First-in-human, Pharmacokinetics (PK) and Pharmacodynamics (PD) Phase I Study of Debio 1143 (AT406) in Patients with Advanced Cancer. Final Results.

#2532

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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.

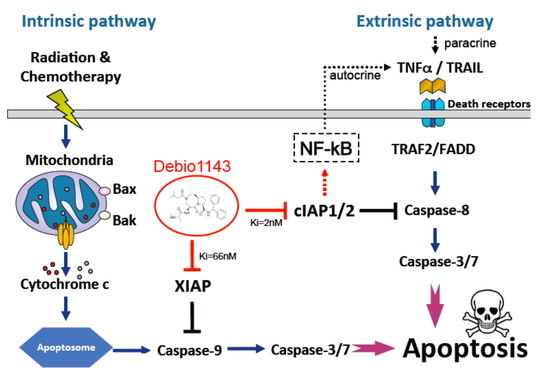


Fig. 1. Debio 1143 facilitates cell death via both intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

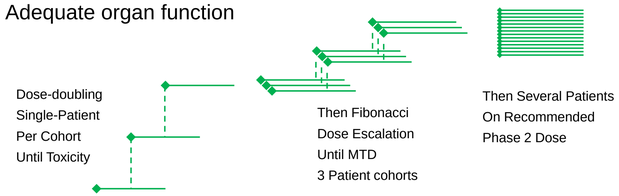
Methods

Eligibility criteria included:

- Age ≥ 18 years
- Cytologically confirmed advanced or metastatic solid tumors or lymphomas
- ECOG performance status 0-2
- Adequate organ function

Study design:

- Schedule: Day 1-5 and 15-19, q 28 days
- Amended to days 1-5, q 21
- Adaptive design for dose titration



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 Cycle 1

Assessments:

- Cardiac safety monitoring including triplicate ECGs and LVEF
- Serial PK assessments performed on day 1 and 5 of Cycle 1
- Serial PD assessments including tumor and surrogate tissue cIAP1 and plasma markers of inflammation and apoptosis
- Tumor assessment performed every two cycles per RECIST criteria

ClinicalTrials.gov identifier: NCT01078649

Results

Patient Characteristics & Safety

The **primary objective** was to characterize the safety and determine the MTD and schedule of Debio 1143 in patients with advanced solid tumors and lymphomas. **Secondary objectives** were to explore PK of Debio 1143, any PD effects, any observable antitumor activity and its correlation with PK.

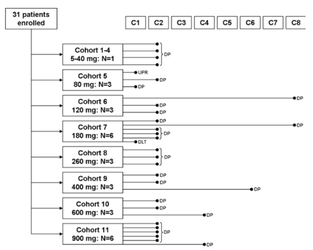


Fig. 2. Patient flow chart.

		N = 31
Age (years)	Mean	52 ± 11
Gender	Male / Female	12 (38.7%)/19 (61.3%)
ECOG PS	1	16
	2	15
Tumor type	Colorectal	14 (45.1%)
	Melanoma	3 (9.7%)
	NSCLC	2 (6.5%)
	Ovarian	1 (4.5%)
	Breast	1 (4.5%)
	Gastro-oesophageal	1 (4.5%)
	Lymphoma	1 (4.5%)
	Other	8 (25.8%)

Table 1. The 31 enrolled patients received 5-900 mg of drug per day

Safety:

- All patients completed at least one cycle (median two cycles).
- Main reason for withdrawal was disease progression.
- AEs were mostly CTCAE Grade 1 or 2; neither incidence nor severity increased with dose.
- Most common toxicity included fatigue (26%), nausea (23%) and vomiting (13%).
- Only one DLT was reported at 180 mg/day (Grade 3 reversible ALT elevation).
- The MTD was not reached at the highest dose of 900 mg.

Debio1143 Dose	DLT	CTCAE Grade	Relatedness	Action	Outcome
180 mg	ALT Increase	3	Possibly Related	Discontinued	Reversed

Table 2. DLT (Dose-limited toxicity).

Pharmacokinetics & Pharmacodynamics

Pharmacokinetics:

- Debio 1143 was rapidly absorbed after oral administration; peak plasma concentration reached within 1-3 h.
- Plasma exposure for parent & metabolite increased with dose.
- Steady-state conditions were reached after the first dose.
- No evidence of drug accumulation

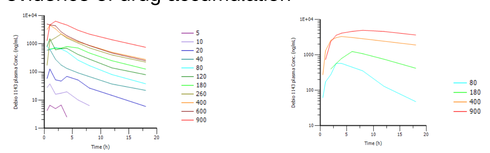
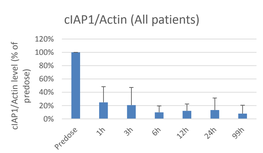


Fig. 3. Debio 1143 (left) and its metabolites MET-1 (right) mean plasma concentrations vs time profile at day 1.

Pharmacodynamics:

- Rapid and strong reduction in cIAP signal observed from 1 h post-dose lasting at least 24 h
- Plasma MCP-1 increased at 3-6 h post-dose and epithelial apoptosis marker CK18-M30 on day 5



All patients			
Hours	mean	SD	N
Predose	100%	0%	22
1 h	25%	24%	19
3 h	21%	27%	19
6 h	10%	10%	20
12 h	12%	10%	9
24 h	13%	18%	19
99 h	8%	13%	18

Fig. 4. Mean ± SD cIAP1 level measured in PBMCs from all. The cIAP1 signal was measured by Western Blot and normalized to Actin signal.

Conclusions

- Debio1143 monotherapy was well tolerated at doses which achieved pre-clinically targeted drug exposure and PD activity.
- MTD has not been reached (highest tested dose 900 mg/day).
- A Phase I-II program of Debio1143 in combination with SOC NSCLC, ovarian, TNBC and LA-SCCHN is in progress.

References

[1]. Hanahan Weinberg RA. 2011. Hallmarks of cancer: the next generation. *Cell* 144: 646-74.
[2]. Fulda S. 2007. Inhibitor of apoptosis proteins as targets for anticancer therapy. *Exp. Rev. Anticancer Ther.* 7: 1255-64.

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