BRIEF REPORT

SWOG S1400C (NCT02154490)—A Phase II Study of Palbociclib for Previously Treated Cell Cycle Gene Alteration–Positive Patients with Stage IV Squamous Cell Lung Cancer (Lung-MAP Substudy)

Martin J. Edelman, MD,[a,*] Mary W. Redman, PhD,[b] Kathy S. Albain, MD,[c] Eric C. McGary, MD,[d] Noman M. Rafique, MD,[e] Daniel Petro, MD,[f] Saiama N. Waqar, M.B.B.S., MSCI,[g] Katherine Minichiello, MS,[b] Jieling Miao, MS,[b] Vassiliki A. Papadimitrakopoulou, MD,[h] Karen Kelly, MD,[i] David R. Gandara, MD,[i] Roy S. Herbst, MD, PhD[j]

[a]*Fox Chase Cancer Center, Philadelphia, Pennsylvania*
[b]*SWOG Statistics and Data Management Center at Fred Hutchinson Cancer Reseach Center, Seattle, Washington*
[c]*Loyola University Chicago Stritch School of Medicine, Maywood, Illinois*
[d]*Kaiser Permanente National Community Oncology Research Program/Kaiser Permanente Medical Group, Los Angeles, California*
[e]*Mercy Medical Center Tri-County Hematology/Oncology Association, Canton, Ohio*
[f]*University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania*
[g]*Washington University School of Medicine, St. Louis, Missouri*
[h]*Thoracic/Head and Neck Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas*
[i]*University of California Davis Cancer Center, Sacramento, California*
[j]*Medical Oncology, Yale Cancer Center, New Haven, Connecticut*

Received 25 February 2019; revised 28 June 2019; accepted 29 June 2019
Available online - 11 July 2019

ABSTRACT

Objective: Lung-MAP (SWOG S1400) is a master platform trial assessing targeted therapies in squamous NSCLC. The objective of study C (S1400C) was to evaluate the response rate to palbociclib, a cyclin-dependent kinase 4 and cyclin-dependent kinase 6 inhibitor, in patients with cell cycle gene abnormalities.

Methods: Patients with squamous NSCLC, a performance status of 0 to 2, and normal organ function who had progressed after at least one prior platinum-based

*Corresponding author.

Disclosure: Dr. Edelman reports grants from Apexigen, Merck, and Bristol-Myers Squibb; personal fees from Armo, BerGen Bio, Syndax, WindMil Therapeutics, and Bristol-Myers Squibb; and stock options from Biomarker Strategies outside the submitted work. Dr. Albain has received personal fees from Novartis, Pfizer, Genomic Health, Myriad, and Genentech/Roche and served as the chair of the independent data monitoring committee of a breast cancer phase III trial for Puma outside of the submitted work. Dr. Waqar reports grants from 1 UM1 CA186704-01 and fees to her institution for serving as a principal investigator from F. Hoffmann-La Roche Ltd, Ariad, Pfizer Pharmaceuticals, Hengrui Therapeutics, Xcovery, EMD Serono Research and Development Institute, Checkpoint Therapeutics, Genentech, Lilly, Stemcentrx, Ignyta, Bristol-Myers Squibb Pharmaceutical, Synermore Biologics, Novartis Pharmaceuticals Corporation, Merck and Company, NewLink Genetics Corporation, and Celegene outside the submitted work. Dr. Papadimitrakopoulou reports service on advisory boards for Nektar Therapeutics, AstraZeneca Pharmaceuticals, Arrys Therapeutics, Merck and Company, Loxo Oncology, Araxes Pharma, F.Hoffman-LaRoche, Janssen Research Foundation, Bristol-Myers Squibb, Clovis Oncology, Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Takeda Pharmaceuticals, AbbVie, TRM Oncology, Exelixis, and Tesaro and research funding and grants from Eli Lilly and Company, Novartis, Merck, AstraZeneca Pharmaceuticals, F. Hoffman-La Roche, Nektar Therapeutics, Janssen, Bristol-Myers Squibb, Checkmate, and Incyte. Dr. Kelly reports personal fees from AstraZeneca and Bristol-Myers Squibb and grants and personal fees from Genentech and Pfizer outside the submitted work. Dr. Gandara reports consulting for Pfizer during the study. Dr. Herbst reports personal fees from AbbVie Pharmaceuticals, Biodesix, Bristol-Myers Squibb, EMD Serrano, Genentech/Roche, Heat Biologics, Jun Shi Pharmaceuticals, Loxo Oncology, Nektar, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Tesaro, Neon Therapeutics, and Infinity Pharmaceuticals and grants and personal fees from AstraZeneca, Eli Lilly and Company, and Merck and Company outside the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Martin J. Edelman, MD, Fox Chase Cancer Center, 333 Cottman Ave., Philadelphia, PA 19111. E-mail: Martin.edelman@fccc.edu

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.06.027

chemotherapy with cyclin-dependent kinase 4 gene (*CDK4*) or cyclin D1 gene (*CCND1*), cyclin D2 gene (*CCND2*), or cyclin D3 gene (*CCND3*) amplifications on tumor specimens were eligible. The study was originally designed as a phase II/III trial comparing palbociclib with docetaxel, but it was modified to a single-arm phase II trial with the primary end point of response when immunotherapy was approved. If two or fewer responses were seen in the first 20 patients, then the study would cease enrollment.

Results: A total of 88 patients (9% of patients screened) were assigned to S1400C, and 53 patients enrolled (including 17 to receive docetaxel). One patient who had been registered to receive docetaxel was re-registered to receive palbociclib after progression while taking docetaxel. The frequencies of cell cycle gene alterations in the eligible patients taking palbociclib (n = 32) were as follows: *CCND1*, 81% (n = 26); *CCND2,* 9% (n = 3); *CCND3*, 6% (n = 2); and *CDK4*, 3% (n = 1). In all, 32 eligible patients received palbociclib. There were two partial responses (response rate 6% [95% confidence interval (CI): 0%–15%]), both with *CCND1* amplification. Twelve patients had stable disease (38% [95% CI: 21%–54%]). The median progression-free survival was 1.7 months (95% CI: 1.6–2.9 months) and the median overall survival was 7.1 months (95% CI: 4.2–12.5).

Conclusion: Palbociclib as monotherapy failed to demonstrate the prespecified criteria for advancement to phase III testing.

Keywords: Lung cancer; Targeted therapy; Squamous NSCLC; Cell cycle gene alteration; Cyclin-dependent kinase; Master protocol

Introduction

Despite substantial progress in identifying targeted agents with activity in advanced nonsquamous NSCLC, there have been few advances in developing such agents in squamous cell NSCLC. Several studies have identified potentially actionable mutations in this subset of disease.[1] The Lung Master Protocol (Lung-MAP, SWOG 1400) was developed with the goal of establishing a mechanism for genomically screening a large, homogeneous population of sqamous NSCLC and subsequently assigning and accruing simultaneously to substudies evaluating agents targeting specific molecular abnormalities.[2] When originally designed, the biomarker-driven substudies in the protocol compared new targeted therapy or targeted therapy combinations with the standard of care therapy (i.e., docetaxel) based on designated therapeutic biomarker-drug combinations, with the ultimate goal of obtaining U.S. Food and Drug Administration approval of new targeted therapies in this setting. In December 2015, because of the rapid development and approval of immunotherapy in NSCLC, the protocol was redesigned to evaluate biomarker-driven therapies by using a single-arm screening design to be followed by randomized assessments if specified levels of activity were met.[3-6]

Substudy C (S1400C) of Lung-MAP tested the concept of targeting cyclin-dependent kinase (CDK) abnormalities with the selective CDK 4 and CDK 6 (CDK4/6) inhibitor palbociclib. Unrestricted proliferation is a hallmark of cancer and frequently results from abnormality in the retinoblastoma (Rb) pathway. In its active, unphosphorylated state, Rb inhibits progression through the cell cycle. For the cell to enter mitosis, Rb is phosphorylated by the cyclin D–CDK4/6 complex. Inactivation of Rb, by deletion, mutation, or increased activation of the cyclin D–CDK4/6 complex, results in unrestricted proliferation. In sqamous NSCLC, Rb itself is rarely mutated. However, abnormalities of cyclin-dependent kinase inhibitor 2A gene (*CDKN2A*), which encodes cyclin-dependent kinase inhibitor 2A (also known as p16 and INK4), the primary inhibitor of the cyclin D–CDK 4/6 complex, are common, as is amplification of D-type cyclins (encoded by cyclin D1 gene [*CCND1*], cyclin D2 gene [*CCND2*], and cyclin D3 gene [*CCND3*]) or CDK4/6. In squamous cell carcinoma, *CCND1* was found to be

Table 1. Patient Demographics and Characteristics of Patients Taking Palbociclib

Characteristic	n (%) (n = 32)
Median age, y (range)	67.3 (53–80.7)
Male sex	21 (66%)
Performance status	
0	13 (41%)
1	18 (56%)
2	1 (3%)
Race/ethnicity	
White	28 (88%)
Black	3 (9%)
Asian	1 (3%)
Hispanic	0 (0%)
No. of prior lines of therapy for stage IV disease	
0	8 (25%)[a]
1	23 (72%)
≥2	1 (3%)
Smoking status	
Current smoker	13 (41%)
Former smoker	18 (56%)
Never-smoker	1 (3%)
Brain metastases	
Present	2(6%)
Absent	30 (94%)

[a]Per protocol, patients were eligible if they received chemotherapy in the adjuvant setting or as part of combined modality therapy within 1 year of enrollment.

amplified in a number of tumors evaluated, including sqamous NSCLC. The Cancer Genome Atlas demonstrated *CCND1* amplification in 12% of squamous cell carcinoma, although these often occur in association with other abnormalities of the CDK4/Rb pathway. In addition, many of these amplifications were associated with loss of p16, contributing to further disruption of the cyclin D–CDK4/6-Rb-p16 axis. Although *Rb* loss was detected in some of the analyzed specimens, there was no overlap with *CCND1* amplifications.[1,7]

Table 2. Gene Alterations Detected by Foundation Medicine Next-Generation Sequencing Screening

Gene Alteration	Palbociclib (n = 32)
CCGA Study gene alterations	
CCND1	26 (81%)
CCND2	3 (9%)
CCND3	2 (6%)
CDK4	1 (3%)
No. of CCGA Study gene alterations	
1	32 (100%)
Other concomitant gene alterations	
Short Variants	
TP53	30 (94%)
CDKN2A, KMT2D	8 (25%)
NFE2L2	6 (19%)
PTEN	4 (13%)
ARID1A, LRP1B, PIK3CA	3 (9%)
APC, BAP1, KRAS	2 (6%)
ATRX, BRCA2, BRIP1, CREBBP, DAXX, DNMT3A, EZH2, FANCA, FBXW7, FLT4, GRIN2A, IGF1, IKZF1, KLHL6, MET, NCOR1, NF1, NF2, NOTCH1, NOTCH3, NOTCH4, SF3B1, STAT4, STK11, TET2, TRRAP, TSC2, WT1	1 (3%)
Copy number alterations	
FGF19, FGF3, FGF4	24 (75%)
SOX2	16 (50%)
PIK3CA	11 (34%)
CDKN2A	10 (31%)
CDKN2B	9 (28%)
FGF12, MYC	6 (19%)
KRAS	5 (16%)
EPHB1, FGFR1, MYST3, REL, ZNF703	3 (9%)
AKT2, EGFR, EMSY, ERBB2, FGF23, FGF6, JAK2, KDM5A, KDR, PTEN	2 (6%)
AKT3, BCL2L2, CCNE1, CDK4, IGF1R, IKBKE, KDM6A, KIT, LRP1B, MDM2, MDM4, NFKBIA, NKX2-1, RICTOR, STK11, TP53	1 (3%)
Rearrangements	
LRP1B	3 (9%)
ABL1, MLH1, MLL2, PIK3R2	1 (3%)

CCND1, cyclin D1 gene; *CCND2*, cyclin D 2 gene; *CCND3*, cyclin D 3 gene; *CDK4*, cyclin-dependent kinase 4 gene; *TP53*, tumor protein p53 gene; *CDKN2A*, cyclin-dependent kinase inhibitor 2A gene; *KMT2D*, lysine methyltransferase 2D gene (also known by the alias *MLL2*); *NFE2L2*, nuclear factor erythroid 2, like 2 gene; *PTEN*, phosphatase and tensin homolog gene; *ARID1A*, AT-rich interaction domain 1A gene; *LRP1B*, LDL receptor related protein 1B gene; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *APC*, APC, WNT signaling pathway regulator gene; *BAP1*, BRCA1 associated protein 1 gene; *ATRX*, ATRX, chromatin reomodeler gene; *BRCA2*, BRCA2, DNA repair associated gene; *BRIP1*, BRCA1 interacting protein C-terminal helicase 1 gene; *CREBBP*, CREB binding protein gene; *DAXX*, death domain associated protein gene; *DNMT3A*, DNA methyltransferase 3 alpha gene; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit gene; *FANCA*, Fanconi anemia complementation group A gene; *FBXW7*, F-box and WD repeat domain containing 7 gene; *FLT4*, fms related tyrosine kinase 4 gene; *GRIN2A*, glutamate ionotropic receptor NMDA type subunit 2A gene; *IGF1*, insulin-like growth factor 1 gene; *IKZF1*, IKAROS family zinc finger 1 gene; *KLHL6*, kelch like family member 6gene; *MET*, MNNG HOS Transforming gene; *NCOR1*, nuclear receptor corepressor 1 gene; *NF1*, neurofibromin 1 gene; *NF2*, neurofibromin 2 gene; *NOTCH1*, notch 1 gene; *NOTCH3*, notch 3 gene; *NOTCH4*, notch 4 gene; *SF3B1*, splicing factor 3b subunit 1 gene; *STAT4*, signal transducer and activator of transcription 4 gene; *STK11*, serine/threonine kinase 11 gene; *TET2*, tet methylcytosine dioxygenase 2 gene; *TRRAP*, transformation/transcription domain associated protein gene; *TSC2*, tuberous sclerosis 2 gene; *WT1*, Wilms tumor 1 gene; *FGF19*, fibroblast growth factor 19 gene; *FGF3*, fibroblast growth factor 3 gene; *FGF4*, fibroblast growth factor 4 gene; *SOX2*, SRY-box 2 gene; *CDKN2B*, cyclin dependent kinase inhibitor 2B gene; *FGF12*, fibroblast growth factor gene; *MYC*, v-myc avian myelocytomatosis viral oncogene homolog gene; *EPHB1*, EPH receptor B1 gene; *FGFR1*, fibroblast growth factor receptor 1 gene; *MYST3*, lysine acetyltransferase 6A gene; *REL*, REL proto-oncogene, NF-κB subunit gene; *ZNF703*, zinc finger protein 703 gene; *AKT2*, AKT/serine threonine kinase 2 gene; *EMSY*, EMSY, BRCA interacting transcriptional repressor gene; *ERBB2*, erb-b2 receptor tyrosine kinase 2 gene; *FGF23*, fibroblast growth factor 23 gene; *FGF6*, fibroblast growth factor 6 gene; *JAK2*, Janus kinase 2 gene; *KDM5A*, lysine demethylase 5A gene; *KDR*, kinase insert domain receptor gene; *AKT3*, AKT/serine threonine kinase 3 gene; *BCL2L2*, BCL like 2 gene; *CCNE1*, cyclin E1 gene; *CDK4*, cyclin-dependent kinase 4 gene; *IGF1R*, insulin-like growth factor 1 receptor gene; *IKBKE*, inhibitor of nuclear factor kappa B kinase subunit epsilon gene; *KDM6A*, lysine demethylase 6A gene; *KIT*, KIT proto-oncogene receptor tyrosine kinase gene; *LRP1B*, LDL receptor related protein 1B gene; *MDM2*, MDM2 proto-oncogene gene; *MDM4*, MDM4 regulator of p53 gene; *NFKBIA*, NFKB inhibitor alpha gene; *NKX2-1*, NK2 homeobox 1 gene; *RICTOR*, RPTOR independent companion of MTOR complex 2 gene; *ABL1*, ABL proto-oncogene 1, non-receptor tyrosine kinase gene; *MLH1*, mutL homolog 1 gene; *PIK3R2* phosphoinositide-3-kinase regulatory subunit 2 gene.

Palbociclib (PD0332991) is an oral, selective CDK4/6 inhibitor that has been tested in multiple phase I, II, and III trials and approved in combination with letrozole for advanced breast cancer. In prior studies, a schedule of 3 weeks on treatment and 1 week off treatment was found to be the best tolerated and active and was therefore chosen for this trial.[8,9]

Patients and Methods

When the trial opened in June 2014, the eligibility criteria specified that patients were allowed to have only a single line of prior therapy for stage III or IV recurrent disease and have a performance status of 0 to 2. In April 2015, the study was amended to allow any number of lines of prior therapy for stage IV NSCLC or for lower-stage disease within 1 year. In December 2015, the study was amended to allow only a performance status of 0 or 1 and was redesigned to be a single-arm study. In addition to these criteria, patients were required to have normal hematologic, hepatic, and renal function. Patients taking strong cytochrome P450 family 3 subfamily A member 4 inhibitors and/or inducers were not allowed to enroll. Because of the known cardiac effects of the drug, patients with a known personal or family history of long or short QT syndrome, Brugada syndrome, or torsade de pointes were excluded. Measurable (by the Response Criteria in Solid Tumors version 1.1) disease was required. Patients with treated brain metastases were allowed as long as (1) the metastases had been locally treated and remained clinically controlled and asymptomatic for at least 14 days after treatment *and* (2) the patient had no residual neurological dysfunction and was no longer taking corticosteroids for at least 1 day before substudy registration. After the modification to a single-arm design, patients previously registered to the docetaxel arm were allowed to re-register to the palbociclib arm. No patient could be enrolled at an institution before review and approval by either the local institutional review board or by the National Cancer Institute Central Institutional Review Board. Written informed consent was required from all patients before enrollment in the master protocol, and a separate consent was required for the specific substudy.

The cell cycle gene alterations required for eligibility were amplifications of cyclin-dependent kinase 4 gene (*CDK4*), *CCND1*, *CCND2*, or *CCND3*. Disease characterized by substitutions or fusion alterations were not eligible. Amplification was defined as at least six estimated copies (or at least seven for triploid or at least eight for tetraploid samples). Mutational analysis was performed on archival formalin-fixed paraffin-embedded tumor specimens by using the Foundation One testing platform.[10]

Palbociclib was administered orally at a dose of 125 mg daily and taken with food. A cycle of treatment was 28 days, with treatment given continuously for 21 days and 7 days with no treatment. Disease assessment occurred every 6 weeks, and treatment could continue until progression. Dose reductions and adjustments were specified in the protocol (see the Supplementary Material) and were to be discussed with the study chair.

Statistical Considerations

S1400C was originally a phase II/III trial with randomization between palbociclib and docetaxel. The primary end point of the phase II component was progression-free survival (PFS), and the study included coprimary end points (PFS and overall survival [OS]), in the phase III component. In December 2015, the design was amended to a single-arm phase II trial and the docetaxel arm permanently was closed to accrual. Patients in the docetaxel arm were not included in the analyses presented in this article. The primary objective for the modified design was to evaluate the objective response rate (ORR) (confirmed and unconfirmed, complete and partial) in patients treated with palbociclib with stage IV refractory sqamous NSCLC. The sample size was based on a design with 91% power to rule out an ORR of 15% at the 5% level if the true rate was 35%. The observation of 10 of 40 responses (a 25% ORR) would be considered evidence to rule out the null hypothesis and evidence to pursue an independent randomized phase III. The design included an interim analysis at 20 patients evaluable for response and would continue accrual if at least three responses were observed. A key secondary objective was an investigator assessment of median PFS (mPFS). If the ORR rate was less than 25% but the mPFS

Table 3. AEs Attributed to Treatment

	n (%) (n = 32)		
AE	3	4	5
AST level increased	1 (3%)		
Anemia	4 (13%)		
Anorexia	1 (3%)		
Chronic kidney disease	1 (3%)		
Dyspnea	1 (3%)		
Fatigue	5 (16%)		
Generalized muscle weakness	1 (3%)		
Hyperglycemia	2 (6%)		
Hyponatremia	1 (3%)		
Hypotension	1 (3%)		
Lung infection	1 (3%)		
Lymphopenia	6 (19%)	3 (9%)	
Neoplasms, all		1 (3%)	
Neutropenia	5 (16%)		
Thrombocytopenia	1 (3%)	1 (3%)	
Leucopenia	6 (19%)		
Maximum grade of any AE	13 (41%)	5 (16%)	0

AE, adverse event; AST, aspartate transaminase.

was at least 4.5 months, this would be considered sufficient evidence to continue to the follow-on phase III. With 40 patients, this design had 90% power to rule out an mPFS of 3 months or less if the true mPFS was 6 months at the 0.05 one-sided level. The observation of an mPFS of at least 4.5 months would be considered evidence to rule out an mPFS of 3 months or less.

Binary proportions and associated 95% confidence intervals (CIs) were estimated. Survival distributions were estimated by using the method of Kaplan-Meier, and the Brookmeyer-Crowley method was used to estimate confidence intervals.

Results

The study was open to accrual from June 15, 2014, to September 1, 2016. In this time, 973 patients were screened for the overall study. A total of 88 patients (9% of those screened while the study was actively accruing) were assigned to S1400C. In all, 53 patients were enrolled (including 17 to receive docetaxel before the study redesign). One patient who had been registered to receive docetaxel re-registered to receive palbociclib after progression while taking docetaxel. The study did not meet the criteria to continue past the interim analysis and was closed to accrual on September 1, 2016. Of the 37 patients enrolled to the palbociclib arm, five were ineligible (four because of inadequate baseline laboratory test results and one who did not progress during prior therapy). The demographics for the 32 eligible and evaluable patients are shown in Table 1. The frequencies of cell cycle gene alterations in the eligible patients treated with palbociclib (n = 32) were as follows: *CCND1*, 81% (n = 26); *CCND2*, 9% (n = 3); *CCND3*, 6% (n = 2); and *CDK4*, 3% (n = 1) (Table 2).

Patients received a median of two cycles of palbociclib (range one to 17). The adverse events (AEs) were as expected for palbociclib (Table 3). Three patients

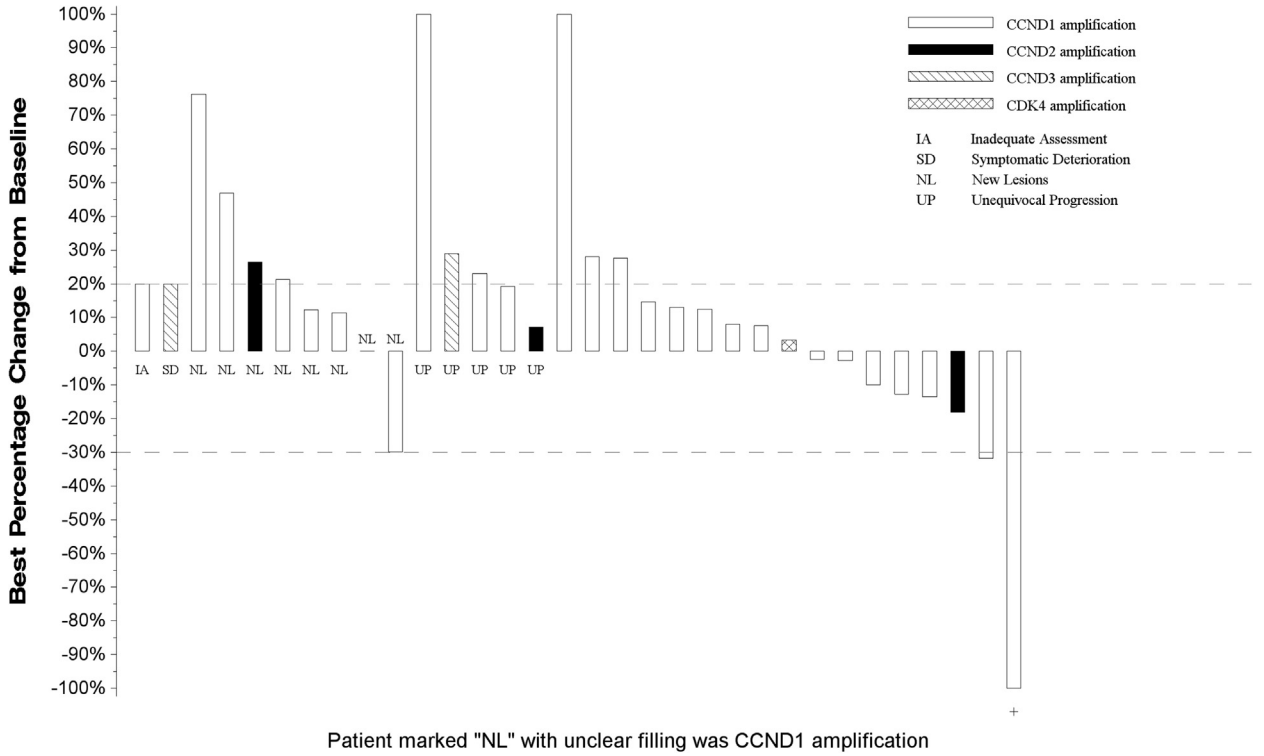

Figure 1. Waterfall plot of response to palbociclib. Each vertical bar represents a patient's best percent decrease in tumor burden when compared with baseline as defined by the Response Criteria in Solid Tumors version 1.1. Only patients with measurable disease at baseline are presented in the plot. Patients who did not have follow-up tumor disease assessment are presented at the very left of the plot marked with a double asterisk. Patients who had new lesions appear at their first follow-up assessment or who died before the first scheduled disease assessment and whose death can reasonably be assumed to be due to disease progression are represented graphically as a 100% increase in tumor burden. Patients who had symptomatic deterioration at first disease assessment are coded as symptomatic deterioration. Negative numbers represent a decrease in tumor burden from baseline whereas positive numbers represent an increase in tumor burden from baseline. Plus sign indicates that the patient had complete disappearance of disease and would have been considered as having a complete response; however, the patient's nontarget brain lesion was removed surgically and per the Response Criteria in Solid Tumors version 1.1 guidelines, the patient is coded as having a partial response. *CCND1*, cyclin D1 gene; *CCND2*, cyclin D2 gene; *CCND3*, cyclin D3 gene; *CDK4*, cyclin-dependent kinase gene.

discontinued therapy because of AEs. Five patients experienced grade 4 AEs, including lymphopenia (three patients), neoplasms (one patient), and thrombocytopenia (one patient). Thirteen others experienced grade 3 treatment-related AEs.

There were two confirmed partial responses observed, for a response rate of 6% (95% CI: 0%–15%). A waterfall plot depicting tumor response is presented in Figure 1. Twelve patients demonstrated stable disease (38% [95% CI: 21%–54%]), for a disease control rate of 44% (95% CI: 27%–61%); response was not assessable in one patient, and one patient had symptomatic deterioration as the best objective response with no follow-up tumor measurements. The mPFS was 1.7 months (95% CI: 1.6–2.9), and the OS was 7.1 months (95% CI: 4.2–12.5) (Fig. 2). The 1- and 2-year estimates of survival were 37.5% and 12.1%, respectively. Of the two patients with partial responses, one has progressed (duration of response 7.7 months) and the other died without evidence of progression (duration of response 12 months). Of note, both of these patients demonstrating partial response had *CCND1* amplification.

Discussion

Palbociclib did not demonstrate antitumor activity in this genomically selected population of patients with sqamous NSCLC. In contrast, well-differentiated or dedifferentiated liposarcoma (WDLD/DDLS) is the paradigm malignancy characterized by *CDK4* amplification and palbociclib has demonstrated growth inhibition in WDLS/DDLS cells in vitro and in xenograft models. Proof of principle that targeting *CDK4*-amplified cancer with palbociclib can be therapeutically important was established in a phase II trial of palbociclib in WDLD/DDLS. In 60 evaluable patients, the 12-week PFS was 57.2%, with an mPFS of 17.9 weeks. One patient had a complete response.[11]

Despite this proof of principle demonstration that CDK/cyclin abnormalities might predict for benefit of this type of agent, it is not clear that such abnormalities are necessary for activity. All three currently approved CDK4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) have primarily demonstrated benefit in hormone-responsive breast cancer when combined with antiestrogens or other hormonally active agents regardless of demonstration of genetic abnormalities.[12] Abemaciclib has demonstrated single-agent activity in hormone receptor–positive breast cancer as well.[13] This likely occurs because the CDK4/6–cyclin D1 complex is a direct target of estrogen receptor signaling.[14]

It is possible that the wrong subgroup of patients with lung cancer was targeted in this trial. Preclinical and early clinical evidence demonstrates that the CDK4/6 inhibitor abemaciclib is particularly active in *KRAS*-mutant lung cancers. These are seen almost exclusively in nonsquamous carcinoma.[15] The results of a study evaluating abemaciclib versus erlotinib in the

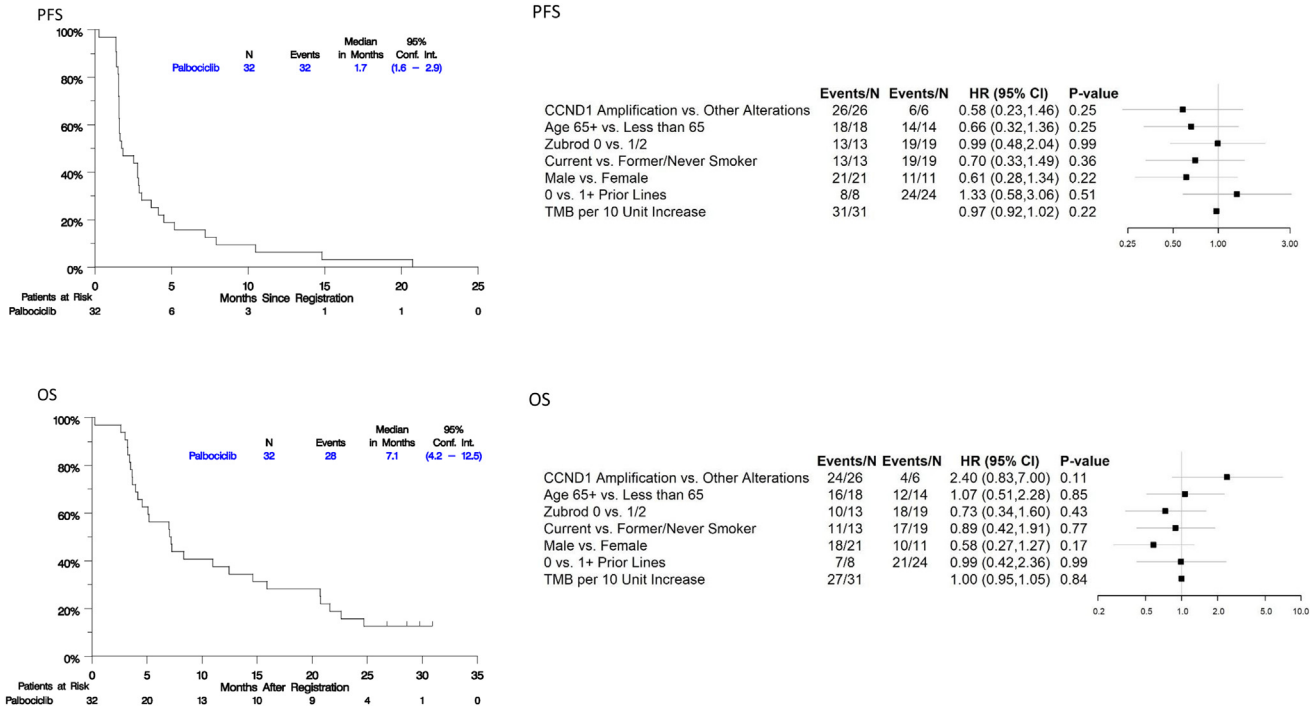

Figure 2. Progression-free survival (PFS) and overall survival (OS). Conf. Int., confidence interval.

second-line treatment of NSCLC with *K-Ras* mutations (and therefore likely adenocarcinoma) were negative for the primary end point of OS. However, abemaciclib demonstrated superior PFS (3.6 months versus 1.9 months [$p < 0.001$]) and a higher response rate (8.9% versus 2.7% [$p = .01$]) compared with erlotinib.[15]

An additional issue is that the postulated mechanism of action for CDK/cyclin agents, namely, inhibition of progression through the cell cycle, is hypothetically more likely to demonstrate cytostatic activity and stable disease as opposed to cytocidal activity and tumor response. For this reason, the secondary end point of mPFS was incorporated into the trial. Unfortunately, this was also negative.

Despite the results of this study, there was some evidence of activity with two partial responses. As noted previously, palbociclib has demonstrated little activity as a single agent in breast cancer but is clearly beneficial when combined with other agents.[12] Additionally, evidence from other trials indicates that additional evaluation of this pathway, possibly in combination with other agents, may still be beneficial in some patients with sqamous NSCLC.

Acknowledgments

This research was supported in part by National Institutes of Health/National Cancer Institute grants CA180888, CA180819, CA180820, CA180821, CA180868, CA189821, CA189812, CA180801, CA189830, CA189872, CA180846, CA189873, CA 189822, CA 189809, CA180828, CA180834, CA190002, CA189954, CA180818, CA180826, CA46368, CA46282, and CA11083 and by Amgen, AstraZeneca, Bristol-Myers Squibb Company, Genentech, and Pfizer through the Foundation for the National Institutes of Health in partnership with Friends of Cancer Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.06.027.

References

1. Cancer Genome Atlas Research Network, Hammerman MS, Lawrence PS, et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489:519–525.
2. Herbst RS, Gandara DR, Hirsch FR, et al. Lung Master Protocol (Lung-MAP)-a biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res*. 2015;21:1514–1524.
3. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
4. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
5. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540–1550.
6. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab monotherapy for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2016;34:2980–2987.
7. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. *J Clin Oncol*. 2006;24:1770–1783.
8. Flaherty KT, Lorusso PM, Demichele A, et al. Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. *Clin Cancer Res*. 2012;18:568–576.
9. Schwartz GK, LoRusso PM, Dickson MA, et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (schedule 2/1). *Br J Cancer*. 2011;104:1862–1868.
10. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31:1023–1031.
11. Dickson MA, Schwartz GK, Keohan ML, et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. *JAMA Oncol*. 2016;2:937–940.
12. DeMichele A, Clark AS, Tan KS, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. *Clin Cancer Res*. 2015;21:995–1001.
13. Patnaik A, Rosen LS, Tolaney SM, 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*. 2016;6:740–753.
14. Yu Q, Sicinska E, Geng Y, et al. Requirement for CDK4 kinase function in breast cancer. *Cancer Cell*. 2006;9:23–32.
15. Goldman JW, Mazieres J, Barlesi F, et al. A randomized phase 3 study of abemaciclib versus erlotinib in previously treated patients with stage IV NSCLC with KRAS mutation: JUNIPER [abstract]. *J Clin Oncol*. 2018;36:9025.