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SPECIAL ARTICLE

Management of Metabolic Effects Associated With Anticancer Agents Targeting the PI3K-Akt-mTOR Pathway

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ABSTRACT

Agents inhibiting the phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (PAM) pathway are currently in various stages of clinical development in oncology, ranging from some in early-phase evaluations to others that have already received regulatory approval for treatment in advanced cancers. The administration of PAM pathway inhibitors has been associated with metabolic toxicities of hyperlipidemia and hyperglycemia. The PAM Task Force of the National Cancer Institute Investigational Drug Steering Committee convened an interdisciplinary expert panel to review the pathophysiology of hyperlipidemia and hyperglycemia induced by PAM pathway inhibitors, summarize the incidence of these metabolic toxicities induced by such agents in the current literature, advise on clinical trial screening and monitoring criteria, and provide management guidance and therapeutic goals on occurrence of these toxicities. The overarching aim of this consensus report is to raise awareness of these metabolic adverse events to enable their early recognition, regular monitoring, and timely intervention in clinical trials. Hyperglycemia and hyperlipidemia are generally not acutely toxic and most often reversible with therapeutic intervention. Dose modifications or discontinuation of PAM pathway inhibitors should only be considered in situations of severe events or if progressive metabolic derangement persists after therapeutic interventions have been attempted for a sufficient duration. Specialty consultation should be sought to aid clinical trial planning and the management of these metabolic adverse events.

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INTRODUCTION

This article focuses on management recommendations for the metabolic toxicities (ie, hyperlipidemia and hyperglycemia) induced by anticancer agents that inhibit signaling in the phosphoinositide 3-kinase (PI3K) –Akt–mammalian target of rapamycin (mTOR; PAM) pathway. Many points along this pathway may be disrupted to achieve a therapeutic effect. The oldest subclass of drugs in this category is composed of the mTOR inhibitors, which have long been used in the postrenal and postcardiac transplantation settings. Thus far, three mTOR inhibitors (temsirolimus, everolimus, and sirolimus) have been approved for marketing in the United States by the US Food and Drug Administration, with several other compounds affecting the PAM pathway in various stages of clinical development.

Concepts of serum lipids and blood glucose management have generally been intended to reduce long-term morbidity and mortality associated with these metabolic abnormalities. In contrast to the population for whom these long-term risk reduction concepts have been studied, PAM pathway inhibitor therapy is currently indicated for patients with advanced cancers who most likely have limited life expectancy. The goals emphasized in this article are targeted to decrease short-term morbidity associated with these metabolic derangements.

Given the limited data with this expanding class of drugs, the recommendations herein for screening, monitoring, and management of hyperglycemia and hyperlipidemia are based on consensus opinion of the task force. This interspecialty panel has reviewed: the published literature, abstracts from major meetings, shared experience with development of PAM therapies, and principles of hyperglycemia and hyperlipidemia management.

PATHOPHYSIOLOGY OF HYPERLIPIDEMIA AND HYPERGLYCEMIA INDUCED BY PAM PATHWAY INHIBITORS

In vitro, in vivo, and clinical studies from the transplantation setting (with the mTOR inhibitor rapamycin) were analyzed in generating pathophysiologic insights. Because mTOR is a downstream component of the

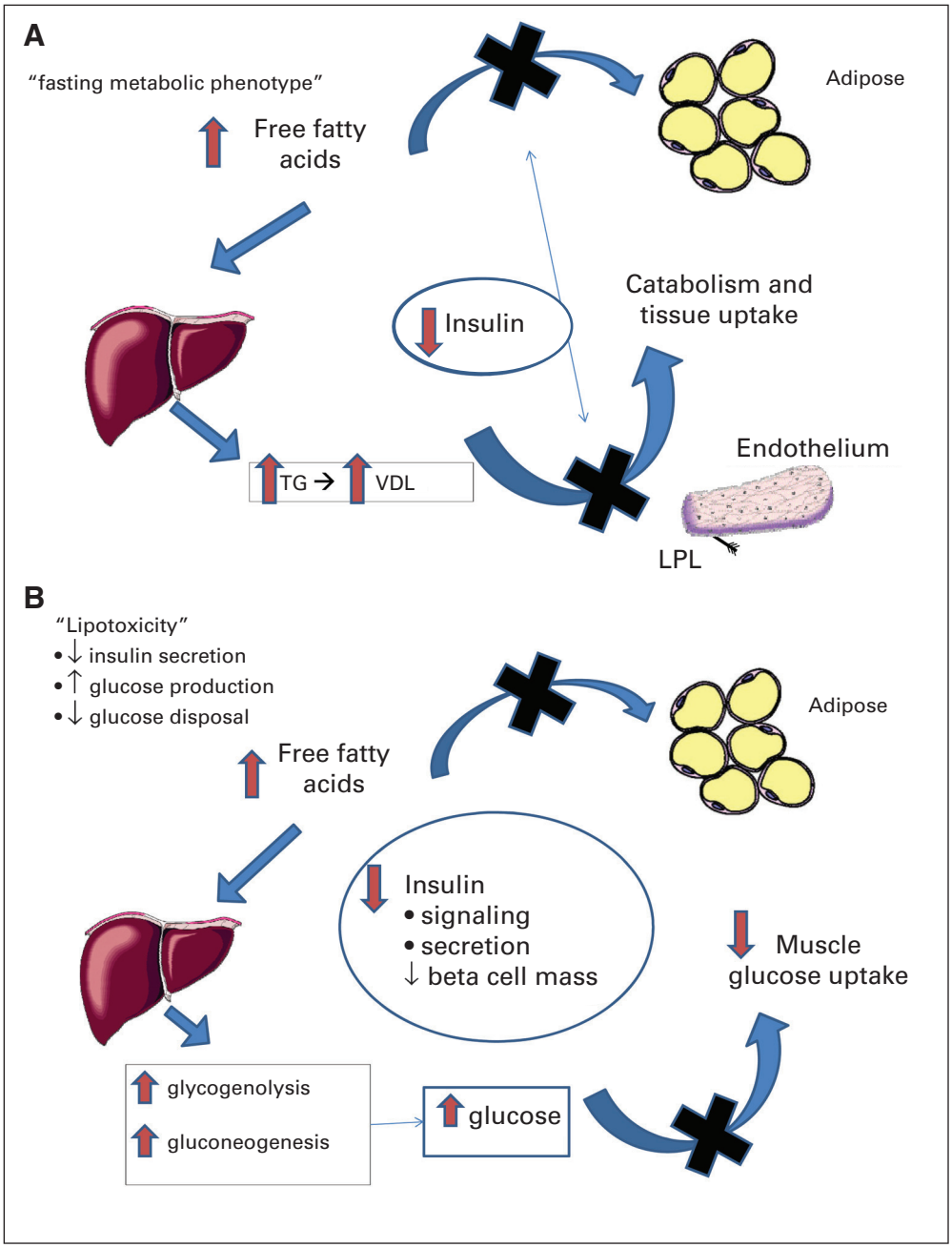

Fig 1. Pathophysiology of (A) mammalian target of rapamycin (mTOR) inhibitor–induced hyperlipidemia and (B) phosphoinositide 3-kinase–Akt–mTOR pathway inhibitor–induced hyperglycemia. LPL, lipoprotein lipase; TG, triglyceride; VDL, very low density lipoprotein.

PAM pathway, drugs affecting earlier steps may produce similar adverse effects. The detailed mechanisms by which PAM pathway inhibitors can cause these metabolic derangements are unclear; some likely mechanisms of these metabolic derangements are described herein.

Insulin is a key hormone regulating metabolism, clearance, and storage of both glucose and lipids. The PAM pathway contains key effectors in the insulin signaling pathway, and it is therefore not surprising PAM pathway inhibitors may produce clinically important metabolic effects. In a mouse model of type 2 diabetes, rapamycin was shown to increase insulin resistance and reduce beta-cell function and mass.[1] The normal physiologic response to hyperglycemia is to increase insulin secretion; this was diminished by rapamycin treatment in mice and patients who had undergone renal transplantation, respectively.[1,2] Induction of insulin resistance and dysregulation of insulin action seem central to the pathophysiology of drug-induced hyperglycemia and hyperlipidemia.

Hyperlipidemia

The pattern of hyperlipidemia seen with mTOR inhibitors involves elevations in total cholesterol, LDL, and triglycerides. Figure 1A represents a schematic summary of probable contributing pathophysiologic factors of PAM pathway inhibitor–induced hyperlipidemia.

The pathophysiology of PAM pathway inhibitor–induced dyslipidemia most likely involves impaired clearance of lipids from the bloodstream as opposed to increased hepatic synthesis.[3] A study in patients who had undergone renal transplantation demonstrated that

rapamycin increases the total free fatty acid pool as well as total cholesterol, LDL cholesterol, and triglyceride levels.[4] Rapamycin has been shown in primary cultures of rat hepatocytes to affect hepatic fatty acid metabolism by promoting β-oxidation while decreasing flux into anabolic storage pathways.[5] Because glucose uptake and glycogen synthesis were decreased, the authors suggested that rapamycin induced a fasting metabolic phenotype,[5] which is characterized by preference for fatty acids as a metabolic fuel and a high rate of lipolysis, leading to high serum levels of fatty acids. In this study, rapamycin affected the transcription of key metabolic enzymes involved in hepatic lipid metabolism in a manner consistent with inhibition of lipogenic pathways, favoring lipolysis.

Another pathophysiologic mechanism whereby PAM pathway inhibitors may cause impaired lipid clearance and hyperlipidemia is via inhibition of insulin-stimulated lipoprotein lipase (LPL).[6] LPL hydrolyzes the triacylglycerol component of circulating lipoprotein particles, thereby mediating the uptake of fatty acids into adipose tissue and muscle. Insulin, a lipogenic hormone, is the principal factor responsible for regulating LPL activity to deposit triglycerides in adipose tissue. In rat adipose cells, the insulin signaling pathway regulating LPL has been shown to be rapamycin sensitive and also sensitive to wortmannin, a specific inhibitor of PI3K.[6] Thus, it is possible that in humans, inhibition of the PAM pathway results in impairment of LPL activity, an enzyme critical for peripheral fatty acid uptake.

Another study in patients who had undergone renal transplantation also supports impaired clearance of triglycerides from the bloodstream as a mechanism of hyperlipidemia mediated by PAM pathway inhibitors. In kidney transplant recipients with rapamycin-related hypertriglyceridemia, Hoogeveen et al[7] demonstrated a significant reduction in the fractional catabolic rate of very LDL apoB100 (a triglyceride-rich lipoprotein) rather than an enhanced very LDL–apoB100 synthesis.

Hyperglycemia

PAM pathway inhibitors have also been shown to cause hyperglycemia in the transplantation and oncologic settings.[2,8-10] The pathophysiology has been better elucidated with mTOR inhibitors compared with other agents. Figure 1B shows a schematic summary of probable contributing pathophysiologic factors of PAM pathway inhibitor–induced hyperglycemia.

Hyperglycemia is in part a result of the induction of a fasted metabolic state characterized by reduced utilization of glucose and preference for fatty acids as a metabolic fuel. Skeletal muscle is a major target for insulin-stimulated glucose disposal and suppression of fatty acid oxidation after a meal. Long-term rapamycin treatment in L6 muscle cells has affected fuel metabolism, promoting β-oxidation of fatty acids while diminishing basal glucose transport and glycogen synthesis.[11] Also, in the presence of rapamycin, the regulatory effects of insulin on glucose and fatty acid metabolism have been diminished.[3] An increase in fatty acid oxidation and decrease in glucose utilization is a behavior characteristic of the fasted metabolic state. Metabolic switching between fatty acids and glucose for energy production is a normal physiologic response. Rapamycin seems to induce a behavior suitable for the fasted environment regardless of circumstances. Rapamycin has increased fatty acid oxidation by 60%, accompanied by increased activities of carnitine palmitoyltransferases I (ie, the primary intracellular regulatory enzyme of the fatty acid oxidation pathway). Glucose transport capacity, glycogen synthesis, and glycolysis have also been reduced by approximately 40%.[7]

Rapamycin-induced hyperglycemia also seems to result from interference with insulin signaling. Di Paolo et al[11] showed an insulin-resistant picture in renal transplant recipients who were administered chronic rapamycin. In vivo expression and activation of PI3K/Akt and insulin receptor substrates (IRS-1 and IRS-2) were investigated. A decrease of basal and insulin-stimulated Akt phosphorylation, which correlated with an increase of patients' insulin resistance, was demonstrated. In addition, an insulin-induced tyrosine phosphorylation pattern mimicking that found in type 2 diabetes was observed. Rapamycin may also interfere with insulin signaling both upstream and downstream of Akt via other mechanisms.

The mechanism of hyperglycemia for the pan-Akt kinase inhibitor GSK690693 was investigated in mice and rats.[12] Increased glucose and insulin levels were noted, with resulting hyperglycemia lasting for approximately 6 hours postdose. An increase in the phosphorylation of the insulin receptor (Tyr^{1150}/Tyr^{1151}) was observed in liver lysates of GSK690693-treated mice 2 hours after compound administration. However, this increased insulin receptor activation was counteracted by a reduction in phospho-GSK-3β (Ser^{9}), consistent with inhibition of Akt kinase activity. Additionally, contrary to normal physiology, glucagon levels transiently increased along with insulin levels after administration. Analysis of animal livers treated with the compound showed dramatically reduced liver glycogen, which the authors suggested might point to an inhibition of glycogen synthesis and/or activation of glycogen breakdown in the liver (ie, glycogenolysis). This hypothesis was supported by the finding that fasting mice for 16 or 20 hours (which lowers liver glycogen stores) before drug administration prevented hyperglycemia, supporting glycogenolysis in the liver as the etiology. Inhibition of peripheral glucose uptake (as demonstrated by micropositron emission tomography imaging) was found to be another mechanism of hyperglycemia. Of importance, hyperglycemia was not responsive to a variety of antidiabetic medications tested and was minimally responsive to insulin infusion in this mouse model; this drug is currently not in human clinical trials.

INCIDENCE OF HYPERLIPIDEMIA AND HYPERGLYCEMIA INDUCED BY PAM PATHWAY INHIBITORS

Incidence data for PAM pathway inhibitor–mediated hyperlipidemia and hyperglycemia are limited at the current time. mTOR inhibitors may increase total cholesterol, triglycerides, and glucose,[9,10,13] as summarized in Table 1. Grades 3 to 4 hyperglycemic events are more frequent than hyperlipidemic events with these agents. Grades 1 to 2 toxicities are included, because management recommendations begin earlier than grade 3 events (described under Management of Hyperlipidemia). The frequency of elevations in LDL, an important atherogenic component of cholesterol, is not known; this is not one of the adverse events listed in the Common Terminology Criteria for Adverse Events (CTCAE; Appendix Table A1, online only), and hence, it is not often reported in clinical trials.

PI3K and Akt inhibitors do not seem to cause hyperlipidemia, although they may cause hyperglycemia. However, only a limited number of patients have been treated with these agents, because most are currently undergoing early development in phase I and II

Table 1. Epidemiology

Drug	Hypertriglyceridemia (%)		Hypercholesterolemia (%)		Hyperglycemia (%)	
	All Grades	Grades 3 to 4*	All Grades	Grades 3 to 4†	All Grades	Grades 3 to 4‡
Approved						
Everolimus	71	< 1	76	3	50	12
Placebo (n = 416)[9]	30	0	32	0	23	1
Temsirolimus	27	3	24	1	26	11
IFN-α (n = 408)[10]	14	1	4	0	11	2
Investigational§						
PI3K inhibitors[14-17]						
GDC-0941	None described		None described		48	2
BKM120	None described		None described		30	5
PI3K/mTOR inhibitors[18-21]						
XL765	None described		None described		10	0
GSK2126458	None described		None described		7	2
GDC-0980	None described		None described		83	14
Akt inhibitors[22-24]						
GDC-0068	None described		None described		41	0
MK-2206	None described		None described		13	3
GSK2141795	None described		None described		19-21	4
mTOR (TORC1 or TORC1/2) inhibitors[25-27]						
Ridaforolimus	41	0	28	0	22-28	6-13

Abbreviations: IFN-α, interferon alfa; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; TC, total cholesterol; TG, triglycerides.
*TG > 500 mg/dL.
†TC > 400 mg/dL.
‡Glucose > 250 mg/dL.
§Data from phase I trials.

trials.[14-27] Of note, given the large and growing population of prediabetics and diabetics, the true incidence of hyperglycemia resulting from these agents in the general cancer population is underestimated from studies that by and large have excluded diabetic and prediabetic patients. In the experience of the panel, these targeted therapies have a higher incidence of metabolic toxicities in patients with insulin resistance, patients with metabolic syndrome phenotype, or those with a family history of such. With a rapid increase in these metabolic disturbances in patients with cancer, the incidence of the metabolic adverse events from these therapies will likely be much greater when applied to later-phase studies (II/III) and postmarketing (phase IV and later).

MANAGEMENT OF HYPERLIPIDEMIA

PAM pathway inhibitors may cause an increase in total cholesterol, LDL, other atherogenic lipoproteins, and triglycerides. Elevation in LDL cholesterol is one of the most important risk factors for the development of cardiovascular diseases and was the number-one cause of death among adults in the United States in 2009.[28] High triglycerides, a component of metabolic syndrome, are independently associated with cardiovascular disease.[29] It is uncertain whether lowering triglycerides reduces cardiovascular events.[30] Statins (HMG CoA reductase inhibitors), which primarily target LDL cholesterol, have reduced cardiovascular risk and death in many randomized trials,[30,31] with benefits observed as early as 6 months.[32] However, the effects of LDL and/or triglyceride lowering in patients with advanced cancer receiving chemotherapy vis-á-vis acute toxicities are unknown.

Screening, Monitoring, and Eligibility

Although the CTCAE only encourages reporting of total cholesterol and triglycerides, the entire fasting lipid panel (FLP; including total cholesterol, triglycerides, LDL, HDL) should be obtained at baseline for all phases of study (fasting blood is prefereable; nonfasting sample is less preferable, because triglyceride levels will be elevated as a result of nonfasting status). LDL cholesterol is often more clinically relevant than total cholesterol and should be monitored and treated as necessary with agents inhibiting the PAM pathway.

Although most studies have suggested that lipids increase in the earlier cycles of therapy, no formal studies have been performed to evaluate the precise timing of onset of hyperlipidemia with these agents. This panel recommends the following for PAM pathway inhibitors that modulate mTOR (because these are the agents shown to cause lipid derangements):

For phase I studies, an FLP should be checked at baseline and monitored once per week for the first two cycles and then once with every cycle if no hyperlipidemia is observed. For phase II and later-phase studies, an FLP should be checked at baseline and monitored with every cycle, unless observations from respective phase I studies suggest otherwise.

For all patients newly initiated on lipid-lowering treatment, an FLP should be rechecked once every cycle or after each experimental drug dose change. If lipids are increasing at the end of a given cycle, therapy may be uptitrated or altered; if lipids are the same or lower at the end of a given cycle, lipid-lowering treatment should not be uptitrated for 6 weeks from initiation of therapy. An FLP should be rechecked once every 3 months after lipids have stabilized. Liver function tests (ALT/AST) should be performed during lipid-lowering

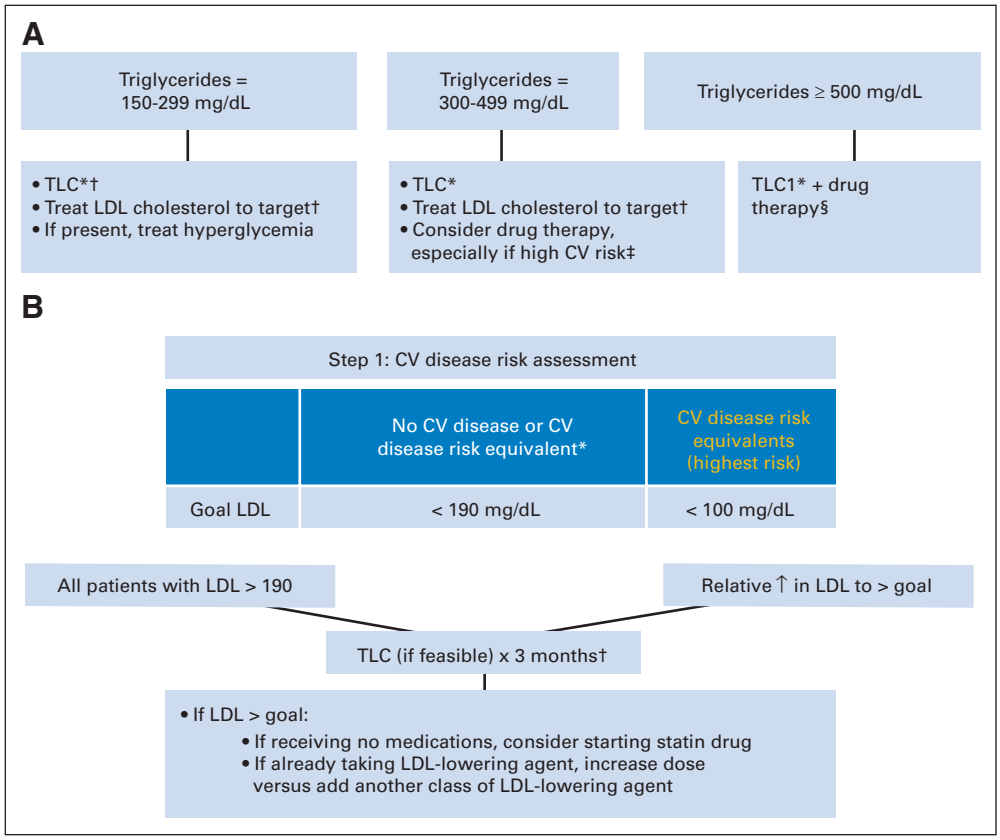

Fig 2. (A) Treatment of phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (PAM) pathway inhibitor–induced hypertriglyceridemia. (*) Therapeutic lifestyle changes (TLC), if appropriate: weight reduction, physical activity, avoid simple sugars (Table 2) and alcohol, consult registered dietician. (†) For triglyceride levels of 150 to 499 mg/dL, triglyceride lowering is secondary to achieving individual LDL cholesterol target. (‡) High risk defined as those continuing to receive PAM pathway inhibitor agent, with anticipated increase in triglycerides, or those with diabetes or cardiovascular (CV) disease (Table 2). (§) Options: fibrates (fenofibrate or gemfibrozil), fish oil (omega-3-ethyl esters), extended-release nicotinic acid. (B) Treatment of PAM pathway inhibitor–induced hypercholesterolemia, if prognosis > 1 year. (*) CV risk equivalents defined in Table 2. (†) TLC in diet and exercise (Table 2).

therapy. Suggested eligibility criteria for clinical trials are: LDL cholesterol < 190 mg/dL and triglycerides < 300 mg/dL.

Treatment of Hyperlipidemia

mTOR inhibitors have been shown to cause elevations in both LDL cholesterol and triglycerides. Elevated LDL cholesterol and triglycerides may need to be managed with different therapies. As per the third report of the guidelines from the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,[33] the primary target of lipid lowering should be to lower LDL cholesterol to reduce cardiovascular effects; secondary targets include triglyceride lowering and increasing HDL cholesterol. If the agent responsible for hyperlipidemia is discontinued, newly initiated lipid-lowering therapies can likely also be stopped in accordance with the half-life of the agent.

Goals of therapy are to keep fasting triglycerides < 300 mg/dL and LDL < 190 mg/dL (lower LDL depending on cardiovascular risk) in those with a life expectancy > 1 year. The goals for fasting triglycerides can be raised to < 500 mg/dL for those in phase I studies or with life expectancy < 1 year. Although there is a paucity of data on the effects of hyperlipidemia and cancer outcomes, the current goals have been chosen to decrease risk of established complications of hypertriglyceridemia (pancreatitis) and hypercholesterolemia (cardiovascular events).

Hypertriglyceridemia. Figure 2A provides a management algorithm of hypertriglyceridemia. Note that all patients should be instructed in therapeutic lifestyle changes (TLC) if clinically appropriate for their situation (Table 2). Hyperglycemia should be treated, because better glycemic control will lower triglycerides. Depending on the magnitude of the triglyceride elevation, drug therapy may be indicated.

In patients with high triglycerides ≤ 500 mg/dL (ie, 200 to 500 mg/dL [CTCAE v.4, grade 1/2]), LDL cholesterol lowering, usually with statin drugs, should be given priority because of extensive clinical evidence showing that statins reduce cardiovascular events. Provided LDL cholesterol is at target level, adding drug therapy to lower triglycerides may be considered. Stronger consideration for treatment should be given to those with diabetes or cardiovascular disease and those continuing to receive the anticancer agent associated with elevated triglycerides, because these patients have a high propensity for further elevation in triglyceride levels.

Drug therapy to specifically lower triglycerides is unequivocally indicated (regardless of LDL cholesterol) in patients with triglyceride levels > 500 mg/dL (CTCAE v.4, grade 3) because of the risk for acute pancreatitis. Options in such cases would be a fibrate (fenofibrate or gemfibrozil), omega-3-acid ethyl esters (fish oil), extended-release niacin, or a combination thereof. In those with estimated survival < 1 year, the goal for lowering triglycerides should be ≤ 500 mg/dL to avoid risk for pancreatitis. For patients with complex oncologic cases such as these, omega-3-acid ethyl esters are a good option, because they are associated with fewer adverse effects and drug interactions. Caution must be taken when prescribing lipid-lowering agents (specifically fibrates), because they may interact with various PAM pathway inhibitors (via competitive inhibition of cytochrome P (CYP) 3A4); the combination of liver metastases and drug interaction may cause increased interaction with these agents.

Table 2. TLC, CHD Risk Equivalents and Major Risk Factors for CHD*

Factor	Description
TLC†	
Diet	Saturated fat < 7% of calories
	Cholesterol < 200 mg per day
	Consider increased viscous (soluble) fiber (10 to 25 g per day) and plant stanols/sterols (2 g per day) to enhance LDL lowering
Weight management	Consider registered dietician consultation
Increased physical activity	
CHD	
Risk equivalents	Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)
	Diabetes
	Multiple risk factors that confer 10-year risk for CHD > 20%
Major risk factors modifying LDL goals‡	Cigarette smoking
	Hypertension (BP ≥ 140/90 mmHg or receiving antihypertensive medication)
	Low HDL cholesterol (< 40 mg/dL)§
	Family history of premature CHD
	CHD in male first-degree relative age < 55 years
	CHD in female first-degree relative age < 65 years
	Age (men, ≥ 45 years; women, ≥ 55 years)

Abbreviations: BP, blood pressure; CHD, coronary heart disease; TLC, therapeutic lifestyle changes.
*Data adapted.[33]
†Implement if feasible, given diagnosis, performance status, and prognosis.
‡Exclusive of LDL cholesterol.
§HDL cholesterol ≥ 60 mg/dL counts as negative risk factor; its presence removes one risk factor from total count.

LDL lowering. For purposes of management of elevated LDL resulting from PAM pathway inhibitors, all patients should be instructed in TLC. All patients with LDL cholesterol levels > 190 mg/dL should be treated with statin therapy if TLC fails. Risk factors that modify LDL cholesterol goals should be assessed (Table 2) and LDL goals adjusted based on presence of two or more cardiovascular risk factors.[34] Consideration to lower goals of LDL cholesterol can be given to those at higher risk of cardiovascular events in the short term (older age, smoking, hypertension, diabetic); lower LDL goals can be based on prognosis and cardiovascular risk, similar to National Cholesterol Education Program recommendations, in those with life expectancy > 1 year.[33] Figure 2B depicts a management algorithm for elevated LDL cholesterol in patients with a prognosis > 1 year. Note that statin drugs are first-line therapy for LDL cholesterol elevation.

Randomized trials have shown that statin therapy reduces cardiovascular events in high-risk patients as early as 6 months.[32] Patients with cancer with a prognosis > 1 year may therefore benefit as early as 6 months with treatment of hyperlipidemia. Any patient with coronary heart disease risk as defined in Table 2 (see CHD risk equivalents) is at high risk and should continue to receive lipid-lowering therapy if feasible, regardless of prognosis.[33] If a high-risk patient experiences an increase in LDL cholesterol to > 100 mg/dL after receiving PAM pathway inhibitor therapy, the following should be considered: uptitration of a lipid-lowering medication, addition of another agent, or appropriate referral. For non–high-risk patients, drug therapy should only be considered in those patients with an estimated survival > 6 months.

Myopathy and, rarely, rhabdomyositis are potential complications of statin therapy. Concomitant treatment with certain CYP450 inhibitors may increase the risk of these complications. Pravastatin is not metabolized by CYP enzymes and may be useful in such situations.

Management in the Clinical Trial Setting

The management recommendations discussed thus far apply to both the standard of care and research settings, but the information in this section is specific to clinical trials (Table 3).

Dose-limiting toxicity: phase I. For phase I studies, if grade 3 or 4 hyperlipidemia (hypertriglyceridemia or hypercholesterolemia) is observed (per protocol guidelines), patients should have a consultation with an endocrinologist or lipidologist (if available). Because therapy can take 4 weeks to lower lipid levels, grade 3 or 4 hyperlipidemia should not constitute a dose-limiting toxicity (DLT) in the first cycle; rather, lipids should be treated aggressively per the guidelines and recommendations of the task force. Persistent hyperlipidemia that does not improve to grade 2 despite treatment within 2 months for grade 3 hyperlipidemia, or within 1 month for grade 4 hyperlipidemia, should be considered dose limiting. However, because hyperlipidemia can occur beyond the typical DLT windows in phase I trials, it would be important to consider such metabolic events in the context of all DLT data at the completion of a phase I trial.

Dose modifications: later-phase trials (phase II or III). For phase II and later-phase studies, the study drug should be continued at current dose and dose reduction implemented if hyperlipidemia does not improve within 2 months in the case of grade 3 hyperlipidemia and 1 month in the case of grade 4 hyperlipidemia.

MANAGEMENT OF HYPERGLYCEMIA

Hyperglycemia and/or diabetes in patients with cancer have been associated with poor outcomes.[35] Large, long-term randomized controlled trials in diabetics have shown that lowering glucose to near-normal levels improves microvascular morbidity[36,37]; these

Table 3. Summary of Glycemic and Lipid Thresholds for Eligibility, Treatment, and Dose-Limiting Toxicity

Factor	Glycemic	Lipid
Eligibility for trials	Do not use HbA1C	LDL cholesterol < 190 mg/dL
	Fasting glucose < 160 mg/dL*	Triglycerides < 300 mg/dL
Goals on trial	HbA1C ≤ 8%†	LDL cholesterol < 190 mg/dL‡
	Fasting glucose < 160 mg/dL	Triglycerides < 300 mg/dL
	Random glucose < 200 mg/dL	
Dose-limiting toxicity	Grade 3 or asymptomatic grade 4 hyperglycemia not improving despite appropriate treatment for 1 week	Grades 3 to 4 hyperlipidemia (total cholesterol > 400 mg/dL or triglycerides > 500 mg/dL) not improving despite appropriate treatment for 4 weeks
	Symptomatic grade 4 hyperglycemia (> 500 mg/dL)	

*If fasting plasma glucose ≥ 160 mg/dL, period of 1 to 2 weeks of reasonable blood sugar control (as deemed by physician review of home blood glucose monitoring) is necessary for subsequent study eligibility.
†HbA1C may not be reliable in states of increased red blood cell turnover and chronic renal failure.
‡Assuming zero to one cardiovascular risk factor present. If ≥ two risk factors present, consider lower LDL goals.

data are of uncertain relevance to patients with cancer with shortened life spans.[36,38,39]

The goals of treatment in oncologic patients with metastatic disease and shortened life expectancy are to preserve quality of life via prevention of acute signs (polyuria, nocturia, polydipsia) and subsequent subacute complications of sustained hyperglycemia such as: infections, hypercoagulability, catabolic weight loss, and osmotic diuresis. The latter occurs when the renal threshold for glucose is overwhelmed and may eventually result in hospital admission for volume depletion, electrolyte abnormalities, and/or hyperosmolar hyperosmotic nonketotic state. Diabetic ketoacidosis, a state of relative or absolute insulin deficiency, may also result from sustained hyperglycemia. Regular blood sugar monitoring and an action plan can help prevent such complications from developing, because they are mainly associated with undetected and untreated hyperglycemia. By analogy, steroid-induced hyperglycemia associated with chemotherapy may often go undetected and eventually necessitate admission. Hypoglycemia is a potentially life-threatening adverse effect of sulfonylurea drugs and insulin; by and large, the blood sugar goals of treatment should be less aggressive in patients with advanced cancer who may experience asthenia, anorexia, stomatitis, and diarrhea. Variable nutrient intake can precipitate hypoglycemia in the setting of sulfonylurea or insulin use. The use of premeal rapid-acting analog insulin allows a patient to eat at flexible meal times and skip meals as needed. Insulin is often the safest option in patients with multiple comorbidities. If a PAM pathway inhibitor is discontinued, the antidiabetic agents should also be stopped and blood glucose observed.

The treatment goals for glycemic control should be: 1) fasting plasma glucose < 160 mg/dL; 2) random plasma glucose < 200 mg/dL; and 3) HbA1c ≤ 8% to prevent the acute symptoms and subacute complications of hyperglycemia, while making every attempt to avoid hypoglycemia.

Screening and Monitoring

No history of diabetes. For monitoring while a patient is receiving PAM pathway inhibitors, we suggest checking fasting (preferably) or random glucose at baseline and every visit. Any nondiabetic patient who has high-risk features of potential for future diabetes (ie, abnormal fasting glucose > 100 mg/dL, random glucose > 140 mg/dL) or is at high risk (ie, overweight [BMI > 25], family history of diabetes, history of gestational diabetes, receiving steroids, hyperlipidemic) should perform home blood glucose monitoring once per day for the first week of cycle one, alternating between before breakfast, lunch, or dinner. Some of these agents may not cause hyperglycemia until cycle two or three; therefore, monitoring blood sugar two or three times per week in cycles two and three is also recommended. In the event of grade 1 or higher hyperglycemia, more frequent monitoring may be necessary, and intervention should be taken as per the algorithm provided (Fig 3). Also, in hyperglycemic patients who develop anion gap metabolic acidosis while receiving PAM pathway inhibitors, in the context of appropriate signs and symptoms, a diagnosis of diabetic ketoacidosis should be considered.

History of diabetes. Monitoring of blood sugars should be continued as patient was doing before starting PAM pathway inhibitors and should be intensified if blood sugars are not at goal.

Management

No history of diabetes. Depending on the pharmacokinetics and schedule of the agent, hyperglycemia may be transient, or it may resolve before a subsequent dose. Transient grade 1 or 2 hyperglycemia does not need to be treated. Metformin is the first-line drug for management of sustained grade 1, grade 2, and asymptomatic grade 3 hyperglycemia (Fig 3). It does not cause hypoglycemia. Metformin is contraindicated in patients with risk factors for lactic acidosis (reduction in glomerular filtration rate < 60 mL/min, significant impairment in liver synthetic function, states of decreased tissue perfusion such as myocardial infarction and sepsis). It should be uptitrated to maximum dose gradually over 1 to 2 weeks to avoid GI adverse effects. Any patient initiated on sulfonylurea or insulin therapy should be instructed on how to recognize and treat hypoglycemia. Sulfonylureas are to be avoided in renal insufficiency (repaglinide and sitagliptin are alternative options in this situation). Patients should call their physician for any blood glucose < 70 mg/dL.

If PAM pathway inhibitors are administered on intermittent schedules, or if they are discontinued, the administration of glucose-lowering agents must be adjusted by close monitoring, because the levels of glucose can fluctuate. Particular caution should be exercised in patients receiving agents capable of causing hypoglycemia (insulin and sulfonylureas); these agents should be stopped in patients with no prior history of use when PAM pathway therapy is interrupted.

The following algorithm provides recommendations on therapeutic interventions if patients develop hyperglycemia while receiving PAM pathway inhibitors:

• Grade 1: fasting glucose > 125 to 160 mg/dL

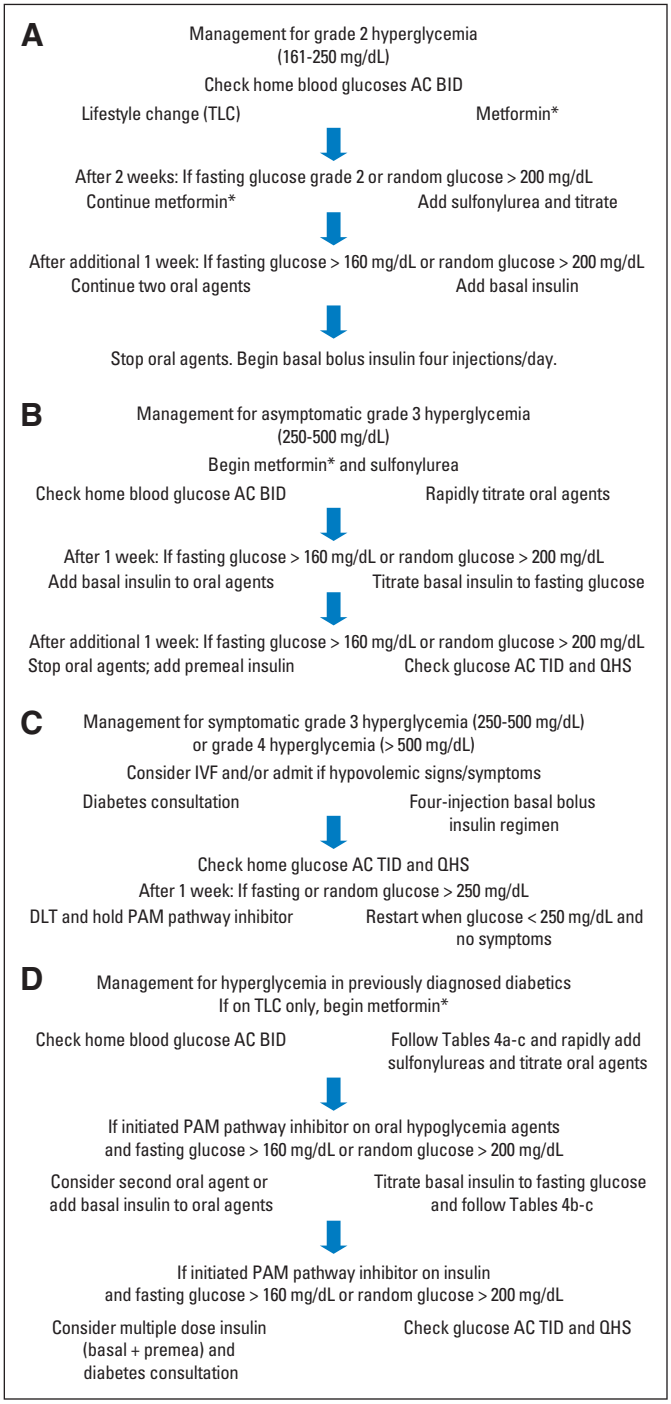

Fig 3. Management of (A) grade 2 hyperglycemia (161 to 250 mg/dL), (B) asymptomatic grade 3 hyperglycemia (250 to 500 mg/dL), (C) symptomatic grade 3 hyperglycemia (250 to 500 mg/dL) or grade 4 hyperglycemia (> 500 mg/dL), and (D) hyperglycemia in previously diagnosed diabetics. NOTE. Recommendations based on experience and expertise of the panel. Some patients are able to stop insulin or sulfonylureas later with therapeutic lifestyle changes (TLC), after acute lowering of blood glucose or after discontinuation of phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (PAM) pathway inhibitors. AC, before meals; DLT, dose-limiting toxicity; IVF, intravenous fluids; QHS, before every bedtime. (*) Do not use metformin if creatine > 1.3 mg/dL (women) or > 1.4 mg/dL (men) or if any state of decreased tissue perfusion or hemodynamic instability is present (eg, heart failure); hold metformin for computed tomography scans; GI symptoms may occur with initiation but usually subside after first week.

Start once-per-day home glucose monitoring (alternate between fasting glucose and predinner glucose); blood glucose log should be assessed by health care provider once each week. If appropriate in clinical context, refer to nutritionist for dietary education on diabetic diet, increase aerobic exercise, and refer to diabetes educator for comprehensive diabetic education on nonpharmaceutical interventions or TLC.

• Grade 2: fasting glucose > 160 to 250 mg/dL

Start twice-per-day home glucose monitoring (before breakfast and dinner) and TLC. Figure 3A illustrates management of grade 2 hyperglycemia.

• Asymptomatic grade 3: fasting glucose > 250 to 500 mg/dL

Start home glucose monitoring before meals twice per day (before breakfast and dinner) and TLC. Figure 3B illustrates management of asymptomatic grade 3 hyperglycemia.

• Symptomatic grade 3 or asymptomatic grade 4: fasting glucose > 500 mg/dL

Consider intravenous fluids because of risk of volume depletion. Check home blood glucoses before meals three times per day and at bedtime. Figure 3C illustrates management of symptomatic grade 3 or asymptomatic grade 4 hyperglycemia.

• Symptomatic grade 4: fasting glucose > 500 mg/dL

DLT; refer to endocrinology or diabetes treating specialist.

History of diabetes. The treatment of those with a history of diabetes is similar to that for patients without, with the exception based on treatment the diabetic patient received before starting PAM pathway inhibitors. The same pre-PAM pathway inhibitor antidiabetic regimen is to be continued if blood glucoses are at goal (fasting < 160 mg/dL; random < 200 mg/dL). Additional therapies in the order described for those without history of diabetes should be incrementally added (Fig 3D).

Management in the Clinical Trial Setting

The management recommendations discussed thus far apply to both the standard of care and research settings, but the information in this section is specific to clinical trials (Table 3).

Eligibility criteria. In trials investigating agents that potentially cause hyperglycemia, diabetics are often excluded. There are multiple problems with the exclusion of diabetics: 1) diabetics are a large and growing part of the cancer population; 2) using a history of diabetes underdiagnoses a large population of truly diabetic patients; 3) depending on what definition of diabetes is used, patients who are mildly hyperglycemic may be unnecessarily excluded, and patients who will still develop a high-grade adverse event, despite no prediagnosis of diabetes, may be included. There are two options for eligibility of diabetics. In the first option, diabetics should not be excluded from trials investigating agents that can cause hyperglycemia; one can consider separating cohorts into diabetics and nondiabetics and then evaluate DLTs separately. In this option, one should have consultation available to aid with management of hyperglycemia, should it be necessary. In option two, diabetics are excluded from early-phase trials and allowed to participate in later-phase trials. Given the large population with diabetes, the experience to date, and reasons provided here, option one is preferred by the authors.

HbA1C should not be used as a screening eligibility criterion. This is because of the fact that HbA1C changes slowly (full change occurs over 3 months), whereas a patient may be brought under reasonable glycemic control as early as 1 to 2 weeks after aggressive

intervention. Therefore, in the case of both diabetic and nondiabetic individuals, we suggest first checking a fasting plasma glucose value. To be eligible for study entry, fasting plasma glucose should be grade 1 hyperglycemia or less (< 160 mg/dL). If fasting plasma glucose value is ≥ 160 mg/dL, a period of 1 to 2 weeks of reasonable blood sugar control (as deemed by physician review of home blood glucose monitoring) should be demonstrated before a patient becomes eligible for study participation.

What constitutes a DLT (hyperglycemic event) during cycle one of PAM pathway inhibitors? Symptomatic grade 4 hyperglycemia constitutes a DLT. Asymptomatic grade 4 hyperglycemia or a grade 3 hyperglycemic event (nonhematologic toxicity) warrants immediate endocrinologist or diabetes treating specialist consult (if available). If glucose levels do not improve within 1 week, the patient should be considered to have a DLT (dose modification and so on should occur).

Early-phase trials (phase I or I/II) with DLT end points. A grade 3 hyperglycemic event (> 250 mg/dL) should result in continuous dosing (case-by-case basis) of the drug, but the patient should have immediate access to consultation with an endocrinologist or specialist. If the event continues for > 1 week after consultation and management, consider this a DLT. For classes of drugs that are likely to cause hyperglycemic DLTs, the research team conducting the phase I study should have an endocrinology collaborator on the trial team.The occurrence of grade 3 hyperglycemia (> 250 mg/dL) or asymptomatic grade 4 hyperglycemia (> 500 mg/dL) should result in a rapid review by the team endocrinologist (by telephone or in person) or the respective algorithm should be followed. The study drug should be held without attempting intervention if a patient experiences a symptomatic grade 4 (> 500 mg/dL) hyperglycemic event.

Later-phase trials (phase II or III) with dose reductions. As stated, dose reductions are not required if grade 3 hyperglycemia or asymptomatic grade 4 hyperglycemia is controllable within 1 week.

RECOMMENDATIONS TO ORGANIZATIONS DETERMINING RESEARCH PRIORITIES AND CLINICAL TRIAL OPERATIONS

Consideration should be given to provide opportunity for research between the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute. A request for proposal should be considered for a more uniform collection of prospective quantitative blood sugar and lipid data to help determine blood levels, drug exposure, pharmacokinetics, and pharmacodynamics and relation to therapeutic levels and outcomes. This would allow for future consensus reports to include the prospectively collected objective data and results for better management of these metabolic toxicities resulting from these agents. This would include blood sugar goals, lipid goals, and choice of agents for the treatment of either adverse events or outcomes.

Consideration should be given by the National Cancer Institute Coordinating Center for Clinical Trials Symptom Management Steering Committee to create a concept for clinical trials to further investigate hyperglycemia and hyperlipidemia toxicities and PAM pathway inhibitors in general. This would help determine if symptom and quality-of-life measures are improved with better control of these metabolic toxicities.

CONCLUSION

Anticancer agents that inhibit signaling in the PAM pathway may be associated with hyperlipidemia and/or hyperglycemia because of their pathophysiologic mechanism of action. All patients should be screened for these metabolic toxicities, because some patients may develop progressive and severe elevations and require interruption of oncologic therapy. In contrast to traditional oncologic adverse events, there are generally no acutely toxic effects to metabolic toxicities (rather, quality of life may be affected and risk for subacute complications increases). Therefore, whether in the clinical trial or clinical practice setting, most metabolic adverse events should be followed by a period of therapeutic intervention with the aid of specialty consultation.

The purpose of this consensus article is to improve the management of adverse events in patients treated with PAM pathway inhibitors. It is not intended to discourage the appropriate use of these potentially lifesaving anticancer therapies. Oncologic therapy should only be interrupted if adverse event management is unsuccessful.

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REFERENCES

1. Fraenkel M, Ketzinel-Gilad M, Ariav Y, et al: MTOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. Diabetes 57:945-957, 2008
2. Teutonico A, Schena PF, Di Paolo S: Glucose metabolism in renal transplant recipients: Effect of calcineurin inhibitor withdrawal and conversion to sirolimus. J Am Soc Nephrol 16:3128-3135, 2005
3. Morrisett JD, Abdel-Fattah G, Hoogeveen R, et al: Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients. J Lipid Res 43:1170-1180, 2002
4. Brown NF, Stefanovic-Racic M, Sipula IJ, et al: The mammalian target of rapamycin regulates lipid metabolism in primary cultures of rat hepatocytes. Metabolism 56:1500-1507, 2007
5. Kraemer FB, Takeda D, Natu V, et al: Insulin regulates lipoprotein lipase activity in rat adipose cells via wortmannin- and rapamycin-sensitive pathways. Metabolism 47:555-559, 1998

6. Hoogeveen RC, Ballantyne CM, Pownall HJ, et al: Effect of sirolimus on the metabolism of apoB100-containing lipoproteins in renal transplant patients. Transplantation 72:1244-1250, 2001

7. Sipula IJ, Brown NF, Perdomo G: Rapamycin-mediated inhibition of mammalian target of rapamycin in skeletal muscle cells reduces glucose utilization and increases fatty acid oxidation. Metabolism 55:1637-1644, 2006

8. Kreis H, Cisterne JM, Land W, et al: Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation 69:1252-1260, 2000

9. Motzer RJ, Escudier B, Oudard S, et al: Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. Lancet 372:449-456, 2008

10. Hudes G, Carducci M, Tomczak P, et al: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271-2281, 2007

11. Di Paolo S, Teutonico A, Leogrande D, et al: Chronic inhibition of mammalian target of rapamycin signaling downregulates insulin receptor substrates 1 and 2 and AKT activation: A crossroad between cancer and diabetes? J Am Soc Nephrol 17:2236-2244, 2006

12. Crouthamel MC, Kahana JA, Korenchuk S, et al: Mechanism and management of AKT inhibitor-induced hyperglycemia. Clin Cancer Res 15:217-225, 2009

13. Sirolimus product monograph. http://www.pfizer.ca/en/our_products/products/monograph/256

14. Jimeno A, Herbst RS, Falchook GS, et al: Final results from a phase I, dose-escalation study of PX-866, an irreversible, pan-isoform inhibitor of PI3 kinase. J Clin Oncol 28:255s, 2010 (suppl 15; abstr 3089)

15. Grana B, Burris HA, Rodon Ahnert J, et al: Oral PI3 kinase inhibitor BKM120 monotherapy in patients (pts) with advanced solid tumors: An update on safety and efficacy. J Clin Oncol 29:204s, 2011 (suppl 15; abstr 3043)

16. Edelman G, Bedell 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 3089)

17. Moreno-Garcia V, Baird RD, Shah KJ, et al: A phase I study evaluating GDC-0941, an oral phosphoinositide-3 kinase (PI3K) inhibitor, in patients with advanced solid tumors or multiple myeloma. J Clin Oncol 29:199s, 2011 (suppl 15; abstr 3021)

18. Burris H, Rodon J, Sharma S, et al: First-in-human phase I study of the oral PI3K inhibitor BEZ235 in patients (pts) with advanced solid tumors. J Clin Oncol 28:234s, 2010 (suppl 15; abstr 3005)

19. LoRusso P, Markman B, Tabernero J, et al: A phase I dose-escalation study of the safety, pharmacokinetics (PK), and pharmacodynamics of XL765, a PI3K/TORC1/TORC2 inhibitor administered orally to patients (pts) with advanced solid tumors. J Clin Oncol 27:221s, 2009 (suppl 15; abstr 3502)

20. Munster PN, van der Noll R, Voest EE, et al: Phase I first-in-human study of the PI3 kinase inhibitor GSK2126458 (GSK458) in patients with advanced solid tumors (study P3K112826). J Clin Oncol 29:198s, 2011 (suppl 15; abstr 3018)

21. Wagner AJ, Bendell JC, Dolly S, et al: A first-in-human phase I study to evaluate GDC-0980, an oral PI3K/mTOR inhibitor, administered QD in patients with advanced solid tumors. J Clin Oncol 29:199s, 2011 (suppl 15; abstr 3020)

22. Yap TA, Yan L, Patnaik A, et al: Final results of a translational phase I study assessing a QOD schedule of the potent AKT inhibitor MK-2206 incorporating predictive, pharmacodynamic (PD), and functional imaging biomarkers. J Clin Oncol 29: 194s, 2011 (suppl 15; abstr 3001)

23. Tabernero J, Saura C, Roda Perez D, et al: First-in-human phase I study evaluating the safety, pharmacokinetics (PK), and intratumor pharmacodynamics (PD) of the novel, oral, ATP-competitive Akt inhibitor GDC-0068. J Clin Oncol 29:199s, 2011 (suppl 15; abstr 3022)

24. Burris HA, Siu LL, Infante JR, et al: Safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of the oral AKT inhibitor GSK2141795 (GSK795) in a phase I first-in-human study. J Clin Oncol 29:194s, 2011 (suppl 15; abstr 3003)

25. Hartford CM, Desai AA, Janisch L, et al: A phase I trial to determine the safety, tolerability, and maximum tolerated dose of deforolimus in patients with advanced malignancies. Clin Cancer Res 15: 1428-1434, 2009

26. Tan DS, Dumez H, Olmos D, et al: First-in-human phase I study exploring three schedules of OSI-027, a novel small molecule TORC1/TORC2 inhibitor, in patients with advanced solid tumors and lymphoma. J Clin Oncol 28:234s, 2010 (suppl 15; abstr 3006)

27. Mita MM, Mita AC, Chu QS, et al: Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. J Clin Oncol 26:361-367, 2008

28. Kochanek KD, Xu JQ, Murphy SL, et al: Deaths: Preliminary data for 2009. Natl Vital Stat Rep 59:1-51, 2011

29. Thompson WG, Gau GT: Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med 169:578-579, 2009

30. Keech A, Simes RJ, Barter P, et al: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. Lancet 366:1849-1861, 2005

31. LaRosa JC, He J, Vupputuri S: Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. JAMA 282:2340-2346, 1999

32. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors: The Pravastatin Multinational Study Group for Cardiac Risk Patients. Am J Cardiol 72:1031-1037, 1993

33. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106:3143-3421, 2002

34. National Cholesterol Education Program (NCEP): Risk assessment tool for estimating your 10-year risk of having a heart attack. http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof

35. Park SM, Lim MK, Shin SA, et al: Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. J Clin Oncol 24:5017-5024, 2006

36. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group. Lancet 352:837-853, 1998

37. ADVANCE Collaborative Group, Patel A, MacMahon S, et al: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358:2560-2572, 2008

38. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial Research Group. N Engl J Med 329:977-986, 1993

39. American Diabetes Association: Standards of medical care in diabetes: 2011. Diabetes Care 34: S11–S61, 2011 (suppl 1)

