

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

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In a Letter to the Editor about our recent publication (1), Haifeng Qiu suggests that further clarification is needed about the relationship between sensitivity to BMN 673 and dysregulated PI3K/mTOR signaling, given the potential association between PTEN loss and PARP inhibitor sensitivity in other cancer types.

Although we agree that PTEN inactivation is common in human malignancies and may be associated with sensitivity to PARP inhibitors in some cancers, PTEN loss is only one of several possible mechanisms by which the PI3K/mTOR pathway can be activated, each of which may have different implications for drug sensitivity. For small cell lung cancer (SCLC), this distinction was illustrated in a recent publication (2) that showed activity of a selective oral phosphoinositide 3-kinase (PI3K) inhibitor, PF-4989216, in SCLC preclinical models harboring activating PIK3CA mutations, but not PTEN loss.

Genomic analysis by Peifer and colleagues (3) indicates that PTEN loss occurs in a minority of SCLC tumors (10%). Of the cell lines used in our analysis, only one—NCI-H2081—carries a PTEN mutation and this cell line was not included in the proteomic analysis. The H2081 cell line fell

in the middle of the range of sensitivities to BMN 673 (6.3 nmol/L; IC₅₀ range, 1.7–15 nmol/L), suggesting that PTEN deficiency was not responsible for the observed sensitivity of our SCLC cell lines to BMN 673, nor was it the cause of greater PI3K/mTOR pathway activation observed in the more resistant lines.

As described in Dr. Qiu's letter, an association between PTEN deficiency and PARP inhibitor sensitivity has been described in other cancers, including breast, prostate, and endometrial cancers. However, even among cancers with PTEN loss, there are likely to be additional factors that affect sensitivity, as suggested by a recent study that showed sensitivity of tumors with PTEN loss was dependent on levels of circulating estrogen (4). Furthermore, the potential benefit of dual PARP–PI3K pathway inhibition has also been suggested in breast cancer based on preclinical models of triple-negative and BRCA-mutated breast cancers (5) and is being explored in an ongoing clinical trial.

In conclusion, we agree with Dr. Qiu that the connection between PARP inhibitors and the PI3K/mTOR pathway warrants further exploration. However, our data indicate that the association between baseline PI3K/mTOR pathway activity and *in vitro* activity of BMN 673 is independent of PTEN and suggests a distinct mechanism of PARP inhibitor activity in SCLC.

Disclosure of Potential Conflicts of Interest

L.A. Byers has received clinical trial funding and is an advisory board member for BioMarin. No potential conflicts of interest were disclosed by the other author.

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References

- Cardnell RJ, Feng Y, Diao L, Fan YH, Masrorpour F, Wang J, et al. Proteomic markers of DNA repair and PI3K pathway activation predict response to the PARP inhibitor BMN 673 in small cell lung cancer. *Clin Cancer Res* 2013;19:6322–8.
- Walls M, Baxi SM, Mehta PP, Liu KK, Zhu J, Estrella H, et al. Targeting small cell lung cancer harboring PIK3CA mutation with a selective oral PI3K inhibitor PF-4989216. *Clin Cancer Res* 2014;20:631–43.
- Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet* 2012;44:1104–10.
- Janzen DM, Paik DY, Rosales MA, Yep B, Cheng D, Witte ON, et al. Low levels of circulating estrogen sensitize PTEN-null endometrial tumors to PARP inhibition *in vivo*. *Mol Cancer Ther* 2013;12:2917–28.
- Alderton GK. Therapeutics: PI3K–PARP combination. *Nat Rev Cancer* 2012;12:658.