Debio 1143 in combination with carboplatin and paclitaxel in patients with non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC) and platinum-refractory epithelial ovarian cancer (EOC). Preliminary results of a Phase I dose-escalation study

Abstract #444

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Background

Drug resistance is a major problem in cancer therapy. The combination of drugs targeting simultaneously multiple critical nodes of the signaling networks controlling growth and survival of cancer cells is necessary to achieve long-lasting responses.

The 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.

The oral monovalent SMAC mimetic Debio 1143 (a.k.a. SM406 and AT406) functions as an antagonist of multiple IAP proteins thus facilitating cell death via both the intrinsic and extrinsic apoptosis pathways by interfering with X-linked IAP (XIAP) and cellular IAP1 and 2 (cIAP1/2), respectively.

As a single agent Debio 1143 exhibits antitumor activity inhibits cell growth and induces apoptosis in a subset of human cancer cell lines and in multiple xenograft models of human cancer, including TNBC, NSCLC and EOC. Debio 1143 works synergistically with conventional chemotherapeutic (such as platins and taxanes), targeted agents, and radiotherapy in non-clinical tumor models. The use of Debio 1143 is of great interest in EOC where carboplatin resistance is induced by an activation of IAPs by the tumor microenvironment.

Debio1143 monotherapy was well tolerated in cancer patients up to 900 mg OD, resulted in rapid and sustained cIAP1 suppression in patient peripheral blood mononuclear cells and in skin biopsies, and achieved exposures that were previously shown to be active in animal models [1]

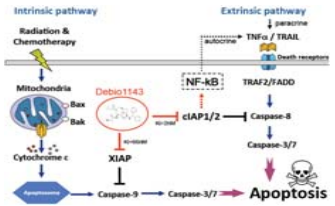
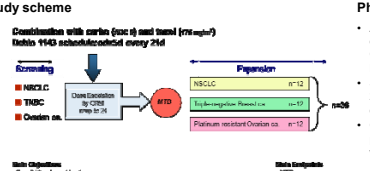


Figure 1. Mechanism of action of Debio 1143. Debio 1143 facilitates cell death via both the intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

Methods

Study scheme



Phase I Dose Escalation

- Adaptive dose-escalation design using a modified Continual Reassessment Method (mCRM)
- Starting dose of Debio was 200 mg/day over 5 days every 21 days
- Carboplatin (AUC6) and paclitaxel (175 mg/m2) were administered on Day 1 of every 21-day cycle.

Definition of DLT

- Non-hematological G3 and 4 toxicity except: alopecia, rash, nausea, vomiting, diarrhea, and electrolyte imbalances with sub-optimal prophylactic and curative therapy. Non-hematological G3 and 4 nausea, vomiting, and diarrhea are considered as DLTs only if they persist despite optimal symptomatic therapy.
- Thrombocytopenia < 25 000/□L lasting ≥ 5 days or < 50 000/□L with bleeding or requiring platelet transfusion.
- G4 neutropenia lasting > 5 days or G ≥ 3 neutropenia with fever > 38.5ºC or
- G ≥ 3 neutropenia with infection.
- Any treatment delay > 2 weeks because of treatment-related AEs occurring during the DLT period.
- Any other life-threatening toxicity.

Preliminary Results: as of October 1, 2014

Demographic and Baseline Characteristics

		Overall N = 17 n	(%)
Gender	Female	15	(88)
Age (year)	median (range)	56.5	(38-78)
ECOG PS	0	9	(52.9)
	1	8	(47.1)
Type of primary tumor	Ovarian cancer	11	
	Triple-Negative breast cancer	4	
	sqNSCLC	2	
Number of prior chemotherapy lines	median (range)	4.2	(1–8)

Determination of MTD

Dose Escalation

Dose Level	Dose of Debio1143	Dose of Carboplatin	Dose of Paclitaxel	N of patients
1	200 mg	AUC6	175 mg/m²	2
2	100 mg	AUC6	175 mg/m²	2
3	100 mg	AUC5	135 mg/m²	2
4	125 mg	AUC5	135 mg/m²	2
5	175 mg	AUC5	135 mg/m²	2
6	200 mg	AUC5	135 mg/m²	7

- Hematological DLT was observed in Dose Level 1 and 2 despite the reduction of the Debio1143 dose to 100 mg.
- The study protocol was amended reducing the doses of carboplatin to AUC5 and paclitaxel to 135 mg/m2

DLTs

Dose Level: Debio1143	Dose Level: carbo/paclitaxel	DLT	CTCAE Grade	Action	Outcome
200 mg	AUC6 175 mg/m²	Febrile neutropenia	4	Dose reduction	Recovered
100 mg	AUC6 175 mg/m²	Febrile neutropenia	4	Discontinued	Recovered
		Thrombocytopenia	4		Recovered
200 mg	AUC5 135 mg/m²	Febrile neutropenia	4	Dose reduction	Recovered

Clinicaltrials.gov identifier: NCT01930292

Safety

Treatment-related Grade ≥ 2 AEs any time on study

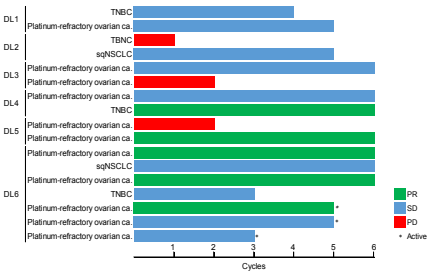
Toxicity, highest grade per patient (N = 17 patients)	Grade 2	Grade 3	Grade 4
Hematologic			
Febrile neutropenia	-	-	3 (17.6%)
Lymphocytes decrease	1 (5.8%)	-	-
Neutropenia	1 (5.8%)	3 (17.6%)	2 (11.8%)
Thrombocytopenia	3 (17.6%)	-	1 (5.8%)
WBC decrease	-	1 (5.8%)	-
Non-hematologic			
Abdominal pain	1 (5.8%)	-	-
Arthralgia/Myalgia	1 (5.8%)	-	-
Anorexia	1 (5.8%)	-	-
Asthenia	5 (29.4%)	-	-
Fatigue	2 (11.8%)	1 (5.8%)	-
Diarrhea	1 (5.8%)	-	-
Nausea	1 (5.8%)	-	-
Infection	1 (5.8%)	-	-
Alkaline phosphatase increased	1 (5.8%)	-	-
Hypomagnesemia	-	1 (5.8%)	-
Hyponatremia	1 (5.8%)	-	-
Hypokalemia	1 (5.8%)	-	-

Efficacy

Best Tumor Response

Tumor Type	PR	SD	PD
Ovarian (n = 11)	4 (36.4%)	4 (36.4%)	3 (27.2%)
Triple-Negative Breast cancer (n = 4)	1 (25.0%)	2 (50.0%)	1 (25.0%)
sqNSCLC (n = 2)	-	2 (100%)	-

Duration of disease control



Pharmacokinetics

PK parameters of DEBIO 1143

DOSE	N	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC (ng*h/mL)	CL/F (L/h)
100 mg	4	6.5 (23%)	[1.0 – 4.6]	486.7 (43%)	5 215 (43%)	19.2 (43%)
125 mg	2	5.9 (14%)	[1.1 – 4.3]	1 036 (165%)	8 215 (49%)	15.2 (49%)
175 mg	2	7.9 (0.5%)	[1.0 – 4.0]	1 796 (28%)	20 017 (29%)	8.7 (29%)
200 mg	9	7.5 (13%)	[1.0 – 4.0]	1 512 (95%)	11 222 (59%)	17.8 (59%)

PK parameters of DEBIO 1143-MET1

DOSE	N	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC (ng*h/mL)
100 mg	4	5.6 (50%)	[4.0 – 8.0]	405.5 (14%)	5 406 (27%)
125 mg	2	8.6 (119%)	8.0	315.5 (127%)	6 564 (53%)
175 mg	2	16.2 (56%)	[8.0 – 8.5]	916.0 (63%)	26 810 (110%)
200 mg	9	9.8 (69%)	[4.0 – 8.0]	702.3 (123%)	14 184 (56%)

Geometric Mean (CV% geomean) except for Tmax [min – max])

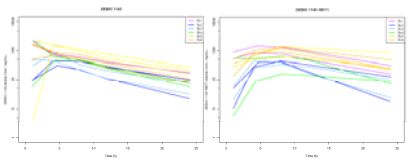


Figure 2. Individual observed plasma concentrations of Debio 1143 and Debio 1143-MET1 in patients from all the dose level cohorts.

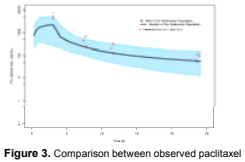
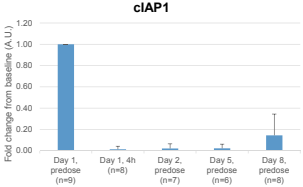


Figure 3. Comparison between observed paclitaxel plasma concentrations in patients from DL1 and DL2 and a population of patients receiving the same chemotherapeutic regimen (paclitaxel 175 mg/m2 + carboplatin AUC 6) [blue zone = 90% CI of concentrations from the reference population]

Pharmacodynamics



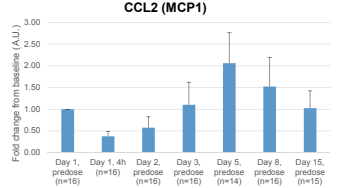


Figure 4. Mean +SD cIAP1/actin level measured in PBMCs (cIAP1 and actin signal were measured by Western Blot)

Figure 5. Mean +SD CCL2 (MCP1) level measured in serum (CCL2 (MCP1) signal was measured by ELISA)

Conclusions

- The MTD has not yet been reached;
- Exposure to Debio 1143 was variable between patients (CV% > 40%), but it was in the range of exposure expected to be active, based on pre-clinical pharmacological models; In general, exposure increased as dose increased;
- A drug-drug interaction between Debio 1143 and paclitaxel was suspected (increased paclitaxel exposure in presence of Debio 1143) then paclitaxel dose was decreased to behave in the therapeutic dose range;
- Carboplatin exposure was in the range of expected exposure (AUC 6 or AUC 5);
- The pharmacodynamics effect of Debio 1143 on cIAP1 degradation in PBMCs was confirmed at doses starting from 100 mg/day;
- Hints of activity was observed in patients with triple-negative breast cancer and platinum-refractory ovarian cancer;

References

[1] H. Hurwitz et al, EJC 48, Suppl.6, 2012; Abstract 76, p. 25

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