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

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Summary

Background At present, there is no established standard treatment for frail older patients with recurrent or metastatic head and neck squamous cell carcinoma. We aimed to compare the efficacy and safety of cetuximab to those of methotrexate (the reference regimen) in this population.

Methods This randomised, open-label, phase 3 trial was done at 20 hospitals in France. Patients aged 70 years or older, assessed as frail by the ELAN Geriatric Evaluation, with recurrent or metastatic head and neck squamous cell carcinoma in the first-line setting and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were eligible for inclusion. Patients were randomly assigned (1:1) to receive cetuximab 500 mg/m² intravenously every 2 weeks or methotrexate 40 mg/m² intravenously every week, with minimisation by ECOG performance status, type of disease evolution, Charlson Comorbidity Index score, serum albumin concentration, and geriatrician consultation. To avoid deterministic minimisation and assure allocation concealment, patients were allocated with a probability of 0·80 to the treatment that most reduced the imbalance. Treatment was continued until disease progression or unacceptable toxicity, whichever occurred first. The primary endpoint was failure-free survival (defined as the time from randomisation to disease progression, death, discontinuation of treatment, or loss of 2 or more points on the Activities in Daily Living scale, whichever occurred first) and was analysed in the intention-to-treat population. 151 failures expected out of 164 patients were required to detect a hazard ratio (HR) of 0·625 with 0·05 alpha error, with 80% power. A futility interim analysis was planned when approximately 80 failures were observed, based on failure-free survival. Safety analyses included all patients who received at least one dose of the study drug. This study is registered on ClinicalTrials.gov (NCT01884623) and was stopped for futility after the interim analysis.

Findings Between Nov 7, 2013, and April 23, 2018, 82 patients were enrolled (41 to the cetuximab group and 41 to the methotrexate group); 60 (73%) were male, 37 (45%) were aged 80 years or older, 35 (43%) had an ECOG performance status of 2, and 36 (44%) had metastatic disease. Enrolment was stopped for futility at the interim analysis. At the final analysis, median follow-up was 43·3 months (IQR 30·8–52·1). At data cutoff, all 82 patients had failure; failure-free survival did not differ significantly between the groups (median 1·4 months [95% CI 1·0–2·1] in the cetuximab group *vs* 1·9 months [1·1–2·6] in the methotrexate group; adjusted HR 1·03 [95% CI 0·66–1·61], p=0·89). The frequency of patients who had grade 3 or worse adverse events was 63% (26 of 41) in the cetuximab group and 73% (30 of 41) in the methotrexate group. The most common grade 3–4 adverse events in the cetuximab group were fatigue (four [10%] of 41 patients), lung infection (four [10%]), and rash acneiform (four [10%]), and those in the methotrexate group were fatigue (nine [22%] of 41), increased gamma-glutamyltransferase (seven [17%]), natraemia disorder (four [10%]), anaemia (four [10%]), leukopenia (four [10%]), and neutropenia (four [10%]). The frequency of patients who had serious adverse events was 44% (18 of 41) in the cetuximab group and 39% (16 of 41) in the methotrexate group. Four patients presented with a fatal adverse event in the cetuximab group (sepsis, decreased level of consciousness, pulmonary oedema, and death of unknown cause) as did two patients in the methotrexate group (dyspnoea and death of unknown cause).

Interpretation The study showed no improvement in failure-free survival with cetuximab versus methotrexate. Patients with an ECOG performance status of 2 did not benefit from these systemic therapies. New treatment options including immunotherapy should be explored in frail older patients with recurrent or metastatic head and neck squamous cell carcinoma, after an initial geriatric evaluation, such as the ELAN Geriatric Evaluation.

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See **Comment** page e166

For the French translation of the abstract see **Online** for appendix 1

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See Online for appendix 2

Introduction

About 30% of patients with head and neck squamous cell carcinoma are aged 70 years or older. Older patients often present with more comorbidities and lower performance status than younger patients, which adversely affects their eligibility for and participation in clinical trials.[1]

In recurrent or metastatic head and neck squamous cell carcinoma, the paucity of trials dedicated to older patients,[2,3] combined with the underrepresentation of older patients in clinical trials, results in a scarcity of evidence-based data for this population.[2] As a result, there is no established standard for systemic palliative treatment, and physicians must find the right balance between treatment efficacy and maintaining patient autonomy and quality of life.[4] It is necessary to accurately assess patients' eligibility for systemic therapy,[5] with tolerance being the main challenge.[6,7] Since performance status and calendar age are not sufficient to assess their ability to receive a systemic therapy,[8] the use of specific geriatric assessments is necessary.[9]

In frail older patients with recurrent or metastatic head and neck squamous cell carcinoma for whom tolerability to polychemotherapy is anticipated to be poor, monotherapy or only best supportive care is recommended.[5,10] Weekly methotrexate is considered to be the accepted standard treatment (proof level I, A, of the European Society for Medical Oncology guidelines),[8] with similar overall survival and progression-free survival to other conventional forms of chemotherapy. However, the objective response rate has remained low (5–10%)[11,12] and tolerance data in older patients with head and neck squamous cell carcinoma are missing. Safety

Research in context

Evidence before this study

We searched PubMed for prospective clinical trial publications, published in English, from April 1, 1992, to April 1, 2022, with the following keywords: "head and neck", "elderly", "carcinoma" or "cancer", and "first-line" and "recurrent", or "metastatic" and "randomised". We found 45 publications, most of which used platinum-based chemotherapy combinations. In frail patients with recurrent or metastatic head and neck squamous cell carcinoma, monotherapy is usually recommended. The eligibility criteria for receiving a systemic treatment are often based on performance status or calendar age, and are thus not sufficient for older patients. When our study was initiated in 2013, methotrexate was considered the standard first-line treatment option in frail older patients with inoperable recurrent or metastatic head and neck squamous cell carcinoma. However, the objective response rate remained low (10% in a large randomised trial). Moreover, methotrexate is associated with chemotherapy-related adverse events. Among molecular targeted therapies, cetuximab is the only drug approved for the treatment of head and neck squamous cell carcinoma. There was no comparative study showing that monotherapy with an anti-epidermal growth factor receptor agent would be more effective than methotrexate. Moreover, survival and treatment response data on these two drugs were not available for frail older patients with recurrent or metastatic head and neck squamous cell carcinoma.

Added value of this study

To the best of our knowledge, this study is the first randomised controlled trial to compare methotrexate and cetuximab in the first-line setting for patients with recurrent or metastatic head and neck squamous cell carcinoma. It is also the first randomised trial dedicated solely to older patients (ie, those aged ≥70 years) with recurrent or metastatic head and neck squamous cell carcinoma who were considered frail using a geriatric evaluation adapted to patients with head and neck cancer. The main endpoint included efficacy, tolerance, and autonomy criteria, which are all relevant for evaluating the impact of treatment in a frail older population. By showing the absence of benefit of cetuximab compared to methotrexate in terms of oncological efficacy and the frequency and grade of adverse events (although with different toxicity profiles), the findings of this trial could help physicians in making treatment decisions for older patients with frailty. This study suggests that older patients with recurrent or metastatic head and neck squamous cell carcinoma who have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 should not be treated with these types of systemic treatments. On the contrary, frail older patients with an ECOG performance status of 0–1 could benefit from an adapted systemic treatment, less toxic than the EXTREME regimen (platinum plus 5-fluorouracil plus cetuximab).

Implications of all the available evidence

Frail older patients with recurrent or metastatic head and neck squamous cell carcinoma constitute a very distinct population with specific treatment challenges. To improve the oncological outcomes of treatments that can be offered to these patients without adversely affecting their quality of life and their autonomy, clinical trials dedicated specifically to older frail populations are needed. In the era of immunotherapy, the possibility of combining chemotherapy and immunotherapy in older frail patients with an ECOG performance status of 0–1 should be studied, as should the efficacy and safety of immunotherapy as monotherapy in older frail patients with an ECOG performance status of 2. The use of specific geriatric assessment tools such as the ELAN Geriatric Evaluation should be systematised not only before older patients with head and neck cancer are included in clinical trials but also before starting these patients on anticancer treatments.

data from patients with CNS lymphoma treated with methotrexate, who were given higher doses than those used in head and neck squamous cell carcinoma, show manageable toxicity in both younger and older patients.[13,14]

Cetuximab is currently considered as a treatment option for head and neck squamous cell carcinoma, although no direct randomised comparisons have been done with methotrexate.[8] As part of a combination regimen with maintenance treatment, cetuximab is usually delivered weekly. Recent trials of cetuximab monotherapy at a dose of 500 mg/m² every 2 weeks in patients with recurrent or metastatic head and neck squamous cell carcinoma have shown comparable efficacy to conventional dosing of cetuximab, without any notable increase in toxicity.[15,16] This schedule allows the frequency of infusions to be decreased, which is especially beneficial for frail or older patients and for long-term maintenance, and was approved in 2021 by the US Food and Drug Administration.[17] To date, the other anti-epidermal growth factor receptor (EGFR) drugs gefitinib and zalutumumab have not shown any advantage over methotrexate in patients with head and neck squamous cell carcinoma.[18]

At the time of initiation of the current trial, methotrexate was the only reference treatment recommended in frail patients with head and neck squamous cell carcinoma and cetuximab was an optional treatment. The tolerance and efficacy of methotrexate and cetuximab in older patients with head and neck squamous cell carcinoma had not been assessed in a randomised setting. We aimed to compare first-line cetuximab with methotrexate in terms of failure-free survival (an endpoint that includes efficacy, tolerance, and autonomy criteria) in older patients with recurrent or metastatic head and neck squamous cell carcinoma, evaluated as frail via a geriatric assessment before randomisation (appendix 2 pp 6–7). This study was part of the French prospective clinical programme ELAN, dedicated to older patients with head and neck squamous cell carcinoma and developed by the GERICO-GORTEC groups and Gustave Roussy (appendix 2 p 5).[19–21]

Methods

Study design and participants

This randomised, open-label, phase 3 trial was sponsored by Gustave Roussy (Villejuif, France) and conducted at 20 hospitals in France (appendix 2 p 2). The study included patients aged 70 years or older, assessed as frail via the ELAN Geriatric Evaluation (mobility tests, situational evaluation, Activities of Daily Living [ADL], Mini Mental-State Examination [MMSE], 4-item Geriatric Depression Scale [GDS-4], and Charlson Comorbidity Index; appendix 2 pp 6–7) followed by an optional comprehensive geriatric assessment conducted by physicians (dependent on the practices of the centre and availability of a geriatrician).

Eligible patients had to have histologically confirmed recurrent or metastatic head and neck squamous cell carcinoma (oral cavity, oropharynx, hypopharynx, or larynx) and not be eligible for local therapy. They had to be eligible for first-line treatment and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Additional key eligibility criteria comprised 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, cervical lymph node metastasis of unknown origin, previous systemic chemotherapy for head and neck squamous cell carcinoma (except if administered as part of a multimodal treatment for locally advanced disease >6 months before study entry), previous EGFR-targeting therapy (except if given in association with radiotherapy >12 months before study entry); surgery or irradiation within the previous 4 weeks, brain metastasis, inadequate haematological and hepatic function (absolute neutrophil count $<1{\cdot}5\times10^9$ cells per L, platelet count $<100\times10^9$ cells per L, haemoglobin concentration less than 9·5 g/dL, bilirubin concentration ≥upper limit of normal [ULN], aspartate and alanine aminotransferase concentrations >1·5 ULN, and alkaline phosphatase concentration >2·5 ULN), and creatinine clearance <50 mL/min per 1·73 m² (as defined by the Modification of Diet in Renal Disease Method). Patients with the following comorbidities were not eligible for inclusion: active severe or uncontrolled cardiovascular disease; myocardial infarction within 12 months before inclusion; unstable angina pectoris; significant arrythmias; and active infections including tuberculosis and HIV. Patients were excluded if they presented with malignancies within 5 years before inclusion, except for adequately treated basal or squamous cell skin cancer and cervix carcinoma in situ. Patients provided written, informed consent before participating in the study.

The study was performed according to 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 [ANSM], Saint-Denis, France) was obtained on Jan 17, 2013, and approval from the ethics committee (Comité de protection de personnes, Ile de France VII, Le Kremlin-Bicêtre, France) was obtained on April 18, 2013, with both obtained before the start of the study. An independent data monitoring committee (IDMC), composed of a statistician, an oncologist, a radiotherapist, and a geriatrician, was established to monitor the ethics and scientific progress of the study. This board met annually and at the time of the interim analysis. Safety was assessed quarterly by the steering committee.

For more on **TenAlea** see https://www.aleaclinical.eu/

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio via the TenAlea website by investigators or duly authorised people to receive cetuximab or methotrexate, with minimisation by Charlson Comorbidity Index (score ≤2 *vs* ≥3), ECOG performance status (0–1 *vs* 2), serum albumin concentration (>34 g/L *vs* ≤34 g/L), type of evolution (locoregional relapse *vs* metastatic disease), and geriatrician consultation performed before patient inclusion (yes *vs* no). To avoid deterministic minimisation and assure allocation concealment, patients were allocated with a probability of 0·80 to the treatment that most reduced the imbalance. Minimisation parameters were defined by the Gustave Roussy Biostatistics Unit (Villejuif, France) in the computerised TenAlea system. Physicians and patients were not masked to treatment group.

Procedures

Cetuximab was given intravenously every 2 weeks at a dose of 500 mg/m² as a 120-min infusion on day 1, as a 90-min infusion at second one on day 14, and as a 60-min infusion for the remaining administrations. Patients received methotrexate 40 mg/m² as an intravenous bolus injection weekly. Treatment was continued until disease progression or unacceptable toxicity. Details on the administration of anti-allergy prophylaxis for cetuximab and dose modifications of cetuximab and methotrexate for the management of adverse events according to protocol-specified criteria are presented in appendix 2 (pp 8–9).

Baseline assessments and the complete study flowchart are presented in appendix 2 (p 10). Study visits took place every 2 weeks during treatment cycles, during which ADLs and instrumental activities of daily living (IADL) and concomitant medications were assessed and adverse events were reported. Tumour response, assessed by CT scan or MRI, and health-related quality of life were assessed at fixed 6-week intervals after the start of treatment. After disease progression, survival status was documented. A safety follow-up visit after treatment cessation was planned 6 weeks after the last dose, during which health-related quality-of-life and ADL/IADL questionnaires were administered. Patients who discontinued treatment for reasons other than disease progression, death, or withdrawal of consent were followed up for assessment of progression-free survival every 6 weeks until documented disease progression or the start of a new cancer treatment, whichever occurred first.

Outcomes

The primary endpoint was failure-free survival, defined as the time from randomisation to disease progression, death, discontinuation of treatment (regardless of cause), or loss of two or more points on the ADL scale, whichever occurred first. Patients who did not have any of these events were censored at the date of the last follow-up. The outcome was assessed at the centre level.

There were three secondary efficacy endpoints: overall survival, progression-free survival, and objective response rate. Overall survival was defined as the time from randomisation to death from any cause. Progression-free survival was defined as the time from randomisation to disease progression or death, whichever occurred first. The objective response rate (complete or partial tumour response) was based on the best response obtained during treatment. Tumour response was evaluated by RECIST 1.1[22] until disease progression. All imaging assessments were reviewed by at least one investigator and radiologist at each centre.

Safety was assessed from the first dose of study treatment, using severity and type of adverse event (as per the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0).

Autonomy was assessed by ADL and IADL scores. Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQ-C30) and the Head and Neck Module (EORTC QLQ-H&N35) questionnaires.[23]

Statistical analysis

The expected median failure-free survival with methotrexate alone was 2·5 months. A 1·5-month improvement with cetuximab was expected, corresponding to a hazard ratio (HR) of 0·625. Assuming a 0·05 two-sided level of statistical significance, we estimated that the observation of 151 failures would provide 80% power to detect this difference. This number of failures was expected from a total of 164 patients (82 per treatment group). A futility interim analysis based on failure-free survival was scheduled when approximately 80 failures occurred (53% of the expected total number of failures). The futility boundary was constructed by using the spending function of Lan-DeMets with O'Brien-Fleming parameters (East software) and was non-binding. The analysis was performed when 79 failures had occurred. The p value boundary for futility was 0·26.

Failure-free survival was estimated with the Kaplan–Meier method. The 95% CIs of the timepoint estimates were calculated with the Rothman method. Comparisons between the two treatment groups were done by Cox's proportional hazards model. Main analyses report HRs adjusted for the minimisation factors and p values of the Wald test. Crude HRs are provided for context. Similar analyses were done for progression-free survival and overall survival. The proportional hazards assumption was assessed by visual inspection of the plots of the log(–log(survival)) versus the log (time).

All tumour responses, regardless of whether they were confirmed on a follow-up scan, were included in the overall response analysis. The best response obtained

during the studied treatment was used in analyses. Patients without response evaluation were regarded as non-responders. The objective response rate (complete and partial response) was compared between the two treatment groups using logistic regression. Odds ratios (ORs) adjusted for minimisation factors and crude odds ratios were reported. Duration of response was estimated with the Kaplan–Meier method in patients who achieved a partial or complete response and was calculated from the date of first response until the date of progression. Patients who died after having an objective response were censored at the date of death. The QLQ-C30 and QLQ-H&N35 questionnaires were scored according to EORTC recommendations, as described in the EORTC QLQ-C30 and QLQ-H&N35 Scoring Manual. Scores were compared between the two treatment groups using linear mixed-effects models to account for repeated measurements of quality of life and the baseline score. The primary endpoint of the quality of life analysis was the global health status/quality of life scale of the QLQ-C30 questionnaire. ADL and IADL scores were also analysed with mixed models adjusted for the baseline score, but due to a small sample size after week 16 the analyses by mixed models were restricted to weeks 2–16.

Adverse events were described by treatment group, according to grade and type. The frequency of patients with severe adverse events (grade 3–5) was compared between the two treatment groups.

A post-hoc analysis of the effect of minimisation factors on overall survival, progression-free survival, and failure-free survival was done using a Cox model stratified by treatment group. A post-hoc analysis was done of grade 4–5 adverse events according to performance status group (ECOG 0–1 *vs* 2).

Analyses of efficacy criteria by subgroups defined by p16/human papillomavirus (HPV) status of oropharyngeal tumours were planned but they were not done due to the small number of patients with p16/HPV-positive oropharyngeal tumours.

Except for the interim analysis, statistical tests were two-sided and p values less than 0·05 were considered statistically significant. All analyses were performed according to the intention-to-treat principle, using SAS version 4.

This trial is registered with ClinicalTrials.gov (NCT01884623) and is completed.

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 or the decision to submit the manuscript for publication.

Results

Between Nov 7, 2013, and April 23, 2018, 82 patients were randomly assigned, 41 to each treatment group. One patient was found to be ineligible as they did not have relapse or metastasis, and one patient withdrew consent after the first administration of cetuximab. All patients were included in the intention-to-treat analyses (figure 1). Baseline patient and disease characteristics are shown in table 1 and appendix 2 (pp 11–13). Of the 82 patients, 60 (73%) were male (29 in the cetuximab group and 31 in the methotrexate group), 37 (45%) were aged 80 years or older, 35 (43%) had an ECOG performance status of 2, and 36 (44%) had metastatic disease.

An interim futility analysis was done in June, 2018, based on 79 failures (ie, 52% of the planned failures) in 81 patients randomly assigned until the end of February, 2018 (41 in the cetuximab group and 40 in the methotrexate group). Median follow-up was 18·1 months (IQR 13·3–28·0). 39 patients had failure in the cetuximab group, as did 40 in the methotrexate group. Median failure-free survival was 1·4 months (95% CI 1·0–2·1) in the cetuximab group versus 2·0 months (1·1–2·5) in the methotrexate group (HR 0·98; 95% CI 0·62–1·53). The futility boundary was crossed. Enrolment was therefore stopped on June 12, 2018, on the recommendation of the IDMC.

In each treatment group, all patients received at least one administration of treatment. Two (5%) of 41 patients in the cetuximab group had a dose reduction; this occurred in four of 389 administrations. For one patient, the dose reduction was related to a technical problem and for the other patient it was an error. 13 (32%) of 41 patients in the methotrexate group had a dose reduction; this occurred in 130 of 482 administrations. The main reasons for methotrexate dose reduction were

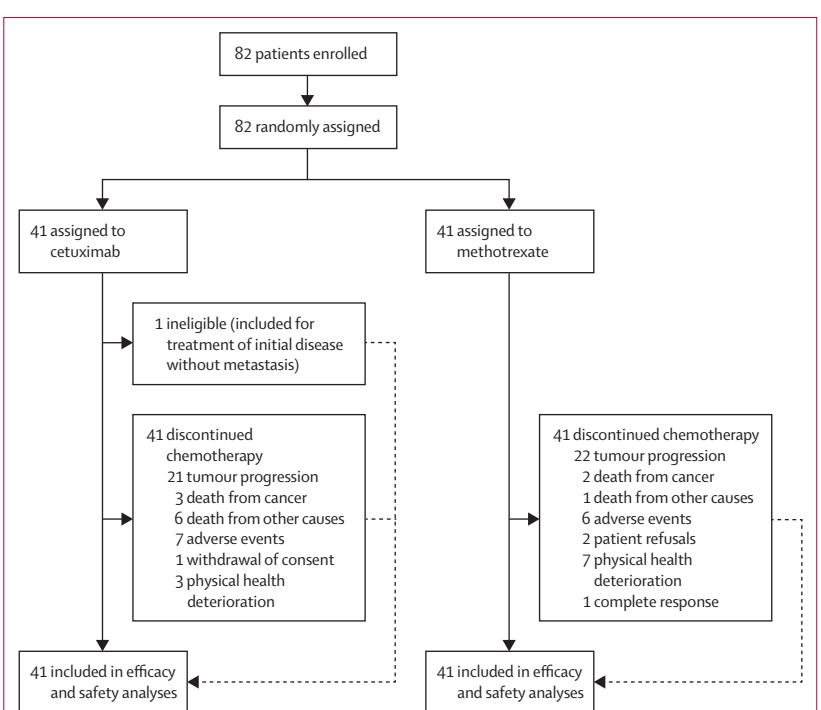

Figure 1: **Trial profile**

	Cetuximab (n=41)	Methotrexate (n=41)	Total (n=82)
Sex			
Male	29 (71%)	31 (76%)	60 (73%)
Female	12 (29%)	10 (24%)	22 (27%)
Age (years)			
Mean (SD)	78·8 (5·4)	79·3 (5·3)	79·0 (5·3)
Median (IQR)	78 (74–82)	79 (76–82)	78 (74–82)
≥80 years	17 (41%)	20 (49%)	37 (45%)
ECOG performance status			
0	3 (7%)	1 (2%)	4 (5%)
1	21 (51%)	22 (54%)	43 (52%)
2	17 (41%)	18 (44%)	35 (43%)
Number of geriatric frailties			
Mean (SD)	2·4 (1·1)	2·4 (1·1)	2·4 (1·1)
Median (range)	2 (0–5)	3 (0–4)	2 (0–5)
≥3	20 (49%)	22 (54%)	42 (51%)
Charlson Comorbidity Index score			
0	10 (24%)	16 (39%)	26 (32%)
1	14 (34%)	17 (41%)	31 (38%)
2	10 (24%)	5 (12%)	15 (18%)
≥3	7 (13%)	3 (7%)	10 (12%)
Serum albumin (g/L)			
Mean (SD)	36·5 (5·1)	36·8 (5·3)	36·7 (5·2)
Median (range)	36·0 (22·0–46·4)	37·0 (21·1–46·0)	37·0 (21·1–46·4)
≤34 g/L	11 (27%)	11 (27%)	22 (27%)
>34 g/L	30 (73%)	30 (73%)	60 (73%)
Comprehensive geriatric assessment performed			
No	15 (37%)	18 (44%)	33 (40%)
Yes	26 (63%)	23 (56%)	49 (60%)
Tobacco consumption			
Never smoked	8 (20%)	16 (39%)	24 (29%)
Former smoker	29 (71%)	22 (54%)	51 (62%)
Current smoker	4 (10%)	3 (7%)	7 (9%)
Alcohol consumption			
Never drank	25 (61%)	23 (56%)	48 (59%)
Former drinker	10 (24%)	10 (24%)	20 (24%)
Current drinker	6 (15%)	8 (20%)	14 (17%)
Type of disease evolution			
Locoregional relapse alone	21 (51%)	24 (59%)	45 (55%)
Metastatic disease	19 (46%)	17 (41%)	36 (44%)
Initial disease without metastasis*	1 (2%)	0	1 (1%)
Initial tumour location			
Oropharynx	15 (37%)	15 (37%)	30 (37%)
Oral cavity	13 (32%)	17 (41%)	30 (37%)
Hypopharynx	6 (15%)	4 (10%)	10 (12%)
Larynx	6 (15%)	4 (10%)	10 (12%)
Other	1† (2%)	1‡ (2%)	2 (2%)

Data are n (%), mean (SD), or median (IQR). ECOG=Eastern Cooperative Oncology Group. *Patient not eligible for inclusion. †Lip. ‡Nodes alone and metastasis.

Table 1: **Patient and tumour characteristics at inclusion**

haematological toxicity (in six patients) and mucositis (in three patients). At the cutoff date of Dec 17, 2021, all patients had discontinued treatment. The main cause of discontinuation was disease progression (21 in the cetuximab group *vs* 22 in the methotrexate group), followed by adverse events (seven *vs* six), physical health deterioration (three *vs* seven), death from a non-cancer cause (six *vs* one), death from cancer (three *vs* two), patient refusal (one *vs* two), and complete response (one in the methotrexate group). There were a median of four administrations in the cetuximab group and eight in the methotrexate group. Six (15%) of 41 patients in the cetuximab group received only one administration versus three (7%) of 41 in the methotrexate group. Median treatment duration was 1·4 months (IQR 0·9–3·8) in the cetuximab group and 1·9 months (0·7–4·0) in the methotrexate group. The treatment duration was up to 1 month in 17 (41%) patients in the cetuximab group and 12 (29%) patients in the methotrexate group, and was longer than 6 months in six (15%) patients in the cetuximab group and five (12%) patients in the methotrexate group, with a maximal duration of 51·8 months in the cetuximab group versus 15·1 months in the methotrexate group.

Median follow-up was 43·3 months (IQR 30·8–52·1). Five patients were alive at their last follow-up. Three of these patients (two in the cetuximab group and one in the methotrexate group) were followed up for more than 3·6 years, one (in the cetuximab group) was lost to follow-up at 2·5 years, and one patient withdrew consent and had only a 1-day follow-up.

At data cutoff, all 82 patients had failure. Failures occurred between 1 day and 51·8 months after randomisation. Disease progression was the most common type of failure in both groups (19 patients in the cetuximab group *vs* 20 in the methotrexate group), followed by discontinuation of treatment due to adverse events (six *vs* five), physical health deterioration (three *vs* six) or patient refusal (one *vs* two), death (seven *vs* three), and a decrease of 2 or more points in ADL score (five *vs* five). Failure-free survival did not differ significantly between the groups (median 1·4 months [95% CI 1·0–2·1] in the cetuximab group *vs* 1·9 months [1·1–2·6] in the methotrexate group; crude HR 1·06 [95% CI 0·68–1·64], adjusted HR 1·03 [0·66–1·61], p=0·89; figure 2A).

37 deaths occurred in the cetuximab group compared with 40 in the methotrexate group. Deaths were related to cancer in 25 patients in the cetuximab group versus 33 in the methotrexate group, related to other causes in ten patients in the cetuximab group and five patients in the methotrexate group, and were of unknown cause in two patients in each group. Overall survival did not differ significantly between the groups (median 4·6 months [95% CI 2·4–7·3] in the cetuximab group *vs* 4·6 months [2·3–7·7] in the methotrexate group; crude HR 0·87 [95% CI 0·55–1·36], adjusted HR 0·82 [0·52–1·29], p=0·39; figure 2B).

79 progression-free survival events (progression or death) occurred, 38 in the cetuximab group and 41 in the methotrexate group. Progression-free survival did not

differ significantly between the groups (median 2·4 months [95% CI 1·5–3·7] in the cetuximab group *vs* 2·7 months [1·4–4·1] in the methotrexate group; crude HR 0·98 [95% CI 0·63–1·52], adjusted HR 0·90 [0·57–1·40], p=0·64; figure 2C).

There was no evidence of violation of the proportional hazards assumption for failure-free survival, overall survival, and progression-free survival.

Tumour response was evaluated in 73 (89%) of 82 patients (35 in the cetuximab group and 38 in the methotrexate group). An objective response was achieved in five patients (12·2%; 95% CI 4·1–26·2) in the cetuximab group and in six patients (14·6%; 5·6–29·2) in the methotrexate group (crude OR 0·81 [95% CI 0·23–2·90], adjusted OR 0·88 [95% CI 0·23–3·26]; p=0·84). The median duration of response was 5·9 months (95% CI 2·8–not reached) with cetuximab and 6·7 months (95% CI 1·3–30·3) with methotrexate.

The proportion of quality-of-life questionnaires returned was 88% (36 of 41) at baseline in the cetuximab group and 93% (38 of 41) at baseline in the methotrexate group, 70% (23 of 33 expected) and 74% (25 of 34 expected) at week 6, and 53% (41 of 77 expected) and 43% (36 of 83 expected) over the period from week 12 to week 30. The analyses of the QLQ-C30 and QLQ-H&N35 questionnaires are presented in appendix 2 (pp 14–25). No significant difference was seen between the treatment groups for the quality of life primary endpoint of global health status/quality-of-life score (p=0·88), nor for the other QLQ-C30 scores; there were no differences between groups on the QLQ-H&N35, except for the sticky saliva item, which was worse in the methotrexate group than in the cetuximab group (p=0·025).

The analyses of the ADL and IADL questionnaires are presented in appendix 2 (pp 26–29). From week 2 to 16, no significant difference was seen between the treatment groups for ADL (p=0·35) or for the IADL score (p=0·88).

Safety results represent all observed adverse events. All patients in the methotrexate group presented with at least one adverse event (table 2). Six patients had a grade 5 adverse event: four in the cetuximab group (sepsis, decreased level of consciousness, pulmonary oedema, and death of unknown cause) and two in the methotrexate group (dyspnoea and death of unknown cause). Ten (24%) of 41 patients in the cetuximab group had an adverse event of grade 4 or worse, compared with nine (22%) of 41 patients in the methotrexate group. In the cetuximab group, 26 (63%) patients had at least one adverse event of grade 3 or worse, compared with 30 (73%) in the methotrexate group (p=0·34). 18 (44%) patients in the cetuximab group had at least one serious adverse event versus 16 (39%) in the methotrexate group. The most common adverse events of any grade (occurring in >20% of all patients) were decreased serum albumin, electrolyte disturbances, haematological adverse events, fatigue, disturbances in liver parameters (aminotransferase, gamma-glutamyltransferase, and alkaline phosphatase), oral

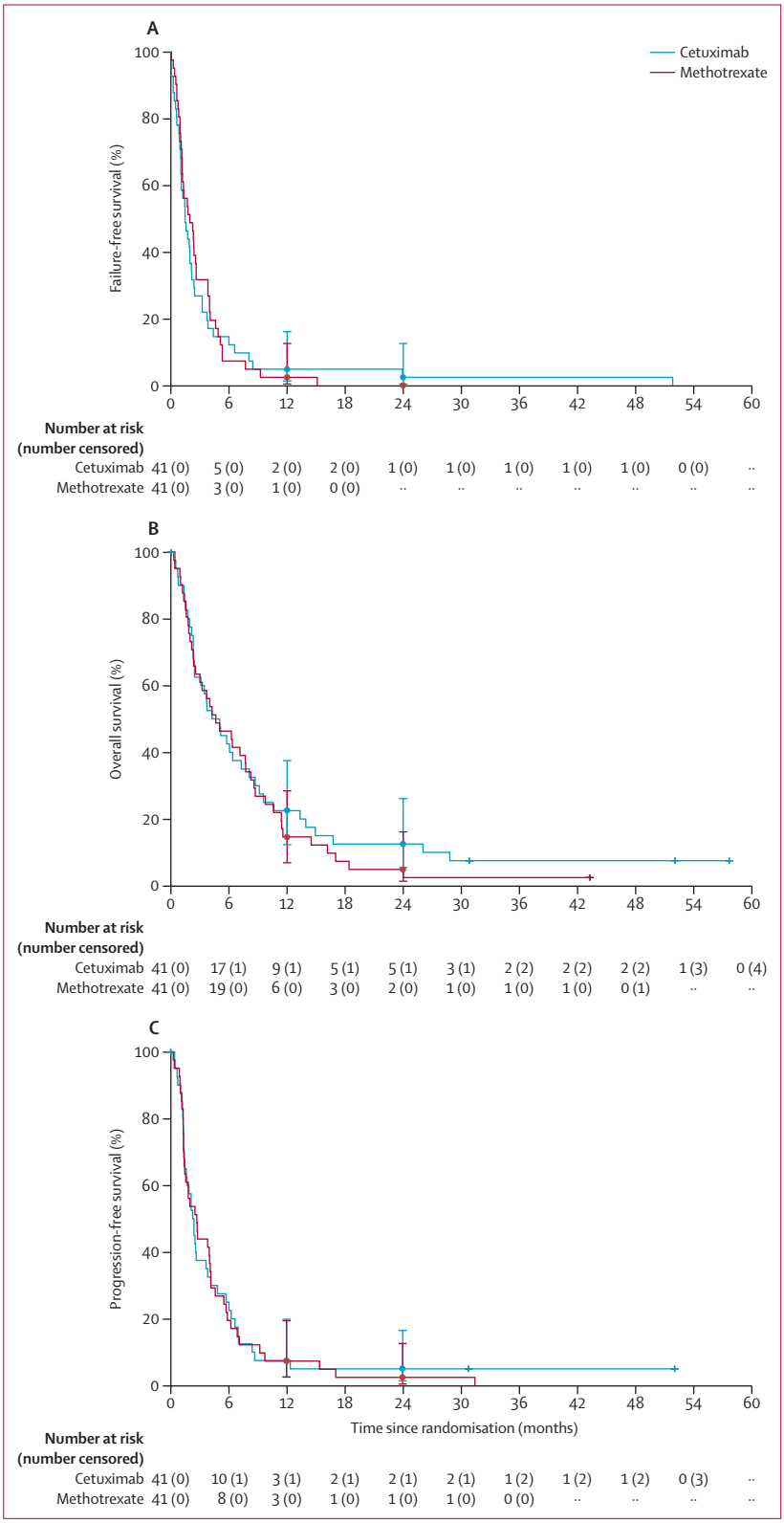

Figure 2: **Kaplan–Meier estimates of failure-free survival (A), overall survival (B), and progression-free survival (C) according to treatment group**

	Cetuximab group (n=41)				Methotrexate group (n=41)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All adverse events								
Maximal grade reached	15 (37%)	16 (39%)	6 (15%)	4 (10%)	11 (27%)	21 (51%)	7 (17%)	2 (5%)
Any type of adverse event*	41 (100%)	24 (59%)	6 (15%)	4 (10%)	40 (98%)	28 (68%)	7 (17%)	2 (5%)
Blood system disorders								
Anaemia	26 (63%)	0	1 (2%)	0	31 (76%)	4 (10%)	0	0
Leukopenia	6 (15%)	0	0	0	15 (37%)	2 (5%)	2 (5%)	0
Thrombocytopenia	6 (15%)	1 (2%)	0	0	11 (27%)	1 (2%)	1 (2%)	0
Neutropenia	2 (5%)	1 (2%)	0	0	5 (12%)	2 (5%)	2 (5%)	0
Febrile neutropenia						1 (2%)	1 (2%)	0
Cardiac and vascular disorders								
Hypotension	2 (5%)	1 (2%)	1 (2%)	0	1 (2%)	0	0	0
Hypertension	1 (2%)	1 (2%)	0	0	1 (2%)	1 (2%)	0	0
Thromboembolic event	0	1 (2%)	0	0	0	1 (2%)	0	0
Heart failure	0	0	0	0	0	1 (2%)	0	0
Ear disorders								
Hearing impaired	0	1 (2%)	0	0	0	0	0	0
Gastrointestinal disorders								
Mucositis oral	6 (15%)	1 (2%)	0	0	16 (39%)	1 (2%)	0	0
Diarrhoea	2 (2%)	0	0	0	11 (27%)	1 (2%)	0	0
Constipation	5 (12%)	2 (5%)	0	0	7 (17%)	0	0	0
Nausea	4 (10%)	0	0	0	8 (20%)	0	0	0
Vomiting	5 (12%)	0	0	0	7 (17%)	0	0	0
Dysphagia	5 (12%)	2 (5%)	0	0	2 (5%)	2 (5%)	0	0
Oral haemorrhage	1 (2%)	0	1 (2%)	0	2 (5%)		0	0
Abdominal pain	0	0	0	0	2 (5%)	1 (2%)	0	0
Oral pain	1 (2%)	0	0	0	1 (2%)	0	1 (2%)	0
Tongue haemorrhage	0	0	0	0	0	0	1 (2%)	0
Small intestinal obstruction	0	1 (2%)	0	0	0	0	0	0
General disorders								
Fatigue	15 (12%)	4 (10%)	0	0	17 (41%)	9 (22%)	0	0
Pain	4 (10%)	2 (5%)	0	0	7 (17%)	0	0	0
Fever	1 (2%)	0	1 (2%)	0	6 (15%)	1 (2%)	0	0
Allergic reaction	1 (2%)	2 (5%)	1 (2%)	0	0	0	0	0
Health status alteration	0	0	1 (2%)	0	1 (2%)	2 (5%)	0	0
Death not otherwise specified	0	0	0	1 (2%)	0	0	0	1 (2%)
Infection								
Lung infection	2 (5%)	2 (5%)	2 (5%)	0	2 (5%)	0	0	0
Sepsis	0	1 (2%)	1 (2%)	1 (2%)	0	0	1 (2%)	0
Bronchial infection	0	0	0	0	2 (5%)	1 (2%)	0	0
Bone infection	0	1 (2%)	0	0	0	0	0	0
Device-related infection	0	1 (2%)						
Other infections	1 (2%)	1 (2%)	0	0	0	1 (2%)	0	0
Investigations								
Increased gamma-glutamyltransferase	16 (39%)	0	1 (2%)	0	13 (32%)	6 (15%)	1 (2%)	0
Increased alkaline phosphatase	15 (37%)	1 (2%)	0	0	11 (27%)	1 (2%)	0	0
Increased aspartate aminotransferase	7 (17%)	0	1 (2%)	0	19 (46%)	0	0	0
Increased alanine aminotransferase	3 (7%)	1 (2%)	0	0	17 (41%)	0	0	0
Decreased creatinine clearance	4 (10%)	0	0	0	10 (24%)	1 (2%)	0	0
Increased blood bilirubin	4 (10%)	0	0	0	6 (15%)	0	0	0

(Table 2 continues on next page)

	Cetuximab group (n=41)				Methotrexate group (n=41)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Metabolism and nutrition disorders								
Decreased serum albumin	36 (88%)	0	0	0	35 (85%)	0	0	0
Natraemia disorder	23 (56%)	3 (7%)	0	0	25 (61%)	3 (7%)	1 (2%)	0
Kalaemia disorder	25 (61%)	0	1 (2%)	0	21 (51%)	2 (5%)	0	0
Calcaemia disorder	23 (56%)	1 (2%)	0	0	23 (56%)	0	0	0
Magnesaemia disorder	29 (71%)	0	0	0	16 (39%)	1 (2%)	0	0
Anorexia	6 (15%)	0	1 (2%)	0	9 (22%)	1 (2%)	0	0
Dehydration	0	0	0	0	1 (2%)	0	1 (2%)	0
Hyperglycaemia	0	1 (2%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders								
Trismus	1 (2%)	0	0	0	3 (7%)	1 (2%)	0	0
Back pain	1 (2%)	1 (2%)	0	0	2 (5%)	0	0	0
Pain in limbs	1 (2%)	1 (2%)	0	0	1 (2%)	0	0	0
Myalgia	1 (2%)	1 (2%)	0	0	0	0	0	0
Hip fracture	0	1 (2%)	0	0	0	0	0	0
Benign and malignant neoplasms								
Tumour pain	4 (10%)	0	0	0	6 (15%)	1 (2%)	0	0
Nervous system disorders								
Depressed level of consciousness	0	0	0	1 (2%)	0	0	0	0
Dizziness	0	0	0	0	0	1 (2%)	0	0
Dysphasia	0	1 (2%)	0	0	0	0	0	0
Psychiatric disorders								
Insomnia	1 (2%)	0	0	0	1 (2%)	2 (5%)	0	0
Hallucinations	0	0	0	0	2 (5%)	1 (2%)	0	0
Respiratory and thoracic disorders								
Dyspnoea	1 (2%)	1 (2%)	1 (2%)	0	3 (7%)	3 (7%)	0	1 (2%)
Cough	5 (12%)	0	0	0	5 (12%)	0	0	0
Voice alteration	1 (2%)	1 (2%)	0	0	0	0	0	0
Pulmonary oedema	0	0	0	1 (2%)	0	0	0	0
Adult respiratory distress syndrome	0	1 (2%)	0	0	0	0	0	0
Pleural effusion	0	0	0	0	0	1 (2%)	0	0
Haemoptisiae	0	0	0	0	0	1 (2%)	0	0
Epistaxis	1 (2%)	0	0	0	0	1 (2%)	0	0
Skin and subcutaneous tissue disorders								
Rash acneiform	16 (39%)	4 (10%)	0	0	2 (5%)	0	0	0

Data are n (%). Adverse events of grade 1 or 2 occurring in ≥10% of patients in either group and all adverse events of grade 3, 4, or 5 are shown. A complete list of adverse events, including all grade 1 or 2 adverse events, is provided in appendix 2 (pp 30–33). *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 2: **Adverse events**

mucositis, acneiform rash, and anorexia. Acneiform rash and magnesium disorders were more frequent in the cetuximab group than in the methotrexate group. Anaemia, leukopenia, increased liver aminotransferases, diarrhoea, and oral mucositis were more frequent in the methotrexate group than in the cetuximab group. Four (10%) patients in the cetuximab group had an allergic reaction to cetuximab, one being grade 4, two grade 3, and one grade 1. The most common grade 3–4 adverse events in the cetuximab group were fatigue (four patients), lung infection (four patients), and rash acneiform (four patients); and the most common 3–4 adverse events in the methotrexate group were fatigue (nine patients), increased gamma-glutamyltransferase (seven patients), natraemia disorder (four patients), anaemia (four patients), leukopenia (four patients), and neutropenia (four patients). All adverse events are presented in appendix 2 (pp 30–33).

Grade 4–5 adverse events were significantly more frequent in the 35 patients with an ECOG performance status of 2 than in the 47 patients with an ECOG

performance status of 0–1 (13 [37%] *vs* six [13%]). Five of the six grade 5 adverse events occurred in patients with an ECOG performance status of 2.

Post-hoc prognostic analyses showed that an ECOG performance status of 2 and metastatic disease were independently associated with worse overall survival, progression-free survival, and failure-free survival (appendix 2 pp 34–37). Median overall survival was 2·1 months (95% CI 1·5–3·2) in patients with an ECOG performance status of 2 compared with 7·3 months (4·6–9·6) in patients with an ECOG performance status of 0–1 (HR for death 2·93; 95% CI 1·80–4·78), and 2·8 months (2·0–4·6) in patients with metastatic disease compared with 7·1 months (4·2–9·1) in those with locoregional relapse alone (HR for death 2·05; 95% CI 1·27–3·31; figure 3). The other minimisation factors (Charlson Comorbidity Index, serum albumin concentration, and whether a geriatrician consultation was done) were not independently associated with overall survival, progression-free survival, or failure-free survival (appendix 2 pp 34–35).

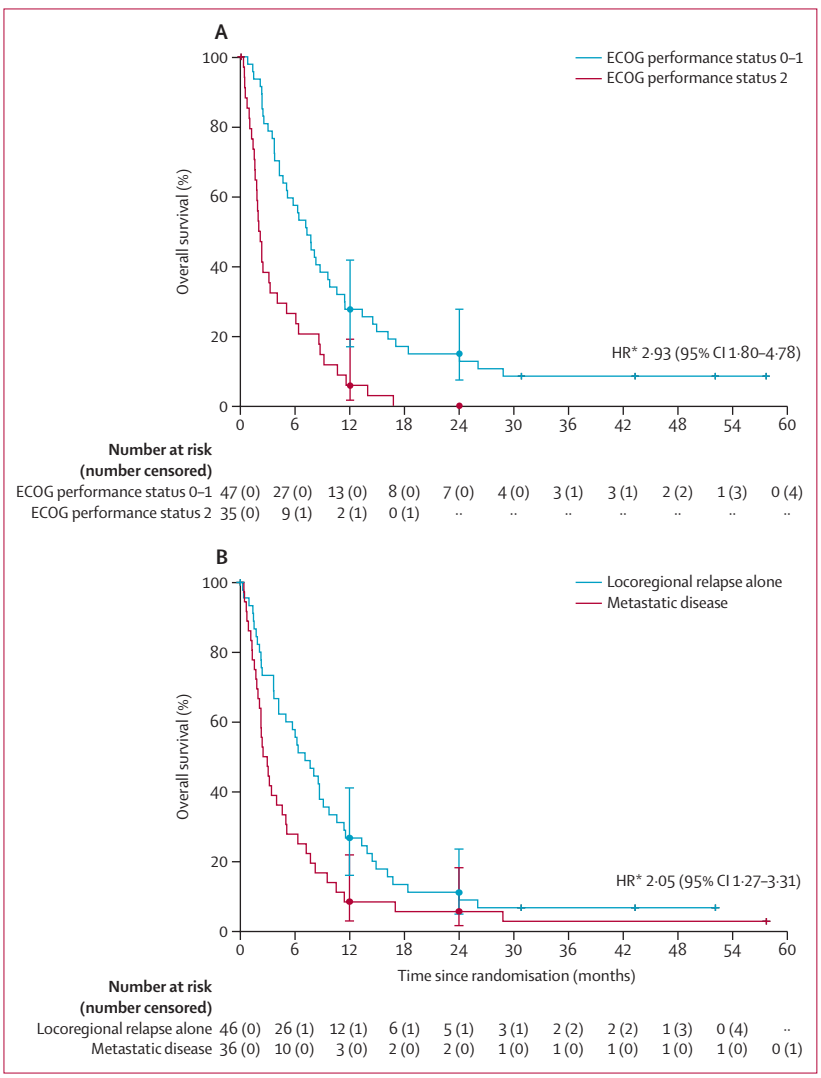

Figure 3: **Kaplan–Meier estimates of overall survival for both treatment groups together, according to ECOG performance status or type of disease evolution at inclusion**

(A) ECOG performance status (2 *vs* 0–1). (B) Metastatic disease versus locoregional relapse alone. Point estimates of overall survival at 12 months and 24 months with Rothman 95% CIs (vertical bars) are shown. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. *HR for death estimated in Cox model including performance status and type of disease evolution and stratified by treatment group.

Discussion

To the best of our knowledge, this study is the first randomised trial to compare methotrexate and cetuximab in the first-line setting in patients with recurrent or metastatic head and neck squamous cell carcinoma. The primary objective was not reached as no benefit of cetuximab compared with methotrexate was observed in terms of failure-free survival in this frail older population. After the interim analysis showing an HR of 0·98 that was indicative of futility, the study was stopped prematurely for futility after half of the planned patients had been enrolled. No differences were observed between the two treatment groups in overall survival, progression-free survival, and objective response rate. The objective response rate was similar to that reported in a previous trial of methotrexate in younger patients with recurrent or metastatic head and neck squamous cell carcinoma in the first-line setting (10%),[12] and similar to that in a trial of cetuximab in patients with platinum-resistant cancer (13%).[24] Disease progression was the most common type of failure in both groups, while only ten (12%) of 82 failures were related to a decrease of 2 or more points in the ADL score. The study confirms the feasibility of administering 500 mg/m² cetuximab every 2 weeks in an older and vulnerable patient population, which supports the approval of this dosing regimen by the US Food and Drug Administration.

The primary endpoint was discussed by geriatricians and oncologists from Unicancer GERICO and H&N groups. Failure-free survival was chosen because it includes efficacy, tolerance, and autonomy criteria, which are all relevant to evaluate the impact of treatment in an older frail population.

Our study had several limitations. Due to the early termination of the trial after the predefined futility criterion was met at the interim analysis, the planned sample size was not reached. Our efficacy hypothesis was an HR of failure of 0·625, whereas the observed HR was 0·98 (95% CI 0·62–1·53) at the interim analysis and 1·03 (0·66–1·61) at the final analysis, when all patients had failure. Although we are confident that it would have been futile to continue enrolment for the primary endpoint hypothesis, the reduction in the number of patients randomly assigned, which resulted from early termination of the study, meant that the power to assess secondary endpoints, including quality of life and autonomy, was reduced. Indeed, data on quality of life and autonomy outcomes are important in the frail older population, especially in this trial in which the frequency of adverse events was similar between the

two groups but the toxicity profile was different. However, due to a scarcity of data, some differences might not have been detected. Moreover, the small sample size compromised our ability to study long-term survival; of the 82 patients randomly assigned, only seven were alive after 2 years, but this number could have been higher if more patients had been enrolled.

In this population of older patients with recurrent or metastatic head and neck squamous cell carcinoma classified as frail according to a geriatric evaluation, two prognostic factors were identified to influence overall survival, progression-free survival, and failure-free survival independently of the treatment group: a metastatic disease status and an ECOG performance status of 2 were unfavourable. Significant differences were observed between patients with an ECOG performance status of 0–1 versus those with a performance status of 2 in terms of overall survival (7·3 months *vs* 2·1 months) and tolerance to treatment (grade 4–5 adverse events in 13% *vs* 37% of patients), suggesting that patients with an ECOG performance status of 2 did not benefit from these standard systemic treatments. On the contrary, patients with an ECOG performance status of 0–1 could benefit from an adapted systemic treatment, less toxic than the EXTREME regimen (platinum plus 5-fluorouracil plus cetuximab).[25] These data underline the importance of a treatment regimen adapted to the level of frailty in patients and the importance of including supportive care to preserve autonomy and manage treatment-related adverse events. Evaluation of a clinico-radiobiological age appears essential in patients with head and neck squamous cell carcinoma to better characterise patients' frailty and to, accordingly, choose the most appropriate treatment.

Immunotherapy targeting PD1 and PD-L1 has been tested in patients with head and neck squamous cell carcinoma, showing an improvement in survival in patients with recurrent or metastatic cancer. Following the results of the KEYNOTE-048 study, pembrolizumab obtained a European marketing authorisation and is now considered the recommended first-line treatment as monotherapy or in combination with platinum and 5-fluorouracil for patients with PD-L1 combined positive score.[26] Few data exist for the older patient population but, in patients with an ECOG performance status of 0–1, the efficacy has been shown to be similar to that observed in younger patients.[27]

As the optimal treatment paradigm in the palliative setting for older patients with head and neck squamous cell carcinoma has not been well defined, the inclusion of older people in dedicated clinical trials, with an adapted geriatric assessment, should be encouraged. New treatment options such as immunotherapy with checkpoint inhibitors should be explored through a suitable evidence-based approach in older frail patients. Pembrolizumab, being a well tolerated treatment, in combination with well tolerated chemotherapy or new immune agents, requires further testing in older patients with an ECOG performance status of 0–1. Patients aged 70 years or older with an ECOG performance status of 0 or 1 may well tolerate an anti-PD-1 agent and carboplatin doublet regimen. For older, frail patients with an ECOG performance status of 2, the comparison of pembrolizumab with best supportive care will be of interest in the first-line setting.

In conclusion, this study did not meet its primary endpoint, with no significant improvement in failure-free survival, nor in overall survival or progression-free survival, observed with cetuximab versus methotrexate. The toxicity profile was different between the two treatments, but the frequency of adverse events was similar. Frail patients with an ECOG performance status of 2 did not benefit from these systemic therapies. New treatment options including immunotherapy should be explored in frail older patients with recurrent or metastatic head and neck squamous cell carcinoma, following an initial geriatric evaluation such as the ELAN Geriatric Evaluation,[28] using an evidence-based approach.

Contributors

Academic advisers and the sponsor designed this study. All data were collected by the investigators and their site personnel. All authors had full access to all the data in the study, vouch for their accuracy, and attest that the study conformed to the protocol. The coordinating investigator (JG) and the statistician (AA) had full access to the data and verified the accuracy. A statistician employed by the sponsor 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 reviewing and amending the manuscript. The corresponding author had final responsibility to submit the publication.

Declaration of interests

JG has been an advisory board member for Bristol Myers Squibb, Hookipa Pharma, MSD, Merck, Nanobiotix, and Roche, outside the submitted work; reports support for attending meetings or travel, or both, from Merck and MSD; and received grant support, paid to his institution, from the GEMLUC (Groupement des Entreprises Monégasques dans la Lutte Contre le Cancer and GEFLUC (Groupement des Entreprises Françaises dans la Lutte contre le Cancer), and the French National Cancer Institute, the Fondation ARC, and the Ligue Contre le Cancer, through the French programme PAIR-VADS. CE reports receiving consulting fees from Bristol Myers Squibb, Elevar, F-star Therapeutics, Innate Pharma, Merck Serono, MSD, and Novartis outside the submitted work; and support for attending meetings or travel, or both, from MSD and Merck Serono. PDe reports personal fees from LEO Pharma and Pfizer, and support for attending meetings or travel, or both, from Pfizer, outside the submitted work. JF reports personal fees from MSD, Merck, Sanofi, Bristol Myers Squibb, Roche, AstraZeneca, Seagen, Hookipa, and Elevar; has been an advisory board member for Roche, Seagen, and Elevar; and reports support for attending meetings or travel, or both, from MSD and Merck, outside the submitted work. ESB 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. PDa reports personal fees from Gilead Science and support for attending meetings or travel from Lilly, or both, and has been an advisory board member for Pfizer, outside the submitted work. CF reports personal fees from Astellas Pharma, AstraZeneca, Biogaran, Bristol Myers Squibb, Chugai Pharma, Clovis Oncology, Eisai, GSK, Leo Pharma, Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Seagen, and Viatris; and non-financial support from AstraZeneca, Janssen Oncology, Đeo Pharma, and Pierre Fabre, outside the submitted work. JB reports support for attending

meetings from Bristol Myers Squibb, Merck, Nanobiotix, and MSD; participated on advisory boards for Merck, MSD, Bristol Myers Squibb, Nanobiotix, and Roche; and reports consulting fees from Bristol Myers Squibb, Merck, Nanobiotix, MSD, and Roche, outside the submitted work. AA has been an advisory member for MSD, outside the submitted work; and received grant support, paid to their institution, from the French National Cancer Institute, the Fondation ARC and the Ligue Contre le Cancer for a study grant through the French programme PAIR-VADS. 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.

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