Combination Paclitaxel and Palbociclib: Results of a Phase I Trial in Advanced Breast Cancer

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Abstract

Purpose: The CDK 4/6 inhibitor palbociclib rapidly and reversibly inhibits the cell cycle. The goal of this study was to exploit the cell cycle through intermittent, alternating dosing with palbociclib/paclitaxel to enhance efficacy. We determined the combination dose-limiting toxicity (DLT) in patients with Rb protein–expressing, advanced breast cancer.

Patients and Methods: This open-label, phase I trial (NCT01320592) enrolled patients to sequential cohorts of palbociclib orally dosed intermittently between days 1 and 19 of a 28-day cycle alternating with weekly paclitaxel. Dose escalation proceeded in a standard 3+3 design. Ten additional patients received the combination at the recommended phase II dose (RP2D). Those who reached response plateau ≥6 cycles could continue on palbociclib alone on a 3 week on/1 week off schedule at one dose level above their combination dose.

Introduction

The G1–S checkpoint is regulated by the CDK 4/6–Cyclin D complex via phosphorylation of the Rb protein (1). In its hypophosphorylated state, Rb binds E2F promoters to prevent transition from G1–S–phase of the cell cycle. When phosphorylated by the complexing of Cyclin D and CDK 4 or CDK 6, Rb is released from E2F, leading to progression through the cell cycle, and ultimately, to cellular proliferation. Components of CDK 4/6–Cyclin D complex are frequently altered in breast cancer. For example, CCND1 is amplified in up to 30% of breast cancers and the endogenous inhibitor of the complex (2), INK4a-p16, is lost in up to half of breast cancers (3). The consequences of these changes are unregulated cellular proliferation.

Therapies targeting the cell cycle have long been in development, and in 2015, palbociclib, a highly potent, oral inhibitor of CDK 4/6, was the first to be FDA approved. In preclinical models, palbociclib-induced, G1 arrest inhibited growth in breast cancer cell lines. The cell lines that were most sensitive to palbociclib-induced growth inhibition were those expressing luminal genes, whereas cell lines expressing basal-like genes were not sensitive to palbociclib-induced growth inhibition (4). Furthermore, synergistic growth inhibition was observed when palbociclib was combined with tamoxifen or trastuzumab. On the basis of these data, palbociclib was studied alone and in combination with endocrine therapy in breast cancer after phase I trials demonstrated safety (5). Palbociclib alone has modest efficacy with an overall response rate (ORR) of 20% among patients with heavily pretreated advanced estrogen receptor (ER)–positive breast cancer (6). The phase III PALOMA-2 trial demonstrated that when combined with letrozole in the first-line metastatic setting, the addition of palbociclib nearly doubled progression-free survival (PFS; ref. 7). Similarly, in the metastatic endocrine-resistant setting, the addition of palbociclib to fulvestrant nearly tripled PFS compared with fulvestrant alone in the PALOMA-3 trial (8) and has shown a survival benefit (9). Two additional CDK 4/6 inhibitors, ribociclib and abemaciclib, are also FDA approved in these settings.

Results: Twenty-seven patients enrolled. Although there was only one DLT (grade 3 alanine aminotransferase/aspartate aminotransferase at 125 mg), neutropenia (NTP) requiring dose modification in cycle 1 (C1) resulted in an RP2D of 75 mg palbociclib/80 mg/m2 paclitaxel. During C1, the most common adverse event was NTP, occurring in 15 patients (55.6%); grade 1 or 2 nausea and peripheral neuropathy were also observed in 8 patients each (29.6%). The clinical benefit rate was 55% at the RP2D; benefit was observed across all receptor subtypes.

Conclusions: Alternating sequential palbociclib/paclitaxel in patients with Rb+ advanced breast cancer is feasible and safe, without evidence of additive toxicity. This represents a new application for CDK 4/6 inhibitors in Rb+ breast cancer regardless of subtype; efficacy trials are warranted.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) are a new class of drugs that are approved alone or in combination with endocrine therapy for advanced estrogen receptor–positive breast cancer. We sought to combine palbociclib with paclitaxel using a novel dosing schedule taking advantage of the mechanism of action of both drugs (G1 arrest for palbociclib and M-phase derangement for paclitaxel) to potentially increase the efficacy of single-agent paclitaxel. Rather than administering these drugs simultaneously (which preclinically is antagonistic), the drugs were sequenced. Administering the drugs on an alternating schedule (never on the same day) potentially enables G1 synchronization by palbociclib—a few days rest without drug allows cells to reenter the cell cycle, increasing the percentage of cells in M-phase when exposed to paclitaxel. This article describes the safety and preliminary efficacy of combination palbociclib/paclitaxel and demonstrates that they can be combined in a mechanistically designed sequence.

Besides showing that combinations of endocrine therapy and palbociclib are synergistic, preclinical work has also shown that palbociclib can be combined with chemotherapy, although results demonstrate either synergy or antagonism, depending on the schedule of administration (10, 11). For example, when palbociclib and paclitaxel are given concurrently to breast cancer cells in colony growth experiments, antagonism was noted compared with paclitaxel alone. However, when cells were intermittently exposed to palbociclib followed by paclitaxel (after a 24-hour period without any drug exposure), synergistic reduction in colony formation was noted compared with either drug alone (11). These results suggest that palbociclib-induced G1 arrest was protecting the breast cancer cells from paclitaxel-induced cell death when the drugs were given concurrently but was potentially synchronizing cells in the cell cycle when given intermittently when cells were released back into S-phase by removing palbociclib. The consequence of synchronization would theoretically lead to a greater proportion of cells in M-phase when exposed to paclitaxel thus causing synergistic cell death and potentiating paclitaxel activity.

Noting the favorable tolerability of palbociclib, as well as the strong preclinical data for intermittent exposure to palbociclib and paclitaxel, we sought to exploit this approach clinically, with the hypothesis that alternating, intermittent dosing would increase paclitaxel activity. We therefore conducted a phase I clinical trial combining palbociclib and paclitaxel in an alternating fashion, taking into account the half-life of palbociclib (27 hours; ref. 5) to assess the feasibility, safety, and tolerability of the combination as well as to obtain preliminary efficacy data.

Patients and Methods

Patient population

Eligible patients had histologically confirmed stage IV breast cancer, with any combination of ER, progesterone receptor (PR), or HER2 expression, measurable disease defined by RECIST 1.1 (12), ≤3 prior cytotoxic chemotherapies in the metastatic setting, adequate organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. Prior taxane (including paclitaxel) for early-stage and/or advanced breast cancer was allowed, although there had to be at least 365 days from the last dose of paclitaxel. Patients with both ER+ and PR+ disease were required to have expression of Rb protein immunohistochemically in either the primary or metastatic tumor; Rb testing was not required for those with ER− and/or PR− disease, as these tumors are nearly universally Rb− (13). Patients with a history of brain metastases were allowed if they had received treatment for known lesions, were off steroids to control symptoms, and had no new or progressing central nervous system (CNS) lesions. Washout from previous therapy was required: 21 days from cytotoxic therapy or radiation, 28 days for an investigational agent, and 24 hours for endocrine therapy.

RB testing. For patients requiring Rb testing, fresh or archival tumor was obtained and sectioned to perform IHC testing for Rb expression, as described previously (6). Tumors were considered positive if there was at least 1+ staining in the nucleus or cytoplasm.

Clinical trial design

This was an investigator-initiated, phase I trial with a 3+3 design, testing escalating doses of palbociclib given in an alternating fashion with a fixed weekly dose of paclitaxel (NCT01320592). The study objectives were to determine the feasibility, toxicity, and safety of the combination. The primary endpoint was the determination of MTD of the combination. Secondary endpoints included adverse event (AE) rates, response rate, and PFS at the recommended phase II dose (RP2D). All participants provided written informed consent. The protocol was approved by the institutional review board at the University of Pennsylvania (Philadelphia, PA) and was conducted in accordance with the Declaration of Helsinki and the US Common Rule. The trial was funded through the University of Pennsylvania-Pfizer Alliance; the senior author (A.M. DeMichele) was the sponsor-investigator, and Pfizer supplied investigational palbociclib.

Dose-escalation cohort

Palbociclib dose was escalated in the following dose cohorts: 50, 75, 100, and 125 mg. Palbociclib was administered on consecutive 5-day intervals on days 2, 3, 4, 5, 6, 9, 10, 11, 12, 13; and 16, 17, 18, 19, 20 of each 28-day cycle (Fig. 1A). Paclitaxel was given weekly on days 1, 8, 15, and 22 in 28-day cycles for the first 3 cycles; at the start of cycle 4, dosing was reduced to days 1, 8, and 15 every 28 days (3 weeks on/1 week off). Critical to the dosing schedule and hypothesis, palbociclib and paclitaxel were never administered on the same day. The 5-day palbociclib dosing duration was selected based upon the known half-life of the drug (27 hours) so that clearance would occur before dosing with paclitaxel. This was supported by preclinical growth inhibition experiments demonstrating synergy when 24 hours separated palbociclib and paclitaxel treatment (11). Patients who reached a response plateau after ≥6 or greater cycles of therapy were given the option to discontinue paclitaxel and start palbociclib maintenance, given at one dose level above their current combination dose of palbociclib. Those who opted to change to palbociclib maintenance were permitted to restart combination therapy if scans demonstrated
progression on palbociclib alone. Growth factors were prohibited; dose reductions of both palbociclib and paclitaxel were utilized in response to toxicity.

**DLT definitions**
DLTs were defined during the dose-escalation phase of the study as any one of the following: (i) grade 4 neutropenia (NTP) lasting for ≥7 days in duration, (ii) grade 4 NTP with fever >38.5°C and/or infection requiring antibiotic or antifungal treatment, (iii) grade 4 thrombocytopenia, (iv) any grade ≥3 non-hematologic toxicity (note exceptions below), including treatment delay of greater than 7 days or (v) missing ≥1 of the 4 weekly doses of paclitaxel or palbociclib in the first cycle due to toxicity. The following were NOT considered DLTs: grade 3 or 4 NTP lasting <7 days and not accompanied by fever or infection; grade 3 nausea, vomiting, diarrhea, dehydration, hyperglycemia that in the opinion of the investigator/sponsor occurred in the setting of inadequate compliance with supportive care measures and lasted less than 48 hours; asthenia; alopecia; inadequately treated hypersensitivity reactions; grade 3 elevated transaminases ≥1 week in duration or in patients with known liver metastases and abnormal liver function tests (LFT) at baseline; grade 3 elevated transaminases ≥2x baseline; and grade 3 total hyperbilirubinemia if <35% is direct component.

**Expansion cohort**
The totality of toxicity data from the dose-escalation cohort was utilized to determine optimally tolerable dose and schedule for the expansion cohort. A 3-day run-in of single-agent palbociclib was added to synchronize cells prior to the first dose of paclitaxel (Fig. 1B). Because of the extent of non-DLT NTP with 5-day palbociclib dosing, palbociclib was decreased to 3-day intervals (days 2, 3, 4; 9, 10, 11; 16, 17, 18) to allow a greater time period (>48 hours) for clearance before dosing paclitaxel (Fig. 1B). In addition, patients with HER2+ disease in the expansion cohort were permitted to receive trastuzumab 6 mg/kg every 3 weeks in addition to palbociclib and paclitaxel. Those patients who were starting or restarting trastuzumab received a one-time loading dose of 8 mg/kg for the first dose.

**Response assessment**
Disease response was defined per RECIST 1.1 (12) and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Response was assessed every 2 cycles (8 weeks) by a radiologist in the RECIST core at the University of Pennsylvania (Philadelphia, PA).

**Results**
A total of 27 patients enrolled onto the trial between June 2, 2011 and May 8, 2015, 15 on the dose-escalation portion, and 12 on the dose-expansion portion. The characteristics of the

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>N = 27 (%)</th>
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</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>53 (33-70)</td>
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<tr>
<td>Receptor status</td>
<td></td>
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<tr>
<td>ER+/HER2−</td>
<td>16 (59.3%)</td>
</tr>
<tr>
<td>ER−/HER2+</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>ER any/HER2+</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Sites of metastatic diseasea</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>18 (66.7%)</td>
</tr>
<tr>
<td>Bone</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>Soft tissue/lymph nodes</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>Prior cytotoxic therapy regimens (metastatic)</td>
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<tr>
<td>0</td>
<td>0-11 (40.8%)</td>
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<tr>
<td>1</td>
<td>1-5 (38.5%)</td>
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<tr>
<td>2</td>
<td>2-6 (22.2%)</td>
</tr>
<tr>
<td>3</td>
<td>3-5 (38.5%)</td>
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<tr>
<td>Prior taxane</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>21 (77.8%)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>19 (70.4%)</td>
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<tr>
<td>Metastatic</td>
<td>5 (18.5%)</td>
</tr>
<tr>
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<tr>
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<td>6 (22.2%)</td>
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<tr>
<td>Reason of study</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>25 (92.6%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Alive</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Deceasedb</td>
<td>17 (63%)</td>
</tr>
</tbody>
</table>

*aSome patients had multiple sites of metastatic disease.*

*bAlive/deceased as of the data cutoff of March 31, 2017.*
study population are shown in Table 1. Sixteen patients (59.3\%) had ER\+/HER2\- disease, 9 patients (33.3\%) had triple-negative breast cancer, and 2 patients (7.4\%) had HER2-overexpressing breast cancer. Most patients (59\%) had received zero or one prior lines of cytotoxic chemotherapy for advanced breast cancer. Notably, 77% percent had received a prior taxane in either the adjuvant (n = 19) or metastatic (n = 5) settings. Two patients discontinued treatment due to toxicity [recurrent (n = 1) or prolonged (n = 1) grade 3 NTP], and the remainder discontinued study participation due to progression of disease. Eight patients elected to discontinue paclitaxel after reaching a response plateau. Two of these patients restarted the combination upon progression on single-agent palbociclib.

Table 2 shows the AEs experienced in cycle 1 (C1). The most common AE was NTP, which occurred in 3 of 9 patients at 75 mg (33\%), 9 of 12 (75\%) at 100 mg, and 3 of 3 (100\%) at the 125 mg dose levels. NTP was also the most common grade 3/4 event occurring in 2 of 9 (22\%), 7 of 12 (58\%), and 2 of 3 (66.7\%) of patients in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively. No DLTs were seen in the 50 mg, 75 mg, or 100 mg cohorts. One of 3 patients experienced a DLT at the highest palbociclib dose level (125 mg), consisting of grade 3 elevation in aspartate aminotransferase (AST) and alanine aminotransferase; ext, extremity; NOS, not otherwise specified.

*All AEs reported regardless of relatedness to study therapy.

Table 3 shows all AEs recorded over the course of the trial in each dose cohort. NTP was the most common grade 3/4 event during C1 and throughout the study occurring in 0/3 (0\%), 2/9 (22\%), 7/12 (58.3\%), and 2/3 (66.7\%) patients during C1 and 1/3 (33.3\%), 4/9 (44\%), 10/12 (83.3\%), and 3/3 (100\%) throughout the trial in the 50 mg, 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3). The median time with grade 3 NTP was 1.9, 6.5 and 9.3 days in the 75 mg, 100 mg, and 125 mg dose cohorts, respectively (Tables 2 and 3).
Day (D) 15 was the most common day for dose holds of paclitaxel and was most common among those receiving higher doses of palbociclib (100 mg and 125 mg); with 2 exceptions, all patients were able to receive D22 of paclitaxel. One patient received concurrent trastuzumab without additional toxicity. To explore preliminary efficacy, we examined response rate and PFS within dose cohorts. The median PFS was 209 days and is depicted in the Kaplan–Meier Curve in Supplementary Fig. S2; the median PFS is 105, 812, 234, and 209 days in the 50, 75, 100, and 125 mg cohorts, respectively. Four patients are not evaluable for response.

Table 4. Dose modifications

<table>
<thead>
<tr>
<th>Palbociclib</th>
<th>Final dose (mg)</th>
<th>N (%)</th>
<th>Paclitaxel</th>
<th>Original dose (mg/m²)</th>
<th>Final dose (mg/m²)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 (n = 3)</td>
<td>50</td>
<td>3 (100%)</td>
<td>80</td>
<td>80</td>
<td>2 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>75 (n = 9)</td>
<td>75</td>
<td>4 (44.4%)</td>
<td>80</td>
<td>80</td>
<td>5 (55.6%)</td>
<td></td>
</tr>
<tr>
<td>100 (n = 12)</td>
<td>100</td>
<td>3 (25%)</td>
<td>80</td>
<td>80</td>
<td>7 (58.3%)</td>
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<tr>
<td>125 (n = 3)</td>
<td>75</td>
<td>1 (33.3%)</td>
<td>80</td>
<td>60</td>
<td>3 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ext, extremity; GERD, gastroesophageal reflux disease.
*AEs that were reported in >1 patient and were felt at least possibly due to study therapy. Serious AEs experienced by 1 patient were pulmonary embolism, pneumonia, and port infection.
Figure 2.
Response assessments. **A**, Waterfall plot. The columns are coded by palbociclib dose cohort: diagonal stripe, 50 mg starting dose; gray, 75 mg starting dose; black, 100 mg starting dose; white, 125 mg starting dose. Characters indicate receptor subtype: Δ, ER any/HER2+; †, ER-/HER2+; no character, ER+/HER2+.

**B**, Swimmers plot depicting days on study by palbociclib dose cohort. The bars are coded by best RECIST response: gray, PD; vertical stripes, SD < 6 months; white, SD ≥ 6 months; black, PR; diagonal stripes, CR; dots, unevaluable. Characters indicate receptor subtype: ‡, ER-/HER2+; Δ, ER any/HER2+; no character, ER+/HER2+.
response because they came off study due to clinical progression (3) or toxicity (1) prior to the end of C2 and did not undergo anatomic reimaging for RECIST review. These patients enrolled in the 50 mg (n = 1), 75 mg (n = 1), and 100 mg (n = 2) dose levels. Figure 2A is a waterfall plot that depicts the best RECIST response in those who are eligible for response assessment. Responses are observed in all dose cohorts and in patients with all receptor subtypes. Figure 2B is a swimmers plot that groups patients by dose cohort and depicts time on study and best response according to RECIST 1.1 by receptor status. Response rates (CR or PR) are 50% (1/2), 44% (4/9), 50% (6/12), and 33.3% (1/3) in the 50 mg, 75 mg, 100 mg, and 125 mg dose cohorts, respectively. Clinical benefit (CR, PR, or SD ≥ 6 months) are 50% (1/2), 55.6% (5/9), 66.7% (8/12), and 66.7% (2/3) in the 50 mg, 75 mg, 100 mg, and 125 mg dose cohorts, respectively. Among the 8 patients who discontinued paclitaxel and took single-agent palbociclib, progression occurred after 2 cycles (n = 3), 3 cycles (n = 1), 9 cycles (n = 2, one of these patients restarted paclitaxel and continued to respond for 6 cycles), 10 cycles (n = 1), and 13 cycles (n = 1, she restarted paclitaxel, but progressed after 2 cycles). Thus, 50% (4/8) of patients who went on to single-agent palbociclib maintenance continued to respond for >6 months.

Discussion

In summary, this trial demonstrated the safety, tolerability, feasibility, and initial activity of the combination of intermittent alternating doses of the CDK 4/6 inhibitor palbociclib and paclitaxel in women with Rb+, advanced breast cancer. The recommended dose and schedule for future studies is 75 mg of palbociclib, given for 3 consecutive days, initiated at least 24 hours after each dose of weekly paclitaxel. Responses were observed at all dose levels and within each receptor subset and were maintained in 50% (4/8) of patients who elected to go onto palbociclib maintenance. Too few patients resumed the combination to draw any conclusions about the success of restarting this therapy.

CDK 4/6 inhibitors, in combination with endocrine therapy for patients with metastatic, ER+ breast cancer, have dramatically improved outcomes and are now FDA approved and widely used for this indication. However, based upon their unique mechanism of action and extremely tolerable safety profile, these agents may have efficacy beyond these combinations (14). The current trial was designed to translate the preclinical findings regarding concurrent versus alternating dosing with chemotherapy (11). We have combined intermittent dosing of palbociclib with weekly paclitaxel, to take advantage of the ability of the CDK 4/6 inhibitor to synchronize the cancer cells so that initial exposure causes a G1 arrest, discontinuation of the drug allows the cells to be released back into the cell cycle, therefore a higher fraction of cells will be in M when exposed to paclitaxel. Given the 27-hour half-life of palbociclib as well as the 24 hours of rest provided to cells in the preclinical growth inhibition experiments, we initially dosed palbociclib for 5 consecutive days to allow a 48-hour rest period during which patients would receive no drug therapy. Although this was tolerable, there was a high frequency of NTP and dose reductions with the addition of paclitaxel. Therefore, in the dose-expansion cohort, palbociclib dosing was shortened to 3 days (resulting in a 96-hour rest period) in an effort to improve tolerability without losing the potential synchronization effect.

Despite the shortened palbociclib-dosing interval, 5 of 6 patients who received palbociclib at 100 mg in the expansion cohort experienced grade 3 NTP which necessitated holding paclitaxel during the first cycle of therapy. Thus, the 75 mg dose level proved to be more feasible and was tolerable and active. Importantly, we did observe NTP in those receiving 75 mg of palbociclib at higher rates than we would expect with paclitaxel alone, which indicates that there is PD effect of palbociclib at this dose level. Furthermore, among those enrolled into the 75 mg dose cohort, not every patient was able to receive all 4 doses of paclitaxel during C1 due to NTP again indicating PD effect. Although palbociclib at 75 mg is the RP2D, additional dose reduction to 50 mg was still necessary to enable some patients to remain on study beyond the first cycle of therapy. Because 50-mg tablets are not commercially available, future studies will need to examine alternative dose modification strategies such as reducing the paclitaxel dose.

This is the first human clinical trial to combine palbociclib and chemotherapy of any kind. We explored the combination with paclitaxel because of its mechanism of action. Our goal with alternating dosing was to exploit the reversible G1 arrest of palbociclib to synchronize the tumor cells in the cell cycle, enable them to later reenter the cycle with a few days of rest, such that a higher fractions would be in M-phase when exposed to paclitaxel. Paclitaxel was also a good partner clinically, because it is a common therapy used for patient with advanced breast cancer. Unfortunately, we do not have any direct PD measure within the trial that could confirm that the mechanism operated as hypothesized.

However, we have demonstrated that the combination of alternating palbociclib and paclitaxel does not appear to modify the safety profile of either agent, and no new safety signals were seen. All AEs observed in this phase I study were expected, and although we did not collect pharmacokinetics to directly assess for drug–drug interactions, the AE severity did not appear to exceed that of the individual agents when used alone based upon historical data. NTP is a well-established toxicity of palbociclib and was the most common AE observed among our patients, occurring with a frequency that is similar to that seen in the PALOMA 2 and 3 trials (7, 15). Furthermore, the rate of neutropathy was consistent with other trials examining paclitaxel (41%–89.9%; ref. 16–18). Although it is difficult for us to draw conclusions about efficacy from this small study of patients receiving different doses of palbociclib in combination with a stable dose of paclitaxel, we did observe a degree of response (33.3%–60% across each dose cohort) that was at least as good as if not better than those seen historically with weekly paclitaxel alone (44.9%–55%; refs. 19–21). It is also notable that patients with all receptor subtypes responded to this therapy, and further exploration in all receptor subtypes is warranted; however, we acknowledge that the responses seen in those with triple-negative breast cancer may be related to paclitaxel alone. A randomized trial comparing the intermittent, alternating palbociclib/paclitaxel strategy to paclitaxel alone will be necessary to determine the relative contribution of the CDK 4/6 inhibitor to this regimen.

Despite the limitations, this trial is important because it demonstrates the successful translation of an alternate dosing strategy combining palbociclib and paclitaxel in patients with Rb+, advanced breast cancer. We can conclude that the alternate dosing schedule of palbociclib and paclitaxel is both safe and
feasible; however, we cannot draw conclusions about any alteration in the cell cycle with this schedule of drug delivery. Given the feasibility of this approach, we are conducting a follow-up trial (NCT02599363) utilizing pharmacodynamic, histologic, and imaging biomarkers to confirm synchronization and schedule, and identify a patient population that benefits from this treatment approach. Ultimately, this combination will require further study in a larger randomized trial with a direct comparison to single-agent paclitaxel to determine whether such a strategy will ultimately improve outcomes for women with advanced breast cancer.

Disclosure of Potential Conflicts of Interest

S.M. Domchek reports receiving commercial research grants from AstraZeneca and is a consultant/advisory board member for AstraZeneca, Clovis, and Bristol-Myers Squibb. K.R. Fox is a consultant/advisory board member for Genomic Health. P.I. O’Dwyer reports receiving commercial research grants from Novartis, Pfizer; receiving other commercial research support from Genentech, Bristol-Myers Squibb, GlaxoSmithKline, Five Prime, FortySeven, BBI, Novartis, Celgene, Incyte, Lilly/Inhibitex, Array, H3, and Talo; is a consultant/advisory board member for Genentech, Celgene, and Boehringer Ingelheim; and reports receiving other remuneration for expert testimony from Bayer. A.M. DeMichele reports receiving commercial research grants from Novartis, Pfizer, Genentech, Calithera, and Menarini; reports receiving speakers bureau honoraria from Pfizer; and is a consultant/advisory board member for Context Therapeutics, Novartis, Calithera, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

References

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