

Phase I, Dose-Escalation Study of BKM120, an Oral Pan-Class I PI3K Inhibitor, in Patients With Advanced Solid Tumors

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ABSTRACT

Purpose

This phase I dose-escalation study investigated the maximum-tolerated dose (MTD), safety, preliminary activity, pharmacokinetics (PK), and pharmacodynamics of BKM120, a potent and highly specific oral pan-Class I PI3K inhibitor.

Patients and Methods

Thirty-five patients with advanced solid tumors received daily BKM120 12.5 to 150 mg. Dose escalation was guided by a Bayesian logistic regression model with overdose control. Assessments included archival tumor molecular status, response by Response Evaluation Criteria in Solid Tumors (RECIST), positron emission tomography tracer uptake ($[^{18}\text{F}]$ fluorodeoxyglucose positron emission tomography [FDG-PET]), fasting plasma C-peptide, and phosphorylated ribosomal protein S6 (pS6) in skin biopsies.

Results

Overall, treatment was well tolerated. Dose-limiting toxicities were grade 2 mood alteration (80 mg), grade 3 epigastralgia, grade 3 rash, grade 2 and grade 3 mood alteration (100 mg), and two grade 4 hyperglycemia (150 mg). The MTD was 100 mg/d. Frequent treatment-related adverse events included rash, hyperglycemia, diarrhea, anorexia, and mood alteration (37% each); nausea (31%); fatigue (26%); pruritus (23%); and mucositis (23%). BKM120 demonstrated rapid absorption, half-life of ~40 hours, ~three-fold steady-state accumulation, dose-proportional exposure, and moderate interpatient variability. One patient demonstrated a confirmed partial response (triple-negative breast cancer); seven patients (20%) were on study for ≥ 8 months. BKM120 demonstrated dose-dependent pharmacodynamic effects on $[^{18}\text{F}]$ FDG-PET, fasting C-peptide, fasting blood glucose, and pS6. No significant trends were seen to correlate tumor molecular alterations with clinical activity.

Conclusion

This study demonstrates feasibility and proof-of-concept of class I PI3K inhibition in patients with advanced cancers. BKM120, at the MTD of 100 mg/d, is safe and well tolerated, with a favorable PK profile, clear evidence of target inhibition, and preliminary antitumor activity.

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INTRODUCTION

The intracellular phosphatidylinositol-3-kinase (PI3K) pathway regulates such cellular functions as cell proliferation, growth, survival, apoptosis, protein synthesis, and glucose metabolism.¹⁻³ Of the three classes of PI3K (I to III), class IA is the most implicated in cancer.⁴ Class-IA PI3K heterodimers comprise a p85-regulatory and a p110-catalytic subunit with several isoforms.⁴ Mutation or amplification of *PIK3CA*, the gene encoding the p110 α isoform, promotes oncogenic activation of the PI3K path-

way and occurs frequently in human cancers.⁴⁻⁸ Inactivation of the phosphatase and tensin homolog (PTEN), a key negative regulator of PI3K, via mutations or loss of protein expression is associated with tumorigenesis and observed in many cancers.^{4,9-11} Moreover, PI3K pathway activation may be associated with resistance to chemotherapy and targeted agents in different cancers.¹²⁻¹⁵ Selective inhibition of the PI3K pathway in cancer represents a promising therapeutic approach and is the focus of significant efforts in research and clinical development of novel agents targeting this pathway.

Preclinical studies of inhibitors of PI3K signaling have shown antiproliferative activity in cancer cells and inhibition of tumor growth in tumor xenograft models.^{4,16-18}

BKM120 (Novartis Pharma AG, Basel, Switzerland) is an oral pyrimidine-derived pan-PI3K inhibitor with specific and potent activity against class I PI3Ks. BKM120 inhibits wild-type and mutant PI3K α isoforms and PI3K β , γ , and δ isoforms at nanomolar concentrations.¹⁹ BKM120 has no inhibitory activity against the class III PI3K, or mammalian target of rapamycin (mTOR).¹⁹ In vitro experiments show a strong antiproliferative effect of BKM120 on human cancer cell lines with alterations in the PI3K pathway. This was confirmed in a screen of more than 400 cancer cell lines (Novartis, data on file), including MCF7-PIK3CA-mutated breast cancer cells.¹⁹ In vivo, BKM120 demonstrated significant antitumor activity in human tumor xenograft models with or without PIK3CA/PTEN mutations, with good correlation between BKM120 exposure and inhibition of PI3K signaling.²⁰

The primary objective of this first-in-human, phase I, dose-escalation study was to determine the maximum-tolerated dose (MTD) of oral BKM120 on a once-daily continuous schedule in adult patients with advanced solid tumors. Secondary objectives included assessment of safety and tolerability of BKM120, preliminary antitumor activity, and characterization of the pharmacokinetic (PK) and pharmacodynamic profiles. Pharmacodynamic assessments to measure clinical PI3K inhibition included tumor metabolic response by [¹⁸F]fluorodeoxyglucose positron emission tomography ([¹⁸F]FDG-PET), fasting plasma C-peptide levels, fasting plasma glucose (FPG), and phosphorylated ribosomal protein S6 (Ser240/244; pS6) in skin biopsies.

PATIENTS AND METHODS

Supplementary methods can be found in the Appendix (online only).

Patient Population

Patients had histologically confirmed advanced tumors failing standard therapy; one or more lesion as defined by Response Evaluation Criteria In Solid Tumors (RECIST); age \geq 18 years; life expectancy \geq 12 weeks; World Health Organization performance status \leq 2; adequate bone marrow, hepatic, and renal function; and FPG levels \leq 140 mg/dL (7.8 mmol/L). A representative tissue specimen for analysis of tumor molecular status was required. Key exclusion criteria were corticosteroid treatment \leq 2 weeks before starting BKM120; clinically manifest diabetes mellitus, including a history of gestational diabetes; and prior treatment with a PI3K inhibitor.

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

Study Design and BKM120 Dose Escalation

This was a phase I, multicenter, open-label, single-agent, dose-escalation study. Patients received oral, once-daily BKM120 capsule(s) starting at 12.5 mg on a 28-day continuous schedule until disease progression, unacceptable toxicity, or consent withdrawal. Assignment to treatment was based on Bayesian inference of a logistic regression model describing the dose-toxicity relationship and was guided by the escalation with overdose control principle.²¹ Dose-limiting toxicities (DLTs) were evaluated during the first treatment cycle (28 days). Main DLTs were defined as Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 \geq grade 3 hematologic or nonhematologic toxicity. Exceptions were \geq grade 2 pancreatitis, \geq 1 grade level increase in neurotoxicity, \geq grade 2 phototoxicity or skin rash necessitating treatment

interruption for more than 21 consecutive days, non-CTCAE grade 2 hyperglycemia not resolved to grade 0 within 14 consecutive days of initiation of oral antidiabetes medications, \geq non-CTCAE grade 3 hyperglycemia (Appendix Table A1, online only), grade 2 mood alteration not resolved to grade 1 within 14 days despite medical treatment (grade 2 anxiety was considered a DLT only if worsened from baseline), and \geq grade 3 mood alteration (per protocol amendment).

The MTD was defined as the highest dose of BKM120 not causing DLT in more than 33% of patients in the first treatment cycle. Twenty-one or more evaluable patients had to be treated before MTD declaration, with six or more evaluable patients treated at the MTD for one cycle. Criteria for evaluation were \geq 21 days BKM120 treatment in cycle 1, sufficient safety evaluation, or early discontinuation owing to DLT.

Safety and Efficacy Assessments

Clinical and laboratory assessments were conducted at baseline and on a weekly basis during cycle 1; on days 8, 15, and 22 of cycle 2; and on days 1 and 15 of subsequent cycles. Safety assessments included electrocardiograph monitoring and monitoring of urine glucose, FPG, plasma glucose per 2-hour 75-g oral glucose tolerance test, and hemoglobin A1C levels. Adverse events were graded using the CTCAE version 3.0, unless otherwise specified (Appendix Table A1). Responses were assessed after two cycles, and every other cycle thereafter, using RECIST version 1.0.²²

Pharmacokinetic Assessments

Plasma levels of BKM120 were determined from samples (collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose on days 1, 8, and 28 of cycle 1) using a validated liquid chromatography–tandem mass spectrometry assay with a lower limit of quantification of 1 ng/mL (Novartis, data on file). Standard PK parameters were determined using a noncompartmental method (WinNonlin; Pharsight, Mountain View, CA).

Pharmacodynamic Assessments

Whole-body [¹⁸F]FDG-PET scans were performed at baseline and on day 28 of cycles 1 and 2. Response thresholds were maximum standardized uptake value changes \geq 25%.²³

pS6 was measured by semiquantitative immunohistochemistry in fresh-frozen postprandial skin biopsies from pretreatment and 2 to 4 hours post-treatment on day 1 of cycle 2.

Blood samples for fasting glucose, insulin, and fasting C-peptide were collected at predose and 0.5, 1, 2, 4, and 24 hours postdose on days 1, 8, and 28 of cycle 1. C-peptide (cleavage product of proinsulin) was chosen over insulin as a more robust and stable pharmacodynamic marker based on its longer half-life (30 v 5 minutes).²⁴

RESULTS

Study Population

Thirty-five patients from three clinical sites were enrolled and treated in dose-escalation cohorts from November 2008 to October 2009 (Table 1). Patients with colorectal (15, 43%) or breast (nine, 26%) cancer constituted the majority. Thirty-three patients (94%) had received prior antineoplastic therapy; 18 patients (51%) had received more than three prior antineoplastic regimens.

Thirty-one tumor samples were found to be evaluable; 16 (46%) had PI3K pathway alterations (Table 1), including a PIK3CA mutation (n = 5) or null or low PTEN protein expression (n = 11). In four patients the mutation involved the H1047R amino acid substitution; in one patient the mutation involved the E545G amino acid substitution. Of 10 patients with tumor KRAS mutations, three had both a KRAS mutation and null or low PTEN protein expression.

Dose Escalation and MTD

Patients received oral, once-daily BKM120 starting at 12.5 mg (12.5, 25, 50, 80, 100, or 150 mg). Inpatient dose escalation

Table 1. Patient Baseline Characteristics and Tumor Molecular Status

Characteristic	No. (N = 35)	%
Age, years		
Median	53	
Range	37-76	
Sex		
Male	14	40
Female	21	60
WHO PS		
0	25	71.4
1	10	28.6
Prior antineoplastic regimens	33	94
No. of regimens		
Median	4	
Range	0-12	
Patients with > 3 prior regimens	18	34.2
Primary tumor		
Colorectal	15	42.8
Breast	9	25.7
Lung	2	5.7
Other*	9	25.7
Tumor molecular status†		
Evaluable for <i>PIK3CA</i> status (n = 29)		
Wild type	24	69
Mutation	5	14
Evaluable for PTEN expression (n = 30)‡		
Protein level not low	19	54
Protein level low or null	11	31
Tumors with PI3K pathway dependence (any <i>PIK3CA</i> /PTEN alterations)	16	46
Evaluable for <i>KRAS</i> status (n = 27)		
Wild type	17	49
Mutation	10	29

Abbreviations: PI3K, phosphatidylinositol-3-kinase; PIK3CA, p110 α catalytic subunit of PI3K; PTEN, phosphatase and tensin homolog; WHO PS, World Health Organization performance status.

*One patient each (2.9%): liver, head and neck, prostate, ovary, kidneys, gall bladder, neuroendocrine tumor, astrocytoma, and angiosarcoma.

†Evaluable samples available for 31 of 35 patients; some analyses were incomplete because of sample quantity or quality.

‡Designations were "low or null" (H-score < 50) and "not low" (H-score \geq 50).

occurred in three patients. DLTs occurred in seven patients of 30 evaluable for DLT (Appendix Table A2): one patient (of six) at 80 mg (grade 2 mood alteration), four patients (of 16) at 100 mg (one each of grade 3 epigastralgia, grade 3 rash, grade 2 mood alteration, and grade 3 mood alteration), and two patients (of three) at 150 mg (both with grade 4 hyperglycemia). Mood alterations consisted of anxiety, euphoria, and depression and were reversible with dose hold and reduction. The 150-mg dose level was evaluated after a single DLT of epigastralgia was observed of five patients at 100 mg. After DLTs of hyperglycemia at the 150-mg dose level, additional patients were enrolled at 100 mg, and an 80-mg cohort was initiated to further explore the mood disorder and overall safety. The 100-mg dose level was defined as the MTD on the basis of the largest posterior probability of DLT rate in the target toxicity interval and with less than 25% risk of overdose. Six patients (17.1%) had dose reductions in cycle 1 and 12 (34.3%) overall in the study. In eight patients overall (22.9%), dose reductions were

due to adverse events. Dosing was delayed in 12 patients (34.3%) in cycle 1 and in 20 patients (57.1%) overall.

Safety Findings

BKM120 was well tolerated. Grade 3/grade 4 adverse events (AEs), regardless of causality, were observed in 22 patients (63%) (Table 2). Of the grade 3/grade 4 AEs regardless of causality, rash (11%), hyperglycemia (9%), performance status decreased (9%), mood alteration (9%; including mood altered [6%] and affective disorder [3%]), and pruritus (6%) were observed in two or more patients (Table 2). The majority of treatment-related AEs were observed at dose levels \geq 100 mg (Table 2).

Rash was primarily a pruritic maculopapular rash concentrated on the torso (Appendix Fig A1). Terms used to describe mood alterations included mood altered, anxiety, depression, emotional disorder, crying episodes, hallucinations, irritability, and affective disorder. After interruption of BKM120, mood alterations resolved within the treatment cycle. Grade 3 mood alterations consisted of anhedonia followed by an increase in anxiety and irritability.

Five patients (14%) experienced serious AEs considered to be treatment related: hyperglycemia (80 mg, 150 mg [n = 2]), skin rash (150 mg), and diarrhea (100 mg). All four deaths on study resulted from disease progression.

Pharmacokinetic Analysis

BKM120 is rapidly absorbed after oral administration, with the median time to reach peak plasma concentrations (T_{max}) between 0.5 and 4 hours post dose (Fig 1, Table 3). T_{max} seemed to be independent of dose and did not change after multiple oral doses. After reaching the peak drug concentration (C_{max}), BKM120 plasma concentrations decreased in a bi-exponential manner (Fig 1) with an apparent long terminal elimination half-life ($T_{1/2}$). Because of the study sampling schedule and the long half-life, $T_{1/2}$ and related PK parameters could not be accurately estimated by noncompartmental analysis.

BKM120 exposure within a dosing interval (AUC_{0-24}) and C_{max} was similar between days 8 and 28 of daily oral dosing, indicating the absence of significant drug accumulation after day 8 (Table 3). BKM120 accumulated ~three-fold in achieving steady-state, consistent with a half-life of ~40 hours. Apparent total body clearance from plasma at steady-state (calculated as dose/ AUC_{0-24}) was low (~5.0 L/h). Approximate dose-proportional increase in C_{max} and AUC_{0-24} was observed across the entire dose range. Interpatient variability (CV%) in C_{max} and AUC_{0-24} differed at each dose level but was moderate and generally approximately 40%.

At the MTD, steady-state levels of BKM120 were in the range predicted to be efficacious based on in vivo preclinical tumor models. Physiologically based models predicted a fraction of absorbed dose and hepatic clearance (CL_{hep}) of BKM120 of approximately 0.95 and 2 to 8 L/h, respectively, with an absolute oral bioavailability of more than 90% (data not shown). These predictions are in close agreement with the oral clearance of 5 L/h found in this study. BKM120 is a low-clearance drug with a first-pass hepatic extraction limited to less than 10% (CL_{hep} < 5 L/h).

Table 2. Adverse Events by Treatment Cohort and Grade

Adverse Events*	BKM120 Dose Cohort																											
	All (N = 35)				12.5 mg (n = 1)				25 mg (n = 2)				50 mg (n = 5)				80 mg (n = 6)				100 mg (n = 17)				150 mg (n = 4)			
	All		G3/G4		All		G3/G4		All		G3/G4		All		G3/G4		All		G3/G4		All		G3/G4		All		G3/G4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total patients experiencing AEs regardless of causality	35	100	22	63	1	100	0		2	100	1	50	5	100	4	80	6	100	3	50	17	100	10	59	4	100	4	100
AEs of G3/G4, regardless of causality, occurring in ≥ 2 patients (6%)																												
Rash	15	43	4	11	0		0		1	50	0		1	20	0		1	17	1	17	10	59	2	12	2	50	1	25
Hyperglycemia	14	40	3	9	1	100	0		0		0		1	20	0		2	33	1	17	8	47	0		2	50	2	50
Performance status decreased	3	9	3	9	0		0		0		0		1	20	1	20	1	17	1	17	1	6	1	6	0		0	
Mood altered	7	20	2	6	0		0		0		0		0		0		3	50	1	17	3	18	1	6	1	25	0	
Pruritus	9	26	2	6	0		0		0		0		0		0		1	17	0		7	41	2	12	1	25	0	
Total patients experiencing AEs suspected to be related to BKM120	33	94	14	40	1	100	0		2	100	1	50	4	80	0		5	83	2	33	17	100	8	47	4	100	3	75
AEs suspected to be related to BKM120 occurring in ≥ 15% of patients																												
Rash	13	37	4	11	0		0		1	50	0		0		0		1	17	1	17	10	59	2	12	1	25	1	25
Hyperglycemia	13	37	3	9	1	100	0		0		0		1	20	0		1	17	1	17	8	47	0		2	50	2	50
Diarrhea	13	37	0	0	0		0		0		0		0		0		1	17	0		11	65	0		1	25	0	
Anorexia	13	37	0	0	0		0		2	100	0		0		0		2	33	0		8	47	0		1	25	0	
Nausea	11	31	0	0	0		0		1	50	0		1	20	0		2	33	0		4	24	0		3	75	0	
Fatigue	9	26	0	0	1	100	0		0		0		1	20	0		2	33	0		5	29	0		0		0	
Pruritus	8	23	2	6	0		0		0		0		0		0		1	17	0		6	35	2	12	1	25	0	
Mucositis	8	23	0	0	0		0		0		0		0		0		3	50	0		5	29	0		0		0	
Mood altered	7	20	2	6	0		0		0		0		0		0		3	50	1	17	3	18	1	6	1	25	0	
Anxiety	6	17	0	0	0		0		0		0		0		0		1	17	0		4	24	0		1	25	0	

Abbreviations: AEs, adverse events; G, grade; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

*All AEs, with the exception of hyperglycemia, were defined according to NCI-CTCAE v3.0 criteria.

Antitumor Activity

Thirty-one of 35 patients were evaluable for response by investigator; baseline and postbaseline target lesion radiologic assessments were available for 24 patients by central review (Fig 2A). One patient with triple-negative breast cancer and a *KRAS* mutation achieved a partial response (PR) on a BKM120 dose of 100 mg/d. Sixteen patients

(of 31; 52%) had stable disease (SD) for more than 6 weeks, including five with colorectal cancer and five with breast cancer. As of August 2010, seven patients had been on the study for ≥ 8 months, most at 100 mg/d (two patients each with breast cancer and colorectal cancer and one patient each with prostate cancer, angiosarcoma, and lung adenocarcinoma). Five of these patients had tumors with PI3K pathway dependence (PTEN low/no protein expression or *PIK3CA* gene mutation).

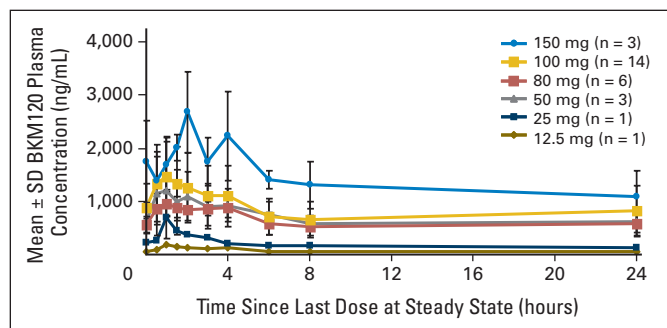


Fig 1. Plasma pharmacokinetic profile of BKM120 in patients with advanced solid tumors. Each line represents the mean BKM120 plasma concentration for a single-dose cohort measured on day 8, cycle 1 (error bars reflect standard deviation of the mean [SD]). Time scale is hours after dose.

Pharmacodynamic Analysis

Nineteen patients were evaluable for [^{18}F]FDG-PET assessments (Fig 2B). A more than 25% decrease in tumor [^{18}F]FDG uptake was observed in 10 patients per central review, three of whom demonstrated tumor shrinkage on CT assessment. Nine patients had a metabolic PR; eight of these patients had received BKM120 doses of ≥ 100 mg.

BKM120 administration was associated with sustained dose-dependent increases in fasting C-peptide. Increases in fasting blood glucose were more evident at higher doses, including hyperglycemia as a DLT at 150 mg/d (Fig 3A).

Assessments of baseline and post-treatment pS6 levels in skin were available for 23 patients (Fig 3B; Appendix Fig A2, online

Table 3. Summary of Pharmacokinetic Parameters by Cohort

BKM120 Dose Cohort*	Study Day in Cycle 1									AR Day 8†	AR Day 28‡
	1			8			28				
	T _{max} (hr)	C _{max} (ng/mL)	AUC ₀₋₂₄ (hr·ng/mL)	T _{max} (hr)	C _{max} (ng/mL)	AUC ₀₋₂₄ (hr·ng/mL)	T _{max} (hr)	C _{max} (ng/mL)	AUC ₀₋₂₄ (hr·ng/mL)		
12.5 mg (n = 1)											
Mean	—	62.3	575	—	185	1,710	—	147	1,650	2.97	2.87
SD	—	—	—	—	—	—	—	—	—	—	—
Median	1.5	62.3	575	1	185	1,710	3	147	1,650	2.97	2.87
25 mg (n = 2)											
Mean	—	268	1,360	—	691	4,570	—	401	4,300	3.2	3.01
SD	—	142	96.4	—	—	—	—	—	—	—	—
Median	1.5	268	1,360	1	691	4,570	0.5	401	4,300	3.2	3.01
50 mg (n = 5)											
Mean	—	661	5,380	—	1,210	16,300	—	1,300	19,700	2.89	3.47
SD	—	243	960	—	629	4,540	—	84.9	4,920	0.869	1.63
Median	1.5	638	5,070	4	1,190	18,400	2.25	1,300	19,700	2.62	3.47
80 mg (n = 6)											
Mean	—	831	7,180	—	1,100	14,800	—	1,470	16,100	2.86	1.92
SD	—	429	5,730	—	198	3,250	—	365	6,710	1.73	0.881
Median	1	908	5,630	1.25	1,120	15,500	1.5	1,470	17,300	2.44	1.67
100 mg (n = 17)											
Mean	—	969	8,720	—	1,700	20,000	—	1,850	22,500	2.58	5.37
SD	—	405	3,670	—	678	9,570	—	575	8,980	1.03	8.09
Median	1	1,010	8,680	1	2,080	22,200	1.25	1,950	22,100	2.75	2.78
150 mg (n = 4)											
Mean	—	1,200	10,900	—	2,730	33,400	—	—	—	2.96	—
SD	—	635	1,340	—	708	10,200	—	—	—	0.863	—
Median	1.75	1,010	10,800	2	2,420	28,600	—	—	—	2.88	—

Abbreviations: AR, accumulation ratio; AUC, area under the plasma concentration time curve; C_{max}, maximum concentration; SD, standard deviation; T_{max}, time of occurrence of C_{max}.

*Number of patients evaluable on day 1 of cycle 1. Not all patients in each cohort were evaluable for all parameters on days 8 and 28.

†AR calculated as AUC₀₋₂₄ on day 8 divided by AUC₀₋₂₄ on day 1.

‡AR calculated as AUC₀₋₂₄ on day 28 divided by AUC₀₋₂₄ on day 1.

only). At BKM120 doses of 80 to 150 mg/d, 15 (80%) of 19 patients demonstrated a 40% to 85% decrease in pS6 levels compared with baseline (Fig 3B).

Expansion Part of the Study

The study has been expanded, and, as of August 20, 2010, five additional patients have been enrolled at 80 mg and 26 additional patients at 100 mg. Median age was 55 years (range, 30 to 77 years). Most common tumor types were colorectal (24 patients), breast (18 patients), lung (three patients), and endometrial (three patients) cancer. Median duration of treatment was 7.5 weeks (range, 0.1 to 69+ weeks), with 17 patients treated for more than 16 weeks. Most frequent AEs of all grades suspected to be related to BKM120 were decreased appetite (33%); rash, diarrhea, nausea (27%); fatigue, hyperglycemia (24%); anxiety (20%); depression (18%); and mucosal inflammation (17%). Most frequent grade 3/grade 4 AEs (> 5%) were transaminase increase (9.1%), asthenia (7.6%), and rash (6.1%). Two patients in the expansion have demonstrated PRs: one patient with estrogen receptor–positive/human epidermal growth factor receptor 2 negative metastatic breast cancer (*PIK3CA* mutation) and one patient (unconfirmed) with parotid cancer (*PIK3CA* mutation and null PTEN). Twenty-six of 45 patients evaluable by CT (58%) had SD as best response. A trend toward better activity was observed at the higher dose cohorts, also

expressed as metabolic FDG-PET response. Eighteen patients had SD lasting for at least 16 weeks, including eight patients who had tumors with either PI3K mutations or low/absent PTEN expression. A more detailed analysis of the expansion cohort will be presented in a separate publication.

DISCUSSION

The results from this dose-escalation study of the novel PI3K inhibitor BKM120 provide evidence of the feasibility of pan-Class I PI3K inhibition in patients with cancer. The MTD of oral BKM120 administered on a continuous daily schedule was defined as 100 mg/d on the basis of DLTs of mood alteration, hyperglycemia, epigastralgia, and rash.

At the MTD, steady-state levels of BKM120 were in the range predicted to be efficacious based on in vivo preclinical tumor models. Given the good absorption properties and apparent low intra- and inter-individual variability, BKM120 shows a favorable pharmacokinetic profile.

BKM120 was well tolerated, with a dose-dependent safety profile. Hyperglycemia, a class effect, is consistent with inhibition of PI3K signaling and has been observed with other PI3K/mTOR/Akt pathway inhibitors.²⁵⁻²⁷ p110-PI3K activity mediates insulin

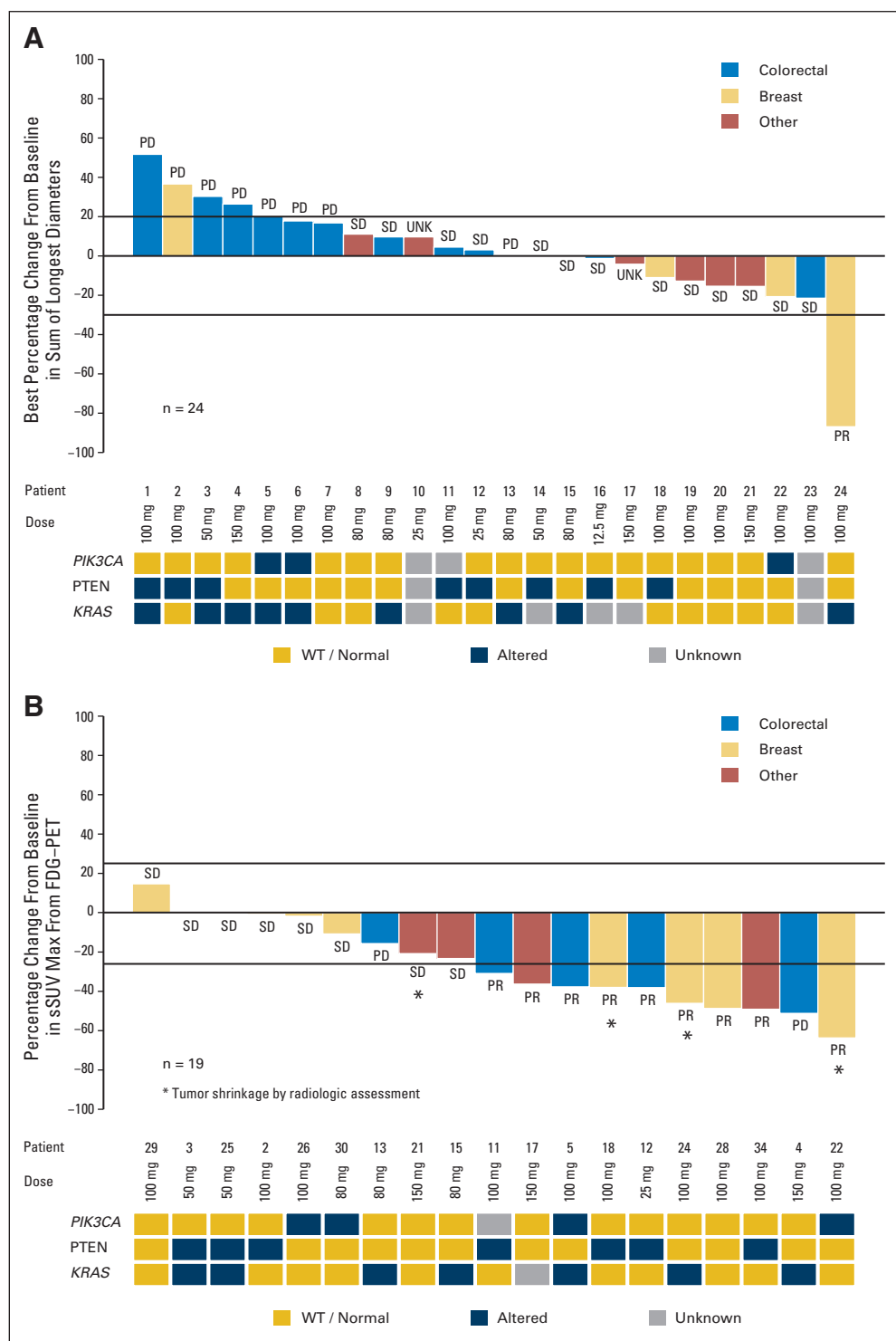


Fig 2. Radiologic response to BKM120 with corresponding status of tumor *PIK3CA*, phosphatase and tensin homolog (*PTEN*), and *KRAS* alterations. Gold indicates no alterations, and dark blue indicates a gene mutation or altered protein expression. Gray shading indicates status unknown. Primary tumor type of colorectal cancer (blue), breast cancer (tan), or other (red) is indicated. (A) Best percentage change from baseline in the sum of the longest diameter and response as per investigator for 24 patients with baseline and postbaseline target lesion assessments. Solid lines indicate Response Evaluation Criteria in Solid Tumors thresholds for response: 30% decrease for partial response (PR) and 20% increase for progressive disease (PD). (B) Best percentage change from baseline to cycle 1, day 28 in the sum of the maximum standardized uptake values (sSUVmax) and metabolic response (mResponse) as per investigator. Patient numbers correlate to those in panel A. The solid line indicates a 25% decrease threshold for mResponse. FDG-PET, [¹⁸F]fluorodeoxyglucose positron emission tomography; SD, stable disease; UNK, unknown; WT, wild type.

signaling; inhibition blocks the metabolic actions of insulin, including glucose transport and glycogen synthesis,^{2,3,28-30} resulting in increased blood glucose and compensatory release of insulin (and C-peptide) from pancreatic β -cells.³ Disturbance of glucose homeostasis as evidenced by hyperglycemia was more common at higher doses and may be attributed to BKM120 inhibition of p110.¹⁶

Hyperglycemia was managed initially with metformin and subcutaneous insulin, when necessary. Hyperglycemia was primarily controlled with metformin. Insulin was used in four patients, including three of whom developed hyperglycemia on starting steroids and one who was unable to tolerate oral medication. At the 150-mg dose level, discontinuation of BKM120 was required to control hyperglycemia.

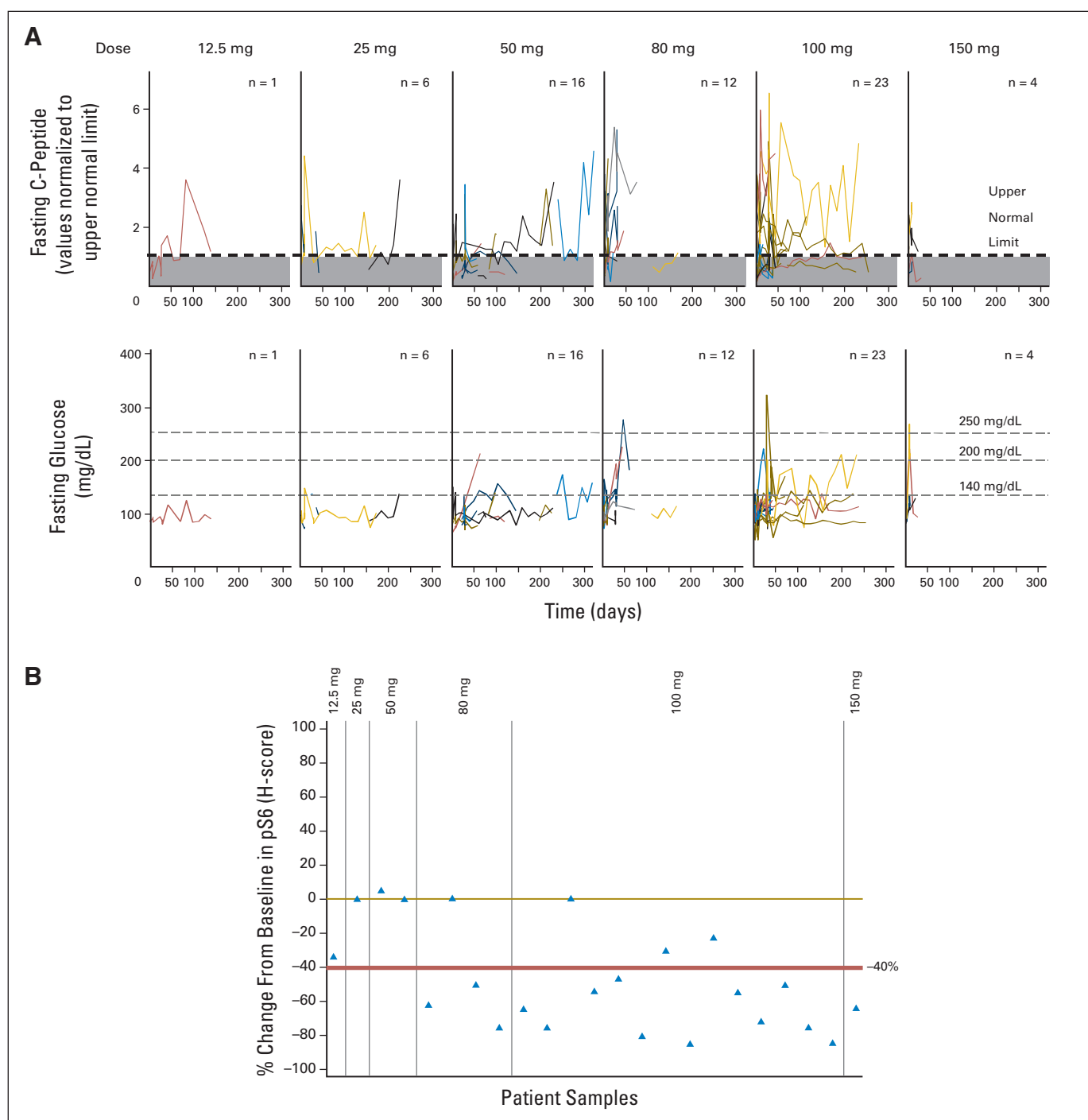


Fig 3. Biomarker assessment in patients receiving oral BKM120. (A) Comparison of plasma fasting C-peptide and fasting glucose levels over time (0 to 300 days) by dose cohort (n corresponds to the number of patients). Each line represents a single patient. Normalized C-peptide values are listed as fold increase from upper limit of normal; glucose values are given in milligrams per deciliter. Ranges for hyperglycemia grade 1 (140 to 199 mg/dL [7.8 to 11.0 mmol/L]), grade 2 (200 to 249 mg/dL [11.1 to 13.8 mmol/L]), and grade 3 (250 to 399 mg/dL [13.9 to 22.2 mmol/L]) are indicated. Analysis time points are at baseline, on days 1, 8, 15, 22, and 28 of cycle 1; day 15 of cycle 2; and days 1 and 15 of subsequent cycles. Increases in C-peptide are evident at all doses tested, whereas increases in glucose become more evident at doses \geq 80 mg. (B) Effect of BKM120 on pS6 (Ser240/244) levels in skin biopsies, by dose cohort. Data are represented as percentage change from baseline of the H-score of the whole epidermis for evaluable paired pre- and post-treatment (day 28) patient samples. Red solid line marks a 40% decrease in pS6 levels from baseline.

Skin rash was a frequent AE potentially related to BKM120 administration in 37% of patients; this may be considered a class effect.^{25,27,31,32} Rash was primarily responsive to antihistamines and topical corticosteroids. Dose interruption was required in severe cases; most patients were able to resume the previous dose level.

Mood alterations seen may reflect effects of PI3K inhibition in the CNS, given that BKM120 can cross the blood–brain barrier (Novartis, data on file; also demonstrated by a 28% shrinkage of a brain metastasis in one patient). Dysfunction of the PI3K pathway in the CNS has been linked to anxiety and low serotonin levels in the

amygdala³³ and to schizophrenia.³⁴ Mood alterations were responsive to BKM120 dose-reduction, dose-hold, and treatment with selective serotonin reuptake inhibitors and anxiolytics. Once mood alterations were identified as potentially drug-related, patients with grade 1 alterations were immediately treated with selective serotonin reuptake inhibitors, and no further mood alterations greater than grade 1 were seen. Future studies of BKM120 will exclude patients with major risk factors for these AEs.

Pharmacodynamic effects suggested dose-dependent inhibition of PI3K signaling. Increases in fasting C-peptide were detected at doses lower than those associated with hyperglycemia, suggesting that increased pancreatic insulin/C-peptide release can effectively compensate for decreased glucose transport and metabolism due to PI3K inhibition at BKM120 doses less than 100 mg. Although glucose has typically been used as a pharmacodynamic marker for PI3K pathway inhibition, C-peptide may be more appropriate. Additionally, significant decrease in pS6, a downstream PI3K target, was observed in a majority of skin biopsies at doses of BKM120 \geq 80 mg. Decreased [¹⁸F]FDG uptake ($> 25\%$) was observed in 53% of evaluable patients; however, the role of PI3K signaling in glucose uptake may skew the use of [¹⁸F]FDG uptake as a marker of tumoricidal effect,²³ as seen with mTOR inhibitors.³⁵ In studies of PI3K pathway inhibitors, [¹⁸F]FDG-PET may reflect pharmacodynamic effects of target inhibition as well as antitumor effects.¹⁶ Similar to the profile of tumor radiologic response, decreases in tumor [¹⁸F]FDG uptake were most significant at BKM120 doses \geq 100 mg/d, suggesting that this effect may be due to a combination of antitumor activity and direct PI3K inhibition.

It is too early to conclude whether tumors with PI3K pathway alterations have a higher probability of response to BKM120. Five of seven patients treated for \geq 8 months had tumors with PI3K pathway dependence. Further clinical studies are needed to evaluate the predictive value of oncogenic alterations in PI3K or PTEN, as well as other mutations such as *AKT1/2* or *PIK3R1*, the regulatory subunit of PI3K, in patient populations selected for PI3K pathway alterations.

Preclinical data suggest *KRAS* mutations may predict resistance to PI3K inhibition³⁶⁻³⁸; however, the PR in a patient with breast cancer suggests that implications of breast cancer *KRAS* mutation may differ from colon cancer, in which it predicts resistance to inhibition of growth factor signaling.³⁹ In our study, one of seven patients with *KRAS* mutant colon cancer had SD for more than 3.5 months; the rest had progressive disease.

In conclusion, this study's findings demonstrate the clinical safety and tolerability, favorable PK profile, consistent pharmacodynamic effects, and early antitumor activity of pan-Class I PI3K inhibition with BKM120 on a continuous daily schedule in patients with advanced solid tumors. Further characterization of BKM120 at the selected dose of 100 mg is ongoing in patients with PI3K pathway-activated tumors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

- Cantley LC: The phosphoinositide 3-kinase pathway. *Science* 296:1655-1657, 2002
- Engelman JA, Luo J, Cantley LC: The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet* 7:606-619, 2006
- Katso R, Okkenhaug K, Ahmadi K, et al: Cellular function of phosphoinositide 3-kinases: Implications for development, homeostasis, and cancer. *Annu Rev Cell Dev Biol* 17:615-675, 2001
- Courtney KD, Corcoran RB, Engelman JA: The PI3K pathway as drug target in human cancer. *J Clin Oncol* 28:1075-1083, 2010
- Lee JW, Soung YH, Kim SY, et al: PIK3CA gene is frequently mutated in breast carcinomas and hepatocellular carcinomas. *Oncogene* 24:1477-1480, 2005
- Bader AG, Kang S, Zhao L, et al: Oncogenic PI3K deregulates transcription and translation. *Nat Rev Cancer* 5:921-929, 2005
- Levine DA, Bogomolny F, Yee CJ, et al: Frequent mutation of the PIK3CA gene in ovarian and breast cancers. *Clin Cancer Res* 11:2875-2878, 2005
- Nosho K, Kawasaki T, Ohnishi M, et al: PIK3CA mutation in colorectal cancer: Relationship with genetic and epigenetic alterations. *Neoplasia* 10:534-541, 2008
- Li J, Yen C, Liaw D, et al: PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* 275:1943-1947, 1997
- Whang YE, Wu X, Suzuki H, et al: Inactivation of the tumor suppressor PTEN/MMAC1 in advanced human prostate cancer through loss of expression. *Proc Natl Acad Sci U S A* 95:5246-5250, 1998
- Salvesen HB, MacDonald N, Ryan A, et al: PTEN methylation is associated with advanced stage and microsatellite instability in endometrial carcinoma. *Int J Cancer* 91:22-26, 2001
- Berns K, Horlings HM, Hennessy BT, et al: A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. *Cancer Cell* 12:395-402, 2007
- Eichhorn PJ, Gili M, Scaltriti M, et al: Phosphatidylinositol 3-kinase hyperactivation results in lapatinib resistance that is reversed by the mTOR/phosphatidylinositol 3-kinase inhibitor NVP-BE225. *Cancer Res* 68:9221-9230, 2008
- Brognard J, Clark AS, Ni Y, et al: Akt/protein kinase B is constitutively active in non-small cell lung cancer cells and promotes cellular survival and resistance to chemotherapy and radiation. *Cancer Res* 61:3986-3997, 2001
- Hu L, Hofmann J, Lu Y, et al: Inhibition of phosphatidylinositol 3'-kinase increases efficacy of paclitaxel in in vitro and in vivo ovarian cancer models. *Cancer Res* 62:1087-1092, 2002

16. Engelman JA: Targeting PI3K signalling in cancer: Opportunities, challenges and limitations. *Nat Rev Cancer* 9:550-562, 2009
17. Serra V, Markman B, Scaltriti M, et al: NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. *Cancer Res* 68:8022-8030, 2008
18. Maira SM, Stauffer F, Brueggen J, et al: Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. *Mol Cancer Ther* 7:1851-1863, 2008
19. Voliva CF, Pecchi S, Burger M, et al: Biological characterization of NVP-BKM120, a novel inhibitor of phosphoinositide-3-kinase in phase I/II trials. Presented at the American Association for Cancer Research Annual Meeting, Washington, DC, April 17-21, 2010 (abstr 4098)
20. Maira M, Menezes D, Pecchi S, et al: NVP-BKM120, a novel inhibitor of phosphoinositide 3-kinase in phase I/II clinical trials, shows significant antitumor activity in xenograft and primary tumor models. Presented at the American Association for Cancer Research Annual Meeting, Washington, DC, April 17-21, 2010 (abstr 4097)
21. Babb J, Rogatko A, Zacks S: Cancer phase I clinical trials: Efficient dose escalation with overdose control. *Stat Med* 17:1103-1120, 1998
22. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
23. Young H, Baum R, Cremerius U, et al: Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 35:1773-1782, 1999
24. Van Cauter E, Mestrez F, Sturis J, et al: Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 41:368-377, 1992
25. Tabernero J, Rojo F, Calvo E, et al: Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: A phase I tumor pharmacodynamic study in patients with advanced solid tumors. *J Clin Oncol* 26:1603-1610, 2008
26. Markman B, Dienstmann R, Tabernero J: Targeting the PI3K/Akt/mTOR pathway: Beyond rapalogs. *Oncotarget* 1:530-543, 2010
27. Yap TA, Patnaik A, Fearon I, et al: First-in-class phase I trial of a selective Akt inhibitor, MK2206 (MK), evaluating alternate day (QOD) and once weekly (QW) doses in advanced cancer patients (pts) with evidence of target modulation and antitumor activity. *J Clin Oncol* 28:235s, 2010 (suppl 15; abstr 3009)
28. Foukas LC, Claret M, Pearce W, et al: Critical role for the p110alpha phosphoinositide-3-OH kinase in growth and metabolic regulation. *Nature* 441:366-370, 2006
29. Taniguchi CM, Emanuelli B, Kahn CR: Critical nodes in signalling pathways: Insights into insulin action. *Nat Rev Mol Cell Biol* 7:85-96, 2006
30. Knight ZA, Gonzalez B, Feldman ME, et al: A pharmacological map of the PI3-K family defines a role for p110alpha in insulin signaling. *Cell* 125:733-747, 2006
31. Edelman G, Bendell C, Shapiro G, et al: A phase I dose-escalation study of XL147 (SAR245408), a PI3K inhibitor administered orally to patients (pts) with advanced malignancies. *J Clin Oncol* 28:234s, 2010 (suppl 15; abstr 3004)
32. Brana I, LoRusso P, Baselga J, et al: A phase I dose-escalation study of the safety, pharmacokinetics (PK), and pharmacodynamics of XL765 (SAR245409), a PI3K/TORC1/TORC2 inhibitor administered orally to patients (pts) with advanced malignancies. *J Clin Oncol* 28:240s, 2010 (suppl 15; abstr 3030)
33. Ackermann TF, Hortnagl H, Wolfer DP, et al: Phosphatidylinositol dependent kinase deficiency increases anxiety and decreases GABA and serotonin abundance in the amygdala. *Cell Physiol Biochem* 22:735-744, 2008
34. Kalkman HO: The role of the phosphatidylinositol 3-kinase-protein kinase B pathway in schizophrenia. *Pharmacol Ther* 110:117-134, 2006
35. Ma WW, Jacene H, Song D, et al: [18F]fluorodeoxyglucose positron emission tomography correlates with Akt pathway activity but is not predictive of clinical outcome during mTOR inhibitor therapy. *J Clin Oncol* 27:2697-2704, 2009
36. Engelman JA, Chen L, Tan X, et al: Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat Med* 14:1351-1356, 2008
37. Ihle NT, Lemos R, Jr., Wipf P, et al: Mutations in the phosphatidylinositol-3-kinase pathway predict for antitumor activity of the inhibitor PX-866 whereas oncogenic Ras is a dominant predictor for resistance. *Cancer Res* 69:143-150, 2009
38. Torbett NE, Luna-Moran A, Knight ZA, et al: A chemical screen in diverse breast cancer cell lines reveals genetic enhancers and suppressors of sensitivity to PI3K isoform-selective inhibition. *Biochem J* 415:97-110, 2008
39. Lièvre A, Bachet JB, Le Corre D, et al: KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 66:3992-3995, 2006
40. Neuenschwander B, Branson M, Gsponer T: Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med* 27:2420-2439, 2008