# Clinical decision making with immunotherapies in advanced or recurrent endometrial cancer

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# Using molecular classification to inform treatment decisions

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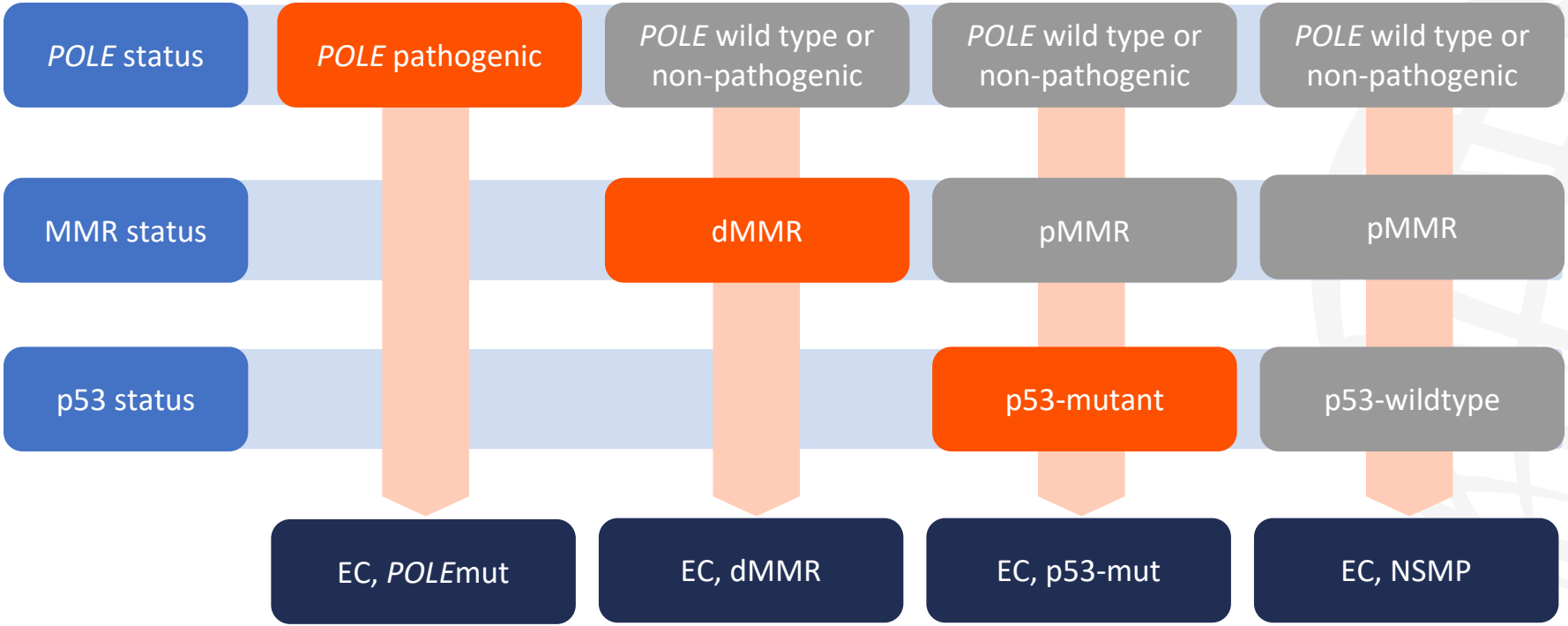
# Which molecular classifications are used to stratify patients with endometrial cancer?

# Molecular classification in EC




dMMR, MMR deficient; EC, endometrial cancer; MMR, mismatch repair; NSMP, no specific molecular profile; pMMR, MMR proficient; POLE, polymerase epsilon; POLEmut, POLE-ultramutated; p-53mut, p53-mutant.

Oaknin A, et al. *Ann Oncol*. 2022;33:860–77.

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# What is the rationale behind molecular classification in advanced or recurrent endometrial cancer?

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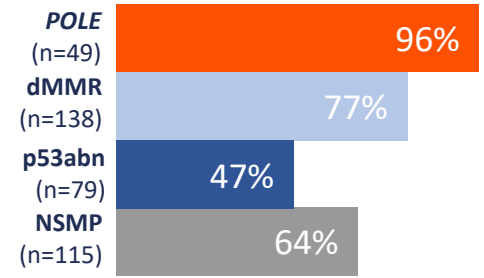
# Clinical outcomes in EC vary depending on the molecular classification

## Five-year RFS[1]

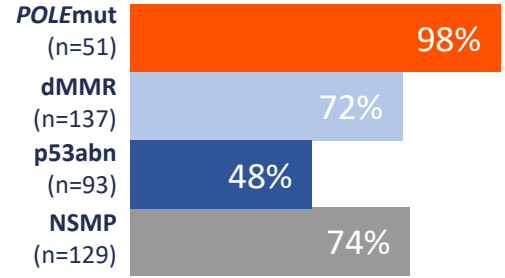
Retrospective analysis of clinical follow-up data for patients with FIGO grade 3 EECs (N=381)




p=0.000001

## Five-year RFS[2]

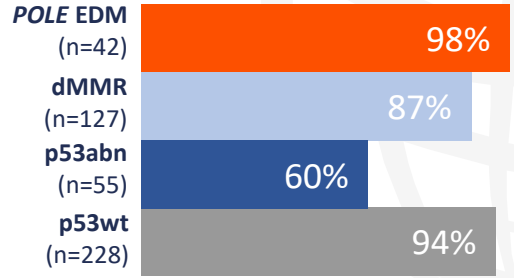
Molecular analysis of patients from the PORTEC-3 trial in high-risk EC (N=410)




p<0.001

## Disease-specific survival[3]

Retrospective analysis of patients with EC treated at a single centre (N=452)




p=0.03

**Direct comparisons between trials should not be made due to differences in trial design.**

dMMR, mismatch repair deficient; EC, endometrial cancer; EEC, endometrioid endometrial carcinomas; EDM, exonuclease domain mutations; FIGO, The International Federation of Gynecology and Obstetrics; NSMP, no specific molecular profile; POLE, polymerase epsilon; POLEmut, POLE-ultramutated; p53abn, p53 abnormal; p53wt, p53 wild type; RFS, recurrence-free survival.

1. Bosse T, et al. *Am J Surg Pathol*. 2018;42:561–8; 2. León-Castillo A, et al. *J Clin Oncol*. 2020;38:3388–97; 3. Kommoss S, et al. *Ann Oncol*. 2018;29:1180–8.

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# What diagnostic tests are required to establish the molecular classification of a tumour?

# Tests required for molecular assessment of EC

## MMR status[1]

**Immunostaining** of at least two MMR proteins:

- PMS2
- MSH6

And ideally four proteins:

- PMS2
- MSH6
- MLH1
- MSH2

**Complete loss of one or more** of these proteins is sufficient for diagnosis of **dMMR**

## p53 status

**p53-mut** diagnosed using **p53 immunostaining[1]**

p53 immunostaining is a good but not perfect surrogate for *TP53* mutation, ESGO/ESTRO/ESP guidelines recommend **integrated analysis combining pathologic and molecular results**[2]

## *POLE* status[1]

***POLEmut*** diagnosed after **detection of pathogenic mutation** in the exonuclease domain of *POLE*

IHC staining recommended as standard practice for all EC pathology specimens regardless of histological type[1]

Should be carried out where available and prioritized where results are relevant to guide treatment recommendations[1]

ESGO, European Society of Gynaecological Oncology; ESP, European Society of Pathology; ESTRO, European SocieTy for Radiotherapy and Oncology; dMMR, MMR deficient; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; POLE, polymerase epsilon; POLEmut, POLE-ultramutated; p53-mut, p53 mutant.

1. Oaknin A, et al. *Ann Oncol*. 2022;33:860–77; 2. Concin N, et al. *Int J Gynecol Cancer*. 2021;31:12–39.

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# What are the latest guideline recommendations regarding molecular classification and treatment selection?

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# ESMO guidelines for the management of advanced/recurrent EC

## First line

**Chemotherapy:**[1]
- 6 cycles of carboplatin + paclitaxel

### Low-grade carcinomas with endometroid histology Low-volume/indolent disease[1]

**Hormonal therapy:**
- Progestins
- Aromatase inhibitors
- Tamoxifen
- Fulvestrant

### MSI-H/dMMR[2]

**ICI therapy:**
- **Dostarlimab plus carboplatin/paclitaxel**

## Second line

### MSI-H/dMMR

**Rechallenge:**[1]
- Platinum-based therapy

**Chemotherapy:**[1]
- Doxorubicin
- Paclitaxel

**ICI therapy:**
- Dostarlimab*[1]
- Pembrolizumab-lenvatinib*†[1]
- **Pembrolizumab**[3]

### MSS/pMMR

**Rechallenge:**[1]
- Platinum-based therapy

**Chemotherapy:**[1]
- Doxorubicin
- Paclitaxel

**ICI therapy:**[1]
- Pembrolizumab-lenvatinib*

Indicates EMA approval after the ESMO guidelines were published

NCCN guidelines already include recommendations for an ICI + CP in first line and pembrolizumab monotherapy in the second line for dMMR tumours[4]

*In patients eligible for further treatment after failure of platinum-based therapy; †FDA approval is restricted to patients whose tumours are not MSI-H or dMMR.
CP, carboplatin plus paclitaxel; dMMR, MMR deficient; EC, endometrial cancer; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; MMR, mismatch repair; MSI-H, microsatellite instability – high; MSS, microsatellite stable; NCCN, National Comprehensive Cancer Network; pMMR, MMR proficient.

1. Oaknin A, et al. *Ann Oncol*. 2022;33:860–77; 2. EMA. Dostarlimab SmPC. Available at: https://bit.ly/3vnfGpR (accessed 20 March 2024); 3. EMA. Pembrolizumab SmPC. Available at: https://bit.ly/3PvRLeN (accessed 20 March 2024); 4. NCCN. Uterine Neoplasms Guidelines Version 2.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (accessed 09 May 2024).

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# Immunotherapy as an established treatment in endometrial cancer

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# What is the current role of immunotherapy in the treatment pathway for endometrial cancer?

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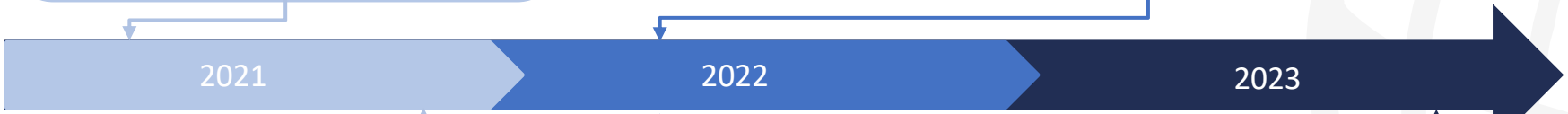
# EMA approvals of ICIs in advanced/recurrent EC

**Monotherapy dostarlimab:**
- dMMR/MSI-H recurrent/advanced EC
  - Progressed on or following prior treatment with a platinum-containing regimen[1]

**Pembrolizumab monotherapy:**
- *In MSI-H or dMMR tumours* including advanced/recurrent EC
  - Disease progression on or following prior treatment with a platinum-containing regimen
  - Not candidates for curative surgery or radiation[2,3]




**Pembrolizumab + lenvatinib:**
- Advanced/recurrent EC
  - Progressed on or following prior treatment with a platinum-containing regimen
  - Not candidates for curative surgery or radiation[2,3]

**Most recent ESMO guidelines update[4]**

**Dostarlimab + carboplatin/paclitaxel:**
- dMMR/MSI-H primary advanced/recurrent EC
  - Candidates for systemic therapy[1,5]

dMMR, mismatch repair deficient; EC, endometrial cancer; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; ICI, immune-checkpoint inhibitors; MSI-H, microsatellite instability – high.

1. EMA. Dostarlimab SmPC. Available at https://bit.ly/3vnfGpR (accessed 20 March 2024); 2. EMA. Pembrolizumab SmPC. Available at: https://bit.ly/3PvRLeN (accessed 20 March 2024); 3. EMA. Pembrolizumab: Procedural steps taken and scientific information after the authorisation. Available at https://bit.ly/3TKXzDM (accessed 20 March 2024); 4. Oaknin A, et al. *Ann Oncol*. 2022;33:860–77; 5. EMA. Dostarlimab: Procedural steps taken and scientific information after the authorisation. Available at: https://bit.ly/3TK0n40 (accessed 20 March 2024).

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# What do the guidelines recommend regarding the use of immunotherapies?

# ESMO guidelines for the management of advanced/recurrent EC

## First line

**Chemotherapy:**[1]
- 6 cycles of carboplatin + paclitaxel

**Low-grade carcinomas with endometroid histology Low-volume/indolent disease**[1]

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**MSI-H/dMMR**[2]

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## Second line

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- Dostarlimab*[1]
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CP, carboplatin plus paclitaxel; dMMR, MMR deficient; EC, endometrial cancer; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; MMR, mismatch repair; MSI-H, microsatellite instability – high; MSS, microsatellite stable; NCCN, National Comprehensive Cancer Network; pMMR, MMR proficient.

1. Oaknin A, et al. *Ann Oncol*. 2022;33:860–77; 2. EMA. Dostarlimab SmPC. Available at: https://bit.ly/3vnfGpR (accessed 20 March 2024); 3. EMA. Pembrolizumab SmPC. Available at: https://bit.ly/3PvRLeN (accessed 20 March 2024); 4. NCCN. Uterine Neoplasms Guidelines Version 2.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (accessed 09 May 2024).

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# What are the efficacy data supporting the current use of immunotherapies in endometrial cancer?

# Efficacy data for first-line ICI use: dMMR population

## RUBY/ENGOT-en6-NSGO/GOG-3031 (NCT03981796)[1]

Phase III: RUBY Part 1 – **dostarlimab + CP followed by dostarlimab** (n=245) vs placebo + CP followed by placebo (n=249) (R 1:1)

**mPFS dMMR/MSI-H** (months)


**HR 0.28**
95% CI 0.16–0.50
p<0.0001

Median duration of follow-up 24.8 months

Dostarlimab + CP | Placebo + CP

## NRG-GY018/KEYNOTE-868 (NCT03914612)[2]

Phase III: **Pembrolizumab + CP* followed by pembrolizumab** vs placebo + CP followed by placebo (pMMR [n=591], dMMR [n=225]; R 1:1)

**mPFS dMMR** (months)


**HR 0.30**
(95% CI 0.19–0.48)
p<0.001

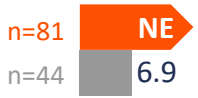
Median duration of follow-up 12 months

Pembrolizumab + CP | Placebo + CP

## AtTEnd/ENGOT-en7/MaNGO (NCT03603184)[3]

Phase III: **Atezolizumab + CP* followed by atezolizumab** (n=360) vs placebo + CP followed by placebo (n=189) (R 2:1)

**mPFS dMMR** (months)




**HR 0.36**
95% CI 0.23–0.57
p=0.0005

Median duration of follow-up 26.2 months

Atezolizumab + CP | Placebo + CP

**Direct comparisons between trials should not be made due to differences in trial design. *Not currently approved for use in EC by the EMA.**

Clinical trial information can be found on ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to the specific trial number (accessed 16 May 2024).

CI, confidence interval; CP, carboplatin-paclitaxel; dMMR, MMR deficient; EMA, European Medicines Agency; HR, hazard ratio; ICI, immune checkpoint inhibitor; m, median; MMR, mismatch repair; MSI-H, microsatellite instability – high; NE, not estimable; NR, not reached, PFS, progression-free survival; pMMR, MMR proficient; R, randomized.

1. Mirza MR, et al. Presented at: SGO 2023, Tampa, FL, USA. 25–28 March 2023. Abstract LBA11; 2. Eskander RN, et al. *N Engl J Med*. 2023;388:2159–70; 3. Colombo N, at al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA40.

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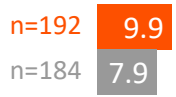
# Efficacy data for first-line ICI use: pMMR population

## RUBY/ENGOT-en6-NSGO/GOG-3031 (NCT03981796)[1]

Phase III: RUBY Part 1 – **dostarlimab + CP followed by dostarlimab** (n=245) vs placebo + CP followed by placebo (n=249) (R 1:1)

**mPFS pMMR/MSS** (months)



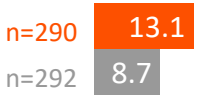

**HR 0.76**
95% CI 0.59–0.98

Dostarlimab + CP | Placebo + CP

## NRG-GY018/KEYNOTE-868 (NCT03914612)[2]

Phase III: **Pembrolizumab + CP* followed by pembrolizumab** vs placebo + CP followed by placebo (pMMR [n=591], dMMR [n=225]; R 1:1)

**mPFS pMMR** (months)




**HR 0.54**
(95% CI 0.41–0.71)
p<0.001

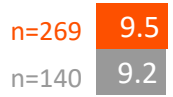
Median duration of follow-up 7.9 months

Pembrolizumab + CP | Placebo + CP

## AtTEnd/ENGOT-en7/MaNGO (NCT03603184)[3]

Phase III: **Atezolizumab + CP* followed by atezolizumab** (n=360) vs placebo + CP followed by placebo (n=189) (R 2:1)

**mPFS pMMR** (months)




**HR 0.92**
95% CI 0.73–1.16

Atezolizumab + CP | Placebo + CP

**Direct comparisons between trials should not be made due to differences in trial design. *Not currently approved for use in EC by the EMA.**

Clinical trial information can be found on ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to the specific trial number (accessed 16 May 2024).

CI, confidence interval; CP, carboplatin-paclitaxel; dMMR, MMR deficient; EMA, European Medicines Agency; HR, hazard ratio; ICI, immune checkpoint inhibitor; m, median; MMR, mismatch repair; MSS, microsatellite stable; PFS, progression-free survival; pMMR, MMR proficient; R, randomized.

1. Mirza MR, et al. Presented at: SGO 2023, Tampa, FL, USA. 25–28 March 2023. Abstract LBA11; 2. Eskander RN, et al. *N Engl J Med*. 2023;388:2159–70; 3. Colombo N, at al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA40.

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# Efficacy data supporting second-line ICI use

## GARNET (NCT02715284)[1]

Phase I: **Dostarlimab** in advanced or recurrent EC

| | dMMR/MSI-H (n=108) | pMMR/MSS (n=156) |
|---|---|---|
| ORR | 43.5% | 14.1% |
| mDOR | Not reached | Not reached |

## KEYNOTE-158 (NCT02628067)[2]

Phase II: **Pembrolizumab** in previously treated advanced MSI-H/dMMR non-colorectal cancers

EC (n=68)

| | |
|---|---|
| ORR | 48.5% |
| mDOR | Not reached |

## KEYNOTE-775 (NCT03517449)[3]

Phase III: **Lenvatinib plus pembrolizumab** in previously treated advanced EC

| | L+P (n=411) | ChT (n=416) | |
|---|---|---|---|
| mOS | 18.7 months | 11.9 months | HR 0.65 95% CI: 0.55–0.77 |
| pMMR | 18.0 months | 12.2 months | HR 0.70 95% CI: 0.58–0.83 |
| mPFS | 7.3 months | 3.8 months | HR 0.56 95% CI: 0.48–0.66 |
| pMMR | 6.7 months | 3.8 months | HR 0.60 95% CI: 0.50–0.72 |

**Direct comparisons between trials should not be made due to differences in trial design.**

Clinical trial information can be found on ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to the specific trial number (accessed 16 May 2024).

ChT, chemotherapy of the treating physician's choice; dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; ICI, immune checkpoint inhibitor; L+P, lenvatinib plus pembrolizumab; m, median; MMR, mismatch repair; MSI-H, microsatellite instability – high; MSS, microsatellite stable; pMMR, MMR proficient; OS, overall survival; PFS, progression-free survival.

1. Oaknin A, et al. *J Immunother Cancer*. 2022;10:e003777; 2. Maio M, et al. *Ann Oncol*. 2022;33:929–38; 3. Makker V, et al. *J Clin Oncol*. 2023;41:2904–10.

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# What are the key safety considerations for immune checkpoint inhibitors?

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# Safety considerations when using ICIs in advanced/recurrent EC

- irAEs can affect any organ system[1]
- ICIs have a different adverse event profile compared with chemotherapy[1]
- irAEs can occur at any point during or up to 12 months after cessation of treatment[1,2]
- When patients present with symptoms of a potential irAE it is important to consider and rule out other causes, including disease progression, allergy, GI infection or hepatotoxicity of other drugs[3]
- All patients and caregivers should be carefully counselled about symptoms of potential irAEs and to report them immediately[1]
- Guidelines have been developed to support the management of irAEs according to grade[2,4]

EC, endometrial cancer; GI, gastrointestinal; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

1. Medina P, et al. *J Pharm Pract*. 2020;33:338–49; 2. Brahmer JR, et al. *J Immunother Cancer*. 2021;9:e002435; 3. Champiat S, et al. *Ann Oncol*. 2016;27:559–74; 4. Haanen J, et al. *Ann Oncol*. 2022;33:1217–38.

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# Future directions for immunotherapy in the first-line setting

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# What is the current role of immunotherapy in first-line treatment of recurrent or advanced endometrial cancer?

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# What other immunotherapy approaches are in development for the first-line treatment of advanced/recurrent endometrial cancer, and what data support their use?

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# First-line ICI + TKI: Efficacy data

## ENGOT-en9/LEAP-001 (NCT03884101)[1,2]

Phase III: **Pembrolizumab + lenvatinib** (n=420) vs CP (n=422)*
Data cut-off: 02 October 2023†

### pMMR population

**mPFS (months)**
n=320 9.6
n=322 10.2
**HR 0.99** (95% CI 0.82–1.21)

**mOS (months)**
n=320 30.9
n=320 29.4
**HR 1.02** (95% CI 0.83–1.26) p=0.246

### dMMR population

**mPFS (months)**
n=100 31.8
n=100 9.0
**HR 0.61** (95% CI 0.40–0.92)

**mOS (months)**
n=100 NR
n=100 NR
**HR 0.57** (95% CI 0.36–0.91)

Pembrolizumab + lenvatinib  CP

**Pembrolizumab + lenvatinib did not meet the prespecified non-inferiority statistical criterion for OS or PFS vs CP in patients with pMMR aEC, so further statistical analysis of other efficacy endpoints was not performed**

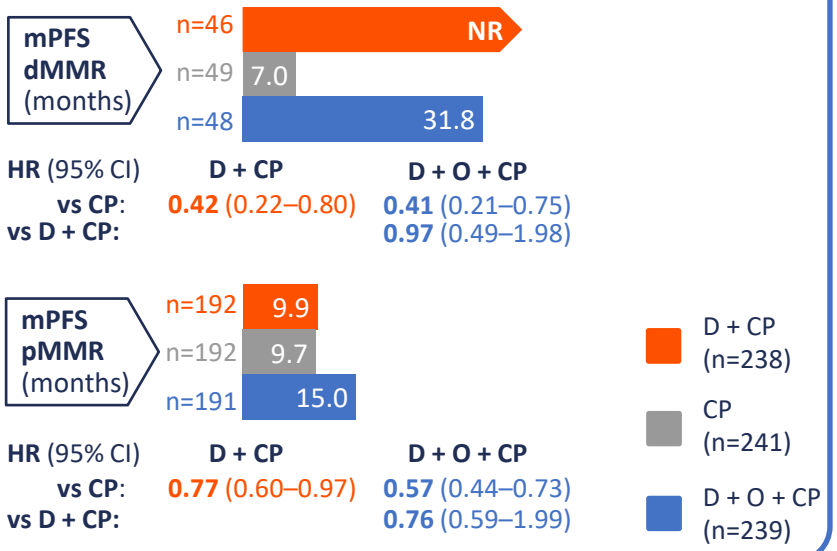
*Patients with prior neoadjuvant or adjuvant chemotherapy included; †Median duration of follow-up 38.4 months. Clinical trial information can be found on ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to the specific trial number (accessed 16 May 2024). aEC, advanced endometrial cancer; CI, confidence interval; CP, carboplatin-paclitaxel; dMMR, MMR deficient; HR, hazard ratio; ICI, immune checkpoint inhibitor; m, median; MMR, mismatch repair; NR, not reached; OS, overall survival; PFS, progression-free survival; pMMR, MMR proficient; TKI, tyrosine kinase inhibitor.

1. Marth C, et al. Presented at: SGO 2024, San Diego, CA, USA. 16–18 March 2024; 2. Marth C, et al. Presented at: ESGO 2024, Barcelona, Spain. 7–10 March 2024. Abstract 88.

# First-line ICI + PARPi: Efficacy data

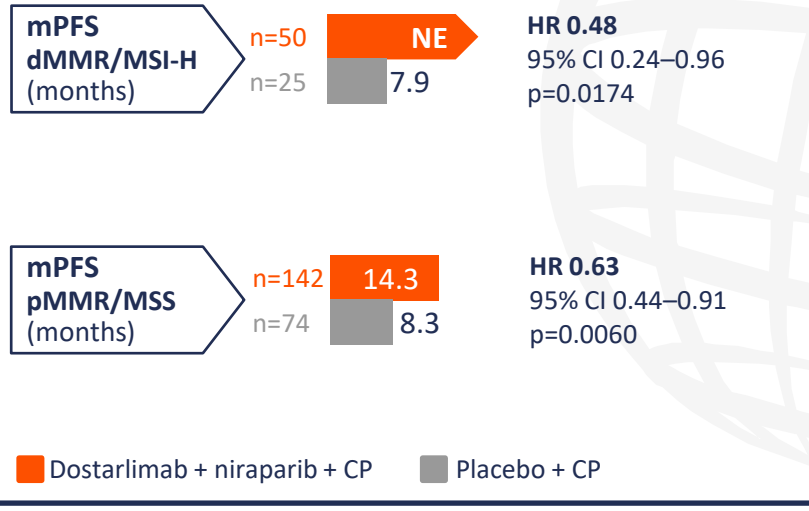
## DUO-E/ENGOT-en10/GOG-3041 (NCT04269200)[1]

Phase III: **Durvalumab + CP followed by durvalumab ± olaparib** vs CP




## RUBY/ENGOT-en6-NSGO/GOG-3031 (NCT03981796)[2]

Phase III: RUBY Part 2 – **dostarlimab + CP followed by dostarlimab plus niraparib** (n=192) vs placebo + CP followed by placebo IV plus placebo PO (n=99)




Clinical trial information can be found on ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to the specific trial number (accessed 16 May 2024).

CI, confidence interval; CP, carboplatin-paclitaxel; D, durvalumab; dMMR, MMR deficient; HR, hazard ratio; ICI, immune checkpoint inhibitor; IV, intravenous; m, median; MMR, mismatch repair; MSI-H, microsatellite instability – high; MSS, microsatellite stable; NE, not estimable; NR, not reached; O, olaparib; PARPi, poly(ADP-ribose) polymerase inhibitors; PFS, progression-free survival; pMMR, MMR proficient; PO, by mouth.

1. Westin SN, et al. Presented at: ESGO 2024, Barcelona, Spain. 7–10 March 2024. Abstract 619; 2. Mirza MR, et al. Presented at: SGO 2024, San Diego, CA, USA. 16–18 March 2024.

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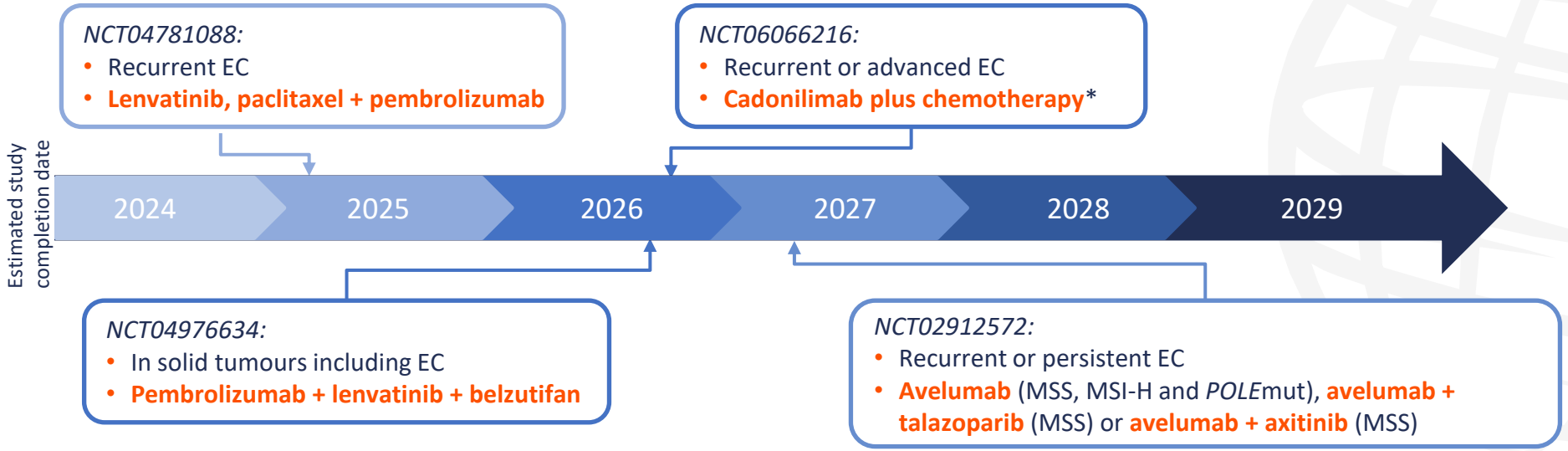
# First-line ICIs under investigation in advanced or recurrent EC – phase II




*Chemotherapy consisting of cisplatin or carboplatin and paclitaxel.
EC, endometrial cancer; dMMR, mismatch repair deficient; MSI-H, microsatellite instability – high; MSS, microsatellite stable; POLEmut, POLE-ultramutated.
ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to specific trial number (accessed 25 March 2024).

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# How will emerging immunotherapy approaches likely impact the treatment landscape?

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