First-in-Human Pharmacokinetic and Pharmacodynamic Study of the Dual m-TORC 1/2 Inhibitor AZD2014

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Abstract

Purpose: AZD2014 is a novel, oral, m-TORC 1/2 inhibitor that has shown in vitro and in vivo efficacy across a range of preclinical human cancer models.

Experimental Design: A rolling six-dose escalation was performed to define an MTD (part A), and at MTD a further cohort of patients was treated to further characterize toxicities and perform pre- and posttreatment biopsies (part B). AZD2014 was administered orally twice a day continuously. Flow cytometry, ELISA, and immunohistochemistry were used to quantify pharmacodynamic biomarkers. Pharmacokinetic analysis was carried out by mass spectrometry.

Results: A total of 56 patients were treated across a dose range of 25 to 100 mg. The MTD was 50 mg twice daily. The dose-limiting toxicities were fatigue and mucositis. At the MTD, the most common adverse events (AE) were fatigue (78%), nausea (51%), and mucositis (49%), but these were equal to or greater than grade 3 in only 5% of patients. Drug levels achieved at the MTD (AUC0-246 6868 ng·h/mL, Cmax 1,664 ng/mL) were consistent with activity in preclinical models. A reduction in p-S6 levels and Ki67 staining was observed in 8 of 8 and 5 of 9 evaluable paired biopsy samples. Partial responses were seen in a patient with pancreatic cancer and a patient with breast cancer, who were found to have a PDGFR and ERBB2 mutation, respectively.

Conclusions: The recommended phase II dose for further evaluation of AZD2014 is 50 mg twice daily, and at this dose it has been possible to demonstrate pharmacologically relevant plasma concentrations, target inhibition in tumor, and clinical responses. Clin Cancer Res; 21(15); 3412–9. ©2015 AACR.

Introduction

The PI3K pathway is deregulated in more than 50% of all cancers. Mechanisms of deregulation include activating mutations in PIK3CA and AKT and loss of function of tumor suppressor genes such as PTEN (1). m-TOR consists of two essential complexes, TORC1 and TORC2 and is a crucial node in the PI3K signaling network (2). Inhibition of TORC1 could lead to inhibition of cell growth and metabolism via inactivation of downstream targets such as p-S6, p-4EBP1, and p-GSK3B (3). In addition, m-TORC2 is critical to AKT signaling (4).

Torvast (hmm)

Drugs such as sirolimus, temsirolimus, and everolimus are allosteric inhibitors of m-TOR. Sirolimus is licensed for use in transplant medicine (5) and other allosteric m-TOR inhibitors such as temsirolimus and everolimus have been licensed for use in a variety of cancers (6–10).

Preclinical studies have suggested that allosteric inhibition of m-TOR by a rapalog inhibits only m-TORC1 and leads to an increase in phosphorylation of AKT due to feedback loops (11) and continued activity of m-TORC2 (12). This has been confirmed clinically in posttreatment biopsy samples in patients treated with rapalogs (13, 14). The activation of AKT is hypothesized to be a mechanism of resistance to these agents.

AZD2014 is a rationally designed ATP competitive m-TORC1/2 inhibitor with an IC50 of 2.81 nmol/L and has shown preclinical activity across a range of in vitro and in vivo preclinical models (15). Preclinical experiments showed a 95% protein binding in human plasma and bioavailability of 29%. [14C]-AZD2014 was extensively metabolized following a single dose in rats with N-hydroxymethyl and desmethyl components accounting for 25% and 10% of parent AUC in plasma, respectively. Urinary and fecal excretion in this model accounted for approximately 2% and 85% of dose radioactivity, respectively. In human hepatocytes and heterologously expressed CYP isozymes, AZD2014 was primarily metabolized by CYP3A5 and CYP2C8 with some contribution from CYP3A4.

The primary aim of this first-in-human study was to investigate the safety and tolerability of AZD2014. The secondary aims...
Phase I Study of AZD2014

Translational Relevance

The m-TOR consists of two essential complexes, m-TORC1 and m-TORC2. Conventional, allosteric m-TOR inhibitors inhibit m-TORC1 but not m-TORC2 function. This may lead to feedback loops activating PI3K via IRS1 and continued phosphorylation of AKT at Ser473 by uninhibited m-TORC2. AZD2014 is a dual m-TORC1 and m-TORC2 kinase inhibitor. This study identified the maximally tolerated dose and schedule for AZD2014 as 50 mg twice daily. It was possible to demonstrate m-TORC1 inhibition in normal tissue and tumor as evidenced by reduction in the phosphorylation of 4EBP1 and S6, respectively, and importantly, m-TORC2 inhibition (reduction in p-AKT) in normal tissue and tumor. Furthermore, there was evidence of reduced metabolism (reduction in SUVmax in FDG PET scans). Other key findings included reduction in proliferation (Ki67 reduction in posttreatment biopsies and two partial responses). The dual m-TORC1/2 inhibitor AZD2014 should be investigated further.

Materials and Methods

This study used a rolling six dose-escalation design during the dose-escalation phase. At the recommended phase II dose, an expansion cohort to further characterize tolerability, PK and PD profiles, including pre- and posttreatment biopsies in a subset of patients, was instituted. Patients were recruited at the Royal Marsden and Christie Hospital NHS Foundation Trust in the UK following ethics committee approvals. Patients with advanced solid tumors who had already received standard-of-care treatment and had adequate organ function were eligible for the study. There was no difference between the eligibility criteria between dose-escalation and -expansion cohorts of the study. Following informed, written consent, patients received a single run-in dose of AZD2014 in a liquid (solution) formulation. During the clinical trial, AZD2014 was administered orally, with patients fasting (except for water) for 2 hours before dosing and 1 hour after dosing. Dose-limiting toxicities (DLT) were evaluated during the run-in dose and the first 21 days of continuous dosing. Common toxicity criteria (CTC) grade 4 hematologic toxicity or any grade 3 or grade 4 non-hematologic toxicity was considered a DLT, with the exception of alopecia, inadequately treated grade 3 or 4 nausea and vomiting or isolated laboratory change without any clinical significance. Concomitant exposure to potent and moderate inhibitors and inducers of CYP3A4/5 and CYP2C8 were not permitted. Details of drugs and washout periods are mentioned in the Supplementary Data. Blood was drawn for PK and PD analysis over 24 hours. The PD samples for the run-in single dose were drawn at pre dose, 2 hours, 6 to 8 hours and 24 hours after dose. The patient then commenced continuous dosing of AZD2014 twice a day, 3 to 7 days later. The length of a cycle was 28 days. Adverse events were recorded using National Cancer Institute Common Toxicity Criteria 3.1. On days 15, 21, and 28, blood was collected over 12 hours to assess steady state PK parameters. Further exposures in patients following a 50 mg starting dose were expected to be consistent with the exposures that caused monitorable and reversible effects in the toxicology studies, with the exception of the testicular changes and partial recovery in bone marrow. Finally, AZD2014 was predicted to have a modest half-life of 4 hours, it was not anticipated that the subsequent repeat dosing phase at 50 mg twice daily (100-mg total-daily dose) would show significant accumulation. Thus, the proposed starting dose was 50 mg twice daily after the washout period.

TORC1/2 inhibitors that are currently under phase 1 evaluation or have completed phase I evaluation include AZD2014 (15), INK-128/MLN-128 (16, 17), DS-3078a (18), OSI-027 (19, 20), and AZD8055 (21, 22).

Results

A total of 56 patients across a dose range of 25 to 100 mg twice daily were treated on this phase I study (n = 23 in part A and n = 33 in part B). Nineteen male and 37 female patients included determining the pharmacokinetic (PK) profile, confirming target engagement by studying changes in pharmacodynamic (PD), proof-of-mechanism (POM), and proof-of-concept (POC) biomarkers in addition to documenting preliminary clinical activity.

The highest severely non-toxic dose in dogs was not established. The highest dose administered to dogs in a 1 month toxicology study was 5 mg/kg/d. The human equivalent dose of one sixth this dose level in a 60 kg human was 27 mg/d. However, the International Conference on Harmonization (ICH) S9 guideline recommended that the starting dose should be “a pharmacologically active dose that is reasonably safe to use.” Using physiologically based pharmacokinetic modeling, the IC50 value demonstrated in the U87-MG mouse xenograft model, and allowing for differences in plasma protein binding in man and mouse, suggests that a single dose of 50 mg would give plasma concentrations close to the IC50 value at maximum concentration (Cmax) in patients. Further exposures in patients following a 50 mg starting dose were expected to be consistent with the exposures that caused monitorable and reversible effects in the toxicology studies, with the exception of the testicular changes and partial recovery in bone marrow. Finally, AZD2014 was predicted to have a modest half-life of 4 hours, it was not anticipated that the subsequent repeat dosing phase at 50 mg twice daily (100-mg total-daily dose) would show significant accumulation. Thus, the proposed starting dose was 50 mg twice daily after the washout period.

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This study used a rolling six dose-escalation design during the dose-escalation phase. At the recommended phase II dose, an expansion cohort to further characterize tolerability, PK and PD...
were treated, and the median age was 59 (range, 33–76). The most common tumor type recruited to the study was breast cancer (15/56). Details of the demographic profile, ECOG performance status, and tumor types treated are listed in Supplementary Table S1.

### Dose escalation

The starting dose was 50 mg twice daily and, as no DLTs were seen in 6 patients, the dose was doubled to 100 mg twice daily. As there were four of four DLTs, an intermediate dose of 70 mg twice daily was explored. A total of 5 patients were dosed in this cohort, but one patient withdrew consent before becoming evaluable for the dose decision. A further two of four evaluable patients had a DLT at 70 mg twice daily, and thus the remaining two patients who had consented to this cohort received 50 mg twice daily. Thus, 50 mg twice daily was considered the maximally tolerated dose. Fifty mg twice daily was declared the recommended phase II dose (RP2D) and a further 33 patients were treated to further characterize PK and PD profiles over a range of doses of AZD2014 that could be used in the future. Subsequently, 50 mg twice daily was declared the recommended phase II dose (RP2D) and a further 33 patients were treated to further evaluate toxicity, PK and PD.

### Dose-limiting toxicities

At the dose of 100 mg twice daily, DLTs were seen in four of four patients. In all instances these were CTC grade 2 or 3 fatigue, occurring within the first week of treatment. The fatigue was reversible on discontinuation of the drug. At a dose of 70 mg twice daily, DLTs were seen in two of four evaluable patients treated, with grade 3 fatigue and grade 3 mucositis in one patient and grade 3 fatigue in another. All events were reversible on cessation of AZD2014.

### Adverse events

The adverse events (AE) that occurred in >15% of patients at the RP2D of 50 mg twice daily are listed in Table 1. All AEs reported in this paragraph pertain to patients treated at 50 mg twice daily on parts A and B (Table 1). Fatigue was the most commonly seen AE in 32 of 41 (78%) patients; however, only 2 of 41 (5%) were grade 3 or higher and this was reversible on discontinuation of the drug. Gastrointestinal symptoms such as nausea, mucositis, diarrhea, and vomiting were seen in 21 of 41 (51%), 20 of 41 (49%), 17 of 41 (42%), and 12 of 41 (29%), respectively; however, less than 5% of these AEs were grade 3 or 4. Nausea and vomiting were well controlled by antiemetics, such as domperidone, if necessary, and the grade 1 and 2 diarrhea did not consistently require treatment. Mucositis was grade 1 and 2 in most instances and patients responded to mouth-washes and did not require dose interruptions due to it. A predominantly maculopapular rash was observed in 17 of 41 (42%) of patients and less than 5% of these were grade 3 or higher. Lower respiratory tract infections were seen in 7 of 41 (17%), and it was grade 3 in only 1 of 41 (2%). Interestingly, no patients were diagnosed with pneumonitis. The most common laboratory abnormality was anemia, with 7 of 41 (17%) having recorded grade 1 and 2 anemia; given the advanced cancer and degrees of comorbidities in these patients, it was difficult to...
attribute this specifically to AZD2014. Hyperglycemia was seen in 5 of 41 (12%), 0 of 5 (0%), and 2 of 4 (50%) of patients treated at 50, 70, and 100 mg twice daily, respectively. At the RP2D of 50 mg twice daily, no grade 3 or 4 hyperglycemia was seen. Furthermore, no grade 3 or above hypercholesterolemia or triglyceridemia was seen in this cohort. ECG monitoring revealed an increase in QT corrected Bazett’s formula (QTCB) and a reduction in QTCB by 30 to 60 msec in 3 of 41 (7%) and 5 of 41 (12%), respectively, thus showing no defined trend for increase or decrease in QTCB. Because of the modest number of patients treated across different dose levels and the standard timing of ECG done, a formally powered testing of the relationship of plasma concentrations to QTCB has not been done. At the RP2D of 50 mg twice daily, 10 of 41 (24.4%) had an interruption and 1 of 41 (2.4%) had a dose reduction due to an AE.

Pharmacokinetics
Following oral administration, AZD2014 was rapidly absorbed, with median time to peak following a single dose between 0.5 and 1 hour across the 25 to 100 mg dose range. Terminal elimination half-life was approximately 3 hours. Geomean exposure (AUC and C_{\text{max}}) increased greater than proportionally with increasing dose and interpatient variability was seen with exposures overlapping across the dose range (Fig. 1A and B and Table 2). At dose of 50 mg twice daily (n = 27), the C_{\text{mean}}

Table 2. Pharmacokinetic profile of AZD2014

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>25 mg</th>
<th>50 mg</th>
<th>70 mg</th>
<th>100 mg</th>
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<tr>
<td>AUC (ng h/mL)</td>
<td>G_{\text{mean}}</td>
<td>1,640</td>
<td>4,015</td>
<td>8,967</td>
<td>9,671</td>
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<tr>
<td></td>
<td>CV (%)</td>
<td>52</td>
<td>78</td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>883-2,730</td>
<td>453-12,600</td>
<td>6,010-14,200</td>
<td>4,770-16,100</td>
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<tr>
<td>C_{\text{max}} (ng/mL)</td>
<td>G_{\text{mean}}</td>
<td>435</td>
<td>1,151</td>
<td>2,382</td>
<td>2,787</td>
</tr>
<tr>
<td></td>
<td>CV (%)</td>
<td>42</td>
<td>57</td>
<td>39</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>221-681</td>
<td>234-2,840</td>
<td>1,440-3,690</td>
<td>1,410-5,050</td>
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<tr>
<td>t_{1/2} (h)</td>
<td>Mean</td>
<td>2.96</td>
<td>2.48</td>
<td>3.11</td>
<td>3.23</td>
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<tr>
<td></td>
<td>SD</td>
<td>2.13</td>
<td>1.42</td>
<td>1.99</td>
<td>2.47</td>
</tr>
<tr>
<td></td>
<td>Range</td>
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<td>0.90-8.04</td>
<td>1.35-5.98</td>
<td>0.82-6.49</td>
</tr>
<tr>
<td>Steady state</td>
<td>N = 6</td>
<td>N = 27</td>
<td>N = 5</td>
<td>N = 4</td>
<td></td>
</tr>
<tr>
<td>AUC_{ss} (ng h/mL)</td>
<td>G_{\text{mean}}</td>
<td>2,984</td>
<td>6,686</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td></td>
<td>CV (%)</td>
<td>79</td>
<td>79</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td></td>
<td>Range</td>
<td>1,000-4,560</td>
<td>1,280-47,800</td>
<td>7,500-22,500</td>
<td>NC</td>
</tr>
<tr>
<td>C_{\text{max, ss}} (ng/mL)</td>
<td>G_{\text{mean}}</td>
<td>747</td>
<td>1,664</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td></td>
<td>CV (%)</td>
<td>72</td>
<td>48</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td></td>
<td>Range</td>
<td>227-1,450</td>
<td>657-6,410</td>
<td>1,500-3,870</td>
<td>NC</td>
</tr>
<tr>
<td>t_{1/2, ss} (h)</td>
<td>Mean</td>
<td>2.89</td>
<td>3.01</td>
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<tr>
<td></td>
<td>SD</td>
<td>1.02</td>
<td>0.96</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td></td>
<td>Range</td>
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<td>1.18-4.80</td>
<td>3.63-4.23</td>
<td>NC</td>
</tr>
</tbody>
</table>

NOTE: The pharmacokinetic parameters across the dose range of 25 to 100 mg twice daily are shown. Abbreviations: t_{1/2}, half-life; a subscript of ss, steady state.
Pharmacodynamics

In samples of patients treated at 50 mg, phosphorylation of 4E-BP1 was reduced in PBMCs to approximately −45% and −41% of baseline at 2 and 6 to 8 hours following a single dose of AZD2014, respectively. Phosphorylation of AKT (S473) in PRP was reduced to −62% and −37% of baseline at 2 and 6 to 8 hrs, respectively. These data indicate inhibition of m-TORC1 and m-TORC2 (Fig. 2A and B). Changes in phosphorylation of 4EBP-1 and AKT were seen at dose levels of 50 to 70 mg and, importantly, changes in phosphorylation of AKT were seen at doses below the MTD (25 mg cohort; Fig. 2C and D). POM PD biomarkers such as p-S6, p-4EBP1 (m-TORC1), and p-AKT (m-TORC2), and POC biomarkers (Ki67) were assessed in pre- and posttreatment biopsies and showed evidence of target inhibition (Fig. 3A–E). Of note, 11 patients in part B (50 mg twice daily) had paired FDG PET scans, 8 of 11 patients showed a reduction of SUVmax with 3 of 11 attaining a PR (30% reduction in SUVmax; Fig. 3F).

Efficacy

There were two PRs in the study. The first was a patient with acinar pancreatic cancer who had previously responded to two lines of gemcitabine-based treatment. The patient had a maintained PR and was on treatment for six cycles. The patient was found to have KRAS, PDGFRA, APC, ERBB4, KIT, and FBXW7 mutations. The second patient to respond was a patient with estrogen receptor (ER)–positive breast cancer who had six prior lines of chemotherapy and one line of hormonal treatment for her metastatic breast cancer. She received AZD2014 treatment for four cycles. Her tumor had a mutation in HRAS, NRAS, TP53, and ERBB2 (Fig. 4). In addition, 2 patients, one each with ovarian and...
endometrial cancer, had prolonged stable disease and remained on treatment for more than 1 year.

Discussion

The toxicity profile of AZD2014 had similarities with other TORC 1/2 inhibitors and more generally with allosteric m-TOR inhibitors and these were rash, mucositis, and fatigue (17, 18, 20, 22–25). At 50-mg twice-daily continuous dosing AZD2014 was well tolerated. Interestingly, in this present study there were no instances of grade 3 and 4 hyperglycemia that had been seen in clinical trials of m-TOR inhibitors (23–25). Patients with diabetes were excluded and all patients had to have a fasting glucose of less than 126 mg/dL (7 mmol/L). Given previous experience of hyperglycemia seen with m-TOR inhibitors, it is not known how AZD2014 would affect glycemic control of patients with type I or type II diabetes. Renal (20), hepatic (22), and left ventricular dysfunction (20) seen with other m-TORC 1/2 inhibitors were not seen in patients treated with AZD2014. Of note, there were no instances of pneumonitis, seen more generally across m-TOR inhibitors (7, 9, 26) in this study. The tolerability of once a day AZD2014 given continuously and twice a day dosing given intermittently (2 days every week) has been subsequently studied and the results will be presented separately when the studies are complete.

The pharmacokinetic profile of AZD2014 showed rapid absorption. Although the elimination half-life of AZD2014 was approximately 3 hours and is shorter than allosteric m-TOR inhibitors such as everolimus, temsirolimus, or ridaforolimus, which have half-lives of approximately 24 hours or longer (23–25), it allows twice-daily dosing and the possibility of more flexible intermittent dosing when used in combination with other anticancer drugs such as cytotoxic chemotherapy or other targeted agents. There are multiple reasons that could give rise to the interindividual pharmacokinetic variability. Preliminary analysis of some of the potential reasons have been investigated and include differences in the percentage of drug bound to protein between patients, but a preliminary investigation using measured AZD2014-free plasma concentrations instead of the usual way of using total plasma concentrations to determine PK parameters...
found that they were equally variable and the relationships with PD no better. It is also not likely to be formulation performance because the drug is a solution, and therefore does not require a dissolution step before being absorbed. It could be hypothesized that differences in CYP metabolizing enzymes and/or transporter enzymes may affect ability to clear and/or distribute the drug in and out of tissue and affect PK variability. The data in this publication relate to the liquid formulation of AZD2014. Further studies have been conducted to evaluate the PK of the tablet formulation and the effect of food on exposure to AZD2014 and found that they were equally variable and the relationships with PD no better. It is also not likely to be formulation performance because the drug is a solution, and therefore does not require a dissolution step before being absorbed. It could be hypothesized that differences in CYP metabolizing enzymes and/or transporter enzymes may affect ability to clear and/or distribute the drug in and out of tissue and affect PK variability. The data in this publication relate to the liquid formulation of AZD2014. Further studies have been conducted to evaluate the PK of the tablet formulation and the effect of food on exposure to AZD2014 and will be submitted for publication once complete. AZD2014 produces >70% total growth inhibition (TGI) at 4,500 nmol/L·h free weekly AUC, and ≥100% TGI at 17,000 nmol/L·h in MCF7 xenograft models and human PK achieved in this trial was in the range that would be efficacious in this model (on average the 50-mg twice-daily solution dose achieved a free weekly AUC of 11,050 nmol/L·h, with the vast majority of patients achieving more than 4,500 nmol/L·h). To provide the comparison of the clinical exposure with the preclinical data, the measured clinical exposure of AZD2014 reported in ng·h/mL of total (bound and unbound) drug was converted to nmol/L·h of free (unbound) drug using the molecular weight of AZD2014 (462.56 g/mol) and the measured human plasma protein binding of 5.47% free (unbound) drug.

The PD profile of AZD2014 showed target engagement in normal tissue. POM biomarkers of m-TORC1 and m-TORC2 inhibition, that is, reduction in levels of p-4EBP1 in PBMCs and p-AKT in PRP, respectively, were seen at 2 to 8 hours but recovered at 24 hours following a single dose of AZD2014, supporting a twice a day schedule. Importantly, reduction in p-AKT was seen at the 25 mg cohort, suggesting PD activity at this dose if dose reductions are necessary in future trials. Substantial interindividual variability was seen in the PK profile and this is likely to influence the PD profile seen in this study. Further studies evaluating PK, PD, and PK–PD profiles of the tablet formulation that will be taken forward into later phase clinical trials are warranted. Crucially, it was possible to demonstrate reduction of p-S6 (m-TORC1 inhibition) in all evaluable posttreatment biopsies. Reduction in p-AKT levels was seen in three of four assessable posttreatment biopsies, and no instances of induction of phosphorylation of AKT were seen in these samples. This is in contrast with increase in phosphorylation of AKT due to a feedback loop via IRS1, which is a possible mechanism of resistance seen when tumor tissue is exposed to allosteric m-TOR inhibitors (13, 14). In addition to the POM PD biomarkers discussed above, more distal, POC biomarkers such as reduction of proliferation (Ki67) and reduction in metabolism (FDG-PET scans) also support evidence of target inhibition in tumor. Overall PD biomarkers have been informative to the trial; normal tissue has shown a PD engagement at 25 to 100 mg twice daily, which will be taken into consideration while designing intermittent schedules and combination studies with dosing a higher or lower doses of AZD2014.

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Single-agent efficacy was seen in a population of heavily pre-treated solid tumors. Interestingly, both patients who responded did not have a PIK3CA or AKT mutation; however, the tumors did have activating mutations upstream of m-TORC1/2.

The recommended phase II dose of AZD2014 took into consideration toxicity, PK and PD findings. At this dose, the drug was well tolerated, exhibited a favorable PK profile, showed robust evidence of target engagement and showed evidence of clinical efficacy as a single agent. PD studies indicated target engagement in normal tissue in the range 25 to 100 mg; thus, these doses could be explored in future intermittent schedules or taken into consideration if dose reductions are necessary. The clinical efficacy of
AZD2014 as a single agent and in combination with other anticancer agents should be explored in clinical trials.

Disclosure of Potential Conflicts of Interest

M. Puglisi is an employee of MSD. W. Burke holds ownership interest (including patents) in AstraZeneca. J. S. de Bono is a consultant/advisory board member for AstraZeneca. M. Ranson reports receiving a commercial research grant from and is a consultant/advisory board member for AstraZeneca. U. Banerji reports receiving a commercial research grant from AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: S. Green, J. S. de Bono, M. Ranson, U. Banerji Development of methodology: E. Dean, M. Puglisi, A. Greystoke, G. Bigley, C. Womack, J. S. de Bono Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Basu, E. Dean, M. Puglisi, A. Greystoke, M. Ong, M. Cavallin, C. Womack, E. A. Harrington, J. S. de Bono, M. Ranson, U. Banerji Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B. Basu, E. Dean, M. Ong, W. Burke, M. Cavallin, C. Womack, E. A. Harrington, J. S. de Bono, M. Ranson, U. Banerji Writing, review, and/or revision of the manuscript: E. Dean, M. Puglisi, A. Greystoke, M. Ong, W. Burke, M. Cavallin, G. Bigley, C. Womack, E. A. Harrington, E. Oelmann, J. S. de Bono, M. Ranson, U. Banerji Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Dean, M. Puglisi, G. Bigley, J. S. de Bono, M. Ranson Study supervision: B. Basu, E. Dean, J. S. de Bono, M. Ranson, U. Banerji Other (project leader, AstraZeneca): S. Green

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References

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