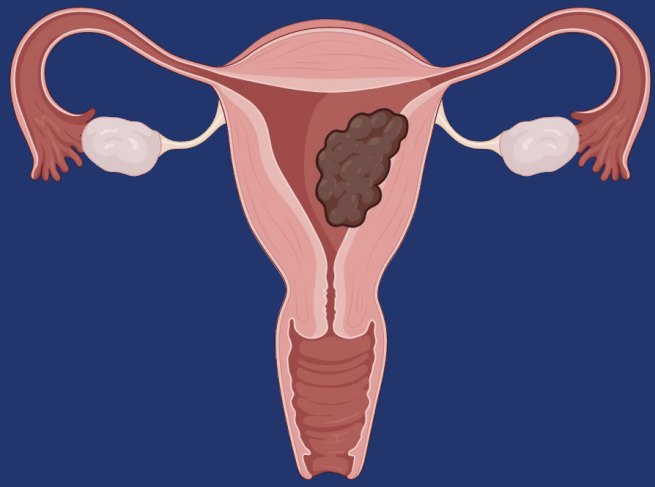
National Cancer Centre Singapore
SingHealth

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
ONCOLOGY

# Management of Advanced Endometrial Cancer



## Cancer ECHO UM
## 7 Aug 2024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# Endometrial Cancer: From “Cinderella Disease” to “Embarrassment of Riches” – or not?

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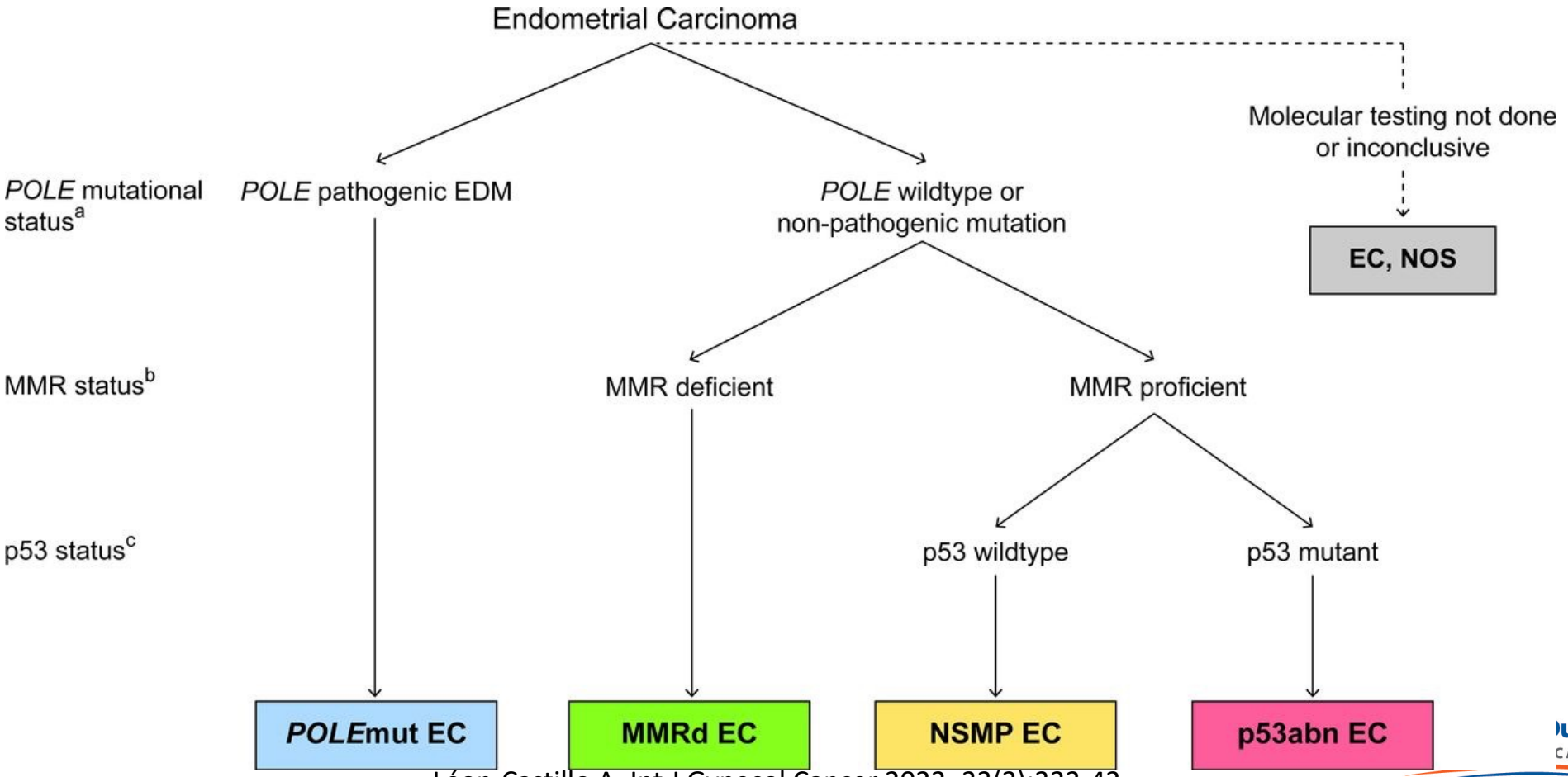
# Molecular Classification of EC




Léon-Castillo A. Int J Gynecol Cancer 2023; 33(3):333-42.

# Scope

- First-line systemic therapies
  - Chemotherapy
  - Trastuzumab for advanced HER2+ uterine serous carcinoma
  - First-line chemoimmunotherapy trials with ICI ± PARP inhibitor maintenance
  - XPO1 inhibitor maintenance
- Later-line systemic therapies
  - Anti–PD-1 for dMMR tumours
  - Pembrolizumab + Lenvatinib
  - Endocrine-based therapies
  - Antibody-drug conjugates

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# First-line Systemic Therapies

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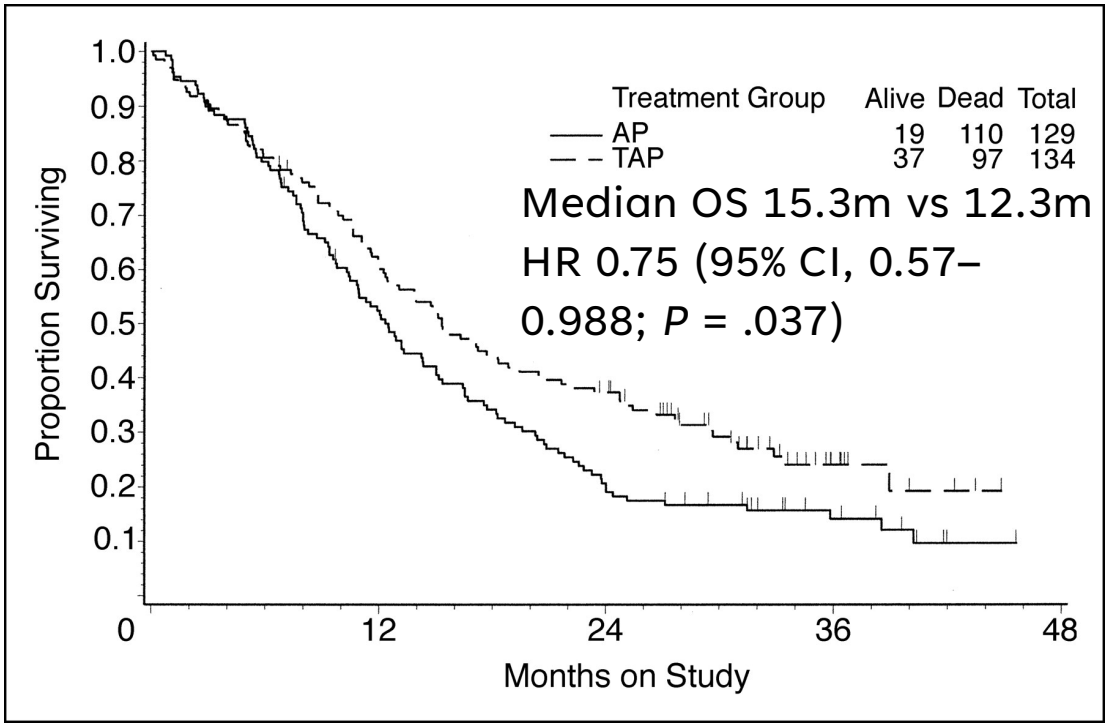
# GOG 177: $T_{160}A_{45}P_{50}$ is Superior to, But More Toxic Than, $A_{60}P_{50}$ x 7#




ORR 57% v 34%; *P* <.01

Median PFS 8.3m vs 5.3m; *P* <.01

5 treatment-related deaths in TAP arm

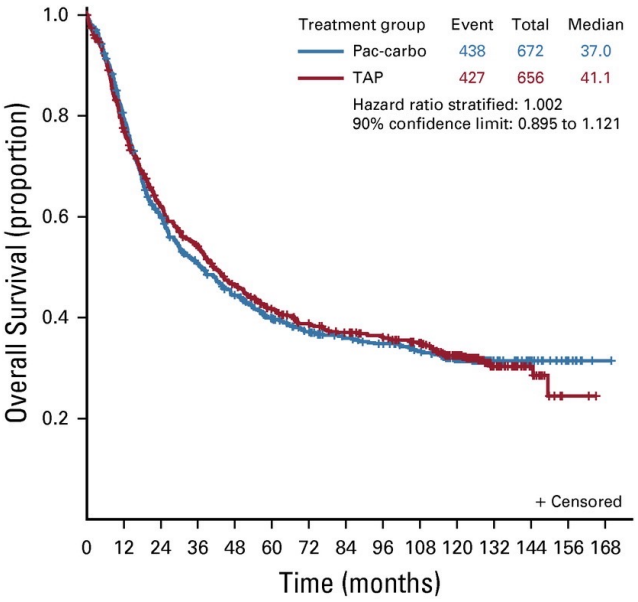
**Table 3.** Grade 2-4 Toxicities

| Toxicity | % of Patients: AP (n = 129) Maximum Grade 2 | AP (n = 129) Maximum Grade 3 | AP (n = 129) Maximum Grade 4 | TAP (n = 131) Maximum Grade 2 | TAP (n = 131) Maximum Grade 3 | TAP (n = 131) Maximum Grade 4 |
|---|---|---|---|---|---|---|
| Neutropenia | 5 | 39 | 50 | 13 | 23 | 36* |
| Thrombocytopenia | 8 | 1 | 2 | 21 | 20 | 2 |
| Auditory | 5 | 0 | 0 | 7 | 0 | 0 |
| LVEF | 11 | 0 | 0 | 10 | 2 | 0 |
| Pulmonary | 1 | 1 | 2 | 5 | 2 | 0 |
| DVT | 1 | 7 | 0 | 1 | 6 | 0 |
| Constitutional | 26 | 6 | 6 | 31 | 10 | 2 |
| Vomiting | 24 | 8 | 0 | 23 | 10 | 2 |
| Diarrhea | 7 | 4 | 0 | 8 | 8 | 1 |
| Mucositis or stomatitis | 5 | 1 | 0 | 7 | 1 | 0 |
| GU/renal | 10 | 1 | 1 | 3 | 3 | 1 |
| Metabolic | 15 | 7 | 2 | 8 | 12 | 7 |
| Sensory peripheral neuropathy | 4 | 1 | 0 | 27 | 12 | 0 |

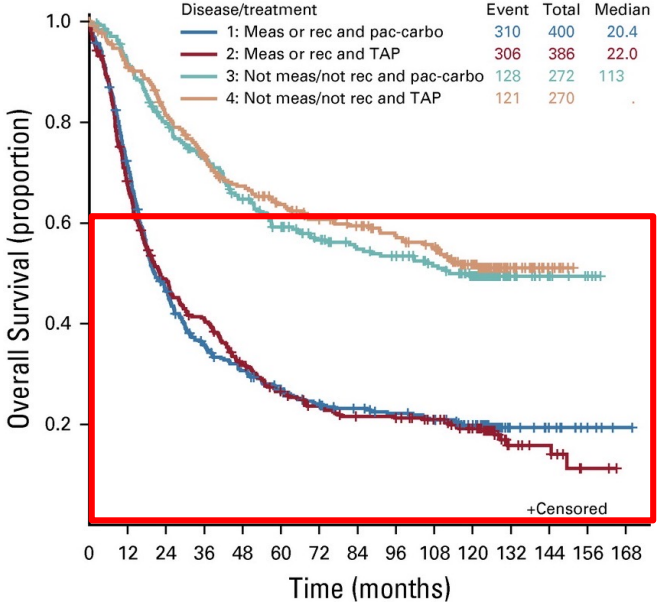
Fleming GF *et al*. J Clin Oncol 2004; 22(11):2159-66.

# GOG 209: $T_{175}C_6$ x 7# is Non-inferior to $T_{160}A_{45}P_{50}$ x 7#

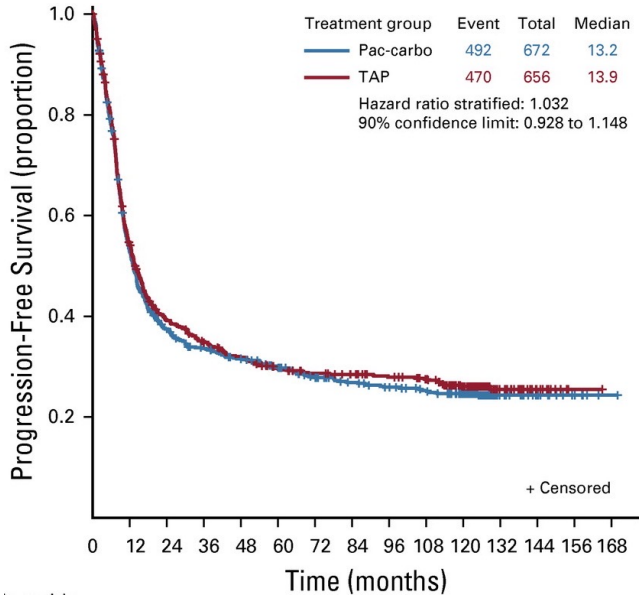
OS




OS for measurable/recurrent disease




PFS




ORR in pts with meas. disease:
52% in both arms
(c.f. 55% / 65% in control arms of LEAP-001 / RUBY Part 1)

More frequent G3-4 thrombocytopaenia, vomiting, diarrhoea and metabolic AEs with TAP
More common neutropaenia (80% vs 52%) with TC than TAP + GCSF
HRQoL favoured TC

Miller DS et al. J Clin Oncol 2020; 38(33): 3841-50.

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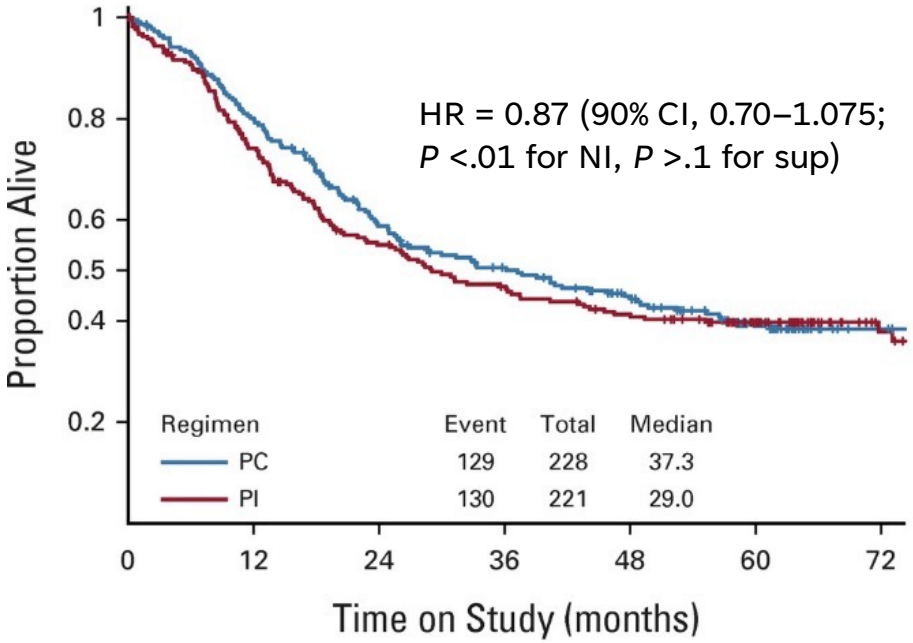
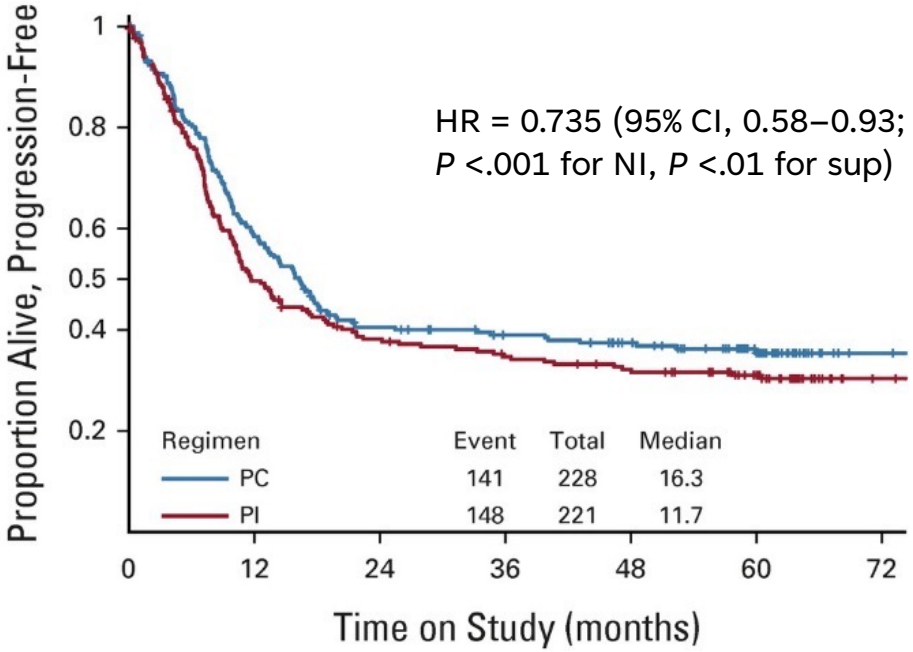
# GOG 261: TC is Non-inferior to Ifos/Pac for Uterine Carcinosarcoma

OS




PFS




Greater frequency of G3-4 haematologic AEs with TC (GCSF given in Ifos/Pac arm)
Greater frequency of confusion and GU haemorrhage with Ifos/Pac

Powell MA *et al*. J Clin Oncol 2022; 40(9):968-77.

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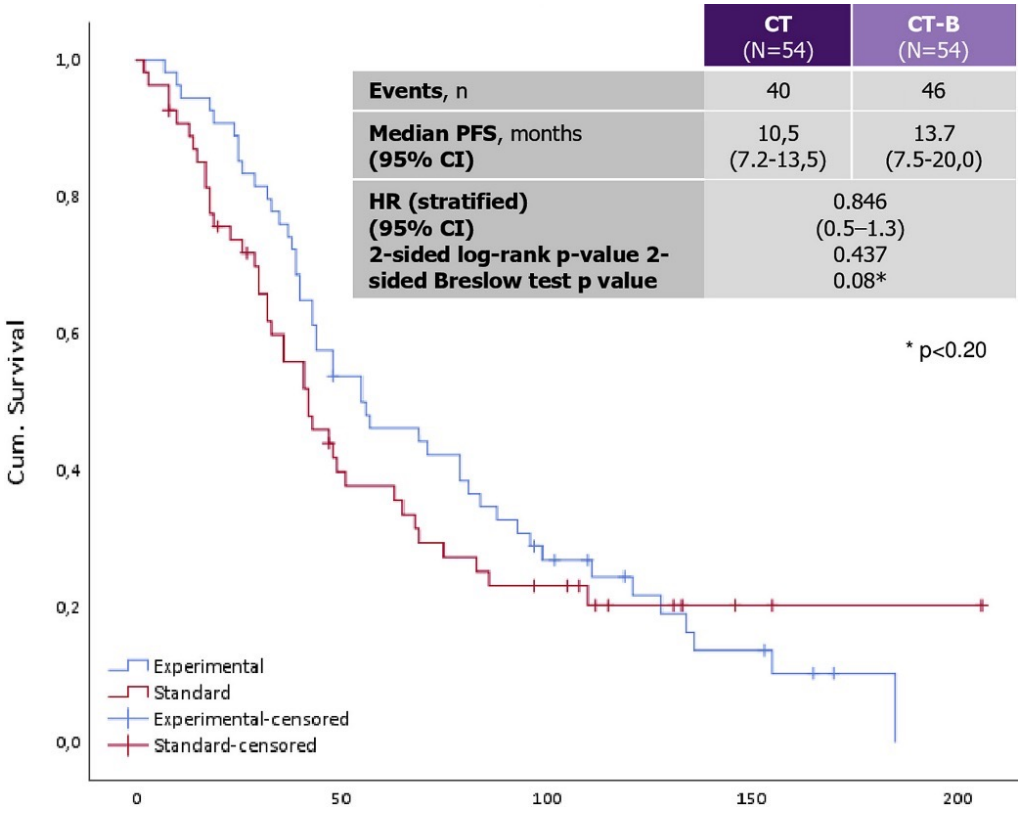
# Bevacizumab: 2 Negative Phase II Trials in 1st & 2nd Lines

## Randomised Phase II MITO END-2: PFS

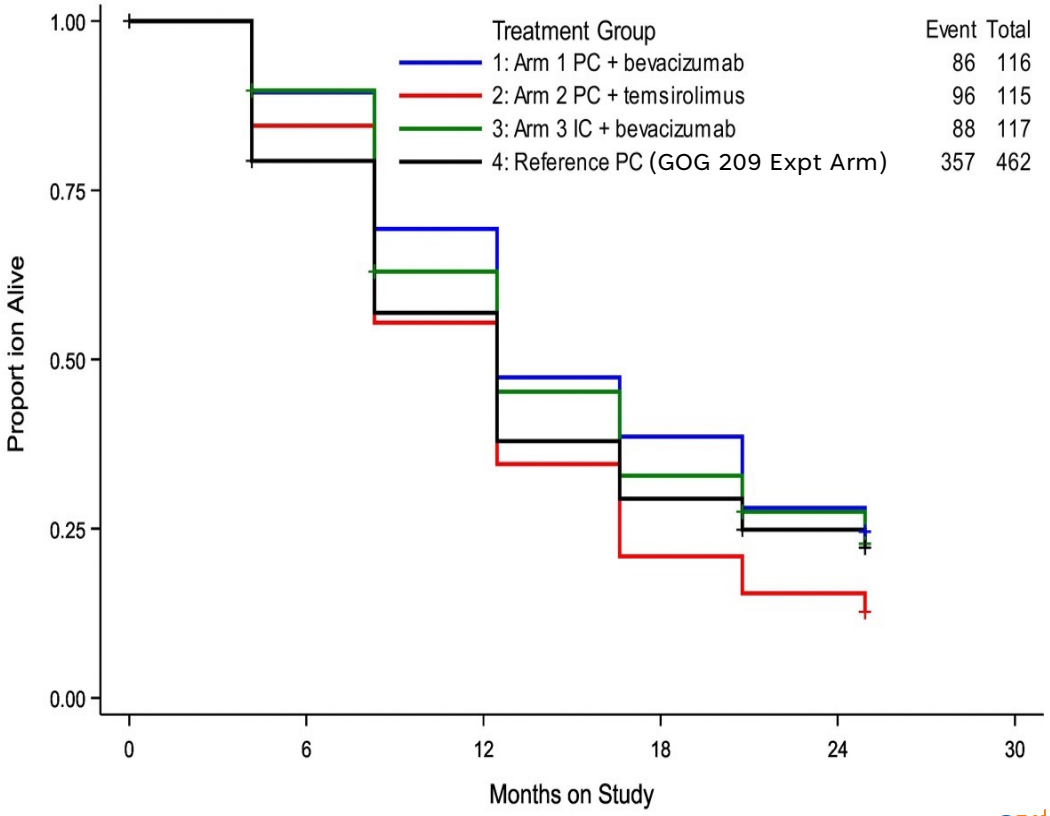
| | CT (N=54) | CT-B (N=54) |
|---|---|---|
| **Events**, n | 40 | 46 |
| **Median PFS**, months **(95% CI)** | 10,5 (7.2-13,5) | 13.7 (7.5-20,0) |
| **HR (stratified) (95% CI) 2-sided log-rank p-value 2-sided Breslow test p value** | 0.846 (0.5–1.3) 0.437 0.08* | |

* p<0.20




Lorusso D *et al*. Gynecol Oncol 2019; 155(3):406-12.

## GOG-86P: PFS



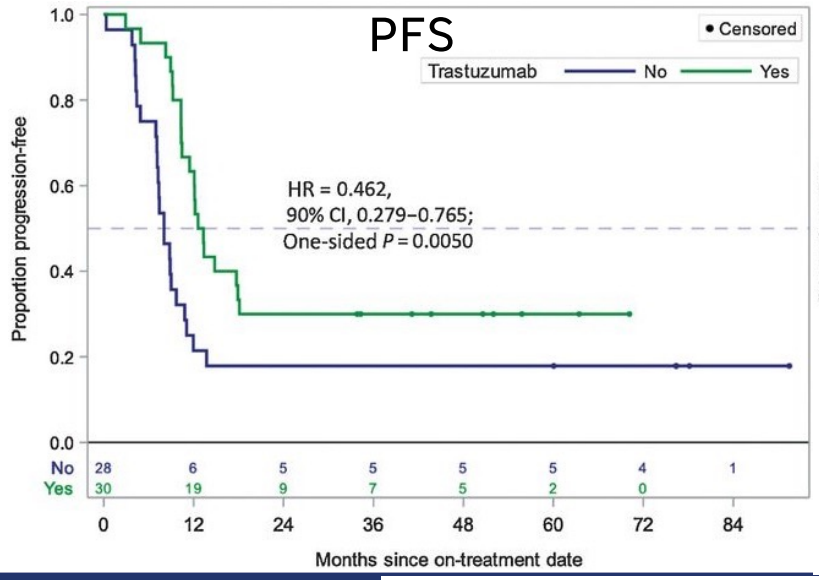

Aghajanian C *et al*. Gynecol Oncol 2018; 150(2):274-81.

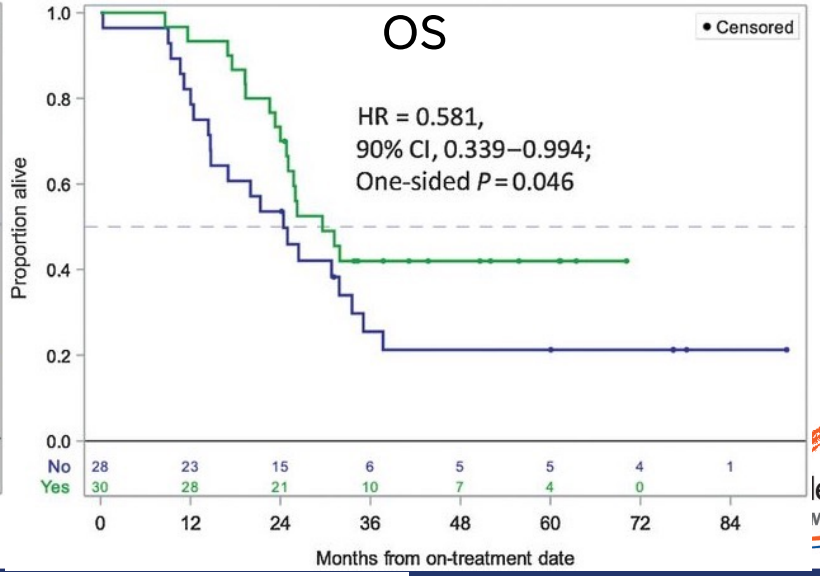
# Randomised Phase II Trial of Trastuzumab for Stage III–IV or Recurrent HER2+ USC

FIGO 2009 stage III-IV or recurrent histologically confirmed USC (≥10% in specimen)
HER2+ as defined by IHC 3+ or 2+ with gene amplification by FISH
N = 61

RANDOMISE (1:1)

- Pac/Carbo + Trastuz x 6# → Trastuz until PD or toxicity
- Pac/Carbo x 6#






Fader A *et al*. Clin Cancer Res 2020; 26(15):3928-35.

# Phase III 1L ICI + Chemo ± PARPi Trials in Advanced EC

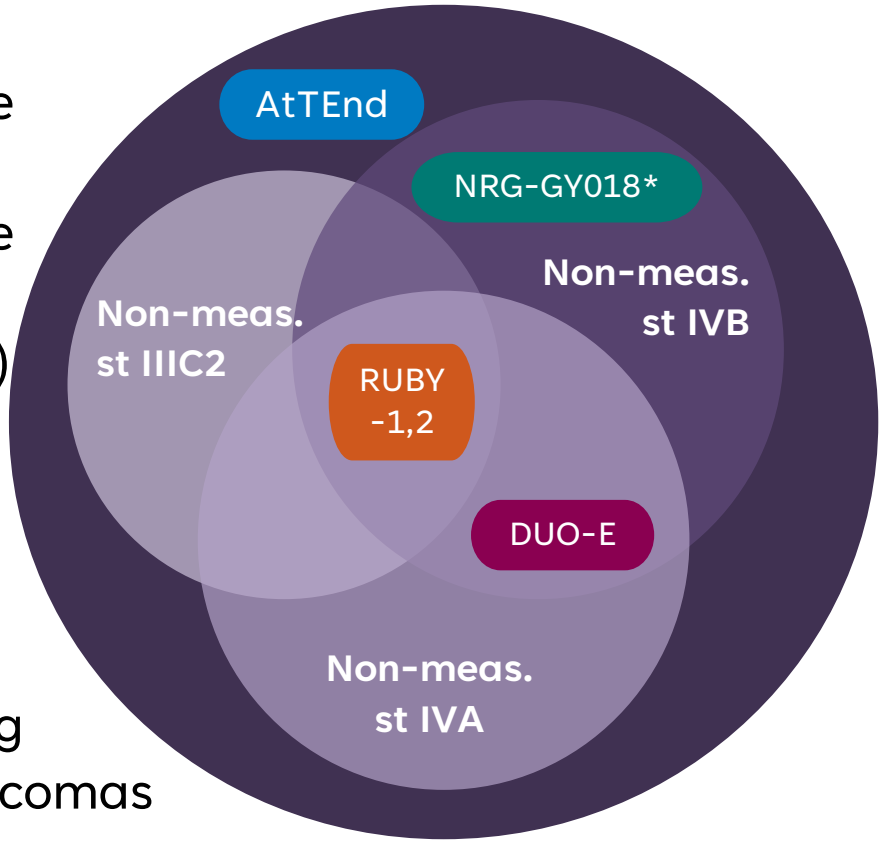
| | RUBY Part 1[1,2] | RUBY Part 2[3] | NRG-GY018[4,5] | AtTEnd[6] | DUO-E[7,8] |
|---|---|---|---|---|---|
| | Dostarlimab 500 mg q3w + TC → Dostar 1000 mg q6w 3y<br><br>Placebo + TC → Placebo | Dostarlimab 500 mg q3w + TC → Dostar 1000 mg q6w 3y<br>+ Niraparib ISD 3y<br><br>Placebo + TC → Placebo + Placebo | Pembrolizumab 200 mg q3w + TC → Pembro 400 mg q6w 2y<br><br>Placebo + TC → Placebo | Atezolizumab 1200 mg q3w + TC → Atezo 1200 mg q3w until PD<br><br>Placebo + TC → Placebo | Durvalumab 1120 mg q3w + TC → Durva 1500 mg q4w<br>+ Olaparib 300 mg BD until PD<br><br>Durva + TC → Durva + Pbo until PD<br><br>Pbo + TC → Pbo/Pbo |
| ⊕ | Statistically significant PFS dMMR and ITT, OS ITT | Statistically significant PFS ITT and PFS pMMR | Statistically significant PFS dMMR and pMMR | Statistically significant PFS dMMR and ITT | Statistically significant PFS ITT for Durva + Pbo and Durva + Ola |
| ⊖ | Not powered for pMMR | Missing ICI + PC arm OS immature | Not powered for OS UCS excluded | pMMR did not benefit OS ITT immature | Not powered for pMMR or dMMR, Durva + Ola vs Durva + Pbo |

1. Mirza MR *et al*. N Engl J Med 2023; 388:2145-58. 2.Powell MA *et al*. Ann Oncol 2024; 35(8):728-38. 3. Mirza MR *et al*. Presented at SGO 2024 Annual Meeting. 4. Eskander RN *et al*. N Engl J Med 2023; 388:2159-70. 5. Eskander RN *et al*. Presented at at SGO 2024 Annual Meeting. 6. Colombo N *et al*. Lancet Oncol 2024: S1470-2045(24)00334-6. [online ahead of print]. 7. Westin SN *et al*. J Clin Oncol 2024; 42(3):283-99. 8. Baurain J-F *et al*. Presented at at SGO 2024 Annual Meeting.

# Summary of Study Designs

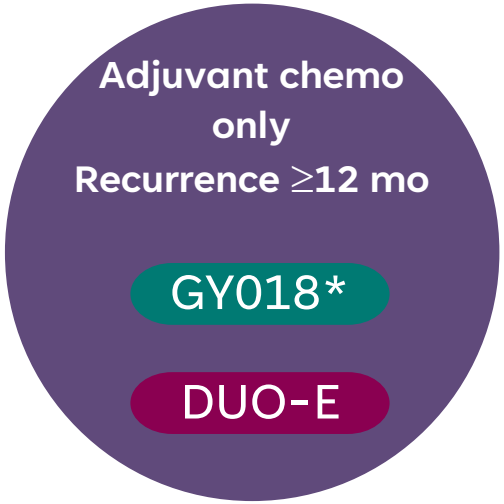
## Disease Inclusion Criteria

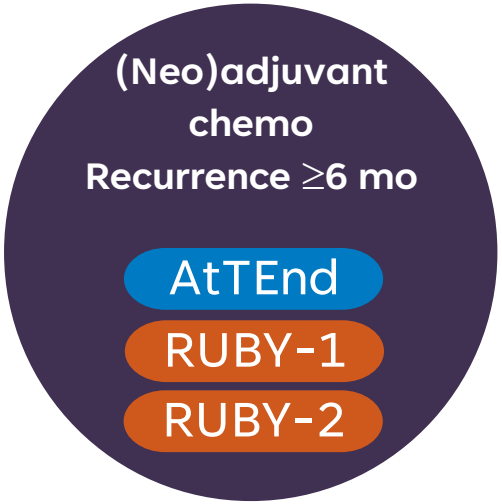
Recurrent, measurable stage III, measurable stage IV (all 5 trials)




* Excluding carcinosarcomas

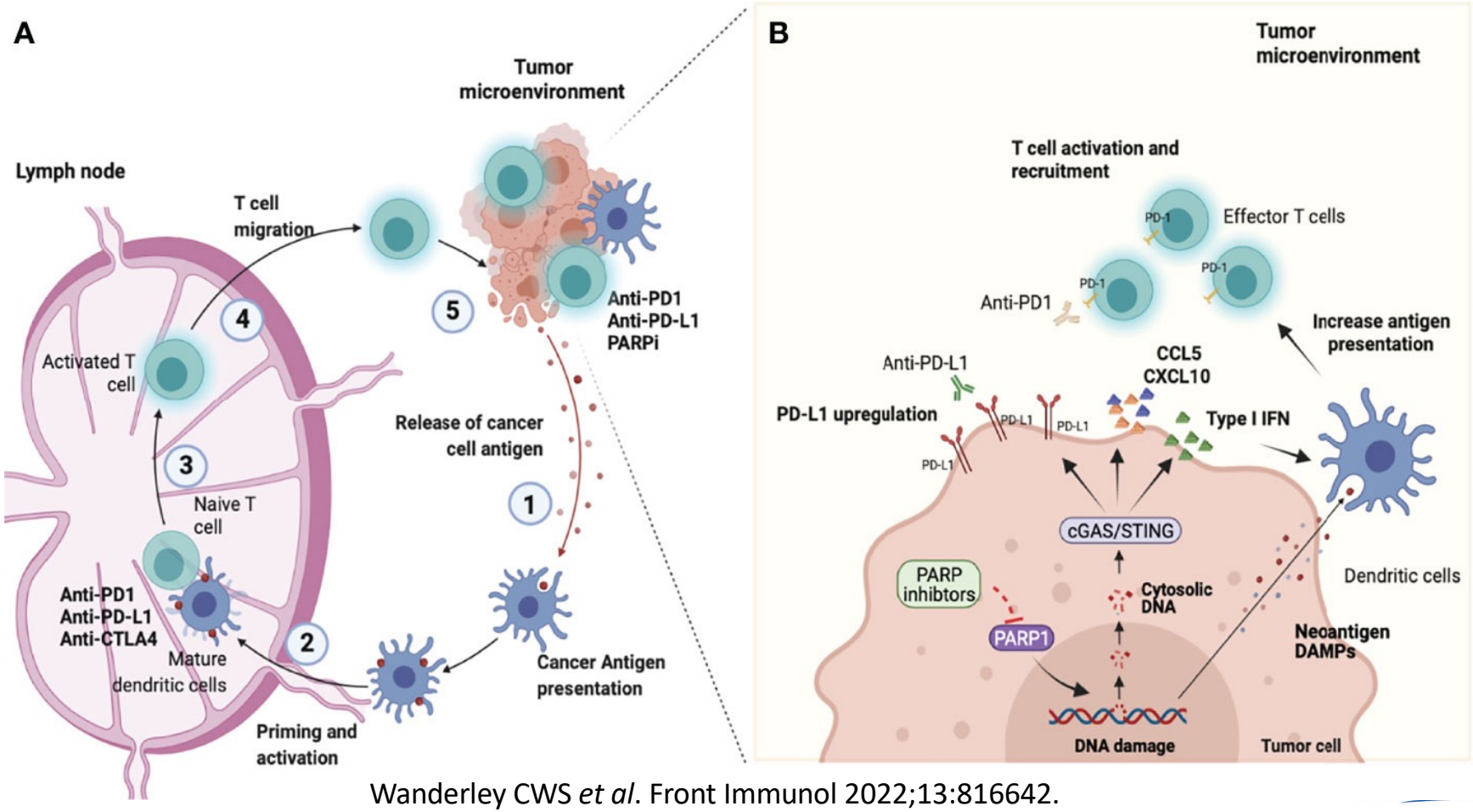
## Prior Therapy Allowable for Inclusion




Not intended for head-to-head comparison. Cross-trial comparisons cannot be made because trials differ in design, size, time period of recruitment, location of study sites etc.

# Combining PARP Inhibitor & ICI



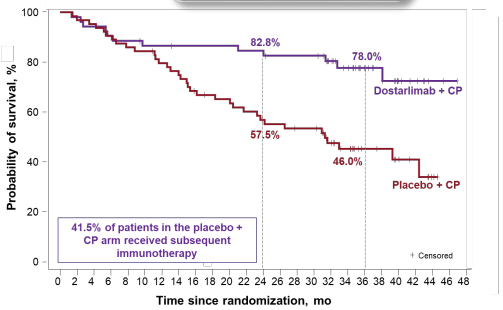

Wanderley CWS *et al*. Front Immunol 2022;13:816642.

# Substantial PFS & OS Benefits of 1L ICI + TC in dMMR EC

## RUBY Part 1[1,2]

**PFS** HR 0.28 (95% CI, 0.16-0.50); *P*<0.001

**OS** HR 0.32 (95% CI, 0.17-0.63); *Nominal P*=0.0002

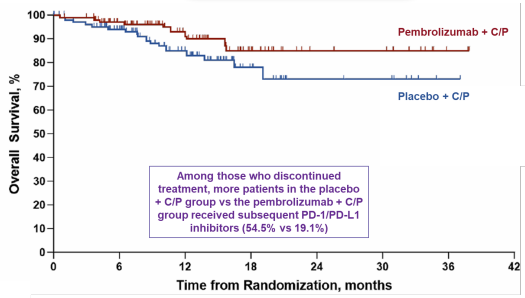



| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Dostarlimab + TC | 22.6 | NE (NE-NE) |
| Placebo + TC | 53.8 | 31.4 (20.3-NE) |
| OS data maturity | 39.8% | |
| Median follow-up, mo | 36.6 | |

## NRG-GY018[3,4]

**PFS** HR 0.30 (95% CI, 0.19-0.48); *P*<0.001

**OS** HR 0.55 (95% CI, 0.25-1.19); *Nominal P*=0.0617

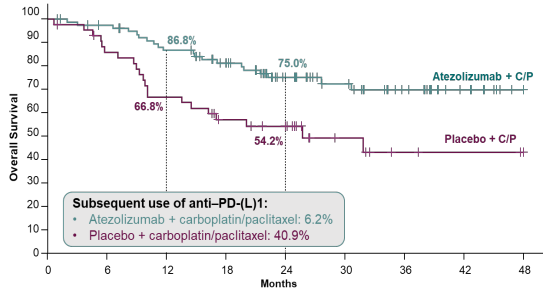



| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Pembrolizumab + TC | 9.1 | NR (NR-NR) |
| Placebo + TC | 15 | NR (NR-NR) |
| OS data maturity | 18% | |
| Median follow-up, mo | 13.3-13.7 | |

## AtTEnd[5]

**PFS** HR 0.36 (95% CI, 0.23-0.57); *P*=0.0005

**OS** HR 0.41 (95% CI, 0.22-0.76)

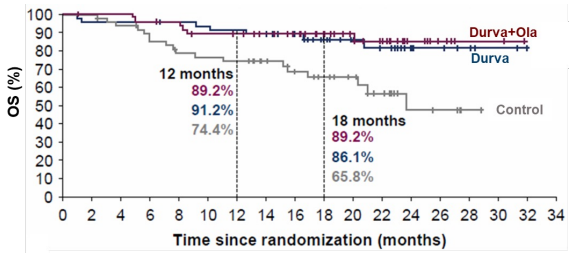



| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Atezolizumab + TC | 24.6 | NE (NE-NE) |
| Placebo + TC | 47.7 | 25.7 (13.5-NE) |
| OS data maturity | -- | |
| Median follow-up, mo | -- | |

## DUO-E[6,7]

**PFS** HR 0.42 (95% CI, 0.22-0.80); *Durva +TC arm*

**OS** HR 0.34 (95% CI, 0.13-0.79) *Durva + TC arm*




| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Durvalumab + TC | 15.2 | NR (NR-NR) |
| Placebo + TC | 36.7 | 23.7 (16.9-NR) |
| OS data maturity | 21.7% | |
| Median follow-up, mo | -- | |

**There are no completed direct head-to-head trials in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials.**


1. Mirza MR *et al*. N Engl J Med 2023; 388:2145-58. 2.Powell MA *et al*. Ann Oncol 2024; 35(8):728-38. 3. Eskander RN *et al*. N Engl J Med 2023; 388:2159-70. 4. Eskander RN *et al*. Presented at at SGO 2024 Annual Meeting. 5. Colombo N *et al*. Lancet Oncol 2024: S1470-2045(24)00334-6. [online ahead of print]. 6. Westin SN *et al*. J Clin Oncol 2024; 42(3):283-99. 7. Baurain J-F *et al*. Presented at at SGO 2024 Annual Meeting.

# No Benefit from Adding PARPi to Anti-PD-(L)1 in dMMR EC

## RUBY Part 2[1,2,3]

### PFS

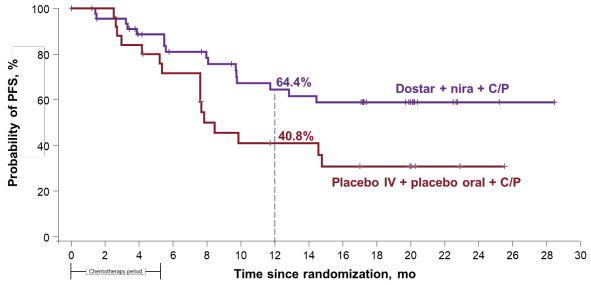
**HR 0.48**
(95% CI, 0.27-0.96);
*Nominal P*=0.0174
Dostar + Nira + TC arm

**HR 0.28**
(95% CI, 0.16-0.50);
*P*<0.001
Part 1 Dostar + TC

### OS

**The trial is ongoing for OS follow-up**

**HR 0.32**
(95% CI, 0.17-0.63);
*Nominal P*=0.0002
Part 1 Dostar + TC




| PFS data | Events, % | Median (95% CI), mo |
|---|---|---|
| Dostarlimab + Niraparib + TC | 32 | NE (11.8-NE) |
| Placebo + TC | 64 | 7.9 (5.4-NE) |
| PFS data maturity | 42.7% | |
| Median follow-up, mo | 18.7 | |

## DUO-E[4,5]

### PFS

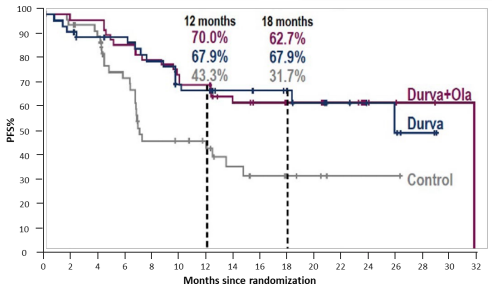
**HR 0.41**
(95% CI, 0.21-0.75)
*Durva + Ola+ TC arm*

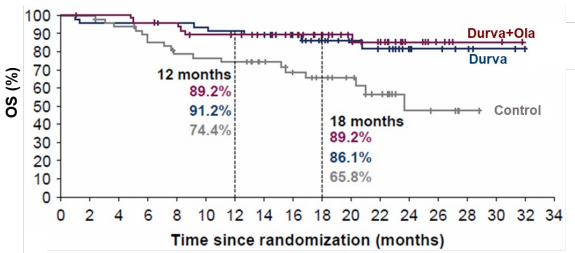
**HR 0.42**
(95% CI, 0.22-0.80)
*Durva + TC arm*

### OS

**HR 0.28**
(95% CI, 0.10-0.68)
*Durva + Ola+ TC arm*

**HR 0.34**
(95% CI, 0.13-0.79)
*Durva + TC arm*




| PFS data | Events, % | Median (95% CI), mo |
|---|---|---|
| Durvalumab + Olaparib + TC | 37.5 | 31.8 (12.4-NR) |
| Durvalumab + TC | 32.6 | NR (NR-NR) |
| Placebo + TC | 51 | 7.0 (6.7-14.8) |
| OS data maturity | -- | |
| Median follow-up, mo | 17.1 (Durva+PC); 17.5 (Durva+Ola+PC) | |

**There are no completed direct head-to-head trials in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials.**

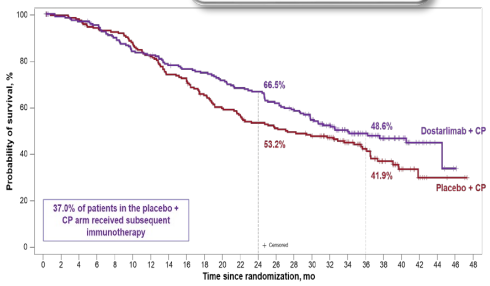

1. Mirza MR *et al*. N Engl J Med 2023; 388:2145-58. 2.Powell MA *et al*. Ann Oncol 2024; 35(8):728-38. 3. Mirza MR *et al*. Presented at SGO 2024 Annual Meeting. 4. Westin SN *et al*. J Clin Oncol 2024; 42(3):283-99. 5. Baurain J-F *et al*. Presented at at SGO 2024 Annual Meeting.

# Clinically Meaningful PFS & OS Benefits of 1L ICI + Chemo in pMMR EC

## RUBY Part 1[1,2]

**PFS** HR 0.76 (95% CI, 0.59-0.98)

**OS** HR 0.79 (95% CI, 0.60-1.04); nominal *P*=0.0493

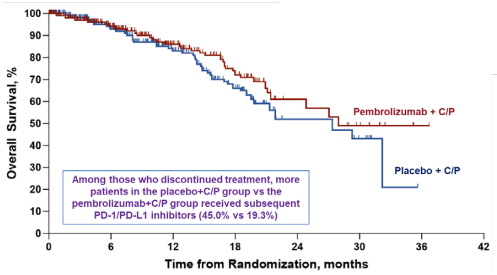



| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Dostarlimab + TC | 50.5 | 34.0 (28.6-NE) |
| Placebo + TC | 59.2 | 27.0 (21.5-35.6) |
| OS data maturity | 54.8% | |
| Median follow-up, mo | 37.5 | |

## NRG-GY018[3,4]

**PFS** HR 0.54 (95% CI, 0.41-0.71); *P*<0.001

**OS** HR 0.79 (95% CI, 0.53-1.17) Nominal P=0.1157

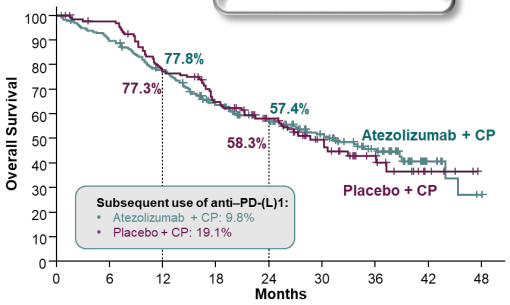



| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Pembrolizumab + TC | 15.3 | 27.9 (21.4-NR) |
| Placebo + TC | 18.3 | 27.4 (19.5-NR) |
| OS Data maturity | 27.2% | |
| Median follow-up, mo | 8.4-8.8 | |

## AtTEnd[5]

**PFS** HR 0.92 (95% CI, 0.73-1.16);

**OS** HR 1.00 (95% CI; 0.74-1.35)

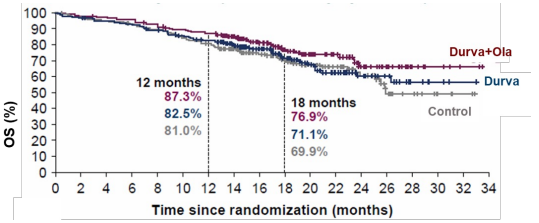



| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Atezolizumab + TC | 47.2 | 31.5 (25.0-38.9) |
| Placebo + TC | 46.4 | 28.6 (22.4-37.2) |
| OS Data maturity | -- | |
| Median follow-up, mo | -- | |

## DUO-E[6,7]

**PFS** HR 0.77 (95% CI, 0.60-0.97); *Durva + TC arm*

**OS** HR 0.91 (95% CI, 0.64-1.30) *Durva + TC arm*




| OS Data | Events, % | Median (95% CI), mo |
|---|---|---|
| Durvalumab + TC | 30.2 | NR (NR-NR) |
| Placebo + TC | 33.3 | 25.9 (25.1-NR) |
| OS Data maturity | 29.2% | |
| Median follow-up, mo | -- | |

**There are no completed direct head-to-head trials in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials.**


1. Mirza MR *et al*. N Engl J Med 2023; 388:2145-58. 2.Powell MA *et al*. Ann Oncol 2024; 35(8):728-38. 3. Eskander RN *et al*. N Engl J Med 2023; 388:2159-70. 4. Eskander RN *et al*. Presented at at SGO 2024 Annual Meeting. 5. Colombo N *et al*. Lancet Oncol 2024: S1470-2045(24)00334-6. [online ahead of print]. 6. Westin SN *et al*. J Clin Oncol 2024; 42(3):283-99. 7. Baurain J-F *et al*. Presented at at SGO 2024 Annual Meeting.

# Possible Benefit from Adding PARPi to Anti-PD-(L)1 in pMMR EC

## RUBY Part 2[1,2,3]

### PFS

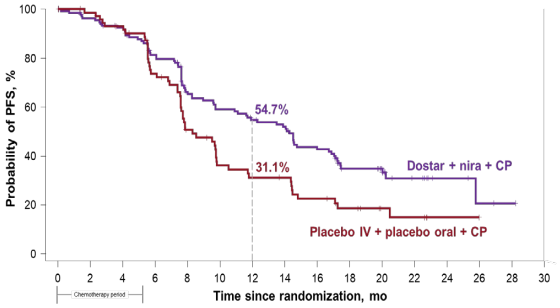
**HR 0.63**
(95% CI, 0.44-0.91);
*P*=0.0060
Dostar + nira + TC arm

**HR 0.76**
(95% CI, 0.59-0.98)
Part 1 Dostar + TC

### OS

**The trial is ongoing for OS follow-up**

**HR 0.79**
(95% CI, 0.60-1.04);
nominal *P*=0.0493
Part 1 Dostar + TC




| PFS data | Events, % | Median (95% CI), mo |
|---|---|---|
| Dostarlimab + Niraparib + TC | 55.6 | 14.3 (9.7-16.9) |
| Placebo + TC | 71.6 | 8.3 (7.6-9.8) |
| PFS data maturity | 61.1% | |
| Median follow-up, mo | 19.1 | |

## DUO-E[4,5]

### PFS

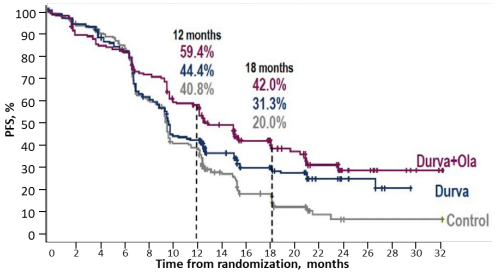
**HR 0.57**
(95% CI, 0.44-0.73);
*Durva + Ola+ TC arm*

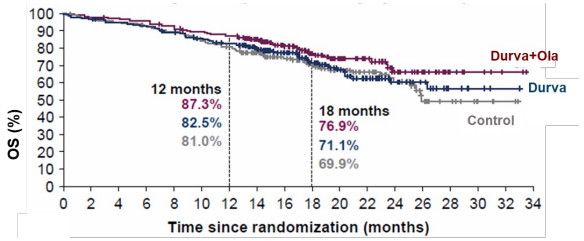
**HR 0.77**
(95% CI, 0.60-0.97);
*Durva + PT arm*

### OS

**HR 0.69**
(95% CI, 0.47-1.00)
*Durva + Ola + TC arm*

**HR 0.91**
(95% CI, 0.64-1.30)
*Durva + TC arm*




| PFS data | Events, % | Median (95% CI), mo |
|---|---|---|
| Durvalumab + Olaparib + TC | 56.5 | 15.0 (12.4-18.0) |
| Durvalumab + TC | 64.6 | 9.9 (9.4-12.5) |
| Placebo + TC | 77.1 | 9.7 (9.2-10.1) |
| PFS data maturity | -- | |
| Median follow-up, mo | 17.1 (Durva+C/P); 17.5 (Durva+Ola+C/P) | |

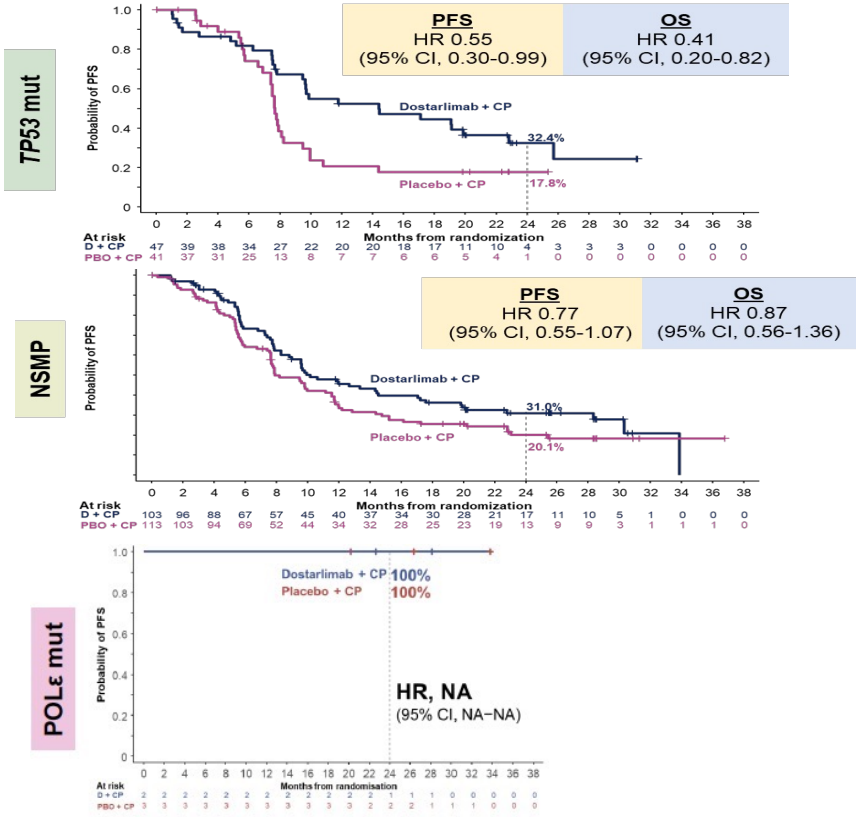
**There are no completed direct head-to-head trials in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials.**


1. Mirza MR *et al*. N Engl J Med 2023; 388:2145-58. 2.Powell MA *et al*. Ann Oncol 2024; 35(8):728-38. 3. Mirza MR *et al*. Presented at SGO 2024 Annual Meeting. 4. Westin SN *et al*. J Clin Oncol 2024; 42(3):283-99. 5. Baurain J-F *et al*. Presented at at SGO 2024 Annual Meeting.

# p53abn or NSMP: Potential Predictive Biomarkers of Benefit from Dostarlimab + Chemo ± PARPi?

## RUBY Part 1[1]

**Molecular subgroup analysis based on 400/494 patients with known molecular classification per WES**




## RUBY Part 2[2]

**Exploratory PFS Molecular Subgroup Analyses in Overall Population**

| | Dostarlimab + niraparib + CP N=192 | Placebo IV + placebo oral + CP N=99 | HR (95% CI) |
|---|---|---|---|
| | *No. of patients with events/No. of patients* | | |
| All patients | 95/192 | 69/99 | 0.59 (0.43–0.81) |
| **Molecular subgroup[a]** | | | |
| POLE | 0/3 | 1/2 | NA |
| dMMR/MSI-H | 12/37 | 10/17 | 0.45 (0.20–1.05) |
| TP53 | 27/39 | 10/10 | 0.29 (0.13–0.63) |
| NSMP | 37/75 | 31/46 | 0.61 (0.38–0.99) |
| Not evaluable[b] | 19/38 | 17/24 | 0.71 (0.37–1.37) |

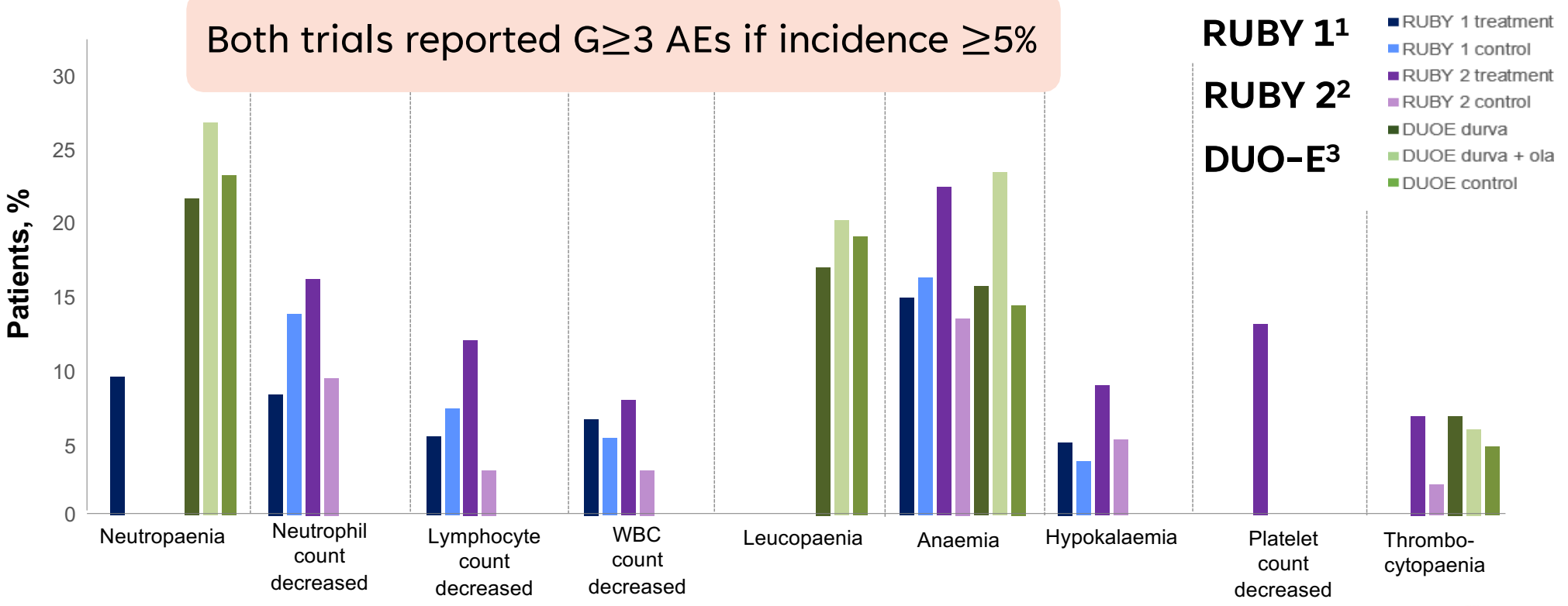
←Dostar + nira + CP better | Placebo + CP better→

0.0156 0.0313 0.0625 0.125 0.25 0.5 1 2 4 8 16


1. Mirza MR et al. Presented at ESMO Congress 2023.
2. Mirza MR *et al*. Presented at SGO 2024 Annual Meeting.

# Safety: RUBY Part 1 & Part 2 and DUO-E

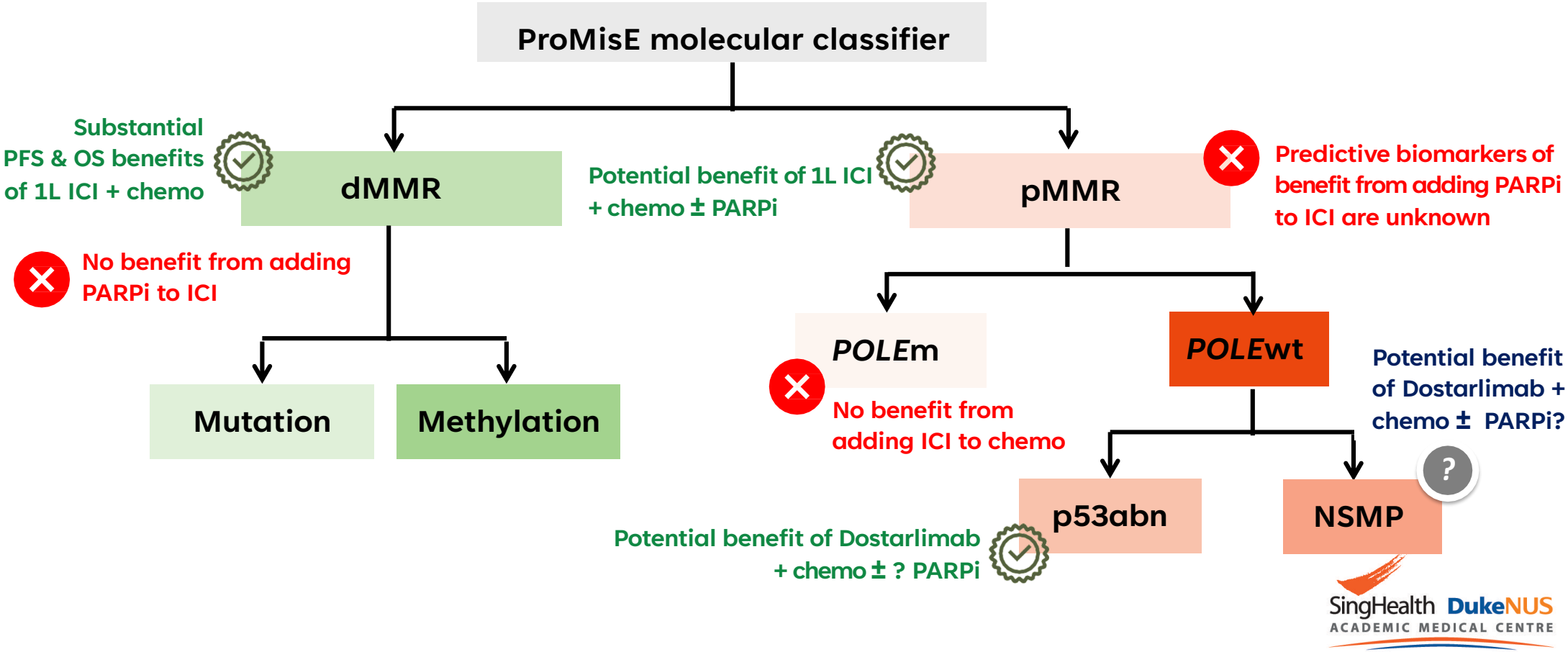
Both trials reported G≥3 AEs if incidence ≥5%




**There are no completed direct head-to-head trials in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials.**

1. Mirza MR *et al*. N Engl J Med 2023; 388:2145-58. 2.Mirza MR *et al*. Presented at SGO 2024 Annual Meeting. 3. Westin SN *et al*. J Clin Oncol 2024; 42(3):283-99.

# Key Takeaways from 1L ICI + Chemo ± PARPi Trials

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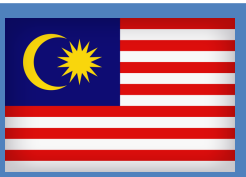
# Approval Status of 1L ICI ± PARPi for Advanced EC C.A.A. 7 Aug 2024

| Drug(s) |  | |  | |  | |  |
|---|---|---|---|---|---|---|---|
| | dMMR/ MSI-H | pMMR/ MSS | dMMR/ MSI-H | pMMR/ MSS | dMMR/ MSI-H | pMMR/ MSS | |
| **Dostarlimab** | Full | Full | Yes | - | Yes | - | - |
| **Pembrolizumab** | Full | Full | - | - | - | - | - |
| **Durvalumab** | Yes | - | Positive EMA CHMP opinion | - | - | - | - |
| **Atezolizumab** | - | - | - | - | - | - | - |
| **Durvalumab + Olaparib** | - | - | - | Positive EMA CHMP opinion | - | - | - |
| **Dostarlimab + Niraparib** | - | - | - | - | - | - | - |

# LEAP-001: 1L Pembrolizumab + Lenvatinib vs TC in Advanced or Recurrent EC

**Patient Population (N = 842)**

- Stage III, Stage IV or recurrent endometrial carcinoma (UCS excluded)
- Radiographically apparent disease - either measurable or non-measurable
- No prior chemotherapy except in the neo/adjuvant setting (≥6m before recurrence)
- ECOG PS 0-1
- Tumour tissue sample for MMR testing

**Stratification Factors**

- pMMR vs dMMR
- If pMMR: ECOG PS, measurable disease, prior chemotherapy and/or chemoradiation

R
1:1

**Pembrolizumab**
200 mg IV Q3W until PD or 35 doses

+

**Lenvatinib**
20 mg PO QD until PD

Paclitaxel 175 mg/m2 IV + Carboplatin AUC 6 IV Q3W X 7 cycles

**Primary Endpoints**

- PFS by BICR per RECIST v1.1
- OS

**Key Secondary Endpoints**

- ORR by BICR per RECIST v1.1
- HRQoL
- Safety

Marth C *et al*. Presented at ESGO Annual Meeting 2024.

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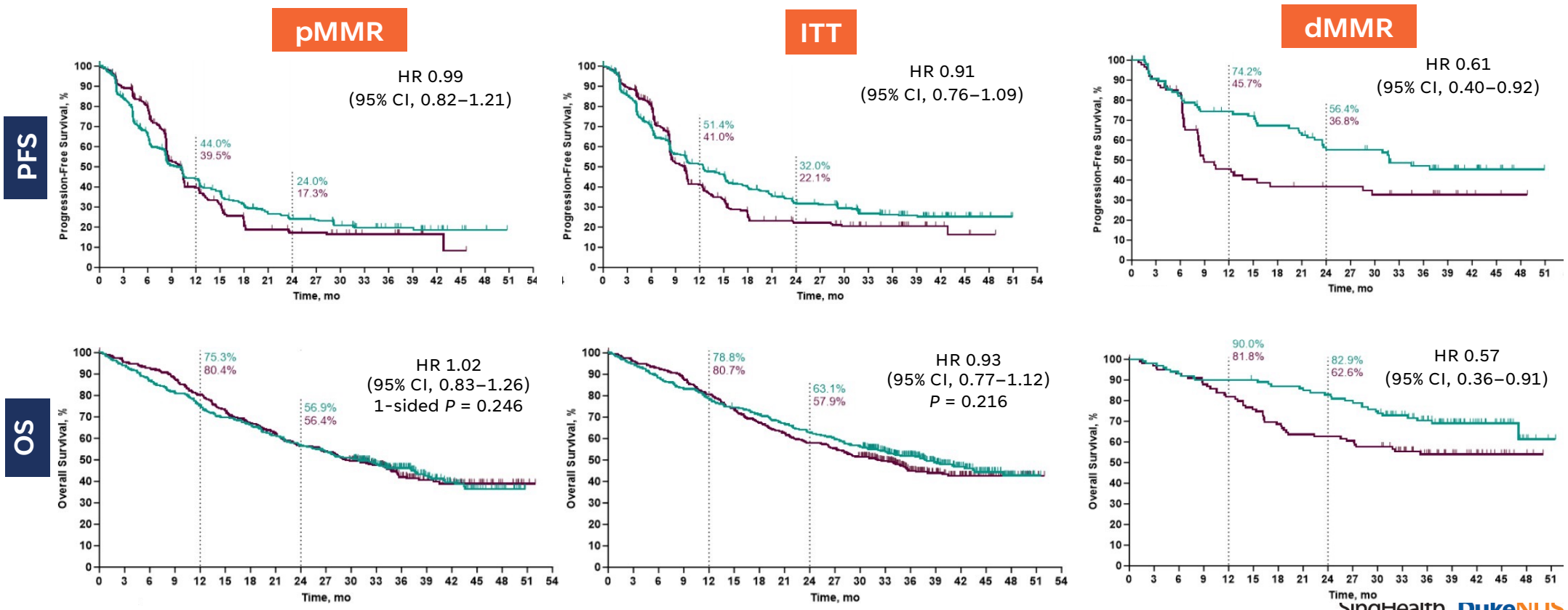
# LEAP-001: 1L Lenvatinib + Pembrolizumab vs TC

**Co-primary endpoints of OS and PFS NOT met in pMMR and ITT populations**




Marth C *et al*. Presented at ESGO Annual Meeting 2024.

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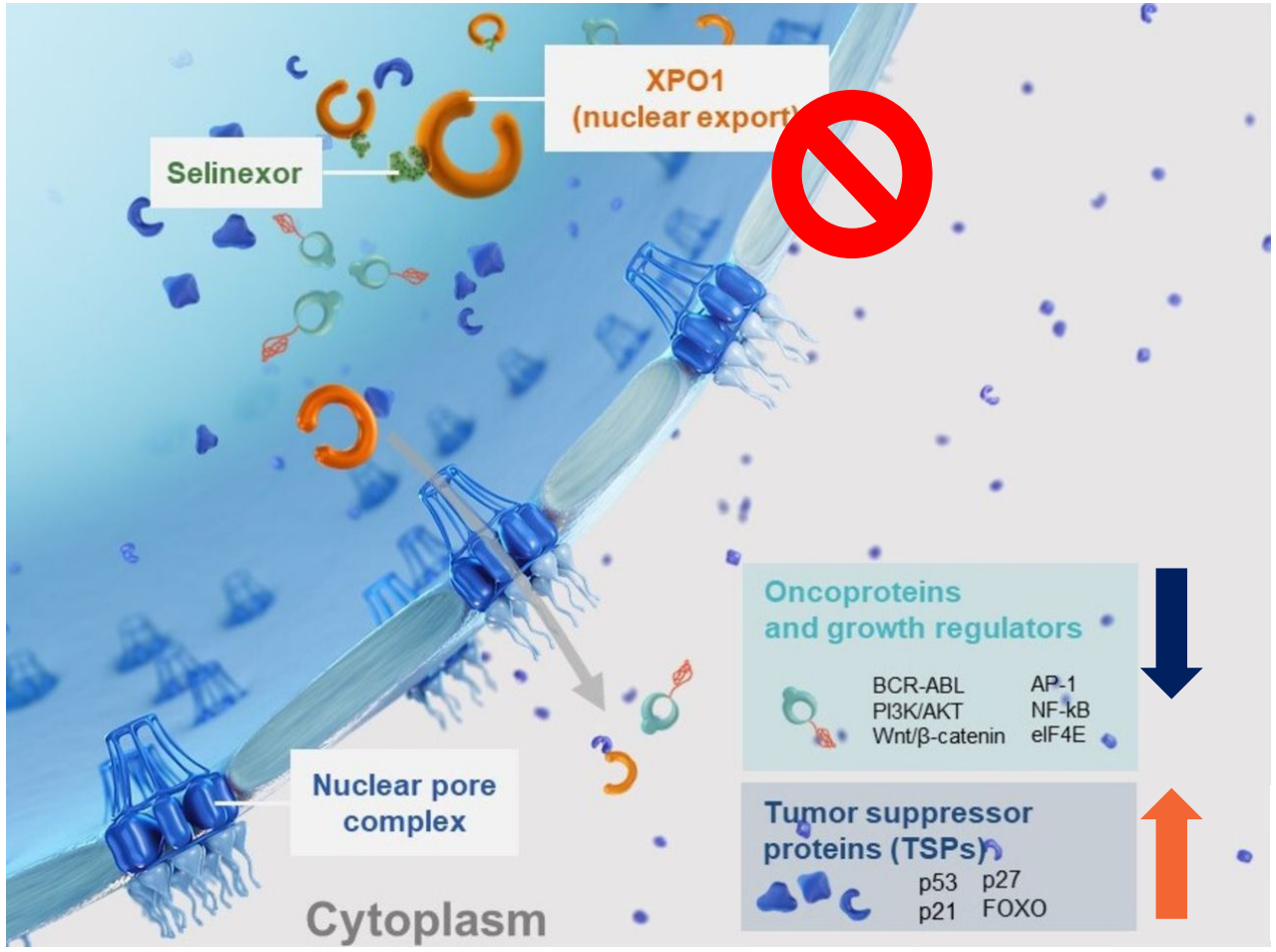
## Ongoing 1L Chemo-free ICI Trials in Primary Advanced or Recurrent EC

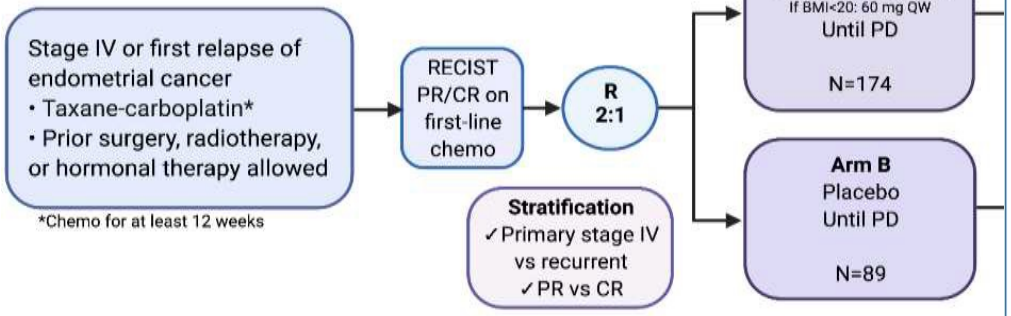
| | DOMENICA/ENGOT-EN13 | KEYNOTE-C93/ENGOT-EN15 |
|---|---|---|
| Experimental arm | Dostarlimab | Pembrolizumab |
| ClinicalTrials.gov Identifier | NCT05201547 | NCT05173987 |
| Control arm | TC | TC |
| Patient population | dMMR | dMMR |
| Study status | Recruitment ongoing | Recruitment complete |
| Sponsor | GINECO | MITO |
| N | 260 | 280 |
| Primary endpoint(s) | PFS (BICR) | PFS (BICR), OS |

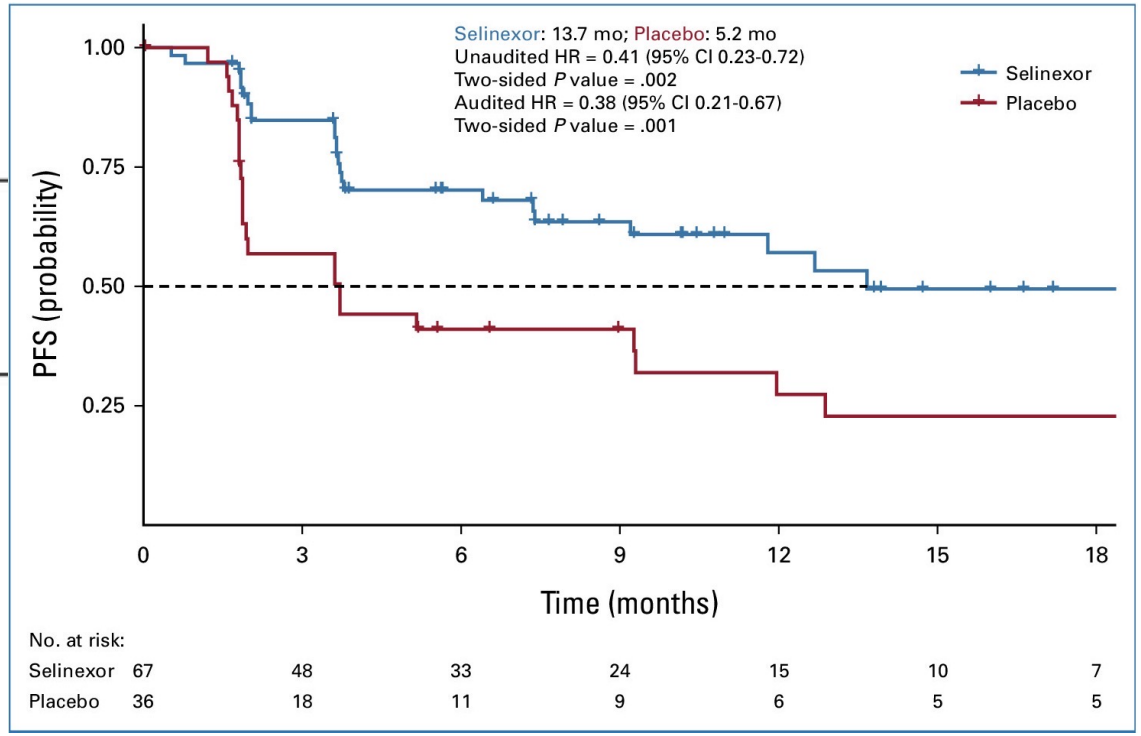
# Selinexor: Oral XPO-1 Inhibitor




Vergote I *et al*. Int J Gynecol Cancer 2024; 34(8):1283-9.

# ENGOT-EN5/GOG-3055/SIENDO: Selinexor Maintenance After 1L Chemotherapy





1. Vergote I *et al*. J Clin Oncol 2023; 41(35):5400-10.
2. Vergote I *et al*. Int J Gynecol Cancer 2024; 34(8):1283-9.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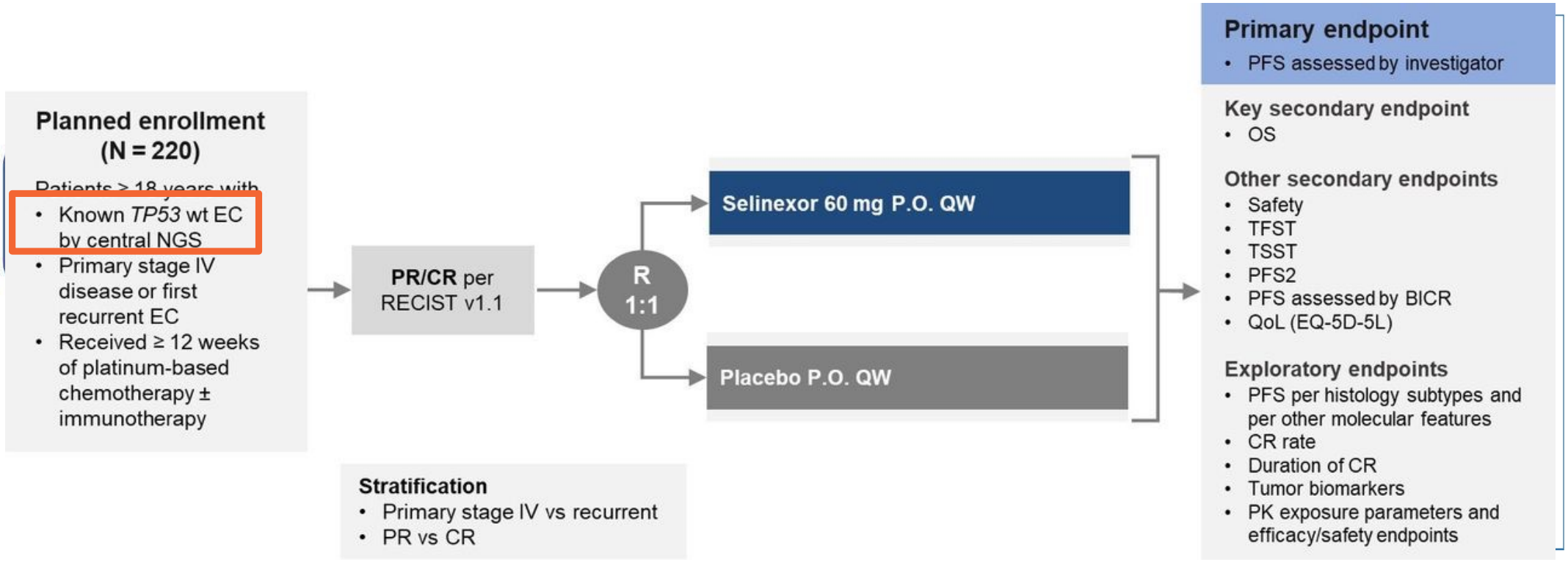
# Ongoing ENGOT-EN20/GOG-3083/XPORT-EC-042: Selinexor Maintenance After 1L Chemotherapy





1. Vergote I *et al*. J Clin Oncol 2023; 41(35):5400-10.
2. Vergote I *et al*. Int J Gynecol Cancer 2024; 34(8):1283-9.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National Cancer Centre Singapore
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ONCOLOGY

# Later-line Systemic Therapies

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PATIENTS. AT THE HEART OF ALL WE DO.®

Singapore General Hospital | Changi General Hospital | Sengkang General Hospital | KK Women's and Children's Hospital | National Cancer Centre Singapore | National Dental Centre Singapore | National Heart Centre Singapore | National Neuroscience Institute | Singapore National Eye Centre | SingHealth Community Hospitals | Polyclinics SingHealth

# What Used to be Done Circa 2010s

- No standard-of-care second-line chemotherapy (ORR 10-15%): doxorubicin and paclitaxel are considered most active[2]
- In patients with long PFI, re-introduction of platinum can be considered based on retrospective studies[3,4]

| GOG Trial | Agent | 6m PFS (%) | ORR (%) |
|---|---|---|---|
| 129-B | Etoposide | 8 | 0 |
| 129-C | Paclitaxel | 21 | 25 |
| 129-E | Dactinomycin | 4 | 11 |
| 129-H | Liposomal doxorubicin | 23 | 9 |
| 129-J | Topotecan | 25 | 7 |
| 129-K | Oxaliplatin | 27 | 13 |
| 229-E | Bevacizumab | 40 | 13.5 |

Adapted from: Slomovitz BM *et al.* J Clin Oncol 2015; 33(8):930-6.


1. Colombo N *et al*. Ann Oncol 2016; 27(1):16-41.
2. Concin N *et al*. Int J Gynecol Cancer 2021; 31(1):12-39.
3. Nagao S *et al*. Gynecol Oncol 2013; 131(3):567-73.
4. Rubinstein M *et al*. Gynecol Oncol Rep 2019; 28:120-3.


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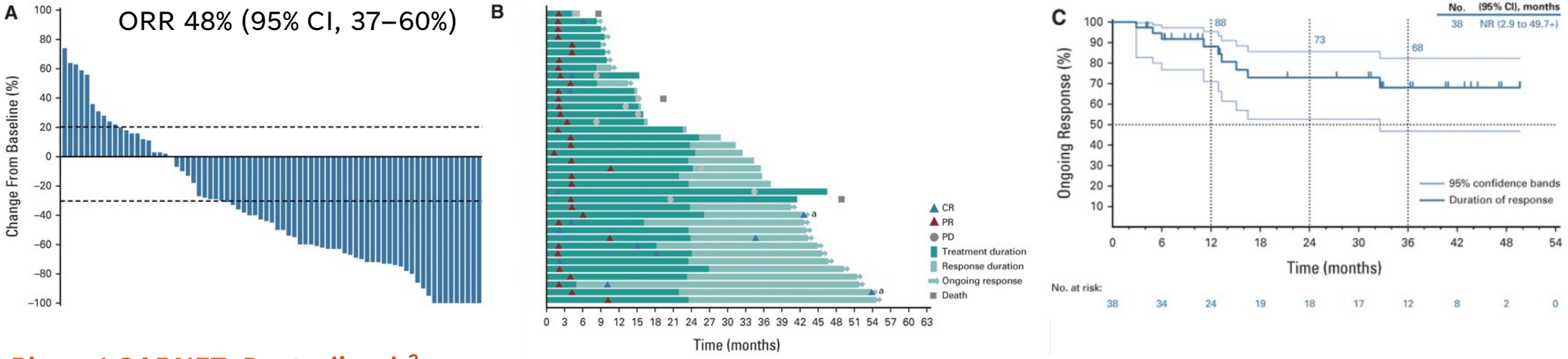
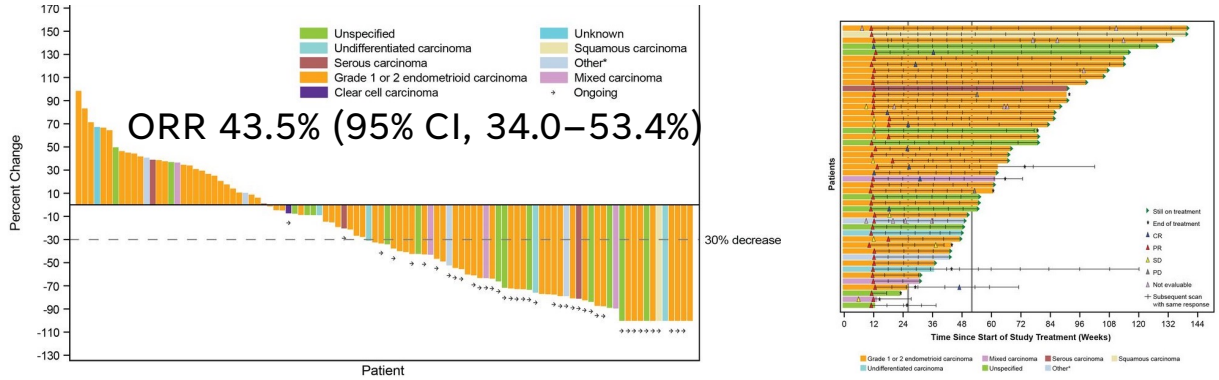
# Anti-PD-1 ICIs are Active Against Previously Treated Advanced or Recurrent MSI-H/dMMR EC

## Phase II KEYNOTE 158: Pembrolizumab[1]




## Phase I GARNET: Dostarlimab[2]

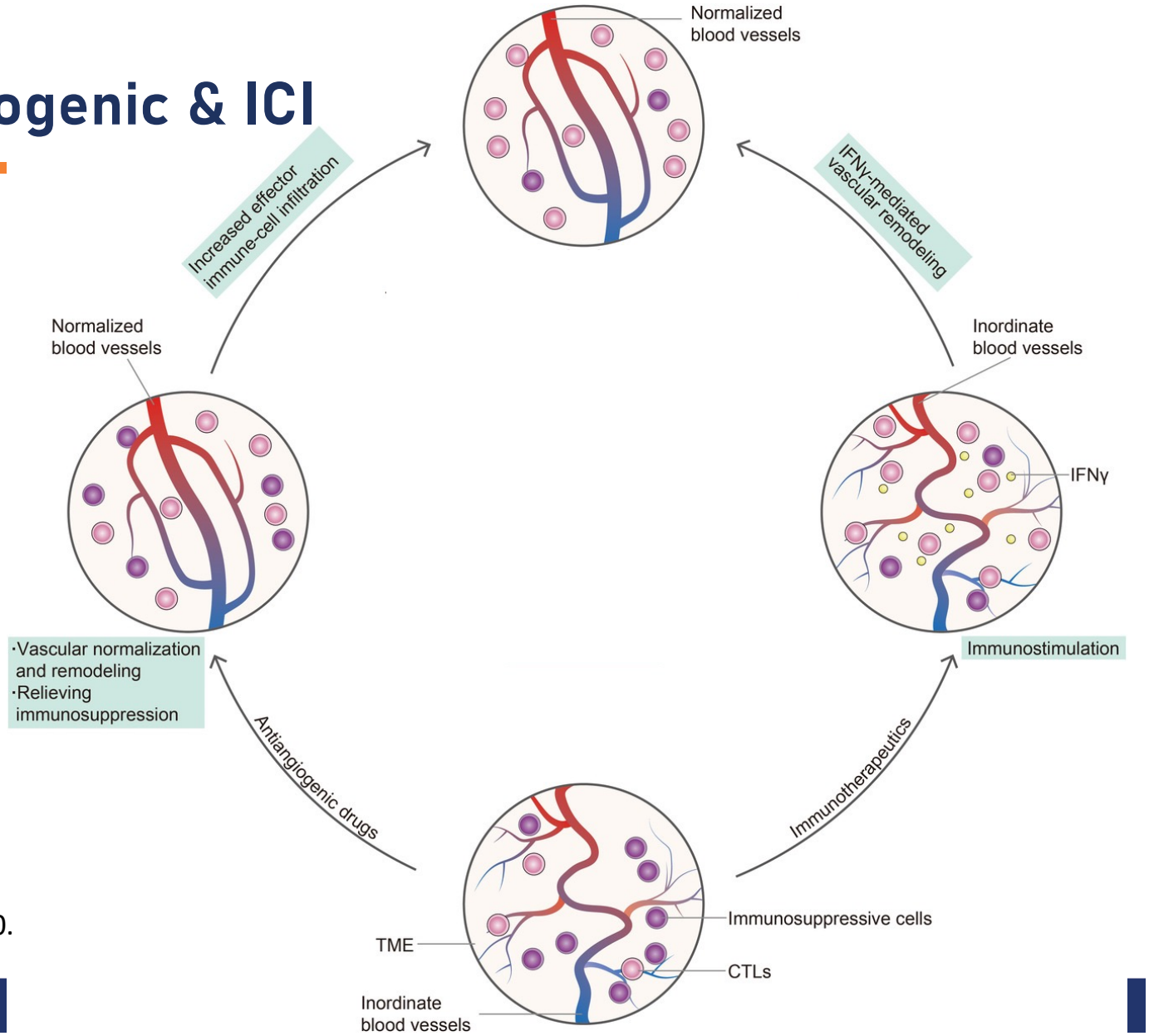







1. O'Malley DM *et al*. J Clin Oncol 2022; 40(7):752-61.
2. Oaknin A *et al*. J Immunother Cancer 2022; 10(1):e003777.

# Combining Anti-angiogenic & ICI




Li S-J *et al*. Cancer Commun (Lond) 2021; 41(9):830-50.

# Study 309/KEYNOTE-775: Pembrolizumab + Lenvatinib vs Chemo in Previously Platinum-treated Advanced EC

**Patient Population (N = 827)**

- Disease progression after 1 prior systemic, platinum-based chemotherapy regimen for advanced, recurrent or metastatic endometrial carcinoma
- Histologically confirmed diagnosis
- 1 prior systemic anticancer treatment
- No prior treatment targeting VEGF-directed angiogenesis or any anti–PD-1, –PD-L1, –PD-L2 agent
- Archival or fresh tumor biopsy specimen available for determination of MMR status

**Stratification Factors**

- pMMR vs dMMR
- If pMMR: ECOG PS, geographic region, prior history of pelvic radiation (yes vs no)

**R 1:1**

n=411

**Pembrolizumab**
200 mg IV Q3W until PD or 35 doses

+

**Lenvatinib**
20 mg PO QD until PD

n=416

**Physician's choice:**
**Doxorubicin**
60 mg/m$^2$ IV Q3W

**OR**

**Paclitaxel**
80 mg/m$^2$ IV
(28-day cycle: 3 weeks on + 1 week off)

**Primary Endpoints**

- PFS by BICR per RECIST v1.1
- OS

**Key Secondary Endpoints**

- ORR by BICR per RECIST v1.1
- HRQoL
- Safety

Makker V *et al*. N Engl J Med 2022; 386(5):437-48.

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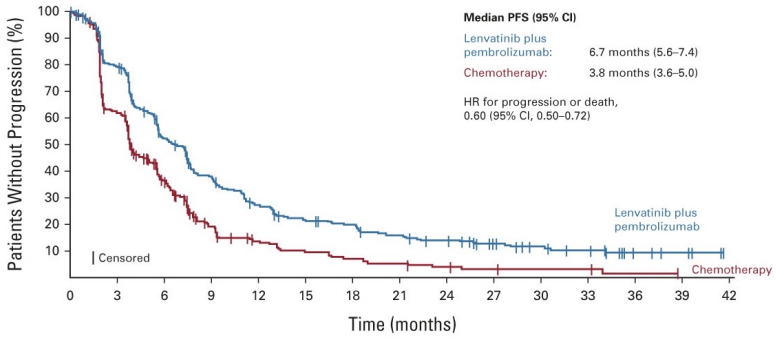
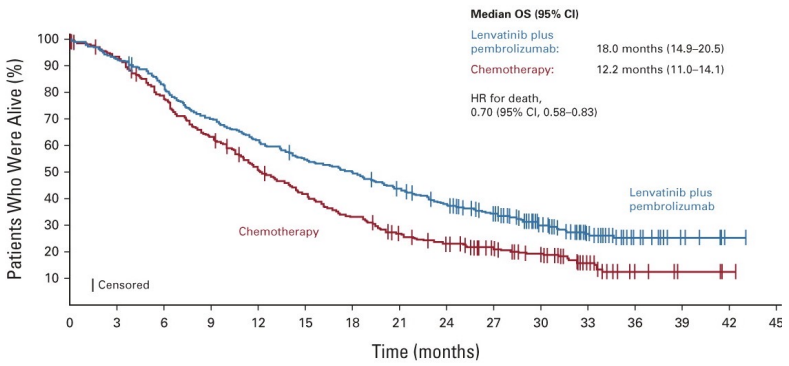
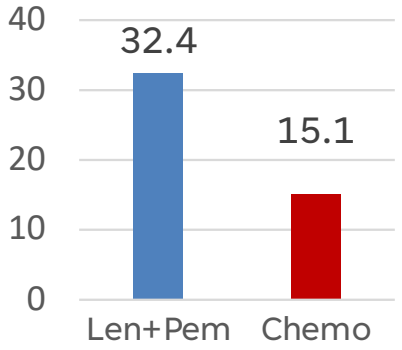
# KEYNOTE-775: Pembrolizumab + Lenvatinib is Superior to Chemo in Previously Platinum-treated Advanced EC

PFS | OS | ORR (%)

pMMR

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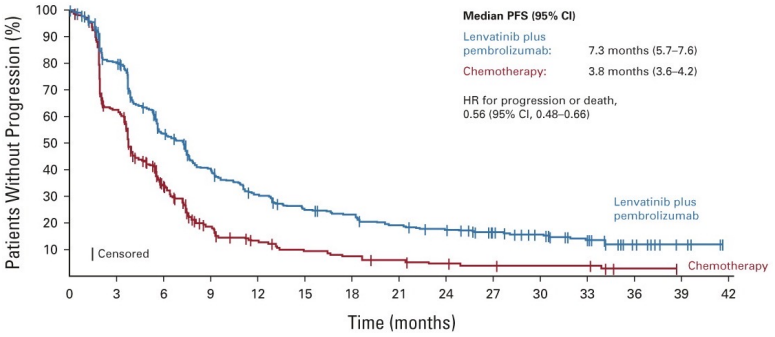
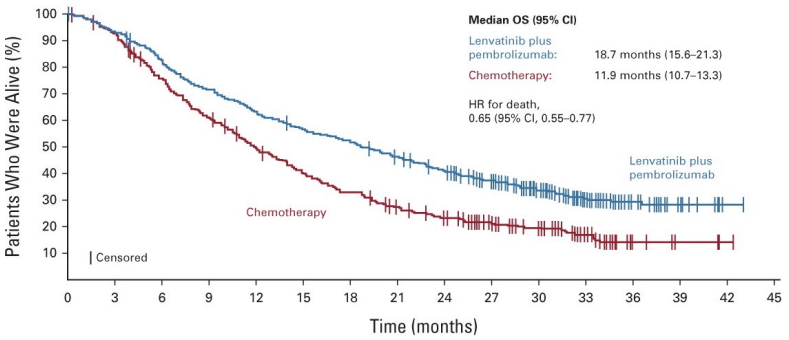
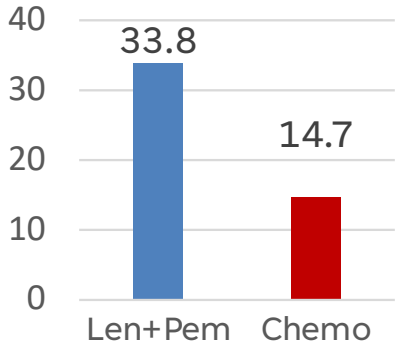



Makker V *et al*. J Clin Oncol 2023; 41(16):2904-10.

[a] Median time to first onset in patients who experienced the adverse reaction
[b] All grades
c Percentages are based on the number of patients with an adverse reaction leading to a dose modification
Abbreviations: PPES, palmar-plantar erythrodysesthesia syndrome; Q1,first quartile; Q3, third quartile

| Adverse Reaction | Incidence[b] n | Incidence[b] % | Lenvatinib Dose Interruption[c] | Lenvatinib Dose Reduction[c] | Lenvatinib Dose Discontinuation[c] | Pembrolizumab Interruption[c] | Pembrolizumab Discontinuation[c] | Median Time to First Onset (weeks)[a] | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| Hypertension | 61 | 65% | 15% | 12% | 0% | 1% | 0% | MIN: 0.1 / Q1: 1.4 / Median: 2.1 / Q3: 5.0 / MAX: 30.1 weeks | 30.1 |
| Musculoskeletal pain | 61 | 65% | 6% | 6% | 0% | 2% | 0% | MIN: 0.3 / Q1: 1.3 / Median: 2.4 / Q3: 9.1 / MAX: 31.3 weeks | 31.3 |
| Proteinuria | 18 | 19% | 4% | 3% | 0% | 0% | 0% | MIN: 1.1 / Q1: 2.7 / Median: 3.2 / Q3: 12.1 / MAX: 38.3 weeks | 38.3 |
| Fatigue | 61 | 65% | 16% | 24% | 1% | 14% | 0% | MIN: 0.1 / Q1: 0.9 / Median: 3.3 / Q3: 8.7 / MAX: 118.4 weeks | 118.4 |
| Nausea | 45 | 48% | 7% | 9% | 0% | 3% | 0% | MIN: 0.1 / Q1: 1.0 / Median: 4.7 / Q3: 11.4 / MAX: 143.1 weeks | 143.1 |
| Diarrhea | 60 | 64% | 14% | 10% | 1% | 6% | 0% | MIN: 0.1 / Q1: 1.0 / Median: 4.8 / Q3: 16.4 / MAX: 55.0 weeks | 55.0 |
| Decreased appetite | 49 | 52% | 5% | 9% | 0% | 6% | 0% | MIN: 0.1 / Q1: 2.0 / Median: 5.1 / Q3: 11.6 / MAX: 37.4 weeks | 37.4 |
| Stomatitis | 40 | 43% | 4% | 5% | 0% | 1% | 0% | MIN: 0.6 / Q1: 1.9 / Median: 5.5 / Q3: 13.3 / MAX: 29.1 weeks | 29.1 |
| Vomiting | 37 | 39% | 11% | 6% | 0% | 4% | 0% | MIN: 0.4 / Q1: 3.0 / Median: 5.9 / Q3: 11.7 / MAX: 96.6 weeks | 96.6 |
| Hypothyroidism | 48 | 51% | 2% | 0% | 0% | 1% | 0% | MIN: 1.0 / Q1: 5.9 / Median: 6.1 / Q3: 15.3 / MAX: 43.1 weeks | 43.1 |
| PPES | 24 | 26% | 5% | 13% | 0% | 1% | 0% | MIN: 1.1 / Q1: 4.2 / Median: 8.1 / Q3: 13.6 / MAX: 70.9 weeks | 70.9 |
| Weight decreased | 34 | 36% | 3% | 3% | 0% | 4% | 0% | MIN: 2.1 / Q1: 7.1 / Median: 9.1 / Q3: 15.1 / MAX: 124.3 weeks | 124.3 |



1. Makker V *et al*. Oncologist 2021; 26(9):e1599-608. 2. Colombo N *et al*. Presented at ESGO 2021, abstract 145.

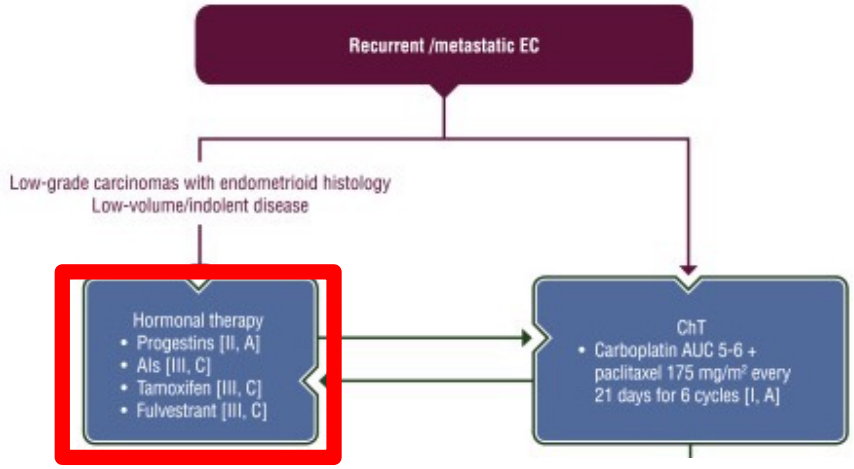
# Endocrine-based Therapies in Advanced EC: Guidelines

## NCCN ver 2.2024

| Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma | |
|---|---|
| **Preferred Regimens**<br>• Megestrol acetate/tamoxifen (alternating)<br>• Everolimus/letrozole | **Other Recommended Regimens**<br>• Medroxyprogesterone acetate/tamoxifen (alternating)<br>• Progestational agents<br>▸ Medroxyprogesterone acetate<br>▸ Megestrol acetate<br>• Aromatase inhibitors<br>• Tamoxifen<br>• Fulvestrant |
| **Useful in Certain Circumstances**<br>• ER-positive tumors<br>▸ Letrozole/ribociclib<br>▸ Letrozole/abemaciclib | |

Based on phase II data, ORRs:
Megestrol acetate 15-20%,
Letrozole <10%,
AI + CDK4/6i ~30%,
Letrozole/Everolimus 22%

## ESMO 2022




Oaknin A *et al*. Ann Oncol 2022; 33(9):860-77.

## ESGO/ESTRO/ESP 2020

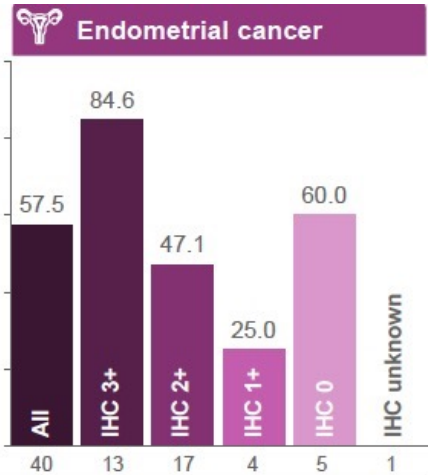
Hormone therapy is the preferred front-line systemic therapy for patients with low-grade carcinomas without rapidly progressive disease (II, A).

Progestogens (medroxyprogesterone acetate 200 (–300) mg and megestrol acetate 160 mg) are recommended (III, A). Alternative options for hormonal therapies include aromatases inhibitors, tamoxifen, fulvestrant (III, C).

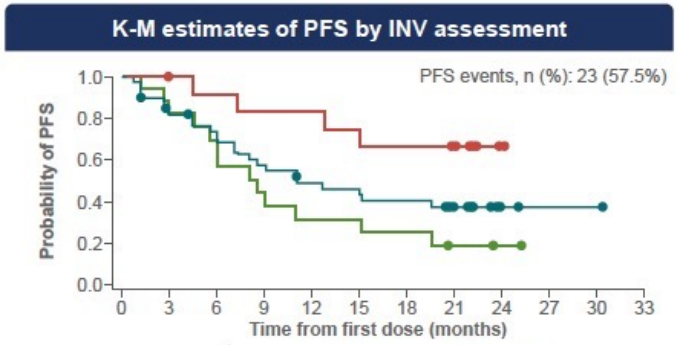
Concin N *et al*. Int J Gynecol Cancer 2021; 31(1):12-39.

# Trastuzumab Deruxtecan: Phase II Trials

## DESTINY-PanTumor02 Part 1: HER2 3+/2+ EC (N = 40)



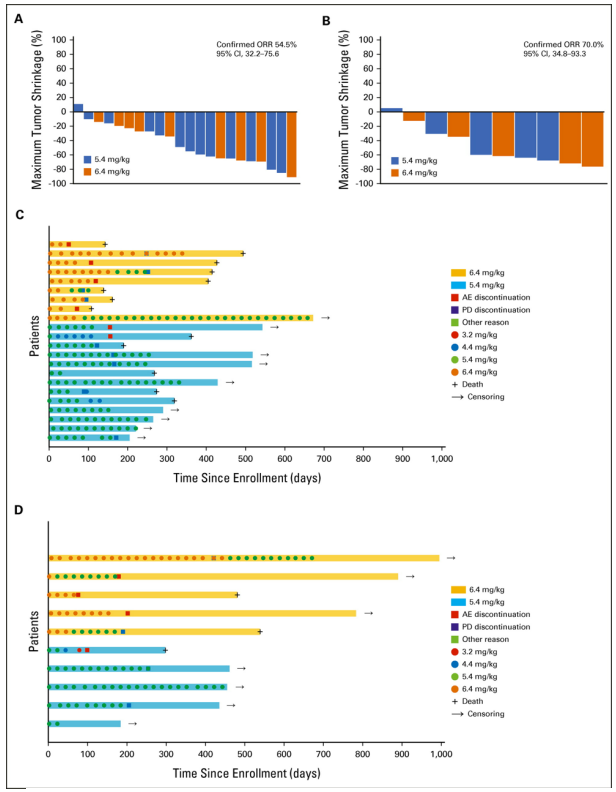

| | All | IHC 3+ | IHC 2+ | IHC 1+ | IHC 0 | IHC unknown |
|---|---|---|---|---|---|---|
| Total n in subgroup | 40 | 13 | 17 | 4 | 5 | 1 |
| n of responders | 23 | 11 | 8 | 1 | 3 | 0 |
| Median DOR, months† | NR | NR | 18.2 | NR | 9.9 | - |
| 95% CI‡ | 9.9, NE | 9.6, NE | 3.0, NE | - | 2.8, NE | - |




| | Median PFS, months (95% CI) | | |
|---|---|---|---|
| | n | INV | ICR |
| All | 40 | 11.1 (7.1, NE) | 14.1 (7.3, NE) |
| IHC 3+ | 13 | NR (7.3, NE) | NR (7.3, NE) |
| IHC 2+ | 17 | 8.5 (4.6, 15.1) | 11.0 (4.6, 20.3) |
| IHC 1+ | 4 | 1.2 (0.8, NE) | 1.2 (0.8, NE) |
| IHC 0 | 5 | 9.1 (2.6, NE) | 11.1 (2.6, NE) |
| IHC unknown | 1 | NR (-) | NR (-) |

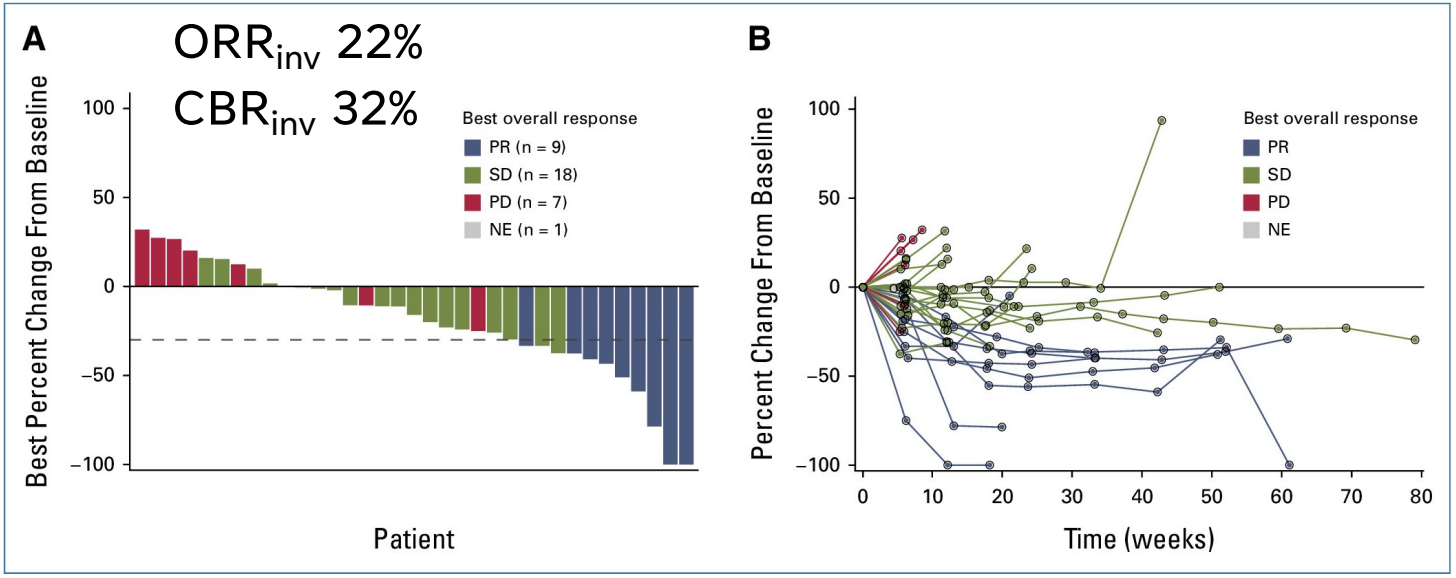
Meric-Bernstam F *et al*. J Clin Oncol 2024; 42(1):47-58.

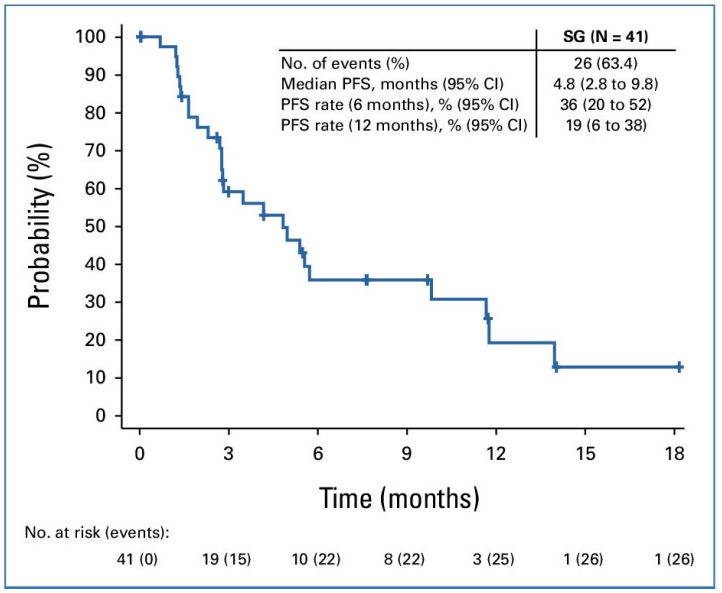
## STATICE: HER2 ≥1+ UCS




Nishikawa T *et al*. J Clin Oncol 2023;4 1(15):2789-99.

# Sacituzumab Govitecan: EC Cohort of Phase II TROPiCS-3




Santin AD *et al*. J Clin Oncol 2024; JCO2302767. [online ahead of print.]

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# Conclusions

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# Key Takeaways

- Paclitaxel/Carboplatin is the chemotherapy backbone in first-line management of advanced EC
  - Consider concurrent-maintenance Trastuzumab in HER2+ USC based on a randomised phase II trial
- Immune checkpoint inhibitors have expanding roles in the first line and beyond of advanced EC
  - 1L: in combination with Pac/Carbo
    - Should be given in dMMR subgroup; unlikely to benefit from additional PARPi.
    - Can be considered in pMMR subgroup. Role of PARPi is less clear (maybe p53abn?).
  - 2+L: as monotherapy (dMMR), or combined with Lenvatinib

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# Unanswered Questions & Unmet Needs in Advanced EC

- Which (molecular) subgroups benefit the most from ICI + PARPi maintenance after response to first-line chemo + ICI?
- How efficacious is 2+L Pem/Len after 1L chemo + ICI ± PARPi?
- What is the optimal 3+L therapy after failure of earlier ICI-based regimen(s)?
  - ADCs are actively investigated e.g. MK-2870-005/ENGOT-en23/GOG-3095 (NCT06132958), ASCENT-GYN-01 (NCT06486441)

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# Thank you for your attention

*Terima kasih banyak-banyak*


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