**Association of Hyperglycemia in Phase 1 Studies Involving PI3K, mTOR, AKT and mTORC1/mTORC2 Inhibitors: The Royal Marsden Experience**

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Manuscript contains 10 text pages, 4tables

Summary: 343 Text word count: 1721

Running Title: Hyperglycemia in Phase 1 studies

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**ABSTRACT:**

**Introduction**

Dysregulation of the PI3K/AKT/mTOR pathway is implicated in human cancer growth and progression. Agents targeting this pathway can be associated with on target effects of hyperglycemia due to partial compensation of the insulin-glucose regulatory axis. Identifying the predictive factors for developing hyperglycemia in patients treated with these agents may help direct future management.

**Materials and Methods**

Clinical characteristics including clinical, laboratory, deomographic data (personal and family history of diabetes, steroid use, body mass index, baseline blood sugar, biochemistiry), and outcomes of patients treated consecutively with PI3K, AKT or mTOR inhibitors in the Drug Development Unit, The Royal Marsden between 2007 and 2012 were recorded. Baseline variables and their association with grade (G) 3 hyperglycemia (CTCAE version 3.0) were analyzed, using the Chi Square test and Fischer Exact test for categorical variables, and binary logistic regression for continuous variables.

**Results**

341 patients were treated on 12 phase I trials of PI3K/AKT/mTOR inhibitors, during the study period.. Overall, 87.4% of patients developed hyperglycemia during treatment. Majority had G1 (n=217, 63.6%) and G2 hyperglycemia (n=61, 17.9%). Development of G ≥3 hyperglycemia was seen in 5.9% of patients (n=20). Using the Chi Square test, age <65 (p=0.03), previous history of diabetes (p=0.003) and treatment with AKT and PI3K/mTOR inhibitors (p=0.00) predicted for the occurrence of G3 hyperglycemia. The majority of patients did not require intervention for hyperglycemia [n=316; 92.7%]; however, metformin [n=20; 5.9%] and/or insulin [n=2; 0.6%] were the most commonly used, where required. There were no permanent drug discontinuations.

**Conclusion**

.Hyperglycaemia was a common finding in patients treated with agents targeting PI3K/AKT/mTOR pathway; however, it can be managed in most cases with close monitoring and early intervention. These predictive factors identified in our series warrant further validation in a prospective setting,

**INTRODUCTION:**

The phosphatidylinositol3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K-AKT-mTOR) signaling pathwayplays a critical role in cell functions including cell growth, differentiation, proliferation, cellular metabolism and cytoskeletal reorganization leading to apoptosis and cell survival[[1](#_ENREF_1), [2](#_ENREF_2)]. PI3K-AKT-mTOR pathway also plays a pivotal role in the metabolic and mitogenic actions of insulin and insulin-like growth factor1 (IGF-1)[[3](#_ENREF_3), [4](#_ENREF_4)]. In the presence of insulin, the insulin receptor (IR) phosphorylates insulin receptor substrate proteins (IRS proteins) that are linked to the activation of two main signalling pathways: the PI3K/AKT pathway, which is responsible for most of the metabolic actions of insulin, and the Ras–mitogen-activated protein kinase (MAPK) pathway, which regulates expression of some genes and cooperates with the PI3K pathway to control cell growth and differentiation[[4](#_ENREF_4)]. Therefore, activation of the PI3K pathway is crucial for aspects of insulin-induced glucose and lipid metabolism, such as translocation of Glucose transporter type 4 (GLUT4) to the cell surface, glucose uptake, glycogen synthesis, suppression of glucose output and triglyceride synthesis as well as insulin-induced mitogenesis [[3](#_ENREF_3), [5](#_ENREF_5)]. As a result, it is not surprising that PI3K-AKT-mTOR pathway inhibitors may result in clinically significant and important metabolic effects. This hypothesis is supported by evidence gained from some preclinical modelssuggesting that the loss of insulin signaling in pancreatic β cells and peripheral tissues through blocking of either of the nodes of the PI3K-AKT-mTOR pathway may result in hyperglycemia and diabetes[[6](#_ENREF_6), [7](#_ENREF_7)].Furthermore, germline deletion of AKT2, an AKT isoform that is abundant in muscle and liver, results in a diabetic phenotype in the mouse models[[7](#_ENREF_7)]. The relevance of this model for human disease is supported by the identification of a point mutation in AKT2 in a familial form of severe insulin resistance[[8](#_ENREF_8)].

Dysregulation of the PI3K-AKT-mTOR pathway has been implicated in various malignancies[[2](#_ENREF_2)] and thus a number of anti-cancer agents targeting this pathway have been developed and tested in early phase clinical trials in last few years [[9](#_ENREF_9)]. Some agents including temsirolimus and everolimus have in fact already met regulatory approvals by European Medicines agency (EMA) and Food and Drug Administration (FDA) for treatment of renal cancer, neuroendocrine, pancreatic tumour and hormone-positive HER-2 negative breast cancer [[10-13](#_ENREF_10)]. Due to the overlapping mechanism of action and interference with insulin-glucose regulatory axis agents targeting PI3K-AKT-mTOR inhibitors may potentially causeon-target effect of hyperglycaemia and hyperinslulinaemia and thus may hamper the clinical development of these agents,Nevertheless, although hyperglycemia has been observed in various early phase clinical trials as a class effect of drugs targeting this pathway [[14-16](#_ENREF_14)], there is serious lack of clinical data to inform us about the degree of hyperglycemia, its clinical implications and management, and impact on the patients treated with agents targeting this pathway. To our knowledge, we hereby report the first series defining the clinical outcome of patients treated with agents targeting the PI3K-AKT-mTOR pathway; we also examined the relevant predictive biomarkers that could be used to better stratify these patients. We have also collected data on the treatment of hyperglycemia and outcomes of our patients on these agents in the hope that this could help to direct future management of patients with significant hyperglycemia treated with this important class of agents.

**PATIENTS AND METHODS:**

***Baseline characteristics***

This is a retrospective study comprising of all patients treated with PI3K-AKT-mTOR (mTORC1/2) inhibitors in the Drug Development Unit, The Royal Marsden National Health Service (NHS) Foundation Trust, Sutton, United Kingdom between 2007 and 2012. Clinical characteristics and outcomes of patients treated consecutively with these agents were recorded from the computerised database. Only patients who had received at least on dose of the experimental agent were included in the study.

Baseline demographic and clinical characteristics including age, gender, height, weight, body mass index, personal history of diabetes mellitus and steroid use, tumour type, type of novel agent used, as well as laboratory results such as fasting blood sugar level at cycle 1 and cycle 2, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), glycated hemoglobin A1c (HBA1c) and calculated creatinine clearance (Cockcroft- Gault Formula) were recorded. All study patients had previously provided written informed consent for participation in the relevant Phase 1 trials as approved by the local Research Ethics Committees.

***Statistical Methods***

Baseline demographic and clinical characteristics and their association with grade (G) 3 hyperglycemia (CTCAE version 3.0) were analyzed, using the Chi Square and Fischer Exact test for categorical variables, and binary logistic regression analysis for continuous variables. Outcomes that included the highest blood sugar level reached, highest grade hyperglycemia during the trial, as well as the intervention for hyperglycemia were also recorded.

**RESULTS:**

***Patients and characteristics*:**

A total of 341 patients were identified and treated in 12 phase 1 trials of PI3K-AKT-mTOR inhibitors during the study period**.(Table 1)** The female/male ratio was 1.0. Majority of patients did not have personal history of diabetes mellitus (99.4%) or history of steroid use (90.6%).. Gastrointestinal tract cancers (33.1%), urological cancers (14.1%), gynaecological cancers (14.1%), and breast cancer (10.9%), were the commonest cancer types. 65.4% of patients received at least 2 cycles of treatment at the point of data cut-off.

***Hyperglycaemia in patients:***

. The majority of patients (76.8%) experienced the highest blood sugar level at cycle 1, with another 12.6% recording the highest blood sugar level at cycle 2. Overall, 87.4% of patients developed any grade of hyperglycemia during the treatment. The majority had Grade 1 (n=217, 63.6%) and Grade 2 (n=61, 17.9%) hyperglycemia. Development of Grade 3 or more hyperglycemia was only seen in 5.9% of patients (n=20).

***Treatment characteristics of patients with hyperglycemia:***

Most of the patients did not require any intervention for hyperglycemia (n=316; 92.7%) **(Table 1).** However, metformin (n=20; 5.9% and/or insulin (n=2; 0.6%) were the most common pharmacological agents used, where required. Only one patient’s blood sugar level failed to resolve to Grade 2 or less after pharmacological intervention and required a dose reduction. There were no permanent drug discontinuations.

The median fasting blood sugar level at cycle 1 day 1 was 5.3mmol/L (range 3.0-8.2mmol/L). The median maximum blood sugar level at cycle 1 was 7.1mmol/L (range 4.7-31.9mmol/L). Of the 341 patients, 244 patients went on to receive 2 or more cycles of treatment. The median fasting blood sugar level at cycle 2 day 1 was 5.4mmol/L (range 3.9-9.4mmol/L), indicating the rise in blood sugar level, if any, was transient. The median highest blood sugar level reached was 7.4mmol/L (range 4.7-34.5mmol/L). **(Table 2)**

***Predictive factors for hyperglycaemia:***

Gender, body mass index, previous history of steroid use and tumour type were not predictive of the risk of developing Grade 3 hyperglycemia. Similar, fasting blood sugar level at cycle 1 day 1, amino-aspartate transferase (AST), gamma-glutamyl transferase (GGT), glycated hemoglobin A1c (HbA1c) and baseline creatinine clearance, which was calculated based on serum creatinine taken at Cycle 1 Day 1, did not predictive for development of significant hyperglycemia.

Using Chi square test, age <65 (p=0.032), previous history of diabetes mellitus (p=0.003) and treatment with an AKT or PI3K/mTOR inhibitor (p=0.00) predicted for the occurrence of Grade 3 hyperglycemia **(Tables 3 and 4)**.

**DISCUSSION:**

The PI3K-AKT-mTOR pathway is a well-established driver in human cancers and therefore blocking different nodes of this pathway is a relevant treatment strategy. Phase I clinical trials are generally offered to patients with metastatic refractory cancers, although the primary aim of these studies is to find the maximum tolerated dose of the treatment. One of the important aspects of management in this patient population should be to preserve the quality of life of these patients and one of the major concerns of treating patients with PI3K-AKT-mTOR pathway, which may hamper the future development of these drugs, is development of hyperglycemia. There are currently no clinical data to inform us about the actual risk of hyperglycemia in patients being treated on various nodes of this pathway. Currently the available data are limited to the adverse events observed in various early phase clinical trials of novel agents targeting this important pathway.

Our study is the largest examination of the patients treated with PI3K-AKT-mTOR inhibitors on various clinical trials. We found that the incidence of clinically significant hyperglycemia (>grade 3) was relatively low than anticipated at 5.9%. The majority of patients develop transient hyperglycemia usually during the initiation of treatment of the novel agents. These episodes of hyperglycemia, in general, do not require pharmacological intervention and do not result in discontinuation of treatment. However, most patients in our series discontinued treatment due to progression at relatively early stage; therefore the long term risk of hyperglycemia can’t be established from our data. Nevertheless, in our experience regular blood sugar monitoring and early intervention can help preventing significant hyperglycemia.

DM can be associated with increased morbidity and mortality due to end-organ damage; certain cancers such as breast and colorectal cancer are also independently known to have been associated with increased risk of developing DM [[17](#_ENREF_17)]. Our study however failed to establish a correlation between development of significant hyperglycemia with a specific tumour type. Insulin resistance and the development of hyperglycemia are hallmarks of metabolic syndrome and are often related to abdominal obesity [[18](#_ENREF_18)]. Body mass index (BMI), however, was also not found to predictive of the risk of Grade 3 or above hyperglycemia in our study. Rise in the liver enzymes such as alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transpeptidase (GGT)have been found to negatively predict for insulin sensitivity[[19](#_ENREF_19), [20](#_ENREF_20)]. Likewise, chronic kidney disease has also been known to be associated with insulin resistance and hyperglycemia in non-diabetic patients[[21](#_ENREF_21)]. We therefore examined these factors in univariate model so see if these were independently predictive of the risk of hyperglycemia in patients treated on PI3K-AKT-mTOR pathway. In our study we did not find any correlation of grade 3 or above hyperglycemia with deranged liver or renal functions. However, most patients in the present study were required to have satisfactory liver and renal functions at baseline, which may have an impact on our study findings.

Combined use of fasting plasma glucose and glycated hemoglobin A1c (HbA1c) has been established to be a sensitive and specific screening tool for identifying individuals with diabetes and impaired glucose tolerance at an early stage[[22](#_ENREF_22)]. However, in our study, fasting blood sugar and HbA1c both failed to predict for the risk of development of Grade 3 or more hyperglycemia.

Although majority of patients in our study did not have history of DM due to exclusion criteria of the trials, this was still established to be an independent risk factor for developing grade 3 hyperglycemia. Patients with DM may represent an important proportion of patients with cancers due to ageing population; therefore it will be unfair to exclude all the patients with DM from novel agents targeting PI3K/AKT/mTOR pathway. However, these patients may require careful monitoring and early intervention in collaboration with endocrinologist to manage their sugar levels.

Interestingly, the only patient in our study, whose hyperglycemia failed to resolve despite pharmacological intervention and required a trial drug dose reduction, was on a selective p110α inhibitor. Some studies using PI3K inhibitors have not reported dramatic hyperglycemia, an effect that may be related to the p110 isoform of the PI3K that is inhibited: a pan class 1A inhibitor may lead to more severe glucose derangement than a selective p110α inhibitor, although the roles of the different p110 isoforms that they play in the metabolic effects of insulin still remains un-determined [[23](#_ENREF_23), [24](#_ENREF_24)]. The range of metabolic alterations observed with inhibitors of PI3K/AKT/mTOR pathway differ suggesting that kinase selectivity among various inhibitors may be responsible for the different levels of glucose and insulin elevation observed with these agents [[23](#_ENREF_23), [25](#_ENREF_25), [26](#_ENREF_26)]. We found that patients on AKT or PI3K/mTOR inhibitors were at higher risk of developing significant hyperglycemia. Inhibition of mTOR in addition to PI3K has been postulated to improve insulin sensitivity, as the mTOR/S6 kinase pathway causes serine phosphorylation of insulin receptor substrate-1, which attenuates signaling [[27](#_ENREF_27)]. Therefore, inhibiting mTOR/S6 kinase activity may reduce some of the insulin resistance caused by PI3K inhibition by relieving the inhibition of serine phosphorylation of insulin receptor substrate-1, allowing tyrosine phosphorylation of insulin receptor substrate-1 and activation of insulin signaling pathway[[27](#_ENREF_27)].

Acknowledging the limitations of highly selected patient population treated in a controlled environment of a specialist unit within the context of phase I studies, our findings may be considered as hypothesis generating and may need validated in prospective larger clinical trials. Nevertheless, our data will be useful in informing the physicians about the risk factors that may warrant careful monitoring of patients treated with PI3K/AKT/mTOR inhibitors.

**CONCLUSION:**

Patients aged <65 years old, with a history of diabetes mellitus, and treated with an AKT or PI3K/mTOR inhibitor are more likely to develop significant hyperglycemia when treated with agents targeting PI3K/AKT/mTOR pathway. These factors should be carefully considered and specialist consultation should be sought earlier in order to aid clinical trial planning and management of metabolic adverse events which may result from treating patients on this pathway. Finally, our findings may not be practice changing but they are indeed reassuring for phase I physicians and industry working scrupulously to develop these compounds further.

Table 1: Baseline Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| Category |  | Frequency | Percent |
| Gender | Female | 171 | 50.1 |
| Male | 170 | 49.9 |
| History of diabetes mellitus | No | 339 | 99.4 |
| Yes | 2 | 0.6 |
| Family history of diabetes mellitus | No record | 339 | 99.4 |
| Yes | 2 | 0.6 |
| History of steroid use | No | 309 | 90.6 |
| Yes | 32 | 9.4 |
| Tumour type | Gastrointestinal tract | 113 | 33.1 |
| Urology | 48 | 14.1 |
| Gynecology | 48 | 14.1 |
| Breast | 37 | 10.9 |
| Lung / Pleura | 27 | 7.9 |
| Others | 68 | 19.9 |
| Pathway inhibited | AKT | 91 | 26.7 |
| mTOR | 84 | 24.6 |
| PDK1/AKT | 12 | 3.5 |
| PI3K | 78 | 22.9 |
| PI3K/mTOR | 33 | 9.7 |
| Dual TORC1/2 | 43 | 12.6 |
| Cycles received by date of data cut-off | 1 | 97 | 28.4 |
| 2 | 126 | 37.0 |
| 3 | 39 | 11.4 |
| 4 | 32 | 9.4 |
| 5 | 11 | 3.2 |
| 6 | 11 | 3.2 |
| 7 | 3 | 0.9 |
| 8 | 5 | 1.5 |
| 9 | 4 | 1.2 |
| 10 | 6 | 1.8 |
| 12 | 3 | 0.9 |
| 15 | 1 | 0.3 |
| 16 | 1 | 0.3 |
| 17 | 1 | 0.3 |
| 34 | 1 | 0.3 |
| Cycle number with highest blood sugar level (mmol/L) | 1 | 262 | 76.8 |
| 2 | 43 | 12.6 |
| 3 | 14 | 4.1 |
| 4 | 10 | 2.9 |
| 5 | 2 | 0.6 |
| 6 | 5 | 1.5 |
| 7 | 2 | 0.6 |
| 9 | 1 | 0.3 |
| 15 | 1 | 0.3 |
| 22 | 1 | 0.3 |
| Grade of highest hyperglycemia reached (CTCAE version 3.0) | 0 | 43 | 12.6 |
| 1 | 217 | 63.6 |
| 2 | 61 | 17.9 |
| 3 | 18 | 5.3 |
| 4 | 2 | 0.6 |
| Intervention for hyperglycemia | Dietary advice | 2 | 0.6 |
| Insulin | 1 | 0.3 |
| Metformin | 20 | 5.9 |
| Metformin and Insulin | 1 | 0.3 |
| None | 316 | 92.7 |
| Trial drug dose reduction | 1 | 0.3 |
| Hyperglycemia resolved to Grade (CTCAE version 3.0) | 0 | 8 | 2.3 |
| 1 | 15 | 4.4 |
| 2 | 1 | 0.3 |
| Not applicable | 316 | 92.7 |
| Not resolved | 1 | 0.3 |
| Trial stopped | No | 341 | 100.0 |
| Fasting blood sugar level at cycle 1 day 1 (mmol/L) | <5.5 | 218 | 63.9 |
| 5.5 - 6.0 | 59 | 17.3 |
| >6.0 | 64 | 18.8 |
| Fasting blood sugar level at cycle 1 day 1 (mmol/L) | <6 | 277 | 81.2 |
| 6 & above | 64 | 18.8 |
| Age at entry (years) | <40 | 30 | 8.8 |
| 41 - 60 | 172 | 50.4 |
| >60 | 139 | 40.8 |
| Age at entry (years) | <65 | 253 | 74.2 |
| 65 & above | 88 | 25.8 |
| Body mass index | <19 | 16 | 4.7 |
| 19.1 - 25 | 136 | 39.9 |
| 25.1 - 30 | 128 | 37.5 |
| >30 | 61 | 17.9 |
| Body mass index | <30 | 276 | 80.9 |
| 30 & above | 65 | 19.1 |
| Baseline creatinine clearance [CockcroftGault Formula] (ml/min) | 50 - 70 | 58 | 17.0 |
| 70 - 90 | 94 | 27.6 |
| >90 | 186 | 54.5 |
| No record | 3 | 0.9 |
| Baseline creatinine clearance [Cockcroft Gault Formula] (ml/min) | <60 | 21 | 6.2 |
| 60 & above | 320 | 93.8 |
| Grade of highest hyperglycemia (CTCAE version 3.9) | Grade <3 | 321 | 94.1 |
| Grade >=3 | 20 | 5.9 |

Table 2: Baseline Characteristics (Median Values)

|  |  |  |  |
| --- | --- | --- | --- |
|  | N=341 | Median | Range |
| Age at Entry (years) | 341 | 58 | 22 - 77 |
| Height (cm) | 341 | 169.4 | 143.5 - 195.5 |
| Weight (kg) | 341 | 73.6 | 41.1 - 123.1 |
| Body mass index (BMI) | 341 | 25.6 | 16.7 - 40.2 |
| Fasting blood sugar level (BSL) at cycle1 day1 (mmol/L) | 341 | 5.3 | 3.0 - 8.2 |
| Maximum blood sugar level during cycle 1 (mmol/L) | 341 | 7.1 | 4.7 - 31.9 |
| Fasting blood sugar level at cycle 2 (mmol/L) | 244# | 5.4 | 3.9 - 9.4 |
| Highest blood sugar level during trial (mmol/L) | 341 | 7.4 | 4.7 - 34.5 |
| Baseline creatinine (μmol/L) | 341 | 70 | 32 - 143 |
| Baseline creatinine clearance [Cockcroft Gault Formula] (ml/min) | 341 | 94.1 | 37.8 - 250.2 |
| AST at cycle 1 day 1 (U/L) | 341 | 24 | 4 - 123 |
| GGT at cycle 1 day1 (U/L) | 341 | 42 | 0 - 958 |
| HbA1c at cycle 1 day1 (mmol/mol) | 341 | 36 | 0 - 56 |

Creatinine (Male) 63-116 umol/l, Creatinine (Female) 54-98 umol/l

Creatinine Clearance (Male) 90-130 ml/min,Creatinine Clearance (Female) 80-120 ml/min,

Aspartate aminotransferase [AST] 10-42   U/l

Gamma glutamyl-transferase [GGT] (Female)  <35 U/l, Gamma-glutamyl-transferase [GGT] (Male)  <54U/l,

Blood sugar level [BSL] 3.9-6.0 mmol/l, Glycated Hemoglobin A1c (HbA1c) 4.0-6.5%

#N=244 patients with fasting blood sugar level recorded for cycle 2

Table 3: Factors Predicting for the Development of Grade 3 Hyperglycemia

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Grade <3 | Grade >=3 | Total | p-value |
| Fasting blood sugar level at cycle 1 day 1 (mmol/L) | <5.5 | 206 | 12 | 218 | 0.344 |
| 5.5 - 6.0 | 57 | 2 | 59 |
| >6.0 | 58 | 6 | 64 |
| Total | 321 | 20 | 341 |
| Fasting blood sugar level at cycle 1 day 1 (mmol/L) | <6 | 263 | 14 | 277 | 0.233 |
| 6 & above | 58 | 6 | 64 |
| Age at entry (years) | <40 | 27 | 3 | 30 | 0.131 |
| 41 - 60 | 159 | 13 | 172 |
| >60 | 135 | 4 | 139 |
| Total | 321 | 20 | 341 |
| Age at entry (years) | <65 | 234 | 19 | 253 | 0.032 |
| 65 & above | 87 | 1 | 88 |
| Gender | Female | 163 | 8 | 171 | 0.368 |
| Male | 158 | 12 | 170 |
| Total | 321 | 20 | 341 |
| Body mass index | <19 | 15 | 1 | 16 | 0.356 |
| 19.1 - 25 | 130 | 6 | 136 |
| 25.1 - 30 | 120 | 8 | 128 |
| >30 | 56 | 5 | 61 |
| Total | 321 | 20 | 341 |
| Body mass index | <30 | 261 | 15 | 276 | 0.553 |
| 30 & above | 60 | 5 | 65 |
| History of diabetes mellitus | No | 321 | 18 | 339 | 0.003 |
| Yes | 0 | 2 | 2 |
| Total | 321 | 20 | 341 |
| History of steroid use | No | 291 | 18 | 309 | 1 |
| Yes | 30 | 2 | 32 |
| Total | 321 | 20 | 341 |
| Tumour type | Gastrointestinal tract | 88 | 7 | 95 | 0.077 |
| Urology | 47 | 1 | 48 |
| Gynecology | 44 | 4 | 48 |
| Breast | 37 | 0 | 37 |
| Lung / Pleura | 23 | 4 | 27 |
| Others | 14 | 0 | 14 |
| Total | 321 | 20 | 341 |
| Baseline creatinine clearance [CockcroftGault Formula] (ml/min) | 50 - 70 | 57 | 1 | 58 | 0.136 |
| 70 - 90 | 89 | 5 | 94 |
| >90 | 173 | 13 | 186 |
| Total | 319 | 19 | 338 |
| Baseline creatinine clearance [CockcroftGault Formula] (ml/min) | <60 | 19 | 2 | 21 | 0.353 |
| 60 & above | 302 | 18 | 320 |
| Pathway | AKT | 81 | 10 | 91 | 0.000 |
| mTOR | 83 | 1 | 84 |
| PDK1/AKT | 12 | 0 | 12 |
| PI3K | 76 | 2 | 78 |
| PI3K/mTOR | 26 | 7 | 33 |
| TORC1/2 | 43 | 0 | 43 |

Table 4: Results of Univariate Analysis

|  |  |  |
| --- | --- | --- |
|  | Odds Ratio (95% CI) | p-value |
| Fasting blood sugar level at cycle day 1 (mmol/L) | 1.24 (0.68 - 2.25) | 0.48 |
| Max blood sugar level in cycle 1 (mmol/L) | 2.28 (1.71 - 3.04) | 0.000 |
| Fasting blood sugar level at cycle 2 (mmol/L) | 1.54 (0.99 - 2.38) | 0.054 |
| AST at cycle 1 day 1 (U/L) | 1 (0.97 - 1.03) | 0.984 |
| GGT at cycle 1 day 1 (U/L) | 1 (0.99 - 1) | 0.546 |
| HbA1c at cycle 1 day 1 (mmol/mol) | 1.03 (0.99 - 1.06) | 0.108 |

Aspartate aminotransferase [AST],Gamma glutamyl-transferase [GGT], Glycated Hemoglobin A1c (HbA1c)

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