Idelalisib

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Contents

1 Introduction 244

2 Structure and Mechanisms of Action 246

3 Preclinical Data 247
3.1 Idelalisib in CLL 247
3.2 Idelalisib in other Hematological Malignancies 248

4 Clinical Data 249
4.1 Clinical Trials with Idelalisib 249
4.2 Idelalisib in CLL 249
4.3 Idelalisib in Relapsed Small Lymphocytic Lymphoma 252
4.4 Idelalisib in Relapsed Follicular Lymphoma 252
4.5 Idelalisib in Other Indolent and Aggressive B-Cell Lymphomas 253
4.6 Idelalisib in Merkel-Cell Carcinoma 254

5 Toxicity 255

6 Drug Interactions 256

7 Biomarkers 257

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8 Summary and Perspectives 258
References 259

Abstract

Idelalisib (GS-1101, CAL-101, Zydelig®) is an orally bioavailable, small-molecule inhibitor of the delta isoform (p110δ) of the enzyme phosphoinositide 3-kinase (PI3K). In contrast to the other PI3K isoforms, PI3Kδ is expressed selectively in hematopoietic cells. PI3Kδ signaling is active in many B-cell leukemias and lymphomas. By inhibiting the PI3Kδ protein, idelalisib blocks several cellular signaling pathways that maintain B-cell viability. Idelalisib is the first PI3K inhibitor approved by the US Food and Drug Administration (FDA). Treatment with idelalisib is indicated in relapsed/refractory chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and small lymphocytic lymphoma (SLL). This review presents the preclinical and clinical activity of idelalisib with a focus on clinical studies in CLL.

Keywords

Idelalisib · Kinase inhibitor · Chronic lymphocytic leukemia (CLL) · PI 3 Kinase

1 Introduction

The management of lymphoid malignancies has greatly evolved during the last decade with the advent of biological, more targeted therapies (Awan and Byrd 2014; Byrd et al. 2014a; Danilov 2013; Jahangiri et al. 2014; Jain and O'Brien 2016; Marini et al. 2017; Molica 2017; Morabito et al. 2015; Niemann et al. 2013; Sanford et al. 2015; Vitale et al. 2017). Since its initial description, the PI3K pathway has been an attractive target for anticancer therapy. The PI3K pathway seems to play an important role in the development of various solid malignancies, such as melanoma, lung, colorectal, and breast cancers (Janku 2017). More recently, the role of the PI3K pathway in the pathophysiology of hematological malignancies has been appreciated (Akinleye et al. 2013; Alinari et al. 2012; Brown 2016; Burger and Okkenhaug 2014; Fruman and Rommel 2011; Gilbert 2014; Gockeritz et al. 2015; Hewett et al. 2016; Macias-Perez and Flinn 2013; Okoli et al. 2015; Pongas and Cheson 2016; Seiler et al. 2016; Vanhaesebroeck and Khwaja 2014; Yap et al. 2015). CLL, a malignancy of mature B lymphocytes, remains the most prevalent leukemia in Western adult patients. Though the clinical outcome has improved considerably through the introduction of immunochemotherapy and presumably better supportive care, CLL treatment may be challenging, particularly as the incidence of CLL increases with age (Rai 2015; Ysebaert et al. 2015). Therefore, new treatment strategies to improve efficacy, survival rate, and safety profile are needed.

The B-cell receptor (BCR) signaling pathway plays a key role in the pathogenesis of CLL (Chiorazzi et al. 2005; Herishanu et al. 2011; ten Hacken and Burger 2016; Duhren-von Minden et al. 2012). BCR signaling is mediated in part by the activation of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ). The delta isoform is one of four catalytic isoforms (p110 α, β, γ, and δ) that differ in their tissue expression, with PI3Kδ being highly expressed in lymphoid cells (Okkenhaug and Vanhaesebroeck 2003) and acting as the most critical isoform for the malignant phenotype in CLL (Herman et al. 2010). It activates the serine–threonine kinases (AKT) and mammalian target of rapamycin (mTOR) and exerts multiple effects on cell metabolism, migration, survival, proliferation, and differentiation (Fig. 1) (Bodo et al. 2013; Hoellenriegel et al. 2011; Lannutti et al. 2011; Maffei et al. 2015; Puri and Gold 2012). Given the functional significance of the BCR, strategies to target BCR signaling have appeared as emerging therapeutic options (Arnason and Brown 2017; Choi and Kipps 2012; Fruman and Cantley 2014; Jerkeman et al. 2017; Jeyakumar and O'Brien 2016; Niemann and Wiestner 2013; Pula et al. 2017; ten Hacken and Burger 2014; Wiestner 2012; Wiestner

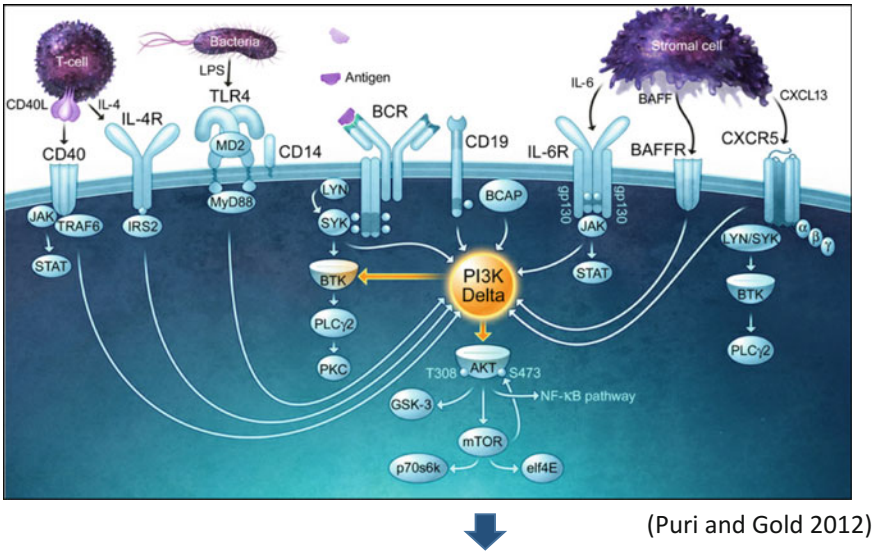

Fig. 1 Pathways utilizing PI3Kδ signaling. PI3Kδ is a central signaling enzyme that mediates the effects of multiple receptors on B cells. PI3Kδ signaling is important for B-cell survival, migration, and activation, functioning downstream of the B-cell antigen receptor (BCR) and its co-receptor CD19, chemokine receptors (CXCR5), and activation/co-stimulatory receptors such as CD40 and Toll-like receptors (TLRs). Cytokines derived from lymphoid stromal cells (BAFF, IL-6) and T cells (IL-4) that are essential for the expansion and survival of B-cells also require PI3Kδ for their actions and bind receptors that activate PI3Kδ. Akt is the major downstream target of PI3Kδ. Once phosphorylated, Akt is activated and in turn phosphorylates other downstream substrates, including mTOR (Puri and Gold 2012)

2014; Wiestner 2015). In fact, inhibitors of BCR signaling, especially those targeting the BCR-associated kinases SYK, BTK, and PI3Ks have shown promising clinical results (Sharman and Di Paolo 2016). Idelalisib (formerly called GS-1101 and CAL-101) is a potent, oral, selective small-molecule inhibitor of PI3Kδ. Idelalisib was approved by the US Food and Drug Administration in July 2014 for the treatment of relapsed CLL, in combination with rituximab, in patients who do not qualify for other chemotherapeutic agents, except rituximab monotherapy due to the presence of comorbidities. Idelalisib also received an accelerated approval for relapsed follicular lymphoma and small lymphocytic lymphoma after failing at least two systemic therapies (Markham 2014; Miller et al. 2015; Traynor 2014; Yang et al. 2015). The European Commission has also granted marketing authorization for idelalisib: (1) in combination with rituximab for the treatment of adult patients with CLL who received ≥ 1 prior therapy or as first-line treatment in the presence of a 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy and (2) as monotherapy in the treatment of adult patients with follicular lymphoma refractory to two prior lines of treatment. The safety profile of idelalisib appeared acceptable in patients with recurrent B-cell lymphomas treated for up to 4 years in the Phase I and II trials (Flinn et al. 2014; Gopal et al. 2014). The most frequent adverse events were diarrhea, nausea, fatigue, and pyrexia. As seen with other inhibitors of BCR signaling, in particular the BTK inhibitor ibrutinib and the SYK inhibitor fostamatinib, idelalisib induces transient lymphocytosis resulting from egress of CLL cells from the microenvironment. This peculiar lymphocytosis, also referred to as "leukemic flare," is not considered to signify disease progression any more (Cheson et al. 2012; Fiorcari et al. 2013). However, a series of upfront trials were terminated early because of an increased risk of fatal infections for patients randomized to combinations containing idelalisib. Idelalisib prescribing information includes now a black box warning for fatal and severe hepatotoxicity, diarrhea or colitis, pneumonitis, fatal and/or serious infections, and intestinal perforation. An understanding of these unusual toxicities, as well as good institutional policies for their management, will gain important as more PI3K inhibitors are approved and become incorporated into routine practice. Many clinical studies with idelalisib in hematological malignancies in different treatment lines and combinations are ongoing. Results are summarized in this review.

2 Structure and Mechanisms of Action

The chemical name for idelalisib is 5-fluoro-3-phenyl-2-[(1S)-1-(9*H*-purin-6-ylamino)-propyl]quinazolin-4(3*H*)-one (Fig. 2) (Somoza et al. 2015). It has a molecular formula of $C_{22}H_{18}FN_7O$ and a molecular weight of 415.42.

Idelalisib was initially developed by ICOS as a potential treatment of inflammatory diseases. Later on, Calistoga Pharmaceuticals and now Gilead Sciences (following its acquisition of Calistoga) performed preclinical testing and phase I clinical trials with a focus on the treatment of hematological cancers.

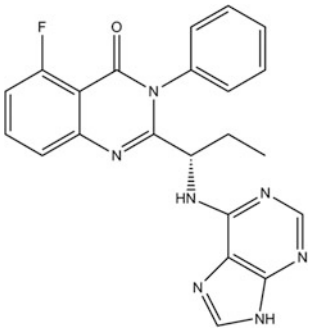

Fig. 2 Chemical structure of idelalisib (5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl] quinazolin-4(3H)-one) (Somoza et al. 2015)

In vitro, Idelalisib showed high potency against PI3Kδ with an IC_{50} value of 2.5 nM (Lannutti et al. 2011). In contrast, the IC_{50} values for PI3Kα, PI3Kβ, and PI3Kγ were 820, 565, and 89 nM, respectively (Lannutti et al. 2011). In cell-based assays, idelalisib blocked FcεRI p110δ-mediated CD63 expression in basophils with an EC_{50} of 8 nM, which was 240- to 2500-fold selective for PI3Kδ over the other class I PI3K isoforms. Idelalisib has a favorable pharmacokinetic profile with a plasma half-life of 8 h, and oral bioavailability of 39 and 79% in rats and dogs, respectively. Using tumor cell lines and primary patient samples representing multiple B-cell malignancies, idelalisib blocks the constitutive activation of the p110δ-dependent PI3K pathway, resulting in decreased phosphorylation of AKT and other downstream effectors.

3 Preclinical Data

3.1 Idelalisib in CLL

Ex vivo treatment of primary CLL cells with idelalisib in various concentrations established that

1. CLL cells express PI3Kδ in abundance at both gene and protein level;
2. idelalisib can induce apoptosis in CLL cells, although responses varied;
3. the induction of apoptosis was selective for CLL cells as compared with normal B cells or other hematopoietic cells;
4. the induction of apoptosis occurred independently of prognostic markers such as cytogenetic abnormality or immunoglobulin heavy chain variable region heavy chain *(IGHV)* mutational status;
5. the mechanism of action seemed to be associated with induction of apoptosis through caspase activation; and

6. CAL-101 antagonized CLL cell survival mechanisms by blocking the protective effect of CD40-ligand (CD40L) and microenvironment stimuli (Herman et al. 2010).

Further experimental studies suggested that idelalisib could overcome both bone marrow stromal cell- (BMSC-) and endothelial cell- (EC-) mediated CLL cell protection, indicating that idelalisib inhibits BMCS- and EC-derived pro-survival signals (Fiorcari et al. 2013). Furthermore, idelalisib can inhibit both the chemotaxis toward CXCL12 and CXCL13 and the migration beneath stroma cell layers, suggesting a potential mobilization effect (Hoellenriegel et al. 2011). Furthermore, idelalisib inhibits chemokine (such as CCL3 and CCL4) and cytokine (such as TNF and interleukin-6) secretion mediated by BCR stimulation or nurse-like cells. Concurrent with these findings, the sensitivity of CLL cells to other cytotoxic drugs (such as fludarabine and bendamustine) was increased (Hoellenriegel et al. 2011; Modi et al. 2017). Similarly, ex vivo data suggested that idelalisib could sensitize stroma-exposed CLL cells to other agents by inhibition of stroma-CLL contact, leading to an increase in mitochondrial apoptotic priming of CLL cells (Davids et al. 2012). In summary, these ex vivo data suggest that idelalisib may be beneficial in the treatment of CLL by directly inducing apoptosis and inhibiting microenvironmental interactions.

Combined inhibition of PI3Kδ by idelalisib and Syk by GS-9973 in primary peripheral blood and bone marrow CLL samples reduced CLL survival, synergistically induced growth inhibition, and further disrupted chemokine signaling at nanomolar concentrations, including in bone marrow derived and poor risk samples (Burke et al. 2014). These data suggest increased clinical activity by simultaneous targeting of these kinases.

3.2 Idelalisib in other Hematological Malignancies

Idelalisib yielded no activity against non-neoplastic mononuclear cells, but 26% of CLL and 23% of B-cell acute lymphoblastic leukemia samples were sensitive to idelalisib (Lannutti et al. 2011). In contrast, only 3% of acute myeloid leukemia and 0% of myeloproliferative neoplasm samples showed sensitivity to idelalisib, indicating that idelalisib has a greater therapeutic potential for lymphoid malignancies. In addition, idelalisib downregulated p-Akt expression in diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL) cell lines, and induced a several-fold increase in the levels of apoptotic markers, such as caspase 3 and poly(ADP-ribose) polymerase cleavage (Lannutti et al. 2011).

High levels of p110δ and p-Akt were also found in five out of five investigated Hodgkin lymphoma (HL) cell lines. Exposure to CAL-101 not only decreased levels of p110δ and p-Akt but also disrupted tumor microenvironment-mediated survival signals mediated by CCL5, CCL17, and CCL22 in co-cultures of HL cells and BMSCs (Meadows et al. 2012).

In plasma cell myeloma (PCM), in vitro experiments demonstrated that

1. All PCM cell lines were shown to express PI3Kδ;
2. Idelalisib was highly selective against p110δ-positive PCM cells by inducing caspase-dependent apoptosis in dose-dependent fashion but with minimal cytotoxicity in p110δ-negative cells;
3. Idelalisib inhibited the Akt phosphorylation in p110δ-positive PCM cells;
4. Idelalisib decreased PCM viability in the presence of BMSCs, and
5. Idelalisib had a synergistic effect with bortezomib, a proteasome inhibitor approved by the FDA for the treatment of PCM and MCL (Ikeda et al. 2010).

The PI3K pathway is known to be closely involved in BCR-ABL transformation and the tumorigenesis of chronic myeloid leukemia (CML), suggesting that PI3K may be a potential target for CML therapy. Idelalisib inhibited proliferation of K562 chronic myeloid leukemia cells and induced apoptosis with increased expression of pro-apoptotic molecules such as Bad and Bax, cleavage of caspase-9, -8, and -3, and PARP, in contrast to downregulation of anti-apoptotic protein Bcl-2 (Chen et al. 2016). In addition, combination of idelalisib with imatinib led to a synergistic anti-proliferative effect on K562 cells, together with enhanced activity of G1 arrest and apoptosis induction, suggesting potential application in CML therapy.

4 Clinical Data

4.1 Clinical Trials with Idelalisib

More than 50 clinical trials have been registered with idelalisib so far (http://www.clinicaltrials.gov). Currently, 20 trials are listed as active, the greater part of which are phase II and III trials in hematological malignancies (Table 1). Idelalisib has shown clinical activity and a tolerable safety profile in phase II and III trials.

4.2 Idelalisib in CLL

The initial efficacy of idelalisib in CLL was demonstrated in a phase I trial treating patients with relapsed or refractory CLL (Brown et al. 2014). Fifty-four patients with adverse characteristics, including bulky lymphadenopathy, extensive prior therapy, refractory disease, unmutated *IGVH*, and deletion of 17p or *TP53* mutations, were included. 81% of patients had a nodal response. Median progression-free survival (PFS) was 15.8 months, but at the recommended phase II dose of 150 mg twice a day or higher, it was 32 months. The most common grade 3 adverse events included pneumonia in 20% of patients and neutropenic fever in 11% of patients (Brown et al. 2014).

Table 1 Registered active interventional clinical trials (phase I–III) with idelalisib

Indication	Phase I	Phase I/II	Phase II	Phase III
B-cell hematological malignancies	3		1	
Indolent B-cell lymphoma (FL, SLL, LPL, MZL)			1	
FL, MCL	1			1
CLL, SLL			1	
CLL	2		2	4
FL				1
Waldenström's macroglobinaemia			1	
MCL		1		
NSCLC		1		

Reference: www.clinicaltrials.gov
FL follicular lymphoma, *MCL* mantle cell lymphoma, *SLL* small lymphocytic lymphoma, *LPL* lymphoplasmacytic lymphoma, *MZL* marginal zone lymphoma, *CLL* chronic lymphocytic leukemia, *NSCLC* non-small cell lung cancer

The approval of idelalisib in combination with rituximab for the treatment of patients with relapsed CLL was based on a randomized, double-blind, placebo-controlled phase III clinical trial (Furman et al. 2014). This clinical trial enrolled 220 patients with relapsed CLL who required treatment and were unable to tolerate standard chemo-immunotherapy due to coexisting medical conditions, reduced renal function or neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents. Patients received idelalisib plus rituximab or placebo plus rituximab until disease progression or unacceptable toxicity. The primary endpoint was PFS. As recommended by the data and safety monitoring board, the trial was stopped early at the pre-specified first interim analysis because of the positive results seen with idelalisib. At 24 weeks, the PFS rate was 93% in patients receiving idelalisib plus rituximab compared with 46% in patients receiving placebo plus rituximab. At 12 months, the overall survival (OS) rate in the idelalisib plus rituximab group (92%) was significantly higher than the OS rate in the placebo plus rituximab group (80%; HR for death, 0.28; 95% CI, 0.09–0.86; $p = 0.02$). In the idelalisib plus rituximab group, the overall response rate (ORR) was 81% compared with 13% in the placebo plus rituximab group ($p < 0.001$). All responses were partial responses (Furman et al. 2014).

Idelalisib treatment has been associated with a dramatic lymph node response, but eradication of disease and relapse in high-risk disease remain challenges. Idelalisib in combination with rituximab and bendamustine (idelalisib BR) as compared to rituximab and bendamustine (BR) was investigated in a randomized, phase III, placebo-controlled, double-blind trial, treating patients with relapsed or refractory CLL (Zelenetz et al. 2017). At a median follow-up of 14 months, the median PFS was 20.8 months in the idelalisib-containing arm and 11.1 months in the placebo arm ($p < 0.0001$). An increased risk of grade 3 or higher infections was

seen in the idelalisib-containing arm (39 vs. 25%). Updated efficacy data recently demonstrated that the combination of idelalisib BR had improved overall survival relative to BR (not reached vs. 41 months, $p = 0.036$) (Zelenetz et al. 2016).

The efficacy and safety of idelalisib in combination with the second-generation anti-CD20 antibody, ofatumumab, was investigated in a randomized phase 3 trial for previously treated CLL patients. The idelalisib plus ofatumumab combination resulted in better PFS compared with ofatumumab alone in patients with relapsed CLL (16.3 months vs. 8 months, adjusted hazard ratio (HR) 0.27, 95% CI 0.19–0.39, $p < 0.0001$), including in those with high-risk disease. Idelalisib in combination with ofatumumab might represent a new treatment alternative for this patient population (Jones et al. 2017).

Given the efficacy seen with idelalisib in patients with relapsed/refractory CLL, and the activity of rituximab in treatment-naive patients, a phase II open-label study of idelalisib in combination with rituximab in older patients with previously untreated CLL or small lymphocytic lymphoma was performed (O'Brien et al. 2015). The ORR was 97%, including 19% complete responses. The ORR was 100% in patients with del(17p)/*TP53* mutations and 97% in those with unmated *IGVH*. PFS was 83% at 36 months. The most frequent adverse events (any grade) were diarrhea (including colitis) (64%), rash (58%), pyrexia (42%), and nausea (38%). Elevated alanine transaminase/aspartate transaminase was seen in 67% of patients (23% grade >3). These data suggest that toxicity rates may be higher in the front-line setting. Concurrent with this, results from a phase II clinical trial of front-line idelalisib used in combination with the anti-CD20 monoclonal antibody ofatumumab indicated frequent occurrence of often severe immune-mediated transaminitis, potentially through inhibition of regulatory T cells (Lampson et al. 2016). In March 2016, Gilead closed seven randomized trials of idelalisib in B-cell malignancies (5 in treatment-naive patients) due to an excess of infectious deaths.

Several studies are actively evaluating idelalisib in CLL in combination with, e.g., Bcl-2 inhibitors, Btk inhibitors, CD19 or CD20 antibodies, or PD-1 inhibitors. These include a phase II investigation of idelalisib with the Bcl-2 inhibitor venetoclax for patients with CLL that have relapsed or are refractory to prior therapy with a BCR pathway inhibitor (NCT02141282). A phase II study to evaluate safety and preliminary efficacy of the Fc-enhanced CD19 antibody MOR00208 combined with idelalisib or venetoclax in adult patients with relapsed or refractory CLL or SLL pretreated with a BTK inhibitor (e.g., ibrutinib) as single agent or as part of combination therapy is also currently underway (NCT02639910). In addition, the combination of the BTK inhibitor tirabrutinib and idelalisib with or without obinutuzumab in adults with relapsed or refractory CLL is currently tested in a phase II study (NCT02968563).

Otlertuzumab (TRU-016) is a novel humanized anti-CD37 protein therapeutic. The safety and efficacy of otlertuzumab is currently evaluated in a Phase Ib trial when administered in combination with rituximab or obinutuzumab, in combination with idelalisib and rituximab, or in combination with ibrutinib in patients with CLL (NCT01644253). The PD-1 inhibitor pembrolizumab it currently explored alone or

with idelalisib or ibrutinib in patients with relapsed or refractory CLL or other low-grade B-cell lymphomas (NCT02332980).

4.3 Idelalisib in Relapsed Small Lymphocytic Lymphoma

Idelalisib is indicated for the treatment of patients with relapsed small lymphocytic lymphoma (SLL), the nodal form of CLL, who have received at least two prior systemic therapies. Accelerated approval was granted for this indication based on ORR. The safety and efficacy of idelalisib in patients with relapsed SLL were explicitly evaluated in the DELTA clinical trial (Gopal et al. 2014). Overall, 26 patients with relapsed SLL received 150 mg of idelalisib orally twice daily until evidence of disease progression or unacceptable toxicity. The study's primary end point was Independent Review Committee-assessed ORR. Among these 26 patients with relapsed SLL, the ORR was 58% (95% CI, 37–77%), and all responses were partial responses (Gopal et al. 2014). An improvement in survival or disease-related symptoms has not yet been established for idelalisib in relapsed SLL.

4.4 Idelalisib in Relapsed Follicular Lymphoma

In relapsed follicular lymphoma (FL), idelalisib was approved under the accelerated approval program based on ORR data. Idelalisib is indicated for the treatment of patients with relapsed FL who received at least two prior systemic therapies.

The safety and efficacy of idelalisib in patients with relapsed FL were evaluated in the DELTA clinical trial, a single-arm, multicenter clinical trial that included 72 patients with relapsed FL who had received at least two prior treatments (Gopal et al. 2014). The primary endpoint was Independent Review Committee-assessed ORR. Among the 72 patients with relapsed FL who received idelalisib, the ORR was 54% (95% CI, 42–66%), including 6 complete responses (8%) and 33 partial responses (46%).

To better characterize the efficacy and safety of idelalisib treatment for patients with refractory FL, a subsequent subgroup analysis of patients enrolled in this study was performed (Salles et al. 2017). The ORR was 55.6% (n = 40/72; 95% CI 43.4–67.3; $p < 0.001$ for testing against the null hypothesis) in patients with FL overall and did not differ when stratified by FL grade. Idelalisib was effective across evaluated patient categories, regardless of the number of prior therapies, refractoriness to previous regimens, bulky disease, and age. Median PFS with idelalisib was 11.0 months (95% CI, 8.0–14.0) overall. At the time of data cutoff, median OS had not been reached. At 24 months, OS was estimated to be 69.8%, and all patients achieving a CR had survived. In these heavily pretreated patients with relapsed/refractory FL, idelalisib monotherapy demonstrated an acceptable and manageable safety profile. Diarrhea, colitis, and transaminase elevations were generally manageable with dose interruption/reduction or drug discontinuation. In

conclusion, these data suggest that patients with high-risk FL may benefit from a targeted therapy such as idelalisib (Salles et al. 2017).

Similarly, a multicenter UK-wide compassionate use program evaluating the efficacy of idelalisib monotherapy in relapsed, refractory FL (n = 79), showed an ORR of 57% (CR/unconfirmed CR 15%; PR 42%) in 65 assessable cases. The median PFS was 7.1 months (95% CI 5.0–9.1 months) and median OS was not reached. This is the only real-world series outlining the efficacy and survival of idelalisib-treated relapsed and refractory FL (Eyre et al. 2017).

Idelalisib treatment in patients with high-risk follicular lymphoma and early relapse after initial chemo-immunotherapy induced an ORR of 56.8% (21 out of 37) with 5 complete responses (13.5%) and 16 partial responses (43.2%). These results are the first to describe the efficacy and safety of idelalisib in patients with FL relapsing early following first-line chemo-immunotherapy and suggest that idelalisib may provide a viable therapeutic option for patients with double-refractory FL with early relapse after initial therapy (Gopal et al. 2017b).

4.5 Idelalisib in Other Indolent and Aggressive B-Cell Lymphomas

The efficacy of idelalisib monotherapy was first reported in a phase I dose-ranging study of 64 patients with previously treated indolent B-cell lymphomas (FL n = 38; SLL n = 11; marginal zone lymphoma (MZL) n = 6; lymphoplasmacytic lymphoma (LPL) n = 9) (Flinn et al. 2014). Patients had received a median of 4 prior therapies, and 58% were refractory to the last prior therapy. The ORR was 47% (n = 30) in the total study population and 59% in patients treated with continuous higher doses. Responding patients had a rapid reduction in lymphadenopathy with a median time to response of 1.3 months. Because the median PFS was longer in patients treated with higher dose continuous therapy (16.8 months; range: 1–37 months) than in patients receiving lower doses or intermittent therapy (3.7 months; range: 0.5–33 months), idelalisib doses of >150 mg twice daily were identified for further study.

In a phase I study of idelalisib in patients with relapsed and refractory MCL, the ORR was 16 of 40 patients (40%), with CR in 2 of 40 patients (5%). Median DOR was 2.7 months, and 1-year PFS was 22%, providing proof of concept that targeting PI3Kd is a viable strategy in MCL (Kahl et al. 2014).

To evaluate the safety and activity of idelalisib in combination with immunotherapy, chemotherapy, or both, 79 patients with relapsed/refractory indolent B-cell lymphoma were enrolled in a phase I study in three treatment groups based on investigators preference: (1) idelalisib + rituximab, (2) idelalisib + bendamustine, or (3) idelalisib + rituximab + bendamustine (de Vos et al. 2016). Lymphoma subtypes included FL (59 patients, 74.7%), SLL (15 patients, 19.0%), and MZL (5 patients, 6.3%). The ORR for the idelalisib + rituximab, idelalisib + bendamustine, and idelalisib + rituximab + bendamustine groups were 75, 88, and 79%, respectively. The median PFS was 37.1 months overall:

29.7 months for idelalisib + rituximab, 32.8 for idelalisib and bendamustine, and 37.1 months for idelalisib + rituximab + bendamustine. The most common grade ≥ 3 adverse events and laboratory abnormalities were neutropenia (41%), pneumonia (19%), transaminase elevations (16%), diarrhea/colitis (15%), and rash (9%). The safety and efficacy reflected in these early data, however, stand in contrast with later observations of significant toxicity in subsequent phase 3 trials in frontline CLL and less heavily pretreated indolent B-cell lymphoma patients. These findings highlight the limitations of phase I trial data in the assessment of new regimens. Therefore, the safety of novel combinations should be proven in phase III trials before adoption in clinical practice.

Similarly, a phase II study evaluating the safety and effectivity of the combination of idelalisib and the Syk inhibitor entospletinib in patients with relapsed or refractory CLL or non-Hodgkin lymphoma including MCL and DLBCL was terminated early due to an unexpectedly high rate of pneumonitis in 18% of patients (severe in 11 of 12 cases) (Barr et al. 2016), whereas the combination of idelalisib and the selective Syk inhibitor GS-9973 has shown promising synergistic preclinical activity (Burke et al. 2014).

The safety and tolerability of idelalisib, lenalidomide, and rituximab was investigated in phase I trials in patients with relapsed and refractory MCL and FL (Smith et al. 2017). The primary endpoint of safety and tolerability was not met due to unexpected dose-limiting toxicities coinciding with rituximab. Both studies were amended to remove rituximab, but two of three additional patients developed grade 3 rashes and one had grade 3 AST elevation. Both trials were then permanently closed.

Recently, results of a phase II study of idelalisib for relapsed and refractory classical Hodgkin's lymphoma (HL) were presented (Gopal et al. 2017a). Twenty-five patients who had previously received a median of five therapies, including 18 (72%) with failed autologous stem cell transplant and 23 (92%) with failed brentuximab vedotin, were enrolled in the study. Idelalisib was tolerable and had modest single-agent activity in these heavily pretreated patients with an ORR of 20% and a median PFS of 2.3 months. Rational combinations with other novel agents may improve response rate and duration of response.

4.6 Idelalisib in Merkel-Cell Carcinoma

Aberrant activation of the PI3K pathway may be a potential therapeutic target in Merkel-cell carcinoma. Indeed, activation of the PI3K pathway was detected both in Merkel-cell polyomavirus-negative tumor tissues and in tumor cells (Nardi et al. 2012; Shao et al. 2013). In a recent case report, a patient with metastatic Merkel-cell carcinoma showing high expression of PI3Kδ in the tumor cells was treated with idelalisib, resulting in a rapid and complete response. Unfortunately, the patient died from other causes before long-term response could be measured (Shiver et al. 2015). Although the cause of high expression of PI3Kδ in Merkel-cell carcinoma is

unclear, the efficacy of idelalisib provides evidence that targeting of PI3Kδ in Merkel-cell carcinoma is warranted.

5 Toxicity

Selective inhibition of the PI3Kδ isoform be idelalisib minimizes adverse events (AEs) from inhibition of other PI3K signaling pathways involved in normal function of the healthy cells. Overall, idelalisib was fairly well tolerated (Falchi et al. 2016) with the most common AEs in patients receiving idelalisib and rituximab being pyrexia, fatigue, nausea, and diarrhea (Keating 2015). Therapy interruption occurred in 3.6% of patients across all studies with 1.3% requiring a dose reduction (Coutre et al. 2015). In the pivotal phase III study, AEs led to treatment discontinuation in 8% of the patients; majority of which were due to gastrointestinal and skin toxicities (Furman et al. 2014).

However, following the initial trials investigating the use of idelalisib in relapsed and refractory CLL, a series of upfront trials were terminated secondary to the observation of increased risk of death related to infection for patients randomized to combinations containing idelalisib. This experience was communicated to healthcare professionals via an FDA alert, and a black box warning for fatal hepatoxicity, severe diarrhea or colitis, pneumonitis, serious infections and intestinal perforation is now included in the idelalisib product insert (http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm). The majority of deaths was due to bacterial sepsis sometimes associated with neutropenia, but pneumocystis jiroveci pneumonia (PJP) and cytomegalovirus (CMV) infections were also seen, leading to the recommendation that patients receiving idelalisib should be on PJP prophylaxis and should be monitored regularly for the development of CMV infection.

In addition to the increased rate of death related to infection, increased likely autoimmune toxicity related to lymphocytic infiltrates was observed in the upfront setting. In a phase II study investigating the combination of idelalisib and ofatumumab as upfront therapy for CLL, 19 out of 24 patients (79%) experienced a grade 1 or higher elevation in transaminases and 13 patients (54%) experienced grade 3 or higher transaminitis (Lampson et al. 2016). The development of transaminitis occurred before the initiation of ofatumumab, at a median time of 28 days. A lymphocytic infiltrate was seen on liver biopsy specimens taken from 2 patients with transaminitis. A decrease in peripheral blood regulatory T cells was seen in patients experiencing toxicity on therapy, which is consistent with an immune-mediated mechanism. All cases of transaminitis resolved either with drug hold or the initiation of immunosuppression, or both. Significant risk factors for the development of hepatotoxicity were younger age and mutated *IGHV* (Lampson et al. 2016). Histopathological examination during idelalisib-associated diarrhea or colitis in relapsed patients revealed similar findings with a mixed appearance with both apoptotic and ischemic and inflammatory features (Louie et al. 2015; Weidner et al. 2015).

One potential mechanism for the development of the hepatic lymphocytic infiltrate is the effects of PI3K inhibition on regulatory T cells (Tregs). PI3K activity has been shown to be critical to Treg development and function. Initial studies with PI3K-deficient mice demonstrated decreased numbers of Tregs and decreased Treg function (Oak et al. 2006; Patton et al. 2006). Furthermore, Tregs from mice with a kinase-dead mutant p110δ PI3K have inferior suppressive capacity relative to wild-type Tregs (Patton et al. 2011). Given the increased risk of infection and risk of death related to infection coupled with significant idelalisib-mediated liver, colonic (Hammami et al. 2017), and pulmonary injury (Barr et al. 2016; Gupta and Li 2016; Haustraete et al. 2016), the use of idelalisib continues to be adapted to these risks (Greenwell et al. 2017).

An expert panel of hematologists and one gastroenterologist has provided further guidance for the management of idelalisib treatment-emergent diarrhea/colitis (Coutre et al. 2015). Based on anecdotal effectiveness, the panel recommended that once infectious source has been ruled out, budesonide or steroid (oral or intravenous) therapy should be initiated and continued until diarrhea resolves. Any patient presenting with pulmonary symptoms should be evaluated for pneumonitis. Additional warnings and precautions from the US prescribing information include severe cutaneous reactions (Gabriel et al. 2017; Huilaja et al. 2017), anaphylaxis, neutropenia, and embryo-fetal toxicity.

6 Drug Interactions

Idelalisib and its major inactive metabolite GS-563117 are implicated in the inhibition or induction of various CYP isoenzymes or transporters (Jin et al. 2015; Liewer and Huddleston 2015).

Midazolam (CYP3A substrate) exposure was significantly increased by the co-administration of idelalisib, reflecting inhibition of CYP3A by GS-563117 (Jin et al. 2015). A drug interaction between idelalisib and diazepam, also a CYP3A4 substrate, resulted in altered mental status and respiratory failure resulting in hospitalization. After discontinuation of both agents, the patient recovered quickly (Bossaer and Chakraborty 2017). Therefore, co-administration of idelalisib with CYP3A substrates should be avoided.

Both idelalisib and GS-563117 exposure were significantly reduced by co-administration of the potent CYP3A inducer rifampicin (Jin et al. 2015). The US prescribing information states that co-administration of idelalisib with strong CYP3A inducers such as rifampicin, phenytoin, hypericum (St John's wort), or carbamazepine should be avoided.

In contrast, idelalisib exposure was increased by co-administration of the strong CYP3A inhibitor ketoconazole. Monitoring for signs of idelalisib toxicity is recommended in patients receiving concomitant therapy with strong CYP3A inhibitors. The EU summary of product characteristics recommends caution when co-administering idelalisib and CYP2C8 substrates with a narrow therapeutic index

(e.g., paclitaxel) or substrates of CYP2C9, CYP2C19, CYP2B6 or UGT with a narrow therapeutic index (e.g., warfarin, phenytoin).

7 Biomarkers

With changing treatment paradigms, particularly the use of oral targeted therapies, the value of predictive and prognostic factors to determine treatment choice are shifting. Traditional risk factors, including disease stage and lymphocyte doubling time, are becoming less relevant for treatment selection, and the predictive value of cytogenetic and molecular markers on response to treatment with novel agents is being redefined based on the outcomes of recent trials.

A number of biomarkers have been developed in CLL that fulfill the definition of prognostic factors, while conversely, few biomarkers meet the definition of predictive biomarkers. The presence of a deletion of chromosome 17p (del17p) and mutated *TP53* represents the most relevant disease characteristics that guide the choice of therapy in patients with CLL. Both del17p and mutated *TP53* are associated with poor response to chemotherapy-based regimens, short PFS, and poor OS, independently of *IGHV* mutation status (Hallek et al. 2010). Recent trials have demonstrated activity of novel targeted agents in patients with del17p/*TP53*-mutant CLL (Furman et al. 2014; Byrd et al. 2014b). These results have significantly changed outcomes for this subgroup for whom previous options to increase the duration of response were largely limited to stem cell transplant in eligible patients. Because leukemic clones may evolve, del17p and *TP53* mutations analyses should be repeated at each disease progression requiring treatment. BCR inhibitors ibrutinib and idelalisib are considered the preferred first-line therapy for patients with del17p/*TP53*-mutant CLL and are a category 1 recommendation for patients with CLL without del17p/*TP53* mutation who are frail, or are ≥ 65 years of age, or younger with significant comorbidities, according to the National Comprehensive Cancer Network (NCCN) guidelines on CLL.

Patients with mutated *IGHV* genes receiving chemo-immunotherapy often maintain disease remission in the long term and almost all *IGHV* unmutated CLL patients are projected to progress after chemo-immunotherapy (Fischer et al. 2016). In contrast, upon treatment with ibrutinib or idelalisib, the PFS of *IGHV* unmutated patients is similar to that of *IGHV* mutated cases (Furman et al. 2014; Burger et al. 2015). Accordingly, the most recent guidelines support *IGHV* mutations analysis as desirable at the time of treatment requirements.

Ibrutinib and idelalisib overcome the relevance of biomarkers reflecting patients' frailty. In the relapsed–refractory setting, patient's age does not affect ibrutinib or idelalisib safety and efficacy (Furman et al. 2014; Byrd et al. 2014b). Though guideline recommendations are lacking and the level of evidence is low, comorbidities support the choice of one novel agents among the others when multiple options are available. Most of the recent trials stratify patient inclusion criteria

according to the cumulative illness rating scale (CIRS) with a cutoff of 6 to define fit and less fit patients (Eichhorst et al. 2016).

Regarding prognostic factors, identified to be significantly associated with CLL outcome, more recently, an international collaboration developed a comprehensive CLL-International Prognostic Index (IPI) (2016). The CLL-IPI score is based on five robust and widely used prognostic biomarkers (age, clinical stage, 17p13 deletion and/or TP53 mutation, *IGHV* mutations status, and β2-microglobulin levels) and incorporates both clinical and biological CLL aspects. Based on these biomarkers, a prognostic index was derived that identified four risk groups with significantly different survival at 5 years. The CLL-IPI score was developed in patients diagnosed in the chemo+/− immunotherapy era. The significant impact of novel targeted agents on patients' survival and the mitigation of historical prognostic factors when these drugs are used prompt the reevaluation and validation of the clinical usefulness of CLL prognostic scores in cohort of patients treated with the new drugs.

8 Summary and Perspectives

Idelalisib, the first FDA-approved PI3Kδ inhibitor, is an important addition to treatment options for patients with B-cell lymphomas. Its use is approved as single agent for patients with FL or SLL relapsed after 2 prior regimens and in combination with rituximab for patients with relapsed CLL for whom single-agent rituximab would be an appropriate therapy. Idelalisib has shown impressive clinical activity both as a single agent and in combination therapy, even in high-risk subtypes of indolent B-cell lymphoma, and is usually well tolerated. PI3Kδ inhibition appears to antagonize both intrinsic and extrinsic cell survival signals, decreases the survival of CLL cells directly, and abrogates cellular interactions between CLL cells and components of the tissue microenvironment that normally sustain leukemia and lymphoma cells in a protective niche.

Recent clinical trial data have demonstrated increased risk of death secondary to infections when idelalisib is used frontline. In addition, idelalisib has been shown to promote the development of immune-mediated colitis, hepatitis, and pneumonitis. Additional research is needed to better understand the mechanisms underlying the off-target toxicities, whether they can be predicted by features of the disease or the patient's genetics, and how they can be minimized. Ongoing clinical studies are evaluating idelalisib in combination studies to potentially expand its utility in B-cell malignancies and solid tumors.

In addition, PI3Kδ also plays a critical role in the activation, proliferation, and tissue homing of self-reactive B cells that contribute to autoimmune diseases, in particular innate-like B-cell populations such as marginal zone (MZ) B cells and B-1 cells that have been strongly linked to autoimmunity. Inhibitors of PI3Kδ, either alone or in combination with B-cell depletion, showed activity in treating autoimmune diseases such as lupus, rheumatoid arthritis, and type 1 diabetes (Puri

and Gold 2012). Further research is needed to determine if PI3K inhibitors specific for other isoforms are effective against autoimmune diseases; however, PI3Kδ inhibitors may represent also a promising therapeutic approach for treating these diseases (Foster et al. 2012; Vyas and Vohora 2017).

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