Randomized phase II study of two intercalated combinations of eribulin mesylate and erlotinib in patients with previously treated advanced non-small-cell lung cancer


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Received 12 September 2013; revised 16 April 2014; accepted 23 April 2014

Background: This phase II, open-label study investigated intercalated combinations of eribulin and erlotinib in unselected patients with advanced non-small-cell lung cancer previously treated with platinum-based chemotherapies.

Patients and methods: Eligible patients were randomized to eribulin mesylate 2.0 mg/m² on day 1 with erlotinib 150 mg on days 2–16 (21-day regimen) or eribulin mesylate 1.4 mg/m² on days 1 and 8 with erlotinib 150 mg on days 15–28 (28-day regimen). The primary end point was objective response rate (ORR).

Results: One hundred and twenty-three patients received ≥1 cycle of therapy (63, 21-day regimen; 60, 28-day regimen). ORRs were 13% [95% confidence interval (CI) 6%–24%] and 17% (95% CI 8%–29%), and disease control rates were 48% (95% CI 35%–61%) and 63% (95% CI 50%–75%) for the 21- and 28-day regimens, respectively. The median progression-free survival and overall survival were similar with both regimens. Both regimens were well tolerated with common grade ≥3 toxicities being neutropenia, asthenia/fatigue, and dyspnoea. Sequential administration of erlotinib did not interfere with the pharmacokinetic profile of eribulin.

Conclusion: Intercalated combination of eribulin and erlotinib demonstrated modest activity and the addition of erlotinib did not appear to improve treatment outcome in an unselected population. The 28-day regimen is suitable for further investigation.

Clinicaltrials.gov identifier: NCT01104155.

Key words: biomarker, eribulin, erlotinib, non-small-cell lung cancer, platinum-based doublet chemotherapy

Introduction

Lung cancer is the most common cause of cancer death worldwide [1]. Most patients are diagnosed at an advanced stage and their 5-year survival rates are low [2]. Standard first-line therapy for patients without a known driver oncogene is platinum-based doublet chemotherapy; second-line therapy is single-agent docetaxel or pemetrexed. However, the magnitude of improvement in overall survival (OS) is limited [3–7].

Combining anti-cancer agents with different mechanisms of action may improve efficacy while maintaining tolerability.

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two chemotherapeutic regimens. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments [15]. A phase II study of single-agent eribulin as second-line therapy for NSCLC reported an objective response rate (ORR) of 10% [16]. We postulated that an intercalated combination of eribulin and erlotinib would be efficacious in patients with advanced NSCLC and unknown EGFR mutation status.

Eribulin mesylate is administered on days 1 and 8 within every 21-day cycle. We modified this regimen to accommodate at least 14 days of erlotinib in the intercalated combination. The objective of this randomized phase II study was to evaluate the efficacy and tolerability of these two intercalated regimens of eribulin and erlotinib in patients with advanced NSCLC previously treated with platinum-based doublet chemotherapy.

patients and methods

study design

In this open-label, multicentre, phase II study, patients were randomized (1:1) to receive eribulin mesylate 2.0 mg/m² (eribulin 1.75 mg/m² expressed as free base) on day 1 with erlotinib 150 mg on days 2–16 of a 21-day cycle or eribulin mesylate 1.4 mg/m² (eribulin 1.23 mg/m² expressed as free base) on days 1 and 8 with erlotinib 150 mg on days 15–28 of a 28-day cycle. Eribulin was administered as an intravenous infusion in 2–5 min and erlotinib given orally. Patients were randomized via a central interactive voice response system. Randomization was stratified by race (Asian, non-Asian), tumour histology (squamous, non-squamous), and smoking history [never smoker (<100 cigarettes ever), history of smoking]. Treatment continued until disease progression, unacceptable toxicity, death, or as long as clinically appropriate. Grade 3 or 4 toxicities were managed by dose reduction or interruption.

Study approval was obtained from participating centres’ Institutional Review Board or Independent Ethics Committee. The study was conducted using Good Clinical Practice in accordance with the Principles of the World Medical Association Declaration of Helsinki 2008, the International Conference on Harmonisation guidelines (CPMP/ICH/135/95), and the United States Code of Federal Regulations (US 21 CFR). All patients provided written informed consent.

patients and study objectives

Key inclusion criteria were: 18 years or older; histologically confirmed NSCLC with measurable disease; ≥1 prior platinum-based doublet chemotherapy for recurrent/advanced NSCLC; disease progression during or after last anti-cancer therapy; Eastern Cooperative Oncology Group performance status ≤2; adequate bone marrow, liver, and renal function. Exclusion criteria included: prior therapy with eribulin or EGFR-TKI; known brain metastases unless treated and stable; and pre-existing neuropathy grade >2.

The primary efficacy end point was ORR. Secondary efficacy end points were PFS, duration of response (DOR), disease control rate (DCR), and OS. Clinical benefit rate (CBR) was an exploratory efficacy end point. Safety, pharmacokinetic (PK), and exploratory biomarker analyses were also carried out.

assessments

efficacy and safety. Tumour response was assessed by the investigator (with Response Evaluation Criteria in Solid Tumors [17]) every 8 weeks or sooner if progressive disease (PD) was suspected. Complete responses (CRs) and partial responses (PRs) required confirmation by scanning after 4 weeks or more. DCR and CBR included CR, PR, or stable disease (SD); ≥7 weeks for DCR; ≥6 months for CBR). DOR was time from first documented evidence of response (CR or PR) until PD or death. PFS was time from randomization until date of PD or death. OS was time from randomization until death due to any cause, last date known alive, or study cut-off (censored).

Adverse events (AEs) and serious AEs (SAEs) were assessed according to the National Cancer Institute Common Terminology Criteria for AEs (version 4). Eribulin pharmacokinetics. Sampling was carried out for the first 12 subjects in each dose regimen enrolled at sites able to perform PK assessments. Blood samples were collected 5 min pre-dose, and 5 min, 0.25, 0.5, 1, 2, 4, 6–8, 24–26, 72–120, and 168 h after day 1 administration of eribulin in cycles 1 and 2. Plasma concentrations of eribulin were quantified by a validated liquid chromatography-tandem mass spectrometry method [18]. PK parameters were estimated using non-compartmental analysis of plasma concentration–time data.

exploratory analyses: biomarker assessments. Archival tumour specimens (paraffin blocks or unstained slides) were sent to a central laboratory (Genzyme Genetics, now LabCorp Integrated Oncology). Formalin-fixed, paraffin-embedded sections were analysed for EGFR expression by standard immunohistochemistry procedure and for EGFR gene amplification and/or high polysomy by fluorescence in situ hybridization using EGFR CEP7® dual-colour DNA probe (Vysis®). Tumour DNA from tissue samples was analysed for KRAS mutation in codons 12 and 13 by single-nucleotide primer extension and for EGFR mutation by polymerase chain reaction amplification and bidirectional gene sequencing of exons 18–21 of the tyrosine kinase domain.

statistical analyses

For efficacy end points, primary analyses were based on the intent-to-treat population (all randomized patients). The safety population included all randomized patients who received at least one dose of study drug, and had at least one post-baseline safety evaluation. The PK population comprised all patients who received at least one dose of study drug and had evaluable PK data. Biomarker analyses were carried out on patients with evaluable biomarker samples.

Approximately 100 patients were to be randomized; however, according to a protocol amendment, enrolment of non-Asian patients was stopped and additional Asian patients were enrolled to allow for the recruitment of ≥30% Asian patients in order to enrol the requisite number of patients with EGFR mutation [19]. For each study arm, the 90% one-sided confidence interval (CI) would have 80% power to exclude the historical control ORR of 9% for erlotinib alone if the sample size was 50 patients and the ORR was 20% for the combination. The decision rule for this study was to identify a combination regimen with a potentially higher ORR than single-agent erlotinib; an observation of the ORR of 20% or above would imply a 90% confidence that there is potential synergy between the two agents. Data cut-off for the primary analysis occurred when the last patient completed the week 16 tumour assessment or was off-study.

The sample size was not powered for formal statistical treatment comparisons; both regimens were experimental. ORRrs were computed with 90% one-sided and 95% two-sided CIs using the Clopper-Pearson method [20]. The median PFS, DOR, and OS were calculated with two-sided 95% CIs using the Kaplan–Meier method. For DCR and CBR, the corresponding exact Clopper-Pearson 95% two-sided CIs were computed. Safety data were summarized using descriptive statistics. Planned exploratory analyses evaluated the correlation between biomarkers and best ORR (Fisher’s exact test; ORR ‘Yes’ defined as ‘CR’ or ‘PR’, ORR ‘No’ defined as ‘SD’ or ‘PD’), PFS (Kaplan–Meier’s curve, log-rank test), and reduction in tumour volume (Wilcoxon’s test).
results

patients
Between 22 February 2010 and 14 December 2010, 123 eligible patients were randomized to the 21-day \( n = 63 \) or 28-day \( n = 60 \) regimen (Figure 1) at 38 sites (23, United States; 15, Asia). Baseline demographics and disease characteristics (Table 1) were similar between arms.

study drug exposure
Of the 123 patients randomized into the study, all patients in both treatment regimens received at least one dose of study drug. The median number of cycles received per patient was 3 (range, 1–44 cycles) for the 21-day and 4 (range, 1–33) for the 28-day regimen. Dose delays, omissions, and reductions were undertaken in 20 (32%), 0, and 20 (32%) patients, respectively, for the 21-day regimen, and in 20 (33%), 7 (12%), and 16 (27%) patients, respectively, for the 28-day regimen.

assessments

efficacy. The ORR was 13% (lower bound of 90% CI, 8; 95% CI, 6–24) for the 21-day and 17% (lower bound of 90% CI, 11; 95% CI, 6–24; one-sided P-value of 0.041 compared with the pre-specified reference ORR of 9%) for the 28-day regimen (supplementary Table S1, available at Annals of Oncology online). The DCR was higher with the 28-day (63%) compared with the 21-day (48%) regimen, although the CBR was similar. The median DOR was 9.4 months (95% CI, 2.7–censored) for the 21-day regimen. The median DOR for the 28-day regimen was 9.7 months (95% CI 5.6–censored). The median PFS was 3.5 and 3.8 months, and the median OS 7.6 and 8.5 months for the 21- and 28-day regimen, respectively (Figure 2A and B).

safety. With both regimens, all patients reported AEs and the incidences of grade ≥3 AEs were 84% for the 21-day regimen and 80% for the 28-day regimen. The total number of deaths considered to be treatment-related was 5 (21-day: febrile neutropenia, acute respiratory failure, and pneumonia; 28-day: febrile neutropenia and pneumonia). Other AEs were mostly disease-related. The incidences of AEs (all grades) are summarized in supplementary Table S2, available at Annals of Oncology online. Most common grade ≥3 AEs for the 21- and 28-day regimens included neutropenia (56% versus 48%), asthenia/fatigue (13% versus 12%), and dyspnoea (10% for both regimens). Febrile neutropenia

Figure 1. CONSORT diagram.
occurred in more patients on the 21-day regimen than the 28-day regimen (17% versus 5%). More patients on the 21-day regimen required dose reductions due to AEs (40% versus 27% for the 28-day regimen), and the incidence of SAEs also appeared to be higher (60% versus 45%), including a higher incidence of SAEs requiring/delaying hospitalization (59% versus 35%). More patients on the 21-day regimen (17% versus 5%) also had AEs leading to study drug withdrawal.

Pharmacokinetics. Eribulin PK parameters were similar to those defined previously [21], and comparable between the 21- and 28-day dosing regimens (supplementary Table S3, available at Annals of Oncology online). The mean elimination half-life in cycle 1 ranged from 27 to 32 h.

There was a dose-related increase in eribulin exposure: the mean area under the concentration–time curve (AUC) from time zero to infinity for cycle 1 was 851.5 and 1276.5 ng h/ml following 1.4 and 2 mg/m² dose administration, respectively. Dose-normalized exposure was similar on day 1 of cycles 1 and 2 of both regimens, indicating lack of eribulin accumulation on subsequent dosing.

**Discussion**

This randomized phase II study confirmed the feasibility of combining eribulin with erlotinib in an intercalated manner with the 28-day regimen meeting our predefined criteria for a positive result. However, ORRs of 13% and 17% suggest similar efficacy for the two regimens, supported by similar survival outcomes. Our findings suggest that addition of the EGFR-TKI erlotinib does not improve the treatment outcome of eribulin in these patients (no selection by biomarker status) with advanced NSCLC. This may best be explained by the fact that most of the patients in this study did not harbour activating EGFR mutations. When this study was designed, it was unclear whether the intercalated combination of chemotherapy and EGFR-TKI would improve treatment outcomes in patients with or without EGFR mutation. Recent data from NVALT-10 [22] and FASTACT 2 [23] suggest that patients without activating EGFR mutations are unlikely to benefit from the combination. In NVALT-10, intercalated combination of single-agent chemotherapy and erlotinib improved PFS of patients with non-squamous cell carcinoma but not those with squamous cell carcinoma. Although biomarker analysis for EGFR mutation was not available in NVALT-10, it is reasonable to postulate that the majority of patients with squamous cell carcinoma had EGFR mutation-negative tumours. Wu et al. [23] reported similar findings in their randomized phase III study, whereby the benefit of intercalated combination of gemcitabine/platinum and erlotinib was confined to patients with EGFR-mutant disease. Thus, our findings also show that addition of EGFR-TKI to chemotherapy fails to improve treatment outcome in patients without EGFR mutation.

Both regimens were generally well tolerated, with no additional safety considerations with the combination. The 21-day regimen was associated with a relatively higher incidence of dose reduction and SAEs. Erlotinib induces cytochrome P450

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**Table 1.** Baseline patient demographics and disease characteristics (intent-to-treat population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>21-day regimen</th>
<th>28-day regimen</th>
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<tr>
<td></td>
<td>(n = 63)</td>
<td>(n = 60)</td>
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<tr>
<td>Age, years [median (range)]</td>
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<td>63.5 (39–87)</td>
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<td>Never smoker</td>
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<tr>
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<td>2</td>
<td>21 (33)</td>
<td>11 (18)</td>
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<tr>
<td>≥3</td>
<td>4 (6)</td>
<td>15 (25)</td>
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</table>

All data are n (%) unless otherwise stated. ECOG, Eastern Cooperative Oncology Group.

**Table 1.** Baseline patient demographics and disease characteristics (intent-to-treat population)
Figure 2. Kaplan–Meier analysis of (A) progression-free survival and (B) overall survival (intent-to-treat population). CI, confidence interval; PFS, progression-free survival.
(CYP)3A4 and decreases exposure (AUC) of co-administered drugs that are CYP3A4 substrates. Eribulin is a CYP3A4 substrate; however, metabolism has been shown to be a minor contribution to eribulin clearance [21]. Prolonged (>7 days) administration of the CYP inducer erlotinib will result in enzyme induction; however, in the current study, eribulin exposure (AUC) and clearance were comparable when eribulin was administered alone (day 1, cycle 1) or after extended administration of erlotinib (day 1, cycle 2). This indicates that CYP3A4 induction does not have a substantial effect on eribulin exposure and that eribulin efficacy will not be compromised when administered with erlotinib according to the dosing regimen tested. These results are in agreement with another study which demonstrated that co-administration with rifampicin, a strong CYP3A4 inducer, also had no effect on eribulin exposure [24]. Given the positive primary result and slightly better tolerance, the 28-day regimen should be considered for future investigation.

The combination of chemotherapy and EGFR-TKI has been controversial. Our study demonstrates the feasibility of combining a novel cytotoxic chemotherapy with EGFR-TKI in an intercalated manner. However, addition of EGFR-TKI is unlikely to improve treatment outcomes in patients without EGFR mutation. Future investigation should explore the combination in patients with EGFR-mutant disease in comparison with single-agent EGFR-TKI.

acknowledgements

We thank all the patients and investigators who participated in this study (see Appendix). We also thank Annette Smith, PhD, from Complete Medical Communications, who provided medical writing support, and Oxford PharmaGenesis™ Ltd (UK), who provided additional medical writing support for the manuscript revisions. All funding for medical writing support was provided by Eisai.

funding

This study was funded by Eisai Ltd (NCT01104155).

disclosure

TSM is an advisor for AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, Bristol-Myers Squibb, BeiGene, AVEO Oncology, Pfizer, Taiho, Boehringer Ingelheim, GlaxoSmithKline Biologics, and Clovis Oncology, is a member of the speakers’ bureau for AstraZeneca, Roche, Eli Lilly, Boehringer Ingelheim, Merck Serono, and Pfizer, and is currently conducting research sponsored by AstraZeneca. LR, BW, PG, FG, and LX are employees of Eisai Ltd. CR has previously been on the speakers bureaus for Boehringer Ingelheim, Eisai, and Genentech. SLG, NI, ST, AS, DS, VL, and WTL have declared no conflicts of interest.

references

SNPs in the transforming growth factor-β pathway as predictors of outcome in advanced lung adenocarcinoma with EGFR mutations treated with gefitinib

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Received 30 March 2014; revised 15 April 2014; accepted 23 April 2014

Background: The aim of this study was to evaluate whether genetic variations in the transforming growth factor-β (TGF-β) pathway influenced clinical outcome of advanced lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations treated with gefitinib.

Patients and methods: Two hundred six patients with advanced lung adenocarcinomas were enrolled in this study. EGFR mutation in these tumors was detected. Among them, 106 patients with EGFR mutation and 37 of 100 patients with wild type were treated with gefitinib. Genotype of 33 single-nucleotide polymorphisms (SNPs) from 13 genes involved in the TGF-β signaling pathway was determined, and their association with survival time was analyzed. Univariate and multivariate analyses were carried out to assess the role of biological/clinical parameters in progression-free survival (PFS) and overall survival (OS) using Pearson’s χ² test, log-rank test, and Cox proportional hazards model.

Results: Among SNPs analyzed, multivariate analysis showed the cytidylate and thymidine (CT) genotype of SMAD3: rs11632964 was associated with a longer OS and PFS when the entire cohort of 143 patients were included; the association was significant in the patients with EGFR mutant tumors (30.8 versus 17.5 months; log-rank P = 0.020; and 20.8

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