


Management of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia

Integrative Cancer Therapies
Volume 21: 1–14
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15347354211073163
journals.sagepub.com/home/ict


Marcus D. Goncalves, MD, PhD¹  and Azeez Farooki, MD²

Abstract

Phosphatidylinositol-3-kinase (PI3K) pathway hyperactivation has been associated with the development of cancer and treatment resistance. PI3K inhibitors are now used to treat hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–), *PIK3CA*-mutated advanced breast cancer. Hyperglycemia, a frequently observed adverse event with PI3K inhibitors (PI3Ki), is regarded as an on-target effect because inhibition of the PI3K pathway has been shown to decrease glucose transport and increase glycogenolysis and gluconeogenesis. PI3Ki-induced hyperglycemia results in a compensatory increase in insulin release, which has been shown to reduce the efficacy of treatment by reactivating the PI3K pathway in preclinical models. Patients with an absolute or relative deficiency in insulin, and those with insulin resistance or pancreatic dysfunction, may experience exacerbated or prolonged hyperglycemia. Therefore, the effective management of PI3Ki-associated hyperglycemia depends on early identification of patients at risk, frequent monitoring to allow prompt recognition of hyperglycemia and its sequelae, and initiating appropriate management strategies. Risk factors for the development of hyperglycemia include older age (≥ 75 years), overweight/obese at baseline, and family history of diabetes. Consultation with an endocrinologist is recommended for patients considered high risk. The management of PI3Ki-induced hyperglycemia requires an integrative approach that combines diets low in carbohydrates and glucose-lowering medications. Medications that do not affect the PI3K pathway are preferred as the primary and secondary agents for the management of hyperglycemia. These include metformin, sodium-glucose co-transporter 2 inhibitors, thiazolidinediones, and α -glucosidase inhibitors. Insulin should only be considered as a last-line agent for PI3Ki-associated hyperglycemia due to its stimulatory effect of PI3K signaling. Clinical studies show that alpelisib-associated hyperglycemia is reversible and manageable, rarely leading to treatment discontinuation. Management of PI3Ki-associated hyperglycemia in patients with breast cancer should focus on the prevention of acute and subacute complications of hyperglycemia, allowing patients to remain on anticancer treatment longer.

Keywords

HR+, HER2– advanced breast cancer, PI3K, alpelisib, hyperglycemia, *PIK3CA*

Submitted August 17, 2021; revised December 6, 2021; accepted December 22, 2021

Introduction

The phosphatidylinositol-3-kinase (PI3K) pathway is an intracellular pathway that integrates extracellular signals to regulate a variety of physiological functions including cell growth, metabolism, survival, angiogenesis, and glucose metabolism (Figure 1).^{1–6} Hyperactivation of this pathway is associated with almost all human cancers.¹ In breast cancer, PI3K pathway hyperactivation has also been implicated in drug resistance to endocrine therapy, human epidermal growth factor receptor-2 (HER2) inhibitors, and cytotoxic agents.^{2,7}

Phosphatidylinositol-3-kinases are heterodimeric lipid kinases that are divided into 3 classes (I, II, III); abnormal activation of class I PI3Ks is observed in breast cancer.^{3,8} The genes *PIK3CA*, *PIK3CB*, and *PIK3CD* encode the

catalytic p110 α , p110 β , and p110 δ subunits of class IA, the PI3K subclass most frequently implicated in human cancer.^{1,3} Among the different mutations that can lead to PI3K pathway activation in breast cancer, phosphatidylinositol-4,5-bisphosphate kinase-3 catalytic subunit alpha (*PIK3CA*) mutation is the most common alteration of this pathway.^{4,9} Mutation of *PIK3CA* occurs in approximately

¹Weill Cornell Medicine, New York, NY, USA

²Memorial Sloan Kettering Cancer Center, New York, NY, USA

Corresponding Author:

Marcus D. Goncalves, Division of Endocrinology, Weill Department of Medicine, Weill Cornell Medicine, 211 East 80th Street, 2nd Floor, New York, NY 10075, USA.

Email: mdg9010@med.cornell.edu



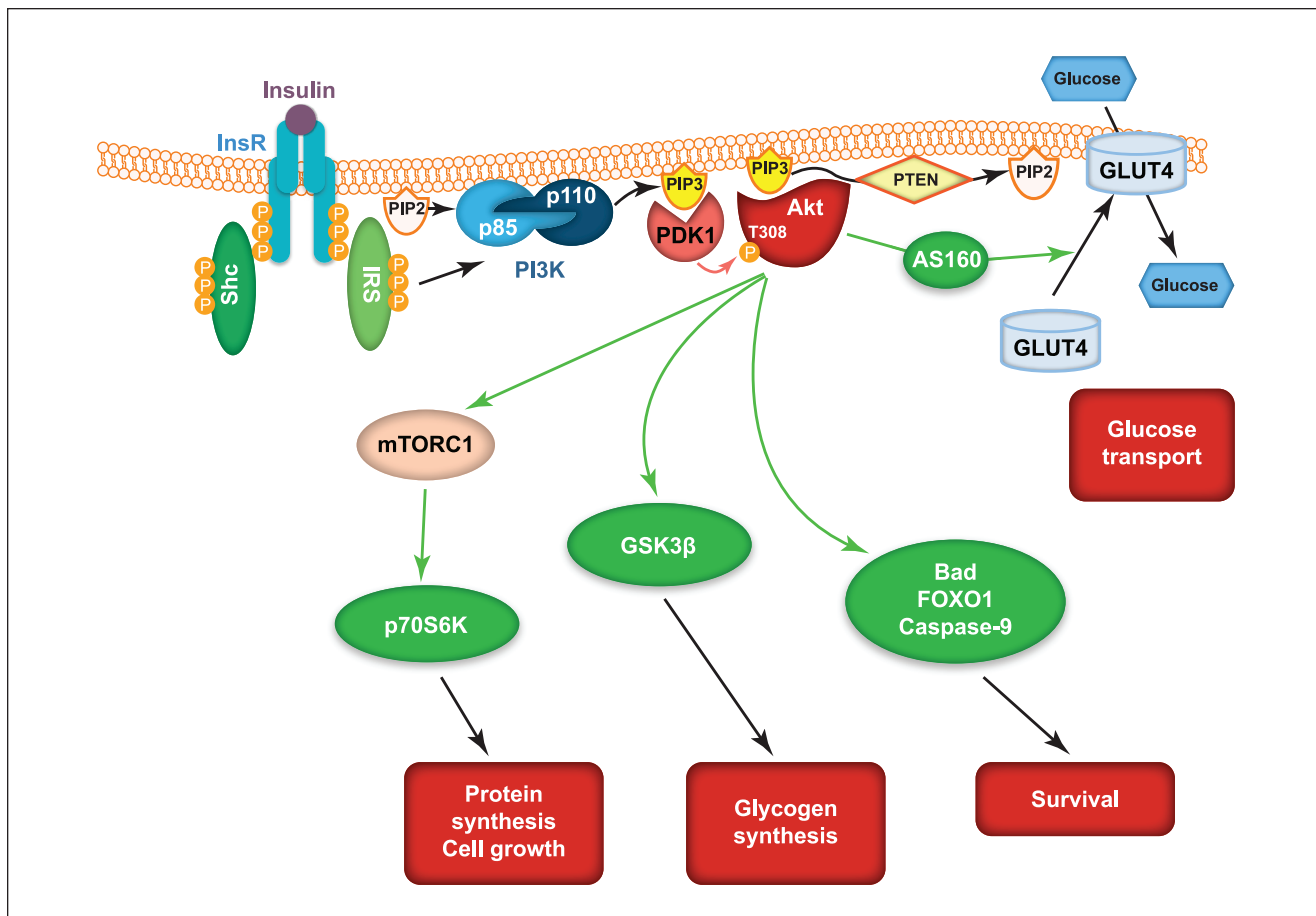


Figure 1. Overview of the PI3K pathway.⁶

Source: Adapted by permission from Kim and Feldman,⁶ Elsevier Ltd, Copyright 2011.

Abbreviations: AKT, protein kinase B; FOXO1, Forkhead Box O1; GLUT4, glucose transporter type 4; GSK3, glycogen synthase kinase-3; InsR, insulin receptor; mTORC1, mammalian target of rapamycin complex 1; p70S6K1, ribosomal protein S6 kinase beta-1; PDK1, pyruvate dehydrogenase kinase; PI3K, phosphatidylinositol-3-kinase; PIP2, phosphatidylinositol 4, 5-bisphosphate; PIP3, phosphatidylinositol 3, 4, 5-trisphosphate; PTEN, phosphatase and tensin homolog.

40% of hormone receptor-positive (HR+), HER2-; up to 40% in HER2+; and in up to 14% of triple-negative breast cancers.¹⁰⁻¹⁵ The majority of *PIK3CA* mutations occur within the helical (E542K and E545K) and kinase (H1047R) domains of p110 α .⁴ In a preclinical study, tumors with novel *PIK3CA* C-terminal frameshift mutations were shown to exhibit sensitivity to p110 α inhibition.¹⁶

Alpelisib is an α -selective PI3K inhibitor (PI3Ki) that is indicated for the treatment of postmenopausal women and men with HR+, HER2- *PIK3CA*-mutated advanced breast cancer (ABC) who progressed on or after endocrine therapy.¹⁷ In the Phase III SOLAR-1 trial, patients treated with alpelisib plus fulvestrant (n=169) had longer progression-free survival (PFS) than those treated with placebo plus fulvestrant (n=172; 11 months vs 5.7 months; hazard ratio [HR] 0.65, $P < .001$).¹⁸ Median overall survival in patients with lung and/or liver metastases (n=170) was 37.2 months versus 22.8 months (HR 0.68; 95% CI, 0.46-1.00) in the alpelisib plus fulvestrant group compared with

the placebo plus fulvestrant group.¹⁹ Hyperglycemia was the most common (64% of patients) alpelisib-associated adverse event (AE) reported in that study.¹⁸

Because many clinicians lack experience with PI3Kis, there is a need for additional guidance on how to prevent, monitor, and manage this on-target effect of PI3K inhibition. This review aims to explore the etiology of hyperglycemia and provide recommendations for the prevention and management of PI3Ki-associated hyperglycemia.

Physiologic Control of Blood Glucose Levels: Insulin and the PI3K Pathway

Glucose homeostasis is regulated by insulin and glucagon, produced by the β - and α -cells of the pancreas, respectively. Insulin functions to lower blood glucose (BG), whereas glucagon is responsible for increasing BG. Insulin secretion is mainly regulated by BG concentrations. After meals, insulin secretion increases. Other factors that stimulate insulin

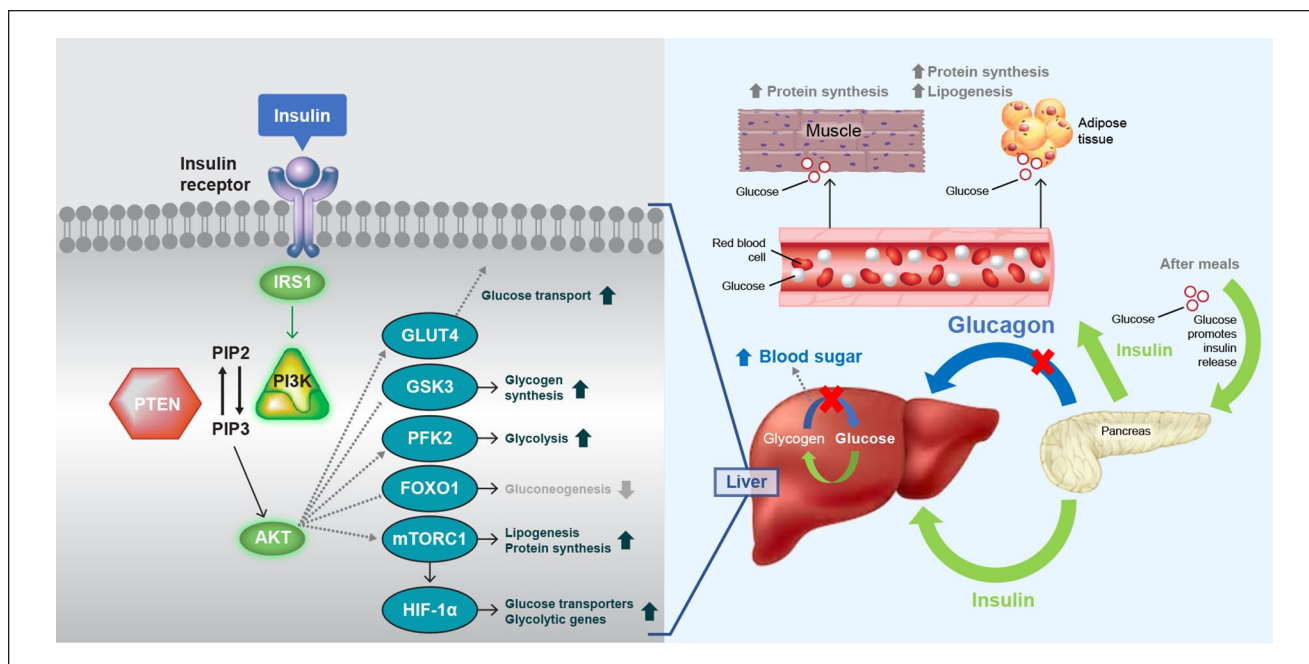


Figure 2. Role of insulin and the PI3K pathway in normal glucose homeostasis.²¹

Source: Adapted by permission from Drullinsky and Hurvitz,²¹ Springer Nature Customer Service Centre, Copyright 2020.

Normally, insulin secreted from the pancreas causes glucose to be stored as glycogen in the liver, and, glucose is taken up by skeletal muscle and adipose tissue.²⁰

Abbreviations: AKT, protein kinase B; FOXO1, Forkhead Box O1; GLUT4, glucose transporter type 4; GSK3, glycogen synthase kinase-3; HIF-1 α , hypoxia-inducible factor 1 α ; IRS1, insulin receptor substrate 1; mTORC1, mammalian target of rapamycin complex 1; PFK2, phosphofructokinase-2; PI3K, phosphatidylinositol-3-kinase; PIP2, phosphatidylinositol 4, 5-bisphosphate; PIP3, phosphatidylinositol 3, 4, 5-trisphosphate; PTEN, phosphatase and tensin homolog.

secretion are increased levels of certain amino acids, postprandial release of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) from the gut, and parasympathetic stimulation. Initially, preformed insulin is released into the bloodstream. This is followed by increased insulin synthesis and subsequent release in response to increased BG.²⁰

Insulin exerts its actions through binding to the insulin receptor (IR) on the cell surface, thereby activating intracellular pathways such as the PI3K pathway (Figure 2).²⁰⁻²² The p110 α isoform of PI3K mediates insulin responses in muscle, liver, and adipose tissues (as shown in the animation [Supplemental File 1]).⁴ The PI3K pathway can also be activated by other mitogens, including insulin-like growth factor (IGF) and epidermal growth factor (EGF), through binding to IGF receptor 1 (IGF-1R) and EGF receptor (EGFR), respectively.²²

Upon PI3K activation, protein kinase B (AKT) induces the translocation of glucose transporters GLUT1 and GLUT4 to the plasma membrane to facilitate glucose uptake.⁵ Intracellularly, AKT promotes glycolysis by stimulating hexokinase and phosphofructokinase-2, and promotes glycogenesis by inhibiting glycogen synthase kinase 3 (GSK3) resulting in glycogen synthase activation.^{21,23} AKT also prevents the nuclear localization of the

transcription factor FoxO1, leading to inhibition of gene transcription needed for gluconeogenesis.²² In addition, insulin-PI3K signaling stimulates protein synthesis in skeletal muscle, and both protein synthesis and lipogenesis in adipose tissue. Activation of AKT also leads to activation of mammalian target of rapamycin complex 1 (mTORC1), which upregulates lipogenesis, protein synthesis, and glucose metabolism through various downstream effectors including hypoxia-inducible factor 1 α .^{22,23}

Mechanism of PI3Ki-Associated Hyperglycemia and Incidence in Preclinical and Clinical Studies

PI3K inhibitors result in hyperglycemia through inhibition of the intracellular response to insulin,²¹ leading to decreased glucose transport and increased glycogenolysis and gluconeogenesis (as shown in the animation [Supplemental File 1]).^{8,22,23} Glucose transport capacity, glycogen synthesis, and glycolysis are reduced to approximately 60% in the presence of a PI3Ki.²⁴ Hence, hyperglycemia can be considered an expected “on-target” effect of PI3K inhibition.²⁵

In a preclinical study of mice treated with either alpelisib, buparlisib, or taselisib, a significant increase in BG was observed in PI3Ki-treated mice compared with

vehicle-treated mice.²⁶ The PI3K-induced hyperglycemia then triggered a compensatory massive release of insulin (insulin feedback) from the pancreas. This hyperinsulinemic state led to partial reactivation of PI3K signaling and glucose uptake into the tumor and the metabolic tissues that restore glucose homeostasis.^{25,26} In addition, the increase in insulin secretion can activate not only IR, but also IGF-1R, providing a mechanism for survival of tumor cells.²⁴ Blocking the release of insulin using therapeutic strategies (diet or drugs) that control PI3Ki-induced hyperglycemia improved the efficacy of the PI3Kis.^{25,26}

Baseline glucose control may impact severity and duration of PI3Ki-induced hyperglycemia. In an insulin-resistance mouse model (MKR mice), mice treated with buparlisib experienced significant hyperglycemia after 2 weeks of treatment. Hyperglycemia was more pronounced in MKR than wild-type mice. Mice treated with buparlisib also experienced hyperinsulinemia, but the increase was higher in MKR than wild-type mice (10- vs 7-fold).²⁷

The perturbations of glucose homeostasis observed in mice have also been found in humans treated with PI3Kis. In SOLAR-1, the incidence of all-grade and grade ≥ 3 hyperglycemia was 64% and 37%, respectively.¹⁸ This was higher than the incidence of grade ≥ 3 hyperglycemia in clinical trials of buparlisib, taselisib, pictilisib, and serabelisib (ranging from 5.5% to 15%), which all stalled in their clinical development except for serabelisib.²⁸⁻³² Similarly, other targeted therapies that affect the PI3K pathway are also associated with hyperglycemia including IGF-1R (cixutumumab, all grade 17%-100%, grade ≥ 3 up to 46%; dalotuzumab, all grade 19%-100%, grade ≥ 3 up to 32%), dual IGF-1R/IR (linsitinib, all grade 3%-37%, grade ≥ 3 up to 5%), and EGFR (gefitinib, grade ≥ 3 up to 5%; panitumumab, all grade up to 5%, grade ≥ 3 up to 5%) inhibitors.^{22,33} As predicted by the mouse models, hyperinsulinemia has also been observed in subjects treated with alpelisib and other PI3Kis in clinical trials and in clinical practice.³⁴⁻³⁷

Similar to the findings from the MKR mice,²⁷ a higher incidence of hyperglycemia was reported in SOLAR-1 subjects who were prediabetic at baseline compared with those with normal baseline glycemic status.³⁸ Along the same lines, the rates of grade 3/4 hyperglycemia (fasting glucose >250 mg/dL or >13.9 mmol/L) were higher in the first half of SOLAR-1 compared with the second half, when the glycosylated hemoglobin (HbA1c) enrollment criterion was $<8.0\%$ instead of $<6.5\%$.³⁸ These data suggest that patients with an absolute or relative insulin deficiency are particularly prone to PI3Ki-induced hyperglycemia.

Results from SOLAR-1 have shown that alpelisib-associated hyperglycemia is reversible, with a median time to onset of 15 days (grade ≥ 2 : fasting glucose [fasting plasma or blood glucose] >160 mg/dL), and a median time to improvement by ≥ 1 grade of 8 and 6 days for grade ≥ 2 and ≥ 3 (fasting glucose >250 mg/dL), respectively.^{17,38}

Prevention and Monitoring of PI3Ki-Associated Hyperglycemia

Baseline Assessment and On-treatment Monitoring

Perform a thorough history and physical examination in patients prior to starting PI3Ki to identify risk factors associated with hyperglycemia (Figure 3A).³⁹ In SOLAR-1, a higher incidence of hyperglycemia was observed in elderly patients (≥ 75 years) and patients who were overweight and obese at baseline treated with alpelisib.³⁸ According to the American Diabetes Association (ADA), other risk factors associated with the development of diabetes include family history of diabetes, race/ethnicity (African American, Latino, Native American, Asian American, Pacific Islander), history of prediabetes, cardiovascular disease, hypertension, polycystic ovarian syndrome or gestational diabetes, high-density lipoprotein (HDL) cholesterol <35 mg/dL (0.9 mmol/L) and/or triglyceride >250 mg/dL (2.82 mmol/L), sedentary lifestyle, and other conditions associated with insulin resistance (such as acanthosis nigricans).³⁹ Additional indications that the patient is at high risk for developing hyperglycemia include pre-existing prediabetes (fasting glucose 100-125 mg/dL or HbA1c 5.7%-6.4%) or diabetes (fasting glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$). Other potential markers include fructosamine >230 μ M and glycated albumin (GA) $>13.35\%$.

The ADA diagnostic criteria for diabetes are included in Figure 3A.³⁹ In the elderly (≥ 65 years) population of the United States, approximately 25% of people have diabetes and nearly half are estimated to have prediabetes.⁴⁰ Approximately 30% of patients with breast cancer have diabetes; pre-existing diabetes was associated with a 49% increased risk of all-cause mortality among patients with breast cancer.⁴¹ Furthermore, diabetes is associated with an increased risk of various cancers, including breast cancer.³⁹

Test fasting plasma glucose (FPG), HbA1c, and optimize BG at baseline. There are insufficient safety data on the use of PI3Kis in patients with type I or uncontrolled type II diabetes; hence, PI3Ki should not be initiated in patients without good glycemic control.¹⁷ Patients with HbA1c $\geq 6.5\%$ (diabetes) were initially allowed to enter SOLAR-1, but the protocol was subsequently amended to exclude patients with HbA1c $>6.5\%$ and FPG >140 mg/dL due to the increased risk of developing severe hyperglycemia in patients with HbA1c 6.5% to 8%.¹⁸ In addition, patients who were prediabetic or diabetic at baseline treated with alpelisib had greater increases in FPG compared with normoglycemic patients.³⁸ Educate all patients on possible signs and symptoms of hyperglycemia such as excessive thirst, frequent urination, blurry vision, and increased appetite with weight loss.

If administering alpelisib, monitor fasting glucose (FPG or fasting BG) at least once a week for the first 2 weeks,

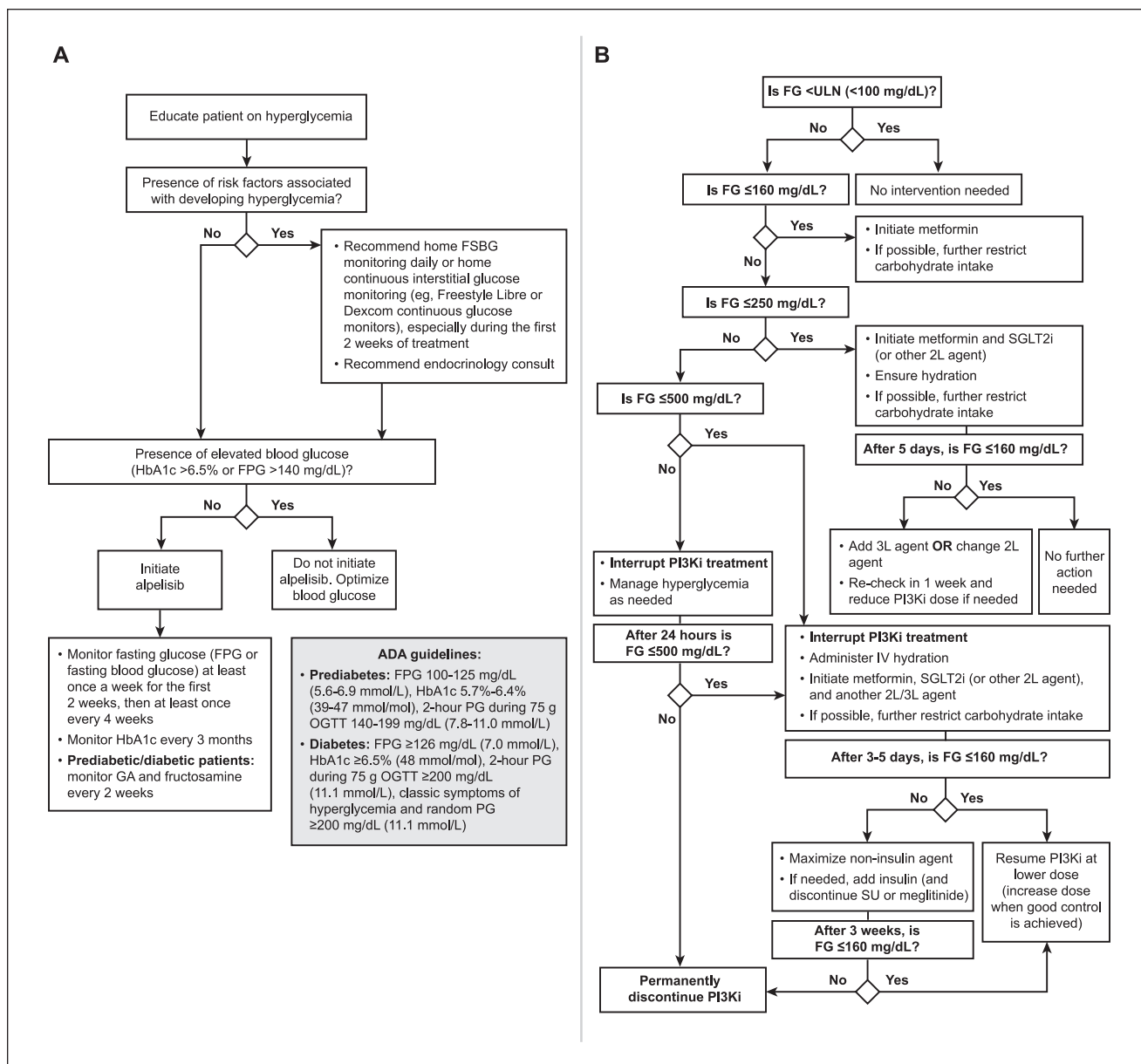


Figure 3. (A) Patient education and baseline assessment and (B) hyperglycemia management (see text and Table 2 for dosing recommendations).³⁹

Abbreviations: 1/2/3L, first/second/third line; ADA, American Diabetes Association; FG, fasting glucose; FPG, fasting plasma glucose; FSBG, fingerstick blood glucose; GA, glycated albumin; HbA1c, glycosylated hemoglobin; IV, intravenous; OGTT, oral glucose tolerance test; PG, plasma glucose; PI3Ki, phosphatidylinositol-3-kinase inhibitor; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; ULN, upper limit of normal.

then at least once every 4 weeks and monitor HbA1c every 3 months. More frequent monitoring may be recommended as clinically indicated.¹⁷ For patients who are considered high risk for developing hyperglycemia, if feasible, recommend home fingerstick blood glucose (FSBG) monitoring daily or home continuous interstitial glucose monitoring (eg, Freestyle Libre or Dexcom continuous glucose monitors) especially during the first 2 weeks of treatment. Collaborative management with an endocrinologist is

highly recommended. Glycated albumin and fructosamine (total glycated serum proteins), which are alternative markers of glycemia that reflect short-term metabolic alterations, may be monitored every 2 weeks for prediabetic or diabetic patients at baseline.⁴²

If a patient develops hyperglycemia, monitor fasting glucose at least twice a week and as clinically indicated until hyperglycemia resolves. Home glucose monitoring should be considered for any patient who develops hyperglycemia

in order to help titrate medication. The frequency of monitoring may vary for each patient depending on the severity of hyperglycemia. Depending on the patient's clinical situation, FSBG should be measured 2 to 4 times daily (eg, once before breakfast and dinner [or before each meal] and at bedtime) or via home continuous interstitial glucose monitoring. For patients already undergoing daily FSBG monitoring, advise to continue at least until hyperglycemia resolves. While on antidiabetic medication, continue fasting glucose monitoring at least daily for 8 weeks (in addition to FSBG monitoring if available), then twice a week thereafter once glucose levels are stable and as clinically indicated.

Hyperglycemia Prevention and Mitigation Strategies: Lifestyle and Dietary Interventions

All patients initiating PI3Ki treatment should be advised to follow ADA and other dietary guidelines at least a week prior to starting PI3Ki treatment. For patients without active gastrointestinal complaints or unintentional weight loss, restrict carbohydrate intake to 130 g/day, and avoiding consumption of foods with added sugar, sugar-sweetened beverages, foods with high glycemic index, and alcohol (<1 drink/day for women, <2 drinks/day for men). Encourage intake of nutrient-dense carbohydrate foods that are high in fiber and/or protein. Further carbohydrate restriction to <100 g/day may be necessary for some patients to prevent hyperglycemia. Advise consultation with a dietitian or nutritionist familiar with low-carbohydrate meal planning.

For PI3Ki-treated patients with significant hyperglycemia who are in relatively good health, more aggressive carbohydrate restriction can be considered. We advocate consideration of a ketogenic diet (<50 g carbohydrate/day) because of its beneficial effects on glucose and because it decreases insulin levels and PI3K activation. This diet has been previously demonstrated to decrease glucose levels, and it lowers insulin quickly—particularly when insulin resistance is present.^{26,43-45} In the fasting state, hepatic glycogen is the main source of glucose, and prolonged fasting or the ketogenic diet depletes glycogen stores (Figure 4).^{25,26,46} In a preclinical study, mice that fasted for 16 to 20 hours showed >90% depletion of liver glycogen. Subsequent treatment with a PI3Ki resulted in minimal increase in BG.⁴⁶ Preclinical evidence demonstrates that the ketogenic diet reduces blood glucose and insulin levels in mice, without altering body weights.⁴⁷ In addition, the ketogenic diet has been demonstrated in mice to decrease spikes in insulin and glucose after treatment with a PI3Ki better than metformin pretreatment.²⁶

In addition to its effect on glucose, some dietary restrictions have also been shown to influence tumor growth. A seminal study of tumor metabolism in 1926 demonstrated that tumors mainly metabolize glucose anaerobically (known as the Warburg effect) and are therefore sensitive to

glucose concentration.^{48,49} As a result, implementation of a ketogenic diet may inhibit tumor growth by restricting carbohydrates.⁴⁸ In a murine model of breast cancer, mice on a ketogenic diet had significantly smaller tumor volumes and had longer median survival than those on standard diet. Mice on a ketogenic diet also had reduced lung metastasis.⁴⁷ The ketogenic diet also improved responses to PI3Ki in various preclinical models of cancer, including *PIK3CA*-mutated breast cancer.²⁶

A pilot study was previously done to evaluate the feasibility and safety of a carbohydrate-restrictive diet to inhibit insulin secretion in patients with advanced, incurable, glucose-dependent cancers. The study hypothesized that inhibiting insulin secretion restricts tumor growth. Patients with prior rapid disease progression who achieved stable disease or partial remission exhibited a 3-fold increase in dietary ketosis compared with patients who continued to have a progressive disease. Ketosis was found to be inversely associated with serum insulin. Calorie deficit and weight loss were not found to be correlated with stable disease or partial remission.⁵⁰

However, there is also some preclinical evidence that shows increased tumor growth with the ketogenic diet in certain tumor types such as in melanoma (BRAF V600-expressing) and tuberous sclerosis.^{51,52} Overall, there is a need for well-designed clinical trials to further evaluate the effect of the ketogenic diet on outcomes in cancer patients; further studies, including patients treated with a PI3Ki, are ongoing (clinicaltrials.gov identifiers NCT03285152, NCT05090358, NCT04231734, NCT04691960, NCT04750941).⁵³

When starting patients on a ketogenic diet, consider the use of a point-of-care (POC) β -hydroxybutyrate (BHB) capillary meter to monitor for ketoacidosis (given case reports of this complication in some patients following a ketogenic diet)^{54,55} (Table 1). Ketoacidosis results in dehydration, high anion gap metabolic acidosis and a hyperosmolar state, which should be monitored.^{56,57} If POC BHB capillary meters are unavailable, determining the presence of ketones in serum and urine using nitroprusside test may be considered. However, this test is semiquantitative and may underestimate ketoacidosis severity as it cannot detect BHB, the main metabolic product in ketoacidosis. The preferred method for the diagnosis of ketoacidosis is still the direct measurement of serum BHB.⁵⁷

Patients should be encouraged to engage in moderate to vigorous aerobic physical activity for ≥ 150 minute, divided into ≥ 3 days/week. Muscle strengthening exercises are recommended to younger patients whereas flexibility and balance training may be recommended to adults greater than 65 years old.³⁹ Exercise has been studied in patients with advanced cancer and is feasible in some patients. It enhances glucose transfer into skeletal muscle through either an insulin-dependent or insulin-independent mechanism.^{59,60} Although PI3Kis block the insulin-dependent mechanism of

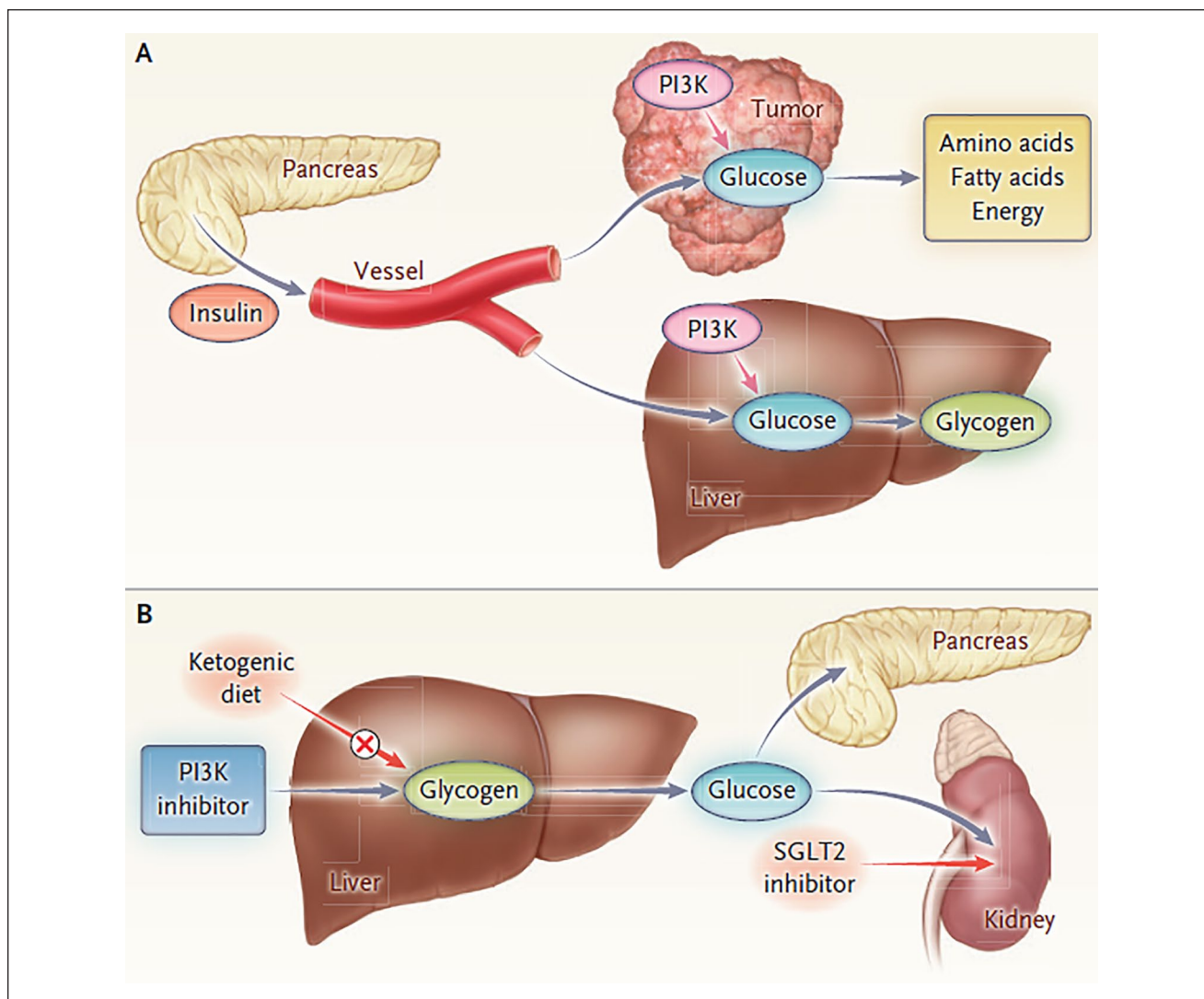


Figure 4. (A) Role of PI3K pathway in glucose metabolism in the liver and in tumors and (B) effect of the ketogenic diet and SGLT2 inhibitors on glucose metabolism in the presence of a PI3K inhibitor.²⁵

Source: From Goncalves et al,²⁵ Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Abbreviations: PI3K, phosphatidylinositol-3-kinase; SGLT2, sodium-glucose co-transporter 2.

glucose transport, they do not inhibit contraction-induced glucose transport.⁶⁰ Exercise has also been shown to enhance insulin sensitivity and increase insulin-stimulated glucose uptake, even in insulin-resistant conditions.⁵⁹ Exercise may also help promote weight loss, which is recommended for overweight or obese patients with prediabetes or diabetes.

Pharmacologic Management of PI3Ki-Associated Hyperglycemia

For management of hyperglycemia, multiple oral agents will often be required and, if needed, can be combined with insulin. When choosing an antihyperglycemic agent, consider possible side effects and onset of action (Table 2),^{39,61,62} as

well as any adverse effects the patient may be experiencing with alpelisib and fulvestrant treatment.

Metformin as First-Line Agent

Metformin acts to suppress hepatic gluconeogenesis, which is up-regulated in patients with diabetes.^{72,73} It does not lead to increased insulin synthesis, but rather improves insulin sensitivity in peripheral tissues (as shown in the animation [Supplemental File 1]).^{73,74} In skeletal muscle, metformin increases IR tyrosine kinase activity and GLUT4 transporters, leading to improved glucose uptake.⁷⁵ In adipose tissue, metformin inhibits lipolysis and promotes esterification of free fatty acids, improving insulin

Table 1. Monitoring for Ketoacidosis Using POC BHB Capillary Meter.

For Patients on a Ketogenic Diet	
BHB, mM ⁵⁸	Recommendations
>3.0	<ul style="list-style-type: none"> • Assess for signs and symptoms of dehydration or acute illness • Alert dietitian and review daily carbohydrate content with the patient • Encourage additional 3 L of oral hydration daily and continue to monitor daily POC BHB
>3.5	<ul style="list-style-type: none"> • Assess for signs and symptoms of dehydration or acute illness • Alert dietitian and review daily carbohydrate content with the patient • If concerning signs and symptoms present, obtain basic metabolic panel to assess for presence of gap metabolic acidosis <ul style="list-style-type: none"> ○ If $\text{HCO}_3^- < 18 \text{ mEq/L}$ with anion gap > 16, hold alpelisib, and refer to acute care medical facility ○ If $\text{HCO}_3^- > 18 \text{ mEq/L}$, encourage additional 3 L of oral hydration daily, reduce carbohydrate restriction by 10 g daily, and continue daily POC BHB monitoring
For Patients Receiving an SGLT2 Inhibitor	
BHB, mM ⁵⁸	Recommendations
>1.5	<ul style="list-style-type: none"> • Assess for signs and symptoms of dehydration or acute illness • If concerning signs and symptoms present, obtain basic metabolic panel to assess for presence of gap metabolic acidosis <ul style="list-style-type: none"> ○ If $\text{HCO}_3^- < 18 \text{ mEq/L}$ with anion gap > 16, hold canagliflozin and alpelisib. Encourage consumption of 3 L of oral hydration and refer to acute care medical facility ○ If $\text{HCO}_3^- > 18 \text{ mEq/L}$, encourage additional 3 L of oral hydration daily and continue daily POC BHB monitoring
>3.0	<ul style="list-style-type: none"> • Hold SGLT2 inhibitor • Refer to acute care medical facility to rule out ketoacidosis

Abbreviations: BHB, β -hydroxybutyrate; POC, point-of-care; SGLT2, sodium-glucose co-transporter 2.

sensitivity.⁷⁶ It is typically low-cost, widely available, does not cause hypoglycemia, and physicians, including oncologists, are familiar with its use.^{39,74} However, metformin may take weeks to work. In addition, in a study of 6 high-risk patients who were treated with alpelisib and subsequently developed hyperglycemia, metformin monotherapy was found to be insufficient in achieving glycemic control.⁷⁷ It is contraindicated in patients with severe renal dysfunction (estimated glomerular filtration rate [eGFR] $< 30 \text{ mL/min/1.73 m}^2$). Potential side effects include diarrhea and nausea, which are also common adverse events associated with alpelisib therapy (any-grade diarrhea = 58% and any-grade nausea = 45% in the SOLAR-1 trial).^{18,39,61} However, in patients receiving alpelisib in SOLAR-1, similar incidence of diarrhea was observed in patients who did and did not receive metformin (49% vs 50%).³⁸ Treatment with metformin can also potentially lead to Vitamin B12 deficiency (Table 2).^{39,61,62}

Second-Line Agents

Sodium-glucose co-transporter 2 inhibitors (SGLT2is). Sodium-glucose co-transporter 2 inhibitors decrease renal reabsorption of glucose (as shown in the animation [Supplemental File 1]),⁶¹ and have a quick onset of action. In a preclinical study, mice treated with an SGLT2i in addition to a PI3Ki had decreased hyperglycemia and reduced insulin that was

released in response to PI3K inhibition.²⁶ In SOLAR-1, 6 patients who had baseline risk factors for the development of hyperglycemia were treated with an SGLT2i. None of these patients discontinued treatment due to hyperglycemia, and the median duration of exposure to alpelisib was longer in these patients (range, 9.5–46.5 months) than the median observed in the overall population (5.5 months).⁷⁷ Check a patient's renal status prior to initiating SGLT2is; although they have recently been shown to protect against declines in renal function, the glycemic-lowering efficacy of SGLT2is decreases in patients with renal dysfunction, and they are contraindicated with GFR $< 30 \text{ mL/min}$. Due to their mechanism of action (loss of glucose in the urine), these agents often cause substantial weight loss—this should be monitored in cancer patients struggling to maintain body weight. There is a small but significant associated increased risk for genitourinary infections (most commonly yeast infections in women; up to 14.5% with canagliflozin)⁷⁸ and, case reports of Fournier's gangrene have led to a U.S. Food & Drug Administration warning.⁷⁹ Volume depletion and hypotension may occur in patients with poor hydration or in patients taking diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers.³⁹ Furthermore, providers should monitor the anion gap [$\text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$], blood/urinary ketones, and/or serum bicarbonate at each visit while the patient is on treatment, as the combination of an SGLT2i and a PI3Ki resulted in euglycemic ketoacidosis in a case

Table 2. Recommended Antihyperglycemic Agents.

Recommended Drug and Dosage ³⁹	Other Treatment Considerations ^{39,61}
Agents That Do Not Affect the PI3K Pathway⁶²	
Biguanide <ul style="list-style-type: none"> Metformin 500-2000 mg AC QD 	<ul style="list-style-type: none"> Onset of action: glucose control observed in 1-2 weeks, maximal effect in 2-3 months⁶³ Risk of modest weight loss GI AEs are common (diarrhea, nausea) Potential for Vitamin B12 deficiency
SGLT2 inhibitors <ul style="list-style-type: none"> Ertugliflozin 15 mg PO OD Dapagliflozin 10 mg PO OD Empagliflozin 25 mg PO OD Canagliflozin 300 mg PO OD 	<ul style="list-style-type: none"> Onset of action: 2 hours, improved variation in blood glucose by 1 week⁶⁴ Risk of weight loss Other associated AEs: DKA (assess for ketoacidosis at each visit), genitourinary infections, hypotension, volume depletion <ul style="list-style-type: none"> For DKA, monitor the anion gap [$\text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$], blood/urinary ketones, and/or serum bicarbonate at each visit Hold SGLT2 inhibitor if with poor hydration and/or concurrent illness Hold SGLT2 inhibitor 5 days prior to surgery or colonoscopy
Thiazolidinediones <ul style="list-style-type: none"> Pioglitazone 45 mg PO OD Rosiglitazone 4 mg PO OD to BID 	<ul style="list-style-type: none"> Onset of action: within 2 weeks, maximal effect in 3 months⁶⁵ Risk of weight gain Use with caution in patients with or at risk for congestive heart failure Associated with risk of fluid retention and bone fractures, bladder cancer
α-Glucosidase inhibitors <ul style="list-style-type: none"> Acarbose 100 mg PO OD to TID 	<ul style="list-style-type: none"> Onset of action: 1 hour⁶⁶ GI AEs are common
Agents That Affect the PI3K Pathway⁶²	
GLP-1 receptor agonists <ul style="list-style-type: none"> Exenatide (extended release) 2 mg powder for suspension or pen SC once a week Exenatide 10 μg pen SC OD to BID Dulaglutide 1.5/0.5 mL pen SC once a week Semaglutide 1 mg pen SC once a week Liraglutide 18 mg/3 mL pen 1.8 mg SC OD 	<ul style="list-style-type: none"> Risk of weight loss Onset of action: glycemic improvement after 2-4 weeks with long-acting agents; greater reduction in postprandial rather than fasting glucose observed for short-acting agents⁶⁷ GI AEs are common (nausea, vomiting, diarrhea) Gradual dose up-titration required to minimize GI AEs Injection-site reactions Do not initiate in patients with history of acute pancreatitis Onset of action: unknown, but peak plasma levels achieved in 1-4 hours⁶⁸ Typically well tolerated Do not initiate in patients with history of acute pancreatitis
DPP-4 inhibitors <ul style="list-style-type: none"> Alogliptin 25 mg PO OD Saxagliptin 5 mg PO OD Linagliptin 5 mg PO OD Sitagliptin 100 mg PO OD 	
Sulfonylureas <ul style="list-style-type: none"> Glimepiride 1-8 mg PO OD Glipizide 5-40 mg PO (OD or split dose BID) Glipizide XR 5-20 mg PO Glyburide 2.5-20 mg OD Glyburide micronized 3-12 mg OD 	<ul style="list-style-type: none"> Onset of action: 30 minutes, peak response within 2-3 hours⁶⁹ Potential AEs include hypoglycemia, weight gain
Meglitinides <ul style="list-style-type: none"> Nateglinide 60-120 mg AC Repaglinide 0.5-4 mg AC 	<ul style="list-style-type: none"> Onset of action: 15-30 minutes⁷⁰ Potential AEs include hypoglycemia, weight gain
Basal insulin <ul style="list-style-type: none"> Insulin glargine 0.2 units/kg/day SC Insulin detemir 0.2 units/kg/day SC 	<ul style="list-style-type: none"> Onset of action: 2 hours⁷¹ Potential AEs include hypoglycemia and weight gain
Increase dose to achieve goal FSBG < 160 mg/dL	
Rapid-acting insulin <ul style="list-style-type: none"> Insulin aspart Insulin lispro Insulin glulisine 	<ul style="list-style-type: none"> Onset of action: 5-15 minutes, peak effect at 45-75 minutes⁷¹ Potential AEs include hypoglycemia and weight gain

Abbreviations: AC, before meals; AE, adverse event; BID, twice daily; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; FSBG, fingerstick blood glucose; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein; OD, once daily; SC, subcutaneous; SGLT2, sodium-glucose co-transporter 2; TID, thrice daily.

Table 3. Glycemic Treatment Goals.³⁹

	Treatment goal		
	HbA1c	Preprandial Glucose	Bedtime Glucose
Patients with good prognosis	<7.5% (58 mmol/mol)	90-130 mg/dL (5.0-7.2 mmol/L)	90-150 mg/dL (5.0-8.3 mmol/L)
Patients with limited life expectancy	<8.5% (69 mmol/mol)	100-180 mg/dL (5.6-10 mmol/L)	110-200 mg/dL (6.1-11.1 mmol/L)

Abbreviation: HbA1c, glycosylated hemoglobin.

report; ketoacidosis is not common with alpelisib, observed only in 2 (0.7%) patients during SOLAR-1 and postmarketing experience.^{17,62} A POC BHB capillary meter may also be used to monitor ketoacidosis (Table 1). Patients should be aware of possible symptoms of ketoacidosis, which include nausea, vomiting, and fatigue.^{62,80} Physicians should have a high index of suspicion for ketoacidosis in these patients, as (1) diagnosis may be missed because these might overlap with alpelisib-associated AEs and (2) the glucose level may be normal (euglycemic diabetic ketoacidosis).¹⁸ Ketoacidosis may also be triggered by physiologic stress such as illness, infection, trauma, or surgical and medical procedures such as colonoscopy.³⁹

Thiazolidinediones. Thiazolidinediones inhibit hepatic gluconeogenesis, and maximal effect may take approximately 6 weeks.²² Use with caution in patients with renal dysfunction due to increased risk of fluid retention, often manifested by worsening peripheral edema. These agents are also associated with increased risk of congestive heart failure, fractures, and bladder cancer.³⁹

α -Glucosidase inhibitors. α -Glucosidase inhibitors impair intestinal absorption of carbohydrates.^{22,61} They have a quick onset, but weak efficacy. Their use is commonly associated with gastrointestinal side effects.⁶¹

Glucagon-like peptide 1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 RA and DPP-4 inhibitors stimulate the release of incretins from the gut, subsequently leading to the release of insulin from the pancreas, and also affect the PI3K pathway.^{22,62} These agents have a quick onset of action. Glucagon-like peptide 1 receptor agonists are associated with risk of gastrointestinal side effects (nausea and vomiting) and increased satiety often leading to substantial weight loss; they are not to be used in patients with a history of pancreatitis.³⁹ Dipeptidyl peptidase-4 inhibitors are extremely well-tolerated drugs but have weaker efficacy than GLP-1 RA; they are also not to be given to patients with history of acute pancreatitis, and some of these agents have been associated with a small increase (3.5%-3.9%) in risk for congestive heart failure, particularly in patients with pre-existing heart or kidney disease.^{39,81}

Third-Line Agents

Meglitinides and sulfonylureas. Meglitinides and sulfonylureas are insulin secretagogues that stimulate pancreatic insulin secretion independent of glucose levels.^{22,39,61} These agents have a quick onset of action and good potency. Both meglitinides and sulfonylureas are associated with hypoglycemia risk and weight gain.⁶¹ However, sulfonylureas are also associated with an increased risk of cardiovascular mortality—the relevance of this finding to advanced cancer patients is uncertain. Certain sulfonylureas such as glyburide should not be initiated in patients with renal impairment.³⁹

Insulin as Last Line of Therapy

Certain chemotherapeutic agents, corticosteroids, and mTOR inhibitors have been associated with the development of hyperglycemia by directly decreasing the production and release of insulin or causing insulin resistance. In most cases, administering insulin constitutes the main strategy for rapidly establishing glycemic control.⁸² In PI3Ki-associated hyperglycemia, insulin should only be recommended as a last-line antihyperglycemic agent. This is because insulin has been shown to partially reactivate the PI3K pathway, despite treatment with a PI3Ki, in various tumor cell lines, leading to cellular proliferation.²⁶ Insulin is associated with an increased risk of hypoglycemia and weight gain.⁶¹

Management Recommendations

Management differs based on the severity of hyperglycemia. A detailed management algorithm is provided in Figure 3B.³⁹ Oncologists should consider consultation with an endocrinologist for hyperglycemia co-management. Glycemic treatment goals (Table 3) should be individualized based on age, life expectancy, and presence of other comorbidities.³⁹ Preprandial and bedtime glucose levels should be 90 to 130 mg/dL (5.0-7.2 mmol/L) and 90 to 150 mg/dL (5.0-8.3 mmol/L), respectively, for patients with good prognoses; for those with limited life expectancies, these levels should be 100 to 180 mg/dL (5.6-10 mmol/L) and 110 to 200 mg/dL (6.1-11.1 mmol/L), respectively. However,

fluctuation in these levels above and below these targets are common and of no concern. Metformin is the recommended first-line antihyperglycemic agent, due to its wide availability and safety profile. For any degree of fasting hyperglycemia (fasting glucose ≥ 100 mg/dL), regardless of baseline glycemic status, start metformin at 500 mg premeal once daily, increasing dose by 500 mg/day weekly up to a maximum dose of 2000 mg/day. For grade 2 hyperglycemia (fasting glucose > 160 -250 mg/dL or > 8.9 -13.9 mmol/L or random BG/FSBG > 200 mg/dL), addition of a second-line antihyperglycemic agent (eg, SGLT2i) is recommended. If after 5 days, fasting glucoses remain > 160 mg/dL (persistent grade 2 hyperglycemia), addition of a tertiary oral antihyperglycemic agent (eg, meglitinides, sulfonylureas) is recommended. Addition of a tertiary oral antihyperglycemic agent is also recommended for grade 3 hyperglycemia (> 250 -500 mg/dL or > 13.9 -27.8 mmol/L or random BG/FSBG > 300 mg/dL). Alternatively, for persistent grade 2 or for grade 3 hyperglycemia, consider changing second-line antihyperglycemic agent. Insulin is generally not recommended due to its effect on the PI3K pathway, but it may be recommended for severe hyperglycemia (persistent grade ≥ 3). Insulin should be administered subcutaneously either as once-daily basal insulin (starting at 0.2 units/kg/day) or prandial rapid-acting insulin sliding scale.

In patients with persistent grade ≥ 2 hyperglycemia despite appropriate treatment with antihyperglycemic medications for 1 week, reduce alpelisib dose to 250 mg/day. For grade ≥ 3 hyperglycemia, alpelisib dose interruption and subsequent dose reduction or permanent discontinuation (if persistent grade ≥ 2 despite adequate antihyperglycemic therapy) is recommended to improve glycemic control. Discontinuation of alpelisib therapy may be necessary in patients who do not respond to various antihyperglycemic medications and/or who are at high risk of developing hyperglycemia-related complications. Continue glucose monitoring when alpelisib is discontinued; consider discontinuing initiated antihyperglycemic medications to avoid hypoglycemia.

Concluding Remarks

Hyperglycemia arising from cancer treatment is not unique to PI3Kis. However, the management of PI3Ki-associated hyperglycemia requires additional considerations because, theoretically, treatment with insulin or insulin-secretagogues (sulfonylureas, etc) may curb antitumor activity. Selection of appropriate antihyperglycemic medication remains at the discretion of the managing physician, but it is important to consider the effect of the drug on endogenous insulin or the PI3K pathway, and subsequently on the tumor. Hyperglycemia occurs within the first few weeks of alpelisib treatment, and with adequate management, rarely leads to treatment discontinuation.^{17,18,38} Importantly, acute

hyperglycemia does not cause acute toxicity (a glucose level of 500 mg/dL is not acutely equivalent to a lab abnormality such as severe hyperkalemia, which can cause arrhythmia), but needs to be detected and acted upon. Early identification of high-risk patients and close monitoring while on treatment are critical to reducing onset and severity of hyperglycemia.

In most patients with diabetes, the goal of treatment is to prevent long-term complications of hyperglycemia, restore quality of life, and avoid hypoglycemia and weight gain.⁶¹ In contrast to the goal in patients with diabetes, the goal of treatment of transient hyperglycemia in patients with cancer shifts from preventing long-term complications to preventing acute and subacute complications such as catabolic weight loss and dehydration.⁸³ Although seemingly rare, diabetic ketoacidosis is a life-threatening complication that has been reported in the context of PI3Ki treatment.^{39,84,85} The aim of managing these complications is to prevent the patient from discontinuing anticancer therapy, thereby maximizing the duration of treatment while weighing patient needs and quality of life.⁸³

Since most randomized clinical trials do not fully represent the patient population and management of PI3Ki-associated hyperglycemia is evolving, there are ongoing trials focused on investigating the effect of antihyperglycemic management on PI3Ki therapy. The Targeting Insulin Feedback to Enhance Alpelisib (TIFA) trial is examining the efficacy and safety of 3 different interventions that target insulin feedback in patients treated with alpelisib (clinicaltrials.gov identifier NCT05090358). In TIFA, patients are randomly assigned to receive alpelisib and fulvestrant with either a ketogenic diet (< 50 g/day), a low-carbohydrate diet (< 100 g/day), or an SGLT2i. The ongoing Phase II METALLICA study (clinicaltrials.gov identifier NCT04300790) is assessing the rate of grade ≥ 3 hyperglycemia and tumor response in patients with and without fasting glycemia who receive alpelisib, fulvestrant, and metformin.

Acknowledgments

Medical editorial assistance was provided by Audrey So, MD, from Healthcare Consultancy Group, LLC, and was funded by Novartis Pharmaceuticals Corporation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Competing interests: M.D. Goncalves: Paid to attend a Novartis-sponsored advisory board, Grants from Pfizer, Personal fees from Petra Pharma; Patent (pending) for Combination Therapy for PI3K-associated Disease or Disorder, and patent for The Identification of Therapeutic Interventions to Improve Response to PI3K Inhibitors for Cancer Treatment pending; Co-founder of and owns stock in Faeth Therapeutics, whose

mission is to produce meal plans for cancer patients. A. Farooki: Personal fees received from Novartis to attend a Novartis-sponsored advisory board and to be a member of a Novartis steering committee.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Novartis Pharmaceuticals Corporation.

ORCID iD

Marcus D. Goncalves  <https://orcid.org/0000-0002-0784-9248>

Supplemental Material

Supplemental file 1 for this article is available online.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

- Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: mechanisms and advances in clinical trials. *Mol Cancer*. 2019;18:26. doi:10.1186/s12943-019-0954-x
- Paplomata E, O'Regan R. The PI3K/AKT/mTOR pathway in breast cancer: targets, trials and biomarkers. *Ther Adv Med Oncol*. 2014;6:154-166.
- Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat Rev Cancer*. 2015;15:7-24. doi:10.1038/nrc3860
- Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. *Cell*. 2017;170:605-635. doi:10.1016/j.cell.2017.07.029
- Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. *Nat Rev Cancer*. 2019;20:74-88. doi:10.1038/s41568-41019-40216-41567
- Kim B, Feldman EL. Insulin resistance in the nervous system. *Trends Endocrinol Metab*. 2012;23:133-141.
- Vasan N, Toska E, Scaltriti M. Overview of the relevance of PI3K pathway in HR-positive breast cancer. *Ann Oncol*. 2019;30:x3-x11. doi:10.1093/annonc/mdz281
- Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet*. 2006;7:606-619. doi:10.1038/nrg1879
- Qin H, Liu L, Sun S, et al. The impact of PI3K inhibitors on breast cancer cell and its tumor microenvironment. *PeerJ*. 2018;6:e5092. doi:10.7717/peerj.5092
- Razavi P, Chang MT, Xu G, et al. The genomic landscape of endocrine-resistant advanced breast cancers. *Cancer Cell*. 2018;34:427-438. doi:10.1016/j.ccell.2018.08.008
- The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490:61-70.
- Di Leo A, Johnston S, Lee KS, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19:87-100.
- Moynahan ME, Chen D, He W, et al. Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR(+), HER2(-) advanced breast cancer: results from BOLERO-2. *Br J Cancer*. 2017;116:726-730.
- Garrido-Castro AC, Lin NU, Polyak K. Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment. *Cancer Discov*. 2019;9:176-198.
- Mollon LE, Anderson EJ, Dean JL, et al. A systematic literature review of the prognostic and predictive value of PIK3CA mutations in HR(+)/HER2(-) metastatic breast cancer. *Clin Breast Cancer*. 2020;20:e232-e243.
- Spangle JM, Von T, Pavlick DC, Khotimsky A, Zhao JJ, Roberts TM. PIK3CA C-terminal frameshift mutations are novel oncogenic events that sensitize tumors to PI3K- α inhibition. *Proc Natl Acad Sci U S A*. 2020;117:24427-24433. doi:10.1073/pnas.2000060117
- Piqray. *Prescribing Information*. Novartis Pharmaceuticals Corporation; 2020.
- André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380:1929-1940. doi:10.1056/NEJMoa1813904
- André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. *Ann Oncol*. 2021;32:208-217. doi:10.1016/j.annonc.2020.11.011
- Aronoff SL, Berkowitz K, Shreiner B, Want L. Glucose metabolism and regulation: beyond insulin and glucagon. *Diabetes Spectr*. 2004;17:183-190. doi:10.2337/diaspect.17.3.183
- Drullinsky PR, Hurvitz SA. Mechanistic basis for PI3K inhibitor antitumor activity and adverse reactions in advanced breast cancer. *Breast Cancer Res Treat*. 2020;181:233-248. doi:10.1007/s10549-020-05618-1
- Goldman JW, Mendenhall MA, Rettinger SR. Hyperglycemia associated with targeted oncologic treatment: mechanisms and management. *Oncologist*. 2016;21:1326-1336. doi:10.1634/theoncologist.2015-0519
- Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. *Int J Biol Sci*. 2018;14:1483-1496. doi:10.7150/ijbs.27173
- Nunnery SE, Mayer IA. Management of toxicity to isoform α -specific PI3K inhibitors. *Ann Oncol*. 2019;30:x21-x26. doi:10.1093/annonc/mdz440
- Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-kinase, growth disorders, and cancer. *N Engl J Med*. 2018;379:2052-2062. doi:10.1056/NEJMra1704560
- Hopkins BD, Pauli C, Du X, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. *Nature*. 2018;560:499-503. doi:10.1038/s41586-41018-40343-41584
- Gallagher EJ, Fierz Y, Vijayakumar A, Haddad N, Yakar S, LeRoith D. Inhibiting PI3K reduces mammary tumor growth and induces hyperglycemia in a mouse model of insulin resistance and hyperinsulinemia. *Oncogene*. 2011;31:3213-3222. doi:10.1038/nc.2011.3495
- du Rusquec P, Blonz C, Frenel JS, Campone M. Targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive

- HER2 negative advanced breast cancer. *Ther Adv Med Oncol*. 2020;12:1758835920940939. doi:10.1177/1758835920940939
29. Juric D, de Bono JS, LoRusso PM, et al. A first-in-human, phase I, dose-escalation study of TAK-117, a selective PI3K α isoform inhibitor, in patients with advanced solid malignancies. *Clin Cancer Res*. 2017;23:5015-5023. doi:10.1158/1078-0432.CCR-16-2888
30. Janku F. Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: from laboratory to patients. *Cancer Treat Rev*. 2017;59:93-101. doi:10.1016/j.ctrv.2017.07.005
31. Vuylsteke P, Huizing M, Petrakova K, et al. Pictilisib PI3Kinase inhibitor (a phosphatidylinositol 3-kinase [PI3K] inhibitor) plus paclitaxel for the treatment of hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study. *Ann Oncol*. 2016;27:2059-2066.
32. Dent S, Cortés J, Im YH, et al. Phase III randomized study of taselisib or placebo with fulvestrant in estrogen receptor-positive, PIK3CA-mutant, HER2-negative, advanced breast cancer: the SANDPIPER trial. *Ann Oncol*. 2021;32:197-207.
33. Moore AM, Einhorn LH, Estes D, et al. Gefitinib in patients with chemo-sensitive and chemo-refractory relapsed small cell cancers: a Hoosier Oncology Group phase II trial. *Lung Cancer*. 2006;52:93-97. doi:10.1016/j.lungcan.2005.10.12.1002
34. Blow T, Hyde PN, Falcone JN, et al. Treating alpelisib-induced hyperglycemia with very low carbohydrate diets and sodium-glucose co-transporter 2 inhibitors: a case series. *Integr Cancer Ther*. 2021;20:15347354211032283.
35. Ando Y, Iwasa S, Takahashi S, et al. Phase I study of alpelisib (BYL719), an α -specific PI3K inhibitor, in Japanese patients with advanced solid tumors. *Cancer Sci*. 2019;110:1021-1031.
36. Sarker D, Ang JE, Baird R, et al. First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. *Clin Cancer Res*. 2015;21:77-86.
37. Patnaik A, Appleman LJ, Tolcher AW, et al. First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Ann Oncol*. 2016;27:1928-1940.
38. Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. *Ann Oncol*. 2020;31:1001-1010. doi:10.1016/j.annonc.2020.05.001
39. American Diabetes Association. Standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43:S1-S212.
40. Centers for Disease Control and Prevention. *National Diabetes Statistics Report*. Centers for Disease Control and Prevention, US Department of Health and Human Services. 2020. Accessed April 8, 2021. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>
41. Pears KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol*. 2011;29:40-46. doi:10.1200/JCO.2009.27.3011
42. Ribeiro RT, Macedo MP, Raposo JF. HbA1c, fructosamine, and glycated albumin in the detection of dysglycaemic conditions. *Curr Diabetes Rev*. 2016;12:14-19. doi:10.2174/1573399811666150701143112
43. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med*. 2008;359:229-241. doi:10.1056/NEJMoa0708681
44. Hall KD, Chen KY, Guo J, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr*. 2016;104:324-333. doi:10.3945/ajcn.116.133561
45. Nuttall FQ, Almokayyad RM, Gannon MC. Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes. *Metabolism*. 2015;64:253-262. doi:10.1016/j.metabol.2014.10.004
46. Crouthamel MC, Kahana JA, Korenchuk S, et al. Mechanism and management of AKT inhibitor-induced hyperglycemia. *Clin Cancer Res*. 2009;15:217-225. doi:10.1158/1078-0432.CCR-08-1253
47. Zou Y, Fineberg S, Pearlman A, Feinman RD, Fine EJ. The effect of a ketogenic diet and synergy with rapamycin in a mouse model of breast cancer. *PLoS One*. 2020;15:e0233662. doi:10.0231371/journal.pone.0233662
48. Fine EJ, Feinman RD. Insulin, carbohydrate restriction, metabolic syndrome and cancer. *Expert Rev Endocrinol Metab*. 2015;10:15-24. doi:10.1586/17446651.2014.960392
49. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. *J Gen Physiol*. 1927;8:519-530. doi:10.1085/jgp.8.6.519
50. Fine EJ, Segal-Isaacson CJ, Feinman RD, et al. Targeting insulin inhibition as a metabolic therapy in advanced cancer: a pilot safety and feasibility dietary trial in 10 patients. *Nutrition*. 2012;28:1028-1035. doi:10.1016/j.nut.2012.05.001
51. Xia S, Lin R, Jin L, et al. Prevention of dietary-fat-fueled ketogenesis attenuates BRAF V600E tumor growth. *Cell Metab*. 2017;25:358-373. doi:10.1016/j.cmet.2016.12.010
52. Liškiewicz AD, Kasprowska D, Wojakowska A, et al. Long-term high fat ketogenic diet promotes renal tumor growth in a rat model of tuberous sclerosis. *Sci Rep*. 2016;6:21807. doi:10.21038/srep21807
53. Weill Cornell Medicine Goncalves Lab. Clinical studies. Last updated September 1, 2021. Accessed January 12, 2022. <https://goncalveslab.com/clinical-studies>
54. von Geijer L, Ekelund M. Ketoacidosis associated with low-carbohydrate diet in a non-diabetic lactating woman: a case report. *J Med Case Rep*. 2015;9:224.
55. Marzban S, Arbee M, Vorajee N, Richards GA. Non-diabetic ketoacidosis associated with a low carbohydrate, high fat diet in a postpartum lactating female. *Oxf Med Case Reports*. 2020;2020:omz026.
56. Westerberg DP. Diabetic ketoacidosis: evaluation and treatment. *Am Fam Physician*. 2013;87:337-346.
57. Fayman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Med Clin North Am*. 2017;101:587-606.
58. Brooke J, Stiell M, Ojo O. Evaluation of the accuracy of capillary hydroxybutyrate measurement compared with other measurements in the diagnosis of diabetic ketoacidosis: a systematic review. *Int J Environ Res Public Health*. 2016;13:837.

59. Cartee GD. Mechanisms for greater insulin-stimulated glucose uptake in normal and insulin-resistant skeletal muscle after acute exercise. *Am J Physiol Endocrinol Metab.* 2015;309:E949-E959. doi:10.1152/ajpendo.00416.2015
60. Brozinick JT, Birnbaum MJ. Insulin, but not contraction, activates Akt/PKB in isolated rat skeletal muscle. *J Biol Chem.* 1998;273:14679-14682. doi:10.1074/jbc.273.24.14679
61. Pfeiffer AF, Klein HH. The treatment of type 2 diabetes. *Dtsch Arztebl Int.* 2014;111:69-82. doi:10.3238/arztebl.2014.0069
62. Bowman C, Abramson V, Wellons M. Ketoacidosis with canagliflozin prescribed for phosphoinositide 3-kinase inhibitor-induced hyperglycemia: a case report. *J Investig Med High Impact Case Rep.* 2017;5:2324709617725351. doi:10.1177/2324709617725351
63. Mayo Clinic. Metformin (oral route). Last updated December 1, 2021. Accessed January 12, 2022. <https://www.mayoclinic.org/drugs-supplements/metformin-oral-route/proper-use/drg-20067074?p=1>
64. Torimoto K, Okada Y, Koikawa K, Tanaka Y. Early effects of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes: study based on continuous glucose monitoring. *Diabetol Metab Syndr.* 2017;9:60.
65. Rendell M. Advances in diabetes for the millennium: drug therapy of type 2 diabetes. *MedGenMed.* 2004;6:9.
66. Hanefeld M. Cardiovascular benefits and safety profile of acarbose therapy in prediabetes and established type 2 diabetes. *Cardiovasc Diabetol.* 2007;6:20.
67. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectr.* 2017;30:202-210.
68. Pathak R, Bridgeman MB. Dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of diabetes. *P T.* 2010;35:509-513.
69. Klein-Schwartz W, Stassinis GL, Isbister GK. Treatment of sulfonylurea and insulin overdose. *Br J Clin Pharmacol.* 2016;81:496-504.
70. Luna B, Feinglos MN. Oral agents in the management of type 2 diabetes mellitus. *Am Fam Physician.* 2001;63:1747-1756.
71. Marín-Peñalver JJ, Martín-Timón I, Sevillano-Collantes C, Del Cañizo-Gómez FJ. Update on the treatment of type 2 diabetes mellitus. *World J Diabetes.* 2016;7:354-395.
72. Basu R, Chandramouli V, Dicke B, Landau B, Rizza R. Obesity and type 2 diabetes impair insulin-induced suppression of glycogenolysis as well as gluconeogenesis. *Diabetes.* 2005;54:1942-1948. doi:10.2337/diabetes.54.7.1942
73. Madiraju AK, Erion DM, Rahimi Y, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature.* 2014;510:542-546. doi:10.1038/nature13270
74. Yang X, Xu Z, Zhang C, Cai Z, Zhang J. Metformin, beyond an insulin sensitizer, targeting heart and pancreatic β cells. *Biochim Biophys Acta Mol Basis Dis.* 2017;1863:1984-1990. doi:10.1016/j.bbdis.2016.09.019
75. Kawanami D, Takashi Y, Tanabe M. Significance of metformin use in diabetic kidney disease. *Int J Mol Sci.* 2020;21:4239. doi:10.3390/ijms21124239
76. Yan Y, Kover K, Moore W. *New Insight Into Metformin Mechanism of Action and Clinical Application.* IntechOpen; 2020. Accessed April 8, 2021. <https://www.intechopen.com/books/metformin/new-insight-into-metformin-mechanism-of-action-and-clinical-application>.
77. Lu YS, Chiu J, Airolidi M, Sodium glucose cotransporter 2 (SGLT2) inhibitors for alpelisib-induced hyperglycemia: a report of 6 cases from SOLAR-1. Presented at: European Society for Medical Oncology Virtual Congress 2020; September 19-21, 2020. Poster 301P.
78. Unnikrishnan AG, Kalra S, Purandare V, Vasawala H. Genital infections with sodium glucose cotransporter-2 inhibitors: occurrence and management in patients with type 2 diabetes mellitus. *Indian J Endocrinol Metab.* 2018;22:837-842. doi:10.4103/ijem.IJEM_159_17
79. U.S. Food and Drug Administration. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. U.S. Food and Drug Administration; 2018. Accessed October 27, 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrences-serious-infection-genital-area-sgl2-inhibitors-diabetes>
80. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. *Diabetes Care.* 2019;42:1147-1154. doi:10.2337/dc18-2316
81. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. U.S. Food and Drug Administration; 2016. Accessed October 27, 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-adds-warnings-about-heart-failure-risk-labels-type-2-diabetes>
82. Hwangbo Y, Lee EK. Acute hyperglycemia associated with anti-cancer medication. *Endocrinol Metabol.* 2017;32:23-29. doi:10.3803/EnM.2017.32.1.23
83. Flory J, Farooki A. Diabetes management in cancer patients. *Oncology.* 2016;30:565-570.
84. Carrillo M, Rodriguez RM, Walsh CL, Mcgarvey M. Alpelisib-induced diabetic ketoacidosis: a case report and review of literature. *AACE Clin Case Rep.* 2021;7:127-131.
85. Farah SJ, Masri N, Ghanem H, Azar M. Diabetic ketoacidosis associated with alpelisib treatment of metastatic breast cancer. *AACE Clin Case Rep.* 2020;6:e349-e351.