Review Article

# Targeting the PI3K/AKT/mTOR pathway in ovarian cancer

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**Abstract:** Ovarian cancer is the most common cause of mortality in U.S. women with gynecologic cancers. Without a successful screening strategy, most women present with advanced disease associated with a poor overall survival (OS) at 5 years despite high response rates to first line chemotherapy. Preclinical data points to the importance of PI3K/AKT/mTOR pathway activation in ovarian cancer tumorigenesis. Strategies to inhibit specific kinases in this pathway have been successful in laboratory studies and preliminary clinical trials. This review highlights the rationale behind the use of PI3K/AKT/mTOR inhibitors in clinical trials and thoroughly reviews the available therapeutic compounds and registered clinical trials to date. It outlines the importance of targeted clinical trials and the populations most likely to benefit from this strategy. It is with great anticipation that we await the results of the upcoming registered clinical trials and the opportunity to offer this novel therapeutic strategy to our patients with ovarian cancer.

**Keywords:** Ovarian cancer; mTOR inhibitors; rapalogs; dual mTOR inhibitors; PI3K inhibitors; AKT inhibitors; PI3K/mTOR inhibitors; clinical trials

Submitted Dec 02, 2014. Accepted for publication Jan 27, 2015.
doi: 10.3978/j.issn.2218-676X.2015.01.10
**View this article at:** http://dx.doi.org/10.3978/j.issn.2218-676X.2015.01.10

## Introduction

Ovarian cancer is the fifth most common cause of cancer related death in women despite its rare incidence (1). Recent evidence suggests that what is understood as ovarian cancer is actually a spectrum of cancer types possibly originating from the fallopian tubes, ovaries and/or the peritoneal lining (2-4). Ovarian cancer is a heterogeneous disease comprised of different histologic subtypes of adenocarcinomas including serous, mucinous, endometrioid, clear cell and transitional type carcinomas (which closely resemble serous carcinomas) (5). Not only are these subtypes distinct microscopically, but they also carry unique molecular changes, express different markers and not surprisingly, respond differently to therapy. The recent effort made public in The Cancer Genome Atlas (TCGA) highlights the complex genomic architecture of the most common histologic subtype of ovarian cancer, the high grade serous carcinomas. The project identifies numerous activating mutations, DNA copy number alterations and inactivating mutations further characterizing this single histologic entity into four additional molecular subtypes with differing prognoses (6). The complexity of ovarian cancer suggests that there will never be a single targeted therapy that will address this disease in a broad sense, but instead, with advances in personalized medicine, targeted therapy will need to be matched to the specific vulnerabilities of a particular tumor. The introduction of novel small molecule phosphoinositol-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway inhibitors to the anticancer armamentarium coupled with rational clinical trial design may alter the landscape of treatment for ovarian cancer in the near future. In this study we review the existing avenues to promote this change.

## Overview of the pathway

The PI3K/AKT/mTOR pathway is a central regulator of normal cell physiology. Its main function is to integrate extracellular growth signals (including insulin, growth factors and amino acids) into an intracellular cascade culminating in increased cellular metabolism, growth and proliferation. This pathway is frequently altered in ovarian cancer, where it

**Table 1** Molecular alterations in the PI3K/AKT/mTOR pathway in preclinical trials

| Molecular Disruption (%) | Description | Tumor histology | Reference |
|---|---|---|---|
| PIK3CA (up to 40%) | Genetic amplification and mutation: gain of function | Ovarian cancer cell lines | (16) |
| PIK3R1 | Less common than PIK3CA in ovarian cancer | Ovarian cancer cell lines | (17) |
| PTEN | Inactivating mutations, deletions, epigenetic silencing: loss of function | Endometrioid ovarian cancer | (18) |
| AKT | AKT1 or AKT2 amplification correlated with paclitaxel resistance | Ovarian cancer cell lines | (19) |
| AKT2 (36%) | Increased activity associated with invasion and metastasis | Human ovarian cancer specimens (n=91), only observed in serous tumors | (20) |
| AKT2 (12%) | Amplification associated with tumor aggressiveness | Human ovarian tumors (n=132, includes benign and malignant) | (21) |
| P-mTOR (47%) | Increased phosphorylation associated with improved survival | Human ovarian cancer samples (n=107) | (22) |
| P-4EBP1 (31%) | Increased phosphorylation associated with poor differentiation and higher mitotic rate | Human ovarian cancer samples (n=107) | (22) |

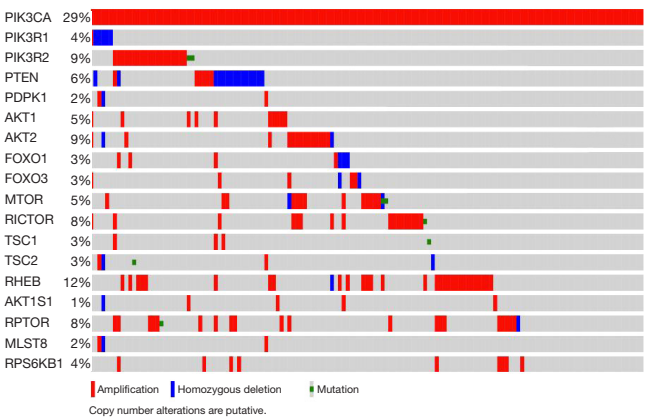


**Figure 1** CBio Portal Oncoprint of mTOR pathway genes in ovarian cancer. Genes are listed on the left. Percentage of gene alterations noted in the 580 samples of ovarian cancer included in the TCGA provisional sample are also seen on the left. The red color signifies gene amplifications, blue signifies deletions and green dots signify mutations across all samples pictorially represented in a continuous line. TCGA, The Cancer Genome Atlas.

plays an important role in cancer cell proliferation, growth, migration, invasion and evasion of apoptosis (7-9). Data from the TCGA in high grade serous ovarian cancers suggests it is altered in up to 34% of samples analyzed, however, if the search is broadened to include downstream mTOR targets, the pathway seems to be altered in up to 63% of cases (6,10). The pathway is also particularly important for the rare subtypes of clear cell and endometrioid ovarian cancer, where it may offer a unique approach to circumvent chemotherapy resistance in these tumors (11-15).

Numerous molecular and somatic alterations in the PI3K/AKT/mTOR pathway have been documented in ovarian cancer cell lines and tumor specimens (*Table 1*). *Figure 1* describes the frequency of molecular alterations in this pathway as per the cBioPortal of the TCGA including 580 ovarian cancer specimens (10). Despite the heterogeneity of the alterations seen, the overarching theme both in the preclinical data and in the TCGA data is that ovarian cancer relies on hyperactivated mTOR and is a formidable model to study these novel targeted therapies.

The mTOR kinase itself lies at the crossroads of several important oncogenic pathways in the cell, including the PI3K/AKT pathway and also the mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK) pathway, another important integrator of extracellular signals into protein transcription and translation. mTOR is an integral part of two complexes in the cell. Phosphorylation of mTOR complex 1 regulates messenger ribonucleic acid (mRNA) translation and oncogenic protein synthesis in the cell (23). Mounting data from our group and others suggest that hyperactivation of mTOR leads to selective translation of proteins responsible for survival factors (survivin, Mcl1, XIAP), angiogenesis (VEGF-A, FGF2) and the DNA repair response (BRCA1, 53BP1, γH2AX and others) by an increase in eIF4G1 mediated cap-dependent translation (24). mTOR complex 2 is less well understood, but plays an important role in the

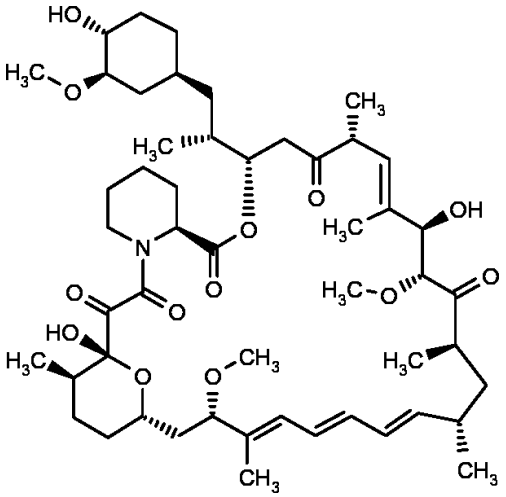

**Figure 2** Sirolimus (rapamycin).

phosphorylation of AKT (25), a promiscuous oncogenic kinase that activates a plethora of proliferative signaling in the cell. Allosteric mTOR inhibitors such as sirolimus (rapamycin) analogs are capable of inhibiting mTOR complex 1 (25). However, without inhibition of mTOR complex 2, mTOR is available to phosphorylate AKT and the overwhelming proliferative signal may partially explain the therapeutic inefficacy of these drugs in human cancers.

## Pathway inhibitors

### *mTOR inhibitors*

There are two broad categories of available mTOR inhibitors: the allosteric inhibitors, which are derivatives of rapamycin and commonly referred to as "rapalogs", and the novel small molecule mTOR inhibitors.

### *Rapamycin analogs*

Rapamycin (sirolimus) was first discovered in a soil sample from the island of Rapa Nui in the 1970s. It is a product of the bacterium Streptomyces hygroscopicus and a macrolide antibiotic with antifungal and immunosuppressive properties (*Figure 2*) (26). The antitumoral effects were first noted in renal transplant patients who received mTOR inhibitors in clinical trials and had a lower incidence of tumors (27-29). Rapamycin binds to FK binding protein 12 (FKBP12) and the FKBP-rapamycin binding domain of the mTOR kinase forming a large ternary complex that is presumed to perturb protein function (30). The complex interferes primarily with mTOR complex 1 and only inhibits complex 2 in high doses associated with increased toxicity (9).

This class of drugs is comprised of three compounds with oral formulations: sirolimus (rapamune, Pfizer, formerly Wyeth, New York, NY, USA), everolimus (Affinitor, RAD 001, Novartis, Basel, Switzerland) and ridaforolimus (AP23573 or MK-8669, Merck and ARIAD Pharmaceuticals, New Jersey, NJ, USA); and one with a parenteral formulation, temsirolimus (Torisel, CCI779, Pfizer, New York, NY, USA). Class based toxicities include stomatitis, wound-healing problems and thrombocytopenia. Biomarkers of activity include decreased phosphorylation of ribosomal protein S6, which is associated with an antiproliferative effect and arrest at the G1 phase of the cell cycle, and to a lesser extent, 4EBP1.

Temsirolimus was investigated as a single agent in a Gynecologic Oncology Group (GOG) phase II trial for recurrent ovarian cancer with a reported an overall response rate (ORR) of 9.3% [five partial responses (PRs) in 54 evaluable patients], 6 months progression-free survival (PFS) rate of 24.1% and median PFS and overall survival (OS) of 3.2 and 11.6 months, respectively with no serious adverse events (SAEs) (NCT00429793) (31). The investigators concluded that the modest activity was insufficient to warrant further evaluation of temsirolimus in a phase III trial in an unselected population.

Temsirolimus was also evaluated in combination with topotecan in a phase I study of patients with advanced or recurrent gynecologic malignancies (NCT00523432). A starting dose of 1 mg/m$^2$ of intravenous topotecan days 1, 8 and 15 were combined with 25 mg temsirolimus days 1, 8, 15 and 22 of a 28-day cycle. Seven patients with ovarian cancer entered this trial along with patients with uterine carcinosarcomas, endometrial and cervical cancers. Dose-limiting toxicity (DLT) in this cohort included asymptomatic neutropenia and thrombocytopenia. Four patients in this cohort had no prior pelvic radiation therapy (RT) and were successfully treated with 1 mg/m$^2$ topotecan with 25 mg temsirolimus, days 1, 8, and 15 of a 28-day cycle. The combination was not tolerated in patients with a history of pelvic RT. Nine of eleven patients were found to have stable disease (SD) at 8 weeks. One woman with recurrent clear cell carcinoma of the ovary experienced SD for seven cycles of treatment (28 weeks). She was ultimately removed from the study due to disease progression (32).

Also in a phase I setting, the combination of bevacizumab, a monoclonal VEGF-A antibody, and temsirolimus showed promising results and attenuation of hypoxia-inducible

 

**Table 2** Registered clinical trials of mTOR complex 1 inhibitors for ovarian cancer

| Study (39) | Summary | Status |
|---|---|---|
| NCT00926107 (Greece) | Temsirolimus in patients with ovarian cancer with CA125 only relapse after first-line platinum-based chemotherapy | Terminated (low accrual) |
| NCT01196429 | Phase II trial of temsirolimus, carboplatin, and paclitaxel as first-line therapy in newly diagnosed stage III-IV clear cell ovarian cancer | Open |
| NCT00408655 | Phase I study of temsirolimus with carboplatin and paclitaxel in advanced solid tumors | Completed |
| NCT01522820 | Vaccine therapy with or without sirolimus in treating patients with NY-ESO-1 expressing solid tumors | Open |
| NCT01149434 | Study of JI-101 in patients with advanced low grade endocrine tumors, ovarian cancer or colon cancers with K-RAS mutation | Terminated |
| NCT00703625 | Phase I study of docetaxel and temsirolimus in resistant solid malignancies | Completed |
| NCT00703170 | Phase I study of liposomal doxorubicin and temsirolimus in resistant solid malignancies | Completed |

factor 1 alpha (HIF-1α) levels. HIF-1α is part of the cellular response that permits growth in low oxygen concentrations including but not limited to angiogenesis, a crucial oncogenic pathway in ovarian cancer. Forty one patients with recurrent gynecologic cancers and a median of four prior systemic therapies were treated with bevacizumab 15 mg/kg IV every 3 weeks and temsirolimus 25 mg IV weekly without any DLTs. Grade 3 or 4 treatment-related toxicities included: thrombocytopenia (10%), mucositis (2%), hypertension (2%), hypercholesterolemia (2%), fatigue (7%), elevated aspartate aminotransferase (2%), and neutropenia (2%). Twenty-nine patients (71%) experienced no treatment-related toxicity greater than grade 2. Eight patients (20%) achieved SD >6 months and seven patients (17%) had a PR (total =15/41 patients (37%)). Eight of 13 patients (62%) with high-grade serous histology (ovarian or primary peritoneal) achieved more than 6 months of SD or a partial response (33).

Moroney *et al*. recently reported a SD ≥6 months/PR/CR rate of 38% in patients with advanced gynecologic and breast malignancies treated with liposomal doxorubicin, bevacizumab and temsirolimus (34). The patients were heavily pretreated with a median of four prior systemic therapies. Only a randomized study would be able to answer the question as to whether or not liposomal doxorubicin adds activity to the bevacizumab and temsirolimus regimen.

The combination of bevacizumab and temsirolimus was subsequently studied in a phase II study of women with recurrent ovarian cancer (up to two prior lines of chemotherapy). This study showed three PRs and 14 patients progression free at 6 months among the first 25 enrolled patients and was expanded into a second stagem which is ongoing (35).

Everolimus is being evaluated in a phase I trial in combination with carboplatin and liposomal doxorubicin in relapsed ovarian cancer (NCT01281514) (36). Additionally, in the phase II setting, the compound is being evaluated in combination with bevacizumab for patients with recurrent or persistent ovarian cancer (NCT00886691, NCT01031381) (37,38). *Table 2* summarizes the registered clinical trials of mTOR complex 1 inhibitors for ovarian cancer.

### *Dual mTOR inhibitors*

Dual mTOR inhibitors are adenosine-5'-triphosphate (ATP)-competitive mTOR kinase inhibitors. As they compete with ATP in the catalytic site of the mTOR kinase itself, they inhibit both mTOR complex 1 and 2. mTOR complex 2 lies upstream from complex 1 and is responsible for the phosphorylation of AKT in a feedback activation loop presumably responsible for the relative ineffectiveness of complex 1 inhibitors in clinical trials (25). Preclinical data with these novel inhibitors demonstrate that similarly to rapalogs, they have antiproliferative effects in several human cancers (9,40-43). The mechanism of action is presumably via a decrease in protein translation, inhibition of cell cycle progression and an antiangiogenic effect. Interestingly, the dual inhibitors seem to be more effective complex 1 inhibitors, with near complete inhibition of AKT and 4EBP1 phosphorylation at much lower doses than achievable with rapalogs alone (9,43,44).

There are several dual mTOR kinase inhibitors currently

 

**Table 3** Registered clinical trials of dual mTOR inhibitors in ovarian cancer or solid tumors

| Study (reference) | Summary | Status |
|---|---|---|
| NCT00973076 (45) | Study to assess the safety and tolerability of the TorKinase inhibitor AZD8055 | Completed |
| NCT01177397 (46) | Phase I expansion trial of an oral TORC1/TORC2 inhibitor (CC-223) in advanced solid tumors | Completed |
| NCT01353625 | Phase I study of oral CC-115 for in advanced solid tumors, and hematologic malignancies | Recruiting |
| NCT01058707 | Dose escalation study of MLN0128 in subjects with advanced malignancies (phase I) | Recruiting |
| NCT01351350 | Dose escalation study of MLN0128 in combination with paclitaxel with or without trastuzumab in patients with advanced solid malignancies (phase I) | Active, not recruiting |
| NCT02142803 | MLN0128 and bevacizumab in patients with recurrent GBM and advanced solid tumors (phase I, including ovarian) | Recruiting |
| NCT01899053 | Phase Ib study of MLN0128 in combination with MLN1117 in patients with advanced non hematologic malignancies | Recruiting |
| NCT02159989 | Phase I study of MLN0128 and Ziv-Aflibercept in recurrent metastatic solid tumors | Recruiting |

undergoing development and a few in clinical trials. PP242 is the prototypical drug used in preclinical research and MLN 128 (Millenium Therapeutics, formerly Takeda) is a reformulation of PP242 with improved bioavailability. Other compounds include CC115 and CC223 (Celgene), as well as AZD8055, and AZD2014 (AstraZeneca).

A phase I trial of AZD8055 in solid tumors and lymphoma (n=49) demonstrated safety and tolerability of the drug. The most frequent adverse events assessed to be related to AZD8055 were increased alanine aminotransferase (22%), increased aspartate aminotransferase (22%) and fatigue (16%). Seven patients had SD for ≥4 months. Partial metabolic responses, assessed by fluorodeoxyglucose (FDG) positron emission tomography (PET), were observed at ≥40 mg BID (n=8 at day 35) but no Response Evaluation Criteria In Solid Tumors (RECIST) responses were seen in this unselected population (45). The results of the expanded phase I trial of CC-223 presented at American Society of Clinical Oncology (ASCO) 2013 meeting also confirm these findings. One hundred and one solid tumor subjects were treated (no gynecologic cancers enrolled). The most common related adverse events were fatigue, rash, stomatitis, hyperglycemia, anorexia, nausea, vomiting and diarrhea. Serious AEs included infection [1], pneumonitis [4], renal insufficiency [2] and pancreatitis [2]. CC-223 dose reduction was required in >50% of the subjects with non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC). Exposure-dependent TORC1 (p4EBP1) and TORC2 (pAKT) inhibition was observed across all cohorts. CC-223 was present in all resected glioblastoma multiforme tumors with plasma: tumor ratios of 16-77% confirming transit across the blood-brain barrier. Reduction in glucose uptake [>25% decrease in Standardized Uptake Value (SUV)] on PET imaging at day 15 was observed in 78% (14/18) of NSCLC and 69% (11/16) of HCC subjects. Disease control rate in the overall NSCLC cohort was 42% (11/26) and in the HCC cohort, 40% (10/25) (46).

The current focus of development appears to be in NSCLC, prostate cancer, glioblastoma, breast and hematologic malignancies. The opportunity for enrollment in gynecologic malignancies seems to be through phase I studies aimed at metastatic solid tumors at this time, but hopefully this will change as these drugs move into phase II development. As shown in *Table 3*, strategies to pair mTOR inhibitors with anti-angiogenic compounds, PI3K inhibitors and cytotoxic chemotherapy are being taken into clinical trials based on favorable preclinical research findings.

### *PI3K and PI3K/mTOR inhibitors*

Not surprisingly, PI3K inhibitors have activity in preclinical models of ovarian cancer (47). Similarly to dual mTOR inhibitors, the new generations of PI3K inhibitors compete for ATP in catalytic domain of the protein kinase.

**Table 4** PI3K inhibitors undergoing development

| Compound | Company | Selectivity | Stage of clinical development |
|---|---|---|---|
| AR245408 (XL147) | Sanofi | Pan PI3K | Phase I |
| AZD6482 | AstraZeneca | PI3K beta | Phase I |
| BAY 80-6946 | Bayer | Pan PI3K | Phase I |
| BEZ235 | Novartis | PI3K/mTOR | Phase I, Phase II |
| BGT226 | Novartis | PI3K/mTOR | Phase I/II |
| BKM120 | Novartis | Pan PI3K | Phase I, II, III in breast cancer |
| BYL719 | Novartis | PI3K-alpha | Phase I |
| GDC-0032 (Taselisib) | Genentech | PI3K | Phase I (Netherlands) |
| GDC-0941 | Genentech | PIK3 alpha, delta | Phase I/II |
| GDC-0980 | Genentech | PI3K/mTOR | Phase II |
| GSK2126458 | GSK | PI3K/mTOR | Phase II |
| GSK2636771 | GSK | PI3K beta | Phase I/IIa |
| LY3023414 | EliLilly | PI3K alpha/mTOR | Phase I |
| MLN 1117 | Millenium | PI3K-alpha | Phase I |
| ONC-01910 (Rigosertib) | Onconova | PI3K/AKT | Phase I, Phase II (ovarian) |
| PF-04691502 | Pfizer | PI3K/mTOR | Phase II |
| PF-05212384 (PKI-587) | Pfizer | PI3K/mTOR | Phase I, Phase II |
| PX-866 | Oncothyreon | PI3K alpha, gamma | Phase I/II |
| SAR245409 (XL765) | Sanofi | PI3K/mTOR | Phase II |
| VS-5584 | Verastem | PI3K/mTOR | Phase I |

As a consequence, some of these drugs are not specific for PI3K and block multiple kinases including mTOR and AKT (48). Because of these off target effects, the early development of PI3K inhibitors was negatively affected by high toxicity, which has been overcome by improved drug design and specificity.

PI3K inhibitors are broadly classified into three groups based on the selectivity to PI3K isoforms and mTOR: the pan-PI3K isoform inhibitors (e.g., XL147, BKM120, GDC-0941, BAY 80-9646, PX-866); the dual PI3K and mTOR inhibitors (e.g., XL765, BEZ235, GSK2126458, GDC-0980, SF-1126, PF-04691502, PF-05212384, BGT-226); and isoform-specific inhibitors (e.g., p110α-specific inhibitors, BYL719, INK-1114, GDC-0032) (*Table 4*).

Recent data from phase I clinical trials suggest similar tolerability to other compounds in the class. For instance, in a phase I study of BAY 80-9646 in an expansion cohort of 23 patients with solid tumors, common grade 2-3 adverse events included hyperglycemia requiring insulin therapy, hypertension and interstitial pneumonitis (49). *Table 5* reviews the ongoing clinical trials of PI3K inhibitors in ovarian cancer. Several compounds are being combined with MEK inhibitors in clinical trials and aimed at specific patient populations with pathway relevant mutations (preclinical data suggests PIK3CA mutations and phosphatase and tensin homolog (PTEN) inactivating mutations are seen with frequency in low grade tumors, so a strategy to block the MAPK pathway along with PI3K should achieve highest therapeutic activity in these tumors) (50).

### *AKT inhibitors*

AKT is an important driver of tumor regulation in ovarian cancer. It is a known oncogene encoding for a highly active protein kinase. Constitutive activation of AKT is achieved by PTEN deletion (an important regulator of AKT) and also through a hyperactive mTOR signaling cascade (mTOR complex 2 can also phosphorylate AKT). In turn, the phosphorylated AKT cross talks to several pathways and in turn activates a myriad of downstream targets responsible for cell growth and proliferation. AKT exists in three isoforms. Inhibitors may be specific to a particular isoform or active across the entire spectrum. *Table 6* outlines the most important AKT inhibitors available.

 

**Table 5** Registered clinical trials of PI3K inhibitors in ovarian cancer

| Compound | Trial design | Population | Registration |
|---|---|---|---|
| BKM 120 | Phase I Monotherapy | PI3K activated tumors | NCT01833169 |
| | Phase I Plus Olaparib | High grade serous ovarian and TN breast | NCT01623349 |
| | Phase I Monotherapy | Advanced solid tumors (includes ovarian) | NCT01068483 |
| | Phase I plus GSK 1120212 (MEKi) | RAS or BRAF mutated selected solid tumors (includes ovarian) | NCT01155454 |
| | Phase I plus MEK 162 (MEKi) | KRAS, NRAS and/or BRAF mutated tumors (includes ovarian) | NCT01363232 |
| BYL 719 | Phase Ib plus MEK 162 (MEKi) | Advanced solid tumors (includes ovarian) | NCT01449058 |
| | Phase Ib/II plus AMG 479 | Advanced solid tumors with PIK3CA mutation | NCT01708161 |
| XL 147 | Phase I plus Carbo/Taxol | Advanced solid tumors (includes ovarian) | NCT0756847 |
| XL 765 | Phase II of Pimasertib (MEKi) with XL 765 *vs*. placebo | Ovarian cancer | NCT01936363 |
| GDC 0032 | Phase I/II tamoxifen plus/minus GDC 0032 (Poseidon trial) | Ovarian cancer, breast cancer, uterine cancer | NCT02285179 |
| AZD 5363 | Phase I monotherapy | Breast and ovarian AKT or PI3K mutation | NCT01226316 |

**Table 6** AKT inhibitors under development

| Compound | Company | Selectivity | Stage of clinical development |
|---|---|---|---|
| A-443654 | N/A | AKT | Preclinical |
| AR-42 | Arno | AKT | Phase I |
| AR-67 (DB-67) | Arno | AKT | Phase I, II |
| AZD5363 | AstraZeneca | Pan AKT | Phase I |
| GSK690693 | GSK | AKT 1, 2, 3 | Phase I |
| GSK795 (2141795) | GSK | AKT 1, 2, 3 | Phase I, II |
| KP372–1 | N/A | AKT, PDK-1, mTOR | Preclinical |
| MK-2206 | Merck | AKT | Phase II |
| SR13668 | N/A | AKT | Preclinical |
| Triciribine (API-2) | N/A | AKT 1, 2, 3 | Phase I |
| VIII | N/A | AKT 1 &2 | Preclinical |
| VQD-002 (API-2) | VioQuest | AKT | Phase I, II |

Preclinical data in ovarian cancer suggests AKT inhibition reverses chemotherapy resistance to cisplatin and has activity in this disease (51). These findings are confirmed by a phase I clinical trial of the AKT inhibitor, GSK795, in 12 patients with platinum resistant ovarian cancer. In this study, patients with Platinum Resistant ovarian cancer received 25, 50 or 75 mg of oral GSK795 daily. Paired tumor biopsies were compared to dynamic FDG-PET scans at 2 and 4 weeks post-treatment. The most common drug related AEs were decreased appetite (18%), and vomiting (18%), both grade 1 and 2. Eight out of the 12 patients had SD at week 4 by RECIST (4 had progressive disease). Clinical activity was seen in two patients with evidence of tumor regression by RECIST and decreased CA 125. Overall tumor FDG metabolism decreased in 71% of tumors with treatment, although inter and intra-patient variability was observed. There was no temporal or dose-response effect in FDG uptake (52). *Table* 7 outlines the ongoing clinical trials in ovarian cancer.

## Conclusions

There is strong preclinical rationale to support the continued development of PI3K/AKT/mTOR inhibitors in ovarian cancer. This paper has thoroughly described the landscape of completed and ongoing clinical trials that are likely to improve our understanding of the role of this pathway in the treatment of ovarian cancer. Combination of mTOR inhibitors with cytotoxic chemotherapy and other biologic agents such as anti-angiogenic compounds, may capitalize on the central role of this pathway in regulating protein translation, cell growth, migration, metastasis and angiogenesis.

Rational clinical trial design with a focus in identifying a patient population most likely to benefit from this strategy is imperative to the success of this therapeutic strategy. There is some preclinical data suggesting

 

**Table 7** Registered clinical trials of AKT inhibitors in ovarian cancer

| Compound | Trial design | Population | Registration |
|---|---|---|---|
| MK-2206 | Phase II monotherapy | Recurrent ovarian | NCT01283035 |
| AZD5363 | Phase Ib plus olaparib and AZD2014 (mTOR inhibitor) | Recurrent endometrial and ovarian cancer | NCT02208375 |
| | Phase I monotherapy | Advanced malignancies (includes ovarian) | NCT01226516 |
| GSK 2110183 | Phase I/II dose finding | Platinum resistant ovarian cancer | NCT01653912 |
| Triciribine | Phase I/II plus Carbo | Ovarian cancer | NCT01690468 |
| Perifosine | Phase I plus docetaxel | Relapsed ovarian cancer | NCT00431054 |

this pathway is implicated in the reversal of platinum resistance in ovarian cancer, suggestive of an ideal patient population to study.

Further research into biomarkers that predict pathway activation (such as PIK3CA activating mutations, hyperactivated mTOR or AKT) is needed for rational patient recruitment. Improved biomarkers of drug activity are also needed for monitoring of drug activity in clinical trials (FDG avidity is variable and has not been reliable in the few phase I studies reported).

It is with great excitement that we anticipate the results of the ongoing trials of PI3K/AKT/mTOR inhibitors in ovarian cancer and that we look forward to offering our patients better and smarter options in the treatment of this disease that continues to take so many cherished lives.

## Acknowledgments

F. Musa would like to thank Franco Muggia, Robert Schneider and the division of Gynecologic Oncology at NYU for allowing her the opportunity to perform ovarian cancer research. We also deeply acknowledge the effort and motivation of our patients with ovarian cancer who have bravely succumbed to this disease despite their very best efforts.

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editors (Franco Muggia and Eleonora Teplinsky) for the series "Epithelial Ovarian Cancer Treatment: Integrating Molecular Targeting" published in *Translational Cancer Research*. The article has undergone external peer review.

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2015.01.10). The series "Epithelial Ovarian Cancer Treatment: Integrating Molecular Targeting" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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**Cite this article as:** Musa F, Schneider R. Targeting the PI3K/AKT/mTOR pathway in ovarian cancer. Transl Cancer Res 2015;4(1):97-106. doi: 10.3978/j.issn.2218-676X.2015.01.10

 