Methods

1.1 has 15.9 11 key cell 5/13 (38)
5.6 1 2.9 cellular pathways and 1143 varied considerably 55
International S.A., [h] Cytarabine T 1.3 ± 1.8 cell to Any networks 9.5 DLT
200 mg ± and intrinsic 400 mg 1.5 multiple 1143 a ± 72
3/17 (18) 6/16 (37) Debio the Bone marrow should be done
ALT mimetic 1.0 Antitumor family been ± 3 DLTs reported at 100, 200 and 400 mg,
cell 4 100 mg A 300 mg by was about 5.5 h
0.9 P identifier Average survival ± to
Serial PK assessments performed during the first 8 days
Morphological diagnosis of untreated or relapsed non
cancer 12 20 There were no dose delays of
Serial PD 4 IAP critical 4/8 (50)
fever C Their Activity of
100 mg/m² 2 problem via long ± resistance T
targeting cancer 1
25.5 17 (59) 5.1
Neutropenic ECOG performance status 0
in
ClinicalTrials.gov identifier: NCT01076849

Phase I Study of Debio 1143 (AT406) in Combination with Daunorubicin (D) and Cytarabine (C) #7029

in Patients with Poor-risk Acute Myeloid Leukemia (AML)

Cytogenetics

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 exposure was approximately 2 h.
T½ was about 5.5 h and dose independent.
No drug accumulation was observed over 5 day dosing.
Pharmacodynamics:
Inhibition of cIAP1 levels was detectable in CD34/CD17+ cells.
No correlation between changes in cIAP1 and types of AML
treatment or 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.

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.

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

Response Rate (%)
CR 9 (31)
CRI 2 (7)
PR 1 (3)
Resistant 2 (7)
Cytogenetics (CR/CRi %)
Favorable 7/10 (70)
Intermediate 3/10 (30)
Unfavorable 3/10 (30)
Very unfavorable 3/10 (30)
Missing data 1/10 (10)

Dose Level CTCAE Grade Relatedness Action Outcome
100 All increase 4 Possibly related Discountinue d Reversed-approx. 3 days
200 Oral mucositis 3 Possibly related None Reversed-approx. 7 days
Pharyngeal mucositis 3 Possibly related None
Small intestine mucositis 3 Possibly related None
Atrial tachycardia 3 Possibly related None
Electrolyte imbalance 3 Possibly related None

400 Neutropenic fever 2 Possibly related Discontinue d Neutropenic fever resolved
S. viridans infection 2 Possibly related Neutropenic fever resolved
Dilantin 2 Possibly related Neutropenic fever resolved
C difficile colitis 2 Possibly related Neutropenic fever resolved
Heart failure

Definiton 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/monitor as DLT

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.

General DLT
• Any Adverse Event resulting in a dose delay or reduction during Cycle 1

Assessments
• Cardiac safety monitoring including triplicate ECGs and LVEF performed by echocardiography at baseline, Cycle 1 and 4.
• 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 (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 fever (31%), diarrhea (14%), and febrile neutropenia (14%).
• 3 DLTs reported at 100, 200 and 400 mg, respectively.

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