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Sponsor/company:	sanofi-aventis	ClinicalTrials.gov Identifier:	NCT00087802
		Study Code:	L_9210
Generic drug name:	Oxaliplatin (Eloxatin)	Date:	15/Jan/2010

Title of the study: A Phase III Randomized Trial of Gemcitabine/Oxaliplatin (GEMOX) versus Carboplatin/Paclitaxel (CP) as First-Line Therapy in Patients with Advanced Non-small Cell Lung Cancer (NSCLC) (L_9210)

Investigator(s): Coordinating Investigator: Charles Weissman, MD, US Oncology Research (USOR)

Study center(s): A total of 113 active centers in the United States

Publications (reference): NA

Study period:

Date first patient enrolled: 04/Mar/2004

Date last patient completed: 15/May/2007

Phase of development: Confirmatory / phase III

Objectives: To determine the relative efficacy, safety and clinical benefit of the GEMOX regimen compared to the standard combination regimen of carboplatin/paclitaxel (CP) as first-line treatment of Stage IIIb and IV NSCLC

Methodology:

This was an open-label, multicenter study in which patients were randomly assigned to treatment with the GEMOX or CP regimen on a 1:1 basis with stratification by disease stage (Stage IIIb versus Stage IV or relapsed disease).

Number of patients: Planned: Total of 480 (240 per treatment arm)

Randomized: Total of 383 (GEMOX=191; CP=192)

Treated: Total of 371 (GEMOX=184; CP=187)

Evaluated:

Efficacy: Intent-to-treat (ITT): 383 (GEMOX=191; CP=192); As-treated (AT): 342 (GEMOX=166; CP=176); Per protocol (PP): 311 (GEMOX=152; CP=159)

Safety (SE): 371 (GEMOX=184; CP=187)

Pharmacokinetics: Not applicable.

Diagnosis and criteria for inclusion: Patients who had: histologically proven, newly diagnosed, Stage IIIb or IV NSCLC for which they had not received prior chemotherapy and/or any other systemic therapy; at least 1 unidimensionally measurable lesion (Response Evaluation Criteria in Solid Tumors [RECIST]); an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate hematologic, renal, and hepatic function; clinically stable brain metastases (if present); peripheral neuropathy ≤ Grade 1 (if present), and were without history of an acute cardiac or central nervous system (CNS) event within 6 months of study entry.

Investigational product: GEMOX: gemcitabine/oxaliplatin

Dose: Gemcitabine, 1000 mg/m^2 and oxaliplatin, 130 mg/m^2

Administration: GEMOX was administered in 21-day cycles as follows:

Gemcitabine: Intravenous (IV) administration over 30 minutes on Days 1 and 8

Oxaliplatin: IV administration over 2 hours on Day 1 (following gemcitabine administration)

Duration of treatment: Treatment consisted of a maximum of six 21-day cycles.

Duration of observation: Observation consisted of a Prestudy Period (within 6 weeks before randomization); a Treatment Period (maximum of six 21-day cycles); and a Follow-up Period (2 years after first administration of study treatment

Reference therapy: CP: carboplatin/paclitaxel

Dose: Carboplatin, dose calculated to produce an area under the concentration time curve (AUC) of 6 and paclitaxel: 225 mg/m^2

Administration: CP was administered in 21-day cycles as follows:

Carboplatin: IV administration over 30 to 60 minutes on Day 1 (following paclitaxel administration)

Paclitaxel: IV administration over 3 hours on Day 1

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was time to tumor progression (TTP).

The secondary efficacy endpoints were:

- Tumor response rate (overall and confirmed) based on RECIST criteria
- Time to treatment failure (TTF)
- Median survival
- Clinical benefit based on assessment of quality of life (Functional Assessment of Cancer Therapy-Lung [FACT-L])

Safety: Prospectively identified safety endpoints included:

- Type, frequency, severity, timing, and relatedness of all adverse events (AEs) during treatment and for 30 days following discontinuation of treatment
- Actual treatment administration as characterized by the median, mean, and range of doses given; dose modifications, omissions, and delays; and actual and relative dose intensity

Pharmacokinetics: Not applicable.

Pharmacokinetic sampling times and bioanalytical methods: Not applicable.

Statistical methods:

Planned analyses included 2 interim analyses and 1 final analysis; the 2 interim analyses were to occur after 154 and 308 patients, respectively, had a documented event of disease progression. One interim analysis in which the Sponsor was blinded with respect to the detailed results was conducted. The study was terminated because the protocol early stopping rule had been met (ie, 20% or more of patients in either treatment group had discontinued study treatment because of unacceptable toxicity). Enrollment was halted, but patients already enrolled in the study were allowed to continue treatment and follow-up procedures.

The study was designed to compare the efficacy and safety of the GEMOX and CP regimens. While primary and secondary endpoints remained as originally described following early termination of the study, no formal statistical analyses for comparing the efficacy endpoints between treatment groups were performed, and only appropriate descriptive statistics were presented for both efficacy and safety data. This was because the number of enrolled subjects was less than that required by the protocol to achieve the desired levels of power for demonstrating statistically significant differences between the 2 treatment groups in terms of the primary efficacy endpoint.

Study analysis populations include: ITT, SE, AT, and PP. The ITT population comprised all randomized patients in accordance with their original treatment group assignment, regardless of whether any or incorrect study medication was administered. The ITT population was used for analysis of efficacy endpoints. The SE population comprised all patients who received at least 1 dose of study medication. The AT population comprised all randomized patients who had taken at least 1 dose of study medication (actual study treatment received) and who provided sufficient efficacy data for at least 1 analysis. The PP population comprised all patients who had received at least 2 cycles of treatment, had at least 1 follow-up tumor assessment, and did not violate the protocol in any fundamental manner related to the evaluation of efficacy. The PP population was used only for the summary of the primary efficacy endpoint. All safety analyses were performed for the SE population (all patients who received at least 1 dose of study medication), and were based on actual treatment received.

The primary efficacy endpoint was TTP, which was defined as the time from randomization to the first documentation of objective tumor progression or death due to any cause in the absence of previous documentation of objective tumor progression. Based on the definition of TTP, it reflected progression-free survival (PFS). Time to tumor progression was estimated using the Kaplan-Meier product limit method presented as a survival curve and as the probability of being progression-free. Time to tumor progression was characterized in terms of median TTP with 95% confidence interval (CI) based on Brookmeyer and Crowley and the probability of being progression free at 6 and 12 months with 95% CIs based on the Greenwood method.

Secondary efficacy endpoints included the best overall response rate, TTF, survival, and quality of life.

The best overall response rate (complete response [CR] and partial response [PR]), ie, the best response recorded from the start of treatment until disease progression/recurrence, was based on tumor measurements and confirmation of response in accordance with RECIST criteria for all subjects included in the presented efficacy population (ITT). The 95% CI for the best overall response rate (CR and PR combined) was calculated using the Exact Binomial.

Time to treatment failure was measured as the time from randomization to the earliest date of withdrawal due to AEs, progressive disease (PD)/insufficient therapeutic response, failure to return, refused treatment/did not cooperate/withdrew consent, started new treatment, or death. Time to treatment failure was estimated using the Kaplan-Meier method. Time to treatment failure was characterized in terms of median TTF with 95% CI based on Brookmeyer and Crowley and the probability of nonfailure at 3 and 6 months with 95% CIs based on the Greenwood method.

Survival was the time from the date of randomization to the date of death from any cause. Survival was estimated using the Kaplan-Meier method, and was characterized in terms of median survival with 95% CI (Brookmeyer and Crowley), the range of observed survival times, and the probability of being alive with 95% CI (Greenwood method) at 12, 18, and 24 months.

Quality of life, assessed by the FACT-L, was analyzed based on subscale scores (5 domains) and the Trial Outcome Index (TOI). These were summarized using descriptive statistics at baseline, each subsequent time point, and the change from baseline.

Assessments of safety were based mainly on the incidence of treatment-emergent AEs (TEAEs) (including serious adverse events [SAEs]) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0; clinical laboratory test values that fell outside predetermined ranges or worsened based on NCI Common Toxicity Criteria (CTC), Version 2.0; and vital sign measurements. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 9.0.

Summary

Efficacy results:

Efficacy results for the primary variable and most secondary variables were similar for both treatment groups based on analyses of efficacy data for the ITT population. However, since the study was terminated prematurely, the number of patients enrolled in the study was less than that required by the protocol to achieve the desired levels of power for demonstrating differences between the treatment groups for the primary efficacy endpoint. For this reason, formal statistical analyses for comparing the efficacy endpoints between treatment groups were not performed, and the statistical presentation was limited to appropriate descriptive statistics for efficacy data. Therefore, statistically significant differences between treatment groups cannot be claimed conclusively.

The primary efficacy variable, TTP, reflected PFS based on its definition. In the primary analysis, performed for the ITT population, median TTP was 4.44 months (95% CI: 4.106, 5.331) for the GEMOX group and 4.67 months (95% CI: 4.172, 5.563) for the CP group. The respective 3-, 6-, and 12-month progression-free rates for the GEMOX group were 0.67 (95% CI: 0.590, 0.732), 0.32 (95% CI: 0.238, 0.398), and 0.10 (95% CI: 0.053, 0.177), while those for the CP group were 0.66 (95% CI: 0.586, 0.726), 0.35 (95% CI: 0.268, 0.430), and 0.09 (95% CI: 0.048, 0.161). The results of a secondary analysis of TTP, performed for the PP population, were similar for both treatment groups and also were similar to the results of the primary analysis (ITT population).

Secondary efficacy variables included best overall response, TTF, survival, and quality of life. The best overall response rate for the GEMOX group, 15.2% (95% CI: 10.410, 21.072), reflected 1 CR and 28 PRs, and was 7% lower than that for the CP group. The best overall response rate for the CP group was 22.4% (95% CI: 16.707, 28.957), based on 43 PRs. The incidence of SD was higher in the GEMOX group (38.2%) than in the CP group (33.9%).

Median TTF was 2.91 months (95% CI: 2.649, 3.642 [GEMOX] and 2.682, 3.543 [CP]) in both treatment groups. Similar 3- and 6-month failure-free rates were observed. For the GEMOX group, the respective 3- and 6-month failure-free rates were 0.50 (95% CI: 0.425, 0.567) and 0.11 (95% CI: 0.073, 0.167). For the CP group, they were 0.49 (95% CI: 0.422, 0.563) and 0.14 (95% CI: 0.095, 0.194).

Median time to death for the GEMOX group, 9.90 months (95% CI: 7.848, 11.623) was slightly longer than that for the CP group, 9.24 months (95% CI: 8.179, 10.894). Similarly, the 12-, 18-, and 24-month survival rates were slightly longer for the GEMOX group than for the CP group. For the GEMOX group, they were 0.43 (95% CI: 0.355, 0.495), 0.27 (95% CI: 0.208, 0.335), and 0.21 (95% CI: 0.159, 0.276), respectively. For the CP group, they were 0.38 (95% CI: 0.310, 0.449), 0.25 (95% CI: 0.189, 0.313), and 0.18 (95% CI: 0.126, 0.235), respectively.

Decreases of similar magnitude in quality of life, as assessed by the FACT-L, were noted for both treatment groups in 2 domains (physical well-being and functional-well being) in the interval from baseline to the final visit. Since the TOI is weighted toward physical aspects of quality of life, the TOI total scores reflected these decreases in physical well-being and functional well-being, with mean decreases in TOI that were slightly less for the GEMOX group (-4.7) than for the for the CP group (-6.4).

Safety results:

Administration of GEMOX and CP for up to 6 cycles as first-line therapy for advanced NSCLC appeared to be tolerated based on achieved exposure, TEAEs, hematology and chemistry laboratory results, and vital sign measurements.

Decreases in the percentage of patients receiving study drug at each cycle were similar between groups, and 37.0% (68/184) and 40.1% (75/187) of patients in the GEMOX and CP groups, respectively, completed 6 cycles. Gemcitabine, which was to be dosed on Days 1 and 8 of each 3-week cycle, appeared to be less well tolerated than the 3 other drugs. The median overall relative dose intensities for oxaliplatin, carboplatin, and paclitaxel were approximately 90% or higher; for gemcitabine the median relative dose intensity was 81.06%. The incidence of dose modifications and/or delays was greatest for gemcitabine (76.1%) and least for oxaliplatin (59.8%). This reflected the incidence of dose modifications due to AEs; these also were greatest for gemcitabine (60.9%) and least for oxaliplatin (33.2%). Dose modifications due to AEs were similar in incidence for carboplatin (41.7%) and paclitaxel (38.5%) and occurred less frequently than for gemcitabine (60.9%). Dose modifications due to hematologic AEs were more prevalent for GEMOX patients, while those due to neurologic AEs were more prevalent for CP patients.

The safety profiles of both combination therapies were consistent with the established safety profiles of the individual drugs. Treatment-related TEAEs seen more often in the GEMOX group were those reflecting gastrointestinal (GI) disorders and blood and lymphatic system disorders. In contrast, treatment-related TEAEs reflecting nervous system disorders and musculoskeletal and connective tissue disorders occurred more often in the CP group.

One or more treatment-related TEAE was reported for 98.4% of patients in each treatment group. The following treatment-related TEAEs (preferred terms) were reported most frequently (incidence ≥20% in either treatment group): nausea, vomiting, diarrhoea, fatigue, peripheral sensory neuropathy, paraesthesia, neuropathy peripheral, thrombocytopenia, anaemia, neutropenia, leukopenia, anorexia, alopecia, myalgia, and arthralgia. Among most frequently reported treatment-related TEAEs, the incidence of nausea, vomiting, diarrhoea, paraesthesia, and thrombocytopenia was greater in the GEMOX group, while the incidence of neuropathy peripheral, neutropenia, alopecia, myalgia, and arthralgia was greater in the CP group. Differences in incidence of treatment-related, Grade 3 or 4 TEAEs between the GEMOX and CP groups were consistent in that an increased incidence in the GEMOX group was noted for thrombocytopenia (GEMOX, 29.9% and CP, 4.8%) and platelet count decreased (GEMOX, 12.0% and CP, 2.7%), while an increased incidence in the CP group was noted for neuropathy peripheral (GEMOX, 0.5% and CP, 7.5%), and peripheral sensory neuropathy (GEMOX, 0.0% and CP, 12.3%). The overall incidence of treatment-related, treatment-emergent SAEs was similar between treatment groups (GEMOX, 16.3% and CP, 13.4%), with SAEs of thrombocytopenia reported exclusively in the GEMOX group and those involving neutropenia and associated sequelae (ie, infection, sepsis) reported only in the CP group. Similar percentages of patients in each group experienced TEAEs leading to treatment discontinuation (GEMOX, 33.7% and CP, 28.3%). For the GEMOX group, these primarily involved blood and lymphatic system disorders; for the CP group, these primarily reflected nervous system disorders. Similarly, TEAEs reflecting blood and lymphatic system disorders that required dose reduction and/or delay occurred more frequently in the GEMOX group, and those reflecting nervous system disorders occurred more frequently in the CP group.

It is important to note that incidence cutoffs were applied to in-text tables summarizing TEAEs, and that statements describing differential TEAE incidence between treatment groups are based on the information presented in in-text tables and do not necessarily reflect all TEAEs.

The SE population consisted of 99 males and 85 females in the GEMOX group and 105 males and 82 females in the CP group. In general, when differences in incidence of TEAEs were noted between males and females, a higher incidence was seen in females.

More than 78% of patients in each treatment group died. Most deaths were due to disease progression (GEMOX, 66.8% and CP, 75.9%), and the majority of deaths occurred >30 days after the last dose of study drug. The incidence of all deaths attributable to AEs was similar between treatment groups (GEMOX, 7.6% and CP, 5.3%). Four deaths (2.2%) in the GEMOX group and 3 deaths (1.6%) in the CP group were considered by the Investigators to be study-related (ie, treatment-related). These included congestive heart failure (CHF), PD, adult respiratory distress syndrome, and thrombocytopenic purpura in the GEMOX group and sepsis (2 deaths), and respiratory failure in the CP group. Treatment-related TEAEs with an outcome of death were reported for 6 patients in the GEMOX group (disease progression [2 patients], cardiac arrest, cardiac failure congestive, thrombocytopenic purpura, and hypersensitivity and pneumonitis) and 3 patients in the CP group (alveolitis allergic, neutropenic sepsis, and neutropenic sepsis and septic shock).

Changes in hematology laboratory test results (ie, shifts from baseline to extreme postbaseline NCI CTC grades) were consistent with the safety profiles based on TEAEs of the treatment groups, with decreases in platelet count more prevalent with GEMOX treatment and decreases in white blood cell count (WBC) and absolute neutrophil count (ANC) more prevalent with CP treatment. Increases in some chemistry variables associated with hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and lactic acid/lactate dehydrogenase [LDH]) were seen primarily in the GEMOX group; however, total bilirubin did not show similar increases.

There were no observations of clinical concern among vital sign measurements. The worsening in ECOG performance status (ie, increase in performance status scores) over time was not unexpected.

Pharmacokinetic results: Not applicable.

Date of report: 06-Jan-2010