OPEN-LABEL, NON-RANDOMIZED, EXPLORATORY PRE-OPERATIVE WINDOW-OF-OPPORTUNITY TRIAL TO INVESTIGATE THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THE SMAC MIMETIC DEBIO 1143 IN PATIENTS WITH RESECTABLE SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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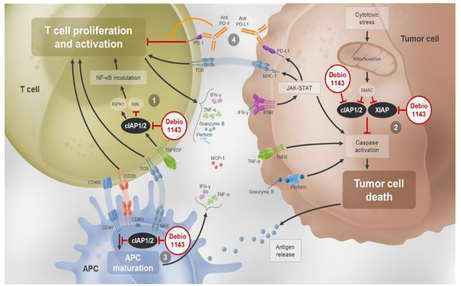
BACKGROUND

- Inhibitor of Apoptosis Proteins (IAPs) regulate apoptosis and modulate NFκB signaling, which in turn drives the expression of genes involved in immune and inflammatory responses.
- Debio 1143 is an orally available antagonist of IAPs with the potential to enhance both the pro-apoptotic effect of chemo-radiotherapy and the anti-tumor immunity with immunotherapeutic agents.

Debio 1143's dual mechanism of action

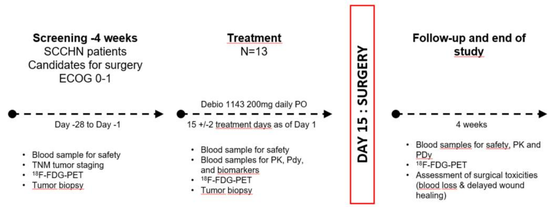


(1) In T cells, cIAPs modulate the NF-kB pathway via regulation of the activities of the kinases RIPK1 (also called RIP1) and NIK. cIAP inhibition by Debio 1143 promotes NIK-dependent non-canonical NF-kB signaling resulting in enhanced T cell stimulation and immune effector molecule secretion (IFN-γ, TNF-α, granzyme B, perforin). (2) In tumor cells, cIAPs and XIAP antagonize cytotoxic stimuli (such as chemo-, radio or immunotherapies) by inhibition of caspases. cIAP and XIAP inhibition by Debio 1143 allows for activation of caspases and cell death induction. (3) Tumor cell death can cause antigen release into the tumor microenvironment and uptake by APCs. Debio 1143 counteracts cIAP-mediated inhibition of CD40 signaling to promote APC maturation and antigen presentation, further activating immune effector cells including T cells. (4) T cell activation is negatively regulated by immune checkpoints such as the PD-1/PD-L1 axis. In a manner complementary to Debio 1143, immune checkpoint inhibitors (such as anti-PD-1 or anti-PD-L1) lead to activation of T cells and combination of Debio 1143 with immune checkpoint inhibitors represents a promising strategy to increase the anti-tumor immune response.

- Debio 1143 is currently being evaluated in a Phase I/II randomized study in combination with concurrent Chemo-Radiation Therapy in patients with LA-SCCHN (NCT01930292).
- This is an open-label, non-randomized, multicenter, exploratory phase 2, 'window of opportunity' study exploring the molecular activity of Debio 1143 in patients with newly diagnosed, SCCHN who were candidates for primary surgical treatment (EudraCT Number: 2014-004655-31).
- We report here the pharmacokinetic and pharmacodynamic effects of Debio 1143 monotherapy (200 mg/day D1-15 +/-2 p.o.) in paired tumor samples collected at diagnosis and at time of surgical resection.

METHODS OVERVIEW

STUDY DESIGN



PK/PDY ASSESSMENTS

- Pharmacokinetic disposition of Debio 1143 was evaluated in tumor samples by quantitative mass spectrometry imaging (QMSI), and in plasma by LC-MS/MS.
- Immunohistochemistry for cellular IAP1 (cIAP1), apoptosis (cleaved caspase-3), proliferation (Ki-67), tumor-infiltrating lymphocytes (TILs), PD-1 and PD-L1 were performed in pre- and post-treatment specimen.
- Exploratory transcriptomic analyses were conducted to assess the effects of Debio 1143 on gene expression in tumor biopsies. Pathways were analyzed using GeneGo by Metacore (Clarivate Analytics).

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic characteristics Safety population

	Number (%) of subjects N=13
Age (years)	
Median	61
Ranges	32-77
Sex	
Male	10 (77)
Female	3

SCCHN tumor characteristics Safety population

	Number (%) of subjects N=13
Localization of the primary tumor	
Oral cavity	12 (92.3)
Oropharynx	1 (7.7)
TNM staging	
Stage II	3 (23)
Stage III	1 (8)
Stage IVa	8 (62)
Stage IVb	1 (8)
T – Tumor	
T2	4 (30.8)
T3	1 (7.7)
T4a	7 (53.8)
T4b	1 (7.7)
Lymph nodes	
N0	7 (54)
N1	1 (8)
N2	5 (38)

- 13 subjects were treated (safety population).
- 12 subjects were included in ITT and per-protocol populations (1 subject discontinued from the study due to a postponed surgery).
- There were no Debio 1143 dose adjustments. 2/13 subjects did not receive the planned (15±2) doses: 1 subject received 9 doses, had no surgery and was replaced; the other subject received 18 doses due to a delay of surgery.

SAFETY

Treatment-Emergent Adverse Events and Maximum Toxicity Grade (Incidence ≥ 10%) Safety Population

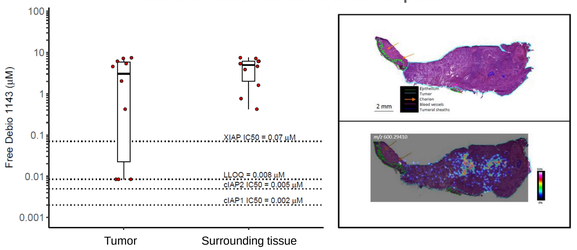
System Organ Class / Preferred Term	Toxicity	N=13 Patients		Events
General disorders and administration site conditions				
Asthenia	Grade 1	3	(23.08%)	3
Gastrointestinal disorders				
Nausea	Grade 1	2	(15.38%)	2
Diarrhea	Grade 1	2	(15.38%)	3
Infections and infestations				
Abscess neck	Grade 3	2	(15.38%)	2
Blood and lymphatic system disorders				
Anemia	Grade 2	3	(23.08%)	4
CNS disorders				
Insomnia	Grade 1	3	(23.08%)	3

Coded using MedDRA 18.1. Includes terms whose incidence is ≥ 10% in at least one dose. If a patient had several AEs for a given term or class, he/she is counted only once

- Debio 1143 monotherapy was well tolerated.
- Mild anemia was the only haematological toxicity observed.
- 1 SAE, unrelated to study drug, was reported for 1 subject who completed the full course of treatment (free flap resumption (laryngeal repair) occurring post-surgery. No deaths occurred in this study.

PHARMACOKINETICS

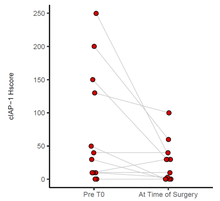
Debio 1143 distribution in tumor biopsies



- Tumor penetration was high, with Debio 1143 concentrations up to 55-fold those found in plasma at the time of the resection (data not shown), indicating Debio 1143 accumulation in tumor and surrounding tissue.

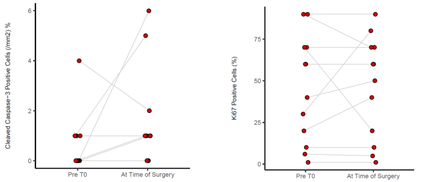
PHARMACODYNAMICS

Effect on cIAP1 in tumor biopsies



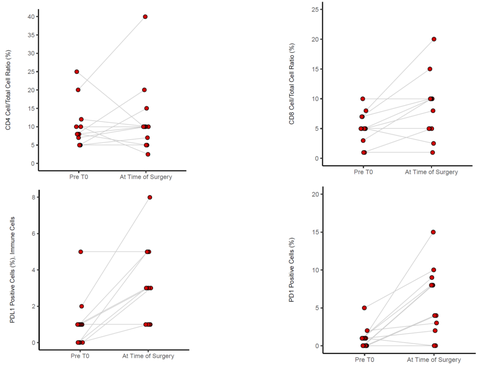
- Upon binding to their targets, IAP inhibitors such as Debio 1143 induce proteasomal degradation of cIAP1.
- cIAP1 levels markedly decreased in most subjects treated with Debio 1143 monotherapy.

Effect apoptosis, necrosis, and proliferation markers in tumors



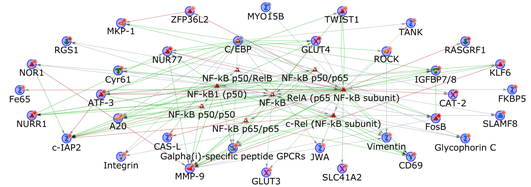
- There was no significant change in apoptosis (cleaved caspase-3), proliferation (Ki67), and necrosis (data not shown) on tumor cells after 14 days of treatment.

Effect on tumor microenvironment



- Overall, the levels of CD8+ TILs, PD-1 and PD-L1 positive immune cells increased significantly ($p < 0.05$) compared to pre-treatment levels.

Exploratory transcriptomic analysis of tumor biopsies



- Changes were observed in the expression of genes related to NFκB signaling, RelA and other components of the canonical NF-kB transcription factor, as related to the 100 top genes affected by Debio 1143.

CONCLUSIONS AND PERSPECTIVES

- This study demonstrates that Debio 1143 p.o. at 200 mg once daily, distributes widely into SCCHN potentially resectable tumors from patients, showing consistent *in vivo* target engagement of cIAP1, and inducing downstream effects that modulate host immunity in the tumor microenvironment.
- The immunomodulatory potential of Debio 1143 is being explored in a phase-Ib dose finding study combining Debio 1143 and avelumab (anti-PD-L1) in patients with advanced solid malignancies and NSCLC (CT# 03270176), and in a phase-Ib/II exploratory basket study combining Debio 1143 with nivolumab in patients with solid tumors who failed prior PD-1/PD-L1 treatment (SMARTPLUS-106, EudraCT# 2018-003546-16).

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