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A phase 1b study of necitumumab in combination with abemaciclib in patients with stage IV non-small cell lung cancer

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ABSTRACT

Objectives: Necitumumab, an anti-EGFR antibody, and abemaciclib, a CDK4/6 inhibitor, have shown activity in patients with non-small cell lung cancer (NSCLC) and have non-overlapping toxicities. A 2-part, single-arm, multicenter, phase 1b trial was conducted to test the safety and efficacy of necitumumab plus abemaciclib in patients with advanced NSCLC who had received ≤2 lines of chemotherapy, including a platinum-based one.
Materials and Methods: Part A was a dose-escalation phase for abemaciclib (100, 150, 200 mg, Q12 H) in combination with necitumumab 800 mg D1D8 Q3W to determine the recommended dose for the expansion cohort, Part B. The primary endpoint was progression-free survival (PFS) rate at 3 months.
Results: Sixty-six patients entered the study: 71% male, 41% squamous histology, 15% never-smokers. In Part A (n = 15), the maximum tolerated dose of abemaciclib was 150 mg Q12H in combination with necitumumab 800 mg. In 57 patients treated at this dose level, the 3-month PFS rate was 32.3% (95% CI: 20.4–44.8); median PFS was 2.14 months (1.41–2.76). The overall response rate (ORR) was 5.3% (1.1–14.6). The median OS was 6.93 months (4.96–12.85). In the exploratory subgroup analysis of EGFR expression-negative patients (n = 10), both the 3-month PFS and ORR were 0.0%. The most common grade 3 treatment-emergent adverse events were fatigue (14%), dyspnea (9%), diarrhea (7%), vomiting (7%), and hypokalemia (7%).
Conclusions: Abemaciclib 150 mg Q12H with necitumumab 800 mg did not produce an additive effect over single-agent activity in patients with Stage IV NSCLC. The safety profile was consistent with the individual study drugs.

1. Introduction

In genetically unselected non–small cell lung cancer (NSCLC) patients, platinum-based doublets in combination with pembrolizumab or atezolizumab or pembrolizumab as monotherapy (patients with tumor cell PD-L1 > 50%) are the preferred first-line therapy [1–3]. Platinum-based chemotherapy in combination with various targeted agents, such as necitumumab and bevacizumab, may be used for the initial treatment in appropriate NSCLC patients [4–8]. Patients with epidermal growth factor receptor (EGFR) or *BRAF, ALK, ROS-1* gene aberrations are candidates for first-line therapy with targeted kinase inhibitors [2,9].

As patients either relapse after first-line therapy or show no initial response, second-line and often third-line treatment options are sought. Second-line treatment options include pemetrexed for patients with nonsquamous NSCLC if not previously used and docetaxel with or without ramucirumab (or in the European Union, nintedanib) [2,10–13]. Immune checkpoint inhibitors may also be chosen if not

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previously used; pembrolizumab is indicated for selected patients with PD-L1 expression and atezolizumab and nivolumab in unselected patients [3,14,15]. Although treatment options for patients with metastatic NSCLC have increased, prolonging patient survival after progression on second-line treatment continues to be an unmet medical need.

Necitumumab is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 that blocks the ligand-binding site of the EGFR that is detectable in most tumors of patients with advanced or metastatic NSCLC [16]. The phase 3 trial (SQUIRE) of necitumumab in combination with gemcitabine plus platinum chemotherapy [4], which referenced the FLEX phase 3 trial with cetuximab [5], demonstrated a statistically significant improvement in survival in the first-line treatment of patients with metastatic squamous NSCLC.

Abemaciclib, a selective and potent small-molecule inhibitor of CDK4/6, prevents cell-cycle progression through the G1 restriction point, thus arresting tumor growth. Abemaciclib has shown single-agent antitumor activity in a Phase 1 trial in heavily pretreated patients with NSCLC [17]. In a phase 1b study, abemaciclib, in combination with pemetrexed, gemcitabine, or ramucirumab, demonstrated an acceptable safety profile and preliminary efficacy in patients with metastatic NSCLC [18]. Abemaciclib exposures remained consistent with those observed in single-agent studies.

Because necitumumab and abemaciclib inhibit tumor progression by different, independent modes of action, they have potential as a combination treatment. To this end, a xenograft tumor cell-line model has shown an add-on effect of necitumumab to abemaciclib where the combination was more effective when compared to the activity of either drug alone. (Eli Lilly and Company, data on file). Importantly, the individual toxicity profile suggests no, or only marginal, overlapping toxicity is expected.

Differing modes of action, preclinical data, and the clinical efficacy of necitumumab, as well as other EGFR mAbs and abemaciclib in NSCLC, provide a rationale for the investigation of necitumumab in combination with abemaciclib in patients with stage IV NSCLC. Thus, the purpose of this phase 1b study with an expansion cohort was to explore the efficacy and safety of necitumumab plus abemaciclib in patients with stage IV NSCLC who have received no more than two lines of chemotherapy of which at least one was platinum-based.

2. Methods

2.1. Study design

A multicenter, nonrandomized, open-label phase 1b trial enrolled patients previously treated for advanced/metastatic NSCLC. The study was comprised of two parts: (A) a dose-escalation phase to determine the maximum-tolerated dose (MTD) of abemaciclib at doses up to 200 mg every 12 h (Q12H) when combined with necitumumab 800 mg on days 1 and 8 of a 3-week cycle (D1D8 Q3W) as measured by the number of patients with a dose-limiting toxicity (DLT) in cycle 1, and (B) an expansion phase to evaluate the efficacy in terms of progression-free survival (PFS) rate at 3 months of the combination therapy using the abemaciclib dose identified in Part A. The secondary objectives of Part A included investigating the safety profile of the combination therapy, examining the pharmacokinetics (PK) of necitumumab and abemaciclib, and determining the immunogenicity of necitumumab. The secondary objectives of Part B included determining PFS, overall survival (OS), overall response rate (ORR), and disease control rate (DCR), safety profile, PK, and immunogenicity of necitumumab. Exploratory objectives included correlating *KRAS* mutation status, EGFR protein expression, and tumor histology to clinical outcomes.

This study was designed by the sponsor and was conducted in accordance with the Declaration of Helsinki ethical principles and International Conference on Harmonization 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 (NCT02411591).

2.2. Patients

Key eligibility criteria included histologically- or cytologically-confirmed stage IV NSCLC of any histology type (Part A) or of squamous and nonsquamous histology (Part B); age ≥ 18 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; measurable disease as defined by Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1); progression after one platinum-based chemotherapy regimen and a maximum of one other prior chemotherapy for advanced and/or metastatic disease or judged by the physician as ineligible for further standard second-line chemotherapy; and no symptomatic brain metastases. Prior treatment with an EGFR tyrosine kinase inhibitor or ALK inhibitors was mandatory in patients with tumors that have *EGFR*-activating mutations or *ALK* translocations.

2.3. Treatments and MTD determination

Fig. 1 outlines treatments and dose-escalation scheme. During Part A, necitumumab 800 mg was administered intravenously (IV) on D1D8 Q3W, followed by abemaciclib orally Q12H on days 1–21 of a 21-day cycle. The necitumumab dosing regimen was consistent with approved dosing in combination with chemotherapy [19]. The dose-finding part

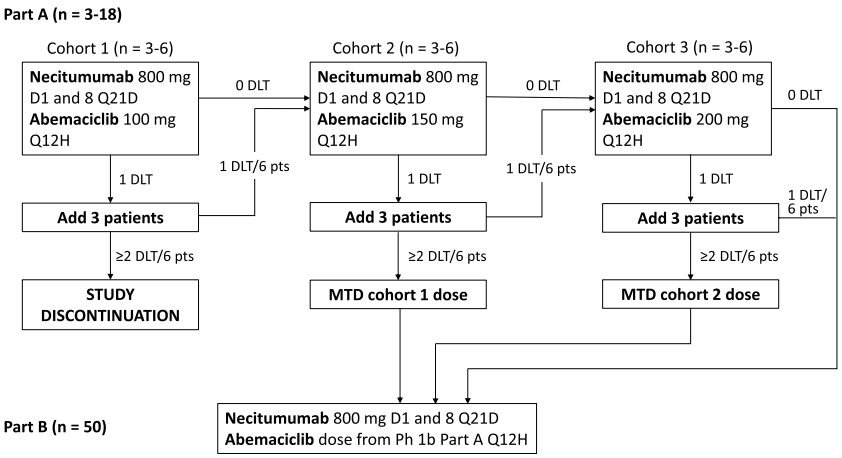

Fig. 1. Study design.

Table 1
Patient demographic and baseline disease characteristics.

	Necitumumab 800 mg + Abemaciclib 150 mg N = 57[a]	Total patients (All dose cohorts) N = 66 [b]
Sex, n (%)		
Female	17 (29.8)	19 (28.8)
Male	40 (70.2)	47 (71.2)
Age (years)		
Median	63	61
Range	37–85	37–85
Country, n (%)		
Belgium	9 (15.8)	11 (16.7)
Spain	3 (5.3)	3 (4.5)
France	45 (78.9)	52 (78.8)
Histological subtype, n (%)		
Non-squamous	29 (50.9)	35 (53.0)
Squamous	27 (47.4)	27 (40.9)
Other	1 (1.8)	4 (6.1)
Disease stage at study entry, n (%)		
Stage IV	57 (100)	66 (100)
Tobacco use, n (%)		
Never	7 (12.3)	10 (15.2)
Current	6 (10.5)	8 (12.1)
Former	44 (77.2)	47 (71.2)
Baseline ECOG performance status, n (%)		
0	11 (19.3)	14 (21.2)
1	45 (78.9)	51 (77.3)
2	1 (1.8)	1 (1.5)
Prior systemic therapy		
Adjuvant	5 (8.8)	7 (10.6)
Neoadjuvant	4 (7.0)	4 (6.1)
Locally advanced	18 (31.6)	19 (28.8)
Metastatic	46 (80.7)	54 (81.8)
Number of lines of prior therapy		
Median	2	2

Abbreviations: n = number of patients in specified category; N = total population size.

[a] The necitumumab 800 mg + abemaciclib 150 mg Q12H population (N = 57) was derived from patients in Part A cohort 2 and all patients in Part B.

[b] The "Total" patient population is derived from Part A, cohorts 1, 2, and 3 (necitumumab 800 mg + abemaciclib 100, 150, 200 mg, Q12H, respectively) and all patients in Part B.

of the study used increasing abemaciclib doses: 100, 150, 200 mg Q12H. The 100-mg starting dose was 50% of the maximum dose administered in monotherapy studies. The study followed a 3 + 3 dose escalation design. Each dose level began with a 3-patient cohort. If no patient experienced a DLT, dose escalation occurred to the next prespecified dose level. If one of the 3 patients experienced a DLT, then 3 additional patients were enrolled at that dose level. If a DLT was observed in ≥2 out of the 6 patients, dose escalation ceased, and the previous dose was declared the MTD for the combination therapy. A DLT was defined as one of the following adverse events (AEs) occurring during cycle 1 of the dose-escalation phase that was considered to be possibly related to necitumumab or abemaciclib or both agents: grade 3 or 4 nausea, vomiting, diarrhea persisting > 2 days despite intervention, any other grade 3 or 4 nonhematological toxicity except electrolyte disturbance, grade 3 thrombocytopenia with bleeding requiring transfusion, grade 4 thrombocytopenia with or without bleeding, grade 4 neutropenia that lasts longer than 5 days, grade 3 or 4 febrile neutropenia, grade 3 or 4 skin toxicity despite best supportive care, and an inability to dose ≥75% of the planned dose for both agents in the first cycle due to toxicity. A full list of defined DLTs and dose delay and reduction criteria are included in the online Supplemental Data.

2.4. Assessments

Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Tumor assessments were performed locally at baseline and every 6 weeks (± 3 days) until evidence of disease progression according to RECIST 1.1.

Blood samples were collected based on a predefined schedule to determine the serum concentrations of necitumumab using a validated enzyme-linked immunosorbent assay (ELISA) method and to determine the plasma concentrations of abemaciclib and its metabolites using a validated liquid chromatography–tandem mass spectrometry method. For abemaciclib, PK parameters were computed by standard non-compartmental methods of analysis using WinNonlin (Professional Edition), including maximum concentration, area under the concentration-time curve, and terminal half-life for Part A and a descriptive summary of exposure for Part B. For necitumumab, PK parameters included a descriptive summary of exposure for Part A and B.

Immunogenicity was assessed by measuring the presence of anti-drug antibodies (ADA) and neutralizing antibodies using two validated ELISAs.

Translational research was undertaken utilizing a tumor tissue block or serial tumor tissue slides obtained at baseline. EGFR protein expression was assessed by an immunohistochemistry (IHC) assay in the archived tumor tissue, using the commercially available Dako EGFR PharmDx kit (Catalog #K1494, Dako, Carpinteria, CA) at Clarient Diagnostic Services, Inc. Positive staining was defined as immunoreactivity of tumor cell membranes at any intensity in > 1% of cells; negative staining was defined as immunoreactivity of tumor cell membranes at any intensity ≤1% of cells.

KRAS mutation status in archived tumor tissue was assessed with the Modaplex KRAS Mutation Analysis Kit (Catalog #510750, QIAGEN, Germantown, MD) at Insight Genetics, Inc. Patients were described as *KRAS* mutation-positive if test results were positive for one or more of the 13 somatic *KRAS* oncogene mutations assessed by the assay; *KRAS* mutation-negative patients had test results that were negative for all mutations assessed.

2.5. Statistical methods

In Part B, the primary outcome of a 3-month PFS rate was estimated by the Kaplan Meier method. Part A patients with squamous or non-squamous NSCLC who received the recommended abemaciclib dose for Part B were included in the Part B portion of the trial. All patients who had at least one dose of study therapy and complete radiographic assessment at baseline were included in the analyses. The statistical null hypothesis stated that the true 3-month PFS rate was 50%, whereas the research hypothesis stated that the true 3-month PFS rate was 65%. The null hypothesis would be rejected at the final analysis only if at least 60% of evaluable patients experience PFS ≥ 3 months. The study had a one-sided alpha level of 0.10, with statistical power of 81% assuming full enrollment of 50 evaluable patients in Part B.

All patients who had at least one dose of study therapy were included in the safety analyses. Data were summarized by dosage group. 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. Statistical Analyses System (SAS) V9 was used to analyze the data.

3. Results

3.1. Patient disposition

From June 2015 through January 2017, 11 centers in Belgium, France, and Spain enrolled 66 patients with stage IV NSCLC in Parts A

Table 2
Extent of exposure to necitumumab and abemaciclib by cohort.

	Cohort 1: Neci 800 mg + Abema 100 mg, N = 3	Cohort 3: Neci 800 mg + Abema 200 mg, N = 6	Cohort 2 + Part B: Neci 800 mg + Abema 150 mg, N = 57[a]	Total patients (All dose cohorts), N = 66[b]
Necitumumab				
Number of patients who received necitumumab	3	6	57	66
Cycles received per patient				
Median	16.0	3.5	3.0	3.0
Range	4–22	1-11	1–21	1–22
Duration of therapy (weeks)				
Median	51.0	11.0	9.0	9.0
Range	12.1–66.6	3.0–33.1	3.0–64.0	3.0–66.6
Relative dose intensity (%)				
Median	96.9	94.9	97.2	97.0
Range	91.2–98.8	67.9–100	54.0–105.0	54.0–105.0
Patients with at least 1 dose adjustment, n (%)	3 (100.0)	4 (66.7)	34 (59.6)	
Patients with at least 1 dose reduction, n (%)	0	1 (16.7)	6 (10.5)	
Patients with at least 1 dose delay, n (%)	3 (100.0)	4 (66.7)	13 (22.8)	
Patients with at least 1 dose omission, n (%)	2 (66.7)	2 (33.3)	26 (45.6)	
Abemaciclib				
Number of patients who received abemaciclib	3	6	57	66
Duration of therapy (weeks)				
Median	51.7	11.1	8.6	9.1
Range	12.0–65.6	2.3–31.3	1.1–59.0	1.1–65.6
Relative dose intensity (%)				
Median	68.1	88.5	84.7	93.1
Range	65.8–96.8	84.6–100	42.7–258.3	42.7–258.3
Patients with at least 1 dose adjustment, n (%)	0	3 (50.0)	32 (56.1)	
Patients with at least 1 dose reduction, n (%)	0	0	13 (22.8)	
Patients with at least 1 dose omission, n (%)	0	3 (50.0)	30 (52.6)	

Abbreviations: Abema = abemaciclib; N = total population size; Neci = necitumumab.
[a] The necitumumab 800 mg + abemaciclib 150 mg Q12H population (N = 57) was derived from patients in Part A, cohort 2 and all patients in Part B.
[b] The "Total" patient population is derived from Part A, cohorts 1, 2, and 3 (necitumumab 800 mg + abemaciclib 100, 150, 200 mg, Q12H, respectively) and all patients in Part B.

or B of the study. All patients were evaluable for safety and efficacy assessment. The median age was 61 (range: 37–85 years); most patients had ECOG PS of 1; 53% of the population exhibited nonsquamous NSCLC; and patients had a median of two lines of prior systemic therapy (Table 1). In the dose-finding Part A, 3 patients were treated in cohort 1, 6 patients in cohort 2, and 6 patients in cohort 3.

As of the data cut-off date (23 June 2017), 5 patients receiving necitumumab 800 mg plus abemaciclib 150 mg Q12H were still on study treatment. The most common reasons for study treatment discontinuation among all patients were progressive disease (PD) (47 patients, 71.2%) and AE (6 patients, 9.1%) (Table S1, online Supplemental Data).

3.2. Exposure

Table 2 summarizes treatment exposure among the three cohorts and the total population. Among the 66 treated patients (Parts A and B), the median number of cycles of necitumumab per patient was three (range, 1–22). The median duration of treatment was 9 weeks for necitumumab (range 3–66.6 weeks) and 9.1 weeks for abemaciclib (range, 1.1–65.6 weeks). The median relative dose intensity for necitumumab was 97% (range 54–105%) and 93.1% for abemaciclib (range 42.7–258.3%).

3.3. Dose escalation and MTD determination

Dosing and DLTs from the dose-escalation portion of the study (Part A) are summarized in Table S2, online Supplemental Data. In Part A, no patients experienced a DLT during cycle 1 of cohort 1. One of 6 patients in cohort 2 experienced a DLT (grade 3 diarrhea). Two of 6 patients in cohort 3 experienced DLTs (grade 3 stomatitis and grade 4 thrombocytopenia). Thus, the MTD was determined to be an absolute dose of necitumumab 800 mg D1D8 Q3W in combination with abemaciclib 150 mg Q12H day 1–21, and this dose was used to treat the 51 patients in Part B.

3.4. Safety

As outlined in Table 3, the most commonly reported (≥50%) treatment-emergent adverse events (TEAEs) among patients receiving abemaciclib 150 mg plus necitumumab 800 mg were grade 1 and 2 with fatigue, diarrhea, skin reactions, and rash. Overall, the most common grade ≥3 TEAEs (occurring in ≥4 patients) were fatigue (n = 8), dyspnea (n = 5), decreased appetite (n = 4), diarrhea (n = 4), hypokalemia (n = 4), hypophosphatemia (n = 4), neutropenia (n = 4), and vomiting (n = 4).

The most common AEs of special interest were skin reactions (any grade: 77.3%; grade ≥3: 10.6%), rash (any grade: 71.2%; grade ≥3: 4.5%), and hypomagnesemia (any grade: 31.8%; grade ≥3: 1.5%).

Six patients discontinued all study treatment because of an AE: 4 of the 57 patients treated with abemaciclib 150 mg Q12H plus necitumumab 800 mg, and 2 of 6 patients treated with abemaciclib 200 mg Q12H plus necitumumab 800 mg (Table S3, online Supplemental Data). Four of the six events were considered by the investigator to be related to treatment: grade 3 anemia, stomatitis, and general physical health deterioration, and grade 4 thrombocytopenia.

There was one disease-related death on study and 12 deaths in the 30-days post discontinuation period: 10 patients died due to study disease, 1 due to pneumonitis, and 1 for an indeterminate reason (Table S4, online Supplemental Data). The death due to pneumonitis occurred in a patient treated with necitumumab 800 mg in combination with abemaciclib 150 mg Q12H, 24 days after the last dose of study

Table 3
Treatment-emergent adverse events (TEAEs) and TEAEs of special interest, regardless of causality.

	Necitumumab 800 mg + Abemaciclib 150 mg N = 57[a]		Total patients (All dose cohorts) N = 66[b]	
TEAEs reported in ≥20% of the safety population	Any grade, n (%)	Grade 3/4/5, n (%)	Any grade, n (%)	Grade 3/4/5, n (%)
Patients with any TEAE	57 (100)	41 (71.9)	66 (100)	46 (69.7)
Fatigue[c]	36 (63.2)	8 (14.0)	43 (65.2)	8 (12.1)
Diarrhea	29 (50.9)	4 (7.0)	33 (50.0)	4 (6.1)
Dermatitis acneiform	26 (45.6)	2 (3.5)	31 (47.0)	3 (4.5)
Decreased appetite	20 (35.1)	3 (5.3)	26 (39.4)	4 (6.1)
Nausea	23 (40.4)	2 (3.5)	26 (39.4)	2 (3.0)
Anemia	20 (35.1)	2 (3.5)	24 (36.4)	2 (3.0)
Dyspnea	20 (35.1)	5 (8.8)	22 (33.3)	5 (7.6)
Vomiting	17 (29.8)	4 (7.0)	21 (31.8)	4 (6.1)
Dry skin	15 (26.3)	0	20 (30.3)	0
Thrombocytopenia[c]	14 (24.6)	2 (3.5)	16 (24.2)	3 (4.5)
Blood creatinine increased	13 (22.8)	2 (3.5)	14 (21.2)	2 (3.0)
Hypokalemia	12 (21.1)	4 (7.0)	17 (25.8)	4 (6.1)
Pyrexia	12 (21.1)	0	16 (24.2)	0
Special interest TEAEs				
Patients with any special interest TEAE	50 (87.8)	11 (19.3)	59 (89.4)	13 (19.7)
Skin reactions[c]	43 (75.4)	5 (8.8)	51 (77.3)	7 (10.6)
Rash[c]	39 (68.4)	2 (3.5)	47 (71.2)	3 (4.5)
Hypomagnesemia	20 (35.1)	1 (1.8)	21 (31.8)	1 (1.5)
Conjunctivitis[c]	7 (12.3)	0	10 (15.2)	0
Venous thromboembolic events[c]	6 (10.5)	2 (3.5)	6 (9.1)	2 (3.0)
Interstitial lung disease (pneumonitis)	3 (5.3)	2 (3.5)	3 (4.5)	2 (3.0)
Arterial thromboembolic event (blindness)	1 (1.8)	1 (1.8)	1 (1.5)	1 (1.5)
Infusion-related reaction	1 (1.8)	0	2 (3.0)	0

Abbreviations: n = number of patients in specified category; N = total population size; TEAE = treatment-emergent adverse event.
[a] The necitumumab 800 mg + abemaciclib 150 mg Q12H population (N = 57) was derived from patients in Part A, cohort 2 and all patients in Part B.
[b] The "Total" patient population is derived from Part A, cohorts 1, 2, and 3 (necitumumab 800 mg + abemaciclib 100, 150, 200 mg, Q12H respectively), and all patients in Part B.
[c] Consolidated terms: fatigue includes asthenia; thrombocytopenia includes platelet count decreased; conjunctivitis includes lacrimation increased, blepharitis, dry eye; skin reactions includes: dermatitis acneiform, paronychia, dry skin, nail infection, pruritus, pyogenic granuloma, skin fissures, skin ulcer, anal abscess, erythema, folliculitis, fungal skin infection, impetigo, nail dystrophy, nail ridging, palmar-plantar erythrodysesthesia syndrome, penile infection, rash maculopapular, rash, seborrheic dermatitis, skin infection, and skin toxicity; rash includes dermatitis acneiform, dry skin, pruritus, erythema, and rash maculopapular; venous thromboembolic events includes deep vein thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, pulmonary embolism, superior vena cava syndrome, and venous thrombosis limb.

treatment, and was related to study treatment as per investigator assessment.

3.5. Efficacy

Of the 57 evaluable patients treated with necitumumab 800 mg in combination with abemaciclib 150 mg Q12H, 47 patients had a PFS event. The PFS rate at 3 months was 32.3% (95% CI = 20.4–44.8). The median PFS was 2.14 months (95% CI = 1.41–2.76) (Fig. 2A). A PFS sensitivity analysis confirmed the robustness of the result. Among the evaluable patients (n = 57), the median OS was 6.93 months (95% CI = 4.96–12.85) (Fig. 2B). The OS rate at 6 months was 57.3% (95% CI = 43.1–69.2).

Among all patients (N = 66), the best overall response was partial response in 5 patients (7.6%) and stable disease in 29 patients (43.9%), with 4 patients (6.1%) not evaluable (Table 4). DCR across all cohorts was 51.5% (95% CI: 38.9–64). Duration of response for the five responders ranged from 2.8 to 12.7 months. All 5 patients were male, with ECOG PS of 1, mixed smoking history, and no clear pattern of EGFR expression. The 4 patients for whom *KRAS* mutation status was available were all *KRAS* negative (Table S5, online Supplemental Data).

Exploratory analysis of PFS, OS, and ORR by histology did not show any consistent trend of association in the efficacy for patients with squamous versus nonsquamous histology. Median PFS was 2.7 months (95% CI: 1.41–5.16) for squamous (n = 27) and 2.05 months (95% CI: 1.31–2.76) for nonsquamous (n = 35). Median OS was 6.93 months (95% CI: 4.44–10.02) for squamous and 11.17 months (95% CI: 4.34–15.74) for nonsquamous. Best ORR was 3.7% for the squamous subgroup (1/27) and 8.6% for the nonsquamous subgroup (3/35).

Twenty patients (30.3%) received at least one additional systemic anticancer therapy after discontinuation from study therapy. Nivolumab (8 patients, 12.1%) was most commonly used.

3.6. Pharmacokinetics

Pharmacokinetic analyses were conducted on patients who received at least one dose of either study drug and had samples collected within the scheduled sampling time windows. Among the 66 patients receiving 800 mg necitumumab, 61 patients had 270 samples that were included in the analysis. Abemaciclib and metabolite concentration-time data were available from 50 patients who received 150 mg Q12H abemaciclib and 800 mg necitumumab. The results of PK were consistent with previous necitumumab and abemaciclib studies and the single-dose PK parameters in this study. There was no particular PK pattern to associate with better tumor response or AEs resulting in treatment discontinuation or death. (data not shown).

3.7. Relationship between EGFR protein expression and efficacy

For exploratory evaluation of EGFR protein expression by IHC, a tissue sample was available for 50 of 57 patients (87.7%) evaluable for Part B and a valid result obtained for 48 patients (84.2%). The PFS rate at 3 months was 32.5% (95% CI = 17.4–48.5) in EGFR expression-positive patients (n = 38) and 0.0% for EGFR expression-negative patients (n = 10). The median PFS was 2.1 months (95% CI = 1.4–2.8) for

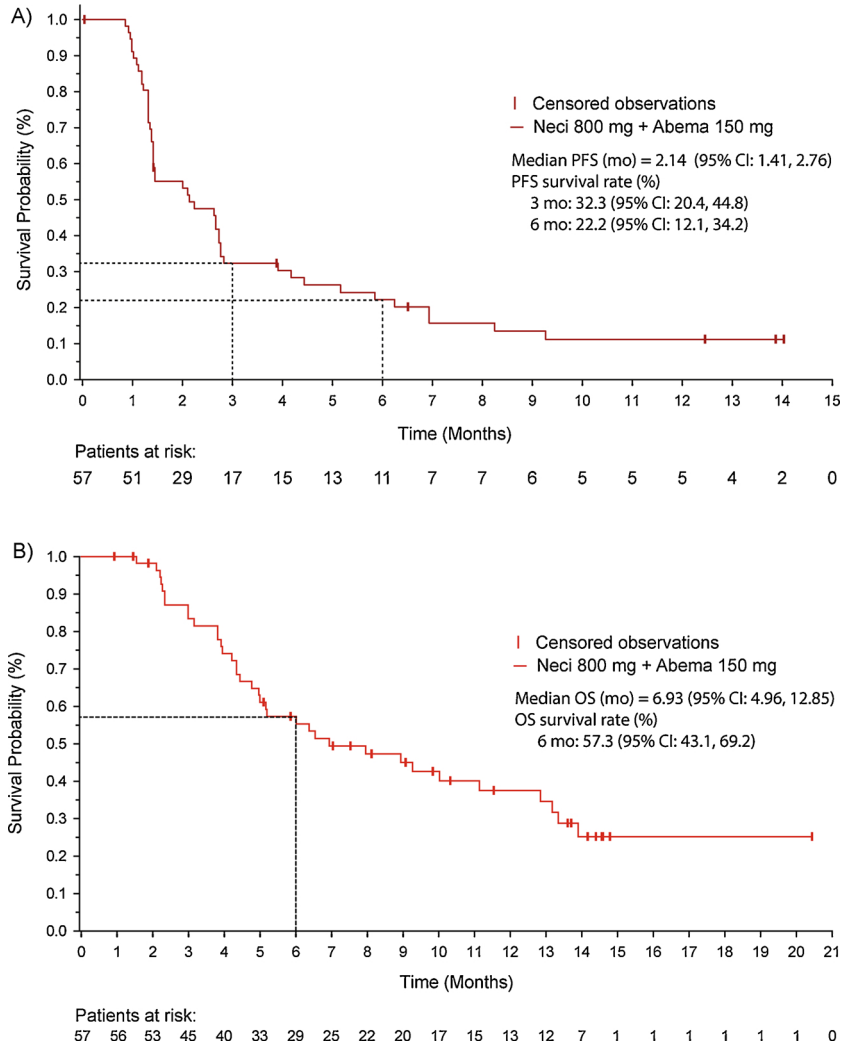

Fig. 2. Kaplan-Meier estimates for (A) PFS and (B) OS.
(A) PFS and (B) OS Kaplan-Meier estimates for the necitumumab plus abemaciclib-treated population are shown. Abbreviations: abema = abemaciclib; CI = confidence interval; mo = month; neci = necitumumab; OS = overall survival; PFS = progression-free survival.

Table 4
Summary of best overall tumor response.

Best overall response, n (%)	Necitumumab 800 mg + Abemaciclib 150 mg N = 57[a]	Total patients (All dose cohorts) N = 66[b]
Complete response (CR)	0	0
Partial response (PR)	3 (5.3)	5 (7.6)
Stable disease (SD)	24 (42.1)	29 (43.9)
Progressive disease	27 (47.4)	28 (42.4)
Not evaluable	3 (5.3)	4 (6.1)
Overall response rate (CR + PR)	3 (5.3)	5 (7.6)
Disease control rate (CR + PR + SD)	27 (47.4)	34 (51.5)

Abbreviations: CI = confidence interval; n = number of patients in specified category; N = total population size.

[a] The necitumumab 800 mg + abemaciclib 150 mg Q12H population (N = 57) was derived from patients in Part A, cohort 2 and all patients in Part B.

[b] The "Total" patient population is derived from Part A, cohorts 1, 2, and 3 (necitumumab 800 mg + abemaciclib 100, 150, 200 mg, Q12H, respectively) and all patients in Part B.

EGFR expression-positive patients and 1.3 months (95% CI = 0.9–2.7) for EGFR expression-negative patients (HR = 0.41, 95% CI = 0.2–0.9; p = 0.02).

In EGFR expression-positive patients, the ORR was 5.3% (95% CI: 1.5–17.3) and the DCR was 52.6% (95% CI: 37.3–67.5). No EGFR expression-negative patients had a response, and the DCR was 10% (95% CI: 1.8–40.4).

3.8. Relationship between KRAS mutation and efficacy

For *KRAS* mutation analysis, a tissue sample was available for 49 of 57 patients (86%) evaluable for Part B and a valid result obtained for 43 patients (75.4%). Although the number of *KRAS* mutation-positive patients (n = 6) was very small, a comparison of this subgroup's PFS rate at 3 months with the KRAS mutation-negative patients (n = 37) showed no meaningful difference (33.3%, 95% CI: 4.6–67.6 versus 30.9%, 95% CI: 15.8–47.4, p = 0.91).

3.9. Immunogenicity analysis

Of the 66 patients who received any amount of necitumumab, 46 patients had ≥1 post-treatment sample analyzed, 9 patients had ≥1 anti-drug antibody (ADA)-positive sample during the study, and no patients were identified as having treatment-emergent anti-drug antibody (TE-ADA)-positive samples. In addition, no patient evaluated for immunogenicity was positive for neutralizing antibodies post-baseline Among the 2 patients who experienced an infusion-related reaction

(grade 1 and grade 2) and were tested for ADA at any time, there was no evidence of TE-ADAs.

4. Discussion

Despite the remarkable advances recently achieved with immunotherapies, new treatment options with better survival and less toxicity are still needed for patients with metastatic lung cancer. Based on previous efficacy and safety data of necitumumab and abemaciclib as monotherapies, targeting the combined inhibition of the EGFR and CDK 4/6 pathways was a clinically reasonable approach.

Part A of the study examined treatment dose, safety, and pharmacokinetics. The MTD of abemaciclib was identified as 150 mg Q12H, day 1–21, when used in combination with an absolute dose of necitumumab (800 mg, D1D8 Q3W). This dose level was also proven tolerable in multiple cohorts of a phase 1b abemaciclib combination study [18]. The DLTs were grade 3 diarrhea (150 mg Q12H dose), and grade 3 stomatitis and grade 4 thrombocytopenia (200mg Q12H dose). Grade 3 stomatitis was also observed as a DLT when abemaciclib 200 mg Q12H was combined with ramucirumab in the other phase 1b study [18]. Further examination of the tolerability of the abemaciclib-necitumumab combination therapy in Part B of the study found it to be generally acceptable, with predominant toxicities of grade 1 or 2.

The observed PK of both compounds was comparable to previous studies of their use as monotherapy in cancer patients, thus confirming a lack of drug-drug interaction.

Part B of the study collected efficacy data on the expansion cohort treated with the MTD identified in Part A. For the 57 evaluable patients treated with necitumumab 800 mg in combination with abemaciclib 150 mg Q12H, the PFS rate at 3 months was 32.3% (95% CI: 20.4–44.8). The 3-month PFS rate does not lead to rejection of the null hypothesis; thus, the study efficacy endpoint was not met. Comparison of the median PFS outcome of the present study with that of the other phase 1b abemaciclib combination study in patients with metastatic NSCLC provides additional context [18]. Median PFS for the present study was 2.14 months (95% CI: 1.41–2.76). In contrast, abemaciclib plus pemetrexed (n = 23) resulted in median PFS of 5.55 months (95% CI: 1.81–10.05), and abemaciclib plus ramucirumab (n = 39) was associated with a median PFS of 4.83 months (95% CI: 2.60–6.93), with 5 patients still receiving abemaciclib/ramucirumab treatment at the time of analysis [18]. The median PFS associated with the combination of abemaciclib and necitumumab is comparable with that of patients treated with abemaciclib plus gemcitabine (n = 24) (1.58 months, 95% CI: 1.15–4.24) [18].

A comparison of the ORR data from the present study with that from other studies showed similarly low values. Treatment with necitumumab and abemaciclib yielded an ORR of 5.3%. This result was comparable to historical data of a phase 2 study of patients with advanced NSCLC treated with single-agent cetuximab, a first-generation anti-EGFR mAb, ORR 4.5% [20]. Likewise, the ORRs in the phase 1b study of abemaciclib combined with pemetrexed, gemcitabine, and ramucirumab were 4%, 4%, and 5%, respectively [18]. While the ORR in these studies is low, the populations were heavily pretreated, with a median of two prior regimens for metastatic NSCLC. Indeed, in the present study, necitumumab/abemaciclib was at least third-line treatment for 77% of the patients, a setting in which traditional chemotherapy has proven to be ineffective [21].

The *KRAS* mutated subgroup efficacy exploration was based on prior preclinical and clinical data, which suggested that patients with NSCLC harboring the *KRAS* mutation are more sensitive to abemaciclib than patients with wild type *KRAS* [17]. The recent phase 3 JUNIPER trial comparing abemaciclib versus erlotinib monotherapy confirmed that abemaciclib monotherapy conferred a PFS benefit (HR 0.58, $p < 0.001$) and ORR benefit (8.9% versus 2.7%, $p = 0.01$) for patients with metastatic NSCLC patients harboring the *KRAS* mutation [22]. In the present phase 1b study, there was no strong association between *KRAS* mutation status and efficacy in the 43 assessable patients. The PFS rate at 3 months was 33.3% for *KRAS* mutation-positive patients (n = 6) and 30.9% for *KRAS* mutation-negative patients (n = 37). Notably, the *KRAS* mutation was found in only six out of 43 available samples, significantly limiting the ability to interpret these results in the context of overall study outcome.

Exploratory analyses were undertaken to examine the impact of histology and EGFR protein expression on the efficacy endpoints in the present study. An examination of the squamous (47.4%) and non-squamous (50.9%) subgroups identified no meaningful efficacy outcome difference, suggesting that histology was not a predictive factor for efficacy for this treatment regimen. However, as before, the small patient numbers preclude a definitive conclusion. Exploratory analysis of EGFR protein expression suggested a trend toward lack of benefit (3 month-PFS rate of 0% in EGFR expression-negative patients); however, no conclusion could be drawn due to the small population (n = 10). Finally, an examination of the characteristics of the five responders did not identify any commonalities. The duration of response did not exhibit any trend of association with the *KRAS* mutation or EGFR expression, where the efficacy of abemaciclib and necitumumab are known to be related.

In summary, due to the DLTs of grade 3 stomatitis and grade 4 thrombocytopenia in cohort 3, the cohort 2 dose of necitumumab 800 mg D1D8 Q3W in combination with abemaciclib 150 mg Q12H day 1–21 was identified as the MTD and the dose to treat patients in the expansion cohort. This combination of necitumumab and abemaciclib had manageable toxicity overall but did not provide remarkably improved benefit over the individual agents or existing treatment options in this disease setting. In this phase 1b study, necitumumab and abemaciclib treatment did not show an add-on effect over single-agent activity.

Declaration of Competing Interest

BB reports grants from Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgène, Eli-Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, and Tiziana Pharma, outside the submitted work. FB reports personal fees from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda, outside the submitted work. JV served on an advisory board for Eli Lilly during the conduct of the study. VS, BF-M, and JSK are employees of Eli Lilly and Company. All other authors have nothing to report.

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Appendix A. Supplementary data

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References

[1] D.S. Ettinger, D.E. Wood, D.L. Aisner, et al., Non–small cell lung cancer, version 5.2017, J. Compr. Canc. Netw. 15 (2017) 504–535.
[2] N. Hanna, D. Johnson, S. Temin, et al., Systemic therapy for stage IV non–small-cell lung cancer: american society of clinical oncology clinical practice guideline update summary, J. Oncol. Pract. 13 (2017) 832–837.
[3] D. Planchard, S. Popat, K. Kerr, et al., Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol. 29 (Supplement_4) (2018) iv192–237.

[4] N. Thatcher, F.R. Hirsch, A.V. Luft, et al., Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial, Lancet Oncol. 16 (2015) 763–774.
[5] R. Pirker, J.R. Pereira, A. Szczesna, et al., Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial, Lancet 373 (2009) 1525–1531.
[6] A. Sandler, R. Gray, M.C. Perry, et al., Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer, N. Engl. J. Med. 355 (2006) 2542–2550.
[7] M. Reck, J. von Pawel, P.V. Zatloukal, et al., Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL), Ann. Oncol. 21 (2010) 1804–1809.
[8] C. Langer, S.M. Gaddgeel, H. Borghaei, et al., Randomized, phase 2 study of carboplatin and pemetrexed with or without pembrolizumab as first-line therapy for advanced NSCLC: KEYNOTE-021 cohort G, Ann. Oncol. (2016) suppl_6:LBA46_PR.
[9] A. Drilon, T.W. Laetsch, S. Kummar, et al., Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children, N. Engl. J. Med. 378 (2018) 731–739.
[10] F.V. Fossella, R. DeVore, R.N. Kerr, et al., Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non–small-cell lung cancer previously treated with platinum-containing chemotherapy regimens, J. Clin. Oncol. 18 (2000) 2354–2362.
[11] N. Hanna, F.A. Shepherd, F.V. Fossella, et al., Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy, J. Clin. Oncol. 22 (2004) 1589–1597.
[12] E.B. Garon, T.E. Ciuleanu, O. Arrieta, et al., Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial, Lancet 384 (2014) 665–673.
[13] M. Reck, R. Kaiser, A. Mellemgaard, et al., Nintedanib (BIBF 1120) plus docetaxel in NSCLC patients progressing after first-line chemotherapy: LUME Lung 1, a randomized, double-blind phase III trial, J. Clin. Oncol. (2013) 31:LBA8011.
[14] A. Rittmeyer, F. Barlesi, D. Waterkamp, et al., Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial, Lancet 389 (2017) 255–265.
[15] H. Borghaei, L. Paz-Ares, L. Horn, et al., Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer, N. Engl. J. Med. 373 (2015) 1627–1639.
[16] G. Fontanini, S. Vignati, D. Bigini, et al., Epidermal growth factor receptor (EGFr) expression in non-small cell lung carcinomas correlates with metastatic involvement of hilar and mediastinal lymph nodes in the squamous subtype, Eur. J. Cancer 31A (1995) 178–183.
[17] A. Patnaik, L.S. Rosen, S.M. Tolaney, et al., Efficacy and safety of abemaciclib, an inhibitor of CDK4 and CDK6, for patients with breast cancer, non–small cell lung cancer, and other solid tumors, Cancer Discov. 6 (2016) 740–753.
[18] E.S. Kim, K. Kelly, L.G. Paz-Ares, et al., Abemaciclib in combination with single-agent options in patients with stage IV non–small cell lung cancer: a phase Ib study, Clin. Cancer Res. 24 (2018) 5543–5551.
[19] Portrazza (Eli Lilly and Company): FDA Package Insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125547s000lbl.pdf, Accessed 10 February 2019.
[20] N. Hanna, R. Lilenbaum, R. Ansari, et al., Phase II trial of cetuximab in patients with previously treated non–small-cell lung cancer, J. Clin. Oncol. 24 (2006) 5253–5258.
[21] E. Massarelli, F. Andre, D.D. Liu, et al., A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small cell lung cancer, Lung Cancer 39 (2003) 55–61.
[22] J.W. Goldman, J. Mazieres, F. Barlesi, et al., A randomized phase 3 study of abemaciclib versus erlotinib in previously treated patients with stage IV NSCLC with KRAS mutation, JUNIPER. J Clin Oncol 36 (2018) 9025.