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Challenges for immunotherapy for the treatment of platinum resistant ovarian cancer

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ABSTRACT

Platinum resistant ovarian cancer, usually defined as progression occurring within 6 months after completing platinum-based therapy, is a heterogeneous disease with poor prognosis and short survival (less than 18 months). It is typically considered as a "cold tumor", characterized by reduced infiltration by immune cells, particularly $CD8^+$ T cells. Response rate to anti-PD1/PD-L1 monotherapy is low, not exceeding 8%. Multiple therapeutic strategies are currently investigated in order to increase response rates to anti-PD1/PD-L1 through adding chemotherapy, anti-angiogenic agents, DNA damage (PARP inhibitors, cyclophosphamide and/or radiotherapy) or other immune checkpoint inhibitors (CTLA-4, etc.). Ovarian clear cell carcinoma, a rare histotype characterized by primary platinum-resistance, recently showed anecdotal but promising response rates to immune checkpoint blockade. Other immunotherapeutic approaches such as adoptive T cell therapy, vaccines and targeting myeloid immune checkpoints like "don't eat me" signal CD47 are currently investigated. Each approach faces distinct challenges that will be reviewed here. Robust immunogenomics studies conducted in parallel of the ongoing trials will help into refining optimal immunotherapy combination for this lethal disease and identify predictive biomarkers.

1. Introduction

Ovarian cancer (OC) is the most lethal gynecological cancer in developed countries and the second cause of death from gynecological malignancies worldwide [1]. In 2018, 295'414 new cases were estimated with 184'799 related deaths [1]. It is a heterogeneous disease at the histological and molecular levels. About ninety percent of the tumors are epithelial and the most common histotype is high-grade serous carcinoma [2]. The majority of patients are diagnosed at advanced stages and cytoreductive surgery followed by platinum and taxane-based chemotherapy is the standard of care [3]. Platinum-resistant ovarian cancer, generally defined as progression occurring within 6 months after completing platinum-based therapy, occur in about 20 % of the patients after first-line platinum-based therapy [4]. This primary platinum-resistance is mainly observed in non-high grade serous ovarian carcinoma (HGSOC) subtypes such as clear cell, mucinous and low-grade serous carcinoma. In contrast, initial response rates in HGSOC are high but most patients will relapse and ultimately develop secondary platinum-resistance leading to death. It is now questionable whether in recurrent disease the historical definition of platinum-sensitivity (or resistance) is still valid for planning subsequent line of chemotherapy. This classification using a 6 months cut-off has several shortcomings: 1) increasing number of patients undergo upfront complete surgical resection making the evaluation of response to platinum-based chemotherapy impossible; 2) use of bevacizumab as a maintenance therapy has delayed relapse changing the profile of platinum-sensitivity; 3) not all patients experiencing a treatment-free interval from platinum (TFIp) longer than 6 months will respond again to platinum (response rates ranging from 47 to 66 %) [5–8]; 3) TFIp shorter than 6 months is not always predictive for the absence of response to platinum-based therapy [9,10]. Recently, the Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup for recurrent disease has proposed to evolve platinum-resistance definition toward a therapy oriented definition and replace it by the therapy-free

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interval [11].

Platinum-resistant ovarian cancer has dismal prognosis. Median survival with single agent chemotherapy and bevacizumab does not exceed 16 months [12]. Alternative therapeutic options are urgently needed. Since OC is immunogenic, there was hope that immunotherapy, a breakthrough therapy for several cancers in the last decade, could transform the course of the disease. In this review, we summarized the biological rationale and available clinical data on immunotherapy in platinum-resistant ovarian cancer and discussed the challenges and future areas of research in the field.

2. Tumor immune microenvironment in platinum-resistant ovarian cancer

The phenotype and functional alterations of tumor immune microenvironment of epithelial ovarian cancer (EOC) has been extensively characterized. Most studies investigating the prognostic value of immune infiltrate used diagnosis or pre/post-neoadjuvant platinum-based chemotherapy biopsies [13]. The prognostic value of tumor-infiltrating lymphocytes (TILs) is well-established in EOC: the presence of intra-epithelial T cells defined as $CD3^+$, and especially $CD8^+$ T cells, is associated with prolonged survival [14–17]. The abundance of $CD8^+$ TILs substantially vary across the 5 major EOC histotypes, according to the large prospective cohort evaluating over 5′500 patients and conducted by the Ovarian Tumor Tissue Analysis consortium [17]. Most HGSOC cases (83 %) had evidence of $CD8^+$ TILs, while intermediate proportion of low-grade serous and endometrioid carcinoma had TILs (73 % and 72 % respectively). Clear-cell and mucinous carcinoma were the least frequently infiltrated histotypes by TILs (52 % and 51 %, respectively). The presence of intra-epithelial $CD8^+$ T cells is associated with prolonged survival in HGSOC, endometroid and mucinous carcinoma [17]. Immunogenomic data revealed that in HGSOC samples with the highest intra-epithelial densities of TILs, there is an active pruning of malignant cell diversity by TILs through subclonal neoepitope recognition, resulting in expansion of clones harboring neoantigens and/or loss of heterozygosity of human leukocyte antigen (HLA) [18,19].

The prognostic value of other immune cell sub-populations has been investigated in smaller cohorts. The presence of $CD163^+$ tumor associated macrophages (TAMs) or plasmacytoid dendritic cells is associated with immunosuppressive microenvironment and poor outcome [20–22] while prognostic value of regulatory T cells (Treg) varied between studies. In the seminal study by Curiel et al., the accumulation of Treg was associated with poor survival whereas another study found that it is the ratio Treg to $CD8^+$ T cells that had prognostic value: patients with high $CD8^+$/Treg ratio had longer survival (57.6 vs 22.6 months; Hazard Ratio [HR = 0.31]; 95 % Confidence Index [CI 0.17−0.58]; $p = 0.0002$) [23]. Intriguingly the impact of Treg on outcome seems to vary depending on the timing of the sampling: higher Treg in primary tumors correlated with decreased time to first recurrence (17.0 versus 28.5 months, $p = 0.022$) while higher Treg frequencies in recurrent tumors correlated with longer overall survival (OS) from recurrence (median survival not reached versus 20 months, $p = 0.022$) [21].

The impact of programmed death-ligand 1 (PD-L1) expression on tumor cells and/or antigen-presenting cells on outcome is not clear [24–29]. Some studies reported a positive impact of PD-L1 expression on tumor cells and/or TAMs on outcome of EOC [27,25–29] while others reported negative impact [24–26]. There is substantial heterogeneity between published studies regarding the methods with different immunohistochemistry (IHC) techniques, scoring systems and antibodies [30]. Further investigation of the prognostic value of PD-L1 in larger cohorts such as the Ovarian Tumor Tissue Analysis consortium are warranted.

Tumor microenvironment (TME) of EOC is substantially changed by neoadjuvant chemotherapy. Immunogenomic analyses of paired biopsies before/after platinum-based chemotherapy revealed an enrichment toward higher cytolytic activity, infiltration by Natural Killer (NK) cells and oligoclonal expansion of T cells [31,32]. Neoadjuvant platinum-based chemotherapy enhances adaptive immune response by increasing activated $CD4^+$ T cells and reducing Treg in good responders but this effect is tempered by increased levels of inhibitory molecules such as programmed death 1 (PD1), PD-L1 and cytotoxic T-lymphocyte antigen-4 (CTLA-4) [33]. It is possible that platinum leads to intra-tumoral migration of T cells through inducing up-regulation of proinflammatory chemokines such as CXCL10 and CXCL11, and class I HLA molecules by cancer cells, as it was shown *in vitro* [31].

Data on TME of platinum-resistant ovarian cancer are scarce. It is clearly a “cold tumor”, characterized by low infiltration by $CD8^+$ T cells [34] and activated $CD4^+$ T cells, increased infiltration by PD-$L1^+$ cells [35], known to promote peritoneal dissemination [36], and increased infiltration by Treg [31] (Fig. 1). Hao et al. developed an immune score by using the transcriptomic of 2’203 advanced EOC samples from publicly available datasets. This immune score takes into account 69 marker genes representative of specific immune cell subtypes and seven antigen-presenting genes [31]. High immune score reflects an overall high expression of favorable prognostic genes. All immune subpopulations of adaptive immune response except Treg cells were associated with high immune score, whereas loss of chemokines and interferon-gamma (IFN-ɣ) pathway genes were associated with low immune score. Patients with low immune score had poorer response to chemotherapy (Fisher exact test, $p < 0.05$) [31] while chemosensitive tumors were enriched in activated $CD4^+$ T cells compared to chemoresistant ones [31].

Few data are available regarding PD-L1 expression in platinum-resistant ovarian cancer. In the phase II trial of nivolumab (n = 20), the majority of samples 16 (80 %) showed high expression of PD-L1 (score of+2 or +3) [35]. In the phase II study evaluating nivolumab and bevacizumab in relapsing EOC, PD-L1 estimated by combined positive score (CPS) $\geq$ 10 was expressed by 33 % (6/18) of platinum-resistant ovarian cancer [37]. In the JAVELIN200 trial, PD-L1 was expressed by 57 % of the cases. PD-L1 staining was considered positive if tumor cells expressing PD-L1 $\geq$ 1% and/or percentage of tumor area populated by PD-$L1^+$ immune cell was $\geq$5% [38]. Importantly, analyses in the three studies were conducted on archival tumor samples with different antibodies and scoring methods. Given TME changes over the time course of the disease [19], emphasized by changes in paired biopsies pre/post-neoadjuvant platinum-based chemotherapy, there is a need for deeper characterization of immune TME landscape of platinum-resistant ovarian cancer on fresh biopsies collected when platinum resistance appears.

3. Immune checkpoint inhibitors for the treatment of platinum-resistant ovarian cancer

Tumor evasion from immune surveillance occur through multiple mechanisms such as disruption of antigen processing and presentation, infiltration by immunosuppressive cells, upregulation of co-inhibitory molecules PD1/PD-L1 related to *in situ* T cell exhaustion or upregulation of CTLA-4, a co-inhibitory regulator of central T cell activation [39]. Targeting immune checkpoint inhibitors (ICI) is among the most extensively investigated immunotherapeutic approaches in the last decade to unleash the immune system and control malignancy and this holds true for platinum-resistant ovarian cancer. ICI have proven efficacy in inflamed tumors. Yet, platinum-resistant ovarian cancer, a “cold tumor”, is characterized by reduced infiltration by effector immune cells, particularly $CD8^+$ T cells and increased infiltration by immune suppressive Treg. This “cold” immune TME could explain the poor efficacy of anti-PD1/PD-L1 as monotherapy as it will be discussed below. The main challenge for ICI in platinum-resistant ovarian cancer is to turn this “cold” tumor into “inflamed” by favoring infiltration of functional cytotoxic T cells. In order to increase response rate, various combinations of anti-PD1/PD-L1 are currently investigated with either chemotherapy to release cancer antigens, anti-angiogenic agents to increase T

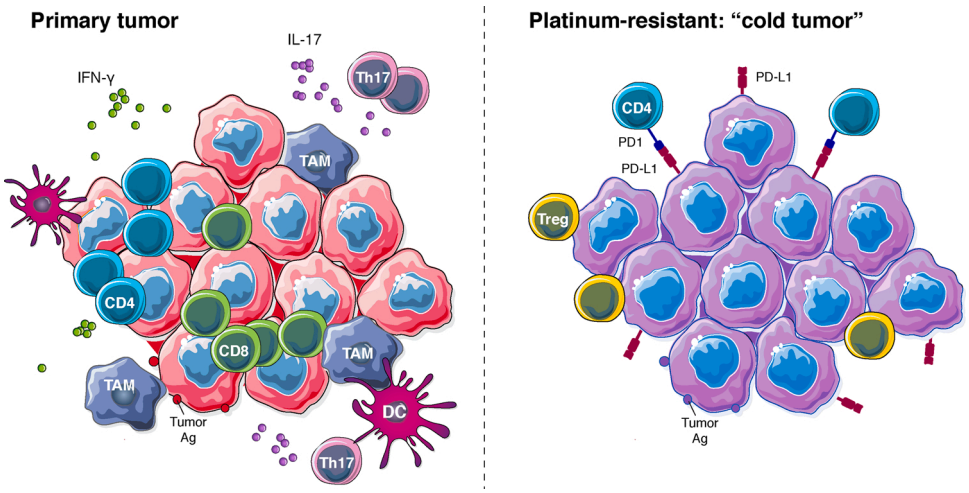

Fig. 1. Tumor microenvironment of platinum-resistant ovarian cancer is "cold". Left panel: Tumor microenvironment (TME) of ovarian cancer is characterized by infiltration of different immune cell subtypes such as $CD8^+$ effector T cells, tumor-associated macrophages (TAM), dendritic cells (DC), IL^+17 T cells (Th17) and $CD4^+$ activated T cells. Right panel: TME of platinum-resistant ovarian cancer is "cold", with less infiltration by $CD8^+$ T cells and increased regulatory T cells (Treg).

cells trafficking into tumors, anti-CTLA-4 to improve priming and activation of effector T cells at lymph nodes, DNA damage agents like Poly (ADP-ribose) polymerase (PARP) inhibitors to activates type I interferon (IFN) response (Fig. 2) or vaccines to enhance neoantigen T cells reactivity. The main results are listed in Table 1. Overall response rate (ORR) varied between platinum-resistant and platinum-sensitive sub-groups. For instance, combination of anti-PD1/PD-L1 with anti-angiogenic agents seemed to be more effective in platinum-sensitive [37] while combination with PARP inhibitors or anti-CTLA-4 are potentially synergistic in platinum-resistant cases [40,41].

A second challenge for ICI in platinum-resistant ovarian cancer is the identification of predictive biomarkers for response such as histologic subtype, the expression and spatial distribution of PD-L1 or genomic alterations. A third challenge is tumor heterogeneity with distinct TME and T-cell receptor (TCR) clones co-existing within the same individual [19].

3.1. Immune checkpoint inhibitors as monotherapy

Although EOC has proven to be immunogenic, no immunotherapy is approved to date and this holds true for platinum-resistant ovarian cancer. As monotherapy, anti-CTLA-4 ipilimumab showed an ORR of 10 % in platinum-sensitive ovarian cancer (NCT01611558). The toxicity was substantial with grade≥3 related adverse events in more than 50 % of the patients. This was probably due to the high dose of ipilimumab, administered at 10 mg/kg [42]. To date, there is no available data on anti-CTLA-4 monotherapy specifically in platinum-resistant ovarian cancer.

The first published study of anti-PD1/PD-L1 in platinum-resistant ovarian cancer (n = 20) showed an ORR of 15 % to anti-PD1 nivolumab [35]. Response rate to anti-PD-L1 avelumab was similar, estimated to 13.6 % (3 of 22 patients; 95 %CI, 2.9 %–34.9 %) in the platinum-resistant sub-group of the EOC cohort (n = 125) of phase Ib JAVELIN solid tumor trial [43]. Larger trials revealed an even lower ORR. As monotherapy, response rate to anti-PD1 pembrolizumab was estimated to 8% in the 376 patients included in the KEYNOTE-100 trial [44]. Platinum-sensitivity did not impact ORR, comparable in platinum-resistant (7.8 %; n = 141), partially platinum-sensitive (7.8 %; n = 128) and platinum-sensitive EOC (5.6 %; n = 18). Importantly, the KEYNOTE-100 study showed that ORR correlates with the expression of PD-L1 estimated by CPS. ORR was 17.1 % (9.7–27.0) in patients with CPS ≥ 10 compared to 5% (2.0–10.0) in those with CPS < 1. In the JAVELIN200 trial, ORR was estimated to be 3.7 % (1.5–7.5) in the 188 platinum-resistant patients who received avelumab alone [38]. Bifunctional fusion proteins such as M7824, a first-in class molecule composed of monoclonal antibody against PD-L1 fused to a Transforming growth factor beta (TGF-β) "trap" showed early signs of efficacy and durable responses in heavily pretreated advanced solid tumors [45]. This therapy could be interesting in platinum-resistant ovarian cancer since TGF-β favors activation of cancer-associated fibroblasts and immunosuppression [46].

3.2. Anti-PD1/PD-L1 and chemotherapy

Anti-PD1/PD-L1 antibodies have been combined with multiple drugs of chemotherapy in order to improve ORR with limited activity (Table 1). To date, the largest trial with reported data in platinum-resistant ovarian cancer is the JAVELIN200 study, a three-arm randomized phase III trial that compared pegylated liposomal doxorubicin (PLD), a standard of care chemotherapy agent in this setting, was compared with avelumab alone or a combination of avelumab + PLD . ORR was higher in the avelumab + PLD arm (13.3 %; 95 % CI, 8.8–19) than PLD alone (4.2 %; 95 % CI, 1.8–8.1, $p = 0.0018$) whereas avelumab had similar ORR with PLD (3.7 %; 95 %CI, 1.5–7.5, $p = 0.8280$). The trial did not meet the pre-specified co-primary end points of progression-free survival (PFS; avelumab+PLD vs PLD alone; 3.7 vs 3.5 months ; HR, 0.78; 95 % CI, 0.59–1.25; $p = 0.0301$) and OS (avelumab+PLD vs PLD alone; 15.7 vs 13.1 months; HR, 0.89; 95 % CI, 0.74–1.24; $p = 0.2082$) [38]. Retrospective sub-group analysis, for which 442 tumor samples were evaluable, revealed that patients with tumors expressing PD-L1 may benefit from avelumab + PLD. Indeed, in the avelumab + PLD arm, patients with $PD\text{-}L1^+$ tumors had higher ORR than those with $PD\text{-}L1^-$ tumors (18.5 % vs 3.4 %). $PD\text{-}L1^+$ patients who received the avelumab combination therapy had a trend toward prolonged PFS (3.7 vs 3 months, HR, 0.65; 95 %CI 0.48−0.91, $p = 0.0143$) and OS (17.7 vs 13.1 months, HR, 0.72; 95 %CI 0.49–1.05, $p = 0.0842$) when compared with $PD\text{-}L1^-$ patients.

3.3. Anti-PD1/PD-L1 and anti-angiogenic drugs

At least three key mechanisms related to vascular endothelial growth factor-mediated immunosuppression: a) inhibition of dendritic cell maturation; b) reduction of tumor infiltration by T cells; and c) promotion of immunosuppressive cells in TME (Treg and myeloid-derived suppressor cells [47]) support the combination of anti-angiogenic agents and anti-PD1/PD-L1 in solid tumors [48]. This was outlined by

Table 1
Immunotherapies evaluated in platinum-resistant ovarian cancer.

Name of the trial Type of therapy Current status Actual study start date	Phase	N (%)			ORR (%)			PFS			OS			Safety Grade ≥3 (%)	Biomarkers	Reference
Anti-PD1/PD-L1 monotherapy																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
KEYNOTE-100 Pembrolizumab Active, not recruiting February, 2016	II	376	141 (37.5)	128 (34.0)	8	7.8	7.8 (NS)	2.1	NA	NA	18	NA	NA	19.7	CPS <1: ORR = 5% 1 ≤ CPS<10: ORR = 5.2 % CPS≥10: ORR = 17.1 %	[44]
Nivolumab Completed September, 2011	II	20	20 (100)	0	15	15	NA	3.5	3.5	NA	20.0	20.0	NA	40.0	PD-L1 status not associated with response	[153]
JAVELIN solid tumors Avelumab Completed January, 2013	Ib	125	22	NA	9.6	13.6	NA	NA	NA	NA	NA	NA	NA	7.2	PD-L1 status not associated with response	[43]
Anti-PD1/PD-L1 + Anti-angiogenic therapy																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
Nivolumab + Bevacizumab Completed February, 2017	II	38	18	20	28.9	16.7	40.0	8.1	5.3	9.4	NA	NA	NA	23.7	PD-L1^{+} tumor % < 1: ORR = 45.5% PD-L1^{+}%≥1: ORR = 14.3 %	[37]
Durvalumab + Cediranib Recruiting June, 2015	I	9	5	4	33.3	0.0	75.0	NA	NA	NA	NA	NA	NA	Hypertension (11.1) Anemia (11.1) Lymphopenia (33.3)	Tumor PD-L1 expression not statistically significant	[50]
Anti-PD1/PD-L1 + Anti-angiogenic therapy + DNA damage agent																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
Pembrolizumab + Bevacizumab + Oral Metronomic Cyclophosphamide Active, not recruiting September, 2016	II	40	30	10	37.5	NA	NA	6mo rate 70 %	6mo rate 59 %	6mo rate 100 % (p = 0.024)	NA	NA	NA	Most common: decreased lymphocyte count and hypertension	NA	[67]
Durvalumab + Cediranib + Olaparib Recruiting June, 2015	I	9	5	2	44.0	40.0	50.0	NA	NA	NA	NA	NA	NA	Anemia (22.2) Hypertension (11.1) Increased creatinine (11.1)	PD-L1^{+} tumor cells (p = 0.03)	[65]
Anti-PD1/PD-L1 + Chemotherapy																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
JAVELIN 200 Avelumab + pegylated liposomal doxorubicin PLD (topoisomerase II inhibitor) Active, not recruiting December, 2015	III	556	556	0	13.3	13.3	NA	3.7	3.7	NA	17.7	17.7	NA	No new safety signals	PD-L1^{-}: ORR = 3.4% PD-L1^{+}: ORR = 18.5%	[38]
Durvalumab + PLD	II	40	40	0	NA	NA	NA	6mo rate 30.0 %	6mo rate	NA	NA	NA	NA	Palmar-plantar erythrod ysesthesia syndrome/rash	NA	[154]

(*continued on next page*)

Table 1 (*continued*)

Name of the trial Type of therapy Current status Actual study start date	Phase	N (%)			ORR (%)			PFS			OS			Safety Grade ≥3 (%)	Biomarkers	Reference
Active, not recruiting May, 2015									30.0 %					Stomatitis Lymphocyte count decreased Lipase increased Anemia		
Pembrolizumab + paclitaxel (anti-microtubule) Active, not recruiting October, 2015	II	37	37	0	51.4	51.4	NA	6.7	6.7	NA	13.4	13.4	NA	NA	NA	[155]
Pembrolizumab+Cisplatin (DNA crosslinker) +gemcitabine (nucleoside analogue) Active, not recruiting November 2015	II	18	18	0	50	50	NA	5.4	5.4	NA	NA	NA	NA	NA	NA	[156]
Anti-PD1 + Anti-CTLA4		**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
NRG GY003 Nivolumab + Ipilimumab Active, not recruiting June, 2015	Randomized II	100	62	38	31.4	NA		3.9	NA	NA	28.1	NA	NA	49.0	NA	[40]
Anti-PD1/PD-L1 + PARP inhibitor		**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
TOPACIO Pembrolizumab + Niraparib Active, not recruiting March, 2016 OVCa	I/II	62	30	15	18.0	21.0	20.0 (NS)	3.4	NA	NA	NA	NA	NA	Anemia (21.0) Thrombocytopenia (9.0) Immune-related AEs (6.0) Anemia (26.0)	1−2 prior lines of therapy: ORR = 28.0 % (14−46) ≥3 prior lines of therapy: ORR = 11.0 % (4−24)	[41]
Durvalumab + Olaparib Recruiting June, 2015	II	35	30	5	15.0	10.0	40.0	NA	NA	NA	NA	NA	NA	Lymphopenia (14.0)	NA	[64]
Anti-PD1 + Antifolate antibody-drug conjugate		**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
Pembrolizumab + Mirvetuximab soravtansine Active, not recruiting December 2015	Ib	14	14	0	43.0	43.0	NA	5.2	5.2	NA	NA	NA	NA	Manageable safety profile	NA	[157]
Cytokine therapy		**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
GM-CSF + Nab-paclitaxel Completed May, 2006	II	21	21	0	72.0 (biochemical)	72.0	NA	4.0	4.0	NA	16.8	16.8	NA	NA	Fewer myeloid derived suppressor cells (MDSC) at enrollment (p = 0.05) T-cell responses to IGF1R-p1332–1346 (r	[158]

(*continued on next page*)

Table 1 (*continued*)

Name of the trial Type of therapy Current status Actual study start date	Phase	N (%)			ORR (%)			PFS			OS			Safety Grade ≥3 (%)	Biomarkers	Reference
Intraperitoneal IL-2 Completed 1995	II	31	31	0	25.0	25.0	NA	NA	NA	NA	25.0	25.0	NA	NA	= 0.827, p = 0.0003) and IGF1R-p1242–1256 (r = 0.850, p = 0.0001) Changes in CD3 counts (p = 0.05) IFN- secreting CD8 T cells at early time points (p = 0.04)	[159]
Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs)																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
Adoptive cell therapy with tumor-infiltrating lymphocytes Completed October, 2015	Pilot study	6	6	0	All patients had stable disease (SD) six weeks after TIL therapy Four patients had SD for 3 months and two patients maintained SD for 5 months	All patients had stable disease (SD) six weeks after TIL therapy Four patients had SD for 3 months and two patients maintained SD for 5 months	NA	NA	NA	NA	NA	NA	NA	Manageable toxicity	Expression of exhaustion markers including LAG3 and PD1 on infused TILs MHCII and PD-L1 expression on tumor samples	[114]
Chimeric antigen receptor T cells (CAR T cells)																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
Anti-mesothelin CAR T cells Completed June, 2014	I	15	5	0	11/15 had stable disease	NA	NA	2.1	NA	NA	NA	NA	NA	One treatment-related death	20 % had expression of mesothelin on ≥75% tumor cells	[124]
Ovarian cancer vaccine therapy																
		All	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**	**All**	**R**	**S**			
NY-ESO-1 Vaccine + Decitabine + PLD Completed April, 2009	I	12	10	1*	10.0	NA	NA	Duration of response: 5.8 mo	NA	NA	NA	NA	NA	Neutropenia Vaccine site reactions (16.7) Febrile neutropenia (8.3)	NA	[160]
Gemcitabine + Pegintron + p53 synthetic long peptide vaccine Completed August, 2011	I/II	18	18	0	11.1	11.1	NA	NA	NA	NA	NA	NA	NA	Nausea/vomiting (22.0) Dyspnea (17.0)	NA	[107]
Durvalumab + folate receptor alpha vaccine TPIV200 Active, not recruiting May, 2016	II	27	27	0	Unconfirmed partial response (3.7) SD (33.3)	Unconfirmed partial response (3.7) SD (33.3)	NA	NA	NA	NA	21.0	21.0	NA	18.5	Loss of FRα expression and upregulation of PD-L1 in a progressing lesion for one patient	[106]

R = platinum-resistant, S = platinum-sensitive, NA = Not available, ORR = Overall response rate, SD = Stable Disease, PFS = progression-free survival, OS = Overall survival, NS = Not Significant, mo = months, PLD = pegylated liposomal doxorubicin *One patient with unavailable information.

data in renal cell carcinoma, where combination of anti-PD-L1 atezolizumab and bevacizumab lead to increase of intra-tumoral antigen-specific T cells, through upregulation of CX3CL1 and class I HLA molecules [49]. In the context of relapsing EOC, bevacizumab in association with nivolumab was evaluated in 38 patients (20 platinum-sensitive and 18 platinum-resistant) [37]. The rate of prior bevacizumab receipt was similar between the two sub-groups (platinum-sensitive, 65.0 %; platinum-resistant, 66.7 %). The ORR was 28 % in the entire cohort: 40 % among platinum-sensitive and 16.7 % for platinum-resistant. The combination seemed safe with 9 patients (23.7 %) experiencing grade ≥3 treatment-related adverse effects but no treatment-related death was observed. The low ORR in platinum-resistant sub-group suggests that alternative combinational strategies might be necessary in this setting.

Another study questioned the benefit of combining anti-PD-L1 agent durvalumab and anti-angiogenic therapy cediranib in a phase I study of gynecological cancers (EOC, cervical cancer, uterine cancer and triple negative breast cancer) [50]. Durvalumab and cediranib were tested in parallel 3 + 3 dose escalations. Only six EOC patients were assessable for ORR, among whom two were platinum-resistant. No objective response was reported in these 2 platinum-resistant patients while 2 out of 4 platinum-sensitive women achieved partial response (PR). However, imbalance was observed between platinum-sensitive and resistant patients for dosages with no patients in the platinum-sensitive group receiving the first dose level versus 2 in the platinum-resistant group. In front-line treatment of newly diagnosed advanced stage OC, combination of anti-PD-L1 atezolizumab and bevacizumab, paclitaxel and carboplatin did not show benefit in PFS according to the press release on phase III trial IMagyn050 [51]. Results from trials combining atezolizumab with bevacizumab and other drugs in platinum-resistant ovarian cancer such acetylsalicylic Acid (NCT02659384), MEK inhibitor (NCT03363867) or chemotherapy (NCT03353831) are awaited before drawing definitive conclusions.

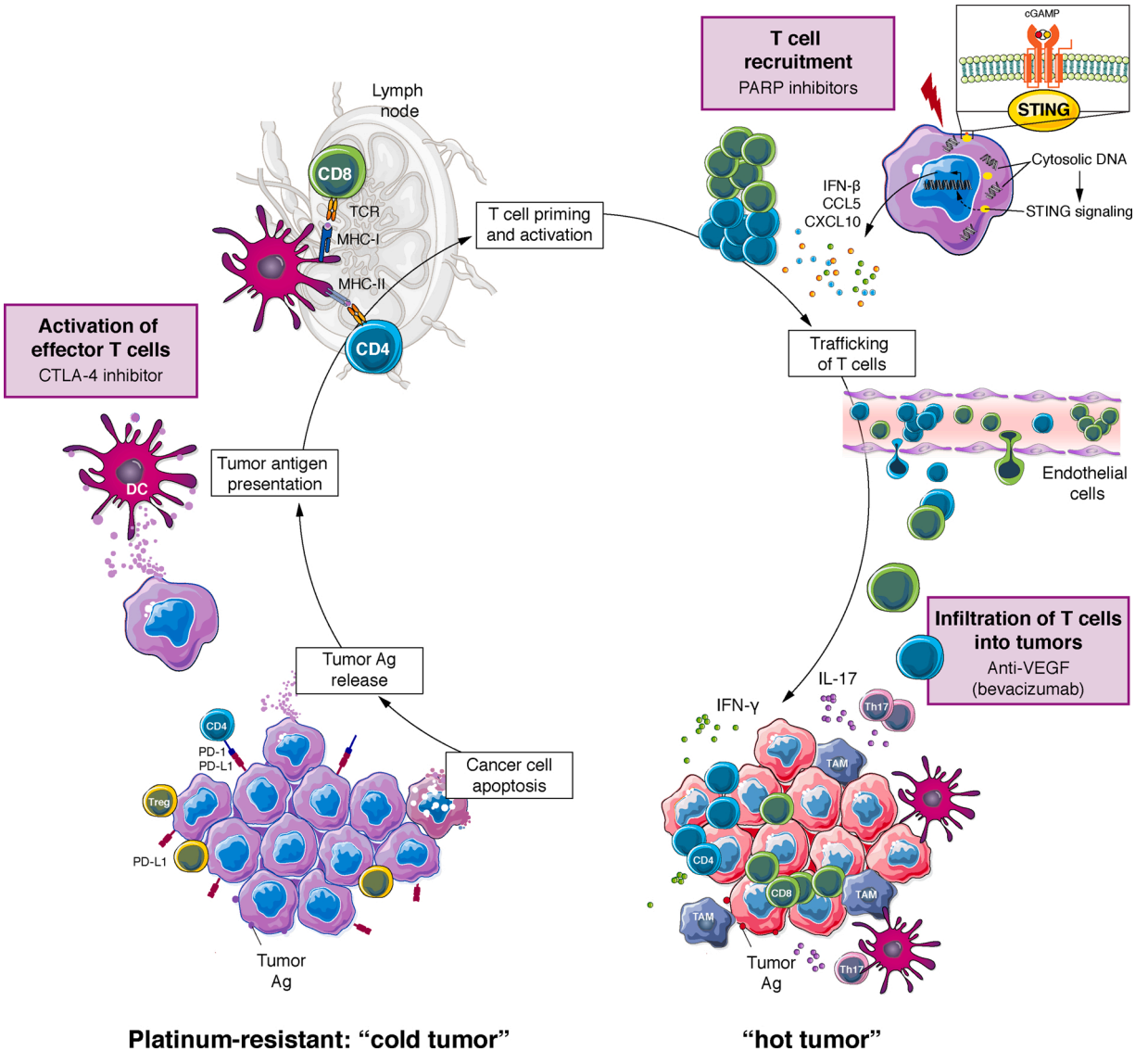

Fig. 2. Different therapeutic strategies for turning TME of platinum-resistant ovarian cancer from "cold" into "hot". TME of platinum-resistant ovarian cancer is "cold" and could be turned into "hot" through combination of anti-PD1/PD-L1 with : a) anti-CTLA-4 antibody in order to boost the priming phase of immune response at lymph nodes; b) PARP inhibitors leading to release of cytosolic DNA in cancer cells, activation of cGAS-STING, and subsequent release of chemokines (CCL5, CXCL10 etc.) attracting immune cells; c) anti-VEGF agents that augments intra-tumoral infiltration by T cells, through vascular normalization and endothelial cell activation.

3.4. Anti-PD1 and anti-CTLA-4

Immune checkpoint inhibitors PD1 and CTLA-4 have distinct regulatory effect during adaptive immune response. PD1 is mainly expressed on $CD8^+$ T cells within tumor during chronic antigen presentation, leading to deterioration of T cell function, named “exhaustion”, while CTLA-4 is expressed on T cells early after antigen presentation in lymphoid organs, inhibiting the priming phase of the immune response [52]. Anti-CTLA-4 ipilimumab (1 mg/kg) combined with anti-PD1 nivolumab (3 mg/kg) was evaluated in the randomized phase II trial NRG-003 [40]. The study included 100 relapsing EOC patients (62 platinum-resistant and 38 platinum-sensitive) [40]. Participants were randomly allocated (1:1) to induction with intravenous nivolumab or nivolumab + ipilimumab for 4 doses, followed by maintenance therapy with nivolumab. ORR was 12.2 % in the nivolumab group vs 31.4 % in the nivolumab + ipilimumab group (odds ratio = OR, 3.28; 95 %CI, 1.54 to infinity; $p = 0.034$). Median PFS was 2 and 3.9 months in the nivolumab and nivolumab+ipilimumab groups, respectively. Median OS was 21.8 and 28.1 months in the nivolumab group and nivolumab plus ipilimumab group, respectively. Interestingly, platinum-resistance seemed to favor the combination arm, with a platinum-free interval (PFI)-stratified HR of 0.53 (95 % CI, 0.34 to 0.82). Grade≥3 related adverse events were more frequent in the combination group (49 %) than in patients receiving nivolumab alone (33 %), as expected.

3.5. Anti-PD1/PD-L1 and PARP inhibitors

There is a strong biological rationale for combining PARP inhibitors and ICI in HGSOC [53,54]. HGSOC is characterized by high genomic instability. Genomic instability often coincides with chronic release of cytosolic double-stranded DNA [55,56]. PARP inhibitors further exacerbate release of cytosolic DNA in cancer cells, which in turn activates the DNA-sensing cyclic GMP-AMP Synthase- Stimulator of Interferon Genes (cGAS-STING), a pathway involved in innate immune response. Activation of cGAS-STING stimulates the production by cancer cells of type I IFNs and upregulates the expression of proinflammatory chemokines CCL5 and CXCL10 (Fig. 2), known to recruit $CD8^+$ T cells into tumors [54,57]. PARP inhibitors activate cGAS-STING in dendritic cells, stimulating antigen presentation and further intra-tumoral recruitment of T cells [53,58]. In parallel, PARP inhibitors up-regulates the expression of PD-L1 on cancer cells. In preclinical studies, combination of PARP inhibitors and anti-PD1 was synergistic in mouse models of EOC independently of *BReast CAncer* gene (*BRCA)* mutation status [53,54] and lead to longer survival than with anti-PD1 alone.

Two trials reported the results of combining PARP inhibitors with anti-PD1/PD-L1 in platinum-resistant ovarian cancer. The TOPACIO phase I/II trial investigated the combination of anti-PD1 (pembrolizumab) with PARP inhibitor (niraparib) in relapsing EOC [41]. This study included patients with platinum-refractory EOC (n = 17, 27 %), platinum-resistant EOC (n = 30, 48 %) and patients with PFI ≥ 6 months but unable to receive further platinum-based chemotherapy (n = 15, 24 %). The majority of patients had wild-type *BRCA* status (n = 49, 79 %). ORR was estimated to 18 % (95CI% 11−29%) in the entire cohort and 21 % (95CI%; 9–37 %) in the platinum-resistant subgroup. Exploratory analyses on archival biopsies indicated that combining niraparib and pembrolizumab resulted in antitumor activity across the study population regardless of *BRCA* mutation status, homologous recombination defects (HRD)-score (by Myriad®), tumor mutational burden [59] or prior treatment with bevacizumab. These results are quite interesting in platinum-resistant population without *BRCA* mutation where the activity of PARP inhibitors alone does not exceed 5% [60,61] and the activity of anti-PD1/PD-L1 alone is expected to be less than 10 % [35,43,44]. No new safety signals were identified with this combination. Targeted sequencing using two different methods (OncoPanel assay and NanoString gene expression profiling) on tumor samples identified two determinants of response: mutational signature 3 reflecting defective homologous recombination DNA repair [62] ($p = 0.02$) and positive immune score as a surrogate of IFN-primed exhausted $CD8^+$ T cells in TME ($p = 0.01$) [59]. Importantly, no objective response was reported in patients whose tumors were negative for both mutational signature 3 and immune score. Using Signature Multivariate Analysis (SigMA), a recently developed computational tool on the OncoPanel sequencing data, the presence of signature 3 was identified in 51 % (20/39) of the patients which corresponds to a larger proportion of tumors with HRD compared to other markers of HRD (*BRCA* mutation, Myriad® HRD-score, BROCA panel or $RAD51^+$ foci by IHC). Signature 3 is distinct from other markers for HRD: it generates a mutational signature characterized by a high number of larger deletions (up to 50 bp) and microhomology overlaps at breakpoint junctions. It was first described in the pan-cancer analysis of mutational signatures [62]. It is strongly associated with *BRCA1/BRCA2* mutations but some cases with a substantial contribution from signature 3 do not have *BRCA1* and *BRCA2* mutations [62]. Its presence reflects the fact that in the presence of HRD, repair of DNA double strand breaks relies on alternative error-prone repair mechanisms [59]. Gene-expression profiling by nanostring ® showed that type I IFN signaling was enriched in samples from patients responding to niraparib + pembrolizumab, while differences in immune TME composition ($CD8^+$, $CD4^+$, macrophages, B cells, neutrophils etc…) were not associated with response. Interestingly, one of the two patients who were extreme responders had amplification of PD-L1 locus (*CD274*), a rare genomic alteration observed in 0.7 % of HGSOC [63].

A second trial, the OVCa phase II trial [64], investigated the efficacy of combining anti-PD-L1 (durvalumab) and a PARP inhibitor (olaparib) in relapsing EOC. The majority of the patients (30/35; 86 %) were platinum-resistant. ORR was estimated to 15 % in this study, consistently with the TOPACIO trial. Paired biopsies at baseline and D15 of cycle 1 were mandatory and RNA-sequencing on these biopsies brought important insights for the *in vivo* effects of combining PARP inhibitor and anti-PD-L1 in ovarian cancer patients’. It revealed that the combination led to increased expression of IFN-ɣ, CXCL9 and CXCL10, two chemokines involved in $CD8^+$ T cells migration into tumors. All 8 responders had an immunoreactive signature in the pre-treatment biopsies compared to none of the non-responders, suggesting that the combination of PARP inhibitor and anti-PD-L1 was not sufficient to induce response in “cold" tumors. Contrary to the preclinical models, the treatment lead to either downregulation or no change of the STING pathway in the majority of patients while baseline STING levels was not associated with clinical benefit. All together, these data suggest that STING pathway activation is unlikely to be a predominant mechanism driving benefit from this combination.

3.6. Triplet anti-PD1/PD-L1 + anti-angiogenic + DNA damage agent

DNA damage could be induced by PARP inhibitors, numerous chemotherapy drugs (platinum and alkylating agents, for instance) and radiation therapy. Trials of triplet combination of PARP inhibitors, anti-PD1/PD-L1 and anti-angiogenic agents are under their way in a number of clinical settings, including platinum-resistant ovarian cancer. The phase I study of durvalumab, olaparib and cediranib showed promising preliminary results (NCT02484404). Overall, nine patients were included with a majority of EOC (n = 6, 5 platinum-resistant and 2 clear cell ovarian carcinoma), one platinum-resistant primary peritoneal cancer, one endometrial carcinoma and one metastatic triple-negative breast cancer [65]. The ORR was estimated to 44 % (4/9), all being PRs and lasting a median duration of 8.5 months (range 7–26 months). Although preliminary, such clinical activity is particularly interesting because these patients were heavily pretreated (number of previous treatments: 2, range [2–6]) recurrent gynecologic cancer population, especially platinum-resistant ovarian cancer where ORR to cediranib monotherapy is expected to be 17 % [66] and less than 5% for olaparib [61]. Further confirmation of the preliminary results of this phase I study are awaited. The combination of durvalumab, olaparib and

another anti-angiogenic agent, bevacizumab, is currently investigated in MEDIOLA phase I/II trial (NCT02734004), BOLD phase II Trial (NCT04015739) and DUO phase III trial (NCT03737643).

Another triplet combination that got attention is the combination pembrolizumab + bevacizumab + oral metronomic cyclophosphamide in relapsing EOC [67]. The rationale for adding cyclophosphamide is its immunomodulatory effects, previously shown to decrease angiogenic cytokines [68] and reduce immune tolerance by lowering the number of circulating Treg, restoring T and NK effector functions [69], promoting type I IFN [70] and influencing dendritic cell homeostasis [71]. However, one should not forget that cyclophosphamide is primary a DNA damage agent, inducing DNA inter-strand crosslinks and subsequent double-strand breaks in cancer cells [72]. ORR to the combination pembrolizumab + bevacizumab + oral metronomic cyclophosphamide was estimated to 37.5 % with 15 patients out of 40 showing PR (30 were platinum-resistant). The 6-months PFS was estimated to 100 % in platinum-sensitive and 59 % in platinum-resistant patients ($p = 0.024$). A recent preclinical study elegantly showed that exposure of cancer cells to mafosfamide, the active metabolite of cyclophosphamide, lead to upregulation of STING-mediated type I IFN expression and paracrine activation of Signal Transducer And Activator Of Transcription 1 (IFN/STAT1) signaling pathway [73]. Thus, it is possible that benefit from the triplet with cyclophosphamide had a similar biological mechanism than PARP inhibitors.

4. Ovarian clear cell carcinoma, an exceptional example of primary platinum-resistant disease, could be a good target for immune checkpoints inhibitors

Ovarian clear cell carcinoma (OCCC) is an endometriosis-associated ovarian carcinoma and accounts for 10 % of EOC. Loss-of-function mutations in *AT-rich Interaction Domain 1A* gene (*ARID1A)* [74,75], a component of the switch/sucrose non-fermentable (SWI/SNF) complex, are early events in the pathogenesis of OCCC and result in dysregulation of chromatin remodeling [74]. These *ARID1A* mutations frequently co-occur with activation of the phosphatidylinositol 3′-kinase(PI3K)-Akt (PI3K/Akt) signaling pathway, through loss of *Phosphatase and TENsin homolog* (*PTEN)* or gain-of-function mutations of the *Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic subunit Alpha (PIK3CA)* gene [76,77]. Immune TME of OCCC is characterized by moderate infiltration by $CD8^+$ T cells that do not have prognostic value [17]. PD-L1 expression is high in 20 % to more than 40 % of OCCC [78–80] and showed a trend toward higher expression than in HGSOC [80]. Unlike HGSOC, OCCC is frequently associated with primary platinum resistance [81] and median OS does not exceed 2 years in stage III patients: when compared with stage III serous histology, clear-cell is associated with decreased adjusted-PFS (HR = 1.35; 95 % CI, 1.16–1.57; $p < 0.0001$) and OS (HR = 1.54; 95 % CI, 1.32–1.8 $p < 0.001$) [82].

Several clinical trials revealed increased sensitivity of OCCC to ICI. A first signal was observed in the phase II trial with nivolumab by Hamanishi and colleagues: two out of twenty cases of platinum-resistant ovarian cancer with a complete response (CR), were OCCC [35,83] (UMIN000005714). Consistently, among the two OCCC patients treated with avelumab in the phase Ib JAVELIN trial, one had a PR and the other one had an immune-related PR [43]. The KEYNOTE-100 study enrolled 376 relapsing EOC, of whom 19 were OCCC. Response rate was 15.8 % (95 % CI 3.4 %–39.6 %) in OCCC, compared to 8.5 % (95 %CI 5.5 %–12.4 %) in HGSOC [44]. Finally, the randomized phase II NRG GY003 trial compared the combination ipilimumab and nivolumab to nivolumab in relapsing EOC. Patients with OCCC (n = 12) had an approximately five fold odds (OR = 5.21; 95 %CI 1.37–19.77) of response compared with the other subtypes (n = 88). These observations, although anecdotal and limited by the number of patients, strongly suggest increased sensitivity of OCCC to ICI and warrant further investigation in larger trials.

5. Genomic alterations and response to immune checkpoint blockade

5.1. Homologous recombination defects

HGSOC is characterized by HR defects in up to 50 % of the cases, through multiple mechanisms that include mutations (either germline or somatic) of *BRCA1/BRCA2* and hypermethylation of the promotor of *BRCA1* or *RAD51C* genes [84]. *BRCA1* mutations are associated with increased immune infiltration [17] and cluster according to gene-expression profile within the C2 immunoreactive molecular subtype [85]. *BRCA2* had distinct TME profile: there is no significant increase of intra-epithelial $CD8^+$ T cells and tumors do not show immunoreactive transcriptomic profile, when compared with wild-type. *BRCA1/BRCA2* mutated HGSOC are characterized by increased expression of PD1/PD-L1 and higher mutational burden [86]. Thus, it was speculated that *BRCA* mutated HGSOC would better respond to ICI but this was not the case [87]. In a single institution series of 103 EOC patients who received ICI (28 % had *BRCA* mutations), median OS was 21.3 months in those with *BRCA* mutations and 19.8 months in those without (HR = 1.00; 95 % CI 0.54–1.87, $p = 0.99$) [88]. In another cohort of pan-cancer patients with (n = 93) or without (n = 2079) *BRCA* mutations treated with ICI, event-free survival from the start of the first line of immunotherapy was similar in both groups (HR = 0.99; 95 % CI 0.78–1.3, $p = 0.9$) [89]. Consistently, response to pembrolizumab in the KEYNOTE-100 study did not correlate with HRD-score of Myriad ® or *BRCA* mutation [90]. It is unclear why *BRCA* mutated tumors do not response better to ICI while they are more infiltrated by T cells, express PD-L1 and harbor upregulation of antigen processing, TCR signaling and cytotoxicity [18]. Most studies investigating TME of *BRCA* mutated tumors used diagnosis biopsies. It is possible that TME of *BRCA* mutated tumors become “cold” when patients develop platinum-resistance.

5.2. Mismatch repair defects

Mismatch repair is a process that corrects mismatched nucleotides in the otherwise complementary paired DNA strands. Its absence results in a large increase of spontaneously occurring mutations, particularly in microsatellite sequences of highly repetitive DNA [91]. Tumors with defects in mismatch repair (dMMR), either germline or somatic, are characterized by high mutational burden [92], infiltration by $CD8^+$ T cells and high response rate to ICI [93]. In gynecological cancers, dMMR are frequently observed in endometrial cancers (up to 18 %) but they are rare in ovarian cancers. They occur only in endometriosis-associated histologic types, mainly endometroid ovarian carcinoma (18 %) and are rare in OCCC (2%) [94]. According to the KEYNOTE-158 study, ORR was estimated to 33 % in the dMMR ovarian cancer cohort (n = 15) [93]. Overall, dMMR represents rare molecular subgroup of EOC, that are mainly diagnosed at early stage and cured by surgery (type I tumors) [94].

5.3. SWI/SNF complex

The *SWI/SNF* complex is composed of 10–15 subunits protein that interact with histones and transcriptional factors. This complex binds to DNA regions via ARID1A and ARID1B to control chromatin accessibility. Recurrent mutations in *SWI/SNF* complex are observed in multiple gynecologic cancers: a) Inactivating mutations of the *SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4* (*SMARCA4)* gene is the driver event of small-cell carcinoma of the ovary, hypercalcemic type; b) *ARID1A* inactivation occurs early during transformation of endometriosis-associated ovarian cancer such as OCCC ; c) mutations in *SMARCA4*, *SMARCB1, ARID1A,* and *ARID1B* genes are late events in the development of endometrial cancer [95]. Overall it seems that *SWI/SNF* subunits act as tumor suppressors.

Recent immunogenomic studies revealed that tumors with loss-of-

function mutations in genes of the *SWI/SNF* complex responded better to ICI. For instance, mutations of Polybromo 1 (*PBRM1)* gene were enriched in clear cell renal cell carcinoma who responded to ICI, either anti-PD1 or anti-CTLA-4 [96]. *iIn vivo* studies in mice models of melanoma with inactivation of *PBRM1,* or the related *SWI/SNF* complex components such as *ARID2* or Bromodomain Containing 7 (*BRD7)* genes, showed that cancer cells with Polybromo-Associated BAF (PBAF) loss are more sensitive to T cell-mediated cytotoxicity compared to their PBAF-intact counterparts [97]. Gene sets related to IFN-ɣ and IFN-α response were significantly enriched among genes up-regulated in *ARID2* and *PBRM1* deficient cells.

Among ovarian cancers, two tumors with frequent inactivating mutations of *SWI/SNF* complex genes' showed increased sensitivity to ICI: small-cell carcinoma of the ovary, hypercalcemic type and OCCC. Small-cell carcinoma of the ovary, hypercalcemic type is a rare and very aggressive tumor that occurs mainly in young women. This monogenic tumor (inactivating mutations of *SMARCA4)* shares histologic and genomic similarities with pediatric rhabdoid tumors, caused by mutations of *SMARCB1* [98]. A case series reported objective and sustained response to anti-PD1 in a cohort of 4 patients with relapsing small-cell carcinoma of the ovary, hypercalcemic type [99]. In another cohort, PD-L1 was detected in 10 of 11 cases of small-cell carcinoma of the ovary, hypercalcemic type (on both stromal and cancer cells), and correlates with infiltration by $CD8^+$ T cells and up-regulation of cytolytic and antigen-presenting genes [99]. Consistently, a recent study in pediatric rhabdoid tumors revealed that they are highly infiltrated by T cells and myeloid cells. Subsets of exhausted effector and clonally expanded tissue resident memory $CD8^+$ T subpopulations were identified, likely representing tumor-specific cells [100] and mouse models of pediatric rhabdoid tumors responded to anti-PD1. The second histotype of EOC with frequent inactivation of SWI/SNF complex is OCCC, characterized by mutations of *ARID1A* resulting in complete loss of ARID1A protein in up to 50 % of the cases [101,102]. OCCC responded better to ICI than the other EOC subtypes as detailed above.

The mechanisms by which cancers harboring *SWI/SNF* deficiency respond to ICI are unclear. *ARID1A* deficiency contributes to impaired mismatch repair, leading to increased tumor mutational burden and increased response to ICI [103–105]. In cancers harboring *ARID1A,* mutations, indels and frameshift mutations are the most common types of mutations. This mutational class is very likely to be immunogenic, triggering increased abundance of neoantigens [105]. Nevertheless, the two cases with OCCC who responded to nivolumab in the early phase II study by Hamanishi and colleagues underwent whole-exome sequencing that did not show *ARID1A* mutation [83]. Pediatric rhabdoid tumors and small-cell carcinoma of the ovary, hypercalcemic type (recently classified as a rhabdoid tumor) are monogenic tumors with very low mutational burden. A raised mechanism for increased sensitivity to ICI in pediatric rhabdoid tumors with *SMARCB1* mutations is re-expression of endogenous retrovirus due to epigenetic dysregulation. This leads to cytosolic release of double-strand RNA and activation of type I/III IFN [100]. Given the frequent alterations of *SWI/SNF* complex in gynecological cancers, a better comprehension of the biological mechanisms underlying sensitivity to ICI is warranted.

6. Vaccine therapy

Vaccine therapy aims at stimulating endogenous tumor-specific T cells by providing tumor-associated antigens and activating signals. There are two main challenges for cancer vaccines. The first challenge is to identify the right antigen, the appropriate immune adjuvant and the delivery method. The second challenge is the immunosuppressive TME that compromises effective anti-tumor response. Early phase trials in platinum-resistant cancer evaluated vaccine that target "shared" tumor-associated antigens (TAA), i.e. antigens that are overexpressed by a subset of EOC (New York Esophageal Squamous Cell Carcinoma-1 [NY-ESO-1], Folate receptor alpha (FRα), or p53 for instance). Different combinations were further tested in order to dampen the immunosuppressive TME such adding anti-PD-L1 [106], use of IFN-α to promote dendritic cell maturity [107], or epigenetic therapy in order to increase the expression of TAA. Despite low ORR, antigen-specific T cell responses occurred and unexpected durable survival was reported. Maybe the most promising vaccine approach for platinum-resistant ovarian cancer is the development of individually mutated neoantigen vaccine [108]. These "private" tumor neoantigens are a class of HLA-bound peptides generated by missense mutations. Thus, they are exclusively tumor specific and highly immunogenic. Combining personalized vaccine with immunomodulation are mandatory for future success of vaccine therapy in platinum-resistant ovarian cancer [109,110].

7. Adoptive T cell therapy

Adoptive T cell (ACT) therapy is based on the passive transfer of a large number of tumor reactive T cells capable of immediate effector functions to eliminate the majority of tumor cells. There are two major forms of ACT: expansion of isolated TILs or genetically modified T cells (collected from peripheral blood) that express a specific TCR or a chimeric antigen receptor. Both approaches were investigated in platinum-resistant ovarian cancer with limited activity so far.

7.1. Autologous tumor infiltrating lymphocytes therapy

ACT based on autologous TILs is a therapeutical strategy that allows the activation and expansion of tumor-reactive T cells for subsequent infusion to lymphodepleted autologous host. They are generated *ex vivo* from processing of freshly removed small fragments (2−3 mm^3) of tumors that are placed in culture with media supplemented with high-dose IL-2 over the course of 2−3 weeks. TILs had achieved durable responses in selected patients with metastatic melanoma [111]. The main challenge for TILs therapy in solid tumors is the generation of highly active anti-tumor T cells in a sufficient number with appropriate effector functions for enabling them to kill cancer cells *in vivo*. With the development of next-generation sequencing, new approaches of neoantigen screening are developed in order to specifically expand neoantigen reactive T cells with known mutation-specific reactivity [112]. Another challenge is T cell exhaustion due to chronic antigen stimulation. Multiple strategies of immunomodulation of TILs before their transfer to patients with ICI targeting PD1, CTLA-4 or Lymphocyte activation 3 (LAG3), for instance, are currently investigated to overcome TILs exhaustion.

In the context of EOC, tumor reactive TILs are present within tumor lesions but the clinical benefit from ACT with TILs in EOC was limited according to the early clinical trials reported in the 1990's. Most patients included in these trials were platinum-resistant (review in [113]). Importantly, these trials did not use current chemotherapy regimens of lymphodepletion and the techniques for TILs expansion have substantially changed since 2000's. Recently, a pilot study included 6 ovarian cancer patients treated with "modern regimen" of TILs expansion and decrescendo IL-2, of whom 3 were platinum-resistant. Still, no objective response was reported but specific antitumor reactivity in $CD8^+$TILs was seen in two out of six patients [114]. In a subsequent phase 1 study from the same group, 6 patients with platinum-resistant ovarian cancer received anti-CTLA-4 ipililumab prior to surgical removal of tumors and *ex vivo* expansion of TILs. One patient achieved PR an another one had prolonged stable disease [115]. When comparing TILs from both trials, pre-treatment with ipilimumab seemed to be associated with higher number of infused T cells, a higher ratio of CD8:CD4 and a better anti-tumor reactivity of TILs. Although preliminary, these observations suggest that *in vivo* immunomodulation of TILs could improve response rate. Ongoing trials are investigating other strategies of immunomodulation such as anti-PD1 (NCT03158935, NCT01174121) or anti-4-1BB (NCT03412526), for instance.

7.2. Chimeric antigen receptor T cells

Chimeric antigen receptor T cells (CAR-T cells) have revolutionized anticancer therapy in the last decade [116]. They are genetically engineered T cells that express a CAR at their surface, thus combining the specificity of a monoclonal antibody with the cytolytic effect of a T cell [117]. CAR-T cells can be designed to recognize any cell-surface antigen. Despite impressive successes in B cell malignancies, CAR-T cells showed limited activity in solid tumors to date. The first step for a successful CAR-T cells therapy is selecting an optimal TAA. The ideal target should meet at least two criteria [118]. First, TAA needs to be selectively expressed on cancer cells at high levels while their expression is restricted to non-vital tissues [117]. Second, the ideal TAA would be expressed by 100 % cancer cells [119,120]. CD19 fits both of these criteria as a target antigen for B cell malignancies. It is expressed by essentially all B cells and has ubiquitous expression on B cell malignancies. To date, most clinical success has been obtained with CAR-T cells targeting CD19 [121,122]. Importantly, patients can live without healthy B cells. The third challenge for CAR-T cells in solid tumors is the immunosuppressive TME that limits intra-tumor trafficking of CARs [117].

Mesothelin is among the most promising TAA candidate for CAR-T cells therapy in EOC. It is a cell surface protein overexpressed by 80 % of HGSOC [123], while expressed at low levels by serosal cells. A first-in-human phase I trial investigated the efficacy of a “second generation” CAR-T cells anti-mesothelin, coupled to the CD3ζ and 4−1BB cytoplasmic signaling domains in 15 patients with chemotherapy refractory solid tumors, of whom 5 had platinum-resistant ovarian cancer [124]. No objective response was observed but one patient with platinum-resistant disease showed 26 % decrease of tumor burden at day 28. This study revealed several challenges facing development of CAR-T cells in solid tumors in general and this holds true for platinum-resistant ovarian cancer: 1) Expression of TAA, here mesothelin, was heterogeneous with only 3 of 15 patients expressing the target on >75 % of tumor cells. Thus, expression of mesothelin by cancer cells became an inclusion criterion in ongoing trials (NCT0354298 and NCT03323944); 2) Cell expansion of anti-mesothelin CAR-T cells was 10-fold less than those previously reported with anti-CD19 CAR-T cells, and they became undetectable in peripheral blood in most patients by 28 days after infusion; 3) Low levels of CAR-T cells were detected within tumors, suggesting poor infiltration, lack of expansion within tumors, or both. To circumvent the challenge of CAR-T cells having to traffic into the tumor, new trials are investigating local delivery of CAR-T cells anti-mesothelin into pleural and peritoneal cavities. A phase I trial tested intra-pleural administration of anti-mesothelin CAR-T cells combined with anti-PD1 in patients with pleural cancers and showed promising response rate with 2 complete metabolic response and 6 PR [125]. Local delivery of CAR-T cells is feasible in platinum-resistant ovarian cancer, through laparoscopy, and could be investigated as an alternative administration route in EOC to overcome barriers for CAR-T cells trafficking to the tumors.

7.3. T-cell receptor engineered T cells

T-cell receptor (TCR) engineered T cells are fundamentally different form CAR-T cells in their mechanism of action. While CAR-based engineering relies on antibody-like-mediated binding to the antigen, independently from HLA presentation, the basic concept of TCR-based ACT is to provide mature T cells with a high affinity TCR, recognizing an epitope of a TAA presented in the context of class I HLA molecules by cancer cells [112]. The main challenge for TCR-engineered T cell therapy is the choice of TAA. Most studies in the context of platinum-resistant ovarian cancer have engineered TCR against “shared” TAA like NY-ESO-1 (NCT02366546, NCT01567891, NCT02457650 or MAGE-A4 (NCT02096614). No objective reponse was reported among the 6 patients included in the sole trial with available data (NCT01567891) investigating TCR-engineered T cell therapy targeting NY-ESO1. Multi-level proteomics identified cancer/testis antigen 45 (CT45), a naturally occurring cancer antigen presented on class I HLA molecules on OC cells, as a novel “shared” TAA candidate for TCR engineered T cells in HGSOC [126]. Data from ongoing trials are awaited before driving definitive conclusions on targeting "shared" TAA with TCR engineered T cells.

With the breakthrough development of next-generation sequencing and new bioinformatics tools that enabled the discovery of tumor neoantigens (i.e. mutation-derived antigens), there is a shift toward targeting “private” TAA rather than “shared” ones, similarly to vaccine therapy. A pilot study has demonstrated the feasibility of the process from identification of neoantigen to manufacturing TCR-engineered T cells specific to neoantigens in EOC [127]. Another challenge for TCR-engineered T cells is their dependency on HLA for binding antigen. Given the frequent abnormalities of HLA class I expression and disruption of antigen presentation machinery by cancer cells [128], and this holds true in HGSOC [18], it is an important disadvantage that renders CAR-T cells more attractive.

8. Targeting myeloid immune checkpoints

Besides ICI that activate adaptive immune response, one of the most appealing possibilities is targeting myeloid immune checkpoints, for instance CD47. CD47 is a transmembrane protein overexpressed on the surface of many types of cancers. It was originally identified as a “don’t eat me” signal because it forms a signaling complex with signal-regulatory protein α (SIRPα) expressed on phagocytic immune cells, enabling the escape of cancer cells from macrophage-mediated phagocytosis [129]. This inhibitory mechanism of CD47 is an attractive therapeutic target for all tumors expressing it [130]. CD47 could be targeted with monoclonal or bispecific antibodies, anti-signal-regulatory protein alpha (SIRPα) antibodies and engineered receptor decoys. Since the CD47/SIRPα axis also limits the efficacy of tumor-opsonizing antibodies, combining anti-CD47 with other anti-cancer antibodies such as rituximab, trastuzumab and cetuximab is synergistic and boosts their effect in several preclinical studies [131]. This synergistic effect was confirmed in a landmark phase Ib clinical trial combining anti-CD47 Hu5F9-G4 and rituximab in non-Hodgkin lymphoma [132].

CD47 is overexpressed by the majority of EOC and correlates with lower complete response rate to platinum-based adjuvant therapy [133]. Its gene locus is amplified in 5% of HGSOC according to The Cancer Genome Atlas (TCGA) cohort and represents an attractive new therapy for EOC. A recent first-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers showed that inhibition of the CD47–SIRPα innate immune checkpoint is safe. Most toxicities were mild to moderate and included transient anemia (57 %) and fatigue (64 %). Importantly, objective responses were observed in 2 women among the 13 cases with EOC included in this phase I study: one with OCCC (5.2 months) and the second with Fallopian tube carcinoma (9.2 months) [134]. This “signal” in favor of anti-tumor effect in EOC warrants further confirming phase II studies. Since the reported toxicities compare favorably with those observed in patients receiving T cell-recruiting therapies such as ICI or CAR-T cells, combination of anti-CD47 with T cell immunotherapies seems feasible. A phase I trial investigating the combination of Hu5F9-G4 with anti-PD-L1 avelumab is ongoing (NCT03558139).

CD24, a novel “don’t eat me” signal capable of directly protecting cancer cells from attack by Siglec-10-expressing macrophages, emerged as the potential dominant myeloid immune checkpoint in EOC. Analyses of pan-cancer RNA-sequencing from the TCGA database revealed that the largest upregulation of *CD24* gene (a log2 fold increase of more than 9) was observed in HGSOC [135]. *CD24* levels were much higher than PD-L1 (*CD274*) or *CD47* genes. Abrogation of CD24 through genetic ablation or therapeutic blockade with monoclonal antibody resulted in a

macrophage-dependent reduction of tumor growth and prolonged survival in breast cancer mouse model.

9. Challenges for preclinical models

Preclinical models are of great importance for future development of anti-cancer immunotherapy. They allow testing numerous immunotherapy combinations and their effect on TME. They face several challenges in the context of EOC. The first challenge is using the appropriate animal models. With the new comprehension that the different histotypes arise from different cells of origin, there is a need for animal models for each histotype. Mice do not develop ovarian cancer spontaneously and have to be genetically modified to do so. Substantial progress was recently achieved with genetically engineered mouse models of HGSOC, obtained through genetic manipulations of the oviduct, the murine equivalent of the human Fallopian tubes, the putative cell of origin of HGSOC [136–138]. They recapitulate the morphology and molecular alterations of the disease. Hence, these engineered mice models were limited by the fact that they were generated in a mixed genetic background, precluding the development of tumor cell lines that can be used for syngeneic studies [139]. New orthotopic models generated from genetically engineered mice models backcrossed in the B6 background recapitulate the morphology and molecular alterations of HGSOC. Still, their TME had substantial differences when compared with their human counterparts with much higher amounts of TAMs and few T cells, limiting their utility for testing immunotherapy targeting T cells [140].

Syngeneic mouse models are another important preclinical model for testing immunotherapy. The most widely used syngeneic mouse model of EOC is ID8. It has several limitations: 1) it is derived from the ovarian surface epithelium, not the oviduct; 2) it does not harbor functional mutations in genes characteristic of HGSOC such as *Trp53* or *Brca1/Brca2; 3)* it demonstrated weak immunogenicity [141]. Genetic engineering of the ID8 model has resulted in a more suitable transplantable model with *Trp53* and *Brca2* deletions leading to immune infiltrate [141].

Egg-laying hen is the only animal model that spontaneously develops ovarian tumors and they develop the four histological types of EOC (serous, endometrioid, mucinous and clear cell), like humans. Although, EOC from laying hen has clinical, histologic and molecular similarities with the human counterpart, there is a controversy on whether the cell of origin being the oviduct or ovarian cell surface [142]. TME of avian EOC mirrored the human counterpart with the infiltration of advanced stage serous carcinoma by T cells. Deeper investigation of TME in this model is warranted before its use a preclinical model for immunotherapy [143].

The second challenge for preclinical models is testing immunotherapy on human tumors. Patient-derived xenografts in mice are suitable for drug screening on rapidly growing tumors but they are not appropriate for testing immunotherapy since xenografts are transferred to immunocompromised animals. An alternative to xenotransplants is *ex vivo* testing of immunotherapy on co-culture of tumor-derived 3-D organoids and autologous immune cells [144–146]. This strategy is attractive in EOC, since the majority of patients are diagnosed at advanced stages and undergo up-front debulking, allowing access to large sampling of tumors and malignant ascites from which autologous immune cells could be isolated and co-cultured with organoids and different combinations of immunotherapies [20,23].

10. What should be the future of research in this setting?

Platinum-resistance is a heterogeneous disease. For HGSOC, multiple biologic mechanisms are involved such as cancer stem cells, miRNA, amplification of cyclin E gene (*CCNE1*), reverse mutations that restore the open-reading frame of *BRCA1/BRCA2* genes [147], loss of *BRCA1* promoter methylation and recurrent promoter fusion associated with overexpression of the drug efflux pump Multi-Drug Resistance 1 (*MDR1)* [148,149]. Besides low infiltration by $CD8^+$ T cells [34], few is known on TME of platinum-resistant ovarian cancer [149,150]. With the recent development of maintenance therapies, the effect of PARP inhibitors and bevacizumab on the biology of platinum-resistant ovarian cancer adds further complexity. A better characterization of the immune landscape of the disease and its correlation with genomic alterations will help into defining the optimal strategy for transforming this “cold” tumor into “hot”. Access to tumor biopsies in platinum-resistant ovarian cancer is among the main challenges for better understanding its biology. This obstacle could be overcome with the ongoing trials of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in platinum-resistant ovarian cancer [151]. Studies with longitudinal and serial biopsies during repeated PIPAC will help into refining its biology (NCT04000906; EudraCT number 2018-003664-31).

Given the low response rate to ICI monotherapy in platinum-resistant ovarian cancer, several combinations of anti-PD1/PD-L1 with other ICI targeting T cells (CTLA-4, TIM-3 etc…) or myeloid cells (CD47), anti-angiogenic molecules, chemotherapy, PARP inhibitors or radiotherapy [152] are ongoing. Robust immunogenomic studies on biopsies collected longitudinally will be an invaluable resource for developing predictive biomarkers and a better comprehension of the biology of the disease, as emphasized by recent clinical trials [44,59].

Declaration of Competing Interest

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