SYNOPSIS

Title of the study: Phase 3 randomized trial of concomitant radiation, cisplatin, and tirapazamine (SR259075) versus concomitant radiation and cisplatin in patients with advanced head and neck cancer

Investigator(s): [redacted]

Study center(s): Europe, North America, South America, Asia, Australia, New Zealand, and South Africa

Publications (reference): Not applicable.

Study period:
Date first patient enrolled: 21 April 2005
Date last patient/last visit: 16 January 2008

Phase of development: 3

Objectives:
***Primary*:** Overall Survival (OS).
Secondary:
- Failure-free survival (FFS).
- Time to locoregional failure (LRF)
- Patterns of failure.
- Toxicity and safety
- Initial response rates
- Final complete response (CR) rate.
- Change in quality of life (QoL)
- Percent of patients who were feeding tube dependant 12 months after completion of therapy
- Pharmacokinetic/Pharmacodynamic (PK/PD) and tissue sample analyses.

Substudies
- Analysis of hypoxia biological marker

Methodology: Phase 3, multicenter, international, randomized, open-label, 2-arm trial in advanced head and neck cancer.

Number of patients: Planned: 550; Randomized: 317; Treated: 314 (3 patients were randomized but never received study drug)
Evaluated: Efficacy: 317 patients in the ITT popoulation were evaluable for efficacy endpoints of OS, FFS, LRF, and CR.
Safety: 314
Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion: Patients with Stage 3 or Stage 4 (excluding T1N1, T2N1 and metastatic disease) previously untreated squamous cell carcinoma of head & neck (H & N), ECOG performance status ≤2 and adequate renal, hepatic, and hematologic function.

Investigational product: Tirapazamine
Dose: Tirapazamine (290 mg/m^2, two-hour infusion), followed after 1 hour by cisplatin (75 mg/m^2, 1-hour infusion) immediately before radiation therapy on Day 1 of Weeks 1, 4, and 7 of radiotherapy. Tirapazamine (160 mg/m^2, two-hour infusion) on Days 1, 3, and 5 of Weeks 2 and 3 of radiotherapy.
Administration: Intravenous (IV) over 1 or 2 hours
Batch number(s): [redacted]

Duration of treatment: Inclusion and treatment planning up to 1 month, 7 weeks of treatment, minimum 2 months of follow up.
Duration of observation: Until locoregional disease progression, death, or study-cutoff date, whichever occurred first. QoL was followed for 3 years after completion of therapy or study cutoff date. All patients to be followed for survival, radiation toxicity, and further therapy until death or study cutoff date.

Reference therapy: Cisplatin
Dose: Cisplatin (100 mg/m^2, 1-hour infusion) immediately before radiation therapy on Day 1 of Weeks 1, 4, and 7 of radiotherapy.
Administration: Intravenous (IV)
Batch number(s): Commercially available

Criteria for evaluation: The current report is an abbreviated report and as such, only the safety results are being presented in full. The following safety criteria were evaluated and analyzed using descriptive statistics: adverse events (AEs), routine symptom assessment, and laboratory determinations.
Pharmacokinetics: Not applicable

Pharmacokinetic sampling times and bioanalytical methods: Not applicable

Statistical methods: A sample size of 275 patients per treatment arm was needed to provide at lease 80% power. The cutoff date for the final analysis of survival was planned to be the date of the 233rd death. The final survival cutoff was expected to occur approximately 2.5 years after the end of accrual. For FFS, the final analysis was to have a cutoff equal to the date of the 217th failure. The final FFS analysis was expected to take place approximately 1 year after the last patient was accrued.

A Cox proportional hazards model with covariates of nodal stage (N0 versus N1-3), hemoglobin (≥13,5 g/dL for men and ≥12.5 g/dL for women versus otherwise); radiation technique (standard/3D conformal versus IMRT planning), and ECOG performance status (0 versus 1,2) was planned to compare the treatment arms for the time related endpoints, OS, FFS, and time to locoregional failure. Categorical parameters such as response rate were to be evaluated using the chi-squared test.

Characteristics of subjects assigned to the 2 treatment arms were to be summarized. These were to include sex, race, age, weight, height, performance status, histology, stage of disease, measurable disease, time since diagnosis, and presence of other disease conditions. The incidence of adverse events and laboratory tests was to be summarized by type of event and toxicity grade.

With early termination of the study for safety concerns and consideration of the efficacy results of EFC4690, efficacy analyses were not done for this study.

Summary: This Phase 3 study enrolled a total of 317 patients; 159 in the control arm (cisplatin) and 158 in the test arm (tirapazamine). Among them, 3 patients did not receive any study drug. The median age was 57 years in the control arm and 56 years in the test arm. The male to female ratio was 270:47 (85.2% male, 14.8% female); 86.8% of the patients were Caucasian, 2.25% Black, and 7.3% Asian.
Efficacy results: The early termination of the study does not allow meaningful analysis of efficacy.

Safety results: Nearly all patients on study experienced an AE; 157 (98.7%) in the control arm and 150 (96.8%) in the tirapazamine arm. There was a higher incidence of serious adverse events (SAEs) in the tirapazamine arm (58.1%) than in the control arm (51.6%), however the number of patients who were withdrawn from study treatment due to AEs was comparable (22 patients in the control arm and 25 patients in the tirapazamine arm); the most common AEs leading to study treatment discontinuation in the tirapazamine arm were muscle spasms, diarrhea, nausea, vomiting, and weight decrease. There were 3 deaths in the control arm and 12 deaths in the tirapazamine arm occurring within 30 days of the last treatment.

Pharmacokinetic results: Not applicable.

Conclusions: [redacted]

Date of report: 24-Nov-2008