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 Hydrochloride		

Title of Study:

A randomized, open-label, multinational phase 3 trial comparing amrubicin versus topotecan in patients with extensive or limited and sensitive or refractory small cell lung cancer after failure of first-line chemotherapy.

Principal Investigator:

Investigators: Refer to the Investigator List for details.

Study center(s): 141 centers in Australia, Austria, Belgium, Bulgaria, Canada, the Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, Switzerland, the United Kingdom, and the US.

Publications:

Jotte R, von Pawel J, Spigel DR et al. Randomized Phase 3 trial of amrubicin versus topotecan as second-line treatment for small cell lung cancer (SCLC). 47th Annual Meeting of the American Society of Clinical Oncology (ASCO). 6-3-2011. June 3-7.

Spigel DR, von Pawel J, Jotte R et al. Cardiac safety of amrubicin in a randomized Phase 3 trial of amrubicin vs topotecan as second-line treatment for small cell lung cancer (SCLC). 14th Biennial World Conference on Lung Cancer of the International Association for the Study of Lung Cancer (IASLC). 7-3-2011. eng, MIS. July 3-7. 6-30-2011.

von Pawel J, Jotte R, Spigel DR et al. Randomized Phase 3 trial of amrubicin versus topotecan as second-line treatment for small cell lung cancer (SCLC). 14th Biennial World Conference on Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) . 7-3-2011. eng, MIS. July 3-7. 6-30-2011.

Studied period (years):	**Phase of development: 3**
Date first patient enrolled: 24 Dec 2007 Date last patient completed: 23 May 2011 Data cutoff date: 19 Jul 2011	

Objectives:

Primary:

- The original primary objective from the study protocol was to demonstrate superiority in overall survival of amrubicin (40 mg/m^2 administered as a 5-minute infusion once daily for 3 consecutive days starting on Day 1 of a 21-day cycle) compared with topotecan (1.5 mg/m^2 administered as a 30-minute infusion once daily for 5 consecutive days starting on Day 1 of a 21-day cycle) in patients with extensive disease (ED) or limited disease (LD) and sensitive or refractory small cell lung cancer (SCLC) after failure of first-line chemotherapy. After unblinding for the overall survival results and following

discussions with both EU Rapporteurs, the primary objective of the study was switched post hoc from demonstrating superiority to demonstrating non-inferiority (see the EMA guidance, *Points to Consider on Switching between Superiority and Non-inferiority*).

Secondary:

The important secondary objectives were to further characterize the clinical benefit of amrubicin compared with topotecan in terms of the following:

- Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0)
- Progression-free survival (PFS)

Additional secondary objectives were to assess or compare the effect of amrubicin relative to topotecan in terms of the following:

- Duration of response (changed from key secondary objective to "additional" secondary objective by Protocol Amendment 7 dated 11 Aug 2009)
- Time to tumor progression
- Quality of life (QoL), assessed using EuroQol-5 dimension [EQ-5D] and the Lung Cancer Symptom Scale (LCSS)
- Safety
- Pharmacokinetics (plasma and whole blood concentrations) in amrubicin-treated patients only

Methodology: This was a phase 3, randomized, open-label, multinational study to determine the superiority in overall survival of amrubicin compared with topotecan when administered to patients with ED or LD and sensitive or refractory SCLC after failure of first-line chemotherapy. Patients were defined as sensitive or refractory based on their response to first line chemotherapy, and the time interval between completion of first-line chemotherapy and the date of relapse or progression. "Sensitive" was defined as a best response to first-line platinum-based chemotherapy of complete response (CR), partial response (PR), or stable disease (SD), and subsequent progression ≥ 90 days after completing first-line chemotherapy; "refractory" was defined as a best response to first-line platinum-based chemotherapy of progressive disease (PD) or progression < 90 days after completing first-line chemotherapy.

Patients were randomized in a 2:1 ratio to:

- Amrubicin 40 mg/m^2/day given as a 5-minute infusion once daily for 3 consecutive days starting on Day 1 of a 21-day cycle
- Topotecan 1.5 mg/m^2/day given as a 30-minute infusion once daily for 5 consecutive days starting on Day 1 of a 21-day cycle

Randomized patients were stratified by type of response to first-line chemotherapy (sensitive vs refractory), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2; prior to Protocol Amendment 5 [dated 03 Oct 2008] only), and disease stage (LD vs ED). After Protocol Amendment 5, patients with ECOG performance status of 2 were no longer eligible for the study; thereafter, stratification was by type of response to first-line chemotherapy and disease stage only.

At each cycle, safety assessments were performed on Days 1 through 4 (Days 1 through 6 for topotecan patients), Day 5 (Cycles 1 and 2 only), Day 8, and Day 15; efficacy assessments were performed on even cycles on or between Day 14 and Day 21; an additional safety measure (left ventricular ejection fraction [LVEF]) was performed after Cycle 3 but before Cycle 4. Patients in both treatment groups were treated for up to 6 cycles in the absence of disease progression, unacceptable toxicity, the patient's withdrawal of consent, or the physician's decision to discontinue treatment. At Cycle 6, patients experiencing SD or better could receive 6 additional cycles (with re-evaluation at the end of Cycle 9 to determine continued eligibility) for a total of up to 12 cycles after discussion with the sponsor if they remained free of progression and had no unacceptable toxicity. Study treatment beyond Cycle 12 was authorized on a

case-by-case basis by the sponsor.

After completion of the treatment phase, patients entered the follow-up phase of the study, which continued until the patient's death, withdrawal of consent for further follow-up, loss to follow-up, or study closure (except for some patients who received more than 12 cycles and who were treated until study discontinuation). During follow-up, patients were followed for survival and new anticancer treatments every 4 weeks, with additional cardiac assessments and tumor measurements at other scheduled timepoints.

Number of patients (planned and analyzed):

Planned: 620 patients

Analyzed: 637

Diagnosis and main criteria for inclusion:

Patients meeting all of the following criteria were considered for enrollment into the study:

1. Histological or cytological diagnosis of SCLC at study entry according to the International Association for the Study of Lung Cancer (IASLC) histopathologic classification. Mixed or combined subtypes according to the IASLC were not allowed.
2. Small cell lung cancer that was either sensitive (defined as a best response to first-line platinum-based chemotherapy of CR, PR, or SD, with subsequent progression ≥ 90 days after completing first-line chemotherapy), or refractory (defined as PD as best response to first-line platinum-based chemotherapy or progression < 90 days after completing first-line chemotherapy) (definitions of sensitive and refractory were revised by Protocol Amendment 6 dated 10 Apr 2009 and Protocol Amendment 7 dated 11 Aug 2009)
3. Extensive or limited disease; however, patients with LD who were candidates for local or regional salvage radiation therapy must have been offered such treatment prior to participation in this study (revised by Protocol Amendment 1 dated 12 Sep 2007)
4. Radiographically documented progression after first-line treatment with platinum-based chemotherapy
5. No more than 1 prior chemotherapy regimen
6. At least 18 years of age
7. ECOG performance status of 0 or 1 (revised by Protocol Amendment 5 dated 03 Oct 2008 to remove ECOG performance status of 2);
8. Measurable disease defined by modified RECIST Version 1.0 as follows:
   a. Measurable disease: The presence of at least 1 measurable lesion
   b. Measurable lesion: Lesions that can be accurately measured in at least 1 dimension with the longest diameter ≥ 20 mm using conventional techniques, or ≥ 10 mm to 16 mm, depending on reconstruction interval, using spiral computed tomography (CT) scans
9. Adequate organ function including the following:
   a. Adequate bone marrow reserve: absolute neutrophil count (ANC) (segmented and bands) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 90 g/L
   b. Hepatic: Bilirubin ≤ 1.5 x the upper limit of normal (ULN), alanine transaminase and aspartate transaminase ≤ 3.0 x ULN
   c. Renal: Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 60 mL/min
   d. Cardiac: LVEF ≥ 50% by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) (revised by Protocol Amendment 6 dated 10 Apr 2009)
10. Negative serum pregnancy test at the time of enrollment for females of childbearing potential
11. For males and females of child-producing potential, use of effective contraceptive methods during

the study

12. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, to understand and complete quality of life (QoL) forms, and agree to abide by the study restrictions and to return for the required assessments.

Patients meeting any of the following criteria were excluded from the study:

1. Pregnant or nursing females
2. Chest radiotherapy with curative intent to the primary disease complex ≤ 28 days prior to first dose, cranial radiotherapy ≤ 21 days prior to first dose, or radiotherapy to all other areas ≤ 7 days prior to first dose (revised by Protocol Amendment 1 dated 12 Sep 2007)
3. Prior anthracycline, topotecan, or irinotecan treatment (revised by Protocol Amendment 2 dated 24 Oct 2007)
4. Treatment with any investigational agent within 28 days or standard chemotherapy within 21 days prior to first dose. Patients must have recovered from all acute adverse effects of prior therapies, excluding alopecia.
5. Patients with previous malignancy treated with chemotherapy and/or radiation (except in situ carcinoma of the cervix, localized low-grade prostate cancer, adequately treated nonmelanomatous skin cancer, or ductal carcinoma in situ of the breast). Patients with a previous malignancy that was treated surgically at least 3 years prior and who had been in remission since that time were allowed.
6. Concurrent severe or uncontrolled medical disease (eg, active systemic infection, diabetes, hypertension, coronary artery disease, congestive heart failure) that, in the opinion of the investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study
7. Symptomatic central nervous system metastases. Patients with asymptomatic brain metastases were allowed. The patient must have been stable for ≥ 2 weeks after radiotherapy; if the patient was on corticosteroids, the dose of corticosteroids must have been stable for ≥ 2 weeks prior to first dose of study treatment, or be in the process of being tapered
8. Suspected, diffuse idiopathic interstitial lung disease or pulmonary fibrosis not related to prior treatment
9. Patients with known history of seropositive human immunodeficiency virus or patients who were receiving immunosuppressive medications that would, in the opinion of the investigator, increase the risk of serious neutropenic complications (added by Protocol Amendment 6 dated 10 Apr 2009)

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

Amrubicin administered intravenously, 40 mg/m^2 over 5 minutes.

Lot numbers:

Duration of treatment:

Patients in both treatment groups were treated for up to 6 cycles unless there was disease progression, unacceptable toxicity, the patient's withdrawal of consent, or the physician's decision to discontinue treatment. At Cycle 6, patients experiencing SD or better could have received 6 additional cycles (with re-evaluation at the end of Cycle 9 to determine continued eligibility) for a total of up to 12 cycles over approximately 8 months after discussion with the sponsor. Study treatment beyond Cycle 12 was available only with the approval of the sponsor.

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

Topotecan administered intravenously, 1.5 mg/m^2/day over 30 minutes

Criteria for evaluation:

Efficacy: Efficacy was assessed by the time to death from any cause (overall survival), objective response based on a modified RECIST Version 1.0 (Confirmed CR + PR) determined by the investigator, time to disease progression or death from any cause (PFS), time from the point that criteria for response are first met to disease progression (duration of response), and time to tumor progression.

Safety: Safety was measured by adverse events (AEs) as well as by clinical laboratory variables; 12-lead electrocardiogram (ECG); ECHO/ MUGA scan for determination of LVEF; physical examinations; and vital signs. ECHO/MUGA scans were reviewed centrally by an independent laboratory to identify patients with significant decline in LVEF (≥ 15% from baseline or ≥ 10% and below 50%) or significant cardiac AEs of interest. ECGs were evaluated centrally by an independent laboratory. Cardiac data for cases with significant decline in LVEF as defined above or with significant cardiac AEs of interest were reviewed by a blinded panel of cardiologists (Independent Cardiac Review Committee [ICRC]).

Study Populations:

- **Intention-to-Treat Population** (n = 424 amrubicin; n = 213 topotecan): The intention-to-treat (ITT) population included all patients randomized to the study. The ITT population was the primary population for all efficacy variables. All patients in the ITT population were analyzed according to the treatment they were randomized to receive.
- **Safety Population** (n = 408 amrubicin; n = 197 topotecan): The safety population consisted of all enrolled patients who received at least 1 dose of study medication and had at least 1 posttreatment safety assessment. Patients were summarized according to the actual treatment received (in case of randomization or treatment errors).
- **Full Analysis Set (ad hoc)** (n = 388 amrubicin; n = 180 topotecan): The full analysis set (FAS) included all patients who received at least 1 dose of study treatment as documented in the study drug administration form of the electronic case report form (eCRF), and who had no violations of inclusion/exclusion criteria also as documented in the appropriate eCRF form. This definition is consistent with the suggested content of a FAS in the ICH-E9 guidance. The FAS is considered intermediate between the ITT and per-protocol (PP) populations and was added as an ad hoc analysis population to address possible concerns over treatment-arm imbalances with respect to patients excluded from the PP population.
- **Per-protocol Population** (n = 348 amrubicin; n = 150 topotecan): The PP population included all ITT patients who experienced none of the following: violation of the inclusion/exclusion criteria; received anticancer therapy (cytotoxic, biologic, or radiation) at any time during the treatment period other than those to which they were randomized, or cranial radiation at any time during the treatment period; had a treatment cycle delayed by more than 28 days; or noncompliance with study medication, defined as receiving less than 75% of the scheduled treatment doses through the first 4 cycles.

Statistical methods:

Two methodologies were used to control possible inflation of type I error due to multiplicity in this study. The first was the Lan-DeMets spending function for the O'Brien-Fleming-type boundary used to assess overall survival at the interim and final analyses of overall survival. The second was a predefined testing sequence in which overall survival was assessed first before key secondary could be assessed. Once the null hypothesis for the primary objective was rejected, multiplicity within the key secondary endpoints was controlled using the Hochberg method. The details were described in the statistical analysis plan.

For table presentation, continuous data were summarized using descriptive statistics: N, mean, standard deviation (Std Dev), minimum, first quartile (Q1), median, third quartile (Q3) and maximum. Categorical data were summarized using counts and percentages. 'Missing' appears as a category (only when applicable) for the following tables: demographics, baseline characteristics, clinical laboratories, ECG, and LVEF. For tables summarizing data for the overall populations (ITT, safety, and PP), the

denominators for percentages were based on the counts of patients in the applicable population as given in the patient disposition tables. For subgroup summaries, denominators were based on the counts of patients in the applicable subgroup as given in the demographics and baseline characteristics tables. For tables summarizing data by cycle, the denominators for each cycle were based on the count of patients starting a cycle as given in the exposure to study treatment tables. When data were summarized for all cycles after Cycle 6, the denominator was based on the count of patients who started Cycle 7.

Demographics:

Age, height, weight, body mass index, and body surface area were summarized using descriptive statistics (N, mean, Std Dev, minimum, Q1, median, Q3, and maximum). The number and percentage of patients by age categories (< 40, 40 to 64, ≥ 65, ≥ 75 years) was reported. The number and percentage of males and females and patients in each race category (White, Black/African American, Asian, American Indian/Alaska Native, native Hawaiian or other Pacific Islander, and combinations of those) were also reported. Ethnicity was reported as Hispanic or Latino vs not Hispanic or Latino.

Efficacy:

The primary objective of the ACT-1 study, time to death from any cause (overall survival), was switched from superiority to non-inferiority. The non-inferiority margin for overall survival in the hazard ratio (HR) scale was 1.111. The null hypothesis for testing non-inferiority was that the $HR_{amrubicin/topotecan}$ for the treatment effect on the overall survival of amrubicin vs topotecan is greater than 1.111, and non-inferiority was tested at the one-sided level of $\alpha = 0.025$. Therefore, if the upper bound of a 95% confidence interval (CI) was less than 1.111, the experimental treatment was declared non-inferior to the control. This method for testing non-inferiority is in accordance with applicable European Medicines Agency (EMA) guidance documents.

The primary efficacy endpoint of overall survival was defined as the number of days from the date of randomization until the date of death from any cause. Patients surviving at the cutoff date for the final analysis (or cutoff date for the interim analysis) were censored at the cutoff date or date of last contact that proved the patient was still alive. If a patient withdrew consent to follow-up or was lost to follow-up, the patient was censored as of the date of last contact that proved the patient was still alive. The primary analysis of overall survival was based on Cox's proportional hazard model with only treatment included in the model. For a superiority test, the p-value from an unstratified log-rank test is equivalent to the p-value generated based on a score test for Cox's proportional hazard model with only treatment in the model. The Cox's proportional hazard model adjusted for stratification factors was presented as a supportive analysis, with type of response to first-line chemotherapy (sensitive/refractory) and disease stage (LD/ED) as stratification factors.

The other objectives of the study remain unchanged. Overall response rate and time to disease progression or death from any cause were key secondary endpoints. For ORR, a patient was defined as a responder if their best overall response to treatment, using RECIST, was either CR or PR. The response was confirmed no less than 4 weeks after the criteria for response were first met. The ORR was defined as the proportion of patients with confirmed responsive disease (CR + PR) and was based on the investigator assessment of disease response. Time to disease progression or death from any cause (whichever occurred first) was defined for all patients in the ITT population as the time from the date of randomization until the date the patient had documented disease progression or died from any cause. The date of disease progression was the earlier of the date of the first CT/magnetic resonance imaging (MRI) scan showing a new lesion or the last date of the CT/MRI scan from which the investigator determined that progression of previously-observed lesions had occurred.

Other secondary endpoints include duration of response (time from the point that criteria for response were first met to disease progression) and time to tumor progression. The analyses were conducted by the same statistical methods as the key secondary analyses.

Safety:

Safety data summarized include AEs, clinical laboratory data, physical examinations, vital signs, ECOG

performance status, 12-lead ECG, and LVEF (ECHO/MUGA scan). All summaries of safety data were conducted using the safety population. Adverse events were classified using the Medical Dictionary for Regulatory Affairs (MedDRA) classification system, Version 10.0. The intensity of AEs was graded 1 to 5 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. AE frequency was tabulated by MedDRA system organ class (SOC) and preferred term. In the by-patient analysis, a patient having the same event more than once was counted only once (except for treatment-emergent adverse events [TEAEs] by patient-months, which report the total number of events, and TEAEs by cycle). Adverse events were listed by worst NCI CTCAE grade, and were summarized by all TEAEs, most frequent TEAEs, intensity/grade, race, age, sex, ≥ Grade 3 TEAEs by cycle onset, relationship to study drug and seriousness, length of exposure to treatment, selected cardiac TEAEs of interest, NADP(H):quinone oxidoreductase 1 polymorphism, non-TEAEs, and cause of death. AEs leading to death or discontinuation from treatment, study-drug-related events, and serious adverse events (SAEs) were summarized separately. Laboratory data were graded according to NCI CTCAE severity grade.

Selected classes of TEAEs were analyzed over the protocol-defined treatment period using generalized estimating equations (GEEs). For this ad hoc analysis, the treatment period was divided into Cycle 1, Cycle 2, Cycles 3 and 4, and Cycles 5 and 6. All TEAEs were counted once for each patient in the segment in which it occurred, and the denominator for each segment was based upon the number of patients treated in that segment. In addition to segment, treatment group, and the segment-by-treatment group interaction, sex, age category (< 65 years/≥ 65 years), previous response (sensitive/refractory), region (North America/Australia/Europe), and baseline ECOG performance score (0/1/2) were also included. Since the GEE model estimates the risk of a binary event (TEAE or no TEAE), odds ratios were used to compare risk between treatment groups. The odds ratios in the GEE tables average the comparative risk over the 4 time segments, and all p-values are 2-sided. Odds ratios that are less than 1.0 favor amrubicin (ie, there is lower risk of a TEAE in the amrubicin group than the topotecan group), and those that are greater than 1.0 favor topotecan.

The summary of LVEF includes descriptive statistics (N, mean, Std Dev, Q1, minimum, median, Q3, and maximum) at each timepoint and descriptive statistics of the change from screening to each timepoint. Frequency distributions of the number and percentage of patients whose LVEF values were below their institution's lower limit of normal, whose values were below 50%, or who met any of the protocol criteria for cardiomyopathy were also provided. The overall ECG interpretations were summarized by presenting the number and percentage of patients with "normal", "abnormal, not clinically significant" and "abnormal, clinically significant" results by treatment arm at screening and for each cycle and the worst on-treatment result over all cycles.

The summary of vital signs data includes descriptive statistics of the on-treatment value by cycle/end of treatment and the worst value on-treatment. Additional descriptive statistics were prepared for the change from baseline to the on-treatment value by cycle and the worst and final on-treatment value.

SUMMARY – CONCLUSIONS

Demographics and baseline characteristics were generally similar between treatment groups, although some slight differences were noted in a number of variables that are predictors of survival; these imbalances favored the topotecan group. For example, patients in the amrubicin group were older (39.9% of patients in the amrubicin group and 34.7% of the patients in the topotecan group were ≥ 65 years of age). Both groups were predominantly white, male, and not Hispanic or Latino. Height, weight, and body mass index were also well balanced between treatment groups.

Overall, protocol compliance was excellent with median daily doses administered as specified in the protocol for both treatment groups, and mean cycle lengths within 2 days of the protocol specified 21 days. Patients in the amrubicin and topotecan groups were treated for a median of 4 cycles (range 1 to 36, amrubicin and 1 to 13, topotecan). The median relative dose intensity was higher in the amrubicin group than in the topotecan group (97.7% vs 89.5%).

EFFICACY RESULTS:

The original intent of the study was to demonstrate superiority in overall survival.

- There was a nonsignificant trend towards improved overall survival in the amrubicin group. Median overall survival was 7.5 months (95% CI = 6.8 to 8.5 months) for amrubicin compared with 7.8 months (95% CI = 6.6 to 8.5 months) for topotecan, p = 0.1701; HR = 0.880 (95% CI = 0.733 – 1.057). Since the point estimate is less than 1, this hazard ratio favors amrubicin.
- In the PP population, overall survival was improved for patients in the amrubicin group compared with patients who received topotecan. Median overall survival was 8.0 months (95% CI = 7.1 to 8.8 months) for amrubicin compared with 7.5 months (95% CI = 6.3 to 8.5 months) for topotecan, p = 0.0428 favoring amrubicin; HR = 0.806 (95% CI 0.654 – 0.994).

Small numerical imbalances in patient characteristics (performance status, age, response to first-line therapy, for example) affected the final survival outcome. In a Cox model that corrected for these imbalances, a significant improvement in survival was demonstrated for the ITT population:

- Results of a Cox model of survival with performance status 0 (yes/no), age, response to first-line platinum-based therapy (refractory/sensitive; CRF-derived), and disease stage (limited/extensive) as covariates showed a treatment effect with a HR of 0.821 (95% CI 0.683 – 0.987), p = 0.036.

The secondary endpoints of ORR and PFS were significantly improved, as were all other endpoints of duration of response, and time to progression.

- The investigator-determined ORR was 31.1% for amrubicin and 16.9% for topotecan (odds ratio 2.223, 95% CI = 1.470 – 3.360), p = 0.0001. The ORR included 7 amrubicin patients (1.7%) who had a CR, compared with 1 topotecan patient (0.5%).
- The median PFS was 4.1 months for amrubicin (95% CI = 3.5 to 4.3 months) and 3.5 months for topotecan (95% CI = 2.9 to 4.2 months), p = 0.018, log rank in favor of the amrubicin group; HR = 0.802 (95% CI = 0.667 – 0.965).
- For patients who had either a CR or PR, the median duration of response was 4.8 months for amrubicin and 4.2 months for topotecan (HR = 0.516, 95% CI = 0.313 - 0.851). There was a 6-fold increase in the proportion of responding patients who had a response duration of at least 6 months in the amrubicin group compared to the topotecan group (KM estimate of 36.5% for amrubicin compared with 6.1% for topotecan).

Given these outcomes, the analysis plan was amended to include a non-inferiority analysis for overall survival. Based on the EMA guidance for switching the objective of a study from superiority to non-inferiority, the results of ACT-1 could be reasonably interpreted when a valid non-inferiority margin was established for the overall survival analyses. Using a non-inferiority margin of 1.111 and the upper bounds of the applicable 95% CI, the non-inferiority of amrubicin with respect to topotecan was concluded from the unstratified log-rank analyses of both the ITT (1.057) and PP (0.994) populations. This claim is substantiated by supportive analyses of overall survival, including the log-rank test stratified by previous response, covariate-adjusted analyses using the Cox proportional-hazards model, and the FAS analyses. The upper bound of the 95% CI was well below the non-inferiority margin of 1.111 for all analyses. For the supportive analyses, all bounds were below 1.05, less than half of the non-inferiority margin. Although the survival curves were similar between treatment groups for the first 12 months, they separated after 12 months, with amrubicin trending toward improved long-term survival compared with topotecan. In addition, amrubicin treatment provided an improvement in overall survival compared with topotecan for among patients with refractory disease.

According to the revised hypothesis testing procedure, the key secondary endpoints could be tested for superiority of amrubicin over topotecan once non-inferiority testing was concluded with respect to overall survival for the ITT and PP populations and superiority for the PP population. Following the Hochberg procedure, the larger of 2 p-values (p = 0.018 for PFS) was compared to $\alpha = 0.05$. Since the p-value was

smaller than the α-level, both PFS and ORR are significant at $\alpha = 0.05$, and amrubicin is superior to topotecan for both PFS and ORR. The stratified and subgroup analyses for both PFS and ORR are also supportive of this conclusion.

Although the treatment effect in PFS was modest (HR of 0.802 for the unstratified analyses with a difference in medians PFS of 0.6 months), a larger proportion of patients was censored in the topotecan group (13.4% for amrubicin vs 21.6% for topotecan). In addition, 35.7% of topotecan patients who were censored for PFS were censored within 6 months of randomization, as opposed to 12.9% for amrubicin ($p < 0.0001$). Both of these factors may have caused the amrubicin treatment effect to be underestimated for PFS. At least a slight underestimation of the treatment effect for PFS is supported by the sensitivity analyses and by most of the stratified analyses. The PFS result is supported by a significant effect for time to progression (HR = 0.758, p = 0.0118).

The ORR result confirms the conclusion of both phase 2 studies conducted by Celgene, which, with a doubling of the response rate seen for amrubicin compared with topotecan, demonstrated that amrubicin is the most active compound tested in this patient population. This finding is especially true in the refractory population, where the response rate from the phase 2 study was duplicated. In addition, durable responses of at least 6 months were reported for 6 times as many patients in the amrubicin group than in the topotecan group (36.5% for amrubicin vs 6.1% for topotecan), a remarkable result given that a relapse of SCLC is nearly inevitable in this population. Consistent with findings from previous studies, the significant improvement in ORR was correlated with a significant improvement in lung cancer symptoms of dyspnea, chest pain, and cough for patients in the amrubicin group. It follows that any treatment that improves and extends tumor response will have a meaningful impact on the lives of SCLC patients.

SAFETY RESULTS:

Results from this study indicate that amrubicin was generally well tolerated as second line therapy (at doses of 40 mg/m^2/day given for 3 consecutive days, every 21 days) in patients with limited or extensive and sensitive or refractory SCLC.

Exposure

Overall, protocol compliance was excellent with median daily doses administered as specified in the protocol for both treatment groups, and mean cycle lengths within 2 days of the protocol specified 21 days. Patients in the amrubicin and topotecan groups were treated for a median of 4 cycles (range 1 to 36, amrubicin and 1 to 13, topotecan). The median relative dose intensity was higher in the amrubicin group than in the topotecan group (97.7% vs 89.5%). This observation is consistent with the fewer dose reductions required in the amrubicin group (patients without a dose reduction: 77.7% in the amrubicin group vs 55.3% in the topotecan group), and suggests better tolerance of the planned amrubicin treatment regimen compared to the planned (and labeled) topotecan regimen.

Most Frequently Reported Treatment-emergent Adverse Events:

The percentage of patients with at least 1 TEAE was comparable in both treatment groups (amrubicin: 97.8%, topotecan: 99.5%). The most common TEAEs (reported in > 40% of patients in either treatment group) included anemia, neutropenia, fatigue, thrombocytopenia, and nausea. Of these, anemia, neutropenia, and thrombocytopenia were reported less frequently in the amrubicin group than in the topotecan group (53.7% vs 70.1%, 50.7% vs 58.9%, and 41.4% vs 70.6%, respectively).

The generalized estimating equations (GEE) analyses corrected for baseline characteristics covariates and exposure period, and indicated that amrubicin patients had a significant decrease in the risk of events in the respiratory disorders SOC (32.8% risk reduction), the Hemorrhagic SMQ (55.5% risk reduction), and the Angioedema SMQ (46.1% risk reduction), with trends toward decreased risk for the asthenia/fatigue higher level term (22.6% risk reduction), the edema higher level term (45.3% risk reduction), and pain-related higher level terms (32.8% risk reduction).

Severe TEAEs (Grade 3 or Higher)

Overall, the percentage of patients with grade 3 or higher TEAEs was lower for amrubicin-treated patients than for patients who received topotecan (amrubicin: 74.0%, topotecan: 89.3%). In both groups, the most frequently reported grade 3 or higher TEAEs were from the blood and lymphatic system disorders SOC. Of these TEAEs, anemia, leukopenia, neutropenia, and thrombocytopenia were reported in a lower percentage of patients in the amrubicin group (15.9%, 15.2%, 41.4%, and 21.1%, respectively) than in the topotecan group (30.5%, 21.8%, 53.8%, and 54.3%, respectively), while febrile neutropenia was reported in a higher percentage of patients in the amrubicin group than in the topotecan group (10.0% vs 3.0%). Of other common grade 3 or higher TEAEs, the preferred term of pneumonia was reported more frequently in the amrubicin group than in the topotecan group (6.6% vs 3.0%).

The GEE analyses demonstrated highly significant decreases in the risk of both grade 3 and higher TEAEs (69.7% risk reduction) and grade 4 and higher TEAEs (67.6% risk reduction) in the amrubicin group compared with the topotecan group.

Most Frequently Reported Treatment-related Treatment-emergent Adverse Events

The most common TEAEs that were considered by the investigator to be related to study treatment were anemia, neutropenia, and thrombocytopenia. While neutropenia was reported as being treatment related in a similar percentage of patients in both treatment groups (50.0% and 57.9% in the amrubicin and topotecan groups, respectively), anemia and thrombocytopenia were reported as being related in a lower percentage of patients in the amrubicin group (49.5% and 41.2%, respectively) than in the topotecan group (65.0% and 69.0%, respectively). The treatment-related TEAEs of febrile neutropenia (10.3% vs 3.6%), stomatitis (22.5% vs 7.1%), and alopecia (20.8% vs 11.2%) were reported more frequently in the amrubicin group compared with the topotecan group.

Cardiac Events of Interest

The percentage of patients reporting any cardiac TEAEs was low in both treatment groups (from 0.2% to 4.1% across preferred terms). The majority of TEAEs from the cardiac disorders SOC were mild or moderate. Tachycardia was the most common of these TEAEs, and was reported by a slightly lower percentage of patients in the amrubicin group than in the topotecan group (3.2% vs 4.1%). The risk of cardiac events of interest of all grades appears to be equal between treatments (17.2% amrubicin; 15.2% topotecan).

Left ventricular ejection fraction decreases were similar in both treatment groups and did not decline even with cumulative doses of amrubicin exceeding 1000 mg/m^2. The median change from baseline in LVEF was minimal and, at the highest cumulative doses (from the end of Cycle 6 onwards), less pronounced in the amrubicin group than in the topotecan group (end of Cycle 9: -1 for amrubicin compared with -5 for topotecan); however, the number of patients for each treatment group was very small after Cycle 6.

On-treatment ECG abnormalities, as assessed by the investigator, occurred in a similar percentage of patients treated with amrubicin and topotecan (50.0% and 49.2%, respectively), but were clinically significant in a slightly higher percentage of patients in the amrubicin group than in the topotecan group (4.7% vs 3.0%).

Deaths and Serious Adverse Events

As would be expected in this patient population, the most common cause of death overall was disease progression (amrubicin: 79.9%, topotecan: 83.8%). Overall, TEAEs resulting in death were reported in 9.8% of amrubicin patients and 12.7% of topotecan patients. Treatment-emergent adverse events resulting in death were mostly from the neoplasms SOC, and were reported in a lower percentage of patients in the amrubicin group than in the topotecan group (3.4% vs 9.6%, respectively).

The percentage of patients with at least 1 serious TEAE during the study was similar between treatment groups (amrubicin: 47.3%; topotecan: 50.3%). The most frequently reported serious TEAEs were in the blood and lymphatic system disorders SOC (similar in both groups: 25.2% for amrubicin and 28.9% for topotecan) and in the infections and infestations SOC (amrubicin 13.7%; topotecan 10.2%); in the neoplasms benign, malignant and unspecified SOC, serious TEAEs were less frequently reported in the

amrubicin group (4.7%) than in the topotecan group (9.6%).

GEE analyses indicated trends in favor of amrubicin in risk of serious TEAEs (a 26.6% decrease) and the risk of TEAEs leading to or prolonging hospitalization (a 25.3% decrease).

Other Significant Adverse Events

The percentage of patients with at least 1 TEAE leading to discontinuation of study drug was comparable in the amrubicin group (18.1%) and the topotecan group (19.8%). SCLC of unspecified stage was the main TEAE leading to study drug discontinuation, and it was reported in a lower percentage of patients in the amrubicin group than in the topotecan group (1.0% vs 5.1%).

Hematologic TEAEs (anemia, leukopenia, neutropenia, and thrombocytopenia) were the most common TEAEs leading to therapy interruption and were reported by a slightly lower percentage of patients in the amrubicin group than in the topotecan group.

The percentage of amrubicin patients with at least 1 TEAE resulting in study drug reduction was slightly more than half that seen in the topotecan group (22.8% vs 40.1%), with a highly significant decrease in the risk of TEAEs resulting in dose reductions (60.4% risk reduction) in the amrubicin group.

Laboratory Assessments and Vital Signs

Hematology analytes

The percentage of patients with NCI CTCAE grade 3 hemoglobin and WBC, and the percentage of patients with NCI CTCAE grade 3 and 4 ANC and platelets was lower in the amrubicin group than in the topotecan group. According to the GEE analyses, the risk of grade 4 values for ANC and platelets was reduced by 58.3% and 88.5%, respectively, for patients in the amrubicin group. The risk of grade 3 or 4 values for WBC and hemoglobin was reduced by 47.1% and 66.8%, respectively, for the amrubicin group. All of these reductions were highly statistically significant.

For all hematology parameters, the median time to first nadir was consistently longer in the amrubicin than in the topotecan group (ANC: 79 days vs 15 days; WBC: 100 days vs 29 days; hemoglobin: not reached vs 266 days; platelets: not reached vs 15 days).

Chemistry analytes

The median changes from baseline in most chemistry parameters were minor and similar between treatment groups.

Vital signs

Median changes from baseline in vital signs were minimal and similar in both treatment groups.

Left Ventricular Ejection Fraction

The majority of LVEF decreases were greater than 10% from baseline, with a final value below the LLN. Decreases in LVEF in this category occurred in 20 patients overall (3.3%), with a similar incidence among patients who received amrubicin (14 patients, 3.4%) and patients who received topotecan (6 patients, 3.0%). A smaller number of patients had decreases that were ≥ 15% with a final value above the LLN, including 9 patients (2.2%) who received amrubicin and 3 patients (1.5%) who received topotecan. In both treatment groups, most of the decreases were asymptomatic. Among all amrubicin-treated patients, the incidence of "definitely" and "possibly" anthracycline-like cardiomyopathy was 4.4% (14 definitely, 4 possibly), compared with 3.6% in topotecan patients (4 definitely, 3 possibly).

Electrocardiograms

A QTc increase (Fridericia correction) from baseline > 30 msec was observed in a higher percentage of patients in the amrubicin group than in the topotecan group (22.3% vs 16.2%). Conversely, all other changes in QTc (according to the Fridericia and Bazett corrections) were observed in a similar percentage of patients in the amrubicin and topotecan groups.

Eastern Cooperative Oncology Group Performance Status

In each cycle, the majority of patients in both treatment groups had an ECOG performance score ≤ 1.

Subgroup Analyses

Age

Overall, in both treatment groups, the frequency of the most common TEAEs was either similar in patients of both age groups (< 65 or ≥ 65 years of age), or it was higher in patients over 65 years. Exceptions to this general trend were found in the topotecan group, where vomiting, bone pain, headache, and insomnia were reported in a higher percentage of patients < 65, compared with patients 65 years or older.

Sex

In the amrubicin group, a higher percentage of females than males experienced some of the most common TEAEs from the blood and lymphatic system disorders SOC (anemia, febrile neutropenia, leukopenia, neutropenia, and thrombocytopenia). Except for anemia, which was reported in a higher percentage of males than females, such TEAEs were reported in a similar percentage of females and males in the topotecan group. In both treatment groups, SCLC of unspecified stage was reported in a higher percentage of males than females.

Previous Response to Treatment

Those patients who did not have disease progression within 90 days of the end of first-line treatment were considered to have sensitive disease. Among patients who received amrubicin, patients with sensitive disease had a higher incidence of many preferred terms compared with patients with refractory. A similar trend was noted among patients who received topotecan, but to a lesser degree. It is noteworthy that the excess risk in severe (grade 3 or higher) infections in the overall safety population was not present for the refractory subgroup, and, in fact, patients with refractory disease appeared to have decreased risk of such events. This trend was also observed for cardiac disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders, suggesting that amrubicin was better tolerated in the refractory subgroup.

Growth Factor Mandate

Early survival rates were found not to have changed as colony stimulating factor recommendations were changed during the study.

CONCLUSION:

Amrubicin administered as a treatment for SCLC was non-inferior to topotecan for the primary endpoint of overall survival. In addition, amrubicin was superior to topotecan for the key secondary endpoints of PFS and ORR, and the additional secondary endpoints of duration of response and time to tumor progression. Amrubicin was relatively well tolerated among patients, with a safety profile that was improved compared with the control treatment, topotecan. Although the incidence of infections was higher among patients who received amrubicin, the risk decreased once the use of colony stimulating factors and antibiotics was mandated. Taken together, the efficacy and safety data provide the basis for a favorable benefit-risk assessment for the proposed indication of SCLC.

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