A First-in-Human Phase 1 Study of LY3023414, an Oral PI3K/mTOR Dual Inhibitor, in Patients with Advanced Cancer

Johanna C. Bendell1, Anna M. Varghese2, David M. Hyman2, Todd M. Bauer1, Shubham Pant3, Sophie Callies4, Ji Lin4, Ricardo Martinez4, Enaksha Wickremesinhe4, Aaron Fink4, Volker Wacheck4, and Kathleen N. Moore3

Abstract

Purpose: The PI3K/mTOR pathway is frequently aberrated in cancer. LY3023414 is a potent and selective ATP-competitive inhibitor of class I PI3K isoforms, mTOR, and DNA-PK. Here we report the dose-escalation results of the first-in-human phase I study of LY3023414.

Patients and Methods: A 3+3 dose escalation for once-daily and twice-daily oral dosing of LY3023414 was followed by an expansion cohort for CYP3A4 drug–drug interaction (DDI) assessment. The primary objective was to determine the recommended phase 2 dose (RP2D). Additional objectives included safety, pharmacokinetics/pharmacodynamics, and antitumor activity.

Results: Forty-seven patients with solid tumors received LY3023414 at once-daily (20–450 mg) or twice-daily dosing (150–250 mg). Dose-limiting toxicities were observed at 450 mg once-daily (thrombocytopenia, hypotension, hyperkalemia) in three of three patients, 250-mg twice-daily dosing (hypophosphatemia, fatigue, mucositis) in three of four patients, and in one of 15 patients at 200 mg twice-daily (nausea). Common related AEs included nausea (38%), fatigue (34%), and vomiting (32%) and were mostly mild or moderate. LY3023414 pharmacokinetics demonstrated dose-dependent increase in exposure with ≥90% target inhibition at doses ≥150 mg. DDI analysis demonstrated LY3023414 to be a weak inhibitor of CYP3A4. Durable partial response was observed in a patient with endometrial cancer harboring PIK3R1 and PTEN truncating mutations, and 13 additional patients (28%) had a decrease in their target lesions by up to 30%.

Conclusions: LY3023414 has a tolerable safety profile and single-agent activity in patients with advanced cancers. The RP2D of LY3023414 monotherapy is 200 mg twice daily based on safety, tolerability, and pharmacokinetic/pharmacodynamic data.

Introduction

The PI3K/AKT/mTOR pathway is a critical signaling cascade that plays a central role in physiologic processes regulating cellular growth, survival, and metabolism. In human tumors, it is reported to be one of the most frequent dysregulated pathways leading to activation of the pathway in >70% cases (1–3). Molecular aberrations leading to activation of PI3K/AKT/mTOR pathway can occur at multiple levels and include mutations of the catalytic subunit of PI3K (PIK3CA), PI3K amplification, loss of PTEN tumor suppressor protein, and kinases downstream of PI3K including AKT, TSC, and mTOR complex 1 and 2 (1, 4). Once activated, PI3K/AKT/mTOR signaling has been reported to lead to a more aggressive tumor phenotype with increased proliferation, angiogenesis, metastases formation, and drug resistance. Consequently, significant efforts have been dedicated to develop inhibitors targeting components of the PI3K/AKT/mTOR pathway (4, 5).

A challenge in targeting the PI3K/AKT/mTOR pathway is the complex feedback loops within the signaling cascade leading to activation of compensatory pathways or shift in isoform dependency upon inhibition of either mTOR or PI3K alone (1, 4, 6). Therefore, it has been suggested that dual inhibitors targeting PI3K/mTOR simultaneously might be a more efficient way to target this pathway and to circumvent these feedback loops (1, 6).

LY3023414 is a novel and selective inhibitor of class I PI3K isoforms, mTORC1/2 and DNA-PK, as demonstrated in biochemical testing against approximately 266 kinases, with high solubility across a wide pH range (7). LY3023414 shows dose-dependent inhibition of phosphorylation of PI3K/Akt/mTOR pathway downstream substrates for 4 to 6 hours in vivo, reflecting the drug’s half-life of 2 hours, and leads to potent antitumor activity in tumor xenograft models (7). An intermittent, “quick-on/quick-off” target engagement mechanism has been suggested to enhance clinical tolerability of PI3K/mTOR inhibitors as well as potentially reduce the emergence of compensatory resistance mechanisms (7, 8). The pharmacokinetic parameters of LY3023414 in rats and dogs suggest that the drug is extensively absorbed at relevant doses and subsequently cleared in part via oxidative metabolism by CYP enzymes (7). CYP3A4 and CYP1A2 are responsible for 82% and
The PI3K/mTOR signaling pathway is one of the most frequently activated pathways in solid and hematologic malignancies and therefore an attractive target for cancer drug development. This first-in-human dose phase I study of the novel and potent PI3K/mTOR dual kinase inhibitor LY3023414 demonstrates a favorable safety profile in patients with advanced solid tumors. In contrast to other PI3K/mTOR dual inhibitors, the high bioavailability and the half-life of 2 hours result in potent in vivo efficacy via intermittent target inhibition ("quick-on/quick-off" effect). Pharmacokinetic/pharmacodynamic analysis demonstrated strong but transient target engagement with ≥90% p4EBP1 inhibition at dose levels of ≥150 mg LY3023414. Patients treated at this biological efficacious dose range demonstrated clinical benefit including a durable partial response lasting >18 months in a patient with endometrial cancer harboring PIK3R1 and PTEN truncating mutations fostering PI3K/mTOR target engagement of LY3023414. These results support further investigation of LY3023414 in patients with advanced cancers.

18% of the CYP-mediated LY3023414 clearance, respectively. In addition, in vitro data suggest that LY3023414 may be a time-dependent inhibitor of CYP3A4 metabolism, which could lead to increased plasma concentration of CYP3A4 substrates (Eli Lilly and Company, data on file). The nonclinical toxicology profile of LY3023414 provided a favorable benefit–risk profile enabling clinical studies of LY3023414.

Herein, we report the results of the first in-human phase I dose escalation trial of LY3023414 in patients with advanced or metastatic cancer. The primary objective of the study was to identify a recommended phase 2 dose (RP2D) of LY3023414 that can be safely administered to patients with advanced and metastatic cancer.

\section*{Patients and Methods}

\subsection*{Study design}

This study was a multicenter, open-label, phase I, first-human-dose (FHHD) dose-escalation study of oral LY3023414 in patients with advanced cancer. The study consisted of a dose-escalation part for once-daily oral administration of LY3023414 (part A) and one for twice-daily dosing of LY3023414 (part A2). Dose escalation followed a 3+3 design and no intrapatient dose escalation was allowed. After completion of the dose-escalation parts, an expansion cohort was initiated to assess a potential CYP3A4 drug–drug interaction (DDI) of LY3023414 using midazolam as substrate (part B1).

The primary objective of this study was to determine a RP2D of LY3023414 that could be safely administered to patients. Secondary objectives included safety and toxicity assessments, pharmacokinetic, DDI, and preliminary antitumor activity, while exploratory objective was to evaluate pharmacodynamic effects of LY3023414 on biomarker indicative of PI3K/mTOR activity. The protocol was approved by Institutional Review Boards before patient recruitment, and each patient provided written informed consent before enrollment. The study was conducted in accordance with Consensus ethics principles derived from international ethical guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guideline and the International Conference on Harmonization E6 Guidelines for Good Clinical Practice (ICH GCP E6). This study was registered at clinicaltrials.gov with the identifier, NCT01655225.

\subsection*{Patient population}

Eligible patients were male or female at ≥18 years age, who had advanced and/or metastatic cancer (solid tumor or lymphoma) and had progressed or failed standard therapy(s), or for whom there was no standard therapy. Other key eligibility criteria included adequate hematologic and organ function, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and having discontinued all previous cancer therapies. Patients had measurable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; ref. 9).

Key exclusion criteria were symptomatic central nervous system malignancy or metastasis, insulin-dependent or history of gestational diabetes, intolerance to any previous treatment with PI3K and/or mTOR compound, or severe uncontrolled cardiac, lung, or liver disease. Patients in the DDI expansion cohort were in addition not allowed to have any concomitant medications that are moderate/strong inhibitors or inducers of CYP3A4 administered 21 days prior to midazolam assessment.

\subsection*{Study treatments}

LY3023414 was orally self-administered with a glass of water with no food consumed at least 1-hour prior and after a dose. In part A, patients received LY3023414 once daily in consecutive cohorts at dose levels of 20, 40, 80, 150, 225, 325, or 450 mg. This dose range was determined on the basis of toxicology results and modeling of pharmacokinetic and pharmacodynamic data from nonclinical studies (7). In part A2, patients received LY3023414 twice daily at 150-, 200-, or 250-mg dose levels in consecutive cohorts. LY3023414 doses were taken in the morning and evening approximately 12 hours apart. Part A2 was initiated after the 325 mg once daily LY3023414 dose in part A was judged to be safe and tolerable.

Following completion of the dose escalation, patients in the DDI expansion cohort (part B1) were treated with LY3023414 200 mg twice daily. In addition, patients received a midazolam probe (0.2 mg as syrup) within 1 week prior to the first LY3023414 dosing and on day 15 of cycle 1 to evaluate potential CYP3A4 DDI based on nonclinical observation.

A cycle was defined as a 21-day period with continuous dosing of LY3023414 (either once daily or twice daily). Patients were treated until a discontinuation criterion was met. LY3023414 was provided by Eli Lilly & Company as capsules.

\subsection*{Safety}

Safety and tolerability were assessed through clinical and laboratory evaluations at weekly intervals for the first two cycles and at least every 2 weeks thereafter. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.0), and were recorded for all patients who received at least one dose of LY3023414. Dose-limiting toxicities (DLTs) were defined as possibly drug-related AEs during cycle 1 if they met one of the following main criteria: grade ≥3 nonhematologic toxicity (except for nausea, vomiting, diarrhea,
constipation, anorexia, and skin rash for ≤ 3 days; asymptomatic electrolyte disturbance responsive to medical treatment, transient ≤ 5 days grade 3 fasting hyperglycemia, grade 3 hypertriglyceridemia or hyperlipidemia without optimal treatment), grade 4 hematologic toxicity of ≥ 7 days duration, febrile neutropenia, grade ≥ 3 thrombocytopenia with ≥ 2 grade 2 bleeding or any other significant toxicity. The MTD was defined as the highest dose of LY3023414 not causing DLT in more than 33% of patients. Pharmacokinetic assessments Blood samples were collected for assessment of LY3023414 concentration profiles (at predose and 0.5, 1, 2, 4, 8, 12, and 24 hours postdose) on three occasions: (i) on day 1 of cycle 1 (single dose), (ii) on day 15 of cycle 1 (continued dosing) and (iii) on day 15 of cycle 2 (prolonged continued dosing; referred to as study day 36 for the purpose of pharmacokinetic analysis). Venous blood was drawn at each time point and collected using (single dose), (ii) on day 15 of cycle 1 (continued dosing) and (iii) 24 hours postdose) on three occasions: (i) on day 1 of cycle 1 0.5, 1, 2, 4, 8, 12 and 24 hours). Pharmacokinetic/pharmacodynamic relationship was investigated using nonlinear mixed effect (NLME) modeling methodology implemented in NONMEM VII level 3 (ICON plc). A sigmoidal Emax model was fitted to the inhibition of p4EBP1 versus LY3023414 exposure. Exploratory biomarkers Available archived tumors were subjected to next-generation sequencing using platforms compliant with Clinical Laboratory Improvement Amendments (CLIA) regulations. Sequencing was performed using the Foundation-One T5 panel consisting of 288 genes as described previously (13). Sequencing was confined to cohorts comprising patients dosed at 200 twice daily or 325 once daily to exclude potentially confounding results arising from dose escalation. Antitumor activity Tumor response was assessed by CT scans or MRI according to RECIST v1.1 (Eisenhauer and colleagues, 2009) at baseline and thereafter every 6 weeks until radiographic documentation of progressive disease. All patients receiving at least one dose of LY3023414 were included in the evaluation of antitumor activity. Statistical methods As a dose-escalation study, the sample size was determined by the number of dose levels explored and the number of patients per dose level following the 3+3 approach. The sample size for the DDI cohort (Part B1, n = 9) was calculated on the basis of an assumed intrasubject coefficient of variation on exposure of 20% for midazolam, leading to at least 90% probability that the precision of the mean effect of LY3023414 on midazolam exposure (i.e., on CYP3A4 activity) will be 26%. The precision of the estimate of DDI is defined as the ratio of the upper 95% confidence limit (two-sided) to the estimated mean. The statistical analyses for this study were descriptive. Data summaries, including demographics and baseline characteristics, safety, pharmacokinetics, and preliminary antitumor activities, were reported by study part and dose groups as appropriate. Continuous variables were summarized using mean and SD. Categorical variables were summarized using frequency and percentages. No formal hypothesis testing was performed. The data cutoff was June 8, 2017. Results Patient disposition and demographics A total of 47 patients were enrolled and received at least one dose of LY3023414 (Table 1). Twenty-five patients were enrolled in the once-daily dose-escalation part (Part A) and were treated at one of the seven LY3023414 dose levels: 20 mg (n = 3), 40 mg (n = 3), 80 mg (n = 3), 150 mg (n = 3), 225 mg (n = 3), 325 mg (n = 7), or 450 mg (n = 3). Thirteen patients received twice-daily dosing of LY3023414 at one of the three dose levels: 150 mg (n = 3), 200 mg (n = 6), and 250 mg (n = 4). Nine patients in the DDI expansion cohort received 200 mg LY3023414 twice daily. Patients were representative for a first human dose study and had exploited standard-of-care treatment options. Baseline patient and disease characteristics are summarized in Table 1.
Safety and tolerability

For once-daily dosing, no DLTs were observed up to the 325-mg dose level. At the next higher dose level of LY3023414 given at 450 mg once daily, DLTs were reported in three of three patients, including one case each of thrombocytopenia (grade 4), hypotension (grade 4), and hyperkalemia (grade 3). Therefore, a dose of 325 mg \( (n = 7) \) was determined as the MTD for LY3023414 once-daily dosing. For twice-daily dosing, DLTs were reported in three of four patients at 250 mg in the form of hypophosphatemia (grade 4), fatigue, and mucositis (both grade 3). At the next lower level of 200 mg, one of six patients experienced a DLT of intolerable grade 2 nausea. Thus, 200 mg was determined as the MTD for twice-daily dosing of LY3023414.

Forty patients (85.1%) experienced at least one adverse event (AE) possibly related to the study drug, 13 patients (27.7%) of whom experienced grade \( \geq 3 \) AEs. The most common possibly study drug-related AEs (in \( \geq 15\% \) of patients) reported across all patients included nausea (38.3%), fatigue (34%), vomiting (31.9%), and diarrhea (21.3%), as well as Table 2. Most of these AEs were of mild or moderate intensity. Grade \( \geq 3 \) related AEs that occurred in more than one patient included hyperglycemia, anemia, and fatigue. Fourteen patients reported serious adverse events (SAEs), including six events possibly related to LY3023414: hypotension and hypophosphatemia (both grade 4 and considered DLTs); nausea, hypernatremia, hyperglycemia, and asthenia (all grade 3). All SAEs possibly related to LY3023414 were reported at dose levels exceeding the MTD. AEs regardless of causality were provided in Supplementary Table S2. At the MTD of 200 mg twice daily, two patients had dose reduction, and one patient had a dose-cycle delay; while at 325 mg once daily, one patient had dose reduction, and two patients had dose-cycle delay. Dose reductions and delays occurred at various time points with no obvious pattern.

Progressive disease was the primary reason for study treatment discontinuation from either dose escalation or the DDI expansion cohort. One patient discontinued study treatment due to an adverse event (grade 3 hypercalcemia, 250 mg twice-daily cohort) not related to study treatment, who later died due to disease progression within 30 days from study treatment discontinuation. There were no deaths on study treatment.

Pharmacokinetics

LY3023414 pharmacokinetic data were available and evaluable for 43 patients including 23 patients with once-daily dosing and 20 patients with twice-daily dosing. LY3023414 was readily absorbed, followed oral administration, and concentrations

### Table 1. Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Age, median (years)</th>
<th>66.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>35 (74.5)</td>
</tr>
<tr>
<td>African American</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (46.8)</td>
</tr>
<tr>
<td>1</td>
<td>24 (51.1)</td>
</tr>
<tr>
<td>( \geq 2 )</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Weight (kg), median</td>
<td>71.2</td>
</tr>
<tr>
<td>Most common types of cancer, n (%)</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Pseudomyxoma peritonei (PEComa)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (34)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>44 (93.6)</td>
</tr>
<tr>
<td>Prior therapy with a PI3K and/or mTOR inhibitor</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>26 (55.3)</td>
</tr>
</tbody>
</table>

### Table 2. Treatment-related adverse events related (all grades occurring in \( \geq 10\% \) patients)^a^, b

<table>
<thead>
<tr>
<th>CTCAE Term, n (%)</th>
<th>20 mg (N = 3)</th>
<th>40 mg (N = 3)</th>
<th>80 mg (N = 3)</th>
<th>150 mg (N = 3)</th>
<th>225 mg (N = 3)</th>
<th>325 mg (N = 3)</th>
<th>450 mg (N = 3)</th>
<th>150 mg BID (N = 3)</th>
<th>200 mg BID (N = 4)</th>
<th>250 mg BID (N = 4)</th>
<th>200 mg BID (Midazolam) (N = 9)</th>
<th>Total (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
<td>(N = 47)</td>
</tr>
<tr>
<td>Patients with any adverse event (AE)</td>
<td>2 (66.7)</td>
<td>3 (100)</td>
<td>5 (100)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>7 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>5 (83.3)</td>
<td>4 (100)</td>
<td>7 (77.8)</td>
<td>40 (85.1)</td>
</tr>
<tr>
<td>Patients with ( \geq 3 ) AEs</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (28.6)</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
<td>4 (100.0)</td>
<td>3 (33.3)</td>
<td>13 (27.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>5 (17.4)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>2 (33.3)</td>
<td>3 (75.0)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>2 (28.6)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (66.7)</td>
<td>3 (75.0)</td>
<td>3 (33.3)</td>
<td>16 (34)</td>
<td>2 (4.3)^d</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>2 (28.6)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (25.0)</td>
<td>3 (33.3)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>2 (28.6)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (25.0)</td>
<td>3 (33.3)</td>
<td>10 (21.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>1 (4.5)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (25.0)</td>
<td>3 (33.3)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>2 (50)</td>
<td>1 (25.0)</td>
<td>0 (0)</td>
<td>7 (14.9)</td>
<td>1 (2.1)^e</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (66.7)</td>
<td>1 (25.0)</td>
<td>0 (0)</td>
<td>5 (10.6)</td>
<td>2 (4.3)^c</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N = cohort size; n = number of events.

^a^Number of patients with treatment-related adverse events over the course of therapy are listed. Patients reporting more than one adverse event were counted only once by highest CTCAE grade. Data reported includes cohorts A, A2, and B1 only.

^b^At 325 mg once daily.

^c^At 450 mg once daily (exceeding MTD).

^d^At 250 mg twice daily (exceeding MTD).

^e^At 200 mg twice daily (exceeding MTD).
LY3023414 reached a maximum value at approximately 1 to 2 hours post-dose. LY3023414 pharmacokinetic profile as displayed in Supplementary Fig. S1, indicate a biphasic (biexponential) decline of LY3023414 concentration following LY3023414 maximum concentration. The inflexion point of the biphasic disposition, from visual inspection of LY3023414 concentration time plot, occur at approximately 8 to 12 hours postdose. After reaching \( C_{\text{max}} \) LY3023414 concentration declined with a mean distribution and terminal elimination half-life of 0.6 and 2.9 hours, respectively, as determined by the two-compartment pharmacokinetic model. The model indicated that the terminal phase of LY3023414 pharmacokinetic profile, under the terminal \( t_{1/2} \), corresponds to a limited percentage (approximately 20%) of the overall AUC. Therefore, the NCA provides reliable estimation of LY3023414 AUC\(_{0-\infty}\) and clearance because the terminal phase of LY3023414 pharmacokinetic has limited contribution to the assessment of LY3023414 AUC. The NCA results indicate mean LY3023414 half-life (\( t_{1/2} \)) of 1.93 hours (43% CV, \( N = 38 \) in the 20- to 325-mg dose range), and a mean clearance of 85 L/hour (56.8 % CV, \( N = 38 \) in the 20- to 325-mg dose range) after single dose (Supplementary Fig. S1). LY3023414 \( C_{\text{max}} \) and AUC\(_{0-\infty}\) increased approximately dose proportionally in the 20- to 325-mg dose range. At a higher dose of 450 mg, a greater than dose-proportional increase in LY3023414 exposure was observed. This corresponded to a lower LY3023414 clearance (median LY3023414 clearance 26 L/hour; range, 12–53 L/hour, \( N = 3 \) at that 450-mg dose) compared with LY3023414 clearance reported for the lower dose range of 20 to 325 mg (Fig. 1; clearance is the inverse of dose normalized AUC). LY3023414 pharmacokinetic parameters are summarized in Table 4.

Following repeated twice-daily dosing, \( C_{\text{max}} \) and AUC\(_{0-\infty}\) increased dose proportionally from 150 mg to 250 mg twice daily (as observed with single dose) and some level of accumulation in LY3023414 exposure is observed relative to single dose [mean accumulation ratio day 15/day1 exposure is 1.50 (CV47% \( N = 16 \))]. LY3023414 clearance after repeated dosing was 64 L/hour (CV46% \( N = 38 \)) in the 20- to 325-mg dose linear range. Exposure was similar following dose on day 15 and 36 indicating that steady state was reached by day 15.

**DDI**

LY3023414 was identified to be a weak inhibitor of the metabolic clearance of drugs metabolized through CYP3A4. The geometric mean ratio of midazolam AUC\(_{0-\infty}\) (midazolam+LY3023414: midazolam alone) was 1.46 (90% CI, 1.21–1.76); and the geometric mean ratio of hydroxymidazolam AUC\(_{0-\infty}\) (midazolam+LY3023414: midazolam alone) was 1.31 (90% CI, 0.95–1.81; see Supplementary Table ST1).

**Pharmacodynamic modulation of the PI3K/mTOR pathway**

LY3023414 demonstrated dose-dependent inhibition of PI3K/mTOR signaling based on pharmacodynamic biomarkers evaluated in this study. A dose-related decrease in phosphorylation of 4EBP1, a downstream target of PI3K/mTOR signaling, was observed in (CD14\(^{+}\)) PBMCs following LY3023414 administration as measured by a validated flow cytometry assay.
Table 3. Best response to LY3023414

<table>
<thead>
<tr>
<th>Response</th>
<th>LY3023414 (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response*, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (31.9)</td>
</tr>
<tr>
<td>PD</td>
<td>20 (42.6)</td>
</tr>
<tr>
<td>NE</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Overall response rate (CR+PR+SD), %</td>
<td>2.1</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD), %</td>
<td>34.0</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; N, total population; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. Data reported includes cohorts A, A2, and B1 only.

*Evaluated using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

(Supplementary Fig. S2A). In parallel to the pharmacokinetic profile of LY3023414, a more than 90% inhibition p4EBP1 was observed lasting for approximately 1.5 hours at LY3023414 doses ≥150 mg (Supplementary Fig. S3).

In line with previous studies for PI3K/mTOR inhibitors (14), changes in glucose level were observed as a mechanistic pharmacodynamic biomarker following LY3023414 dosing. A dose-related increase in glucose levels and C-peptide by up to approximately 25% relative to baseline was noted in the first 4 hours under fasting conditions (Supplementary Fig. S2B and S2C).

Antitumor activity

Of the 47 patients receiving LY3023414, 38 patients had measurable disease allowing evaluation of tumor response according to RECIST criteria. Patients treated with LY3023414 completed a median of 3.0 cycles (range, 1–39). There was one confirmed PR according to RECIST v.1.1 in an endometrial cancer patient that lasted for >18 months (Supplementary Fig. S4A). An additional 15 patients (31.9%) exhibited SD as their best response to therapy for a disease control rate (DCR) of 34.0% (Table 3). Thirteen of 23 patients (57%) treated at or above LY3023414 MTD dose levels of 325 mg once daily or 200 mg twice daily demonstrated a decrease in the sum of target lesions relative to baseline (Fig. 2A) relative to one of 15 patients (7%) at dose levels below the MTD.

Exploratory biomarker

In an effort to explore any potential association between genetic alterations and clinical activity of LY3023414, archival tumor tissue was subject to next-generation sequencing and data from this retrospective analysis aligned to clinical antitumor activity (Fig. 2B). Among the patients whose genetic mutation data were available, the only patient with a PR observed in this study was a patient with endometrial cancer detected to have a PIK3R1 mutation (PIK3R1 K448_Y452 del) and a truncating PTEN mutation (PTEN L193fs*6) which both leading to activation of the PI3K/mTOR pathway according to literature (15). The next three patients with the most decrease in tumor size and tumor tissue available for analysis correspond also to endometrial cancers two of which displayed potentially activating pathway alterations in PI3K/mTOR pathway genes (e.g., AKT1, AKT3, TSC2). Consistent with the high frequency of ARID1A mutations in endometrial cancer (16), two of five patients with this tumor type featured this alteration. However, mutations described to lead to activation of

Table 4. Pharmacokinetic parameters of LY3023414 [cycle 1, day 1 and day 15 and cycle 2 day 15 (day 36)]

<table>
<thead>
<tr>
<th>LY3023414 Treatment</th>
<th>Day (N)</th>
<th>t_{max} a (hr)</th>
<th>C_{max} (ng/mL)</th>
<th>AUC_{0–t} b (ng·h/mL)</th>
<th>t_{1/2} b (hr)</th>
<th>CI/F (L/h)</th>
<th>V2/F (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg QD</td>
<td>1 (3)</td>
<td>1 (1–1)</td>
<td>65.2 (49)</td>
<td>155 (40)</td>
<td>1.66 (1.47–1.81)</td>
<td>129 (40)</td>
<td>308 (48)</td>
</tr>
<tr>
<td></td>
<td>15 (3)</td>
<td>2 (0.5–2)</td>
<td>49.8 (176)</td>
<td>162 (65)</td>
<td>1.70 (1.53–1.90)</td>
<td>123 (65)</td>
<td>302 (74)</td>
</tr>
<tr>
<td></td>
<td>36 (3)</td>
<td>0.5 (0.5–1)</td>
<td>84.4 (34)</td>
<td>184 (22)</td>
<td>2.00 (1.44–3.31)</td>
<td>109 (22)</td>
<td>314 (72)</td>
</tr>
</tbody>
</table>

20 mg QD
1 (3) 2 (0.5–2) 49.8 (176) 162 (65) 1.70 (1.53–1.90) 123 (65) 302 (74)
15 (3) 2 (0.5–2) 129 (187) 408 (98) 1.71 (1.41–2.57) 98.1 (98) 243 (150)
36 (3) 0.5 (1) 42.4 (52) 550.1 (706) 1.38 (1.76) 73 (37) 140 (90)

40 mg QD
1 (3) 2 (1–2) 244 (56) 895 (58) 1.43 (1.01–1.78) 89.4 (58) 185 (52)
15 (3) 2 (1–2) 162 (104) 959 (48) 1.98 (1.86–2.06) 83.4 (58) 238 (44)
36 (3) 0.5 (0–2) 267 (75) 915 (27) 1.85 (1.54–2.08) 88 (28) 233 (15)

150 mg ALL
1 (6) 2 (0.5–4) 397 (65) 1460 (62) 1.94 (1.14–4.35) 103 (65) 287 (45)
150 mg QD
1 (3) 2 (2–2) 480 (102) 1940 (66) 2.57 (1.86–4.35) 77.4 (66) 287 (48)
150 mg BID
1 (3) 2 (0.5–4) 329 (24) 1100 (50) 1.46 (1.14–1.81) 136 (50) 287 (29)
150 mg QD
1 (3) 2 (2–4) 827 (27) 3390 (13) 3.84 (3.18–4.26) 44.2 (13) 245 (22)
36 (3) 1.2 807 (810) 3708 (2640) 3.16 (1.66) 40.5 (56.9) 180 (140)

150 mg BID
1 (3) 1 (0.5–2) 714 (45) 1980 (22) 1.74 (1.5–2.16) 75.8 (22) 191 (30)
36 (3) 4.1 329 (231) 1520 (1230) 1.57 (2.08) 99.1 (122) 220 (160)
200 mg QD
1 (14) 1 (0.5–4) 814 (55) 2500 (68) 1.88 (1.08–3.74) 80.0 (68) 218 (44)
15 (15) 2 (0.5–4) 941 (59) 3670 (28) 1.90 (1.59–2.67) 54.5 (28) 148 (23)
36 (5) 1.2 1082 (54) 4002 (62) 1.73 (1.26–2.18) 50.0 (62) 124 (44)

225 mg QD
1 (3) 2 (0.5–4) 810 (70) 2870 (82) 2.74 (1.65–4.44) 78.4 (82) 310 (107)
36 (3) 1.0 2550 (912) 5570 (1880) NC (160) 40.4 (119) NC (280)

250 mg BID
1 (3) 0.5 (0.5–1) 967 (107) 3500 (10) 2.41 (1.72–4.64) 72 (12) 252 (74)
325 mg QD
1 (5) 1 (0.5–2) 1710 (27) 4960 (32) 2.18 (1.20–3.69) 65 (32) 215 (63)
15 (7) 2 (0.5–2) 1450 (92) 5580 (58) 3.4 (1.31–5.07) 58.3 (38) 286 (82)
36 (7) 2 (1–4) 1406 (67) 5710 (43) 3.17 (1.92–5.91) 56.9 (43) 253 (67)

450 mg QD
1 (3) 0.5 (0.5–2) 4140 (152) 17500 (85) 3.17 (2.02–4.89) 26 (85) 117 (141)

NOTE: Not all patients in each cohort were evaluable for all parameters at all timepoints.

Abbreviations: hr, hour; QD, once daily.

*Median (range).

**Geometric mean (range).

At 200 mg BID and 325 mg QD, one and two subject's pharmacokinetic parameters, respectively, were excluded from summary statistic reporting due to being outliers with very low exposure.

*Individual data reported as only two patients' data.

Bendell et al.
PI3K/mTOR signaling were also observed in patients with best response of progressive disease (e.g., AKT1, STK11, PIK3CA) but, noted here was the presence of concurrent MAPK pathway alterations (e.g., KRAS, BRAF).

Discussion
In this FHID dose-escalation study in patients with advanced cancer, the oral PI3K/mTOR dual inhibitor LY3023414 was demonstrated to be safe and tolerable when given up to 325 mg once daily or 200 mg twice daily. The RP2D for LY3023414 monotherapy was determined to be 200 mg twice daily based on safety and tolerability and supported by pharmacokinetic/pharmacodynamic and preclinical observations.

The majority of possibly LY3023414-related AEs observed in this study were mild or moderate in intensity and included nausea, fatigue, diarrhea, and vomiting as the most common reported possibly related AEs (that is ≥20% of patients). No grade ≥ 3 AE possibly related to LY3023414 was observed more than once in patients treated up to the MTDs supporting the tolerability of LY3023414 at the RP2D level. The safety profile observed in patients receiving LY3023414 for prolonged period of time was similar as for the overall patient population supporting the long-term tolerability of LY3023414 at the RP2D. Upper gastrointestinal toxicity and fatigue has been previously reported as a common AE for other PI3K/mTOR dual inhibitors with a dose-dependent safety profile (17). Potentially due to LY3023414’s short half-life with intermittent target inhibition, rash and...
hyperglycemia were infrequently observed, which contrasts with the toxicity profiles of other PI3K/mTOR inhibitors that commonly report higher rates for these adverse events. Notably, no AEs indicative for mood alteration were reported for LY3023414 as reported for another pan-PI3K inhibitor (14). Rafi and colleagues (18) reported increased risk of bacterial infections in patients treated with inhibitors to components of the PI3K/mTOR pathway. While this risk might be of particular interest for PI3K/mTOR inhibitors coadministered with myelosuppressive agents, there was no increased rate of bacterial infections noted in the current monotherapy study. However, careful monitoring of this toxicity will continue to be performed for LY3023414 combinations with other drugs in subsequent clinical trials.

LY3023414 pharmacokinetic analysis showed a dose-proportional increase in LY3023414 exposure (AUC) at tolerated dose levels (from 20 to 325 mg). At a higher dose of 450 mg, a greater than dose-proportional increase in LY3023414 exposure was observed. The estimation of LY3023414 t1/2 using classical NCA method was impeded by limited pharmacokinetic information available in the terminal phase of the LY3023414 pharmacokinetic profile: (i) for patients receiving once-daily dosing, the LY3023414 concentration at the 24-hour postdose sampling time point were below the lower limit of quantification for lower dose levels (i.e., LY3023414 dose ≤ 80 mg); (ii) for patients receiving twice-daily dosing, the pharmacokinetic profile was limited to the 12-hour dosing interval leading to at most two pharmacokinetic points in the terminal phase. These limitations in the assessment of the terminal half-life were mitigated by using modeling analysis, which confirmed that the t1/2 of LY3023414 was short (2.9 hours). Furthermore, the modeling analysis enabled to determine that the terminal elimination phase of LY3023414 contributed to only a small percentage of the overall AUC and therefore reinforce LY3023414 clearance and AUC output from the NCA analysis. Pharmacokinetic data from the DDI analysis with midazolam indicated that LY3023414 is only a weak inhibitor of CYP3A4. As LY3023414 is also a substrate of CYP3A4, it remains to be elucidated whether the weak CYP3A4 inhibitory effect by LY3023414 may contribute to the mild accumulation observed in LY3023414 exposure following repeated dosing. Further analysis on repeated dosing of LY3023414 is warranted and additional DDI studies are planned to investigate DDI with LY3023414 as CYP3A4 victim.

Pharmacodynamic analysis suggest that LY3023414 exposure obtained is in a biological active dose range even below the RP2D of 200 mg twice daily. Dose-related target inhibition with ≥50% and ≥90% of p4EBP1 in peripheral mononuclear cells was observed following single dosing of LY3023414 at 100 mg and 150 mg, respectively. In parallel with the short half-life of LY3023414 of about 2 hours, dephosphorylation by ≥50% of 4EBP1 lasted for about 4 hours and returned to baseline after 6 hours postdose. While this pharmacodynamic data in PBMCs can be only considered as surrogate for the pharmacodynamic effects in patients tumor tissue, the target inhibition kinetics are consistent with data in tumor xenograft models showing intermittent target inhibition in tumors to be associated with single-agent activity of LY3023414 (7). Therefore, assessment of PBMCs was considered a scientifically acceptable and clinically feasible surrogate approach to reflect pharmacodynamic effects of LY3023414 in patient’s tumors in phase I study. A further established pharmacodynamic biomarker for PI3K/mTOR inhibitors is change in blood glucose given the central role of PI3K/mTOR signaling in regulating insulin-mediated cellular metabolism. In line with this, we observed a dose-dependent and transient increase in median blood glucose in patients treated with LY3023414 that followed the short half-life of the molecule. While this on-target effect fosters the mechanism of action of LY3023414 as a PI3K/mTOR inhibitor, its modest and short-lived nature might have led to low frequency of hyperglycemic AEs observed in the current study and is hypothesized to reduce the risk of impaired glucose tolerance as one major toxicities of other PI3K inhibitors (14). Moreover, increased glucose levels due to PI3K/mTOR inhibition have been suggested to result in unintended activation of the PI3K/mTOR pathway due to induction of insulin growth factor (IGF) receptor signaling as a feedback loop to PI3K/mTOR inhibition (19). PI3K/mTOR molecules leading to only modest and short-lived blood glucose elevations might also reduce this potential mechanism of compensatory pathway activation.

Beside the observation that LY3023414 at 200 mg twice daily resulted in less pronounced transient glucose elevation relative to 325 mg once daily but still ≥90% inhibition of p4EBP1 in PBMCs, the decision for 200 mg twice-daily dosing as RP2D for LY3023414 over 325 once daily was further informed by preclinical data. In vivo studies show that tumor growth inhibition by LY3023414 is dependent on the total daily dose administered but independent of the dosing schedule (7). The same total daily dose of LY3023414 resulted in similar antitumor activity regardless of whether it was administered as a single or two separate doses in various tumor xenograft models (7). Considering the MDs identified for once daily (i.e., 325 mg) and twice daily (200 mg) dosing in this phase I study, the 200 mg twice daily schedule allowed to administer a higher total daily dose of LY3023414 in patients with a monitorable and manageable side-effect profile and was therefore determined as RP2D over 325 mg once daily. Further alternative dosing schedules (e.g., thrice daily dosing of LY3023414) in view of the relative short half-life of LY3023414 were not explored considering the schedule-independent activity of LY3023414 in preclinical models (7) and the dose-dependent duration and intensity of p4EBP1 target inhibition observed in PBMCs.

In line with previous studies for PI3K/mTOR inhibitors, this dose finding study demonstrated only moderate single-agent activity for LY3023414 in the unselected patient population enrolled. While the observation that more than half of the patients treated at or above the MTD dose levels of once-daily or twice-daily dosing demonstrated a decrease in the sum of target lesions is encouraging, the single confirmed partial response fosters the notion that only selected patients might receive major benefit from single-agent treatment with PI3K/mTOR-targeting compounds.

Predictive biomarker(s) for clinical activity to monotherapy with PI3K/mTOR inhibitors is an active area of research and has been shown to be challenging (2). Across all preclinical tumor models studied and in line with previous studies (5, 20), no obvious predictive marker for sensitivity to LY3023414 in vivo or in vitro was identified (7). In the current study, of note, the only patient with a confirmed partial response according to RECIST and lasting >18 months was a patient with endometrial cancer harboring a truncation mutation in PTEN and a deletion in the regulatory protein PIK3R1, two events with the potential to engender pathway activation and dependence. PI3K pathway alterations occur at a high frequency in endometrial tumors
(>80%; refs. 16, 21) and three of five endometrial patients in our study with evaluable tumor tissue displayed alterations in this pathway. The PIK3R1 mutation observed in the patient with the confirmed PR, K448_M452del, localizes to the intervening SH2 domain of the p85 regulatory subunit, a site prone to recurrent deletions that result in enhanced pathway activation (AktSer^{473} phosphorylation; ref. 22). The two patients with endometrial cancer with the next-best reduction in tumor size displayed a truncation in ARID1A, a gene observed mutated in endometrial cancer at a frequency of about 35% (16, 23). ARID1A deficiency has been reported to enhance sensitivity to PI3K-targeted agents (23). The biomarker data from this small phase I study can be considered of anecdotal value only. The possibility that clinical activity to LY3023414 in patients with (or without) PI3K pathway activating mutations is countered by MAPK pathway alterations (3 KRAS mutation, one low-level BRAF amplification; Fig. 2B) in patients that did not receive clinical benefit in the current study. KRAS mutations singly or concurrent with PIK3CA or PTEN mutations were found also in patients displaying pharmacodynamics in a phase I study of BKM120, a pan-class I PI3K inhibitor (14) and preclinical observations support a role for KRAS mutations in resistance to PI3K inhibitors (24, 25). Cotargeting PI3K and MAPK pathways might provide an opportunity to overcome such resistance as demonstrated by synergistic antitumor efficacy in preclinical models of endometrial cancer (26).

However, any molecular profile associations with clinical activity of LY3023414 is strongly hindered by the small size of the sequenced cohort, the diverse tumor types enrolled, and the use of archival tumor samples for molecular analysis in the current study. As variations in preanalytic parameters (e.g., cold ischemia time, temperature before and during tissue fixation, and sample type) may profoundly affect phosphopeptides (27) and procurement and preservation of tumor tissue was not standardized, it was intentionally decided to forego assessment of phosphopeptides to confirm mutational activation at the protein level from archival tumor samples collected in this study. The potential contribution of the observed genetic alterations to LY3023414 activity awaits further studies involving larger cohorts of patients and using ideally fresh tumor biopsies.

In summary, the current study demonstrated that LY3023414 has a tolerable safety profile and single-agent activity in patients with advanced cancers. Pharmacodynamic analysis shows intermittent but strong target engagement with >90% pathway inhibition at the RP2D of 200 mg twice-daily LY3023414. On the basis of the observed activity in patients with endometrial cancer in this phase I study, a phase II study has been initiated to further explore the single-agent activity of LY3023414 in patients with recurrent or persistent endometrial cancer with tumors harboring a known PI3K pathway activating mutation (NCT02549989). Further ongoing clinical trials are investigating the effect of LY3023414 in combination with endocrine therapy for hormone receptor–positive breast cancer (NCT02057133) and castration-resistant prostate cancer (NCT02407054).

Disclosure of Potential Conflicts of Interest
A. M. Varghese reports receiving commercial research grants from Lilly, and reports receiving other commercial research support from Lilly, Verastem, Bristol, Myers, Squibb, and Sileseed. D. M. Hyman reports receiving commercial research grants from Lono Oncology, AstraZeneca, and Puma Biotechnology, and is a consultant/advisory board member for Atar Biotherapeutics, Chugai Pharma, CytoxM, AstraZeneca, Pfizer, Bayer, Debiopharm Group, arQule, and Genentech. T. M. Bauer is a consultant/advisory board member for Lono Oncology, Ignyta, Pfizer, GuardantHealth, and Moderna. V. Wacheck holds ownership interest (including patents) in Eli Lilly and Company. K. N. Moore is a consultant/advisory board member for Advaxis, AstraZeneca, Clovis, Immunogen, VBL Therapeutics, and Genentech/Roche. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Conception and design: A. M. Varghese, S. Callies, V. Wacheck
Development of methodology: R. Martinez, E. R. Wickremesinhe
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. C. Bendell, A. M. Varghese, D. M. Hyman, T. M. Bauer, S. Pant, R. Martinez, A. Fink, K. N. Moore
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. M. Varghese, S. Pant, S. Callies, J. Lin, R. Martinez, A. Fink, V. Wacheck, K. N. Moore
Writing, review, and/or revision of the manuscript: J. C. Bendell, A. M. Varghese, D. M. Hyman, T. M. Bauer, S. Pant, R. Martinez, A. Fink, K. N. Moore
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Pant, R. Martinez, A. Fink
Study supervision: S. Pant, A. Fink, V. Wacheck, K. N. Moore

Acknowledgments
We thank the patients, their families and the study personnel across all sites for participating in this study. The authors would like to thank Christine Martersteck for reviewing biomarker data, Elizabeth Smith Labell for her work on the pharmacokinetic analysis, and Gregory P. Donohoo for critical review of the manuscript and editorial assistance. Anindya Chatterjee provided writing assistance funded by Eli Lilly and Company. C.M., E.S.L., G.P.D, A.C. are employees of Eli Lilly and Company. The study was sponsored by Eli Lilly and Company.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 15, 2017; revised March 2, 2018; accepted April 3, 2018; published first online April 10, 2018.
A First-in-Human Phase 1 Study of LY3023414, an Oral PI3K/mTOR Dual Inhibitor, in Patients with Advanced Cancer

Johanna C. Bendell, Anna M. Varghese, David M. Hyman, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-17-3421

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2018/04/10/1078-0432.CCR-17-3421.DC1

Cited articles
This article cites 27 articles, 12 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/24/14/3253.full#ref-list-1

Citing articles
This article has been cited by 6 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/24/14/3253.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://clincancerres.aacrjournals.org/content/24/14/3253.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.