original reports

# Palbociclib in Patients With Non–Small-Cell Lung Cancer With *CDKN2A* Alterations: Results From the Targeted Agent and Profiling Utilization Registry Study

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abstract

**PURPOSE** The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a phase II pragmatic basket trial evaluating antitumor activity of commercially available targeted agents in patients with advanced cancer with genomic alterations known to be drug targets. Results in a cohort of patients with non–small-cell lung cancer (NSCLC) with *CDKN2A* alterations treated with palbociclib are reported.

**METHODS** Eligible patients were ≥ 18 years old with advanced NSCLC, no remaining standard treatment options, measurable disease, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate organ function. Patients with NSCLC with *CDKN2A* alterations and no *Rb* mutations received palbociclib 125 mg orally once daily for 21 days, followed by 7 days off. Simon's two-stage design was used with a primary study end point of objective response or stable disease (SD) of at least 16 weeks in duration. Secondary end points are progression-free survival (PFS), overall survival (OS), and safety.

**RESULTS** Twenty-nine patients were enrolled from January 2017 to June 2018; two patients were not evaluable for response but were included in safety analyses. One patient with partial response and six patients with SD were observed, for a disease control rate of 31% (90% CI, 19% to 40%). Median PFS was 8.1 weeks (95% CI, 7.1 to 16.0 weeks), and median OS was 21.6 weeks (95% CI, 14.1 to 41.1 weeks). Eleven patients had at least 1 grade 3 or 4 adverse event (AE) or serious AE (SAE) possibly related to palbociclib (most common, cytopenias). Other AEs or SAEs possibly related to the treatment included anorexia, fatigue, febrile neutropenia, hypophosphatemia, sepsis, and vomiting.

**CONCLUSION** Palbociclib monotherapy demonstrated evidence of modest antitumor activity in heavily pretreated patients with NSCLC with *CDKN2A* alterations. Additional investigation is necessary to confirm efficacy and utility of palbociclib in this population.

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## INTRODUCTION

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) encodes the p16INK4a protein, which plays an important role in cell-cycle regulation through inhibition of cyclin-dependent kinases (CDK) 4/6 and p14(ARF) that protects the p53 protein from degradation. The major target for the CDKs in the cell cycle is the retinoblastoma (*Rb*) protein, and tumors with *Rb* loss as a driver of malignancy would be expected to be resistant to CDK inhibitors. Indeed, palbociclib is inactive in preclinical tumor models that lack functional *Rb*.[1] *CDKN2A* loss or mutation is found in a wide array of malignancies and may lead to increased CDK activity. Palbociclib was the first oral CDK inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of metastatic hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer in combination with antihormonal therapy.

*CDKN2A* loss or mutation occurs commonly in non–small-cell lung cancer (NSCLC). In a large-scale project to characterize copy number alterations in primary lung adenocarcinomas, 371 tumors were analyzed using dense single nucleotide polymorphism arrays.[2] Chromosome 9p arm deletion (*CDKN2A* is on 9p21.3) was one of the most frequently observed chromosome deletions, occurring in 42.9% of tumors. Focal deletions in *CDKN2A/CDKN2B* were seen in 3% of all samples tested. *CDKN2A* genomic alterations (most commonly deletion events) were observed in 24.5% of epidermal growth factor receptor (*EGFR*)–mutated NSCLC,[3,4] and studies are inconclusive as to

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

**Key Objective**

The Targeted Agent and Profiling Utilization Registry (TAPUR) Study aims to identify signals of drug activity when US Food and Drug Administration–approved drugs are matched to prespecified genomic targets in patients with advanced cancer, outside of their approved indication.

**Knowledge Generated**

This article reports the outcomes of a cohort of patients with non–small-cell lung cancer (NSCLC) with *CDKN2A* alterations treated with palbociclib, which demonstrates antitumor activity in this heavily pretreated population.

**Relevance**

Monotherapy with palbociclib demonstrated evidence of modest antitumor activity in heavily pretreated patients with NSCLC with *CDKN2A* loss or mutation, indicating a need for further study to confirm the efficacy and utility of palbociclib in this patient population.

whether such alterations are less prevalent in non–*EGFR*-mutated NSCLC.[2] Several phase II studies have recently been published testing a CDK inhibitor as monotherapy in NSCLC demonstrating modest antitumor activity and suggesting better outcomes in patients with *KRAS*-mutant tumors.[5-7]

The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a phase II, pragmatic basket trial designed to identify signals of antitumor activity of commercially available targeted agents in patients with advanced cancers that harbor genomic alterations known to be drug targets. In this analysis, data for a cohort of patients with NSCLC with *CDKN2A* loss or mutation treated with single-agent palbociclib are reported.

## METHODS

The rationale and study design of the TAPUR Study have been previously reported in detail.[8] The methods specific to the data collection and analysis of this cohort are the same as previously reported for a cohort of patients with pancreatic and biliary cancer with *CDKN2A* loss or mutation treated with palbociclib in this trial.[9]

### Study End Points

The primary end point is disease control (DC) defined as complete response (CR) or partial response (PR) observed at 8 weeks or later or stable disease (SD) lasting for at least 16 weeks as determined by RECIST version 1.1. Secondary end points are progression-free survival (PFS), overall survival (OS), and toxicity per Common Terminology Criteria for Adverse Events (version 4.0).

### Trial Design

Patients with advanced cancer and no standard treatment options are eligible if they have a tumor that harbors a genomic alteration known to be a target of or to predict sensitivity to one of the available study treatments. Patients are matched to one of the study drugs according to prespecified protocol matching rules based on genomic testing performed by laboratories selected by clinical sites. All laboratories must have certification under the Clinical Laboratory Improvement Amendments and accreditation from the College of American Pathologists or New York state accreditation, if services are offered in New York. Patients may not be matched to treatments that are already approved by the FDA for their cancer type. Treating physicians may choose to consult with the TAPUR Molecular Tumor Board for treatments options where none or multiple possible treatment matches are identified by the tumor genomic profile or if the treating physician would like to propose a treatment match outside of the TAPUR matching rules. Study treatments are administered per the treating physician in accordance with the recommended dose and schedule described in the package insert of each drug. Study treatment is continued until documentation of progressive disease or withdrawal as a result of patient preference or physician recommendation. Radiographic assessment and clinical evaluation for response are performed at 8 and 16 weeks after treatment initiation and then every 12 weeks while the patient remains on treatment. Radiographic assessment and clinical evaluation for response are also performed at the end of study treatment when possible.

For analysis, patients are placed in multiple parallel cohorts defined by study drug, tumor type, and genomic alteration. Simon's optimal two-stage approach is used in the design of each cohort. The trial was designed to have 85% power and a type I error rate of 10% to reject the null hypothesis of a DC rate (DCR) of 15% when the true DCR is 35%. In the first stage, 10 patients are required to be enrolled, and if fewer than two patients have DC, the cohort is permanently closed. If at least two patients experience DC, the cohort expands to stage II and enrolls an additional 18 patients. The null hypothesis is rejected if at least seven patients have DC and it is concluded that a signal of activity has been identified.

### Patients

Detailed inclusion and exclusion criteria for patients treated with palbociclib in this study have been previously reported.[8] Eligible patients are required to meet both

 

**TABLE 1.** Baseline Demographic and Clinical Characteristics of 29 Enrolled Patients

| Characteristic | No. of Patients (N = 29; %)[a] |
|---|---|
| Median age, years (range) | 63 (41-78) |
| Sex | |
| Male | 15 (52) |
| Female | 14 (48) |
| Race | |
| White | 26 (90) |
| Black | 3 (10) |
| Ethnicity | |
| Non-Hispanic or non-Latino | 27 (93) |
| Hispanic or Latino | 2 (7) |
| ECOG performance status | |
| 0 | 5 (17) |
| 1 | 19 (66) |
| 2 | 5 (17) |
| Prior treatments | |
| Radiation therapy | 17 (59) |
| Systemic therapies | |
| 0-1 | 3 (10) |
| 2 | 6 (21) |
| ≥ 3 | 20 (69) |
| Histology | |
| Adenocarcinoma | 19 (65) |
| Squamous carcinoma | 8 (28) |
| Neuroendocrine carcinoma | 2 (7) |
| Co-mutation status | |
| *KRAS* mutation | 7 (24) |
| *BRAF* mutation | 1 (3) |
| *EGFR* alteration: C7975, exon 19 deletion (E746_A750del), T790M exon 19 deletion amplification, exon 19 deletion (L747_P753>S amplification) | 4 (14) |
| *ALK* fusion | 1[b] (3.5) |
| *ROS1* alteration | 0 (0) |
| Genomic test performed | |
| FoundationOne (Foundation Medicine, Cambridge, MA) | 19 (66) |
| Caris Mi Profile X (Caris Life Sciences, Irving, TX) | 5 (17) |
| Guardant Health (Redwood City, CA) | 3 (10) |
| Local test by Intermountain Healthcare (Salt Lake City, UT) | 1 (3.5) |
| Local test by University of Nebraska (Lincoln, NE) | 1 (3.5) |

NOTE. Twenty-seven were included in efficacy analysis; 29 were included in safety analysis.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[a]Except for age, which is a continuous variable and reported as median and range (in parentheses).

[b]One patient had two fusions reported in their tumor.

general and drug-specific inclusion and exclusion criteria. General eligibility criteria include advanced or metastatic solid tumors; measurable or evaluable disease per RECIST version 1.1; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2; and a protocol-specified genomic target identified by an eligible laboratory. TAPUR permits enrollment of patients age 12 years or older; however, to meet eligibility criteria specific to palbociclib, patients must be 18 years of age or older. To match to palbociclib, patients must have an advanced cancer type other than breast cancer that has *CDKN2A* loss or mutation or amplification of *CDK4*, *CDK6*, or cyclin D1 (*CCND1*) and no *Rb* mutations because these have been associated with lack of activity of palbociclib. Patients must not have received food or drugs that are known to be CYP3A4 inhibitors or inducers within 7 days before the start of study treatment. Patients must also avoid chronic immunosuppressive therapies and herbal medicines.

Patients were treated with standard doses of palbociclib (125 mg orally daily for 21 days followed by 7 days off treatment to complete a 28-day cycle) until disease progression or discontinuation as a result of an adverse event (AE) or patient withdrawal of consent. Radiographic tumor evaluations were performed at 8 and 16 weeks after treatment initiation and every 12 weeks thereafter until disease progression.

### Trial Oversight

The TAPUR Study protocol was reviewed and approved by a central institutional review board and, in some cases, by a local institutional review board at participating sites (Appendix Table A1). Patients provided written consent before any screening activities or data collection. The TAPUR Study was designed by ASCO staff with input from ASCO volunteer members and participating pharmaceutical companies. The TAPUR Data and Safety Monitoring Board (DSMB) is an independent board appointed by ASCO and meets biannually to monitor the study and review the safety and efficacy findings. The DSMB reviews all cohorts after stage I enrollment is complete and recommends cohorts for either closure or expansion. For expanded cohorts, the DSMB reviews all completed cohorts before release of the cohort data. In the case of the cohort reported herein, the DSMB reviewed the safety and efficacy data and determined the cohort should expand and complete stage II enrollment. Once stage II enrollment was complete, the DSMB determined that protocol-specified criteria were met to declare a signal of activity and recommended the findings be released.

### Data Analysis

Analysis of DC, OR, PFS, and OS was conducted for the evaluable patients in the palbociclib cohort, known as the efficacy population. The primary end point was summarized as a proportion, and 90% CIs were computed based on the exact binomial test for Simon's two-stage design, which

accounts for the interim futility assessment.[10] The Kaplan-Meier approach was used to estimate the PFS and OS distributions, along with median estimates with 95% CIs. All enrolled patients are included in the safety analyses.

## RESULTS

Twenty-nine patients with advanced NSCLC with *CDKN2A* loss or mutation were enrolled from January 2017 to June 2018 across 20 clinical sites in the United States. Two patients were not evaluable for response; one of the patients had brain metastases requiring immediate radiation before target lesion evaluation, and the second patient was found to have an *Rb* mutation after completion of the study protocol and was declared ineligible. Both patients were included in safety analyses. The median age was 63 years (range, 41-78 years); 56% of patients were male; and 93% were White and 7% were Black. Nineteen percent, 67%, and 15% of patients had an ECOG PS of 0, 1, and 2, respectively. Most patients were previously treated, with 70% of patients having received three or more prior systemic regimens. Sixty-seven percent of patients had adenocarcinoma, 30% squamous carcinoma, and 4% neuroendocrine carcinoma. Detailed demographic and clinical characteristics are listed in Table 1.

Patient tumors or peripheral blood were tested for alterations using the next-generation sequencing platforms listed in Table 1, with the most frequent test being FoundationOne (66%; Foundation Medicine, Cambridge, MA). The specific tumor specimen tested was at the discretion of the treating physician, and archival tissue was acceptable. Detailed information regarding the specific *CDKN2A* variants identified is provided in Table 2.

Best tumor response is shown in Figure 1. For the seven patients with clinical progression but for whom no tumor measurements were available, a 20% increase from baseline was assigned. One patient had PR, and six had SD of at least 16 weeks duration, for an estimated DCR of 31% (90% CI, 19%-40%). Notably, four of these seven patients had received an immune checkpoint inhibitor as their most recent therapy before initiation of palbociclib, including the patient with a PR of long duration. The interval from last receipt of the immune checkpoint inhibitor to initiation of palbociclib ranged from 0.89 to 3.75 months. However, each patient had documented disease progression before initiation of palbociclib treatment. Of the 21 patients who did not respond to palbociclib, 10 received an immune checkpoint inhibitor as the therapy immediately before starting

**TABLE 2.** Type and Variant of *CDKN2A* Alterations Reported for Evaluable Patients

| ***CDKN2A* Alteration Type and Variant** | **NGS Test Name/Platform** | **No. of Patients** |
|---|---|---|
| Loss (44%) | | |
| *CDKN2A* loss exons 1-2 and *CDKN2B* | FoundationOne (Foundation Medicine, Cambridge, MA) | 1 |
| *CDKN2A/B* | FoundationOne | 10 |
| *CDKN2A* p16INK4a loss exons 2-3 and p14ARF loss | FoundationOne | 1 |
| Mutation (56%) | | |
| A60fs | Navican Precision Cancer Care, Intermountain Healthcare (Salt Lake City, UT) | 1 |
| D14fs | Guardant 360 (Guardant Health, Redwood City, CA) | 1 |
| Exon 2 c151-2A>T | Caris Mi Profile X (Caris Life Sciences, Irving, TX) | 2 |
| Exon 2 R112fs | Caris Mi Profile X | 1 |
| Exon 2 W110X | Caris Mi Profile X | 1 |
| p16INK4a A17fs*26 | FoundationOne | 1 |
| p16INK4a D74N and p14ARF R88Q | FoundationOne | 1 |
| p16INK4a D84Y and p14ARF R98L | FoundationOne | 1 |
| p16INK4a G1010W and p14ARF R115L, p16INK4a R103fs*17, and p14ARF A117fs*44 | FoundationOne | 1 |
| p16INK4a G23fs*3 | FoundationOne | 1 |
| p16INK4a H66fs*52 and p14ARF P80fs*53+ | FoundationOne | 1 |
| p161NK4a H83Y and p14ARF A97V | FoundationOne | 1 |
| R80* c238C>T | 50 Gene Cancer Panel by University of Nebraska (Lincoln, NE) | 1 |
| W15fs | Guardant 360 | 1 |

NOTE. *CDKN2A* alterations are listed as reported on the genomic test reports that qualify each patient to participate in this Targeted Agent and Profiling Utilization Registry Study cohort.

Abbreviation: NGS, next-generation sequencing.

 

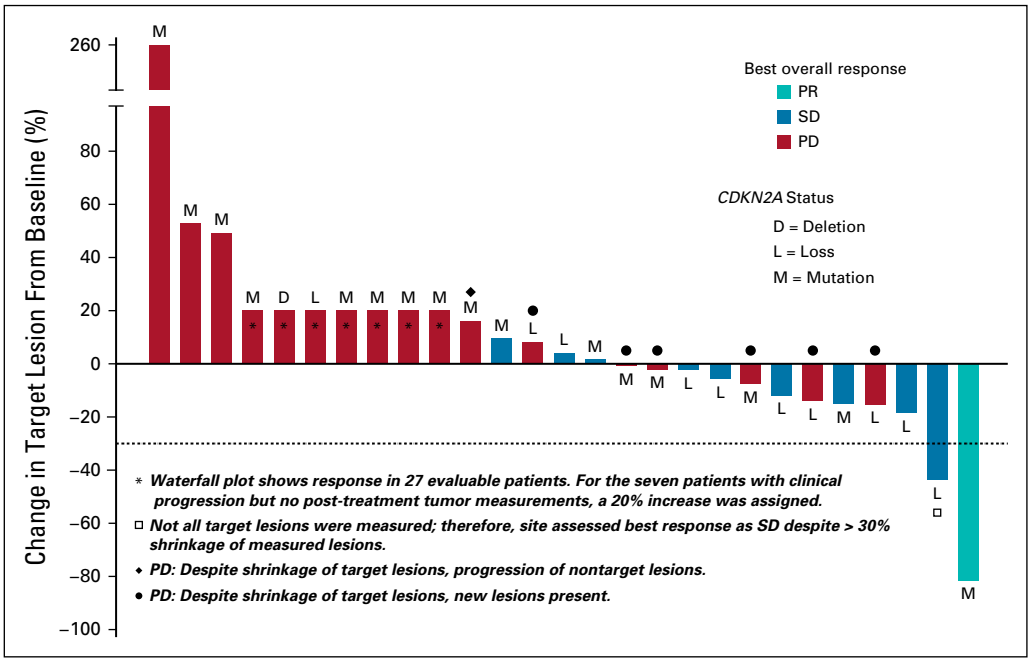


**FIG 1.** Maximum percent change from baseline in target lesion size (N = 27). PD, progressive disease; PR, partial response; SD, stable disease.

palbociclib. For all patients, the median PFS was 8.1 weeks (95% CI, 7.1 to 16.0 weeks; Fig 2A), and the median OS was 21.6 weeks (95% CI, 14.1 to 41.1 weeks; Fig 2B). The shortest time on treatment of a patient with SD or PR was 18.6 weeks, and the longest time on treatment was 40.1 weeks. The percent change from baseline tumor measurements over time for each patient is shown in Figure 3. The single patient with PR is a former smoker, White male diagnosed with stage IV adenocarcinoma, with *CDKN2A* p16INK4a A17fs*26 and no reported alterations in *ALK*, *EGFR*, *KRAS*, and *ROS1*. This patient had two prior lines of therapy after a right upper lung lobectomy, with the most recent being nivolumab administered 27 days before initiation of palbociclib but with apparent progression of disease (increased retroperitoneal adenopathy) before start of palbociclib.

All 29 patients were included in the analysis for safety. Eleven patients (37.9%) had at least one grade 3 or 4 AE or serious AE (SAE) at least possibly related to palbociclib, with the most common being neutropenia (Table 3). Other grade 3-4 AEs or SAEs at least possibly related to palbociclib included anorexia, fatigue, febrile neutropenia, hypophosphatemia, sepsis, and vomiting. Of these 11 patients, seven experienced AEs, two experienced SAEs, and two reported both AEs and SAEs. All reported events were consistent with the label for palbociclib except for hypophosphatemia.

## DISCUSSION

This phase II study of 27 evaluable patients with NSCLC and *CDKN2A* loss or mutation treated with single-agent palbociclib met predefined criteria to declare clinical activity when seven of 27 patients had either PR or SD of at least 16 weeks in duration for a DCR of 31% (90% CI, 19% to 40%). Using the same criteria, we previously reported lack of clinical activity for palbociclib in treatment of patients with pancreatic and biliary cancer with *CDKN2A* loss or mutation,[9] raising the possibility that *CDKN2A* loss or mutation is not a relevant predictive biomarker for palbociclib activity or that other features of the genomic milieu of the tumor affect the activity of palbociclib in the presence of *CDKN2A* loss or mutation. It is also possible that the genomic profiling results did not reflect the mutational status of the tumor at the time of treatment because archived specimens could have been selected by the treating physicians instead of performing new tumor biopsies.

Several phase II studies have recently been published testing a CDK inhibitor as monotherapy in NSCLC with similar findings. Abemaciclib was studied in 49 patients with NSCLC who had a median of four prior systemic therapies. DCR was 50% (PR, 4%; SD, 46%), with a trend for higher DCR in patients with *KRAS*-mutant NSCLC. *CDKN2A* loss or mutation was not described in this study nor was it a prerequisite for enrollment.[5]

SWOG S1400C enrolled 32 patients with squamous NSCLC with *CDK4*, *CCND1*, cyclin D2 (*CCND2*), or cyclin D3 (*CCND3*) amplifications on treatment with palbociclib monotherapy after progression on docetaxel. Two patients (6%) had a PR, both with *CCND1* amplification. Twelve patients (38%) had SD. Median PFS was 1.7 months, and palbociclib failed to meet prespecified criteria for further study.[6]

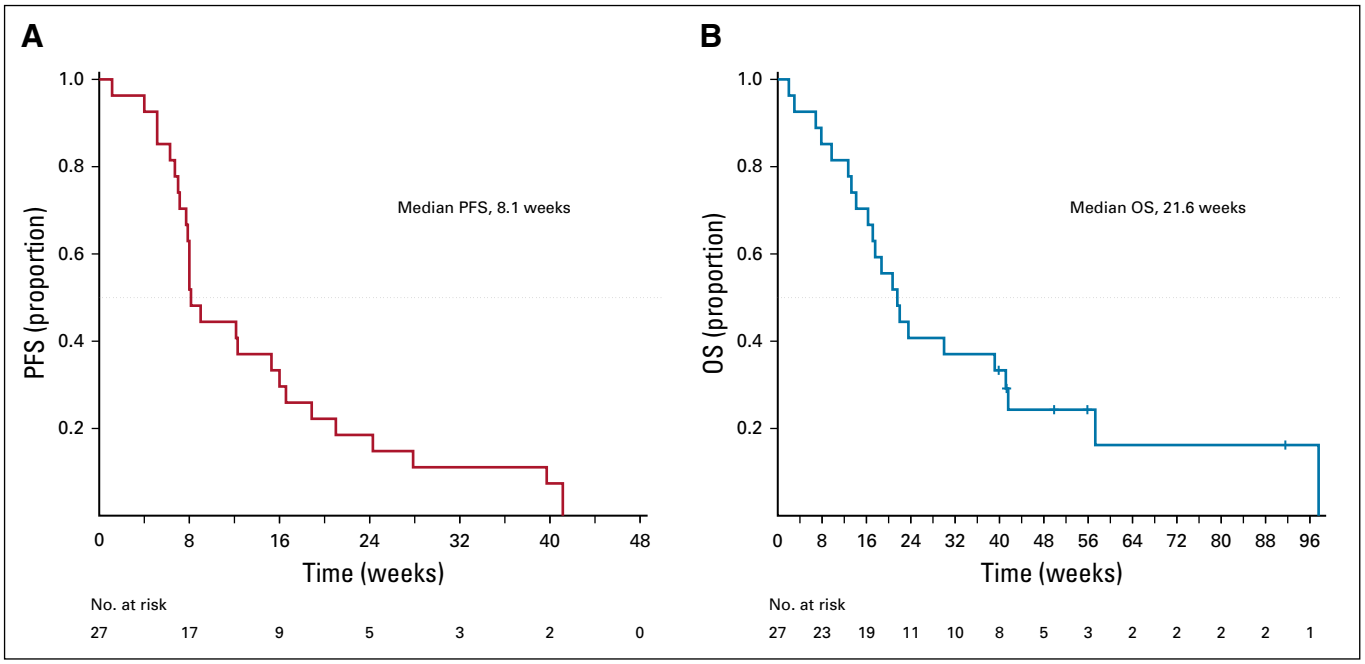


**FIG 2.** (A) Progression-free survival (PFS) and (B) overall survival (OS) in cohort of 27 patients with non–small-cell lung cancer treated with palbociclib targeting *CDKN2A* loss or mutation.

SD with palbociclib monotherapy in NSCLC was also reported in another study of 16 patients with NSCLC whose tumors were p16 null by immunohistochemistry. None of the patients had an objective response, but eight patients (50%) had SD lasting from 4 to 10.5 months.[11]

A phase III study presented in 2018[6] reported 453 patients with NSCLC and *KRAS* mutation who were randomly assigned 3:2 to treatment with either abemaciclib or erlotinib. The OS was not significantly different in patients treated with abemaciclib versus erlotinib (7.4 *v* 7.8 months, respectively),

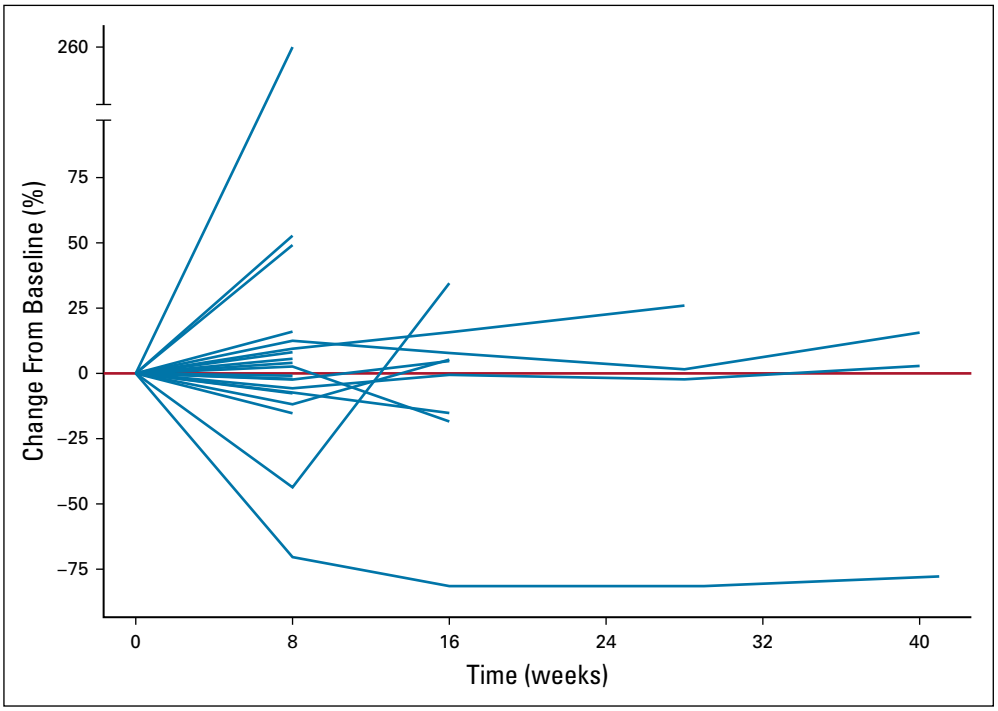


**FIG 3.** Spider plot of tumor burden changes (percent change from baseline) during palbociclib treatment in 21 patients targeting *CDKN2A* loss or mutation. Six patients with clinical progressive disease and no postbaseline tumor assessments are not included in this figure.

**TABLE 3.** Summary of Grade 3-4 AEs and SAEs (at least possibly related to palbociclib) Experienced by 11 Patients

| AE | Total No. of Events | All Grade 3 AEs (No. of SAEs) | All Grade 4 AEs (No. of SAEs) |
|---|---|---|---|
| Neutrophil count decreased | 5 | 4 (2) | 1 (1) |
| WBC decreased | 3 | 3 (1) | |
| Platelet count decreased | 2 | 1 | 1 (1) |
| Anemia | 2 | 2 (1) | |
| Lymphocyte count decreased | 2 | 2 | |
| Febrile neutropenia | 1 | | 1 (1) |
| Sepsis | 1 | | 1 (1) |
| Fatigue | 1 | 1 (1) | |
| Anorexia | 1 | 1 (1) | |
| Myocardial infarction | 1 | 1 (1) | |
| Vomiting | 1 | 1 (1) | |
| Hypophosphatemia | 1 | 1 | |

Abbreviations: AE, adverse event; SAE, serious adverse event.

although the PFS was greater with abemaciclib (3.6 *v* 1.9 months, respectively). DCR with abemaciclib was 54.4%.

The results of this TAPUR cohort are hypothesis generating and require confirmation. Additional analyses of the types of *CDKN2A* alterations and coexisting mutations could be performed to see whether there are associations of response with homozygous versus heterozygous deletion of *CDKN2A* function. Through the study of 45 lung adenocarcinoma tissue samples and 40 NSCLC cell lines, Tam et al[12] identified that 55% of the samples had p16 inactivation, and the mechanism was homozygous deletion in 55%, methylation of the promoter region in 30%, and single point mutation in 15%. Because promoter methylation was seen primarily in *KRAS*-mutated NSCLC, additional studies of palbociclib in patients with *KRAS* wildtype NSCLC with *CDKN2A* alterations might be warranted.

Given the limited, although not absent, activity of CDK4/6 inhibitors in NSCLC identified in this and other studies, consideration could be given to combining these agents with other drugs just as they are used in combination with antiestrogen therapy in metastatic hormone receptor–positive breast cancer. Recent studies suggest that CDK inhibitors might have a role in myelopreservation during doublet chemotherapy regimens,[13] sensitization to radiation treatments,[14] or augmentation of antitumor immunity with immune checkpoint blockade[15] and may perhaps extend the duration of response or restore response to oral tyrosine kinase inhibitors (TKIs) used for *EGFR*-mutated NSCLC.

In preclinical cell culture and xenograft models, Nie et al[16] demonstrated that palbociclib combined with the second-generation TKI afatinib reversed acquired resistance to afatinib. In a single-institution study of 33 patients with *EGFR*-mutated NSCLC who were treated with first-generation TKIs,[17] 78% had at least one concomitant genomic alteration, with the most common being *TP53* mutations (30.3%) and *CDK4* (24.2%) or *CDKN2A* (21.2%) copy number alterations. PFS was markedly worse for those with versus without *CDKN2A* copy number loss (6.5 *v* 13.4 months, respectively), and patients with any concomitant genomic alteration had worse OS (24.1 months *v* 40.8 months for patients without a concomitant genomic alteration). In addition, in a study that reviewed the genomic analysis of 1,122 *EGFR*-mutant lung cancer cell-free DNA samples and whole-exome analysis of seven longitudinally collected tumor samples from a patient with *EGFR*-mutant lung cancer, the authors identified pathways limiting EGFR inhibitor response, with cell-cycle gene mutations such as *CDK4/6* being prominent.[3]

Although the outcomes of patients with *CDKN2A*-altered NSCLC treated with single-agent palbociclib met our protocol-specified criteria for clinical activity, these results require confirmation because most patients experienced clinical or radiographic progression at the time of the first protocol-specified evaluation (8 weeks) or shortly thereafter. Patients with a signal of activity tended to have a performance status of 0-1 and had *KRAS* wildtype tumors. Notably, the sole patient with a PR of long duration in our study, as well as three of six patients with SD of at least 16 weeks in duration, had been treated with an immune checkpoint inhibitor as their most recent therapy before beginning palbociclib. Even though each patient had documented disease progression before initiation of palbociclib treatment, a possible delayed antitumor effect of these agents cannot be ruled out. It seems clear from this and other studies that CDK4/6 inhibitors used as single agents have modest antitumor activity in patients with advanced NSCLC. It is not clear, however, that patient selection using *CDK4/6* genomic target alterations is a necessary or effective strategy to identify patients most likely to benefit from treatment. Additional research is necessary to explore other potential biomarkers of drug sensitivity in these patients.

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## CLINICAL TRIAL INFORMATION

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## APPENDIX

**TABLE A1.** Clinical Site Names and Locations

| Site Name | Location |
|---|---|
| Cancer Research Consortium of West Michigan | |
| Mercy Health Campus | Muskegon, MI |
| Munson Medical Center | Traverse City, MI |
| Cancer Treatment Centers of America | |
| Eastern Regional Medical Center | Philadelphia, PA |
| Midwestern Regional Medical Center | Zion, IL |
| Southeastern Regional Medical Center | Newnan, GA |
| Western Regional Medical Center | Goodyear, AZ |
| Carolinas Healthcare System | |
| Levine Cancer Institute–Charlotte | Charlotte, NC |
| Levine Cancer Institute–Ballantyne | Charlotte, NC |
| Levine Cancer Institute–Monroe | Monroe, NC |
| Levine Cancer Institute–Stanly Regional Medical Center | Albemarle, NC |
| Inova Hospital System | |
| Inova Fairfax Hospital | Fairfax, VA |
| Intermountain Healthcare | |
| Intermountain Precision Genomics Cancer Research Clinic | Salt Lake City, UT |
| Michigan Cancer Research Consortium | |
| Genesys Hurley Cancer Institute | Grand Blanc, MI |
| Sparrow Health System | Lansing, MI |
| St Joseph Mercy Health System | Ann Arbor, MI |
| St Joseph Mercy Hospital | Pontiac, MI |
| Sanford Health | |
| Sanford Health | Sioux Falls, SD |
| University of Miami | |
| Sylvester Comprehensive Cancer Center | Miami Beach, FL |
| Sylvester Comprehensive Cancer Center | Deerfield Beach, FL |
| University of Nebrasa Medical Center | |
| University of Nebraska Medical Center | Omaha, NE |

 