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REVIEW

Investigational agents in development for the treatment of ovarian cancer

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Summary Although significant success has been achieved in the treatment of advanced and recurrent ovarian cancer, there is clearly room for improvement. The use of targeted agents in this patient population has the promise to provide improved survival and quality of life. There are a myriad of relevant pathways under exploration in all settings of ovarian cancer. Clinical trial data are accumulating for antiangiogenic therapy, including vascular endothelial growth factor (VEGF)-specific inhibitors and multiple angiogenic signaling target inhibitors, as well as poly-ADP-ribose polymerase (PARP) inhibitors. Other types of tumorigenic pathway inhibitors, including those that target phosphatidylinositol-3-kinase (PI3K), mammalian target of rapamycin (mTOR), protein kinase B (AKT), Src, folate receptor alpha, and insulin-like growth factor-1 receptor (IGF-1R) pathways are in earlier phases of development for ovarian cancer. Attempts to target the epidermal growth factor receptor (EGFR) of ovarian tumors have been met with limited success; however, newer agents that inhibit this pathway show promise. Finally, with recognition of the role of Wee-1 in p53-deficient tumors, an inhibitor of this tyrosine kinase is being evaluated in recurrent ovarian cancer. The logistical challenge is to determine the optimal timing and proper combinations of novel agents independently as well as concomitantly with conventional chemotherapeutics. Reported results have been modest; however, our growing understanding of these pathways will be potentially reflected in greater impact on response and survival.

Keywords Ovarian cancer · Targeted therapy · Personalized therapy · Resistance · Angiogenesis

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Introduction

Ovarian cancer is the second most common gynecologic cancer and the most frequent cause of gynecologic cancer-related death in the United States. Current estimates for 2012 suggest that 22,280 women will be diagnosed with ovarian cancer and 15,500 will die of their disease [1]. It is encouraging that the incidence of ovarian cancer has remained stable since 1992 and death rates decreased by 1.9 % per year from 2004 to 2008. However, the majority of patients (63 %) are still diagnosed with distant disease and 5-year survival rates only reach 27 % [1]. These dismal rates occur despite the high chemosensitivity of ovarian cancer, where 50–80 % of patients will achieve a response or lack of progression of disease after treatment with primary therapy [2–5], which generally includes a combination of surgical cytoreduction and platinum and taxane-based chemotherapy [6]. High rates of relapse in the first 2 years following therapy and the emergence of drug resistance highlight the key barriers to improving clinical outcomes [2].

Interestingly, there is currently no therapeutic agent recommended as the treatment of choice for platinum-resistant

recurrent ovarian cancer [6]. This underscores the critical need to develop novel agents and combinations in this population to impact overall survival (OS) while preserving quality of life. The use of targeted agents which act on pathways involved in tumorigenesis promises to reduce mortality from ovarian cancer while reducing morbidity associated with treatment by focusing on abnormal rather than normal tissues. The majority of current research in advanced and recurrent ovarian cancer focuses on the inhibition of signal transduction pathways and targeting DNA repair mechanisms. This review will discuss investigational agents in development for the treatment of ovarian cancer, including therapies targeted at single (with tyrosine kinase inhibitors [TKIs] or monoclonal antibodies) or multiple (with TKIs) signaling pathways in angiogenesis, cellular survival, and DNA repair (Table 1). Special attention will be paid to the development of resistance to these therapies, and the need for rational combinations to avoid further disappointments in the treatment of ovarian cancer.

Table 1 Targeted investigational agents in development for ovarian cancer

Investigational agent	Target(s)	Phase of development in ovarian cancer
Bevacizumab	VEGF	III
Aflibercept (VEGF-Trap)	VEGF	III
Cediranib	VEGFR-1, -2, -3, PDGFR-α/β, FGFR-1, c-kit	III
Nintedanib (BIBF 1120)	VEGFR-1, -2, -3, PDGFR-α/β, FGFR-1, -2, -3, Src family, Flt-3	III
Pazopanib	VEGFR-1, -2, -3, PDGFR-α/β, FGFR-1, -3, c-kit	III
Sorafenib	VEGFR-2, -3, PDGFR-β, c-kit, Flt-3, Raf	II
Sunitinib	VEGFR-2, PDGFR-β, c-kit, Flt-3, RET	II
Cabozantinib (XL184)	VEGFR-2, c-kit, RET, MET	II
Olaparib (AZD2281)	PARP	II
Iniparib (BSI-201)	PARP	II
MK-4827	PARP	I
ABT-888	PARP	I/II
XL147	PI3K	I/II (advanced solid tumors; endometrial cancer)
PX-866	PI3K	I (advanced solid tumors)
Everolimus	mTOR	II
Temsirolimus	mTOR	II
Perifosine	AKT	I
Dasatinib	Src	II
Saracatinib (AZD0530)	Src	II/III
Erlotinib	EGFR	III
MM-121	EGFR (ErbB3)	II
Vandetanib	VEGFR-2, EGFR	II
Farletuzumab (MORab-003)	α-FR	III
AMG 479	IGF-1R	II

α-FR alpha folate receptor; *AKT* protein kinase B; *c-kit* stem cell factor receptor; *EGFR* epidermal growth factor receptor; *FGFR* fibroblast growth factor receptor; *Flt-3* fms-like tyrosine kinase-3; *IGF-1R* insulin-like growth factor-1 receptor; *MET* mesenchymal-epithelial transition; *mTOR* mammalian target of rapamycin; *PARP* poly-ADP-ribose polymerase; *PDGFR* platelet-derived growth factor receptor; *PI3K* phosphatidylinositol-3-kinase; *Raf* v-raf 1 murine leukemia viral oncogene homolog 1; *RET* rearranged during transfection; src, v-src sarcoma viral oncogene homolog; *VEGFR* vascular endothelial growth factor receptor

Targeting angiogenesis

Arguably, the greatest success in targeted therapy for ovarian cancer to date has been among agents that target angiogenesis (Fig. 1). Angiogenesis is critical for normal ovarian physiology and plays a fundamental role in the pathogenesis of ovarian cancer by promoting tumor growth, progression, and metastatic spread [7, 8]. Vascular endothelial growth factor (VEGF) and its receptor, VEGFR, are expressed in many tumor types, including ovarian cancer [8, 9]. High levels of expression of VEGFR in ovarian cancer have been associated with increased tumor growth, metastases, and higher mortality rates [10, 11]. Furthermore, increased VEGF expression has been found in malignant ascites and is associated with its development [8, 12].

VEGF-specific inhibitors in ovarian cancer

Bevacizumab (Avastin®, Genentech; South San Francisco, CA, USA), a humanized monoclonal antibody to human VEGF, is the most widely studied targeted agent in ovarian cancer. Unlike in other tumor types [13], bevacizumab has demonstrated single-agent activity in ovarian cancer, likely explained by the dual antitumor and antiangiogenic activity induced by VEGF inhibition [14]. Two phase II trials of bevacizumab as a single agent in heavily pretreated patients with relapsed ovarian cancer yielded response rates (RRs) of 16 % and 21 %, with a median progression-free survival (PFS) of 4.4 and 4.7 months, respectively [15, 16]. In the study by Burger and colleagues, 40.3 % of patients had a PFS of at least 6 months, with patients receiving a median number of 7 cycles (1 or 2 prior regimens required) [16]. However, activity of bevacizumab in these trials was offset by higher toxicity, with 4 of 44 (11 %) patients in the Cannistra study having gastrointestinal perforation (GIP), leading to early termination for toxicity concerns. The risk of perforation was higher in those patients with more prior chemotherapy treatments and in whom impending bowel obstruction was suspected; however, a clear risk-based model has yet to be elucidated and may vary by clinical setting where the agent is studied [15]. Further studies are ongoing to define a clear set of risk factors for perforation in the setting of bevacizumab therapy.

The combination of bevacizumab with cytotoxic agents has great promise in recurrent ovarian cancer. Bevacizumab was

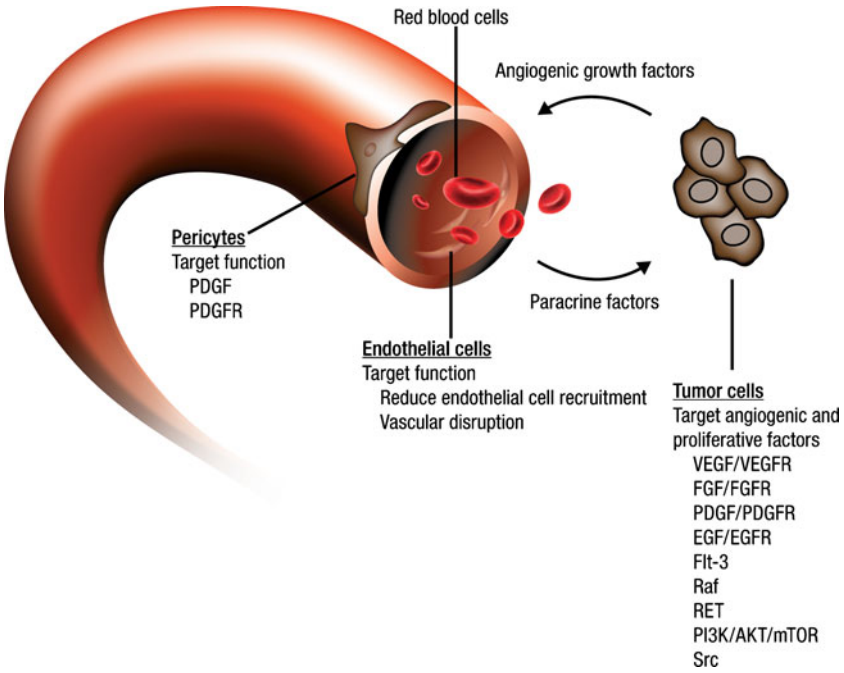

Fig. 1 Key angiogenic targets in ovarian cancer. *AKT* protein kinase B; *EGF* epidermal growth factor; *EGFR* epidermal growth factor receptor; *FGF* fibroblast growth factor; *FGFR* fibroblast growth factor receptor; *Flt-3* fms-like tyrosine kinase-3; *mTOR* mammalian target of rapamycin; *PDGF* platelet-derived growth factor; *PDGFR* platelet-derived growth factor receptor; *PI3K* phosphatidylinositol-3-kinase; *Raf* v-raf 1 murine leukemia viral oncogene homolog 1; *RET* rearranged during transfection; *src* v-src sarcoma viral oncogene homolog; *VEGF* vascular endothelial growth factor; *VEGFR* vascular endothelial growth factor receptor

combined with metronomic oral cyclophosphamide in a cohort of patients with multiple prior lines of chemotherapy. With minimal toxicity, this study achieved a RR of 24 % at a median follow up of 23.2 months. Further, PFS at 6 months was 56 % [17]. A single-arm trial of bevacizumab with carboplatin and pegylated liposomal doxorubicin (PLD) in platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer yielded an objective RR of 72.2 % among 54 patients. PFS was 14.1 months and median response duration was 12.1 months, with 13 patients experiencing drug-related serious adverse events (gastrointestinal, infectious, procedural, respiratory, and/or vascular) [18]. The OCEANS trial combined bevacizumab with at least 6 cycles (up to 10 cycles allowed) of standard carboplatin and gemcitabine followed by bevacizumab (or placebo) maintenance in the treatment of platinum-sensitive recurrent ovarian cancer. The bevacizumab arm demonstrated a 4-month improvement in PFS compared with placebo (hazard ratio [HR], 0.484; 95 % confidence interval [CI], 0.388–0.605; $P<0.0001$); OS data are not mature [19]. Gynecologic Oncology Group (GOG) 213 is an ongoing bifactorial randomized study to evaluate the impact of bevacizumab in addition to paclitaxel and carboplatin on OS in platinum-sensitive patients (NCT00565851). Additionally, the study examines the role of secondary surgical cytoreduction in this patient population.

In the platinum-resistant setting, the fully accrued AURELIA trial is comparing bevacizumab in combination with standard recurrent disease chemotherapy agents, including paclitaxel, PLD, or topotecan, to the standard agent alone (NCT00976911). Other studies have combined bevacizumab with cyclophosphamide [17, 20], topotecan [21], PLD [22], nab-paclitaxel [23], and docetaxel (Table 2) [24].

Bevacizumab has also been combined with other biologics in recurrent Müllerian cancers. A phase II trial combined with erlotinib, a TKI to epidermal growth factor receptor (EGFR), demonstrated a RR of 15 % and 54 % had stable disease (SD). However, there was no clear benefit over single-agent bevacizumab and the rate of GIP was quite high (15 %) [25].

Given the activity of bevacizumab in combination with paclitaxel and carboplatin in early phase trials in the frontline setting [26, 27], 2 large phase III trials have been recently completed in previously untreated advanced ovarian cancer (Table 2) [28, 29]. In the GOG 218 study, patients who received bevacizumab and cytotoxic chemotherapy followed by maintenance bevacizumab had significantly improved PFS versus those who received chemotherapy alone (median 14.1 vs. 10.3 months; HR, 0.717; 95 % CI, 0.625–0.824; $P<0.001$). Of note, there was no significant difference in PFS between patients who received bevacizumab and chemotherapy without maintenance bevacizumab compared with those who received chemotherapy alone (median 11.2 vs. 10.3 months; HR, 0.908; 95 % CI, 0.795–1.040; $P=0.16$) suggesting duration of exposure may be important to the treatment strategy [28].

Although the design is somewhat different, primary results from the International Collaborative Ovarian Neoplasm (ICON) 7 trial support a PFS benefit among patients in the arm treated with bevacizumab in addition to standard chemotherapy followed by maintenance bevacizumab after a 19.4-month median follow-up (19.0 vs. 17.3 months; HR, 0.81; 95 % CI, 0.70–0.94; $P=0.004$) [30], with similar findings after an updated analysis (after a 28-month median follow-up) [29]. Survival data are not yet mature for either trial; however, preliminary results reveal no OS benefit for

Table 2 Efficacy and safety in Phase II/III trials of antiangiogenic agents in combination with chemotherapy

Trial	Setting	Treatment	RR, %	SD, %	Outcomes	Reported grade 3 to 4 AEs
Bevacizumab – relapsed/refractory						
Garcia [17]; phase II (N=70)[a]	Recurrent EOC/PPC; ≤3 prior regimens	Bev+cyclo	24 (PR)	63	TTP, 7.2 mo. OS, 16.9 mo.	Hypertension, proteinuria
del Carmen [18]; phase II (N=54)[b]	Recurrent EOC/PPC/FTC; relapse-free interval >6 mo. after first-line platinum regimen	Bev+carbo/PLD	72 (NR)	NR	PFS, 14.1 mo.	Blood/lymphatic system, gastrointestinal, vascular disorders, hand-foot syndrome, DVT, and small intestinal perforation
McGonigle [21]; phase II (N=40)	Recurrent OC/PPC; ≤2 prior regimens	Bev + topo	25 (PR)	35	PFS, 7.8 mo. OS, 16.6 mo.	Hypertension, neutropenia, gastrointestinal toxicity, pain, metabolic toxicity, bowel obstruction, cardiotoxicity
Kudoh [22]; phase II (N=30)	Recurrent EOC; ≥1 prior regimen	Bev + PLD	7 (CR); 27 (PR)	40	PFS, 6 mo.	Hand-foot syndrome, GIP
Tillmans [23]; phase II (N=48)[b]	Recurrent EOC/PPC; ≥1 prior regimen	Bev + nab-pac	46.1 (PR)	30.8	PFS, 8.3 mo. OS, 16.5 mo.	NR
Wenham [24]; phase II (N=27)[b]	Recurrent OC; ≤3 prior regimens	Bev + doc	5 (CR); 53 (PR)	37	PFS, 21 % at 6 mo.	Leukopenia, neutropenia, infection, fatigue, anorexia, rash, metabolic fistula, GIP
OCEANS [19]; phase III (N=484)	Recurrent platinum-sensitive EOC/PPC/ FTC; 1 prior regimen	Carbo/gem vs. carbo/gem + bev → bev	57.4 vs. 78.5 (P <0.0001)	NR	PFS, 8.4 vs. 12.4 mo. OS, 35.2 vs. 33.3 mo.[c]	Neutropenia, hypertension, proteinuria, bleeding (non-CNS), venous thrombolic event, left ventricular dysfunction/congestive heart failure, wound healing complication[d]
Bevacizumab – first line						
Micha [26]; phase II (N=18)	Chemonaive advanced EOC/PPC/FTC	Bev + pac/carbo	30 (CR); 50 (PR)	5	NR	Neutropenia, hypertension, neuropathy
Penson [27]; phase II (N=62)	Chemonaive EOC/FTC/ PPC/ UPC	Bev + pac/carbo → bev maintenance	21 (CR); 55 (PR)	21	PFS, 29.8 mo.	Hypertension, musculoskeletal pain, proteinuria, metabolic, thrombocytopenia
GOG 218 [28]; phase III (N=1,873)	Chemonaive EOC/PPC/ FTC	Pac/carbo vs. bev + pac/ carbo vs. bev + pac/ carbo → bev maintenance	NR	NR	PFS, 10.3 vs. 11.2 (HR=0.908; 95 % CI, 0.795-1.040; P=0.16) vs. 14.1 mo. (HR=0.717; 95 % CI, 0.625-0.824; P<0.001) OS, 39.3 vs. 38.7 (HR=1.036; 95 % CI, 0.827–1.297; P=0.76) vs. 39.7 mo. (HR=0.915; 95 % CI, 0.727–1.152; P=0.45)	Proteinuria, neutropenia, non-CNS bleeding (other AEs were reported based on grade ≥2 or all-grade incidences)
ICON7 [29]; phase III (N=1,528)	Chemonaive EOC/PPC/ FTC	Pac/carbo vs. bev + pac/ carbo → bev maintenance	48 vs. 67 (P <0.001)	46 % vs. 29 %	PFS, HR=0.81 (95 % CI, 0.70–0.94); P=0.004 favoring bev arm OS, HR=0.85 (95 % CI, 0.69–1.04); P=0.11	Bleeding, abscess and fistula, GIP, hypertension, proteinuria, thromboembolic event, neutropenia, febrile neutropenia, thrombocytopenia, congestive heart failure, wound healing complication
Aflibercept						
Coleman [34]; phase II (N=46)	Recurrent EOC/PPC/FTC; ≤2 prior regimens	Aflibercept + doc	54	24	PFS, 6.4 mo. OS, 26.6 mo.	Neutropenia, leukopenia, fatigue, dyspnea, stomatitis, reduced magnesium, elevated creatinine, GIP, sensory neuropathy, TIA, headache
Sorafenib						
Ramasubbaiah [72]; phase I/II (N=30)	Platinum-resistant EOC/ PPC	Sorafenib + topo	16.7 (PR)	46.7	PFS, 3.7 mo. OS, 14.0 mo.	Neutropenia, thrombocytopenia, anemia, fatigue, nausea, vomiting
Welch [73]; phase II (N=43)	Platinum-refractory EOC	Sorafenib + gem	4.7 (PR)	18.3	TTP, 5.4 mo. OS, 13.0 mo.	Lymphopenia, neutropenia, thrombocytopenia, hand-foot syndrome, fatigue, hypokalemia, diarrhea

AEs adverse events; *bev* bevacizumab; *carbo* carboplatin; *CI* confidence interval; *CNS* central nervous system; *CR* complete response; *cyclo* cyclophosphamide; *doc* docetaxel; *DVT* deep-vein thrombosis; *EOC* epithelial ovarian carcinoma; *FTC* fallopian tube cancer; *gem* gemcitabine; *GIP* gastrointestinal perforation; *HR* hazard ratio; *nab-pac* nab-paclitaxel; *NR* not reported; *OC* ovarian cancer; *OS* overall survival; *pac* paclitaxel; *PFS* progression-free survival; *PLD* pegylated liposomal doxorubicin; *PPC* primary peritoneal cancer; *PR* partial response; *RR* response rate; *SD* stable disease; *topo* topotecan; *TIA* transient ischemic attack; *TTP* time to progression; *UPC* uterine papillary serous carcinoma

[a] Trial was closed early due to rate of GIP (11.4 %). A total of 3 treatment-related deaths occurred

[b] Represents interim data

[c] OS data are immature, with only 48.6 % of patients having had an event

[d] Selected AEs described

bevacizumab plus chemotherapy followed by maintenance bevacizumab versus the control arm (HR, 0.0915 [95 % CI, 0.727–1.152; P=0.45] and 0.84 [95 % CI, 0.69–1.04; P=0.11] for GOG 218 and ICON7, respectively) [28, 29]. Adverse events associated with bevacizumab in GOG 218 and ICON7 were similar. The frequency of most adverse events was comparable between the bevacizumab and control arms aside from increased incidence of hypertension among bevacizumab recipients in both studies [28, 29]. Additional studies are ongoing to explore bevacizumab in combination with chemotherapy to determine its optimal role in ovarian cancer therapy (NCT00951496 [GOG 252], NCT01167712 [GOG 262], NCT01081262, NCT00483782).

Aflibercept (VEGF Trap, Regeneron; Tarrytown, NY, USA) is a manufactured protein engineered through fusion of the ligand-binding domains of human VEGFR-1 and VEGFR-2 with the constant region of IgG. This agent binds all isoforms of VEGF as well as placental growth factor [31]. Two phase II studies of aflibercept as a single agent in platinum-resistant ovarian cancer have demonstrated promising results given a heavily pretreated population [32, 33]. In a study of 162 patients, the RR was 11 % with 5 partial responses (PRs) and no mention of SD [33]. As a treatment for malignant ascites, Gotlieb and colleagues found that the mean time to repeat paracentesis was prolonged with aflibercept (P=0.019) compared with placebo; however, the incidence of fatal gastrointestinal events was higher with aflibercept (3 intestinal perforations) versus placebo (1 intestinal fistula leading to sepsis) [32]. Due to promising results in phase I trials, Coleman and colleagues recently reported the results of a phase II trial of aflibercept in combination with docetaxel in recurrent ovarian cancer. Overall the confirmed RR was 54 % (11 CRs and 14 PRs among 46 evaluable patients), with impressive response in platinum-sensitive (77 % [10 of 13]) and platinum-resistant (45 % [15 of 33]) patients. Median duration of response was 6.0 months and median PFS and OS in the entire group were 6.4 months and 26.6 months, respectively. Adverse events were mostly of grade 1/2 severity; the most common grade 3/4 events (≥5 % of patients) were fatigue, dyspnea, neutropenia, leukopenia, and stomatitis [34].

Although RRs have been quite impressive with the use of anti-VEGF therapies, there are patients that do not respond to initial treatment and also those that develop resistance to these therapies. There are multiple excellent reviews on the topic of antiangiogenic therapy resistance as a thorough discussion is beyond the scope of this article [35–37]. Briefly, it appears there are multiple mechanisms at work, including development of tumor hypoxia that may lead to more aggressive behavior and sustained survival. In addition, it appears that other angiogenic pathways are stimulated when VEGF blockade is achieved, leading to compensatory activation of angiogenesis. Finally, the tumor microenvironment, including fibroblasts and pericytes, protect tumor cells from the action of agents targeting VEGF. Targeting other angiogenic signaling pathways is one option to overcome the development of resistance to these therapies.

Other angiogenic targets of importance

Although VEGF and related receptors have been the primary focus for clinical targets heretofore, the development of resistance and the failure to achieve CR have led to great interest in other members in the antiangiogenic cascade. Several other targets have gained focus in light of their apparent importance in ovarian cancer and the potential for successful inhibition. For example, higher levels of platelet-derived growth factor (PDGF) have been found in ovarian carcinomas than in benign tissue and in malignant ascites, and have been associated with poor survival [38–44]. In addition, the fibroblast growth factor (FGF) pathway has also been implicated in angiogenesis and ovarian physiology [45–50] and ascites [48]. Furthermore, both PDGF [41, 51, 52] and FGF signaling [36, 53, 54] have been implicated in resistance to VEGF inhibition, suggesting that combined inhibition of VEGF and PDGF and/or FGF would more effectively block angiogenesis than isolated VEGF inhibition [52, 55–57].

The inhibition of multiple angiogenic signaling targets is characteristic of several drugs currently under development, some with potentially promising early results. Cediranib (Recentin™, AstraZeneca; Wilmington, DE, USA) demonstrates strong inhibition of VEGFR-1, -2, -3 and c-kit, in addition to lower affinity inhibition of PDGFR-α/β, and fibroblast growth factor receptor 1 (FGFR-1) [58]. In a study of this agent in 46 patients with recurrent ovarian cancer, a clinical benefit rate of 30 % was achieved with acceptable toxicity. Successful outcomes included 8 patients with PR, 6 patients with SD, and a median PFS of 5.2 months [59]. Hirte and colleagues reported a 41 % RR in platinum-sensitive patients and a 29 % RR in patients with platinum-resistant ovarian cancer treated with cediranib. The median time to progression and OS in the cohort were 4.1 and 11.9 months, respectively [60]. A phase II/III trial is evaluating cediranib in combination with paclitaxel and carboplatin and as maintenance therapy in platinum-sensitive recurrent ovarian cancer (NCT00544973 [ICON6]). Blinded safety results for 60 patients treated in stage I (for which safety was the primary outcome) have been published, supporting trial expansion to stage II [61].

Nintedanib (BIBF 1120, Boehringer Ingelheim; Ingelheim, Germany) is a triple angiokinase inhibitor that targets several key angiogenic receptors including VEGFR-1, -2, and -3, PDGFR-α/β, and FGFR-1, -2, and -3. In addition, this agent has activity against members of the v-src sarcoma viral oncogene homolog (Src) family and fms-like tyrosine kinase 3 (Flt-3) [62]. A phase I study of nintedanib combined with paclitaxel and carboplatin in patients with advanced or

recurrent gynecologic malignancies had promising results with 5 of 7 patients with measurable disease demonstrating response and 2 achieving SD. Of the patients with response, 3 had recurrent ovarian cancer. Overall, the treatment was well tolerated with primarily gastrointestinal adverse events that were grade 1 to 2 in severity [63]. Nintedanib has also been assessed as a maintenance therapy among patients with recurrent ovarian cancer who responded to their last chemotherapy regimen, defined as CR, PR, or 50 % reduction in CA125. Treatment with nintedanib yielded a 36-week PFS rate of 16.3 % compared with 5.0 % in patients treated with placebo (HR, 0.65; 95 % CI, 0.42–1.02; P=0.06). Patients receiving nintedanib maintenance experienced significantly more nausea, vomiting, and diarrhea (mostly of grade 1/2 severity) compared with those treated with placebo [64]. Grade 3/4 adverse events were similar between groups, with the exception of grade 3 liver enzyme elevations (51.2 % with nintedanib vs. 7.5 % with placebo). These results led to the development of a randomized phase III study of nintedanib in combination with paclitaxel and carboplatin in the upfront setting for advanced ovarian cancer followed by nintedanib monotherapy as maintenance (NCT01015118 [AGO-OVAR12/LUME-Ovar1]). Treatment with nintedanib is to be continued until toxicity, disease progression, or a maximum of 120 weeks is reached. Two ongoing phase I studies are investigating the combination of nintedanib with carboplatin and PLD in platinum-sensitive relapsed ovarian cancer (NCT01329549; NCT01314105).

Pazopanib (GlaxoSmithKline; London, UK) is an agent that inhibits signaling through VEGFR-1, -2, and -3, PDGFR-α/β, FGFR-1 and -3, and c-kit [65, 66]. This small molecule inhibitor has been evaluated in a phase II study of 31 patients with recurrent ovarian cancer with elevated CA125 and non-bulky disease. This study reported a 31 % RR by CA125 level and a 56 % SD rate. Among 17 patients with measurable disease, 18 % achieved a PR [67]. Phase II studies in relapsed/resistant ovarian cancer of pazopanib as a single agent (NCT01262014, NCT01227928) and in combination with chemotherapy (NCT01238770, NCT01035658) are ongoing. In addition, a phase III study evaluating single-agent pazopanib maintenance after first-line chemotherapy has recently completed enrollment (NCT00866697).

Sorafenib (Nexavar®, Bayer; Leverkusen, Germany) is an interesting small molecule inhibitor that effectively inhibits several angiogenesis-related receptors (VEGFR-2 and -3, PDGFR-β, c-kit, Flt-3) as well as Raf [68]. Matei and colleagues reported a phase II trial of this agent in recurrent ovarian cancer after 1 or 2 prior therapies. Twenty-two of 59 patients achieved PR or SD with common toxicities of gastrointestinal, constitutional, and dermatologic events. Fourteen patients with measurable disease were progression free for 6 months or greater [69]. A phase I study of the combination of sorafenib with bevacizumab had an impressive RR of 46 % in heavily pretreated ovarian cancer. Toxicity was common in this study, including diarrhea, fatigue, hypertension, hand-foot syndrome, and transaminitis, leading to dose-reduction in the majority (74 %) of patients [70]. A subsequent phase II study of intermittently dosed sorafenib with bevacizumab yielded clinical benefit in 88 % of the first 25 response-evaluable patients (including 6 PRs and 16 patients with SD) with recurrent ovarian cancer. The most common grade 3/4 adverse events included hypertension and thrombosis [71]. Phase II studies combining sorafenib with traditional second-line chemotherapy, including topotecan [72] and gemcitabine [73], have yielded similar clinical benefit rates with minimal additional toxicity. Sorafenib is under evaluation in several phase II trials in combination with chemotherapy (NCT00096200, NCT01047891) in recurrent ovarian cancer, in the first-line setting in combination with standard chemotherapy (NCT00390611), and as a maintenance therapy after complete clinical response (NCT00791778).

Sunitinib (Sutent®, Pfizer; New London, CT, USA) inhibits VEGFR-2, PDGFR-β, c-kit, Flt-3, and the rearranged during transfection (RET) proto-oncogene [74–78]. Single-agent sunitinib has been evaluated in 3 phase II studies in patients with recurrent or refractory ovarian cancer [79–81]. RRs among the 3 trials ranged between 3.3 % to 19 % [79–81] and SD rates were between 19 % and 53 % [79–81]. Common side effects were hand-foot reaction, gastrointestinal symptoms, fatigue, hypertension, and mucositis [80]. The utility of this agent in all types of ovarian cancer is unclear; however, sunitinib is under exploration for the treatment of advanced and recurrent ovarian cancer of clear cell histology (NCT00979992 [GOG 254]).

Cabozantinib (XL-184, Exelixis, Inc; South San Francisco, CA, USA) is new chemical entity that targets multiple receptor tyrosine kinases promoting angiogenic, invasive and metastatic properties, including RET, mesenchymal-epithelial transition (MET), VEGFR-2, and c-kit. It has demonstrated preclinical and clinical activity across a number of solid tumors, including ovarian, medullary thyroid, and castrate-resistant prostate cancer. A recent phase II randomized discontinuation trial of cabozantinib in recurrent, previously treated ovarian cancer was stopped early based on an encouraging 12-week RR of 24 % in a mixed population (18 % in platinum-resistant, 29 % in platinum-sensitive patients) [82]. The median duration of response and PFS had not been reached after a median follow-up of 4 months. Grade ≥3 adverse events were hand-foot syndrome and diarrhea. A placebo-controlled phase II trial of cabozantinib for progressive recurrent or advanced solid tumors (including ovarian) is ongoing (NCT00940225).

Targeting DNA repair with poly-ADP-ribose polymerase (PARP) inhibition

Increased signaling through DNA damage repair pathways is a known mechanism of chemoresistance. PARP1 is an

enzyme that plays a critical role in the repair of DNA single-strand breaks through base-excision repair [83]. Loss of PARP1 activity leads to accumulation of single-strand breaks, subsequent double-stranded breaks, and cellular death. In normal cells, double-stranded breaks are repaired through homologous recombination [84].

Defects in DNA repair occur in carriers of *breast cancer susceptibility gene 1 (BRCA1)* and *BRCA2* gene mutations, whether germline or somatic, as well as in patients with defects in the homologous recombination pathway [85, 86]. The use of PARP inhibitors in patients with defects in DNA repair is a rational approach, as PARP inhibition in these tumor cells leads to double-stranded DNA accumulation and cell death via a process known as synthetic lethality. Germline *BRCA1* and *BRCA2* mutations occur in approximately 5 % to 10 % of patients with ovarian cancer [87–89]. In addition, recent findings indicate that somatic mutations in *BRCA1* and *BRCA2* are also common, suggesting that additional patients may be sensitive to PARP inhibition [90]. Furthermore, the hypermethylation of DNA leading to loss of function of the *BRCA1* gene has also been observed in up to 31 % of sporadic ovarian cancers [91]. Certain histology types, such as high grade serous adenocarcinoma, may respond to PARP inhibitors in the absence of *BRCA* mutation. Recent studies have attempted to identify patients with a "BRCAness" phenotype to determine those that might benefit most from treatment with these agents [90, 92].

While several PARP inhibitors are currently being investigated (Table 3), the most experience to date in ovarian cancer is with olaparib (AZD2281, AstraZeneca; Wilmington, DE, USA) in patients with *BRCA1* and *BRCA2* mutations. In an ongoing phase II trial evaluating 2 doses of olaparib in 57 patients with *BRCA1* and *BRCA2* mutations and platinum-resistant ovarian cancer, the RR was 33 % in patients receiving olaparib 400 mg twice daily and 13 % in patients receiving 100 mg twice daily [93]. Additional phase II studies of olaparib in recurrent serous ovarian cancer have confirmed favorable response in patients with and without *BRCA* mutations[94, 95].

PARP inhibitors are fairly well tolerated, with most common adverse events consisting of fatigue, nausea, and vomiting. Cognitive dysfunction and mood alterations have been described as a dose-limiting toxicity [93–96]. Dose reduction has been necessary in early trials combining PARP inhibitors with cytotoxic chemotherapy secondary to increased toxicity. Further, it is unclear if these agents outperform chemotherapy in germline *BRCA* mutation carriers. A randomized phase II trial comparing olaparib versus PLD in patients with *BRCA* mutations and progression within 12 months of platinum chemotherapy revealed higher RRs in the patients treated with olaparib. However, the primary endpoint of PFS was not reached, with only a slight improvement with olaparib (6.5 and 8.8 months for olaparib 200 and 400 mg, respectively, vs. 7.1 months for PLD; HR for combined doses, 0.88; 80 % CI, 0.51–1.56; P=0.66) [97].

The use of olaparib as a maintenance therapy in the platinum-sensitive recurrent setting was recently published with promising findings. Patients, who were not required to carry a germline mutation in *BRCA1* or *BRCA2*, were treated with olaparib or placebo until disease progression after any response to platinum agent. This phase II study found a clear improvement in PFS (HR, 0.35; 95 % CI, 0.25–0.49; P<0.001), with a toxicity profile consistent with previous studies [98]. Several ongoing phase II trials are evaluating olaparib in ovarian cancer, including its use in combination with carboplatin and paclitaxel in the recurrent platinum-sensitive setting (NCT01081951).

Several other PARP inhibitors are being evaluated in clinical trials for ovarian cancer. A phase II trial of iniparib (BSI-201, BiPar Sciences; South San Francisco, CA, USA) in combination with carboplatin and gemcitabine in platinum-sensitive ovarian cancer yielded improved RR over historical RRs for chemotherapy alone (70.6 % vs. 47.2 %) [99]. Iniparib has also been evaluated in combination with carboplatin and gemcitabine in patients with platinum-resistant ovarian cancer. Among the first 19 evaluable patients in a single-arm phase II trial, this combination demonstrated a RR of 31.6 % and median PFS of 5.9 months with no unexpected toxicities [100]. Additional studies of iniparib both as a single agent in patients with *BRCA1* or *BRCA2*-associated ovarian cancer are ongoing (NCT00677079). Interestingly, 2 recent publications reported that the antitumor activity of iniparib is not consistent with PARP inhibition, indicating a need for further preclinical assessment of this agent [101, 102]. Other PARP inhibitors are in early phase trials include MK-4827 (Merck & Co., Inc.; Whitehouse Station, NJ, USA), ABT-888 (Abbott Laboratories; Abbott Park, IL, USA), AG-14699 (rucaparib, Pfizer; New London, CT, USA), and BMN-673 (Biomarin; Novato, CA, USA).

There are patients with *BRCA* mutations that are resistant to PARP inhibition despite defects in base excision repair. Preclinical data indicate that resistance to this therapy is related to upregulation of other DNA repair pathways [103]. Additional proposed mechanisms of resistance to PARP inhibition are the loss of *BRCA2* mutations or development of secondary *BRCA2* mutations that restore BRCA function [104, 105].

Targeting the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway

The PI3K pathway plays a key role in tumorigenesis through stimulation of several downstream mediators, including AKT. AKT acts on a variety of targets affecting cellular proliferation, survival, and evasion of apoptosis. mTOR is a critical target of AKT that subsequently activates proteins such as S6 kinase, impacting protein translation and progression of the cell cycle [106–108]. This pathway may

Table 3 Efficacy and safety in Phase II/III trials of PARP inhibitors

Trial	Setting	Treatment	RR, %	SD, %	Outcomes	Reported grade 3 to 4 AEs
Olaparib						
Audeh [93]; phase II (*N*=57)	Recurrent EOC/PPC/FTC with confirmed *BRCA1* or *BRCA2* mutations	Olaparib 400 or 100 mg BID	33 (400 mg); 13 (100 mg)	36 (400 mg); 29 (100 mg)	PFS, 5.8 mo. (400 mg); 1.9 mo. (100 mg)	Nausea, fatigue, anemia, vomiting, neutropenia, GERD, lymphopenia
Gelmon [94]; phase II (*N*=90)	Advanced high-grade se rous and/or undifferenti ated and/or known *BRCA*-mutated OC/PPC/ FTC (*n*=64) or triple-negative BC (*n*=26)	Olaparib 400 mg BID	29 (OC only)	38 (OC only)[a]	PFS, 219 d (OC only)	Nausea, fatigue, decreased appetite, diarrhea, abdominal pain (OC only)
Ang [95]; phase II (*N*=26)[b]	Advanced *BRCA1/ 2*-deficient OC	Olaparib followed by CT at progression	54 (olaparib only, before CT)	NR	NR	NR
Kaye [97]; phase II (*N*=97)	Recurrent OC within 12 mo. of platinum therapy and confirmed *BRCA1* or *BRCA2* mutations	Olaparib 200 mg BID vs. olaparib 400 mg BID vs. PLD	25 vs. 31 vs. 18 (*P* = NS)	47 vs. 59 vs. 52[a]	PFS, 6.5 vs. 8.8 vs. 7.1 mo. (HR for combined doses=0.88; 80 % CI, 0.51–1.56; *P*=0.66) OS, HR (200 mg vs. PLD)=0.66 (95 % CI, 0.27–1.55); HR (400 mg vs. PLD)= 1.01 (95 % CI, 0.44–2.27)	Nausea, fatigue, abdominal pain, vomiting, constipation (olaparib only), diarrhea (PLD only), asthenia, urinary tract infection (PLD only), anemia (olaparib only), rash/PPE (PLD only), stomatitis (PLD only)
Ledermann [98]; phase II (*N*=265)	Platinum-sensitive, relapsed, high-grade serous OC/ PPC/FTC; ≥2 prior regimens and PR/CR to most recent regimen	Maintenance olaparib 400 mg BID vs. placebo	12 vs. 4	NR	PFS, 8.4 vs. 4.8 mo. (HR=0.35; 95 % CI, 0.25–0.49; *P* <0.001) OS, 29.7 vs. 29.9 mo. (HR=0.94; 95 % CI, 0.63–1.39; *P*=0.75)[b]	Nausea, fatigue, vomiting, diarrhea, abdominal pain, anemia, asthenia, back pain
Iniparib						
Penson [99]; phase II (*N*=41)[b]	Platinum-sensitive EOC/PPC/FTC	Iniparib + carbo/gem	70.6[c]	NR	NR	NR
Birrer [100]; phase II (*N*=48)[b]	Platinum-resistant EOC/PPC/FTC	Iniparib + carbo/gem	31.6[d]	NR	PFS, 5.9 mo.[d]	NR

AE adverse event; *BC* breast cancer; *BID* twice daily; *BRCA* breast cancer susceptibility gene; *carbo* carboplatin; *CI* confidence interval; *CR* complete response; *CT* chemotherapy; *EOC* epithelial ovarian carcinoma; *FTC* fallopian tube cancer; gem, gemcitabine; *GERD* gastroesophageal reflux disease; *HR* hazard ratio; *NR* not reported; *NS* not significant; *OC* ovarian cancer; *OS* overall survival; *PARP* poly-ADP-ribose polymerase; *PFS* progression-free survival; *PLD* pegylated liposomal doxorubicin; *PPC* primary peritoneal cancer; *PPE* palmar-plantar erythrodysesthesia; *PR* partial response; *RR* response rate; *SD* stable disease

[a] Stable disease for ≥8 weeks

[b] Represents interim data

[c] RR based on first 17 evaluable patients

[d] Efficacy reported for first 19 evaluable patients

be activated in ovarian cancers, serving as a potential mechanism of drug resistance [109]. Thus, inhibition of the PI3K pathway appears to be an attractive target for the treatment of ovarian cancer. Further, certain ovarian histology types such as low grade serous, clear cell, and endometrioid adenocarcinomas, are more likely to demonstrate aberrations in this pathway [110–112]. Thus, there is the potential for higher levels of clinical activity with appropriate patient selection during trial design.

PI3K inhibitors

First-generation PI3K inhibitors were largely unsuccessful in preclinical studies because of high toxicity, likely due to an absence of selectivity [106]. There are multiple PI3K inhibitors currently under exploration, although few have reached phase II clinical development. XL147 (Exelixis, Inc.; South San Francisco, CA, USA) is a reversible, highly selective PI3K inhibitor that has shown dose-dependent inhibition of the PI3K pathway in multiple tumor xenografts [106]. A phase I study of single-agent XL147 in patients with advanced solid tumors showed the agent had durable clinical benefit and was well tolerated, with skin rash being the most common drug-related toxicity [113]. An ongoing phase Ib/II trial (NCT00756847) is evaluating the combination of XL147 and paclitaxel and carboplatin in patients with advanced solid tumors; preliminary results suggest the combination is well tolerated and induces tumor regression in a heavily pretreated patient population. Favorable responses in ovarian cancer have led to a dose expansion in this tumor type [114]. PX-866 (Oncothyreon Inc.; Seattle, WA, USA) is an irreversible PI3K inhibitor that has shown preclinical activity in ovarian cancer cell lines [115]. In a phase I (first-in-human) study, PX-866 was well tolerated,

with adverse effects consisting primarily of grade 1/2 nausea, vomiting, and diarrhea [116]. Further phase I studies with PX-866 are ongoing in patients with advanced solid tumors.

mTOR inhibitors

mTOR may be considered the most important target of AKT, mediating the regulation of translation of different effectors involved in cell growth [106]. There are several agents of great interest that inhibit mTOR. Everolimus (Afinitor®, RAD001, Novartis Pharmaceuticals Corporation; East Hanover, NJ, USA) has shown preclinical activity in ovarian cancer models [117–119], and is currently being evaluated in phase II studies in combination with bevacizumab for patients with recurrent or persistent ovarian cancer (NCT00886691, NCT01031381). In addition, a phase I study evaluating everolimus plus carboplatin and PLD in relapsed ovarian cancer is ongoing (NCT01281514).

Temsirolimus (Torisel®, Pfizer; New London, CT, USA [formerly Wyeth]; Philadelphia, PA, USA) was evaluated in a phase I study in combination with topotecan in patients with advanced or recurrent gynecologic malignancies. This combination was well tolerated, with the dose-limiting toxicity of myelosuppression; 9 of 11 patients achieved SD at 8 weeks [120]. In an ongoing phase II trial combining temsirolimus with bevacizumab in recurrent ovarian cancer patients with up to 2 prior lines of therapy, there were 3 PRs and 14 patients progression free at 6 months among the first 25 enrolled patients. This trial has opened for second stage accrual [121]. A GOG phase II trial of single-agent temsirolimus for recurrent ovarian or primary peritoneal cancer reported an overall RR of 9.3 % (5 PRs in 54 evaluable patients), 6-month PFS rate of 24.1 %, and median PFS and OS of 3.2 months and 11.6 months, respectively. The investigators concluded that this activity, albeit modest, was insufficient to warrant further evaluation of temsirolimus in a phase III trial in an unselected population [122]. Additional phase II trials are currently evaluating temsirolimus in combination with PLD (NCT00982631) in relapsed ovarian cancer as well as temsirolimus in patients with platinum-refractory ovarian cancer (NCT01460979).

AKT inhibitors

Activation of downstream AKT is the most important PI3K function for onset and progression of tumor cells [106]. Furthermore, the inhibition of mTOR results in upregulation of AKT phosphorylation [123]. Thus, AKT is a rational target alone or in combination with other agents for ovarian cancer. Perifosine (Keryx Biopharmaceuticals, Inc; New York, NY, USA), an alkylphospholipid, is known to inhibit AKT by prevention of its recruitment to the cellular membrane. This agent has demonstrated activity in phase I studies in advanced solid tumors [124–126]. Results from a phase I study of perifosine in combination with docetaxel in patients with relapsed ovarian cancer suggest further study of the combination in patients with defined PI3K pathway mutational status is warranted [127]. MK-2206 (Merck & Co., Inc.; Whitehouse Station, NJ, USA), an allosteric inhibitor of Akt, is now in phase II investigation for platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer in a biomarker-assessed clinical trial (NCT01283035).

As noted above, the inhibition of only 1 target in the PI3K/AKT pathway may not be sufficient for an objective tumor response, given the extensive cross-talk and feedback loops found in this pathway. Furthermore, the PI3K/AKT pathway appears tightly linked to the retrovirus-associated DNA sequences (Ras)/v-raf 1 murine leukemia viral oncogene homolog 1 (Raf)/mitogen-activated protein kinase (MAPK) pathway that regulates cellular survival, proliferation, and avoidance of apoptosis. The Ras/Raf/MAPK pathway has been implicated in resistance to multiple targeted therapies, including those agents targeting the PI3K pathway [128]. For example, recent data demonstrate that cell lines with activating *Ras* mutations demonstrated resistance to everolimus in vitro [129]. Pairing drugs that target this pathway, such as mitogen -activated protein/extracellular signal-regulated kinase kinase (MEK) inhibitors, with agents that target the PI3K pathway may be a rational way to overcome poor RRs and resistance. This combination was recently described in *KRAS*-mutated ovarian cancer cell lines and resulted in significant tumor regression [130]. To date, MEK inhibitors have not yet been explored in high-grade serous ovarian cancer, although preliminary activity in low-grade serous ovarian cancer was recently demonstrated for one agent (selumetinib [AZD6244], AstraZeneca; Wilmington, DE, USA) in a phase II trial (GOG-239) [131].

Targeting Src

Src is a downstream nonreceptor tyrosine kinase that mediates cancer cell growth, migration, adhesion, invasion, and angiogenesis [87, 132]. Overexpression of Src has been observed in ovarian cancer cell lines [133] and in late-stage cancers [134]. Src inhibition has been shown to reverse chemoresistance and enhance the activity of paclitaxel and platinum treatment in ovarian cancer cell lines [135, 136].

Dasatinib (Sprycel®, Bristol-Myers Squibb Company; Princeton, NJ, USA) is a strong inhibitor of the Src family of kinases, as well as other targets at higher doses, including BCR-ABL, c-kit, and PDGF. Preclinical data strongly support further investigation of dasatinib as a single agent or in combination with chemotherapy in patients with ovarian

cancer [137, 138]. A phase II study is evaluating dasatinib as monotherapy (NCT00671788) and a phase I study is evaluating dasatinib combined with paclitaxel and carboplatin (NCT00672295) for persistent or recurrent ovarian cancer.

Saracatinib (AZD0530, AstraZeneca; Wilmington, DE, USA) is an orally bioavailable inhibitor of Src. A phase II study of saracatinib plus carboplatin and paclitaxel versus chemotherapy alone in patients with platinum-sensitive ovarian cancer revealed a similar PFS (median, 8.3 vs. 7.8 months, respectively; HR, 0.99; 80 % CI, 0.76–1.31) and overall RR (53.4 % vs. 51.7 %; HR, 0.91; 80 % CI, 0.62–1.36) in both groups. The most common adverse events were neutropenia, febrile neutropenia, thrombocytopenia, and anemia, which were usually reported during the chemotherapy period [139]. An ongoing phase II study is evaluating saracatinib in advanced ovarian cancer (OVERT-1; NCT00610714) and a phase II/III study in combination with weekly paclitaxel in platinum-resistant ovarian cancer has begun recruitment (NCT01196741).

Targeting other novel pathways

Initial interest was high in the EGFR pathway in ovarian cancer secondary to the high but variable level of overexpression (4–100 %) found in this tumor type [140]. Activation of the EGFR pathway has impact on invasion and metastasis as well as cell survival through the PI3K/AKT and Ras/Raf pathways [141, 142]. Unfortunately, agents targeting this pathway have not demonstrated significant activity in ovarian cancer.

Several monoclonal antibodies targeting EGFR or another ErbB family member (e.g., cetuximab [Erbitux®, Bristol-Myers Squibb; New York, NY, USA], trastuzumab [Herceptin®, Genentech; South San Francisco, CA, USA], lapatinib [Tykerb®, GlaxoSmithKline; London, UK], pertuzumab [Genentech; South San Francisco, CA, USA]) and TKIs (e.g., erlotinib [Tarceva®, Genentech; South San Francisco, CA, USA], gefitinib [Iressa®, AstraZeneca; Wilmington, DE, USA]) have been investigated in ovarian cancer, but have demonstrated only minimal activity as monotherapy or in combination with standard chemotherapy [143–156]. This may be secondary to recent data that indicate that response to EGFR-directed therapy is related to mutations in *EGFR*, which are rare in ovarian cancer, rather than overexpression of EGFR [157]. Despite weak evidence supporting the benefit of inhibiting EGFR, the European Organization for Research and Treatment of Cancer (EORTC) has recently completed enrollment of a phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platinum-based therapy (EORTC 55041; NCT00263822).

One alternative strategy in this pathway is based on efforts to block EGFR activation through prevention of specific receptor dimerizations. One agent, MM-121 (Merrimack Pharmaceuticals Inc.; Cambridge, MA, USA), which is designed to block dimerization of ErbB3, has shown promising preclinical and phase I data [158], which is supporting a randomized phase II trial in combination with weekly paclitaxel for platinum-resistant/refractory advanced ovarian cancer (NCT01447706).

The agent vandetanib is a TKI that has dual action on VEGFR-2 and EGFR to target angiogenesis and cellular survival mechanisms. Unfortunately, a study of vandetanib as a single agent for recurrent ovarian cancer had no activity, resulting in study closure after first stage accrual. Molecular testing that was performed on tissues after treatment was significant for blockage of the EGFR pathway but had no impact on VEGFR [159]. Based on preclinical studies that indicated enhanced activity of antivascular therapy in combination with docetaxel [160], a trial combining docetaxel with vandetanib is now underway for the treatment of recurrent ovarian cancer (NCT00872989).

Folate receptor alpha (α-FR) is involved with folate transport and binds the folate receptor with high affinity. This is an attractive target in ovarian cancer, as greater than 70 % of primary and 82 % of recurrent ovarian tumors overexpress α-FR [161]. Farletuzumab (MORAb-003, Morphotek, Inc.; Exton, PA, USA), a humanized monoclonal antibody against α-FR, was generally safe and well tolerated in a phase I study of heavily pretreated patients with ovarian cancer. There were no severe adverse events; the majority of toxicity was mild including hypersensitivity, fatigue, and diarrhea [162]. In addition, a phase II study of farletuzumab alone with subsequent addition of carboplatin and taxane at the time of disease progression in patients with platinum-sensitive ovarian cancer in first relapse had promising results. Approximately 90 % of patients receiving combination therapy achieved normalized CA125 and approximately 70 % had a response. Farletuzumab was well tolerated as a single agent, with no additive toxicity combined with chemotherapy [163]. A phase III randomized, double-blind, placebo-controlled study was performed to farletuzumab in combination with weekly paclitaxel in patients with platinum-resistant or refractory ovarian cancer (NCT00738699) [164]. Unfortunately, this study was closed to accrual after failure to meet predefined efficacy endpoints at interim analysis. This agent is currently under evaluation in combination with carboplatin and taxane in an ongoing phase III study in patients with platinum-sensitive ovarian cancer in first relapse (NCT00849667). EC145 (Endocyte, Inc.; West Lafayette, IN) is a conjugate of folic acid and desacetylvinblastine that binds to the folate receptor with high affinity. This agent demonstrated a significant improvement in PFS in combination with PLD (21.7 weeks)

compared to PLD alone (11.7 weeks) in patients with platinum-resistant ovarian cancer in a phase II trial [165], prompting an ongoing randomized phase III trial (NCT01170650).

Activity of the insulin-like growth factor (IGF) family impacts cell proliferation and tumorigenesis among many solid tumors, including ovarian cancer [166, 167]. IGF can activate the PI3K/AKT pathway leading to cellular survival and metastasis [166]. Microarray studies have demonstrated that upregulation of this pathway correlates with poor OS in ovarian cancer [168]. Currently, a humanized monoclonal antibody that targets the IGF-1 receptor, AMG 479 (Amgen Inc.; Thousand Oaks, CA, USA), is under exploration as a single agent in platinum-sensitive ovarian cancer (NCT00719212) and in combination with standard cytotoxics as first-line therapy (NCT00718523). In addition, a dual IGF and PI3K/Akt/mTOR blockade strategy is being pursued with dalotuzumab (Merck & Co., Inc.; Whitehouse Station, NJ, USA) in combination with either an mTOR inhibitor or an Akt inhibitor (either ridaforolimus or MK-2206, respectively [both also Merck & Co, Inc]) in advanced malignancies, with preliminary antitumor activity to be assessed in a subgroup of patients with metastatic or recurrent platinum-resistant ovarian cancer (NCT01243762).

Serous ovarian cancer is characterized by near universal aberration in the P53 tumor suppressor gene [169]. Normally p53 plays an important role as a cell cycle checkpoint regulator, particularly at the G1 checkpoints. While protecting normal cells from DNA injury, this regulator mechanism can also allow tumor cells to repair induced DNA damage—thereby reducing the effectiveness of chemotherapy. Cells that lack normal p53 function are known to rely on other checkpoints for cell cycle regulation. Wee-1 is a tyrosine kinase that regulates the G2 cell cycle checkpoint. It gains prominence when p53 function is perturbed. As inhibition of Wee-1 in p53-deficient tumors leads to reduced capacity for tumor cell repair of induced DNA damage (e.g., chemotherapy, radiation) [170], it represents a potential target for p53-mutant ovarian cancer. Accordingly, a randomized, placebo-controlled phase II study is evaluating paclitaxel and carboplatin with or without the Wee-1 tyrosine kinase inhibitor MK-1775 (Merck & Co, Inc; Whitehouse Station, NJ, USA) in women with p53 mutation-positive platinum-sensitive recurrent ovarian cancer.

Conclusions

Given the limited success of traditional cytotoxic chemotherapy in the treatment of ovarian cancer, recent clinical studies have focused more heavily on molecular targeted therapy. There are a number of promising pathways in ovarian cancer that may prove to advance OS while minimizing quality of life impact. Current study designs will continue to clarify the role of these agents, specifically use in the upfront versus recurrent settings, as well as development of rational combinations to overcome resistance. Certainly, close analysis of factors that predict adverse events of these agents will be necessary as our knowledge continues to expand.

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