Therapeutic Advances in Medical Oncology Review

Immunotherapy as a treatment strategy in advanced stage and recurrent endometrial cancer: review of current phase III immunotherapy clinical trials

Ther Adv Med Oncol
2021, Vol. 13: 1–9
DOI: 10.1177/17588359211001199

Ramez N. Eskander and Matthew A. Powell

***Abstract*:** The treatment of advanced stage, metastatic or recurrent endometrial cancer remains a clinically difficult scenario. Although combination carboplatin and paclitaxel is an effective standard-of-care regimen, alternate strategies have shown promise, particularly in biomarker select populations. In an effort to improve oncologic outcomes, investigators are exploring novel immunotherapy combinations. In this review, we discuss the clinical rationale and design of current phase III immuno-oncology clinical trials in patients with advanced stage or recurrent endometrial cancer.

Keywords: antiangiogenic therapy, chemotherapy, combination therapy, endometrial cancer, immune checkpoint inhibition, immunotherapy, tumor mutational burden

Received: 2 February 2021; revised manuscript accepted: 15 February 2021.

Introduction

Endometrial cancer (EC) remains the only gynecologic malignancy with a rising incidence and mortality. In 2021, it is anticipated that 66,570 new cases of uterine cancer will be diagnosed in the United States, with approximately 12,940 deaths.[1] Despite excellent outcomes in patients with early-stage disease, those with metastatic or recurrent EC have limited options, representing an opportunity for therapeutic drug development.

To date, combination carboplatin and paclitaxel remains the preferred chemotherapy regimen in the front-line treatment of EC. The Gynecologic Oncology Group (GOG) 209 compared the combination regimen of paclitaxel and carboplatin to paclitaxel, doxorubicin, and cisplatin (TAP) in patients with stage 3, stage 4 or recurrent EC. The study enrolled over 1300 patients and demonstrated less toxicity and a noninferior progression-free survival (PFS) and overall survival (OS) with the doublet regimen, rendering paclitaxel and carboplatin a suitable backbone for future clinical trials.[2]

Second-line chemotherapy options for EC have been historically less effective, although recent advances show promise. Given the frequency of phosphoinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) aberrations in EC as well as the established importance of estrogen signaling in type I EC, Slomovitz and colleagues examined the combination of letrozole and everolimus in a cohort of 38 patients with progressive or recurrent EC who had received up to two prior chemotherapeutic regimens.[3] A promising clinical benefit rate of 40% was identified with a 32% objective response rate (ORR). Importantly, patients with CTNNB1 mutations appeared to respond particularly well to the drug combination in exploratory translational studies.[3]

An alternate biomarker-driven approach was examined in a prospective phase II trial examining trastuzumab in combination with carboplatin and paclitaxel in HER2/neu overexpressing uterine serous cancer.[4] A total of 61 patients with primary stage III or IV or recurrent HER2/neu-positive disease were enrolled on the trial. Median PFS was 8.0 months in the control arm

Correspondence to:
Ramez N. Eskander
Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, University of California San Diego Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, USA
reskander@health.ucsd.edu

Matthew A. Powell
Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Washington University School of Medicine, St. Louis, MO, USA

versus 12.6 months with addition of the anti-HER2 agent [$p = 0.005$; hazard ratio (HR) 0.44; 90% confidence interval (CI), 0.26–0.76]. The results of these two trials led to the National Comprehensive Cancer Network compendium listing of both letrozole plus everolimus as well as the trastuzumab-containing regimen in the treatment of EC. More recently, Fader *et al.*[5] reported on OS, showing a striking benefit in patients with stage 3 or 4 disease treated with trastuzumab in combination with chemotherapy [24.4 months (control) *versus* not reached (experimental), $p = 0.041$, HR = 0.49, 90% CI 0.25–0.97].

Perhaps the greatest enthusiasm in the treatment of patients with EC stemmed from the identification of immunotherapy as an effective treatment strategy. Catalyzed by the clinical observation of one dramatic responder in two separate colorectal cancer clinical trials, the efficacy of immunotherapy, particularly in mismatch-repair-deficient (dMMR) solid tumors, was described in patients with colon cancer as well as a mixed dMMR solid tumor population.[6,7] These findings led to US Food and Drug Administration (FDA) accelerated approval of the anti-PD-1 antibody pembrolizumab (MK-3475, Keytruda®) in May 2017 as monotherapy in patients with dMMR or microsatellite instability-high (MSI-H) solid tumors, whose disease has progressed following prior therapy, and who have no satisfactory alternative treatment options. This achievement represented the first disease-site agnostic and histology independent cancer drug approval, in which treatment is based on a shared tumor biomarker rather than on the anatomic site of origin.

The phase II Keynote-158 study ultimately included 27 different tumor types, with endometrial, gastric, cholangiocarcinoma, and pancreatic cancers being the most common.[8] In the entire population, the ORR was 34.3% (95% CI, 28.3–40.8%), the median PFS was 4.1 months (95% CI, 2.4–4.9 months) and the median OS was 23.5 months (95% CI, 13.5 months to not reached). Within the EC cohort ($n = 49$), the ORR was 57.1% (95% CI 42.2–71.2) and, importantly, the median OS and median duration of response were not reached.[8]

Despite the above findings, and dramatic progress in the dMMR/MSI-H populations, response to single-agent checkpoint inhibition in mismatch-repair-proficient (pMMR) or microsatellite-stable recurrent EC has been disappointing. As detailed in several single-agent trials, response rates have range from 6 to 13%, with short-lived PFS gains.[9–12] In an effort to improve response rates, and oncologic outcomes in this patient population, clinical trialists are examining novel combinatorial approaches in conjunction with immune checkpoint inhibition. In this article, we will discuss the current phase III clinical trial landscape as it relates to immunotherapeutic regimens in the treatment of EC, highlighting the clinical rationale while discussing future drug development opportunities.

Chemotherapy and immunotherapy

In order to improve on the number of patients responding to checkpoint inhibitors, investigators are assessing combination regimens involving cytotoxic chemotherapy and PD-1/PD-L1 inhibition. Although no randomized controlled trials comparing single-agent checkpoint inhibition to combination regimens with cytotoxic agents have reported in patients with gynecologic malignancies, preclinical data as well as emerging clinical data support such an approach.[13,14]

Several preclinical studies have suggested that cytotoxic chemotherapy may result in robust immune stimulation[14] (Table 1). Platinum agents, including oxaliplatin, have been shown to result in immunogenic cell death (ICD), producing a favorable milieu for immune activation within tumor tissues.[15] Furthermore, taxanes, including docetaxel and paclitaxel, are known to modulate the antitumor immune response. As an example, concurrent paclitaxel therapy was shown to significantly enhance radiation-induced ICD in breast cancer cell lines.[16] The antitumor effects of cytotoxic chemotherapy may additionally be immunologic, with a reduction in regulatory T-cell activity and an enhanced presentation of tumor cell-specific antigens.[14,17,18] Cytotoxic agents also appear to directly influence immune checkpoint expression.[19,20] Therefore, combining chemotherapy and immunotherapy may lead to enhanced antitumor effects.

Additional data supporting the investigation of a combinatorial approach comes from the lung, head and neck, as well as the breast cancer arena. CheckMate 012 was conducted to explore the safety and efficacy of nivolumab in combination with current standard therapies in first-line advanced non-small cell lung cancer (NSCLC).[21]

Table 1. Rationale for combinatorial approaches in the endometrial cancer space in an effort to expand checkpoint inhibition beyond biomarker select populations.

Combination	Rationale
Immunotherapy + chemotherapy	Immune cell stimulation
	Immunogenic cell death
	Enhanced presentation of tumor-specific antigens
	Increased T-cell activation by DCs
Immunotherapy + antiangiogenic Therapy	Reduction in T_{reg} activity
	Reversal of immunosuppressive effects of VEGF
	Improved T-cell trafficking and infiltration of $CD8^+$ T-cells and macrophages into the tumor bed
	Increased immune cell recruitment
Immunotherapy + PARPi	Increased TILs
	Enhance DNA damage, with increased $CD8^+$ T-cells
	Potential synergy with PARPi

DC, Dendritic Cells; PARPi, poly (ADP-ribose) polymerase inhibitor; TIL, Tumor Infiltrating Lymphocytes; T_{reg}, regulatory T-cell; VEGF, vascular endothelial growth factor.

The paclitaxel + carboplatin + nivolumab regimen was associated with a favorable toxicity profile, and median OS was not reached during follow-up (range 8.8–30.1+ months).[21] The most common toxicities reported for the combination were those anticipated with platinum doublet therapy alone.[21]

In the phase II cohort of the open-label Keynote-021 study, researchers enrolled a total of 123 patients with stage 3B/4 chemotherapy-naïve, nonsquamous, NSCLC, to receive four cycles of carboplatin and pemetrexed, with or without 24 months of treatment with pembrolizumab.[22] Patients receiving pembrolizumab + chemotherapy exhibited a significantly greater ORR (55% *versus* 29%, $p = 0.0016$) and an improved PFS (13 *versus* 8.9 months; HR 0.53; 95% CI 0.31–0.91). Perhaps most strikingly, the incidence of potentially immune-mediated adverse events in the pembrolizumab + chemotherapy group of the as-treated population (22%), was similar to that seen with pembrolizumab monotherapy in Keynote-010 (20% in the 2 mg/kg cohort; 19% in the 10 mg/kg cohort).

Lastly, in Keynote 189, a double-blind, randomized (2:1) phase III trial, 616 patients with NSCLC were randomized to receive platinum chemotherapy and pemetrexed with pembrolizumab or placebo and up to 2 years of pemetrexed maintenance with pembrolizumab or placebo.[23] At a median follow-up of 10.5 months, the ORR (47.6%, 95% CI, 42.6–52.5 *versus* 18.9% 95% CI, 13.8–25.0; $p < 0.001$), PFS (HR 0.52; 95% CI, 0.43–0.64; $p < 0.001$) and OS (HR 0.49; 95% CI, 0.38–0.64; $p < 0.001$) favored the pembrolizumab arm.[23]

There are currently four prospective, phase III clinical trials examining the impact of the addition of an immune checkpoint inhibitor to standard 3-weekly carboplatin + paclitaxel in patients with advanced stage and recurrent EC (Table 2). NRG GY018 (ClinicalTrials.gov identifier: NCT03914612), was designed to specifically evaluate the therapeutic impact of pembrolizumab, when given in combination with chemotherapy in both pMMR and dMMR cohorts in the front-line, adjuvant setting, or in patients who completed adjuvant therapy ⩾12 months prior to study entry. Enrolled patients are required to have central MMR immunohistochemistry (IHC) assessment prior to randomization, which will also permit correlation of local and central testing results. Eligibility requirements include measurable stage 3 or 4A disease as well as

Table 2. Active phase III combination immunotherapy trials in patients with advanced stage and recurrent endometrial cancer.

Study	Drug regimen	Anticipated accrual	Study endpoint
NRG GY018 (NCT03914612)	Carboplatin + paclitaxel + placebo *versus* Carboplatin + paclitaxel + pembrolizumab	*N* = 590 (pMMR) *N* = 220 (dMMR)	Investigator-assessed PFS
RUBY (NCT03981796)	Carboplatin + paclitaxel + placebo *versus* Carboplatin + paclitaxel + dostarlimab	*N* = 470	Investigator-assessed PFS
AtTEnd (NCT03603184)	Carboplatin + paclitaxel + placebo *versus* Carboplatin + paclitaxel + atezolizumab	*N* = 550	Investigator-assessed PFS and OS
Keynote 775 (NCT03517449)	Pembrolizumab + lenvatinib *versus* either doxorubicin or paclitaxel (physician choice)	*N* = 770	BICR-assessed PFS
ENGOT-EN9/LEAP-001 (NCT03884101)	Pembrolizumab + lenvatinib *versus* carboplatin + paclitaxel	*N* = 720	BICR-assessed PFS
DUO-E (NCT04269200)	Carboplatin + paclitaxel + placebo *versus* Carboplatin + paclitaxel + durvalumab *versus* Carboplatin + paclitaxel + durvalumab + olaparib	*N* = 699	Investigator-assessed PFS

BICR, blinded independent central review; dMMR, mismatch repair deficient; NCT, ClinicalTrials.gov identifier; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient.

stage 4B or recurrent disease, irrespective of the presence of a measurable lesion.

In an analogous manner, the RUBY trial (ClinicalTrials.gov identifier: NCT03981796) is randomizing patients with advanced stage or recurrent EC to a carboplatin + paclitaxel backbone, with or without dostarlimab (IgG4 anti-PD-1). Although similar in design, the RUBY study permits enrollment of patients with carcinosarcoma histology and does not mandate a minimum number of dMMR EC patients.

The AtTEnd trial (ClinicalTrials.gov identifier: NCT03603184) was designed to determine if the addition of atezolizumab (IgG1 anti PD-L1) to carboplatin and paclitaxel, and then continued as maintenance will translate into improved cancer outcomes when compared to placebo in patients with advanced stage or recurrent EC and measurable disease. It is anticipated that a total of 550 patients will be enrolled on study, with coprimary endpoints of OS and PFS.

Lastly, DUO-E (ClinicalTrials.gov identifier: NCT04269200), the most recently activated of the above clinical trials, is a three-arm study that expands the therapeutic question by adding olaparib, an oral poly (ADP-ribose) polymerase inhibitor (PARPi), to immunotherapy in the maintenance setting (Table 2).There is mounting evidence to support the rationale of PARPi in combination with immunotherapy. The accumulation of DNA errors in homologous recombination-deficient tumors, which appears to be prevalent in EC, may result in somatic mutations and neoantigen production triggering an immune response.[24,25] In fact, BRCA-mutated tumors have been found to have an increased tumor mutation burden, $CD3^+$ and $CD8^+$ immune cell infiltration, and increased expression of PD-L1 and PD-1 in the intraepithelial and peritumoral immune cell compartment compared to non-BRCA-mutated tumors.[26]

Antiangiogenic therapy and immunotherapy

In an effort to expand therapeutic options, cooperative group studies have explored antiangiogenic therapy with bevacizumab in patients with advanced stage or recurrent EC. A single-arm phase II study conducted by the GOG (GOG 229-E), examined bevacizumab at a dose of 15 mg/kg given intravenously every 3 weeks in patients with persistent or recurrent EC and ⩽2 prior lines of chemotherapy.[27] A total of 56 patients were enrolled, and although the response rate was modest (13.5%), a promising 6-month PFS rate of 40.4% was identified, with median PFS and OS of 4.2 and 10.5 months, respectively. Importantly, no gastrointestinal fistulae or perforations were reported on study (55.8% of patients

on GOG 229-E received prior radiation therapy).

There results prompted further investigation of antiangiogenic therapy in this disease setting. The therapeutic benefit of bevacizumab in the front-line treatment of advanced stage, metastatic, or recurrent EC was examined in the phase II GOG 86P study.[28] This three-arm study randomized 349 patients to either: (1) carboplatin (C) + paclitaxel (P) + bevacizumab *versus* (2) CP + temsirolimus *versus* (3) C + ixabepilone + bevacizumab. The CP + bevacizumab triplet regimen compared favorably to the other treatment arms, with a 59.5% ORR (24.7% with complete response). In addition, when compared to a matched group from the GOG protocol 209 (CP arm), the triplet regimen of CP + bevacizumab showed a significant improvement in OS (34 *versus* 22.7 months; $p < 0.039$).[28] Grade $\geqslant 3$ adverse events (AEs) occurring in $>5\%$ of patients on the CP + bevacizumab regimen were limited to hypertension and proteinuria. Furthermore, an Italian study presented at the 2015 American Society of Clinical Oncology annual meeting reported the triplet regimen of CP + bevacizumab was superior to CP alone in patients with recurrent EC; ORR 71.7 *versus* 54.3 %, median PFS 13 *versus* 8.7 months, median OS 23.5 *versus* 18 months, respectively.[29]

There is a strong scientific and therapeutic rationale for combining immune checkpoint inhibitors and antiangiogenic therapy (Table 1). Completion and presentation of results from both the IMpower150 (NSCLC) and IMmotion151 (renal cancer) studies suggest added therapeutic efficacy with the addition of atezolizumab (anti-PD-L1) to a bevacizumab-containing regimen with acceptable toxicity.[30,31] Furthermore, results of the IMbrave150 trial (ClinicalTrials.gov identifier: NCT03434379), results in US FDA approval of atezolizumab and bevacizumab in patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy. The translational and mechanistic rationale of this approach originally stemmed from data in the melanoma and renal cell cancer arena. In an early study examining the combination of ipilimumab (anti-CTLA-4) and bevacizumab in patients with metastatic melanoma, Hodi *et al.*[32] reported that on treatment biopsies demonstrated increased $CD8^+$ and macrophage cell infiltration in tumor beds. Additionally, extensive morphological changes were identified in $CD31^+$ endothelial cells, with widespread immune cell infiltration on the combination regimen.

Additionally, Wallin *et al.*[33] detailed, in a cohort of 10 subjects with metastatic renal cell carcinoma treated on GP28328, that combination atezolizumab and bevacizumab resulted in increased intratumoral $CD8^+$ T-cells, with a related increase in intratumoral MHC-1, natural killer cells, type 1 helper T-cells, T-effector markers and chemokines (CX3Cl1; fractalkine). These synergistic effects are hypothesized to stem from the proinflammatory impact of vascular endothelial growth factor (VEGF) blockade, as well as hypoxia in the tumor microenvironment. Aside from its direct antiangiogenic effects, bevacizumab may result in more robust antitumor immunity by inhibiting VEGF-related regulatory T-cell function while promoting immune cell trafficking and T-cell priming/activation. Thus, the combination regimen may enhance the immunogenic response in patients with advanced stage or recurrent EC. Additionally, no concerning safety signals have emerged across clinical trials examining this therapeutic drug combination in conjunction with cytotoxic chemotherapy.

Although no phase III studies have specifically examined bevacizumab in combination with immunotherapy in the EC space, alternate multitargeted antiangiogenic tyrosine kinase inhibitors have shown significant promise. Lenvatinib is an oral multikinase inhibitor that targets VEGF receptor-1–3, fibroblast growth factor receptor-1–4, platelet-derived growth factor-α, and the oncogenes RET and KIT.[34] Early phase II clinical trials of lenvatinib, as monotherapy, in patients with recurrent EC showed a response rate of 14%, with a median PFS of 5.4 months (95% CI 8.8–21.4).[35]

In an effort to augment response, lenvatinib was combined with pembrolizumab in a phase II, open-label, single-arm, multicenter clinical trial (study 111/Keynote 146).[36] A total of 53 enrolled patients were included in the analysis, with the primary endpoint defined as the proportion of patients with an objective response (complete or partial response) at the week-24 tumor assessment as assessed by investigators according to the immune-related Response Evaluation Criteria In Solid Tumors. Eligible patients were aged 18 years or older and had metastatic EC (unselected for microsatellite instability or PD-L1 expression),

had a good performance status, and no more than two previous systemic therapies.[36] The ORR was 39.6% ($n = 21$; 95% CI 26·5–54·0), although serious treatment-related AEs occurred in 16 (30%) patients, and 1 treatment-related death was reported (intracranial hemorrhage).[36] The most frequently reported any-grade treatment-related AEs were hypertension (58%), fatigue (55%), diarrhea (51%), and hypothyroidism (47%). The most common grade 3 treatment-related AEs were hypertension (34%) and diarrhea (8%).

At the 2019 European Society of Medical Oncology meeting, Makker *et al.*[37] presented updated outcomes data on a total of 108 EC patients treated with the combination regimen. In the cohort of patients who were not MSI-H or dMMR ($n = 94$), the ORR was 38.9% (7.4% complete response and 31.5% partial response; 95% CI 29.7–48.7). Strikingly, although nearly half of the enrolled patients had received two or more prior treatment regimens, the median duration of response was 21.2 months (7.6 to not reached).[37] Once again, however, toxicity remained an issue with treatment-related AEs occurring in 105 (97%) of patients (90% ⩽ grade 3, 7% ⩾ grade 4). Treatment-related AEs led to study-drug interruption of one or both drugs in 78 (72%) patients and resulted in dose reductions of lenvatinib in 70 (65%) patients on trial; 20 (19%) patients discontinued one or both drugs due to a treatment-related AE. Analogous to the earlier study, the most common ⩾grade 3 AEs were hypertension (32%), fatigue (8%), and diarrhea (7%).

Despite issues with tolerability, and the frequent need for dose interruption or dose reduction, these clinical findings reflected remarkable progress when compared to historical controls in the EC space. On September 17, 2019, the US FDA granted accelerated approval to the combination of pembrolizumab plus lenvatinib for the treatment of patients with advanced EC that is not MSI-H or dMMR and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation. This approval was conducted under Project Orbis, and allowed simultaneous review and approval in the United States, Australia and Canada.

Subsequently, Keynote 775 was developed (ClinicalTrials.gov identifier: NCT03517449) (Table 2). This parallel, open-label, multicenter phase III study randomized patients with recurrent EC, and at least one prior platinum-based regimen, to receive either pembrolizumab and lenvatinib or physician's choice chemotherapy (doxorubicin or paclitaxel), with a total target accrual of 780 patients. The coprimary endpoints of this trial are PFS (determined by blinded independent central review) and OS, with a recent press release in December 2020, indicating that the study met its dual primary endpoints, as well as a key secondary endpoint of ORR.

Furthermore, the ENGOT-EN9/LEAP-001 study (ClinicalTrials.gov identifier: NCT03884101) is a phase III, randomized, open-label, active-controlled trial comparing combination therapy with pembrolizumab and lenvatinib to carboplatin and paclitaxel in patients with newly diagnosed stage III–IV or recurrent EC (Table 2).[38] Approximately 720 patients not previously treated with systemic chemotherapy (except as part of a chemoradiation regimen), antiangiogenic agents, PD-1 or PD-L1 inhibitors, or other T-cell receptor-targeted agents will be randomized 1:1 to each arm. Patients will be stratified by pMMR *versus* dMMR, and pMMR patients will be further stratified by Eastern Cooperative Oncology Group performance status (0 *versus* 1), measurable disease (yes *versus* no), and prior chemoradiation (yes *versus* no). This trial may reflect a paradigm shift in EC therapeutics, as the findings may lead to the replacement of cytotoxic chemotherapy in the front-line setting.

Conclusions

While identification of effective treatment strategies in the EC arena has been historically difficult, tremendous gains have been realized with the incorporation of immune checkpoint inhibitors. To date, the greatest efficacy has been seen in the dMMR or MSI-H populations, with the combination regimen of lenvatinib and pembrolizumab showing synergistic effects in pMMR cohorts.

Translational studies accompanying contemporary trials will be important in helping inform mechanisms of resistance and alternate treatment opportunities. As detailed in the phase II PHAEDRA trial, analysis of dMMR tumors that failed to respond to checkpoint inhibition revealed mutations of JAK1 or B2M, possibly reflecting biallelic inactivation of these genes, which have been associated with resistance.[12] In parallel, trials examining options in patients who have progressed after prior immune checkpoint inhibition, particularly in the dMMR population, will be critical. Recently, Leureux and colleagues reported

on the combination of cabozantinib plus nivolumab at the 2020 American Society of Clinical Oncology virtual meeting.[39] Although the study size was small ($n=76$), an exploratory cohort of post-immune checkpoint inhibitor progressors was included, with three MSI-H patients experiencing a response after prior progression on single-agent nivolumab.

We eagerly await the results of the discussed phase III clinical trials to determine whether alternate drug combinations hold promise. It will also be important to explore drug sequencing as additional treatment options become available. Certainly, the magnitude of benefit with the various combinations will inform treatment decisions as we attempt to weigh oncologic gains against treatment-related side effects.

Conflict of interest statement

Dr. Eskander has received consulting and honoraria fees from Genentech, AstraZeneca Oncology, Clovis Oncology, Pfizer and Merck. Dr. Powell has received consulting fees from Merck, Eisai, AstraZeneca, Clovis Oncology, Tesaro/GSK.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Siegel RL, Miller KD, Fuchs HE, *et al.* Cancer statistics, 2021. *CA Cancer J Clin* 2021; 71: 7–33.
2. Miller DS, Filiaci VL, Mannel RS, *et al.* Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). *J Clin Oncol* 2020; 38: 3841–3850.
3. Slomovitz BM, Jiang Y, Yates MS, *et al.* Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. *J Clin Oncol* 2015; 33: 930–936.
4. Fader AN, Roque DM, Siegel E, *et al.* Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. *J Clin Oncol* 2018; 36: 2044–2051.
5. Fader AN, Roque DM, Siegel E, *et al.* Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III–IV) or recurrent uterine serous carcinomas that overexpress Her2/neu (NCT01367002): updated overall survival analysis. *Clin Cancer Res* 2020; 26: 3928–3935.
6. Le DT, Durham JN, Smith KN, *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; 357: 409–413.
7. Diaz LA Jr and Le DT. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; 373: 1979.
8. Marabelle A, Le DT, Ascierto PA, *et al.* Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. Epub ahead of print 4 November 2019. DOI: 10.1200/JCO.19.02105.
9. Ott PA, Bang YJ, Berton-Rigaud D, *et al.* Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. *J Clin Oncol* 2017; 35: 2535–2541.
10. Antill YC, Kok PS, Robledo K, *et al.*; Australia New Zealand Gynaecological Oncology Group (ANZGOG). Activity of durvalumab in advanced endometrial cancer (AEC) according to mismatch repair (MMR) status: the phase II PHAEDRA trial (ANZGOG1601). *J Clin Oncol* 2019; 37(Suppl. 15): 5501.
11. Oaknina A, Sullivanc RJ, Pothuri B, *et al.* Preliminary safety, efficacy, and pharmacokinetic/pharmacodynamic characterization from GARNET, a phase I/II clinical trial of the anti-PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-h and MSS endometrial cancer. *Gynecol Oncol* 2019; 154(Suppl. 1): abstract 33.
12. Konstantinopoulos PA, Luo W, Liu JF, *et al.* Phase II study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer. *J Clin Oncol* 2019; 37: 2786–2794.
13. Postow MA, Callahan MK and Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015; 33: 1974–1982.
14. Zitvogel L, Kepp O and Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. *Nat Rev Clin Oncol* 2011; 8: 151–160.

15. Tinhofer I, Budach V, Johrens K, *et al*. The rationale for including immune checkpoint inhibition into multimodal primary treatment concepts of head and neck cancer. *Cancers Head Neck* 2016; 1: 8.

16. Golden EB, Frances D, Pellicciotta I, *et al*. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. *Oncoimmunology* 2014; 3: e28518.

17. Galluzzi L, Buque A, Kepp O, *et al*. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell* 2015; 28: 690–714.

18. Apetoh L, Ladoire S, Coukos G, *et al*. Combining immunotherapy and anticancer agents: the right path to achieve cancer cure? *Ann Oncol* 2015; 26: 1813–1823.

19. Lesterhuis WJ, Punt CJ, Hato SV, *et al*. Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice. *J Clin Invest* 2011; 121: 3100–3108.

20. Peng J, Hamanishi J, Matsumura N, *et al*. Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor-kappaB to foster an immunosuppressive tumor microenvironment in ovarian cancer. *Cancer Res* 2015; 75: 5034–5045.

21. Rizvi NA, Hellmann MD, Brahmer JR, *et al*. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2016; 34: 2969–2979.

22. Langer CJ, Gadgeel SM, Borghaei H, *et al*. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016; 17: 1497–1508.

23. Gandhi L, Rodriguez-Abreu D, Gadgeel S, *et al*. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; 378: 2078–2092.

24. Birkbak NJ, Kochupurakkal B, Izarzugaza JM, *et al*. Tumor mutation burden forecasts outcome in ovarian cancer with BRCA1 or BRCA2 mutations. *PLoS One* 2013; 8: e80023.

25. Hansen JM, Ring K, Hu W, *et al*. Homologous recombination deficiency score testing in endometrial cancer. *Gynecol Oncol* 2020; 159: 225.

26. Strickland KC, Howitt BE, Shukla SA, *et al*. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. *Oncotarget* 2016; 7: 13587–13598.

27. Aghajanian C, Sill MW, Darcy KM, *et al*. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2011; 29: 2259–2265.

28. Aghajanian C, Filiaci V, Dizon DS, *et al*. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. *Gynecol Oncol* 2018; 150: 274–281.

29. Lorusso D, Ferrandina G, Colombo N, *et al*. Randomized phase II trial of carboplatin-paclitaxel (CP) compared to carboplatin-paclitaxel-bevacizumab (CP-B) in advanced (stage III–IV) or recurrent endometrial cancer: the MITO END-2 trial. *J Clin Oncol* 2015; 33(Suppl. 15): 5502.

30. Socinski MA, Jotte RM, Cappuzzo F, *et al*. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018; 378: 2288–2301.

31. Rini BI, Powles T, Atkins MB, *et al*. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet* 2019; 393: 2404–2415.

32. Hodi FS, Lawrence D, Lezcano C, *et al*. Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res* 2014; 2: 632–642.

33. Wallin JJ, Bendell JC, Funke R, *et al*. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun* 2016; 7: 12624.

34. Matsui J, Yamamoto Y, Funahashi Y, *et al*. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. *Int J Cancer* 2008; 122: 664–671.

35. Vergote I, Teneriello M, Powell MA, *et al*. A phase II trial of lenvatinib in patients with advanced or recurrent endometrial cancer: angiopoietin-2 as a predictive marker for clinical outcomes. *J Clin Oncol* 2013; 31(Suppl. 15): 5520.

36. Makker V, Rasco D, Vogelzang NJ, *et al*. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis

of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019; 20: 711–718.

37. Makker V, Taylor MH, Aghajanian C, *et al*. Lenvatinib (LEN) and pembrolizumab (PEMBRO) in advanced endometrial cancer (EC). *Ann Oncol* 2019; 30(Suppl. 5): v404–v405.

38. Marth C, Vulsteke C, Rubio MJ, *et al*. ENGOT-EN9/LEAP-001: a phase 3, randomized, open-label study of pembrolizumab plus lenvatinib versus chemotherapy for first-line treatment of advanced endoemtrial cancer. *Ann Oncol* 2019; 30(Suppl. 5): v433.

39. Lheureux S, Matei D, Konstantinopoulos PA, *et al*. A randomized phase II study of cabozantinib and nivolumab versus nivolumab in recurrent endometrial cancer. *J Clin Oncol* 2020; 38(Suppl. 15): 6010.