Received: 5 October 2020 | Revised: 26 January 2021 | Accepted: 28 January 2021

DOI: 10.1111/cts.13002

BRIEF REPORT

Exploratory window-of-opportunity trial to investigate the tumor pharmacokinetics/pharmacodynamics of the IAP antagonist Debio 1143 in patients with head and neck cancer

Carlos Gomez-Roca[1] | Caroline Even[2] | Christophe Le Tourneau[3] | Neus Basté[2] | Jean-Pierre Delord[1] | Jerome Sarini[4] | Sebastien Vergez[4] | Stephane Temam[2] | Caroline Hoffmann[3] | Philippe Rochaix[5] | Edith Borcoman[3] | Bruno Gavillet[6] | Elisabeth Rouits[6] | Annick Ménétrey[6] | Franck Brichory[6] | Daniela Purcea[6] | Gregoire Vuagniaux[6] | Claudio Zanna[6]

[1]Clinical Research Unit, Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

[2]Institut Gustave-Roussy, Villejuif, France

[3]Department of Drug Development and Innovation (D3i), Institut Curie, Paris and Saint-Cloud, France

[4]Surgery Department, Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

[5]Pathology Department, Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

[6]Debiopharm International S.A, Lausanne, Switzerland

Correspondence
Claudio Zanna, Debiopharm International S.A., Forum "après-demain," Chemin Messidor 5-7, Case postale 5911, 1002 Lausanne, Switzerland.
Email: Claudio.Zanna@debiopharm.com

Funding information
This study and the cost of the publication were funded by Debiopharm International S.A.

Abstract

Inhibitor of apoptosis proteins (IAPs) regulate apoptosis and modulate NF-κB signaling thereby driving expression of genes involved in immune/inflammatory responses. The orally available IAP antagonist Debio 1143 has potential to enhance tumor response to chemoradiotherapy and/or immunotherapy. Patients with preoperative squamous cell carcinomas of the head and neck (SCCHN) received: Debio 1143 monotherapy (200 mg/day [D]1–15 +/- 2); Debio 1143 (200 mg/day D1–15 +/- 2) plus cisplatin (40 mg/m^2 D 1 and 8); cisplatin alone (40 mg/m^2 D 1 and 8; EudraCT: 2014-004655-31). Pharmacokinetic/pharmacodynamic effects were assessed in plasma and resected tumors. Primary end point; effect of Debio 1143 on cellular IAP-1 (cIAP-1). Levels of cIAP-1/-2, X-linked inhibitor of apoptosis protein (XIAP), tumor infiltrating lymphocytes (TILs), including CD8+ T cells, programmed cell death protein 1 (PD-1), PD-ligand 1 (PD-L1), and gene expression were also analyzed. Twenty-three of 26 patients completed treatment. In the Debio 1143 monotherapy cohort ($n = 13$), mean tumor concentrations of Debio 1143 were 18-fold (maximum 55.2-fold) greater than in plasma, exceeding the half-maximal inhibitory concentration for cIAPs and XIAP by 100 to 1000-fold, with significant engagement/degradation of cIAP-1 ($p < 0.05$). Overall, levels of CD8+ TILs, PD-1, and PD-L1 positive immune cells increased significantly ($p < 0.05$) following Debio 1143 treatment. Changes were observed in the expression of genes related to NF-κB signaling. Treatments were well-tolerated. Debio 1143 penetrated SCCHN tumors, engaged cIAP-1, and induced immune inflammatory changes in the tumor microenvironment. Based on the mode of action demonstrated here and in previous studies, these data support future combinations of Debio 1143 with immune-checkpoint agents.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Inhibitors of apoptosis proteins (IAPs) are a class of proteins that can negatively regulate apoptosis and influence a multitude of other cellular processes that are frequently deregulated in human cancers. The IAP antagonist Debio 1143 is being developed in combination with chemoradiotherapy for the treatment of high-risk locoregionally advanced squamous cell carcinomas of the head and neck (SCCHN). Debio 1143 sensitizes for radiotherapy and synergizes with cisplatin in models of SCCHN and the host immune system integrity is a major contributor to radiosensitization effects.

WHAT QUESTION DID THIS STUDY ADDRESS?

We investigated pharmacokinetic and pharmacodynamic parameters in paired SCCHN tumor samples and plasma pre and post-treatment.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The recommended phase II dose of Debio 1143 (200 mg/daily for 15 days), distributed widely into SCCHN tumors engaging with IAPs to induce effects that could potentially modulate immunity in the tumor microenvironment.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our findings support the potential therapeutic effects of Debio 1143 in patients with SCCHN and provide a rationale for combinations with immune-checkpoint agents.

INTRODUCTION

Dysfunction in cellular apoptosis is a hallmark of cancer.[1] Inhibitors of apoptosis proteins (IAPs) are a class of proteins that can negatively regulate apoptosis. Cellular IAPs 1 and 2 (cIAP-1 and cIAP-2) play critical roles in the regulation of death-receptor-mediated apoptosis and X-linked IAP (XIAP) is a central regulator of both the death-receptor-mediated and the mitochondria-mediated apoptosis pathways. IAPs also influence a multitude of other cellular processes that are frequently deregulated in human cancers, including activation of nuclear factor-kappaB (NF-κB), which regulates gene expression during inflammatory and immune responses.[2] IAPs are highly expressed in a range of human cancers, including squamous cell carcinoma of the head and neck (SCCHN) where they are believed to play a prominent role in cancer cell resistance to anticancer treatments. IAPs thus represent promising therapeutic targets[3,4] and direct binding of IAPs has been shown to moderate their anti-apoptotic effects through restoration of treatment sensitivity.[5,6]

The small molecule Debio 1143 (AT-406, SM-406, xevinapant) is a potent orally active IAP antagonist with the potential to promote apoptosis in tumor cells via restoration of caspase activity through blockade of IAPs (XIAP, cIAP-1, and cIAP-2) and regulation of the immune response by modulation of NF-κB and tumor necrosis factor alpha (TNFα) effects. Consequently, Debio 1143 may be considered a multi-IAP antagonist. Debio 1143 has been shown to sensitize to radiotherapy, improve the effects of platinum derivatives in multiple SCCHN tumor models,[7–9] and to significantly enhance activation of CD4+ and CD8+ T cells in a concentration-dependent manner following anti-CD3/CD28 stimulation. Furthermore, the combination of Debio 1143 with an anti-programmed cell death protein 1 (PD-L1) antibody significantly decreased tumor growth and increased survival.[10] Debio 1143 augmented the tumor-specific adaptive immunity induced by ablative radiotherapy, whereas reversing host immunosuppressive cell infiltrates in the tumor microenvironment in a TNF-α, IFNγ, and CD8+ T cell-dependent manner.[8] Debio 1143 has been evaluated in a phase I/II randomized trial in combination with standard concurrent chemoradiotherapy in patients with locally advanced (LA)-SCCHN. The recommended phase II dose (RP2D) of Debio 1143 was 200 mg/day for 14 days q3w when combined with concomitant q3w high-dose cisplatin (100 mg/m^2) chemoradiotherapy. In addition, Debio 1143 improved locoregional control compared with chemoradiation alone.[11]

To investigate the molecular activity of Debio 1143 in patients with newly diagnosed resectable SCCHN, we conducted an open-label, nonrandomized, multicenter, exploratory phase II window of opportunity study. We assessed the activity of Debio 1143 monotherapy at the RP2D (200 mg/day [D] 1–14 of 21) for 2 consecutive weeks, Debio 1143 at the same dose combined with weekly cisplatin (40 mg/m^2 D 1 and 8), and weekly cisplatin alone at the same dose in patients with SCCHN who were candidates for primary surgery (EudraCT Number: 2014-004655-31). Here, we report the pharmacokinetic (PK) disposition in tumor tissue and in plasma and

pharmacodynamic (PD) observations in paired tumor samples collected at diagnosis and at the time of surgical resection.

METHODS

Patients

Our study was concordant with the Declaration of Helsinki and local laws. Patients who met the following criteria were eligible for inclusion; age greater than or equal to 18 years, squamous cell carcinoma of the nasopharynx, nasal cavity, paranasal sinuses, oral cavity, oropharynx, hypopharynx or larynx, Eastern Cooperative Oncology Group performance status 0–1 and adequate performance and organ function.

Treatment plan

Patients were divided into three cohorts: Debio 1143 monotherapy, Debio 1143 plus cisplatin, or cisplatin alone. Regimens were administered over 15 days immediately prior to surgery. Debio 1143 (200 mg daily) was administered orally as capsules for 15 (±2) days, and cisplatin was administered i.v. (40 mg/m^2) on days 1 and 8. Surgery was scheduled on day 15 (±2 days) following the final dose of Debio 1143. Follow-up evaluations were 4 weeks postsurgery.

The primary end point was an assessment of the effects of Debio 1143 as monotherapy, and in combination with cisplatin, on levels of cIAP-1. Secondary objectives included; safety, Debio 1143 PK disposition in plasma and in tumor tissue, early biological response, assessment of apoptosis, necrosis, proliferation, and immune signaling in tumor biopsies. No formal efficacy assessments were planned (per Response Evaluation Criteria in Solid Tumors criteria) due to the short duration of treatment and to avoid delaying surgery. (Details of further assessments are included in Table S1.)

RESULTS

Patients and disease characteristics at baseline are shown in Table S2.

Pharmacokinetic assessments

Median plasma concentrations of Debio 1143 reached a time of maximum plasma concentration within 2-h of dosing (Figure S1). Extent of plasma exposure, reflected by area under the curve, was comparable after the first administration and at steady-state (8760 and 8950 ng·h/ml, respectively), indicating an absence of accumulation and consistent with a terminal half-life of 6–7 h. Plasma PK profiles for Debio 1143 with and without cisplatin were essentially similar (data not shown).

On the day of surgery, ~ 4 h after dosing, median plasma concentrations of Debio 1143 were 784.5 ng/ml (range 117–2200) and 608.5 ng/ml (428–1370) in the monotherapy and combination cohorts, respectively. Median concentrations of Debio 1143 in tumor tissue were 11.7 μg/g (0–26.40) and 27.8 μg/g (0.8–50.6) in the in the Debio 1143 and combination cohorts, respectively (Figure 1). Consequently, the median tumor to plasma ratio of Debio 1143 concentration was 16:1 (0–55) and 25:1 (1–103) in the Debio 1143 and combination cohorts, respectively.

Pharmacodynamic assessments

In the Debio 1143 cohort, the median cIAP-1 H-score in total tumoral cells reduced in a statistically significant manner from 35 (0–250) at baseline to 20 (0–100) at the time of surgery ($p < 0.05$, *t*-test, post hoc analysis), a median change of −18.5 (−220 to 20), a median reduction of −70% (−100% to 200%), and a median fold change of 0.3 (0–3; Figure 2a).

We did not observe a significant trend in the degradation of cIAP-1 in the combination or cisplatin alone cohorts (Figure S2) and we did not observe a significant trend in the degradation of cIAP-2 (Figure S3) or XIAP (data not shown) in any of the treatment cohorts.

Overall, there was a significant increase in the levels of CD8+ TILs, and in both PD-1 and PD-L1 positive immune cells ($p < 0.05$; post hoc analysis) in the Debio 1143 monotherapy cohort compared with pretreatment levels (Figure 2b).

An approximately two-fold increase in CD8 count, or any increase from a near-zero baseline value, was considered relevant and beneficial. In the Debio 1143 cohort ~ 40% (5/12) of the evaluable patients had an increase in CD8 count. In the combination cohort, 2 of 5 patients had a compelling change in CD8 count and in the cisplatin cohort 3 of 6 evaluable patients had an increase in CD8 count (Figure S4).

Post-treatment levels of PD-1 positive immune cells increased within tumor biopsies in most patients regardless of the treatment received. Increased levels of PD-L1+ immune cells within tumor biopsies were also noted in the combination cohort, whereas in the cisplatin alone cohort, 5 of 6 patients maintained baseline values or had modest increases in levels of PD-L1 (Figure S5). A trend for tumor cell expression of PD-L1 was also observed, with 8 of 12 patients in the Debio 1143 cohort maintaining baseline levels, and 5 of 6 patients in the cisplatin alone cohort displaying increased levels.

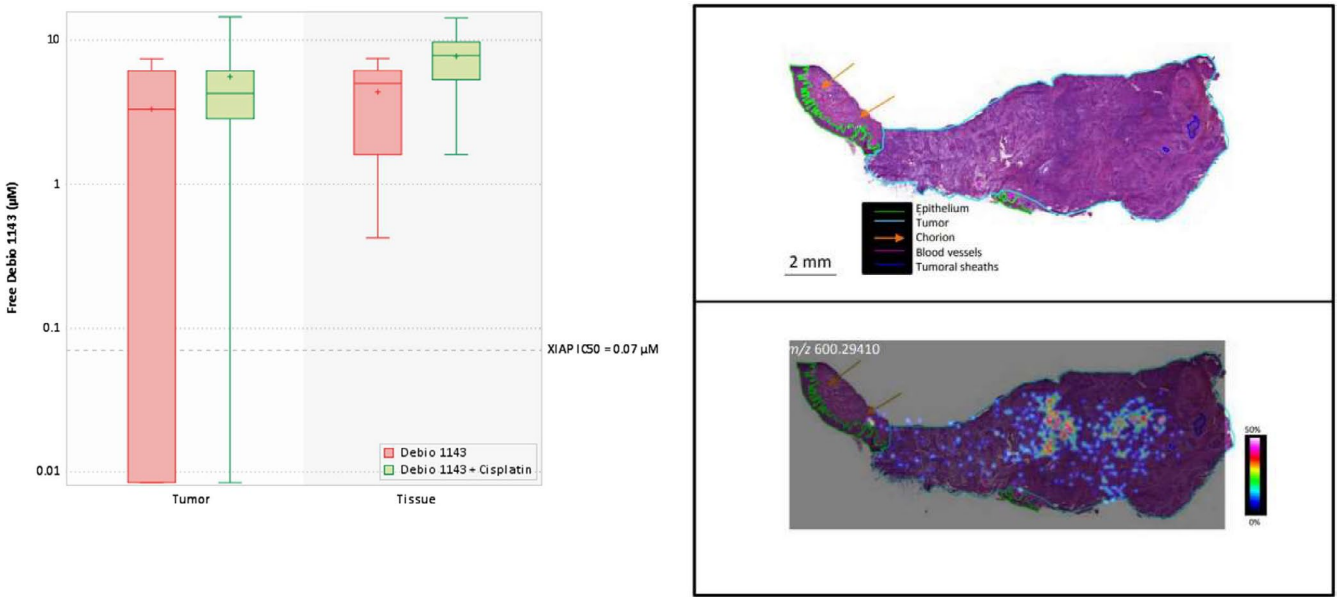

FIGURE 1 Concentrations of Debio 1143 in tumor biopsies and surrounding tissue at the time of resection (safety population). Left panel: $n = 13$ in Debio 1143 cohort, $n = 6$ in the Debio 1143 + cisplatin cohort (analysis performed in triplicate). Right panel: Representative image of histological analysis (top; hematoxylin-eosin staining) and Debio 1143 distribution (bottom; detected by matrix-assisted desorption/ionization-mass spectrometry detection) as observed in tumor bulk section. The color scale in the image represents the intensity of the Debio 1143 signal in the section (dark blue, lowest Debio 1143 concentration; pink, highest Debio 1143 concentration). IC_{50}, half-maximal inhibitory concentration

Significant changes in levels of cleaved caspase-3 or Ki67 were not observed in any of the treatment arms. Compared with baseline levels, on the day of surgery an overall increase in levels of caspase-cleaved cytokeratin (CK) 18 fragment M30 antigen (CK18-M30), a marker of epithelial cellular apoptosis and cytokines/chemokines, was observed in serum samples from the Debio 1143 monotherapy and combination cohorts at 4 h postdose (data not shown). Although not statistically significant, a trend in increased levels was observed for the following cytokines/chemokines that reflect potential signs of NF-κB pathway modulation by Debio 1143 monotherapy: IL12/IL23 p40, IFNγ, IP10, MCP1, MCP4, MDC, and TNFα (data not shown).

Pharmacogenomics

Analyses of tumor biopsies from the Debio 1143 monotherapy cohort only revealed changes in the expression of genes related to NF-κB signaling, transcription factor p65 (RELA) and other components of the canonical NF-κB transcription factor, as related to the 100 top genes affected by Debio 1143 (Figure S6).

Safety

Eleven of 13 patients in the Debio 1143 monotherapy cohort (no documentation of Debio dosing $n = 1$; patient forgot to attend $n = 1$) and all of the patients in the combination cohort received the planned doses of Debio 1143, no dose adjustments were required. With one exception in the cisplatin-only cohort, all patients received the planned cumulative dose of cisplatin (80 mg/m^2) and no dose adjustments were required. There were no treatment discontinuations due to adverse events (AEs) in the Debio 1143 cohort or the combination cohort. AEs were recorded in 25/26 (96.2%) patients. There were no grade 4 treatment emergent AEs (TEAEs) that were considered to be treatment-related. There were 3/26 (11.5%) SAEs, 1 in the Debio 1143 monotherapy cohort (post-surgical laryngeal repair) and 2 in the cisplatin alone cohort (grade 3 acute coronary syndrome and grade 4 pneumonia). All SAEs were resolved during the study, none were related to study treatment. No deaths were reported (TEAEs by cohort are reported in Table S3).

DISCUSSION

Our findings clearly demonstrate that daily oral administration of Debio 1143, at the predetermined RP2D of 200 mg/day, led to rapid and diffuse penetration of Debio 1143 into SCCHN tumors with concentrations up to 55-fold those found in plasma at the time of surgical resection. These concentrations largely exceed the IC_{50} for the cIAP-1 and -2 and XIAP targets by 100 to 1000-fold.

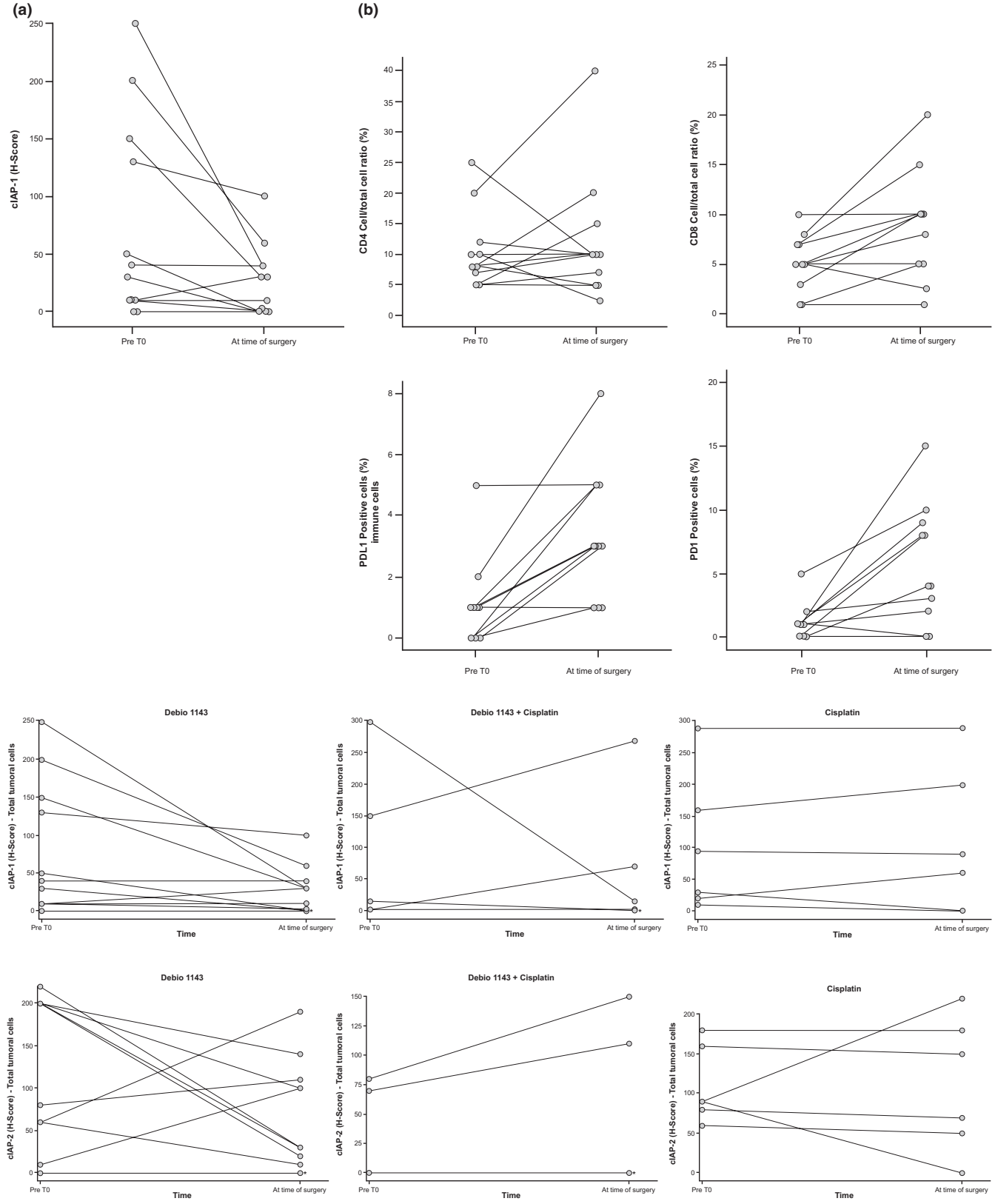

FIGURE 2 Changes in pharmacodynamic parameters at baseline and at time of tumor resection (a) individual patient cIAP-1 H-scores from tumors (total tumoral cells) at baseline (pre T0) and resected following the final dose of Debio 1143, per protocol population ($n = 12$, 1 section per patient), in the Debio 1143 monotherapy cohort. (b) Changes in levels of CD4+ TILS, CD8+ TILs, PD-L1 positive immune cells, and PD-1 positive immune cells in the tumor, at baseline (Pre T0) and time of surgery in the Debio 1143 monotherapy cohort (per protocol population) ($n = 12$, 1 section per patient)

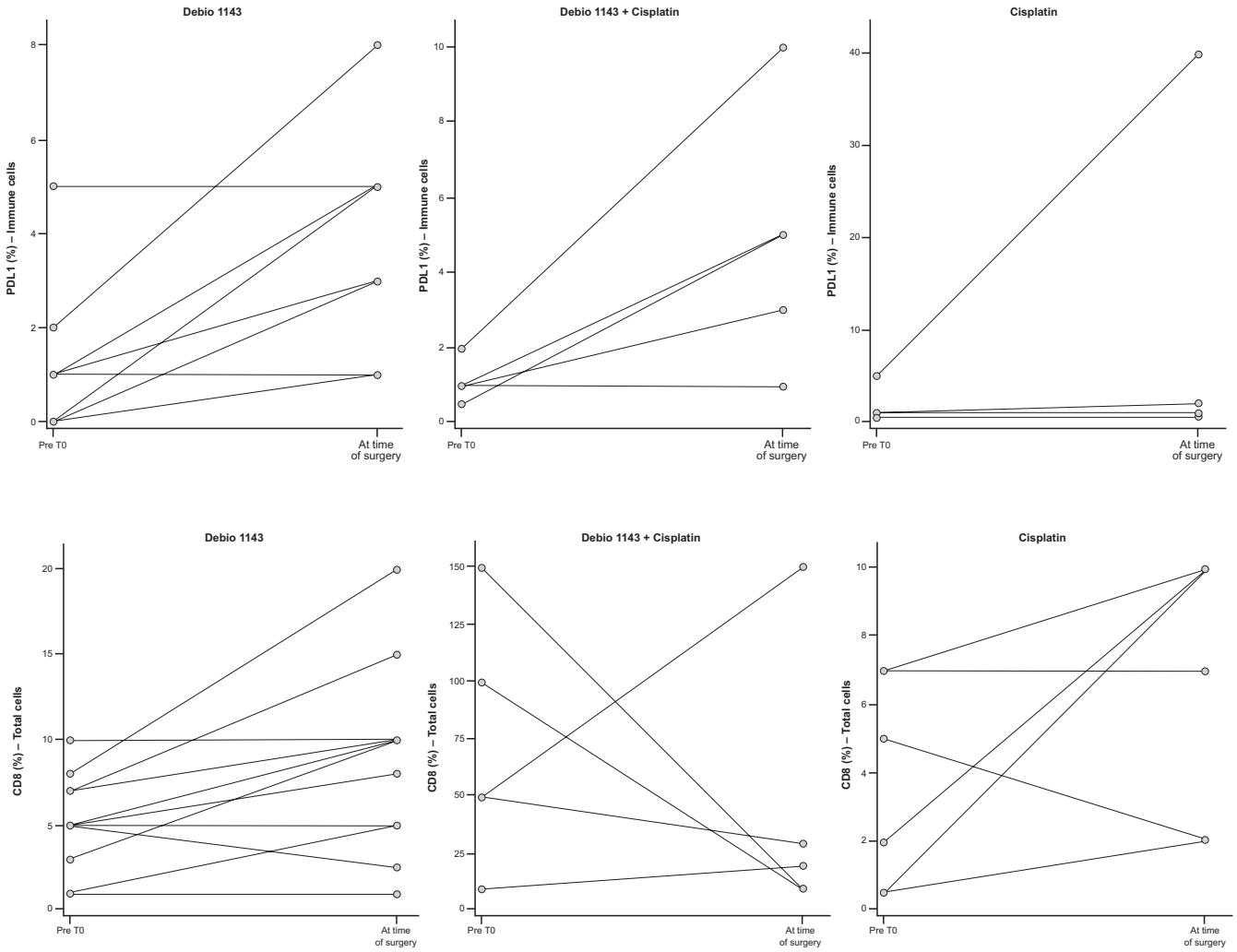

FIGURE 2 Continued.

Furthermore, systemic Debio 1143 PK disposition was broadly similar between the monotherapy and combination cohorts, further evidence supporting the utility of Debio 1143 200 mg/day in combination with standard cisplatin based chemoradiotherapy in this refractory population.

Results from a phase II trial of daily Debio 1143 at this same dose in combination with cisplatin based chemoradiotherapy, in patients with high-risk LA-SCCHN were recently published.[11] The primary endpoint of at least 20% improvement in locoregional control rate 18-months after treatment was met, compared with the control cohort (chemoradiotherapy + placebo) ($p = 0.026$). Furthermore, progression-free survival was significantly improved in the Debio 1143 group ($p = 0.007$) and the toxicity profile of Debio 1143 in this combination was predictable and manageable.

The primary endpoint of our study was met in the Debio 1143 monotherapy cohort. PD analysis of tumor biopsies revealed target engagement as evidenced by degradation of cIAP-1 in tumors from patients treated with Debio 1143 monotherapy. The lack of a significant trend in the reduction of cIAP-1 and -2 H-scores in the combination cohort was potentially due to the limited number of evaluable patients and to relatively low expression levels of cIAP-1 and -2 in this group.

Overall, an increase in the levels of CD8+ TILs, PD-1 positive immune cells and PD-L1 positive immune cells was observed in the monotherapy cohort compared with pretreatment levels. A trend towards increased levels of serum cytokines/chemokines was also observed, which may reflect NF-κB pathway modulation by Debio 1143 monotherapy. We also observed a positive trend between free Debio 1143 concentrations in tumor tissue and CD-positive cell ratio relative change from baseline, in line with the immunomodulatory properties of Debio 1143 described previously.

The pharmacogenomic analyses of samples from the Debio 1143 monotherapy cohort revealed changes in the expression of genes related to NF-κB signaling, RELA and other components of the canonical NF-κB transcription factor (Figure S6). These findings are in line with the mechanism of action of an IAP antagonist which turns

on the expression of genes involved in immune and inflammatory responses through modulation of NF-κB signaling. Although the results were significant based on the false discovery rate threshold, we acknowledge that these analyses were exploratory and require confirmation in a larger independent cohort. We also recognize that, given the small number of patients in our study, inter-cohort comparisons are indicative only. The safety profile of Debio 1143 as monotherapy and also in combination with cisplatin was predictable and manageable in our study. Debio 1143 monotherapy was very well-tolerated with only grade 1 alanine aminotransferase/aspartate aminotransferase increases in some patients; these increases did not affect overall treatment compliance and no dose reductions were necessary. These data are in line with previous findings[11,12] and there were no changes to the Debio 1143 safety profile as a result of this study.

We acknowledge that despite the potential for Debio 1143 to enhance the pro-apoptotic effect of cisplatin, changes in the levels of cleaved caspase-3, necrosis, or cell proliferation fraction in tumor biopsies were not apparent. Detection of apoptosis markers in clinically derived samples can be challenging given their elusive nature and the rate of molecular change in the tumor microenvironment. Furthermore, our sampling was performed 24–72 h post-treatment, which is after the time when peak chemotherapy-induced apoptosis may reasonably be expected and may explain the absence of a signal in these samples.[13] In previous studies, Debio 1143 has successfully demonstrated antitumor activity in preclinical cancer models, including SCCHN,[7–9] and also in patients with SCCHN.[11] However, it should be noted that the focus of this window study was not efficacy but the application of a clinical model to support the mode of action of Debio 1143, potentially leading to efficacy in SCCHN clinical trials. In the clinical studies reported to date, Debio 1143 monotherapy has not demonstrated significant efficacy, we anticipate that future trials of Debio 1143 will be in combination with other agents.

In summary, our data corroborate the established RP2D of Debio 1143 in combination with cisplatin-based chemoradiotherapy for patients with LA-SCCHN and support the rationale for future combinations of Debio 1143 with immune checkpoint agents.

ACKNOWLEDGMENTS

The authors would like to thank Silvano Brienza, Sebastien Del Rizzo, Catalina Barceló, Dalit Rechavi-Robinson, Kathrin Gollmer, Vincent Bize, Marc Dupuis, Marc Messier, Amina Haouala, Brandon Gonzales, and Luke Piggott. Medical writing support was provided by Dr Shaun Villa of Cancer Communications and Consultancy Ltd. (Knutsford, UK) with funding from Debiopharm International S.A.

CONFLICT OF INTERESTS

C.G.-R. declares no conflict for this study. Outside this study grant/research support from BMS and Roche/Genentech, advisory board participation for BMS, Roche/Genentech, Pierre Fabre, Erytech, MSD, Astra-Zeneca, Sanofi-Aventis, Novartis; accommodations and travel support from BMS, Roche/Genentech, Pierre Fabre and MSD. C.E. declares no conflict for this study, however, outside this study advisory board, he has participation for BMS, Innate Pharma, MSD, and Merck Serono. C. L.T. has participated in advisory boards for MSD, BMS, Merck Serono, Astra Zeneca, Roche, GSK, Celgene, Rakuten, Seattle Genetics, Novartis, and Nanobiotix. N.B. has participated in advisory boards for Nanobiotix, Merck Serono, MSD, BioNtech, Roche, and BMS. J.-P.D. has consulting or advisory roles in boards for MSD, Novartis, Roche, Genentech, and BMS; research fundings (Institution) from Genentech, Roche, MSD, Debiopharm, and BMS. C.H. has no conflict of interest for this study, and has participated in advisory boards for Nanobiotix. B.G. is an employee of Debiopharm International S.A. E.R. is an employee of Debiopharm International S.A. A.M. is an employee of Debiopharm International S.A. F.B. is an employee of Debiopharm International S.A. D.P. is an employee of Debiopharm International S.A. G.V. is an employee of Debiopharm International S.A. C.Z. is an employee of Debiopharm International S.A. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

C.G.R., C.E., C.L.T., N.B., J.P.D., J.S., S.V., S.T., C.H., P.R., E.B., B.G., E.R., A.M., F.B., D.P., G.V., and C.Z. wrote the manuscript. C.G.R., C.E., C.L.T., N.B., J.P.D., J.S., S.V., S.T., C.H., E.R., B.G., G.V., and C.Z. designed the research. C.G.R., C.E., C.L.T., N.B., J.P.D., J.S., S.V., S.T., C.H., P.R., E.B., B.G., E.R., A.M., and F.B. performed the research. D.P. analyzed the data.

REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.
2. Gyrd-Hansen M, Meier P. IAPs: from caspase inhibitors to modulators of NF-kappaB, inflammation and cancer. *Nat Rev Cancer*. 2010;10:561-574.
3. Fulda S, Vucic D. Targeting IAP proteins for therapeutic intervention in cancer. *Nat Rev Drug Discov*. 2012;11:109-124.
4. Cancer Genome Atlas. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015;517:576-582.
5. Yang X-H, Feng Z-E, Yan M, et al. XIAP is a predictor of cisplatin-based chemotherapy response and prognosis for patients with advanced head and neck cancer. *PLoS One*. 2012;7(3):e31601.
6. Yu J, Zhang L. Apoptosis in human cancer cells. *Curr Opin Oncol*. 2004;16:19-24.

7. Thibault B, Genre L, Le Naour A, et al. DEBIO 1143, an IAP inhibitor, reverses carboplatin resistance in ovarian cancer cells and triggers apoptotic or necroptotic cell death. *Sci Rep*. 2018;8(1):17862.
8. Matzinger O, Viertl D, Tsoutsou P, et al. The radiosensitizing activity of the SMAC-mimetic, Debio 1143, is TNFalpha-mediated in head and neck squamous cell carcinoma. *Radiother Oncol*. 2015;116:495-503.
9. Serova M, Tijras-Raballand A, Albert S, et al. Debio 1143, an oral antagonist of the inhibitor of apoptosis proteins (IAPs) improves the effects of platinum derivatives in multiple SCCHN tumor models. European Congress on Head & Neck Oncology. European Congress on Head & Neck Oncology (ECHNO-14). Abstract P231 (2014).
10. Attinger A, Gavillet B, Chessex AV, Wiedemann N, Vuagniaux G. The inhibitor of apoptosis protein (IAP) antagonist Debio 1143 enhances the immune response to anti-PD1/L1 inhibitors in vitro and in vivo. American Association for Cancer Research (AACR) Annual Meeting. Abstract 4703 (2018).
11. Sun XS, Tao Y, Le Tourneau C, et al. Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study. *Lancet Oncol*. 2020;21(9):173-187.
12. Tao Y, Le Tourneau C, Bouchaab H, et al. Phase 1 Study of Debio 1143 with Concurrent Chemo-Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck. European Society for Radiotherapy and Oncology (ESTRO) Annual Meeting. Poster Abstract PV-0518; 2016.
13. Belhocine T, Steinmetz N, Li C, Green A, Blankenberg F. The imaging of apoptosis with the radiolabeled annexin V: optimal timing for clinical feasibility. *Technol Cancer Res Treat*. 2004;3(1):23-32.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Gomez-Roca C, Even C, Le Tourneau C, et al. Exploratory window-of-opportunity trial to investigate the tumor pharmacokinetics/pharmacodynamics of the IAP antagonist Debio 1143 in patients with head and neck cancer. *Clin Transl Sci*. 2022;15:55–62. https://doi.org/10.1111/cts.13002