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Emerging growth factor receptor antagonists for ovarian cancer treatment

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1. Background

Epithelial ovarian cancer (EOC) represents the seventh most common cancer and the eighth most common cancer-related cause of death in women [1]. EOC is associated with the highest mortality rate in women between all gynecological malignancies. Annually, approximately 240,000 women are diagnosed with ovarian cancer in the world, with approximately 150,000 dying of their disease. Regrettably, only 45% will be alive 5 years from diagnosis [1].

Outcomes in EOC have improved modestly over the past three decades, despite aggressive surgical treatment and initial chemo-sensitivity, with initial response rates to first line platinum-based chemotherapy of about 60–75% in high-grade histologies [2]. Poor clinical outcome in EOC may be attributed to factors such as advanced stage at diagnosis (Stage III, IV) with extensive peritoneal involvement [3,4] as well as a high risk of recurrent disease after initial treatment, with rather low response rates on subsequent treatment [5,6]. The introduction of novel treatment strategies such as antiangiogenic agents [7] and poly ADP ribose polymerase (PARP) inhibition [8] have conferred survival benefits in specific subgroups. Platinum-based chemotherapy remains the backbone of systemic therapy for EOC. Sensitivity to platinum chemotherapy stands as one of the most important prognostic factors for EOC, and influences treatment sequence during the entire disease course.

The intense search for new treatment options over the last several decades has brought new knowledge of disease biology [9]. For example, as a result of The Cancer Genome Atlas (TGCA) project identified molecular pathways aberrations that may represent attractive disease targets for future drug development.

Six main biological capabilities are acquired during development of human tumors, well described by Hanahan & Weinberg and that have laid the roadmap for drug development. These include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [10]. Subsequently, deregulating cellular energetics and avoiding immune destruction were added as fundamental emerging hallmarks of disease [11]. These principles consolidated an accurate framework for understanding the complexity of cancer development and also established the notion of the indispensable role of tumor microenvironment in the generation, proliferation and spread of cancer, engaging inflammation and angiogenesis among other essential functions. These hallmarks originate by the influence of two cancer enabling conditions – tumor genome instability, which is responsible for causing genetic variations that ultimately become transduced to a functional hallmark phenotype; and inflammation involving the immune system in the tumor progression processes [11]. Development of ovarian cancer involves these same hallmarks as well as the essential
interaction with the tumor microenvironment by induction of angiogenesis and avoidance of immune destruction (Figure 1).

EOC is now recognized as a heterogeneous disease with five identified histological subtypes, each with different molecular characteristics generated from specific genetic alterations that determine a unique anatomic site of origin as well as a distinctive disease course, prognosis and treatment predictive response. High-grade serous carcinoma (HGSC) is thought to originate from the fallopian tube and behaves aggressively [12], has a high degree of genomic instability, and is characterized by TP53 mutations [13] as well as mutations in homologous repair genes, such as BRCA 1 and 2 and NF1. [14] Low-grade serous carcinoma (LGSC) usually with a stable genomic profile, originates from borderline tumors and typically behaves with a slow disease progression course [15]. Genomically, LGSC is characterized by mitogen-activated protein kinase (MAPK) pathway mutations, in KRAS or BRAF [16] responsible for cell division regulation. Endometrioid carcinoma (EC), potentially related to endometriosis and is molecularly similar to Clear cell carcinomas (CCC). EC has been found to have inactivating mutations in the tumor suppressor gene ARID1A [17], PI3K activation, PTEN inactivation, and MMR abnormalities [5]. Mucinous carcinomas (MC) harbor 19% amplification of ERBB2[18], associated to KRAS/BRAF/MEK pathway activation [12].

We performed a comprehensive review of growth factor receptor antagonists for EOC treatment presently in different stages of development. English peer-reviewed articles and abstracts were searched in MEDLINE, PubMed, Embase and major conferences. Epub Ahead of Print and In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) were also included, as well as related clinical trials available information though clinicaltrials.gov site. We focused our search on agents that antagonize growth factors promoting tumor or tumor-associated microenvironment, responsible for sustained proliferative signaling, angiogenesis and evasion of immune destruction by blocking the receptor or its stimulating factors, and thus inactivating the specific pathways.

2. Medical need

High mortality rates and an overall 5-year survival below 45% stand as prominent proof of the unmet medical need that renders EOC a lethal malignancy. Many factors influence the poor outcome of patients with EOC, as discussed previously [5,6].

Time of disease relapse after first-line chemotherapy with platinum-based chemotherapy serves as one of the main prognostic factors for EOC clinical outcome as well as a predictive factor of response to re-challenge to platinum-based chemotherapy [9]. Investigations to better understand the biology behind treatment resistance with the objective to identify early biomarkers as better predictors of response remain an active area of interest and exploration.

Superior treatment strategies are warranted for women with EOC in order to allow for better disease control, survival and quality of life. Toward this end, recent advances in EOC research have identified critical pathogenesis pathways involved in EOC as well as key genetic alterations occurring during this process [18] that could potentially serve as prognostic or predictive factors, or targets for future therapeutic development. Many of these potential targets, are represented by key growth factors that are overexpressed in the different EOC subtypes as result of specific genetic alterations.

Multiple cancer hallmarks are driven by these growth factors [11]. Growth factors usually activate tumor development process by interacting with tumor associated molecules or receptors, present in the cell membrane to ultimately induce activation of intracellular downstream signaling to allow tumor cell and associated microenvironment cells to proliferate and survive. These tumor-associated molecules and receptors are frequently overexpressed in cancer cells as opposed to
normal cells. Targeting these molecules represents a tumor-specific opportunity for EOC treatment, proven to be effective in multiple other malignancies either through development of specific monoclonal antibodies or tyrosine kinase inhibitors [19,20].

3. Market review

Focusing on systemic treatment, chemotherapy remains the backbone of treatment at all EOC disease stages. Most used chemotherapy compounds include platinum (carboplatin, cisplatin), taxanes, liposomal doxorubicin, gemcitabine and cyclophosphamide. Platinum treatment for EOC, was established in the late seventies and early eighties [21]. Shortly thereafter, cisplatin was changed to carboplatin, based on the evidence of same efficacy with a more tolerable toxicity profile [22]. Since the platinum introduction in the EOC treatment algorithm, platinum-free interval disease progression, constitutes a valuable prognostic factor, predictive for platinum-based treatment response, used as a guide for treatment decision. In the late nineties, early 2000s, taxanes were introduced in the first-line EOC treatment setting [23].

The monoclonal antibody (mAb) Bevacizumab was the first anti-angiogenic targeted therapy that showed efficacy in EOC in the first line followed by maintenance treatment in 2011 [24,25]. Achieving significant improvement in progression-free survival (PFS) in all treated population and overall survival in poor prognosis disease patients, with 34.5 months with standard chemotherapy vs. 39.3 months with bevacizumab, with an absolute mean survival time improvement of 4.8 months, in high-risk EOC patients treated with bevacizumab [25]. In clinical practice, bevacizumab use in the neoadjuvant setting is limited as it may impose delays in the timing of debulking surgery, recovery and possibly initiation of further adjuvant treatment, due to risk of complication such as gastrointestinal perforations and delayed wound healing [26,27]. Although different bevacizumab doses have been assessed in first line, the most widely used dose in first line setting is 7.5 mg/kg; head-to-head dose comparison to 15 mg/kg has not yet been performed. Bevacizumab has also shown activity in the EOC recurrence setting of platinum sensitive and platinum resistant EOC [28,29]. Bevacizumab is currently approved by the European Medicines Agency (EMA) for EOC first line and disease recurrence while in the USA, the Food Drug Administration (FDA) agency only recently approved bevacizumab for platinum-resistant EOC.

In 2014, the PARP inhibitor olaparib was the first-in-class approved compound for the treatment of EOC. The approval was based on significant outcomes improvement in specific patient populations (germ line or somatic BRCA1/2 mutation carriers) in the maintenance treatment setting, with a significant absolute median progression-free survival improvement of 3.6 months from randomization on completion of chemotherapy for olaparib over placebo, in this patient population [8]. More recently in December 2016, rucaparib was approved for the same indication as olaparib [30]. Niraparib, also a PARP inhibitor, was granted FDA approval in 27 March 2017, based on results of a phase III trial that randomized 553 patients with recurrent platinum-sensitive EOC, fallopian tube or primary peritoneal cancer post response to platinum-based chemotherapy, regardless of the presence or absence of germ line BRCA (gBRCA) mutations or homologous repair deficiency (HRD) received maintenance niraparib vs. placebo. Significant median PFS improvement in patients treated with niraparib compared to placebo was documented in patients with gBRCA mutations, 21 months PFS in the niraparib arm vs. 5.5 months in the placebo arm. Likewise, a significant improvement in PFS of 9.3 months was seen in patients without gBRCA mutations treated with niraparib vs. 3.9 months with placebo [31]. A fourth PARP inhibitor, velaparib, was assessed in a phase II clinical trial of patients with recurrent EOC gBRCA mutated, and showed median PFS of 18.8 months [32](Table 1).

Whilst various chemotherapy combinations and schedules are used in the different EOC settings [33], platinum remains the most essential treatment, either in combination or as single agent. Other compounds can be used as single agents in the platinum-resistant setting, while hormonal treatment is reserved for advanced treatment in low grade serous cancer and granulosa tumors. Clinical trials represent one of the most essential sources of treatment opportunities.

4. Current review goals

Our main objective is to comprehensively review emerging molecules for EOC treatment, targeting recognized growth factor pathways responsible for tumor sustaining proliferative signaling by antagonizing their receptor activation, through direct blockage of the receptor or receptor-specific stimulating factors. We also include molecules that target proliferative pathways involved in the functions of tumor-associated microenvironment, by antagonizing the activation of their specific receptors or stimulating factors, to achieve EOC tumor control. Furthermore, we objectively estimate the potential role and impact that these novel compounds could have in the future treatment of EOC, and their likelihood to be integrated in current EOC treatment paradigm that remain defined by platinum sensitivity status.

Receptor antagonists, are molecules that target the receptor or its specific stimulating factors; either monoclonal antibodies or fusion-proteins, have been developed for the treatment of EOC, targeting associated pathways in three out of the ten cancer hallmarks described by Hanahan and Weinberg [11]: sustained proliferative signaling inhibition, angiogenesis inhibition, and evasion of immune destruction.

5. Sustained proliferative signaling inhibition in EOC

Sustained proliferation is the most important quality of cancer cell generation and survival [11]. Normal tissues are capable of balancing growth-promoting signals that direct cell cycle proliferation, keeping normal tissue structure and homeostasis. Conversely, cancer cells enable uncontrolled cell proliferation through deregulation of these growth-promoting signals, activated by growth factors that bind to cell membrane receptors, that are usually overexpressed in tumor cells [18]. These receptors contain an intracellular tyrosine kinase domain. Once binding of growth factor to receptor has occurred, intracellular signaling pathways are activated to induce cell proliferation,
Recently EOC-approved standard treatment options.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Approval status</th>
<th>Trials</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>EMA first-line maintenance</td>
<td>GOG 218</td>
<td>1. IV Carboplatin (AUC 5) + IV Paclitaxel (175 mg/m2) + IV placebo followed by maintenance placebo Q3 weeks</td>
<td>Median PFS 10.3 vs. 11.2 vs. 14.1 mos. HR 0.717; 95% CI 0.625–0.824; p = 0.001</td>
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<td></td>
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<td>2. IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m2) + IV bevacizumab (15 mg/kg) + IV placebo maintenance Q3 weeks</td>
<td>Median OS 39.3 vs. 38.7 vs. 39.7 mos. HR 0.915C; 95% CI 0.727–1.15</td>
</tr>
<tr>
<td></td>
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<td>3. IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m2) + IV bevacizumab (15 mg/kg) + IV bevacizumab maintenance Q3 weeks</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>ICON 7</td>
<td></td>
<td>1. IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m2)</td>
<td>PFS 11.2 mos (m)/5.6 mos (wt)</td>
<td>p = 0.00001</td>
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<td></td>
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<td>2. IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m2) + IV bevacizumab (15 mg/kg) + IV bevacizumab maintenance Q3 weeks</td>
<td>For placebo: 3 mos (m)/5.5 mos (wt) p = 0.007</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3. IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m2) + IV bevacizumab (15 mg/kg) + IV bevacizumab maintenance Q3 weeks</td>
<td>No OS differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chemotherapy as above plus IV Bevacizumab (15 mg/kg) Q3 weeks</td>
<td>PFS for Rucaparib 12·8 mos (95% CI 9·0 – 17·6 mos) (HR 0·27, 95% CI 0·17 to 0·41) vs. 5·7 mos (5·3–6·1 mos) in the non-gBRCA cohort HRD (HR 0·38, 95% CI 0·24 to 0·59) and 9.3 mos vs. 3.9 mos in non-gBRCA cohort (HR 0·45; 95% CI 0·34 to 0·61; P &lt; 0.001 for all three comparisons)</td>
</tr>
<tr>
<td>FDA after platinum resistant recurrence</td>
<td>AURELIA</td>
<td>Platinum-resistant recurrence; ≤ 2 prior chemotherapy regimens; no e/o recto-sigmoid involvement; 361 patients; ECOG PS 0–2 [24]</td>
<td>1. Niraparib 300 once a day</td>
<td>PFS 21.0 vs. 5.5 mos in the gBRCA cohort (HR, 0.27; 95% CI 0.17 to 0.41), vs. 12.9 mos vs. 3.8 mos in non-gBRCA cohort HRD (HR, 0.38; 95% CI, 0.24 to 0.59) and 9.3 mos vs. 3.9 mos in non-gBRCA cohort (HR, 0.45; 95% CI, 0.34 to 0.61; P &lt; 0.001 for all three comparisons)</td>
</tr>
<tr>
<td>Olaparib</td>
<td>FDA after 2 or 3 previous lines in BRCA mutated</td>
<td>Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer both Germ line BRCA and sporadic 265 patients; ECOG PS 0–2 [8]</td>
<td>1. Olaparib 400 mg BID Q3 weeks</td>
<td>PFS 11.2 mos (m)/5.6 mos (wt)</td>
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<td></td>
<td></td>
<td></td>
<td>Given as maintenance following platinum-based chemotherapy</td>
<td>For placebo: 4.3 mos (m)/5.5 mos (wt) p = 0.007</td>
</tr>
<tr>
<td>Niraparib</td>
<td>FDA after complete of partial response to platinum based chemotherapy</td>
<td>Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer 553 patients; ECOG PS 0–2 [31]</td>
<td>2. Placebo</td>
<td>No OS differences</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Given as maintenance following platinum-based chemotherapy</td>
<td>PFS for Rucaparib 12.8 mos (95% CI 9.0–14.7) in the BRCA (m) subgroup, 5–7 mos (5.3–7.6) in the LOH high subgroup, and 5–2 mos (3.6–5.5) in the LOH low subgroup. PFS BRCA (m) (HR 0.27, 95% CI 0.16–0.44, p &lt; 0.001) vs. 0.001) subgroups compared with the LOH low subgroup.</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>FDA after 2 or 3 previous lines in BRCA mutated</td>
<td>ARIEL 2</td>
<td>1. Rucaparib 600mg BID Q2 weeks</td>
<td>PFS for Rucaparib 12.8 mos (95% CI 9.0–14.7) in the BRCA (m) subgroup, 5–7 mos (5.3–7.6) in the LOH high subgroup, and 5–2 mos (3.6–5.5) in the LOH low subgroup. PFS BRCA (m) (HR 0.27, 95% CI 0.16–0.44, p &lt; 0.001) vs. 0.001) subgroups compared with the LOH low subgroup.</td>
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<td>2. Placebo</td>
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</table>

BID: twice a day; BRCA: breast cancer susceptibility gene; CI: confidence interval; ECOG: Eastern cooperative; EMA: European medicines agency; FDA: food drug administration; GOG: gynecologic oncology group; HR: hazard ratio; HRD: homologous repair deficiency; IV: intravenous; kg: kilogram; LOH: loss of heterozygosity; mg: milligrams; mos: months; m: mutated; m2: meter square; OS: overall survival; ORR: overall response rate; PFS: progression free survival; PS: performance status; Q: every; wt: wild type.
Table 2. Ovarian cancer proliferative-related hallmarks, receptor ligand-mediated pathways, targets and compounds.

<table>
<thead>
<tr>
<th>Hallmark</th>
<th>Receptor pathway</th>
<th>Targeting antagonist</th>
</tr>
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<tbody>
<tr>
<td>Sustained proliferative signaling</td>
<td>EGFR/HER</td>
<td>Cetuximab, Panitumumab, Pertuzumab, Matuzumab, Trastuzumab, Seribantumab</td>
</tr>
<tr>
<td></td>
<td>Folate Receptor Alpha (FR alpha)</td>
<td>Farletuzumab, IMGN853 (Mirvetuximab Soravtatin)</td>
</tr>
<tr>
<td></td>
<td>EPHRIN-A4 (EFNA4) Delta-like ligand 4 (DLL4) NOTCH Receptor</td>
<td>PF-06647263, Demicizumab</td>
</tr>
<tr>
<td>Angiogenesis induction</td>
<td>VEGFR/VEGF</td>
<td>Bevacizumab, Volociximab, Afibercept, Olaratumab, Siltuximab, Tocilizumab, Pembrolizumab, Nivolumab, BMS-936,559, Avelumab, Durvalumab, Atezolizumab</td>
</tr>
<tr>
<td>Evasion of immune destruction</td>
<td>PD-1 and PD-L1</td>
<td>DLL4: Delta-like ligand 4; EGFR: epithelial growth factor receptor; Erb/HER: epithelial growth receptor; FR alpha: Folate receptor alpha; Her 2: human epidermal growth factor receptor 2; IL-6: Interleukin 6; PD-1: programmed cell death protein; PD-L1: programmed cell death ligand 1; PDGFR: platelet-derived growth factor receptor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.</td>
</tr>
</tbody>
</table>

Cetuximab is a chimeric IgG1 monoclonal antibody (mAb) that targets the extracellular domain of Erb1/HER1 (EGFR), currently indicated for the treatment of advanced head and neck tumors and metastatic colorectal carcinoma. In EOC preclinical models, Cetuximab has shown antitumor activity and increased efficacy when combined with different chemotherapies [45]. In the clinical setting, cetuximab activity and safety has been evaluated as a single agent and in combination with chemotherapy in phase II clinical trials. A Cetuximab single-agent phase II clinical trial included patients with persistent/recurrent ovarian or primary peritoneal carcinoma. Dose escalation based On cutaneous toxicity and a comprehensive evaluation of 100 biomarkers was performed in this small patient population. Although the trial did not achieve its primary objective, 12 markers: SAA, cytokeratin 19, IL-8, HSP27, HE4, IL-6, MMP7, fibrinogen, GH, CA 72-4, TNF-α and KLK10 were found elevated at baseline and significantly and persistently elevated in progressing patient compared to the PR/SD group, suggesting a prognostic role for these proteins [46].

Two additional phase II studies assessed Cetuximab with chemotherapy and both consistently demonstrated combination tolerability but dichotomous efficacy results [42,43]. One in combination with paclitaxel and carboplatin in advanced EOC patients as first line treatment [47], did not reveal prolonged PFS compared to previous data. The second trial in relapsed platinum-sensitive ovarian cancer patients demonstrated objective response in 9 of 29 patients, while 8 patients had SD [48].

5.1. Epidermal growth factor receptor family inhibitors

The epidermal growth factor receptor (EGFR) family includes four transmembrane receptors with tyrosine kinase intracellular domains, Erb1/HER1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. These are expressed normally in the cell membrane of epithelial cells. Receptor dimerization follows by tyrosine auto-phosphorylation that cascades in downstream signaling ultimately induces tumor cell proliferation, survival motility, and invasion, and can be induced by ten different ligands that bind selectively to each receptor hetero- or homodimer [34].

Expression of EGFR in EOC is related with poor patient outcomes and resistance to cisplatin [35,36]. Erb1/HER1 is expressed in 25–50% of ovarian cancers and ErbB2/HER2 expression range is estimated to be 5–66% [11] and may be a target for EOC treatment [37]. Erb1/HER1 has been the subject of extensive research in EOC, as its expression is marked in high-grade ovarian cancer and appears early in the development of this malignancy [38]. Erb1/HER1 is responsible for upregulation of survivin, an apoptosis inhibitor protein [39]. Based on preclinical data, Erb1/HER1 is associated with the regulation of cancer cell adhesion proteins linked to cell invasion and migration, such as laminin-1, E-catherin and MMP-9 [40,41]. ErbB2/HER2 higher frequencies of amplification have been reported in clear cell and mucinous carcinomas studies [42], suggesting the possible interest of ErbB2/HER2 therapy for patients with specific histology [43,44]. In the last two decades, many monoclonal antibodies as well as tyrosine kinase inhibitors, targeting EGFR family had been developed. These data have led to multiple clinical trials targeting the EGFR pathway in EOC patients.

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5.1.2. Panitumumab

A human recombinant IgG2 mAb, Panitumumab prevents activation of EGFR/HER1 by binding to the receptor extracellular domain [49], currently indicated for the treatment of metastatic colorectal cancer patients. A phase I study of 32 patients with advanced solid tumors evaluating Panitumumab in combination with everolimus and bevacizumab showed that three patients diagnosed with EOC had disease control from 11 to >40 months [50].

In the phase II setting, 43 platinum-resistant, K-RAS wild-type, EOC patients received panitumumab in combination
with pegylated liposomal doxorubicin, and found 9.3% of patients had a partial response (PR), 18.6% had stable disease (SD) and 39.5% progressed on treatment, based on RECIST evaluation. About half of the patients developed treatment-related grade 3 skin toxicities, representing the major cause for dose reduction and compromise of patient quality of life [51]. Most recently, a phase II trial aimed to assess Panitumumab combination with gemcitabine safety and efficacy in patients with recurrent platinum-refractory/resistant EOC, single-arm trial. This trial was ended due to poor accrual (NCT01296035).

5.1.3. Pertuzumab
Pertuzumab is a humanized IgG1 mAb that inhibits heterodimerization of ErbB2/HER2 with ErbB1/HER1 or ErbB3/HER3, by binding to the extracellular domain II of ErbB2/HER2, indicated for advanced ErbB2/HER2 overexpressing breast cancer. In a phase I trial evaluating this compound in patients with advanced solid tumors, 2 out of 21 patients, including 1 diagnosed with EOC, reached a partial response (PR) [52]. A randomized phase II trial in platinum-resistant EOC patients of pertuzumab in combination with gemcitabine compared to gemcitabine plus placebo showed that objective response rate (ORR) was 13.8% in the combination arm compared to 4.6% in the placebo arm. Correlation with ErbB3/HER3 mRNA and ErbB3/HER3 tumor expression, showed increased benefit of pertuzumab in patients with lower HER3 mRNA expression. Patients with high ErbB3/HER3 tumor expression benefited less from the combination treatment. Additionally, in the combination arm, greater incidence of grade 3 and 4 toxicity was seen, neutropenia 35% in the combination arm vs. 22% in the control, diarrhea 11% vs. 2% and back pain 9% vs. 2%, respectively [53]. A small nonrandomized phase II trial assessing pertuzumab as a single agent in platinum-resistant EOC found 14.5% of patients achieved clinical benefit [54].

In the platinum-sensitive setting, a phase II trial assessing pertuzumab in combination with carboplatin and paclitaxel or gemcitabine showed no significant differences in PFS or other secondary end points between arms [55].

Taken together, no strong data have shown benefit of HER target in EOC; however, selection of patients based in HER3 expression is warranted in future investigations [56]. Two important ongoing clinical trials in this area are eagerly awaited. The phase III study evaluating pertuzumab in combination with standard chemotherapy in platinum-resistant EOC with low HER3 mRNA expression (NCT01684878), and the phase II trial evaluating HER2 activation on pertuzumab efficacy in advanced EOC, which has already completed accrual and data analysis is pending (NCT00058552).

5.1.4. Matuzumab
Matuzumab (EMD72000) is a humanized IgG1 mAb that antagonizes EGFR/HER1 by binding to the receptor extracellular domain at the ligand-binding region, activating the antibody-dependent cell-mediated cytotoxicity (ADCC) against tumor cells [57]. There are no indications approved for this agent to date. A phase II trial evaluated matuzumab in 37 patients with EGFR-positive recurrent EOC, with a median of four previous treatment lines and found no responses (Response Rate (RR) = 0%, 95% CI: 0–9.5%) were detected. Stable disease was observed in 7 patients (21%) for more than 3 months and treatment was related with tolerable side effects [58].

5.1.5. Trastuzumab
Trastuzumab is a humanized IgG1 mAb that inhibits activation of ErbB2/HER2 receptor intracellular tyrosine kinase proliferative pathways, as well as additional interaction with other EGF receptors by binding to the receptor extracellular domain [19]. Trastuzumab is currently indicated for the treatment of patients with ErbB2/HER2 overexpressing advanced breast cancer and gastric cancer.

A phase II trial evaluated trastuzumab in recurrent or persistent EOC patients selected on the basis of high ErbB2/HER2 tumor expression by immunohistochemistry [59]. Treatment was well tolerated and no dose-limiting toxicities (DLT) were reported. Overall response rate (ORR) of 7.3% and 39% stable disease (SD) rate was detected. Interestingly, some of the patients that reached PR or SD, continued treatment for over a year and no correlation between ErbB2/HER2 expression level and trastuzumab response was detected [60].

Two phase I studies assessing trastuzumab in combination with interleukin-12 have also been performed but results have not yet been reported (NCT00028535, NCT00040704).

Finally, a phase III trial evaluating trastuzumab in triplet or doublet treatment combinations with paclitaxel and carboplatin in patients with stage III or IV EOC stratified by extend of residual disease or plan for interval debulking have achieved planned accrual; results are pending (NCT00011986).

5.1.6. Seribantumab
Seribantumab (MM-121, SAR256212) is a human IgG2 mAb that antagonizes ErbB3/HER3 function, preventing ErbB2/HER2 and ErbB3/HER3 dimerization, ultimately resulting in intracellular downstream pathway impairment; is not yet approved for any indication [57]. A randomized phase II trial evaluated seribantumab in combination with weekly paclitaxel in advanced platinum-resistant or refractory recurrent/advanced EOC and fallopian tube cancer. Two of the following pretreatment biomarkers (BM): heregulin (HRG), betacellulin, EGFR, ErbB2, and ErbB3, were found positive in 34% of all the assessed patients. Treatment was tolerable, yet PFS was not improved by the combination. PFS was improved in the combination arm, in BM-positive patients HR 0.37 [0.2–0.8] [61].

5.2. Folate receptor alpha inhibitor
Folate receptor alpha (FRA) is a glycosylphosphatidylinositol (GPI)-anchored membrane protein, responsible of folate transport via receptor-mediated endocytosis [62]. In EOC, FRA is overexpressed in 80–90% of tumors [59]. The high expression level of FRA constitutes a marker of tumor aggressiveness and is possibly a poor prognostic factor in serous epithelial ovarian carcinoma (SEOC) [63,64].

Overexpression of FRα by cancer cells possibly induces tumor progression by increased cell proliferation due to folate
uptake modulation and regulatory signals, through enhancing DNA synthesis [65]. This has been supported by EOC preclinical models, which show that abolition of FRα expression leads to inhibition of folate-mediated cell proliferation, migration, and invasion [66]. FRα overexpression has been related to chemo-resistance in EOC and low chemotherapy-induced apoptosis levels by downregulation of caspase 3 and 7, increased Bcl-2 expression and decreased Bax expression [52–55]. FRα is thought to support ovarian carcinoma progression by inhibition of the tumor suppressor gene, caveolin-1, responsible to inhibit cell cycle progression and anchorage-independent growth [67]. Taken together, FRα represents an ideal anticancer therapy target [68] due to the many functions that FRα overexpression impacts and that ultimately induce tumor cell proliferation and survival. This is in addition to the fact that FRα high expression is almost exclusive for tumor cells [63].

5.2.1. Farletuzumab
Farletuzumab (MORAb003), a humanized IgG1 antibody that antagonizes FRα was first assessed in a phase I study as a single agent in platinum-resistant EOC patients [69]. A further phase Ib trial, in combination with carboplatin and pegylated liposomal doxorubicin (PLD) followed by maintenance in patients with platinum-sensitive EOC, 1st or 2nd recurrence, showed similar safety profile as that reported for carboplatin and pegylated liposomal doxorubicin (PLD) [70].

A phase II study evaluated farletuzumab single agent or in combination with carboplatin and taxane in platinum-sensitive EOC patients, followed by farletuzumab maintenance therapy. Toxicity was acceptable in both arms, no additional toxicity to that expected from carboplatin and taxane combination was detected. Farletuzumab infusion reactions were grade 1 or 2 were controlled with antihistamines and antipyretics. In total, 75% of the patients in the combination therapy achieved complete response (7 patients, 3%), partial response (30 patients, 7%), and stable disease (9 patients, 21%) [71].

Two phase III trials have been performed to further evaluate farletuzumab activity. A large phase III trial with 1100 EOC patients with platinum-sensitive recurrence compared carboplatin and taxane with or without two doses of farletuzumab (1.25 mg/kg or 2.5 mg/kg) and maintenance. Primary endpoint of improvement in PFS was not met, with 9.0, 9.5, and 9.7 months for the placebo, farletuzumab 1.25 mg/kg, and farletuzumab 2.5 mg/kg groups. Nevertheless, better PFS and OS were seen in patients with higher farletuzumab dose and CA-125 levels not more than three times the ULN [72]. A second phase III study enrolled platinum-resistant EOC patients compared weekly paclitaxel alone, or in combination with farletuzumab (NCT00738699). This trial was stopped in the interim analysis, because did not meet pre-specified criteria for continuation.

Phase II study is assessing farletuzumab with carboplatin and paclitaxel or with carboplatin and pegylated liposomal doxorubicin (NCT02289950), with stratification by CA 125 levels.

FRα levels of expression in the tumor cells might represent a biomarker for farletuzumab expression and future trials are currently designed to identify an EOC-specific population with this consideration.

5.2.2. IMGN853 (mirvetuximab soravtansine)
IMGN853 (mirvetuximab soravtansine) is an antibody-drug conjugate that targets FRα. IMGN853 is composed by a humanized FRα-binding antibody conjugated to a potent antimitotubule compound, maytansinoid, DM4 [73].

A phase I study in heavily pretreated FRα-positive solid tumors, including EOC patients, showed tolerable toxicity profile. Preliminary activity showed 11 of 44 patients with clinical benefit, 26% response rate, including CA125 response, PR (11), CR (1) or SD. PFS 4.8 months and median duration of response 19.1 weeks [74].

An ongoing phase Ib in FRα-positive advanced EOC, peritoneal cancer, fallopian tube cancer or endometrial cancer, is currently assessing IMGN853 with bevacizumab, carboplatin, or PLD (NCT02606305). An additional phase II study is recruiting patients with FRα-positive advanced EOC, primary peritoneal cancer or fallopian tube cancer to compare IMGN853 with investigator’s choice chemotherapy (NCT02631876).

5.2.3. Mov18 IgE
MOv18 IgE, a chimeric IgE antibody FRα-specific obtained from mouse/human chimeric IgG1 (MOV18-IgG1) antibodies modification. A phase I clinical study (NCT02546921) is assessing the hypothetical concept that created Fc regions of the IgE class antibodies may have improved specific features compared to IgG antibodies [75]. This was previously shown in vivo EOC models [76].

5.3. EPHRIN-A4 (EFNA4) inhibitor
Ephrin-A4 (EFNA4), a tumor antigen and receptor, is often overexpressed in a variety of tumors including EOC. EFNA4 is a member of the Ephrin (Eph) receptor family and is also expressed in tumor-initiating cells (TIC), constituting a potential target for these cells. TICs are related to tumor proliferation and resistance to treatment [77].

5.3.1. PF-06647263
PF-06647263, an antibody-drug conjugate, that combines a humanized IgG2 mAb (huE22) that targets specifically EFNA4, and calicheamicin that causes DNA strand scission.

A phase I study evaluated PF-06647263 in advanced solid tumors patients, regardless of EFNA-4 expression levels. Two patients had a PR, one of them with EOC. DLT and grade 4 neutropenia were determined in one patient [78].

5.4. Delta-like ligand 4 (DLL4) inhibitor
Notch is a transmembrane receptor and its activation leads to a signaling pathway normally involved in many essential cell functions such as embryonic development, cell survival, tissue repair, hematopoiesis and stem cell homeostasis maintenance in endothelial and gut epithelium [79,80]. Notch also has a role in carcinogenesis, through modulation of tumor stem cells functioning and tumor angiogenesis [81]. Delta-like ligand 4 (DLL4) is responsible for Notch pathway activation inducing
angiogenesis in endothelial cells; DLL4 therefore represents a relevant anti-angiogenesis target [82].

5.4.1. Demicizumab

Demicizumab (OMP-21M18), is a humanized IgG2 mAb targeting DLL4.

A phase I trial showed demicizumab single-agent activity and durable responses. A patient with ovarian granulosa cell carcinoma had SD with clinical benefit for 17 months [83]. Nevertheless, long exposure in this particular patient, resulted in cardiotoxicity and tumor bleeding, which led to trial closure.

An open phase Ib/II study (NCT01952249) is currently enrolling platinum-resistant EOC, primary peritoneal carcinoma or fallopian tube cancer, to assess demicizumab in combination with paclitaxel.

6. Ovarian cancer angiogenesis inhibition

Tumor growth and metastasis is dependent upon angiogenesis [11]. The formed tumor vessels not only supply nutrients and oxygen to the tumor but also serve as route for metastasis. Tumor angiogenesis takes place through a complex process, which engages the tumor and its microenvironment, involving proliferation of endothelial cells, followed by migration and capillary development [84]. A pro-angiogenic signaling cascade is induced by a tumor hypoxic state, which activates hypoxia-inducible factor (HIF)-1α that forms a complex with HIF-1β within the nucleus [85]. The HIF-1 complex works as a transcription factor for many genes that ultimately generate essential angiogenesis receptors and their growth factors, like vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF) and also induce downregulation of thrombospondin-1 and angiostatin that are both anti-angiogenic factors [86]. This review highlights EOC angiogenic signaling pathways that are activated through specific receptor stimulation and compounds that antagonize this action.

6.1. VEGFR/VEGF inhibitors

Vascular endothelial growth factor (VEGF) interaction with specific tyrosine kinase receptors (VEGFRs) drives the activation of pathways ultimately resulting in new blood vessel formation via endothelial cell proliferation and survival, endothelial cells migration and invasion [87]. The tumoral VEGF pathway also downregulates tumor microenvironment immune response, which contributes to the deceleration of immune cell maturation such as T lymphocytes. High VEGF levels in EOC might be associated to worse disease prognosis and more aggressive disease behavior. Therefore, VEGF might constitute an EOC potential prognostic factor [88]. In fact, targeting VEGF in EOC has achieved improvements in outcomes despite the mechanisms of action is not clearly established but may be related to the tumor vascular system normalization, that allows better delivery of chemotherapy to tumor cells.

6.1.1. Bevacizumab

Bevacizumab is a humanized monoclonal IgG1 antibody specific to VEGF-A. The effectiveness and safety of Bevacizumab has been widely assessed in EOC treatment. Promising results were obtained since early development phases, including complete responses in patients with recurrent disease [89]. Phase II showed encouraging results achieving ORR over 20% and 6 months PFS of 40–50% [89], leading to design of large phase III trials that have evaluated bevacizumab as upfront treatment as well as in the recurrent EOC setting.

In the GOG 218 trial, 1873 women with optimally or sub-optimally debulked EOC, primary peritoneal carcinoma or fallopian tube cancer were randomized to carboplatin paclitaxel treatment with placebo, followed by maintenance placebo or carboplatin paclitaxel and bevacizumab and placebo maintenance or carboplatin paclitaxel with bevacizumab, and maintenance bevacizumab. Treatment with bevacizumab 15 mg/kg was well tolerated and had a significant PFS of 14.1 months for the combination plus maintenance bevacizumab arm vs. chemotherapy alone; however, no significant difference in OS was seen between arms [90]. Another large pivotal phase III trial, the ICON 7 study, assessed carboplatin and paclitaxel alone or in combination with concurrent bevacizumab at 7.5 mg/kg followed by bevacizumab maintenance. Again, PFS was significantly improved in the combination arm achieving 17.3 months vs. 19 months [91], although no significant difference in OS was detected between the arms at 39.7 months vs. 30.3, respectively.

Two phase III trials have assessed the efficacy of bevacizumab in the EOC recurrence setting. The OCEANS phase III clinical trial that randomized patients with platinum-sensitive recurrence disease, to carboplatin and gemcitabine with or without bevacizumab, significant better PFS in the bevacizumab arm was achieved, with 8.4 months vs. 12.4 months [92]. The AURELIA trial included patients with recurrent platinum-resistant EOC, randomized to chemotherapy with weekly paclitaxel, pegylated liposomal doxorubicin (PLD) or topotecan alone or combined with bevacizumab. The combination treatment arm showed statistically significant improvement in PFS, 3.4 months vs. 6.7 months, respectively [24].

6.1.2. Volociximab

Volociximab is a chimeric IgG4 mAb that antagonizes human α5β1 integrin. α5β1 integrin has a central role in angiogenesis, it also regulates angiogenesis by interacting with endostatin, VEGFR-1, Angiopoietin-2 and Tie-2 [25]. Positive preclinical studies showed increased survival in ovarian cancer animal models by inhibition of neovascularization induced by VEGF and α5β1 integrin [28].

In a phase I study, no DLTs were experienced. In total, 20 patients with multiple malignancies were evaluable, 1 renal cell carcinoma patient had minimal response and other 5 durable SD [93].

A single-arm phase II trial assessed volociximab in two stages in platinum-resistant EOC or primary peritoneal cancer. Of 14 patients, only one had SD at 8 weeks, 13 patients had PD. Adverse events consistent with fatigue and headache were reported in 75% [94]. An additional phase II trial in EOC
patients was conducted and patients were randomized between PLD, volociximab or both, patients and stratified by platinum sensitivity. Similar response rates and safety was detected in the three arms, no CRs. Trial was closed due to low probability to detect meaningful difference for the combination [95].

6.1.3. Afilimeter
Afilimeter is a recombinant fusion protein formed by VEGF-binding areas to VEGF receptor 1 (VEGFR-1) and VEGFR-2 extracellular domains, fused to the human IgG1 Fc portion [96]. Afilimeter is currently approved for the treatment of patients with neovascular (Wet) age-related macular degeneration and metastatic colorectal cancer resistant or progressing to oxaliplatin-containing treatment.

A phase I trial evaluated afilimeter single agent, in 47 patients with multiple malignancies. Dose for phase II trial was determined to be 4 mg/kg every 2 weeks, DLT were rectal ulceration and proteinuria at the 7.0 mg/kg dose. PR was demonstrated in three recurrent EOC patients [97].

Subsequently, phase II trials, assessed afilimeter in platinum-resistant EOC patients [98]. One trial, demonstrated malignant ascites control with single agent afilimeter. Afilimeter combination with docetaxel showed ORR of 54% [99,100]. Finally, a parallel arm, double-blind phase II trial that assessed two doses of afilimeter 2 mg/kg or 4 mg/kg in heavily pretreated platinum-resistant advanced EOC patients, did not meet its primary end point of radiological response, achieving an ORR of less than 5%, although afilimeter had a good tolerability profile [101].

6.2. PDGFR ALPHA inhibitor
Platelet-derived growth factor receptor-α (PDGFRα) is activated by binding of platelet-derived growth factor (PDGF), subsequently receptor dimerization occurs, conducting to activation of intracellular pathways, to tumor cell proliferation, apoptosis inhibition, influencing many stromal functions as well including angiogenesis regulation [102]. In EOC, PDGFRα activation by PDGF constitutes an autocrine mechanism of tumor cell proliferation [103]. PDGFRα levels of expression had been correlated with EOC prognosis, and had been detected in many EOC histologic types including serous, mucinous and epithelial subtype [104,105].

6.2.1. Olaratumab
Olaratumab (IMC-3G3), a human IgG1 mAb that antagonizes PDGFRα, inhibits PDGFR binding. In preclinical studies, olaratumab showed to improve chemotherapy effect against EOC cells [106].

A phase I trial evaluated olaratumab in different solid tumors, SD was detected in 12 out of 19 evaluable, and no PR or CR was observed. Treatment with olaratumab was tolerated well, no maximal-tolerated dose (MTD) was determined due to the absence of DLT [107].

A phase II trial (NCT00913835) is currently assessing PLD single agent or in combination with olaratumab in platinum-resistant or refractory EOC patients.

6.3. IL-6 inhibitor
Normal follicle development in the ovary is in part mediated by IL-6 cytokine [108]. In the tumor, IL-6 is considered to induce tumor growth, improve chemotactic and chemokinetic cell action, and increase invasiveness [109]. In EOC, IL-6 is considered to have an autocrine effect in tumor cells increasing proliferation pathways, like JAK/STAT, Ras/MEK/Erk and PI3K/Akt, inducing also angiogenesis [110,111]. This effect occurs primarily by IL-6 binding to its receptor, triggering the intracellular signal transduction. IL-6 levels in serum and ascitic fluid in EOC patients have been correlated with disease tumor burden. Therefore, high serum levels of IL-6 represent a poor prognostic factor for EOC. Additionally, high level of IL-6 are also predictive for low response to chemotherapy [112,113]. The role of IL-6 in EOC proliferation represents an opportunity for targeting treatment [114].

Clear cell carcinoma of the ovary (CCC) has been differentiated by its chemoresistance and therefore poor prognosis. Recently CCC has been characterized by having overexpression of IL-6/IL-6R-signal transducer and activator of transcription 3 (Stat3) signaling pathway, and there is some evidence that overstimulation of this pathway may be related to CCC progression. Targeting IL-6/IL-6R mediated signaling pathway in CCC with Tocilizumab has showed reduction in cell invasion as well as cytotoxic response restoration. This represents a valuable opportunity for improving outcomes in patients with CCC [115].

6.3.1. Siltuximab
Siltuximab (CNTO 328, cCLB8) is a chimeric mAb that targets IL-6 preventing its binding to the specific receptor. Siltuximab is currently indicated for the treatment of Multicentric Castleman’s Disease (MCD).

A phase Ib/II trial assessed siltuximab in different solid tumors, including recurrent platinum-resistant EOC patients. From 84 patients heavily pretreated enrolled, 29 had EOC, although siltuximab monotherapy was well tolerated, no clinical activity was detected including KRAS-mutated EOC, this although Interleukin (IL)-6 has been identified to have an essential in mutant Kirsten rat sarcoma-2 (KRAS)-driven tumorigenesis [116].

6.3.2. Tocilizumab
Tocilizumab, a humanized mAb that targets interleukin-6 (IL-6), inhibits its binding to receptor (IL-6R), subsequently preventing IL-6 signal transduction pathway, inhibiting the production of inflammatory mediators to promote B and T cells.

A phase I trial combining carboplatin/doxorubicin with tocilizumab and interferon-α2b in patients with recurrent epithelial ovarian cancer, enrolled 23 patients, no DLT was established. The most frequent grade 3/4 adverse events reported included neutropenia (23%), febrile neutropenia (19%), and ileus (19%). No treatment-related deaths occurred. In terms of disease response, 11 of 21 patients had a response, 6 had stable disease and 3 progressive disease. Patients receiving the highest dose of tocilizumab, 8 mg/kg, showed increased levels of IL-6, as well as decreased levels of pSTAT3. [117]
7. Ovarian cancer evasion of immune destruction

Modulation of the immune system as an approach to developing cancer therapeutics has resulted in paradigm changes for several malignancies [118–120]. Immunotherapy also stands as a potential tool for the treatment of ovarian cancer. Tumor immunity is impacted by the many interactions that take place between the tumor cells and the tumor microenvironment. The tumor microenvironment contains a variety of immune cells including: CD8+ T cells, CD4+ helper 1 T cells (TH1), NK cells, M1 macrophages and dendritic cells that work against the tumor whereas regulatory T cells (T reg), M2 macrophages, myeloid-derived suppressor cells (MDSC), CD4 helper 2 T cells (TH2) cells promote tumor growth [121]. This immune-induced cancer pro- and anti-proliferative actions constitute a delicate balance that occurs in three distinct phases namely Elimination, Equilibrium, and Escape [111]. The elimination phase, engages innate and adaptive immunity to eliminate new cancer cells. Cancer cells able to evade elimination proceed to the equilibrium phase, in which tumor and immune cells interaction keeps the tumor in a latent state of control. Last, in the escape phase, a hallmark of cancer, cancer cells resist immune control leading to disease progression [122].

7.1. PD-1 and PD-L1 inhibitors

The programmed death-1 (PD-1) receptor (CD279) and its ligands, PD-L1 and PD-L2 (B7-DC; CD273), represent a novel pathway that regulates the balance between stimulatory and inhibitory signals needed for effective immunity and the maintenance of self-tolerance and T cell homeostasis [123]. In normal tissues, PD-1 constrains self-reactive effector T cell functions against non-hematopoietic tissues and by suppressing tissue-reactive T cells, facilitates tissue tolerance and defends against immune-mediated tissue injury [124,125]. In discordance to the crucial beneficial PD-1 role in preserving T cell homeostasis, following interaction of PD-1 and its expressed ligands on malignant tumors, PD-1 leads to effective inhibitory signals that prevent the expansion of T effector cells and have detrimental effects on antitumor immunity [125,126].

PD-1 blocks cell cycle progression in the G1 phase. PD-1 does not affect G1 phase cyclins or cyclin-dependent kinases (Cdk5s) expression; it does however target Ras and PI3K/Akt signaling to inhibit transcription of Skp2 and to activate Smad3 as an integral component of a pathway that regulates blockade of cell cycle progression in T lymphocytes [127]. The PD-1 and PD-L1 pathway represents an inhibitory pathway of tumor-associated T lymphocytes, its blockade by antagonism of PD-1 and PD-L1 receptors, induces activation of proliferative pathways resulting in T cell expansion.

PD-1 and PD-L1 inhibitors toxicity profile is characterized mainly by immune-related adverse events (irAEs). IrAEs may include involvement of any organ, most frequently dermatologic, gastrointestinal, hepatic and endocrine inflammatory events. These toxicities are related to augmentation of the immune system primarily due to the activity of these immunomodulatory compounds. They are also usually responsive to treatment with corticosteroids and in some cases requiring tumor necrosis factor-alpha antagonists.

Although PD-1 and PD-L1 inhibition objective is to achieve better immune response against the tumor through proliferation induction and not inhibition, we consider it important to include in this review the emerging data of PD-1 and PD-L1 activity in the treatment of EOC.

7.1.1. Pembrolizumab

Pembrolizumab is a mAb that targets PD-1 thus preventing the binding of PD-L1 and PD-L2 ultimately allowing T cell activation against the tumor cells [128]. A multicohort phase Ib trial assessed pembrolizumab 10 mg/kg activity in multiple solid tumors expressing PD-L1 26 patients enrolled in the ovarian cancer cohort, including advanced EOC, primary peritoneal carcinoma or fallopian tube cancer after disease progression of previous treatment. CR was detected in one patient, 2 patients achieved partial response and 6 patients had stable disease. ORR was 11.5%, treatment was tolerable [129].

7.1.2. Nivolumab

Nivolumab is a human anti-PD-1 IgG4 mAb blocks binding of PD-1 and has shown [130] marked activity in malignant melanoma and lung cancer, and is indicated for the treatment of both malignancies advance disease stage [131–133].

A phase I trial that assessed nivolumab activity in patients with advanced tumors, 17 patients with EOC were included, 6% had PR and 18% had SD [134]. A subsequent phase II trial in patients with platinum-resistant EOC, nivolumab ORR was 15%, disease control rate was 45% and median OS was 20 months. Similar to nivolumab trials in other malignancies, PD-L1 expression was not helpful to predict response. Grade 3–4 treatment related AEs and SEAs occurred in 40 and 10% of the patients [135].

7.1.3. BMS-936,559

BMS-936,559 is a human IgG4 mAb anti-PD-L1. A phase I study assessed BMS-936,559, included patients with ovarian cancer. In this study, PR in 6% and SD for over 24 weeks in 18% was achieved in patients receiving the MTD of 10 mg/kg. [136]

7.1.4. Avelumab

Avelumab, a human IgG1 mAb targeting PD-L1, additionally, due to its functional IgG1 Fc region, avelumab is also capable to facilitate tumor cells.

A phase I study evaluated avelumab in patients with advanced refractory cancers, including EOC, which ultimately led to a phase IIb study in patients with recurrent or refractory ovarian cancer (NCT01772004). Findings from the phase IIb showed that PR was achieved in 17.4% of patients and SD in 47.8%, respectively [137]. Presently, a phase III trial is recruiting advanced platinum-resistant or refractory EOC patients to evaluate single-agent avelumab in comparison to avelumab in combination with PLD or PLD alone (NCT02580058).

7.1.5. Durvalumab

Durvalumab, a human IgG1 mAb targeting PD-L1.
In a phase I/II clinical trial (NCT02484404), currently ongoing, assesses durvalumab combination with either olaparib a PARP inhibitor or with cediranib a VEGFR TKI inhibitor. In this trial, 1 out of 9 patients treated with durvalumab in combination with olaparib, achieved a partial response for more than 11 months and in the arm assessing combination of durvalumab with cediranib, 1 out of 5 patients achieve a partial response for 7 months. Main side effects reported were lymphopenia and anemia, and in the durvalumab and cediranib arm, lymphopenia and anemia, nausea diarrhea, pulmonary embolism and fatigue [138].

7.1.6. Atezolizumab
Atezolizumab, a humanized IgG1 mAb targeting PD-L1.

An ongoing phase III randomized, double-blinded, compara- tive, multicenter clinical trial (NCT02891824), the ATALANTE trial is currently enrolling patients with EOC, primary peritoneal and/or fallopian tube adenocarcinoma, with platinum-sensitive recurrence, to assess the efficacy of atezolizumab in combination with platinum-based chemotherapy plus bevacizumab.

8. Competitive environment

Table 3 Competitive Environment of Emerging Growth Factor Receptor Antagonists for Ovarian Cancer treatment in phase I/ II, phase II, or phase III of development.

9. Potential development issues

As we move forward in the knowledge of EOC pathogenesis, finding potential targets for treatment, new essential ques- tions arise, adding complexity to the ongoing building treat- ment path.

One fundamental view regarding future successful develop- ments in EOC therapeutics recognizes the significance of finding treatment targets, ideally those determined by disease driving mutations, and subsequently finding highly specific targeting agents. Nevertheless, it is equally or even more important to be able to quantify the functionality of the target, before and after exposure to the specific treatment.

10. Conclusion

EOC encompasses a wide variety of pathologies and as such, changes in the paradigm of care have been long and complex. Our contemporary understanding of disease etiology and pathogenesis has improved and has resulted in the development of novel EOC treatment options. This new knowledge has helped guide the development of novel therapies target- ing EOC growth factor pathways by antagonizing effect of their driving receptor. Several of these molecules are in differ- ent stages of development, many still struggling to find the ideal patient population and treatment-specific protocol combi- nation to achieve meaningful EOC patient outcomes. Based on our review, we found that the most promising growth factor receptor antagonists for EOC treatment involve folate receptor alpha inhibitors, IL-6 and VEGF inhibition, and immu- nomodulation. The ultimate success of these treatments in achieving disease control and maybe cure, depends upon the identification of biomarkers as well as good understanding of different targets modulating their synergy.

It is apparent that treatment of EOC is rapidly evolving to a more personalized standard. Basing treatment decisions on unique tumor molecular features in patients is requisite to target those hallmarks of disease that enable tumor growth and survival. Nevertheless, many of these treatments are cur- rently in late stages of development, and hopefully will be approved for EOC treatment, ultimately achieving better treatment outcomes.

11. Expert opinion

Receptor signaling has been well characterized for most of the hallmarks of cancer. Growth receptor antagonist molecules are mainly represented by high receptor affinity monoclonal antib- oodies that have been established as one of the most specific and successful treatments in cancer over the last two decades. Monoclonal antibodies cause tumor cell death by several mechanisms including: (i) direct action of the antibody either through receptor blockade, induction of an agonist activity or by the ability to deliver a cytotoxic agent, (ii) immu- nemediated cell killing mechanisms via activation of antibody- dependent cellular cytotoxicity (ADCC) and complement- dependent cytotoxicity (CDC) as well as direct regulation of T cell function and (iii) via specific antibody effects on tumor microenvironment (stroma and vasculature). Growth receptor antagonism by way of monoclonal antibody targeting has been shown to be especially effective when a related predic- tive biomarker of response is identified. Therefore, along with the promising development of novel receptor antagonists or modulators in EOC treatment, targeting essential growth path- ways in the tumor and associated microenvironment, biomar- kers discovery remains crucial towards improving clinical responses in EOC.

There is a strong scientific rationale to target Erb1/HER1 in EOC treatment. Although Cetuximab treatment is tolerable, no significant improvements in outcomes were recorded either as single agent or in combination with chemotherapy [50–52]. Nevertheless, current evidence of cetuximab in EOC treatment is based upon clinical trials performed in small heterogeneous populations of EOC in different treatment settings. Therefore, a more thoughtful investigation of Erb1/HER1 in EOC treat- ment should be considered, with better patient population specification, treatment setting as well as mandatory tumor/ patient assessment for biomarkers. For such clinical trials evalu- ating new generations of Erb1/HER1 monoclonal antibodies, fully humanized, is suggested. Moreover, combination with additional treatment modalities, such as antiangiogenic ther- apy or immunomodulatory agents is warranted.

FRα targeting, stands as one of the most promising EOC treatment alternatives. As for other treatment strategies, find- ing a biomarker predictive of FRα targeting treatment response appears to be particularly essential for achieving success using these agents. This will probably be a key factor in demonstrating efficacy in platinum-resistant EOC. For this purpose, it is necessary to pursue novel approaches to assess receptor expression as possible predictive biomarker, to
<table>
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<tr>
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<th>Structure</th>
<th>Indication</th>
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<td>Targets Erb1/HER1 (EGFR)</td>
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<tr>
<td>Avelumab</td>
<td>Merck KGaA, Pfizer, Eli Lilly</td>
<td>Human IgG1 mAb</td>
<td>Metastatic Merkel cell carcinoma</td>
<td>Phase III</td>
<td>Antagonizes PD-L1</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Medimmune/ AstraZeneca Genentech</td>
<td>Human IgG1 mAb</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>Phase II/II</td>
<td>Antagonizes PD-L1</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Genentech</td>
<td>Humanized IgG1 mAb</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>Phase III</td>
<td>Antagonizes PD-L1</td>
</tr>
</tbody>
</table>

DL14: Delta-like ligand 4; EGFR: epithelial growth factor receptor; Erb1/HER1: epithelial growth factor receptor; FR alpha: Folate receptor alpha; Her 2: human epidermal growth factor receptor 2; HHV: Human herpes virus; HIV: Human immunodeficiency virus; HNSCC: Head and Neck squamous cell carcinoma; IgG: Immunoglobulin G; mAb: Monoclonal antibody; NSCLC: Non-small cell lung cancer; PD-1: programmed cell death protein; PD-L1: programmed cell death ligand 1; PDGFR: platelet-derived growth factor receptor; VEGF A: vascular endothelial growth factor A.
overcome potential factors affecting receptor expression, such as tumor heterogeneity and receptor variability. The new conjugate molecules stand as a promise to improve outcomes by better chemotherapy delivery and immune targeting united.

Targeting of angiogenesis continues to be an essential component of EOC tumor control, allowing not only better cytotoxic treatment delivery by normalizing tumor vasculature but also by directly blocking tumor growth stimuli. One of the values of the evidence accumulated in VEGF pathway EOC targeting, is that it included patients with performance status 2 and some of the trials also included histologies with limited treatment options, this research approach, approximates these results to the real-world clinical experience.

We are living in an exciting time in oncology as well as in EOC, changing treatment paradigms through the fast introduction of novel compounds that have changed the perspective of how to evaluate outcomes and clinical benefit. The introduction of new concepts in EOC treatment such as the value of maintenance treatment with antiangiogenic agents and PARP inhibitors has generated additional questions focusing on different compound combination strategies that are being tested in large randomized controlled trials. These new treatment approaches will impose new challenges, such as determining ideal treatment schedules, management of toxicities, as well as requiring the thoughtful introduction of pharmacogenomic and response assessment through conventional imaging. This will probably require the parallel development of novel targeted imaging strategies.

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Declaration of interest
L Bonilla is a fellow at University Health Network. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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