

CLINICAL COMMUNICATIONS

Senior Vice President

Jeff Prescott, PharmD

**Assistant Director,
Content Services**

Angelia Szwed

**Senior Clinical
Project Manager**

Ida Delmendo

Project Manager

Lindsay Caporrino

Associate Editor

Hayley Fahey

Assistant Editor

Daniel Greaves

COPY & PRODUCTION

Copy Chief

Jennifer Potash

Copy SupervisorsRachelle Laliberte
Paul Silverman**Scientific & Medical
Quality Review Editor**

Stacey Abels, PhD

Senior Copy Editor

Kelly King

Copy EditorsCheney Baltz
Georgina Carson
Rebekah Harrison
Kirsty Mackay
Ron Panarotti**Creative Director,
Publishing**

Melissa Feinen

Art Director

Julianne Costello

SALES & MARKETING

Vice President

Gil Hernandez

**Senior National
Account Managers**Ben Baruch
Megan Halsch**National Account
Managers**Robert Foti
Ryan O'Leary**National Account
Associate**

Kevin George

OPERATIONS & FINANCE

Circulation Director

Jon Severn

circulation@mjhassoc.com

**Vice President,
Finance**

Leah Babitz, CPA

Controller

Katherine Wyckoff

CORPORATE

Chairman & Founder

Mike Hennessy Sr

Vice Chairman

Jack Lepping

President & CEO

Mike Hennessy Jr

Chief Financial Officer

Neil Glasser, CPA/CFE

Chief Marketing Officer

Michael Baer

**Executive Vice
President, Global
Medical Affairs &
Corporate Development**

Joe Petrozello

**Senior Vice President,
Content**

Silas Inman

**Senior Vice President,
Operations**

Michael Ball

**Senior Vice President,
I.T. & Enterprise
Systems**

John Moricone

**Vice President,
Human Resources
and Administration**

Shari Lundenberg

**Vice President,
Mergers & Acquisitions**

Chris Hennessy

**Executive
Creative Director,
Creative Services**

Jeff Brown

This publication was supported by Debiopharm International SA.

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

This AJMC® Clinical Brief provides key information regarding a study by Sun et al, the results of which were originally published in *Lancet Oncology* (doi:10.1016/S1470-2045(20)30327-2). The authors of the original publication are Sun XS, Tao Y, Le Tourneau C, et al. Please consult the full publication for complete study information and author affiliations.

BACKGROUND

Standard treatment for unresectable locoregionally advanced squamous cell carcinomas of the head and neck (SCCHN) consists of thrice-weekly cisplatin chemotherapy (100 mg/m²) with concomitant radiotherapy.¹ However, high-dose cisplatin chemotherapy plus radiotherapy is commonly associated with serious treatment-related toxicity.² Also, treatment resistance is a substantial challenge, and more so for patients with human papillomavirus (HPV)-negative SCCHN, which is associated not only with resistance to therapy, but also higher risk of recurrence and poorer overall survival (OS).³ Among those with HPV-negative oropharyngeal squamous cell carcinoma, the 5-year survival rate ranges from 45% to 50%, compared with 75% to 80% among those with HPV-positive disease.⁴ At present, there are no treatments indicated specifically for HPV-negative oropharyngeal cancers.¹ Treatment failure or relapse after treatment occur in more than half of patients with advanced SCCHN, whether resectable or not.⁵ There are few treatment options after relapse, and prognosis for these patients is often poor. Thus, for patients with HPV-negative SCCHN, there is an unmet need for treatment options with greater efficacy.²

SCCHN, like many cancers, is characterized by impairment of programmed cell death, which allows for cancer cells to avoid apoptosis that would otherwise be induced by chemotherapy and/or radiotherapy, thus promoting treatment-resistant clones.^{1,6} Inhibitor of apoptosis proteins (IAPs) are a class of proteins involved in numerous cellular processes, including regulation of apoptosis and mediation of inflammatory and immune responses. IAPs include X chromosome-linked IAP (XIAP), cellular IAP1 (cIAP1, also called BIRC2), and cIAP2.¹ SCCHNs are notable for a high degree of IAP expression, and SCCHNs are broadly associated with a high frequency of deregulated gene encoding specific to the apoptosis pathway.^{7,8} The use of therapeutic agents to inhibit IAPs by direct binding has been shown to increase apoptosis and enhance sensitivity to treatment.^{9,10}

Debio 1143 (also called AT-406 and SM-406) is an orally administered, small-molecule IAP antagonist that acts upon XIAP, cIAP1, and cIAP2, among other IAPs. In numerous preclinical SCCHN models, use of Debio 1143 improved the efficacy of both radiotherapy and platinum-based chemotherapy.¹¹⁻¹³ In a previous phase 1 study in 14 patients with locoregionally advanced SCCHN, the safety profile of Debio 1143 combined with chemoradiation treatment was shown to be consistent with that of chemoradiation alone.^{11,14} The results of that phase 1 study were used to determine the recommended dose for a phase 2 trial.¹ The present study is that phase 2 trial.

AJMC
THE AMERICAN JOURNAL OF MANAGED CARE

© 2020 Managed Care & Healthcare Communications, LLC

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Managed Care & Healthcare Communications, LLC, the editorial staff, or any member of the editorial advisory board. Managed Care & Healthcare Communications, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Managed Care & Healthcare Communications, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

METHODS

This phase 2, randomized, double-blind trial (NCT02022098) was funded by Debiopharm and conducted by the French Head and Neck Radiotherapy Oncology Group at 19 centers in France and Switzerland.¹ Eligible patients were aged 18 to 75 years with previously untreated locoregionally advanced SCCHN (stage III, IVA, or IVB, limited to T_{≥2}, N0-3, and M0 per the American Joint Committee on Cancer TNM staging system, version 7.0), measurable disease per RECIST version 1.1, a smoking history of more than 10 pack-years, and creatinine clearance at least 60 mL/min.¹

Patients were randomized 1:1 to treatment with Debio 1143 plus standard chemoradiotherapy or placebo plus standard chemoradiotherapy, using stochastic minimization with stratification based on the following factors: node involvement (N0-N1 vs N2-N3) and primary tumor site (oropharynx vs others), as well as HPV-16 status in patients with a primary tumor site.¹ Patients were administered Debio 1143 (200 mg) or placebo once daily on days 1 to 14 of a 21-day treatment cycle, for 3 cycles. Cisplatin 100 mg/m² was given intravenously, once per cycle for each of the 3 cycles (on days 2, 23, and 44), and administered 1 hour prior to the radiation fraction and 30 minutes to 3 hours after Debio 1143 or placebo administration. Fractionated intensity-modulated radiotherapy was directed to the primary tumor and involved nodes on 5 days of each week for 7 weeks.¹ Tumor assessment was conducted by CT scan or MRI or both; ¹⁸F-fluorodeoxyglucose PET scans were optional.¹ In the case of treatment-emergent adverse events (TEAEs), dose reduction of chemoradiotherapy and/or Debio 1143 was permissible.¹

The study's primary end point was the proportion of patients who had achieved locoregional control 18 months after the end of chemoradiotherapy. This was defined as the absence of locoregional failure based on either a blinded assessment by an investigator with subsequent confirmation by biopsy, or RECIST.¹ Key secondary end points included progression-free survival (PFS), duration of locoregional control, time to distant relapse, and OS.¹ Efficacy end points were assessed in the intention-to-treat population (primary analysis), and the primary end point was assessed at a 2-sided significance level of 0.20; other end points were assessed at a 0.05 level.¹ Safety outcomes were assessed for all patients who received at least 1 dose of the study drug.¹

RESULTS

Efficacy

A total of 96 patients were randomized to the Debio 1143 and placebo groups (n = 48 for each), but 1 patient in the placebo group never received a study treatment, leaving 95 patients included in the safety analysis. The 2 groups were well balanced regarding disease stage, tumor size, and lymph node involvement. Median follow-up was 25.0 versus 24.2 months in the Debio 1143 and placebo groups, respectively.¹ There were 7 discontinuations (15%) in the Debio 1143 group: 4 due to toxicity, 2 due to study withdrawal, and 1 because the patient found the study drug to have a bitter taste. Six patients in the

placebo group discontinued: 3 withdrew from the study, 2 discontinued radiotherapy, and 1 discontinued due to toxicity.¹

The primary end point, locoregional control 18 months after the end of chemoradiotherapy, was achieved (and was ongoing at the time of publication) in 26 patients (54%) in the Debio 1143 group (95% CI, 39%-69%) and 16 patients (33%) in the placebo group (95% CI, 20%-48%), as shown in the [Figure](#).¹ Kaplan-Meier estimates of the primary end point were 78% (95% CI, 61%-88%) versus 67% (95% CI, 48%-80%) in the Debio 1143 and placebo groups, respectively (difference = 11% [95% CI, -10% to 32%]; P = .311).¹ A sensitivity analysis indicated that at 24 months after randomization, locoregional control (per Kaplan-Meier estimates) was 78% (95% CI, 61%-88%) for patients in the Debio 1143 group and 63% (95% CI, 43%-77%) in the placebo group, a difference of 15% (95% CI, 7%-37%; P = .171). The median duration of locoregional control, according to this analysis, was not reached for either group.¹ Five of 9 locoregional failures in the Debio 1143 group were cases of disease progression and 4 were treatment failures. In the placebo group, 10 of the 11 locoregional failures were disease progression and 1 was treatment failure.¹

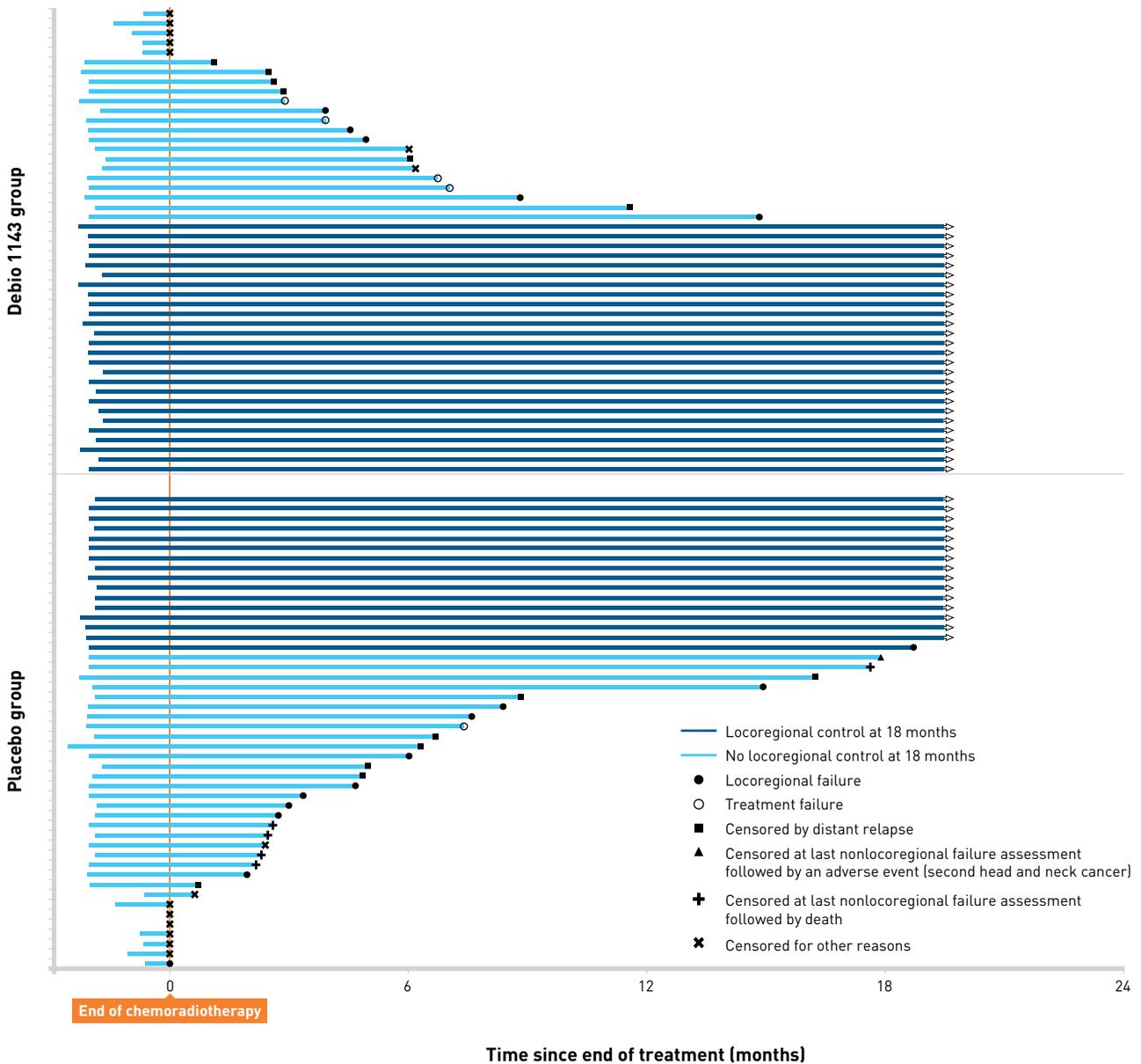
Among secondary end points, PFS was 16.9 months in the placebo group (95% CI, 6.8 to not estimable) and was not reached for the Debio 1143 group, producing a PFS HR of 0.37 (95% CI, 0.18-0.76; P = .0069). At 24 months, 72% (95% CI, 56%-84%) of patients in the Debio 1143 group were progression free compared with 41% (95% CI, 25%-55%) in the placebo group (difference = 32% [95% CI, 11%-53%]; P = .0026).¹ At the time of data cutoff, distant relapse was observed in 6 patients (13%) in the Debio 1143 group compared with 9 patients (19%) in the placebo group. At 18 months after the end of chemoradiotherapy, no distant relapse was observed in 85% (95% CI, 69%-93%) and 71% (95% CI, 51%-84%) of the Debio 1143 and placebo groups, respectively, a difference of 14% (95% CI, -6% to 34%; P = .172). Median time to distant relapse was not reached in either the Debio 1143 or placebo groups.¹

OS at 24 months was not significantly different between the 2 groups: 73% (95% CI, 58%-84%) in the Debio 1143 group versus 65% (95% CI, 48%-77%) in the placebo group (HR, 0.65; P = .243). Median OS was not reached in either group. Fourteen patients (29%) in the Debio 1143 group died during the study and 17 patients (35%) in the placebo group died. No deaths were deemed to be related to treatment.¹ At the first evaluation (approximately 11 weeks after chemoradiotherapy), a complete response was reported in 17 patients (35%) in each group, while a partial response was seen in 13 patients (27%) and 15 patients (31%) in the Debio 1143 and placebo groups, respectively. At the second evaluation (6 months after chemoradiotherapy), 25 patients (52%) in the Debio 1143 group experienced complete response and 7 (15%) experienced partial response. Among patients in the placebo group, 18 (38%) experienced a complete response and 5 (10%) experienced a partial response at 6 months.¹

Safety

The addition of Debio 1143 to cisplatin and radiotherapy was generally well tolerated and the AE profile was consistent with the AE profile of chemoradiotherapy alone, as shown in the [Table](#).¹ Every patient in the

Figure. Swimmer Plot of Locoregional Control Data 18 Months From the End of Chemoradiotherapy¹



Reprinted from *Lancet Oncology*, 21(9), Sun XS, 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, 1173-1187, Copyright 2020, with permission from Elsevier.

study experienced at least 1 TEAE, while TEAEs of grade 3 or greater were observed in 41 patients (85%) in the Debio 1143 group and 41 (87%) in the placebo group. Dysphagia, mucositis, and anemia were the most common TEAEs, and more frequently manifested as grade 3 in the Debio 1143 group than in the placebo group.¹ With the exception of grade 1/2 tinnitus, treatment with Debio 1143 was not associated with an increase in cisplatin-related AEs, such as renal insufficiency, febrile neutropenia, thrombocytopenia, peripheral sensory neuropathy, or severe vomiting.¹

CONCLUSIONS

The results of this phase 2 study demonstrate that in patients with nonresected, high-risk SCCHN, Debio 1143 combined with standard-of-care chemoradiotherapy confers greater treatment efficacy compared with chemoradiotherapy alone, with a predictable safety profile.¹ Patients in the Debio 1143 group experienced superior outcomes versus those receiving chemoradiotherapy only, as measured by the primary end point, locoregional control at

Table. Most Common Treatment-Emergent Adverse Events¹

	Debio 1143 (n=48)				Placebo (n=47)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Mucositis	21 (44%)	15 (31%)	0	0	22 (47%)	10 (21%)	0	0
Dysphagia	10 (21%)	24 (50%)	0	0	19 (40%)	10 (21%)	0	0
Anemia	12 (25%)	17 (35%)	0	0	15 (32%)	11 (23%)	0	0
Weight loss	27 (56%)	0	0	0	22 (47%)	0	0	0
Radiation skin injury	24 (50%)	1 (2%)	0	0	17 (36%)	3 (6%)	0	0
Nausea	19 (40%)	2 (4%)	0	0	16 (34%)	1 (2%)	0	0
Xerostomia	19 (40%)	1 (2%)	0	0	18 (38%)	0	0	0
Dermatitis	16 (33%)	2 (4%)	0	0	17 (36%)	1 (2%)	0	0
Asthenia	15 (31%)	2 (4%)	0	0	13 (28%)	4 (9%)	0	0
Neutropenia	4 (8%)	7 (15%)	4 (8%)	0	4 (9%)	11 (23%)	2 (4%)	0
Constipation	15 (31%)	0	0	0	15 (32%)	1 (2%)	0	0
Vomiting	13 (27%)	2 (4%)	0	0	9 (19%)	3 (6%)	0	0
Tinnitus	15 (31%)	0	0	0	10 (21%)	0	0	0
ALT increased	7 (15%)	6 (13%)	0	0	6 (13%)	2 (4%)	0	0
Dysgeusia	12 (25%)	0	0	0	14 (30%)	0	0	0
Decreased appetite	10 (21%)	2 (4%)	0	0	11 (23%)	1 (2%)	0	0
Odynophagia	7 (15%)	3 (6%)	0	0	6 (13%)	3 (6%)	0	0
Acute kidney injury	8 (17%)	2 (4%)	0	0	3 (6%)	4 (9%)	0	0
Pyrexia	7 (15%)	2 (4%)	0	0	10 (21%)	0	0	0
Stomatitis	5 (10%)	4 (8%)	0	0	6 (13%)	3 (6%)	0	0
Neck pain	5 (10%)	4 (8%)	0	0	6 (13%)	1 (2%)	0	0
Fatigue	6 (13%)	3 (6%)	0	0	5 (11%)	1 (2%)	0	0
AST increased	6 (13%)	3 (6%)	0	0	2 (4%)	1 (2%)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Reprinted from *Lancet Oncology*, 21(9), Sun XS, 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):1173-1187. Copyright 2020, with permission from Elsevier.

18 months, in addition to the secondary end points of PFS and distant relapse.¹ A limitation of the present study was its small sample size, making it insufficiently powered to detect significant differences in OS or locoregional control as assessed by Kaplan-Meier.¹ •

Address correspondence to: Debiopharm International SA via email at info@debiopharm.com.

REFERENCES

- 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):1173-1187. doi:10.1016/S1470-2045(20)30327-2
- Voorntman J. Chemoradiotherapy plus a SMAC mimetic for locally advanced squamous cell carcinoma of the head and neck. *Lancet Oncol*. 2020;21(9):1126-1128. doi:10.1016/S1470-2045(20)30383-1
- Alshafiq E, Begg K, Amelio I, et al. Clinical update on head and neck cancer: molecular biology and ongoing challenges. *Cell Death Dis*. 2019;10(8):540. doi:10.1038/s41419-019-1769-9
- Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35. doi:10.1056/NEJMoa0912217
- Magnes T, Egle A, Greil R, Melchardt T. Update on squamous cell carcinoma of the head and neck: ASCO annual meeting 2017. *Memo*. 2017;10(4):220-223. doi:10.1007/s12254-017-0358-9

- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(4):646-674. doi:10.1016/j.cell.2011.02.013
- Cheng H, Yang X, Si H, et al. Genomic and transcriptomic characterization links cell lines with aggressive head and neck cancers. *Cell Rep*. 2018;25(5):1332-1345.e5. doi:10.1016/j.celrep.2018.10.007
- Derakhshan A, Chen Z, Van Waes C. Therapeutic small molecules target inhibitor of apoptosis proteins in cancers with deregulation of extrinsic and intrinsic cell death pathways. *Clin Cancer Res*. 2017;23(6):1379-1387. doi:10.1158/1078-0432.CCR-16-2172
- Yang XH, Feng ZE, 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. doi:10.1371/journal.pone.0031601
- Yu J, Zhang L. Apoptosis in human cancer cells. *Curr Opin Oncol*. 2004;16(1):19-24. doi:10.1097/00001622-200401000-00005
- Gomez-Roca C, Even C, Le Tourneau C, et al. 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. *Cancer Res*. 2019;79(suppl 13):abstr 5001. doi:10.1158/1538-7445.AM2019-5001
- 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. doi:10.1038/s41598-018-35860-z
- Matzinger O, Viertl D, Tsoutsou P, et al. The radiosensitizing activity of the SMAC-mimetic, Debio 1143, is TNF α -mediated in head and neck squamous cell carcinoma. *Radiother Oncol*. 2015;116(3):495-503. doi:10.1016/j.radonc.2015.05.017
- Tao Y, Le Tourneau C, Bouchaab H, et al. Phase 1 study of Debio 1143 with concurrent chemo-radiotherapy in LA-SCCHN [locally advanced squamous cell carcinoma of the head and neck]. *European Society for Radiotherapy and Oncology* 35; Turin, Italy; April 30, 2016. Abstract PV-0518. Accessed November 19, 2020. https://www.debiopharm.com/wp-content/uploads/2018/09/2016-ESTRO-Debio1143_Final.pdf