2. S111 Synopsis

Clinical Study Report Synopsis: Study H3E-CR-S111

Title of Study: Pemetrexed with Simplified Folate and Dexamethasone Supplementation versus Pemetrexed with Standard Supplementation as Second-Line Chemotherapy for Patients with Non-Squamous Non-Small Cell Lung Cancer	
Number of Investigators: This multicenter study included 14 principal investigators.	
Study Centers: This study was conducted at 14 study centers in 4 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date first patient enrolled: 22 February 2008 Date last patient completed: 09 June 2010	**Phase of Development:** 2

Objectives:

Primary objective:

The primary objective of the study was based on comparing the proportion of patients who experienced any drug-related Grade 3 or 4 toxicity on a simplified vitamin and steroid schedule plus pemetrexed versus the standard vitamin and steroid schedule plus pemetrexed in patients with advanced non-squamous non-small cell lung cancer (NSCLC) who had been previously treated with chemotherapy. The intent of the study was to demonstrate noninferiority of the simplified supplementation regimen compared with the standard supplementation regimen.

Secondary objectives:

The secondary objectives of the study were as follows:

- to compare the following time-to-event variables between patients receiving the 2 vitamin/steroid schedules:
  - time to first drug-related Grade 3/4 toxicity
  - time to first treatment-emergent Grade 3/4 toxicity
  - time to first drug-related Grade 3/4 hematologic toxicity
  - time to first treatment-emergent Grade 3/4 hematologic toxicity
  - time to first drug-related Grade 3/4 nonhematologic toxicity
  - time to first treatment-emergent Grade 3/4 nonhematologic toxicity
  - time to first appearance of treatment-emergent Grade 3/4 rash
- to compare the tumor response rate between the patients receiving a simplified vitamin and steroid schedule plus pemetrexed and those receiving the standard vitamin and steroid schedule plus pemetrexed
- to compare overall survival (OS) and progression-free survival (PFS) between the patients receiving a simplified vitamin and steroid schedule plus pemetrexed and those receiving the standard vitamin and steroid schedule plus pemetrexed
- to assess the relationship between patient toxicity and possible predictors (i.e., folate status, type of first-line chemotherapy received, response to first-line chemotherapy).

Approval Date: 09-Jun-2011 GMT

Study Design:
Study H3E-CR-S111 was a multicenter, randomized, parallel-arm, open-label, Phase 2 study in patients with advanced non-squamous NSCLC who had been previously treated with chemotherapy. A total of 110 patients were to be enrolled into the study per protocol and randomly assigned (1:1) to one of 2 treatment arms: the standard vitamin and steroid schedule plus pemetrexed arm or the simplified vitamin and steroid schedule plus pemetrexed arm. Details regarding the vitamin and steroid schedules can be found in the study drug/comparator, dose, and mode of administration sections below.

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0 or 1 versus 2) and country. Study therapy continued up to a maximum of 6 pemetrexed cycles or until disease progression, unacceptable toxicity, or any other protocol-specified reasons for study therapy discontinuation. Patients were followed for survival for 12 months and for tumor response until disease progression or the start of a new anticancer therapy.

Number of Patients:
Planned per protocol: 110
Randomized: 112 (57 simplified supplementation, 55 standard supplementation)
Treated (at least 1 dose): 111 (57 simplified supplementation, 54 standard supplementation)
Completed study treatment (6 cycles): 35 (17 simplified supplementation, 18 standard supplementation)

Diagnosis and Main Criteria for Inclusion:
Eligible patients were men or women, at least 18 years of age, who had a histologic or cytologic diagnosis of NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB, or IV), as defined by the American Joint Committee on Cancer Staging Criteria for NSCLC. NSCLC patients with predominantly squamous histology could have been eligible for enrollment into the study prior to implementation of protocol amendment S111(a), which subsequently restricted enrollment to patients with non-squamous histology; however, patients with squamous histology were not included in the primary analysis population. Patients must have failed only 1 prior chemotherapy regimen and must have been considered to be eligible for further chemotherapy. Other inclusion criteria included: the presence of measurable disease at baseline, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST); an ECOG performance status of 0 to 2; an estimated life expectancy of at least 8 weeks; and adequate organ function (as defined in the protocol). Prior radiation therapy or surgery must have been completed at least 2 weeks (4 weeks for surgery) prior to randomization. The complete list of inclusion and exclusion criteria can be found in the protocol.

Study Drug, Dose, and Mode of Administration:
The simplified vitamin and steroid supplementation schedule included the following:

- oral folic acid supplement (350 to 1000 μg/day) the day before and the day of the first dose of pemetrexed, then daily throughout pemetrexed treatment until 3 weeks after the last dose of pemetrexed
- dexamethasone 4 mg orally (or equivalent) twice daily on the day of pemetrexed administration
- pemetrexed 500 mg/m^2 intravenous infusion on Day 1 of each 21-day cycle
- standard vitamin B_{12} supplementation

Comparator, Dose, and Mode of Administration:
The standard vitamin and steroid supplementation schedule included the following:

- oral folic acid supplement (350 to 1000 μg/day) on at least 5 days during the 7-day period before the first dose of pemetrexed, then daily throughout pemetrexed treatment until 3 weeks after the last dose of pemetrexed
- dexamethasone 4 mg orally (or equivalent) twice daily, the day before, the day of, and the day after pemetrexed administration
- pemetrexed 500 mg/m^2 intravenous infusion on Day 1 of each 21-day cycle
- standard vitamin B_{12} supplementation

Duration of Treatment: Patients in both arms received up to 6 cycles of pemetrexed treatment. A cycle was defined as an interval of 21 days.

Variables:
The primary endpoint (safety) was the proportion of patients who experienced any drug-related Grade 3 or Grade 4 toxicity event while on study treatment. Secondary safety endpoints were time-to-events of Grade 3/4 toxicities (including hematologic toxicities, nonhematologic toxicities, rash, and overall). Secondary efficacy endpoints were tumor response rate, OS, and PFS.

Additional safety endpoints included the incidence of adverse events (AEs) (including serious adverse events [SAEs]), study drug discontinuation due to AEs, hospitalizations and transfusions, use of key concomitant medications and growth factors, number of treatment cycles, and dose intensity per cycle.

Statistical Evaluation Methods:
Analysis populations: The Q-ITT analysis population, which included all randomized patients with non-squamous histology who complied with their pretreatment folic acid and steroid supplementation schedule and received at least 1 dose of pemetrexed, was used for all primary and secondary analyses, with the exception of tumor response rate, which used the qualified intention-to-treat tumor analyzable (Q-ITT-TA) population. The safety population consisted of all patients who received at least 1 dose of pemetrexed.
Primary and Secondary Analyses: The study was designed as a noninferiority study with the primary analysis that noninferiority in the toxicity rate in the simplified supplementation arm compared with the standard supplementation would be demonstrated if the upper limit of the observed 95% confidence interval (CI) for the absolute difference between the simplified and standard supplementation groups in the proportion of patients experiencing a drug-related grade 3 or 4 toxicity was less than 14%. The sample size was calculated for there to be 72% power for demonstrating noninferiority if there was no difference in the proportion of patients experiencing a drug-related grade 3 or 4 toxicity; specifically, 12% for both the simplified and standard supplementation groups. However, the planned sample size in the protocol was incorrectly calculated as 110 patients, with 55 patients per supplementation group, corresponding to a power of just over 50%. This was not detected until after enrollment had been completed; therefore, the study had less power than planned for evaluation of the primary endpoint.
The time-to-event endpoints were analyzed using Kaplan-Meier techniques and a Cox proportional hazards model both unadjusted and adjusted for selected prognostic variables. The tumor response rate was defined as the number of patients with a documented complete response or partial response divided by the number of patients in the Q-ITT-TA population.
Additional Safety Analyses: In addition to summarizing AEs by system organ class and preferred term, AEs were graded and summarized using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The incidence of AEs was compared between the 2 treatment groups.

Summary:
A total of 116 patients entered the study; of these, 112 were randomized to receive either pemetrexed plus a simplified vitamin and steroid regimen (n=57) or pemetrexed plus a standard vitamin and steroid regimen (n=55). The baseline characteristics were balanced between the treatment arms. In the Q-ITT population, the median age was 61.8 years, and a majority of patients were male (61.2%) and Caucasian (70.4%). Most patients in both supplementation groups had non-squamous histology, with adenocarcinoma being the predominant pathological diagnosis (78.7% and 84.3% in the simplified supplementation and standard supplementation groups, respectively). Nearly all patients had an ECOG performance status of 0 or 1, while 2 patients in the simplified supplementation arm had an ECOG performance status of 2.

One randomized patient did not receive study treatment; therefore, the safety population included 111 patients. A total of 98 patients (47 in the simplified supplementation arm and 51 in the standard supplementation arm) were included in the Q-ITT and the Q-ITT-TA analysis populations.

Across both treatment arms, a similar proportion of patients in the Q-ITT population completed all 6 cycles of study treatment (36.2% and 35.3% in the simplified supplementation and standard supplementation arms, respectively).

The primary reason for premature discontinuation of treatment in both the simplified supplementation and standard supplementation arms was inadequate response (44.7% and 41.2%, respectively). The definition of inadequate response was prespecified in the protocol and included evidence of progressive disease or the patient, for any reason, required another tumor treatment.

For the primary endpoint, the proportion of patients with drug-related Grade 3/4 toxicity was 38.3% (95% CI: 24.5 to 53.6) in the simplified supplementation group and 29.4% (95% CI: 17.5 to 43.8) in the standard supplementation group. The difference in the percentage of patients with drug-related Grade 3/4 toxicity for the simplified supplementation arm versus the standard supplementation arm was 9% (95% CI: -10 to 28). A higher proportion of drug-related toxicities were observed in the simplified supplementation group compared with the standard supplementation group, with the upper end of the 95% CI exceeding the predefined threshold of 14%. Consequently, the simplified supplementation group did not show a similar or noninferior toxicity profile compared with the standard supplementation group.

The median time to drug-related Grade 3/4 toxicity was 3.7 months for the simplified supplementation group and was not calculable for the standard supplementation group (Table S311.2.1). The hazard ratio (HR) for the time to drug-related Grade 3/4 toxicity was 1.63 (95% CI: 0.80 to 3.33), suggesting an increased risk of drug-related Grade 3/4 toxicity in the simplified supplementation group. Additional time-to-event analyses are summarized in Table S311.2.1. Only 1 patient had an event of Grade 3 or Grade 4 rash; therefore, an analysis for the time to first appearance of Grade 3/4 rash was not applicable.

Table S311.2.1. Summary Table for Primary and Secondary Toxicity Endpoints (Q-ITT Population)

	Proportion (%) and 95% CI		
Parameter	**Simplified Supplementation Arm (N=47)**	**Standard Supplementation Arm (N=51)**	**Difference[a] (%), 2-sided 95% CI**
Drug-related Grade 3/4 toxicity	38.3 (24.5, 53.6)	29.4 (17.5, 43.8)	9 (-10, 28)
	Median (range) in months		
Parameter	**Simplified Supplementation Arm (N=47)**	**Standard Supplementation Arm (N=51)**	**HR[a,b], 2-sided 95% CI**
Time to drug-related Grade 3/4 toxicity	3.7 (0.2, 5.2)	NC (0.2, 5.8)	1.63 (0.80, 3.33)
Time to treatment-emergent Grade 3/4 toxicity	3.0 (0.1, 5.2)	1.8 (0.2, 5.8)	0.99 (0.58, 1.70)
Time to drug-related Grade 3/4 hematological toxicity	NC (0.2, 5.6)	NC (0.2, 5.8)	1.54 (0.70, 3.39)
Time to treatment-emergent Grade 3/4 hematological toxicity	NC (0.2, 5.6)	NC (0.2, 5.8)	1.47 (0.72, 2.98)
Time to drug-related Grade 3/4 nonhematological toxicity	NC (0.3, 5.6)	NC (0.3, 5.8)	1.98 (0.66, 5.92)
Time to treatment-emergent Grade 3/4 nonhematological toxicity	3.7 (0.1, 5.2)	3.5 (0.3, 5.8)	0.96 (0.52, 1.78)

Abbreviations: CI = confidence interval; HR = hazard ratio; NC = not calculable; Q-ITT = qualified intention-to-treat.

[a] Simplified supplementation versus standard supplementation.

[b] Unadjusted.

Source: Table S111.11.8.1, Table S111.11.9.1, Table S111.11.10.1, Table S111.11.10.2, Table S111.11.10.3, Table S111.11.10.4, Table S111.11.10.5, Table S111.11.10.6, Table S111.11.11.1, Table S111.11.12.1, Table S111.11.13.1, Table S111.11.14.1, Table S111.11.15.1, Table S111.11.16.1.

The tumor response rate was 6.4% (95% CI: 1.3 to 17.5) and 11.8% (95% CI: 4.4 to 23.9) in the simplified and standard supplementation groups, respectively. No patient had a complete response; all responses were partial responses. The proportion of patients with a best overall response of stable disease was 38.3% and 37.3% in the simplified supplementation and standard supplementation groups, respectively.

In the simplified supplementation and standard supplementation groups, respectively, median OS was 9.2 months (95% CI: 7.6 to 11.3) and 8.2 months (95% CI: 5.4 to 11.7), and median PFS was 3.8 months (95% CI: 1.8 to 5.9) and 3.7 months (95% CI: 2.9 to 4.9).

In the safety population, the mean (standard deviation) number of days from the first dose of folic acid to the first dose of pemetrexed was 1.33 (1.39) days in the simplified supplementation group and 7.72 (4.80) days in the standard supplementation group. Dexamethasone adherence, which was monitored using patient diaries and medical interview by site staff, was 100% in both supplementation arms. The median (range) number of cycles completed was 4 (1, 6) in both supplementation groups. Additionally, the proportions of patients who had dose reductions and dose delays were similar between the simplified and standard supplementation arms. The median (range) relative dose intensity per cycle of pemetrexed was 1.00 (0.74, 1.04) and 1.00 (0.81, 1.04) in the simplified supplementation and standard supplementation groups, respectively.

Study drug-related TEAEs were experienced by 84.2% and 64.8% of patients in the simplified supplementation and standard supplementation groups, respectively. The most common (≥10% of all patients) drug-related AEs were anemia (29.7%), neutropenia (26.1%), nausea (22.5%), leukopenia (21.6%), lymphopenia (13.5%), thrombocytopenia (12.6%), rash (12.6%), and alanine aminotransferase increased (10.8%). The proportion of patients with drug-related leukopenia was 29.8% in the simplified supplementation arm and 13.0% in the standard supplementation arm.

No deaths occurred while on study therapy. Ten deaths (7 in the simplified supplementation arm and 3 in the standard supplementation arm) occurred within 30 days of the last dose of study therapy. Of these 10 patients, 1 patient (Patient 3301) in the simplified supplementation arm died due to a study drug-related AE of acute pulmonary edema. This patient was a 56-year-old woman with squamous cell carcinoma, an ECOG performance status of 1, and morbid obesity (body mass index of 47.7 kg/m^2) who experienced severe pancytopenia followed by acute pulmonary edema approximately 1 week after the second cycle of pemetrexed. The patient was fully compliant with vitamin and dexamethasone premedication.

The incidence of possibly drug-related SAEs was similar between the simplified supplementation group (14.0%) and the standard supplementation group (11.1%). Three patients (5.3%) in the simplified supplementation group and 4 patients (7.4%) in the standard supplementation group discontinued treatment due to an AE, regardless of causality. Three patients discontinued study treatment due to possibly drug-related SAEs, including 2 patients in the simplified supplementation group (events of acute pulmonary edema, erythema multiforme, and febrile neutropenia) and 1 patient in the standard supplementation group (laryngeal edema).

For drug-related CTCAE Grade 3 and Grade 4 toxicities, the incidence of patients with at least 1 toxicity was higher in the simplified supplementation group compared with the standard supplementation group (38.6% and 29.6%, respectively). Differences in the incidence of individual drug-related Grade 3/4 CTCAE hematological toxicities were observed for hemoglobin, leukocytes, lymphopenia, neutrophils/granulocytes, and febrile neutropenia. These events, with the exception of drug-related Grade 3/4 hemoglobin toxicity, occurred more frequently in the simplified supplementation arm than the standard supplementation arm. No notable differences were observed between

treatment arms for any individual Grade 3/4 nonhematological toxicity. Drug-related Grade 1/2 gastrointestinal toxicity occurred more frequently in the simplified supplementation arm compared with the standard supplementation arm (33.3% and 16.7%, respectively). There was no Grade 3/4 diarrhea in either group, and 1 patient in the simplified supplementation group experienced Grade 3 mucositis.

The incidence of drug-related rash (by preferred term) was 12.3% in the simplified supplementation arm and 13.0% in the standard supplementation arm. No patient in the simplified supplementation group experienced Grade 3/4 rash, compared with 1 patient in the standard supplementation group.

Conclusions:

- A simplified vitamin and steroid supplementation schedule accompanying pemetrexed treatment was not shown to be similar (noninferior) and resulted in a higher incidence of toxicity compared with the standard supplementation schedule.
- The study was not designed to detect differences in efficacy endpoints with acceptable power; however, tumor response rate, median OS, and median PFS appeared similar between the simplified and standard vitamin and steroid supplementation schedules.