Debio 1143, an oral antagonist of the inhibitor of apoptosis proteins, synergistically enhances the effects of multiple standard care agents in human lung cancer models

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Summary

- The oral monovalent IAP antagonist Debio 1143 displays single agent activity across lung cancer models in vitro and in vivo.
- Pathways targeted by Debio 1143 and docetaxel are different.
- The combination of Debio 1143 and docetaxel synergized in vivo in mouse NSCLC xenograft models, where the combination caused marked antitumor activity that was superior for both monotherapy and combination therapy.
- The synergy observed in vitro correlated with superior antitumor efficacy in vivo.

Results

Debio 1143 displays differential anti-proliferative activity in vitro lung cancer PDX models of different lung histotypes

Using clonogenic assays the anti-proliferative activity of Debio 1143 was assessed in a panel of 104 human non-small lung cancer (NSCLC) xenografts, which included a total of 16 lung cancer models representing different lung cancer histotypes. The response to Debio 1143 was evaluated in vitro in adenocarcinoma and squamous cell lung cancer xenografts. Across all tumor xenografts, the most sensitive cell lines were adenocarcinoma-derived xenografts, whereas mesenchymal cell xenografts derived from squamous cell xenografts were less sensitive to Debio 1143.

Debio 1143 synergizes with NSCLC SOC compounds to inhibit growth of human NSCLC cell lines in vitro

To test whether Debio 1143 synergizes with NSCLC SOC compounds also in vitro, the combination of Debio 1143 and several NSCLC SOC compounds (e.g. docetaxel) was evaluated in vitro. The synergistic activity was observed in vitro in several NSCLC SOC compounds, which included the following agents: docetaxel, gemcitabine, and vinorelbine.

Debio 1143 displays synergy in combination with the NSCLC SOC compounds paclitaxel, vinorelbine, gemcitabine and perhexiline.

Methods

In vitro drug efficacy testing

PDX maintenance. PDX experiments were performed according to Christof, Freiburg, Germany. Solid human tumor xenografts in nude mice were maintained in vitro by sequential xenografts in nude mice. For xenograft maintenance, tumors were harvested, digested with dispase, counted and resuspended in saline.

Clonogenic PDX assay. Tumor cell suspensions were plated at 100 cells per well in 24-well format. The plates were incubated at 37°C in 5% CO\(_2\). After 21 days, the plates were stained with crystal violet. The number of colonies was counted.

In vivo drug efficacy testing

Xenograft mouse models. Xenografts were performed using the guidelines for the care and use of laboratory animals. In total, 5-7 nude mice were included in each of the four groups (2 weeks old female nude mice (BALB/c-nu)).

AUC3. Debio 1143 concentrates were tested against a group of lung cancer PDX xenografts in a single agent or combination therapy. The ratio of AUC for Debio 1143 to the AUC of the better of the two single agents was calculated and compared to the AUC synergy score of the combination. The AUC synergy score of the combination was calculated as the difference between the AUC AUC synergy score of the combination and the better of the two single agents.

Figure 2. Debio 1143 exhibits differential single agent activity across human lung cancer PDX models.

Figure 3. Combination therapy sensitized adenocarcinoma NSCLC cell lines to Debio 1143.

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 NSCLC SOC compounds also in vivo, the combination of Debio 1143 and docetaxel was assessed in mouse xenografts of human AS41 NSCLC adenocarcinoma cells. The combination was found to be superior to either monotherapy in vivo.

The increased Debio 1143 monotherapy efficacy observed in vivo may indicate involvement of host-mediated processes relevant for the Debio 1143 mechanism of action.

Background / Aim of the study

Debio 1143 is a monovalent IAP antagonist facilitating induction of apoptosis

The oral monovalent IAP antagonist Debio 1143 (aka SMAC mimetic and ATPase) inhibits multiple IAP proteins: the pro-hypothetical cell death executioner XIAP and the caspase-8 activator cIAP1/2. Debio 1143 is currently in clinical development for cancer treatment. The aim of this study was to evaluate the activity of Debio 1143 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).

Drug resistance is a major problem in cancer therapy. The combination of drugs targeting simultaneously multiple distinct cellular targets that contribute to cancer cell survival and cell killing in vitro has been shown to achieve long-lasting responses (1-2). The mechanisms of the inhibitor of apoptosis (IAP) family are key negative 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.

Debio 1143 synergizes with NSCLC SOC compounds to inhibit growth of human NSCLC cell lines in vitro

In clinical trials in several cancer types (ClinicalTrials.gov Identifier: NCT01930292).

It was to evaluate the activity of Debio 1143 alone and in combination therapy, an in vitro high-throughput combination screen (cHTS) was performed using the 6 compounds in a cell viability assay at 72h performed in duplicates (CellTiter-GLO). Synergy was assessed in vitro using an AUC-based analysis in order to capture curve shifts, which represent increased potency and/or efficacy of the combination compared to the better of the two single agents.

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Acknowledgements

*These authors contributed equally to this work.

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

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References


Contact

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