**ANTITUMOR ACTIVITY OF THE NOVEL ORAL HIGHLY SELECTIVE WEE1 INHIBITOR DEBIO 0123**

Colin O’Dowd¹, Gerald Gavory², Frank Burkamp¹, Adam Treder¹, Caroline Boyd¹, Tim Harrison¹, Frederic Massièrêt, Astrid Glück², Anïta Thorimbert², Christophe Chardonnens², Andréa Zaffalon², Stefania Rigotti², Robert Mader², Grégoire Vuagniaux², Anne Vaslin³

¹Aimaco Discovery, Belfast, UK, ²Debiopharm International S.A., Lausanne, Switzerland

**ABSTRACT #4423**

The WEE1 tyrosine kinase is activated upon DNA damage and regulates the G2-M cell cycle checkpoint. Inhibition of WEE1, in conjunction with additional genetic alterations and/or addition of a DNA-damaging agent, results in mitotic catastrophe and apoptosis of cancer cells, offering an attractive approach to treat cancer. Only one WEE1 inhibitor, AZD1775, is currently in clinical development. The aim of the present study was to characterize the pharmacological properties of the newly discovered, orally available, and highly selective Wee1 inhibitor Debio 0123.

**RESULTS**

Debio 0123 is a potent and selective Wee1 Inhibitor

Debio 0123 anti-proliferative activity in a large panel of cell lines

Debio 0123 induced dose-dependent antiproliferative activity and was well tolerated at all doses tested. At 30 mg/kg, treatment with Debio 0123 resulted in tumor regressions in a NSCLC cancer model, with a median IC50 value of 1.23 µM (range: 0.109 to 7.08 µM), showing a good response of cancer cells to Debio 0123 across various histotypes. While some cell lines are sensitive to Debio 0123 as monotherapy, further work is currently ongoing aiming at identification of potential predictive biomarkers and at exploring potential combinations.

**SUMMARY**

**Cell free assay:**
- Experiments were performed using a cell-free system. Debio 0123 was highly selective to Wee1. As compared to AZD1775, it does not inhibit Plk1 and Plk2, as also reported in recent publications for AZD1775.

**In vitro proliferation assay:**
- The in vitro growth inhibition activity of Debio 0123 was assessed in a large panel of cell lines.

**Western blot:**
- Effects on downstream Wee1 signaling were analyzed by ELISA profiling of Debio 0123 was performed on 465 selected kinases in a cell-free system.

**CONCLUSIONS**

- Debio 0123 is a highly selective and potent Wee1 inhibitor able to prevent CDC2/Cdc14 phosphorylation and to induce senescence through multiple cell cycle entry checkpoints, resulting in accumulation of unreplicated DNA damage both in vitro and in vivo, resulting in tumor regression.
- Debio 0123 is currently being evaluated in combination with various agents.
- The achievement of Debio 0123 into clinical studies may provide improved therapeutic outcomes for patients with cancer.

**REFERENCES**


**CONTACT**

Lausanne, Switzerland.

Debiopharm International S.A.,
www.debiopharm.com