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Incorporating immune checkpoint inhibitors in epithelial ovarian cancer☆

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HIGHLIGHTS

- Immune checkpoint inhibitors (CPIs) have shown limited efficacy in epithelial ovarian cancer.
- The combination of CPIs with chemotherapy is not validated and does not induce immunogenic cell death.
- Further evidence is required to evaluate the role of CPIs in combination with PARP inhibitors and bevacizumab.

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ABSTRACT

Objective. Therapeutic interventions for epithelial ovarian cancer (EOC) have increased greatly over the last decade but improvements outside of biomarker selected therapies have been limited. There remains a pressing need for more effective treatment options that can prolong survival and enhance the quality of life of patients with EOC. In contrast to the significant benefits of immunotherapy with immune checkpoint inhibitors (CPI) seen in many solid tumors, initial experience in EOC suggests limited efficacy of CPIs monotherapy.

Methods. A systematic review of phase III studies testing the role of CPIs in ovarian cancer was performed.

Results. Seven randomized trials testing CPIs in newly diagnosed ($n = 3$) and recurrent ($n = 4$) EOC are evaluated. Overall, those trials included data of 5671 patients. Single-agent PD-L1 inhibitor trials have not shown significant efficacy in newly diagnosed ovarian cancer. Triplet maintenance with bevacizumab plus olaparib and

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Immunity
PARP inhibitors

durvalumab is associated with longer progression-free survival than maintenance with bevacizumab alone in patients without tumor BRCA mutations. CPIs were not effective in platinum-sensitive ($n = 1031$) and platinum-resistant ($n = 1420$) EOC.

Conclusions. The value of adding CPI to standard treatment including poly (ADP-ribose) polymerase (PARP) inhibitors with or without bevacizumab remains unclear and is being addressed in ongoing clinical trials. The combination of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitors may enhance the efficacy of immunotherapy in EOC and studies are underway to investigate the combination of CPI with other emerging treatment modalities.

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Contents

1. Introduction

Epithelial ovarian cancer (EOC) is one of the most lethal gynecological malignancies, with a death-to-incidence ratio higher than 0.6 [1]. It is estimated that 324,603 new cases of EOC and 206,956 cancer-related deaths occurred in 2022 worldwide [1]. Over the last decade, there have been growing efforts to improve the prognosis of patients with EOC [2–6]. In particular, maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors (alone or in combination with bevacizumab) has shown remarkable efficacy in newly diagnosed patients following platinum-based treatment [4–6]. *BRCA* mutation and homologous recombination deficiency (HRD) represent the two most important biomarkers predicting a benefit from PARP inhibitors [4–6]. However, despite the introduction of innovative treatment algorithms and new agents, the outcomes for EOC patients remain poor [2,3]. Treatment options for patients with recurrent disease become increasingly limited with each line of therapy [7–10]; therefore, there is an unmet need to identify new treatments for patients with EOC.

Immune checkpoint inhibitors (CPI) are an effective therapy for several solid tumors (including cervical and endometrial cancers) and have been incorporated into standard of care as a new treatment paradigm [11,12]. The aim of these therapies is to enhance the anti-cancer response of the immune system and reduce cancer burden through cell killing. However, the tumor response to immunotherapy with CPI varies greatly between different types of cancers and even among different patients. Factors such as histology, tumor microenvironment, tumor mutational burden, and expression of immune checkpoint proteins, as well as genetic and epigenetic factors, influence the effectiveness of immunotherapy. The complex interplay of these factors contributes to the heterogeneity in the response to immunotherapy among different tumors and individuals [11–14].

In the present paper, we discuss the emerging evidence on incorporating CPI in the treatment of EOC. We reviewed systematically available evidence regarding immunotherapy (alone or in combination with other agents) in different patient segments (PROSPERO registration ID: CRD42024536017). In **Supplemental Material 1** we reported the methodological details about the process of the systematic review. We address (i) the effect of CPI agents in EOC subtypes; (ii) the role of CPI in newly diagnosed cases, (iii) platinum-sensitive disease, and (iv) platinum-resistant disease; as well as (v) innovative approaches to implement CPI in EOC patients.

1.1. Rationale, biology and biomarkers

Immunogenicity, defined as the capacity to provoke adaptive immune responses, has been extensively investigated through experiments involving in vitro and in vivo cancer cells. Two main predictors of response to CPI have been identified [15]. The first predictor involves the genomic and molecular characteristics of the tumor cells, including microsatellite instability/mismatch repair defects, tumor mutational load, and neoantigen load. The second predictor is related to extracellular components, such as tumor immune microenvironments (TME), tumor-infiltrating lymphocytes (TILs), and tertiary lymphoid structures (TLSs) [16,17].

Early studies suggested the presence of intra-tumoral T cells is associated with molecular evidence of activation of antitumor mechanisms and with a survival advantage in ovarian cancer, thus supporting the potential benefit of immune checkpoint inhibitors in ovarian tumors [18,19]. However, more recent studies suggested that EOC is characterized by limited responsiveness to immunotherapy due to its tendency to be immunologically "cold" [17]. Ovarian cancer often lacks the immune cell infiltration seen in other "hot" tumors and is characterized by a low tumor mutational burden (TMB), coupled with limited anticancer immunity and active immune suppression. Intra-tumoral TLSs have been associated with improved outcomes in several cancer types by enhancing tumor-directed immunity [16,20,21]. However, recent research by Kasikova et al. demonstrated that mature TLSs are expressed only in a minority of high-grade serous EOC cases (about 16 %) and are associated with an increased intratumor density of CD8+ effector T cells and $TIM3^{+}PD1^{+}$ cells and a low density of follicular helper T cells, leading to poor responsiveness to immunotherapeutic agents [18]. Ovarian cancer is also associated with increased levels of

myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells that promote an immunosuppressive environment and induce the proliferation of regulatory T cells (T-reg) suppressing the effector T cells [20,21].

High-grade serous EOC is a molecularly heterogeneous cancer [22,23]. Tothill et al. identified different molecular subtypes of EOC using gene expression profiling [22]. Four molecular subtypes were observed in patients with high-grade serous EOC, each with distinct biological and clinical differences [22]. Moreover, The Cancer Genome Atlas (TCGA) Research Network reviewed genomic and epigenomic abnormalities of 489 high-grade serous EOC in 2011, corroborating the presence of four subtypes: mesenchymal, immunoreactive, differentiated, and proliferative [23]. The immunoreactive subtype exhibits high expression levels of the T-cell chemokine ligands CXCL11, CXCL10, and CXCR3, while the other subtypes (accounting for about 80 % of high-grade serous EOC cases) do not present a favorable immune microenvironment. Interestingly, the difference in T-cell expression in BRCA-mutated tumors is not significantly different from that of BRCA-wild type tumors, in line with the fact that BRCA-mutated tumors did not reveal more CPI sensitivity than their wild-type counterpart [24]. Further studies are needed to test the incorporation of immunotherapy in patients with immune-reactive profile, but also in other cancer types.

Ovarian cancers represent a heterogeneous entity. Hence, further evidence is needed to identify ovarian cancer patients who might benefit from immune checkpoint inhibitors and to determine surrogate biomarkers.

1.2. Immunotherapy in newly diagnosed ovarian cancer

There is a growing interest in identifying new combination strategies for newly diagnosed EOC. Although the introduction of PARP inhibitors (with or without bevacizumab) has represented a game-changer opportunity for ovarian cancer patients [25–27], there are two main unmet needs: (i) patients who develop resistance to treatments and (ii) *BRCA*-wild type, HRD-test-negative tumors who experience limited benefit from these treatments [25–27]. With the aim of improving response rates to primary medical treatments, new combinations with immunotherapeutic agents have been developed.

The landscape of studies focusing on first-line treatment of EOC has evolved significantly over recent years. Initially, the focus was to add CPI to chemotherapy [28]. However, the limited efficacy observed in broader patient populations prompted a shift towards combination therapies. This progression stemmed from a need to enhance treatment responses and overcome resistance seen with chemotherapy plus immunotherapy [28]. Consequently, researchers began exploring combinations of CPI with other agents such as bevacizumab and PARP inhibitors [29–33]. These combinations aimed to exploit multiple pathways involved in tumor growth and survival, thus offering a more comprehensive approach to treatment. Table 1 reports the main studies (mostly ongoing) investigating the role of immunotherapy with anti-programmed death-ligand 1 (anti-PD-L1) monoclonal antibodies—in newly diagnosed ovarian cancer.

The open-label, three-arm, parallel, randomized, phase III trial JAVELIN Ovarian 100 (NCT02718417) tested the role of avelumab (anti-PD-L1) in newly diagnosed ovarian cancer. The study randomized 998 patients to receive: (A) chemotherapy plus avelumab followed by avelumab maintenance ($n = 331$), (B) chemotherapy followed by avelumab maintenance ($n = 332$), and (C) chemotherapy alone (control; $n = 335$) [28]. The trial did not meet either of its two primary objectives of improving progression-free survival with two avelumab regimens with chemotherapy versus chemotherapy alone. The stratified hazard ratio (HR) for progression-free survival was 1.43 (95 % CI: 1.05–1.95; $p = 0.99$) with the avelumab maintenance and HR of 1.14 (95 % CI: 0.83–1.56; $p = 0.79$) with the avelumab combination regimen versus control treatment [27]. The study was stopped due to the unfavorable HRs [28].

The placebo-controlled double-blind randomized phase III IMagyn050/GOG3015/ENGOT-OV39 trial (NCT03038100) randomized patients 1:1 to receive 3-weekly cycles of atezolizumab (anti-PD-L1) or placebo (day 1, cycles 1–22), with paclitaxel plus carboplatin (day 1, cycles 1–6) plus bevacizumab (day 1, cycles 2–22). The study enrolled 1301 patients who had primary cytoreductive surgery (with residual disease) or received neoadjuvant chemotherapy plus interval debulking surgery [29]. The data suggested that adding immunotherapy did not improve median progression-free survival in the intention-to-treat population (19.5 versus 18.4 months with atezolizumab versus placebo, respectively; HR: 0.92; 95 % CI: 0.79–1.07). A potential benefit was observed in the PD-L1-positive (60 % of the whole study population) cohort (20.8 versus 18.5 months, respectively; HR: 0.80; 95 % CI: 0.65–0.99; $p = 0.038$). Adding atezolizumab to standard therapy did not improve median overall survival in the intention-to-treat population (50.5 versus 46.6 months with atezolizumab versus placebo, respectively; HR: 0.92; 95 % CI: 0.78–1.09), and in the PD-L1-positive population (not estimable versus 49.2 months, respectively; HR: 0.83; 95 % CI: 0.66–1.06). Interestingly, a trend towards improved survival was observed in patients with *BRCA* mutations (HR: 0.68; 95 % CI: 0.42–1.10), but not in HRD-positive tumors (HR: 0.92; 95 % CI: 0.67–1.27). The incidence of grade 3+ adverse events was numerically higher with atezolizumab than placebo (79 % versus 73 %). Discontinuation of any treatment occurred in 26 % and 22 % in the atezolizumab and placebo group, respectively [29]. Interestingly, in a subanalysis of the IMagyn050/GOG3015/ENGOT-OV39 trial, Mhawech-Fauceglia P et al. evaluated histopathologic characteristics in patients who received neoadjuvant chemotherapy. These data highlighted the importance of inflammation in predicting outcomes (46.9 months vs. 36.3 months for extensive and no extensive inflammation, respectively; HR 0.65; $p = 0.02$) and the response to chemotherapy, bevacizumab, and immunotherapy ($p < 0.01$) [30]. Similarly, the translational results of the phase II NeoPembrOV trial (NCT03275506), exploring the association of neoadjuvant chemotherapy with pembrolizumab [31], suggested that combination therapy results in a significant increase in intraepithelial CD8 + PD-1+ T cells, and that targeting regulatory T cells and endothelial cells may help overcome the immune resistance of ovarian cancers [32].

The DUO-O study (NCT03737643) tested the efficacy and safety of treatment combinations including standard chemotherapy, bevacizumab, durvalumab (anti-PD-L1 antibody) and olaparib in newly diagnosed advanced EOC. Depending on the tumor *BRCA* mutation status, patients were included in two independent cohorts. Patients with *BRCA*-wild type tumors were randomized (1:1:1) to receive (i) chemotherapy plus bevacizumab plus placebo followed by bevacizumab maintenance plus doublet placebo maintenance; (ii) chemotherapy plus bevacizumab plus durvalumab followed by bevacizumab and durvalumab maintenance plus placebo maintenance; and (iii) chemotherapy plus bevacizumab plus durvalumab followed by bevacizumab, durvalumab and olaparib maintenance. Moreover, the DUO-O included an open-label cohort of patients with *BRCA*-mutated tumors who received chemotherapy plus durvalumab followed by durvalumab and olaparib maintenance in a single arm. The use of bevacizumab was optional in this latter cohort. Interim data from the non-*BRCA*-mutated cohort of the DUO-O study (presented at the SGO 2024) assessed the safety and effectiveness of chemotherapy followed by maintenance therapy with bevacizumab alone versus bevacizumab plus durvalumab and olaparib. The triplet maintenance therapy correlated with a statistically significant improvement in median progression-free survival compared to bevacizumab alone in the HRD-positive population (HR: 0.49; 95 % CI: 0.34–0.69; $p < 0.001$) and in the intention-to-treat population (HR: 0.63; 95 % CI: 0.52–0.76; $p < 0.001$). Although it was not an analytic endpoint, the triplet maintenance strategy also correlated with improved progression-free survival, even when focusing only on HRD-negative tumors (HR: 0.68; 95 % CI: 0.54–0.86) [33]. Preliminary analysis comparing a doublet versus single maintenance strategy

Table 1
The incorporation of immune checkpoint inhibitors in newly diagnosed ovarian cancer.

Study	Identifier	Standard of care	CPI during chemotherapy	CPI maintenance	Bevacizumab	PARP inhibitors	Population	No residual tumor at PDS	BRCAm/HRD	PD-L1 positive	Median DFS (months, 95 % CI)	Median OS (months, 95 % CI)
JAVELIN Ovarian 100 [28]	NCT02718417	Chemotherapy ($n = 335$)	No	No	No	No	Stage III-IV, all histologies	105 (31 %)	NR	169 (50 %)	NE (18.2–NE)	11.8 (8.5–15.6)*, **
		Chemotherapy (n = 332)	No	Avelumab	No	No	Stage III-IV, all histologies	105 (32 %)	NR	158 (48 %)	16.8 (13.5–NE)	12.6 (9.1–16.0)*, **
		Chemotherapy (n = 331)	Avelumab	Avelumab	No	No	Stage III-IV, all histologies	105 (32 %)	NR	160 (48 %)	18.1 (14.8–NE)	12.6 (9.5–16.1)*
IMagyn050 [29]	NCT03038100	Chemotherapy ($n = 650$)	No	No	Yes	No	Stage III-IV, all histologies	41 (6.3 %)	NR	393 (60 %)	18.4 (17.2–19.8)	NE*
		Chemotherapy ($n = 651$)	Atezolizumab	No	Yes	No	Stage III-IV, all histologies	31 (4.7 %)	NR	391 (60 %)	19.5 (18.1–20.8)	NE*
DUO-O (non-tBRCAm) [33]	NCT03737643	Chemotherapy ($n = 378$)	No	No	Yes	No	Stage III-IV, high-grade histology	NR	HRD: 143 (37.8 %)	NR	19.3	NR*
		Chemotherapy ($n = 374$)	Durvalumab	Durvalumab	Yes	No	Stage III-IV, high-grade histology	NR	HRD: 148 (39.6 %)	NR	20.6	NR*
		Chemotherapy (n = 378)	Durvalumab	Durvalumab	Yes	Olaparib	Stage III-IV, high-grade histology	NR	HRD: 140 (37 %)	NR	24.2	NR*
DUO-O (tBRCAm) [33]	NCT03737643	Chemotherapy	Durvalumab	Durvalumab	Optional	Olaparib	Stage III-IV, high-grade histology	NR	All patients with BRCAm	NR	NR	NR*
NeoPembrOV [31]	NCT03275506	Chemotherapy ($n = 30$)	No	No	Optional	No	Stage III-IV, high-grade histology	0	BRCAm: 4 (13 %) HRD: 8 (27 %)	CPS ≥10: 11 (37 %)	20.8 (15.0–25.7)	35.3 (27.1–NE)
		Chemotherapy ($n = 61$)	Pembrolizumab	Pembrolizumab	Optional	No	Stage III-IV, high-grade histology	0	BRCAm: 15 (25 %) HRD: 19 (31 %)	CPS ≥10: 19 (31 %)	19.4 (17.0–26.7)	49.8 (36.1–NE)

Abbreviation: BRCAm, BReast CAncer gene mutated; CI, confidence interval; CPI, immune checkpoint inhibitors; CPS, combined positive score of PD-L1 expression; DFS, disease-free survival; HRD, homologous recombination deficiency; NE, not estimable; NR, not reported; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PDS, primary debulking surgery; tBRCAm, tumor BRCA mutated.

* Data on overall survival are not mature.

** Data about median follow-up for overall survival.

(bevacizumab plus durvalumab vs. bevacizumab) did not show differences in median progression-free survival (HR: 0.87; 95 % CI: 0.74–1.03; $p = 0.11$) [33]. The trial design did not compare the efficacy of the doublet combination between olaparib plus durvalumab. Data on overall survival are not yet mature. At this stage, no statistically difference in overall survival was observed. No new safety signals were reported in this preliminary analysis. Notably, 35 % of patients receiving triplet maintenance experienced adverse events leading to discontinuation of one or more medications [33]. Looking at the preliminary data of the DUO-O study, we have to point out two important considerations: (i) in the HRD-positive group, DUO-O showed that adding PARP inhibitors to bevacizumab improves outcomes (as expected due to the results of the PAOLA-1 trial [4]); (ii) due to the absence of an appropriate control arm, it is not possible to isolate the effects of durvalumab by comparing the experimental triplet therapy to the olaparib/bevacizumab combination.

Fig. 1 summarizes the results of the main studies testing the incorporation of immune checkpoint inhibitors in newly diagnosed ovarian cancer. Other ongoing trials are testing single (immunotherapy) or doublet maintenance therapy (immunotherapy plus PARP inhibitors) in newly diagnosed ovarian cancer undergoing platinum-based chemotherapy. The MK-7339-001/KEYLYNK-001/ENGOT-ov43/GOG-3036 (NCT03740165) is a phase III, randomized, double-blind, active- and placebo-controlled study of chemotherapy plus pembrolizumab followed by doublet pembrolizumab/olaparib maintenance for first-line treatment of *BRCA*-wild type advanced EOC [34]. Overall, more than 1300 patients will receive chemotherapy plus pembrolizumab + olaparib, pembrolizumab + placebo for olaparib, or placebo for pembrolizumab + placebo for olaparib [34]. Similarly, the ongoing ENGOT-OV44/FIRST (NCT03602859) study enrolled patients ($n = 1402$) with stage III (with residual disease) and IV non-mucinous ovarian cancer, randomized 1:1:2 to chemotherapy (with or without bevacizumab) with (A) placebo plus 3-year maintenance with doublet placebo; (B) placebo plus 3-year maintenance with niraparib plus placebo; and (C) dostarlimab plus 3-year maintenance with niraparib and dostarlimab. Patients are stratified per PD-L1, bevacizumab use, and BRCA/HRD status [35]. Recent announces reported benefits in term of progression-free survival for the immunotherapy arm, in the KEYLINK-001 and FIRST studies. However, until now, no data are still published. Another phase III trial, ATHENA (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy) trial is trying to assess the role of immune CPI (nivolumab) and PARP inhibitor (rucaparib) in a 4-arm randomized study. The study consists of two independent comparisons: (A) ATHENA-MONO: testing the efficacy of frontline maintenance with rucaparib versus placebo; (B) ATHENA-COMBO: testing the efficacy of the combination rucaparib plus nivolumab versus rucaparib alone. The results of the ATHENA-MONO cohort have already been published [27,36], while the data of ATHENA-COMBO were presented at ESMO 2024 [36]. The primary endpoint of investigator-assessed progression-free survival comparing the combination of rucaparib and nivolumab with rucaparib monotherapy was not met in the intent-to-treat population [36]. ATHENA-COMBO concluded that the addition of nivolumab to rucaparib was associated with increased toxicity, earlier discontinuation rates and inferior progression-free survival [36]. Other studies are ongoing testing various strategies for the incorporation of immune checkpoint inhibitors in newly diagnosed ovarian cancer (**Supplemental Material 2**).

Single-agent PD-L1 inhibitor trials have not shown significant efficacy in newly diagnosed ovarian cancer. Triplet maintenance with bevacizumab plus olaparib and durvalumab is associated with longer progression-free survival than maintenance with bevacizumab monotherapy in patients without tumor BRCA mutations. Further research into combination strategies is warranted.

1.3. Immunotherapy in patients with platinum treatment-free interval ≥ 6 months

Several studies have tested the combination of immune checkpoint inhibitors with other agents in platinum-sensitive EOC [37]. Here, we present two phase III studies focusing the first on standard chemotherapy plus immunotherapy and bevacizumab and the second on chemotherapy plus immunotherapy and PARP inhibitors (Table 2).

The ATALANTE/ENGOT-ov29 (NCT02891824) trial randomized patients 2:1 to receive atezolizumab (1200 mg once every 3 weeks or equivalent) or placebo for up to 24 months, combined with bevacizumab and six cycles of chemotherapy (carboplatin alone or in combination with paclitaxel or gemcitabine), stratified by platinum-free interval, PD-L1 status, and chemotherapy regimen [38]. Patients received platinum-based chemotherapy with bevacizumab and atezolizumab/placebo during chemotherapy followed by bevacizumab and atezolizumab/placebo maintenance. At the primary analysis cut-off date (October 2021), median progression-free survival was 13.5 vs. 11.3 months with atezolizumab vs. placebo, respectively (HR: 0.83; 95 % CI: 0.69–0.99). Data on overall survival are still immature. Median overall survival was 35.5 vs. 30.6 months with atezolizumab vs. placebo, respectively (HR: 0.81; 95 % CI: 0.65–1.01). Updated results will be presented at ESMO 2024. Focusing on the PD-L1 positive tumors (38 % of the whole population), atezolizumab did not improve survival outcomes. To date, the data from ATALANTE suggest that adding atezolizumab did not improve progression-free survival in the intention-to-treat and PD-L1 positive populations [38].

Trial	Chemotherapy	CPI (type)	Bevacizumab	CPI maintenance	Bevacizumab maintenance	PARP inhibitor maintenance	Disease-free survival	Overall survival
JAVELIN Ovarian 100 [28] (experimental arm B)	Yes	No	No	Yes (anti PD-L1)	No	No	Negative results	Negative results*
JAVELIN Ovarian 100 [28] (experimental arm C)	Yes	Yes (anti PD-L1)	No	Yes	No	No	Negative results	Negative results*
IMagyn050 [29] (experimental arm)	Yes	Yes (anti PD-L1)	Yes	Yes	Yes	No	Negative results	Negative results*
DUO-O [33] (experimental arm 2)	Yes	Yes (anti PD-L1)	Yes	Yes	Yes	No	Negative results	Negative results*
DUO-O [33] (experimental arm 3)	Yes	Yes (anti PD-L1)	Yes	Yes	Yes	Yes	Positive results	Negative results*

Fig. 1. Randomized trials testing immunotherapy vs. standard of care in newly diagnosed ovarian cancer.
Abbreviation: CPI, immune checkpoint inhibitors; PARP, poly (ADP-ribose) polymerase; *no mature results available

Table 2
The incorporation of immune checkpoint inhibitors in ovarian cancer with platinum-free interval ≥ 6 months.

Study	Identifier	Treatment	CPI during chemotherapy	CPI maintenance	Bevacizumab	PARP inhibitors	Population	BRCAm/HRD	PD-L1 positive	Median DFS (months, 95 % CI)	Median OS (months, 95 % CI)
ATLANTE [38]	NCT02891824	Chemotherapy ($n = 204$)	No	No	Yes	No	Non-mucinous ovarian cancer	NR	77 (37.7 %)	11.3 (11.0–13.5)	30.6 (27.9–33.6)
		Chemotherapy ($n = 410$)	Atezolizumab	No	Yes	No	Non-mucinous ovarian cancer	NR	156 (38 %)	13.5 (12.2–14.2)	35.5 (32.4–41.3)
ANITA/ENGOT-ov41 [39]	NCT03598270	Chemotherapy ($n = 208$)	No	No	No	Yes	Stage III-IV, high-grade	15 % BRCAm	73 (35 %)	10.1 (9.2–11.2)	NR*
		Chemotherapy ($n = 209$)	Atezolizumab	Atezolizumab	No	Yes	Stage III-IV, high-grade	13 % BRCAm	76 (37 %)	11.2 (10.1–12.1)	NR*

Abbreviation: BRCAm, BReast CAncer gene mutated; CI, confidence interval; CPI, immune checkpoint inhibitors; DFS, disease-free survival; HRD, homologous recombination deficiency; NE, not estimable; NR, not reported; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1.
* Data on overall survival are not mature.

The ENGOT-ov41/GEICO69-O/ANITA (NCT03598270) trial evaluates the addition of atezolizumab to carboplatin-based chemotherapy followed by maintenance niraparib in ovarian cancer with a platinum-free interval ≥ 6 months [39]. The interim results of the ongoing ANITA trial were presented during the 2023 ESMO congress. According to preliminary data, adding atezolizumab to platinum-based chemotherapy and niraparib did not improve median progression-free survival in the intention-to-treat population (11.2 vs. 10.1 months, in the atezolizumab and placebo arm, respectively; HR: 0.89; 95 % CI: 0.71–1.10) [39]. Fig. 2 summarizes the main results of randomized controlled trials testing immunotherapy vs. standard of care in patients with platinum -free interval ≥ 6 months. **Supplemental Material 3** shows ongoing studies for patients with a platinum-free interval ≥ 6 months.

Other studies are testing novel immunotherapeutic agents (other than CPI) in this setting, including therapeutic cancer vaccines [40,41]. The ENGOT-OV56/NSGO-CTU-DOVACC trial is testing UV1 (a therapeutic cancer vaccine directed against telomerase). The study aims to demonstrate the efficacy of UV1-olaparib-durvalumab combination maintenance therapy against olaparib in maintenance after platinum combination therapy for *BRCA*-wild type patients with relapsed ovarian cancer [40]. The three-arm TEDOVA study aims at evaluating the neoepitope-based vaccine (OSE2101) in HLA-A*02-positive patients (45 % of ovarian cancer population) as a maintenance treatment, alone or in combination with pembrolizumab, versus best supportive care in patients with first or second platinum-sensitive recurrent ovarian cancer with controlled disease after platinum-based chemotherapy and who have already received both bevacizumab and a PARP inhibitor [41].

Preliminary data regarding the addition of immunotherapy to standard of care for platinum-sensitive relapsed ovarian cancer failed to demonstrate a significant improvement in survival across all patient groups. New treatment strategies deserve to be explored.

1.4. Immunotherapy in patients with platinum treatment-free interval ≤ 6 months

Several studies have investigated the role of immunotherapy as a standalone treatment for patients with a platinum-free interval of less than 6 months. Table 3 shows the main studies investigating the role of immune checkpoint inhibitors for PROC. Preliminary experiences supported the investigation of single-agent CPI [42]. The phase Ib KEYNOTE-028 trial reported outcomes of 26 patients with PD-L1-positive advanced metastatic ovarian cancer who received pembrolizumab. These data suggested that CPI might be a valuable treatment for PROC, being characterized by a durable antitumor activity with manageable safety and toxicity [42]. Then, a few phase II and III trials were designed to test the value of CPI in PROC. The phase II KEYNOTE-100 (NCT02674061) demonstrated only modest activity for single-agent pembrolizumab in advanced recurrent ovarian cancer [43]. This trial included two cohorts: cohort A consisted of 285 patients who received ≤2 prior chemotherapy lines with a treatment-free interval between 3 and 12 months, while cohort B comprised 91 patients who received 3 to 5 prior lines with a treatment-free interval of ≥3 months. The objective response rate was low in both cohorts: 8.1 % in cohort A and 9.9 % in cohort B. Median progression-free survival was 2.1 months for both cohorts. Median overall survival was 18.7 months in cohort A and 17.6 months in cohort B. PD-L1 expression (measured as combined positive score [CPS]) correlated with response rate (4.1 % for CPS <1, 5.7 % for CPS ≥1, and 10.0 % for CPS ≥10), suggesting that patient selection may play a role in identifying candidates for CPI [43]. However, the value of PD-L1 expression as a predictive biomarker seems limited in ovarian cancer, as also confirmed in IMagyn050 [29], JAVELIN Ovarian 100 [28], JAVELIN Ovarian 200 [44], and ATALANTE [38] trials. In particular, an analysis of the ATALANTE trial showed negative results in the PD-L1+/CD8+ subpopulation in terms of progression-free survival, suggesting that if there is a subpopulation that benefits from

Trial	Chemotherapy	CPI (type)	Bevacizumab	CPI maintenance	Bevacizumab maintenance	PARP inhibitor maintenance	Disease-free survival	Overall survival
ATALANTE [38] (experimental arm)	Yes	Yes (anti PD-L1)	Yes	Yes	Yes	No	Negative results	Negative results*
ANITA/ENGOT-ov41 [39] (experimental arm)	Yes	Yes (anti PD-L1)	No	Yes	No	Yes	Negative results	Not reported

Fig. 2. Randomized trials testing immunotherapy vs. standard of care in patients with platinum-free interval ≥ 6 months.
Abbreviation: CPI, immune checkpoint inhibitors; PARP, poly (ADP-ribose) polymerase; *no mature results available

immunotherapy, currently available immunohistochemistry analyses are unable to identify these patients. Moreover, although chemotherapy has been associated with T cell "exhaustion", a dysfunctional state due to persistent antigenic stimulation, the number of prior chemotherapy lines did not play a relevant role [14]. Several studies have highlighted the impotence of PD-L1 expression in solid tumors. The binding between PD-1 and PD-L1 leads to a suppression of anti-tumor immunity. Consequently, this suppression is mediated through induction of T cell apoptosis and functional exhaustion in the tumor microenvironment. Moreover, recent evidence supported that PD-L1/PD-1 activation requires myeloid cells to suppress antitumor immunity. However, the ovarian cancer microenvironment is characterized by an inherent resistance to immune checkpoint inhibitors [44]. Indeed, similar results were observed in the Japanese phase III NINJA trial (JapicCTI153004) [45]. In this trial, nivolumab was tested as a monotherapy versus single-agent chemotherapy (gemcitabine or pegylated liposomal doxorubicin) in patients with a platinum-free interval of <6 months. The study enrolled 316 patients, and results showed that nivolumab did not improve overall survival and was associated with worse progression-free survival compared to gemcitabine or pegylated liposomal doxorubicin. Median progression-free survival was 2.0 and 3.8 months with nivolumab and chemotherapy, respectively (HR: 1.5; 95 % CI: 1.2–1.9). Median overall survival was 10.1 and 12.1 months with nivolumab and chemotherapy, respectively (HR: 1.0; 95 % CI: 0.8–1.3) [45].

With the aim that conventional chemotherapies might potentially synergize with immunotherapy by causing immunogenic cell death and releasing tumor antigens, several trials were designed [44,46]. The phase III JAVELIN Ovarian 200 (NCT02580058) trial assessed the role of avelumab (alone or in combination with chemotherapy) in platinum-resistant or platinum-refractory ovarian cancer. Patients were randomized 1:1:1 to avelumab, avelumab plus pegylated liposomal doxorubicin, or pegylated liposomal doxorubicin alone. Neither avelumab alone nor avelumab plus chemotherapy significantly improved progression-free and overall survival compared to chemotherapy alone [46]. Median progression-free survival was 3.7, 1.9, and 3.5 months in the avelumab plus chemotherapy, avelumab, and chemotherapy groups, respectively. Median overall survival was 15.7, 11.8, and 13.1 months in the avelumab plus chemotherapy, avelumab, and chemotherapy groups, respectively [46]. Similarly, the ongoing ENGOT-ov65/KEYNOTE-B96 (NCT05116189) randomized PROC patients to receive pembrolizumab versus placebo plus paclitaxel with optional bevacizumab. The estimated completion date is June 30, 2025 [47]. Fig. 3 summarizes the main results of randomized controlled trials testing immunotherapy vs. standard of care in patients with platinum-free interval < 6 months.

Other combinations have been explored. The phase II TOPACIO/KEYNOTE-162 trial (NCT02657889) evaluated the combination of pembrolizumab plus niraparib in 60 previously treated recurrent ovarian

Table 3
The incorporation of immune checkpoint inhibitors in ovarian cancer with platinum-free interval < 6 months.

Study	Identifier	Phase	Prior Lines	PFI (months)	Treatment	Bevacizumab	PARP inhibitors	BRCA m/HRD	PD-L1 positive	ORR	Median DFS (months, 95 % CI)	Median OS (months, 95 % CI)
KEYNOTE-100 [43]	NCT02674061	II, Cohort A	1–3	3–12	Pembrolizumab ($n = 285$)	No	No	NR	NR	7.4 %	2.1 (2.1–2.2)	NE
		II, Cohort B	4–6	3 or more	Pembrolizumab ($n = 91$)	No	No	NR	NR	9.9 %	2.1 (2.1–2.6)	17.6
TOPACIO [46]	NCT02657889	I/II	1–5	<6	Pembrolizumab ($n = 62$)	No	Niraparib	11 (17.7 %)	NR	25 %	NR	NR
JAVELIN Ovarian 200 [44]	NCT02580058	III	1–3	0-6	Chemotherapy ($n = 190$)	No	No	NR	88 (46 %)	4 %	3.5 (2.1–4.0)	13.1 (11.8–15.5)
			1–3	0–6	Chemotherapy plus avelumab ($n = 188$)	No	No	NR	100 (53 %)	13 %	3.7 (3.3–5.1)	15.7 (12.7–18.7)
			1–3	0–6	Avelumab (n = 188)	No	No	NR	100 (53 %)	4 %	1.9 (1.8–1.9)	11.8 (8.9–14.1)
NINJA [45]	JapicCTI153004	III	>1	0–6	Chemotherapy ($n = 159$)	No	No	NR	58 (36.5 %)	7.6 %	3.8 (3.6–4.2)	12.1 (9.3–15.3)
			>1	0–6	Nivolumab ($n = 157$)	No	No	NR	65 (41.4 %)	13.2 %	2.0 (1.9–2.2)	10.1 (8.3–14.1)
NRG-GY003 [53]	NCT02498600	II	1–3	<12	Nivolumab ($n = 49$)	No	No	NR	6/21 (28.5 %)	12.2 %	2.0 (NR)	21.8 (NR)
			1–3	<12	Nivolumab plus ipilimumab ($n = 51$)	No	No	NR	5/31 (16.1 %)	31.4 % (33 %*)	3.9 (NR)	28.1 (NR)

Abbreviation: BRCAm, BReast CAncer gene mutated; CI, confidence interval; DFS, disease-free survival; HRD, homologous recombination deficiency; NR, not reported; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PFI, platinum-free interval.
* In the NRG-GY003, one additional (unconfirmed) response was observed after 6 months.

Trial	Chemotherapy	CPI (type)	Bevacizumab	PARP inhibitor	Disease-free survival	Overall survival
NINJA [45] (experimental arm)	No	Yes (anti PD-1 monotherapy)	No	No	Negative results	Negative results
JAVELIN Ovarian 200 [44] (experimental arm A)	No	Yes (anti PD-L1 monotherapy)	No	No	Negative results	Negative results
JAVELIN Ovarian 200 [44] (experimental arm B)	Yes	Yes (anti PD-L1)	No	No	Negative results	Negative results

Fig. 3. Randomized trials testing immunotherapy vs. standard of care in patients with platinum-free interval < 6 months.
Abbreviation: CPI, immune checkpoint inhibitors; PARP, poly (ADP-ribose) polymerase

cancer patients [48]. This study reported an objective response rate of 25 % and a response rate of 45 % in *BRCA*-mutated patients, suggesting the potential efficacy of this combination [48]. Another experience combining dostarlimab and niraparib was recently published. The MOONSTONE/GOG 3032 trial (NCT03955471) was terminated due to the low objective response rate (7.3 %) observed for patients with recurrent advanced platinum-resistant ovarian cancer [49]. The results of the phase III NItCHE-MITO33 (NCT04679064), evaluating the same combination (dostarlimab and niraparib vs. physician's choice chemotherapy) will clarify the value of this combination [50]. The phase 2, multi-cohort, LEAP-005 trial evaluated lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors [51]. Recently, the results of 31 patients in the ovarian cancer cohort have been published. As fourth-line therapy, lenvatinib plus pembrolizumab was associated with an objective response rate of 35 % (according to blinded independent central review). Median (95 % CI) progression-free survival and overall survival were 6.2 (4.0–8.5) months and 21.3 (11.7–32.3) months, respectively [51]. The FORWORD II (NCT02606305) study is investigating potential combinations involving mirvetuximab soravtansine (the new standard of care for patients with a platinum-free interval of <6 months and with high expression of folate receptor alpha) and other drugs, including pembrolizumab [3]. Preliminary data on 14 patients showed no new safety signals and encouraging oncologic outcomes with an objective response rate of 43 %, median duration of response of 6.9 months, and a median progression-free survival of 5.2 months. However, these results are similar to those achieved with mirvetuximab soravtansine alone in the MIRASOL (NCT04209855) trial (objective response rate of 42.3 %, median duration of response of 6.77 months, and a median progression-free survival of 5.62 months) [52]. Combining different immunotherapic agents might enhance antitumor immune responses by targeting multiple immune escape pathways. The randomized, phase II, NRG-GY003 (NCT02498600) trial tested the association of CTLA-4 inhibitor (ipilimumab) plus PD-1 inhibitor (nivolumab) compared with PD-1 inhibitor (nivolumab) alone in women with persistent or recurrent ovarian cancer with a platinum-free interval < 12 months (62 % of patients had a platinum-free interval < 6 months) [53]. The study included 100 patients (49 receiving nivolumab and 51 receiving nivolumab plus ipilimumab). Six-month response rate was higher in the ipilimumab plus nivolumab in comparison to nivolumab alone (31.4 % vs. 12.2 %). The median progression-free survival was 2 and 3.9 months in the nivolumab and nivolumab plus ipilimumab arms, respectively [53].

Other investigational drugs are testing how to enhance the effects of immunotherapy. Indeed, medications targeting the tumor microenvironment (e.g., olvimulogene nanivacirepvec) and enhancing the immune response (e.g., nemvaleukin alfa) are being tested in this setting [54,55]. In particular, the ARTISTRY-7 (NCT05092360) trial highlights the potential limitations of single-agent CPI. Preliminary data suggest that single-agent CPI may be insufficient in certain settings, underscoring the need for combination approaches [55]. Bispecific antibodies, such as ubamatamab (anti-MUC16xCD3) tested in the ongoing R4018-ONC-1721 study (NCT03564340), represent another interesting class of immunotherapeutic drugs worth exploring [56]. **Supplemental Material 4** outlines ongoing studies for patients with a platinum-free interval < 6 months.

As of now, there are no data to support the integration of immunotherapy either alone or in combination with chemotherapy for patients with a platinum-free interval of less than 6 months. Combining PD-1 and CTLA-4 inhibitors might result in a clinical improvement, as reported by the NRG-GY003 trial. Additional evidence is required to evaluate other combination strategies involving PARP inhibitors or investigational drugs, such as antibody-drug conjugates.

1.5. Immunotherapy for other ovarian cancer histologies

Most studies investigating immunotherapy in advanced or recurrent ovarian cancer patients typically include high-grade, non-mucinous ovarian cancer [28–32]. Most of the high-grade tumors are serous-type as other high-grade tumors are less common. For instance, there is much less information on the activity of immunotherapy in high-grade endometrioid tumors. Accumulating data suggest the prognostic value of microsatellite instability-high (MSI-H) and/or mismatch repair deficiency (MMRd) in predicting the response to immunotherapy. MSI occurs in approximately 13 % and 7 % of endometrioid and clear cell ovarian cancer, respectively. Conversely, the expression of MSI-H/MMRd in low-grade serous, high-grade serous, and mucinous ovarian cancer is negligible [57]. In 2023, the Food and Drug Administration (FDA) granted full approval to pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H/MMRd tumors that have progressed following previous treatment and who have no satisfactory alternative options. Therefore, immunotherapy may be considered as an option in a selected group of endometrioid and clear cell ovarian cancers [57].

At ASCO 2024, Dizon et al., reported the final results of the phase 2 BrUOG 354 trial (NCT03355976) demonstrating that nivolumab plus ipilimumab elicited higher response rates vs. nivolumab monotherapy and improved outcomes for patients with ovarian or other extra-renal clear cell carcinomas. Combination therapy showed a 33.3 % response rate vs. 14.3 % with monotherapy. Median progression-free survival was 5.6 months for combination therapy vs. 2.2 months for monotherapy [58]. Another noteworthy study is the ENGOT-GYN2/GOG-3051/BOUQUET (NCT04931342), which is project aimed to evaluate multiple treatments in biomarker-selected patients with rare epithelial ovarian cancers (non-high-grade serous/non-high-grade endometrioid ovarian cancer). Patients who are ineligible for any open biomarker-selected arm receive atezolizumab plus bevacizumab. Interim results presented

at the 2023 ESMO congress included 21 patients who received atezolizumab plus bevacizumab, showing complete and partial responses in 0 % and 14 % of patients, respectively, with a 6-month progression-free survival rate of 75 %, the greater benefit being observed in clear cell and low-grade serous ovarian cancers [59]. The final results will provide insights into the role of immunotherapy and biomarker-driven therapies for rare ovarian cancers [59]. Interestingly, immunotherapy is under evaluation for patients with rare ovarian cancer types including small cell ovarian cancer (e.g., pembro-SCCOHT (NCT04602377)) [60].

To date, no mature data about the effectiveness of immunotherapy in non-high-grade serous ovarian cancer are available. Further studies are needed for the identification of the optimal management of those patients.

2. Conclusions

Immunotherapy has emerged as a breakthrough treatment in many solid tumors, but the results of immunotherapy with immune checkpoint inhibitors in ovarian cancer have been disappointing. Numerous trials have investigated and continue to investigate the incorporation of immune checkpoint inhibitors in these patients. However, ovarian cancer is a heterogeneous malignancy, presenting challenges for treatment strategies. The current landscape of cancer immunotherapy underscores the complexity of single-agent and combination strategies. While biomarkers such as TMB, dMMR, and MSI may offer valuable predictive insights, the efficacy of immune checkpoint inhibitors remains modest in the absence of these markers. The search for synergistic combinations continues, with PARP inhibitors, antiangiogenic agents and chemotherapy not yet providing consistent benefits as the only partners to CPI. The validated success of combined regimens with CTLA-4 inhibitors and the ongoing exploration of PARP inhibitor combinations highlight the dynamic and evolving nature of cancer immunotherapy research. To date, immunotherapy (alone or in combination) does not improve overall survival in newly diagnosed, platinum-sensitive, and platinum-resistant ovarian cancer. Consequently, the available results of phase III studies are not supporting the incorporation of immunotherapy. The definitive results of ongoing trials and new innovative approaches will clarify the role of promising combination therapies in ovarian cancer treatment.

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