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Towards personalized treatment for high risk endometrial cancer

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Chapter 5

PARP and PD-1/PD-L1 checkpoint inhibition in recurrent or metastatic endometrial cancer

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ABSTRACT

The prognosis of recurrent or metastatic endometrial cancer is poor, with five-year survival of only 10–20%. First-line therapy consists of either platinum-based chemotherapy or hormonal therapy. No standard subsequent-line therapy has been identified. In recent years, significant progress has been made in the knowledge on underlying molecular biology of endometrial cancer and potential targets for therapy have been identified. Targeted therapies as poly (ADP-ribose) polymerase (PARP) inhibitors and immunotherapy as PD-1/PD-L1 checkpoint inhibitors have the potential to be effective against specific subtypes of endometrial cancer. Preclinical studies have shown that combining these agents may result in a synergistic effect. In this review, we focus on the molecular basis of checkpoint inhibition and targeted therapy as PARP inhibition in endometrial cancer and summarize available clinical data, and ongoing and planned clinical trials that investigate these agents as mono- or combination therapies in endometrial cancer and where relevant, other gynecological cancers.

1. Introduction

Endometrial cancer is the most common gynecological cancer in developed countries, and its incidence is gradually rising due to increased obesity and ageing of the population. In contrast to the declining trends for many common cancers, mortality has remained roughly the same for endometrial cancer.[1, 2] Although endometrial cancer is most often diagnosed at an early stage and the prognosis is generally good, a small (but notable) proportion of patients present with or develop metastatic or recurrent disease not amenable to localized therapies; these women have an unfavorable prognosis. First-line therapy for metastatic disease consists of platinum-based chemotherapy, especially carboplatin-paclitaxel,[3] or hormonal therapy in case of low grade, hormone receptor positive tumors.[4, 5] There are no standard subsequent-line therapies. Five-year survival is only 10-20% for women with non-locally recurrent or metastatic disease.[2, 6-8] Consequently, new treatment strategies and paradigms are urgently needed for these patients. Among these, checkpoint inhibition and targeted therapies, such as Poly (ADP-ribose) polymerase (PARP) inhibition, are of interest with the current understanding of the molecular biology of endometrial cancer.

Here, we focus on the molecular basis of checkpoint and PARP inhibition in endometrial cancer and present an overview of the current and future clinical trials that investigate the potential of PARP- and checkpoint inhibition as mono- or combination therapy in advanced endometrial cancer and where relevant, other gynecological cancers. We also discuss the hypothesis of combination therapy induced synergistic anti-tumor effect and trials exploring the efficacy of this combination, such as the Durvalumab and Olaparib in Metastatic or recurrent Endometrial Cancer (DOMEC; NCT03951415) trial.

2. Molecular background

Significant progress in unraveling the underlying molecular biology of endometrial cancer has been made since the extensive molecular-genetic analysis by The Cancer Genome Atlas group (TCGA). The TCGA has identified four distinct molecular subgroups with prognostic significance:[9] (i) Endometrial cancer with pathogenic mutations in the exonuclease domain of DNA polymerase-epsilon (*POLE)* with an extremely high mutational load and an excellent prognosis; (ii) endometrial cancer with microsatellite instability (MSI) caused by mismatch repair deficiency with a high mutational load and an intermediate prognosis; (iii) a copy-number low (CNL) group with no specific molecular profile (NSMP), a low mutational load and an intermediate prognosis and; (iv) a group with frequent *TP53*-mutation characterized by extensive somatic copy-number alterations (SCNAs; CNH), a relatively low mutational load and a poor prognosis.

Subsequent studies have identified surrogate markers that can be used to classify endometrial cancer into four molecular subgroups analogous to the TCGA subclasses. This novel classification of endometrial cancer not only provides important prognostic information, it also yields biologically defined subgroups that may show different responses to specific drugs. For example, *POLE* ultramutated and mismatch repair deficient (MMRd) endometrial cancer are attractive candidates for immune checkpoint inhibition strategies, as they are associated with a high mutational burden and a prominent immune infiltrate.[10, 11] The immune checkpoint inhibitor pembrolizumab has been approved by the Food and Drug Administration (FDA) for unresectable or metastatic MSI or MMRd solid tumors. Secondly, CNH endometrial cancers are characterized by alterations in the actionable p53 pathway.[12, 13] This pathway alteration is associated with a high prevalence of homologous recombination deficiency (HRD).[14] Generally, HRD tumors are likely to respond to PARP inhibitors.[15] For patients with ovarian cancer and metastatic breast cancer PARP inhibitors are becoming part of standard-of-care therapy; PARP inhibition effect is largest in patients with *BRCA*-mutated tumors and those that are HRD.[16-21]

Research on differences between molecular alterations in primary and recurrent or metastatic endometrial cancer tumors is limited. In a Memorial Sloan Kettering Cancer Center (MSK) cohort, including 189 patients with recurrent and metastatic endometrial cancer analyzed for molecular characterization, the most frequent somatic alterations were similar to the TCGA cohort, although *TP53* mutations were more common and *PTEN* alterations were less common in the MSK cohort. These differences were largely explained by the histologic subtypes, with inclusion of carcinosarcomas and clear cell tumors and a higher proportion of serous and grade 3 tumors in the MSK cohort compared to the TCGA cohort.[22] Thus far, studies have indicated that the molecular classification according to TCGA subgroups is generally stable from primary to metastatic lesions.[22-24] However, in a small proportion of cases a shift from CNL to MMRd was seen[23] and *PTEN* mutations are less commonly observed in metastatic lesions compared to their matched primary tumor.[22] Gibson et al. found that abdominal metastases are more closely related to each other than to the primary tumor biopsy, so they might have arisen from a limited fraction of these cancers. Despite a notable heterogeneity between silent mutations of the primary tumor and their metastases, the overlap in non-silent mutations between the primary tumor and their metastases is large.[24]

Especially following therapy, derangements in multiple oncogenic or tumor-promoting pathways may occur. This should be considered when evaluating targeted therapies in the recurrent setting. Moreover, metastases to anatomical sites outside the abdominopelvic area might present with different actionable alterations. The large number of genetic co-alterations in advanced tumors can be a challenge in choosing targeted therapies.

Combining agents targeting different pathways attempts to circumvent these problems. Checkpoint and Poly (ADP-ribose) polymerase (PARP) inhibition are two promising treatment modalities for endometrial cancer. These agents can be combined, and it is hypothesized that this combination delivers a synergistic effect. This synergistic effect is discussed later in this review.

3. Checkpoint inhibition: anti-PD-(L)1 antibodies

Immune checkpoint inhibitors, particularly agents targeting the programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) pathway, are being increasingly explored as a potential treatment strategy in various cancers. Checkpoint inhibition could prevent PD-1/PD-L1 interaction by blocking PD-1 or its ligand PD-L1.[25] The PD-1 receptor is a transmembrane protein expressed on the surface of activated T-cells.[26] Once PD-L1, commonly over-expressed on many tumor cells and hematopoietic cells, binds to PD-1 the immunological response is suppressed and apoptosis is inhibited. Checkpoint inhibition based on anti-PD-1/PD-L1 pathway antibodies can be subdivided in PD-1 blockers and PD-L1 blockers. PD-1 blockers which have established activity in several cancer types are nivolumab, pembrolizumab and cemiplimab.[27] PD-L1 blockers which have been shown to be effective are atezolizumab, avelumab and durvalumab. Theoretically, anti-PD-L1 has a less immune related toxicity profile compared to anti-PD-1, since they do not block binding of the other PD-1 ligand, PD-L2. PD-L2 is expressed on hematological cells, and interaction with PD-1 generates an inhibitory signal affecting the immune response. In addition, PD-L2 binds to repulsive guidance molecule b (RGMb), which regulates respiratory immunity.[28] No direct comparison has been made between PD-1 and PD-L1 inhibitors. Pembrolizumab has been approved by the FDA for unresectable or metastatic MSI or MMRd solid tumors that have progressed following prior treatment without satisfactory alternative treatment options, which include selected endometrial carcinomas.[29] Particularly tumors with a high mutational burden (e.g. *POLE*/MMRd subgroups) may be susceptible to PD-1/PD-L1 inhibitors.[30, 31] In endometrial cancer the MMRd subgroup are expected to benefit most, since *POLE* ultramutated endometrial cancer is associated with an extremely favorable prognosis and very rare disease recurrence.[12, 22] The PD-1 inhibitor dostarlimab is currently undergoing FDA review for advanced endometrial cancer.

The response to checkpoint inhibition seems to be more pronounced in patients with tumors that express PD-L1.[32-35] PD-L1 expression is higher among MMRd than MMR proficient endometrial cancer,[36, 37] although PD-L1 expression is not exclusive to the MMRd group.[38] The largest study on PD-L1 expression in endometrial cancer, including 700 patients, reported expression of PD-L1 in approximately 30% of MMRd tumors and less than 5% in MMR proficient tumors. Other studies report larger expression percentages

up to 53% in MMRd.[37, 39] Differences in reported percentages are probably explained by the heterogeneity in used methods and thresholds. There is no established cut-off for PD-L1 positivity in endometrial cancer. Although, in a basket trial enabling routine genomic testing for advanced cancer patients, the Strata Trial (NCT03061305), an RNA expression score of more than 22 (scale 0 -100) was validated as 100% sensitive and 70% specific for predicting PD-L1 tumor proportion score of ≥50%.[40] PD-L1 expression in lung cancer and breast cancer has proven to select patients that benefit most from checkpoint-inhibition, this has not yet been established for endometrial cancer.

The few trials published on PD-L1 or PD-1 inhibition in recurrent gynecological cancer showed clinical efficacy and an acceptable safety profile in endometrial cancer,[29, 41] cervical cancer[42] and ovarian cancer.[43-45] However, last update of the three-arm phase 3 JAVELIN Ovarian 100 and 200 trials in both patients with primary stage III or IV ovarian cancer and patients with platinum resistant or refractory ovarian cancer showed no significant difference in progression free survival (PFS) or overall survival (OS) after evaluating avelumab in combination with and/or following platinum-based chemotherapy, and avelumab with pegylated liposomal doxorubicin monotherapy, respectively.[46, 47] Le et al. [41] investigated pembrolizumab in patients with advanced MMRd cancers across 12 different tumor types. Of all tumor types, the highest frequency of MMRd was seen in endometrial cancer (17%). Objective response rate (ORR) was 53%, and complete responses were achieved in 21% of the 86 patients, of whom 15 had endometrial cancer. Pembrolizumab demonstrated a durable antitumor activity in 24 patients with heavily pretreated advanced PD-L1-positive endometrial cancer in the KEYNOTE-028.[29] Objective radiographic responses were observed in 13%, and stable disease also in 13%. No complete responses were observed and median PFS was 1.8 months (95% CI 1.6–2.7 months). Among all 19 tumor samples evaluable for MSI status the only tumor with MSI-high status had a partial response. The other two patients with a partial response had non-MSI-high status; one of them was *POLE*-mutated. This indicates that treatment effect is most pronounced in the MMRd subgroup, but it is not limited to this subgroup. Monotherapy is generally tolerated,[29, 35, 41-44, 48, 49] although awareness of immune-related adverse events is warranted.

Several phase 1 and 2 studies are currently recruiting patients with recurrent endometrial cancer to investigate anti PD-1 (NCT02628067, NCT02899793, NCT02728830, NCT03241745, NCT03474640, NCT02715284) or anti PD-L1 monotherapy (NCT03212404) in a single group design or compared to the combination with a monoclonal antibody against CTLA-4 in a randomized open label trial (NCT03015129). Two recruiting phase 3 trials are to investigate the addition of anti-PD-L1 therapy to the usual chemotherapy treatment (paclitaxel and carboplatin) in advanced or recurrent endometrial cancer (NCT03914612, NCT03981796).

4. PARP inhibition

Currently, PARP inhibitors are part of standard-of-care therapy for selected patients with ovarian cancer and metastatic breast cancer. PARP facilitates DNA damage repair in case of single-strand DNA breaks. Inhibition of PARP leads to accumulation of DNA damage and double-strand DNA breaks (DSBs). DSBs are repaired by two major pathways: homologous recombination repair and the more error prone 'nonhomologous end joining'. In patients whose tumors exhibit homologous recombination-deficiency (HRD), DNA repair is impaired and consequently these patients may be more sensitive to PARP inhibition.[15]

The various PARP inhibiting agents include olaparib, niraparib, rucaparib, talazoparib, and veliparib.[19] In December 2018, olaparib was approved as frontline maintenance therapy for germline *BRCA1/2* mutation associated ovarian cancer with response to platinum-based chemotherapy. Approval was based on the SOLO-1 trial,[50] that showed an improvement of median PFS after olaparib compared to placebo (49.9 versus 13.8 months, HR 0.30, 95% CI 0.23–0.41; $p < .01$). Recent phase 3 trials confirm the effectivity of PARP inhibition as frontline therapy after response to platinum-based chemotherapy[19] even in HR-proficient tumors (although to a lesser extent).[20] Moreover, olaparib, niraparib and rucaparib have been approved for maintenance therapy in patients with recurrent ovarian cancer regardless of *BRCA*-status, who responded to platinum-based chemotherapy based on the SOLO-2, NOVA and ARIEL-3 trials.[16-18] In addition, olaparib and talazoparib have received FDA approval for treating patients with *BRCA*-mutated metastatic breast cancer, based on PFS improvement in the phase 3 EMBRACA[51] and OlympiAD trials.[52] Adverse events, including fatigue, gastro-intestinal and hematologic adverse events, were generally acceptable and manageable with dose modifications and delays.[16-21, 50-52] An overview of these studies is displayed in Appendix Table A1.

The hypothesized benefit of PARP inhibition in endometrial cancer is based on the observed effect in *BRCA1/2* mutated and HRD tumors mentioned above. Whether endometrial cancer should be considered part of germline *BRCA*-associated syndrome is under debate.[53] Nevertheless, previous research pointed out molecular similarities of serous-like/SCNA-high endometrial cancer and both basal-like breast cancer and high-grade serous ovarian cancer, including a high number of SCNAs and frequent *TP53* mutations.[12] Serous-like/SCNA-high endometrial cancers also frequently are HRD.[14] In general, HRD tumors are sensitive to platinum-based chemotherapy and PARP inhibitors.[54, 55]

Currently, no clinical trials on PARP inhibition in endometrial cancer have been published. However, there are three upcoming or currently recruiting trials in recurrent or metastatic endometrial cancer. In a single group phase 2 trial, the efficacy of niraparib is being

investigated in 44 patients (NCT03016338). Two planned randomized placebo-controlled trials will investigate the activity of rucaparib (NCT03617679) and olaparib (NCT03745950) in respectively 138 and 147 patients with metastatic endometrial cancer.

5. Combination therapy

There is growing interest in combining immunotherapy with other targeted agents and with chemotherapy in all endometrial cancer subtypes. However, only one clinical trial combining immunotherapy with other targeted therapy in endometrial cancer has been published. Makker and Taylor et al.[56, 57] investigated the combination of pembrolizumab and lenvatinib, a multikinase inhibitor targeting VEGFR, FGFR, and PDGFR in a phase 2 study in selected solid tumors, including endometrial cancer, irrespective of MMRd or PD-L1 expression status. Grade 3 or higher treatment related adverse events occurred in 67–68%. Dose interruptions (70%) or dose reductions (63–64%) were needed to manage adverse events in the majority of patient; 15–16% of the patients discontinued the study due to adverse events.[56, 57] The ORR at 24 weeks among the 108 patients with metastatic endometrial cancer was 38% (95% CI 29–48%) and median PFS was 7.4 months (95% CI 5.3–8.7).[57] ORRs for participants with MMRd (94 patients) and MMR proficient (11 patients) endometrial cancer were 36% and 64%, respectively. As a result of the high anti-tumor activity the FDA has approved this combination for metastatic endometrial cancer that is not MSI-H or MMRd in September 2019. Two randomized phase 3 trials (KEYNOTE-775/NCT03517449, ENGOT-EN9/LEAP-001/NCT03884101) are currently recruiting.

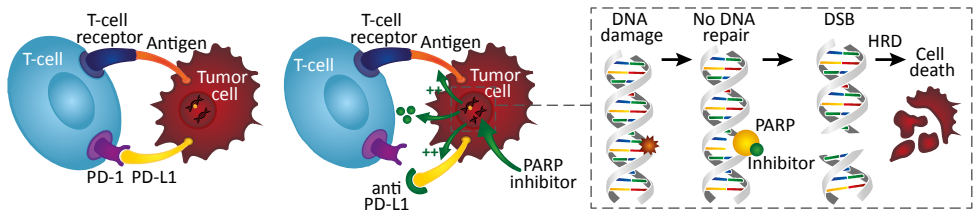

Figure 1. Effect of anti-PD-L1 and PARP inhibition.
Interaction of PD-1 and PD-L1 inhibts cytotoxic T lymphocytes (CTLs) activity, allowing the cancer cells to escape immune detection. Poly (ADP-ribose) polymerase (PARP) inhibitors and anti-PD-L1 antibodies synergize and may enhance an antitumor immune response mediated by specific activated CTLs against tumor antigens. Inhibition of PARP leads to accumulation of DNA damage and double-strand DNA breaks (DSBs). In patients whose tumors exhibit homologous recombination-deficiency (HRD), DNA repair is impaired which can lead to apoptotic death. In addition, DNA damage due to PARP inhibition causes upregulation of chemokines and neo-antigen expression (green arrows) and induces an immune response mediated by CTLs. Anti-PD-L1 can reverse the potential immune escape of tumor cell mediated by the PD-L1 upregulation induced by PARP inhibitors. *Reprinted with permission from Ned Tijdschr Oncol 2019;14:(8).*

Both PARP inhibition and PD-1/PD-L1 inhibition have the potential to show activity in specific subgroups of endometrial cancer as monotherapy. The combination of these two agents is promising and currently being investigated among several tumor types (Table 1). Preclinical studies have shown that the combination can have additive or even synergistic effects. The accumulation of DNA damage caused by PARP inhibition may complement anti-tumor activity of immune checkpoint blockade by expanding neoantigen expression and greater immune recognition of the tumor.[58-60] *In vitro* and *in vivo* breast cancer models have shown that PARP inhibitors inactivate glycogen synthase kinase 3, which in turn up-regulates PD-L1 expression.[61] Another study does not show upregulation of PD-L1 expression, although high PD-L1 expression was seen in the models that did not respond to PARP inhibition.[62] Checkpoint inhibition can theoretically restore antitumor immunity and enhance the antitumor activity of PARP inhibitors (Figure 1). The benefit may be expected the most in *TP53* mutated endometrial cancer. Moreover, a substantial part of MMRd tumors harbor one or more mutations in key components of the cellular DNA damage response pathway such as At-rich interactive domain 1A (ARID1A) or meiotic recombination 11 (MRE11),[63, 64] which may sensitize cancer cells to PARP inhibitors.[65] Together, although data is still limited, these preclinical studies support the potential added (or even synergistic) effect of combining PARP inhibitors and checkpoint inhibitors.

There are only few published clinical trials on combined checkpoint and PARP inhibition, predominantly in ovarian cancer. The recently published phase 1/2 TOPACIO study showed promising response to niraparib combined with pembrolizumab in triple negative breast cancer or ovarian cancer, irrespective of *BRCA* mutation status or PD-L1 expression. They reported an ORR of 18% and a disease control rate (DCR) of 65% in 62 patients with ovarian cancer and respectively 21% and 49% in 55 patients with triple negative breast cancer.[66, 67] A dose-escalation phase 1 trial by Jung-Min et al.[68] reported an ORR of 17% and a DCR of 83% without any dose-limiting toxicity with the durvalumab-olaparib combination in 12 patients with ovarian cancer or triple negative breast cancer. Preliminary results of the first 32 *BRCA* mutated platinum-sensitive relapsed ovarian cancer patients in the MEDIOLA-trial showed promising efficacy with a particularly high ORR of 72% with a total of seven complete responses. Most common grade 3 or higher adverse events were anemia (17.6%), elevated lipase (11.8%), neutropenia (8.8%), and lymphopenia (8.8%). Five patients discontinued olaparib and three discontinued durvalumab due to an adverse event.[69, 70] This treatment regimen also demonstrated efficacy and acceptable toxicity in metastatic castration-resistant prostate cancer.[71] In the randomized phase 3 JAVELIN Ovarian PARP 100 trial patients with primary stage III or IV ovarian cancer were randomized to chemotherapy and avelumab followed by maintenance avelumab and talazoparib versus an active comparator. Despite a good safety profile, efficacy interim analysis did not support continuation of the avelumab-talazoparib combination in an unselected patient population.[72]

Several studies are ongoing to investigate the safety and efficacy of combining PARP inhibition and PD-1/PD-L1 pathway inhibition in gynecological cancers. The current recruiting studies are displayed in Table 1. Three of these studies include patients with recurrent or persistent endometrial cancer. The open-label two-group phase 2 study (NCT02912572) [73] is designed for 70 patients previously treated with at least one line of chemotherapy. Cohort-1, including MSI-H and/or *POLE*-mutant endometrial cancers, are to receive avelumab monotherapy. Cohort 2, which includes microsatellite stable tumors with negative or unknown *POLE*-mutation status, will receive the combination therapy of avelumab and talazoparib. Secondly, the combination of PARP inhibition with a PD-1 blocker is investigated in a phase 1/2 study among 60 patients with either recurrent endometrial cancer or castration resistant prostate cancer (NCT03572478).

The combination of PARP inhibition and PD-L1 blocking is investigated among all molecular subgroups of endometrial cancer in the DOMEC trial (NCT03951415; Figure 2). This study has been initiated by the Dutch Gynecological Oncology Group. It is a multi-center, single arm phase 2 trial for 55 patients with metastatic, refractory or recurrent endometrial cancer (including carcinosarcoma) to investigate the efficacy of the combination therapy of olaparib and durvalumab. Patients who have not responded to or who have relapsed after at least one prior line of chemotherapy or who are not able/willing to get chemotherapy are eligible for the study. The primary endpoint is PFS.

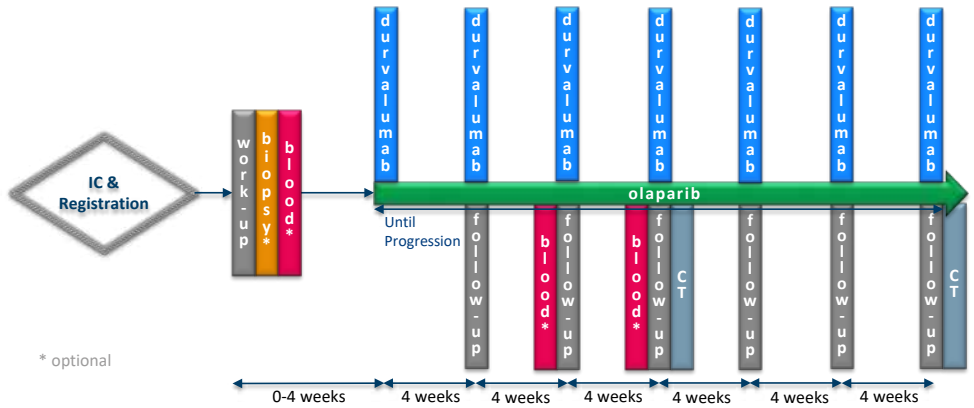

Figure 2. Participant timeline DOMEC-trial.
CT = CT scan of the abdomen and chest (or MRI when indicated); IC = Informed consent; Work-up consists of: history, physical examination, blood including chemistry and hematology, electrocardiogram and imaging; Follow-up consists of: history, physical examination, blood chemistry and hematology.
*Optionally an additional blood sample for immune-monitoring or an additional fresh frozen biopsy.

Table 1. Ongoing trials combining PARP inhibitors and PD-L1/PD-1 pathway inhibitors in gynecological cancers

Drug	NCT number Acronym	Conditions		*N*	Phase	Design	Country
Olaparib + Durvalumab	NCT03951415 DOMEC	RP	Advanced Endometrial Cancer	55	2	Single Group	NL
	NCT03737643 DUO-O	ND	Advanced OC	1056	3	Randomized Blinded	US + 15
	NCT03699449 AMBITION	RP	Platinum-resistant OC	68	2	Randomized Open Label	KR
	NCT02734004 MEDIOLA	RP	Advanced Solid tumors (incl. OC)	427	1/2	Single Group	US + 6
Avelumab + Talazoparib	NCT02912572	RP	Advanced Endometrial Cancer (cohort2: MSS)	70	2	Non-Randomized Open label	US
	NCT03330405	RP	Locally Advanced or Metastatic tumors	242	2	Sequential Open label	US + 6
Rucaparib + nivolumab	NCT03572478	RP	Advanced Endometrial Cancer (and CRPC)	60	1b/2a	Single Group / Randomized	US
	NCT03522246 ATHENA	ND	Platinum-responsive Advanced OC	1012	3	Randomized Blinded	US + 8
	NCT03824704	RP	OC*	139	2	Non-Randomized Open label	US
Niraparib + TSR-042	NCT03602859 FIRST	ND	Advanced OC	960	3	Randomized Blinded	US + 8
	NCT03574779 OPAL	ND RP	High-grade OC	40	2	Single group	US
Niraparib + Atezolizumab	NCT03598270 ANITA	RP	Advanced OC	414	3	Randomized Blinded	ES
Rucaparib + Atezolizumab	NCT03101280	RP	Advanced OC and TNBC	48	1	Non-Randomized Open Label	AU + 3

Several studies have multiple treatment arms to compare to standard treatment, mono therapy and/or other novel drug combinations. Advanced disease is defined as stadium III-IV; AU = Australia; BC = breast cancer; BE = Belgium; CRPC = castrate-resistant prostate cancer; ES = Spain; KR = Korea; TNBC = triple negative breast cancer; NL = the Netherlands; MSS = microsatellite stable ND = newly diagnosed; OC = ovarian cancer; RP = recurrent or persistent; US = United States.
*or locally advanced unresectable/metastatic transitional cell urothelial carcinoma

6. Conclusion

In conclusion, both PARP inhibitors and checkpoint inhibitors are promising effective novel modalities in cancer treatment. PARP inhibitors are part of standard-of-care therapy for ovarian cancer and metastatic breast cancer. Checkpoint inhibition by anti-PD-1/PD-L1 pathway antibodies is indicated for unresectable or metastatic MSI or MMRd solid tumors. Combining these agents in the treatment of recurrent and metastatic endometrial cancer seems promising as these agents may have a synergistic effect. This combination is currently investigated in phase 2 setting. Depending on the results of those studies subsequent phase 3 trials of PARP and checkpoint inhibition in advanced endometrial cancer will be conducted.

References

1 Cronin KA, Lake AJ, Scott S, Sherman RL, Noone A-M, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. 2018;124(13):2785-800.

2 IKNL. Dutch cancer figures [Cijfers over Kanker]. Available from: http://www.cijfersoverkanker.nl [Accessed Nov 2019].

3 Miller D, Filiaci V, Fleming G, Mannel R, Cohn D, Matsumoto T, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol. 2012;125(3):771.

4 Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. Int J Gynecol Cancer. 2007;17(5):964-78.

5 Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999;17(6):1736-44.

6 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.

7 Francis SR, Ager BJ, Do OA, Huang YJ, Soisson AP, Dodson MK, et al. Recurrent early stage endometrial cancer: Patterns of recurrence and results of salvage therapy. Gynecol Oncol. 2019;154(1):38-44.

8 de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019.

9 Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

10 Eggink FA, Van Gool IC, Leary A, Pollock PM, Crosbie EJ, Mileshkin L, et al. Immunological profiling of molecularly classified high-risk endometrial cancers identifies POLE-mutant and microsatellite unstable carcinomas as candidates for checkpoint inhibition. Oncoimmunology. 2017;6(2):e1264565.

11 van Gool IC, Eggink FA, Freeman-Mills L, Stelloo E, Marchi E, de Bruyn M, et al. POLE Proofreading Mutations Elicit an Antitumor Immune Response in Endometrial Cancer. Clin Cancer Res. 2015;21(14):3347-55.

12 Levine DA, The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67.

13 Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, et al. Oncogenic Signaling Pathways in The Cancer Genome Atlas. Cell. 2018;173(2):321-37 e10.

14 de Jonge MM, Auguste A, van Wijk LM, Schouten PC, Meijers M, Ter Haar NT, et al. Frequent Homologous Recombination Deficiency in High-grade Endometrial Carcinomas. Clin Cancer Res. 2019;25(3):1087-97.

15 Lim JSJ, Tan DSP. Understanding Resistance Mechanisms and Expanding the Therapeutic Utility of PARP Inhibitors. Cancers (Basel). 2017;9(8).

16 Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274-84.

17 Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-64.

18 Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10106):1949-61.

19 Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med. 2019;381(25):2403-2415.

20 Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019;381(25):2391-2402.

21 Ray-Coquard IL, Pautier P, Pignata S, Pérol D, González-Martín A, Sevelda P, et al. Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. Ann Oncol. 2019;30(Supplement_5).

22 Soumerai TE, Donoghue MTA, Bandlamudi C, Srinivasan P, Chang MT, Zamarin D, et al. Clinical Utility of Prospective Molecular Characterization in Advanced Endometrial Cancer. Clin Cancer Res. 2018;24(23):5939-47.

23 Ashley CW, Da Cruz Paula A, Kumar R, Mandelker D, Pei X, Riaz N, et al. Analysis of mutational signatures in primary and metastatic endometrial cancer reveals distinct patterns of DNA repair defects and shifts during tumor progression. Gynecol Oncol. 2019;152(1):11-9.

24 Gibson WJ, Hoivik EA, Halle MK, Taylor-Weiner A, Cherniack AD, Berg A, et al. The genomic landscape and evolution of endometrial carcinoma progression and abdominopelvic metastasis. Nat Genet. 2016;48(8):848-55.

25 Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and Characterization of MEDI4736, an Antagonistic Anti–PD-L1 Monoclonal Antibody. Cancer Immunol Res. 2015;3(9):1052.

26 Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and Its Ligands in Tolerance and Immunity. Annu Rev Immunol. 2008;26(1):677-704.

27 Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2018;379(4):341-51.

28 Xiao Y, Yu S, Zhu B, Bedoret D, Bu X, Francisco LM, et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. J exp med. 2014;211(5):943-59.

29 Ott PA, Bang YJ, Berton-Rigaud D, Elez E, Pishvaian MJ, Rugo HS, 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(22):2535-41.

30 Nebot-Bral L, Brandao D, Verlingue L, Rouleau E, Caron O, Despras E, et al. Hypermutated tumours in the era of immunotherapy: The paradigm of personalised medicine. Eur J Cancer. 2017;84:290-303.

31 Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;372(26):2509-20.

32 Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515:558.

33 Rizvi NA, Brahmer JR, Ou S-HI, Segal NH, Khleif S, Hwu W-J, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). J Clin Oncol. 2015;33(15_suppl):8032.

34 Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol. 2015;33(15_suppl):3011.

35 Dirix LY, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, Forero-Torres A, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2018;167(3):671-86.

36 Li Z, Joehlin-Price AS, Rhoades J, Ayoola-Adeola M, Miller K, Parwani AV, et al. Programmed Death Ligand 1 Expression Among 700 Consecutive Endometrial Cancers: Strong Association With Mismatch Repair Protein Deficiency. Int J Gynecol Cancer. 2018;28(1):59-68.

37 Sloan EA, Ring KL, Willis BC, Modesitt SC, Mills AM. PD-L1 Expression in Mismatch Repair-deficient Endometrial Carcinomas, Including Lynch Syndrome-associated and MLH1 Promoter Hypermethylated Tumors. Am J Surg Pathol. 2017;41(3):326-33.

38 Luchini C, Bibeau F, Ligtenberg MJL, Singh N, Nottegar A, Bosse T, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol. 2019;30(8):1232-43.

39 Sungu N, Yildirim M, Desdicioglu R, Basaran Aydogdu O, Kilicarslan A, Tatli Dogan H, et al. Expression of Immunomodulatory Molecules PD-1, PD-L1, and PD-L2, and their Relationship With Clinicopathologic Characteristics in Endometrial Cancer. Int J Gynecol Pathol. 2018.

40 Sobecki-Rausch J, Barroilhet L. Anti-programmed Death-1 Immunotherapy for Endometrial Cancer with Microsatellite Instability-High Tumors. Curr Treat Options Oncol. 2019;20(11):83.

41 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-13.

42 Chung HC, Schellens JHM, Delord J-P, Perets R, Italiano A, Shapira-Frommer R, et al. Pembrolizumab treatment of advanced cervical cancer: Updated results from the phase 2 KEYNOTE-158 study. J Clin Oncol. 2018;36(15_suppl):5522.

43 Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, et al. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol. 2015;33(34):4015-22.

44 Varga A, Piha-Paul S, Ott PA, Mehnert JM, Berton-Rigaud D, Morosky A, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. Gynecol Oncol. 2019;152(2):243-50.

45 Disis ML, Taylor MH, Kelly K, Beck JT, Gordon M, Moore KM, et al. Efficacy and Safety of Avelumab for Patients With Recurrent or Refractory Ovarian Cancer: Phase 1b Results From the JAVELIN Solid Tumor Trial. JAMA Oncol. 2019;5(3):393-401.

46 E. Pujade-Laurainea, K. Fujiwarab, J.A. Ledermannc, A.M. Ozad, R.S. Kristeleitc, I.L. Ray-Coquarde, et al., editors. Avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: Primary and biomarker analysis of the phase III JAVELIN Ovarian 200 trial. Abstracts 50th Annual Meeting of the Society of Gynecologic Oncology; 2019; Honolulu.

47 Merck and Pfizer Provide Update on JAVELIN Ovarian 100 Trial of Avelumab in Previously Untreated Advanced Ovarian Cancer2018 11-10-2019 11-10-2019]. Available from: https://www.merckgroup.com/en/news/javelin-ovarian-100-21-12-2018.html.

48 Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018;379(22):2108-21.

49 Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol. 2016;34(21):2460-7.

50 Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379(26):2495-505.

51 Litton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753-63.

52 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-33.

53 de Jonge MM, Ritterhouse LL, de Kroon CD, Vreeswijk MPG, Segal JP, Puranik R, et al. Germline BRCA-associated Endometrial Carcinoma is a Distinct Clinicopathologic Entity. Clin Cancer Res. 2019;25(24):7517-7526.

54 Stewart RA, Pilie PG, Yap TA. Development of PARP and Immune-Checkpoint Inhibitor Combinations. Cancer Res. 2018;78(24):6717-25.

55 Mendes-Pereira AM, Martin SA, Brough R, McCarthy A, Taylor JR, Kim JS, et al. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med. 2009;1(6-7):315-22.

56 Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, et al. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. J Clin Oncol. 2020;38(11):1154-63.

57 Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients With advanced endometrial cancer. J Clin Oncol. 2020;38(26):2981-2992.

58 Cesaire M, Thariat J, Candeias SM, Stefan D, Saintigny Y, Chevalier F. Combining PARP inhibition, radiation, and immunotherapy: A possible strategy to improve the treatment of cancer? Int J Mol Sci. 2018;19(12):3793.

59 Ding L, Kim HJ, Wang Q, Kearns M, Jiang T, Ohlson CE, et al. PARP Inhibition Elicits STING-Dependent Antitumor Immunity in Brca1-Deficient Ovarian Cancer. Cell Rep. 2018;25(11):2972-80 e5.

60 Pantelidou C, Sonzogni O, De Oliveria Taveira M, Mehta AK, Kothari A, Wang D, et al. PARP Inhibitor Efficacy Depends on CD8(+) T-cell Recruitment via Intratumoral STING Pathway Activation in BRCA-Deficient Models of Triple-Negative Breast Cancer. Cancer Discov. 2019;9(6):722-37.

61 Jiao S, Xia W, Yamaguchi H, Wei Y, Chen M-K, Hsu J-M, et al. PARP Inhibitor Upregulates PD-L1 Expression and Enhances Cancer-Associated Immunosuppression. Clin Cancer Res. 2017;23(14):3711.

62 Pellegrino B, Llop-Guevara A, Pedretti F, Cruz C, Castroviejo M, Cedro-Tanda A, et al. PARP inhibition increases immune infiltration in homologous recombination repair (HRR)-deficient tumors. Ann Oncol. 2019;30(Supplement_5).

63 Giannini G, Rinaldi C, Ristori E, Ambrosini MI, Cerignoli F, Viel A, et al. Mutations of an intronic repeat induce impaired MRE11 expression in primary human cancer with microsatellite instability. Oncogene. 2004;23(15):2640-7.

64 Bosse T, ter Haar NT, Seeber LM, Diest PJv, Hes FJ, Vasen HFA, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. Modern Pathology. 2013;26(11):1525-35.

65 Shen J, Peng Y, Wei L, Zhang W, Yang L, Lan L, et al. ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors. Cancer Discov. 2015;5(7):752-67.

66 Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Tan AR, et al. Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. JAMA Oncol. 2019;5(8):1132-1140.

67 Konstantinopoulos PA, Waggoner S, Vidal GA, Mita M, Moroney JW, Holloway R, et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. JAMA Oncol. 2019 ;5(8):1141-1149.

68 Lee JM, Cimino-Mathews A, Peer CJ, Zimmer A, Lipkowitz S, Annunziata CM, et al. Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study. J Clin Oncol. 2017;35(19):2193-202.

69 Drew Y, de Jonge M, Hong SH, Park YH, Wolfer A, Brown J, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline BRCA-mutated (gBRCA) platinum-sensitive relapsed (PSR) ovarian cancer (OC). Gynecol Oncol. 2018;149:246-7.

70 Drew Y, Kaufman B, Banerjee S, Lortholary A, Hong SH, Park YH, et al. Phase II study of olaparib + durvalumab (MEDIOLA): Updated results in germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer (OC). Ann Oncol. 2019;30(Supplement_5).

71 Karzai F, VanderWeele D, Madan RA, Owens H, Cordes LM, Hankin A, et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J Immunother Cancer. 2018;6(1):141.

72 Merck Kgaa, Darmstadt, Germany, and Pfizer Announce Discontinuation of Phase III Javelin Ovarian PARP 100 Trial in Previously Untreated Advanced Ovarian Cancer2019. Available from: https://www.pfizer.com/news/press-release/press-release-detail/merck_kgaa_darmstadt_germany_and_pfizer_announce_discontinuation_of_phase_iii_javelin_ovarian_parp_100_trial_in_previously_untreated_advanced_ovarian_cancer.

73 Konstantinopoulos PA, Liu JF, Barry WT, Krasner CN, Buss MK, Birrer MJ, et al. Phase 2, two-group, two-stage, open-label study of avelumab in patients with microsatellite stable, microsatellite instable and POLE-mutated recurrent or persistent endometrial cancer. J Clin Oncol. 2017;35(15_suppl):TPS5615-TPS.

APPENDIX A

A1. Search strategy

A comprehensive search in PubMed and clinicaltrials.gov was performed for clinical studies published or posted in English on February 28, 2019, with the terms and synonyms of "gynecological cancer" OR "endometrial cancer" OR "ovarian cancer" OR "cervical cancer" OR "breast cancer" AND "PARP inhibitor" OR "checkpoint inhibitor". References of relevant records were also evaluated for cross-referencing. We identified 5 relevant (phase 3) trial publications for PARP inhibition monotherapy (0 in endometrial cancer), 8 relevant (phase 1-2) published trials for PD-1/PD-L1 blocking monotherapy (2 in endometrial cancer) and 1 relevant (phase 1) trial publication for the combination therapy (0 in endometrial cancer). An updating PubMed search was performed on May 22, 2019, resulting 1 additional relevant (phase 2) trial publication for PARP or checkpoint inhibitor combined with another immunotherapy or targeted therapy agent in endometrial cancer. A last update was done on August 15, 2019 resulting in addition of the TOPACIO trial publications (combined treatment in ovarian and breast cancer). Finally, relevant abstracts presented at ESMO Congress 2019 were included in the manuscript.

Table A1. Overview of phase 3 PARP inhibition studies in gynecological cancer and breast cancer

	Conditions						
	BRCAm			***N***	**Phase**	**Agents**	**endpoint**
SOLO-1 *Moore, 2018*	ND	+	OC*	391	3	Olaparib vs placebo (2:1)	mPFS 49.9 vs 13.8m; HR 0.30 (0.23-0.41); *p*<0.01
SOLO-2 *Pujade, 2019*	RP	+	OC	295	3	Olaparib vs placebo (2:1)	mPFS 19.1 vs 5.5m; HR 0.30 (0.22-0.41); *p*<0.01
NOVA *Mirza, 2016*	RP	+/-	OC	553	3	Niraparib vs placebo (2:1)	BRCA+: mPFS 21.0 vs 5.5m; HR 0.27 (0.17-0.41) BRCA-, HRD: mPFS 12.9 vs 3.8m; HR 0.38 (0.24-0.59) BRCA-: mPFS 9.3 vs 3.9m; HR 0.45 (0.34-0.61) *p*<0.01
ARIEL-3 *Coleman, 2017*	RP	+/-	OC	564	3	Rucaparib vs placebo (2:1)	BRCA+: mPFS 16.6 vs 5.4m; HR 0.23 (0.16-0.34); HRD: mPFS 13.6 vs 5.4m; HR 0.32 (0.24-0.42); BRCA+/-: mPFS 10.8 vs 5.4m; HR 0.37 (0.30-0.45); *p*<0.01
VELIA *Coleman, 2019*	ND	+/-	OC	1140	3	CT + veliparib followed by placebo / veliparib vs CT + placebo followed by placebo (1:1:1)	BRCA+: mPFS 34.7 vs 22.0 HR 0.44 (0.28-0.68) HRD: mPFS 31.9 vs 20.5 HR 0.57 (0.43-0.76) *p*<0.01 HRP: HR 0.81 (0.60-1.09)
PRIMA *González, 2019*	ND	+/-	OC*	733	3	Niraparib vs placebo (2:1)	HRD: mPFS 21.9 vs 10.4 HR 0.43 (0.31-0.59) HRP: HR 0.68 (0.49-0.94)** *p*<0.01
PAOLA-1 *Ray-Coquard, 2019*	ND	+/-	OC	806	3	Olaparib + bevacizumab vs placebo + bevacizumab (2:1)	BRCA+: mPFS 37.2 vs 21.7 HR 0.31 (0.20-0.47) BRCA-: mPFS 28.9 vs 16.0 HR 0.71 (0.58-0.88) BRCA+, HRD: mPFS 37.2 vs 17.7 HR 0.33 (0.25-0.45) BRCA0, HRD: mPFS 28.1 vs 16.6 HR 0.43 (0.28-0.66) HRP/unk: mPFS16.9 vs 16.0 HR 0.92 (0.72-1.17)
EMBRACA *Litton, 2018*	RP	+	BC	431	3	Talazoparib vs physician's choice single agent (2:1)	mPFS 8.6 vs 5.6m; HR 0.54 (0.41-0.71); *p*<0.01
OlympiAD *Robson, 2017*	RP	+	BC	302	3	Olaparib vs physician's choice single-agent (2:1)	mPFS 7.0 vs 4.2m; HR 0.58 (0.43-0.80); *p*<0.01

BC = breast cancer; BRCA+ = breast cancer gene mutation; BRCA- = no breast cancer gene mutation; CT = chemotherapy with carboplatin and paclitaxel; HR = hazard ratio; HRD = homologue recombinant deficient; HRP = homologue recombinant Proficient; m = months; mPFS = median progresion free survival; ND = newly diagnosed; OC = ovarium cancer; RP = recurrent or persistent.

* Advanced OC after complete/partial response platinum-based chemotherapy.

** NB In the homologue recombinant not determined group the hazard ratio was 0.83 (0.51-1.43).

A2. Design and eligibility criteria of the DOMEC-trial

Summary

The Durvalumab and Olaparib in Metastatic or recurrent Endometrial Cancer (NCT03951415; DOMEC) trial has been initiated by the Dutch Gynecological Oncology Group. The study is designed as a prospective, multi-center, single arm phase II study for 55 patients with metastatic, refractory or recurrent endometrial cancer (including carcinosarcoma of the uterus) to investigate the efficacy of the combination therapy of olaparib 300mg PO BID and durvalumab 1500mg IV q4w. Patients who have not responded to or who have relapsed after at least one prior line of chemotherapy or who are not able/willing to get chemotherapy are eligible for the study. The primary endpoint is progression free survival (PFS). Efficacy is defined as a median PFS of 6 months (compared to the estimated 30% PFS at 6 months without treatment). Forty-six evaluable patients are needed to test the null hypothesis according to Simon's two-stage design. With an expected drop-out rate of 20%, 55 patients will be entered into the trial. Interim analysis will be performed on the first 15 evaluable patients. Secondary endpoints include objective response rate (ORR) according to RECIST 1.1 criteria; overall survival (OS); adverse events assessed by NCI Common Terminology Criteria for adverse Events (CTCAE) version 5.0; and predictive biomarkers. Optional secondary endpoints are: baseline HRD assay and immunological effects of PARP-1 inhibition measured by tests for T cell and APC functionality and predictive biomarkers for PD-L1 blocking in blood. Baseline assessment consists of medical history including toxicity assessment, blood chemistry, hematological screening, a pregnancy test (in women of child-bearing potential), ECG, imaging (e.g. CT thorax/abdomen or MRI) and complete physical examination (incl. height, weight, WHO performance status and vital signs). Diagnosis will be centrally confirmed by the LUMC's Department of Pathology. Extra tumor biopsies will be performed for RAD51 testing (only at baseline) and at 3 times blood samples for immunomonitoring (50cc) will be taken; patients will be able to opt out of the extra biopsies and/or blood samples. Every 4 weeks during treatment and at completion of therapy physical examination, blood chemistry and hematology and imaging will be performed. Three months after last treatment, WHO performance status, hematology, chemistry and tumor assessment will be reported. Participant timeline is schematically shown in *Article Figure 2*. Treatment will be continued until disease progression, patient's request to discontinue or unacceptable toxicity. Total recruitment time is assumed to be 30 months. Follow-up after inclusion of the last subject will be 6 months, resulting in a total study duration of 36 months.

Eligibility criteria

To be eligible for the DOMEC-trial, patients must be (1) at least 18 years old, (2) have a WHO performance score of 0-1, and (3) have histologically confirmed diagnosis of EC (including carcinosarcoma of the uterus). There must be (4) a documented progressive disease (metastatic or locally advanced) according to RECIST 1.1 criteria. (5) Disease must be not amendable to local therapy, chemotherapy and hormonal therapy (or patient is not be able/willing to get chemotherapy). (6) Organ system function should be adequate, defined as adequate bone marrow function (Haemoglobin ≥ 10.0 g/dL, Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L, Platelet count ≥ 100 x 10^9 /L), liver function (Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 2.5 x ULN (in case of lever metastases ≤ 5x ULN) and kidney function (creatinine clearance ≥51 mL/min calculated according to Cockcroft-Gault or 24 hour urine clearance). (7) Life expectancy must be at least 16 weeks.

Patients with (1) history of leptomeningeal carcinomatosis, symptomatic brain metastases (uncontrolled despite of corticosteroids) or spinal cord compression are not eligible. Other exclusion criteria are (2) severe concomitant diseases; (3) active or prior documented autoimmune or inflammatory disorders; (4) active primary immunodeficiency; (5) active infections including tuberculosis, HIV, hepatitis B or C or (6) other malignant disease (except adequately treated non-melanoma skin cancer, lentigo maligna or carcinoma in situ without evidence of disease). (7) Prior treatment with PARP, PD1 or PD-L1 inhibitor; (8) prolonged QTc interval or family history of long QT syndrome; (9) severe psychiatric illness; (10) irreversible grade ≥2 toxicity from previous anti-cancer therapy; (11) major surgery in the last 2 weeks; (12) prior allogeneic bone marrow transplantation or double umbilical cord blood transplantation; (13) inability to swallow oral medication; (14) concurrent treatment with another investigational agent during the conduct of the trial or (15) known intolerance to olaparib or durvalumab will prohibit inclusion; as well as (16) pregnancy or breast feeding.

For more details see https://clinicaltrials.gov/ct2/show/NCT03951415.