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Gynecologic Oncology 165 (2022) 223–229

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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

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HIGHLIGHTS

- DOMEC is the first to report on efficacy and safety of combined PD-L1 and PARP inhibition for advanced endometrial cancer.
- The primary endpoint to reach PFS of ≥6 months in 50% was not reached; median PFS was 3.4 months.
- The objective response rate was 16% including 2% with a complete response; some patients had a durable ongoing response.
- Combined durvalumab-olaparib was well tolerated, with 16% treatment-related grade 3 adverse events and no grade 4 or 5.

ARTICLE INFO

Article history:
Received 2 February 2022
Accepted 28 February 2022
Available online 11 March 2022

Keywords:
Immune checkpoint inhibitor
PARP inhibitor
Durvalumab
Olaparib
Endometrial cancer

ABSTRACT

Background. Patients with advanced endometrial cancer have a poor prognosis, and treatment options are limited. The investigator-initiated, multicenter, phase II 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.

Abbreviations: DOMEC, Durvalumab with olaparib in metastatic or recurrent endometrial cancer; ER, Estrogen receptor; MMRd, Mismatch repair-deficient or microsatellite unstable; MMRp, Mismatch repair-proficient; NSMP, No specific molecular profile; OR, Objective response; OS, Overall survival; PARP, Poly (ADP-ribose) polymerase; PD-1, Programmed cell death-protein 1; PD-L1, Programmed cell death-ligand 1; PFS, Progression-free survival; PFS6, Progression-free survival at 6 months; POLE, Polymerase epsilon; RECIST, Response Evaluation Criteria in Solid Tumors.

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https://doi.org/10.1016/j.ygyno.2022.02.025

Conclusion. 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.

1. 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, *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: p53-abnormal 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 I and II trials [21,22], but has not been studied before in endometrial cancer.

The phase II 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.

2. Methods

2.1. Study design and patients

The DOMEC trial was an investigator-initiated multicenter, open-label, single-arm phase II 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.

2.2. 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].

2.3. 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.

3. Results

3.1. 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, 84.0%) and/or endocrine therapy (13/50, 26%). The most common histologic subtypes of disease were serous carcinoma (38.0%), endometrioid adenocarcinoma (32.0%; International Federation of Gynecology and Obstetrics [FIGO] grade 1 or 2, 20.0%; FIGO grade 3, 12.0%), clear cell carcinoma (12.0%) and carcinosarcoma (14.0%). Twenty-nine (58.0%) tumors were classified as p53-abnormal, 10 (20.0%) as MMRd, 10 (20.0%) as NSMP and none as *POLE*mut endometrial cancer (Table 1). Two of the NSMP endometrial cancers were ER-positive.

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, No. (%)	
0	13 (27.7)
1	34 (72.3)
Histologic subtype, No. (%)	
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, No. (%)	
p53-abnormal EC	29 (59.2)
MMRd EC	10 (20.4)
NSMP EC	10 (20.4)
*POLE*mut EC	0 (0.0)
ER positive	23 (46.9)
ER negative	26 (53.1)
Prior chemotherapy, No. (%)	42 (84.0)
Number of lines chemotherapy, No. (%)	
1	29 (69.0)
2	11 (26.2)
3	2 (4.8)
Prior endocrine therapy, No. (%)	13 (26.0)
Number of lines endocrine therapy, No. (%)	
1	8 (66.7)
2	3 (25.0)
5	1 (8.3)
Prior radiotherapy, No. (%)	34 (68.0)

EC, Endometrial cancer; ER, Estrogen receptor; MMRd, Mismatch repair deficiency; NSMP, Non-specific molecular profile; *POLE*mut, *POLE*-ultramutated, WHO, World Health Organization.

3.2. 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; $p = 0.82$; 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 p53-abnormal 3.0 months (2.8 to 7.8; $p = 0.67$; 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).

There were no significant differences in characteristics between responders and non-responders. Objective response to treatment was seen in 6 tumors classified as p53-abnormal 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).

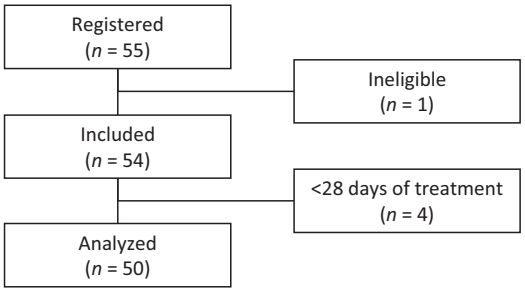

Fig. 1. CONSORT diagram of study enrollment.

3.3. 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.

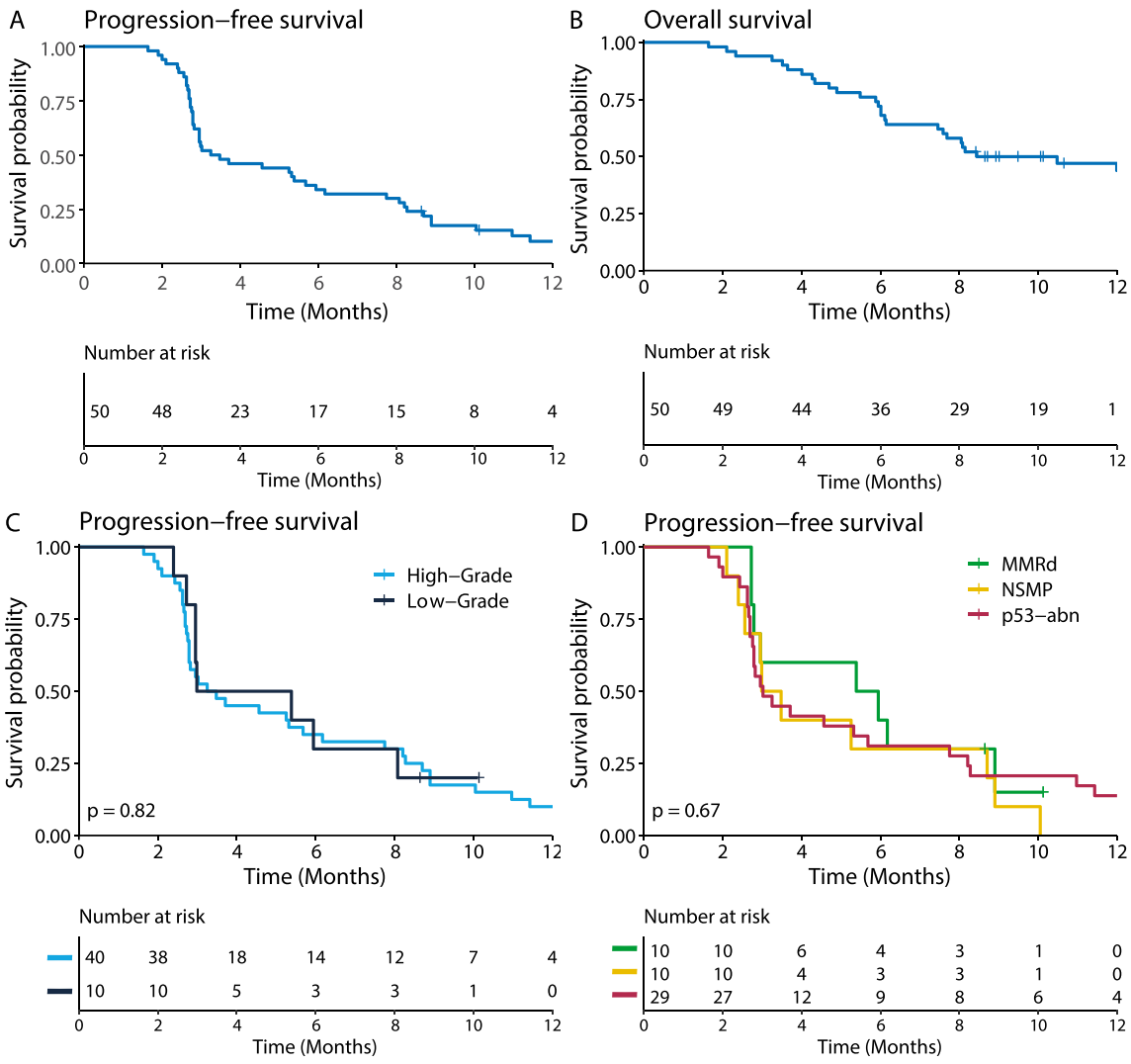

Fig. 2. Kaplan-Meier curves for progression-free survival (A) and overall-survival (B) of the evaluable population, and progression-free survival by histological subtype (C) and molecular subgroup (D).
MMRd, Mismatch Repair deficiency; NSMP non-specific molecular profile; p53-abn, p53-abnormal.

4. 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 II 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.

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

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

KM, Kaplan-Meier; NA, not available.

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 p53-abnormal, 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 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 p53-abnormal are often

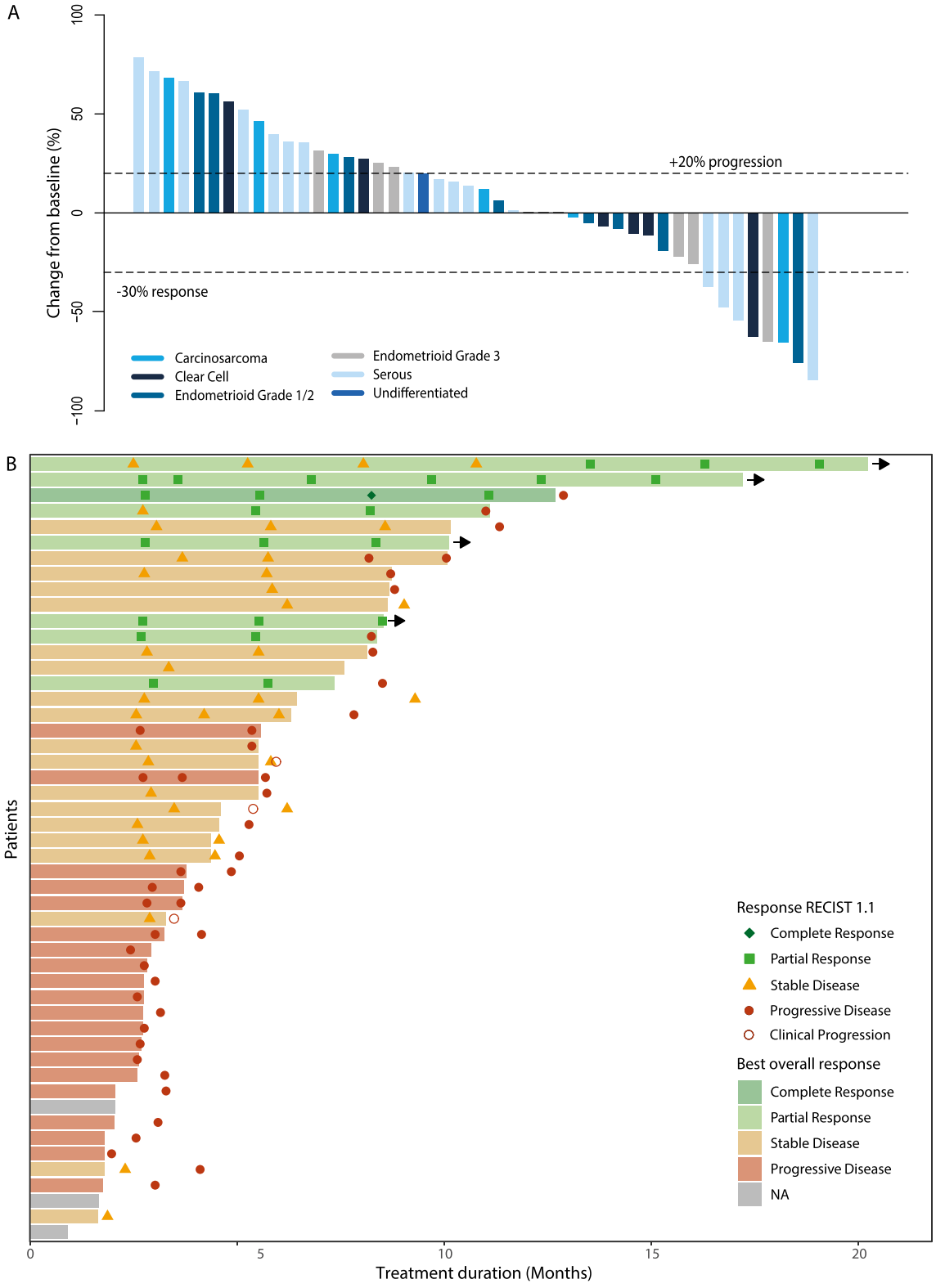

Fig. 3. Best percentage change from baseline in sum of diameters of target lesions stratified by histology (A), and time on treatment with best overall tumor response per patient (B). Each bar represents one patient. The black arrows indicate patients that were still on treatment at time of data cut-off.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

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

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)
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 presented 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).

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 p53-abnormal endometrial cancer, hormone receptor-negative NSMP endometrial cancer, and also MMRd tumors without durable response to checkpoint inhibition [17,20]. Within the p53-abnormal endometrial cancers, specifically, tumors with HRD are of interest. This was supported by a good response in 3 patients with p53-abnormal endometrial cancer with known *BRCA 1* germline mutations. Another interesting finding was that one of the seven unfavorable p53-abnormal 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.

Funding

This work was supported by AstraZeneca [Study drugs and an unrestricted grant].

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Credit authorship contribution statement

C.C.B. Post: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Project administration, Writing – original draft, Writing – review & editing, Visualization. **A.M. Westermann:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Funding acquisition. **I.A. Boere:** Resources, Writing – review & editing. **P.O. Witteveen:** Resources,

Writing – review & editing. **P.B. Ottevanger:** Resources, Writing – review & editing. **G.S. Sonke:** Resources, Writing – review & editing. **R.I. Lalisang:** Resources, Writing – review & editing. **H. Putter:** Methodology, Validation, Formal analysis, Resources, Writing – review & editing. **E. Meershoek-Klein Kranenbarg:** Validation, Formal analysis, Data curation, Project administration, Writing – review & editing. **J.P.B.M. Braak:** Validation, Formal analysis, Data curation, Project administration, Writing – review & editing. **C.L. Creutzberg:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision. **T. Bosse:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Funding acquisition. **J.R. Kroep:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

Study drugs and an unrestricted grant were supplied by AstraZeneca. Outside this work: JRK has received study grants from AstraZeneca and Novartis and is a steering committee member for AstraZeneca, GSK, Novartis and Pfizer. GSS reports institutional research support from Agendia, AstraZeneca, Merck, Novartis, Roche and Seagen. CLC has received research support to institution from Varian, Elekta, and compensation to institution for time spent on IDMC membership from Merck and on invited presentations from GSK.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.02.025.

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