CLINICAL SAFETY, PHARMACOKINETICS AND EARLY EVIDENCE OF ACTIVITY OF THE ORAL IAPS INHIBITOR DEBIO 1143 IN COMBINATION WITH CARBOPLATIN AND PACLITAXEL: A PHASE 1 STUDY

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BACKGROUND

Debio 1143 is an oral monovalent SMAC mimetic

Resistance to apoptosis is a typical hallmark of cancer. Inhibitor of Apoptosis Proteins (IAPs) block caspase activation, modulate NF-kB signaling pathways, and are involved in resistance to standard chemo and radiation therapies. As such, IAPs antagonism represents an attractive target for therapeutic intervention. [1]

Debio 1143 is a potent orally-available monovalent SMAC mimetic antagonist of IAPs currently in clinical development. A previous phase I study showed Debio 1143 was well tolerated up to 900 mg QD as a single agent, with strong evidence of pharmacodynamic (PD) activity and appropriate pharmacokinetic (PK) parameters [1].

This Phase I study defined the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, PK, and PDy of Debio 1143 in combination with carboplatin and paclitaxel.

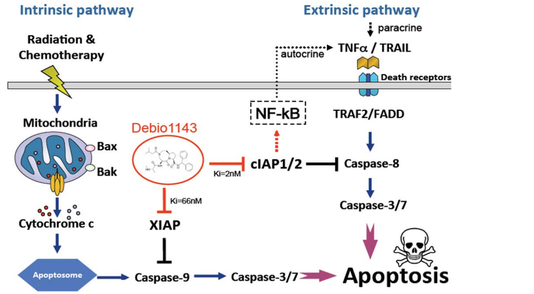
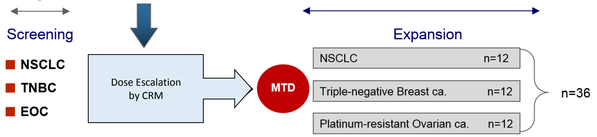


Figure 1.
Mechanism of action of Debio 1143. Debio 1143 facilitates cell death via both the intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

METHODS

Study Schema



Phase I Dose Escalation

- Adaptive dose-escalation design using a modified Continual Reassessment Method (mCRM)
- Target toxicity choosen at 40% to address the high toxicity of the combination therapy
- Starting dose of Debio was 200 mg/day on days 1-5 combined to Carboplatin (AUC6) and paclitaxel (175 mg/m2) administered on Day 1 of every 21-day cycle.

Definition of DLT

- Non-haematological G3 and 4 toxicity except: alopecia, rash, nausea, vomiting, diarrhoea, and electrolyte imbalances with sub-optimal prophylactic and curative therapy. Non-haematological G3 and 4 nausea, vomiting, and diarrhoea are considered as DLTs only if they persist despite optimal symptomatic therapy.
- Thrombocytopenia < 25 000/µL lasting ≥ 5 days or < 50 000/µL 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.

DLT period defined as the first treatment cycle

Clinicaltrials.gov identifier: NCT01930292

RESULTS AS OF OCTOBER 5TH, 2015

Demographics & Baseline Characteristics

	Safety population (N=27)
Median age, years (range)	62 (31 - 78)
ECOG performance status 0/1, n (%)	17 (63) / 9 (33)
Diagnosis, n (%)	
Ovarian	20 (74)
TNBC	6 (22)
sqNSCLC	1 (4)
Prior surgery, n (%)	24 (89)
Prior radiotherapy, n (%)	7 (26)
Prior regimens, n (%)	
Platinum-containing regimen	22 (82)
Taxane-containing regimen	27 (100)
Monoclonal AB (Bev) containing regimen	16 (59)
Median # of prior chemotherapy lines from diagnosis, n (range)	4 (1 - 8)

MTD and Recommended phase 2 dose (RP2D)

PK interaction between Debio 1143 and paclitaxel resulted in increased paclitaxel exposure with hematological DLTs observed in 2/4 patients in the first two dose-levels despite the reduction of Debio 1143 dose to 100mg. Thus, the backbone chemotherapy was reduced to paclitaxel 135 mg/m^2 and Carboplatin AUC=5 after 4 patients enrolled.

DLTs at paclitaxel 135mg/m^2 and carboplatin AUC=5

Debio 1143 Dose Level (DL)	DLT evaluable patients N=24	Patients with DLTs N=4	Event (CTCAE)	CTCAE Grade	Action	Outcome
100mg	2	0				
125mg	2	0				
175mg	2	0				
200mg	6	1	Febrile neutropenia	4		Recovered
225mg	4	0				
250mg*	8	3	Febrile neutropenia	3	Dose reduction	Recovered
			Febrile neutropenia +	4	''	''
			AST increase	3	''	''
			ALT increase	3	Withdrawn due to delayed recovery	''

***MTD, established by CRM**

3 patients were not DLT evaluable and replaced:

- One patient at 200mg received prohibited con-med (Amiodaron). This patient completed the planned 6 cycles at full dose (1 SAE grade 3 hypotension, not related)
- One patient at 225mg received prohibited con-med (G-CSF). This patient completed the planned 6 cycles at full dose (no SAE)
- One patient at 250mg was withdrawn by the investigator at C1D2 due to symptomatic carcinomatosis (1 SAE nausea/vomiting, not related)

Final CRM simulation

Dose level	A posteriori tox (%)	Patients	Toxicity
200	**13.91**	**6**	**1**
225	24.14	4	0
250	38.71	8	3
275	42.22	0	0

Debio 1143 at 200mg QD appears to be safe with an estimated toxicity probability of 13.9% and was selected as RP2D

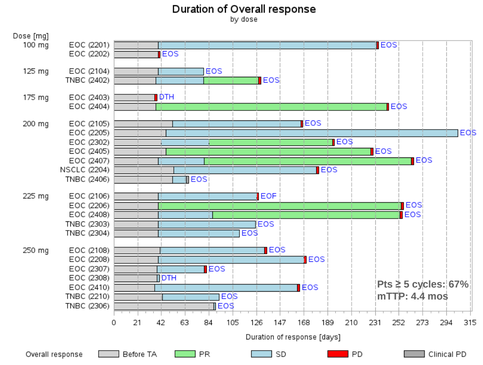
Safety population

	Highest grade per patient								
	All DL (N=27) n, (%)				Debio 200mg (N=6) n			Debio 250mg (N=8) n	
Hematologic	**All grades**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Neutropenia	18 (67)	-	-	2	3	1	-	1	3
Febrile Neutropenia	*4 (15)*	-	-	-	2[1DLT]	-	-	1[1DLT]	1[1DLT]
Anemia	18 (67)	3	2	-	-	2	4	-	-
Thrombocytopenia	12 (44)	3	1	-	-	2	1	1	-
WBC Decreased	9 (33)	1	1	2	-	-	1	-	-
Neutrophil Count ↓	7 (26)	1	1	0	1	-	1	-	-
Lymphocyte Count ↓	6 (22)	1	1	1	-	-	1	-	-
Non-hematologic									
Diarrhea	13 (48)	2	2	-	-	2	2	2	-
Constipation	12 (44)	2	2	-	-	5	0	-	-
Nausea	13 (48)	3	-	-	-	6	1	-	-
Abdominal Pain	9 (33)	1	2	-	-	3	2	-	-
Vomiting	9 (33)	2	1	-	-	2	-	1	-
Asthenia	18 (67)	0	3	-	-	4	3	-	-
Fatigue	8 (30)	1	2	-	-	0	1	-	-
Pyrexia	4 (15)	-	-	-	-	3	-	-	-
Hypomagnesemia	14 (52)	2	2	-	-	1	2	1	-
Decreased appetite	12 (44)	5	1	-	-	2	0	-	-
ALT increased	8 (30)	1	-	-	-	1	2	1[1DLT]	-
AST increased	7 (26)	2	-	-	-	-	1	1[1DLT]	-
Myalgia	5 (19)	2	-	-	-	-	-	-	-
Peripheral Neuropathy	10 (37)	1	2	-	-	2	1	-	-
Epistaxis	6 (22)	2	-	-	-	2	-	-	-
Alopecia	9 (33)	1	2	-	-	-	-	-	-
Pruritis	7 (26)	-	-	-	-	-	2	-	-

Efficacy

Best Tumor response All dose levels	PR	SD	PD
Tumor Type			
sqNSCLC (n=1)	0	1	0
TNBC (n=6)	1	5	0
Ovarian (n=18)	6	10	2
Total (n=25)	7	16	2

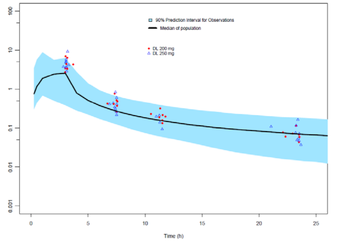
DURATION OF DISEASE CONTROL



Post-AMD patients. BIOSTAT / 05OCT2015 data

Pharmacokinetics

PK parameters of DEBIO 1143				
Combination with paclitaxel = 175 mg/m^2 and carboplatin AUC6				
DOSE	**N**	**C_{max} (mg/L)**	**AUC (mg*h/L)**	**MetRauc**
100 mg	2	0.371 (27%)	4.67 (64%)	1.2
200 mg	2	1.88 (18%)	13.2 (22%)	1.3
Combination with paclitaxel = 135 mg/m^2 and carboplatin AUC5				
100 mg	2	0.639 (40%)	5.84 (36%)	0.99
200 mg	6	1.40 (130%)	10.2 (72%)	1.07
250 mg	8	2.16 (62%)	21.3 (19%)	0.8



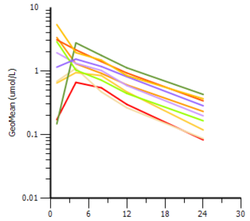


Figure 2. Mean observed plasma concentrations of Debio 1143 by cohort.

PK parameters of Paclitaxel		
DOSE	**N**	**AUC (mg*h/L)**
175 mg/m2	4	22.4 (26%)
135 mg/m^2	27	15.2 (31%)

Figure 3. Comparison between observed paclitaxel plasma concentrations in patients from DL200 and DL250 with paclitaxel 135 mg/m2 and a historical population of patients receiving paclitaxel 175 mg/m2 without Debio 1143 [blue zone = 90% CI of concentrations from the reference population]

Pharmacodynamics

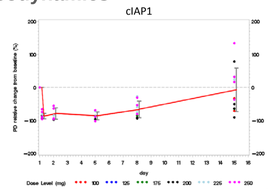


Figure 4. Mean ±SD cIAP1/actin level measured in PBMCs (cIAP1 signal was measured by Western Blot and normalized to Actin signal)

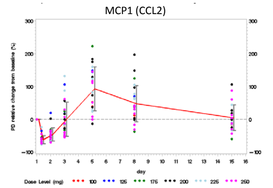


Figure 5. Mean ±SD MCP1 (CCL2) level measured in serum (MCP1 signal was measured by ELISA)

CONCLUSIONS

Safety and RP2D

- Safety profile of the combination is largely consistent with the safety profile known from the backbone treatment; Debio 1143 at 200mg QD days 1-5 in combination with taxol/carbo was selected as RP2D (MTD = 250mg)

Pharmacokinetics

- Debio 1143 exposure increased as dose increased. Exposure to Debio 1143 was variable between patients (CV% > 40%), but it was in the range of exposure expected to be active;
- A drug-drug interaction between Debio 1143 and paclitaxel was demonstrated with increased paclitaxel exposure in presence of Debio 1143 thus paclitaxel dose was decreased to behave in the therapeutic exposure range;
- Carboplatin exposure was in the range of expected exposure (AUC 6 or AUC 5)

Pharmacodynamic

- At all dose levels, the PD effect of Debio 1143 was evidenced by the degradation of cIAP1 in PBMCs (target engagement). Following an initial decrease at days 1-2 probably due to glucocorticoid comedication, an overall increase in serum MCP1 level (NF-kB modulation) was observed up to day 8.

Efficacy

- Encouraging signs of activity were observed mainly in heavily pre-treated platinum-refractory ovarian cancer patients
- As chemo-sensitizer, Debio1143 warrants further evaluation in disease settings where taxol/carbo is indicated

ACKNOWLEDGMENTS

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REFERENCES

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

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