Advancements in Endometrial Cancer Research in 2024

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Summary

Endometrial cancer is one of the most common gynaecological cancers in high-income countries and, for many years, has been associated with poor outcomes for patients with advanced-stage disease. The results from the Phase III studies, RUBY Part 1 with dostarlimab, NRG-GY018 with pembrolizumab, and DUO-E with durvalumab, in patients with advanced or recurrent endometrial cancer in 2023 were practice-changing. The addition of immunotherapy to carboplatin–paclitaxel chemotherapy, followed by immunotherapy maintenance, led to a marked improvement in progression-free survival (PFS), particularly in patients with mismatch repair deficient, microsatellite stability-high (dMMR/MSI-H) disease, and has transformed the treatment landscape for these patients. This article discusses the latest advancements in endometrial cancer research in 2024, including highlights from the Society for Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer 2024 in March, the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting in May and June, the European Society for Medical Oncology (ESMO) Congress 2024 in September, and the Annual Global Meeting of the International Gynecologic Cancer Society (IGCS) 2024 in October. The article highlights the pivotal research conducted in 2024 in the chemotherapy–immunotherapy space, including the statistically significant and clinically meaningful overall survival (OS) benefit with dostarlimab in the overall population in RUBY Part 1. The PFS benefit with pembrolizumab, regardless of mismatch repair (MMR) status, and the early OS data in NRG-GY018 are also discussed. Additional topics covered in this year-in-review article include the effect of adding a poly adenosine diphosphate ribose polymerase (PARP) inhibitor to chemotherapy–immunotherapy combinations in DUO-E and RUBY Part 2, the unmet need in

patients with MMR proficient/microsatellite stable (pMMR/MSS) disease, and the potential importance of adding PARP inhibitor for the pMMR/MSS population. 2024 was a pivotal year in endometrial cancer research, building on the first-line data that emerged in 2023 from key studies including RUBY, NRG-GY018, and DUO-E, and firmly establishing chemotherapy–immunotherapy combinations as the new standard of care for patients with dMMR disease. Other important developments in the endometrial cancer space in 2024 include the data from LEAP-001, which further support the use of chemotherapy-free combination treatment in patients with pMMR advanced or recurrent endometrial cancer after progression on systemic adjuvant or neoadjuvant chemotherapy.

INTRODUCTION

Endometrial cancer is one of the most common gynaecological cancers in high-income countries[1] and, for many years, has been associated with poor outcomes for patients with advanced-stage disease.[2,3] The practice-changing results from the Phase III studies, RUBY Part 1 with dostarlimab and NRG-GY018 with pembrolizumab, in patients with advanced or recurrent endometrial cancer were the first important highlights of endometrial cancer research in 2023,[4,5] and were considered by experts to be two of the most striking trials ever seen in gynaecological oncology research.[6,7] The addition of immunotherapy to carboplatin–paclitaxel chemotherapy, followed by immunotherapy maintenance, led to a marked improvement in PFS (a dual primary endpoint in RUBY Part 1,[4] and the primary endpoint in NRG-GY018),[5] which appeared to be sustained over time, and the treatment regimens were well tolerated, with no new safety signals.[4,5,7] Furthermore, the similar findings in DUO-E with durvalumab[8] support the results from RUBY Part 1 and NRG-GY018. The results of these trials were key in the regulatory approval of dostarlimab, durvalumab, and pembrolizumab in 2024.

The results from RUBY Part 1, NRG-GY018, and DUO-E were particularly important because, historically, chemotherapy alone has had limited and short-lived efficacy in patients with endometrial cancer.[7,9,10] Combining chemotherapy and immunotherapy was shown in 2023 to be particularly effective in patients with dMMR/MSI-H disease,[4,5,8] transforming the treatment landscape for these patients.[11,12] Indeed, some authors have hinted at the potential for cure with the addition of immunotherapy in the context of prolonged response even after discontinuation.[11]

The considerable progress in the endometrial cancer research space in 2023 laid the foundation for further research developments in 2024. This article highlights the pivotal research presented in 2024 at the SGO Annual Meeting on Women's Cancer, ASCO Annual Meeting, ESMO Congress, and Annual Global Meeting of the IGCS in the chemotherapy–immunotherapy space, including the OS benefit in RUBY Part 1 and NRG-GY018, and the effect of adding PARP inhibitors to chemotherapy–immunotherapy combinations in DUO-E and RUBY Part 2. The unmet need in the pMMR/MSS population is also explored, including the use of chemotherapy-free combination treatment in patients with pMMR advanced or recurrent endometrial cancer after progression on systemic adjuvant or neoadjuvant chemotherapy in LEAP-001.

UPDATE OF THE ESGO–ESTRO–ESP GUIDELINES IN 2025

In 2023 and 2024, the results from RUBY Part 1, NRG-GY018, and DUO-E changed the treatment landscape in first-line advanced and recurrent endometrial cancer. This has led to regulatory approvals and is now reflected in new treatment guidelines.

An update of the guidelines on the management of endometrial cancer from the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) was presented at the ESGO 2025 Congress in February 2025.[13]

The updated ESGO–ESTRO–ESP guidelines emphasise the importance of the molecular profile in treatment decision-making for patients with endometrial cancer, including using the molecular profile as a prognostic factor and stratifying patients based on the molecular profile.[13] These guidelines also merge the classification from the International Federation of Gynaecology and Obstetrics (FIGO) 2023 guidelines[14] with the molecular profile and the class of risk of the patient, and indicate treatment in the adjuvant and advanced disease settings according to this new classification.[13]

New treatment recommendations in the guidelines include the addition of immunotherapy to chemotherapy in dMMR and pMMR populations, the addition of PARP inhibitor to chemotherapy–immunotherapy (specifically olaparib in combination with chemotherapy–durvalumab) in patients with pMMR disease, and chemotherapy–immunotherapy combinations in the adjuvant setting in the dMMR population based on data from the KEYNOTE-B21 study with pembrolizumab.[13,15,16]

OVERALL SURVIVAL BENEFIT WITH DOSTARLIMAB IN RUBY PART 1 WAS A HIGH POINT OF 2024

There was an early signal from the RUBY Part 1 interim data in 2023 that the observed PFS benefit may translate into an OS benefit, with a 36% reduction in the risk of disease progression or death at 24 months in the overall population (24-month hazard ratio [HR]: 0.64; 95% CI: 0.46–0.87; p=0.0021).[4,17]

The results from a second interim analysis of RUBY Part 1 data, presented at the SGO Annual Meeting on Women's Cancer 2024,[18] confirmed that the PFS benefit translated to an OS benefit in RUBY Part 1.[19] The results showed that dostarlimab plus chemotherapy was associated with a statistically significant and clinically meaningful improvement in OS compared with placebo plus chemotherapy in the overall patient population.[19] The dual primary endpoint for OS was met in the overall population (51% OS maturity), with a statistically significant 31% reduction in the risk of death (HR: 0.69; 95% CI: 0.54–0.89; p=0.0020), and a clinically meaningful improvement in median OS of 16.4 months (44.6 versus 28.2 months) in patients who received dostarlimab plus carboplatin–paclitaxel compared with those who received carboplatin–paclitaxel alone.[19] The risk of death was lower in the dostarlimab arm versus the placebo arm in the dMMR/MSI-H population (40% OS maturity; HR: 0.32; 95% CI: 0.17–0.63; nominal p=0.0002).[19] Median OS was not reached (NR) for the dostarlimab arm and was 31.4 months for the placebo arm in this population.[19] In addition, there was a trend in favour of dostarlimab in the pMMR/MSS population, indicating a 21% reduction in the risk of death (55% OS maturity; HR: 0.79; 95% CI: 0.60–1.04; nominal p=0.0493), with a clinically meaningful improvement in median OS of 7 months (34.0 months in the dostarlimab arm versus 27.0 months in the placebo arm).[19]

In a study of post-progression survival outcomes in patients from RUBY Part 1, subsequent use of immunotherapy in the overall and pMMR/MSS populations showed limited impact on OS benefits, supporting frontline use of dostarlimab plus chemotherapy as standard of care in patients with advanced or recurrent endometrial cancer.[20] Further support was provided by a post hoc exploratory analysis of the impact of investigator-assessed objective response at 3 months on OS in the intent-to-treat (ITT) population from RUBY Part 1, which showed that outcomes associated with response in the dostarlimab arm were favourable compared with those associated with response in the placebo arm, reflecting the durability of benefit with dostarlimab.[21]

RUBY Part 1 showed that duration of response (DOR) was improved with the addition of dostarlimab to chemotherapy.[4] Data published in 2023 showed that median DOR overall was 10.6 months (95%

CI: 8.2–17.6) in the dostarlimab group versus 6.2 months (95% CI: 4.4–6.7) in the placebo group.[4] This improvement was seen in both the dMMR (not estimable versus 5.4 months) and pMMR (8.6 versus 6.3 months) populations.[4]

The OS results in RUBY Part 1 were accompanied by a safety profile for dostarlimab plus carboplatin and paclitaxel that was consistent with the first interim analysis assessing PFS.[18,19] The majority of the most common treatment-related adverse events (TRAEs) (≥30%) and Grade ≥3 TRAEs (≥10%) in both arms occurred within the first 3–6 months of treatment, which was consistent with receipt of chemotherapy.[22] The onset of new TRAEs after 12 months in the dostarlimab arm was uncommon.[22] The most commonly reported TRAEs in both treatment arms were alopecia, fatigue, nausea, peripheral neuropathy, and anaemia.[22] Grade ≥3 anaemia was reported in ≥10% of patients in the dostarlimab arm.[22]

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL BENEFITS WITH PEMBROLIZUMAB IN NRG-GY018 SUPPORT CHEMOTHERAPY–IMMUNOTHERAPY COMBINATIONS

As presented at the SGO Annual Meeting on Women's Cancer 2024, PFS benefits were seen in both the dMMR and pMMR populations in NRG-GY018 (40% data maturity).[23,24] In the dMMR population, the investigator-assessed median PFS was not reached (95% CI: 30.7–NR) in the pembrolizumab arm and 8.3 months (95% CI: 6.5–12.3) in the placebo arm (HR: 0.34; 95% CI: 0.22–0.53; p<0.0001).[23,24] The blinded independent central review (BICR)-assessed median PFS was not reached (95% CI: NR–NR) in the pembrolizumab arm and 14.1 months (95% CI: 8.5–NR) in the placebo arm (HR: 0.45; 95% CI: 0.27–0.73; p=0.0005).[23,24] In the pMMR population, the investigator-assessed median PFS was 13.1 months (95% CI: 10.6–19.5) in the pembrolizumab arm and 8.7 months (95% CI: 8.4–11.0) in the placebo arm (HR: 0.57; 95% CI: 0.44–0.74; p<0.0001).[23,24] The BICR-assessed median PFS was 19.5 months (95% CI: 13.1–28.0) in the pembrolizumab arm and 11.0 months (95% CI: 9.0–11.5) in the placebo arm (HR: 0.64; 95% CI: 0.49–0.85; p=0.0008).[23,24] Although investigator-assessed and BICR-assessed data show some variation, these findings support the addition of pembrolizumab to chemotherapy as a first-line treatment for patients with advanced or recurrent endometrial cancer, regardless of MMR status.

OS data with the addition of pembrolizumab to chemotherapy in NRG-GY018[5] were provided at the SGO Annual Meeting on Women's Cancer 2024.[23,24] OS was a secondary endpoint in the NRG-GY018 study,[5] and the OS data in the interim analysis were not mature (27.2% and 18.0% for patients with pMMR and dMMR disease, respectively, based on information fraction).[23,25,26] The median OS was not reached in either treatment arm in patients with dMMR disease (HR: 0.55; 95% CI: 0.25–1.19; p=0.0617).[23,25,26] In patients with pMMR disease, the median OS was 27.96 months (95% CI: 21.42–NR) in the pembrolizumab arm versus 27.37 months (95% CI: 19.52–NR) in the placebo arm (HR: 0.79; 95% CI: 0.53–1.17; p=0.1157).[23,25,26]

Response data for NRG-GY018 presented in 2023 showed that median DOR was significantly improved with the addition of pembrolizumab to chemotherapy, with 28.7 versus 6.2 months in patients with dMMR disease (HR: 0.22; 95% CI: 0.13–0.37; p<0.0001) and 9.2 versus 6.2 months in patients with pMMR disease (HR: 0.47; 95% CI: 0.34–0.64; p<0.0001).[27]

Updated response data from an ad hoc analysis published in 2025 showed that median DOR in the dMMR population was not reached (range: 0.0+ to 41.8+; + indicates no progressive disease at last disease assessment) in the pembrolizumab arm and 4.8 (range: 0.0+ to 42.2+) months in the placebo arm.[26] In the pMMR population, median DOR was 8.1 (range: 0.0+ to 40.9+) and 6.4 (range: 0.0+ to 28.3+) months, respectively.[26]

Safety data from the ad hoc analysis showed that there were no safety concerns with longer follow-up in the NRG-GY018 study.[26] The rates of chemotherapy-related adverse events (AEs) were not increased with the addition of pembrolizumab.[26] In both treatment arms, rates of immune-mediated AEs and infusion reactions were slightly higher in this ad hoc analysis (39.6% in the pembrolizumab arm, 26.3% in the placebo arm) than in the primary publication (34.8% and 21.6%, respectively).[5,26] In the dMMR plus pMMR population, AEs were reported in 99.2% of patients in the pembrolizumab arm and 99.7% in the placebo arm, and Grade ≥3 AEs were reported in 65.7% and 49.2%, respectively.[26] The most common AEs (≥20% of patients in either treatment arm) were fatigue, anaemia, alopecia, nausea, and constipation.[26] TRAEs occurred in 96.9% of patients in the pembrolizumab arm and 96.1% in the placebo arm and were Grade ≥3 in 49.9% and 34.0%, respectively.[26] Study treatment was discontinued because of AEs in 18.2% and 7.2% of patients in the pembrolizumab and placebo arms, respectively.[26]

OBSERVATIONS FROM POST HOC ANALYSES IN RUBY PART 1 AND NRG-GY018

MMR deficiency is caused by aberrant expression of MMR proteins that mediate DNA repair.[28] This deficiency results from epigenetic regulation (epi-dMMR), in which hypermethylation of the MLH1 promoter prevents MLH-1 expression, or mutation (mut-dMMR), where MMR proteins are lost through deleterious mutations.[28] Epigenetic regulation and mutation account for 70–75% and 25–30% of dMMR/MSI-H endometrial cancers, respectively.[28] A post hoc analysis of PFS and OS in RUBY Part 1 showed that the mechanism of MMR protein loss (epi-dMMR or mut-dMMR) does not appear to be a significant predictor of clinical benefit for dostarlimab treatment in patients with primary advanced or recurrent dMMR endometrial cancer.[28]

The mechanism of MMR loss was also not a significant predictor of clinical benefit for pembrolizumab treatment in NRG-GY018: 85% of patients with MMR protein loss secondary to gene mutation were progression-free at 12 months versus 75% of patients with MLH1 promoter hypermethylation.[27]

In a post hoc exploratory analysis by age subgroups in RUBY Part 1, dostarlimab plus carboplatin and paclitaxel was shown to prolong PFS in patients aged <70 years (HR: 0.71; 95% CI: 0.54–0.94) and ≥70 years (HR: 0.50; 95% CI: 0.32–0.77), with a consistent safety profile across the age groups, and no increase in toxicity with increasing age.[29] These results indicate that this treatment combination is effective and well tolerated in patients with primary advanced or recurrent endometrial cancer, including those aged ≥70 years.[29] These results are supported by the age subgroup analysis in DUO-E showing the benefit of durvalumab in patients aged <65 years and ≥65 years.[30] The further benefit of adding olaparib to durvalumab was also confirmed in patients aged <65 years and ≥65 years in DUO-E.[30]

Post hoc analysis of RUBY Part 1 data compared differences in patient-reported quality of life among responders and non-responders in the dostarlimab versus placebo arms in the ITT population, regardless of MMR status.[31] Trends in the data indicated a higher and sustained quality of life improvement in the dostarlimab arm versus the placebo arm in responders and non-responders, further supporting the combination of dostarlimab plus chemotherapy as a treatment option for patients with endometrial cancer.[31]

ADDITION OF PARP INHIBITOR TO CHEMOTHERAPY–IMMUNOTHERAPY COMBINATION IN DUO-E

PARP inhibitors induce DNA damage and further immune priming,[32] which may promote more robust antitumour immunity and potentially more durable benefit.[33] The addition of a PARP inhibitor, such as olaparib, to chemotherapy–immunotherapy combinations may improve outcomes in patients with specific malignancies.[34]

DUO-E was a Phase III study in patients with newly diagnosed advanced or recurrent endometrial cancer who were randomised in a 1:1:1 ratio to control arm (durvalumab placebo plus carboplatin and paclitaxel, then durvalumab placebo plus olaparib placebo); durvalumab arm (durvalumab plus carboplatin and paclitaxel, then durvalumab plus olaparib placebo); or durvalumab plus olaparib arm (durvalumab plus carboplatin and paclitaxel, then durvalumab plus olaparib).[8]

The dual primary endpoints in DUO-E were met, showing a statistically significant and clinically meaningful improvement in PFS for the durvalumab (HR: 0.71; 95% CI: 0.57–0.89; p=0.003) and durvalumab plus olaparib (HR: 0.55; 95% CI: 0.43–0.69; p<0.0001) arms versus the control arm.[8] Prespecified, exploratory subgroup analyses showed PFS benefit in the dMMR subgroup for the durvalumab (HR: 0.42; 95% CI: 0.22–0.80) and durvalumab plus olaparib (HR: 0.41; 95% CI: 0.21–0.75) arms versus the control arm, with these results indicating that there is no added benefit of olaparib for patients with dMMR disease.[8] Durvalumab showed a PFS benefit in the pMMR subgroup versus the control arm, with an HR of 0.77 (95% CI: 0.60–0.97).[8] The addition of olaparib enhanced this benefit, with an HR of 0.57 (95% CI: 0.44–0.73) for the durvalumab plus olaparib arm versus the control arm.[8]

Interim OS results (approximately 28% maturity) were supportive of the primary outcomes, with an HR of 0.77 (95% CI: 0.56–1.07; p=0.120) and 0.59 (95% CI: 0.42–0.83; p=0.003) for the durvalumab arm versus the control arm and the durvalumab plus olaparib arm versus the control arm, respectively.[8]

A post hoc exploratory analysis of PFS results from DUO-E showed that there was a clinical benefit in the durvalumab plus olaparib arm versus the control arm in the ITT and pMMR populations irrespective of *BRCA1*/*BRCA2* mutation status.[35] The prevalence of *BRCA* mutations was low overall, with the majority of mutations being in the dMMR subpopulation (dMMR: 12.6% *BRCA*m, 61.5% non-*BRCA*m, 25.9% unknown; pMMR: 4.0% *BRCA*m, 65.9% non-*BRCA*m, 30.1% unknown).[35] These results indicate that *BRCA*m is a passenger mutation in this patient population.

Further biomarker analyses in DUO-E showed that the pMMR subpopulation was highly heterogenous with frequent overlap of biomarkers and histology.[36] Programmed death ligand 1 (PD-L1)-positive (tumour area positivity ≥1%) and *TP53* mutation (*TP53*m) were the most prevalent biomarkers (56% and 59%, respectively). A total of 84% of the patients were positive for at least one biomarker.[36] The PFS benefit provided by the addition of olaparib maintenance to durvalumab was observed across a range of biomarker and histological subgroups.[36]

Post hoc exploratory PFS subgroup analyses by key clinical factors (age, BMI, Eastern Cooperative Oncology Group performance status, prior treatment) from DUO-E generally showed benefit for the durvalumab arm and the durvalumab plus olaparib arm versus the control arm in the ITT population.[30] Furthermore, there was consistent PFS benefit for the durvalumab arm versus the control arm in the dMMR population (HR<1.00 in all subgroups).[30] In the pMMR population, there was generally a benefit in the durvalumab arm versus the control arm, with PFS consistently enhanced by the addition of olaparib (HR<1.00 for the durvalumab plus olaparib arm in all subgroups).[8,30] These DUO-E subgroup analyses support prior PFS analyses and show that the addition of olaparib enhanced PFS benefit in the pMMR population.[8,30]

Durvalumab increased the DOR in both the dMMR and pMMR populations. These results are in line with the DOR results from RUBY and NRG-GY018. The addition of olaparib in DUO-E further extended the DOR. The addition of durvalumab plus olaparib to chemotherapy (durvalumab plus olaparib arm) more than doubled the median DOR compared with chemotherapy alone (control arm) in patients with pMMR advanced or recurrent endometrial cancer (18.7 versus 7.6 months).[37,38] The corresponding results for the dMMR population were 29.9 versus 10.5

months.[37,38] Median DOR was not reached in the durvalumab arm in the dMMR population.[37,38]

Safety findings in DUO-E were generally consistent with the known safety profiles of carboplatin, paclitaxel, durvalumab, and olaparib.[39] The four most common AEs, regardless of relatedness to treatment, were anaemia, alopecia, nausea, and fatigue.[39] These AEs were mostly low-grade and led to few discontinuations or dose modifications/interruptions.[39] There was no increase in immune-mediated AEs with the addition of olaparib, and AE profiles were generally consistent across MMR subgroups.[39]

These results support the addition of PARP inhibitor maintenance to immunotherapy in the treatment of newly diagnosed pMMR advanced or recurrent endometrial cancer.

UNMET NEED IN PATIENTS WITH PMMR ENDOMETRIAL CANCER

Approximately 69–75% of patients with endometrial cancer have pMMR/MSS tumours.[40,41] The OS data from RUBY Part 1 presented in 2024 are pivotal, showing a 68% reduction in the risk of death in the dostarlimab arm compared with the placebo arm in the dMMR/MSI-H population;[19] however, only a 21% reduction in the risk of death was indicated in the pMMR/MSS population.[19] The immature OS data for NRG-GY018 also indicate a smaller OS benefit with pembrolizumab versus placebo (both plus chemotherapy) in the pMMR population compared with the dMMR population.[23,25]

These results clearly show that the pMMR population is less responsive to chemotherapy–immunotherapy regimens than the dMMR population.[19,23,25] Hence, the pMMR population represents an area of unmet need that merits further exploration.

Inhibition of PARP results in greater levels of DNA damage, neoantigens, and a more immunogenic tumour microenvironment, promoting infiltration of cytotoxic T cells to drive antitumour immune responses, which may be held in check by PD-L1.[32,42,43] The addition of olaparib to durvalumab could result in simultaneous enhancement of antitumor immune responses to drive clinical response in patients with pMMR tumours. Data presented from DUO-E in 2024,[30] described herein, indicate that adding a PARP inhibitor to chemotherapy–immunotherapy combinations may provide additional benefits for the pMMR patient subgroup. Further evidence for this additional benefit was provided by RUBY Part 2.[44,45]

As presented at the SGO Annual Meeting on Women's Cancer 2024, the primary endpoint was met in RUBY Part 2.[44] There was a significant and clinically meaningful improvement in PFS with dostarlimab plus chemotherapy followed by dostarlimab plus niraparib (a PARP inhibitor) as maintenance versus placebo plus chemotherapy followed by placebo, particularly in patients with pMMR/MSS disease.[44,46] At 19 months' median follow-up, the median PFS in the overall population was 14.5 months (95% CI: 11.8–17.4) for the dostarlimab–niraparib arm and 8.3 months (95% CI: 7.6–9.8) for the control arm.[44-46] A total of 57.0% and 33.7% of patients, respectively, were progression-free at 12 months (HR: 0.60; 95% CI: 0.43–0.82; p=0.0007).[44-46] In the pMMR/MSS population, median PFS was 14.3 months (95% CI: 9.7–16.9) and 8.3 months (95% CI: 7.6–9.8) for the dostarlimab–niraparib and control arms, respectively, with 54.7% and 31.1% progression-free, respectively (HR: 0.63; 95% CI: 0.44–0.91; p=0.0060).[44-46] These outcomes indicate a potential role for PARP inhibitor maintenance in patients receiving dostarlimab plus chemotherapy, particularly for patients with pMMR/MSS disease.[44,46]

In RUBY Part 2 exploratory analyses, a clinically relevant benefit was observed in patients with dMMR/MSI-H disease (HR: 0.48; p=0.0174).[44-46] However, given the absence of a single-agent immunotherapy arm in this study, the relative contribution of PARP inhibitor to immunotherapy in the dMMR population cannot be defined. Furthermore, there were no predictive biomarkers of PARP efficacy identified in RUBY Part 2[44-46] or DUO-E.[8,30,35]

Immunotherapy is recognised as part of the standard of care in the first line for dMMR endometrial cancer.[47] The benefit of adding immunotherapy to chemotherapy has also been shown in patients with pMMR disease, although the effect is not as pronounced as for dMMR disease. This benefit is reflected in the updated ESGO–ESTRO–ESP guidelines, which recommend chemotherapy–immunotherapy or chemotherapy–immunotherapy–PARP inhibitor combinations for the pMMR patient population.[13]

FURTHER UPDATES IN ENDOMETRIAL CANCER RESEARCH PRESENTED AT CONGRESSES IN 2024

Interim analysis results of the KEYNOTE-B21 study of pembrolizumab or placebo in combination with adjuvant chemotherapy, with or without radiotherapy, after surgery with curative intent, showed that pembrolizumab plus adjuvant chemotherapy did not improve disease-free survival (primary endpoint) in patients with newly diagnosed, high-risk endometrial cancer (HR: 1.02; 95% CI: 0.79–1.32; p=0.570).[48] However, in subgroup analyses, this combination led to clinically meaningful improvements in disease-free survival in patients with dMMR tumours (HR: 0.31; 95% CI: 0.14–0.69), with less favourable results in those with pMMR tumours (HR: 1.20; 95% CI: 0.91–1.57).[48]

In the Phase III LEAP-001 study, first-line lenvatinib plus pembrolizumab did not meet the prespecified statistical criteria for PFS or OS versus chemotherapy in pMMR advanced or recurrent endometrial cancer.[49] However, a subgroup analysis showed improved PFS and OS in the ITT and pMMR populations who had received prior adjuvant or neoadjuvant chemotherapy.[50] The LEAP-001 data are further evidence supporting the new ESGO–ESTRO–ESP guideline recommendation of pembrolizumab–lenvatinib for patients with pMMR who are contraindicated for chemotherapy and had received prior adjuvant or neoadjuvant chemotherapy.[13]

Wild-type *TP53* (*TP53*wt) is found in over 50% of advanced or recurrent endometrial cancers, with 40–55% of these being pMMR/MSS.[51] Long-term follow-up analysis of a prespecified *TP53*wt exploratory subgroup of ENGOT-EN5/GOG-3055/SIENDO[52] showed PFS improvement with selinexor (an oral exportin 1 [XPO1] inhibitor)[52] versus placebo as maintenance treatment in patients who had responded to chemotherapy, regardless of microsatellite stability status.[51] The strong PFS signal observed in the *TP53*wt/pMMR/MSS subgroup was encouraging, considering this is a patient population with high unmet need. A randomised, Phase III confirmatory study is ongoing.[53]

REAL-WORLD TREATMENT PATTERNS IN ADVANCED ENDOMETRIAL CANCER

MMR/MSI testing has evolved from being a key biomarker for the diagnosis and molecular classification of endometrial cancer (alongside POLε and p53 testing) to now also being a predictive marker for guiding treatment. Molecular profiling of MMR/MSI has emerged as a valuable tool for guiding treatment decisions in advanced or recurrent endometrial cancer; however, real-world data on the use of this tool and the shifting treatment paradigm are limited.[54] A retrospective study using data from the Flatiron Health database showed that MMR/MSI testing was common; however, the use of second-line immunotherapy for dMMR (51%) and immune checkpoint inhibitor plus vascular endothelial growth factor for pMMR (23%) was lower than expected and may reflect slow uptake of recently approved, molecular profile-specific therapies.[54] Furthermore, MMR/MSI testing gaps were noted, particularly in underrepresented populations, and may be a barrier to the adoption of new therapies.[54]

REGULATORY APPROVALS IN 2024 MARK SIGNIFICANT PROGRESS IN ENDOMETRIAL CANCER TREATMENT

The results from the pivotal clinical trials presented in 2024 have translated into new approved treatment options for patients with endometrial cancer in the first-line setting. There are three immune checkpoint inhibitors approved for treatment in chemotherapy–immunotherapy combinations in first line: dostarlimab, durvalumab, and pembrolizumab. The European Medicines Agency [EMA] has approved dostarlimab, pembrolizumab, and durvalumab–olaparib in patients with pMMR disease. Please note, data included in this report are based on EU data and may vary depending on local approval in each country. Please refer to your local prescribing information.

On 27th June 2024, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, based on a prespecified exploratory subgroup analysis by MMR status from DUO-E,[8] recommending a change to the terms of the marketing authorisation for durvalumab (AstraZeneca AB).[55] The CHMP adopted a new indication: durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in dMMR disease, and durvalumab in combination with olaparib in pMMR disease.[55] The European Commission approved this indication on 14th August 2024.[56]

On 19th September 2024, the EMA CHMP adopted positive opinions, based on results from NRG-GY018,[5] recommending changes to the terms of the marketing authorisation for pembrolizumab (Merck Sharp & Dohme B.V., Rahway, New Jersey, USA).[57] The CHMP adopted a new indication for the management of cervical cancer (not discussed herein) and endometrial cancer, as follows: pembrolizumab, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adult patients who are candidates for systemic therapy.[57] The European Commission approved this indication on 24th October 2024.[58]

On 12th December 2024, the EMA CHMP adopted a positive opinion, based on the OS results of RUBY Part 1,[19] recommending a change to the terms of the marketing authorisation for dostarlimab (GlaxoSmithKline [Ireland] Limited, Dublin).[59] The CHMP adopted an extension to an existing indication to now include pMMR/MSS tumours.[60] The full indication is as follows: dostarlimab is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, and dostarlimab is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[59] On 20th January 2025, the European Commission expanded dostarlimab plus chemotherapy approval to all adult patients with primary advanced or recurrent endometrial cancer.[60]

On 14th June 2024, the U.S. FDA approved durvalumab in combination with carboplatin plus paclitaxel, followed by single-agent durvalumab, for adult patients with primary advanced or recurrent endometrial cancer that is dMMR.[61]

On 17th June 2024, the U.S. FDA approved pembrolizumab in combination with carboplatin and paclitaxel, followed by pembrolizumab monotherapy, for adult patients with primary advanced or recurrent endometrial carcinoma, regardless of MMR status.[62]

On 1st August 2024, the U.S. FDA expanded the approval for dostarlimab plus chemotherapy to include adult patients with primary advanced or recurrent endometrial cancer, regardless of MMR or MSI status.[63]

CONCLUSION

2024 was a pivotal year in endometrial cancer research, building on the practice-changing, first-line data that emerged in 2023 from key studies including RUBY, NRG-GY018, and DUO-E, and firmly establishing chemotherapy–immunotherapy combinations as the new standard of care for patients with dMMR disease. In particular, OS data from RUBY Part 1 with dostarlimab and NRG-GY018 with pembrolizumab in 2024 support the chemotherapy–immunotherapy approach in dMMR endometrial cancer. In the era before the data from these pivotal trials were presented, patients were treated with chemotherapy, which resulted in short-lived responses and poor outcome. Chemotherapy–immunotherapy combinations are associated with substantially improved DOR, particularly in patients with dMMR disease. These treatment combinations also improve the DOR in patients with pMMR disease, with the addition of PARP inhibitor further extending the DOR in the pMMR setting. The pMMR subgroup represents an area of unmet need that merits further exploration. The results from DUO-E and RUBY Part 2 presented in 2024 support the addition of PARP inhibitors to chemotherapy–immunotherapy combinations in the pMMR population. Several treatment options received approval from the EMA and FDA in 2024, marking significant progress in endometrial cancer treatment, and updated ESGO–ESTRO–ESP guidelines were presented in February 2025. Further developments in endometrial cancer research in 2025 that expand the significant knowledge accrued in 2024, and continue to drive endometrial cancer care and improve patient outcomes, are awaited with interest.

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