2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Amrubicin		
Name of Active Ingredient: Amrubicin		

Title of Study: Randomized Phase II Study of Amrubicin as Single Agent or in Combination With Cisplatin Versus Etoposide-Cisplatin as First-line Treatment in Patients with Extensive Stage SCLC (ES)

Principal Investigator:

Investigators:

Study center(s): Subjects were randomized at 16 sites in Europe (4 in Belgium, 2 in Italy, 1 in Poland, 2 in The Netherlands, and 7 in the United Kingdom.

Publications (reference): O'Brien M, Jassem J, Lorigan P, et al.: Randomized phase II study (EORTC 08062) of amrubicin as single agent or in combination with cisplatin versus etoposide-cisplatin as first-line treatment in patients (pts) with extensive disease small cell lung cancer (ED SCLC). [Abstract] J Clin Oncol 28 (Suppl 15): A-7052, 2010.

Studied period (years):	**Phase of development**:
Date first subject enrolled: 09 Nov 2006 Date last subject completed: 07 Sep 2010	2

Objectives:

Primary:

To investigate the activity and safety of single-agent amrubicin, amrubicin combined with cisplatin (amrubicin/cisplatin), and etoposide combined with cisplatin (cisplatin/etoposide) as first line treatment in ED-SCLC.

Secondary:

To evaluate toxicity (including cardiotoxicity), progression-free survival (PFS), and overall survival (OS) in each of the three treatment groups.

Methodology:

This was a multicenter, randomized, open-label, active-comparator, 3-arm parallel-group late phase 2 study conducted in Europe by the European Organisation for Research and Treatment of Cancer (EORTC) that investigated the use of amrubicin alone, amrubicin combined with cisplatin, and etoposide combined with cisplatin as first line treatment of ED-SCLC in subjects ≥ 18 years of age. The study consists of one treatment phase with no limitation on the number of treatment cycles. Subjects were randomized 1:1:1 utilizing the EORTC On-Line Randomized Trials Access (ORTA) system to 1 of

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3 treatment arms:

- Treatment with amrubicin alone (herein referred to as the amrubicin arm)
- Treatment with amrubicin and cisplatin (herein referred to as the amrubicin/cisplatin arm)
- Treatment with cisplatin and etoposide (herein referred to as the cisplatin/etoposide arm)

Subjects were stratified at randomization by Eastern Cooperative Oncology Group (ECOG) performance status (PS), sex, and institution.

The treatment period began (Day 1 of the study) when the first dose of study medication was administered. The length of each treatment cycle was 21 days (3 weeks). Subjects were treated until progressive disease, excessive toxicity, subject refusal, or clinical decision.

The primary endpoint was response rate following Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Tumor response was evaluated by computed tomography (CT) scan. A one-stage Fleming design was used to design the study.

Number of patients (planned and analyzed):

Planned: 81 subjects randomized in a 1:1:1 ratio to the amrubicin, amrubicin/cisplatin, or cisplatin/etoposide arms (27 subjects to each arm)
Enrolled: 99 subjects - 33 subjects randomized to each arm
Analyzed: 99 (intent-to-treat [ITT] population), 95 subjects (safety population), and 88 subjects (per protocol [PP] population)

Diagnosis and main criteria for inclusion: Histologically/cytologically proven small cell lung cancer, extensive stage as defined by Harris; WHO performance status 0-2; measurable disease (RECIST); age ≥ 18 years; normal baseline cardiac function; adequate hematological function (absolute neutrophil count [ANC] ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, Hb ≥ 9 g/dL), and creatinine clearance: > 60 ml/min; adequate hepatobiliary function (ALT/AST < 2.5 x upper limit of normal); no prior systemic chemotherapy for small cell lung cancer (SCLC); no radiotherapy for SCLC within 14 days before treatment; no history of interstitial lung disease or pulmonary fibrosis; no history of prior malignancy unless subject was disease free for >5 years, or the tumor was a non-melanoma skin cancer or in-situ carcinoma of the cervix; absence of uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association Class III or IV heart failure, uncontrolled angina, clinical significant pericardial disease or cardiac amyloidosis; absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; no pregnancy or breast feeding; men and women of child bearing potential had to agree to use an appropriate method of contraception if the risk of conception existed; written informed consent before randomization

Test product, dose and mode of administration, batch number:

Amrubicin arm (Arm 1):	amrubicin 45 mg/m^2 IV on Day 1-3 of a 3-week cycle
Amrubicin/cisplatin arm (Arm 2):	amrubicin 40 mg/m^2 IV on Day 1-3 of a 3-week cycle + cisplatin 60 mg/m^2 IV on Day 1 of a 3-week cycle

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Celgene supplied amrubicin as 50 mg a lyophilized preparation for injection. Cisplatin was supplied by the local pharmacy.

Duration of treatment: There was no maximum number of cycles. Subjects were treated until progressive disease, excessive toxicity, subject refusal, or clinical decision. Each cycle was a 21-day (3-week) cycle.

Reference therapy, dose and mode of administration, batch number:

Cisplatin/etoposide arm (Arm 3): cisplatin 75 mg/m^2 IV on Day 1 of a 3-week cycle + etoposide 100 mg/m^2 IV on Day 1 followed by 200 mg/m^2 oral administration on Days 2 and 3 of a 3-week cycle or etoposide 100 mg/m^2 IV on Days 1-3 of a 3-week cycle

Cisplatin and etoposide were supplied by the local pharmacy.

Criteria for evaluation:

Efficacy: Best overall tumor response, duration of response, PFS, and OS

Safety: Incidence of adverse events, clinical laboratory evaluations (hematology and clinical chemistry), and vital signs, including measurement of left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)

Statistical methods: The study was not powered to perform inferential testing, therefore formal statistical assumption testing were not performed. Inferential assessments to support study objectives are not presented.

In each arm, the response rate together with its 80% and 95% 2-sided confidence interval were computed. Response was analyzed for the ITT and PP populations, and the baseline ECOG PS 0-1 strata within the ITT and PP populations.

For each type of toxicity, the worst grade was tabulated. The percent of subjects with any grade 3 or grade 4 toxicities were estimated and a 95% confidence interval calculated.

PFS and OS were estimated using the Kaplan-Meier estimators. Kaplan Meier curves were plotted and fixed time point estimates were accompanied by 95% confidence intervals.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The best overall response rate in the PP population by investigator evaluation was highest in the amrubicin/cisplatin arm at 76.7% (80% CI [63.9%, 86.5%]), followed by the cisplatin/etoposide arm at 63.3% (80% CI [50.0%, 75.2%]), and the amrubicin arm at 60.7% (80% CI [46.8%, 73.3%]). The amrubicin/cisplatin arm was the only treatment group to exceed a minimum lower limit of 55% for the 80% CI (alpha = 0.1) set forth in the protocol as the minimum criteria for satisfying the decision rule.

Response rates by investigator evaluation were comparable across analysis populations. The best overall response rate for the amrubicin/cisplatin arm was 75.8% (80% CI [63.6, 85.3]) in ITT population, 75.9% (80% CI [62.8, 86.0]) in the ECOG PS 0-1 ITT population, and 74.1% (80% CI [60.3, 84.9]) in the ECOG PS 0-1 PP population.

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The robustness of the response outcome is further supported by a sensitivity analysis comparing response rates between the investigator evaluation an independent reviewer, who evaluated response for only subjects in the PP population given a best response of CR, PR, or SD by investigator evaluation. Within this population of subjects (non-responders excluded), the overall response rate (CR + PR) for all subjects (all treatments arms) combined were similar between independent review (80.3%) and the investigator evaluation (83.1%).

Duration of response (median 7.0, 6.5, and 6.0 months), PFS (median 6.8, 7.4, and 6.9 months), and OS (median 11.1, 11.1, and 10.0 months) were comparable in the ITT population across the amrubicin, amrubicin/cisplatin, and cisplatin/etoposide arms, respectively.

SAFETY RESULTS:

Amrubicin was generally safe and well tolerated at doses of 45 mg/m^2/day for 3 consecutive days every 21 days or at a dose of 45 mg/m^2/day for 3 consecutive days every 21 days in combination with 60 mg/m^2 cisplatin once every 21 days. Subjects were treated with amrubicin for a median of 6 cycles (range: 1 to 22 cycles) and a duration of 3.55 months (range: 0 to 14.8 months).

Almost every subject in the amrubicin, amrubicin/cisplatin, and cisplatin/etoposide arms experienced at least 1 TEAE (96.7%, 100.0%, and 100.0%, respectively) and 1 study drug-related TEAE (90.0%, 93.9%, and 100.0%). The most commonly recorded TEAEs were non-hematologic, including fatigue, alopecia, and nausea. Toxicities were generally manageable throughout the study, especially hematologic toxicities with the use of growth factor therapy. The intensities of TEAEs were similar between the amrubicin and amrubicin/cisplatin arms, and slightly lower overall in the cisplatin/etoposide arm. Grade 3-5 events were experienced in 66.7%, 60.6%, and 43.8% of subjects in each arm, and study drug-related grade 3-5 events were experienced in 50.0%, 48.5%, and 28.1% of subjects. Serious TEAE were reported for 63.3%, 54.5%, and 43.8% of subjects. There were 10 deaths overall reported during treatment (occurred during the study or within 30 days after the last administration of any study medication): 2 (6.7%) subjects in the amrubicin arm, 5 (15.2%) subjects in the amrubicin/cisplatin arm, and 3 (9.4%) subjects in the cisplatin/etoposide arm.

Interpretation of TEAEs must be addressed with caution. Elements of the CRF design may have led to under reporting of certain TEAEs that were not included in a checklist style design. Some of the most frequently reported TEAEs were included on the AE CRF page and were not affected by this bias. These TEAEs included fatigue (73.3%, 66.7%, and 75.0%, respectively), alopecia (70.0%, 69.7%, 59.4%), and nausea (46.7%, 57.6%, and 68.8%). Although stomatitis (50.0%) was more prevalent in subjects in the amrubicin arm compared to the amrubicin/cisplatin (39.4%) and cisplatin/etoposide (25.0%) arms, treatment arms containing cisplatin tended to be associated with an increased frequency and severity of gastrointestinal disorders; grade 3 and grade 4, study drug-related gastrointestinal AEs were observed in 18.2% and 15.6% of subjects in the amrubicin/cisplatin and cisplatin/etoposide arms compared to 6.7% subjects in the amrubicin arm.

Hematologic events were not included on the CRF page and the substantial under reporting of hematologic TEAEs is confirmed through blood hematology results, which provide a conservative estimate of hematologic abnormalities in the study. For example, 6.7%, 9.1%, and 12.5% of subjects in the amrubicin, amrubicin/cisplatin, and cisplatin/etoposide arms were reported as experiencing the TEAE neutropenia. In comparison, 83.3%, 84.8%, and 81.3% of subjects, respectively, were reported with

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≥ grade 2 ANC (neutropenia) at any time during treatment. The frequency of subjects with ≥ grade 2 abnormalities at any time during treatment was also higher for leukopenia (83.3%, 78.8%, and 62.5%), anemia (50.0%, 63.6%, and 46.9%), and thrombocytopenia (30.0%, 27.3%, and 21.9%). A large proportion of these subjects had abnormalities ≥ grade 3 for neutropenia (73.3%, 72.7%, and 68.8%), leukopenia (50.0%, 57.6%, and 37.5%), anemia (10.0%, 18.2%, and 3.1%), and thrombocytopenia (16.7%, 15.2%, and 9.4%). Importantly, myelosuppression was controllable with concomitant growth factor therapy. Most subjects discontinued treatment due to the completion of 6 cycles of chemotherapy or disease progression.

No clinically significant differences were observed between gender or age stratification. No new safety signals were identified for amrubicin and there were no grade 3 or 4 cardiac events.

CONCLUSION:

Overall, based on the known safety profile for amrubicin, no new safety or cardiotoxicity concerns were identified for amrubicin alone or in combination with cisplatin. The amrubicin/cisplatin arm was the only treatment group to exceed a minimum lower limit of 55% for the 80% CI (alpha = 0.1) set forth in the protocol and therefore warrants further study on the basis of the protocol-defined efficacy criteria.

Date of the report: 07 Dec 2011