Dose-finding quantitative FDG PET imaging study with the oral pan-AKT inhibitor GSK2141795 in patients with gynecological malignancies

Hatice Gungor¹, Azeem Saleem², Syed Babar³, Roberto Dina⁴, Mona A. El-Bahrawy⁴, Nona Rama¹, Michele Chen¹, Emily Pickford¹, Roshan Agarwal¹, Sarah Blagden¹, Sabin Carme⁵, Cristian Salinas², Sam Madison⁶, Elizabeth Krachey⁶, Ademi Santiago-Walker⁶, Deborah A. Smith⁶, Shannon R. Morris⁶, Euan A. Stronach¹, Hani Gabra¹

¹Ovarian Cancer Action Research Centre, Dept. of Surgery and Cancer, Imperial College London, London UK; ²Imanova Centre for Imaging Sciences (formerly GSK Clinical Imaging Centre), Hammersmith Hospital, London, UK; ³Department of Radiology, Imperial College Healthcare NHS Trust, London, UK; ⁴Department of Histopathology, Imperial College London, London, UK; ⁵AVIESAN, Strategic Valorization, Paris, France; ⁶GlaxoSmithKline, Collegeville, PA and Research Triangle Park, NC, USA.

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**Corresponding Author:**

Name: Hatice Gungor  
Address: Ovarian Cancer Action Research Centre,  
Dept. of Surgery and Cancer,  
Imperial College London,  
London UK  
Telephone: +44 208 383 8377  
Fax: +44 207 594 2154  
Email: h.gungor@imperial.ac.uk

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GSK employees: Sam Madison  
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Abstract

BACKGROUND:
AKT regulates many cellular processes contributing to cytotoxic drug resistance. This study’s primary objective examined the relationship between GSK2141795, an oral, pan-AKT inhibitor, and FDG-PET markers of glucose metabolism in tumor tissue to determine if FDG-PET could be used to guide personalized dosing of GSK2141795. Biomarker analysis of biopsies was also undertaken.

METHODS

Twelve patients were enrolled in three cohorts; all had dynamic FDG-PET scans and serial pharmacokinetic sampling at baseline, Week 2 (W2) and Week 4 (W4) with tumor biopsies pre-treatment and at W4. Response was evaluated by RECIST v1.1 and GCIG criteria. Biopsy samples were analyzed for mutations and protein expression.

RESULTS

GSK2141795 did not significantly influence blood glucose levels. No dose-response relationship was observed between GSK2141795 pharmacokinetics (PK) and FDG-PET pharmacodynamic (PD) measures; however an exposure-response-relationship was seen between maximum drug concentrations and maximal decrease in FDG uptake in the best responding tumor. This relationship also held for pharmacokinetic parameters of exposure and 1,5-anhydroglucitol (a systemic measure of glucose metabolism). Phospho-AKT up-regulation at W4 in biopsies confirmed AKT inhibition by
GSK2141795. Single agent activity was observed with clinical benefit rate of 27% (3/11) and 30% (3/10) CA125 response in the study’s platinum-resistant ovarian patients. AKT pathway activation by PIK3CA/PIK3R1 mutation did not correlate with clinical activity, whereas RAS/RAF pathway mutations did segregate with resistance to AKT inhibition.

**CONCLUSION**

GSK2141795 demonstrated an exposure-response relationship with decreased FDG uptake and is active and tolerable. This study’s design integrating FDG-PET, PK and biomarker analyses demonstrate the potential for clinical development for personalized treatment.

**Introduction**

The serine-threonine kinase AKT plays a central role in multiple cellular processes important to carcinogenesis, making it an attractive anti-cancer therapeutic target.\(^1\), \(^2\)

The PI3K/AKT pathway also plays an evolutionarily-conserved role in glucose metabolism where it acts to transduce intracellular signals downstream of insulin and the insulin-like-growth factor.\(^3\) The three AKT isoforms (AKT1, 2 and 3) are highly homologous yet differ in quantitative levels of tissue-specific expression, which determines the relative contribution of each isoform to glucose metabolism and insulin signaling.\(^4\), \(^5\), \(^6\)
GSK2141795 is a potent, oral, ATP-competitive inhibitor of all three AKT isoforms. In the first-time-in-human (FTIH) study, the maximum tolerated dose of GSK2141795 was 75mg daily; however the level of tumor target engagement at this dose was not elucidated. The study described in this manuscript was designed to answer this question.

Preclinical data indicate that knockout of AKT2 in mice results in insulin resistance with a diabetes-mellitus like syndrome.\textsuperscript{7, 8} In contrast; AKT1-deficient mice display an opposing phenotype with increased insulin sensitivity.\textsuperscript{9} AKT also has a direct effect on tumor glucose metabolism by stimulating aerobic glycolysis and survival. Tumors with PI3K/AKT pathway activation have robust \[^{18}\text{F}]\text{ fluorodeoxyglucose (FDG)} \text{ uptake by positron emission tomography (PET) scanning suggesting that PI3K/AKT pathway inhibition should inhibit glucose metabolism and decrease FDG-PET avidity.}\textsuperscript{10}

This study hypothesized that inhibition of glucose uptake visualized by FDG-PET imaging could be used as a PD marker of AKT inhibition at the tumor level; and that if a relationship could be established between GSK2141795 exposure and glucose inhibition in tumors, FDG-PET imaging could be used as a surrogate marker of GSK2141795 PK. In this way FDG-PET imaging could enable a physician to personalize dosing of GSK2141795 and theoretically optimize the risk/benefit profile for each patient.
The primary objective of this study was to explore the relationship between changes in glucose metabolism at the tumor level [FDG-PET], and systemically [1,5-anhydroglucitol (1,5-AG)], with pharmacokinetic parameters of GSK2141795 exposure. Secondary objectives included characterization of PK, safety, tolerability and clinical activity of GSK2141795. Additional exploratory objectives included (1) evaluation of paired pre-treatment and on-treatment tumor biopsies using immunohistochemistry (IHC) and reverse phase protein array (RPPA) to explore the association of changes in tumor glucose uptake seen on FDG-PET imaging with changes in the PI3K/AKT pathway and (2) evaluation of tumor tissue for genetic markers of pathway activation (e.g. KRAS mutation, PIK3CA mutation, etc) as potential predictive markers of response to GSK2141795.

Materials and Methods

Patient Population
This was an open-label, 2-stage, Phase-I study conducted at Imperial College London. FDG-PET imaging was conducted at the GlaxoSmithKline Clinical Imaging Centre. Detailed entry and exclusion criteria are summarized in the study protocol [SD (Supplementary Document)-1]. Eligible patients had a histologically or cytologically confirmed diagnosis of FDG-PET-positive recurrent or persistent ovarian cancer or endometrial cancer, measurable disease ≥2 cm, Eastern Cooperative Oncology Group performance status of 0, 1 or 2, adequate organ function manifested by certain prospectively-defined laboratory parameters, and left-ventricular-ejection fraction ≥50%. The protocol and informed consent document were approved by the West London
Research Ethics Committee and registered as NCT01266954 at ClinicalTrials.gov. Approval was also obtained from the UK Administration of Radioactive Substances Advisory Committee. All subjects provided written informed consent.

**Study Design**

The study was conducted in two stages; stage 1 evaluated whether continuous dosing of GSK2141795 would confound interpretation of sequential FDG-PET scans and whether FDG-PET could be used as an imaging biomarker for AKT-targeted therapy. Stage 2 assessed dose-response relationships between GSK2141795 and tumor metabolism using sequential PET scans. The study design and decision making algorithm for progression from Stage 1 to Stage 2 is included in SD-1.

**Study Drug Administration**

Twelve patients were enrolled in the study. Four were enrolled in Stage 1 and administered 50mg oral GSK2141795 daily for 4 weeks (Cohort 1) followed by dose escalation to 75mg daily. Four additional patients were enrolled in each of 2 sequential cohorts of 75mg daily continuously (Cohort 2), or 25mg for 2 weeks followed by dose escalation to 75mg daily (Cohort 3). On the day of the W2 and W4 scans, GSK2141795 was administered 2-3 hours before scan start to ensure that the scan was performed at Cmax (maximum plasma concentration). Dose modifications were made for clinically significant adverse events (AE) as determined by the investigator. Specific dose modification guidelines were provided for QTc prolongation, liver chemistry abnormalities, hypoglycemia and hyperglycemia.
Study Assessments

Study assessments included collection of archival tumor samples, safety evaluations, limited-field-of-view (FoV) dynamic PET scans, laboratory tests including 1,5-AG, optional biopsies, and disease assessments at time points outlined in SD-1. Arterial blood sampling was performed concurrent with PET scans for patients enrolled in Cohort 1. Blood samples for PK analysis were obtained at W2 and W4 pre-dose and at 1, 2, 3, 4, 5, 8 and 24 hours post-dose.

Pharmacokinetics

Plasma samples were analyzed using a validated method based on liquid-liquid extraction followed by high-pressure liquid chromatography-mass spectrometry/mass spectrometry analysis. The lower and higher limits of quantification for GSK2141795 were 1ng/mL and 1000ng/mL respectively using a 100μL aliquot of human plasma. GSK2141795 plasma concentrations and actual sample time data were analyzed using non-compartmental methods (WinNonlin V6.3).

Quantitative FDG-PET

PET-CT scans were acquired on Siemens® HiRez 6 (FoV = 22 cm) or TruePoint PET-CT scanners (FoV = 16 cm). Patients fasted for at least 6 hours before each scan. A CT attenuation scan followed by dynamic 90 minute PET imaging focused on the tumors was performed after administration of 300 MBq of [18F] FDG. PET images were reconstructed and corrected for motion during PET acquisition using a rigid body algorithm. Tumor and normal regions of interest (ROI) on PET-CT were defined on the summated PET images using Analyze® software and applied to the dynamic images to obtain radioactivity versus time curves, which were normalized for injected radioactivity.
and patient’s body weight. (Supplementary Table (ST)-1 details the anatomic tumor locations). The semi-quantitative parameter SUVmax(60-90) (the maximal standardized uptake value between 60 and 90 minutes) was calculated.

The quantitative parameters, Ki, and the metabolic rate of FDG (MRfdg) were also calculated.\textsuperscript{12, 13} Ki represents the rate of $[^{18}\text{F}]$ FDG trapping in a specific tissue and is a combined measurement of $[^{18}\text{F}]$ FDG transport across the cell membrane and the rate of $[^{18}\text{F}]$ FDG phosphorylation, while MRfdg is a product of Ki and blood glucose.

An image-derived input function (IDF; blood radioactivity over time) obtained from aortic activity within the PET camera’s field of view was used to model plasma radioactivity (input) versus tissue radioactivity (output) over time to obtain quantitative parameters for all patients. The use of IDF for modeling was validated in this study against an arterial input function (AIF) obtained from radial arterial sampling of blood from patients in cohort 1.

**Exploratory Biomarker Studies**

Three core biopsies were taken at pre-treatment and W4 for each patient; two were fixed (one formalin fixed/paraffin embedded (FFPE), one ethanol (70%) fixed) and one was fresh frozen for mutation and proteomic analysis.\textsuperscript{15, 16} Fixed samples were assessed for tumor cellularity, heterogeneity, and expression levels of candidate PD biomarkers by immunohistochemistry (IHC). Analyses were performed by Mosaic Laboratories (Lake Forest, CA USA) and Imperial College London Histopathology Laboratories using standard methods and antibodies as outlined in ST 2.
Following intra and inter-biopsy heterogeneity assessment of paraffin-embedded biopsies as a reference point, RPPA data derived from the fresh frozen biopsies (pre-treatment and W4), were generated as described previously\textsuperscript{17} (MD Anderson Cancer Center, TX, USA) and evaluated for changes in AKT and phosphoAKT.

DNA was isolated from archival FFPE samples (Response Genetics, Los Angeles, California, US) and analyzed (Expression Analysis, Durham, North Carolina, US) using a custom genotyping assay on the Illumina Golden Gate platform covering 78 genes and 480 probes/mutations (ST 3). DNA was also isolated from cell pellets produced during protein extraction and from archival FFPE paraffin shavings. These samples were subjected to hot spot mutation detection by a mass spectroscopy-based approach evaluating single nucleotide polymorphisms using Sequenom's MassARRAY platform covering 17 genes and 147 mutations at MD Anderson Cancer Center (ST 4).

**Tumor Response Evaluation**

Tumor response was evaluated according to RECIST (Response Evaluation Criteria for Solid Tumors) 1.1\textsuperscript{15} and the 2005 Gynecological Cancer Intergroup (GCIG) criteria for CA125 (which was not prospectively defined in the protocol).\textsuperscript{16}

**Statistics**

For FDG-PET analyses using SUVmax(60-90), Ki, and MRfdg, raw and mean values (over tumor locations) for each patient at each time point were descriptively explored. Post-baseline mean and percent-change from baseline of the mean PET parameters (across tumor locations) were considered missing if any baseline tumor location was
missing post-baseline. GSK2141795 PK parameters were summarized descriptively. Exploratory analyses including simple linear regression models were performed to assess the potential relationship between GSK2141795 exposure and PD endpoints including changes in FDG-PET parameters and 1,5-AG. IHC and genetic mutation data were each descriptively explored. RPPA data was investigated post hoc; paired t-tests comparing pre-treatment and W4 AKT and phospho-AKT protein expression levels were evaluated.

Results

Patient characteristics

Twelve patients (11 ovarian and 1 endometrial) were enrolled between June and November 2010 (median age 64.5 years, range 45 to 78 years). All ovarian cancer patients were platinum resistant\textsuperscript{17, 18} and had received at least 1 line of prior therapy (median 3.5 lines). 8/11 (73\%) of the patients with ovarian cancer had serous histology and all had measurable disease.

Safety and tolerability

Of the 12 patients enrolled, 3 were withdrawn because of an AE and 9 were withdrawn due to disease progression. 9 patients had GSK2141795 interrupted due to AEs (3 ‘being drug related) and 2 patients were dose-reduced due to AEs. All patients reported at least one AE, with nausea and lethargy being the most commonly reported (Table 1). 7 patients experienced Grade 3/4 AEs (four Grade 3 AEs were attributed to study drug). Three Grade 4 events (renal failure, thrombocytopenia and vomiting) were reported in 2 patients. No fatal events were reported on study drug.
**Pharmacokinetic Results**

Since the majority of patients only had PK sampling up to 5 hrs post-dose (the optional 8 and 24h post-dose time points were infrequently obtained), AUC5 was used in the analysis. Cmax occurred 1 to 5.5 hours post-dose. AUC and Cmax generally increased with increasing dose, although values across dose groups overlapped. Exposures (AUC5 and Cmax) were approximately 1.2-fold (range 0 to 1.5) higher at W4 versus W2 when the same dose was given for 4 weeks, suggesting that GSK2141795 was not at steady state in all patients at W2 (Table 2). The apparent half-life is approximately 2 to 4 days.\(^{11}\)

**FDG-PET Analysis**

All 12 patients administered GSK2141795 underwent dynamic FDG-PET scans. PET scans were not obtained on W4 for three patients; W2 PET scan for one patient was terminated prematurely because the patient felt unwell. The strong correlation between Ki-derived input functions AIF and IDF for Cohort 1 [Supplementary Figure (SF)-1A] validated the use of IDF to derive quantitative parameters precluding the need to obtain further radial arterial samples in subsequent cohorts.

Although there was considerable heterogeneity in FDG uptake (Ki, SUVmax(60-90) and MRfdg) among individual tumors in each patient (Figures 1A-C), the mean change from W2 to W4 SUVmax(60-90) in the 3 Stage 1 patients who had both W2 and W4 scans was <15%. This observation suggested that changes in FDG uptake from W2 to W4 were within physiological variability and unlikely to be due to the cumulative effect of continuous repeat doses of GSK2141795.
All patients had pre-PET scan fasting blood glucose levels < 7.5 mmol/L. Overall, the impact of blood glucose on tumor FDG measurements was predicted to be minimal, an observation supported by the high degree of correlation between SUVmax(60-90) and the quantitative parameter Ki, ($r^2 = 0.89$) (Figure 1D).\textsuperscript{14, 19, 20}

**PK/PD Analysis**

The potential exposure-response relationships between various PK parameters for GSK2141795 and both tumor and systemic markers of glucose metabolism were explored.

**FDG-PET**

The strongest linear relationships between PK and FDG-PET PD parameters were observed between the best PET-responding tumor in each patient regardless of time point, i.e., the individual tumor within each patient demonstrating the greatest percent change from baseline in Ki, SUVmax(60-90), and MRfdg values and the Cmax value for that same patient chronologically closest to the FDG-PET parameter ($p=0.001$, $r^2=0.6593$; $p=0.002$, $r^2=0.6186$; $p=0.0018$, $r^2=0.639$, respectively). The relationship was weaker if the greater mean percent change from baseline of each FDG-PET parameter averaged across tumors was used [Ki example in Figures 2A- B; SUVmax(60-90) and MRfdg in Figure 3] ($p=0.0946$, $r^2=0.2542$; $p=0.03298$, $r^2=0.3793$; $p=0.1297$, $r^2=0.2502$, respectively).
**1,5-AG**

1,5-AG, a metabolically-inert, naturally-occurring 1-deoxy form of glucose competes with glucose for re-absorption in the kidney\(^1\), such that increased blood glucose levels result in decreased 1,5-AG blood levels. 8/12 patients had a decrease from baseline in 1,5-AG (-5% to -88%). 2 patients with the greatest decreases in 1,5-AG (-88% and -87%) also had AEs of hyperglycemia.

The relationships between 1,5-AG percent change from baseline and PK parameters were evaluated for W2 and W4 separately using all available data. 3 patients with missing data on Week 4 were not included in the Week 4 analysis. In general, the inverse linear relationships between 1,5-AG and PK variables at W4 had greater \(r^2\) values and were statistically significant (\(p<0.05\)) as compared to W2. This observation suggests that either the changes in 1,5-AG did not reach steady state until at least W4 (Figure 2C-D) and/or that the increase in dose from 25mg to 75mg (Cohort 3) led to greater effects on 1,5AG. While the fit for all 3 PK parameters was similar, the best fit was the relationship between 1,5-AG percent change from baseline versus Ct (pre-dose) \((p=0.0021, r^2=0.8156)\) (examples in Figure 2C-D; AUC5 and Cmax data in ST 5).

**Exploratory Biomarker Studies**

Archival samples were collected from all patients enrolled on the trial. Core biopsies were performed as follows: Pre-treatment (n=12); Week 4 (n=10). Of the 58 core biopsies obtained; only one complication, a self-limiting intra-abdominal hematoma, was encountered (1.7%).
Proteins
AKT protein levels in paired biopsies (pre-treatment and W4 on-treatment) were evaluated by RPPA and IHC. Decreases in total AKT (p=0.05) and increases in the phospho-AKT/total AKT ratio (p=0.05) at W4 compared to baseline by RPPA were observed across all patients regardless of response to GSK2141795, an observation consistent with PD target engagement.

Genetics
PIK3CA (p110alpha) and/or PIK3R1 (p85 gamma) mutations were seen in 5/11 of patients with ovarian cancer (Figure 3). Co-occurring RAS/RAF mutations (KRAS, HRAS or BRAF) were observed in 2/5 ovarian cancer patients with either a PIK3CA or PIK3R1 mutation. Concurrent PIK3R1 and PIK3CA mutations were observed in 3 of 4 ovarian cancer patients. Of the 6 patients with PIK3CA and/or PIK3R1 mutations, only one (clear cell) had a response to GSK2141795. The other clear cell patient with co-occurring RAS mutations did not respond.

Clinical Response
All 12 patients had measureable disease by RECIST; one partial response (PR) was reported (overall response rate 8%) although 2 additional patients continued on trial for >6 months (clinical benefit rate 25%) (Figure 3). 10 of 11 patients with ovarian cancer were evaluable based upon CA125 GCIG criteria\textsuperscript{11}; 3/10 had a CA125 response.
Discussion

GSK2141795 is an oral nanomolar pan-AKT kinase inhibitor which influences glucose uptake and inhibits cellular proliferation in preclinical cell line and xenograft models. The purpose of this trial was to explore whether GSK2141795 could decrease tumor glucose metabolism, and whether a relationship could be established between changes in glucose metabolism in tumors (measured with FDG-PET) and PK parameters. If such a relationship could be established, it would be possible to use FDG-PET to guide personalized dosing of GSK2141795.

We did not observe a dose-response relationship between GSK2141795 and FDG-PET uptake in this study. However, for the first time, an exposure-response relationship was demonstrated between maximal drug concentrations and FDG uptake in the best responding tumor within each patient, confirming our hypothesis regarding the utility of FDG-PET as a PD marker of AKT inhibition. A similar relationship between various PK parameters of GSK2141795 exposure and 1,5-AG was also demonstrated, thereby providing additional evidence of target modulation. These surrogate measures of target inhibition were confirmed by demonstration (via IHC and RPPA) of increased phospho-AKT levels which presumably result from feedback inhibition after administration of GSK2141795.

Unfortunately, the heterogeneity in FDG uptake between the various tumors both within and between individual patients, as well as the amount of overlap between the PK parameters measured at each dose negated a more easily generalizable dose-
response relationship. It is not surprising that significant variation was seen in FDG uptake by individual tumors given recent data suggesting significant intra-tumor spatial and linear heterogeneity.  

As AKT inhibition by GSK2141795 can cause hyperglycemia, thereby altering FDG tissue uptake, we acquired dynamic FDG-PET scans to derive quantitative PET parameters which can account for the confounding effects of plasma glucose levels and scan timing. Although hyperglycemia adverse events and decreased 1,5-AG levels were observed in this study, fasting blood glucose levels measured prior to scans were within limits unlikely to affect the evaluation of FDG uptake in tumors using semi-quantitative parameters—a conclusion supported by the high degree of correlation between quantitative and semi-quantitative PET parameters. This observation suggests that semi-quantitative FDG-PET parameters (e.g. SUV) which are more easily obtained at most clinical imaging centres would be suitable in the development of GSK2141795.

In general, GSK2141795 administered at doses of ≤75mg daily was tolerable and demonstrated single agent activity in this difficult-to-treat group of patients. On a genetic level, PIK3CA/PIK3R1 mutations did not obviously segregate with response to GSK2141795 as measured by RECIST and/or GCIG CA125 criteria; however RAS/RAF pathway mutations did coincide with lack of response to AKT inhibition.

There are some caveats to this study that could influence interpretation of the results. Firstly, it is possible that the changes in FDG-PET avidity seen in tumors at W2 and W4
do not represent the influence of AKT on glucose metabolism but rather a decrease in
the number of viable cancer cells present within the tumor. Whilst this is theoretically
possible, it is unlikely since GSK2141795 and other AKT inhibitors are primarily
cytostatic in cell culture\textsuperscript{28} and that there was minimal change in the sum of the
diameters of the target lesions at W4 (range from -15\% to +24\%). A second issue is that
the PK parameters used in the PK/PD (FDG-PET) analysis were calculated based on
sampling over a limited time period in the post-dose setting. While this approach
underestimates the actual AUC of GSK2141795, data from the FTIH study indicate that
AUC\textsubscript{0-5} is proportional to AUC\textsubscript{0-24} which suggests that the PK/PD (FDG-PET)
relationship observed would still be observed if AUC0-24 data had been available.

Regardless of the caveats, this highly-focused, exploratory, translational medicine study
is the first attempt to guide personalized dosing of a targeted agent based on changes
in glucose uptake visualized by FDG-PET and represents the potential future of
precision medicine.
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of screening PET scans; Brandon Whitcher and Jennifer Gauvin: statistical advice;
Gordon B. Mills and Katherine Stemke Hale: sequencing analysis.
REFERENCES


Table 1  Summary of All Adverse Events with Relatedness by Maximum Toxicity Grade Occurring in ≥ 25% of Patients (n = 12), n (%)  

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1Preferred term for related AE of rash was rash macular-papular
Table 2  Summary of Derived GSK2141795 Pharmacokinetic Parameters

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<td>week 4</td>
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<td>[6.84]</td>
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<tr>
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<td>(2031,2327)</td>
</tr>
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<td>3</td>
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<td>(561,1414)</td>
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<td>[39.20]</td>
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<td>(1682,3294)</td>
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Abbreviations: AUC, area under the concentration-time curve; Cmax, maximum observed concentration; Cmin, minimum observed concentration; Ct(pre-dose), pre-dose concentration; max, maximum; min, minimum; PK, pharmacokinetics; Tmax, time to maximum observed concentration

1. Cohort 1: 50 mg/75 mg treatment cohort
2. Cohort 2 75 mg/75 mg treatment cohort
3. Cohort 3 25 mg/75 mg treatment cohort
4. Subjects in this cohort received 50 mg for 4 weeks, then 75 mg; therefore, Week 4 PK was determined after subjects received 50 mg doses not 75 mg.
5. Presented as geometric mean [\%CVb] (min, max)
6. Presented as median (min, max)
FIGURE LEGENDS

Figure 1:

FDG uptake parameters Ki (1A), SUVmax(60-90) (1B) and MRfdg (1C) over time. Each patient is represented in an individual panel with individual tumors represented by separate lines. The X axis represents the time points (baseline, Week 2 and Week 4) at which the parameters, Ki [(mL of plasma/mL of tissue)/min], SUVmax(60-90) (g/ml), MRfdg (μmol/mL of tissue/min) were determined. Scatter plot of the Mean SUVmax(60-90) Versus Mean Ki by Time (1D) shows good correlation ($r^2 = 0.89$). Baseline, week 2 and week 4 values are represented in black, red, and green, respectively.

Fig. 2: Linear Regression Analysis of PK/PD Relationships. The greatest percent change from baseline for Ki averaged over tumors (A) and for an individual tumor (B) versus Cmax. The percent change from baseline in 1,5-AG at Week 2 (C) and Week 4 (D) versus Ct(pre-dose). Each point represents data from one patient. The solid line represents the linear regression line with the dotted lines representing 90% confidence intervals.

Fig. 3: Plot of Duration of Treatment and Responses by Tumor Type (All-Treated Population). Corresponding RAS/RAF and PI3K pathway mutations detected in Sequenom and Illumina platform from archival (black and white) and pre-treatment biopsy samples (red) i.e. gain of mutations which were not detected in the archival samples but detected in pre-study samples, are provided. The corresponding response
statuses of each patient (RECIST and GCIG) are provided. CBR: Clinical Benefit Rate:
PFS: Progression Free Survival, RECIST- PR: Partial Response, SD: Stable Disease,
PD: Progressive disease. GCIG- CR Complete Response, R: Response, NR: Non-
Response, N/E Not Evaluable.
Figure 1A: Ki Values over Time.
Figure 1B: SUVmax(60-90) Values over Time.

<table>
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<th>Patient</th>
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<th>Week 4</th>
<th>Baseline</th>
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<td>-5</td>
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Note: The table and graph display the maximum SUV values for different subjects over time.
Figure 1C: MRfdg Values over Time.
Figure 1D: Scatter plot of the Mean SUV_{max}(60-90) Versus Mean Ki by Time.
Figure 2: Linear Regression Analysis of PK/PD Relationships.

A

\[ y = -0.1021x + 32.319 \]
\[ r^2 = 0.2542 \]
\[ p = 0.0946 \]

B

\[ y = -0.1414x + 27.275 \]
\[ r^2 = 0.6593 \]
\[ p = 0.001 \]
Figure 3: Plot of Duration of Treatment and Response by Tumor Type (All Treated Population).