PI3Kα in cardioprotection: Cytoskeleton, late Na⁺ current, and mechanism of arrhythmias

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ABSTRACT

PI 3-kinase α (PI3Kα) is a lipid kinase that converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). PI3Kα regulates a variety of cellular processes such as nutrient sensing, cell cycle, migration, and others. Heightened activity of PI3Kα in many types of cancer made it a prime oncology drug target, but also raises concerns of possible adverse effects on the heart. Indeed, recent advances in preclinical models demonstrate an important role of PI3Kα in the control of cytoskeletal integrity, Na⁺ channel activity, cardioprotection, and prevention of arrhythmias.

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Introduction

Phosphoinositide 3-kinases (PI3Ks) phosphorylate phosphatidylinositol lipids in intracellular membranes at the 3' position of the inositol ring. Class I PI3Ks act at the plasma membrane by phosphorylating phosphatidylinositol-4,5-bisphosphate (PIP2) to produce phosphatidylinositol-3,4,5-triphosphate (PIP3). In addition to catalytic functions, class I PI3Ks also act as scaffold proteins to create regulatory complexes independent of the kinase action of PI3Ks [1–3]. Class I PI3Ks have four isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) consisting of a p110 catalytic and regulatory subunit. Based on the regulatory subunit preference, class I PI3Ks are grouped into class IA enzymes (p110β, p110γ, and p110δ), which bind to a p85 family regulatory subunit, and the class IB PI3K (p110γ), which binds to p84 or p101 regulatory subunit. PIP3 produced by these PI3Ks binds with effectors that have a PI3K-lipid-binding pleckstrin homology (PH) domain. These effector proteins, including the AKT Ser/Thr protein kinase, regulate various biological processes such as nutrient sensing, survival, cell cycle, migration, and others [3–8]. Different isoforms are activated by distinct mechanisms: PI3Kα and PI3Kδ are activated by receptor tyrosine kinase (RTK) and Ras small GTPases, PI3Kγ is activated by Gαq subunits released following G protein-coupled receptor (GPCR) activation and by Ras, and PI3Kα can be activated by RTKs, Gαq and the Cdc42 and Rac small GTPases. The catalytic subunits, p110β, p110γ, and p110δ, are encoded by the PIK3CA, PIK3CB, PIK3CG, and PIK3CD genes, respectively. Upregulation of class IA PI3K signaling is frequently found in cancer and occurs through various mechanisms, including inactivation of the PI3K antagonist phosphatase and tensin homolog (PTEN), overactivation of RTKs upstream of PI3K and gain-of-function somatic mutations in genes coding for catalytic subunits [9–11]. Among PI3K gene mutations, mutations in PIK3CA are the most frequent, with much lower frequency in PIK3CB and PIK3CD [12]. The crucial role of the PI3K pathway in cancer development and progression made this pathway a promising target for cancer treatment [13–15]. However, the development of PI3K-targeted drugs has raised a need to investigate the role of PI3K isoforms in wider physiology and pathophysiology. Recent preclinical studies have revealed that PI3Ks play a critical role in hypertrophy, electrical remodeling, cardiovascular diseases, including cytoskeletal regulation during heart failure, cardioprotection from ischemic injury, and channel...
activity regulation [6–8,16,17]. In this review, we will focus on the novel role of PI3Kα as a modulator of cytoskeletal integrity, channel activity, Ca\(^{2+}\) cycling, and the mechanisms underlying arrhythmogenicity upon PI3Kα inhibition.

**PI3K inhibitors in cancer therapy**

The involvement of various PI3K isoforms in cancer made them a prime target for cancer therapies [13–15]. The PI3Kα isoform is the main target for solid tumors, and PI3Kδ is targeted in hematological tumors, whereas PI3Kα and PI3Kγ receiving less attention (Table 1). Since PI3Kα is the functionally-dominant isoform expressed in the heart, in this review, we will focus on the cardiac effects of PI3Kα inhibition.

Clinical trials of inhibitors that block PI3Kα commonly reported hyperglycemia as the major side effect [18–30], which is unsurprising considering the critical involvement of PI3Kα in insulin signaling [31,32]. Corrected QT (QTc) prolongation was observed for alpelisib (BYL719) [18,23], but not for sarolbesib (MLN1117) [26] or tasselisib (GDC0032) [27] (Table 1). General inhibition of PI3K and/or tyrosine kinase activity had been linked to cardiotoxicity and drug-related heart failure [13,14]. Pan-PI3K inhibitors exhibit similar cardiac side effects as PI3Kα inhibition suggesting that the effects might be due to inhibition of this PI3K. So far, arrhythmogenic side effects are known for the pan-PI3K inhibitor copanlisib [15]. For copanlisib, which now has regulatory approval, prolonged QTc (ΔQT\(_{c}\) ≥ 60 ms) was found in 6.6% of patients, prompting a request by the FDA for further monitoring [15].

Tyrosine kinase inhibitors may indirectly suppress PI3Kα. Inhibition of PI3Kα has been put forward as an explanation of the arrhythmogenic effects of ibrutinib [33]. Only ibrutinib (Bruton tyrosine kinase inhibitor) has been linked to instances of atrial fibrillation, ventricular arrhythmias, and sudden cardiac death [34–36].

**Cardiac effects of PI3Kα inhibition in diabetes**

In murine models of diabetes, reduced sensitivity to insulin is associated with diminished PI3Kα activity which has been linked to both hyperglycemia and arrhythmias [37,38]. Prolongation of the action potential and QTc interval was observed in different animal models of diabetes [39,40]. The reduced PI3Kα activity causes the dis-inhibition (activation) of late Na\(^{+}\) current leading to prolongation of the action potential [37,38]. Conversely, upregulation of PI3Kα activity in the heart has been shown to protect from ventricular arrhythmias and sudden death associated with pathological hypertrophy and heart failure [17,41].

**PI3Kα in cardioprotection**

PI3Kα signaling has recently emerged as an important cardioproteective pathway. In murine animal models, PI3Kα pathway has been shown to be protective in the model of tamoxifen toxicity [42] and various models of heart failure [6,43,44]. For pressure overload model of heart failure, a recent study by Patel et al. [6]. elucidated a mechanism underlying the accelerated progression of heart failure observed in a murine model of PI3Kα deficiency, suggesting that PI3Kα activation is part of a compensatory response during heart failure. They also reported reduced PI3Kα activity in human and dog hearts with dilated cardiomyopathy, additionally suggesting that PI3Kα is a part of compensatory response mechanisms to maintain heart function under adverse conditions [6]. In the murine model of ischemic preconditioning, PI3Kα was also found to be the key PI3K isoform to limit myocardial infarct size [43]. In the murine model of doxorubicin-induced heart failure, the loss of PI3Kα exacerbates cardiac atrophy, leading to biventricular atrophy associated with right ventricular dysfunction [44]. Similarly, patients receiving anthracyclines and trastuzumab, which indirectly inhibits PI3Kα activity, exhibit biventricular dysfunction and reduced heart mass [45]. Taken together, the PI3Kα pathway appears to play a crucial cardioprotective role.

**PI3Kα in compensatory response during heart failure**

Under quiescent conditions, lack or reduced PI3Kα activity does not significantly affect heart function [6,46,47], but lack of PI3Kα activity is known to accelerate heart failure progression in the pressure
| Agent   | Target | Phase | Cancer type/Condition                          | Major Toxicities                                           | Cardiac specific | Notes                                                                 | Ref       |
|---------|--------|-------|-----------------------------------------------|------------------------------------------------------------|-----------------|-----------------------------------------------------------------------|-----------|
| Alpelisib | PI3Ka  | I     | Advanced breast cancer                        | Hyperglycemia, dermatologic adverse effects, gastrointestinal discomforts, fatigue | QTc prolongation |                                                                       | [18–20]  |
|         |        | I     | Advanced solid tumors                        |                                                            |                 | QTc prolongation                                                      | [21,22]  |
|         |        | I     | Advanced colorectal cancer                    |                                                            |                 |                                                                       | [23]      |
|         |        | I     | Advanced ovarian, fallopian tube, primary peritoneal, or breast cancer |                                                            |                 |                                                                       | [24]      |
|         |        | II    | Early Breast cancer                           |                                                            |                 | No additional benefits with letrozole                                  | [25]      |
| serabelisib |        | I     | Advanced solid tumors                        | As above, with in addition elevated AST/ALT                |                 |                                                                       | [26]      |
| Taselisib |        | I     | Advanced solid tumors                        | Gastrointestinal discomforts, fatigue, hyperglycemia, dermatologic adverse effects, stomatitis, colitis |                 | Target mutant PI3Ka isoform > wild-type PI3Kα, δ, γ > PI3Kβ          | [27]      |
|         |        | I     | Advanced solid tumors, HR-positive advanced breast cancer |                                                             |                 |                                                                       | [28]      |
|         |        | II    | Advanced HER2-negative, HR-positive breast cancer |                                                             |                 |                                                                       | [29]      |
|         |        |       | Estrogen receptor-positive, PIK3CA-mutant, locally advanced or metastatic breast cancer |                                                             |                 |                                                                       | [30]      |
| GSK2636771 | PI3Kβ | I     | Advanced solid tumors                        | Gastrointestinal discomforts, fatigue, hypophosphatemia, hypocalcemia |                 |                                                                       | [73]      |
| IPI-549  | PI3Ky  | I     | Advanced solid tumors                        | Gastrointestinal discomforts, dermatologic adverse effects, pyrexia, elevated AST/ALT |                 |                                                                       | [74]      |
| Umbralisib | PI3Kδ  | I     | Relapsed or refractory chronic lymphocytic leukemia or lymphoma | Gastrointestinal discomforts, fatigue, dermatologic adverse effects, hypokalemia, hematological toxicities (neutropenia, anemia, thrombocytopenia), elevated AST/ALT, pneumonia, colitis |                 | Inhibits casein kinase 1ε as well                                       | [75]      |
|         |        | I     | Relapsed or refractory chronic lymphocytic leukemia or mantle cell lymphoma |                                                             |                 |                                                                       | [76]      |

(Continued)
| Agent     | Target | Phase | Cancer type/Condition                      | Major Toxicities                                                                 | Cardiac specific                                                                 | Notes                                                                                           | Ref            |
|-----------|--------|-------|--------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------|
| Idelalisib| I, II  | Relapsed indolent non-Hodgkin lymphoma (NHL) | fatigue, gastrointestinal discomforts, dermatologic adverse effects, pyrexia, hematological toxicities (neutropenia, anemia, thrombocytopenia), elevated AST/ALT, pneumonia, colitis | Combined with lenalidomide and rituximab: hepatotoxicity and immune suppression    | [78–81]                                                                                         |                                                                                                  |                |
|           | I, III | Relapsed or refractory CLL                   |                                                                             | Hypokalemia                                                                      |                                                                                      |                                                                                                  | [82–85]       |
|           | II     | Chronic lymphocytic leukemia or small lymphocytic leukemia |                                                                             |                                                                                 |                                                                                      | treatment-naive older patients; AEs-related death: pneumonia, sepsis                          | [86,87]       |
|           | II     | Relapsed or refractory CLL or NHL             |                                                                             |                                                                                  |                                                                                      | terminated early due to pneumonitis in 18% of patients; 2 AE-related death: pneumonitis        | [88]          |
|           | I      | Relapsed mantle cell lymphoma and relapsed follicular lymphoma |                                                                             |                                                                                  |                                                                                      | 60% deaths during the study or long term follow up (1 death occurred on study – hypoxia)     | [89]          |
|           | –      | B-cell prolymphocytic leukemia                |                                                                             |                                                                                  |                                                                                      | Case study n = 5                                                                               | [90]          |
| Nemiralisib| I    | Allergic rhinitis                            | Nasopharyngitis, myalgia                                                   |                                                                                  |                                                                                      |                                                                                                  | [91]          |
| Copanlisib| I     | Advanced solid tumors and non-Hodgkin’s lymphomas | Hyperglycemia, gastrointestinal discomforts, hypertension, dermatologic adverse effects, fatigue, mucositis, elevated aspartate aminotransferase and alanine aminotransferase, thrombocytopenia, neutropenia, anemia, pneumonitis | Hypertension                                                                      |                                                                                                  | As above with atrial fibrillation, sinus tachycardia                                         | [94]          |
|           | I     | Advanced or refractory solid tumors          |                                                                             |                                                                                  |                                                                                      |                                                                                                  | [95]          |
|           | I     | Advanced cancer                              |                                                                             |                                                                                  |                                                                                      |                                                                                                  | [96]          |
|           | II    | Indolent or aggressive malignant lymphoma     | As above with pancreatitis, infection                                       |                                                                                  |                                                                                      | As above with cardiac disorders (not being specified in the article)                          | [97]          |
| Agent          | Target          | Phase | Cancer type/Condition                        | Major Toxicities                                                                 | Cardiac specific | Notes                                                                 | Ref |
|----------------|-----------------|-------|----------------------------------------------|---------------------------------------------------------------------------------|------------------|-----------------------------------------------------------------------|-----|
| Buparlisib     |                 | I     | Advanced solid tumors                        | Gastrointestinal discomforts, hyperglycemia, fatigue, dermatologic adverse effects, stomatitis, elevated transaminase, hypertension, psychiatric disorders, confusion, increased lipase, increased serum amylase | Hypertension     | 7 in 28 patients discontinued therapy because of toxicity            | [98]|
| (BKM120)       |                 | Ib    | HER2-positive advance or metastatic breast cancer |                                                                                  |                  |                                                                       | [99]|
|                |                 | I     | Metastatic renal cell carcinoma               |                                                                                  |                  |                                                                       | [100]|
|                |                 | I, III| Hormone receptor-positive metastatic breast cancer |                                                                                  |                  |                                                                       | [101–103]|
|                |                 | I     | Relapsed/refractory acute leukemias           |                                                                                  |                  |                                                                       | [104]|
|                |                 | II    | Advanced or recurrent endometrial carcinoma   |                                                                                  |                  | Stopped before end of recruitment for toxicity                        | [105]|
|                |                 | II    | Recurrent glioblastoma                        |                                                                                  |                  |                                                                       | [106]|
|                |                 | I     | Metastatic breast cancer                      | As above with neutropenia, peripheral neuropathy                                |                  |                                                                       | [107]|
|                |                 | II/III| Advanced or metastatic breast cancer          |                                                                                  |                  |                                                                       | [108]|
|                |                 | I     | High-grade ovarian and breast cancer          | As above with thrombocytopenia, leukopenia, anemia, lymphopenia                  |                  |                                                                       | [109]|
|                |                 | I     | Advanced solid tumors                        |                                                                                  |                  |                                                                       | [110]|
|                |                 | Ib    | Advanced solid tumors                        | As above with increased creatine kinase                                          |                  |                                                                       | [111]|

AST/ALT, the ratio of aspartate transaminase (AST) to alanine transaminase (ALT); CCL, chronic lymphocytic leukemia; HR, hormone receptor; NHL, non-Hodgkin lymphoma.
overload model of heart failure [6,47]. However, the exact mechanisms of this increased susceptibility to heart failure were unknown. Recently, Patel et al [6]. proposed that in response to biomechanical stress, PI3Kα is recruited to intercalated disks and the plasma membrane where it produces PIP3, which is required to suppress the activity of gelsolin (GSN), an actin-severing protein. When PI3Kα activity is suppressed, GSN activity is markedly increased, leading to lower levels of actin polymerization and a less resilient actin cytoskeleton. Tissue of human and dog hearts with dilated cardiomyopathy also showed reduced levels of actin polymerization, and in human samples, there was a negative correlation between cardiac function and actin depolymerization (the lower ejection fraction corresponded to higher depolymerization levels) [6]. In addition, human and canine hearts with dilated cardiomyopathy showed reduced PI3Kα activity. In a murine dilated cardiomyopathy model, the exacerbation of cardiac dysfunction in PI3Kα-deficient mice was prevented by experimental GSN deficiency, suggesting that PI3Kα is an important in vivo cytoskeletal regulator during cardiac remodeling in pressure overload heart failure. In the proposed framework [6], PI3Kα produces PIP3 which suppresses GSN activity, preventing depolymerization of the actin cytoskeleton by GSN (Figure 1a). In the case of heart failure, reduced PI3Kα activity leads to low PIP3 levels and increased GSN activity, which in turn favors the depolymerization of the actin cytoskeleton (Figure 1b). Another possible mechanism of cardioprotection mediated by PI3Kα is suppression of late Na+ current by PI3Kα-generated PIP3 [7,48]. Since activation of late Na+ current accompanied heart failure in the pressure overload model[49], lack of PI3Kα activity and the ensuing reduction in PIP3 to suppress late Na+ current may contribute to the accelerated transition to heart failure. The link between PI3Kα inhibition, late Na+ current, Ca2+ cycling, and arrhythmias is discussed in more detail below.

**PI3Kα and QT prolongation**

**PI3Kα upregulation and QT.** PI3Kα activity controls expression levels of many channel forming proteins (K+: Kir, Kv, TASK; Ca2+: Cav1; Na+: SCN5A). In murine models, an increase in PI3Kα activity, for example, due to exercise leads to an increase in the protein levels of K+, Ca2+, and Na+ channels as well as their current densities [17]. Increasing PI3Kα activity via expression of constitutively-active PI3Kα also produces higher protein levels and current densities [41]. Overall, upregulation of PI3Kα due to exercise or overexpression did not affect QT interval due to balanced increase in protein levels of both repolarizing K+ channels (Kir, Kv, TASK) and depolarizing channels (Ca2+: Cav1; Na+: SCN5A). Moreover, PI3Kα upregulation was protective against arrhythmias, pathological hypertrophy, and dilated cardiomyopathy [16,17,41].

**PI3Kα inhibition prolongs QT.** Over the last decade, there has been a steady accumulation of observations linking pharmacological inhibition of PI3Kα to activation of late Na current (I_{Na,L}). Apparently, some classical blockers of rapidly-activating delayed rectifier K+-channels, such as dofetilide and E4031, can also inhibit PI3Kα activity and activate I_{Na,L} [50]. In patients, ibrutinib (inhibitor of Bruton tyrosine kinase)
kinase, an upstream effector of PI3Ka) increased cardiac disorders (2-fold) and atrial fibrillation (3-fold) [34], as well as instances of sudden death and ventricular arrhythmias [35,36]. In mice, high doses of ibrutinib produce analogous results (an increase in susceptibility to induced atrial and ventricular arrhythmias) and was associated with inhibition of PI3Ka activity [51].

In murine models, inhibition of PI3Ka produced QT prolongation or long-QT (LQT) and was associated with activation of $I_{\text{Na,L}}$ [50], whereas in canine cardiac myocytes the use of pan PI3K inhibitors lead to inhibition of delayed rectifier $K^+$ currents and activation of $I_{\text{Na,L}}$ [52]. The isoform-specific PI3Ka inhibitor (BYL719) increased $I_{\text{Na,L}}$ and resulted in a triggered activity in murine cardiomyocytes [48] and isolated murine hearts [7,53], but had no effect on murine $K^+$ currents [7]. These results suggest a straightforward link between PI3Ka activity, the prolongation of the action potential, and QT interval (Figure 2).

In this framework, an indirect inhibition of PI3Ka activity by cancer therapies via receptor tyrosine kinase-based therapies (e.g., ibrutinib) [34–36] or directly (e.g., alpelisib) [18,23] may reduce PI3Ka activity leading to reduced PIP3. Since PIP3 suppresses $I_{\text{Na,L}}$, a reduction in PIP3 levels will dis-inhibit (activate) $I_{\text{Na,L}}$, which as a depolarizing current will promote action potential and result in QT prolongation (Figure 2). This QT prolongation due to PI3Ka inhibition may be somewhat compensated in large mammals (including humans) by the influence of PIP3 on L-type $Ca^{2+}$ current ($I_{\text{Ca,L}}$). Indeed, PIP3 has stimulatory effects on depolarizing L-type $Ca^{2+}$ current ($I_{\text{Ca,L}}$); therefore, the reduction of PIP3 levels due to PI3Ka inhibition will promote QT prolongation via $I_{\text{Na,L}}$ and counteract it via $I_{\text{Ca,L}}$ (Figure 2).

A promising approach therefore to prevent QT prolongation is to block the activation of $I_{\text{Na,L}}$ with adjuvant therapy (e.g., ranolazine) (Figure 2) [7]. Besides direct pro-arrhythmic effects of $I_{\text{Na,L}}$ activation, the increased $I_{\text{Na,L}}$ may potentially contribute to the development dilated cardiomyopathy since increased influx of $Na^+$ due to gain-of-function mutations in $SCN5A$ and $SCN10$ (genes encoding $Na^+$ channels) has been implicated in the development of heart failure in rodents [49] and was associated with dilated cardiomyopathy [54] as well as sudden cardiac death [55,56]. Another implication of increased $I_{\text{Na,L}}$ activity is sarcoplasmic reticulum $Ca^{2+}$ overload, which we will discuss below.

**PI3Ka, $Ca^{2+}$ cycling, and triggered arrhythmias**

Dis-inhibition of $I_{\text{Na,L}}$ due to inhibition of PI3Ka [7,48,50,52] can exacerbate $Ca^{2+}$ overload by modulating $Ca^{2+}$ cycling and $\alpha$-adrenergic stimulation [7], both of which are important contributors to the development of several arrhythmias [56–58]. In this framework, dis-inhibited $I_{\text{Na,L}}$ will produce an additional $Na^+$ influx ($I_{\text{Na,L}}$; see 1 in Figure 3a), which will increase cytosolic $Ca^{2+}$ either via a reverse mode of $Na^+-Ca^{2+}$ exchanger at the plateau of action potential (2) or by reduction of $Ca^{2+}$ extrusion via forward mode during resting potential. Increase in cytosolic $Ca^{2+}$ will facilitate $Ca^{2+}$ uptake to the sarcoplasmic reticulum (SR) via SERCa2 (3) leading to $Ca^{2+}$ overload (4) (Figure 3a,b) [7]. This $Ca^{2+}$ overload will promote prolongation of the action potential, abnormal automaticity, early and delayed afterdepolarization, and increased dispersion of repolarization [59,60]. This increase in SR $Ca^{2+}$ load is additive to $\alpha$-adrenergic stimulation [7] and thus will create a risky situation similar to catecholaminergic polymorphic ventricular

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**Figure 2.** Cancer therapies prolong QT interval via inhibition of PI3Ka. Inhibition of PI3Ka activity either at receptor tyrosine kinase (RTK) step or directly at PI3Ka will lead to a reduction in PIP3 levels, which exert an inhibitory effect on late $I_{\text{Na}}$. In the absence of PIP3-related inhibition, additional depolarizing $I_{\text{Na}}$ will prolong action potential and QT interval. The QT prolongation could be moderated in large mammals due to the opposite effect of PIP3 on L-type $Ca^{2+}$ current ($I_{\text{Ca,L}}$). Reduction in PIP3 levels will translate in the smaller amplitude of depolarizing current $I_{\text{Ca,L}}$, which will favor QT shortening.
tachycardia (CPVT) [58,61]. The combined effect of I_{Na-L} and α-adrenergic stimulation will lead to an excessive Ca^{2+} load that may result in spontaneous Ca^{2+} release, which will promote the influx of Ca^{2+} via Na^{+}-Ca^{2+} exchanger (NCX) (2). Increased Ca^{2+} influx and thus increased cytosolic Ca^{2+} will stimulate additional Ca^{2+} uptake via sarcoplasmic reticulum Ca^{2+} ATPase type 2 (SERCa2) (3) leading to increased Ca^{2+} levels in sarcoplasmic reticulum or Ca^{2+} overload (4). (b) Schematic representation of the sequence of the events depicted in A. (c) Interaction of activation of late I_{Na} and α-adrenergic stimulation. Both late I_{Na} and α-adrenergic stimulation are known to contribute to sarcoplasmic (SR) Ca^{2+} overload. The SR Ca^{2+} overload may result in spontaneous Ca^{2+} release (increase in cytoplasmic Ca^{2+}) via ryanodine receptor channels (RYR2). An increase in cytoplasmic Ca^{2+} will produce depolarizing current via the forward mode of NCX (NCX(F)) leading to arrhythmogenic delayed afterdepolarization (DAD).

**FIGURE 3.** Effect of PI3Kα on Ca^{2+} cycling, α-adrenergic stimulation, and arrhythmias. (a) Effect of the PI3Kα inhibition on Ca^{2+} cycling. Inhibition of PI3Kα (1) reduces the inhibitory action of PIP3 on late Na^{+} current (I_{Na-L}). Increased I_{Na-L} will generate an influx of Na^{+}, which will promote the influx of Ca^{2+} via Na^{+}-Ca^{2+} exchanger (NCX) (2). Increased Ca^{2+} influx and thus increased cytosolic Ca^{2+} will stimulate additional Ca^{2+} uptake via sarcoplasmic reticulum Ca^{2+} ATPase type 2 (SERCa2) (3) leading to increased Ca^{2+} levels in sarcoplasmic reticulum or Ca^{2+} overload (4). (b) Schematic representation of the sequence of the events depicted in A. (c) Interaction of activation of late I_{Na} and α-adrenergic stimulation. Both late I_{Na} and α-adrenergic stimulation are known to contribute to sarcoplasmic (SR) Ca^{2+} overload. The SR Ca^{2+} overload may result in spontaneous Ca^{2+} release (increase in cytoplasmic Ca^{2+}) via ryanodine receptor channels (RYR2). An increase in cytoplasmic Ca^{2+} will produce depolarizing current via the forward mode of NCX (NCX(F)) leading to arrhythmogenic delayed afterdepolarization (DAD).

**PI3Kα inhibition and heart failure in the clinic**

Besides the arrhythmogenic effects of PI3Kα inhibition associated with I_{Na-L} activation and related Ca^{2+} overload, these processes may contribute to the development and exacerbate heart failure. The activation of I_{Na-L} and increased Ca^{2+} influx via NCX have been linked to the development of heart failure in a murine pressure overload model [49] via hypertrophic calcineurin-NFAT signaling [62]. In heart failure, when α-adrenergic signaling is upregulated to maintain cardiac output [63], an additional Ca^{2+} from I_{Na,L}-NCX axis would compound with the effects of α-adrenergic stimulation resulting in the accelerated progression of heart failure. Pro-arrhythmic effects of PI3Kα inhibition will be amplified because of the higher levels of Na^{+}-Ca^{2+} exchanger protein observed both in human failing heart [64] and in rodent models of heart failure [65]. This means that the risk of cardiac-specific side effects of PI3Kα inhibition will be greater in the elderly patients who are more likely to suffer from heart failure or preexisting cardiac dysfunctions [66]. Polymorphisms in genes involved in all steps that produce Ca^{2+} overload (Figure 3a,b) could also contribute to susceptibility of PI3Kα-dependent cardiac
side effects. Polymorphisms and mutations in SCN5A and SCN10A (genes that are responsible for Na⁺ influx via I_{Na-L}) have already been linked to dilated cardiomyopathy, arrhythmias, and sudden cardiac death [54–56,67]. Other LQT-related polymorphisms and mutations may aggravate QT prolongation due to PI3Kα inhibition exacerbating arrhythmic risk. Additionally, since PI3Kα inhibition leads to Ca²⁺ overload, polymorphisms and mutations related to CPVT, especially the ones that increase sensitivity to Ca²⁺ overload [58], will also magnify arrhythmogenic effects PI3Kα inhibition. The link between genetic background and arrhythmogenic effects of PI3Kα inhibition warrants further in-depth studies.

Currently, there are two possible approaches to mitigate cardiotoxicity related to PI3Kα inhibition. One is the use of an I_{Na-L} blocker (e.g., ranolazine) that will prevent AP prolongation and Ca²⁺ overload resulting from inhibition of PI3Kα [7,68]. Ranolazine is known to improve heart function in heart failure patients (not related to drug-induced cardiotoxicity) [69–71] as well as to prevent anthracycline-induced cardiotoxicity [72]. The other less explored approach is to block the reverse mode of NCX; however, currently, there are no approved drugs to achieve this effect.

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References

[1] Vanhaesebroeck B, Ali K, Bilancio A, et al. Signalling by PI3K isoforms: insights from gene-targeted mice. Trends Biochem Sci. 2005;30:194–204.
[2] Hirsch E, Braccini L, Ciracolo E, et al. Twice upon a time: PI3K’s secret double life exposed. Trends Biochem Sci. 2009;34:244–248.
[3] Bilanges B, Posor Y, Vanhaesebroeck B. PI3K isoforms in cell signalling and vesicle trafficking. Nat Rev Mol Cell Biol. 2019;20:515–534.
[4] Hawkins PT, Stephens LR. PI3K signalling in inflammation. Biochim Biophys Acta. 2015;1851:882–897.
[5] Fruman DA, Chiu H, Hopkins BD, et al. The PI3K Pathway in Human Disease. Cell. 2017;170:605–635.
[6] Patel VB, Zhabyeyev P, Chen X, et al. PI3Kα-regulated gelsolin activity is a critical determinant of cardiac cytoskeletal remodeling and heart disease. Nat Commun. 2018;9:5390.
[7] Zhabyeyev P, McLean B, Chen X, et al. Inhibition of PI3Kα inotrope-alpha is pro-arrhythmic and associated with enhanced late Na⁺ current, contractility, and Ca²⁺ release in murine hearts. J Mol Cell Cardiol. 2019;132:98–109.
[8] Chen X, Zhabyeyev P, Azad AK, et al. Endothelial and cardiomyocyte PI3Kβ divergently regulate cardiac remodelling in response to ischaemic injury. Cardiovasc Res. 2019;115:1343–1356.
[9] Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov. 2014;13:140–156.
[10] Thorpe LM, Yuzugullu H, Zhao JI. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015;15:7–24.
[11] Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol. 2018;15:273–291.
[12] Arafeh R, Samuels Y. PIK3CA in cancer: the past 30 years. Semin Cancer Biol. 2019. DOI:10.1016/j.semcancer.2019.02.002
[13] McLean BA, Zhabyeyev P, Pituskin E, et al. PI3K inhibitors as novel cancer therapies: implications for cardiovascular medicine. J Card Fail. 2013;19:268–282.
[14] Mayer IA, Arteaga CL. The PI3K/akt Pathway as a Target for Cancer Treatment. Annu Rev Med. 2016;67:11–28.
[15] Curigliano G, Shah RR. Safety and Tolerability of Phosphatidylinositol-3-Kinase (PI3K) Inhibitors in Oncology. Drug Saf. 2019;42:247–262.
[16] Yang KC, Tseng YT, Nerbonne JM. Exercise training and PI3Kα-induced electrical remodeling is independent of cellular hypertrophy and Akt signaling. J Mol Cell Cardiol. 2012;53:532–541.
[17] Yang KC, Foeger NC, Marionneau C, et al. Homeostatic regulation of electrical excitability in physiological cardiac hypertrophy. J Physiol. 2010;588:5015–5032.
[18] Mayer IA, Abramson VG, Formisano L, et al. A phase 1b study of alpelisib (BYL719), a PI3Kα-specific inhibitor, with letrozole in ER+/HER2- metastatic breast cancer. Clin Cancer Res off J Am Assoc Cancer Res. 2017;23:26–34.
[19] Jain S, Shah AN, Santa-Maria CA, et al. Phase I study of alpelisib (BYL-719) and trastuzumab emtansine (T-DM1) in HER2-positive metastatic breast cancer (MBC) after trastuzumab and taxane therapy. Breast Cancer Res Treat. 2018;171:371–381.

[20] Juric D, Janku F, Rodn J, et al. Alpelisib plus fulvestrant in PIK3CA-altered and PIK3CA-wild-type estrogen receptor-positive advanced breast cancer: A Phase Ib clinical trial. JAMA Oncol. 2018;18:184475. DOI: 10.1001/jamaoncol.2018.4475

[21] Juric D, Rodon J, Tabernero J, et al. Phosphatidylinositol 3-Kinase alpha-Selective inhibition with alpelisib (BYL719) in PIK3CA-altered solid tumors: results from the first-in-human study. J Clin Oncol. 2018;36:1291–1299.

[22] Rodon J, Curigliano G, Delord J-P, et al. A Phase Ib, open-label, dose-finding study of alpelisib in combination with paclitaxel in patients with advanced solid tumors. Oncotarget. 2018;9:31709–31718.

[23] van Geel R, Xiao J, Lin H, et al. A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer. Cancer Discov. 2017;7:610–619.

[24] Konstantinopoulos PA, Barry WT, Birrer M, et al. Olaparib and alpha-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase Ib trial. Lancet Oncol. 2019;20:570–580.

[25] Mayer IA, Prat A, Egle D, et al. A phase II randomized study of neoadjuvant letrozole plus alpelisib for hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (NEO-ORB). Clin Cancer Res off J Am Assoc Cancer Res. 2019;25:2975–2987.

[26] Juric D, de Bono JS, LoRusso PM, et al. A first-in-human, phase I, dose-escalation study of TAK-117, a selective PI3Kalpha isoform inhibitor, in patients with advanced solid malignancies. Clin Cancer Res off J Am Assoc Cancer Res. 2017;23:5015–5023.

[27] Juric D, Krop I, Ramanathan RK, et al. Phase I dose-escalation study of taselisib, an oral PI3K inhibitor, in patients with advanced solid tumors. Cancer Discov. 2017;7:704–715.

[28] Tamura K, Kodaia M, Shimizu C, et al. Phase I study of taselisib in Japanese patients with advanced solid tumors or hormone receptor-positive advanced breast cancer. Cancer Sci. 2018;109:1592–1601.

[29] Dickler MN, Saura C, Richards DA, et al. Phase II study of Taselisib (GDC-0032) in combination with fulvestrant in patients with HER2-negative, hormone receptor-positive advanced breast cancer. Clin Cancer Res off J Am Assoc Cancer Res. 2018;24:4380–4387.

[30] Baselga J, Dent SF, Cortés J, et al. Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): primary analysis from SANDPIPER J Clin Oncol. 2018;36:LBA1006–LBA1006.

[31] Foukas LC, Claret M, Pearce W, et al. Critical role for the p110alpha phosphoinositide-3-OH kinase in growth and metabolic regulation. Nature. 2006;441:366–370.

[32] Knight ZA, Gonzalez B, Feldman ME, et al. A pharmacological map of the PI3-K family defines a role for p110alpha in insulin signaling. Cell. 2006;125:733–747.

[33] McMullen JR, Boey EJH, Ooi JYY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124:3829–3830.

[34] Byrd JC, Brown JR, O’Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213–223.

[35] Tomcsanyi J, Neney Z, Matrai Z, et al. Ibrutinib, an approved tyrosine kinase inhibitor as a potential cause of recurrent polymorphic ventricular tachycardia. JACC Clin Electrophysiol. 2016;2:847–849.

[36] Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibritinib. Blood. 2017;129:2581–2584.

[37] Lu Z, Jiang Y-P, Wu C-YC, et al. Increased persistent sodium current due to decreased PI3K signaling contributes to QT prolongation in the diabetic heart. Diabetes. 2013;62:4257–4265.

[38] Ballou LM, Lin RZ, Cohen IS. Control of cardiac repolarization by phosphoinositide 3-kinase signaling to ion channels. Circ Res. 2015;116:127–137.

[39] Lengyel C, VIRAG L, BIRO T, et al. Diabetes mellitus attenuates the repolarization reserve in mammalian heart. Cardiovasc Res. 2007;73:512–520.

[40] Zhang Y, Xiao J, Lin H, et al. Ionic mechanisms underlying abnormal QT prolongation and the associated arrhythmias in diabetic rabbits: a role of rapid delayed rectifier K+ current. Cell Physiol Biochem. 2007;19:225–238.

[41] Yang KC, Jay PY, McMullen JR, et al. Enhanced cardiac PI3Kalpha signalling mitigates arrhythmogenic electrical remodelling in pathological hypertrophy and heart failure. Cardiovasc Res. 2012;93:252–262.

[42] McLean BA, Zhabyeyev P, Patel VB, et al. PI3Kalpha is essential for the recovery from Cre/tamoxifen cardiotoxicity and in myocardial insulin signalling but is not required for normal myocardial contractility in the adult heart. Cardiovasc Res. 2015;105:292–303.

[43] Rossello X, Riquelme JA, He Z, et al. The role of PI3Kalpha isoform in cardioprotection. Basic Res Cardiol. 2017;112:66.

[44] McLean BA, Patel VB, Zhabyeyev P, et al. PI3Kalpha pathway inhibition with doxorubicin treatment results in distinct biventricular atrophy and remodeling with right ventricular dysfunction. J Am Heart Assoc. 2019;8:e010961.
and trastuzumab have biventricular dysfunction and reduced heart mass. J Am Coll Cardiol. 2018;72:1872–1873.

[46] Shioi T, Kang PM, Douglas PS, et al. The conserved phosphoinositide 3-kinase pathway determines heart size in mice. Embo J. 2000;19:2537–2548.

[47] McMullen JR, Shioi T, Zhang L, et al. Phosphoinositide 3-kinase: p110alpha) plays a critical role for the induction of physiological, but not pathological, cardiac hypertrophy. Proc Natl Acad Sci U S A. 2003;100:12355–12360.

[48] Yang T, Meoli DF, Moslehi J, et al. Inhibition of the alpha-subunit of phosphoinositide 3-Kinase in heart increases late sodium current and is arrhythmogenic. J Pharmacol Exp Ther. 2018;365:460–466.

[49] Toischer K, Hartmann N, Wagner S, et al. Role of late sodium current as a potential arrhythmogenic mechanism in the progression of pressure-induced heart disease. J Mol Cell Cardiol. 2013;61:111–122.

[50] Yang T, Chun YW, Stroud DM, et al. Screening for acute IKr block is insufficient to detect torsades de pointes liability: role of late sodium current. Circulation. 2014;130:224–234.

[51] Tuomi JM, Xenocostas A, Jones DL. Increased susceptibility for atrial and ventricular cardiac arrhythmias in mice treated with a single high dose of ibritinib. Can J Cardiol. 2018;34:337–341.

[52] Lu Z, Wu C-YC, Jiang Y-P, et al. Suppression of phosphoinositide 3-kinase signaling and alteration of multiple ion currents in drug-induced long QT syndrome. Sci Transl Med. 2012;4:131ra150.

[53] Zhabyeyev P, McLean B, Vanhaesebroeck B, et al. Acute Pharmacological Inhibition of PI3K alpha by the Novel Cancer Drug, BYL-719, Has a Pro-arrhythmic Effect. Circulation. 2016;134:A15697.

[54] Walsh R, Thomson KL, Ware JS, et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet Med. 2017;19:192–203.

[55] Kääb S, Schulze-Bahr E. Susceptibility genes and modifiers for cardiac arrhythmias. Cardiovasc Res. 2005;67:397–413.

[56] Zhabyeyev P, Oudit GY. Reference module in biomedical sciences (ed M. Caplan). Amsterdam, Netherlands: Elsevier; 2017.

[57] Antzelevitch C, Burashnikov A. Overview of basic mechanisms of cardiac arrhythmia. Card Electrophysiol Clin. 2011;3:23–45.

[58] Priori SG, Chen SR. Inherited dysfunction of sarcoplasmic reticulum Ca2+ handling and arrhythmogenesis. Circ Res. 2011;108:871–883.

[59] Shryock JC, Song Y, Rajamani S, et al. The arrhythmogenic consequences of increasing late INa in the cardiomyocyte. Cardiovasc Res. 2013;99:600–611.

[60] Antzelevitch C, Nesterenko V, Shryock JC, et al. The role of late INa in development of cardiac arrhythmias. Handb Exp Pharmacol. 2014;221:137–168.

[61] Zhabyeyev P, Hiess F, Wang R, et al. S4153R is a gain-of-function mutation in the cardiac Ca2+ release channelryanodine receptor associated with catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation. Can J Cardiol. 2013;29:993–996.

[62] Dewenter M, von der Lieth A, Katus HA, et al. Calcium signaling and transcriptional regulation in cardiomyocytes. Circ Res. 2017;121:1000–1020.

[63] Najafi A, Sequeira V, Kuster DW, et al. Beta-adrenergic receptor signalling and its functional consequences in the diseased heart. Eur J Clin Invest. 2016;46:362–374.

[64] Flesch M, Schwinger RHG, Schiffer F, et al. Evidence for functional relevance of an enhanced expression of the Na+-Ca2+ exchanger in failing human myocardium. Circulation. 1996;94:992–1002.

[65] O’Rourke B, Kass DA, Tomaselli GF, et al. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. Circ Res. 1999;84:562–570.

[66] Sarfati D, Koczwar B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin. 2016;66:337–350.

[67] Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. Genome Med. 2017;9:20.

[68] Fischer TH, Herting J, Mason FE, et al. Late INa increases diastolic SR-Ca2+-leak in atrial myocardium by activating PKA and CaMKII. Cardiovasc Res. 2015;107:184–196.

[69] Hale SL, Shryock JC, Belardinelli L, et al. Late sodium current inhibition as a new cardioprotective approach. J Mol Cell Cardiol. 2008;44:954–967.

[70] Sossalla S, Wagner S, Rasenack ECL, et al. Ranolazine improves diastolic dysfunction in isolated myocardium from failing human hearts—role of late sodium current and intracellular ion accumulation. J Mol Cell Cardiol. 2008;45:32–43.

[71] Maier LS, Layug B, Karwatowska-Prokopczuk E, et al. RANOLaZIne for the treatment of diastolic heart failure in patients with preserved ejection fraction: the RALI-DHF proof-of-concept study. JACC Heart Fail. 2013;1:115–122.

[72] Minotti G. Pharmacology at work for cardiac-oncology: ranolazine to treat early cardiotoxicity induced by anti-tumor drugs. J Pharmacol Exp Ther. 2013;346:343–349.

[73] Mateo J, Ganji G, Lemech C, et al. A first-time-in-human study of GSK2636771, a Phosphoinositide 3 Kinase beta-selective inhibitor, in patients with advanced solid tumors. Clin Cancer Res off J Am Assoc Cancer Res. 2017;23:5981–5992.

[74] Sullivan RJ, Hong DS, Tolcher AW, et al. Initial results from first-in-human study of IPI-549, a tumor macrophage-targeting agent, combined with nivolumab in advanced solid tumors. J Clin Oncol. 2018;36:3013–3013.
therapy in relapsed refractory CLL and

[75] Burris HA 3rd, Flinn IW, Patel MR, et al. Umbralisib, a novel PI3Kdelta and casein kinase-epsilon inhibitor, in relapsed or refractory chronic lymphocytic leukaemia and lymphoma: an open-label, phase I, dose-escalation, first-in-human study. Lancet Oncol. 2018;19:486–496.

[76] Davids MS, Kim HT, Nicotra A, et al. Umbralisib in combination with ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia or mantle cell lymphoma: a multicentre phase 1-1b study. Lancet Haematol. 2019;6:e58–e47.

[77] Cheah CY, Amison RT, Riffo-Vasquez Y, et al. Lenalidomide, idelalisib, and rituximab are unacceptably toxic in patients with relapsed/refractory indolent lymphoma. Blood. 2015;125:3357–3359.

[78] Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-delta, as therapy for previously treated indolent non-Hodgkin lymphoma. Blood. 2014;123:3406–3413.

[79] de Vos S, Wagner-Johnston ND, Coutre SE, et al. Combinations of idelalisib with rituximab and/or bendamustine in patients with recurrent indolent non-Hodgkin lymphoma. Blood Adv. 2016;1:122–131.

[80] Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370:1008–1018.

[81] Salles G, Schuster SJ, De Vos S, et al. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. Haematologica. 2017;102:e156–e159.

[82] Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. Blood. 2014;123:3390–3397.

[83] Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370:997–1007.

[84] Jones JA, Robak T, Brown JR, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol. 2017;4:e114–e126.

[85] Zelenetz AD, Barrientos JC, Brown JR, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2017;18:297–311.

[86] O’Brian SM, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib plus rituximab in treatment-naive older patients with chronic lymphocytic leukemia. Blood. 2015;126:2686–2694.

[87] Thompson PA, Stingo F, Keating MJ, et al. Outcomes of patients with chronic lymphocytic leukaemia treated with first-line idelalisib plus rituximab after cessation of treatment for toxicity. Cancer. 2016;122:2505–2511.

[88] Barr PM, Sayers GB, Spurgeon SE, et al. Phase 2 study of idelalisib and entospletinib: pneumonitis limits combination therapy in relapsed refractory CLL and NHL. Blood. 2016;127:2411–2415.

[89] Gopal AK, Fanale MA, Moskowitz CH, et al. Phase II study of idelalisib, a selective inhibitor of PI3Kdelta, for relapsed/refractory classical Hodgkin lymphoma. Ann Oncol. 2017;28:1057–1063.

[90] Eyre TA, Fox CP, Shankara P, et al. Idelalisib-Rituximab induces clinical remissions in patients with TP53 disrupted B cell prolymphocytic leukaemia. Br J Haematol. 2017;177:486–491.

[91] Smith SM, Pitcher BN, Jung S-H, et al. Safety and tolerability of idelalisib, lenalidomide, and rituximab in relapsed and refractory lymphoma: the Alliance for Clinical Trials in Oncology A051201 and A051202 phase I trials. Lancet Haematol. 2017;4:e176–e182.

[92] Horak F, Puri KD, Steiner BH, et al. Randomized phase I study of the phosphatidylinositol 3-kinase delta inhibitor idelalisib in patients with allergic rhinitis. J Allergy Clin Immunol. 2016;137:1733–1741.

[93] Khindri S, Cahn A, Begg M, et al. A multicentre, randomized, double-blind, placebo-controlled, cross-over study to investigate the efficacy, safety, tolerability, and pharmacokinetics of repeat doses of inhaled nebulised idelalisib in adults with persistent, uncontrolled asthma. J Pharmacol Exp Ther. 2018;367:405–413.

[94] 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.

[95] Doi T, Fuse N, Yoshino T, et al. A Phase I study of intravenous PI3K inhibitor copanlisib in Japanese patients with advanced or refractory solid tumors. Cancer Chemother Pharmacol. 2017;79:89–98.

[96] Kim RD, Alberts SR, Pena C, et al. Phase I dose-escalation study of copanlisib in combination with gemcitabine or cisplatin plus gemcitabine in patients with advanced cancer. Br J Cancer. 2018;118:462–470.

[97] Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. Ann Oncol. 2017;28:2169–2178.

[98] Rodon J, Braña I, Siu LL, et al. Phase I dose-escalation and -expansion study of buparlisib (BKM120), an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. Invest New Drugs. 2014;32:670–681.

[99] Saura C, Bendell J, Jerusalem G, et al. Phase Ib study of Buparlisib plus Trastuzumab in patients with HER2-positive advanced or metastatic breast cancer that has progressed on Trastuzumab-based therapy. Clin Cancer Res off J Am Assoc Cancer Res. 2014;20:1935–1945.

[100] McKay RR, De Velasco G, Werner L, et al. A phase I study of buparlisib and bevacizumab in patients with
metastatic renal cell carcinoma progressing on vascular endothelial growth factor-targeted therapies. Cancer. 2016;122:2389–2398.

[101] Ma CX, Luo J, Naughton M, et al. A phase I trial of BKM120 (Buparlisib) in combination with fulvestrant in postmenopausal women with estrogen receptor-positive metastatic breast cancer. Clin Cancer Res off J Am Assoc Cancer Res. 2016;22:1583–1591.

[102] Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18:904–916.

[103] 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.

[104] Ragon BK Kantarjian H, Jabbour E, et al. Buparlisib, a PI3K inhibitor, demonstrates acceptable tolerability and preliminary activity in a phase I trial of patients with advanced leukemias. Am J Hematol. 2017;92:7–11.

[105] Heudel PE, Fabbro M, Roemer-Becuwe C, et al. Phase II study of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma: a stratified type I-type II study from the GINECO group. Br J Cancer. 2017;116:303–309.

[106] Wen PY, Touat M, Alexander BM, et al. Buparlisib in patients with recurrent glioblastoma harboring Phosphatidylinositol 3-Kinase pathway activation: an open-label, multicenter, multi-arm, phase II trial. J Clin Oncol. 2019;37:741–750.

[107] McRee AJ Marcom PK, Moore DT, et al. A phase I trial of the PI3K inhibitor buparlisib combined with capecitabine in patients with metastatic breast cancer. Clin Breast Cancer. 2018;18:289–297.

[108] Martin M, Barrios CH, Kim TM, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2-advanced breast cancer (BELLE-4). Ann Oncol. 2017;28:313–320.

[109] Matulonis UA, Barrios CH, Kim TM, et al. Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. Ann Oncol. 2017;28:512–518.

[110] McRee AJ, Sanoff HK, Carlson C, et al. A phase I trial of mFOLFOX6 combined with the oral PI3K inhibitor BKM120 in patients with advanced refractory solid tumors. Invest New Drugs. 2015;33:1225–1231.

[111] Bedard PL Tabernero, J, Janku, F, et al. A phase Ib dose-escalation study of the oral pan-PI3K inhibitor buparlisib (BKM120) in combination with the oral MEK1/2 inhibitor trametinib (GSK1120212) in patients with selected advanced solid tumors. Clin Cancer Res off J Am Assoc Cancer Res. 2015;21:730–738.