Phase 1 Study of Debio 1143 with Concurrent Chemo-Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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BACKGROUND

Debio 1143 is an Oral Monovalent SMAC Mimetic

Inhibitors of Apoptosis Proteins (IAPs) are expressed in various cancers and are able to block caspase activation and modulate NF-kB signalling pathways. As such, they represent attractive targets to overcome resistance to both chemo- and radio-therapy. Debio 1143 is a potent orally IAP antagonist currently in clinical development that is able to radiosensitise and ameliorate the effects of platinum derivatives in multiple SCCHN models both in vitro and in vivo. A previous Phase I study showed that Debio 1143 as a single agent was well tolerated up to 400 mg/day on days 1-14 every 3 weeks, with strong evidence of pharmacodynamic (PDy) activity and appropriate pharmacokinetic (PK) disposition.[1]

This Phase I study defined the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, PK, PDy and preliminary efficacy of Debio 1143 administered orally in combination with conventional CRT.

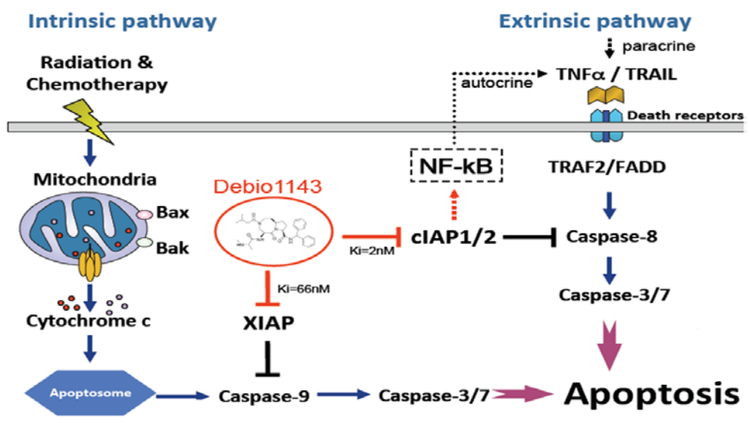
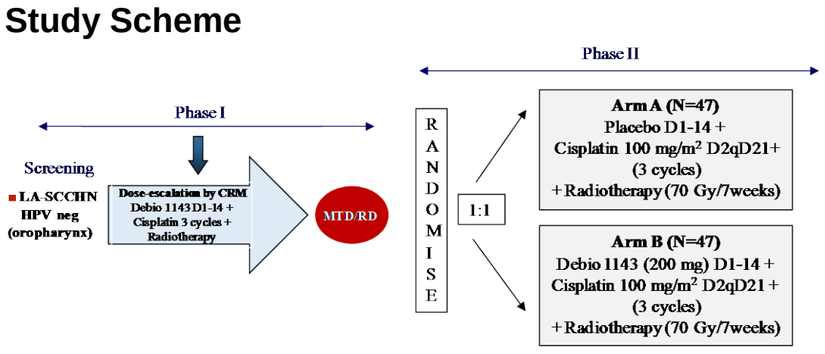


Figure 1: Mechanism of action of Debio 1143. Debio 1143 facilitates cell death via both the intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

METHODS

Study Scheme



Phase I Dose-Escalation

- Adaptive dose-escalation design using a modified continual reassessment method (mCRM) with a minimum of 6 patients to be treated at the recommended phase 2 dose (RP2D).
- Debio 1143 doses were escalated from 100 mg QD until MTD, based on the DLTs observed within the first 9 weeks from start of study drug administration.
- Dose-escalation decision and RP2D were determined by an independent safety committee.

Definition of DLT

- Non-haematological G3 and G4 toxicity (G ≥ 2 for ototoxicity); G3 and G4 nausea, vomiting, and diarrhoea were considered as DLTs only if they persisted despite optimal symptomatic therapy.
- Thrombocytopenia < 25 000/µL for ≥ 5 days or < 50 000/µL with bleeding or requiring transfusion.
- G4 neutropenia lasting ≥ 7 days or G ≥ 3 neutropenia with fever > 38.5ºC or infection.
- G4 skin or mucosal reactions.
- G ≥ 2 worsening of serum creatinine and/or creatinine clearance < 45 mL/min.
- Any treatment delay > 2 weeks for treatment-related AEs.
- Any other life-threatening toxicity.

The study is ongoing. Patients are followed up for 2 years from treatment start, with tumour response evaluated quarterly starting 10-12 weeks after end of treatment. This analysis presents all data recorded up to 29 February 2016: all patients had been followed up for at least 6 months from end of treatment.

RESULTS

Demographics and Baseline Characteristics

Safety population	(N = 14)
Median age, years (range)	64.5 (47 - 71)
Female / male	2 /12
ECOG performance status 0 /1, n (%)	5 (36) / 9 (64)
Localisation of primary tumour, n (%)	
Oral cavity	2 (14)
Oropharynx	4 (29)
Hypopharynx	6 (43)
Larynx	2 (14)
Tumour stage III / IVa, n (%)	4 (29) / 10 (71)
Lymph node N0-1 / N2, n (%)	5 (36) / 9 (64)

MTD and Recommended Phase 2 Dose

The MTD was reached at the Debio 1143 dose of 200 mg. This dose was also selected as RP2D based on acceptable safety.

DLTs						
Debio 1143 dose level	**Patients N = 14**	**Patients with DLTs N = 5**	**Event (study day of onset)**	**NCI-CTCAE Grade**	**Action taken with Debio1143**	**Outcome**
100 mg	5	1	Amylase increase (D4) Anaemia (D50) Eosophagitis (D56)	3 4 3	None Drug withdrawn NA (already withdrawn)	Recovered Recovered Sequelae
200 mg*	6	2	AST increase (D4) ALT increase (D5) Tubular necrosis (D5) Febrile neutropenia (D15) Lipase increase (D15)	3 3 3 4 3	Drug withdrawn None Drug withdrawn Drug withdrawn None	Recovered Recovered Ongoing Recovered Recovered
300 mg	3	2	ALT increase (D64) Amylase increase (D36) Lipase increase (D36)	3 3 4	NA (already completed) None Drug withdrawn	Recovered Recovered Recovered

* **MTD established by mCRM**

Final mCRM Simulation

Debio 1143 at a dose of 200 mg appears to be tolerable with an estimated toxicity probability of 38% (a target toxicity rate of 40% had initially been selected to address the high toxicity of the combined chemotherapy and radiotherapy).

Dose level	A posteriori tox (%)	Patients	Toxicity
100 mg	22	5	1
200 mg	38	6	2
300 mg	48	3	2

Treatment Compliance

Overall treatment exposure (i.e., ratio cumulative dose/planned dose) is presented in the table below.

Treatment	Compliance	
	All DL (N = 14)	Debio 200 mg (N = 6)
Debio 1143	83%	82%
Cisplatin	83%	83%
Radiotherapy	102%	104%

Safety

All adverse events reported in at least 4 patients

	Highest grade per patient				
	All DL (N = 14) n (%)	Debio 200 mg (N = 6) n			
Haematological	**All grades**	**G1**	**G2**	**G3**	**G4**
Anaemia	9 (64)	1	1	1	-
Neutropenia	8 (57)	-	3	-	-
Lymphopenia	6 (43)	-	-	1	1
Leukopenia	4 (29)	-	-	-	-
Non-haematological					
Asthenia	12 (86)	2	3	-	-
Radiation skin injury	12 (86)	2	2	2	-
Dysgeusia	10 (71)	2	4	-	-
Dysphagia	10 (71)	1	-	2	-
Mucosal inflammation	10 (71)	1	2	1	-
Constipation	8 (57)	1	1	-	-
Nausea	8 (57)	6	-	-	-
Weight decreased	8 (57)	2	2	-	-
Cough	7 (50)	2	-	-	-
Decreased appetite	6 (43)	-	3	-	-
Tinnitus	6 (43)	2	-	-	-
Dry mouth	5 (36)	2	1	-	-
ALT increased	4 (29)	1	-	1	-
Diarrhoea	4 (29)	1	-	-	-
Dysphonia	4 (29)	1	-	-	-
Headache	4 (29)	1	-	1	-
Odonyphagia	4 (29)	-	-	1	-

Transient increases of pancreatic enzymes amylase and lipase were each observed in 3 patients (21%).

Three patients experienced 5 Debio 1143-related SAEs. One patient experienced G4 anaemia, G3 colitis and G3 oesophagitis, one patient G2 asthenia and one patient G4 increased lipase. As of the cut-off date, no patient had died on study.

Preliminary Efficacy Data

At the time of data cut-off, ten patients were still in follow-up. The best overall responses according to RECIST as recorded by the cut-off date, in all dose levels combined, were as follows:

	CR n	PR n	PD n
Best overall response (N=14)	7	5	2

ACKNOWLEDGMENTS

The authors would like to thank the patients who participated in this study and their families as well as staff at all the investigational sites.

REFERENCE

[1] H. Hurwitz et al, Safety, pharmacokinetics and pharmacodynamic properties of oral Debio1143 (AT-406) in patients with advanced cancer: results of a first-in-man study. Cancer Chemother Pharmacol. **2015**; 75(4):851-9

Pharmacokinetics

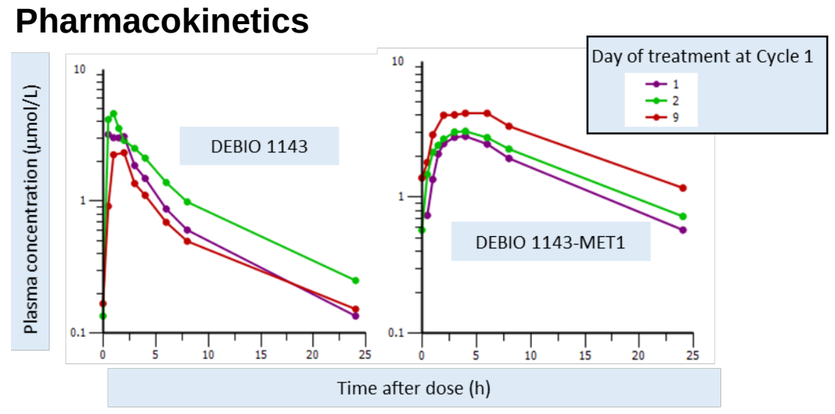


Fig. 2: Geometric mean plots of Debio 1143 and Debio 1143 MET-1 plasma concentration (µmol/L) after the 200 mg dose at the indicated day of administration.

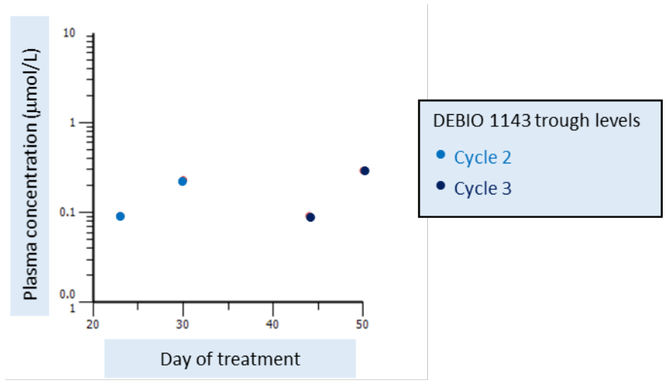


Fig. 3: Geometric mean trough plasma concentration of Debio 1143 at Cycle 2 and Cycle 3 after the 200 mg dose.

On average, Debio 1143 plasma concentrations decreased slightly after multiple dosing at Cycle 1 essentially because of increased metabolism. However, this did not jeopardise overall PK disposition over the treatment period because trough concentrations remained stable at Cycles 2 and 3.

Pharmacodynamics

Upon binding to their targets, IAP inhibitors such as Debio 1143 have the ability to induce proteasomal degradation of some members of the IAP family such as cIAP1. The cIAP1 level in PBMCs was therefore measured to demonstrate target inhibition. IAP inhibitors also modulate NF-κB signaling, which was assessed by measuring the level of the NF-κB-induced chemokine MCP1 (a.k.a. CCl2).

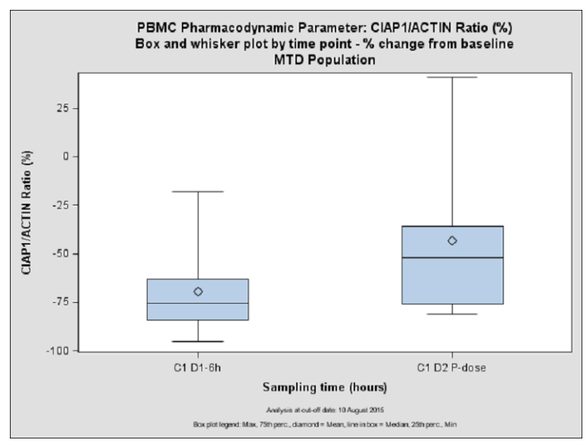


Figure 4: cIAP1/actin level measured in peripheral blood mononuclear cells (PBMCs) (cIAP1 signal was measured by Western Blot and normalised to actin signal).

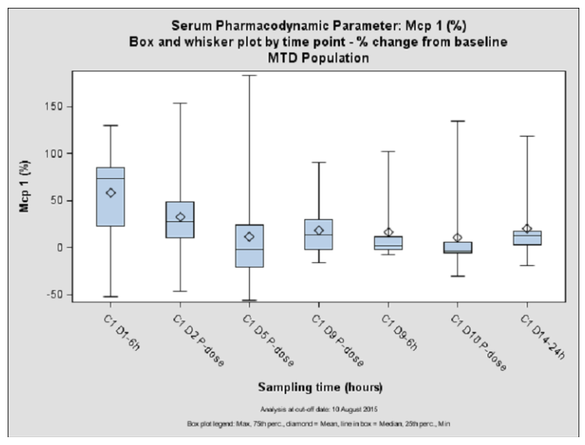


Figure 5: MCP1 (CCL2) level measured in serum (MCP1 signal was measured by ELISA).

A median reduction of circa 75% at Cycle 1/Day 6 hours and circa 50% at Cycle 1/Day 2 pre-dose was measured in cIAP1/actin ratio demonstrating the cIAP1 target engagement of Debio 1143 in PBMCs. A trend towards an increase in median MCP1 level was observed at Cycle 1/Day 1 6 hours and Cycle 1/Day 2 pre-dose, in line with the expected pharmacological effects of Debio 1143.

CONCLUSIONS

Safety and RP2D

The safety profile of the combination is largely consistent with the safety profile known from the backbone treatment; the RP2D (=MTD) of Debio 1143 to be combined with conventional CRT is 200 mg/day on days 1-14. This dose is now being used in the randomised phase 2 part of the study initiated by GORTEC to evaluate the antitumor activity of this combination in LA-SCCHN.

Pharmacokinetics

PK disposition of Debio 1143 is compatible with the multiple dosing schedule (Days 1-14 every 3 weeks). Throughout the treatment period, plasma levels were consistent enough to produce a PDy effect.

Pharmacodynamics

The PDy effect of Debio 1143 was evidenced by the degradation of cIAP1 in PBMCs and a trend in an increase of serum MCP1.

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