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SGO Journal Club Commentary

Advanced endometrial cancer—The next generation of treatment: A society of gynecologic oncology journal club clinical commentary

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ABSTRACT

In February of 2024, the Society of Gynecologic Oncology (SGO) hosted a journal club focused on new treatment options for the management of advanced and metastatic endometrial cancer. This clinical commentary is intended to provide a summary report of that presentation. The session described the importance of molecular characterization shown in the work of The Cancer Genome Atlas (TCGA). The updated 2023 FIGO staging of endometrial cancer was reviewed. The panel then described the role of upfront immunotherapy for the treatment of advanced or recurrent endometrial cancer as demonstrated in four recent trials (RUBY, NRG-GY018, AtTEnd, and DUO-E studies). The DUO-E study uniquely examined the combination immunotherapy with a PARP inhibitor. The trials had unique differences in inclusion criteria, primary outcomes, and length of maintenance therapy, but all boasted similarly promising results particularly in mismatch repair deficient (dMMR) endometrial cancer. This era of rapid innovation in advanced and recurrent endometrial cancer will hopefully enhance individualized treatment approaches and improved outcomes for patients with endometrial cancer.

1. Introduction

The Society of Gynecologic Oncology (SGO) Journal Club webinar series is an open forum that provides members with input from national experts to discuss the literature pertaining to important topics in gynecologic oncology. On February 12, 2024, SGO hosted a journal club focused on new treatment options for the management of advanced and metastatic endometrial cancer. Our discussants included Drs. Anthony Karnezis, Dana Chase, and Todd Tillmanns. They reviewed the advances in molecular characterization of endometrial cancer and the updated 2023 FIGO staging criteria; followed by a review of the clinical trials investigating upfront immunotherapy and PARP inhibitors. This clinical commentary serves as a summary of the journal club presentation.

The mortality rate of endometrial cancer has been increasing in the United States (Somasegar et al., 2023). While 5-year survival in localized disease can be as high as 95 %, it is 70 % for those with regional disease and 18 % in those with distant stage disease (Society AC, 2024). For over a decade, treatment strategies for patients with advanced or recurrent endometrial cancer were stagnant and largely dependent on carboplatin and paclitaxel in the frontline and recurrent settings. However, with increasing availability of molecular tumor characterization, new treatment strategies specific to molecular subtypes have emerged. Within the past five years, developments in immunotherapy targeting the programmed death ligand (PD-L) pathway have brought the checkpoint inhibitors pembrolizumab and dostarlimab to the forefront of recurrence therapy for patients with MSI-H tumors following progression on carboplatin and paclitaxel. Within the past two years, landmark clinical trials have demonstrated the success of immunotherapy in the frontline setting for advanced or recurrent endometrial cancer.

The Cancer Genome Atlas (TCGA) marked a major advance in the field by comprehensively examining DNA mutations, gene expression, miRNA expression, DNA copy number alterations, microsatellite analysis, DNA methylation, and protein expression of 373 endometrioid and serous carcinomas. The TCGA established four molecular subtypes, termed copy-number high (serous-like), copy-number low,

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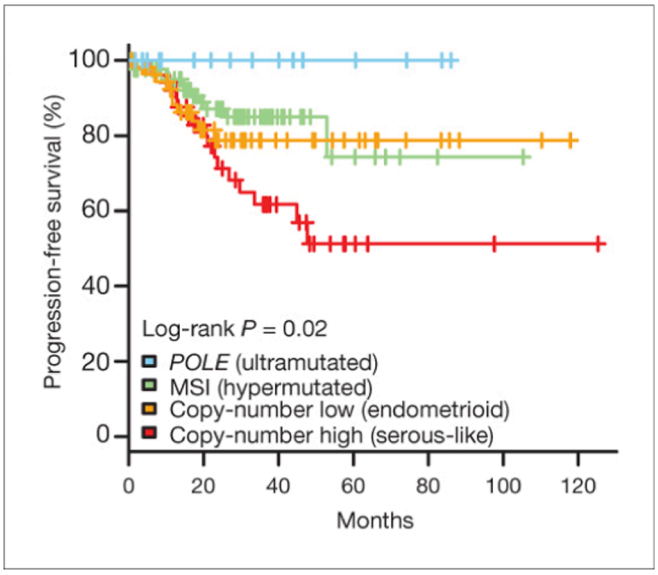

Fig. 1. Progression-free survival of endometrial carcinoma patients stratified by TCGA molecular subtype, established by comprehensive genomic analyses. Reproduced from reference (3).

microsatellite instability (MSI, hypermutated), and *POLE* (ultra-mutated) (Cancer Genome Atlas Research et al., 2013). Copy-number high tumors comprise all serous carcinomas and many high-grade (FIGO grade 3) endometrioid carcinomas. These tumors are characterized by high levels of DNA copy number alterations, high frequency of *TP53* mutations, and relatively poor prognosis (Fig. 1). In contrast, copy-number low tumors consist almost exclusively of low-grade (FIGO grades 1 and 2) endometrioid carcinomas that are essentially devoid of *TP53* mutations and have stable genomes with low tumor mutation burden (TMB, i.e. low number of mutations per megabase of DNA). MSI hypermutated tumors consist of both low-grade and high-grade endometrioid carcinomas, which are characterized mostly by *MLH1* promoter hypermethylation, rare *TP53* mutations, and ~ 10-fold higher TMB than copy-number low (or copy-number high) tumors. Both copy-number low and MSI (hypermutated) tumors have an intermediate prognosis (Fig. 1).

A significant discovery by TCGA was the identification of a new molecular subtype defined by hotspot mutations in the exonuclease domain of the *POLE* gene, which encodes the catalytic subunit of DNA polymerase epsilon. Mutations in the exonuclease (proofreading) domain, which occurred in approximately 7 % of the tumors tested, results in the inability to correct mismatched bases inserted during DNA replication. As a result, the genomes of *POLE* tumors have more mutations than even MSI (hypermutated) tumors (hence the ultra-mutated nomenclature). Though *POLE* tumors consist of both low-grade and high-grade endometrioid carcinomas that often harbor *TP53* mutations, patients with this molecular subtype typically have excellent outcomes (Fig. 1).

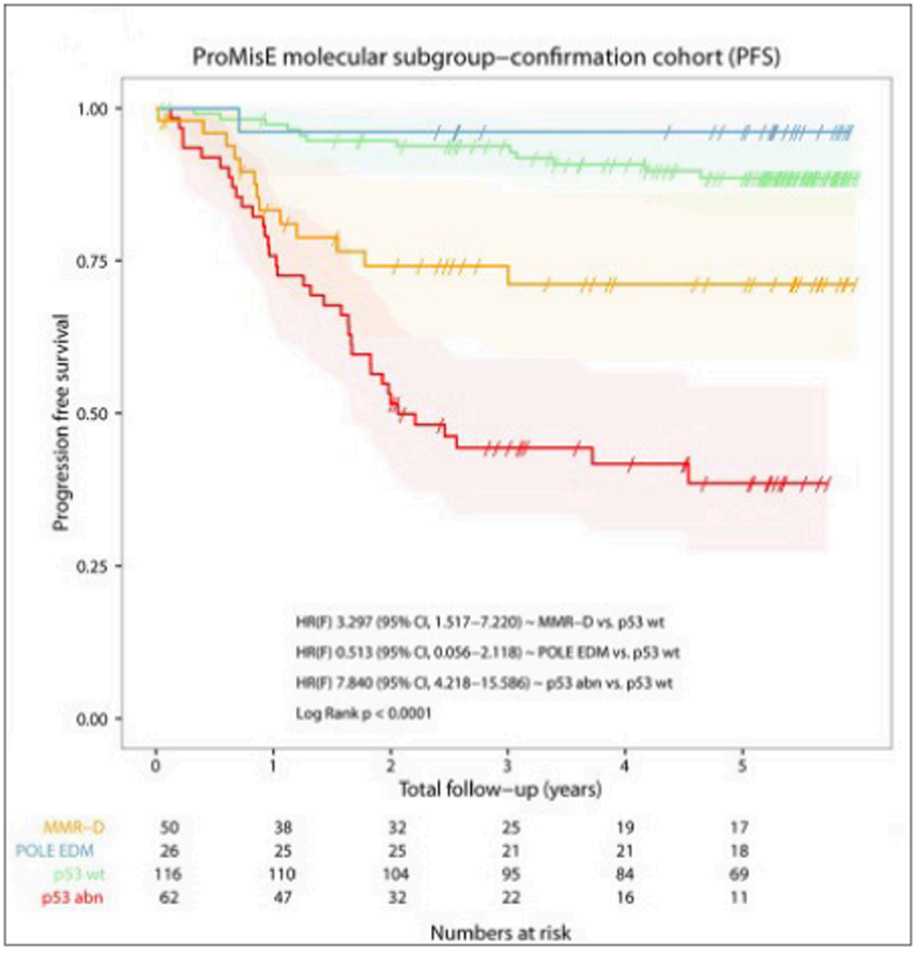

Fig. 2. Progression-free survival of endometrial carcinoma patients stratified by simplified molecular subtype, established by mismatch repair protein and p53 immunohistochemistry and POLE hotspot sequencing. (5).

Table 1
Comparison chart of patient characteristics by study design.

	NRG-GY018	RUBY	AtTEnd	DUO-E
Checkpoint Inhibitor	Pembrolizumab	Dostarlimab	Atezolizumab	Durvalumab
Mechanism of Action	PD-1 inhibitor	PD-1 inhibitor	PD-L1 inhibitor	PD-L1 inhibitor
PARP-inhibitor	None	None	None	Olaparib
Trial Design				
Dosing Frequency	Q3w on treatment, q6w on maintenance	Q3w on treatment, q6w on maintenance	Q3w on treatment and maintenance	Q3w on treatmemt and maintenance Q4w
Maintenance timeframe	14 cycles or until progression (Max of 20 cycles total)	For three years (26 cycles) or until progression	No maximum, until progression	No maximum, until progression
Randomization	1:1	1:1	2:1	1:1:1
Platinum-free Interval	12 months	6 months	6 months	12 months
Stage/Histology	Measurable: Stage III & IVA Non-measurable: Stage IVB or recurrent Excluded carcinosarcoma	Meeting RECIST criteria: Stage IIIA, IIIB, or IIIC1 Non-measurable: Stage IIIC2 or IV or Stage IIIC1 carcinosarcoma, clear cell, serous, or mixed	Stage III & IV Carcinosarcoma included	Stage III & IV Epithelial: Carcinosarcoma included Excluded sarcomas
Patient Characteristics				
Sample Size	816 (225 dMMR)	494 (118 dMMR)	549 (125 dMMR)	718 (143 dMMR)
Study sites in European Union	−	+	−	+
Study sites in United States	+	+	−	+
Median Age	dMMR- 66 pMMR- 65.5	dMMR- 61–66 All comers- 64–65	dMMR- 64 All comers- 65–67	All comers 63–64
Percentage of Asian/Black/ White/other/No Response Patients	dMMR- 3.1 %/8.9 %/79.1 % pMMR- 5.3 %/16.3 %/72.1 %	dMMR- 1.7 %/8.4 %/84.7 % All comers- 3.0 %/11.9 %/76.9 %	dMMR- 17.6 %/0%/82.4 % All comers- 20 %/UNK/ 78.7 %	All comers 30 %/5%/57 % /6%/2%
Percentage of Hispanic patients	dMMR- 4.9 % pMMR- 6.3 %	Not Reported	Not Reported	Not Reported
Primary Endpoints				
	PFS in dMMR and pMMR cohorts	Hierarchical: PFS in dMMR cohort > PFS in all-comers > OS in all-comers	PFS in dMMR and all-comers, OS in all-comers	PFS in dMMR: maint with Durvalumab (D) −vs- Durvalumab + Olaparib (DO)
PFS Hazard Ratio dMMR cohort	0.30 (95 % CI 0.19–0.48)	0.28 (95 % CI 0.16–0.50)	0.36 (95 % CI 0.23–0.57)	D-0.42 (0.22 to 0.80) DO-0.41 (0.21 to 0.75)
PFS Hazard Ratio pMMR cohort	0.54 (95 % CI 0.41–0.71)			D- 0.77 (0.60 to 0.97) DO-0.57 (0.44 to 0.73)
PFS Hazard Ratio All-comers		0.64 (95 % CI 0.51–0.80)	0.74 (95 % CI 0.61–0.91)	D-0.71 (0.57 to 0.89); P=.003 DO-0.55 (0.43 to 0.69); P<.0001 Intention To Treat
OS Hazard Ratio all-comers		0.64 (95 % CI 0.46–0.87)	0.82 (95 % CI 0.63–1.07)	OS did not reach significance at first interim analysis at 18.5 mos D-0.77 (0.56–1.07) DO-0.59 (0.42–0.83)

2. Simplified molecular classification

Due to time and cost considerations, the comprehensive TCGA genomic analyses are not practical for a clinical setting. However, three immunohistochemistry (IHC) stains and sequencing of the exonuclease domain (EDM) of *POLE* can identify the 4 molecular subtypes and give similar prognostic information as the full TCGA-style analysis (Fig. 2). (Talhouk et al., 2015; Talhouk et al., 2017; Kommoss et al., 2018; Stelloo et al., 2016) Defective mismatch repair (MMR) protein status (MMRd) (MLH1, PMS2, MSH2, or MSH6) by IHC is used as a surrogate for MSI (hypermutated) tumors. Since MMR proteins function as heterodimeric complexes (MLH1/PMS2 and MSH2/MSH6), a 2-antibody screening approach can be used as a highly sensitive and cost-saving alternative to conventional 4-antibody IHC to identify MMRd tumors (Aiyer et al., 2022); if either protein is lost, its heterodimeric partner can then be tested. Alternatively, MSI testing can be used to directly identify MSI status to define the MMRd/MSI molecular subtype (Stelloo et al., 2016). p53 IHC is highly sensitive and specific for *TP53* mutation status (Kobel et al., 2019) and can identify p53 abnormal/mutant tumors (p53abn or p53mut) as a surrogate for copy-number high (serous-like) tumors. *POLE* EDM sequencing identifies *POLE*-mutant tumors (POLEmut or POLE-EDM); approximately 5 % of endometrial cancers are POLE-mutated (PMID 37922951). A tumor is classified as POLEmut regardless of whether it also shows defective MMR IHC or abnormal p53 IHC (rare so-called "double classifier tumors") (Leon-Castillo et al., 2020). POLE IHC cannot be used to identify POLEmut tumors since mutation does not necessarily cause loss of protein expression. Tumors that show neither *POLE* EDM mutation nor abnormal MMR or p53 IHC are designated as p53 wild type / no specific molecular profile (p53wt or NSMP), which is a surrogate of copy-number low tumors. Similar molecular subtypes have been identified in endometrial clear cell carcinoma. (DeLair et al., 2017; Baniak et al., 2019; Kim et al., 2020).

This simplified molecular classification system shows higher concordance between diagnostic specimens and final hysterectomy specimens than conventional histotype and grade, which suggests it has the potential to guide both operative and postoperative management. (Talhouk et al., 2016) Importantly, molecular classification more accurately predicts patient prognosis, in particular for high-grade (FIGO grade 3) endometrioid carcinomas, which fall into all four molecular subtypes with very distinct outcomes. (Bosse et al., 2018).

3. 2023 FIGO staging system

Whereas prior FIGO staging systems stratify risk by pathologic and anatomical tumor location only, the new 2023 FIGO staging system uses ESGO/ESTRO/ESP guidelines as a template to integrate the anatomical location of the tumor with histotype (with tumors stratified into low-risk vs high-risk histotypes), presence and extent of LVSI and, when available, molecular subtype information into a comprehensive risk stratification system (Bosse et al., 2018). The goal of the new integrated staging

system is to improve its prognostic power, which will lead to better clinical decision making. However, it is not without controversy, including concern over the dichotomization of histotypes (lumping of FIGO grade 3 endometrioid carcinoma with non-endometrioid types into a single high-risk category), criteria and reproducibility of LVSI, lack of molecular testing in resource-limited environments, potential bottleneck for *POLE* send out testing, the non-intuitive nature of the new system, potential difficulty explaining historical clinical trials to patients in the context of the new staging system, the resulting confusion when a patient's assigned stage is changed with the new system, and others (Leitao Jr., 2024; McCluggage et al., 2023). Despite these concerns, it is increasingly clear that molecular classification is useful for stratifying patient prognosis and predicting response to differing treatment options for end0etrimental cancer patients.

4. Recently investigated immunotherapy agents

Dr. Chase continued the discussion with a review of recently investigated immunotherapy agents. Dostarlimab is a PD-1 inhibitor that has been approved by the FDA for treatment of endometrial cancer. Dostarlimab was first granted accelerated approval in the second line setting as a single agent in recurrent mismatch repair deficient endometrial cancer in April 2021, with full approval granted in February of 2023 (Administration USFD). This approval was based on the GARNET trial which demonstrated an overall response rate of 42.3 % (Oaknin et al., 2020). The RUBY trial was a phase 3, placebo controlled randomized control trial comparing carboplatin, paclitaxel and dostarlimab followed by dostarlimab maintenance to carboplatin and paclitaxel as frontline management of advanced or recurrent endometrial cancer. Progression-free survival in mismatch repair deficient tumors had a hazard ratio of 0.28. Improvement in PFS and overall survival for all patients was also improved with hazard ratios of 0.64 (Table 1) (Mirza et al., 2023). Based on findings from the RUBY Trial, in July of 2023 the FDA granted approval to dostarlimab in combination with carboplatin and paclitaxel followed by dostarlimab maintenance, in the frontline setting for recurrent or advanced mismatch repair deficient or microsatellite instability-high endometrial cancer. ((FDA) USFDA, 2024) Dostarlimab is not currently FDA approved for mismatch repair proficient tumors.

Pembrolizumab is another PD-1 inhibitor that has been approved by the FDA for treatment of endometrial cancer; to date this is for patients with dMMR tumors in the second line setting. Most recently, the NRG-GY018 phase 3, placebo controlled, randomized control trial has been published. This trial evaluated pembrolizumab in combination with carboplatin and paclitaxel followed by pembrolizumab maintenance in the frontline treatment of advanced or recurrent endometrial cancer. The primary outcome was progression free survival among MMR proficient and MMR deficient patients. PFS hazard ratio in the dMMR group was 0.30 and in the pMMR group was 0.58 (Table 1) ((FDA) USFDA, 2024). The FDA recently approved pembrolizumab with carboplatin and paclitaxel followed by pembrolizumab maintenance in the front line setting.

Similar to dostarlimab and pembrolizumab, atezolizumab is a checkpoint inhibitor which has been evaluated in conjunction with carboplatin and paclitaxel followed by a maintenance regimen in the front-line setting for advanced or recurrent endometrial cancer. Atezolizumab differs from dostarlimab and pembrolizumab in that it is a PD-L1 inhibitor rather than a PD-1 inhibitor, and it currently has no FDA approved use in endometrial cancer. The AtTEnd study is a phase 3 placebo controlled randomized control trial, like the RUBY trial and NRG-GY018. The AtTEnd study compares the above regimen to carboplatin and paclitaxel. While study results have not been published, preliminary results were presented at the European Society for Medical Oncology (ESMO) National Meeting in October 2023. Primary end points were PFS in both the dMMR and entire cohort and overall survival in the study cohort. Results in the dMMR population are promising with a hazard ratio of 0.36 for PFS. For all patients, PFS hazard ratio was 0.74 and OS hazard ratio was 0.82 (Colombo, 2023).

While there are many similarities in trial design and statistical analyses of the three trials noted above (RUBY, NRG GY-018, AtTENd), there are differences particularly in stated primary outcomes, inclusion of measurable vs non-measurable disease, and inclusion criteria with regard to histology. Differences and similarities are outlined in Table 1. Importantly, all of these trials utilized the prior FIGO staging system for inclusion criteria, not the updated FIGO 2023 staging. Overall, these phase 3 clinical trials have demonstrated significant patient benefit with the inclusion of immunotherapy in the frontline setting for these patients, particularly those with dMMR tumors.

5. Combination of PARP inhibition and immunotherapy

Dr. Tillmanns next addressed the role of combining immunotherapy with PARP inhibition in the DUO-E trial. DUO-E was an international, randomized phase 3 study for advanced stage and recurrent uterine cancer that evaluated the addition of durvalumab to paclitaxel and carboplatin with and without olaparib compared to standard paclitaxel and carboplatin and placebo maintenance. DUO-E built upon prior immunotherapy trials of durvulamab in endometrial cancer for patients with both pMMR and dMMR tumors (Westin et al., 2024). It was hypothesized that combining poly(ADP-ribose) polymerase (PARP) inhibitor with an immune checkpoint inhibitor may improve outcomes in both dMMR and pMMR tumors (Lee and Konstantinopoulos, 2019; Li et al., 2019; Stewart et al., 2018; Wanderley et al., 2022).

The study included three arms and 710 patients enrolled were randomized in a 1–1–1 fashion. All histological subtypes were eligible for enrollment, including carcinosarcoma. The control arm received paclitaxel and carboplatin followed by placebo maintenance. The durvalumab arm consisted of paclitaxel and carboplatin plus durvalumab followed by maintenance durvalumab. Lastly the durvalumab and olaparib arm consisted of paclitaxel and carboplatin plus durvalumab followed by maintenance durvalumab and olaparib (D+O). Patients received standard dosing of paclitaxel and carboplatin every 3 weeks.

In the intention to treat population, the durvalumab arm had a statistically and clinically significant lower risk of progression to death compared to the control arm (HR, 0.71 [95 % CI, 0.57 to 0.89]; $p = 0.003$. This was also noted to be improved in the D+O arm with HR, 0.55 [95 % CI, 0.43 to 0.69]; $p < 0.0001$ compared to control.

DUO-E also included prespecified subgroups for analysis including pMMR, dMMR, PD-L1 positive, PD-L1 negative, and homologous recombination deficiency/proficiency. In exploratory subgroup PFS analyses, all HR point estimates favored the durvalumab and D+O arms though not all findings were statistically significant. It seems that the addition of olaparib to durvalumab in dMMR patients may not yield substantial gains in PFS over placebo; however, in pMMR patients the addition of D+O appears to improve the PFS benefit above that of durvalumab alone. Further, the PD-L1 positive subgroup revealed a PFS benefit in both the durvalumab and D+O arms compared with control; however, these findings were not seen in the PD-L1 negative subgroup. In the PD-L1 positive group the HR for PFS in the durvalumab arm was 0.63 (95 % CI, 0.48 to 0.83) with median PFS 11.3 months. For the same group in the durvalumab + olaparib arm the HR for PFS was 0.42 (95 % CI, 0.31 to 0.57) and median PFS was 20.8 months.

The first interim analysis for overall survival took place for all 3 arms at an average of 18.5 months. Though hazard ratios for both investigational arms favored the experimental arms, neither reached statistical significance. The hazard ratio for durvalumab versus the control was 0.77 and that for durvalumab plus olaparib was 0.59.

In terms of safety and toxicity profiles for the three arms, myelosuppression was similar across groups. Grade three or higher anemia was also similar in the control and durvalumab arms but jumped in the durvalumab plus the olaparib group, which is consistent with known effects of PARPi on blood counts. The serious adverse events overall were 31 % in the control group, 31.1 % in the durvalumab group, and

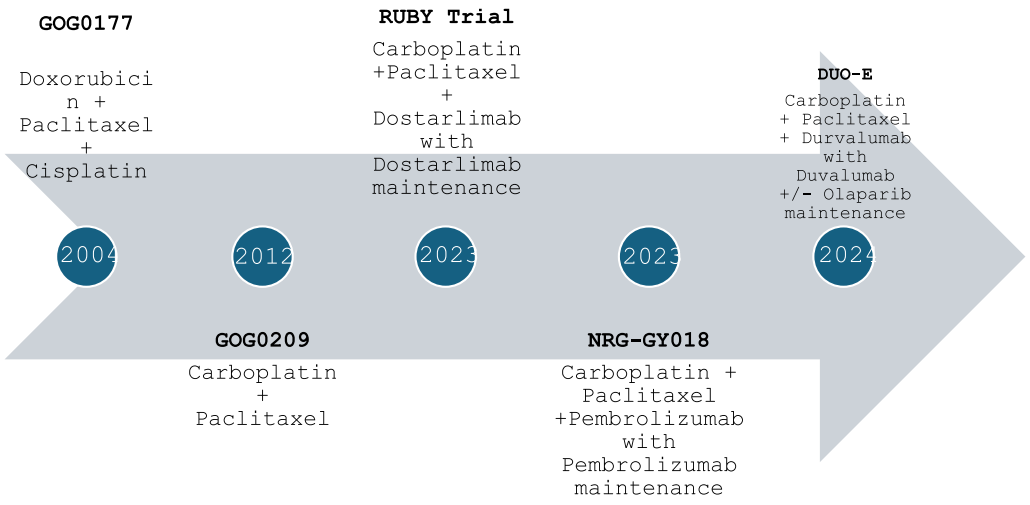

Fig. 3. Timeline of frontline treatment in advanced or recurrent endometrial cancer.

36 % in the durvalumab plus the Olaparib group. Adding more agents as expected slightly increased adverse events. Fatal events occurred in 3.4 % of the control group, 1.7 % of the durvalumab group and 2.1 % of the durvalumab plus olaparib groups. Importantly there were no cases of MDS or AML.

DUO-E results indicate a statistically significant PFS benefit with the addition of durvalumab to front line chemotherapy followed by maintenance durvalumab with or without olaparib. Dr. Tillmanns proposed consideration of the addition of olaparib in patients that are either PD-L1 positive or pMMR, otherwise durvalumab with durvalumab maintenance alone will suffice. There may also be a role to evaluate HRD status independently to consider addition of olaparib, though this remains to be determined. A thorough cost analysis may shed light on the real-world benefits of these combination therapies.

6. Discussion

The options in the treatment of advanced or recurrent endometrial cancer have come a long way; with so many options so quickly, it can be difficult to determine the best plan of care for each individual patient (Fig. 3). Pembrolizumab, dostarlimab, atezolizumab and durvalumab have all shown promise when included with carboplatin and paclitaxel in the frontline setting. However, no trial has compared one to another. Each checkpoint inhibitor has shown excellent reduction in progression or death in patients with dMMR tumors with more variable results in pMMR tumors.

PARP-inhibitors have shown great efficacy in breast and ovarian tumors demonstrating homologous recombination deficiency (HRD), but data supporting PARP-i use in endometrial cancer is limited, particularly for the indication of maintenance. Siedel, et al demonstrated that presence of HRD in endometrial tumors was associated with lower disease-free survival and that uterine cancer cell lines with high HRD score responded to olaparib in vivo (Siedel et al., 2021). As discussed above, data from the DUO-E pre-specified homologous recombination repair gene mutated subgroup utilizing olaparib and durvalumab maintenance are also promising. The RUBY-2 clinical trial is in process and evaluates the combination of the PARP-i niraparib and dostarlimab in the maintenance setting (RUBY, 2024).

Our Journal Club discussion centered on a hypothetical case of a new patient with advanced endometrial cancer. The option of including systemic therapy targeting HER2 was brought up as an option. Trastuzumab has been shown in a phase 2 trial to provide clinical benefit in conjunction with a chemotherapy backbone in HER2 positive uterine serous carcinoma. (Fader et al., 2018) Depending on the testing methodology and criteria for amplification, HER2 positivity can range from 10-20 % of uterine serous carcinomas. (Navarro Sanchez et al., 2023) Webinar participants in the Journal Club noted that the trial assessing the role of trastuzumab was a phase 2 trial; however, the biology of HER2/neu amplification may be important to recognize and target with therapy.

As additional treatment options become available, the role of molecular characterization of tumors plays a crucial role, as the choice of immunotherapy, PARP inhibitor or HER-2 directed agents will be dictated by molecular profile. The choice of which agent to add to chemotherapy is complex but the panel shared the gratitude of the audience that patients with endometrial cancer can look forward to individualized therapy with the goal of improved outcomes.

CRediT authorship contribution statement

Todd Tillmanns: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation. **Amal Masri:** Methodology, Data curation. **Chelsea Stewart:** Methodology, Data curation. **Dana Chase:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Anthony Karnezis:** Writing – review & editing, Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Lee-may Chen:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Renata Urban:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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