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Towards personalized treatment for high risk endometrial cancer

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Citation
Post, C. C. B. (2023, June 13). *Towards personalized treatment for high risk endometrial cancer*. Retrieved from https://hdl.handle.net/1887/3620169

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3620169

Note: To cite this publication please use the final published version (if applicable).

Chapter 6

Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase 2 DOMEC trial)

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Gynecologic Oncology 2022; 165(2):223-229.

ABSTRACT

Background

Patients with advanced endometrial cancer have a poor prognosis, and treatment options are limited. The investigator-initiated, multicenter, phase 2 DOMEC trial (NCT03951415) is the first trial to report data on efficacy and safety of combined treatment with PD-L1 and PARP inhibition for advanced endometrial cancer.

Patients and methods

Patients with metastatic or recurrent endometrial cancer were enrolled. Patients received durvalumab 1500 mg intravenously q4w and olaparib 300 mg 2dd until disease progression, unacceptable toxicity, or patient withdrawal. Patients with at least 4 weeks of treatment were evaluable for analysis. The primary endpoint was progression-free survival at 6 months. Evidence for efficacy was defined as progression-free survival at 6 months in ≥50% of patients. Secondary endpoints included safety, objective response and overall survival.

Results

From July 2019, through November 2020, 55 patients were enrolled. At data cut-off (September 2021), 4 of the 50 evaluable patients were still on treatment. Seventeen patients (34%) were progression-free at 6 months. Objective response rate was 16% (95% CI 8.3 to 28.5) with 1 complete and 7 partial responses. With a median follow-up of 17.6 months, median progression-free survival was 3.4 months (95% CI 2.8 to 6.2) and median overall survival was 8.0 months (95% CI 7.5 to 14.3). Grade 3 treatment-related adverse events occurred in 8 patients (16%), predominantly anemia. There were no grade 4 or 5 treatment-related adverse events.

Conclusions

The combination of durvalumab and olaparib was well tolerated, but did not meet the prespecified 50% 6-month progression-free survival in this heterogeneous patient population with advanced endometrial cancer.

Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. Treatment options for advanced disease after initial platinum-taxane based chemotherapy, and endocrine therapy in case of hormone receptor positive tumors, are scarce.[1-6] Recently, immunotherapy using checkpoint inhibition has been studied and registered as monotherapy[7-12] and in combination with angiogenesis inhibition[5, 6] with promising response rates.

The endometrial cancer molecular classification introduced by The Cancer Genome Atlas[13] provides a basis for individualized risk stratification and treatment. The significant prognostic and predictive differences among the four molecular subgroups in early-stage disease have been replicated in standard diagnostic pathology materials using surrogate markers, identifying similar subgroups: p53-abnormal (p53abn), *POLE*-ultramutated, mismatch repair-deficient or microsatellite unstable (MMRd), and no specific molecular profile (NSMP) endometrial cancer.[14-16] However, predictive significance in recurrent/advanced setting has not been well characterized to date.

MMRd advanced endometrial cancer, which is characterized by a high number of somatic mutations and increased immunogenicity, has been shown to potentially benefit from single-agent programmed cell death-ligand or protein 1 (PD-[L]1) inhibitors with reported objective tumor response rates varying between 27% and 57%.[7-11] Nevertheless, the majority of advanced endometrial cancers will likely be relatively resistant to single-agent checkpoint inhibitors.[10-12] Inducing an immune response to checkpoint inhibitors by combining them with other treatment modalities may be a more rational approach for these tumors.[5, 6, 17]

Poly (ADP-ribose) polymerase (PARP) inhibition has been raising interest as treatment modality in endometrial cancer. As monotherapy, particularly in the molecular subgroup with the worst clinical outcome: p53abn endometrial cancer, in which homologous recombination deficiency (HRD) has been reported.[18, 19] Moreover, the combination of checkpoint inhibition with PARP inhibition has the potential of synergy and thus might be of interest in all types of advanced endometrial cancer. The accumulation of DNA damage caused by PARP inhibition may complement anti-tumor activity with alteration in immune-checkpoint receptor expression that could predispose to response to checkpoint inhibition.[17, 20] The combination of checkpoint inhibition plus PARP inhibition has already been shown to be safe with promising activity in phase 1 and 2 trials,[21, 22] but has not been studied before in endometrial cancer.

The phase 2 DOMEC trial was initiated to investigate the efficacy and safety of combined immune-checkpoint and PARP inhibition for patients with metastatic, persistent or recurrent endometrial cancer.

Methods

Study design and patients

The DOMEC trial was an investigator-initiated multicenter, open-label, single-arm phase 2 study (ClinicalTrials.gov identifier: NCT03951415) of the Dutch Gynecology Oncology Group (DGOG) evaluating the efficacy and safety of combination treatment with durvalumab and olaparib in patients with advanced (recurrent, persistent or metastatic) endometrial cancer. Patients were enrolled at 7 sites in the Netherlands. Data were collected from the first registry date, July 9, 2019, through September 24, 2021. Women with histologically confirmed endometrial cancer including uterine carcinosarcoma were eligible if they had received at least one prior platinum-based chemotherapeutic regimen or were not able or willing to receive chemotherapy. Eligible patients should have documented progressive disease not amenable to local therapy or endocrine therapy, measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria before enrollment. Other key eligibility criteria included WHO performance status 0 or 1, adequate organ function, no previous treatment with PARP inhibitor or PD-(L)1 inhibitor, and no other active primary malignancy. Inclusion was irrespective of molecular subtype. Detailed eligibility criteria are described in Appendix A1. Written informed consent was obtained from all patients prior to enrollment. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee (METC LDD) and the institutional review board of each participating clinical site. Study drugs and an unrestricted grant were supplied by AstraZeneca.

Procedures and outcomes

Patients received durvalumab 1500 mg intravenously once every 4 weeks and olaparib tablets 300 mg twice daily orally until disease progression, treatment discontinuation due to toxicity, or patient withdrawal of consent. Disease progression was based on RECIST v1.1 or documented clinical progression. Radiographic tumor assessment by CT or MRI was performed every three months and at the end of treatment. If radiologic imaging showed disease progression by RECIST v1.1 while the patient was clinically stable and had clinical benefit, study treatment could be continued awaiting radiologic confirmation of disease progression 4 weeks later. Secondary tumor assessment according to irRECIST criteria was performed to account for delayed response and pseudo-progression. Progression-free survival (PFS) was defined as the time from registration to the first documented disease progression or death from any cause; overall survival (OS) was defined as the time from registration to the date of death from any cause; objective response (OR) was defined as a confirmed complete or partial response (best response from study start until the end of treatment) using RECIST v1.1. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The primary endpoint was PFS at 6 months (PFS6). Secondary endpoints included PFS, OS, OR, and safety of combined durvalumab and olaparib.

Central pathology revision was performed after registration. Estrogen receptor (ER) immunohistochemical staining with a 10% cut-off was performed. Tumors were classified according to the diagnostic algorithm of the molecular classification of endometrial cancer;[23] KASPar competitive allele-specific polymerase chain reaction (LGC Genomics, Berlin, Germany) was performed to screen for *POLE* hotspot variants at codons 286, 297, 411, 456, and 459, and immunohistochemical staining of p53 and MMR proteins (PMS2 and MSH6)[24, 25] were performed as previously described.[16]

Statistical analysis

Simon's optimal two-stage design was used with 15 patients evaluable for efficacy in the first phase. If there were at least 6 patients with PFS6, the additional 31 patients would be enrolled in the second stage for 46 evaluable patients. With an expected drop-out of 20%, 55 patients had to be enrolled in the trial. Evidence for sufficient efficacy would be PFS6 in at least 50% of patients, which is equivalent to a median PFS of at least 6 months. Assuming a baseline PFS6 of 30% and improved PFS6 of 50%, this study had 80% power at a 5% significance level.

The data cut-off date was September 24, 2021. Baseline characteristics, safety and efficacy results were summarized descriptively. All evaluable patients, defined as having at least 28 days (1 cycle) of treatment, were included in the primary analysis. PFS and OS were evaluated with the Kaplan-Meier method. Patients who did not experience a PFS or OS event were censored at their last assessment. Subgroup analyses for molecular group, histology and responders versus non-responders were performed using Fisher's exact test, Mann-Whitney U test and log-rank test.

Results

Patients

Between July 9, 2019, and November 25, 2020, 55 patients with advanced endometrial cancer from 7 sites in the Netherlands were enrolled. The drop-out rate was lower than expected, providing 50 patients evaluable for efficacy and safety analysis (Figure 1). The median age of evaluable patients was 69.0 years (IQR 64.3 to 73.0), and the majority had

received prior chemotherapy (42/50, 84%) and/or endocrine therapy (13/50, 26%). The most common histologic subtypes of disease were serous carcinoma (38%), endometrioid adenocarcinoma (32%; International Federation of Gynecology and Obstetrics [FIGO] grade 1 or 2, 20%; FIGO grade 3, 12%), clear cell carcinoma (12%) and carcinosarcoma (14%). Twenty-nine (58%) tumors were classified as p53abn, 10 (20%) as MMRd, 10 (20%) as NSMP and none as *POLE*mut endometrial cancer (Table 1). Two of the NSMP endometrial cancers were ER-positive.

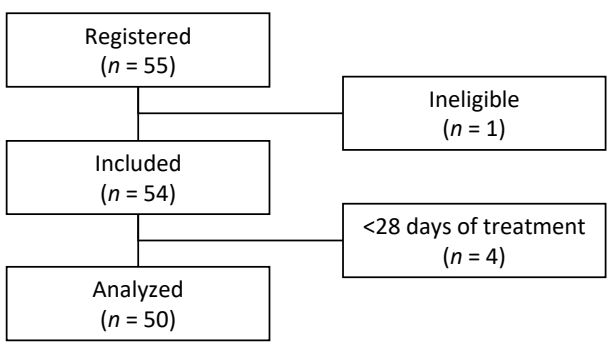

Figure 1. CONSORT diagram of study enrollment

Efficacy

Among the 50 evaluable patients, 17 patients (34%) were free from progression at 6 months (18 [36%] when using irRECIST), and thus did not meet the predefined threshold of 50% 6-month PFS. Under the hypothesis of 50% 6-month PFS, the probability of having 17 out of 50 patients with PFS6, the *p*-value for Simon's two-stage design, equals 0.016. The median follow-up time was 17.6 (95% CI 10.1 to 20.2) months. Median PFS was 3.4 months (95% CI 2.8 to 6.2; Figure 2A) and median OS was 8.4 months (7.5 to 14.3; Figure 2B). Median PFS for low-grade endometrial cancer patients was 4.2 months (95% CI, 3.0 to NR) and for high-grade endometrial cancer patients 3.4 months (2.8 to 7.8; $p = .82$; Figure 2C). When compared by molecular subgroup, median PFS for MMRd endometrial cancer patients was 5.7 months (95% CI 2.8 to NR), for NSMP 3.2 months (2.6 to NR), and for p53abn 3.0 months (2.8 to 7.8; $p = .67$; Figure 2D).

There was objective response in 8 out of 50 patients (ORR 16%, 95% CI 8.3 to 28.5; Table 2 and Figure 3A); One patient (2%) had a confirmed complete response (CR), and 7 patients (14%) had a confirmed partial response (PR). There were no significant differences when using irRECIST. Four patients were still receiving protocol treatment at the data cut-off date (Figure 3B).

Table 1. Baseline characteristics

Characteristics	*N* = 50
Median age (IQR), years	69.0 (64.3, 73.0)
Median BMI (IQR)	27.9 (22.4, 31.5)
WHO performance status	
0	13 (27.7)
1	34 (72.3)
Histologic subtype	
Endometrioid EC Grade 1/2	10 (20.0)
Endometrioid EC Grade 3	6 (12.0)
Serous EC	19 (38.0)
Clear Cell Carcinoma	6 (12.0)
Carcinosarcoma	7 (14.0)
Undifferentiated EC	2 (4.0)
Molecular classification	
p53-abnormal EC	29 (59.2)
MMRd EC	10 (20.4)
NSMP EC	10 (20.4)
*POLE*mut EC	0 (0.0)
Hormonal status	
ER positive	23 (46.9)
ER negative	26 (53.1)
Prior chemotherapy	42 (84.0)
Number of lines chemotherapy	
1	29 (69.0)
2	11 (26.2)
3	2 (4.8)
Prior endocrine therapy	13 (26.0)
Number of lines endocrine therapy	
1	8 (66.7)
2	3 (25.0)
5	1 (8.3)
Prior radiotherapy	34 (68.0)

NOTE. Data reported as No. (%) unless otherwise indicated.

EC = endometrial cancer; ER = estrogen receptor; MMRd = mismatch repair deficiency; NSMP = non-specific molecular profile; *POLE*mut = *POLE*-ultramutated; WHO = World Health Organization.

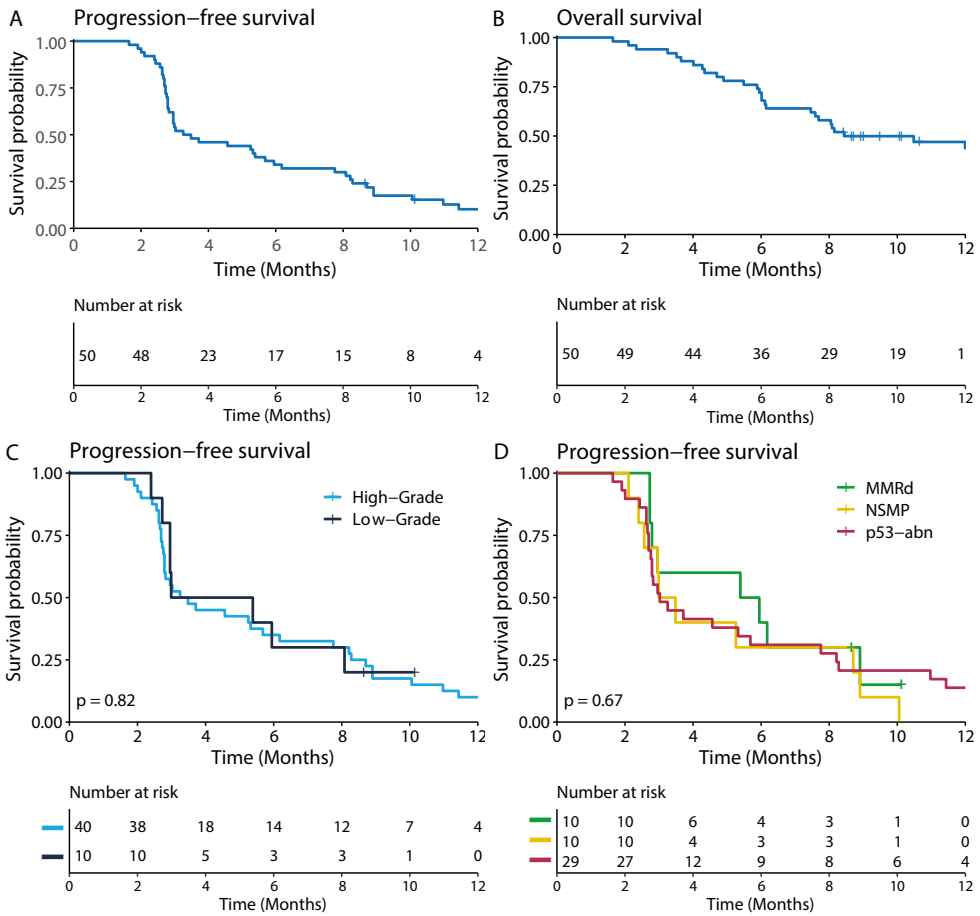

Figure 2. Kaplan-Meier curves for progression-free survival (A) and overall-survival (B) of the evaluable population, and progression-free survival by histological subtype (C) and molecular subgroup (D). MMRd = mismatch repair deficiency; NSMP = non-specific molecular profile; p53-abn = p53-abnormal.

There were no significant differences in characteristics between responders and non-responders. Objective response to treatment was seen in 6 tumors classified as p53abn and 2 classified as MMRd endometrial cancer. The three patients in whom *BRCA 1* germline mutations were already known all showed objective response (1 CR with progression after 12.9 months, 1 PR with progression after 8.3 months and 1 PR who was still receiving protocol treatment at data cut-off after 20 months).

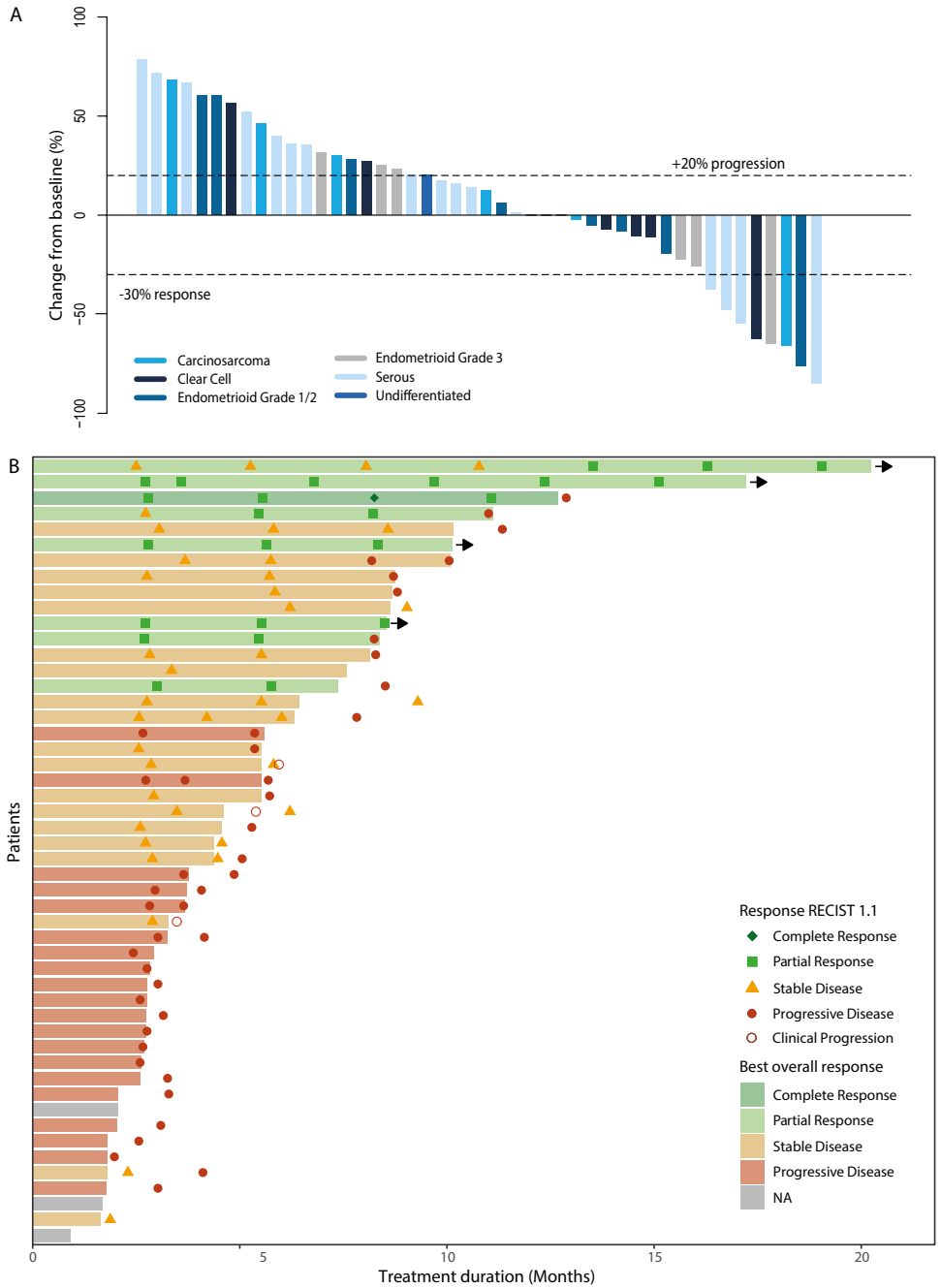

Figure 3. Best percentage change from baseline in sum of diameters of target lesions stratified by histology (A), and time on treatment with best overall tumor response per patient (B).
Each bar represents one patient. The black arrows indicate patients that were still on treatment at time of data cut-off. Each symbol represents a CT-scan with response according to RECIST v1.1

Table 2. Best overall response as per RECIST version 1.1 and progression-free survival estimate

Evaluable patients	***N* = 50**		
Best overall response, No. (%)		**Objective response**	
Complete Response	1 (2.0)	No. (%; 95% CI)	8 (16.0; 8.3 - 28.5)
Partial Response	7 (14.0)	Progression-free survival	
Stable Disease	19 (38.0)	6 m KM estimate, % (95% CI)	34.0 (23.1 - 50.0)
Progressive Disease	20 (40.0)	Median KM estimate, m (95% CI)	3.4 (2.8 - 6.2)
NA	3 (6.0)		

KM = Kaplan-Meier; NA = not available; m = months.

Safety

Of the evaluable patients, 44 (88%) had a treatment-related adverse event (TRAE) of any grade (Table 3). The most frequently reported (≥10%) TRAEs of any grade were fatigue (44%), nausea (38%), anemia (32%), diarrhea (26%), anorexia (24%), vomiting (16%), dysgeusia (16%), renal events (10%) and flu-like symptoms (10%). Grade 3 TRAEs occurred in 8 patients (16%), most frequently (10%) anemia. There were no grade 4 and 5 TRAEs.

One patient (2%) had to discontinue olaparib due to a treatment-related renal event and 12 patients (24%) had a dose reduction of olaparib due to TRAEs (1 patient with dose reduction to 100 mg, 2 to 150 mg, 7 to 200 mg and 2 to 250 mg BID). Three other patients (6%) had to interrupt olaparib due to TRAEs, but could resume treatment on the initial dose of 300 mg twice daily. One patient (2%) had to discontinue durvalumab early due to treatment-related diarrhea.

Table 3. Treatment-related adverse events

CTCAE term	**Any Grade**	**≥ Grade 2**	**Grade 3**
Any	44 (88)	28 (56)	8 (16)
Anemia	16 (32)	12 (24)	5 (10)
Fatigue	22 (44)	4 (8)	2 (4)
Renal events[a]	5 (10)	4 (8)	1 (2)
Nausea	19 (38)	3 (6)	1 (2)
Anorexia	12 (24)	3 (6)	1 (2)
Hepatotoxicity[b]	3 (6)	2 (4)	1 (2)
Leukopenia[c]	2 (4)	1 (2)	1 (2)
Infections[d]	4 (8)	4 (8)	0 (0)
Diarrhea	13 (26)	2 (4)	0 (0)
Vomiting	8 (16)	2 (4)	0 (0)
Flu like symptoms[e]	5 (10)	2 (4)	0 (0)
Abdominal pain[f]	3 (6)	2 (4)	0 (0)

Table 3. Treatment-related adverse events *(continued)*

CTCAE term	**Any Grade**	**≥ Grade 2**	**Grade 3**
Dysgeusia	8 (16)	1 (2)	0 (0)
Hypothyroidism	4 (8)	1 (2)	0 (0)
Edema limbs	2 (4)	1 (2)	0 (0)
Peripheral motor neuropathy	2 (4)	1 (2)	0 (0)
Hypertension	1 (2)	1 (2)	0 (0)
Gastrointestinal other[g]	6 (12)	0 (0)	0 (0)
Pain[h]	3 (6)	0 (0)	0 (0)
Respiratory disorders[i]	3 (6)	0 (0)	0 (0)
Dizziness	2 (4)	0 (0)	0 (0)
Dry skin	2 (4)	0 (0)	0 (0)
Pruritus[j]	2 (4)	0 (0)	0 (0)
Allergic reaction	1 (2)	0 (0)	0 (0)
Anosmia	1 (2)	0 (0)	0 (0)
Colitis	1 (2)	0 (0)	0 (0)
General disorders other	1 (2)	0 (0)	0 (0)
Hyperglycemia	1 (2)	0 (0)	0 (0)
Hypomagnesemia	1 (2)	0 (0)	0 (0)
Peripheral sensory neuropathy	1 (2)	0 (0)	0 (0)
Vaginal hemorrhage	1 (2)	0 (0)	0 (0)

NOTE. Adverse events graded according to the Common Terminology Criteria for Adverse Events (version 5.0). Data are reported as No. (%). The denominator to all calculated percentages is 50, the number of evaluable patients. No grade 4 or 5 treatment-related adverse events were reported.

a Renal event basket (including creatinine increased, acute kidney injury, chronic kidney disease)

b Hepatotoxicity basket (including alanine aminotransferase increased, aspartate aminotransferase increased and alkaline phosphatase increased)

c Leukopenia (including white blood cell and neutrophil count decreased)

d Infections (including eye, urinary tract, wound and pleural infections)

e Flu like symptoms basket (including predominantly fever, chills and flu like symptoms)

f Abdominal pain basket (including abdominal pain and stomach pain)

g Gastrointestinal other (including constipation, dry mouth, dysphagia, oral pain and salivary duct inflammation)

h Pain basket (including pain, facial pain and headache)

i Respiratory disorders basket (including cough and dyspnea)

j Pruritus basket (including pruritus and urticaria)

Discussion

The DOMEC trial is the first to report the efficacy and safety of combined immune-checkpoint inhibition and PARP inhibition for patients with metastatic, persistent or recurrent endometrial cancer including uterine carcinosarcoma. In this investigator-initiated phase 2 study, the combination of PD-L1 inhibitor durvalumab and PARP inhibitor olaparib did not meet the prespecified threshold of 50% 6-month PFS. The trial included a heterogeneous group of advanced endometrial cancers and PFS at 6 months was 34%. Nevertheless, some patients benefited with prolonged response and were still on treatment at the data cut-off date. The combined treatment was well tolerated without any grade 4 or 5 treatment-related adverse events and grade 3 in 16% of the patients.

Comparison with other studies that investigated new agents in advanced endometrial cancer is challenging due to the variety in study population and RECIST version used. Our study included patients with relatively unfavorable characteristics (e.g. worse WHO performance status, 80% high-grade endometrial cancer including 14% carcinosarcomas, 59% molecularly classified as p53abn, and 80% of NSMP endometrial cancers were ER-negative). Reported response rates of single-agent PD-(L)1 inhibitors strongly depend on MMR status in endometrial cancer. Studies investigating checkpoint inhibition in MMRd advanced endometrial cancer patients showed a median PFS of 4.4 to 25.7 months with ORR of 26.7 to 57.1%.[7, 9-11] These outcomes were better than those of the DOMEC trial, both in the MMRd subgroup and in our overall population. In the setting of immunotherapy, endometrial cancers classified as *POLE*mut, NSMP and p53abn are often referred to as MMR-proficient (MMRp). The response rates in our study seem to be better than those of studies with checkpoint inhibition monotherapy in MMRp endometrial cancer; Those studies report median PFS of 1.8 to 1.9 months and ORR of 3.0 to 13.4%, while reported rates of grade 3 or higher TRAEs were similar (13.5 to 19%).[9-12] The combination of pembrolizumab with the multitarget angiogenesis inhibitor lenvatinib, which has been approved by the FDA for advanced MMRp endometrial cancer, provided better outcomes irrespective of MMR status, with median PFS of 18.8 and 7.4 months and ORRs of 63.6 and 37.2% in MMRd and MMRp advanced endometrial cancer, respectively. However, more grade 3 or higher TRAEs (67%) were observed using this combination therapy.[5, 26]

The combination of durvalumab and olaparib was well tolerated. One patient had to discontinue olaparib and one patient had to discontinue durvalumab treatment due to TRAEs. Treatment modifications were made in 34% of the patients. The most common TRAEs of any grade were fatigue (44%), nausea (38%) and anemia (32%), and the most common grade 3 TRAE was anemia (10%). No olaparib-related adverse events of special interest (pneumonitis, myelodysplastic syndromes, or new primary malignancies) were reported. The most commonly reported durvalumab-related adverse events of special interest were diarrhea, renal events and hepatotoxicity. No new safety signals were observed, in line with those previously observed in respective combination and monotherapy studies.[10, 27-30]

The main strength of our study is that it is the first to report the efficacy and safety of combined immune-checkpoint inhibition and PARP inhibition for patients with metastatic or recurrent endometrial cancer. All tumors were molecularly classified.[23] This treatment combination has a rationale from preclinical and correlative data.[20] Although some molecular subgroups could be expected to benefit more than others, a synergistic effect could potentially occur in all types of advanced endometrial cancer. Therefore, an all-comer design was chosen. On the other hand, this study design introduced limitations. This study is limited by its heterogeneous patient, prior treatment and tumor characteristics. Due to the heterogeneity and the absence of a control group, it is difficult to put the clinical efficacy into perspective and draw any hard conclusions. In addition, the sample size was too small to perform powered subgroup analyses to make mature recommendations on patient selection for future clinical trials.

In order to generate recommendations on precision (combination) therapy, translational studies are needed to enhance knowledge on biomarkers. Given the good tolerance and suggestion of better performance than anti-PD(L)1 monotherapy in MMRp advanced endometrial cancer, the combination of durvalumab and olaparib might be of interest in a selected group of patients despite insufficient efficacy in the overall DOMEC population. Subgroups of interest might be the p53abn endometrial cancer, hormone receptor-negative NSMP endometrial cancer, and also MMRd tumors without durable response to checkpoint inhibition.[17, 20] Within the p53abn endometrial cancers, specifically, tumors with HRD are of interest. This was supported by a good response in 3 patients with p53abn endometrial cancer with known *BRCA 1* germline mutations. Another interesting finding was that one of the seven unfavorable p53abn carcinosarcomas had a durable response of >17 months, whereas she previously had only a short duration of disease control after primary treatment with surgery and chemotherapy. Additional exploratory analyses on *BRCA* mutational status, HRD and immunomonitoring is being planned, and will potentially set directions for future research. Further insight could be obtained from the currently recruiting phase 3 RUBY (NCT03981796) and DUO-E (NCT04269200) trials. These studies investigate the combination of platinum-based chemotherapy, checkpoint inhibitors and PARP inhibitors in the first-line treatment of advanced endometrial cancer. The *Trans*PORTEC consortium is initiating the RAINBO program in early-stage endometrial cancer, consisting of four academic trials for each of the four molecular subgroups.[31, 32] This approach should be extended to the advanced setting to identify the best molecularly

based systemic therapy for every patient with endometrial cancer.

In conclusion, the combination of checkpoint inhibitor durvalumab and PARP inhibitor olaparib was well tolerated in our group of patients with metastatic or recurrent endometrial cancer, but did not reach the 6-month PFS of 50%, and was therefore insufficient to recommend for a phase 3 trial in the overall patient population. However, with further knowledge on predictive biomarkers, this combination might be of interest in a selected group of patients with advanced endometrial cancer.

Acknowledgments

We thank all clinical research teams at participating sites and the women who participated in the trial. We thank Tessa Rutten and Natalja T. ter Haar (Leiden University Medical Center) for their excellent technical support.

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APPENDIX A1. ELIGIBILITY CRITERIA

Inclusion criteria

1 Written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up assessments.
2 Age $\geq$ 18 years old
3 Histologically confirmed diagnosis of endometrial cancer or carcinosarcoma of the endometrium. Besides central revision, a tumor block or 20 slides are asked for TR.
4 Metastatic disease or locally advanced tumor not amenable to local therapy.
5 Documented progressive disease before enrolment.
6 Measurable lesions outside irradiated field *or* progressive measurable lesions in irradiated area
7 Not eligible for hormonal therapy (because of negative hormone receptor/poor differentiation, or after failure of hormonal therapy).
8 Previous failure of chemotherapy, or refusal to undergo chemotherapy or chemo-naive patients not suitable for chemotherapy.
9 WHO performance 0-1
10 Adequate organ system function as measured within 28 days prior to administration of study treatment, as defined below:
   - Hemoglobin ≥ 10.0 g/dL, with no blood transfusion in the past 28 days.
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (not applicable to Gilbert's syndrome)
   - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x ULN unless liver metastases are present in which case they must be ≤ 5x ULN
   - Patients must have creatinine clearance estimated of ≥51 mL/min estimated using the Cockcroft-Gault equation or 24 hr urine clearance.
11 Expected adequacy of follow-up
12 Life expectancy of at least 16 weeks.
13 Measurable disease as defined by RECIST 1.1 criteria
14 Able to swallow and retain oral medication.
15 Body weight > 30 kg

Exclusion criteria

1 Participation in another clinical study with an investigational product during the last month or previous enrolment in the present study.
2 Any previous treatment with PARP inhibitor, including olaparib and/or any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.
3 History of another primary malignancy that could conceivably be active evaluated by the study physician. Examples include, but are not limited to:
   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease.

4 History of leptomeningeal carcinomatosis. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids (maximum 2 mg/day) before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
5 Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
6 Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.
7 Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

8 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
   - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
   - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab and olaparib may be included only after consultation with the Study Physician.

9 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
10 Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
11 Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.
12 History of active primary immunodeficiency
13 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   - Patients with vitiligo or alopecia
   - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
   - Any chronic skin condition that does not require systemic therapy
   - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
   - Patients with celiac disease controlled by diet alone

14 Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

15 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16 Patients with an expected or known hypersensitivity to olaparib or durvalumab or any of the excipients of the products.
17 Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
18 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
19 Female patients who are pregnant or breastfeeding or patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.