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Targeting the PI3K pathway and DNA damage response as a therapeutic strategy in ovarian cancer

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ABSTRACT

Ovarian cancer is the most lethal gynecological malignancy worldwide although exponential progress has been made in its treatment over the last decade. New agents and novel combination treatments are on the horizon. Among many new drugs, a series of PI3K/AKT/mTOR pathway (referred to as the PI3K pathway) inhibitors are under development or already in clinical testing. The PI3K pathway is frequently upregulated in ovarian cancer and activated PI3K signaling contributes to increased cell survival and chemoresistance. However, no significant clinical success has been achieved with the PI3K pathway inhibitor(s) to date, reflecting the complex biology and also highlighting the need for combination treatment strategies. DNA damage repair pathways have been active therapeutic targets in ovarian cancer. Emerging data suggest the PI3K pathway is also involved in DNA replication and genome stability, making DNA damage response (DDR) inhibitors as an attractive combination treatment for PI3K pathway blockades. This review describes an expanded role for the PI3K pathway in the context of DDR and cell cycle regulation. We also present the novel treatment strategies combining PI3K pathway inhibitors with DDR blockades to improve the efficacy of these inhibitors for ovarian cancer.

Introduction

Ovarian cancer is the deadliest gynecologic malignancy in industrialized countries [1]. Most women with ovarian cancer are diagnosed at advanced stages and recurrence is common after initial platinum-based chemotherapy leading to incurable disease with limited treatment options [2]. Therefore, a critical need remains for new effective therapeutic strategies.

The phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) pathway (referred to as the PI3K pathway) is the most frequently altered signaling, found in ~70% of ovarian cancer [2,3]. PI3K pathway activation is associated with aggressive phenotypes, chemoresistance and poor prognosis in ovarian cancer [2,3], making it an important target for treatment. However, only limited clinical activity has been observed with PI3K pathway inhibitors thus far despite the high frequency of PI3K pathway activation in ovarian cancer [4]. Hence, it is necessary to develop new combination strategies to improve the efficacy of PI3K pathway blockades.

DNA damage response (DDR) pathways are active therapeutic targets in ovarian cancer. The successful introduction of poly (ADP-ribose) polymerase inhibitor (PARPi) has led to a new treatment paradigm in this disease, particulary for those with *BRCA* mutations [5]. Also, blockades of ataxia-telangiectasia and Rad3-related (ATR)/cell cycle checkpoint kinase 1 (CHK1) cell cycle pathway are currently being investigated in ovarian cancer [6]. Therefore, an improved understanding of the mechanisms underlying the PI3K pathway and its interactions with other pathways becomes more important to identify the optimal combination treatment candidates. In line with this, emerging preclinical data suggest synergistic cytotoxicity of the combination of PI3K pathway inhibitors and DDR blockades in high-grade serous ovarian cancer (HGSOC) [7–9]. Here, we briefly review the PI3K and DDR pathways with a focus on the relevance to preclinical evidence and clinical development of dual inhibition of these two pathways. We use HGSOC as an example and refer to other rare subtypes, *i.e.,* clear cell or endometrioid ovarian cancer where appropriate this review.

Alteration of PI3K pathway in ovarian cancer

Fig. 1 illustrates an overview of the PI3K pathway. Briefly, upon activation, active PI3K phosphorylates PI(4,5)P2 to PI(3,4,5)P3, which consequently activates AKT and its downstream effector mTOR, leading to the entire pathway activation and cell growth. There is a positive feedback loop between AKT and mTORC2 while PTEN and INPP4B negatively regulate the PI3K pathway by converting active PI(3,4,5)P3

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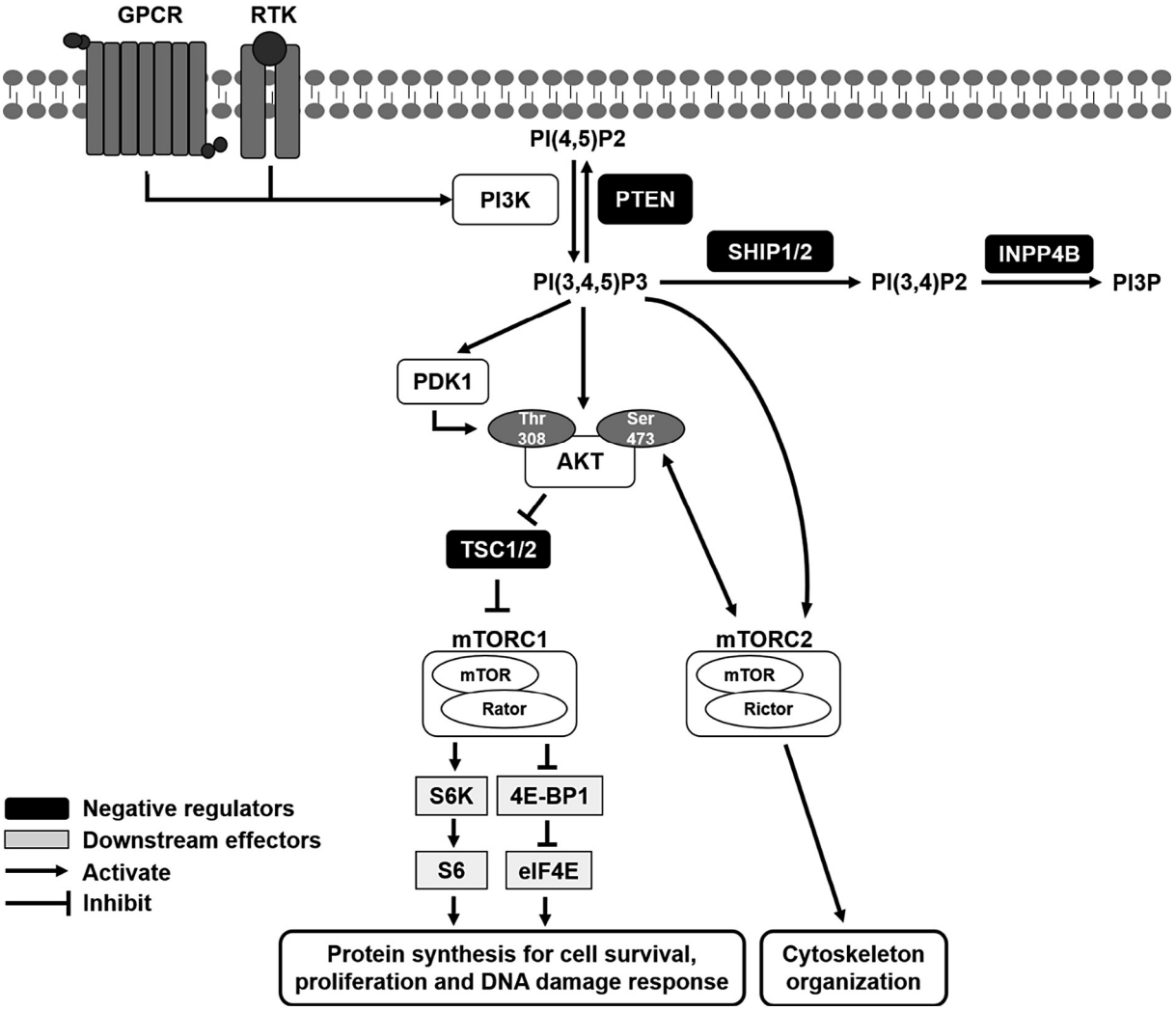

Fig. 1. An overview of the PI3K pathway. Upon RTK activation induced by growth factors, PI3K phosphorylates PI(3,4)P2 to generate PI(3,4,5)P3. PI(3,4,5)P3 then recruits PDK1 to activate AKT. Individual isoforms of PI3K or AKT are not shown here. mTOR is downstream of AKT. The mTOR complex consists of two components; mTORC1-Raptor and mTORC2-Rictor. AKT directly activates mTOR via phosphorylating mTORC1 or indirectly activates mTORC1 by inhibiting TSC 1/2. mTORC1 phosphorylates the 4E-BP1 and the S6K, which consequently enhances the translation of mRNA encoding proteins, responsible for cell survival (*i.e.,* survivin), proliferation (*i.e.,* Forkhead box O family) and DNA damage response (*i.e.,* BRCA1). There are positive and negative feedback loops for active PI3K signaling. mTORC2 triggers positive feedback on PI3K pathway activation by phosphorylating AKT at Ser473. PTEN and INPP4B negatively regulate the PI3K pathway *via* converting PI(3,4,5)P3 back to inactive forms, thus impairing AKT activation. Abbreviations: 4E-BP1 = eukaryotic initiation factor 4E binding protein 1; eIF4E = eukaryotic initiation factor 4E; GPCR = G-protein coupled receptor; INPP4B = inositol Polyphosphate 4-phosphatase type II; mTORC = mammalian target of rapamycin complex; PDK1 = phosphoinositide dependent kinases 1; PI3K = phosphatidylinositol 3-kinase; PI3P = phosphatidylinositol 3-phosphate; PI(3,4)P2 = phosphatidylinositol-3,4-bisphosphate; PI(4,5)P2 = phosphatidylinositol-4,5-bisphosphate; PI(3,4,5)P3 = phosphatidylinositol-3,4,5-trisphosphate; PTEN = tumor suppressor phosphatase and tensin homolog; RTK = receptor tyrosine kinase; S6 = ribosomal protein S6; S6K = ribosomal protein S6 kinase; SHP1/2 = SH-2 containing inositol 5′ polyphosphatase 1/2; TSC1/2 = tuberous sclerosis complex 1 and 2.

to inactive forms [3].

The prevalence of aberrant PI3K pathway activations in ovarian cancer varies depending on the histology. The main histologic subtypes are epithelial in origin and include HGSOC (~70%), endometrioid carcinoma (10–15%), ovarian clear cell carcinoma (OCCC, 5–10%), low-grade serous carcinoma (3%), and mucinous carcinoma (2–8%) [2,3]. *PIK3CA* mutations and *PTEN* deletion are more prevalent in OCCC (20–46% and 20%, respectively) and endometrioid carcinoma (12–20% and 40%, respectively) while they occur rarely in HGSOC (2.3–3.7% and 7%, respectively) [2,3]. Although *PIK3CA*, *AKT* or inactivating *PTEN* mutations are rare in HGSOC, the genomic amplification of *PIK3CA* (~20%) and *AKT* isoforms (10–15%), or deletions of *PTEN* (5%) are not uncommon in HGSOC [2,3]. Also, approximately one-quarter to one-third of HGSOC express the phosphorylated eukaryotic initiation factor 4E binding protein 1 (4E-BP1) and ribosomal protein S6 kinase (S6K), downstream targets of mTOR, suggesting enhanced active PI3K signaling in subsets of HGSOC [10]. Accordingly, analysis of the Cancer Genome Atlas data indicates that higher expressions of *AKT* or *MTOR* are associated with poor clinical outcome in advanced HGSOC [11]. Hence, utilizing PI3K pathway inhibitors may have broader clinical applicability in ovarian cancer, regardless of its histological subtypes.

The initial preclinical studies evaluating PI3K pathway inhibitors demonstrate that chemical inhibition of PI3K pathway induces cell killing in ovarian cancer models, in particular, those with *PIK3CA* or *PIK3R1* activating mutations, or *PTEN* loss-of-function [12]. However, the clinical application of PI3K pathway inhibitors has been limited in ovarian cancers, even among tumors with *PIK3CA*-activating mutations, reflecting the complex biology [13,14]. Currently, work has been focused on identifying selective pathway inhibitors and studying

combined treatments to enhance the efficacy of PI3K pathway inhibitors [3]. The focus of this review will be combination therapy of PI3K pathway and DDR blockades.

Interactions of PI3K pathway with DDR and therapeutic opportunities

Active PI3K signaling promotes cell survival partly by regulating DDR [15]. DDR pathway is triggered by DNA damage sensors *e.g.,* PI3K-like kinases (PIKKs). Three PIKKs include DNA-dependent protein kinase (DNA-PK), ataxia-telangiectasia mutated (ATM), and ATR. ATR is activated by DNA single-strand breaks (SSBs), specifically via persistent single-stranded DNA (ssDNA) coated with replication protein A, which is present at stalled replication forks [16]. Conversely, ATM and DNA-PK are mainly activated by DNA double-strand breaks (DSBs) via MRE11-RAD50-NBS1 complex and Ku-bound DSB ends, respectively [16]. Moreover, preclinical studies indicate that active PI3K signaling is involved in DNA replication, and thus PI3K pathway inhibition induces replication stress [17]. In support, mTORC1/2 inhibition (PP242) is found to prolong S phase arrest and increase γ-H2AX foci formation in *TP53* and *BRCA1* mutant SUM149 breast cancer cells [18]. Similarly, the mTOR/PIKK inhibitors (Torin2 and its chemical analogs) and a dual PI3K/mTOR inhibitor (PI3K/mTORi) omipalisib increase replication catastrophe and cell death during S and G2 phases in PI3K-activated triple-negative breast cancer (TNBC) cells [19]. The following section will describe the roles of PI3K signaling in the context of specific cell cycle phases and DNA repair pathways, and show the preclinical evidence of dual inhibition of PI3K signaling and cell cycle regulators in various cancers including ovarian cancer models.

DNA replication, cell cycle checkpoints and PI3K signaling

ATR/CHK1 pathway is essential for successful completion of DNA replication. Cell cycle checkpoints monitor the structural integrity of chromosomes before progression through crucial cell cycle stages. Fig. 2 shows a schematic view of cell cycle control pathways.

The PI3K pathway is important in maintaining genomic stability by involving DNA replication and cell cycle regulation [17]. Accordingly, PI3K inhibition causes genomic instability and mitotic catastrophe by decreasing the activity of Aurora kinase B, a spindle assembly checkpoint protein, thus increasing the occurrence of lagging chromosomes during prometaphase [20]. PI3K blockage also increases replication stress and subsequent DNA damage by depleting deoxynucleoside triphosphates (dNTP) in BRCA1-deficient TNBC models [21].

Similarly, mTOR inhibition interferes the DNA replication process. The mTOR inhibitor (mTORi) AZD8055 dislodges replication helicase minichromosome maintenance complex proteins 2–7 (MCM2-7) and proliferating cell nuclear antigen (PCNA) from chromatin and reduces the levels of replication factor CDC6, leading to replication stress and consequent ATR/CHK1 activation [22]. Similarly, a recent study in OVCAR3 and SKOV3 ovarian cancer cell lines shows that a pan-mTORi INK128 decreases the levels of DNA replication-related proteins *i.e.,* POLQ and cell cycle regulators, *i.e.,* FBXW7 [23], causing replication stress.

AKT also regulates the progression of DNA replication. In response to replication stress, AKT is required for efficient PCNA ubiquitylation, as shown in homologous recombination (HR)-deficient TNBC and colon cancer cells [24]. As such, a pan-AKT inhibitor (AKTi) C11 or a pan-PI3K inhibitor (PI3Ki) LY294002 blocks the recruitment of translesion synthesis polymerases at sites of DNA damage, thus hindering the progression of DNA replication forks after UV irradiation, leading to replication stress and cell death [24]. Together, these data indicate crosstalk between PI3K signaling and DNA replication process for genomic stability, therefore, the PI3K pathways is an actionable target to induce replication stress and genomic instability in cancer cells.

AKT has an expanded role in interacting with major cell cycle regulators. Active AKT inhibits CHK1 by directly phosphorylating CHK1 at Ser280 which causes non-functioning cytoplasmic sequestration of CHK1, leading to premature mitotic entry and mitotic catastrophe in *BRCA* wild-type cell lines including MCF7 breast cancer, human epithelial and mouse embryonic stem cells [25,26]. Similarly, in BRCA1-deficient mouse embryo fibroblasts, AKT1 depletion increases CHK1 nuclear localization and RAD51 foci formation for DNA repair and cell survival following irradiation-induced DSBs [27]. It appears that AKT has a similar inhibitory role on CHK1 in both BRCA-deficient and -proficient settings, unlike its conflicting function on HR repair in

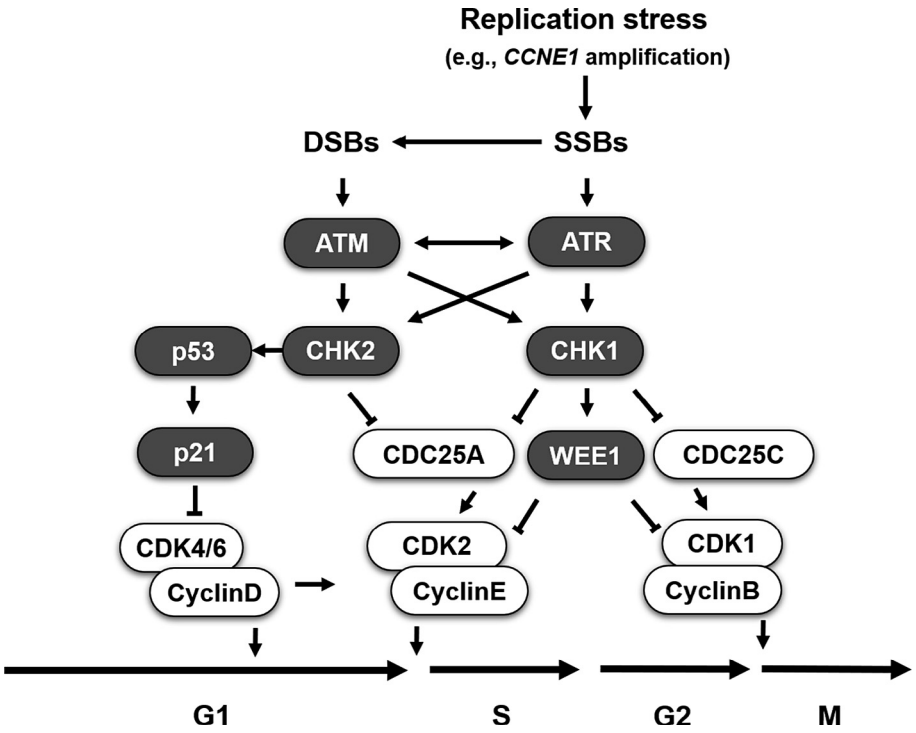

Fig. 2. Cell cycle checkpoints. Checkpoints occur at entry into S phase (the G1/S checkpoint), during replication (intra-S checkpoints) and entry into mitosis (the G2/M checkpoint). For S and G2/M phase checkpoints, ATR activates CHK1 following replication stress-induced SSBs, which subsequently activates WEE1 or inhibits CDC25 phosphatases, leading to deactivation of CDKs. The attenuated CyclinB/CDK1 activity results in the stoppage of G2 to M transition. For G1/S checkpoint, ATM activates CHK2 following DNA DSBs, which in part activates p53. Active p53 transcriptionally induces expression of the CDK inhibitor p21, leading to inhibition of CyclinD/CDK4/6 and CyclinE/CDK2 complexes, thus causing G1 arrest. Proteins contributing to cell-cycle progression are indicated in white boxes, and cell-cycle arrest in gray boxes. Abbreviations: ATM = ataxia-telangiectasia mutate; ATR = ataxia-telangiectasia and Rad3-related; CDC25 = cell division cycle 25; CDK = cyclin-dependent kinase; CHK = cell cycle checkpoint kinase; DSBs = double-strand breaks; SSBs = single-strand breaks.

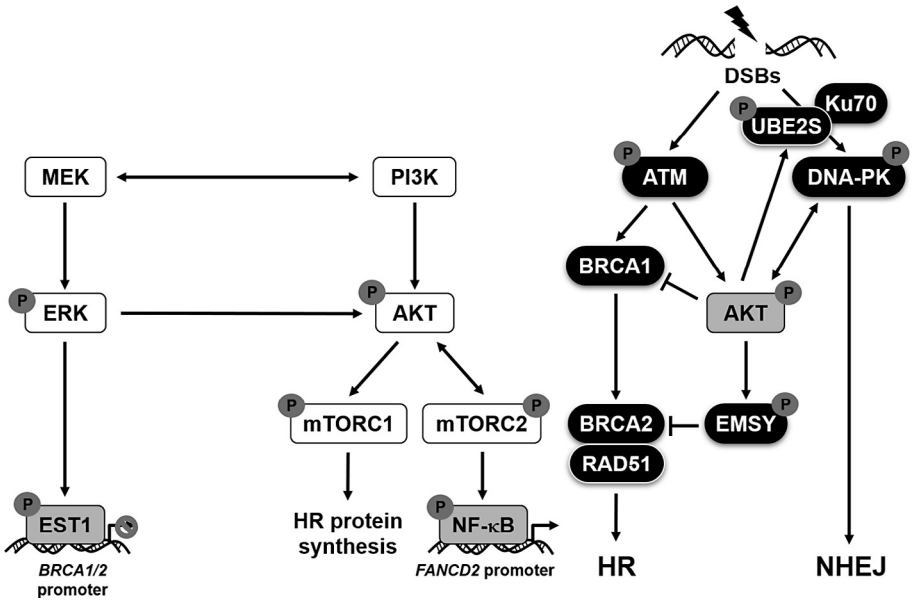

Fig. 3. Crosstalk between PI3K signaling and DNA damage repair pathways. Cytoplasmic PI3K signaling can regulate HR pathway via mTOR-mediated protein synthesis and gene transcription of HR repair while nuclear PI3K signaling can regulate both HR and NHEJ pathways via active AKT. Upon PI3K pathway activation, mTORC1 increases protein synthesis of HR repair proteins *e.g.,* BRCA1, RAD50, RAD51 and FANCD2 by phosphorylating 4E-BP1 and S6K. mTORC2 also increases FANCD2 transcripts by phosphorylating NF-κB which consequently increases its loading onto the promoter region of *FANCD2*. In addition, PI3K can indirectly downregulate the BRCA1 and BRCA2 transcriptions through compensatory MEK/ERK/EST1 pathway activation. Separately, DNA damage sensors including ATM and DNA-PK induce nuclear AKT activation in response to DSBs. Active AKT blocks nuclear translocation of BRCA1 from cytoplasm leading to impaired HR repair. It also indirectly inhibits BRCA2 via EMSY phosphorylation, resulting in the downregulation of HR pathway. For NHEJ repair, active AKT enhances NHEJ pathway by promoting autophosphorylation of DNA-PKcs. It also stabilizes UBE2S thereby enhances its association with Ku70. Active Ku70 then recruits DNA-PKcs to DSBs sites leading to activation of DNA-PKcs kinase to initiate NHEJ repair process. White boxes represent cytoplasmic proteins, gray boxes are nuclear proteins and black boxes indicate DNA repair proteins. Abbreviations: 4E-BP1 = eukaryotic initiation factor 4E binding protein 1; ATM = ataxia-telangiectasia mutated; DNA-PK = DNA-dependent protein kinase; DNA-PKcs = DNA-dependent protein kinase; DSBs = DAN-double stranded breaks; EMSY = BRCA2-interacting transcriptional repressor; EST1 = transcriptional repressor E26 transformation-specific-1; FANCD2 = Fanconi Anemia complementation group D2; HR = homologous recombination; mTORC = mammalian target of rapamycin complex; NHEJ = non-homologous end joining; PI3K = phosphatidylinositol 3-kinase; S6K = ribosomal protein S6 kinase; UBE2S = ubiquitin-conjugating enzyme E2S.

different preclinical models which will be described later.

AKT also downregulates CDK activity via activating the CDK inhibitors p21 and p27 [28]. AKT directly phosphorylates p21 at Ser146 and further increases the assembly of CyclinD/CDK4 complex for G1/S transition [28]. Separately, AKT phosphorylates p27 at Thr157 thus relocates p27 to the cytoplasm. This relocation of p27 consequently releases the nuclear substrates CyclinE/CDK2 and CyclinA/CDK2 from p27, inducing cell cycle progression [28].

It is noteworthy that each isoform of AKT (referred to as AKT unless an isoform-specific function is noted) has distinct roles in tumorigenesis. In murine ID8 ovarian cancer cells, AKT1 or AKT3 knockdown shows impaired tumor growth and metastasis, whereas AKT2 knockdown results in increased tumor proliferation and metastasis [29]. Cristiano *et al.* also found that total AKT activity for cell proliferation was mainly driven by AKT3. In OVCA429 and DOV13 ovarian cancer cells which have higher total AKT activity, AKT3 but not AKT1 activity is required to induce cell growth by activating CDK1 and G2/M transition [30]. The distinct roles of AKT need more mechanistic investigation in various ovarian cancer models as the different AKT isoforms may exert independent, even opposing effects under physiological and pathological conditions.

PI3K pathway inhibitors in combination with cell cycle blockade as a therapeutic strategy

Blocking ATR/CHK1 signaling has been hypothesized to promote replication stress, lethal DNA damage and cell death in p53-deficient tumors including HGSOC [31–33]. As discussed earlier, the PI3K pathway blockades can enhance replication stress. In support, we and other groups found that the CHK1 inhibitor (CHK1i) prexasertib yielded a synergistic anti-tumor effect when combined with a dual PI3K/mTORi LY3023414 in TNBC patient-derived xenografts [34] and HGSOC cell lines and xenograft models [7,8], possibly by causing greater replication stress compared to monotherapy [8]. Similarly, the combinations of mTORi AZD8055 with ATR inhibitor AZ20 or CHK1i rabusertib showed synergistic cytotoxicities *via* inducing replication stress in PI3K-activated TNBC cell models with an activating *PIK3CA* mutation (H1047R) or low levels of PTEN and/or INPP4B [19]. In OCCC and HGSOC cell lines, BEZ235, a dual PI3K/mTORi that also targets ATR, decreased cell proliferation and resensitized cisplatin-resistant cells to cisplatin [35,36].

WEE1 is another key checkpoint at the G2/M transition [32]. WEE1 inhibitor AZD1775 in combination with mTORi ridaforolimus is synergistically cytotoxic in HGSOC and OCCC cell lines independent of their *BRCA* and *KRAS* mutation status [9]. Similarly, WEE1 serves as an adaptive resistant kinase after PI3K inhibition in glioblastoma cell and *in vivo* models, where the combination treatment of WEE1 inhibition (AZD1775) with pan-PI3Ki buparlisib caused a synergistic cytotoxic effect [37]. Kuzu *et al.* also reported that knockdown of AKT3 and WEE1 synergistically inhibited melanoma cell proliferation and xenograft tumor growth [38].

Moreover, HGSOC with *CCNE1* amplification, which accounts for approximately 20% of HGSOC [2], may serve as a synthetically lethal model of HGSOC for this dual pathway blockade. CyclinE1/CDK2 complex promotes DNA replication and chromosome segregation by activating S phase-specific genes, *i.e.,* CDC6 and MCM2-7, thus facilitating the formation of DNA replication complexes for S phase entry [39]. This increased premature S-phase entry leads to replication stress and consequent cell death in HGSOC cell lines [40]. As such, AKT inhibition by MK-2206 or GSK2110183 showed synergistic cytotoxicity with a CDK2 inhibitor dinaciclib in *CCNE1*-amplified HGSOC cell lines [40]. Notably, this synergism was not observed with other PI3Ki or mTORi, implying the interaction with *CCNE1* may be specific to AKT [40] since AKT directly phosphorylates CDK2 and therefore causes a temporary cytoplasmic localization of the CyclinA/CDK2 complex [28].

Overall, these results support that inhibition of ATR, CHK1, WEE1, or their downstream kinase CDK2 can be a promising combination treatment strategy to increase the efficacy of PI3K pathway inhibitors given its interactions with DNA replication and G2/M cell cycle checkpoints, requiring further evaluation in the clinical setting.

Roles of the PI3K pathway in DNA repair pathways

DNA repair process occurs during cell cycle arrest. DSBs are

repaired by two major pathways including non-homologous end-joining (NHEJ) and HR repair. HR repair facilitates error-free repair of DSBs primarily during the S and G2 phases, while NHEJ is the preferred DSB repair pathway in the G1 phase [41]. The following section will elaborate on the interaction between these two repair signalings and the PI3K pathway. Fig. 3 shows the interactions between PI3K and DNA repair pathways.

HR repair and PI3K signaling

HGSOC is characterized by universal *TP53* mutation and half of them harbors defects in HR repair genes [2]. The essential role of BRCA1 and BRCA2 proteins in HR repair has been extensively documented [42]. In brief, BRCA1 acts at an early HR step to promote end resection, and then recruits PALB2 to assist BRCA2 chromatin localization at a later step [42]. BRCA2 subsequently loads RAD51 recombinase onto the resection site to form a RAD51-ssDNA filament. RAD51-ssDNA filaments are necessary for HR partly by preventing the engagement of the 3′-ssDNA into the deleterious single-strand annealing pathway [42]. It has been well known that cancer cells including ovarian cancer with deficient BRCA1 or BRCA2 are highly sensitive to PARP1 inhibition or knockdown [43]. Now, PARPis are one of the most active new drug families in the drug armamentarium for ovarian cancer. Good reviews have been published describing PARPi, therefore, it will not be summarized here [5,44].

PI3K inhibition can induce BRCA-deficient phenotype in tumors with *BRCA* wild-type. Mechanistically, PI3K inhibition triggers a compensatory upregulation of MEK/ERK signaling, as shown in breast and ovarian cancer models [45–47]. This activated MEK/ERK signaling induces the binding of the transcriptional repressor E26 transformation-specific-1 to the *BRCA1* and *BRCA2* promoter regions, resulting in decreased BRCA1 and BRCA2 transcripts and proteins [45–47].

The roles of AKT1 in HR repair are contradictory in literature. In HR-proficient models, AKT1 inhibits HR repair by reducing the nuclear foci formation of BRCA1 and RAD51 following irradiation-induced DNA damages, as shown in BRCA-proficient MCF7 breast cancer cells [48] and hamster ovary cells [49]. However, AKT1 is also reported to promote HR in other studies. AKT1 phosphorylates BRCA1 at Ser694 following hormone stimulation, thus protecting BRCA1 from proteasomal degradation, and also promotes nuclear assembly of BRCA1 complexes in MCF7 breast cancer cells [50]. AKT1 also increases nuclear RAD51 foci formation at the DSBs, thus inducing HR repair in lung cancer cells [51]. In HR-deficient cells, AKT1 partly impairs HR by suppressing CHK1 nuclear localization, which disrupts the interaction between CHK1 and RAD51 [27]. Furthermore, AKT1 indirectly downregulates HR by activating BRCA2-interacting transcriptional repressor EMSY, resulting in decreased function of BRCA2 [52]. More studies are needed to better understand the interactions between AKT and BRCA in HR repair to guide the combination treatment approaches using AKTi.

NHEJ repair and PI3K signaling

AKT is also involved in NHEJ-mediated DSB repair. AKT enhances NHEJ repair by forming a complex with DNA-PKcs (DNA-PK catalytic subunit) and stimulating its autophosphorylation [53]. AKT can also increase the stability of ubiquitin-conjugating enzyme E2S (UBE2S) as well as its association with Ku70 which is essential for the activation of DNA-PKcs kinase [54]. Consistently, AKT depletion results in decreased NHEJ repair in non-small cell lung cancer cells [55]. Moreover, DNA-PK can act as an upstream signal for AKT activation following genotoxic stress [53]. Stronach *et al.* reported that DNA-PKcs specifically phosphorylated nuclear AKT at Ser473 in platinum-resistant OCCC and HGSOC cells but not platinum-sensitive cells [55]. There, authors showed that inhibition of DNA-PK (NU7026 and siRNA against DNA-PK) but not mTORC2 (rapamycin and siRNA against Rictor subunit of mTORC2), reversed the activating phosphorylation of AKT at Ser473, thus restoring platinum-sensitivity. This effect appears to be restricted to DNA damage-mediated activation of AKT [56]. Notably, the development of platinum-resistance was associated with different AKT isoform activation, *i.e.,* for cisplatin resistance, HGSOC PEO23 and OCCC SKOV3 require AKT1, HGSOC PEA2 requires AKT2, whereas HGSOC PEO4 requires AKT3, respectively [56]. Together, these data suggest that the PI3K pathway plays an active role in promoting DNA DSB repair through HR or DNA-PK-dependent NHEJ.

PI3K pathway inhibitors in combination with DNA repair blockades as a therapeutic strategy

The initial concept of combining PARPi with PI3K/mTOR pathway inhibitors is based on the reduction of HR repair-related proteins in HR-proficient tumors. In *BRCA* wild-type HGSOC cell lines, pan-PI3Ki (buparlisib) resulted in attenuated HR repair by downregulating BRCA2 or RAD51, making cells more sensitive to PARPi [46]. This synergism was seen in both *PIK3CA* mutant OCCC and wild-type HGSOC ovarian cancer cells [45,46]. Buparlisib also reduced RAD51 foci formation and sensitizes *PTEN* mutant endometrial cancer cells to PARPi olaparib [57]. These data suggest that tumors with *PIK3CA* mutation alone may not predict the response to PI3K blockade and PARPi combination in the clinical setting reflecting the complex biology. In addition, pan-AKT activity is upregulated at baseline in BRCA-deficient ovarian cancer cells (SKOV3 with *BRCA1*-knockdown and *BRCA2*-mutated PEO1) which enhances cell survival despite the absence of HR, making an important target for treatment [58]. As such, a pan-AKTi MK-2206 and olaparib combination induced synergistic cytotoxicity in BRCA-deficient HGSOC cells [58].

Overall, preclinical data suggest PI3K signaling blockades can induce synthetic lethality with DNA repair or cell cycle inhibitors in ovarian cancer. More preclinical studies are necessary for various ovarian cancer models to dissect the interactions between PI3K signaling and HR, and also to develop possible predictive biomarkers to optimize patient selection for treatment.

PI3K pathway inhibitors in clinical trials

Several PI3K pathway inhibitors are approved by the United States Food and Drug Administration (FDA) for various cancers [59–61], however, no PI3K pathway inhibitor has been approved by the FDA for the treatment of gynecologic cancers. Here, we will focus on the use of this drug class, either as monotherapy or in combination, in gynecologic cancers.

PI3K pathway blockade monotherapy in ovarian cancer

Early trials of single-agent PI3K pathway inhibitors have produced disappointing results despite the high prevalence of PI3K pathway aberrations in ovarian cancer and strong preclinical rationale for their use. Studies have ubiquitously reported overall response rates (ORR; complete + partial responses) of $< 10\%$ in advanced or recurrent ovarian cancer and are similarly low across all advanced solid tumor types (Table 1). Few monotherapy trials of PI3K pathway inhibition remain ongoing in this disease (Table 2).

One potential limitation is toxicities leading to suboptimal dosing/schedules or early cessation of trials [62]. In a phase II study of mTORi everolimus in endometrial cancer, 49% (17/35) of patients required a dose reduction and 5 patients were unevaluable after < 1 cycle due to toxicities including stomatitis, hyperglycemia, thrombocytopenia, hypertriglyceridemia, rash and fever [63]. Similarly, in a phase II trial of mTORi ridaforolimus, treatment was discontinued in 33% of patients due to adverse events (AEs) predominantly diarrhea, hyperglycemia, and anemia [64] while another study of ridaforolimus reported dose modifications in 29 of 34 (85%) patients and removal of 7 from the trial for hematologic events, sepsis and most commonly, mucositis [65].

Table 1
PI3K pathway inhibitor monotherapy clinical trials including ovarian and/or endometrial cancer with results.

Drug	Mechanism	Phase	Patients	Dose and schedule	Enrollment biomarker	Common (> 10%) adverse events	ORR (RECIST)
PI3K inhibitor							
Buparlisib [71], Rodon 2014	Pan-class I PI3K inhibitor	I	Advanced solid tumors (n = 83) OC (n = 3)	12.5–150 mg PO qd	Mutated/amplified *PIK3CA* and/or mutated/null/low *PTEN* protein expression (expansion cohort n = 43)	G1/2: anorexia, diarrhea, nausea, hyperglycemia, rash, fatigue, stomatitis, asthenia, pruritis, anxiety, depression G3/4: none	4.8% overall/0% OC
Pictilisib [89], Sarker 2015	Pan-class I PI3K inhibitor	I	Solid tumors (n = 60) OC (n = 3)	15–450 mg PO qd for days 1–21/q28 330–400 mg PO qd for 28/28 days	None	G1/2: nausea, diarrhea, vomiting, anorexia, dysgeusia, rash, stomatitis, xeroderma, fatigue G3/4: none	1.6% overall/0% OC
Pilaralisib [90], Matulonis 2015	Pan-class I PI3K inhibitor	II	Advanced or recurrent endometrial carcinoma (n = 67)	600 mg capsules or 400 mg tablets qd	None	G1/2: rash, diarrhea, fatigue, nasuea, hyperglycemia, anorexia, G3/4: none	6%
Buparlisib [70], Heudel 2017	Pan-class I PI3K inhibitor	II	Advanced or recurrent endometrial carcinoma (n = 40)	100 mg PO qd (n = 16*) 60 mg PO qd (n = 24)	None	G1/2: rash, hyperglycemia, mucositis, nausea, vomiting, constipation, diarrhea, abdominal pain, anorexia, dyspnea, depression, anxiety, fatigue, infection, pain, anemia, lymphopenia, hepatic cytolysis, increased ALP, increased GGT hypercholesterolemia, renal toxicity G3/4: rash, hypertension, hyperglycemia	0%
Alpelisib [72], Juric 2018	PI3Kα-selective inhibitor	Ia	Advanced solid tumors (n = 134) OC (n = 14)	30–450 mg PO qd (n = 108) 120–200 mg PO BID (n = 26)	*PIK3CA* mutation (n = 125, 93.3%)	G1/2: hyperglycemia, nausea, anorexia, diarrhea, vomiting, fatigue, stomatitis G3/4: hyperglycemia	6% overall/0% OC
AKT inhibitor							
GSK2141795 [91], Gungor 2015	Pan-AKT isoform inhibitor	I	Recurrent/persistent OC (n = 11) or EC (n = 1)	50–75 mg PO qd	None	G1/2: nausea, anorexia, vomiting, diarrhea, rash, constipation, lethargy, dizziness, insomnia G3/4: none	8%
Perifosine [14], Hasegawa 2017	Pan-AKT isoform inhibitor	II	Recurrent gynecologic cancer (n = 71) *PIK3CA* mutant OC (n = 5) *PIK3CA* wild-type OC (n = 16) *PIK3CA* mutant EC (n = 7) *PIK3CA* wild-type EC (n = 17)	600 mg PO day 1 followed by 100 mg PO qd	*PIK3CA* mutation	G1/2: anemia, nausea, vomiting, diarrhea, anorexia, malaise, weight loss, hypoalbuminemia, increased creatinine, pain G3/4: diarrhea, anorexia	0% overall
Capivasertib [73], Hyman 2017	Pan-AKT isoform inhibitor	I	Advanced solid malignancy in tumors with AKT1 mutations (n = 58) OC (n = 7) EC (n = 8)	480 mg BID for 4 days, followed by 3 days off, in 21-day cycles	*AKT1* mutation	G1/2: diarrhea, nausea, fatigue vomiting, hyperglycemia, rash, abdominal pain, anorexia, pyrexia, dizziness, back pain, elevated AST, cough, dry mouth, headache, edema, congestion, constipation, hypertension, pruritis, myalgia, hypokalemia G3/4: hyperglycemia, diarrhea, rash	24% overall/0% OC 25% EC
Capivasertib [13], Banerji 2018	Pan-AKT isoform inhibitor	I	Dose escalation and dose-expansion cohort: advanced solid tumors (n = 90) OC (n = 4) Expansion cohort: *PIK3CA* mutant breast (n = 31) and gynecologic cancers (n = 28) OC (n = 6) EC (n = 10)	Dose-escalation 80–600 mg BID, 480–640 mg BID 4/7 days, 640–800 mg 2/7 days Expansion 480 mg BID for 4/7 days	*PIK3CA* mutation (expansion cohort)	G1/2: diarrhea, nausea, vomiting, fatigue, anorexia, hyperglycemia, rash, constipation, abdominal pain, pyrexia, headache, anemia, increased creatinine, proteinuria, asthenia, hypomagnesemia G3/4: hyperglycemia	0% Dose-escalation and expansion cohorts 8% *PIK3CA* mutant gyn cancer expansion cohort
MK-2206 [92], Myers 2019	Pan-AKT isoform inhibitor	II	Recurrent endometrial cancer (n = 36)	200 mg PO qw	*PIK3CA* mutation (n = 9, 25%)	G1/2: constipation, nausea, vomiting, fatigue fever, hyperglycemia, rash G3/4: rash	6% overall (1 *PIK3CA* mutant, 1 *PIK3CA* wt)
mTORC1/2 inhibitor							
MKC-1 [93],Elser 2009	mTORC2 inhibitor	II	Metastatic or recurrent platinum-resistant OC	125 mg/m2 PO BID for 14 days in 28-day cycles	None	G1/2: fatigue, nausea, anorexia, transaminitis, vomiting, diarrhea, anemia G3/4: neutropenia	0% overall

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Table 1 (*continued*)

Drug	Mechanism	Phase	Patients	Dose and schedule	Enrollment biomarker	Common (> 10%) adverse events	ORR (RECIST)
			(n = 21) and advanced EC (n = 21)				
Everolimus [63], Slomovitz 2010	mTORC1 inhibitor	II	Recurrent endometrial carcinoma (n = 35)	10 mg PO qd	None	G1/2: anorexia, constipation, fatigue, mucositis, nausea, pain, rash, anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, hypercholesterol, hyperglycemia, hypertriglyceride G3/4: fatigue, nausea, lymphopenia	0% overall
Temsirolimus [94],Behbakht 2011	mTORC1 inhibitor	II	Recurrent/persistent epithelial OC or primary peritoneal cancer (n = 54)	25 mg IV weekly	None	G1/2: leukopenia, thrombocytopenia, neutropenia, anemia, fatigue, nausea, gastrointestinal, metabolic, neurosensory, pain G3/4: gastrointestinal, metabolic, pain	9.3%
Temsirolimus [95], Oza 2011	mTORC1 inhibitor	II	Recurrent or metastatic endometrial cancer (n = 60) Chemo-naïve (n = 33) Chemo-treated (n = 27)	25 mg IV weekly	None	G1/2: fatigue, acne, dry skin, pruritis, rash, diarrhea, anorexia, mouth dryness, nausea, vomiting, cough, lymphopenia, neutropenia, thrombocytopenia, anemia, elevated creatinine, hypokalemia, elevated AST G3/4: fatigue, diarrhea	9% overall
Everolimus [96], Ray-Coquard 2013	mTORC1 inhibitor	II	Advanced or metastatic endometrial cancer (n = 44)	10 mg PO qd	None	G1/2: fatigue, nausea, rash, mucositis, vomiting, anorexia, diarrhea, infection, constipation, edema, dyspnea, hemorrhage, anemia, lymphopenia, leukopenia, neutropenia, thrombocytopenia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, transaminitis, hypercalcemia G3/4: fatigue, anorexia, diarrhea, infection, thromboembolism, anemia, lymphopenia, hyperglycemia	9%
Ridaforolimus [97], Colombo 2013	mTORC1 inhibitor	II	Recurrent or persistent endometrial cancer (n = 45)	12.5 mg IV/day, d1-5 every 2 weeks	None	G1/2: mouth sores, anemia, fatigue, diarrhea, nausea, vomiting, asthenia, anorexia, dysgeusia, anorexia G3/4: anemia	11%
Ridaforolimus [65], Tsoref 2014	mTORC1 inhibitor	II	Recurrent or metastatic endometrial cancer (n = 34)	40 mg/day; d1-5 of a 7 day cycle	None	G1/2: fatigue, dry skin, nail changes, pruritis, rash, anorexia, diarrhea, mucositis, nausea, dysgeusia, vomiting, edema, dizziness, cough, dyspnea, pneumonitis, weight loss, anemia, neutropenia, thrombocytopenia, lymphopenia, elevated creatinine, elevated ALP, transaminitis, hyperglycemia G3/4: fatigue, weight loss, hyperglycemia	8.8%
Ridaforolimus [64], Oza 2015	mTORC1 inhibitor	II	Advanced endometrial cancer (n = 64 received ridaforolimus)	40 mg/day; d1-5 of a 7 day cycle	None	G1/2: diarrhea, mucositis, anorexia, asthenia, nausea, hyperglycemia, vomiting, abdominal pain, stomatitis, fatigue, anemia, rash, pyrexia, hyper cholesterol G3/4: diarrhea, hyperglycemia, anemia	0%
Temsirolimus [98], Emons 2016	mTORC1 inhibitor	II	Platinum-refractory/resistant OC (n = 22) or advanced/ recurrent EC (n = 22)	25 mg IV weekly	None	G1/2: nausea, abdominal pain, diarrhea, stomatitis, constipation, vomiting, fatigue, mucositis, edema, rash, nail disorder, urinary tract infection, dyspnea, headache, neuropathy, anemia, thrombocytopenia, anorexia G3/4: none	4.8% OC 10% EC
PI3K/mTOR inhibitor							
SF1126 [99],Mahadevan 2012	Pan-class I PI3K and mTOR inhibitor	I	B-cell malignancies (n = 5) and Advanced solid tumors (n = 39) OC (n = 5) EC (n = 1)	90–1110 mg/m2/day IV on days 1 and 4 weekly	None	G1/2: nausea, fatigue, vomiting, diarrhea, pyrexia, anorexia, anemia, pruritis, headache G3/4: edema, diarrhea, weakness, hypoglycemia, anemia, pruritis, hypokalemia, hypersensitivity	0% among all solid tumors
BGT226 [100], Markman 2012	PI3Kα/β/γ and mTOR inhibitor	I	Advanced solid tumors (n = 57) OC (n = 2) EC (n = 4)	2.5–125 mg/day TIW	None	G1/2: nausea, diarrhea, vomiting, anorexia, ftigue, anemia, abdominal pain G3/4: diarrhea	0% overall
		II		8 mg PO qd	None		

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Table 1 (*continued*)

Drug	Mechanism	Phase	Patients	Dose and schedule	Enrollment biomarker	Common (> 10%) adverse events	ORR (RECIST)
PF-04691502 [66], Del Campo 2016	Pan-class I PI3K and mTOR inhibitor		Recurrent endometrial cancer (n = 18)			G1/2: diarrhea, fatigue, hyperglycemia, nausea, anorexia, dry mouth, hypokalemia, mucositis, stomatitis, dysgeusia, dyspnea, pneumonitis, rash G3/4: diarrhea, dyspnea, fatigue, hyperglycemia, hypokalemia, pneumonia, pneumonitis, rash, stomatitis	Trial terminated early due to AEs
Gedatolisib [66], Del Campo 2016	Pan-class I PI3K and mTOR inhibitor	II	Recurrent endometrial cancer (n = 40)	154 mg IV qw	None	G1/2: nausea, mucositis, anorexia, diarrhea, fatigue, dysgeusia, vomiting, rash, stomatitis, hyperglycemia, asthenia, dry mouth G3/4: fatigue	16%
Apitolisib [101], Makker 2016	Pan-class I PI3K and mTOR inhibitor	II	Recurrent or persistent endometrial cancer (n = 56)	40 mg PO qd	None	G1/2: hyperglycemia, rash, fatigue, diarrhea, anorexia, vomiting, stomatitis, weight loss, dysgeusia, hypokalemia, hypomagnesemia, abdominal pain, anemia, constipation, dehydration, dry mouth, mucositis, pyrexia G3/4: hyperglycemia, rash, diarrhea	9%
BEZ235 [74],Rodon 2018	Pan-class I PI3K and mTOR inhibitor	I/Ib	Solid tumors (n = 153) OC (n = 8) EC (n = 5)	BEZ235 hard gelatin capsule 10–1200 mg/day BEZ235 solid dispersion system capsule 400–1000 mg/day	*PIK3CA* and/or *PTEN* molecular alterations (expansion cohort)	G1/2: nausea, diarrhea, vomiting, anorexia, fatigue, stomatitis, asthenia, anemia, weight loss, dehydration, dyspnea, abdominal pain, cough, pyrexia, rash, creatinine increase, pruritis G3/4: none	0% overall
LY3023414 [75], Rubinstein 2019	Pan-class I PI3K and mTOR inhibitor	II	Advanced endometrial cancer (n = 28)	200 mg PO BID in 21-day cycles	Loss of function mutation in *PTEN* or known activating mutation in *PIK3CA, AKT1, PIK3R1, PIK3R2,* or *MTOR*	G1/2: anemia, hyperglycemia, hyboalbuminemia, hypophosphatemia, transaminitis, leukopenia, hypomagnesemia, thrombocytopenia, nausea, hypocalcemia, hypokalemia, constipation, hyponatremia, increased creatinine, fatigue G3/4: anemia, hyperglycemia, hypophosphatemia, thrombocytopenia, lymphopenia, hypokalemia, hyponatremia	16%

*Trial dose was lowered to 60 mg daily after the first 16 patients experienced high rates of toxicities (cutaneous rash 54%, depressive events 47%, anxiety 40%).

Abbreviations: ALP = alkaline phosphatase; BID = twice daily; CBR = clinical benefit rate; EC = endometrial cancer; G1/2 = grade 1 or 2; G3/4 = grade 3 or 4; GGT = gamma-glutamyltransferase; gyn = gynecologic; IV = intravenous; OC = ovarian cancer; ORR = overall response rate; mg = milligram; PO = oral; PR = partial response; qd = once daily; qw = once weekly; SD = stable disease; TIW = three times weekly; wt = wild-type.

Table 2
Ongoing monotherapy clinical trials targeting the PI3K pathway including ovarian cancer patients.

Drug	Target	Year opened	Phase	Name	Disease	Biomarker	NCT#	Status
GDC-0077	PI3Kα selective inhibitor	2016	I	A Phase I, Open-Label, Dose-Escalation Study Evaluating the Safety, Tolerability, and Pharmacokinetics of GDC-0077 as a Single Agent in Patients With Locally Advanced or Metastatic *PIK3CA*-Mutant Solid Tumors and in Combination With Endocrine and Targeted Therapies in Patients With Locally Advanced or Metastatic *PIK3CA*-Mutant Hormone-Receptor Positive Breast Cancer	Advanced solid tumors	*PIK3CA* mutant	03006172	Recruiting
IPI-549	PI3Kγ selective inhibitor	2015	I/Ib	A Phase 1/1b First-In-Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IPI-549 Monotherapy and in Combination With Nivolumab in Subjects With Advanced Solid Tumors	Advanced solid tumors	None	02637531	Recruiting
YY-20394	PI3Kδ selective inhibitor	2019	I	A Single-Arm, Open-Label, Multi-Center, Phase I Study of YY-20394 in Patients With Advanced Solid Tumors	Advanced solid tumors	None	04049929	Not yet recruiting,as of 12/31/2019
ARQ 751	Pan-AKT inhibitor	2016	Ib	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination With Other Anti-Cancer Agents in Adult Subjects With Advanced Solid Tumors With *PIK3CA / AKT / PTEN* Mutations	Advanced solid tumors	*PIK3CA*, *AKT* or *PTEN* mutations	02761694	Recruiting
TAS-117	Pan-AKT inhibitor	2017	II	A Phase II Study of TAS-117 in Advanced Solid Tumors With PI3K/AKT Gene Aberration	Advanced solid tumors	PI3K or AKT aberration	03017521	Recruiting
Sirolimus	mTORC1	2017	IV	Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors	Refractory solid tumors	*PIK3CA* mutation, *PIK3CA* amplification, *PIK3CA-AKT* pathway aberration (H1047R, E542K, E545K, *PTEN* loss)	0688881	Recruiting
Capivasertib Ipatasertib Sapanisertib GSK2636771 BAY 80–6946	AKT AKT mTOR PI3Kβ Pan-class I PI3K	2015	II	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	Lymphomas, multiple myeloma or solid tumors including ovarian carcinoma	*AKT* mutation *AKT* mutation mTOR, TSC1 or TSC2 mutation *PTEN* mutation/deletion/loss *PIK3CA* mutation, *PTEN* mutation/loss	02465060	Recruiting

Moreover, the development of dual PI3K/mTORi PF-04691502 was terminated due to safety concerns including the high rate (22%) of treatment-related pneumonitis observed in a phase II study [66].

The underlying mechanisms of toxicities related to PI3K pathway blockade are partly understood. Hyperglycemia, a common dose-dependent toxicity seen with pan-PI3K, PI3Kα, mTOR and AKT inhibitors (Table 1), occurs because the PI3K pathway mediates insulin-driven glucose uptake [62,67]. It occurs in diabetics and non-diabetics, often leading to early discontinuation of treatment. The mechanism of neuropsychiatric effects including anxiety and depression observed with the pan-PI3Ki buparlisib remains incompletely understood but has served to limit its clinical application [68–70].

Additionally, lack of or poor patient selection may further contribute to unsatisfactory results. Several studies have applied biomarker criteria for improved patient selection to address the low efficacy seen in these trials. However, ORRs have remained low despite application of genomic biomarkers such as *PIK3CA* mutation, as detailed in Table 1. For instance, the phase I trials of pan-PI3Ki buparlisib and PI3Kα-selective inhibitor alpelisib, which enrolled patients with *PIK3CA* mutant advanced solid tumors, reported ORRs < 10% overall [71,72]. Similarly, a phase II study of pan-AKTi perifosine in recurrent gynecologic cancer recruited *PIK3CA* mutant ovarian (n = 5), endometrial (n = 7) and cervical (n = 10) as well as *PIK3CA* wild-type ovarian (n = 16), endometrial (n = 17) and cervical cancer patients (n = 16). No complete or partial responses were observed, regardless of *PIK3CA* status [14]. A multi-arm study of pan-AKTi capivasertib (AZD5363) examined the impact of both *PIK3CA* and *AKT1* mutations (Table 1; NCT01226316) [13,73]. The expansion cohort recruiting *PIK3CA* mutant gynecologic cancers, including endometrial (n = 10) and ovarian cancer (n = 6), reported an 8% ORR [13]. Another arm of this trial assessed whether activating *AKT1* mutations enhance sensitivity to direct AKT inhibition with capivasertib. Limited efficacy was again reported, with a 17% ORR among *AKT1* mutated gynecologic cancers (2/8 endometrial, 1/3 cervical and 0/7 ovarian cancer partial responses) [73]. Consistently low response rates (RRs) were also seen with dual PI3K/mTOR inhibition, including a phase I trial of BEZ235 in *PIK3CA* or *PTEN* mutated advanced solid tumors reporting a 0% ORR [74] and a phase II of LY3023414 in advanced endometrial cancer with activating *PI3K* pathway mutations reporting at 16% ORR [75]. Insufficient activity of single-agent PI3K pathway targeting despite the application of genomic biomarkers suggests more research is needed to identify improved biomarkers of response [62]. Moreover, it highlights potential pathway redundancy and compensatory feedback loops resulting in resistance to treatment with PI3K pathway inhibitors [4,62].

Therefore, combination therapies are currently under investigation as a strategy to address these challenges. There are many active and moderately promising studies looking at the combination of PI3K pathway inhibitors with classic chemotherapies, including carboplatin and paclitaxel, as well as with targeted therapies such as the circulating VEGF antibody bevacizumab, which have been detailed in reviews and studies [3,4,76,77]. The focus of this section will be combination therapy with PI3K pathway and DDR inhibitors.

Clinical benefit of targeting PI3K pathways and DDR

Therapeutic combinations of PI3K and DDR inhibitors are actively being investigated in clinical trials (Tables 3 and 4). Available results suggest the combinations are generally tolerable and show modestly promising early signs of improved activity compared to single-agent PI3K pathway inhibition, though further research and final reports from ongoing trials are eagerly awaited.

Combining PI3K pathway inhibitors with DNA repair inhibitors

To date, only 1 trial has published results of a PI3K pathway inhibitor with a DDR inhibitor, specifically with the PARPi olaparib. In

Table 3
Trials of PI3K pathway inhibitors in combination with DDR inhibitors in gynecologic cancers with results.

Drugs	Mechanism of PI3K pathway inhibitor	Phase	Patients	Dose and schedule	Biomarker	Common (> 10%) adverse events	Response in OC
PI3K inhibitor							
Buparlisib + olaparib [69], Matulonis 2017	Pan-class I PI3K inhibitor	I	Recurrent HGSOC, fallopian tube, or primary peritoneal cancer (n = 46); TNBC (n = 24)	Buparlisib 40-50mq qd + olaparib 100–300 mg BID	None	G1/2: nausea, fatigue, hyperglycemia, anorexia, depression, diarrhea, anxiety, mucositis, vomiting, transaminitis, anemia, thrombocytopenia, lymphopenia G3/4: none	ORR 29% 12 PR (8 with *gBRCA*m), 20 SD (13 with *gBRCA*m)
Alpelisib + olaparib [81], Konstantinopoulos 2019	PI3Kα-selective inhibitor	I	Recurrent epithelial OC (n = 28); breast cancer (n = 4)	Alpelisib 200–300 mg qd + olaparib 100–200 mg BID	None	G1/2: nausea, hyperglycemia, fatigue, diarrhea, vomiting, anorexia, headache, anemia, constipation, elevated creatinine, thrombocytopenia, rash, increased amylase, abdominal pain, dry skin, dysgeusia, dyspnea, mucositis G3/4: hyperglycemia	ORR 36% 10 PR (3 with *gBRCA*m), 14 SD (7 with *gBRCA*m)

Abbreviations: BID = twice daily; G1/2 = grade 1 or 2; G3/4 = grade 3 or 4; gram = germline BRCA mutation; ORR = overall response rate; PR = partial response; ad = once daily; SD = stable disease; TNBC = triple negative breast cancer

Table 4
PI3K pathway inhibitors in combination with DDR inhibitors under clinical development in advanced tumors including gynecologic cancers.

Drugs	Mechanism of PI3K pathway inhibitor	Year opened	Phase	Name	Diseases	Biomarker	NCT#	Status
PI3K inhibitor								
Copanlisib + niraparib	Pan-class I PI3K inhibitor	2018	Ib	A Phase Ib Study of the Oral PARP Inhibitor Niraparib With the Intravenous PI3K Inhibitor Copanlisib for Recurrent Endometrial and Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Recurrent endometrial, ovarian, primary peritoneal or fallopian tube cancer	None	03586661	Recruiting
Copanlisib + olaparib + durvalumab	Pan-class I PI3K inhibitor	2019	Ib	A Phase Ib Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors	Advanced solid tumors	*PTEN* mutation; or *PIK3CA* mutation; or mutation in DDR genes: *ARID1A, ATM, ATRX, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, MRE11A, MSH2, PALB2, PARP1, POLD1, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L, XRCC2*	03842228	Recruiting
AKT inhibitor								
Capivasertib + olaparib	Pan-AKT isoform inhibitor	2014	Ib	A Phase Ib Study of the Oral PARP Inhibitor Olaparib With the Oral mTORC1/2 Inhibitor AZD2014 or the Oral AKT Inhibitor AZD5363 for Recurrent Endometrial, Triple Negative Breast, and Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Recurrent endometrial, TNBC, and ovarian, primary peritoneal, or fallopian tube cancer	None	02208375	Active, not recruiting
Capivasertib + olaparib	Pan-AKT isoform inhibitor	2015	I	A Phase I Multi-centre Trial of the Combination of Olaparib (PARP Inhibitor) and AZD5363 (AKT Inhibitor) in Patients With Advanced Solid Tumours	BRCA1/2 mutant cancersor TNBC, HGSOC, CRPC, and tumors with somatic mutations or other aberrations known to result in a hyperactivated PI3K/AKT pathway	None	02338622	Unknown on CT.govas of 12/31/2019
Capivasertib + olaparib	Pan-AKT isoform inhibitor	2015	II	A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination with AZD1775, AZD5363, or AZD6738 in Advanced Solid Tumors	Advanced solid tumors	*PTEN*, *PIK3CA*, *AKT*, or *ARID1A* mutation	02576444	Recruiting
mTORC1/2 inhibitor								
Vistusertib + olaparib	mTORC1/2 inhibitor	2014	Ib	A Phase Ib Study of the Oral PARP Inhibitor Olaparib With the Oral mTORC1/2 Inhibitor AZD2014 or the Oral AKT Inhibitor AZD5363 for Recurrent Endometrial, Triple Negative Breast, and Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Recurrent ovarian, primary peritoneal, or fallopian tube cancer, endometrial cancer, breast cancer	None	02208375	Active, not recruiting
Everolimus + niraparib	mTORC1 inhibitor	2017	I	A Phase 1 Evaluation of the Safety and Tolerability of Niraparib in Combination With Everolimus in Advanced Ovarian and Breast Cancer	Ovarian cancer, breast cancer	None	03154281	Recruiting
PI3K/mTOR inhibitor								
LY3023414 + Prexasertib	Pan-class I PI3K /mTORC1/2 inhibitor	2014	I	A Study of Prexasertib (LY2606368) With Chemotherapy or Targeted Agents in Participants With Advanced Cancer	Advanced or metastatic cancer	*PIK3CA* mutations	02124148	Active, not recruiting
Gedatolisib + Palbociclib	Pan-class I PI3K /mTORC1/2 inhibitor	2017	II	Phase I Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	Solid tumors	None	03065062	Recruiting

Abbreviations: CRPC = castration resistant prostate cancer; ER+ = estrogen receptor positive; HER2- = human epidermal growth factor receptor 2 negative; HGSOC = high grade serous ovarian cancer; TNBC = triple negative breast cancer.

the first arm of this phase I trial (NCT01623349), the pan-class I PI3Ki buparlisib was combined with olaparib. 69 patients with women's cancers were enrolled, 46 of whom had recurrent HGSOC [69]. The combination resulted in dose-limiting toxicities (DLTs) of grade 3 transaminitis and depression, consistent with the neuropsychiatric AEs observed with buparlisib monotherapy, requiring attenuation of the buparlisib dose. Moreover, depression and anxiety were observed in 36% and 28% of patients, respectively, prompting future evaluation of α-specific PI3Ki alpelisib (BYL719), which has no known central nervous system (CNS) toxicity, in the second arm. ORR with the olaparib and buparlisib combination was 29% in germline *BRCA* mutated (gBRCAm) and 12% in germline *BRCA* wild-type (gBRCAwt) HGSOC patients. Of the 24 patients included in the breast cancer cohort, RRs were 33% and 20% in gBRCAm and gBRCAwt patients, respectively. No difference in RRs was observed based on platinum-sensitivity, as is typically described with PARP inhibition [78,79]. However, as RRs to single-agent olaparib in the BRCAm population are approximately 30%, data suggest the combination did not provide added benefit in the BRCAm setting [79,80].

The alpelisib plus olaparib arm of this trial enrolled patients with recurrent epithelial ovarian (n = 28) or breast cancer (n = 4). DLTs included hyperglycemia and neutropenic fever. An expansion cohort was enrolled at the maximum tolerated dose (MTD) of alpelisib 200 mg once daily plus olaparib 200 mg twice daily (BID) [81]. Common (> 10%) AEs are listed in Table 3; notably, there were no CNS issues. Early signs of clinical activity were observed among ovarian cancer patients, with responses in 4 of 12 (33%) BRCAwt, platinum-resistant patients and 3 of 10 (30%) gBRCAm [81], requiring further investigation.

In light of these findings, several ongoing trials are now investigating the PI3K pathway and PARPi combination (Table 4). Two phase I trials investigating combination therapy with copanlisib, a pan-class I PI3Ki, are actively recruiting patients as of 12/31/2019. One trial is investigating copanlisib with PARPi niraparib in recurrent gynecologic cancers (NCT03586661), while the other is exploring potential for synergy with immunotherapy by testing the triplet of copanlisib, olaparib and anti-programmed death ligand-1 (PD-L1) durvalumab in advanced solid tumors with *PTEN*, *PIK3CA*, or DDR gene mutations (NCT03842228; Table 4).

AKT inhibition is also being combined with PARPi in several ongoing trials (Table 4). A dose escalation (n = 20) and dose expansion (n = 33) phase I trial of capivasertib, an AKTi, with olaparib enrolled 53 patients with advanced cancers, including 19 with ovarian and 16 with breast cancer (NCT02338622). Recommended phase 2 doses (RP2D) were established as 300 mg olaparib BID and 400 mg capivasertib BID for 4 of 7 days or 300 mg olaparib BID and 640 mg capivasertib BID for 2 of 7 days [82,83], the latter of which are the MTDs of both drugs when used as monotherapy [13,84]. The only DLT was a grade 3 rash, while grade 3 non-DLT toxicities included anemia, diarrhea, vomiting and proteinuria in the 4 of 7 day schedule and transaminitis, nausea, fatigue, anemia, rash, hyperglycemia, and diarrhea in the 2 of 7 day schedule [82,83]. There was a 27% (10/37) ORR, including responses in platinum-resistant gBRCAm ovarian (n = 2), BRCAwt ovarian (n = 2), gBRCAm breast (n = 4) and BRCAwt TNBC (n = 1) [83], although final results have yet to be published.

Similarly, in an ongoing phase Ib dose-escalation and expansion study for patients with recurrent endometrial, ovarian, or TNBC (NCT02208375), preliminary results from 38 enrolled patients reported DLTs of diarrhea and vomiting, establishing the RP2D as 300 mg BID olaparib and 400 mg BID capivasertib 4 of 7 days as above [85]. Similar AE profiles as described above were observed. A 24% RR was seen in 30 evaluable patients (7/30), including 1 ovarian, 4 endometrial and 2 TNBC patients, with translational studies ongoing. The results of an ongoing phase II trial of olaparib with capivasertib in patients with advanced solid tumors with *PIK3CA*, *AKT*, or *ARID1A* mutations will provide important information regarding the clinical activity of this combination as well as the potential benefits of patient selection based on molecular characteristics (NCT02576444).

Lastly, several trials are exploring the combination of PARP and mTOR inhibition. An active phase I trial of olaparib with mTORC1/2 inhibitor vistusertib (AZD2014) in recurrent ovarian, endometrial and TNBC (NCT02208375) enrolled 74 patients, predominantly BRCAwt (89%). One arm tested olaparib with continuous vistusertib at 5 dose levels (DL) and the second tested olaparib with 4 DL of vistusertib 2 days on, 5 days off. DLTs included neutropenia, thrombocytopenia, allergic reaction, fatigue, and hyperglycemia. The RP2D of arm 1 was olaparib 200 mg BID with continuous vistusertib 50 mg BID while RP2D of arm 2 was olaparib 300 mg BID with vistusertib 100 mg BID 2 of 7 days. Other common AEs (> 40%) included nausea, anemia, hyperglycemia, fatigue, leukopenia, increased creatinine, headache, vomiting, and hypercholesterolemia [86]. ORR was 19% among 64 evaluable patients across all DL, with ORRs of 20% and 27% in ovarian and endometrial cancer patients, respectively [86]. Final results of this trial will help determine if combination with mTOR inhibition can enhance RRs to PARPi among BRCAwt patients and the planned correlative molecular analyses may serve to identify biomarkers of response.

A phase I trial of mTORi everolimus with niraparib is actively recruiting patients with advanced breast and ovarian cancer (NCT03154281). Together, these ongoing clinical trials of PARPi and PI3K pathway inhibitors and related biomarker work will hopefully pave the way for improved therapeutic options for PI3K pathway blockades.

Combining PI3K pathway inhibitors with cell cycle checkpoint inhibitors

The dual PI3K/mTORi gedatolisib is currently being investigated in combination with CDK4/6 inhibitor palbociclib and endocrine therapy (letrozole or fulvestrant) in a phase Ib trial of women with estrogen receptor-positive (ER+) metastatic breast cancer (NCT02684032). Preliminary reports from the dose-escalation arm found DLTs of grade 3 neutropenia, stomatitis, febrile neutropenia, mucositis and abdominal pain, while nausea, stomatitis, fatigue, and neutropenia were the most common AEs overall. Early antitumor activity was reported, with RRs of 33% and 20% in the letrozole and fulvestrant arms, respectively, while the dose-expansion phase remains ongoing [87]. Similarly, a phase I trial of gedatolisib with palbociclib for patients with advanced solid tumors is recruiting patients (NCT03065062; Table 4).

Based on promising preclinical evidence of enhanced antitumor activity in TNBC models [34], a phase I trial in advanced or metastatic cancer is actively investigating the safety of the CHK1i prexasertib with the dual PI3K/mTORi LY3023414 (NCT02124148). 50 patients were enrolled, including 13 in a dose-escalation cohort and 9 in an initial dose-expansion cohort at the MTD of prexasertib 105 mg/m2 every 14 days plus LY3023414 200 mg BID. Although no DLTs were observed in the dose-escalation cohort, 2 patients experienced DLT-equivalent toxicities in the expansion group (anemia, neutropenia, thrombocytopenia, oral mucositis, abdominal pain, fatigue), leading to a reduced LY3023414 dose of 150 mg BID in subsequent cohorts [88]. The final two cohorts of this trial included 15 participants with *PIK3CA*-mutated solid tumors and 13 TNBC patients [88]. Common AE included leukopenia/neutropenia, thrombocytopenia, nausea, stomatitis, vomiting, and anemia. Febrile neutropenia was reported in 25% of patients and dose reductions were common, suggesting the prophylactic growth factor support may be necessary. Of the preliminarily evaluable patients across all four cohorts, 5 achieved a partial response, although final analysis remains pending [88]. Results from these studies will be the first available clinical data on the safety and activity of PI3K pathway inhibitors in combination with cell cycle checkpoint inhibition.

Conclusions

Although the precise mechanisms of oncogenicity of the PI3K

pathway and DDR are still under investigation, this signaling cascade is an attractive therapeutic target because of the high frequency of aberrations in ovarian cancers. In this review, we have discussed that DDR inhibition may represent potential synthetically lethal therapeutic approaches with PI3K pathway blockades. While dual inhibition of PARP or cell cycle checkpoint inhibitors with PI3K pathway inhibition represents a promising preclinical anti-tumor effect in ovarian cancers, the therapeutic possibilities for this combination need to be proven. Another concern would be acquired or *de novo* resistance to these therapies which we did not discuss details here. Understanding more about the molecular abnormalities involved in PI3K pathway-dysregulated tumors, exploring novel therapeutic trial designs and drug combinations, and defining potential predictive biomarkers, are necessary to rapidly advance the field of PI3K pathway inhibitor therapy for ovarian cancer. This is a field rich in opportunity, and the coming years should see a better understanding of which ovarian cancer patients we should treat with PI3K pathway and DDR blockade combinations and where these agents should be best applied during the treatment course of this disease.

Author contributions

T.T.H., E.J.L., C.C., and J.M.L wrote the manuscript and made the tables.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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