Role of PI3K/AKT pathway in cancer: the framework of malignant behavior

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Abstract
Given that the PI3K/AKT pathway has manifested its compelling influence on multiple cellular process, we further review the roles of hyperactivation of PI3K/AKT pathway in various human cancers. We state the abnormalities of PI3K/AKT pathway in different cancers, which are closely related with tumorigenesis, proliferation, growth, apoptosis, invasion, metastasis, epithelial–mesenchymal transition, stem-like phenotype, immune microenvironment and drug resistance of cancer cells. In addition, we investigated the current clinical trials of inhibitors against PI3K/AKT pathway in cancers and found that the clinical efficacy of these inhibitors as monotherapy has so far been limited despite of the promising preclinical activity, which means combinations of targeted therapy may achieve better efficacies in cancers. In short, we hope to feature PI3K/AKT pathway in cancers to the clinic and bring the new promising to patients for targeted therapies.

Keywords PI3K · AKT · PTEN · Cancer · Targeted therapy

Abbreviations

| ABC | Activated B cell-like |
| AI | Aromatase inhibitor |
| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloid leukemia |
| AKT | Protein kinase B |
| ATC | Anaplastic thyroid cancer |
| ATL | Adult T cell leukemia/lymphoma |
| AYA | Adolescent and young adult |
| BC | Breast cancer |
| BCBM | Breast cancer brain metastases |
| BCL | B-cell lymphoma |
| BTKi | BTK inhibitors |
| ccfDNA | Circulating cell-free DNA |
| CHL | Classical Hodgkin lymphoma |
| CLL/SLL | Chronic lymphocytic leukemia or small lymphocytic lymphoma |
| CRC | Colorectal carcinoma |
| CRPC | Castration resistant prostate cancer |
| CSC | Cancer stem cell |
| EBV | Epstein–Barr virus |
| EC | Endometrial cancer |
| EEC | Endometrioid type of EC |
| EMT | Epithelial–mesenchymal transition |

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Background

Cancer is considered as the major cause of mortality in the worldwide. According to the global cancer statistics of the Global Cancer Observatory (GCO), there will be 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018 (World Health Organization. Cancer. 2018; https://gco.iarc.fr/). The top 5 most prevalent cancers in the world are lung cancer (LC), breast cancer (BC), prostate cancer (PCa), colon cancer and gastric cancer (GC, Table 1). In China, LC and liver cancer were two of the top five causes of death leading to years of life lost (YLLs) in 2017 [1]. Environmental and genetic risk factors have been recognized as the two major risk factors resulting in various tumorigenesis and cancer progression. Recent decades have witnessed the molecular understanding of the mechanisms of numerous genetic factors in human cancer, such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), P53, NF-κB, STAT3, COX-2 and c-Myc. Apparently, PI3K/AKT pathway has gradually gotten a major focus of attention as it plays a crucial role in regulating diverse cellular functions, including metabolism, growth, proliferation, survival, transcription and protein synthesis.

The PI3Ks are a family of heterodimeric lipid kinases, which are grouped into class I, II, and III isoforms. Class IA subgroup of PI3Ks activated by receptor tyrosine kinases consist of a p110 catalytic subunit (p110α, PIK3CA; p110β, PIK3CB; p110δ, PIK3CD) and one of five p85-like regulatory subunits (p85α, p55α, p50α, PIK3R1; p85β, PIK3R2; p55γ, PIK3R3). Class IB subgroup of PI3Ks activated by G protein-coupled receptors consist of the catalytic subunit (p110γ, PIK3CG) and regulatory subunits (p85α, p55α, p50α, PIK3R1; p85β, PIK3R2; p55γ, PIK3R3). Class IC subgroup of PI3Ks activated by G protein-coupled receptors consist of the catalytic subunit (p110γ, PIK3CG) and regulatory subunits (p85α, p55α, p50α, PIK3R1; p85β, PIK3R2; p55γ, PIK3R3).
Table 1 Incidence, mortality and genetic alteration of PI3K/AKT pathway by cancer site (https://gco.iarc.fr; https://www.cbioportal.org/)

| System                          | Incidence rate (%) | Mortality rate (%) | Subtype of cancer | Genetic alteration of PI3K/AKT pathway (%) |
|---------------------------------|--------------------|--------------------|-------------------|------------------------------------------|
|                                 |                    |                    |                   | PIK3CA | PIK3R1 | PIK3R2 | AKT1 | AKT2 | PTEN |
| Brain and Central Nervous Tumors |                    |                    |                   |        |        |        |      |      |      |
| Tumors                          | 1.6                | 2.5                | GBM               | 7      | 6      | 0.7    | 0.9  | 0.3  | 22   |
|                                 |                    |                    | MBM               | 2      | 0.3    | 0.3    |      |      | 1.3  |
| Endocrine                       |                    |                    | TC                | 1.8    | 0.3    | 0.5    | 0.5  | 0.5  | 2.3  |
|                                 |                    |                    | ATC               | 18     | 0      | 3      |      |      | 15   |
|                                 |                    |                    | PDTC              | 2      | 1      | 0      |      |      | 4    |
| Respiratory                     |                    |                    |                   |        |        |        |      |      |      |
| NPC                             | 0.7                | 0.8                |                   | 1.8    |        |        |      |      |      |
| LC                              | 11.6               | 18.4               | NSCLC             | 17     | 1.8    | 1.6    | 2.1  | 3    | 6    |
|                                 |                    |                    | SCLC              | 3      | 2      | 1.5    | 0.5  | 1.5  | 8    |
| Digestive                       |                    |                    |                   |        |        |        |      |      |      |
| ESCA                            | 3.2                | 5.3                |                   | 24     | 2.7    | 1.6    | 3    | 1.6  | 7    |
| GC                              | 5.7                | 8.2                |                   | 17     | 4      | 2.5    | 1.4  | 2.8  | 11   |
| Colon cancer                    | 6.1                | 5.8                |                   | 21     | 4      | 4      | 2.2  | 3    | 9    |
| CRC                             | 3.9                | 3.2                |                   | 22     | 5      | 2.2    | 1.8  | 1.5  | 8    |
| HCC                             | 4.7                | 8.2                |                   | 3      | 1.2    | 1.5    | 0.7  | 1.1  | 4    |
| GBC                             | 1.2                | 1.7                |                   | 10     | 0.8    | 0      | 1.5  | 1.5  | 2.3  |
| PC                              | 2.5                | 4.5                |                   | 2.3    | 0.7    | 1.2    | 2.2  | 3    | 1.9  |
| Breast and female reproductive  |                    |                    |                   |        |        |        |      |      |      |
| BC                              | 11.6               | 6.6                |                   | 37     | 3      | 1.9    | 5    | 1.6  | 8    |
| OC                              | 1.6                | 1.9                |                   | 29     | 5      | 9      | 5    | 8    | 7    |
| CC                              | 3.2                | 3.3                |                   | 39     | 4      | 1.1    | 4    | 5    | 13   |
| EC                              | 2.1                | 0.94               |                   | 34     | 19     | 5      | 3    | 5    | 32   |
| Genitourinary                   |                    |                    |                   |        |        |        |      |      |      |
| PCa                             | 7.1                | 3.8                |                   | 6      | 4      | 1.9    | 2.5  | 1.3  | 18   |
| BLCA                            | 3.0                | 2.1                |                   | 24     | 3      | 1.1    | 3    | 2.5  | 6    |
| KC                              | 2.2                | 1.8                |                   | 2.8    | 0.4    | 0.3    | 0.5  | 0.6  | 4    |
| Te Ca                           | 0.39               | 0.1                |                   | 3      | 1.3    |        | 0.7  |      |      |
| Hematologic                     |                    |                    |                   |        |        |        |      |      |      |
| HL                              | 0.44               | 0.27               |                   | 0.4    | 0.5    | 0.1    | 0.1  | 0.1  | 1.1  |
| NHL                             | 2.8                | 2.6                |                   | 0.88   | 1.1    |        |      |      |      |
| 0.6                              | 0.6                | 0.4                |                   |        |        |        |      |      | 0.1  |
| Leukemia                        | 2.4                | 3.2                |                   | 7/59 [366] | 0.5 |
| Bone and soft tissue            |                    |                    |                   |        |        |        |      |      |      |
| OS                              | 1/59               | 1/59               |                   | 1/59   | 1/59   | 1/59   |      |      | 7/59 |
| EWS                             | 1.4                | 0.5                |                   |        |        |        |      |      | 0.5  |
| Skin                            |                    |                    |                   |        |        |        |      |      |      |
| Melanoma                        | 1.6                | 0.64               |                   | 5      | 2      | 1.5    | 1.7  | 1.7  | 12   |

BC breast cancer, BLCA bladder cancer, CRC colorectal carcinoma, EC endometrial cancer, ESCA esophageal cancer, EWS Ewing’s sarcoma, GBM glioblastoma, GC gastric cancer, HCC hepatocellular carcinoma, HL Hodgkin’s lymphoma, KC kidney cancer, LC lung cancer, MBM medulloblastoma, MM multiple myeloma, NHL non-Hodgkin’s lymphoma, NSCLC non-small cell lung cancer, OC ovarian cancer, OS osteosarcoma, PC pancreatic cancer, PCa prostate cancer, SCLC small cell lung cancer, TC thyroid cancers, Te Ca testicular cancer
single class III PI3K is hVPS34 (PIK3C3). When PI3K is activated by a variety of upstream cell-surface receptors, including growth factor, antigen, costimulatory, cytokine, chemokine, and Toll-like receptors (TLRs), class I PI3Ks catalyzes the conversion of phosphatidylinositol 4,5-biphosphate (PI(4,5)P₂) with phosphorylation at the D3 position of the inositol ring to the second messenger phosphatidylinositol 3,4,5-triphosphate (PIP₃). Two PIP₃-binding Pleckstrin homology (PH) domain-containing proteins linked to PI3K activity in all cells, including B cells, are the serine/threonine kinases AKT and phosphoinositide-dependent kinase-1 (PDK-1) [2–5].

AKT is an evolutionarily conserved serine protein kinase from the protein kinase AGC subfamily, which is composed of three conservative structure domains, including N-terminal PH domain, a short C-terminal tail containing a regulatory hydrophobic motif (HM) and a linker region with a central kinase catalytic domain [6]. AKT contains three highly conserved homologous subtypes, AKT1/PKBα (AKT1), AKT2/PKBβ (AKT2) and AKT3/PKBγ (AKT3). On the cell membrane, AKT is recruited via its PH domain ascribing to the accumulation of PI(3,4,5)P₃ and PI(3,4)P₂ (less extent), and plays a catalytic role by activating two regulatory sites, including a threonine phosphorylated by PDK1 at Thr308(AKT1), Thr309(AKT2), Thr305(AKT3) and a serine phosphorylated by the mammalian Target of Rapamycin (mTOR) Complex mTORC2 at Ser473(AKT1), Ser474(AKT2), Ser472(AKT3) respectively as well as specifically [7, 8]. Massive researches have shown that AKT regulates vital downstream effector molecules, such as FOXO, mTOR, GSK3b, and many other effectors via phosphorylation cascade reaction, which is modulated by lipid and protein phosphatases, to control cell growth, proliferation, survival, genome stability, glucose metabolism, and neovascularization [9–12]. However, the activities of these phosphatases are frequently lost or inactivated evidently in human cancer, followed by the result of AKT hyperactivation.

When talking about PI3K/AKT pathway, we have to mention phosphatase and tensin homolog deleted on chromosome 10 (PTEN), the primary negative regulator of the PI3K/AKT pathway. As a lipid phosphatase, PTEN directly suppresses the activation of PI3K/AKT pathway via converting the PIP₃ generated by PI3K back to PIP₂. The p85α regulatory subunit has a dual effect on the p110α catalytic subunit, since p85α inhibits the activity of p110α while it plays an important role in the stability of p110α. In addition, the p85α regulatory subunit has been known to directly bind PTEN and enhance its activity to promote the conversion of PIP₃ to PIP₂ [13, 14]. Indeed, the abnormality of PTEN have been validated in diverse cancers, even directly related with carcinogenesis in some cancers.

Following the emerging alterations of PI3K/AKT pathway genes have been widely reported in cancers recently, the inhibitors of PI3K/AKT pathway have brought a new era for targeted therapy of cancer. Since the first approval of idelalisib (CAL-101) validated the druggability of the PI3K pathway, more and more PI3K inhibitors have been created. They are generally divided into pan-PI3K (targeting all four isoforms of class I PI3K), isoform-selective (targeting single isoform of class I PI3K) and dual inhibitors (highlighted by dual PI3K/mTOR inhibitors). Comparatively, the number of AKT inhibitors which have been explored in clinical trials is less than that of PI3K inhibitors. AKT inhibitors mainly include two separate classes: Allosteric inhibitors and ATP-competitive inhibitors. The former prevents localisation of AKT by PH domain to the plasma membrane, thereby blocking AKT phosphorylation and activation. The latter targeting the phosphorylated conformation of AKT include first generation and second generation inhibitors [15, 16]. These PI3K/AKT inhibitors have shown their various aptitude for anticancer in preclinical experiments or clinical trials, even druggable value for the anticancer treatment.

In this review, we present the comprehensive work of PI3K/AKT pathway with a new perspective in various cancer sites, in which elevated PI3K/AKT pathway is considered as a hallmark. Firstly, we state the abnormalities of PI3K/AKT pathway and summarize the roles of PI3K/AKT in aberrant signaling cascades in human cancers. Furthermore, we list the involvement of the PI3K/AKT inhibitors in the clinical trials of targeted therapies in cancers. Meanwhile, we briefly provide preliminary findings in the context of resistance to targeted therapies. Finally, we discuss the confusion and the future of the PI3K/AKT pathway.

Recent studies and results

Profiling the PI3K/AKT pathway in the brain and central nervous system tumors

Considering that the incidence and mortality of the brain and central nervous system tumors is 1.6% and 2.5% respectively in the worldwide (https://gco.iarc.fr/, Table 1), particularly the most common primary malignant tumor, glioblastoma multiforme (GBM), contributes to the poor prognosis partly for its tolerance of radiation therapy, hyper-activation of PI3K/AKT pathway in GBM caused by the mutations of PIK3CA or PIK3R1 (18.3%) and other PI3K family genes (6.8%) has urged researchers to seek novel targeted treatments to control the disease [17–19]. Moreover, knockdown of PIK3CA or PIK3R1 significantly inhibits cell viability, migration and invasion in GBM cells via hypo-activation of AKT and FAK [20]. In addition, overexpression of p110β is more frequently detected in a series of GBM cell lines.
than in the patient tumor samples. **PIK3CB** knockdown suppresses cell proliferation and induces caspase-dependent apoptosis in GBM in *vitro* and *vivo* instead of suppressing GBM cell migration [21–23]. Therefore, PI3K inhibitors have been seriously studied in GBM for decades and some have achieved significant success in treating GBM.

As a matter of fact that more than 50 PI3K inhibitors have been designed and produced for cancer treatment, but only a minority of them such as BKM120, XL147, XL765 and GDC-0084 have successfully entered into clinical trials for GBM treatment (https://clinicaltrials.gov, Table 2) [18]. Some p110α isoform-selective inhibitors, such as A66 or PIK-75, could effectively suppress the GBM cell growth, survival and migration in *vitro* [24], while inhibition of p110β by TGX-221 only arrests cell migration, and inhibition of p110δ by IC87114 or CAL-101 moderately blocks cell proliferation and migration [22, 25]. However, PI3K inhibitors including A66 and BEZ235 are observed to increase the expression of cancer stem cell (CSC) genes (SOX2, OCT4 and MSI1) in GBM CSC models, which exhibit therapy resistance [26].

By the way, although AKT isoforms are observed to play different roles in GBM, including AKT3 delays tumor progression [27], as a matter of fact, the AKT inhibitor perifosine is tolerable but ineffective as monotherapy for GBM progression [27], as a matter of fact, the AKT inhibitor perifosine is tolerable but ineffective as monotherapy for GBM [28]. AKT inhibitors remain elusive and bear the weight of further examination in treating GBM.

Notably, building on that 22% genetic alterations of **PTEN** was detected in GBM (https://www.cbioportal.org, Table 1), especially deep deletion, which caused the loss of function of PTEN tumor suppressor, PTEN was deeply involved in the pathological effects of PI3K/AKT pathway in GBM [29]. Meanwhile, genetic loss of **PTEN** is associated with each subtype of GBM [30].

Additionally, glucose regulated protein 78 (GRP78) interacts with α2-macroglobulin to activate AKT1 via PDK1, as well as mTOR to enhance cancer cell proliferation and radiotherapy resistance in GBM [31–33]. Anti-GRP 78 antibody can restore cancer cells to sensitivity to radiation therapy, which inhibits cell proliferation and enhances apoptosis, and has the advantage of targeting against cancer cells without affecting normal cells. Moreover, combination of anti-GRP 78 antibody and radiation therapy (XRT) shows better inhibitory effect on tumor [31].

Compared to GBM, the genetic alteration of **PIK3CA** (2%) and **PIK3R1** (0.3%) in medulloblastoma (MBM, Table 1), which is the most aggressive malignant brain tumor that highly occurs in children and survival rate can reach 70% after active treatment, are less frequently observed [34]. However, enhance phosphorylation of AKT via PI3K or mTOR to restrain GSK3 in MBM, which lead to SOX9 degradation is reduced due to the facts that FBW7 degrades SOX9 under the guidance of GSK3. The loss of FBW7 function increases SOX9 protein levels, increasing the malignancy of cancer and resistance to cisplatin [35]. As a major oncoprotein inhibitor, once FBW7 is deleted or mutated, it can cause tumors to occur directly [36, 37]. So targeted inhibition of the PI3K pathway has a bright therapeutic potential in MBM. Moreover, experiments show that combination of PI3K inhibitor, mTOR inhibitor and cisplatin can achieve better therapeutic effect [35], and how well LY3023414 works in recurrent MBM is being tested in an ongoing clinical trial (NCT03213678, Table 2).

**Aberration of the PI3K/AKT pathway in the cancer of endocrine system**

Thyroid cancer (TC) is the most common malignancy in the endocrine system with a global incidence rate of 3.1% but a relatively lower lethality (0.4%, Table 1). In view of the fact that follicular epithelial cell–derived TC accounts for >95% of all thyroid malignancies, TC histologically comprises papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) [38]. Although PDTC and ATC only account for approximately 5%–10% of TC, but they have brought great clinical challenges since they beget two-thirds of TC-related deaths [39]. Obviously, the overall genetic alterations of PI3K/AKT pathway in TC is inconspicuous (Table 1), but genetic mutations in PI3K/ AKT pathway are common in PDTC and ATC, specifically more common in ATC than in PDTC. Besides **PIK3CA** (18% vs. 2%) and **PTEN** (15% vs. 4%), mutations of **PIK3C2G** (6% vs. 1%), **PIK3CG** (6% vs. 1%), **PIK3C3** (0 vs. 1%), **PIK3R1** (0 vs. 1%), **PIK3R2** (3% vs. 0), **AKT3** (0 vs. 1%) are also observed in ATC and PDTC respectively [40]. REC8, TEKT4, ING5, c-Met, HIPPI, PIG3, TBX1, CRLF1, INPP4B, MAPK4, miR-34a, -125b, -126, -145, -146b, -148a and -176, as well as lncRNA LINCO03121, ABHD11-AS1, H19 and XIST regulate TC cell growth, tumor progression, migration, metastasis or epithelial–mesenchymal transition (EMT) through activating PI3K/AKT pathway [41–61]. Actually, exclusive activating mutations of **BRAF** (60% vs. 33% and 38%) in PTC are more frequently observed than in PDTC and ATC [40], while mice experiments show that co-mutation of **BRAF** and **PIK3CA** can promote the development of lethal ATC, but neither **BRAF** nor **PIK3CA** mutations alone can [62]. In addition, mutations in **BRAF** and **PIK3CA** can activate the MAPK pathway and the PI3K/ AKT pathway respectively and lead to the occurrence of ATC, whereas dual blocking PI3K and MAPK pathways can effectively inhibit ATC [63]. Dual PI3K/HDAC inhibitor CUDC-907 inhibits TC growth and metastases, and may be a promising treatment strategy for advanced, metastatic TC [64]. Moreover, whether CUDC-907 was safe and effective in ATC and PDTC patients had been attempted in a
Table 2  Clinical trial of PI3K Inhibitors in cancers (as of December 2019) (https://clinicaltrials.gov)

| System                | Cancer  | Subunit | Inhibitors | Characteristic                                                                                     | Clinical trials                  |
|-----------------------|---------|---------|------------|---------------------------------------------------------------------------------------------------|----------------------------------|
| Brain and central nervous | GBM     | Pan-    | BKM120     | To assess the safety and the dose of the combination of INC280 and BKM120, as well as the anti-tumor activity of the combination, in patients with recurrent GBM with mutations or homozygous deletion of PTEN or PTEN negative by IHC | I/II NCT01870726                |
|                       |         |         | XL147      | To measure what effect XL147 has on tumor tissue in subjects with recurrent GBM who are candidates for surgical resection | I NCT01240460                    |
|                       |         | Dual    | GDC-0084   | To assess the safety, PK and Efficacy of GDC-0084 in newly-diagnosed GBM                         | II NCT03522298                   |
|                       |         |         | XL765      | To measure what effect XL765 has on tumor tissue in subjects with recurrent GBM who are candidates for surgical resection | I NCT01240460                    |
| MBM                   | Dual    | LY3023414 |           | To study how well LY3023414 works in treating patients with recurrent MBM2                       | II NCT03213678                   |
| UM                    | IS      | BYL719   |            | Phase Ib Trial of AEB071 in combination with BYL719 in patients with metastatic UM                 | I NCT02273219                    |
| Endocrine             | TC      | Pan-    | BKM120     | Evaluating the efficacy and safety of BKM120 in the treatment of patients with advanced or metastatic differentiated TC | II NCT01830504                   |
|                       |         | Dual    | CUDC-907   | To see if CUDC-907 will shrink tumors in people with advanced TC                                  | II NCT03002623                   |
|                       | IS      | BYL719   |            | To study the safety and efficacy of BYL719 with Everolimus or BYL719 with Everolimus and Exemestane in advanced PNETs | I NCT02077933                    |
| Respiratory           | SCLC    | Pan-    | BKM120     | Combine BKM120 with cisplatin and etoposide may kill more tumor cells                            | I NCT02194049                    |
|                       | NSCLC   | Pan-    | BKM120     | BKM120 and pemetrexed disodium may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Giving BKM120, carboplatin, and pemetrexed disodium together may kill more tumor cells | I NCT01723800                    |
|                       |         |         |            | The safety, tolerability and RP2D of the combination of gefitinib and BKM120 will be determined | I NCT01570296                    |
|                       |         |         |            | Giving BKM120, gemcitabine hydrochloride, and cisplatin may be a better treatment for solid tumors | I NCT01971489                    |
|                       |         |         |            | To determine the MTD/RP2D of BKM120 in combination with docetaxel. Subsequently the MTD/RP2D will be investigated in a Phase II randomized trial in patients with advanced or metastatic squamous NSCLC | I NCT01911325                    |
|                       |         |         |            | GDC-0032 To explore the effects of GDC-0032 in treating patients with stage IV squamous cell lung cancer | II NCT02785913                    |
|                       |         |         |            | GDC-0941 This is an open-label, multicenter, Phase Ib dose-escalation study to assess the safety, tolerability and PO of GDC-0941 | I NCT00974584                    |
| System | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|--------|---------|------------|---------------|-----------------|
| IS | CAL-101 | IS | CAL-101 | To determine the safety and effectiveness of the combination of pembrolizumab and CAL-101 in NSCLC patients who has stopped responding to immune therapy and see if adding CAL-101 to pembrolizumab will increase response rates vs. pembrolizumab alone | I/II NCT03257722 |
| BYL719 | IS | BYL719 | To evaluate the overall response rate of NSCLC patients | II NCT02276027 |
| AZD8186 | IS | AZD8186 | To explore the efficacy of AZD8186 as monotherapy or in combination with abiraterone acetate or AZD2014 in patients with squamous NSCLC | I NCT01884285 |
| Dual | PKI-587 | Dual | PKI-587 | Study of PD-0332991 in combination with PKI-587 for patients with advanced squamous cell lung solid tumors | I NCT03065062 |
| PKI-587 | Dual | PKI-587 | To determine if PKI-587 given in combination with paclitaxel and carboplatin will work against unresectable NSCLC | I/II NCT02920450 |
| LY3023414 | IS | LY3023414 | To find a recommended dose level and schedule of dosing LY3023414 that can safely be taken by participants with advanced or metastatic cancer | I NCT01655225 |
| NPC | Pan- | NPC | BKM120 | To study the SE and BD of BKM120 in combination with cetuximab and how well it works in treating patients with recurrent or metastatic head and neck cancer | I/II NCT01816984 |
| LSCC | Pan- | LSCC | BKM120 | To assess tolerability of the combining standard chemoradiotherapy with weekly cisplatin and BKM120 in high risk patients with locally advanced SCCHN | I NCT02113878 |
| Digestive | ESCC | Digestive | Pan- | BKM120 | BKM120 is currently tested in clinical trials, and it is used for patients with ESCC after failure of first line chemotherapy | II NCT01806649 |
| IS | BYL719 | IS | Byl719 | During or after palliative first-line platinum-based chemotherapy, patients with ESCC will be screened for NGS-based molecular screening. The patients with the genetic alteration of PI3Ks will be treated with Byl719 and be observed its efficacy | II NCT03292250 |
| GC | Pan- | GC | BKM120 | To determine the MTD and/or RP2D of a combination of imatinib and BKM120 in the treatment of 3rd line GIST patients | I NCT01468688 |
| IS | GSK2636771 | IS | GSK2636771 | To evaluate the safety, PK and clinical activity of GSK2636771 administered in combination with Paclitaxel in advanced GC having alterations in PI3K pathway genes | I/II NCT02615730 |
| GSK2636771 | IS | GSK2636771 | To evaluate the ORR of patients targeted study agent(s) in patients with advanced refractory cancers | II NCT02465060 |
| BYL719 | IS | BYL719 | To investigate the safety of BYL719 and AUY922 in patients with advanced GC, and to determine the MTD and/or RDE of both drugs in combination | I NCT01613950 |
| System | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|--------|---------|------------|----------------|-----------------|
| **CRC** | Pan- | BKM120 | To determine whether treatment with BKM120 demonstrates sufficient efficacy in patients with PI3K-activated tumors, such as CR, OC to warrant further study | II | NCT01833169 |
| IS | BYL719 | To assess the safety and efficacy of LGX818 when combined with cetuximab or combined with cetuximab and BYL719 in patients with BRAF mutant metastatic CRC | I/II | NCT01719380 |
| TAK-117 | Dual | To test if combining TAK-117 with canagliflozin will improve efficacy in the treatment of advanced solid tumors | I/II | NCT04073680 |
| **GIST** | Pan- | BKM120 | To determine the MTD and/or RP2D of a combination of imatinib and BKM120 in the treatment of 3rd line GIST patients | I | NCT01468688 |
| IS | BYL719 | To determine the MTD and/or RP2D of a combination of imatinib and BYL719 in the treatment of 3rd line GIST patients | I | NCT01735968 |
| **HCC** | Dual | SF1126 | To determine the MTD or MRD and the RP2D of SF1126 in combination with nivolumab in adult patients with advanced HCC | I | NCT03059147 |
| IS | GSK2636771 | To evaluate the ORR of patients targeted study agent(s) in patients with advanced refractory cancers | II | NCT02465060 |
| **PC** | Pan- | BKM120 | To investigate the safety, PK and PD of BKM120 plus GSK1120212 in advanced RAS or BRAF mutant PC patients | I | NCT01155453 |
| | | To investigate the safety, PK and PD of BKM120 plus MEK162 in advanced RAS or BRAF mutant PC patients | I | NCT01363232 |
| IS | GSK2636771 | To evaluate the ORR of patients targeted study agent(s) in patients with advanced refractory cancers | II | NCT02465060 |
| BYL719 | Dual | To see primarily if BYL719 is safe to be given to patients in combination with gemcitabine and nab-paclitaxel in locally advanced and metastatic PC | I | NCT02155088 |
| PKI-587 | PKI | To study PD-0332991 in combination with PKI-587 for patients with advanced PC solid tumors | I | NCT03065062 |
| BEZ235 | Dual | To study the safety, PK and PD of BEZ235 Plus MEK162 in advanced PC solid tumor patients | I | NCT01337765 |
| LY3023414 | | To evaluate the safety and efficacy of abemaciclib alone and in combination with other drugs including LY3023414 in participants with previously treated metastatic PDAC | II | NCT02981342 |
| **Reproductive BC** | BC | BKM120 | Evaluating the clinical activity of BKM120 in patients with metastatic TNBC | II | NCT01629615 |
| | | Evaluating BKM120 in combination with trastuzumab and paclitaxel in HER2+ primary BC | II | NCT01816594 |
Table 2 (continued)

| System | Cancer       | Subunit | Inhibitors | Characteristic                                                                 | Clinical trials                          | Phase | Gov identifier |
|--------|--------------|---------|------------|--------------------------------------------------------------------------------|------------------------------------------|-------|---------------|
|        |              |         |            | Evaluating the safety profile/tolerability and preliminary anti-tumor effect of BKM120 and endocrine therapy combination and BEZ235 and endocrine therapy combination in postmenopausal patients with HR + MBC | I                                           |       | NCT01248494   |
|        |              |         |            | To determine whether treatment with BKM120 plus letrozole led to an increase in pathologic clinical response and ORR compared to treatment with placebo plus letrozole in patients with BC | II                                          |       | NCT01923168   |
|        |              |         |            | To assess the MTD and/or RP2Ds, safety and tolerability, the single and multiple dose PK profile and assess the preliminary antitumor activity of BYL719 and BKM120 in combination with tamoxifen plus goserelin acetate in premenopausal advanced HR + BC patients | I                                           |       | NCT02058381   |
|        |              |         |            | BKM120 and anti-HER2 therapy may have a synergistic antitumor activity in preclinical model of HER2 + BC | I/II                                        |       | NCT01589861   |
|        |              |         |            | To determine the MTD and/or RP2D and schedule for BKM120 given in combination with GSK1120212 in patients with selected, advanced solid tumors | I                                           |       | NCT01155453   |
|        |              |         |            | Inhibition of PI3K by BKM120 may enhance apoptosis in ER + BC cells | I                                           |       | NCT01339442   |
|        |              |         |            | To look for MTD, and also to see if the combination of BKM120 or BYL719 and olaparib is effective in treating BC | I                                           |       | NCT01623349   |
|        |              |         |            | To explore the efficacy and safety of BKM120 in combination with tamoxifen in patients with ER/PR +, HER2- BC with prior exposure to antihormonal therapy | II                                          |       | NCT02404844   |
|        |              |         |            | To determine the efficacy and safety of treatment with BKM120 plus Fulvestrant vs. Placebo plus Fulvestrant in postmenopausal women with HR +, HER2-, AI-treated, locally MBC whose disease progressed on or after mTORi-based treatment | III                                         |       | NCT01633060   |
|        |              |         |            | Consistent, dose-dependent PD activity has been demonstrated and clear signs of anti-tumor activity have been seen with BKM120 | I                                           |       | NCT01513356   |
|        |              |         |            | GDC-0941 | Examining how well the combination of GDC-0941 and cisplatin work in treating patients with metastatic AR- TNBC | I/II                                         |       | NCT01918306   |
|        |              |         |            | Assessing the safety, tolerability and efficacy of GDC-0032 or GDC-0941, in combination with PAIbociclib, with the subsequent addition of Fulvestrant in PIK3CA-mutant BCs | I                                           |       | NCT02389842   |
|        |              |         |            | To assess the safety, tolerability, and PO of pictilisib administered with letrozole or IV paclitaxel with and without IV bevacizumab or IV trastuzumab in participants with locally recurrent or metastatic BC | I                                           |       | NCT00960960   |
| System | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|--------|---------|------------|----------------|----------------|
| GDC 0032 | AR + TNBC | GDC 0032 is given together with enzalutamide and to see how well they work in treating patients with metastasis AR + TNBC | I/II | NCT02457910 |
|         |        |         |            | Assessing the safety, tolerability and efficacy of GDC-0032 or GDC-0941, in combination with PaBiciclib, with the subsequent addition of Fulvestrant in PIK3CA-mutant BCs | I | NCT02389842 |
|         |        |         |            | To determine RP2D of GDC-0032 plus tamoxifen in HR +, HER2-MBC patients who have progressed after prior endocrine treatment | I/II | NCT02285179 |
| BAY 80–6946 |         |         |            | To study the SE and how well BAY 80–6946 works when given together with fulvestrant in treating postmenopausal patients with ER + and HER2- BC that has spread to other places in the body and progressing after prior treatment | I/II | NCT03803761 |
|         |        |         |            | The addition of BAY 80–6946 to the usual treatment (trastuzumab and pertuzumab) could shrink the cancer or stabilize it for longer duration as compared to the usual treatment alone | I/II | NCT04108858 |
|         |        |         |            | Adding BAY 80–6946 to the usual therapy of Fulvestrant and abemaciclib may work better than giving Fulvestrant and abemaciclib alone in treating patients with BC | I/II | NCT03939897 |
|         |        |         |            | BAY 80–6946 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | II | NCT03377101 |
|         |        |         |            | Giving BAY 80–6946, letrozole, and palbociclib may work better in treating patients with BC | I/II | NCT03128619 |
| BYL719 |         |         |            | IS | BYL719 in combination with letrozole may kill more tumor cells | I | NCT01791478 |
|         |        |         |            | BYL719 is an oral drug that may help T-DM1 to work better | I | NCT02038010 |
|         |        |         |            | Determining the MTD, safety and effectiveness of BYL719 combined with Nab-Paclitaxel in treating patients with HER2-BC, along with the determination of how long this drug combination will keep the disease from getting worse | I/II | NCT02379247 |
|         |        |         |            | A Study of BYL719 in combination with paclitaxel in advanced solid tumors followed by two expansion phases in locally chemotherapy naive HER2-MBC patients and in recurrent and metastatic HNSCC patients pre-treated with platinum-based therapy | I | NCT02051751 |
|         |        |         |            | To determine whether treatment with BYL719 plus letrozole led to an increase in pathologic clinical response and ORR compared to treatment with placebo plus letrozole in patients with BC | II | NCT01923168 |
|         |        |         |            | To assess the MTD and/or the RP2D(s), safety, tolerability, the single and multiple dose PK profile and the preliminary anti-tumor activity of BYL719 and BKM120 in combination with tamoxifen plus goserelin acetate in premenopausal advanced HR + BC patients | I | NCT02058381 |
|         |        |         |            | To describe safety and tolerability of the BYL719 and everolimus or BYL719, everolimus and exemestane combinations | I | NCT02077933 |
| System  | Cancer    | Subunit | Inhibitors | Characteristic                                                                                                                                                                                                 | Clinical trials                                                                 |
|---------|-----------|---------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|         |           |         |            | To study BYL719 monotherapy in adult patients with advanced MBC progressing after first line therapy                                                                                                         | II NCT02506556                                                                   |
|         |           |         |            | BKM120, BYL719 and olaparib are drugs that may stop cancer cells from growing abnormally                                                                                                                     | I NCT01623349                                                                   |
|         |           |         |            | BYL719 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth                                                                                                              | I NCT03207529                                                                   |
|         |           |         |            | Assessing the efficacy and safety of BYL719 plus Fulvestrant or letrozole, based on prior endocrine therapy, in patients with PIK3CA mutation with advanced BC who have progressed on or after prior treatments | II NCT03056755                                                                   |
|         |           |         |            | To investigate combination of BYL719 with Fulvestrant in post-menopausal patients with locally advanced or MBC whose tumors have an alteration of the PIK3CA gene                                                                 | I NCT01219699                                                                   |
|         |           |         |            | MEN1611 To identify the appropriate dose of MEN1611 to be used in combination with Trastuzumab with/without Fulvestrant for the treatment of HER2 + MBC                                                                 | I NCT03767335                                                                   |
|         |           |         |            | BAY80-6946 It will determine the MTD and the RP2D of BAY80-6946 in combination with paclitaxel                                                                                                               | I NCT01411410                                                                   |
|         |           |         |            | XL147 Phase 1 will evaluate the MTD of XL147 or XL765 when given in combination with letrozole. Phase 2 will evaluate the efficacy and safety of these combinations in subjects with BC refractory to a non-steroidal aromatase inhibitor that is ER+/PGR+ and HER2- | I/II NCT01082068                                                                  |
|         |           |         |            | TAK-117 To test if combining TAK-117 with canagliflozin will improve efficacy in the treatment of advanced solid tumors                                                                                       | I/II NCT04073680                                                                  |
| Dual    | BEZ235    |         |            | Evaluating the safety profile/tolerability and preliminary anti-tumor effect of BKM120 and endocrine therapy combination and BEZ235 and endocrine therapy combination in postmenopausal patients with HR + MBC | I NCT01248494                                                                   |
|         |           |         |            | This is a first-in-human, phase I/II clinical research study with BEZ235                                                                                                                                  | I NCT00620594                                                                   |
|         | CUDC-907  |         |            | Evaluating the safety, tolerability and PK of CUDC-907 administered orally to subjects with advanced/relapsed solid tumors                                                                                   | I NCT02307240                                                                   |
|         | LY3023414 |         |            | To investigate the safety of prexasertib in combination with other anti-cancer drugs including LY3023414 in participants with advanced or metastatic cancer                                                                 | I NCT02124148                                                                   |
|         | PF-04691502|         |            | The combination of PF-04691502 and exemestane might mitigate resistance to hormonal therapy and result in greater clinical benefit than exemestane alone in women with advanced ER + BC | II NCT01658176                                                                   |
|         |           |         |            | Published data support the hypothesis that a PF-04691502 in combination with letrozole might mitigate the intrinsic or acquired resistance to hormonal therapy and restore hormone sensitivity in high risk patient population of hormone-sensitive BCs | I NCT01430585                                                                   |
| System | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|--------|---------|------------|----------------|-----------------|
|        |        |         | PKI-587    | Preclinical and first-in-human studies have shown a manageable safety profile with predictable toxicity for this class of drugs | I NCT02626507 |
|        |        |         | XL765      | Phase 1 will evaluate the MTD of XL147 or XL765 when given in combination with letrozole. Phase 2 will evaluate the efficacy and safety of these combinations in subjects with BC refractory to a non-steroidal aromatase inhibitor that is ER+ / PGR+ and HER2- | I/II NCT01082068 |
|        |        |         | PQR309     | To evaluate clinical safety, efficacy and PK of PQR309 in combination with standard dose of eribulin in patients with locally advanced or metastatic HER2-TNBC | I/II NCT02723877 |
| OC     | Pan    |         | BAY 80–6946| Niraparib and BAY 80–6946 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | I NCT03586661 |
|        |        |         | BKM120     | To look for MTD, and also to see if the combination of BKM120 or BYL719 and olaparib is effective in treating OC | I NCT01623349 |
| IS     |        |         | BYL719     | To look for MTD, and also to see if the combination of BKM120 or BYL719 and olaparib is effective in treating OC | I NCT01623349 |
| Dual   |        |         | CUDC-907   | Evaluating the safety, tolerability and PK of CUDC-907 administered orally to subjects with advanced/relapsed solid tumors | I NCT02307240 |
| FTC    | Pan    |         | BAY 80–6946| Niraparib and BAY 80–6946 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | I NCT03586661 |
| EC     | Pan    |         | BAY 80–6946| Niraparib and BAY 80–6946 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | I NCT03586661 |
|        |        |         | BAY 80–6946| BAY 80–6946 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | II NCT02728258 |
| IS     |        |         | TAK-117    | To test the hypothesis that combining TAK-117 with canagliflozin will improve efficacy in treating patients with advanced EC | I/II NCT04073680 |
|        |        |         | MLN1117    | Study of MLN0128, combination of MLN0128 with MLN1117, Paclitaxel and combination of MLN0128 with Paclitaxel in women with EC | II NCT02725268 |
| Dual   |        |         | PF-04691502| To investigate the individual safety and efficacy of PF-04691502 in patients with recurrent EC | II NCT01420081 |
|        |        |         | PKI-587    | To investigate the individual safety and efficacy of PKI-587 in patients with recurrent EC | II NCT01420081 |
|        |        |         | LY3023414  | To determine the effectiveness and the side effects of LY3023414 in treating the EC | II NCT02549989 |
|        |        |         | DS-7423    | To determine the MTD in subjects with advanced solid tumors and measure the effects of DS-7423 on the patients with advanced EC | I NCT01364844 |
### Table 2 (continued)

| System          | Cancer | Subunit | Inhibitors | Characteristic                                                                 | Clinical trials |
|-----------------|--------|---------|------------|---------------------------------------------------------------------------------|-----------------|
| Genitourinary   | PCa    | Pan-    | BKM120     | To evaluate BKM120 with cabazitaxel in the treatment of patients with advanced PCa | II NCT02035124  |
|                 | IS     |         | AZD8186    | To explore the efficacy of AZD8186 as monotherapy or in combination with abiraterone acetate or AZD2014 in patients with CRPC | I NCT01884285  |
|                 |        |         | GSK2636771 | To determine the RP2D for the combination GSK2636771 with enzalutamide in male subjects with metastatic CRPC | I NCT02215096  |
|                 |        | Dual    | LY3023414  | To evaluate the safety and effectiveness of LY3023414 in combination with enzalutamide in men with PCa | II NCT02407054  |
|                 |        |         | GDC-0980   | Phase Ib is to determine RP2D of ipataserib administrated in combination with abiraterone and of GDC-0980 administrated in combination with abiraterone | I/II NCT01485861 |
| RCC             | IS     |         | BYL719     | To describe safety and tolerability of the BYL719 and everolimus or BYL719, everolimus and exemestane combinations | I NCT02077933  |
|                 |        |         | MLN1117    | To evaluate the efficacy and safety of single-agent MLN0128 and the combination of MLN0128 + MLN1117 compared with everolimus in the treatment of adults with advanced or metastatic Clear-Cell RCC | II NCT02724020 |
|                 |        |         | GSK2636771 | To evaluate the ORR of patients targeted study agent(s) in patients with advanced refractory cancers | II NCT02465060  |
| BLCA           | Pan-   |         | BKM120     | To learn what effects, good and/or bad, BKM120 has on advanced urothelial cancer | II NCT01551030  |
|                 | IS     |         | GSK2636771 | To evaluate the ORR of patients targeted study agent(s) in patients with advanced refractory cancers | II NCT02465060  |
| Hematologic    | Lymphoma | Pan-   | BAY80-6946 | To study the SE and BD of BAY 80–6946 and nivolumab in treating patients with metastatic solid tumors or lymphoma | I NCT03502733  |
|                 |        |         |            | To investigate safe, feasible and beneficial of BAY80-6946 in pediatric patients with recurrent or refractory lymphoma | I/II NCT03458728 |
|                 |        |         |            | To evaluate the ORR of patients targeted study agent(s) in patients with advanced refractory cancers | II NCT02465060  |
|                 |        |         | BKM120     | To find out what effects, good and/or bad, BKM120 has on lymphoma and the central nervous system | II NCT02301364  |
|                 |        |         | TGR-1202   | Phase I is to determine the MTD, DLT, safety and toxicity of the combinations of TGR-1202 and carfilzomib in participants with R/R NHL and HL. If the combination is found to be feasible, phase II consisting of a 2-stage design of the combination will be initiated | I/II NCT02867618 |
|                 |        |         | IPI-145    | To evaluate the safety and PK of IPI-145 in Japanese participants with R/R lymphoma | I NCT02598570  |
|                 |        |         |            | To characterize the safety, MTD and preliminary efficacy profile of IPI-145 given in combination with rituximab, or bendamustine plus rituximab, to subjects with select R/R hematologic malignancies | I NCT01871675  |
Table 2 (continued)

| System | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|--------|---------|------------|---------------|-----------------|
| Dual   | PQR309 | To determine the MTD, RP2D and preliminary antitumor activity of PQR309 administered orally, as once daily capsules continuously and on intermittent schedule in patients with R/R lymphomas | II | NCT02249429 |
|        | VS-5584| To evaluate the safety (including the RP2D), PK and the anti-cancer activity of VS-5584 | I | NCT01991938 |
|        | WX390  | WX390 is a novel oral small molecular that has demonstrated potent inhibitory effects on multiple human tumor xenografts | I | NCT03730142 |
|        | GSK1059615| To define the RP2D, toxicity profile, PK and biologically active dose range of GSK1059615 | I | NCT00695448 |
|        | CUDC-907| To assess the safety, tolerability and PK of orally administered CUDC-907 in subjects with R/R lymphoma | I/II | NCT01742988 |
|        | GSK2126458| To determine the RP2D of GSK2126458 based on safety and tolerability, PK, PD and preliminary evidence of clinical activity | I | NCT00972686 |
| HL     | IS     | TGR-1202| To evaluate the safety and effectiveness of TGR-1202 in combination with brentuximab vedotin in patients with HL. | I | NCT02164006 |
|        | RP6530 | To evaluate safety, tolerability and to establish the MTD for RP6530 in combination with Pembrolizumab in patients with CHL. | I/II | NCT03471351 |
| NHL    | Pan-   | BAY80-6946| BAY80-6946 in combination with standard immunochemotherapy vs. standard immunochemotherapy in patients with relapsed iNHL. To assess the safety of BAY80-6946 in Rituximab-refractory iNHL. Part A is to evaluate the efficacy and safety of BAY80-6946 in patients with indolent or aggressive NHL, who have progressed after standard therapy. Part B is to evaluate the efficacy and safety of BAY80-6946 in patients with R/R FL. To study BD and how well BAY80-6946 plus nivolumab works in patients with Richter's transformation or transformed iNHL. To study the BD of BAY80-6946 plus chemotherapy in patients with R/R DLBCL or relapsed grade 3b FL after 1 prior line therapy. | III | NCT02626455 |
|        | BKM120 | BKM may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth | I | NCT01719250 |
|        | GDC-0941| To assess the safety, tolerability, and PK of orally administered GDC-0941 administered QD | I | NCT00876122 |
|        | GDC-0032| To assess the safety, tolerability, and PK of GDC-0032 in participants with NHL. | I | NCT01296555 |
| System | Cancer Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|----------------|------------|----------------|-----------------|
|        |                | IPI-145    | To assess the safety, PK, drug-drug interactions, and RP2D of co administered IPI-145 and Venetoclax in subjects with R/R CLL/SLL or iNHL who have not previously received a Bcl-2 or PI3K Inhibitor. Examine the effects of predefined 2 weeks IPI-145 dose holidays on tumor responses and safety/tolerability. To evaluate the safety and efficacy of IPI-145 in subjects with iNHL that is refractory to rituximab and to either chemotherapy or RIT. To evaluate the efficacy and safety of DBR vs PBR in subjects with previously-treated iNHL. | Phase | Gov identifier |
|        |                |            |                | I | NCT02640833 |
|        |                |            |                | II | NCT04038359 |
|        |                |            |                | II | NCT01882803 |
|        |                |            |                | III | NCT02576275 |
|        |                |            |                | III | NCT01796470 |
|        |                |            |                | III | NCT01732926 |
|        |                |            |                | II | NCT03711578 |
|        |                |            |                | I | NCT02006485 |
|        |                |            |                | II | NCT03127020 |
|        |                |            |                | II | NCT03213678 |
|        |                |            |                | I | NCT02049541 |
|        |                |            |                | III | NCT02367040 |
|        |                |            |                | I | NCT03886649 |
| System | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials |
|--------|--------|---------|------------|---------------|----------------|
|        |        |         | CAL-101    | To evaluate the safety of CAL-101 as post-transplantation maintenance in patients with BCL undergoing an allogeneic HSCT | I NCT03151057 |
|        |        |         |            | To assess the overall response rate, the efficacy and safety of CAL-101 in participants with previously treated iNHL that is refractory both to rituximab and to alkylating-agent-containing chemotherapy | II NCT01282424 |
|        |        |         | RP6530     | To evaluate the safety and efficacy of RP6530 in patients with hematologic malignancies | I NCT02017613 |
|        |        |         | KA2237     | To evaluate safety/tolerability, PK and PD effects of KA2237 in patients with BCL and determine the MTD in Part I of the study. In Part II, patients with BCL will be treated with KA2237 at the MTD to evaluate safety and efficacy in the patient population | I NCT02679196 |
|        |        |         | YY-20394   | To assess the tolerability, PK and efficacy of YY-20394 in patients with relapse or refractory BCL | I NCT03757000 |
| TCL    | IS     | RP6530  | To evaluate the safety, PK and efficacy of RP6530 in patients with R/R TCL | I NCT02567656 |
|        |        |         |            | To evaluate the safety and efficacy of RP6530 in patients with hematologic malignancies | I NCT02017613 |
|        |        |         |            | To characterize safety, tolerability and to establish the MTD of RP6530 in combination with Romidepsin in patients with R/R TCL. | I/II NCT03770000 |
|        |        |         | IPI-145    | This is a study of IPI-145 in patients with R/R PTCL | II NCT03372057 |
|        |        |         |            | To determine the MTD of IPI-145 with romidepsin and IPI-145 with bortezomib in R/R TCL. | I NCT02783625 |
| FL     | Pan    | BAY80-6946 | Part B is to evaluate the efficacy and safety of BAY80-6946 in patients with R/R FL | II NCT01660451 |
|        |        |         |            | To see if BAY80-6946 plus rituximab is effective at slowing the growth of FL. | II NCT03789240 |
|        | IS     | IPI-145 | To evaluate the safety and efficacy of IPI-145 administered in combination with rituximab vs. placebo in combination with rituximab in patients with previously treated CD20+FL who are not suitable candidates for chemotherapy | III NCT02204982 |
|        |        |         |            | To evaluate the safety and efficacy of IPI-145 in combination with rituximab or obinutuzumab in subjects with untreated CD20+FL. | I/II NCT02391545 |
|        |        |         | TGR-1202   | To determine the overall response rate of TGR-1202 in FL | II NCT03178201 |
|        |        |         | CAL-101    | To establish a safe and effective dosing regimen of CAL-101 in participants with R/R FL who have no other therapeutic options | III NCT02536300 |
|        |        |         | INCBO50465 | To assess the ORR of INCBO50465 treatment in patients with R/R BL | II NCT03126019 |
|        |        |         | ME-401     | A Three-Arm Study of ME-401 in subjects with R/R FL or CLL/SLL. | I NCT02914938 |
| System  | Cancer | Subunit | Inhibitors | Characteristic | Clinical trials | Phase | Gov identifier |
|---------|--------|---------|------------|---------------|----------------|-------|----------------|
| NK/TCL  | Pan-   | BAY80-6946 | BAY 80–6946 has demonstrated activity in R/R, aggressive NHLs, suggesting an ORR of 50% for TCL. BAY 80–6946 plus gemcitabine will exhibit early elimination of rapidly growing tumor cells and be a rational therapeutic modality for use in R/R PTCLs, if the overlapping toxicities can be managed | I/II | NCT03052933 |
| CLL/SLL | Pan-   | BAY80-6946 | To study how well bendamustine and rituximab in combination with BAY80-6946 work in treating patients with CLL/SLL | II | NCT04155840 |
|         | IS     | BKM120   | To find out the effects of BKM120 in CLL | II | NCT02340780 |
|         | IS     | CAL-101  | The CLL2-BCG-trial is a prospective, open-label, multicenter phase-II-trial | II | NCT02445131 |
|         |        |          | To evaluate a combination of drugs called Ofatumumab and CAL-101 as a possible treatment for CLL and SLL | II | NCT02135133 |
|         |        |          | To determine the preliminary efficacy and safety of the combination of tibrucitinib and CAL-101 with obinutuzumab in adults with R/R CLL | II | NCT02968563 |
|         | IS     | IPI-145  | To study IPI-145 and Venetoclax in subjects with R/R CLL/SLL or iNHL who have not previously received a Bcl-2 or PI3K Inhibitor | I | NCT02640833 |
|         |        |          | To examine the efficacy of IPI-145 monotherapy vs. ofatumumab monotherapy in subjects with R/R CLL/SLL | III | NCT02004522 |
|         |        |          | To examine the efficacy of IPI-145 monotherapy or ofatumumab monotherapy in subjects with CLL/SLL who experienced disease progression after treatment with IPI-145 or ofatumumab in study IPI-145–07 | III | NCT02049515 |
|         |        |          | To study IPI-145 in patients with CLL/SLL who have previously been treated with ibrutinib or another BTK Inhibitor and R/R to such therapy or discontinued such therapy due to toxicity | II | NCT03370185 |
|         |        |          | To test safety, PK and PD of IPI-145 in combination with obinutuzumab in patients with CLL/SLL previously treated with a BTKi | I | NCT02292225 |
|         | IS     | TGR-1202  | TGR-1202 may stop cancer cells from growing and this drug may help to kill cancer cells when coupled with ibrutinib | I | NCT02268851 |
|         |        |          | A study of TGR-1202 administered as a single agent in CLL patients who are intolerant to prior BTKi or prior PI3Kδ inhibitors | II | NCT02742090 |
| MCL     | IS     | INCB050465 | Evaluating efficacy and safety of 2 INCB050465 treatment regimens in subjects with R/R MCL treated either with or without a BTKi | II | NCT03235544 |
| MZL     | Pan-   | BAY80-6946 | To test the toxicity and efficacy of BAY 80–6946 in combination with Rituximab in patients with newly diagnosed or relapsed MZL | II | NCT03474744 |
|         | IS     | INCB050465 | To study INCB050465 in subjects with R/R MZL with or without prior exposure to CITADEL-204 | II | NCT03144674 |
| System | Cancer   | Subunit | Inhibitors         | Characteristic                                                                 | Clinical trials       |
|--------|----------|---------|-------------------|-------------------------------------------------------------------------------|-----------------------|
|        |          |         |                   |                                                                               | Phase | Gov identifier |
| DLBCL  | Pan-     | BAY80-6946 | To study how well BAY 80–6946 hydrochloride and nivolumab work in treating patients with R/R DLBCL or PMBLC | II     | NCT03484819   |
|        |          |         | To assess efficacy of BAY80-6946 in R/R DLBCL patients and the relationship between efficacy and a predictive biomarker | II     | NCT02391116   |
|        | IS       | INCB050465 | To assess the safety and efficacy of INCB050465 in subjects with R/R DLBCL | II     | NCT02998476   |
|        |          |         | To evaluate the safety and tolerability of INCB053914 in combination with INCB050465 in R/R DLBCL | I      | NCT03688152   |
|        | Dual     | CUDC-907  | To evaluate the efficacy and safety of CUDC-907 in subjects 18 years and older with R/R MYC-altered DLBCL | II     | NCT02674750   |
|        | PCNSL    | Pan-     | BAY80-6946        | To test the safety of combined use of the study drugs, BAY80-6946 and ibrutinib, in people with PCNSL | I/II   | NCT03581942   |
|        | MM       | IS       | BYL719            | To estimate the MTD and/or RP2D of the combination of LGH447 and BYL719 administered orally to adult patients with R/R MM | I      | NCT02144038   |
|        | Leukemia | Pan-     | BKM120            | To find the MTD of BKM120 that can be given to patients with R/R leukemia | I      | NCT01396499   |
|        |          | IS       | CAL-101           | To provide CAL-101 to individuals with relapsed, previously treated CLL who have limited treatment options | NCT02136511   |
|        |          |         | To evaluate the effect of the addition of CAL-101 to bendamustine + rituximab on PFS in participants with previously treated CLL | III    | NCT01569295   |
|        |          |         | To evaluate the effect of idelalisib in combination with rituximab on the onset, magnitude, and duration of tumor control in participants previously treated for CLL | III    | NCT01539512   |
|        |          |         | To evaluate the effectiveness of CAL-101 and rituximab in adults with CLL in a real world setting | NCT03582098   |
|        |          |         | Obtaining more in-depth information on how patients with CLL treated with CAL-101 and rituximab react to treatment | NCT03545035   |
|        |          |         | To study how well pembrolizumab alone or with CAL-101 or ibrutinib works in treating patients with CLL or other iB-NHL | II     | NCT02332980   |
|        |          |         | To evaluate efficacy, safety, tolerability and PD of entospletinib and CAL-101 in patients with CLL, FL, MCL, DLBCL, or iB-NHL | II     | NCT01796470   |
|        |          |         | To confirm the hypothesis that CAL-101 may represent a new therapeutic alternative for patients with ALL in a set of particularly complex scenarios: relapsed, refractory to conventional treatments, and old age | I/II   | NCT03742323   |
|        |          |         | To investigate the safety and clinical activity of CAL-101 in combination with chemotherapeutic agents, immunomodulatory agents and anti-CD20 mAb in subjects with R/R iNHL, MCL or CLL | I      | NCT01088048   |
|        |          |         | To investigate the safety, PK, PD, and clinical activity of CAL-101 in patients with select, R/R Hematologic Malignancies | I      | NCT00710528   |
Clinical trials

| System                           | Cancer               | Subunit | Inhibitors                        | Characteristic                                                                 | Clinical trials |
|----------------------------------|----------------------|---------|-----------------------------------|--------------------------------------------------------------------------------|-----------------|
|                                  |                      |         |                                   |                                                                                |                 |
| Bone and soft tissue             | OS or EWS Pan-       | BAY80-6946 | YY-20394                          | To determine how well the test can be used to select personalized kinase inhibitor therapy in combination with standard chemotherapy in treating patients with newly diagnosed AML and ALL | I               |
|                                  |                      |         |                                   |                                                                                | NCT02779283     |
|                                  |                      |         |                                   | To assess the tolerability, PK and efficacy of YY-20394 in patients with relapse or refractory B cell malignant hematological tumor | I               |
|                                  |                      |         |                                   |                                                                                | NCT03757000     |
|                                  |                      |         |                                   | To establish the MTD and the RP2D of BEZ235 when administered twice daily as a single agent in patients with R/R acute leukemia | I               |
|                                  |                      |         |                                   |                                                                                | NCT01756118     |
|                                  |                      |         |                                   | Phase II open-label single-arm prospective multicentric clinical trial of PKI-587 delivered by intravenous route | II              |
|                                  |                      |         |                                   |                                                                                | NCT02438761     |
|                                  |                      |         |                                   | Bone and soft tissue OS or EWS Pan-                                      | I/II             |
|                                  |                      |         |                                   | To investigate safe, feasible and beneficial of BAY80-6946 in pediatric patients with recurrent or refractory OS, EWS or lymphoma |                 |
|                                  |                      |         |                                   |                                                                                | NCT03458728     |
|                                  |                      |         |                                   | To study how well LY3023414 works in treating patients with recurrent OS, EWS or NHL | II              |
|                                  |                      |         |                                   |                                                                                | NCT03213678     |
| Skin                             | Melanoma Pan-        | BKMI20  | LY3023414                          | To study how well LY3023414 works in treating patients with recurrent OS, EWS or NHL | II              |
|                                  |                      |         |                                   |                                                                                | NCT03213678     |
|                                  |                      |         |                                   | Phase I/II study of PX-866 combined with Vemurafenib in patients with BRAF-mutant cancer including advanced melanoma | I/II             |
|                                  |                      |         |                                   |                                                                                | NCT01616199     |
| IS                               | GSK2636771           |         |                                   | To determine how well the test can be used to select personalized kinase inhibitor therapy in combination with standard chemotherapy in treating patients with newly diagnosed AML and ALL | I               |
|                                  |                      |         |                                   |                                                                                | NCT03131908     |

Table 2 (continued)

| System                          | Cancer       | Subunit | Inhibitors | Characteristic                                                                 | Clinical trials |
|---------------------------------|--------------|---------|------------|--------------------------------------------------------------------------------|-----------------|
|                                  |              |         | BAY80-6946 | To investigate safe, feasible and beneficial of BAY80-6946 in pediatric patients with recurrent or refractory OS, EWS or lymphoma | I/II            |
|                                  |              |         | LY3023414  | To study how well LY3023414 works in treating patients with recurrent OS, EWS or NHL | II              |
|                                  |              |         | PX-866     | Phase I/II study of PX-866 combined with Vemurafenib in patients with BRAF-mutant cancer including advanced melanoma | I/II            |
|                                  |              |         | GSK2636771 | To determine how well the test can be used to select personalized kinase inhibitor therapy in combination with standard chemotherapy in treating patients with newly diagnosed AML and ALL | I               |

AI aromatase inhibitor, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, BC breast cancer, BCL B-cell lymphoma, BD best dose, BLCA bladder cancer, BTKi BTK inhibitors, CHL classical Hodgkin lymphoma, CLL/SLL chronic lymphocytic leukemia or small lymphocytic lymphoma, CRC colorectal carcinoma, CRPC Castration-Resistant Prostate Cancer, DBR duvelisib in combination with bendamustine and rituximab, DLT dose limiting toxicity, EC endometrial cancer, ESCC esophageal squamous cell carcinoma, EWS Ewing’s sarcoma, FL fallopian lymphoma, FTC fallopian tube carcinoma, GBM Glioblastoma multiforme, GC gastric cancer, GIST gastrointestinal stromal tumor, HCC hepatocellular carcinoma, HL Hodgkin’s lymphoma, HNSCC head-and-neck squamous cell carcinoma, HR hormone receptor, HSTC hematopoietic stem cell transplant, iB-NHL indolent B cell non-Hodgkin’s lymphoma, iNHL indolent non-Hodgkin’s lymphoma, IS isoform-selective, IV intravenous, KC kidney cancer, MBC metastatic Breast Cancer, MBM medulloblastoma, MCL mantle cell lymphoma, MM multiple myeloma, MRD maximum recommended dose, MTD maximum tolerated dose, mTORi rapamycin inhibitor, MZL marginal zone lymphoma, NHL non-Hodgkin’s lymphoma, NSCLC non-small cell lung cancer, NK/TCL NK/T cell lymphomas, OC ovarian cancer, ORR objective response rate, OS osteosarcoma, PBR placebo in combination with bendamustine and rituximab, PC pancreatic cancer, PCu prostate cancer, PCNSL primary central nervous system lymphoma, PD pharmacodynamics, PDAC pancreatic ductal adenocarcinoma, PFS progression-free survival, PK pharmacokinetics, PMLBCL primary mediastinal large B-cell lymphoma, PNETs pancreatic neuroendocrine neoplasms, PO pharmacokinetics of oral, PTCL peripheral T-cell lymphoma, RCC renal cell cancer, RIT radioimmunotherapy, RP2D recommended phase 2 dose, R/R relapsed and/or refractory, SCLC small cell lung cancer, SE side effects, TC thyroid cancers, TCD T-cell lymphoma, TNBC triple negative breast cancer, UM uveal melanoma

terminated clinical trial (NCT03002623) besides the clinical trial of BKMI20 in patients with advanced or metastatic differentiated TCs (NCT01830504, Table 2).

**Characterization of the PI3K/AKT pathway in the respiratory system tumor**

The respiratory system tumors are composed of the upper respiratory tract tumors, such as nasopharyngeal carcinoma (NPC) and laryngeal cancer, and the lower respiratory tract tumors, which mainly refer to LC. Compared to the NPC and laryngeal cancer, LC is witnessed as the gender-free and world-wide cancer with the highest morbidity (11.6%) and mortality (18.4%, Table 1).

LC is classified into two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) including three subtypes: adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC) [65]. In the light of the fact that genetic alterations of PIK3CA (3% vs. 17%), PIK3R1 (2% vs. 1.8%), PIK3R2 (1.5% vs. 1.6),
AKT1 (0.5% vs. 2.1%), AKT2 (1.5% vs. 3%) and PTEN (8% vs. 6%) are observed in SCLC and NSCLC respectively (Table 1), the studies of treatment strategies of LC targeting PI3K/AKT pathway are in full swing. Apart from those widely recognized alterations, such as EGFR and KRAS gene mutations, MET amplification, EML4-ALK rearrangements in NSCLC, somatic mutations and amplification in PIK3CA are described in 3–10% vs. 35% of SCC and 0–2.7% vs. 7% of ADC respectively [66]. What’s more, the expression of PIK3IP1, a negative regulator of PI3K, which can combine the p110 catalytic subunit of PI3K heterodimers to inhibits the activity of PI3K catalytic, is significantly lower in ADC and other tumors tissues [67]. ROCK1, GPX1, PAX6-ZEB2 axis, miR-93 and -496, as well as LINC00665 participate in regulation of the growth, migration, tumorigenesis or chemoresistance of NSCLC through PI3K/AKT pathway [68–73]. Furthermore, IGF-1 activates PI3K/AKT/β-catenin axis, which promotes the symmetric cell division of lung CSC and expands CSC pool, to maintain tumorigenesis [74, 75]. Interestingly, GRP78 plays the same role in radiation resistance and survival of cells in NSCLC by activating AKT1 as in GBM [31]. Currently, the potential of PI3K/AKT inhibitors has been clinically evaluated in a considerable number of studies (Tables 2 and 3) with NSCLC patients. On the other hand, MCAM and EPHA3 mediate chemoresistance in SCLC via the PI3K/AKT pathway [76, 77]. Whether combining daily BKM120 with cisplatin and etoposide was safe and effective in extensive stage SCLC patients had been attempted in a completed clinical trial (NCT02194049, Table 3).

NPC is a unique cancer prevalent in South-East Asia with strong etiological association with Epstein–Barr virus (EBV) exposure [78]. As expected, NPC has a relatively lower mutational burdens with PIK3CA mutations of 1.8% (Table 1), however, there are still numerous of researches involved in PI3K/AKT pathway in NPC. Not only is hyperactivation of PI3K/AKT pathway in relation to NPC progression and prognosis [79], but FOXO1, CHL1, PNOTS, VPS33B interacts with NESG1, RBM3, ARHGAP42 and LncRNA ZFAS1 also display their influence on the proliferation, growth, invasion, metastasis, EMT, chemosensitivity or radio-resistance of NPC cells via PI3K/AKT pathway [80–86]. Moreover, miR-205-5p induces EMT by targeting PTEN via PI3K/AKT pathway in cisplatin-resistant NPC cells [87].

Typically presenting as a form of squamous cell carcinoma, laryngeal cancer is one of common malignancies in the head and neck, which is partly associated with human papillomavirus (HPV) [78, 88, 89]. A series of studies show the mutational events of PI3K pathway (30.5%) in 151 head and neck squamous cell carcinomas (HNSCCs) containing 29 laryngeal squamous cell carcinomas (LSCCs), particularly PIK3CA mutations of 12.6% [90–92]. Furthermore, profiling 279 HNSCCs containing 72 LSCCs, alteration events of PIK3CA (34% vs. 56%), PIK3R1 (1 vs. 3%) and PTEN (12% vs. 6%) are displayed in 243 HPV (−) and 36 HPV (+) HNSCCs respectively [93]. Additionally, MMP2/3, MEOX2, miR-145 and -138 regulate the growth, apoptosis or migration of LSCC cells by targeting the PI3K/AKT pathway [94–97].

Herein, clinical trials of BKM120 (Table 2) in NPC and LSCC patients may provide the feasibility of new treatment strategies. Even more, the safety and efficacy of AKT inhibitor MK2206 in NPC patients had been evaluated in a completed clinical trial (Table 3).

### Deregulation of the PI3K/AKT pathway in digestive system tumors

It’s well established that the global health status is jeopardized by digestive system tumors, and the incidence and mortality rate of major digestive system tumors including esophageal cancer (ESCA), GC, colorectal cancer (CRC), as well as hepatocellular, gallbladder and pancreatic cancer (PC) are listed in Table 1.

Esophageal squamous cell carcinoma (ESCC) is the most frequent ESCA subtype internationally. In general, the genetic alterations of PIK3CA (24%), and PTEN (7%) are observed in ESCA (Table 1), especially the somatic mutations of PIK3CA (7.2% vs 12.5%), PIK3CA (0.7% vs. 0), PIK3CG (2.9% vs. 4.2%) and PIK3CG (0 vs. 37.5%) are observed respectively in 139 paired ESCC cases and 24 cell lines [98]. Even more, PIK3CA mutations are frequent in ESCC associated with chagasic megaesophagus and are associated with a worse patient outcome [99]. HERG1, LSD1, CEP55, CACNA2D3, CircVRK1 and lncRNA GAS5 affect the proliferation, migration, invasion or radioresistance of ESCC cells via the PI3K/AKT pathway [100–105]. After all, a limited number of clinical trials of PI3K inhibitors BYL719 and BKM120 in ESCC patients may bring efficacious therapeutic proposals (Table 2).

The incidence (5.7%) of GC, in which gastric adenocarcinoma (GAC) is the dominant subtype, has continued to decline worldwide due to the *H pylori* treatment [106], but the mortality rate (8.2%) remains the second most common cause of cancer death worldwide (Table 1). As shown in Table 1, the overall genetic alterations of PI3K/AKT pathway are observed with main digestive system tumors including esophageal cancer (ESCA), GC, colorectal cancer (CRC), as well as hepatocellular, gallbladder and pancreatic cancer (PC) are listed in Table 1.

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| System                  | Cancer       | Subunit    | Inhibitors      | Characteristic                                                                                     | Clinical trials |
|------------------------|--------------|------------|-----------------|---------------------------------------------------------------------------------------------------|-----------------|
| Brain and central nervous | GBM         | Allosteric | Perifosine      | 30 adults with recurrent GBM were treated with a loading dose of 600 mg Perifosine followed by     | II (24)         |
|                        |              |            |                 | 100 mg daily until either disease progression or intolerable toxicity. Perifosine is tolerable but  |                 |
|                        |              |            |                 | ineffective as monotherapy for GBM. Preclinical data suggests synergistic effects of Perifosine in |                 |
|                        |              |            |                 | combination with other approaches, and further study is ongoing                                  |                 |
| UM                     | ATP-comp     | GSK2141795 | Trametinib      | Trametinib and GSK2141795 may stop the growth of tumor cells by blocking some of the enzymes       | II NCT01979523  |
|                        |              |            |                 | needed for cell growth. It is not yet known whether trametinib is more effective with or without  |                 |
|                        |              |            |                 | GSK2141795 in treating patients with metastatic UM                                                |                 |
| Respiratory            | NSCLC        | Allosteric | MK2206          | MK2206 and gefitinib hydrochloride may stop the growth of tumor cells by blocking some of the     | II NCT01294306  |
|                        |              |            |                 | enzymes needed for cell growth                                                                   |                 |
|                        |              |            |                 | Combination of MK2206 and gefitinib for the treatment of patients with NCLC who have failed      | I NCT01147211   |
|                        |              |            |                 | prior chemotherapy and an EGFR-TKI                                                                 |                 |
|                        |              |            |                 | Whether it helps to control NSCLC with drug combinations (Erlotinib + MK2206 or AZD6244 + MK2206) | II NCT01248247  |
|                        |              |            |                 | and the safety of these drug combinations remains to be studied                                   |                 |
|                        |              |            | Perifosine       | To determine the MTD of perifosine that can be administered to people without gastrointestinal     | I/II NCT00399789 |
|                        |              |            |                 | toxicity and obtain preliminary information on the response rate of perifosine in NSCLC         |                 |
| Digestive              | GC           | Allosteric | MK2206          | To study how well MK2206 works in treating patients with advanced GC or GEJC                       | II NCT01260701  |
|                        |              |            |                 | To study the side effects and BD of MK2206 and lapatinib ditosylate when given together with     | I NCT01705340   |
|                        |              |            |                 | trastuzumab in treating patients with locally advanced or metastatic GC, or GEC that cannot      |                 |
|                        |              |            | ATP-comp         | To determine the MTD and RP2D for the combination of GSK2110183 and paclitaxel in subjects with   | I NCT02240212   |
|                        |              |            | GSK2110183       | recurrent HER2-GC, and further assess safety and preliminary efficacy of combination at the RP2D  |                 |
|                        |              |            |                 | To evaluate the efficacy of GDC-0068 in combination with oxaliplatin, 5-fluorouracil, and        | II NCT01896531  |
|                        |              |            |                 | leucovorin chemotherapy in participants with advanced or metastatic GC or GEJC                    |                 |
| System          | Cancer          | Subunit | Inhibitors | Characteristic                                                                 | Clinical trials                                      | Phase | Gov identifier |
|-----------------|-----------------|---------|------------|--------------------------------------------------------------------------------|------------------------------------------------------|-------|---------------|
| CRC             | Allosteric      | MK2206  |            | To evaluate the safety and effectiveness of MK-2206 and AZD6244 in individuals with advanced CRC that has not responded to standard treatments | II NCT01333475                                      | II    |               |
|                 |                 |         |            | To study how well MK2206 works in treating patients with previously treated CRC that has spread from the primary site to other places in the body or nearby tissue or lymph nodes and cannot be removed by surgery | II NCT01802320                                      | II    |               |
|                 |                 |         |            | MK2206 is being tested in a subgroup of patients with CRC whose tumors have changes in certain genes that may make them more likely to respond to MK2206 | II NCT01186705                                      | II    |               |
|                 | ATP-comp        |         | GSK2141795 | GSK2141795 given together with dabrafenib and trametinib may be a better treatment for cancer | I/II NCT01902173                                     | I/II  |               |
| HCC             | Allosteric      | MK2206  |            | MK2206 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | II NCT01239355                                      | II    |               |
|                 |                 |         |            | How well MK2206 works in treating patients with advanced or non-resectable HCC | II NCT01425879                                      | II    |               |
| GBC             | Allosteric      | MK2206  |            | To study how well selumetinib and MK2206 work in treating patients with refractory or advanced GBC that cannot be removed by surgery | II NCT01859182                                      | II    |               |
|                 |                 |         |            | How well MK2206 works in treating patients with Stage IV GBC | II NCT01425879                                      | II    |               |
| PC              | Allosteric      | MK2206  |            | Selumetinib and MK2206 may stop the growth of tumor cells. To find if selumetinib and MK2206 are more effective than oxaliplatin and fluorouracil in treating patients with metastatic PC | II NCT01658943                                      | II    |               |
| Female Reproductive BC | Allosteric | MK2206  |            | To study how well MK2206 works in treating patients with BC that has spread to other places in the body and usually cannot be cured or controlled with treatment | II NCT01277757                                      | II    |               |
|                 |                 |         |            | To study the side effects and BD of MK2206 when given together with paclitaxel and to see how well they work in treating patients with MBC | I NCT01263145                                       | I     |               |
|                 |                 |         |            | Giving MK2206 together with anastrozole, fulvestrant may kill more tumor cells | I NCT01344031                                       | I     |               |
|                 |                 |         |            | Giving MK-2206, anastrozole, and goserelin acetate together may kill more tumor cells | II NCT01776008                                      | II    |               |
|                 |                 |         |            | MK2206 may stop the growth of MBC cells by blocking some of the enzymes needed for cell growth when combined with Lapatinib ditosylate | I NCT01281163                                      | I     |               |
|                 |                 |         |            | To study the side effects and BD of MK2206 and lapatinib ditosylate when given together with trastuzumab in treating patients with locally advanced or metastatic HER2 + BC that cannot be removed by surgery | I NCT01705340                                      | I     |               |
| System | Cancer  | Subunit | Inhibitors | Characteristic                                                                                                                                                                                                 | Clinical trials |
|--------|---------|---------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| ATP-comp | GSK2141795 | Trametinib and GSK2141795 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | II | NCT01964924 |
|        | AZD5363  | AZD5363 may stop the growth of tumor cells by blocking some of the enzymes needed for advanced BC cell growth | I | NCT02077569 |
|        | GSK2141795 | AZD5363 in combination with paclitaxel can be used in triple negative advanced or MBC | II | NCT02423603 |
|        | GDC-0068 | Combine GDC-0068 with paclitaxel chemotherapy to treat BC | II | NCT02301988 |
| Indirect* | ONC201  | ONC201 is able to target tumor cells to get rid of them without affecting normal cells. Giving ONC201 and a MR diet may work better in treating participants with BC | I | NCT03733119 |
| OC     | Allosteric | Perifosine | Perifosine may help docetaxel be more effective in causing cancer cells to die | I | NCT00431054 |
|        | Triciribine | Investigate the safety and tolerability, and determine the maximum tolerated dose of triciribine when combined with carboplatin in women with platinum-resistant, recurrent or persistent OC | I/II | NCT01690468 |
|        | MK2206  | How effective MK2206 is in treating OC with mutations in PI3K/AKT or low levels of PTEN | II | NCT01283035 |
| ATP-comp | AZD5363  | Olaparib and AZD5363 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | I/II | NCT02208375 |
|        | GSK2110183 | GSK2110183 in combination with carboplatin and paclitaxel for the treatment of recurrent platinum-resistant OC | I/II | NCT01653912 |
|        | GSK2141795 | GSK2141795 given together with dabrafenib and trametinib may be a better treatment for cancer | I/II | NCT01902173 |
|        | Investigate the PK and PD of GSK2141795 by 18F FDG PET Analysis | I | NCT01266954 |
| FTC    | Allosteric | MK2206 | How effective MK-2206 is in treating FTC where there are mutations in PI3K or AKT or low levels of PTEN | II | NCT01283035 |
| ATP-comp | AZD5363  | Olaparib and AZD5363 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | I/II | NCT02208375 |
|        | ARQ 092  | Whether ARQ 092 and anastrozole can treat EC remains to be studied | I/II | NCT02476955 |
| EC     | ATP-comp | ARQ 092 | Trametinib and GSK2141795 may stop the growth of tumor cells. It is not yet known whether trametinib is a more effective treatment for EC when given with or without GSK2141795 | I | NCT01935973 |
|        | GSK2141795 | GSK2141795 may stop the growth of EC cells by blocking some of the enzymes needed for cell growth | II | NCT01307631 |
| CC     | ATP-comp | GSK2141795 | To evaluate the combination of GSK1120212 and GSK2141795 as a possible treatment for recurrent or persistent CC | II | NCT01958112 |
Table 3 (continued)

| System        | Cancer | Subunit   | Inhibitors | Characteristic                                                                 | Clinical trials |
|---------------|--------|-----------|------------|---------------------------------------------------------------------------------|-----------------|
|               |        |           |            |                                                                                 |                 |
| Genitourinary | KC     | Allosteric| MK2206     | To study the side effects and the BD of MK2206 together with hydroxychloroquine in treating patients with advanced KC | I NCT01480154   |
|               |        |           |            |                                                                                 |                 |
|               |        |           |            | To study the side effects and how well MK2206 or everolimus works in treating patients with KC that does not respond to treatment | II NCT01239342  |
|               | PCa    | Allosteric| MK2206     | To study the side effects and the BD of MK2206 together with hydroxychloroquine in treating patients with advanced PCa | I NCT01480154   |
|               |        |           |            |                                                                                 |                 |
|               |        |           |            | To study the side effects and BD of dinaciclib and MK2206 in treating patients with PCa that cannot be removed by surgery | I NCT01783171   |
| Hematologic   | HM     | ATP-comp  | GSK2110183 | To investigate the safety, tolerability, PK, and PD of GSK2110183 in subjects with any HM | I/II NCT00881946 |
| Lymphoma      | Allosteric | MK2206 |            | To study how well MK2206 works in treating patients with relapsed lymphoma | II NCT01258998  |
|               |        | ATP-comp  | GSK690693  | To investigate the safety, tolerability, PK, and PD of GSK690693 given on various schedules in subjects with solid tumors or lymphoma | I NCT00493818   |
| NHL           | Indirecta | ONC201  |            | ONC201 may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth | I/II NCT02420795 |
| DLBCL         | Allosteric | MK2206 |            | MK2206 may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth | II NCT01481129  |
| MM            | ATP-comp | GSK2141795 | GSK2110183 | Studying how well trametinib and GSK2141795 work in treating patients with relapsed/refractory MM | II NCT01989598  |
|               |        |           | GSK2110183 | To evaluate safety, tolerability, PK, PD and clinical activity of GSK2110183 dosed in combination with bortezomib and dexamethasone in MM subjects who have failed at least one line of systemic treatment | I NCT01428492   |
|               |        |           |            | To investigate the safety, PK, PD, and clinical activity of GSK1120212 in combination with GSK2110183 in MM patients | I NCT01476137   |
|               | Allosteric | KRX-0401 |            | To assess the efficacy and safety of KRX-0401, Bortezomib and Dexamethasone in MM patients | III NCT01002248 |
| Leukemia      | Allosteric | MK2206 |            | To study the SE, best way to give, and BD of MK2206 in treating patients with recurrent or refractory solid tumors or leukemia | I NCT01231919   |
| AML           | ATP-comp | GSK2141795 |            | To study how well trametinib and GSK2141795 work in treating patients with AML | II NCT01907815  |
|               |        | Allosteric | MK2206     | Studying how well MK2206 works in treating patients with relapsed or refractory AML | II NCT01253447  |
| CLL/SLL       | Allosteric | MK2206 |            | Giving MK2206 with bendamustine hydrochloride and rituximab may be an effective treatment for relapsed CLL/SLL | I/II NCT01369849 |
and PRL-3, miR-19a, 21, 34a, 137 and 196b, as well as lncRNA MALAT1, STXBP5-AS1 and PICART1 are involved in modulating biological functions of GC cells via PI3K/AKT pathway [109–122]. A lot of clinical trials of PI3K inhibitors (BKM120, BLY719 and GSK2636771. Table 2) and AKT inhibitors (MK2206, GSK2110183 and GDC-0068. Table 3) in GC patients try to save their lives, especially the patients with advanced or metastatic GC.

Although CRC screening has reduced the incidence and mortality nowadays [123], CRC remains one of the main reasons of tumor-related deaths worldwide (Table 1). The overall genetic alterations of PI3K/AKT pathway in CRC are observed as follows: PIK3CA (22%), PIK3R1 (5%), PIK3R2 (2.2%), AKT1 (1.8%), AKT2 (2.5%) and PTEN (8%, Table 1). Contrary to predictions, PIK3CA mutations do not predict aggressive clinicopathological characteristics in CRC, whereas they are closely associated with KRAS mutations, as well as PIK3CA exon 9 and 20 mutations show different tendencies with respect to BRAF mutation and MSI status [124]. Similar to ADC, the expression of PIK3P1 is also significantly lower in CRC tissues [67]. CXCL12, NLRRC3, Wnt/β-catenin target genes including BAMB1, BOP1, CKS2 and NFIL3, as well as miRNA-135b, Linc00659 and CRNDE are associated with the proliferation, invasion or metastasis of CRC cells via PI3K/AKT signaling [125–130]. As shown in Tables 2 and 3, multiple clinical trials of PI3K/AKT inhibitors in CRC patients try to yield useful inhibitors for treatment [131].

As the most common mesenchymal tumor of the digestive system, gastrointestinal stromal tumors (GISTs) mainly harbor mutually exclusive KIT or PDGFRA mutations, which lead to constitutive activation of the encoded receptor tyrosine kinase (RTK) and activation of downstream pathways including PI3K/AKT pathway [132, 133]. Genetic alterations of PIK3CA and PTEN are observed more frequently in malignant GISTs than in less malignant GISTs in 65 GIST samples with 14/65 overall genetic alterations of PI3K/AKT pathway [134]. It is noted that FASN overexpression often occurs in high-risk and metastatic GISTs, whereas combination therapy with imatinib and C75 targeting FASN has been demonstrated in vitro and vivo to down-regulate the phosphorylation levels of the KIT and PI3K/AKT/mTOR pathway [135, 136]. MiR-374b modulates proliferation and apoptosis of GIST cells through PI3K/AKT pathway [137]. Combination of imatinib mesylate (IM) and MK2206 provide obviously greater efficacy than treatment with IM or MK2206 alone in vitro and vivo preclinical study of GIST [138]. Furthermore, clinical trials of combination of Imatinib and BKM120 (NCT01468688) or BYL719 (NCT01735968, Table 2) were tested in GIST patients.

Being the third most common cause of cancer death worldwide with the mortality rate of 8.2%, hepatocellular
cancer (HCC) is a distinct tumor of the digestive system and exhibits a different genetic alteration pattern of PI3K/AKT pathway, such as PIK3CA (3%), PIK3R1 (1.2%), PIK3R2 (1.5%), AKT1 (0.7%), AKT2 (1.1%) and PTEN (4%) respectively (Table 1). Similarly, PIK3IP1 also suppresses the development of HCC [67, 139]. Moreover, APLN, miR-7, -367, -1296, and -3691-5p as well as lncRNA PTTG3P and LINC01133 are associated with the proliferation, invasion, metastasis or EMT of HCC cells via PI3K/AKT pathway [140–146]. A small amount of clinical trials of PI3K inhibitors (SF1126, GSK2636771) and AKT inhibitors (MK2206) in HCC patients may give them an opportunity for relief (Tables 2 and 3).

Regarding gallbladder cancer (GBC) is the most common malignancy of the biliary tract, the general genetic abnormalities of PIK3CA (10%) and PTEN (2.3%) are found (Table 1), especially the PIK3CA E545K mutation rate (6.15%) [147]. Due to ErbB2 and ErbB3 mutations at a frequency of 7–8% in GBC, ErbB2/ErbB3 mutation inducing PD-L1 overexpression can mediate immune escape of tumor cells via PI3K/AKT pathway in vitro [148]. In addition, EIF3d, UB53, BRD4, TRIM31 and LINC01152 are demonstrated to contribute to cell growth or tumor metastasis of GBC cells via PI3K/AKT pathway [149–153]. Currently, only MK2206 was tested in clinical trials (NCT01859182 and NCT01425879) in GBC patients.

Pancreatic cancer (PC) is a fatal malignancy in the digestive system tumors and takes the first place among asymptomatic cancers (Table 1). Take into consideration that more than 90% of PC is pancreatic ductal adenocarcinoma (PDAC) with the 5-year overall survival (OS) rate less than 5–10% [154], novel targeting therapies are in urgent need. In contrast to the well-known genetically inactivated of KRAS (90%) and Her2 (4–50%) in PDAC [155–159], the overall genetic aberrations of PI3K/AKT members (PIK3CA, 2.3% and PTEN 1.9%, Table 1) are less frequently. Interestingly, pancreatic cell plasticity and cancer initiation induced by Kras is completely dependent on wild-type p110α [160], and PAK4 interacts with p85α can affect the migration of PDAC cells [161]. Significantly, the mutations of PIK3CG in PDAC are also revealed [156]. EG-VEGF, TMEM158, miR-107, as well as LncRNA ABHD11-AS1, SNHG1 and AB209630 are involved in proliferation, apoptosis, metastasis or carcinogenesis of PDAC cells through PI3K/AKT pathway [156–161]. Plenty of clinical trials of PI3K inhibitors (BKM120, BYL719, GSK2636771, PKI-587, BEZ235 and LY3023414. Table 2) and AKT inhibitor (MK2206. Table 3) in PDAC patients may reveal promising therapeutic activities.

Abnormalities of the PI3K/AKT pathway in breast and female reproductive system tumor

BC, which is Estrogen (ER)-related cancer, is the second common cancer in the world (mortality of 11.6%) but in the first place and the most frequent cause of cancer death (mortality of 6.6%) among women worldwide (Table 1). Compared to the recognized genetically diverse of Her2 and TOP2A of BCs, the overall genetic alterations of PI3K/AKT pathway are not uncommon, especially PIK3CA (37%) and PTEN (8%, Table 1). Remarkably, hotspot mutations in PIK3CA are frequent in ER+BCs, which account for up to 80% of BCs, and Her2 mutations hyperactivate the HER3/PI3K/AKT/mTOR axis, leading to anti-ER resistance in ER+BCs. Hence, dual blockade of the Her2 and ER pathways is necessary for the treatment of ER+/Her2 mutant BCs [168]. Moreover, PIK3CA and MAP3K1 alterations reveal Luminal A status in ER+ metastatic BCs and the patients are likely to clinically benefit from BKM120 [169]. On the other hand, top to 70% of patients with breast cancer brain metastases (BCBM) show the activated PI3K pathway [170], and GDC-0084 induces apoptosis of PIK3CA-mutant BCBM cells by suppressing activation of AKT and p70 S6 kinase [171]. Additionally, PRLR/Jak2/STAT5 is the main signaling pathway for activation in mammary gland, and PRLR-triggered pro-tumorigenic pathways in BC include the PI3K/AKT pathway [172]. As well, numerous studies have shown that IRS4, CDK12, SPC24, Mfn2, Transglinin 2, STX3, SOX4, PAK4, TPX2, MEG3 and miR-21, -93, -106b, -130b, -214, -361-5p, -489, -511, -564 as well as lncRNA-HOTAIR and MALAT1 regulate tumorigenesis, proliferation, apoptosis, invasion, migration, paclitaxel resistance or anti-Her2 therapy (trastuzumab) resistance of BC cells through PI3K/AKT pathway [173–191]. And then, PI3K/AKT inhibitors have gained wide attentions, and a large number of clinical trials may have provided tremendous promises in the treatment of BC patients (shown in Tables 2 and 3).

Globally, the incidence and mortality rate of ovarian cancer (OC), which is the most frequently fatal cancer in female reproductive tract with a wide-range of pathological subtypes, are 1.6% and 1.9% respectively (Table 1). Ovarian serous cystadenocarcinoma (OSC), the leading common subtype of epithelial ovarian cancers (EOC) accounting for 90% of OC, harbors overall genetic alterations of PIK3CA (29%), PIK3R1 (5%), PIK3R2 (9%), AKT1 (5%), AKT2 (8%) and PTEN (7%, Table 1) besides the mutant p53 in high-grade OSC (HGOCS), germline BRCA1 and BRCA2 mutations. Furthermore, another subtype of EOC, ovarian clear cell carcinomas (OCCC), shows more frequently mutations of PIK3CA (33%) and PTEN (5%) in overall 97 OCCC cases, especially mutations of PIK3CA (46%) in the 28 cases of affinity purified OCCCs and OCCC cell lines [192], than
the mutation of PIK3CA and PTEN (both <5%) in HGOSC [193]. Huge amounts of studies have shown YAP, PAK II, SIK2, SERPINF1, miR-15b, -21, -150, -222-3p, -337-3p, -497, -503 and -936, as well as LncRNA MALAT1 and JPX modulate proliferation, apoptosis, invasion, migration, angiogenesis, progression, glucose metabolism or drug resistance of OC cells by PI3K/AKT pathway [194–207]. Some clinical trials of PI3K/AKT inhibitors or in combination with chemotherapy drugs listed in Tables 2 and 3 may help relieve the patients of OC.

Along with recent compelling evidence that OSC actually arises from the epithelial lining of fallopian tube, the true incidence of primary fallopian tube carcinoma (PFTC) has been substantially underestimated, which was previously considered as a rare neoplasm accounting for 0.14–1.8% of genital malignancies [208, 209]. Furthermore, aberrant p53/KRASV12/c-Myc or p53/KRASV12/PI3K/AKT signaling is the minimum requirement for fallopian tube secretory epithelial cells (FTSECs) carcinogenesis [210], and increased copy number of PIK3CA has been observed in six fallopian tube carcinomas (FTCs) [211]. Thus, although the studies of PI3K/AKT signaling in FTC are numbered, there are still several clinical trials of PI3K/AKT inhibitors trying to treat patients with FTCs (Tables 2 and 3).

Cervical cancer (CC) is a prominent example of HPV-related cancer, accounting for 3.2% of all human cancers with the mortality rate of 3.3% (Table 1). A litany of genetic alterations induced by HPVs in CC activate four major upstream pathways (GFR, Notch receptor, RAS isoforms and p110α) to stimulate host cell survival, proliferation and carcinogenesis through the PI3K/AKT/mTOR pathway. Considerable overall genetic alterations of PI3K/AKT pathway in CC have emerged with PIK3CA (39%) and PTEN (13%, Table 1). In particular, the mutations of PIK3CA E542K and E545K promote glycolysis and proliferation of CC in vitro and vivo [212]. NBPF1, ARHGAP17, miR-99b, -181a2/181b2, -338, -383, -433 and -489, as well as LncRNA ANRIL, CRNDE, NEAT1 and LINCO1305 are involved in the proliferation, invasion, autophagy or EMT via PI3K/AKT pathway [213–224]. Currently, only preclinical trials of PI3K inhibitor LY294002 has revealed it significantly radiosensitized CC cell lines in vitro and vivo [225, 226], and the terminated clinical trials of AKT inhibitor GSK2141795 (NCT01958112, Table 3) has tried to display a novel treatment approach to patients of CC.

Attributed to the global incidence (2.1%) and mortality rate (0.94%) of corpus uteri cancer, which is usually referred to endometrial cancer (EC), EC researches have gained a big momentum in recent years. Particularly, the endometrioid type of EC (EEC) progressing from intraepithelial endometrial neoplasia in a large proportion of cases belongs to ER-related cancer, and is directly associated with inactivation of PTEN. Hereby, the remarkable overall genetic alterations of PI3K/AKT pathway are shown in EC, such as: PIK3CA (34%), PIK3R1 (19%), PIK3R2 (5%), AKT1 (3%) and AKT2 (5%), especially PTEN (32%, Table 1). What’s more, it’s revealed that the majority of the G3 EC samples have exhibited PIK3CA mutations (39%) and PTEN mutations (67%) [227]. Moreover, JQ1, NEDD4, PDCD4, miR-101, -494-3p, Lnc RNA LINP1 and MEG3 have shown their aptitudes for controlling tumorigenesis, proliferation, apoptosis, invasion, progression of EC cells via PI3K/AKT pathway [228–234]. Thus, EC patients may get benefit from the mounting clinical trials of PI3K/AKT inhibitors listed in Tables 2 and 3.

Dysregulation of the PI3K/AKT Pathway in the genitourinary system tumors

The morbidity of PCa ranks third in the world (7.1%) since men obtain a small but finite benefit from PCa screening in terms of PCa-specific mortality, which is estimated as 3.8% globally [235] (Table 1). Seeing that loss of function of PTEN, resulting in dysregulated activation of the PI3K signaling network, is recognized as one of the most common driving events in PCa development [236], the overall genetic alterations of PI3K/AKT pathway in PCa have demonstrated with PIK3CA (6%), and visible PTEN (18%, Table 1). Sexual hormones have been historically associated with PCa for the androgen deprivation therapy (ADT), but scientific evidences including the increasingly emerging of castration resistant prostate cancer (CRPC) are inconsistent to decide whether their involvement is aetiological or a phenotype component of the disease. However, similar to BC, PRLR/Jak2/STAT5 is also the main signaling pathway for activation in prostate gland, and PRLR-triggered pro-tumorigenic pathways in PCa include PI3K/AKT [172]. In addition, AEP, SCL/TAL1, SIRT3, Snail, MED15, ST6Gal-I, Glyoxalase 2, ASF1B, GPCR48/LGR4, AP4, GCN5, SAG/RBX2 E3, miR-7, -101, -129, -133a-3p, and -4638-5p, as well as LncRNA HCG11 and ATB govern tumorigenesis, progression, metastasis, EMT or castration resistant of PCa cells via PI3K/AKT pathway [237–256]. Preclinical trial of dual BRD4/PI3K inhibitor SF2523 [257] as well as a few of clinical trials of PI3K/AKT inhibitors may develop new therapeutic strategies for PCa patients (Tables 2 and 3).

Kidney cancer (KC) is a malignancy originating in the urinary tubular epithelial system of the renal parenchyma, which mainly means renal cell carcinoma (RCC). Accompanying with the recent hunt for the genetics causes of KC, such as TFE3, TFEB, or MITF gene fusions, the overall genetic alterations of PI3K/AKT pathway comprising PIK3CA (2.8%), PIK3R1 (0.4%), PIK3R2 (0.3%), AKT1 (0.5%), AKT2 (0.6%) and PTEN (4%, Table 1) are captured in KC. To a further extent, PI3K/AKT/mTOR is identified as a highly enriched pathway in translocation RCC with
**Description of the PI3K/AKT pathway in the hemato-immune system tumors**

Hematologic cancers are associated with hemato-immune system, which comprise lymphomas, myelomas and leukemias. Lymphoma, which is classified with Hodgkin’s lymphoma (HL) and non-Hodgkin’s lymphoma (NHL), and multiple myeloma (MM) emanate from the cells of the immune system, while leukemia originates from blood-forming tissues such as the bone marrow [291, 292].

HL is a rare B-cell malignant neoplasm approximately accounting for 0.44% of all new cancers annually, which is classified into two discrete disease entities: classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). With four subgroups including nodular sclerosis (NSCHL), mixed cellularity (MCCHL), lymphocyte depletion (LDCHL), and lymphocyte-rich (LRCHL), CHL is relatively less known about genetic lesions owing to the fact that the neoplastic Hodgkin and Reed-Sternberg (HRS) cells constituting only a small proportion of the tumor tissue [293]. But the prevalence of EBV in HRS cells varies according to the histological subtype and epidemiologic factors from highest frequency in MCCHL to the lowest in NSCHL, and EBV-encoded LMP1 utilizes the PI3K/AKT/mTOR signaling axis to induce ectopic CD137 expression in HRS cells, which results in enhancing the proliferation rate of HRS cells [294, 295]. Furthermore, differences related to EBV status or histological subtypes are observed for PI3K signaling in pediatric HL patients by using hybrid capture-targeted next-generation sequencing of circulating cell-free DNA (ccfDNA), where MCCHL and EBV+ cases were less frequently affected by mutations in ITK/PB and GNA13 genes [296]. Recent evidences revealing that germinal center B-cells (GCB cells) are the cellular origin of HRS cells [294, 296], and the facts that PRMT5 is upregulated by B-cell receptor signaling and forms a positive-feedback loop with PI3K/AKT in both activated B cell-like (ABC) and GCB cells of diffuse large B cell lymphoma (DLBCL) [297] suggest that PI3K/AKT may promote lymphomagenesis of GCB cells in HL, which is a remarkable coincidence with the other evidences that the PI3K/AKT pathway plays a pathogenetic role in HL [298, 299]. Thus, novel therapeutic options targeted PI3K/AKT pathway promote apoptosis or cell death, as well as regulate tumor microenvironment (TME) of HL cells in preclinical studies [300–302], and patients may get beneficial strategy in clinical trials of PI3K/AKT inhibitors (Tables 2 and 3).

As the most common malignancies of hemato-immune system in the world, NHL represents a wide spectrum of illnesses that vary from the most indolent to the most aggressive malignancies, which encompasses 2 main type: mature B-cell neoplasms (B-NHL, 85–90%) and mature T-cell and natural killer (NK)-cell neoplasms (T/NK-NHL, 10–15%; 2016 WHO). Indolent B-cell lymphomas (iB-NHL) represents 35–40% of NHL, and the most common subtypes include follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), a fraction of mantle cell lymphoma (MCL) cases, extramedullary, nodal and splenic marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL). On the other hand, the most common subtypes of aggressive B-NHL are large
B-cell lymphomas, which is composed of DLBCL, not otherwise specified (NOS, 80%) and additional 13 specific variants of DLBCL (20%) including anaplastic (ALK + LBC) and primary mediastinal lymphoma (PMLBCL), and other variants of DLBCL [303–306]. Anyway, the overall genetic alterations of PIK3CA (0.4%), PIK3R1 (0.5%), PIK3R2 (0.1%), AKT1 (0.1%), AKT2 (0.1%) and PTEN (1.1%, Table 1) are observed statistically in NHL.

Apparently, two specific lymphomas, FL and DLBCL, account for about 65% of all NHL, and more importantly, the genomic profile of transformed FL shares similarities with that of GCB de novo DLBCL, and thus a thorough knowledge of these two entities related with PI3K/AKT pathway is essential [307–309]. Despite the recognized fact that overwhelming majority of FL cases have the characteristic (14;18) translocation involving the IgH/bcl-2 genes, while B-cells "arrested" in germinat centers of FL acquire dozens of additional genetic aberrations that influence key pathways controlling their physiological development including B Cell Receptor (BCR) signaling, PI3K/AKT pathway, and so on [310, 311]. Especially, the facts that deletion of PIK3CD results in decreased number of marginal zone (MZ) B cells and pleural/peritoneal cavities in mice, as well as the evidences that PIK3CD-depleted B cells also fail to proliferate in vitro in response to BCR or CD40 signals and have impaired both humoral T-cell-dependent and T-cell-independent responses suggest that PI3CD plays a critical role in B cell homeostasis and function [312–314]. Consequently, following with the world’s first selective PI3Kδ inhibitor CAL-101 was approved by the FDA for the treatment of FL, CLL and SLL in 2014 [315] (NCT01282424, NCT02136511), the PI3K/AKT inhibitors have shown remarkable activity in an increasing subset of patients with NHL [316] (Tables 2, 3). Copanlisib (BAY 80-6946) and Duvelisib (IPI-145) are newly approved PI3K inhibitors that offer objective, although relatively short-lasting, responses in patients with heavily pre-treated FL and other NHL, and more such targeted agents may be approved soon [307, 317–320] (Tables 2 and 3).

As aforementioned, DLBCL is a highly aggressive heterogeneous disease with two subtypes: GCB and ABC [297]. One study shows that deregulation of the PI3K/AKT pathway by the inactivation of PTEN is found in 55% of GCB-DLBCL cases, but only in 14% of non-GCB-DLBCL and worsens prognosis in 248 primary DLBCL patients [308]. Another study finds the PIK3CA amplification of 12.7% and PTEN loss of 12.2% in DLBCL [321]. Furthermore, upregulation of PRMT5 and CXCR4 are involved in lymphomagenesis or resistance mechanism via the PI3K/AKT pathway in DLBCL cells [297, 322]. Preclinical trial of BAY80-6946 in DLBCL cells [323] and the clinical trials of BAY80-6946, INCB050465, CUDC-907 and MK2206 in patients with DLBCL have improved our ability to manage patients with this disorder (Table 2).

T/NK-NHL is a heterogeneous group of malignancies often associated with poor clinical outcomes, and each malignancy within this group is characterized by unique clinicopathologic features, while T cell receptor/NFκB (TCR/NFκB) signaling highly enriched and dysregulation of JAK/STAT pathway, specifically aberrant STAT3 activation, are the common feature among these lymphomas [324–326]. A study with 426 adult T cell leukemia/lymphoma (ATL) cases associated with human T cell leukemia virus type-1 (HTLV-1) infection shows that PI3KCD mutation is also observed in 9 of 370 (2.4%) cases besides the highly enriched for TCR/NFκB signaling, T cell trafficking and other T cell-related pathways [324]. In addition, the alterations of PI3K signaling are involved in the multilobulated nucleus formation and cell proliferation in ATL cells [327]. Therefore, preclinical trial of CAL-101 inducing apoptosis in ATL cells [328] and a series of clinical trials of PI3K/AKT inhibitors are expected to offer new treatment regimens for patients with T/NK-NHL [316] (Tables, 2, 3).

MM accounts for 0.88% of all cancers with the mortality rate (1.1%). Almost all MM patients evolve from an asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS). Despite that hotspot mutations of PIK3CA (E542K, E545K and H1047R) and AKT1 genes (E17K) are absent in MM [329], the R310C mutation of PIK3CA gene [330] is identified in some cases of MM, as well as ROR2 drives the interaction of MM cells with TME through AKT activation [331]. Furthermore, only the blockade of PIK3CA is sufficient to induce cell death in a sizeable subgroup of MM samples, and PIK3CA inhibitor BYL-719 in combination treatments with other compounds establishes anti-myeloma agents resulted in strongly enhanced MM cell death [332]. Therefore, some preclinical studies have examined PI3K/AKT pathway inhibitors in MM, such as TAS-117, PI-103 and BEZ235 [333–335]. Fortunately, some of the clinical trials of PI3K/AKT inhibitors have demonstrated encouraging clinical activity in relapsed and relapsed/refractory (R/R) MM [336–339] (NCT01002248; NCT01476137; NCT00881946) (Tables 2 and 3).

The definition of leukemia is increasingly employed that an aberrant hyper-proliferation of immature blood cells either of the myeloid or lymphoid lineages forms liquid cancer, which is classified with acute or chronic. With morbidity (2.4%) and mortality rate (3.2%) across the world (Table 1), leukemia is a series of life-threatening malignant diseases, particularly in the adolescent and young adult (AYA) population, in which the acute leukemias are most prevalent [340]. Apart from the iconic BCR/ABL oncogene formation in chronic myeloid leukemia (CML) and the genetic abnormalities frequently linked to treatment resistance and...
poor patient outcome in acute myeloid leukemia (AML), for example the unique PML-RARA fusion in acute promyelocytic leukaemia (APL; AML M3), the PI3K/AKT pathway can function as a prosurvival factor in leukemia stem cells and early committed leukemic precursors with the following facts: Firstly, the overall genetic alterations of PIK3CA (0.6%), PIK3R1 (0.6%), PIK3R2 (0.4%), AKT1 (0.5%), AKT2 (0.1%) and PTEN (0.7%; Table 1) are observed in leukemia (Table 1). Secondly, PTEN plays critical roles in regulating not only hematopoietic stem cell activity through a Niche-dependent mechanism, but also hematopoiesis and leukemogenesis [341–343]. Furthermore, TAL1, c-Jun, EZH2, TRIM22, ETV6/RUNX1, miR-7, -22, -26b, -103, -125b, -126, -139-5p, -181c, -193a, -628, and -3142, as well as LncRNA HULC, UCA1, linc00239 and LINC00265 control leukemogenesis, proliferation, apoptosis or chemoresistance via PI3K/AKT pathway [344–363]. Hereafter, PI3K/AKT pathway inhibition is regarded as a therapeutic approach [364, 365] followed by the preclinical studies in leukemia cells [366, 367] in spite of the upregulated expression of P2RY14 in acute leukemia cells resistant to PI3K/mTOR inhibition [368]. Since CAL-101 has been approved for marketing in patients with CLL/SLL, the clinical trials of PI3K/AKT inhibitors such as: BAY80-6946, KM120, YY-20394, BEZ235, PKI-587, IPI-145, CAL-101, TGR-1202, MK2206 and GSK2141795 try to seek new therapeutic approach in relapse or refractory patients with CLL or newly diagnosed AML and acute lymphocytic leukemia (ALL, Tables 2 and 3).

**Featuring the PI3K/AKT pathway in the bone and soft tissue tumors**

Osteosarcoma (OS) is the most frequent primary solid malignancy of bone with the presence of malignant mesenchymal cells which produce osteoid and/or immature bone. The incidence of OS is higher in adolescence (8–11/million/year) than in the general population (2–3/million/year), and > 90% of OS patients died from pulmonary metastases before polychemotherapy. Although the biological and genetic studies of OS have made substantial progress, there has been no qualitative breakthrough in treatment over the past 30 years. Besides the alterations of TP53, RB1, ATRX and DLG2 in OS, total genetic alterations in the PI3K/AKT/mTOR pathway are observed in 14 of 59 (24%) OS patients, and PIK3CA and mTOR are vital for the proliferation and survival of OS cells [369] (Table 1). Furthermore, dual PI3K/mTOR inhibitors are effective at inducing apoptosis in primary OS cell cultures in vitro in both human and mouse OS, while specific PI3K or mTOR inhibitors are not effective [370], which is consistent with the preclinical study’s result that BEZ235 inhibits proliferation and tumor development of OS cells in vivo [371].

Ewing’s sarcoma (EWS), the second most common bone tumor in children and adolescents, is identified by the characteristic t (11;22) chromosomal translocation and resulting oncogenic EWS–FLI1 fusion, for which no cure is currently available. Overall genetic alterations of the PI3K/AKT pathway are observed in EWS cases with PIK3CA (1.4%), PIK3R1 (0.5%) and PTEN (0.5%, Table 1), which play an important role in EWS pathogenesis [372]. Moreover, SOX2, Ski, miR-30d and -185 regulate proliferation, apoptosis, migration or progression of EWS cells though PI3K/AKT pathway [373–376]. In addition, hnRNPM motifs are significantly enriched under the inhibition of the PI3K/AKT/mTOR pathway by BEZ235 in EWS cells. On the other hand, hnRNPM down-expression revokes the BEZ235-induced splicing changes including hnRNPM binding sites, enhanced BEZ235 cytotoxicity and limited the clonogenicity of EWS cells [377].

Currently, pediatric patients of OS or EWS may be benefitted from the ongoing clinical trials of BAY80-6946 (NCT03458728) and LY3023414 (NCT03213678, Table 2).

**The trait of the PI3K/AKT pathway in skin cancer**

Skin cancer is the most common carcinoma, affecting millions worldwide annually, which generally divided into malignant melanoma and non-melanoma skin cancer. Cutaneous melanoma ranks 20th among most common cancers worldwide and rapidly becomes life-threatening once it has spread. Even though solar ultraviolet exposure is the main environmental risk factor for cutaneous melanoma development, there are still genetic susceptibility factors, such as germline mutations in p16 or CDK4, and genesis of melanoma, such as the main genetic drivers BRAF, NF1 and NRAS mutations [378, 379]. Since BRAFV600E-mutated melanomagenesis is often accompanied by silencing of PTEN [380], the increasing genetic alterations in PI3K/AKT pathway have been observed in melanoma including: PIK3CA (5%) and PTEN (12%, Table 1). Notably, dysfunction mutations of NF1 induce BRAF inhibitor resistance by activating RAS and its downstreams including both MAPK and PI3K/AKT/mTOR pathways in cutaneous melanoma [381, 382]. Even more, the onset of MEK1/2 inhibitor resistance in BRAF-mutated melanoma can be forestalled by PI3K blockade [383]. Other than that, ROR1, FOXC1, MIF, TGFβ, LncRNA SNHG17, MIAT, MHCNCR, OR3A4 and H19 regulate proliferation, progression, migration, invasion, metastasis or EMT-like transition though PI3K/AKT pathway in melanoma cells [384–392]. And now, a limited number of clinical trials of PI3K/AKT pathway inhibitors (BKM120, PX-866, GSK2636771, GSK2141795 and MK2206) try to find new ways other than current classic RAF/MEK/MAPK pathway inhibitors to treat the patients with metastatic or advanced melanomas (Tables 2 and 3).
Points of dispute or unanswered questions

In general, ATC, NSCLC, EC, GC, CRC, BC, OC, CC, EC and BLCA exhibit higher frequencies of PIK3CA mutations than other tumors, while PTEN mutations are predominantly found in GBM, EC and PCa (Fig. 1, Table 1). No matter what kind of the genetic alteration happens in PI3K/AKT pathway, or the factor influences cellular behaviors via PI3K/AKT pathway, it leads to the hyperactivation of PI3K/AKT pathway. Growing evidences have shown that the hyper-activation of PI3K/AKT pathway in malignant tumor influences the tumorigenesis, proliferation, growth, apoptosis, invasion, metastasis, EMT, stem-like phenotype, immune microenvironment,
drug resistance of tumor cells (Fig. 1). Interestingly, some protein may play a dual role in PI3K/AKT pathway. For instance, unlike the previous understanding that INPP4B is a negative regulator of PI3K/AKT pathway in TC cells in vivo [49], the tumor-promoting features of INPP4B have yet been observed in leukemia and BC [393–395]. Why and how the INPP4B is a double-edged sword in PI3K/AKT pathway is still a puzzle and it needs further research to evaluate the evidences.

Potential research/future

More and more promising PI3K/AKT pathway inhibitors seem to be useful to overcome malignant tumor, especially CAL-101 treated in patients with hemato-immune system tumors has achieved exhilarating results. Obviously, CAL-101 not only causes a rapid and sustained reduction in lymphadenopathy, but also regulates the immune environment in CLL [396, 397]. However, things are more complicated than our envisage and there is always coexist with abnormal activity of other pathways interacted with PI3K/AKT pathway in tumors. For example, AKT inhibition induces the expression and phosphorylation of multiple RTKs, and the activated RTK signaling may attenuate their antitumor activity in BC cells, which suggest that combined inhibition of AKT and HER kinase activity is more effective than either alone [398]. There are some other embarrassments findings that small molecule PI3K/AKT pathway inhibitors could promote the (re)phosphorylation of AKT2 which is linked to the redistribution and adaptive reprogramming of mitochondria, contributing to drug resistance and metastasis in GBM cells [399, 400]. Thence, novel combination therapies that target mitochondrial adaption and PI3K pathway may achieve better efficacies than either alone in the clinic.

Collectively, we hope to feature PI3K/AKT pathway in cancers to the clinic and bring the promise of the novel inhibitors to the patients for targeted therapies.

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Compliance with ethical standards

Conflict of interest
No competing financial interests exist.

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