

Paclitaxel and cisplatin with or without cetuximab in metastatic esophageal squamous cell carcinoma: a randomized, multicenter phase II trial

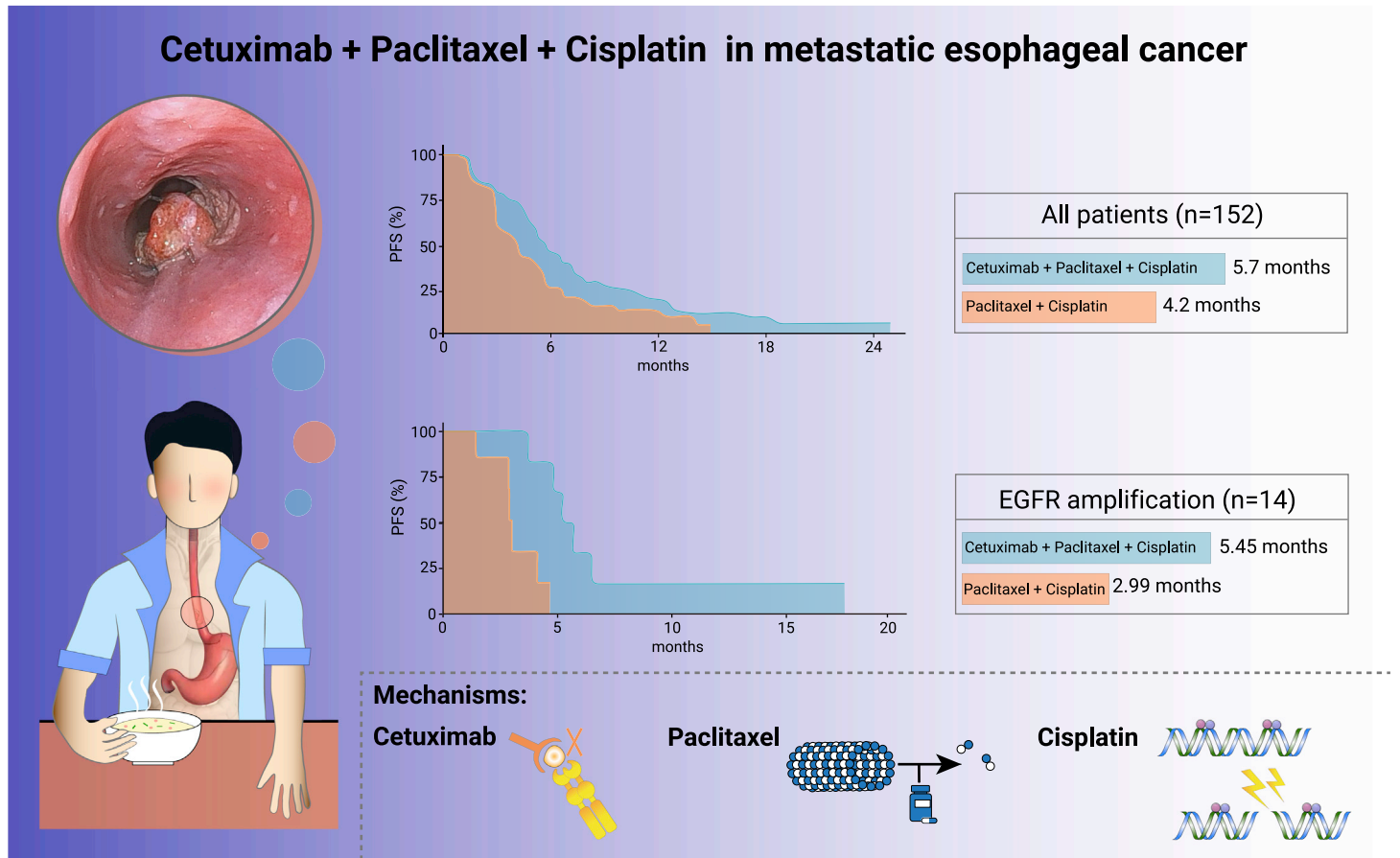
Zhihao Lu,^{1,15} Yanqiao Zhang,^{2,15} Qingxia Fan,^{3,15} Yueyin Pan,⁴ Da Jiang,⁵ Ping Lu,⁶ Jingdong Zhang,⁷ Xianglin Yuan,⁸ Jifeng Feng,⁹ Shujun Yang,¹⁰ Wenbin Yue,¹¹ Lin Zhao,¹² Yunhua Xu,¹³ Jinhua Luo,¹⁴ and Lin Shen^{1,*}

*Correspondence: shenlin@bjmu.edu.cn

Received: December 14, 2021; Accepted: April 4, 2022; Published Online: April 4, 2022; <https://doi.org/10.1016/j.xinn.2022.100239>

© 2022 This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Compare the effect of Cetuximab + chemotherapy with chemotherapy alone in ESCC
- CTP regimen improves progression-free survival with a manageable safety profile
- ESCC patients with EGFR amplification obtain greater therapeutic benefit from CTP
- CTP regimen represents a new treatment option for ESCC



Paclitaxel and cisplatin with or without cetuximab in metastatic esophageal squamous cell carcinoma: a randomized, multicenter phase II trial

Zhihao Lu,^{1,15} Yanqiao Zhang,^{2,15} Qingxia Fan,^{3,15} Yueyin Pan,⁴ Da Jiang,⁵ Ping Lu,⁶ Jingdong Zhang,⁷ Xianglin Yuan,⁸ Jifeng Feng,⁹ Shujun Yang,¹⁰ Wenbin Yue,¹¹ Lin Zhao,¹² Yunhua Xu,¹³ Jinhua Luo,¹⁴ and Lin Shen^{1,*}

¹Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China

²Department of Gastrointestinal Medical Oncology, Harbin Medical University Cancer Hospital, Harbin 150081, China

³Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China

⁴Department of Oncology, Anhui Province Hospital, Hefei, Anhui 230088, China

⁵Department of Medical Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei Province 050011, China

⁶Department of Medical Oncology, First Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan 453199, China

⁷Medical Oncology Department of Gastrointestinal Cancer, Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, Shenyang 110042, China

⁸Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

⁹Department of Oncology, Jiangsu Cancer Hospital, Nanjing, Jiangsu 210009, China

¹⁰Department of Medical Oncology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan 450003, China

¹¹Department of Oncology, Puyang Oilfield General Hospital Puyang, Henan, China

¹²Department of Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

¹³Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

¹⁴Department of Thoracic Surgery, Jiangsu Province Hospital, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

¹⁵These authors contributed equally

*Correspondence: shenlin@bjmu.edu.cn

Received: December 14, 2021; Accepted: April 4, 2022; Published Online: April 4, 2022; <https://doi.org/10.1016/j.xinn.2022.100239>

© 2022 This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Citation: Lu Z., Zhang Y., Fan Q., et al., (2022). Paclitaxel and cisplatin with or without cetuximab in metastatic esophageal squamous cell carcinoma: a randomized, multicenter phase II trial. *The Innovation* 3(3), 100239.

Lack of effective targeted therapy in metastatic esophageal squamous cell carcinoma (ESCC) underscores the urgent need for identifying new treatment approaches for this challenging disease. We sought to assess the addition of cetuximab to paclitaxel-cisplatin chemotherapy for first-line treatment in patients with metastatic ESCC. In this randomized, multicenter, open-label, phase II clinical trial, patients were randomized to receive paclitaxel-cisplatin (TP) (paclitaxel [175 mg/m² intravenously (i.v.) on day 1 of every 3-week cycle] and cisplatin [75 mg/m² i.v. on day 1 of every 3-week cycle]) and TP plus cetuximab (CTP) (cetuximab, 400 mg/m² i.v. on day 1 of week 1, followed by 250 mg/m² weekly), respectively. Targeted next-generation sequencing (NGS) was performed on 89 tumor samples for biomarker exploration. The primary endpoint was progression-free survival (PFS) in the intention-to-treat population. With a median follow-up of 22.6 months, median PFS was 5.7 months (95% confidence interval [CI]: 4.8–7.0) in patients administered CTP versus 4.2 months (95% CI: 3.0–5.3) in the TP group (hazard ratio [HR] = 0.61; 95% CI: 0.40–0.93; p = 0.02). Median overall survival was 11.5 months (95% CI: 7.9–13.1) in the CTP group and 10.5 months (95% CI: 9.0–13.2) in the TP arm (HR = 0.98; 95% CI: 0.67–1.44; p = 0.91). The most common reported greater than or equal to grade 3 adverse events were neutropenia (35.2% versus 22.4%) and leukopenia (25.4% versus 13.2%). In patients with epidermal growth factor receptor (EGFR) amplification tumors (15.7%), PFS was improved with CTP compared with TP treatment (HR = 0.11; 95% CI: 0.01–0.98; p = 0.018). First-line CTP significantly improves PFS, with a manageable safety profile in patients with metastatic ESCC.

INTRODUCTION

Esophageal cancer (EC) is the seventh most common malignancy and the sixth leading cause of cancer deaths worldwide.¹ Importantly, more than 50% of global EC cases occur in China, with most of them diagnosed as an advanced stage.² Platin-based chemotherapy is the most commonly used first-line regimen for advanced esophageal squamous cell carcinoma (ESCC), with a reported median progression-free survival (PFS) of 3.6–6.0 months and a median overall survival (OS) of approximately 10 months.^{3–7} These data underscore the need for identifying new treatment approaches for this disease.

It has been reported that epidermal growth factor receptor (EGFR) overexpression is frequently observed in ESCC, with an incidence of 50%–70%,^{7–9} suggesting EGFR as a potential therapeutic target in ESCC. Previously, a random-

ized trial assessing first-line treatments for metastatic ESCC demonstrated that patients administered cetuximab plus 5-fluorouracil (5-FU) and cisplatin have a trend of improved PFS and OS compared with the chemotherapy alone group.⁷ However, the paclitaxel and cisplatin (TP) regimen is another active treatment option, which is widely used in China.^{4,10} Whether addition of cetuximab to the TP regimen (CTP) could be applied to first-line treatment in ESCC remains to be elucidated. Therefore, we performed a randomized phase II study to assess the clinical efficacy and safety of cetuximab added to chemotherapy for first-line treatment in metastatic ESCC.

RESULTS

Patient characteristics

Between April 10, 2017 and Oct 17, 2018, a total of 159 patients with metastatic ESCC in 14 study centers were screened for participation, of whom 152 patients were randomly assigned to the CTP (n = 74) and TP (n = 78) arms (Figure 1). Finally, PFS, OS, time to progression (TTP), objective response rate (ORR), and disease control rate (DCR) were analyzed in 152 patients. Safety profile was assessed in 147 of the 152 patients. Demographic and baseline characteristics are listed in Table 1.

At the cutoff date on April 21, 2020, a total of 113 (74%) patients had died, and no patient was lost to follow-up. The median follow-up time was 22.6 months (95% confidence interval [CI]: 21.5–25.6).

Efficacy

In the intention to treat (ITT) population (n = 152), median PFS was 5.7 months (95% CI: 4.8–7.0) in the CTP arm versus 4.2 months (95% CI: 3.0–5.3) in the TP arm (hazard ratio [HR] = 0.61; 95% CI: 0.40–0.93; p = 0.02; Figure 2A). In most of the predefined subgroups, PFS was improved in the CTP group versus TP-treated patients, particularly in men, patients with more than one metastasis, and below 65 years old (Figure 3).

Median TTP was 6.6 months (95% CI: 5.2–7.9) in patients administered CTP versus 4.3 months (95% CI: 3.0–5.5) in the TP group (HR = 0.58; 95% CI: 0.37–0.91; p = 0.02; Figure S1). Median OS was 11.5 months (95% CI: 7.9–13.1) in patients administered CTP versus 10.5 months (95% CI: 9.0–13.2) in the TP group (HR = 0.98; 95% CI: 0.67–1.44; p = 0.91; Figure 2B).

The ORR data were based on a subset of 64 of the 74 patients in the CTP arm and 60 of the 78 patients administered TP. In terms of overall response, 43 patients (58.1%; 95% CI: 46.9–69.3) showed response in the CTP arm versus 36 patients (46.2%; 95% CI: 35.1–57.3) in the TP arm (Table 2). The DCR was 78.4%

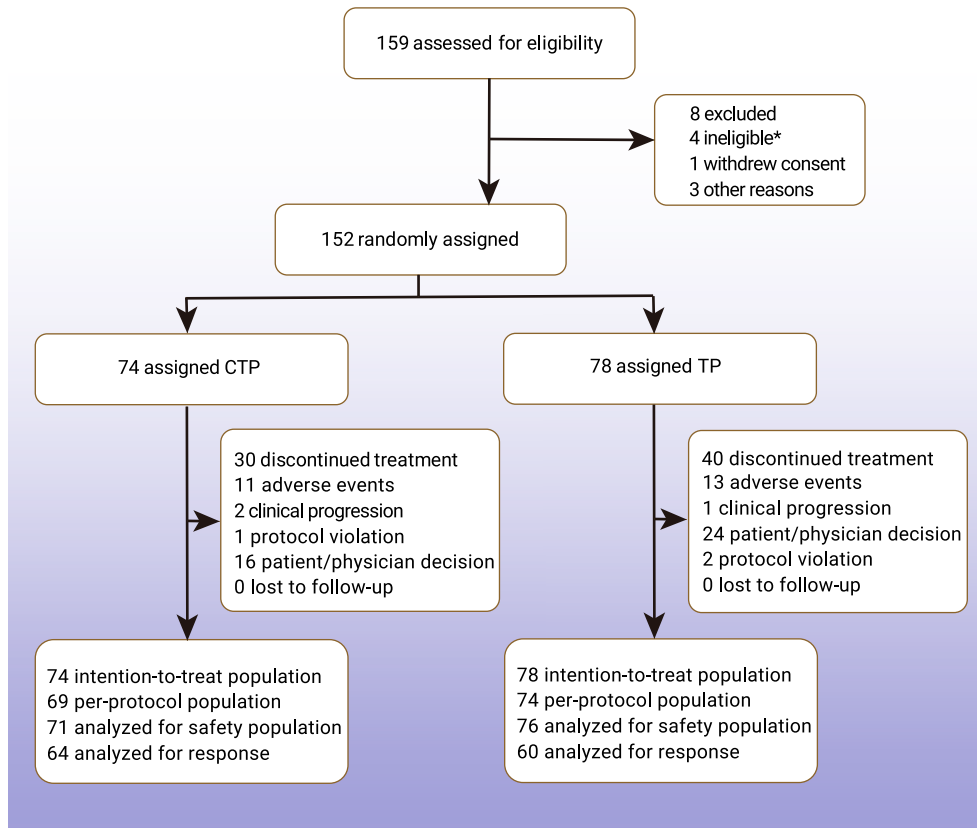


Figure 1. CONSORT diagram of patient selection
Asterisk indicates a major deviation occurred, because one patient was still randomized.

95% CI: 0.22–0.85; $p = 0.013$; Figure 4D), but OS analysis did not reach significance in this subset of patients (Figure S3). The processed data are displayed in Table S2, and the analysis of the other genetic biomarkers are shown in Figure S4.

DISCUSSION

This is a randomized trial comparing the efficacy and safety of CTP and TP alone as first-line treatment in patients with metastatic ESCC. The results showed that addition of cetuximab significantly improved PFS. Furthermore, this combinational regimen showed an acceptable toxicity profile. Jointly, these findings formed the basis for further phase III trials evaluating the CTP regimen as first-line treatment in metastatic ESCC.

Anti-EGFR treatment has been previously investigated in combination with chemotherapy regimens in metastatic ESCC, but no significant benefit was associated with the addition of cetuximab or panitumumab, as reported in the AIO and POWER studies.^{6,7} The present study provides the first proof of concept that cetuximab addition to chemotherapy resulted in increased PFS in metastatic

ESCC. Two important factors might contribute to this difference. The first parameter is the selected chemotherapy backbone. Lorenzen et al. employed the cisplatin and 5-FU regimen as the chemotherapy backbone,^{6,7} while this study used the cisplatin and paclitaxel regimen instead. There are strong biological and mechanistic rationales for this combination, because addition of cetuximab to paclitaxel and cisplatin may have highly synergistic activities due to non-overlapping cell-killing mechanisms.¹⁴ Specifically, cetuximab inhibits the cell cycle and induces pro-apoptotic molecules,¹⁵ paclitaxel promotes mitosis arrest,¹⁶ and platinum triggers the formation of DNA adducts,¹⁷ all leading to apoptosis. In addition, docetaxel has been previously shown to induce immunogenic cell death in cancer cells and elicit various immunogenic actions in the tumor microenvironment,^{18–21} which may exacerbate cetuximab's immunostimulatory effects.¹⁴ Beyond these preclinical observations, several phase III clinical trials have evaluated the added benefit of combining immunotherapy and chemotherapy in the first-line setting for ESCC patients. According to recently released results,^{22–26} chemoimmunotherapy combinations using TP regimen appear to confer better survival than using 5-FU and cisplatin regimen, indicating that TP regimen could generate a more favorable tumor microenvironment to maximize the immunotherapy or targeted therapy efficacy and might be more suitable for combination. Notably, evidence from clinical studies of head and neck squamous cell carcinoma also supported the combination of cetuximab and the TP regimen, reporting a slightly longer time to treatment failure (TTF) and improved safety profile with a taxane versus 5-FU in combination with anti-EGFR antibody and platinum.^{27–30} Together with available evidence, the present study suggests that cetuximab combined with the cisplatin and paclitaxel regimen may be preferable to the 5-FU and cisplatin regimen. The second potential factor is the heterogeneity in different races. Specifically, the AIO and POWER trial was conducted in Germany alone, whereas this study was based on the Chinese population. ESCC is a highly heterogeneous disease with a distinct molecular basis among races.^{12,31} Therefore, it is plausible that racial factors may account for the different results of this study versus previous reports.

Safety

Adverse events are summarized in Table 3. The incidence rates of all grades adverse events (AEs) were 94.4% (67/71) in the CTP arm and 73.7% (56/76) in the TP arm. The most commonly reported AEs were anemia (52.1% of patients administered CTP versus 51.3% in the TP group), neutropenia (52.1% versus 39.5%) and leukopenia (52.1% versus 40.8%). AEs of grade 3 or worse occurred in 39 (54.9%) of 71 patients in the CTP arm and 24 (31.6%) of 76 cases in the TP arm. The most frequently reported AEs greater than or equal to grade 3 were neutropenia (35.2% versus 22.4%) and leukopenia (25.4% versus 13.2%). In addition, rash occurred in 19/71 (26.8%) patients administered CTP versus 2/76 (2.6%) in the TP arm. No patients experienced greater than or equal to grade 3 rash in either arm. No fatal event related to cetuximab was documented.

Biomarker exploration

To identify potential biomarkers associated with treatment benefit, a total of 89 baseline tumor samples were profiled by targeted next-generation sequencing. In samples from 42 patients in CTP group and 47 patients from TP group, gene mutations or amplification were successfully detected in at least one of the analyzed exons. The genetic landscape presented in our study was robustly consistent with previous reports,^{11–13} demonstrating the high frequency of mutations in TP53, NOTCH1, and amplifications in Myc and CCND1 (Figure 4A; Table S1). Notably, in EGFR amplification patients ($n = 14$; 15.7%), PFS benefit was observed in patients who received CTP compared with those who received TP (5.45 versus 2.99 months; HR = 0.11; 95% CI: 0.01–0.98; $p = 0.018$; Figure 4B). A similar trend of improved OS was also associated with CTP treatment in EGFR-amplified cases (17.18 versus 6.01 months; HR = 0.35; 95% CI: 0.1–1.27; $p = 0.097$; Figure 4C). Response rate was higher in CTP group than TP group for EGFR amplification patients, but difference did not reach the statistical significance (Figure S2).

We also identified PFS was improved in 11q13-amplified patients who received CTP compared with those who received TP (5.19 versus 2.96 months; HR = 0.43;

Although cetuximab added to the TP regimen chemotherapy failed to improve the median OS in patients with metastatic ESCC, we did observe a

Table 1. Baseline characteristics

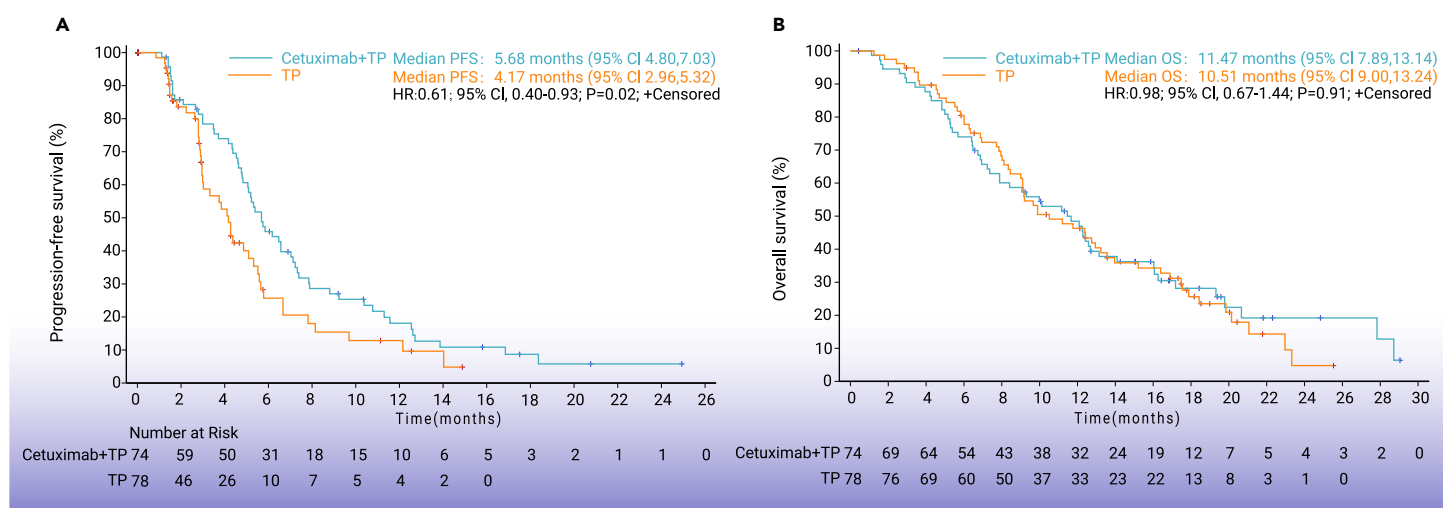
| | Cetuximab + TP (n = 74) | TP (n = 78) |
|------------------------------|-------------------------|--------------|
| Age (years) | | |
| Median (range) | 61 (44–78) | 60.5 (40–76) |
| Sex | | |
| Male | 62 (83.8%) | 69 (88.5%) |
| Female | 12 (16.2%) | 9 (11.5%) |
| ECOG | | |
| 0 | 33 (44.6%) | 33 (42.3%) |
| 1 | 41 (55.4%) | 45 (57.7%) |
| Number of metastases | | |
| 1 | 16 (21.6%) | 3 (28.2%) |
| ≥2 | 58 (78.4%) | 5 (71.8%) |
| Tumor location | | |
| Upper | 9 (12.2%) | 7 (9.0%) |
| Middle | 36 (48.6%) | 31 (39.7%) |
| Lower | 23 (31.1%) | 35 (44.9%) |
| NA | 6 (8.1%) | 5 (6.4%) |
| Previous surgery | | |
| Yes | 27 (36.5%) | 27 (34.6%) |
| No | 47 (63.5%) | 51 (65.4%) |
| Previous radiotherapy | | |
| Yes | 17 (23.0%) | 21 (26.9%) |
| No | 57 (77.0%) | 57 (73.1%) |

“tail” on the OS curve in CTP group, suggesting a subset of patients would derive long-term benefit from CTP regimen. Based on the previous preclinical and clinical reports,^{32–36} we hypothesized that those patients whose tumors were driven by EGFR signaling would accordingly benefit from anti-EGFR treatment. Notably, our biomarker program demonstrated the patients with EGFR amplification derive greater therapeutic benefit from CTP treatment, further providing insights of EGFR signaling alterations in guiding the selection of ESCC patients treated by EGFR-directed monoclonal antibodies (mAbs).³⁶

This is very similar to the results observed in lung squamous cell carcinoma,^{37,38} which also found that EGFR-directed mAbs in combination with chemotherapy are associated with greater clinical benefits in selected patients with high EGFR expression and/or increased EGFR gene copy number. It provided an important basis for future large-scale study accessing EGFR amplification as a biomarker to select advanced ESCC patients, who would benefit from CTP treatment. In addition, we also found patients with 11q13 amplification obtain more PFS benefit when treated with CTP, indicating that ESCC with aberrations in cell cycle pathway may also be susceptible to EGFR-directed mAbs. Previous studies found that 11q13 amplification is associated with poor prognosis in ESCC.¹¹ Our results suggest that CTP treatment strategy may represent an alternative treatment for this subset patients, which should be validated in the future.

Recently, programmed cell death-1 (PD-1) blockade has emerged as a standard second-line treatment option for metastatic ESCC.^{39–41} Moreover, the recently reported results of the KEYNOTE-590 study (pembrolizumab combined with chemotherapy versus chemotherapy alone) in the first-line setting are really promising and could revolutionize the treatment algorithm for metastatic ESCC.²⁴ However, the survival benefit of immunotherapy is correlated with PD-L1 expression status, with only a subset of patients possibly deriving long-term survival benefit from these immunotherapeutic treatment options.^{24,41} Notably, it was observed that PD-L1 expression either on tumor-infiltrating immune cells or tumor cells is negatively associated with EGFR expression in ESCC.⁴² Meanwhile, EGFR is considered a target of anti-EGFR antibodies.^{34,35} Therefore, the patients who could not benefit from PD-1 and PD-L1 blockade treatment would probably be suitable for anti-EGFR antibodies. Moreover, pembrolizumab combined with cetuximab has yielded a promising efficacy in recurrent and metastatic head and neck squamous cell carcinoma.⁴³ It has also been reported that EGFR is a potential drug target for combinatorial immunotherapy with strong scientific rationale.⁴⁴ These findings provided a novel implication that targeting EGFR in combination with immune checkpoint inhibitor may bring more survival benefit in patients with ESCC.

In this study, the safety profile showed that grade 3–5 AEs seem higher in the CTP arm than TP arm (54.9% versus 31.6%), which was similar with previous reports, including ESCC and colorectal cancer.^{7,45} Specifically, dermatologic toxicity, such as rash, was the most frequently observed AE after addition of cetuximab, with 38% of patients experiencing grade 1/2 and no grade 3–5 dermatologic AEs. However, 28 (40%) patients in CTP group and 27 (36%) patients in TP group have taken the administration with the maximum six courses, suggesting the toxicities of CTP did not delay the course of treatment and the CTP treatment had manageable safety profiles. Compared with the 5-FU and cisplatin chemotherapy backbone,^{6,7} the paclitaxel-based combination had low rates of blood system and gastrointestinal disorders. This was generally consistent with our historical data, which might be associated with pretreatment with glucocorticoids while using paclitaxel

**Figure 2.** Survival outcomes (A) Kaplan-Meier plot of overall survival. (B) Kaplan-Meier plot of progression-free survival.

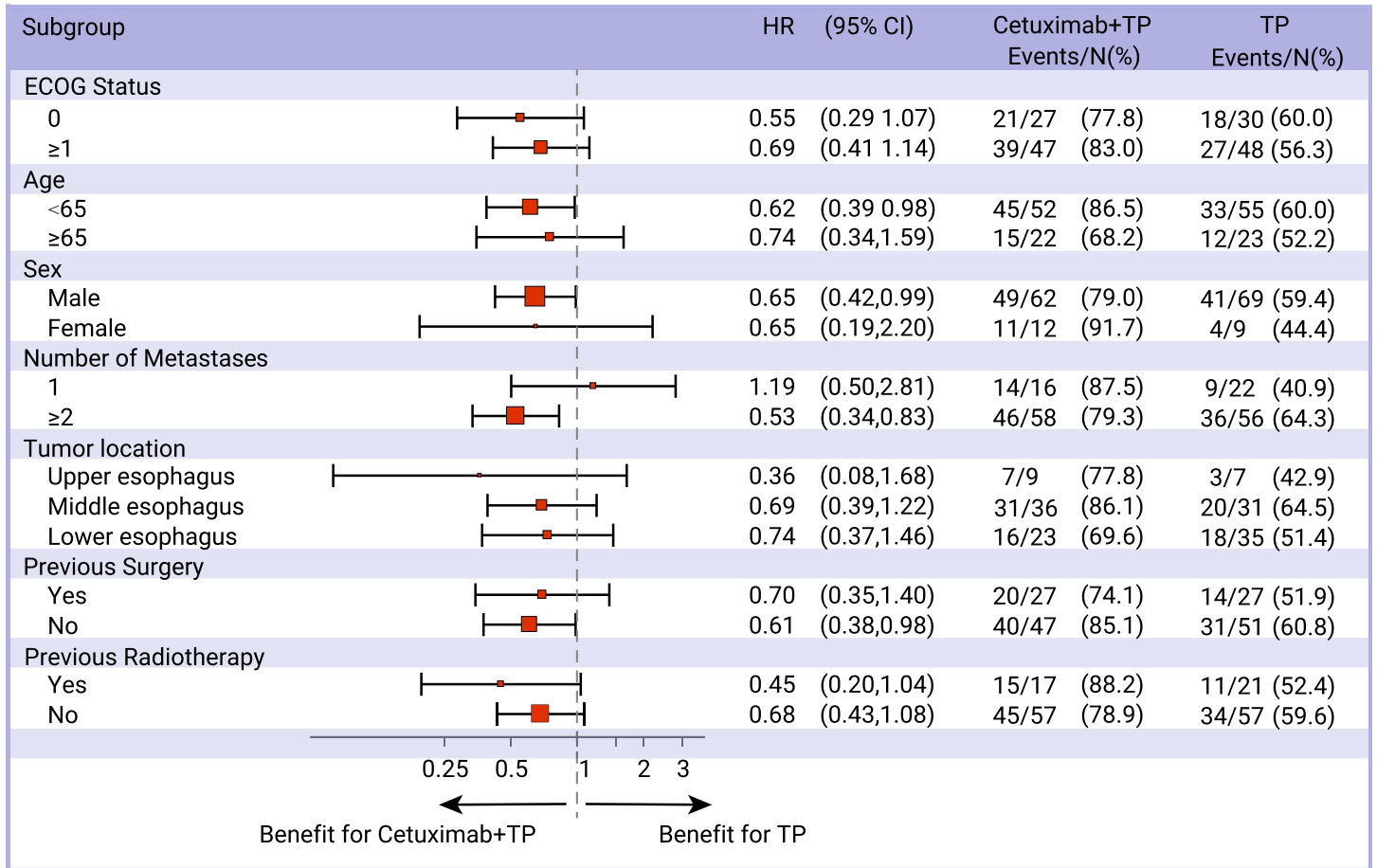


Figure 3. Forest plot for subgroup analyses of progression-free survival

and our highly experienced management of adverse events.^{10,46} These findings further support the favorable safety profile of paclitaxel-based regimens for combination with cetuximab.

This study had some limitations. First, the sample size was relatively small, and the study was not powered enough to detect a difference in OS. A large, randomized phase III trial is warranted to further confirm these results. Secondly, although our post hoc analysis identified a fraction of patients with EGFR or 11q13 amplification may derive more PFS benefit from CTP than TP, the observation needs to be further validated in the future prospective study with a large subset of this specific population.

In conclusion, the combination of cetuximab with the TP regimen is safe and effective, with significantly improved PFS, as first-line treatment in metastatic ESCC. A randomized, biomarker-driven, phase III study is warranted for further confirming the efficacy of this combination in ESCC patients.

MATERIALS AND METHODS

Study design and patients

This was an open-label, randomized, multicenter phase II trial (NCT03126708) evaluating the efficacy and safety of CTP versus TP alone for the first-line treatment of Chinese patients with metastatic ESCC.

Inclusion criteria were histologically confirmed squamous cell carcinoma of the esophagus, 18 years of age or older, metastatic ESCC not suitable for local-regional treatment, no (neo)adjuvant chemotherapy within 6 months of study entry or prior chemotherapy for metastatic disease, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Patients with prior EGFR-targeted therapy were excluded.

This study was approved by the medical ethics committee of Peking University Cancer Hospital (2016YJZ47-ZY01). The study was performed in accordance with the Declaration

Table 2. Best overall responses by RECIST

| | Cetuximab + TP (n = 74) | TP (n = 78) |
|------------------------------|-------------------------------|-------------------------------|
| Best overall response | | |
| Complete response | 0 | 0 |
| Partial response | 43 (58.1%) | 36 (46.2%) |
| Stable disease | 15 (20.3%) | 18 (23.1%) |
| Progressive disease | 6 (8.1%) | 6 (7.7%) |
| Not assessable | 10 (13.5%) | 18 (23.1%) |
| Objective response | 43 (58.1%; 95% CI: 46.9–69.3) | 36 (46.2%; 95% CI: 35.1–57.3) |
| Disease controlled | 58 (78.4%; 95% CI: 69.0–87.8) | 54 (69.2%; 95% CI: 59.0–79.4) |

Table 3. Adverse events

| | Cetuximab + TP (n = 71) | | TP (n = 76) | |
|--------------------------------------|-------------------------|------------------|------------------|------------------|
| | All grades n (%) | Grades 3–5 n (%) | All grades n (%) | Grades 3–5 n (%) |
| Any | 67 (94.4) | 39 (54.9) | 56 (73.7) | 24 (31.6) |
| Neutropenia | 37 (52.1) | 25 (35.2) | 30 (39.5) | 17 (22.4) |
| Anemia | 37 (52.1) | 4 (5.6) | 39 (51.3) | 1 (1.3) |
| Leukopenia | 37 (52.1) | 18 (25.4) | 31 (40.8) | 10 (13.2) |
| Thrombocytopenia | 10 (14.1) | 3 (4.2) | 1 (1.3) | 0 |
| Constipation | 4 (5.6) | 0 | 3 (3.9) | 0 |
| Diarrhea | 7 (9.9) | 0 | 2 (2.6) | 0 |
| Mouth ulceration | 5 (7.0) | 0 | 0 | 0 |
| Nausea | 10 (14.1) | 1 (1.4) | 3 (3.9) | 1 (1.3) |
| Vomiting | 9 (12.7) | 4 (5.6) | 3 (3.9) | 0 |
| Alanine aminotransferase increased | 12 (16.9) | 2 (2.8) | 4 (5.3) | 0 |
| Aspartate aminotransferase increased | 7 (9.9) | 1 (1.4) | 3 (3.9) | 0 |
| Hypoesthesia | 8 (11.3) | 0 | 6 (7.9) | 1 (1.3) |
| Rash | 19 (26.8) | 0 | 2 (2.6) | 0 |

of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent before enrollment.

Randomization and treatment

Randomization was performed by the stratified block randomization method, according to previous treatment (previous surgery or radiotherapy versus no previous treatment), ECOG performance status (0 versus 1), and the number of metastatic sites (one versus greater than or equal to two affected organs). Patients were randomly assigned (1:1) to the TP (paclitaxel [175 mg/m² i.v. on day 1 of every 3-week cycle] and cisplatin [75 mg/m² i.v. on day 1 of every 3-week cycle]) and CTP (Eributix; Merck KGaA, Darmstadt, Germany) arms. Cetuximab was administered at a dose of 400 mg/m² (i.v. on day 1 of week 1), followed by 250 mg/m² weekly. Cisplatin was replaced by carboplatin (area under the plasma concentration-time curve [AUC] 5) in case of intolerance. All patients received a maximum of six cycles of chemotherapy. After six cycles of treatment, the patients in the CTP arm who had clinical benefits continued treatment with cetuximab as monotherapy. Tumor assessment was performed by computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and every 6 weeks. Treatment was continued until disease progression (defined according to RECIST version 1.1), unacceptable toxicity, patient withdrawal, or investigator decision, whichever occurred first. Further details regarding study design, procedures, and assessment are summarized in the supplement.

Outcomes

The primary endpoint was PFS, defined as the time from randomization to radiological disease progression or death from any cause. The secondary endpoints were OS, TTP, ORR, DCR, and safety profile. OS was defined as the time from randomization to death from any cause. TTP was defined from the date of randomization until the first confirmed evidence of disease progression, death due to progressive disease, or censoring. Tumor response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST version 1.1. ORR cases were defined as patients with PR or CR as the best overall response. The DCR was defined as the number of patients whose best response was CR, PR, or SD, divided by the number of patients belonging to the trial set of interest. Adverse events were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Samples collection and targeted DNA sequencing

Baseline formalin-fixed, paraffin-embedded (FFPE) tissue samples and matched peripheral blood mononuclear cells (PBMCs) were collected retrospectively. All patients provided written informed consent for the biomarker analysis of their tissue specimens.

Genomic DNA (gDNA) from FFPE and paired PBMC (germline) samples were isolated by using the Maxwell 16 FFPE Plus Lev DNA Purification Kit according to the manufacturer's instructions. Before library construction, gDNA was sheared to 200-

to 250-bp fragments with a Covaris LE220 ultrasonicator. Libraries were prepared using the KAPA Library Preparation Kit (Kapa Biosystems, Wilmington, MA, USA). A 1,021-gene panel with potential clinical relevance was used to capture target regions.⁴⁷ DNA sequencing was carried out with paired-end reads on the DNBSEQ-T7 sequencing system.

Sequencing data processing and mutation calling

Terminal adaptor sequences and low-quality reads were removed separately from raw data of paired samples using realSeq (version 3.1.0; in house) and NCFILTER (version 2.0.0; in house). Burrows-Wheeler Aligner (BWA) (version 0.7.15-r1140) tool was used to align clean reads to the reference human genome (hg19). Duplicate reads of cancer sample derived from PCR amplification were marked using realSeq, which was designed to retain reads containing rare events by treating unique molecular indices, and the normal sample was marked using Picard tools (version 2.6.0).

Single-nucleotide variants (SNV) and indels were detected by comparing tumor-normal pairs using TNSCOPE (version 201,808) and RealDcaller (version 1.8.1; in house), a software developed in house to review hotspot variants, and the results of these analyses were merged using NCHOT (version 2.7.2; in house) and then annotated to multiple public databases using NCANNO (version 1.14; in house). For somatic copy-number alteration, an in-house software CNVKIT (version 0.9.2) was performed, and the matched peripheral blood cell samples served as matched controls. Significant copy number variations were calculated as the ratio of adjusted depth between case gDNA and control gDNA. An in-house algorithm NCSV (0.2.3; in house) was used to identify split-read and discordant read-pair to identify structural variants (SVs). All candidate variants were manually verified with the integrative genomics viewer browser.⁴⁸

The WES-FASTQ files data were deposited at Genome Sequence Archive, <https://ngdc.cncb.ac.cn/gsa-human/browse/HRA001904> (BioProject: PRJCA007995; accession GSA: HRA001904). The raw sequence data will be available via controlled access by reasonable request.

Statistical analysis

This study was designed to have an 80% power with a two-sided type I error rate of 0.2 to detect a median PFS HR of 0.66 in favor of CTP. Concurrent with the randomization ratio (1:1) and a predicted dropout rate of 1% per month, the required number of patients was 150.

Survival and efficacy analyses were performed in the ITT population. All patients who received one or more doses of treatment were included in safety analyses. Baseline characteristics were presented as mean and standard deviation (SD) for continuous variables or number and percentage for categorical variables. Differences between study groups in baseline characteristics were assessed by two-sample t test for continuous variables and the Fisher exact test for categorical ones. PFS, OS, and TTP were estimated by the Kaplan-Meier

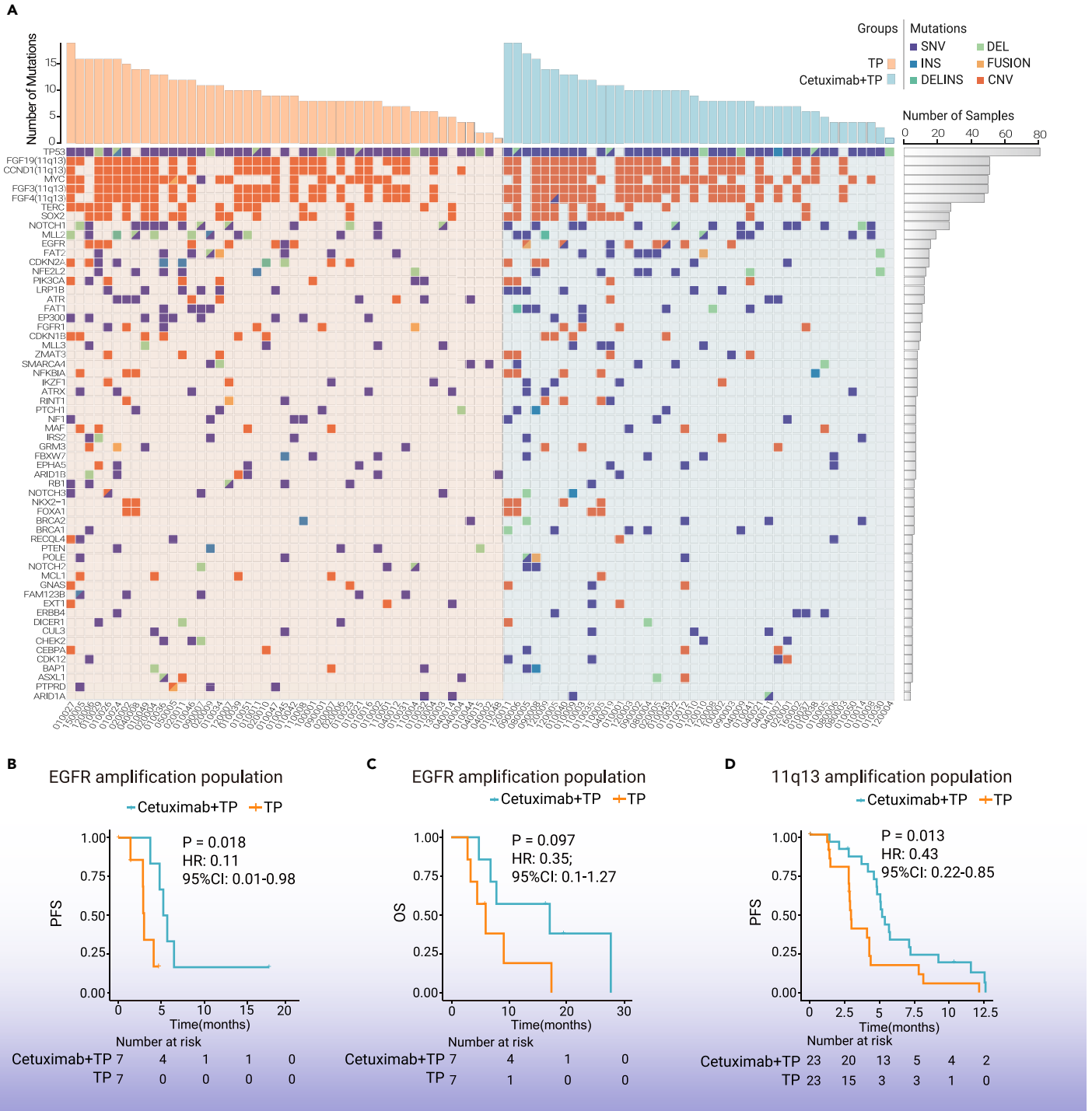


Figure 4. Biomarker analysis (A) Genetic landscape of 89 patients with sufficient pretreatment tumor material for targeted NGS. (B and C) Kaplan-Meier curves of progression-free survival (B) and overall survival (C) for patients with EGFR amplification. (D) Kaplan-Meier curves of progression-free survival in patients with 11q13 amplification.

method. Comparisons between groups in PFS, OS, and TTP were assessed by two-sided stratified log rank test. HRs and their associated 95% CIs were calculated using Cox proportional hazards models, adjusted for stratification factors. The corresponding 95% CIs of ORRs and DCRs were calculated by the Clopper-Pearson method. Statistical analyses were carried out with SAS 9.4. Two-sided $p < 0.05$ was considered statistically significant.

REFERENCES

- 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**, 394–424.
- He, Y., Li, D., Shan, B., et al. (2019). Incidence and mortality of esophagus cancer in China, 2008-2012. *Chin. J. Cancer Res.* **31**, 426–434.

- Qin, T.J., An, G.L., Zhao, X.H., et al. (2009). Combined treatment of oxaliplatin and capecitabine in patients with metastatic esophageal squamous cell cancer. *World J. Gastroenterol.* **15**, 871–876.
- Cao, W., Xu, C., Lou, G., et al. (2009). A phase II study of paclitaxel and nedaplatin as first-line chemotherapy in patients with advanced esophageal cancer. *Jpn. J. Clin. Oncol.* **39**, 582–587.
- Wang, F.H., Wang, Y., Sun, G.P., et al. (2017). Efficacy and safety of recombinant human lymphotoxin- α derivative with cisplatin and fluorouracil in patients with metastatic esophageal squamous cell carcinoma: a randomized, multicenter, open-label, controlled, phase 2b trial. *Cancer* **123**, 3986–3994.
- Moehler, M., Maderer, A., Thuss-Patience, P.C., et al. (2020). Cisplatin and 5-fluorouracil with or without epidermal growth factor receptor inhibition panitumumab for patients with non-resectable, advanced or metastatic oesophageal squamous cell cancer: a prospective, open-label, randomised phase III AIO/EORTC trial (POWER). *Ann. Oncol.* **31**, 228–235.

7. Lorenzen, S., Schuster, T., Porschen, R., et al. (2009). Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann. Oncol.* **20**, 1667–1673.
8. Gibault, L., Metges, J.P., Conan-Charlet, V., et al. (2005). Diffuse EGFR staining is associated with reduced overall survival in locally advanced oesophageal squamous cell cancer. *Br. J. Cancer* **93**, 107–115.
9. Hanawa, M., Suzuki, S., Dobashi, Y., et al. (2006). EGFR protein overexpression and gene amplification in squamous cell carcinomas of the esophagus. *Int. J. Cancer* **118**, 1173–1180.
10. Zhang, X., Shen, L., Li, J., et al. (2008). A phase II trial of paclitaxel and cisplatin in patients with advanced squamous-cell carcinoma of the esophagus. *Am. J. Clin. Oncol.* **31**, 29–33.
11. Cui, Y., Chen, H., Xi, R., et al. (2020). Whole-genome sequencing of 508 patients identifies key molecular features associated with poor prognosis in esophageal squamous cell carcinoma. *Cell Res.* **30**, 902–913.
12. Cancer Genome Atlas Research, Analysis Working Group, Asan, U., Agency, B.C.C., et al. (2017). Integrated genomic characterization of oesophageal carcinoma. *Nature* **541**, 169–175.
13. Lin, D.C., Hao, J.J., Nagata, Y., et al. (2014). Genomic and molecular characterization of esophageal squamous cell carcinoma. *Nat. Genet.* **46**, 467–473.
14. Guigay, J., Tahara, M., Licitra, L., et al. (2019). The evolving role of taxanes in combination with cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: evidence, advantages, and future directions. *Front. Oncol.* **9**, 668.
15. Hotz, B., Keilholz, U., Fusi, A., et al. (2012). In vitro and in vivo antitumor activity of cetuximab in human gastric cancer cell lines in relation to epidermal growth factor receptor (EGFR) expression and mutational phenotype. *Gastric Cancer* **15**, 252–264.
16. Abal, M., Andreu, J.M., and Barasoain, I. (2003). Taxanes: microtubule and centrosome targets, and cell cycle dependent mechanisms of action. *Curr. Cancer Drug Targets* **3**, 193–203.
17. Siddik, Z.H. (2003). Cisplatin: mode of cytotoxic action and molecular basis of resistance. *Oncogene* **22**, 7265–7279.
18. Galluzzi, L., Humeau, J., Buqué, A., et al. (2020). Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat. Rev. Clin. Oncol.* **17**, 725–741.
19. Tsavaris, N., Kosmas, C., Vadiaka, M., et al. (2002). Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. *Br. J. Cancer* **87**, 21–27.
20. Garnett, C.T., Schlom, J., and Hodge, J.W. (2008). Combination of docetaxel and recombinant vaccine enhances T-cell responses and antitumor activity: effects of docetaxel on immune enhancement. *Clin. Cancer Res.* **14**, 3536–3544.
21. Pfannenstiel, L.W., Lam, S.S., Emens, L.A., et al. (2010). Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. *Cell Immunol.* **263**, 79–87.
22. Shen, L., Lu, Z., Wang, J., et al. (2021). LBA52 Sintilimab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced or metastatic esophageal squamous cell cancer: first results of the phase III ORIENT-15 study. *Ann. Oncol.* **32**, S1330.
23. Wang, Z., Cui, C., Yao, J., et al. (2022). Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): a multi-center phase 3 trial. *Cancer Cell* **40**, 277–288e3.
24. Sun, J.M., Shen, L., Shah, M.A., et al. (2021). Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* **398**, 759–771.
25. Doki, Y., Ajani, J.A., Kato, K., et al. (2022). Nivolumab combination therapy in advanced esophageal squamous cell carcinoma. *N. Engl. J. Med.* **386**, 449–462.
26. Luo, H., Lu, J., Bai, Y., et al. (2021). Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. *JAMA* **326**, 916–925.
27. Vermorken, J.B., Mesia, R., Rivera, F., et al. (2008). Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N. Engl. J. Med.* **359**, 1116–1127.
28. Bossi, P., Miceli, R., Locati, L.D., et al. (2017). A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Ann. Oncol.* **28**, 2820–2826.
29. Tahara, M., Kiyota, N., Yokota, T., et al. (2018). Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02). *Ann. Oncol.* **29**, 1004–1009.
30. Tsakonas, G., Specht, L., Kristensen, C.A., et al. (2020). Randomized phase II study with cetuximab in combination with 5-FU and cisplatin or carboplatin vs. cetuximab in combination with paclitaxel and carboplatin for treatment of patients with relapsed or recurrent squamous cell carcinoma of the head and neck (CETMET Trial). *Cancers (Basel)* **12**, 3110.
31. Sawada, G., Niida, A., Uchi, R., et al. (2016). Genomic landscape of esophageal squamous cell carcinoma in a Japanese population. *Gastroenterology* **150**, 1171–1182.
32. Petty, R.D., Dahle-Smith, A., Stevenson, D.A.J., et al. (2017). Gefitinib and EGFR gene copy number aberrations in esophageal cancer. *J. Clin. Oncol.* **35**, 2279–2287.
33. Janmaat, M.L., Gallegos-Ruiz, M.I., Rodriguez, J.A., et al. (2006). Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. *J. Clin. Oncol.* **24**, 1612–1619.
34. Ramos-Suzarte, M., Lorenzo-Luaces, P., Lazo, N.G., et al. (2012). Treatment of malignant, non-resectable, epithelial origin esophageal tumours with the humanized anti-epidermal growth factor antibody nimotuzumab combined with radiation therapy and chemotherapy. *Cancer Biol. Ther.* **13**, 600–605.
35. Chen, Y., Wu, X., Bu, S., et al. (2012). Promising outcomes of definitive chemoradiation and cetuximab for patients with esophageal squamous cell carcinoma. *Cancer Sci.* **103**, 1979–1984.
36. Zhu, H., Wang, C., Wang, J., et al. (2018). A subset of esophageal squamous cell carcinoma patient-derived xenografts respond to cetuximab, which is predicted by high EGFR expression and amplification. *J. Thorac. Dis.* **10**, 5328–5338.
37. Herbst, R.S., Redman, M.W., Kim, E.S., et al. (2018). Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. *Lancet Oncol.* **19**, 101–114.
38. Bonomi, P.D., Gandara, D., Hirsch, F.R., et al. (2018). Predictive biomarkers for response to EGFR-directed monoclonal antibodies for advanced squamous cell lung cancer. *Ann. Oncol.* **29**, 1701–1709.
39. Huang, J., Xu, J., Chen, Y., et al. (2020). Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol.* **21**, 832–842.
40. Kato, K., Cho, B.C., Takahashi, M., et al. (2019). Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* **20**, 1506–1517.
41. Kojima, T., Shah, M.A., Muro, K., et al. (2020). Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J. Clin. Oncol.* **38**, 4138–4148.
42. Zhang, W., Pang, Q., Zhang, X., et al. (2017). Programmed death-ligand 1 is prognostic factor in esophageal squamous cell carcinoma and is associated with epidermal growth factor receptor. *Cancer Sci.* **108**, 590–597.
43. Sacco, A.G., Chen, R., Worden, F.P., et al. (2021). Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: an open-label, multi-arm, non-randomised, multicentre, phase 2 trial. *Lancet Oncol.* **22**, 883–892.
44. Feng, B., Shen, Y., Pastor, H.X., et al. (2020). Integrative analysis of multi-omics data identified EGFR and PTGS2 as key nodes in a gene regulatory network related to immune phenotypes in head and neck cancer. *Clin. Cancer Res.* **26**, 3616–3628.
45. Maughan, T.S., Adams, R.A., Smith, C.G., et al. (2011). Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomized phase 3 MRC COIN trial. *Lancet* **377**, 2103–2114.
46. Lu, M., Wang, X., Shen, L., et al. (2016). Nimotuzumab plus paclitaxel and cisplatin as the first line treatment for advanced esophageal squamous cell cancer: a single center prospective phase II trial. *Cancer Sci.* **107**, 486–490.
47. Ai, X., Cui, J., Zhang, J., et al. (2021). Clonal architecture of EGFR mutation predicts the efficacy of EGFR-tyrosine kinase inhibitors in advanced NSCLC: a prospective multicenter study (NCT03059641). *Clin. Cancer Res.* **27**, 704–712.
48. Thorvaldsdóttir, H., Robinson, J.T., and Mesirov, J.P. (2013). Integrative genomics viewer (IGV): high-performance genomics data visualization and exploration. *Brief Bioinform.* **14**, 178–192.

ACKNOWLEDGMENTS

This work was supported by the Merck KGaA (Darmstadt, Germany), the Clinical Medicine Plus X - Young Scholars Project of Peking University (PKU2020LCXQ008), the Digestive Medical Coordinated Development Center of Beijing Hospitals Authority (no. XXT19), and Beijing Hospitals Authority Youth Programme (QML20191102).

AUTHOR CONTRIBUTIONS

Z.L., Y.Z., and Q.F. contributed equally to this work. L.S. designed the study. Y.P., D.J., P.L., J.Z., X.Y., J.F., S.Y., W.Y., L.Z., Y.X., and J.L. provided study material or patients. Z.L., Y.Z., Q.F., and L.S. contributed to the data collection, analysis, and interpretation. All authors contributed to editing the text and discussed the scientific questions.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xinn.2022.100239>.

LEAD CONTACT WEBSITE

www.pku-shenlab.cn

The Innovation, Volume 3

Supplemental Information

**Paclitaxel and cisplatin with or without cetuximab
in metastatic esophageal squamous cell
carcinoma: a randomized, multicenter phase II trial**

Zhihao Lu, Yanqiao Zhang, Qingxia Fan, Yueyin Pan, Da Jiang, Ping Lu, Jingdong Zhang, Xianglin Yuan, Jifeng Feng, Shujun Yang, Wenbin Yue, Lin Zhao, Yunhua Xu, Jinhua Luo, and Lin Shen

Supplementary materials

Paclitaxel and Cisplatin with or without Cetuximab in metastatic esophageal squamous cell carcinoma: A randomized, multicenter, open-label Phase II trial

Contents:

Table S1

Figure S1-S4

Study procedure

Table S1. Number and Frequency of the common genetic variants

| Gene | Number of genetic variants | Frequency of genetic variants |
|-------------|-----------------------------------|--------------------------------------|
| TP53 | 81 | 91.01% |
| CCND1 | 51 | 57.30% |
| FGF19 | 51 | 57.30% |
| MYC | 50 | 56.18% |
| FGF3 | 50 | 56.18% |
| FGF4 | 48 | 53.93% |
| TERC | 28 | 31.46% |
| NOTCH1 | 27 | 30.34% |
| SOX2 | 27 | 30.34% |
| MLL2 | 19 | 21.35% |
| EGFR | 16 | 17.98% |
| CDKN2A | 15 | 16.85% |
| FAT2 | 15 | 16.85% |
| NFE2L2 | 13 | 14.61% |
| ATR | 12 | 13.48% |
| LRP1B | 12 | 13.48% |
| PIK3CA | 12 | 13.48% |
| EP300 | 11 | 12.36% |
| FAT1 | 11 | 12.36% |
| FGFR1 | 10 | 11.24% |
| CDKN1B | 10 | 11.24% |
| MLL3 | 9 | 10.11% |
| IKZF1 | 8 | 8.99% |
| SMARCA4 | 8 | 8.99% |
| ATRX | 8 | 8.99% |
| NFKBIA | 8 | 8.99% |
| ZMAT3 | 8 | 8.99% |
| ARID1B | 7 | 7.87% |
| FBXW7 | 7 | 7.87% |
| EPHA5 | 7 | 7.87% |
| GRM3 | 7 | 7.87% |
| RINT1 | 7 | 7.87% |
| PTCH1 | 7 | 7.87% |
| NF1 | 7 | 7.87% |
| IRS2 | 7 | 7.87% |
| MAF | 7 | 7.87% |
| BRCA2 | 6 | 6.74% |
| RB1 | 6 | 6.74% |
| NOTCH3 | 6 | 6.74% |
| BRCA1 | 6 | 6.74% |
| FOXA1 | 6 | 6.74% |
| NKX2-1 | 6 | 6.74% |

| | | |
|---------|---|-------|
| PTEN | 5 | 5.62% |
| ERBB4 | 5 | 5.62% |
| CHEK2 | 5 | 5.62% |
| CUL3 | 5 | 5.62% |
| POLE | 5 | 5.62% |
| ASXL1 | 5 | 5.62% |
| EXT1 | 5 | 5.62% |
| CDK12 | 5 | 5.62% |
| GNAS | 5 | 5.62% |
| BAP1 | 5 | 5.62% |
| FAM123B | 5 | 5.62% |
| DICER1 | 5 | 5.62% |
| RECQL4 | 5 | 5.62% |
| NOTCH2 | 5 | 5.62% |
| CEBPA | 5 | 5.62% |
| MCL1 | 5 | 5.62% |

Figure S1. Kaplan-Meier plot of time to progression.

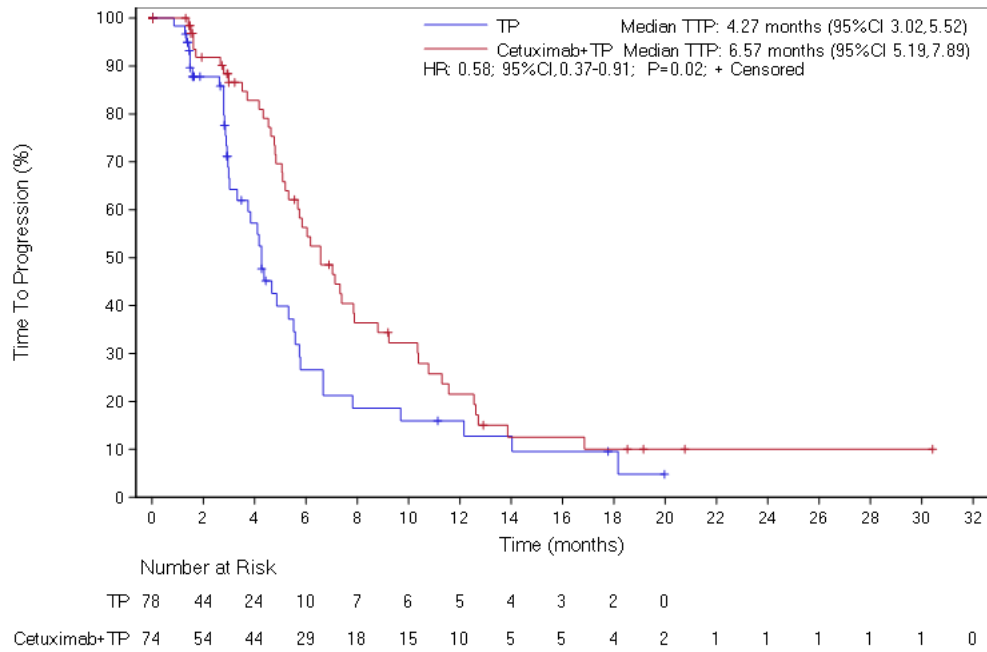


Figure. S2. Overall response rate in patients with EGFR amplification.

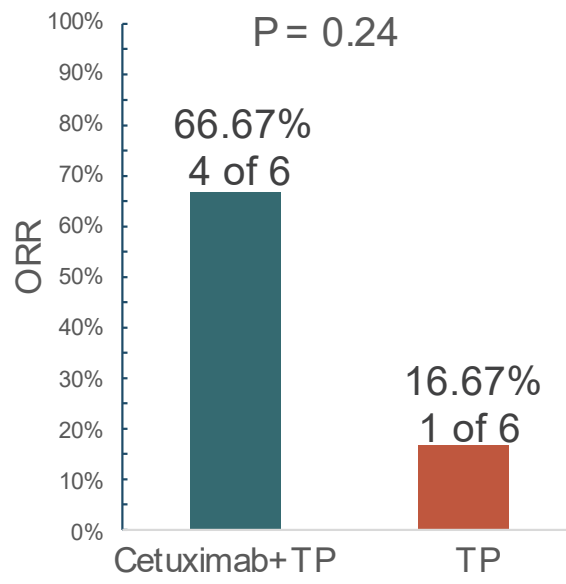


Figure S3. Kaplan-Meier curves of overall survival for patients with 11q13 amplification.

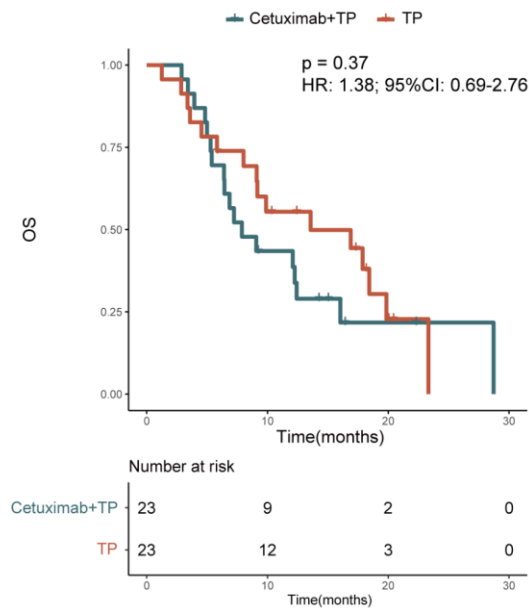
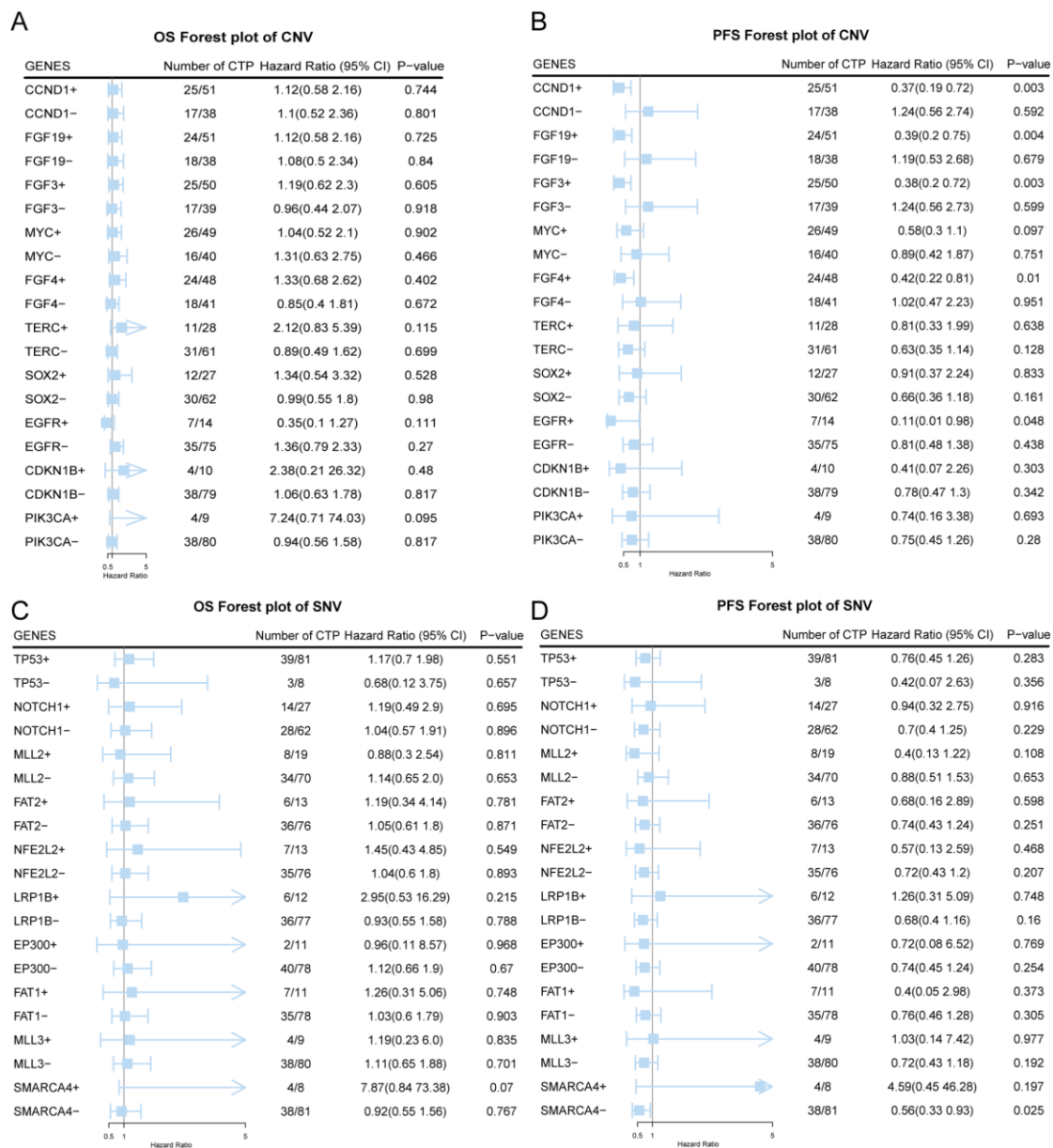


Figure S4. Forest plot showing the effect of treatment (Cetuximab+TP versus TP) on PFS and OS separated by subgroups according to copy-number alteration (A and B) and single nucleotide variants (C and D).



Clinical Trial Protocol

A phase II, multicenter, open-Label, randomized, controlled study to assess efficacy and safety of cetuximab in combination with paclitaxel plus cisplatin versus paclitaxel plus cisplatin alone for the first-line treatment of Chinese patients with metastatic esophageal squamous cell carcinoma (ESCC)

| | |
|--|---|
| Clinical trial protocol number | MS062202_0063 |
| Clinical trial protocol version | V1.0 |
| Date | 06Dec2016 |
| Investigational medicinal product | Cetuximab(Erbitux®) |
| Sponsor | Prof. Lin Shen Beijing Cancer Hospital, No.52, Fucheng Road, Haidian District, Beijing |
| Principal investigator | Prof. Lin Shen Beijing Cancer Hospital, No.52, Fucheng Road, Haidian District, Beijing |
| Study phase | Phase II |

-Confidential -

Content

| | | |
|-------|---|----|
| 1 | Protocol Synopsis..... | 9 |
| 2 | Background..... | 18 |
| 2.1 | Esophageal Cancer and Squamous Cell Carcinoma..... | 18 |
| 2.2 | Background on study treatment..... | 18 |
| 2.2.1 | Epidermal growth factor receptor in Cancer | 18 |
| 2.2.2 | Cetuximab | 19 |
| 2.3 | Trial rationale | 21 |
| 3 | Objectives of the trial..... | 22 |
| 3.1 | Primary objective..... | 22 |
| 3.2 | Secondary objectives | 22 |
| 3.3 | Exploratory objective | 22 |
| 4 | Study design | 23 |
| 4.1 | Overall Trial design and plan | 23 |
| 4.2 | definition of the end of trial | 25 |
| 4.3 | rationale for study design | 25 |
| 5 | Materials and methods | 26 |
| 5.1 | Trial population | 26 |
| 5.1.1 | Inclusion Criteria | 26 |
| 5.1.2 | Exclusion Criteria | 26 |
| 5.2 | Study treatment | 27 |
| 5.2.1 | Investigational medicinal product..... | 27 |
| 5.2.2 | Dosage and administration..... | 27 |
| 5.2.3 | Noninvestigational medicinal products to be used | 28 |
| 5.2.4 | Other Drugs | 29 |
| 5.2.5 | Packaging and labelling of the investigational medicinal product..... | 29 |
| 5.2.6 | Preparation, handling and storage of the investigational medicinal product..... | 29 |
| 5.2.7 | Investigational medicinal product accountability..... | 30 |
| 5.2.8 | Medical care of patients after end of trial | 31 |
| 5.3 | Concomitant medications and therapies..... | 31 |
| 5.3.1 | Permitted Medicines | 31 |
| 5.3.2 | Prohibited Medicines..... | 31 |
| 5.3.3 | Medication after the trial termination..... | 31 |
| 5.4 | Trial Procedures and Assessments | 32 |
| 5.4.1 | Schedule of Assessments | 32 |
| 5.4.2 | Screening Visit..... | 32 |
| 5.4.3 | Weekly Cetuximab Administration Visit | 32 |
| 5.4.4 | Start of Each Cycle Visit (Day 1 of Each 21-Day Cycle)..... | 32 |
| 5.4.5 | 6-Weekly Evaluation Visit..... | 33 |
| 5.4.6 | End of Efficacy Assessment Visit..... | 33 |
| 5.4.7 | Safety Follow-Up Visit | 34 |
| 5.4.8 | Survival Follow-Up..... | 34 |
| 5.5 | Demographic and Other Baseline Characteristics..... | 34 |

| | | |
|-------|---|----|
| 5.5.1 | Demographic Data..... | 34 |
| 5.5.2 | Diagnosis of Primary Tumor | 34 |
| 5.5.3 | Medical History | 34 |
| 5.5.4 | Viral Serology..... | 35 |
| 5.5.5 | Pregnancy Testing and Contraception | 35 |
| 5.5.6 | Echocardiogram | 35 |
| 5.5.7 | Creatinine Clearance | 35 |
| 5.5.8 | Other Baseline Assessments | 35 |
| 5.6 | Efficacy Assessment..... | 35 |
| 5.6.1 | Documentation of Tumor Assessments..... | 35 |
| 5.6.2 | Criteria for Tumor Response Evaluation..... | 36 |
| 5.7 | Criteria for patient withdrawal..... | 36 |
| 5.7.1 | Withdrawal from Trial Therapy | 36 |
| 5.7.2 | Withdrawal from the Trial | 37 |
| 5.8 | Premature Termination of the trial..... | 37 |
| 6 | Assessment of Safety..... | 38 |
| 6.1 | Safety plan..... | 38 |
| 6.1.1 | Toxicities Associated with Cetuximab and Dose Reductions..... | 38 |
| 6.1.2 | Dose Reductions of Chemotherapy..... | 40 |
| 6.1.3 | Adverse Events..... | 42 |
| 6.1.4 | Clinical Laboratory Assessments | 45 |
| 6.1.5 | Exploratory biomarker assessments..... | 46 |
| 6.1.6 | Vital Signs, Physical Examinations, and Other Assessments | 46 |
| 7 | Statistics..... | 47 |
| 7.1 | Sample Size..... | 47 |
| 7.2 | Randomization..... | 48 |
| 7.3 | Endpoints | 48 |
| 7.3.1 | Primary Endpoint..... | 48 |
| 7.3.2 | Secondary Endpoints | 48 |
| 7.3.3 | Safety Endpoints | 48 |
| 7.4 | Analysis Sets..... | 49 |
| 7.5 | Description of Statistical Analyses..... | 49 |
| 7.5.1 | General Considerations | 49 |
| 7.5.2 | Analysis of Primary Endpoint | 50 |
| 7.5.3 | Analysis of Secondary Endpoints..... | 51 |
| 7.5.4 | Analysis of Safety..... | 51 |
| 7.6 | Additional Planned Analyses..... | 52 |
| 8 | Trial Management | 52 |
| 8.1 | Case Report Form..... | 52 |
| 8.2 | Source Data and Patient Files..... | 52 |
| 8.3 | Investigator Site File and Archiving | 52 |
| 8.4 | Monitoring AND Quality Assurance of the study..... | 53 |
| 8.5 | Changes to the Clinical Trial Protocol | 53 |
| 8.6 | Clinical Trial Report and Publication Policy | 53 |

| | | |
|-------|---|----|
| 8.6.1 | Clinical Trial Report | 53 |
| 8.6.2 | Publication..... | 53 |
| 9 | Ethical Aspects | 54 |
| 9.1 | Local Regulations/Declaration of Helsinki | 54 |
| 9.2 | Patient Information and Informed Consent..... | 54 |
| 9.3 | Clinical Trial Insurance and Compensation to Patients | 54 |
| 10 | References Cited in the Text..... | 54 |
| 11 | Appendices..... | 56 |

List of Abbreviations

| | |
|-----------|--|
| ADCC | antibody-dependent cell-mediated cytotoxicity |
| AE | Adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AREG | amphiregulin |
| AST | aspartate aminotransferase |
| AUC | area under serum concentration time curve |
| CBC | complete blood count |
| CR | complete response |
| CRS | cytokine release syndrome |
| CRT | Chemoradiotherapy |
| DCR | Disease control rate |
| DVT | deep vein thrombosis |
| EAC | Esophageal adenocarcinoma |
| EC | Esophageal carcinoma |
| ECF | epirubicin, cisplatin and 5-FU |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EGFR | Epidermal growth factor receptor |
| EOEA | end of efficacy assessment |
| EoTV | End of Treatment Visit |
| EREG | epiregulin |
| ESCC | Esophageal squamous cell carcinoma |
| FOLFOX | 5-FU, folinic acid, oxaliplatin |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HCG | β -human chorionic gonadotropin |
| IB | investigator's brochure |
| IC | cisplatin/irinotecan |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medicinal Product |
| IV | intravenously |
| IVRS | interactive voice response system |
| LA | locally-advanced |
| moAb | monoclonal antibody |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| ORR | Objective response rate |
| OS | Overall survival |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PR | Partial response |
| R/M | Recurrent or metastatic |
| RCT | randomized controlled trial |
| RECIST | Response Evaluation Criteria in Solid Tumors |

| | |
|-------|--|
| RT | radiotherapy |
| SAE | Serious Adverse Event |
| SCCHN | squamous cell carcinoma of the head and neck |
| ULN | upper limit of normal |
| Vd | volume of the distribution |

Signature Page-Coordinating Investigator

Trial Title: A phase II, multicenter, open-Label, randomized, controlled study to assess efficacy and safety of cetuximab in combination with paclitaxel plus cisplatin versus paclitaxel plus cisplatin alone for the first-line treatment of Chinese patients with metastatic esophageal squamous cell carcinoma (ESCC)

Clinical trial protocol date/version: 06 December 2016 /version 1.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

Signature

Date

| | |
|-----------------------|--|
| Name, academic degree | Shen Lin, MD |
| Function/Title: | Medical Oncology Department |
| Institution: | Beijing Cancer Hospital |
| Address: | No.52, Fucheng Road, Haidian District, Beijing |
| Telephone number: | +8613911219511 |
| Email address: | linshenpku@163.com |

Signature Page - Investigator

Trial Title: A phase II, multicenter, open-Label, randomized, controlled study to assess efficacy and safety of cetuximab in combination with paclitaxel plus cisplatin versus paclitaxel plus cisplatin alone for the first-line treatment of Chinese patients with metastatic esophageal squamous cell carcinoma (ESCC)

Clinical trial protocol date/version: 06 December 2016 /version 1.0

Center Number:

Principal Investigator

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

Signature

Date of Signature

Name, academic degree

Function / Title

Institution

Address

Telephone number

E-mail address

1 PROTOCOL SYNOPSIS

| | |
|---|--|
| Study title | A phase II, multicenter, open-Label, randomized, controlled study to assess efficacy and safety of cetuximab in combination with paclitaxel plus cisplatin versus paclitaxel plus cisplatin alone for the first-line treatment of Chinese patients with metastatic esophageal squamous cell carcinoma (ESCC). |
| Sponsor | Prof. Lin Shen |
| Principal investigator | Prof. Lin Shen Beijing Cancer Hospital, No.52, Fucheng Road, Haidian District, Beijing |
| Study phase | Phase II |
| Study center(s)/country(ies) | 15-20/ CHINA |
| Planned study period (first enrollment-last patient out) | Q4 2016 Q2 2019 |
| Study objectives | <p>Primary objective: The primary objective of this trial is to evaluate whether PFS time, as assessed by the investigator, in patients receiving cetuximab in combination with paclitaxel plus cisplatin is longer than that in patients receiving paclitaxel plus cisplatin alone in the first-line treatment of metastatic ESCC.</p> <p>Secondary objectives: To evaluate the efficacy of cetuximab in combination with paclitaxel plus cisplatin in 1st line ESCC in terms of OS, ORR, DCR and safety. To assess the tolerability of cetuximab in combination with paclitaxel plus cisplatin in 1st line ESCC.</p> <p>Exploratory objectives: To investigate potential biomarkers for the prediction of efficacy and selection of R/M ESCC patients likely to benefit from cetuximab. EGFR expression analysis by IHC will be conducted on the primary tissue, analysis of EGFR ligands, amphiregulin (AREG)/ epiregulin (EREG) mRNA expression will be conducted on the primary tissue sample and/or blood sample.</p> |

| | |
|--|--|
| <p>Study design and plan</p> | <p>This is an open-label, randomized, and controlled trial. At the end of a 28-day screening period, all eligible patients will be randomly assigned into treatment Arm A or B in a 1:1 ratio. Patients in Arm A will receive a maximum of 6 cycles of chemotherapy (cisplatin plus paclitaxel) and cetuximab weekly in the absence of both disease progression (PD) and unacceptable toxicity, as assessed by the Investigator. After 6 cycles of treatment, patients who derive clinical benefit will continue treatment with cetuximab as monotherapy until either PD or unacceptable toxicity. Patients in Arm B will receive the same chemotherapy regimen as Arm A alone for a maximum of 6 cycles in the absence of both PD and unacceptable toxicity.</p> <p>Tumor assessment will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations will be performed every 6 weeks (\pm 3 days) starting from the first dose of trial treatment until occurrence of PD regardless of any cycle delay.. If treatment is discontinued for reasons other than PD, patients will continue to have tumor assessments every 6 weeks until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss to follow up, whichever comes first. If symptoms are suggestive of PD, patients will be evaluated by imaging studies within 1 week for documentation and confirmation of the tumor responses.</p> <p>A safety evaluation will be performed 30 days (\pm 2 days) after the last dose of trial treatment or immediately before starting any new antitumor treatment (End of Treatment Visit [EoTV]). All patients in Arm A and B will be followed up continuously for safety and efficacy every 6 weeks (\pm 3 days) starting from the first dose of trial treatment until the end of efficacy assessment (EOEA). During the treatment period, additional safety evaluations will be on a weekly basis including physical examination, vital signs, documentation of adverse events and concomitant medications, and also at the start of each cycle for Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram, hematology, biochemistry and urinalysis. Survival data will be collected every 3 months after the EOEA until either death, loss to follow up, or the termination of the trial, whichever comes first.</p> |
| <p>Planned number of patients</p> | <p>Total number of patients: 150</p> <p>Number of patients per center: 10</p> <p>Number of patients per treatment arm: 75</p> |
| <p>Diagnosis</p> | <p>Patients with metastatic ESCC, not suitable for local-regional treatment and having not received prior chemotherapy in the metastatic setting.</p> |

| | |
|---|---|
| Criteria for inclusion | <ul style="list-style-type: none"> • Signed written informed consent. • ≥18 years of age. • Histologically proven squamous cell carcinoma of the esophagus. • Metastatic ESCC, not suitable for local-regional treatment. • Presence of at least 1 measurable lesion according to RECIST version 1.1. • ECOG performance status of 0 or 1. • Adequate bone marrow, hepatic, renal and metabolic function. |
| Criteria for exclusion | <ul style="list-style-type: none"> • Prior chemotherapy in the metastasis setting. • Prior chemotherapy within 6 months before entering this study. • Previous exposure to EGFR-targeted therapy. • Known central nervous system metastasis and/or leptomeningeal disease. • Cardiac disease within the previous 12 months • Patients with any concurrent medical condition or disease that will potentially compromise the conduct of the trial at the discretion of investigator. |
| Investigational therapy: product / dosing schedule / mode of administration | <p>Product A: Cisplatin (If intolerable, can be replaced by Carboplatin)</p> <p>Dosing schedule: Cisplatin 75mg/m², every 3 weeks or Carboplatin AUC5, every 3 weeks</p> <p>Mode of administration: IV</p> <p>Product B: Paclitaxel</p> <p>Dosing schedule: 175mg/m², every 3 weeks</p> <p>Mode of administration: IV</p> <p>Product C: Cetuximab</p> <p>Dosing schedule: 400mg/m² for initial dose then 250mg/m² weekly</p> <p>Mode of administration: IV</p> |
| Reference (comparator) therapy: product / dosing schedule / mode of administration | <p>Product A: Cisplatin (If intolerable, can be replaced by Carboplatin)</p> <p>Dosing schedule: Cisplatin 75mg/m², every 3 weeks or Carboplatin AUC5, every 3 weeks</p> <p>Mode of administration: IV</p> <p>Product B: Paclitaxel</p> <p>Dosing schedule: 175mg/m², every 3 weeks</p> <p>Mode of administration: IV</p> |
| Planned treatment duration per patient | Cetuximab treatment until progression or unacceptable toxicity Cisplatin/Carboplatin plus Paclitaxel max 6 cycles |
| Primary target variable | PFS by investigator assessment (RECIST V. 1.1) |
| Secondary efficacy target variables | OS, ORR, DCR, safety |

| | |
|--|---|
| Tolerability/safety variable(s) | <p>Exposure to cetuximab, cisplatin or carboplatin, and paclitaxel in terms of duration of therapy, cumulative dose, dose intensity and relative dose intensity, number of dose reductions, dose delays, and premature drug discontinuation will be calculated.</p> <p>Safety profile. All adverse events will be recorded and graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC AE version 4.03.).</p> <p>Safety laboratory tests graded by CTCAE (version 4.03) where applicable will be recorded.</p> |
| Exploratory analysis | <p>EGFR expression analysis by IHC will be conducted on the primary tissue; the analysis of AREG/EREG mRNA expression will be conducted on the primary tissue sample and/or blood samples.</p> |
| Statistical methods | <p>A two-sided stratified log-rank test will be used to test the equality of PFS between the experimental cetuximab treatment group and the control group. This log-rank test will be regarded as primary analysis, and decision making will also be based on this result. Furthermore, a Cox proportional hazards regression model adjusted for the stratification factors, will be used to obtain an estimation of hazard ratio and its 95% confidence interval.</p> <p>Stratification factors are previous treatment (previous surgery or radiotherapy vs. no previous treatment; ECOG performance status 0 vs 1 and the number of metastatic sites (1 vs ≥ 2 organs).</p> <p>For the analysis of time to event endpoint, such as OS, two-sided stratified log-rank test and Cox proportional hazards regression model adjusted for stratification factors will be used.</p> <p>For binary endpoints, such as ORR, DCR, both descriptive analysis (frequency, proportion) and hypothesis test by using Fisher's exact test will be used.</p> |
| Sample size calculation and explanation | <p>The sample size requires 150 patients to collect 105 PFS events and ensure 80% power with a two-sided significance level of 20% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio (HR) of 0.66. Furthermore, a median PFS time of 6 months in the control group and 9.09 months in the cetuximab treatment group is expected.</p> |
| Date | |
| Version | 1.0 |

| | Screen | | Treatment Period Until Disease Progression or Death ± 3 days | | | | | | | | | | Survival follow-up ⁵ | | | |
|--|------------|-----------|---|---|----|-----------|---|----|-----------------------|---|----|--|------------------------------------|-------------------|-----------|--|
| | D-28 to -1 | D-7 to -1 | Cycle 1 | | | Cycle 2-6 | | | 6 Cycles ¹ | | | Every 2 cycle (every 6 weeks) ² | EoTV ³ | EOEA ₄ | 3 monthly | |
| | | | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | (until PD) | | | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Randomization ⁶ | | | X | | | | | | | | | | | | | |
| Demographics, Height | X | | | | | | | | | | | | | | | |
| Physical exam, Weight | | X | X | X | X | X | X | X | X | X | X | X | | X | | |
| Vital signs ⁷ | | X | X | X | X | X | X | X | X | X | X | X | | X | | |
| Medical history and HBV HCV HIV test ⁸ | X | | | | | | | | | | | | | | | |
| ECOG performance status | | X | X | | | X | | | X | | | X | X | X | | |
| ECG ⁹ | X | | X ¹⁸ | | | X | | | X | | | X | X | X | | |

| | | | | | | | | | | | | | | | |
|---|--------------|--------------------------------------|-----------------|--|--|----|--|--|---|--|--|---|---|---|---|
| Echocardiogram | X | | | | | | | | | | | | | | |
| Brain scan | If indicated | | | | | | | | | | | | | | |
| Bone scan | If indicated | | | | | | | | | | | | | | |
| Hematology and Biochemistry ¹⁰ | | X | X ¹⁸ | | | X | | | X | | | X | X | X | |
| Urinalysis ¹¹ | | X | X ¹⁸ | | | X | | | X | | | X | X | X | |
| Creatinine clearance AND Serum pregnancy test ¹² (if Applicable) | X | | | | | | | | | | | | | | |
| Inclusion Exclusion criteria | X | | | | | | | | | | | | | | |
| Tumor assessment ¹³ | X | Will be done 6 weekly(\pm 3 days) | | | | | | | | | | | | X | |
| Survival Information | | | | | | | | | | | | | X | | X |
| Blood samples for biomarker analysis ¹⁴ | | X | | | | X* | | | | | | | X | X | |
| Tissue samples for biomarker analysis ¹⁵ | X | | | | | | | | | | | | | | |
| Cisplatin ¹⁶ and Paclitaxel | | | X | | | X | | | | | | | | | |

| | | | | | | |
|-----------------------------------|--|---|--|--|--|--|
| Concomitant Disease and Treatment | | x | | | | |
| AE/SAE | | | | | | |
| Cetuximab (qw) ¹⁷ | | | | | | |

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CT: computed tomography, ECG: electrocardiogram, ECOG: Eastern

Cooperative Oncology Group, EOEa: end of efficacy assessment, GGT: gamma-glutamyl transferase, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human

immunodeficiency virus, MRI: magnetic resonance imaging, PD: disease progression, RECIST: Response Evaluation Criteria in Solid Tumors.

1. Arm A only: until PD or unacceptable toxicity.
2. All patients in Arm A and B will be followed up continuously for safety and efficacy every 6 weeks starting from the first dose of trial treatment until the EOEa visit.
3. Arm A: EoTV is 30±2 days after last treatment administration of chemotherapy or cetuximab, whichever is later.
Arm B: EoTV is 30±2 days after last treatment administration of chemotherapy.
4. EOEa visit will be performed on the day of the last efficacy assessment, whether or not at the end of a cycle. The day of the last efficacy assessment is defined as the day on which it is determined that the patient will no longer be followed up for efficacy. PD or immediately before commencing the start of any new anticancer treatment.
5. Survival follow-up (telephone contact) will be performed every 3 months after the EOEa visit until death or the termination of the trial, whichever comes first.
6. If the Investigator is willing to administer prophylactic tetracycline to reduce the incidence of Grade 3 skin reactions related to cetuximab, randomization and the initiation of prophylactic tetracycline should be performed on Day -1 (1 day before the initiation of cetuximab treatment).

7. Heart rate and blood pressure will be measured in a supine position after 5 minutes at rest. For those in Arm A, vital signs must be continuously monitored before, during, and up to 1 hour after each cetuximab infusion.
8. Viral serology will be performed only if clinically indicated.
9. All 12-lead ECGs will be performed after the patient has rested for 5 minutes.
10. The results of all safety laboratory parameters must be available within 3 days before start of next cycle. Required hematologic parameters include hemoglobin, red blood cell count, white blood cell count and differential count, and platelet count. Required biochemistry parameters include creatinine, AST, ALT, GGT, total bilirubin (including direct bilirubin if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, glucose, blood urea, and uric acid. Blood samples will be collected after fasting for at least 8 hours.
11. Urinalysis dipstick will be followed by microscopic examination if results are abnormal.
12. Only for female patients of childbearing potential, including those who have had a tubal ligation. Performed within 7 days before the first dose of the trial treatment. Regular urine pregnancy tests are also recommended during the trial for female patients of childbearing potential.
13. Tumor assessment will be performed according to RECIST version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. The CT or MRI with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations will be assessed every 6 weeks starting from the first dose of trial treatment until occurrence of PD regardless of any cycle delay. If treatment is discontinued for reasons other than PD, patients will continue to have tumor assessments until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss to follow up, whichever comes first. If symptoms are suggestive of PD, patients will be evaluated by imaging studies within 1 week for documentation and confirmation of the tumor responses. Imaging must include CT or MRI of the neck (base skull to clavicles), chest, and abdomen. A CT or MRI of the brain and a bone scan or positron emission tomography should be considered for patients who have possible central nervous system metastasis and possible bone metastasis, respectively. Tumor assessment should include a complete assessment of all target and non-target lesions.

14. Blood samples for biomarkers analysis include 10 ml EDTA-anticoagulant blood and 3 ml clotted blood, will be collected at baseline, after 2 cycles and end of treatment. All the samples for each center should be sent to GI laboratory in Peking University Cancer within 24 hours after collection.
15. Tissue samples for biomarkers analysis include 10 unstained slides. All the samples for each center should be sent to GI laboratory in Peking University Cancer before randomization.
16. Arm A and B for a maximum of 6 cycles in the absence of both PD or unacceptable toxicity. If cisplatin results in a non-hematologic toxicity, cisplatin may be replaced by carboplatin in the subsequent cycles.
17. Arm A only: until PD or unacceptable toxicity.
18. Only if screening/last assessments were performed more than 7 days before Cycle 1, Day 1.

2 BACKGROUND

2.1 ESOPHAGEAL CANCER AND SQUAMOUS CELL CARCINOMA

Esophageal cancer (EC) is a highly aggressive tumor and is the sixth leading cause of cancer-related death in USA and UK, and the fourth leading cause of cancer-related death in China (1-2). The estimated incidence of EC in China is 477.0 per 100,000 with a mortality of 375 per 100,000 in 2015. Issued data illustrated that in some areas of China, the incidence of esophageal cancer is 10 to 100-fold more than that of USA (3). Esophageal cancers are classified into two histological types with distinct clinical and pathologic characteristics: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the main histological type and accounts for 80% of cases of EC in China (4). Alcohol and tobacco are major risk factors for ESCC (5). Only 15-25% of patients with ESCC survive for 5 years after diagnosis (6). More than 50% of patients with EC already have incurable metastatic disease at the time of diagnosis and the 5-year survival rate for advanced stage EC is less than 15% (5,7). For locally recurrent or metastatic EC, depending on patients' performance status, systemic therapy or best supportive care are applied (8). For recurrent/metastatic esophageal carcinoma, several phase II trials of palliative chemotherapy regimens have been investigated and shown to have at least some activity, with responses ranging from 20% to 48% and 5-year survival rates of approximately 15% with significant toxicity rates (9). Current NCCN guidelines recommend the combination of fluorouracil and cisplatin, either alone or in combination with a third drug such as epirubicin or a taxane, as the most effective first-line treatment option (8). There is a high unmet need for drug development for esophageal cancer patients in terms of the high incidence, mortality worldwide and lack of good therapeutic options.

2.2 BACKGROUND ON STUDY TREATMENT

2.2.1 Epidermal growth factor receptor in Cancer

The human epidermal growth factor receptor (EGFR) as a member of HER family, is a 170 kDa protein with an extracellular ligand-binding domain, a transmembrane domain, and a cytosolic tyrosine kinase domain (10). Upon binding of its ligands such as transforming growth factor- α or epidermal growth factor, it will be activated by internalization of homodimerized or heterodimerized HER family member receptors, leading to autophosphorylation of the intracellular tyrosine kinase domain and subsequent activation of downstream proto-oncogenic signalling pathways (11). The EGFR signalling pathway plays a vital role in tumorigenesis, including cell cycle progression, angiogenesis, metastasis as well as evasion of apoptosis (12). Due to its aberrant activation as a result of gene amplification, overexpression and mutation, it is identified as an important contributor to tumorigenesis and poor prognosis of various cancer types. Aberrant high expression of EGFR or gene copy number is frequently observed in a series of cancers including colorectal, pancreatic, renal, head and neck and non-small cell lung cancers (13-15). In ESCC and EAC, comparison of the 5-10% EGFR mutations, the 20-30% EGFR amplification and the 30-80% overexpression rate suggests that amplification and overexpression rather than mutations may be a driving cause of EC (16-17). In ESCC, the range of EGFR overexpression is found to be 50-70% and has been correlated with prognosis (18).

2.2.2 Cetuximab

Cetuximab, an IgG1 chimerized, monoclonal antibody (moAb), binds specifically to EGFR on both normal and tumor cells and competitively inhibits the binding of EGF and other ligands of EGFR (19). Binding of cetuximab to EGFR blocks phosphorylation and activation of receptor-associated kinases as well as stimulating EGFR internalization and degradation, resulting in inhibition of cell growth and proliferation, induction of apoptosis, decreased ability of cell metastasis, depression of angiogenesis and induction of antibody-dependent cell-mediated cytotoxicity (ADCC) (20-23). Cetuximab is also found to be able to sensitize cancer cells to chemotherapy (24).

Cetuximab has been approved and authorized in 90 countries (including the United States, European Union, and Canada). In metastatic colorectal cancer, the indications for cetuximab are in combination with FOLFIRI for first-line treatment, and in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, and/or as monotherapy in patients who have failed oxaliplatin and irinotecan-based chemotherapy or who are intolerant to irinotecan. In squamous cell carcinoma of the head and neck (SCCHN), cetuximab is indicated in combination with radiotherapy for locally advanced SCCHN, and in combination with platinum-based chemotherapy and 5-fluorouracil (5-FU) in recurrent locoregional disease or metastatic SCCHN, and/or as monotherapy for patients with recurrent or metastatic SCCHN after platinum-based therapy.

2.2.2.1 Cetuximab in the Treatment of esophageal squamous cell carcinoma

Several phase II studies have been performed with cetuximab in combination with chemotherapy in advanced esophageal cancer. In a randomized phase II trial, cetuximab was added to three chemotherapy regimens including ECF (epirubicin, cisplatin and 5-FU), IC (cisplatin/irinotecan), and FOLFOX (5-FU, folinic acid, oxaliplatin) (25). The results showed response rates of 58%, 38% and 51% in the 3 arms, respectively. Of note, the study included only 9% patients with ESCC. Another randomized phase II study compared cisplatin 100 mg/m², day 1 and 5-fluorouracil (5-FU) 1000 mg/m²/d continuous infusion, days 1-5 every 4 weeks with or without cetuximab 250 mg/m² weekly (after a loading dose of 400 mg/m²) in the first line metastatic ESCC setting (26). A trend towards longer progression-free survival (PFS) (5.9 m vs 3.6 m) and overall survival (OS) (9.5 m vs 5.5 m) was noted in the cetuximab arm. Furthermore, cetuximab did not exacerbate grade 3 or 4 toxicities, except for rash and diarrhea.

Overall, studies showed cetuximab can be safely administered with chemotherapy in locally-advanced or recurrent/metastatic (R/M) ESCC patients with certain clinical activity.

2.2.2.2 Related Adverse Events

In the Investigator's Brochure, safety data for cetuximab are summarized for all phase I trials and for phase II and III trials by indication. Cetuximab has been investigated in four randomized controlled trials (RCTs) with more than 3000 metastatic colorectal cancer patients either alone or in combination with various types of chemotherapy including irinotecan, oxaliplatin plus 5-FU/folinic acid. Additionally, in SCCHN cetuximab was investigated with radiotherapy or in combination with platinum-based chemotherapy. Safety data of all these 6 trials are available and the known side effects of cetuximab are listed below in Table 2.1.

Table 2.1 Adverse events found associated with cetuximab*

| | |
|--------------------------|---|
| Nervous system disorders | Headache (common) Aseptic meningitis (frequency not known) |
|--------------------------|---|

| | |
|--|---|
| Eye disorders | Conjunctivitis (common) Blepharitis, keratitis (uncommon) |
| Respiratory, thoracic, and mediastinal disorders | Pulmonary embolism (uncommon) Interstitial lung disease (rare) |
| Gastrointestinal disorders | Diarrhea, nausea, vomiting (common) |
| Skin and subcutaneous tissue disorders | Skin reactions (very common) Stevens-Johnson syndrome/toxic epidermal necrolysis (very rare) Superinfections of skin lesions (frequency not known) |
| Metabolism and nutrition disorders | Hypomagnesaemia (very common) Dehydration, hypocalcaemia, anorexia which may lead to weight decrease (common) |
| Vascular disorders | Deep vein thrombosis (uncommon) |
| General disorders and administration site conditions | Mild or moderate infusion-related reactions comprising symptoms such as fever, chills, dizziness, or dyspnoea (very common) Mucositis, in some cases severe. Mucositis may lead to epistaxis (very common) Severe infusion-related reactions (common), in rare cases with fatal outcome Fatigue (common) |
| Hepatobiliary disorders | Increase in liver enzyme levels (aspartate amino transferase, alanine aminotransferase, and alkaline phosphatase) (very common) |

*: The expected frequencies in brackets are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$) frequency not known (cannot be estimated from the available data).

Skin reactions: Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first 3 weeks of treatment. Following the recommended adjustments in dose regimen, these skin reactions generally resolve without sequelae over time after the end of treatment. According to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, Grade 2 skin reactions are characterized by rash affecting up to 50% of body surface area (BSA), while Grade 3 reactions affect equal or more than 50% of BSA. Skin lesions induced by cetuximab may predispose patients to superinfections (e.g. with *Staphylococcus aureus*), which may lead to subsequent complications, e.g. cellulitis, erysipelas or potentially fatal outcomes such as staphylococcal scalded skin syndrome or sepsis.

Infusion-related reactions: Mild or moderate infusion-related reactions are very common and present with symptoms such as fever, chills, dizziness, or dyspnea mainly during the first cetuximab infusion. Severe infusion-related reactions may occur commonly, but the outcome is rarely fatal. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). They usually develop during or within 1 hour of the initial cetuximab infusion, but may occur

after several hours or with subsequent infusions. Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature and may include symptoms such as bronchospasm, urticaria, decrease or increase in blood pressure, loss to consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

Combination with platinum-based chemotherapy: If cetuximab is used in combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia, and sepsis compare to platinum-based chemotherapy alone.

2.3 TRIAL RATIONALE

In China, the 5-year survival rate of ESCC remains dismal despite improvements in treatments modalities. EGFR overexpression was found in 30-80% of ESCC and is related with poor prognosis, which provided the rationale for targeting EGFR in ESCC (17). The tumor biology of ESCC is comparable to squamous cell carcinoma in head and neck cancer, in which cetuximab together with platinum based chemotherapy have demonstrated a survival benefit in the recurrent/metastatic setting. The phase III pivotal randomized controlled trial EXTREME consisting of 442 recurrent and/or metastatic SCCHN patients evaluated the addition of cetuximab to platinum-based chemotherapy in first-line treatment (29). The results showed a significantly improved OS when cetuximab was added to the chemotherapy alone (median 10.1 versus 7.4 months; hazard ratio: 0.80; $p=0.04$). Accordingly, PFS was also significantly improved in the cetuximab arm (5.6 months) compared with chemotherapy alone (3.3 months; HR=0.54, $p<0.001$). Furthermore, a significant increase in response rate in the cetuximab-containing arm compared with chemotherapy alone was also observed. With all these significantly improved survival benefits, cetuximab addition only slightly changed the AE profile of platinum-based chemotherapy and did not have a negative impact on quality of life. Owing to these observations, it is desirable to consider the clinical application of cetuximab in ESCC.

Several phase II studies have been performed with cetuximab in combination with chemotherapy in advanced esophageal cancer, with a response rate ranging from 38% to 58% (25). A randomized phase II study evaluating chemotherapy with or without cetuximab in the first line metastatic ESCC setting have revealed a trend towards longer progression-free survival (PFS) (5.9 m vs 3.6 m) and overall survival (OS) (9.5m vs 5.5m) when cetuximab was added (26). Furthermore, cetuximab did not aggravate grade 3 or 4 toxicities, except for rash and diarrhea.

Cisplatin is one of the most active agents with a single-agent response rate consistently at 20% or greater (8). The combination of cisplatin with fluorouracil is commonly used for EC patients, resulting in response rates of 20% to 50%. However, severe mucosal toxicities are often observed when 5-FU is included. Paclitaxel has important single-agent activity in ESCC demonstrated in several phase II studies (30-31). In these trials, the CR rates (35%-47%) and survival are comparable to those in cisplatin/5-FU/radiation regimens. In addition, less esophagitis occurred with the regimen of cisplatin and paclitaxel (< 5% grade 4 esophagitis).

Therefore, this trial aims to assess efficacy and safety of cetuximab in combination with paclitaxel plus cisplatin versus paclitaxel plus cisplatin alone for the first-line treatment of Chinese patients with metastatic esophageal squamous cell carcinoma.

EGFR expression may be predictive for cetuximab treatment in ESCC patients. In a study which investigated cetuximab added to CRT in 29 Chinese ESCC patients, EGFR

expression was found in 55.2% of patients using immunohistochemical staining (26). The patients with EGFR-expressing tumor had a significantly higher CR rate of 75.0% compared with 61.5% in those with negative EGFR expression ($p=0.024$). In addition, the PFS for patients with EGFR-expressing tumors was longer compared with the PFS of patients with negative EGFR (1-year PFS rate, 87.1% vs 83.9%), although the difference was not significant. These results suggest that further analysis of EGFR expression using immunohistochemistry might be an effective way to predict the efficacy of ESCC treatment with cetuximab. Moreover, since high EGFR expression has shown to be an adverse prognostic factor for EC patients, it is reasonable to speculate patients with positive EGFR expression might achieve a better clinical outcome when treated with cetuximab. Besides EGFR expression, the mRNA expression of epiregulin (EREG) ligands and amphiregulin (AREG), which are both EGFR ligands, has also shown a correlation with the efficacy of cetuximab (32). Therefore in this study, EGFR expression analysis by immunohistochemistry and analysis of AREG/EREG mRNA expression will be conducted to identify potential predictive biomarkers for selection of R/M ESCC patients likely to benefit from cetuximab.

3 OBJECTIVES OF THE TRIAL

3.1 PRIMARY OBJECTIVE

The primary objective of this trial is to evaluate whether PFS time, as assessed by the investigator, in patients receiving cetuximab in combination with paclitaxel plus cisplatin is longer than that in patients receiving paclitaxel plus cisplatin alone in the first-line treatment of metastatic ESCC.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this trial are to compare the two treatment arms regarding the following terms:

- OS time
- Objective response rate (ORR)
- Disease control rate (DCR)
- Safety

3.3 EXPLORATORY OBJECTIVE

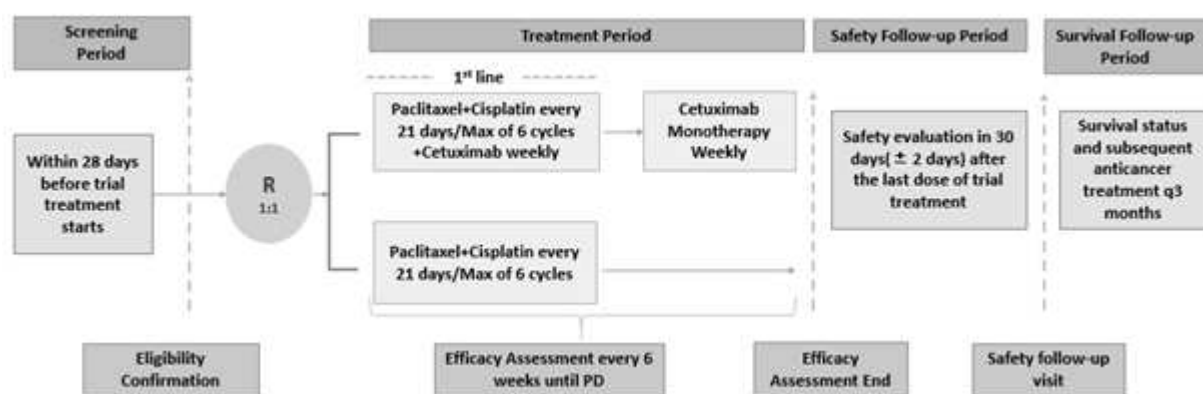
An exploratory objective is to investigate potential biomarkers for the prediction of efficacy and selection of R/M ESCC patients likely to benefit from cetuximab. EGFR expression analysis by IHC will be conducted on the primary tissue sample and analysis of AREG/EREG mRNA expression will be conducted on the primary tissue sample and/or dynamic blood samples.

4 STUDY DESIGN

4.1 OVERALL TRIAL DESIGN AND PLAN

This multicentre, open-label, randomized controlled phase II trial will randomize approximately 150 patients with metastatic ESCC and involve about 20 trial centres in China. The overall trial design is illustrated in Figure 4.1

Figure 4.1 Schematic Trial Design



At the end of a 28-day screening period, all eligible patients will be randomized to one of the treatment arms in a 1:1 ratio:

- Arm A (cetuximab plus chemotherapy): Combination of paclitaxel plus cisplatin for a maximum of 6 cycles and weekly cetuximab in the absence of both disease progression (PD) as assessed by the Investigator and unacceptable toxicity. Patients who derive clinical benefit (at least stable disease) will continue treatment with cetuximab as monotherapy until either PD or unacceptable toxicity.
- Arm B (chemotherapy alone): paclitaxel and cisplatin only for a maximum of 6 cycles in the absence of both PD as assessed by the Investigator and unacceptable toxicity.

Assignment to Treatment Arms: Randomization will be performed using web-based randomization or an interactive voice response system (IVRS). Patient screening information will be collected and eligible patients who have signed the informed consent form (ICF) will be randomized in a 1:1 ratio to either Arm A or Arm B. Randomization will be stratified according to: previous treatment (previous surgery or radiotherapy vs. no previous treatment), ECOG performance status (0 versus 1) and the number of metastatic sites (1 vs ≥ 2 organs).

Definition of Treatment Cycle: The cycle in each arm is 21 days and is determined by the chemotherapy as follows:

Arm A: 1 treatment cycle consists of dosing with chemotherapy (paclitaxel with cisplatin) plus cetuximab on Day 1, and doses of cetuximab on Day 8 and 15, with follow-up until Day 21 of the cycle.

Arm B: 1 treatment cycle consists of dosing with chemotherapy (paclitaxel with cisplatin) on Day 1 for each cycle.

Duration of Treatment for Patients in Arm A: Patients with absence of both PD as assessed by the Investigator, and unacceptable toxicity will receive a maximum of 6 cycles of chemotherapy (paclitaxel with cisplatin) and weekly cetuximab. Patients with an unacceptable toxicity due to one of the trial drugs will receive other trial drug(s) without unacceptable toxicity until either PD (cetuximab) or completion of a maximum of 6 cycles of chemotherapy. If treatment with cetuximab is delayed because of a related toxicity, the 21-day rhythm of chemotherapy will be retained. A maximum of 2 consecutive cetuximab infusions can be withheld (no more than 21 days without cetuximab infusions) due to unacceptable toxicity, otherwise the patient must discontinue cetuximab treatment. If treatment is delayed because of toxic effects of the chemotherapy, the 7-day rhythm of cetuximab infusions will be retained. Chemotherapy can be delayed for a maximum of 21 days; after this, the patient must discontinue the chemotherapy treatment. The patient may still continue cetuximab monotherapy treatment (if deriving clinical benefit).

Duration of Treatment for Patients in Arm B: Patients without both PD as assessed by the Investigator, and unacceptable toxicity will receive up to a maximum of 6 cycles of chemotherapy (paclitaxel with cisplatin). Patients with unacceptable toxicity due to one of the trial drugs will receive other trial drug(s) without unacceptable toxicity until either PD or completion of 6 cycles of chemotherapy. Chemotherapy can be delayed for a maximum of 21 days; after this, the patient must discontinue the chemotherapy treatment.

Tumor Assessment: Tumor assessment will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations, which must use the same technique as baseline, will be assessed every 6 weeks (\pm 3 days) starting from the first dose of trial treatment until occurrence of PD regardless of any cycle delay. If treatment is discontinued for reasons other than PD, patients will continue to have tumor assessments until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss to follow up, whichever comes first. If symptoms are suggestive of PD, patients will be evaluated by imaging studies within one week for documentation and confirmation of the tumor status.

End of Treatment visit: A safety evaluation will be performed 30 days (\pm 2 days) after the last dose of trial treatment or immediately before starting any new antitumor treatment.

Safety Follow-up Period: All patients in Arm A and B will be followed up continuously for safety and efficacy every 6 weeks (\pm 3 days) starting from the first dose of trial treatment until the end of efficacy assessment (EOEA). During the treatment period, additional safety evaluations will be on a weekly basis for physical examination, vital signs, documentation of adverse events and concomitant medications, and also at the start of each cycle for Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram, hematology, biochemistry and urinalysis. Survival data will be collected every 3 months after the EOEA until either death, loss to follow up, or the termination of the trial, whichever comes first.

Primary and Secondary Endpoints: The primary endpoint of this trial is PFS time as assessed by the Investigator. Secondary endpoints include OS, ORR, DCR and safety.

Duration of the Whole Trial: The anticipated duration of the recruitment period is from the third quarter, 2016 to the third quarter, 2017. The main statistical analysis is event driven, i.e. at least 105 PFS events have to be observed patient. The trial will be terminated on the date of last patient last visit, which is anticipated in June, 2018. Final results based on all data recorded until the end of the trial will

be presented in a clinical trial report. The actual duration of the recruitment period will depend on the trial set-up process.

4.2 DEFINITION OF THE END OF TRIAL

The end of the trial will occur when the following conditions are met:

At least 12 months of follow up after the randomization of the last patient AND

At least 105 PD events have been reported in this trial.

4.3 RATIONALE FOR STUDY DESIGN

In SCCHN, which has a tumor biology comparable to ESCC, cetuximab together with platinum based chemotherapy have demonstrated a survival benefit in the recurrent/metastatic setting. The phase III pivotal randomized controlled trial EXTREME consisting of 442 recurrent and/or metastatic SCCHN patients and evaluated the addition of cetuximab to platinum-based chemotherapy in first-line treatment (29). The results showed significantly improved OS when cetuximab was added to the chemotherapy compared to chemotherapy alone (median 10.1 versus 7.4 months; hazard ratio: 0.80; $p=0.04$). Similarly, PFS was also significantly improved in the cetuximab arm (5.6 months) compared with chemotherapy alone (3.3 months; HR=0.54, $p<0.001$). Furthermore, a significant increase in response rate in the cetuximab-containing arm compared with chemotherapy alone was also observed with slightly increased but tolerable toxicity. The addition of cetuximab had no impact on quality of life.

Several phase II studies have been performed with cetuximab in combination with chemotherapy in advanced esophageal cancer, with the response rates ranging from 38% to 58% (25). A randomized phase II study, in 62 patients, evaluating chemotherapy with or without cetuximab in the first line metastatic ESCC setting, revealed a trend towards longer progression-free survival (PFS) (5.9m vs 3.6m) and overall survival (OS) (9.5m vs 5.5m) when cetuximab was added (26). Furthermore, cetuximab did not exacerbate grade 3 or 4 toxicities, except for rash and diarrhea.

The dosage of paclitaxel and cisplatin is in accordance with the recommendations from NCCN guideline (2015, v3) (8). If cisplatin results in nonhematologic toxicity, it may be replaced by carboplatin in the subsequent cycles and the dose of carboplatin is the same as recommended by NCCN guideline (2015, v3).

The primary endpoint in this trial is PFS time, as assessed by the Investigator. While OS time is still considered the 'gold standard' of clinical efficacy, PFS can reflect tumor growth and be assessed before the determination of a survival benefit. Especially in China, OS time data may be confounded by a cross-over and/or second and third-line treatments, while the treatment effect on PFS time is not confounded by these factors. The PFS as primary endpoint is well recognized and has been accepted as a surrogate endpoint by the Chinese Health Authority. Therefore, PFS is considered as an acceptable primary endpoint for this trial.

5 MATERIALS AND METHODS

5.1 TRIAL POPULATION

5.1.1 Inclusion Criteria

Patients should fulfil all of the following inclusion criteria:

- Signed written informed consent.
- ≥18 years of age.
- Histologically proven squamous cell carcinoma of the esophagus.
- Metastatic ESCC, not suitable for local-regional treatment.
- At least 4 weeks after prior surgery, except for diagnostic biopsy.
- At least 2 weeks after prior radiotherapy for bone lesions.
- At least 4 weeks after prior radiotherapy for non-target lesions, except for a target lesion that has progressed after prior radiotherapy.
- Presence of at least 1 measurable lesion according to RECIST version 1.1, in a non-irradiated field.
- ECOG performance status of 0 or 1.
- Adequate bone marrow function: Absolute neutrophil count (ANC) ≥ 1.500 cells/mm³, platelet count ≥100,000 cells/mm³, and hemoglobin ≥ 90 g/L.
- Adequate renal function: Creatinine ≤ 1.5 mg/dl, or 24-hour creatinine clearance ≥ 60 ml/minute
- Adequate hepatic function: Bilirubin ≤1.5 × upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3×ULN
- Serum corrected calcium, potassium and magnesium corrected within normal range (electrolyte correction is permitted during screening).
- Effective contraception if potential for pregnancy exists.

5.1.2 Exclusion Criteria

Patients are not eligible for this trial if any of the following criteria are met:

- Prior chemotherapy in the metastatic setting.
- Prior chemotherapy within 6 months before entering this trial.
- Previous exposure to EGFR-targeted therapy.
- Patients with any concurrent medical condition or disease that would potentially compromise the conduct of the trial at the discretion of the Investigator.
- Known central nervous system metastasis and/or leptomeningeal disease.
- Known allergic reaction against any of the components of the trial treatment.
- Known uncontrolled diabetes mellitus, pulmonary fibrosis, interstitial lung diseases, acute pulmonary diseases, or liver failure.
- Active infection resulting in impaired liver function, or cirrhosis.
- Asymptomatic severe hypertension or hypertensive crisis defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥110 mmHg under resting conditions
- Impaired cardiac function including following: serious arrhythmia, unstable angina and/or congestive heart failure requiring hospitalization or myocardial infarction within the last 12 months before trial entry, pericardial effusion or LVEF < 0.45.
- Patients with obvious ulceration of the esophagus, esophageal perforation or moderate thoracic and dorsal pain.
- Hearing impairment and severe peripheral neuropathy.
- Psychiatric disease.

- History of organ allograft, autologous/allogeneic stem cell transplantation, and renal replacement therapy.
- Past or current history of neoplasm other than ESCC within 5 years, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years.
- Any investigational medical treatment within 30 days of trial entry.
- Female patients who are pregnant (confirmed by serum β -human chorionic gonadotropin [HCG] test) or breast feeding.
- Concomitant treatment with prohibited medication (see section 5.3).

5.2 STUDY TREATMENT

5.2.1 Investigational medicinal product

Cetuximab (Erbix[®]) will be manufactured and supplied by Merck KGaA. The re-labelling, distribution of Erbitux for clinical trial use will be the sponsor's responsibility in compliance with local regulations and Good Manufacturing Practice (GMP) requirements. Cetuximab will be available in ready-to-use 20 mL vials containing 5 mg/ml solution.

Batch numbers will be provided in the certificates of release. The retrace of the composition and quality should be available through the documentation of cetuximab in accordance with GMP.

Cetuximab will be provided free of charge for all eligible patients in this trial.

5.2.2 Dosage and administration

5.2.2.1 Treatment Arms

Patients in Arm A (treatment arm) will receive cetuximab (400 mg/m² as initial dose on Day 1 and subsequently 250 mg/m² weekly, intravenously [IV]) with paclitaxel (175 mg/m², IV, on Day 1, every 3 weeks) and cisplatin (75 mg/m², IV, on Day 1, every 3 weeks). Cetuximab will be administered first, followed by paclitaxel and then the cisplatin infusion. Chemotherapy (paclitaxel plus cisplatin) will be administered together with cetuximab for a maximum of 6 cycles in the absence of both PD assessed by the Investigator and unacceptable toxicity. After 6 cycles, with the presence of clinical benefit achievement, cetuximab as monotherapy will be administered until either PD assessed by the Investigator or unacceptable toxicity.

Patients in Arm B (reference group), only paclitaxel (175 mg/m², IV, on Day 1, every 3 weeks) and cisplatin (75 mg/m², IV, on Day 1, every 3 weeks) will be administered for a maximum of 6 cycles in the absence of both PD assessed by the Investigator and unacceptable toxicity.

5.2.2.2 Dose and Schedule of Cetuximab

Cetuximab will be infused intravenously from day 1 and be given every 7 days until Investigator assessed PD or unacceptable toxicity. If possible, the cetuximab infusion should be performed on the same day of each week. The initial dose of cetuximab will be 400 mg/m², with the infusion duration over 120 minutes and the maximum infusion rate no more than 5 mg/minute. The following weekly dosage of cetuximab will be 250 mg/m² with the infusion duration over 60 minutes and the maximum

infusion rate not exceeding 10 mg/minute. Flushing of the line with saline solution (0.9%) at the end of infusion is necessary.

Premedication with an antihistamine and a corticosteroid is mandatory before the first cetuximab administration and is recommended before all the following weekly cetuximab infusions.

Patients administered with cetuximab must be closely monitored during the whole infusion process for AE by a physician.

All patients allocated to Arm A will be treated with cetuximab until PD as assessed by the Investigator, or unacceptable toxicity occurrence, or withdrawal of consent. Regardless of chemotherapy discontinuation, cetuximab may still continue to be administered weekly according to original trial schedule.

5.2.3 Non-investigational medicinal products to be used

5.2.3.1 Chemotherapy

Chemotherapy will be administered for a maximum of 6 cycles in the absence of both PD assessed by the Investigator and unacceptable toxicity, with each cycle consisting of 3 weeks (21 days). The start of each cycle will be defined by the start of cisplatin infusion or carboplatin infusion if as an alternative for cisplatin. Chemotherapy should be administered on the same day of each cycle if possible. In the event of chemotherapy discontinuation, cetuximab may still continue to be administered weekly according to original trial schedule.

5.2.3.2 Dose and Schedule of Chemotherapy

5.2.3.2.1 Paclitaxel

Paclitaxel is a commercially available antitumor agent. The formulation, preparation and administration should follow the instructions in locally approved package insert.

In this study, paclitaxel will be administered after the cetuximab infusion and before the cisplatin infusion. There must be at least 1 hour between the end of the cetuximab infusion and the start of the paclitaxel infusion. Paclitaxel will be given intravenously over 3 hours at a dose of 175 mg/m² on Day 1 every 3 weeks for a maximum of 6 cycles.

Patients will be closely observed during the whole process of infusion. Premedication to prevent severe hypersensitivity reactions should be given prior to paclitaxel administration including corticosteroids, diphenhydramine, and H₂ antagonists. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before paclitaxel. If patients have premedication for cetuximab before the paclitaxel infusion, the administration of diphenhydramine and Dexamethasone is not necessary.

All the infusions and medications given must be documented in the eCRF. The actual doses, dates, start and end times of infusions should be documented accurately.

5.2.3.2.2 Cisplatin

Cisplatin is a common first-line antitumor treatment for EC patients. The formulation, preparation and administration should follow the instructions in the locally approved package insert.

In this study, cisplatin will be administered after the cetuximab and paclitaxel infusions. There must be at least 1 hour between the end of the paclitaxel infusion and the start of the cisplatin infusion.

Cisplatin will be given intravenously over 1 hour at a dose of 75 mg/m² on Day 1 every 3 weeks for a maximum of 6 cycles. Intravenous pre-hydration should be performed following the local practice and the locally approved package insert. Antiemetic prophylaxis is mandatory to prevent acute and delayed nausea and vomiting caused by cisplatin. Premedication as described in 5.2.3.2.1 for paclitaxel is recommended if it is not administered before the paclitaxel infusion.

All the infusions and medications given must be documented in the eCRF. The actual doses, dates, start and end times of infusions should be documented accurately.

5.2.3.2.3 Carboplatin

If cisplatin results in non-hematologic toxicity (see Section 5.2.3.2.2), carboplatin at a dose of target AUC of 5 may be used as a replacement of cisplatin in the subsequent cycles.

Carboplatin will be administered after the cetuximab and paclitaxel infusions. There must be at least 1 hour between the end of paclitaxel infusion and the start of a carboplatin infusion. Carboplatin will be given intravenously over 1 hour on Day 1 every 3 weeks for a maximum of 6 cycles (including the previous cisplatin cycles). The dose of carboplatin will be calculated considering the renal function of patients using the Calvert formula or the Chatelut formula, with the target AUC 5.

All the infusions and medications given must be documented in the eCRF. The actual doses, dates, start and end times of infusions should be documented accurately.

5.2.4 Other Drugs

For patients who will receive cetuximab, administration of corticosteroid and antihistamine prior to first cetuximab is mandatory, and is recommended before all the following weekly cetuximab infusions. All pretreatment must be documented in the eCRF.

The administration of other premedication, prophylactic drugs and hydration treatment will be based on locally approved package insert of each treatment and description in section 5.2.3.2. All these drugs and infusions must be documented in the eCRF.

5.2.5 Packaging and labelling of the investigational medicinal product

The packaging, labelling, and documentation of the cetuximab will be according to applicable local regulatory requirements and applicable GMP Guidelines. This will ensure the retrace of the composition and pharmaceutical quality. All labels are given in the Trial File. The Principle investigator, Peking University Cancer Hospital is responsible to re-label the IMP according to local regulation and requirement.

5.2.6 Preparation, handling and storage of the investigational medicinal product

Instructions for the preparation and handling of cetuximab will be provided. For

chemotherapy, it will be in accordance with the locally-approved package insert.

Cetuximab treatment boxes will be stored safely and separately from other drugs. Cetuximab must be stored in the refrigerator at 2 °C to 8 °C. Increased particulate formation may occur at temperatures at or below 0 °C. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2 °C to 8 °C and up to 8 hours at controlled room temperature (20 °C to 25 °C).

Paclitaxel should be stored at a temperature of 2 °C to 25 °C and avoiding light.

Cisplatin should be stored at room temperature.

The IMP must not be used for any purpose other than the trial. The Investigator (or the designated person) will maintain the following record for the IMP:

- Receipt of treatment boxes at the trial centre
- Inventory at the centre
- Administration to each patient enrolled in the trial
- Destruction of unused IMPs
- Storage temperature records

The IMP should not be used if the expiry date has been exceeded.

Once the trial has been completed or terminated, with the approval from monitor, the Investigator should destroy all the unused IMP on site or as per the site's specific procedures for handling and disposing of hazardous drugs. The specific procedures for destruction will be provided to monitor and verified by the monitor. The Investigator should provide the monitor with a copy of the inventory record form for filing and the record of the used, unused and destroyed clinical supplies. The following information should be included in this form: all administered units, all unused units, all units destroyed at the end of the trial, date of destruction, name and signature of the Investigator.

5.2.7 Investigational medicinal product accountability

The investigator is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Once the IMP is received, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialling and dating the appropriate documentation and returning it to the specified location. A copy will be archived for the Investigator Site File.
- IMP dispensing will be accurately recorded on the appropriate drug accountability forms. Accurate records should be available for verification at each monitoring visit.
- Trial centre IMP accountability records will include the following:
 - ✧ Confirmation of IMP receipt in good condition and at appropriate temperature for storage.
 - ✧ The inventory of IMP provided for clinical trial and prepared at the centre.
 - ✧ The use of each dose by each patient.
 - ✧ The study number of the patient to whom the IMP was dispensed.
 - ✧ The disposition (including return) of any unused IMP.
 - ✧ Dates, quantities, batch numbers, vial numbers, expiry dates, and the individual patient trial numbers.
 - ✧ Storage temperature records

The Investigator center should maintain records, which adequately document that patients were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No residual IMP that is dispensed to a patient may be re-dispensed to a different patient.

A Trial Monitor will periodically collect the IMP accountability forms and will check all

returns (both unused and used containers) before authorizing their destruction by the trial centre.

5.2.8 Medical care of patients after end of trial

After a patient has completed the trial or has withdrawn early, usual treatment according to the standard of care of the trial centre and general medical practice should be administered, depending on the individual medical needs of the patient.

5.3 CONCOMITANT MEDICATIONS AND THERAPIES

5.3.1 Permitted Medicines

Patients may receive all concomitant therapy (except those excluded by the protocol in Section 5.3.2) deemed necessary to provide adequate support to manage pain, infection and other complications caused by the tumor or its treatment, which should not interfere with the trial medication. In case of febrile neutropenia or documented infection, intravenous antibiotics may be administered for curative purposes. Prophylactic use of quinolone is also permitted in cases of recurrent febrile neutropenia despite dose reduction of chemotherapy. In addition, myeloid growth factors are permitted only to treat grade 4 neutropenia.

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication and in the eCRF.

5.3.2 Prohibited Medicines

Prohibited medicines include additional concurrent systemic immune treatment, chemotherapy, radiotherapy (other than a short course of palliative radiotherapy for pain, radiotherapy for primary tumor or target lesions is taken as indicating disease progression), hormone treatment for cancer treatment (other than corticosteroids as antiemetic treatment and gestagens for tumor cachexia), or any other investigational agent that may not be administered to patients in this trial.

5.3.3 Medication after the trial termination

After PD or the termination of the trial, patients will receive appropriate treatments based on local medical practice.

5.4 TRIAL PROCEDURES AND ASSESSMENTS

5.4.1 Schedule of Assessments

Before performing any trial assessments that are not part of routine medical care for the patient, the Investigator will obtain written informed consent as described in Section 9.2.

This section summarizes the types of assessment to be performed by visit type. A complete schedule of assessments is given in Table 1.1.

5.4.2 Screening Visit

The screening visit (baseline) must take place in the 28 days before the start of trial treatment.

The following tests and procedures will be performed at this visit:

- Written informed consent.
- Primary tumor diagnosis (see Section 5.5.2).
- Documentation of AEs starting from the date of first signature of informed consent.
- Documentation of demographic data, height, and relevant medical history (see Section 5.5.3).
- Documentation of prior and concomitant medications (see Section 5.3).
- Check of inclusion and exclusion criteria (see Section 5.1).
- Physical examination, check of vital signs, and assessment of ECOG performance status (see Section 6.1.5).
- ECG (to be repeated if performed more than 7 days before the first dose of trial treatment) (see Section 6.1.5.4).
- Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (hematology and biochemistry [see Section 6.1.4]), and to be repeated if performed more than 7 days before the first dose of trial treatment.
- Urinalysis (to be repeated if performed more than 7 days before the first dose of trial treatment) (see Section 6.1.4).
- Creatinine clearance based on serum and urine creatinine (see Section 5.5.7).
- Serum pregnancy test (if applicable) (see Section 5.5.5).
- HBV antigen and antibody test, HCV antibody test, and HIV test (see Section 5.5.4).
- Echocardiogram (see Section 5.5.6).
- Tumor assessment (see Section 5.6.1).

5.4.3 Weekly Cetuximab Administration Visit

For patients in Arm A, the following procedures and investigations will be performed at weekly intervals (± 3 days) until the last dose of cetuximab:

- Physical examination (see Section 6.1.5).
- Check of vital signs.
- Documentation of AEs and concomitant medications.
- Administration of cetuximab (based on BSA).

5.4.4 Start of Each Cycle Visit (Day 1 of Each 21-Day Cycle)

For all patients in Arm A and B, the following procedures and investigations will be performed on Day 1 of each 21-day chemotherapy cycle. A visit window of 3 days is acceptable.

- Randomization (for Cycle 1 only, see Section 6.3).
- Physical examination, check of vital signs, and assessment of ECOG performance status (see Section 6.1.5).
- ECG (see Section 6.1.5.4).
- Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (within 3 days before start of each cycle) (see Section 6.1.4).
- Urinalysis (within 3 days before start of each cycle) (see Section 6.1.4).
- Documentation of AEs and concomitant medications.
- Administration of cetuximab (based on BSA) only for patients in Arm A.
- Administration of cisplatin (cisplatin may be replaced by carboplatin in subsequent cycles if there are cisplatin-related nonhematologic toxicities) and paclitaxel (based on BSA) for patients in Arm A and B for a maximum of 6 cycles.
- Exploratory biomarker assessments (see Section 6.1.5)

Note: ECG and laboratory safety results must be available at start of each cycle visit.

Note: If the patient is not able to visit the Investigator for this evaluation or misses the scheduled visits, the Investigator should attempt to contact the patient or the referring physician by appropriate means to determine the patient's well-being.

5.4.5 6-Weekly Evaluation Visit

For all patients in Arm A and B, the following procedures and investigations will be performed at 6-week intervals starting from the first dose of trial treatment until the EOE. A visit window of 3 days is acceptable.

- Physical examination, check of vital signs, and assessment of ECOG performance status (see Section 6.1.5).
- ECG (see Section 6.1.5.4).
- Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (within 3 days before start of each cycle) (see Section 6.1.4).
- Urinalysis (within 3 days before start of each cycle) (see Section 6.1.4).
- Documentation of AEs and concomitant medications.
- Tumor assessment (see Section 5.6.1).
- Exploratory biomarker assessments (see Section 6.1.5)

Note: Exploratory biomarker assessments during the study treatment will be only collected at the end of cycle 2 of study treatment.

5.4.6 End of Efficacy Assessment Visit

Patients are to attend the EOE visit on the day of the last efficacy assessment. The last efficacy assessment is defined as the day on which it is determined that the patient will no longer be followed up for efficacy as a result of PD or immediately before commencing the start of any new anticancer treatment. A visit window of 3 days is acceptable. The following procedures and investigations will be performed:

Physical examination, check of vital signs, and assessment of ECOG performance status (see Section 6.1.5).

ECG (see Section 6.1.5.4).

Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (see Section 6.1.4).

Urinalysis (see Section 6.1.4).

Documentation of AEs and concomitant medications.

Tumor assessment (see Section 5.6.1).

Exploratory biomarker assessments (see Section 6.1.5)

5.4.7 Safety Follow-Up Visit

Patients are to attend the safety follow-up visit 30 days (\pm 2 days) after the last dose of trial treatment or immediately before commencing the start of any new anticancer treatment (see Section 5.3 for details). The planned procedures and investigations, except tumor assessment, are the same as the EOE visit (see Section 5.4.6).

5.4.8 Survival Follow-Up

The following assessments will be performed every 3 months after the EOE until death or termination of the trial, whichever comes first. This follow-up can take the form of a telephone contact to the patient or the patient's family, or their referring doctor.

- Survival status.
- Documentation of subsequent antitumor treatment after the end of the trial treatment.
- Outcome and resolution date of skin reactions.
- Resolution of ongoing SAEs (see Section 6.1.3.4).

5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.5.1 Demographic Data

At screening, the following demographic data will be collected: date of birth, sex, and ethnic origin data.

5.5.2 Diagnosis of Primary Tumor

At the screening visit, the following data will be recorded for the primary tumor:

- Date of initial diagnosis and date of recurrence and/or metastasis.
- Histology.
- Localization.
- Recurrence or metastasis.
- Classification at initial diagnosis, according to AJCC TNM staging system, 7th edition, 2010.

5.5.3 Medical History

The following medical history data will be documented:

- Relevant previous and concomitant disease(s), other than ESCC.
- Previous treatments, other than cancer treatment, administered in the 14 days before trial entry.
- Previous treatment for ESCC.

5.5.4 Viral Serology

The antigen and antibody test for HBV, antibody test for HCV, and HIV test will be performed if clinically indicated. Patients with known and declared HIV infection, as well as patients with an active HBV or HCV infection resulting in impaired liver function or cirrhosis will be excluded from the trial. These patients will be identified during screening by either elevation of serum transaminases (i.e. not meeting inclusion criteria for enrollment) (Section 5.1.1) and/or by the presence of a combination of markers of liver fibrosis (e.g. clinical, laboratory abnormalities, serologic markers, radiological). Chronic asymptomatic HBV/HCV carriers are permitted to enter the trial.

5.5.5 Pregnancy Testing and Contraception

All female patients of childbearing potential must have a negative blood pregnancy test at screening, which should be done within 7 days before the initiation of the trial treatment. Regular urine pregnancy tests are also recommended during the trial for female patients of childbearing potential. All patients, male or female, must practice medically-accepted contraception throughout the trial and for 3 months after last treatment administration, if the risk of conception exists. The investigator will decide together with the patient on adequate methods of contraception.

5.5.6 Echocardiogram

The left ventricular ejection fraction will be measured at screening by echocardiogram. Patients with left ventricular ejection fraction less than 45% will be excluded from the trial.

5.5.7 Creatinine Clearance

The creatinine clearance will be calculated based on serum and urine creatinine according to local practices. Patients with creatinine clearance less than 60 mL/minute will be excluded from the trial.

5.5.8 Other Baseline Assessments

Other baseline assessments include physical examination, measurement of vital signs, assessment of ECOG performance status, ECG, CT or MRI of the brain (only if clinically indicated), neck, chest, and abdomen, safety laboratory assessments (hematology, clinical chemistry, electrolytes, urinalysis). Biomarker assessments (Tissue samples for EGFR expression level. Tissue and/or blood samples for AREG/EREG mRNA expression)

As these assessments are also performed at subsequent visits during the trial, refer to the relevant subsections of Sections 5.6 and 6 below for details of any method to be used.

5.6 EFFICACY ASSESSMENT

5.6.1 Documentation of Tumor Assessments

A CT or MRI with contrast enhancement is recommended for tumor assessment.

Imaging, including CT or MRI of the brain (only if clinically indicated), neck (base skull to clavicles), chest, and abdomen, must be performed at baseline in order to review potential metastasis (≤ 28 days before trial treatment is acceptable). A bone scan and/or positron emission tomography (PET) scan should be considered for patients who have possible bone metastasis at baseline or if bone metastasis is suspected during the trial; however, The same method, CT or MRI, must be used for tumor assessment at baseline and at subsequent visits. The bone scan or PET cannot be used for measurement of target lesions.

At baseline, the organs with metastatic disease and the target and non-target lesions should be documented. Evaluation of lesions should be performed at baseline and then every 6 weeks (± 3 days), regardless of any delays in trial treatment, until PD, as assessed by the Investigator.

Tumor assessments should be conducted at each tumor assessment time point including a complete assessment of all target and non-target lesions (see Table 1.1).

In the case of skin lesions, clinical evaluation should be made with a caliper and photos must be taken and made available.

All measurements should be recorded in metric notation.

Confirmation of progression needs to be based on radiological measurements. Clinical symptoms/signs suggestive of progression need radiological confirmation of PD. Patients with a global deterioration of health status requiring discontinuation of treatment without radiological evidence of PD should be classified as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment (i.e. the patient needs to return for a final tumor assessment).

5.6.2 Criteria for Tumor Response Evaluation

Tumor response evaluation will be performed according to RECIST version 1.1 (see Appendix I) by using CT or MRI and other modalities at a 6-week interval starting from the first dose of trial treatment. In the case of symptoms suggesting progression, patients should be evaluated by imaging within 1 week for documentation and confirmation of the tumor responses.

Evaluation of lesions should be based on images obtained by either CT or MRI. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the trial. All assessments should be provided by the same physician or radiologist if possible during the trial.

Evaluation criteria for possible combinations of tumor responses (e.g. target lesion, non-target lesion, new lesion, and overall response) are provided in Appendix I.

5.7 CRITERIA FOR PATIENT WITHDRAWAL

5.7.1 Withdrawal from Trial Therapy

Patients must be withdrawn from all trial treatment in any of the following circumstances:

- Occurrence of an exclusion criterion that affects the patient's safety and discontinuation is necessary as judged by the Investigator.
- Occurrence of AEs and discontinuation of trial treatment is considered necessary by the Investigator.
- Occurrence of pregnancy during trial treatment.

- Treated with prohibited medication defined in Section 5.3.2, if judged necessary by the Investigator.
- Noncompliance/insufficient compliance.

Patients must be withdrawn from chemotherapy treatment but may still use cetuximab alone under the following circumstances:

- A delay of chemotherapy treatment of more than 21 days due to toxicity.
- More than two dose reductions of chemotherapy with paclitaxel and cisplatin or more than one dose reduction of chemotherapy with carboplatin.
- Occurrence of AEs, if discontinuation of chemotherapy is desired by the patient or if deemed necessary by the Investigator.

Patients must be withdrawn from cetuximab but may still continue treatment of chemotherapy under following conditions:

- More than 2 consecutive cetuximab infusions withheld due to toxicity.
- Occurrence of any Grade 4 toxicities related to cetuximab.
- Second episode of any cetuximab infusion-related reaction following a 50% reduction in the infusion rate.
- Diagnosis of interstitial lung disease during the trial.
- Occurrence of AEs, if discontinuation of cetuximab is desired by the patient or if deemed necessary by the Investigator.

Patients with premature withdrawal from the trial treatment for reasons other than PD will be asked to follow scheduled visits until an assessment of PD, followed by the safety follow-up visit and survival contacts.

5.7.2 Withdrawal from the Trial

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Patients must be withdrawn under the following circumstances:

- Patient withdrawal of consent at any time
- Participation in another clinical trial
- Termination of the trial
- Patient noncompliance

5.8 PREMATURE TERMINATION OF THE TRIAL

The trial may be discontinued prematurely. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient recruitment is unsatisfactory.
- Discontinuation of production of investigational medicinal product (IMP).
- Sponsor's decision that continuation of the trial is unsuitable for medical or ethical reasons.

The Investigator (sponsor) has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment within an acceptable time frame.
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

6 ASSESSMENT OF SAFETY

6.1 SAFETY PLAN

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each patient will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the patient (see Section 6.1.3.1). The reporting period of AEs is described in Section 6.1.3.2.

6.1.1 Toxicities Associated with Cetuximab and Dose Reductions

Cetuximab IB 20.0 used as reference safety information in this study.

6.1.1.1 Skin Reactions

Prophylactic medication with tetracyclines is recommended for patients in Arm A to reduce the incidence of Grade 3 skin reactions (30) [100mg minocycline daily or 100mg doxycycline twice daily is recommended for 6-8 weeks]. The administration of these prophylactic agents should begin 1 day before administration of first dose of cetuximab (30-31).

For patients with grade 1 or 2 acne-like rash (defined in the CTCAE v4.03), treatment with topical antibiotics such as benzoyl peroxide or erythromycin or systemic antibiotics such as tetracyclines can be considered. For skin reactions greater than Grade 3, a dermatologist should be consulted. In case of pruritus, an oral antihistamine is recommended.

If a patient experiences a severe skin reaction (\geq grade 3, defined in the CTCAE v4.03), cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to grade 2 or less. Cetuximab may be delayed for up to 14 days (which means 1 or 2 planned treatments missed) without changing the dose level.

With the second and third occurrences of severe skin reactions (\geq grade 3, defined in the CTCAE v4.03), cetuximab therapy must again be interrupted for up to 14 days. Treatment may only be resumed at a lower dose level (200 mg/m² after the second occurrence and 150 mg/m² after the third occurrence), if the reaction has resolved to grade 2 or less.

If severe skin reactions occur a fourth time or do not resolve to grade 2 within 14 days of treatment, permanent discontinuation of cetuximab treatment is required.

6.1.1.2 Infusion-related Reactions

A close monitoring of patients particularly during the first administration is required.

Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first cetuximab infusion. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms or signs of an infusion-related reaction occur. Symptoms may include bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped immediately. Before subsequent infusion of cetuximab, consideration should be taken of whether the patient may have performed IgE antibodies.

If an infusion-related reaction develops later during the infusion or at a subsequent infusion, further management will depend on its severity:

- Grade 1 (mild): Decrease cetuximab infusion rate by 50% and monitor closely. The total infusion time for cetuximab should not exceed 240 minutes.
- Grade 2 (moderate): Stop cetuximab infusion and immediately administer treatment for symptoms. Resume infusion at 50% of the previous rate once the infusion-related reaction has resolved to Grade 1 or less, and monitor closely.
- Grade 3 and 4 (severe or life-threatening): Stop cetuximab infusion immediately. Treat symptoms vigorously and contraindicate further use of cetuximab.

6.1.1.3 Respiratory Disorders

Cases of interstitial lung disease have been reported, with the majority of patients from the Japanese population. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient should be treated appropriately.

6.1.1.4 Electrolyte disturbances

Progressively decreasing serum magnesium levels have been observed leading to severe hypomagnesaemia in some patients. Hypomagnesaemia is reversible following discontinuation of cetuximab. Depending on severity, other electrolyte disturbances, mainly hypocalcaemia or hypokalaemia, have also been observed. Determination of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate

6.1.1.5 Other Conditions

If the patient develops an interim illness that according to the Investigator must be treated, treatment might be interrupted which can last for no more than 2 continuous cetuximab infusions. In such delayed situation, subsequent dosage of cetuximab will remain as 250 mg/m² weekly or same as the last dose before interruption if the dose had been reduced.

In the case that cetuximab must be stopped for a longer period of time (more than 2 continuous cetuximab infusions), cetuximab treatment will be permanently discontinued

6.1.2 Dose Reductions of Chemotherapy

Dose reductions for paclitaxel, cisplatin and carboplatin are based on the dose level changes outlined below (Table 6.1). Two dose reductions for paclitaxel and cisplatin and 1 dose reduction for carboplatin are allowed. If further toxicity occurs or the treatment cannot be resumed within 1 cycle (21 days), the patient must be withdrawn from chemotherapy treatment.

Table 6.1 Dose Reductions for Chemotherapy

| | Dose reduction levels | Dosage¹ |
|-------------|------------------------------------|---------------------------|
| Paclitaxel | 0 | 175 mg/m ² |
| | -1 (decreased by 20%) | 140 mg/m ² |
| | -2(decreased by 20% from level -1) | 112 mg/m ² |
| Cisplatin | 0 | 75 mg/m ² |
| | -1 (decreased by 20%) | 60 mg/m ² |
| | -2(decreased by 20% from level -1) | 48 mg/m ² |
| Carboplatin | 0 | AUC 5 |
| | -1 (decreased by 20%) | AUC 4 |

¹ The doses which have been reduced for toxicity must not be re-escalated.

Dose modification will be made with regard to the greatest degree of toxicity, which will consider the lowest haematology values and the highest degree of nonhematologic toxicities experienced by the patient during previous cycle. If more than one toxicity occurs, the dose reduction will be made based on the most severe toxic effect decided by the Investigator.

For patients in Arm A, chemotherapy will not be delayed due to cetuximab-related toxicities.

For paclitaxel, bone marrow suppression is the major dose-limiting toxicity with neutropenia, febrile neutropenia, anemia and infections. Other major toxicities observed for paclitaxel when combined with cisplatin include: hypersensitivity reaction, skin reaction, nausea and vomiting, myalgia/arthralgia, diarrhea, neurotoxicity with peripheral neuropathy, asthenia and alopecia. Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in polyoxyl 35 castor oil.

For cisplatin, the major toxicities include: nephrotoxicity, ototoxicity, myelodepression with leukopenia, thrombocytopenia and anemia, infectious complications, nausea and vomiting and peripheral neuropathy. Cisplatin is contraindicated in patients with pre-existing hearing deficiency.

For carboplatin, the major toxicity include: myelodepression with thrombopenia, leucopenia, neutropenia and anemia, infectious complications, nausea and vomiting, ototoxicity, and peripheral neuropathy.

6.1.2.1.1 Hematologic Toxicities of Chemotherapy

Based on results of the patient's blood sample test on the scheduled day of treatment, if any of the hematologic criteria listed in Table 6.2 are met, a dose reduction of chemotherapy should be applied.

Table 6.2 Criteria for Dose Reductions Based on Hematologic Results on Scheduled Day of Treatment

| | |
|---|--|
| ANC \geq 1500/ μ l AND Platelet count \geq 100,000/ μ l | Full dose paclitaxel, cisplatin or carboplatin |
| ANC 500-999/ μ l OR Platelet count 50,000-75,000/ μ l | Hold paclitaxel and cisplatin or carboplatin. Recheck complete blood count (CBC) weekly. When ANC $>$ 1000/ μ l and platelet count $>$ 100,000/ μ l, resume paclitaxel and cisplatin at -1 dose reduction level (20% dose reduction) |
| ANC $<$ 500/ μ l OR Platelet count $<$ 50,000/ μ l | Hold paclitaxel, cisplatin or carboplatin. Recheck CBC weekly. When ANC $>$ 500/ μ l and platelet count $>$ 75,000/ μ l resume paclitaxel and cisplatin at -2 dose reduction level. |
| Febrile Neutropenia (ANC $<$ 1000/ μ l fever with a single temperature \geq 38.3 °C or a sustained temperature \geq 38.0 °C) | 1) The first episode of febrile neutropenia or documented infection will require antibiotic treatment and 1 level dose reduction by 20% for paclitaxel and cisplatin or carboplatin. 2) If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics (quinolone) during the subsequent cycles. 3) If there is a third episode, the patient will be withdrawn from the trial. |

6.1.2.1.2 Nonhematologic Toxicities of Chemotherapy

If a patient has a Grade 3 or 4 toxicity defined in Table 6.3, after 2 dose reductions, or if the delay is longer than 3 weeks (21 days), the chemotherapy treatment should be discontinued based on the Investigator's decision.

Table 6.3 Criteria for Dose Reductions Based on Nonhematologic Toxicities on the Scheduled Day of Treatment

| Toxicity | Grade (as defined in CTCAE v4.03) | Action to be taken |
|---------------------------------|-----------------------------------|---|
| Hypercreatinemia Ototoxicity | \geq Grade 1 | Delay chemotherapy until Grade 0, change cisplatin to carboplatin |
| | Grade 2 | Dose reduction by 1 |

| | | |
|-----------------------------------|-----------|--|
| | | level (20% reduction) for all chemotherapy |
| Hypercreatinemia | > Grade 2 | Delay chemotherapy until ≤ Grade 2, change cisplatin to carboplatin |
| Sensory neuropathy | Grade 2 | Dose reduction by 1 level (20% reduction) for all chemotherapy |
| | > Grade 2 | Change cisplatin to carboplatin |
| | > Grade 3 | Stop cisplatin/carboplatin |
| Other organ toxicity ¹ | Grade 2 | Delay chemotherapy treatment until Grade 0 |
| | > Grade 2 | Delay chemotherapy treatment until Grade 0 ² ; Dose reduction by 1 level (20% reduction) for all chemotherapy |

1 Except asymptomatic increase in transaminases, cetuximab-induced skin reactions and medically irrelevant side effects (e.g. nausea, vomiting, alopecia, etc.)

2 Nonhematologic chemotherapy-related toxicities have resumed to <Grade 1 or baseline (excluding skin reactions, paronychia, alopecia, fatigue or neurotoxicity which must have resumed to <Grade 2)

6.1.3 Adverse Events

6.1.3.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE. Investigators will reference the National Cancer Institute - CTCAE, version 4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild.
- Grade 2 or Moderate.
- Grade 3 or Severe.
- Grade 4 or Life-threatening.
- Grade 5 or Death.

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMP/trial treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions.

Decisive factors for the assessment of causal relationship of an AE to the IMP/trial treatments include, but may not be limited to, temporal relationship between the AE and the IMP/trial treatments, known side effects of IMP/trial treatments, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP/trial treatments. The AE could not medically (pharmacologically/clinically) be attributed to the IMP/trial treatments under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP/trial treatments. The AE could medically (pharmacologically/clinically) be attributed to the IMP/trial treatments under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the patient is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.)

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE and described in Section 6.1.3.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration treatment application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

In this trial, PD is the only medically anticipated clinical event which is considered as a clinical efficacy outcome rather than an AE. No other medically anticipated events are defined in this trial as efficacy outcomes.

However, if adverse signs or symptoms occur in association with PD then these should be recorded as AEs.

AE/SAEs Observed in Association with Disease Progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms should not be reported as AEs.

However, if adverse signs and symptoms occur in association with disease (tumor) progression, such as dyspnea, tumor pain, bleeding etc., then these should be recorded as AEs or reported SAEs, if they meet criteria for seriousness.

6.1.3.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the patient will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the patient's condition will be recorded as AEs, whether reported by the patient or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 6.1.3.4.

It is important that each AE report includes a description of the event, its duration (onset and resolution dates [and times when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose reduction or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

6.1.3.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the patient is initially included in the trial (date of first signature of informed consent) and continues until the Safety Follow-up Visit.

Any SAE assessed as related to cetuximab must be reported whenever it occurs, irrespective of the time elapsed since the last administration of cetuximab.

6.1.3.4 Procedure for Reporting Adverse Events

The principle investigator will be responsible for consolidating a safety report consisting of AEs and abnormal lab results on a monthly basis and sending it to Merck.

6.1.3.5 Procedure for Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) report all SAEs irrespective of causal relationship to study medication to the Sponsor or its designee in writing, ethics committee, national and province center for ADR monitoring and Merck China. All written reports should be transmitted using the Merck SAE Report Form, which must be completed by the Investigator following specific completion instructions.

For each SAE, all relevant medical information should be documented on the SAE report form.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the trial-specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant medications). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

6.1.3.6 Safety Reporting to Health Authorities

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable center-specific requirements related to the reporting of SAEs (particular deaths) involving trial patients to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor will inform the Investigator of “findings that could adversely affect the safety of patients, impact the conduct of the trial or alter the IEC’s/IRB’s approval/favorable opinion to continue the trial.”

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or center-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

6.1.4 Clinical Laboratory Assessments

Blood and urine samples will be collected for hematology, biochemistry, electrolytes, and urinalysis following the timing noted in the Schedule of Assessments (Table 1.1). The results of all safety laboratory parameters must be available within 3 days before start of each cycle.

Category Parameters

Hematology hemoglobin, red blood cell count, white blood cell count and differential count, platelet count Biochemistry creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total bilirubin (including direct bilirubin if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, glucose, blood urea, uric acid Electrolytes sodium, potassium, chloride, calcium, magnesium, Urinalysis* pH value, specific gravity, protein, glucose, red blood cell, white blood cell

* Urinalysis dipstick will be followed by microscopic examination if results are abnormal.

All samples should be clearly identified. Blood samples will be collected after fasting for at least 8 hours. All laboratory assessments will be performed at local laboratories and will comply with local requirements. Analysis of additional laboratory parameters is at the discretion of the Investigator. Viral serology tests will be performed if clinically indicated (see Section 7.2.4).

At the screening visit, female patients of childbearing potential including those who have had tubal ligation must additionally have a blood pregnancy test performed within 7 days before the first dose of trial treatment.

All laboratory test results obtained (including any potential repeat tests) must be documented in the eCRF.

Any laboratory result leading to an interruption or dose reduction of trial treatments will be considered as an untoward medical occurrence and therefore has to be documented as an AE (see Section 6.1.3).

6.1.5 Exploratory biomarker assessments

Tissue samples for biomarkers analysis include 10 unstained slides. All the tissue samples from each center should be sent to GI laboratory in Peking University Cancer before randomization. Blood samples for biomarkers analysis include 10 ml EDTA-anticoagulant blood and 3 ml clotted blood at baseline (after the patient has been determined to be eligible for the study but before the first administration of study medication), at the end of cycle 2 and at the end of the study treatment. All the blood samples for each center should be sent to GI laboratory in Peking University Cancer in 24 hours after collection.

6.1.6 Vital Signs, Physical Examinations, and Other Assessments

6.1.6.1 Vital Signs

Vital signs will be assessed at the time points outlined in Table 1.1 and must include axillary temperature, heart rate and blood pressure (measured in a supine position after 5 minutes at rest), and respiratory rate. For those in Arm A, vital signs must be continuously monitored before during, and up to 1 hour after each cetuximab infusion.

6.1.6.2 Physical Examination

Physical examination will be performed at the time points outlined in Table 1.1 and must include the following: height (screening only), weight, general appearance, skin, head, neck, ears, eyes, nose, mouth, throat, respiratory/pulmonary, cardiovascular, gastrointestinal/abdominal, genitourinary, neurological, musculoskeletal/extremities, and lymphatic systems, and any other that may be relevant.

For physical examinations after the screening visit, only new findings compared to the previous one have to be documented in the eCRF.

6.1.6.3 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status of each patient will be reviewed at the time points outlined in Table 1.1 and will be graded according to the following:

Grade 0 Fully active, able to carry on all pre-disease performance without restriction.

Grade 1 Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.

Grade 2 Ambulatory and capable of all self-care, but unable to carry out any work activities up and about more than 50% of waking hours.

Grade 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

Grade 4 Completely disabled, cannot carry on any self-care, totally confined to bed or chair.

Grade 5 Dead

6.1.6.4 Electrocardiogram

A computerized 12-lead ECG must be obtained at the time points outlined in Table 1.1 and as clinically indicated. An ECG should be performed after the patient has rested for 5 minutes.

Each lead shall be recorded for at least 3 beats at a speed of 25 mm/second.

The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval.

At screening, the Investigator must assess the ECG for signs of cardiac disease that could exclude the patient from the trial. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented in the eCRF. The ECG results must be available at start of each cycle visit.

7 STATISTICS

7.1 SAMPLE SIZE

Assuming a median PFS time as 6 months in the control group and 9.09 months in the experimental cetuximab treatment group, the sample size requires 150 patients to collect 105 PFS events and ensure 80% power with a two-sided significance level of 20% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio (HR) of 0.66. Assuming the median PFS time above and a recruitment period of 12 months, then the number of 105 PFS events will be observed within 21 months, if the withdrawal rate per month in both groups is not higher than 1%.

7.2 RANDOMIZATION

Patients will be randomized to one of the 2 treatment arms, cetuximab plus chemotherapy versus chemotherapy alone, at a 1:1 ratio stratified by the following:

- ECOG performance status: 0 versus 1
- Previous treatment: previous surgery or radiotherapy versus. no previous treatment
- Number of metastatic sites (1 versus ≥ 2)

A central stratified permuted block randomization procedure will be employed via IVRS to balance prognostic factors between treatment arms.

7.3 ENDPOINTS

7.3.1 Primary Endpoint

The primary endpoint of this trial is PFS time, as assessed by the Investigator. The primary endpoint is defined as the duration (in months) from the date of randomization until first observation of PD, or death due to any cause whichever is first. Only those deaths will be considered, which occurred within 60 days after the last tumor assessment or randomization (whichever occurred earlier). Any patient without either assessment of the tumor after baseline, or death date (within 60 days after last tumor assessment and the first dose of trial treatment) will be censored on the date of last tumor assessment or the first dose of trial treatment. A patient who has not received trial treatment and for whom no date of progression or death is known will be censored on the date of the first dose of trial treatment (Day 1) or date of last tumor assessment, whichever comes later.

7.3.2 Secondary Endpoints

The secondary endpoints include OS time, ORR, and DCR.

- OS time is defined as the time (in months) from the date of randomization to the date of death. If a patient is alive at the time of analysis, survival time will be censored at the last date when the patient was known to be alive.
- Overall Response Rate (ORR): overall response (complete response [CR] or partial response [PR], according to the RECIST 1.1). The date of response is the date that the response is first observed.
- The DCR will be based on imaging and classified according to RECIST version 1.1 criteria. The DCR defined as the number of patients whose best response is either CR, PR or SD, divided by the number of patients belonging to the trial set of interest.

7.3.3 Safety Endpoints

The safety and toxicity of the treatment will be evaluated in terms of the following safety variables:

Exposure to cetuximab, cisplatin or carboplatin, and paclitaxel in terms of duration of therapy, cumulative dose, dose intensity and relative dose intensity, number of dose reductions, dose delays, and drug discontinuation.

- Incidence and type of AEs in terms of:
 - ✧ All treatment-emergent adverse events (TEAEs);
 - ✧ Related TEAEs;
 - ✧ Treatment emergent SAEs;

- ◇ Related treatment emergent SAEs;
- ◇ CTCAE (version 4.03) Grade 3 and 4 TEAEs;
- ◇ Related CTCAE (version 4.03) Grade 3 and 4 TEAEs;
- ◇ TEAEs leading to withdrawal, dose modification, or drug discontinuation will be summarized by treatment arm.
- Incidence and reasons for deaths in each treatment arm.
- Safety laboratory tests graded by CTCAE (version 4.03) where applicable.
- Vital signs, physical examinations and ECOG performance status.

7.4 ANALYSIS SETS

All screened patients: The population of all screened patients will include all patients who signed the ICF.

Safety population (all treated patients): All patients who received at least 1 dose of any trial treatment (cetuximab, cisplatin, or paclitaxel). Patients will be allocated as treated.

Intent to Treat (ITT) population (full analysis set - all randomized patients): All patients who were randomized to trial treatment. Patients will be allocated as randomized.

Per protocol (PP) population: All ITT patients who meet all of the following criteria:

- Compliance with main entry criteria;
- Absence of major protocol violations with respect to factors likely to affect the primary efficacy of treatment;
- Adequate compliance with trial medication.

Further details on major protocol deviation leading to exclusion from PP population will be specified in the Statistical Analysis Plan.

The following subgroups are considered of interest to comparatively explore the treatment effect for the definition of subgroups, data as documented in the eCRF will be taken.

- Age: <65 years versus \geq 65 years
- Sex: Male versus Female
- Baseline ECOG performance status: 0 versus 1
- Primary tumor location: cervical/upper versus median versus lower
- Time from initial ESCC diagnosis: < median versus \geq median
- Histology: well/moderately versus poorly differentiated
- Extent of disease at trial entry: non-metastatic recurrent versus non-recurrent metastatic versus metastatic including recurrent
- Prior antitumor therapy:
 - ◇ Any: yes versus no;
 - ◇ Prior neoadjuvant/induction: yes versus no;
 - ◇ Prior radiotherapy: yes versus no;
 - ◇ Prior radiochemotherapy: yes versus no;
 - ◇ Prior surgery: yes versus no;
 - ◇ Prior platinum-containing treatment for ESCC: yes versus no.

7.5 DESCRIPTION OF STATISTICAL ANALYSES

7.5.1 General Considerations

The ITT population will be primarily used in the analysis of baseline characteristics and efficacy.

Selected efficacy analyses will be repeated for the PP population and for subgroups.

The Safety population will be considered for safety analyses.

All statistical tests comparing treatment arms will be performed 2-sided and the p-values will be considered as exploratory statistics, with the exception of the stratified log-rank test for the primary endpoint using a significance level (α) of 20%. . If CIs are to be calculated, these will be 2-sided with a confidence level of 95%, unless otherwise specified.

Continuous variables will be summarized using descriptive statistics, i.e. number of patients (N), mean, median, standard deviation, 25th and 75th percentiles (Q1, Q3), minimum and maximum.

Qualitative variables will be summarized by means of counts and percentages. Unless otherwise stated the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

7.5.2 Analysis of Primary Endpoint

The primary endpoint of this trial is PFS time as assessed by the investigator.

The PFS time assessed by the investigator is defined as the duration (in months) from the date of randomization until first observation of PD, or death due to any cause whichever is first. Only those deaths will be considered, which occurred within 60 days after the last tumor assessment or randomization (whichever occurred earlier). Any patient with neither assessment of tumor progression, nor death date within 60 days after last tumor assessment and the first dose of trial treatment will be censored on the date of last tumor assessment or the first dose of trial treatment. A patient who has not received trial treatment and for whom no date of progression or death is known will be censored on the date of the first dose of trial treatment (Day 1).

The analysis will be performed on the basis of the ITT principle on the ITT population.

The treatment effect expressed as hazard ratio of cetuximab plus chemotherapy to chemotherapy alone including 95% CI on PFS time will be estimated using a stratified Cox proportional hazard model, including treatment and the randomization strata (as specified in the IVRS), ECOG performance status (0 versus 1) and previous surgery or radiotherapy vs. no previous treatment and the number of metastatic sites (1 vs ≥ 2). Furthermore, a two-sided stratified log-rank test p-value will be presented to demonstrate the likelihood of the observed or a greater difference in survival distribution between treatment arms. The underlying superiority test considers the null hypothesis that the distribution of PFS time is the same under treatment with cetuximab plus chemotherapy compared to chemotherapy alone, with the alternative hypothesis being that the distributions are different. For this phase II trial, a significance level of 20% is considered sufficient to obtain initial information as to whether the combination of cetuximab plus chemotherapy might be superior to chemotherapy alone in patients with ESCC receiving first line treatment.

The PFS time of the 2 treatment arms will be described by means of Kaplan-Meier survival curves (product-limit estimates) and associated summary statistics (e.g. median PFS time, 95% CI, survival estimates at certain time points, and number of patients under risk).

Secondary Analyses of Primary Variable

All secondary analyses of the primary variable will be performed to support the robustness of the primary analysis and regarded as exploratory. Such analyses will comprise:

- Sensitivity Analyses.

Sensitivity analysis will be employed to explore the robustness of the primary confirmatory analyses to assess the impact of analysis populations, the validity of model assumptions by

- ✧ Executing per-protocol analysis. If PP population includes more than 90% of the ITT population, additional efficacy analyses on the PP population will be omitted.

- ◇ Conducting an unstratified log-rank test
- Subgroup analyses to investigate the effect in subgroups (see subgroup as given in Section 7.4).

Subgroup analyses will comprise univariable unstratified analysis considering the subgroups as defined in Section 7.4. To assess the heterogeneity of treatment effects across the subgroups levels Cox proportional hazards model will be performed for PFS time as dependent variable and with subgroup type, the treatment arm and the treatment by subgroup type interaction as explanatory variables.

P-values for the interaction test will be provided together with the hazard ratios and 95% CI for each subgroup.

- Exploratory analyses to investigate the treatment effect when adjusted for explanatory variables of potential prognostic values.

Multivariable Cox regression analysis will be used to assess and adjust the treatment effect for potential baseline prognostic factors (see subgroup as given in Section 7.4).

7.5.3 Analysis of Secondary Endpoints

The secondary efficacy analyses considered below are used as supporting evidence to underline the clinical benefit of cetuximab plus chemotherapy versus chemotherapy only. The analyses will be exploratory, and no adjustment for multiple comparisons will be made.

The analysis of time-to-event variables (e.g. OS time), will follow standard methodology by employing Kaplan-Meier estimates (product-limit estimates), Cox's proportional hazard model to estimate stratified hazard ratios and corresponding 95%CI, and subgroup analyses will be performed for predefined baseline factors (see subgroup as given in Section 7.4).

Duration of response will be presented descriptively.

For the analysis of dichotomous variables (e.g. DCR), the stratified Cochran-Mantel-Haenszel test will be performed.

7.5.4 Analysis of Safety

Safety analyses will be performed according to the as-treated principle. Any TEAEs will be summarized, i.e. those events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state and with onset dates occurring within the first dosing day of trial treatment until 30 days after the last dose of trial treatment. No formal statistical comparisons are planned.

The extent of exposure for cetuximab, cisplatin or carboplatin, and paclitaxel will be characterized by duration (weeks), cumulative dose, dose intensity, relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

The severity of AEs will be graded using CTCAE toxicity grades. The incidence and type of AEs, SAEs, trial treatment-related AEs and SAEs, trial treatment-related AEs by CTCAE toxicity grade, CTCAE Grade 3 and 4 AEs, trial treatment-related CTCAE Grade 3 and 4 AEs, AEs leading to death, AEs leading to discontinuation of trial treatment, will be summarized in total and for each treatment arm.

All deaths, deaths within 60 days after first dose of trial treatment and deaths within 30 days after last dose of trial treatment as well as reasons for deaths will be tabulated.

Laboratory results will be classified according to the CTCAE (version 4.03) when applicable.

The worst on trial grade after the first dose of trial treatment will be summarized. Shifts in toxicity grading from treatment start to highest grade will be displayed. Results for laboratory variables that were not part of the CTCAE (version 4.03) will be presented as below, within, and above the normal limits of the local laboratory.

Vital signs (temperature, heart rate, blood pressure, respiratory rate) will be descriptively presented.

The baseline results of the physical examination will be presented. Clinically significant, abnormal findings from the physical examination are to be reported as AEs.

7.6 ADDITIONAL PLANNED ANALYSES

Biomarker analysis will be performed to explore different EGFR expression levels, AREG/EREG mRNA expression levels and their correlation with responses to cetuximab treatment. Response will be measured using RECIST (Response Evaluation Criteria in Solid Tumors, V. 1.1) criteria. The relation between ligand expression levels and outcome will be evaluated using logistic regression for response and Cox regression for survival data.

8 TRIAL MANAGEMENT

8.1 CASE REPORT FORM

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely way. The data in the eCRF should be consistent with the relevant source documents. For each patient enrolled, the Case Report Form must be completed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the Case Report Form. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome of the AE.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. Portable Document Format files of the eCRFs will be provided to the Investigators at the completion of the trial.

8.2 SOURCE DATA AND PATIENT FILES

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when Case Report Forms are inconsistent or when errors in data transcription are suspected.

8.3 INVESTIGATOR SITE FILE AND ARCHIVING

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The

documents to be archived include the Patient Identification List and the signed patient ICFs. If archiving of the Investigator Site File is no longer possible at the center, the Investigator must notify the Sponsor/designee.

All original patient files (medical records) must be stored at the center (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

8.4 MONITORING AND QUALITY ASSURANCE OF THE STUDY

This trial will be monitored in accordance with the ICH GCP and any other applicable regulations. The center Monitor will perform visits to the trial center at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be patient to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the center, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each patient.

8.5 CHANGES TO THE CLINICAL TRIAL PROTOCOL

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the center. Any amendment that could affect the patient's agreement to participate in the trial requires the patient's informed consent before implementation following the process as described in Section 9.2.

8.6 CLINICAL TRIAL REPORT AND PUBLICATION POLICY

8.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor/designee in consultation with the Coordinating Investigators following the guidance in ICH Topic E3.

8.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial centers. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the center. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

9 ETHICAL ASPECTS

9.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of China, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the patient.

9.2 PATIENT INFORMATION AND INFORMED CONSENT

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

9.3 CLINICAL TRIAL INSURANCE AND COMPENSATION TO PATIENTS

Insurance coverage shall be provided. Insurance conditions shall meet good local practices, as applicable.

10 REFERENCES CITED IN THE TEXT

1. Chen W, Zheng R, et al. Cancer Statistics in China, 2015. *Ca Cancer J Clin*. 2016; 66(2): 115-132.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J clin*. 2012; 62: 10-29.
3. Tran GD. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*. 2005; 113:456-63.
4. Kamangar F, Dores GM, et al. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Onco*. 2006; 24: 2137-2150.
5. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med*. 2003; 349:2241-2252.
6. Pennathur A, Farkas A, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. *Ann Thorac Surg*. 2009; 87: 1048-1054.
7. Wu AH, Wan P, et al. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). *Cancer Causes Control*. 2001;12(8):721-732.
8. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers. Version V3.2015. http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
9. Grunberger B, metastatic esophageal cancer. *Anticancer Res*. 2007 Jul-Aug;27(4C):2705-14.
10. Ferguson KM. Structure-based view of epidermal growth factor receptor regulation. Annual review of biophysics. 2008; 37:353-373.
11. Franklin WA, Veve R, Hirsch FR, Helfrich BA, Bunn PA, Jr. Epidermal growth factor receptor family in lung cancer and premalignancy. *Seminars in oncology*. 2002; 29:3-14.
12. Harari PM, Allen GW, Bonner JA. Biology of interactions: Antiepidermal growth factor receptor agents. *J Clin Oncol*. 2007; 25: 4057-4065.
13. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol*. 2006; 24:4170-4176.
14. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004; 351: 337-345.
15. Salomon DS, Brandt R, Ciardiello F, et al. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*. 1995; 19: 183-232.
16. Guo M, Liu S, Lu F. Gefitinib-sensitizing mutations in esophageal carcinoma. *N Engl J Med*. 2006; 354: 2193-2194.
17. Cronin J, McAdam E, Danikas A, Tselepis C, Griffiths P, Baxter J, Thomas L, Manson J, Jenkins G. Epidermal growth factor receptor (EGFR) is overexpressed in high-grade dysplasia and adenocarcinoma of the esophagus and may represent a biomarker of histological progression in Barrett's esophagus (BE). *The American journal of gastroenterology*. 2011; 106: 46-56.
18. Liao Z, Cox JD, Komaki R. Radiochemotherapy of esophageal cancer. *J Thorac Oncol*. 2007;2:553-568.
19. Wu X, Fan Z, Masui H, et al. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. *J Clin Invest*. 1995; 95:1897-1905.
20. Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. *Nat Rev Cancer* 2006; 6(9):714-727.
21. Waksal HW. Role of an anti-epidermal growth factor receptor in treating cancer. *Cancer Metastasis Rev*. 1999; 18:427-436.
22. Hadari YR, Doody JF, Wang Y, et al. The IgG1 monoclonal antibody cetuximab induces degradation of the epidermal growth factor receptor. *ASCO GI meeting 2004; Abstract 234*.
23. Friedlander E, Barok M, Szollosi J and Vereb G: ErbB-directed immunotherapy: antibodies in current practice and promising new agents. *Immunol Lett*. 2008; 116: 126-140.
24. Schmitz KR and Ferguson KM: Interaction of antibodies with ErbB receptor extracellular regions. *Exp Cell Res*. 2009; 315: 659-670.
25. Enzinger PC, Burtness B, Hollis D, et al: CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. *J Clin Oncol*. 2010; 15S:4006.
26. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol*. 2009; 20:1667-1673.
27. Chen Y, Wu X, Bu S, et al. Promising outcomes of definitive chemoradiation and cetuximab for patients with esophageal squamous cell carcinoma. *Cancer Sci*. 2012; 103(11): 1979-1984.
28. Crosby T, Hur CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicenter, phase 2/3 randomised trial. *Lancet Oncol*. 2013; 14: 627-637.

29. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008; 359:1116-1127.
30. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer.* 2011; 19(8):1079-1095.
31. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010;28(8):1351-1357.
32. Jacobs, B, De Roock W, Piessevaux H, et al. Amphiregulin and epiregulin mRNA expression in primary tumors predicts outcome in metastatic colorectal cancer treated with cetuximab. *J Clin Oncol.* 2009; 27(30): 5068-5074.

11 APPENDICES