# Endometrial Cancer:
# Immunotherapy: The standard of care after platinum failure

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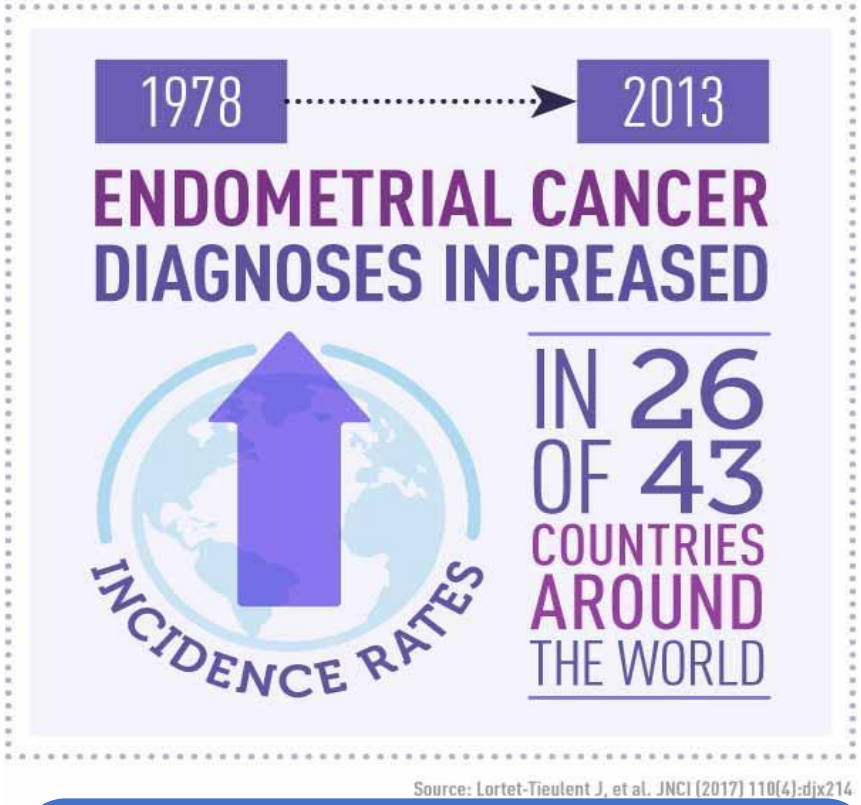
# Endometrial Cancer: Facts and Figures

VHIO VALL D'HEBRON Institute of Oncology

**65,950**
New Cases Uterine Cancer Projected in U.S. for 2022[1]

**122,000**
New Cases Uterine Cancer Projected in U.S. for 2030[2]

**1.8%**
ANNUAL Increase in Uterine Cancer Mortality Rates in U.S. 2010-2017[3]



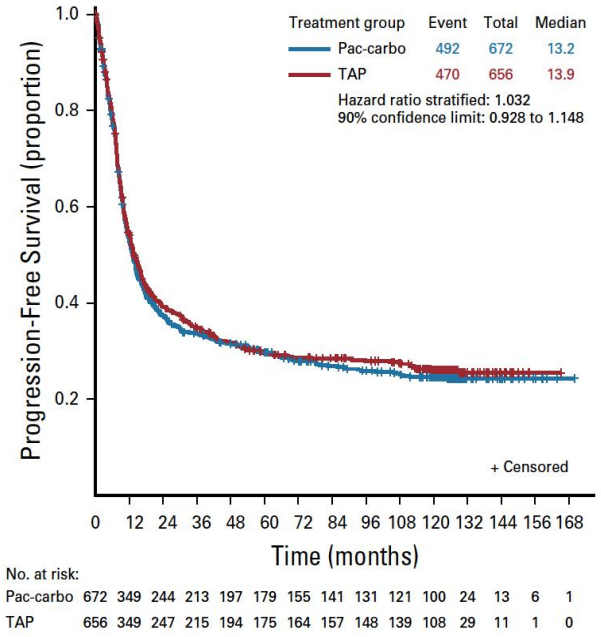

Worldwide in 2020[4]:
417,000 New Cases
97,000 Deaths

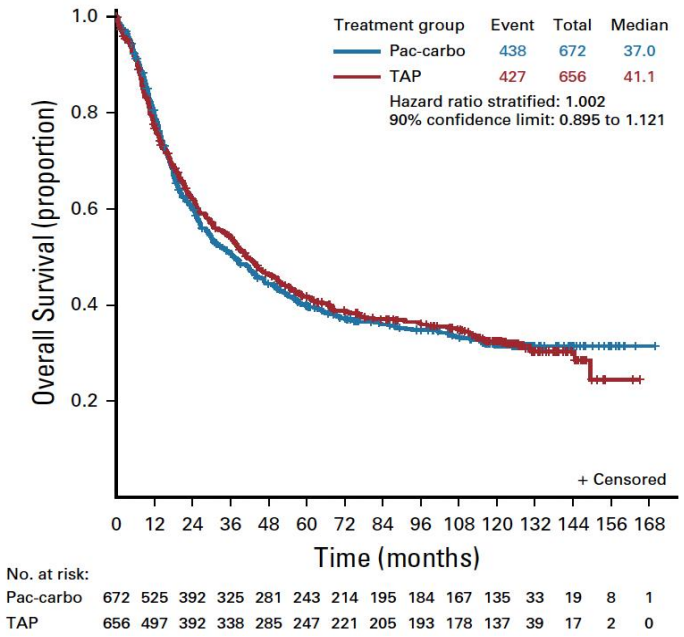
[1] Siegel et al. *CA Cancer J Clin* 2022;72:7–33
[2] Rahib et al. *Cancer Res* 2014; 74(11); 2913–21.
[3] Clarke et al. *JAMA Oncol.* Published online May 5, 2022. doi:10.1001/jamaoncol.2022.0009
[4] https://www.wcrf.org/cancer-trends/endometrial-cancer-statistics/

# Standard First Line Therapy for Advanced Endometrial Cancer: Carboplatin and Paclitaxel(GOG#209) or Hormonotherapy:

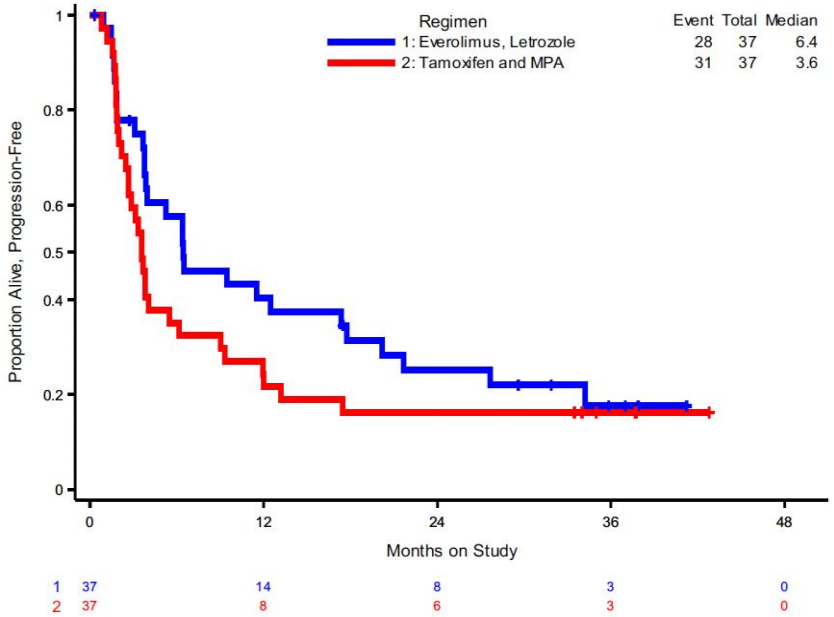
## Limited Efficacy

### GOG#209




### Phase II everolimus and letrozole vs. hormonal therapy




Miller D. et al J Clin Oncol 38:3841-3850; 2020B.M. Slomovitz et al;Gynecologic Oncology 164 (2022) 481–491

# Poor Response to 2nd Line Therapy

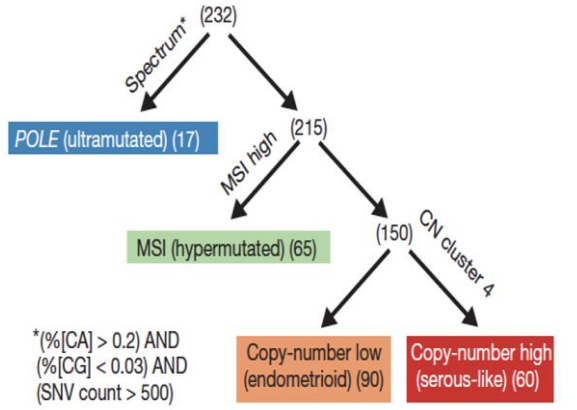
**Table 2.** Selected GOG Phase II Trials of Cytotoxic Agents as Second-Line Therapy for Recurrent Endometrial Cancer

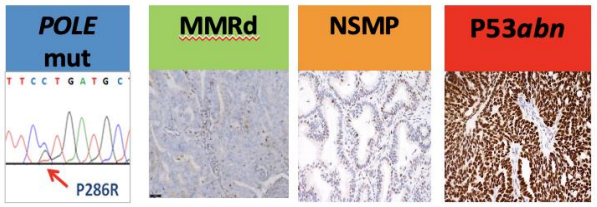
| Agent | Reference | RR (%) |
|---|---|---|
| Paclitaxel* | Lincoln et al[8] | 27 |
| Docetaxel, once per week† | Garcia et al[24] | 7.7 |
| Liposomal doxorubicin | Muggia et al[25] | 9.5 |
| Topotecan | Miller et al[26] | 9 |
| Oxaliplatin | Fracasso et al[27] | 13.5 |
| Ixabepilone | Dizon et al[28] | 12 |
| Pemetrexed | Miller et al[29] | 4 |
| Gemcitabine | Tait et al[30] | 4 |

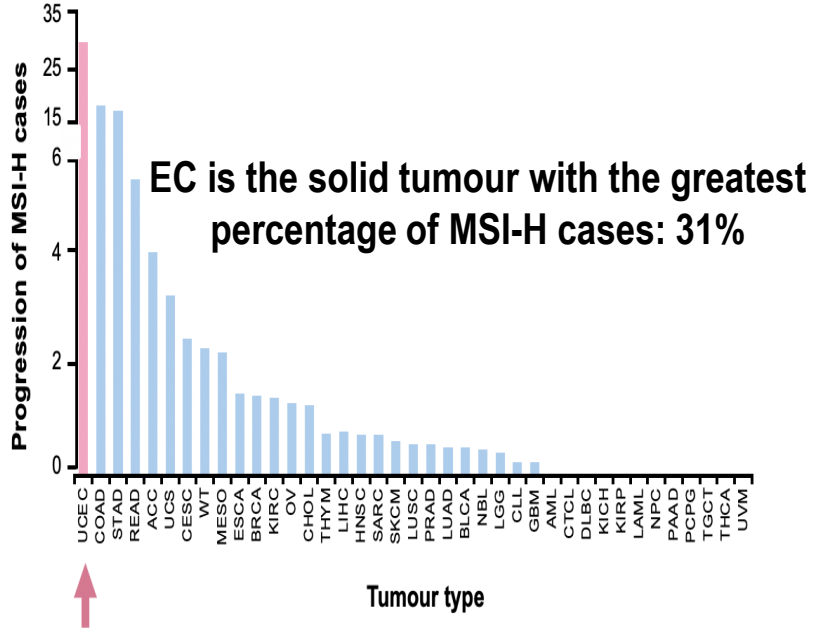
Abbreviation: GOG, Gynecologic Oncology Group; RR, response rate.
*Patients had no prior paclitaxel.
†Patients had received prior paclitaxel.

Fleming GF. *J Clin Oncol.* 2015;33(31):3535-3540.

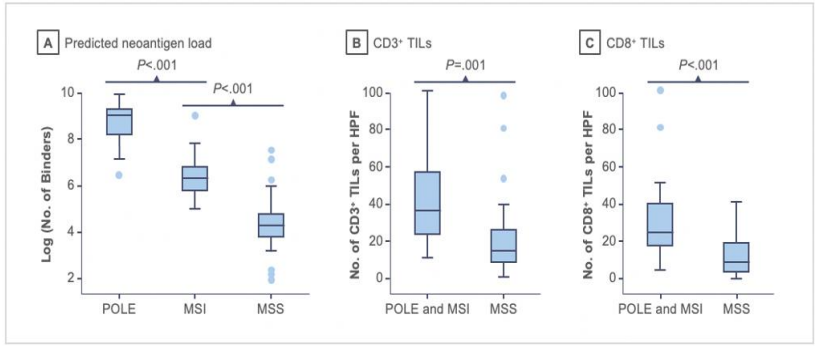
# The Tipping Point: Bringing Biology Into the Clinic

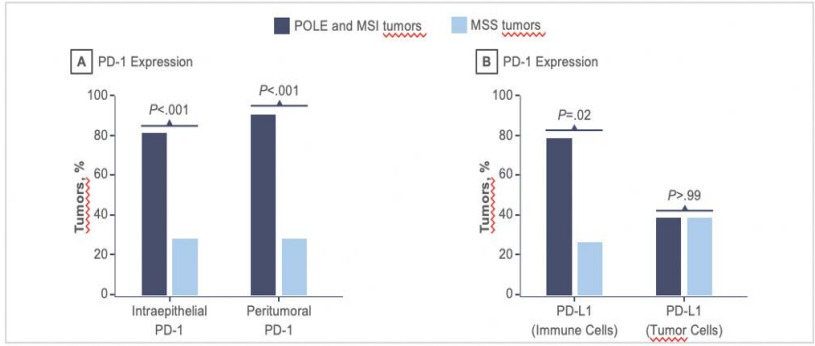



**EC is the solid tumour with the greatest percentage of MSI-H cases: 31%**




**In this scenario, Immunotherapy emerges as a game changer in the management of EC.**


The Cancer Genome Atlas Research Network. *Nature* 2013; 497: 67–73; 3. Talhouk A, *et al*. *Cancer* 2017; 123: 802–813;Luchini C, *et al*. *Ann Oncol* 2019; 30: 1232–1243; Bonneville R, *et al*. *JCO Precis Oncol* 2017; 1: PO.17.00073. Howitt BE, *et al*. *JAMA Oncol* 2015; 1: 1319–1323;

# Single-Agent Immunotherapy Approaches

**Monotherapy immune checkpoint inhibition is an effective strategy for biomarker-selected patients with advanced or recurrent endometrial cancer**

**Phase 2 KEYNOTE-158**
Pembrolizumab[1]

**Phase 1 GARNET**
Dostarlimab[2]

| FDA Approval | Pembrolizumab Single-Agent Indication |
|---|---|
| **2017[a]; 2023[b]** | Tissue-agnostic approval for the treatment of unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment |
| **2020[a]** | Tissue-agnostic approval for TMB-H tumors following progression on prior treatment |
| **2022[b]** | Advanced endometrial carcinoma that is dMMR following progression on prior treatment |
| **FDA Approval** | **Dostarlimab Single-Agent Indication** |
| **2021[a]; 2023[b]** | Recurrent or advanced endometrial cancer that is dMMR following progression or prior treatment |
| **2021[a]** | Tissue-agnostic approval for dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment |

[a] Accelerated FDA approval. [b] Full FDA approval.

1. Keytruda (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s136lbl.pdf.
2. Jemperli (dostarlimab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761174s003s004lbl.pdf.

# Phase 2 KEYNOTE-158: Pembrolizumab Monotherapy for Advanced Endometrial Cancer[1,2]

**Key Inclusion Criteria**

- Aged ≥18 years
- MSI-H/dMMR advanced endometrial cancer
  - Cohort D: endometrial cancer, regardless of MSI status and excluding sarcomas and mesenchymal tumors
  - Cohort K: any MSI-H/dMMR advanced solid tumor except colorectal
- Progression on or intolerance to ≥1 line of standard treatment for unresectable and/or metastatic disease
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Provision of a tumor sample for biomarker assessment

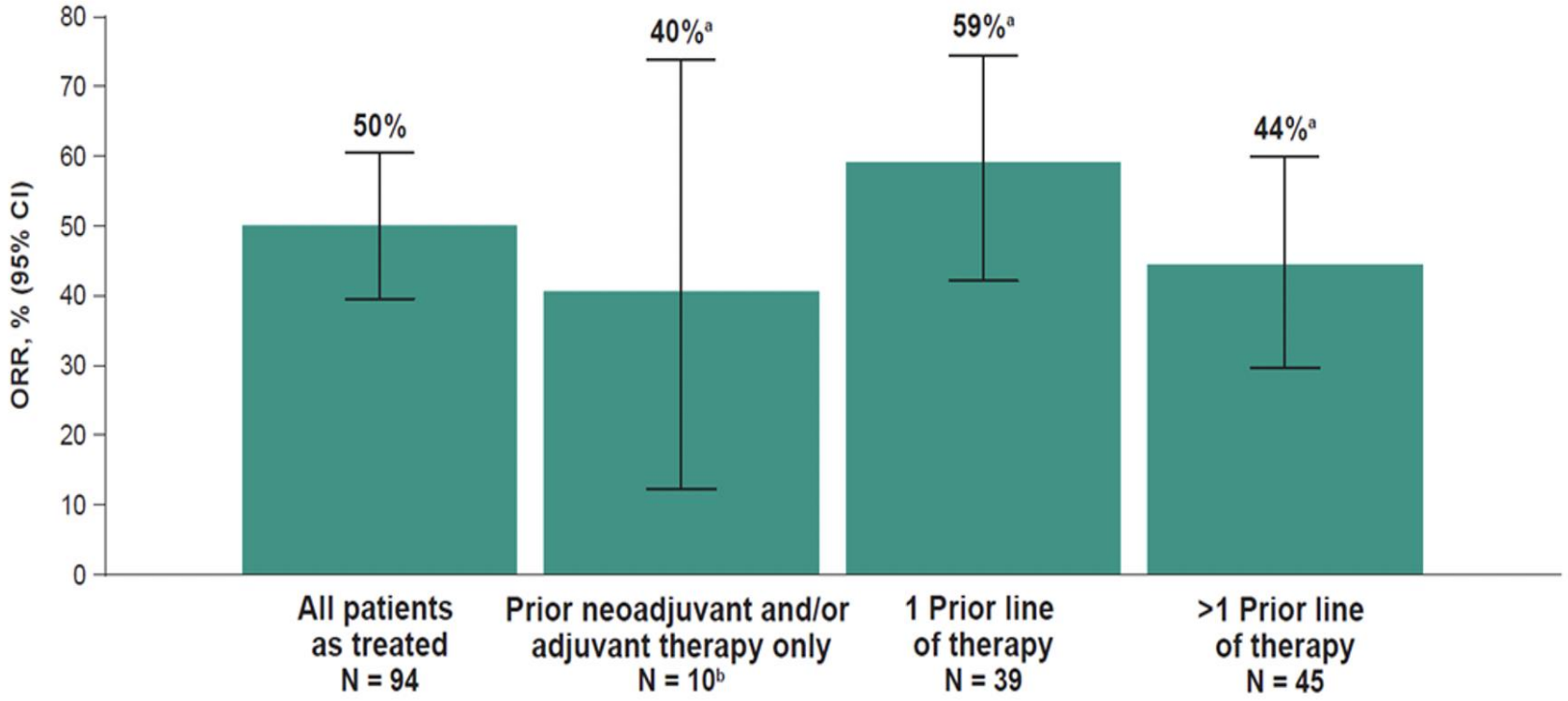
→ **Pembrolizumab**
200 mg IV Q3W →

For 35 cycles (approximately 2 y) or until disease progression, intolerable toxicity, investigator decision, or patient withdrawal

- **Primary endpoint:** ORR per RECIST v1.1 by ICR
- **Secondary endpoints:** DOR and PFS per RECIST v1.1 by ICR, OS, safety

1. https://clinicaltrials.gov/ct2/show/NCT02628067.
2. Keytruda (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s136lbl.pdf.

# KEYNOTE-158
# PEMBROLIZUMAB IN DMMR/MSI-H ENDOMETRIAL CANCER COHORT
## 1º END-POINT: ORR BY RECIST V1.1(ICR)



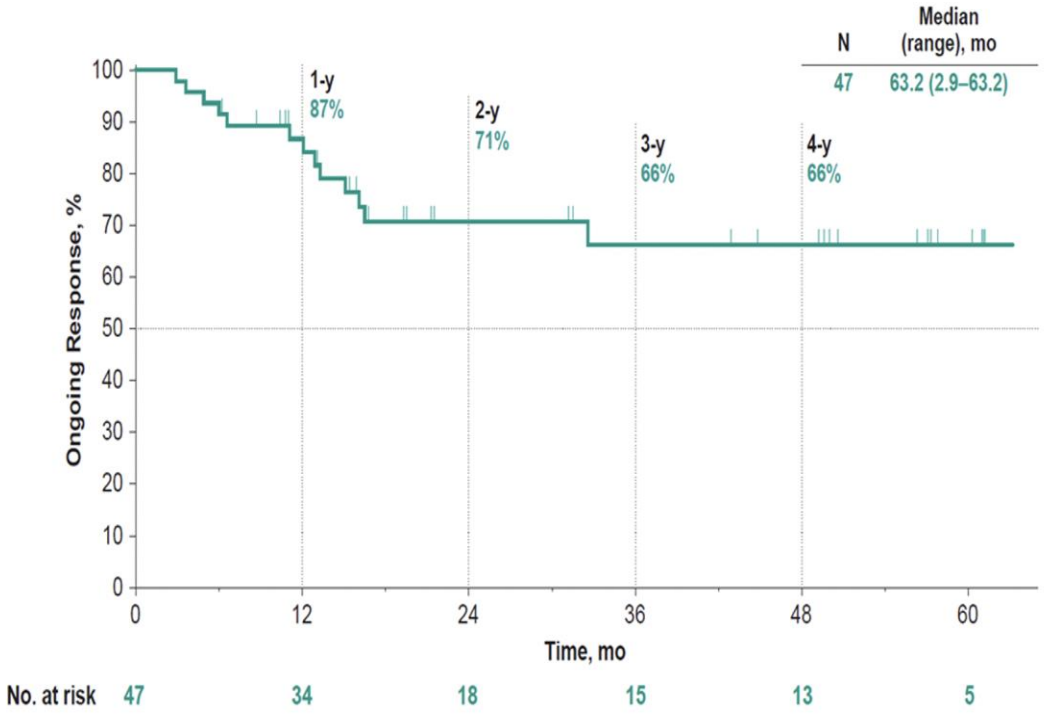

[a]Percentage based on number of patients in subgroup.
[b]9 patients received only adjuvant therapy and 1 patient received both neoadjuvant and adjuvant therapy.

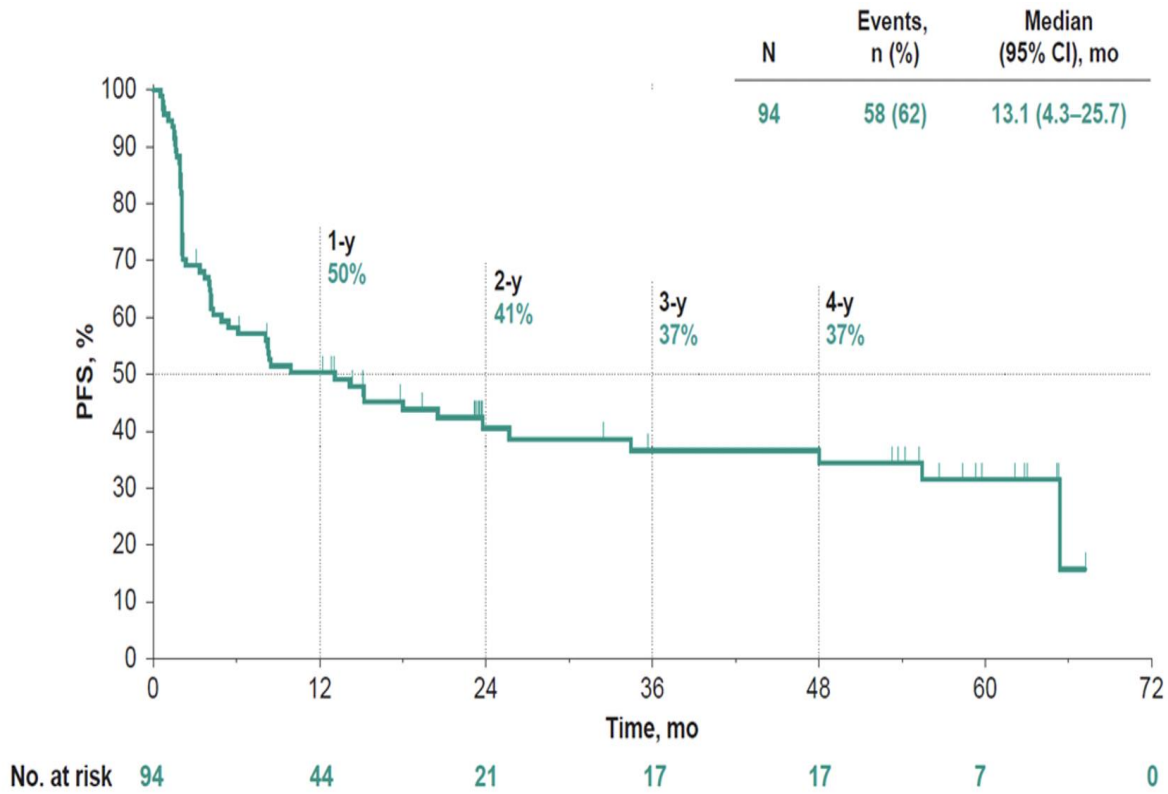
ICR: Independent Central Review

ClinicalTrials.gov : NCT02628067

O'Malley D, et al. J Clin Oncol 2022; 40: 752−761
O'Malley D, et al Presented at ESMO Congress 2022. .

# KEYNOTE-158
# PEMBROLIZUMAB IN DMMR/MSI-H ENDOMETRIAL CANCER COHORT
## 2º END-POINTS: DOR*,PFS




Median follow-up of 54.5(14.7-71.4) months

*Duration of Response

O'Malley D, et al. J Clin Oncol 2022; 40: 752−761
O'Malley D, et al Presented at ESMO Congress 2022.

# KEYNOTE-158
# Pembrolizumab in dMMR/MSI-H Endometrial Cancer Cohort
# Safety Profile

- **9.0% discontinued therapy due to a TRAE**

## Treatment-Related AE(TRAE)

| | N=94 | |
|---|---|---|
| Event, n (%) | Any grade | Grade 3 or 4[a] |
| Any treatment-related AE[b] | 71 (76) | 13 (14) |
| Occurring in ≥5% of patients | | |
| Pruritus | 24 (26) | 0 |
| Fatigue | 19 (20) | 0 |
| Diarrhea | 16 (17) | 0 |
| Arthralgia | 15 (16) | 0 |
| Hypothyroidism | 13 (14) | 0 |
| Nausea | 13 (14) | 0 |
| Rash | 11 (12) | 1 (1) |
| Decreased appetite | 8 (9) | 0 |
| Myalgia | 7 (7) | 0 |
| Maculopapular rash | 7 (7) | 0 |
| Hyperthyroidism | 6 (6) | 0 |
| Aspartate aminotransferase increased | 5 (5) | 0 |
| Dry mouth | 5 (5) | 0 |
| Vomiting | 5 (5) | 0 |

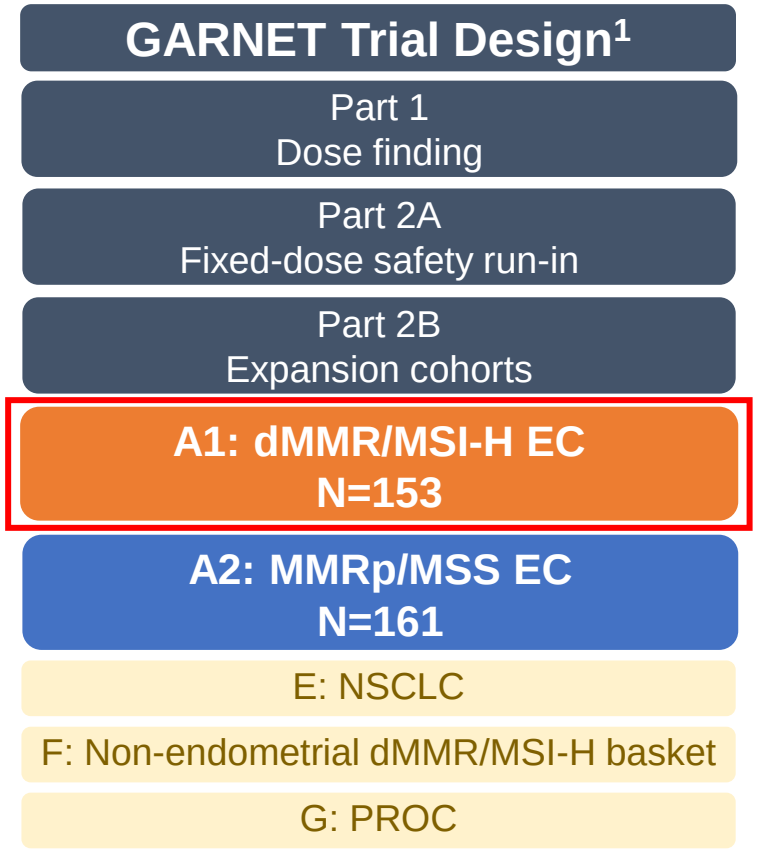
## Immune-Mediated AE

| | N=94 | |
|---|---|---|
| Event, n (%) | Any grade | Grade 3 or 4[a] |
| Any immune-mediated AE or infusion reaction[b] | 28 (30) | 8 (9) |
| Hypothyroidism | 15 (16) | 0 |
| Hyperthyroidism | 7 (7 ) | 0 |
| Colitis | 4 (4) | 2 (2) |
| Infusion reactions | 3 (3) | 0 |
| Severe skin reactions | 3 (3) | 3 (3) |
| Type 1 diabetes mellitus | 2 (2) | 1 (1) |
| Pneumonitis | 2 (2) | 0 |
| Hepatitis | 1 (1) | 1 (1) |
| Myositis | 1 (1) | 0 |
| Adrenal insufficiency | 1 (1) | 1 (1) |
| Uveitis | 1 (1) | 0 |

O'Malley D, et al Presented at ESMO Congress 2022.

# GARNET trial[1]

- GARNET is a Phase I, multicentre, open-label, single-arm study of JEMPERLI monotherapy in patients with advanced or recurrent solid tumours
- Patients were enrolled on cohort A1 (dMMR/MSI-H) or cohort A2 (MMRp/MSS) based on MMR immunohistochemistry (IHC) assessment
- Patients received 500 mg IV JEMPERLI every 3 weeks for 4 cycles, followed by 1000 mg IV every 6 weeks until disease progression, discontinuation or withdrawal
- Primary endpoints were evaluation of anti-tumour activity (in terms of objective response rate (ORR) and duration of response (DOR) by BICR) and safety




BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; IV, intravenous; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NSCLC, non–small cell lung cancer; ORR, objective response rate; PROC, platinum-resistant ovarian cancer.

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Oaknin A at al. Presented at ASCO Meeting 2022 Oaknin A. et al J Immunother Cancer. 2022 Jan;10(1):e003777; Oaknin A. *et al.* Presented at IGCS 2021. [Poster 2564].

# Demographics and baseline characteristics (dMMR/MSI-H)

| Characteristic, n (%) | dMMR/MSI-H EC N=143 |
|---|---|
| Age, median (range), years | 65.0 (39–85) |
| FIGO disease stage at diagnosis | |
| Stage I or II | 62 (43.4) |
| Stage III or IV | 81 (56.6) |
| Histology | |
| Grade 1 or 2 endometrioid carcinoma | 92 (64.3) |
| Serous | 7 (4.9) |
| Grade 3 endometrioid | 21 (14.7) |
| Clear cell | 1 (0.7) |
| Squamous | 1 (0.7) |
| Undifferentiated | 4 (2.8) |
| Carcinosarcoma | 0 |
| Mixed carcinoma | 7 (4.9) |
| Unspecified | 4 (2.8) |
| Other* | 4 (2.8) |
| Unknown | 2 (1.4) |

| Characteristic, n (%) | dMMR/MSI-H EC N=143 |
|---|---|
| Prior anticancer treatment | 143 (100) |
| Prior lines of therapy, n (%)† | |
| 1 | 90 (62.9) |
| 2 | 35 (24.5) |
| ≥3 | 18 (12.6) |
| Patients with only adjuvant or neoadjuvant therapy | 49 (34.3) |
| Neoadjuvant setting only | 3 (2.1) |
| Adjuvant setting only | 44 (30.8) |
| Only adjuvant and neoadjuvant | 2 (1.4) |
| Prior radiation, n (%) | 101 (70.6) |

*Other includes dedifferentiated, endometrial adenocarcinoma, endometrial adenocarcinoma NOS, endometrial neuroendocrine carcinoma, high Grade uterine carcinoma, and undifferentiated clear cell carcinoma.[1] †Includes lines of therapy in the adjuvant setting.[1]
dMMR, mismatch repair deficient; EC, endometrial cancer; FIGO, International Federation of Gynaecology and Obstetrics; NOS, not otherwise specified.



Oaknin A at al. Presented at ASCO Meeting 2022 Oaknin A. et al J Immunother Cancer. 2022 Jan;10(1):e003777; Oaknin A. *et al.* Presented at IGCS 2021. [Poster 2564].

# Primary endpoint analysis:
## ORR and DOR by BICR per RECIST v1.1 (dMMR/MSI-H)

| | dMMR/MSI-H EC<br>N=143 |
|---|---|
| Median follow-up time, months | **27.6** |
| **ORR**, % (95% CI; n/N)<br>Complete response, n (%)<br>Partial response, n (%)<br>Stable disease, n (%)<br>Progressive disease, n (%)<br>Not evaluable, n (%) | **45.5%** (37.1–54.0; 65/143)<br>**23** (16.1)<br>**42** (29.4)<br>21 (14.7)<br>51 (35.7)<br>6 (4.2) |
| Median time from Cycle 1 Day 1 to best overall response, months<br>Complete response<br>Partial response | <br>2.79<br>2.69 |
| Disease control rate, % (95% CI; n/N) | 60.1% (51.6–68.2; 86/143) |
| Response ongoing, n (%) | 54 (83.1) |
| **Median DOR (range), months** | **NR** (1.18+ to 47.21+) |
| Probability of maintaining response, %<br>6 months<br>12 months<br>24 months | <br>96.8<br>93.3<br>83.7 |

BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability-high; NR, not reached; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumours.

Oaknin A at al. Presented at ASCO Meeting 2022 Oaknin A. et al J Immunother Cancer. 2022 Jan;10(1):e003777; Oaknin A. *et al.* Presented at IGCS 2021. [Poster 2564].

# DOR in responders (dMMR/MSI-H)

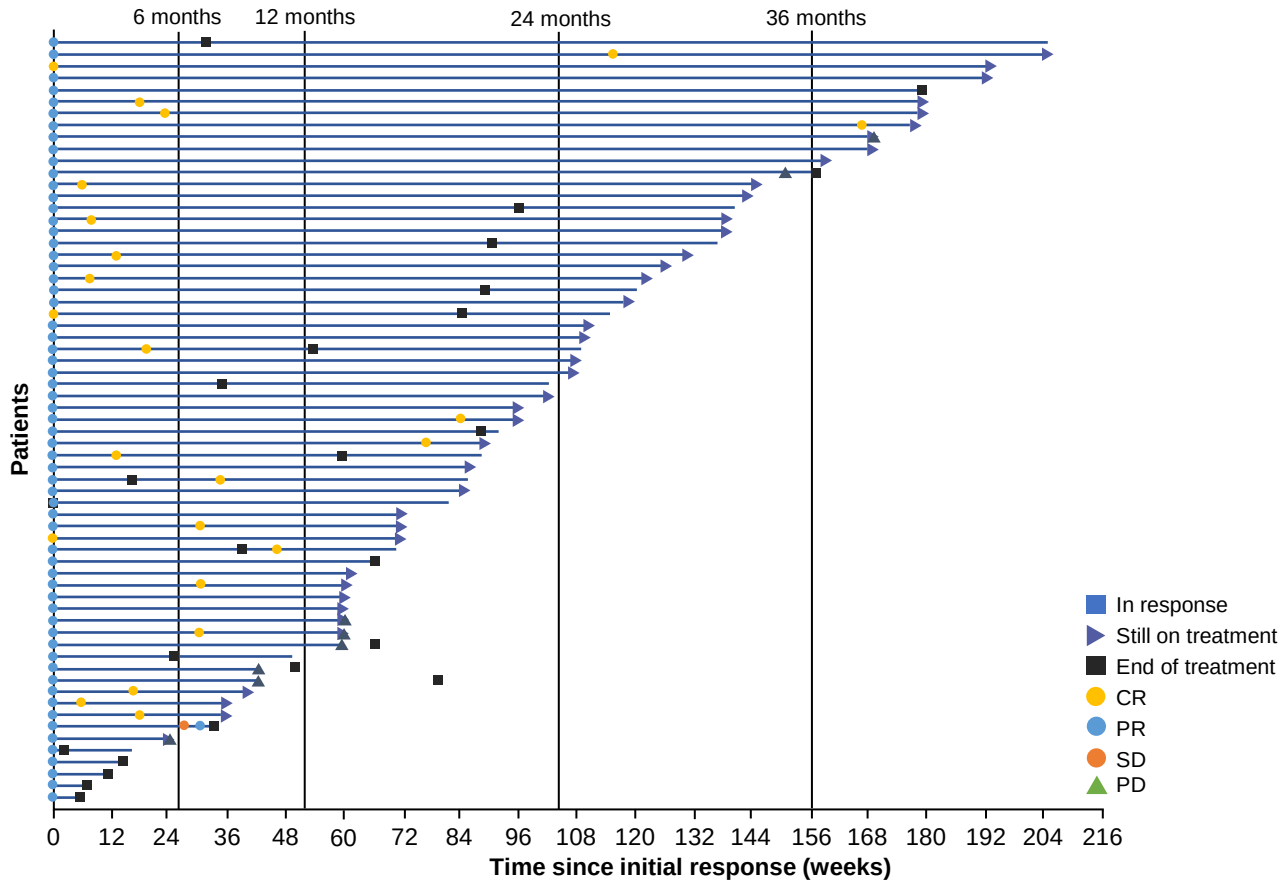



Figure adapted from Oaknin A, *et al*. 2022.[2]

With increased median duration of follow-up of 27.6 months responses were durable.

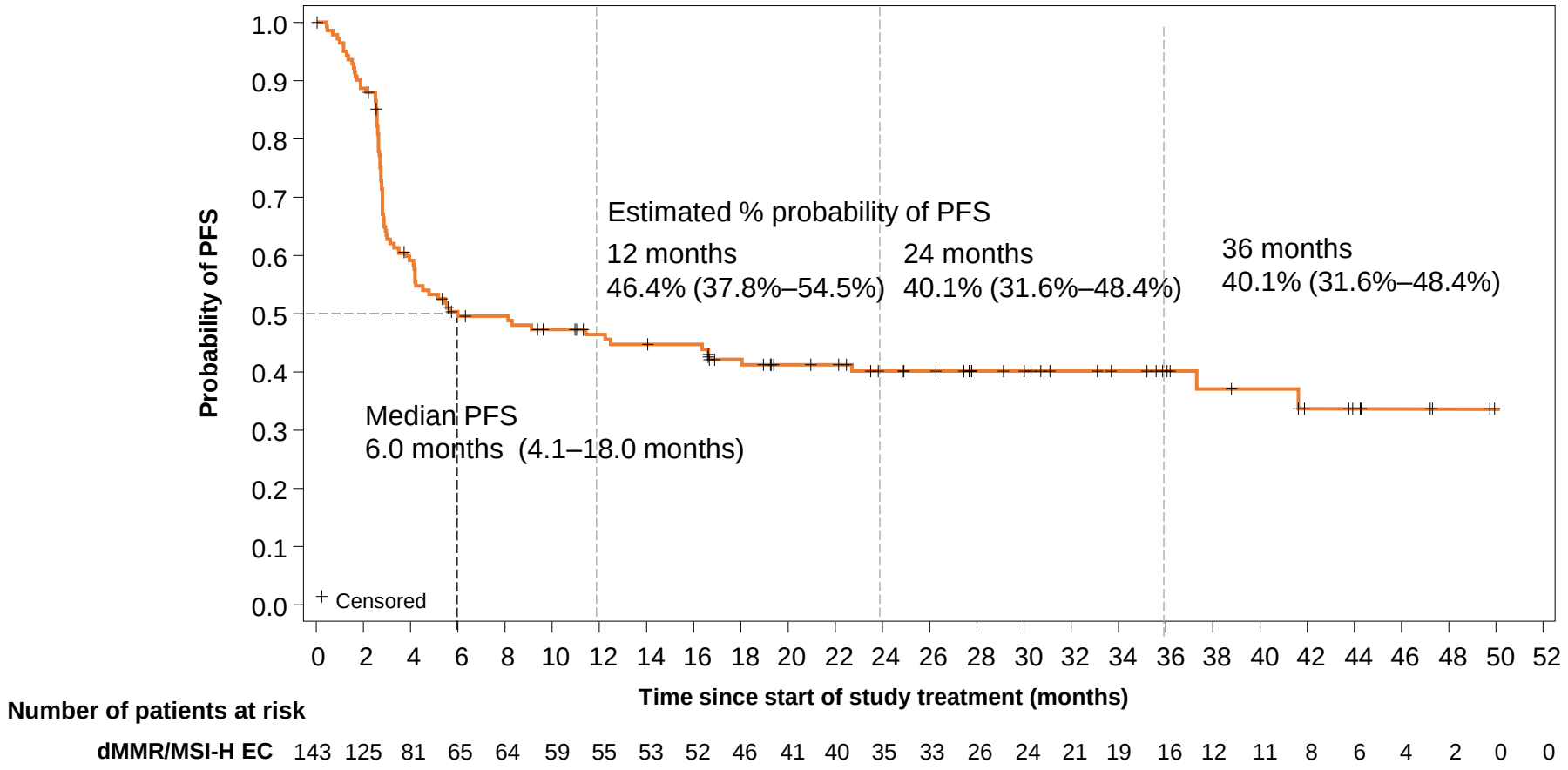
Median duration of response was not reached.

Probability of remaining in response at 24 months was 83.7%.

CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; MSI-H, microsatellite instability-high; PD, progressive disease; PR, partial response; SD, stable disease.

Oaknin A at al. Presented at ASCO Meeting 2022

# Probability of progression-free survival (PFS): dMMR/MSI-H




dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability-high; PFS, progression-free survival.



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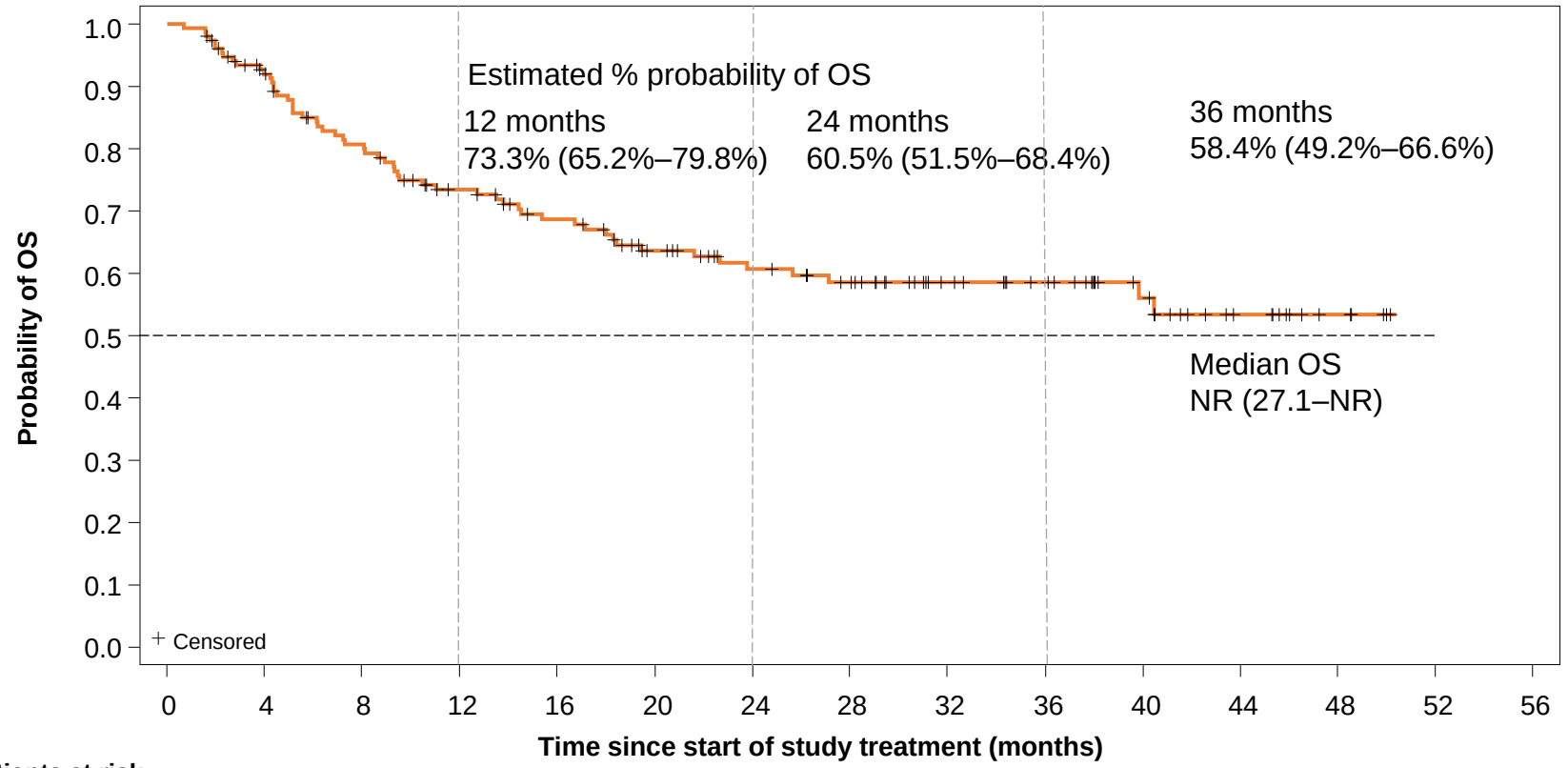
# Probability of overall survival (OS): dMMR/MSI-H




**Number of patients at risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **dMMR/MSI-H EC** | 153 | 132 | 112 | 95 | 84 | 70 | 60 | 52 | 38 | 32 | 22 | 13 | 5 | 0 | 0 |

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability-high; NR, not reached; OS, overall survival.

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Oaknin A at al. Presented at ASCO Meeting 2022

# GARNET Trial
## Safety Summary in both EC Cohorts

- The safety population included all patients with EC who had received ≥1 dose of dostarlimab
- Most TRAEs were grade 1 or 2 and were manageable
- 27 (8.6%) patients discontinued treatment because of a TRAE
- No deaths associated with dostarlimab were reported in any EC cohorts in the GARNET trial.

| Parameter, n (%) | dMMR/MSI-H EC N=153 | MMRp/MSS EC N=161 | Overall N=314 |
|---|---|---|---|
| Any TEAE | 152 (99.3) | 161 (100) | 313 (99.7) |
| Grade ≥3 TEAE | 87 (56.9) | 95 (59.0) | 182 (58.0) |
| Any-grade TRAE | 108 (70.6) | 115 (71.4) | 223 (71.0) |
| Grade ≥3 TRAE | 27 (17.6) | 33 (20.5) | 60 (19.1) |
| Any irTRAE | 42 (27.5) | 31 (19.3) | 73 (23.2) |
| Grade ≥3 irTRAE | 16 (10.5) | 9 (5.6) | 25 (8.0) |
| Treatment-related SAE | 18 (11.8) | 14 (8.7) | 32 (10.2) |
| Any TRAE leading to discontinuation | 13 (8.5) | 14 (8.7) | 27 (8.6) |
| TRAE leading to death | 0 | 0 | 0 |

dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune related; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Oaknin A. et al . Presented at ASCO Meeting 2022

# GARNET Trial
## Safety Summary in both EC Cohorts

| Preferred term, n (%) | dMMR/MSI-H EC N=153 | MMRp/MSS EC N=161 | Overall N=314 |
|---|---|---|---|
| **Any-grade TRAEs occurring in ≥10% of patients** | | | |
| Fatigue | 21 (13.7) | 35 (21.7) | 56 (17.8) |
| Diarrhea | 25 (16.3) | 21 (13.0) | 46 (14.6) |
| Nausea | 19 (12.4) | 24 (14.9) | 43 (13.7) |
| Asthenia | 24 (15.7) | 13 (8.1) | 37 (11.8) |
| **Grade ≥3 TRAEs occurring in ≥1% of patients** | | | |
| Anemia | 7 (4.6) | 3 (1.9) | 10 (3.2) |
| Alanine aminotransferase increased | 3 (2.0) | 3 (1.9) | 6 (1.9) |
| Amylase increased | 1 (0.7) | 4 (2.5) | 5 (1.6) |
| Diarrhea | 3 (2.0) | 2 (1.2) | 5 (1.6) |
| Aspartate aminotransferase increased | 0 | 4 (2.5) | 4 (1.3) |
| Fatigue | 1 (0.7) | 3 (1.9) | 4 (1.3) |
| Hyperglycemia | 1 (0.7) | 3 (1.9) | 4 (1.3) |
| Lipase increased | 3 (2.0) | 1 (0.6) | 4 (1.3) |
| Pneumonitis | 2 (1.3) | 1 (0.6) | 3 (1.0) |

| Preferred term, n (%) | dMMR/MSI-H EC N=153 | MMRp/MSS EC N=161 | Overall N=314 |
|---|---|---|---|
| **Grade ≥2 irTRAEs occurring in ≥2% of patients[a]** | | | |
| Hypothyroidism | 13 (8.5) | 13 (8.1) | 26 (8.3) |
| Alanine aminotransferase increased | 5 (3.3) | 3 (1.9) | 8 (2.5) |
| Aspartate aminotransferase increased | 2 (1.3) | 5 (3.1) | 7 (2.2) |
| Arthralgia | 6 (3.9) | 4 (2.5) | 10 (3.2) |
| **Grade ≥3 irTRAEs occurring in ≥1% of patients** | | | |
| Alanine aminotransferase increased | 3 (2.0) | 3 (1.9) | 6 (1.9) |
| Aspartate aminotransferase increased | 0 | 4 (2.5) | 4 (1.3) |
| Pneumonitis | 2 (1.3) | 1 (0.6) | 3 (1.0) |
| **Any-grade TRAE leading to discontinuation in ≥1% of patients** | | | |
| Alanine aminotransferase increased | 2 (1.3) | 3 (1.9) | 5 (1.6) |
| Aspartate aminotransferase increased | 1 (0.7) | 2 (1.2) | 3 (1.0) |
| Pneumonitis | 2 (1.3) | 1 (0.6) | 3 (1.0) |

[a]Immune-related AEs were defined as grade 2 and above from a predefined list.
AE, adverse event; dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune related; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable; TRAE, treatment-related adverse event.

Oaknin A. et al . Presented at ASCO Meeting 2022

Dostarlimab no está aprobado en la población con cáncer de endometrio pMMR/MSS.

Dostarlimab en proceso de negociación de precio y reembolso

# dMMR/MSI-H ECs originate from different pathways
## Does this matter?

### Immunohistochemistry
### A 4-panel IHC test for MLH1, MSH2, MSH6 and PMS2

- If the MSH2, MSH6 or isolated PMS2 IHC results are abnormal

↓

genetic testing of germline DNA to confirm Lynch syndrome

- If MLH1 (or MLHI and PMS2) are abnormal

↓

MLH1 promoter hypermethylation testing on tumour DNA

↓

**Methylation of the MLH1** promoter: **Sporadic**

↓

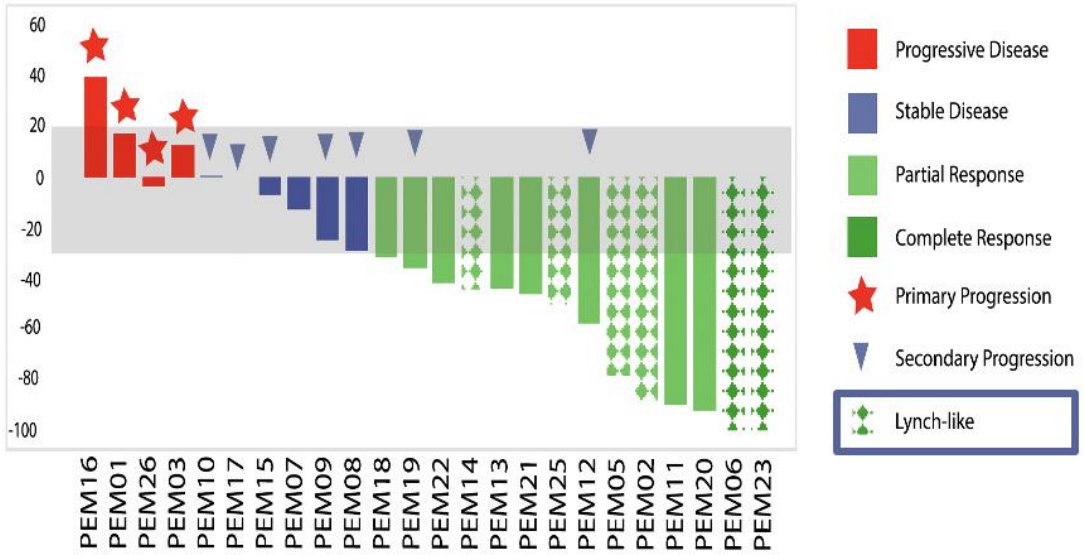
**No Methylation of the MLH1** promoter: **Confirm Lynch Sd by genetic testing**

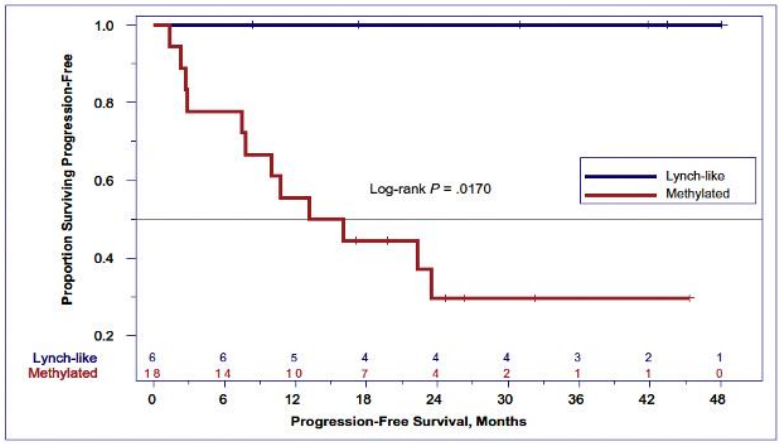
Borden et al. Am J Clinical Path, 2022.

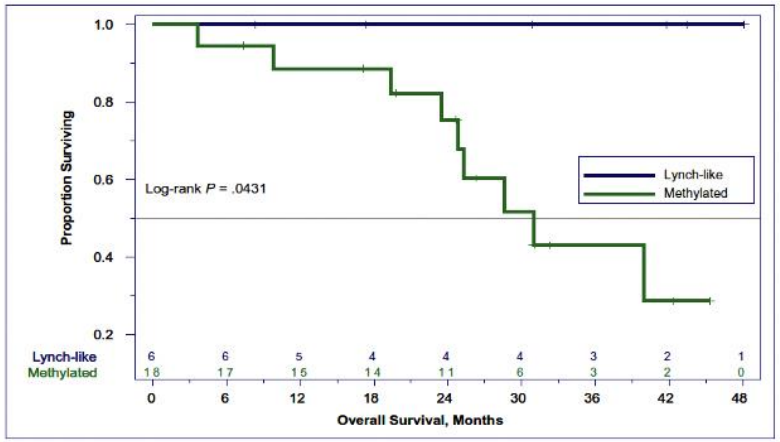
# COULD MECHANISMS UNDERLYING DMMR/MSI-H EC ALTER RESPONSES TO ICI?
## DATA FROM PEMBROLIZUMAB STUDIES

-Study enrollment = 25 patients
-24 evaluable for response
-14 CR/PR = 58.3%
-Clinical Benefit = 83.3%

**6** somatic loss MMR prot: **Lynch-Like**
**19** Methylated



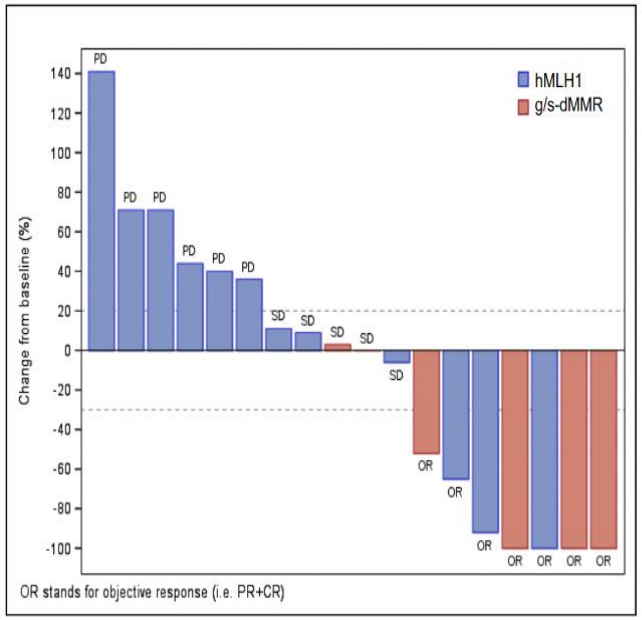

Median follow-up was 25.8 months


Bellone S. et al. Cancer. 2022 Mar 15;128(6):1206-1218.
Bellone S. et al. Annals of Oncology, Vol 32, Issue 8,2021, 1045-1046;


ClinicalTrial.gov: NCT02899793

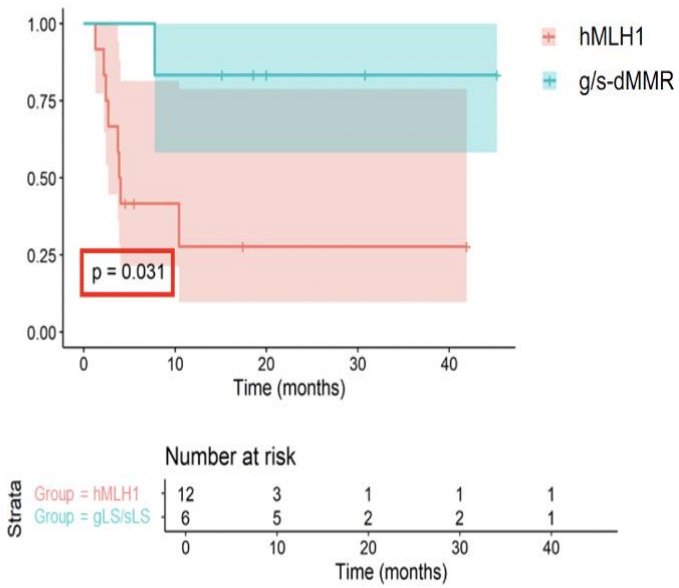
# COULD MECHANISMS UNDERLYING DMMR/MSI-H EC ALTER RESPONSES TO ICI?
## DATA FROM PEMBROLIZUMAB STUDIES(2)

### Objective Response Rates



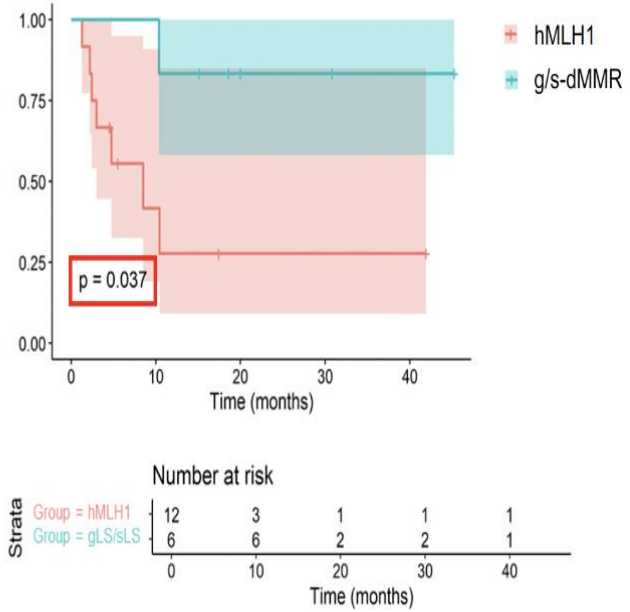

**ORR:** 38.8%(7/18 pts)
**g/s-dMMR:66.7%**(4/6 pts)
**hMLH1:25.0%**(3/12pts)
P = 0.141

### Recurrence-Free Survival




**Median RFS**
hMLH1: 4.0 mos
g/s-dMMR: NR

### Overall Survival




**Median OS**
hMLH1: 8.5mos
g/s-dMMR: NR

Lindsay Borden et al. Presented at SGO Meeting, March 2022

Median follow-up: 9.5 months

# COULD MECHANISMS UNDERLYING DMMR/MSI-H EC ALTER RESPONSES TO ICI?
## DATA FROM POST-HOC ANALYSIS GARNET( DOSTARLIMAB)

- No differences in ORR or DOR by MMR heterodimer loss pattern

| MMR protein staining pattern (IHC) | Patients, N | Responders, n | ORR, % (95% exact CI) | DOR median (95% CI), mo |
|---|---|---|---|---|
| Cohort A1 (dMMR/MSI-H EC) | 143 | 65 | 45.5 (37.1–54.0) | NR (38.9–NR) |
| MLH1–PMS2 dimer loss | 94 (66%) | 46 | **48.9** (38.5–59.5) | NR (34.7–NR) |
| MSH2–MSH6 dimer loss | 16 (11%) | 9 | **56.3** (29.9–80.2) | NR (13.9–NR) |
| Other[a] | 33 (23%) | 10 | 30.3 (15.6–48.7) | NR (13.7–NR) |

[a]Other: any other pattern of loss that is not exclusively MLH1–PMS2 or MSH2–MSH6 dimer loss. This group includes 17 patients with loss of expression of 1 MMR protein, 13 with loss of 3 proteins, 1 with loss of 2 proteins that are not a canonical dimer, and 2 with MMR unknown/MSI-H status

Anna V. Tinker et al. Presented at IGCS Meeting, NYC 2022

# COULD MECHANISMS UNDERLYING DMMR/MSI-H EC ALTER RESPONSES TO ICI?
## DATA FROM POST-HOC ANALYSIS GARNET( DOSTARLIMAB)

- No difference in ORR or DOR in those with MLH1 loss by mutation status

| | Patients, N | Responders, n | ORR, % (95% exact CI) | DOR median (95% CI), mo |
|---|---|---|---|---|
| Cohort A1 (dMMR/MSI-H EC) | 143 | 65 | 45.5 (37.1–54.0) | NR (38.9–NR) |
| Cohort A1 patients with available mutation data | 101 | — | — | — |
| MLH1 loss **by** IHC (any pattern)[a] | 78 | 31 | 39.7 (28.8–51.5) | NR (38.9–NR) |
| **MLH1 loss by IHC (any pattern) and mutation in *MLH1* or *PMS2* genes** | 7 (9%) | 3 | 42.9 (9.9–81.6) | NR (NR–NR) |
| **MLH1 loss by IHC (any pattern) and no mutation in *MLH1* or *PMS2* genes** | 71 (91%) | 28 | 39.4 (28.0–51.7) | NR (38.9–NR) |

MMR protein status (presence or loss of expression) was determined **by local or central IHC; MMR gene mutation** status was determined by central testing **with Foundation One**

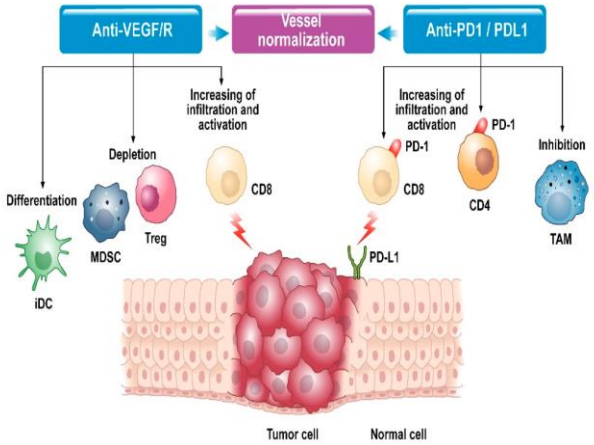
Ana Oaknin MD PhD

Anna V. Tinker et al. Presented at IGCS Meeting, NYC 2022

# Combination Approaches: Leveraging ICI's Activity

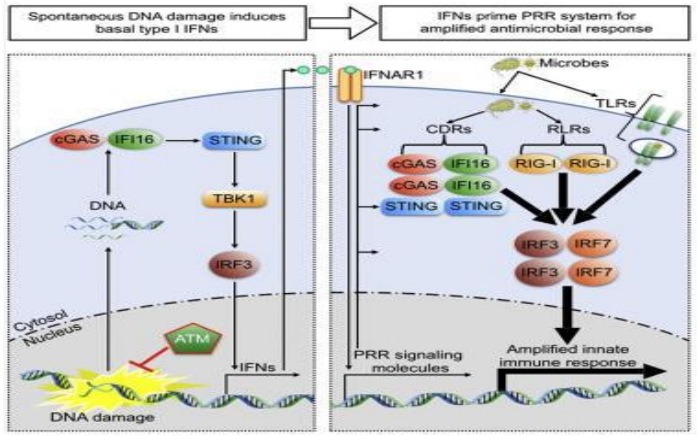
## Antiangiogenic Agents

- Reduction in Treg activity
- Reversal of immunosuppressive effects of VEGF
- Improved T-cell trafficking and infiltration of CD8+ into the tumor bed



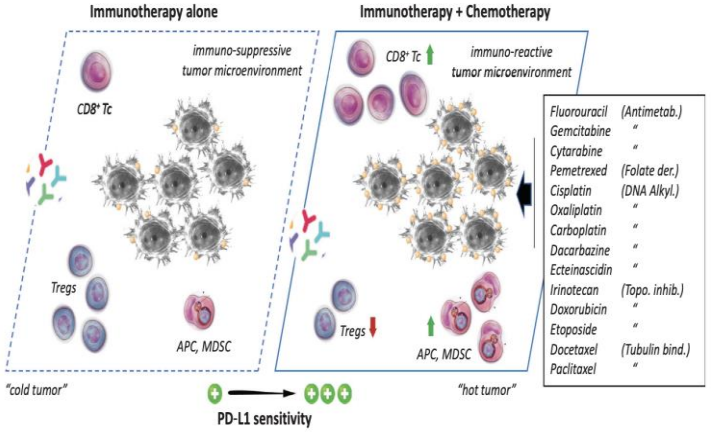

## PARP inhibitors

- Enhanced DNA Damage with increased CD8+T Cells
- Potential Synergistic antitumor activity partly mediated by STING pathway




## Chemotherapy

- Immunogenic cell death
- Enhanced presentation of tumor specific antigens
- Increased T-Cell activation by DC




DC: Dendritic Cells
STING: Stimulator of Interferon Genes

Ciciola P, et al. J Clin Med. 2020; Bailly C, et al. NAR Cancer. 2020;Huang J.,et al. *Biochem and Biophy Res Comm*. 2015; 463:551-6; Sen et al. Cancer Discov 2019

# KEYNOTE-775: Study design

**Phase III trial to compare the efficacy and safety of lenvatinib + pembrolizumab vs. treatment of physician's choice in participants with advanced EC**

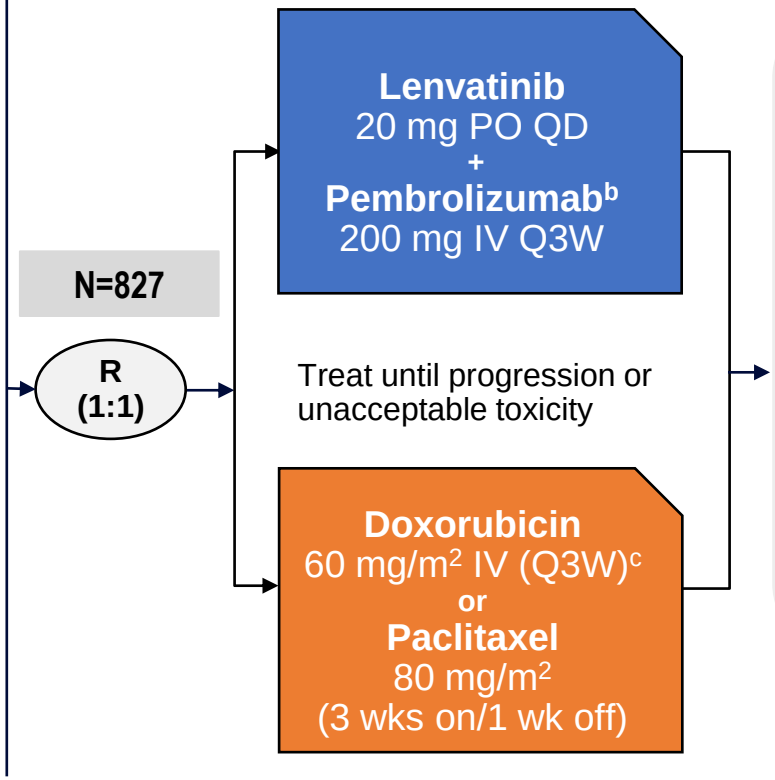
**Key eligibility criteria**

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- One prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

**Stratification factors**

**MMR status** (pMMR vs dMMR) & further stratification within pMMR by:

- Region (1: Europe, USA, Canada, Australia, NZ, and Israel vs 2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)




**Primary endpoints**
- PFS by BICR
- OS

**Secondary endpoints**
- ORR
- HRQoL
- PK
- Safety

**Key exploratory endpoint**
- DOR

[a]Patients may have received up to two prior platinum-based CT regimens if given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m².
BICR, Blinded Independent Central Review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status;
DOR, duration of response; HRQoL, health-related quality of life; pMMR, mismatch repair-proficient; ORR, objective response rate; PK, pharmacokinetics.

Makker V, *et al. N Engl J Med* 2022; 386: 437–448.

# KEYNOTE-775: Baseline Characteristics

| | LEN + pembro (n = 411) | TPC (n = 416) |
|---|---|---|
| Median age (range), years | 64 (30-82) | 65 (35-86) |
| MMR status: pMMR / dMMR, % | 84.2 / 15.8 | 84.4 / 15.6 |
| Prior history of pelvic radiation, % | 40.9 | 41.6 |
| ECOG 0 / 1, %[a] | 59.9 / 39.9 | 57.9 / 42.1 |
| Race: White / Black / Asian / other, %[b] | 63.5 / 4.1 / 20.7 / 2.9 | 59.1 / 3.4 / 22.1 / 4.8 |
| Histology at diagnosis, %[c] | | |
| Endometrioid carcinoma High-grade / low-grade / not specified[d] | 22.9 / 14.4 / 21.9 | 21.6 / 13.0 / 26.4 |
| Serous carcinoma | 25.1 | 27.6 |
| Clear cell carcinoma | 7.3 | 4.1 |
| Mixed | 5.4 | 3.8 |
| Prior lines of systemic treatment 1 / ≥ 2, % | 72.3 / 27.7 | 66.6 / 33.4 |
| Prior lines of platinum-based treatment 1 / 2, %[e] | 79.3 / 20.2 | 75.7 / 24.3 |
| Prior neo-adjuvant and/or adjuvant treatment, % | 54.5 | 60.3 |

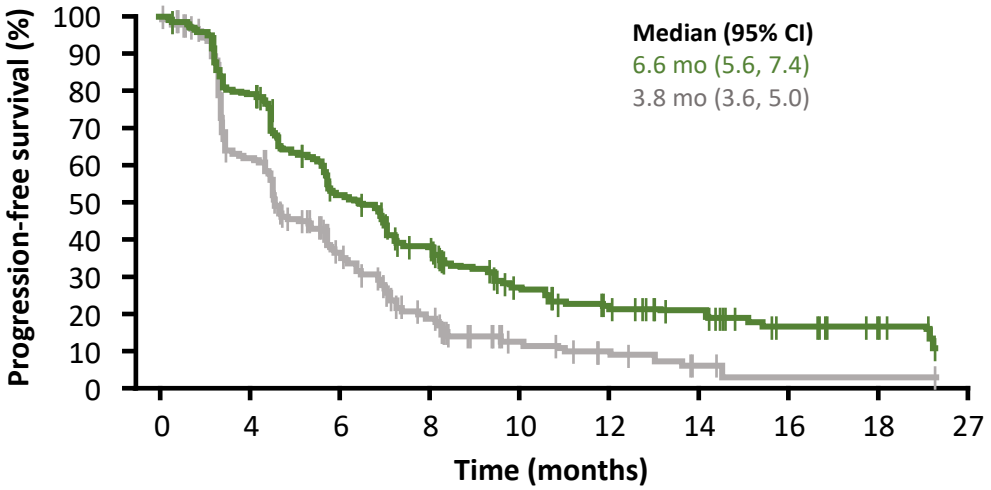
[a]0.2% of patients in the lenvatinib plus pembrolizumab group had an ECOG score deviation of 3. [b]Includes American Indian or Alaska native, native Hawaiian or other Pacific islander. 8.8% of patients in the LEN + pembro group and 10.6% of patients in the TPC group were missing information on race. [C]Other histology at diagnosis included mucinous, undifferentiated, and neuroendocrine (LEN + PEMBRO: 1.7%; TPC: 0.96%). Histology was unclassified for 0% patients in the LEN + PEMBRO arm, and 0.7% in the TPC arm. [d]Endometrioid Histology includes: Low Grade, High Grade, Endometrioid, and Endometrioid with Squamous Differentiation. Tx, treatment.

Makker V, *et al. N Engl J Med* 2022; 386: 437–448.

# KEYNOTE-775: 1º End-Point

## PFS in pMMR and All-Comers

### pMMR

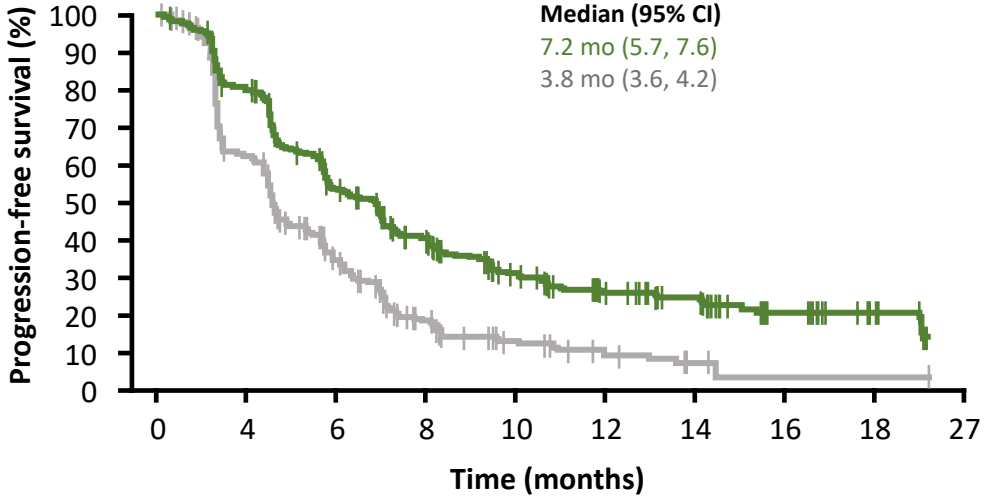



No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 346 | 264 | 165 | 112 | 60 | 39 | 30 | 12 | 5 | 0 |
| 351 | 177 | 83 | 37 | 15 | 8 | 3 | 1 | 1 | 0 |

| | Events | HR (95% CI) | p-value |
|---|---|---|---|
| LEN + pembro | 247 | 0.60 (0.50, 0.72) | < 0.0001 |
| TPC | 238 | | |

### All-Comers




No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 411 | 316 | 202 | 144 | 86 | 56 | 43 | 17 | 6 | 0 |
| 416 | 214 | 95 | 42 | 18 | 10 | 4 | 1 | 1 | 0 |

| | Events | HR (95% CI) | p-value |
|---|---|---|---|
| LEN + pembro | 281 | 0.56 (0.47, 0.66) | < 0.0001 |
| TPC | 286 | | |

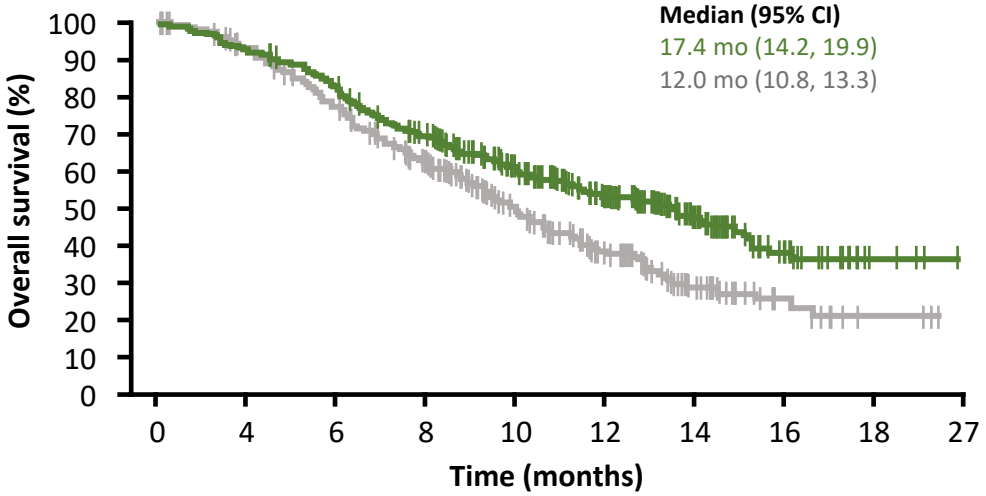
Makker V, *et al. N Engl J Med* 2022; 386: 437–448.

aEC, advanced EC; HR, hazard ratio; LEN, lenvatinib; pembro, pembrolizumab; TPC, treatment of physician's choice.

# KEYNOTE-775: 1º End-Point

## OS in pMMR and All-Comers

### pMMR

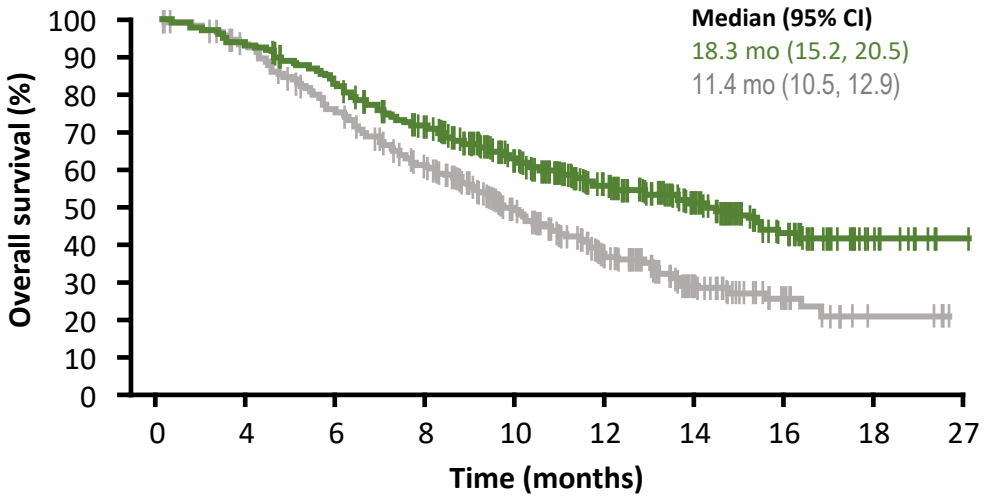



No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 346 | 322 | 285 | 232 | 160 | 109 | 62 | 28 | 5 | 0 |
| 351 | 319 | 262 | 201 | 120 | 70 | 33 | 11 | 3 | 0 |

| | Events | HR (95% CI) | p-value |
|---|---|---|---|
| LEN + pembro | 165 | 0.68 (0.56, 0.84) | < 0.0001 |
| TPC | 203 | | |

### All-Comers




No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 411 | 383 | 337 | 282 | 198 | 136 | 81 | 40 | 7 | 0 |
| 416 | 373 | 300 | 228 | 138 | 80 | 40 | 11 | 3 | 0 |

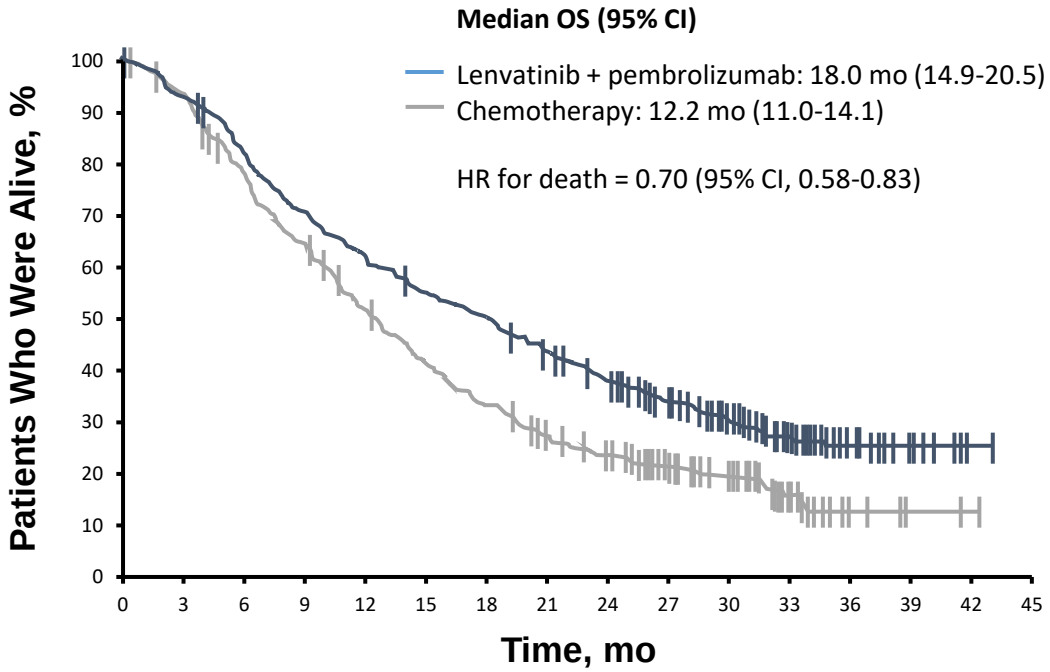
| | Events | HR (95% CI) | p-value |
|---|---|---|---|
| LEN + pembro | 188 | 0.62 (0.51, 0.75) | < 0.0001 |
| TPC | 245 | | |

Median follow-up: 11.4 months

Makker V, *et al. N Engl J Med* 2022; 386: 437−448.

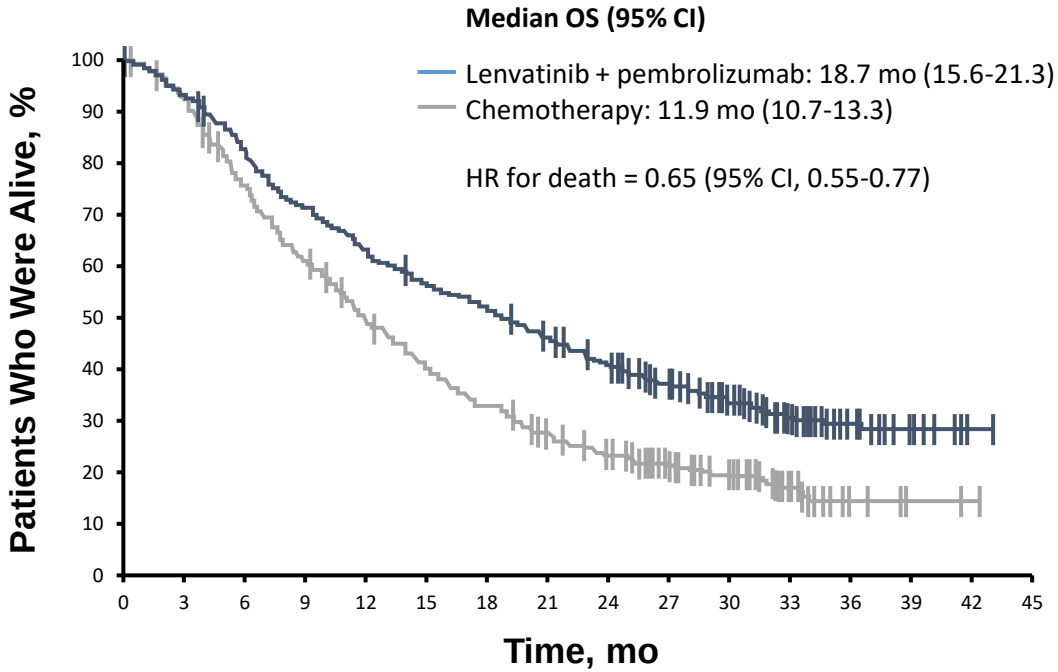
# KEYNOTE-775:
# Final Prespecified Analysis for Overall Survival

## pMMR Population




| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + pembrolizumab | 346 | 322 | 285 | 242 | 214 | 188 | 171 | 148 | 124 | 95 | 65 | 41 | 20 | 7 | 2 |
| Chemotherapy | 351 | 324 | 267 | 217 | 171 | 138 | 111 | 86 | 71 | 53 | 40 | 21 | 6 | 3 | 1 |

## All-Comer Population



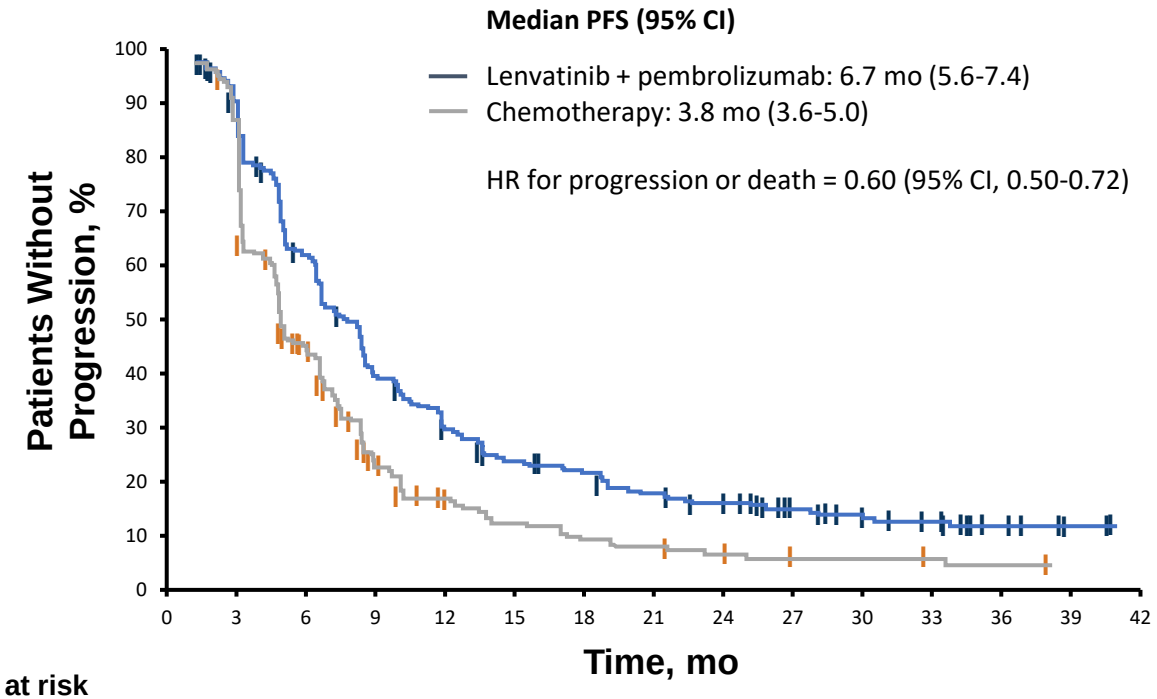

| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + pembrolizumab | 411 | 383 | 337 | 292 | 258 | 229 | 211 | 186 | 160 | 125 | 91 | 58 | 30 | 10 | 2 |
| Chemotherapy | 416 | 378 | 305 | 246 | 196 | 158 | 129 | 104 | 84 | 64 | 49 | 28 | 6 | 3 | 1 |

[a] In the chemotherapy arm, 10.0% of patients in the pMMR population and 8.7% of patients in the all-comer population received subsequent lenvatinib plus pembrolizumab. After excluding these patients, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71). Median follow-up time: 14.7 months (data cutoff date: 1 March 2022; >16 months of additional follow-up from initial publication).

1. Makker V et al. *N Engl J Med* 2022;386:437-448. 2. Makker V et al. ESMO 2022. Abstract 525MO; Makker V et al J Clin Oncol 00. 

# KEYNOTE-775:
# Update PFS With Longer Follow-Up

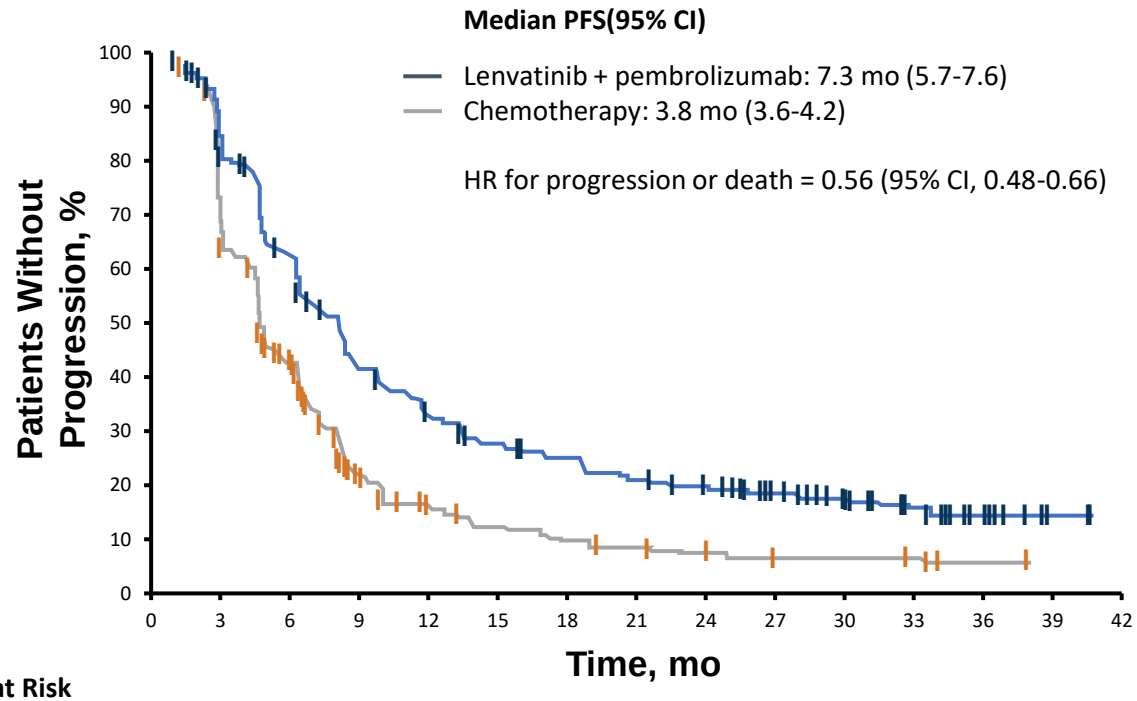
## pMMR Population




**No. at risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + pembrolizumab | 346 | 265 | 166 | 116 | 80 | 61 | 55 | 43 | 36 | 24 | 18 | 14 | 6 | 4 | 0 |
| Chemotherapy | 351 | 177 | 83 | 38 | 23 | 16 | 12 | 9 | 6 | 4 | 3 | 3 | 1 | 0 | 0 |

## All-Comer Population




**No. at Risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + pembrolizumab | 411 | 317 | 203 | 148 | 109 | 87 | 79 | 65 | 57 | 45 | 35 | 23 | 10 | 4 | 0 |
| Chemotherapy | 416 | 214 | 95 | 43 | 27 | 19 | 15 | 11 | 8 | 6 | 5 | 5 | 1 | 0 | 0 |

[a] Median follow-up time: 14.7 months; data cutoff date: 1 March 2022; >16 months of additional follow-up from initial publication. PFS by BICR per RECIST v1.1.

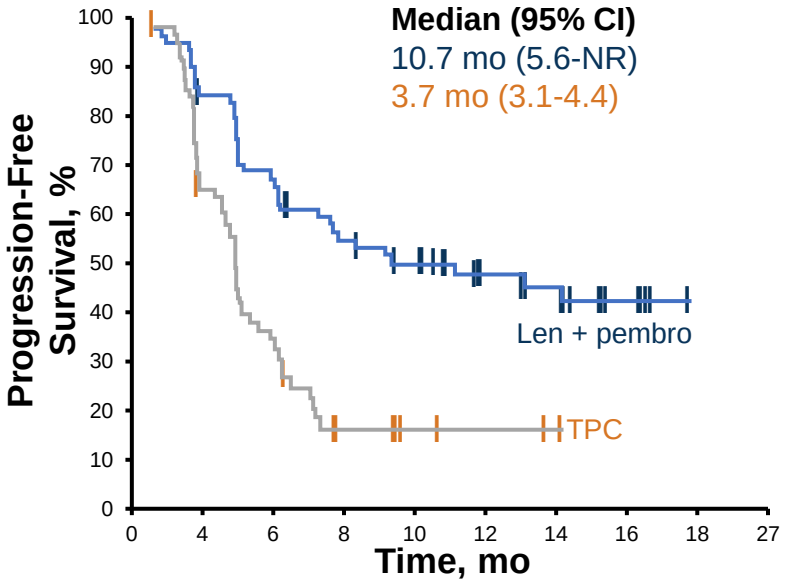
# KEYNOTE-775: Response Rates

| | pMMR | | All-Comer Population | |
|---|---|---|---|---|
| | **LEN + Pembro** (n = 346) | **Chemotherapy** (n = 351) | **LEN + Pembro** (n = 411) | **Chemotherapy** (n = 416) |
| **ORR**, % (95% CI) | **32.4** (27.5, 37.6) | **15.1 (11.5, 19.3)** | **33.8** (29.3, 38.6) | **14.7 (11.4, 18.4)** |
| **BOR**, % (95% CI) | | | | |
| Complete response | **5.8** (3.6, 8.8) | 2.6 (1.2, 4.8) | **7.5** (5.2, 10.5) | 2.6 (1.3, 4.7) |
| Partial response | **26.6** (22.0, 31.6) | 12.5 (9.3, 16.5) | **26.3** (22.1, 30.8) | 12.0 (9.1, 15.5) |
| Stable disease | 46.5 (41.2, 51.9) | 39.6 (34.4, 44.9) | 45.0 (40.1, 50.0) | 40.1 (35.4, 45.0) |
| Progressive disease | 15.6 (11.9, 19.9) | 30.8 (26.0, 35.9) | 14.8 (11.5, 18.7) | 29.6 (25.2, 34.2) |
| Not evaluable | 0.6 (0.1, 2.1) | 2.0 (0.8, 4.1) | 1.2 (0.4, 2.8) | 1.9 (0.8, 3.8) |
| No assessment | 4.9 (2.9, 7.8) | 12.5 (9.3, 16.5) | 5.1 (3.2, 7.7) | 13.7 (10.5, 17.4) |
| **Disease control rate**, % (95% CI) | 72.0 (66.9, 76.6) | 46.4 (41.1, 51.8) | 72.3 (67.7, 76.5) | 46.6 (41.8, 51.6) |
| **Median DOR**, mo (range) | 9.3 (1.6+ to 39.5+) | 5.7 (0+ to 37.1+) | 12.9 (1.6+ to 39.5+) | 5.7 (0+ to 37.1+) |
| **Median TTR**, mo (range) | 2.1 (1.5 to 23.0) | 3.5 (1.0 to 7.4) | 2.1 (1.5 to 23.0) | 2.1 (1.0 to 7.4) |

1. Makker V et al. *N Engl J Med* 2022;386:437-448. 2. Makker V et al. ESMO 2022. Abstract 525MO ; .

# Exploratory Analysis in the dMMR Population

## PFS

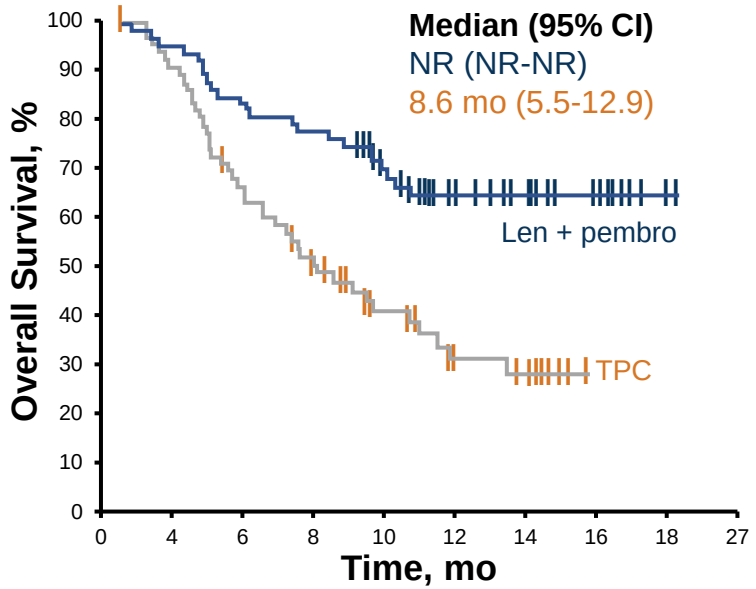



No. at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 65 | 52 | 37 | 32 | 26 | 17 | 13 | 5 | 1 | 0 |
| 65 | 37 | 12 | 5 | 3 | 2 | 1 | 0 | 0 | 0 |

| | Events | HR (95% CI) | *P* |
|---|---|---|---|
| LEN + pembro | 34 | 0.36 (0.23-0.57) | < .0001 |
| TPC | 48 | | |

## OS




No. at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 65 | 61 | 52 | 50 | 38 | 27 | 19 | 12 | 2 | 0 |
| 65 | 54 | 38 | 27 | 18 | 10 | 7 | 0 | 0 | 0 |

| | Events | HR (95% CI) | *P* |
|---|---|---|---|
| LEN + pembro | 23 | 0.37 (0.22-0.62) | < .0001 |
| TPC | 42 | | |

## ORR

| | Len + Pembro (n = 65) | TPC (n = 65) |
|---|---|---|
| **Objective response, % (95% CI)** | 40 (28-52.9) | 12.3 (5.5-22.8) |
| Difference vs TPC, %; *p* value | 27.7 (12.9-41.7); .0002 | |
| **Best overall response, %** | | |
| Complete response | 14 | 3 |
| Partial response | 26 | 9 |
| Stable disease | 38 | 43 |
| Progressive disease | 11 | 23 |
| Not evaluable/assessed | 5/6 | 2/20 |
| **Median DOR, mo (range)** | NR (2.1-20.4) | 4.1 (1.9-15.6) |
| **Median time to response, mo (range)** | 2.9 (1.7-16.3) | 1.9 (1.8-3.7) |
| **Disease control rate, %** | 74 | 48 |

1. Makker V et al. *New Engl J Med* 2022;386:437-448. 2. Makker V et al. IGCS 2021. Abstract O002/43.

# KEYNOTE-775: Treatment exposure, safety and discontinuation

## All-comers population

| | LEN + PEMBRO (n = 406) | TPC (n = 388) |
|---|---|---|
| Median duration of treatment, days (range) | 231 (1-817) | 104.5 (1-785) |
| Patients with any TEAEs (%) | 99.8 | 99.5 |
| Grade ≥ 3 | 88.9 | 72.7 |
| Patients with any TEAEs leading to dose reductions (%)[a] | 66.5 | 12.9 |
| Patients with any grade TEAEs leading to discontinuation (%)[b] | 33.0 | 8.0 |
| LEN[c] | 30.8 | -- |
| Pembro[c] | 18.7 | -- |
| LEN + pembro | 14.0 | -- |
| Patients with any grade TEAEs leading to interruption (%)[b] | 69.2 | 27.1 |
| LEN[c] | 58.6 | -- |
| Pembro[c] | 50.0 | -- |
| LEN + pembro | 30.8 | -- |

[a]Includes LEN only or TPC; [b]Includes LEN or pembro or LEN + pembro or TPC; [c]Regardless of action taken with the other drug in the combination arm.
LEN + pembro, lenvatinib plus pembrolizumab; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

Makker V, et al. New Engl J Med 2022; 386:437–448.

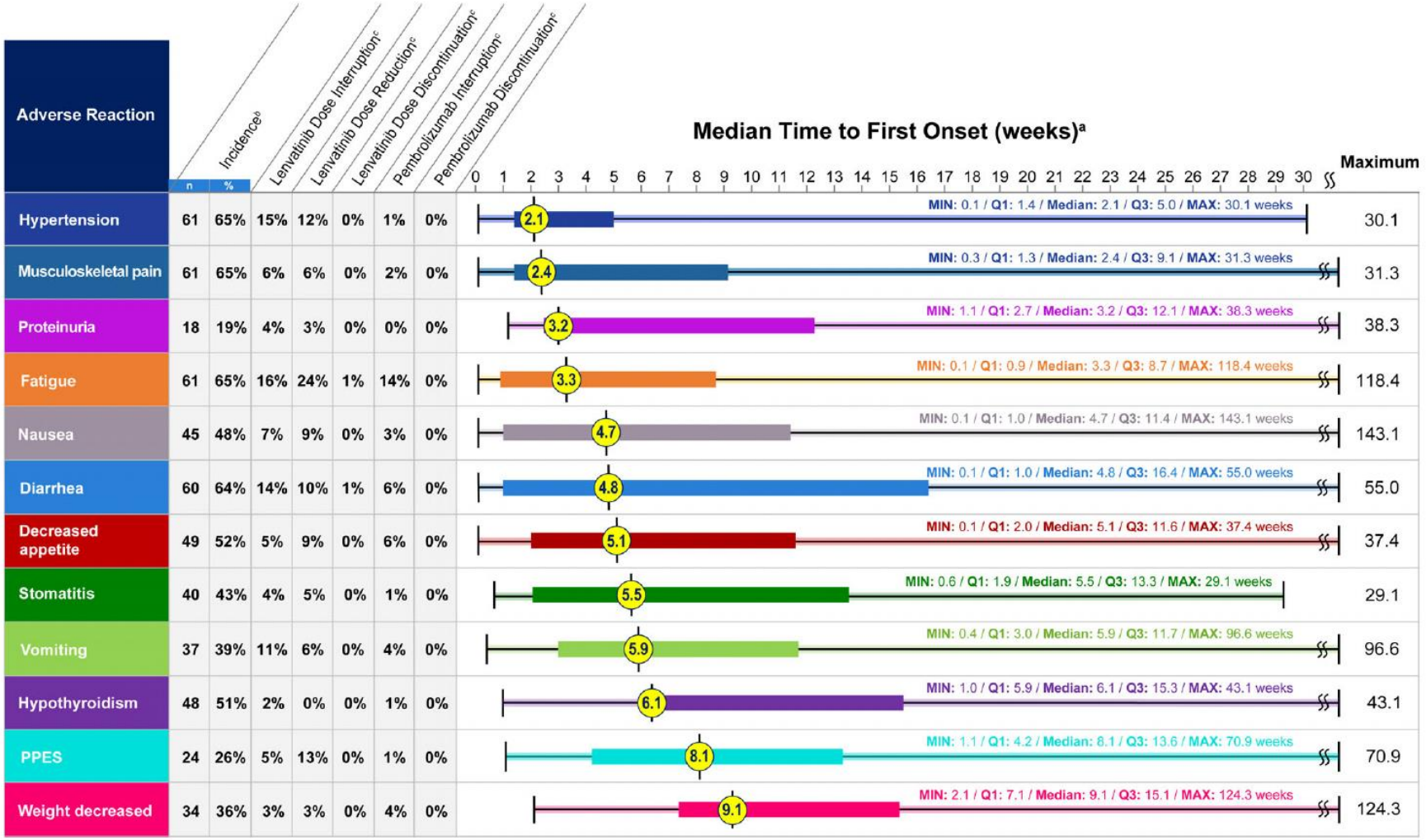
# KEYNOTE-775: TEAEs with frequency ≥25% in all-comers

| | LEN + PEMBRO (n = 406) | | TPC (n = 388) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3a | Any Grade | Grade ≥3a |
| Patients with any TEAEs (%) | 99.8 | 88.9 | 99.5 | 72.7 |
| Hypertension | 64.0 | 37.9 | 5.2 | 2.3 |
| Hypothyroidism** | 57.2 | 1.2 | 0.8 | 0.0 |
| Diarrhea | 54.2 | 7.6 | 20.1 | 2.1 |
| Nausea | 49.5 | 3.4 | 46.1 | 1.3 |
| Decreased appetite | 44.8 | 7.9 | 21.1 | 0.5 |
| Vomiting | 36.7 | 2.7 | 20.9 | 2.3 |
| Weight decrease | 34.0 | 10.3 | 5.7 | 0.3 |
| Fatigue | 33.0 | 5.2 | 27.6 | 3.1 |
| Arthalgia | 30.5 | 1.7 | 8.0 | 0.0 |
| Proteinuria | 28.8 | 5.4 | 2.8 | 0.3 |
| Anemia | 26.1 | 6.2 | 48.7 | 14.7 |
| Constipation | 25.9 | 0.7 | 24.7 | 0.5 |
| Urinary tract infection | 25.6 | 3.9 | 10.1 | 1.0 |
| Headache | 24.9 | 0.5 | 8.8 | 0.3 |
| Asthenia | 23.6 | 5.9 | 24.5 | 3.9 |
| Neutropenia | 7.4 | 1.7 | 33.8 | 25.8 |
| Alopecia | 5.4 | 0.0 | 30.9 | 0.5 |

[a]Includes LEN only or TPC; [b]Includes LEN or pembro or LEN + pembro or TPC; [c]Regardless of action taken with the other drug in the combination arm.
LEN + pembro, lenvatinib plus pembrolizumab; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

Makker V, et al. New Engl J Med 2022; 386:437–448.

# Safety Profile Lenvatinib Plus Pembrolizumab:
## Median time to First Onset of Adverse Events




Makker V et al.The Oncologist 2021;26:e1599–e1608

[a]Median time to first onset in patients who experienced the adverse reaction.

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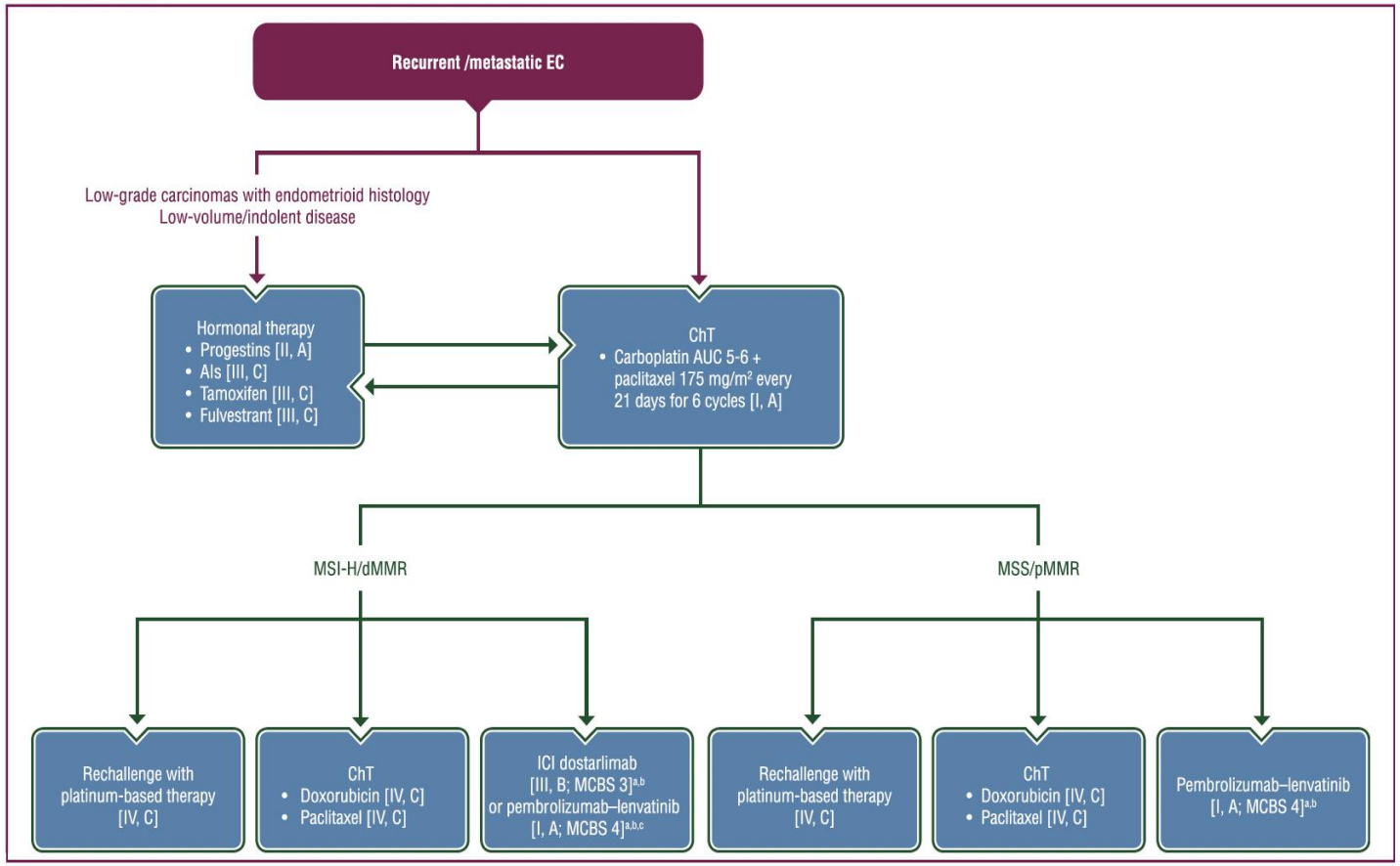
SPECIAL ARTICLE

# Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆




Oaknin A. et al Ann Oncol. 2022 Sep;33(9):860-877;

# Conclusions:

- Endometrial cancers have relatively high proportions of TMB-H and MSI-H/dMMR tumors, providing rationale for treatment with checkpoint inhibitors.
- The MSI-H/dMMR phenotype has emerged as a predictive biomarker for checkpoint inhibitor therapy.
- A number of checkpoint inhibitors  such as Dostarlimab and Pembrolizumab have shown clinically meaningful activity in MSI-H/dMMR EC as monotherapy
- Further research is needed to determine whether the origin of MSI-H/dMMR phenotype will have therapeutic implications.
- Checkpoint inhibitors in combination with antiangiogenic drug have shown compelling activity, which has led to regulatory approval.
- There are a large number of clinical trials studying ICI in different EC settings that will continue paving the treatment pathway.