

## Proteomic Markers of DNA Repair and PI3K Pathway Activation Predict Response to the PARP Inhibitor BMN 673 in Small Cell Lung Cancer—Letter

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In a recent article, Cardnell and colleagues reported that BMN 673 (a novel PARP inhibitor) exhibited striking activities in small cell lung cancer (SCLC) cell lines and xenografts, and that cellular sensitivity to BMN 673 was associated with high baseline expression of several DNA repair proteins. Furthermore, the authors also detected that greater drug resistance was observed in SCLC models with baseline activation of the PI3K/mTOR pathway (1). However, we have some concerns about these findings.

As a tumor suppressor, PTEN is frequently inactivated in human malignancies, which then activates PI3K/mTOR signaling and promotes tumor progression. In contrast to the report of Cardnell and colleagues, another recent study

found that BMN 673 selectively targeted tumor cells with PTEN deficiency both *in vitro* and *in vivo* (2). In 2012, a Japanese research group reported that PTEN-deficient lung cancer cells were more sensitive to olaparib (AZD2281, another PARP inhibitor), and PTEN restoration suppressed the PI3K/mTOR pathway and induced cellular resistance to PARP inhibition (3). More findings from endometrial cancer supported that sensitivity to PARP inhibitors was PTEN dependent (4). Nonetheless, a recurrent endometrial cancer patient with PTEN deficiency responded well to olaparib (5). All these findings are in contrast to the finding of Cardnell and colleagues that SCLC cell lines with more active phosphoinositide 3-kinase (PI3K) signaling are less sensitive to BMN 673.

In summary, we believe it is necessary to clarify the association between sensitivity to BMN 673 and dysregulated PI3K/mTOR signaling, to help select patients for future clinical trials.

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### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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