Abstract

Cellular proliferation is tightly controlled by several cell-cycle checkpoint proteins. In cancer, the genes encoding these proteins are often disrupted and cause unrestrained cancer growth. The proteins are over-expressed in many malignancies; thus, they are potential targets for anti-cancer therapies. These proteins include cyclin-dependent kinase, checkpoint kinase, WEE1 kinase, aurora kinase and polo-like kinase. Cyclin-dependent kinase inhibitors are the most advanced cell-cycle checkpoint therapeutics available. For instance, palbociclib (PD0332991) is a first-in-class, oral, highly selective inhibitor of CDK4/6 and, in combination with letrozole (Phase II; PALOMA-1) or with fulvestrant (Phase III; PALOMA-3), it has significantly prolonged progression-free survival, in patients with metastatic estrogen receptor-positive, HER2-negative breast cancer, in comparison with that observed in patients using letrozole, or fulvestrant alone, respectively. In this review, we provide an overview of the current compounds available for cell-cycle checkpoint protein-directed therapy for solid tumors.

Key words: aurora kinase, CDK4/6 inhibitor, cell-cycle check-point, cyclin-dependent kinase, palbociclib, polo-like kinase

Introduction

The standard eukaryotic cell cycle is divided into four phases, viz., G1, S (DNA synthesis), G2 and M (mitosis) phase (1). In the G1 phase, the cell is preparing for DNA synthesis and growth, and the diploid cell has 2n chromosomes. In the subsequent S phase, DNA duplication occurs and the DNA content reaches 4n. Before cells undergo mitosis, they continue into the G2 phase, during which the cells grow and prepare for cell division. In the M phase, two daughter cells are formed after mitotic separation. Cells that are in G0 phase (quiescence) are removed from the regular active cell cycle for repair of errors, in order to avoid inappropriate cell proliferation.

The key regulators of the G1/S transition are cyclin-dependent kinases (CDKs) 4 and 6 (2). Cyclin D1 forms a complex with CDK4/6, which then phosphorylates and inactivates retinoblastoma (Rb) protein. The inactivated Rb protein is released from its complex with the transcription factor E2F, and the reaction promotes G1/S transition. CDK1 forms a complex with cyclin B, which then regulates G2/M transition. The CDK1/cyclin-B complex is activated by CDC25 phosphatase, and is inactivated by WEE1 and membrane-associated CDK1-inhibitory kinase (MYT1) kinases.

Because unrestrained cancer growth is caused by abrogation of appropriate cell-cycle control, and because many cell-cycle kinases are amplified or over-expressed in malignancy, they are potential targets for anti-cancer therapies (3). In the 1990s, CDK inhibiting drugs (such as flavopiridol, UCN-01, Roscovitine and CDC25 phosphatase inhibitor) have shown anti-cancer activity in preclinical and clinical trials; however, these drugs were not investigated in late-phase clinical trials because of their unfavorable anti-tumor activities. In the 2000s, the first-generation aurora kinase (AURK) inhibitor E7070, a novel chloroindolyl sulfonamide, was also assessed in a clinical trial, but was also found to be ineffective and showed significant toxicity caused by non-specific pharmaceutical effects. The possible reason for failures of these early cell-cycle check point inhibitors is their weak selective inhibition of the targets.
In the 2010s, highly selective CDK inhibitors, targeting novel cell-cycle proteins, including CHK1/2 kinase, WEE1 kinase, AURK and polo-like kinase (PLK), were discovered, opening further windows for drug discovery (Table 1, Fig. 1).

### Table 1. Molecular targets and cancer types in clinical trials of cell-cycle checkpoint inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Cancer type</th>
<th>Clinical trial</th>
</tr>
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<tbody>
<tr>
<td><strong>CDK4/6 inhibitors</strong></td>
<td></td>
<td>Breast</td>
<td>Phase III</td>
</tr>
<tr>
<td>PD0332991</td>
<td>CDK4/6</td>
<td>Breast</td>
<td>Phase III</td>
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<tr>
<td>LY2835219</td>
<td>CDK4/6</td>
<td>Breast</td>
<td>Phase III</td>
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<tr>
<td>LEE011</td>
<td>CDK4/6</td>
<td>Breast</td>
<td>Phase III</td>
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<tr>
<td><strong>Pan-CDK inhibitors</strong></td>
<td></td>
<td>Solid tumor</td>
<td>Phase I</td>
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<tr>
<td>Flavopiridol</td>
<td>Pan CDK</td>
<td>Solid tumor</td>
<td>Phase I</td>
</tr>
<tr>
<td>AT7519</td>
<td>CDK1/2/4/5/9</td>
<td>Solid tumor</td>
<td>Phase I</td>
</tr>
<tr>
<td>R-roscovitine</td>
<td>CDK1/2/7/9</td>
<td>Solid tumor</td>
<td>Phase I</td>
</tr>
<tr>
<td>PHA793887</td>
<td>CDK1/2/4</td>
<td>Solid tumor</td>
<td>Phase I</td>
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<tr>
<td>AZD5438</td>
<td>CDK1</td>
<td>Solid tumor</td>
<td>Phase I</td>
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<tr>
<td>MK-7965</td>
<td>CDK1/2/5/9</td>
<td>NSCLC</td>
<td>Phase II</td>
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<tr>
<td><strong>CHK1 inhibitors</strong></td>
<td></td>
<td>Solid tumor</td>
<td>Phase I</td>
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<tr>
<td>AZD7762</td>
<td>CHK1</td>
<td>Solid tumor</td>
<td>Phase I</td>
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<tr>
<td>MK-8776</td>
<td>CHK1</td>
<td>AML</td>
<td>Phase II</td>
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<tr>
<td><strong>WEE1 inhibitor</strong></td>
<td></td>
<td>Ovarian</td>
<td>Phase II</td>
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<tr>
<td>MK-1775</td>
<td>WEE1</td>
<td>Ovarian</td>
<td>Phase II</td>
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<tr>
<td><strong>AURK inhibitors</strong></td>
<td></td>
<td>Ovarian</td>
<td>Phase II</td>
</tr>
<tr>
<td>PHA-739358</td>
<td>Pan-AURK</td>
<td>CML</td>
<td>Phase II</td>
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<tr>
<td>MLN8237</td>
<td>AURK A</td>
<td>Ovarian</td>
<td>Phase II</td>
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<tr>
<td>AZD1152</td>
<td>AURK B</td>
<td>AML</td>
<td>Phase II</td>
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<tr>
<td><strong>PLK inhibitor</strong></td>
<td></td>
<td>AML</td>
<td>Phase III</td>
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<tr>
<td>Volasertib</td>
<td>PLK</td>
<td>AML</td>
<td>Phase III</td>
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</tbody>
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CDK4/6 inhibitors

CDK4/6 activity is closely related to the action of estrogen (4). One of the reasons for resistance to endocrine therapy is persistent cyclin D1 expression and Rb phosphorylation in estrogen receptor (ER)-positive breast cancer. Genetic aberrations of the cyclin D1–CDK4/6 pathway are associated with a poor clinical outcome in ER-positive breast cancer.

PD0332991 (palbociclib)

The most advanced CDK inhibitor available is PD0332991 (palbociclib, Pfizer), a first-in-class, oral, highly selective inhibitor of CDK4/6 kinase (IC$_{50}$ = 11 nmol/l; K$_i$ = 2 nmol/l) (5). Palbociclib has broad activity against a wide range of breast cancer cell lines in vitro, particularly against ER-positive luminal breast cancer cell types (6). A Phase I study was conducted to identify the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) (7). One hundred and twenty-five milligrams once daily for 21 days every 28 days (3/1 schedule) was the recommended dose for Phase II, and DLT was neutropenia. A Phase II study was conducted in Rb-positive metastatic breast cancer. The median overall progression-free survival (PFS) was 3.7 months, but was significantly longer for those with ER-positive vs. ER-negative disease ($P = 0.03$) and for those who had previously undergone endocrine therapy for advanced disease ($P = 0.02$) (8). A large randomized Phase II study (PALOMA-1) was then performed with 165 patients randomized to palbociclib plus letrozole vs. letrozole alone as first-line therapy for metastatic ER-positive, HER2-negative breast cancer (9). A striking and statistically significant improvement in PFS, from 10.2 to 20.2 months [HR = 0.49; 95% confidence interval (CI) = 0.32–0.75; $P < 0.001$], was observed (Table 2). The response rate in the combination therapy group (55.4%) was significantly higher than that in the monotherapy group (39.4%). Palbociclib has recently been approved by the FDA (February 2015), and is indicated for...

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**Figure 1.** Cell-cycle checkpoint inhibitors. Cell cycle is controlled by several key proteins, including CDKs (cyclin-dependent kinases) which combine with cyclin proteins, CHK1, WEE1, PLK (polo-like kinase) and AURK (aurora kinase). This figure shows that each compound selectively inhibit each cell-cycle checkpoint protein, respectively.
advanced ER-positive, HER2-negative, post-menopausal breast cancer under the accelerated review process as a breakthrough therapy. Currently, the data of randomized Phase III study (PALOMA-3) were open published. Five hundred and twenty-one patients were randomized to palbociclib plus fulvestrant vs. placebo plus fulvestrant as a second-line therapy for metastatic ER-positive, HER2-negative breast cancer (10). Primary endpoint, PFS in palbociclib arm (9.2 months) was statistically significant longer than that in placebo arm (3.8 months) (HR = 0.42; 95% CI = 0.32–0.56; P < 0.001) (Table 3B).

Palbociclib was tested against CDK4-amplified liposarcoma in a Phase II study (11), providing an encouraging PFS of 66% at 12 weeks, and was tested against mantle cell lymphoma, a disease characterized by cyclin D1 overexpression.

Early study using 20 glioblastoma xenograft cells reported that palbociclib was sensitive with cell lines which have a loss of p16, or phosphorylation of Rb (12). Other study using 25 renal cancer carcinoma cell lines (13) showed that the loss of p16, p15 and E2F1 was significantly associated with high sensitivity each, but Rb status was not. Additional studies are needed to estimate the biomarker to predict clinical efficacy.

Previous reports suggested that palbociclib showed a synergistic anti-tumor effect with tamoxifen, trastuzumab and paclitaxel in ER+ and HER2+ breast cancer cell lines. Palbociclib should be tested in adjuvant and neoadjuvant settings in the future concurrent combining with endocrine therapy, or sequential combining with trastuzumab/paclitaxel. For advanced diseases, targeted population should be more enriched not only by the ER status, but also by a biomarker, for example, loss of p16. Additionally, palbociclib also should be tested in pre-menopausal patients.

LY2835219 (abemaciclib)

Another selective CDK4/6 inhibitor is LY2835219 (abemaciclib, Eli Lilly). This is also an orally bioavailable drug that selectively inhibits CDK4/6 (IC50 = 2 nM for CDK4 and 9.9 nM for CDK6). Abemaciclib demonstrates activity in human xenograft models of non-small cell lung cancer (NSCLC), ovarian cancer and mantle cell lymphoma (14). The drug has also been shown to cross the blood–brain barrier (15). A Phase I study of abemaciclib was conducted in 75 patients with advanced solid tumors; the MTD was 200 mg, administered twice daily. The principle adverse events were diarrhea, fatigue, nausea and neutropenia (16). Early activity was observed in NSCLC, breast cancer, ovarian cancer and in melanoma. Two simultaneous Phase III studies of this drug are currently ongoing, viz., abemaciclib plus a non-steroidal aromatase inhibitor vs. placebo plus the aromatase inhibitor as first-line therapy (Monarch 3), or abemaciclib plus fulvestrant inhibitor vs. placebo plus fulvestrant as second-line therapy (Monarch 2) in ER-positive advanced breast cancer. The primary endpoint of both trials is PFS.

**Table 2. Summary of the result of PALMA-1**

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib + letrozole</th>
<th>Letrozole alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>347</td>
<td>142</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>10.4% (95% CI 7.5–7.5)</td>
<td>6.3% (95% CI 3.5–5.5)</td>
</tr>
<tr>
<td>Clinical benefit rate</td>
<td>34% (CR + PR)</td>
<td>19% (CR + PR + SD)</td>
</tr>
<tr>
<td>G3/4 neutropenia</td>
<td>62%</td>
<td>0.6%</td>
</tr>
<tr>
<td>G4 neutropenia</td>
<td>8.7%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

**Table 3. Summary of the result of PALMA-3**

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib + fulvestrant</th>
<th>Placebo + fulvestrant</th>
</tr>
</thead>
<tbody>
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</tr>
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</tr>
<tr>
<td>Response rate</td>
<td>34% (CR + PR)</td>
<td>19% (CR + PR + SD)</td>
</tr>
<tr>
<td>G3/4 neutropenia</td>
<td>62%</td>
<td>0.6%</td>
</tr>
<tr>
<td>G4 neutropenia</td>
<td>8.7%</td>
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**LEE011 (ribociclib)**

A third selective inhibitor of CDK4/6 is LEE011 (ribociclib, Novartis); this orally bioavailable small-molecule inhibits CDK4/6 at a nanomolar concentration. Ribociclib causes G1 arrest and demonstrated anti-tumor activity in several models, including melanoma with BRAF or NRAS mutations and in breast cancer. Both intermittent and continuous doses were evaluated in a Phase I trial, and the recommended dose was 600 mg daily (continuous) and 900 mg daily for 3 of 4 weeks (intermittent) (17). Development of ribociclib is continuing as well in advanced trials in metastatic breast cancer. MONALEESA-2 is a Phase III trial randomizing patients with metastatic HR+/HER2- disease in the first-line setting to letrozole with or without ribociclib. In the pre-operative setting, MONALEESA-1 is evaluating the contribution of ribociclib to neoadjuvant aromatase inhibitor. Encouraging responses were observed in breast cancer and melanoma.

Ribociclib-sensitized PIK3CA mutant breast cancer cell to PI3K inhibitor. Combination ribociclib and PI3K inhibitor is a hopeful regimen for PIK3CA mutant breast cancer, which is ∼30% of the total breast cancer.

**Other CDK inhibitors**

Several CDK inhibitors have been evaluated against solid tumors in Phase I clinical trials; however, these have achieved only a modest response in monotherapy, despite favorable preclinical data. Flavopiridol, a pan-CDK inhibitor, resulted in a partial response in one patient with renal cancer, and a complete response in one patient with gastric cancer (18). AT7519, a CDK1/2/4/5/9 inhibitor, resulted in a partial response in one patient with NSCLC (19), while seliciclib (CYC202; R-roscovitine), a CDK1/2/7/9 inhibitor, yielded a partial response in one patient with hepatocellular carcinoma (20). PHA739387 (21), a CDK1/2/7 inhibitor, yielded a partial response in one patient with hepatocellular carcinoma and AZD5438, a CDK1/2 inhibitor, did not result in any objective responses in a Phase I trial.

Dinaciclib (MK-7965, formerly known as SCH72965), a novel, small-molecule inhibitor of CDK, was assessed in a Phase I trial in patients with solid tumors, and in a randomized, multicenter Phase II trial in which dinaciclib was compared with erlotinib in patients who had been previously treated for NSCLC. Unfortunately, no objective responses were observed in either study.

One of the reasons these classical CDK inhibitors have failed in early stage of the development was their weak selectivity of the CDKs. They have failed to focus 'the targeted disease', type of cancers, population of responders by the biomarker. In contrast, novel CDK4/6 inhibitors were tried to evaluate at least in the enriched population by...
ER+/HER2-, post-menopausal and breast cancer. An additional biomarker to predict to response is needed to get more clinical benefit.

### CHK1 inhibitor

The ataxia telangectasia-mutated and the ataxia telangectasia-related kinases are activated in response to double-stranded DNA breaks and, in turn, activate the checkpoint kinases CHK1 and CHK2. CHK1 then inhibits CDC25A phosphatase, which results in cell-cycle arrest in G2, and activates the RAD51 and related pathways to accomplish DNA repair. CHK2 also inhibits CDC25C phosphatase, allowing it to bind to 14-3-3 protein. This leads to nuclear export and cytoplasmic sequestration of CDC25C, effectively inactivating its phosphatase activity and preventing entry of the cell into M phase.

AZD7762 (AstraZeneca) is a potent and selective ATP-competitive CHK1 kinase inhibitor that increases sensitivity of the cell to DNA-damaging agents. A Phase I study of this drug was conducted in 42 patients with advanced solid tumors as monotherapy or in combination with gemcitabine (22). Two NSCLC patients achieved partial responses.

Phase I study of MK-8776 (SCH900776), a potent, selective checkpoint kinase 1 (Chk1) inhibitor, as monotherapy and in combination with gemcitabine with advanced solid tumor malignancies was conducted (23). Early evidence of clinical efficacy was observed. The recommended Phase II dose was MK-8776 200 mg plus gemcitabine 1000 mg/m² on Days 1 and 8 of a 21-day cycle. MK-8776 given along with timed sequential cytarabine produced a complete response in 33% of patients with relapsed/refractory acute myelogenous leukemia (AML) in Phase I trials (24), and increased H2A.X phosphorylation in bone marrow blast cells, which was consistent with unrepaired DNA damage. A randomized Phase II study comparing cytarabine plus MK-8776 to cytarabine alone is currently ongoing in patients with relapsed or refractory AML.

### WEE1 kinase inhibitor

WEE1, a protein kinase, regulates the G2 checkpoint in response to DNA damage. Preclinical studies have elucidated the role of WEE1 in DNA damage repair and the stabilization of replication forks. Overexpression of WEE1 has been observed in several malignancies, including hepatocellular carcinoma, luminal and HER-2-positive breast cancer, glioblastoma and malignant melanoma (25).

MK-1775 is a selective and potent small-molecule inhibitor of WEE1 (26). Preliminary data from Phase I studies testing escalating single and multiple doses of MK-1775 in combination with gemcitabine, cisplatin or carboplatin in patients with advanced solid tumors have shown promising activity, resulting in stable disease in 14 of 28 evaluable patients, with a manageable toxicity profile. Two Phase II studies of MK-1775 are currently underway: a combination of MK-1775 and carboplatin tested in patients in whom p53-mutated epithelial ovarian cancer had progressed despite prior paclitaxel/carboplatin therapy, and a randomized study evaluating the combination of MK-1775 with paclitaxel and carboplatin vs. placebo with paclitaxel and carboplatin in patients with p53-defective ovarian, fallopian tube and primary peritoneal tumors. MK-1775 abrogates the radiation-induced G2 block, especially in p53-defective cells, and enhanced radiosensitivity (27,28). Studies of MK-1775 in combination with radiation are currently in progress in patients with glioma (NCT01849146, NCT01922076), cervical cancer (NCT01958658) and pancreas (NCT02037230). MK-1775 also abrogates the cisplatin-induced G2 block in p53-defective cells but not in wild-type p53 (29). These data suggested that p53 mutation was a potent predictive biomarker for response to the WEE1 kinase inhibitor. Concurrent or sequence combination of WEE1 kinase inhibitor with radiation, or with cisplatin based chemotherapy are needed to be evaluated in the future study.

### AURK inhibitors

AURKs are known to play multiple roles in mitosis, and their distribution correlates strongly with their functions. Aurora A is involved in mitotic entry, aurora B is involved in chromosomal bi-orientation and aurora C exhibits functions similar to those assigned to aurora B. The gene encoding aurora A has been found to be amplified in breast cancer and gliomas. Overexpression of aurora B is associated with malignant progression of anaplastic thyroid carcinoma. A functional polymorphism, Ser295Ser (885 A>G), in the C-terminal end of aurora B has been associated with an elevated risk of familial breast cancer.

PHA-739358 (danusertib) is a pan-AURK inhibitor. Phase II studies have been conducted in various types of advanced solid tumors, including breast, ovarian, pancreatic and colorectal cancers, SCLC and NSCLC (30). As a single agent, danusertib showed a response in one ovarian cancer patient and one squamous NSCLC patient. Danusertib has also been shown to inhibit BCR-ABL kinase. Many patients with chronic myeloid leukemia (CML) acquire resistance to the BCR-ABL inhibitor imatinib by specific BCR-ABL mutations, particularly the Thr315Ile gate-keeper mutation. Danusertib inhibits both wild-type BCR-ABL and the Thr315Ile-mutated protein in kinase assays. In a Phase II study of CML patients, danusertib achieved a complete hematological response in two CML patients with the Thr315Ile mutation, and a complete cytogenetic response in one CML patient.

MLN8237 (Alisertib) has been reported to be a highly specific, second-generation inhibitor of Aurora A (IC₅₀ = 1 nM). Even more promising in acute lymphoblastic leukemia, a sustained complete response was achieved in three of seven neuroblastoma models, and the activity was much higher than that with standard anti-cancer agents. Phase I study was conducted in East Asian patients with advanced solid tumors or lymphomas. Steady-state exposure of MLN8237 was 70% higher in East Asian patients than previous estimates in Western patients, resulting in lower MTD dose [30 mg b.i.d; twice a day (BID)] in comparison with that (50 mg BID) in Western patients (31). In Phase II studies of MLN8237 in patients with platinum-resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal carcinoma was conducted (32), and revealed modest single-agent anti-tumor activity.

Aurora B kinase plays a prominent role in mitosis and its inhibition by AZD1152 produced a 25% response rate in poor-risk AML and a 45% response rate in older patients with AML when given along with low-dose cytarabine.

Both WEE1 inhibitor and aurora kinase inhibitor acts G2/M which is well known as a radio-sensitizing phase. Sequence of combination of these cell-cycle checkpoint drugs and radiation, or M phase-dependent cytotoxic drug (for example, paclitaxel or eribulin etc.) might be promising.

### PLK inhibitors

PLKs are a group of highly conserved serine/threonine protein kinases that play a key role in processes such as cell division and checkpoint regulation in mitosis. About 80% of human tumors, of various
origins, express high levels of PLK transcripts. Overexpression of PLK is associated with a poor prognosis in several tumor types and a lower overall survival rate.

Volasertib is a potent and selective PLK1 inhibitor. A first-in-man Phase I trial involved a dose-escalation study in 65 patients with progressive advanced or metastatic solid tumors (33). Dose-limiting toxicities involved neutropenia and thrombocytopenia. This first-in-man trial also revealed signs of anti-tumor activity, three patients (urothelial cancer, ovarian cancer and melanoma) achieved partial responses and 26 (40%) achieving stable disease.

A Phase II trial of volasertib was undertaken in 50 patients with metastatic urothelial cancer following platinum failure. Although patients were heavily pretreated, volasertib demonstrated anti-tumor activities with seven (14%) patients achieving a partial response and 13 (26%) achieving stable disease as the best response (34). Two Phase II trials of volasertib are ongoing in advanced ovarian cancer and advanced NSCLC.

A randomized Phase II study of volasertib plus low-dose cytarabine (LDAC) vs. LDAC alone in older patients with AML resulted in improvement in the response rate and overall survival with the combination (31.0% vs. 13.3%, \( P = 0.052 \); overall survival 8.0 vs. 5.2 months, \( P = 0.047 \) (35)). These encouraging data from the Phase II have prompted the initiation of a Phase III trial of volasertib in patients with AML (POLO-AML-2). This trial was designed to evaluate, in a randomized, double-blind setting, the efficacy and safety of volasertib plus LDAC vs. placebo plus LDAC in AML patients older than 65 years. The primary endpoint of the POLO-AML-2 trial is an objective response.

Summary

Novel CDK4/6 inhibitors have shown evidence that supports its use as standard care in ER-positive, HER2-negative advanced breast cancer. Danusertib, a pan-AURK inhibitor has achieved promising results in CML patients with the Thr315Ile gate-keeper mutation, which results in acquired resistance to imatinib. Moreover, volasertib, a PLK1 inhibitor, has shown efficacy in a randomized, double-blind Phase III trial comparing volasertib plus LDAC vs. placebo plus LDAC in elderly patients with AML. All these drugs show potent activity against other types of malignancy. However, the mechanisms underlying their efficacies in specific tumor types remain unclear, hampering identification of biomarkers predicting responses to these drugs. Selection of the targeted population by biomarker is crucially needed to bring up the drug which provides real clinical benefit. And, prescreening multi-gene alteration by the next-generation sequence form the identification of biomarkers predicting responses to these drugs against other types of malignancy. However, the mechanisms under.

Conflict of interest statement

None declared.

References


