**ABSTRACT**

We evaluated the safety, pharmacokinetic profile, pharmacodynamic effects, and antitumor activity of abemaciclib, an orally bioavailable inhibitor of cyclin-dependent kinases (CDK) 4 and 6, in a multicenter study including phase I dose escalation followed by tumor-specific cohorts for breast cancer, non–small cell lung cancer (NSCLC), glioblastoma, melanoma, and colorectal cancer. A total of 225 patients were enrolled: 33 in dose escalation and 192 in tumor-specific cohorts. Dose-limiting toxicity was grade 3 fatigue. The maximum tolerated dose was 200 mg every 12 hours. The most common possibly related treatment-emergent adverse events involved fatigue and the gastrointestinal, renal, or hematopoietic systems. Plasma concentrations increased with dose, and pharmacodynamic effects were observed in proliferating keratinocytes and tumors. Radiographic responses were achieved in previously treated patients with breast cancer, NSCLC, and melanoma. For hormone receptor–positive breast cancer, the overall response rate was 31%; moreover, 61% of patients achieved either response or stable disease lasting ≥6 months.

**SIGNIFICANCE:** Abemaciclib represents the first selective inhibitor of CDK4 and CDK6 with a safety profile allowing continuous dosing to achieve sustained target inhibition. This first-in-human experience demonstrates single-agent activity for patients with advanced breast cancer, NSCLC, and other solid tumors. *Cancer Discov; 6(7); 740–53. © 2016 AACR.*

**Corresponding Authors:** Amita Patnaik, South Texas Accelerated Research Therapeutics, 4383 Medical Drive, San Antonio, TX 78229. Phone: 210-593-5250; Fax: 210-615-1121; E-mail: amita.patnaik@start.stoh.com; and Geoffrey Shapiro, Early Drug Development Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Mayer 446, 450 Brookline Avenue, Boston, MA 02215. Phone: 617-632-4942; Fax: 617-632-1977; E-mail: geoffrey_shapiro@dfci.harvard.edu

doi: 10.1158/2159-8290.CD-16-0095
© 2016 American Association for Cancer Research.

**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**


1 South Texas Accelerated Research Therapeutics, San Antonio, Texas. 2 University of California, Los Angeles, California. 3 Dana-Farber Cancer Institute, Boston, Massachusetts. 4 Eli Lilly and Company, Indianapolis, Indiana. 5 Massachusetts General Hospital, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).


Current address for J.F. Hilton: University of Ottawa, Ottawa, Ontario, Canada.

www.aacrjournals.org
INTRODUCTION

Cyclin-dependent kinases (CDK) 4 and 6 interact with D-type cyclins to phosphorylate the retinoblastoma (RB) tumor suppressor protein and promote G1 to S phase cell-cycle progression (1). The activity of these kinases is regulated by the phosphorylation, ubiquitination, and binding of endogenous cellular inhibitors from the INK4 family (2–5). The INK4–CDK4/CDK6–cyclin D axis is often disrupted in cancer by both genetic and epigenetic mechanisms, resulting in increased kinase activity (6–8). In addition, excessive CDK4 or CDK6 activity may suppress senescence and directly contribute to both initiation and maintenance of the transformed state (9–15). Ectopic expression of INK4-inhibitory proteins in cancer cells reverses these tumorigenic effects, indicating the potential of CDK4 and CDK6 as antineoplastic drug targets (16). Furthermore, mouse models lacking D-type cyclins or CDK4 or CDK6 demonstrate context-specific roles for these proteins in proliferation that is restricted by cell type, suggesting a therapeutic window for inhibition of CDK4 and CDK6 as an anticancer strategy (17–20).

Abemaciclib (LY2835219) is a small-molecule inhibitor of CDK4 and CDK6 (21). Consistent with its activity against CDK4 and CDK6, abemaciclib inhibits RB phosphorylation and leads to G1 arrest in RB-proficient cell lines (21). In a colorectal cancer xenograft model used to develop an integrated pharmacokinetic/pharmacodynamic model, abemaciclib can be dosed orally on a continuous schedule to achieve sustained target inhibition and demonstrates not only durable cell-cycle inhibition but also single-agent antitumor activity (21, 22). Tumor growth inhibition is observed in multiple other human cancer xenograft models, including those derived from non–small cell lung cancer (NSCLC), melanoma, glioblastoma, and mantle cell lymphoma (21–23). Abemaciclib distributes across the blood–brain barrier and prolongs survival in an intracranial glioblastoma xenograft model (24), suggesting potential efficacy against primary and metastatic tumors involving the central nervous system.

Based on preclinical investigations, we conducted a multicenter study including phase I dose escalation and tumor-specific cohorts. The primary objective was to evaluate safety and tolerability of abemaciclib when administered orally on a continuous schedule to patients with advanced cancer. Secondary objectives were to determine pharmacokinetics, evaluate biomarkers, document antitumor activity, and establish a recommended dose range for patients with cancer.
RESULTS

Enrollment

A total of 225 patients with advanced cancer were enrolled between December 28, 2009, and April 28, 2014. Thirty-three patients were enrolled in dose escalation (Supplementary Table S1) and 192 patients in tumor-specific cohorts for breast cancer (n = 47, single-agent therapy with abemaciclib), NSCLC (n = 68), glioblastoma (n = 17), melanoma (n = 26), colorectal cancer (n = 15), and hormone receptor (HR)-positive breast cancer (n = 19, combination therapy with abemaciclib + fulvestrant). Baseline patient and disease characteristics are summarized by cohort and in aggregate for the tumor-specific cohorts in Supplementary Table S2. Notably, most patients had ≥2 metastatic sites and had received multiple prior systemic therapies for advanced cancer.

Dose Escalation

During dose escalation, both once-daily (n = 13) and twice-daily (n = 20) schedules were investigated. On the once-daily (Q24H) schedule, sequential cohorts of patients received abemaciclib at dose levels of 50 mg (n = 4), 100 mg (n = 3), 150 mg (n = 3), or 225 mg (n = 3). Dose-limiting toxicity (DLT) was not observed, and the maximum tolerated dose (MTD) was not reached. On the twice-daily (Q12H) schedule, sequential cohorts of patients received abemaciclib at dose levels of 75 mg (n = 3), 100 mg (n = 4), 150 mg (n = 3), 200 mg (n = 7), and 275 mg (n = 3). Febrile neutropenia was not observed on either schedule. At 200 mg Q12H, 1 of the 7 patients experienced DLT of grade 3 fatigue. At 275 mg Q12H, 2 of the 3 patients experienced DLT of grade 3 fatigue. Therefore, the MTD for the twice-daily schedule was established at 200 mg Q12H. Both the MTD and 150 mg Q12H were further investigated in the tumor-specific cohorts.

Table 1. Possibly related treatment-emergent adverse events (>10% all grades) for tumor-specific cohorts

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All grades (n = 173)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>75 (43%)</td>
<td>25 (15%)</td>
<td>9 (5%)</td>
<td>0</td>
<td>109 (63%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>59 (34%)</td>
<td>15 (9%)</td>
<td>4 (2%)</td>
<td>0</td>
<td>78 (45%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (22%)</td>
<td>27 (16%)</td>
<td>5 (3%)</td>
<td>0</td>
<td>70 (41%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31 (18%)</td>
<td>10 (6%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>43 (25%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9 (5%)</td>
<td>17 (10%)</td>
<td>17 (10%)</td>
<td>0</td>
<td>43 (25%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (12%)</td>
<td>7 (4%)</td>
<td>12 (7%)</td>
<td>0</td>
<td>40 (23%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (4%)</td>
<td>15 (9%)</td>
<td>16 (9%)</td>
<td>2 (1%)</td>
<td>39 (23%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (8%)</td>
<td>14 (8%)</td>
<td>7 (4%)</td>
<td>0</td>
<td>34 (20%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22 (13%)</td>
<td>8 (5%)</td>
<td>0</td>
<td>0</td>
<td>30 (17%)</td>
</tr>
<tr>
<td>Increased creatinine‡</td>
<td>12 (7%)</td>
<td>7 (4%)</td>
<td>0</td>
<td>0</td>
<td>19 (11%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>14 (8%)</td>
<td>4 (2%)</td>
<td>0</td>
<td>0</td>
<td>18 (10%)</td>
</tr>
</tbody>
</table>

NOTE: Data are represented as n (%).

*No grade 4 events were reported.

‡Includes all tumor-specific cohorts receiving single-agent abemaciclib for NSCLC, glioblastoma, breast cancer, melanoma, or colorectal cancer.

Safety

In the single-agent tumor-specific cohorts (n = 173), the most common (>10%) treatment-emergent adverse events (TEAE) possibly related to abemaciclib involved fatigue and the gastrointestinal (diarrhea, nausea, vomiting, anorexia, and weight loss), renal (increased creatinine), or hematopoietic (leukopenia, neutropenia, thrombocytopenia, and anemia) systems (Table 1). These events occurred early, within 1 to 2 weeks of initiating treatment, and were reversible. There were no study-related deaths and only 2 grade 4 events (both neutropenia). Among the 173 patients, febrile neutropenia was observed in 1 patient with breast cancer who received abemaciclib at a dose of 150 mg Q12H. In the tumor-specific cohorts, grade 3 events involving the gastrointestinal and hematopoietic systems occurred in ≤5% and ≤10% of patients, respectively; grade 3 events involving the renal system were not observed, with grade 1 and 2 events occurring in 7% and 4% of patients, respectively. Due to the incidence of grade 1 and 2 diarrhea at 200 mg Q12H, the alternate starting dose of 150 mg Q12H was also explored. Among the 173 patients, dose reductions were required for 17 of 81 patients (21%) receiving a dose of 150 mg Q12H and 40 of 92 patients (43%) receiving a dose of 200 mg Q12H.

For patients with HR-positive breast cancer receiving combination therapy with abemaciclib plus fulvestrant (n = 19), the most common possibly related TEAEs were similar to those observed in the single-agent cohorts (Supplementary Table S3). There were no study-related deaths and no grade 4 events. Although grade 1 or 2 diarrhea was common and grade 3 diarrhea occurred in 1 patient (5%), no patients discontinued due to diarrhea. Grade 3 neutropenia occurred in 6 patients (32%); however, febrile neutropenia was not
Abemaciclib in Breast Cancer, Lung Cancer, and Other Tumors

and at steady state after multiple doses between 50 and 225 mg Q24H or 75 and 200 mg Q12H (Fig. 1B). Relevant pharmacokinetic parameters are summarized in Supplementary Tables S4 and S5. The time course was characterized by a slow absorption phase with a median time from oral dose to maximum plasma concentration (t<sub>max</sub>) ranging from 4 to 6 hours. Abemaciclib was extensively cleared and distributed. The mean terminal elimination half-life (t<sub>1/2</sub>) ranged from 17.4 to 38.1 hours with no apparent dose-dependent change in clearance. After multiple doses, the mean area under the plasma concentration–time curve over 24 hours at steady state (AUC<sub>24,ss</sub>) reached 4,280 and 5,520 ng-h/mL for 150 mg and 200 mg Q12H, respectively. The mean maximum plasma concentration at steady state (C<sub>max</sub>) reached 249 ng/mL and 298 ng/mL for 150 mg and 200 mg Q12H, respectively.

Both cerebrospinal fluid and unbound plasma concentrations of abemaciclib were obtained on day 15 for 10 patients (Fig. 1C). Cerebrospinal fluid samples were collected for logistical reasons at variable time points (2–8 hours postdose), whereas plasma samples were obtained at a time point (4 hours postdose) approximating mean maximum plasma concentration (C<sub>max</sub>). Notably, abemaciclib concentrations in the cerebrospinal fluid (range, 2.2–14.7 nmol/L) exceeded the dissociation constant (K<sub>i</sub> = 0.6 nmol/L) for the CDK4/cyclin D1 complex and approached unbound plasma concentrations for all these patients.

Pharmacodynamics

In both the dose-escalation and tumor-specific cohorts, phosphorylated RB (pRB) and topoisomerase II alpha (TopoIIα, specific for S phase) were evaluated in epidermal keratinocytes (a proliferative cell population) as integrated pharmacodynamic biomarkers to monitor CDK4/6 inhibition and cell-cycle progression, respectively. Evidence of target engagement, as exemplified by reduced pRB, was observed postdose at steady state on both schedules; however, Q12H dosing was selected for the tumor-specific cohorts to achieve more sustained pharmacodynamic inhibition over the dosing interval. At doses of both 150 mg and 200 mg Q12H, pRB (Fig. 2A; P < 0.0001) and TopoIIα expression (Fig. 2B; P < 0.0001) was reduced following treatment with abemaciclib. At steady state, reductions in these parameters were comparable whether assessed predose or postdose, indicating sustained CDK inhibition over the dosing interval. The magnitude of pharmacodynamic effect was comparable for 150 mg and 200 mg Q12H across both biomarkers, thereby identifying an oral dose range associated with consistent in vivo target inhibition. Importantly, similar pharmacodynamic effects were also observed for pRB (Fig. 2C) and TopoIIα (Fig. 2D) in fresh tumor biopsies collected whenever clinically feasible from patients receiving oral abemaciclib.

To test the hypothesis that a threshold pharmacodynamic effect predicts for disease control, we analyzed maximal percent change in tumor size as a function of percent change in pRB in skin for patients with HR-positive breast cancer in the single-agent cohort (Fig. 2E). This analysis revealed that a decrease in pRB ≥60% separated most patients with stable disease or response from those with progressive disease (P < 0.0001) and defined a threshold pharmacodynamic effect that in the absence of biological modifiers involved in

---

**Figure 1.** Concentrations of abemaciclib in plasma and cerebrospinal fluid (CSF). Geometric mean time course of abemaciclib plasma concentration (A) after single oral dose of abemaciclib ranging from 50 to 275 mg and (B) at steady state on once-daily (Q24H) and twice-daily (Q12H) schedules. Observations below the limit of quantitation of the assay were excluded from the analysis. (C) Paired plasma and cerebrospinal fluid concentrations of abemaciclib at steady state.

---

observed. In combination with fulvestrant, the MTD for abemaciclib was also 200 mg Q12H.

Overall, febrile neutropenia was rare and occurred in only 1 of the 225 patients (0.4%) treated in this study.

**Pharmacokinetics**

Abemaciclib plasma concentrations increased with dose following a single dose between 50 and 275 mg (Fig. 1A)
Figure 2. Pharmacodynamic inhibition of phosphorylated retinoblastoma protein (pRB) and topoisomerase II α (TopoIIα) in skin and tumor biopsies. Serial skin biopsies were collected at baseline, predose at steady state, and postdose at steady state for patients who received abemaciclib at 150 mg or 200 mg Q12H. Expression of pRB (A) and TopoIIα (B) decreased postdose and remained suppressed predose, indicating sustained pharmacodynamic effect over the 12-hour dosing interval. The magnitude of pharmacodynamic inhibition was similar for the 150-mg and 200-mg dose groups. Serial tumor biopsies were collected pretreatment and posttreatment to evaluate intratumoral expression of pRB and TopoIIα for a patient with breast cancer who received abemaciclib (150 mg Q12H) for 16 cycles without radiographic progression (C and D, respectively). Pharmacodynamic effect was observed for both biomarkers and this patient achieved a partial response. E, analysis of maximal percent change in tumor size as a function of percentage change in pRB in skin for patients with HR-positive breast cancer receiving abemaciclib in the single-agent cohort. A decrease in pRB levels ≥60% compared with baseline (indicated by vertical dotted line) separated most patients with stable disease or response from those with progressive disease. n, number of patients with evaluable sample for marker of interest; PD, progressive disease; PR, partial response; Pre, predose; Post, postdose; Q12H, every 12 hours (twice daily); Q24H, every 24 hours (once daily); SD, stable disease.
resistance may be associated with optimal clinical activity. Within this cohort, 1 patient with an increase in pRB achieved a partial response and 1 patient with a decrease in pRB ≥60% experienced progressive disease as best response; this latter patient had an HR-positive, HER2-negative breast carcinoma characterized by CCND1 amplification, CDKN2A mutation, and TP53 mutation.

Breast Cancer

Because CDK4 activity is particularly important to the proliferation of luminal HR-positive tumors (25, 26), we tested the activity of abemaciclib in relevant HR-positive breast cancer models. In a representative estrogen receptor (ER)-positive and HER2-negative human breast cancer xenograft (T47D), abemaciclib demonstrates antitumor activity as a monotherapy (Fig. 3A). Consistent with these preclinical results, radiographic responses were observed among patients with previously treated HR-positive breast cancer receiving abemaciclib as a single agent. Importantly, these responses were not limited to patients with HER2-negative disease and also included those with HR-positive, HER2-positive breast cancer (Fig. 3B).

Figure 3. Breast cancer. A, antitumor activity of abemaciclib in a human xenograft model (T47D) of ER-positive, HER2-negative breast cancer. Athymic nude mice implanted with human xenograft tumors (T47D) were treated orally once daily for 21 days with vehicle (1% hydroxyethyl cellulose [HEC] shown in black), or abemaciclib mesylate (75 mg/kg/d; shown in blue). The horizontal red bar below the x-axis indicates the treatment period. B, patient with HR-positive, HER2-positive breast cancer and extensive hepatic metastases who received oral abemaciclib (200 mg every 12 hours). She had recurrence after adjuvant chemotherapy plus endocrine therapy and had received treatment for metastatic disease with vinorelbine, trastuzumab, gemcitabine, lapatinib plus capcitabine, liposomal doxorubicin, and eribulin. C, waterfall plot of maximal percentage change in tumor size for the cohort of patients receiving abemaciclib for advanced breast cancer. Patients with at least 1 posttreatment radiographic assessment were included. Positive values indicate tumor growth, and negative values indicate tumor reduction. The upper and lower dashed lines depict thresholds defined in RECIST v1.1 for progressive disease and partial response, respectively. Genetic features (as determined by next-generation sequencing) and clinical markers (as reported by investigators) for each patient are summarized in the accompanying heat map. PR, progesterone receptor; NA, not available. D, duration of therapy with abemaciclib for patients with breast cancer. E, mapping of mutations in the tumor suppressor protein p53 identified among the patients with breast cancer. All mutations mapped to the DNA-binding domain of p53 (protein domain map modified from ref. 47). Mutations identified in this study are indicated below the protein domain map and included R273 mutations (location indicated in orange above the protein domain map), which alter contact of p53 with DNA DBD, DNA-binding domain; PR, proline-rich domain; Reg, carboxy-terminal regulatory domain; TA, transactivation domain; TET, tetramerization domain.
To extend these findings, we characterized the clinical activity of abemaciclib in a cohort of 47 patients with advanced breast cancer who had received a median of 7 (range, 2–16) prior systemic therapies. Ten of the 47 patients who had progression on prior endocrine therapy continued endocrine therapy with the addition of abemaciclib. The disease control rate [complete response (CR) + partial response (PR) + stable disease (SD)] was higher for HR-positive tumors (29 of 36 patients, 81%) versus HR-negative tumors (3 of 9 patients, 33%), and radiographic responses occurred exclusively in the HR-positive population (Table 2). Among the 36 patients with HR-positive breast cancer, 11 (31%) achieved partial response (4 of whom had continued prior endocrine therapy) and 18 (50%) achieved stable disease, including 11 (31%) with stable disease for ≥24 weeks; thus, the clinical benefit rate (CR + PR + SD for ≥24 weeks) was 61%. Of the 11 responses in the HR-positive population, 7 were observed among 25 patients (28%) with HER2-negative disease and 4 occurred among 11 patients (36%) with HER2-positive disease. For the overall HR-positive population, median duration of response was 13.4 months (95% CI, 3.7–13.4) and median progression-free survival (PFS) was 8.8 months (95% CI, 4.2–16.0). Change in tumor size at best response, along with genetic features and clinical markers, is depicted graphically for the single-agent breast cancer cohort (Fig. 3C) and highlights the activity of abemaciclib in HR-positive breast cancer. Duration of therapy is also summarized for these patients (Fig. 3D) and is notable for the durability of disease control in the absence of radiographic progression. Nonresponding breast tumors were more likely to harbor TP53 mutations, with all mutations observed occurring in the region encoding the p53 DNA-binding domain (Fig. 3E). Importantly, abemaciclib demonstrated clinical activity in HR-positive breast cancers with or without PIK3CA mutations.

To evaluate the potential for combining abemaciclib with endocrine agents for the treatment of HR-positive breast cancer, we investigated combination therapy with abemaciclib plus fulvestrant, an antiestrogen that induces selective degradation of the estrogen receptor. The 19 patients in the combination cohort for HR-positive breast cancer had received a median of 4 (range, 1–11) prior systemic therapies, and all patients had received prior endocrine therapy. Both abemaciclib (200 mg Q12H) and fulvestrant (500 mg once monthly) were given at MTD. Partial responses were observed in 4 patients, resulting in a response rate of 21% (4 of 19 patients) for all patients (measurable or nonmeasurable disease) and a response rate of 36% (4 of 11 patients) for those patients with measurable disease. Although the disease control rate (15 of 19 patients, 79%) and clinical benefit rate (12 of

Table 2. Efficacy for single-agent breast cancer cohort, overall and by HR and HER2 status

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Breast cancer overall (N = 47)</th>
<th>HR-positive (N = 36)</th>
<th>HR-negative (N = 9)</th>
<th>HR-positive, HER2-positive (N = 11)</th>
<th>HR-positive, HER2-negative (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (23%)</td>
<td>11 (31%)</td>
<td>0 (0%)</td>
<td>4 (36%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>SD</td>
<td>22 (47%)</td>
<td>18 (50%)</td>
<td>3 (33%)</td>
<td>8 (72%)</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>≥24 weeks</td>
<td>5 (14%)</td>
<td>7 (19%)</td>
<td>2 (22%)</td>
<td>2 (18%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>&lt;24 weeks</td>
<td>10 (21%)</td>
<td>11 (31%)</td>
<td>1 (11%)</td>
<td>5 (45%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (23%)</td>
<td>5 (14%)</td>
<td>6 (67%)</td>
<td>0</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (6%)</td>
<td>2 (6%)</td>
<td>0</td>
<td>0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR (95% CI)</td>
<td>23% (12.3–38.0)</td>
<td>31% (16.3–48.1)</td>
<td>0% (0–33.6)</td>
<td>36% (10.9–69.2)</td>
<td>28% (12.1–49.4)</td>
</tr>
<tr>
<td><strong>Clinical benefit rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR + SD (≥24 weeks) (95% CI)</td>
<td>49% (34.1–63.9)</td>
<td>61.1% (43.5–76.9)</td>
<td>11.1% (0.3–48.2)</td>
<td>54.5% (23.4–83.3)</td>
<td>64% (42.5–82.0)</td>
</tr>
<tr>
<td><strong>Disease control rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR + SD (95% CI)</td>
<td>70% (55.1–82.7)</td>
<td>81% (64.0–91.8)</td>
<td>33% (7.5–70.1)</td>
<td>100% (71.5–100.0)</td>
<td>72% (50.6–87.9)</td>
</tr>
<tr>
<td><strong>Median duration of response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(months)</td>
<td>13.4 (9.0–13.4)</td>
<td>13.4 (3.7–13.4)</td>
<td>NA</td>
<td>4.6, 10.0, 9.2, 5.3 (4 patients)</td>
<td>13.4 (3.7–13.4)</td>
</tr>
<tr>
<td><strong>Median PFS (95% CI), months</strong></td>
<td>5.8 (2.9–10.9)</td>
<td>8.8 (4.2–16.0)</td>
<td>1.1 (0.6–4.0)</td>
<td>7.2 (2.8–12.0)</td>
<td>8.8 (2.9–18.0)</td>
</tr>
</tbody>
</table>

NOTE: Data are represented as n (%), unless otherwise specified. Abbreviations: CI, confidence interval; NA, not available.

*Two patients had unknown HR status.

**All 11 patients with breast cancer who had a partial response were HR-positive.

*Median duration of response is reported if ≥5 patients had a response in each category. If <5 patients had a response, individual values are presented.

*Duration of response was not available for patients with HR-negative breast cancer as none of these patients had a partial response.
19 patients, 63%) were comparable to those among HR-positive patients in the single-agent cohort, several important factors (such as differences in eligibility criteria, nonrandomized design, and sample sizes for these cohorts) limit the ability to compare efficacy for abemaciclib plus fulvestrant versus abemaciclib alone.

**NSCLC**

In a genetically engineered mouse model of KRAS-mutant NSCLC, genetic ablation of CDK4 induces senescence and prevents tumor progression (14). In complementary pharmacologic experiments, we tested whether abemaciclib preferentially inhibits growth of KRAS-mutant versus wild-type NSCLC xenografts. Among 6 human xenograft models of NSCLC, tumors with KRAS mutation were more sensitive to abemaciclib than KRAS wild-type tumors (Fig. 4A). Consistent with these preclinical results, evidence of single-agent antitumor activity was observed among patients with previously treated KRAS-mutant NSCLC (Fig. 4B).

To extend these findings, we evaluated the clinical activity of abemaciclib in a cohort of 68 patients with NSCLC who had received a median of 4 (range, 1–10) prior systemic

---

**Figure 4.** NSCLC. A, antitumor activity of abemaciclib in 4 KRAS-mutant (NCI-H358, NCI-H2122, NCI-H441, NCI-H460) and 2 KRAS wild-type (WT, NCI-H1650, NCI-H1975) human xenograft models of NSCLC. Athymic nude mice implanted with human NSCLC xenograft tumors were treated orally once daily for 21 days with vehicle (1% HEC) or abemaciclib mesylate (25, 50, or 100 mg/kg/d). Tumor growth inhibition compared with the vehicle control group was determined after 21 days of oral dosing with abemaciclib mesylate. B, patient with KRAS-mutant NSCLC and symptomatic left upper lobe primary tumor who received abemaciclib (200 mg orally Q12H). He had previously received first-line treatment with paclitaxel plus carboplatin and second-line treatment with pemetrexed. C, waterfall plot of maximal percentage change in tumor size for the cohort of patients receiving abemaciclib for advanced NSCLC. Patients with at least 1 posttreatment radiographic assessment were included. Positive values indicate tumor growth and negative values indicate tumor reduction. The upper and lower dashed lines depict thresholds defined in RECIST v1.1 for progressive disease and partial response, respectively. Genetic features (as determined by next-generation sequencing) for each patient are summarized in the accompanying heat map. NA, not available. D, duration of therapy with abemaciclib for patients with NSCLC.
theties, including 29 patients who had tumors harboring KRAS mutations. For the overall population (68 patients), the disease control rate (CR + PR + SD) was 49% (33 of 68 patients). Thirty-one of 68 patients (46%) achieved stable disease, including 15 patients (22%) with stable disease lasting for ≥24 weeks. The 6-month PFS rate was 26% (95% CI, 16%–38%), with 4 patients receiving single-agent abemaciclib without progression for ≥12 months (Supplementary Table S6). Partial response was achieved for 1 patient with KRAS-mutant NSCLC and for 1 patient with KRAS wild-type squamous NSCLC bearing copy-number loss of CDKN2A.

KRAS mutations most often involved codon 12 or 13, but tumors with less-frequent mutations (Q61H, A146V) were also detected and associated with decreases in tumor size for 16%–38%, with 4 patients receiving single-agent abemaciclib without progression for ≥12 months (Supplementary Table S6). The clinical activity of abemaciclib was also investigated in patients receiving the drug. Previous reports have identified KRAS mutations most likely to respond, and early initiation of confirma
tory phase III studies. We therefore tested whether abemaciclib could prolong survival in a human xenograft model (SKOV3-Luciferase) that recapitulates the characteristic intraperitoneal dissemination of ovarian cancer in patients (Fig. 5A). In this orthotopic model, oral abemaciclib induced a dose-dependent prolongation of survival with no deaths at the highest dose level. Consistent with these preclinical results, we observed 2 patients with ovarian cancer who achieved stable disease based on RECIST version 1.1 for 4 and 6 cycles (abemaciclib 225 mg Q24H and 200 mg Q12H, respectively) and one patient with ovarian cancer who achieved a rapid and durable CA-125 response based on criteria of the Gynecological Cancer Intergroup (30) and received single-agent therapy (abemaciclib 150 mg Q24H) for 24 cycles without radiographic progression (Fig. 5B).

The clinical activity of abemaciclib was also investigated in tumor-specific cohorts for cancers characterized by relevant pathway alterations, including glioblastoma, colorectal cancer, and melanoma (Fig. 5C and Supplementary Table S7; refs. 31-33). Consistent with detection of abemaciclib in cerebrospinal fluid from patients at concentrations associated with target inhibition (CDK4/cyclin D1 Ki = 0.6 nmol/L), 3 patients with glioblastoma achieved stable disease, and 2 of these patients have continued to receive ongoing treatment without progression for 19 and 23 cycles, respectively. Both glioblastomas with durable disease control on single-agent abemaciclib had TP53 mutations, and one also had a frameshift mutation in the gene encoding the epidermal growth factor receptor (EGFR). These results are compatible with distribution of abemaciclib to the central nervous system. In the colorectal cancer cohort, 2 patients achieved stable disease, including 1 patient with a tumor that harbored both KRAS and TP53 mutations. In the melanoma cohort, 1 patient achieved RECIST partial response and 6 patients achieved stable disease, for a disease control rate of 27% (7 of 26 patients). Among the 16 patients with melanoma and available next-generation sequencing results, tumors harboring BRAFV600E/K mutations were relatively uncommon (2 patients) with corresponding enrichment for NRAS mutations (6 patients). Notably, the patient with metastatic melanoma who achieved a partial response had a tumor with molecular alterations (NRAS mutation and copy-number loss at the INK4 locus) that induced aberrant kinase activity of CDK4 and CDK6.

**DISCUSSION**

This report encompasses the first-in-human experience with abemaciclib, a dual inhibitor of CDK4 and CDK6 with greater selectivity for CDK4. Clinical development of this drug has utilized systematic integration of pharmacokinetic parameters with pharmacodynamic biomarkers across preclinical (22) and clinical studies in order to optimize dose, schedule, and antitumor efficacy. The combination of traditional phase I and II design elements, as well as the incorporation of biomarkers and genomic profiling, has allowed refinement of dosing to achieve sustained target inhibition, detection of efficacy signals in multiple tumor types, generation of hypotheses for tailoring abemaciclib therapy to patient populations most likely to respond, and early initiation of confirmatory phase III studies.

We have established that abemaciclib can be dosed safely on a continuous schedule. Among treatment-emergent adverse events, fatigue was dose limiting, but gastrointestinal, renal, and hematopoietic effects were also observed. Diarrhea was manageable with anti-diarrheal agents or dose reduction and did not result in patient discontinuation. Because abemaciclib inhibits renal efflux transporters [multidrug and toxin extrusion (MATE) 1 and 2-K] that mediate active secretion of creatinine from the proximal tubule, increases in serum creatinine during therapy with abemaciclib may not accurately reflect renal function, and measures of glomerular filtration rate that are independent of active tubular secretion via renal efflux transporters (such as cystatin C) may yield a more accurate estimate of renal function than serum creatinine for patients receiving the drug. Previous reports have identified neutropenia as an adverse event associated with dual inhibition of CDK4 and CDK6 (34–39). However, abemaciclib given...
Figure 5. Other tumors. A, abemaciclib prolongs overall survival in an intraperitoneal model of ovarian cancer. Athymic nude mice implanted with human ovarian xenograft tumors (SKOV3-Luciferase) were treated once daily (beginning on day 10 after implantation) for 21 days with vehicle (1% HEC) or abemaciclib mesylate (25, 50, or 100 mg/kg/d). Mean survival ± SEM (in days) following the 21-day dosing interval was 36.2 ± 2.0 (vehicle control), 39.5 ± 1.5 (25 mg/kg/d), 39.8 ± 1.3 (50 mg/kg/d), and >45 (100 mg/kg/d), respectively. No deaths were observed in the group treated with abemaciclib mesylate at 100 mg/kg. Survival was significantly different from the vehicle control group compared with the groups treated with abemaciclib mesylate at 50 mg/kg/d (P = 0.0462) and 100 mg/kg/d (P < 0.0001). B, abemaciclib (150 mg once daily) induced durable CA-125 response for a patient with advanced ovarian cancer. She had recurrence after first-line treatment with paclitaxel plus carboplatin, and had received second-line treatment with paclitaxel plus carboplatin, and third-line treatment with topotecan. C, waterfall plot of maximal percent change in tumor size for the cohorts of patients receiving abemaciclib for advanced colorectal cancer, glioblastoma, or melanoma. Patients with at least 1 posttreatment radiographic assessment were included. Positive values indicate tumor growth, and negative values indicate tumor reduction. The upper and lower dashed lines depict thresholds defined in RECIST v1.1 for progressive disease and partial response, respectively. Genetic features (as determined by next-generation sequencing) are summarized in the accompanying heat map. CRC, colorectal cancer; GBM, glioblastoma; MEL, melanoma; NA, not available.
previous findings in mouse xenograft models (22), a decrease in pRB 260% identified a group of patients with HR-positive breast cancer who were likely to achieve stable disease or response. Although pharmacodynamic effects were observed at both dose levels, fewer dose reductions were required among those patients who initiated treatment at 150 mg Q12H. However, the broad dose range associated with clinical efficacy and the presence of interpatient pharmacokinetic variability support the concept that some patients may derive optimal antitumor efficacy from dosing at 200 mg Q12H. Therefore, the recommended starting dose for abemaciclib as a single agent is 200 mg Q12H, with supportive measures or dose reduction if necessary to achieve acceptable tolerability for an individual patient. In certain clinical contexts, however, it may be reasonable to initiate therapy with abemaciclib at 150 mg Q12H to limit toxicity and to consider dose escalation to 200 mg Q12H for an individual patient with acceptable tolerability but suboptimal response. Abemaciclib was also detectable in the cerebrospinal fluid of patients at concentrations approximating those of unbound drug in plasma, and 2 patients with glioblastoma have achieved prolonged PFS. Accordingly, abemaciclib is being investigated in a clinical trial for patients with brain metastases (NCT02308020).

KRAS mutations are found in approximately 30% of lung adenocarcinomas and confer an adverse prognosis compared with KRAS wild-type tumors (40). Among the heavily pretreated patients in the NSCLC cohort, responses were uncommon, but the disease control rate was greater in the KRAS-mutant population compared with the KRAS wild-type population, due in large part to more than a doubling of the number (and also the percentage) of patients with stable disease lasting ≥24 weeks. Moreover, the majority of tumor regressions in the group with stable disease also occurred in KRAS-mutant patients. Although outcomes from ongoing clinical trials will be required to confirm whether the presence of KRAS mutation identifies a population with NSCLC sensitive to abemaciclib, the results from the current study are consistent with the greater sensitivity of KRAS-mutant versus KRAS wild-type NSCLC xenografts, as well as the synthetic lethal interaction observed with genetic inactivation of CDK4 in KRAS-driven mouse models of lung adenocarcinoma (14). The activity observed in the KRAS/LKB1 (XL) subset is particularly noteworthy, as this group has recently been associated with aggressive phenotype (41) and was poorly responsive to other therapeutic approaches in preclinical models, including taxane-based chemotherapy and MEK inhibition (42). Collectively, these findings support the investigation of abemaciclib for patients with KRAS-mutant NSCLC in an ongoing phase III trial (NCT02152631).

Similar to NSCLC, colorectal cancer frequently harbors KRAS mutation. Although stable disease was achieved for some patients with colorectal cancer, durability was relatively short, and progressive disease was typical for most patients. In this regard, it is important to emphasize that synthetic lethality between KRAS mutation and CDK4 inhibition may depend upon tumor type and molecular context (14).

For melanoma, abemaciclib as a single agent achieved a disease control rate of 27% and induced a partial response for 1 patient with metastatic melanoma harboring both NRAS mutation and copy-number loss at the INK4 locus. However, the relatively low representation of BRAF-mutant disease in the current study may have limited the opportunity to observe maximal clinical activity, as preclinical studies with abemaciclib in models of human melanoma indicate that the drug may have particular clinical application in reversing resistance to selective BRAF inhibitors in melanomas characterized by BRAFV600E/K mutations (23).

Preclinical studies in breast cancer models utilizing genetic or pharmacologic ablation of CDK4 activity have predicted the efficacy of CDK4 inhibitors in both HR-positive and HER2-positive disease (11, 26). Clinical investigation with palbociclib as a single agent in patients with HR-positive breast cancer showed an overall response rate (ORR) of 6% (2 of 33 patients), a clinical benefit rate (CBR) of 21% (7 of 33 patients), and a median PFS of 4.5 months (43). Among patients with HR-positive disease enrolled in the breast cancer cohort of the current clinical trial (Fig. 3C and D), abemaciclib therapy demonstrated an ORR of 31% (11 of 36 patients), a CBR of 61% (22 of 36 patients), and a median PFS of 8.8 months. Based on these results, abemaciclib is currently under active clinical investigation for patients with HR-positive advanced breast cancer in a phase II study as a single agent (NCT02102490) and in two phase III studies in combination with either fulvestrant (NCT02107703) or aromatase inhibitors (NCT02246621).

TP53 mutations localized to the region encoding the DNA-binding domain of p53 and were enriched among breast cancers with increase in tumor size at best response. Although it is not yet known whether these mutations confer intrinsic resistance in breast cancer, it is intriguing that p53 plays a role in triggering senescence, which may represent an important mechanism for the antitumor effects of agents that inhibit CDK4 or CDK6 (44).

Although partial responses were observed for HER2-positive or PIK3CA-mutated breast cancers in the context of HR-positive disease, further work will be required to define the role for abemaciclib in tumors with these molecular features. To investigate potential therapeutic opportunities, abemaciclib is being studied for patients with breast cancer in combination with both endocrine therapies and agents targeting the HER2 or PI3K-AKT-mTOR pathways (23).

In summary, the results of this clinical trial demonstrate the safety and antitumor activity of abemaciclib as a single agent and support its further development both as monotherapy and in rational combinations. Furthermore, these findings validate CDK4 and CDK6 as antitumor drug targets and translate preclinical predictions regarding therapeutic targeting of cell-cycle derangements in cancer into clinical efficacy.

METHODS

Preclinical Studies

All cell lines were authenticated by genetic testing (IDEXX Bioresearch) and were obtained from the centralized cell bank maintained by Eli Lilly and Company. For human xenograft studies, athymic nude mice were implanted with human tumor cells either subcutaneously or directly into the peritoneal cavity. After tumors were established in vivo, cohorts of mice were treated orally with either vehicle or abemaciclib mesylate (range, 25–100 mg/kg/d) for a period of approximately 21 days. Tumor measurements were performed quantitatively by physical measurement (subcutaneous models) or noninvasive imaging (intraperitoneal model) at regular intervals. All animal studies were...
Abemaciclib in Breast Cancer, Lung Cancer, and Other Tumors

performed in accordance with American Association for Laboratory Animal Care institutional guidelines, and all protocols were approved by the Eli Lilly and Company Animal Care and Use Committee.

Study Design
Dose escalation was performed using a 3+3 design. Two continuous administration schedules were studied: 50, 100, 150, or 225 mg orally every 24 hours (Q24H) and 75, 100, 150, 200, or 275 mg orally every 12 hours (Q12H). After determination of the single-agent MTD, abemaciclib (150 mg Q12H or 200 mg Q12H) was assessed in tumor-specific cohorts for breast cancer, NSCLC, glioblastoma, melanoma, and colorectal cancer. An additional cohort for HR-positive breast cancer evaluated combination safety for abemaciclib plus fulvestrant. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation. The protocol was approved by all institutional review boards, and written informed consent was collected from all patients before conducting study procedures. This study is registered with ClinicalTrials.gov (NCT01394016).

Patients
Eligible patients were 18 years or older with advanced cancer, no longer receiving benefit from available standard therapies, with adequate organ function and Eastern Cooperative Oncology Group performance status of 1 (dose escalation) or 2 (tumor-specific cohorts). Measurable disease was required in the single-agent tumor-specific cohorts and was defined by RECIST version 1.1 (45). Prior cancer treatments must have been discontinued 14 or 21 days for nonmyelosuppressive and myelosuppressive therapies, respectively; however, patients in the single-agent breast cancer cohort who had progressed on endocrine therapy were permitted to continue that specific therapy. Patients with disease in the central nervous system were excluded from dose escalation but permitted in tumor-specific cohorts if there was radiographic and clinical stability for at least 14 days.

Procedures
During dose escalation, cohorts of 3 patients were sequentially enrolled at successive dose levels. A single dose of abemaciclib was administered on day –3 for determination of single-dose pharmacokinetics, with continuous dosing beginning on day 1. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE; Version 4.0). Dose escalation was guided by safety during cycle 1 and informed by pharmacokinetic data. DLT was defined as the following possibly drug-related events occurring during cycle 1: grade 3 or 4 nonhematologic toxicity (except for nausea, vomiting, diarrhea, or electrolyte disturbance, which were considered dose limiting only if they persisted >2 days despite maximal supportive intervention); grade 4 hematologic toxicity that persisted >5 days; grade 3 or 4 thrombocytopenia with bleeding; and grade 3 or 4 neutropenia with fever. Dose adjustments were required for patients with possibly related grade 3 nonhematologic toxicity or grade 4 hematologic toxicity and were permitted for patients with omission of >25% of doses in a single cycle due to tolerability. MTD was defined as the highest dose level at which <33% of patients experienced DLT.

Tumor response was assessed every 2 cycles by investigators, and retrospectively by independent central review for patients with investigator-assessed stable disease or response, using either computed tomography (CT) or MRI scans in accordance with RECIST version 1.1 (45).

Pharmacokinetics
Pharmacokinetic sampling was performed from plasma and, in a subset of patients, from cerebrospinal fluid. Drug concentrations were assayed using a validated method for liquid chromatography with tandem mass spectrometry. For plasma, sampling was performed on day –3 (predose and 1, 2, 4, 6, 8, and 10 hours postdose), day –2 (24 hours postdose), day –1 (48 hours postdose), and day 1 (72 hours postdose), day 15 (predose and 1, 2, and 4 hours postdose), day 22 (predose), and day 28 (predose and 1, 2, 4, 6, 8, 10, and 24 hours postdose). For cerebrospinal fluid, sampling was performed at baseline (day 14 to day –3) and on day 15 (2–8 hours postdose).

Pharmacodynamic and Genomic Analyses
Skin biopsies were performed pretreatment and on day 15 (predose and 4 hours postdose) and analyzed for pRB (Ser780; BD Biosciences #558385) and TopoII (Epitomics #1826-1) by immunohistochemistry to quantitate expression by H-score (H-score = weighted sum of % 1+ cells, twice % 2+ cells, and three times % 3+ cells; range, 0–300). Paired tumor biopsies were obtained from selected patients before treatment (between days –14 and –4) and on treatment (between days 8 and 22) during cycle 1. Available archived tumors were subjected to next-generation sequencing using platforms compliant with Clinical Laboratory Improvement Amendments (CLIA).

Sample Size and Statistical Analysis
Although at least 15 patients were to be enrolled in each of the tumor-specific expansions, up to 45 to 60 patients could be enrolled in each tumor-specific expansion. The target sample size of up to 45 to 60 patients was based on differentiating 34.5% to 40% from 5% (uninteresting) ORR in tumors with (marker present) and without (marker absent) a relevant tumor biomarker, respectively (that is, ORRmarker present = 34.5%–40% and ORRmarker absent = 5%). Examples of relevant tumor biomarkers included KRAS status (mutant versus wild-type; NSCLC) and HR status (positive versus negative; breast cancer). Assuming an equal number of patients having tumors with and without the biomarker, 45 or 60 patients provided approximately 85% power to differentiate 40% or 34.5% from 5% ORR, respectively. To maximize the power to detect the ORR difference between the biomarker groups, enrollment to a tumor-specific expansion could be adjusted to achieve approximately an equal number of patients having tumors with and without the biomarker.

All patients who received at least 1 dose of abemaciclib were included in safety and efficacy analyses. Patient results were summarized by dose level (escalation) or tumor-specific cohort. Pharmacokinetic parameters were computed by standard noncompartmental methods. For analysis of pharmacodynamic response during drug treatment, a paired Wilcoxon test was used to compare the distributions of pRB or TopoII expression in skin at baseline versus during treatment (predose or postdose) on day 15. An unpaired Wilcoxon test was used to compare the distributions of maximal percent change in tumor size in subgroups of patients with HR-positive breast cancer with <60% versus 260% decrease in pRB expression in skin (predose) on day 15. Median duration of response and median PFS were estimated using the Kaplan–Meier method (46).

Disclosure of Potential Conflicts of Interest
L.S. Rosen reports receiving commercial research support from Eli Lilly and Company. A.W. Tolcher is a board member for Symphogen and a consultant/advisory board member for Arqule, Asten, Bayer Schering Pharma, Bind Therapeutics, Blend, Celator, Dicerca, Janssen, Merus, Nanobiotix, Pharmacycles, Pierre Fabre, Valentin, Heron, Johnson & Johnson, Asana, Akemia, Gemmah, AP Pharma, Mersana, Endoxygen, Proximagen, Upsher-Smith, Eli Lilly and Company, Idea Pharma, LiquidNet, MedImmune, and Symphogen. L. Gandhi reports receiving a commercial research grant from BMS, and is a consultant/research support from BMS, and is a consultant/
advisory board member for Genentech/Roche, AstraZeneca, AbbVie, Merck, and Pfizer. D. Rasco is a consultant/advisory board member for TaiRx. R. Beckmann has ownership interest (including patents) in Eli Lilly and Company. T.S. Nguyen has ownership interest (including patents) in Eli Lilly and Company. M. Frenzel has ownership interest (including patents) in Eli Lilly and Company. D.M. Cronier has ownership interest (including patents) in Eli Lilly and Company. E.M. Chan has ownership interest (including patents) in Eli Lilly and Company. G.I. Shapiro reports receiving a commercial research grant from Eli Lilly and Company and other commercial research support from Pfizer, and is a consultant/advisory board member for Eli Lilly and Company, G1 Therapeutics, Vertex Pharmaceuticals, and Syros Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Patnaik, A.W. Tolcher, L. Gandhi, A. Nasir, A.D. Fulford, L.Q. Li, M. Frenzel, D.M. Cronier, E.M. Chan, P.Y. Wen, G.I. Shapiro


Other (design of biomarker assay, training/supervision of CRO staff in analytical validation of the assays to evaluate modulation of PD biomarkers): A.D. Fulford

Acknowledgments

The authors thank the patients and families who participated in this study and the staff who cared for these patients at the investigative sites. Eli Lilly and Company funded the medical writing support provided by Stephanie Brillhart, who is an employee of inVent Health Clinical.

Grant Support

All funding was provided by Eli Lilly and Company.

Received January 20, 2016; revised April 22, 2016; accepted April 26, 2016; published OnlineFirst May 23, 2016.

REFERENCES


Downloaded from cancerdiscovery.aacrjournals.org on July 31, 2017. © 2016 American Association for Cancer Research.
Abemaciclib in Breast Cancer, Lung Cancer, and Other Tumors
