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OBSTETRICS & GYNECOLOGY CONNECT ANIMATED VIDEO

CURRENT TREATMENT OPTIONS IN ADVANCED/RECURRENT ENDOMETRIAL CANCER: EXPLORING THE IMPACT OF MOLECULAR SUBTYPES

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JANUARY 2025

EDUCATIONAL OBJECTIVES

- Understand current treatment options for advanced or recurrent endometrial cancer and their place in the treatment landscape
- Explore treatment decisions in advanced or recurrent endometrial cancer based on molecular subtypes
- Embrace the importance of clear communication with patients and agreement on the end goal of the treatment

CLINICAL TAKEAWAYS

- Molecular classification is crucial not only for prognosis but also for guiding personalised treatment decisions
- ICI and ChT combination, including with maintenance olaparib, demonstrates PFS benefits and manageable safety in patients with non-dMMR advanced/recurrent endometrial cancer, with greater efficacy observed in dMMR populations
- Lenvatinib plus pembrolizumab is a viable option not only as 2nd line therapy but also as 1st line treatment for patients with non-dMMR advanced/recurrent endometrial cancer who have progressed after prior systemic therapy in any setting
- Shared decision-making, supported by patient education, is essential for optimising treatment outcomes

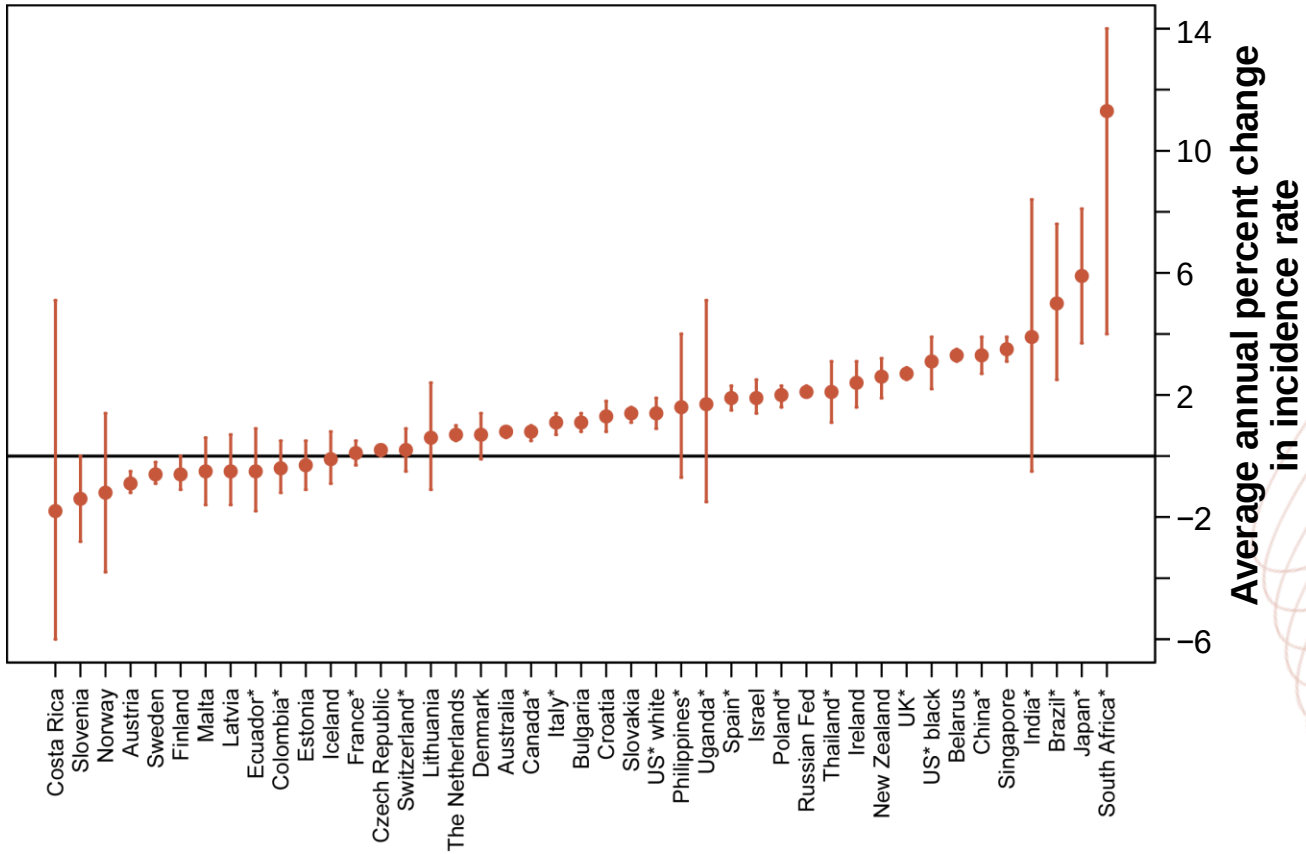
ChT, chemotherapy; ICI, immune checkpoint inhibitor; PFS, progression-free survival; p/dMMR, proficient/deficient mismatch repair

ENDOMETRIAL CANCER EPIDEMIOLOGY & CURRENT TREATMENT GUIDELINES

ENDOMETRIAL CANCER: EPIDEMIOLOGY

- Endometrial cancer (EC) is the most common gynecologic cancer and the fourth most common cancer among women in the United States[1,2]
- The majority of EC (66%) is diagnosed in early stages[2]
- However, 15% to 20% of these carcinomas will recur with unfavourable prognosis[3,4]

AVERAGE ANNUAL PERCENT CHANGE IN AGE-STANDARDISED ENDOMETRIAL CANCER INCIDENCE RATES[5]

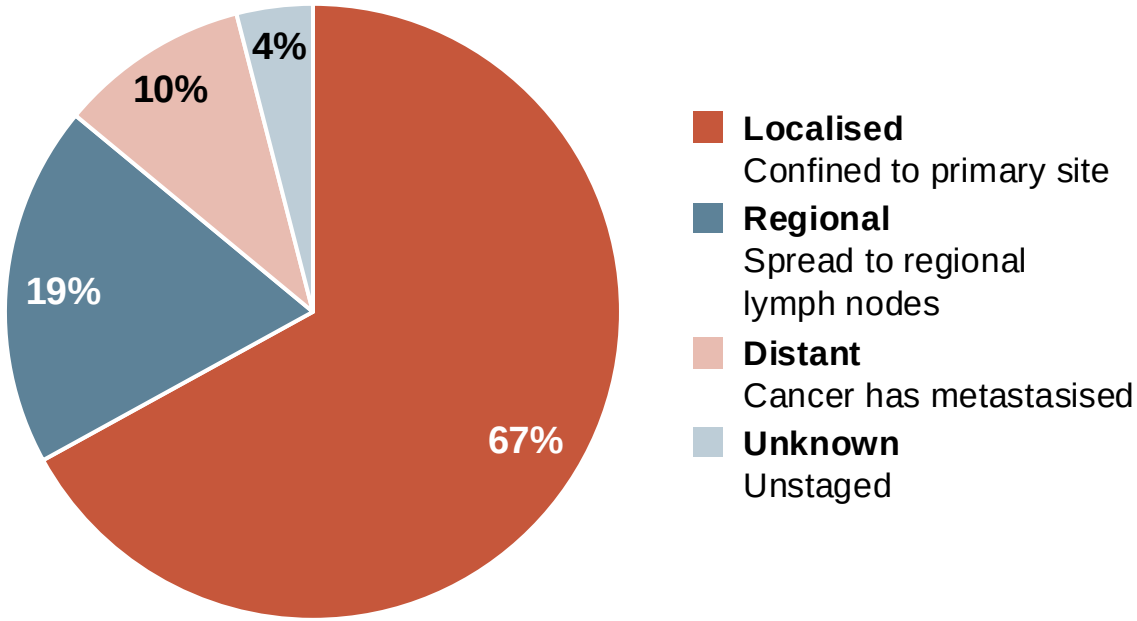


1. Liu L, et al. JNCI Cancer Spect. 2023;7:pkad001; 2. Cancer Facts and Figures 2022. American Cancer Society (2022). Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf (accessed October 2024); 3. Beavis AL and Fader AN. J Clin Oncol. 2022;40:3790-3795; 4. van den Heerik ASVM, et al. Int J Gynecol Cancer. 2021:31:594-604; 5. Lortet-Tieulent J, et al. J Natl Cancer Inst. 2018;110:354-361

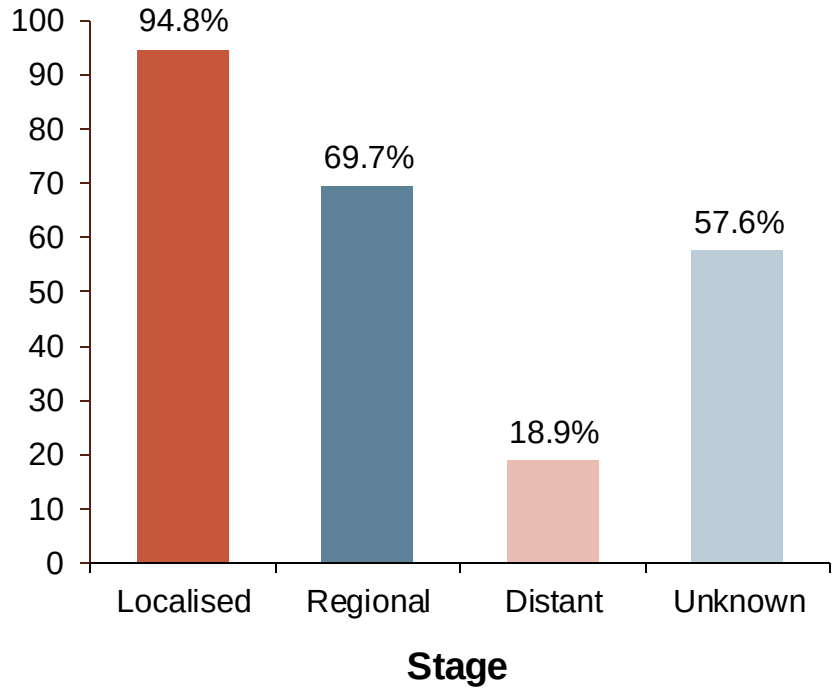
ENDOMETRIAL CANCER: SURVIVAL BY CANCER STAGE

- **Overall, 5-year survival rate** for endometrial cancer is **81.1%**
- **Survival rate varies significantly by stage:** Patients with distant metastases have **five times lower** chances of 5-year survival compared to those with localized EC

PERCENT OF CASES BY STAGE AT DIAGNOSIS



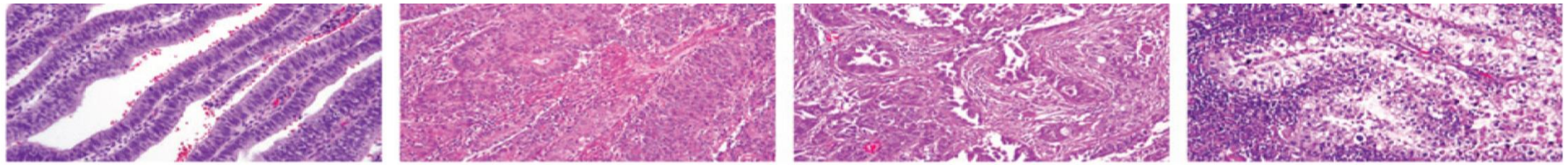
5-YEAR RELATIVE SURVIVAL



EC, endometrial cancer

Cancer stat facts: Uterine Cancer. *National Cancer Institute*. 2022. https://seer.cancer.gov/statfacts/html/corp.html (accessed in November 2024)

ENDOMETRIAL CANCER GENOMIC AND HISTOPAHTOLOGICAL FEATURES



Histological type	Endometrioid	Endometrioid	Serous	Clear cell
Histological grade	Low	High	High	High
Metastasis	Uncommon	Lymph nodes Distant organs	Lymph nodes Peritoneal Distant organs	Lymph nodes Peritoneal −/+
Prognosis	Favourable	Poor	Poor	Poor
Molecular markers				
ER/PR expression	+	+/−	−/+	−
PTEN expression	−/+	−/+	+	+
DNA MMR loss	−/+	−/+	−	−/+
Aberrant P53	−	−/+	+	−/+
Ki-67/MIB-1	Low	High	High	Low or high

DNA, deoxyribonucleic acid; ER, estrogen receptor; Ki-67, marker of proliferation Kiel-67; MIB-1, mindbomb e3 ubiquitin protein ligase 1; MMR, mismatch repair; P53, tumour protein p53; PR, progesterone receptor; PTEN, phosphatase and tensin homolog

Murali R, et al. *Lancet Oncol.* 2014;15:e268-e278

MOLECULAR CLASSIFICATION AND TREATMENT IMPLICATIONS

Molecular classification not only **provides prognostic value** but also serves as a **factor in selecting appropriate treatments**

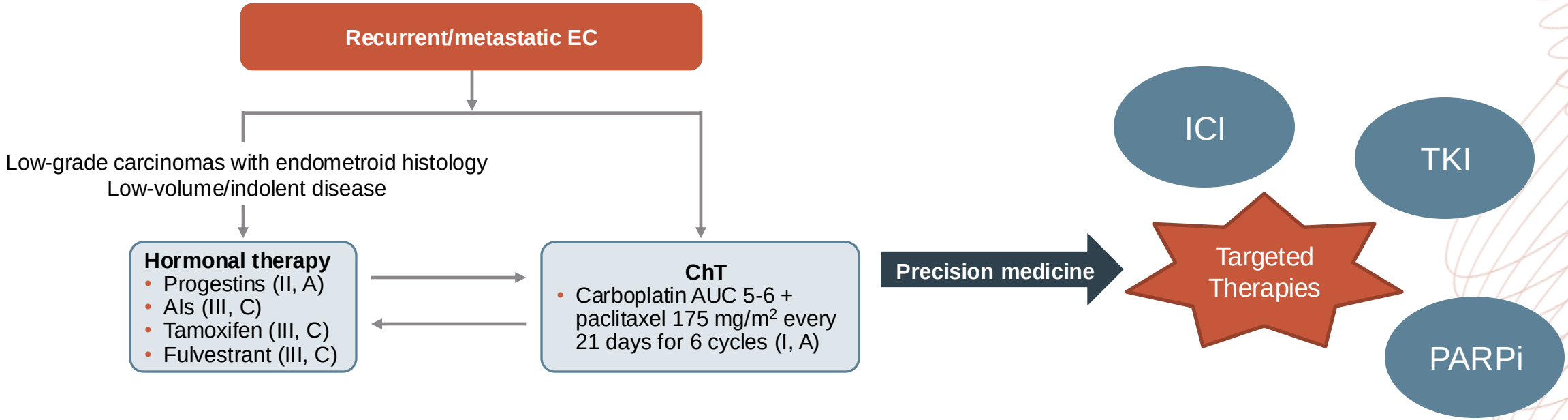
Molecular Group	Identifying features	Predominant Hystotypes	Prognosis (PFS at 5 yrs)	Treatment Implications
POLEmut	⇧⇧ Mutational load	All expect serous carcinomas	92-100%	Adjuvant treatment may not be required
dMMR	⇧ Mutational load	Endometroid carcinomas	80-90%	Limited ChT benefit, improved response to IO
p53abn	⇩ Mutational load ⇧ CNV	Serous, high grade endometroid carcinomas	50%	Benefit from ChT + radiotherapy, PARPi or IO[2]
NSMP	⇩ Mutational load ⇩ CNV	Low grade endometroid	75%-80%	May benefit from hormonal therapy

ChT, chemotherapy; CNV, copy number variation; dMMR, deficient mismatch repair; IO, immuno-oncology; NSMP, no specific molecular profile; p53abn, p53 abnormal; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; POLEmut, polymerase epsilon mutation; yrs, years

1.Baker-Rand H and Kitson SJ. *Cancers (Basel).* 2024;16:1028; 2. Yang Y, et al. *Int J Gynaecol Obstet.* 2024 Feb;164(2):436-459

METASTATIC EC: CURRENT 1L TREATMENT GUIDELINES

- The latest ESMO guidelines (2022) recommend hormonal therapy or ChT as the 1st line treatment for metastatic EC[1]
- Recent research has focused on precision medicine, leading to the development of various targeted therapies, including Immune checkpoint inhibitors (ICI),[2,3] tyrosine kinase inhibitors (TKIs)[4] and PARP inhibitors (PARPis)[5,6]
- Many of these therapies have now received EMA and/or FDA approval, with expectations of their integration into clinical guidelines in the near future[7-11]



1L, first-line; AI, aromatase inhibitor; AUC, area under the curve; ChT, chemotherapy; EC, endometrial cancer; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, United States Food and Drug Administration

1. Oaknin A, et al. *Ann Oncol.* 2022;33:860-77; 2. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158; 3. Eskander RN, et al. *N Engl J Med.* 2023;388:2159-2170; 4. Marth C, et al. Int J Gynecol Cancer. 2022;32(1):93-100; 5. Westin SN, et al. *J Clin Oncol.* 2024;42:283-299; 6. Westin SN, et al. *J Clin Oncol.* 2024;42:3262; 7. GSK press release (December 2023). Available here (accessed November 2024). 8. GSK press release (August 2024). Available here (accessed November 2024); 9. Merck press release (October 2024). Available here (accessed November 2024); 10. Flaherty C (August 2024). Available at: https://www.onclive.com/view/durvalumab-based-combos-win-eu-approval-for-advanced-recurrent-endometrial-cancer (accessed November 2024); 11. Ryan C (June 2024). Available at: https://www.onclive.com/view/fda-approves-durvalumab-plus-chemotherapy-for-dmmr-primary-advanced-or-recurrent-endometrial-cancer (accessed November 2024)

CLINICAL SCENARIO

PATIENT CASE: p53abn & pMMR METASTATIC EC

PATIENT
Jane D.
AGE: 54 years

Which first-line targeted therapy options are available to patients like Jane?

DIAGNOSIS ENDOMETRIAL CANCER
2021

Stage: FIGO Ib
Histology: G2 Endometrioid adenocarcinoma
LVSI: None
L1-CAM: Positive
Bilateral SLNB: Negative

1L TREATMENT
2021

Surgery:
- TLH
- BSO

Adjuvant ChT:
Carboplatin + Paclitaxel

METASTATIC PROGRESSION
2024

Metastases: Liver & lung
Histology: G3 Endometroid carcinoma
Hormonal status: HR+/HER2-
Molecular classification: p53abn & pMMR

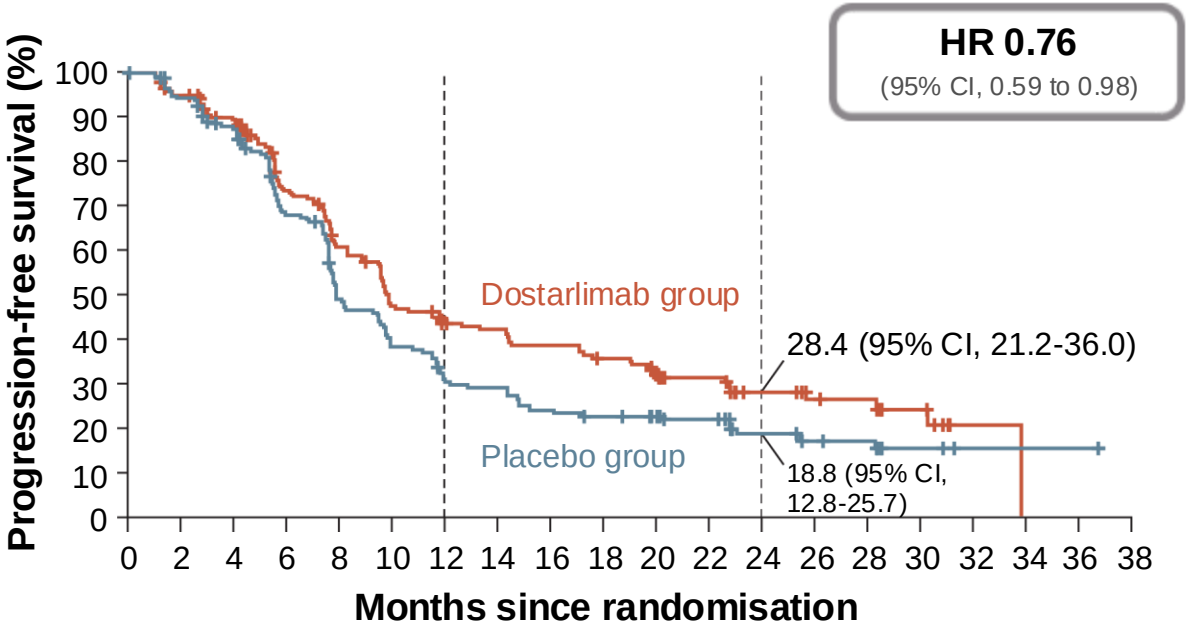
1L, first line; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; EC, endometrial cancer; FIGO Ib, International Federation of Gynecology and Obstetrics stage Ib; G2/3, grade 2/3; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; L1-CAM, L1 cell adhesion molecule; LVSI, lymphovascular space invasion; p53abn, p53 abnormality; pMMR, proficient mismatch repair; SNLB, sentinel lymph node biopsy; TLH, total laparoscopic hysterectomy

IMMUNO CHECKPOINT INHIBITORS

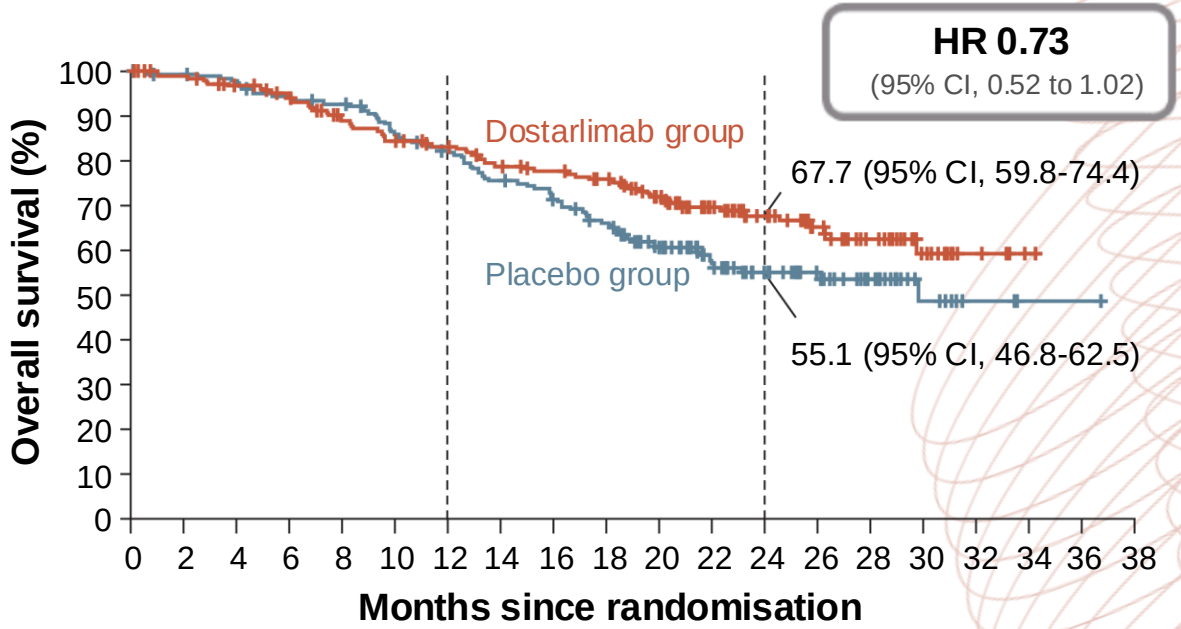
RUBY TRIAL: DOSTARLIMAB + ChT SHOWED IMPROVED PFS & OS RESULTS IN pMMR POPULATION VS ChT ALONE

Dostarlimab benefit in pMMR–MSS population: Although **less pronounced than in the dMMR–MSI-H group**, efficacy was consistent for progression-free and overall survival

PFS RESULTS



OS RESULTS



- Safety analysis in the overall population showed a 10% higher incidence of grade ≥3 AEs with dostarlimab, while chemotherapy discontinuation rates and QoL remained similar between the two groups

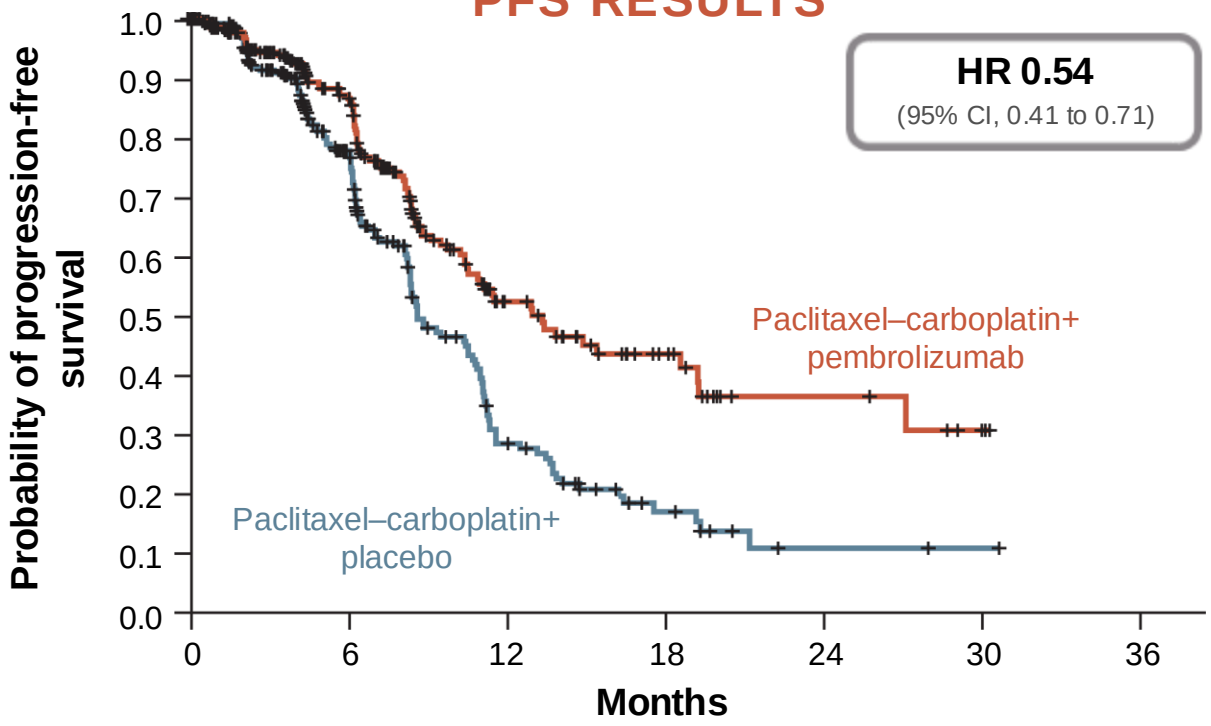
Aes, adverse events; ChT, chemotherapy; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; pMMR, proficient mismatch repair; PFS, progression-free survival; QoL, quality of life

Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158

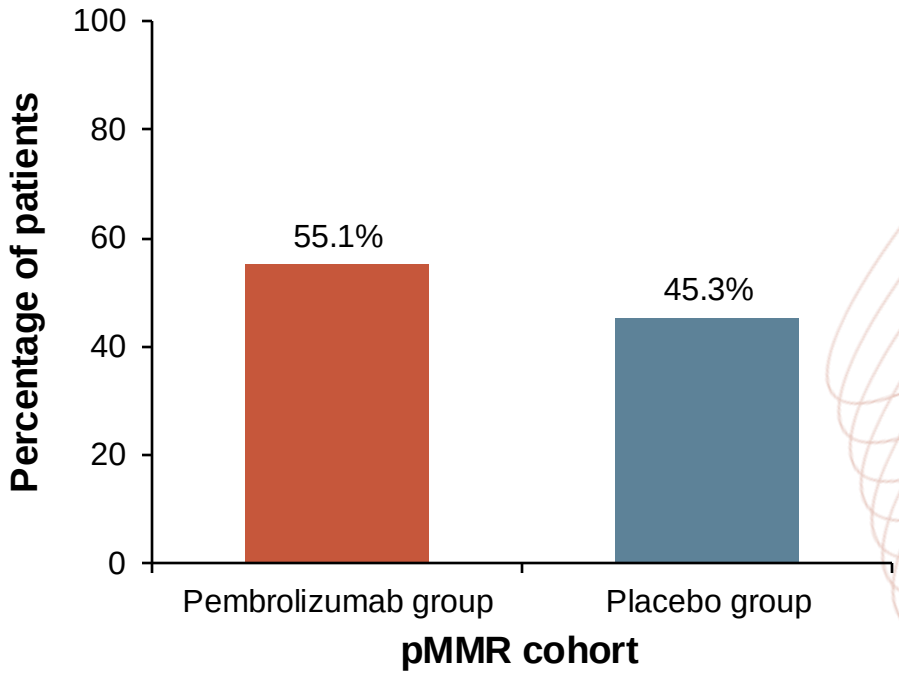
NRG-GY018 TRIAL: SUBGROUP ANALYSIS OF PFS IN pMMR POPULATION FAVORS PEMBROLIZUMAB + ChT VS ChT ALONE

PEMBRO + ChT was **associated with longer PFS** compared to placebo in **patients with pMMR endometrial cancers**, although **greater benefits** were observed in **dMMR population**

PFS RESULTS



GRADE ≥3 ADVERSE EVENTS



- Frequency of grade ≥3 AEs increased with the addition of pembrolizumab to combination chemotherapy

AE, adverse event; ChT, chemotherapy; HR, hazard ratio; PEMBRO, pembrolizumab; PFS, progression-free survival; p/dMMR, proficient mismatch repair

Eskander RN, et al. *N Engl J Med.* 2023;388:2159-2170

TYROSINE KINASE INHIBITORS

ENGOT-en9/LEAP-001 TRIAL DESIGN: PEMBROLIZUMAB + LENVATINIB IN 1L TREATMENT OF ENDOMETRIAL CANCER[1,2]

Key eligibility criteria

- Stage III, Stage IV or recurrent endometrial carcinoma[a]
- Radiographically apparent disease – either measurable or non-measurable
- No prior chemotherapy except in the neo/adjuvant setting[b]
- ECOG PS 0-1
- Tumour tissue sample for MMR testing

Stratification factors

MMR status (pMMR vs dMMR)

- If pMMR
  - ECOG PS (0 vs 1)
  - Measurable disease (yes vs no)
  - Prior chemotherapy and/or chemoradiation (yes vs no)

R (1:1)
N=842[2]

Lenvatinib 20 mg orally QD until PD
+
Pembrolizumab 200 mg IV Q3W until PD or ×35 cycles

Paclitaxel 175 mg/m^2 IV Q3W
+
Carboplatin AUC 6 IV Q3W ×7 cycles[c]

Endpoints

- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DoR per RECIST v1.1 by BICR

[a] Carcinosarcoma (malignant mixed Müllerian tumour), endometrial leiomyosarcoma or other high-grade sarcomas, or endometrial stromal sarcomas excluded

[b] 1 prior line of neoadjuvant and/or adjuvant chemotherapy in the setting of curative-intent resection was permitted if recurrence occurred ≥6 months after last dose; prior radiotherapy with or without chemotherapy, or prior hormonal therapy were also permitted

[c] Patients with ongoing clinical benefit could continue chemotherapy beyond 7 cycles if approved by sponsor

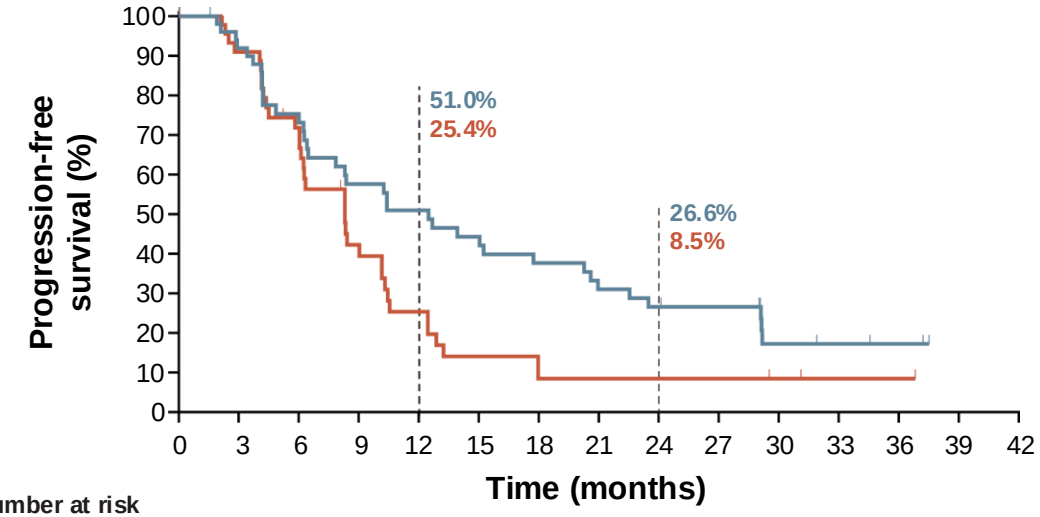
1L, first-line; AUC, area under the curve; BICR, blinded independent central review; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; (p/d)MMR, (proficient/deficient) mismatch repair; PFS, progression-free survival; QD, once daily; Q3W, every 3 weeks; R, randomised; RECIST, Response Evaluation Criteria In Solid Tumours

1. Marth C, et al. *Int J Gynecol Cancer.* 2022;32:93-100; 2. Marth C, et al. Gynecol Oncol. 2024;190 (suppl. 1):S63-S64. Presented at SGO Annual Meeting on Women's Cancer 2024 (22 [LBA])

ENGOT-en9/LEAP-001 TRIAL: PFS & OS IMPROVED WITH LEN/PEMBRO VS TPC IN PRIOR (NEO)ADJUVANT ChT pMMR SUBGROUP

LEN/PEMBRO was **approved based on the KEYNOTE-775** trial for **aEC (non-MSI-H/dMMR) after prior systemic therapy in any setting.**[1] The ENGOT-en9/LEAP-001 trial further **confirms its effectiveness as a 1st line option** in this population

PFS RESULTS[2]

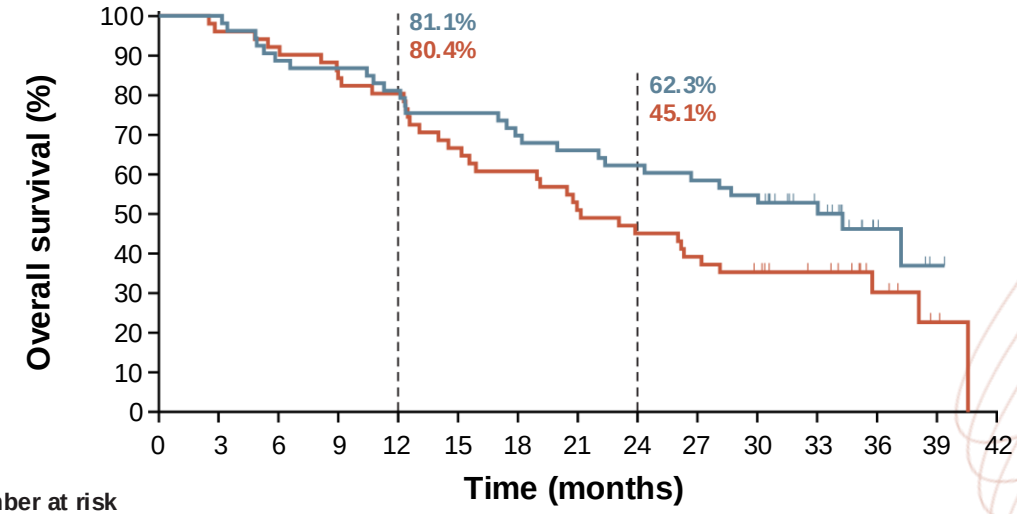


Number at risk

LEN/PEMBRO	53	45	34	26	23	20	17	14	12	11	4	3	2	0	0
TC	51	40	28	15	9	5	3	3	3	3	2	1	1	0	0

	LEN/PEMBRO	TPC
Events, n/N	37/53	35/51
Median PFS (95% CI), mo	12.5 (6.5-20.3)	8.3 (6.1-10.2)
HR (95% CI)	0.60 (0.37-0.97)	

OS RESULTS[2]



Number at risk

LEN/PEMBRO	53	53	47	46	43	40	37	35	33	31	28	18	6	1	0
TC	51	49	47	43	41	34	31	26	23	20	17	13	6	2	0

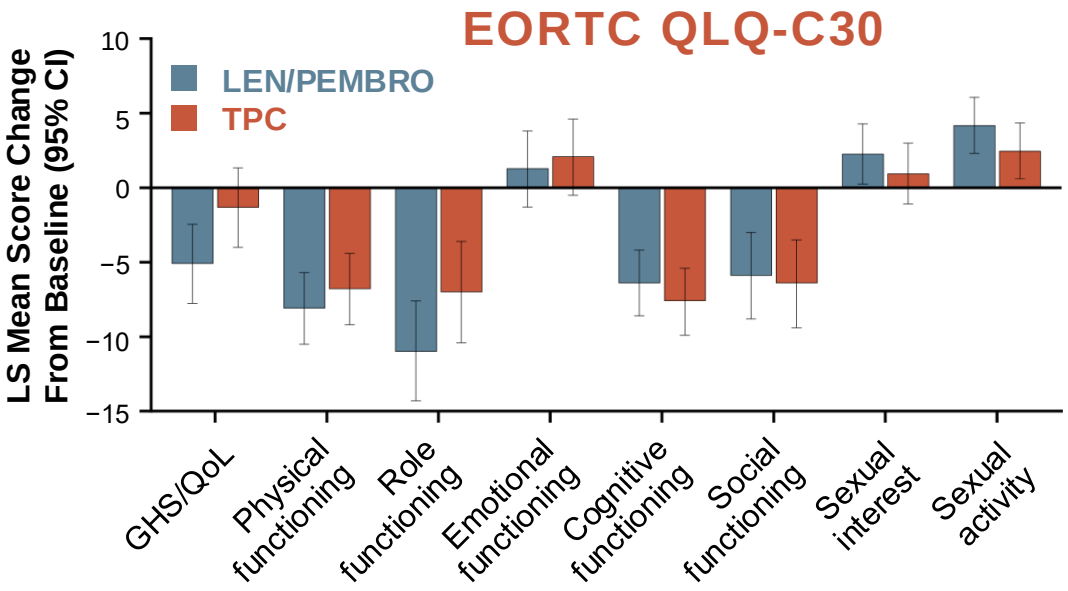
	LEN/PEMBRO	TPC
Events, n/N	28/53	36/51
Median OS (95% CI), mo	34.2 (22.0-NR)	21.1 (15.1-28.1)
HR (95% CI)	0.67 (0.41-1.11)	

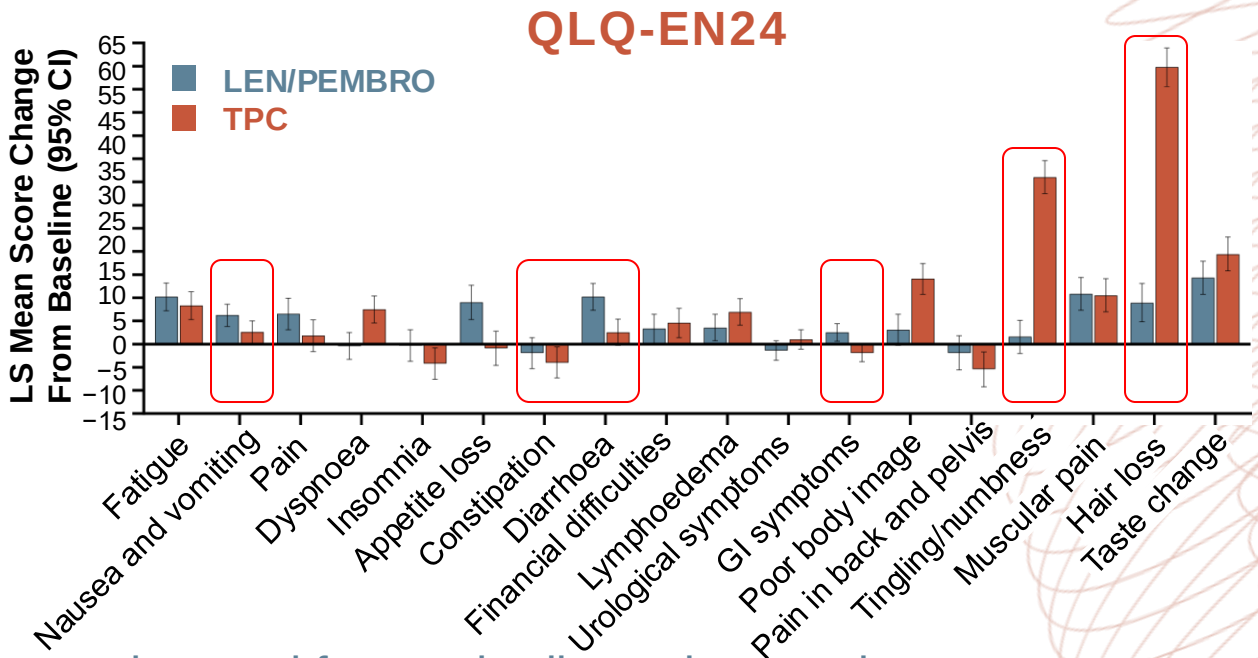
ChT, chemotherapy;CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; mo, months; MSI-H, microsatellite instability-high; NR, not reached; OS, overall survival; p/dMMR, proficient/deficient mismatch repair; PEMBRO, pembrolizumab; PFS, progression-free survival; TPC, treatment of physician's choice

1. FDA grants regular approval to pembrolizumab and lenvatinib for advanced endometrial carcinoma. Available here (accessed November 2024); 2. Marth C, et al. Gynecol Oncol. 2024;190 (suppl. 1):S63-S64. Presented at SGO Annual Meeting on Women's Cancer 2024 (22 [LBA])

ENGOT-en9/LEAP-001 TRIAL: CHANGES IN EORTC QLQ-C30 & QLQ-EN24 SCALE SCORES FROM BASELINE TO WEEK 18 IN pMMR COHORT

HRQoL outcomes were similar between LEN/PEMBRO and TPC across most QoL scales; however, **LEN/PEMBRO was associated with lower incidences of neuropathy and alopecia compared to TPC**





- AEs of interest were generally consistent with those observed for pembrolizumab monotherapy with exception of increased rates of thyroid abnormalities (hypo/hyperthyroidism) and colitis

AE, adverse event; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; HRQoL, health-related quality of life; LEN, lenvatinib; LS, least squares; PEMBRO, pembrolizumab; pMMR, proficient mismatch repair; QLQ-C30, quality of life questionnaire core 30; QLQ-EN24, quality of life questionnaire endometrial cancer module 24; QoL, quality of life; TPC, treatment of physician's choice

Marth C, et al. *Gynecol Oncol.* 2024;190 (suppl. 1):S63-S64. Presented at SGO Annual Meeting on Women's Cancer 2024 (22 [LBA])

PARP INHIBITORS

PARP, poly (ADP-ribose) polymerase

DUO-E TRIAL DESIGN: DURVALUMAB + ChT FOLLOWED BY DURVALUMAB +/- OLAPARIB AS 1L TREATMENT FOR aEC

Patients

- Newly diagnosed FIGO stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas

R
1:1:1

Stratified by:

- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs RoW)

Chemotherapy phase
6 cycles

Maintenance phase

	Chemotherapy phase	Maintenance phase
Control	Paclitaxel-carboplatin q3w + durvalumab placebo IV q3w	Durvalumab placebo IV q4w + olaparib placebo tablets bid
Durvalumab	Paclitaxel-carboplatin q3w + Durvalumab 1,120 mg IV q3w	Durvalumab 1,500 mg IV q4w + olaparib placebo tablets bid
Durvalumab + olaparib	Paclitaxel-carboplatin q3w + Durvalumab 1,120 mg IV q3w	Durvalumab 1,500 mg IV q4w + olaparib 300 mg tablets bid

Patients without disease progression

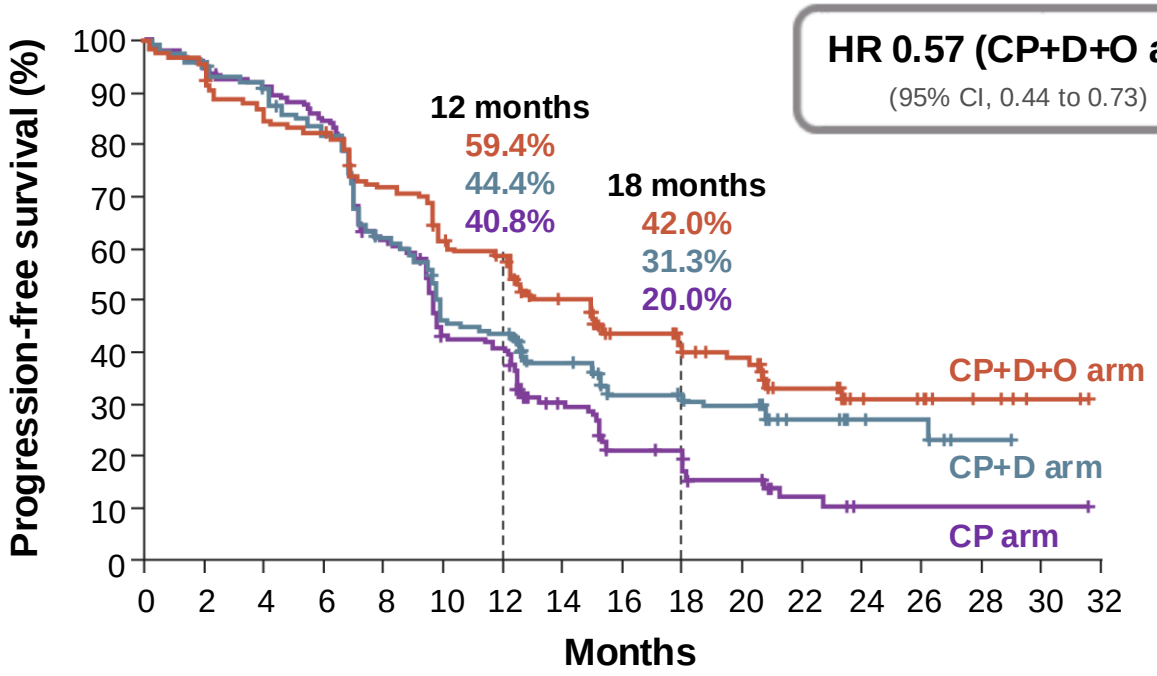
Maintenance therapy continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met

1L, first-line; aEC, advanced endometrial cancer; bid, twice daily; ChT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; IV, intravenous; MMR, mismatch repair; PARP, poly (ADP-ribose) polymerase; q3/4w, every 3/4 weeks; R, randomised; RoW, rest of world

Westin SN, et al. *J Clin Oncol.* 2024;42:283-299 (including supplement); Westin SN, et al. *J Clin Oncol.* 2024;42:3262

DUO-E TRIAL: DURVALUMAB IMPROVED PFS VS CONTROL IN pMMR SUBGROUP WITH ADDED BENEFIT FROM MAINTENANCE OLAPARIB

PFS benefit was observed for durvalumab + olaparib arm versus control in **pMMR subgroup**, although the **greatest benefit was seen in the dMMR subgroup**



Summary of AEs in the overall population

	Overall[a]			Maintenance Phase		
	D + O (n=238)	D (n=235)	CP (n=236)	D + O (n=192)	D (n=183)	CP (n=169)
Grade ≥3 AE (%)	67.2	54.9	56.4	41.1	16.4	16.6
AE leading to death (%)	2.1	1.7	3.4	1.6	0	1.2
Immune-mediated AEs (%)	23.5	28.1	6.8	14.1	14.8	3.6
AEs leading to discontinuation (%)	24.4	20.9	18.6	14.1	6.0	4.1

- In the overall population, although there was a higher rate of grade ≥3 AEs in the durvalumab + olaparib arm, the safety profiles of each arm were generally consistent with the known profiles of individual components of the regimen

[a] ChT Phase + Maintenance Phase

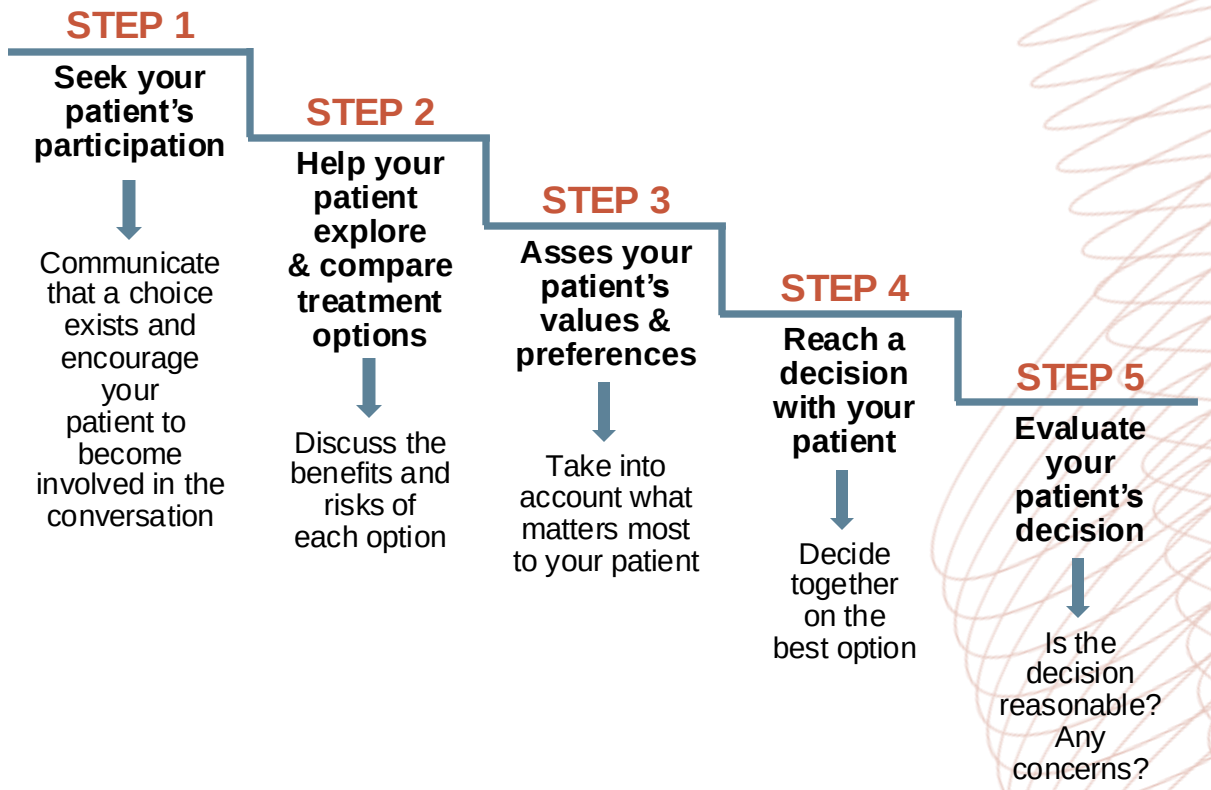
AE, adverse events; CP, carboplatin; D, durvalumab; O, olaparib; PFS, progression-free survival; p/dMMR, proficient/deficient mismatch repair; HR, hazard ratio

Westin SN, et al. *J Clin Oncol.* 2024;42:283-299

PATIENT COMMUNICATION & SHARED DECISION-MAKING

THE SHARE APPROACH—ESSENTIAL STEPS OF SHARED DECISION-MAKING (SDM)

- **The SHARE Model** guides effective SDM in clinical practice, with patient education as the core focus. Key topics for patients with aEC include[a]:
  1. **Molecular Classification**
     Simplify the explanation of molecular subtypes and their impact on treatment options to empower informed decisions and build trust
  2. **Risks and Benefits of Combination Therapy**
     Explain targeted combinations (e.g. DURV/OLA, LEN/PEMBRO) and their side effects transparently. Discuss QoL outcomes to help patients weigh pros and cons and engage in SDM



[a]Expert input

aEC, advanced endometrial cancer, DUR, durvalumab; LEN, lenvatinib; OLA, olaparib; PEMBRO, pembrolizumab; QoL, quality of life

SHARE approach. *AHRQ*. 2020. Available at: https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tool/resource-2.html#ref1 (accessed October 2024)

CONCLUSION

CONCLUSION

- Molecular classification is essential for both prognosis and guiding personalised treatment decisions[1]
- The combination of an ICI and ChT has demonstrated benefits for patients with pMMR status, including with maintenance olaparib. However, the greatest benefit for this combination is seen in the dMMR population[2-5]
- Lenvatinib plus pembrolizumab is a viable option for advanced or recurrent endometrial cancer, particularly for pMMR patients who have progressed after any prior systemic therapy, including (neo)adjuvant treatments[6]
- Shared decision-making, reinforced by patient education, is crucial for optimising treatment outcomes[7]

aEC, advanced endometrial cancer; ChT, chemotherapy; ICI, immune checkpoint inhibitor; p/dMMR, proficient/deficient mismatch repair

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