Abstract #317

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

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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 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 (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 by interfering with X-linked IAP (XIAP) and cellular IAP1 and 2 (cIAP1/2), respectively (Fig. 1). 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 *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).

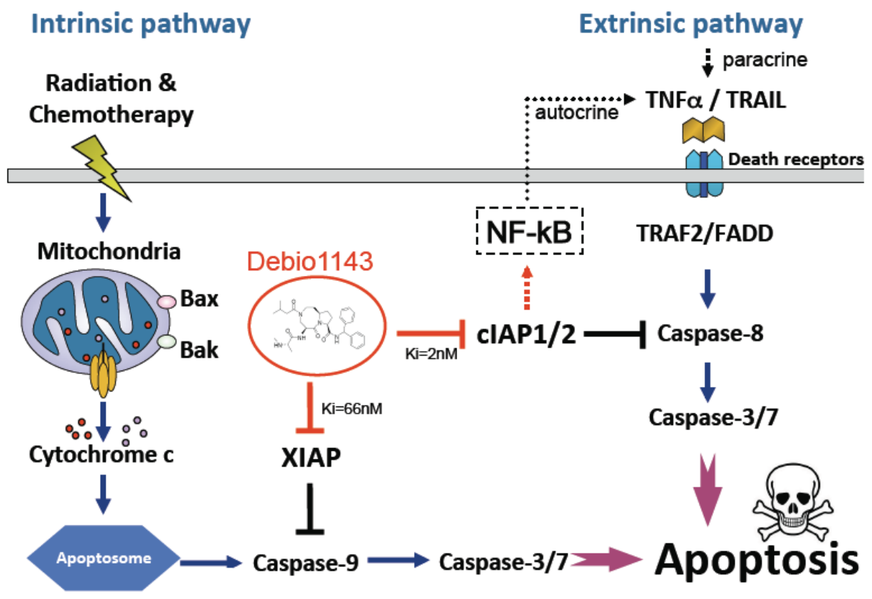


Figure 1. Mechanism of action of Debio 1143. Debio 1143 facilitates cell death via both the intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

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).**

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 patient-derived xenograft (PDX) 3D cultures, which included 49 lung cancer models representing small-cell, large-cell, adeno and squamous lung cancer histotypes. Increased activity of Debio 1143 was observed in small, large and squamous histotypes, whereas adenocarcinoma-derived samples were less responsive as compared to the mean activity across the full PDX panel (Fig. 2).

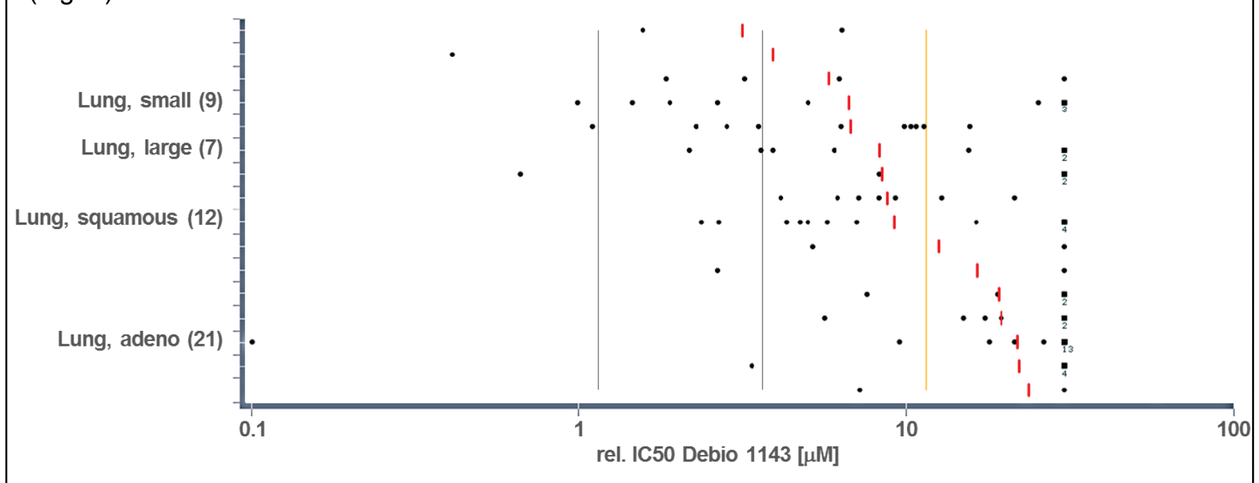


Figure 2. Debio 1143 exhibits differential single agent activity across human lung cancer PDX of different histotypes in clonogenic assays. Yellow line: geometric mean relative IC50 across all samples; red lines: geometric mean relative IC50 within each histotype.

Debio 1143 synergizes with SOC compounds on human adeno NSCLC cell lines *in vitro*

Previous results indicated that adeno NSCLC models are insensitive to Debio 1143 monotherapy (Fig.1 and unpublished results). To test if this histotype could be sensitized to Debio 1143 an *in vitro* high-throughput combination screen (cHTS) was performed using the 6 human adeno NSCLC cell lines displayed in Fig. 4, assessing pairwise combinations of Debio 1143 with 128 oncology compounds in a cell viability assay. In order to identify and quantify curve shifts indicative of synergy or antagonism the dose-response curves of single agents and combinations were analyzed by quantifying the area under the curve (AUC). This identified several NSCLC SOC compounds as synergistic combination partners for Debio 1143 when looking at the average effects across all 6 cell lines (Fig. 3 only combinations with positive AUC score are shown).

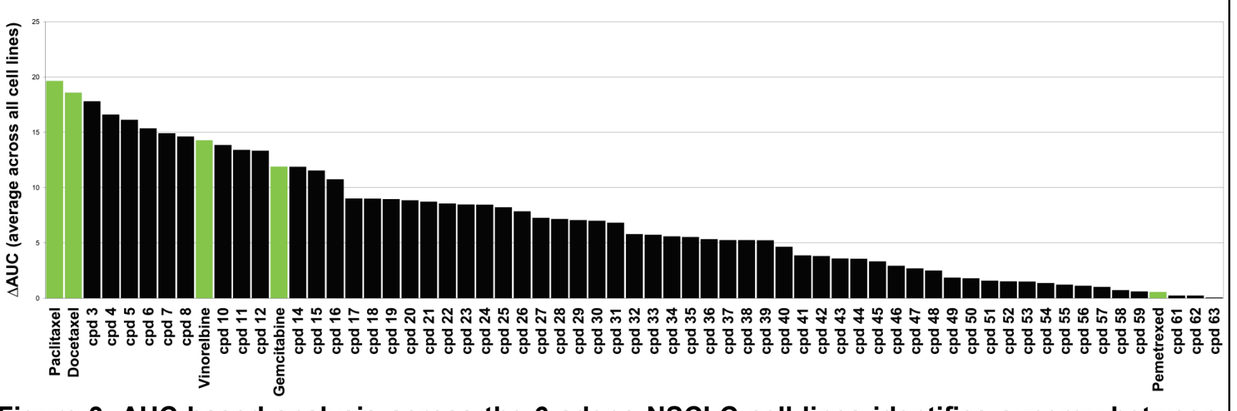
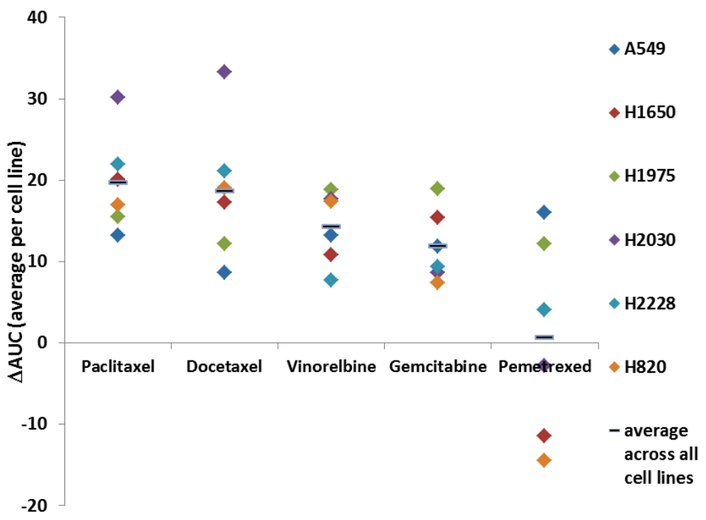


Figure 3. AUC-based analysis across the 6 adeno NSCLC cell lines identifies synergy between Debio 1143 and several NSCLC SOC compounds. cpd: compound.

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

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



Cell line	Genotype
A549	KRAS mut, CDKN2A mut
H1975	EGFR mut (L858R, T790M mutations)
H2228	EML4-ALK fusion, TP53 mut, CDKN2A mut, RB1 mut
H2030	KRAS mut, TP53 mut
H1650	EGFR mut (E746_A750del), TP53 mut, CDKN2A mut
H820	EGFR mut (ΔE746-A749, T790M mutations)

Figure 4. Debio 1143 displays synergy in combination with the NSCLC SOC compounds paclitaxel, docetaxel, vinorelbine, gemcitabine and pemetrexed *in vitro*. AUC scores and genotypes for the individual adeno NSCLC cell lines are displayed.

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 was assessed in mouse xenografts of human A549 NSCLC adenocarcinoma cells. While both 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.

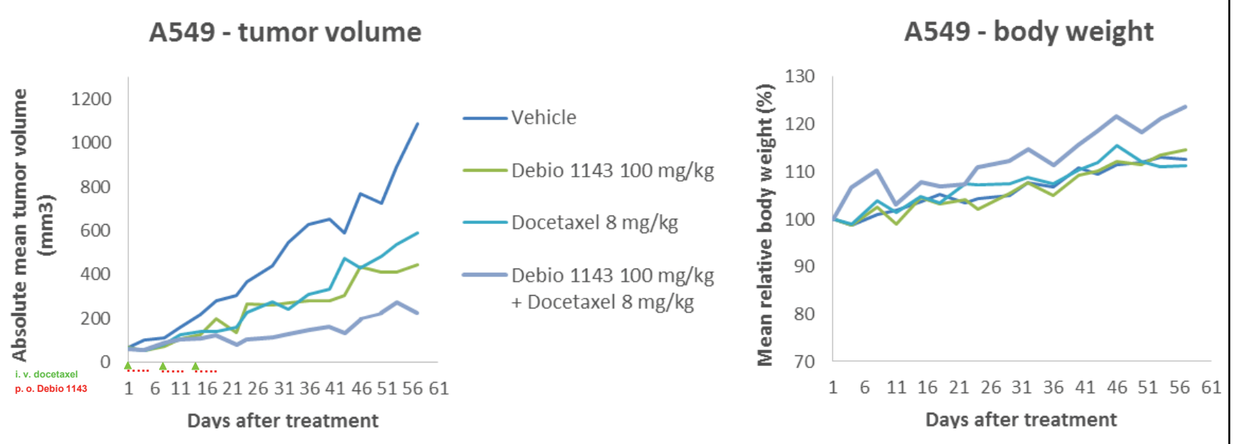


Figure 5. *In vivo* synergy between Debio 1143 and docetaxel on A549 human NSCLC xenografts in nude mice.

Methods

PDX maintenance. PDX experiments were performed by Oncotest, Freiburg, Germany. Solid human tumor xenografts grown subcutaneously (s.c.) in serial passages in NMRI nu/nu mice were removed, disaggregated, filtered, counted and frozen in nitrogen.

Clonogenic PDX assays. A three-layer soft agar assay was used in a 24-well format: 10k cells were seeded and continuously exposed to test compounds for up to 20 days when colonies with a diameter of > 50 µm were counted.

cHTS. 3 Debio 1143 concentrations were tested against a 5-log concentration range of the candidate compounds in a cell viability assay at 72h performed in duplicates (CellTiter-GLO). Synergy was assessed using an AUC-based analysis in order to capture curve shifts, which represent increased potency and/or efficacy. The AUC score was calculated in R using the natural log of the candidate concentration range (to allow comparison of compounds despite different dosing). The ΔAUC was calculated as the difference between the AUC scores of the combination and the better of the two single agents and used as a synergy measure.

Xenograft mouse models. Xenografts were performed in accordance with the guidelines for the care and use of laboratory animals. In brief, 5 × 10e6 cells were injected s.c. into the right flank of 4-6 week old female nude mice (BALB/c- nu/nu).

Treatment schedules: Debio 1143 was given p.o. daily 5 days a week for 3 weeks (d1-5; d8-12; d15-19); docetaxel (Taxotere; NorthCarolina Chemlabs) was injected i.v. once per week for 3 weeks (d1; d8; d15) using a dosing volume of 10 mL/kg (0.2 mL/mouse). Tumor volume and body weight was monitored every 3-4 days.

References

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Acknowledgements

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