

## CASE REPORT

### Pulmonary squamous cell carcinoma and sorafenib

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#### Key Clinical Message

Pulmonary squamous cell carcinomas are not often thought to sensitive to targeted agents, like their cousin the adenocarcinoma of the lung. With appropriate testing of molecular markers, squamous cell carcinomas, like adenocarcinomas of the lung, melanomas, and renal cell carcinomas, may be found to be sensitive to newer, targeted agents.

#### Keywords

BRAF mutants, nonsmall cell lung cancer, squamous cell carcinoma, targeted therapy.

## Introduction

No longer are all advanced nonsmall cell cancers considered different histologic manifestations of inconsequential genetic mutations, deletions, and translocations [1–4]. The advances made with pulmonary adenocarcinomas – identifying KRAS and ALK mutations as markers for in vivo sensitivity to the targeted agents erlotinib and crizotinib, respectively – have revolutionized the treatment of lung cancers. There are still markers that have not had targeted therapy found for them, including MEK [5–8]. Further, there appear to be distinct sensitivities amongst adenocarcinomas for platinum salts and pemetrexed, whereas squamous cell carcinomas may have increased sensitivities to taxane-based treatments.

## Presentation of Case

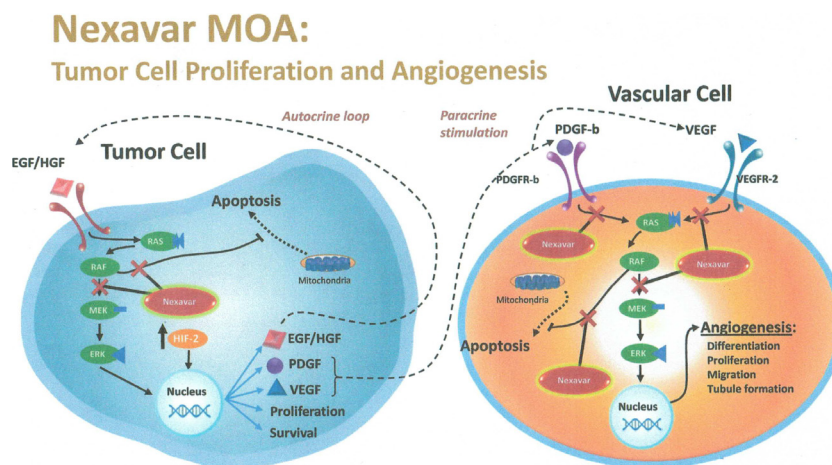
A 69-year-old female, a long time smoker, presented with widely metastatic squamous cell carcinoma involving the right upper lobe, bones, and lymph nodes throughout the mediastinum and retroperitoneum. She was initially treated with carboplatin (AUC=5) and paclitaxel (175 mg/m<sup>2</sup>) q 3 weeks for six cycles. She then received radiation directed at L4, cGy 3750 in 15 fractions. She also received zoledronic acid. Although her performance status

remained excellent, she developed progressive disease in pre-existing sites, sparing the central nervous system. The results of a lung cancer molecular prognostic diagnostic panel are shown on Table 1.

The patient was not felt to be a candidate for either erlotinib or crizotinib based on the squamous histology; however, sorafenib was felt to possibly have some efficacy for this patient in the second-line setting (Fig. 1). Sorafenib is a small molecular inhibitor of several tyrosine protein kinases (vascular endothelial growth factor receptor and platelet-derived growth factor receptor) and Raf kinases (more avidly C-Raf than B-Raf). The rationale is as follows: Some non-V600E BRAF mutations in melanoma cell lines signal through CRAF (gene that encodes enzyme with serine-threonine kinase activity in normal mammalian cells), which, in contrast to BRAF, regulates apoptosis through mitochondrial localization where it binds to

Table 1: Biomarkers were analyzed for common mutations found in nonsquamous lung cancers.

EGFR mutation not detected
KRAS mutation not detected
BRAF Exon 11 (G469R) mutated (non-V600E mutation)
ALK no mutation at 2p23; increased number suggesting polysomy chromosome 2



**Figure 1.** Nexavar inhibits both VEGFR and PDGFR receptor tyrosine kinases along the RAF/MEK/ERK pathway.

Bcl-2 and phosphorylates Bcl-2-associated death promoter (BAD) [9]. Sorafenib was found to induce a time-dependent reduction in both BAD phosphorylation and Bcl-2 expression in the D594G/G469E lines through CRAF inhibition. In experimental systems knockdown of CRAF using a lentiviral shRNA suppressed both Bcl-2 expression and induced apoptosis in the D594G melanoma line but not in a V600E-mutated cell line. Based on the in-vitro data, sorafenib, typically used for kidney cancer, was prescribed for our patient. She developed hypertension so the dose had to be reduced from 800 mg to 400 mg/day after 1 month. She subsequently was followed with positron emission tomography (PET) scans. She recurred in the central nervous system (left frontal lobe) and underwent craniotomy followed by whole brain irradiation. She was then evaluated by PET scan. The patient had stabilization of all areas of disease, with decrease in size and uptake in all areas of involvement. She has continued to have stable disease for over 18 months.

Studies of chemotherapy in combination with targeted agents have not been conclusive [10–13]. Scagliotti et al. have previously shown a decrement in overall survival when sorafenib was given with combination chemotherapy. This study, known as Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in NSCLC (ESCAPE), involved 926 patients. Median overall survival was similar in the two treatment groups (10.7 months with carboplatin/paclitaxel/sorafenib and 10.6 months with carboplatin/paclitaxel).

In patients with refractory NSCLC, sunitinib plus erlotinib did not improve as compared with erlotinib alone, but the combination was associated with a statistically significantly longer progression free survival and greater overall response rate. The incidence of grade 3 or higher toxicities was greater with combination therapy. There are data that

sunitinib has only nominal activity in previously treated nonsmall cell lung cancers. Sorafenib may have some role in squamous cell patients with the proper genetic signature who have failed combination chemotherapy. Molecular profiling, which has been used mostly for adenocarcinomas and adenosquamous carcinomas of the lung, should be also applied to squamous cell carcinomas.

Tailored medical therapy involves the application of diagnostic and prognostic molecular studies to determine the optimal treatment for lung cancer patients. Thus far, mutations in the epidermal growth factor receptor gene and ALK gene have resulted in clinical applications for targeted therapies, specifically in the use of Xalkori and erlotinib. BRAF gene mutations, albeit a distinct mutation utilized for malignant melanoma patients, may be an additional mutation of clinical importance for patients with squamous cell carcinoma who thus far have not benefited from molecular diagnostics as have those diagnosed with nonsquamous cell lung tumors. In the future, it may be possible to type and subtype RAS mutations, ROS1 translocations, MET overexpressors, MEK 1 mutations, RET translocations, and other possible targets [14, 15]. Such profiling would lessen the relative guesswork associated with choosing optimal therapies and in an era of limited resources would not waste benefits on expensive and futile therapies. A panel of useful molecular markers taken at diagnosis with prospectively prognostic value would seem most reasonable; it should become a necessity for even squamous cell carcinomas to be typed in the same way that adenocarcinomas are as more is learned about the translation of in-vitro sensitivity data to clinical case scenarios.

### Conflict of Interest

None declared.

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