Response to rapamycin analogs but not PD-1 inhibitors in PTEN-mutated metastatic non-small-cell lung cancer with high tumor mutational burden

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Abstract: In non-small-cell lung cancer (NSCLC) refractory to standard therapy and which lacks well-known oncogenic drivers, genomic profiling can still identify genomic alterations that may suggest potential sensitivity to targeted therapy. PTEN mutation in NSCLC may be sensitizing to analogs of rapamycin such as everolimus or temsirolimus, but more investigation is needed. We report the case of a patient with metastatic NSCLC harboring a PTEN mutation as well as high tumor mutational burden and PD-L1 positivity with a durable response to temsirolimus, but refractory to a checkpoint inhibitor. Even in the event of failure of treatment with checkpoint inhibitors in the background of a case with a higher tumor mutational burden and PD-L1 positivity, targeting specific genomic alterations may still result in patient benefit.

Keywords: genomic profiling, temsirolimus, targeted therapy, immunotherapy

Introduction
Lung cancer is one of the most common cancers diagnosed in the US. The 5-year survival upon diagnosis of stage IV lung cancer is 4%.1 Comprehensive genomic profiling is being used more frequently to help identify mutations in an individual patient’s non-small-cell lung cancer (NSCLC) to suggest benefit from targeted therapy or immunotherapy. We present the case of a patient with metastatic NSCLC found to harbor PTEN and STK11 alterations using comprehensive genomic profiling who responded to matched targeted therapy in the background of higher tumor mutational burden.

Case history
The patient is a 62-year-old woman with a 60 pack-year smoking history who presented with stage IV lung adenocarcinoma in September 2012. She was found to have bilateral disease in her lungs, a right adrenal mass, and osseous metastasis. EGFR and ALK were queried by single gene molecular testing. The patient enrolled in a clinical trial and was treated with carboplatin, paclitaxel, and bevacizumab. She responded to therapy and was then placed on maintenance bevacizumab. She had disease progression in February 2013 and was treated with pemetrexed. Her disease progressed in November 2013, and so she was treated with docetaxel. Her computed tomography scans showed response at 3 months and 6 months; however, by 9 months, she had further disease progression including a new intracranial metastasis. She received stereotactic
radiation to her intracranial metastasis in May 2014. She was then started on gemcitabine and found to have disease progression after 3 cycles.

To identify opportunities for possible benefit from targeted therapy, comprehensive genomic profiling (Foundation-One, Foundation Medicine, Inc., Cambridge, MA, USA) was performed on a biopsy of a right upper lobe lesion collected in December 2013, which revealed the following genomic alterations: PTEN D268fs*30, STK11 splice site 465-1G>T, p53 G293R, KEAP1 G480W, and LRP1B G528W, as well as tumor mutational burden of 18.9 mutations/megabase. On the basis of PTEN and STK11 alterations, the decision was made to treat the patient with weekly temsirolimus 25 mg IV weekly in analogy to dosing for advanced renal cell carcinoma. After 3 months of treatment, she showed significant clinical improvement in her breathing and overall functional status. Although her radiologic response was not formally evaluated by RECIST criteria, it was analogous to a robust partial response with significant reduction of a right lung mass and reduction of a pleural mass (Figure 1). She remained on treatment for almost 20 months until March 2016 when her scans showed disease progression with increase in size of right-sided lung mass as well as increase in pleural effusion. Her treatment was then changed to nivolumab, on which the right-sided lung mass as well as increase in pleural effusion.

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**Discussion**

The exceptional response to a rapamycin analog in this patient and the underlying mechanism likely hinges on the mutations of PTEN and possibly, to a lesser extent, on STK11, which are both regulators of the downstream mTOR pathway, and the former is known to confer sensitivity to rapamycin analogs in vivo. Given that PTEN is a tumor suppressor, loss of heterozygosity (LOH) was queried on a research basis for both loci, but due to low sample purity could not be determined for either PTEN or STK11 (data not shown).

Loss of function of PTEN, a lipid phosphatase, has long been posited as being sensitizing to rapamycin due to ensuing hyperactivation of mTORC1. In particular, biallelic loss of function of PTEN should be more sensitizing than mutation of a single allele.

STK11 is also upstream of mTOR, and loss of function alterations of STK11 also hyperactivate mTORC1, albeit through the intermediary of AMPK activity. However, in preclinical models of STK11-driven dysplasia and neoplasia, only some of these entities are rapamycin sensitive, such as the polyps of juvenile polyposis and observation in PIN. Overall, whether STK11 alteration confers sensitivity to rapamycin analogs remains poorly understood.

A significant limitation in this study is the inability to identify whether PTEN is under LOH, which would offer a compelling explanation for the efficacy of temsirolimus. The specimen purity did not permit LOH assessment, and no additional specimens were available including original sample (data not shown). Future investigation, whether on the basis of an exceptional responder to rapamycin analog like the patient here or in the context of clinical investigation where the therapeutic hypothesis is a similar question, should incorporate genomic assessment of both alleles of PTEN to help further explain the mechanism of the effect seen here. Studies of both temsirolimus and everolimus in unselected prostate cancer populations did not show an effect, but the latter trended toward some efficacy in a population with PTEN alteration.

One aspect of note is the relatively high tumor mutational burden observed with high PD-L1 staining, but lack of durable response to checkpoint inhibitor. This failure increases the impact of observing a prolonged response to genomically matched targeted therapy for this patient.
In conclusion, the exceptional response observed here suggests that further assessment and investigation is warranted for PTEN status in NSCLC lacking known oncogenic drivers.

The authors apologize to all the investigators whose work cannot be cited here due to limitations of format. Written informed consent was provided by the patient to have the case details published.

Disclosure
ABS, LAA, VAM, PJS, and SMA are employees of and have equity interest in Foundation Medicine Inc. The authors report no other conflicts of interest in this work.

References