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Journal

Cancer Chemotherapy and Pharmacology, 74(2)

ISSN

0344-5704

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Publication Date

2014-08-01

DOI

10.1007/s00280-014-2510-0

Peer reviewed

Published in final edited form as:

Cancer Chemother Pharmacol. 2014 August ; 74(2): 359–365. doi:10.1007/s00280-014-2510-0.

Impact of Patient Ethnicity on the Metabolic and Immunologic Effects of PI3K-mTOR Pathway Inhibition in Patients with Solid Tumor Malignancies

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Abstract

Purpose—Inhibition of the phosphatidylinositol 3-kinase (PI3K)/mammalian target of Rapamycin (mTOR) pathway is associated with metabolic and immunologic perturbations that impact drug tolerability. Here, we studied whether PI3 kinase/mTOR pathway inhibitors are associated with greater metabolic impact and decreased tolerability in Asian patients.

Methods—A retrospective analysis was conducted of consecutive patients with advanced malignancies treated on Phase 1 trials of PI3K/mTOR inhibitors. Adverse events related to PI3K/mTOR inhibition, fasting plasma glucose (FPG), insulin, and cpeptide levels, hemoglobin A1c (HgbA1c), and T-cell subsets, were prospectively collected. Mann-Whitney and chi-squared tests were used to compare continuous and categorical variables, respectively, between Asian and Caucasian patients.

Results—A total of 103 patients (31 Asian; 72 Caucasian) were treated consecutively across five clinical trials. Baseline age, gender distribution, and metabolic parameters were comparable with the exception of lower median body mass index (BMI) in Asian patients (23.0 vs. 24.8 kg/m^2, p=0.024). There were no differences in drug tolerability, adherence or duration of therapy. Asian patients experienced a higher incidence of grade ≥ 2 hyperglycemia (40.4% vs. 18%, p = 0.03), and greater increases in FPG, HgbA1c, and insulin resistance. No differences in incidence or severity of mucositis, rash, or pneumonitis were observed. Drug effects on neutrophils, lymphocytes and T-cell subsets were similar.

Conclusions—PI3K/mTOR inhibitors have greater glycemic impact in Asian patients, despite similar baseline metabolic parameters, comparable dose intensity, and a lower median BMI. Further studies are warranted to explore the mechanisms underlying these differences and optimize dosing in Asian patients.

Keywords

PI3 kinase; mammalian target of rapamycin; ethnicity; glycemic indices; adverse effects

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The authors do not have any financial support or conflicts of interest to disclose.

Introduction

The phosphatidylinositol 3-kinase (PI3K)/mammalian target of Rapamycin (mTOR) pathway is critical for numerous cellular processes, including glucose uptake and metabolism, regulation of catabolic pathways, cellular proliferation, and response to environmental stressors [1–3]. Over-activation of the PI3K/mTOR pathway is implicated in the progression of numerous cancer types, and inhibitors of the pathway have achieved regulatory approval in the United States and Europe in the treatment of various solid tumor malignancies, including kidney and breast cancer [4,5]. However, effects of PI3K/mTOR pathway inhibition in normal tissues lead to numerous perturbations in cellular metabolism and inflammatory processes, including inhibition of glucose uptake, inhibition of cellular immunity predisposing to intra-cellular pathogens, and induction of an inflammatory state leading to expected toxicities including rash, mucositis, and colitis [6,7]. Cumulatively, these metabolic and inflammatory toxicities can significantly impact the tolerability and dose intensity of targeted inhibitors of the PI3K/mTOR pathway.

Preliminary data suggest that Asian patients may be particularly predisposed to the adverse effects of PI3K/mTOR pathway inhibition. A small phase 1 dose-finding study of everolimus in Chinese patients, suggested that the incidence of hyperglycemia was higher than observed in prior studies of everolimus in predominantly Caucasian patient populations [8]. In a subset analysis of the phase 3 clinical trial of exemestane with or without everolimus in patients with advanced hormone receptor positive breast cancer, the incidence of any grade pneumonitis was higher in Asian versus non-Asian patients, despite a similar duration of drug exposure and dosing intensity [9].

Prior retrospective analyses in cancer patient populations examining the impact of patient ethnicity have focused primarily upon first generation, predominantly TORC 1 complex inhibitors such as everolimus and other rapalogs. It is unknown whether a similar differential pattern of toxicity exists with next generation dual TORC complex 1 + 2 inhibitors as well as other targeted PI3K pathway inhibitors in clinical development. It is unclear whether the development of more potent and more selective PI3K/mTOR pathway inhibitor will accentuate or ameliorate the differential metabolic and immunologic impact across patient ethnicities. As these emerging targeted anti-cancer therapies are evaluated in varied patient populations, these data will be critical to inform drug development and optimize dosing strategies across patient populations. The current study was designed to analyze the metabolic and immunologic impact of PI3K/mTOR pathway inhibition, including second-generation inhibitors, in Asian and Caucasian patients treated on Phase I clinical trials.

Methods

Study Population and Assessment Schedule

A retrospective analysis was undertaken of data collected from consecutive Asian and Caucasian patients enrolled onto five early phase clinical trials of targeted PI3K/mTOR pathway inhibitors at the University of California San Francisco between the dates of January 1st, 2010 and December 31st, 2012. Common eligibility criteria across clinical trials excluded patients with history of pneumonitis or known diabetes, and required an ECOG

performance status of 0–2. Patient ethnicity was determined by patient self-report at the time of study enrollment using a validated questionnaire.

The five clinical trials included two clinical trials of dual TORC1 + 2 inhibitors, a clinical trial of a pan-isoform PI3K inhibitor, and two clinical trials of TORC1 inhibitors (given in combination with sorafenib and an Akt inhibitor respectively). Adverse events were captured prospectively and graded in severity using Common Toxicity Criteria. Baseline and on-study laboratory assessments captured included fasting glucose, complete blood count + differential, creatinine, total bilirubin, aspartate aminotransferase, and albumin levels. Fasting insulin and c-peptide levels, hemoglobin A1c, and circulating T lymphocyte subsets were collected in a subset of patients treated with dual TORC 1 + 2 inhibition. Patients were required to be fasting for at least 10 hours prior to laboratory assessment. The study pharmacist captured the formal pill count and drug diary to assess drug adherence and dose intensity from all patients on study.

Each patient had signed an institutional review board (IRB)-approved, protocol-specific informed consent form in accordance with federal and institutional guidelines prior to initiating protocol therapy. The subsequent retrospective review of outcomes by patient ethnicity was approved by the local IRB.

Statistical Methods and Data Analysis

Data collected prospectively during the course of protocol therapy included baseline patient characteristics at the time of study entry, including age, gender, patient ethnicity, height, weight, body surface area, body mass index, ECOG performance status, and starting dose level. Laboratory parameters were collected at baseline and at minimum every 4-week cycle as discussed above. The maximal percent change from baseline in each of the laboratory parameters was determined for each patient, using all measurements obtained during the course of protocol therapy. Dose intensity during the first two cycles of therapy was determined using patient reported dosing through returned pill counts, which were used to calculate the actual versus expected cumulative dosing. For patients who discontinued protocol therapy prior to completion of two cycles of therapy (8 weeks) for reasons other than adverse events/drug toxicity, the expected cumulative dose was calculated using the dates of therapy initiation and discontinuation.

Fisher’s exact test and Chi-squared test was used to compare baseline categorical variables and the incidence of selected adverse events of interest between patient ethnicities. The Mann-Whitney test [10] was used to compare baseline continuous variables between patient cohorts, as well as the maximal change from baseline in the laboratory parameters discussed above. No adjustments were made for multiple comparisons for this retrospective analysis.

Results

Baseline Patient Characteristics

Between March 3rd, 2010 and November 27th, 2012, a total of 31 Asian and 72 Caucasian patients were consecutively enrolled onto five trials of targeted inhibitors of the PI3K/mTOR pathway, including two trials of dual TORC1 + 2 inhibitors, a trial of a pan-class PI3K

inhibitor, and two trials with TORC 1 inhibition (given in combination with sorafenib and an Akt inhibitor respectively). The distribution of study drug and treatment exposure across the five studies was similar between Asian and Caucasian patients (Table 1). Baseline patient characteristics were comparable between patient cohorts, except for the median baseline weight, body mass index, and body surface area, which were lower in Asian compared with Caucasian patients (Table 1). The median baseline fasting plasma glucose level was less than 100 mg/dL across the study cohorts with a baseline hemoglobin A1c in the normal range in both groups. There were no significant differences in any laboratory parameters, including baseline fasting plasma glucose, between Asian and Caucasian patient cohorts.

Incidence of Adverse Events of Interest and Dose Intensity Between Patient Ethnicities

The median dose intensity during the first eight weeks of therapy and total duration of protocol therapy for the Asian and Caucasian patient cohorts were 79% and 84% of target drug exposure (p-value for difference = 0.401). No differences in drug adherence and discontinuations were seen between the groups. Dose modifications were comparable to both groups. Despite the similar dose intensity and duration of therapy, and lower baseline body mass index, Asian patients were significantly more likely to experience grade 2 or higher hyperglycemia (fasting plasma glucose > 160 mg/dL) during protocol therapy (37.5% vs. 18.1%, p-value = 0.032) (Table 2).

Other select adverse events of interest, including grade 2 or higher grade rash, mucositis, and diarrhea, were common in both patient cohorts with incidences ranging from 25–40%; there were no significant differences between Asian and Caucasian patients. The incidence of any grade pneumonitis was slightly higher in Asian than in Caucasian patients but the difference was not statistically significant (6.5% vs. 2.8%; p = 0.36).

Impact of PI3K/mTOR Pathway Inhibition on Metabolic Parameters

Asian patients experienced a greater metabolic impact of PI3K/mTOR pathway inhibition. Within 8 weeks or less, the median maximal increase from baseline in fasting plasma glucose on study was 42 mg/dL for Asian patients versus 18 mg/dL in Caucasian patients (p = 0.0164) (Figure 1a). Likewise, Asian patients experienced significantly higher percent increase in hemoglobin A1c (18.9% versus 9.4%, p = 0.044 (Figure 1b) and insulin resistance index as assessed by the HOMA-IR instrument (3.88 versus 1.68, p = 0.0278) (Figure 1c). There was no difference in maximal increase from baseline in fasting c-peptide levels between patient cohorts (4.50 ng/mL median increase from baseline in Asian patient cohort versus 5.30 ng/mL increase in Caucasian cohort; p = 0.70) (Figure 1d).

The impact of specific pathway inhibitor (PI3K, TORC1, or TORC 1+2) on maximal change from baseline in fasting plasma glucose levels is shown in Table 3. In each subgroup the median maximal change from baseline in fasting plasma glucose was higher in Asian than Caucasian patients, though the difference was only significant in the subgroup of patients treated with pan-class PI3K inhibition.

Impact of PI3K/mTOR Pathway Inhibition on Hematologic Parameters and Organ Function

There were no significant changes from baseline observed for hemoglobin, absolute neutrophil count, platelet count, or markers of liver and renal function, nor were there differences between patient ethnicities with respect to these variables (Figure 2a–c). Circulating CD4+ and CD8+ T cells declined significantly from baseline in the sub group of patients treated with dual TORC 1 + 2 inhibition; however there were no significant differences between Asian and Caucasian cohorts (Figure 2d–e).

Discussion

The results of the current analysis demonstrated that the glycemic impact of PI3K/mTOR pathway blockade was significantly greater in Asian versus Caucasian patient populations. Asian patients experienced significantly greater increases in fasting glucose and hemoglobin A1c levels, along with a greater increase in insulin resistance, compared with Caucasian patients. These findings were observed despite similar starting dose levels, dose intensities, duration of therapy, baseline metabolic parameters between cohorts, and a lower body mass index in the Asian patient cohort. Differences between patient ethnic groups were not observed with respect to the inflammatory and immunologic impact of PI3K/mTOR pathway inhibition, including inflammation-related adverse events and changes in circulating T cell subsets, which suggests that there is a specific interaction between patient ethnicity and glucose metabolism related to PI3K/mTOR pathway inhibition. The lack of observed differences in fasting cpeptide level between patient ethnicities suggests that the difference in glucose metabolism between patient ethnicity may be linked to peripheral tissue utilization of glucose and insulin metabolism, rather than effects on pancreatic beta-cell secretion, though the small sample size precludes definitive conclusions.

Previous studies with first generation rapalogs have provided mixed evidence for a differential metabolic impact of PI3K/mTOR pathway inhibition in Asian patients. In a phase 1 study of everolimus in Chinese patients, the incidence of hyperglycemia was nearly 50%, and in a separate retrospective analysis of 22 Korean patients treated with everolimus, the incidence of grade 3 or higher (> 250 mg/dL) hyperglycemia was 17%, exceeding rates observed in studies carried out in Caucasian patient populations by cross study comparison [8,11]. In contrast, in a subset analysis of the BOLERO-2 study, a randomized phase 3 study of exemestane with or without everolimus in women with advanced hormone receptor positive breast cancer, the Asian patient subset (N = 143) demonstrated a 7% incidence of grade 2 or higher hyperglycemia, as compared with a 12% incidence in non-Asian patients [9]. Similarly, there was no difference in incidence of grade 2 or higher hypercholesterolemia in Asian versus Caucasian patients. Several differences in treatment regimen may account for these discrepant findings, including differences in the potency of pathway inhibition with everolimus versus second-generation inhibitors, as well as the use of concomitant hormonal therapy exemestane that may have influenced metabolic impact of PI3K/mTOR pathway blockade. Furthermore, no data on baseline weight was reported in the different ethnic cohorts.

Though the current analysis is retrospective in nature, the study data were captured prospectively on phase I clinical trials in a tightly controlled fashion, with careful and

detailed assessment of the impact of PI3K/mTOR pathway inhibition on metabolic and inflammatory parameters, along with systematic assessment of adverse events and subjective toxicity. Drug adherence and dosing intensity were captured using both drug diaries and pill counts, and there was limited impact of concomitant medications and no confounding baseline diabetes or use of glucose-lowering medications.

The current analysis has several limitations, including the absence of germline polymorphism and pharmacokinetic data that limits the ability to investigate underlying mechanisms explaining ethnic differences in metabolic toxicity observed with PI3K/mTOR pathway inhibition. Examples of both environmental and genetic etiologies for observed ethnic differences in drug toxicity exist with other classes of anti-cancer therapies, including the increased toxicity with capecitabine observed in North American patient populations with higher folate diets than European populations [12], and the increased risk of irinotecan in patients with select polymorphisms in the glucoronidating UGT1A1 gene [13]. Rapalogs are metabolized by the CYP3A system, and potentially functional, non-synonymous single nucleotide polymorphisms in CYP3A5, among others, have been implicated in variable everolimus metabolism that may account for some of the observed differences in drug toxicity with mTOR pathway inhibition [14]. This warrants prospective evaluation in future studies.

Another limitation of the study is the relatively limited sample size and heterogeneous cohort drawn from multiple phase 1 studies of various pathway inhibitors administered at varying dose levels. The sample size precludes the ability to perform a multivariate analysis to determine which baseline factors are most strongly predictive of the development of subsequent metabolic toxicity with PI3K/mTOR pathway inhibition. Furthermore, the relatively short duration of therapy (less than 2 months in both cohorts) for most patients limits the ability to determine the long-term metabolic impact of therapy which may likely be further exacerbated with longer durations of treatment and follow-up. The negative glycemic impact may be even more striking in patients with borderline or overt diabetes. This will be an important consideration in future studies, especially as PI3K/mTOR pathway inhibitors are utilized in less advanced metastatic disease and increasingly in adjuvant disease settings with longer expected durations of therapy. The recommended Phase II doses for Asian patients may have to be reconsidered in those settings.

The analysis is the first to our knowledge to examine the differential metabolic impact of second-generation PI3K/mTOR pathway inhibitors across Asian versus Caucasian patient populations. The findings, if validated in prospective studies, are likely to become of increasing relevance as novel targeted agents are evaluated in Asian patient populations. The first generation rapalog everolimus was approved for use in renal cell carcinoma patients in China in 2013, and the evaluation of second-generation pathway inhibitors in predominantly Asian patient populations are underway. The current analysis may have a significant impact on the development of these targeted PI3K/mTOR pathway inhibitors, and serve as a reminder that consideration of environmental and potential germline polymorphisms and pharmacogenetic differences in drug metabolism across patient ethnicities may significantly impact observes rates of toxicity. As drug development proceeds in Asian populations, and

other populations underrepresented in the registrational trials of these anti-cancer therapies, this bears important consideration.

Conclusion

The adverse glycemic impact of second generation PI3K/mTOR pathway inhibition was greater in Asian than in Caucasian patients, despite similar baseline fasting laboratory assessment, comparable dose intensity, drug adherence, and a lower body mass index at study entry. Other known on-target adverse events such as rash, mucositis and lymphopenia induced by this class of agents were not significantly different in these patients. An in-depth assessment of the degree, long-term impact and mechanism of glucose dysregulation should be evaluated in future studies involving inhibitors of the energy sensing pathway. Careful consideration should be given to pharmacogenetic differences in drug and glucose metabolism and transport, and environmental factors including diet and potential drug-drug interactions.

Acknowledgements

The authors would like to acknowledge Alyson Cockerill for help with data collection.

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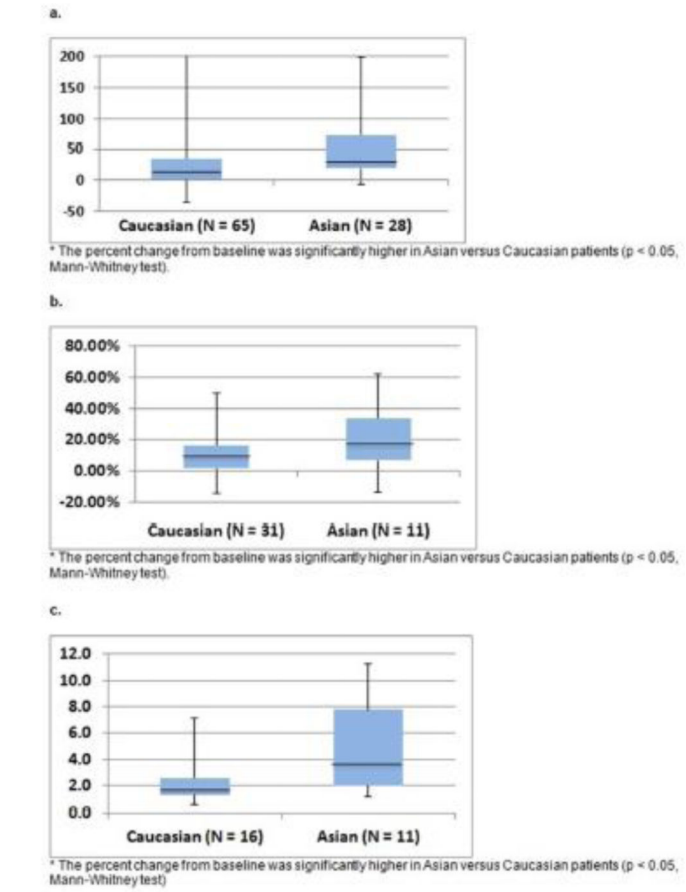


Figure 1. Glycemic Impact of PI3K/mTOR Pathway Inhibition By Patient Ethnicity

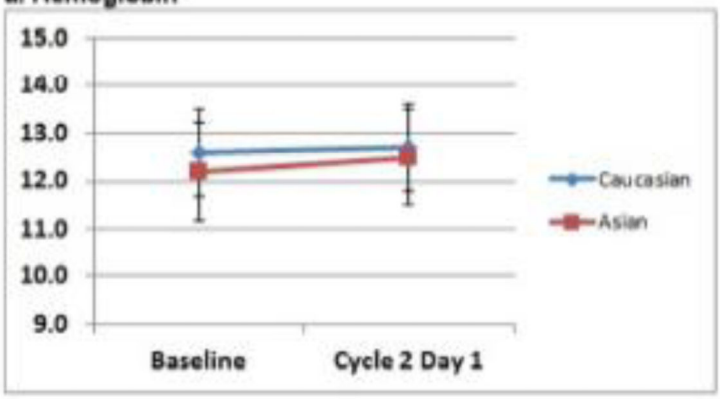
a. Maximal Change From Baseline in Fasting Plasma Glucose (mg/dL)

b. Maximal Percent Change From Baseline in Hemoglobin A1c

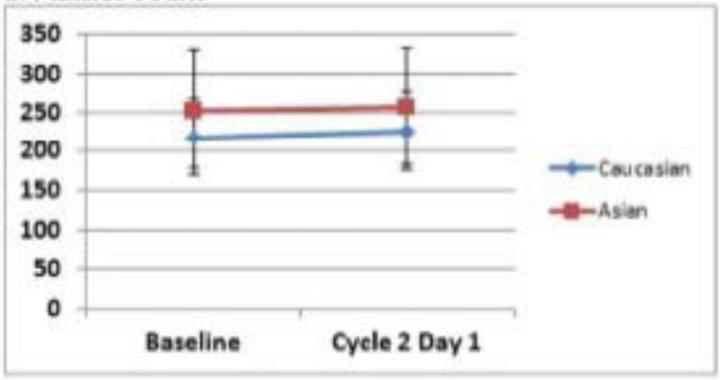
c. Maximal Change From Baseline in Insulin Resistance Index (HOMA-IR)

d. Maximal Change From Baseline in Fasting Serum C-Peptide Level (ng/mL)

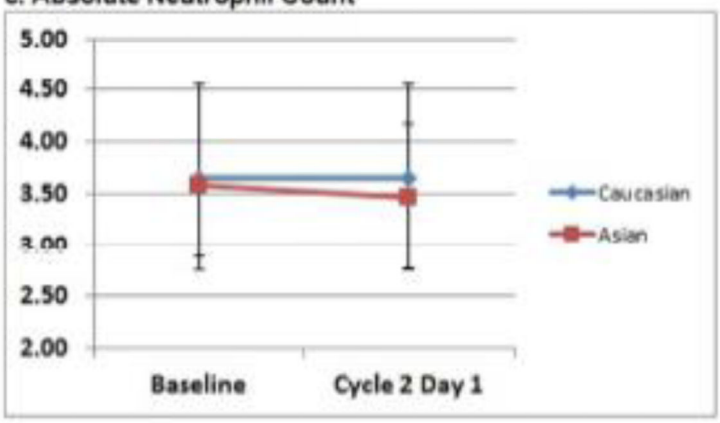
a. Hemoglobin



b. Platelet Count



c. Absolute Neutrophil Count



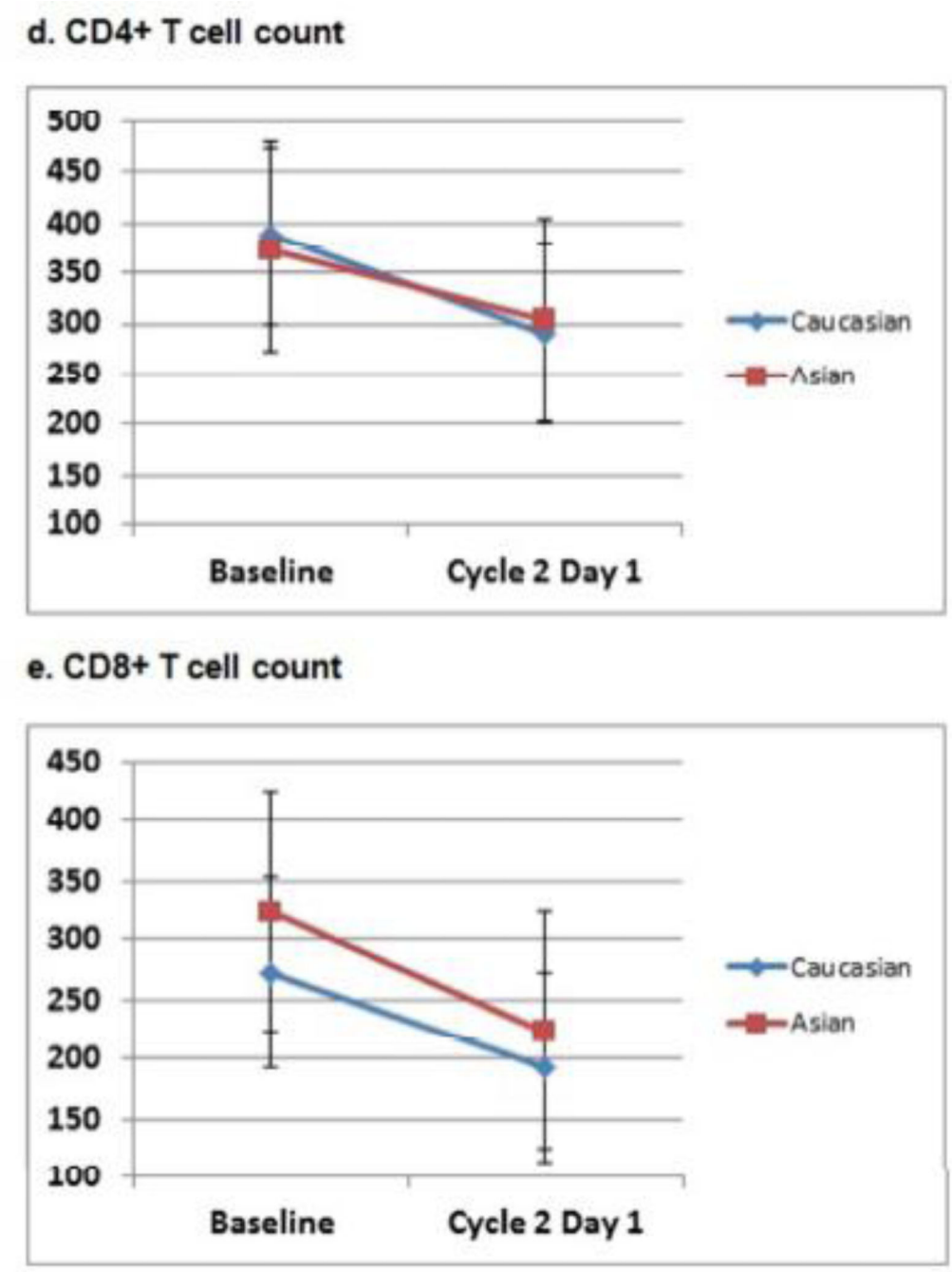


Figure 2.
Change in Hematologic Parameters By Patient Ethnicity

Table 1

Baseline Characteristics

	Asian Patients (N = 31)	Caucasian Patients (N = 72)	P-Value*
Median Age (range)	57 (22–77)	61 (22–84)	0.10
Gender (male, %)	50%	51%	0.90
Median Weight, kg (range)	61.6 (41.7–93)	75.0 (45.5–119.3)	**< 0.001**
Median Body Surface Area, m^2 (Mosteller)	1.66 (1.35–1.99)	1.89 (1.41–2.31)	**< 0.001**
Median Body Mass Index, kg/m^2 (range)	23.0 (16.9–32.4)	24.8 (18.3–49.7)	**0.024**
Predominant Drug Target			
PI3-kinase	29.0%	45.8%	
TORC1	22.6%	15.3%	0.12
TORC1 + 2	48.4 %	38.9%	
Number of Patients Treated at Dose Level			
I	10 (32%)	21 (29%)	
II	8 (26%)	15 (21%)	
III	6 (19%)	18 (25%)	0.96
IV	4 (13%)	10 (14%)	
V or Higher	3 (10%)	8 (11%)	
Median Fasting Plasma Glucose, mg/dL (range)	96 (86–144)	97 (77–143)	0.70
Median Hemoglobin A1c, % (range)	5.6 (4.4–8.2)	5.4 (4.1–6.6)	0.47
Median HOMA-IR Score (range)	0.48	0.57	0.95
Median Fasting C-peptide Level, ng/mL (range)	1.70	1.67	0.93
Median Blood Count Parameters (range)			
Hemoglobin (g/dL)	12.2 (8.9–16.5)	12.6 (9.4–15.8)	0.76
Absolute neutrophil count	3.58 (1.31–12.97)	3.65 (1.73–12.95)	0.87
Platelet Count	251 (78–570)	224 (104–513)	0.77
CD4+ T cell Count	403 (156–1048)	357 (46–918)	0.73
CD8+ T cell Count	323 (117–913)	296 (102–994)	0.36
Median Serum Creatinine, mg/dL (range)	0.76 (0.40–1.66)	0.78 (0.43–1.46)	0.93
Median Liver Function Tests (range)			
Total bilirubin	0.9 (0.2–1.6)	0.8 (0.3–2.2)	0.37
Aspartate aminotransferase	30 (12–101)	28 (10–219)	0.87
Albumin	3.6 (2.4–4.8)	3.6 (2.4–4.7)	0.93

Table 2

Dose Delivery, Tolerability and Incidence of Adverse Events Related to PI3K/mTOR Inhibition By Patient Ethnicity

Asian			
Patients			
(N = 31)	**Caucasian Patients**		
(N = 72)	**P-Value***		
Median Duration of Therapy, weeks (range)	7.2 (1–63)	7.0 (1–37)	0.77
Mean Dose Intensity During First 8 Weeks of Protocol Therapy	79%	84%	0.401
Incidence of Grade ≥ 2 Hyperglycemia	37.5%	18.1%	**0.032**
Incidence of Grade ≥ 2 Mucositis	25.0%	27.8%	0.77
Incidence of Grade ≥ 2 Rash	28.1%	22.3%	0.35
Incidence of Grade ≥ 2 Fatigue	40.6%	36.1%	0.66
Incidence of Any Grade Pneumonitis	6.5%	2.8%	0.36

* Chi-squared test used for comparisons between Asian and Caucasian patients.

* Mann-Whitney test used for continuous variables and chi-squared or Fisher's exact test for categorical variables.

Table 3

Impact of Specific PI3K/mTOR Pathway Inhibitor on Fasting Plasma Glucose Levels

Type of Pathway Inhibitor	Sample Size (Caucasian/ Asian)	Maximal Median Change From Baseline in FPG (g/dl) (range)		P-value
		Caucasian	Asian	
PI3K	33/9	20 (−19–202)	69 (−6–198)	**0.03**
TORC 1	11/7	7 (−35–32)	17 (−4–40)	0.38
TORC 1 + 2	28/15	18 (−13–161)	42 (7–100)	0.38