



A Randomized Phase III Study of Abemaciclib Versus Erlotinib in Patients with Stage IV Non-small Cell Lung Cancer With a Detectable KRAS Mutation Who Failed Prior Platinum-Based Therapy: JUNIPER

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Introduction: JUNIPER compared the efficacy and safety of abemaciclib, a selective cyclin-dependent kinase 4 and 6 inhibitor, with erlotinib in patients with non-small cell lung cancer (NSCLC) harboring a Kirsten rat sarcoma (*KRAS*) mutation.

Methods: JUNIPER was a Phase III, multicenter, randomized, open-label trial of abemaciclib versus erlotinib in patients with stage IV NSCLC and a detectable mutation in codons 12 or 13 of the *KRAS* oncogene, who progressed after platinum-based chemotherapy and 1 additional therapy (could include immune checkpoint inhibitor therapy). Randomized patients (3:2) received either 200 mg abemaciclib twice daily or 150 mg erlotinib once daily with best supportive care until disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS); secondary endpoints included overall response rate (ORR), progression-free survival (PFS), and safety.

Results: Between December 2014 and April 2017, 453 patients were randomly assigned to receive abemaciclib (N = 270) or erlotinib (N = 183). Median OS was 7.4

months (95% confidence interval [CI]: 6.5, 8.8) with abemaciclib and 7.8 months (95% CI: 6.4, 9.5) with erlotinib (hazard ratio [HR] = 0.968 [95% CI: 0.768, 1.219]; $p = .77$). Median PFS was 3.6 months (95% CI: 2.8, 3.8) with abemaciclib and 1.9 months (95% CI: 1.9, 2.0) with erlotinib (HR = 0.583 [95% CI: 0.470, 0.723]; $p < .000001$). ORR was 8.9% and 2.7% ($p = .010$), and the disease control rate was 54.4% and 31.7% ($p < .001$) with abemaciclib and erlotinib, respectively. Safety results reflected the known safety profiles of abemaciclib and erlotinib.

Conclusions: In this study, the primary endpoint of OS was not met; PFS and ORR were improved with manageable toxicity in the abemaciclib arm. The increases in response rates and PFS support further investigation of abemaciclib in other NSCLC subpopulations or in combination with other agents.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT02152631

Keywords: platinum-resistant, erlotinib, abemaciclib, KRAS, NSCLC

INTRODUCTION

The Kirsten rat sarcoma (*KRAS*) and epidermal growth factor receptor (EGFR) mutations play an important role in the pathogenesis of most lung adenocarcinomas and are, with rare exceptions, mutually exclusive, and vary by geography (1). *KRAS* is the most commonly mutated oncogene in non-small cell lung cancer (NSCLC), occurring mainly in lung adenocarcinomas (30%) and less frequently in squamous cell carcinoma (5%) (2, 3). Treatments directed toward *KRAS* mutations are not available because of limited efficacy resulting from failure to inhibit the protein directly, or inhibit its downstream effectors (4). Platinum-based doublets have been the first-line standard of care therapy for more than 2 decades. Irrespective of first-line response, patients with continued good performance status (PS) often proceed to second-line therapy (5, 6). Such therapy yields an approximately 5- to 8-month overall survival (OS) for patients with *KRAS* mutation positive (*KRAS*+) NSCLC tumors (7–9). Until recently, erlotinib use in second- or subsequent-line treatment in NSCLC had no limitation with regard to *EGFR* mutation status, and erlotinib was frequently used as salvage therapy in unselected patients (10–13). Approvals of immune checkpoint inhibitors [nivolumab (14), pembrolizumab (15), and atezolizumab (16)] changed the standard of care in first-line therapy and after platinum-based treatment failure; however, these agents do not specifically target patients with metastatic *KRAS*-mutated NSCLC, which continues to be an area of significant unmet medical need.

The cyclin-dependent kinase (CDK) 4 and 6-retinoblastoma (Rb) pathway is frequently dysregulated in NSCLC and therefore represents an attractive therapeutic target. Abemaciclib is a potent and selective inhibitor of CDK 4 and 6, approved for treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer, as monotherapy or with endocrine

therapy. In preclinical studies, a synthetic lethal interaction between *KRAS* mutation and CDK4 inhibition indicates a potential therapeutic application for CDK4 and 6 inhibitors in NSCLC (17). In a Phase I study of abemaciclib in patients with advanced NSCLC, those with *KRAS*-mutated tumors had improved disease control rate (DCR) compared to those with *KRAS* wild-type tumors (18). CDK4 and 6 negatively regulate Rb activity through phosphorylation and inactivation of this tumor suppressor protein; therefore, it is possible that only tumors containing Rb-proficient cells may be sensitive to CDK4 and 6 inhibition (19).

In the current study, we compared abemaciclib to erlotinib, both in combination with best supportive care, in patients with stage IV NSCLC who had *KRAS*-mutated tumors and had progressed after platinum-based chemotherapy plus one other anti-cancer therapy.

METHODS

Patients and Study Design

JUNIPER was a Phase III, international, randomized, open-label, controlled trial of abemaciclib versus erlotinib in patients who had a confirmed diagnosis of stage IV NSCLC, a detectable mutation in codons 12 or 13 of the *KRAS* oncogene, and had progressed after 2 prior systemic therapies of which 1 was platinum-based. Initially, patients who received a prior immune checkpoint inhibitor in addition to a regimen of platinum-based therapy required 1 additional prior systemic therapy for eligibility. With the approval of immune checkpoint inhibitors as second-line therapy after progression on platinum-based therapy, the study was amended in July 2015 to include the immune checkpoint inhibitor as the second therapy regimen for eligibility without the need for additional anti-cancer therapy. Patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumors

(RECIST) v1.1; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; adequate organ function; and to have recovered from the acute effects of previous therapy. Main exclusion criteria included the presence of unstable central nervous system metastases, prior treatment with a CDK4 and 6 inhibitor or *EGFR*-targeted therapy in any setting for NSCLC, or a serious pre-existing medical condition that the investigator judged should preclude participation. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent prior to any study-related procedures.

Eligible patients were randomized 3:2 to receive either 200 mg of abemaciclib orally twice daily, or 150 mg erlotinib orally once daily, with best supportive care until disease progression or unacceptable toxicity (Figure 1A). Randomization, via computer-generated random sequence using an interactive web response system, was stratified according to the number of prior chemotherapy regimens, ECOG PS, sex, and *KRAS* mutation. The primary objective was OS, defined as the duration from the date of randomization to the date of death from any cause. Secondary objectives included overall response rate (ORR), progression-free survival (PFS), and safety. Responders were patients exhibiting partial response (PR) or complete response (CR) by RECIST v1.1. ORR was the proportion of patients with best overall response of CR or PR. PFS was the time from the date of randomization to the date of investigator-determined objective progression (20) or the date of death due to any

cause, whichever was earlier. DCR was the proportion of patients with best overall response of CR, PR, or stable disease (SD).

Tumor status was assessed radiographically at screening and approximately every 8 weeks until disease progression. Pharmacogenetic and biomarker samples were requested for all patients where regulatory approval was obtained, and pharmacokinetic (PK) studies were performed on patients who received abemaciclib.

KRAS Mutation Status

KRAS mutation status was determined at baseline by the central laboratory using the QIAGEN® *therascreen*® *KRAS* Rotor-Gene Q Polymerase Chain Reaction Kit for NSCLC with formalin-fixed paraffin embedded tumor tissue collected by surgical biopsy, fine needle aspirate, or core needle biopsy.

Statistical Analysis

The study planned to enroll 450 patients and the results were to be analyzed when approximately 304 OS events had been observed. Assuming an OS hazard ratio (HR) of 0.72, this sample size would yield approximately 80% statistical power to detect superiority of abemaciclib over erlotinib with a two-sided log-rank test and alpha level of 0.05. Efficacy analyses were based on all patients randomized to study treatment (intent-to-treat [ITT] population). Safety analyses were based on all randomized patients receiving at least one dose of any study drug (safety population). Interim patient safety analyses occurred

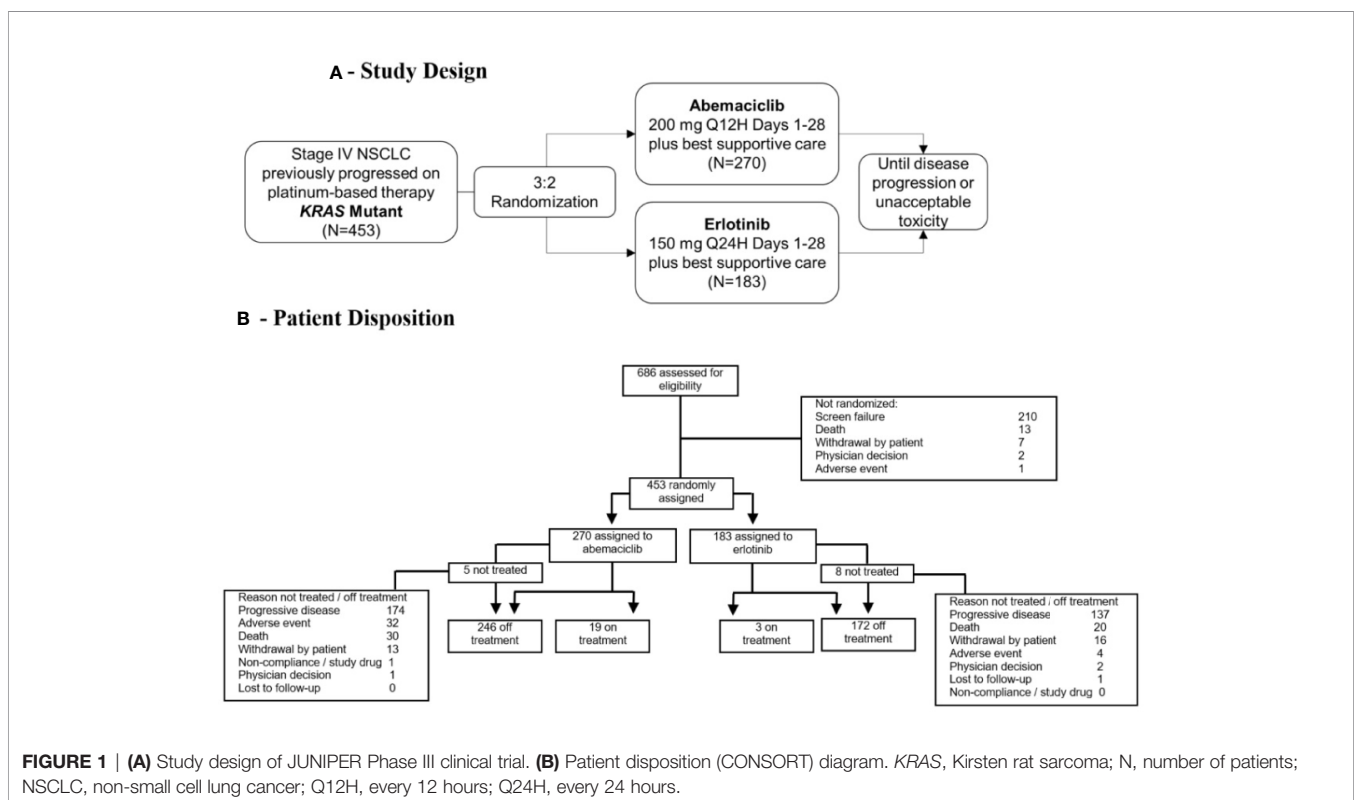


FIGURE 1 | (A) Study design of JUNIPER Phase III clinical trial. **(B)** Patient disposition (CONSORT) diagram. *KRAS*, Kirsten rat sarcoma; N, number of patients; NSCLC, non-small cell lung cancer; Q12H, every 12 hours; Q24H, every 24 hours.

approximately every 6 months by an independent Data Monitoring Committee. A protocol defined futility analysis was conducted after approximately 100 PFS events occurred.

The comparison of OS and PFS between treatment groups was conducted using a stratified log-rank test. The Kaplan-Meier method was used to estimate OS and PFS curves. The Cox proportional hazard model with treatment as a factor, stratified by the randomization stratification factors, was used to estimate the HR and its corresponding 95% confidence interval (CI). Prespecified subgroup analyses for OS and PFS included all the stratification factors, age, geographical region, prior use of immunotherapy, and smoking status. Cochran-Mantel-Haenszel test adjusted by all stratification factors was used to evaluate and compare the treatment effects in ORR and DCR. All tests of treatment effects were conducted at a two-sided alpha level of 0.05. All statistical analyses were performed using the software SAS version 9.2.

Immunohistochemistry for Retinoblastoma Status

Immunohistochemistry (IHC) for Rb was performed on formalin-fixed, paraffin-embedded tissues where sufficient residual tumor cells were present, using the Rb (4H1) mouse monoclonal antibody (Cell Signaling Technology), and reviewed by a board certified pathologist. Cases were adjudicated Rb+ if weak (1+ on a 0, 1+, 2+, 3+ scale) or stronger intensity, and with specific staining identified in $\geq 10\%$ of tumor cells.

Genetic Variant Analysis

An exploratory analysis by cancer gene sequencing of 53 tumor samples representing the best and worst change in tumor size was performed for the abemaciclib arm. Foundation Medicine (Cambridge, MA) sequenced 404 cancer-related genes and characterized them for genetic variants including: base substitutions, short insertions and deletions, copy number alterations, and select fusions. Analysis focused on genetic variants with known or likely functional consequences as defined by Foundation Medicine.

RESULTS

Patients

Of the 2747 samples tested for a *KRAS* mutation at the central laboratory using the QIAGEN[®] *KRAS* kit (97%) or a local laboratory (3%), 850 (31%) were positive. From the *KRAS*-positive samples, 686 patients were screened for inclusion in this study (Figure 1B). The distribution of amino acid changes among the positive samples is given in Table S1.

Of the 686 patients screened for inclusion, 453 patients were eligible and randomly assigned to receive study treatment (Figure 1B). A total of 270 patients were randomized in the abemaciclib arm and 183 patients in the erlotinib arm. Baseline characteristics were similar between treatment groups in the ITT population (Table 1). In the advanced/metastatic setting, prior chemotherapy was received in 98.9% of all randomized patients, targeted therapy in 26.5% of patients, and immunotherapy in

TABLE 1 | Baseline Demographic and disease characteristics (ITT population).

Characteristic	Abemaciclib N = 270	Erlotinib N = 183
Sex, male, n (%)	163 (60.4)	109 (59.6)
Age, y, median (range)	62 (36-89)	63 (39-83)
Race, n (%)		
White	165 (61.1)	106 (57.9)
Asian	56 (20.7)	41 (22.4)
Other/not reported	49 (18.1)	36 (19.7)
Ethnicity, n (%)		
Hispanic or Latino	13 (4.8)	12 (6.6)
Not Hispanic or Latino	197 (73.0)	132 (72.1)
Not Reported	60 (22.2)	39 (21.3)
Region, n (%)		
Europe	160 (59.3)	106 (57.9)
Asia	54 (20.0)	41 (22.4)
North America	48 (17.8)	29 (15.8)
Other	8 (3.0)	7 (3.8)
Pathological diagnosis, n (%)		
Adenocarcinoma	243 (90.0)	165 (90.2)
Squamous	9 (3.3)	6 (3.3)
Other	18 (6.7)	12 (6.6)
Smoking status		
Past smoker	198 (73.3)	127 (69.4)
Current smoker	44 (16.3)	28 (15.3)
Never smoked	28 (10.4)	26 (14.2)
Missing	0	2 (1.1)
ECOG performance status		
0	64 (23.7)	44 (24.0)
1	206 (76.3)	139 (76.0)
KRAS mutation stratification factor		
G12C	145 (53.7)	96 (52.5)
Others	125 (46.3)	87 (47.5)
Number of prior systemic chemotherapy regimens for locally advanced/metastatic disease		
1	108 (40.0)	75 (41.0)
2	157 (58.1)	104 (56.8)
3	2 (0.7)	2 (1.1)
Number of prior systemic immunotherapy regimens for locally advanced/metastatic disease		
1	46 (17.0)	29 (15.8)
2	0	1 (0.5)
Number of prior target therapy regimens for locally advanced/metastatic disease		
1	65 (24.1)	42 (23.0)
2	7 (2.6)	6 (3.3)

ECOG, Eastern Cooperative Oncology Group; G12C, mutation in codon 12 of the *KRAS* gene resulting in an amino acid substitution from glycine to cysteine; ITT, intent-to-treat; *KRAS*, Kirsten rat sarcoma; N, number of patients in the population; n, number of patients in the specified category.

16.8% of patients. Five patients assigned to abemaciclib and eight patients assigned to erlotinib did not receive study treatment; therefore, 440 patients comprised the safety population (Figure 1B). The majority of patients (68.7%) discontinued treatment because of progressive disease (PD) across both treatment arms (abemaciclib arm, 64.4%; erlotinib arm, 74.9%). There were 32 (11.9%) and 4 (2.2%) patients who discontinued study treatment because of an adverse event (AE) in the abemaciclib and erlotinib arms, respectively. AEs resulting in treatment discontinuation in ≥ 3 patients included lung infection, anemia, acute kidney injury, and diarrhea. At the time of data cut-off, 19 patients in the

abemaciclib arm and 3 patients in the erlotinib arm remained on treatment.

Primary and Secondary Objectives

The median follow-up time was 17.3 months (abemaciclib arm, 17.4 months; erlotinib arm, 17.3 months). A total of 189 (70%) OS events occurred in the abemaciclib arm and 127 (69.4%) in the erlotinib arm. The median OS was 7.4 months (95% CI: 6.5,

8.8) with abemaciclib and 7.8 months (95% CI: 6.4, 9.5) with erlotinib (HR = 0.968 [95% CI: 0.768, 1.219]; $p = .77$) (Figure 2A). The results were consistent in all prespecified subgroup analyses (Figure 2B).

The median PFS in the abemaciclib arm was 3.6 months (95% CI: 2.8, 3.8) versus 1.9 months (95% CI: 1.9, 2.0) in the erlotinib arm (HR = 0.583 [95% CI: 0.470, 0.723]; $p < .000001$) (Figure 2C). In the subgroup analyses, HRs favored the abemaciclib arm in all groups (Figure 2D).

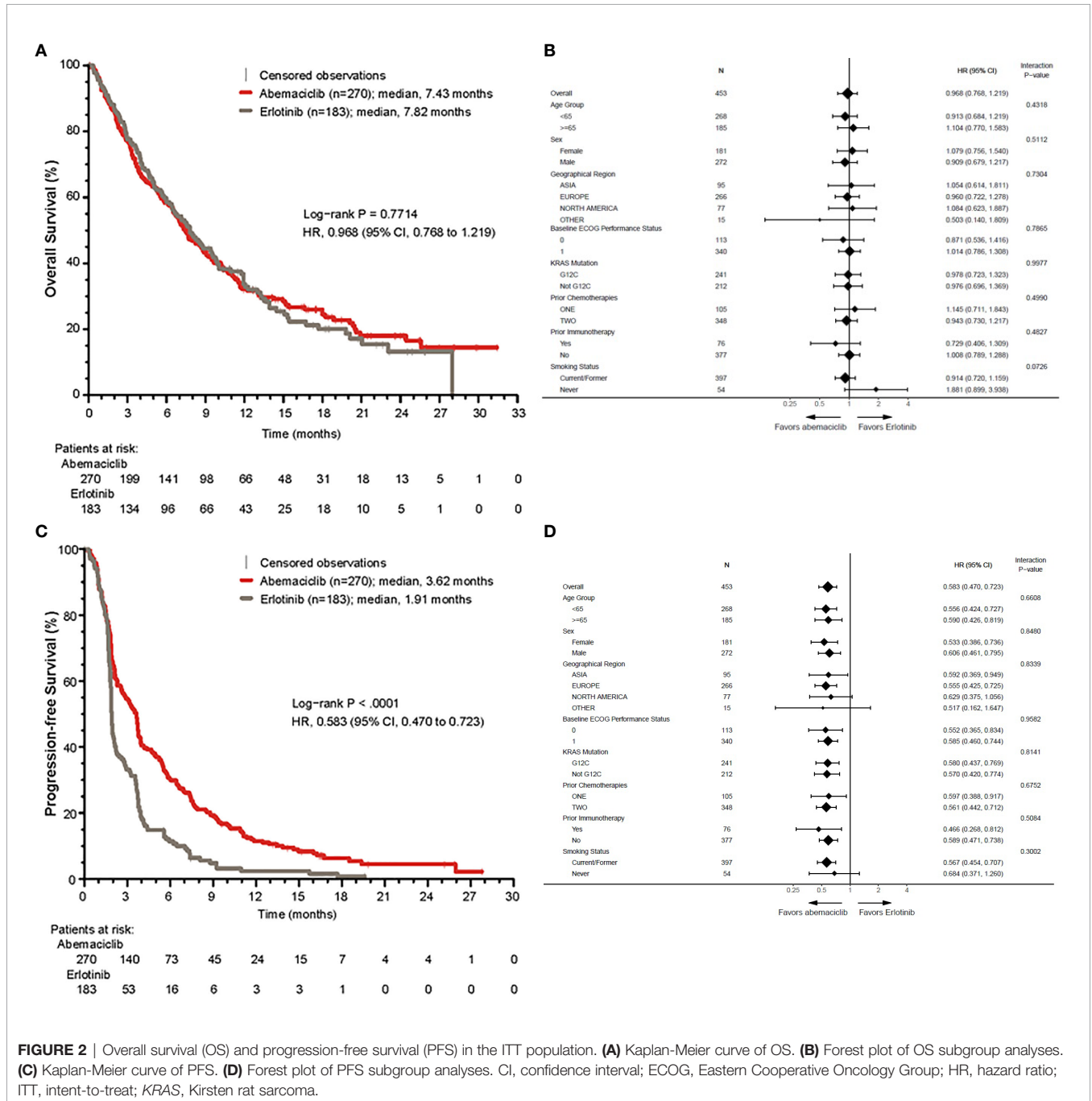


FIGURE 2 | Overall survival (OS) and progression-free survival (PFS) in the ITT population. **(A)** Kaplan-Meier curve of OS. **(B)** Forest plot of OS subgroup analyses. **(C)** Kaplan-Meier curve of PFS. **(D)** Forest plot of PFS subgroup analyses. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; KRAS, Kirsten rat sarcoma.

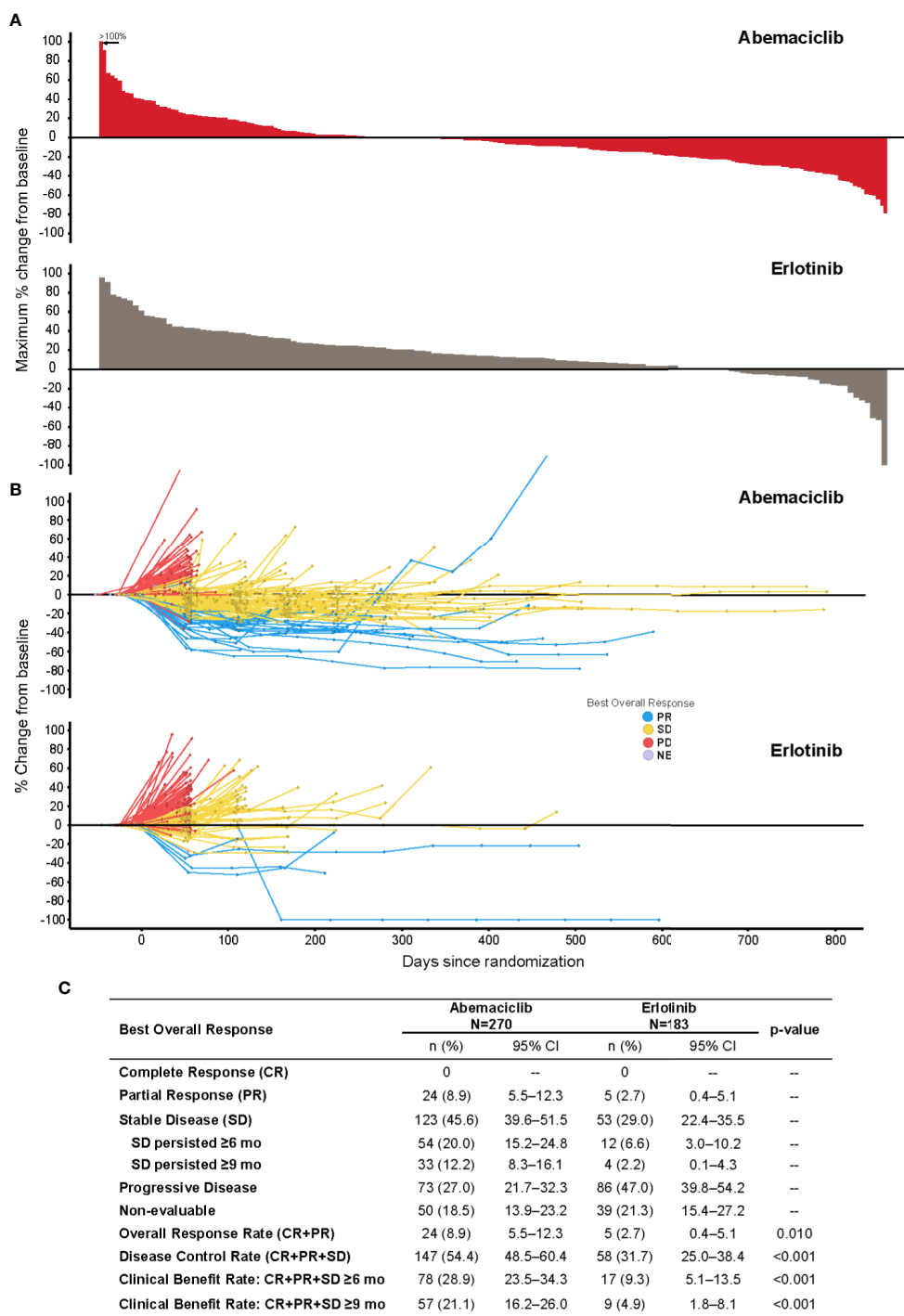


FIGURE 3 | Response to treatment (ITT population). **(A)** Maximum percent change from baseline in tumor size in individual patients: top, abemaciclib; bottom, erlotinib. **(B)** Percent change from baseline in tumor size in individual patients over the course of treatment: (top) abemaciclib; (bottom) erlotinib. **(C)** Table of best overall responses by treatment. CI, confidence interval; ITT, intent-to-treat; mo, months; NE, non-evaluable; PD, progressive disease.

A waterfall plot of maximum percent change in tumor size and a spider plot showing the best overall response by treatment arm are shown in **Figures 3A, B**, respectively. A summary of best ORRs is given in **Figure 3C**. The plurality of

patients on abemaciclib had a best response of SD [abemaciclib (45.6%) versus erlotinib (29.0%)]. A PR was observed in 24 patients in the abemaciclib arm and 5 patients in the erlotinib arm, resulting in a higher ORR with abemaciclib (8.9%) than

with erlotinib (2.7%; $p = .010$). No patients exhibited a CR. The DCR and the clinical benefit rate (CBR), defined as patients with a PR or SD at 6 and 9 months of treatment, were also significantly higher with abemaciclib compared to erlotinib ($p < .001$).

Post-Study Treatment

Post-discontinuation systemic therapy was received by 98 (36.3%) patients in the abemaciclib and 74 (40.4%) patients in the erlotinib arms. The median time from randomization to post-discontinuation therapy initiation was 4.4 months for patients in the abemaciclib arm and 2.8 months in the erlotinib arm. The most common systemic therapies included nivolumab (15.9%), gemcitabine (7.9%), and docetaxel (7.9%) (Table S2). Post-discontinuation radiotherapy was received by 12.8% of patients. An exploratory analysis of patients with or without post-discontinuation therapy was performed to assess the impact of post-discontinuation systemic therapy on OS (Figure S1). The distribution of post-discontinuation therapy was similar between arms (data not shown).

An exploratory analysis of OS was performed by censoring survival time at post-discontinuation therapy initiation. With 125 events in the abemaciclib arm and 82 in the erlotinib arm, median OS was 8.2 and 6.6 months, respectively (HR = 0.767 [95% CI: 0.575, 1.025]; $p = .0713$) (Figure S2). This numerical difference in median OS was not statistically significant.

Pharmacokinetic Analyses and Results

Plasma concentration-time data for abemaciclib and its major active metabolites M2 and M20 were available from 265 patients. The time

course of the observed plasma concentrations for abemaciclib, M2, and M20 demonstrate that the PK observations in JUNIPER were consistent with those in MONARCH 1 (21), which used the same starting dose of 200 mg twice daily.

Safety Results

In the abemaciclib arm, 31.7% of patients had dose reductions and 57.0% had dose omissions, while in the erlotinib arm, patients had 14.3 and 26.9%, respectively. Diarrhea was the most frequent AE requiring a dose omission (10.9%) or dose reduction (8.3%) for patients on abemaciclib. Treatment-emergent adverse events (TEAEs) occurring in $\geq 10\%$ of patients are summarized in Table 2. Notable differences in the incidence of Grade ≥ 3 TEAEs were reflective of the known safety profile differences between abemaciclib and erlotinib. These included hematologic toxicity (anemia, thrombocytopenia, neutropenia), gastrointestinal toxicity (diarrhea, nausea, vomiting), fatigue, increases of alanine aminotransferase and aspartate aminotransferase, decreased appetite, and dehydration observed more frequently in the abemaciclib arm. Skin reactions (dermatitis acneiform and rash) were observed more frequently in the erlotinib arm (45.7 and 10.3%, respectively, versus 3.0 and 2.6% in the abemaciclib arm). Serious adverse events occurred more frequently in the abemaciclib arm (42.3%) than in the erlotinib arm (24.6%), with lung infection reported most frequently for both arms (Table 3). Treatment-related AEs occurring in $\geq 10\%$ of the safety population are reported in Table S3.

Most deaths were due to study disease. Thirty-one deaths on therapy or within 30 days of treatment discontinuation were due to an AE (18 patients on abemaciclib [6.8%]; 13 patients on

TABLE 2 | Treatment-emergent adverse events occurring in $\geq 10\%$ of patients in the abemaciclib arm—safety population.

Preferred Term	Abemaciclib N = 265			Erlotinib N = 175		
	CTCAE Grade					
	Grade 3	Grade 4	Any	Grade 3	Grade 4	Any
Patients with ≥ 1 TEAE, n (%)	130 (49.1)	24 (9.1)	256 (96.6)	60 (34.3)	6 (3.4)	167 (95.4)
Diarrhea	23 (8.7)	0	172 (64.9)	9 (5.1)	0	69 (39.4)
Fatigue ^a	26 (9.8)	NA	112 (42.3)	7 (4.0)	1 (0.6)	43 (24.6)
Decreased appetite	15 (5.7)	0	97 (36.6)	2 (1.1)	0	42 (24.0)
Nausea ^a	13 (4.9)	NA	96 (36.2)	2 (1.1)	NA	30 (17.1)
Anemia	28 (10.6)	1 (0.4)	89 (33.6)	5 (2.9)	0	26 (14.9)
Dyspnea	18 (6.8)	2 (0.8)	63 (23.8)	7 (4.0)	0	27 (15.4)
Vomiting	8 (3.0)	0	62 (23.4)	1 (0.6)	0	16 (9.1)
Neutropenia	27 (10.2)	4 (1.5)	60 (22.6)	0	1 (0.6)	3 (1.7)
Thrombocytopenia	12 (4.5)	6 (2.3)	59 (22.3)	2 (1.1)	0	6 (3.4)
Increased blood creatinine	1 (0.4)	0	47 (17.7)	0	0	2 (1.1)
Abdominal pain ^a	3 (1.1)	NA	44 (16.6)	1 (0.6)	NA	11 (6.3)
Decreased weight ^a	2 (0.8)	NA	42 (15.8)	0	NA	17 (9.7)
Cough ^a	2 (0.8)	NA	38 (14.3)	0	NA	21 (12.0)
Leukopenia	9 (3.4)	0	38 (14.3)	3 (1.7)	0	4 (2.3)
Pyrexia	1 (0.4)	0	35 (13.2)	1 (0.6)	0	12 (6.9)
Constipation	2 (0.8)	0	29 (10.9)	0	0	15 (8.6)
Lung infection	7 (2.6)	2 (0.8)	29 (10.9)	5 (2.9)	0	10 (5.7)

CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects in safety population; n, number of subjects in the specified category; NA, not applicable per CTCAE^a; TEAE, treatment-emergent adverse event.

^aCTCAE version 4.0 does not provide a definition for Grade 4: fatigue, nausea, abdominal pain, decreased weight, and cough.

TABLE 3 | Serious adverse events by preferred term in $\geq 1\%$ of patients—safety population.

Preferred term	Abemaciclib N = 265	Erlotinib N = 175
Patients with ≥ 1 serious adverse event, n (%)	112 (42.3)	43 (24.6)
Lung infection	18 (6.8)	7 (4.0)
Acute kidney injury	11 (4.2)	1 (0.6)
Dehydration	10 (3.8)	1 (0.6)
Diarrhea	10 (3.8)	1 (0.6)
Dyspnea	8 (3.0)	7 (4.0)
Nausea	7 (2.6)	0
Sepsis	6 (2.3)	3 (1.7)
Embolism^a	5 (1.9)	2 (1.1)
Respiratory failure	5 (1.9)	1 (0.6)
Vomiting	5 (1.9)	2 (1.1)
Pneumonitis	4 (1.5)	5 (2.9)
Anaemia	3 (1.1)	3 (1.7)
Confusional state	3 (1.1)	0
Decreased appetite	3 (1.1)	1 (0.6)
Fatigue	3 (1.1)	1 (0.6)
General physical health deterioration	3 (1.1)	1 (0.6)
Hyponatraemia	3 (1.1)	1 (0.6)
Pleural effusion	3 (1.1)	2 (1.1)
Thrombocytopenia	3 (1.1)	0
Hyperglycaemia	1 (0.4)	2 (1.1)
Pneumothorax	1 (0.4)	2 (1.1)
Back pain	0	2 (1.1)

DVT, deep vein thrombosis; N, number of patients in the enrolled population; n, number of patients with a serious adverse event.

^aPulmonary embolism (4 patients [1.5%] in abemaciclib arm; 2 patients [1.1%] in erlotinib arm); DVT (1 patient [0.4%] in abemaciclib arm).

erlotinib [7.4%]). The most common AEs resulting in death across both study arms were lung infection (seven patients), respiratory failure (four patients), and dyspnea (three patients).

Rb Expression

Immunohistochemical staining for Rb status was evaluated for 392 tumor samples (230 in the abemaciclib arm and 162 in the erlotinib arm). The population with Rb-stained samples was representative of the ITT population with respect to OS and PFS, with 231 of 392 (58.9%) tumor samples staining positive. However, no association between Rb status (either positive or negative) and OS or PFS for either treatment was observed.

Genetic Assessments

A subset of tumor samples from the abemaciclib arm representing extreme change in tumor size were sequenced to identify genetic variants that may associate with treatment response. Skoulidis et al. (22) previously identified three gene expression subgroups within *KRAS*-mutated adenocarcinomas, and reported that these subgroups were independently associated with co-mutation genomic alterations in *KRAS* and the tumor suppressor genes *TP53*, *STK11*, or *CDKN2A*. In our study, patients with such co-mutations demonstrated similar treatment effects in PFS and tumor size changes relative to the ITT population (**Figure S3**). Genomic variants in the Rb pathway genes *RBI* and *CCNE1* were observed in few patients.

The 2 *RBI* mutated tumors had best overall response of PD, while the 1 tumor with *CCNE1* amplification had SD.

DISCUSSION

In the JUNIPER study, abemaciclib did not demonstrate a statistically significant improvement in the primary endpoint of OS versus erlotinib. However, analyses of the secondary endpoints of both PFS and ORR showed evidence of abemaciclib monotherapy activity in *KRAS*+ population.

Historically, a median OS of 5.3 to 6.7 months was noted for erlotinib therapy in unselected patients who progressed after one or two prior chemotherapy regimens (8, 12, 13). The erlotinib arm in JUNIPER had longer OS than previously reported; however, considering the poor PFS and DCR, this did not seem attributable to erlotinib treatment. Patients on erlotinib discontinued treatment and started post-discontinuation therapies sooner, including recently US Food and Drug Administration (FDA)-approved immunotherapy agents, which may have affected the comparison of OS rates in this study.

Despite the lack of an OS benefit with abemaciclib in this trial, the PFS differences and ORR results suggest abemaciclib demonstrated some antitumor activity in this patient population. The abemaciclib arm showed a higher DCR (54.4%), CBR for ≥ 6 months (28.9%), and CBR for ≥ 9 months (21.1%) than the erlotinib arm (31.7, 9.3, and 4.9%, respectively).

In spite of *KRAS* being the most commonly mutated oncogene in NSCLC (2, 3), there are no available treatments for *KRAS* mutations, resulting in a significant unmet medical need. Recently, G12C inhibitors have shown encouraging benefit in a subset of patients with *KRAS*-mutated NSCLC. The G12C inhibitor AMG 510 (now called sotorasib) has shown promising clinical efficacy and a tolerable safety profile (23), and a Phase 3 study is ongoing to evaluate this agent in patients with previously treated *KRAS*-mutated NSCLC (NCT04303780). MRTX849, another G12C inhibitor, has demonstrated encouraging anti-tumor activity in an ongoing Phase 1/2 open-label trial (24).

The abemaciclib dose used in this study (200 mg every 12 hours) was the maximum tolerated dose and achieved plasma concentrations associated with efficacy in other disease states such as metastatic breast cancer (21). However, in this study, an improvement in OS in *KRAS*-mutated NSCLC was not observed in patients taking abemaciclib, and optimization of the single agent dose in this disease setting is not expected to affect OS.

In general, safety data obtained in this trial were consistent with the safety profile expected for a CDK4 and 6 inhibitor in patients with advanced NSCLC. The overall death rate due to AEs was low and similar between treatment arms. Consistent with the overall safety observations for abemaciclib, diarrhea was frequently reported in patients receiving abemaciclib; however, the incidence observed in this trial was lower than in MONARCH 1, a single-agent trial in HR+, HER2- metastatic breast cancer patients (64.9 versus 90.2%) (21).

Prior characterization of NSCLC tumor samples showed negative Rb protein stains in 46% of NSCLC adenocarcinomas (25). Rb negative tumors were expected to be resistant to abemaciclib treatment, since CDK4 and 6 inhibitors inhibit upstream of Rb; however, abemaciclib effects were not associated with Rb expression status. Potential explanations could include: correlation of Rb expression to cell cycle progression (i.e., quiescent tumors may not express detectable quantities of Rb protein), Rb loss or expression present only among tumor subclones possibly geographically missed by the biopsy needle track, or some *RBI* gene variants that may not have eliminated the IHC epitope. Alternatively, only small amounts of Rb, below the detection threshold of IHC, may need to be present for biological effect.

Subgroups of *KRAS*-mutated NSCLC tumors defined by their co-mutations respond differentially to programmed cell death protein 1 (PD-1) blockade (26) and have different prognoses. The *KRAS+TP53* and *KRAS*-only tumors (lack *TP53* or *STK11* co-mutations) are more sensitive to PD-1/programmed death-ligand 1 (PD-L1) inhibitors, while *KRAS+STK11* are least sensitive (26). DNA mutation assessments on a subset of tumors to identify any associations with specific *KRAS* co-variant subgroups were performed; however, no observed association between NSCLC *KRAS* co-mutation subgroups and abemaciclib sensitivity or resistance was noted.

Limitations of the present study included the comparator choice of erlotinib (a tyrosine kinase inhibitor of *EGFR*) in this population for which available clinical data have been limited and inconsistent (7, 27–31). Initially, erlotinib was indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (11); and National Comprehensive Cancer Network guidelines supported erlotinib as a subsequent second- or third-line treatment option. Given the differences in available treatment toxicity profiles, and the limited treatment options for *KRAS* mutant NSCLC patients, erlotinib was considered an acceptable option in the selected geographies (32, 33) and the only approved third-line agent to use as a control arm at the time of initiation of the current study in selected geographies. However, during trial accrual in 2016, the erlotinib FDA label was modified to include use only in those patients whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations (34). Meanwhile, the availability of immune checkpoint inhibitors further changed the standard of care in the second-line setting and beyond.

In summary, abemaciclib did not improve OS compared to erlotinib in patients with stage IV NSCLC harboring *KRAS* mutations. However, the increases in response rates and PFS may warrant additional studies of abemaciclib in other NSCLC subpopulations or in combination with other agents. Indeed, ongoing studies in NSCLC with abemaciclib may provide additional information on the potential efficacy and effects of immunotherapy and abemaciclib, including on *KRAS*-mutated tumors.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data are available to request 6 months after the indication

studied has been approved in the US and EU and after primary publication acceptance, whichever is later. Requests to access the datasets should be directed to www.vivli.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committees and institutional review boards at each trial site approved this study. This includes the following name/affiliation of each approval site, by country, listed below:

- Argentina (Comite de Etica Independiente en Invest.Clinica, Ciudad Autonoma de Buenos Air; Centro de Oncologia e Investigacion Buenos Aires, Buenos Aires).
- Austria (EK der Medizinischen Universität Graz, Steiermark; Ethikkommission Oberösterreich, Oberösterreich; Ethikkommission für das Bundesland Salzburg, Salzburg).
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- Germany (Ethikkommission der Universität Ulm, Baden-Wuerttemberg).
- Greece (National Ethics Committee, Athens; SOTIRIA General Hospital, Athens; University General Hospital of Patras Rio, Patras; Metaxa Hospital, Athens).
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AUTHOR CONTRIBUTIONS

JG contributed to study conception and design, collection and assembly of data, data analysis and interpretation, and preparation and critical revision of the manuscript. JM contributed to collection and assembly of data, data analysis and interpretation, and preparation and critical revision of the manuscript. FB contributed to study conception and design, collection and assembly of data, data analysis and interpretation, and preparation and critical revision of the manuscript. KD contributed to collection and assembly of data, and preparation and critical revision of the manuscript. MK contributed to collection and assembly of data, data analysis and interpretation, and preparation and critical revision of the manuscript. TG contributed to collection and assembly of data, data analysis and interpretation, and preparation and critical revision of the manuscript. ABC contributed to collection and assembly of data, and preparation and critical revision of the manuscript. NG contributed to collection and assembly of data, data analysis and interpretation, and preparation and critical revision of the manuscript. CW contributed to collection and

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2020.578756/full#supplementary-material>

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