First-in-Human Phase I Study of Pictilisib (GDC-0941), a Potent Pan-Class I Phosphatidylinositol-3-Kinase (PI3K) Inhibitor, in Patients with Advanced Solid Tumors

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Abstract

Purpose: This first-in-human dose-escalation trial evaluated the safety, tolerability, maximal-tolerated dose (MTD), dose-limiting toxicities (DLT), pharmacokinetics, pharmacodynamics, and preliminary clinical activity of pictilisib (GDC-0941), an oral, potent, and selective inhibitor of the class I phosphatidylinositol-3-kinases (PI3K).

Patients and Methods: Sixty patients with solid tumors received pictilisib at 14 dose levels from 15 to 450 mg once-daily, initially on days 1 to 21 every 28 days and later, using continuous dosing for selected dose levels. Pharmacodynamic studies incorporated [18F]-FDG-PET, and assessment of phosphorylated AKT and S6 ribosomal protein in platelet-rich plasma (PRP) and tumor tissue.

Results: Pictilisib was well tolerated. The most common toxicities were grade 1–2 nausea, rash, and fatigue, whereas the DLT was grade 3 maculopapular rash (450 mg, 2 of 3 patients; 330 mg, 1 of 7 patients). The pharmacokinetic profile was dose-proportional and supported once-daily dosing. Levels of phosphorylated serine-473 AKT were suppressed >90% in PRP at 3 hours after dose at the MTD and in tumor at pictilisib doses associated with AUC >20 h·μmol/L. Significant increase in plasma insulin and glucose levels, and >25% decrease in [18F]-FDG uptake by PET in 7 of 32 evaluable patients confirmed target modulation. A patient with V600E BRAF-mutant melanoma and another with platinum-refractory epithelial ovarian cancer exhibiting PTEN loss and PI3CA amplification demonstrated partial response by RECIST and GCIG-CA125 criteria, respectively.

Conclusion: Pictilisib was safely administered with a dose-proportional pharmacokinetic profile, on-target pharmacodynamic activity at dose levels ≥100 mg and signs of antitumor activity. The recommended phase II dose was continuous dosing at 330 mg once-daily. Clin Cancer Res; 21(1); 77–86. ©2014 AACR.

Introduction

Phosphatidylinositol-3-kinase (PI3K) regulates processes involved in the hallmark traits of cancer, such as cell growth, survival, metabolism, invasion, and metastases (1). Multiple isoforms of PI3K exist in mammalian cells and these isoforms are subdivided into three classes based on structural features and lipid substrate preferences (1). The class IA isoforms (p110α, β, and γ) are responsible for the production of the second messenger phosphatidyl-inositol-3,4,5 triphosphate (PIP3; refs. 2, 3). PI3K activation initiates a signal transduction cascade, of which the major effectors are the kinases AKT and mTORC1 (4). PTEN is a tumor-suppressor gene that functions as a phosphatase, and is the
Primary negative regulator of PI3K, through hydrolysis of PIP3 (5). Deregu-lation of the PI3K pathway has been frequently implicated in a wide range of malignancies, including glioma, prostate, breast, ovarian, and endometrial cancer (6). Alteration of the pathway commonly occurs through mutation or amplifica-
tion of PIK3CA that encodes the p110α catalytic subunit, loss of function of PTEN (through deletion, mutation, or reduced expres-
sion), alterations in the INPP4B and PHLPP phosphatases, muta-
tions of the PI3K regulatory subunits encoded by PIK3R1 and PIK3R3, or through activation of upstream receptor tyrosine kinases or cross-talk with the RAS pathway (3, 6, 7).

Pictilisib (GDC-0941; Genentech Inc.) is an oral, potent, selective pan-inhibitor of class I PI3K (IC50 against purified recombinant human PI3K isoforms: p110α = 3 nmol/L, p110β = 33 nmol/L, p110δ = 3 nmol/L, and p110γ = 75 nmol/L) with 193-fold less activity against mTOR compared to p110α (8). Antitumor activity was demonstrated in human tumor xenograft mouse models; at an oral dose of 150 mg/kg, pictilisib achieved 98% and 80% growth inhibition in PI3K pathway-activated U87MG glioblastoma and IGROV1 ovarian cancer xenografts, respectively (9). At this dose level, pictilisib achieved plasma concentrations in tumor tissue that exceeded those observed in plasma (10). In addition, tumor-to-plasma concentrations were well tolerated at biologically active doses. Comprehensive pharmacodynamic biomarker evaluation showed suppression of AKT and S6 phosphorylation in platelet-rich plasma (PRP) and tumor, together with significant changes in plasma insulin and glucose levels, and decreases in 18F-FDG uptake by PET. In addition, there was preliminary evidence of antitumor activity. These results provide the basis for further evaluation of pictili-
sib in rationally designed monotherapy or combination trials. In addition, this phase I trial of pictilisib exemplifies the use of “Pharmacological Audit Trail” guidelines for molecularly targeted therapy in cancer.

**Translational Relevance**

The phosphatidylinositol-3-kinase (PI3K) pathway is one of the most commonly deregulated in cancer and is currently a major focus for anticancer drug development. This article describes the first-in-human phase I trial of pictilisib (GDC-0941), one of the very first pan-class I selective PI3K inhibitors evaluated in patients with advanced cancer. Pictilisib demonstrated a favorable pharmacokinetic profile and was well tolerated at biologically active doses. Comprehensive pharmacodynamic biomarker evaluation showed suppression of AKT and S6 phosphorylation in platelet-rich plasma (PRP) and tumor, together with significant changes in plasma insulin and glucose levels, and decreases in 18F-FDG uptake by PET. In addition, there was preliminary evidence of antitumor activity. These results provide the basis for further evaluation of pictilisib in rationally designed monotherapy or combination trials. In addition, this phase I trial of pictilisib exemplifies the use of “Pharmacological Audit Trail” guidelines for molecularly targeted therapy in cancer.

**Patients and Methods**

This single-center trial was conducted in accordance with the Declaration of Helsinki at The Royal Marsden NHS Foundation Trust (London, United Kingdom) after approval by local Institutional Review Boards. Informed consent from all patients was obtained.

**Eligibility**

Patients of ages ≥18 years with histologically confirmed solid tumors and no conventional treatment option were eligible. Other inclusion criteria included fasting serum glucose ≤120 mg/dL, HbA1c, upper limit of normality, prior chemotherapy or radiotherapy completed ≥4 weeks previously, toxicity from prior therapy resolved to grade ≤1, an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, expected life expectancy ≥12 weeks, and adequate organ functions. Significant exclusion criteria included diabetes mellitus requiring medication, significant respiratory disease (requiring supplemental oxygen or predicted diffusion capacity of carbon monoxide (DLCO) ≤50%), and use of anticoagulation or chronic corticosteroid.

**Study design**

This was an open-label, single-center, phase I study using a modified 3+3 dose-escalation design. During dose escalation, the dose of pictilisib was doubled until drug-related toxicity of grade ≥2 was observed. Dose escalations from this point were limited to ≤50% of the previous dose (if grade ≤2) or 33% in the event of grade ≥3 toxicities.

Pictilisib was administered on day 1, followed by a 1-week washout to evaluate single-dose pharmacokinetics and pharma-
codynamics. Dosing was once-daily for 21 or 28 days every 28 days (21/28 or 28/28 schedule, respectively). The recommended starting dose in humans of 15 mg once-daily was chosen on the basis of the no observed adverse effect level and MTD in 28-day rodent and dog species studies. The 21/28 starting schedule was chosen to implement a drug-free period to allow recovery from acute toxicities and limit cumulative toxicities to maximize the administered dose of pictilisib. A continuous dosing schedule (28/28) was implemented to further explore safety and pharma-
codynamics of dose levels of 330 to 400 mg.

**Definitions of DLT and MTD**

DLTs were based on toxicities observed in the first cycle and assessed by the investigator as possibly related to pictilisib. A DLT was defined as grade 4 neutropenia for >5 days or accompanied by fever >38.5°C, grade 4 thrombocytopenia, or grade 3 nonhematologic toxicity of any duration with the exception of alopecia. Grade 3–4 nausea, vomiting, and diarrhea were only considered DLTs if they occurred despite optimal medical management. Grade ≥3 total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were considered DLTs except when preexisting grade 1 values and were <7.5x ULN due to known liver metastases. Decreases in DLco ≥20% were also considered DLTs. The MTD was defined as the highest dose at which ≤1 of 6 DLTs (<33%) patients experienced DLT at that dose level.

**Safety and efficacy**

Clinical and laboratory assessments were conducted at baseline and weekly thereafter. Safety assessments included medical
Phase I Trial of Potent and Selective Pan–PI3K Inhibitor Pictilisib

Table 1. Demographics and clinical characteristics of all treated patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>Patients, n (%)</th>
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<tbody>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>30 (50)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td>ECOG performance status at screening</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>28 (47)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32 (55)</td>
<td></td>
</tr>
<tr>
<td>Primary cancer diagnosis</td>
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<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>16 (27)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>9 (15)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>7 (12)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
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<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>16 (27)</td>
<td></td>
</tr>
<tr>
<td>Prior lines of systemic therapies (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–16</td>
<td></td>
</tr>
</tbody>
</table>

DLTs and MTD

The MTD was exceeded at 450 mg once-daily (21/28 schedule) with a DLT of grade 3 rash in 2 patients. This was a maculopapular rash covering 70% to 80% of the body surface area that presented approximately 2 weeks after commencement of daily pictilisib dosing and resolved spontaneously 2 weeks after treatment discontinuation. At 330 mg once-daily (21/28 schedule), the grade 3 maculopapular rash observed in 1 of 7 patients had a similar temporal pattern of onset and resolution; this was also declared as a DLT. On the 28/28 schedule, no DLT was observed.

Safety and tolerability

Pictilisib was well tolerated up to 330 mg (21/28 schedule); most AEs were mild to moderate in severity with no treatment-related deaths (Table 2). At the assessed dose levels, there did not appear to be a significant difference in the toxicity profile between the 21/28 and 28/28 schedules. Treatment-related AEs that occurred in ≥10% of patients included: nausea, diarrhea, vomiting, fatigue, dysgeusia, decreased appetite, and rash. In addition to the two DLts of grade 3 rash at the 450-mg dose level, the third patient at this dose level experienced grade 2 rash; nonetheless, this patient received 8 months of pictilisib with concomitant use of oral antihistamines and skin emollients. Of 10 patients treated with 330 mg once-daily (28/28 schedule), grade 1 or 2 rash was observed in 2 patients, and grade 3 rash (occurring after the DLT-defining window) in 2 patients; these similarly resolved with the introduction of drug holidays and supportive medications including emollients and corticosteroids.

Other clinically relevant drug-related AEs ≥grade 3 were grade 4 hyperglycemia (n = 1; 130 mg) and grade 3 pneumonitis (n = 1; 340 mg). The grade 4 hyperglycemia was transient, uncomplicated by clinically significant symptoms, signs or acidosis, and occurred in a patient with cholangiocarcinoma and previous pancreatico-duodenectomy who started low-dose prednisolone 2 days before the event. Grade 3 pneumonitis was observed at the end of cycle 1 in a patient with breast cancer previously treated with chest radiotherapy who developed grade 1 dyspnea, reduced DLCO, and a ground glass appearance on HRCT; these resolved.

Patients Patient characteristics

Sixty patients with confirmed progressive cancer at study entry were enrolled, most of whom were heavily pretreated [median of 3 prior systemic therapies (range, 0–16); Table 1]. All patients were included in the safety analysis.

Treatment and dose escalation

Sixty patients were treated in 14 dose schedules (Table 2). Dose escalation on the 21/28 schedule proceeded through 11 dose levels from 15 mg. At 450 mg, 2 of 3 patients experienced DLTs. The dose level of 330 mg was then evaluated with 1 DLT observed in 7 patients treated at this dose level on a 21/28 schedule. Subsequently, the dose levels of 330, 340, and 400 mg on the 28/28 schedule were assessed.

PI3K pathway alteration biomarkers

PIK3CA mutations were identified in circulating tumor plasma DNA (ctDNA) using a site-specific molecular characterization protocol (11). Archival and fresh tumor samples were analyzed using the SEQUENOM OncoCarta Panel (Sequenom Inc.). PIK3CA amplification was assessed by fluorescence in situ hybridization (FISH) and PTEN status by immunohistochemistry (12).

Results

Patient characteristics

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Treatment and dose escalation

Sixty patients were treated in 14 dose schedules (Table 2). Dose escalation on the 21/28 schedule proceeded through 11 dose levels from 15 mg. At 450 mg, 2 of 3 patients experienced DLTs. The dose level of 330 mg was then evaluated with 1 DLT observed in 7 patients treated at this dose level on a 21/28 schedule. Subsequently, the dose levels of 330, 340, and 400 mg on the 28/28 schedule were assessed.

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following 2 weeks of drug interruption and concomitant use of prednisolone. When pictilisib was reintroduced at 240 mg, the dyspnea and HRCT changes recurred; these subsequently resolved following permanent discontinuation of pictilisib due to disease progression.

Pharmacokinetics

Pharmacokinetic parameters of pictilisib were estimated for all dose cohorts and are summarized in Table 3 and Supplementary Table S1. Under fasting conditions, pictilisib was rapidly absorbed after oral administration [median $T_{\text{max}}$ of 2 hours (range, 0.5–8)]; this was independent of dose and was unchanged after multiple doses. Terminal plasma elimination half-life ($T_{1/2}$) on day 1 ranged between 13.1 and 24.1 hours. Dose-proportional increases in exposure (C$_{\text{max}}$ and AUC$_{0-24}$) was observed across the dose levels studied (Fig. 1). Similar pharmacokinetic characteristics were seen on day 15. The accumulation index (AUC$_{\text{Day15}}$/AUC$_{\text{Day1}}$) ranged from 1.2 to 2.2, suggesting modest accumulation following multiple doses.

Pharmacodynamics

We observed a dose- and concentration-dependent decrease in phospho-AKT in PRP on days 1 and 15 (Fig. 2). Inhibition up to 90% of phospho-AKT level in PRP was demonstrated 1

Table 2. Summary of AEs

<table>
<thead>
<tr>
<th>Dose level (mg)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>130</th>
<th>180</th>
<th>245</th>
<th>330</th>
<th>340</th>
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<td>21/28</td>
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<td>21/28</td>
<td>21/28</td>
<td>21/28</td>
<td>21/28</td>
<td>21/28</td>
<td>21/28</td>
<td>28/28</td>
<td>28/28</td>
<td>28/28</td>
<td>21 or 28/28</td>
</tr>
<tr>
<td>No. of patients</td>
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<td>3</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>Toxicity grade</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

NOTE: AEs possibly or likely treatment-related that occurred in $\geq$10% of patients according to maximum grade for each patient by dose level and grade. AEs grades $\geq$3 are presented in separate columns for each dose-schedule only when observed.

Table 3. Key pharmacokinetic parameters of pictilisib on days 1 and 15

<table>
<thead>
<tr>
<th>Dose level (mg)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>130</th>
<th>180</th>
<th>245</th>
<th>330</th>
<th>340</th>
<th>400</th>
<th>All</th>
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<tbody>
<tr>
<td>Schedule</td>
<td>21/28</td>
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<td>21 or 28/28</td>
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<tr>
<td>No. of patients</td>
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<td>3</td>
<td>4</td>
<td>4</td>
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<td>5</td>
<td>3</td>
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<td>3</td>
<td>7</td>
<td>7</td>
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<td>60</td>
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<tr>
<td>Toxicity grade</td>
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<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

NOTE: AEs possibly or likely treatment-related that occurred in $\geq$10% of patients according to maximum grade for each patient by dose level and grade. AEs grades $\geq$3 are presented in separate columns for each dose-schedule only when observed.

aIncluding preferred terms of rash, rash maculo-papular, rash macular, rash pruritic, rash erythematous, and rash papular.

bIncluding preferred terms of stomatitis, mucosal inflammation, mouth ulceration.
to 3 hours after dose at the recommended phase II dose (RP2D); this effect was sustained (50% of baseline) at 24 hours after dose. Reductions in S6 and AKT phosphorylation in tumor biopsies were greatest at the highest exposure level of pictilisib (AUC $>20 \text{ mol/L}$), with all 3 patients in this cohort showing ≥75% decrease in S6 phosphorylation and 2 patients also exhibiting a 100% decrease in AKT phosphorylation (Fig. 3). Following pictilisib treatment at 330 mg on cycle 1 day 1, there was a statistically significant increase in plasma insulin and glucose levels at 1 hour from baseline with mean fold change (i.e., ratio of post- over pretreatment level) in plasma insulin and glucose levels of 3.58 [95% confidence interval (CI), 2.33–5.49] and 1.18 (95% CI, 1.10–1.26), respectively (Supplementary Fig. S1).

18F-FDG-PET imaging showed a reduction from baseline of 18F-FDG-tracer uptake at dose levels ≥45 mg with an overall median change in maximum standardized uptake value (SUV$_{\text{max}}$) of −13% (range, −47 to 22; Supplementary Fig. S2). Seven of 32 evaluable patients (22%) achieved a metabolic partial response by EORTC-PET criteria (>25% reduction in mean SUV$_{\text{max}}$ without new lesions) on 18F-FDG-PET (10).

Antitumor activity
One patient with BRAF V600E–mutated metastatic melanoma, but no detected PI3K pathway deregulation, achieved a confirmed RECIST partial response; she received pictilisib at 330 mg once-daily (21/28 schedule) for 9.5 months. She had previously been treated sequentially with paclitaxel and dacarbazine, but had not received a BRAF or MEK inhibitor. A heavily pretreated, platinum-refractory advanced epithelial ovarian cancer patient with PIK3CA amplification (with high polysomy and >60% of tumor cells harboring four copies of PIK3CA) and loss of PTEN achieved radiologic stable disease for 4 months with GCIG-CA125 partial response (Supplementary Fig. S3; ref. 13) associated with 36% reduction in SUV$_{\text{max}}$ on 18F-FDG-PET and 75% reduction in tumor phospho-S6 expression. A patient with cKIT exon 9 mutant gastrointestinal stromal tumor but no evidence of PI3K pathway deregulation achieved stable disease for 7.5 months on pictilisib 450 mg once-daily, and this was associated with pharmacodynamic changes of 47% reduction in SUV$_{\text{max}}$ on 18F-FDG-PET and 75% reduction in tumor phospho-S6 expression.

Of 60 patients, 12 (20%) remained on study for >3 months and 2 (3%) for >6 months. Supplementary Table S2 shows the
pharmacokinetic–pharmacodynamic–clinical relationship of patients who demonstrated a partial response by RECIST, GCIG-CA125, or 18F-FDG-PET EORTC criteria.

Discussion

In this first-in-human dose-escalation phase I study, we confirm the feasibility of safely inhibiting class I PI3K in patients with solid tumors. Pictilisib was well tolerated at doses shown here to modulate PI3K signaling in normal and tumor tissues, and demonstrated dose-proportional pharmacokinetics. The most common drug-related toxicities included grade 1–2 nausea, fatigue, diarrhea, vomiting, dysgeusia, and reduced appetite. The RP2D of oral pictilisib was 330 mg continuous once-daily dosing. DLT was grade 3 maculopapular rash occurring in 2 of 3 patients treated at 450 mg/day and 1 of 7 patients at 330 mg/day. Our data indicate that the severity of the rash was not clearly related to higher exposures of pictilisib (Supplementary Fig. S4) and resolved with discontinuation of pictilisib. The rash was maculopapular but not acniform or blistering, did not show a predilection for sun-exposed areas, and was similar to the rash observed with other PI3K, AKT, and mTOR inhibitors, thereby pointing to a mechanism-based toxicity (14–16). Although this toxicity could be a potential pharmacodynamic biomarker of pictilisib, its underlying pathophysiology remains unclear and warrants further evaluation.

Our study design incorporated the use of the "Pharmacological Audit Trail" guidelines using appropriate pharmacokinetic–pharmacodynamic biomarkers (17, 18). The audit trail has been used by both academia (19) and industry (20) as a guideline to help answer critical "go/ no-go" decisions based on scientifically measurable and rigorous endpoints. This audit trail has utility in providing broad guidance for drug development, even though the same precise effects in preclinical models may not be exactly reproduced in patients, as demonstrated in this trial. The favorable preclinical PK properties of pictilisib were reproduced in this phase I trial (9). Preclinical pharmacokinetic–pharmacodynamic modeling based on MDA-MB-361, a human breast cancer xenograft with HER2 amplification and PIK3CA 1633G>A mutation, predicted the minimal target plasma AUC to be 6 μmol/L·h (3000 ng·h/mL) to achieve ≥90% tumor growth inhibition; this target AUC was achieved in most patients treated at doses >80 mg following 1 week of consecutive dosing and support the view that pictilisib is associated with biologically meaningful activity at these dose levels and exposures, especially at the RP2D. On the basis of these preclinical data, we additionally postulated that ≥90% inhibition of AKT phosphorylation is needed to inhibit cancer cell proliferation (9, 21). We demonstrate here a dose–response relationship between drug exposure and target modulation in normal tissue, with up to 90% decrease in AKT phosphorylation in PRP at up to 3 hours after dose at the RP2D. Although a direct correlation between pictilisib exposure and decrease in S6 and AKT phosphorylation in tumor is less clear, at the highest level of drug exposure [AUC >20 h (μmol/L)] there was clear evidence of pharmacodynamic effect, with >75% decrease in S6 phosphorylation and 100% reduction in AKT phosphorylation in 2 of 3 patients. The lack of consistent target modulation in tumor at lower drug exposures contrasts with the consistent dose–response relationship in PRP and is possibly related to different assay conditions that likely favor greater inhibition in the latter, together with disparities in drug concentrations between normal and tumor tissues due to probable differences in tissue architecture and hemodynamics. Such differences highlight the complexity of accurately defining the pharmacokinetic–pharmacodynamic relationship of molecularly targeted drugs, along with additional important issues including extrapolation of preclinical models to predict effects in patients, intratumoral and intertumor heterogeneity, and differences in analytic sensitivity/methodology in PRP versus tumor biopsies. All of these are likely to be important, highlighting the importance of evaluating different pharmacodynamic biomarkers to increase confidence in the overall pharmacologic effects of a drug within the audit trail framework, as we have done here.

To this end, at the RP2D of 330 mg, we demonstrate multimodal pharmacodynamic evidence of target modulation including the reduction of 18F-FDG-PET tracer uptake, inhibition of phospho-AKT in PRP and phospho-S6 in tumor tissue as well as increase in plasma glucose and insulin levels. These pharmacodynamic changes were observed regardless of molecular genetic status and from dose levels ≥100 mg. PI3K signaling regulates insulin sensitivity, and hyperglycemia has been predicted to be a hallmark toxicity of PI3K inhibition (6, 22, 23). However, pictilisib-related hyperglycemia was limited to grade 1–2 elevations in this study with grade ≥3 hyperglycemia being observed in only 1 patient with an extratherapeutic cholangiocarcinoma who had undergone a
previous pancreatic resection and was commenced on a corticosteroid 2 days before the AE. We confirmed target and pathway modulation at the RP2D with observations of convincing pharmacodynamic changes in phospho-S6 and 18FDG-PET in tumor, and phospho-AKT, glucose and insulin in plasma. Nonetheless, it is possible that homeostatic mechanisms via negative feedback loops may cause drug resistance and account for the lack of more significant hyperglycemia.

The toxicity profile of pictilisib is in contrast to BKM120 (another pan-class I PI3K inhibitor) where rash, hyperglycemia, and mood alterations were the observed DLTs (15). Apart from rash, the latter two were not significant toxicities of pictilisib. One would not have expected such differences if these DLTs are mechanism-based toxicities, especially when the observed in vitro potency of pictilisib is higher than that of BKM120 (24). Pictilisib has a lower central nervous system (CNS) penetration than

Figure 3. Pharmacodynamic analysis in tumor biopsies. A, phospho-S6 (pS6) and phospho-AKT (pAKT) levels in baseline and on-treatment paired tumor biopsies grouped according to AUC0–24 h (µmol/L) on day 15. pS6 staining levels were measured using a standard H-Score method, and pAKT staining levels were measured using a validated, qualitative scoring method (represented on y-axis). Pre- and on-treatment samples from the same patient were stained in the same experiment and examined blind. Arrows indicate patient 50036. B, immunohistochemistry images of pS6 and pAKT from patient 50036. C, percentage change from baseline of pS6 and pAKT levels. Tumor biopsies for three patients were not evaluable for phospho-AKT and are indicated with an “x.” All patients received doses of >60 mg of pictilisib with the exception of patient 50008 who received 45 mg.
BKIM120 while the targeted disruption of insulin signaling in the brain has been shown to lead to a diabetes mellitus phenotype (15, 25–28). It is likely that the marked hyperglycemia observed with BKIM120 is due to the synergistic inhibition of PI3K signaling in peripheral tissues (e.g., muscle and adipose tissues) with non-canonical insulin-targeted tissues (including the brain), and the lack of CNS penetration may have enhanced the clinical therapeutic index of pictilisib relative to BKIM120. The other pan-class I PI3K inhibitors that have undergone phase I clinical evaluation include SAR245408 and the irreversible wortmannin derivative PX-866 (29, 30). Both drugs were associated with minimal hyperglycemia but differences were observed in the frequency of rash, which occurred in 26% of patients treated with SAR245408 (all grades) and in none of the patients treated with PX-866. The importance of the therapeutic window of the pan-class I inhibitors with regards to their pharmacodynamic effect is critical, and in this respect our hypothesis that ≥90% inhibition of AKT phosphorylation is needed to inhibit cancer cell proliferation reveals potentially important differences between pictilisib and the other drugs in this class, with SAR245408 reporting a 40% to 80% reduction in tumor AKT phosphorylation, in comparison to pictilisib achieving 100% AKT inhibition in two patients at the MTD.

There is currently no validated predictive biomarker for PI3K pathway inhibitors. Somatic mutational sequencing and assessment of PTEN expression status were therefore undertaken. Our results highlight ongoing difficulties in the attempt to identify predictive biomarkers for pan-class I PI3K inhibitors, with no clear relationship between PI3K mutation/amplification or PTEN expression status and response to pictilisib (3). In this trial, PI3K pathway alterations were identified in 9 of 60 patients (15%), comprising 3 PTEN negative: 1 PTEN negative and PIK3CA amplification by FISH; and 5 PIK3CA mutations. Of these, one achieved a RECIST-based response and only 1 achieved a response by GCIG-CA125 criteria. This suggests the prediction of sensitivity may require more complex biomarker signatures rather than single mutational events (3, 21). In addition, an association between 18F-FDG-PET changes and RECIST response was not detected, in keeping with results from an earlier study of mTOR inhibitors (31).

We note the modest response rates in this trial and therefore, while we postulate that approximately 90% inhibition of AKT phosphorylation for several hours is needed to inhibit cancer cell proliferation based on our preclinical tumor phosphorylation data (9), the exact duration and magnitude to which the pathway should be inhibited remains unclear and more work is required to relate the extent of downstream phosphoprotein biomarker modulation to efficacy in patients. We also believe that important distinctions should be made between the utility of reduction in AKT phosphorylation as a pharmacodynamic and predictive biomarker of response. The best RECIST-responder in this study bore a BRAF V600E-mutant melanoma with no demonstrable PI3K mutation; she achieved a radiologic partial response by RECIST and remained on pictilisib for 9.5 months (she was not previously treated with a BRAF inhibitor and this was not therefore a withdrawal response). Responses to PI3K pathway inhibitors have been reported in BRAF-mutated cancer cell lines, including those without any known PI3K pathway aberration (32). Although these cancer cell lines are primarily dependent on RAS–RAF–MEK–ERK signaling for their proliferation, they are likely to have a degree of codependence on the PI3K-AKT pathway for their proliferation and survival, possibly explaining the response to pictilisib in this patient. In addition, there may be other activating effects in the PI3K pathway that we have been unable to assess that predispose to sensitivity including potential immunomodulatory effects given that T-cell receptor signaling involves the PI3K pathway (33).

An increasing understanding of potential resistance mechanisms (21) and promising preclinical data from combinatorial use of pictilisib (34–36) has led to clinical trials of pictilisib in combination with drugs including erlotinib, fulvestrant, trastuzumab emtansine (Kadcyla), GDC-0973 (a MEK inhibitor), paclitaxel, and chemotherapy regimens comprising paclitaxel/bevacizumab, carboplatin/paclitaxel/bevacizumab, and cisplatin/pemetrexed. Results from these ongoing studies are awaited.

In summary, pictilisib was safely tolerated at doses up to the RP2D which is 330 mg once-daily administered continuously. Displaying favorable pharmacokinetic properties, the plasma exposure levels achieved with ≥80 mg once-daily dosing were consistent with those associated with effective target modulation and antitumor activity predicted by preclinical in vivo pharmacokinetic-pharmacodynamic modeling. Analysis of pharmacodynamic biomarkers in peripheral blood and tumor tissue crucially provided evidence of significant PI3K pathway modulation at the RP2D. There is also evidence of clinical antitumor activity. Overall, these data provide strong support for the continued clinical evaluation of pictilisib.

Disclosure of Potential Conflicts of Interest
J. de Bono is a consultant/advisory board member for AstraZeneca, Chugai, Genentech, Merck and Millennium, and Pfizer, and reports receiving a commercial research grant from Genentech. R. Baird is a consultant/advisory board member for, and receives speakers’ bureau honoraria and commercial research grants from Genentech. P. Clarke reports receiving commercial research grants from Astellas Pharma and Piramal Pharma. M.K. Derynck, J. Fredrickson, L. Friedman, M. Lackner, and J. Spoerke are employees of and have ownership interests (including patents) in Genentech. K. Mazina has ownership interests (including patents) in Genentech. J. Ware has ownership interests in Roche. P. Workman reports receiving a commercial research grant from Astellas Pharma and Piramal Pharma; has ownership interest in Chroma Therapeutics and Piramed Pharma; and is a consultant/advisory board member for Chroma Therapeutics, Nextech Invest, NuVilolution, Piramed Pharma, and Wilux. Note: P. Workman, P. Clarke, F. Raeynaud, and J. de Bono are current employees of AstraZeneca. J.S. de Bono has ownership interests in Roche. R. Kristeleit, K. Shah, V. Moreno and S. Kaye are employees of Valeant Pharmaceuticals. Of the patients treated with PX-866, the importance of the therapeutic window of the pan-class I inhibitors with regards to their pharmacodynamic effect is critical, and in this respect our hypothesis that ≥90% inhibition of AKT phosphorylation is needed to inhibit cancer cell proliferation reveals potentially important differences between pictilisib and the other drugs in this class, with SAR245408 reporting a 40% to 80% reduction in tumor AKT phosphorylation, in comparison to pictilisib achieving 100% AKT inhibition in two patients at the MTD.

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Other (pharmacokinetic assessment of pictilisib (GDC-0941)): J.A. Ware

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References


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