# Practical Management Pearls for Immunotherapy for the Treatment of Gynecologic Cancer: Endometrial Cancer

SITC CPG Webinar

Thursday September 7, 2023

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# Case 1:

- 56 yo with recurrent metastatic endometrioid adenocarcinoma of the uterus on pembrolizumab and lenvatinib
  - Develops non-bloody diarrhea 4 weeks into treatment
  - 6 episodes above baseline

What are your next steps?

a. Hold lenvatinib
b. Hold pembrolizumab
c. Stop both pembrolizumab and lenvatinib
d. Dostarlimab

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- 56 yo with recurrent metastatic endometrioid adenocarcinoma of the uterus on pembrolizumab and lenvatinib
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What are your next steps?

a. Hold lenvatinib
b. Hold pembrolizumab
c. Stop both pembrolizumab and lenvatinib
d. Give Dostarlimab

# Uterine Cancer 2023

**Estimated New Cases**

| | Males | | | Females | |
|---|---|---|---|---|---|
| Prostate | 288,300 | 29% | | Breast | 297,790 | 31% |
| Lung & bronchus | 117,550 | 12% | | Lung & bronchus | 120,790 | 13% |
| Colon & rectum | 81,860 | 8% | | Colon & rectum | 71,160 | 8% |
| Urinary bladder | 62,420 | 6% | | Uterine corpus | 66,200 | 7% |
| Melanoma of the skin | 58,120 | 6% | | Melanoma of the skin | 39,490 | 4% |
| Kidney & renal pelvis | 52,360 | 5% | | Non-Hodgkin lymphoma | 35,670 | 4% |
| Non-Hodgkin lymphoma | 44,880 | 4% | | Thyroid | 31,180 | 3% |
| Oral cavity & pharynx | 39,290 | 4% | | Pancreas | 30,920 | 3% |
| Leukemia | 35,670 | 4% | | Kidney & renal pelvis | 29,440 | 3% |
| Pancreas | 33,130 | 3% | | Leukemia | 23,940 | 3% |
| **All Sites** | **1,010,310** | **100%** | | **All Sites** | **948,000** | **100%** |

**4th most common malignancy**

**Estimated Deaths**

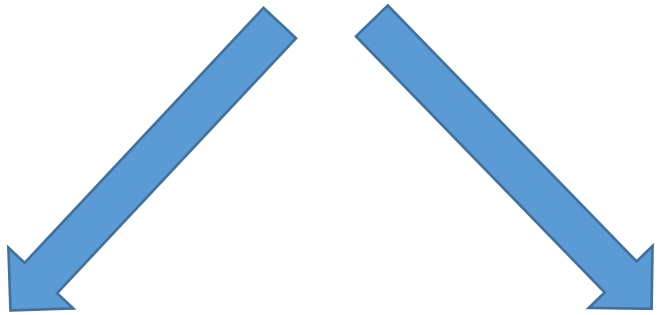
| | Males | | | Females | |
|---|---|---|---|---|---|
| Lung & bronchus | 67,160 | 21% | | Lung & bronchus | 59,910 | 21% |
| Prostate | 34,700 | 11% | | Breast | 43,170 | 15% |
| Colon & rectum | 28,470 | 9% | | Colon & rectum | 24,080 | 8% |
| Pancreas | 26,620 | 8% | | Pancreas | 23,930 | 8% |
| Liver & intrahepatic bile duct | 19,000 | 6% | | Ovary | 13,270 | 5% |
| Leukemia | 13,900 | 4% | | Uterine corpus | 13,030 | 5% |
| Esophagus | 12,920 | 4% | | Liver & intrahepatic bile duct | 10,380 | 4% |
| Urinary bladder | 12,160 | 4% | | Leukemia | 9,810 | 3% |
| Non-Hodgkin lymphoma | 11,780 | 4% | | Non-Hodgkin lymphoma | 8,400 | 3% |
| Brain & other nervous system | 11,020 | 3% | | Brain & other nervous system | 7,970 | 3% |
| **All Sites** | **322,080** | **100%** | | **All Sites** | **287,740** | **100%** |

**6th most common cause of cancer deaths**

# Endometrial Cancer 2023

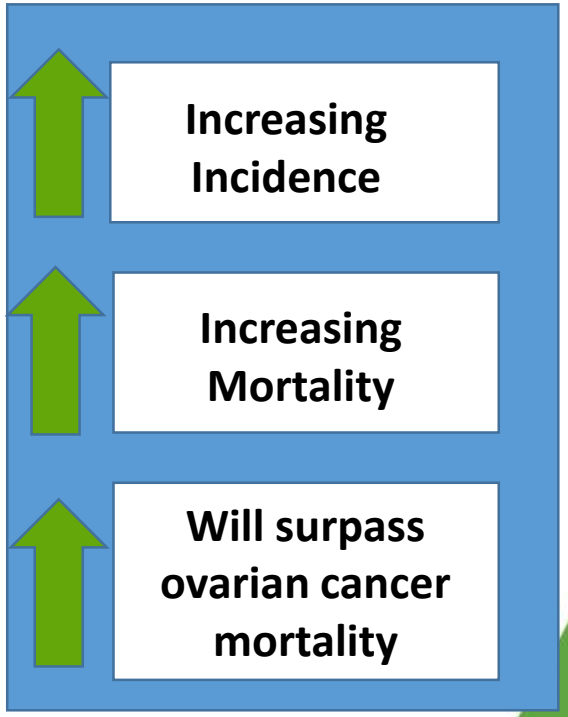
66,200 New Cases

13,030 Deaths



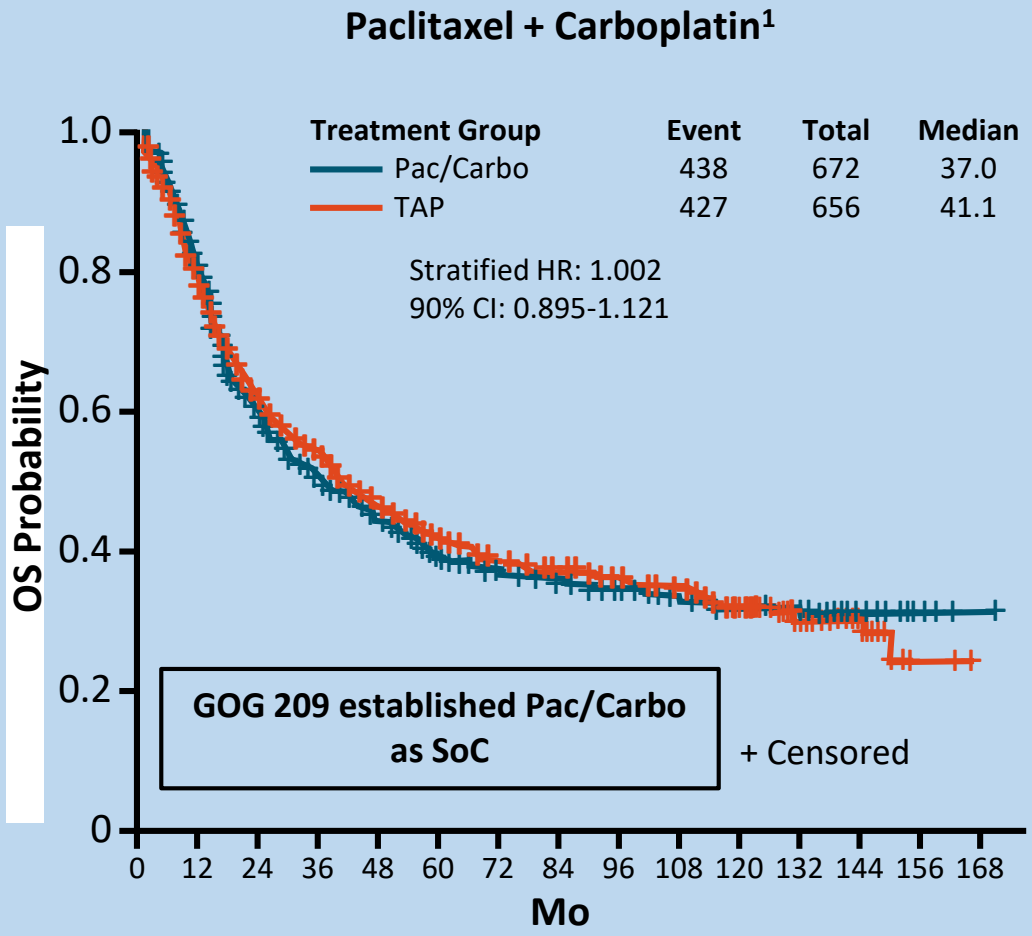
~ 2/3 will be early stage, low grade cancers

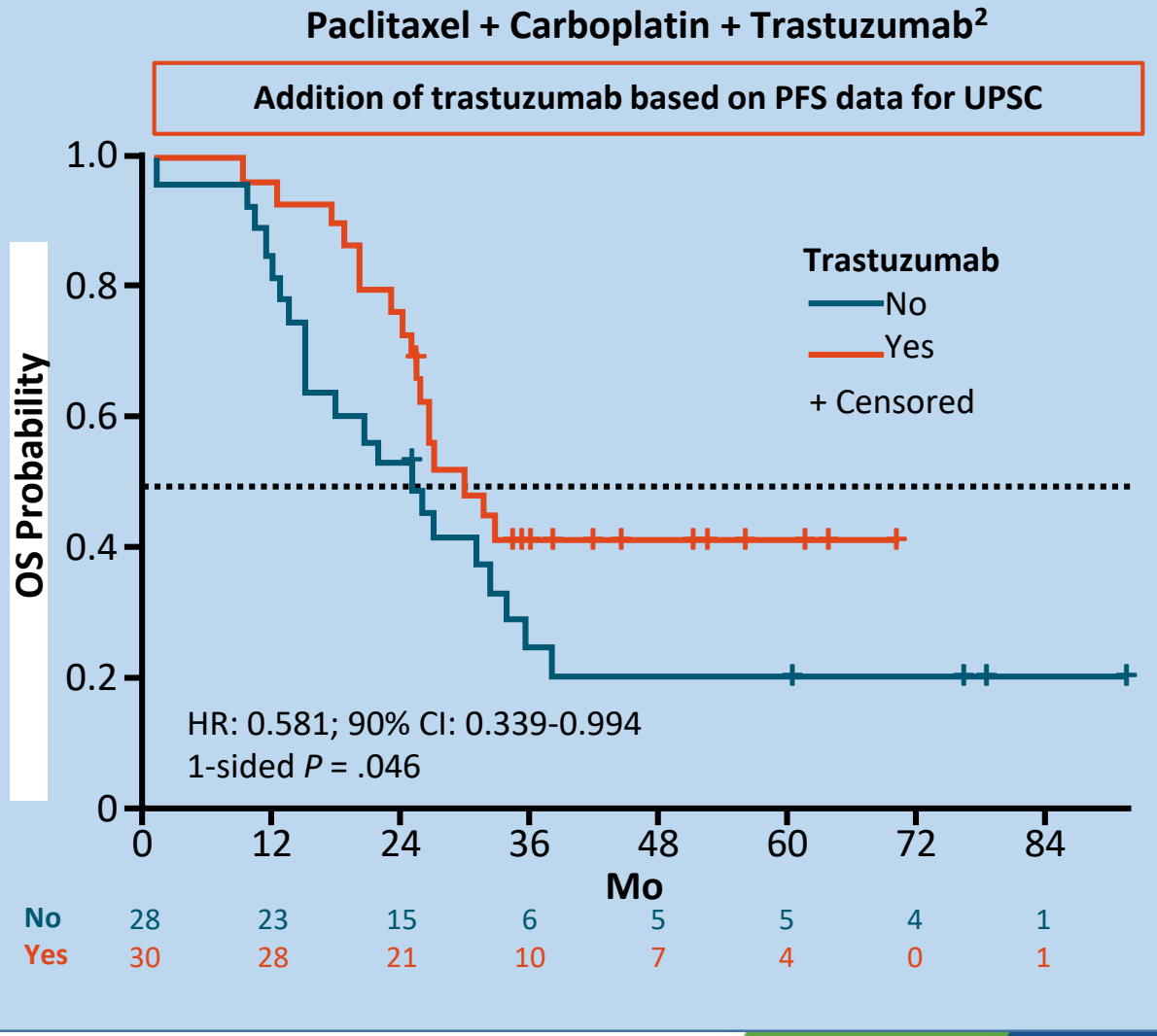
~ 1/3 will be high grade or advanced stage/metastatic disease




Siegel et al. Cancer Statistics 2023
Cancer Facts & Figures 2023. American Cancer Society. www. Cancer. org

# OS with Paclitaxel/Carboplatin for Advanced/Recurrent Endometrial Cancer




1. Miller. JCO. 2020;38:3841. 2. Fader. Clin Cancer Res. 2020;26:3928.

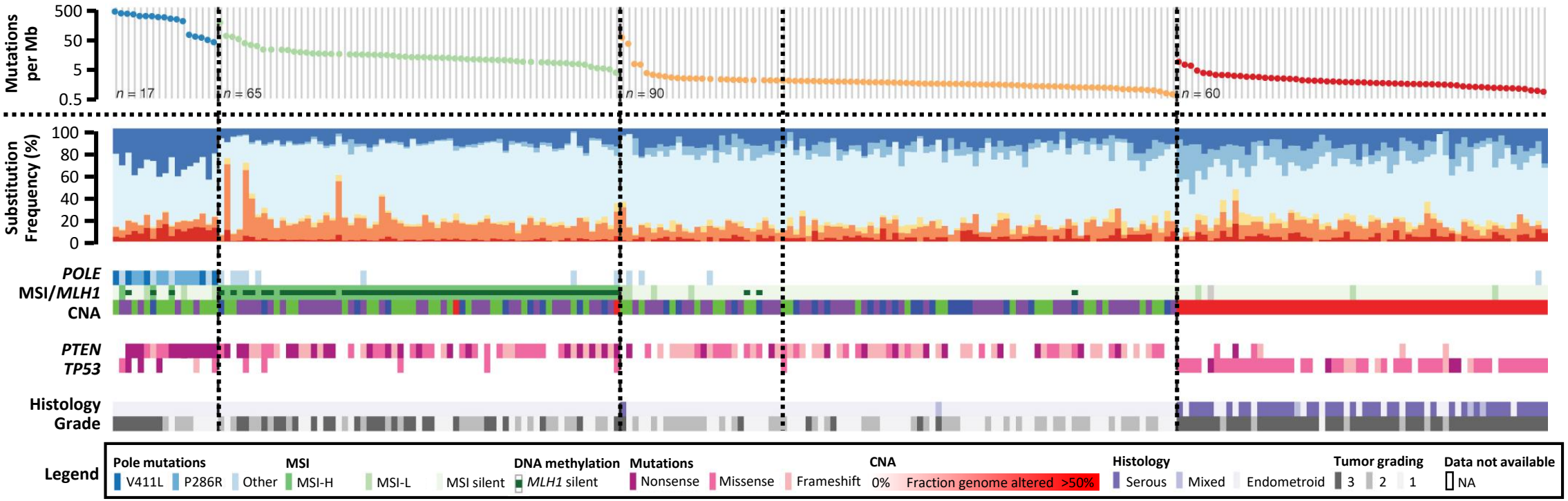
# Integrated Molecular Classification of Endometrial Cancer

*POLE* mutations are ultramutated, 100-500 mut/Mb, endometrioid, *PTEN*

MSI-H group with 10-20 mut/Mb, endometrioid, *PTEN* mutations, mixed grade

CN low: 2-3 mut/Mb, endometrioid, *PTEN* and *CTNNB1* mutations, G1

CN high: 2-3 mut/Mb, *TP53* mutations, high grade




TCGA. Nature. 2013;22;500:415.

# PD1/PDL1 Inhibitor Activity in MMRp Endometrial Cancers had been modest….

- **Keynote-028** Pembrolizumab: (n=24)
  - Advanced stage or metastatic, PDL1+ tumors (n=24)
  - ORR 13%
- **PHAEDRA trial** Durvalumab: (n=36)
  - Advanced stage or metastatic
    - ORR in pMMR 13%
- **GARNET** study Dostarlimab (n=94)
  - Recurrent, advanced stage
  - ORR in pMMR: 13.9%
- **Ph II Avelumab study** (n=16)
  - Advanced stage or metastatic
  - ORR 6.25%

Ott PA et al. J Clin Oncol. 2017;35(22):2535.
Antill PSK et al Jclin Oncol 2019.
Oaknin A et al. Gynecol Oncol 2019.
Konstantinopoulos PA et al. J Clin Oncol 2019
Pothuri et al. SGO Annual Meeting 2021

# Endometrial Cancer Enters the Immunotherapy Era: Phase II studies

- Fader et al. Previously treated dMMR-recurrent or persistent Endometrial CA
  - Pembrolizumab 10mg/kg every 2 weeks
  - **ORR=56%**

**FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication in MSI-H and dMMR cancers May 2017**

- Mismatch repair d ors to PD-1 blockade
  - Endometrial Ca (n=15) **ORR: 53%**
  - Disease Control Rate: 73%

- Phase II KEYNOTE-158 study: pembrolizumab in MSI-H/dMMR
  - Endometrial Ca (n=49) **ORR=57%**

Fader AN, et al. Presented at SGO, 2016.
Le DT et al. Science. 2017 Jul 28;357(6349):409-413.
Marabelle A et al. J Clin Oncol. 2020;38(1):1.

# GARNET Cohorts A1 + A2: Dostarlimab Monotherapy in Patients With dMMR/MSI-H or pMMR/MSS EC

| Variable | Cohort A1: dMMR/MSI-H EC | | | Cohort A2: pMMR/MSS EC | | |
|---|---|---|---|---|---|---|
| | dMMR | MSI-H and MMR-Unk | Overall | pMMR | MSS and MMR-Unk | Overall |
| | (n = 106) | (n = 2) | (n = 108) | (n = 142) | (n = 14) | (n 156) |
| Median follow-up, mo | 13.8 | 11.1 | 16.3 | 11.5 | 10.4 | 11.5 |
| Objective responses, n (%) [95% CI] | 46 (43.4) | 1 (50) | 47 (43.5) | 19 (13.4) | 3 (21.4) | 22 (14.1) |
| | [33.8-53.4] | | | | .8] | [9.1-20.6] |
| Best confirmed response, n (%) | 11 (10.4) | | | | | 3 (1.9) |
| CR | 35 (33.0) | | | | 4) | 19 (12.2) |
| PR | 13 (12.3) | | | | ) | 32 (20.5) |
| SD | 39 (36.8) | | | | 1) | 85 (54.5) |
| PD | 8 (7.5) | 1 (50.0) | 9 (8.3) | 15 (10.6) | 2 (14.3) | 17 (10.9) |
| Not evaluable | | | | | | |
| Disease control rate, n (%) | 59 (55.7) | 1 (50.0) | 60 (55.6) | 50 (35.2) | 4 (28.6) | 54 (34.6) |
| Median duration of response, mo | NR | NR | NR | NR | NR | NR |

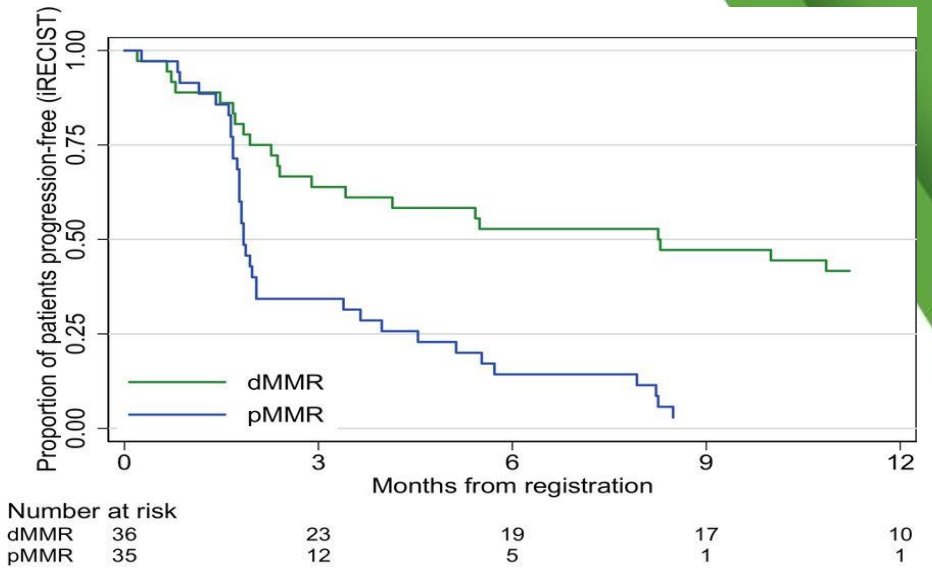
**Dostarlimab granted accelerated FDA approval for those with dMMR-recurrent or advanced endometrial cancer who progressed on or following prior therapy**
**April 2021**

Oaknin. IGCS 2021. Abstr 149. Oaknin. ESGO 2021. Abstr 272. NCT02715284.
Oaknin A. J Immunotherapy of Ca. 2022. 10

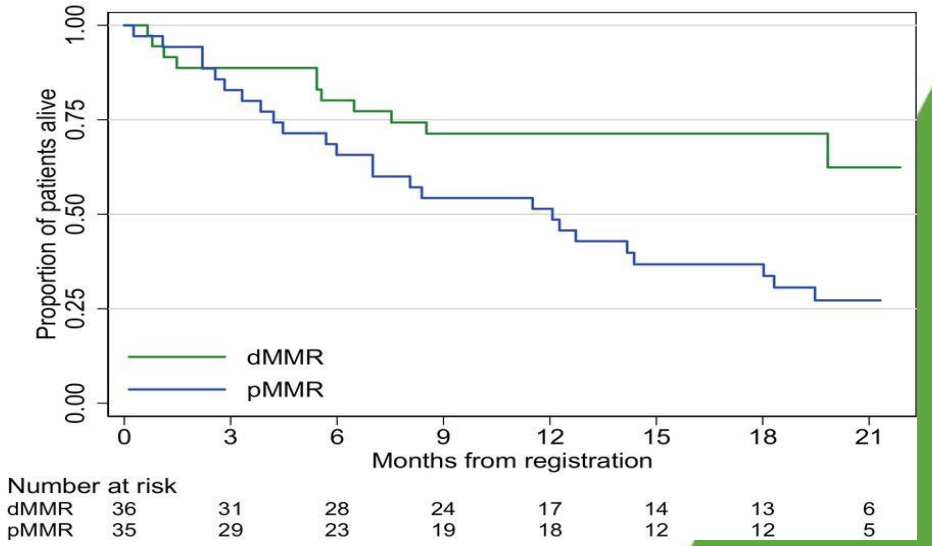
# Phase 2 PHAEDRA: Durvalumab in dMMR and pMMR advanced EC

| Variable | dMMR EC (n = 36) | pMMR EC (n = 35) |
|---|---|---|
| Median follow-up, mo | 19 | 21 |
| ORR, % | 47 | 3 |
| CR, % | 17 | 0 |
| PR, % | 31 | 3 |
| SD, % | 17 | 29 |
| PD, % | 36 | 66 |
| mPFS, mo | 8.3 | 1.8 |
| Estimated PFS at 6 mo, % | 53 | 14 |
| mOS, mo | NR | 12.1 |
| Estimated OS at 1 y, % | 71 | 51 |

**PFS**




**OS**




Anthill Y et al. J Immunotherapy Cancer. 2021; 9.

# Safety of Single-Agent Immunotherapies in EC

| Grade 3/4 AEs, % | KEYNOTE-158[1] MSI-H, All Cancers (N = 233) | GARNET[2,3] dMMR EC (n = 104) |
|---|---|---|
| Fatigue | 0.9 | 1 |
| Pruritus | 0 | 1 |
| Diarrhea | 0 | 2 |
| Nausea or vomiting | 0 | 0 |
| Arthralgia or myalgia | 0 | 0 |
| **Any Grade irAEs, %** | | |
| Hypothyroidism | 9.0 | 5.6* |
| Hyperthyroidism | 5.2 | 1.8* |
| Pneumonitis | 3.9 | 1.1* |
| Colitis | 3.9 | 1.4 |

*Out of 444 patients evaluated.

- Single-agent immunotherapy is associated with manageable, mostly low-grade AEs

1. Marabelle. JCO. 2020;38:1. 2. Oaknin. ESMO 2020. Abstr LBA36. 3. Dostarlimab PI.

# Only ~ 28% of endometrial cancers are MSI-H/MMRd
# so what do we do with those that are not?

**Checkpoint Inhibitors Plus Antiangiogenic Agents**

KEYNOTE-146[1]

KEYNOTE-775 (phase III)[2]

Makker et al. J Clin Oncol 2020. 38:2981-2992
Makker V. N Engl J Med 2022; 386:437-448

# Keynote146/Study111- Lenvatinib and Pembrolizumab in Patients With Advanced Endometrial Cancer

Makker et al. J Clin Oncol 2020. 38:2981-2992.

| ORR | PFS | OS |
|---|---|---|
| MSS = 36% | 7.4 mos | 16 mos |
| MSI-H = 63% | 18.9 mos | Not Reached |

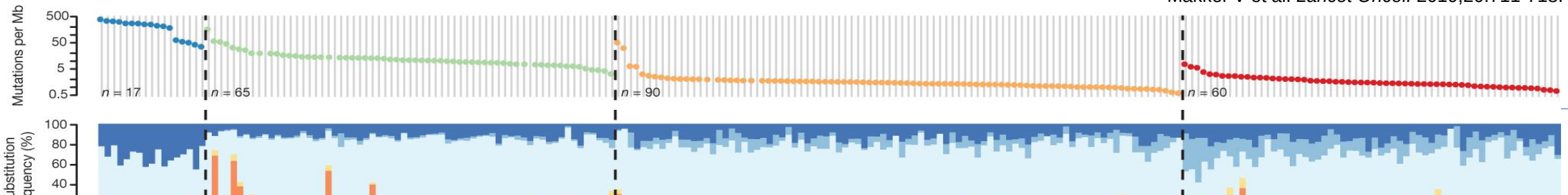
**Levatinib + Pembrolizumab**

**Better PFS**
**Hot Tumors**

**Worse PFS**
**Cold Tumors**

**POLE** | **MSI Hypermutated** | **Copy-number low (endometrioid) MSS** | **Copy-number high (serous-like)**

Makker V et al. *Lancet Oncol.* 2019;20:711-718.



# Phase II KEYNOTE-146: Safety

| Parameter | Previously Treated EC (n = 108), n (%) |
|---|---|
| **Patients with any treatment-related TEAEs** | 105 (97.2) |
| **Patients with treatment-related TEAEs leading to study drug discontinuation** | 20 (18.5) |
| Both lenvatinib and pembrolizumab | 10 (9.3) |
| Lenvatinib | 17 (15.7) |
| Pembrolizumab | 14 (13.0) |
| **Patients with treatment-related TEAEs leading to study drug dose reduction of lenvatinib** | 70 (64.8) |
| **Patients with treatment-related TEAEs leading to study drug interruption** | 78 (72.2) |
| Both lenvatinib and pembrolizumab | 30 (27.8) |
| Lenvatinib | 73 (67.6) |
| Pembrolizumab | 43 (39.8) |

Makker. JCO. 2020;38:2981.

Most common grade ≥3 TEAEs were:

-Hypertension (32.4%)

-Fatigue (8.3%)

-Diarrhea (6.5%)

Any grade irAEs occurred in 57.4% of patients; most common was hypothyroidism (47.2%)

Most common grade ≥3 irAE was severe skin reactions (4.6%)

# Study 309/Keynote-775: Lenvatinib and Pembrolizumab vs. Physician's Choice Chemotherapy

FDA Accelerated Approval September 2019
FDA Priority Review May 2021
For patients with endometrial cancer who are not MSI-H or dMMR

*Stratified by MMR status (pMMR vs dMMR); within pMMR by region, ECOG PS 0 vs 1, prior history of pelvic radiation*

Patients with advanced, metastatic, or recurrent endometrial cancer with measurable disease after 1 previous platinum-based CT; ECOG PS 0/1; tissue available for MMR testing
(N = 827)

R
(1:1)

**Lenvatinib** 20 mg PO QD +
**Pembrolizumab** 200 mg IV Q3W
(n = 411)

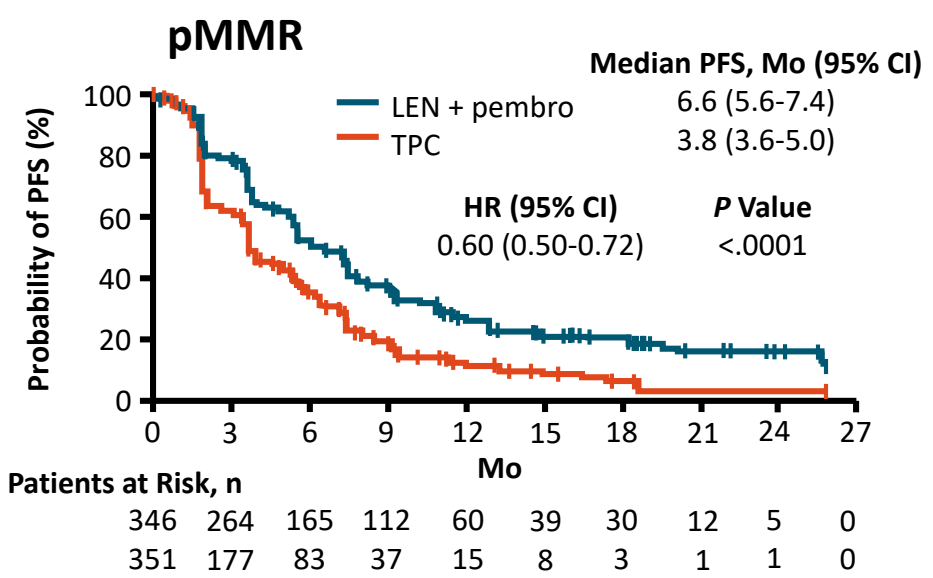
**Doxorubicin** 60 mg/m$^2$ IV Q3W or
**Paclitaxel** 80 mg/m$^2$ IV QW 3 wk on/1 wk off
(n = 416)

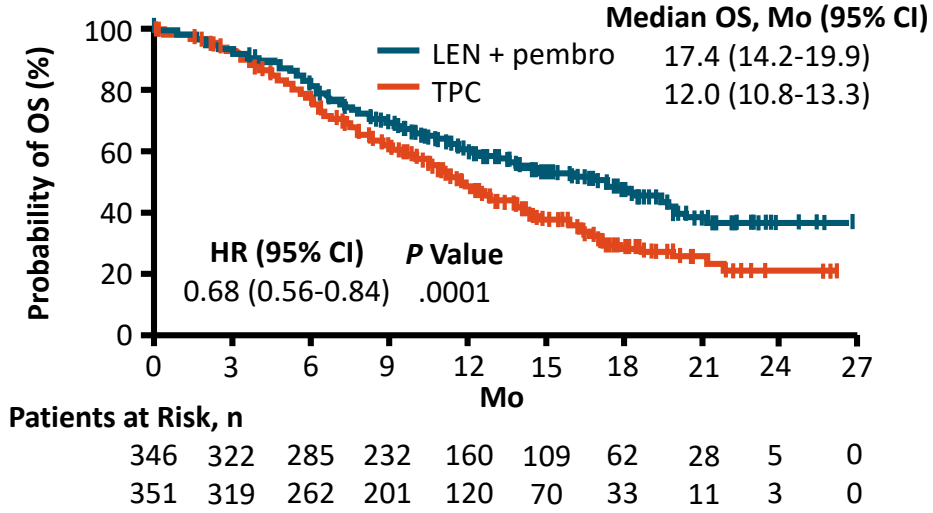
*Until PD or unacceptable toxicity*

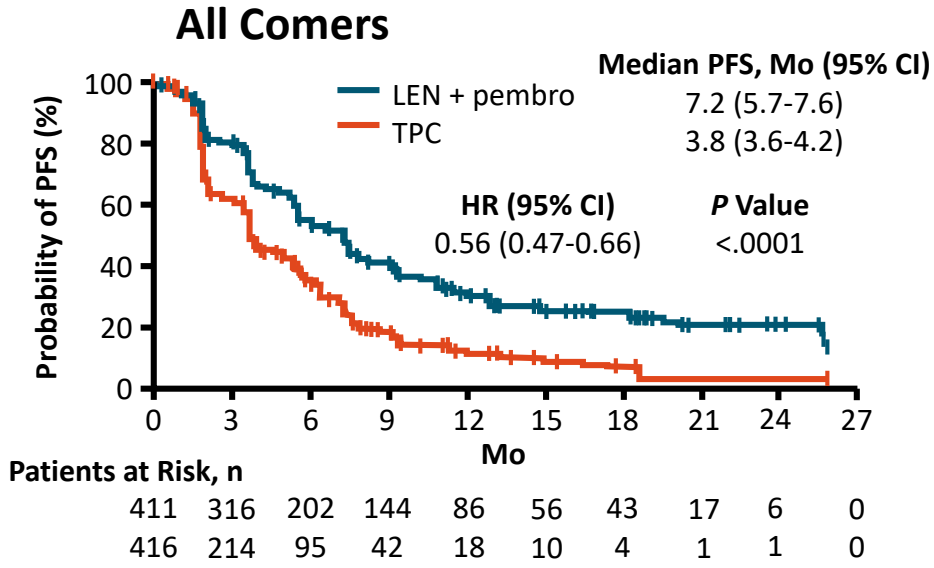
- **Primary endpoints:** PFS by BICR, OS
- **Secondary endpoints:** ORR, health-related quality of life, pharmacokinetics, safety
- **Key exploratory endpoint:** DoR

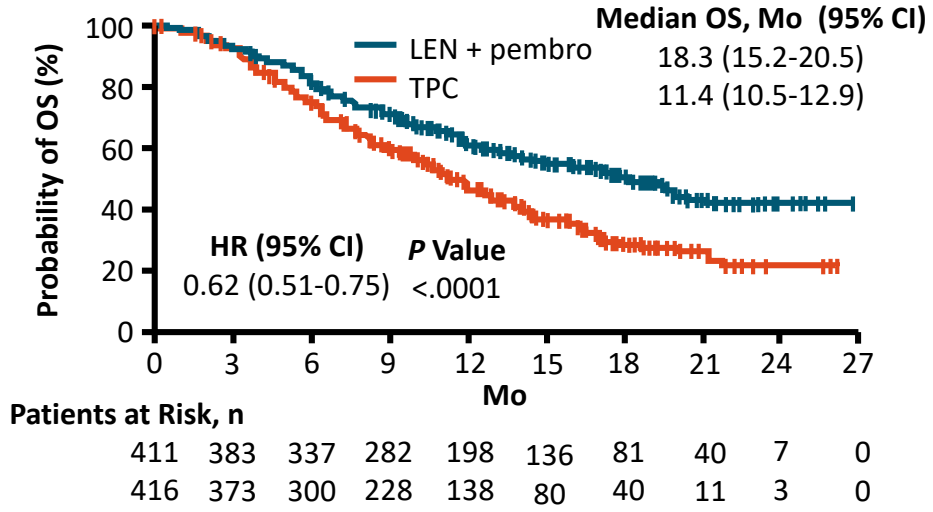
Makker V. N Engl J Med 2022; 386:437-448

# Study 309/KEYNOTE-775: PFS and OS Benefit




Makker V. N Engl J Med 2022; 386:437-448

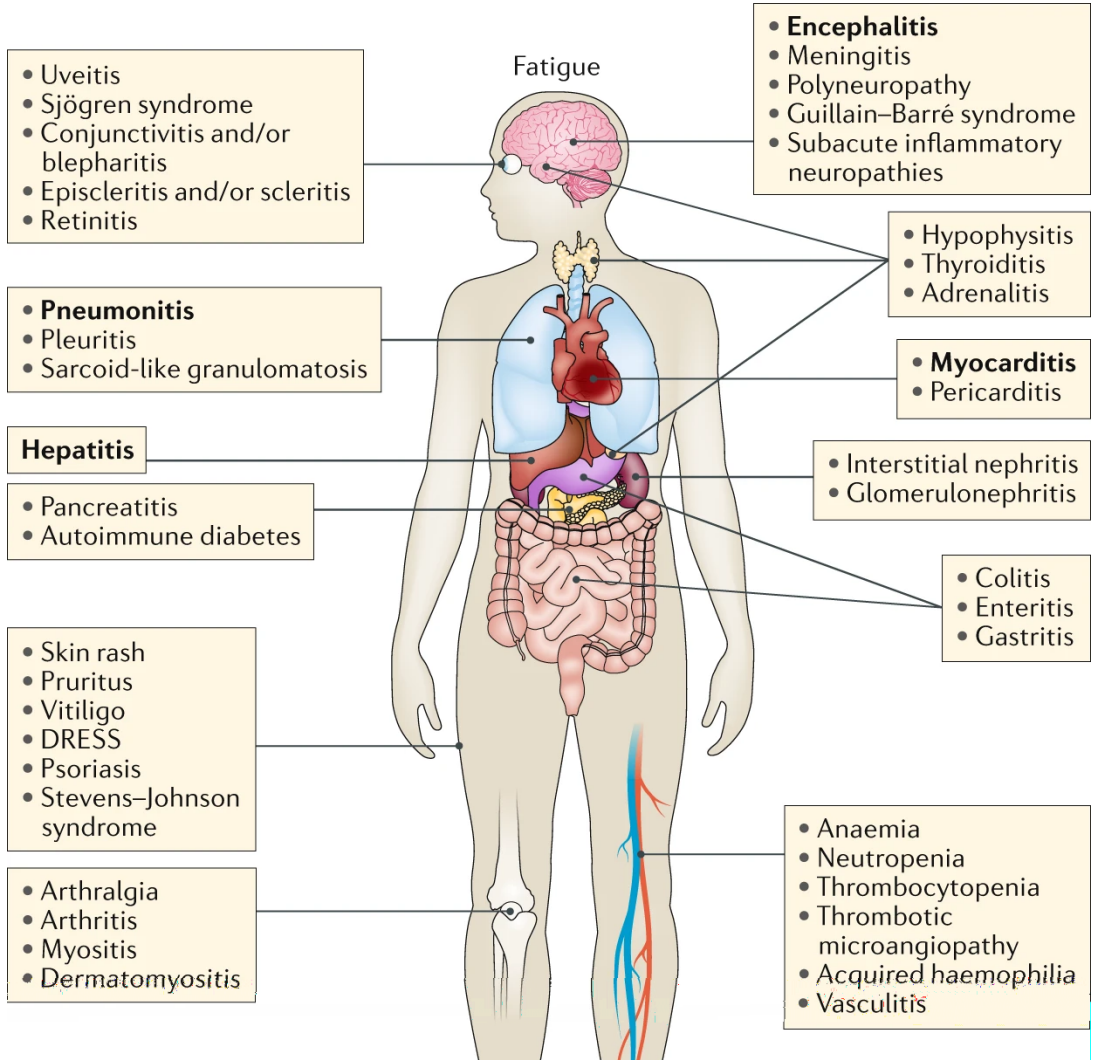
# Study 309/KEYNOTE-775: TEAEs

| TEAE, % | Lenvatinib + Pembrolizumab (n = 406) | | Doxorubicin or Paclitaxel (n = 351) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3* | Any Grade | Grade ≥3* |
| Hypertension | 64.0 | 37.9 | 5.2 | 2.3 |
| Hypothyroidism | 57.4 | 1.2 | 0.8 | 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 |
| Arthralgia | 30.5 | 1.7 | 8.0 | 0 |

| TEAE, % | Lenvatinib + Pembrolizumab (n = 406) | | Doxorubicin or Paclitaxel (n = 351) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3* | Any Grade | Grade ≥3* |
| 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 |
| UTI | 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 | 30.9 | 0.5 |

*In the lenvatinib and pembrolizumab arm, 5.7% of patients suffered grade 5 AEs (including events of gastrointestinal disorder [1.2%], cardiac disorder [0.5%], general disorder [1.5%], and infections [0.7%]), and 4.9% of patients in the TPC arm suffered grade 5 AEs (including cardiac disorder [1%], general disorder [1.3%], infections [1.5%], and subdural hematoma [0.3%]).

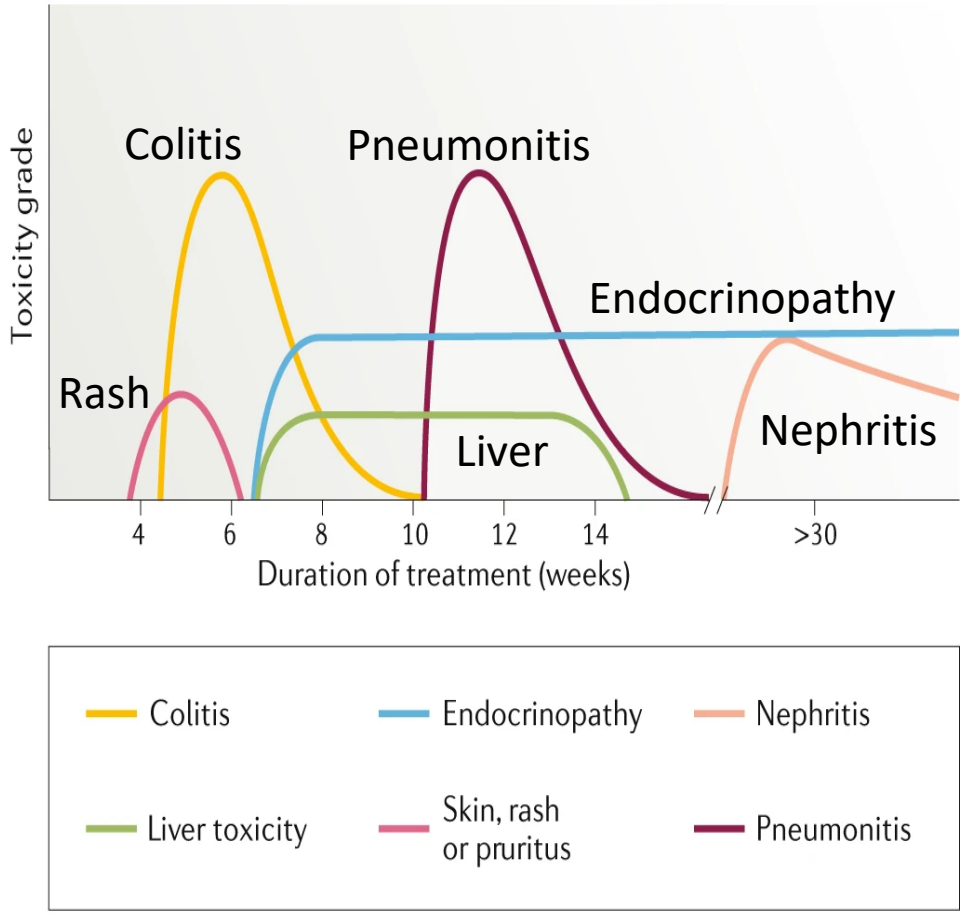
# The Spectrum of Immune-Related AE's by Organ




- T cell expansion
- Can affect any organ
- irAE's contributing to most fatalities:
  - Pneumonitis
  - Encephalitis
  - Myocarditis
  - Hepatitis

Martins et al. Nat Rev Clin Oncol 16, 563-580 (2019)

# Immune-Related Adverse Events

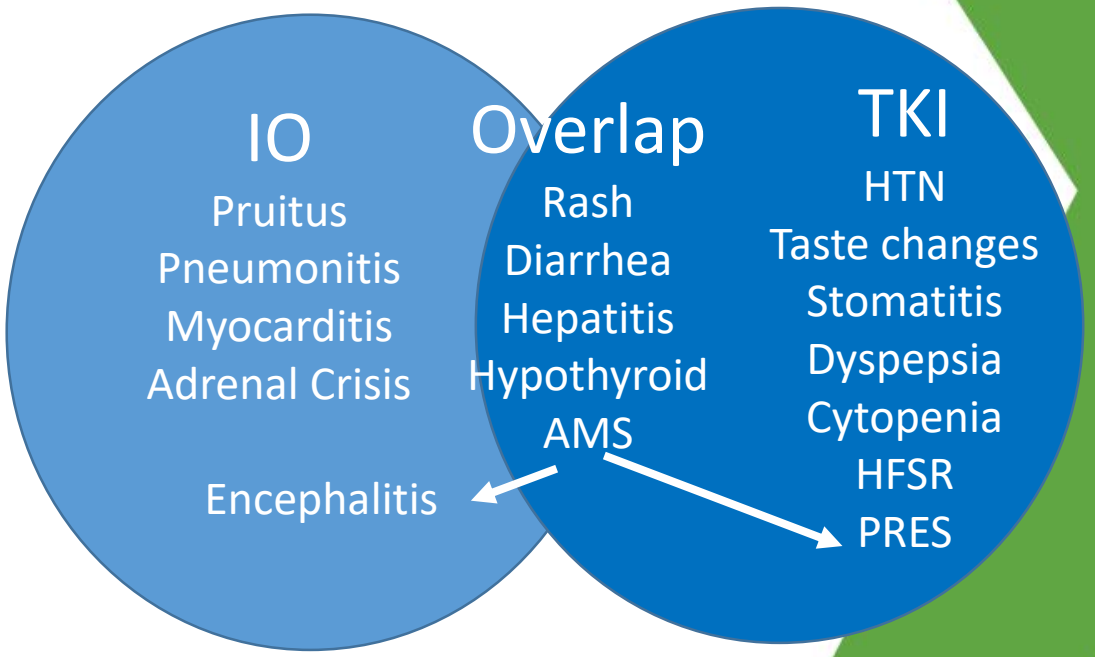



- Variable timing of irAE's
- Kinetics of appearance important for management and safety of treatment resumption
- Early recognition is critical

Martins et al. Nat Rev Clin Oncol 16, 563-580 (2019)

# Management of AE's in IO + TKI Combinations

- Two mechanisms of action
- Two sets of AE's that overlap
- Must determine which is causing AE
- Holding TKI first as shorter half-life than CPI
  - If symptoms resolve in a few days likely the TKI causing AE




**Consult irAE management guidelines: SITC**

Makker V et al. Oncologist 2021; 26:e1599-e1608
How JA et al. Gynecol Oncol 2021; 162: 24-31.

# Primary Advanced Endometrial Cancer

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

## Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

Mirza MR et al. DOI: 10.1056/NEJMoa2216334

Mirza MR et al. N Engl J Med 2023; 388:2145-2158.

The NEW ENGLAND JOURNAL of MEDICINE

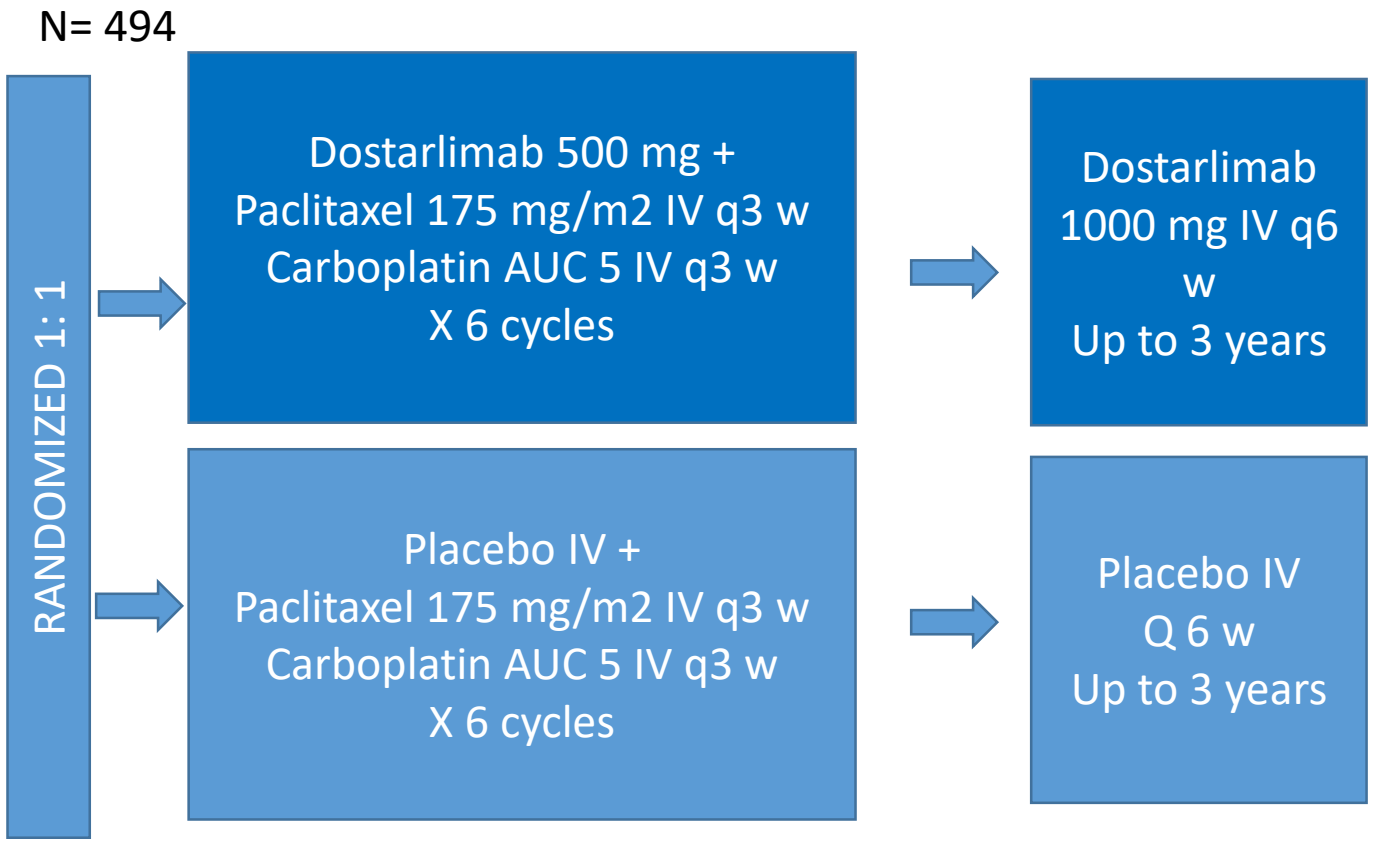
ORIGINAL ARTICLE

## Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

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

Two NEJM articles published this year for first-line advanced endometrial cancer!

# GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC (Part 1)




**Key Eligibility Criteria**

- Advanced/recurrent EC
- ECOG PS 0-1
- No prior Chemo except adjuvant chemo if completed ≥6 mo before study

**Stratification**

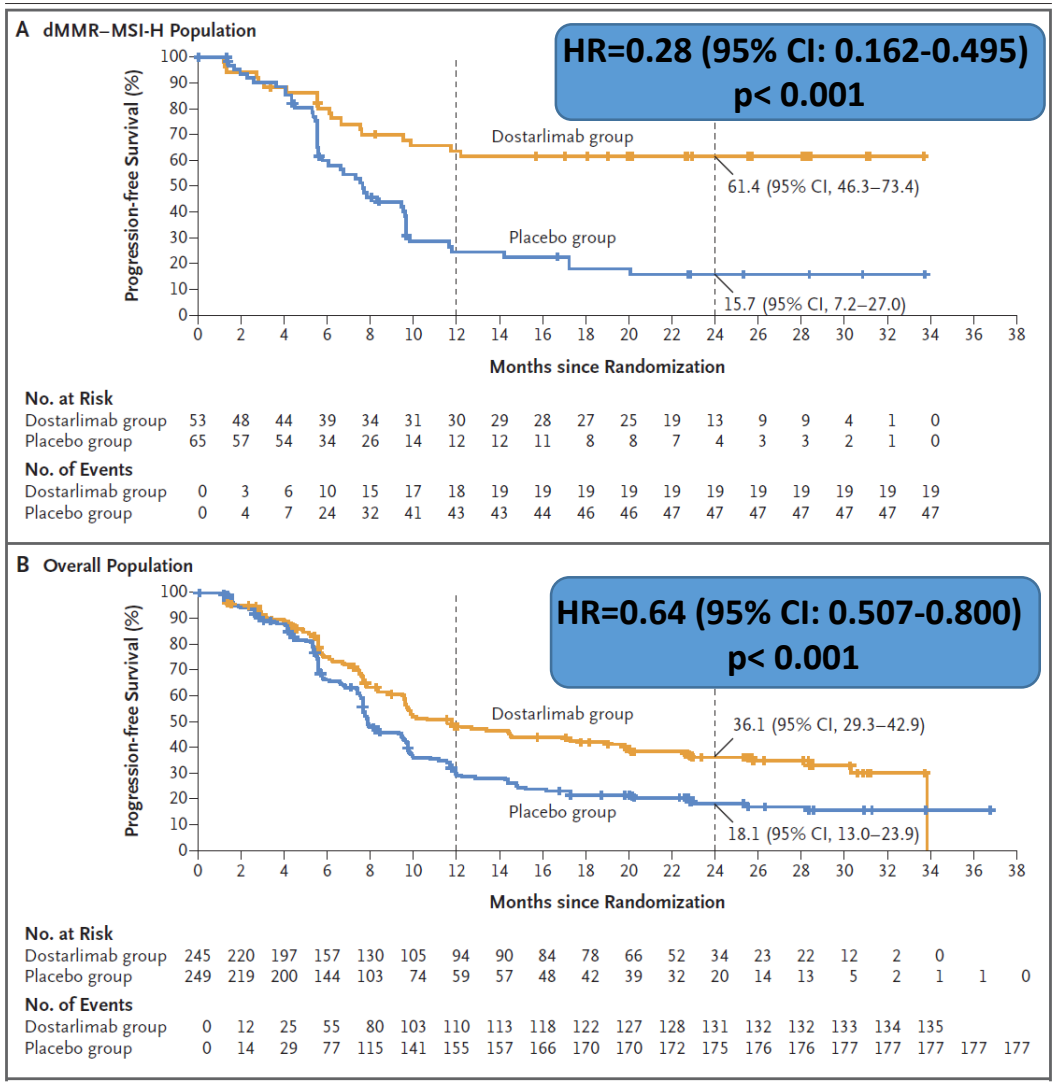
- MSI-H vs. MSS
- Stage III vs. IV vs. recurrent
- Prior pelvic RT (yes/no)

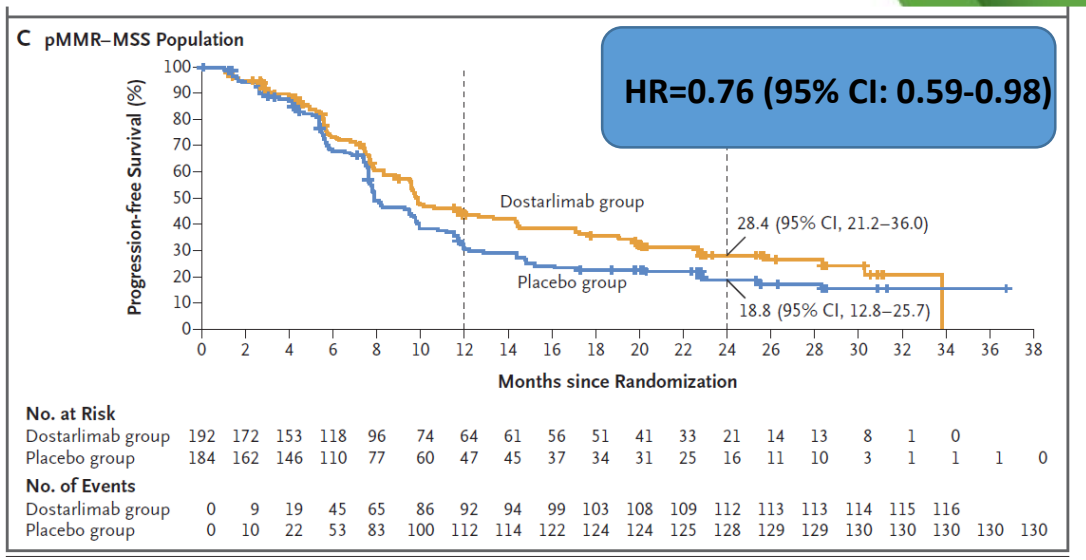
**July 31, 2023**
**FDA granted approval primary advanced or recurrent dMMR or MSI-H EC**

Mirza MR et al. N Engl J Med. 2023. June 388;23.

# GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC

## PFS




**PFS dMMR/MSI-H: Dostarlimab + T/C arm**

- 24 mos PFS: 61.4% vs. 15.7%

**PFS Overall Population**

- 24 mos PFS: 36.1% vs. 18.1%

**OS dMMR/MSI-H**

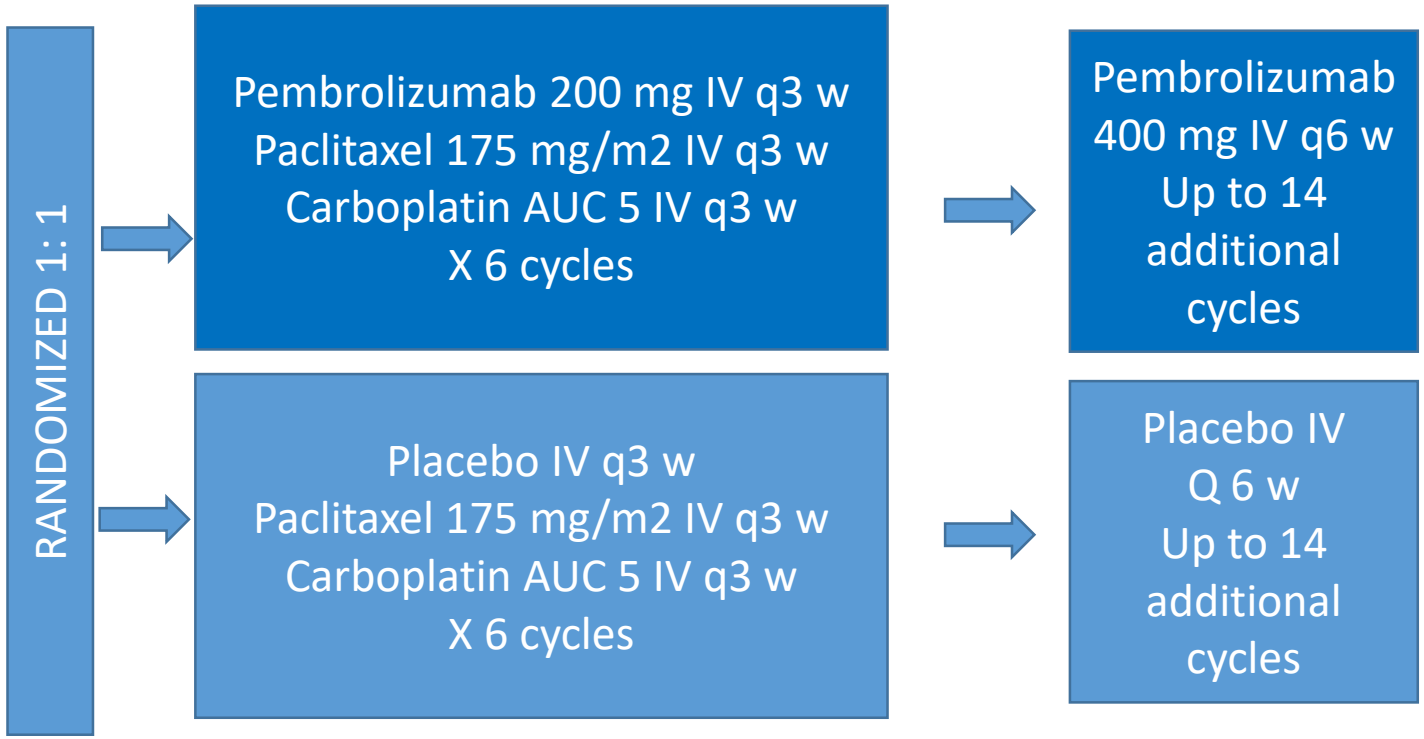
- 24 mos OS: 83.3% vs. 58.7% (HR=0.30 (95%CI:0.127-0.699)

**OS Overall Population (33% maturity)**

- 24 mos OS: 71.3% vs. 56% (HR=0.64 (95% CI:0.464-0.870) P=0.0021

Mirza MR et al. N Engl J Med. 2023. 388;23.

# NRG GY018: Ph 3 Trial of Pembrolizumab + T/C in measurable Stage 3, 4a, 4b or recurrent EC




Stratified by MMR status, ECOG and prior adjuvant chemo

**dMMR (n=225)** **pMMR (n=588)**

**Key Eligibility Criteria**

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent EC
- MMR IHC testing
- ECOG PS 0-2
- No prior Chemo except adjuvant Chemo if completed ≥12 mo before study

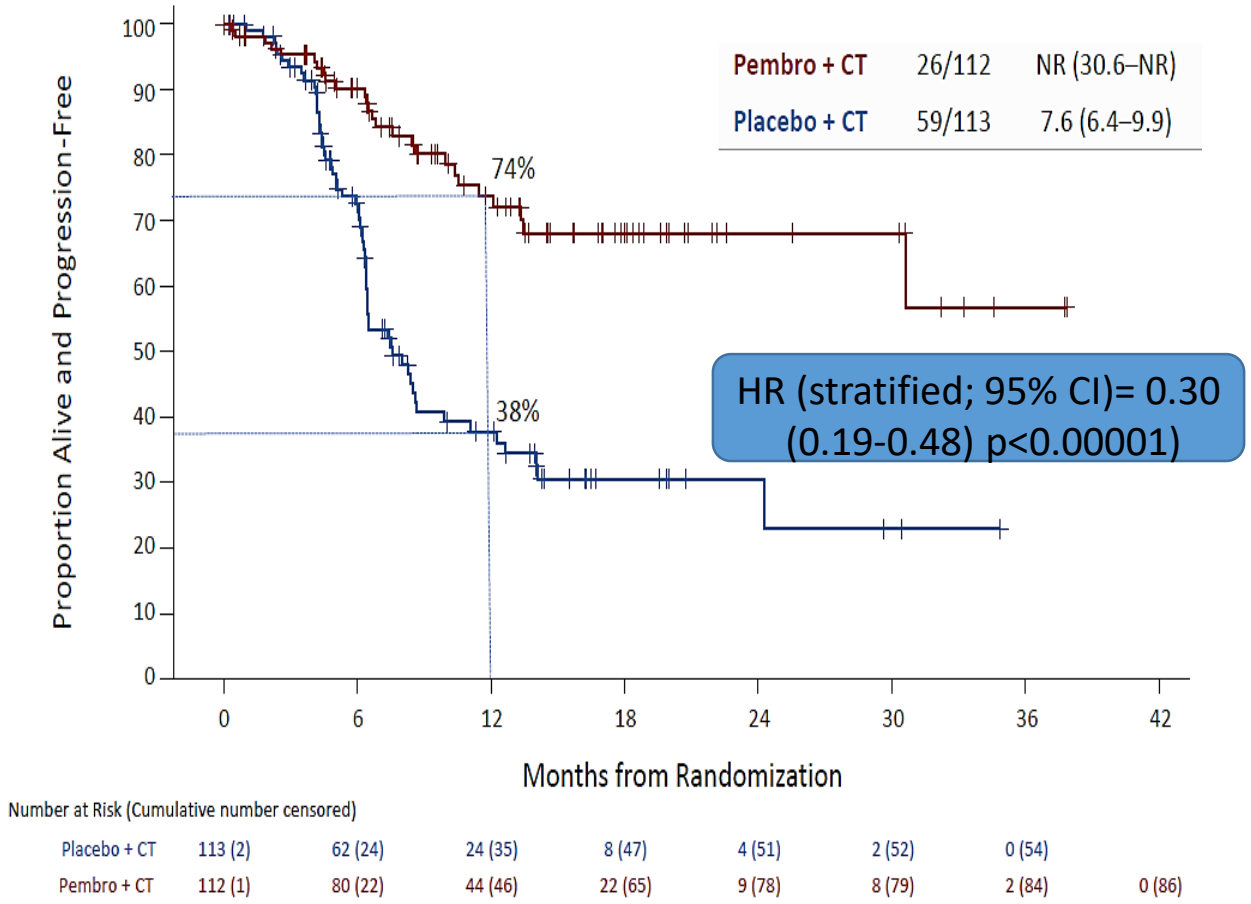
**Primary endpoints**: PFS
**Secondary endpoints**: Safety, ORR/DOR, OS, PRO/QoL, concordance of MMR testing results

Eskander R, et al. N Eng J Med. March 2023

# NRG GY018: PFS

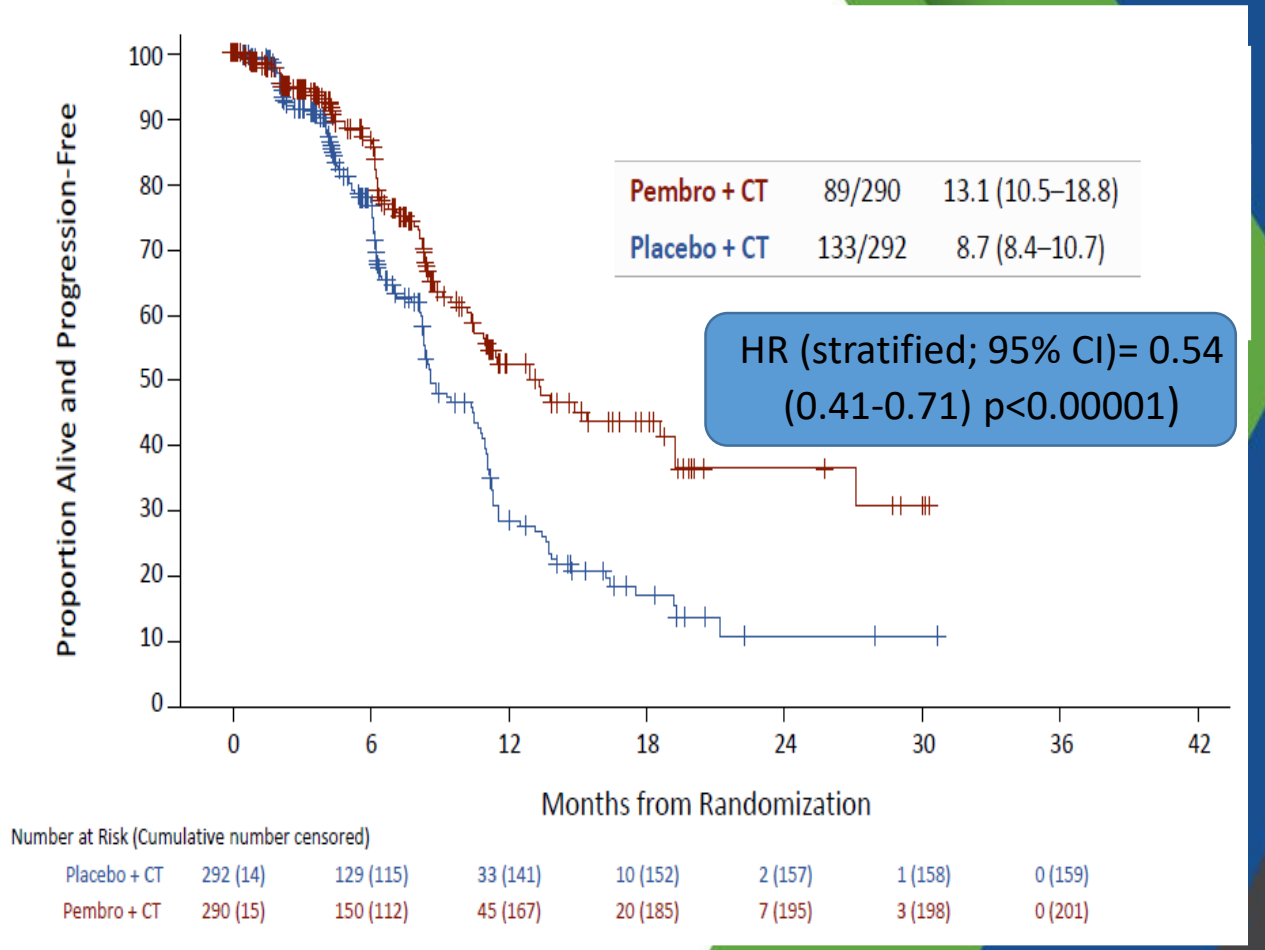
Eskander R, et al. N Eng J Med. March 2023

## dMMR




dMMR 12 mos: PFS 74% VS. 38%

## pMMR




pMMR 12 mos PFS: 74% VS. 38%

# Phase III Trials of Front Line Immunotherapy Combinations in Advanced/Recurrent EC

| Name (NCT) | Setting | Treatment Arms | Primary Endpoint(s) |
|---|---|---|---|
| **NRG-GY018 (NCT03914612)** | 1L | Pembro + carboplatin-paclitaxel vs placebo + carboplatin-paclitaxel ± pembro maintenance | PFS ★ |
| **RUBY/ENGOT-EN6 (NCT03981796)** | 1L | Carboplatin-paclitaxel ± dostarlimab followed by placebo or dostarlimab (Part 1), or niraparib + dostarlimab (Part 2) | PFS ★ |
| **AtTEnd/IRFMN-EN-7556 (NCT03603184)** | 1L | Atezolizumab + carboplatin-paclitaxel vs placebo + carboplatin-paclitaxel | OS, PFS |
| **DUO-E/ENGOT-EN10 (NCT04269200)** | 1L | Durvalumab + carboplatin-paclitaxel followed by maintenance durvalumab ± olaparib | PFS ★ |
| **LEAP-001/ENGOT-EN9 (NCT03884101)** | 1L and 2L | Lenvatinib + pembrolizumab vs carboplatin + paclitaxel dMMR and pMMR | PFS, OS |
| **Keynote-C93** | | Pembrolizumab vs. carboplatin + paclitaxel dMMR | PFS, OS |
| **Domenica** | | Dostarlimab vs. carboplatin + paclitaxel dMMR | PFS |

Clinicaltrials.gov.

# Conclusions

- Biomarker testing is imperative
- Pembrolizumab and Durvalumab approved for second line dMMR/MSI-H tumors
- Pembrolizumab/lenvatinib approved for second line pMMR tumors
- Paclitaxel/carboplatin/dostarlimab approved for front-line, advanced stage dMMR/MSI-H EC.
- irAE's manageable but early recognition and patient education critical
- Treatment sequences may change now that CPI approved for first-line therapy-will we be able to get rid of chemotherapy?
- Prioritize clinical trial enrollment