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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

Johann S. de Bono, Debashis Sarker, Joo Ern Ang, et al.

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ORIGINAL REPORT

TITLE: 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

AUTHORS: Debashis Sarker^{1,2*}, Joo Ern Ang^{1,2*}, Richard Baird^{1,2}, Rebecca Kristeleit^{1,2}, Krunal Shah^{1,2}, Victor Moreno^{1,2}, Paul A. Clarke², Florence I. Raynaud¹, Gallia Levy³, Joseph A Ware³, Kathryn Mazina³, Ray Lin³, Jenny Wu³, Jill Fredrickson³, Jill M Spoerke³, Mark R Lackner³, Yibing Yan³, Lori S. Friedman³, Stan B. Kaye^{1,2}, Mika K. Derynck³, Paul Workman², Johann S. de Bono^{1,2}

*These authors have contributed equally and are joint first authors

AFFILIATIONS:

¹The Royal Marsden National Health Service (NHS) Foundation Trust, Sutton, Surrey, United Kingdom;

²The Institute of Cancer Research, London, United Kingdom;

³Genentech Inc., South San Francisco, California, United States of America

CORRESPONDING AUTHOR:

Professor Johann S. de Bono, MB ChB, MSc, FRCP, PhD, FMedSci

Professor of Experimental Cancer Medicine

Division of Clinical Studies, The Institute of Cancer Research

Drug Development Unit, The Royal Marsden NHS Foundation Trust

Downs Rd

Sutton, Surrey SM2 5PT

United Kingdom

Telephone: +44 (0)2087224028

Fax: +44 (0)2086427979

Email: johann.de-bono@icr.ac.uk

RUNNING HEAD: FIH Phase I trial of potent and selective pan-PI3K inhibitor pictilisib

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DISCLOSURES:

The following authors have no conflicts of interest to declare: Debashis Sarker, Jooern Ang, Rebecca Kristeleit, Krunal Shah, Victor Moreno, Gallia Levy, Jenny Wu, Stan Kaye.

The following authors have relevant conflicts of interest to declare:

Richard Baird has received honoraria and research funding from Genentech Inc.

Paul Clarke has received royalties from The Institute of Cancer Research ‘Rewards to Inventors’ scheme for development of PI3K inhibitors.

Florence Raynaud has received royalties from The Institute of Cancer Research ‘Rewards to Inventors’ scheme for development of PI3K inhibitors, and is a consultant for ELARA pharmaceuticals.

Johann De-Bono has served on advisory boards for Genentech, GSK, Merck, Pfizer, AstraZeneca, Millenium, Chugai.

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Joseph Ware, Ray Lin, Jill Fredrickson, Mark Lackner, Yibing Yan, Lori Friedman and Mika Derynck are all currently employed by Genentech Inc, and have stock ownership in Roche.

Jill Spoerke is currently employed by Genentech Inc.

Kathryn Mazina was a prior employee at Roche and has stock ownership in Roche

Mika Derynck has the following relevant patent to disclose: Methods of treating mesothelioma with a PI3K Compound, patent no. P4665R1.

Paul Workman was a founder of, consultant to, and Scientific Advisory Board member of Piramed Pharma (acquired by Roche); has been a founder of, consultant to and Scientific Advisory Board and Main Board member of Chroma Therapeutics; is on the Medical Advisory Board of WILEX; is a Member of the Scientific Advisory Board of Nextech Invest and Nuevolution; and was formerly an employee of AstraZeneca.

Paul Workman, Paul Clarke, Florence Raynaud, Johann de Bono are current employees of The Institute of Cancer Research, which has a commercial interest in the development of PI3K inhibitors, including pictilisib (GDC-0941), and operates a rewards-to-inventors scheme. Paul Workman, Paul Clarke and Florence Raynaud have previously been involved in a commercial collaboration with Yamanouchi (now Astellas Pharma) and with Piramed Pharma and intellectual property arising from the program has been licensed to Genentech. Debashis Sarker, Joo Ern Ang, Richard Baird, Rebecca Kristeleit, Krunal Shah, Victor Moreno and Stan Kaye are previous employees of The Institute of Cancer Research and are not part of the rewards-to-inventors scheme for pictilisib.

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ABSTRACT

Purpose: This first-in-human dose-escalation trial evaluated the safety, tolerability, maximal tolerated dose (MTD), dose limiting toxicities (DLTs), 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 450mg once-daily, initially on days 1-21 every 28 days and later, utilizing continuous dosing for selected dose levels. Pharmacodynamic studies incorporated ^{18}F -FDG-PET, and assessment of phosphorylated AKT and S6 ribosomal protein in platelet-rich plasma and tumor tissue.

Results: Pictilisib was well-tolerated. The most common toxicities were grade 1-2 nausea, rash and fatigue while the DLT was grade 3 maculopapular rash (450mg, 2 of 3 patients; 330mg, 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 platelet rich plasma at 3 hours post-dose at the MTD and in tumor at pictilisib doses associated with AUC >20uM.hr. Significant increase in plasma insulin and glucose levels, and >25% decrease in ^{18}F -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 PIK3CA 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 $\geq 100\text{mg}$ and signs of antitumor activity. The recommended Phase II dose was continuous dosing at 330mg once-daily.

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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 manuscript describes the first-in-man 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 and tumor, together with significant changes in plasma insulin and glucose levels, and decreases in ¹⁸F-FDG uptake by PET. In addition, anti-tumor activity is reported in patients with PI3K pathway deregulation. 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.

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 (p110 α , β and δ) are responsible for the production of the second messenger phosphatidyl-inositol-3,4,5 triphosphate (PIP₃).^{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 which functions as a phosphatase, and is the primary negative regulator of PI3K, through hydrolysis of PIP₃.⁵ Deregulation 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

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through mutation or amplification of *PIK3CA* which encodes the p110 α catalytic subunit, loss of function of PTEN (through deletion, mutation or reduced expression), alterations in the INPP4B and PHLPP phosphatases, mutations of the PI3K regulatory subunits encoded by *PIK3R1* and *PIK3R3*, or through activation of upstream receptor tyrosine kinases or crosstalk with the RAS pathway.^{3,6,7}

Pictilisib (GDC-0941; Genentech Inc., South San Francisco, CA) is an oral, potent, selective pan-inhibitor of class I PI3K (IC₅₀ against purified recombinant human PI3K isoforms: p110 α =3 nM, p110 β =33 nM, p110 δ =3 nM, p110 γ =75 nM) with 193-fold less activity against mTOR compared to p110 α .⁸ Antitumor activity was demonstrated in human tumor xenograft murine models; at an oral dose of 150mg/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 >GI₅₀-antiproliferative concentrations for >8 hours and demonstrated downstream PI3K pathway biomarker changes such as time- and dose-dependent inhibition of phosphorylation of AKT (Ser⁴⁷³) and P70S6 kinase (Thr⁴²¹/Ser⁴²⁴).⁹ These data led us to conduct a first-in-human Phase I dose-escalation study of pictilisib in patients with advanced solid tumors to evaluate safety and tolerability, define dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of pictilisib administered orally. Secondary objectives included characterization of pharmacokinetics, assessment of pharmacodynamics including changes in tumor ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake (by positron emission tomography [PET] studies), tumor expression of phosphorylated (Ser²³⁵/Ser²³⁶) S6 ribosomal protein (phospho-S6) in mandatory pre- and on-treatment biopsies and phosphorylated (Ser⁴⁷³) AKT (phospho-AKT) in platelet-rich plasma (PRP), and preliminary evaluation of antitumor activity.

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PATIENTS AND METHODS

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

Eligibility

Patients aged ≥ 18 years with histologically confirmed solid tumors and no conventional treatment option were eligible. Other inclusion criteria included: fasting serum glucose ≤ 120 mg/dl, HbA_{1c} \leq 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 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 [DL_{CO}] $\leq 50\%$), and use of anticoagulation or chronic corticosteroid.

Study Design

This was an open-label, single-centre, Phase I study utilizing 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 $\leq 50\%$ 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 pharmacodynamics. 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 15mg once-daily was chosen based on 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

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implemented to further explore safety and pharmacodynamics of dose levels 330-400mg.

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 non-hematologic 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, AST, ALT were considered DLTs except when pre-existing Grade 1 values and were <7.5x ULN due to known liver metastases. Decreases in DLco $\geq 20\%$ 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 history, physical examination, electrocardiogram, hematology, biochemistry (including fasting glucose and HbA_{1C}), and assessment of pulmonary toxicity with pulse oximetry, DL_{CO}, and high resolution CT (HRCT) of the chest. Adverse events were graded using CTCAE (Common Toxicity Criteria for Adverse Events) version 3.0. Tumor assessments were performed at the end of cycles 1 and 2, and then every 2 cycles using RECIST guidelines.¹⁰

Pharmacokinetics

Plasma levels of pictilisib were determined from samples collected on day 1: pre-dose, and 0.5, 1, 2, 3, 4, 8, 24, 48 and 72 hours post-dose; and on day 15: pre-dose, and 0.5, 1, 2, 3, 4, 8, and 24 hrs post-dose. Pharmacokinetic samples for pictilisib were analyzed using a validated HPLC/MS/MS method. Standard pharmacokinetic parameters were determined using a non-compartmental method (WinNonlin version 5.2.1; Pharsight Corporation, Mountain View, CA)

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Pharmacodynamics

Platelet-rich plasma was obtained from patients pre-dose, and at 1, 3, 8, 24 hours post-dose on days 1 and 15 of cycle 1 for analysis of phospho-AKT (Ser⁴⁷³) using an electrochemiluminescence assay (Luminex xMAP, Luminex Corp, Austin, TX). Wherever feasible, patients underwent tumor biopsies pre-treatment and 1-4 hours post-dose on day 15; samples were fixed, sectioned and stained with haematoxylin and eosin, and for phospho-S6 using anti-phospho-S6 (Ser^{235/236}) (Cell Signaling Technology Inc., Beverly, MA), or anti-phospho-AKT (Serine 473) clone D9E (Cell Signaling Technology). Plasma was obtained pre-dose and at 1 hour post-dose on cycle 1 day 1 for analysis of glucose and insulin levels at dose levels ≥ 100 mg. Whole body ¹⁸F-FDG-PET scans were performed at baseline, 1-4 hours post-dose between day 22 and the end of cycle 1 as well as between day 50 and the end of cycle 2.

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., San Diego, CA). *PIK3CA* amplification was assessed by fluorescence in-situ hybridization (FISH) and PTEN status by immunohistochemistry.¹²

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RESULTS

Patient characteristics

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

Treatment & 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 15mg. At 450mg, 2 of 3 patients experienced DLTs. The dose level of 330mg 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 330mg, 340mg and 400mg on the 28/28 schedule were assessed.

DLTs and MTD

The MTD was exceeded at 450mg once-daily (21/28 schedule) with a DLT of grade 3 rash in 2 patients. This was a maculopapular rash covering 70-80% 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 330mg 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 330mg (21/28 schedule); most adverse events 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 adverse events that occurred in $\geq 10\%$ of patients included: nausea, diarrhea, vomiting, fatigue, dysgeusia, decreased appetite and rash. In addition to the 2 DLTs of grade 3 rash at the 450mg 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 330mg once-daily

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(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 adverse events \geq grade 3 were grade 4 hyperglycemia (n=1, 130mg) and grade 3 pneumonitis (n=1, 340mg). The grade 4 hyperglycemia was transient, unaccompanied by clinically significant symptoms, signs or acidosis, and occurred in a patient with cholangiocarcinoma and previous pancreatoco-duodenectomy who started the use of low-dose prednisolone 2 days prior to the event. Grade 3 pneumonitis was observed at the end of cycle 1 in a breast cancer patient previously treated with chest radiotherapy who developed grade 1 dyspnea, reduced DL_{CO} and a ground glass appearance on HRCT; these resolved following 2 weeks of drug interruption and concomitant use of prednisolone. When pictilisib was reintroduced at 240mg, 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 1**. Under fasting conditions, pictilisib was rapidly absorbed after oral administration (median T_{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_{max} and AUC₀₋₂₄) was observed across the dose levels studied (**Figure 1**). Similar pharmacokinetic characteristics were seen on day 15. The accumulation index (AUC_{Day15}/AUC_{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 platelet rich plasma on days 1 and 15 (**Figure 2**). Inhibition up to 90% of phospho-

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AKT level in platelet rich plasma was demonstrated 1 to 3 hours post-dose at the RP2D; this effect was sustained (50% of baseline) at 24 hours post-dose. Reductions in S6 and AKT phosphorylation in tumor biopsies was greatest at the highest exposure level of pictilisib (AUC >20uM.hr on day 15), with all three patients in this cohort showing $\geq 75\%$ decrease in S6 phosphorylation and 2 patients also exhibiting a 100% decrease in AKT phosphorylation (**Figure 3**). Following pictilisib treatment at 330mg 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 pre-treatment level) in plasma insulin and glucose levels of 3.58 (95%CI: 2.33-5.49) and 1.18 (95%CI: 1.10-1.26), respectively (**Supplementary figure 1**). ^{18}F -FDG-PET imaging showed a reduction from baseline of ^{18}F -FDG-tracer uptake at dose levels $\geq 45\text{mg}$ with an overall median change in maximum standardized uptake value (SUV_{max}) of -13% (range -47 to 22) (**Supplementary figure 2**). Seven of 32 evaluable patients (22%) achieved a metabolic partial response by EORTC-PET criteria ($>25\%$ reduction in mean SUV_{max} without new lesions) on ^{18}F -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 330mg 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 4 copies of *PIK3CA*) and loss of PTEN achieved radiological stable disease for 4 months with GCIG-CA125 partial response¹³ (**Supplementary Figure 3**) associated with 36% reduction in SUV_{max} on ^{18}F -FDG-PET and 56% 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 450mg once-daily, and this was associated with pharmacodynamic changes of 47% reduction in SUV_{max} on ^{18}F -FDG-PET and 75% reduction in tumor phospho-S6 expression.

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

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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 330mg continuous once-daily dosing. Dose limiting toxicity was grade 3 maculopapular rash occurring in 2 of 3 patients treated at 450mg/day and 1 of 7 patients at 330mg/day. Our data indicate that the severity of the rash was not clearly related to higher exposures of pictilisib (**Supplementary Figure 4**) and resolved with discontinuation of pictilisib. The rash was maculopapular but not acneiform 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} Our study design incorporated the use of the pharmacological audit trail guidelines using appropriate pharmacokinetic-pharmacodynamic biomarkers. The audit trail has been used by both academia¹⁹ and industry²⁰ as a guideline to help answer critical 'go/ no-go' decisions based on scientifically measurable and rigorous end points. This audit trail has utility in providing broad guidance of the drug development process, 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 6uM*hr (3000 ng*hr/ml) in order to achieve ≥90% tumor growth inhibition; this target AUC was achieved in most patients treated at doses >80mg following one week of consecutive dosing and support the view that

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pictilisib is associated with biologically meaningful activity at these dose levels and exposures, especially at the RP2D. Based on these preclinical data, we additionally postulated that $\geq 90\%$ 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 platelet rich plasma at up to 3 hours post-dose at the RP2D. Whilst 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 $> 20\mu\text{M}/\text{hr}$) 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 platelet-rich plasma and is possibly related to different assay conditions which likely favour greater inhibition in the latter, together with disparities in drug concentrations between normal and tumor tissues due to likely differences in tissue architecture and haemodynamics. 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, inter-patient variation due to host pharmacogenomic variation, intra- and inter-patient tumour heterogeneity, and differences in analytical sensitivity/methodology in platelet-rich plasma versus tumour biopsies. All of these are likely to be important, highlighting the importance of evaluating different pharmacodynamic biomarkers to increase confidence in the overall pharmacological effects of a drug within the audit trail framework, as we have done here.

To this end, at the RP2D of 330mg we demonstrate multimodal pharmacodynamic evidence of target modulation including the reduction of ^{18}F -FDG-PET tracer uptake, inhibition of phospho-AKT in platelet-rich plasma 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 $\geq 100\text{mg}$.

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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 extrahepatic cholangiocarcinoma who had undergone a previous pancreatic resection and was commenced on a corticosteroid 2 days prior to the adverse event. We confirmed target and pathway modulation at the RP2D with observations of convincing pharmacodynamic changes in phospho-S6 and ¹⁸F-FDG-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 BKM120 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 BKM120 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 BKM120. The other pan-Class I PI3K inhibitors which have undergone Phase I clinical evaluation include SAR245408 and the irreversible wortmanin derivative PX-866.^{29,30} Both drugs were associated with minimal hyperglycaemia 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 $\geq 90\%$ inhibition of AKT phosphorylation is needed to inhibit cancer cell proliferation reveals potentially important differences between pictilisib and the other drugs in this class,

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with SAR245048 reporting a 40-80% 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, none 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} Additionally, 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, whilst we postulate that ~90% inhibition of AKT phosphorylation for several hours is needed to inhibit cancer cell proliferation based on our preclinical tumor phosphorylation data⁹ 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 radiological 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 signalling for their

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proliferation, they are likely to have a degree of co-dependence 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 signalling involves the PI3K pathway.³³

An increasing understanding of potential resistance mechanisms²¹ and promising preclinical data from combinatorial use of pictilisib³⁴⁻³⁶ 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 330mg 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.

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Figure Legend

Figure 1. Pharmacokinetic profile of pictilisib.

(A) Plasma concentration versus time profile for all dose levels.

(B) Maximum plasma concentration (C_{max}) versus dose

(C) area under the curve (AUC) versus dose. Solid and dashed lines represent the fitted regression lines for days 1 and 15, respectively

Figure 2:

(A) Percentage change in levels of phosphorylated AKT (pAKT) in platelet-rich plasma (PRP) and plasma level of pictilisib up to 24 hours following administration of pictilisib (at RP2D of 330mg) on days 1 and 15 of cycle 1 (n=8).

(B) Pictilisib concentration-dependent inhibition of phosphorylated AKT (pAKT) in platelet-rich plasma (PRP) following systemic exposure to pictilisib. Data represent available concentration-matched PRP pAKT inhibition from duration of Phase I investigation

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 (hr* μ M) 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) Percent 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 >60mg of pictilisib with the exception of patient 50008 who received 45 mg.

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Table 1. Demographics and clinical characteristics of all treated patients.

Characteristic	All patients	
	No. of patients	%
Sex		
Male	30	50
Female	30	50
Age, years		
Median	59	
Range	27-77	
ECOG performance status at screening		
0	28	47
1	32	53
Primary cancer diagnosis		
Colorectal	16	27
Breast	9	15
Soft tissue sarcoma	7	12
Melanoma	5	8
Ovarian	3	5
Gastric	2	3
Prostate	2	3
Others	16	27
No. of prior lines of systemic therapies		
Median	3	
Range	0 - 16	

Abbreviation: ECOG: Eastern Cooperative Oncology Group

Table 2. Summary of adverse events (AEs).

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 ≥ 3 are presented in separate columns for each dose-schedule only when observed.

Dose level (mg)	15	30	45	60	80	100	130		180	245	330		450		330		340		400	All	
Schedule	21/28	21/28	21/28	21/28	21/28	21/28	21/28		21/28	21/28	21/28		21/28		28/28		28/28		28/28	21 or 28/28	
No. of patients	4	3	4	4	3	5	3		3	3	7		3		10		7		1	60	
Toxicity grade	All	All	All	All	All	All	≥ 3	All	All	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3	All	All	≥ 3	All
Any adverse event	2	1	2	2	3	3	1	1	2	3	2	7	2	3	2	10	2	6	1	9	46
Gastrointestinal																					
Nausea	1	0	0	2	1	3	0	0	0	1	0	4	0	2	0	9	0	4	1	0	28
Diarrhea	0	0	2	1	1	1	0	0	1	2	0	3	0	0	1	7	0	1	0	1	19
Vomiting	0	0	0	2	1	0	0	0	0	0	0	3	0	2	0	3	0	4	0	0	15
Decreased appetite	0	0	0	0	0	0	0	0	1	1	0	2	0	1	0	6	0	3	0	0	14
Dysgeusia	1	0	1	0	1	0	0	0	1	0	0	1	0	1	0	5	0	2	0	0	13
Skin & mucosa																					
Rash*	0	0	0	0	0	0	0	0	1	0	1	4	2	3	2	4	0	1	1	5	14
Stomatitis**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	2	1	0	7
Xeroderma	0	0	0	0	0	0	0	0	0	1	0	2	0	1	1	4	0	0	0	1	8
Constitutional																					
Fatigue	0	0	0	0	2	1	0	0	1	1	0	4	0	2	0	6	0	3	1	0	21

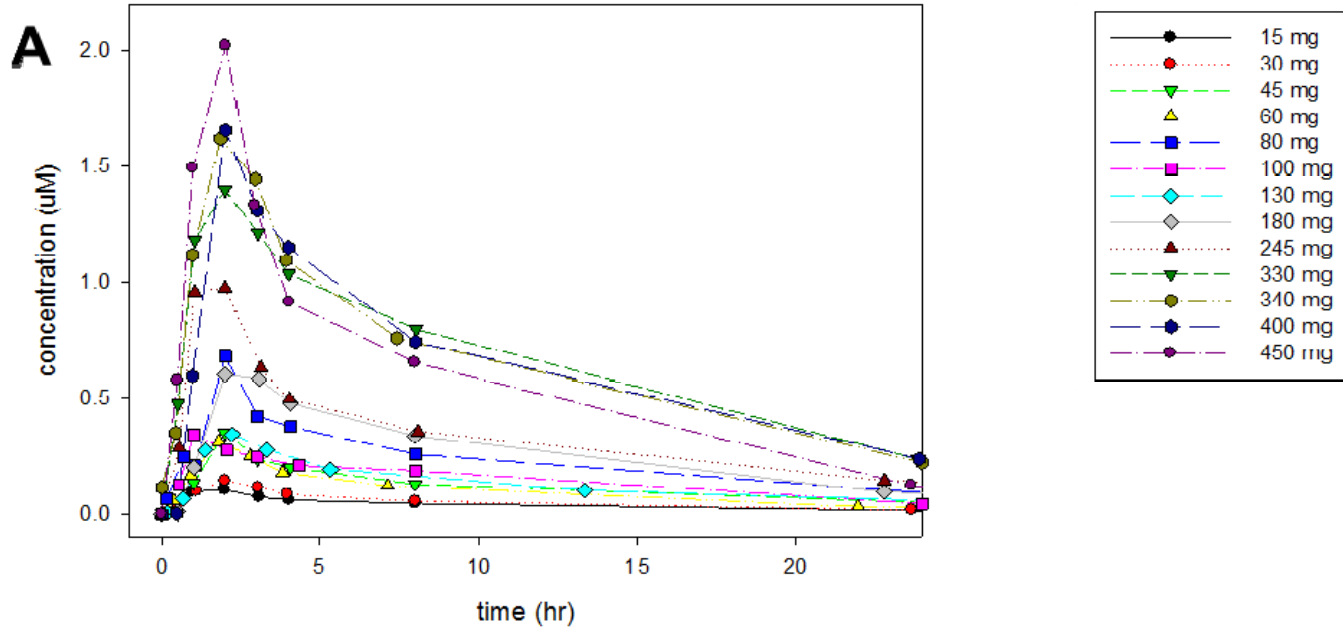
*Including preferred terms of rash, rash maculo-papular, rash macular, rash pruritic, rash erythematous, and rash papular.

** Including preferred terms of stomatitis, mucosal inflammation, mouth ulceration.

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

Day	No. of patients	Elimination half-life (hr) Geometric mean	T _{max} (hr)		C _{max} (μM) Geometric mean	AUC 0-24 (hr*μM) Geometric mean
			Median	Range		
Day 1						
15 mg QD	4	19.2	2	1-2	0.112	0.978
30 mg QD	3	24.1	2	1-2	0.144	1.18
45 mg QD	4	19.5	2	2	0.362	2.77
60 mg QD	4	18.8	2	1-2	0.242	2.02
80 mg QD	3	20.1	2	1-2	0.632	5.45
100 mg QD	5	14.6	2	1-8	0.362	3.19
130 mg QD	3	13.1	2	1-2.5	0.359	2.99
180 mg QD	3	17.1	2	2-3	0.611	5.95
245 mg QD	3	16.8	2	1-2	0.994	8.18
330 mg QD	17	15.7	2	0.5-8	1.52	14.4
340 mg QD	7	20.9	2	1-4	1.68	14.9
400 mg QD	1	14.8	2	2	1.65	15.6
450 mg QD	3	15.0	2	1-2	1.95	13.9
Day 15						
15 mg QD	4		1.5	1-4	0.116	1.35
30 mg QD	3		1	0.5-4	0.179	1.90
45 mg QD	4		2	2	0.436	4.09
60 mg QD	3		3	2-4	0.27	2.78
80 mg QD	3		3	3-4	0.779	9.86
100 mg QD	3		2	1-3	0.751	5.64
130 mg QD	3		1	1-2	0.457	5.03
180 mg QD	3		1	1-3	0.783	8.25
245 mg QD	3		1	1-3	1.37	11.3
330 mg QD	17		3	0-8	2.07	22.8
340 mg QD	6		1	1-4	1.95	16.5
450 mg QD	3		2	1-3	2.64	23.5

Figure 1



Pictisilib Cmax versus Dose

Pictisilib AUC versus Dose

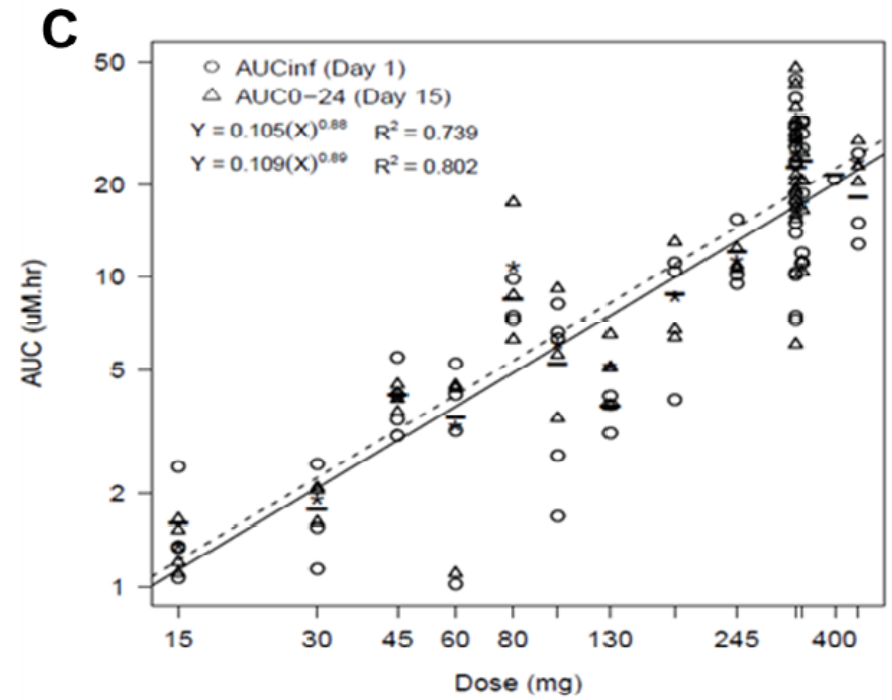
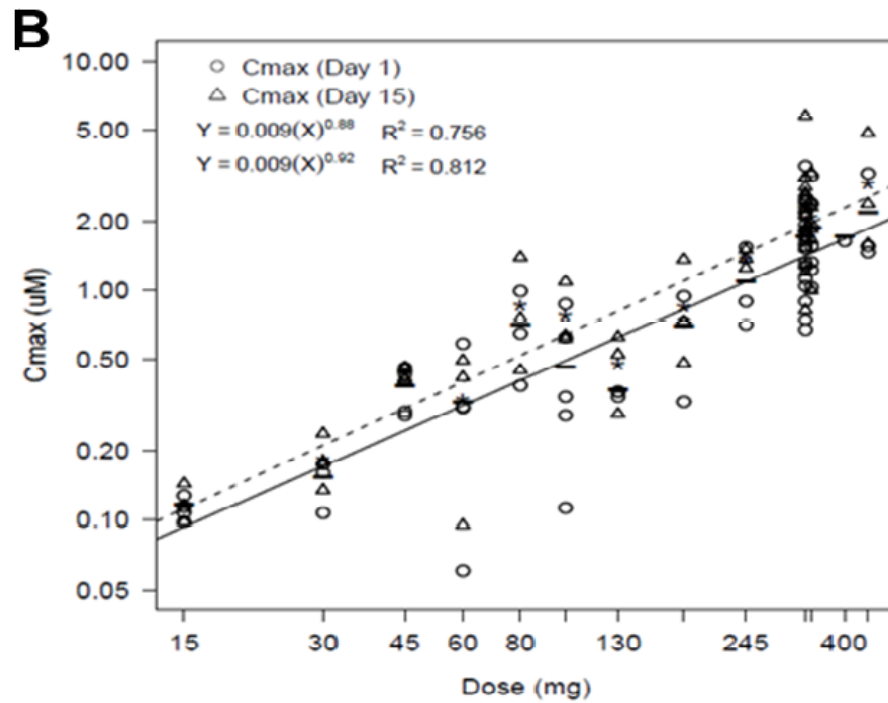


Figure 2

