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

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Summary

Background Debio 1143 is an orally available antagonist of inhibitor of apoptosis proteins with the potential to enhance the antitumour activity of cisplatin and radiotherapy. The radiosensitising effect of Debio 1143 is mediated through caspase activation and TNF, IFNγ, CD8 T cell-dependent pathways. We aimed to investigate the efficacy and safety of Debio 1143 in combination with standard chemoradiotherapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck.

Methods This double-blind, multicentre, randomised, phase 2 study by the French Head and Neck Radiotherapy Oncology Group (GORTEC) was run at 19 hospitals in France and Switzerland. Eligible patients were aged 18–75 years with locoregionally advanced, squamous cell carcinoma of the head and neck (characterised as non-metastatic, measurable stage III, IVa, or IVb [limited to T ≥2, N0–3, and M0] disease), Eastern Cooperative Oncology Group performance status of 0 or 1, a history of heavy tobacco smoking (>10 pack-years) with no previous or current treatment for invasive head and neck cancer, and no previous treatment with inhibitor of apoptosis protein antagonists. Patients were randomly assigned (1:1) to receive oral Debio 1143 (200 mg per day on days 1–14 of 21-day cycles, for three cycles) or oral placebo (20 mg/mL, administered at the same dosing schedule) using a stochastic minimisation technique according to node involvement and primary tumour site, and HPV-16 status in patients with an oropharyngeal primary tumour site. All patients received standard high-dose cisplatin chemoradiotherapy. The primary endpoint was the proportion of patients with locoregional control 18 months after chemoradiotherapy, analysed in the intention-to-treat population (primary analysis), and repeated in the per-protocol population. Responses were assessed according to Response Evaluation Criteria in Solid Tumors (version 1.1). This trial is registered with ClinicalTrials.gov, NCT02022098, and is still active but not recruiting.

Findings Between Jan 25, 2016, and April 24, 2017, 48 patients were randomly assigned to the Debio 1143 group and 48 to the placebo group (one patient in the placebo group did not receive the study drug and was not included in the safety analysis). Median duration of follow-up was 25·0 months (IQR 19·6–29·4) in the Debio 1143 group and 24·2 months (6·6–26·8) in the placebo group. Locoregional control 18 months after chemoradiotherapy was achieved in 26 (54%; 95% CI 39–69) of 48 patients in the Debio 1143 group versus 16 (33%; 20–48) of 48 patients in the placebo group (odds ratio 2·69 [95% CI 1·13–6·42], p=0·026). Grade 3 or worse adverse events were reported in 41 (85%) of 48 patients in the Debio 1143 group and in 41 (87%) of 47 patients in the placebo group. The most common grade 3–4 adverse events were dysphagia (in 24 [50%] patients in the Debio 1143 group *vs* ten [21%] in the placebo group), mucositis (in 15 [31%] *vs* ten [21%]), and anaemia (in 17 [35%] *vs* 11 [23%]). Serious treatment-emergent adverse events were recorded in 30 (63%) of 48 patients in the Debio 1143 group and 28 (60%) of 47 in the placebo group. In the placebo group, two (4%) deaths were due to adverse events (one multiple organ failure and one asphyxia; neither was considered to be related to treatment). No deaths due to adverse events occurred in the Debio 1143 group.

Interpretation To our knowledge, this is the first treatment regimen to achieve superior efficacy in this disease setting against a high-dose cisplatin chemoradiotherapy comparator in a randomised trial. These findings suggest that inhibition of inhibitor of apoptosis proteins is a novel and promising approach in this poor prognostic population and warrant confirmation in a phase 3 study with the aim of expanding the therapeutic options for these patients.

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Research in context

Evidence before this study

We searched PubMed and major congress abstracts for studies published up to Nov 1, 2019, using the terms "inhibitor of apoptosis proteins (IAPs)", "locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN)", "chemoradiotherapy", "cancer", and "treatment". No language restriction was applied. The results of this search showed that, so far, concurrent administration of chemotherapy and radiotherapy has demonstrated the greatest survival benefit for patients with locoregionally advanced squamous cell carcinoma of the head and neck. This search also revealed that inhibitor of apoptosis proteins are highly expressed in squamous cell carcinoma of the head and neck cancers and that direct binding of these proteins with inhibitory agents has been shown to moderate their anti-apoptotic effects.

Added value of this study

To our knowledge, this phase 2 study is the first to establish the clinical efficacy and safety profile of Debio 1143 in combination with standard chemoradiotherapy in patients with locoregionally advanced squamous cell carcinoma of the head and neck. It demonstrates the clinical potential of this therapeutic approach, in a particularly poor prognostic patient population, as evidenced by the improved locoregional control 18 months after treatment and improvement in progression-free survival.

Implications of all the available evidence

Locoregionally advanced squamous cell carcinomas of the head and neck are a refractory group of cancers in which the activity of Debio 1143 was durable and tolerable. The clinical activity demonstrated here warrants further development in randomised clinical trials, as is currently planned.

Introduction

The broad geographical variation in the incidence of squamous cell carcinoma of the head and neck is predominantly attributable to regional patterns of tobacco and alcohol use and, together, these habits contribute to the development of almost 80% of cases worldwide.[1] Human papillomavirus (HPV) infection status has become increasingly important in the epidemiology and prognosis of squamous cell carcinoma of the head and neck.[2] Most patients diagnosed with squamous cell carcinoma of the head and neck present with the locoregionally advanced form of disease.[3] Although potentially curable, the management of patients with locoregionally advanced squamous cell carcinoma of the head and neck poses a complex challenge due to the requirement for combined-modality therapy.[4] In patients with an unresectable form of this disease, three-weekly high-dose cisplatin (100 mg/m²) with concurrent radiotherapy is a standard treatment. More than half of patients with locoregionally advanced squamous cell carcinoma of the head and neck relapse or have treatment failure, the majority locoregionally and within 2 years of completing treatment.[5] Treatment resistance remains a major challenge, especially in those with HPV-negative oropharyngeal cancers.[6] HPV status is a strong, independent prognostic indicator in patients with oropharyngeal cancer, with 5-year survival rates of 75–80% in patients with HPV-positive disease, compared with 45–50% for those with HPV-negative cancers.[7] Currently, no therapies are indicated specifically for patients with HPV-negative oropharyngeal cancers, and these patients, usually heavy tobacco smokers, have the poorest prognoses and represent an unmet medical need.

In numerous cancer types, including squamous cell carcinoma of the head and neck, regulation of programmed cell death is impaired, allowing cancer cells to evade apoptosis in response to potentially lethal standard chemoradiotherapy exposure, thereby contributing to the emergence of treatment-resistant clones.[8] Inhibitor of apoptosis proteins (IAPs), including X chromosome-linked IAP (XIAP), cellular IAP1 (cIAP1; also known as BIRC2), and cIAP2, are a class of proteins that can negatively regulate apoptosis, modulate immune and inflammatory responses, and affect a multitude of other cellular processes that are frequently deregulated in human cancers. IAPs are highly expressed in several human tumours, including squamous cell carcinoma of the head and neck.[7,9] Squamous cell carcinomas of the head and neck are among the cancers with the highest frequency of deregulation in genes encoding constituents of the cell death pathway, with more than 40% of HPV-negative and more than 30% of HPV-positive cases showing deregulation of FADD, cIAP1, CASP8, and TRAF3.[7] Direct binding of IAPs with inhibitory agents has been shown to moderate their anti-apoptotic effects through promotion of apoptosis and restoration of treatment sensitivity.[10,11] cIAP1 and cIAP2 are also modulators of NF-κB signalling, which plays an important part in T-cell activation and proliferation, and inhibition of cIAP1 and cIAP2 with IAP antagonists has resulted in antitumour activity through modulation of innate and adaptive immunity.[12]

Debio 1143 (also known as AT-406 and SM-406) is an orally available, small-molecule antagonist of IAPs, including XIAP, cIAP1, and cIAP2. Debio 1143 has been shown to enhance the effect of chemoradiotherapy in several preclinical models of cancer, including squamous cell carcinoma of the head and neck, sensitising for radiotherapy and improving the effects of platinum

derivatives in multiple squamous cell carcinoma of the head and neck tumour models.[13–16] Furthermore, the antitumour host immune system was shown to contribute to the radiosensitisation effect of Debio 1143, and was dependent on CD8 cells, TNF, and IFNγ.[14] In a window-of-opportunity study, high concentrations of Debio 1143 were achieved in squamous cell carcinoma of the head and neck tumours (up to 55 times those found in plasma), largely exceeding the half maximal inhibitory concentration for XIAP and cIAPs by 100 to 1000 times, resulting in cIAP1 target engagement and downstream effects on CD8 tumour-infiltrating lymphocytes.[16]

In the phase 1 part of this study, the safety profile of Debio 1143 in combination with standard chemoradiotherapy was largely consistent with that of chemoradiotherapy alone in 14 patients with locoregionally advanced squamous cell carcinoma of the head and neck.[17] In this setting, we established the safety profile, dose-limiting toxicities, maximum tolerated dose, pharmacokinetics, pharmacodynamics, and preliminary antitumour activity of Debio 1143. The recommended phase 2 dose (RP2D) of Debio 1143 (200 mg once daily, administered on days 1–14 of 21-day cycles) was also defined (detailed findings will be reported elsewhere). Here, we aimed to investigate the efficacy and safety of Debio 1143 at the RP2D in combination with standard chemoradiotherapy in patients with high-risk locoregionally advanced squamous cell carcinoma of the head and neck.

Methods

Study design and participants

This double-blind, multicentre, randomised, phase 2 study (GORTEC 2015-03) was run by the French Head and Neck Radiotherapy Oncology Group (GORTEC) at 19 hospitals in France and Switzerland. Patients were eligible to participate if they were aged 18–75 years with a histologically confirmed diagnosis of previously untreated locoregionally advanced squamous cell carcinoma of the head and neck (stage III, IVa, and IVb, limited to T ≥2, N0–3, and M0 [according to the 2010 American Joint Committee on Cancer [AJCC] Tumour Node Metastasis [TNM], version 7.0, staging system]) of one or more of the following sites: oral cavity, oropharynx, hypopharynx, and larynx. Patients also had to fulfil the following inclusion criteria: measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1);[18] tumour HPV status for patients with oropharyngeal cancer determined by p16 immunohistochemistry; a tobacco smoking history of more than 10 pack-years; no medical history of hepatitis B or hepatitis C virus infection; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; no clinically significant cardiac disease; no clinically significant hearing impairment that would contraindicate the use of chemotherapy with high-dose cisplatin; QTcF interval of ≤450 ms; no previous treatment with IAP inhibitors; no use or requirement for use of aspirin or aspirin-containing products with more than 160 mg of aspirin per day; no history of gastrointestinal bleeding within 1 year; no active rheumatoid arthritis, active inflammatory bowel disease, chronic infections, or any other disease or condition associated with chronic inflammation; and adequate haematological, renal, and hepatic function. Adequate haematological, renal, and hepatic function was defined as calculated creatinine clearance (≥60 mL/min) as determined by the modified method of Cockcroft and Gault or by the EDTA method, absolute neutrophil count (≥1500 cells per µL), platelet count (≥100 000 cells per µL), haemoglobin (≥10 g/dL), aspartate aminotransferase and alanine aminotransferase concentration (less than three times the upper limit of normal), total bilirubin (≤2·0 mg/dL), and serum albumin (>35 g/L).

Exclusion criteria included any previous or current treatment for invasive head and neck cancer of any kind (including, but not limited to, previous tyrosine kinase inhibitors, previous neoadjuvant therapy, previous surgical resection, or use of any investigational agent); weight loss of more than 10% during the previous month; non-compensated liver cirrhosis; gastrointestinal disorders that could affect drug absorption; concurrent treatment with any other systemic anticancer therapy or concurrent treatment with any drug on the prohibited medication list; history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure; history of another malignancy within the past 5 years with the exception of completely resected basal or squamous cell skin cancer or successfully treated in-situ carcinoma; and history of non-invasive lesion or in-situ carcinoma, including in the head and neck region, which was successfully treated with surgery.

The protocol was approved by the institutional review boards or ethics committees of all 19 participating centres. The study was carried out in accordance with the protocol, the principles expressed in the Declaration of Helsinki, and applicable regulatory requirements. All patients provided written informed consent in advance of study-specific procedures.

Randomisation and masking

Patients were randomly assigned (1:1) to receive Debio 1143 plus standard chemoradiotherapy (Debio 1143 group) or placebo plus standard chemoradiotherapy (placebo group) by a stochastic minimisation technique according to the following stratification factors: node involvement (N0–N1 *vs* N2–N3) and primary tumour site (oropharynx *vs* others), as well as HPV-16 status (positive *vs* negative, as determined by p16 immunohistochemistry) in patients with an oropharyngeal primary tumour site. Randomisation codes were generated centrally by an external supplier (via an interactive response technology). Participants, personnel administering the interventions, and investigators assessing outcomes were masked to group assignment. However, the data assessed by the

biostatistician from the Efficacy and Safety Evaluation Committee (ESEC) were unblinded.

Procedures

Patients received either Debio 1143 (200 mg) or placebo (20 mg/mL) in active pharmaceutical ingredient solution in single-dose glass vials containing 10 mL of solution orally or via a feeding tube (according to nutritional status and swallowing capability) once daily on days 1–14 of 21-day treatment cycles, for three cycles (taken fasted 1 h before or 2 h after a meal). Cisplatin 100 mg/m^2 was administered intravenously over 60 min before the irradiation fraction, once in every cycle for 3 cycles (on days 2, 23, and 44) and between 30 min and 3 h after patients had received Debio 1143 or placebo. Conventional fractionated intensity-modulated radiotherapy was delivered to the gross tumour volume (primary tumour and involved nodes), to a total dose of 70 Gy in 2 Gy daily fractions, for 5 days per week over 7 weeks. Primary and neck nodal areas with no tumour involvement (elective or prophylactic irradiation areas) received a total dose of 50 Gy. In accordance with the European Society for Medical Oncology guidelines,[19] patients received prophylactic treatment with granisetron or palonosetron, dexamethasone, and aprepitant before and after cisplatin to prevent renal damage and emesis. Tumour assessments were done at screening when patients were evaluated and tumours were staged using AJCC TNM (version 7.0). A CT scan or MRI (or both) of the head and neck region, and chest CT and an optional ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET scan were also performed. During the study, tumour response assessments by investigators were performed according to RECIST (version 1.1) guidelines.[18] ^{18}F-FDG PET scan imaging, although not mandatory, was indicated if there was doubt about whether residual disease existed, or to identify new lesions, which were then to be confirmed by CT, biopsy, or surgery. No central review was planned or performed. The end of treatment visit was 10 days after the final treatment had been received (±3 days). A safety follow-up was scheduled for 30–40 days after the final treatment, and the first efficacy follow-up was scheduled 11 weeks (±1 week) after the end of treatment visit, followed by re-evaluation every 3 months until 2 years after randomisation. Patients who were still in follow-up at that point were asked to enter the extended follow-up, which continues for all patients until the last patient has reached 3 years since randomisation. During the extended follow-up, assessments were done at 3-monthly to 6-monthly intervals. Patients remained on efficacy follow-up until disease progression, patient withdrawal of consent, adverse events (eg, an intercurrent illness that would affect assessments of clinical status to a substantial degree), patient non-compliance, patient loss to follow-up, crucial and relevant protocol violation, use of prohibited medication, non-drug-related reasons, or emergency code break, or if the sponsor or independent ethics committee decided to terminate the study.

Where an adverse event could reasonably be attributed to chemoradiotherapy, adjustments to chemoradiotherapy were attempted before adjusting the Debio 1143 or placebo dose. In patients with Debio 1143-related toxicities requiring dose reduction, Debio 1143 or placebo was reduced by 50 mg at each occurrence; a maximum of two dose reductions were permitted. If a further dose reduction was indicated, Debio 1143 or placebo was discontinued; re-escalation was not permitted.

Medical history and demographics were collected at screening. Physical examination was done at screening, on day 1 of each cycle, at the end of the study visit, at the safety follow-up visit, and at each subsequent efficacy follow-up visit. Adverse events and co-medication were monitored throughout the study from signature of informed consent (28 days before the first dose) until 30 days after the last dose of study drug. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). All information pertaining to unusual manifestations or adverse events was collected by the investigator at each visit. The investigator was required to notify the sponsor or delegate of any serious adverse event, irrespective of reason, within 24 h of being informed of its occurrence. Late toxicities were defined in the protocol and reported throughout the efficacy follow-up period until the end of study visit. Blood samples for laboratory safety tests that included coagulation, prothrombin time, partial prothrombin time, and fibrinogen were collected at screening, on days 1, 8, and 15 of cycles 1 and 2, and days 1 and 8 of cycle 3, at the end of treatment, at the safety follow-up visit, at each standard efficacy follow-up visit (not during extended follow-up), and at the end of the study. Haematology tests included haemoglobin, white blood cells, absolute neutrophil count, and platelet count, and were done at screening, on days 1, 8, and 15 of cycles 1 and 2, and days 1 and 8 of cycle 3, at the end of treatment, at the safety follow-up visit, at each standard efficacy follow-up visit, and at the end of the study. Biochemical tests included aspartate aminotransferase; alanine aminotransferase; γ-glutamyl transferase; alkaline phosphatase; amylase; lipase; glucose; conjugated, unconjugated, and total bilirubin; electrolytes (sodium, potassium, calcium, magnesium, and phosphate); urea; creatinine; creatinine clearance calculated using the Cockcroft and Gault formula; total protein; albumin; and lactate dehydrogenase. The biochemical tests were done at screening, on days 1, 8, and 15 of cycles 1 and 2, and days 1 and 8 of cycle 3, at end of treatment, at the safety follow-up visit, at each standard efficacy follow-up visit and at end of study. Quality control of contouring and dosimetry was performed by independent expert radiation oncologists.

Outcomes

The primary endpoint was the proportion of patients achieving locoregional control at 18 months from the end of chemoradiotherapy, defined as the documented absence of locoregional failure up to and including that timepoint. Locoregional failure was recorded by the investigator, either according to RECIST (version 1.1) or based on the investigator's blinded clinical assessment and confirmation by biopsy. Treatment failure events (ie, locoregional failures without progression, but with some residual tumour cells at the time of resection or biopsy) were counted as events for analysis of locoregional control in addition to locoregional progressions. Key secondary endpoints were progression-free survival, duration of locoregional control, time to distant relapse, and overall survival. Progression-free survival was defined as time from initiation of chemoradiotherapy to death from any cause or disease progression, whether locoregional or distant; treatment failures, as defined previously, were not counted as events. Duration of locoregional control was defined as the time from the end of chemoradiotherapy to occurrence of locoregional relapse. Time to distant relapse was defined as the time from the end of chemoradiotherapy to occurrence of distant relapse, and overall survival was defined as the time from randomisation to death from any cause. Other secondary endpoints were complete response (by RECIST, version 1.1) at 6 months after completion of chemoradiotherapy; best overall response; the proportion of patients with a response at 11 weeks and 6 months after completion of chemoradiotherapy; the proportion of patients with locoregional control at 6 months and 1 year after completion of chemoradiotherapy; the proportion of patients with progression-free survival at 1 year, 18 months, and 2 years after the initiation of chemoradiotherapy; distant relapse at 6 months, 1 year, and 18 months after completion of chemoradiotherapy; the proportion of patients with disease-specific survival at 1 year and 2 years after the initiation of chemoradiotherapy; the proportion of patients alive at 1 year and 2 years after the initiation of chemoradiotherapy; duration of response (for patients who achieve a best overall response, partial response, or complete response); change in vital signs and ECOG performance status; incidence of serious adverse events; incidence and severity of adverse events and laboratory abnormalities graded according to CTCAE (version 4.03); incidence of late toxicity; incidence of treatment discontinuations and treatment modifications due to adverse events; exploration of pharmacodynamic biomarkers of Debio 1143 activity in serum and saliva; and pharmacokinetic parameter estimation of Debio 1143 and Debio 1143 metabolite, including intra-individual and inter-individual variability (including potential variability due to chemoradiotherapy and, if appropriate, Debio 1143 exposure (or any other relevant pharmacodynamic parameter of the investigational drug) correlated with any marker of response (pharmacodynamic, efficacy, or safety).

Statistical analysis

The null hypothesis was that there is no difference between the experimental and control treatment groups, and the alternative hypothesis was that there is a difference between the treatment groups. We calculated the sample size for a comparison of two independent binomial proportions using Pearson's χ^2 statistic with a two-sided significance level of 0·2, in line with literature recommendations for phase 2 studies.[20] The planned sample size of 47 patients per treatment group would achieve a power of 0·8 or more to detect a 20% difference between groups in the proportions of patients with locoregional control achieved at 18 months after chemoradiotherapy treatment. The primary endpoint was assessed at a two-sided significance level of 0·20, whereas all other endpoints were assessed at the 0·05 level. No adjustments were made for multiple comparisons.

All efficacy endpoints were assessed in the intention-to-treat population and repeated in the per-protocol population, with the exception of disease-specific survival. The analysis in the intention-to-treat population was considered the primary analysis. The per-protocol population included patients who had measurable disease, according to RECIST (version 1.1), and underwent a baseline disease assessment and at least one post-baseline assessment, but excluded those who fulfilled any of the following conditions: violation of clinically relevant inclusion or exclusion criteria, administration of non-permitted concomitant treatments, did not receive at least 70% of the planned Debio 1143 dose, did not receive at least 100 mg/m² of cisplatin, and did not receive at least 70% of the planned dose of radiotherapy.

Safety was analysed in all patients who received at least one dose of study drug according to treatment received. We compared the primary endpoint between treatment groups using logistic regression with adjustment for randomisation stratification factors. Patients with missing data were included as having treatment failure in the primary endpoint analysis. We did a sensitivity analysis for the primary endpoint, whereby patients with missing data were excluded from the analysis rather than treated as having treatment failure. We analysed time-to-event endpoints (including locoregional control) using the Kaplan-Meier method, and we compared the survival curves between treatment groups using Cox regression, adjusted for the randomisation stratification factors. The assumption of proportional hazards was verified by means of a correlation test between the weighted Schoenfeld residuals and ranked failure times. Best overall response was considered as an ordinal endpoint and therefore compared between groups using the Mann-Whitney test.

We did a sensitivity analysis to evaluate locoregional control when measured from randomisation rather than the end of chemoradiotherapy. Derivations for this endpoint followed the rules defined for locoregional control, but the chemoradiotherapy end date was

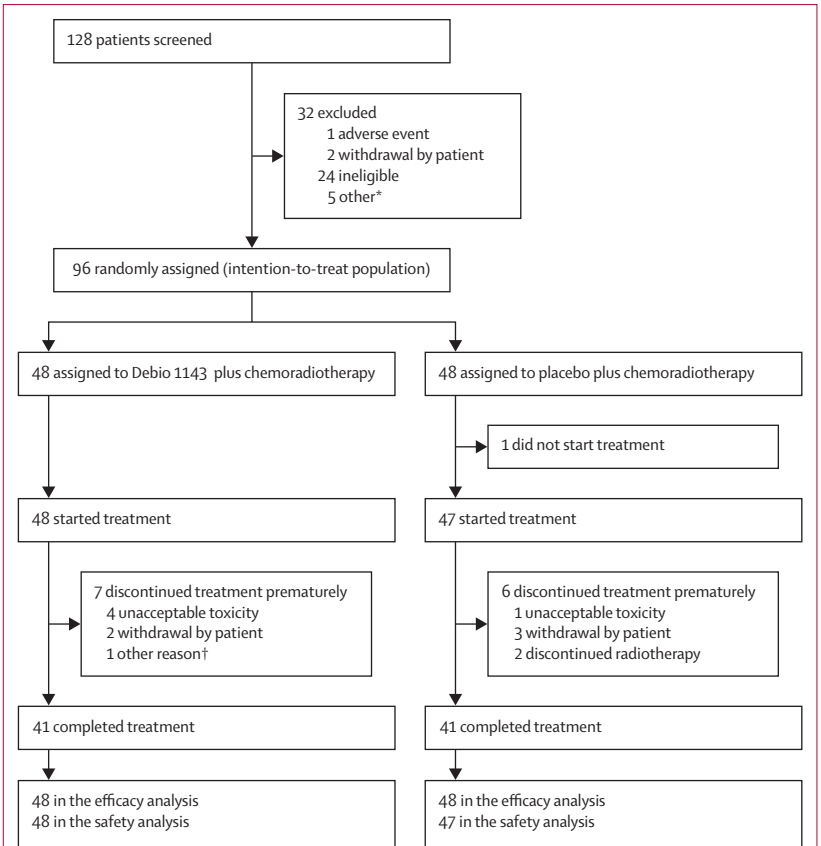


Figure 1: **Trial profile**
*Other reasons were investigator decision (left ventricular ejection fraction was <50%), death of patient, respiratory insufficiency due to tumour, investigator decision (due to comorbidities), and a logistical reason. †Patient found the taste of the study drug too bitter.

	Debio 1143 group (n=48)	Placebo group (n=48)
Age, years	57 (53–61; 39–70)	59 (56–63; 46–74)
Sex		
Male	37 (77%)	41 (85%)
Female	11 (23%)	7 (15%)
Smoking history		
Current or former smoker	48 (100%)	48 (100%)
Total pack-years	40 (30–45; 15–104)	40 (30–55; 11–90)
Alcohol history		
Drinks per week	21 (12–28; 1–50)	21 (12–35; 3–140)
ECOG performance status		
0	27 (56%)	27 (56%)
1	20 (42%)*	21 (44%)
Primary tumour localisation		
Hypopharynx	7 (15%)	10 (21%)
Larynx	8 (17%)	2 (4%)
Oral cavity	2 (4%)	3 (6%)
Oropharynx: HPV-16 negative	28 (58%)	28 (58%)
Proportion of the oropharynx population	28/31 (90%)	28/33 (85%)
Oropharynx: HPV-16 positive	3 (6%)	5 (10%)
Proportion of the oropharynx population	3/31 (10%)	5/33 (15%)
TNM stage		
III	7 (15%)	8 (17%)
IVa	35 (73%)	32 (67%)
IVb	6 (13%)	8 (17%)
Staging T—tumour stage		
T2	9 (19%)	12 (25%)
T3	21 (44%)	12 (25%)
T4a	14 (29%)	19 (40%)
T4b	4 (8%)	5 (10%)
Staging N—lymph nodes		
N0	4 (8%)	7 (15%)
N1	8 (17%)	6 (13%)
N2	32 (67%)	31 (65%)
N3	4 (8%)	4 (8%)
Staging M—metastases		
M0	48 (100%)	48 (100%)

Data are median (IQR; range), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. TNM=Tumour Node Metastasis. M0=no metastases. *One patient was ECOG 1 at screening (3 weeks before first dose), but was ECOG 3 on the first day of treatment.

Table 1: **Demographic and baseline characteristics of the intention-to-treat population**

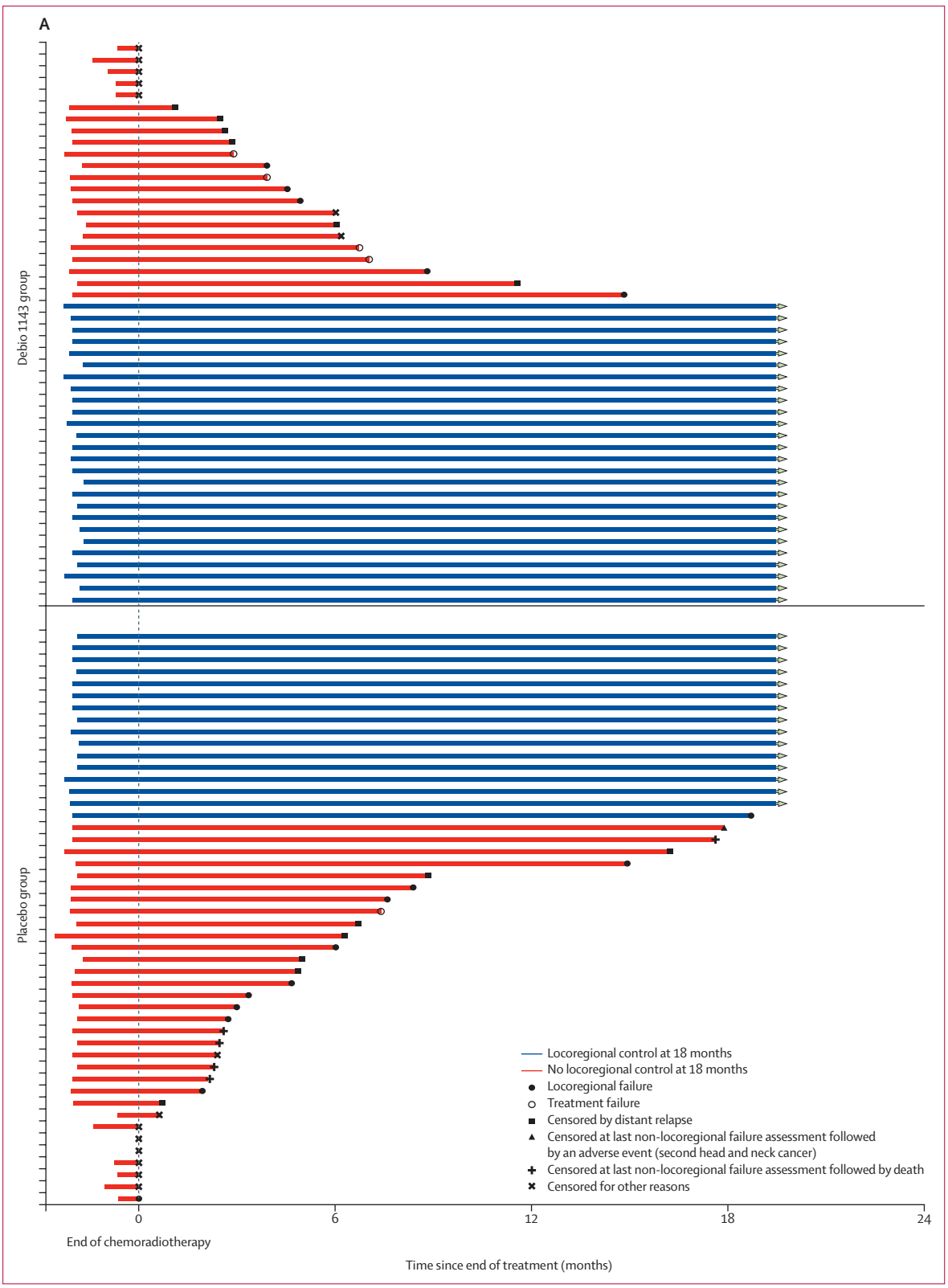
replaced with the date of randomisation. An interim analysis of progression-free survival and overall survival was done once all patients had completed at least 12 months of follow-up; the results were presented to the ESEC as well as an internal unblinded committee, but not shared with the study team or the investigators.

All data analyses were done with SAS (version 9.4) and Phoenix WinNonlin Professional (version 8.2).

This trial is registered with ClinicalTrials.gov, NCT02022098.

Role of the funding source

This study was funded by Debiopharm, in partnership with GORTEC. Debiopharm was responsible for data management, commissioning of laboratory investigations, and statistical analyses. The study was designed by Debiopharm, GORTEC, and the ESEC. Debiopharm was responsible for electronic case report form data collection; site monitoring was outsourced to a clinical research organisation. Data were analysed by an independent biostatistician from the ESEC. The internal unblinded committee, which included Debiopharm authors SS, ER, and AZ, had access to unblinded individual-level data after the 24-month analysis was completed. This committee had no further access to the clinical database, and no further involvement in study conduct after receiving the results of the interim analysis at 12 months. The funder interpreted the data in collaboration with the authors and supported the development of this report by commissioning medical



(Figure 2 continues on next page)

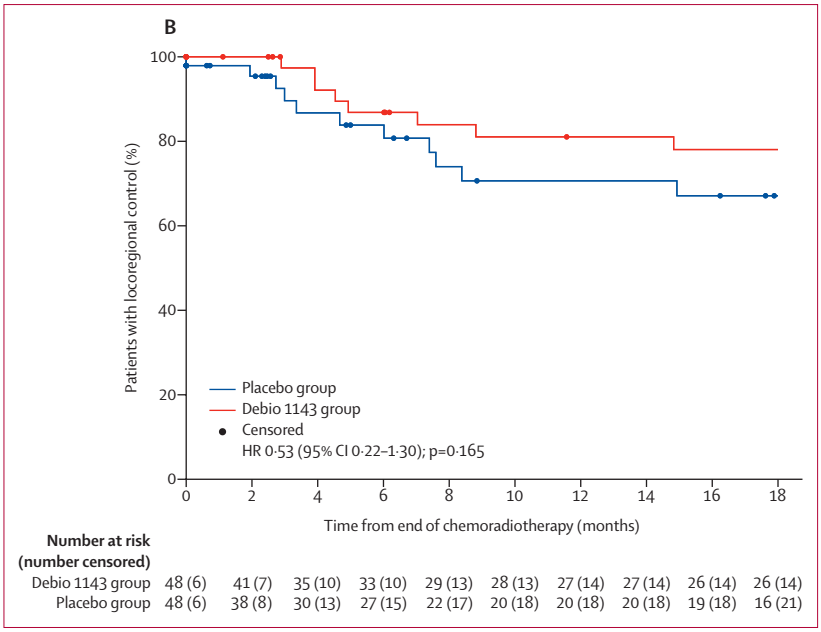


Figure 2: **Locoregional control in the intention-to-treat population**
(A) Swimmer plot of locoregional control data 18 months from the end of chemoradiotherapy (appendix p 4). (B) Kaplan-Meier estimates of duration of locoregional control. One patient in the placebo group had died of disease progression at the end of treatment (baseline timepoint). HR=hazard ratio.

See Online for appendix

writing assistance. Debiopharm authors had access to all raw blinded data from all hospitals, and all other authors, including the corresponding author, had access to raw blinded data from their own hospital. The corresponding author had the final responsibility for the decision to submit for publication.

Results

Between Jan 25, 2016, and April 24, 2017, 96 patients were enrolled and randomly assigned to the Debio 1143 group (n=48) or the placebo group (n=48); these patients constituted the intention-to-treat population. One patient from the placebo group did not receive study treatment; thus, 95 patients were included in the safety population (figure 1). Baseline characteristics are in table 1. Eight (17%) of 48 patients in the Debio 1143 group versus two (4%) of 48 patients in the placebo group had primary tumours of the larynx, and three (6%) patients in the Debio 1143 group versus five (10%) patients in the placebo group had HPV-positive oropharyngeal cancer, although disease stages, as well as tumour size and lymph node involvement, were well balanced.

Data cutoff was on July 15, 2019. Median duration of follow-up was 25·0 months (IQR 19·6–29·4) in the Debio 1143 group and 24·2 months (6·6–26·8) in the placebo group. The median total cumulative dose of Debio 1143 was 7425 mg (IQR 5180–8400) and that of placebo was 8200 (5600–8600). The median total cumulative dose of cisplatin was 288 mg/m² (IQR 200–300) in both groups, and 42 (88%) of 48 patients received two or more cycles of cisplatin in the Debio 1143 group versus 39 (82%) of 47 patients in the placebo group (appendix p 3). 28 (58%) patients in the Debio 1143 group and 25 (53%) patients in the placebo group received all three cycles of cisplatin. The median total cumulative dose of radiotherapy (intensity-modulated radiotherapy) delivered to the gross tumour volume was 70 Gy (IQR 70–70) in both groups, and the median dose delivered to the elective lymph nodes regionally was 51·8 Gy in both groups (IQR 50·0–54·4 in the Debio 1143 group and 50·0–51·8 in the placebo group). Seven (15%) of 48 patients discontinued treatment prematurely in the Debio 1143 group: four (8%) because of unacceptable toxicity, two (4%) because of withdrawal from the study, and one (2%) because the patient found the taste of the study drug too bitter. Six (12%) of 47 patients discontinued treatment prematurely in the placebo group: one (2%) because of unacceptable toxicity, three (6%) because of withdrawal from the study, and two (4%) because of discontinued radiotherapy.

At the 18-month timepoint, locoregional control was achieved and ongoing in 26 (54%; 95% CI 39–69) of 48 patients in the Debio 1143 group versus 16 (33%; 20–48) of 48 patients in the placebo group (odds ratio 2·69 [95% CI 1·13–6·42], p=0·026). No evidence of non-proportional hazards between the treatment groups was observed (appendix p 7). Kaplan-Meier estimates of locoregional control at 18 months after the end of chemoradiotherapy were 78% (95% CI 61–88) in the Debio 1143 group versus 67% (48–80) in the placebo group (a difference of 11% [–10 to 32]; p=0·311; figure 2; appendix p 8). The median duration of locoregional control was not reached in either treatment group (hazard ratio [HR] 0·53 [95% CI 0·22–1·30], p=0·165). Results of the sensitivity analysis of the primary endpoint in which patients with missing data were excluded from the analysis rather than treated as having treatment failure are presented in the appendix (p 4). Results of the sensitivity analysis of the primary endpoint in which locoregional control was measured from randomisation rather than from the end of chemoradiotherapy are presented in the appendix (p 8).

Median progression-free survival was not reached for the Debio 1143 group and was 16·9 months (95% CI 6·8 to not estimable) for the placebo group (HR 0·37 [95% CI 0·18–0·76], p=0·0069; figure 3A). 72% (95% CI 56–84) of patients in the Debio 1143 group compared with 41% (25–55) of patients in the placebo group were progression free at 24 months (difference 32% [11–53], p=0·0026). In the Debio 1143 group, five of the nine locoregional failures were progressions and four were treatment failures, compared with ten progressions and one treatment failure out of 11 locoregional failures in the placebo group. The number of events for progression-free survival in the Debio 1143 group was therefore 11 disease progressions (five locoregional, including one death, and six distant relapse) and no other deaths, whereas for the placebo group there were 24 events, consisting of 17 progressions

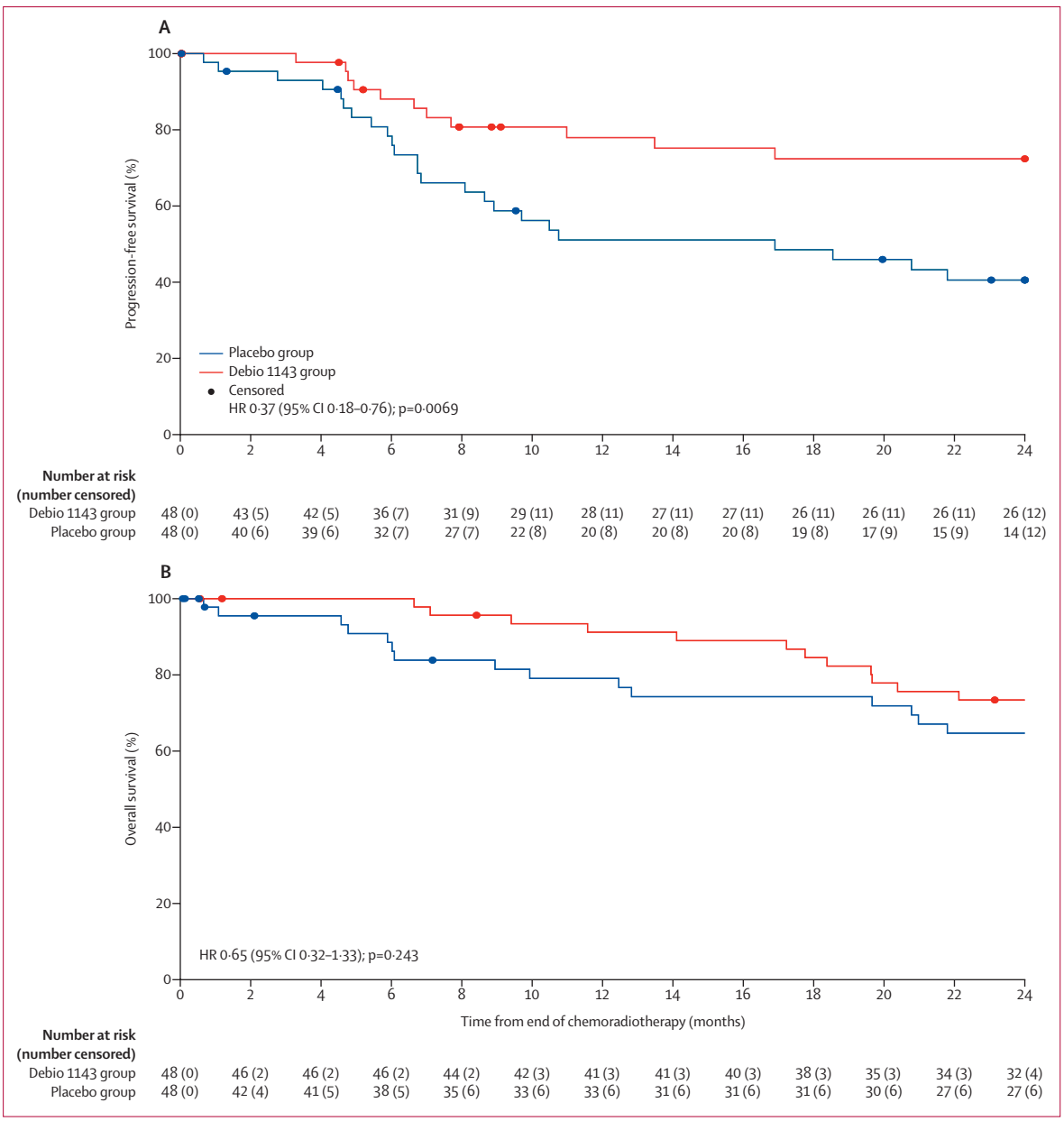


***Figure 3*: Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)**
HR=hazard ratio.

(ten locoregional and seven distant relapse) and seven deaths. Six (13%) patients had distant relapse events in the Debio 1143 group versus nine (19%) patients in the placebo group by data cutoff. At 18 months from end of chemoradiotherapy, 85% (95% CI 69–93) of patients in the Debio 1143 group compared with 71% (51–84) of patients in the placebo group had no distant relapse, with a difference of 14% (–6 to 34; p=0·172; appendix p 9). The median time to distant relapse was not reached in either treatment group for distant relapse (HR 0·57 [95% CI 0·20–1·60], p=0·286). A sensitivity analysis showed that, at 24 months from randomisation, Kaplan-Meier estimates of locoregional control were 78% (95% CI 61–88) for the Debio 1143 group versus 63% (43–77) for the placebo group; a difference of 15% (7–37; p=0·171). In this sensitivity analysis, the median duration of locoregional control was not reached in either group.

There was no significant difference in overall survival between treatment groups at 24 months (73% [95% CI 58–84] in the Debio 1143 group *vs* 65% [48–77] in the placebo group; HR 0·65 [0·32–1·33], p=0·243; figure 3B). In the Debio 1143 group, 14 (29%) patients died versus 17 (35%) in the placebo group; no deaths were considered to be treatment related. Median overall survival was not

	Debio 1143 group (n=48)				Placebo group (n=47)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	7 (15%)	32 (67%)	9 (19%)	0	6 (13%)	29 (62%)	10 (21%)	2 (4%)
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
Anaemia	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
Thrombocytopenia	7 (15%)	0	0	0	5 (11%)	3 (6%)	0	0
Leukopenia	5 (10%)	2 (4%)	0	0	3 (6%)	3 (6%)	1 (2%)	0
Diarrhoea	6 (13%)	1 (2%)	0	0	6 (13%)	0	0	0
GGT increased	5 (10%)	2 (4%)	0	0	4 (9%)	1 (2%)	0	0
Oropharyngeal pain	6 (13%)	1 (2%)	0	0	4 (9%)	0	0	0
Anxiety	7 (15%)	0	0	0	3 (6%)	0	0	0
Oral pain	5 (10%)	2 (4%)	0	0	1 (2%)	2 (4%)	0	0
Hypokalaemia	4 (8%)	2 (4%)	0	0	3 (6%)	1 (2%)	1 (2%)	0
Cough	5 (10%)	0	0	0	6 (13%)	0	0	0
Dysphonia	5 (10%)	0	0	0	6 (13%)	0	0	0
Hypoalbuminaemia	5 (10%)	0	0	0	5 (11%)	1 (2%)	0	0
Fungal infection	5 (10%)	0	0	0	3 (6%)	1 (2%)	0	0
Insomnia	5 (10%)	0	0	0	4 (9%)	0	0	0
White blood cell count decreased	1 (2%)	3 (6%)	1 (2%)	0	3 (6%)	0	0	0
Trismus	5 (10%)	0	0	0	0	1 (2%)	0	0
Alopecia	4 (8%)	0	0	0	7 (15%)	0	0	0
Headache	4 (8%)	0	0	0	5 (11%)	2 (4%)	0	0
Blood creatinine increased	4 (8%)	0	0	0	5 (11%)	1 (2%)	0	0
Blood urea increased*	3 (6%)	0	1 (2%)	0	4 (9%)	0	0	0
Oral candidiasis	4 (8%)	0	0	0	5 (11%)	0	0	0
Renal failure	3 (6%)	1 (2%)	0	0	5 (11%)	0	0	0
Salivary hypersecretion	4 (8%)	0	0	0	5 (11%)	0	0	0
Lipase increased	1 (2%)	3 (6%)	0	0	1 (2%)	0	0	0
Hypomagnesaemia	2 (4%)	1 (2%)	0	0	5 (11%)	2 (4%)	1 (2%)	0
Malnutrition	0	3 (6%)	0	0	5 (11%)	0	1 (2%)	0
Dyspnoea	3 (6%)	0	0	0	4 (9%)	1 (2%)	0	0

(Table 2 continues on next page)

	Debio 1143 group (n=48)				Placebo group (n=47)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Hypertension	1 (2%)	2 (4%)	0	0	1 (2%)	3 (6%)	0	0
Oesophagitis	0	3 (6%)	0	0	3 (6%)	1 (2%)	0	0
Polyuria	1 (2%)	2 (4%)	0	0	0	2 (4%)	1 (2%)	0
Chronic kidney disease	2 (4%)	1 (2%)	0	0	0	2 (4%)	0	0
Febrile neutropenia	0	2 (4%)	1 (2%)	0	0	1 (2%)	1 (2%)	0
Hyperglycaemia	2 (4%)	1 (2%)	0	0	0	0	1 (2%)	0
Lymphopenia	1 (2%)	1 (2%)	1 (2%)	0	0	0	0	0
Amylase increased	1 (2%)	1 (2%)	0	0	2 (4%)	2 (4%)	1 (2%)	0
Blood phosphorus decreased	1 (2%)	1 (2%)	0	0	2 (4%)	0	0	0
Dermatitis acneiform	1 (2%)	1 (2%)	0	0	2 (4%)	0	0	0
Confused mental state	2 (4%)	0	0	0	0	1 (2%)	0	0
Hyperamylasaemia	0	2 (4%)	0	0	0	0	0	0
Hyperlipasaemia	0	2 (4%)	0	0	0	0	0	0
Sepsis	0	1 (2%)	1 (2%)	0	0	0	0	0
Hyponatraemia	0	1 (2%)	0	0	3 (6%)	3 (6%)	0	0
Device-related infection	0	1 (2%)	0	0	1 (2%)	2 (4%)	0	0
Lymphocyte count decreased	0	0	1 (2%)	0	0	2 (4%)	0	0
Dehydration	0	1 (2%)	0	0	0	1 (2%)	0	0
Hyperuricaemia*	0	0	1 (2%)	0	0	0	0	0
Hypocalcaemia	1 (2%)	0	0	0	0	1 (2%)	0	0
Lung disorder	0	1 (2%)	0	0	0	1 (2%)	0	0
Neutrophil count decreased	0	0	1 (2%)	0	0	1 (2%)	0	0
Platelet count decreased	0	0	1 (2%)	0	1 (2%)	0	0	0
Aplasia	0	1 (2%)	0	0	0	0	0	0
Cerebrovascular accident	0	1 (2%)	0	0	0	0	0	0
Diabetic ketoacidosis	0	1 (2%)	0	0	0	0	0	0
Febrile bone marrow aplasia	0	1 (2%)	0	0	0	0	0	0
Gastrointestinal haemorrhage	0	1 (2%)	0	0	0	0	0	0
Hepatobiliary disease	0	1 (2%)	0	0	0	0	0	0
Hypoxia	0	1 (2%)	0	0	0	0	0	0
Loss of consciousness	0	1 (2%)	0	0	0	0	0	0
Lung infection	0	1 (2%)	0	0	0	0	0	0
Nutritional condition abnormal	0	1 (2%)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (2%)	0	0	0	0	0	0
Pyelonephritis	0	1 (2%)	0	0	0	0	0	0
Rash	0	1 (2%)	0	0	0	0	0	0
Staphylococcal infection	0	1 (2%)	0	0	0	0	0	0
Transitional cell carcinoma	0	1 (2%)	0	0	0	0	0	0
Ulcerative keratitis	0	1 (2%)	0	0	0	0	0	0
Hypophosphataemia	0	0	0	0	1 (2%)	1 (2%)	1 (2%)	0
Blood magnesium decreased	0	0	0	0	1 (2%)	1 (2%)	0	0
Blood potassium decreased	0	0	0	0	1 (2%)	1 (2%)	0	0
Hypotension	0	0	0	0	1 (2%)	1 (2%)	0	0
Asphyxia	0	0	0	0	0	0	0	1 (2%)
Central venous catheterisation	0	0	0	0	0	1 (2%)	0	0
Faecaloma	0	0	0	0	0	0	1 (2%)	0
Hepatic failure	0	0	0	0	0	0	1 (2%)	0
Hypoprothrombinaemia	0	0	0	0	0	1 (2%)	0	0

(Table 2 continues on next page)

	Debio 1143 group (n=48)				Placebo group (n=47)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Ischaemic stroke	0	0	0	0	0	0	1 (2%)	0
Mouth haemorrhage	0	0	0	0	0	1 (2%)	0	0
Multiple organ dysfunction syndrome	0	0	0	0	0	0	0	1 (2%)
N-terminal prohormone brain natriuretic peptide increased	0	0	0	0	0	1 (2%)	0	0
Osteonecrosis	0	0	0	0	0	0	1 (2%)	0
Parenteral nutrition	0	0	0	0	0	1 (2%)	0	0
Procedural pain	0	0	0	0	0	1 (2%)	0	0
Tongue haemorrhage	0	0	0	0	0	1 (2%)	0	0
Urine output decreased	0	0	0	0	0	1 (2%)	0	0

Data are n (%). Shown are treatment-emergent adverse events regardless of relation to study drugs of grade 1–2 occurring in at least 10% of patients and all grade 3, 4, and 5 events in the safety population. Treatment-emergent adverse events are coded by the Medical Dictionary for Regulatory Activities (version 19.0) and graded by worst severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Patients with two or more incidences of a particular adverse event are counted only once according to the maximum grade. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyltransferase. *Missing data for one patient in the placebo group.

Table 2: **Treatment-emergent adverse events in the safety population**

reached in either group by 24 months. Additional blinded follow-up is ongoing and will be reported elsewhere. The first tumour evaluation occurred approximately 11 weeks after chemoradiotherapy: a complete response was observed in 17 (35%) of 48 patients in both groups and a partial response was observed in 13 (27%) patients in the Debio 1143 group versus 15 (31%) patients in the placebo group (appendix p 5). At the subsequent tumour evaluation, 6 months after chemoradiotherapy, there was a complete response in 25 (52%) of 48 patients in the Debio 1143 group versus 18 (38%) of 48 in the placebo group, and a partial response in seven (15%) patients in the Debio 1143 group versus five (10%) patients in the placebo group (appendix pp 1, 5). Results on the duration of response are presented in the appendix (p 10).

Overall, the addition of Debio 1143 to chemoradiotherapy was well tolerated and consistent with the safety profile of chemoradiotherapy alone. Documented treatment-emergent adverse events are presented in table 2 and the appendix (pp 11–12). All patients had at least one treatment-related adverse event. Adverse events of grade 3 or worse were reported in 41 (85%) of 48 patients in the Debio 1143 group and 41 (87%) of 47 patients in the placebo group. The most common events were dysphagia, mucositis, and anaemia, with grade 3 occurrences of these three events being more frequent in the Debio 1143 group than in the placebo group. In the Debio 1143 group, nine (19%) patients had grade 4 events, and no patients had fatal adverse events. In the placebo group, grade 4 events were reported in ten (21%) patients, and two (4%) patients died (one from multiple organ failure and one from asphyxia). Serious treatment-emergent adverse events were recorded in 30 (63%) patients in the Debio 1143 group, the most common of which were mucositis in four (8%) patients, pyrexia in three (6%), and malnutrition in three (6%) patients. In the placebo group, serious treatment-emergent adverse events were recorded in 28 (60%) patients, the most common being acute kidney injury in five (11%) patients, pyrexia in four (9%) patients, and polyuria in three (6%) patients (appendix p 12).

Dose reductions of Debio 1143 and placebo due to adverse events were reported in two (4%) patients in the Debio 1143 group and in one (2%) patient in the placebo group. Full details of treatment modifications due to adverse events are in the appendix (p 15).

Debio 1143 treatment did not increase the frequency or severity of cisplatin-associated adverse events (renal insufficiency, febrile neutropenia, thrombocytopenia, peripheral sensory neuropathy, or severe vomiting), with the exception of grade 1–2 tinnitus in 15 (31%) patients versus ten (21%) in the placebo group. Grade 3 increases in aspartate aminotransferase and alanine aminotransferase were higher in the Debio 1143 group than in the placebo group (table 2); however, no association between aminotransferase increase and Debio 1143 exposure (in terms of area under the receiver operating characteristic curve) was clearly identified (data not shown). No grade 4 aminotransferase increases and no grade 3 bilirubin increases were reported in the Debio 1143 group. There was a higher incidence of grade 3 anaemia and a higher incidence of grade 4 neutropenia in the Debio 1143 group than in the placebo group. However, the frequencies of grade 3–4 febrile neutropenia reported as a treatment-emergent adverse event were similar between the two treatment groups (table 2). We found no significant difference in plasmatic carboxy-terminal collagen cross-

links peptide (appendix p 2) and no evidence of increased skeletal-related events between the treatment groups (data not shown).

Overall, the incidence of late toxicity was balanced between the groups (appendix p 12) and grade 3 or worse late toxicity was relatively rare in both treatment groups. Late toxicities were recorded in 35 (73%) of 48 patients in the Debio 1143 group and 31 (66%) of 47 patients in the placebo group. The most common late toxicities were xerostomia in 15 (31%) of 48 patients in the Debio 1143 group and 11 (23%) of 47 in the placebo group, and trismus in six (13%) of 48 patients and two (4%) of 47 patients, respectively. With regard to toxicities with potential for unblinding, we only observed minor differences in the frequency of treatment-emergent adverse events that were directly attributable to Debio 1143 (increases in aspartate aminotransferase, alanine aminotransferase, bilirubin, and lipase; appendix p 13). Treatment-emergent adverse events more frequently observed in the Debio 1143 group than in the placebo group were generally related to radiotherapy (dysphagia, mucositis, and anaemia). Furthermore, because of the small number of patients treated per site (only three sites recruited more than eight patients), the potential for unblinding at the level of a participating centre was negligible.

Changes in pharmacodynamic effects are shown in the appendix (p 16). In line with the dual mechanism of action of Debio 1143, an increase in the epithelial cell death marker (indicated by the area under the receiver operating characteristic curve of cytokeratin-18 M30 fragment) and an effect on NF-κB signalling (indicated by the increase in MCP-1 [also known as CCL2] and TNF concentrations) were observed in the Debio 1143 group. The results of the pharmacokinetic analyses are shown in the appendix (pp 15–16). Data relevant to the remaining secondary outcomes and the results of the per-protocol analyses are presented in the appendix (pp 4–10, 14).

Discussion

The key findings from our placebo-controlled, randomised study provide, to our knowledge, the first proof of concept that the addition of Debio 1143 to standard-of-care chemoradiotherapy resulted in superior clinical outcomes, compared with chemoradiotherapy alone, in a cohort of patients with non-resected, high-risk locoregionally advanced squamous cell carcinoma of the head and neck. Our results in this poor prognostic population suggest that inhibition of IAPs is a novel and promising approach in this patient group, and provides strong evidence that Debio 1143 has the potential to sensitise high-risk locoregionally advanced squamous cell carcinoma of the head and neck cancers to standard concurrent chemoradiotherapy without affecting treatment compliance or compromising patient safety.

Our primary endpoint of locoregional control at 18 months after treatment was initially based on the results of a systematic review of randomised trials of modified radiotherapy, in patients with head and neck cancer.[21] This review reported a significant correlation between locoregional control and overall survival, and suggested that a 10% improvement in 2-year (post-randomisation) locoregional control predicted a significant improvement (6·7%) in 5-year overall survival. A study of data from 93 randomised trials, in more than 17 000 patients with previously untreated squamous cell carcinoma of the head and neck, suggested that the majority of the benefit derived from concurrent platinum-based chemoradiotherapy is from improved locoregional control, even if event-free or progression-free survival were better indicators of patient benefit in larger chemoradiotherapy trials.[4] The available data analysis demonstrates that the improved locoregional control reported in our study is consistent with the findings of others and underscores the compelling improvement in progression-free survival reported here. Because the study is ongoing, the Kaplan-Meier analysis will be repeated with additional estimations, and the differences in the probability of locoregional control will be estimated at several later timepoints.

Median progression-free survival was 16·9 months in the placebo group and not yet reached in the Debio 1143 group (HR 0·37 [95% CI 0·18–0·76], p=0·0069), which is in line with the phase 1[17] part of our study (74% [95% CI 38–91]; data not shown). The overall survival data are not yet mature enough to be interpreted robustly; additional follow-up is ongoing, and these data will be published at a later date.

Although we acknowledge that our study population included a relatively high number of patients with ECOG performance status of 0, these patients were balanced, with 27 (56%) in each treatment group. The outcomes in our comparator group are consistent with those reported in two phase 3 studies in patients with intermediate-risk or high-risk locoregionally advanced squamous cell carcinoma of the head and neck.[22,23] Conducted in parallel within the GORTEC network, these studies recruited a patient population similar to that of our study in terms of primary tumours and tobacco smoking history. The similar results in the comparator groups suggest that the clinical benefits derived from the addition of Debio 1143 to standard therapy in our study are attributable to the novel regimen and not the result of unusually poor outcomes in our comparator group. The addition of Debio 1143 to chemoradiotherapy was feasible, with a predictable safety profile and a high compliance to both cisplatin and radiotherapy, without compromising delivery of these mainstay treatments. Indeed, more than half of the patients received all three cycles of cisplatin. Even with this high level of chemoradiotherapy compliance, the treatment safety profile was manageable. Dysphagia, mucositis, and anaemia were the most common adverse events in both treatment groups, with grade 3 events being more frequent in the Debio 1143 group. Although

these events should not be underestimated, they are not uncommon in patients receiving radiotherapy treatment. Moreover, grade 3 or worse late toxicity was relatively rare in both groups, potentially as a result of the high-quality planning and use of intensity-modulated radiotherapy in all treated patients. The most common late toxicities were xerostomia (balanced between groups) and trismus (slightly higher in the Debio 1143 group).

Despite preclinical observations suggesting that treatment with IAP antagonists might lead to increased bone resorption, we found no significant difference in plasmatic carboxy-terminal collagen crosslinks peptide (a marker of bone resorption) and no evidence of increased skeletal-related events among the treatment groups.

At the 24-month follow-up, information on the anticancer treatments administered following progression or relapse had not been systematically collected; these data will be collected retrospectively and during subsequent follow-up, and presented at a later date. Limitations of this study include the relatively small sample size, meaning that the study was not powered to detect differences in overall survival or in the Kaplan-Meier analysis of locoregional control; the use of a dichotomised locoregional control endpoint, resulting in loss of information in the timing of events; the high level of imputation for missing data in the dichotomised primary endpoint, leading to lower estimated rates of locoregional control at 18 months compared with the Kaplan-Meier estimates and also compared with those seen in the literature; and the fact that no centralised imaging review was done. However, local investigators and radiologists were masked with regard to treatment regimen and no toxicities with obvious unblinding potential were observed. Finally, the inclusion of only very few patients with HPV-positive oropharyngeal disease advocates caution in terms of generalising our findings to these patients.

In summary, the addition of concurrent Debio 1143 to standard-of-care chemoradiotherapy resulted in superior antitumour activity in this high-risk patient population without compromising the delivery of high-dose cisplatin or radiotherapy, and the safety profile of the combination was predictable and manageable. A confirmatory phase 3 study of Debio 1143 with standard chemoradiotherapy in patients with high-risk locoregionally advanced squamous cell carcinoma of the head and neck is warranted to expand the therapeutic options for these patients.

Contributors

X-SS, MA, LM, JM, J-FR, J-PD, PC, ER, KG, and SS contributed to data collection, data analysis, data interpretation, and writing of the manuscript. YT and M-CK contributed to data collection, data interpretation, and writing of the manuscript. CLT participated in the conception of the study, patient inclusion, data interpretation, and writing of the manuscript. YP, AC, PB, FR, JV, EG, FN, CL, GB, VC, and LG contributed to data collection and data interpretation. CS contributed to recruitment, randomisation, treatment, and follow-up of patients, study design, data collection, data analysis, data interpretation, and writing of the manuscript. FC contributed to data collection and writing of the manuscript. NM contributed to data collection, data analysis, and data interpretation. OE was involved in patient recruitment and treatment, data collection, writing of the manuscript, and approval of the final version of the submitted manuscript. BC contributed to data collection. AZ contributed to data interpretation and writing of the manuscript. CZ and JB contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript. SB contributed to the study design, data collection, and data analysis.

Declaration of interests

YT reports a grant from Debiopharm during the conduct of the submitted work and grants and other financial support from Merck Sharp & Dohme (MSD), Merck Serono, and Pfizer outside the submitted work. CLT reports personal fees outside the submitted work from MSD, Bristol-Myers Squibb (BMS), Merck Sereno, AstraZeneca, Rakuten, Nanobiotix, GlaxoSmithKline, Roche, and Celgene. M-CK receives personal fees from Novartis, Merck, EMD Sereno, AstraZeneca, and Merck outside the submitted work. FC reports a grant from AstraZeneca, and personal fees and non-financial support from Roche, BMS, Lilly, AstraZeneca, and Merck outside the submitted work. OE reports personal fees from MSD International, Merck Serono, and AstraZeneca outside the submitted work. AZ, CZ, SB, PC, ER, KG, and SS are employees of Debiopharm International. JB reports personal fees outside the submitted work from BMS, MSD, AstraZeneca, and Merck Serono. All other authors declare no competing interests.

Data sharing

Availability of the data underlying this publication will be determined according to Debiopharm's commitment to the European Federation of Pharmaceutical Industries and Associations–Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing. This pertains to scope, timepoint, and process of data access. As such, Debiopharm commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and EU as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the USA and EU regulatory agencies on or after Jan 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help to advance medical science or improve patient care. Information on the Debiopharm criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Debiopharm is not involved in the decisions made by the independent review panel. Debiopharm will take all necessary measures to ensure that patient privacy is safeguarded.

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