CLINICAL STUDY REPORT

CETMET
Randomised phase II study with cetuximab (Erbitux®) in combination with 5-FU and cisplatin or carboplatin versus CETuximab (Erbitux®) in combination with paclitaxel and carboplatin for treatment of patients with relapsed or METastatic squamous cell carcinoma of the head and neck.

EudraCT number:	2010-022924-57
Registration in public database:	ClinicalTrials.gov identifier NCT01830556
Investigational Product:	Cetuximab (Erbitux®)
Indication:	Relapsed or metastatic squamous cell carcinoma of the head and neck
Sponsor:	Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden
Sponsor Representative and Principal Investigator:	Signe Friesland, MD, PhD Address: Radiumhemmet, Karolinska University hospital, 171 76 Stockholm Tel: +46 8 517 725 39 Fax: +46 8 517 733 92 E-mail: signe.friesland@karolinska.se
Study initiation date (first patient first visit):	22-November-2011
Date for study closure:	06-July-2020
Date of this report:	17-June-2021 (comments added 07-October-2021) Rev TP_CJ_AZ (comments added 24-November-2021 and 09 December 2021)

The clinical study was conducted, and essential documentation archived, in compliance with the requirements of the ICH Guideline for Good Clinical Practice.

Name of Sponsor/Company: Radiumhemmet

Name of investigational product: Cetuximab (Erbitux®)

Title of study:
Randomised phase II study with cetuximab (Erbitux®) in combination with 5-FU and cisplatin or carboplatin versus CETuximab (Erbitux®) in combination with paclitaxel and carboplatin for treatment of patients with relapsed or METastatic squamous cell carcinoma of the head and neck.

Principal Investigator: Signe Friesland, MD, PhD

Study centres:
Karolinska University Hospital, Stockholm, Sweden
Sahlgrenska University Hospital, Gothenburg, Sweden
Umeå University Hospital, Umeå, Sweden
Rigshospitalet, Copenhagen, Denmark

Study period:
First patient in: 22-November-2011
Last treatment visit: 22-May-2017
Last maintenance treatment visit: 25-May-2020
Last follow-up visit: 06-July-2020

Phase of development:
Phase II

Objectives:
The primary objective was to investigate in patients with relapsed or metastatic squamous cell carcinoma of the head and neck whether progression free survival (PFS) in the arm with cetuximab and paclitaxel based chemotherapy is not markedly worse than PFS in the arm with cetuximab and 5-FU based chemotherapy.

The secondary objectives were to compare in patients with relapsed or metastatic squamous cell carcinoma of the head and neck the following study variables between the treatment arms:

- Best overall response
- Duration of response
- Time to treatment failure
- Overall survival
- Safety

Methodology:
An open-labelled randomised, controlled, multicentre phase II study.

Number of patients (planned and analysed):
Planned: 120; enrolled: 85; analysed: 85

Diagnosis
Relapsed or metastatic squamous cell carcinoma of the head and neck.

Inclusion criteria

Only patients that met all of the following inclusion criteria were eligible for the study:

- ≥18 years
- Histologically or cytologically confirmed SCCHN, relapsed and/or metastatic
- Patient must have a life expectancy of at least 3 months, allowing adequate follow-up toxicity evaluation
- Clinical examination
- 1 unidimensional lesion according to RECIST 1.1
- PS WHO 0-1 at study entry
- Adequate haematological function defined as WBC ≥ 3 x 10^9/L and platelets ≥100 x 10^9/L, ANC > 1.5 x 10^9/L and Hb > 100 g/L
- Adequate liver function; bilirubin < 1.5 x UNL, ALAT or ASAT<3.0 UNL, alkaline phosphates < 2.5 UNL
- Creatinine clearance > 50mL/min when treatment with Cisplatin
- Written informed consent must be obtained according to the local Ethics committee

Exclusion criteria:

The presence of any of the following criteria excluded the patient from participating in the study:

- >75 years
- Nasopharyngeal cancer and cancer of the paranasal sinuses
- Inability to follow the treatment and evaluation schedule
- Any other condition or therapy which in the investigator's opinion may pose a risk to the patient or interfere with the study objectives
- Pregnant or nursing females, or male or female of child-bearing potential not using adequate methods of birth-control
- Patients with active infections or any other serious underlying medical condition, which would impair the ability of the patients to receive the protocol treatment
- Known hypersensitivity to any of the components of the treatment
- Legal incapacity
- Clinically significant cardiovascular disease, e.g. cardiac failure of New York Heart Association classes III-IV, uncontrolled coronary artery disease, cardiomyopathy, uncontrolled arrhythmia, uncontrolled hypertension or history of myocardial infarction in the last 6 months.
- Patients with clinically relevant neuropathy
- Previously treated for relapsed or metastatic SCCHN, except radiotherapy for previously treated relapse if terminated > 3 months before start of treatment
- Previously treated with cetuximab, cisplatin/carboplatin, 5-FU or taxanes for locally advanced SCCHN within 3 months before study entry

Investigational product, dosage and mode of administration:

The investigational treatment (arm B) included intravenous injections of cetuximab, paclitaxel (175 mg/m^2) and carboplatin (AUC 5). The initial dose of cetuximab was 400 mg/m^2 and thereafter given as a weekly dose of 250 mg/m^2.

Duration of treatment:

The ideal cycle in each group was 21 days long and one treatment cycle consisted of dosing with chemotherapy plus cetuximab on day 1, and doses of cetuximab on days 8 and 15. Next cycle started at day 22, i.e. day 1 in cycle 2 etc. A maximum of 6 cycles was given.

Active control, dosage and mode of administration:

The control treatment (arm A) included intravenous injections of cetuximab and cisplatin (100 mg/m^2) or carboplatin (AUC 5), and 1000 mg/m^2 5-FU administered by infusion pump or gravity drip. The initial dose of cetuximab was 400 mg/m^2 and thereafter given as a weekly dose of 250 mg/m^2.

Maintenance treatment

Patients with at least stable disease after treatment with chemotherapy in combination with cetuximab could continue with maintenance cetuximab within 30 days from last given cetuximab infusion, administered at a dose of 500 mg/m^2 every second week until PD or unacceptable toxicity.

Criteria for evaluation:

The primary endpoint was progression free survival, defined as the period from randomisation until first observation of progressive disease (PD), or death due to any cause. This was assessed by magnetic resonance imaging (MRI) or computed tomography (CT) at baseline, after cycle 2, 4 and 6 and thereafter every 3rd month after start of maintenance treatment during a maximum of 2 years post randomisation, thereafter every 6 months until 3 years post randomisation, or progressive disease.

The secondary endpoints were:

- **Overall response**, was determined for patients whose best response was either complete response (CR) or partial response (PR).
- **Duration of response**, in months, was determined for patients whose best response was either CR or PR. It is was defined as the time from the first assessment of CR or PR until the date of the first occurrence of PD, or until the date of death. If a patient had not had PD, then the duration of response was censored on the date of last known tumour assessment.
- **Time to treatment failure**, was defined as the time in months from randomisation until the date of the first occurrence of one of the events defining treatment failure: PD assessed by the investigator, discontinuation of treatment due to PD or an adverse event (AE), initiation of a new anticancer treatment therapy or withdrawal of consent or death within 60 days of the last tumour assessment or randomisation.
- **Overall survival** was defined as the time from the day of randomisation to death from any cause.

The secondary endpoint of **safety and toxicity** considered the following safety variables:

- Extent of drug exposure: cetuximab, paclitaxel, cisplatin, carboplatin and 5-FU
- Incidence of AEs in terms of any:
    - AEs related to study treatment
    - Related AEs of grade 3-5 according to NCI-CTC, v. 4.0
    - Serious AEs (SAEs)
    - Related SAEs of grade 3-5 according to NCI-CTC, v. 4.0
    - AEs leading to discontinuation from all study medication
    - AEs leading to dose modification or discontinuation of any study drug of the combination therapy

Statistical methods

Patient inclusion was stopped prematurely, March 1, 2017, due to too slow an inclusion rate. The original aim was to include 120 patients in two treatment arms (1:1). The study was designed as a non-inferiority approach between the two treatment arms with the power of 80% to reject the null hypothesis and with a total number of 110 PFS events (progression or death) observed.

A simulation based on 1000 runs with four scenarios based on number of patients enrolled showed that if there is no difference between the two treatment arms regarding PFS, including 35-40 patients per group with observed PFS events in 80-90% of the patients, the hazard ratios would be between 0.6 and 1.7. Furthermore, when calculating the absolute number of the PFS events and the power for the study with 80 patients, the calculation shows that for 2x40 patients with 74 PFS events, the power would be of 67.7% to reject the null hypothesis under the assumption that the two treatments have the same efficacy in terms of PFS.

Continuous variables were to be summarised using descriptive statistics, i.e. number of patients (N), mean, median, standard deviation (Stdv), standard error of the mean (SEM), minimum, and maximum. Qualitative variables were to be summarised by means of counts and percentages. Reasons for discontinuation were to be displayed for the safety population together with the number of patients still on treatment and/or alive at the time of data cut-off.

Summary - Conclusions

Patient Demography and Disposition:

Baseline characteristics including age, gender, Tumour Node Metastasis (TNM) staging at initial diagnosis, localisation, Human Papilloma Virus (HPV) status, smoking status and performance status (PS) were well balanced between the two treatment arms. The median age for the whole study population was 60.9 years, with a male predominance (69.4%). The vast majority of the study population had non-hypopharyngeal tumours which were HPV-negative).

In total, 23 (54.8%) patients received cisplatin, 17 (40.5%) patients received carboplatin and 2 (4.7%) patients did not receive any treatment. A total of 14 patients in arm A (33%) vs. 26 patients in arm B (61%) received all 6 planned cycles of chemotherapy. All patients had received radiotherapy as a part of their primary treatment. All radiotherapy treated patients had received doses ≥65 + Gy (the vast majority 68 Gy) and a few patients had received neoadjuvant treatment. Six patients (14%) in arm A and three patients (6.7%) in arm B had received concomitant radiotherapy with cetuximab, whereas 18 patients (40%) in arm A and 15 patients (33.3%) in arm B had received concomitant radiotherapy with cisplatin ($p = 0.53$).

Efficacy results:
Efficacy analysis was performed on the intention-to-treat population considering the patients as randomised (arm A: n=42; arm B: n=43).

Median time to PFS was 4.32 months for arm A, and 6.48 months for arm B (5.7 months for both arms). Median PFS in arm A was 4.37 months (95% CI: 2.9–5.9 m) and 6.5 months (95% CI: 4.8–8.2 m) in arm B, (p = 0.064, non-stratified log rank test). PFS HR for arm B was 0.65 (95% CI: 0.41–1.03), therefore not significantly worse than arm A and showing a trend in favour of arm B.

Best overall response was similar in both arms (20 vs. 22 patients). However, there were proportionally more patients with a complete response (CR) in arm B vs. arm A: 7 vs. 2 patients, and less with partial response (PR): 13 vs. 20, resulting in a statistically significant difference between the 2 arms (p = 0.041).

Median duration of response for arm A was 6.44 months (95% CI: 4.38–8.51) and 7.37 months (95% CI: 4.84–9.89) for arm B, HR = 0.51 (95% CI: 0.25–1.06)

Median Time to Treatment Failure (TTF) for arm A was 3.95 months (95% CI: 1.92–5.96), whereas for arm B it was 5.87 months (95% CI: 3.02–8.69). TTF was longer for arm B, HR = 0.63 (95% CI: 0.40–0.99), p=0.046.

Median overall survival (OS) was 8.4 months (95% CI: 5.3–11.5 m) in arm A and 10.2 months (95% CI: 5.4–15 m) in arm B, (HR = 0.71; 95% CI: 0.43–1.16).

Safety results:

The safety population included all patients who received at least one dose of study medication (arm A: n=40; arm B: n=42). In addition to the 2 patients who received no treatment, one enrolled patient was excluded for not meeting inclusion criteria and was never treated in the study.

Adverse events:
A total number of 76 patients reported 535 adverse events (AEs) during the study period starting at the day of randomisation. 188 of these events were assessed as being possibly related or related to the chemotherapy treatment while 171 were considered possibly related or related to the cetuximab treatment.

In total there were 97 Serious Adverse Events (SAEs) reported in 56 patients. Twenty SAEs were assessed as being possibly related or related to cetuximab. Patients in arm A receiving cisplatin/carboplatin and 5-FU reported 12 SAEs possibly related to 5-FU, of which 4 were also possibly related to the cisplatin/carboplatin treatment. All 10 SAEs related to the cisplatin treatment were also related or possibly related to 5-FU. Patients in arm B, treated with carboplatin and paclitaxel reported 6 SAEs possibly related to and 5 related to the carboplatin and paclitaxel treatment. The most frequently affected system organ classes were gastrointestinal disorders followed by infections and respiratory and thoracic disorders. However, none of the respiratory disorders reported as SAEs were related to the treatment.

There were 12 fatal SAEs. One of 12 fatal SAEs was characterized as SUSAR, related to cetuximab and chemotherapy (patient 504). There were two further fatal SAEs (patients 106 and 107) which were initially assessed as SUSARs. Due to follow-up information providing the reason for death in these two fatal patients, the fatal SAEs were assessed as not related to either cetuximab or chemotherapy. Therefore, these two fatal SAEs were no longer considered SUSARs.

Overall conclusion:
The combination of cetuximab and paclitaxel/carboplatin may have similar efficacy and less toxicity compared to cetuximab and 5-FU/cisplatin or carboplatin, rendering it a favourable treatment option for the first-line treatment of RM-SCCHN. This less toxic treatment should be tested along with immunotherapy in future trials, in order to offer a broader subset of patients a chance for treatment completion and durable response. The results of our trial should be validated in a larger randomised phase 3 trial.

Date of report: 17-June-2021