International Journal of Clinical Oncology (2021) 26:51–58
https://doi.org/10.1007/s10147-020-01788-6

ORIGINAL ARTICLE

Phase II trial of combination treatment with S-1/cetuximab in patients with platinum-ineligible recurrent and/or metastatic squamous cell carcinoma of the head and neck

Jun Taguchi[1] · Yasushi Shimizu[1] · Shin Ariga[1] · Tomohiro Goda[1] · Yoshihito Ohhara[1] · Rio Honma[1] · Takuro Noguchi[1] · Satoshi Takeuchi[1] · Ichiro Kinoshita[1] · Toraji Amano[1,2] · Takatsugu Mizumachi[3] · Satoshi Kano[3] · Miki Takahara[4] · Takahisa Abe[5] · Akihiro Homma[3] · Hirotoshi Dosaka-Akita[1]

Received: 29 April 2020 / Accepted: 10 September 2020 / Published online: 29 September 2020

Abstract

Background The standard of care for first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in patients who cannot tolerate platinum-based regimens has not been clarified. We aimed to develop a new treatment regimen for patients with R/M SCCHN who are ineligible for platinum-based therapy, by evaluating the effects and safety of tegafur/gimeracil/oteracil (S-1) and cetuximab.

Methods Platinum-ineligibility was defined as: elderly (aged ≥ 75 years), poor PS, comorbidity, platinum resistance and refusal to undergo platinum-based therapy. Patients received S-1 (80 mg/m^2/day for 14 days followed by a seven-day break) and cetuximab (initial dose, 400 mg/m^2, followed by 250 mg/m^2 weekly) until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR).

Results Between September 2014 and September 2018, we enrolled 23 patients. Among the 21 patients who were evaluable, 20 were male [median age, 69 years (range 49–82)]. The ORR was 9 (43%) of 21 patients [95% confidence interval (CI) 22–66]. One and eight patients achieved complete response (CR) and partial response (PR), respectively. The median overall survival (OS) was 13.7 months (95% CI 9.0–18.3) and progression-free survival (PFS) was 5.7 months (95% CI 3.1–8.2). Grade 3/4 adverse events included acneiform rash and skin reactions (33%), hypomagnesemia (19%), hand-foot syndrome (14%), fatigue (14%), mucositis (10%), and anorexia (10%).

Conclusions Combination treatment with S-1 and cetuximab was effective and tolerated well by patients with platinum-ineligible R/M SCCHN.

Registered clinical trial number: UMIN000015123

Keywords S-1 · Cetuximab · Head and neck · Recurrent · Metastatic · Squamous cell carcinoma

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-020-01788-6) contains supplementary material, which is available to authorized users.

✉ Yasushi Shimizu
y-simz@med.hokudai.ac.jp

[1] Department of Medical Oncology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, North 15 West 7, Kita-ku, Sapporo 060-8638, Japan

[2] Hokkaido University Hospital Clinical Research and Medical Innovation Center, North 14 West 5, Kita-ku, Sapporo 060-8648, Japan

[3] Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, North 15 West 7, Kita-ku, Sapporo 060-8638, Japan

[4] Department of Otolaryngology Head and Neck Surgery, Asahikawa Medical University, Midorigaoka East 2-1-1-1, Asahikawa 078-8510, Japan

[5] Department of Otolaryngology, Hirosaki University Graduate School of Medicine, Honcho 53, Hirosaki 036-8563, Japan

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is a common malignancy worldwide, with more than 800,000 new patients being diagnosed annually [1]. An estimated 60% of such patients present with locally advanced stage III/IV disease. Although multidisciplinary treatment of locally advanced SCCHN has progressed, disease recurs in > 50% of patients within 3 years [2–4]. Some patients are eligible for salvage therapy with surgery or chemoradiotherapy, but the only therapy available for most patients with recurrent and/or metastatic disease is palliative treatment [5].

The standard treatment for patients with recurrent and/or metastatic (R/M) SCCHN is a combination of platinum, 5-FU, and cetuximab; namely, the EXTREME regimen [6]. Adding cetuximab to the combination of platinum and 5-FU (FP) as a first-line treatment for R/M SCCHN has significantly improved survival over FP alone [7]. However, the prevalence of grade 3 or 4 toxicity under this regimen is high. Therefore, patients must have good performance status (PS), organ function, and physical status, which means that not all patients can tolerate this therapy. Because the prognosis of R/M SCCHN is poor, the therapeutic target is not a complete cure for cancer, but rather improved survival and palliative care to optimize their quality of life (QOL). Thus, a more appropriate regimen for patients who are contraindicated for platinum-based therapy is needed.

The orally active therapy referred to as S-1 comprises a 1:0.4:1 molar ratio of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits fluorouracil phosphorylation in the gastrointestinal tract, thus reducing the gastrointestinal toxic effects of fluorouracil) [8, 9]. It is presently used alone or in combination with anti-cancer agents to treat various cancers, such as gastric [9, 10], colon [11, 12], pancreas [13, 14], lung [15, 16], breast [17] and head and neck cancer [18, 19] in adjuvant or systemic chemotherapy setting and it has demonstrated survival benefits with lower toxicity. Because of its lower toxicity and improved radiation sensitivity by gimeracil [20], S-1 has also been used with triplet chemotherapy [21] and radiotherapy [22]. Both in vitro and in vivo studies have demonstrated that a combination of S-1 and cetuximab confers greater antitumor activity than S-1 alone [23, 24], suggesting that cetuximab induces the downregulation of thymidylate synthase (TS). A phase II study of patients with KRAS wild-type unresectable metastatic colorectal cancer showed that this combination treatment was effective and tolerable [25]. The present phase II study evaluates the effects and safety of S-1/cetuximab as a first-line treatment for platinum-ineligible patients with R/M SCCHN.

Patients and methods

Study design

The eligibility criteria were as follows: platinum-ineligible, age ≥ 20 years, histologically confirmed R/M SCCHN, measurable disease according to RECIST, no suitable local therapy, Eastern Cooperative Oncology Group (ECOG) PS 0 to 2, adequate hematological, hepatic and renal functions, predicted survival > 3 months, and no prior chemotherapy other than curative chemoradiotherapy and immunotherapy. We also defined platinum-ineligibility as at least one of the following six criteria: age ≥ 20 to < 70 years with PS 2; age ≥ 70 to < 75 years with PS 1-2; age ≥ 75 years with PS 0-2; comorbidity, platinum-refractory (tumor progression within six months of platinum-based therapy) and refusal to undergo platinum-based therapy.

Key exclusion criteria included previous systemic chemotherapy for R/M SCCHN (except for immune checkpoint inhibitors), surgery (except for diagnostic biopsies and port-a-cath implantation) or radiotherapy within four weeks before study entry (except for palliative radiotherapy administered over two weeks previously), simultaneous or metachronous double cancers within five years before study entry except for carcinoma in situ or intramucosal tumor, symptomatic central nervous system metastases, HBV virus infection, uncontrolled comorbidities (such as severe heart failure, cerebrovascular disease, pulmonary fibrosis, renal failure, liver failure, active peptic ulcer, uncontrolled diabetes mellitus, uncontrolled hypertension), and prior treatment with cetuximab or anti-epidermal growth factor receptor (EGFR) inhibitor.

The ethics committees at the participating centers approved the study protocol and the trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participating in the study. This trial was registered in the UMIN clinical trials Registry as UMIN000015123.

Treatment

Chemotherapy consisted of S-1 (80 mg/m^2/day, daily for 14 days followed by a seven-day break) and cetuximab (initial dose 400 mg/m^2, followed by 250 mg/m^2 weekly) until disease progression or unacceptable toxicity.

Dose reductions and delays

Chemotherapy doses were modified when hematological or non-hematological toxicity became intolerable. Cetuximab was reduced in the event of ≥ grade 3 skin toxicity or hypomagnesemia. If a patient experienced grade 3 skin

toxicity for a second or third time, cetuximab was delayed for up to three consecutive weeks, followed by dose reductions to 200 mg/m^2 and then 150 mg/m^2. The infusion rate of cetuximab was reduced when grades 1 or 2 infusion-related reactions (IRRs) occurred, and cetuximab was discontinued when grade 3 or 4 IRRs or any grade of cetuximab-related interstitial pneumonia developed. S-1 was gradually reduced by 20 mg/day if the neutrophil count reached < 500/mm^3, the platelet count reached < 50,000/mm^3 or ≥ grade 3 non-hematological adverse events developed. The dose of each drug was reduced according to dose reduction protocols.

Assessments

Tumor response was assessed using RECIST version 1.1 criteria [26] and computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and every six weeks after the start of treatment until progressive disease (PD). Adverse events were monitored weekly throughout the study and evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Design and statistics

This single-arm, multicenter, phase II study evaluated the effects and safety of S-1/cetuximab as a first-line treatment for R/M SCCHN. The primary endpoint was the overall response rate (ORR) based on RECIST version 1.1. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF) and the relative dose intensity of each chemotherapeutic drug.

We defined PFS as the elapsed time between the initial administration of the protocol treatment until PD or death. Overall survival was defined as the elapsed time between the initial administration of the protocol treatment until death from any cause. The primary objective of the study was to establish proof-of-concept for S-1/cetuximab by evaluating ORR. We assumed that the ORR of S-1/cetuximab was 34%, based on an S-1 phase II study [27], and the EXTREME study [7]. Thus, a two-sided test with $\alpha = 0.05$ and power of 80% required a sample size of 58 patients. Confidence intervals (CI) for ORR were estimated using the binominal method. We analyzed PFS, OS, and TTF using Kaplan–Meier curves. Primary analyses included the full analysis set (FAS) population defined as all registered patients excluding those who were deemed ineligible after enrollment, and no data for efficacy endpoints due to events that were obviously unrelated to the protocol treatment. Safety analyses were conducted for all registered patients who received at least one dose of the protocol treatment. The data cutoff point for OS, PFS, and safety analyses was March 31, 2019. Statistical analyses were performed using SPSS version 22. We initially planned two years of recruitment, but extended the registration period for two more years.

Results

Patient characteristics

Between September 2014 and September 2018, we accrued 23 patients from four sites (Supplementary Fig. S1). The trial was stopped early due to slow accrual. Two patients withdrew before being administered with the S-1/cetuximab combination therapy due to protocol noncompliance ($n = 1$) and poor PS due to disease progression ($n = 1$). Thus, data from 21 patients were analyzed. Table 1 shows the characteristics of the patients (male, $n = 20$; female, $n = 1$; median age 69 years [range 49–82]). Eighteen patients had good PS (0 or 1) and three patients had poor PS (2). The primary sites were hypopharynx ($n = 8$), oropharynx ($n = 6$), oral ($n = 3$), larynx ($n = 2$), and other ($n = 2$). Nineteen patients

Table 1 Patient characteristics (n=21)

Variable	No. of patients	%
Age		
Age (years) - median, range	69 (49–82)	
< 70 years	9	43%
≥ 70 years	12	57%
Sex		
Female	1	5%
Male	20	95%
PS		
0	4	19%
1	14	67%
2	3	14%
Primary site		
Hypopharynx	8	38%
Oropharynx	6	28%
Oral cavity	3	14%
Larynx	2	10%
Maxillary sinus	1	5%
External auditory canal	1	5%
Extent of disease		
Only locoregionally recurrent	8	38%
Metastatic with or without locoregional recurrence	13	62%
Platinum - ineligible reason (overlapped)		
PS2	3	14%
Elderly (≥75 years old)	6	28%
Comorbidity	9	43%
Platinum resistance	9	43%
Refuse platinum therapy	2	10%

Table 2 Response (n=21)

Response	No. of patients	(%)
Complete response	1	(5%)
Partial response	8	(38%)
Stable disease	10	(47%)
Progressive disease	2	(10%)
Overall response rate	9	(43%)

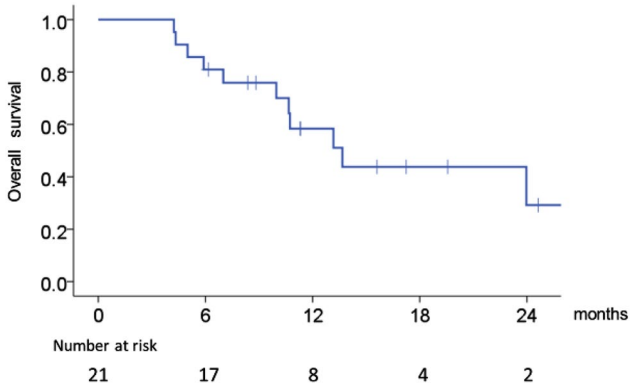

Fig. 1 Overall survival

had previously been treated with definitive radiotherapy ($n=3$) or concurrent chemoradiotherapy with cisplatin ($n=16$). Among them, two patients received nivolumab due to recurrence after chemoradiotherapy. Thirteen patients had distant metastases with or without locoregional recurrence, and eight had locoregional recurrence. Platinum therapy was contraindicated because of PS 2 ($n=3$), age > 75 years ($n=6$), comorbidity ($n=9$), platinum resistance ($n=9$), and refusal of platinum therapy ($n=2$).

Efficacy

Twenty-one patients were assessed for efficacy (Table 2). The ORR was 43% (95% CI 22–66), with one patient (5%) achieving complete response (CR), eight patients (38%) achieving partial response (PR), and ten patients (47%) achieving stable disease (SD). The disease control rate (CR, PR plus SD) was 90% (95% CI 77–100). The median follow-up was 10.7 months (range, 4.2–29.3) for all patients, and the median OS was 13.7 months (95% CI 9.0–18.3) with 12 (57%) deaths (Fig. 1). The median PFS was 5.7 months (95% CI 3.1–8.2) (Fig. 2).

Safety

Treatment-related grade 3/4 adverse events (AEs) were reported in 13 patients (62%) (Table 3). They were acneiform rash and skin reactions (33%), hypomagnesemia

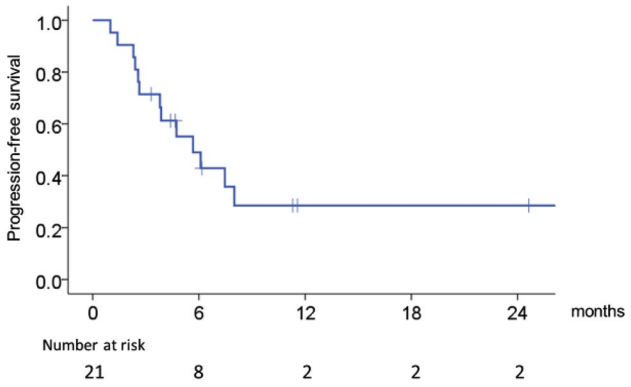

Fig. 2 Progression-free survival

Table 3 Adverse events during S-1/Cetuximab (n=21)

Adverse events	No. of patients				
	Gr1	Gr2	Gr3	Gr4	%Gr3-4
Neutropenia	1	3	1	0	5%
Anemia	15	4	1	0	5%
Thrombocytopenia	7	0	0	0	0%
AST/ALT increase	4	1	0	0	0%
Cr increase	1	1	0	0	0%
Hypomagnesemia	1	3	3	1	19%
Hypocalcemia	3	2	0	0	0%
Hyponatremia	16	0	0	0	0%
Hypokalemia	8	0	0	0	0%
Hyperkalemia	4	0	0	0	0%
Hypoalbuminemia	14	5	0	0	0%
Hyperbilirubinemia	3	0	0	0	0%
Acneiform rash	9	7	3	0	14%
Skin reactions*	5	10	4	0	19%
Hand-Foot Syndrome	2	0	3	0	14%
Fatigue	4	1	3	0	14%
Mucositis	4	2	2	0	10%
Anorexia	3	5	2	0	10%
Diarrhea	1	0	1	0	5%
Nausea	0	2	0	0	0%
Pruritus	5	6	0	0	0%
Dysgeusia	3	1	0	0	0%
Pneumonitis	1	2	0	0	0%
Shingles	0	0	1	0	5%
IRRs**	0	2	0	0	0%
Alopecia	2	0	0	0	0%

*Excluded acneiform rash**IRR, infusion-related reaction

(19%), hand-foot syndrome (14%), fatigue (14%), mucositis (10%), anorexia (10%), neutropenia (5%), anemia (5%), diarrhea (5%), and shingles (5%). Grade 2 IRR developed in two patients and grade 1 interstitial pulmonary pneumonia associated with cetuximab developed in one patient. No

AE-related deaths were recorded and the treatment was generally well tolerated.

Treatment compliance

The study treatment was discontinued due to disease progression ($n=10$), AEs ($n=8$), and patient's refusal ($n=2$). One patient was still under S-1/cetuximab therapy at the time of the cutoff. The median time to treatment failure (TTF) was 4.3 months (95% CI 2.9–5.7) (Supplementary Figure S2). The median number of treatment cycles was 5 (range 1–13). The median relative dose intensity of S-1 and cetuximab was 91.3% (range 52–100) and 87.8% (range 61.1–100), respectively.

Subsequent treatment

One patient was untraceable after hospital transfer. Eleven patients received the following therapy after the experimental regimen was discontinued: off-protocol S-1/cetuximab after long-term discontinuation due to an treatment-unrelated AE ($n=1$), S-1 ($n=2$), cetuximab ($n=1$), paclitaxel plus cetuximab ($n=1$), nivolumab ($n=3$), docetaxel ($n=2$), and carboplatin plus 5-FU ($n=1$) because the general status of this patient improved.

Discussion

The results of this phase II study showed that S-1/cetuximab might be an effective combination for treating platinum-ineligible R/M SCCHN, with an ORR of 43%. This combination showed promise in terms of better survival, with a median PFS of 5.7 months and a median OS of 13.7 months. Although the sample size was smaller than planned, our findings were essentially the same as those in the EXTREME trial. Moreover, toxicity was manageable, and the regimen was well tolerated on an outpatient basis with dosage adjustment as necessary.

Given that the phase III EXTREME trial provides gold standard data with a median OS of 10.1 months, a PFS of 5.6 months, and a response rate of 36% [7], it is the most frequently recommended treatment regimen for platinum-eligible patients. However, a certain portion of patients encountered during routine medical practice cannot tolerate platinum-based treatment due to various medical issues. Some recent clinical trials have included the concept of 'platinum-refractoriness', defined as tumor progression or recurrence within 6 months after the last dose of platinum-based chemoradiotherapy, adjuvant therapy or systemic chemotherapy as eligibility criteria for patients with R/M SCCHN. The prognosis for such patients is poor [28] and administering another platinum-based regimen results in limited antitumor effects [29, 30]. The response rate of the nine patients with platinum-refractory R/M SCCHN in the present study was 33%, including PR ($n=3$) and SD ($n=5$). This finding indicated that S-1/cetuximab is effective against platinum-refractory R/M SCCHN. On the other hand, PD-1 immune checkpoint inhibitors have recently been administered to treat platinum-refractory R/M SCCHN [31, 32], and treatment for R/M SCCHN is rapidly changing. Therefore, we included patients treated with a PD-1 immune checkpoint inhibitor for platinum-refractory R/M SCCHN in the present study. Two patients were enrolled after treatment with a PD-1 immune checkpoint inhibitor, including PR ($n=1$) and SD ($n=1$). Recent data suggest that exposure to an immune checkpoint inhibitor improves response to chemotherapy in various cancer types [33–35] including head and neck cancer [36]; therefore, a PD-1 immune checkpoint inhibitor followed by S-1/cetuximab might be an appropriate treatment option for platinum-ineligible patients with R/M SCCHN. Recently, the KEYNOTE-048 study showed that pembrolizumab monotherapy was effective in patients with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) of 1 or more and was well tolerated as a first-line treatment for R/M SCCHN [37]. However, the efficacy of pembrolizumab monotherapy was insufficient compared to the EXTREME regimen in the PD-L1-negative population (CPS < 1) and its response rate was 17% in the full population, lower than that of S-1/cetuximab combination treatment. Therefore, S-1/cetuximab combination treatment may be more appropriate than pembrolizumab monotherapy for patients who are PD-L1-negative and/or who require early tumor shrinkage because of good response rate.

Platinum-ineligible patients are often elderly, have comorbidity or poor PS, and are usually treated with single agents, such as taxanes, cetuximab, or methotrexate. However, single agents have limited effectiveness and responses are transitory [5]. Few reports have described combination regimens without platinum for platinum-ineligible patients. Hitt et al. [38] described a prospective phase II study of combination of cetuximab and weekly paclitaxel as a first-line treatment for patients with R/M SCCHN that was promising, as the ORR was 54%, and the median PFS and OS were 4.2 and 8.1 months, respectively. As a background to these findings, although cetuximab is only about 13% effective as a single agent [39], combining it with a cytotoxic agent might result in a synergistic effect. This notion was addressed in the EXTREME trial, which showed that adding cetuximab to FP improved survival compared with FP [7]. We found that S-1/cetuximab was also promising, with an ORR of 43% in platinum-ineligible patients with R/M SCCHN. Thus, S-1/cetuximab treatment might be a beneficial alternative to paclitaxel/cetuximab in the setting of platinum-ineligibility for the following reasons. The frequency of myelosuppressive toxicity was low. Only one (5%) patient each developed

grade 3 neutropenia and anemia. Peripheral neuropathy is a common AE associated with paclitaxel, but it did not arise in the present study. This is very important for maintaining the therapeutic effect and patient QOL, because severe neuropathy often results in treatment discontinuation. Pre-treatment steroids to prevent IRRs were discontinued after a second infusion of cetuximab in the present study. Cetuximab is unlikely to cause IRRs after a few doses, but pre-treatment steroids need to be continued to suppress allergic reactions to paclitaxel. Thus, our regimen helped to maintain stable blood sugar levels in patients with diabetes. The frequency of alopecia was very low during treatment with S-1/cetuximab, as only two patients developed grade 1 alopecia. This is also beneficial for patients who participate in social activities. On the other hand, 8 patients in our study discontinued treatment due to AEs. Specifically, 5 patients discontinued due to treatment-related AEs including grade 1 cetuximab-related pneumonitis. However, 2 of these 5 were able to switch to S-1 or cetuximab monotherapy after discontinuation. The other 3 of the 8 patients discontinued due to grade 2 radiation pneumonitis, aspiration pneumonia, and off-protocol S-1/cetuximab after long-term discontinuation due to trouble with gastrostomy. Although treatment-related grade 3/4 AEs were reported in 13 patients (62%), the treatment was generally well tolerated with appropriate dose reductions and administration delays according to dose reduction protocols. Two patients refused to continue treatment due to personal reasons unrelated to AEs: one for economic reasons and the other because of durable complete response. Based on the above evidence, S-1/cetuximab might be an appropriate treatment option for platinum-ineligible patients with R/M SCCHN.

Limitations

This study was prematurely closed due to slow accrual, and it was underpowered to determine statistical significance for the primary endpoint due to the small patient cohort. On the other hand, we did confirm survival data and the safety profile of S-1/cetuximab. Factors that contributed to the insufficient closure comprised competing trials in Japan at the time, strict patient criteria, and an overlap with the approval of nivolumab in routine medical practice for R/M SCCHN.

Conclusions

Our study suggests that S-1/cetuximab might be an effective first-line treatment (or after therapy with an immune checkpoint inhibitor) for patients with R/M SCCHN. Whereas platinum/5-FU/cetuximab remains one of the standard first-line treatments, S-1/cetuximab is an appropriate alternative for platinum-ineligible patients with R/M SCCHN.

Acknowledgements This study did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest Hirotoshi Dosaka-Akita received scholarship donations from Taiho Pharmaceutical Company. The remaining co-authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424. https://doi.org/10.3322/caac.21492
2. Pignon JP, le Maitre A, Maillard E et al (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92(1):4–14. https://doi.org/10.1016/j.radonc.2009.04.014
3. Bernier J, Domenge C, Ozsahin M et al (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350(19):1945–1952. https://doi.org/10.1056/NEJMoa032641
4. Cooper JS, Pajak TF, Forastiere AA et al (2004) Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350(19):1937–1944. https://doi.org/10.1056/NEJMoa032646
5. Vermorken JB, Specenier P (2010) Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol. https://doi.org/10.1093/annonc/mdq453
6. National Comprehensive Cancer Network Head and Neck Cancers (Version 3.2019) https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck_blocks.pdf. Accessed February 23, 2020
7. Vermorken JB, Mesia R, Rivera F et al (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359(11):1116–1127. https://doi.org/10.1056/NEJMoa0802656
8. Shirasaka T, Nakano K, Takechi T et al (1996) Antitumor activity of 1 M tegafur-04 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. Cancer Res 56(11):2602–2606
9. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357(18):1810–1820. https://doi.org/10.1056/NEJMoa072252
10. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9(3):215–221. https://doi.org/10.1016/S1470-2045(08)70035-4
11. Yamada Y, Takahari D, Matsumoto H et al (2013) Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 14(13):1278–1286. https://doi.org/10.1016/S1470-2045(13)70490-X

12. Muro K, Boku N, Shimada Y et al (2010) Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 11(9):853–860. https://doi.org/10.1016/S1470-2045(10)70181-9
13. Uesaka K, Boku N, Fukutomi A et al (2016) Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 388(10041):248–257. https://doi.org/10.1016/S0140-6736(16)30583-9
14. Ueno H, Ioka T, Ikeda M et al (2013) Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 31(13):1640–1648. https://doi.org/10.1200/JCO.2012.43.3680
15. Kubota K, Sakai H, Katakami N et al (2015) A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial. Ann Oncol 26(7):1401–1408. https://doi.org/10.1093/annonc/mdv190
16. Okamoto I, Yoshioka H, Morita S et al (2010) Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. J Clin Oncol 28(36):5240–5246. https://doi.org/10.1200/JCO.2010.31.0326
17. Takashima T, Mukai H, Hara F et al (2016) Taxanes versus S-1 as the first-line chemotherapy for metastatic breast cancer (SELECT BC): an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 17(1):90–98. https://doi.org/10.1016/S1470-2045(15)00411-8
18. Yokota T, Onozawa Y, Boku N et al (2011) S-1 monotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck after progression on platinum-based chemotherapy. Jpn J Clin Oncol 41(12):1351–1357. https://doi.org/10.1093/jjco/hyr147
19. Kubota A, Nakatani E, Tsukahara K et al (2018) Adjuvant chemotherapy with S-1 after curative chemoradiotherapy in patients with locoregionally advanced squamous cell carcinoma of the head and neck: reanalysis of the ACTS-HNC study. PLoS ONE 13(6):e0198391. https://doi.org/10.1371/journal.pone.0198391
20. Sakata K, Someya M, Matsumoto Y et al (2011) Gimeracil, an inhibitor of dihydropyrimidine dehydrogenase, inhibits the early step in homologous recombination. Cancer Sci 102(9):1712–1716. https://doi.org/10.1111/j.1349-7006.2011.02004.x
21. Tahara M, Araki K, Okano S et al (2011) Phase I trial of combination chemotherapy with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer. Ann Oncol 22(1):175–180. https://doi.org/10.1093/annonc/mdq298
22. Tahara M, Kiyota N, Mizusawa J et al (2015) Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci 106(6):726–733. https://doi.org/10.1111/cas.12657
23. Fukuda K, Saikawa Y, Takahashi M et al (2012) Antitumor effect of cetuximab in combination with S-1 in EGFR-amplified gastric cancer cells. Int J Oncol 40(4):975–982. https://doi.org/10.3892/ijo.2011.1279
24. Nukatsuka M, Saito H, Nakagawa F et al (2012) Combination therapy using oral S-1 and targeted agents against human tumor xenografts in nude mice. Exp Ther Med 3(5):755–762. https://doi.org/10.3892/etm.2012.484
25. Takahashi T, Emi Y, Oki E et al (2016) Multicenter phase II study of combination therapy with cetuximab and S-1 in patients with KRAS exon 2 wild-type unresectable colorectal cancer previously treated with irinotecan, oxaliplatin, and fluoropyrimidines (KSCC 0901 study). Cancer Chemother Pharmacol 78(3):585–593. https://doi.org/10.1007/s00280-016-3109-4
26. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026
27. Inuyama Y, Kida A, Tsukuda M et al (2001) Late phase II study of S-1 in patients with advanced head and neck cancer. Gan kagaku ryoho Cancer Chemother 28(10):1381–1390
28. Saloura V, Cohen EE, Licitra L et al (2014) An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol 73(6):1227–1239. https://doi.org/10.1007/s00280-014-2459-z
29. Baselga J, Trigo JM, Bourhis J et al (2005) Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 23(24):5568–5577. https://doi.org/10.1200/JCO.2005.07.119
30. Herbst RS, Arquette M, Shin DM et al (2005) Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 23(24):5578–5587. https://doi.org/10.1200/JCO.2005.07.120
31. Ferris RL, Blumenschein G Jr, Fayette J et al (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 375(19):1856–1867. https://doi.org/10.1056/NEJMoa1602252
32. Cohen EEW, Soulieres D, Le Tourneau C et al (2019) Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet 393(10167):156–167. https://doi.org/10.1016/S0140-6736(18)31999-8
33. Schvartsman G, Peng SA, Bis G et al (2017) Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. Lung Cancer 112:90–95. https://doi.org/10.1016/j.lungcan.2017.07.034
34. Szabados B, van Dijk N, Tang YZ et al (2018) Response Rate to Chemotherapy After Immune Checkpoint Inhibition in Metastatic Urothelial Cancer. Eur Urol 73(2):149–152. https://doi.org/10.1016/j.eururo.2017.08.022
35. Rossi C, Gilhodes J, Maerevoet M et al (2018) Efficacy of chemotherapy or chemo-anti-PD-1 combination after failed anti-PD-1 therapy for relapsed and refractory Hodgkin lymphoma: a series from Lysa centers. Am J Hematol. https://doi.org/10.1002/ajh.25154
36. Saleh K, Daste A, Martin N et al (2019) Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Eur J Cancer 121:123–129. https://doi.org/10.1016/j.ejca.2019.08.026
37. Burtness B, Harrington KJ, Greil R et al (2019) 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 394(10212):1915–1928. https://doi.org/10.1016/S0140-6736(19)32591-7
38. Hitt R, Irigoyen A, Cortes-Funes H et al (2012) Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic

squamous cell carcinoma of head and neck. Ann Oncol 23(4):1016–1022. https://doi.org/10.1093/annonc/mdr367

39. Vermorken JB, Trigo J, Hitt R et al (2007) Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 25(16):2171–2177. https://doi.org/10.1200/JCO.2006.06.7447