Clinical Cancer Research

First-in-Human Phase I Study of GSK2126458, an Oral Pan-Class I Phosphatidylinositol-3-Kinase Inhibitor, in Patients with Advanced Solid Tumor Malignancies

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Abstract

Purpose: GSK2126458 (GSK458) is a potent inhibitor of PI3K (α, β, γ, and δ), with preclinical studies demonstrating broad antitumor activity. We performed a first-in-human phase I study in patients with advanced solid tumors.

Materials and Methods: Patients received oral GSK458 once or twice daily in a dose-escalation design to define the maximum tolerated dose (MTD). Expansion cohorts evaluated pharmacodynamics, pharmacokinetics, and clinical activity in histologically and molecularly defined cohorts.

Results: One hundred and seventy patients received doses ranging from 0.1 to 3 mg once or twice daily. Dose-limiting toxicities (grade 3 diarrhea, $n = 4$; fatigue and rash, $n = 1$) occurred in 5 patients ($n = 3$ at 3 mg/day). The MTD was 2.5 mg/day (MTD with twice daily dosing undefined). The most common grade ≥ 3 treatment-related adverse events included diarrhea (8%) and skin rash (5%). Pharmacokinetic analyses demonstrated increased duration of drug exposure above target level with twice daily dosing. Fasting insulin and glucose levels increased with dose and exposure of GSK458. Durable objective responses (ORs) were observed across multiple tumor types (sarcoma, kidney, breast, endometrial, oropharyngeal, and bladder cancer). Responses were not associated with *PIK3CA* mutations (OR rate: 5% wild-type vs. 6% mutant).

Conclusions: Although the MTD of GSK458 was 2.5 mg once daily, twice-daily dosing may increase duration of target inhibition. Fasting insulin and glucose levels served as pharmacodynamic markers of drug exposure. Select patients achieved durable responses; however, *PIK3CA* mutations were neither necessary nor predictive of response. Combination treatment strategies and novel biomarkers may be needed to optimally target PI3K. *Clin Cancer Res; 22(8); 1932–9. ©2015 AACR.*

Introduction

The PI3K pathway is an important mediator of glucose metabolism, and in tumors, of cancer cell growth, survival, and metabolism (1–4). Upregulation of the pathway via activating mutations (e.g., *PIK3CA*), loss of suppressor proteins (e.g., PTEN), or activation of upstream receptor tyrosine kinases (e.g., Insulin-like growth receptor and HER family) has been implicated in the initiation and progression of numerous cancer subtypes, suggesting its role as a therapeutic target across multiple solid tumor malignancies and in preclinical models (5–9).

Several agents targeting the PI3K pathway (e.g., TORC1 inhibitors) of various potency as well as narrow-target specificity have been tested (10). GSK2126458 (GSK458) is a reversible, selective, pan-PI3K ATP-competitive inhibitor with a K_i for the catalytic p110α subunit in the subnanomolar range, with similar potency against three somatic "hotspot" mutant forms of PI3K p110α (E542K, E545K, and H1047R).

In vitro studies indicated antiproliferative effects of GSK458 across a broad panel of cancer cell lines. Breast cancer cell lines harboring activating mutations in *PIK3CA* were among the most sensitive to GSK458, whereas cell lines harboring *RAS/RAF* mutations were associated with poor response. Preclinical pharmacodynamic analyses demonstrated a dose-dependent decrease in phospho-AKT, a key downstream mediator of the PI3K signal transduction pathway. *In vivo*, GSK458 displayed dose-dependent delays in tumor growth across a range of xenograft models and tumor regression in HCC1954 xenografts (*PIK3CA*-mutant and *KRAS* wild-type breast cancer cell line). The biologic relevance of wild-type or mutated *PIK3CA* and the correlation with on-target side effects such as glycemic dysregulation has remained an unanswered question.

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Translational Relevance

The results demonstrate a subset of patients with durable responses to single-agent therapy, including two patients with ongoing tumor responses lasting more than 4 years in duration. The data highlight the need to better define the molecular profile of these "exceptional responders." Notably, *a priori* selection of predictive biomarkers, including somatic *PIK3CA* mutations, failed to enrich for clinical benefit or objective response, highlighting the importance of developing novel functional biomarkers to enrich for therapeutic benefit. The modest single-agent activity observed calls into question the development of PI3K inhibitors as monotherapy for advanced solid tumor malignancies and suggests that combination therapy will be required.

The primary objective of this first-in-human phase I dose-escalation study was to determine the recommended phase II dose (RP2D) of GSK458; secondary objectives included characterization of pharmacokinetic and pharmacodynamic profiles and to explore the relationship between pharmacokinetics, pharmacodynamics, response prediction biomarkers, and clinical outcomes. Pharmacodynamic biomarkers included 2[18F]fluoro-2-deoxy-D-glucose (FDG)–PET, immunohistochemical assessment of intratumoral protein phosphorylation of downstream effectors of the PI3K pathway (AKT, ERK, and S6), and fasting serum insulin and glucose levels.

Materials and Methods

Patient population

Patients were required to have advanced solid tumor malignancies that had progressed on standard therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function including absolute neutrophil count $> 1.5 \times 10^9$/L, total bilirubin $< 1.5 \times$ ULN, creatinine < 2 mg/dL or creatinine clearance > 40 mL/min, fasting serum glucose < 126 mg/dL, and cardiac ejection fraction $>$ LLN. Patients with prior treatment with a PI3K inhibitor were excluded.

Study approval was obtained from the ethics committees at the participating institutions and regulatory authorities. All patients gave written informed consent. The study followed the Declaration of Helsinki and good clinical practice guidelines.

Study design and treatment schedule

This was a phase I, multicenter, open-label, single-agent, dose-escalation study of GSK458. The starting dose of GSK458 was 0.1 mg/day. The initial once-daily dosing schedule was based upon *in vivo* xenograft data demonstrating improved efficacy with once or twice-daily dosing compared with every 2-day dosing schedule. Twice-daily dosing of GSK458 was subsequently tested after initial pharmacokinetic/pharmacodynamic data suggested that once-daily dosing did not achieve target serum concentrations over a 24-hour interval.

The dose-escalation portion of the study used a 3+3 escalation schema, and also took into account predicted doses as determined by Escalation with Overdose Control Bayesian Adaptive Design Methodology (11). The MTD was defined as the exposure expected to produce some degree of medically unacceptable dose-limiting toxicitiy (DLT, θ). For this study, the probability of DLT (θ) was set as θ = 0.25.

Additional patient cohorts consisted of the following: (i) pharmacodynamic expansion cohorts, including (a) patients who underwent paired tumor biopsies and (b) patients who underwent FDG-PET scans, (ii) predictive marker cohorts including *PIK3CA*-mutated breast and urothelial carcinoma and *KRAS* wild-type endometrial carcinoma, (iii) safety profile expansion cohort to better characterize safety profile and define RP2D, (iv) exploratory cohorts consisting of patients with renal cell, bladder, and endometrial carcinoma enrolled without selection based upon tumor genotyping. Dosing for the expansion cohorts occurred at or below the MTD defined by the dose-escalation cohorts. Availability of archival tumor tissue was required for patients enrolled into the predictive markers cohorts and optional for all others.

Sample size justification

The planned total sample size was between 175 to 225 patients. The sample size of the dose-escalation cohort was based upon the 3+3 dose-escalation schema as outlined above. Up to 12 patients per dose level were enrolled in the safety expansion cohorts to better define the safety profile and RP2D of GSK458. The planned sample size of each planned pharmacodynamic cohort was 15 evaluable patients to achieve 80% power with α = 0.05 in detecting an effect size of 0.7 in percent change from baseline in prespecified pharmacodynamic markers.

For each predictive and exploratory cohort, it was assumed that the maximum objective response (OR) rate for an ineffective drug was 0.1, and the minimum OR rate for an effective drug was 0.3. Simon optimal two-stage design was used to test the null hypothesis of 10% response proportion with 80% at α = 0.05. If one or fewer responses were observed in the first 10 patients enrolled per cohort, and also upon review of the number of additional patients with tumor regressions classified as stable disease, the cohort was closed to accrual.

The actual final planned analyses were performed after 167 patients completed study treatment and the database was locked on December 12, 2012.

Safety and efficacy assessments

Clinical and laboratory assessments were conducted at baseline and weekly during cycle 1 (28-day cycle length) and once per cycle thereafter. Ambulatory blood glucose monitoring occurred daily during cycle 1. Tumor response by RECIST 1.0 criteria was assessed at baseline and every 2 cycles thereafter. Adverse events were graded using Common Toxicity Criteria version 3.0.

Pharmacodynamic assessments

In selected pharmacodynamic cohorts, paired tumor biopsies and FDG-PET scans were performed within 14 days prior to starting GSK458 and repeated during days 2 to 4 of cycle 1. Pre- and postdose biopsies were evaluated by IHC for protein expression of total and phosphorylated forms of AKT, ERK, and P70s6K, phospho-histone 3, phosphorylated proline-rich AKT, and Ki67 proliferation index. Serial fasting glucose and insulin samples were collected.

Pharmacokinetic assessments

Blood samples for GSK458 concentrations were obtained predose and up to 24 hours postdose on days 1 and 15 of cycle 1 for patients treated with the daily dosing schedule. For the twice-daily

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dosing schedule, samples were obtained up to 12 hours after each dose (am and pm) on days 1 and 15. GSK458 blood concentration was determined using validated LC/MS-MS. The lower limit of quantification of GSK458 was 0.5 ng/mL. Standard pharmacokinetic parameters were computed by noncompartmental methods (WinNonLin). Values assessed were area under the plasma-concentration time curve from time 0 to 24 or 12 hours (AUC_{0-24}) and (AUC_{0-12}) for once- or twice-daily dosing, respectively, and maximum blood concentration (C_{max}) and time to C_{max} (t_{max}). Accumulation was determined by AUC day 15/AUC day 1.

Results

Study population

A total of 170 patients were enrolled between September 2009 and August 2012. Baseline characteristics of the enrolled patients are shown in Table 1. Seventy percent of patients received three or more prior lines of therapy in the advanced setting. Overall, *PIK3CA* mutation status was known in 68 patients (40%), of which 18 patients (26%) harbored somatic *PIK3CA* mutations at the time of study enrollment.

Patient disposition is shown in Table 2. Sixty-five patients (38%) enrolled onto the daily or twice-daily dose-escalation phase, and 105 patients enrolled into one of the prespecified expansion cohorts. The majority (79%) of patients discontinued study therapy for disease progression. Two patients remained on study treatment (>4 years' duration).

Table 1. Patient characteristics (N = 170)

Gender, *n* (%)	
Female	84 (49)
Male	86 (51)
Age in years, mean (range)	56.7 (22–85)
Race, *n* (%)	
Caucasian	154 (91)
Asian	8 (5)
African American	6 (4)
Unknown	2 (1)
Ethnicity, *n* (%)	
Hispanic	(2)
Non-hispanic	(98)
Body mass index, kg/m^2 mean (range)	26.8 (18.2–48.5)
ECOG performance status, *n* (%)	
0	57 (34)
1	113 (66)
Tumor histology, *n* (%)	
Colon/rectum	31 (18)
Renal cell	24 (14)
Breast	22 (13)
Bladder	17 (10)
Endometrial	15 (9)
Melanoma	8 (5)
Ovary/primary peritoneal	6 (4)
Pancreas	4 (2)
Prostate	4 (2)
Other	39 (23)
Known *PIK3CA* mutation status at study entry, *n* (%)	
Positive	18 (11)
Negative	50 (29)
Unknown	102 (60)
Number of lines of prior anticancer therapy, *n* (%)	
1	20 (12)
2	29 (17)
3	35 (21)
4	24 (14)
5+	60 (35)

Table 2. Patient disposition

Number of subjects enrolled per cohort, *n* (%)	
Daily dosing–escalation cohort	43 (25)
Twice-daily dosing–escalation cohort	22 (13)
Safety expansion cohort	20 (12)
PD expansion cohort	36 (21)
Exploratory cohort (renal, endometrial, and bladder cancer)	40 (24)
Breast cancer with *PIK3CA* mutation	9 (5)
Reasons for study discontinuation, *n* (%)	
Disease progression	136 (80)
Withdrawal of consent	12 (7)
Adverse event	9 (5)
Other	11 (7)
Therapy ongoing	2 (1)
Number of patients included in study populations, *n* (%)	
Safety/toxicity	170 (100)
PK population	166 (98)
PD (blood)	170 (100)
PD (tumor)	25 (15)

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics.

Determination of MTD

In the once-daily dose-escalation part of the study, 8 dose levels were explored (Table 3). The first DLT (grade 3 diarrhea) occurred at the 1.5 mg once-daily dose. This cohort was expanded without further dose limiting events. Three DLTs (all grade 3 diarrhea events) occurred at the 3 mg once-daily dose level, rendering this the nontolerated dose (NTD). Patients were subsequently treated at dose levels of 2 mg and 2.5 mg once daily without any observed DLTs, establishing 2.5 mg as the MTD with once daily dosing schedule.

Because of the observation of a shorter duration of GSK458 drug levels above target range with daily dosing, twice-daily dose escalation was initiated at a dose of 0.75 mg twice daily, and 5 dose levels were studied (Table 3). No DLTs were observed at the 2 mg twice-daily dose level. One of the three patients experienced a DLT (grade 3 fatigue + grade 3 rash) at 2.5 mg twice daily; however, due to the decision to discontinue single-agent testing of GSK458, further patients were not treated at this dose level; and therefore, the MTD with twice-daily dosing could not be determined.

Safety results

The most common adverse events (any grade severity) experienced on study were fatigue (45%), diarrhea (45%), nausea (42%), decreased appetite (30%), and vomiting (26%; Table 4). The most common grade ≥ 3 adverse events included diarrhea (8%), hyperglycemia (>250 mg/dL; 6%), and skin rash (5%). Nine patients (5%) experienced a treatment-related serious adverse event, including four patients with diarrhea. Diarrhea appeared to be an intermittent, self-limiting event for most patients, with resolution reported in 82% of patients. Rash was noted in 21 patients (12%), with most patients experiencing a single occurrence (81%). The most common type of rash was maculopapular in appearance; acneiform rash was rare (2 patients). Hyperglycemia was noted in 37 patients (22%), was mostly grade 1 or 2 in severity, and did not require dose adjustment in the majority of patients (92%). Cardiac toxicity was minimal with 2 (1%) patients experiencing post-baseline decreases in ejection fraction below the lower limit of normal and >10% from baseline. There were no significant effects on mood noted. There were no treatment-related grade 5 adverse events.

Table 3. Summary of DLTs by dose level

Dose (mg)	Frequency	Treated (n)	Number of DLTs	DLT
0.1	Once daily	7	0	
0.2	Once daily	4	0	
0.4	Once daily	5	0	
0.75	Once daily	9	0	
1.5	Once daily	14	1	Grade 3 diarrhea ($n = 1$)
3.0	Once daily	9	3	Grade 3 diarrhea ($n = 3$)
2.0	Once daily	38	0	
2.5[a]	Once daily	57	0	
0.75	Twice daily	3	0	
1.0	Twice daily	5	0	
1.5	Twice daily	8	0	
2.0	Twice daily	8	0	
2.5	Twice daily	3	1	Grade 3 fatigue + grade 3 rash ($n = 1$)

[a]2.5 mg once daily established as MTD for single daily dosing. MTD for twice-daily dosing schedule not determined.

Pharmacokinetic analyses

Following single daily dosing, the median t_{max} ranged from 1 to 4 hours. Mean $AUC_{0-24hrs}$ and C_{max} increased approximately in proportion with doses from 0.1 to 0.4 mg daily and then from 0.75 mg to 3.0 mg/day but not across the whole dose range (Supplementary Table S1 and Fig. 1A). As expected due to accumulation of GSK458, the mean $AUC_{0-12hrs}$ and C_{max} were generally higher following the second dose versus the first dose with the twice-daily dosing schedule. The average time spent > 20 ng/mL (the target dose level based on preclinical data) was greater with twice-daily than once-daily dosing (21.2 hours at 2 mg twice daily vs. 14.5 hours at the once-daily MTD of 2.5 mg; Fig. 1B). The terminal $T_{1/2}$ and $AUC_{0->\infty}$ could not be determined due to the large %AUC extrapolation in >20% of patients. Because of between-subject variability, pharmacokinetic values overlapped across doses.

The repeat dose (day 15) pharmacokinetics of GSK458 demonstrated that predose (C_{tau}) levels generally increased with dose, but values were variable and overlapped across doses. C_{tau} values were higher on twice-daily versus once-daily dosing schedule for comparable cumulative daily doses (e.g., 2 mg daily vs. 1 mg twice daily). The mean accumulation ratio with daily and twice daily dosing schedules was approximately 1.4.

Pharmacodynamic analyses

Putative biomarkers of the PI3K signaling pathway were prospectively investigated. The approach included measurement of phosphorylation levels of various downstream kinases in a prospectively identified cohort of patients harboring tumors with activating somatic *PIK3CA* mutations. Baseline and post-dose tumor biopsies for immunohistochemichal analysis were obtained in a total of 24 patients, with 13 patients having paired evaluable biopsies. Eleven of the 13 patients were treated with GSK458 once daily. The percent change from baseline in p-AKT H-score was inconsistent and did not correlate with the *PIK3CA* mutation status or with dose level of a patient (Fig. 2A).

For the subset of patients with both pharmacokinetic and pharmacodynamic data available, the correlation between drug exposure (AUC) and percent change from baseline in phosphorylated-AKT H-score by IHC was weak and not significant

Table 4. Summary of adverse events (any grade severity) in ≥10% of patients across dose levels

	Subjects, n (%)													
	Once-daily dosing								Twice-daily dosing					
	0.1	0.2	0.4	0.75	1.5	2.0	2.5	3.0	0.75	1.0	1.5 mg	2.0 mg	2.5 mg	Total
Event	n = 7	n = 4	n = 5	n = 9	n = 14	n = 38	n = 57	n = 9	n = 3	n = 5	n = 8	n = 8	n = 3	N = 170
Any event	7 (100)	4 (100)	5 (100)	9 (100)	14 (100)	38 (100)	57 (100)	9 (100)	3 (100)	5 (100)	8 (100)	8 (100)	3 (100)	170
Diarrhea	0	0	0	6 (67)	3 (21)	15 (39)	32 (56)	6 (67)	0	2 (40)	6 (75)	4 (50)	3 (100)	77 (45)
Fatigue	2 (29)	1 (25)	1 (20)	2 (22)	9 (64)	14 (37)	32 (56)	5 (56)	1 (33)	2 (40)	3 (38)	2 (25)	3 (100)	77 (45)
Nausea	2 (29)	0	0	2 (22)	6 (43)	17 (45)	28 (49)	4 (44)	1 (33)	3 (60)	3 (38)	3 (38)	2 (67)	71 (42)
Decreased appetite	1 (14)	1 (25)	0	1 (11)	5 (36)	9 (24)	17 (30)	4 (44)	1 (33)	4 (80)	4 (50)	3 (38)	1 (33)	51 (30)
Vomiting	0	0	0	1 (11)	4 (29)	10 (26)	23 (40)	4 (44)	0	0	0	2 (25)	0	44 (26)
Hyperglycemia	0	1 (25)	1 (20)	0	2 (14)	5 (13)	12 (21)	4 (44)	0	1 (20)	2 (25)	2 (25)	1 (33)	31 (18)
Dyspnea	1 (14)	0	0	2 (22)	2 (14)	8 (21)	10 (18)	2 (22)	0	1 (20)	0	1 (13)	0	27 (16)
Pyrexia	1 (14)	0	1 (20)	1 (11)	5 (36)	1 (3)	12 (21)	2 (22)	0	1 (20)	1 (13)	0	0	25 (15)
Constipation	0	1 (25)	0	0	1 (7)	7 (18)	7 (12)	2 (22)	2 (67)	2 (40)	1 (13)	1 (13)	0	24 (14)
Mucositis	0	0	0	0	1 (7)	5 (13)	6 (11)	4 (44)	0	2 (40)	4 (50)	1 (13)	1 (33)	24 (14)
Back pain	0	1 (25)	0	2 (22)	0	7 (18)	8 (14)	0	1 (33)	3 (60)	0	1 (13)	0	23 (14)
Urinary tract infection	1 (14)	0	0	0	2 (14)	5 (13)	10 (18)	1 (11)	0	0	2 (25)	2 (25)	0	23 (14)
Abdominal pain	0	0	0	1 (11)	1 (7)	3 (8)	11 (19)	1 (11)	1 (33)	1 (20)	1 (13)	0	0	22 (13)
Rash	0	0	0	1 (11)	0	4 (11)	7 (12)	4 (44)	0	0	1 (13)	1 (13)	3 (100)	21 (12)
Cough	0	0	0	1 (11)	0	3 (8)	10 (18)	3 (33)	1 (33)	0	0	1 (13)	1 (33)	20 (12)
Peripheral edema	0	0	0	0	1 (7)	5 (13)	11 (19)	0	0	1 (20)	1 (13)	1 (13)	0	20 (12)
Anemia	0	1 (25)	0	1 (11)	2 (14)	4 (11)	5 (9)	3 (33)	2 (67)	0	0	1 (13)	0	19 (11)
Headache	2 (29)	0	1 (20)	3 (33)	1 (7)	3 (8)	3 (5)	2 (22)	0	1 (20)	2 (25)	1 (13)	0	19 (11)
Aspartate aminotransferase	0	1 (25)	2 (40)	0	2 (14)	1 (3)	6 (11)	1 (11)	0	1 (20)	1 (13)	2 (25)	0	17 (10)

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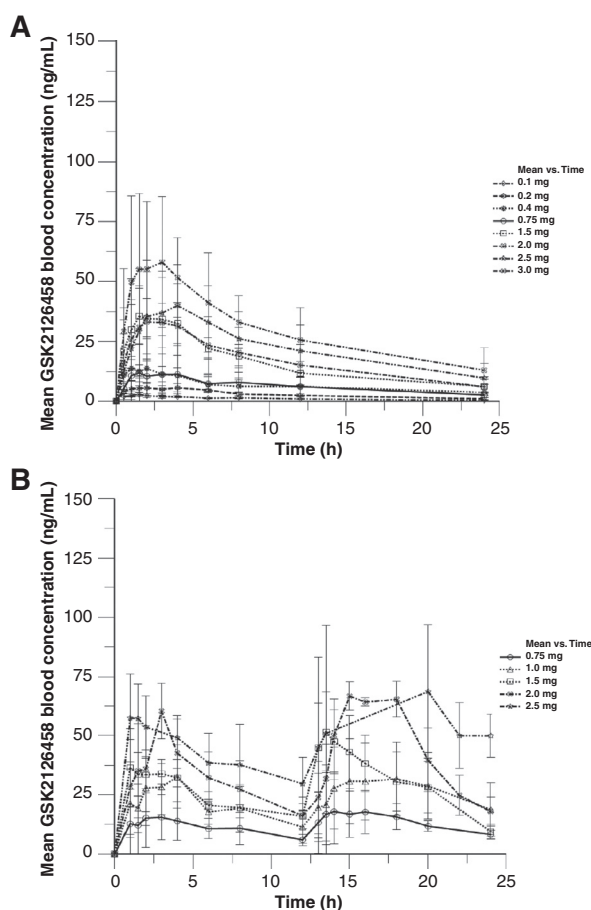
Figure 1.
A, mean blood concentration versus time on day 1 with single daily dosing. B, mean blood concentration versus time on day 1 with twice-daily dosing.

($r = -0.27$; Fig. 2B). Similar patterns were observed for phosphorylated P70s6K and ERK (data not shown).

Paired FDG-PET scans were performed in 14 patients, all of whom were treated with GSK458 once daily (Fig. 2C). Overall, decrease in FDG avidity upon initiation of GSK458 treatment was observed in 28 of 38 evaluable metastatic lesions (74%). There was no consistent dose–effect relationship on FDG-PET scans by metastatic lesion. The median change from baseline in sum of SUV_{max} by patient varied from -3.1 to 0.1 across the 0.75 mg to 3 mg once-daily dosing levels.

In contrast, the percent change from baseline in fasting plasma glucose levels on day 1 of study therapy was significantly associated with GSK458 dose level (Fig. 2D). Likewise, the fold increase in insulin from baseline to 6 hours postdose on cycle 1 day 1 was significantly associated with dose and serum concentration of GSK458 (data not shown).

Efficacy analyses

The maximum percent change from baseline in tumor measurements is shown in Fig. 3. Forty-three patients (25%) had nonmeasurable disease and/or discontinued study prior to first restaging scans and thus were not evaluable for assessment of OR. Overall, ORs were seen in 9 patients (5%; Supplementary Table S2). Two of the nine ORs were observed in the twice-daily dosing

cohort ($N = 27$; 7% response rate). In the expansion cohort of 84 patients enrolled with breast, renal cell, bladder, or endometrial cancer, there were a select group of patients with prolonged OR or disease stabilization, including 5 (6%) patients treated with GSK458 for greater than 6 months without disease progression (Supplementary Fig. S1). Two patients with bladder and renal cell carcinoma remain on therapy with ongoing partial and complete responses, respectively, for more than four years duration.

Importantly, there did not appear to be enrichment for tumor responses or prolonged disease stabilization in *KRAS* wild-type endometrial cancer patients or in patients with tumors harboring somatic *PIK3CA* mutations, with objective tumor response rates of 7% and 6% respectively in these two prespecified expansion cohorts.

Discussion

The dose-escalation/expansion study of the pan-class I PI3K inhibitor GSK458 demonstrates that targeting the PI3K pathway directly with this small-molecule inhibitor is well tolerated and associated with single-agent activity in a small percentage of patients across multiple tumor types in a heavily pretreated patient population. Prolonged objective tumor responses and disease stabilization was observed in several tumor types including bladder and renal cell carcinoma. Overall, however, limited single-agent activity was observed and *a priori* selection of molecularly defined tumor subtypes including *PIK3CA*-mutant breast and bladder cancer and *KRAS* wild-type endometrial cancer did not enrich for tumor response or prolonged disease stabilization. In accounting for these findings, several points warrant consideration.

First, in contrast to prior reports (12–17), activating somatic *PIK3CA* mutations did not appear to be a predictive biomarker of clinical benefit in the expansion cohort, and the responses seen in nonmutated patients suggest that in our population, *PIK3CA* mutations were neither predictive nor necessary for response. Baseline and early changes in FDG uptake on PET scan were likewise neither associated with dose nor with subsequent clinical response. The PI3K pathway is essential for many cellular functions, and the on-target effects of GSK458 treatment on plasma glucose and serum insulin levels suggest a strong inhibition of the wild-type PI3K pathway. These results highlight the need for more effective biomarkers to predict which subset of tumors are highly dependent on PI3K/mTOR signaling for proliferation and therefore more likely to respond to targeted PI3K inhibition. Without such biomarkers, the clinical development of targeted PI3K/mTOR pathway inhibitors will be hindered.

Emerging evidence indicates that PI3K inhibitors may have limited single-agent activity in tumors with *PIK3CA* mutations due to compensatory activation of alternative signaling pathways including mitogen-activated protein (MAP) kinase, particularly in tumors harboring coexisting *RAS* mutations (18). Other α isoform-specific and pan-class inhibitors of PI3K, including BYL719 and BKM120, respectively, have also demonstrated limited single-agent activity across a variety of solid tumor malignancies including those harboring *PIK3CA* mutations (19, 20). In contrast to activating mutations in other oncogenes (e.g., *EGFR* and *BRAF*) in which significant single-agent activity is observed, combination treatment strategies may be necessary to effectively target the PI3K pathway. In a prior retrospective review of *PIK3CA*-mutant tumors treated with single-agent PI3K inhibitors versus
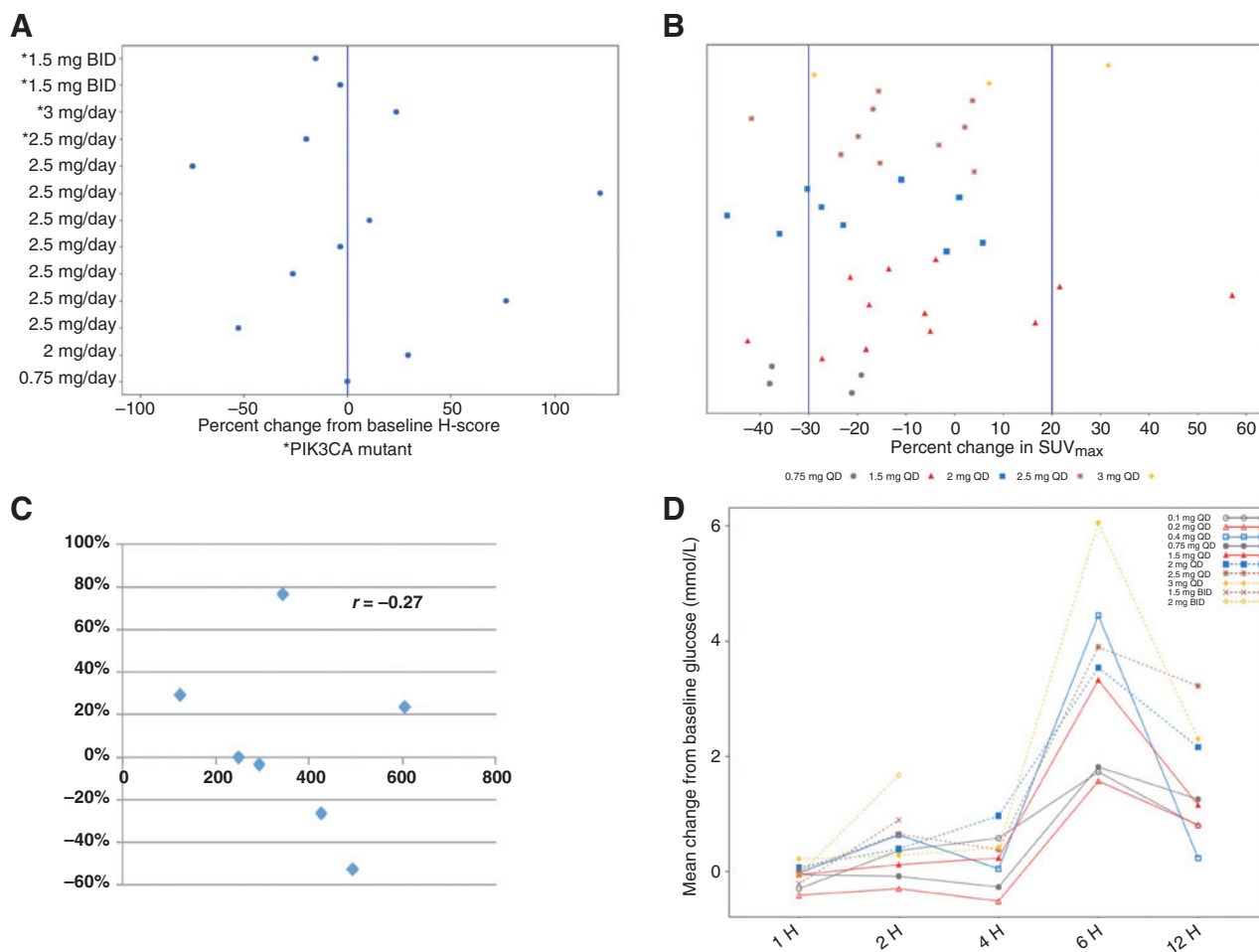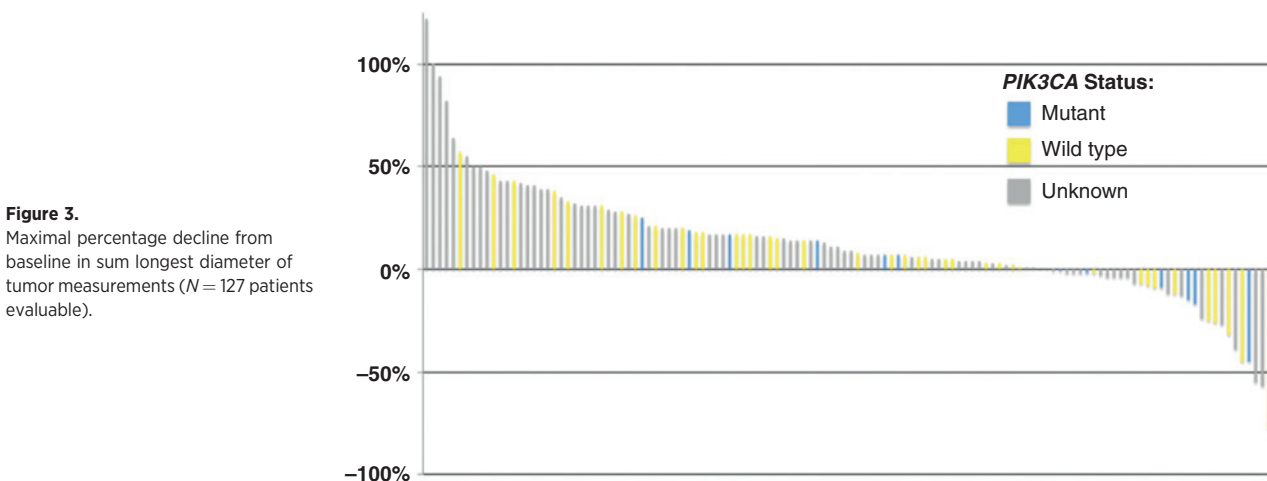
Figure 2.
A, change from baseline in level of expression of phosphorylated AKT by dose level and *PIK3CA* mutation status. B, percent change from baseline in phospho-AKT by H-score versus drug exposure (AUC; $N = 7$ patients evaluable). C, maximal percent SUV change from baseline on FDG-PET by metastatic lesion ($N = 14$ patients). D, change from baseline in fasting glucose levels on cycle 1 day 1 dosing. QD, once daily.

combination therapy (including cotargeting of MAP kinase pathway), progression-free survival was significantly longer with combination therapy (18). A prospective clinical trial combining GSK458 with the MEK inhibitor trametinib recently demonstrat-ed prolonged disease stabilization in a subset of tumors harboring *KRAS* mutations (21).

The study results also highlight the importance of pharmaco-kinetic/pharmacodynamic data to define the optimal biologic

Figure 3.
Maximal percentage decline from baseline in sum longest diameter of tumor measurements ($N = 127$ patients evaluable).

dose in a first-in-patient study of a targeted anticancer therapy. Pharmacokinetic/pharmacodynamic modeling using mouse BT474 xenografts yielded a sustained mean target serum concentration of >20 ng/mL as the expected IC_{67} for AKT phosphorylation with range of 6.6 to 60 ng/mL to account for potential translation differences between mice and humans. Pharmacokinetic data from the daily dosing schedule suggested that the target serum concentration of >20 ng/mL was not being sustained over a 24-hour interval. In addition, significant interpatient variability in drug exposure was observed across the once-daily dosing levels. These two factors likely contributed to the lack of dose- and exposure-dependent effect observed in the pharmacodynamic analyses with daily dosing of GSK458 and may have impacted the observed antitumor activity. The twice-daily dosing schedule achieved more consistent serum levels above the target exposure. Whether twice-daily dosing of GSK458 translates into more effective target inhibition and enhanced antitumor activity requires further clinical evaluation as pharmacodynamic analyses were nearly entirely limited to the once-daily dosing cohort and the MTD was not reached with twice-daily dosing.

GSK458 was fairly well tolerated. The frequency of adverse events appeared to be similar with once-daily versus twice-daily dosing. Diarrhea was a common clinical event; however, it was largely grade 1–2 in severity for most patients, with grade 3 diarrhea (>7 stools above baseline/day) observed in 8% of enrolled patients. Diarrhea appeared to be self-limiting and responsive to temporary dose interruptions and resolved in more than 80% of patients at the time of last study reporting. Hyperglycemia, a class effect (and potential pharmacodynamic biomarker) of PI3K pathway inhibition, was observed in 18% of patients on study and was mostly grade 1–2 in severity. Hyperglycemia was commonly managed with oral agents (e.g., metformin); the initiation of insulin during protocol therapy was a rare event. Other class effects of PI3K pathway inhibition were observed, including rash and mucositis, both managed effectively with temporary dose holds and/or initiation of topical steroid treatment. Interestingly, in contrast to other PI3K inhibitors such as BKM120, effects on mood were uncommon, suggesting potentially a differential penetration across the blood–brain barrier or other off-target differences in receptor inhibition (20).

Conclusion

The MTD with daily dosing of GSK458 is 2.5 mg/day. However twice-daily dosing may optimize target inhibition across a 24-hour interval. Pharmacodynamic analyses showed a dose-dependent increase in fasting insulin and glucose levels that may serve as a pharmacologic biomarker of drug exposure. Antitumor activity of GSK458 was not enriched in *KRAS* wild-type endometrial cancer or in *PIK3CA*-mutant cancers in this study, highlighting the need for more effective predictive biomarkers of the PI3K signaling pathway. GSK458 is being evaluated in combination with other targeted agents as well as in noncancerous indications in which PI3K upregulation is implicated in disease etiology (e.g., idiopathic pulmonary fibrosis; NCT01725139).

Disclosure of Potential Conflicts of Interest

Authors' Contributions

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Grant Support

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First-in-Human Phase I Study of GSK2126458, an Oral Pan-Class I Phosphatidylinositol-3-Kinase Inhibitor, in Patients with Advanced Solid Tumor Malignancies

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