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Review article

The fate of ovarian cancer in an era of immunotherapy

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Abstract:

Ovarian cancer is the leading cause of death from gynecologic malignancies with an overall 5-year survival rate of <45%. Most patients are diagnosed at stage III/IV due to the lack of adequate screening biomarkers and the paucity of early symptoms. The gold standard of treatment is aggressive debulking surgery, followed by platinum-based chemotherapy. However, ovarian cancer has a high recurrence rate. Recently, the emergence of immunotherapy has shown promising results in the treatment of various cancers. This has led to the exploration of possible immunotherapeutic options as a second-line treatment for recurrent ovarian cancer. This review focuses on the mechanisms of tumor evasion and the emerging immunotherapeutic options that can improve clinical outcomes.

Key words: ovarian neoplasms, immunotherapy, tumor escape, chemotherapy

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INTRODUCTION:

In the United States, ovarian cancer is the leading cause of death from gynecologic malignancies with an overall five-year survival rate of <45%. In 2017, 22440 new cases and 14080 deaths were expected, making ovarian cancer the fourth most common cause of cancer-related deaths in females.[2] The high mortality rate of ovarian cancer patients is due to the lack of adequate screening biomarkers and the paucity of early symptoms. As a result, three quarter of patients are diagnosed at stage III/IV based on the International Federation of Gynecology and Obstetrics (FIGO) classification.[3]

The current standard treatment for newly diagnosed patients comprises of aggressive debulking surgery, followed by adjuvant intravenous or intra-peritoneal platinum-based chemotherapy (cisplatin/carboplatin) in combination with paclitaxel. Despite a high initial response rate to the standard therapy, there is a significant risk for recurrence following primary treatment. Up to 80% of these patients will develop chemo-resistance, eventually leading to disease progression and death.[4] At present, the standard of care for patients who relapse 6 months after completing adjuvant therapy is platinum-based combination chemotherapy. For patients with a platinum free interval of less than 6 months, sequential single agent chemotherapy (pegylated liposomal doxorubicin (PLD), paclitaxel, and topotecan) is recommended with only a modest improvement in overall survival (OS).[5]

[2] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *Cancer J Clin* 2017; 67:7–30.

[3] American Cancer Society. Cancer Facts & Figures 2015. Atlanta: *American Cancer Society*; 2015.

[4] Salani R, Backes FJ, Fung MF, et al. Post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am. J. Obstet. Gynecol.,* 204 (2011), pp. 466-478

[5] Hardwick N, Frankel PH, Cristea M. New Approaches for Immune Directed Treatment for Ovarian Cancer Approaches for Immune Directed Treatment for Ovarian Cancer. *Curr. Treat. Options in Oncol.* (2016) 17: 14

During the past two decades, immunotherapy has emerged as the possible new paradigm for cancer therapy. It has shown promising results for solid tumors such as metastatic melanoma, non-small cell lung carcinoma, renal cell cancer, urothelial cancer and lymphoma.[6] In 2003, Zhang et al. provided the first evidence about the role of the immune system in the prognosis of ovarian cancer. The authors concluded that tumors harboring CD3+ T cells had an improved 5 years-OS compared to those without CD3+ T cells (38% vs. 4.5%, P<0.001).[7] In 2014, the AURELIA open-label randomized phase III trial demonstrated that the combination of Bevacizumab and chemotherapy in platinum-resistant patients could significantly improve the progression-free survival (PFS) and the objective response rate (ORR) without considerable improved OS.[8]

Immunotherapy certainly seems appealing to face the current challenges in the management of ovarian cancer. In this review, we will discuss about the mechanisms of tumor evasion and the emerging immunotherapeutic options that can possibly improve clinical outcomes.

1. Mechanisms of tumor evasion

Ovarian cancer is characterized by a unique tumor microenvironment (TME) that enables specific and efficient metastatic routes, impairs immune surveillance and mediates therapy resistance.[9] One of the key features in the ovarian TME is the presence of a large accumulation of ascitic fluid rich in

[6] Martin-Liberal J, Ochoa de Olza M, Hierro C, et al. The expanding role of immunotherapy. *Cancer Treat Rev* 54: 74-86, 2017.

[7] Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intra-tumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med.* 2003;348(3):203–213.

[8] Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014; 32 D13:302–308.

[9] Worzfeld T, Pogge von Strandmann E, Huber M, et al. The Unique Molecular and Cellular Microenvironment of Ovarian Cancer. *Onc.* 2017.00024

tumor-promoting soluble factors,[10] extracellular vesicles,[11] highly tumorigenic cancer cells,[12] different types of T cells and other host cells.

The following section includes a brief description of some of the possible mechanisms that promote tumor cell evasion.

1.1 Tumor-infiltrating lymphocytes (TILs):

TILs are now known to be present in ovarian cancer and are associated with better prognosis. Although Zhang et al. have proposed a survival benefit in patients with high CD3+ T cells,[7] a larger number of studies suggest that CD8+ TILs are the cells responsible for the increased survival benefit in ovarian cancer. In a study conducted by Sato et al., the authors concluded that intraepithelial CD8+ TILs were associated with a favorable prognosis in epithelial ovarian cancer while no association with CD3+ TILs was observed.[13] A 2017 meta-analysis by Jun Li et al. sought to assess the impact of different TILs subsets on the PFS and the disease free survival (DFS) in ovarian cancer. Overall analysis of the 2903 ovarian cancer patients revealed that intraepithelial CD3+, and CD8+ TILs were strongly associated with improved PFS/DFS (HR= 0.53, for CD3+ TILs; and HR= 0.50, for CD8+ TILs).[14] Therefore it can be concluded that the presence of TILs represent a positive factor in the prognosis of ovarian cancer, while the specific subset involved remains arguable.

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[10] Kulbe H, Chakravarty P, Leinster DA, et al. A dynamic inflammatory cytokine network in the human ovarian cancer microenvironment. *Cancer Res* (2012) 72(1):66–75.

[11] Peng P, Yan Y, Keng S. Exosomes in the ascites of ovarian cancer patients: origin and effects on anti-tumor immunity. *Oncol Rep* (2011) 25(3):749–762.

[12] Latifi A, Luwor RB, Bilandzic M, et al. Isolation and characterization of tumor cells from the ascites of ovarian cancer patients: molecular phenotype of chemoresistant ovarian tumors. *PLoS One* (2012) 7(10):e46858.

[13] Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. *Proc Natl Acad Sci* USA 2005; 102:18538–18543;

[14] Li J, Wang J, Chen R, et al. The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. *Oncotarget*, 2017, Vol. 8, (No. 9), pp: 15621-15631

The role of CD8+ T cells as cytotoxic killer cells of the immune system is well established. However, there are other types of T cells that are known to counteract the effects of CD8+ T cells and thus, participate in the evasion of tumor cells. Various studies have shown that the presence of regulatory T cell (Treg) in the TME is associated with a poor prognosis.[15,16] Curiel et al. described a study of 104 ovarian cancer patients in which the recruitment of Treg cells mediated by the chemokine, CCL22 by the tumor is associated with high death hazard and reduced survival.[17] In the aforementioned study by Sato et al., TIL subgroups with higher CD8/CD4 ratios showed better prognosis in terms of survival, suggesting an inhibitory role for Tregs.[15]

The above-mentioned studies imply that Tregs hinder the clearance of cancer cells by the immune system. Consequently, targeted immunotherapy aiming to reduce the number of Tregs and to increase the number of CD8+ TILs in the TME could represent the basis of future ovarian cancer treatment.

1.2 Cytotoxic T-lymphocyte associated protein 4(CTLA-4):

CTLA-4 is a member of the CD28:B7 immunoglobulin super-family, typically low-expressed on the surface of naïve effector T-cells and Tregs.[18] CTLA-4 plays a vital role in regulating T-

[15] Kryczek I, Wei S, Zhu G, et al. Relationship between B7-H4, regulatory T cells, and patient outcome in human ovarian carcinoma. *Cancer Res* 2007; 67:8900–8905;

[16] Wolf D, Wolf AM, Rumpold H, et al. The expression of the regulatory T cell- specific forkhead box transcription factor FoxP3 is associated with poor prognosis in ovarian cancer. *Clin Cancer Res* 2005;

[17] Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med* 2004; 10:942–949;

[18] Peggs KS, Quezada SA, Chambers CA, et al. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. J Exp Med. 2009; 206 (8): 1717–1725.

cell activation.[19] Activation is triggered through antigen recognition by the T-cell receptor (TCR), but co-stimulatory and co-inhibitory signaling dictates the magnitude of the resulting response. The cell surface molecule CD28 and its ligands CD80(B7-1) and CD86 (B7-2) are the primary sources of co-stimulatory signaling.[20] However, CD80 and CD86 do not exclusively induce activating signals, they are also the ligands of CTLA-4, a key negative regulator of T-cell activation.[21] CTLA-4 directly competes with CD28 for binding to CD80 and CD86. CTLA-4 ligation results in the termination of the T-cell activation, cell cycle arrest, and T-cell anergy. By limiting or reversing T-cell activation, CTLA-4 serves as an important immune checkpoint that helps contain immune responses. Thus, in the immunosuppressive TME, blocking CTLA-4 has the potential to directly activate CD4+ and CD8+ effector T-cells leading to tumor clearance.[22]

1.3 Programmed cell death-1 (PD-1):

PD-1 also known as CD279 is usually expressed on the surface of activated T cell, whereas its ligands, PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273), are commonly expressed on the surface of dendritic cells or macrophages. PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can limit the development of the T cell response. PD1/PD-L1 interaction ensures that the immune system is timely activated in order to minimize the

[19] Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. *Cancer Cell* 2014; 25(6): 846–859.

[20] Hathcock KS, Laszlo G, Pucillo C, et al. Comparative analysis of B7-1 and B7-2 costimulatory ligands: expression and function. *J Exp Med* 1994;180 (2):631–640.

[21] Chambers CA, Kuhns MS, Egen JG, et al. CTLA-4 mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. *Annu Rev Immunol* 2001;19: 565–594.

[22] Venkatesh Krishnan, Jonathan S.Berek, Oliver Dorigo. Immunotherapy in ovarian cancer. *Curr Probl Cancer* 41, 48-63

possibility of chronic autoimmune inflammation. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune-checkpoint pathway as a mechanism to evade detection and inhibit the immune response. PD-L1 is commonly over expressed on tumor cells or on non-transformed cells in the TME.[23]

PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, which leads to inhibition of the cytotoxic T cells. These deactivated T cells remain inhibited in the TME. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.[24] Maine et al. focused on the expression of PD-L1/PD-1 on monocytes in the ascites and blood of ovarian cancer patients and found that PD-L1 expression correlates with poor clinical outcome.[25] Therefore, a disruption of the PD-1/PD-L1 interaction using antibodies to either molecule can potentially restore T-cell function leading to an enhanced anti-tumor immune response.[26]

2. PASSIVE IMMUNOTHERAPY IN OVARIAN CANCER

2.1 IMMUNE CHECKPOINT INHIBITORS:

2.1.1 CTLA-4 inhibitors:

CTLA-4 acts as a checkpoint blockade, preserving self-tolerance and preventing autoimmunity, but may also act as a barrier against immunotherapies.[27] Inhibition of CTLA-4 offers a

[23] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; 12: 252-264.

[24] Chinmoy K.Bose. Immune checkpoints, their control by immunotherapy and ovarian cancer. *Contemp Oncol* (Pozn) 2017; 21 (3): 189–196

[25] Maine CJ, Aziz NH, Chatterjee J, et al. Programmed death ligand-1over-expression correlates with malignancy and contributes to immune regulation in ovarian cancer. *Cancer Immunol Immunother* 2014;63(3):215–224.

[26] J. Sunshine, J.M. Taube. PD-1/PD-L1 inhibitors. *Curr. Opin. Pharmacol.* 23 (2015) 32–38.

[27] Korman AJ, Peggs KS, Allison JP. Checkpoint blockade in cancer immunotherapy.

mechanism to enhance antitumor TIL responses by promoting T-cell proliferation.[28] The success of anti-CTLA-4 therapy in preclinical models revitalized interest in the field of immunotherapy. This resulted in the 2011 FDA approval of the anti-CTLA-4 mAb Ipilimumab (Yervoy, Bristol-Meyers, Squibb) for the treatment of metastatic melanoma.[29] Documented efforts to test Ipilimumab in ovarian cancer started with Hodi et al. The authors reported significant antitumor effects in a few patients, one having marked regression of tumor and 3 achieving stable disease after 6 months. In a phase 2 study using Ipilimumab in recurrent platinum-sensitive ovarian cancer subjects, the investigators aimed at analyzing the safety and efficacy of the drug (NCT01611558). Out of 40 patients, 20 had a grade 3 or higher drug-related adverse events and the best overall response rate (BORR) was 10.3 (2.9-34.2). At present there are other trials exploring the use of CTLA-4 inhibitor combined with other immunotherapeutic options such as TILs or other immune checkpoint inhibitors, and are now recruiting (NCT03287674, NCT03342417).

2.1.2 PD-1/PD-L1 inhibitors:

The validation of antibodies targeting the PD-1/PD-L1 axis came in late 2014, when the FDA granted accelerated approval to Pembrolizumab (Keytruda, Merck). Pembrolizumab is an anti-PD1 mAb that achieved an ORR of 26% in patients with Ipilimumab-refractory advanced melanoma.[30] A rationale for targeting PD-1/PD-L1 pathway in gynecologic malignancies was initially demonstrated in a phase 1 study of anti-PD-L1

Adv Immunol 2006; 90:297–339;

[28] Egen JG, Kuhns MS, Allison JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. *Nat Immunol* 2002; 3:611–618;

[29] Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. *Clin Cancer Res* 2011;17 (22):

[30] Robert C, Ribas A,Wolchok JD, et al.Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. *Lancet* 2014;384(9948):1109–1117.

antibody in patients with advanced cancer, which included 17 patients with ovarian cancer. Of the ovarian cancer cohort, 22% of the patients had evidence of objective response or stable disease, lasting at least 24 weeks.[31] During the past few years, many clinical trials started using PD-1/PD-L1 inhibitors in ovarian cancer patients. In the KEYNOTE-028 phase 1b study (NCT02054806), Pembrolizumab was administered to 26 patients. The objective response rate was 11.5%, with 1 CR, 2 partial responses (PR) and 23% stable disease (SD). Durable responses were noted and the median time to response was 8 weeks.[32]

Nivolumab is another monoclonal antibody targeting the PD-1/PD-L1 axis and was first studied in the setting of ovarian cancer by Haminishi et al. Nivolumab was administered every 2 weeks to patients with advanced or relapsed platinum-resistant ovarian cancer. 15 patients were treated with Nivolumab (1mg/Kg, n=10; 3mg/Kg, n=5) and evaluated. Grade 3 or 4 adverse events occurred in 8 patients (20%) and two experienced severe adverse events (grade 3 disorientation, gait disorder, fever in 1 patient and grade 3 fever, deep venous thrombosis in the other). The best overall response was 15%. 4 patients experienced prolonged disease control (2 patients in each dose cohort) with 2 patients in the 3mg/Kg cohort experiencing a durable complete response (CR).[33] While response rates were similar to what has been seen with chemotherapy in platinum resistant disease, the durable responses are atypical in this disease and a cause for

[31] Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012; 366:2455-2465

[32] Varga A, Piha-Paul SA, Ott PA, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study. *J Clin Oncol*. 2015:33 Suppl; abstr 5510

[33] Hamanishi J, Mandai M, Ikeda T, et al. Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO- 4538) in patients with platinum-resistant ovarian cancer. *J Clin Oncol* 2014;32 15 Suppl:5511.

enthusiasm particularly in a very heavily pre-treated population.[34]

Avelumab is a fully humanized monoclonal antibody directed against PD-L1, which prevents interaction with its receptor PD-1. This may restore immune function through the activation of cytotoxic T-lymphocytes targeted to PD-L1-overexpressing tumor cells. The phase 1b of the JAVELIN solid tumor clinical trial investigated the use of Avelumab in 124 patients with recurrent/refractory epithelial ovarian cancer. The preliminary results reported at ASCO 2016 showed an acceptable safety profile (grade 3/4 AEs reported in 6.5% of patients) and clinical activity: mPFS 11.3 weeks (95% CI: 6.1, 12.0) and mOS 10.8 (95% CI: 7.0, 16.1).[35] Differences in median PFS and OS were not statistically significant. 12 patients experienced a partial response for an ORR of 9.7%. Disease control rate (DCR, defined as ORR + SD) was 54%. ORR was 12.3% in PD-L1+ tumors and 5.9% in PD-L1- tumors (based on > =1% threshold). There are currently 2 phase 3 trials using Avelumab for ovarian cancer: one is testing Avelumab as first line therapy (JAVELIN OVARIAN 100, clinicaltrials.gov NCT02718417) and the other one is analyzing Avelumab in platinum-resistant/refractory disease (PLD, pegylated liposomal doxorubicin, plus Avelumab vs PLD alone, clinicaltrials.gov NCT02580058).

The evidence above shows that there are many factors to be addressed before the use of immune checkpoint inhibitors can be used in the setting of ovarian cancer treatment. We have not only noted a low response rate, but a high level of toxicity as well. More researches are required to evaluate the efficacy of immune checkpoint inhibitors in the context of ovarian cancer as a future immunotherapeutic option.

[34] Gaillard SL, Secord AA, Monk B. The role of immune checkpoint inhibition in the treatment of ovarian cancer. *Gynecol Oncol Res Pract.* (2016) 3:11.

[35] Disis ML, Patel MR, Pant S, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN Solid Tumor phase Ib trial: Safety and clinical activity. *J Clin Oncol* 2016; 34 Suppl; abstr 5533

2.2 POLY ADP RIBOSE POLYMERASE INHIBITORS (PARP-Inhibitors)

There are currently three PARP inhibitors that have been FDA-approved for use—olaparib (Astra Zeneca, London, UK), rucaparib (Clovis Oncology, Boulder, CO, USA), and niraparib (Tesaro Inc., Waltham, MA, USA).

Olaparib was the first PARP inhibitor to be approved by the EMA and FDA authorities for treatment of patients with *BRCA1/2* mutant ovarian cancers. Clear activity of single-agent Olaparib in BRCA-mut was demonstrated in Study 42, a multi-centre phase 2 trial that enrolled 298 patients with germline BRCA1/2 mutations and recurrent breast, ovarian, pancreatic or prostate cancers.[36] Within this trial, there were 193 patients who had received greater than 3 lines of chemotherapy for ovarian cancer, and the overall response rate was 34%, with a median duration of response of 7.9 months.[37] Another study conducted by Ledermann et al. evaluated the use of Olaparib as maintenance therapy in patients with platinum-sensitive relapsing high-grade serous ovarian cancer. Patients received olaparib 400mg twice daily or placebo. PFS was significantly longer with olaparib than with placebo (8.4 months vs. 4.8 months, respectively).[38] According to the retrospective analysis of the phase 2 trial in advanced ovarian cancer with BRCA 1/2 mutations, there was a significantly prolonged PFS in the olaparib group compared to the placebo group (11.2 months vs. 4.3 months, respectively).[39] On the basis

[36] Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. *J Clin Oncol* 2015;33(3):244e50.

[37] Domchek SM, Aghajanian C, Shapira-Frommer R, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. *Gynecol Oncol* 2016;140(2): 199e203.

[38] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382-1392.

[39] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. *Lancet Oncol* 2014;15: 852-861.

of these data, the US FDA granted approval for single-agent olaparib in advanced BRCA1/2 –mutant ovarian cancer.

In December 2016, rucaparib, another PARP-inhibitor, gained approval by the FDA following the ARIEL2 study, which confirmed that rucaparib prolonged PFS in patients with platinum-sensitive recurrent ovarian cancer.[40] ARIEL2 prospectively tested a novel next-generation sequencing-based homologous recombination deficiency (HRD) assay and algorithm to predict rucaparib sensitivity by assessing tumor BRCA status and genome-wide loss of heterozygosity (LOH). The patients received rucaparib (600 mg twice daily) in three pre-defined HRD subgroups: tumor $BRCA^{mut}$, $BRCA^{wt}/LOH^{high}$, and $BRCA^{WT}/LOH^{low}$. Efficacy data indicated ORRs of 69%, 39%, and 11%, respectively. Responses occurred in both germ-line $BRCA^{mut}$ (14/19, 74%) and somatic $BRCA^{mut}$ (10/16, 63%) tumors. The current ARIEL3 study (NCT01968213) aims at investigating the efficacy of rucaparib as maintenance therapy in platinum-sensitive ovarian cancer.

Niraparib is the most recent PARP-inhibitor approved by the FDA, based on the phase 3 NOVA study that investigated the role of this PARP 1/2 inhibitor as maintenance therapy for patients with platinum-sensitive, recurrent ovarian cancer. In this study, patients with platinum-sensitive disease were included regardless of germline BRCA1/2 mutation and HRD status, while results were stratified to investigate the role of HRD biomarkers for response. Improvement in PFS was observed regardless of germline BRCA1/2 mutation or HRD status, although improvement in PFS was mostly marked in the germline BRCA1/2 mutant group (HR 0.27, confidence interval (CI) 0.17–0.41). In addition the PFS in the HRD group

[40] Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 part 1): An international, multi-centre, open-label, phase 2 trial. *Lancet Oncol.* 2017, 18, 75–87.

(HR 0.38, CI 0.24–0.59) was slightly better than the non-germline BRCA1/2 mutant cohort (HR 0.45, CI 0.34–0.61).[41]

The current challenges being faced by the use of PARP-inhibitors, is the emergence of resistance.[42] New strategies are needed to make optimal use of PARP-inhibitors. Investigators are now looking at the prospect of combination therapies. For example, in a phase 2 study of patients with recurrent platinum-sensitive ovarian cancer, the combination of cediranib and olaparib found an improved PFS compared to single agent olaparib (HR=, p=0.0005).[43] A current phase 2 trial aims at investigating the above- mentioned combination in platinum-resistant ovarian cancer patients. (NCT02889900)

2.3 VEGF-inhibitors

Vascular endothelial growth factor (VEGF) is a key mediator of developmental angiogenesis and regulates the vascularization of tumors.[44] Bevacizumab (Avastin, Roche) is a humanized mAb that binds to all isoforms of the VEGF receptor ligand. Results from the AURELIA trial[8] demonstrated that ovarian cancer is a promising candidate for VEGF therapy. In the ICON-7 trial, 1528 ovarian cancer patients with stages IIIC and IV were enrolled. At a median follow-up time of 36 months, patients in the bevacizumab arm showed a significant improvement in median PFS (2 months). The maximal effect of this trial was observed at 12 months but decreased after 24 months. A recently updated analysis showed similar PFS and OS benefits in the bevacizumab group.[45] The OCEANS trial was a

[41] Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med.* 2016, 375, 2154–2164.

[42] Edwards SL, Brough R, Lord CJ, et al. Ashworth, A. Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 2008, 451, 1111–1115.

[43] Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: A randomised phase 2 study. *Lancet Oncol.* 2014, 15, 1207–1214.

[44] Ferrara N, Gerber HP, Le Couter J. The biology of VEGF and its receptors. *Nat Med* 2003;9(6):669–676.

[45] Oza AM, Cook AD, Pfsterer J, et al. Standard chemotherapy with or without

randomized, multi-center, blinded, placebo-controlled phase III trial. Patients were randomly assigned to carboplatin plus gemcitabine combined with bevacizumab or placebo for 6 to 10 cycles. PFS for the bevacizumab arm was superior to that of the placebo arm (12.4 months vs. 8.4 months, respectively). In addition, bevacizumab therapy caused a significant improvement in the ORR (78.5% vs. 57.4%, respectively) and duration of response (10.4 months vs. 7.4 months, respectively). There was no OS benefit for patients who received bevacizumab compared to the placebo arm (33.6 months vs. 32.9 months, respectively).[46] The AURELIA trial was the first randomized phase 3 trial to evaluate bevacizumab in combination with chemotherapy in platinum-resistant ovarian cancer. A 3-month prolongation of PFS was observed with the addition of bevacizumab. Even though the difference in OS was not significant, the ORR was higher in the bevacizumab arm compared to the one without bevacizumab (11.8% vs. 27.3%, respectively).[8]

3. ACTIVE IMMUNOTHERAPY IN OVARIAN CANCER

3.1 Adoptive cell therapy:

ACT is an immunotherapeutic technique that uses autologous or allogenic antitumor lymphocytes to induce cancer regression. Given the favorable prognostic value of TILs in ovarian cancer, various attempts have been made to exploit its use. ACT relies on the isolation of TILs from fresh tumor resections, selection of tumor-reactive subpopulation, activation and expansion of TILs to large numbers ex vivo. The engineered TILs are

bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015; 16: 928- 936

[46] Aghajanian C, Blank SV, Gof BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; 30: 2039-2045.

subsequently administered to the patient.[22] The disadvantage of ACT is the limited availability of tumor-specific lymphocytes. Genetically engineered T cells provide an alternative strategy that avoids the need to isolate sufficient number of TILs. The autologous lymphocytes isolated from peripheral blood are transduced either with a T cell receptor recognizing a specific tumor antigen by the MHC, or with a chimeric antigen receptor (CAR) recognizing a tumor-associated surface antigen.[47] ACT with tumor infiltrating lymphocytes (TIL) has achieved impressive clinical results with durable complete responses in patients with metastatic melanoma. However, in the case of ovarian cancer, studies are currently underway. In a recent phase 1 study involving 6 patients with metastatic ovarian cancer, TILs were isolated from the patients' own tumor tissue followed by in vitro expansion and activation for around 4-6 weeks. Before TIL infusion, the patients received 1 week of preconditioning chemotherapy with Cyclophosphamide and Fludarabine. After the TIL infusion, Interleukin-2 was administered to support T cell activation and proliferation in vivo. The investigators found that TIL therapy in patients with metastatic ovarian cancer is feasible and tolerable (NCT02482090). Since the clinical responses were transient, phase 2 consists of the combination of TIL with checkpoint inhibitors in an attempt to improve the clinical outcome (NCT03287674).

While the numerous advantages conferred by ACT seem plausible, significant toxicities were noticed: cytokine release syndrome (CRS) can lead to a range of clinical toxicities, including fever, hypotension, hypoxia and neurologic toxicities, requiring prompt recognition and treatment with steroids or anti-interleukin-6 receptor antibody tocilizumab.[48] Therefore,

[47] Smith EL, Zamarin D, Lesokhin AM. Harnessing the immune system for cancer therapy. Curr Opin Oncol. 2014; 26:600-7

[48] Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med.* 2014; 6 224ra25

these concerns should be addressed when engineering T cells to improve the safety profile of ACT.

CONCLUSION

In an era where precision medicine is emerging, the "one size fits all" mindset is gradually becoming obsolete. The need to explore new horizons in the management of ovarian cancer is becoming obvious with the increasing mortality rate. At present, there is a plethora of opportunities open for research in the field of immunotherapy and this certainly makes the future of cancer therapy look brighter. However, immunotherapy in the treatment of ovarian cancer is still in its infancy with multiple trials failing to provide convincing evidence to implement its use. Therefore, strategies to improve treatment outcome and minimize immune-related toxicities are necessary and will more likely require an individualized approach. Furthermore, we need to develop a better understanding of the molecular mechanism of ovarian cancer to design new therapies that can overcome resistance and thus help clinicians to conquer this disease. Tailored treatment based on individual sensitivity and molecular characteristics could be the cornerstone of future therapy.