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EGFR/HER-targeted therapeutics in ovarian cancer

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Abstract

Despite decades of research and evolving treatment modalities, survival among patients with epithelial ovarian cancer has improved only incrementally. During this same period, the development of biologically targeted therapeutics has improved survival for patients with diverse malignancies. Many of these new drugs target the human epidermal growth factor receptor (EGFR/HER/ErbB) family of tyrosine kinases, which play a major role in the etiology and progression of many carcinomas, including epithelial ovarian cancer. While several HER-targeted therapeutics are US FDA approved for the treatment of various malignancies, none have gained approval for the treatment of ovarian cancer. Here, we review the published literature on HER-targeted therapeutics for the treatment of ovarian cancer, including novel HER-targeted therapeutics in various stages of clinical development, as well as the challenges that have limited the use of these inhibitors in clinical settings.

Ovarian cancer is the most lethal gynecological malignancy in the USA. It is estimated that in the USA in 2012, 22,280 women will be diagnosed with **epithelial ovarian cancer** (EOC), and 15,500 women will die of the disease in 2012; by comparison, it is estimated that 47,130 women will be diagnosed with endometrial cancer in 2012, and 8010 women will die of the disease [1]. The high mortality rate associated with EOC is attributed to the intrinsically aggressive nature of the disease process and our limited ability to detect early-stage disease. In contrast to breast or cervical cancer, current imaging and available markers are inadequate for diagnosis and preclude population-based screening; unlike uterine cancer, the most common symptoms associated with EOC (e.g., bloating, abdominal pain and early

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Supplementary data

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satiety) are classically nonspecific and may portend advanced disease at the time of clinical presentation, precluding early evaluation based on common symptoms. This translates into a clinical reality that >70% of patients have the advanced-stage disease (e.g., spread beyond the pelvis, i.e., stage III or IV) at the time of initial diagnosis. The 5-year survival rate for patients with advanced EOC is only approximately 30%, while that of patients diagnosed with early disease (e.g., localized to the ovary or pelvis, stage I or II) may exceed 90%.

Significant advances have been made in EOC treatment over the past three decades, including the establishment of cytoreductive surgery and combination platinum- and taxane-based chemotherapy as standard of care for first-line management of advanced disease. However, debate continues in regards to the timing and extent of surgical resection compared with the timing and duration of chemotherapy in patients with advanced tumors (primary cytoreductive surgery vs three to six cycles of initial [i.e., 'neoadjuvant'] chemotherapy with interval debulking surgery), and there is no accepted regimen for management of recurrent, relapsed or refractory disease. The role of intraperitoneal chemotherapy continues to evolve and the utility of interval debulking surgery is still under discussion. We may be approaching the limits of our ability to optimize treatment of EOC using conventional chemotherapeutics. Improvements in EOC morbidity and mortality will likely occur with improvements in the early detection of this disease [2], as well as through the application of biologically targeted therapeutics.

While it was initially predicted that therapeutics targeting the HER/ErbB family of receptors would be effective for the treatment of EOC patients based on *in vitro* studies demonstrating a critical role for HER family members in ovarian cancer cell growth, as well as on the frequent expression of HER family members in ovarian tumors, these new drugs have not achieved target levels of efficacy in early stage clinical trials. While recent reviews have summarized recent studies on the use of biologically targeted inhibitors for the treatment of EOC, including EGFR inhibitors [3–5], the purpose of this report is to present a comprehensive overview of the potential of HER/ErbB-targeted therapeutics for the treatment of EOC, the challenges that have been encountered, and opportunities for overcoming these challenges. In this review, we discuss the current state of EOC treatment, focusing on chemotherapeutic intervention; the current repertoire of HER-targeted therapeutics; and the therapeutic potential of these drugs in EOC patients. Finally, we address the limitations of these early trials and present recommendations for future studies, including new strategies for the design of clinical trials to test this new family of **biologically targeted cancer therapeutics** for the treatment of EOC.

Overview of epithelial ovarian cancer treatment

Many women have asymptomatic pelvic masses that are detected during routine clinical care. While the majority of these masses will be benign, the limitations of available imaging and diagnostic techniques necessitate surgical resection for pathology confirmation of clinically suspected malignancy. For some patients diagnosed with early-stage EOC, optimal surgical debulking alone may be curative. However, a significant body of evidence suggests that even in patients with early-stage disease, histopathology suggestive of a high probability of recurrence (e.g., poor differentiation) and/or disease extending beyond the confinement of

the ovarian capsule (i.e., stage 1C or greater) should prompt consideration of adjuvant chemotherapy [6].

Unfortunately, most patients with EOC present with advanced (stage III or IV) disease, and the remainder of this review is focused on the treatment of these women. The standard management in patients with advanced EOC is cytoreductive surgery followed by cytotoxic chemotherapy to eradicate residual or micrometastatic disease. Multiple studies suggest that minimizing tumor burden confers better patient outcome than suboptimal tumor resection, regardless of subsequent chemotherapeutic treatment. The Gynecologic Oncology Group (GOG) defines optimal debulking as having 1 cm or less of identifiable, macroscopic disease at any site at the completion of surgical resection [7]. The standard initial cytotoxic regimen for management of advanced EOC is a platinum and taxane combination, with intraperitoneal administration gaining increased consideration in patients who are optimally debulked. A myriad of treatment regimens are employed in the management of patients who have significant residual disease after initial surgery and/or have recurrent disease.

Optimal management of recurrent EOC remains elusive. The role of interval cytoreductive surgery is currently under investigation through the GOG and the potential role of radiation therapy in patients with recurrent EOC is unclear. Systemic therapy is, therefore, the mainstay of treatment for these patients, and is largely dependent on the time to disease recurrence following initial platinum-based treatment. Treatment during this phase of the disease is typically administration of successive rounds of various chemotherapeutic agents, with increasing palliative intent, until a point at which unacceptable toxicity/impaired quality of life is reached or no further tumor response is elicited.

Patients with advanced disease have a response rate of 73–77% to first-line therapy with platinum and taxol, which is standard of care in this population. Even among responders, the median progression-free interval is 16–18 months and median survival is 35–38 months [6,8]. Further systemic treatment options for patients are selected based on tumor response to platinum. In addition to established chemotherapeutics, a new generation of biologically targeted therapeutics is being explored for the treatment of EOC. This review focuses on a new category of therapeutics that targets the **EGFR/HER** receptor family signaling axis.

HER family & ovarian cancer

The HER family of type I transmembrane receptor tyrosine kinases consists of four structurally related members: EGFR/ErbB1/HER-1, ErbB2/HER-2/neu, ErbB3/HER-3 and ErbB4/HER-4 [9]. HER proteins are structurally subdivided into an extracellular domain (ECD), a transmembrane domain and a cytoplasmic or intracellular domain containing an ATP-binding tyrosine kinase domain and a carboxy-terminal domain (Figure 1). The unliganded ECD exists in an ‘open’ conformation, capable of binding ligands specific for each HER family member [10]. Following ligand binding, the ECD adopts a ‘closed’, hetero- or homodimerization conformation. HER receptor dimerization induces transphosphorylation of carboxy-terminal sequences, which function as docking sites for a variety of adaptor proteins and substrates, including STAT-3, STAT-5, PI3K, Ras-GAP, phospholipases C γ , Grb2, Grb7, Grb10, Nck, Crk, Cbl, Abl, Shp1, Shp2, Eps8 and Eps15

[11–15]. HER family members can activate an overlapping but distinct repertoire of signaling pathways, resulting in both cell type- and tissue-specific signal transduction [16].

The prototypic ligand-dependent HER activation pathway applies to EGFR and HER4. Although recent reports suggest that membrane MUC4 can act as a ligand for HER2 [17–19], HER2 has no known soluble ligand, and is maintained in the closed, receptor-competent state. HER2, therefore, functions as a HER co-receptor and is the preferred heterodimerization partner of EGFR, HER3 and HER4 [20]. Conversely, HER3 has no intrinsic tyrosine kinase activity and, as a result, can only activate ligand-mediated signaling in the context of a HER heterodimer.

HER ligands are synthesized as transmembrane precursors that are proteolytically shed from the cell surface and can be classified by their HER binding patterns. EGF, TGF- α and amphiregulin bind specifically to EGFR. Betacellulin, heparin-binding EGF and epiregulin bind to both EGFR and HER4. Heregulin/neuregulin (HRG/NRG)-1 and HRG-2 bind both HER3 and HER4, while HRG-3 and HRG-4 bind only to HER4.

In addition to full-length transmembrane HER family members, each HER receptor has also been described as a soluble isoform, lacking the TMD and ICD. Soluble isoforms arise from either proteolytic processing of full-length HER holoreceptor or via alternate transcription events [21]. Alternate transcripts of the *EGFR*, *HER2*, and *HER3* genes incorporating alternate exons (i.e., splice variants) or intron sequences give rise to ‘soluble’ EGFR, HER2 and HER3 isoforms (sEGFR, sHER2 and sHER3, respectively). Proteolytic processing of HER2 and HER4 can also give rise to both soluble and truncated membrane-bound HER receptor isoforms [21]. Soluble HER isoforms impart another level of complexity to the regulation of HER signaling, and sEGFR/sHER expression has been shown to influence tyrosine kinase activity, cell cohesion/compaction, cell survival, proliferation, differentiation and migration [21–23].

In addition, two ECD-truncated membrane-associated HER isoforms (tHER) [21] have a role in the etiology of human malignancies. First, EGFRvIII, a constitutively kinase-active EGFR variant lacking 268 amino acids of the ECD, is frequently expressed in numerous cancers [24]. However, the role of EGFRvIII expression in EOC is controversial. While an early study reported that approximately 73% of ovarian cancers express EGFRvIII [25], subsequent studies have failed to detect EGFRvIII expression in malignant ovarian tumors [26–28]. Second, p95 tHER2 is a HER2 isoform lacking almost all of the ECD and, freed from ECD-mediated autoinhibition, is a constitutively active kinase; its expression is associated with poor prognosis and resistance to trastuzumab (Herceptin®; a monoclonal antibody that binds to an extracellular domain of HER2) in breast cancer patients [29,30]. Two distinct mechanisms that give rise to p95 tHER2 have been identified. Full-length HER2 can be proteolytically cleaved by a metalloprotease, releasing most of the ECD [31–33]. Other more recent studies have identified an alternate *HER2* transcript that incorporates an alternate transcription start codon and encodes a p95 tHER2 isoform lacking most of the ECD [34]. While the contribution of p95 tHER2 to the etiology of EOC is unclear, expression of p95 tHER2 has been identified in diverse EOC-derived cell lines [35,36].

HER family in normal ovaries

The HER family of receptors and their ligands control numerous cellular processes including growth, differentiation, adhesion, migration, and survival. As recently reviewed by our group [21], HER family members and their ligands display complex expression patterns in the normal human ovary. ‘HER expression’ as assessed by immunohistochemistry (IHC) is highly dependent on the choice of primary antibody, as studies using different HER-directed antibodies have yielded disparate results. Moreover, previous studies have not used methods that would allow isoform-specific HER expression patterns to be determined. Most studies have shown that EGFR and HER2 are expressed at moderate levels in the epithelium of the ovary, but at only low or undetectable levels in the ovarian stromal compartment. In the few studies that have examined localization of HER3 and HER4 in human ovary, HER3 was not detected in either the epithelium or stroma, and HER4 was expressed at only low levels in the epithelium and was not detected in stromal tissue.

While the role of the HER family in the biology and etiology of EOC has been extensively studied (see below), relatively little is known about the function of HER family members in normal ovaries. In one notable IHC study, EGFR expression increased during follicular maturation; high EGFR expression was initially noted in primary oocytes, followed by theca interna and granulosa cells, and finally in the corpora lutea during mid-luteal phase, after which time EGFR expression became undetectable [37]. In contrast, another study demonstrated strong HER3 expression in developing follicles and surrounding granulosa cells, but only weak HER3 expression in luteinized granulosa [38]. The observation that HER expression varies throughout the ovulatory cycle suggests an association between HER expression and steroid/gonadotropin hormone levels in the ovary. Indeed, an association between steroid/gonadotropin levels and ovarian HER receptor and/or ligand expression has been demonstrated *in vitro* and in animal models [21], and circulating HER receptor isoforms have also been correlated with steroid/gonadotropin hormone levels [39,40]. The mechanistic basis for these relationships has not yet been determined.

HER family in epithelial ovarian cancer

We have recently reviewed the expression of HER family members and their ligands in malignant ovarian tissue and derived cell lines [21], and salient results are briefly summarized here. EGFR expression ranges from 4–100% in malignant ovarian tissue as demonstrated by IHC, with an average expression frequency of approximately 48%. The utility of EGFR expression as an independent prognostic indicator in EOC patients is controversial, with multiple reports suggesting both that EGFR is [26,41–46] and is not [47–55] a reliable marker of survival or responsiveness to therapy.

HER2 is expressed in approximately 40% of EOC tumors as evaluated by IHC [21], and has been identified as a negative prognostic indicator in EOC [56]. Since this observation, multiple studies have reported contradictory results, regarding the utility of HER2 expression as an indicator of responsiveness to therapy and survival in EOC patients [49,51,53,57–83].

In one study, HER3 and HER4 expression was detected by IHC in approximately 48 and 71% of EOC tumors, respectively [20]; the expression of these two receptors in EOC has been examined in far fewer studies than EGFR and HER2. HER3 expression has been independently associated with overall survival in EOC [44,84,85], while HER4 expression has not been correlated with survival [86].

Despite the role of the HER family and its cognate ligands in the development and progression of EOC, there is significant controversy regarding the role of HER family members as prognostic indicators in EOC patients. The reasons underlying these discrepancies include a multitude of potential technical and methodological issues, including choice of antibody, the use of frozen versus paraffin-embedded sections, antigen retrieval methods, sample size, degree of observational concordance between pathologists in scoring labeled tumor cells and the potential confounding effects of disease stage, tumor grade and histology, patient age, race and treatment regimen, among others. Another potential confounding factor may be the co-expression of multiple immunoreactive isoforms of HER family members that are indistinguishable by IHC, including soluble and truncated HER isoforms (sHERs/tHERs). The prospective roles of these alternate HER isoforms in the pathophysiology of EOC, as well as their potential utility as diagnostic markers in EOC, have previously been reviewed [21,87,88].

HER-targeted therapeutics

Given the central role of HER oncogenic signaling in the development and progression of a number of human cancers, substantial resources have been focused on the development of HER-targeted inhibitors for cancer treatment. HER-targeted therapeutics can be divided into two main categories (Figure 1): small-molecule **tyrosine kinase inhibitors** (TKIs) and therapeutic antibodies (see Table 1 for a list of HER inhibitors reviewed). Other drugs that indirectly target HER pathways, such as geldanamycin (an inhibitor of the HER2-stabilizing chaperone HSP90), have recently been reviewed by others [89].

The 4-anilinoquinazolines and their derivatives comprise the largest class of HER-targeted low-molecular weight TKIs. The first such reported compound was PD153035, a 4-(3-bromoanilino)-6,7-dimethoxyquinazoline, which selectively inhibits EGFR via reversible, competitive binding to the ATP-binding domain of EGFR's tyrosine kinase domain [90]. Numerous anilinoquinazolines (including analogs with alkylated side chains for irreversible binding to the ATP pocket), as well as pyrimidines, triazines and triazols, are in various stages of development in clinical trials for the treatment of human malignancies.

HER-directed therapeutic antibodies can be divided into overlapping categories. The first class of antibodies inhibits HER ligand binding, and includes cetuximab and panitumumab (Figure 1). The second class includes antibodies that inhibit HER dimerization, such as matuzumab [91] and pertuzumab [92]. HER-targeted antibodies also may function by recruiting immune cells to induce antibody-dependent cell toxicity (e.g., trastuzumab [93–95], 2B1 [96,97] and cetuximab [98,99]) or by inducing HER internalization/degradation (e.g., trastuzumab [100–102] and cetuximab [103]).

Effect of HER inhibitors on epithelial ovarian cancer-derived cells *in vitro*

More than 100 reports have detailed the effects of HER inhibitors on a range of ovarian carcinoma-derived cell lines. In **Supplementary Table 1**, we summarize these studies and distinguish between a drug's ability to inhibit ligand-dependent versus ligand-independent cell growth. It is worth noting that growth inhibition in the absence of ligand may either reflect inhibition of endogenously produced growth factor signaling or may also highlight ligand-independent HER-mediated survival signaling in association with extracellular matrix components [104].

While the majority of reports on a given HER inhibitor in a particular cell line are consonant, a number of discrepancies also exist in the literature in terms of inhibitor efficacy and inhibition phenotype (**Supplementary Table 1**). Possible explanations for these discrepancies include differences in assay method, assay duration, drug batch/formulation and handling of HER inhibitor, as well as statistical methods used for data analysis. Other factors include cell line history and culture conditions; passage number of LNCaP prostate cells, for example, is inversely correlated with response to the anti-androgen bicalutamide [105], and trastuzumab growth inhibition of OVCAR-3 cells is dependent on concentration of culture serum [106].

HER-targeted therapeutics have been shown to interact with other compounds to influence EOC cell growth in an additive or synergistic manner (**Supplementary Table 1**). In addition to growth inhibition, EGFR inhibitors have been shown to alter migration and/or gene expression patterns in EOC cell lines. For example, PD153035 [107–110] inhibits the migration of CaOV3 cells, and gefitinib inhibits the migration of OVCAR3 and cisplatin-resistant A2780 cells [111,112]. Gefitinib inhibits the production of TGF- α , bFGF and VEGF in OVCAR-3 cell lines [113], while PKI-166 inhibits expression of the antiapoptotic protein c-FLIP_L in HEYA8 cells, as well as in SKOV-3 cells [114]. Trastuzumab can alter the phosphorylation pattern of a number of noncanonical proteins of the HER2 signaling axis in certain EOC-derived cell lines [115–117]. To date, however, the mechanistic basis for these myriad effects has not been fully characterized for the inhibitors described.

HER inhibitors for the treatment of epithelial ovarian cancer patients

Standard frontline treatment of EOC patients consists of platinum- and taxane-based combination chemotherapy, most often carboplatin and paclitaxel. Following initial remission, patients may receive maintenance therapy to extend progression-free survival (PFS). After varying cycles of disease relapse and remission, EOC typically becomes platinum-resistant or refractory, at which point salvage therapy is often employed. Clinical trials are continuing to evaluate the role of HER-targeted therapeutics during each stage of cancer treatment, including use as postsalvage monotherapy after even palliative therapy options have been exhausted.

When evaluating clinical trials that incorporate HER-targeted therapeutics into the management of EOC patients, we must assess them within the context of the associated treatment regimens and patient populations. Induction therapy for EOC typically has a very high response rate (73–76%) [6,8]; therefore, the addition of an HER-targeted therapeutic in

the context of a clinical trial must further improve this response rate to be considered clinically meaningful. In contrast, salvage and postsalvage therapies have rapidly diminishing response rates, and the addition of an HER-targeted therapeutic need not induce a response in the majority of patients to be considered successful. Some argue that stable disease (SD) in response to a postsalvage therapy should be considered encouraging; indeed, certain modified indices of therapeutic response include a clinical benefit algorithm consisting of complete response to treatment (CR), partial response to treatment (PR) and SD rates. Furthermore, trials of HER inhibitors do not uniformly select for patients whose tumor expresses the therapeutic target. As shown in **Supplementary Table 2**, only a minority of HER inhibitor trials for the treatment of EOC required tumor expression of EGFR or HER2 as an inclusion criterion. However, even when evaluated with these modified indices, few clinical trials of HER inhibitors for the treatment of ovarian cancer have provided clear evidence of superior efficacy when compared with use of established chemotherapeutic treatment regimens alone. The results of published trials are summarized in **Supplementary Table 2**. Below, we discuss instances where ovarian cancer patient treatment regimens incorporating HER inhibitors have provided promising, albeit modest, indications of improved efficacy, as well as considerations for the design of future trials using these inhibitors.

TKIs

Gefitinib (EGFR inhibitor)—Gefitinib plus chemotherapy has not proven superior to chemotherapy alone in any published study in terms of PFS and OS. However, several clinical trials of gefitinib monotherapy have shown modest efficacy. Baselga *et al.* reported the results of a Phase I trial of daily gefitinib (4-week cycles) for the treatment of advanced solid tumors, including EOC [118]. Of the 23 EOC patients enrolled in this study, one (4%) achieved SD lasting 36 weeks. In a similar Phase I trial of daily gefitinib (2 weeks treatment and 2 weeks off treatment per cycle) for the treatment of patients with advanced solid tumors, one of eight (13%) EOC patients achieved SD at 6 months [119]. In a Phase II trial of daily gefitinib (4-week cycles) for patients with advanced solid tumors judged to be EGFR positive (methods not presented), Vergote *et al.* reported that one of 33 (3%) patients achieved PR and nine out of 33 (27%) patients achieved SD at 2 months [120]. In a Phase II trial of daily gefitinib (4-week cycles) for the treatment of patients with persistent or recurrent EOC, three of 27 achieved SD (11%) at 6 months, and one achieved PR (4%) [121]. Interestingly, a mutation in the tyrosine kinase domain of EGFR, often observed in NSCLC, was observed in the one patient that achieved SD in this trial. In another Phase II trial of daily gefitinib (4-week cycles) for the treatment of refractory or recurrent EOC, nine of 24 (38%) of patients achieved SD at 2 months [122]. Taken together, these Phase I and II clinical trials suggest that a subset of EOC patients benefit from gefitinib monotherapy.

Erlotinib (EGFR inhibitor)—Blank *et al.* described a three-stratum, Phase II study of daily erlotinib in combination with paclitaxel and carboplatin (3-week cycles, up to six cycles) as frontline therapy for patients with stage III or IV EOC; efficacy was initially assessed at 8 weeks of treatment [123]. Patients in each stratum received erlotinib as follows: stratum I received therapy after optimal debulking surgery; stratum II received therapy after suboptimal debulking surgery; and stratum III received neoadjuvant therapy

prior to debulking. Among patients with optimally resected EOC, ten of 20 (50%) demonstrated a CR (PR data not provided) and, of patients with suboptimally resected disease, three of 21 (14%) had a CR. Among patients receiving neoadjuvant treatment, three of five (60%) achieved a CR, and one of five (20%) achieved SD. The addition of erlotinib to paclitaxel and carboplatin appears to be favorable for patients with optimally resected disease compared with paclitaxel and carboplatin treatment alone as frontline therapy (CR 28%, PR 31%) [124], but optimism must be tempered by the small number of patients enrolled in this trial and lack of randomization.

A Phase II trial of daily erlotinib and single agent carboplatin administered every 3 weeks among patients with recurrent EOC was described by Hirte *et al.* [125]. Among patients with platinum-resistant disease, 7% PR and 71% SD were achieved. However, among patients with platinum-sensitive disease, this regimen achieved 10% CR, 47% PR and 43% SD, which is comparable with the 11% CR, 24% PR and 39% SD achieved among EOC patients receiving single agent carboplatin every 3 weeks, as reported by Pfisterer *et al.* [126].

Finally, Gordon *et al.* described a Phase II study of daily erlotinib monotherapy (48 weeks or until disease progression or dose-limiting toxicity) for patients with advanced EOC. Erlotinib monotherapy resulted in PR and SD of 6 and 44%, respectively, at 8 weeks [127,128]. Perplexingly, the only patients who achieved PR in response to erlotinib monotherapy had EGFR-negative ovarian tumors as determined by IHC.

Lapatinib (EGFR/HER2 inhibitor)—Daily lapatinib in combination with weekly topotecan has been evaluated in two Phase II trials of patients with recurrent EOC. In the first study (4-week cycles, up to eight cycles), Joly *et al.* reported that among patients with platinum-sensitive disease versus platinum-resistant disease, this combination yielded a 11% PR and 50% SD, 0% PR and 37% SD, respectively [129]. Werooha *et al.*, in contrast, enrolled only patients with platinum-resistant or refractory disease (4-week cycles, daily lapatinib and weekly topotecan 3 weeks out of 4, up to 13 cycles); of 15 evaluable patients, one achieved PR (7%) and three achieved SD (20%) [130]. An ongoing Phase I/II clinical trial of daily lapatinib and weekly (3 weeks out of 4 per cycle) paclitaxel and carboplatin until disease progression in patients with relapsed stage III/IV EOC has shown 17% CR, 25% PR and 46% SD rates at 8 weeks [131,132].

Efficacy of lapatinib monotherapy for patients with persistent or recurrent EOC has been addressed in one Phase II trial. Garcia *et al.* reported an SD of 16%, with no objective responses [133].

Cancertinib (EGFR/HER2/HER4/EGFRvIII inhibitor)—In a Phase II trial of daily cancertinib monotherapy (21 of 28 days per cycle, up to 18 cycles) for patients with relapsed EOC, 0% CR, 0% PR and 30% SD were observed at 2 months [134]. No associations were observed between expression of HER family members and disease stability.

Vandetanib (EGFR/VEGFR2/ret inhibitor)—Annunziata *et al.* recently reported the results of a Phase II trial of daily vandetanib monotherapy (4-week cycles, up to 22 weeks) for patients with recurrent or refractory EOC [135]. Of the 12 enrolled patients, ten had

platinum-resistant disease. No responses were noted among these 12 patients but four patients (33%) did achieve SD at 16 weeks (one of two patients with platinum-sensitive EOC and three of ten patients with platinum-resistant disease).

Leflunomide (PDGFR/FGFR/EGFR inhibitor)—The PDGFR/FGFR/EGFR inhibitor leflunomide was tested as a weekly monotherapy for patients with advanced solid tumors in a Phase I study. In this study, one EOC patient achieved SD but the number of enrolled EOC patients was not specified [136].

In another Phase I/II trial of weekly leflunomide for patients with advanced EOC, NSCLC or prostate cancer, one of eight EOC patients (12.5%) achieved PR lasting 22 months or longer [137]. In a follow up Phase II study of weekly leflunomide therapy (up to 11 weeks) for patients with advanced EOC, one patient of 15 (7%) achieved PR at 6 weeks [138].

Therapeutic antibodies

Cetuximab (EGFR inhibitor)—Secord *et al.* reported the results of a Phase II trial of weekly cetuximab and carboplatin every 3 weeks (until disease progression or dose-limiting toxicity) for patients with relapsed, platinum-sensitive EOC [139]. This treatment regimen resulted in 12% CR, 23% PR and 31% SD, a modest improvement compared with the 6% CR and 25% PR response rate to singleagent carboplatin reported by Pfisterer *et al.* [140]. However, median PFS was 9.1 versus 5.8 between these trials. Interestingly, Secord *et al.* noted the lack of correlation between tumor EGFR expression and response to this treatment regimen; of particular note, both patients whose tumors were judged to be EGFR negative had a clinical response.

Schilder *et al.* reported the results of a Phase II trial of weekly cetuximab monotherapy (3-week cycles, up to 11 cycles) for the treatment of patients with persistent or recurrent EOC [141]. This patient population achieved a 0% CR, 4% PR and 36% SD.

Matuzumab (EGFR inhibitor)—Seiden *et al.* reported the results of a Phase II trial of weekly matuzumab monotherapy (eight up to 30 weeks) for the treatment of patients with platinum-resistant EOC [142]. Of the 23 patients who completed at least 8 weeks of treatment, 0% CR, 0% PR and 21% SD were observed.

Trastuzumab (HER2 inhibitor)—Ray-Coquard *et al.* reported the results of a Phase II study of paclitaxel, carboplatin and trastuzumab every 3 weeks (up to six cycles) for the treatment of patients with advanced EOC judged to be HER2-positive by IHC and/or fluorescence *in situ* hybridization [143]. In this small trial of seven patients, the CR rate was 43% and the SD rate was 29%. While little can be inferred from such a small treatment group, a 43% CR rate using a platinum-containing regimen for platinum-resistant disease is impressive compared with previous reports [144,145].

In contrast, Bookman *et al.* reported the results of a Phase II trial of weekly trastuzumab monotherapy (up to 53 weeks) for the treatment of patients with recurrent or refractory EOC judged to be HER2-positive by IHC [146]. Of the 41 subjects treated, a CR of 2%, PR of 5% and SD of 39% were reported. Recently, McAlpine *et al.* reported that one of three patients

with HER2-positive mucinous ovarian cancer experienced CR and another experienced PR following trastuzumab therapy with or without carboplatin [147]. Of note, none of the patients in the trial reported by Bookman *et al.* presented with mucinous EOC, so it was not possible to assess the effect of tumor histology on treatment response to trastuzumab in this study.

Pertuzumab (HER2 inhibitor)—Makhija *et al.* reported the results of a doubleblind, placebo-controlled Phase II trial of either gemcitabine plus placebo or gemcitabine plus pertuzumab (2 out of every 3 weeks until disease progression or dose-limiting toxicity) for the treatment of patients with platinum-resistant EOC [148]. Patients in the pertuzumab arm had an hazard ratio of 0.66 (0.43, 1.03; $p = 0.07$) for disease progression compared with the placebo control group when adjusted for Eastern Cooperative Oncology Group performance status, number of prior platinum-containing regimens, and measurable disease (by Response Evaluation Criteria in Solid Tumors criteria), and median PFS was 2.9 versus 2.6 months. Patients in the pertuzumab treatment arm experienced 14% PR, compared with 5 % PR in the placebo arm. Low tumor expression of HER3 (as determined by quantitative real-time polymerase chain reaction) was associated with improved PFS in patients treated with pertuzumab (HR: 0.32 [0.17, 0.59; $p = 0.0002$]). Among those patients in the lowest quartile of tumor HER3 expression, five of 13 patients demonstrated a clinical response to gemcitabine plus pertuzumab, while none of the 17 patients responded to gemcitabine plus placebo.

Similarly, Kaye *et al.* reported the findings of a Phase II trial for treatment of patients with platinum-sensitive EOC with pertuzumab plus carboplatin and, at the investigator's discretion, either paclitaxel or gemcitabine [149]. Patients were randomized to receive pertuzumab plus chemotherapy or chemotherapy alone. No differences in survival were observed between the four treatment arms. However, the authors did note an improvement in 6–12 month PFS in response to pertuzumab plus chemotherapy versus chemotherapy alone among patients with low tumor expression levels of HER3; however, this effect was not statistically significant (HR: 0.554; $p = 0.16$).

Agus *et al.* evaluated pertuzumab monotherapy every 3 weeks in a Phase I trial of patients with solid tumors, including three patients with EOC [150]. One of the three EOC patients achieved a PR and another achieved SD. Oddly, the tumor of the EOC patient with a PR did not overexpress HER2.

Gordon *et al.* described the results of a Phase II trial of pertuzumab every 3 weeks for the treatment of recurrent EOC [151]. A PR of 4%, SD of 7% for at least 6 months and SD of 6% for less than 6 months were observed. Assays for phosphorylated HER2 were performed in the 28 women in cohort 1 with fresh tumor biopsies. PR and SD rates of 4 and 7%, respectively, were achieved, respectively. Although the median PFS was longer for patients ($n = 8$) with HER2-positive tumors (20.9 weeks) versus those ($n = 20$) with HER2-negative tumors (5.8 weeks), this effect was not statistically significant ($p = 0.14$).

Summary & conclusion

In summary, a stark contrast exists between the *in vitro* evaluation of HER-targeted therapeutics and predicted clinical outcomes in EOC patients treated with HER-targeted therapeutics. One conclusion from these studies is that the stringency of cell line-based assays for predicting successful EOC treatment is insufficient for effective translation into the clinic. Several new animal models that mimic this disease have only recently been developed and have been underutilized in such preclinical drug studies. Moreover, most clinical trials using biologically targeted therapeutics have not optimally integrated potential predictive biomarkers and, critically, these drugs have largely been tested in heavily pretreated patients. One could argue that under these test conditions, finding responsive patients is not only unlikely, but may preclude the future testing of candidate drugs that may be highly effective in the treatment of this disease.

In spite of the serious limitations in previous studies, several HER-targeted therapeutics have shown promise in the frontline setting. As adaptive design and other emerging clinical trial strategies better suited to the testing of biologically targeted therapeutics are developed, optimal clinical trial design will increasingly be dependent on the discovery and development of positive predictive biomarkers for the effective stratification of patients for therapy. In this regard, analogous studies in both lung and breast cancer have resulted in the identification of significant subsets of patients who are responsive to EGFR/HER-targeted therapeutics [152,153]. Such patient selection strategies have been vital to the successful testing and approval of new treatment options for these patients, and serve as a useful paradigm for future studies in ovarian cancer. In general, greater investment in and emphasis on optimizing the testing of biologically targeted therapeutics for cancer patients is consonant with the notion that the next major advance in health care, in general, will be dependent on the advent of diagnostics-driven 'precision medicine' [154].

Future perspective

Despite decades of research and hundreds of clinical trials, late-stage EOC remains a largely intractable disease. While the introduction of biologically targeted therapeutics represents a true revolution in the treatment of some cancers, this revolution has not yet significantly impacted the treatment and survival outcome for ovarian cancer patients. Here, we speculate on the future role of HER inhibitors in the treatment and management of EOC.

Evaluating HER inhibitor efficacy in epithelial ovarian cancer patient populations

Since most biologically targeted therapeutics are tested in the context of heavily pretreated (and relapsed) patients, the clinical utility of HER-targeted therapeutics in patients with primary, previously untreated EOC has not been well studied. This shortcoming, in addition to the (relatively) low incidence of ovarian cancer, has 'left behind' this patient population in our increasing ability to more effectively treat patients with adult solid tumors with biologically targeted therapeutics. The apparent need for improvements in this area are illustrated by the high mortality rate for EOC patients, in spite of the relatively low incidence of this disease.

For example, because the efficacy of monoclonal antibodies relies, at least in part, on activation of an uncompromised host immune system [155], heavy pretreatment of EOC patients with multiple regimens of immunosuppressive chemotherapy may limit the clinical efficacy of mAbs in this study population. The importance of an uncompromised immune system to the success of testing biologically targeted therapeutics has been highlighted by others [156]. Moreover, combinations of biologically targeted therapeutics may offer the best treatment strategy, but such studies, to date, have been limited in the study of improved treatment methods for EOC. The interpretation of the effectiveness of previous HER-targeted clinical trials must take all of these considerations into account.

Many clinical studies of HER-targeted therapeutics have addressed chemoresistant disease in a salvage setting, where CR and PR are increasingly unrealistic goals and where SD (prolonged PFS) might reasonably be considered a success. In this setting, CR and PR are increasingly unrealistic goals, and one might reasonably consider SD (prolonged PFS) a success. As shown in **Supplementary Table 2**, SD in response to HER-targeted therapy is common in this context; however, one must also consider the financial burden and quality of life of such treatment strategies. Nonetheless, the development of such strategies for breast cancer patients over the past decade has resulted in a significant increase in the 10-year survival rate for this disease, shifting disease treatment for this disease site to a chronic disease management strategy.

In this regard, while numerous trials of HER inhibitors in EOC have failed to reach ‘target clinical efficacy,’ we question whether these goals, in retrospect, were realistic. As one illustration of this point, the ‘success’ of the recent spate of bevacizumab trials for EOC treatment remains controversial. For example, the recent GOG 218 Phase III trial of frontline paclitaxel/carboplatin versus paclitaxel/carboplatin/bevacizumab versus paclitaxel/carboplatin/bevacizumab plus bevacizumab maintenance reported PFS of 10.3, 11.2 and 14.1 months, respectively [157], and the improvement between paclitaxel/carboplatin versus paclitaxel/carboplatin/bevacizumab did not achieve statistical significance. On the other hand, Konner *et al.* reported good response rates for EOC patients treated with carboplatin, paclitaxel and cetuximab as frontline therapy [158]; in this study, PFS was 14.4 months, which compares favorably with the GOG 218 trial, though it must be stressed that this trial was not randomized. Erlotinib in combination with carboplatin and either paclitaxel [123] or docetaxel [159] appears as efficacious or slightly more so than chemotherapy alone and is well tolerated. Given that the difference in PFS of incorporating bevacizumab into frontline treatment in GOG 218 was a statistically insignificant 0.9 months, one could argue that HER-targeted inhibitors may be equally well justified for inclusion in frontline therapy trials. We propose here that HER inhibitors should be incorporated more often into trials of chemonaïve EOC patients, rather than judging the clinical utility of these candidate drugs solely in heavily pretreated patient populations.

Indeed, cautious optimism may be justified for continued trials of HER inhibitors for the treatment of EOC. HER inhibitors, in general, are well tolerated (a notable exception being the combination of erlotinib and bevacizumab [160]). While these Phase II trials have not reached target efficacy, objective responses have, nevertheless, been observed in previous EOC trials using these drugs. As noted above, interesting response rates and clinical benefit

were observed among patients treated with cytotoxic chemotherapy in concert with erlotinib, cetuximab, trastuzumab or pertuzumab. As described below, the challenge of effectively incorporating HER inhibitors into routine EOC treatment may depend on more reliable methods of predicting patient response to this new family of drugs.

Predicting responsiveness to HER-targeted therapeutics for epithelial ovarian cancer

ML Hensley, a GOG clinical oncologist, recently stated, “we will serve our patients best by designing trials that permit us to identify which patients have the highest likelihood of deriving a meaningful survival benefit from a novel agent” [161]. Despite the non-ideal setting for testing of most novel biologically targeted therapeutics, responders are regularly identified, even in the salvage setting, demonstrating that a significant subpopulation of ovarian cancers is dependent on EGFR/HER signaling. Given the enormous cost of clinical trials of novel therapeutics and the relatively small population of newly diagnosed ovarian cancer patients, it is imperative that we begin to use the results of previous correlative studies to identify prospective responders for biologically targeted therapeutics, as part of the study design. This concept is dramatically reinforced by statistical considerations regarding the early clinical trials on trastuzumab for the treatment of HER2-positive breast cancer; if no HER2 test had been available, and one assumed that HER2-negative patients had no benefit from treatment with trastuzumab, the sample size required for this study would have been 23,586 patients – 50-times more patients than were enrolled in this original trastuzumab study [162].

These early studies, as well as the past decade of research on other biologically targeted therapeutics, have taught us that it is unrealistic to expect any therapeutic to be a ‘magic bullet’ for all EOC patients. The true challenge in effectively translating these lessons into improved clinical practice will rely on the discovery and implementation of biomarkers capable of predicting response to novel HER-targeted therapeutics.

In this regard, the coupled dogmas that overexpression of a transforming oncogene is necessary for malignant transformation and, that levels of expression of a drugable target necessarily correlate with response, are rapidly eroding. While HER-targeted therapeutics have not been tested as extensively in ovarian cancer patients as they have been in other malignancies (i.e., non-small-cell lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer and breast cancer, each of which is associated with at least one FDA-approved HER-targeted therapeutic), clues regarding treatment efficacy can be inferred from clinical studies in each of these malignancies. For example, Paik *et al.* recently demonstrated that patients with breast tumors expressing even low levels of HER2 (by central reference laboratory standards) may gain benefit from trastuzumab therapy [163]. Others have shown that responsiveness to cetuximab among CRC patients is negatively correlated with *KRAS* and *BRAF*, rather than being a direct function of ‘EGFR expression.’ In fact, in most of these malignancies, EGFR/HER receptor expression levels, at least as currently measured, are not reliable as positive predictive markers of response [164–167].

Our group, therefore, initiated a meta-analysis aimed at correlating expression of HER expression in ovarian carcinoma-derived cell lines with response to HER-targeted therapeutics. Expression of HER family members [21] was classified as low, medium or

high, and correlated with response (yes or no) to inhibitor as presented in **Supplementary Table 1**. As presented in Table 2 & **Supplementary Table 3**, we observed no statistically significant association between HER expression and responsiveness to any HER inhibitor. While conditional analyses suggest a possible association between high expression of HER2 and response to HER2-directed TKIs, similar associations were not noted between expression of EGFR and EGFR-directed TKIs or EGFR-directed antibodies, or between HER2 and HER2-directed antibodies. This observation is consonant with our observations, and those of others, demonstrating that HER expression does not, in general, predict ovarian cancer cell responsiveness to any HER-directed inhibitors, as discussed in greater detail below.

The lack of correlation between HER expression and drug responsiveness *in vitro* is perhaps counterintuitive and may be attributable to many factors. Technical factors include the broad range of methods (radioimmunoassay, immunoblot, ELISA, IHC, immunofluorescence and flow-assisted cell sorting) used to detect expression and/or activity of HER family members, including choice of antibodies and their related epitopes, methods of antigen retrieval and diverse methods of measuring cell proliferation, apoptosis, xenograft tumor growth, activation of receptor and downstream effectors. Clearly, there is no standardized method for HER detection or for measuring responsiveness to these inhibitors. Despite the lack of standardization for HER expression and/or related HER inhibitor assays, one must also consider the possibility that a lack of association between HER expression and response to inhibitor may be related to potential ‘offtarget’ mechanisms of activity, and/or complex facets of ovarian cancer cell biology; that is, does expression of an HER family member necessarily imply critical oncogenic function? Using a systems biology approach, Friedman and Perrimon describe cell signaling components as gradient of interconnected hubs, and observed that blockade of one signaling pathway may be overcome by compensatory signaling [168]. Alternatively, recent studies have demonstrated that HER-targeted therapeutics may cause subtle changes in a cell’s phenotype without directly inhibiting cell growth in a variety of carcinoma-derived cell lines (including ovarian), including the induction of *de novo* sensitivity to other HER-targeted therapeutics [117,169,170]. In this review, we have noted the frequent lack of correlation between HER expression in malignant ovarian tumors (by IHC) and responsiveness to various HER-targeted therapeutics. For example, low objective response rates were observed in EOC patients with EGFR-positive tumors treated with matuzumab [142] or gefitinib [120] monotherapy, or HER2-positive tumors treated with trastuzumab monotherapy [146]. Furthermore, no correlation between EGFR expression and responsiveness to gefitinib plus carboplatin and paclitaxel chemotherapy was observed in patients with recurrent EOC by Pautier *et al.* [171–173], and no correlation between HER expression and responsiveness to cancertinib monotherapy was observed Campos *et al.* [134].

Identifying target pathways & tissues of HER inhibitors

Might the lack of association between HER expression and therapeutic responsiveness be explained in terms of function, rather than stoichiometry? In addition to the recent unexpected and controversial biomarker developments regarding EGFR in CRC [174,175], there is an interesting report by Matulonis and colleagues demonstrating that tumor HER3

expression, and not HER2 expression, is associated with responsiveness to pertuzumab in patients with EOC [148]. In this regard, it is possible that noncanonical signaling functions of HER family members may influence responsiveness to therapy. HER signaling is not only regulated by association with other tyrosine kinases (e.g., Met, IGFR-I) [176,177], but also by interactions with various signaling adaptors (e.g., paxillin) and ECM/integrin interactions [178–180]; as such, HER proteins may signal independently of ligand, acting as a noncanonical transducer of signals by other kinases/cell-surface proteins. Finally, steady drug access to HER members can be influenced by steric associations between HERs and other proteins (e.g., integrins) and/or by perturbations in HER internalization kinetics [181], as shown by the recent finding that ligand-independent EGFR internalization is mediated via PKA/phosphatidic acid signaling [182]. The applicability of these noncanonical functions and/or regulators of HER family members in EOC remain understudied and, as such, represent a rich venue for future investigation.

In this regard, studies on the detailed mechanism of action of these drugs in the context of other potential biological targets for the treatment of EOC, such as BRCA1 or BRCA2, are limited. For example, the observation that *BRCA1* mutations have been correlated with reduced HER2 expression in breast cancer suggests these two signaling pathways share important convergence points that have not yet been identified [183]. The obvious potential for combined therapy using multiple biologically targeted therapeutics, as this field evolves, will require a better understanding of such convergence points in cancers such as breast and ovarian cancer.

Regardless of whether canonical or noncanonical HER signaling pathways are considered, recent controversies regarding the origin of EOC also lead us to question the utility and reliability of existing models of EOC. Recent evidence suggests that aggressive, high-grade EOC arises, at least in part, from secretory cells of the fallopian tube [184,185]. Drapkin *et al.* have shown that a series of simple genetic manipulations of human primary cultures of fallopian tube secretory epithelial cells (including knockdown of p53 and protein phosphatase 2A, and induced expression of hTERT, myc and constitutively active CDK4) results in a phenotype that recapitulates high grade EOC *in vitro* and also in xenograft models [186]. This provocative finding argues in favor of testing fallopian tube-derived models of EOC [187] during the preclinical testing phase of candidate drugs for the treatment of ovarian cancer. While a handful of reports have evaluated the expression of HER family members and ligands in human fallopian tube (including menstrual cycle-dependent expression) [188–195], and provide an excellent foundation for future studies, renewed interest in the fallopian tube model for the origin of EOC will undoubtedly spark new investigations regarding the role of the HER family in the biology and pathobiology of the fallopian epithelium. Whatever the anatomical origin of EOC, few studies on the role of HER family members in EOC have considered how HER receptor signaling in non-malignant cells/tissues (e.g., stromal, vascular, immune and stem) may also mediate clinically beneficial and/or synergistic effects of combination therapies; for example, by regulating the epithelial–mesenchymal transition of EOC cells, by stabilizing tumor microvasculature, by enhancing antitumor immunity and/or by sensitizing ovarian cancer stem cells.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Terms

Epithelial ovarian cancer	Most lethal form of gynecologic malignancy. Epithelial ovarian cancer is characterized by exquisite sensitivity and responsiveness to cytotoxic chemotherapy, typically followed by relapse with aggressive, chemoresistant disease. Newer models of highgrade serous ovarian carcinoma, the most common subtype of malignant epithelial ovarian cancer, may arise, at least in part, from secretory epithelial cells in the fallopian tube
Biologically targeted cancer therapeutics	Certain gene products, such as EGFR/HER, play a pivotal role in driving the growth and metastasis of cancer cells. Rational targeting of these key cancer cell growth pathways using protein-based ‘biologic’ therapeutics, such as antibodies, and small-molecule inhibitors, such as tyrosine kinase inhibitors, represent the vanguard of cancer therapy, and are in various stages of clinical development/practice
EGFR/HER	Prototypic receptor tyrosine kinase family, consisting of four distinct cell surface receptors: the epidermal growth factor receptor (EGFR)/HER1, HER2, HER3 and HER4. All four members of the HER family are oncogenic <i>in vitro</i> and <i>in vivo</i> , and are frequently overexpressed and/or mutated in diverse solid tumors, where they play a critical role in both the etiology and progression of these malignancies
Tyrosine kinase inhibitor	Small molecule that reversibly or irreversibly binds within the ATP-binding pocket of a tyrosine kinase (e.g., EGFR/HER family members), reducing kinase activity

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Executive summary

Background

- Most women diagnosed with epithelial ovarian cancer (EOC) present with late-stage disease.
- Advanced EOC is highly sensitive to traditional chemotherapy, but typically recurs as an aggressive, chemotherapy-resistant disease.
- Epithelial ovarian cancers frequently express HER tyrosine kinases that are druggable with novel HER-targeted therapeutics.

Overview of epithelial ovarian cancer treatment

- Contemporary EOC patient management consists of debulking surgery and platinum-plus-taxol chemotherapy.
- Most EOC patients respond to first-line chemotherapy.
- Successive cycles of disease relapse may necessitate second- or third-line chemotherapy.

HER family & ovarian cancer

- The HER family of receptor tyrosine kinases plays a crucial role in ovarian development and also in normal ovarian tissue homeostasis.
- Aberrant HER expression and activation are common in ovarian cancer.
- Lack of standardized measurement of HER family members and their transcripts confound studies associating HER expression and disease characteristics.

HER-targeted therapeutics

- Numerous HER-directed therapeutics, including reversible tyrosine kinase inhibitors, irreversible tyrosine kinase inhibitors and therapeutic antibodies, are in various stages of development for clinical use.

Effect of HER inhibitors on epithelial ovarian cancer-derived cells in vitro

- HER-targeted therapeutics inhibit numerous malignant processes *in vitro*, including cell proliferation, survival, anchorage-independence and activation of mitogenic and survival signaling pathways.
- Lack of congruence between apparent HER expression levels and response to novel therapeutics may depend on: the mechanism of drug action; compensatory activity of other signal pathways; and reliability of 'HER expression' testing methods, among others.

HER inhibitors for the treatment of epithelial ovarian cancer patients

- Clinical trials of HER-targeted therapeutics for the treatment of ovarian cancer over the past decade have yielded only modest results to date.

- Lack of randomization, especially in frontline trials in combination with platinum and taxane chemotherapy, make it difficult to assess the clinical utility of HER-targeted therapeutics for the treatment of ovarian cancer.

Future perspective

- A meta-analysis suggests no association between HER expression in ovarian carcinoma-derived cells and responsiveness to HER-directed therapeutics.
- Some ovarian cancer patients respond to HER-targeted therapeutics; these observations suggest that future studies targeting this receptor family remain a viable option for more effective treatment of a significant subpopulation of ovarian cancer patients.
- Improved methods for identification of this subpopulation will be required for optimal testing of these new candidate drugs.
- Information regarding the complexities of HER receptor signaling, as well as the limitations of current methods for assessing HER expression, has not been optimally integrated into clinical trial design strategies for the testing of HER-targeted drugs.
- Use of new *in vitro* and *in vivo* (animal) models of epithelial ovarian cancer may improve methods of selection for patients potentially responsive to HER-targeted therapeutics.

Figure 1. Design of HER-directed therapeutics

HER family members consist of an extracellular domain (divided into subdomains I–IV, with subdomains I and III regulating ligand binding), a transmembrane domain and an intracellular domain containing an ATP-binding tyrosine kinase domain. Ligand binding induces HER dimerization and transphosphorylation of intracellular domains, initiating signal cascades. Therapeutic antibodies, directed against HER extracellular domains, inhibit ligand binding and/or receptor dimerization, deliver toxic conjugates, and/or recruit immune cells. Small-molecule HER inhibitors reversibly or irreversibly inhibit HER tyrosine kinase activity. Each therapeutic antibody or small-molecule inhibitor shown has been tested *in vitro*, *in vivo* or in clinical studies of epithelial ovarian cancer. Cartoon structures of HER family members are not drawn to scale and not based on reported crystal structures.

Table 1

HER-targeted therapeutics used for *in vitro* studies or in epithelial ovarian cancer clinical trials.

Compound	Manufacturer	Type	Target	Development status	
				EOC	Any cancer
PD153035	Parke Davis/Pfizer	Reversible AQ	EGFR	Preclinical	Imaging
Gefitinib (ZD 1839, Iressa)	Astra Zeneca	Reversible AQ	EGFR	Phase II	US FDA-approved (NSCLC)
Erlotinib (OSI-774, Tarceva)	OSI/Genentech/Roche	Reversible AQ	EGFR	Phase II	FDA-approved (NSCLC, pancreatic cancer)
Pelitinib (EKB-569)	Wyeth	Irreversible AQ	EGFR	Preclinical	Phase II
CP-724,714	OSI/Pfizer	Reversible AQ	HER2	Preclinical	Phase II
ARRY-380	Array Biopharma	Reversible AQ	HER2	Preclinical	Phase I
Mubritinib (TAK-165)	Takeda	Irreversible TRZ	HER2	Phase I	Phase I
Lapatinib (Tykerb)	GlaxoSmithKline	Reversible TAQ	EGFR/HER2	Phase I/II	FDA approved (breast)
Varlitinib (ARRY 543)	Array Biopharma	Reversible AQ	EGFR/HER2	Phase I	Phase I/II
Neratinib (HKL-272)	Wyeth	Irreversible AQ	EGFR/HER2	Phase I	Phase III
HKL-357	Wyeth	Irreversible AQ	EGFR/HER2	Preclinical	Phase I
Afatinib (BIBW 2992, Tovok)	Boehringer Ingelheim	Irreversible AQ	EGFR/HER2	Phase I	Phase III
PKI-166	Novartis	Reversible PP	EGFR/HER2	Phase I	Phase I
PD158780	Parke Davis/Pfizer	Reversible PZ	EGFR/HER2/HER4	Preclinical	NR
AC480 (BMS-599,626)	Bristol-Myers Squibb	Reversible PT	EGFR/HER2/HER4	Preclinical	Phase I
Canceritinib (CI-1033, PD-183085)	Parke Davis/Pfizer	Irreversible AQ	EGFR/HER2/HER4/EGFRvIII	Phase II	Phase II
Dacomitinib (PF-00299804)	Pfizer	Irreversible AQ	EGFR/HER2/HER4	Phase I	Phase III
XL-647	Exelixis	Reversible AQ	EGFR/HER2/HER4/VEGFR2/Eph4	Phase I	Phase III
AEE 788	Novartis	Reversible PP	EGFR/HER2/VEGFR/EGFRvIII	Preclinical	Phase II
Vandetanib (ZD-6474, Zactima)	Astra Zeneca	Reversible AQ	EGFR/VEGFR2/ret	Phase I	Phase IV
Leflunomide (Arava)	Sugen	Reversible FCA	EGFR/FGFR/PDGFR	Phase II	Phase III
Cetuximab (225, Erbitux)	ImClone/Bristol-Myers Squibb	Humanized IgG1	EGFR	Phase II	FDA-approved (CRC and head and neck cancer)
Panitumumab (ABX-EGF, Vectibix)	Amgen	Human IgG2	EGFR	Phase I	FDA-approved (CRC)
ICR-62	Rat IgG2b		EGFR	Preclinical	Phase I

Compound	Manufacturer	Type	Target	Development status	
				EOC	Any cancer
Nimotuzumab (hR3, TheraCim)	YM Biosciences	Humanized IgG2	a EGFR	Phase I	Phase III
Necitumumab (IMC-11F8)	ImClone	Human IgG1	EGFR	Phase I	Phase III
Matuzumab (EMD-72000)	EMD Chemicals	Humanized IgG2	EGFR	Phase II	Phase II
scFv(FRPS)-ETA	NA	Single-chain fusion	HER2	Preclinical	Phase I
Trastuzumab (4D5, Herceptin)	Genentech	Humanized IgG1	HER2	Phase II	FDA-approved (breast cancer)
Pertuzumab (2C4, Omnitarg)	Genentech	Humanized IgG1	HER2	Phase II	Phase III
MDX-447	Medarex	Crosslinked F(ab) hybrid	EGFR and Fc γ R1	Phase I	Phase I
2B1	Chiron	Murine quadroma	HER2 & Fc γ RIII	Phase I	Phase II
MDX-210	Medarex	Crosslinked F(ab) hybrid	HER2 & Fc γ R1	Phase I	Phase I
MDX-H210	Medarex	Humanized crosslinked F(ab) hybrid	HER2 & Fc γ R1	Phase I	Phase I
MM-121	Merrimack Pharmaceuticals	Human IgG2	HER3	Preclinical	Phase II

AQ: Anilinoquinazoline; CRC: Colorectal cancer; EOC: Epithelial ovarian cancer; FCA: 5-methyl-N-[4-(trifluoromethyl)phenyl]-1,2-oxazole-4-carboxamide; NA: Not applicable; NR: Not reported; NSCLC: Non-small-cell lung cancer; PP: Pyrolopyrimidine; PT: Pyrolotriazine; PZ: Pyrolozopyrimidine; TAQ: Thiazoloquinazoline; TRZ: Triazole.

Table 2

HER expression does not associate with response to inhibitor in epithelial ovarian cancer cell lines.

Response to any HER-targeted therapeutic					
EGFR expression	Measurable response		HER2 expression	Measurable response	
	Yes	No		Yes	No
High	26 (0.65)	14 (0.35)	High	81 (0.71)	33 (0.29)
Moderate	123 (0.70)	53 (0.30)	Moderate	48 (0.72)	19 (0.28)
Low	93 (0.69)	41 (0.31)	Low	111 (0.66)	57 (0.34)
High			High	2 (0.500)	2 (0.500)
			Moderate	15 (0.790)	4 (0.210)
			Low	7 (0.467)	8 (0.533)
Moderate			High	74 (0.718)	29 (0.282)
			Moderate	22 (0.667)	11 (0.333)
			Low	26 (0.684)	12 (0.316)
Low			High	0	0
			Moderate	11 (0.733)	4 (0.267)
			Low	78 (0.678)	37 (0.322)

Fisher exact test, $p = 0.82$; Fisher exact test, $p = 0.59$.

Likelihood ratio (degrees of freedom = 4), $p = 0.73$; EGFR (df = 2), $p = 0.61$; HER2 (degrees of freedom = 2), $p = 0.51$. Expression of EGFR and HER in ovarian carcinoma-derived cell lines was assigned to high, moderate, and low categories by consensus of literature [97,106,111,117,187–285]. Association between HER expression and response to inhibitor was determined by contingency table analysis using chi-square or Fisher's exact test and logistic regression. Measurable response was defined as any inhibitory response reported in **Supplementary Table 1**. Contingency table sub-analyses are reported in **Supplementary Table 3**.