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Chemotherapy resistance in epithelial ovarian cancer: Mechanisms and emerging treatments

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ABSTRACT

Ovarian cancer (OC) remains a fatal malignancy because most patients experience recurrent disease, which is resistant to chemotherapy. The outcomes for patients with platinum-resistant OC are poor, response rates to further chemotherapy are low and median survival is lower than 12 months. The complexity of platinum-resistant OC, which comprises a heterogeneous spectrum of diseases, is indeed far from being completely understood. Therefore, comprehending tumors' biological behaviour to identify reliable biomarkers, which may predict responses to therapies, is a demanding challenge to improve OC management. In the age of precision medicine, efforts to overcome platinum resistance in OC represent a dynamic and vast field in which innovative drugs and clinical trials rapidly develop. This review will present the exceptional biochemical environment implicated in OC and highlights mechanisms of chemoresistance. Furthermore, innovative molecules and new therapeutic opportunities are presented, along with currently available therapies and ongoing clinical trials.

1. Introduction

Ovarian cancer (OC) represents the most fatal tumor of the female reproductive system. In 2020, 313,959 women worldwide were diagnosed with this disease and 207,252 died from it, resulting in the fourth cause of female cancer death [1]. From a global perspective, the OC incidence is twice as high in more developed countries compared with developing countries, whereas the cumulative mortality risk is almost similar [2]. Its poor prognosis is mainly due to diagnosis at advanced disease stages (International Federation of Gynecology and Obstetrics, FIGO stage III and IV) and chemotherapy resistance.

An optimal cytoreductive surgery followed by adjuvant chemotherapy with or without maintenance therapy (bevacizumab or poly adenosine diphosphate ribose polymerase (PARP) inhibitors) represents the gold standard of treatment in most of the cases [3]. Despite this, 70 % of the patients still experience recurrence within 2 years from primary diagnosis and the death rate reaches around 50 % of women within five years from primary diagnosis [4]. Clinical response to second-line chemotherapy significantly depends on platinum-free interval (PFI) [5]. While the treatment strategy is clear for patients who respond initially to platinum-based adjuvant chemotherapy, other treatment lines in the platinum-resistant population are not well defined [6]. Providing appropriate answers is difficult since relevant scientific literature is ranked at a lower evidence level [6]. This review provides a comprehensive overview of emerging treatments and predictive biomarkers in platinum-resistant cases, based on the considerations mentioned above. Firstly, platinum sensitivity is defined, and mechanisms and biomarkers of resistance are shown mainly for high-grade serous ovarian carcinoma (HGSOC). Subsequently, new strategies to improve survival rates and ameliorate the quality of life in platinum-resistant OC patients are discussed and new directions for future research are presented.

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2. Recurrence and platinum sensitivity

At initial diagnosis, the standard approach with complete cytoreductive surgery and platinum-based chemotherapy grants an optimal response, even in advanced stages. Nonetheless, an 18-month progression-free survival (PFS) is expected with a disease recurrence in 80 % of the patients [7].

Patients with recurrent disease have traditionally been stratified into two groups: platinum-sensitive and platinum-resistant cases [8]. This stratification is based on PFI. PFI refers to the time elapsed between the last date of platinum-based adjuvant therapy and the date of radiological or symptomatic recurrence diagnosis. The cut-off time is set at six months, defining platinum-sensitive disease (PFI $>$ 6 months) and platinum-resistant disease (PFI $\leq$ 6 months). Overall, platinum-sensitive patients are supposed to have a median survival of 2 years (from 3 months up to 10 years), while the survival rate of platinum-resistant patients ranges between 9 months and 12 months, with $<$ 15 % of cases showing chemo-sensitivity to following treatments [9].

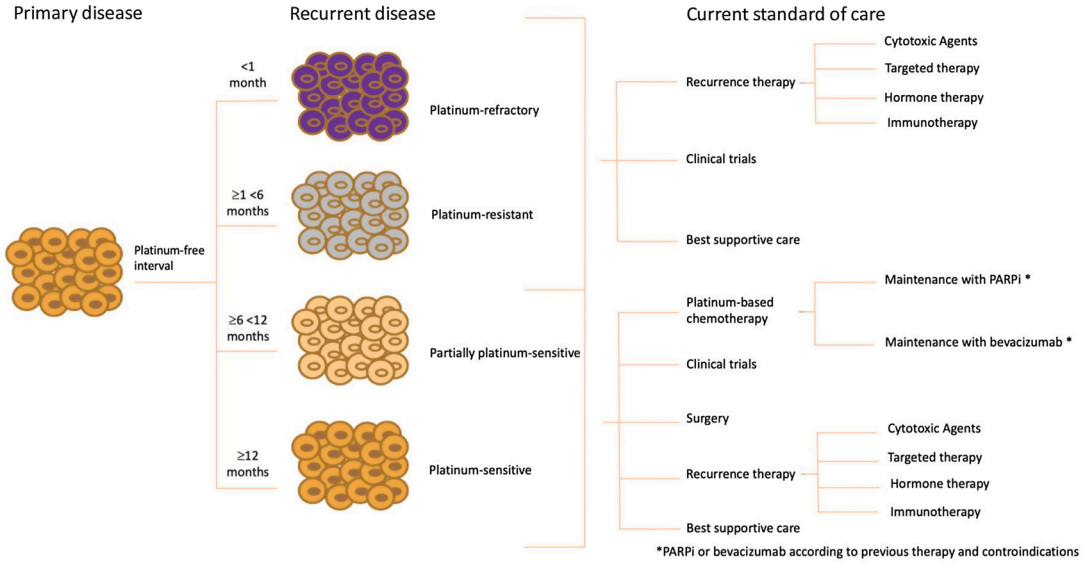
At present, two other categories have been recognized by the Gynecologic Cancer InterGroup (GCOG) consensus: patients with platinum-refractory disease (PFI $<$ 1 month) and patients with partially platinum-sensitive relapse (PFI between 6 and 12 months) [8]. A schematic representation of these platinum-subgroups – refractory (PFI $<$ 1 month), resistant (PFI $>$ 1 month and $<$6 months), partially sensitive (PFI 6–12 months) or sensitive (PFI $>$ 12 months) – is shown in Fig. 1. Nonetheless, it should be underlined that in some trials, platinum-resistant disease has been categorized into two groups, including patients with a PFI between 3−6 months and patients with a PFI shorter than 3 months (including refractory patients) [9].

Moreover, this PFI stratification is expected to evolve in the treatment-free interval (TFI) stratification shortly. According to this TFI concept - as proposed at the fifth OC Consensus Conference in Tokyo in November 2015 - treatment of relapsed OC and its response to chemotherapy depends on the specific tumor histological type, Breast Cancer gene (*BRCA*) mutation status, type of prior therapy and the time elapsed from the last systemic therapy [10]. Based on current knowledge, on the European Society for Medical Oncology (ESMO) and the European Society of Gynecological Oncology (ESGO) OC consensus conference, it was suggested to divide patients with recurrences into patients for whom platinum-based re-challenge appears to be appropriate and patients who may benefit from another treatment (Fig. 1) [11].

3. Sensitivity to chemotherapy in ovarian cancer subtypes

Fundamentally, malignant tumors arising from the ovary are classified into two different tumor types: i) malignant epithelial tumors (90 % of cases), including HGSOC, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and low-grade serous ovarian cancer (LGSOC); ii) primitive germ cell tumors (3 % of OCs) and potentially malignant sex cord-stromal tumors (7 % of cases) [12–14].

Data on chemoresistance mostly come from HGSOC. However, while most HGSOCs are initially platinum-sensitive and become platinum-resistant over treatment time resulting in an overall poor prognosis, LGSOC, clear cell carcinoma and mucinous carcinoma are non-responsive to chemotherapy but have a better prognosis than HGSOC ultimately. The high level of chemoresistance in these subtypes is predominantly related to their cellular architecture, molecular profile and genetic alterations [15].



	PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER		PLATINUM-RESISTANT RECURRENT OVARIAN CANCER		
Platinum-based chemotherapy	Carbopaltin ±gemcitabine or liposomal doxorubicin or paclitaxel ±bevacizumab Cisplatin + gemcitabine		--		
Cytotoxic Agents	Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan	Paclitaxel Paclitaxel albumin bound Pemetrexed Vinorelbine Oxaliplatin	Cyclophosphamide ± bevacizumab Docetaxel Etoposide Gemcitabine Liposomal doxorubicin ± bevacizumab	Paclitaxel ± bevacizumab Topotecan ± bevacizumab Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan	Melphalan Paclitaxel albumin bound Pemetrexed Vinorelbine Oxaliplatin Sorafenib + topotecan
Targeted therapy	Bevacizumab Olaparib Rucaparib Niraparib ± bevacizumab Pazopanib	Trametinib (for LGSOC) Entrectinib or larotrectinib (for NTRK gene fusion-positive tumors)	Bevacizumab Niraparib Olaparib Rucaparib	Pazopanib Trametinib (for LGSOC) Entrectinib or larotrectinib (for NTRK gene fusion-positive tumors)	
Hormone therapy	Aromatase inhibitors (anastrozole, exemestane, letrozole)	Leuprolide acetate Megestrol acetate Tamoxifen Fulvestrant (for LGSOC)	Aromatase inhibitors (anastrozole, exemestane, letrozole)	Leuprolide acetate Megestrol acetate Tamofifen Fulvestrant (for LGSOC)	
Immunotherapy	Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥ 10 mutations/megabase and no satisfactory alternative treatment options)		Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥ 10 mutations/megabase and no satisfactory alternative treatment options)		

Fig. 1. Classification of recurrent OC and its management according to NCCN [6] and ESMO-ESGO [11] guidelines.
Abbreviations. dMMR: Mismatch repair deficient. LGSOC: Low-grade serous ovarian cancer. MSI-H: Microsatellite instability-high. NTRK: Neurotrophic tyrosine receptor kinase. PARPi: Poly (ADP-ribose) polymerase (PARP) inhibitors. TMB-H: Tumor mutational burden-high.

Patients with LGSOC harbor Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS)* or v-raf murine sarcoma viral oncogene homolog B1 (*BRAF)* mutations and/or mitogen-activated protein kinase (*MAPK*) [16,17] more frequently compared to HGSOC. Regarding the role of MAPK pathway (with the activation of BRAF and KRAS), it generally leads to the transcription of genes related to cellular proliferation, survival and angiogenesis. It is still unclear how the activation of MAPK cascade affects the platinum sensitivity; however, it was shown to control hypoxia-inducible factor-1α (HIF1α) transcriptional activation, which has been associated with chemoresistance [18,19]. This evidence suggests an active response to BRAF kinase inhibitor and/or mitogen-activated protein (MEK) inhibitors in LGSOC [16].

More frequently than in serous and mucinous histotype, patients with clear cell carcinoma mainly express mutations of Phosphatidylinositol-4,5-Bisphosphate 3-Kinase catalytic subunit α (*PIK3CA)* and subsequent the phosphatidylinositol 3-kinase (PI3K) / protein kinasi B (AKT) / mammalian target of the rapamycin (mTOR) pathway over-activation. Generally, the PI3K/AKT pathway leads to activating several mechanisms including stimulating cell proliferation, preventing apoptosis and modulating metabolism. In fact, the PI3K/AKT pathway is related to multidrug resistance because of complex and numerous mechanisms, as mTOR phosphorylates and activates AKT. First of all, the cascade regulates the gene expression of ATP binding cassette (ABC) transporters (through nuclear factor kappa-light-chain-enhancer of activated B cells NF-κB) that facilitate the efflux of anticancer drugs outside the cell. The PI3K/AKT pathway has been proved to suppress the activity of caspase-3, inhibiting apoptosis and, finally, the P13 K/AKT/mTOR may also induce dysregulation of miRNA and consequently multidrug resistance [20]. Therefore, PI3K/AKT/mTOR inhibitors seem to have an antitumor effect in this context. Similarly, vascular endothelial growth factor (*VEGF*) expression has been described in platinum-resistant mucinous OC, suggesting a potential role of multi-targeted receptor tyrosine kinase inhibitor (TKI), such as sunitinib [21].

Although its mechanism has not yet been clearly elucidated, also the mitochondrial function seems to be implicated in drug resistance in clear cell carcinoma. In particular, the mitochondrial biogenesis is influenced by the function of the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator-1 α (PGC1a) which regulates the nuclear respiratory factor (NRF) 1−2 [15] and then the mitochondrial transcription factor A (TFAM) [22,23]. TFAM plays a crucial role in preserving the mitochondrial deoxyribonucleic acid (mtDNA) and the efficient replication and transcription of related genes [24,25]. Moreover, mitochondrial biogenesis has been linked to oestrogen receptor α (ERα) [26,27]. It was shown that the expression of these genes varies significantly between histotypes of OC: HGSOC expresses *PGC1a, TFAM* and *Erα*, and is more responsive to platinum-based treatment. Conversely, clear cell carcinoma generally does not express them and is less sensitive to chemotherapy. Interestingly, the same author found a loss of PGC1a/TFAM and ERα also in a non-clear cell epithelial OC cell line highly resistant to platinum in vitro [28].

Furthermore, it is assumed that low cell proliferation in clear cell carcinoma OC is involved in its platinum resistance. The nuclear antigen Ki-67 is expressed in all cell cycle phases except in resting cells in G0. Thus, its low expression in clear cell carcinoma and the higher level in HGSOC suggest that clear cell carcinoma has low tumor proliferation activity and consequently chemoresistance [29].

Regarding mucinous carcinoma, it is extremely rare histology (< 4 %). Approximately 20 % of mucinous carcinomas express *KRAS* or human epidermal growth factor receptor 2 (*HER2*)/ neuro/glioblastoma derived oncogene homolog (*ERBB2)* [30]. Based on its histopathological similarity with colon carcinoma, several strategies have been explored, including oxaliplatin and capecitabine, with or without bevacizumab, but no definitive results have been reached.

Finally, a significantly improved clinical outcome has been demonstrated in patients with FIGO stage III endometrioid OC compared with those with serous tumors (PFS hazard ratio HR 0.76, 95 % confidence interval CI: 0.64−0.92, p value 0.004 and OS (HR 0.79, 95 % CI: 0.65−0.97, p value 0.02) and other histotypes, after surgery and first-line chemotherapy [31]. However, the majority of advanced high-grade endometriod OCs recurs, with eventual resistance to most effective agents. The underlying mechanisms are multiple and not well-known. However, interestingly, some authors identified a novel pathway: the high expressed cluster of differentiation (CD) 55 in endometrioid cancer stem cells (CSCs) can activate lymphocyte-specific protein tyrosine kinase (LcK) and induce DNA repair gene, leading to platinum resistance. Thus, a possible pathway of platinum resistance in endometrioid OC was hypothesized, which deserves further investigation [32].

4. Current treatment of platinum-resistant ovarian cancer

Currently, treatment strategies for platinum-refractory or platinum-resistant disease include non-platinum drugs, delivered sequentially as single agents. The main compounds are pegylated liposomal doxorubicin (PLD), paclitaxel, gemcitabine and topotecan. These compounds assure comparable response rates (ranging from 10 % to 15 %) and survival outcomes, such as PFS (3–4 months) and overall survival (OS) around 1 year [33]. Therefore, therapy choice mainly depends on residual toxicities of previously received treatments, treatment cost, accessibility and the patient-physician agreement.

In order to reduce drug-related impairment, weekly administration has been proposed. Among possible drugs, paclitaxel seems to be particularly effective and better tolerated, reducing neurotoxicity, when administered once a week compared with three administrations per week [34].

Other options have been taken into consideration in the last 20 years. One of the most relevant treatments is bevacizumab. It is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor-A (VEGFA) and it has demonstrated effectiveness both in terms of single-agent activity and in association with chemotherapy. The randomized Avastin use in platinum-resistant OC (AURELIA) trial tested a single-agent scheme +/- bevacizumab in patients with platinum-resistant disease without bowel obstruction. The AURELIA trial showed a significant improvement of the PFS rate (3.4 versus 6.7 months; HR 0.48, 95 % CI: 0.38−0.60, p value < 0.001) in the bevacizumab arm, with apparently no impact on OS (13.3 versus 16.6 months; HR 0.85, 95 % CI: 0.66–1.08, p value 0.171) [35]. The highest improvement in health-related quality of life and patient-reported outcomes was recorded in those patients with ascites [35]. Interestingly, the greatest benefit was found when bevacizumab was administered with the weekly dose of paclitaxel, with an increase in response rate (53.3 % in paclitaxel + bevacizumab versus 30.2 % with weekly paclitaxel alone), median PFS (10.4 months in paclitaxel + bevacizumab versus 3.9 months with weekly paclitaxel alone) and OS (22.4 months in paclitaxel + bevacizumab versus 13.2 months with weekly paclitaxel alone). Because of this trial, the European Medicines Agency and Food and Drug Administration approved bevacizumab plus chemotherapy to treat women with platinum-resistant OC [36,37].

A possible limitation of bevacizumab could be its toxicity profile. Bowel perforation has been reported in 11 % of patients even if administered alone [38]. Other less frequent and yet reported bevacizumab-related toxicities are hypertension, proteinuria, hemorrhage and thrombosis. Moreover, neither predictive markers of response, allowing for an appropriate selection of patients, nor resistance mechanisms hampering the use of bevacizumab have been found. Therefore, patients are still exposed to eventually ineffective treatments with the risk of non-negligible toxicities

5. Mechanisms of resistance

It should be underlined that most platinum-sensitive patients in

advanced stages finally become platinum-resistant. Acquired chemotherapy resistance can be related to different molecular mechanisms, and the most frequent are summarized in Table 1. A large body of literature focuses on the identification of platinum resistance mechanisms, especially in HGSOC. Firstly, in platinum-based chemotherapy, both cisplatin and carboplatin induce cell apoptosis and crosslink with the purine bases on the deoxyribonucleic acid (DNA), thus causing DNA damage. Every step in this complex mechanism, from drug release into cell cytoplasm [39] to DNA binding or signal transduction pathways induced by the drug, can be impaired in platinum-resistant cells. Moreover, the susceptibility of a cancer cell to DNA alkylating-like agents is determined by its ability to detect and repair DNA damage. Therefore, cells, which are able to repair DNA at the beginning or restore originally impaired DNA repair systems, can resist chemotherapy. Once this target has been achieved, immune checkpoint genes are activated to induce apoptosis. For instance, the relation between p53 and immune checkpoints is linked to p53's ability to induce cycle arrest and apoptosis in impaired cells promoting T-cell receptor over-expression. Alterations in this complex mechanism seem to correlate with platinum chemotherapy resistance [40–42].

Other mechanisms of resistance are the CSCs [43] and the epithelial-to-mesenchymal transition (EMT) process [44,45]. The specific resistance mechanism is mainly uncharacterized, but it has been assumed that quiescence CSCs and mesenchymal-like cells may regrow after a complete clinical response to chemotherapy.

Epigenetic changes, such as methylation and histone acetylation, have been described in women with acquired platinum resistance [46–48]. Finally, tumor microenvironment, remarkably immune cell infiltration, angiogenesis and hypoxia, might induce platinum chemoresistance. Recently, micro ribonucleic acids (miRNAs) have also been advocated as possible targets of new drugs. MiRNAs are short (18−25 nucleotides) non-coding fragments of ribonucleic acid (RNA) that regulate protein expression, including proteins related to platinum resistance mechanisms [49]. All these factors are currently under investigation and not completely understood.

The ambition of establishing biomarkers should help physicians in cancer management towards effective and tolerable targeted therapies. Details of mechanisms of resistance are discussed below and summarized in Fig. 2.

5.1. Transport system

Transport system refers to those mechanisms that involve steps preceding the binding of a platinum compound to its DNA target. Different pre-target resistance mechanisms have been described. The high-affinity copper uptake protein 1 (Ctr1) has a role in the uptake of cisplatin. Elevated platinum concentration down-regulates Ctr1 by internalization, which is probably responsible for secondary platinum resistance [50]. Other ways to avoid DNA damage include increased drug efflux caused by adenosine triphosphate copper transporter α (ATP-7A) and β (ATP-7B) [51], multidrug resistance protein 2 (MRP2) [52] and increased drug inactivation due to glutathione (GHS) [53,54].

5.2. DNA repair and homologous recombination deficiency involved mechanism

Platinum therapy mainly works by binding DNA, and producing inter- and intra-strand DNA adducts, causing apoptosis [55]. The susceptibility of a cancer cell to DNA alkylating-like agents is determined by its ability to detect and repair DNA damage [56]. In simple words, the more the cell can repair DNA, the lower are the chances of chemo-response. Human cells have different DNA repair systems: homologous recombination repair (HRR), nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), non-homologous end joining (NHEJ) and Fanconi Anemia (FA) system [57]. Despite HRR is a ubiquitous repair cellular mechanism particularly

Table 1
Mechanisms of chemoresistance and potential target therapy in ovarian cancer.

	Mechanism of action
TRANSPORT SYSTEM	
Reduced uptake	
SLC31A1 [139]	Cisplatin plasma membrane copper-transporter. SLC31A1 depletion increases CDDP resistance.
Increased efflux	
ATP7A/ATP7B [142]	Copper-extruding P-type ATPases. Up-regulated in CDDP-resistant OC.
MRP2 [52]	Member of ABC ATPases. Increased CDDP efflux
Increased inactivation	
GSH/7-GCS/GST [141]	GST conjugates GSH to CDDP, facilitating its extrusion
DNA REPAIR SYSTEM	
Increased NER proficiency	
ERCC1 [232]	Single-strand endonuclease. Removing intrastrand crosslinks produced by CDDP
MMR deficiency	
MLH1 [95]	Component of multiprotein complex that excides and repairs DNA mismatches. MLH1 deficiency is sometimes associated with CDDP resistance.
MSH2 [96]	Detect DNA lesions. Mutated or under expressed in some tumors with acquired CDDP resistance
Increased HRR proficiency	
BRCA1/BRCA2 [146]	Components of the HRR DNA system.
CELL CYCLE CHECKPOINT	
p53 [154]	Tumor suppressor gene, mutated in >50 % of human cancers that has lost its anti proliferative and apoptotic abilities. It seems that its binding with HSP90 is responsible for platinum resistance in OC.
WEE1 [153]	Tyrosine kinase which regulates the G_2-M cell-cycle checkpoint control.
RB1 [41]	It plays a crucial role in regulating the cell cycle at the G1/S checkpoint. In OC, it is inactivated by a mechanism of gene breakage and is probably responsible for resistance to platinum based chemotherapy.
PTEN [74]	This gene plays an important role in the negative regulation of the cell cycle, survival and apoptosis and this pathway has been lost in 27 % of epithelial cancers of the ovary especially in endometrioid and clear cell histotypes.
CANCER STEM CELLS AND EPITHELIAL-TO-MESENCHYMAL TRANSITION	
CSCs [78]	CSCs are self renewal and can give rise to more differentiated progeny.
EMT [88]	During tumor progression, neoplastic cells switch from an epithelial-like state to gain mesenchymal properties, contributing to invasiveness and stemness.
GENES EXPRESSION AND EPIGENETIC CHANGES	
Hypermethylation [96]	DNA methylation is a key epigenetic regulator of gene expression. The onset of resistance has been linked with increased DNA methylation of specific genes, such hMLH1, which encodes a mismatch repair enzyme associated with apoptosis.
Histone acetylation [99]	HDACs actively mediate the level of acetylation of histone structures. When high deacetylation is present the result is suppression of gene expression, responsible for chemoresistance.
IMMUNE SYSTEM	
TAMs [103]	They secrete multiple metastasis-promoting cytokines including IL-6, IL-10,

(continued on next page)

Table 1 (*continued*)

	Mechanism of action
	CCL18, CCL22, TNFα, and TGFβ.
PD-1/ PD-L1 [72]	PD is expressed on the surface of T, B, and NK. PD-L1 is considered to be a crucial immunological escape mechanism that results in tumor cell growth, proliferation and metastasis.
CTLA-4 [233]	CTLA-4 regulates T-cell priming and activation, is a negative regulator which attenuate normal T-cell activation to prevent pathologic over-activation.
B7 family checkpoint molecules [119]	B7-H3, B7S1 and B7-H5 (VISTA) are a co-signaling receptors family that determines T cell function or tolerance. Their overexpression in chemo-resistant OC is correlated with a worst prognosis.
MDSCs [115]	MDSCs are recruited by pro-inflammatory cytokines secreted by malignant cells, to create an immunosuppressive microenvironment.
Treg [110]	Tregs are T cells that modulate the immune system. $CD4^+$ and $CD25^+$ Tregs inhibit TAA-specific immunity and allow uncontrolled tumor growth.
ANGIOGENESIS	
VEGF family [35]	Blocking the VEGF pathway promotes recruitment of vascular progenitors and vascular modulators such TAMs. Tumor hypoxia is a major molecular controller of an "angiogenic switch".
PDGF family [196]	PDGF isoforms and receptors are overexpression or have altered function in chemoresistant cancer cells. The PDGFRb-EGFR heterodimerization is implicated in mechanisms underlying of multiple drugs resistance.
HER family	
HER-2 [216]	The HER2/HER3 heterodimer activates HER signaling, with activation of various pathways as PI3K.
MICRO RIBONUCLEIC ACIDS (miRNAs)	
Let-7b, miRNA-9, miRNA-370, miRNA-199b-5p, and miRNA-449a, miRNA-21 and miRNA-93 [49]	miRNAs are short (18−25 nucleotides) non-coding fragments of RNA that bind to and inhibit mRNA, targeting drug-resistance-related genes.
ANTIBODY DRUG CONJUGATES (ADCs)	
FRα [222]	Folate metabolism is important for the replication of the DNA. FRα is overexpressed in OC, with correlation of poor prognosis.

Abbreviations. ABC: ATP-binding cassette. ATP7A: ATPasi copper transporter α. ATP7B: ATPasi copper transporter β. BRCA: Breast related cancer antigens. CCL: Chemochine ligand. CD: cluster of differentiation. CDDP: Cisdiamminedichloridoplatinum/cisplatin. CSC: Cancer stem cell. CTLA-4: Cytotoxic T lymphocyte-associated antigen 4. CTR-1: High affinity copper uptake protein 1. DNA: Deoxyribonucleic acid. EGFR: Epidermal growth factor receptor. EMT: Epithelial-To-Mesenchymal Transition. ERCC1: Excision Repair Cross-Complementation Group 1. FRα: Folate receptor α. GCS: Gamma-glutamylcysteine synthetase. GSH: Glutathione. GST: Glutathione S-transferase. HDAC: Histone deacetylases. HER2/ERBB2: Human epidermal growth factor receptor 2/ neuro-glioblastoma derived oncogene homolog. HER: Human epidermal growth factor receptor. hMLH1: Human MutL homolog 1 gene. HRR: Homologous recombination repair. HSP: Heat shock protein. IL: Interleukin. MDSCs: Myeloid-derived suppressor cells. miRNAs: Micro ribonucleic acids. MMR: Mismatch repair. MRP2: Multidrug resistance protein 2. MSH2: MutS homolog 2. NER: Nucleotide excision repair. NK: Natural killer. OC: Ovarian cancer. PDGF: Platelet-derived growth factor. PDGFR: Platelet-derived growth factor receptor. PD-1: Programmed cell death protein 1. PD-L1: Programmed cell death protein ligand 1. PI3K: Phosphatidylinositol 3-kinase. PTEN: Phosphatase and TENsin. RB1: Retinoblastoma gene. SLC31A1: Solute Carrier Family 31 Member 1. TAA: Tumor-associated antigens. TAMs: Tumor-associated macrophages. TGF: Transforming growth factor. TNF: Tumour necrosis factor. Treg: regulatory T cells. VEGF: Vascular endothelial growth factor. VISTA: V-domain immunoglobulin suppressor of T cell activation. WEE1: WEE1 G2 checkpoint kinase.

in non-cancerous cells, mutations in HRR genes, including *BRCA* gene 1 and 2 (*BRCA1, BRCA 2), RAD51*, ataxia telangiectasia and rad3 related serine/threonine kinase (*ATR*), ataxia telangiectasia mutated serine/threonine kinase (*ATM*) and checkpoint kinase 2 (*CHK2*), are reported in approximately 30 % of HGSOC [58]. Consequently, OC is extremely sensitive to platinum drugs because the impairment of a DNA repair system causes death after platinum damage [59].

Chemoresistance might be associated with tumors that are HRR proficient at the beginning of the disease (platinum-refractory or platinum-resistant at first line) or restored after chemotherapy (platinum-resistant from the second line onwards). Recently, it has been hypothesized that in *BRCA* mutated (m*BRCA*) patients, platinum resistance can occur with a second somatic mutation of originally germline mutation carriers (reversion mutations) [60] or with increased *BRCA1* expression through reduction of *BRCA1* promoter methylation [41].

In addition to reversed mutation, other mechanisms of platinum-resistance in m*BRCA* patients were reported in the literature, including protection or re-start of replication fork [61–63] and the inhibition of NHEJ system [64]. These processes were recently summarized in a special issue [65,66].

The NER system has also shown impairment in about 8 % of epithelial OC, conferring better prognosis than patients without NER alterations; thus, women who have acquired NER system proficiency might have developed potential platinum resistance as wild-type *BRCA* (wt*BRCA*) [67].

Despite microsatellite instability (MSI) was also reported in serous histotype (7.9 %, 95 % CI: 4.5–12.3) [68], MMR deficiency, especially human mutL homolog 1 (*MLH1*) deficiency or mutation in mutS homolog 2 (*MSH2*), is more frequent in endometrioid and clear cell OC [69,70]. In particular, since platinum complexes interfere with the normal MMR activity preventing the repair of DNA damage caused by chemotherapy, when MMR is deficient, OC cells can escape the mechanism of apoptosis, continue to proliferate and finally become drug-resistant [71].

As a result, a patient's immune system produces tumor-infiltrating lymphocytes (TILs) expressing high levels of programmed cell death protein 1 (PD-1), which is the target of therapy [72].

5.3. Cell cycle checkpoint

The cell cycle consists of four distinct phases (G1, S, G2, and M) that occur in a subsequent order to complete cell replication. In order to go through this process, checkpoint mechanisms between every phase play a role to halt the cell cycle in case of replication damage [73]. Different genes are implicated in cell cycle regulation. Among them, the tumor protein p53 (*TP53)* gene, retinoblastoma 1 (*RB1*) gene, neurofibromin-1 (*NF1*) gene and phosphatase and tensin homolog (*PTEN*) gene, are often impaired in HGSOC [74]. *TP53* is an onco-suppressor gene that plays a crucial role at the G1/S checkpoint level, like *RB1*. However, it should be considered that 96 % of platinum-resistant HGSOC, which are *TP53* mutated tumors, could simply be due to the high percentage of *TP53* somatic mutated HGSOC, rather than represent a potential role of *TP53* in platinum sensitivity [75,76]. Mutations in *NF1* and *RB1* have been found in 20 % and 17.5 % of recurrent OC, respectively [41]. *PTEN* mutation is less frequent.

5.4. Cancer stem cells and epithelial-to-mesenchymal transition

CSCs are a population of cells from solid tumor with stem cell properties. They can self-renew and differentiate along multiple lineages, creating phenotypic and functional intratumoral heterogeneity.

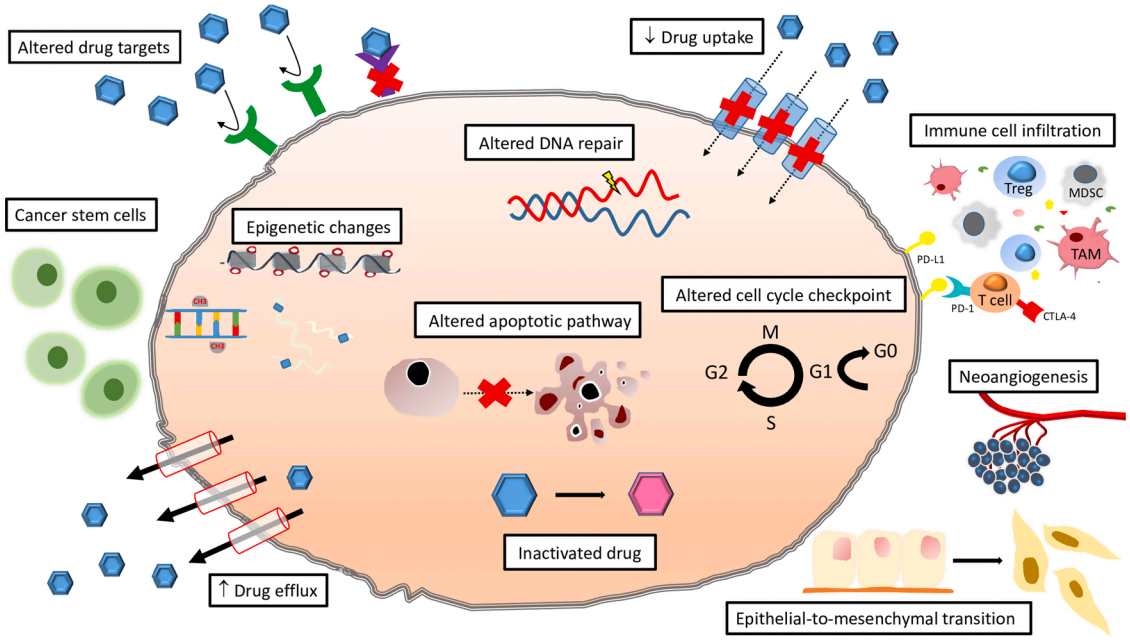


Fig. 2. Mechanisms of resistance to therapy in OC.
Abbreviations. CTLA-4: Cytotoxic T lymphocyte-associated antigen 4. DNA: Deoxyribonucleic acid. MDSC: Myeloid-derived suppressor cell. PD-1: Programmed cell death protein 1. PD-L1: Programmed cell death protein ligand 1. TAM: Tumor-associated macrophage. Treg: Regulatory T cell.

These CSCs seem to have a role in the development of metastases and chemotherapy resistance [77]. It is believed that after debulking surgery and chemotherapy, the presence of residual CSCs in their niche can lead to cancer relapse. In this regard, it seems that chemoresistant CSCs can remain quiescent for prolonged periods in metastatic sites and, after being triggered, can reactivate and proliferate. Besides this, normal tissue stem cells can transform into a new population of cells [78]. In the literature, controversial opinions on the role of CSCs in OC can be found. However, many studies have demonstrated the correlation between CSCs and OC prognosis [79]. Although it is difficult to identify markers of CSCs, reliable markers of OC CSCs have been recently proposed [80], such as CD 133+, aldehyde dehydrogenase (ALDH)+, CD44+/CD117+, CD44+/MyD188+, CD24, and the epithelial cell adhesion molecule (EPCAM) [81–84]. Several mechanisms have been reported to explain treatment resistance in ovarian CSCs. An increased repair DNA system has been demonstrated in CSCs of different solid tumors [85], and recently, an increased HRR proficiency has been found in ovarian CSCs of PARP inhibitor-resistant patients [86]. Another mechanism involved in generating resistance to therapy is enhanced drug efflux by the *ATP binding cassette (ABC)* gene family. In fact, the DNA integrity defense system in normal stem cells is partially granted by these efflux transporters. These pumps allow more effective preservation of the normal stem cell genome against chemical mutagens (chemotherapy) in an attempt to prevent carcinogenesis, avoiding drug penetration. Ovarian CSCs may derive resistance to chemotherapy through a higher expression of drug efflux pumps [87]. In addition, ALDH enzymes are highly expressed in CSCs. These enzymes catalyse the oxidation of aldehydes (oxygen, carbon, and hydrogen) to carboxylic acids to preserve DNA. ALDH activates different pathways such as Wingless-related integration site (Wnt)/β-catenin or hedgehog signaling, which are currently under investigation as targeted therapy in OC. CSCs are also related to another well-known mechanism of resistance to platinum, namely EMT. EMT is a process in which epithelial cells differentiate into mesenchymal cells, increasing some characteristics, such as their invasiveness and motility [88]. EMT cells are related to high malignancy. Indeed, several studies, identifying 6 molecular subtypes of OC [89], demonstrated poor prognosis in both C1 and C5 subtypes, the former representing the high stromal response, the latter the mesenchymal low immune signature [90]. Different mechanisms control the EMT process. The transforming growth factor (TGF) β pathway seems to play a more important role in this transition. Recently, a study on 23 platinum-resistant patients identified a strong association between TGFβ-mediated EMT and chemoresistance [30].

Nonetheless, although EMT seems to play an essential role in HGSOC progression, it is not easy to develop targeted therapy. The PI3K/ AKT/ mTOR signaling represents another possible pathway involved in chemoresistance. In particular, these proteins are responsible for regulating different cellular processes, including cell growth, proliferation, motility, cell adhesion, angiogenesis and inhibition of apoptosis. They even seem to be involved in EMT reversal. Besides, stimulation of PI3K signaling could activate DNA damage response proteins, resulting in DNA repair [91].

5.5. *Epigenetic changes*

DNA methylation is associated with epigenetic silencing genes, which accounts for drug chemoresistance. In cisplatin-resistant cancer cells, multiple DNA methylation changes have been reported [92–94], especially in *MLH1* and *MSH2* mismatch repair genes. Gene silencing has been correlated with poor prognosis in both genes [95,96]. Interestingly, reversal of *MLH1* and *MSH2* epigenetic silencing by demethylation was demonstrated to re-sensitize tumor cells to subsequent treatment [97–99]. Histone deacetylation is another way to silence genes. DNA transcription is favored by a more relaxed state of chromatin, which occurs in the presence of acetylated lysine residues. Therefore, deacetylation is linked to gene silencing [100]. Of note, poor prognosis in endometrioid OC and endometrial carcinomas has been correlated to high expression of class 1 histone deacetylases (HDAC1, 2, and 3) [101].

5.6. *Immune system*

The tumor microenvironment (TME) is a complex network composed of stromal and immune cells and it plays a crucial role in resistance to therapy and disease progression, especially by promoting immunosuppression [102]. Indeed, both innate and adaptive immune system cells

affect chemotherapy response and OC prognosis. In patients with ascites, the most representative myeloid cells are tumor-associated macrophages (TAMs). TAMs promote immune suppression and their expression of CD163 has been correlated to increased interleukin (IL) -6 and IL-10 levels in ascites, which is inversely correlated with PFS in HGSOC [103,104]. Besides macrophages, other myeloid and natural killer (NK) cells are also involved in immune escape [105]. Suppression of NK cells in HGSOC ascites by either macrophage migration inhibitory factor (MIF) or B7-H6 is associated with lower OS [106]. As far as the adaptive response is concerned, increased intra-tumoral CD3+ cells (TILs) are associated with a better prognosis in OC [107]. This benefit is associated with an increased release of interferon γ (IFN-γ) [108]. Among TILs, it has recently been clarified that CD8 + T cells are associated with better prognosis [109] compared with CD4+, which are associated with worse prognosis. Accordingly, the overexpression of a subpopulation of CD4+, known as regulatory T cells (Tregs), suppresses the production of IFN-γ and IL-2 by CD8+ cells, thus triggering tumor growth in serous OC [110]. The correlation between Treg density and epithelial OC survival has been widely debated. With this regard, there are still conflicting views, some in favour of a negative correlation [111, 112], others against it [113,114]. The TME may also recruit other cells. Recently, a new member of tumor-host interacting cells has acquired increasing interest, which are suppressor cells derived from myeloid progenitors (myeloid-derived suppressor cells, MDSCs). This heterogeneous cell population is composed of myeloid line cells at different stages of differentiation that do not express myeloid markers on their surface. MDSCs have a suppressive immune response role, as they directly inhibit the cytotoxic effects of NK cells and T cells [115]. Regarding epithelial OC, a potential association between MDSCs and up-regulation of insuline-like growth factor (IGF)-1 has been observed, which may drive proliferative function among cancer cells and migration for invasion and metastasis among these cells. Other studies reported the correlation between ascites fluid and MDSCs, measuring IL-6 and IL-10 in ascites. Their findings suggested that IL-6 and IL-10 in ascites could activate MDSCs in epithelial OC patients [116]. The cyclic GMP-AMP synthase (cGAS)-Stimulator of interferon genes (STING) pathway has been linked to cancer immune response, as it can activate adaptive and immune responses. In fact, primary cGAS-STING activation promotes the continuous release of IFN. This chronic inflammation potentially leads to the development of an immunosuppressive environment and thus to drug resistance. Agonist and antagonist STING drugs are under investigation [117].

Platinum-resistant OC has been described as a “cold” tumor, because of low TIL concentrations; thus, the objective is to enhance immune cells into the tumor, to get immunotherapy efficacy. Different drug mechanisms of action are reviewed elsewhere [118]; in a subsequent chapter, we briefly present the main results for platinum-resistant OC. Traditionally, the most used targets are PD-1, programmed cell death protein ligand 1 (PD-L1) and Cytotoxic T-lymphocyte antigen 4 (CTLA-4). PD-1 is expressed both on lymphocytes and other cells of the immune system. Its activation through the link with PD-L1 or CTLA-4 leads to immune response suppression. Other receptors have been identified on immune cells as co-stimulators or co-inhibitors, which have been used as targets for new drugs; among them, a new receptor class caused interest in researchers, which is the B7 family composed of 10 receptors, including the PD-L1. Amongst, B7-H4 and B7-H6 expression is significantly associated with poor outcomes in patients with OC, due to the inhibition of TILs activation [106,119].

Further research dealing with the immune system might help to deeper understand chemoresistance, and, eventually, create future clinical testing opportunities. Moreover, the TME has recently started to be considered both as a potential target to re-sensitise tumors to platinum-based compounds and as an alternative therapy for platinum-resistant OC [120].

5.7. miRNAs

As previously stated, miRNAs are short (18−25 nucleotides) non-coding fragments of RNA that bind to and inhibit mRNA. Most of the over 1000 human miRNAs have been linked to mRNA regulation in normal and pathological processes.

In many studies, miRNAs played a role in tumor cells’ drug resistance. They may target drug-resistance-related genes and/or influence genes related to cancer spread. miRNA often targets a small number of genes of a specific gene tissue. It has been shown that miRNAs, such as let-7 [121], miRNA-9 [122], miRNA-370 [123,124], miRNA-199b-5p [125] and miRNA-449a [126] are likely to reduce the cisplatin resistance of OC cells. Some other miRNAs, such as miRNA-21 [127] and miRNA-93 [128] might enhance OC cells’ resistance to cisplatin. Intriguingly, due to the peculiar ability of miRNA to target multiple genes, even with different regulatory effects on chemoresistance, some other miRNAs, such as miRNA-106a and miRNA-130a [129,130], induce OC cell resistance to cisplatin, and correspondingly improve cells’ sensitivity to cisplatin, which complicates the understanding of their mechanism.

Attempts to target miRNAs are still ongoing. The small molecule inhibitors (SMIRs) [131,132] seem to be the most encouraging therapeutic mark for miRNAs. Other targets include miR-622 [133], which targets the Ku-complex and downregulates non-homologous end joining (NHEJ), miR-484, which targets vascular endothelial growth factor-B (*VEGFB),* vascular endothelial growth factor receptor 2 (*VEGFR2)/* kinase insert domain receptor *KDR)* pathways and tumor vasculature [134] and a miRNA profile of 9 miRNAs, which are involved in the regulation of EMT and TGF/Wnt signaling [135].

Holistic understanding of how miRNAs may induce drug resistance will facilitate the development of new strategies to regulate them effectively. This process will lead to better translation of miRNAs into clinics, transforming their functions into encouraging approaches to cancer therapy.

6. Overcoming platinum resistance

This section focuses on new molecules, which are likely to provide therapeutic opportunities in platinum-resistant OC in the near future. Drug choice should be based on clinical efficacy, quality of life and financial costs. For each of the resistance mechanisms mentioned above, drugs tested in OC are presented. Following that, drugs without the same platinum targets, as in case of angiogenesis, which showed potential effectiveness in platinum-resistant treatment, are discussed. Completed and significant ongoing studies for the treatment of platinum-resistant OC are reported in Tables 2 and 3, respectively.

6.1. Targeting pre-platinum target resistance

Data on pre-platinum targets are still in a preclinical phase. Epigallocatechin-3-gallate (EGCG), an active polyphenol in green tea, has been largely studied in cancer prevention and therapy. It has already been proven that it can enhance the effect of conventional cancer therapies through different mechanisms as induction of apoptosis [136], inhibition telomerase expression [137] or regulation of microenvironment [138]; recently the effect on cisplatin uptake has also been studied [139]. The study hypothesis is that EGCG could enhance Solute Carrier Family 31 Member 1 *(SLC31A1)* gene expression, inhibiting the degradation induced by cisplatin. Preliminary results demonstrated increased accumulation of cisplatin in OC cells if associated with EGCG of xenograft mice, placing it as a possible cisplatin-adjuvant drug in the OC treatment.

SLC31A1 function was also targeted by bortezomib and theaflavin-3,30-digallate (TF3). While the first is a proteasome inhibitor, thus keeps the *SLC31A1* protein in function despite high cisplatin concentrations [140], the second up-regulates the expression of *SLC31A1* gene

Table 2
Significant innovative studies including platinum resistant ovarian cancer.

Drug	Target	Phase	Primary endpoint	Results	Reference
PLATINUM PRE-TARGET RESISTANCE					
Reduced uptake/increased inactivation					
EGCG + CDDP	SLC31A1	Pre-clinical study	CDDP uptake	Enhance cisplatin uptake	Wang et al. (2014) [139]
Bortezomib	SLC31A1	Pre-clinical study	CDDP uptake	Enhance cisplatin uptake	Jandial et al. (2009) [140]
Theaflavin-3,3'-digallate + Cisplatin	SLC31A1 and GSH	Pre-clinical study	CDDP uptake	Enhance cisplatin uptake	Pan et al. (2018) [141]
Increased efflux					
DOPC + CDDP	ATP7A and ATP7B	Pre-clinical study	ATP7A and ATP7B expression	Enhance CDDP effect	Calandrini et al. (2014) [142]
Octeotride	MRP2	Pre-clinical study	Reduced MRP2 and EGFR expression	Enhance CDDP effect	Shen et al. (2012) [143]
DNA REPAIR SYSTEM					
Increased NER proficiency					
siRNA	miR-770-5p-ERCC1	Pre-clinical study	CDDP chemo-sensitivity	Restoration of CDDP chemo-sensitivity	Zhao et al. (2018) [232]
Increased HR proficiency					
Niraparib 300 mg NCT02354586	PARP	II	ORR	ORR: 27 % m*BRCA*, 10% in HRD, 3% in HRR proficient or unknown	Moore et al. (2019) [151]
Rucaparib 600 mg b.i.d. NCT01482715 (Study 10) NCT01891344 (ARIEL2)	PARP	I/II	ORR	ORR: 25 %	Oza et al. (2017) [150]
Veliparib 400 mg b.i.d. NCT01540565	PARP	II	ORR Safety	ORR: 20 %	Coleman et al. (2015) [152]
Olaparib 300 mg b.i.d. + Tremelimumab 10 mg/kg NCT02571725	PARP + CTLA-4	I	Safety and Tolerability	No grade 3 AEs	Adams et al. (2017) [233]
Olaparib + Cediranib NCT02345265	PARP + VEGF	II	Biomarkers of response ORR	ORR: 20 % in PR	Liu et al. (2018) [234]
Olaparib 400 mg b.i.d. NCT01078662.	PARP	II	TRR	TRR: 31% in PR, 40% in SD at 8 weeks.	Kaufman et al. (2015) [148]
Olaparib + Cediranib or paclitaxel NCT03314740	PARP+VEGF	II	PFS Safety	PFS: 5.7 m	Colombo et al. (2019) [235]
Olaparib 200–600 mg b.i.d. NCT00516373	PARP	II	ORR	ORR: 32 %	Fong et al. (2010) [149]
Olaparib + Cediranib NCT02681237	PARP + VEGF	Clinical – traslational study	PFS OS	PFS (16 w): 50% OS (1y): 64.8%	Lheureux et al. (2019) [236]
CELL CYCLE CHECKPOINT					
Ganetespib 150 mg/m^2 + Paclitaxel 80 mg/m^2 NCT02012192	p53	I/II	Safety ORR	ORR: 20% Death: 10% AEs: 30%	Ray-Coquard et al. (2019) [154]
AKT inhibitor MK-2206 NCT 01283035	PI3K/AKT pathway inhibitor overexpressed in PTEN loss	II	ORR	ORR: 0 % SD of 19 weeks in 1 patient	Lee et al. (2020) [155]
CSC and EMT					
Metformin	ALDH	Pre-clinical study	CDDP efficacy	Increased CDDP ability	Shank et al. (2012) [161]
AZD5363 and AZD8835	PI3K/AKT/mTOR	Pre-clinical study	Sensibilation of CDDP and paclitaxel	Enhance efficacy of CDDP + Paclitaxel	Wu et al. (2020) [164]
Sonidegib 800 mg + Paclitaxel 80 mg/m^2 NCT01954355	Hedgehog	I	Dose Safety	ORR: 22 %	Stathis et al. (2017) [156]
Defactinib 400 mg B.I.D. + PTX80 mg/m^2 NCT01778803	FAK inhibitor	Ib	Safety	ORR:11 %	Patel et al. (2017) [160]
Afuresertib 125 mg/day + Carboplatin AUC5 + Paclitaxel 175 mg/m^2 NCT01653912	PI3K/AKT/mTOR	Ib	Safety ORR	ORR: 32 %	Blagden et al. (2019) [177]
EPIGENETIC CHANGES					
Azacitidine 75 mg/m2+ Valproic acid 20 mg/m2 + Carboplatin AUC3 NCT00529022	DNA methylation + histone deacetylase	I	Safety	SD: 30 %	Falchook et al. (2013) [182]
Azacitidine 75 mg/m^2 sc for 5 days + Carboplatin AUC 4/5	DNA methylation	I/II	ORR, PFS	ORR: 13 % PFS: 3.7 m OS: 14 m	Fu et al. (2011) [181]

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Table 2 (*continued*)

Drug	Target	Phase	Primary endpoint	Results	Reference
Decitabine 10 mg/m^2 d1-5 + Carboplatin AUC 5	DNA methylation	II	ORR	ORR: 35 %	Matei et al. (2016) [179]
IMMUNE CHECKPOINT INHIBITORS and IMMUNOTHERAPIES					
Avelumab 10 mg/kg NCT01772004	PD-L1	Ib	Safety ORR	ORR: 13,6 %	Disis et al. (2015) [184]
Nivolumab 1−3 mg/kg UMIN000005714	PD-1	Ib	ORR	ORR:15 % PFS: 3 m OS: 20 m	Hamanishi et al. (2015) [183]
Pembrolizumab 200mg NCT02674061	PD-1	II	ORR	ORR: 7.4 % PFS: NA OS: NA	Matulonis et al. (2019) [187]
Pembrolizumab 200 mg NCT02628067	PD-1	II	ORR	ORR: 33 % in dMMR PFS: 2.3 m	Marabelle et al. (2019) [185]
Nivolumab + Bevacizumab NCT02873962	PD-1 + VEGF	II	ORR	ORR: 16.7 % PFS: 5.3 m OS: NA	Liu et al. (2018) [190]
Durvalumab 10 mg/kg + Cediranib15−20 mg + Olaparib 300 mg b.i.d. NCT02484404	PD-L1	I	ORR	ORR: 40 % PFS: NA OS: NA	Zimmer et al. (2019) [191]
Pembrolizumab + Bevacizumab + oral metronomic cyclophosphamide NCT02853318	PD-1 + VEGF + DNA damage	II	Safety ORR PFS	ORR: NA 6 m PFS: 59 %	Zsiros et al. (2019) [186]
Avelumab 10 mg/mq +/- PLD NCT02580058	PD-L1 +/- topoisomerase II	III	PFS OS	ORR: 13.3 m PFS: 3.7 m OS: 17.7 m	Pujade-Lauraine et al. (2019) [237]
Durvalumab + PLD NCT02431559	PD-1 + topoisomerase II	II	PFS	ORR:NA 6m PFS: 30 % OR: NA	O'Cearbhaill et al. (2018) [230]
Pembrolizumab + paclitaxel NCT02440425	PD-1+ microtubule	II	ORR PFS OS	ORR:51.4 % PFS:6.7 m OS:13.4 m	Duska et al. (2018) [188]
Pembrolizumab + Cisplatin + gemcitabine NCT02608684	PD-1 + DNA crosslinker + nucleoside analogue	II	ORR PFS	ORR: 50 % PFS: 5.4 m OR: NA	Walsh et al. (2019) [231]
Nivolumab 3 mg/kg vs Nivolumab 3 mg/kg + Ipilimumab mg/kg NCT02498600	PD-L1 + CTLA-4	II	ORR Toxicity	ORR: 12.2 % at 6 m in the nivolumab group and 31.4 in the nivolumab + ipilimumab group PFS: NA OS: NA 49 % Grade $\geq$ 3 related AE	Zamarin et al. (2020) [238]
Pembrolizumab 200 mg + Niraparib 200 mg NCT02657889	PD-1 + PARP	I/II	ORR	ORR: 21 % PFS: NA OS: NA	Konstantinopoulos et al. (2019) [192]
Pembrolizumab + Mirvetuximab soravtansine NCT02606305	PD-1 + folate	Ib	ORR	ORR:43 % PFS:5.2 OS:NA	Matulonis et al. (2018) [193]
INHIBITORS OF ANGIOGENESIS					
Pazopanib 800 mg/d+ W Paclitaxel 80 mg/m^2 NCT01644825.	VEGFR 1-2-3, PDGFR, c-KIT	II	ORR PFS OS	ORR: 50 % PFS: 6.3 m OS:18.7 m	Pignata et al. (2015) [198]
Pazopanib 800 mg /d + W Paclitaxel 80 mg/m^2 NCT01468909	VEGFR 1-2-3, PDGFR, c-KIT	II	PFS OS	ORR: 31.8 % PFS: 7.5 m OS: 23.3 m	Richardson et al. (2018) [199]
Cediranib 45 mg/day NCT00275028	VEGFR 1-2-3, PDGFR, c-KIT	II	ORR PFS	ORR: 17 % PFS 5.2 m OS: 16.3 m No difference in PFS between PS and PR	Matulonis et al. (2009) [200]
Cediranib 45 mg/day NCT00278343	VEGFR 1-2-3, PDGFR, c-KIT	II	ORR PFS	ORR: 29 % PFS: 4.1 m OS: 11.9 m no responses in PR and 23 (66 %) SD	Hirte et al. (2015) [201]
Aflibercept 2−4 mg/kg every 2 weeks NCT0032717	VEGFR 1-2	II	ORR PFS	ORR: 12.3 % PFS: 3.1 m OS: 13.7 m	Tew et al. (2014) [202]
Sunitinib malate 37.5 mg/d NCT00768144	VEGFR-1-2-3, PDGFR, RET, FLT3, c-KIT and CSF-1R	II	ORR PFS	ORR: 8.3 % PFS: 2.3 m	Campos et al. (2013) [203]
MCy 100 mg/d +/-Nintedanib NCT01610869	VEGF/PDGF/FGFR + MCy	II	OS	OS: 6.4 m	Hall et al. (2018) [205]
		II	ORR		Matulonis et al. (2019) [206]

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Table 2 (*continued*)

Drug	Target	Phase	Primary endpoint	Results	Reference
Cabozantinib 60 mg /day NCT01716715	RTK + VEGFR, RET, GAS6 receptor			ORR: 7 % OS: 19.4 m PFS worse in PR than in PS (p = 0.06)	
Bevacizumab 10 mg/kg or 15 mg/kg NCT00976911	VEGF	III	PFS	PFS: 6.7 m OS: 16.6 m	Pujade-Lauraine et al. (2014) [35]
Combretastatin A4 phospphate 63 mg/m^2 + carboplatin AUC 5 and paclitaxel 175 mg/m^2	Tubuline	II	Safety ORR	ORR: 29 %	Zweifel et al. (2011) [207]
Trabectedin 1.3 mg/mq every 3 weeks	DNA	II	ORR	ORR: 31 %	Lorusso et al. (2016) [213]
Lurbinectedin 3.2 mg/mq every 3 weeks	DNA	III	ORR	ORR: 14 %	Gaillard et al. (2018) [215]
HER 2 INHIBITORS					
Gemcitabine 800 mg/m2 +/- Pertuzumab 840/410 mg NCT00096993	HER2	II	ORR PFS	ORR: 13.8 % PFS: 5.3 m	Makhija et al. (2010) [217]
Pertuzumab 840/410 mg + topotecan or w-paclitaxel or gemcitabine NCT01684878	HER3	III	PFS OS	PFS: 4.3 m No OS differences	Kurzeder et al. (2016) [218], Lorusso et al. (2019) [219]
ADCs					
Mirvetuximab soravtansine NCT02631876	FR-α	III	Safety and clinical activity PFS	26 % experienced a grade 3 AE PFS: 4.1 m	Moore et al. (2019) [227]
Tamrintamab pamozirine+/- budigalimab 0.025−0.4 mg/kg NCT 02539719	DPEP3	I	Toxicity	100 % experienced ≥1 AEs. 66 % experienced serous AEs. ORR: 4 %	Hamilton et al. (2020) [239]
Lifastuzumab vedotin 2.4 mg/kg or PLD NCT01991210	NaPi2b	II	PFS	PFS: 5.3 m	Banerjee et al. (2018) [228]
Anetumab ravtansine + PLD NCT02751918	Mesothelin	Ib	Dose Toxicity	Serous AEs: 9.5% PR: 52% (11) SD: 33% (7)	Bulat et al. (2018) [240]

Abbreviations. ADCs: Antibody-Drug Conjugates. AE: Adverse events. AKT: Protein kinase B. ALDH: Aldehyde dehydrogenase. ATP7A: ATPasi copper transporter α. ATP7B: ATPasi copper transporter β. b.i.d: twice daily. BRCA: Breast Related Cancer Antigenes. DPEP3: Dipeptidase 3. c-KIT: Receptor tyrosine kinase. CDDP: Cis-diamminedichloridoplatinum/cisplatin. CSF-1R: Colony-stimulating factor 1 receptor. CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen 4. DCR: Disease control rate. DLT: Dose limiting toxicity. dMMR: Mismatch repair deficient. DNA: Deoxyribonucleic acid. DOPC: Neutral nanoliposome 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine. EGCG: Epigallocatechin-3-gallate. EGFR: Epidermal growth factor receptor. ERCC1: Excision Repair Cross-Complementation Group 1. FAK: Focal adhesion kinase-1. FGFR: Fibroblast growth factor receptor. FLT3: fms related receptor tyrosine kinase 3. FR-α: Folate receptor-α. GAS6: Growth arrest specific 6. GSH: Glutathione. HER: Human epidermal growth factor receptor. HRD: Homologous recombination deficiency. HRR: Homologous recombination repair. M: months. MCy: Metronomic cyclophosphamide. MRP2: Multidrug resistance-associated protein 2. mTOR: Mammalian target of the rapamycin. NA: Not available. ORR: Objective response rate. OS: Overall survival. PARPi: Poly (ADP-ribose) polymerase (PARP) inhibitors. PD-1: Programmed cell death protein 1. PD-L1: Programmed cell death protein ligand 1. PDGFR: Platelet-derived growth factor receptor. PFS: Progression free survival. PI3K: Phosphatidylinositol 3-kinase. PLD: Pegylated liposomal doxorubicin. PR: Platinum resistant. PS: Platinum sensitive. PTEN: Phosphatase and TENsin. RET: Rearranged during transfection. RP2D: Recommended phase 2 doses. RR: Response rate. RTK: Receptor tyrosine kinase. SD: Stable disease. siRNA: Small interfering RNA. SLC31A1: Solute Carrier Family 31 Member 1. TRR: Tumor response rate. VEGF: Vascular endothelial growth factor. VEGFR: Vascular endothelial growth factor receptor. WNT: Wingless-related integration site.

and down-regulates cellular GSH levels [141]. Both treatments seem to increase cisplatin uptake. Before cisplatin binds to DNA, there are still two molecules involved in its intracellular concentration. ATP-7B was targeted by a small interfering RNA (siRNA) [142] and MRP2 by octreotide [143]. As in previous studies, both treatments enhance cisplatin efficacy, but more data are needed to draw conclusions.

6.2. Targeting DNA repair system: PARP inhibitors

PARP inhibitors are a class of drugs that inhibit the activity of an alternate DNA repair pathway. Physiologically, DNA damage can involve single-strand breaks (SSBs) and double-strand breaks (DSBs). The mechanism of SSBs and DSDs DNA repair depends on two relatively independent processes. The SSBs activate the recruitment of the protein complex ATR [144]. Subsequently, a series of signal transduction cascades are initiated, and, finally, the NER, MMR, or BER pathways occur. In response to DSBs, two distinct pathways, including HRR and NHEJ are implicated. NHEJ is an error-prone process, which can occur during the entire cell cycle but is dominant in G0/G1 and G2 phases [144]. NHEJ involves the DNA-dependent protein kinase that recruits other proteins in a coordinated sequence to ensure that the broken ends bind, while HRR is a more accurate, error-free repair process, and most active in the late S/G2 phases of the cell cycle [144,145]. HRR entails many proteins, including RAD51, BRCA1, BRCA2 and ATM, to allow strand exchange and DNA break resolution. Despite SSBs and DSBs initiate different signaling pathways, the activated p53 is their common node and controls both damage responses in transcriptional and non-transcriptional regulation [144]. Activated p53 mediates cell cycle arrest to repair DNA lesions or activates the apoptotic proteins to induce apoptosis, if DNA damage is severe [144].

Lesions in DSBs DNA repair pathways, including HRR and NHEJ, have a significant role in platinum chemotherapy response. Platinum-based drugs cause DSBs due to intra- and inter-strand crosslinks. It is evident that BRCA1 and BRCA2 participate in making orderly HRR easier and thereby maintain genomic integrity. In the presence of *BRCA1/2* defective genes, critical events at the beginning of the HRR pathways are impaired, and repair and replication errors increase quickly with each cell cycle. Interestingly, according to the Cancer Genome Atlas (TCGA) project data, up to 51 % of HGSOC cases are characterized by defective HRR pathway [146].

Table 3
Ongoing active clinical trials testing target therapy drugs, including platinum-resistant recurrent OC.

ClinicalTrials.gov Identifier	Agent investigated	Biomarker target/mechanism of action	Phase	Number of patients enrolled	Estimated study completion date
Targeting Angiogenesis					
NCT02839707	PLD + Atezolizumab/Bevacizumab	Anti-VEGF+ anti-PD-L1 + topoisomerase inhibitor	II/III	488	July 2027
NCT03596281	Pemrolizumab + Bevacizumab + PLD	Anti-PD-1 Anti-VEGF + topoisomerase inhibitor	I	40	June 2024
NCT04787289	Bevacizumab + Chemotherapy	Anti-VEGF	II	244	January 2025
NCT04753216	Bevacizumab + Irinotecan liposome	Anti-VEGF + Topoisomerase I inhibitor	II	30	July 2024
NCT04670978	Bevacizumab + Abraxane	Anti-VEGF + antimucrotubule agent	II	96	December 2024
NCT04556071	Niraparib + Bevacizumab	PARPi + Anti-VEGF	II	32	October 2022
NCT03639246	AVB-S6-500/ Paclitaxel/PLD	Anti-AXL + microtubule inhibitor + topoisomerase inhibitor	I/II	53	December 2022
NCT04019288	AVB-S6-500 + Durvalumab	Anti-AXL+ Anti-PD-L1	I/II	36	September 2020
NCT03170960	Cabozantinib + Atezolizumab	Multi targeting TKI + anti-PD-L1	I/II	1732	December 2021
NCT03398655	Ofranergene Obadenovec/Paclitaxel	Fusion protein combining TNFR1 and FasR, driving cell death in the endothelium + microtubule inhibitor	II	400	June 2023
NCT04348032	Apatinib/PLD	VEGFR2 inhibitor + DNA topoisomerase inhibitor	II	150	June 2021
NCT04000295	Apatinib + Etoposide vs Paclitaxel	VEGFR2 inhibitor + topoisomerase II inhibitor + microtubule inhibitor	III	280	July 2022
NCT03942068	Apatinib/Paclitaxel	VEGFR2 Inhibitor + microtubule inhibitor	II	35	December 2020
NCT03648489	Paclitaxel/ sapanisertib	mTORC inhibitor + microtubule inhibitor	II	126	March 2022
NCT02641639	Bevacizumab + Combretastatin A4	Anti-VEGF + Tubulin inhibitor	II/III	91	2018: Interim analysis failed to show efficacy benefit but final results pending
NCT04376073	Anlotinib + Niraparib	Multi targeting TKI: VEGFR, FGFR, PDGFR, and c-KIT + PARPi	II	40	March 2022
NCT03924882	Anlotinib	Multi targeting TKI: VEGFR, FGFR, PDGFR, and c-KIT.	II	30	April 2022
Targeting DNA repair					
NCT03924245	Olaparib + Entinostat	PARPi + HDAC inhibitors	I/II	73	March 2025
NCT03992131	Rucaparib + other anticancer agents	PARPi	I/II	329	March 2024
NCT03955471	Niraparib + Dostarlimab	PARPi + Anti-PD-1	II	150	October 2024
NCT03467178	Decitabin+ Carboplatin	Nucleic Acid Synthesis Inhibitor + microtubule inhibitor	II	119	April 2021
NCT00529022	Azacytidine + Valproic acid + Carboplatin	DNMT inhibitor+ HDAC inhibitor + microtubule inhibitor	I	36	October 2012
NCT04217798	Niraparib+ Oral etoposide	PARPi + topoisomerase II inhibitor	II	35	January 2022
NCT03335241	Fludarabine+ PLD	Purine analog that interrupts DNA synthesis + DNA topoisomerase inhibitor	II	140	December 2022
NCT02953457	Olaparib/Durvalumab/ Tremilimumab	PARPi + Anti-PD-L1 + Anti-CTLA-4	II	36	December 2021
NCT02502266	Standard cht vs Olaparib vs Cediranib vs Olaparib + Cediranib	PARPi + Anti-VEGF	II/III	680	June 2023
NCT04679064	Niraparib + dostarlimab vs chemotherapy	PARPi + Anti-PD-1	III	427	January 2025
NCT03586661	Niraparib + Copansilib	PARPi + PI3K inhibitor	I	44	April 2022
NCT02208375	Olaparib + Vistusertib vs Olaparib + Capivasertib	PARPi + mTORC inhibitor or AKT inhibitor	I/II	159	November 2021
NCT03154281	Niraparib + Everolimus	PARPi + kinase inhibitor	I	24	June 2022
Targeting Immune Checkpoints					
NCT02963831	ONCOS102 + Durvalumab	Anti-PD-L1 + GM-C SF-encoding adenovirus	I/II	78	October 2022
NCT04205227	ENB003+ Pembrolizumab	Endothelin B receptor antagonist + Anti-PD-1	I/II	130	November 2023
NCT03287674	TILs and IL2 after Cyclophosphamide And Fludarabine with prior treatment with ipilimumab and nivolumab	ACT with TILs	I/II	20	October 2023
NCT04068974	Camrelizumab/ Apatinib	Anti-PD-1+VEGFR2 Inhibitor	II	28	June 2022
NCT03699449	Durvalumab + Olaparib/ Tremelimumab/ standard cht	Anti-PD-L1+ PARPi/ Anti-CTLA-4	II	86	September 2022
NCT03539328	Pembrolizumab + standard chemotherapy vs standard chemotherapy	Anti-PD-1	II	138	April 2022
NCT03113487	Pembrolizumab + P53MVA	Anti-PD-1 + Modified Vaccinia Virus Ankara Vaccine Expressing p53	II	28	January 2021
NCT02659384	Atezolizumab, Bevacizumab and Acetylsalicylic Acid	Anti-PD-L1	II	122	February 2023

(*continued on next page*)

Table 3 (*continued*)

ClinicalTrials.gov Identifier	Agent investigated	Biomarker target/mechanism of action	Phase	Number of patients enrolled	Estimated study completion date
NCT03363867	Atezolizumab/ Bevacizumab/ Cobimetinib	Anti-PD-L1+ Anti-VEGF+ MEK inhibitor	II	29	February 2024
NCT03430700	Pembrolizumab following w Paclitaxel	Anti-PD-1	II	28	November 2022
NCT03026062	Durvalumab and Tremelimumab	Anti-PD-L1 + Anti-CTLA4	II	100	March 2022
NCT03029403	Pembrolizumab/ DPX-Survivac Vaccine/ Cyclophosphamide	Anti-PD-1 + survivin-based synthetic peptide antigens.	II	42	February 2024
NCT02554812	Avelumab + other immune modulators	Anti-PD-L1	II	620	February 2024
NCT03038100	Standard chemotherapy + Atezolizumab/ Placebo	Anti-PD-L1	III	1300	February 2022
Antibody Drug Conjugated Targeting PR-recurrent ovarian cancer					
NCT03657043	Tisotumab Vedotin	ADC targeting TF	II	222	August 2022
NCT03587311	Bevacizumab + Anetumab Ravtansine/ Paclitaxel	Anti-VEGF + ADC targeting mesothelin + microtubule inhibitor	II	96	October 2021
NCT04296890	Mirvetuximab Soravtansine	ADC targeting FRα	III	110	July 2022
NCT04209855	Mirvetuximab Soravtansine vs standard chemotherapy	ADC targeting FRα	III	430	November 2022
NCT03319628	Upifitamab rilsodotin	ADC targeting NaPi2b	I/II	420	December 2022
NCT04152499	SKB264	ADC targeting TROP-2	I/II	78	December 2022
Targeting serine/threonine protein kinase pathways					
NCT04055649	ONC201 + Paclitaxel	Inhibitor of the serine/threonine protein kinase AKT and ERK	II	62	June 2020
NCT04374630	Afuresertib and Paclitaxel	Inhibitor of the serine/threonine protein kinase B + microtubule inhibitor	II	141	January 2023
NCT03462342	Olaparib + AZD6738	PARPi + inhibitor of the Serine/Threonine protein kinase ATR	II	86	December 2021
NCT02101775	Adavosertib	WEE1 TKI	II	100	December 2020
NCT01164995	Adavosertib + carboplatin	WEE1 TKI	II	21	September 2013
NCT04840589	Nivolumab+ Ipilimumab+ ZEN003694	Anti-CTLA-4 + BET inhibitor	I	51	January 2023

Last updated November 21 st 2020

Abbreviations. ACT: Adoptive T cell therapy. ADC: Antibody-drug conjugate. AKT: Protein kinase B. ATR: Ataxia telangiectasia and rad3 related serine/threonine kinase. BET: Bromodomain and extraterminal domain. c-KIT: Receptor tyrosine kinase. CTLA-4: Cytotoxic T-Lymphocyte Antigen 4. DNA: Deoxyribonucleic acid. DNMT: DNA methyltransferases. ERK: Extracellular signal-regulated kinase. FGFR: Fibroblast growth factor receptor. FasR: Fas receptor. FRα: folate receptor α. GM-CSF: granulocyte-macrophage colony stimulating factor. HDAC: Histone deacetylase. MEK: Mitogen-activated protein. mTORC: Mammalian target of rapamycin complex. NaPi2b: Sodium-dependent phosphate transporter 2B. Poly (ADP-ribose) polymerase (PARP) inhibitors. PD-1: Programmed cell death protein 1. PD-L1: Programmed cell death protein ligand 1. PDGFR: Platelet-derived growth factor receptor. PI3K: Phosphatidylinositol 3-kinase. PLD: Pegylated liposomal doxorubicin. TILs: Tumor infiltrating lymphocytes. TF: Tissue factor. TKI: Tyrosine kinase inhibitor. TNFR: Tumor necrosis factor receptor. TROP2: Trophoblast cell-surface antigen 2. VEGF: Vascular endothelial growth factor. VEGFR: Vascular endothelial growth factor receptor. WEE1: WEE1 G2 checkpoint kinase.

Considering that *BRCA1* and *BRCA2* are largely restricted to the HGSOC subtype and are mainly a risk factor for this histotype -notably 25 % HGSOC harbor somatic and germline *BRCA1/2* mutations [147] - the subsequent homologous recombination deficiency (HRD) promotes platinum sensitivity due to an accumulation of double-strand breaks after platinum chemotherapy. In addition, m*BRCA* patients can also be sensitive to other DNA damage-inducing regimens, such PARP inhibitors, because of the deficiency in HRR. Limited data are available on PARP inhibitors in platinum-resistant OC. PARP inhibitors have mostly shown encouraging clinical efficacy in several phase I/II trials [148, 149]. In particular, Kaufman et al. reported an objective response rate (ORR) of 31.1 % (95 % CI: 24.6–38.1) and a stable disease (SD) rate of 40.4 % (95 % CI: 33.4–47.7) in patients with *BRCA1* and *BRCA2* associated platinum-resistant OC with oral olaparib 400 mg twice per day. Olaparib was reasonably well-tolerated and in order to manage most of its toxicity, the dose was interrupted or reduced to 200 mg twice per day or 100 mg twice per day [148]. Similarly, Fong et al. found an ORR of 33.5 % among 24 platinum-resistant patients treated with olaparib in a phase I trial. None of 13 platinum-refractory patients had partial or complete response to treatment, while in 13 patients with platinum-sensitive disease, the ORR was 46.2 % [149]. More recently, other PARP inhibitor drugs, such as veliparib, niraparib and rucaparib have been tested in platinum-resistant OC patients. In total, results supported a favourable tolerance profile and showed an ORR around 20–27 %, especially in m*BRCA* patients [150–152].

These data showed that, despite platinum and PARP inhibitors resistance may involve similar mechanisms, patients with platinum-resistant disease still have the potential to favourably respond to this treatment, especially m*BRCA* women. Thus further investigation in phase III trials is warranted.

Recently, attention has been put in studying combination therapy with PARP inhibitors in platinum-resistant disease. The rationale is to use different agents to cease the growth of tumor cells. The vast majority of studies are phase I/II trials. Details are listed in Table 3. Interestingly, the OVM 1405 is a phase II/III trial (NCT02502266) that randomizes 1:1:2 platinum-resistant OC patients to the PARP inhibitor olaparib or the anti-angiogenic agent cediranib or the combination of drugs (NCT02502266). The OVM 1405 trial is still recruiting. The primary endpoint is PFS. The estimated primary completion date is planned for June 30, 2023 (NCT02502266).

Lately, the association of PARP inhibitor and immunotherapy has been arousing interest. Among ongoing studies, the NItCHE-MITO 33

trial is designed to evaluate the combination of dostarlimab and niraparib versus chemotherapy at physician choice in patients with recurrent ovarian, tube or primary peritoneal cancer when platinum is not an option of treatment (NCT04679064). In this phase III randomized study, the primary outcome is OS. The study completion date is expected for January 1, 2025.

6.3. Targeting cell cycle-checkpoint inhibitors

During cell cycle, checkpoint pathways inhibit the transmission of errors, which are likely to arise during cell replication. New therapeutic approaches against cell-cycle checkpoints are in development.

One of the most studied and promising cell cycle checkpoint inhibitors in OC treatment is the WEE1 G2 checkpoint kinase. It acts as a critical regulator of the G_2-M cell-cycle checkpoint control by regulating the phosphorylation of the CDC2-cycline B complex [153]. In case of DNA damage, WEE1 inactivates CDC2, leading the cell to G_2 arrest to allow time to repair damaged DNA. In this context, WEE1 tyrosine kinase inhibitors play a key role due to their ability to abrogate the G_2–M checkpoint and thus determine the mitotic catastrophe (a premature mitotic entry and subsequent cell death) [153]. Since OC can retain p53-related G1 checkpoint abnormalities, it becomes dependent on the G2 checkpoint. Therefore, with the inhibition of the G2 checkpoint, the p53 deficient OC cells become more susceptible to cytotoxic drugs that cause DNA damage, such as radiation therapy or some cytotoxic agents. Based on this assumption, adavosertib (MK1775), a WEE1 tyrosine kinase inhibitor has been tested in p53 mutated refractory and resistant OC patients, associated with carboplatin (NCT01164995). However, results are still pending. Similarly, an active, non-recruiting phase II trial (NCT02101775), planned to enroll 100 patients, is designed to compare gemcitabine with or without MK1775 in women with platinum-resistant OC. The primary endpoint is PFS.

Heat shock protein 90 (HSP90) inhibition makes cell cycle arrest easier in all cell cycle checkpoints, based on malignancy grade and cellular context. In a phase I/II study, ganetespib, an anti-HSP 90 was associated with weekly paclitaxel in platinum-resistant OC [154]. In patients with p53 mutation, HSP90 blockage induced degradation of p53 and hence cell apoptosis. Ganetespib 150 mg/m^2 with paclitaxel 80 mg/m^2 administered once a week, for 3 out of 4 weeks, was generally well-tolerated. Nonetheless, one patient died due to digestive hemorrhage, and grade 3/4 adverse events (AEs) of diarrhea (in 30 % of the patients) and neutropenia (in 20 % of patients) were recorded [154]. However, an ORR of 20 % was achieved.

No trial has been published targeting NF1 and RB1, while a phase II study was recently published on the inhibition of the pathway activated by PTEN. Despite promising results in a phase I study, this phase II study did not show any objective response; only 5 patients were enrolled, and 80 % experienced grade 3 maculopapular rash. Further investigations are needed to understand if the low ORR of cell cycle target is due to inefficacy of the tested drugs, or if next-generation sequencing could identify patients with altered pathways, who are potential beneficiaries of these treatments [155].

6.4. Targeting cancer stem cells and epithelial-to-mesenchymal transition

Despite the extraordinary results achieved by PARP inhibitors, patients treated with olaparib relapsed because cells overcame DNA repair deficiency. A recent study highlighted that resistant cell lines express CD133 and CD117, typical markers of CSCs [86]. Some emerging therapies, which aim at targeting the escape mechanisms of CSCs, are under investigation.

Sodinegib and vismodegib are two new drugs, which inhibit hedgehog pathways. Sodinegib was tested in a phase I study, showing a good toxicity profile at 800 mg daily dose combined with paclitaxel 80 mg/m per week [156]. Eighteen solid tumor patients were enrolled; only in 6 % a grade 3 anemia and in 11 % grade 3 diarrhea were registered. In OC women, an ORR of 22 % was achieved [156]. Vismodegib was tested alone after second- or third-line chemotherapy, in patients who had achieved complete response with previous chemotherapy treatment [157], but PFS (primary endpoint) was not improved in patients who received vismodegib maintenance.

Other pathways, such as Wnt and focal adhesion kinase inhibitor (FAK), have been tested in phase I studies [158–160]. Data about ipafricept have been positive in platinum-sensitive patients and studies on platinum-resistant OC are under possible exploration [161]. FAK is a cytoplasmic protein overexpressed in CSCs, which activate intracellular signaling cascades. It has been studied that the blockade of FAK inhibits tumor cell survival, proliferation, invasion and tumor angiogenesis, thus reducing tumor growth and metastasis. Cancer stem cells have also been shown to reduce because of FAK inhibitors.

Targeting FAK was investigated in a phase I/Ib trial of defactinib 400 mg twice daily, in 18 advanced or refractory OC patients in association with weekly paclitaxel.

The combination treatment was well-tolerated. Toxicity grade 3 was reported in 27 % of women for neutropenia, 16 % for hyperbilirubinemia and only 5 % for anemia, leukopenia, nausea and vomiting, without any grade 4/5 toxicity. ORR was 11 % [160]. One woman had a complete response according to Response Evaluation Criteria in Solid Tumors (RECIST), one had an ongoing partial response of >6 months and one had SD for longer than 8 months. Therefore, the combination of defactinib and weekly paclitaxel was considered well-tolerated, although it still requires further analysis.

Furthermore, metformin, an anti-diabetic drug, in combination with carboplatin and/or paclitaxel has been proven to induce apoptosis in OC cells, leading to cell cycle arrest in the G0/G1 and S phase. In particular, the down-regulation of B cell lymphoma 2 (*BCL2*) and up-regulation of BCL2 associated X (*BAX*) expression induce apoptosis in OC cells [162]. After achieving interesting results in preclinical studies, metformin in association with cisplatin was explored in the clinical setting and it was found to significantly synergize with cisplatin, restricting the growth and proliferation of OC stem cells in vitro and in vivo, probably due to the reduction of ALDH + in CSCs [161]. Thirty-eight women were enrolled in a phase II study comparing chemotherapy with or without 100 mg metformin in an upfront strategy. Primary endpoints were ALDH + CD133+ CSC and relapse-free survival (RFS) at 18 months. Final analysis showed a reduction of ALDH + CD133+ cells in the metformin arms compared with controls and an RFS at 18 months of 59 % (95 % CI 38.6–70.5) [163].

As mentioned above, the PI3K/ AKT/ mTOR pathway is involved in chemoresistance. Considering that *PIK3CA* mutations occur in 20 % of OC [21], PI3K/AKT/mTOR inhibitors may offer an effective therapeutic approach to OC management [164]. Thus, this family of drugs was investigated in several clinical trials for OC, including platinum-resistant disease. Results in orthotopic animal models demonstrated that AZD5363/capivasertib and AZD8835 (two compounds that inhibit PI3K/AKT signaling pathway) sensitized chemoresistant cells to treatment with cisplatin and paclitaxel [164].

However, in clinical phase I studies, different pan-PI3K inhibitors (such as buparlisib, pictisilib and alpelisib) in monotherapy, showed limited ORR (0%) and a high toxicity in OC [165–167]. Similarly, for mammalian target of rapamycin complex (mTORC1) inhibitors [168–170] and AKT inhibitors [171,172], phase II studies showed an ORR < 10 % in OC (including also platinum-resistant disease). Differently, the association with PARP inhibitors seems promising and needs to be further investigated [173]. Until now, only two studies have been published regarding PI3K inhibitors. The association of buparlisib 40−50 mg with olaparib 100−300 mg BID was tested on 46 recurrent HGSOC (57 % with platinum-resistant disease, 70 % m*BRCA*); the ORR reported was 29 % in germline m*BRCA* women and 27 % in platinum-resistant patients [174]. These results are slightly lower than ones derived from a trial testing the association of alpelisib and olaparib in 28 OC patients (23 platinum-resistant recurrences, 3

platinum-refractory recurrences, 10 m*BRCA* patients). This phase I trial demonstrated an ORR of 36 % (33 % in m*BRCA* and 31 % in wt*BRCA* patients with platinum-resistant disease) [175]. Several ongoing trials are investigating the real benefit of PI3K/ AKT/ mTOR inhibitors in association with PARP inhibitors, (NCT03586661, NCT02208375, NCT03154281), considering that olaparib alone has a similar ORR (around 30 % in m*BRCA*) [148,176].

Some authors have evaluated PI3K/ AKT/ mTOR inhibitors also in combination with cytotoxic agents (NCT04374630) or immunotherapy (NCT04840589). Among them, Blagden et al. investigated the safety and tolerability of afuresertib -a pan-AKT kinase inhibitor- in combination with paclitaxel and carboplatin in patients with platinum-resistant OC. The study had two parts: part I, including 29 patients, was a 3 + 3 dose escalation; part II, with 30 women, aimed to assess efficacy [177]. The maximum tolerated dose of afuresertib in combination with 175 mg/mq paclitaxel and area under the curve (AUC) 5 carboplatin, administered every 3 weeks for six cycles, was defined at 125 mg/day. Main toxicity included alopecia, neutropenia, neuropathy, and arthralgia. In total, an ORR of 32 % (95 % CI: 15.9–52.4) was observed, with a clinical benefit rate of 71 %. The response was durable with a median PFS of 7.1 months (95 % CI: 6.3–9.0) [177].

Until now, no significant benefit of PI3K/ AKT/ mTOR inhibitors was demonstrated in Phase III clinical trials. Thus, further well-designed clinical trials are required to explore and support their use in the setting of platinum-resistant disease, toward an individualized, precision-medicine approach [178].

6.5. Targeting epigenetic change

DNA methylation or deacetylation are associated with epigenetic silencing genes. Therefore, DNA methyltransferases (DNMT) inhibitors and HDAC inhibitors have been studied to restore platinum sensitivity. Decitabine is the first DNMT inhibitor tested in HGSOC. Results concerning its efficacy are contradictory [179,180]; indeed, one study conducted on a small sample of platinum-sensitive OC closed earlier due to lack of efficacy [179]. However, in the setting of platinum resistance, 17 women were treated with decitabine 10 mg/mq before carboplatin (AUC5) and an ORR of 35 % was achieved with an acceptable toxicity profile (grade 3–4 AEs neutropenia in 23 % of women and thrombocytopenia, leukopenia, anemia in 11 % each) [180]. Another ongoing study has completed enrollment and results are awaited (MITO 29) (NCT03467178).

Azacytidine, another DNMT inhibitor, is a possible promising drug. It was tested on 30 OC women in a phase I/II study. Platinum-resistant/-refractory patients were treated with a dose of 75 mg/mq azacytidine subcutaneously administered daily for 5 days before carboplatin (AUC 4 or 5) four weekly. ORR was 14 % (4/29; 95 % CI: 10.1–17.5) with a median PFS of 3.7 months and OS of 14 months. The most common grade 3–4 AEs were leukopenia (20 %) and fatigue (30 %) [181]. Good results have also been obtained combining azacytidine at the same dosage with carboplatin AUC 3 and valproic acid, an HDAC inhibitor (NCT00529022). Out of ten patients, 30 % achieved a partial response or SD in terms of ORR [182]. Currently, no drugs belonging to this class are yet approved in OC. However, future research should focus on patient selection to maximize efficacy, as these drugs have the advantage of an easy administration.

6.6. Targeting immune system

Immunotherapy is a field of research with wide scope in recent decades and gains recognition in OC treatment. However, drugs are not yet approved for women with OC because the results obtained in terms of ORR are still not satisfactory. The most exploited targets in immunotherapy are PD-1 with its receptor PD-L1 and CTLA-4. PD-1 is expressed both on lymphocytes and other cells of the immune system. Its activation through the link with PD-L1 or CTLA-4 leads to a suppression of the immune response.

Immunotherapy aims to increase the activity of the immune system against the tumor, avoiding the link between the ligand and its receptor. In this regard, it has been shown that the presence of TILs is connected to a better prognosis in OC.

The safety and tolerability of different anti-PD-1 and anti-PD-L1 were evaluated in several phase I studies. All medications (avelumab, nivolumab, pembrolizumab) showed an acceptable toxicity profile. There was no evidence of treatment-related death and severe toxicity (grade $\geq$ 3) was recorded in 10 % of cases. Overall, nivolumab showed the highest ORR rate (15 %) compared with other drugs (7–14 %) [183]. PFS and OS were similar to standard single-agent chemotherapy used in clinical practice for resistant OC [35,184–187]. Nonetheless, in tumors with deficit in DNA mismatch repair, an ORR rate of 33 % was reached after pembrolizumab administration [185], suggesting that MSI OC might achieve the greatest benefit from this drug class. In order to increase treatment efficacy, further combinations of immunotherapy with chemotherapy have been investigated, hypothesizing a synergistic effect. The combination of pembrolizumab with paclitaxel has recently reached an ORR of 51.4 % [188], which is similar to the 53 % response rate seen in the AURELIA trial [35] when bevacizumab is added to standard chemotherapy.

Moreover, promising results are emerging with the association of immune checkpoint inhibitors with targeted agents, such as anti-angiogenic drugs and/or PARP inhibitors. Indeed, it has been suggested that targeting the tumor vasculature by anti-angiogenic drugs can be a potential solution to enhance anti-cancer immunity and overcome resistance to immune checkpoint inhibitors. On the other side, DNA damage by DNA repair inhibitors promotes activation of systemic anti-tumor immune responses, potentially enhancing immunotherapy activity [189–191]. In platinum-resistant patients, double treatment resulted in an ORR of 16 % and 17 %, respectively [190,191]. No ORR benefit was demonstrated when pembrolizumab was associated with niraparib (25 % versus 21 %) [192]. Anti-folate antibody-drug conjugates were also associated with pembrolizumab, reaching an ORR of 43 % and 5.2 months in PFS [193].

6.7. Inhibitors of angiogenesis signaling pathways

Angiogenesis describes the process needed for the growth and development of new blood vessels and it is mostly regulated by the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) [194].

a **Bevacizumab**

Bevacizumab is a recombinant humanized monoclonal antibody. It targets all VEGFA isoforms. Bevacizumab received both U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in 2014 to treat platinum-resistant OC in association with chemotherapy [35–38]. The standard dose of bevacizumab is not clearly established; for platinum-resistant OC, only 15 mg/kg doses are allowed. An ongoing clinical trial, with two arms, will clarify if a low dose (7.5 g mg/kg) combined with standard chemotherapy is effective as treatment with high doses in platinum-resistant disease (NCT04787289). Other possible combinations with bevacizumab are currently under investigation, including cytotoxic drugs like irinotecan liposome (NCT04753216) and abraxane (NCT04670978). The aim is to clarify if these associations might have a synergistic effect. Also, the combination with PARP inhibitors is examined; specifically, a phase II study is currently exploring the efficacy and safety of niraparib combined with bevacizumab in platinum-resistant OC and it has started to recruit in November 2020; thirty-two patients are planned to be enrolled (NCT04556071). Regarding immune system, some authors have proposed a synergistic effect of anti-angiogenic activity with immune checkpoint inhibitor (NCT03596281, NCT02839707), but data are still

immature. The combination of paclitaxel and bevacizumab with or without emactuzumab enriches the picture of ongoing studies on the immune system. Indeed, emactuzumab is a new monoclonal antibody, which targets TAMs and it has been proposed that its administration together with bevacizumab might enhance the anti-angiogenic effect. In fact, chemoresistance to anti-VEGF agents is mediated by TAMs, which are recruited in the tumor microenvironment following hypoxia; emactuzumab that targets colony-stimulating factor (CSF-1)-mediated signaling via its receptor (CSF-1R) reduces TAMs migration and proliferation into the tumor [195].

Finally, in the BEACON trial, platinum-resistant or -refractory HGSOCs patients are randomized to receive cobimetinib, bevacizumab and atezolizumab. Cobimetinib is a drug that blocks the mitogen-activated protein kinase involved in the multiplication of cancer cells. By binding to the MEK protein, cobimetinib is supposed to stop the growth of cancer cells (NCT03363867). Efficacy and safety are the main endpoints of this trial.

Other agents interfering with tumor vascularization are discussed in the following paragraphs.

b Tyrosine kinase inhibitors

TKIs, alone or in combination therapy, are evaluated in platinum-resistant OC. TKIs target the VEGFR, the fibroblast growth factor (FGF) and the platelet-derived growth factor (PDGF). Pazopanib is an oral TKI, which blocks multiple receptors such as i) VEGFR1/ fms related receptor tyrosine kinase 1 (FLT1), VEGFR2/KDR, and VEGFR3/ fms related receptor tyrosine kinase 4 (FLT4); ii) platelet-derived growth factor receptors (PDGFR) α and β; iii) proto-oncogene receptor tyrosine kinase (*c-KIT*). In recurrent OC, pazopanib has been tested as monotherapy [196], maintenance therapy after upfront chemotherapy for advanced disease [197] and lastly in combination with paclitaxel in patients with refractory or recurrent OC [198,199]. Overall, data do not allow a clinical recommendation for pazopanib use in the OC management. The effect of pazopanib in platinum-resistant disease has been directly studied in the phase II MITO 11 trial [198]. In particular, 73 patients with platinum-resistant or -refractory OC received pazopanib (800 mg/day) plus weekly paclitaxel (80 mg/mq on day 1,8 and 15 in a 28-day cycle). This study indicated that the combination of pazopanib with weekly paclitaxel was related to a significant 2.86-month improvement in PFS compared with weekly paclitaxel alone (6.35 months versus 3.49 months; HR 0.42, 95 % CI: 0.25−0.69, p value 0.0002) [198]. The addition of pazopanib to weekly paclitaxel increased toxic effects, especially leucopenia, neutropenia, epistaxis, hypertension, fatigue, diarrhea, mucositis, sensory neuropathy and increased aspartate/alanine aminotransferase concentrations. Hypertension, fatigue, diarrhea, bleeding and liver toxicity are known adverse effects of anti-angiogenic agents; whereas neutropenia, mucositis, and neurotoxic effects were attributed to the potential synergistic effect of the combination therapy [198]. Richardson et al. have recently released the results of a similar randomized phase II trial [199]. The trial has shown that the combination of pazopanib and weekly paclitaxel increased overall toxicity (mainly severe hypertension and severe neutropenia) and did not yield better outcomes than weekly paclitaxel alone [199]. About half of the patients (n = 52, 49.1 %) had platinum-sensitive disease and this finding was relevant to evaluate the risk-benefit ratio in platinum-resistant OC cases adequately. Interestingly, a suggestive connection was identified between single-nucleotide polymorphisms VEGF and response to therapy. Although no difference was observed in PFS between the paclitaxel with and without pazopanib groups (HR 0.84, 90 % CI: 0.57–1.22, p value 0.20), platinum-resistant patients with VEGFA CC genotype were more resistant to weekly paclitaxel than those with the AC or AA genotype, with 7 %, 20 % and 50 % responding, respectively [199]. Further and larger studies are needed to establish whether single-nucleotide polymorphisms VEGF can be used as predictive markers in pazopanib treatment.

Cediranib is an oral multi-potent TKI of VEGFR1/FLT1, VEGFR2/KDR, VEGFR3/FLT4, PDGFRα and c-KIT. A phase II study showed encouraging anti-cancer activity in platinum-resistant OC, with 20 % of partial response and 13.3 % of SD. Patients experienced higher rates and severity of hypertension, fatigue and gastro-intestinal toxicities (diarrhea, nausea/vomiting) [200].

Similar results in platinum-resistant population were recently confirmed in a phase II study conducted by the Princess Margaret Phase II Consortium in collaboration with the University of Chicago and the California Cancer Consortia [201]. In the mentioned study, an overall 66 % of clinical benefit and cediranib-related toxicities, were recorded in platinum-resistant patients [202]. Overall, several considerations were shared. The anti-cancer responses in platinum-resistant disease suggested that cediranib therapy can circumvent pathways of platinum resistance. As far as drug-related toxicity is concerned, its severity may be a predictive marker but whether or not cediranib-related toxic effects should be related to the clinical outcome still remains to be confirmed.

Other multi-targeted TKIs, used as monotherapy or in combination therapy, have been tested in different trials involving the platinum-resistant population [202–206]. The mentioned multi-targeted TKIs include aflibercept (a fusion protein of the Fc portion of human IgG1 with the extracellular ligand-binding domains of VEGFR1/FLT1 and VEGFR2/KDR, which modulates the availability of VEGF ligand), sunitinib malate (a VEGFR1/FLT1, VEGFR2/KDR, VEGFR3/FLT4, PDGFR, RET, fms related receptor tyrosine kinase 3 FLT3, c-KIT and CSF-1R inhibitor), cabozantinib (tyrosine-protein kinase Met c-MET, VEGFR2/KDR, Rearranged during transfection RET, AXL tyrosine kinase, FLT3 and TIE-2/TEK tyrosine kinase inhibitor) and nintedanib (VEGF, FGF, and PDGF inhibitor). Collectively, these anti-angiogenic agents in platinum-resistant disease showed modest activity in terms of response if compared with the remarkable frequency and consistency of the observed toxic effects. Based on detrimental results of a phase II NRG Oncology/Gynecologic Oncology Group study, treatment with cabozantinib was even deemed clinically uninteresting and not worthy of further investigation to treat recurrent OC, either platinum-resistant or platinum-sensitive [206]. The cabozantinib 60 mg regimen compared with weekly paclitaxel showed worse clinical outcomes (OS, PFS, response rate) and worse toxicity profile (mainly nausea, diarrhea, abdominal pain and vascular disorders).

c Vascular disrupting agents

Vascular disrupting agents specifically target the existing neovasculature. Combretastatin A4 is a microtubule-depolymerizing agent that binds to tubulin causing morphological changes in endothelial cells [195]. A phase II trial was carried out to assess the activity of combretastatin A4 (63 mg/mq) in association with carboplatin (AUC 5) and paclitaxel (175 mg/mq) in patients with platinum-resistant OC [207]. The treatment was well-tolerated, with a relatively good level of response (29 %) [208]. A randomized trial is needed to confirm these promising results. A phase II/III study has already been designed to test both efficacy and safety of physician's choice chemotherapy plus bevacizumab and combretastatin A4 versus physician's choice chemotherapy plus bevacizumab and placebo in patients with platinum-resistant OC (NCT02641639). Interim analysis failed to show efficacy benefit, but, at present, definitive results are still pending. This approach, targeting both ligand (bevacizumab) and receptor (combretastatin A4), could potentially improve the antitumor activity, as it has been demonstrated in other combinations that it blocks the vertical VEGF pathway or two different horizontal pathways [208]. Careful attention should be paid in cumulative toxicities monitoring. For instance, a trial of the Chicago, PMH, and California Phase II Consortia, which aimed at testing the association of bevacizumab and erlotinib in recurrent OC, was stopped [208]. The first accrual stage showed no strong evidence that the anti-VEGF/anti- epidermal growth factor receptor (EGFR) agent combination was superior to single-agent

bevacizumab; furthermore, the rate of gastro-intestinal perforation was higher [208].

Other two drugs deserve attention. Trabectedin is a marine-derived antitumor agent discovered in the Caribbean tunicate Ecteinascidia turbinata, with multiple mechanisms of action. Indeed, his cytotoxic effect is due to the binding of the minor groove of DNA, avoiding the activation of DNA repair process and further enhanced by protein inhibition production as VEGF [209].

The efficacy and safety of trabectedin in OC were demonstrated in different phase I-II trials. Although the ORR is always higher in platinum-sensitive OC, it also seems to have a role in treating platinum-resistant OC. A standard dose has not been established. In fact, trabectedin was tested in a first study at a dose of 1.3 mg/mq as a 3-h intravenous infusion every three weeks in 30 platinum-resistant OC with an ORR of 7 % [210] and at a dose of 0.58 mg/mq as a 3-h intravenous infusion every four weeks in 81 platinum-resistant OC patients with an ORR of 6 % [211].

Moreover, it seems that its efficacy is even higher in m*BRCA* patients because the lack of HRR, resulting in the inability to repair DSBs, enhances the trabectedin effect [212]. In the MITO 15 trial, a total of 100 patients with recurrent m*BRCA* OC and/or BRCAness phenotype (more than two previous responses to platinum) were treated with trabectedin 1.3 mg/mq every three weeks. In the platinum-resistant group (n = 48) the ORR was 31 %. No differences were found between m*BRCA* and wt*BRCA* [213].

Lurbinectedin (PM01183) is a synthesized protein derived from trabectedin; as the latter, it binds the DNA minor groove, resulting in cell death. It was tested in OC in phase II-III studies. In a phase II multicenter study, 22 patients with platinum-resistant OC received 7 mg of lurbinectedin every three weeks. In a second step of the study, other patients were randomized to receive lurbinectedin (30 patients) or topotecan (29 patients) on days 1−5 every three weeks or weekly every 4 weeks. In the subgroup of 33 platinum-resistant OC women treated with lurbinectedin, the ORR and PFS were 30 % (95 % CI: 16–49) and 5 months (95 % CI: 2.7–6.9 months) respectively, compared to no ORR in the topotecan group [214].

As the results were promising, a phase III randomized trial was conducted from 2015 (CORAIL trial). Women with platinum-resistant OC were randomized to receive lurbinectedin 3.2 mg/mq every three weeks or other drugs depending on the investigator's choice among PLD 50 mg/mq every four weeks or topotecan 1.5 mg/mq/day from day 1 to day 5 every three weeks. However, preliminary results did not confirm an advantage in terms of PFS (3.5 versus 3.6 months, HR 1.04, 95 % CI: 0.84–1.29), OS (1.2 versus 11.1 months, HR 0.97, 95 % CI: 0.77–1.23) and ORR (14.0 % versus 12.2 %, p value <0.05) when lurbinectedin was administered [215].

d **HER2/ERBB2**

HER2/ERBB2 is a type I growth factor receptor tyrosine kinase. *HER2/ERBB2* is over-expressed in carcinogenesis and approximately 20 % of OC patients have a tumor that over-expresses this receptor [216]. Based on the encouraging results in breast cancer, there has been an increasing interest in targeting HER2/ERBB2 in OC. Pertuzumab is a recombinant, humanized monoclonal antibody that inhibits HER2/ERBB2. In a phase II clinical study, 130 patients with advanced platinum-resistant OC were treated with gemcitabine with (n = 65) or without (n = 65) pertuzumab [217]. Patients receiving pertuzumab exhibited a superior ORR (13.8 % versus 4.6 %). Interestingly, low (below median) tumor HER3 mRNA expression was associated to a higher PFS rate in the gemcitabine plus pertuzumab arm compared with gemcitabine alone (HR 0.32, 95 % CI: 0.17−0.59, p value 0.0002; median PFS, 5.3 months with pertuzumab versus 1.4 months with placebo) [217]. Patients treated with gemcitabine plus pertuzumab presented more severe toxicities including neutropenia, diarrhea and back pain. These observations lead the Arbeitsgemeinschaft Gynä kologische Onkologie OC Study Group (AGO-OVAR) and the European Network for Gynecological Oncological Trial Groups (ENGOT) to plan a phase III study [218]. The PENELOPE trial was a placebo-controlled double--blind, randomized phase III study, assessing pertuzumab combined with the investigator's choice in platinum-resistant low HER3 mRNA OC [218]. Of note, despite the widely used clinical categorization of refractory disease (< 1 month) and resistant disease (1−6 months), in the PENELOPE trial, patients were stratified according to PFI < 3 (platinum-refractory cohort) and 3−6 months (platinum-resistant cohort). The primary endpoint was PFS. No different PFS rate was identified between groups (HR 0.74, 95 % CI: 0.50–1.11, p value 0.14), although, globally, a lower proportion of events were recorded in patients treated with pertuzumab. Notably, a significant PFS benefit with pertuzumab was recorded in those patients with a PFI between 3−6 months (HR 0.61, 95 % CI: 0.40−0.92, p value 0.02), but not in patients with a PFI shorter than 3 months (HR 1.61, 95 %CI: 0.79−3-29). Recently, the final OS results have been published [219]. Pertuzumab did not significantly improve OS (HR 0.90, 95 % CI: 0.61–1.32, p value 0.60). In addition, consistently with the preliminary results, the addition of pertuzumab did improve neither PFS nor OS in low tumor HER3 mRNA-expressing platinum-resistant OC [219]. The effect on the quality of life was also evaluated using four validated patient-reported outcome measures (PROMs): i) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core module, ii) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire OC-specific module, iii) the Hospital Anxiety Depression Scale, and iv) the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index [219]. Overall, pertuzumab had only a negative impact on diarrhea (profile difference 21.2, 95 % CI: 10.1–32.3) [219]. Taken together, these results merit further investigations to identify better a subset of platinum-resistant patients who might benefit from this class of drugs.

6.8. *Antibody-drug conjugates*

Antibody-Drug Conjugates (ADCs) are an emerging class of molecules that consist of a monoclonal antibody that specifically recognizes a tumor cell's surface target antigen conjugated to a strong cytotoxic agent (payload). Because they are composed of three elements, the antibody, the linker and the payload, they can remain stable in the extracellular environment and target cancer tissue preferentially [220]. ADCs have a hypothetically good toxicity profile since they deliver the molecule directly into tumor, limiting systemic effect. However, adverse events occurred in platinum-resistant OC patients treated in clinical trials with ADCs and they were distinguishable based on the used payloads [221]. Currently, further studies that evaluate the toxicity profile of ADCs in comparison to chemotherapy are missing. Even if there are no approved ADCs in OC, some data were presented at the ESMO congress 2019. Mirvetuximab soravtansine is the first ADC entering clinical testing in platinum-resistant OC; it targets the folate receptor α (FRα). Folate metabolism is essential to replicate the DNA [222], and different receptors have been described (isoform α, β and γ). In particular, isoform α is overexpressed in OC [223] and its presence has been linked with poor prognosis [224]. In HGSOC, FRα is expressed in 76 % of patients, and is a marker of better prognosis, while in other subtypes, such as mucinous cancer, it is expressed in only 11 % of patients, and is a marker of worse prognosis [225].

Because of the promising results of a phase I study [226], FORWARD I, a phase III trial, was designed to randomize 366 patients with platinum-resistant OC to receive mirvetuximab soravtansine or single-agent chemotherapy. Unfortunately, preliminary data presented at the ESMO congress in 2019, showed that the trial failed to reach its primary endpoint of PFS [227]. However, in the same trial, promising and consistent efficacy measures were observed in the predefined subset of patients with high Folate-Reptor α expression treated with mirvetuzimab.

Therefore, two multicentre phase III trials (NCT04296890 SORAYA and NCT04209855 MIRASOL) are currently actively recruiting. Thus, a firmer conclusion on its efficacy could be drawn in the future. Additional ADCs are under evaluation in platinum-resistant OC, which include agents targeting tissue factor (TF), sodium-dependent phosphate transporter 2B (NaPiB2), dipeptidase 3 (DPEP3) and mesothelin in phase I and II clinical trials. While a few drugs, such as lifastuzumab vedotin DNIB0600A, an anti- NaPi2b antibody, were already tested in comparison with PLD, not demonstrating any benefit in terms of PFS (5.3 versus 3.1 months, HR 0.79, 95 % CI: 0.46–1.31, p value 0.34) [228], others are still under investigation (NCT03657043, NCT03319628, NCT04152499, NCT03587311). Although ADCs are attractive drugs, higher efficacy and toxicity results must be reached in ongoing trials to further consider these drugs in the treatment algorithm of OC, alone or in combination with other agents.

7. Conclusions and prospects

Chemoresistance results from intricate and not fully understood mechanisms, combining multiple concurrent intra- and extra cellular factors. This complexity can significantly hamper the management of drug-resistant disease. In platinum-resistant OC, the medical treatment is challenging and its failure is ultimately responsible for nearly all deaths from this cancer, as the role of secondary surgery is not yet well defined [229]. Sequential use of single non-platinum chemotherapy drugs remains the standard of care for patients with platinum-refractory/-resistant OC, limited to palliative care in most cases. The addition of bevacizumab to single-agent chemotherapy improves response rate and PFS. However, the combination with this anti-angiogenic drug showed no significant effect on OS and, additionally, it is not prescribable for platinum-resistant OC worldwide. Unfortunately, no other drugs gained approval in this setting of disease in the last decade. Thus, scant effective therapeutic options remain for platinum-resistant OC. In this scenario, extensive investigations have been recently performed to evaluate new approaches that can overcome chemoresistance exploiting different mechanisms such as the improvement of drug delivery, the re-sensitization to platinum, the enhancement of immune responses and the modulation of cell cycle. Several trials have been conducted on alternative strategies to cytotoxic chemotherapy (e.g. immune checkpoint inhibitors, anti-angiogenic agents, PARP inhibitors, cell cycle modulators). Among them, some encouraging evidence on PARP inhibitors in platinum-resistant OC are available, with better results in m*BRCA* or HRD positive disease. At present, some phase I-II studies on PARP inhibitors and their combinations are ongoing, also involving wt*BRCA* patients. These trials will probably clarify if PARP inhibitors' mechanism of action is related only to *BRCA* mutation and other DNA-damage repair deficiency, or if this class of drugs exploits the immune response as well. If the real efficacy of PARP inhibitors in platinum-resistant OC is confirmed by new evidence, subsequent phase III and randomized trials will be necessary. The role of immune checkpoint inhibitors, which have been proven effective in tumors with MSI, is under investigation in platinum-resistant OC. Even if monotherapy is not promising, combination of immune checkpoint inhibitors with chemotherapy [188,230,231] and PARP inhibitors [192] seems favourable and deserves further exploration. Of note, pembrolizumab alone, reached an ORR of 33 % in tumors with DNA MMR deficit [185], improving the response rate to 51 % when combined with paclitaxel [188], similar to 53 % response rate seen in the AURELIA trial, with the association of bevacizumab and standard cytotoxic drugs. Moreover, mirvetuximab, an antibody-drug conjugate, which targets FRα, has shown positive results in a phase I study and, albeit a randomized trial did not confirm efficacy data, after FDA revision, two studies, one pivotal and the other confirmatory, have been planned to clarify this issue definitely. Finally, mTOR inhibitors could also enter the clinical setting if the optimum results in terms of efficacy will be confirmed in phase III studies. [175].

As platinum resistance is a major impediment in managing OC patients, we summarized the potential predictive biomarkers to facilitate the detection of personalized therapy in those patients without platinum agent response. Nonetheless, the heterogeneity and marked adaptability of the cancer genome, especially in HGSOC, show that overcoming resistance to therapy requires many different approaches. In fact, it seems that the combinations of different classes of drugs have shown promising results, since associations can allow counteracting more mechanisms of resistance simultaneously. Innovations in tumor genomic sequencing technology and in the development of drugs targeting molecular alterations, might be the key and should rely on genome-driven oncology care. Moreover, designing basket studies or histology-agnostic clinical trials in genomically selected platinum-resistant OC patients might represent a crucial research tool. In our view, the advent of precision medicine in OC should not be limited to patients with better prognosis. However, it should carefully involve chemoresistant patients, because the lower is the survival, the greater should be the scientific commitment. In the future, a greater understanding of the biology of platinum-resistant disease and the detection of relative biomarkers are expected to pave the way towards the identification of women that can mostly benefit from novel tailored approaches. Besides, the development of new drugs should also deal with cost issue, since only a real significant benefit can justify high costs of treatment. Thus, also cost-effectiveness analysis in platinum-resistant OC is needed. Finally, it should be underlined that some of the most important intents of treatment for platinum-resistant OC should remain the preservation of quality of life and symptoms improvement and these measures, other than survival and response rates, should be relevant for final drug approval. Meanwhile, awaiting new approved and effective agents for platinum-resistant disease, participation in clinical trials must be strongly encouraged, possibly where translational analysis is planned.

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