2. S123 Synopsis

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Clinical Study Report Synopsis: Study H3E-MC-S123

Title of Study: A Phase 2 Study of Pemetrexed in Combination with Cisplatin and Cetuximab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck	
Number of Investigator(s): This multicenter study included 12 principal investigators.	
Study Center(s): This study was conducted at 12 study centers in 5 European countries.	
Publication(s) Based on the Study: There are no publications based on this study at this time.	
Length of Study: 720 days Date of first patient enrolled: 03 March 2010 Date of last patient visit: One patient remains on study (data cutoff was April 18, 2012)	**Phase of Development:** 2

Objectives: The primary objective of this study was to estimate progression-free survival (PFS) for the combination of pemetrexed plus cisplatin and cetuximab followed by optional pemetrexed plus cetuximab maintenance therapy.

Secondary objectives of the study were:

- to estimate overall survival (OS)
- to estimate the overall objective response rates (ORR) according to the Response Evaluation Criteria in Solid Tumors, version 1 (RECIST; Therasse et al. 2000)
- to examine the safety and toxicity profile of study treatment
- to assess health status using the patient-reported European Quality of Life -5 Dimension questionnaire (EQ-5D) and the physician-assessed performance status scale for head and neck cancer (PSS-HNC)
- to assess biomarkers relevant to the safety, efficacy, and mechanism of action of pemetrexed, cetuximab, and cisplatin
- to assess the association between biomarkers and clinical outcome

Study Design: This was an open-label, single-arm, multicenter, Phase 2 study evaluating pemetrexed and cisplatin plus cetuximab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN), who had not received more than 1 prior systemic therapy for locally advanced disease and no prior systemic therapy for metastatic disease. Patients were to receive up to a maximum of 6 cycles of triplet therapy. After a minimum of 4 cycles of triplet therapy, patients had the option to receive maintenance therapy with pemetrexed plus cetuximab. During maintenance therapy, at the discretion of the investigator, either pemetrexed or cetuximab monotherapy was given if the other drug was discontinued due to any toxicity.

Maintenance therapy ended when the patient met 1 of the following prespecified reasons for discontinuation:

- patient had evidence of disease progression
- patient had an unacceptable toxicity
- other withdrawal criteria had been met

Number of Patients: The study was planned to enroll 65 patients; 73 patients entered the trial and signed informed consent.

Treated: 66 patients received at least 1 dose of triplet therapy; 27 received at least 1 dose of maintenance therapy.

Completed: There is still 1 patient receiving treatment with pemetrexed and cetuximab as of the data cut-off date of 18 April 2012.

Diagnosis and Main Criteria for Inclusion: Patients who were at least 18 years of age or older, with a histologic diagnosis of SCCHN, that was either recurrent and/or metastatic, and not amenable to local therapy, were eligible for this study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and measurable or nonmeasurable disease defined by RECIST criteria, version 1 (Therasse et al. 2000). Patients could have no more than 1 prior systemic therapy, as part of multimodal treatment for locally advanced disease (induction chemotherapy and subsequent concurrent chemoradiation were considered as 1 regimen), OR no prior systemic therapy for metastatic disease. Patients had to have a life expectancy ≥12 weeks.

Dose, and Mode of Administration: Triplet Combination Treatment: Pemetrexed 500 mg/m^2 intravenous (iv) on Day 1, and Cisplatin 75 mg/m^2 iv Day 1, both given every 21 days; plus cetuximab given at a loading dose of 400 mg/m^2 initially and then as 250 mg/m^2 iv weekly for a maximum of 6 cycles. Folic acid 350 to 1000 µg was taken orally starting approximately 7 days preceding the first dose of pemetrexed and continuing daily. Vitamin B_{12} 1000 µg intramuscular injection was given the week preceding the first dose of pemetrexed and every 9 weeks thereafter. Dexamethasone (or equivalent) 4 mg, was taken orally twice per day (BID) on the day before, the day of, and the day after each dose of cetuximab and pemetrexed. An antihistamine of 50 mg was given iv within 1 hour before each dose of cetuximab. Ciprofloxacin 500 mg BID or equivalent was given to prevent infection. Optional maintenance therapy with pemetrexed 500 mg/m^2 iv every 21 days and cetuximab 250 mg/m^2 weekly was permitted after at least 4 cycles of triplet therapy were received.
There was a safety lead-in cohort consisting of the first 12 patients and a second safety lead-in consisting of 35 patients in this study who were dosed in accordance with the study treatment listed above.

Duration of Treatment: Patients were scheduled to receive up to 6 cycles of pemetrexed, cisplatin, and cetuximab therapy and could optionally continue into maintenance therapy.
Maintenance Therapy: Patients who completed at least 4 cycles of triplet combination treatment could continue to receive pemetrexed plus cetuximab in the maintenance setting, or either as monotherapy, in the absence of progressive disease (PD), unacceptable toxicity, or any other withdrawal criterion.

Variables:
Efficacy: PFS was assessed from the date of first dose of study drug (any dose of pemetrexed, cisplatin or cetuximab) to the date of first documented objective PD or death from any cause. Patients not known to have died or to have objective PD as of the data inclusion cutoff date were censored at the date of the last objective progression-free disease assessment. OS was assessed from the date of first dose of study drug (which was any dose of pemetrexed, cisplatin or cetuximab) to the first date of documented objective PD or death from any cause. OS duration was censored at the date of the patient's last contact prior to the cutoff date. ORR was based on the patient's best response of CR or PR, according to RECIST criteria, version 1 (Therasse et al. 2000).
Safety: All adverse events (AEs) were graded at each visit (until at least 30 days after discontinuation of study therapy) using Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0.
Translational Research: Translational research analyses were performed on relevant biomarkers to correlate them with clinical outcome and will be reported in an addendum to this study report.
Health Outcomes: Assessment of patient responses to the PSS-HNC was collected at baseline and each visit during triplet treatment and every other visit in the maintenance setting. EQ-5D was summarized at baseline, at either the point of disease progression or the final visit in the triplet phase, and either at disease progression or the end of maintenance phase for each of the 5 dimensions.

Methods:

Efficacy: The primary outcome measure in this Phase 2 study was PFS. This was estimated by the Kaplan-Meier technique (Kaplan and Meier 1958) used to assess PFS. Quartiles, PFS rates at appropriate time points, and corresponding 95% confidence intervals (CIs) were calculated. Additional efficacy and health-outcome analyses included the following:

- Kaplan-Meier techniques to assess OS. Quartiles and survival rates at appropriate time points, and corresponding 95% CIs, were calculated.
- ORR was summarized, and a 2-sided alpha and 95% CI were computed. Tumor response was rated according to RECIST criteria, version 1 (Therasse et al. 2000). The number and percentage of patients with each type of response (complete response, partial response, stable disease, PD, or unknown) were reported.

Safety: Safety analyses were performed for all patients who received at least 1 dose of any study drug. Safety analyses included the following:

- summaries of exposure to study drugs
- serious adverse events (SAEs)
- treatment-emergent adverse events (TEAEs)
- discontinuations due to SAEs, deaths, and maximum CTCAE grades for laboratory and nonlaboratory toxicities
- Summaries for treatment-related events (as reported by the investigator) and all events regardless of relationship to study treatment

Health Outcomes: PSS-HNC and EQ-5D findings were summarized for all treated patients at baseline; at each applicable cycle of treatment during triplet therapy for eligible patients; at each applicable cycle of treatment during the maintenance phase; and at applicable study postdiscontinuation visits. For the EQ-5D, responses for the 3 levels of the 5 dimensions were summarized. Mean EQ-5D utility scores were calculated. For the PSS-HNC, frequency distributions, including measures of central tendency and variability, were calculated for individual items and for the total scale. The changes from baseline in EQ-5D (EQ-5D index score and visual analog scale [VAS] score) and PSS-HNC scores were analyzed using a 1-sample t-test and are summarized by visit.

Bioanalytical: The distribution of biomarkers with continuous measures, such as gene expression, will be described for the total population in a separate pharmacogenomics addendum to the study report. Summary statistics include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as IHC-staining-assessed protein expression or genotype locus, will be summarized in frequency tables for the total population.

Summary:

Patients in this study were required to have a relatively good ECOG performance status of 0 or 1 (19 patients with PS of 0; 47 patients with PS of 1). The majority of patients were male (n=53; 80.3%) and had a diagnostic category of oropharyngeal carcinoma (n=30). The study consisted of 4 to 6 cycles of triplet therapy followed by optional maintenance therapy with pemetrexed and cetuximab or monotherapy with either drug if toxicity occurred. Maintenance therapy was initiated only after 4 cycles of triplet therapy were completed, and there was no evidence of PD. Twenty-seven patients received the optional maintenance therapy. All 66 (100%) patients completed at least 1 cycle of triplet treatment and were therefore qualified for efficacy and safety analyses.

The study was well conducted and had a total of 3 protocol amendments. The last of these amendments, protocol amendment (c), was implemented due to a high number of infection-related AEs and deaths. This amendment added a requirement for an antibiotic (ciprofloxacin or equivalent) in order to prevent the infections noted by the Safety Assessment Committee in March 2011. The infection-related AEs and deaths were reviewed by the Safety Assessment Committee, and measures were implemented at all sites.

Efficacy:

Given the cytostatic activity of pemetrexed and the efficacy of cetuximab and cisplatin in SCCHN, PFS was chosen as the primary endpoint. Median PFS in the All Treated Patients (ATP) in this study was 4.4 months (range, 3.6, 5.4). This rate falls short of the median PFS of 5.6 months reported with cisplatin, 5-fluorauracil, and cetuximab observed by Vermorken and colleagues (2008). The PFS of 5.6 months reported by Vermorken et al. was chosen as the comparative rate for PFS for this study. Cisplatin, 5-fluorauracil, and cetuximab are the current standard treatment for recurrent and/or metastatic SCCHN. The sensitivity analysis of PFS without censoring for post-discontinuation therapy showed similar results to PFS with censoring in the ATP.

Median OS in this study was 9.7 months (95% CI: 6.5, 13.1), slightly shorter than the median OS of 10.1 months (95% CI: 0.64, 0.99) observed in the study by Vermorken and colleagues (2008). However, PFS and OS results observed in this study were longer than those observed in a study by Urba et al. (2012), wherein patients who received cisplatin and pemetrexed for up to 6 cycles, had median PFS of 3.6 months and median OS of 7.3 months.

Exploratory analyses were performed for several subgroups for PFS and OS: age (years) <50 versus ≥50 and for age (years) <65 and ≥65, male versus female, ECOG PS, diagnostic category, and patients who received maintenance therapy versus those who did not receive maintenance therapy.

PFS was not significantly different for the 2 age groups analyzed (<50 and ≥50, p = .57; <65 and≥65, p = .78), and for ECOG PS (p = .61) and gender (p = .07). OS for the 2 age groups was also not significantly different (<50 and ≥50, p = .94; <65 and ≥65, p = .91), and for ECOG PS (p = .93) and gender (p = .84).

Regarding diagnostic category, the exploratory analysis showed that patients with larynx tumors (n=16) had a slightly longer median PFS compared to patients with non-larynx tumors (n=50), (5.2 versus 4.2 months) and significantly longer median OS (20.8 versus 8.5 months). However, this may be explained by the fact that more patients with larynx tumors received postdiscontinuation therapy compared with non-larynx tumor patients (81% versus 46%).

Patients who did receive maintenance (n=27) had a median PFS of 6.2 months (95% CI: 5.5, 8.7). Patients who didn't receive maintenance (n=39) had a median PFS of 2.6 months (95% CI: 1.5, 3.1). OS in the maintenance setting was 15.0 months for the 27 patients who received maintenance and 5.9 months for those who didn't receive maintenance (n=39).

The ORR in this study was 29%. One patient achieved a complete response (1.7%), 16 patients had partial responses (27.6%), 23 patients had stable disease (39.7%), 12 had PD (20.7%), and 6 patients had an unknown status (10.3%).

The majority of patients in this study reported no problems with mobility, self-care, usual activities, and anxiety/depression at baseline. The exception to this was pain/discomfort, with 59.1% of patients reporting moderate or extreme problems. Conclusions cannot be drawn from the EQ-5D and the PSS-HNC questionnaires due to compliance with completion at the chosen cycles.

Safety:

Infection-Related Events

Eight patients (12.1%) died due to AEs while on study. Three patients (4.5%) died due to other AEs that were not considered treatment related, and 5 patients (7.5%) died due to treatment-related events (1 death unknown, 1 respiratory failure and septic shock, 1 aspiration pneumonia leading to respiratory failure; 1 sepsis, respiratory failure and tumor emboli; 1 aspiration and respiratory failure). This is higher than the 3% reported both in the standard treatment of cisplatin, 5-fluorouracil, and cetuximab (Vermorken et al. 2008), and in treatment with cisplatin and pemetrexed (Urba et al. 2012). Complications from infection were the most common reason for death (7.6%). Five of 8 deaths occurred at 1 site that enrolled 7 patients. In individual cases at this site, well-known risk factors that are often seen in SCCHN might have played a role in the ultimate death of these patients.

Adverse Events Related to Study-Drug(s)
Grade 3/4 neutropenia was reported in 22 patients (33.4%), and grade 3/4 leukopenia occurred in 23 patients (34.8%). Grade 3/4 anemia was reported in 6 patients (9.1%) and anemia (all grades) occurred in 27 patients (40.9%); 33.3% of these patients required red blood cell transfusions. Anemia is a common side effect of pemetrexed and cisplatin combination therapy. Grade 3/4 hypomagnesemia, a common side effect of cetuximab, was reported in 7 patients (10.6%).
Grade 3-4 fatigue was the most common nonlaboratory CTCAE, reported in 16 patients (24.2%). Grade 3/4 anorexia was reported in 8 patients (12.1%).
Anemia was also the most commonly reported SAE possibly related to study drug, in 4 patients (6.1%). Serious adverse events were also reported in patients with febrile neutropenia, as well as neutropenia, pneumonia, and leukopenia in 3 patients each (4.5%).
Fatigue was the most commonly reported TEAE in 40 patients (60.6%), as well as neutropenia in 26 patients (39.4%), leukopenia in 25 patients (37.9%), and anemia in 24 patients (36.4%).

Conclusions:
The combination of pemetrexed, cisplatin, and cetuximab had modest activity with a median PFS of 4.4 months. This study did not meet the prespecified goal of a median PFS of 5.5 months. Median OS was 9.7 months.
A high number of deaths was observed (n=8; 12.1%). Five of 8 patients who died had active infection.
Most toxicities reported were Grade 1 or 2; however, there were drug-related Grade 3 and 4 leukopenia (34.8%), neutropenia (33.4%), and hypomagnesemia (10.6%).
The majority of patients in this study reported no problems with mobility, self-care, usual activities, and anxiety/depression at baseline. The exception to this was pain/discomfort, with 59.1% of patients reporting moderate or extreme problems. The EQ-5D utility score was 0.76 on a scale of -0.594 to 1.000, and the VAS rating was 70 on a scale of 0 to 100 which indicated relatively good quality of life in patients at baseline. Missing data was an issue for the EQ-5D interpretation.
Missing data was also an issue for the physician-reported PSS-HNC. Scores at baseline were all above the median of 50 for all 3 categories, and scores at Cycle 4 were similar, but there were 25 missing assessments in Cycle 4. At Cycle 6, there were 42 missing assessments, and therefore no conclusions can be drawn from this data.