Molecular Therapy
Oncolytics
Review

Targeting receptor tyrosine kinases in ovarian cancer: Genomic dysregulation, clinical evaluation of inhibitors, and potential for combinatorial therapies

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Epithelial ovarian cancer (EOC) remains one of the leading causes of cancer-related deaths among women worldwide. Receptor tyrosine kinases (RTKs) have long been sought as therapeutic targets for EOC, as they are frequently hyperactivated in primary tumors and drive disease relapse, progression, and metastasis. More recently, these oncogenic drivers have been implicated in EOC response to poly(ADP-ribose) polymerase (PARP) inhibitors and epigenome-interfering agents. This evidence revives RTKs as promising targets for therapeutic intervention of EOC. This review summarizes recent studies on the role of RTKs in EOC malignancy and the use of their inhibitors for clinical treatment. Our focus is on the ERBB family, c-Met, and VEGFR, as they are linked to drug resistance and targetable using commercially available drugs. The importance of these RTKs and their inhibitors is highlighted by their impact on signal transduction and intratumoral heterogeneity in EOC and successful use as maintenance therapy in the clinic through suppression of the VEGF/VEGFR axis. Finally, the therapeutic potential of RTK inhibitors is discussed in the context of combinatorial targeting via co-inhibiting proliferative and anti-apoptotic pathways, epigenomic/transcriptional programs, and harnessing the efficacy of PARP inhibitors and programmed cell death 1/ligand 1 immune checkpoint therapies.

INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for more than 90% of human ovarian cancer cases and is one of the leading causes of cancer-related deaths among women worldwide.[1,2] In 2021, there were approximately 13,000 EOC-related deaths in the United States alone.[3] Alarmingly, the majority (70%) of these patients initially present with advanced disease and face 5-year survival rates as low as 50%. The mainstay of management of EOC involves surgical debulking combined with systemic platinum-/taxane-based chemotherapy in either a neoadjuvant or adjuvant setting.[4–6] Despite diverse targeted therapies aiming to cure EOC, 75% of women still experience a relapse or recurrence of the disease.[7,8] Hence, more effective therapies and treatment regimens are needed to improve patient survival and outcomes.

Conventional platinum- and taxane-based chemotherapies are known to disrupt EOC via impairing microtubule-mediated cell division and DNA synthesis/replication process, respectively. Poor patient response to such treatment regimens is increasingly linked to broad heterogeneity among EOC tumors in terms of oncogenic activation or dysregulation at cellular, genetic, and epigenetic levels.[3,9] To date, 75% of the EOC diagnosed in the clinic belong to the high-grade serous ovarian cancer (HGSOC) subtype. HGSOC is further stratified into four major subgroups: *proliferative*, *mesenchymal*, *immunoreactive*, and *differentiated*, which markedly differ in their cellular origin, morphology, and

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composition, as well as response to the current therapies.[1] There are also less common histological subtypes of EOC, including low-grade serous ovarian cancer, mucinous, clear cell, and endometroid.[1,9] Because of high intrinsic genomic instability, EOC tumors possess unusually high numbers of oncogenic mutations, as well as extensive rearrangements of chromosomal segments, causing gene deletion, amplification, and fusion.[9–14] In addition, a high degree of intratumoral heterogeneity in EOC tumors occurs at genetic and epigenetic levels.[15,16] These lines of dysregulation empower ovarian tumors to counteract traditional chemotherapies, and to fuel disease recurrence and shorter duration of patient survival.[10,17–19] Importantly, they also expose various vulnerabilities to diverse therapeutic targeting.

A variety of molecular targeting strategies have been pursued for EOC treatment, ranging from direct inhibition of the oncogenic pathways to co-targeting of molecular machinery involved in chromatin remodeling and repair of damaged DNA.[1,19–23] Of high promise to clinical application, however, is the disruption of oncogenic signaling of receptor tyrosine kinases (RTKs) and their downstream effectors, which are extensively dysregulated in nearly half of the HGSOC tumors, according to large-scale genomic analyses of patient biopsies.[11,19] Through elevated transcription or protein translation, RTKs become highly expressed on the surface of tumor cells. Upon ligand-based stimulation or overexpression they undergo clustering/aggregation and autophosphorylation to become activated and to allow the recruitment of diverse substrates and assembly of the multi-functional protein complexes. These changes, in turn, stimulate the pro-proliferative and/or anti-apoptotic pathways and expression of cell mitosis-related genes.[24] Meanwhile, they also lead to reprogramming of cell-cell and cell-extracellular matrix (ECM) adhesion toward epithelial-mesenchymal transition (EMT) phenotype, avoidance of programmed cell death, and immune surveillance.[24] Conceivably, ovarian carcinomas driven by various RTK oncogenes are targetable via their small-molecule inhibitors or function-blocking antibodies.[25]

To date, a number of RTK antagonists have been explored as potential monotherapy or part of the combination therapies for EOC.[26–30] Particularly, they have been evaluated through pairing with other treatment options, notably poly(ADP-ribose) polymerase (PARP) inhibitors used to treat a subgroup of EOC patients carrying genetically inherited mutations or low expression of the BRCA1/2 gene.[31–33] Extensive studies have found that ovary and other tissues/organs from these patients are highly dependent on the PARP-driven pathway for repairing damaged DNA, avoidance of senescence and apoptosis or death.[26,34] These findings prompt the development of contemporary PARP inhibitor-based therapy for such a group of EOC patients.[35–37] Intriguingly, when prolonged PARP inhibitor treatment is applied, some RTKs seem to become activated in a feedback manner.[38] Moreover, RTK targeting is viewed valuable to EOC treatment from the angle of harnessing the efficacy of immune checkpoint based or inhibitors of the epigenetic regulators such as azacytidine or bromodomain and extra-terminal (BET) inhibitors.[39–42]

With accumulating evidence on the impact of the ERBB family, a subgroup of druggable RTKs, on disease progression and drug resistance, this review concentrates on therapeutic evaluation of these RTKs and their antagonists for EOC. Given the growing promise of combinatorial therapy for EOC, we have discussed the scope and efficacy of ERBB inhibitors in the wake of co-targeting with various chemo- and targeted therapies such as PARP inhibitors and programmed cell death 1/ligand 1-based immune checkpoint therapies.

ONCOGENIC ACTIVATION AND SIGNAL TRANSDUCTION OF THE ERBBs

A glance at protein structure, enzymatic activity, and oncogenic activation

While many RTKs exist in the human kinome, members of the ERBB family are the most frequently dysregulated oncogenic drivers across human epithelial cancers, including EOC.[24,43–45] As the prototype of druggable RTKs, the ERBB family consists of four members: EGFR (ERBB1/HER1), ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4.[24] Structurally, members of the ERBB family are composed of an extracellular ligand-binding domain, a cell membrane-spanning region, and an intracellular tyrosine kinase domain (Figure 1). Within the family, only EGFR and ERBB4 become activated through their extracellular domain interaction with the ligands, such as epidermal growth factor, transforming growth factor α, amphiregulin, and heregulin.[46] All the family members, with the exception of ERBB3, possess enzymatic activities and are activated upon homodimerization/polymerization or heterodimerization with ERBB3 or the ligand-activated form of EGFR, ERBB4, or c-Met on the cell surface.[24] Thus, in human carcinomas, EGFR, ERBB2, and ERBB4 frequently become oncogenic once amplified, mutated, or overexpressed at the genomic or protein level, but rarely through structural alteration or gene fusion.[47]

Like most of RTKs, the pro-tumorigenic and pro-metastatic roles of ERBB receptors are achieved by eliciting arrays of downstream signaling cascades (Figure 1), highlighted by the activation of PI3K/Akt/mTOR and Ras/Raf/MEK/ERK pathways, PLC-γ1, STATs, and Src.[24] Aside from promotion of nutrient uptake and biosynthesis (e.g., glucose, amino acids, and nucleotides), these signaling cascades markedly upregulate expression of many pro-proliferative and pro-cell survival genes at the epigenetic, transcriptional, and post-transcriptional levels.[48–50] It is also worth noting that members of the ERBB family and c-Met impact tumor growth and progression via intricate crosstalk with other mediators such as inflammation- and integrin-dependent signaling or epigenetic machinery.[51–54] Inhibiting their signaling cascades leads to cell-cycle arrest, apoptosis, impaired tumor cell growth, and pro-invasive behavior.[30,51] ERBB receptors are also known as crucial players in tumor metastasis, as they promote EMT, tumor invasiveness, angiogenesis, and distant metastatic progression. [55]

There is evidence that RTKs become activated through a feedback loop in tumor cells after prolonged treatment with traditional chemotherapies or targeted therapies. Notably, several activated RTKs were detected upon sustained inhibition of the RAS/RAF/MEK pathway or transcription/epigenetic mediator BRD4, a member of the BET

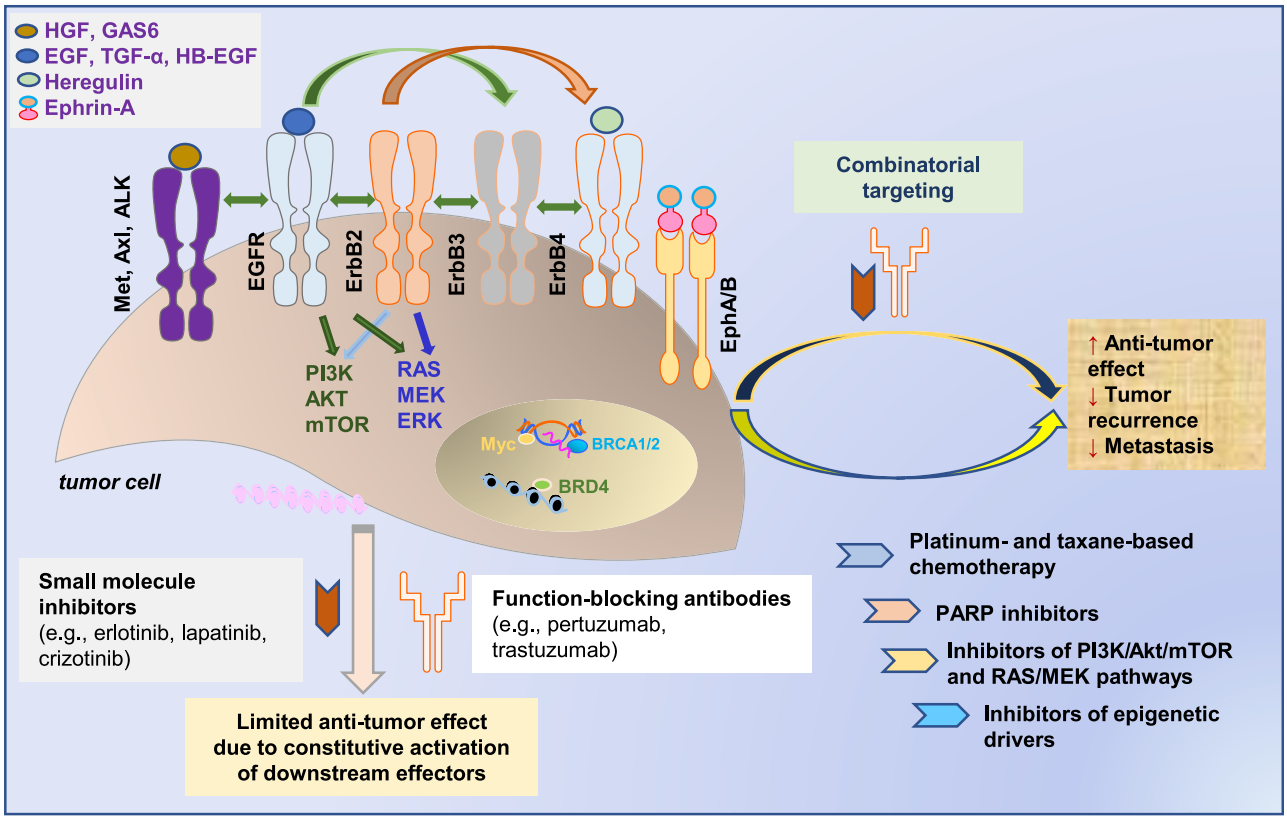

Figure 1. Schematic illustration of the signaling and functional roles of the major druggable RTKs in epithelial ovarian tumor cells

Physiological ligands and dimerization (homo- and hetero-), signaling pathways and cellular roles are highlighted for ERBB receptors and other RTKs. Ligands for some common RTKs are listed in the top left corner and include the following: EGF, epidermal growth factor; HB-EGF, heparin-binding EGF-like growth factor; HGF, hepatocyte growth factor; PARP, poly(ADP-ribose) polymerase inhibitors; TGF-α, transforming growth factor α.

family.[40,56] In line with this evidence, FAK, an integrin-linked non-RTK and a key downstream signaling effector of ERBB2 and other RTKs, modulates tumor cell responses to pharmacological inhibition of BRD4, according to our recent study.[23,52,57] In addition, RTKs may contribute to poor prognosis and drug resistance by promoting expression or activity of the drug transporters.[58,59] In these scenarios, RTK antagonists could serve as a second line of therapy for EOC patients after acquiring drug resistance.

Genomic dysregulation and signaling alteration of the druggable ERBBs in EOC tumors

Members of the ERBB family have been strongly implicated as key drivers of EOC malignancy (Figure 1).[24] Notably, EGFR is overexpressed in 30%–98% of EOC and is linked to poor clinical outcomes.[60,61] ERBB2 is overexpressed or amplified in about 20%–66% of the biopsies across multiple EOC patient cohorts.[62,63] The dysregulation of ERBB receptors and other RTKs in EOC is also readily detectable at the mRNA level (Figure 2), in contrast to the point mutations in their cytoplasmic domains of RNA splicing as seen in other cancer types (e.g., EGFR in glioblastoma).[51] Interestingly, the genomic and mRNA alterations seem mutually exclusive for c-MET and the ERBB receptors (Figure 2). Importantly, the altered gene copy number or expression of the ERBB family possesses diagnostic value. In particular, ERBB2 expression correlates with poor prognosis of EOC.[64] In addition, despite the lack of independent kinase activity, the ERBB3 gene is frequently amplified in EOC, and this alteration correlates with poor progression-free survival (PFS).[43,65,66] Exceptionally, ERBB4 forms a fusion gene with IKZF2 in some EOC tumors.[26]

Besides genomic alterations, the importance of the ERBB receptors in EOC is underscored by frequent activation of their downstream signaling intermediates (Figure 3). Notably, the PI3K/Akt/mTOR and Ras/Raf/MEK/ERK pathways, which are two common sets of pathways downstream of ERBB receptors, are constitutively activated in approximately 70% of ovarian tumors at rates second only to DNA repair pathways.[19] This dysregulated signaling is oncogenic and drives tumor cell proliferation, migration, survival, invasion, and chemotherapy resistance.[67,68] In addition, ERBB receptors are implicated in regulating DNA damage response and disease progression in EOC.[64] Collectively, in EOC tumors, members of the ERBB family undergo extensive genomic alterations or mutations, and their signaling pathways are markedly rewired or dysregulated, fueling their therapeutic utility.

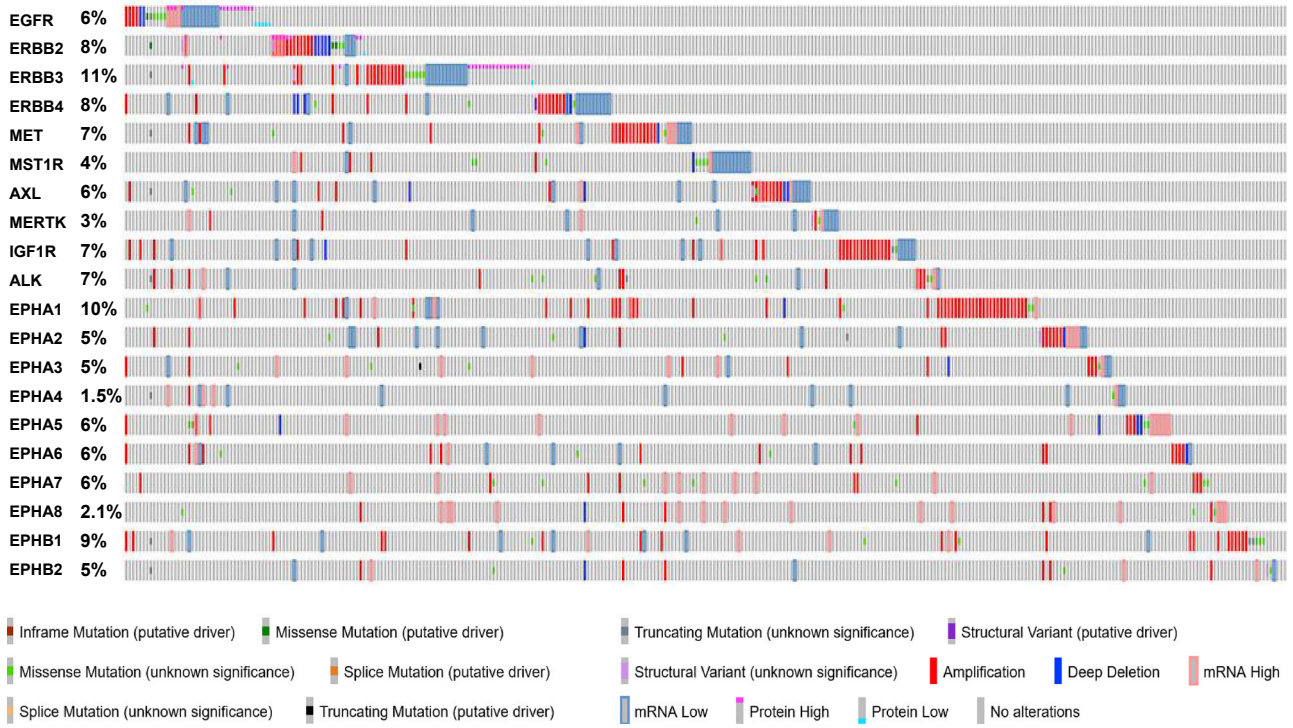

Figure 2. Profiling analysis of genomic and mRNA alterations of the ERBB receptors and other druggable receptor tyrosine kinases in patients with ovarian serous cystadenocarcinoma (TCGA, Pan Cancer Atlas; patients/samples: n = 585)

EGFR, ERBB2, and 26 other genes were profiled in terms of fusions, mutations, protein expression (*Z* scores [RPPA]), putative copy-number alterations from GISTIC, mRNA expression (relative to all samples, log RNA Seq V2 RSEM).

Other RTKs in EOC

Besides ERBB receptors, other RTKs, including c-Met, AXL, PDGFR, members of the EPH family, and VEGFR, are regarded as potential valuable targets for EOC treatment (Figure 2). These RTKs are activated in mechanisms similar to the ERBB receptors, presumably due to their structural similarity.[33,56,69,70] In particular, c-Met activation is implicated as part of a feedback loop under prolonged exposure to traditional chemotherapies or targeted therapies. In addition, there is a feedback-type activation of several druggable RTKs implicated during sustained inhibition of the RAS/RAF/MEK pathway or transcription/epigenetic modulators such as BRD4.[40,56]

CLINICAL EVALUATION OF THE ERBB ANTAGONISTS AS MONOTHERAPY

Thus far, a number of ERBB antagonists, including humanized monoclonal antibodies and small-molecule kinase inhibitors, have been tested as monotherapy for EOC (Table 1). Mechanistically, these agents act via two distinct modes: (1) interference of the extracellular ligand binding or receptor dimerization and (2) competitive inhibition of the ATP-binding capability of the kinase domain (Figure 1). In the first mode, monoclonal antibody drugs block the ligand binding of the ERBB receptors on the cell surface or facilitate receptor internalization and degradation to prevent clustering/aggregation-dependent oncogenic activation. In the second mode, small-molecule-based tyrosine kinase inhibitors (TKIs) directly impair autophosphorylation and kinase activities of the ERBB receptors. Upon treatment with these inhibitors, signal transduction of the ERBB oncogenes is blocked, leading to diminished protein translation and transcription for many critical genes involved in nutrient supply, cell proliferation, and survival.[60] Given the marked difference in their modes of action, the function-blocking antibodies and TKIs may exert divergent anti-tumor effects, making them attractive candidates for combinatorial targeting therapies.[36]

To date, many small-molecule inhibitors of ERBB2, EGFR, and MET have been clinically investigated for EOC, as these RTKs are frequently dysregulated in primary tumors according to analyses of the TCGA data (Figures 2 and 3) and other published patient cohorts.[61] Notably, erlotinib, a small-molecule inhibitor of EGFR, has been shown to inhibit growth of EOC cells and to modulate their sensitivity to cytotoxic agents such as carboplatin.[71] Lapatinib and poziotinib, two common inhibitors of ERBB2, have also been studied regarding their role in modulating EOC resistance to taxane-based regimens.[72,73] In a more recent preclinical study, afatinib, a third-generation small-molecule inhibitor of ERBB oncogenes, was found to have moderate efficacy against EOC.[74] Interestingly, these RTK inhibitors seem particularly effective against a subgroup of EOC cells overexpressing ERBB2 receptor.[75] Based on this evidence, clinical trials with several inhibitors of EGFR and ERBB2 have been carried out in EOC patients (Table 1).

Table 1. A selected list of the clinical trials with ERBB-targeted agents as monotherapy in ovarian/genitourinary cancers

Target	Intervention	Clinical setting	Trial ID	Phase	Enrollment
EGFR	gefitinib	recurrent or persistent ovarian epithelial cancer or primary peritoneal cancer	NCT00023699	II	30
	erlotinib	epithelial ovarian, primary peritoneal or fallopian tube cancer (high-risk stage I or stage II–IV) with responding or stable disease after first-line platinum-based chemotherapy	NCT00263822	III	835
	erlotinib	recurrent metastatic or unresectable non-small lung cancer, ovarian cancer, or squamous cell carcinoma of the head and neck	NCT00063895	I/II	80
	erlotinib	persistent or recurrent squamous cell carcinoma of the cervix	NCT00031993	II	51
	matuzumab	recurrent ovarian cancer following treatment for primary or secondary platinum-refractory disease with evidence of tumor EGFR (HER1) expression	NCT00073541	II	38
ERBB2	lapatinib	persistent or recurrent ovarian epithelial or peritoneal cancer	NCT00113373	II	28
		recurrent or persistent endometrial cancer	NCT00096447	II	31
	trastuzumab	recurrent or persistent endometrial cancer	NCT00006089	II	34

Again, afatinib was highly effective against patients carrying ERBB2 mutations.[76–78] Unexpectedly, lapatinib exhibited poor efficacy when used as a monotherapy in persistent or recurrent EOC.[79]

Besides small-molecule inhibitors, function-blocking monoclonal antibodies of EGFR and ERBB2 have been clinically tested in EOC (Table 1). These agents, including trastuzumab, pertuzumab, and matuzumab, inhibit activity of the ERBB receptors by interfering with their homo- or hetero-dimerization-mediated activation in tumor cells.[24,43] In line with the notion, ovarian tumor cells expressing high levels of ERBB2 proteins are sensitive to the effect of trastuzumab, the first generation of humanized ERBB2 monoclonal antibody, and to taxane-based agents.[80,81] Mechanistically, trastuzumab appears to exert a pro-apoptotic effect through inhibition of the PI3K/AKT axis.[82] Also, pertuzumab, a humanized monoclonal antibody that disrupts the heterodimerization between ERBB2 and other members of the ERBB family, is shown to suppress growth of ovarian cancer cells both *in vitro* and *in vivo*.[83,84] Furthermore, cetuximab, a monoclonal antibody against EGFR, was investigated as monotherapy for patients with primary peritoneal cancers or recurrent EOC.[85] Unfortunately, this agent exhibited poor efficacy among patients with recurrent EOC.

Overall, the initial findings from the above clinical studies suggest that ERBB inhibitors may provide limited efficacy in EOC. Nevertheless, these agents could have potential value for EOC treatment if suitable biomarkers are developed to stratify the EOC patient populations according to expression level or activity of ERBB receptors.

BIOMARKERS AND CLINICAL EVALUATION OF THE ERBB INHIBITORS AS PART OF COMBINATORIAL THERAPIES

Aside from being evaluated as monotherapy, a number of ERBB inhibitors have been clinically pursued for EOC treatment in conjunction with conventional chemotherapies or other targeting agents. Notably, multiple clinical trials have been performed to evaluate efficacy of TKIs of multiple ERBB members for EOC (Tables 1 and 2). Interestingly, one of these trials is the phase II study (NCT00436644) investigating the impact of the combination of lapatinib and topotecan in patient populations with platinum-refractory/-resistant peritoneal or ovarian carcinomas (Table 2). Unfortunately, the data from analysis of correlative markers did not show dramatic predicted benefit. In addition, disruption of the ERBB signaling with lapatinib appears insufficient to overcome topotecan resistance.

In conjunction with systemic chemotherapeutic agents

The most clinically relevant trials of the ERBB antagonists are investigations of both drug efficacy and biomarkers for erlotinib-based combinatorial therapies. One such trial (NCT0030446) is a phase II study of the combination of erlotinib plus carboplatin in patients with recurrent EOC (Table 2).[86] This drug combination appears effective for EOC patients with platinum-sensitive disease only. In a phase III trial (NCT00263822), an effort was made toward development of better biomarkers for analysis of erlotinib efficacy in a cohort of ovarian cancer patients who underwent first-line platinum-based treatment (Table 2).[87] The results from this trial showed that the PFS and overall survival (OS) of the EOC patients were strongly associated with copy number gain of EGFR gene, as the patients carrying amplified EGFR exhibited poorer OS than their counterparts.[87,88] This finding implies that delineating EGFR mutations alone may not be sufficient to foresee patient response to erlotinib treatment, nor do the gain-of-function mutations in EGFR-associated signaling cascades (e.g., KRAS, BRAF, NRAS, and PIK3CA). Furthermore, patient populations with at least one mutation in either KRAS, NRAS, BRAF, or PIK3CA exhibited longer PFS than those without any of these genetic mutations. Together, these trial results implicate an uphill challenge for

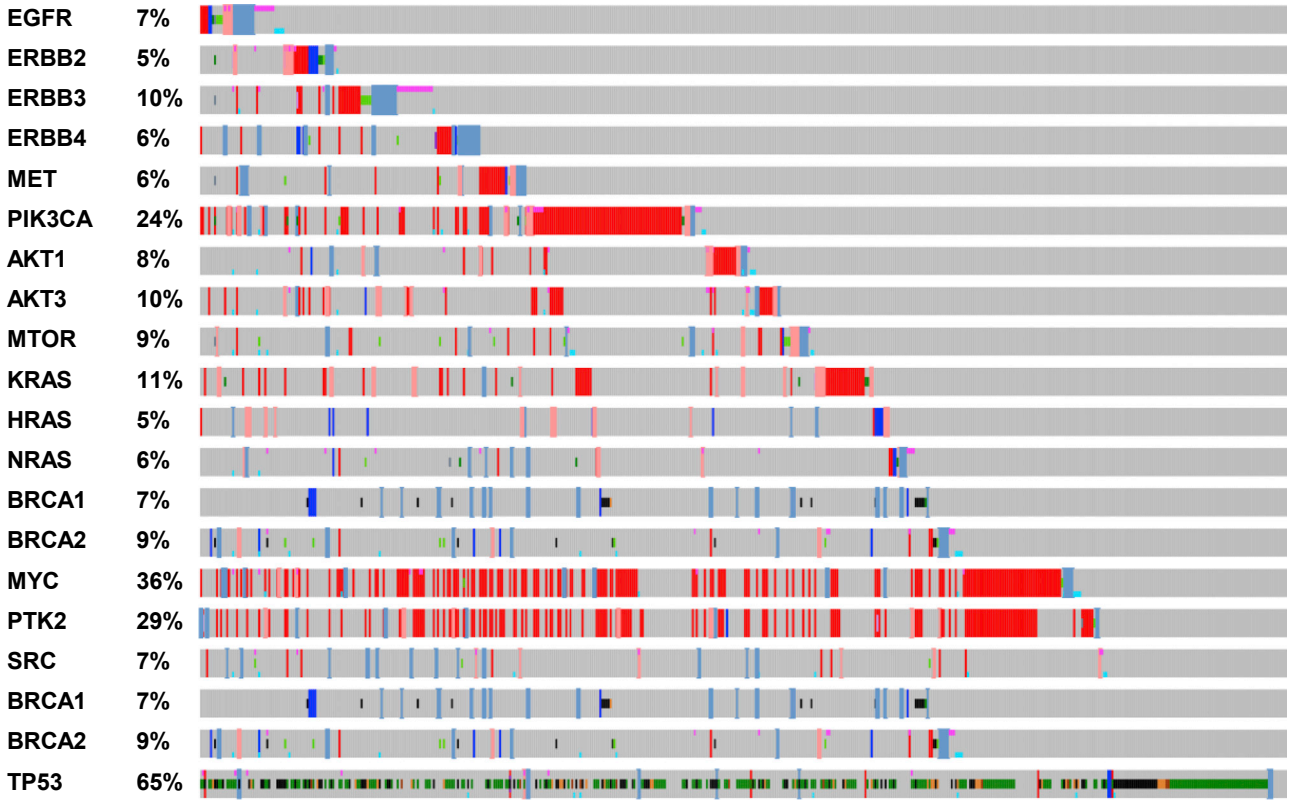

Figure 3. Profiling analysis of genomic and mRNA alterations of the druggable downstream effectors of the RTK-dependent signaling pathways in ovarian serous cystadenocarcinoma

The output was obtained through analysis of the TCGA cohort (Pan Cancer Atlas, patients/samples: n = 585) described in Figure 2.

pursuing clinical application of small-molecule inhibitors of ERBB receptors for EOC treatment, regardless of being used as monotherapy or in association with chemotherapies.[89]

Aside from small-molecule inhibitors, several RTK-blocking antibodies have been sought for EOC treatment in the context of combining with chemotherapies. Notably, in the PENELOPE trial (NCT01684878), adding pertuzumab did not significantly improve PFS in the patient cohort with platinum-resistant tumors and low expression of ERBB3.[43] The results from a subgroup analysis, however, revealed better efficacy of pertuzumab treatment in conjunction with gemcitabine and paclitaxel.[90] In addition, cetuximab was tested in combination with carboplatin for patients with recurrent ovarian cancer.[85] It was also tested in combination with paclitaxel/carboplatin for the patient population with advanced-stage peritoneal lesions or fallopian tube cancer.[91] Collectively, these trials indicate that cetuximab has some beneficial effect for patients with EGFR-positive and platinum-sensitive ovarian carcinomas.

Combination of chemical inhibitors and antibody blockers

The simultaneous administration of two inhibitors against the same ERBB target has also been explored for EOC treatment. This type of strategy is sometimes referred to as "dual blockade" as it disrupts oncogenic activity through simultaneous targeting of extracellular and intracellular domains of ERBB receptors. Notably, in one experimental study, the combination of afatinib and trastuzumab yielded an additive/synergistic effect on the ERBB2^{+} breast cancer cells.[92] Intriguingly, this effect appeared independent of tumor cell sensitivity to trastuzumab. Instead, afatinib appears to act on tumor cell resistance to trastuzumab by blocking the compensatory signaling pathway. Whether this phenomenon also occurs *in vivo* or in the clinical setting, however, remains elusive. One major concern is the high prevalence of constitutive activation of the PI3K/Akt pathway in EOC tumors due to PIK3CA mutation or PTEN loss or Akt amplification, as highlighted in the TCGA patient population (Figure 3). This is also consistent with a recent genomic study.[19] To some extent, knowing such genomic landscape may aid in foreseeing intrinsic resistance to the ERBB antagonist-based therapies in EOC patient population. It may also fuel the co-administration of PI3K or AKT inhibitors and trastuzumab as a new line of targeted therapy for EOC patients.[30,93]

TOWARD SYNTHETIC LETHAL TARGETING

In combination with PARP inhibitors

One of the most exciting advances in targeted therapy for EOC over the past decade is the clinical application of small-molecule

Table 2. A selected list of the clinical trials with combinations of ERBB-targeted agents and chemotherapy in ovarian/genitourinary cancers

Target	Intervention	Clinical setting	Trial ID	Phase	Enrollment
EGFR	gefitinib + tamoxifen	epithelial ovarian cancer, cancer of the fallopian tube or peritoneum refractory or resistant to platinum- and taxane-based chemotherapy	NCT00189358 (AGO-OVAR 2.6)	II	49
	topotecan then erlotinib	topotecan-treated epithelial and/or serous ovarian cancer	NCT01003938	II	6
	erlotinib with docetaxel/carboplatin followed by maintenance therapy of erlotinib	newly diagnosed stage III or IV epithelial ovarian, primary peritoneal cavity or fallopian tube cancer	NCT00217529	I/II	30
	carboplatin + erlotinib	recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer for which no standard curative therapy exists	NCT00030446	II	50
	paclitaxel/carboplatin + erlotinib	first-line treatment of stage III or IV ovarian, fallopian tube, or primary peritoneal cancer	NCT00059787	II	56
	cetuximab + carboplatin	recurrent, platinum-sensitive epithelial ovarian or primary peritoneal cancer	NCT00086892	II	29
ERBB2	lapatinib + topotecan	platinum-refractory/resistant epithelial ovarian or primary peritoneal cancer	NCT00436644	II	18
	paclitaxel + pertuzumab + topotecan paclitaxel + pertuzumab + placebo gemcitabine + paclitaxel + pertuzumab + topotecan gemcitabine + paclitaxel + placebo + topotecan	platinum-refractory/resistant epithelial ovarian, primary peritoneal, and/or fallopian tube cancer with low HER3 expression	NCT01684878 (PENELOPE)	III	208
	placebo comparator: placebo + gemcitabine active comparator: pertuzumab + gemcitabine	platinum-refractory/resistant ovarian, primary peritoneal, or fallopian tube carcinoma	NCT00096993	II	131
	experimental: chemotherapy (paclitaxel + gemcitabine + carboplatin) + pertuzumab active comparator: chemotherapy (paclitaxel + gemcitabine + carboplatin)	platinum-sensitive recurrent ovarian cancer	NCT02004093	II	149
ERBB3	experimental: seribantumab + paclitaxel active comparator: paclitaxel alone	platinum resistant/refractory advanced ovarian cancer	NCT01447706	II	233

inhibitors of PARP enzymes, which appears particularly effective in treatment of the patient population carrying functionally defective BRCA1/2 genes.[3,8] Thus far, several RTK inhibitors have been explored for treatment of metastatic EOC in conjunction with the PARP inhibitors. Neratinib, which irreversibly inhibits activities of multiple members of the ERBB family through disruption of autophosphorylation and signal transduction, has been approved for use in treatment of metastatic breast cancer.[94] This pan-ERBB inhibitor also seems capable of downregulating expression of ERBB1/2/4, c-MET, PDGFR, and mutant RAS proteins via the autophagic degradation route.[95] In a recent study, the combination of neratinib with niraparib, a PARP inhibitor, was found to have a synergistic effect in cisplatin-resistant or multi-drug-resistant ovarian cancer cells.[96] Mechanistically, this drug combination appears to induce the ATM-dependent activation of AMPK in tumor cells, which in turn alters signal transduction, autophagy induction and pro-tumorigenic roles of mTOR, ULK1, and ATG13.[97] There is an ongoing phase I trial (NCT04502602) to investigate optimal dosing for the combination of neratinib and niraparib in platinum-resistant ovarian cancer.

EGFR and Met have also been implicated in modulation of PARP inhibitor sensitivity.[32,98] Since multiple inhibitors of these RTKs are clinically used for treatment of non-EOC types and exhibit non-overlapping toxicities with the PARP inhibitors, combining these two classes of drugs may represent a line of rapid bench-to-bedside drug development for EOC. It is of particular attraction, since there are growing cases of clinical resistance to the PARP inhibitors in EOC patient populations.[99,100]

Co-inhibition with transcriptional and epigenetic mediators

Another hurdle in applying RTK inhibitors for EOC treatment is frequent activation of their downstream transcriptional and epigenetic mediators. Notably, a large portion of ovarian tumors exhibit Myc amplification.[23,101] This type of clinical malignancy seems vulnerable to the targeting of BRD4, a transcriptional and epigenetic mediator and a member of the bromodomain-containing protein family, based on our study and others.[22,23,102] Yet, sustained treatment with BRD4 inhibitor, JQ1, an investigational inhibitor interfering with the interaction between BRD4 and the transcription factor Myc and histone proteins, leads to an adaptive response of

Table 3. A glimpse of the clinical trials with dual blockade of the VEGF/VEGFR axis and the ERBB receptors in ovarian/genitourinary cancers

Targets	Intervention	Clinical setting	Trial ID	Phase	Enrollment
VEGF & EGFR	bevacizumab + erlotinib	advanced, refractory ovarian cancer	NCT00130520	II	40
	bevacizumab + erlotinib	recurrent or metastatic ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer	NCT00126542	II	35
	experimental: carboplatin + paclitaxel + bevacizumab then bevacizumab experimental: carboplatin + paclitaxel + bevacizumab then bevacizumab + erlotinib	first-line treatment of newly diagnosed advanced ovarian, fallopian tube, primary peritoneal cancer and papillary serous or clear cell Mullerian tumors	NCT00520013	II	60
VEGFR & ERBB2	experimental: combination arm (pazopanib plus lapatinib) active comparator: lapatinib monotherapy (lapatinib) active comparator: pazopanib monotherapy (pazopanib)	recurrent or persistent advanced metastatic cervical cancer	NCT00430781	II	228

several RTKs.[51] In addition, there is evidence that members of the BET family drive resistance to MEK inhibitors in ovarian cancer cells through activation of RTKs, notably ERBB3.[56] Hence, the concomitant targeting of the RTKs and epigenetic drivers may constitute another line of promising synthetic lethal therapy for EOC treatment.

FUNCTIONAL ROLES AND TARGETING OF THE NON-ERBB RTKs

VEGF/VEGFR-driven pathways and angiogenesis

Thus far, the most successful clinical targeting of the RTKs in EOC has been through the monoclonal antibody-based inhibition of the VEGF-VEGFR axis.[103] There is a growing consensus that tumor growth and dissemination are highly dependent on the formation of new blood vessels, a process called angiogenesis.[104] In human ovarian tumors, the VEGFR2 signaling pathway is highly activated.[55] This receptor drives angiogenesis in an autocrine fashion through physical interaction with its ligand, VEGF-A.[104,105] In EOC, tumor angiogenesis is highly prone to inhibition by the VEGF-neutralizing monoclonal antibody, bevacizumab (Table 3).[106] In addition, bevacizumab appears to have a growth-suppressive impact on EOC tumors.[25] This inhibitory effect seems markedly enhanced when co-administered with chemotherapy.[107,108] Intriguingly, such a drug offers a limited impact on patient survival duration.[42,103] Nonetheless, bevacizumab is now widely used together with olaparib, a PARP inhibitor, as maintenance therapy for women with tumors exhibiting the BRCA mutation or genomic instability and/or who have shown response to platinum-based chemotherapy.[109] In contrast, the use of bevacizumab in conjunction with the immune checkpoint inhibitors appears to have limited clinical benefit based on a recent study.[42]

c-MET and its inhibitors

Next to the ERBB family, c-Met has received the most attention regarding the clinical prognosis and therapeutic targeting in human cancers. This kinase is upregulated in 10% of the ovarian cancer cases in a previous study, as well as in our TGCA cohort (Figure 2), and it is strongly implicated in promotion of tumor progression and metastasis.[110,111] Recently, c-Met has been linked to tumor resistance to the PARP inhibitors.[100,112] This resistance can readily be overcome by combining the PARP inhibitor talazoparib with the multi-kinase inhibitor crizotinib.[32] Mechanistically, it may involve c-Met-mediated phosphorylation of the PARP1 proteins.[113] Meanwhile, the combined inhibition of c-Met and EGFR has been found to sensitize tumor cells response to alazoparib, a PARP inhibitor, in breast cancer.[32,33] Consistent with this evidence, the combination of EGFR and c-Met inhibitors exhibited additive or synergistic inhibitory effects on tumor growth and metastatic potential.[110,111] Conceivably, simultaneous targeting of c-Met and EGFR may provide an alternative strategy for sensitizing some EOC tumors to the PARP inhibitors.

Other RTK inhibitors

Another class of RTKs, the Eph family, has also been linked to EOC malignancy.[27] EPH kinases are activated upon interaction/binding with their ligands on the surface of the opposing stroma cells (Figure 1).[70] In the TCGA cohort, several members of the Eph family are upregulated (Figure 2), consistent with recent studies.[27,69] There is also evidence that some members of the Eph family are dysregulated at the protein level and correlate with patient survival.[27,69] To date, multiple inhibitors, including NVP-BHG712 and a class of xanthine-based chemical inhibitors, have been developed to target EPHB4 kinase in EOC.[114,115].

It is worth noting that additional RTKs, such as ALK and AXL, have been found to be active or overexpressed in EOC (Figure 1).[116,117] They are altered at the genomic level in 10% of EOC tumors (Figure 2). These RTKs appear to play a role in metastasis through regulation of the tumor microenvironment.[118] Recently, APG-2449, a promising inhibitor of ALK kinase, has been tested for EOC targeting in a preclinical model.[119] BGB324, a small-molecule inhibitor of AXL, has been shown to increase tumor sensitivity to paclitaxel and carboplatin in a PDX model-based EOC study.[120]

STRATEGIES FOR OVERCOMING CLINICAL RESISTANCE TO RTK TARGETING

Co-inhibition of RTKs and constitutively active PI3K/Akt-dependent pathways

It is increasingly clear that intrinsic or acquired resistance to ERBB2 or other RTK inhibitors across human cancer types is strongly tied to constitutive activation of their downstream effectors, particularly intermediates of the PI3K/AKT/mTOR pathway.[30,38] This concept is supported by our analysis of the TCGA cohort (Figures 2 and 3). One straightforward approach to overcoming such resistance to ERBB targeting is to combine inhibitors of both ERBB2 and PI3K/AKT or mTOR kinases for EOC treatment (Figures 1 and 3). Thus far, several inhibitors of the PI3K/AKT/mTOR pathway have been evaluated for EOC in combination with the ERBB antagonists.[30,121] Notably, in a recent randomized phase II trial, the combination of buparlisib, a pan-PI3K inhibitor, and trastuzumab plus paclitaxel is associated with a higher overall patient response rate as compared with the placebo arm.[122] Meanwhile, the efficacy of this combinatorial targeting may be boosted by co-targeting estrogen-dependent functions/pathways, as this hormone is elevated in >60% of ovarian cancer cases and is consistently implicated in onset and progression of ovarian cancer.[123,124] Conceivably, with the aid of ER-based stratification, $ER^+/ERBB2^+$ patient populations are likely more responsive to co-inhibition of ERBB2 and PI3K, and acquire the ability to overcome intrinsic resistance to the ERBB2 antagonists.

Co-inhibition of RTKs and constitutively activated RAS/MEK pathways

Another signaling pathway behind EOC resistance to ERBB targeting is the RAS/MAPK pathway (Figure 1). A number of intermediates of this oncogenic pathway have been found to be mutated and/or constitutively activated in EOC tumors, and are associated with resistance to traditional chemotherapies and rapid disease progression.[56,125] In addition, several RTKs were found activated in NF1-deficient ovarian tumor cells after prolonged MEK inhibitor treatment.[56] Hence, the combination of ERBB antagonists and inhibitors of the RAS-MEK pathway may represent another viable targeting option for EOC treatment.

Co-targeting of RTKs and pro-cell survival pathways

Co-inhibition of the anti-apoptotic pathways: ERBB oncogenes are also known to drive drug resistance in the clinic through activation of the anti-apoptotic pathways. This scenario is confounded by the evidence that many of the anti-apoptotic mediators, such as Bcl-2, a well-known anti-apoptotic factor, are actually dysregulated at the genomic level.[126] Hence, co-targeting of this pathway and ERBB receptors could improve efficacy of the RTK antagonists in EOC.

Co-targeting the integrin/FAK axis: another pro-survival pathway utilized by cancer cells is the integrin/FAK signaling axis. This axis has long been recognized to crosstalk with multiple ERBB receptors during tumor development and progression.[57] In addition, it is strongly activated in the ovarian tumor cells carrying TP53 mutations.[127] Conceivably, dual blockade of the ERBB- and integrin-dependent signal transduction may synergistically hinder tumor growth. Meanwhile, FAK, a key effector of integrin signaling, is extensively amplified with the Myc oncogene in many ovarian tumors.[22,23] Clinically, such genomic landscape may also represent a distinct class of EOC malignancy, as tumors with such genomic characteristics are highly refractory to traditional chemotherapies based on *in vitro* studies.[23,128] In addition, tumor cells carrying the FAK-associated 8q24 amplicon appear more susceptible to PARP inhibition.[26] In line with this notion, MRCKA has been shown to drive the activity of the integrin/FAK axis to impact EOC malignancy, presenting an alternative targeting strategy.[128] This finding and the data from an evaluation with a MEK inhibitor, are consistent with our recent study on co-targeting of FAK and Myc in EOC.[23,56] Overall, co-targeting of the ERBB oncogenes and the integrin/FAK axis may represent another potential therapeutic option for EOC.

Co-suppression of the inflammatory pathways: the activation of inflammatory pathways through the NF-κB-based signaling network is also implicated in tumor resistance to RTK inhibitors in ovarian cancer.[54] Recently, JAK2 has been shown to promote resistance to the RTK inhibitors in EOC cells.[54,129] The NF-κB-based network may also indirectly impact EOC resistance to RTK inhibitors through FAK-mediated recruitment of stromal cells, such as myeloid-derived suppressive cells.[130]

PERSPECTIVE ON THERAPEUTIC TARGETING OF THE RTKs

Owing to significant toxicities and rapid development of drug resistance to standard chemotherapy encountered during EOC treatment, recent research efforts have been directed toward development of individualized therapies. This endeavor is heightened by broad heterogeneity among EOC tumors. However, such a therapeutic strategy becomes increasingly achievable with powerful multi-omics technologies to rapidly profile key genetic alterations and activation of oncogenic pathways in the EOC patient biopsies. It will also provide rapid detection and quantification of dysregulated RTK signaling in tumor cells, mediators of resistance to the RTK inhibitors or state of re-activated RTKs, thereby fueling the RTK antagonists as a potential second or third line of therapy for EOC. In addition, the ERBB2-based antibody conjugates may represent another therapeutic option for EOC.[131–133] This class of ERBB2 drugs is particularly appealing, as they are target specific and possess a favorable toxicity profile.[134]

Decades of experimental and clinical studies have accumulated evidence that any single agent-based targeting is usually insufficient for eradication of EOC, as the disease is propelled by a wide range of oncogenic dysregulation and intrinsic resistance to traditional chemotherapies. This clinical challenge is further aggravated by acquired drug resistance through influx of cancer stem cells, evolving microenvironments, and expansion of intratumoral heterogeneity.[15,117,126,135–138] Despite such a complex landscape, EOC tumors sometimes appear particularly vulnerable to certain targeting. Notably, the BRCA1/2

mutated ovarian tumors are highly susceptible to inhibition of the PARP enzyme-dependent pathway, as such a pathway is essential for DNA repair and cell survival. As a result, PARP inhibitors provide a line of synthetic lethal targeting for EOC.[9,139] Based on recent advances in genomic understanding of EOC, such a strategy may be enhanced by adding RTK inhibitors in the wake of overcoming adaptive therapeutic resistance.[23] Finally, there is still promise for developing targeted therapies through combination of RTK antagonists and immune checkpoint inhibitors. This strategy may exert dual therapeutic impact on EOC, as some RTK-targeting agents simultaneously mediate antitumor activity of immune cells, including natural killer cells.[140]

CONCLUSIONS

In conclusion, the oncogenic ERBB members and other RTKs are frequently dysregulated in EOC at the genomic and expression levels. Their oncogenic signaling is strengthened by diverse genomic alterations or mutations of key intermediates of the PI3K/AKT and RAS/MAPK pathways during onset, growth, and progression of EOC. Some RTK signaling pathways are also revoked in the course of prolonged use of systemic and targeted therapeutic agents. As a result, the RTK inhibitors are well positioned as potential second- or third-line therapy for EOC treatment in the context of combinatorial targeting.

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AUTHOR CONTRIBUTIONS

Y. Wei, S.E., D.S., R.d.G., J.Q., J.S., and K.C. performed literature and database search and analyses, and wrote the manuscript. X.H.Y., F.U., B.B.Y., R.C., L.A.B., Y. Wu, T.O., B.Z., Y.Z., W.Z., and D.W. contributed to the development of the scientific concept, critical discussion on recent experimental studies, pharmacological analyses and clinical application of the RTK inhibitors, and their potential use for combinatorial targeting. These authors were all involved in the supervision of writing and editing of the manuscript. X.H.Y. and B.B.Y. are the lead contacts and coordinated the manuscript preparation and submission, and related scientific and clinical discussion.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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