Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): a multicentre, open-label, randomised, phase 2 trial

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Summary

Background Results from a phase 2 trial of the TPEx chemotherapy regimen (docetaxel–platinum–cetuximab) showed promising results, with a median overall survival of 14·0 months in first-line recurrent or metastatic head and neck squamous-cell carcinoma (HNSCC). We therefore aimed to compare the efficacy and safety of the TPEx regimen with the standard of care EXTREME regimen (platinum–fluorouracil–cetuximab) in this setting.

Methods This was a multicentre, open-label, randomised, phase 2 trial, done in 68 centres (cancer centres, university and general hospitals, and private clinics) in France, Spain, and Germany. Eligible patients were aged 18–70 years with histologically confirmed recurrent or metastatic HNSCC unsuitable for curative treatment; had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1; and had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less. Participants were randomly assigned (1:1) using the TenAlea website by investigators or delegated clinical research associates to the TPEx regimen or the EXTREME regimen, with minimisation by ECOG performance status, type of disease evolution, previous cetuximab treatment, and country. The TPEx regimen consisted of docetaxel 75 mg/m² and cisplatin 75 mg/m², both intravenously on day 1, and cetuximab on days 1, 8, and 15 (intravenously 400 mg/m² on day 1 of cycle 1 and 250 mg/m² weekly subsequently). Four cycles were repeated every 21 days with systematic granulocyte colony-stimulating factor (G-CSF) support at each cycle. In case of disease control after four cycles, intravenous cetuximab 500 mg/m² was continued every 2 weeks as maintenance therapy until progression or unacceptable toxicity. The EXTREME regimen consisted of fluorouracil 4000 mg/m² on day 1–4, cisplatin 100 mg/m² on day 1, and cetuximab on days 1, 8, and 15 (400 mg/m² on day 1 of cycle 1 and 250 mg/m² weekly subsequently) all delivered intravenously. Six cycles were delivered every 21 days followed by weekly 250 mg/m² cetuximab as maintenance therapy in case of disease control. G-CSF support was not mandatory per the protocol in the EXTREME regimen. The primary endpoint was overall survival in the intention-to-treat population; safety was analysed in all patients who received at least one dose of chemotherapy or cetuximab. Enrolment is closed and this is the final analysis. This study is registered at ClinicalTrials.gov, NCT02268695.

Findings Between Oct 10, 2014, and Nov 29, 2017, 541 patients were enrolled and randomly assigned to the two treatment regimens (271 to TPEx, 270 to EXTREME). Two patients in the TPEx group had major deviations in consent forms and were not included in the final analysis. Median follow-up was 34·4 months (IQR 26·6–44·8) in the TPEx group and 30·2 months (25·5–45·3) in the EXTREME group. At data cutoff, 209 patients had died in the TPEx group and 218 had died in the EXTREME group. Overall survival did not differ significantly between the groups (median 14·5 months [95% CI 12·5–15·7] in the TPEx group and 13·4 months [12·2–15·4] in the EXTREME group; hazard ratio 0·89 [95% CI 0·74–1·08]; p=0·23). 214 (81%) of 263 patients in the TPEx group versus 246 (93%) of 265 patients in the EXTREME group had grade 3 or worse adverse events during chemotherapy (p<0·0001). In the TPEx group, 118 (45%) of 263 patients had at least one serious adverse event versus 143 (54%) of 265 patients in the EXTREME group. 16 patients in the TPEx group and 21 in the EXTREME group died in association with adverse events, including seven patients in each group who had fatal infections (including febrile neutropenia). Eight deaths in the TPEx group and 11 deaths in the EXTREME group were assessed as treatment related, most frequently sepsis or septic shock (four in each treatment group).

Interpretation Although the trial did not meet its primary endpoint, with no significant improvement in overall survival with TPEx versus EXTREME, the TPEx regimen had a favourable safety profile. The TPEx regimen could

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See Online for appendix

provide an alternative to standard of care with the EXTREME regimen in the first-line treatment of patients with recurrent or metastatic HNSCC, especially for those who might not be good candidates for up-front pembrolizumab treatment.

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Introduction

When this trial was initiated in 2014, the EXTREME regimen (platinum, fluorouracil, and cetuximab followed by weekly 250 mg/m² cetuximab maintenance) was considered the first-line standard treatment option in patients with recurrent or metastatic head and neck squamous-cell carcinoma (HNSCC) not suitable for locoregional curative treatment.[1,2] Treatment goals in this setting are to prolong survival and delay progression, while maintaining quality of life.[3] However, survival results with the EXTREME regimen were far from satisfactory, with median overall survival of 10·1 months and median progression-free survival of 5·6 months.[1] In this context, the development of new therapies is important to improve these outcomes. Several targeted therapies, tested alone or in combination, have failed to do so.[4–7] With the advent of immunotherapy, the standard of care EXTREME regimen was replaced in 2020 by pembrolizumab, which improves overall survival but not progression-free survival, alone or in combination with platinum and fluorouracil for patients with a PD-L1 combined positive score of 1 or more.[8,9] However, in some countries, such as the USA, pembrolizumab has also been approved for patients with a combined positive score of less than 1, even though subgroup analyses do not support benefit in these patients.[8–10]

On the basis of preclinical data suggesting a synergistic effect of taxanes and cetuximab,[11] combinations of taxanes and cetuximab with or without platinum have been studied with promising antitumour efficacy.[12–21] The GORTEC 2008-03 TPEx phase 2 study evaluating the TPEx regimen (four cycles of docetaxel in combination

Research in context

Evidence before this study

We searched prospective clinical trial publications, published in English and indexed in PubMed from Sept 1, 2008, to Sept 1, 2020, for the title or abstract terms "head and neck" and "carcinoma", or "cancer" and "first-line" and "recurrent", or "metastatic" and "randomised". The search returned 47 publications, most of which used chemotherapy–cetuximab-based combinations. When our trial was initiated in 2014, the EXTREME regimen (platinum, fluorouracil, and cetuximab followed by weekly cetuximab maintenance) was considered the first-line standard option in patients with recurrent or metastatic head and neck squamous-cell carcinoma (HNSCC) not suitable for locoregional curative treatment. However, survival results were far from satisfactory, and new therapies are needed to improve outcomes. With the advent of immunotherapy, the first-line standard of care EXTREME regimen was replaced by pembrolizumab, which improves overall survival but not progression-free survival, alone or in combination with platinum and fluorouracil for patients with a PD-L1 combined positive score of 1 or more. Based on preclinical data suggesting a synergistic effect of taxanes and cetuximab, combinations of taxanes with or without platinum and cetuximab have been studied with promising antitumour efficacy. The GORTEC 2008-03 TPEx phase 2 study evaluating four cycles of docetaxel in combination with cisplatin and cetuximab followed by cetuximab maintenance every 2 weeks (the TPEx regimen) showed promising results with a median overall survival of 14·0 months (which compared favourably with the EXTREME regimen). The substitution of fluorouracil by a taxane offered several advantages: shorter treatment duration, easier delivery in daily practice, and fewer contraindications than the standard fluorouracil–cisplatin combination used in the EXTREME regimen.

Added value of this study

This randomised trial assessed the efficacy and safety of the TPEx regimen in first-line treatment of patients with recurrent or metastatic HNSCC compared with the EXTREME regimen. We showed good survival results of the TPEx regimen, similar to those observed in the initial phase 2 trial, but did not show a significant improvement in overall survival compared with the EXTREME regimen. Compared with the EXTREME regimen, the TPEx regimen included a shorter course of chemotherapy (four cycles instead of six cycles), a less frequent cetuximab maintenance treatment schedule (every 2 weeks instead of weekly doses), and was better tolerated and provided better quality of life.

Implications of all the available evidence

Although our trial did not meet its primary endpoint, the results are informative and could potentially change practice, because the TPEx regimen could be an alternative to the EXTREME regimen in first-line treatment of patients with recurrent or metastatic HNSCC, especially for those with a negative PD-L1 combined positive score, those who might not be good candidates for up-front pembrolizumab because of immunologically relevant comorbidities, patients with high tumour burden or symptoms that mean a rapid response is a key treatment goal, or patients with contraindication to fluorouracil.

with cisplatin and cetuximab followed by 500 mg/m² cetuximab maintenance every 2 weeks) showed promising results, with a median overall survival of 14·0 months[19] (compared with the EXTREME regimen's median overall survival of about 10 months[1,8]). The substitution of fluorouracil by a taxane offered several advantages: shorter treatment duration, easier delivery in daily practice, and fewer contraindications than fluorouracil (which is contraindicated in patients with conditions such as dihydropyrimidine dehydrogenase deficiency and ischaemic cardiac disease).

Based on this rationale, our aim was to assess the efficacy and safety of the TPEx regimen in the first-line treatment of patients with recurrent or metastatic HNSCC compared with the standard of care EXTREME regimen.

Methods

Study design and participants

This was a multicentre, open-label, randomised, phase 2 trial, done in 68 centres (cancer centres, university and general hospitals, and private clinics) in France, Spain, and Germany (appendix pp 2–3). Eligible patients were aged 18–70 years; had histologically confirmed squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, with metastases or recurrence not suitable for locoregional curative treatment; had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less; were eligible to receive cisplatin; had clearance of creatinine more than 60 mL/min per 1·73 m² (by the Modification of Diet in Renal Disease method); absolute neutrophil count of more than $1·5\times10^9$ cells per L; platelet count of more than 100×10^9 per L; haemoglobin concentration of at least 9·5 g/dL; bilirubin concentration at or below the upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase concentrations of less than 1·5 times the ULN; and alkaline phosphatase concentration of less than 2·5 times the ULN. Exclusion criteria included: previous systemic chemotherapy for HNSCC (except if administered as part of a multimodal treatment for locally advanced disease more than 6 months before study entry); surgery or radiotherapy within the previous 6 weeks; previous dose of cisplatin more than 300 mg/m²; treatment with EGFR-targeting therapy within the previous 12 months; clinically significant cardiovascular disease; other malignancies within 5 years before randomisation, with the exception of adequately treated basal skin cancer and carcinoma in situ of the cervix; active infection requiring intravenous antibiotic drugs; tuberculosis infection; and HIV infection (complete list of inclusion and exclusion criteria are available in the protocol). All patients gave written informed consent before any study procedure.

The study was done in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and was approved by competent authorities and ethics committees in July, 2014 (France), October, 2014 (Spain), and May, 2015 (Germany). An international, independent data and safety monitoring committee, which included two oncologists and one statistician, monitored progress and interim analysis reports.

Randomisation and masking

Patients were randomly assigned (1:1) using the TenAlea website by investigators or delegated clinical research associates to receive the TPEx regimen or the EXTREME regimen with minimisation by ECOG performance status (0 *vs* 1), type of disease evolution (locoregional relapse alone *vs* metastatic disease), previous cetuximab treatment (no *vs* yes), and country (France *vs* Germany *vs* Spain). To avoid deterministic minimisation and assure allocation concealment, the treatment that minimised the imbalance was assigned with a probability of 0·80. Minimisation parameters were defined by the Gustave Roussy Biostatistics Unit (Villejuif, France) in the TenAlea system. Physicians and patients were not masked to treatment group.

For the **TenAlea system** see https://prod.tenalea.net/igr/dm/

Procedures

The TPEx regimen (appendix p 4) consisted of docetaxel 75 mg/m² as a 1 h intravenous infusion on day 1, cisplatin 75 mg/m² as a 1 h intravenous infusion on day 1, and cetuximab on days 1, 8, and 15 (400 mg/m² at 5 mg/min maximum speed intravenous infusion on day 1 of cycle 1 and 250 mg/m² at 10 mg/min maximum speed intravenous infusion weekly on subsequent administrations). Cetuximab infusion ended at least 1 h before the start of cisplatin followed by docetaxel infusion. Four cycles were repeated every 21 days with systematic granulocyte colony-stimulating factor (G-CSF; lenograstim was recommended, but filgrastim was also authorised according to local guidelines in investigational sites) support at each cycle. In case of disease control after four cycles, intravenous cetuximab 500 mg/m² was continued every 2 weeks as maintenance therapy until progression or unacceptable toxicity.

The EXTREME regimen (appendix p 4) consisted of fluorouracil 4000 mg/m² as a 96 h continuous intravenous infusion on days 1–4, cisplatin 100 mg/m² as a 1 h intravenous infusion on day 1, and cetuximab on days 1, 8, and 15 (400 mg/m² at 5 mg/min maximum speed intravenous infusion on day 1 of cycle 1 and 250 mg/m² at 10 mg/min maximum speed intravenous infusion weekly on subsequent administrations). Six cycles were delivered every 21 days followed by weekly 250 mg/m² cetuximab as maintenance therapy in case of disease control. According to the summary of product characteristics of cetuximab and standard recommendations, G-CSF support was not mandatory per protocol in the EXTREME group.

For the **protocol** see https://www.gortec.net/protocoles/TPExtreme_Protocole_V5.0_22_12_2016_version_finale.pdf

In both groups, in case of toxicity prohibiting chemotherapy continuation, maintenance with cetuximab could be started after two cycles of chemotherapy if patients had stable disease or an objective response.

Tumour response was assessed every 8 weeks after the start of treatment by CT scan for the neck, chest, and abdomen or MRI for the neck until disease progression. Determination of human papillomavirus (HPV) status for patients with oropharyngeal primary tumour was analysed centrally by chromogenic in-situ hybridisation (CISH) for DNA of HPV 16, HPV 18, and HPV 33. HPV DNA CISH has higher specificity than p16 expression by immunohistochemistry, with the trade-off of lower sensitivity in oropharyngeal primaries. Therefore, HPV DNA CISH was favoured for the study.

Health-related quality of life (QOL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire core module QLQ-C30 at baseline, and at weeks 12, 18, and 26.

Adverse event monitoring was done weekly during the chemotherapy phase and every 2 weeks during maintenance therapy using physical examination, check of vital signs, and blood sampling for haematological and biochemistry assessments. Adverse events were collected and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Occurrence of a severe infusion-related reaction required immediate and permanent discontinuation of cetuximab therapy. A grade 1, mild, transient reaction (transient flushing or rash or drug fever <38°C) required a decrease of the cetuximab infusion rate by 50% and close monitoring for any worsening; the infusion rate was further decreased if the reaction persisted. Modifications to the doses of chemotherapy were based on toxicity observed during the previous cycle. In case of neutropenia, thrombocytopenia grade 3–4, or both, without fever, docetaxel was stopped until normalisation. Chemotherapy was stopped for 7 days in case of fever higher than 38·5°C or a grade 3–4 adverse event; in these cases, further doses of docetaxel were reduced by 20%. Only two dose modifications were permitted per patient. Study treatment was definitively stopped in case of absence of normalisation at day 36 despite a previous decrease of docetaxel doses. Non-haematological chemotherapy-related toxicities had to be resolved to grade 0 (excluding skin reactions, paronychia, alopecia, fatigue, ototoxicity, or neurotoxicity, which must have resolved to grade ≤2). In case of cisplatin-related nephrotoxicity of grade 1 or worse, ototoxicity of grade 3 or worse, or neurotoxicity of grade 3 or worse, cisplatin was replaced by intravenous carboplatin with an area under the curve of 5 in the following cycles, with a maximum dose of 750 mg per cycle. Details on permitted dose modifications and adverse event monitoring are provided in the protocol. The only criterion for patient removal from the study was consent withdrawal.

Outcomes

The primary endpoint was overall survival, defined as the interval between randomisation and death from any cause. Secondary endpoints were progression-free survival, defined as the interval between randomisation and first disease progression (investigator assessed according to RECIST 1.1) or death, whichever occurred first; time to progression, defined as the minimum time from randomisation to progression, with censoring in case of death from a cause other than cancer without previous progression (investigator assessed); objective response rate (complete or partial response according to RECIST 1.1) at week 12 evaluated by independent central review; investigator-assessed best overall response according to RECIST 1.1 during treatment; QOL as assessed by the QLQ-C30 questionnaire; compliance with chemotherapy and cetuximab; and safety. A medico-economic study is ongoing, the results of which will be reported elsewhere.

Statistical analysis

Sample size was calculated for detecting a hazard ratio (HR) between the TPEx regimen and EXTREME regimen groups of 0·72 for death, which corresponds to an increase of median overall survival time from 10·1 months to 14·0 months. Under the assumption that deaths follow an exponential distribution, and at a two-sided level of statistical significance of 0·05, 374 deaths would provide 88% power, which would be expected to occur out of a total of 540 patients. Initially, the trial was designed with 80% power (that required 295 deaths and 416 patients), which was increased to 88% in December, 2016, because the rate of enrolment was high so a power increase was authorised without extending the accrual period. One interim futility analysis of overall survival was planned when around 50% of total expected deaths had occurred. The z-score futility boundary was constructed using the spending function of Lan-DeMets and was non-binding.

Time-to-event endpoints (overall survival, progression-free survival, and time to progression) were estimated using the Kaplan-Meier method. The 95% CIs of the point estimates at 12, 24, and 36 months of overall survival and progression-free survival were calculated with the Rothman method. HRs were estimated using the Cox model. Crude HRs and HRs from the Cox model stratified for country and adjusted for the other minimisation factors (ECOG performance status, type of disease evolution, and previous cetuximab treatment) are reported. The proportional hazards assumption for the Cox models was assessed by plotting the log-negative-log of the Kaplan-Meier estimates of the survival function versus the log of time and there was no indication that this assumption had been violated for overall survival or progression-free survival. The rate of objective response at week 12 by independent central review was estimated as the number of patients with complete or partial response among all patients with imaging provided by centres, even those with imaging that was not evaluable.

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The rate of best overall response by investigator assessment was estimated as the number of patients with complete or partial response at any time during treatment among all patients, even those who were not evaluable or not evaluated. Comparisons of these rates between treatment groups were done using a χ^2 test.

The proportion of patients receiving the planned number of chemotherapy cycles and the proportion of patients receiving the planned number of cetuximab administrations were compared between treatment groups using a χ^2 test.

Efficacy was analysed in the intention-to-treat population according to the randomly assigned treatment group. Safety was analysed in all patients who received at least one dose of chemotherapy or cetuximab. The protocol planned to use the χ^2 test to compare between the two groups the distribution of patients according to their worst adverse events into three categories (no adverse events, highest grade 1–2, highest grade ≥3). The scores of the different scales of the EORTC QLQ-C30 questionnaire were compared between the two groups using a mixed model for repeated measures of QOL and taking into account the baseline value before treatment.

Exploratory prespecified subgroup analyses of efficacy outcomes by baseline characteristics (sex; age; ECOG performance status; type of disease evolution; tumour location; and, in patients with oropharyngeal carcinoma, HPV DNA status) were done using the Cox model, including treatment group, baseline characteristic, and term for interaction between treatment group and baseline characteristic. Several post-hoc analyses were done: a sensitivity analysis of the primary endpoint excluding ineligible patients; a multivariable prognostic analysis of overall survival and progression-free survival; a comparison of overall survival between patients in second-line treatment by immunotherapy and by chemotherapy; and, in the EXTREME regimen group, comparison of the week 12 objective response rate and the best objective response rate, and an analysis of the association between G-CSF administration and overall survival. The multivariable prognostic analysis studied initial patient and tumour characteristics (age, sex, ECOG performance status, tobacco consumption, HPV DNA status, type of disease evolution, and previous cetuximab use) using the Cox model stratified for country.

All p values were two-sided at a significance level of 0·05. Only the comparison of overall survival between the groups is considered a confirmatory statistical test; all other statistical tests are supportive or of exploratory nature. Analyses were done with SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02268695.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

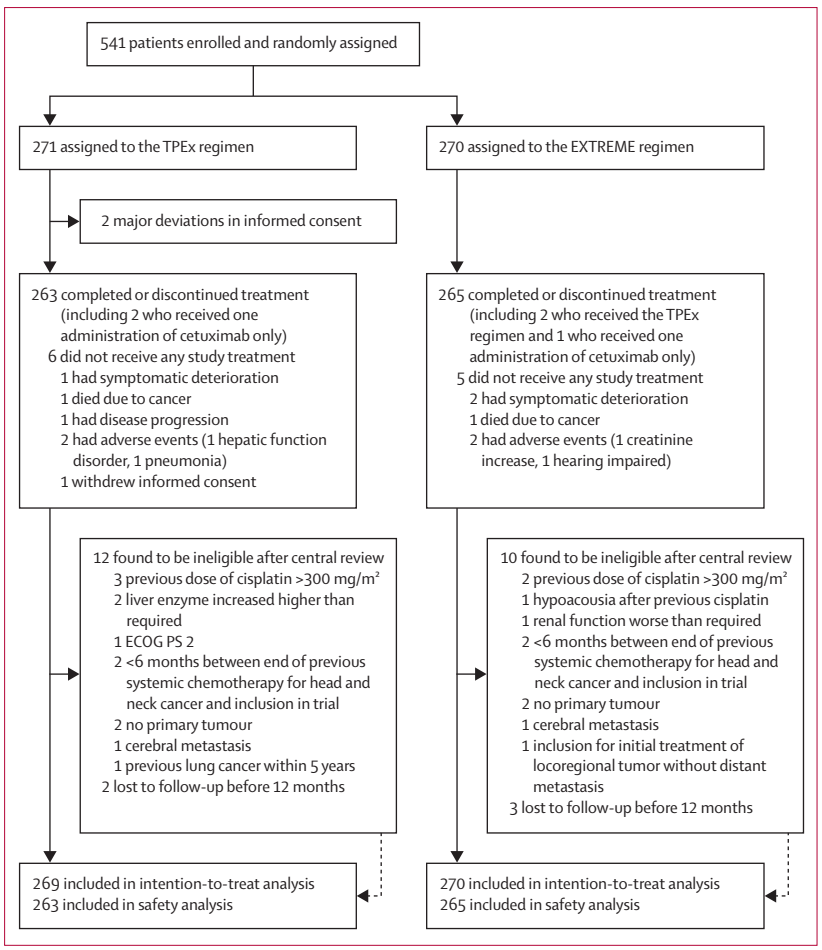


Figure 1: **Trial profile**
ECOG PS=Eastern Cooperative Oncology Group performance status. EXTREME=cisplatin, fluorouracil, and cetuximab. TPEx=docetaxel, cisplatin, and cetuximab.

Results

Between Oct 10, 2014, and Nov 29, 2017, 541 patients were enrolled and randomly assigned to the two treatment groups (TPEx regimen n=271, EXTREME regimen n=270). Major deviations in informed consent forms were noted for two patients in the TPEx group who were consequently removed from the study after starting treatment and were not included in the intention-to-treat analysis. 539 patients were included in the primary and secondary analyses (figure 1). Deviations from the eligibility criteria occurred in 22 patients; these patients were found to be ineligible on central review after randomisation but were still analysed as per the intention-to-treat principle (figure 1). Baseline characteristics are shown in table 1.

525 (97%) of 539 patients received at least one course of chemotherapy (figure 1). Two patients allocated to the EXTREME group received the TPEx regimen by mistake. These patients were included in the EXTREME group in all analyses.

An interim futility analysis was done on April 10, 2017, when 174 deaths had occurred (ie, 46·5% of the planned

	TPEx regimen group (n=269)	EXTREME regimen group (n=270)
Sex		
Female	29 (11%)	39 (14%)
Male	240 (89%)	231 (86%)
Age, years		
Median	60 (55–64)	60 (55–63)
≥65	56 (21%)	47 (17%)
ECOG performance status		
0	86 (32%)	86 (32%)
1	183 (68%)	184 (68%)
Regular alcohol consumption		
No	58 (22%)	77 (29%)
Yes (current or past)	206 (77%)	193 (71%)
Missing data	5 (2%)	0
Smoker		
No	14 (5%)	27 (10%)
Yes (current or former)	255 (95%)	243 (90%)
Primary tumour site		
Oropharynx	120 (45%)	96 (36%)
Oral cavity	57 (21%)	52 (19%)
Hypopharynx	54 (20%)	63 (23%)
Larynx	34 (13%)	57 (21%)
Multiple locations*	3 (1%)	0
Other	0	1 (<1%)
Unknown primary	1 (<1%)	1 (<1%)
Type of disease evolution at inclusion		
Metastasis alone	110 (41%)	118 (44%)
Locoregional relapse alone	94 (35%)	98 (36%)
Metastasis and locoregional relapse	65 (24%)	54 (20%)
Previous cancer treatment		
No	43 (16%)	53 (20%)
Yes	226 (84%)	217 (80%)
Previous platinum agent administration		
No	113 (42%)	130 (48%)
Yes	156 (58%)	140 (52%)
HPV DNA positivity among patients with oropharyngeal carcinoma†		
No	84/104 (81%)	62/76 (82%)
Yes	20/104 (19%)	14/76 (18%)

Data are n (%), median (IQR), n/N (%). Percentages might not total 100% due to rounding. ECOG=Eastern Cooperative Oncology Group. EXTREME=cisplatin, fluorouracil, and cetuximab. HPV=human papillomavirus. TPEx=docetaxel, cisplatin, and cetuximab. *Multiple initial locations including oropharyngeal site for two patients. †HPV DNA test was not done in 18 patients with oropharyngeal carcinoma in the TPEx regimen group and in 20 patients with oropharyngeal carcinoma in the EXTREME regimen group.

Table 1: **Patient characteristics**

deaths) among 393 patients randomly assigned until Jan 31, 2017: 195 in the TPEx group and 198 in the EXTREME group. Median follow-up was 13·2 months (IQR 6·6–18·2) in the TPEx group and 13·9 months (7·0–18·4) in the EXTREME group. 82 patients had died in the TPEx group and 92 patients had died in the EXTREME group. Median overall survival was 14·8 months (95% CI 11·5–17·1) in the TPEx group versus 13·3 months (12·6–15·8) in the EXTREME group. The crude HR for death was 0·91 (95% CI 0·67–1·22). The futility boundary was not crossed and the independent data safety monitoring committee recommended the trial to continue after this analysis.

At final analysis (data cutoff Nov 29, 2019), median follow-up was 34·4 months (IQR 26·6–44·8) in the TPEx group and 30·2 months (25·5–45·3) in the EXTREME group. At data cutoff, 427 patients had died: 209 in the TPEx group and 218 in the EXTREME group (deaths related to cancer n=161 in the TPEx group *vs* n=173 in the EXTREME group; deaths from unknown causes n=17 *vs* n=19; deaths from other causes n=31 *vs* n=26). Overall survival did not differ significantly between the groups (median overall survival 14·5 months [95% CI 12·5–15·7] in the TPEx group *vs* 13·4 months [12·2–15·4] in the EXTREME group; HR 0·89 [95% CI 0·74–1·08], p=0·23 [figure 2A]; adjusted HR 0·91 [0·75–1·10]).

At data cutoff, there were 503 disease progression events or deaths across both groups: 248 in the TPEx group (225 progression events and 23 deaths) and 255 in the EXTREME group (231 progression events and 24 deaths). Progression-free survival did not differ significantly between the groups (figure 2B); adjusted HR 0·90 (95% CI 0·75–1·07). Time to progression also did not differ significantly between the two groups (appendix p 7).

According to the independent central review of imaging examinations done at week 12, the rates of objective response did not differ significantly between the two groups: at week 12, 108 (57%) of 190 patients in the TPEx group had an objective response (eight complete response, 100 partial response) compared with 106 (59%) of 179 patients in the EXTREME group (11 complete response, 95 partial response; p=0·64). Best overall response was also not significantly different between treatment groups (p=0·89). Few patients progressed without any previous stabilisation or response in both groups (table 2).

Details of chemotherapy administration are in table 2 and in the appendix (pp 5–6). The median duration of chemotherapy was 11·1 weeks (IQR 9·0–11·3) in the TPEx group and 15·5 weeks (7·6–18·5) in the EXTREME group. The proportion of patients receiving the planned number of cycles was significantly higher in the TPEx group than in the EXTREME group (194 [72%] of 269 *vs* 119 [44%] of 270; p<0·0001). 92 (10%) of 907 chemotherapy cycles in the TPEx group were delayed, compared with 308 (27%) of 1143 in the EXTREME group. Doses of chemotherapy were less frequently reduced in the TPEx group than in the EXTREME group (appendix pp 5–6). Cisplatin was less frequently replaced by carboplatin in the TPEx group than in the EXTREME group; toxicity-related replacement of cisplatin with carboplatin was lower in the TPEx group than in the EXTREME group (16 patients [renal toxicities n=9, ototoxicities n=2, other toxicities n=5] *vs* 67 patients [renal toxicities n=31, ototoxicities n=10, other toxicities n=26]). More patients received the planned number of cetuximab administrations during chemotherapy in the

TPEx group than in the EXTREME group (137 [51%] of 269 *vs* 82 [30%] of 270; p<0·0001).

Among the patients who received chemotherapy, more started maintenance therapy in the TPEx group than the EXTREME group (p<0·0001; table 2). The main reasons patients did not receive maintenance therapy in both groups were adverse events and disease progression (appendix p 6). The median duration of maintenance was 14·1 weeks in both groups (IQR 8·1–30·0 in the TPEx group, 6·1–26·3 in the EXTREME group). 18 patients in the EXTREME group received cetuximab administrations every 2 weeks during maintenance therapy (instead of every week per protocol). Among patients who stopped maintenance, the main reason for maintenance discontinuation was disease progression in both groups (appendix p 6).

The proportion of QOL questionnaires returned was similar in the two groups: 247 (92%) of 269 expected at baseline, 153 (63%) of 242 expected at week 12, 100 (43%) of 232 expected at week 18, and 81 (38%) of 215 expected at week 26 in the TPEx group; 241 (89%) of 270 expected at baseline, 143 (59%) of 244 expected at week 12, 105 (46%) of 227 expected at week 18, and 81 (40%) of 205 expected at week 26 in the EXTREME group. The QOL results for all scores of the QLQ-C30 are in the appendix (pp 20–23). Better quality of life was seen in the TPEx group than in the EXTREME group for global health status, physical functioning, and role functioning, but no significant difference was seen between the groups for the remaining QLQ-C30 scores (appendix p 23).

Safety was assessed in 528 patients who received at least one dose of chemotherapy or cetuximab, 263 in the TPEx group and 265 in the EXTREME group (table 3; appendix pp 9–18). 37 patients died in association with adverse events: 16 (eight treatment related) in the TPEx group and 21 (11 treatment related) in the EXTREME group (for the full list of treatment-related deaths see appendix p 8). Seven patients in each group had fatal infections (including febrile neutropenia). Deaths assessed as treatment related were most frequently fatal infections, six in each group, including four sepsis or septic shock in each group. Although it was planned that safety would be assessed in three categories (no adverse events, highest grade 1–2, highest grade ≥3), because only one patient had no adverse events, this patient was analysed with patients with grade 1–2 adverse events. Fewer patients had at least one adverse event of grade 3 or worse in the TPEx group (214 [81%] of 263 patients) than in the EXTREME group (246 [93%] of 265 patients; p<0·0001). 95 (36%) of 263 patients in the TPEx group had adverse events of grade 4 or worse, compared with 138 (52%) of 265 patients in the EXTREME group. The most common grade 3 or worse adverse events were haematological events and electrolyte disturbances in both groups. These adverse events occurred less frequently in the TPEx group than in the EXTREME group: neutropenia (65 [25%] of 263 patients *vs* 130 [49%] of 265 patients), leukopenia

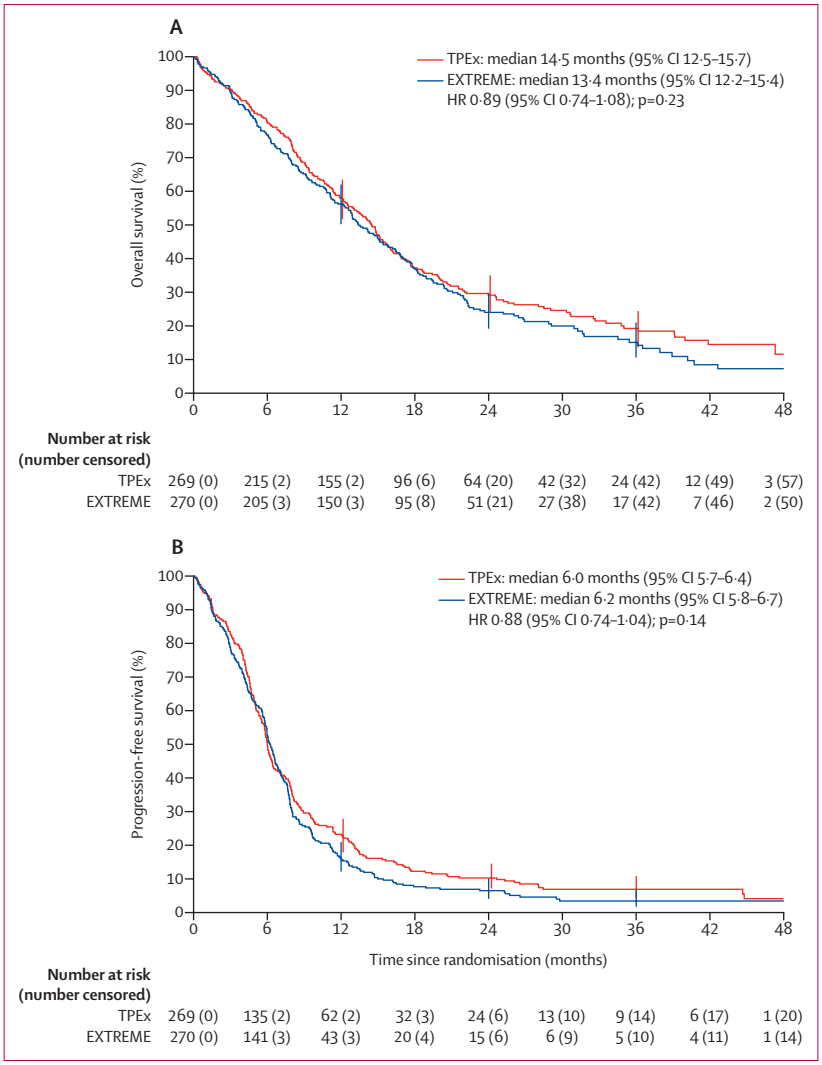


***Figure 2*: Kaplan-Meier estimates of overall survival and progression-free survival**
(A) Overall survival. (B) Progression-free survival. Point estimates of overall survival and progression-free survival at 12, 24, and 36 months with Rothman 95% CIs (vertical bars) are shown.

(60 [23%] *vs* 100 [38%]), thrombocytopenia (six [2%] *vs* 52 [20%]), anaemia (22 [8%] *vs* 53 [20%]), kalaemia disorder (25 [10%] *vs* 60 [23%]), and magnesaemia disorder (34 [13%] *vs* 58 [22%]). In the TPEx group, 118 (45%) of 263 patients had at least one serious adverse event versus 143 (54%) of 265 patients in the EXTREME group. We observed more hearing toxicity, of all grades combined, in the EXTREME group than in the TPEx group (table 3). The most common serious adverse events were infections (37 [14%] in the TPEx group *vs* 41 [15%] in the EXTREME group), febrile neutropenia (21 [8%] *vs* ten [4%]), vomiting (seven [3%] *vs* 20 [8%]), and general physical health deterioration (ten [4%] *vs* 17 [6%]; appendix p 19).

Post-hoc sensitivity analyses excluding the 22 non-eligible patients showed similar results to the main analyses for overall survival and progression-free

	TPEx regimen group (n=269)	EXTREME regimen group (n=270)
Number of chemotherapy cycles received		
0	8 (3%)	6 (2%)
1	23 (9%)	32 (12%)
2	27 (10%)	29 (11%)
3	16 (6%)	25 (9%)
4	194 (72%)	32 (12%)
5	1 (<1%)	27 (10%)
6	0 (<1%)	119 (44%)
Median	4 (3–4)	5 (3–6)
Reason for chemotherapy discontinuation*†		
End of chemotherapy period	191 (73%)	117 (44%)
Adverse event	31 (12%)	57 (22%)
Tumour progression	13 (5%)	35 (13%)
Death	10 (4%)	21 (8%)
Patient refusal or lost to follow-up	7 (3%)	19 (7%)
Other reason	8 (3%)	14 (5%)
Maintenance therapy with cetuximab†		
No	72 (28%)	126 (48%)
Yes	189 (72%)	138 (52%)
Best tumour response during treatment		
Complete response	25 (9%)	15 (6%)
Partial response	130 (48%)	139 (51%)
Stable disease	69 (26%)	62 (23%)
Progressive disease	21 (8%)	29 (11%)
Not evaluable or not evaluated	24 (9%)	25 (9%)

Data are n (%) or median (IQR). Percentages might not total 100% due to rounding. EXTREME=cisplatin, fluorouracil, and cetuximab. TPEx=docetaxel, cisplatin, and cetuximab. *Reason unknown for one patient in each group. †Reason for discontinuation and starting of maintenance therapy shown only in patients who started chemotherapy (TPEX n=261, EXTREME n=264).

Table 2: **Treatment and tumour response**

survival (crude HR for death 0·89 [95% CI 0·73–1·08], crude HR for progression events or deaths 0·89 [0·74–1·06]).

Prespecified exploratory subgroup analyses of overall survival and progression-free survival did not show a difference between groups according to sex, age, tumour location, type of evolution, or HPV status in patients with oropharyngeal carcinoma (figure 3). However, in patients with an ECOG performance status of 0, there was a greater difference in overall survival and progression-free survival between the TPEx regimen and the EXTREME regimen than in patients with an ECOG performance status of 1 (figure 3). In the EXTREME group, a post-hoc exploratory analysis comparing overall survival for patients who received G-CSF support during the chemotherapy phase with those who did not suggested that G-CSF support could improve overall survival (pp 28–29). In the EXTREME group, in the post-hoc analysis of the local investigator evaluation, 109 (40%) of 270 patients had an objective response at week 12, increasing to a best objective response in 154 (57%) patients during therapy. In a post-hoc multivariable analysis, independent prognostic factors for overall survival were ECOG performance status and HPV DNA status (appendix pp 24–25). Independent prognostic factors for progression-free survival were age, ECOG performance status, and type of evolution (appendix pp 24–25).

501 patients were evaluable for post-hoc analysis of second-line treatment: 245 in the TPEx group and 256 in the EXTREME group. 157 (64%) of 245 patients in the TPEx group received second-line treatment versus 164 (64%) of 256 patients in the EXTREME group. Overall

	TPEx regimen group (n=263)					EXTREME regimen group (n=265)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Any type of adverse event†	263 (100%)	260 (99%)	193 (73%)	87 (33%)	16 (6%)	264 (100%)	258 (97%)	231 (87%)	123 (46%)	21 (8%)
Blood system disorders										
Anaemia	204 (78%)	182 (69%)	19 (7%)	2 (1%)	1 (<1%)	216 (82%)	163 (62%)	51 (19%)	2 (1%)	0
Neutropenia	110 (42%)	45 (17%)	22 (8%)	43 (16%)	0	181 (68%)	51 (19%)	70 (26%)	60 (23%)	0
Leukopenia	118 (45%)	58 (22%)	38 (14%)	22 (8%)	0	171 (65%)	71 (27%)	77 (29%)	23 (9%)	0
Thrombocytopenia	98 (37%)	92 (35%)	4 (2%)	1 (<1%)	1 (<1%)	166 (63%)	114 (43%)	34 (13%)	18 (7%)	0
Febrile neutropenia	26 (10%)	2 (1%)	13 (5%)	8 (3%)	3 (1%)	16 (6%)	1 (<1%)	7 (3%)	8 (3%)	0
Metabolism and nutrition disorders										
Magnesaemia disorder	156 (59%)	122 (46%)	25 (10%)	9 (3%)	0	178 (67%)	120 (45%)	41 (15%)	17 (6%)	0
Kalaemia disorder	135 (51%)	110 (42%)	19 (7%)	6 (2%)	0	176 (66%)	116 (44%)	46 (17%)	14 (5%)	0
Calcaemia disorder	153 (58%)	138 (52%)	7 (3%)	8 (3%)	0	148 (56%)	132 (50%)	12 (5%)	4 (2%)	0
Natraemia disorder	127 (48%)	108 (41%)	17 (6%)	2 (1%)	0	142 (54%)	111 (42%)	28 (11%)	3 (1%)	0
Phosphataemia disorder	128 (49%)	108 (41%)	19 (7%)	1 (<1%)	0	140 (53%)	112 (42%)	25 (9%)	3 (1%)	0
Hyperglycaemia	48 (18%)	46 (17%)	2 (1%)	0	0	64 (24%)	52 (20%)	9 (3%)	3 (1%)	0
Anorexia	86 (33%)	73 (28%)	13 (5%)	0	0	85 (32%)	70 (26%)	14 (5%)	1 (<1%)	0
Weight loss	52 (20%)	50 (19%)	2 (1%)	0	0	58 (22%)	54 (20%)	4 (2%)	0	0

(Table 3 continues on next page)

	TPEx regimen group (n=263)					EXTREME regimen group (n=265)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)										
Investigations										
Gamma-glutamyltransferase increased	115 (44%)	104 (40%)	11 (4%)	0	0	139 (52%)	123 (46%)	12 (5%)	4 (2%)	0
Serum albumin decreased	137 (52%)	132 (50%)	5 (2%)	0	0	133 (50%)	125 (47%)	8 (3%)	0	0
Alkaline phosphatase increased	64 (24%)	64 (24%)	0	0	0	66 (25%)	66 (25%)	0	0	0
Alanine aminotransferase increased	58 (22%)	57 (22%)	1 (<1%)	0	0	58 (22%)	57 (22%)	0	1 (<1%)	0
Aspartate aminotransferase increased	56 (21%)	55 (21%)	1 (<1%)	0	0	54 (20%)	51 (19%)	1 (<1%)	2 (1%)	0
Creatinine increased	69 (26%)	60 (23%)	4 (2%)	4 (2%)	1 (<1%)	119 (45%)	98 (37%)	17 (6%)	4 (2%)	0
General disorders										
Fatigue	179 (68%)	144 (55%)	34 (13%)	1 (<1%)	0	195 (74%)	147 (55%)	47 (18%)	1 (<1%)	0
Fever	31 (12%)	25 (10%)	5 (2%)	0	1 (<1%)	32 (12%)	29 (11%)	2 (1%)	1 (<1%)	0
General physical health deterioration	12 (5%)	4 (2%)	7 (3%)	0	1 (<1%)	21 (8%)	5 (2%)	14 (5%)	2 (1%)	0
Allergic reaction	12 (5%)	6 (2%)	3 (1%)	3 (1%)	0	20 (8%)	7 (3%)	7 (3%)	5 (2%)	1 (<1%)
Skin and subcutaneous tissue disorders										
Rash acneiform	168 (64%)	156 (59%)	11 (4%)	1 (<1%)	0	167 (63%)	150 (57%)	16 (6%)	1 (<1%)	0
Dry skin	74 (28%)	74 (28%)	0	0	0	72 (27%)	71 (27%)	1 (<1%)	0	0
Palmar–plantar erythrodysesthesia syndrome	28 (11%)	25 (10%)	3 (1%)	0	0	36 (14%)	32 (12%)	4 (2%)	0	0
Alopecia	60 (23%)	58 (22%)	1 (<1%)	1 (<1%)	0	31 (12%)	31 (12%)	0	0	0
Gastrointestinal disorders										
Mucositis oral	122 (46%)	102 (39%)	16 (6%)	4 (2%)	0	153 (58%)	118 (45%)	34 (13%)	1 (<1%)	0
Nausea	135 (51%)	125 (48%)	10 (4%)	0	0	173 (65%)	145 (55%)	28 (11%)	0	0
Vomiting	84 (32%)	74 (28%)	9 (3%)	1 (<1%)	0	116 (44%)	87 (33%)	29 (11%)	0	0
Diarrhoea	116 (44%)	102 (39%)	14 (5%)	0	0	94 (35%)	77 (29%)	16 (6%)	1 (<1%)	0
Constipation	61 (23%)	61 (23%)	0	0	0	76 (29%)	75 (28%)	1 (<1%)	0	0
Dysphagia	33 (13%)	24 (9%)	9 (3%)	0	0	48 (18%)	32 (12%)	16 (6%)	0	0
Infection (any type)	90 (34%)	48 (18%)	29 (11%)	8 (3%)	5 (2%)	89 (34%)	43 (16%)	29 (11%)	10 (4%)	7 (3%)
Ear disorders										
Tinnitus	14 (5%)	13 (5%)	1 (<1%)	0	0	33 (12%)	30 (11%)	3 (1%)	0	0
Hearing impairment or hypoacusis	10 (4%)	9 (3%)	1 (<1%)	0	0	30 (11%)	24 (9%)	6 (2%)	0	0
Other events										
Hypotension	22 (8%)	17 (6%)	5 (2%)	0	0	25 (9%)	19 (7%)	6 (2%)	0	0
Peripheral sensory neuropathy	29 (11%)	28 (11%)	1 (<1%)	0	0	26 (10%)	25 (9%)	1 (<1%)	0	0
Dyspnoea	25 (10%)	17 (6%)	4 (2%)	2 (1%)	2 (1%)	32 (12%)	28 (11%)	2 (1%)	1 (<1%)	1 (<1%)

Data are n (%). Percentages might not total 100% due to rounding. EXTREME=cisplatin, fluorouracil, and cetuximab. TPEx=docetaxel, cisplatin, and cetuximab. *Includes grade 1 or 2 adverse events occurring in ≥10% of patients in either group, and grade 3, 4, or 5 adverse events occurring in ≥2% patients in either group. A complete list of grade 3–5 adverse events is in the appendix (pp 9–18). †Patients who had different adverse events of different grades are counted in each grade for which they had at least one adverse event; therefore, the number of patients with adverse events of any grade is not the sum of patients with adverse events of grades 1–2, 3, 4, and 5.

Table 3: **Adverse events during the chemotherapy phase***

survival results were encouraging in patients who received TPEx or EXTREME followed by immunotherapy. Detailed results of the post-hoc analysis of second-line treatment are in the appendix (pp 26–27).

Discussion

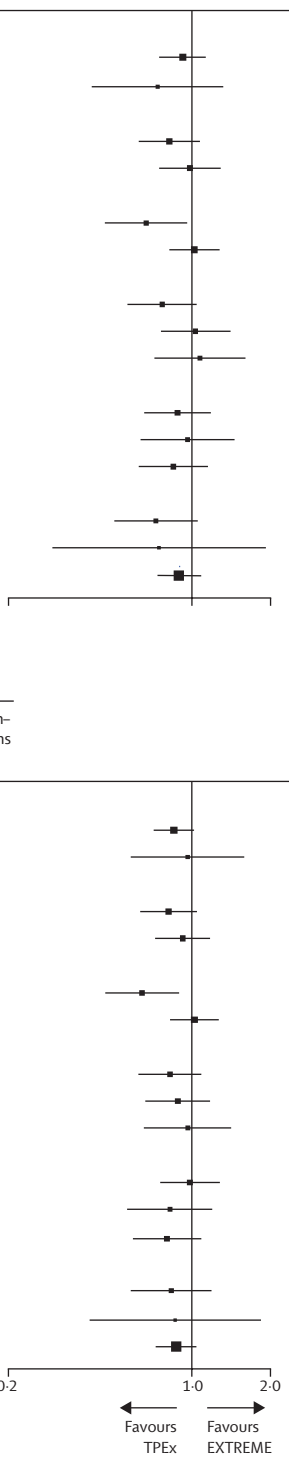
Our study did not show a benefit of TPEx compared with EXTREME in terms of overall survival in patients with recurrent or metastatic HNSCC, and the primary objective was not met. However, median overall survival of patients in the TPEx group was long (14·5 months), in line with our previous phase 2 trial.[19] In the EXTREME group, median overall survival was also long (13·4 months), compared with the median overall survival of 10·1 months with the EXTREME regimen in the trial by Vermorken and colleagues.[1] There is no clear reason for such a variation in median overall survival beyond possible gradual improvements of outcomes due to improved supportive care since the previous study in 2008, but several differences between the two studies can be emphasised. First, initial treatments received before trial enrolment differed between the two studies: 41% of patients in Vermorken and colleagues' study[1] were exposed to a previous platinum drug, compared with 52% in our EXTREME regimen group. Improved imaging technology in the past few years (CT and PET scans) could have led to

A

	TPEx		EXTREME		Hazard ratio (95% CI)	p value
	Deaths/ patients	Median overall survival, months (95% CI)	Deaths/ patients	Median overall survival, months (95% CI)		
Sex						
Male	189/240	14·1 (12·2–15·4)	190/231	13·4 (11·5–15·8)	0·91 (0·74–1·11)	0·53
Female	20/29	19·9 (11·0–32·7)	28/39	13·6 (8·5–20·4)	0·73 (0·41–1·32)	
Age, years						
<60	94/127	14·1 (11·4–15·9)	109/133	12·9 (11·1–15·4)	0·81 (0·62–1·07)	0·39
≥60	115/142	14·8 (12·4–17·2)	109/137	15·0 (11·3–17·3)	0·97 (0·74–1·26)	
ECOG performance status						
0	56/86	20·9 (14·9–33·5)	67/86	17·6 (15·0–21·7)	0·66 (0·46–0·95)	0·072
1	153/183	12·5 (9·8–14·8)	151/184	11·3 (9·2–13·6)	1·01 (0·81–1·27)	
Tumour location						
Oropharynx	89/123	15·2 (12·5–17·6)	76/96	12·5 (9·6–15·8)	0·76 (0·56–1·04)	0·28
Larynx or hypopharynx	71/88	14·1 (11·5–17·4)	97/120	15·0 (12·9–17·8)	1·02 (0·75–1·39)	
Oral cavity or other	49/58	11·3 (9·1–15·2)	45/54	12·6 (8·5–17·6)	1·06 (0·71–1·60)	
Type of evolution						
Metastasis alone	80/110	14·5 (11·3–18·7)	93/118	16·4 (12·8–18·2)	0·87 (0·65–1·18)	0·91
Metastasis and locoregional relapse	53/65	11·5 (8·0–15·2)	42/54	9·6 (6·3–15·8)	0·95 (0·63–1·43)	
Locoregional relapse alone	76/94	15·1 (12·6–16·9)	83/98	12·9 (9·3–15·4)	0·84 (0·62–1·15)	
HPV status in patients with oropharyngael carcinoma						
HPV DNA negative	64/84	14·5 (11·1–16·9)	53/62	11·3 (8·6–15·2)	0·72 (0·50–1·04)	0·99
HPV DNA positive	10/20	36·2 (15·2–NR)	8/14	21·1 (9·6–NR)	0·74 (0·29–1·88)	
Overall	**209/269**	**14·5 (12·5–15·7)**	**218/270**	**13·4 (12·2–15·4)**	**0·89 (0·74–1·08)**	

B

	TPEx		EXTREME		Hazard ratio (95% CI)	p value
	Events/ patients	Median progression–free survival, months (95% CI)	Events/ patients	Median progression–free survival, months (95% CI)		
Sex						
Male	221/240	6·0 (5·6–6·4)	220/231	6·1 (5·8–6·6)	0·86 (0·72–1·04)	0·72
Female	27/29	6·3 (4·7–8·8)	35/39	7·3 (5·6–8·0)	0·97 (0·59–1·61)	
Age, years						
<60	113/127	6·1 (5·4–7·7)	124/133	6·2 (5·6–6·8)	0·82 (0·64–1·06)	0·38
≥60	135/142	5·8 (5·1–6·4)	131/137	6·5 (5·6–7·1)	0·93 (0·73–1·19)	
ECOG performance status						
0	74/86	8·1 (6·1–9·7)	81/86	6·6 (5·8–7·7)	0·65 (0·47–0·90)	0·021
1	174/183	5·5 (4·7–6·0)	174/184	6·0 (5·1–6·9)	1·03 (0·83–1·27)	
Tumour location						
Oropharynx	110/123	6·0 (5·3–7·1)	90/96	6·1 (5·1–6·9)	0·83 (0·63–1·10)	0·71
Larynx or hypopharynx	83/88	6·1 (4·9–7·9)	114/120	6·4 (5·7–7·2)	0·89 (0·67–1·19)	
Oral cavity or other	55/58	5·9 (5·1–8·0)	51/54	6·4 (4·7–7·9)	0·97 (0·66–1·42)	
Type of evolution						
Metastasis alone	103/110	5·8 (5·0–6·1)	114/118	6·6 (6·0–7·1)	0·99 (0·76–1·30)	0·57
Metastasis and locoregional relapse	61/65	5·6 (4·3–6·5)	49/54	5·1 (4·0–6·5)	0·83 (0·57–1·21)	
Locoregional relapse alone	84/94	7·8 (6·0–8·6)	92/98	6·2 (4·8–7·8)	0·81 (0·60–1·09)	
HPV status in patients with oropharyngael carcinoma						
HPV DNA negative	75/84	6·2 (5·5–7·9)	58/62	6·1 (4·7–7·7)	0·84 (0·59–1·18)	0·91
HPV DNA positive	17/20	6·3 (4·5–21·6)	12/14	6·2 (4·4–12·7)	0·87 (0·41–1·84)	
Overall	**248/269**	**6·0 (5·7–6·4)**	**255/270**	**6·2 (5·8–6·7)**	**0·88 (0·74–1·04)**	



earlier detection of relapse or metastases in our study (47% of patients presented with metastases in Vermorken and colleagues' study[1] *vs* 64% in our EXTREME group). Second, patients with an ECOG performance status of 2 were excluded from our study, whereas they represented 12% of patients in Vermorken and colleagues' study.[1] Third, G-CSF administration, which was mandatory in the TPEx group in our study, was also used in 43% of patients (33% of the cycles) in the EXTREME group. Our study was done in countries with widespread experience with the EXTREME regimen, and perhaps more routine use of G-CSF in this setting. An exploratory analysis suggested an increased overall survival for patients who received G-CSF support during the chemotherapy phase, compared with those who did not. This outcome could be related to a decreased toxicity of the chemotherapy–cetuximab combination, and in favour of a systematic use of G-CSF support. In agreement with the overall survival analysis, progression-free survival and objective response rates did not differ between the two groups. In both groups, the proportion of patients who had disease progression without any previous stabilisation or response was very low (8% in the TPEx group *vs* 11% in the EXTREME group). However, the substitution of fluorouracil by docetaxel in the TPEx regimen led to interesting findings regarding compliance and toxicity. Treatment compliance was better in the TPEx group than the EXTREME group, with significantly more delays in chemotherapy, more dose adjustments, and more frequent switch to carboplatin in the EXTREME group. Carboplatin switches could cause an excess of haematological toxicity in this group, even higher than that found by Vermorken and colleagues.[1] The fact that all patients in our study started with cisplatin might have affected the safety profile by causing a higher electrolyte toxicity than in the study by Vermorken and colleagues. The better compliance in the TPEx group compared with the EXTREME group was observed even during the first four cycles of treatment. The TPEx regimen was shorter and the proportion of patients who received the planned treatment was significantly higher than in the EXTREME group, with a significantly higher proportion of patients entering the maintenance phase. Another advantage of the TPEx regimen, other than limiting the chemotherapy at four cycles, is the cetuximab maintenance every 2 weeks instead of weekly, which reduces patient constraints without jeopardising efficacy.

TPEx was also substantially less toxic than EXTREME and patients in the TPEx group had fewer adverse events of grade 3 or worse, which might be due in part to more G-CSF support, the substitution of fluorouracil by docetaxel, and a lower dose of cisplatin. However, the TPEx regimen is still a chemotherapy-based regimen with clinically significant toxicities and should be reserved for fit patients in whom a rapid tumour response is needed. Consistent with the toxicity results and with the shorter duration of chemotherapy, analysis of QOL also suggested benefits in some scales on the QLQ-C30 (global health status, physical functioning, and role functioning) in favour of TPEx compared with EXTREME, with the other scales showing no significant differences between the groups.

Other first-line taxane-based combinations such as paclitaxel–carboplatin with cetuximab have been tested in several studies but have not been compared against the standard of care in large randomised trials as has been done in our trial. These studies also showed promising safety and efficacy results for fit or unfit patients.[21]

PD-1 inhibition has previously shown promising results[22] in the second-line treatment of recurrent or metastatic HNSCC. In 2019, the Keynote 048 randomised phase 3 trial[8] compared the EXTREME regimen with pembrolizumab alone or pembrolizumab combined with platinum–fluorouracil and reported significant overall survival improvements in both pembrolizumab groups for patients with a combined positive score for PD-L1 expression of 1 or more compared with the EXTREME group (median overall survival in the patient population with a combined positive score for PD-L1 expression of 1 or more: pembrolizumab alone 12·3 months; cisplatin–fluorouracil–pembrolizumab 13·6 months; EXTREME 10·4 months), although there were no significant differences in progression-free survival across the three groups.[8–10] Consequently, the EXTREME regimen was replaced in 2020 by this new standard of care of pembrolizumab alone or combined with platinum and fluorouracil for patients with a PD-L1 combined positive score of 1 or more.

Our study has some limitations. The proportion of patients in our population who were HPV DNA positive was low, and possibly somewhat underestimated by the HPV DNA test used. However, the study was done in countries where most patients with HNSCC are current or former smokers, with a lower HPV incidence compared with the USA or Scandinavia. The trial was designed for efficacy, not for non-inferiority because of the very promising overall survival results obtained in the initial phase 2 study (median overall survival of 14·0 months[19]) compared with the median overall survival of 10·1 months with the EXTREME regimen at that time. However, overall survival in the EXTREME group in our trial was much longer than previously reported and expected. Long-term data on QOL are not available, because QOL questionnaires were only completed until week 26, but this fully covered the period of chemotherapy as well as the early maintenance treatment phase. The study was started before the introduction of

Figure 3: **Subgroup analysis of overall survival and progression-free survival**
(A) Overall survival. (B) Progression-free survival. The area of each square is proportional to the number of events in the subgroup. ECOG=Eastern Cooperative Oncology Group. EXTREME=cisplatin, fluorouracil, cetuximab. HPV=human papillomavirus. NR=not reached. TPEx=docetaxel, cisplatin, cetuximab.

immunotherapy for HNSCC and the EXTREME regimen is no longer the standard of care for all patients in this setting. However, pembrolizumab alone or combined with platinum–fluorouracil is not available for all patients with recurrent or metastatic HNSCC and is not beneficial to all patients. The European Medicines Agency did not approve pembrolizumab alone or added to platinum–fluorouracil for patients with a negative PD-L1 combined positive score.[9]

Based on all these data, the TPEx regimen might offer an alternative to the EXTREME regimen in first-line treatment of many patients with recurrent or metastatic HNSCC, especially for those with a negative PD-L1 combined positive score, those who might not be good candidates for up-front pembrolizumab due to immunologically relevant comorbidities, patients with a high tumour burden or symptoms that mean a rapid response is a key treatment goal,[10] or for patients with contraindication to fluorouracil. The post-hoc analysis on second-line therapies showed good overall survival results for patients in the TPEx group who received second-line immunotherapy with PD-1 inhibitors or PD-L1 inhibitors (median overall survival 21·9 months). Although this was a post-hoc analysis, this is an interesting finding and suggests that a treatment sequence of TPEx followed by anti-PD-1 or anti-PD-L1 requires further testing. Alternatively, inhibitors of PD-1 or PD-L1 could be introduced earlier into the TPEx regimen in association with cetuximab in the maintenance phase.

In conclusion, this randomised trial confirmed the good survival results of the TPEx regimen previously observed in the initial phase 2 trial. Compared with the EXTREME regimen, TPEx did not show a significant benefit in overall survival, but was a shorter and better-tolerated treatment regimen, and showed a better QOL. The TPEx regimen might offer an alternative to the EXTREME regimen or pembrolizumab in first-line treatment of fit patients with recurrent or metastatic HNSCC.

Contributors

JG, AA, and JB contributed to the conception and design of the study and statistical analysis plan, and have accessed and verified the data. AA did the statistical analyses. CC-C assembled the data and has accessed and verified the data. AF has accessed and verified the data and took part in the statistical analyses. JG, JF, ES-B, CL, MT, LG, LM, OC, DC, HC, DV, PS, AJ, CEve, CS, SD, CEvr, J-PD, BL, SZ, UK, JB, and RM treated patients and collected data. FL contributed to the writing of the manuscript. LS managed the project. All authors contributed to the data analysis and interpretation. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the drafting of the manuscript or critical revision of the manuscript for important intellectual content. All authors provided final approval of the manuscript, and had final responsibility for the decision to submit for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

JG has received research grants from Boehringer Ingelheim, Bristol Myers Squibb (BMS), Chugai, GlaxoSmithKline (GSK), Merck Serono, and Sanofi and has been an advisory board member for AstraZeneca, BMS, Innate Pharma, and Merck, all outside the submitted work. AA has received grant support, paid to her institution, from the Groupe d'Oncologie Radiotherapie Tête et Cou (GORTEC; French Radiation and Oncology Group for Head and Neck) for this study and has received grant support, paid to her institution, from F Hoffmann–La Roche, outside the submitted work. JF has received grants, personal fees, and non-financial support from AstraZeneca and BMS, personal fees and non-financial support from Merck Sharp & Dohme (MSD), and personal fees from Merck and Innate, outside the submitted work. AF has received grant support, paid to his institution, from the GORTEC for this study. UK has received grants and personal fees from Merck, outside the submitted work. JB participated in advisory boards for MSD, BMS, Debiopharm, Merck, and AstraZeneca, outside the submitted work. RM has received research grants from Merck-Serono and has been an advisory board member for AstraZeneca, BMS, Rakuten, Merck-Serono, MSD, Nanobiotics, Bayer, and Roche, all outside the submitted work. PS has received personal fees from Merck Serono, outside the submitted work. CEve has received personal fees from AstraZeneca, BMS, Innate Pharma, MSD, and Merck Serono, all outside the submitted work. LG has received personal fees from BMS, IPSEN, Merck Serono, MSD, and Pfizer, outside the submitted work. BL has received personal fees from AstraZeneca, BMS, IPSEN, Janssen, MSD, and Roche, outside the submitted work. All other authors declare no competing interests.

Data sharing

Individual participant data and other data and documents will not be shared.

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