Research update on the anticancer effects of buparlisib (Review)

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Abstract. Buparlisib is a highly efficient and selective PI3K inhibitor and a member of the 2,6-dimorpholinopyrimidine-derived family of compounds. It selectively inhibits four isomers of PI3K, PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ, by competitively binding the lipid kinase domain on adenosine 5'-triphosphate (ATP), and serves an important role in inhibiting proliferation, promoting apoptosis and blocking angiogenesis, predominantly by antagonizing the PI3K/AKT pathway. Buparlisib has been confirmed to have a clinical effect in patients with solid tumors and hematological malignancies. A global, phase II clinical trial with buparlisib and paclitaxel in head and neck squamous cell carcinoma has now been completed, with a manageable safety profile. Buparlisib currently has fast-track status with the United States Food and Drug Administration. The present review examined the biochemical structure, pharmacokinetic characteristics, preclinical data and ongoing clinical studies of buparlisib. The various mechanisms of influence of buparlisib in tumors, particularly in preclinical research, were summarized, providing a theoretical basis and direction for basic research on and clinical treatment with buparlisib.

Contents

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1. Introduction

PI3K is an evolutionarily conserved lipid kinase family, with a dual activity (serine/threonine and phosphatidylinositol kinase activities). It interacts with receptors on the cell membrane and mediates the transmission of external signals into the cells. According to their protein domain structure and lipid substrate specificity, they are divided into three categories, each with different functions and mechanisms, and participate in the regulation of several intracellular processes (1,2).

Class I includes heterodimer proteins, which mainly exist in the cytoplasm. These can be further systematically divided into IA and IB. Class IA is mainly activated by tyrosine kinase receptor, which is composed of catalytic subunit p110 and regulatory subunit p85 (3). The catalytic subunit p110 includes p110α, p110β and p110δ, which are encoded by PIK3CA, PIK3CB and PIK3CD, respectively (4). The regulatory subunit P85 includes p85α, p85β, p55α, p55γ and p50α (5). The binding of the catalytic and regulatory subunits has a dual activity (lipid and protein kinase activities). The IB class includes catalytic subunit p110γ and regulatory subunits p101, p84 and p87, which are mainly activated by upstream G protein-coupled receptors (6,7). Class II consists of the C2α, C2β and C2γ subunits, including the PI3KC2a, PI3KC2b and PI3KC2c subunits, and appears to have an important role in insulin signal transduction, neuronal survival, growth factor signal transduction and angiogenesis (8). Class III PI3K includes Vps34-VPS15 heterodimers, which are involved in a variety of intracellular transport activities, including protein synthesis and autophagy (3). Compared with class II and class III, class I is the most widely studied. Studies have shown that these kinases are closely associated with tumor occurrence and development, growth and metabolism, and tumor microenvironment (2,4,5). In mammals, four subtypes of p110 exist, of which the p110α and p110β catalytic subunits are widely distributed in the majority of cell types, while p110γ and p110δ are significantly enriched in immune cells (9). Several mutations in the PIK3CA gene encoding the p110α subunit

have been found in various types of cancer, including breast cancer, medulloblastoma and hepatocellular carcinoma (4,5). In breast cancer, >85% of the mutations in the PI3KCA gene occur in E542K and E545K, which encode helical domains, and H1047R, which encodes catalytic domains (10,11).

Following ligand receptor activation, class I PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2), resulting in phosphatidylinositol 3,4,5-trisphosphate (PIP3) (12-15). It should be noted that tumour suppressor PTEN can hydrolyse PIP3 and convert it into PIP2, a negative regulator of the PI3K signalling pathway (16,17). PIP3 is often referred to as the second messenger. Its pleckstrin homology domain can bind with 3-phosphoinositide-dependent kinase-1 (PDK1) and AKT and recruit them to the cell membrane (13,18). At that time point, AKT has been shown to be activated by PDK1 through the phosphorylation of threonine 308 and serine 473 (19). mTOR is one of the downstream effectors of AKT. mTOR complex (mTORC) 1 and mTORC2 have different structures and functions. AKT mainly affects mTORC1, when it phosphorylates and activates its downstream ribosomal protein S6 kinase β-1 (p70S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), which leads to cell cycle regulation and increased ribosomal protein translation and synthesis, a process that stimulates a series of major drivers of cell growth, proliferation and angiogenesis (20,21). mTORC2 regulates ion transport and cytoskeleton morphology, among other processes, through serine/threonine-protein kinase, protein kinase C α and RAS (22,23). In addition, mTORC2 is directly regulated by PI3K and has a feedback regulation on AKT.

The uncontrolled activation of the PI3K/AKT/mTOR pathway, which is closely associated with several types of cancer, is involved in tumorigenesis, proliferation, invasion, cell cycle progression, apoptosis, metastasis and chemotherapy resistance (2,24,25). Recent studies have shown that the PI3K/AKT/mTOR pathway is also associated with angiogenesis, cytoskeleton, inflammatory response and oxidative stress (26-28). This pathway has a wide range of physiological and pathological functions, and is one of the most important oncogenic pathways in human cancer. At present, PI3K, AKT, mTORC1/2 and mTOR/PI3K inhibitors are the most widely used inhibitors in treatment targeting the PI3K/AKT/mTOR pathway. PI3K inhibitors include pan-PI3K inhibitors, targeting all four PI3K class I subtypes (PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ), as well as allosteric PI3K inhibitors, which are specific to one isomer (29). Buparlisib is a pan-PI3K inhibitor.

The present review summarized the biochemical structure, pharmacokinetic characteristics, preclinical data and ongoing clinical studies of buparlisib. Particularly in preclinical research, the present article reviewed the current knowledge on various molecular factors and signaling pathways affected by buparlisib, which may provide a theoretical basis and direction for basic research and clinical treatment of cancer involving buparlisib.

2. Pan-PI3K inhibitors

Pan-PI3K inhibitors have a wide range of activities against class I PI3K subtypes (PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ). Several pan-PI3K inhibitors have entered clinical trials.

Copanlisib (BAY80-6946). Copanlisib was developed by Bayer AG and approved for listing by the United States Food and Drug Administration (FDA) in 2017. Its trade name is Aliqopa. Copanlisib, which acts on PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ, is a competitive pan-PI3K inhibitor of ATP used in adult patients with recurrent follicular lymphoma, who have received at least two systematic treatments. Copanlisib has an obvious inhibitory activity against two PI3Kα and PI3Kδ subtypes expressed in malignant B cells (30).

Pictilisib (GDC-0941). Pictilisib was developed by Piramed Limited and licensed to Genentech in 2005. It has been shown to have a significant inhibitory effect on PI3Kα and PI3Kδ and a moderate selectivity for p110β and p110γ (31). At a dose of 150 mg/kg, oral pictilisib had an inhibitory effect of >80% on the growth of glioma and ovarian tumors in animals (32). Pictilisib has been shown to have minor side effects in previous clinical studies, and has been used in phase II clinical trials of breast cancer and non-small cell lung cancer (NSCLC) (33).

Buparlisib (BKM120). Buparlisib was developed by Novartis International AG, and it targets PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ for the treatment of metastatic estrogen receptor $(ER)^+$/human epidermal growth factor receptor 2 $(HER2)^-$ breast cancer (34). Novartis is also conducting phase II clinical studies for the treatment of follicular lymphoma, gastrointestinal stromal tumors, mantle cell lymphoma, prostate cancer, diffuse large B-cell lymphoma, ovarian cancer, NSCLC, hepatocellular carcinoma, bone marrow fibrosis, advanced endometrial cancer, melanoma, bladder, pancreatic cancer and malignant gliomas (35-38).

Taselisib (GDC-0032). Taselisib was developed by Genentech, Inc., and is an effective PI3K inhibitor. It targets mutant PI3KCA and can inhibit the activity of PI3Kα, PI3Kβ and PI3Kγ (39,40). At present, phase III clinical studies for the treatment of ER^+ breast cancer in postmenopausal women and NSCLC are underway.

Pilaralisib (XL147, SAR245408). Pilaralisib was developed by Exelixis, Inc., and Sanofi S.A. was granted the right to treat solid tumors in 2009. Pilaralisib is an oral biocompatible PI3K inhibitor that can inhibit PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ. It has been in a phase I clinical trial for the treatment of lymphoma and solid tumors (41-43).

ZSTK474. Jointly developed by Nippon Pharmaceutical Industry Co., Ltd. and the Japan Cancer Research Institute, ZSTK474 targets class I PI3K and has the most significant effect on PI3Kδ (44). Studies on the use of ZSTK474 for the treatment of advanced solid malignancies are in phase I clinical trials (45).

Sonolisib (PX-866). Developed by Oncothyreon Inc., sonolisib can covalently bind to Lys802 residues in the ATP binding site of p110 kinase catalytic subunit and irreversibly inhibit class I PI3K. It exerts an inhibitory activity against PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ. Sonolisib is mainly used in the treatment of pleomorphic glioblastoma and metastatic prostate cancer, and has been entered into phase II clinical trials (46,47).

AMG511. An orally effective class I pan-PI3K inhibitor, AMG511 has a strong inhibitory effect on PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ, and can produce a strong anticancer effect in many tumor cell lines by inducing G_1 phase arrest. In xenografts with PTEN deletion, KRAS mutation and HER2 amplification, AMG511 can significantly inhibit tumor growth (48).

PA799. Developed by Chugai Pharmaceutical Co., Ltd. and later granted the right of early oncology research to Menarini Group, PA799 selectively inhibits class I PI3K (PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ), but has a lower inhibitory effect on class II and III PI3K. PA799 has a stronger inhibitory effect on tumors with PIK3CA mutations compared with tumors with wild type PI3KCA, and can reduce the phosphorylation level of p70S6K, 4E-BP1 and other factors downstream of AKT (49).

3. Biochemical properties of buparlisib

Buparlisib is a highly efficient and selective pan-class I PI3K inhibitor that belongs to the family of 2,6-dimorpholino-pyrimidine-derived compounds (34). It selectively inhibits four isomers of PI3K, PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ, by competitively binding to the lipid kinase domain on ATP, and it has an important role in inihibiting proliferation, promoting apoptosis and inihibiting angiogenesis, by antagonizing the PI3K/AKT pathway (50,51). Due to the similarity in their catalytic domain, buparlisib is considered to also inhibit mTOR.

In clinical studies, buparlisib is often used in combination with other drugs or methods, the most common being synergistic treatment with the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in BRCA1-related triple negative breast cancer (52,53). The combined use of drugs is prone to serious side effects. In order to avoid this issue and also ensure the therapeutic effect, researchers found through the detailed analysis of the chemical structure of buparlisib that, in addition to the binding region of ATP, there is also an idle morpholine group in buparlisib; therefore, a connector could be used to replace it and combine it with PARP inhibitors (54).

4. Pharmacokinetic characteristics of buparlisib

In a variety of animal models, it has been found that buparlisib has a fast absorption rate, high bioavailability and excellent pharmacokinetic characteristics (50). Following the oral administration of buparlisib at a dose of 60 mg/kg, the peak of pharmacokinetics was reached in tumor tissue and plasma within 1 h, and the phosphorylation of AKT was fully inhibited (55). This phase I clinical study also demonsstrated that buparlisib was rapidly absorbed following oral administration, and reached the peak concentration within 1.5 h (55). Next, the plasma concentration of buparlisib decreased doubly exponentially. In addition, buparlisib has been reported to efficiently break through the blood-brain barrier (56,57). A phase I/II study showed that the combined use of buparlisib and trastuzumab did not affect the pharmacokinetic characteristics of buparlisib (58).

5. Preclinical research on buparlisib

Inducing apoptosis, blocking cell cycle progression and promoting cell death is one of the key goals in the treatment of the majority of tumors. Buparlisib has been proven to have an effect in apoptosis and cell cycle in breast, ovarian and intestinal cancer, glioma, lung cancer, head and neck squamous cell carcinoma (HNSCC) and several other cancer types. In addition, buparlisib has also been closely associated with oxidative phosphorylation, inflammation, cytoskeleton and other biological processes. The in-depth study of buparlisib has also provided data on its combination with other drugs for the treatment of a variety of cancer types, providing more directions for the clinical treatment of cancer.

Buparlisib induces apoptosis and inhibits proliferation. Bavelloni *et al* (59) showed that inhibition of the cell cycle induced by buparlisib in osteosarcoma varied slightly depending on the cell line. For example, HOS cells were arrested at the G_2/M phase, U2OS cells were arrested at the G_1 phase, while MG-63 cells were arrested at the sub-G_1 phase, following buparlisib treatment (59). The buparlisib-induced apoptosis of osteosarcoma cells was characterized by an increase in endogenous caspase-3 activity (59). In addition, a specific apoptosis-promoting mechanism that inhibits the triggering of PI3K in lymphoid carcinoma was reported by Müller *et al* (60). This study showed that buparlisib could change the conformation of Bax and Bcl-2 homologous antagonist killer (Bak), lead to N-terminal exposure and protein activation, and then affect the transcription of p53 upregulated modulator of apoptosis and Harakiri, Bcl-2 interacting protein, accompanied by the destruction of mitochondrial membrane potential and mitosis block; this indicated that buparlisib induced apoptosis in mitochondria (60). Buparlisib has also been shown to induce apoptosis in neuroblastoma, and the induction of apoptosis depends on the caspase-mediated pathway, which is associated with caspase 3/7 and cleaved-PARP (61). A previous study has shown that buparlisib can lead to cell cycle arrest and apoptosis in the G_2/M phase of T-cell acute lymphoblastic leukaemia (TALL) cells and T lymphoblasts in patients, and that changes in the expression of cleaved-caspases 2/3/9 occur in a time and concentration-dependent manner (62). Even when co-cultured with MS-5 stromal cells simulating the bone marrow microenvironment, buparlisib was shown to maintaine its proapoptotic activity against Jurkat cells. In addition, buparlisib has been shown to have a synergistic effect with chemotherapeutic drugs currently used to treat patients with TALL without any toxicity (62). In ovarian cancer, the combined inhibition of SH2 containing protein tyrosine phosphatase-2 and PI3K synergistically inhibited cell proliferation and survival, partly by activating proapoptotic Bcl-2 interacting mediator of cell death and inhibiting c-Myc (63). Buparlisib is most widely used in breast cancer and HNSCC. In addition to affecting the growth and cell cycle arrest of breast cancer cells (64,65), buparlisib can also be combined with the inhibition of the c-Myc-mediated human telomerase reverse transcriptase (hTERT) to enhance the arsenic trioxide (ATO)-induced anti-proliferative effect (66). In a study on colorectal cancer, Solberg *et al* (67) found that buparlisib can block HCT-15 cells at the G_1 phase, accompanied by a decrease in c-Myc and

cyclin D1 and increase in cyclin-dependent kinase inhibitor (CDKN) 1A and CDKN1B. Buparlisib can block the cell cycle of A549 and H522 lung cancer cells at the G_1/S and G_2 phase, respectively (68). Compared with another pan-PI3K inhibitor PX-866 (G_0/G_1), the cell cycle arrest effect of buparlisib on Jurkat cells mainly occurred at the G_2/M phase, and the apoptosis induced by buparlisib was more significant (69). A previous study has shown that buparlisib is involved in two main pathways of cell death in leukemic cells: Death receptor and mitochondrial mediation (70). The increase of FAS and the cleavage of procaspase-8 and procaspase-3 suggest that the exogenous pathway of apoptosis is activated. At the same time, it was observed that, following buparlisib treatment, the change in cleaved-procaspase-9, decrease in Bad phosphorylation and upregulation of Bax/Bcl-2 ratio were all associated with mitochondrial apoptosis (71). The regulation of cleaved-caspase-3 by buparlisib was also observed in the Cal27 and Scc25 oral squamous cell carcinoma cells lines (72).

In the aforementioned studies, buparlisib directly inhibited the proliferation or apoptosis pathway to exert its pharmacological effect. Recent studies have indicated that buparlisib can also affect other targets. Certain studies have shown that PTEN may be the key to determining the therapeutic effect of buparlisib. In endometrial carcinoma, PTEN deletion/mutation has been shown to increase the effect of buparlisib plus PARP inhibitors *in vivo* and *in vitro* (73,74). Mutation of p53 is closely associated with the apoptosis of tumor cells. When evaluating the exogenous apoptosis pathway, Bashash *et al* (75) found that the inhibition of PI3K could increase the positive percentage of intracellular Annexin-V/PI and the reactive oxygen species (ROS) levels in p53 mutant NB4 and p53 wild-type NALM-6 cells in a concentration-dependent manner. Buparlisib could inhibit the expression of the NF-κB target gene in NB4 cells, in which the expression of p-IκB was downregulated in a concentration-dependent manner, and inhibit the transcriptional activity of the apoptosis target gene. In NALM-6 cells, buparlisib lead to changes in the transcriptional activities of p73 and FOXO3a, which may be associated with ROS-mediated apoptosis (75).

As a member of the NAD^+-dependent class III histone deacetylase family, sirtuin (SIRT) 1 acts as an important negative regulator of p53 and an anti-apoptotic element (76). Of note, later studies by Bashash *et al* (75,77) have shown that buparlisib can reduce the transcriptional level of hTERT in NB4 cells, significantly enhance the effect of ATO on cells, reduce the expression of SIRT1, expand the effect of changes in factors such as MCL1, X-linked inhibitor of apoptosis, cellular inhibitor of apoptosis protein 1, Bcl-2, Bax and Bad on apoptosis, and induce G_1-phase arrest (77). Certain studies have shown that the sensitivity of leukemic cells to isomer-specific PI3K inhibitors has nothing to do with the mutation/inactivation of PTEN. Similarly, in myeloma, it was found by Safaroghli-azar *et al* (78) that there was no significant correlation between the effect of buparlisib and the state of PTEN in cells. Buparlisib can upregulate the expression of SIRT1 in cells, inhibit the activity of NF-κB and block the G_2/M phase of the cell cycle (78). SIRT6, the downstream target of FoxO3a, is also one of the new targets of buparlisib. SIRT6 can activate Bax and the mitochondrial pathway to promote cell apoptosis. It was reported by Zhang *et al* (79) that buparlisib can reduce the levels of phosphorylated FOXO3a and increase the expression of SIRT6 in colorectal cancer cells and patient tissue samples; the possible mechanism underlying this effect appears to be that buparlisib can dephosphorylate FoxO3a and increase the levels of FoxO3a on the SIRT6 promoter, triggering SIRT6 transcription. Activated SIRT6 acetylates the histone H3K9 site of survivin and other factors, downregulates its transcription and finally initiates mitochondrial apoptosis (79).

Certain studies have shown that the anticancer effect of buparlisib is associated with the PIK3CA mutation status. In a xenograft model of bone metastasis established using PIK3CA-mutated NCI-H460-luc2 cells, buparlisib could induce apoptosis in tumor tissues (80). Of note, with the exception of the upregulation of caspase-3 activity, no change in the expression levels of other pro or antiapoptotic proteins, such as Bcl-2 and Bax, was observed (80). It has been suggested that buparlisib may affect the occurrence of apoptosis through other mechanisms. It is worth noting that the study by Trautmann *et al* (81) in myxoid liposarcoma demonstrated that the effect of buparlisib on apoptosis was more significant in cells with a PIK3CA-H1047R mutation.

Combination therapy of buparlisib. A study on colorectal cancer showed that buparlisib could significantly increase the expression of p53 in HCT-15 cells, and did not induce the apoptosis phenotype in COLO320DM cells (67). By contrast, when combined with the tankyrase inhibitor G007-LK, buparlisib significantly induced apoptosis, regardless of the nuclear catenin and FOXO3a levels (67). Buparlisib alone blocked the G_1/S phase of A549 cells, but its combination with MEK162 (MEK1/2 inhibitor) was more effective in inducing G_1 phase arrest (68). In a study on biliary tract cancer, it was found that buparlisib buparlisib did not inhibit cell proliferation, migration and cell cycle progression in cells harbouring PI3KCA/KRAS mutations. However, when combined with MEK162, the resistance of PI3KCA/KRAS-mutant cells to buparlisib was overcome (82). Prima-1Met is a low molecular weight compound that can restore the transcriptional function of mutant p53 (83). Buparlisib and Prima-1Met can serve a combined role in thyroid cancer cells, and the possible mechanisms include the activation of the caspase apoptosis pathway and the inhibition of the PI3K/AKT/mTOR and cleavage and polyadenylation specific factor 4/hTERT pathways (84). Aasen *et al* (85) studied the role and mechanism of buparlisib using BRAF-mutant cells extracted from patients with melanoma brain metastases. Following the use of buparlisib alone, the expression of cytochrome C, TRAIL-R2 and Fas increased, while that of heat shock protein 27 decreased. In combination with the MEK1/2 inhibitor trametinib, the expression of apoptosis proteins Bad, caspase-3, p27/kip1 and TNFR1 was significantly increased, and that of apoptosis inhibitors such as Bcl-2, cellular inhibitor of apoptosis protein 1, claspin, hypoxia-inducible factor 1-α, 70-kDa heat shock protein and survivin was significantly downregulated following single or combined treatment (85).

Tumor cell cycle arrest and apoptosis induced by buparlisib have also been demonstrated in gliomas and undifferentiated thyroid carcinomas. Buparlisib increased the expression of cleaved-caspase-3 and Bax in C6 glioma cells treated with

the chemotherapy agent temozolomide (TMZ) (86). *In vitro*, apoptosis could be induced by the inhibition of PI3K and the use of volasertib, an experimental small molecule inhibitor of the polo-like kinase 1 protein (87). Of note, it was found by Sai *et al* (88) that buparlisib had an effect on the immune system *in vivo,* through orthotopic and allogeneic breast tumor transplantation models. Sai *et al* (88) showed that buparlisib effectively abrogated lung metastasis of breast cancer cells, as well as significantly altered the composition of tumor-infiltrating leukocytes at the primary or metastatic tumor site. By increasing the number of antitumor leukocytes in the tumor site, buparlisib could change the microenvironment and further hinder the growth of tumor cells (88). For that reason, buparlisib and the checkpoint inhibitor blocker anti-PD1 antibody may have potential as a combined therapy. Of note, buparlisib did not significantly reduce the cytotoxicity of T cells to target 4T1 tumor cells (88).

Although several studies have reported that buparlisib can induce apoptosis, Anisuzzaman *et al* (89) found that buparlisib alone did not induce apoptosis in HNSCC cells, but when combined with erlotinib it inhibited the Bcl-2 protein through 4E-BP1, thus connecting the mTOR protein translation and the intrinsic apoptotic pathways (89). Notably, other studies have also shown a contrary role for buparlisib alone in HNSCC cells. Yun *et al* (90) reported that buparlisib treatment upregulated interleukin (IL-6) levels and then activated ERK and STAT3 to promote the growth of HNSCC cells. Blocking the autocrine IL-6 signaling pathway with small interfering RNA or neutralizing antibody for IL-6 receptor completely eliminated the buparlisib-induced activation of ERK and STAT3 and expression of c-Myc (90).

The combined use of PI3K and bromodomain and extra-terminal domain protein (BET) inhibitors has also been reported. The combination of buparlisib and JQ1 synergistically inhibited the EGFR and c-Myc pathways in SACC-83 salivary gland adenoid cystic carcinoma cells and promoted the occurrence of apoptosis (91). Sakakibara *et al* (92) found that buparlisib strongly induced apoptosis and inhibited cell proliferation in individual myeloid/lymphoblastic leukemia cell lines resistant to binimetinib, a MEK1/2 inhibitor. It is worth noting that there was a higher level of phosphorylated AKT in binimetinib-resistant strains (92).

Finally, the most-well known mechanism for combination treatment of buparlisib is for PARP inhibitors. Certain studies have shown that buparlisib combined with PARP inhibitors can increase the γ-H2A.X variant histone in various types of cancer, decrease the expression of homologous recombinant (HR) repair protein RAD51 and destroy the HR repair ability of cells (73,74,93). Another study demonstrted that the lack of AT-rich interaction domain 1A (ARID1A) expression renders gastric cancer cells sensitive to PI3K and PARP inhibitors (94).

Other functions. Several studies have revealed a variety of additional anticancer effects of buparlisib. Speranza *et al* (50) demonstrated for the first time that buparlisib may be associated with the cytoskeleton. Speranza *et al* (50) have shown that buparlisib significantly inhibited the adhesion of G9-copGFP cells, indicating that it can affect the ability of cells to form firm contact. Following treatment of U251 cells with buparlisib for 24 h, the cells became round, which indicated that buparlisib may destroy the microtubule cytoskeleton. It is known that there are tumor-inititating cell (TIC) subsets in cancer with an ability for self-renewal, very similar to that of embryonic stem cells (95). These TIC subsets can regenerate themselves and other cancer cells in appropriate microenvironmental niches (95). Cells that express both aldehyde dehydrogenases $(ALDH)^+$ and cluster of differentiation (CD) $44^+/CD24^-$ may have the strongest carcinogenesis and self-renewal abilities (95). A previous study has shown that buparlisib can selectively target $CD44^+/CD24^-$ in $ALDH^+$ MDA-MB231 cell subsets (96). Buparlisib can also affect non-homologous end joining (NHEJ), an error-prone repair mechanism that leads to the accumulation of damaged DNA, which in turn leads to cell death. Zhao *et al* (97) showed that, although buparlisib had little effect on the cell cycle of CAL51 and MDA-MB-231 cells, it promoted the repair of NHEJ and inhibited the growth of breast cancer cell lines. Buparlisib can also exert its anti-tumor effects by inhibiting the expression of golgi membrane protein 1 (GOLM1) in prostate cancer cells (98). GOLM1 has been identified as a new biomarker for the diagnosis of prostate cancer (99). Compared with control cells, buparlisib treatment attenuated the apoptosis inhibition of DU145 cells caused by the overexpression of GOLM1 (98). In gliomas, buparlisib upregulated the expression of TRAIL-R2, thus promoting the TRAIL-induced apoptosis in gliomas, but does not upregulate the expression of TRAIL-R1, another major TRAIL-associated death receptor (100).

6. Ongoing clinical trials on buparlisib

Several clinical trials are currently evaluating buparlisib alone or as part of combination therapy in patients with cancer. Phase III trial NCT04338399 plans to recruit 483 adult patients with recurrent or metastatic HNSCC who failed to receive cisplatin or anti-PD1-based treatment. The survival of patients treated with paclitaxel alone or in combination with buparlisib will be examined. The completion time of the study is tentatively scheduled for December 2023. NCT01551030 is an ongoing pharmacodynamic study on buparlisib in patients with metastatic urothelial cancer (phase II clinical trial). The aim of the first part of the trial is to examine whether drugs can reduce or slow down cancer growth in patients. The aim of the second part is to explore whether buparlisib can reduce or slow down the growth of urothelial tumors in patients with certain genetic mutations that cause such tumors. NCT02756247 is an ongoing Phase Ib clinical trial. The purpose of the study is to examine whether the combination of buparlisib and ibrutinib can achieve a superior therapeutic effect in patients with recurrent or refractory follicular lymphoma, mantle cell lymphoma or diffuse large B-cell lymphoma. The NCT02113878 trial, which is being conducted in patients with locally advanced HNSCC, is also in phase Ib; its aim is to determine the maximum dose of buparlisib/cisplatin that can be combined with radiotherapy and to evaluate the tolerance of this combination in high-risk patients with locally advanced HNSCC.

A phase I clinical trial (NCT01623349) of recurrent triple-negative breast cancer and high-grade serous ovarian cancer is underway to determine the safety of drug combinations. The aim of that study is to determine the highest dose that can be safely administered, and to explore whether a

combination of buparlisib/BYL719 and olaparib is effective for both cancer types. It is worth noting that the phase II NCT02220855 trial showed that patients with recurrent or refractory thymoma took oral buparlisib for a median of 11.1 months, and >70% of the patients developed fatigue and anorexia. In addition, >60% of patients developed skin and subcutaneous tissue-related diseases, such as itching, rashes and acne. Unfortunately, due to a lack of funding, the study originally planned to recruit 16 patients, but only 14 patients were actually recruited (101). NCT02049541, a phase I clinical trial, studied the side effects and optimal dose of buparlisib in conjunction with rituximab for the treatment of patients with recurrent or refractory low-grade B-cell lymphoma, and evaluated the efficacy of the combination of the two drugs. Finally, the multicenter, open label phase II clinical trial NCT02159066 is evaluating the antitumor activity of advanced LGX818/MEK162 therapy in combination with targeted drugs (buparlisib, LEE011, BGJ398 or INC280) in advanced melanoma with BRAF mutations, as well as the safety and tolerance of the new triple combination. A summary of ongoing clinical trials involving buparlisib is shown in Table I.

7. Conclusion

In recent years, increasing attention has been paid to tumor-targeted therapies. The clinical benefit of buparlisib has been demonstrated in patients with solid tumors and hematological malignancies. A global clinical phase II trial using paclitaxel in HNSCC has been completed with a manageable safety profile. Buparlisib currently has fast-track status with the FDA. In addition, it has been shown to have a good brain permeability, independent of the blood-brain barrier efflux transporter (57). These characteristics make buparlisib an ideal option for intracranial targeted therapeutic strategies involving PI3K inhibition. Buparlisib in combination with TMZ has been shown to enhance the ability of TMZ to induce apoptosis (86,87). Therefore, it can be hypothesized that it is more likely to be used in combination with existing chemotherapeutic agents in cases where the efficacy of buparlisib is not satisfactory due to tumor resistance, a hypothesis that can provide new directions for the clinical therapy of glioma.

In basic research studies, the main function of buparlisib is to induce an apoptotic phenotype in tumor cells (Table II). Mechanistically, buparlisib has been shown to affect various apoptosis-related factors, including caspases, NF-κB, Fas, FOX3a and ROS. The effects on the cell cycle also ranged from arrest in the sub-G_1 to the G_2/M phases, which appeared to depend on the cancer type and cellular background. A previous study on the chemical structure of buparlisib has indicated that buparlisib interacts with Tyr55, the catalytic residue of Aldo-keto reductase family 1 member C3 (AKR1C3), through trifluoromethyl (102), an aldehyde and ketone reductase widely distributed in human tissues (103). AKR1C3 is closely associated with several types of cancer and is involved in several metabolic pathways, implying that buparlisib may serve a potential role in metabolic regulation.

Jiang *et al* (104) found that EGFR/KRAS mutations do not appear to affect the sensitivity of cancer cells to buparlisib treatment. Buparlisib can induce apoptosis and increased caspase-3 activity in PIK3CA-mutated NCI-H460 lung cancer

Table I. Ongoing clinical trials involving buparlisib.

Identifier	Phase	Type of cancer	Patient numbers	Interventions	Status	Estimated study completion date
NCT04338399	III	Recurrent or metastatic HNSCC	483	Buparlisib 100 mg PO, Paclitaxel 80 mg/m^2 IV	Not yet recruiting	December 2023
NCT01551030	II	Metastatic urothelial carcinoma	35	Buparlisib 100 mg PO	Active, not recruiting	March 2021
NCT02756247	Ib	Mantle cell lymphoma, follicular lymphoma and diffuse large B cell lymphoma	37	Buparlisib, Ibrutinib	Active, not recruiting	May 2021
NCT02113878	Ib	Locally advanced HNSCC	23	Buparlisib 40 mg PO, Cisplatin 30 mg/m^2 IV	Active, not recruiting	March 2021
NCT01623349	I	Recurrent triple negative breast cancer, high grade serous ovarian cancer	118	Buparlisib 40 mg PO, Olaparib 50/100 mg PO, BYL719 250 mg PO	Active, not recruiting	July 2020
NCT02220855	II	Relapsed or refractory thymomas	14	Buparlisib 100 mg PO	Active, not recruiting	December 2019
NCT02049541	I	Relapsed or refractory indolent B-cell lymphoma	18	Buparlisib, Rituximab	Active, not recruiting	December 2020
NCT02159066	II	Locally advanced or metastatic BRAF V600 melanoma	140	Buparlisib, LGX818 MEK162, LEE011 BGJ398, INC280	Active, not recruiting	June 2022

HNSCC, head and neck squamous cell carcinoma; PO, orally; IV, intravenously.

Table II. List of studies demonstrating the effect of buparlisib in cancer cell apoptosis.

First author, year	Type of cancer	Main factors[a]	(Refs.)
Bavelloni *et al*, 2019	Osteosarcoma	Endogenous cas3	(59)
Müller *et al*, 2018	B-cell non-Hodgkin lymphoma	Bax/Bak, Puma, Hrk	(60)
Zhao *et al*, 2017	Medulloblastoma	Cas3/7, Clv-cas3, Clv-PARP	(61)
Lonetti *et al*, 2014	Acute lymphoblastic leukaemia	Clv-cas2/3/9	(62)
Sun *et al*, 2019	Ovarian cancer	Bim, Bad	(63)
Pereira *et al*, 2015	Acute lymphoblastic leukaemia	Clv-procas3/8/9, Fas, Bad, Bax/Bcl-2	(71)
Liu *et al*, 2019	Oral squamous cell carcinoma	Clv-cas3	(72)
Bashash *et al*, 2016	Acute leukaemia	Bax, Bad	(75)
Bashash *et al*, 2018	Acute promyelocytic leukaemia	Bax, Bad, Bcl-2, survivin, MCL1, XIAP, c-IAP1	(77)
Safaroghli-Azar *et al*, 2019	Multiple myeloma	Cas3, MCL1, Bcl-2, c-IAP1, c-IAP2, survivin	(78)
Zhang *et al*, 2019	Colon cancer	Cyto-c, Clv-cas3/9, survivin	(79)
Wang *et al*, 2019	Non-small cell lung cancer	Cas3	(80)
Trautmann *et al*, 2019	Myxoid liposarcoma	Clv-PARP, cas3/7	(81)
Li *et al*, 2018	Thyroid cancer	Cyto-c	(84)
Aasen *et al*, 2019	Melanoma	Clv-cas3, c-IAP1, Clv-P, XIAP, survivin, Fas	(85)
Li *et al*, 2017	Glioblastoma	Clv-cas3, Bax	(86)
Anisuzzaman *et al*, 2017	Head and neck squamous cell carcinoma	Bcl-2, Bcl-xL, MCL1	(89)
Liu *et al*, 2019	Adenoid cystic carcinoma	Clv-cas3	(91)
Sakakibara *et al*, 2019	Acute myeloid leukaemia	Clv-P, Bcl-2, Bcl-xL, Bcl-Xs	(92)
Bian *et al*, 2018	Endometrial cancer	Clv-PARP, Clv-cas3	(73)
Wang *et al*, 2016	Ovarian cancer	Clv-PARP, Clv-cas3	(93)
Yang *et al*, 2018	Gastric cancer	Clv-PARP	(94)
Zhao *et al*, 2018	Triple-negative breast cancer	Clv-PARP	(97)
Foster *et al*, 2015	Malignant glioma	Clv-PARP, Clv-cas3/7/8/9, Bcl-2, Bcl-xL, MCL1	(100)

[a]Main factors, the apoptotic factors that were directly affected by buparlisib. Puma, p53 upregulated modulator of apoptosis; Hrk, harakiri BCL2 interacting protein; Cas, caspase; Clv, cleaved; PARP, poly (ADP-ribose) polymerase; procas, procaspase; XIAP, X-linked inhibitor of apoptosis; c-IAP, cellular inhibitor of apoptosis protein; Cyto-c, cytochrome-c.

cells, but the expression levels of the apoptosis-related proteins Bcl-2 and Bax were unaffected (80); this suggests that buparlisib may affect the occurrence of apoptosis through other mechanisms. In combination, these findings indicate that the mechanism of buparlisib-induced apoptosis in different tumor cells has not been fully elucidated, therefore further studies will be required to uncover more targets and clinical applications of buparlisib.

Of note, the most common side effect of buparlisib described in early clinical trials is hyperglycemia, which is a common adverse reaction to PI3K inhibitors (55). Later trials have shown that buparlisib also appears to have effects on the respiratory, digestive and immune systems (NCT01385293, NCT01487265). Therefore, the immunosuppressive characteristics of buparlisib should be taken into account when using it in basic or clinical studies in the future, to minimize its adverse effects on immune function. It has been shown that buparlisib impairs tumor cell growth by regulating leukocytes. By contrast, buparlisib was not found to significantly reduce the cytotoxic effect of T cells on 4T1 tumor cells (88). This suggests that the effects of buparlisib on the human immune system are complex and diverse, and additional evidence on the combination of buparlisib and immune drugs is required.

In conclusion, the potential beneficial role of buparlisib in the therapy of various types of cancer has been increasingly recognized, but the uderlying mechanisms remain to be fully elucidated. The present review aimed to summarize the current knowledge on buparlisib, highlighting that buparlisib has the potential to serve as an effective, novel and efficient cancer treatment.

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JX and JY conceived the review and wrote the manuscript. YG and JY collected the relevant literature and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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