Immunotherapy in the Treatment of Advanced or Recurrent Endometrial Cancer

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Abstract: The standard treatment of patients with advanced or recurrent endometrial cancer has not significantly changed over the past few decades, reflecting a major unmet clinical need. Fortunately, the arrival of immune checkpoint inhibition is rapidly changing this dismal scenario. This review discusses the most recent results from clinical trials evaluating the use of immune checkpoint inhibitors, either as monotherapy or in combination therapy, in both the post-platinum and frontline settings. Additionally, a section is devoted to the future clinical development of immune checkpoint inhibitors in advanced or recurrent endometrial cancer.

Introduction

Endometrial cancer (EC) represents the sixth most frequently diagnosed cancer among women, with an incidence of 4.5% and 417,000 new cases in 2020, mainly in Western countries.[1] In the last 20 years, its incidence has slowly increased by approximately 1% per year among postmenopausal women, accompanied by an increase in mortality rates.[2] Although early-stage disease is associated with an excellent prognosis, patients with advanced or recurrent disease have poor survival outcomes, with a 5-year overall survival (OS) rate of 20% to 25%. For patients progressing on or after first-line chemotherapy (carboplatin/paclitaxel), treatment alternatives are very limited.[3] Novel effective therapies are needed for this poor-prognosis population, and immunotherapy using immune checkpoint inhibitors (ICIs) is considered one of the most promising. This review article vets the current immunotherapy strategies, with a deep analysis of the latest clinical trial outcomes analyzing the role of ICIs for advanced or recurrent EC.

Biological Rationale for the Use of ICIs in Endometrial Cancer

The Cancer Genome Atlas (TCGA) Research Project identified 4 EC molecular subtypes, including DNA polymerase epsilon

Table 1. Main Clinical Trials Evaluating ICIs in Advanced or Recurrent EC in the Post-Platinum Progression Setting

Trial	Design	Drugs	N, population	ORR, % (95% CI)	mPFS, mo (95% CI)	HR (95% CI)	mOS, mo (95% CI)	HR (95% CI), P value
KEYNOTE-158[17,18]	Phase 2	Pembrolizumab	94, MMRd/MSI-H	50 (39.5-60.5)	13.1 (4.3-25.7)	-	65.4 (29.5-NR)	-
GARNET[22,23]	Phase 1	Dostarlimab	143, MMRd/MSI-H	45.5 (37.1-54.0)	6.0 (4.1-18.0)	-	NR (25.7-NR)	-
			156, MMRp/MSS	15.4 (10.1-22.0)	2.7 (2.6-2.8)	-	16.9 (13.0-21.8)	-
KEYNOTE-775[26,27]	Phase 3, randomized	Pembrolizumab + lenvatinib vs chemotherapy of physician's choice	827, all-comers	33.8 vs 14.7	7.3 vs 3.8	0.56 (0.48-0.66), P<.001	18.7 vs 11.9	0.65 (0.55-0.77), P<.001
			697, MMRp	32.4 vs 15.1	6.7 vs 3.8	0.60 (0.50-0.72), P<.001	18.0 vs 12.2	0.70 (0.58-0.83), P<.001
			130, MMRd	41.5 vs 12.3	10.7 vs 3.7	0.39 (0.25-0.60)	31.9 vs 8.6	0.43 (0.28-0.68)

HR, hazard ratio; MMRd, mismatch repair–deficient; MMRp, mismatch repair–proficient; mo, months; MSI-H, microsatellite instability-high; MSS, microsatellite stable; ICIs, immune checkpoint inhibitors; ITT, intention-to-treat population; NA, not available; NR, not reached; ORR, overall response rate; mOS, median overall survival; mPFS, median progression-free survival.

(POLE)-mutated or -ultramutated, microsatellite instability (MSI)-hypermutated, copy number low, and copy number high.[4] Each of these 4 subgroups showed distinctive molecular and pathological characteristics, along with striking differences in prognosis. As a result, the TCGA classification is rapidly changing EC categorization and treatment. The TCGA classification requires a complex and expensive methodology that does not allow a wide implementation in routine practice, so a simplified classification has been developed. The Proactive Molecular Risk Classifier for EC (ProMisE) is a more straightforward molecular classification based on the immunohistochemical markers MSH6, PMS2, and p53, along with targeted tumor sequencing using POLE hotspot analysis.[5-7] The ProMisE classification identified 4 subgroups that are analogous but not identical to the TCGA classification: POLE-mutated, mismatch repair–deficient (MMRd), p53 abnormal (p53abn), and nonspecific molecular profile (NSMP).[3,8,9]

The TCGA and ProMisE classifications identified 2 EC molecular subgroups that are particularly immunogenic. These are the POLE-ultramutated group and the MSI-high (MSI-H)/MMRd-hypermutated group, which account for approximately 7% and 30% of all EC cases, respectively.[4] Pathogenic mutations in the

POLE exonuclease domain characterize the ultramutated tumor subgroup, whereas the hypermutated tumors have an MSI phenotype owing to a deficient DNA MMR mechanism.[4,7] This MMR deficiency arises from germline (Lynch syndrome) or somatic (Lynch-like) mutations in MMR genes (MLH1, MSH2, MSH6, or PMS2), or more likely, from the biallelic silencing of MLH1 owing to promoter hypermethylation.

Both the POLE-mutated and MMRd EC subgroups harbor common distinctive biological features. They feature a high mutational rate that results in an increased number of potential neoantigens, and consequently a greater CD8+ T-cell infiltration. This immune-reactive microenvironment leads to a tumoral adaptive immune-resistance response, defined by immune checkpoint protein upregulation in the tumor and immune cells, such as programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1), making these 2 EC subtypes ideal candidates for immunotherapy.[10] Interestingly, other EC molecular subgroups characterized by a low tumor mutational burden, namely p53abn and NSMP, can also harbor a significant proportion of high-lymphocyte phenotype tumors.[11] This has certainly allowed for enlarging of the target population, beyond MMRd and POLE-mutated tumors, supporting the clinical development of immunotherapy

in the all-comer population.

A major breakthrough in cancer immunotherapy was the discovery of immune checkpoint proteins, potent immune suppressors through multiple mechanisms. In the last decade, great efforts have been undertaken to develop therapeutic approaches targeting these immune checkpoint proteins, promoting effective antitumor immunity. As a result, ICIs are currently the leading immunotherapy strategy in multiple solid tumor types, including EC. Among the immune checkpoint blockade approaches, the 2 that are the most developed are blocking cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; expressed by CD4+ and CD8+ T cells), and targeting PD-1 (expressed by activated T-cells) and PD-L1 (mainly expressed by T cells, antigen-presenting cells, and tumor cells). Monoclonal antibodies against CTLA-4 promote T-cell activation during the priming phase and wind down regulatory T-cell differentiation, whereas anti–PD-1/PD-L1 monoclonal antibodies increase T-cell activation during the effector phase of the immune cycle. Multiple agents targeting other immune checkpoint molecules, such as T-cell immunoglobulin and mucin domain–containing protein (TIM3), lymphocyte activation gene 3 (LAG3), or indoleamine 2,3-dioxygenase 1 (IDO1), are also under clinical development in the EC population.[12]

ICIs for Advanced or Recurrent Endometrial Cancer After Platinum Failure

Until recently, treatment alternatives for patients with recurrent or advanced EC after progression on carboplatin/paclitaxel remained limited and modestly active. Hormonal therapy and single-agent chemotherapy were among the most common therapeutic options, yielding an overall response rate (ORR) of less than 20% and a median progression-free survival (mPFS) of less than 3 months. Immunotherapy with ICIs has emerged as an effective therapeutic approach in this dismal scenario. Some ICIs have gained regulatory approval in this setting.[13,14]

ICI Monotherapy

The first evidence for the clinical activity of an ICI in metastatic EC was obtained from a phase 2 clinical trial enrolling patients with MSI-H/MMRd cancer (colorectal and noncolorectal) treated with the anti–PD-1 agent pembrolizumab (Keytruda, Merck). The ORR for the noncolorectal subgroup was 71% (95% CI, 29-96), including 2 responses in EC patients.[15] A subsequent combined analysis of 149 patients with MSI-H/MMRd advanced cancer treated with pembrolizumab demonstrated an ORR of 36%.[16] Based on these results, pembrolizumab was granted accelerated approval from the US Food and Drug Administration (FDA) in May 2017 for patients with unresectable or metastatic MSI-H/MMRd solid tumors whose disease has progressed following prior therapies and who do not have satisfactory alternative treatment options.

The KEYNOTE-158 trial was a confirmatory trial of pembrolizumab clinical activity in a previously treated MSI-H/MMRd advanced cancer population, including EC. A recently published update of this trial, with a median follow-up of 54.5 months, reported an ORR of 50% (95% CI, 39.5-60.5), an mPFS of 13.1 months (95% CI, 4.3-25.7), and an mOS of 65.4 months (95% CI, 29.5 to not reached) in the MSI-H/MMRd EC subgroup (n=94; Table 1). Regarding the safety profile, 14% of treated patients had grade 3/4 adverse events (AEs). Immune-mediated AEs or infusion reactions occurred in 30% of patients. The discontinuation rate owing to AEs was 7%.[17,18] Following these data, the FDA and the European Medicines Agency (EMA) approved single-agent pembrolizumab for patients with advanced endometrial carcinoma that is MSI-H or MMRd who have disease progression upon previous systemic therapies.

Beyond pembrolizumab, the clinical activity of several anti–PD-1/PD-L1 antibodies has been assessed in different phase 1/2 trials. Remarkably, all these trials have shown consistent outcomes, with the greatest benefit in the MMRd subgroup.

The phase 2 PHAEDRA study assessed the efficacy and safety of the anti–PD-L1 agent durvalumab (Imfinzi, AstraZeneca) in 2 cohorts of 35 MMRd and 36 mismatch repair–proficient (MMRp) EC patients. The objective tumor response rate by Immune Response Evaluation Criteria in Solid Tumors (iRECIST) was 47% (95% CI, 32-63) and 3% (95% CI, 1-15) in the MMRd and MMRp cohorts, respectively. In the MMRd cohort, durvalumab yielded greater efficacy outcomes in patients receiving this agent as first-line therapy (21/36; 58%) vs those treated in the second line (14/36; 39%), with an objective tumor response rate of 57% vs 38%.[19]

A phase 2 study, with a 2-stage Simon design, assessed the clinical activity of the anti–PD-L1 agent avelumab (Bavencio, EMD Serono/Pfizer). In all, 31 patients with previously treated advanced or recurrent endometrial carcinoma were enrolled in 2 different cohorts according to MMR status. The MMRp cohort was closed owing to futility (ORR, 6.25%), whereas the MMRd cohort showed an ORR of 26.7% (95% CI, 7.8-55.1) and a 6-month PFS of 40% (95% CI, 16.3-66.7). It is important to note that the patients were heavily pretreated, with 60% of MMRd patients having received 2 or more prior lines of therapy, which may explain the lower ORR compared with other ICI monotherapies.[20]

The safety and clinical activity of atezolizumab (Tecentriq, Genentech) in pretreated advanced or recurrent

uterine cancers were evaluated in a phase 1 clinical trial. The confirmed ORR was 13.3% (95% CI, 1.7-40.5) for all 15 evaluable patients in the cohort. Unlike in previous clinical trials, eligible patients were not selected based on the tumor MMR status, and only 1 patient had an MSI-H tumor.[21]

The phase 1 GARNET trial was a dose-escalation and cohort-expansion study evaluating the safety and efficacy of the anti–PD-1 agent dostarlimab (Jemperli, GSK) in patients with advanced solid tumors. After establishing the recommended dose for expansion cohorts, 2 cohorts of patients with recurrent or advanced EC were run: cohort A1 for MMRd patients and cohort A2 for MMRp patients. Patients were required to have received at least 1 and up to 2 prior platinum-based regimens. The MMR status was determined locally by immunohistochemistry. The MMRd cohort included a total of 143 evaluable patients and showed an ORR of 45.5% (95% CI, 37.1-54.0). At a median follow-up of 27.6 months, the median duration of response had not been reached. In contrast, the MMRp cohort included a total of 156 evaluable patients and showed an ORR of 15.4% (95% CI, 10.1-22.0). At a median duration of follow-up of 33.0 months, the median duration of response was 19.4 months (Table 1). Most AEs were grade 1/2, with fatigue (17.8%), diarrhea (14.6%), and nausea (13.7%) being the most common. Hypothyroidism (8%) was the most common any-grade immune-related adverse event. Overall, 8.6% of patients discontinued treatment owing to treatment-related AEs (TRAEs).[22,23] In light of these data, both the FDA and EMA have recently approved dostarlimab for women with MSI-H/MMRd EC that has progressed on or after prior platinum-based therapy.

ICI Combination Approach
A large proportion of patients with advanced or recurrent EC still do not benefit from ICIs, particularly those with MSS/MMRp tumors. To overcome this lack of activity, multiple clinical trials over the last few years have been exploring combination approaches to find a synergistic effect with ICIs that might enhance their clinical activity.

Antiangiogenic Agents and ICI Combinations. A robust biological rationale has supported the clinical development of the combination of antiangiogenic agents and ICIs. Indeed, antiangiogenic agents may modulate the immune tumor microenvironment through multiple mechanisms, such as the increase of CD8+ T-cell infiltration and activation, the depletion of regulator T cells and myeloid-derived suppressor cells, and the induction of dendritic cell differentiation.[24]

Various combinations of antiangiogenic agents and ICIs have been already assessed in EC, namely pembro-

lizumab/lenvatinib (Lenvima, Eisai), nivolumab (Opdivo, Bristol Myers Squibb)/cabozantinib, and atezolizumab/bevacizumab.

Following the promising efficacy data of the combination of the multitarget tyrosine kinase inhibitor lenvatinib and pembrolizumab in the early KEYNOTE-146 clinical trial, the randomized phase 3 KEYNOTE-775 trial was launched to compare the combination of lenvatinib and pembrolizumab with physician's choice chemotherapy (doxorubicin or weekly paclitaxel).[25] A total of 827 patients with advanced or recurrent EC who had received at least 1 prior platinum-based regimen were randomly assigned in a 1:1 ratio to receive the experimental combination or chemotherapy. Patients were stratified according to MMR status. The study evaluated the efficacy of the 2 regimens using 2 coprimary endpoints, PFS and OS, with a hierarchical analysis for the MMRp and all-comers cohorts. The combination of pembrolizumab and lenvatinib was demonstrated to be statistically and clinically superior to chemotherapy in terms of PFS and OS. In the MMRp cohort, the mOS was 18.0 months with lenvatinib plus pembrolizumab vs 12.2 months with chemotherapy (hazard ratio [HR], 0.70; 95% CI, 0.58-0.83), and a mPFS of 6.7 months vs 3.8 months (HR, 0.60; 95% CI, 0.50-0.72). In the all-comer cohort, the mOS was 18.7 months with the experimental combination vs 11.9 months with chemotherapy (HR, 0.65; 95% CI, 0.55-0.77), and the mPFS was 7.3 months vs 3.8 months, respectively (HR, 0.56; 95% CI, 0.48-0.66). The main efficacy outcomes are summarized in Table 1. In an exploratory analysis, the combination of pembrolizumab and lenvatinib was also found to be effective in the MMRd subgroup. The confirmed ORR in this cohort was 41.5% (95% CI, 29.4-54.4), which is similar to the ORR with ICI monotherapies in a comparable patient population.

The most frequent AEs were hypertension (65.0%) with lenvatinib plus pembrolizumab and anemia (48.7%) with chemotherapy. Grade 3 or higher AEs occurred in 90.1% of patients receiving lenvatinib plus pembrolizumab and 73.7% of those receiving chemotherapy, with the most common being hypertension (39.2%) and neutropenia (26.0%), respectively. Patients receiving combination therapy also had a higher incidence of dose reduction (67.2% vs 12.6%), drug interruption (71.9% vs 28.4%), and discontinuation owing to AEs (31.5% vs 5.9%) compared with those receiving chemotherapy. Up to 25.4% of patients discontinued lenvatinib only, 12.1% discontinued pembrolizumab alone, and 5.9% discontinued both drugs; these rates are higher than the discontinuation rates of ICI monotherapies.[26,27]

Based on the KEYNOTE-775 trial's data, pembrolizumab and lenvatinib were approved by the FDA for patients with advanced EC who do not have MSI-H

Table 2. Main Clinical Trials Evaluating ICIs in Advanced or Recurrent EC in the Frontline Setting

Trial	Design	Drugs	N, population	ORR, % (95% CI)	mPFS, %	HR (95% CI)	mOS, % (95% CI)	HR (95% CI)
ENGOT-EN6-NSGO/ GOG-3031/ RUBY[39]	Phase 3, randomized	Carboplatin + paclitaxel + dostarlimab vs carboplatin + paclitaxel + placebo followed by dostarlimab/ placebo for up to 3 y	494, ITT	NA	24-mo PFS: 36.1 vs 18.1	0.64 (0.51-0.80), $P<.001$	24-mo OS: 71.3 vs 56.0	0.64 (0.46-0.87), $P=.0021$
			118, MMRd/ MSI-H	NA	24-mo PFS: 61.4 vs 15.7	0.28 (0.16-0.50), $P<.001$	24-mo OS: 83.3 vs 58.7	0.30 (0.13-0.70)
NRG-GY018[40]	Phase 3, randomized	Carboplatin + paclitaxel + pembrolizumab vs carboplatin + paclitaxel + placebo followed by pembrolizumab/placebo for up to 14 cycles	591, MMRp	NA	13.1 vs 8.7	0.54 (0.41-0.71), $P<.001$	NA	NA
			225, MMRd/ MSI-H	NA	NR vs 7.6	0.30 (0.19-0.48), $P<.001$	NA	NA
AtTEnd/EN GOT-EN7[41]	Phase 3, randomized	Carboplatin + paclitaxel + atezolizumab vs carboplatin + paclitaxel + placebo followed by atezolizumab/ placebo until PD	125, MMRd	82.4 (71.0-89.5) vs 75.7 (56.3-84.7)	NR vs 6.9	0.36 (0.23-0.57), $P=.0005$	NR vs 25.7	0.41 (0.22-0.76)
			549, all-comers	75.0 (65.5-77.2) vs 74.6 (62.4-78.6)	10.1 vs 8.9	0.74 (0.65-0.91), $P=.0219$	38.7 vs 30.2	0.82 (0.63-1.07), $P=.0483$
DUO-E/ GOG-3041/ ENGO T-EN10[42]	Phase 3, randomized	Carboplatin + paclitaxel + durvalumab + placebo followed by durvalumab/ placebo + olaparib/placebo	718, ITT (575 MMRp; 143 MMRd	NA	9.6 (control) vs 10.2 (durvalumab) vs 15.1 (durvalumab + olaparib)	Durvalumab vs control: HR 0.71 (0.57-0.89), $P=.003$ Durvalumab + olaparib vs control: HR 0.55 (0.43-0.69), $P<.0001$	25.9 (control) vs NR (durvalumab) vs NR (durvalumab + olaparib)	Durvalumab vs control: HR 0.77 (0.56-1.07), $P=.120$ Durvalumab + olaparib vs control: HR 0.59 (0.42-0.83), $P=.003$

EC, endometrial cancer; HR, hazard ratio; ICIs, immune checkpoint inhibitors; ITT, intention-to-treat population; MMRd, mismatch repair–deficient; MMRp, mismatch repair–proficient; mo, months; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NA, not available; NR, not reached; ORR, overall response rate; mOS, median overall survival; mPFS, median progression-free survival; PD, progression of disease.

or MMRd tumors, and by the EMA for patients with advanced EC, regardless of MMR status. Both approvals include patients with disease progression on or following platinum-based therapy.

Another antiangiogenic agent plus ICI combination that is worth mentioning is nivolumab plus cabozantinib. A phase 2 trial evaluated this approach in a cohort of heavily pretreated patients with EC, a majority of whom

had MSS tumors. Eligible patients were randomized in a 2:1 ratio to receive nivolumab plus cabozantinib (arm A; n=36) or nivolumab alone (arm B; n=18). Women with carcinosarcoma or prior ICI treatment received the combination treatment (arm C). The combination therapy significantly improved PFS, with an mPFS of 5.3 months (90% CI, 3.5-9.2) vs 1.9 months (90% CI, 1.6-3.4) in the monotherapy arm (HR, 0.59; 90% CI, 0.35-0.98; log-rank P=.09), meeting the prespecified statistical significance criteria. Interestingly, immunotherapy rechallenge with nivolumab plus cabozantinib (n=20, arm C) yielded an ORR in 25% of patients, whereas only 1 patient in the carcinosarcoma subgroup (n=10, arm C) achieved a durable partial response and 5 had stable disease.[28] These provocative data may pave the way to the possibility of retreating EC patients with immunotherapy, but the optimal selection of patients benefiting from rechallenge warrants further investigation.

Fascinating data come from a phase 2 single-arm trial analyzing the clinical activity of an atezolizumab/bevacizumab doublet in 57 patients with pretreated advanced EC (87% were MMRp). The ORR was 30% (95% CI, 18-43) in the whole population and 33% (95% CI, 20-48) in the MMRp subgroup. The median duration of response was 15 months (95% CI, 2.9-34). The rate of grade 3 AEs related to atezolizumab was 7% and the rate of those related to bevacizumab was 22%. The discontinuation rate was 16%.[29] Acknowledging the preliminary nature of these data and the limitations of cross-trial comparisons, it seemed that the combination of atezolizumab/bevacizumab exhibited efficacy outcomes comparable to those of pembrolizumab/lenvatinib, with better tolerability. Further research on this combination in larger controlled randomized trials is needed to confirm these results.

PARP Inhibition Plus ICI Combinations. Preclinical data support the synergistic antitumor activity for combinations of poly(ADP-ribose) polymerase inhibitors (PARPis) with anti–PD-1/PD-L1 agents, which is partially mediated by the activation of the stimulator of interferon genes pathway (STING pathway), regardless of homologous recombination repair (HRR) deficiency status in a disease-agnostic manner.[30] Several PARPi plus ICI combinations have already demonstrated preliminary signals of clinical activity in the pretreated recurrent or advanced EC population.

The combination of talazoparib (Talzenna, Pfizer) plus avelumab was evaluated in a single-arm phase 2 trial enrolling 35 previously treated patients with recurrent MSS EC. The ORR was 11.4% (95% CI, 3.2-26.7) and the PFS at 6 months was 22.9% (95% CI, 10.4-40.1). Interestingly, patients with HRR-altered tumors were more likely to derive clinical benefit compared with non–HRR-altered

tumors (P=.01). The most common grade 3/4 TRAEs were anemia, thrombocytopenia, and neutropenia.[31]

The phase 2 DOMEC trial evaluated a combination of durvalumab and olaparib (Lynparza, AstraZeneca) in a cohort of 50 women with pretreated EC. Overall, only 20% of patients had MMRd tumors. The ORR was 16% (95% CI, 8.3-28.5) and the 6-month PFS rate was 34% (95% CI, 23.1-50.0). The MMRd subgroup treated with combination therapy had a trend for higher mPFS, but no relevant differences were detected among the different molecular subgroups. Grade 3 TRAEs occurred in 16% of patients, predominantly as anemia.[32]

The clinical activity of niraparib (Zejula, GSK) with or without dostarlimab was evaluated in a nonrandomized, 2-cohort phase 2 pilot trial enrolling patients with pretreated recurrent EC. Niraparib monotherapy (cohort 1; n=25) and the combination of niraparib plus dostarlimab (cohort 2; n=22) both showed modest activity, with a clinical benefit rate at 16 weeks of 20% (95% CI, 9-39) and 31.8% (95% CI, 16-53), respectively. Overall, only 3 patients had MMRd tumors, and 1 patient had a *POLE* mutation (all of them treated with combination therapy). Biomarker exploratory analysis did not show a correlation between *PTEN* loss or HRR gene alterations and increased clinical benefit.[33]

Following preliminary efficacy data on the synergistic combination of an anti–PD-L1 agent with either a PARPi or an antiangiogenic agent, a triplet regimen was developed. An open-label, nonrandomized phase 2 trial assessed the triplet of atezolizumab/rucaparib (Rubraca, Clovis Oncology)/bevacizumab in a cohort of 30 patients with pretreated advanced EC. The ORR was 43.5% and the overall median event-free survival was 5.3 months (95% CI, 2.7-7.9). As expected, median event-free survival was longer in the MMRd patients (11.9 months). Grade 3/4 TRAEs occurred in 50% of patients.[34]

Further clinical data from large, randomized trials are required to confirm the benefit of adding a PARPi to ICIs vs single-agent strategies. Patient stratification based on molecular classifications will be crucial in future trial designs to optimize the efficacy and avoid unnecessary toxicities of these combination approaches.

Dual Immune Checkpoint Blockade
Dual immune checkpoint blockade is another therapeutic approach that has been investigated in advanced or recurrent EC to overcome resistance to single-agent anti–PD-1/PD-L1 therapy and improve efficacy outcomes by increasing T-cell activation and reversing T-cell exhaustion.

Recently, a single-center, randomized, open-label, phase 2 study compared durvalumab alone (arm 1) vs the combination of durvalumab plus the anti–CTLA-4 agent tremelimumab (arm 2) and reported modest ORRs

in both treatment arms: 10.8% (90% CI, 4.8-100) in arm 1 and 5.3% (90% CI, 1.4-100) in arm 2. This study did not meet the prespecified efficacy threshold. Of note, the population enrolled in this trial was predominantly MMRp, with only 9 patients having MMRd tumors.[35]

Additional early-phase clinical trials are evaluating the combination of nivolumab and the anti–CTLA-4 agent ipilimumab (Yervoy, Bristol Myers Squibb; NCT03508570, NCT02982486, and NCT05112601).

In addition, nivolumab has been evaluated in combination with an IDO1 inhibitor in the recently reported CA017-056 phase 2 trial. Patients with pretreated MSS/MMRp recurrent or persistent EC were randomized to receive either nivolumab alone (n=12) or nivolumab plus the IDO1 inhibitor BMS-986205. No responses were observed in the nivolumab monotherapy arm, whereas the combination approach elicited an ORR of 8.3% (90% CI, 0.9-100), with an acceptable safety profile.[36]

ICIs for Advanced or Recurrent Endometrial Cancer in the Frontline Setting

Platinum-based agents and paclitaxel have both been found to potentially modulate the immune tumor microenvironment, favoring synergy with ICIs.[37-39] Combining anti–PD-1/PD-L1 agents with carboplatin/paclitaxel has shown efficacy and a tolerable safety profile in advanced non–small cell lung cancer.[38] As discussed earlier, the efficacy of ICI monotherapy has been proven in EC after progression to platinum-based chemotherapy, mainly in the MMRd population. Notably, better efficacy was observed when patients were treated earlier in the disease course.[17,23] Recognizing the potential that immunotherapy can bring to frontline treatment, recent clinical trials have assessed the efficacy of PD-1/PD-L1 agents in combination with platinum-based chemotherapy for advanced or recurrent EC. Table 2 summarizes the main phase 3 trials exploring ICIs in combination with chemotherapy in the frontline setting.

MITO END-3 Trial

The MITO END-3 trial is an open-label, randomized, phase 2 study aiming to evaluate the efficacy of the anti–PD-L1 agent avelumab in combination with carboplatin/paclitaxel as first-line therapy for EC. This multicenter trial randomized 125 patients in a 1:1 ratio to receive avelumab at 10 mg/kg concurrently with carboplatin/paclitaxel followed by avelumab maintenance or carboplatin/paclitaxel followed by standard surveillance. In the avelumab arm, 41% of patients had MMRd/MSI-H tumors, and 50% in the standard arm had the same. In the intention-to-treat (ITT) population, the mPFS was 9.6 months (95% CI, 7.2-17.7) in the avelumab arm vs 9.9 months (95% CI, 6.7-12.1) in the standard group (HR, 0.78; 60% CI, 0.65-

0.93; P=.085). Conversely, avelumab showed significant clinical benefit among the dMMR/MSI-H population: the 12-month PFS rate was 60% (95% CI, 38-76) with avelumab vs 35% (95% CI, 18-52) with standard therapy, whereas the OS rate at 12 months was 87% (95% CI, 65-96) and 79% (95% CI, 59-90), respectively. Regarding the MMRp/MSS population, the PFS and OS rates were numerically inferior in the experimental arm compared with the standard arm. These outcomes should be interpreted with caution because the trial design was not powered to demonstrate statistical differences in the MMRp population. MITO END-3 was the first trial to report efficacy data of an ICI in combination with chemotherapy as frontline therapy for EC patients.

ENGOT-EN6-NSGO/GOG-3031/RUBY, Part 1

ENGOT-EN6-NSGO/GOG-3031/RUBY is a double-blind, randomized, placebo-controlled, multicenter phase 3 trial consisting of 2 parts. Part 1 aims to evaluate the addition of dostarlimab to carboplatin/paclitaxel in the frontline setting of EC (Table 2), whereas part 2 explores the role of niraparib plus dostarlimab as maintenance therapy in the frontline setting.[39]

Patients eligible for part 1 had either primary advanced International Federation of Gynecology and Obstetrics (FIGO) stage IIIA to IIIC1 with measurable disease as per RECIST 1.1, or primary advanced stage IIIC2 to IV, regardless of measurable disease. If systemic therapy or radiotherapy was completed at least 6 months prior, patients with recurrent disease could be enrolled. Patients were randomized in a 1:1 ratio to dostarlimab or placebo added to carboplatin/paclitaxel, followed by dostarlimab or placebo every 6 weeks for up to 3 years. Following a multiplicity control strategy, the coprimary endpoints for the study included the PFS assessed by the investigator among patients who had MMRd/MSI-H tumors and in the ITT population. Additionally, OS in the ITT population was evaluated.

Overall, 245 patients were randomized to dostarlimab and 249 to placebo. About 24% of patients had MMRd/MSI-H tumors. In the whole population, 47.8% had recurrent disease, whereas 33.6% and 18.6% had primary stage IV and III disease, respectively. The most common histologic subtype was endometrioid (54.7%), followed by serous (20.6%). In the MMRd/MSI-H population, with a median follow-up of 24.8 months (19.2-36.9), the 24-month PFS rate was 61.4% (95% CI, 46.3-73.4) with dostarlimab and 15.7% (95% CI, 7.2-27.0) with placebo (HR, 0.28; 95% CI, 0.16-0.50; P<.001). In the ITT population, with a median follow-up of 25.4 months (19.2-37.8), the 24-month PFS rate was 36.1% (95% CI, 29.3-42.9) and 18.1% (95% CI, 13.0-23.9), respectively (HR, 0.64; 95% CI, 0.51-0.80; P<.001). The

Table 3. Ongoing Clinical Trials Evaluating Anti–PD-1/PD-L1 in the Frontline Setting of Advanced or Recurrent EC

	ENGOT-EN6-NSGO/ GOG-3031/RUBY, part 2[45]	ENGOT-en9 /LEAP-001[46]	KEYNOTE-C93/ GOG-3064/ ENGOT-en15[47]	ENGOTen13/ GINECO/ DOMEN-ICA[48]
Identifier	NCT03981796	NCT03884101	NCT05173987	NCT05201547
Study design	Phase 3, randomized, placebo-controlled (2:1), double-blinded	Phase 3, randomized, open-label (1:1)	Phase 3, randomized, open-label (1:1)	Phase 3, randomized, open-label (1:1)
Experimental arm	Dostarlimab 500 mg q3w + paclitaxel/ carboplatin for 6 cycles followed by dostarlimab 1000 mg q6w and niraparib for up to 3 years or PD	Pembrolizumab 200 mg q3w for 35 cycles + lenvatinib 20 mg qd	Pembrolizumab 400 mg q6w for 18 cycles (2 y)	Dostarlimab 500 mg q3w for 4 cycles followed by dostarlimab 1000 mg q6w for up to 24 mo or PD
Comparator	Placebo + paclitaxel/ carboplatin for 6 cycles followed by placebo	Paclitaxel/carboplatin	Paclitaxel/carboplatin; crossover to pembrolizumab is allowed after PD by BICR	Paclitaxel/carboplatin; cross-over to dostarlimab is allowed after PD
Estimated sample size	270	875	350	260
Population	Primary stage III/IV or recurrent disease	Stage III/IV with measurable or radiographically apparent disease	Confirmed MMRd, stage III/IV, or recurrent disease with radiographically evaluable disease	MMRd-MSI, stage III/IV, or recurrent disease
Carcinosarcoma permitted	Yes	No	Yes	Unkown
Previous neo/adjuvant therapy permitted	Yes	Yes	Yes (after protocol amendment)	Yes
Stratification factors	MMR/MSI status, prior pelvic RT, disease status (stage III, IV, or recurrent)	MMR status, MMRp; will be further stratified by ECOG, measurable disease, and prior adjuvant therapy	Disease status and histology	Prior adjuvant chemotherapy, prior adjuvant radiotherapy, disease status
Primary endpoint	PFS, all-comers	PFS and OS (dual)	PFS and OS (dual)	PFS
Expected data release	To be determined	To be determined	Still recruiting	Still recruiting

BICR, blinded independent central review; bid, twice a day; ECOG, Eastern Cooperative Oncology Group performance status; MMRd, mismatch repair–deficient; MMRp, mismatch repair–proficient; MSI, microsatellite instability; MSS, microsatellite stable; OS, overall survival; PD, progression of disease; PFS, progression-free survival; RT, radiation therapy; y, years.

24-month OS rate in the ITT population was 71.3% (95% CI, 64.5-71.1) with dostarlimab, and 56.0% (95% CI, 48.9-62.5) with placebo (HR, 0.64; 95% CI, 0.46-0.87; P=.0021).

Upon the prespecified subgroup analysis, the addition of dostarlimab also demonstrated a PFS benefit in the MMRp/MSS population (HR, 0.76; 95% CI, 0.59-0.98). More granularity of the MMRp/MSS population characteristics could help us hypothesize who would benefit the most or least from immunochemotherapy.

Despite the low maturity of OS data (33% at data cut-off), there was a trend in favor of dostarlimab in both

subpopulations, MMRd/MSI-H and MMRp/MSS.

The dostarlimab safety profile did not differ substantially when combined with carboplatin/paclitaxel compared with that described previously with dostarlimab monotherapy. Grade 3 or more AEs were higher with dostarlimab (70.5%) than placebo (59.8%). The most common immune-related AEs were hypothyroidism (11.2%), rash (6.6%), and arthralgia (5.8%). Seventeen percent of patients discontinued dostarlimab, and 9.3% discontinued placebo owing to AEs of any grade.[39]

In conclusion, dostarlimab added to carboplatin/ paclitaxel improved PFS with tolerable safety profile in

advanced or recurrent EC, especially in the MMRd/MSI-H population, setting a new standard of care for this group of patients. Longer follow-up is needed to assess the definitive effect of this new regimen on OS.

NRG-GY018

NRG-GY018 is a phase 3 randomized, double-blind, placebo-controlled study designed to assess the benefit of adding pembrolizumab to paclitaxel/carboplatin in the frontline setting for patients with recurrent or metastatic EC (Table 2).[40] The trial enrolled patients with newly diagnosed stage III or IVA disease with measurable disease or stage IVB or recurrent EC with or without measurable disease. All histologic subtypes, except carcinosarcoma, were included. Additionally, prior adjuvant chemotherapy was allowed if the chemotherapy-free interval was at least 12 months.

A total of 816 patients were randomly assigned in a 1:1 ratio to receive pembrolizumab or placebo plus carboplatin/paclitaxel followed by pembrolizumab or placebo every 6 weeks for up to 14 cycles. Patients were stratified into 2 cohorts according to MMR status. PFS assessed by investigators was the primary endpoint in both cohorts (MMRd and MMRp). All endpoints were evaluated independently in MMRd and MMRp populations.

Overall, 225 patients were included in the MMRd cohort and 591 in the MMRp cohort. Endometrioid carcinoma was the most common histologic subtype in both cohorts. Approximately 6% of MMRd patients had received adjuvant chemotherapy, compared with 25.3% of MMRp patients. In the MMRd cohort (median follow-up of 12 months), the 12-month PFS rate was 74% with pembrolizumab and 38% with placebo (HR, 0.30; 95% CI, 0.19-0.48; $P<.001$). In the MMRp cohort (median follow-up of 7.9 months), the mPFS was 13.1 months with pembrolizumab and 8.7 months with placebo (HR, 0.54; 95% CI, 0.41-0.71; $P<.001$). To date, no OS data have been reported. The safety profile of pembrolizumab plus carboplatin/paclitaxel exhibited consistency with the known safety profiles of the individual drugs. The incidence of grade 3 or more AEs was lower with pembrolizumab in both cohorts.[40]

In brief, adding pembrolizumab to carboplatin/paclitaxel significantly improved PFS in both cohorts. This supports its use as a first-line therapy in the MMRd population. Longer follow-up for the MMRp subgroup is required to confirm the PFS benefits.

AtTEnd/ENGOT-EN7

AtTEnd/ENGOT-EN7 is a phase 3, double-blind, randomized placebo-controlled trial that evaluated the addition of atezolizumab to standard frontline carboplatin/paclitaxel for 6 cycles, followed by maintenance therapy with atezolizumab or placebo until disease progression or unacceptable toxicity, in women with advanced (FIGO stage III-IV) or recurrent EC (Table 2).[41] Both PFS and OS were coprimary endpoints of the study. PFS was evaluated in the MMRd subgroup and in all-comers and OS was evaluated in the entire population, following a hierarchical order. A total of 185 patients were randomized to the placebo arm and 356 to the atezolizumab arm. In an interim analysis presented at the 2023 European Society for Medical Oncology (ESMO) Congress, with a median follow-up of 26.2 months, atezolizumab positively impacted PFS in the MMRd subgroup, with the mPFS not reached (95% CI, 12.3 months to not reached) in the atezolizumab arm vs 6.9 (95% CI, 6.2-9.0) months in the placebo arm (HR, 0.36; 95% CI, 0.23-0.57; $P=.0005$). In the all-comer population, the mPFS was significantly higher in those patients treated with atezolizumab (10.1 vs 8.9 months; HR, 0.74; 95% CI, 0.61-0.91; $P=.0219$). The positive effect of atezolizumab on PFS in all-comers was consistent in most of the subgroups analyzed. Beyond MMRd status, a trend for a greater benefit is observed in the White population and in PD-L1–positive tumors. In the coprimary endpoint of OS in all-comers, a trend for improvement for atezolizumab was observed (median OS, 38.7 vs 30.2 months; HR, 0.82; 95% CI, 0.63-1.07; $P=.0483$), despite the fact that 24% of patients in the placebo arm received subsequent immunotherapy. Data for OS were not mature at this interim analysis (data maturity, 43%), and the trial will continue as planned to complete OS assessment. Regarding toxicity, the safety profile of atezolizumab was manageable and consistent with expected toxicities.

DUO-E/GOG-3041/ENGOT-EN10

The DUO-E/GOG-3041/ENGOT-EN10 is a phase 3, randomized, placebo-controlled, 3-arm trial that explores the addition of durvalumab to first-line carboplatin/paclitaxel for 6 cycles, followed by durvalumab with or without olaparib, as maintenance therapy (until disease progression or unacceptable toxicity), in women with advanced (FIGO stage III-IV) or recurrent EC (Table 2).[42] The primary endpoint of the study was PFS in the ITT population as assessed by the investigator in the durvalumab arms vs the control arm, and using a multiple testing procedure with an equally split 5% alpha error in the durvalumab/olaparib arm vs the control arm. If PFS was statistically significant in either comparison, the alpha error was recycled to the corresponding OS (secondary endpoint) comparison in the ITT population. Overall, 718 patients were randomized in a 1:1:1 ratio to the following arms of treatment: (1) control arm: carboplatin/paclitaxel plus placebo followed by placebo for both durvalumab and olaparib; (2) durvalumab arm: carboplatin/paclitaxel plus durvalumab followed

by durvalumab along with a placebo for olaparib; and (3) durvalumab + olaparib arm: carboplatin/paclitaxel plus durvalumab followed by durvalumab plus olaparib. Both the primary analysis of PFS and the first preplanned interim analysis of OS were recently presented at the 2023 ESMO Congress. In the ITT population, with a 61.0% data maturity, DUO-E showed a statistically significant improvement in PFS for the durvalumab (mPFS, 10.2 vs 9.6 months; HR, 0.71; 95% CI, 0.57-0.89; P=.003) and the durvalumab/olaparib arms (mPFS, 15.1 vs 9.6 months; HR, 0.55; 95% CI, 0.43-0.69; P<.0001) compared with the control arm. In a predefined exploratory analysis, the PFS benefit with durvalumab was greatest in the MMRd subgroup (20% of the population), with no relevant differences between the durvalumab and the durvalumab/olaparib arms (12-month PFS, 70% vs 67.9%). Besides, in the MMRp subgroup (80% of the population), the addition of olaparib to durvalumab seemed to enhance the PFS benefit compared with durvalumab alone (12-month PFS, 59.4% vs 44.4%). The interim OS data showed a positive trend in both experimental arms, with an overall data maturity of 27.7%. Regarding toxicities, the safety profiles across treatment arms were generally consistent with the known profiles of each agent.

Ongoing Clinical Trials Exploring Immune Checkpoint Inhibitors in the Frontline Setting

Various phase 3 trials are further evaluating the role of ICIs, alone or in combination, in the frontline setting (Table 3). Part 2 of the ENGOT-EN6-NSGO/GOG-3031/RUBY trial is evaluating dostarlimab plus chemotherapy followed by dostarlimab plus niraparib maintenance, and its results are awaited.[43]

In addition, there is rising interest in completely omitting chemotherapy from the frontline scenario in the dMMR EC population.[44-46] The DOMENICA and KEYNOTE-C93 trials were designed to address the pivotal question of whether a chemotherapy-free regimen is efficacious as first-line therapy. However, the current data showing that pembrolizumab or dostarlimab added to paclitaxel/carboplatin are superior to chemotherapy alone may undermine these 2 trials because the comparator arm could now be deemed suboptimal.

Conclusions

ICIs are currently considered the treatment of choice for advanced or recurrent EC, either as monotherapy or in combination with lenvatinib after platinum therapy has failed, or with paclitaxel/carboplatin following the compelling efficacy data shown in the 2 large phase 3 trials, RUBY and NRG-018. The role of the addition of a PARPi

to frontline therapy will be elucidated by the release of data from 2 phase 3 clinical trials, DUO-E and RUBY part 2. The option of a chemotherapy-free regimen will rely on the robustness of the outcomes of upcoming trials that include LEAP, DOMENICA, and KEYNOTE-C93.

The future clinical development of immunotherapy in EC may largely depend on an optimal patient stratification based on molecular biomarkers that optimizes its efficacy and avoids unnecessary toxicities. A thorough analysis of predictive biomarkers is essential to understand immune escape mechanisms and develop novel therapeutic targets.

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