European Journal of Cancer 156 (2021) 35–45

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

First-line treatment with chemotherapy plus cetuximab in Chinese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: Efficacy and safety results of the randomised, phase III CHANGE-2 trial

Ye Guo [a,1], Yi Luo [b], Qingyuan Zhang [c], Xiaoming Huang [d], Zhengdong Li [e], Liangfang Shen [f], Jifeng Feng [g], Yan Sun [h], Kunyu Yang [i], Minghua Ge [j], Xiaodong Zhu [k], Lin Wang [l], Yanyan Liu [m], Xiaohui He [n], Chunmei Bai [o], Kai Xue [p], Yan Zeng [q,2], XinYing Chang [q], Wenfeng Chen [q], Tongyu Lin [r,*]

[a] *Medical Oncology Department, Fudan University Cancer Center, Shanghai, People's Republic of China*
[b] *Hunan Cancer Hospital, Hunan Sheng, People's Republic of China*
[c] *Harbin Medical University Cancer Hospital, Harbin, People's Republic of China*
[d] *Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China*
[e] *Liaoning Cancer Hospital and Institute, Liaoning Sheng, People's Republic of China*
[f] *Xiangya Hospital, Central South University, Hunan Sheng, People's Republic of China*
[g] *Jiangsu Cancer Hospital, Nanjing, People's Republic of China*
[h] *Peking University Cancer Hospital, Beijing, People's Republic of China*
[i] *Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China*
[j] *Zhejiang Provincial People's Hospital, Hangzhou, People's Republic of China*
[k] *The Affiliated Tumor Hospital of Guangxi Medical University, Guangxi, People's Republic of China*
[l] *Hai Nan General Hospital, Internal Medicine One, Hainan, People's Republic of China*
[m] *Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, People's Republic of China*
[n] *Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China*
[o] *Peking Union Medical College Hospital, Beijing, People's Republic of China*
[p] *Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China*
[q] *Merck Serono Co., Ltd., Merck KGaA, Beijing, China*
[r] *Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China*

* *Corresponding author*: Department of Medical Oncology, Sun Yat-sen University Cancer Center, No. 651, Dongfeng East Road, Guangzhou, 510060, People's Republic of China. Fax: +86 20 87343294.

E-mail addresses: pattrickguo@gmail.com (Y. Guo), luoyi702@163.com (Y. Luo), 13313612989@163.com (Q. Zhang), xiaoming.huang@126.com (X. Huang), 1349946150@qq.com (Z. Li), slf1688@sina.com (L. Shen), fjif@vip.sina.com (J. Feng), ysunemail@yahoo.com (Y. Sun), yangky71@aliyun.com (K. Yang), gemingh@163.com (M. Ge), zhuxiaodong83@163.com (X. Zhu), wanglin7209@163.com (L. Wang), yyliu@zzu.edu.cn (Y. Liu), xiaohuih2008@163.com (X. He), baichunmei1964@163.com (C. Bai), xuekaishanghai@126.com (K. Xue), rcc_china@163.com (Y. Zeng), helena.chang@merckgroup.com (X. Chang), wenfeng.chen@merckgroup.com (W. Chen), tongyulin@hotmail.com (T. Lin).

[1] Current affiliation: Department of Medical Oncology, Shanghai East Hospital, Tongji University, Shanghai, People's Republic of China. [2] Current affiliation: Everest Medicines, Beijing, People's Republic of China.

https://doi.org/10.1016/j.ejca.2021.06.039

0959-8049/© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Received 3 September 2020; received in revised form 10 June 2021; accepted 27 June 2021

KEYWORDS
Cetuximab;
China;
EXTREME;
First-line;
Recurrent and/or metastatic squamous cell carcinoma of the head and neck

Abstract ***Background:*** The EXTREME regimen (chemotherapy [CT; cisplatin/carboplatin and 5-fluorouracil]) plus cetuximab is a standard-of-care first-line (1L) treatment for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN), as supported by international guidelines. The phase III CHANGE-2 trial assessed the efficacy and safety of a modified CT regimen (with a reduced dose of both components) and cetuximab versus CT for the 1L treatment of Chinese patients with R/M SCCHN.
Methods: Patients were randomised to receive up to six cycles of CT plus cetuximab followed by cetuximab maintenance until progressive disease or CT alone. The primary end-point was the progression-free survival (PFS) time assessed by the independent review committee (IRC).
Results: Overall, 243 patients were randomised (164 to CT plus cetuximab; 79 to CT). The hazard ratios for PFS by IRC and overall survival (OS) were 0.57 (95% CI: 0.40–0.80; median: 5.5 versus 4.2 months) and 0.69 (95% CI: 0.50–0.93; median: 11.1 versus 8.9 months), respectively, in favour of CT plus cetuximab. The objective response rates (ORR) by IRC were 50.0% and 26.6% with CT plus cetuximab and CT treatment, respectively. Treatment-emergent adverse events of maximum grade 3 or 4 occurred in 61.3% (CT plus cetuximab) and 48.7% (CT) of patients.
Conclusions: CHANGE-2 showed an improved median PFS, median OS and ORR with the addition of cetuximab to a modified platinum/5-fluorouracil regimen, with no new or unexpected safety findings, thereby confirming CT plus cetuximab as an effective and safe 1L treatment for Chinese patients with R/M SCCHN.
Clinical trial registration number: NCT02383966.
© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Head and neck cancers are a group of commonly diagnosed malignancies affecting the upper aerodigestive tract [1]. In 2018, there were >880,000 estimated new cases of head and neck cancers worldwide, with approximately 293,000 occurring in the Asia–Pacific region alone [2–4]. Ninety percent of head and neck cancers are squamous cell carcinoma (SCCHN) [1]. While the treatment landscape for patients with recurrent and/or metastatic (R/M) SCCHN is changing, the EXTREME regimen (up to six cycles of chemotherapy [CT; cisplatin/carboplatin plus 5-fluorouracil {5-FU}] plus cetuximab followed by cetuximab maintenance until progressive disease [PD]) remains a standard-of-care first-line (1L) treatment option for patients with non-nasopharyngeal R/M SCCHN as per current international guidelines [5–7]. Previous results from the phase III EXTREME trial in the 1L R/M disease setting showed that the addition of cetuximab to platinum/5-fluorouracil-based chemotherapy improved the overall survival (OS; 10.1 versus 7.4 months) [8].

While the EXTREME regimen was initially evaluated in European patients [8], other single-arm trials have found similar results in Asian patients with R/M SCCHN [9,10]. One of these Asian studies was the CHANGE trial, which used a modified EXTREME regimen (a 25% dose reduction of cisplatin and a 6.25% total dose reduction of 5-FU for 5 days, instead of the four-day schedule used in the EXTREME study) due to ethnic differences in CT tolerability [8,9]. This trial had reduced rates of grade 3 or 4 treatment-related adverse events (TRAEs) compared with a similar Japanese trial that used the standard EXTREME regimen (44.1% versus 97.0%) [9,10]. Furthermore, the treatment modifications used in the CHANGE trial did not reduce efficacy: both Asian studies showed clinical benefit with either the modified or standard EXTREME regimen [9,10].

The CHANGE-2 trial was a randomised phase III study to assess the efficacy and safety of CT plus cetuximab for the 1L treatment of R/M SCCHN in China, a region with a high incidence of head and neck cancers and a need for more effective therapies [9,11,12]. This was a bridging trial designed to evaluate the influence of ethnic factors that may alter the response to or tolerability of a treatment that was assessed in another population and to extrapolate the previous findings to new populations [13]. The primary end-point was the progression-free survival (PFS) time assessed by an independent review committee (IRC). This trial would be regarded as positive if the point estimation of

the stratified hazard ratio (HR) for the primary endpoint was ≤0.77, thereby retaining ≥50% of the estimated treatment effect seen in the EXTREME study [8].

2. Methods

2.1. Patients

CHANGE-2 (NCT02383966) was a multicentre, randomised, open-label, parallel-group, phase III trial for Chinese patients with histologically or cytologically confirmed diagnosis of R/M SCCHN that was not suitable for local-regional treatment, with ≥1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Eligible patients may not have received prior systemic chemotherapy except if given as part of a multimodal treatment for locally advanced SCCHN that was completed > 6 months before randomisation. Patients with recurrent SCCHN without metastases must have received prior radiotherapy, either as an adjuvant treatment after surgery or as a treatment for locally advanced SCCHN; radiotherapy must have been completed >6 months before randomisation. All patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤1. Key exclusion criteria included nasopharyngeal carcinoma and previous treatment with monoclonal antibody or signal transduction inhibitors targeting EGFR. Further details on eligibility criteria are given in the Supplementary Appendix.

2.2. Study design and treatment

Patients were randomised at a ratio of 2:1 to receive either CT plus cetuximab or CT alone (Fig. 1). Randomisation was stratified by ECOG PS and the primary tumour site. The intent-to-treat (ITT) population included all randomised patients, and the safety analysis set (SAS) population included all patients who received ≥1 dose of any trial treatment.

Treatment cycles consisted of 21 days and were continued up to six cycles until the investigator-assessed PD or unacceptable toxicity. All patients received cisplatin 75 mg/m^2 intravenously (IV) on day 1, followed by 5-FU 750 mg/m^2 IV on days 1–5. All patients were initially treated with cisplatin. A switch to an equivalent dose of carboplatin (at an area under the curve of 5) was permitted in the case of cisplatin-related non-haematologic toxicity.

For patients in the CT plus cetuximab group, cetuximab was given on days 1, 8 and 15 of each cycle (400 mg/m^2 for the first dose; 250 mg/m^2 for all subsequent weekly doses). At the end of six cycles, patients who had at least stable disease after six cycles of treatment with CT plus cetuximab could continue cetuximab as a maintenance treatment. The maintenance treatment was continued until PD or unacceptable toxicity. Further details are given in the Supplementary Appendix.

The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Topic E6 Good Clinical Practice and applicable regulatory requirements. Written informed consent was obtained from all patients. The study protocol and statistical analysis plan can be accessed on ClinicalTrials.gov.

2.3. Assessments

Tumours were assessed at a screening visit (within 28 days before the start of treatment) and every 6 weeks (±3 days) starting from the first dose of trial treatment until PD. During the treatment period, safety evaluations were performed at the start of each treatment cycle and on a weekly basis for patients receiving CT plus cetuximab. Patients who discontinued treatment for reasons other than PD continued to have tumour

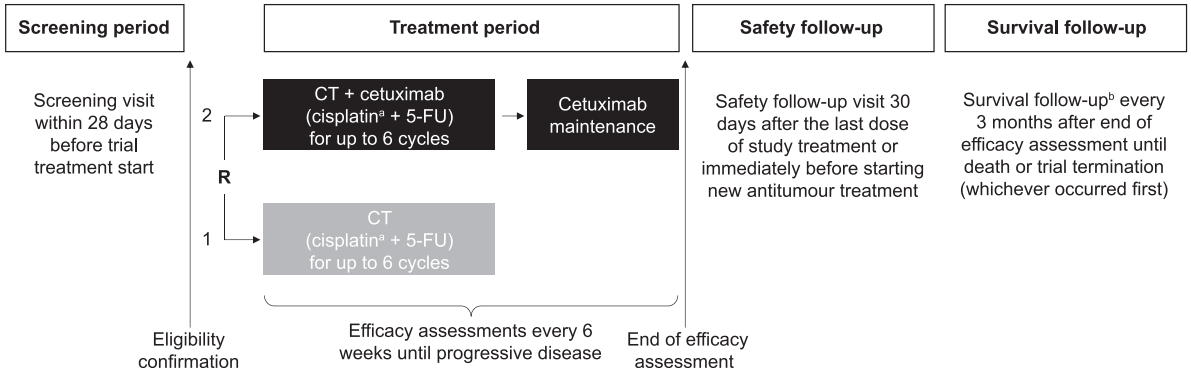

Fig. 1. **Study Design**. 5-FU, 5-fluorouracil; CT, chemotherapy; R, randomisation. [a]Switching to carboplatin from cisplatin was permitted in the case of cisplatin-related non-haematologic toxicity. [b]Information on new antitumour treatments was also collected.

assessments until PD, loss of follow-up, trial termination, the start of new antitumour treatment, or death. Further details are given in the Supplementary Appendix.

2.4. Study end-points

The primary end-point was IRC-evaluated PFS time, defined as the time from randomisation until the first observation of PD based on IRC-assessed imaging, or death due to any cause when the death occurred ≤60 days after the last tumour assessment or randomisation (whichever was later). Secondary efficacy end-points included investigator-assessed PFS time, OS time, best overall response (BOR), disease control rate (DCR) and the duration of response (DOR). Tumour assessments were performed according to RECIST 1.1. Further details on end-points are given in the Supplementary Methods.

Safety end-points were evaluated in terms of exposure to trial treatments and incidence and type of adverse events (AEs), including deaths, safety laboratory tests where applicable, vital signs, physical examinations and ECOG PS. AEs were coded according to Medical Dictionary for Regulatory Affairs (MedDRA) version 21.0, and severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

2.5. Statistical analysis

A total of 240 subjects were planned to be randomised in a 2:1 ratio during an expected accrual period of 16 months and a follow-up period of 6 months after the last subject was randomised. A 60% event rate was expected at the clinical cut-off date for PFS (i.e. 144 events) with respect to the primary end-point. The main analysis was performed after the trial collected >144 events, defined as PD (per imaging assessed by IRC) or death (occurring within 60 days of randomisation or last tumour assessment, whichever was later). The HR for PFS time was estimated using a stratified Cox proportional hazards model, including treatment and randomisation

Table 1
Patient baseline characteristics.

Characteristic	CT plus cetuximab $n = 164$	CT $n = 79$	Total $N = 243$
Age, years			
Mean ± SD	57.1 ± 9.5	57.0 ± 9.0	57.1 ± 9.3
Median	57.0	58.0	57.0
Range	28–82	34–77	28–82
Age category			
<65 years	126 (76.8)	62 (78.5)	188 (77.4)
≥65 years	38 (23.2)	17 (21.5)	55 (22.6)
Sex			
Male	146 (89.0)	67 (84.8)	213 (87.7)
Female	18 (11.0)	12 (15.2)	30 (12.3)
ECOG PS			
0	48 (29.3)	21 (26.6)	69 (28.4)
1	116 (70.7)	58 (73.4)	174 (71.6)
Primary tumour site			
Oral cavity	46 (28.0)	21 (26.6)	67 (27.6)
Oropharynx	25 (15.2)	17 (21.5)	42 (17.3)
Hypopharynx	42 (25.6)	19 (24.1)	61 (25.1)
Larynx	40 (24.4)	18 (22.8)	58 (23.9)
Other	11 (6.7)	4 (5.1)	15 (6.2)
Extent of disease			
Recurrent only	73 (44.5)	41 (51.9)	114 (46.9)
Non-recurrent metastatic	47 (28.7)	16 (20.3)	63 (25.9)
Recurrent with metastases	44 (26.8)	22 (27.8)	66 (27.2)
Nicotine consumption[a]			
Never used	36 (22.0)	18 (22.8)	54 (22.2)
Regular user	20 (12.2)	7 (8.9)	27 (11.1)
Occasional user	2 (1.2)	0	2 (0.8)
Former user	48 (29.3)	18 (22.8)	66 (27.2)
Missing	58 (35.4)	36 (45.6)	94 (38.7)
Alcohol consumption[a]			
Yes	38 (23.2)	10 (12.7)	48 (19.8)
No	66 (40.2)	32 (40.5)	98 (40.3)
Missing	60 (36.6)	37 (46.8)	97 (39.9)

CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
Note: Data are *n* (%) unless otherwise indicated.
[a] Nicotine and alcohol consumption were recorded only for patients who enrolled after a protocol amendment (version 2.0).

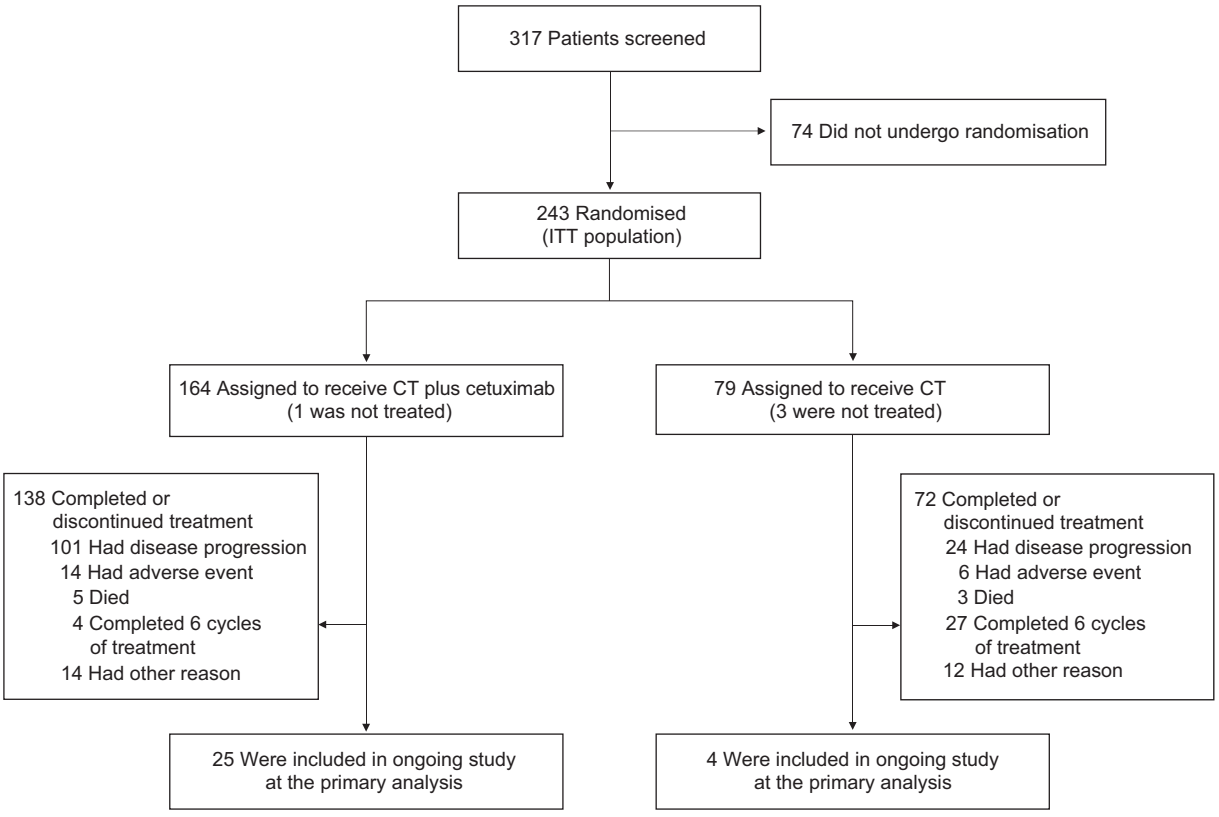

Fig. 2. **Patient Disposition at the Primary Analysis**. CT, chemotherapy; ITT, intent-to-treat.

strata. The trial had a ≥ 83% probability to observe an effect size if the true HR was 0.65 with 144 events. The *P* values provided were not used for decision-making or trial interpretation and were calculated only for exploratory analyses. A separate final analysis of OS was planned after ≥180 deaths (representing ≥75% of the randomised patients) had been reported or ≤12 months after the last patient was randomised. Subgroup analyses based on predefined baseline factors were performed for median PFS and OS. Analysis of time-to-event end-points followed a standard methodology by employing Kaplan–Meier estimates, a Cox proportional hazards model to estimate stratified HRs and corresponding 95% CIs. Only the primary end-point was assessed via statistical analysis, although this was not pre-planned. Further details are given in the Supplementary Appendix.

3. Results

3.1. Patient demographics and disease characteristics

Between 22 July 2015 and 7 December 2017, 317 patients were screened at 29 sites across China and 243 were randomised at a ratio of 2:1 to receive either CT plus cetuximab (n = 164; 67.5%) or CT alone (n = 79; 32.5%). Four enrolled patients did not receive treatment and were not included in the SAS (CT plus cetuximab, n = 163; CT, n = 76). At the cut-off time for primary analysis (19 January 2018), 25 patients in the CT plus cetuximab arm and four patients in the CT arm remained on treatment (Fig. 2). The median follow-up was 16.6 months (95% CI: 8.4–23.4) and 15.3 months (95% CI: 6.9–27.7) for the CT plus cetuximab and CT arms, respectively. The two treatment groups were well balanced with respect to patient baseline characteristics (Table 1). For example, 23.2% and 21.5% of patients in the CT plus cetuximab and CT treatment arms were ≥65 years old, respectively. The human papilloma virus (HPV) status was documented only if known at enrolment and was not assessed for the trial.

3.2. Compliance

At the time of the primary analysis, the median duration of the cetuximab treatment was 21.0 weeks (range: 1.0–91.9), with most patients (81.0%) receiving ≥10 infusions and 97.5% receiving a relative dose intensity of ≥80% following the first dose of cetuximab. More than half of the patients (57.7%) treated with CT plus cetuximab could continue to receive cetuximab maintenance treatment for a median of 6.0 weeks (range: 1.0–73.0). Patients in the CT plus cetuximab arm were treated with cisplatin and 5-FU for a median of 18.1 weeks (range: 3.0–24.6 and 2.9–24.6, respectively) and a median of 6.0 cycles (range: 1.0–6.0). In total, 92.6% and 89.0% of patients received cisplatin and 5-FU at a

relative dose intensity of ≥80%, respectively. In the CT group, patients received cisplatin and 5-FU for a median of 12.6 weeks (range: 3.0–23.7 and 2.4–23.7, respectively) and a median of 4.0 cycles (range: 1.0–6.0). Most patients (92.1% and 88.2%) received cisplatin and 5-FU, respectively, at a relative dose intensity of ≥80%. Four patients—three in the CT plus cetuximab arm and one in the CT arm—switched from cisplatin to carboplatin. Of these patients, 75.0% received carboplatin at a relative dose intensity of ≥80%.

3.3. Efficacy

As of the primary analysis, the primary end-point of PFS time per IRC assessment was met, with a stratified HR of 0.57 (95% CI: 0.40–0.80; *P*: 0.001). The IRC-assessed median PFS was 5.5 months (95% CI: 5.4–5.6) in the CT plus cetuximab arm and 4.2 months (95% CI: 3.0–5.3) in the CT alone arm (Table 2; Fig. 3A). The 6- and 12-month PFS rates were 32.3% (95% CI: 24.1–40.8) and 6.7% (95% CI: 2.7–13.2), respectively, for the CT plus cetuximab arm and were 13.4% (95% CI: 5.7–24.4) and 6.0% (95% CI: 1.3–16.0) for the CT arm (Table 2, Fig. 3A). The investigator-assessed median PFS was in line with IRC results (Supplemental Fig. 1).

Per-protocol final analysis of OS was performed after ≥180 deaths had occurred (4 January 2019 data cut-off). At this time, the stratified HR for OS was 0.69 (95% CI: 0.50–0.93), with a median OS of 11.1 months (95% CI: 9.7–12.7) in the CT plus cetuximab arm and 8.9 months (95% CI: 6.8–10.9) in the CT arm (Table 2; Fig. 3B). OS data from the primary analysis are provided in Supplemental Fig. 2A.

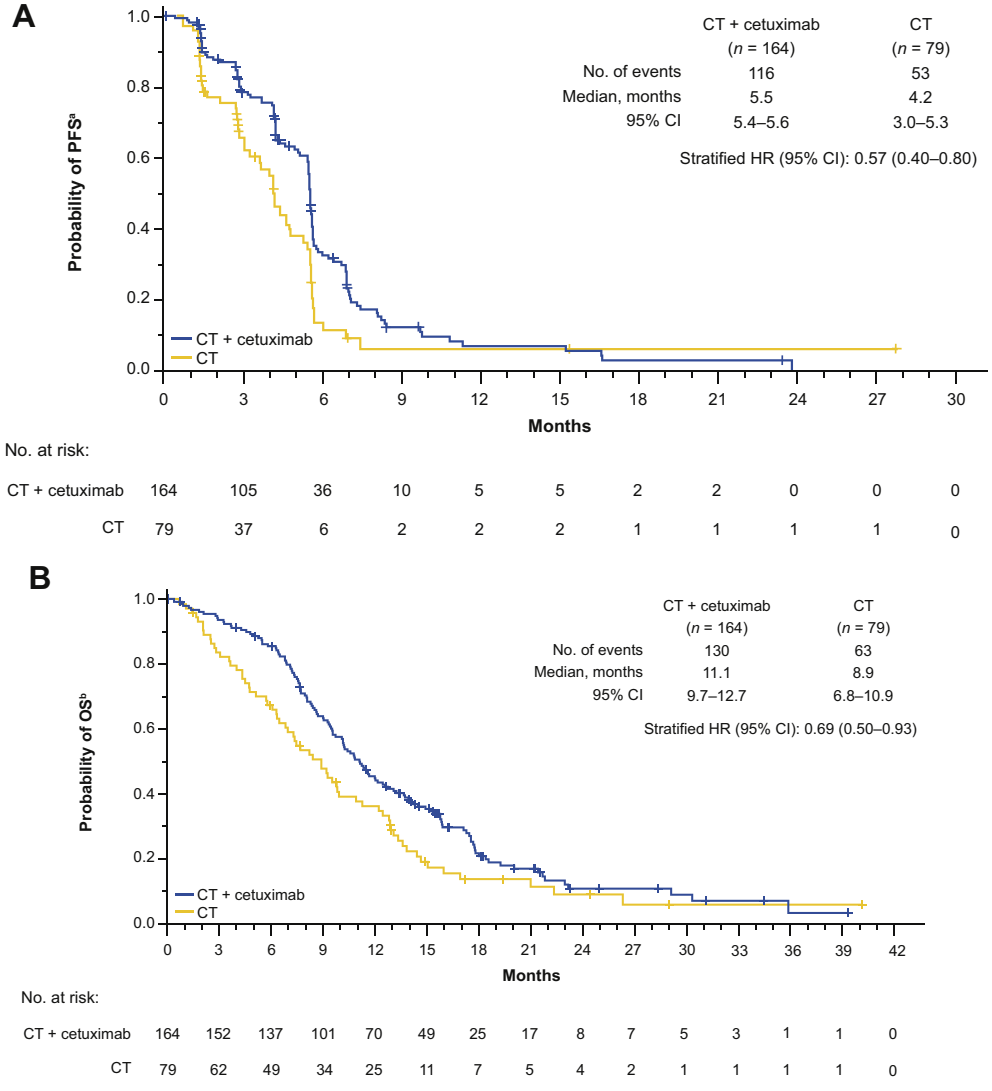

Fig. 3. **IRC Assessment of PFS (A) and OS (B) for the ITT Population**. CT, chemotherapy; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival. [a]As of the primary analysis. [b]As of the final analysis of OS.

Table 2
Efficacy in the ITT population.

Efficacy	CT plus cetuximab $n = 164$	CT $n = 79$
PFS		
No. of events (PD or death), *n* (%)[a]	116 (70.7)	53 (67.1)
HR (95% CI)	0.57 (0.40–0.80)	
PFS time[b]		
Median (95% CI), months	5.5 (5.4–5.6)	4.2 (3.0–5.3)
6-month rate	32.3 (24.1–40.8)	13.4 (5.7–24.4)
12-month rate	6.7 (2.7–13.2)	6.0 (1.3–16.0)
OS[c]		
No. of events (deaths), *n* (%)	130 (79.3)	63 (79.7)
HR (95% CI)[c]	0.69 (0.50–0.93)	
OS time[b,c]		
Median (95% CI), months	11.1 (9.7–12.7)	8.9 (6.8–10.9)
6-month rate	86 (79–90)	68 (56–77)
12-month rate	45 (37–53)	37 (26–48)
Best overall response, *n* (%)		
Complete response	10 (6.1)	3 (3.8)
Partial response	72 (43.9)	18 (22.8)
Stable disease	42 (25.6)	26 (32.9)
Progressive disease	21 (12.8)	18 (22.8)
Non-complete response/non-progressive disease/not evaluable	19 (11.6)	14 (17.7)
ORR, *n* (%)	82 (50.0)	21 (26.6)
95% CI	42.1–57.9	17.3–37.7
Odds ratio (95% CI)	2.76 (1.52–5.45)	
DOR (95% CI), weeks[b]	18.1 (13.1–20.3)	13.9 (8.7–18.1)
DCR, *n* (%)	124 (75.6)	47 (59.5)
95% CI	68.3–82.0	47.9–70.4

CT, chemotherapy; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
Note: Other than OS, data per IRC assessment as of the primary analysis are presented.
[a] Death occurring within 60 days after the last tumour response assessment or randomisation date.
[b] Product-limit (Kaplan–Meier) estimates.
[c] As of the final analysis of OS.

Predefined subgroup analyses based on patient demographics and disease characteristics were performed for IRC-assessed PFS and OS using data from the primary analysis (Fig. 4). Similar to observations from the EXTREME study [8], patients with oral cavity tumours who received CT plus cetuximab ($n = 46$) had a better median PFS (5.5 versus 3.0 months; HR: 0.2 [95% CI: 0.1–0.4]) than similar patients in the CT arm ($n = 21$). ECOG PS is also a known prognostic factor for patients with R/M SCCHN, with an ECOG PS of 1 (versus 0) acting as an independent unfavourable predictor of objective response and OS with cisplatin-based chemotherapy [14]. In the CHANGE-2 study, patients in the CT plus cetuximab arm with an ECOG PS of 1 ($n = 116$) had better median PFS (5.5 versus 4.0 months; HR: 0.4 [95% CI: 0.3–0.6]) than corresponding patients in the CT arm ($n = 58$). Similar OS results were observed in these subgroups (Supplemental Fig. 2B). However, these results could be due to chance and they should be interpreted cautiously.

At primary analysis, ORR and DCR were higher among patients treated with CT plus cetuximab compared with those who received CT, with a longer median DOR in the former (median: 18.1 weeks [95% CI: 13.1–20.3]) for CT plus cetuximab compared with the CT alone group (median: 13.9 weeks [95% CI: 8.7–18.1]) (Table 2; Supplemental Fig. 3).

3.4. Safety

At the primary analysis, 61.3% ($n = 100$) of patients in the CT arm plus cetuximab and 48.7% ($n = 37$) of patients in the CT arm had experienced treatment-emergent AEs (TEAEs) of maximum grade 3 or 4 (Table 3). A total of 35 patients ($n = 27$ [16.6%] in the CT plus cetuximab arm; $n = 8$ [10.5%] in the CT arm) discontinued treatment due to TEAEs. TRAEs that were of maximum grade 3 or 4 were slightly higher with the combination of cetuximab (51.5% [$n = 84$] and 48.7% [$n = 37$] of patients in the CT plus cetuximab and CT arms, respectively). Skin and subcutaneous tissue disorders were more common in patients who received CT plus cetuximab versus CT alone (77.3% [$n = 126$] and 17.1% [$n = 13$]). These events were of grade 3 in 3.7% of patients ($n = 6$) in the CT plus cetuximab arm; there were no grade 3 skin or subcutaneous tissue

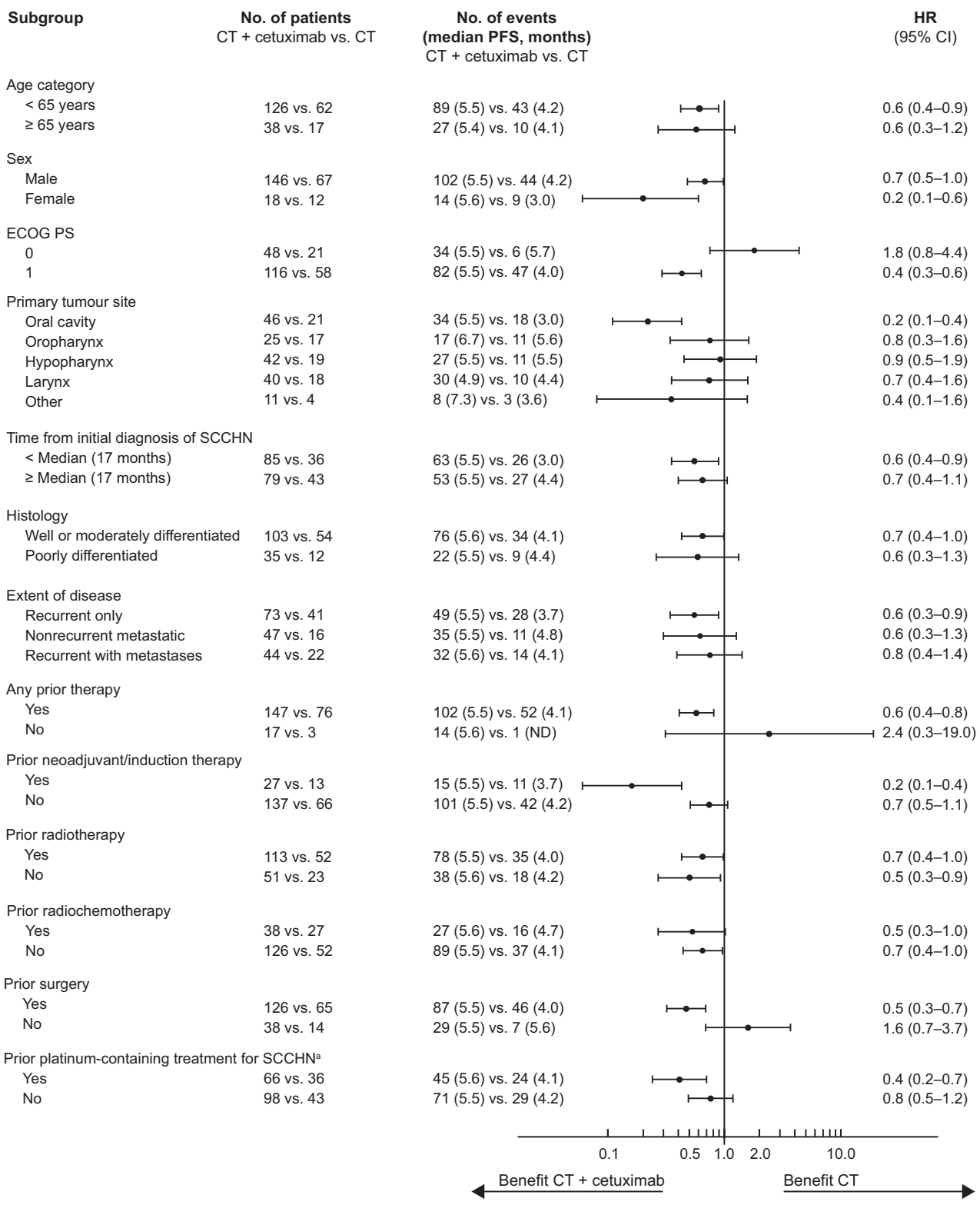

Fig. 4. **Subgroup Analysis for IRC-Assessed PFS in the ITT Population**. CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; ND, not determinable; PFS, progression-free survival; SCCHN, squamous cell carcinoma of the head and neck. Note: Data as of the primary analysis are presented. [a]Prior systemic CT must have been given as part of the multimodal treatment for locally advanced SCCHN that was completed > 6 months before randomisation.

Table 3
Overview of adverse events in the SAS.

Preferred term, *n* (%)[a]	CT plus cetuximab *n* = 163		CT *n* = 76	
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4
Any TEAE[b]	100 (61.3)	14 (8.6)	37 (48.7)	7 (9.2)
Neutropenia	21 (12.9)	2 (1.2)	5 (6.6)	0
Hypokalaemia	20 (12.3)	1 (0.6)	9 (11.8)	1 (1.3)
Hyponatraemia	19 (11.7)	3 (1.8)	10 (13.2)	1 (1.3)
Anaemia	19 (11.7)	0	8 (10.5)	0
Leukopenia	18 (11.0)	0	6 (7.9)	0
Hypomagnesaemia	17 (10.4)	9 (5.5)	4 (5.3)	0
Lung infection	15 (9.2)	0	3 (3.9)	0
Decreased WBC count	12 (7.4)	0	5 (6.6)	2 (2.6)
Decreased neutrophil count	10 (6.1)	0	9 (11.8)	2 (2.6)
Stomatitis	10 (6.1)	0	5 (6.6)	1 (1.3)
Decreased RBC count	0	0	4 (5.3)	0
Atrial fibrillation	0	0	1 (1.3)	1 (1.3)
Obstructive airways disorder	0	0	1 (1.3)	1 (1.3)
Septic shock	0	0	1 (1.3)	1 (1.3)

CT, chemotherapy; SAS, safety analysis set; TEAE, treatment-emergent adverse event; WBC, white blood cell.
Note: Data as of the primary analysis are presented.
[a] TEAEs of maximum grade 3 or 4 that occurred in ≥5% of patients in either treatment group and maximum grade 4 TEAEs that occurred in ≥1% of patients in either treatment group.
[b] TEAEs that were of maximum grade 3 or 4, regardless of frequency.

disorders with CT alone and no grade 4 skin and subcutaneous tissue disorders in either of the treatment groups. Specifically, there was a ≥10% difference between treatment arms in the percent of patients who experienced dermatitis acneiform (21.5% [*n* = 35] and 0%) or rash (47.2% [*n* = 77] and 1.3% [*n* = 1]), with both events being more common with CT plus cetuximab. Two treatment-related deaths occurred in each group (CT plus cetuximab: dyspnoea [*n* = 1] and unknown reasons [*n* = 1]; CT alone: lung infection [*n* = 1] and renal failure [*n* = 1]). The rates of CT-related AEs of any grade were similar between treatment arms (97.5% and 97.4% in the CT plus cetuximab and CT arms, respectively).

4. Discussion

Although the treatment landscape for R/M SCCHN is evolving, the EXTREME regimen of CT plus cetuximab has a long history as a safe and effective preferred treatment option for 1L treatment of R/M SCCHN [5–8]. Results from the TPExtreme trial showed no significant difference in OS between EXTREME and TPEx (platinum and docetaxel plus cetuximab) in the 1L treatment of R/M SCCHN [15]. In the global, phase III KEYNOTE-048 study, pembrolizumab monotherapy significantly improved median OS for patients with a PD-L1 combined positive score of ≥1 (median 12.3 versus 10.3 months; HR 0.78 [95% CI: 0.64–0.96], *P* = 0.0086) or ≥20 (median 14.9 versus 10.7 months, HR 0.61 [95% CI: 0.45–0.83]; *P* = 0.0007) when compared with those who received EXTREME; however, there was no significant difference between these treatments for the overall, unselected population (median 11.6 versus 10.7 months; HR 0.85 [95% CI: 0.71–1.03]) [16]. Additionally, across all populations, patients who were given pembrolizumab plus CT (platinum and 5-FU) or EXTREME in KEYNOTE-048 had a similar median PFS and ORR, with the definitive results showing a statistically significant improvement in median OS with the former treatment (13.0 versus 10.7 months; *P*: 0.003) [16]. However, it is important to note that only 20% of patients in KEYNOTE-048 were Asian, making it difficult to determine whether these treatments are effective in Chinese patients [17].

The CHANGE-2 study met the primary end-point, with a stratified HR for PFS of 0.57 (median PFS time: 5.5 versus 4.2 months in the CT plus cetuximab versus CT arms). Similar results were observed in the EXTREME trial with patients who received CT plus cetuximab having a longer median PFS compared with those treated with CT alone (5.6 versus 3.3 months; HR: 0.54) [8]. However, not only lower chemotherapy dosages were used in CHANGE-2, but also all patients started with cisplatin in CHANGE-2, whereas only 67% of patients had cisplatin as the initial platinum compound in the cetuximab-containing arm of EXTREME. Additional improvements were observed across secondary efficacy end-points in the CHANGE-2 study with CT plus cetuximab. These findings show that 1L

treatment with CT plus cetuximab improved survival and response outcomes in Chinese patients with R/M SCCHN compared with CT alone.

Safety results of the CHANGE-2 study showed no new or unexpected findings. Compared with the EXTREME study, both treatment arms in CHANGE-2 had fewer grade 3 or 4 TEAEs, potentially explained by reductions in the doses of CT [8,9]. The current trial had a lower rate of haematological toxicities, possibly due to restrictions on the use of carboplatin, which was only permitted in the event of cisplatin-related toxicity [8,18]. Skin toxicity data were consistent with the known safety profile of cetuximab. Patients treated with cetuximab in combination with CT are at a higher risk of infections. In CHANGE-2, the incidence of grade 3/4 lung infection was 9.2% in the cetuximab + CT group compared with 3.9% in the CT-treated group. Additionally, in contrast to the EXTREME trial, where sepsis was significantly increased in the cetuximab-containing arm, there was no incidence of sepsis in the cetuximab-containing arm in CHANGE-2, which could be the result of more experience of using the approved regimen by the investigators.

Limitations of this study include the open-label design, which could potentially influence investigator assessments. Additionally, no analyses were performed based on the tumour HPV infection status, which may have yielded interesting results. Previous retrospective analysis of the EXTREME trial showed that the addition of cetuximab to CT improved survival regardless of the tumour p16 or HPV status; however, within treatment arms, patients with p16-positive or HPV-positive tumours had longer OS times than those with negative disease [19]. A similar analysis could not be performed for CHANGE-2, as information regarding patient HPV status was collected only from participants who knew their infection status at screening.

The results of the CHANGE-2 trial show that CT plus cetuximab was effective and well tolerated in Chinese patients, supporting the recent approval of this regimen by the National Medical Products Administration of China for the 1L treatment of R/M SCCHN [20].

Sources of support

This study was funded by Merck (CrossRef Funder ID: 10.13039/100009945).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis and data interpretation. The authors had access to all data in the study and had final responsibility for the decision to submit for publication.

Authors' contributions

Y. Guo, T. Lin, Y. Zeng and W. Chen contributed to study concepts. Y. Guo, T. Lin, Y. Zeng and W. Chen contributed to the study design. Y. Guo, Y. Luo, Q. Zhang, X. Huang, Z. Li, L. Shen, J. Feng, Y. Sun, K. Yang, M. Ge, X. Zhu, L. Wang, Y. Liu, X. He, C. Bai, K. Xue and T. Lin contributed to data acquisition. W. Chen and X. Chang contributed to quality control of data and algorithms. Y. Guo, Y. Luo, Q. Zhang, X. Huang, Z. Li, L. Shen, J. Feng, Y. Sun, K. Yang, M. Ge, X. Zhu, L. Wang, Y. Liu, X. He, C. Bai, K. Xue and T. Lin contributed to data analysis and interpretation. W. Chen provided statistical analysis. All authors contributed equally to manuscript preparation, editing and review and approved the final version for submission.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Y. Guo received speaker honoraria from Merck Serono Co., Ltd., Beijing, China, an affiliate of Merck KGaA, Roche, Celgene, Janssen, and Bayer; and served on scientific advisory boards for Merck Serono Co., Ltd., Beijing, China, an affiliate of Merck KGaA, and Boehringer Ingelheim. X. Chang is an employee of Merck Serono Co., Ltd., Beijing, China, an affiliate of Merck KGaA. W. Chen and Y. Zeng are former employees of Merck Serono Co., Ltd., Beijing, China, an affiliate of Merck KGaA. All remaining authors have no potential conflicts to disclose.

Acknowledgements

We thank the patients and their families, investigators, co-investigators, and study teams at each of the participating sites and at Merck (CrossRef Funder ID: 10.13039/100009945), and Merck Serono Co., Ltd., Beijing, China, an affiliate of Merck KGaA. The authors thank Yuanyuan Cao and Johannes Nippgen for their support. This study was funded by Merck (CrossRef Funder ID: 10.13039/100009945). Medical writing support was provided by Lauren Rusnak, PhD, of ClinicalThinking, Hamilton, NJ, and was funded by Merck (CrossRef Funder ID: 10.13039/100009945).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.06.039.

References

[1] D'cruz A, Lin T, Anand AK, Atmakusuma D, Calaguas MJ, Chitapanarux I, et al. Consensus recommendations for management of head and neck cancer in Asian countries: a review of international guidelines. Oral Oncol 2013;49:872–7.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[3] Miranda-Filho A, Bray F. Global patterns and trends in cancers of the lip, tongue and mouth. Oral Oncol 2020;102:104551.

[4] World Health Organization: International Agency for Research on Cancer. Cancer Today. Accessed August 6, 2021. [https://gco.iarc.fr/]

[5] National Comprehensive Cancer Network. Head and Neck Cancers (Version 1.2020). Accessed August 6, 2021. [https://www.nccn.org/guidelines/guidelines-process/transparency-process-and-recommendations/GetFileFromFileManager?fileManagerId=7573]

[6] Machiels J-P, Leemans CR, Golusinski W. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1462–75.

[7] Oosting SF, Haddad RI. Best practice in systemic therapy for head and neck squamous cell carcinoma. Front Oncol 2019;9:815.

[8] Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.

[9] Guo Y, Shi M, Yang A, Feng J, Zhu X, Choi Y-J, et al. Platinum-based chemotherapy plus cetuximab first-line for Asian patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: results of an open-label, single-arm, multicenter trial. Head Neck 2015;37:1081–7.

[10] Yoshino T, Hasegawa Y, Takahashi S, Monden N, Homma A, Okami K, et al. Platinum-based chemotherapy plus cetuximab for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: results of a phase II trial. Jpn J Clin Oncol 2013;43:524–31.

[11] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.

[12] Global Cancer Observatory: Cancer today. [https://gco.iarc.fr/today].

[13] Agency EM. ICH E5(R1): ethnic factors in the acceptability of foreign clinical data. September 1998.

[14] Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. Cancer 2004;101:2222–9.

[15] Guigay J, Auperin A, Fayette J, Saada-Bouzid E, Lafond C, Taberna M, 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.

[16] Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro Jr G, 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.

[17] Merck. FDA Approves Two New Indications for Merck's KEYTRUDA® (pembrolizumab). Accessed August 6, 2021. [https://www.merck.com/news/fda-approves-two-new-indications-for-mercks-keytruda-pembrolizumab/]

[18] Guan J, Li Q, Zhang Y, Xiao N, Chen M, Zhang Y, et al. A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). Oncotarget 2016;7:7110–9.

[19] Vermorken JB, Psyrri A, Mesía R, Peyrade F, Beier F, de Blas B, et al. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. Ann Oncol 2014;25:801–7.

[20] PR Newswire. ERBITUX approved for first-line use in China in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Accessed August 6, 2021. [https://www.prnewswire.com/in/news-releases/erbitux-r-approved-for-first-line-use-in-china-in-patients-with-recurrent-and-or-metastatic-squamous-cell-carcinoma-of-the-head-and-neck-r-m-scchn–839770456.html]