ID: 01007
Type: Oral Comunication
Topic: Tumor treatment

Preclinical evidence of the therapeutic potential of ABTL0812 in endometrial cancer

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Introduction: Endometrial cancer (EC) is the most frequent of the infiltrating tumors of the female genital tract. The clinical setting of EC is reasonably favorable for patients diagnosed with the tumor confined to the uterus. However, the 5-year survival rate of patients with regional and distant dissemination of endometrioid and non-endometrioid histologies declines to 50-60% and 10-15%, respectively. In those cases, the response rate to the standard treatment, based on a combination of carboplatin and paclitaxel, is very limited. This situation strongly reflects the need for new and efficient therapeutic strategies.

Recently, many reports demonstrated the mechanism of action of new agents acting against specific targets. The PI3K/AKT/mTOR pathway is frequently overactivated in women with EC due to the loss of PTEN, mutations in the PKI3CA receptor, or AKT amplification. Treatment with new alternative inhibitors of the PI3K/AKT/mTOR pathway may result in a significant therapeutic benefit for EC patients. At this respect, ABTL0812, a new first-in-class molecule has a unique mechanism of action to inhibit the PI3K/AKT/mTOR pathway, which has been successfully tested in lung and pancreatic cancers.

Objective: Assess the efficacy of ABTL0812 treatment in endometrial cancer.

Methodology: By MTT, western blot and immune-fluorescence assays we evaluate ABTL0812 effect on viability, apoptosis and autophagy in a wide panel of endometrioid (Ishikawa, AN3CA, and HEC-1A) and non-endometrioid (ARK1 and ARK2) EC cell lines. Similarly, organoid 3D murine endometrial cells culture was also tested. By the generation of a tamoxifen-inducible PTEN-KO murine model, cell line- and patient-derived xenograft (PDX) models; we evaluated ABTL0812 efficacy in tumor onset and progression. Finally, in a Phase I/II clinical trial, TRIB3 mRNA was evaluated in whole blood.

Results: We demonstrated that ABTL0812 treatment reduces viability of EC cell lines, with IC50 values ranging from 5.03 ± 0.12 to 36.86 ± 3.31 mmol/L. We showed that ABTL0812 sensitizes cancer cell lines though inhibition of the PI3K/AKT/mTORC1 axis, by upregulation of TRIB3 expression. Similarly, we confirmed the induction of autophagy in EC cell lines upon ABTL0812 treatment by the decrease of phosphorylation of p70S6k. We also tested the effect of ABTL0812 on endometrial glandular 3D cultures on PTEN-KO conditional cells. We observed a significant decreased of positive BrdU-incorporating cells and glandular size in PTEN-deficient cells compared to control. We also observed nuclear fragmentation/condensation and caspase activation, due to ABTL0812 treatment. TRIB3 levels were also significantly increased. The therapeutic benefit of ABTL0812 was also confirmed *in vivo*. We found that ABTL0812 treatment led to a marked reduction in tumor growth ($p < 0.05$), in a cell line-derived xenograft model. Moreover, ABTL0812 treatment impaired the initial progression of endometrial tumorigenesis in the PTEN-KO conditional mouse model. Histopathological evaluation revealed

that ABTL0812-treated PTEN-KO mice had endometrial lesions to a significantly lower extent than untreated mice. In addition, uteri from those animals expressed significantly higher TRIB3 mRNA levels than their counterparts treated with placebo. Furthermore, two EC patient-derived xenograft (PDX) models bearing PTEN mutations showed that ABTL0812 treatment inhibited tumor progression with a comparable efficacy to the standard first-line chemotherapy treatment of carboplatin-paclitaxel. In the ongoing phase 1b/2a, TRIB3 mRNA levels were increased in the whole blood of the three recruited patients after 8h of ABTL0812 treatment.

Conclusion: Our results demonstrate that induction of autophagy is involved in the mechanism by which ABTL0812 treatment promotes the activation of the pro-apoptotic pathway, thus ending in cell-death. Collectively, we provide strong preclinical evidence of the therapeutic benefit of ABTL0812 as monotherapy or in combination with the current first-line treatment in endometrioid and serous ECs. ABTL0812 promotes cell death through TRIB3 activation, which inhibits the PI3k/AKT/mTOR pathway and induces autophagy, specifically on tumor cells but not in non-pathogenic cells. In fact, ABTL0812 treatment delayed the initial progression of endometrial tumorigenesis. Our findings present a novel and clinically applicable therapeutic strategy for EC and suggest the potential use of TRIB3 expression as a pharmacodynamic biomarker to monitor ABTL0812 treatment.

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