

Accepted Manuscript

PI3K blockage synergizes with PLK1 inhibition preventing endoreduplication and enhancing apoptosis in anaplastic thyroid cancer

Daniela De Martino, Emrullah Yilmaz, Arturo Orlacchio, Michela Ranieri, Ke Zhao, Antonio Di Cristofano



PII: S0304-3835(18)30581-0

DOI: [10.1016/j.canlet.2018.09.024](https://doi.org/10.1016/j.canlet.2018.09.024)

Reference: CAN 14069

To appear in: *Cancer Letters*

Received Date: 29 July 2018

Revised Date: 11 September 2018

Accepted Date: 14 September 2018

Please cite this article as: D. De Martino, E. Yilmaz, A. Orlacchio, M. Ranieri, K. Zhao, A. Di Cristofano, PI3K blockage synergizes with PLK1 inhibition preventing endoreduplication and enhancing apoptosis in anaplastic thyroid cancer, *Cancer Letters* (2018), doi: <https://doi.org/10.1016/j.canlet.2018.09.024>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Abstract

Anaplastic thyroid cancer (ATC) is among the most lethal malignancies. The mitotic kinase PLK1 is overexpressed in the majority of ATCs and PLK1 inhibitors have shown preclinical efficacy. However, they also cause mitotic slippage and endoreduplication, leading to the generation of tetraploid, genetically unstable cell populations.

We hypothesized that PI3K activity may facilitate mitotic slippage upon PLK1 inhibition, and thus tested the effect of combining PLK1 and PI3K inhibitors in ATC models, *in vitro* and *in vivo*. Treatment with BI6727 and BKM120 resulted in a significant synergistic effect in ATC cells, independent of the levels of AKT activity. Combination of the two drugs enhanced growth suppression at doses for which the single drugs showed no effect, and led to a massive reduction of the tetraploid cells population. Furthermore, combined treatment in PI3K^{high} cell lines showed a significant induction of apoptosis.

Finally, combined inhibition of PI3K and PLK1 was extremely effective *in vivo*, in an immunocompetent allograft model of ATC.

Our results demonstrate a clear therapeutic potential of combining PLK1 and PI3K inhibitors in anaplastic thyroid tumors.

Download English Version:

<https://daneshyari.com/en/article/11025938>

Download Persian Version:

<https://daneshyari.com/article/11025938>

[Daneshyari.com](https://daneshyari.com)