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REVIEW ARTICLE

Safety and Tolerability of Phosphatidylinositol-3-Kinase (PI3K) Inhibitors in Oncology

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Abstract

Activation of phosphatidylinositol-3-kinase (PI3K) and downstream signalling by AKT/mammalian target of rapamycin (mTOR) modulates cellular processes such as increased cell growth, cell proliferation and increased cell migration as well as deregulated apoptosis and oncogenesis. The PI3K/AKT/mTOR pathway (particularly Class I PI3K isoforms) is frequently activated in a variety of solid tumours and haematological malignancies, making PI3K an attractive therapeutic target in oncology. Inhibitors of PI3K also have the potential to restore sensitivity to other modalities of treatments when administered as part of combination regimens. Although many PI3K inhibitors have reached different stages of clinical development, only two (idelalisib and copanlisib) have been currently approved for use in the treatment of B cell lymphoma and leukaemias. While these two agents are effective clinically, their use is associated with a number of serious class-related as well as drug-specific adverse effects. Some of these are immune-mediated and include cutaneous reactions, severe diarrhoea with or without colitis, hepatotoxicity and pneumonitis. They also induce various metabolic abnormalities such as hyperglycaemia and hypertriglyceridaemia. Not surprisingly, therefore, many new PI3K inhibitors with a varying degree of target selectivity have been synthesised in expectations of improved safety and efficacy, and are currently under clinical investigations for use in a variety of solid tumours as well as haematological malignancies. However, evidence from early clinical trials, reviewed herein, suggests that these newer agents are also associated not only with class-related but also other serious and unexpected adverse effects. Their risk/benefit evaluations have resulted in a number of them being discontinued from further development. Cumulative experience with the use of PI3K inhibitors under development suggests that, compared with their use as monotherapy, combining them with other anticancer therapies may be a more effective strategy in improving current standard-of-care and clinical outcomes in cancers beyond haematological cancers. For example, combination of alpelisib with fulvestrant has recently demonstrated unexpectedly superior efficacy compared to fulvestrant alone. Furthermore, the immunomodulatory activity of PI3Kδ and PI3Kγ inhibitors also provides unexpected opportunities for their use in cancer immunotherapy, as is currently being tested in several clinical trials.

Key Points

Phosphatidylinositol-3-kinase (PI3K) inhibitors are a welcome addition to therapies for treating various lymphomas and leukaemias, but the only two currently approved PI3K inhibitors carry risks of serious and potentially fatal adverse events.

New PI3K inhibitors under development are anticipated to offer exciting prospects for treating other malignancies, especially when used in combination with other anticancer modalities.

Available evidence suggests, however, that these new agents are also associated with class-related as well as other serious safety issues, impacting adversely on their risk/benefit evaluation.

Part of a theme issue on "Safety of Novel Anticancer Therapies: Future Perspectives". Guest Editors: Rashmi R. Shah, Giuseppe Curigliano.

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1 Introduction

The phosphatidylinositol (PI)-3-kinase (PI3K)-based pathway is an intracellular signalling pathway that responds to a number of hormones and growth factors. Its downstream mediators include AKT and mammalian target of rapamycin (mTOR), both of which are serine–threonine protein kinases. These three components, PI3K, AKT and mTOR, are connected so intricately that they are often regarded as constituting a single unique pathway, the PI3K/AKT/mTOR pathway [1]. Activation of this pathway modulates cellular processes such as increased cell growth, cell proliferation and survival, and increased cell migration as well as deregulated apoptosis and oncogenesis [1, 2]. The reader is referred to a review by Fruman et al. [3] for a comprehensive account of this pathway and its significance for human disease. In this review, we focus only on the PI3K node of this pathway.

Structurally, PI3K enzymes share a common core motif, consisting of a C2 domain, a helical domain and a catalytic (kinase) domain. In mammals, these enzymes are divided into three classes (I, II and III) based on their coding genes, distinct structures and substrate preference [4–6]. Class I PI3Ks are further divided into two subclasses: subclass IA (includes isoforms PI3Kα, PI3Kβ and PI3Kδ) and subclass IB (includes only isoform PI3Kγ) [7–9]. Genes (and their protein catalytic effectors) for the three class IA PI3Ks are designated *PIK3CA* (p110α), *PIK3CB* (p110β) and *PIK3CD* (p110δ) and that for the only class 1B PI3K is designated as *PIK3CG* (p110γ). Class IA PI3Ks are constitutive heterodimers of their corresponding 110 kDa catalytic subunits (p110) with one of the five regulatory adaptor proteins (p85α, p55α, p50α, p85β or p55γ, collectively called 'p85s') that recruits the p110 to intracellular locations of tyrosine kinase activation. Class 1B PI3K complexes with the p101 or p84 adapter protein [10].

The three isoforms of subclass IA are usually (but not always) activated by activation of receptors with protein tyrosine kinase activity, whereas the isoform in subclass IB is usually activated by activation of G protein-coupled receptors (GPCRs) [5, 11, 12]. Activation of tyrosine kinase receptors by their ligand growth factors results in autophosphorylation on tyrosine residues, which results in recruitment of PI3Ks to the cellular membrane [1, 2, 4]. PI3Ks are a family of lipid kinases that phosphorylate inositol lipids at the 3′-position of the inositol ring, generating PI-3-phosphate (PI(3)P1), PI-3,4-bisphosphate (PI(3,4)P2) and PI-3,4,5-trisphosphate (PI(3,4,5)P3). PI(3,4,5)P3 acts as a docking site for AKT [2, 10, 13] for further downstream signalling. Physiologically, the PI3K activity is counterbalanced by phosphatase and tensin homolog (referred to as PTEN). The main lipid substrate of PTEN is PI(3,4,5)P3, converting it to PI(4,5)P2, thereby terminating/deactivating PI3K/AKT-mediated signalling [1, 14]. Thus, PTEN acts as a negative regulator of PI3K/AKT signalling.

The four class I isoforms differ in terms of their tissue distribution and function and play a central role in the signalling pathway. PI3Kα is ubiquitously expressed and essential for angiogenesis, insulin signalling and maintaining glucose homeostasis. PI3Kβ is also ubiquitously expressed but plays a non-redundant role in phagocytosis and reactive oxygen species (ROS) production in macrophages and neutrophils and is involved in the development of thrombotic diseases by activating platelets. PI3Kδ and PI3Kγ are expressed mainly in the leukocytes [11] and are involved in inflammatory and autoimmune diseases [10, 11, 15]. PI3Kδ signalling is critical for activation, proliferation and survival of B cells. It has an important role in their homing to, and retention in, lymphoid tissues. The critical role of p110δ in B cells has led to the development of highly p110δ-specific inhibitors for treatment of B cell malignancies. In addition, PI3Kδ has important roles in T cells and regulates adaptive immune system, whereas PI3Kγ is more important in the innate immune response. Accumulating evidence suggests that inhibition of PI3Kδ leads to activation of immune response through its selective inhibitory effect on regulatory T cells over helper T cells [16, 17]. As discussed in Sect. 3.1, this activation of immune response has important clinical implications with regard to the toxicity associated with PI3Kδ-selective inhibitors.

Activation of the PI3K/AKT/mTOR pathway is often associated with a variety of solid tumours and haematological malignancies [2, 18–21]. Common mechanisms of PI3K/AKT/mTOR pathway activation include (1) activating mutations and/or amplification of *PIK3CA* gene, which encodes for the catalytic subunit PI3Kα; (2) mutations or loss of PTEN; (3) mutation and/or amplification of genes encoding tyrosine receptor kinases such as epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2); and (4) mutation and/or amplification of AKT [22]. PI3Kα plays important roles in oncogenesis and has been detected with persistent mutations and amplification in most human cancers, including breast, ovarian and colorectal cancers [23–26]. PTEN is also frequently mutated in several advanced human cancers [24, 25] and loss of PTEN activity leads to permanent activation of the PI3K/AKT pathway [27]. Dysregulation of the class 1A PI3K signalling pathway is also associated with the development of resistance to a variety of anticancer therapies, including chemotherapy, radiotherapy, hormone therapy and targeted agents [25, 28–30].

Therefore, PI3Ks are an attractive therapeutic target in oncology and their inhibitors also have the potential to restore sensitivity to other modalities of treatments when administered as part of combination regimens [30, 31]. The first generation of PI3K inhibitors (such as Wortmannin

and LY294002) bind to all PI3K isoforms in class I and are referred to as 'pan–PI3K inhibitors'. Second-generation inhibitors are more potent and have greater isoform-selective activity. Appreciation of the potential advantages of combined inhibition of two oncogenic targets has also led to the synthesis of compounds with dual activity (at PI3K and mTOR), referred to as 'dual PI3K/mTOR inhibitors' (third-generation inhibitors). The molecular and pharmacological rationale supporting the synthesis of these dual inhibitors is a high degree of sequence homology shared by the catalytic sites of PI3K and mTOR, and therefore, the anticipation that this combined activity may lead to much stronger inhibition of the whole PI3K/AKT/mTOR pathway. A number of pan–PI3K inhibitors targeting all four isoforms of class I PI3K as well as isoform-selective inhibitors and dual PI3K/mTOR inhibitors are currently under clinical development [14, 20, 32–35].

This review summarises some of the serious adverse effects associated with PI3K inhibitors that have been approved as well as those under development. The only PI3K inhibitors currently approved are idelalisib, which selectively inhibits PI3Kδ and copanlisib, a highly selective and potent inhibitor of PI3Kδ and PI3Kα. We emphasise that we have deliberately chosen to discuss only the PI3K inhibitors and not the inhibitors of other nodes in the PI3K/AKT/mTOR pathway. Our review is based on drug evaluation reports and prescribing information provided by the US Food and Drug Administration (FDA) [36] and European Medicines Agency (EMA) [37], complemented by review of published literature where indicated. It is worth emphasising that the frequency and severity of an adverse effect varies across different trials, especially when there are different patient populations or indications under investigation and different treatment regimens investigated in relatively small study populations [38]. Therefore, only broadly applicable estimates of frequency of various adverse effects are provided in what follows. Locally approved prescribing information as well as guidelines and consensus statements from expert groups and societies should be consulted to evaluate and manage these adverse effects.

2 Pharmacology and Indications of Currently Approved Phosphatidylinositol-3-Kinase (PI3K) Inhibitors

As of 31 July 2018, only two PI3K inhibitors, idelalisib (coded CAL-101 or GS-1101) and copanlisib (coded BAY 80-6946), have been approved.

Idelalisib is available as tablets for oral use and was approved in July 2014 by the FDA and in September 2014 by the EMA. It is indicated for use in a well-defined setting and subsets of patients with relapsed chronic lymphocytic leukaemia (CLL), relapsed follicular B cell non-Hodgkin lymphoma and relapsed small lymphocytic lymphoma. The indications approved by the EMA are more specific in terms of patient selection.

Copanlisib is available as intravenous formulation for infusion and was approved in September 2017 by the FDA. It has not yet been approved by the EMA. It is indicated for use in the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.

2.1 Primary Pharmacodynamics

Both idelalisib and copanlisib are isoform selective but their selectivity varies substantially. Their pharmacological mechanisms of action are summarised below:

- Idelalisib is a selective inhibitor of PI3Kδ kinase, which is expressed in normal and malignant B cells. Its concentration of drug producing 50% inhibition (IC_{50}) values for PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ isoforms are 820, 56.5, 89 and 2.5 nmol/L, respectively. It also inhibits several cell signalling pathways, including B cell receptor (BCR) signalling and the C-X-C chemokine receptor (CXCR) 4 and CXCR5 signalling, which are involved in trafficking and homing of B cells to the lymph nodes and bone marrow.
- Copanlisib is an inhibitor of PI3Kδ as well as PI3Kα isoforms, both of which are expressed in normal and malignant B cells. Its IC_{50} values for PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ isoforms are 0.5, 3.7, 6.4 and 0.7 nmol/L, respectively. It also inhibits several key cell signalling pathways, including BCR signalling, CXCR12-mediated chemotaxis of malignant B cells and nuclear factor (NF)-κB signalling in lymphoma cell lines.

2.2 Pharmacokinetics and Drug Interactions

2.2.1 Idelalisib

Following oral administration of a single dose of idelalisib in the fasted state, the median time to maximum concentration (t_{max}) is observed at 1.5 h. Administration of idelalisib with a high-fat meal increases its exposure (area under the concentration–time curve [AUC]) 1.4-fold. Idelalisib is metabolised to its major metabolite GS-563117 via aldehyde oxidase and cytochrome P450 (CYP) 3A, the metabolite being inactive. Idelalisib also undergoes minor metabolism by UDP glucuronyltransferase (UGT) 1A4. Its terminal elimination half-life is 8.2 h.

Idelalisib exposure is unaffected by age, sex, race or body weight. Its pharmacokinetics in a paediatric population have not been studied. Clinical studies show that idelalisib exposure is unaffected by severe renal impairment but its AUC is increased up to 1.7-fold in subjects with mild hepatic impairment. Patients with baseline hepatic impairment should be monitored for signs of idelalisib toxicity and its dose modified as appropriate.

Rifampicin, a strong inducer of CYP3A4 and P-glycoprotein (P-gp), decreased the geometric mean idelalisib AUC by 75% and the geometric mean maximum concentration (C_{max}) by 58%. Ketoconazole (a strong CYP3A4 and P-gp inhibitor) increased the geometric mean AUC of idelalisib by 1.8-fold without any change in the geometric mean C_{max}. It is therefore recommended that coadministration of idelalisib be avoided with strong CYP3A4 and P-gp inducers and that patients taking concomitant CYP3A inhibitors should be monitored for signs of idelalisib toxicity and its dose modified as appropriate.

In vitro studies have shown that idelalisib inhibits CYP2C8, CYP2C19, CYP3A and UGT1A1 and induces CYP2B6, whereas GS-563117 inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A and UGT1A1. Clinically, idelalisib is a strong inhibitor of CYP3A4; it increased the geometric mean midazolam C_{max} by 2.4-fold and the geometric mean AUC by 5.4-fold. Therefore, coadministration of idelalisib with CYP3A-sensitive substrates should be avoided. Indeed, there is a post-marketing report of severe diazepam-induced altered mental status and respiratory failure resulting in hospitalisation following coadministration of diazepam (a CYP3A4 substrate) with idelalisib; this resolved on stopping both drugs and the patient tolerated a combination of lorazepam (not a CYP3A4 substrate) and idelalisib [39]. Clinical studies have not revealed any significant effect on pharmacokinetics of rosuvastatin (an organic-anion-transporting polypeptide [OATP] 1B1 and OATP1B3 substrate) or digoxin (a P-gp substrate).

2.2.2 Copanlisib

More than 90% of copanlisib metabolism is mediated by CYP3A and < 10% by CYP1A1. Its terminal elimination half-life is 39.1 (range 14.6–82.4) h. The M-1 metabolite of copanlisib accounts for 5% of total radioactivity AUC and its pharmacological activity against PI3Kα and PI3Kδ is comparable with that of the parent compound. Pharmacokinetics of copanlisib are not affected to any clinically significant extent by age, sex, race, smoking status, body weight, mild hepatic impairment or mild to moderate renal impairment. The pharmacokinetics of copanlisib in patients with moderate to severe hepatic impairment, severe renal impairment or end-stage renal disease with or without dialysis have not been studied.

Since copanlisib is principally metabolised by CYP3A4, it is recommended that the use of copanlisib be avoided in combination with strong CYP3A4 inducers or inhibitors. Concomitant use of copanlisib with such agents has been shown to decrease or increase, respectively, copanlisib AUC and C_{max} values. If concurrent use of a CYP3A4 inhibitor cannot be avoided, either the dose of copanlisib must be reduced or the patient carefully monitored for toxicity.

Copanlisib does not inhibit any of the major CYP isoforms, UGT, dihydropyrimidine dehydrogenase (DPD), P-gp or various transporters at therapeutic concentrations. Neither does it induce CYP1A2, CYP2B6 and CYP3A.

3 Serious and Life-Threatening Adverse Effects

Although PI3K inhibitors are associated with a whole range of frequent adverse effects such as nausea, vomiting, fatigue, cough, fever, headache and anorexia, these are not usually serious or severe enough to discontinue therapy. Clinically, they are easily managed and are not discussed in this review. We discuss here only the serious adverse effects that present clinical challenges associated with these agents.

Serious adverse reactions were reported in 65 (59%) patients treated with idelalisib plus rituximab. The most frequent serious adverse reactions reported for patients treated with idelalisib plus rituximab were pneumonia (23%), diarrhoea (10%), pyrexia (9%), sepsis (8%), and febrile neutropenia (5%). Adverse reactions that led to discontinuation of idelalisib occurred in 19 (17%) patients. The most common adverse reactions that led to treatment discontinuations were hepatotoxicity and diarrhoea/colitis. 42 (38%) patients had dose interruptions and 16 (15%) patients had dose reductions due to adverse reactions or laboratory abnormalities. The most common reasons for dose interruptions or reductions were pneumonia, diarrhoea, colitis, rash and elevated transaminases.

In pre-approval clinical trials, serious adverse reactions were reported in 44 (26%) patients treated with copanlisib. Adverse reactions resulted in dose reduction in 36 (21%) and discontinuation in 27 (16%) patients receiving copanlisib. The most common reasons for drug discontinuation were pneumonitis (2%) and hyperglycaemia (2%).

Considering that idelalisib is a selective inhibitor of PI3Kδ and copanlisib is a selective inhibitor of PI3Kδ and PI3Kα isoforms, serious adverse effects induced by these two PI3K inhibitors can be conveniently divided into those that are likely class-related to PI3Kδ inhibition and those that are more drug-specific. These are discussed in Sects. 3.1 and 3.2 as reported in association with the two currently approved PI3K inhibitors.

3.1 Class-Related Effects

As a class, both idelalisib and copanlisib are associated with serious dermatological, myelosuppressive, metabolic, gastrointestinal and respiratory adverse effects. Unlike p110α and p110β, which are ubiquitously expressed, p110δ is mainly expressed in leukocytes and therefore, the PI3Kδ pathway and its inhibitors have attracted much attention for their likely involvement in immune disorders. As stated in Sect. 1, inhibition of PI3Kδ leads to activation of immune response [16, 17], which is believed to account for some of the adverse reactions to these agents, especially the PI3Kδ-selective idelalisib [12]. Idelalisib-induced colitis, hepatitis and pneumonitis are believed to be immune-mediated effects [12, 17, 38, 40, 41]. These effects are more frequently observed in first-line patients who are more immunocompetent, are associated with T cell infiltrates and can often be treated by administration of corticosteroids. One review reported data showing higher incidences of idelalisib-induced diarrhoea, pneumonitis and raised hepatic transaminases in previously untreated patients than in those who were previously treated [42], the former group being immunocompetent. Neither is it surprising that the pattern of idelalisib-induced immune-mediated toxicity is similar to that of checkpoint-blocking antibodies [43, 44]. The FDA-approved label of idelalisib includes a detailed black box warning concerning its potential for "Fatal and Serious toxicities: Hepatic, severe diarrhoea, colitis, pneumonitis, infections and intestinal perforations".

3.1.1 Dermatological Reactions

Fatal cases of Stevens–ohnson syndrome and toxic epidermal necrolysis have occurred in patients treated with idelalisib. If either of these effects is confirmed to be due to idelalisib, treatment with idelalisib should be permanently discontinued. Other severe or life-threatening (grade ≥ 3) cutaneous reactions have been reported in 25% of idelalisib-treated patients and have included exfoliative dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, pruritic rash and exfoliative rash.

Grades 3 and 4 cutaneous reactions occurred in 2.8% and 0.6%, respectively, of 317 patients treated with copanlisib monotherapy. Serious cutaneous adverse events were reported in 0.9%. The reported events included exfoliative dermatitis, exfoliative rash, pruritus and rash (including maculopapular rash).

3.1.2 Myelosuppression and Infections

Treatment-emergent grade 3 or 4 neutropenia occurred in 25% of patients treated with idelalisib monotherapy and 58% of patients treated with idelalisib in combination with rituximab or with unapproved combination therapies. Thrombocytopenia and anaemia have also been reported as laboratory abnormalities in about 27% (all grades) of patients treated with idelalisib. Fatal and/or serious infections occurred in 21% of patients treated with idelalisib monotherapy and 48% of patients treated with idelalisib in combination with rituximab or with unapproved combination therapies. The most common infections were pneumonia, sepsis and febrile neutropenia. Upper respiratory tract infections were reported in 12% of the 146 patients receiving idelalisib monotherapy.

Following copanlisib monotherapy, grade ≥ 3 neutropenia occurred in 24% of 317 patients. Serious neutropenic events occurred in 1.3%. In 168 patients treated with copanlisib, leukopenia, neutropenia (including febrile neutropenia) and thrombocytopenia of any grade were reported in 36, 32 and 22%, respectively. The corresponding figures for grade ≥ 3 events were 27, 25 and 8%, respectively. Serious, including fatal, infections occurred in 19% of 317 patients treated with copanlisib monotherapy. The most common serious infection was pneumonia.

3.1.3 Metabolic Effects

Both idelalisib and copanlisib are reported to cause hyperglycaemia and hypertriglyceridaemia, although copanlisib is by far the more potent in this respect.

Idelalisib plus rituximab was associated with hyperglycaemia (all grade) in 54% of 110 patients compared with 46% of 108 patients who received placebo plus rituximab. This small difference between the frequencies in the two arms suggests that idelalisib has a low potential for inducing hyperglycaemia. The corresponding frequencies for hypertriglyceridaemia in the two treatment arms were 56% and 34%, respectively.

Due to the central role of PI3Kα in regulating glucose homeostasis, PI3K inhibition in patients often gives rise to hyperglycaemia and/or hyperinsulinaemia. Not surprisingly, grade 3 or 4 hyperglycaemia occurred in 41% of 317 patients treated with copanlisib monotherapy. Serious hyperglycaemic events occurred in 2.8% of patients. Blood glucose levels typically peaked 5–8 h post-infusion and subsequently declined to baseline levels in majority of the patients; however, blood glucose levels had remained elevated in 17.7% of patients 1 day after copanlisib infusion. Of the 155 patients with baseline glycosylated haemoglobin (HbA_{1c}) < 5.7%, 16 (10%) patients had HbA_{1c} > 6.5% at the end of treatment. Of the 20 patients with diabetes mellitus (treated with copanlisib in one of the studies), seven developed grade 4 hyperglycaemia and two discontinued treatment as a result. Therefore, it is recommended that patients with diabetes mellitus should only be treated with copanlisib following

adequate glucose control and should be monitored closely. In 168 patients receiving copanlisib monotherapy, hypertriglyceridaemia was reported in 58% (any grade) and 5% (grade ≥ 3).

3.1.4 Gastrointestinal Reactions

Among the serious gastrointestinal reactions, the most troublesome clinically are diarrhoea, colitis and stomatitis.

In 146 patients treated with idelalisib monotherapy, diarrhoea was reported in 47% (any grade). Severe diarrhoea or colitis (grade 3 or higher) occurred in 14% of patients treated with idelalisib monotherapy and 20% of patients treated with idelalisib in combination with rituximab or with unapproved combination therapies. Diarrhoea can occur at any time and responds poorly to antimotility agents. Among idelalisib-treated patients who reported diarrhoea or colitis, the median time to onset of any grade diarrhoea or colitis was 1.9 months (range 0.0–29.8 months), of grade 1 or 2 was 1.5 months (range 0.0–15.2 months) and of grades 3 or 4 was 7.1 months (range 0.5–29.8 months). Median time to resolution ranged between 1 week and 1 month across trials following interruption of idelalisib therapy and, in some instances, use of corticosteroids. Stomatitis was reported in 6% of 110 patients treated with idelalisib plus rituximab and 1% of 108 patients treated with placebo plus rituximab. The FDA-approved label carries a black box warning explicitly warning that "fatal and/or serious and severe diarrhoea or colitis occurred in 14% to 20% of idelalisib-treated patients".

Histologically, the colon biopsies in all 11 cases reported by Louie et al. [45] showed some degree of apoptosis within crypts, with five cases showing moderate to severe apoptosis involving the majority of the crypts with loss of goblet cells. In another study of 50 patients, 23 (46%) patients experienced diarrhoea during treatment with idelalisib, including eight with severe symptoms (≥ 7 stools/day above baseline and/or requiring hospitalization) [46]. 14 patients underwent colonoscopic examination with mucosal biopsy. 12 (86%) of these had colitis characterised by intraepithelial lymphocytosis, crypt cell apoptosis and neutrophilic infiltration of crypt epithelium. Eleven patients had symptoms severe enough to warrant drug withdrawal, including nine who were also treated with corticosteroids. Hammami et al. [47] have reported the case of a 56-year-old male who developed severe diarrhoea with a skin eruption mimicking graft-versus-host disease 6 months after starting idelalisib. Colonoscopy revealed normal colon and terminal ileum and biopsies showed mild active ileitis, colitis and proctitis with frequent epithelial apoptosis. Recently, Yeung et al. [48] reported evidence of T cell dysregulation and a substantial infectious component in association with idelalisib-related diarrhoea/colitis.

With regard to idelalisib and the toxic effects listed in the black box of the FDA label, an expert panel has provided guidance on management of these toxic effects [43]. Interestingly, this panel concluded that there are two types of diarrhoea observed in idelalisib clinical trials. The first type of diarrhoea tended to be self-limiting. This type generally occurs within the first 8 weeks and is typically mild or moderate (grades 1–2) and responsive to common antidiarrheal agents. The second type of diarrhoea tends to occur relatively late (although a few cases happened early) and responds poorly to antidiarrheal or empiric antimicrobial therapy. This second type of diarrhoea is most likely related to idelalisib-induced colitis. Recently, de Weerdt et al. [42] have also provided recommendations for the management of idelalisib-induced adverse respiratory and hepatic effects.

In 168 patients treated with copanlisib monotherapy, diarrhoea was reported in 36% (any grade) and 5% (grade ≥ 3) of patients. The corresponding frequencies for stomatitis were 14% and 2%, respectively. Colitis does not seem to have been a problem associated with copanlisib during clinical trials.

3.1.5 Pneumonitis

Fatal and serious pneumonitis has been reported in patients treated with idelalisib. Pneumonia (including non-infectious pneumonitis) was reported in 25% (any grade) and 16% (grade ≥ 3) of 146 patients treated with idelalisib monotherapy. In randomised clinical trials of combination therapies, pneumonitis (manifested by interstitial infiltrates and organising pneumonia) occurred in 4% of patients treated with idelalisib compared with 1% on the comparator arms. Time to onset of pneumonitis ranged from < 1 to 15 months. Patients with pneumonitis thought to be caused by idelalisib have been treated by discontinuing idelalisib and administration of corticosteroids.

Haustraete et al. [49] have reported five patients with idelalisib-induced pneumonitis. All patients complained of cough, dyspnoea and fever. Four had progression of their clinical symptoms over 3–9 weeks, whereas one had progression over 5 days. Four patients had crackles on physical examination and one had a normal examination. A lung computed tomography scan showed diffuse ground-glass opacities ($n = 3$), consolidations ($n = 2$), diffuse micronodules ($n = 1$) and pleural effusions ($n = 2$). Three of the patients had a bronchoalveolar lavage. Lymphocytic alveolitis was found in two patients (mean lymphocyte proportion 71 ± 5%), whereas one patient had neutrophilic alveolitis (77% neutrophils, 1% lymphocytes). Broad-spectrum antibiotics were ineffective in all five patients. Idelalisib was stopped in all patients and four received corticosteroids. Among patients who received corticosteroids, three had a resolution of pneumonitis and one patient died 12 days after admission due to multi-organ failure. The patient who was

not treated with corticosteroids had a favourable outcome after the interruption of idelalisib.

Non-infectious pneumonitis occurred in 5% of 317 patients treated with copanlisib monotherapy. Its features included pulmonary symptoms such as cough, dyspnoea, hypoxia or interstitial infiltrates on radiologic examination. These patients have been managed by withholding copanlisib and administration of systemic corticosteroids.

3.2 Agent-Specific Adverse Effects

Each of the two PI3K inhibitors currently approved is also associated with specific additional adverse effects that are not shared by the other member in the class.

3.2.1 Hepatotoxicity

Idelalisib is reported to induce anaphylaxis, hepatotoxicity, intestinal perforation and hyponatraemia. Idelalisib is contraindicated in patients who have a history of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis. Fatal and/or serious hepatotoxicity occurred in 18% of patients treated with idelalisib monotherapy and 16% of patients treated with idelalisib in combination with rituximab or with unapproved combination therapies. Elevations in ALT or AST greater than 5 times the upper limit of normal were reported and these findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. Therefore, it is recommended that patients should be monitored for hepatic function prior to and during treatment. Rates of recurrent toxicity were lower in patients taking corticosteroids when idelalisib was re-initiated. The advice is to discontinue idelalisib for recurrent hepatic injury or hepatotoxicity. The reader is referred to a review of idelalisib-induced hepatotoxicity for further details of the mechanisms and histological changes involved [41]. Fatal and serious intestinal perforation occurred in idelalisib-treated patients. At the time of perforation, some patients had moderate to severe diarrhoea. As stated earlier, the FDA-approved label of idelalisib includes a black box warning on its potential for hepatotoxicity and intestinal perforation.

In clinical trials with copanlisib, 20–30% of the patients experienced elevations of serum transaminases but there were no cases of clinically relevant hepatic injury [50].

3.2.2 Hypertension

Copanlisib has some activity at PI3Ky, an isoform which has been implicated in blood pressure (BP) homeostasis [12, 15]. Not surprisingly, copanlisib monotherapy induced grade 3 hypertension in 26% of 317 patients treated. Serious hypertensive events occurred in 0.9% of 317 patients. The mean change of systolic and diastolic BP from baseline to 2 h post-infusion on day 1 of cycle 1 was 16.8 and 7.8 mmHg, respectively. The mean BP started decreasing approximately 2 h post-infusion; BP remained elevated for 6–8 h after the start of infusion. It is recommended that optimal BP control should be achieved before starting each infusion and BP should be monitored pre- and during infusion. Depending on the severity and persistence of hypertension, therapy with copanlisib should be withheld, the dose reduced or treatment discontinued. Raised serum levels of lipase and uric acid and hypophosphataemia were reported as laboratory abnormalities in 21, 25 and 44%, respectively, of 168 patients treated with copanlisib monotherapy.

3.2.3 Cardiac Effects Including QT Interval Prolongation

Across clinical trials with copanlisib, there were other cardiac adverse effects, including atrial fibrillation (1.8%), tachycardia, bradycardia and arrhythmia (0.06%). There was one patient with an event of syncope, but was not associated with QT interval prolongation.

In patients with indolent non-Hodgkin's lymphoma, no patients had a QTcB (QT correction with Bazett formula) or QTcF (QT correction with Fridericia formula) > 500 ms. At subsequent visits during treatment, four of 137 patients (2.9%) and two of 118 patients (1.7%) had a QTcB and QTcF > 500 ms, respectively. Further, nine of 137 patients (6.6%) and two of 118 (1.7%) had a QTcB and QTcF > 480–500 ms, respectively. Three patients (2.2%) experienced a QTcB increase ≥ 60 ms and five patients (4.2%) had a QTcF ≥ 60 ms. It should be noted that copanlisib inhibits the PI3Kα isoform and PI3Kα inhibition is potentially arrhythmogenic [51]. The FDA has therefore required a post-marketing commitment from the sponsor to complete and submit results of a study to determine the effect of copanlisib on QT/corrected QT (QTc) interval in subjects with advanced solid tumours and non-Hodgkin's lymphoma.

In a partially blinded, randomised, placebo- and positive-controlled crossover study, conducted in 46 healthy volunteers to evaluate the effect of idelalisib on the QT/QTc interval, no significant QTc interval prolongation was observed at idelalisib doses of 150 or 400 mg. Neither was there any concentration–QT response relationship.

4 Post-Marketing Safety of Idelalisib

Table 1 provides a summary of selected adverse events associated with idelalisib contained in EMA's EudraVigilance Database of spontaneous reports. It is stressed that in

compiling this table, these reports have not been validated or evaluated for causality but, nevertheless, the table provides a perspective of the safety of idelalisib in the real world.

There were only handful of reports of hyponatraemia ($n = 5$), intestinal perforation ($n = 3$), anaphylaxis ($n = 1$), hyperglycaemia ($n = 1$) and hypertriglyceridaemia ($n = 1$). It appears from these spontaneous reports that the safety observed in clinical trials correlates and predicts the safety during routine clinical use of the drug.

Reports of atrial fibrillation in association with idelalisib were unexpected and their significance is unclear. Interestingly, ibrutinib (another small-molecule agent used to treat B cell lymphomas and leukaemias) and idelalisib share a number of common safety issues [42]. Ibrutinib has been associated with high rates of atrial fibrillation. As of July 2018, there were a total of 7344 reports of adverse events associated with ibrutinib in the EMA's EudraVigilance Database and, of these, 699 (9.5%) were of atrial fibrillation. In a pooled safety analysis of four randomised trials involving 756 ibrutinib-treated and 749 comparator-treated patients, O'Brien et al. [52] found that atrial fibrillation was reported in 6% of ibrutinib-treated versus 2% of comparator-treated patients; grade 3/4 atrial fibrillation occurred in 3% versus < 1%, respectively. In an earlier analysis by the same investigators, the incidence of ibrutinib-induced atrial fibrillation was 9% with a median time on ibrutinib of 46 months [53]. Thus, this potentially serious arrhythmia is unlikely to be identified during short-term clinical trials.

Table 1 Reporting rates of selected events related to idelalisib in the European Medicines Agency's EudraVigilance database as of 31 July 2018

Adverse event	Reporting rate [*n* (% of total reports)]
Total number of reports for the drug	1775
Diarrhoea	372 (21.0)
Colitis	140 (7.9)
Pneumonia	126 (7.1)
Neutropenia	119 (6.7)
Raised transaminases	87 (4.9)
Thrombocytopenia	38 2.1)
Hepatocellular injury	20 (1.1)
Hepatitis	15 (0.8)
Atrial fibrillation	14 (0.8)
Pruritus	14 (0.8)
Generalised exfoliative dermatitis	11 (0.6)
Stomatitis	9 (0.5)
Generalised rash	9 (0.5)
Stevens–Johnson syndrome	7 (0.4)

The search was limited to idelalisib because copanlisib has not yet been approved by the European Medicines Agency. The search strategy was focused on spontaneous reports of serious adverse events discussed in Sect. 3

There are other aspects of idelalisib safety that merit consideration. Furman et al. [54] reported very early on that the combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival (PFS), response rate and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy. Various reviews have also concluded that patients treated with single-agent therapies with PI3K inhibitors have lower efficacy outcomes than those treated with combination therapies [8, 38, 55]. For example, an international, multicentre, double-blind, placebo-controlled trial [56] in 416 adult patients with relapsed/refractory CLL requiring treatment for their disease randomised 207 patients to idelalisib and 209 to the placebo arm; both in combination with bendamustine and rituximab. The median PFS was 20.8 months in the idelalisib arm and 11.1 months in the placebo arm [56]. However, in March 2016, the FDA alerted healthcare professionals to reports of an increased rate of adverse events, including deaths, in clinical trials with idelalisib in combination with other cancer medicines [57]. The sponsor confirmed that they were stopping six clinical trials in patients with CLL, small lymphocytic lymphoma and indolent non-Hodgkin lymphomas. At the same time, the FDA emphasised that idelalisib is not approved for previously untreated CLL. In order to further mitigate the risks, the FDA recently required the sponsor of idelalisib to publish in six designated professional journals an information piece that included the risks of fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhoea or colitis, fatal and serious pneumonitis, and serious intestinal perforation associated with idelalisib treatment [58].

Since idelalisib-induced PI3Kδ inhibition leads to activation of immune response [16, 17], it is interesting to note that Novak et al. [59]. have reported a case of a heavily pretreated CLL patient with an atypically high immunoglobulin production who developed clinically significant immunoglobulin flare following idelalisib treatment. Interestingly, Castillo et al. [60] have also reported high incidence of idelalisib-induced hepatotoxicity in patients with Waldenström macroglobulinaemia. A recent study has also highlighted the potential of idelalisib to increase the risk of adverse effects of radiotherapy (strong grade 2 radiodermatitis and grade 3 mucositis) [61]. In December 2017, a safety review by Health Canada identified nine international reports of progressive multifocal leukoencephalopathy (PML) in patients treated with idelalisib [62]. In eight of the nine reports, the link between PML and the use of idelalisib was considered to be possible. The review of the literature suggested that a possible link may be explained by the actions of idelalisib on the immune system. However, other factors such as the type of cancer the patient had and the use of other medications

at the same time or in the recent past may have also played a role.

5 Later Generations of PI3K Inhibitors in the Pipeline

PI3K inhibitors have the potential to be a major therapeutic class of drugs in the treatment of various cancers, especially haematological malignancies. They have the potential to reverse resistance to a variety of anticancer therapies, including chemotherapy, radiotherapy, hormone therapy and targeted agents. Not surprisingly, there are no less than 50 PI3K inhibitors have been synthesised and are under investigation. Newer agents are more potent and have greater isoform-specific selective activity (second-generation inhibitors).

Among the many candidates either in the pipeline or discontinued are alpelisib (BYL719), apitolisib (GDC-0980), bimiralisib (PQR309), buparlisib (BKM120), dactolisib (BEZ235), dezapelisib (INCB040093), duvelisib (IPI-145), gedatolisib (PF-5212384), nemiralisib (GSK-2269557), omipalisib (GSK2126458), pictilisib (GDC-0941), pilaralisib (XL147 or SAR245408), serabelisib (INK-1117), sonolisib (PX-866), taselisib (GDC-0032), tenalisib (RP6530), umbralisib (TGR-1202) and voxtalisib (XL765 or SAR245409). These compounds display a range of activities, as shown in Table 2. The IC_{50} values for many of these novel inhibitors have been listed by other publications [14, 22, 34]. These agents are being investigated as monotherapy as well as in combination with other therapies.

These newer agents do not appear to be free from the major class-related serious adverse effects typically associated with currently available PI3K inhibitors. Table 3 summarises the overall adverse effects profiles, gathered from various sources, of some of these newer PI3K inhibitors. Many of these agents have been studied in early phase first-in-human studies and phase I/II clinical trials investigating their maximum tolerated doses, dose-limiting toxicities and early evidence of efficacy, often in combination with other chemotherapeutic agents. The study samples are often small and, therefore, the data on their safety profile should be considered only indicative of potential risks. Nevertheless, it is evident that these newer agents do not appear to have a particularly more favourable safety profile than their older counterparts; indeed, some of them appear to have a risk of unexpected adverse effects, such as renal failure and peripheral neuropathy, hitherto not associated with the two currently approved PI3K inhibitors (idelalisib or copanlisib). Consequently, the development of many of these new agents has been discontinued [33].

6 Future Challenges in the Development of PI3K Inhibitors

Given the efficacy and the pattern of serious adverse effects associated with PI3K inhibitors, both those approved and those in development, four clinical settings can be envisioned for their clinical use, with each setting requiring a careful assessment of the risks involved and potential benefits. When it comes to selecting an agent that targets the PI3K-mediated pathway, there are complex pharmacological considerations [22, 23].

Firstly, PI3K inhibitors could be used as monotherapy. However, although PI3K signalling is commonly activated in tumour cells, PI3K inhibitors have shown only modest therapeutic efficacy as monotherapy in solid tumours. Janku [9] has summarised efficacy and safety data on various PI3K inhibitors that have been investigated in haematological as well as solid tumours and concluded that challenges to the therapeutic effectiveness of some PI3K inhibitors include the absence of reliable and effective biomarkers, their limited efficacy as single agents, insufficient development of rational therapeutic combinations, the use of schedules with a broad spectrum of associated off-target adverse effects and suboptimal therapeutic exposures. Similarly, Lampson and Brown [38] have also reviewed efficacy and safety data on a number of PI3K inhibitors, focusing on agents with significant selectivity for PI3Kα and PI3Kδ that have entered clinical trials for the treatment of lymphoma. They concluded that while PI3K inhibitors, particularly those that target p110δ, have

Table 2 Primary pharmacological activity of selected new phosphatidylinositol-3-kinase inhibitors synthesised

Type of inhibitor	PI3K inhibitors synthesised
Pan–PI3K inhibitors	Buparlisib, pictilisib, pilaralisib, sonolisib
Isoform-selective inhibitors	Alpelisib and serabelisib (for PI3Kα)
	Dezapelisib, nemiralisib and umbralisib (for PI3Kδ)
	Duvelisib and tenalisib (for PI3Kδ and PI3Kγ)
	Taselisib (for PI3Kα, PI3Kδ and PI3Kγ)
Dual PI3K/mTOR inhibitors	Apitolisib, bimiralisib, dactolisib, gedatolisib, omipalisib, voxtalisib

mTOR mammalian target of rapamycin, *PI3K* phosphatidylinositol-3-kinase

Table 3 Safety profile of selected phosphatidylinositol-3-kinase inhibitors that are under development or discontinued

Drug name	Adverse events (% of study population)						Reference(s)
	Rash	Diarrhoea	Hepatic	Stomatitis	Hyperglycaemia	Other notable events	
Pan–PI3K inhibitors							
Buparlisib[a]	43	55	17	28	41	Depression (25)	[63]
	11	28	25		36	Anaemia (60)	[64]
						Thrombocytopenia (50)	
						Hypertriglyceridaemia (39)	
						Raised creatinine (26)	
						Depression (29)	
						Anxiety (25)	
						Agitation (7)	
	55	37	64	25	69	Hypercholesterolaemia (61)	[65]
						Depression (42)	
						Renal toxicity (42)	
						Anaemia (30)	
						Anxiety (21)	
						Hypertension (21)	
Pictilisib[a]	23	32		12			[66]
Pilaralisib[a]	26	20			7		[67]
	40	37	12		15		[68]
	18	41	27		23		[69]
Sonolisib	57	64	48	14			[70]
Isoform-selective PI3K inhibitors							
Alpelisib	45	80	20	10	55		[71]
	43	40		20	69		[72]
Duvelisib	30	42	39			Neutropenia (39)	[73]
						Thrombocytopenia (23)	
						Colitis (6)	
						Pneumonitis (4)	
	23	31	57			Neutropenia (20)	[74]
						Raised creatinine (17)	
	42	55	58	16		Neutropenia (39)	[75]
						Thrombocytopenia (19)	
Taselisib	18	44		29	38	Pneumonitis (3)[b]	[76]
						Renal failure (3)[b]	
						Colitis (6)	
						Peripheral neuropathy (6)	
	56	44		44			[77]
Dual PI3K/mTOR inhibitors							
Apitolisib[a]	51	59	11	26	25	Pneumonitis (12)	[78]
	55	41		26	57		[79]
Bimiralisib	46	54	14	11	86	Hypertension (32)	[80]
						Pruritus (29)	
						Range of neuropsychiatric effects	

Table 3 (continued)

Drug name	Adverse events (% of study population)						Reference(s)
	Rash	Diarrhoea	Hepatic	Stomatitis	Hyperglycaemia	Other notable events	
Dactolisib[a]	20	90	30	50	50	Raised lipase (40) Hypertriglyceridaemia (20) Peripheral neuropathy (10) Hyperuricaemia (10)	[81]
	40	45	5	30	5	Renal failure (10)	[82]
	21	74	32	42	21	Arthralgia (32) Acute renal failure (26) Thrombocytopenia (26)	[83]
Gedatolisib	14	14	12	55	26	Hypertriglyceridaemia (10)	[84]
	23	38		20	18	Hypertension (8)[b]	[85]
Voxtalisib[a]	6	22	19		13	Cataracts (3)	[86]
	20	24	13			Thrombocytopenia (26) Convulsions (22) Neutropenia (11)	[87]
	28	37	19		63	Thrombocytopenia (20) Neutropenia (13)	[88]

Blank cells denote absence of information in the published report

mTOR mammalian target of rapamycin, *PI3K* phosphatidylinositol-3-kinase

[a]Development discontinued (for details, see Rodon and Tabernero [33])

[b]Grade ≥ 3 (all other values refer to events of any grade)

robust efficacy, their clinical use is limited by their infectious and autoimmune toxicities.

Secondly, these drugs can assist in managing resistance to anticancer therapies. Activation or dysregulation of the class 1A PI3K signalling pathway has been found to be a major contributor to resistance against a diverse range of anticancer agents, including chemotherapy, radiotherapy, hormone therapy and targeted agents [25, 28–30, 89, 90]. Loss of PTEN is known to promote resistance to T cell-mediated immunotherapy [91]. PI3K inhibitors have the potential to restore sensitivity to other modalities of treatments when administered as part of combination regimens and, therefore, PI3K inhibition may be positioned as another important combination strategy [30, 31]. Cancer cells are very effective at resisting PI3K inhibition and can activate the PI3K pathway in many ways, thus limiting the power of specific PI3K pathway mutations in predicting drug sensitivity [23]. Also, inhibition of one isoform can be compensated by activation of another [92, 93]. Pan–class I PI3K inhibitors are less likely than isoform-selective class I PI3K inhibitors to allow compensation by other PI3K isoforms. Therefore, they may be expected to be more effective than isoform-selective inhibitors. However, because of their wider off-target effects, they are associated with serious adverse effects, precluding their long-term use. Early indications are that isoform-selective PI3Kα inhibitors may have a more favourable safety profile than pan–class I PI3K inhibitors but it is difficult to administer them in high enough doses for the desired efficacy. All in all, the relative merits of pan–class I versus isoform-selective class I PI3K inhibitors in the clinical setting remain unclear. As inhibition of PI3K upregulates or activates a number of tyrosine kinases, combination of targeted tyrosine kinase inhibitors with PI3K inhibitors is potentially another strategy to optimise antitumour effect. The challenge is to identify the most rational combinations with acceptable safety and tolerability.

PI3K inhibitors are also being studied in combination with other anticancer drugs from different pharmacologic classes, and a large number of these studies are in progress [26]. Breast cancer is an example where multiple mechanisms of resistance to endocrine therapy has led to investigations of combinations of a wide range of drugs [94]. Li et al. [95] have reported a meta-analysis of 46 randomised controlled trials which suggested that the addition of the PI3K pathway inhibitors to the therapy regiment for advanced solid tumours significantly improves PFS. Fulvestrant illustrates well the added-value of combination therapy. It is a selective estrogen receptor antagonist first approved by the FDA in April 2002 for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Subsequently, its indication was extended to include its combination with

palbociclib or abemaciclib following clinical trials demonstrating much improved efficacy of the combinations. More importantly, approximately 40% of HR-positive (HR+) advanced breast cancer patients have *PIK3CA* mutations, and the PI3K pathway is the most commonly mutated pathway associated with tumour progression in HR+ advanced breast cancer. Interestingly, Hoste et al. [96] recently reported a postmenopausal patient who was successfully treated with fulvestrant and alpelisib (a PI3Kα-selective agent with an IC_{50} of 5 nmol/L) following six lines of therapy. The tumour showed two uncommon *PIK3CA* mutations, and with the combination of alpelisib and fulvestrant the patient went from Eastern Cooperative Oncology Group (ECOG) grade 3 before the start of this therapy to ECOG grade 1 during treatment until progressive disease after 6 months. This combination has been studied in a large phase III (SOLAR-1) trial [97] and recently announced results from this trial have indicated that the combination of fulvestrant and alpelisib almost doubled the median PFS in patients with *PIK3CA*-mutated HR+/HER2-advanced breast cancer compared with fulvestrant alone [98]. Whilst these efficacy results demonstrating the value of combination therapy are welcome, it is noted that in the same study, the combination was associated with much higher incidences of hyperglycaemia, diarrhoea and skin reactions as well as higher incidence of treatment discontinuation. PI3Kα-specific inhibitors, including alpelisib, are associated with high frequency of diarrhoea and hyperglycaemia [71, 99] and PI3Kα inhibition is potentially arrhythmogenic [51]. SANDPIPER was a similar randomised, double-blind phase III study [100] investigating fulvestrant plus placebo versus the combination of fulvestrant with taselisib (a PI3K inhibitor with IC_{50} values of 0.29/0.12/0.97 nmol/L for PI3Kα/δ/γ). In this study, after randomisation of 516 patients, efficacy was modest but the most common grade ≥3 adverse events in the combination arm were diarrhoea (12%), hyperglycaemia (10%), colitis (3%) and stomatitis (2%). Adverse events led to more taselisib discontinuations (17% vs. 2%) and dose reductions (37% vs. 2%) than placebo [100]. The development of this combination has been discontinued [101].

Finally, in terms of improving clinical response and increasing overall survival, new immunotherapy agents that target the cytotoxic T lymphocyte-associated antigen (CTLA) 4 or programmed cell death (PD) 1 inhibitory receptors on T cells, or PD1 ligands on tumour cells have been very effective [102–104]. However, so far, only select patient populations benefit from this form of immunotherapy. Recent findings indicate that PI3K inhibitors could also be used to target the immune system as well as the cancer stroma (non-cancerous cells that also form the tumour mass), in particular the vasculature. Available data indicate that PI3Kδ inhibitors, such as idelalisib, have the potential to be used as cancer immunotherapeutic agents. It seems unlikely that monotherapy with PI3Kδ inhibitors will be sufficient as effective immunotherapy in order to eliminate the cancer. When used together with other immunotherapies or conventional therapies, PI3Kδ inhibitors may prove to be highly effective in promoting anticancer immune responses [17, 26, 105]. While combining PI3Kδ inhibitors with immunotherapy also seems attractive, recent non-clinical studies have demonstrated that that the immune response to different tumours can be highly distinct, which dictates their response to each therapeutic strategy [106]. The mechanisms by which PI3Kδ inhibition promotes antitumour immunity is distinct from that mediated by immune checkpoint blockade and this needs to be considered as PI3Kδ inhibitors are being developed for immunotherapy [106].

7 Conclusions

Knowledge of the PI3K isoforms and their distribution in tissue may help clinicians to anticipate toxicities. Notably, novel isoform-selective PI3K inhibitors have the potential for therapeutic efficacy with improved toxicity profiles compared with non-isoform-selective agents. However, there is no evidence at present to indicate that newer or more targeted PI3K inhibitors have any better safety profile. In addition, there are challenges to the therapeutic use and effectiveness of some PI3K inhibitors. Among others, these challenges include satisfactory management of a variety of serious adverse effects. More importantly, there are no validated biomarkers to identify patients who may respond satisfactorily to, or those who may be troubled by serious adverse effects of, PI3K inhibitors. Neither is there any current evidence of improved safety or efficacy as a result of two targets being combined in dual PI3K/mTOR inhibitors. Monotherapy with most PI3K inhibitors has now been shown to be of limited efficacy compared to their combination with other therapeutic modalities. Data from the SOLAR-1 trial, referred to in Sect. 6, provided evidence of greater benefit from alpelisib when combined with fulvestrant in molecularly selected metastatic breast cancer patients harbouring *PI3KCa* mutations on primary or metastatic tumours. However, combination of taselisib with fulvestrant was associated with unacceptable risks. Furthermore, reports of an increased rate of adverse events, including deaths, in clinical trials of idelalisib in combination with other cancer medicines (as alerted by the FDA in March 2016) are a matter of concern since they suggest that even combinations of PI3K inhibitors with other therapies may not be free of unacceptable hazards.

The clinical development of many PI3K inhibitors has been discontinued due to insufficient efficacy, problematic toxicities and the absence of biomarkers that correlate with clinical activity. There remain many questions on their

optimal use, including the choice of the most appropriate drug in specific cancer, the dosing schedules and possible rational combination strategies. The next step in the clinical development of PI3K inhibitors might be to focus on exploration of new dosing schedules that are better tolerated and more efficacious, the investigation of new rational combinations that overcome PI3K resistance or act in synergy, and the identification of predictive biomarkers of clinical activity. Arising from the toxicity profiles of novel PI3K inhibitors, it is also clear that while guidelines have been established for dealing with toxicities associated with idelalisib and copanlisib (that target PI3Kδ), there will arise a need for the development and wider dissemination of formal guidelines for identification and management of (additional) toxicities associated with these agents with different target selectivity and/or their novel combinations with agents in other pharmacologic classes.

Compliance with Ethical Standards

Ethical Standards This is a review of data in the public domain and the authors declare compliance with all ethical standards.

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