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Review Article

The VEGF/VEGFR2 system in ovarian cancer: From functional to pharmacological significance

Elisabetta Grillo [a,*], Chiara Romani [b], Victoria M. Ettorre [c], Alessandro D. Santin [c], Stefania Mitola [a,*]

[a] Department of Molecular and Translational Medicine, University of Brescia, Via Branze 39, 25123 Brescia, Italy
[b] Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy
[c] Department of Obstetrics, Gynecology, and Reproductive Sciences, Division of Gynecologic Oncology, Yale University School of Medicine, New Haven, CT 06520, United States of America

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ABSTRACT

The vascular endothelial growth factor receptor 2 (VEGFR2) is a tyrosine kinase receptor regulating a variety of biological processes, including embryonic development, angiogenesis, tissue homeostasis and cancer. VEGFR2 is activated by canonical VEGFs and non-canonical ligands, triggering intracellular signaling cascades that mediate its biological activity. Preclinical studies show that VEGFR2 plays a complex yet pivotal role in the progression of ovarian cancer (OC), a deadly disease with a global burden of more than 320,000 women in 2022. Several inhibitors of the VEGF/VEGFR2 axis have been developed and are currently approved or included in clinical trials/preclinical studies for the therapy of different subtypes of OC. Originally developed as anti-angiogenics, anti-VEGF/VEGFR2 drugs are now well-known to also affect tumor cells, immune cells and cancer-associated fibroblasts (CAFs), also in OC. In this review we address the specific role of the VEGF/VEGFR2 axis in OC cells, and, from this perspective, we discuss the therapeutic significance of VEGFR2 targeting. Dissection of the molecular landscape modulated by the VEGF/VEGFR2 system in tumor cells in addition to stromal ones will facilitate ongoing translational efforts directed toward OC therapy.

Significance statement: Anti-angiogenics blocking the VEGF/VEGFR2 axis are widely used to treat ovarian cancer, although resistance and poor response occur. Recent advances reveal that anti-VEGF/VEGFR2 drugs act on multiple compartments, including ovarian cancer cells. This review discusses the functional and pharmacological significance of the VEGF/VEGFR2 axis in ovarian cancer cells highlighting insights from preclinical and clinical studies. A deeper understanding of this pathway is essential for a safe/efficacious usage of anti-angiogenics targeting the VEGFR2 pathway in ovarian cancer.

1. Ovarian cancer

1.1. Ovarian cancer epidemiology

Ovarian cancer (OC) is the seventh most common cancer in women and the eighth most common cause of cancer death globally, with five-year survival rates below 45 % (https://ocrahope.org). The median age of onset is 62 years old. The incidence has slightly decreased by 1–2 % per year from 1990 to mid-2010s and by up to 3 % per year from 2015 to 2019, possibly due to increased use of oral contraceptives and less use of hormone replacement therapy [1]. OC mortality has decreased by 40 % since 1975. Despite this and the increased the awareness of OC, curative and survival trends remain largely unsatisfactory, when compared to other female tumors, because OC remains difficult to diagnose in the early stage. This is due in part to the lack of a definitive screening tool and partially to vague signs and symptoms overlapping with other non-malignant conditions [2]. Consequently, about 75–80 % of the patients present an advanced disease at the diagnosis. The presence of metastases already at the time of diagnosis is an independent predictor of reduced overall survival (OS) [3].

Several risk and protective factors for OC have been identified such as medical history, body size, lifestyle, reproductive history and exogenous hormone use. Among the protective factors there are oral contraceptives and tubal ligation. Instead, family history of ovarian or

* Corresponding authors at: Department of Molecular and Translational Medicine, University of Brescia, Viale Europa 11, Brescia 25123, Italy.
E-mail addresses: elisabetta.grillo@unibs.it (E. Grillo), stefania.mitola@unibs.it (S. Mitola).

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breast cancers, endometriosis, older menopausal age, menopausal hormone therapy, obesity and smoking increase the risk of OC [2].

1.2. Ovarian cancer classification

OC encompasses heterogeneous diseases with specific clinicopathologic features and prognosis. Most epithelial ovarian cancers (EOCs), in particular high-grade serous ovarian cancer (HGSOC) are believed to originate from epithelial cells in the fallopian tube fimbriae and are classified based on morphological and immunohistochemical features [4]. HGSOC represents the largest histological type (68 %), followed by clear cell (12 %), endometrioid (11 %), mucinous (3 %) and low-grade serous carcinoma (3 %) as well as other rare types (3 %). These differ in epidemiology, risk factors, dissemination patterns, genetic alterations, response to therapy and prognosis. Integrated pan-genomic studies show a convergence of genomic alterations into EOC subgroups [5]. More than 90 % of HGSOC is characterized by mutation of TP53 and/or by germline or somatic mutations of BRCA1 and BRCA2. Clear cell carcinoma, which has a close association with endometriosis, contains mutations in PTEN and PIK3CA. Mutations involving ARID1A (AT-rich interactive domain 1A gene) are documented, as well as in endometrioid carcinoma, which also present β-catenin alterations (CTNNB1, 38 %) and PTEN alterations (14 %). The mutations most frequently found in mucinous tumors are those that affect KRAS, present in approximately 40 % of cases. Low-grade serous carcinoma does not have p53 and BRCA mutations but, in approximately $^{2}/_{3}$ of cases, it harbors BRAF and KRAS mutations.

More recently, transcriptional TCGA studies suggested four EOCs subtypes based on their expression profiles: immunoreactive, differentiated, proliferative and mesenchymal. This classification can predict prognosis, and the different subtypes are associated with drug response. The immunoreactive subtype selectively expresses CXCR3 and CXCR7 receptors, while the proliferative one highly expresses HMGA2, SOX11, MCM2 and PCNA with the reduction of the ovarian markers MUC1 and MUC16. On the contrary, the differentiated subtype maintains the expression of MUC1, MUC16 and SLP1. Finally, the mesenchymal form presents high expression of HOX genes and the markers FAP, ANGPTL2 and, ANGPTL1 [6]. The proliferative and mesenchymal subtypes share an angiogenic signature and respond better to the anti-angiogenic drug bevacizumab.

1.3. Ovarian cancer pathogenesis

The pathogenesis of OC remains poorly understood up to date, and this partially explains the limitations in its early detection and the lack of treatments efficacious in the long-term. Originally, OC was thought to originate from the tumorigenic transformation of the epithelium of the ovary that, stimulated by hormones, undergoes uncontrolled proliferation. However, precancerous lesions cannot be found in most cases. Also, this hypothesis cannot explain the pathogenesis of the diverse histological and molecular subtypes of OC. More recently it has been suggested that OC is a heterogenous disease, where only a small percentage originates in the ovary. Type I OCs, comprising low grade serous, low-grade endometrioid, clear cell and mucinous carcinomas, are genetically stable, wild-type for *TP53* and remain confined to the ovary at diagnosis. They have been proposed to originate from benign ovarian cystic neoplasms. Type II OCs, including HGSOC, are highly aggressive and diagnosed at an advanced stage. They display *TP53* mutation in over 80 % of cases. They originate outside the ovary (fallopian tube) and ovarian colonization occurs secondarily (see below). Endometrioid and clear cell tumors are associated with endometriosis and the endometrium could be the source of these tumors [7,8]. However, further studies are ongoing to clarify these aspects as there is a lack of consensus about the cellular and molecular events that drive OC development.

1.4. Ovarian cancer metastatic dissemination

The dissemination of OC usually follows routes that are alternative to hematogenous and lymphatic metastasis. Indeed, approximately 77 % of OC disseminates within the abdominal cavity *via* the peritoneum (*i.e.* transcoelomic dissemination). Transcoelomic dissemination is facilitated by the proximity of the site of origin to the peritoneal cavity, and allows dissemination into the peritoneal cavity, omentum and abdominal organs [9]. Briefly, cancer cells exfoliate from the primary tumor, acquire the capacity to resist anoikis, form multicellular aggregates, and invade the mesothelial barrier, thus homing and colonizing metastatic sites. In the adipocyte-rich omentum, a metabolic crosstalk between metastatic OC cells and adipocytes has been reported [10] and could contribute to the progression of metastatic OC. Proteolytic molecules, such as metalloproteases (MMPs), and pro-angiogenic factors including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs) and angiopoietin contribute to the metastatic events.

Together with transcoelomic metastasis, hematogenous dissemination to distant organs also occurs and further worsen the prognosis of OC patients. Less frequent (3–24 %) metastatic sites are pancreas, spleen, stomach, and even more rarely (1–12 %) thyroid, bones, brain, skin, heart, breast and kidney. Clinically, an increased risk of central nervous system (CNS) distant metastasis in patients treated with intraperitoneal chemotherapy after optimal debulking surgery [11] or undergoing inferior vena cava (IVC) filter placement after surgery, has been observed [12]. S. Pradeep et al. experimentally described preferential hematogenous spread of OC cells into the omentum driven by the interaction between the Erb-B2 receptor tyrosine kinase 3 (ERBB3) expressed by OC cells and its ligand neuregulin-1 expressed by the omentum [13]. OC cells also have tropism for lymph nodes, sustained by VEGFR3. By immunohistochemical analyses of VEGF-A, VEGF-C and VEGF-D in OC samples, Kuerti and colleagues demonstrated that an increased expression of VEGF-C correlated with the presence of retroperitoneal lymph node metastasis and reduced OS, supporting the role of VEGFR3/VEGF-C axis in lymphatic invasion [14].

More than 90 % of patients with stage III-IV develop abdominal inflammatory ascites. Ascites containing tumor spheroids, macrophages, fibroblasts, and soluble factors including cytokines (IL6, IL10, CCL18, CCL22, TNF-alpha, TGF-beta) and components of the ECM significantly contribute to tumor progression and dissemination. Ascites is associated with pain, discomfort, damage to abdominal organs, and often requires repeated paracentesis to drain the excess fluid [15].

Although much effort has been put into understanding the mechanisms of OC spread, the metastatic cascade of OC is not completely characterized. The identification of the mechanisms involved in OC dissemination will help the development of novel therapeutic strategies.

1.5. Ovarian cancer therapy

The therapeutic approach is based on several factors such as age and stage at diagnosis. The standard treatment is a complete surgical resection of uterus, cervix, omentum, fallopian tubes and ovaries followed by adjuvant platinum-based chemotherapy, in association with carboplatin or paclitaxel. Alternatively, in patients with widespread abdominal disease involving the upper abdomen, multiple comorbidities or stage IV disease, neoadjuvant chemotherapy is administered before the surgery, followed by interval cytoreductive surgery, and by additional platinum/taxane chemotherapy [1]. Unfortunately, 70 % of the patients relapse within 2–3 years.

In recent years, therapies to target specific molecules (*e.g.* mutations, gene amplifications) have been developed to complement surgery and chemotherapy. Among others, the antiangiogenic agent bevacizumab, a humanized monoclonal antibody targeting VEGF was the first biological drug studied in OC. Indeed, OC releases an excessive amount of VEGF, a potent and well-known activator of endothelial cells (ECs) promoting

tumor vascularization. FDA approved bevacizumab for the frontline and maintenance treatment in OC in 1998. However, several side effects were described including venous thromboembolism, hypertension and proteinuria. Also, clear effects of anti-VEGF treatment for OC have not been established. In addition, an increased risk of metastasis following bevacizumab treatment has been described in other tumor types, thus requiring a better evaluation of the use of anti-VEGF/VEGFR2 drugs in cancer, including OC [16–19].

Finally, several poly ADP-ribose polymerase (PARP) inhibitors including but not limited to olaparib, niraparib and rucaparib, have been developed. Olaparib, the first PARP inhibitor to be granted approval, is currently indicated as maintenance monotherapy in OC patients with relapsed disease and mutated Breast Cancer Genes (BRCAs) who have reached a complete or partial resistance to platinum-based chemotherapy [20]. Randomized clinical trials showed significant benefits in terms of progression-free survival, with acceptable tolerability and no deleterious effects on quality of life.

1.6. *High-grade serous ovarian carcinoma (HGSOC)*

HGSOC is the most frequent and aggressive subtype of OC, it causes almost 80 % of OC deaths. It accounts for about two-thirds of all OC cases. The late diagnosis of HGSOC may be due to the lack of consensus on its site of origin, which negatively impacts screening strategies. Putative precursor lesions that resemble HGSOC (morphologically and molecularly) have been detected into the fallopian tube, designated as serous intraepithelial tubal carcinoma (STIC). These lesions harbor TP53 mutation in over 80 % of cases. This suggests that HGSOC originates from a STIC in the fimbriae of the fallopian tube that extends onto the ovary [21]. HGSOC rapidly disseminates to the abdomen, and becomes symptomatic only at a high stage, resulting in poor outcome.

Morphologically, HGSOC is composed of ciliated columnar cells that form papillae, solid masses, or slit-like spaces with high-grade nuclear atypia [22]. HGSOC is a molecularly heterogeneous disease. Somatic mutation of *TP53* is an early event in HGSOC carcinogenesis and occurs in the vast majority of cases. About 15–20 % of tumors have germ mutations in BRCA1 and BRCA2 that have become predictive prognostic factors. In addition, somatic mutations of BRCA1/2, loss of the oncosuppressors NF1, RB1, and PTEN, and copy number variations are frequently found [20,23,24]. Recently, a rare and biologically aggressive variant of HGSOC has been identified as claudin-low subtype (CL-HGSOC), similarly to claudin-low breast cancers [25,26]. CL-HGSOC exhibits stem-like chemo-resistant features [25]. The altered function of claudins compromises cell cohesion, increases invasiveness and inhibits cell differentiation. Furthermore, claudin-7 expression in primary HGSOC correlates with clinicopathological features, including the site of metastasis and the route of dissemination [27].

During HGSOC progression, cancer cells undergo epithelial-to-mesenchymal transition (EMT) with the expression of vimentin, EB1, TWIST, Slug and Snail [28]. In this context, cancer cells upregulate the expression of metalloproteinase (MMPs), and modify the repertoire of adhesion molecules, thus supporting cell dissemination [28,29]. Moreover, metastatic HGSOC cells increase the expression of L1CAM. This adhesion molecule, interacting with its receptor neuropilin-1 (NRP-1), favors cell adhesion to the mesothelium [28]. HGSOC metastasis is further facilitated by the upregulation of $\alpha_5\beta_1$ and $\alpha_V\beta_3$ integrins. During the EMT of HGSOC cells claudins are also dysregulated and mislocalized [30]. For example, claudin 3 is unengaged in the formation of tight junctions [31], and it has been proposed as a diagnostic and therapeutic biomarker. Disruption of tight junctions is necessary for detachment of cancer cells from the primary tumor to start tumor dissemination. On the other hand, claudins facilitate collective migration, which promotes the mutual survival of cancer cells. Claudins can finally play a role in the establishment of new metastases given their involvement in the reverse EMT, called “mesenchymal-to-epithelial transition” (MET), occurring at metastatic sites [30].

2. The VEGF/VEGFR system

The vascular endothelial growth factors (VEGFs) are secreted factors that control numerous physiological processes, including vessel permeability, and angiogenesis. The VEGF family comprises VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor (PlGF). VEGFs exert their biological functions by binding VEGF receptors (VEGFR1–3) on the surface of target cells and activating intracellular signaling pathways. In this review we focus on VEGFR2.

VEGFR2 is expressed in endothelial, mesothelial cells, hepatocytes, smooth muscle cells, fibroblasts, macrophages and adipocytes. Its function on ECs is very well characterized. VEGFR2 activation leads to an increase in vessel permeability. At the same time, VEGFR2 activation promotes the pro-angiogenic activation of ECs, characterized by an increase in the ability to degrade the basement membrane, migrate/invade, proliferate and form new blood vessels [32]. Thus, VEGFR2 promotes physiological angiogenesis.

VEGFR2 is a typical receptor tyrosine kinase (RTKs) expressed on the surface of different cell types and characterized by 7 extracellular immunoglobulin-like domains, a single transmembrane region and an intracellular tyrosine kinase domain. Several ligands have been identified including the different isoforms of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and the non-canonical ligands gremlin-1 and HIV-1-Tat [33,34]. Upon ligand binding, VEGFR2 dimerizes, favoring the activation of the intracellular kinase domains and the rapid autophosphorylation of tyrosine residues. These residues become docking sites for second intracellular messengers. These events eventually result in the activation of intracellular signaling pathways supporting physiological and pathological processes, including cell survival, proliferation, differentiation, regulation of metabolism and migration. Several major phosphorylation sites are involved in cellular signaling mediated by the kinase domain of VEGFR2, including Y951, Y1054, Y1059, Y1175 and Y1214 (Takahashi et al., 2001; Matsumoto et al., 2005). Phosphorylation of Y951 is essential for downstream signaling by the activated kinase. Phosphorylation of Y1054 and Y1059 induces the autophosphorylation of Y801 which enhances the VEGFR2 kinase activity. Indeed when Y801 is unphosphorylated the activation loop interacts with the kinase domain inhibiting the enzymatic activity [35,36]. Another important region in the VEGFR2 activation and signaling is the carboxyl terminus domain which contains two key autophosphorylation sites, Y1175 and Y1214 along with putative serine phosphorylation sites [37]. The activation of VEGFR2 is regulated through different mechanisms: i) ligand-receptor selectivity; ii) engagement of co-receptors (neuropilin-1 [38,39], integrins [40], heparan sulfate proteoglycans [41]; iii) receptor hetero-dimerization with VEGFR1 [42,43]; iii) sequestration of ligands by the soluble receptor forms (*i.e.* sVEGFR1-2) [44]. Activated VEGFR2 recruits several intracellular messengers and adaptors molecules including phospholipase C-γ (PLC-γ), protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the extracellular signal-regulated kinases (Erk) [32] as well as the adaptors SHB and SCK [45]. The interaction with ligand drives VEGFR2 dimerization, activation and transphosphorylation at specific tyrosine residues, leading to recruitment of adaptor proteins and activation of downstream signaling pathways. The PLCγ pathway is initiated by phosphorylation at Y1175 promoting EC proliferation, migration, and gene transcription [46]. VEGFR2 signaling also involves the Ins-P3, PI3-kinase and MAP kinase pathway. Specifically, PLCγ catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) at the plasma membrane, generating inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) which in turn respectively activate protein kinase C (PKC), and induce Ca^{2+} release from the endoplasmic reticulum [47,48]. VEGFR2 phosphorylation at Y799 and Y1175 triggers the activation of PI3K–Akt pathway, supporting ECM remodeling, EC survival, migration, and vascular permeability. Cell adhesion and vascular permeability are also modulated by Src pathway, which is activated by the interaction with phosphorylated Y951 of VEGFR2. Particularly, Src

modulates cytoskeletal dynamics and cell–cell adhesion by phosphorylation of FAK and VE-cadherin [49,50].

The VEGF/VEGFR2 axis also regulates the activation and nuclear translocation of different transcriptional factors involved in EC differentiation including ETS1, ETS2, ERG, ELK3, FLI1, ETV1, ETV2, ETV5, and ETV6 [51–53].

2.1. The VEGF/VEGFR2 system in cancer beyond angiogenesis

During tumor progression, tumor cells acquire the ability to produce high amounts of pro-angiogenic factors (the so-called "*angiogenic switch*"), including VEGF-A. In this context, VEGFR2 expressed on ECs mediates the aberrant and chaotic process of formation of new blood vessels that are necessary to provide tumor cells with oxygen, nutrients and access to the vascular system for metastasis [see [54,55] and references therein]. On these bases, therapeutic targeting of the VEGF/VEGFR2 axis has been developed and is routinely recommended or under clinical evaluation for a variety of tumors, including ovarian cancer (see below).

However, the function of VEGFR2 in cancer is not limited to angiogenesis but also contributes to key aspects of tumorigenesis, including the development of cancer stem cells, tumor initiation and progression. Here we focus on the role of the VEGF/VEGFR2 specifically in tumor (ovarian cancer) cells, as emerging literature has highlighted that cancer cells have an active VEGF/VEGFR2 axis that regulate fundamental biological processes. Indeed, VEGFR2 is highly expressed on tumor cells in multiple types of human solid tumors, including glioma, lung, breast, renal, ovarian and gastrointestinal tract carcinomas. A VEGF/VEGFR2 autocrine loop promotes the growth, survival, migration and invasion of cancer cells [56,57] through the activation of the JAK2/STAT3 pathways, the modulation of ECM [58] or the inactivation of p21, eventually preventing senescence in colon cancer cells [59]. VEGFR2 also supports cancer stem cells (CSCs) self-renewal *via MYC* and *SOX2* upregulation in breast and lung cancer cells [60]. In glioblastoma, a persistent autocrine signaling through VEGF/VEGFR2/Neuropilin-1 loop promotes CSC viability and enhances mouse survival [61]. In the same setting, direct targeting of VEGFR2 *via* knockdown or pharmacologic inhibitors consistently reduces stem cell properties [62,63].

The VEGF/VEGFR2 axis is recurrently hyperactivated in tumor cells, leading to the propagation of oncogenic signaling and aberrant cell growth, migration and invasion [64,65]. VEGFR2 activation could occur as a consequence of point mutations, gene amplifications, upregulation of its expression or overexpression of its ligands, or gene translocations.

Scattered reports have highlighted possible anti-tumoral roles of VEGFR2. For example, in non-small cell lung cancer the presence of VEGFR2 limits ephrin receptor signaling thus blocking tumor cell invasion [66]. Other studies showed that the inhibition of the VEGF/VEGFR2 axis in certain tumors leads to an increase in aggressiveness and an increase in the formation of metastases in breast, melanoma, glioblastoma and pancreatic carcinoma [16]. Thus, the role of VEGFR2 in cancer needs further evaluation for the efficacious and safe use of anti-angiogenics in clinical practice and could be context dependent.

2.2. The VEGF/VEGFR2 system in ovarian cancer

VEGF over-expression is an early event in OC tumorigenesis and supports tumor progression and spread. Indeed, OC is richly vascularized and dependent on VEGF-driven angiogenesis. Also, high VEGF levels contribute to increase the vascular permeability, sustaining OC-associated ascites. VEGF expression is also found in omental metastases and represents a negative prognostic factor [67]. This has substantiated the use of anti-VEGF approaches in OC (bevacizumab, see below). However, VEGF/VEGFR2 system plays pleiotropic functions in OC beyond angiogenesis. Indeed, this system has emerged to regulate other stromal compartments, including immune cells and extracellular matrix, the latter possibly by regulating remodeling enzymes (*e.g.* MMPs) [68]. The hypoxia-induced elevated levels of VEGF found in OC reduce local immunity, by inducing myeloid-derived suppressor cell proliferation and immunosuppressive properties (*e.g.* favoring the conversion of naive $CD4^+$ T cells into regulatory T cells) [69], by directly suppressing T cell activation [70] or by inhibiting natural killer T cell-mediated antitumor response [71]. Consequently, interrupting the VEGF/VEGFR2 axis with various anti-VEGF/VEGFR2 agents reverts immunosuppression in different OC models. Moreover, the immunomodulatory effects of VEGF could in turn modulate the extent of angiogenesis by promoting EC activation. In addition, and relevant to the scope of the present review, numerous studies have shown that OC cells themselves express VEGFR2 and have an active VEGF/VEGFR2 axis [72,73]. In the SK-OV-3 cell line, VEGF administration activates all the canonical signaling pathways downstream to VEGFR2, including pERK, pp38, pPLCγ, pAkt, pFAK and pSrc [74]. Also, *in vitro* experiments showed a VEGF/pVEGFR2/pSTAT3 signaling axis in OC cell lines [75]. Consistently, the expression of VEGF, VEGFR1 and VEGFR2 are correlated with that of p-STAT3 in ovarian carcinomas [56]. A VEGF/VEGFR2 autocrine loop of stimulation promotes OC initiation through a Src-DNMT3A mediated mechanism [76]. VEGFR2 protects OC cells from anoikis [77]. Also, VEGFR2 sustains cell survival proliferation *via* a metabolism-dependent mechanism, as demonstrated by the effects of the VEGFR2-targeted TKi Apatinib [78]. VEGFR2 silencing suppresses lysophosphatidic acid (LPA)-induced OC invasion [79]. This data, together with the inhibitory effects of the TKi Tivozanib on OC cell motility [80], confirms the role of VEGFR2 in promoting OC initiation, growth, motility, invasion and metastatic dissemination (Fig. 1).

The role of co-receptors in the regulation of VEGFR2 activity in OC remains mostly unknown. However, VEGFR2 silencing *in vitro* possibly modulates the expression levels of neuropilin-1, integrins, and N-cadherin [81]. This suggests a cross-talk with these receptors that remain to be functionally validated. Moreover, VEGFR2 blockade in HGSOC cell lines modulates focal adhesion dynamics, FAK and mechanotransduction, possibly resulting in altered motility [82].

VEGFR2 is differentially expressed in OC compared to normal tissue [73]. Activated VEGFR2 in tumor cells has been associated with increased incidence of ascites and reduced OS. This has been linked to the activation of the AKT/mTOR/p70S6K1 signaling pathway [83].

Despite this evidence, scattered studies point to a tumor restraining role of VEGFR2 in OC, as already demonstrated in lung cancer [66]. Indeed, VEGFR2 silencing promotes HGSOC cell proliferation and motility. VEGFR2 downregulation alters the expression of cell-ECM adhesion molecules (*i.e.* integrins α5, β1, β3) and changes the mechanosensitivity of OC cells, and these changes possibly sustain, through FAK activation, the increased motility [81,82] (Fig. 1). In keeping with these observations, the overexpression of VEGFR2 correlates with long-term PFS in patients with advanced HGSOC, and patients with high expression of VEGFR2 may be less likely to experience disease recurrence within 5 years after primary chemotherapy [84].

3. The VEGF/VEGFR2 axis as a therapeutic target in OC: state of the art and new challenges

Given its important role in tumor progression, the VEGF/VEGFR2 axis has become an important therapeutic target for the treatment of multiple types of cancer. Anti-VEGF/VEGFR2 approaches were originally developed to counteract the VEGF/VEGFR2 system in ECs, thus blocking tumor angiogenesis. As such, anti-angiogenic drugs are routinely recommended for the treatment of metastatic colorectal and renal cell cancers, recurrent glioblastoma, pancreatic and stomach cancer and ovarian, fallopian tube and peritoneal cancer, among others. However, growing knowledge has clearly demonstrated that these drugs have the capability of targeting also other stromal cells (*e.g.* CAFs, immune cells) and the tumor parenchyma which often have an active VEGF/VEGFR2 axis (Fig. 2). The pathway can be targeted by sequestering the ligand, by neutralizing the receptor-ligand interaction or by

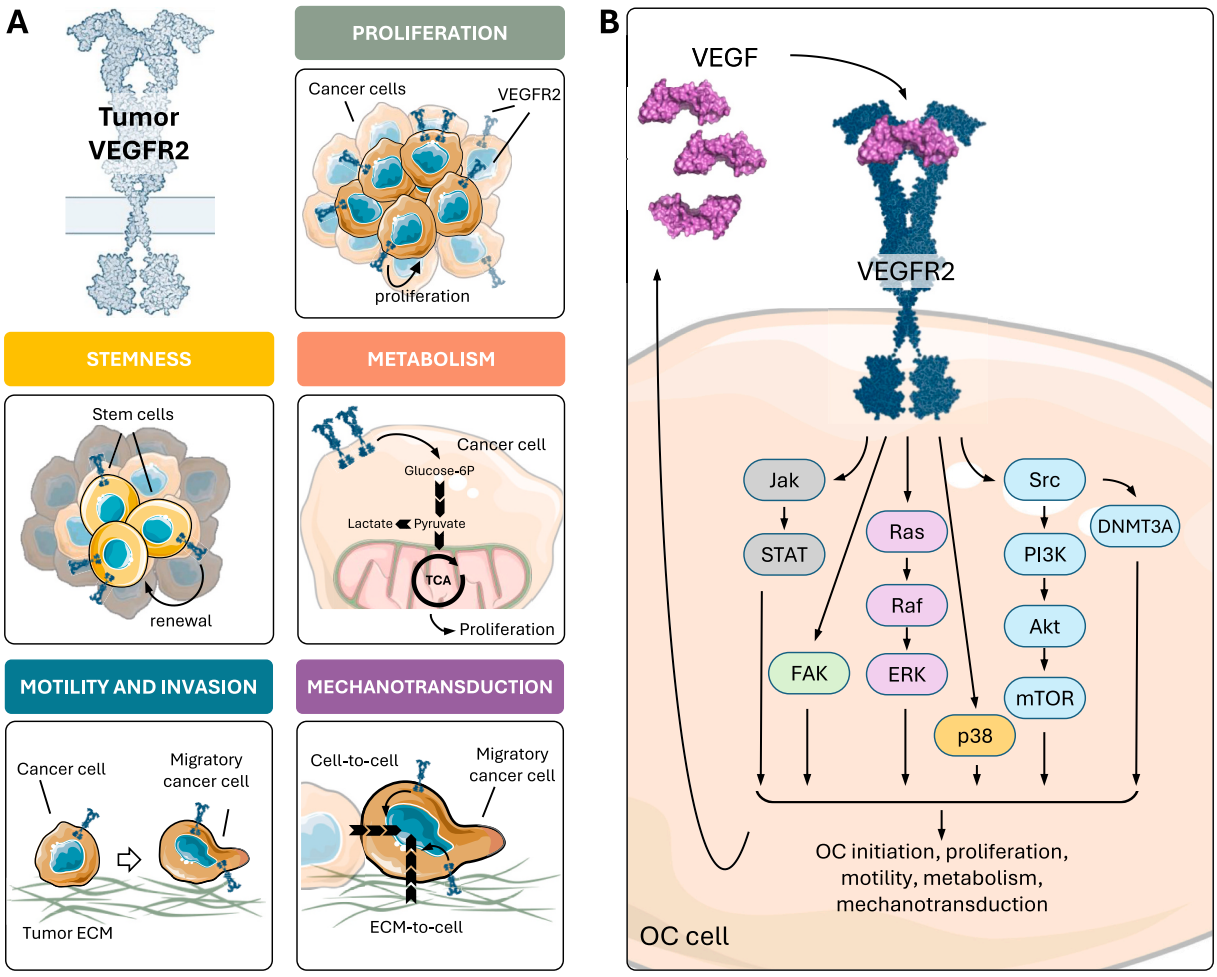

Fig. 1. The VEGF/VEGFR2 system in ovarian cancer. **A**, VEGF/VEGFR2 axis is involved in controlling multiple hallmarks of OC. **B**, Intracellular signaling of the VEGF/VEGFR2 in OC cells.

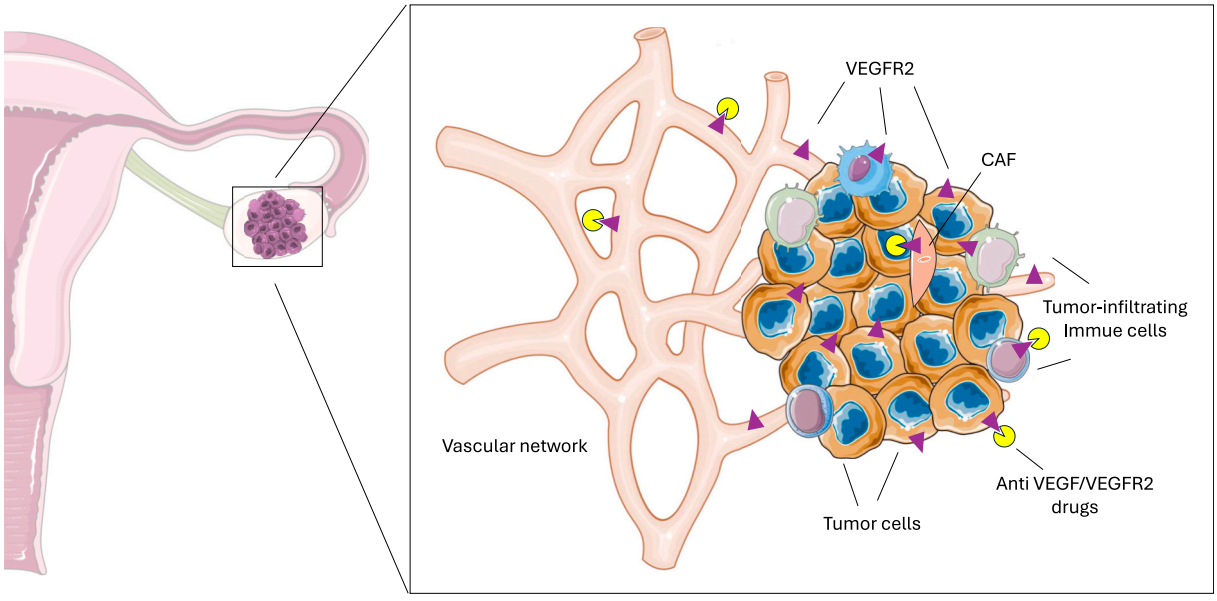

Fig. 2. The multi-compartment effects of therapeutics targeting the VEGF/VEGFR2 axis in OC. Anti VEGF/VEGFR2 drugs (*e.g.* bevacizumab, TKi, etc.) are used/in clinical trials as anti-angiogenics for OC patients. However, a large body of literature has proven that anti-VEGFR2 drugs directly target OC cells, affecting, among others, cell proliferation and motility. In addition, in other solid tumors the VEGF/VEGFR2 axis also regulates immune cells infiltrating the tumors as well as cancer associated fibroblasts (CAFs). Together, this data suggests that anti-VEGF/VEGFR2 drugs could exert multi-compartment effects in OC that deserve further pre-clinical/clinical investigation.

inhibiting the kinase activity of the receptor. In the next paragraphs we will cover the VEGF/VEGFR2-targeted pharmacological approaches that are in clinical practice or under clinical investigation for OC, focusing on their effects on tumor cells. Also, we will discuss the preclinical data regarding the use of anti-VEGF/VEGFR2 drugs using OC cell models.

3.1. Bevacizumab

As stated above, OCs produce huge amounts of VEGF. This factor induces tumor angiogenesis as well as it increases vascular permeability, leading to the development of ascites. This substantiates the use of the monoclonal antibody bevacizumab (Avastin), which sequesters VEGF-A, in OC patients [67]. Bevacizumab prevents VEGFR2 activation, and it was the first anti-angiogenic drug used in clinical practice. Nowadays it is recommended for treating multiple cancer types, including first-line treatment of metastatic breast cancer, renal cancer and primary ovarian, fallopian tube and peritoneal cancers at advanced stages. In OC, bevacizumab is administered in the frontline together with platinum-based chemotherapy and it is associated with increased survival rates [85]. However, bevacizumab administration has shown scarce and highly variable efficacy, possibly due to the lack of reliable predictive markers (see below) as well as to the high frequency of resistance. In this context, the tumor histotype and the individual molecular features may significantly impact on the patient response and thus should be considered carefully. A greater risk of peritoneal tumor spread was observed following bevacizumab treatment [86]. Also, a higher rate of extra-abdominal disease, especially pleura and lung, has been reported [87]. Similar increased malignancy after angiogenesis inhibitors was indeed reported in other cancer types and related to secondary mechanisms, like inflammation or the emergence of compensatory proangiogenic pathways that sustain neovascularization, and that need to be further clarified [88]. In OC the resistance to bevacizumab has different possible explanations. Among these, overexpression of EphB4 RTK has been proposed to mediate the resistance to bevacizumab, as confirmed by the sensitizing effects of EphB4 blocker NVP-BHG712 [89]. Moreover, resistant tumors display a marked infiltration of myeloid-derived suppressor cells and a reduction of $CD8^+$ lymphocytes that was found to be driven by an upregulation of GM-CSF. Consistently, inhibition of GM-CSF improves anti-VEGF therapy efficacy [90]. Finally a tumor cell autonomous interplay among VEGFR2, c-MET and $\alpha_5\beta_1$ has been proposed as a mediator of bevacizumab resistance [91–93]. Further research efforts are required to elucidate better the mechanism of action of bevacizumab (and resistance) in OC beyond inhibition of angiogenesis. This will clarify the therapeutic significance of sequestering VEGF in OC.

Therapeutic approaches similar to bevacizumab entailing only the Fab portion of anti-VEGF antibodies (Ranibizumab, Lucentis) or chimeric extracellular VEGFR1/VEGFR2 protein (Aflibercept) have been developed but are not recommended for OC treatment.

3.2. Ramucirumab

Ramucirumab is a fully human antibody that binds VEGFR2, impeding VEGF binding. Again, the use of this drug for the treatment of OC would be justified by the high VEGF levels detected in OC patients. For this reason this antibody is under clinical evaluation for OC patients. A phase II clinical trial has assessed its anti-tumor effect in patients with persistent or recurrent ovarian, fallopian tube, or primary peritoneal carcinomas (NCT00721162). Although some anti-tumor activity was observed, ramucirumab did not meet the predetermined endpoints (*i.e.* progression-free survival at 6 months and confirmed objective response rate) [94].

3.3. VEGFR2-targeted tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKi) are small molecules that inhibit the enzymatic function of the tyrosine kinase domain. Four different classes of TKi are available. The first class includes covalent inhibitors that usually have a binding, a linker and a warhead module that binds close to ATP binding site. Covalent TKis target the Lys residue within the active site or a Cys residue around the ATP binding site. Inhibitors belonging to this class have shown impressive clinical efficacy. However, mutation of the Cys residue, which is dispensable for the structure and function of kinases, could limit their binding and function. To date, no covalent VEGFR2-targeted TKi is approved or in clinical trials for OC patients.

Non-covalent inhibitors are instead sub-classified into 3 groups based on their mode of binding. Type-1 TKi are ATP-competitive inhibitors that bind to active kinases, where the conserved Asp-Phe-Gly (DFG) motif of the activation loop of the kinase domain is buried within the ATP-binding pocket (called DFG-in conformation). Pazopanib, Nintedanib, Cediranib and Suinitinib, all under clinical investigation for OC, are type-I TKis. Type-2 TKi are instead ATP-competitive inhibitors that bind kinases in their DFG-out inactive conformation. Sorafenib is the only Type-2 TKi directed toward VEGFR2 and under clinical investigation for the treatment of OC. Apatinib, tivozanib, cabozantinib and axitinib, which have been preliminarily evaluated in preclinical studies for OC, belong to this class. Finally, Type-3 inhibitors constitute a heterogeneous group of molecules that allosterically bind sites of the kinases that are remote from the ATP binding site (non-ATP-competitive). As expected, these inhibitors display the highest degree of selectivity. Up to date, no allosteric inhibitor of VEGFR2 is being considered for OC therapy [95].

3.3.1. VEGFR2-targeted TKi in OC: preclinical and clinical data

The preclinical activity of VEGFR2-targeted TKi has been validated on several OC cell models *in vitro* and *in vivo*. The histotypes and molecular heterogeneity of the OC cell lines, whose characterization is often debated, could represent a limitation in the translation of preclinical findings into the clinic. Despite this, the use of VEGFR2-targeted TKi has unambiguously proven to be a promising strategy to restrain OC cells (Table 1). Of note, VEGFR2-targeted TKis, when tested *in vivo*, exert a dual-compartment function, acting both on tumor parenchyma and tumor stroma. In these experimental setups it is difficult to estimate the relative contribution that blocking tumor cell proliferation *vs* blocking tumor angiogenesis or the inflammatory compartment or CAFs gives to the blockade of tumor growth.

At the moment, no VEGFR2-targeted TKi is approved for OC treatment. However, several clinical trials have evaluated or are evaluating the therapeutic potential of these drugs in different OC subtypes. Table 2 summarizes the main information regarding the VEGFR2-targeted TKis under clinical investigation for OC treatment. In the next paragraphs, we will list and describe all the VEGFR2-targeted drugs that have been tested on OC in preclinical and clinical studies and their broad spectrum of activities.

Apatinib is a selective VEGFR2 type-2 TKi. It suppresses the viability, favoring ROS-dependent apoptosis of OC cells *in vitro* and *in vivo* as well as glycolysis by inhibiting the VEGFR2/AKT1/SOX5/GLUT4 signaling pathway [78,96]. Apatinib also inhibits the cell migration and EMT of OC cells and restrains tumor growth *in vivo* [97], possibly by targeting both tumor cells and angiogenesis. Apatinib-treated OC cells display increased sensitivity to cisplatin treatment. Of note, apatinib remains effective even in cancer cells with low VEGFR2 expression, suggesting VEGFR2-independent anti-tumoral effects [96]. This mechanism needs to be clearly elucidated. However, it may imply that also patients with low VEGFR2 levels may benefit from apatinib treatment.

Tivozanib, a type-2 TKi selective for VEGFRs (1–3), reduces the proliferation and invasive potential of platinum-resistant OC cells and synergistically potentiate the anti-tumor effect of the EGFR-targeted inhibitor erlotinib [80].

Axitinib, a potent type-2 inhibitor of VEGFRs, inhibits OC cell viability, motility, increases apoptosis and reduces the *in vivo* growth of

Table 1
VEGFR2-targeted TKis investigated in preclinical studies.

Drug name	Targets	Type	Effects	Type of study	OC cell model employed	References
Apatinib	VEGFR2	2	Reduces cell viability, migration, proliferation. Rewires cell metabolism. Promotes cell apoptosis.	*In vitro/ in vivo*	Hey, OVCA433, SKOV3, HO-8910, CAOV-3, A2780	[78,96,97]
Tivozanib	VEGFR1, 2, 3	2	Reduces cell proliferation and invasion.	*In vitro*	EOC exhibiting multi-drug resistance (OVCAR3, SKOV3, A2780-CIS)	[80]
Axitinib	VEGFR1, 2, 3	2	Reduces cell viability, migration, proliferation. Promotes cell apoptosis.	*In vitro/ in vivo*	Platinum-sensitive EOC cell lines (A2780), Ovarian clear cell carcinoma cells (RMG1) and platinum-sensitive PDXs. **Not effective** on platinum resistant EOC cells (HeyA8-MDR) and refractory PDXs.	[98]
Anlotinib	VEGFR2, 1, 3, PDGFR β and c-kit	n.a.	Blocks cell cycle. Decreases proliferation and migration. Promotes apoptosis.	*In vitro/ in vivo*	Cisplatin-sensitive (A2780; SKOV3) and cisplatin-resistant OC cells (A2780-CIS; DDP-res SKOV3).	[99–101]
Cabozantinib	VEGFR2, MET, Axl, RET, FLT3, c-kit	2	Reduces cell viability and tumor growth.	*In vitro/ in vivo*	Ovarian clear cell carcinoma cells (RMG1)	[107]
Pazopanib	VEGFR1, 2, 3, PDGFRα, β and c-kit	1	Reduces tumor growth and angiogenesis	*In vivo*	Hey8A, SKOV3ip1, A2780	[108]
Cediranib	VEGFR1, 2, 3, PDGFRα, β and c-kit	1	Reduces tumor growth and angiogenesis	*In vivo*	SKOV3	[118]
SU6668	VEGFR2, FGFR1, PDGFRβ	na	Reduces ascites formation and peritoneal tumor spread	*In vivo*	Orthotopic model of OC using HOC22 and HOC79 ascites-producing human ovarian carcinoma xenografts	[161]
KRN951	VEGFR2, PDGFRβ and c-kit	na	Reduces tumor growth and angiogenesis	*In vivo*	OVCAR3, SKOV3	[162]
Sunitinib-c (AmpRGD)	VEGFR2/$\alpha_v\beta_3$	na	Reduces tumor cell proliferation, migration and tumor growth	*In vitro/ in vivo*	IGROV-1 and cisplatin resistant IGROV-1/Pt1	[163]

Table 2
VEGFR2-targeted TKis under clinical investigation for OC treatment.

Drug name	Targets	Type	Approved indications	Phase of clinical trials	Adaptation in OC
Pazopanib	VEGFR1, 2, 3, PDGFRα, β and c-kit	1	Approved by FDA for advanced renal cell cancer, and advanced soft tissue sarcoma	Phase I, II	Recurrent (bevacizumab/platinum resistant) OC. Used in combination with chemotherapy (topotecan, etoposide, cyclophosphamide, gemcitabine).
Lenvatinib	VEGFR1–3, FGFRs, PDGFRα, KIT and RET	1	Thyroid cancer, unresectable hepatocellular carcinoma, advanced renal cell carcinoma and endometrial cancer (+ pembrolizumab).	Phase I, II	Platinum sensitive recurrent OC, clear cell OC and serous OC (in combination with pembrolizumab). Platinum-resistant recurrent OC (in combination with toripalimab).
Nintedanib	VEGFR, FGFR, PDGFR-α, β, FLT3, Lck, Lyn, Src	1	Approved by FDA for idiopathic pulmonary fibrosis	Phase I, II and III	Recurrent (bevacizumab-resistant) OC. Used in combination with chemotherapy (cyclophosphamide, carboplatin/paclitaxel, etc).
Cediranib	VEGFR1, 2, 3, c-kit, PDGFRα, β	1	Not yet approved	Phase I, II, III	Recurrent platinum sensitive OC. Used in combination with platinum-based chemotherapy. Tested also in combination with olaparib or durvalumab. The association with BRCA mutation is being evaluated.
Sunitinib	PDGFR, VEGFR, Flt3, and c-kit	1	Approved by FDA for GIST, RCC, pNET	Phase I, II	Recurrent platinum-sensitive/resistant OC, clear cell ovarian carcinoma.
Sorafenib	VEGFR, PDGFR, Raf, MEK, and ERK	2	Approved by FDA for HCC, RCC, and for metastatic thyroid cancer	Phase I, II	Both platinum-resistant/refractory or platinum-sensitive recurrent OC. Used in combination with chemotherapy (carboplatin/paclitaxel, gemcitabine, topotecan). Also evaluated in combination with bevacizumab.
Anlotinib	VEGFR, PDGFR, FGFR, c-Kit	1	Approved in China for NSCLC	Phase I, II	Platinum-resistant/refractory (recurrent) OC.

platinum-sensitive EOC cell lines, ovarian clear cell carcinoma cells and platinum-sensitive patient derived xenografts (PDXs). In the *in vivo* settings, the anti-tumor effect of axitinib could be also due to its anti-angiogenic activity. Axitinib is instead ineffective on the *in vivo* growth of platinum resistant cells and pretreated/refractory PDXs [98].

Anlotinib mainly blocks VEGFR2, and, to a lesser extent, VEGFR3, VEGFR1, c-Kit and PDGFRβ. This inhibitor blocks the cell cycle, proliferation, and migration and promotes apoptosis of both cisplatin-sensitive and cisplatin-resistant OC cells [99–101]. *In vivo*, it acts by inhibiting cell proliferation and angiogenesis. Again, the anti-tumor effect of anlotinib is maintained in cisplatin-resistant OC cells [99–101]. When translated into clinical studies, anlotinib [approved only in China for the treatment of non-small cell lung cancers (NSCLC)] has shown therapeutic efficacy in gynecological cancers [102] and in chemo-resistant OC [103]. Also, a case report of a 45-year-old patient with recurrent platinum-resistant OC treated with oral anlotinib/etoposide showed therapeutic efficacy with no evidence of disease progression for 18 weeks [104]. Moreover, anlotinib showed promising antitumor activity on platinum-resistant/refractory OC in a phase-1b trial (in combination with immunotherapy) [105] (NCT04236362) and in a prospective phase II trial [106].

Cabozantinib, a multi-kinase type-2 inhibitor that targets MET, Axl, RET, FLT3, c-KIT and VEGFR2 inhibits cell viability and tumor growth in a xenograft model of ovarian clear cell cancer [107], possibly acting simultaneously on tumor and stromal compartments.

Pazopanib, a type-I multi-target inhibitor, inhibits angiogenesis and

tumor growth in an *in vivo* orthotopic model of OC both as monotherapy and in combination with metronomic topotecan [108]. This inhibitor, which is clinically approved for soft tissue sarcoma and advanced renal carcinoma, has been evaluated in phase I/II clinical trial for platinum-resistant OC (NCT01600573) in combination with topotecan [109]. The survival rate was not improved by pazopanib administration. Similarly, pazopanib does not significantly improve the overall survival of OC patients in other trials [110–112] (NCT02055690, NCT00866697, NCT01468909). Also, in patients relapsing during the maintenance therapy with bevacizumab, pazopanib increases the toxicity and compromises the chemotherapy delivery [113] (NCT02383251). A systematic assessment of the use of pazopanib in combination with chemotherapy (518 patients in 5 different studies) recently concluded that the drug does not improve the survival of OC patients, being instead associated with the occurrence of adverse events [114]. However, a phase II randomized controlled trial (CTRI/2017/10/010219) showed that pazopanib in combination with metronomic chemotherapy (etoposide, cyclophosphamide) improved PFS and OS, with a well-tolerated toxicity profile [115]. These findings confirmed previous studies on the association of pazopanib with cyclophosphamide [116] (NCT01610206). When Pazopanib is added to gemcitabine, it increases the anti-OC activity [117]. From a clinical perspective, the therapeutic effects of pazopanib need further clarification.

Cediranib (also known as AZD2171), a type-I TKi with pronounced selectivity for VEGFR2, reduces the growth and vascularization of OC (SKOV3) xenografts in mice [118]. Multiple phase II clinical trials showed that Cediranib has anti-tumor activity in recurrent (after platinum) OC with a toxicity similar to that of other TKi [119,120]. The ICON6 (NCT00532194) phase III trial suggested that Cediranib added to chemotherapy improves PFS in patients with relapsed platinum-sensitive OC [121,122]. A phase I trial (NCT01116648) anticipated the activity of Cediranib in combination with olaparib in recurrent EOC [123]. Phase II studies confirmed the anti-tumor activity of cediranib + olaparib treatment. This treatment increases the PFS of platinum-sensitive HGSOC and platinum-resistant OC when compared to olaparib + chemotherapy thus offering an alternative to chemotherapy [124–127]. Also, the EVOLVE phase II trial (NCT02681237) assessed the efficacy of cediranib combined with olaparib after progression on a PARP inhibitor and demonstrated that the efficacy profile was variable based on the mechanism of resistance to PARP inhibitors [128]. Other studies showed poor-to-non-clinical improvement in women treated with cediranib/olaparib combination compared to chemotherapy [129,130]. HDR gene mutations have been ambiguously associated with the response to cediranib/olaparib treatment [129–131], thus further studies are required to clarify this aspect. The ICON-9 phase III trial is now evaluating the effects of cediranib+olaparib compared to olaparib alone in platinum-sensitive OC and results are expected in 2025 [132]. A combination of cediranib with olaparib and the PD-L1 inhibitor durvalumab has also been tested and found to be tolerable and with preliminary activity in recurrent female cancers [133,134].

Lenvatinib is a multikinase type-1 TKi that targets VEGFR1–3, FGFRs, PDGFRα, KIT and RET, approved for the treatment of thyroid cancer, HCC, renal cancer and recurrent uterine cancer that is not Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) (in combination with pembrolizumab). Lenvatinib binds the DFG-in conformation of VEGFR2 interacting also with the region neighboring the ATP binding site. This specific and peculiar interaction may help to prolong the residence time in complexes with VEGFR2, modifying its anti-angiogenic activity [135]. In OC, lenvatinib is administered in combination with pembrolizumab, based on the safety and efficacy of this regimen assessed by different studies/case reports [136,137]. Various phase II clinical trials are ongoing to evaluate the anti-cancer effects of lenvatinib in combination with immunotherapy in different subtypes of OC (clinicaltrials.gov) (Table 2). Despite this, the role of lenvatinib in controlling OC biology (and possible mechanisms of resistance) is far from being understood. A recent report suggested that OC-derived primary CAFs could mediate the resistance to lenvatinib administration in terms of angiogenesis [138].

Nintedanib is a multi-target TKi approved by FDA for the treatment of idiopathic pulmonary fibrosis. The first randomized phase II placebo-controlled clinical trial with nintedanib after chemotherapy for relapsed OC dates back to 2011 [139]. Two different studies confirmed that in OC patients nintedanib is well tolerated and improves PFS when administered in combination with docetaxel [140]. Dynamic MRI assessment showed that nintedanib reduces intratumoral blood flow in more than 50 % OC patients [141]. However, the GINECO double-blind randomized phase II CHIVA trial (NCT01583322) showed that nintedanib + neoadjuvant chemotherapy worsens PFS while increasing therapy toxicity in advanced epithelial OC [142]. Nintedanib in combination with metronomic low-dose oral cyclophosphamide in patients with relapsed OC showed no improvement in OS and PFS [143] (NCT01610869). Again, nintedanib showed minimal activity in patients with bevacizumab-resistant recurrent OC. Despite a modest improvement in PFS (17.6 *vs* 16.6 months), nintedanib in combination with carboplatin/paclitaxel chemotherapy showed no effect on a small cohort of patients with mucinous OC [144]. Overall, the treatment with nintedanib has limited prognostic benefit and non-negligible toxic effects, suggesting that it is not suitable for the treatment of OC [55,141].

Sunitinib is a type-1 TKi that blocks PDGFR, VEGFR, Flt3, and c-kit approved for the treatment of recurrent gastrointestinal stromal tumors, advanced renal cell carcinoma and advanced/metastatic well-differentiated pancreatic neuroendocrine tumors. Phase II clinical trials showed that sunitinib has only moderate/minimal efficacy in recurrent EOC [145,146] and in relapsed platinum-resistant OC [147]. Sustained clinical and functional imaging responses were observed in two patients with chemotherapy-resistant cell ovarian carcinoma who were treated with sunitinib [148]. However, sunitinib had only minimal efficacy in a phase II trial on clear cell ovarian carcinoma patients [149].

Sorafenib is a type-2 multi-target TKi that blocks VEGFRs, PDGFR, Raf, MEK and ERK. It is approved for the treatment of advanced renal cell carcinoma, unresectable hepatocellular carcinoma and more recently for treating patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment. The phase II TRIAS trial evaluated sorafenib in combination with topotecan chemotherapy in platinum-resistant/refractory OC patients and demonstrated statistically and clinically significant improvements in PFS [150]. When compared the effects of sorafenib alone or in combination with carboplatin/paclitaxel chemotherapy, sorafenib inhibits tumor growth while the combination improved the PFS in patients with recurrent platinum-sensitive epithelial ovarian, peritoneal, or fallopian tube cancers. However, this was accompanied by increased toxicities [151]. Modest efficacy of sorafenib (alone or in combination with chemotherapy) with substantial toxicity in advanced/recurrent OC, tested as neoadjuvant, first-line, third-line or maintenance therapy has been highlighted in phase II studies [152–157].

Another study showed that sorafenib plus gemcitabine has encouraging rates of prolonged stable disease [158]. In combination with bevacizumab, the toxicity of sorafenib was improved in EOC patients [159], anticipating the clinical efficacy of this combination in OC. However, a phase II trial showed unsatisfactory results with only modest clinical activity of sorafenib plus bevacizumab combination in heavily-pretreated bevacizumab-naive patients with platinum-resistant OC [160].

Novel VEGFR2-targeted TKi, including **SU6668** and **KRN951** inhibit angiogenesis and OC progression in preclinical models alone and in combination with paclitaxel [161,162]. Finally, double inhibitors have been developed to combine more therapeutic effects into a single drug. Sunitinib conjugated to a selective binder of $\alpha_v\beta_3$ integrin effectively blocks the growth, migration and invasion of both platinum-sensitive and platinum-resistant OC cells [163] (Table 1).

Despite encouraging preclinical results, clinical trials have generally provided evidence that drugs targeting the VEGF/VEGFR2 system

marginally improve the outcome of OC patients.

Also, inconsistencies in survival benefits and variable clinical outcomes following anti-VEGF/VEGFR2 therapeutics clearly emerge from clinical trials. A recent systematic review and meta-analysis combined the results of 8 clinical trials evaluating the effects of bevacizumab, sorafenib, cediranib, pazopanib or apatinib in combination with chemotherapy and/or PARPi for patients with platinum-resistant OC. Pooled data from randomized controlled trials demonstrated that VEGF/VEGFR inhibitors in combination with chemotherapy yield better clinical outcomes compared to chemotherapy alone [164], indicating that these therapeutics are valuable opportunities for advanced OC patients. The clinical benefit is counterbalanced by resistance, which emerges over time with only partially identified mechanisms (*e.g.* EphB4-mediated, GM-CSF-mediated, CAF-mediated, see above) and associated toxicity. Unlike antibodies, TKi, are generally associated with additional toxicity. Preclinical and clinical studies have shown that TKi synergize with parp-inhibitors through hypoxia-induced down-regulation of HRD genes, although with non-negligible toxicity [127]. Conversely, the known toxic effects associated with bevacizumab were not exacerbated by the addiction of olaparib, whose combination as first-line maintenance significantly improved PFS in patients with HRD [165]. The antiangiogenic-induced vascular normalization may boost the infiltration of immune effector cells into the tumor, providing the rationale for the combined use of immune ceckpoint inhibitor (ICI) and antiangiogenic therapy, currently being tested in platinum-resistant/recurrent OC [166]. Understanding the mechanistic bases of resistance to anti-VEGF/VEGFR2 drugs will be crucial in the future to predict treatment outcome in OC patients receiving targeted therapy.

Remarkably, the mRNA VEGFR2 levels are found significantly lower in OC compared to normal ovarian surface epithelium [96]. Also, the VEGFR2 protein levels detected in tumor cells show a positive significant correlation with PFS in advanced-stage HGSOC [84]. In accordance with this and similarly to other cancer types, VEGFR2 knockdown induces HGSOC cells to acquire an aggressive phenotype leading to increased proliferation, invasion *in vitro* and *in vivo* [66,81,82]. This data is consistent with the preclinical observation that short-term treatment with VEGFR2-targeted TKi inhibitors accelerate metastases in different tumor models [16,167]. These bodies of evidence question the prevailing perception of tumor VEGFR2 as an oncogene, suggesting instead that it may act as a tumor brake in OC. This implies that inhibition of tumor VEGF/VEGFR2 axis by targeted drugs might be detrimental, possibly explaining the variable response/limited efficacy of these drugs in OC. On these bases, there is an urgent need to clarify the promoting *vs* suppressive role of tumor VEGF/VEGFR2 axis in OC. The identification of a molecular signature for the stratification of OC patients may support the clinical decision.

4. Biomarkers predictive of the sensitivity/response to VEGF/VEGFR2 inhibitors in OC

A lot of efforts have been done in the last years to identify biomarkers that could predict the sensitivity to bevacizumab [55]. Among others, the expression of CCNE1 or VEGF-B predicts the efficacy of bevacizumab. Similarly, YKL-40, OPN, IL-6, Ang-2, MSLN, FLT4, AGP, and CA-125 were suggested as predictive markers. Also, the circulating level of miR-200b, and miR-200c could predict bevacizumab efficacy. Moreover, subcutaneous fat area or density and visceral fat density could predict the PFS and OS of OC patients treated with bevacizumab. Finally, CT perfusion biomarkers have been identified. On the other hand, expression of VEGFR2, VEGF-A, VEGF-D do not predict the efficacy of bevacizumab in terms of PFS and OS [55].

As for TKi, OPN, IL-6, TIMP-1, and Ang-2 are correlated with PFS in OC patients treated with olaparib + cediranib. Low expression of miR-34a-5p and miR-93-5p are associated with PFS and OS improvements in OC patients with the treatment of chemotherapy ± nintedanib [55]. Also, soluble VEGFR2 and IL-8 predict the therapeutic efficacy of pazopanib [168]. Despite this, there is a lack of consensus about the reliability of these markers. This limits the efficacious application of anti-VEGF/VEGFR2 drugs in OC. Also, it paves the way for new research to identify reliable biomarkers of sensitivity and response to anti-VEGF/VEGFR2 approaches for OC patients.

5. Future directions

The use of anti-VEGF/VEGFR2 drugs in OC has changed the landscape of treatment specifically for recurrent cases. As we have previously noted, however, the addition of these medications do not always provide the improvement in survival that is so desperately needed for this aggressive disease. Many doublet combinations of anti-VEGF/VEGFR2 drugs with chemotherapy, PARP inhibitors, and ICI have been studied and continue to be studied in clinical trials, however, the discussion on the possible triple combination of these three drug classes is also being studied in trials.

The first of these trials, NCT02484404, is currently in phase II and has looked at the combination of olaparib with durvalumab (anti-PDL1) and cedirinib. The phase I data from this trial [133] showed that the 44 % of patients experienced a partial response, 3 had stable disease >6 months, showing a clinical benefit rate of 67 %. Another study, DUO-O (NCT03737643), is currently in phase III with study results recently presented at the 2023 ASCO annual meeting (https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA5506). In this study, patients receive carboplatin/paclitaxel, with bevacizumab and durvalumab and in the maintenance setting receive bevacizumab, durvalumab, and olaparib. For the patients that received this regimen, there was statistically significant improvement in PFS for the HRD^{+}, HRD^{-} and ITT populations in comparison to the group treated with carboplatin/paclitaxel + bevacizumab with durvalumab + placebo maintenance.

Third, the MEDIOLA trial (NCT02734004), completed phase II of its trial in January 2024 and studied the use of Olaparib and durvalumab with or without bevacizumab in PARPi-naive, platinum sensitive OC recurrent patients [169]. For those with germline BRCA mutations, the ORR was 92.2 %, and the disease control rate at 24 months for the non-mutated patients was 28.1 % in the doublet of Olaparib + durvalumab *vs.* 74.2 % for the triplet treated patients.

The use of triplet combinations shows promise, as they can overcome some of the potential resistance mechanisms developed with use of anti-VEGF/VEGFR2 therapies over time. For example, anti-angiogenic medications can induce hypoxia in tumor cells, which ultimately allows them to be susceptible to PARP inhibition. This mechanism of treatment, however, can ultimately be overcome as HIFI alpha is produced, which increases the production of angiogenic factors once again [170]. Elevations in PD-1/PD-L1 are also present after PARP inhibition [171], so addition of ICI makes sense to fully maximize targeted treatments and facilitate ways of overcoming resistance mechanisms to each individual component of these triplet combinations. Additionally, the promise of these triple combinations has identified PD1 status, easily calculated as a CPS score on pathologic specimens, as a potential biomarker for treatment success.

6. Concluding remarks

OC remains a deadly and difficult to treat tumor. Defining the molecular mechanisms underlying its onset, progression and response/resistance to current treatment modalities remains of paramount importance.

In this context, the VEGF/VEGFR2 axis is gaining increasing attention in the OC field.

As reviewed in the present work, the VEGF/VEGFR2 axis, beside mediating OC angiogenesis and immune suppression, is a master regulator of different cellular functions of OC cells, including cell viability/apoptosis, division, motility and metabolism, all processes that substantially contribute to OC progression. This substantiates the

application of therapeutic strategies to block this axis in both stromal and parenchymal compartments of OC. The pleiotropic function of the VEGF/VEGFR2 system in OC requires that clinical results are interpreted from this tumor cell-centered perspective for a more comprehensive understanding of the clinical efficacy/resistance of this class of anti-cancer drugs.

Beside classical anti-VEGF neutralizing antibodies or VEGFR2-targetd TKi, unconventional approaches have been also tested in OC. Among these, nanomaterials, harmine derivatives, peptides and gene therapy approaches with soluble VEGFR2 showed therapeutic efficacy in *in vitro*/pre-clinical models [172–176]. However, the clinical efficacy (and the possible resistance phenomena) of these therapeutics remains to be evaluated. Instead, classical inhibitors have been thoroughly evaluated in preclinical and clinical studies. Unfortunately, promising preclinical results were followed by inconsistent, variable and unsatisfactory results when the drugs were translated into the clinic. Thus, further basic research efforts and more clinical trials are necessary to clarify the role of the VEGF/VEGFR2 axis and its inhibition in OC. First, the role of this axis should be investigated more thoroughly, to explain in which contexts it acts as a tumor accelerator and in which others it functions as a tumor brake. This becomes of primary importance to avoid unwanted and detrimental effects when administering anti-VEGF/VEGFR2 drugs to OC patients. Second, the VEGF/VEGFR2 axis controls not only the behavior of tumor cells, but also that of stromal cells like ECs, CAFs and immune cells. This aspect should be carefully considered when setting up OC models to assess the effects of inhibitors of the axis or when designing clinical trials and/or administering these drugs to patients. The net result of inhibiting the VEGF/VEGFR2 pathway in all these cell populations, that may respond in a different way to treatment, becomes difficult to predict. Finally, the introduction of triple combination therapies can allow us to overcome eventual resistance mechanisms developed by OCs. Antibody drug conjugates have promise in the future of OC treatment and could be useful to specifically deliver the drugs to target cells thus overcoming the limitations of the multi-compartment effects of anti-VEGF/VEGFR2 approaches. Many of these options are now in development in pre-clinical studies. Finally, new and efficacious markers predictive of response to anti-VEGF/VEGFR2 drugs and/or indicative of their curative effects are pivotal for the stratification of patients to guide these novel therapeutic choices.

Declaration of competing interest

The authors declare that they have no competing interests.

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Data availability

No data was used for the research described in the article.

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