclitaxel is also attractive in patients with taxane hypersensitivity or a contraindication to high-dose steroids used to prevent allergic reactions.

Track 12

DR LOVE: I'm curious about your thoughts on afatinib and in what clinical situations you would administer it — up front instead of erlotinib or later line, for example?

DR PAIK: Afatinib, for me, is still a gray area. The combined analysis of the LUX-Lung 3 and LUX-Lung 6 trials was recently presented at ASCO 2014, and a modest OS benefit was reported with afatinib versus chemotherapy in the first-line setting (Yang 2014; [2.3]). This has not been observed before with an EGFR TKI. However, because of the issues that occur after a patient crosses over, the data are not sufficient as of yet for me to replace erlotinib as the standard.

In terms of afatinib in the acquired resistance setting, the response rate is low, about 8% (Katakami 2013). This 8% is not a true reflection of activity, as part of this response is from re-treatment effects — patients who have been off TKI therapy and then resumed treatment and experienced a response.

The afatinib/cetuximab data are compelling (Janjigian 2012), but the combination is associated with a fair amount of dermatologic toxicity, which is a real limitation. Owing to the toxicity, I'm reluctant to use the combination in the first-line setting. ■

2.3

LUX-Lung 3 and LUX-Lung 6: Combined Overall Survival Analysis of Phase III Studies of Afatinib versus Chemotherapy in EGFR Mutation-Positive Advanced Non-Small Cell Lung Cancer

Patient group	Afatinib (n = 419)	Chemotherapy (n = 212)
Common mutations: del(19)/L858R Median OS	27.3 mo	24.3 mo
Hazard ratio (*p*-value)	0.81 (0.0374)	
	(n = 236)	(n = 119)
Del(19) subgroup Median OS	31.7 mo	20.7 mo
Hazard ratio (*p*-value)	0.59 (0.0001)	
	(n = 183)	(n = 93)
L858R subgroup Median OS	22.1 mo	26.9 mo
Hazard ratio (*p*-value)	1.25 (0.1600)	

OS = overall survival

Yang JCH et al. *Proc ASCO* 2014;**Abstract 8004**.

SELECT PUBLICATIONS

Janjigian YY et al. **Activity of afatinib/cetuximab in patients (pts) with EGFR mutant non-small cell lung cancer (NSCLC) and acquired resistance (AR) to EGFR inhibitors.** *Proc ESMO* 2012;**Abstract 1227O**.

Katakami N et al. **LUX-Lung 4: A phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both.** *J Clin Oncol* 2013;31(37):3335-41.

Rekhtman N. **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.

Socinski MA et al. **Weekly *nab*-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial.** *J Clin Oncol* 2012;30(17):2055-62.

Thatcher N et al. **A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC).** *Proc ASCO* 2014;**Abstract 8008**.