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Clinical Investigation of Receptor and Non-Receptor Tyrosine Kinase Inhibitors for the Treatment of Epithelial Ovarian Cancer

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Abstract

Introduction—Epithelial ovarian cancer (EOC) is the second most common gynecologic malignancy and the leading cause of death from gynecologic cancer in the United States. EOC is an exquisitely chemo-sensitive disease with response rates of over 75% in the upfront setting. Despite this, due to high rates of recurrence and development of chemo-resistance, the overall survival of EOC remains about 25%. Thus, there is a great need for new therapeutic approaches to render more durable responses. Based on preclinical and early phase clinical studies, key targeted pathways include targets that drive angiogenesis and chemo-resistance. Receptor tyrosine kinases and non-receptor tyrosine kinases play important roles in these processes and several small molecule tyrosine kinase inhibitors (TKIs) are in clinical development.

Areas covered—This review summarizes clinical rationale, mechanisms of action, and clinical data for the TKIs under evaluation in the phase III setting for EOC.

Expert opinion—Despite reasonable preclinical activity, small molecule TKIs are unlikely to improve patient survival as single agent therapies in an unselected EOC population. Incorporation of tissue evaluation during ongoing clinical trials is required to identify molecularly defined groups that respond to single agents and direct rational combination strategies based on mechanisms of resistance to improve outcomes in EOC.

Keywords

Angiogenesis; ovarian cancer; phase III; signaling; targeted therapy; tyrosine kinase inhibitor

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Declaration of Interest

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1. Introduction

Ovarian cancer remains the second most common gynecologic malignancy and the leading cause of death from gynecologic cancers in the United States [1]. Epithelial ovarian cancer (EOC), comprised primarily of high grade serous histology, accounts for 95% of ovarian malignancies. Although rates of initial chemosensitivity approach 75% in EOC, the majority of patients develop recurrent disease and despite improvements in progression free survival (PFS) overall survival (OS) rates for advanced disease remain poor at 27% [2–5]. Thus there is an urgent need for more effective therapies. Advancements in the molecular classification of EOC have identified potential targets and patient subgroups that may derive maximal benefit, however these still lack sufficient power to warrant implementation of most targeted therapeutics, at least as monotherapy. Newer compounds targeting signal transduction pathways and their upstream receptor tyrosine kinases (RTK) have shown promise in phase I–II clinical trials. We describe the major aberrant signaling pathways in ovarian cancer with a focus on small molecule tyrosine kinase inhibitors (TKIs) advancing to phase III clinical trials.

2. Current Therapies

Nearly 75% of women with ovarian cancer present at advanced stage (Stage III or IV) in which disease involves the peritoneal cavity, regional lymph nodes or other organs. The large amount of disease present at presentation combined with underlying genomic instability leads to the presence of multiple different tumor subclones likely contributing to the development of resistance to therapy. Current evidence-based upfront treatment combines cytoreductive (de-bulking) surgery and chemotherapy. To date, the literature has not demonstrated a difference in outcomes based on the sequencing of surgery and chemotherapy [6]. This is a critical area of ongoing clinical investigation in EOC.

Gynecologic Oncology Group (GOG) 172 established the survival benefit of combination intravenous (IV) and intraperitoneal (IP) platinum/taxane chemotherapy in optimally debulked stage III EOC, and subsequent meta-analyses have confirmed a roughly sixteen month improved survival compared to IV only therapy [4, 7, 8]. The issue of optimal cytoreduction is pertinent, as IP therapy has limited penetration into residual peritoneal deposits >1cm in volume [9]. For patients not deemed suitable for the IV/IP GOG 172 regimen, IV platinum/taxane combination therapy is the standard of care. Based on a Japanese GOG phase III trial, carboplatin area under the curve (AUC) of 6 on day 1 and weekly paclitaxel 80mg/m^2 on days 1, 8, and 15 of a 21 day cycle may provide survival benefit over carboplatin AUC 6 on day 1 with paclitaxel 180mg/m^2 day 1 of a 21 day cycle [10–12]. These three regimens provide the backbones for ongoing taxane and platinum combination trials investigating whether addition of small molecule tyrosine kinase inhibitors to first line therapy can improve outcomes (table 1).

As in many solid tumors, the amount of residual disease is a key indicator of overall outcome after completion of therapy. The achievement of no gross, or microscopic, residual disease (R_0) is associated with clear improvement in progression free and overall survival [6, 13–15]. This factor holds up regardless of the timing of surgery or chemotherapy. In fact,

in a randomized study of neoadjuvant chemotherapy versus primary surgical cytoreduction followed by adjuvant chemotherapy, complete resection of all macroscopic disease was the strongest independent predictor of overall survival [6]. Thus, the incorporation of targeted agents in either of the settings, neoadjuvant or adjuvant, is reasonable providing that the combination improves the chance of achieving no gross residual disease.

Regardless of residual disease status, the majority of patients with EOC will achieve a complete clinical response to primary therapy. However, a large proportion of these patients will recur, despite upfront chemosensitivity. This has led to the exploration of a variety of maintenance strategies including, additional low dose and high dose chemotherapy, radiation, bevacizumab, and vaccine therapy [16–19]. Unfortunately, none of these trials have demonstrated a significant improvement in overall survival, however, current NCCN guidelines suggest that bevacizumab maintenance is reasonable in the upfront setting. Consolidation therapy beyond completion of standard adjuvant chemotherapy for EOC may provide another opportunity to determine whether targeted agents will improve outcomes in ovarian cancer (Table 1).

Treatment of recurrent ovarian cancer is based upon the time to recurrence from the last treatment with a platinum agent. Somewhat arbitrarily, recurrence after 6 months is considered platinum-sensitive and less than 6 months is platinum resistant. Disease that recurs or progresses during platinum–based therapy is considered platinum refractory. In platinum-sensitive recurrence, the standard of care is carboplatin in combination with another cytotoxic such as liposomal doxorubicin, gemcitabine, or a taxane. Although response rates can approach 50%, these responses are often short lived likely due to the selection and expansion of chemotherapy resistant clones during the initial chemotherapy regimen [20–22]. There is no current evidence-based standard for platinum resistant or refractory disease [23]. Based on expert consensus, acceptable regimens include, but are not limited to, liposomal doxorubicin, gemcitabine, docetaxel, topotecan, weekly paclitaxel or bevacizumab. Given that response rates are limited and the chance of cure is extremely low, these patients could also be considered for experimental therapy.

Bevacizumab is a humanized monoclonal antibody that targets angiogenesis through blocking the ability of VEGF to bind to its receptors. Bevacizumab has objective anti-tumor activity in ovarian cancer in the recurrent setting, highlighting the importance of angiogenesis pathways as therapeutic targets. Bevacizumab has been tested both in combination with cytotoxic therapy followed by maintenance bevacizumab as adjuvant therapy in stage III or IV EOC (GOG 218 and ICON7), as well as first line therapy for recurrent disease [18,19]. Improvement of progression free survival has been consistent across these trials with the addition of bevacizumab. The overall survival benefit of bevacizumab remains less clear, creating controversy in clinical recommendations for its use in the front line setting. The details of the contradicting expert views are beyond the intent of this review, suffice to say there remains ample room to improve overall outcomes in the treatment of advanced ovarian cancer.

3. Angiogenesis

Induction of angiogenesis and sustained proliferative signaling are hallmarks of malignancy and common therapeutic targets [24, 25]. As in many other malignancies, angiogenesis plays a role in promoting ovarian cancer through tumor growth and induction of a metastatic phenotype [26–28]. Elevated levels of vascular endothelial growth factor (VEGF) are associated with more aggressive disease, increased mortality and malignant ascites [29–33]. Briefly, VEGF is secreted in response to acidosis, hypoxia, and mechanical stress, and secreted VEGF binds to one of the three VEGF tyrosine kinase receptors VEGFR1-3. Following ligand binding, the activated VEGF receptor initiates a cascade of downstream signaling events to promote vascular endothelial cell migration, blood vessel formation and proliferation (figure 1) [34, 35]. The VEGF receptors, specifically VEGFR1 and VEGFR2, are major regulators of angiogenesis, although several other receptor tyrosine kinases (RTKs) can initiate pro-angiogenic signaling programs (figure 1) [34]. Targeting angiogenesis is often approached via either decreasing the presence of ligand, inhibiting an upstream receptor tyrosine kinase (RTK), inhibiting intracellular signaling kinases, or a combination strategy (figure 1). Evidenced by objective anti-tumor activity of bevacizumab in recurrent ovarian cancer, the angiogenesis pathway is a clinically relevant target. Whether other strategies to target these pathways will be more effective remains an area of active investigation.

The clinical observation that anti-angiogenesis monotherapies are uncommonly successful and that initial response is followed by relapse has driven investigation in resistance to anti-angiogenesis compounds. One option to maximize pathway blockade and potentially decrease or delay the development of resistance is to target multiple nodes in a signal transduction pathway. Signal transduction pathways commonly converge at multiple nodes and are highly plastic with extensive negative feedback loops and built in redundancies. Preclinical work has established several resistance mechanisms and provides rationale for TKIs targeting multiple pro-angiogenic kinases. The adaptive up-regulation of alternative (i.e. not inhibited) proangiogenic signaling circuits such as fibroblast growth factor 1 (FGF-1), ephrin A1 and angiopoietin has been shown to re-establish tumor neovascularization after initial inhibition [36, 37]. Inhibition of angiogenesis leads to tumor microenvironment hypoxia and up-regulation of proangiogenic factors such as hypoxia inducible factor 1-alpha (HIF1α) [38, 39]. Further tumor hypoxia leads to recruitment of vascular (endothelial and pericyte) progenitor cells as well as proangiogenic monocytes which can restore vascularization and abrogate the effect of angiogenesis inhibitors [40–42]. Beyond adaptive resistance mechanisms, some tumors may be inherently resistant to anti-angiogenic therapies based on pre-existing genomic alterations or constitutively active redundant pro-angiogenic signaling cascades [36].

Preclinical work and phase II–III clinical trials have attempted to establish predictive and prognostic biomarkers in ovarian cancer. Tumor biopsies from patients enrolled in a phase II trial of bevacizumab in recurrent EOC (GOG-170D) suggested high baseline CD-31 microvessel density may be associated with a poor response to the anti-VEGF agent bevacizumab, as well as decreased median survival [33]. Biomarker studies measuring VEGF have yielded inconsistent results and serum VEGF measurements are not used

outside of the research setting [33, 43, 44]. Retrospective analyses have identified putative biomarkers of response and resistance to angiogenesis inhibitors. However additional validation studies are needed prior to their use as prospective selective biomarkers or as therapeutic targets [45–48].

There are five TKI that have advanced or are advancing to Phase III clinical trials. AZD-2171, BIBF1120, and GW786034 target RTKs including VEGFR 1, 2, and 3 and are proposed to work via antiangiogenic mechanisms. AZD0530 is non-receptor TKI that targets Src, based on the Src pathway being involved in multiple cancer promoting processes including angiogenesis and resistance mechanisms and src being activated in ovarian cancer. OSI-774 targets the RTK EGFR, which indirectly activates angiogenic pathways, in addition to stimulating tumorigenic processes such as cell proliferation, survival and migration. Although the majority of the compounds entering phase III trials in EOC are proposed to work partly by impacting angiogenesis, there are other small molecule inhibitors targeting the DNA repair pathways, and the phosphoinositol-3-kinase pathway which are in earlier phase clinical development **and not** discussed here. TKIs offer the potential for oral dosing, more targeted mechanism of action, conserved and manageable toxicity profiles versus monoclonal antibodies such as bevacizumab.

4. AZD-2171 (Cediranib)

Inhibition of VEGFR signaling after ligand binding has been targeted using small molecules that bind the ATP-binding pocket in the intracellular kinase domain to prevent ATP catalysis and propagation of receptor signaling. Cediranib is an oral small molecule ATP-competitive inhibitor of VEGFR-2 (IC_{50} <1nmol/L), VEGFR-1 (IC_{50} = 5nmol/L), and VEGFR-3 (IC_{50} = 3nmol/L) with cross reactivity against c-kit and platelet derived growth factor receptor beta (PDGFR-β) [49, 50]. Since PDGFR may contribute to angiogenesis through impact on pericytes and the microenvironment and provide a mechanism of bypass for anti-VEGFR targeted therapies, this cross reactivity may be important for the activity of cediranib. Several phase I studies demonstrated safety and tolerability of cediranib at daily doses of 45mg, which produced a mean terminal half-life of 22 hours [51–53]. A phase II trial of 46 patients with recurrent EOC given cediranib 30mg daily demonstrated a clinical benefit rate (defined as complete response (CR), partial response (PR) or stable disease (SD) >16 weeks, or CA-125 non-progression >16wks) of 30% with a 17% PR rate [54]. In the population of patients achieving clinical benefit, the mean response duration was 3.9 months, and nearly all patients who achieved clinical benefit had serous histology [54]. Among the phase II–III trials of cediranib across several malignancies, the most common grade 3/4 adverse events include hypertension, fatigue, diarrhea, nausea, and hypothyroidism [54–58].

The UK-based Medical Research Council, in conjunction with AstraZeneca, is now conducting a randomized phase III trial of cediranib 20mg daily or placebo in combination with standard platinum-based chemotherapy in women with platinum sensitive relapsed ovarian cancer (table 1) (NCT00532194). This three-arm study randomized patients 2:3:3 to either carboplatin + paclitaxel every 3 weeks for 6 cycles plus placebo for the duration of chemotherapy followed by 18 months of placebo (Arm A), carboplatin + paclitaxel every 3 weeks for 6 cycles plus cediranib 20mg daily for the duration of chemotherapy followed by

18 months of placebo (Arm B), or carboplatin + paclitaxel every 3 weeks for 6 cycles plus cediranib 20mg daily for the duration of chemotherapy followed by 18 months of cediranib 20mg daily maintenance (Arm C). The primary endpoint is progression free survival (PFS) with secondary endpoints including overall survival (OS), toxicity, and quality of life (QOL) assessments. This trial has completed accrual and we await the results to better inform the role of anti-angiogenesis TKI therapy in relapsed EOC.

5. BIBF1120 (Nintedanib)

Although VEGFR1, 2, and 3 are the primary drivers of angiogenesis, the fibroblast growth factor (FGF) and platelet derived growth factor (PDGF) receptors play important supportive roles in blood vessel formation. FGF receptor (FGFR) is primarily expressed on smooth muscle and endothelial cells and FGFR signaling can stabilize developing blood vessels [37, 59, 60]. PDGFR expression and signaling is central to pericyte survival and maintenance of the pericyte-endothelial interaction important to angiogenesis [61–63]. Nintedanib is an oral indolinone derivative “triple angiokinase” small molecule ATP competitive inhibitor of VEGFR1-3, FGFR1-3, and PDGFRα,β with IC_{50}s ranging from 20–100nmol/L [64]. In addition, nintedanib inhibits the Src family of kinases including Lck, Lyn, and Src, which may contribute to angiogenesis. Preclinical models demonstrated a broad range and in-vitro and in-vivo activity in human cancer cell line angiogenesis models and tumor xenografts [64]. Phase I clinical trials confirmed safety and tolerability at doses of up to 300mg orally twice daily, and suggested a mean terminal half-life of 13–19 hours with a suggested phase II dose of 200–250mg orally twice per day [65]. In phase II trials, the most common side effects have been nausea, vomiting, diarrhea, and transaminitis [66]. Combination studies with nintedanib up to 250mg twice daily with carboplatin AUC 5 and paclitaxel 175mg/m^2 given every three weeks was safe and well tolerated [67]. A subsequent phase II trial of nintedanib 250mg PO twice daily in 43 patients with advanced EOC who had recently responded to chemotherapy but were considered at high recurrence risk demonstrated a 36 week PFS of 16.3% (n=43) compared to 5% for placebo (n=41) [66].

Nintedanib is now being studied in the LUME-Ovar 1 randomized phase III clinical trial of nintedanib or placebo in combination with carboplatin and paclitaxel for first line therapy in advanced EOC (Table 1) (NCT01015118). The primary endpoint is PFS at 41 months with secondary endpoints of OS, time to progression (TTP), overall response rate (ORR), and safety. This trial is estimated to complete in July 2016 and provide information regarding the added benefit of blockade of FGF and PDGF beyond VEGFR inhibition.

6. GW786034 (Pazopanib)

Pazopanib is an orally bioavailable small molecule inhibitor of VEGF receptors 1–3, PDGFR-α/β, FGFR-1 and -3 and c-kit [82]. As noted in the discussion of nintedanib, this agent likely acts on both the tumor cell as well as the cells supporting the vasculature. In phase I studies a pazopanib dose of 800mg once daily achieved a mean elimination half life of 31.1 hours with a mean plasma trough concentration of 34μmol/L, and a monotherapy dose of 800mg once daily was determined for further testing [83]. In a non-randomized phase II study of thirty six patients with recurrent EOC who had not received prior

angiogenesis inhibitors, pazopanib at a dose of 800mg daily for 28 day cycles demonstrated a 31% CA-125 response rate and an overall response rate of 18% (based on CA-125 and RECIST) [84]. Also notable was a 56% stable disease rate that lasted a median of 80 days. The most common grade II–III side effects included fatigue, diarrhea, elevated liver transaminases, and hypertension, consistent with previously published pazopanib side effects [83, 84]. Based on this phase II study, and data from other small molecule TKIs in EOC pazopanib was tested in a phase III trial. The phase III AGO-OVAR16 trial evaluated the effect of pazopanib monotherapy versus placebo in women with stage II–IV EOC that had not progressed after surgery and at least 5 cycle of platinum-taxane first line chemotherapy (NCT00866697)(table 1). Pazopanib was given at 800mg daily for up to 2 years. The primary endpoint was PFS by RECIST, with secondary endpoints including OS, QOL and safety. Of the 940 randomized patients, 91% had stage III/IV disease at diagnosis. Early data with a median follow up of 24 months demonstrated a PFS of 17.9 months for the pazopanib maintenance group versus 12.3 months ($p = 0.0021$) for the placebo group [85]. Data for overall survival are not mature and will be reported in the future. Mature data from the AGO-OVAR16 trial, and data from the LUME-OVAR1 trial of nintedanib will help define the potential benefit of blockade of FGF and PDGF beyond VEGFR inhibition.

7. AZD0530 (Saracatinib)

The Src family of non-receptor tyrosine kinases provides a convergence point downstream of multiple cell surface receptors leading to phosphorylation and activation of multiple signaling pathways that contribute to the pathophysiology of cancer. Increased Src activity promotes angiogenesis via up-regulating the pro-angiogenic cytokines VEGF and interleukin 8 (IL-8), and Src inhibition has been shown to decrease tumoral VEGF and IL-8 production and tumor proliferation [68, 69]. In addition to a role in angiogenesis, Src also stimulates cell growth, adhesion and invasion (Figure 2) [70, 71]. Src family members are overexpressed and activated in multiple cancer cells lines, including ovarian cancer lines, and Src inhibition has been shown to sensitize ovarian cancer cells to taxane and platinum [72–74]. Saracatinib is an orally bioavailable anilinoquinazoline with selectivity for Src family kinases and Abl kinases with in-vitro IC_{50} ranging from 76–149nmol/L [75]. More recent analysis suggests that tumors harboring mutations in the helical (E542K and E545K) and kinase (H1047R) domains of the PIK3CA gene may be particularly sensitive to Src inhibition with saracatinib [76]. A phase I trial of 30 patients with advanced solid tumors suggested safety and tolerability at doses of 175mg daily with a mean half-life of roughly 40 hours. Activity was limited with 11 of 81 patients demonstrating confirmed stable disease at 6 weeks [77]. Daily saracatinib at doses up to 175mg has also been safely combined with paclitaxel 175mg/m^2 and carboplatin AUC 5 across several tumor types. This study found an objective response rate of 11% (5/44), including two patients with ovarian cancer [78]. Results from phase I–II trials suggest common adverse events include fatigue, diarrhea, nausea, transaminitis, and lymphopenia [77–80]. The SaPPrOC phase II–III randomized trial of saracatinib 175mg daily or placebo in combination with weekly paclitaxel (80mg/m2 6wk on/2wk off) in patients with platinum resistant EOC was recently reported in abstract form (Table 1)(NCT01196741). The primary study endpoint was 6 month PFS with secondary assessment of OS at 2 years, ORR by RECIST 1.1, duration of response, TTP and QOL

endpoints. With enrollment of 107 patients, the 6 month PFS rate was 29% for the saracatinib group and 35% for the placebo group, and there were no statistically significant improvements in median PFS (3.9 versus 5.3 months, p=0.86) or OS (12.7 versus 12.8 months, p=0.36)(table 1) [81]. Future correlative studies may help to identify a subgroup of patients who may derive benefit from this combination.

8. OSI-774 (Erlotinib)

The epidermal growth factor receptor (EGFR) is expressed in up to 70% of advanced EOC and increased expression has been correlated with poor survival. EGFR stimulates cell survival, invasion, and metastasis through activation of multiple cell signaling pathways, including the src, PI3K/AKT and RAS/RAF pathways [86–88]. In general, agents targeting this receptor have failed to demonstrate significant activity in EOC as single agents. As EGFR is wild type in ovarian cancer and mutations appear to predict response to agents targeting EGFR [89] in other diseases, this may account in part for the limited single agent activity. Erlotinib is an orally bioavailable small molecule TKI of the EGFR with in-vitro IC_{50} ranging from 2–20nmol/L [90]. In a phase II trial of 34 EOC patients who failed platinum/taxane based therapy, erlotinib 150mg daily was well tolerated with the most common adverse events being rash (≈65%) and diarrhea (≈40%). However, objective response rate was 6% with a stable disease rate of 44% [91] leading to limited interest of further evaluation of this agent as a monotherapy in this setting. A phase II trial testing the combination of bevacizumab and erlotinib in recurrent EOC demonstrated a response rate of 15%, although there were two fatal gastrointestinal perforations resulting in study closure [43].

The established safety and experience with erlotinib monotherapy in non-small cell lung cancer combined with a lack of viable options for maintenance therapies after treatment for upfront therapy led to interest in the use of erlotinib in this setting. The European Organization for Research and Treatment of Cancer (EORTC) launched a randomized phase III trial investigating the role of erlotinib maintenance (150mg Daily) after first line platinum based chemotherapy for EOC (EORTC 55041, NCCT00263822, table 1). At a median follow up of 51 months, the PFS for erlotinib maintenance was 12.7 months and 12.4 months for placebo (p = 0.52) and OS was 50.8 months for erlotinib and 59.4 months in the observation arm[92]. Post-hoc subgroup analysis is ongoing and may identify patients who could derive benefit from erlotinib.

9. Conclusions

There is strong rationale for targeting angiogenesis pathways in EOC. Though a role for bevacizumab in the upfront setting remains controversial, its anti-tumor activity in the recurrent patient population remains proof of concept for targeting angiogenesis [18, 19, 93–95]. The RTK and non receptor TKIs offer a different strategy for inhibition of angiogenesis. Recognition of druggable signaling cascades has translated into numerous phase I–II trials using small molecule TKIs as monotherapy or in combination with approved cytotoxic therapies in many tumor lineages [96]. Despite the large number of phase I–II trials, there is a relative paucity of completed phase III investigations, and

significant opportunities to improve survival remain. Rational incorporation of tumor and serum collection into clinical trial design is necessary to aid in biomarker discovery and retrospective understanding of patient subgroups likely to derive maximum benefit and those likely to be resistant to a given targeted therapy. Ongoing molecular and genomic understanding leading to patient stratification holds the potential to translate to improved response rates and, ultimately, survival advantages.

10. Expert Opinion

The landscape of advanced ovarian cancer has changed substantially in the last ten years, and continues to be informed by improved biologic understanding. Importantly, large-scale genomic characterization efforts such as afforded by the Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC) and the Australian Ovarian Cancer Study Group have provided an atlas of the abnormalities in EOC demonstrating that the most prevalent and aggressive subtype, high grade serous ovarian cancer, is driven primarily by copy number aberrations with almost universal p53 mutations and mutations in the homologous recombination pathway including BRCA1/2. While no other aberrations are found with a frequency of more than 7%, over 50% of high grade serous ovarian cancer patients have aberrations present in potentially targetable genes providing an opportunity for the future. In contrast patients with low grade disease, clear cell and endometrioid cancers have a completely different spectrum of genomic aberrations with events targeting ARID1A as well as the PI3K and RAS pathways in different subsets providing potential targets for therapy.

To date, small molecule TKIs are largely used as single agents, and several phase III trials continue to investigate these agents as monotherapies. With the established role of angiogenesis in ovarian cancer, multiple compounds have been developed with goal of improving upon targeting angiogenesis either through improved binding affinity and/or simultaneous inhibition of multiple pro-angiogenic kinases. As is being seen in renal cell carcinoma (RCC), improved targeting of angiogenesis alone with the current generation of TKIs has not significantly improved overall survival compared to earlier generation TKIs [97–100]. Ongoing efforts to better characterize signaling and genomic alterations in ovarian cancer will increase the potential for rational combination studies with angiogenesis inhibitors. The plasticity and intratumoral heterogeneity of ovarian cancer argues that single agent multi-kinase TKIs are unlikely to improve survival as single agents. Although there is justifiable concern for toxicities resulting from combining multiple TKIs, it is becoming clear that targeting multiple pathways to overcome pre-existing and acquired resistance and, in particular, adaptive resistance seems to hold the greatest potential for success. Further, the combination of targeted agents with existing cytotoxic therapies is a necessary step to achieving greater benefit. Although generally these agents have fewer overlapping toxicities, therapeutic doses of each agent in combination may be difficult to achieve. Exploration of unique schedules of incorporation of targeted agents, including in the neoadjuvant or lead-in settings, may improve the opportunities for successful combinations in EOC.

Key advancements in molecularly targeted therapy in ovarian cancer are likely to arise from concerted efforts to probe tumor biopsy samples and establish response biomarkers that may

ultimately allow a more individualized treatment approach. The current molecular landscape of high grade serous ovarian cancer has not identified a dominant driver pathway to which inhibition produces reliable and durable clinical responses translating into survival benefit. TKI-based therapies have historically been most successful in homogeneous malignancies in which the malignant phenotype is intimately linked, or “addicted”, to a single pathway with a biomarker able to select the patients most likely to benefit [101–108]. Incorporation of tissue assessment, including biopsies at baseline as well as at the time of response and progression, is essential in ongoing trial development. This will allow for identification of molecular subtypes that are more homogenous and likely to respond to a single agent or novel resistance mechanisms and biomarkers to drive the development of combination therapies.

Relatively recently, it has been appreciated that mutations affecting the DNA damage sensing and repair machinery are common in ovarian cancer, and may offer a therapeutic target in some patients [109–114]. Targeted agents such as PARP inhibitors that capitalize on defects in the homologous recombination pathway have demonstrated activity in high grade serous ovarian cancer, particularly patients with germline mutations with BRCA1/2. Whether combinations of TKIs and PARP inhibitors will be efficacious and well tolerated warrants investigation. Much of the preclinical ovarian cancer work has sought to identify genomic and signaling alterations underlying platinum and taxane resistance, with fewer studies dedicated to identifying TKI biomarkers [115–117]. Further preclinical work may identify potentially synergistic small molecule combinations with non-overlapping toxicities [118]. It likely remains that the future of small molecule TKIs in ovarian cancer is not as single agents, but rather in combination with other molecularly targeted agents. Ultimately, early phase clinical trials designed around known genomic and signaling aberrations are most likely to spawn phase III trials demonstrating improved overall survival.

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List of abbreviations

TKIs	tyrosine kinase inhibitors
EOC	Epithelial ovarian cancer
IV	intravenous
IP	intraperitoneal
AUC	area under the curve
VEGF	vascular endothelial growth factor
RTK	receptor tyrosine kinase
FGF-1	fibroblast growth factor 1

HIF1α	hypoxia inducible factor 1-alpha
PDGFR-β	platelet derived growth factor receptor beta
CR	complete response
PR	partial response
SD	stable disease
PFS	progression free survival
OS	overall survival
QOL	quality of life
FGF	fibroblast growth factor
TTP	time to progression
ORR	overall response rate
EORTC	European Organization for Research and Treatment of Cancer
RCC	renal cell carcinoma
Src	Proto-oncogene tyrosine-protein kinase Src

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Highlights

- Emerging small molecule tyrosine kinase inhibitors are unlikely to improve survival in EOC as monotherapy.
- Further translational tissue studies may identify patient subgroups most likely to benefit from small molecule TKI therapy.
- As with other targeted therapies, an understanding of conserved resistance mechanisms is important to maximize efficacy.
- Improved molecular understanding of EOC is needed to identify new targets.

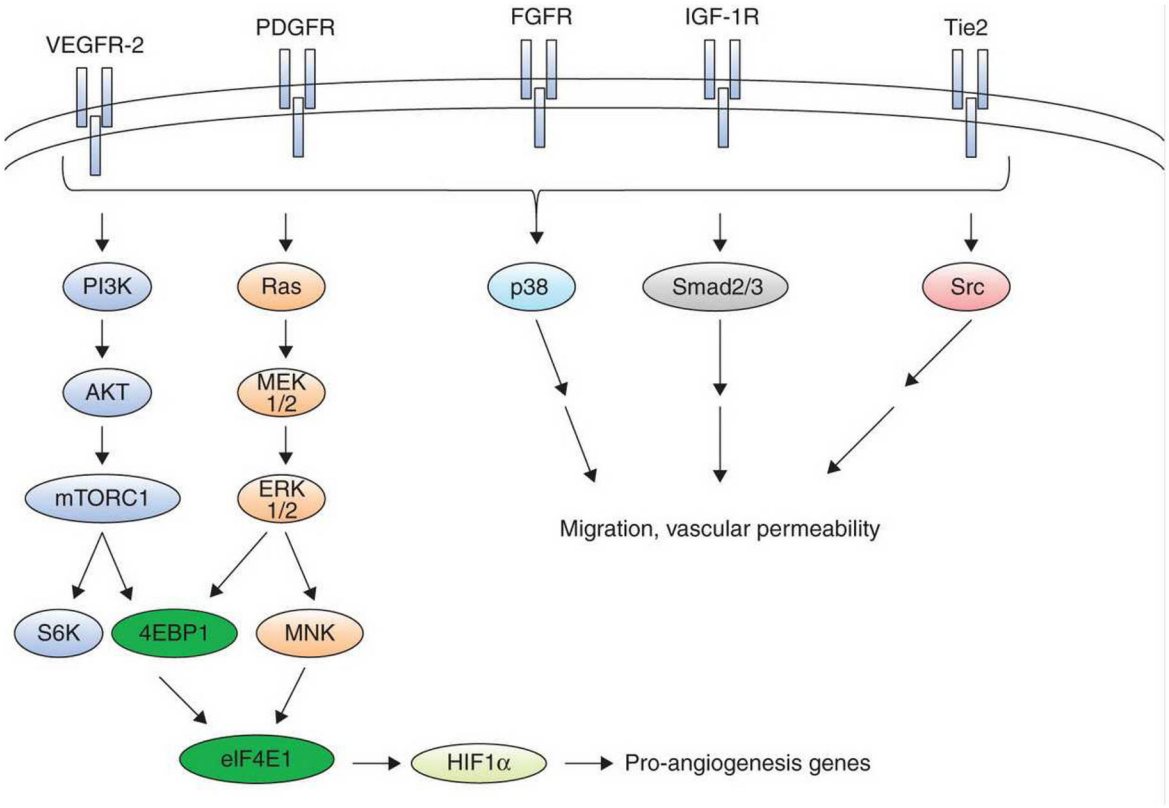

Figure 1.

Signaling pathways involved in driving angiogenesis in ovarian cancer. Vascular endothelial growth factor receptor 2, VEGFR2; platelet derived growth factor receptor, PDGFR; fibroblast growth factor receptor, FGFR; insulin-like growth factor 1 receptor, IGF-1R; angiopoietin-1 receptor, Tie2; phosphoinositide-3-kinase, PI3K; protein kinase B, AKT; mammalian target of rapamycin complex 1, mTORC1; ribosomal protein S6 kinase, S6K; eukaryotic translation initiation factor 4E-binding protein 1, 4EBP1; MAP kinase-interacting kinase, MNK1; eukaryotic translation initiation factor 4E, eIF4E; hypoxia inducible factor 1-alpha, HIF1a; p38 mitogen activated protein kinase, p38; Proto-oncogene tyrosine-protein kinase Src, Src; receptor-regulated Smad 2 and 3, Smad2/3; rat sarcoma, Ras; mitogen-activated protein kinase kinase 1 and 2, MEK1/2; Extracellular signal-regulated kinase 1 and 2, ERK1/2.

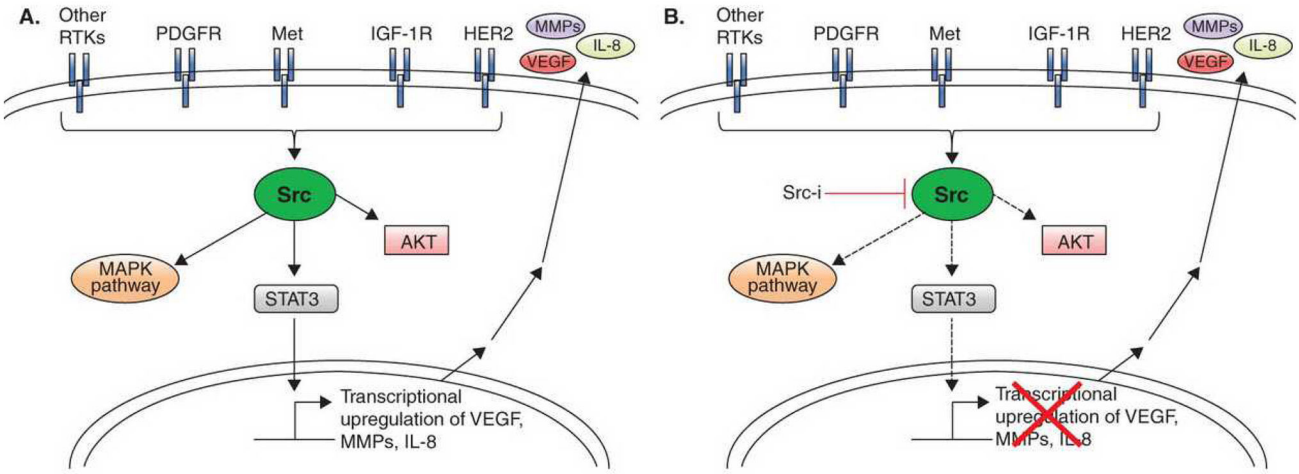

Figure 2.

Major pathways involved in canonical Src signaling in cancer. Panel A demonstrates basal inputs and downstream effectors of Src signaling. Inhibition of Src activity with Src inhibitors (Src-i) reduces downstream target activity and promotes increased sensitivity to cytotoxic therapy (panel B). Mitogen-activated protein kinase, MAPK; protein kinase B, AKT; signal transducer and activator of transcription 3, STAT3; platelet derived growth factor receptor, PDGFR; insulin-like growth factor 1 receptor, IGF-1R; human Epidermal Growth Factor Receptor 2, HER2; hepatocyte growth factor receptor, Met; interleukin 8, IL-8; matrix metalloproteinases, MMPs; vascular endothelial growth factor, VEGF; Proto-oncogene tyrosine-protein kinase Src, Src.

Table 1

Phase III clinical trials investigating the role of tyrosine kinase inhibitors in epithelial ovarian cancer. All trials are registered with the NIH clinical trials registry, ClinicalTrials.gov.

Compound	Compound Targets	Phase III Clinical Trial	Results	ClinTrial Identifier
AZD2171 (Cediranib)	**VEGFR1-3, PDGFRβ, c-kit**	Trial of Concurrent (With Platinum Based Chemotherapy) and Maintenance Cediranib in Women With Platinum Sensitive Relapsed Ovarian Cancer.	Not Reported	NCT00532194
BIBF-1120 (Nindetanib)	**VEGFR1-3 PDGFRα,β FGFR1-3**	BIBF 1120 in Combination With Carboplatin and Paclitaxel Compared to Placebo Plus Carboplatin and Paclitaxel in Patients With Advanced Ovarian Cancer.	Not Reported	NCT01015118
GW786034 (Pazopanib)	**VEGFR1-3 PDGFR-α/β FGFR1,3 c-kit**	**Pazopanib maintenance versus placebo for advanced EOC that has not progressed after first line platinum-taxane chemotherapy.**	**Abstract Reported**	**NCT00866697**
AZD0530 (Saracatinib)	Src family kinases	Saracatinib (AZD0530) Plus Weekly Paclitaxel in Platinum Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer	**Abstract Reported**	NCT01196741
OSI-774 (Erlotinib)	EGFR	Erlotinib vs. Observation After First Line Chemotherapy in Ovarian, Peritoneal, or Fallopian Tube Cancer.	Abstract Reported	NCT00263822