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Abstract

Purpose: Lung-MAP (SWOG S1400) is a master platform trial assessing targeted therapies in squamous non-small cell lung cancer (sqNSCLC). The objective of study C (S1400C) was to evaluate the response rate to palbociclib, a CDK 4/6 inhibitor, in patients with cell cycle gene abnormalities.

Methods: Patients with sqNSCLC, Performance status (PS) 0-2, normal organ function, who had progressed after at least one prior platinum-based chemotherapy with CDK 4 or CCND1/2/3 amplifications on tumor specimens were eligible. The study was originally designed as a phase II/III trial comparing palbociclib to docetaxel, but was modified to a single arm phase II trial with primary endpoint of response when immunotherapy was approved. If two or fewer responses were seen in the first 20 pts, then the study would cease enrollment.

Results: Eighty-eight patients (9% of patients screened) were assigned to S1400C, and 53 patients enrolled (including 17 to docetaxel). One patient registered to docetaxel was re-registered to receive palbociclib after progression on docetaxel. The frequency of cell cycle gene alterations in the eligible palbociclib patients (N=32) were: CCND1 (n=26, 81%), CCND2 (n=3, 9%), CCND3 (n=2, 6%), CDK4 (n=1, 3%). Thirty-two eligible patients received palbociclib. There were two partial responses (6% RR, 95% CI: 0%-15%), both with CCND1 amplification. Twelve patients had stable disease (38%, 95% CI: 21%-54%). Median progression-free survival was 1.7 months (95% CI: 1.6-2.9 months) and median overall survival was 7.1 months (95% CI: 4.2-12.5).

Conclusions: Palbociclib as monotherapy failed to demonstrate the pre-specified criteria for advancement to phase III testing.

Introduction

Despite substantial progress in identifying targeted agents with activity in advanced non-squamous non-small cell lung cancer (NSCLC), there have been few advances in developing such agents in squamous cell NSCLC (sqNSCLC). 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 sqNSCLC and subsequently assigning and accruing simultaneously to sub-studies evaluating agents targeting specific molecular abnormalities.[2] When originally designed, biomarker-driven sub-studies in the protocol compared new targeted therapy or targeted therapy combinations to standard of care therapy (i.e., docetaxel) based on designated therapeutic biomarker-drug combinations, with the ultimate goal of obtaining FDA approval of new targeted therapies in this setting. In December 2015, due to the rapid development and approval of immunotherapy in NSCLC, the protocol was re-designed to evaluate biomarker-driven therapies using a single arm screening design to be followed by randomized assessments if specified levels of activity were met.[3-6]

Sub-study C (**S1400C**) of Lung-MAP tested the concept of targeting cyclin dependent kinase (CDK) abnormalities with the selective CDK4/6 inhibitor palbociclib. Unrestricted proliferation is a hallmark of cancer and frequently results from abnormality in the retinoblastoma (Rb) pathway. Rb in its active, unphosphorylated state, inhibits progression through the cell cycle. For the cell to enter mitosis, Rb is phosphorylated by the cyclin D-CDK 4/6 complex. Inactivation of Rb, by deletion, mutation or increased activation of the cyclin D-CDK 4/6 complex results in unrestricted proliferation. In sqNSCLC, Rb itself is rarely mutated. However, abnormalities of CDKN2, which encodes p16 (INK4), the primary inhibitor of the cyclin D-CDK 4/6 complex are common, as is amplification of D-type cyclins (encoded

by *CCND1,2,3*) or CDK-4/6. In squamous cell carcinoma, *CCND1* was found to be amplified in a number of tumors evaluated, including sqNSCLC. The Cancer Genome Atlas (TCGA) 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, they did not overlap with CCND1 amplifications.[1, 7]

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/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 (PS) = 0-2. 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 one year. In December 2015, the study was amended to only allow PS 0-1 and redesigned to be a single arm study. In addition to these criteria, patients were required to have normal hematologic, hepatic and renal function. Patients on strong CYP3A4 inhibitors and/or inducers were not allowed to enroll. Due to 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 disease (by RECIST 1.1) was required. Patients with treated brain metastases were allowed as long as (1) metastases had been locally treated and remained clinically

controlled and asymptomatic for at least 14 days following treatment, AND (2) patient had no residual neurological dysfunction and was off corticosteroids for at least one day prior to sub-study registration. Following 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 prior to review and approval by either the local Institutional Review Board or by the National Cancer Institute Central IRB. Written informed consent was required from all patients prior to enrollment in the master protocol and a separate consent was required for the specific sub-study.

The cell cycle gene alterations required for eligibility were amplifications of *CDK4, CCND1*, *CCND2*, or *CCND3*. Disease characterized by substitutions or fusion alterations were not eligible. Amplification was defined as $\geq$ 6 estimated copies (or $\geq$ 7 for triploid or $\geq$8 for tetraploid samples). Mutational analysis was performed on archival formalin-fixed paraffin-embedded tumor specimens 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 off treatment. Disease assessment occurred every six weeks, and treatment could continue until progression. Dose reductions and adjustments were specified in the protocol (supplemental materials) and were to be discussed with the study chair.

Statistical Considerations

S1400C originally was a phase II/III trial with randomization between palbociclib and docetaxel. The primary endpoint of the phase II component was progression free survival (PFS) and the study included

co-primary endpoints, 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 closed to accrual. Patients on the docetaxel arm were not included in the analyses presented in this paper. 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 sqNSCLC. 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 were 35%. The observation of 10/40 (25% ORR) would be considered evidence to rule out the null ORR 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 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 a median PFS of 3 months or less, if the true mPFS was 6 months, at the 0.05 1-sided level. The observation of an mPFS of at least 4.5 months would be considered evidence to rule out a mPFS of 3 months or less.

Binary proportions and associated 95% confidence intervals were estimated. Survival distributions were estimated 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. Eighty-eight patients (9% of those screened while the study was

actively accruing) were assigned to S1400C. Fifty-three patients were enrolled (including 17 to docetaxel before the study redesign). One patient registered to docetaxel re-registered to palbociclib after progression on docetaxel. The study did not meet the criterion 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 inadequate baseline labs, one did not progress on prior therapy). The demographics for the 32 eligible and evaluable patients are shown in Table 1. The frequency of cell cycle gene alterations in the eligible palbociclib patients (N=32) were as follows: *CCND1* (n=26, 81%), *CCND2* (n=3, 9%), *CCND3* (n=2, 6%), *CDK4* (n=1, 3%), Table 2.

Patients received a median of two cycles (range = 1-17) of palbociclib. The AEs were as expected for palbociclib (Table 3). Three patients discontinued therapy due to AEs. Five patients experienced Grade 4 AEs including lymphopenia (3), neoplasms (1) and thrombocytopenia (1). 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 their best objective response with no follow-up tumor measurements. The median progression free survival was 1.7 months (95% CI: 1.6-2.9) and overall survival was 7.1 months (95% CI: 4.2-12.5) (Figure 2). The one- and two-year estimates of survival are 37.5% and 12.1%, respectively. Of the two partial responses, one has progressed (duration of response, 7.7 months), and one 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 patient population with sqNSCLC. 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% and median PFS 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 CDK 4/6 inhibitors (palbociclib, abemaciclib, ribociclib) have primarily demonstrated benefit in hormone responsive breast cancer when combined with anti-estrogens 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 lung cancer patients 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 almost exclusively seen in non-squamous carcinoma.[15] A study evaluating abemaciclib versus erlotinib in the second line treatment of NSCLC with K-*Ras* mutations (and therefore likely adenocarcinoma) was negative for the primary endpoint of OS, however

demonstrated superior PFS (3.6 months vs. 1.9 months, p <.001) and higher response rate (8.9% vs. 2.7%, p =.01).[15]

An additional issue is that the postulated mechanism of action for CDK/cyclin agents, 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 endpoint 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. It should be noted that 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 that indicates that additional evaluation of this pathway, possibly in combination with other agents, may still be beneficial in some patients with sqNSCLC.

Tables and Figures

Table 1: Patient Demographics and Characteristics

	N (%) (N = 32)
Age Median (range)	67.3 (53-80.7)
Male Gender	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%)
Number of Prior Lines of Therapy for Stage IV Disease	
0	8 (25%)*
1	23 (72%)
2 or more	1 (3%)
Smoking Status	
Current Smoker	13 (41%)
Former Smoker	18 (56%)
Never Smoker	1 (3%)
Brain Metastases	
Present	2(6%)
Absent	30 (94%)

***** per protocol, patients were eligible if they received chemotherapy in the adjuvant or as part of combined modality therapy within one year of enrollment.

Table 2: Gene Alterations Detected on FMI NGS Screening

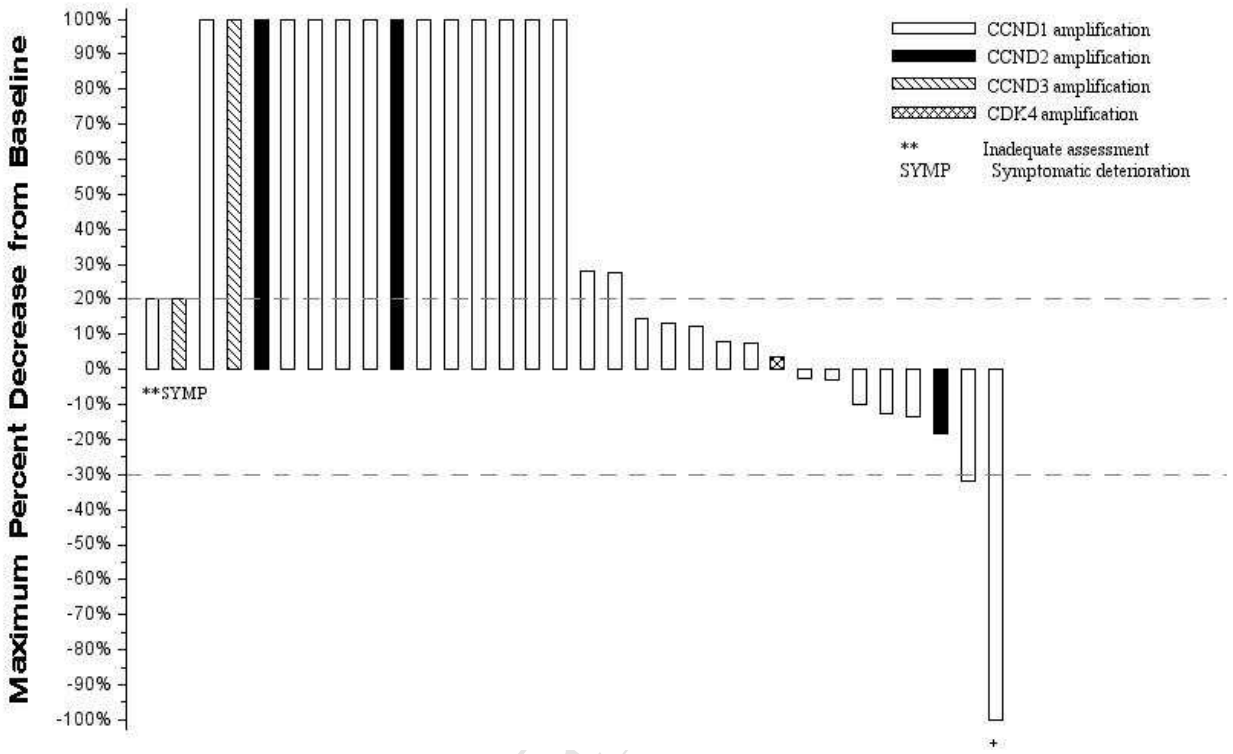
	Palbociclib (n=32)
CCGA Study Gene Alterations	
CCND1	26(81%)
CCND2	3(9%)
CCND3	2(6%)
CDK4	1(3%)
Number of CCGA Study Gene Alterations	
1	32(100%)
Other Concomitant Gene Alterations	
Short Variants	
TP53	30(94%)
CDKN2A, MLL2	8(25%)
NFE2L2	6(19%)
PTEN	4(13%)
ARID1A, LRP1B, PIK3CA	3(9%)
APC, BAP1, KRAS	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,	2(6%)

KDR, PTEN	
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%)

Table 3: Adverse Events Attributed to Treatment

Adverse event	**Grade of AE** N = 32		
	3	**4**	**5**
AST 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**

Figure 1. Waterfall plot of response to palbociclib

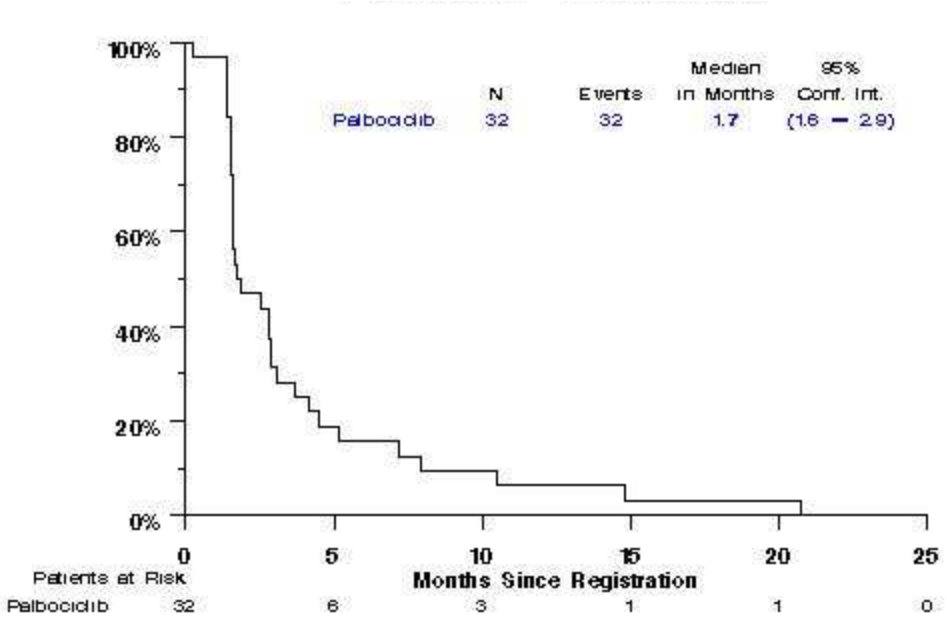


Each vertical bar represents a patient's best percent decrease in tumor burden when compared to baseline as defined by RECIST 1.1. Only patients with measurable disease at baseline are presented in the plot. Patients who did not have follow up tumor disease assessment are presented at the very left of the plot marked with '**'. Patients who had new lesions appear at their first follow-up assessment or who expired prior to the first scheduled the disease assessment and the 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 decrease in tumor burden from baseline while positive numbers represent increase in tumor burden from baseline.

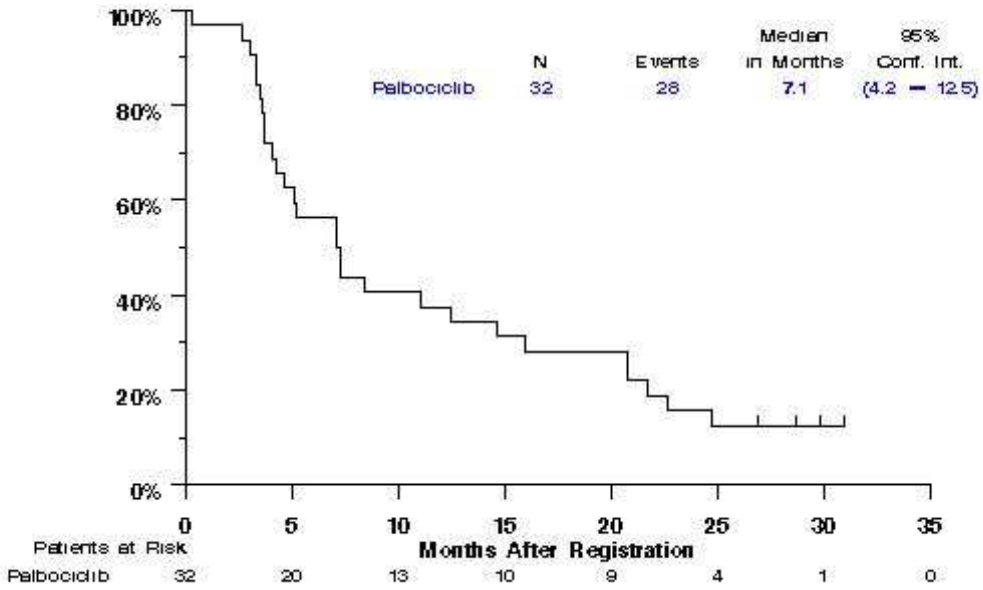
+ this patient had complete disappearance of disease and would have been considered a CR, however, the patient's non-target brain lesion was removed surgically and per RECIST 1.1 guidelines is coded as having a partial response.

Figure 2: Progression-free Survival and Overall Survival

2a: Progression-Free Survival



2b: Overall Survival



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