Phase I Study of Debio 1143 (AT406) in Combination with Daunorubicin (D) and Cytarabine (C) in Patients with Poor-risk Acute Myeloid Leukemia (AML)

#7029

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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. 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.

Overexpression of IAPs and its impact on survival and chemo-resistance has been shown. 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.

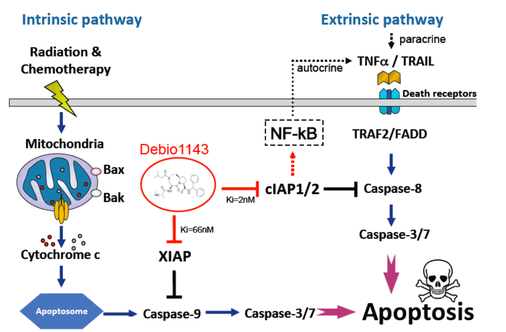

Fig. 1. Debio 1143 facilitates cell death via both intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

Methods

Patient Characteristics & Safety

Eligibility criteria included:

- Age ≥ 18 ≤ 75 years
- Morphological diagnosis of untreated or relapsed non-M3 AML per WHO Criteria
- Patients with prior autologous or allogeneic HSCT are eligible if relapse occurs > 6 months following transplantation.
- Prior treatment for MDS or AML with hypomethylating agents (decitabine, azacitadine) is permitted.
- Patients must exhibit at least one poor-risk feature.
- ECOG performance status 0-1
- Adequate organ function

Dose & Schedule: Patients received an induction cycle of

- Debio 1143 orally on days 1-5 (starting dose 100 mg)
- Daunorubicin 90 mg/m² intravenously on days 1-3
- Cytarabine 100 mg/m² by continuous infusion on days 1-7

Dose Level	Dose of AT-406 Days 1-5	Dose of Cytarabine Days 1-7	Dose of Daunorubicin Days 1-3
-1	100 mg, days 1-3	100 mg/m² c.i.v.	90 mg/m²
1	100 mg	100 mg/m² c.i.v.	90 mg/m²
2	200 mg	100 mg/m² c.i.v.	90 mg/m²
3	300 mg	100 mg/m² c.i.v.	90 mg/m²
4	400 mg	100 mg/m² c.i.v.	90 mg/m²

Definition of DLT

Non-hematologic DLT:

- Any Grade 4 or 5 of non-hematologic toxicity at any time
- Any Grade 3 non-hematologic toxicity
- Any Debio1143-related ≥ Grade 3 hypersensitivity or anaphylactic reactions
- Any toxicity considered by investigator/medical monitor as DLT

General DLT

- Any Adverse Event resulting in a dose delay or reduction during Cycle 1

Hematologic DLT:

- Grade 4 thrombocytopenia at day 42 in the absence of AML
- Grade 4 neutropenia at day 42 in the absence of AML
- Bone marrow should be done by day 42 even if heme recovery has not occurred, however, a day 42 bone marrow examination in a patient with persistent Grade 4 neutropenia will be considered as DLT.

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Assessments

- Cardiac safety monitoring including triplicate ECGs and LVEF
- Serial PK assessments performed during the first 8 days
- Serial PD assessments including PBMC expression of cIAP1, XIAP, CD34 and CD117, and markers (TNFα, MCP-1, and IL-18)

Results

29 Patients: 17 (59%) men, 12 (41%) women, mean age 55.5± 12.9 years

Safety:

- All patients completed the induction; 3 (10%) patients did not receive the planned dose of Debio 1143.
- There were no dose delays of Debio 1143 and daunorubicin, one for cytarabine.
- The MTD was 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 nausea (31%), diarrhea (14%), and febrile neutropenia (14%).
- 3 DLTs reported at 100, 200 and 400 mg, respectively.

Dose Level	DLT	CTCAE Grade	Relatedness	Action	Outcome
100	ALT increase	4 3	Possibly related	Discountinued	Reversed-approx. 3 days
200	Oral mucositis Pharyngeal mucositis Small intestine mucositis Atrial tachycardia Electrolyte imbalance	3 3 3 3 3	Possibly related	None	Reversed-approx. 7 days
400	Neutropenic fever *S. viridans* infection Sepsis *C. difficile* colitis Heart failure	3 2 2 2 4	Possibly related	Discontinued	Neutropenic sepsis resolved Heart failure worsened

PK/PD & Antitumor Activity

Pharmacokinetics

- Cmax and AUC increased greater than proportional with the Debio 1143 dose in the range from 100 to 400 mg.
- Plasma concentrations of Debio 1143 varied considerably among individuals.
- Average T_{max} was approximately 2 h.
- $T_{1/2}$ was about 5.5 h and dose independent.
- No drug accumulation was observed over 5 day dosing.

Dose	Day	N	C_{max} [mg/l]	T_{max}* [h]	$T_{1/2}$ [h]	AUC_{0-tf} [mg*h/l]
100 mg	1	8	1.2 ± 0.7	2.6	5.0 ± 1.1	6.0 ± 3.5
	5	8	8.3 ± 0.8	2.9	13.0 ± 2.9	8.5 ± 5.7
200 mg	1	12	3.0 ± 1.8	1.5	5.6 ± 0.9	18 ± 9
	5	12	2.4 ± 1.3	1.5	18.0 ± 5.1	24 ± 14
300 mg	1	4	4.4 ± 1.7	1.2	4.9 ± 1.0	25 ± 12
	5	4	2.5 ± 4.0	2.0	15.9 ± 3.4	24 ± 11
400 mg	1	4	9.5 ± 4.5	1.0	5.9 ± 1.4	55 ± 20
	5	4	5.6 ± 1.8	2.5	25.5 ± 3.7	72 ± 20

Pharmacodynamics:

- Inhibition of cIAP1 levels was detectable in CD34/CD117⁺ cells.
- No correlation between changes in cIAP1 and types of AML or treatment outcome was observed.

Antitumor activity:

- A total of 11 (38%) achieved CR, the majority in the 100 mg dose cohort (5 out of 8 patients: 68%).
- Correlative subgroup analysis between disease remission and cytogenetic variants were inconclusive.

Response Rate n (%)	
CR	9 (31)
Cri	2 (7)
PR	1 (3)
Resistant	17 (59)
Cytogenetics (CR/Cri %)	
Favorable	===
Intermediate	7/10 (70)
Unfavorable	3/17 (18)
Very unfavorable	===
Missing data	1/2 (50)
Previous treatment	
Untreated	7/21 (33)
Relapsed	4/8 (50)
Age (CR/CRi %)	
< 60 yrs	6/16 (37)
≥ 60 yrs	5/13 (38)

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