ID: 01066
Type: Poster
Topic: Tumor treatment

# Pharmacological targeting of PLK1 induces apoptosis in triple neg

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Triple negative breast cancer (TNBC) is the most aggressive form of breast cancer. These tumours have limited therapeutic options, as no targeted therapies are currently available. Thus, chemotherapy is the first-line of treatment. But its effectiveness is insufficient and the rise of resistance frequently leads to cancer recurrences. This fact makes the search of novel compounds targeting TNBC a necessity.

Bromodomain and extraterminal domain inhibitors (BETi) have shown antitumor activity in this disease through the modulation of the expression of several transcription factors. As, TNBC is characterized by a high proliferation rate and an increase in cell division, targeting protein kinases involved in the mitotic spindle formation, such as polo-like kinase (PLK), might have a relevant role in this cancer. In fact, the combination of BETi with PLK inhibitors (PLKi) has showed a synergistic effect, being very effective in TNBC cells. As development of drugs resistance is a constant rule in TNBC, patients might be susceptible to develop invulnerability to BETi. To explore the effect of PLKi in this context, we generated two BETi-resistant TNBC cell lines using pulse-selection with JQ1, a well-known BETi.

qPCR and Western-B studies on parental (sensitive) and JQ1-resistant MDA-MB-231 and HS578T revealed higher Plk1 expression levels in resistant cell lines, suggesting this kinase could be a potential vulnerability on these cells. The use of the Plk1 inhibitor, volasertib, displayed a marked decrease on cell proliferation on resistance cells, even at higher levels than in the parental ones. Then, we investigated the effect of volasertib, alone and in combination with JQ1, in cell cycle and apoptosis. Results showed that both volasertib treatment and the combination exhibited a greater cell arrest in G2 / M and a considerable increased apoptosis in JQ1-resistant cells when compare to sensitive cells.

To confirm these *in vitro* results, we performed pre-clinical *in vivo* studies in mice. Thus, JQ1-resistant MDA-MB-231 were orthotopically injected in the mammary gland of female balb-c nude mice (6 weeks). Treatment with JQ1 and volasertib was started when tumours reached a volume of 150 $mm^3$. Mice treated with JQ1 alone were insensitive to treatment and, therefore, tumours continued growing. Conversely, mice treated with volasertib showed a striking decrease on tumour volume.

Overall, our results suggest that we might have found an escape route to reverse BETi resistances by using PLKi. Our data set a scenario to pursue with preclinical studies that eventually allow to confirm that Plk1 is a good candidate for targeted-treatment in TNBC with acquired resistance to BET inhibitor.

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