Abstract #2531

Phase I Dose-escalation Study with Extended Daily Administration of Debio 1143, an Oral Inhibitor of Apoptosis Protein Inhibitor, in Patients with Solid Tumors.

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Background

Debio 1143 is a monovalent SMAC mimetic targeting IAPs to induce apoptosis

Drug resistance is a major problem in cancer therapy. The combination of drugs targeting simultaneously multiple critical sites of the signaling networks controlling growth and survival of cancer cells is necessary to achieve long-lasting responses [1]. 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 [2].

The oral monovalent SMAC mimetic Debio 1143 (AT406) functions as an antagonist of multiple IAPs thus facilitating cell death via both intrinsic and extrinsic apoptosis pathways by interfering with X-linked IAP (XIAP) and cellular IAP1 and 2 (cIAP1/2), respectively.

Debio 1143 - administered daily x 5, every 21 days – was well tolerated in cancer patients up to 900 mg QD [3].

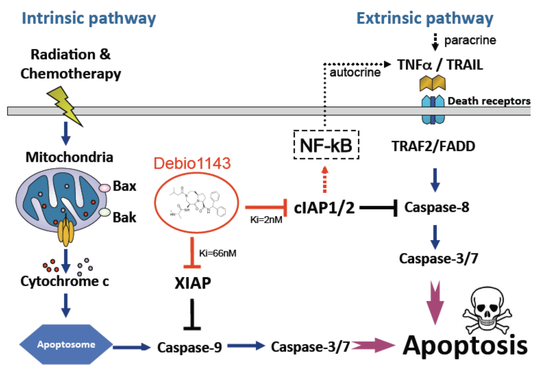


Fig. 1. Debio 1143 facilitates cell death via both intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

Methods

Eligibility criteria included:

- Age ≥18 years
- Cytologically confirmed advanced or metastatic solid tumors or lymphomas
- ECOG performance status 0-1
- Adequate organ function

Dose & scheduling:

- Debio 1143 orally on days 1-14, every 21 days
- Starting dose 200 mg

Definition of DLT & Assessments

Non-hematologic DLT:

- Any ≥ Grade 3 non-hematologic toxicity excluding nausea, vomiting, diarrhea
- ≥ Grade 3 nausea, vomiting or diarrhea uncontrolled by maximal antiemetic/anti- diarrheal therapy for ≥ 24 h
- Any toxicity considered by investigator/medical monitor as DLT

Hematologic DLT:

- ≥ Grade 3 anemia
- ≥ Grade 3 neutropenia
- Thrombocytopenia of any Grade if associated with clinically significant bleeding
- Grade 4 thrombocytopenia

General DLT:

- Any Adverse Event resulting in a dose delay or reduction during the first Cycle

Assessments:

- Cardiac safety monitoring including triplicate ECGs and LVEF
- Serial PK assessments performed on plasma and urine (10 patients) at day 1 and 11 of Cycle 1
- Serial Pdy assessments including tumor and surrogate tissue IAP-1 and serum markers of apoptosis and inflammation
- Tumor assessment performed every two cycles per RECIST criteria

Clinicaltrials.gov identifier: NCT01078649

Results

Patient Characteristics & Safety

16 Patients: 7 (44%) men, 9 (56%) women, mean age 57.4 ± 10.1 years (range: 42-73 years)

Cohort/Dose	N. patients enrolled	Pat. ID	Sex	Age	Tumor type
200 mg	6	001-5004	F	63	Ovarian cancer
		001-5005	M	60	Colon cancer
		001-5006	M	73	Bladder cancer
		131-5001	F	61	Ovarian cancer
		132-5002	F	42	Malignant peripheral nerve sheath
		132-5003	M	53	Chondrosarcoma
300 mg	3	131-5011	F	70	NSCLC
		132-5010	F	47	Cholangiocarcinoma
		132-512	F	44	Adenoid cystic carcinoma
400 mg	7	001-5023	F	57	Leiomyosarcoma
		001-5024	F	70	Gallbladder
		001-5025	M	67	Colon cancer
		001-5027	F	59	Ovarian cancer
		131-5022	M	42	NSCLC
		131-5026	M	51	NSCLC
		132-5021	M	59	Unknown squamous cell carcinoma

Table 1. Patient characteristics

Safety:

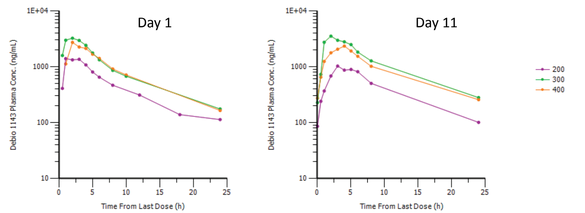
- 15 patients (94%) completed at least one cycle (median duration of exposure: 35 days; range: 7-78 days)
- Main reason for withdrawal was disease progression (87.5%).
- MTD not reached (at 400 mg). AEs were mostly CTCAE Grade 1 or 2 and neither incidence nor severity increased with dose.
- Most common AEs of any grade deemed related to treatment were fatigue (31%), nausea (29%), decreased appetite (20%), vomiting (16%), diarrhea (14%), and rash (14%).
- Only one DLT at 200 mg/day (ALT and ALP elevation)

Debio 1143 Dose	DLT	CTCAE Grade	Relatedness	Action	Outcome
200 mg	ALT increase ALP increase	G3 G3	Possibly related	Discontinued	Reversed

Table 2. DLT (Dose-limited toxicity).

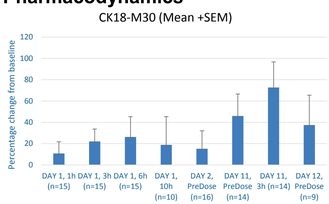
PK/PD & Antitumor Activity

Pharmacokinetics

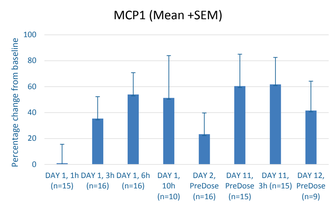


Geometric mean of plasma concentration of Debio 1143 after 200, 300 and 400 mg single dose (Day 1) administration and at steady-state (Day 11). PK inter-individual variability accounts for overlapping exposures after 300 and 400 mg doses.

Pharmacodynamics



CK18-M30 protein level in plasma was measured by ELISA. Following Debio 1143 treatment, an increase in CK18-M30 was observed at all timepoints.



MCP1 protein level in plasma was measured by ELISA. Following Debio 1143 treatment, an increase in MCP1 was observed at most timepoints.

Reduction in cIAP1 levels in PBMCs was observed from Day 1, 1h up to Day 12 in all patients

Antitumor Activity

No responses were observed in 15 evaluable patients.

Conclusions

- The extended schedule administration of oral Debio1143 was well tolerated with significant PD activity at the doses investigated.
- MTD has not been reached at the highest tested dose 400 mg/day.
- A Phase Ib trial of this extended schedule of Debio1143 in combination with concurrent chemo-radiation in H&N squamous carcinoma is in progress.

References

[1]. Hanahan Weinberg RA. 2011. *Cell* 144: 646-74.
[2]. Fulda S. 2007. *Exp. Rev. Anticancer Ther.* 7: 1255-64.
[3]. Hurwitz Het al. 2015. *Cancer Chemotherapy and Pharmacology* 75(4): 851-859

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