# Abemaciclib in Combination with Single-Agent Options in Patients with Stage IV Non–Small Cell Lung Cancer: A Phase 1b Study

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**Abbreviations:** AE, adverse event; $AUC_{(0–last)}$, area under the concentration time curve from time 0 to last observed concentration; CDK, cyclin-dependent kinase; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; DCR, disease control rate; DLT, dose-limiting toxicity; DET, DLT-equivalent toxicity; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; PFS, progression-free survival; SAS, Statistical Analyses System; TEAE, treatment-emergent adverse event.

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**Potential Conflicts of Interest**
ESK reports personal fees from Eli Lilly during the conduct of the study, and personal fees from Celgene, AstraZeneca, and Boehringer Ingelheim, outside the submitted work. KK reports personal fees from Lilly Advisory Board outside the submitted work. LGP-A reports personal fees and serving in a Medical Advisory capacity for Roche, Eli Lilly, MSD, BMS, Novartis, AstraZeneca, Boehringer Ingelheim, Pfizer, Amgen, and Clovis, outside the submitted work. PG is on the Advisory Board for Eli Lilly, Roche, Astra-Zeneca, MSD, AbbVie, Boehringer, BMS, Pfizer, and Guardant; has received personal fees from Roche, MSD, Boehringer, and BMS, and a grant from Guardant. MG reports personal fees from Eli Lilly outside the submitted work. MP reports investigational funds from Lilly. JWG has received research grants and is on an Advisory Board for Eli Lilly and Company. ELJ, PKT, SRPK, RB, AH, WJJ are employees of Eli Lilly and Company. All other authors have nothing to disclose.

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## Translational Relevance

Despite advances in prolonging survival of patients with metastatic NSCLC, treatment options after progression on second-line treatment remain an area of significant unmet medical need. Pemetrexed, gemcitabine, and ramucirumab are indicated for advanced NSCLC treatment. The addition of abemaciclib to single-agent chemotherapy or antiangiogenic therapy already approved in NSCLC may achieve additional clinical benefit. Preclinical studies in NSCLC models indicated potential additive benefit for the combination of single-agent treatments with abemaciclib. The JPBA phase 1 study demonstrated abemaciclib monotherapy activity in NSCLC, and recently, abemaciclib received Food and Drug Administration approval as single-agent or in combination with endocrine therapy for breast cancer. The objective of the JPBJ phase 1b study was to identify a tolerable abemaciclib dose, characterize its pharmacokinetics, and evaluate its antitumor activity when combined with single-agent chemotherapy or antiangiogenic therapy for the treatment of metastatic NSCLC. These results have potential as a foundation for future clinical development.

## Abstract

**Introduction:** Abemaciclib, a dual inhibitor of cyclin-dependent kinases 4 and 6, has demonstrated preclinical activity in non–small cell lung cancer (NSCLC). A multicenter, nonrandomized, open-label phase 1b study was conducted to test safety, maximum tolerated dose (MTD), pharmacokinetics, and preliminary antitumor activity of abemaciclib in combination with other therapies for treatment in patients with metastatic NSCLC.

**Methods:** An initial dose escalation phase was used to determine the MTD of twice-daily oral abemaciclib (150, 200 mg) plus pemetrexed, gemcitabine, or ramucirumab, followed by an expansion phase for each drug combination. Pemetrexed and gemcitabine were administered according to label. The abemaciclib plus ramucirumab study examined two dosing schedules.

**Results**: The three study parts enrolled 86 patients; all received ≥1 dose of combination therapy. Across arms, the most common treatment-emergent adverse events were fatigue, diarrhea, neutropenia, decreased appetite, and nausea. The trial did not identify an abemaciclib MTD for the combination with pemetrexed or gemcitabine but did so for the combination of abemaciclib with days 1,8 ramucirumab (8mg/kg). Plasma sample analysis showed that abemaciclib did not influence the pharmacokinetics of the combination agents and the combinations agents did not affect abemaciclib exposure. The disease control rate was 57% for patients treated with abemaciclib-pemetrexed, 25% for abemaciclib-gemcitabine, and 54% for abemaciclib-ramucirumab. Median progression-free survival was 5.55, 1.58, and 4.83 months, respectively.

**Conclusions**: Abemaciclib demonstrated an acceptable safety profile when dosed on a continuous twice-daily schedule in combination with pemetrexed, gemcitabine, or ramucirumab. Abemaciclib exposures remained consistent with those observed in single-agent studies.

## Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related mortality (1). Non–small cell lung cancer (NSCLC) accounts for >80% of all lung cancer cases, with most patients initially diagnosed with advanced or metastatic disease (2).

Platinum-based doublets are the standard first-line therapy for NSCLC in unselected patients; and in appropriate patients, these may be combined with bevacizumab, necitumumab, or pembrolizumab (3–6). Patients with sensitizing mutations of EGFR or BRAF, or ALK or ROS-1 gene rearrangement are candidates for first-line therapy with targeted oral kinase inhibitors (2).

Unfortunately, not all patients respond to first-line therapy and even patients who initially respond will likely relapse. Many patients are candidates for second-line and eventually third-line therapy. Available second-line treatment options in unselected patients include: docetaxel (with or without ramucirumab, or nintedanib in the European Union), and pemetrexed or gemcitabine if not previously used (2, 7–11). In addition, immune checkpoint inhibitors may be used following disease progression on or after platinum-based chemotherapy: pembrolizumab is indicated for selected patients with PD-L1 expression, and nivolumab and atezolizumab in unselected patients (12–14).

Despite these advances in prolonging survival of patients with metastatic NSCLC, after progression on second-line treatment, there are few options. Third-line treatment continues to be challenging, and subsequent treatment options for patients with metastatic NSCLC remains an area of significant unmet medical need.

Because cell cycle dysregulation occurs in >90% of lung cancers (15), disrupting the cell proliferation machinery may control the growth of advanced NSCLC. During the cell cycle, the G1 restriction point controls entry into S phase (16). Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) form a complex with D-type cyclins to advance the cell cycle through the G1 restriction point through phosphorylation of the Rb tumor suppressor protein (17). Inhibiting CDK4 and CDK6 prevents cell cycle progression, halting tumor growth and promoting senescence.

Abemaciclib is a selective and potent small molecule inhibitor of CDK4 and CDK6 with broad antitumor activity in preclinical models, acceptable physical and pharmacokinetic (PK) properties, and acceptable toxicity profile in nonclinical species (18,19). Preclinical data showed that *KRAS*-mutant NSCLC xenograft models (NCI-H2122, NCI-H358, and NCI-H441) had greater sensitivity to abemaciclib compared with models expressing a wild-type *KRAS* gene (NCI-H1975 and NCI-H1650) (20). In addition, preclinical studies conducted in *KRAS*-mutant NSCLC models (NCI-H441 and NCI-H2122) indicated potential additivity when agents such as pemetrexed, gemcitabine, or DC101 (a mouse surrogate of ramucirumab) were combined with abemaciclib. In these studies, the combination therapies demonstrated greater tumor growth inhibition as well as longer duration of growth inhibition following treatment cessation compared with abemaciclib single-agent therapy (21).

In the JPBA phase 1 study, single-agent abemaciclib showed acceptable safety/tolerability as well as early evidence of clinical activity in multiple tumor types, including patients with heavily pretreated metastatic NSCLC (20). Fatigue was the dose limiting toxicity across all tumor types. The most common treatment-emergent adverse events (TEAEs) were gastrointestinal and hematopoietic and were manageable with dose adjustments and supportive care. The disease control rate (DCR) among abemaciclib-treated patients was 49% (33 of 68 patients); 2 patients achieved partial responses. The DCR was greater in the *KRAS*-mutant population (55%) compared to that in the *KRAS* wild-type population (39%).

Based on preclinical and clinical data, we conducted a multicenter phase 1b clinical study to test the safety and tolerability of oral abemaciclib combination therapy in patients with metastatic NSCLC. The secondary objectives of the study included determination of the pharmacokinetic profile for each combination therapy and assessment of antitumor activity.

## Methods

A multicenter, nonrandomized, open-label phase 1b trial enrolled patients previously treated for advanced/metastatic NSCLC. The study comprised multiple study parts, each with an initial dose escalation phase to determine the maximum tolerated dose (MTD) of abemaciclib plus pemetrexed (part A), gemcitabine (part B), or ramucirumab (part C), followed by an expansion phase for each study part. Part C also included investigation of an alternative ramucirumab dosing schedule. Two additional parts of the study, abemaciclib in combination with LY3023414 (PI3K/mTOR dual inhibitor) and pembrolizumab, have not been concluded and will be reported separately.

This study was designed by the sponsor and was conducted in accordance with the Declaration of Helsinki ethical principles and International Conference on Harmonisation Guidelines for Good Clinical Practice. Site-specific institutional review boards or ethics committees approved the study protocol and amendments. All patients provided written informed consent. The study is registered at www.ClinicalTrials.gov (NCT02079636).

### Patients

Key eligibility criteria included previously treated advanced/metastatic NSCLC, age ≥18 years, Eastern Cooperative Oncology Group performance status ≤1, and adequate hematologic and end organ function. Eligibility was not restricted based on molecular features; however, all patients with EGFR-activating mutations or ALK alterations should have progressed on or after an EGFR or ALK tyrosine kinase inhibitor prior to enrollment.

Part A required nonsquamous histology and one to three prior therapies, including one platinum-based chemotherapy for advanced/metastatic NSCLC. Pemetrexed received as first-line or maintenance therapy must have been completed ≥3 months prior to study entry. Part B allowed any histological subtype and required one to three prior therapies for advanced/metastatic NSCLC. Part C allowed any histological subtype and required two to three prior therapies for advanced/metastatic NSCLC. Study allowed patients with measureable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors v1.1 (22). (The online appendix lists eligibility requirements.)

**Treatments and MTD determination**

Table S1 (online appendix) outlines treatments and dose escalation scheme. During the dose escalation phase, cohorts of three to six patients enrolled at each of the planned dose levels. Abemaciclib was administered orally every 12 hours (Q12H) on days 1 through 21 of a 21-day cycle at 150 or 200 mg (the established single-agent MTD) until disease progression or other study discontinuation criteria were met. Pemetrexed (part A) and gemcitabine (part B) were administered according to label: day 1 for pemetrexed, days 1 and 8 for gemcitabine. Ramucirumab (part C) was administered on two different schedules on day 1 or on days 1 and 8 of a 21-day cycle. The ramucirumab days 1 and 8 regimen was developed based on pharmacokinetic simulations with the expectation to produce higher trough concentrations relative to the standard dosing regimen (22). Dose adjustments (omission and reduction) were permitted for each drug for specific toxicities (see online appendix for details). Patients discontinued from study treatment upon progression, unacceptable toxicity, or decision by the patient, physician, or sponsor. Post-study treatment evaluation occurred 30 ± 7 days from the last dose of study drug.

Safety assessments guided the dose escalation phase during the first 21 days of treatment for all patients in each cohort. If no patient experienced a dose-limiting toxicity (DLT), dose escalation occurred to the next prespecified dose level. If one of three patients at any cohort experienced a DLT, then three additional patients were enrolled at that dose level. If a DLT was observed in ≥2 out of a maximum of six patients at any given dose, dose escalation ceased, and either the previous dose was declared the MTD for the combination therapy or additional patients were treated at the previous dose level to ensure <2 DLTs out of 6 patients occurred at that dose level. If more than 2 of 6 patients experienced a DLT at 150 mg Q12H, then the dose of abemaciclib was to be de-escalated to 100 mg Q12H. After the MTD for each combination therapy was identified in each study part in the dose escalation phase, each study part enrolled 12 additional patients for the confirmation phase of the study. Part C (ramucirumab) included a second dose escalation and a 6-patient confirmation cohort to evaluate an alternate dosing schedule for ramucirumab.

A DLT was defined as an adverse event (AE) occurring during cycle 1 of the dose escalation phase that was possibly related to either abemaciclib or the combination therapy and fulfilled any of the following criteria: grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte disturbance persisting >2 days despite intervention, any other grade 3 or 4 nonhematological toxicity, grade 4 hematological toxicity that lasted longer than 5 days, grade 3 or 4 thrombocytopenia with evidence of bleeding, or febrile neutropenia. A DLT-equivalent toxicity (DET) was defined as an AE that would have met the criteria for DLT if it had occurred during cycle 1 of the dose escalation phase, but that occurred in a later cycle or during any cycle of the dose confirmation phase.

**Assessments**

Safety was assessed by AEs, DLTs, central laboratory tests, and local electrocardiograms. Adverse events were assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (23). Radiological tumor assessments were performed locally at baseline and then every 6 weeks thereafter until evidence of disease progression. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors v1.1 (24).

Pharmacokinetic samples were collected for all patients to measure concentrations of abemaciclib and its metabolites (LSN2839567, LSN3106729, and LSN3106726). Separate blood samples were collected to measure concentrations of pemetrexed (part A), gemcitabine plus its metabolite 2′,2′-difluorodeoxyuridine (dFdU) (part B), and ramucirumab (part C).

Pharmacokinetic samples were collected at predose, immediately postdose (cycle 1, day 1 only), and at 1, 2, 4, 6, 8, 10 hours postdose of abemaciclib on cycle 1, day 1 and on cycle 2, day 1 for abemaciclib and combination agents. Additional samples were collected at predose of cycle 1, day 8 (for abemaciclib and its metabolites, gemcitabine plus its metabolite, and ramucirumab) and cycle 1, day 15 (for abemaciclib and its metabolites). Pharmacokinetic analyses were conducted on patients who had received at least 1 dose of study drug and had adequate samples collected. Plasma concentrations of abemaciclib and its metabolites were assayed at Q2 Solutions (Ithaca, New York). Plasma samples were analyzed for pemetrexed and gemcitabine and its metabolite at BASi (West Lafayette, IN USA). Serum

concentrations of ramucirumab were assayed at Intertek Pharmaceutical Services (San Diego, CA, USA). Pharmacokinetic parameter estimates were computed for abemaciclib, its metabolites, and whenever possible, for pemetrexed, gemcitabine, and ramucirumab). Pharmacokinetic parameters were computed by standard noncompartmental methods using WinNonlin (Professional Edition). The primary parameters for analysis were maximum concentration ($C_{max}$) and area under the concentration-time curve from time zero to the last observation ($AUC_{0-tlast}$).

**Statistical methods**

All patients who had at least 1 dose of study therapy were included in the analyses. Data were summarized by study part and dose group, as appropriate. For continuous variables, summary statistics included mean, median, standard deviation, and range. Categorical endpoints such as baseline characteristics, safety, and tumor response were summarized as frequency and percentages. Progression-free survival (PFS) was analyzed using Kaplan-Meier methodology (25). Statistical Analyses System (SAS) V9 was used to analyze the data.

## Results

From April 2014 through March 2016, 10 centers in the United States and Spain enrolled 86 patients with stage IV NSCLC in parts A, B, or C of the study based on prior therapy or histology. All patients were evaluable for safety and efficacy assessment. At the time of data cutoff (August 24, 2016), all patients except five (all on part C) had discontinued study treatment (Table S2, online appendix). The median age was 64–66 years across study parts (range: 43–83 years), with a median of 2 prior lines of therapy for advanced/metastatic disease (Table 1).

All patients received abemaciclib (150 or 200 mg, twice daily) while on study in combination with either pemetrexed (part A), gemcitabine (part B), or ramucirumab (part C) on a 21-day cycle. Median number of cycles was 1.5–3.0 and range: 1–30 (Table S3, online appendix). Abemaciclib dose reductions occurred in 11 of 23 (48%) patients in part A, 8 of 24 (33%) patients in part B, and 14 of 39 (36%) patients in part C. Dose omissions occurred in 15 patients in both parts A and B (65% and 63%, respectively), and in 21 patients (54%) in part C. The relative dose intensity of abemaciclib was 75–93% among the various treatment and dosage groups (Table S3, online appendix).

### Dose escalation and MTD determination

#### *Part A*

The MTD was not reached for the abemaciclib-pemetrexed combination. At the 150-mg abemaciclib dose level, eight patients were enrolled; two of the initial three patients were deemed not evaluable and replaced. One patient experienced DLTs at 150 mg abemaciclib. No other DLTs occurred in part A at the 150-mg abemaciclib dose level (Table 2). At the 200-mg abemaciclib dose level, no DLTs were observed during cycle 1; one DET of grade 3 febrile neutropenia occurred during cycle 2. During cycle 2 of the 200-mg abemaciclib confirmation phase, one patient experienced grade 3 febrile neutropenia, and two patients experienced grade 4 neutropenia lasting longer than 5 days.

#### *Part B*

The MTD was not reached for the abemaciclib-gemcitabine combination. At the 150-mg abemaciclib dose level, no DLTs reported (Table 2). At the 200-mg abemaciclib dose level, one DLT of

grade 3 fatigue occurred and four DETs, including grade 3 fatigue, grade 3 diarrhea, and two patients with grade 3 infections (grade 4 sepsis; grade 4 neutropenia/febrile neutropenia).

***Part C***

Part C evaluated two different dose schedules for ramucirumab. The first part C dosing schedule evaluated abemaciclib 150 or 200 mg twice daily in combination with ramucirumab 10 mg/kg on day 1 of a 21-day schedule (hereafter referred to as day 1 regimen). The second dosing schedule evaluated abemaciclib 150 mg twice daily in combination with ramucirumab 8 or 10 mg/kg on days 1 and 8 of a 21-day schedule (hereafter referred to as day 1, 8 regimen).

The MTD was not reached for the day 1 regimen. At the 150-mg abemaciclib dose level (ramucirumab 10 mg/kg day 1), four patients enrolled; one of the initial three patients was not evaluable and replaced. No DLTs were reported and one DET of grade 3 hyponatremia occurred during cycle 9. At the 200-mg abemaciclib dose level (ramucirumab 10 mg/kg day 1), two DLTs were reported in a single patient, grade 4 neutropenia and grade 4 leukopenia, and therefore the MTD was not achieved. DETs included grade 3 diarrhea, grade 4 hypokalemia, and grade 3 stomatitis (Table 2).

For the day 1,8 regimen, 12 patients enrolled at the 8 mg/kg ramucirumab days 1, 8 dose level and 4 patients at the 10 mg/kg ramucirumab days 1, 8 dose level. At the 8 mg/kg days 1, 8 dose level, 1 DLT of grade 3 stomatitis and 2 DETs of grade 3 fatigue occurred. At the 10 mg/kg days 1, 8 dose level, 4 DLTs occurred (3 patients), 1 DLT each of grade 4 embolism, and grade 3 myocardial infarction, and two DLTs of grade 3 fatigue. Thus, the MTD declared for part C second dosing schedule was abemaciclib 150 mg twice daily and ramucirumab 8 mg/kg on days 1 and 8 of a 21-day cycle.

**Safety**

***Part A***

Among patient receiving the combination of abemaciclib and pemetrexed, the most common nonhematologic TEAEs (any grade) were fatigue (74%), diarrhea, (78%), decreased appetite (57%), nausea (48%), dyspnea (39%), increased blood creatinine (39%), stomatitis (30%), and vomiting (22%) (Table 3). The most common hematologic TEAEs (any grade) were neutropenia (65%), anemia (74%),

thrombocytopenia (44%), and leukopenia (30%). All-cause grade 3–4 TEAEs in ≥10% of patients were neutropenia (65%), anemia (26%), leukopenia (22%), dyspnea (22%), and thrombocytopenia (17%). Table S3 explains dose reduction information for part A.

***Part B***

Abemaciclib plus gemcitabine yielded a similar pattern of TEAEs as observed in part A. The most common nonhematologic TEAEs (any grade) were fatigue (75%), nausea (67%), diarrhea (58%), decreased appetite (33%), vomiting (29%), dyspnea (21%), and increased blood creatinine (21%) (Table 3). The most common hematologic TEAEs (any grade) were neutropenia (54%), thrombocytopenia (46%) anemia (42%), and leukopenia (21%). All-cause grade 3–4 TEAEs in ≥10% of patients were neutropenia (33%), anemia (25%), dyspnea (21%), and leukopenia (13%). High-grade diarrhea was greater in part B than part A (17% and 4%, respectively). Table S3 explains dose reduction information for part B.

***Part C***

Among patients receiving the combination of abemaciclib and ramucirumab, across dose schedules, the most common nonhematologic TEAEs (any grade) were diarrhea (72%), fatigue (62%), nausea (49%), decreased appetite (41%), vomiting (31%), dyspnea (23%), and stomatitis (21%) (Table 3). The most common hematologic TEAEs (any grade) were neutropenia (23%), thrombocytopenia (21%), anemia (13%), and leukopenia (8%). All-cause grade 3 to 4 TEAEs in ≥10% of patients were fatigue (23%), diarrhea (10%), neutropenia (10%), and thrombocytopenia (10%). High-grade diarrhea was exclusively associated with the 200-mg abemaciclib dose level combined with ramucirumab 10 mg/kg (day 1 regimen). Table S3 explains dose reduction information for part C.

**Pharmacokinetics**

Figure 1 shows the mean plasma concentration-time profiles of abemaciclib and metabolites when administered in combination with other therapies, after a single abemaciclib dose, and at steady state after multiple twice-daily abemaciclib doses. Following 150-mg repeated doses (Table 4), the steady-state, geometric mean abemaciclib $C_{max}$ was 164 to 492 ng/mL and $AUC_{(0–tlast)}$ was 1300 to 3460 (hr*ng/mL). Following the 200-mg repeated doses, the geometric mean abemaciclib $C_{max}$ was 227 to 483

ng/mL and $AUC_{(0–tlast)}$ was 1380 to 3460 (hr*ng/mL). Considering the high variability of the abemaciclib and metabolite pharmacokinetic parameters among the patient plasma samples, the exposure parameters for abemaciclib appeared similar among different combination therapies.

Pharmacokinetic parameters for pemetrexed and mean plasma concentration-time profiles are presented in Table S4 and Figure S1, respectively (online appendix). Pharmacokinetic parameters for gemcitabine metabolite and mean plasma concentration-time profiles are presented in Table S5 and Figure S2, respectively (online appendix). Considering the long half-life of ramucirumab and the limited sampling schedule (up to 10 hours postdose), no pharmacokinetics parameters were estimated for ramucirumab. Figure S3 presents mean serum concentration-time profiles of ramucirumab. Taken together, the results of this study indicate that there is no effect of abemaciclib on the pharmacokinetics of combination agents and that combination agents have no effect on the pharmacokinetics of the abemaciclib.

**Response**

The addition of abemaciclib to pemetrexed, gemcitabine, or ramucirumab resulted in a response rate of 4–9% (all partial responses) (Table 5). However, the combination of abemaciclib with pemetrexed and ramucirumab resulted in a DCR of 57% and 54%, respectively. In contrast, the DCR the gemcitabine group was 25%. Median PFS results mirrored this trend. PFS for patients treated with abemaciclib plus pemetrexed was 5.55 months (95% CI: 1.81–10.05) and for patients treated with abemaciclib plus ramucirumab was 4.83 months (95% CI: 2.60–6.93), with five patients still receiving study treatment with abemaciclib plus ramucirumab at the time of analysis. In contrast, PFS for patients treated with abemaciclib plus gemcitabine was 1.58 months (95% CI: 1.15–4.24).

Examination of treatment duration as a function of *KRAS* status (mutant versus wild type) did not reveal any relationship between patients receiving longer or shorter treatment and *KRAS* mutation (Figure S4, online appendix). Likewise, there was no apparent relationship between change in tumor size and *KRAS* status (Figure S5, online appendix). However, this interpretation was hampered by the large number of patients (51 of 85, 60%) with unknown *KRAS* status.

## Discussion

Treatment options for patients with metastatic NSCLC are limited considerably after progressing on or after first-line treatment. Among the available treatments, historical median PFS is only 2.0–4.5 months for second-line and likely shorter for later lines of treatment (8, 26). This trial gathers initial data regarding possible new drug combinations for second-line (or additional lines) treatment for metastatic NSCLC. Based on preclinical and clinical data, we conducted a multicenter phase 1b clinical study to test the safety and tolerability of oral abemaciclib combination therapy in patients with metastatic NSCLC.

Maximum tolerated dose was not reached for combinations of abemaciclib with gemcitabine or pemetrexed. Both combination treatments used a maximum abemaciclib dose of 200 mg twice daily. The combination of abemaciclib and ramucirumab 10 mg/kg on day 1 of a 21-day cycle did not reach a MTD. However, the day 1, 8 regimen declared an MTD at abemaciclib 150 mg twice daily plus ramucirumab 8 mg/kg on days 1 and 8 of 21-day cycle.

Abemaciclib was well tolerated in patients across study parts. The safety findings are consistent with AEs expected when combining abemaciclib with single-agent chemotherapy or antiangiogenic therapy. Treatment-related toxicities were generally manageable with dose adjustments and supportive care as needed. No unexpected safety signals or significant differences in AEs or serious adverse events were observed across study parts. Across combination treatments, 17–25% patients had all-cause high-grade (3/4) fatigue. High-grade diarrhea appeared dose dependent and was well managed with antidiarrheal treatments and/or dose adjustments. In part A, one patient discontinued from treatment due to diarrhea. Overall, the incidence of AEs that resulted in treatment discontinuation of one or both study drugs was approximately 16%. In addition, safety findings for parts A and B are consistent with AEs expected when combining myelosuppressive agents with abemaciclib, resulting in an increased myelosuppressive effect (65% and 33% grade 3–4 neutropenia, respectively). As expected, the ramucirumab and abemaciclib combination had lower hematologic toxicity with a 23% overall incidence of neutropenia and 10% incidence of grade 3–4 neutropenia, which is consistent with the safety profile of single-agent abemaciclib (20). Across study parts, grade 3-4 TEAEs were generally reversible upon dose

omission and/or dose reduction. The overall safety and tolerability of abemaciclib combination therapy are important in this heavily pretreated metastatic NSCLC population.

In general, abemaciclib can be dosed on a continuous twice-daily schedule when combined with single-agent chemotherapy or antiangiogenic therapy. The range of abemaciclib exposures achieved when combined with pemetrexed, gemcitabine, or ramucirumab is consistent with that observed in single-agent studies. There is no evidence of an effect of abemaciclib on the pharmacokinetics of pemetrexed, gemcitabine, or ramucirumab. The abemaciclib steady state exposures achieved in this current study have been associated with inhibition of Rb phosphorylation and G1 cell cycle arrest in xenograft models (19). Furthermore, when used as a single agent in patients with cancer, abemaciclib doses of 150 or 200 mg Q12H were associated with sustained biochemical inhibition (reduced phosphorylated Rb) and phenotypic G1 arrest (as assessed by reduced topoisomerase II alpha) expression in skin keratinocytes and tumor biopsies (20).

Tumor response data for the combinations of pemetrexed and ramucirumab with abemaciclib demonstrated preliminary antitumor activity relative to the abemaciclib and gemcitabine combination. The DCR for abemaciclib plus pemetrexed was 57% ($n$ = 23), abemaciclib plus gemcitabine was 25% ($n$ = 24), and abemaciclib plus ramucirumab was 54% ($n$ = 39). As expected, the median PFS data followed the same trend as the DCR, namely greater for the pemetrexed combination (5.55 months) and ramucirumab combination (4.83 months) across dosing schedules, and lesser for the gemcitabine combination (1.58 months). No relationship was identified between *KRAS* mutation status and treatment duration or tumor response for the abemaciclib combinations explored among the 40% of patients with *KRAS* status by local testing. Earlier studies found that among abemaciclib-treated patients, the DCR was greater in the *KRAS*-mutant population compared with the *KRAS* wild-type population, due largely to an increase in stable disease (20). Additionally, *KRAS*-mutant NSCLC xenografts were found to be more sensitive to abemaciclib than wild-type NSCLC xenografts (20), also supporting the concept that the *KRAS* mutation identifies a population of NSCLC tumors sensitive to abemaciclib. However, no definitive efficacy conclusions can be reached due to the nonrandomized design and small sample size.

In summary, this trial confirmed the safety and tolerability of abemaciclib combined with single-agent chemotherapy or antiangiogenic therapy in previously treated unselected patients with advanced/metastatic NSCLC.

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# TABLES

## Table 1. Demographic profile of study populations

| | Part A Abemaciclib +Pemetrexed (N=23) | Part B Abemaciclib +Gemcitabine (N=24) | Part C Abemaciclib +Ramucirumab (N=39) |
|---|---|---|---|
| **Age, (years)** | | | |
| Median (range) | 64 (43-83) | 66 (43-80) | 66 (43-82) |
| ≥65 years, n (%) | 11 (48) | 13 (54) | 16 (62) |
| **Male, n (%)** | 14 (61) | 13 (54) | 23 (59) |
| **Race** | | | |
| American Indian | 0 | 2 (8) | 0 |
| Asian | 1 (4) | 2 (8) | 1 (3) |
| Black | 1 (4) | 1 (4) | 0 |
| White | 21 (91) | 19 (79) | 38 (97) |
| **Country** | | | |
| Spain | 9 (39) | 6 (25) | 13 (33) |
| USA | 14 (61) | 18 (75) | 26 (67) |
| **ECOG PS** | | | |
| 0 | 11 (48) | 12 (50) | 10 (26) |
| 1 | 12 (52) | 12 (50) | 29 (74) |
| **Histology** | | | |
| Adenocarcinoma[a] | 21 (91) | 19 (79) | 28 (76) |
| Large Cell Carcinoma | 0 (0) | 1 (4) | 1 (3) |
| Squamous[b] | 0 (0) | 3 (13) | 6 (16) |
| Lung, Other/Not otherwise specified[c] | 2 (9) | 1 (4) | 2 (5) |
| **Median duration of disease from initial diagnosis, months, (range)** | 16 (4–50) | 19 (6–119) | 19 (6–102) |
| **Prior systemic therapies, median (range)** | | | |
| Any intent | 2 (1–5) | 2.5 (1–5) | 2 (1–6) |
| Advanced/metastatic | 2 (1–3) | 2 (1–4) | 2 (1–6) |

[a] 2 patients had incomplete data for Part C histology. Percentages are based on the number of patients with data.
[b] Includes squamous and adenosquamous (predominantly squamous). Only patients with nonsquamous histology were eligible for Part A.
[c] Includes: bronchioalveolar, adenosquamous (not specified), and lung – not otherwise specified.

**Table 2. Dose-limiting toxicities and DLT-equivalent toxicities**

| Abemaciclib dose (mg) | No. of patients treated | No. of patients with DLT or DET | Cohort[a] | DLT or DET[b] | Cycle |
|---|---|---|---|---|---|
| **Part A: Abemaciclib + Pemetrexed** | | | | | |
| 150 mg Q12H | 8 | 1 | Escalation | Acute kidney injury, Gr 3<br>Blood creatinine increased, Gr 3<br>Fatigue, Gr 3 | 1 |
| 200 mg Q12H | 15 | 4 | Escalation | Febrile neutropenia, Gr 3 | 2 |
| | | | Confirmation | Febrile neutropenia, Gr 3 | 1 |
| | | | Confirmation | Neutropenia, Gr 4 | 2 |
| | | | Confirmation | Neutropenia, Gr 4 | 2 |
| **Part B: Abemaciclib + Gemcitabine** | | | | | |
| 150 mg Q12 H | 3 | 0 | -- | None | -- |
| 200 mg Q12 H | 21 | 5 | Escalation | Fatigue, Gr 3 | 1 |
| | | | Confirmation | Fatigue, Gr 3 | 1 |
| | | | Confirmation | Diarrhea, Gr 3 | 1 |
| | | | Confirmation | Scrotal infection, Gr 3 | 1 |
| | | | Confirmation | Neutropenia, Gr 4<br>Sepsis, Gr 4<br>Febrile neutropenia, Gr 4<br>Lung infection, Gr 3 | 2 |
| **Part C: Abemaciclib + Ramucirumab** | | | | | |
| 150 mg Q12H + Ram 10 mg/kg day 1 | 4 | 1 | Escalation | Hyponatraemia, Gr 3 | 9 |
| 200 mg Q12H + Ram 10 mg/kg day 1 | 19 | 3 | Escalation | Leukopenia, Gr 4<br>Neutropenia, Gr 4 | 1 |
| | | | Escalation | Diarrhea, Gr 3<br>Hypokalaemia, Gr 4 | 2,3<br>3 |
| | | | Confirmation | Stomatitis Gr 3 | 1 |
| 150 mg Q12H<br>Ram 8 mg/kg days 1,8 | 12 | 2 | Escalation | Stomatitis, Gr 3<br>Fatigue, Gr 3 | 1<br>2 |
| | | | Confirmation | Fatigue, Gr 2 | 2 |
| 150 mg Q12H + Ram 10 mg/kg Days 1,8 | 4 | 3 | Escalation | Embolism, Gr 4<br>Fatigue, Gr 3 | 1 |
| | | | Escalation | Myocardial infarction, Gr 3 | 1 |
| | | | Escalation | Fatigue, Gr 3 | 1,6 |

[a] Each cohort listing represents a different patient. Some patients exhibited >1 DLT/DET or the same DLT/DET in >1 cycle.
[b] A DLT was defined as one of a list of specific adverse events occurring during cycle 1 of the dose-escalation phase that was possibly related to abemaciclib or the combination therapy. A DET was defined as an adverse event that would have met the criteria for DLT if it had occurred during cycle 1 for a patient enrolled in the dose-escalation phase, but that occurred in a later cycle or during any cycle for a patient in the dose-expansion phase.
Abbreviations: DET, DLT-equivalent toxicity; DLT, dose-limiting toxicity; Gr, grade; No., number; Q12H, every 12 hours.

**Table 3. Treatment-emergent adverse events regardless of causality, by grade and doses.**

| | **Part A: Abemaciclib + Pemetrexed (*N* = 23)** | | **Part B: Abemaciclib + Gemcitabine (*N* = 24)** | | **Part C: Abemaciclib + Ramucirumab (*N* = 39)** | |
|---|---|---|---|---|---|---|
| **Adverse event[a] (N = 73)** | **Grade 3/4, *n* (%)** | **All grades, *n* (%)** | **Grade 3/4, *n* (%)** | **Grade 3/4, *n* (%)** | **All grades, *n* (%)** | **Grade 3/4, *n* (%)** |
| Diarrhea | 1 (4) | 18 (78) | 4 (17) | 14 (58) | 4 (10) | 28 (72) |
| Fatigue | 4 (17) | 18 (78) | 6 (25) | 18 (75) | 9 (23) | 24 (62) |
| Nausea | 1 (4) | 11 (48) | 2 (8) | 16 (67) | 2 (5) | 21 (54) |
| Neutropenia | 15 (65) | 15 (65) | 8 (33) | 13 (54) | 4 (10) | 9 (23) |
| Anemia | 7 (30) | 18 (78) | 6 (25) | 10 (42) | 1 (3) | 5 (13) |
| Decreased appetite | 2(9) | 13 (57) | 1 (4) | 9 (38) | 2 (5) | 16 (41) |
| Thrombocytopenia | 4 (17) | 10 (44) | 2 (8) | 11 (46) | 4 (10) | 8 (21) |
| Vomiting | 0 (0) | 5 (22) | 0 (0) | 8 33) | 0 | 16 (41) |
| Blood creatinine increased | 1 (4) | 9 (39) | 0 (0) | 5 (21) | 1 (3) | 8 (21) |
| Dyspnea | 5 (22) | 9 (39) | 5 (21) | 5 (21) | 1 (3) | 9 (23) |
| Leukopenia | 5 (22) | 7 (30) | 3 (13) | 5 (21) | 2 (5) | 3 (8) |
| Stomatitis | 1 (4) | 8 (35) | 0 (0) | 2 (8) | 3 (8) | 8 (21) |
| **Abemaciclib dose Adverse event, grades 3/4[a]** | **150 mg *N* = 8 *n* (%)** | **200 mg *N* = 15 *n* (%)** | **150 mg *N* = 3 *n* (%)** | **200 mg *N* = 21 *n* (%)** | **150 mg[b] *N* = 20 *n* (%)** | **200 mg[b] *N* = 19 *n* (%)** |
| Diarrhea | 0 (0) | 1 (7) | 0 (0) | 4 (19) | 0 | 4 (21) |
| Fatigue | 3 (38) | 1 (7) | 1 (33) | 5 (24) | 5 (25) | 4 (21) |
| Nausea | 1 (13) | 0 (0) | 1 (33) | 1 (5) | 0 | 2 (11) |
| Neutropenia | 6 (75) | 9 (60) | 2 (67) | 6 (29) | 1 (5) | 3 (16) |
| Anemia | 2 (25) | 4 (27) | 0(0) | 6 (29) | 0 | 1 (5) |
| Decreased appetite | 1 (13) | 1 (7) | 0 (0) | 1 (5) | 1 (5) | 1 (5) |
| Thrombocytopenia | 2 (25) | 2 (13) | 0 (0) | 2 (10) | 1 (5) | 3 (16) |
| Vomiting | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 | 0 |
| Blood creatinine increased | 1 (13) | 0 (0) | 0 (0) | 0 (0) | 0 | 1 (5) |
| Dyspnea | 1 (13) | 4 (27) | 1 (33) | 4 (19) | 1 (5) | 0 |
| Leukopenia | 2 (25) | 3 (20) | 0 (0) | 3 (15) | 0 | 2 (11) |
| Stomatitis | 1 (13) | 0 (0) | 0 (0) | 0 (0) | 2 (10) | 1 (5) |

[a]TEAEs that occurred in ≥30% (all grades) in ≥1 part of the study are listed. No grade 5 events occurred for the TEAEs listed.
[b]Among part C patients who received 150 mg abemaciclib, 4 patients received 10 mg/kg ramucirumab on day 1; 12 patients received 8 mg/kg ramucirumab on days 1 and 8; and 4 patients received 10 mg/kg ramucirumab on days 1 and 8. Patients who received 200 mg abemaciclib, received 10 mg/kg ramucirumab on days 1 and 8.

**Table 4. Summary of abemaciclib exposure following oral administration every 12 hours in combination with therapies in patients with stage IV NSCLC.**

| | | Geometric Mean (CV%)[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Single dose | | | Multiple dose | | |
| Combination therapy | Abemaciclib[b] | $C_{max}$ (ng/mL) | $t_{max}$[c] (hr) | $AUC_{(0\text{-last})}$ (hr*ng/mL) | $C_{max}$ (ng/mL) | $t_{max}$[c] (hr) | $AUC_{(0\text{-last})}$ (hr*ng/mL) |
| Pemetrexed | 200 mg BID (n = 15) | 212 (80) | 7.67 (4.00–10.00) | 1050 (95) | 483[d] (41) | 4.00[d] (0.00–9.67) | 3460[d] (49) |
| | 150 mg BID (n = 8) | 114 (67) | 6.09 (3.82–9.73) | 654 (66) | 146.40, 183.23[e] | 7.88, 0.00[e] | 1060, 1600[e] |
| | 100 mg BID (n =2) | | | | 81.17, 46.43[e] | 4.00, 8.00[e] | 435, 190[e] |
| Gemcitabine | 200 mg BID (n = 19) | 206 (73) | 7.85 (3.92–10.00) | 1150 (77) | 304[f] (66) | 6.85[f] (0.00–7.88) | 2100[f] (58) |
| | 150 mg BID (n = 3) | 80.6 (15) | 9.75 (8.00–10.67) | 509 (28) | 288[g] (71) | 5.53[g] (4.00–8.00) | 2060[g] (66) |
| Ramucirumab 10 mg/kg day 1 | 200 mg BID (n = 19) | 195 (86) | 6.00 (2.08–8.00) | 919 (112) | 227[h] (17) | 5.01[h] (0.00–8.00) | 1380[h] (144) |
| | 150 mg BID (n = 4) | 312 (11) | 6.00 (4.33–8.17) | 1830 (18) | 492[i] (117) | 1.00[i] (0.00–7.97) | 3460[i] (125) |
| Ramucirumab 10 mg/kg days 1, 8 | 150 mg BID (n = 4) | 159 (73) | 7.00 (2.00–10.00) | 885 (67) | 377.41[I] | 10.00[I] | 3420[I] |
| | 100 mg BID (n = 1) | | | | 86.14[j] | 6.00[j] | 534[j] |
| Ramucirumab 8 mg/kg days 1, 8 | 150 mg BID (n = 12) | 103 (97) | 7.91 (4.00–8.00) | 549 (108) | 246 (86) | 2.00 (0.00–8.00) | 1730 (95) |

[a]Geometric mean and geometric CV% are provided for $n \geq 3$; otherwise, actual values are provided.
[b]Patients were started on 150 or 200 mg; later, doses were reduced to 100 mg due to dose reductions.
[c]Median and range are provided for $t_{max}$.
[d]$N = 9$.
[e]$N = 2$.
[f]$N = 6$.
[g]$N = 4$.
[h]$N = 8$.
[i]$N = 5$.
[j]$N = 1$.

Abbreviations: $AUC_{(0\text{–last})}$, area under the concentration time curve from time 0 to last observed concentration; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; n, number of observations.

**Table 5. Summary of efficacy measures**

| | Part A: Abemaciclib + Pemetrexed (*N* = 23) | Part B: Abemaciclib + Gemcitabine (*N* = 24) | Part C: Abemaciclib + Ramucirumab (*N* = 39) |
|---|---|---|---|
| **Best overall response, n (%)[a]** | | | |
| Complete response (CR) | 0 (0) | 0 (0) | 0 (0) |
| Partial response (PR) | 1 (4) | 1 (4) | 2 (5) |
| Stable disease (SD) | 12 (52) | 5 (21) | 19 (49) |
| Progressive disease (PD) | 3 (13) | 9 (38) | 6 (15) |
| Unknown | 7 (30) | 9 (38) | 12 (31) |
| Disease control rate (CR + PR + SD) | 13 (57) | 6 (25) | 21 (54) |
| **Progression-free survival** | | | |
| Number of events, n (%) | 11 (48) | 15 (63) | 19 (49) |
| Number of patients censored, n (%) | 12 (52) | 9 (38) | 20 (51) |
| Median PFS, months (95% CI) | 5.55 (1.81, 10.05) | 1.58 (1.15, 4.24) | 4.83 (2.60, 6.93) |

[a]Response criteria RECIST1.1 was used to determine response. Radiological tumor assessments were performed locally at baseline and then every 6 weeks thereafter until evidence of disease progression. Confirmation of complete or partial response was required for determination of best overall response. Stable disease required at least one post-baseline measurement at a minimum interval of 6 weeks after the first dose.

Abbreviations: CI, confidence interval; n, number of observations; PFS, progression-free survival.

## FIGURE LEGEND

**Figure 1. Abemaciclib plasma concentration over time.** Mean plasma concentrations of abemacilcib is shown over time following single dose (left panel) and multiple dose (right panel) administration of abemaciclib (100, 150, or 200 mg) every 12 hours in combination with other agents as treatment for patients with stage IV NSCLC.

Figure 1