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

HI Hurwitza, HC Pitotb, DC Smithc, J Brillf, G Vuagnaus, E Rouita, C Zanna, M Sorensena

aDuke University, Durham, USA; bMayo Clinic, Rochester, USA; cUniversity of Michigan, Ann Arbor, USA; dAscenta Therapeutics, Malvern, USA; eDebiopharm International SA, Lausanne, Switzerland

Methods

Eligibility criteria included: Age ≥ 18 years, Cytologically confirmed advanced or metastatic solid tumors or lymphomas, ECOG performance status 0-2, Adequate organ function, All patients completed at least one cycle (median two cycles).

Study design: Scheduled: Day 1-5 and 15-19, q28 days, Adapted design for dose titration, Cardiac safety monitoring including triplicate ECGs and LVEF.

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 reversible antitumor activity and its correlation with PK.

Safety:

- All patients completed at least one cycle (median two cycles).
- Main reason for withdrawal was disease progression.
- AE 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.

Results

Pharmacokinetics & Pharmacodynamics:

- 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.

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.

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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

References


Contacts

Debiopharm International S.A. Lausanne, Switzerland
claudio.zanna@debiopharm.com

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