CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

Title of Study: A Phase 2 Trial of Single-Agent Amrubicin in Patients With Extensive Disease Small Cell Lung Cancer That is Refractory or Progressive Within 90 Days of Completion of First-Line Platinum-Based Chemotherapy

Investigators: Multicenter/International

Study center(s): This study was conducted at 37 centers.

Publications (reference): Ettinger DS, Jotte R, Lorigan P, Gupta V, Garbo L, Conkling P, et al. Results of a phase II trial of single-agent amrubicin (AMR) in patients with extensive disease small cell lung cancer (ED-SCLC) refractory to first-line platinum-based chemotherapy: An update. Abstract 8103. J Clin Oncol 2009;27:7s.

Ettinger DS, Jotte RM, Gupta V, Allen AR, Oliver JW. A phase II trial of single-agent amrubicin (AMR) in patients with extensive disease small cell lung cancer (ED-SCLC) that is refractory or progressive within 90 days of completion of first-line platinum-based chemotherapy. American Society of Clinical Oncology Annual Meeting, May 30 – June 3, 2008. Abstract 8041. J Clin Oncol 2008;26:May 20s

Ettinger A, Jotte R, Lorigan P, Gupta V, Garbo L, Alemany C, et al. Amrubicin monotherapy in patients with extensive disease small cell lung cancer (EDSCLC) refractory to first-line platinum-based chemotherapy: Updated results of a Phase 2 trial [abstract]. Proceedings of the IASLC 13th World Conference on Lung Cancer 2009a; July 31-August 4; San Francisco, CA: Abstract #D6.5.

Studied period (years): Date first patient enrolled: 04 Dec 2006 Date last patient completed (treatment phase): 14 May 2008	**Phase of development:** 2

Objectives: For amrubicin administered intravenously daily x 3 every 21 days:

Primary:

- To determine the objective tumor response rate using Response Evaluation Criteria in Solid Tumors [RECIST])

Secondary – to determine:

- Duration of overall response
- Time to tumor progression
- Progression-free survival
- Overall survival

CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

- Various indicators of acute treatment toxicity
- Incidence of cardiomyopathy
- Pharmacokinetic parameters

Exploratory – to determine:

- Overall response rate based on prior response to first-line therapy
- Disease control rate (overall response rate by RECIST plus stable disease x 12 weeks)
- Duration of disease control

Methodology: This was an international Phase 2, single-arm, open-label study conducted in refractory extensive-disease small cell lung cancer (ED-SCLC) patients with progressive disease as best response to first-line platinum-based chemotherapy or disease progression within 90 days of completion of first-line chemotherapy. Patients were to receive treatment with amrubicin hydrochloride 40 mg/m^2/day for 3 consecutive days starting on Day 1 of each 21-day cycle.

Safety measures were performed at each cycle on Days 1 through 3, and on Days 8 and 15 (± 1 day); efficacy measures were performed on even cycles on or after Day 14, and additional safety measures were also performed every 2 or 3 cycles. Patients who achieved a complete response (CR), partial response (PR), or stabilization of disease were to receive up to 6 cycles in the absence of disease progression, unacceptable toxicity, or death. Patients could continue treatment beyond 6 cycles if the investigator determined that additional treatment would provide further benefit and the toxicity remained acceptable; those who experienced unacceptable toxicity or withdrew consent for any reason were to discontinue treatment. Upon discontinuation from the study, patients were to be followed monthly for survival until the patient died or was lost to follow-up.

Blood samples were to be collected from patients on Day 1 of Cycle 1 prior to dosing for NADP(H):quinone oxidoreductase (NQO) 1 genotyping. In addition, serial blood sampling for plasma pharmacokinetic (PK) analyses (Cycle 1) and serial electrocardiograms (ECGs) (all cycles) were to be performed in a subset of 18 patients prior to dosing and at several time points post-dosing.

Number of patients (planned and analyzed): 63 patients evaluable for efficacy were to be enrolled; 75 patients were enrolled and analyzed

Diagnosis and main criteria for inclusion: Patients ≥ 18 years; histological or cytological diagnosis of SCLC, extensive-disease (at the time of enrollment); refractory to first-line platinum-based chemotherapy (defined as progressive disease as a best response to first-line platinum-based chemotherapy or progression within 90 days of the last dose of first-line chemotherapy); Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; measurable disease defined by RECIST criteria; no prior anthracycline treatment or symptomatic central nervous system metastases

Test product, dose and mode of administration, batch number: Vials contained lyophilized amrubicin hydrochloride 50 mg, which were to be reconstituted using 10 mL of physiological saline or 5% glucose for injection. Patients were to receive 40 mg/m^2/day for 3 consecutive days starting on Day 1 of each 21-day cycle; the solution was to be administered as a slow IV push or infusion over

CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

approximately 5 minutes. The dose could be modified based on predefined hematologic and nonhematologic toxicities. Batch numbers:

Duration of treatment: Patients with complete response, partial response, or stable disease, were to receive up to 6 cycles in the absence of disease progression, unacceptable toxicity, or death. Patients could continue treatment beyond 6 cycles if the investigator determined that additional treatment would provide further benefit and the toxicity remained acceptable.

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was overall response rate; secondary endpoints were time to tumor progression, progression-free survival, overall survival, duration of overall response, duration of disease control, and response rate based on prior response to first-line therapy. Extent of disease was measured by the investigator using computed tomography [CT] or magnetic resonance imaging [MRI]).

Safety: Safety evaluations included adverse events, clinical laboratory data, left ventricular ejection fraction (LVEF) determined by echocardiography or multigated acquisition scan (MUGA), electrocardiograms (ECGs), ECOG performance status, vital signs, and physical examinations. The intensity of adverse events and laboratory abnormalities was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 3.0).

Statistical methods:

Determination of the patient sample size was based on the Fleming Single-Stage Design methodology. Efficacy was to be measured by the overall response rate (complete and partial responses). Amrubicin would be considered promising if the true overall response rate of 6% or less could be ruled out in this refractory population.

Patient accrual was to continue until at least 63 refractory patients received at least one full cycle of Amrubicin (Day 1 to 3 administration) and either had the Cycle 2 tumor assessment performed or had early tumor progression. If 7 or fewer responses (CR + PR) were observed in this group of 63, the hypothesis that the true response rate was less than or equal to 6% could not be rejected. If 8 or more responses were achieved, the hypothesis that the true response rate was less than or equal to 6% would be rejected and this regimen would be considered worthy of further testing. This design yielded 0.90 probability of a positive result if the true response rate was 18% or higher and 0.05 probability of a positive result if the true response rate was 6% or lower.

Efficacy Analyses: Efficacy analyses were performed using the intent-to-treat (ITT) population (all patients registered to the study) and the efficacy-evaluable population (those who received 1 full cycle of study drug and had at least 1 response assessment or discontinued before having a response assessment due to rapid disease progression or death) as supportive. Response rates were presented using descriptive statistics. In addition, a 1-sided 95% confidence limit (Clopper-Pearson) and the 2-sided 95% confidence interval (CI) (Wilson Score method) were calculated for the best overall response rate. Time-to-event endpoints (duration of response, time to tumor progression, progression-free survival, overall survival) were characterized using Kaplan-Meier (KM) methodology; medians and 95% CIs were calculated using the Brookmeyer and Crowley method, and 95% CIs were presented for point

CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

estimates (1 month, 3 months, 6 months, 1 year, 2 years) using the Kalbfleisch and Prentice method.

Pharmacokinetic parameters were estimated from the concentration-time profiles for all PK population patients; descriptive statistics were used to summarize PK parameters. As the data allowed, exploratory analysis were to be performed to correlate the concentrations of amrubicin and amrubicinol with the ECG parameters (QT, QTcF [Fredericia's], and QTcB [Bazett's]).

If results allowed, efficacy, PK, and toxicity endpoints were to be summarized as described above by NQO1 genotype (all patients who consented to enzyme genotyping).

Exploratory: Response rates based on prior response to first-line therapy and disease control rates were summarized using the same methodology as described for the primary efficacy analysis; duration of disease control was summarized as described above for the time-to-event summaries (ITT and efficacy-evaluable populations).

Safety Analyses: All safety analyses were performed using the safety-evaluable population, defined as all patients who received at least 1 dose of amrubicin.

SUMMARY – CONCLUSIONS

STUDY CONDUCT:

A total of 75 patients (ITT population) with the following characteristics were enrolled: median age of 63 years (range: 43 to 88 years), 93.3% white, and 52% female. The ECOG performance status score was 0 in 32.0% of the patients, 1 in 50.7% of patients, and 2 in 17.3% of patients. The majority of patients had distant metastases, including to the liver (43 patients, 57.3%), bone (19 patients, 25.3%), adrenal gland (13 patients, 17.3%), and brain (5 patients, 6.7%), noted at baseline. The prior platinum-containing regimen was carboplatin for 51 patients and cisplatin for 19 patients; 5 patients received 1 regimen and were switched to the other regimen because of poor tolerance (considered a single regimen in these 5 patients). Fifty-three percent of patients received prior radiation therapy. The response rate to prior first-line chemotherapy was 42.7% (5.3% CR, 37.3% PR); 29.3% had progressive disease as best response. The median time to progression following the first-line chemotherapy regimen was 39 days (range: 0 to 98 days). The efficacy-evaluable population (all enrolled patients that were treated with at least 1 dose of amrubicin and who had at least 1 efficacy assessment, or progressed or died prior to assessment) comprised 67 patients. Fifty-eight patients consented to NQO1 genotyping, and 3 patients participated in the PK sampling. Seventy-one patients were followed until their death.

EFFICACY AND PHARMACOKINETIC RESULTS:

Primary Endpoint

- The overall response rate was 21.3% (Clopper-Pearson 95% confidence interval [CI]: 13.6%, 31.9%), which met the primary endpoint of the study. A complete response (CR) was achieved in 1 patient (1.3%), and a partial response (PR) in 15 patients (20%).

Secondary Endpoints

- The median duration of response (CR or PR) was 4.2 months (95% CI: 3.0 months, 4.4 months); at 6 months, the progression-free rate in patients with CR or PR was 18.3%.
- 55 patients progressed during the on-treatment period of the study. The median time to progression (measured from first dose) was 3.5 months (95% CI: 2.6 months, 4.0 months); and at 6 months, the

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

progression-free rate was 12.2.%.

- The median progression-free survival (time to either progression or death) was 3.2 months (95% CI: 2.4 months, 4.0 months); and the rate of progression-free survival at 6 months was 14.7%.
- The median overall survival was 6.0 months (95% CI: 4.8 months, 7.1 months). At 12 months, 15.7% of patients were living; the last death was documented at 23.3 months.

The results in the efficacy-evaluable analysis were comparable to the results in the ITT population shown above and support the primary analysis.

Exploratory Endpoints

Subgroup Analysis by Response to First-line Therapy:

- Patients who previously responded to first-line platinum-based therapy had a response rate of 28.1%. Patients who had progressive disease or stable disease as best response to a platinum-based chemotherapy doublet had a response rate of 16.3% to single-agent amrubicin.

Disease Control:

- The rate of disease control (CR, PR, or stable disease for at least 12 weeks) was 52.0% (95% CI: 40.9%, 62.9%).
- The median duration of disease control was 4.4 months (95% CI: 4.0 months, 5.1 months).

Results by NQO1 Genotype

The NQO1 genotype was NQO1 *1/*1 (normal enzyme activity, wild type) in 49.3% of patients, NQO1 *2/*1 (intermediate enzyme activity, heterozygotes) in 21.3%, and NQO1 *2/*2 (poor enzyme activity, homozygotes) in 6.7%.

- Median overall survival in patients with the wild type genotype (NQO1 *1/*1) was 7.8 months; median survival in patients with the heterozygotes genotype (NQO1 *2/*1) and the homozygote mutant genotype (NQO1 *2/*2) was 5.6 months and 6.0 months, respectively.
- The response rate in patients with the wild type genotype (NQO1 *1/*1) was 16.2%, in patients with the heterozygotes genotype (NQO1 *2/*1) was 25.0 %, and in patients with the homozygote mutant genotype (NQO1 *2/*2) was 40%.

Pharmacokinetics

In the limited number of SCLC patients who provided PK samples, the following pharmacokinetic properties were observed:

- The trough amrubicinol concentration was higher than the trough amrubicin concentration on all days and in all matrices (plasma, whole blood, and RBCs). The trough amrubicinol concentration in RBCs was 3- to 6-fold higher than that in plasma, while the trough amrubicin concentration was comparable between RBCs and plasma.
- Plasma amrubicin concentrations fell by approximately 60% to 80% 10 minutes after the end of the infusion, with a terminal half-life of 3 to 4 hours. Three consecutive daily doses did not cause amrubicin to accumulate in plasma. A similar profile was observed in whole blood for armubicin.
- Plasma amrubicinol concentrations declined slowly after reaching the peak level, with a terminal

CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

half-life being 10 to 15 hours on Day 1 and 25 to 40 hours on Day 3. Three consecutive daily doses led to the accumulation of amrubicinol in plasma. Prolonged terminal half life and increased exposure after multiple doses were also observed in whole blood for amrubicinol.

SAFETY RESULTS:

- The 69 patients who received a median of 4 cycles (range: 1 to 12 cycles) of amrubicin over a median of 2.6 months (range: 0 to 8.4 months) comprise the safety population. The percentage of patients receiving 5 cycles and 8 cycles was 47.8% and 15.9%, respectively. Total duration of treatment exposure (all patients combined) was 276.3 patient-months.
- The majority of patients had no dose reductions (62.3%; 43/69) or had 1 dose reduction (33.3%; 23/69); 1 patient had 2 reductions and 2 patients had 3 reductions each. Most first reductions occurred in Cycle 2 (17/62 patients treated; 27.4%) and Cycle 3 (5/46 patients treated; 10.9%).
- The most commonly reported TEAEs were neutropenia (72.5%), anemia (66.7%), fatigue (60.9%), and nausea (55.1%); other frequently reported events included thrombocytopenia, weight decreased, leukopenia, constipation, pyrexia, dehydration, and diarrhea. Events of neutropenia, anemia, nausea, thrombocytopenia, and fatigue were also most often considered possibly related to study drug. In general, based on the known effects of amrubicin, these frequently reported events are consistent with the known safety profile of amrubicin.
- Of the TEAEs that were assessed as Grade 3 or 4, neutropenia and thrombocytopenia were the most frequently reported Grade 4 events (53.6% and 26.1%, respectively); anemia and fatigue were the most frequently reported Grade 3 events (26.1% and 20.3%, respectively). In general, the most frequently reported Grade 3 and 4 TEAEs tended to be first reported in Cycle 1 and/or 2, and then decreased with subsequent cycles; this trend was also observed with respect to the frequency of any occurrence of these events across cycles. In addition, there were no Grade 3 or 4 TEAEs that appeared to increase in frequency over time. These findings suggest a lack of cumulative toxicity and/or improved management of these TEAEs.
- Because of the association of cardiac effects with other anthracycline drugs, the occurrence of cardiac TEAEs (preferred terms from the cardiac disorders SOC and selected preferred terms from the investigations SOC) were summarized in greater detail. Twenty-seven patients (39.1%) experienced at least 1 cardiac TEAE of interest; all but 2 were Grade 1 or 2: one Grade 3 event of ejection fraction decreased was reported (medically important, possibly related) and a fatal (Grade 5) event of myocardial infarction was reported (unlikely related).
- Within the safety population, there were 65 patients followed until death; 57 were due to progressive disease. Seven of the deaths occurred on treatment or within 35 days after the last dose of study drug, 4 of which were associated with disease progression and not considered to be related to study therapy. Of the 3 other on-treatment deaths, one was due to "pulmonary hemorrhage due to small cell lung cancer" in 1 patient assessed as possibly related, one was due to acute myocardial infarction assessed as unlikely related, and one was due to interstitial lung disease assessed as not related (this patient had a medical history of chronic obstructive pulmonary disease).
- Slightly more than half of the patients (56.5%) experienced at least 1 serious adverse event; these were most often from the SOC blood and lymphatic system disorders (26.1%) and the majority were

CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

considered possibly related to study drug.

- Fourteen patients (20.3%) experienced TEAEs which resulted in discontinuation of study drug; the majority were serious adverse events and most often included metastases to central nervous system (3 patients) and small cell lung cancer stage unspecified (2 patients). More frequently than discontinuations, TEAEs led to either interruption of therapy or dose reduction (40.6% each). Of these events leading to dose reduction or interruption of therapy, the majority of the events were hematological, which is consistent with the dose-reduction criteria specified in the protocol.
- Hematological nadir values tended to improve with continued treatment with amrubicin:
  - Median ANC nadir values were 0.59 x 10^3/μL, 1.96 x 10^3/μL, and 2.51 x 10^3/μL in Cycles, 1, 3, and 6, respectively. Grade 3 or 4 neutropenia was reported as an adverse event in 55.1%, 17.4%, and 10.3% of patients in Cycles 1, 3, and 6, respectively. The increasing ANC nadirs in Cycles 1, 3, and 6 were likely due to the appropriate use of amrubicin dose reductions and supportive use of WBC growth factors.
  - Hemoglobin nadir values decreased in Cycles 1 and 3, reaching their lowest values in Cycle 4, then increasing in value, with median nadir values of 104 g/L, 100 g/L, and 111 g/L in Cycles 1, 3, and 6, respectively. Grade 3 or 4 anemia was reported as an adverse event in 10.1%, 6.5%, and 3.4% of patients in Cycles, 1, 3, and 6, respectively.
  - Platelet nadir values were the lowest in Cycle 1, then increased with continued therapy, with median nadir values of 99 x 10^3/μL, 138 x 10^3/μL, and 132 x 10^3/μL in Cycles 1, 3, and 6, respectively. Grade 3 or 4 thrombocytopenia was reported as an adverse event in 26.1%, 6.5%, and 13.8% of patients in Cycles 1, 3, and 6, respectively.
- The majority of nadir values for ANC, platelets, hemoglobin, and WBCs occurred in the second and third weeks of a cycle. Across the cycles, the lowest mean and median nadir values for ANC, platelets, and WBCs occurred during Cycle 1; for hemoglobin, the lowest mean and median values occurred during Cycle 4.
- The median time to first onset of a Grade 3 or 4 event was similar for ANC and WBCs, 2.1 and 2.3 weeks, respectively, but was longer for platelets at 14.6 weeks. There were too few Grade 3/4 hemoglobin values to estimate time to onset. The median time from onset to resolution of the events for all 4 analytes was 1.0 to 1.1 weeks.
- The percentages of patients with shifts in chemistry analytes from Grade 0, 1, or 2 at baseline to Grade 3 or 4 during treatment were small.
- Changes in blood pressure, pulse, respirations, and temperature were small and generally consistent across the cycles; no trends were observed.
- The median baseline and end-of-study LVEF were both 60.0%; the median change at the end of the study was a drop of 0.05 absolute percentage points. In 22 patients who received cumulative doses of ≥ 720 mg/m^2, the median change was 0; the median LVEF for these patients was normal and unchanged from baseline. There was one Grade 3 TEAE reported of ejection fraction decreased (considered medically important and reported as a serious adverse event); in this patient, LVEF was 55.0% at baseline, and decreased to 29.0% at end-study in the setting of progressive disease and

CELGENE PROPRIETARY INFORMATION

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 hydrochloride		
Name of Active Ingredient: Amrubicin		

atrial flutter. One other patient had a decrease of 11 absolute percentage points at Cycle 6 to an LVEF of 47.0% (which was not reported as a serious adverse event nor considered medically important by the investigator). Other decreases were < 15 points and LVEF remained ≥ 50%.

- Of the patients with baseline and postbaseline ECGs, across the first 6 cycles, the percentages of patients that shifted from normal ECG readings at baseline to abnormal readings postbaseline were variable, but ≤ 25%. There was no obvious trend observed. The ECG abnormalities were reported as TEAEs in 13 patients. The events for 2 of these patients were considered to be possibly related to study drug (bradycardia and ventricular extrasystoles in 1 patient, tachycardia in another).
- Overall, just over half of the patients (53.7%) who had both baseline and on-treatment ECOG performance status scores either maintained or improved their baseline status during the treatment period; 8 patients (11.9%) worsened to an ECOG score of 3 (1 patient with a baseline score of 0, 4 patients with baseline scores of 1, and 3 with baseline scores of 2).
- Summaries by NQO1 genotype demonstrated the following:
  - Duration of exposure was slightly higher for the wild type (NQO1 *1/*1; median of 3.09 months) than the other 2 genotypes.
  - There were no apparent trends in TEAEs by NQO1 genotype, although the numbers were small within each subgroup.
  - The summary of ANCs < 500 x 10^9/L versus < 1000 x 10^9/L suggested that the frequency of both abnormalities was higher in the homozygote (NQO1 *2/*2) group than in the other 2 genotypes, although the numbers are small and any generalization is difficult to make.

CONCLUSION:

This study enrolled 75 patients with extensive or limited stage small cell lung cancer that was refractory to first-line platinum-based chemotherapy and was extensive at the time of enrollment. The median time from completion of first-line therapy to progression was only 39 days. More than one-quarter of the patients had progressive disease as best response to their first-line therapy. In this refractory population, treatment with amrubicin administered intravenously at a starting dose of 40 mg/m^2 daily for 3 days every 3 weeks led to an overall response rate of 21.3% with a median duration of response of 4.2 months. Responses were observed in patients who never responded to their first-line platinum-containing chemotherapy doublet. In addition, treatment with amrubicin led to a median overall survival of 6.0 months, which compares favorably with historical data. The safety profile observed in this trial is consistent with the known effects of amrubicin summarized from Japanese studies. The most common adverse events are due to the myelosuppressive effects of amrubicin, which are effectively managed with the use of WBC growth factors and dose reduction or delays. Amrubicin is effective in refractory SCLC patients and is generally well tolerated. Data from this study suggest that amrubicin may have an improved early cardiomyopathy profile relative to typical anthracyclines, although long-term effects are unknown.

Date of the report: 10 Nov 2009

CELGENE PROPRIETARY INFORMATION