**Background / Aim of the study**

Drug resistance is a major problem in cancer therapy and response to therapy varies between histotypes and within the same histotype. Resistance may be overcome by the combination of drugs simultaneously targeting multiple critical nodes of the signaling networks controlling growth and survival of cancer cells (1, 2). The members of the inhibitor of apoptosis protein (IAP) family are key regulators of programmed cell death. Their frequent overexpression in most cancer types contributes to tumor cell survival and resistance to cancer therapy making IAPs attractive therapeutic targets (3). The oral monovalent IAP antagonist Debio 1143 (a.k.a. SM406 and AT406) inhibits multiple IAP proteins thus facilitating cell death via both the intrinsic and extrinsic apoptosis pathways interfering with XIAP and c-IAP1/2, respectively. Debio 1143 is currently in clinical development for cancer treatment. The aim of the study was to evaluate the activity of Debio 1143 alone and in combination with standard of care (SOC) agents in vitro and in vivo lung cancer models of different histotypes and to identify novel synergistic combination partners for Debio 1143 in non-small cell lung cancer (NSCLC).

**Methods**

PDX maintenance. PDX experiments were performed by Oncotest, Freiburg, Germany. Solid human tumor xenografts grown subcutaneously (s.c.) in 6-week old female nude mice (BALB/c- nu/nu). A total of 10-12 mice were randomized and continuously exposed to X-irradiation for up to 20 days at doses with a dose threshold of apoptosis thereby increasing the effect of cytotoxic therapies.

**Results**

Debio 1143 monotherapy displays selective anti-proliferative activity in the majority of lung cancer models in vitro

Using clonogenic assays the anti-proliferative activity of Debio 1143 was assessed on a panel of 104 human adenocarcinoma xenograft (3D) cell cultures, which included 46 lung cancer models representing small-cell, large-cell, adenoid squamous lung histotypes. Increased activity of Debio 1143 was observed in small and large squamous histotypes, whereas adenocarcinoma-derived samples were less responsive as compared to the mean activity across the full PDX panel (Fig. 2).

Debio 1143 combined with NSCLC SOC compounds displays differential synergy across NSCLC cell lines in vitro

The synergy observed in the h(HTS) between Debio 1143 and NSCLC SOC compounds varies between the 6 adenocarcinoma NSCLC cell lines. Interestingly, a pronounced combination effect is observed for both taxanes in the cell line H2030 (Fig. 4).

Debio 1143 displays anti-tumor activity as a monotherapy and synergizes with the lung cancer SOC compound docetaxel in vivo

To test whether Debio 1143 synergizes with SOC compounds also in vivo, the combination of Debio 1143 and docetaxel displayed moderate anti-tumor activity as single agents, the combination caused marked anti-tumor activity that was superior to either monotherapy (Fig. 5). No significant effects on body weights were observed.

**References**


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*These authors contributed equally to this work.

**Contact**

Debiopharm International S.A., Lausanne, Switzerland.

Norbert.Wiedemann@debiopharm.com

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**Activity of IAP antagonist Debio 1143 as a monotherapy and in combination with standard of care agents in human lung cancer of different histotypes**

N Wiedemann1,*, CG Langdon1, MA Held2, JT Platt2, F Levy1, D Robichon1, C Zanna1,

G Vuagniaux1, M Sorensen1, S Wang4, MW Bosenberg2, DF Stern2

1Debiopharm International SA, Switzerland; 2 Yale University, USA;

3Ascenta Therapeutics, USA; 4University of Michigan Cancer Center, USA

**Summary**

- Debio 1143 is an oral monovalent antagonist of multiple IAP proteins and is currently in clinical development for cancer treatment.
- Debio 1143 facilitates cell death by lowering the threshold of apoptosis thereby increasing the effect of cytotoxic therapies.
- In vitro, Debio 1143 monotherapy displays selective anti-proliferative activity in the majority of lung cancer models and synergizes with lung cancer SOC compounds.
- In vivo, using xenograft mouse models, Debio 1143 displays anti-tumor activity as a monotherapy and synergizes with the lung cancer SOC compound docetaxel without causing significant toxicity.
- Clinical trials are currently evaluating Debio 1143 in combination with paclitaxel in various cancer types (ClinicalTrials.gov Identifier: NCT01930292).