



HAL
open science

Adapted **EXTREME** regimen in the first-line treatment of fit, older patients with recurrent or metastatic head and neck squamous cell carcinoma (ELAN-FIT): a multicentre, single-arm, phase 2 trial

Joël Guigay, Hervé Le Caer, François-Régis Ferrand, Lionel Geoffrois, Esma Saada-Bouزيد, Jérôme Fayette, Christian Sire, Didier Cupissol, Emmanuel Blot, Pierre Guillet, et al.

► To cite this version:

Joël Guigay, Hervé Le Caer, François-Régis Ferrand, Lionel Geoffrois, Esma Saada-Bouزيد, et al.. Adapted EXTREME regimen in the first-line treatment of fit, older patients with recurrent or metastatic head and neck squamous cell carcinoma (ELAN-FIT): a multicentre, single-arm, phase 2 trial. *The Lancet. Healthy longevity*, 2024, 5 (6), pp.e392-e405. 10.1016/S2666-7568(24)00048-5 . hal-04578230

HAL Id: hal-04578230

<https://u-picardie.hal.science/hal-04578230v1>

Submitted on 8 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Adapted EXTREME regimen in the first-line treatment of fit, older patients with recurrent or metastatic head and neck squamous cell carcinoma (ELAN-FIT): a multicentre, single-arm, phase 2 trial



Joël Guigay, Hervé Le Caer, François-Régis Ferrand, Lionel Geoffrois, Esma Saada-Bouziid, Jérôme Fayette, Christian Sire, Didier Cupissol, Emmanuel Blot, Pierre Guillet, Julien Pavillet, Laurence Bozec, Olivier Capitain, Frédéric Rolland, Philippe Debourdeau, Yoann Pointreau, Claire Falandry, Stéphane Lopez, Alexandre Coutte, Thierry Chatellier, Pierre Dalloz, Cécile Ortholan, Cécile Michel, Benjamin Lacas, Nadir Cheurfa, Dominique Schwob, Jean Bourhis, Cécile Mertens, Anne Aupérin, on behalf of the ELAN Group including Gustave Roussy, Unicancer GERICO and H&N groups, and GORTEC*



Summary

Background A standard treatment for fit, older patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) is yet to be established. In the previous EXTREME trial, few older patients were included. We aimed to evaluate the efficacy and tolerance of an adapted EXTREME regimen in fit, older patients with recurrent or metastatic HNSCC.

Methods This single-arm, phase 2 study was done at 22 centres in France. Eligible patients were aged 70 years or older and assessed as not frail (fit) using the ELAN Geriatric Evaluation (EGE) and had recurrent or metastatic HNSCC in the first-line setting that was not eligible for local therapy (surgery or radiotherapy), and an Eastern Cooperative Oncology Group performance status of 0–1. The adapted EXTREME regimen consisted of six cycles of fluorouracil 4000 mg/m² on days 1–4, carboplatin with an area under the curve of 5 on day 1, and cetuximab on days 1, 8, and 15 (400 mg/m² on cycle 1–day 1, and 250 mg/m² subsequently), all intravenously, with cycles starting every 21 days. In patients with disease control after two to six cycles, cetuximab 500 mg/m² was continued once every 2 weeks as maintenance therapy until disease progression or unacceptable toxicity. Granulocyte colony-stimulating factor was systematically administered and erythropoietin was recommended during chemotherapy. The study was based on the two-stage Bryant and Day design, combining efficacy and toxicity endpoints. The primary efficacy endpoint was objective response rate at week 12 after the start of treatment, assessed by central review (with an unacceptable rate of ≤15%). The primary toxicity endpoint was morbidity, defined as grade 4–5 adverse events, or cutaneous rash (grade ≥3) that required cetuximab to be discontinued, during the chemotherapy phase, or a decrease in functional autonomy (Activities of Daily Living score decrease ≥2 points from baseline) at 1 month after the end of chemotherapy (with an unacceptable morbidity rate of >40%). Analysis of the coprimary endpoints, and of safety in the chemotherapy phase, was based on the per-protocol population, defined as eligible patients who received at least one cycle of the adapted EXTREME regimen. Safety in the maintenance phase was assessed in all patients who received at least one dose of cetuximab as maintenance therapy. The study is registered with ClinicalTrials.gov, NCT01864772, and is completed.

Findings Between Sept 27, 2013, and June 20, 2018, 85 patients were enrolled, of whom 78 were in the per-protocol population. 66 (85%) patients were male and 12 (15%) were female, and the median age was 75 years (IQR 72–79). The median number of chemotherapy cycles received was five (IQR 3–6). Objective response at week 12 was observed in 31 patients (40% [95% CI 30–51]) and morbidity events were observed in 24 patients (31% [22–42]). No fatal adverse events occurred. Four patients presented with a decrease in functional autonomy 1 month after the end of chemotherapy versus baseline. During chemotherapy, the most common grade 3–4 adverse events were haematological events (leukopenia [22 patients; 28%], neutropenia [20; 26%], thrombocytopenia [15; 19%], and anaemia [12; 15%]), oral mucositis (14; 18%), fatigue (11; 14%), rash acneiform (ten; 13%), and hypomagnesaemia (nine; 12%). Among 44 patients who received cetuximab during the maintenance phase, the most common grade 3–4 adverse events were hypomagnesaemia (six patients; 14%) and acneiform rash (six; 14%).

Interpretation The study met its primary objectives on objective response and morbidity, and showed overall survival to be as good as in younger patients treated with standard regimens, indicating that the adapted EXTREME regimen could be used in older patients with recurrent or metastatic HNSCC who are deemed fit with use of a geriatric evaluation tool adapted to patients with head and neck cancer, such as the EGE.

Funding French programme PAIR-VADS 2011 (sponsored by the National Cancer Institute, the Fondation ARC, and the Ligue Contre le Cancer), Sandoz, GEFLUC, and GEMLUC.

Lancet Healthy Longev 2024;
5: e392–405

Published Online
May 14, 2024
[https://doi.org/10.1016/S2666-7568\(24\)00048-5](https://doi.org/10.1016/S2666-7568(24)00048-5)

See [Comment](#) page e380

For the French translation of the abstract see [Online](#) for appendix 1

*Members listed in appendix 2 (p 3)

Partnerships and Clinical Development—Early Assets, GORTEC, Tours, France (Prof J Guigay MD); Medical Oncology Unit, Hospital Centre of Saint-Brieuc, Saint-Brieuc, France (H Le Caer, MD); Medical Oncology Unit, Gustave-Roussy Institute, Villejuif, France (F-R Ferrand MD); Medical Oncology Unit, Lorraine Cancerology Institute, Nancy, France (L Geoffrois MD); Medical Oncology Department, Centre Antoine Lacassagne, University Côte d'Azur, Nice, France (E Saada-Bouziid MD); Medical Oncology Unit, Cancer Research Centre Léon Bérard, Lyon, France (J Fayette MD); Oncology-Radiotherapy Unit, Hospital Group South Bretagne, Lorient, France (C Sire MD); Medical Oncology Unit, Cancer Institute of Montpellier, Montpellier, France (D Cupissol MD); Medical Oncology Unit, ELSAN Group, Private Hospital Océane, Vannes, France (E Blot MD); Medical Oncology Unit, Intercommunal Hospital Centre, La Seyne-sur-Mer, France (P Guillet MD); Medical Oncology Unit, Hospital Centre, Grenoble, France (J Pavillet MD); Medical Oncology Unit, Curie Institute,

Saint Cloud, France (L Bozec MD); Medical Oncology Unit, West Cancerology Institute, Angers, France (O Capitain MD); Medical Oncology Unit, West Cancerology Institute, Saint Herblain, France (F Pointreau MD); Medical Oncology Unit, Sainte Catherine Institute, Avignon, France (P Debourdeau MD); Radiation Oncology Unit, Inter-regional Cancerology Institute, Jean Bernard Center, Le Mans, France (Y Pointreau MD); Victor Hugo Private Clinic, Sarthe Cancer Center, Le Mans, France (Y Pointreau); Medical Oncology Unit, Hospital Centre of South Lyon, Pierre Bénite, France (C Falandry MD); Medical Oncology Unit, Hospital Centre of Annecy Genevois, Pringy, France (S Lopez MD); Medical Oncology Unit, South Hospital Centre of Amiens, Amiens, France (A Coutte MD); Medical Oncology Unit, Mutualist Clinic of the Estuary, Saint Nazaire, France (T Chatellier MD); Medical Oncology Unit, Centre Jean Perrin, Clermont-Ferrand, France (P Dalloz MD); Oncology-Radiotherapy Unit, Hospital Centre Princesse-Grace, Monaco (C Ortholan MD); Centre Antoine Lacassagne, FHU OncoAge, University Côte d'Azur, Nice, France (C Michel MSc); Biostatistics and Epidemiology Office, Gustave-Roussy, Inserm U1018 Oncostat, Labelled Ligue Contre le Cancer, University Paris-Saclay, Villejuif, France (B Lacas PhD, N Cheurfa PhD, D Schwob MSc, A Aupérin PhD); Radiotherapy Unit, University Hospital Center of Valdois, Lausanne, Switzerland (Prof J Bourhis MD); Oncogeriatrics Unit, Bergonié Institute, Bordeaux, France (C Mertens MD)

Correspondence to: Prof Joël Guigay, Partnerships and Clinical Development—Early Assets, GORTEC, 37000 Tours, France
joel.guigay@gortec.fr
See Online for appendix 2

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an Open Access article under CC BY-NC-ND 4.0 license.

Introduction

In 2022 in the EU, 38% of individuals who had incident carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were aged 70 years or older.¹ The scarcity of dedicated studies^{2,3} combined with under-representation of the older population in clinical trials due, in part, to the presence of comorbidities⁴, has led to an absence of evidence-based data to establish standard systemic palliative treatment for this population.² Age-related factors, such as comorbidity, frailty, polypharmacy, and cognitive impairment, add to an already poor prognosis and limited treatment options when the head and neck cancer becomes recurrent or metastatic. Furthermore, the management of HNSCC in a geriatric context is complex due to the high risk of treatment toxicity, requiring treatment de-escalation or temporary or permanent cessation. In older patients, care needs to be optimised in a way that helps physicians and patients to find the right balance between treatment efficacy and maintenance of autonomy,⁵ and balance between efficacy and quality of life.^{6,7} The eligibility of patients for systemic therapy⁸ must therefore be assessed, beyond the simple criteria of performance status and chronological age.⁹

At the time of initiation of the present study, the platinum-based EXTREME regimen (platinum plus fluorouracil [5-FU] plus cetuximab) was the standard of care in the first-line treatment of fit patients with

recurrent or metastatic HNSCC.⁸⁻¹¹ Based on results of previous trials,^{10,12,13} carboplatin is recommended instead of cisplatin in older patients with HNSCC who are eligible for chemotherapy. In daily practice, most older patients with recurrent or metastatic HNSCC are treated with monotherapy. The EXTREME trial, which compared the EXTREME regimen to the same chemotherapy drugs without cetuximab, included only a small number of patients aged 70 years or older (77 [17%] of 442 aged ≥65 years, including 39 treated in the EXTREME group) and found a higher hazard ratio of death with the addition of cetuximab in patients aged 65 years or older versus younger patients (1.07 [95% CI 0.65–1.77] and 0.74 [0.59–0.94], respectively). Therefore, the efficacy and safety of the EXTREME regimen need to be assessed in a larger population of older patients classified as fit.

The objective of this study was therefore to assess the tolerance and efficacy of an adapted EXTREME regimen in which cisplatin was replaced by carboplatin, followed by maintenance therapy with cetuximab 500 mg/m² once every 2 weeks. A novel component of our study is the addition of a specific geriatric assessment adapted to patients with head and neck cancer (the ELAN Geriatric Evaluation [EGE]) that was done before inclusion (appendix 2 p 4)¹⁴ to select patients who were fit for polychemotherapy. This tool can be completed in 20 min by non-geriatricians with higher sensitivity (95% vs 91%) and specificity (60% vs 30%) than the Geriatric-8 tool (at

Research in context

Evidence before this study

We searched prospective clinical trial publications, published in English, and indexed in PubMed, from April 1, 1992 to April 1, 2022, with the following keywords: “head and neck” and “older” and (“carcinoma” or “cancer”) and “first-line” and (“recurrent” or “metastatic”). The search returned 45 publications, most of which reported on platinum-based chemotherapy combinations. In fit patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), the EXTREME regimen (platinum plus 5-fluorouracil plus cetuximab) is usually recommended. According to previous results, the less toxic carboplatin has been recommended instead of cisplatin in older patients with HNSCC who are eligible to receive chemotherapy. In this study, we assessed the tolerance and efficacy in patients aged 70 years or older of an adapted EXTREME regimen in which cisplatin is replaced by carboplatin followed by maintenance cetuximab 500 mg/m² once every 2 weeks.

Added value of this study

To the best of our knowledge, this study is the first prospective trial to assess a systemic polychemotherapy regimen in the

first-line setting for fit, older patients with recurrent or metastatic HNSCC. The results indicate that, after selection of non-frail (fit) patients using a geriatric frailty assessment tool tailored for patients with head and neck cancer (the ELAN Geriatric Evaluation), an adapted EXTREME regimen can be used in the first-line treatment of these patients, with similar results to those reported for the EXTREME regimen or TPEX regimen (docetaxel plus platinum plus cetuximab) in younger patients.

Implications of all the available evidence

The use of specific geriatric assessment tools before starting anticancer treatments in older patients with head and neck cancer should be standardised and used systematically. The adapted EXTREME regimen can be used in fit older patients, but the search for the most suitable treatments for patients with recurrent or metastatic HNSCC and an Eastern Cooperative Oncology Group performance status of 0–1 should be continued, in particular integrating immunotherapy, in rigorous clinical trials.

cutoff ≤ 14 with Geriatric-8) to detect frailty in older patients.^{5,15}

Methods

Study design and participants

This single-arm, phase 2 trial was sponsored by GORTEC (Tours, France) and conducted in 22 centres in France (cancer centres, university or general hospitals, and private clinics; appendix 2 p 2). The study was part of the large French prospective programme ELAN, which is dedicated to older patients with HNSCC and developed by GERICO, GORTEC, and Gustave Roussy (appendix 2 p 5).^{16–18} The study included patients aged 70 years or older, assessed by an oncologist as not frail (fit) by the EGE tests (mobility tests, social evaluation, Activities of Daily Living [ADL], Mini Mental-State Examination [MMSE], 4-item Geriatric Depression Scale [GDS-4], and Charlson Comorbidity Index [CCI]; appendix 2 p 4). These assessments were followed by an optional comprehensive geriatric assessment by a geriatrician at the investigator's discretion (comprising a series of at least eight tests at the geriatrician's discretion: social evaluation, timed get up and go test, ADL, Instrumental Activities of Daily Living [IADL], Mini Nutritional Assessment, MMSE, 15-item Geriatric Depression Scale, and CCI). The G8 screening questionnaire was also completed for all patients but its score was not taken into account as an inclusion criterion.¹⁹ A patient was considered fit if none of the following conditions according to EGE assessment were met: at least one fall within the past year or monopodal station less than 4 s assessed via the mobility tests; a total score on the social evaluation higher than 0; a score on the ADL lower than 6; a score on the MMSE of 23 or lower; a score on the GDS-4 of 1 or higher; and CCI score higher than 2 (excluding HNSCC) for patients aged 80 years or older or higher than 3 for patients aged 70–79 years. The EGE was done in the ELAN-ONCOVAL study; geriatric patients who were assessed as fit in ELAN-ONCOVAL were subsequently enrolled in the ELAN-FIT study (subject to meeting other trial eligibility requirements). Patients were required to have histologically confirmed recurrent or metastatic HNSCC that was not eligible for local therapy (ie, surgery of the primary tumour not feasible due to local extension [lymph node dissection authorised] and radiotherapy of the primary tumour not feasible due to metastatic extension or already performed and no indication for re-irradiation of the primary tumour). Other inclusion requirements were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of at least 3 months, and a measurable lesion by CT scan or MRI, as defined by Response Evaluation Criteria in Solid Tumours, version 1.1. (RECIST 1.1). Key exclusion criteria were: nasopharyngeal or paranasal sinus cancer, 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), previous EGFR-targeting therapy, irradiation within 4 weeks before study entry, symptomatic brain metastasis, inadequate haematological and hepatic function (absolute neutrophil count $\leq 1.5 \times 10^9$ cells per L, platelet count $\leq 100 \times 10^9$ cells per L, haemoglobin concentration ≤ 9.5 g/dL, total bilirubin $\geq 1.25 \times$ upper limit of normal [ULN], serum glutamic oxaloacetic transaminase or serum glutamate pyruvate transaminase $\geq 5 \times$ ULN, and alkaline phosphatase $\geq 5 \times$ ULN), creatinine clearance lower than 50 mL/min per 1.73 m^2 (as defined by the Modification of Diet in Renal Disease Method), active severe or uncontrolled cardiovascular disease (myocardial infarction within 12 months before inclusion, uncontrolled cardiac insufficiency, high-risk uncontrolled arrhythmias, or clinically significant coronary artery disease), active infection, known dihydropyrimidine dehydrogenase deficiency, and malignancies within 5 years before inclusion (except adequately treated basal or squamous cell skin cancer and cervix carcinoma in situ). Full protocol eligibility criteria are provided in appendix 2 (pp 6–7).

Patients provided written, informed consent, and the study was done in accordance with the International Conference on Harmonisation of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Authorisation of the competent authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé, Saint-Denis, France) was obtained on Jan 8, 2013, and approval from the ethics committee (Comité de Protection de Personnes, Ile de France VII, Le Kremlin-Bicêtre, France) was obtained on Feb 1, 2013, with both obtained before the start of the study. The study protocol is available online. An independent data monitoring committee composed of a statistician, an oncologist, a radiation oncologist, and a geriatrician, was established to monitor study progress on ethical and scientific grounds. This board met annually and at the time of the interim analysis. Safety was assessed quarterly by the steering committee.

Procedures

The adapted EXTREME regimen (appendix 2 p 8) consisted of fluorouracil (5-FU) 4000 mg/m² as a 96-h continuous intravenous infusion on days 1–4, carboplatin with an area under the curve of 5 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 infusion on subsequent administrations). Epoetin alfa (Binocrit; Sandoz) at 40000 international units once a week was recommended according to the summary of product characteristics guidelines. Haematopoietic growth factor (granulocyte colony stimulating factor [G-CSF]) was administered systematically as a prophylactic measure after each cycle of chemotherapy. Recombinant G-CSF, filgrastim (Zarzio;

For the study protocol see https://www.gortec.net/protocoles/ELAN-FIT-short%20protocol_English_version_20240219.pdf

Sandoz), was administered (at a dose of 0·5 million units MU)/kg or 30 MU or 48 MU depending on weight) per day by subcutaneous injection, on days 6–11 after the start of each cycle (summary of product characteristics document sent to each investigator). A maximum of six cycles could be delivered, with cycles starting every 21 days, followed by maintenance therapy in cases of disease control (complete response, partial response, or stable disease per RECIST 1.1) with 500 mg/m² cetuximab once every 2 weeks, at 5 mg/min maximum speed intravenous infusion. For patients with disease control after the two first chemotherapy cycles, two additional cycles were administered and, if disease was still controlled, two more cycles were administered. However, in the event of chemotherapy toxicity that did not allow chemotherapy to be continued, starting maintenance with cetuximab was authorised at any time after two cycles, provided that disease was controlled (response or stable disease). In the event of progressive disease, treatment was at the investigator's discretion.

Adverse events were assessed from the first dose of study treatment according to system organ class and by type of adverse event and grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (CTCAE 4.0; including MedDRA system organ class). Chemotherapy was temporarily interrupted for 7 days in the event of fever (>38·5°C) or CTCAE grade 3–4 adverse events related to chemotherapy drugs. Chemotherapy could be delayed for a maximum of 14 days to allow resolution of fever or the adverse event related to chemotherapy drugs, or discontinued if the event did not resolve after 14 days. Cetuximab administrations could be continued during temporary discontinuation of chemotherapy; thus the number of cetuximab administrations could exceed 18 during the chemotherapy phase. Modalities of cetuximab and chemotherapy adaptations are presented in appendix 2 (pp 9–11). Chemotherapy could also be stopped in the event of intercurrent disease or general status alteration that contraindicated chemotherapy administration, or in the event of disease progression or patient refusal. Maintenance therapy with cetuximab was continued until disease progression or unacceptable toxicity related to cetuximab (skin adverse event grade ≥ 3 or infusion reaction). Maintenance could also be permanently stopped in the event of patient refusal, general status alteration, or investigator decision for the benefit of the patient.

The schedule of study assessments is presented in appendix 2 (pp 12–13). Tumour response was assessed by CT scan or MRI at fixed 6-week intervals after the start of treatment, whenever disease progression was suspected, and at the end of treatment or withdrawal visit. ADL questionnaires were administered before each chemotherapy cycle and then every 4 weeks during maintenance. We also planned to routinely collect IADL questionnaires, however IADL results are not reported because baseline

IADL scores were available for only 46 patients who had a comprehensive geriatric assessment before inclusion in the trial. Quality of life questionnaires (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module [EORTC QLQ-C30] and the Head and Neck Cancer Module [QLQ-HN35]) were completed at baseline, the end of chemotherapy, and 12 weeks after the end of chemotherapy. In addition, the EORTC QLQ-C30 was completed at 6 and 12 weeks since the start of chemotherapy. After the end of trial treatment, follow-up assessments of survival status and assessments of disease course according to RECIST 1.1 took place every 2 months until 1 year after the end of the treatment or until death, whichever occurred first.

Fresh or archived tumour tissues were collected at baseline for patients with oropharyngeal cancer to assess for the presence of human papillomavirus (HPV; types 16, 18, and 33) by chromogenic in situ hybridisation within tumour tissue, and for p16 status assessment by immunohistochemistry (IHC). IHC analysis was done on a BenchMark ULTRA automated slide staining system (Ventana-Roche) with use of an ultraView Universal DAB Detection Kit, prediluted CINtec antibody, and CC1 buffer (all from Roche) for antigen retrieval. Analyses were done by the Gustave Roussy Morphological Pathology Unit (Villejuif, France).

In this paper, we report sex as documented in the medical records of the patients. The collection of ethnicity data requires authorisation in France and must be justified to be necessary for the study aims, which was not the case in this study.

Outcomes

The trial was planned according to the two-stage Bryant and Day design²⁰ to assess efficacy and toxicity. The primary efficacy endpoint was objective response rate at week 12 after the start of treatment, assessed by independent central review according to RECIST 1.1 criteria and defined as the percentage of patients with partial response or complete response. Central review was done by independent radiologists specialised in HNSCC imaging. Patients starting another antitumoral treatment before week 12 were considered not evaluable regardless of their response to the new treatment. These patients, along with patients who were not evaluable due to disease progression before week 12 or who died before week 12, were considered to have not met the primary efficacy endpoint.

The primary toxicity endpoint was grade 4–5 adverse events, or cutaneous rash (grade ≥ 3) requiring cetuximab to be discontinued (appendix 2 p 10), during the chemotherapy phase, or functional autonomy decrease (ADL score decrease ≥ 2 points from baseline) at 1 month after the end of chemotherapy. This score decrease threshold was proposed by Unicancer GERICO. The occurrence of at least one of these three types of events was defined as morbidity in this study. Initially, grade 3

adverse events were also considered in this endpoint; however, an amendment was made during the first stage of the study to not consider these events in the toxicity criteria because, in the first 27 patients, the most frequent grade 3 adverse events were haematological and electrolyte abnormalities that did not alter patient functional autonomy nor have an impact on chemotherapy compliance. The competent authority and the ethics committee authorised this modification.

Secondary efficacy endpoints included overall survival, defined as the interval between trial inclusion and death from any cause, and progression-free survival, defined as the interval between inclusion and first disease progression (per RECIST 1.1) or death. Two other secondary efficacy endpoints were the proportion of patients who obtained an objective response during treatment, regardless of when it was obtained (best overall response), and the duration of objective response among patients who obtained an objective response. An additional secondary efficacy endpoint of objective response rate at 18 weeks is not reported herein.

Other secondary endpoints were functional autonomy and health-related quality of life over time. Functional autonomy was assessed by ADL score (also by IADL score, not reported herein). Health-related quality of life was assessed with the EORTC QLQ-C30 and the QLQ-HN35. The EORTC QLQ-C30 is composed of 30 questions. 24 questions are used to create nine multi-item scales: five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea or vomiting, and pain), and a global health status/quality-of-life scale. Five questions assess additional symptoms commonly reported by patients with cancer (dyspnoea, insomnia, loss of appetite, constipation, and diarrhoea), and one question concerns perceived financial impact of the disease. The QLQ-HN35 consists of 35 questions relating to disease symptoms specific to head and neck cancer and side effects typical of treatment with chemotherapy and radiotherapy. 24 questions are used to create seven multi-item scales (oral pain, swallowing, senses [taste and smell], speech, social eating, social contact, and sexuality). The remaining questions are single-item scales describing specific concerns related to head and neck cancer (problems with teeth, problems opening mouth, dry mouth, sticky saliva, cough, feeling ill, painkiller use, nutritional supplement use, feeding tube use, weight loss, and weight gain). We also assessed grade 3–5 adverse events during chemotherapy and adverse events during maintenance therapy as individual secondary endpoints under the remit of our safety analysis.

Statistical analysis

Applying the two-stage Bryant and Day design,²⁰ an interim analysis, corresponding to the analysis of the first stage, could allow for early termination of the trial in the event of insufficient efficacy or excessive morbidity. On the basis of the results of previous trials,^{11,21} the

sample size was calculated assuming that an objective response rate of 35% was acceptable, while 15% was unacceptable, and that a morbidity rate higher than 40% was unacceptable while a rate of 25% was acceptable. With one-sided alpha values of 0·05 for efficacy and 0·09 for morbidity and a power of 90%, a total of 80 patients was required, with the interim analysis based on 37 patients according to the Bryant and Day methodology.²⁰ The steering committee checked the eligibility of patients recruited into the study to be included in the analysis, when the number of patients included approached the number of patients required for the first stage and then with each new patient until the required number of patients actually eligible for the analysis of the first stage was reached. The same process was done for the second stage of the trial. Among the 85 patients recruited into the study, four patients were deemed ineligible for analysis and one patient was deemed not analysable while the inclusion period was still ongoing, and two additional patients were identified as ineligible after enrolment had closed. As only 78 patients were deemed eligible for analysis, the design was modified in terms of the one-sided alpha error for morbidity (0·08) and power (89%). For the interim analysis of 37 patients, we considered treatment to have insufficient efficacy or to cause excessive morbidity in the first stage if six or fewer patients had an objective response or if 14 or more patients had a morbidity event. If these thresholds were not reached, the trial continued into the second stage. At the end of the second stage, on the basis of all 78 patients, we considered the treatment to be acceptable if 18 or more patients had objective responses and 25 or fewer patients had a morbidity event, according to the Bryant and Day methodology.²⁰

Analysis of the two primary endpoints, of overall survival, progression-free survival, and best overall response, and of duration of response among those who obtained an objective response, were based on eligible patients who received at least one cycle of the adapted EXTREME regimen (per-protocol population). Safety in the chemotherapy phase was assessed in the per-protocol population. Safety in the maintenance phase was assessed in all patients who received at least one dose of cetuximab as maintenance therapy.

Objective response rate and morbidity rate were presented with 95% CI estimated using Wilson's score method. These outcome measures were presented for the overall sample and by sex. Duration of objective response was estimated in patients who obtained an objective response using the Kaplan–Meier method, defined as the interval from the first evaluation of objective response until progression occurrence (per RECIST 1.1). Patients without progression were censored at the date of last follow-up. 95% CIs for the proportions of patients who still had an objective response at 6, 12, and 18 months were calculated with the Rothman method.²² Progression-free survival and overall survival

were estimated using the Kaplan–Meier method from the date of inclusion. For progression-free survival, patients who did not have disease progression or die were censored at the date of last follow-up. For overall survival, patients alive at the date of last follow-up were censored at this date. The 95% CIs of the survival proportions were calculated with the Rothman method. Due to the Bryant and Day design,²⁰ cutoff dates for analyses could not be known in advance. Adverse events were described according to system organ class, type of adverse event, and grade, separately for the chemotherapy phase and the maintenance phase.

The EORTC QLQ-C30 and QLQ-HN35 questionnaires were scored according to the EORTC recommendations described in the scoring manual. The number of patients who completed questionnaires is reported. We calculated the differences in scores over time, from before chemotherapy to during chemotherapy (at week 6 and week 12, for QLQ-C30 only); from before chemotherapy to the end of chemotherapy; and from before chemotherapy to 12 weeks after the end of chemotherapy. The differences in scores were presented as mean differences, with 95% CIs calculated with normal approximation, and assessed with the sign test. Differences were also presented graphically in boxplots at the different timepoints. For interpretation of the results of the EORTC QLQ-C30 analysis, we considered the p values of the sign test and the minimally important differences (MID) proposed by Musoro and colleagues.²³ As MIDs are not available for QLQ-HN35 scores, we used a minimum difference of 20 points, which is considered to be a large change in QLQ-C30 scores.²⁴ For functional autonomy analysis, the number of completed ADL questionnaires is presented and ADL scores are presented at the different assessment timepoints. The proportions of patients with different ADL scores (those with a score of 6; those with a score of 5·5 or 5; and those with a score <5) are reported for the different assessment timepoints. No imputation was done for missing quality of life and ADL scores.

A planned prognostic analysis of the effect of p16 status (oropharynx or unknown primary site p16-positive cases vs oropharynx or unknown primary site p16-negative and other sites) on overall survival and progression-free survival was done with use of log-rank tests. Due to the low number of patients with oropharynx or unknown primary site with known HPV status (19 of 31), we did not perform the analysis according to HPV status. Exploratory post-hoc analyses of the prognostic value of age (70–74 years vs 75–79 years vs ≥80 years), sex, performance status (ECOG 0 vs 1), and type of disease evolution at trial inclusion (locoregional relapse only vs metastases only vs both) for overall survival and progression-free survival were also done.

Analyses were done with SAS (version 4). All provided p values were two-sided at a significance level of 0·05. The study was registered with ClinicalTrials.gov, NCT01864772.

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.

Results

The analysis in the first stage of the study was done on Aug 13, 2016, and was based on 37 patients as of a cutoff date of July 29, 2016. In this analysis, 17 patients had an objective response at week 12 and 12 patients had a morbidity event. As the thresholds for insufficient efficacy or excessive morbidity were not crossed, the study continued.

Between Sept 27, 2013, and June 20, 2018, a total of 85 patients were enrolled (appendix 2 p 14). Seven patients were not analysable: six were found to be ineligible (two with previous EGFR-targeting therapy, two without relapse or metastasis, one treated by local treatment, and one with hepatocellular carcinoma instead of HNSCC metastasis) and one received a 5-FU dose that was not per protocol. The final analyses were therefore based on 78 patients as of a cutoff date of Feb 6, 2023.

Baseline patient and disease characteristics are shown in table 1 and appendix 2 (p 15). 66 (85%) patients were male and 12 (15%) were female. 47 (60%) had an ECOG performance status of 1. Median age was 75 years (IQR 72–79); 14 (18%) patients were aged 80 years or older. 42 (54%) patients presented with metastases and 36 (46%) had locoregional progression alone. 25 (32%) patients had previously received platin-based chemotherapy. 26 (33%) patients exhibited frailty on one or two of the EGE tests. 20 of these individuals were evaluated by geriatricians in a comprehensive assessment, who assessed them as being fit for the study. The other six patients were not evaluated by geriatricians but had exhibited frailty on only one test (three with a GDS-4 score of 1 or 2, one with monopodal station <4 sec, one with an ADL score of 5·5, and one with an MMSE score of 22) and were considered by the physicians to be fit for the study.

The median number of chemotherapy cycles received by patients was five (IQR 3–6), ranging from one to six (table 2). 30 (38%) of 78 patients received all six chemotherapy cycles. The median percentage of the dose received by patients compared with the theoretical dose expected with six full cycles was 67% (IQR 34–92) for 5-FU and 73% (50–100) for carboplatin. For the 48 patients who received fewer than six cycles, the main reasons for chemotherapy discontinuation were toxicity (14 patients), general status alteration according to investigator's clinical evaluation (11 patients), and tumour progression (nine patients). Of the 30 patients who received six cycles, 18 (60%) received at least 18 cetuximab administrations during the chemotherapy phase. Among all 78 patients, the median number of cetuximab administrations during the chemotherapy

phase was 14 (IQR 7–18). Four (5%) patients received only one administration of cetuximab due to an allergic reaction at first administration. The median duration of the chemotherapy phase was 14·1 weeks (IQR 7·1–17·9).

44 (56%) of 78 patients started maintenance treatment with cetuximab. Of these 44 patients, 27 (61%) started maintenance treatment after six chemotherapy cycles, seven (16%) after five cycles, eight (18%) after four cycles, and two (5%) after two cycles. The median number of cetuximab administrations was 7·5 (IQR 5·0–15·0). The median duration of maintenance treatment was

3·3 months (IQR 1·8–6·6). One patient was still receiving maintenance treatment with cetuximab at database lock (Feb 6, 2023). The main reason for maintenance treatment discontinuation was tumour progression (34 [79%] of 43 patients).

Tumour response at week 12 was evaluated by central review in 63 (81%) of 78 patients, as six patients had died due to cancer before week 12, eight had progression before week 12, and one patient was not evaluable at week 12 (chemotherapy was stopped for radiotherapy after partial response was obtained before week 12); these patients were considered to have not met the primary efficacy endpoint. In the analysis population of 78 patients, objective response (complete or partial response) was observed in 31 patients (40% [95% CI 30–51]). Stable disease was observed in 25 (32%) patients. At week 12, seven (9%) patients had progressive disease; thus, the overall number of patients with progressive disease or death due to cancer at or before week 12 was 21 (27%; table 2, appendix 2 p 16). The trial objective was met based on the objective response rate criteria (ie, ≥ 18 patients

Patients (n=78)	
Sex	
Male	66 (85%)
Female	12 (15%)
Age, years	
Median (IQR)	75 (72–79)
Range	70–89
≥ 80 years	14 (18%)
ECOG performance status	
0	31 (40%)
1	47 (60%)
G8 score	
≤ 14	46 (59%)
> 14	32 (41%)
EGE tests	
Social evaluation score ≥ 1	2 (3%)
Functional status—autonomy: ADL < 6	3 (4%)
Cognitive evaluation: MMSE ≤ 23	5 (6%)
Comorbidity: CCI > 2 for age ≥ 80 years or CCI > 3 for age < 80 years	2 (3%)
Motricity altered: ≥ 1 fall within the past year or monopodal station < 4 s	10 (13%)
Depression evaluation: GDS-4 score ≥ 1	13 (17%)
Number of frailties	
0	52 (67%)
1	17 (22%)
2	9 (12%)
Tobacco consumption	
Never	17 (22%)
Former	51 (65%)
Current	10 (13%)
Alcohol consumption	
Never	31 (40%)
Former	26 (33%)
Current	21 (27%)
Primary tumour location*	
Oropharynx	30 (38%)
Oral cavity	17 (22%)
Hypopharynx	9 (12%)
Larynx	18 (23%)
Unknown primary site	1 (1%)
Other	3 (4%)

(Table 1 continues in next column)

Patients (n=78)	
(Continued from previous column)	
p16/HPV status of oropharyngeal carcinoma or unknown primary site	
p16 positive	12/26 (46%)†
p16 negative	14/26 (54%)†
p16 unknown status	5/31 (16%)‡
Type of disease evolution at inclusion	
Locoregional progression alone	36 (46%)
Locoregional progression and metastases	19 (24%)
Metastatic disease alone	23 (29%)
Number of metastatic sites	
1	32 (41%)
2	9 (12%)
3	1 (1%)
Previous cancer treatments	
No	9 (12%)
Yes	69 (88%)
Platin-based chemotherapy for HNSCC	24 (31%)
Platin-based chemotherapy for other cancer	1 (1%)
Medical history	
Cardiovascular disease	60 (77%)
Diabetes	17 (22%)
Other head and neck carcinoma	6 (8%)
Other cancer	12 (15%)

Data are n (%) unless otherwise indicated. ADL=Activities of Daily Living. CCI=Charlson Comorbidity Index. ECOG=Eastern Cooperative Oncology Group. EGE=ELAN Geriatric Evaluation. GDS-4=4-item Geriatric Depression Scale. HNSCC=head and neck squamous cell carcinoma. MMSE=Mini Mental-State Examination. *All squamous cell carcinomas were located in the head and neck region excluding the nasopharynx and paranasal sinus. †Denominator is patients with known p16 status. ‡Denominator is patients with oropharyngeal carcinoma and/or unknown primary site.

Table 1: Patient, tumour, and previous treatment characteristics at inclusion

with objective response at week 12). Objective response at week 12 was recorded in 24 (36%; 95% CI 26–48) of the 66 male patients and in seven (58%; 32–81) of the 12 female patients. Regarding best overall response, 36 (46%) patients had an objective response at some point during treatment; of these patients, one received two chemotherapy cycles (partial response), eight received four cycles (eight partial response), nine received five cycles (eight partial response and one complete response), and 18 received six cycles (17 partial response and one complete response). In these 36 patients, the median duration of response was 6.2 months (95% CI 4.7–9.6; appendix 2 p 16).

During the chemotherapy phase, 19 (24%) of 78 patients had at least one adverse event of grade 4. No

fatal (grade 5) adverse event occurred. Four (5%) patients had grade 3 skin toxicity that required cetuximab interruption. Four (5%) patients had an ADL score decrease of more than 2 points from baseline, 1 month after the end of chemotherapy. In total, 24 patients (31% [95% CI 22–42]) had at least one morbidity event. The trial objective based on morbidity criteria (ie, ≤25 patients with a morbidity event) was reached. 22 (33%; 95% CI 23–45) of 66 male patients and two (17%; 5–45) of 12 female patients had at least one morbidity event.

Median follow-up in the per-protocol population was 71.8 months (IQR 46.5–not reached). Seven (9%) patients were alive at their last follow-up, four of whom had been followed up for more than 2 years since trial enrolment. Six of the seven patients had reached the end of the planned follow-up specified in the protocol (1 year after the end of trial treatment), and the remaining patient was followed up until the end of maintenance treatment, which the patient received for 3.5 years. The median follow-up of these seven patients was 27.2 months (IQR 19.7–46.5). Among the 71 deaths,

Patients (n=78)	
Number of chemotherapy cycles received	
1	6 (8%)
2	8 (10%)
3	8 (10%)
4	14 (18%)
5	12 (15%)
6	30 (38%)
Number of cetuximab administrations during chemotherapy phase	
Median (IQR)	14 (7–18)
Range	1–22
Number of dose modifications* during chemotherapy phase	
5-FU	
0	50 (64%)
1	22 (28%)
2	4 (5%)
3	2 (3%)
Carboplatin	
0	60 (77%)
1	13 (17%)
2	2 (3%)
3	2 (3%)
4	1 (1%)
Chemotherapy duration, weeks	
Median (IQR)	14.1 (IQR 7.1–17.9)
Range	<1–25
Primary reason for chemotherapy discontinuation	
End of chemotherapy period (six cycles received)	30 (38%)
Toxicity	14 (18%)
General status alteration†	11 (14%)
Tumour progression per RECIST 1.1	9 (12%)
Patient refusal to continue	6 (8%)
Death	1 (1%)
Other reason‡	5 (6%)
Maintenance therapy with cetuximab	
No	34 (44%)
Yes	44 (56%)

(Table 2 continues in next column)

Patients (n=78)	
(Continued from previous column)	
Number of cetuximab administrations during maintenance§	
Median (IQR)	7.5 (5.0–15.0)
Range	1–88
Maintenance duration, months§	
Median (IQR)	3.3 (1.8–6.6)
Range	0–43¶
Primary reason for cetuximab maintenance discontinuation§	
Tumour progression per RECIST 1.1	34/43 (79%)
Skin toxicity	2/43 (5%)
General status alteration†	2/43 (5%)
Patient refusal to continue	2/43 (5%)
Death	1/43 (2%)
Physician decision for a maintenance break and subsequently discontinuation	2/43 (5%)
Tumour response per RECIST 1.1 at week 12	
Complete response	2 (3%)
Partial response	29 (37%)
Stable disease	25 (32%)
Progressive disease	7 (9%)
Not evaluable due to death or progressive disease before week 12	14 (18%)
Not evaluable due to switch to radiotherapy before week 12	1 (1%)
Data are n (%) unless otherwise indicated. RECIST 1.1=Response Evaluation Criteria in Solid Tumours, version 1.1. 5-FU=fluorouracil. *Excluding non-administration. †General status alteration is an adverse event but not always related to treatment toxicity particularly in the older population. ‡Other reasons were angina, infection, tumour haemorrhage, second malignancy, and radiotherapy (one patient each). §Among 43 patients who stopped maintenance treatment; one patient was still receiving treatment (88 cetuximab administrations received in 3.5 years) at the database lock (Feb 6, 2023). ¶Shortest duration was 1 day.	

Table 2: Treatment summary and tumour response

62 (87%) were related to cancer; 55 were due solely to cancer and seven were in association with a second cause. Median overall survival was 15.8 months (95% CI 11.0–18.9; figure). Overall survival rates were as follows: at 1 year, 59.0% (95% CI 47.9–69.2); at 2 years, 21.3% (13.5–31.9); at 3 years, 10.3% (5.0–19.9); at 4 years, 6.4% (2.4–15.7); and at 5 years, 4.3% (1.3–13.4).

74 progression-free survival events (64 progressions and ten deaths as the first event) occurred among the 78 patients in the per-protocol population. 13 (17%) of 78 patients progressed while on chemotherapy and 35 (45%) while on maintenance therapy. Median progression-free survival was 6.0 months (95% CI 4.9–7.3; figure). Progression-free survival rates were as follows: at 1 year, 17.9% (95% CI 11.0–27.9), at 2 years, 7.7% (3.6–15.8), and at 3 years, 5.1% (1.7–14.1).

Age, sex, ECOG performance status, type of disease evolution at inclusion (all analysed post-hoc), and p16 status (prespecified analysis) were not indicated to be prognostic factors for overall survival or progression-free survival (appendix 2 pp 17–21); however, the study was not powered for prognostic analysis.

Quality of life questionnaires were completed by 73 (94%) of 78 patients at baseline, 51 (67%) of 76 patients alive at week 6, 45 (63%) of 72 alive at week 12, 25 (36%) of 69 alive at the end of chemotherapy, and 28 (44%) of 64 alive at 12 weeks after the end of chemotherapy (appendix pp 22, 28). The numbers of patients with evaluable questionnaire scores are presented for the different timepoints in appendix 2 (pp 23, 28–29).

Considering the MIDs proposed by Musoro and colleagues²³ for the EORTC QLQ-C30 scores, social functioning (MID –8) showed the greatest decline among functional domains at all timepoints, showing significant differences compared with baseline at all timepoints apart from at the end of chemotherapy (appendix pp 24–27). A deterioration that exceeded the MID of –5 was also observed for the global quality of life score at week 12, at the end of chemotherapy, and at 12 weeks after the end of chemotherapy, though this was not statistically significant. The score for fatigue showed a statistically significant increase at all timepoints, but the increase only exceeded the MID of 15 at week 12. Physical functioning scores showed statistically significant decreases from week 12 onwards, but the decreases were smaller than the MID of –11. The score for nausea or vomiting significantly increased, but was slightly below the MID of 6, at week 6. At week 12 since the start of chemotherapy and at 12 weeks after the end of chemotherapy, the score for dyspnoea was significantly increased and this increase exceeded the MID of 7.

25 patients completed the QLQ-HN35 questionnaires at the end of chemotherapy and 28 patients completed questionnaires 12 weeks after the end of chemotherapy, thus reducing the statistical power to evaluate changes in scores. MIDs were not available for QLQ-HN35

scores. However, using a cutoff score of 20, changes were apparent for weight control at the end of chemotherapy and at 12 weeks after the end of chemotherapy compared with baseline, with a decrease in weight loss at the end of chemotherapy and an increase in weight gain at 12 weeks after the end of chemotherapy, but these changes were not statistically significant (appendix pp 30–33).

Between week 3 and week 18, the proportion of patients with an ADL score below five was maximal at week 6 (seven [13%] of 55 patients with available questionnaires) and decreased to 0% at week 18 (none of 22 patients). During the chemotherapy phase, 12 (17%) of 70 patients who completed at least one ADL questionnaire during the phase had an ADL score below five at least once. Detailed results are presented in appendix 2 (pp 34–35).

During the chemotherapy phase, all patients had at least one adverse event. No fatal (grade 5) adverse events occurred. 65 (83%) of 78 patients had at least one adverse event of grade 3 or 4 (table 3). The most common grade 3–4 adverse events were haematological events (leukopenia [22 patients; 28%], neutropenia [20; 26%], thrombocytopenia [15; 19%], and anaemia [12; 15%]), oral

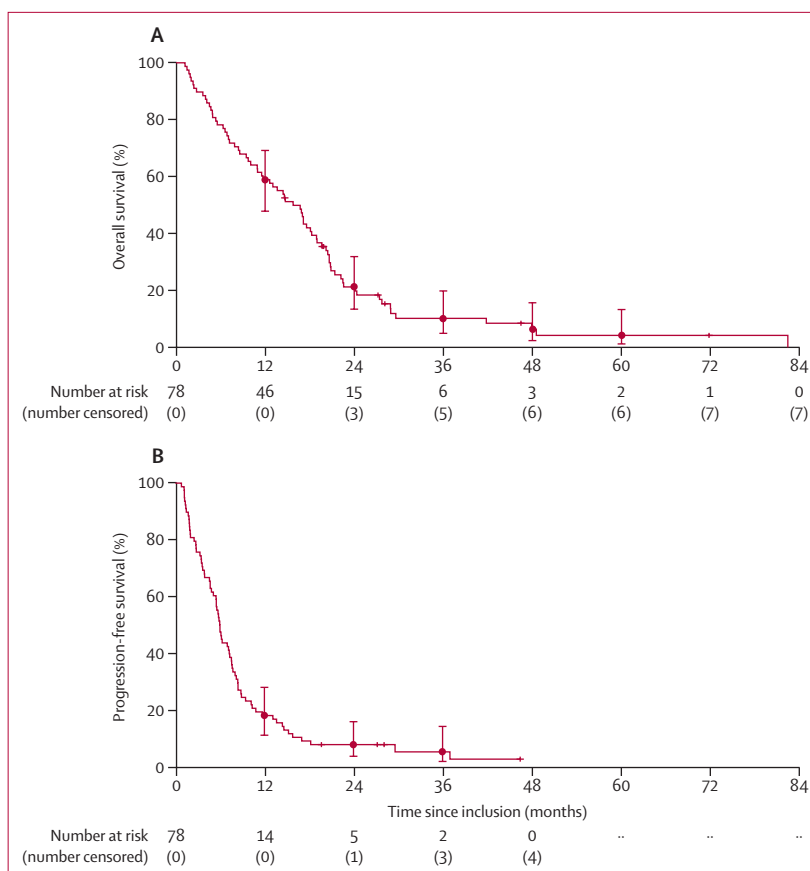


Figure: Kaplan-Meier estimates of overall survival (A) and progression-free survival (B)

Vertical bars are the Rothman 95% CIs of overall survival and progression-free survival estimates. Crosses represent censored patients.

mucositis (14; 18%), fatigue (11; 14%), rash acneiform (ten; 13%), and hypomagnesaemia (nine; 12%).

During maintenance therapy, all 44 patients who received cetuximab had at least one adverse event during the therapy. No fatal (grade 5) adverse events occurred. 25 (57%) patients had at least one adverse event of grade 3 or 4 (table 3), but only two (5%) discontinued maintenance therapy due to skin toxicity (grade 3 rash acneiform). The most common grade 3–4 adverse events were hypomagnesaemia (six patients; 14%) and acneiform rash (six; 14%). All

adverse events that occurred during the chemotherapy and maintenance phases are presented in appendix 2 (pp 36–40).

	Grade 1–2	Grade 3	Grade 4	Grade unspecified
Chemotherapy phase (n=78)				
Maximal adverse event grade reached by patient	13 (17%)	46 (59%)	19 (24%)	NA
Any type of adverse event*	78 (100%)	64 (82%)	19 (24%)	7 (9%)
Grade 1–2 adverse events occurring in ≥10% of patients and all grade ≥3 adverse events†				
Blood system disorders				
Anaemia	62 (79%)	9 (12%)	3 (4%)	0
Leukopenia	41 (53%)	18 (23%)	4 (5%)	0
Thrombocytopenia	50 (64%)	13 (17%)	2 (3%)	0
Neutropenia	21 (27%)	15 (19%)	5 (6%)	0
Febrile neutropenia	0	1 (1%)	1 (1%)	0
Cardiac and vascular disorders				
Temporary electrocardiogram changes	0	1 (1%)	0	0
Pulmonary embolism	0	1 (1%)	1 (1%)	0
Atrial fibrillation	0	1 (1%)	0	0
Cardiac chest pain	0	1 (1%)	0	0
Carotid artery stenosis	0	1 (1%)	0	0
Eye disorders				
Conjunctivitis	0	1 (1%)	0	1 (1%)
Gastrointestinal disorders				
Mucositis oral	3 (4%)	13 (17%)	1 (1%)	0
Diarrhoea	0	5 (6%)	0	0
Nausea	2 (3%)	1 (1%)	0	1 (1%)
Vomiting	0	2 (3%)	0	0
Dysphagia	1 (1%)	2 (3%)	0	0
Intestinal perforation	0	1 (1%)	0	0
Oesophageal stent-graft migration	0	1 (1%)	0	0
General disorders				
Fatigue	2 (3%)	11 (14%)	0	0
General status alteration	0	3 (4%)	1 (1%)	0
Infection				
Infection	1 (1%)	4 (5%)	3 (4%)	0

(Table 3 continues in next column)

	Grade 1–2	Grade 3	Grade 4	Grade unspecified
(Continued from previous column)				
Investigations				
Gamma-glutamyl transferase increased	25 (32%)	4 (5%)	1 (1%)	0
Alkaline phosphatase increased	25 (32%)	0	0	0
Aspartate or alanine aminotransferase increased	22 (28%)	1 (1%)	0	0
Creatinine increased	10 (13%)	0	0	0
Creatinine clearance decreased	34 (44%)	1 (1%)	0	0
Blood bilirubin increased	11 (14%)	0	0	0
Weight loss	0	1 (1%)	0	0
Immune system disorders				
Allergic reaction	5 (6%)	4 (5%)	0	1 (1%)
Metabolism and nutrition disorders				
Hypoalbuminaemia	31 (40%)	1 (1%)	0	0
Hyponatraemia	34 (44%)	6 (8%)	1 (1%)	0
Hypernatraemia	24 (31%)	1 (1%)	1 (1%)	0
Hypokalaemia	23 (29%)	6 (8%)	1 (1%)	0
Hyperkalaemia	29 (37%)	1 (1%)	0	0
Hypocalcaemia	51 (65%)	3 (4%)	0	0
Hypomagnesaemia	53 (68%)	4 (5%)	5 (6%)	0
Hypoglycaemia	0	1 (1%)	0	0
Anorexia	2 (3%)	3 (4%)	0	0
Acidosis (diabetic)	0	1 (1%)	0	0
Dehydration	0	2 (3%)	1 (1%)	0
Nervous system disorders				
Dysgeusia	0	1 (1%)	0	0
Seizure	0	0	1 (1%)	1 (1%)
Cognitive disturbance	1 (1%)	0	1 (1%)	0
Psychiatric disorders				
Insomnia	0	1 (1%)	0	0
Renal disorders				
Acute kidney injury	0	0	1 (1%)	0
Respiratory, thoracic, and mediastinal disorders				
Bronchospasm	0	1 (1%)	0	0
Voice alteration	0	1 (1%)	0	0
Pneumopathy	0	1 (1%)	1 (1%)	0
Skin and subcutaneous tissue disorders				
Rash acneiform	1 (1%)	10 (13%)	0	1 (1%)
Palmar-plantar erythrodysesthesia syndrome	0	1 (1%)	0	0
Cervical skin necrosis	0	1 (1%)	0	0

(Table 3 continues in next column)

Discussion

The present study showed that fit, older patients with recurrent or metastatic HNSCC could benefit from an

adapted, carboplatin-based EXTREME regimen, with similar results to those observed in younger patients. The adapted regimen showed efficacy in our trial population, with an objective response rate of 40% (95% CI 30–51) at week 12, and higher than expected median overall survival and progression-free survival (15·8 months [95% CI 11·0–18·9] and 6·0 months [4·9–7·3], respectively); these rates were similar to those reported in younger patients treated with a TPEX regimen (docetaxel plus cisplatin plus cetuximab; overall survival of 14·5 months [12·5–15·7] and progression-free survival of 6·0 months [5·7–6·4])²⁵ or with the new standard of care regimen of pembrolizumab plus platinum plus 5-FU (KEYNOTE-048; overall survival of 13·0 months [10·9–14·7] and progression-free survival of 4·9 months [4·7–6·1]).²⁶ Furthermore, the carboplatin-based EXTREME regimen compares favourably against other approaches previously studied in older patients with recurrent or metastatic HNSCC, which used systemic cisplatin-based combinations with paclitaxel or 5-FU (median overall survival 5·3 months)¹² or monotherapy with methotrexate (ELAN-UNFIT trial; 4·6 months [2·3–7·7]).²⁷ No prognostic factors were

	Grade 1-2	Grade 3	Grade 4	Grade unspecified
(Continued from previous column)				
Maintenance phase (n=44)				
Maximal adverse event grade reached by patient	19 (43%)	20 (45%)	5 (11%)	NA
Any type of adverse event*	44 (100%)	21 (48%)	5 (11%)	29 (66%)
Grade 1-2 adverse events occurring in ≥10% of patients and all grade ≥3 adverse events†				
Blood system disorders				
Anaemia	34 (77%)	1 (2%)	0	0
Leukopenia	16 (36%)	1 (2%)	0	0
Thrombocytopenia	14 (32%)	0	0	0
Neutropenia	3 (7%)	2 (5%)	0	0
Cardiac and vascular disorders				
Cardiac insufficiency	0	1 (2%)	0	0
Ear and labyrinth disorders				
Hearing impaired	2 (5%)	1 (2%)	1 (2%)	0
Eye disorders				
Conjunctivitis	7 (16%)	0	0	0
Gastrointestinal disorders				
Mucositis oral	8 (18%)	0	0	0
Diarrhoea	5 (11%)	0	0	0
Dysphagia	4 (9%)	2 (5%)	0	1 (2%)
Oral pain	8 (18%)	0	0	0
Gastrostomy tube complication	0	1 (2%)	0	0
General disorders				
Fatigue	17 (39%)	2 (5%)	0	1 (2%)
Fever	4 (9%)	0	0	2 (5%)
General status alteration	1 (2%)	1 (2%)	0	1 (2%)
Oedema	4 (9%)	0	0	0
Pain	5 (11%)	0	0	2 (5%)
Infection				
Infection	4 (9%)	3 (7%)	2 (5%)	1 (2%)
Investigations				
Gamma-glutamyl transferase increased	20 (45%)	0	0	0
Alkaline phosphatase increased	10 (23%)	1 (2%)	0	0
Aspartate or alanine aminotransferase increased	10 (23%)	0	0	0
Creatinine increased	12 (27%)	0	0	0
Creatinine clearance decreased	23 (52%)	0	0	0
Immune system disorders				
Allergic reaction	2 (5%)	1 (1%)	0	0

(Table 3 continues in next column)

	Grade 1-2	Grade 3	Grade 4	Grade unspecified
(Continued from previous column)				
Metabolism and nutrition disorders				
Hypoalbuminaemia	9 (20%)	0	0	0
Hyponatraemia	6 (14%)	1 (2%)	0	0
Hypernatraemia	20 (45%)	0	0	0
Hypokalaemia	4 (9%)	2 (5%)	0	0
Hyperkalaemia	16 (36%)	1 (2%)	0	0
Hypocalcaemia	21 (48%)	0	0	0
Hypomagnesaemia	33 (75%)	4 (9%)	2 (5%)	0
Nervous system disorders				
Peripheral sensory neuropathy	4 (9%)	1 (2%)	0	0
Respiratory, thoracic, and mediastinal disorders				
Dyspnoea	3 (7%)	1 (2%)	1 (2%)	0
Voice alteration	1 (2%)	1 (2%)	0	0
Pneumopathy	1 (2%)	2 (5%)	0	0
Skin and subcutaneous tissue disorders				
Rash acneiform	25 (57%)	6 (14%)	0	1 (1%)
Dry skin	0	0	0	21 (48%)
Fissures	4 (9%)	0	0	15 (34%)
Nail disorders	5 (11%)	0	0	6 (14%)
Hair disorders	6 (14%)	0	0	0
Proud flesh	0	1 (2%)	0	0

Data are number of patients (%). Adverse events are categorised by system organ class and type of event per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. NA=not applicable. *Patients who had different adverse events of different grades are counted for every 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 and 4. †A complete list of adverse events, including all grade 1-2 adverse events, is provided in appendix 2 (pp 36-40).

Table 3: Adverse events during chemotherapy and maintenance therapy

identified; all subgroups defined according to age, sex, ECOG performance status, p16 status, and type of disease evolution had a median overall survival greater than 13·6 months (appendix 2 pp 17–21). Regimen efficacy was accompanied by acceptable tolerance, with 54 (69%) of 78 patients not having a morbidity event. Most patients showed preservation of functional autonomy, no patients had grade 5 adverse events, and fewer patients had grade 4 adverse events during chemotherapy (19 [24%] of 78) than younger patients with the EXTREME regimen (123 [46%] of 265) or TPEX regimen (87 [33%] of 263).²⁵ 30 (38%) of 78 patients received the six chemotherapy cycles, similar to previously reported proportions with the EXTREME regimen.^{25,28} In delivering combination chemotherapy in older patients, G-CSF and erythropoietin are recommended to maintain the dose intensity and reduce the haematological toxicity.^{29,30} We applied these precautionary measures in the present study, and patients were able to receive a median percentage of the expected dose (based on six cycles) of 73% of carboplatin and 67% of 5-FU.

As part of a combination regimen with maintenance treatment, cetuximab is usually delivered weekly. Trials of cetuximab monotherapy at a dose of 500 mg/m² once every 2 weeks in recurrent or metastatic HNSCC indicate similar efficacy to conventional dosing of cetuximab in this population without increased toxicity.^{25,28,31} The schedule of 500 mg/m² once every 2 weeks is now widely used to decrease the frequency of infusions, especially for frail or older patients, and for long-term maintenance, and this schedule has been recently approved by the US Food and Drug Administration.³²

To the best of our knowledge, this study is the first prospective trial in the first-line setting among fit, older patients with recurrent or metastatic HNSCC. Furthermore, the study was original on two levels: the selection of patients according to not only age and ECOG performance status but also comorbidities and frailty, assessed using the EGE tests adapted for patients with HNSCC; and the use of co-primary endpoints evaluating oncological efficacy and tolerance, which are highly relevant in the oncogeriatric population.³³

Our study has several limitations. First, though morbidity initially included grade 3–5 adverse events occurring during the chemotherapy phase, grade 3 adverse events were removed from this endpoint. At the final analysis, 64 (82%) of 78 patients had experienced at least one grade 3 adverse event during chemotherapy but only 14 (18%) patients had stopped chemotherapy due to toxicity and only 12 (17%) of 70 with ADL score available had a ADL score below five during chemotherapy. Thus, the modification of the toxicity endpoint did not risk patient safety.

Second, of a total of 85 patients, only 78 patients were eligible and could be included in the final analysis. We regularly checked patient eligibility and evaluability throughout the study. We included 85 patients to allow

for 80 eligible and evaluable patients. Unfortunately, after stopping inclusion, we found that a total of seven patients were not eligible for analysis. To address this issue, we slightly revised the statistical design of the study by changing the one-sided alpha error for morbidity from 0·09 to 0·08 and the power from 90% to 89% but without changing the null and alternative hypotheses. However, despite these modifications, which could have resulted in a negative trial, the trial analysis showed that efficacy and tolerance were reached with regard to the defined hypotheses.

Third, it is feasible but remains difficult to conduct clinical trials in older patients with head and neck cancer. The present study required 22 centres and five years to accrue only 78 patients. The main reasons for the difficulties in conducting this trial were the time needed to organise a trial at a national level; the need for educational support to assess EGE scores; the need for multiple centres because older patients, even those deemed clinically fit, are often reluctant to travel to a distant centre for treatment; the preference of some clinicians to deliver another regimen, such as carboplatin plus cetuximab without 5-FU, for these older patients; and, finally, the fact that not all fit older patients were eligible (contraindication to 5-FU; eg, DPD deficiency or cardiovascular disease) and that some older patients and their families declined enrolment in the clinical trial.

Finally, the analysis of quality of life is limited by the large quantity of questionnaires that were not completed by patients, mainly at the end of the chemotherapy phase and thereafter. This gradual reduction in completing the questionnaires over time is common, and makes it difficult to extrapolate results to the entire population meeting the inclusion criteria of the study, particularly beyond week 12. During the early trial period (weeks 6 and 12), the study showed a deterioration of social functioning and an increase of fatigue, nausea or vomiting, and dyspnoea.

As we noted previously, the trial results highlight the importance of considering the frailty level of the population and adapting treatment accordingly, and the importance of including supportive care to preserve autonomy and manage treatment toxicities. The EGE test, a geriatric tool specific for patients with HNSCC, shows greater specificity in identifying patients who can benefit from chemotherapy compared with G8.¹⁵ The EGE test¹⁴ was recently added to the American Society of Clinical Oncology Educational Book⁵ and the present results show that it could be widely used for the selection and stratification of patients in future studies. The ELAN UNFIT trial of monotherapy showed that frail older patients with recurrent or metastatic HNSCC and an ECOG performance status of 2 did not benefit from cetuximab or methotrexate.²⁷ Thus, collectively the results suggest that only fit older patients with recurrent or metastatic HNSCC should receive an adapted EXTREME regimen. This trial provides data that present the benefits

and risks of the adapted EXTREME regimen in fit older patients with recurrent or metastatic HNSCC, which could help future patients make an informed decision on whether or not to receive this treatment when it is indicated.

As an optimal treatment paradigm in the palliative setting for older patients with HNSCC has not been well defined, inclusion in dedicated clinical trials (which include an adapted geriatric assessment; appendix 2 p 4)¹⁴ should be routinely offered and encouraged. New treatment options such as taxanes instead of 5-FU, or immunotherapy with checkpoint inhibitors, should be explored through a suitable evidence-based approach for older patients.

In conclusion, the adapted EXTREME regimen was indicated to be a valid treatment option in terms of efficacy and safety while maintaining functional autonomy in older patients with recurrent or metastatic HNSCC screened as fit by the EGE.¹⁵ Therefore, the adapted EXTREME regimen could become the standard regimen in case of a PD-L1-combined positive score lower than one, which is the biomarker ineffectiveness threshold for immunotherapy in first-line treatment in Europe.³⁴ The decision remains to be that of the patient after having received complete information on the risk-to-benefit ratio.

Contributors

Academic advisers and the sponsor (GORTEC) designed this study. All data were collected by the investigators and their site personnel. All authors had full access to the data, vouch for their accuracy, and attest that the study conformed to the protocol. A statistician employed by one of the sponsors of the ELAN programme analysed the data, which were subsequently interpreted by all authors. A medical writer contracted by the sponsor provided assistance in preparing the manuscript. All authors contributed to the reviewing and amending of the manuscript. All authors had final responsibility for the decision to submit for publication. AA and JB assessed and verified the data.

Declaration of interests

JG has been an advisory board member for BMS, Hookipa, MSD, Merck, Nanobiotix, and Roche, outside the submitted work; reports personal fees from MSD, outside the submitted work; and has received grant support during the study, paid to his institution, from the GEMLUC and GEFLUC, and the French National Cancer Institute, the Fondation ARC, and the Ligue Contre le Cancer, through the French programme PAIR-VADS 2011. F-RF reports travel support for congress from Merck Serono, outside the submitted work. ES-B reports personal fees from MSD and Merck Serono, and support for attending meetings or travel, or both, from MSD and Merck Serono, outside the submitted work. JF reports personal fees and non-financial support from MSD and Merck, and personal fees from AstraZeneca, BMS, Roche, Rakuten, Elevar, Hookipa, Sanofi, and Seagen, during the conduct of the study; and has been an advisory board member for Roche, Seagen, and Elevar, outside the submitted work. FR reports personal fees and non-financial support from Merck, outside the submitted work. CF reports personal fees from Astellas Pharma, AstraZeneca, Biogaran, BMS, Chugai Pharma France, Clovis Oncology, Eisai, GSK, Leo Pharma, Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Seagen, and Viartis, and non-financial support from AstraZeneca, Janssen Oncology, Leo Pharma, and Pierre Fabre, outside the submitted work. TC reports personal fees from Merck and has been an advisory board member for MSD outside the submitted work. PDA reports personal fees from Lilly and has been advisory board member for Pfizer and MSD, outside the submitted work. SL has participated on advisory boards of Merck and BMS, outside the submitted work. AA reports grants from the French programme

PAIR-VADS 2011 funded by the French National Cancer Institute, the Fondation ARC, and the Ligue Contre le Cancer, and grants from Sandoz, during the conduct of the study, and other from MSD, outside the submitted work; all paid to her institution. All other authors declare no competing interests.

Data sharing

Individual participant data will not be shared as the informed consent signed by patients does not allow data sharing. The study protocol is available on the GORTEC website (https://www.gortec.net/protocoles/ELAN-FIT-short%20protocol_English_version_20240219.pdf).

Acknowledgments

We thank the patients, the investigators (appendix 2 p 2), the GERICO group for geriatric expertise (Etienne Brain and authors Emmanuel Blot and Cécile Mertens), the independent data monitoring committee members (Bernard Asselain, Isabelle Martel Lafay, Valérie Quipourt, and Frédérique Rousseau), Caroline Brard Moufida Debbah, and Rabia Boulhassas for their contribution. We also thank Cécile Michel for his help in manuscript preparation. We would like to also thank the French National Cancer Institute, the Fondation ARC, and the Ligue Contre le Cancer for the study grant provided through the French programme PAIR-VADS 2011, the associations GEFLUC and GEMLUC for the study grant, and Sandoz (grant number MA-21732-2014).

References

- Global Cancer Observatory. Incidence, both sexes, in 2022. <https://gco.iarc.fr/today/en/dataviz/tables?mode=population> (accessed April 14, 2024).
- Le Saux O, Falandry C, Gan HK, You B, Freyer G, Péron J. Inclusion of elderly patients in oncology clinical trials. *Ann Oncol* 2016; **27**: 1799–804.
- Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003; **21**: 1383–89.
- Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol* 2019; **5**: 326–33.
- Corry J, Ng WT, Ma SJ, Singh AK, de Graeff P, Oosting SF. Disadvantaged subgroups within the global head and neck cancer population: how can we optimize care? *Am Soc Clin Oncol Educ Book* 2022; **42**: 1–10.
- DuMontier C, Loh KP, Soto-Perez-de-Celis E, Dale W. Decision making in older adults with cancer. *J Clin Oncol* 2021; **39**: 2164–74.
- Sarris EG, Harrington KJ, Saif MW, Syrigos KN. Multimodal treatment strategies for elderly patients with head and neck cancer. *Cancer Treat Rev* 2014; **40**: 465–75.
- Sacco AG, Cohen EE. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. *J Clin Oncol* 2015; **33**: 3305–13.
- Grégoire V, Lefebvre J-L, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNES-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v184–86.
- Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; **359**: 1116–27.
- Peyrade F, Cupissol D, Geoffrois L, et al. Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: review of the literature and proposal for management changes. *Oral Oncol* 2013; **49**: 482–91.
- Argiris A, Li Y, Murphy BA, Langer CJ, Forastiere AA. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. *J Clin Oncol* 2004; **22**: 262–68.
- Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005; **23**: 8646–54.
- Mertens C, Guigay J. ELAN Geriatric Evaluation (EGE score). 2022. https://recherche.unicancer.fr/wp-content/uploads/sites/2/2022/10/ege-elan-gerico_2022_03.pdf (accessed April 14, 2024).

- 15 Mertens C, Le Caer H, Ortholan C, et al. ELAN-ONCOVAL (Elderly Head and Neck Cancer-Oncology Evaluation) study: evaluation of the G8 screening tool and the ELAN geriatric evaluation (EGE) for elderly patients (pts) with head and neck squamous cell carcinomas (HNSCC). *J Clin Oncol* 2019; **37** (suppl): 11541.
- 16 Guigay J, Auperin A, Mertens C, et al. Personalized treatment according to geriatric assessment in first-line recurrent and/or metastatic (R/M) head and neck squamous cell cancer (HNSCC) patients aged 70 or over: ELAN (Elderly Head and Neck Cancer) FIT and UNFIT trials. *Ann Oncol* 2019; **30**: v450.
- 17 Guigay J, Le Caer H, Mertens C, et al. Elderly Head and Neck Cancer (ELAN) study: personalized treatment according to geriatric assessment in patients age 70 or older: first prospective trials in patients with squamous cell cancer of the head and neck (SCCHN) unsuitable for surgery. *J Clin Oncol* 2014; **32** (suppl): TPS6099 (abstr).
- 18 Guigay J, Le Caer H, Ortholan C, Aupérin A, Michel C, Mertens C. Treatment of inoperable elderly head and neck cancer patients. *Curr Opin Oncol* 2019; **31**: 152–59.
- 19 Soubeyran P, Bellera C, Goyard J, et al. Validation of the G8 screening tool in geriatric oncology: the ONCODAGE project. *J Clin Oncol* 2011; **29** (suppl): 9001 (abstr).
- 20 Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics* 1995; **51**: 1372–83.
- 21 Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005; **23**: 3562–67.
- 22 Rothman KJ. Estimation of confidence limits for the cumulative probability of survival in life table analysis. *J Chronic Dis* 1978; **31**: 557–60.
- 23 Musoro JZ, Coens C, Singer S, et al. Minimally important differences for interpreting European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scores in patients with head and neck cancer. *Head Neck* 2020; **42**: 3141–52.
- 24 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health related quality of life scores. *J Clin Oncol* 1998; **16**: 139–44.
- 25 Guigay J, Aupérin A, Fayette J, et al. 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. *Lancet Oncol* 2021; **22**: 463–75.
- 26 Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019; **394**: 1915–28.
- 27 Guigay J, Ortholan C, Vansteene D, et al. Cetuximab versus methotrexate in first-line treatment of older, frail patients with inoperable recurrent or metastatic head and neck cancer (ELAN UNFIT): a randomised, open-label, phase 3 trial. *Lancet Healthy Longev* 2024; **5**: e182–93.
- 28 Guigay J, Chamorey E, Lefebvre G, et al. Observational, prospective, phase 4 study in patients with first-line recurrent and/or metastatic squamous cell carcinoma of the head and neck treated with cetuximab and platinum-based therapy: DIRECT. *Cancer Rep (Hoboken)* 2022; **5**: e1467.
- 29 Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *Eur J Cancer* 2004; **40**: 2201–16.
- 30 Wedding U, Honecker F, Bokemeyer C, Pientka L, Höffken K. Tolerance to chemotherapy in elderly patients with cancer. *Cancer Control* 2007; **14**: 44–56.
- 31 Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann Oncol* 2015; **26**: 1941–47.
- 32 US Food and Drug Administration. FDA approves new dosing regimen for cetuximab. 2021. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-cetuximab> (accessed Nov 20, 2022).
- 33 Wildiers H, Mauer M, Pallis A, et al. End points and trial design in geriatric oncology research: a joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society Of Geriatric Oncology position article. *J Clin Oncol* 2013; **31**: 3711–18.
- 34 Peyrade F, Borel C, Daste A, Even C, Saada-Bouزيد E, Guigay J. Systemic treatment of metastatic squamous cell carcinoma of the head and neck: proposal for management changes. *Curr Opin Oncol* 2021; **33**: 160–67.