Debio 1143 is a monovalent SMAC mimic 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 cancer types contributes to tumor cell survival and resistance to cancer therapy making IAP's attractive therapeutic targets [2].

The oral monovalent SMAC mimic 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.

**Methods**

**Eligibility criteria included:**
- Age ≥ 18 years
- Tumor assessment performed every two cycles per RECIST criteria
- Plasma exposure for parent Debio1143
- Cytologically and histologically confirmed advanced or metastatic solid tumors or lymphomas
- ECOG performance status 0-2
- Adequate organ function
- Most common toxicity included fatigue (26%), nausea (23%)
- Cardiac safety monitoring including triplicate ECGs and LVEF
- Plasma MCP
- Adequate tumor tissue for cIAP1/Actin level (% of signal) was measured by investigator/medical monitor as DLT
- Any toxicity considered by investigator/medical monitor as DLT

**Study design:**
- Scheduled: Day 1 and 5 of Cycle 1
- 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 uncontrollable 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

**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 and any observable 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's 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/day.

**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

**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**


**ClinicalTrials.gov identifier:** NCT0178649

**Fig. 1:** Debio 1143 facilitates cell death via both intrinsic and extrinsic apoptosis pathways by interfering with XIAP and cIAP1/2, respectively.