# Multidisciplinary Approaches to Cancer Symposium

## Gynecologic Systemic Therapies Update

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# Disclosures

- Consultant for Astra Zeneca and Immunogen

*This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.*

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

*This presentation has been peer-reviewed and no conflicts were noted.*

**The off-label/investigational use of trastuzumab deruxtecan will be addressed.**

# Learning Objectives

- To understand the current use of PARP inhibitors in ovarian cancer
- To delineate different maintenance strategies in the initial management of advanced stage ovarian cancer
- To identify indications for use of immunotherapy in metastatic and recurrent endometrial cancer
- To discuss indications for use of immunotherapy in cervical cancer
- To review novel antibody drug conjugates in the management of gynecologic cancer

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

**STATE LAW:**

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

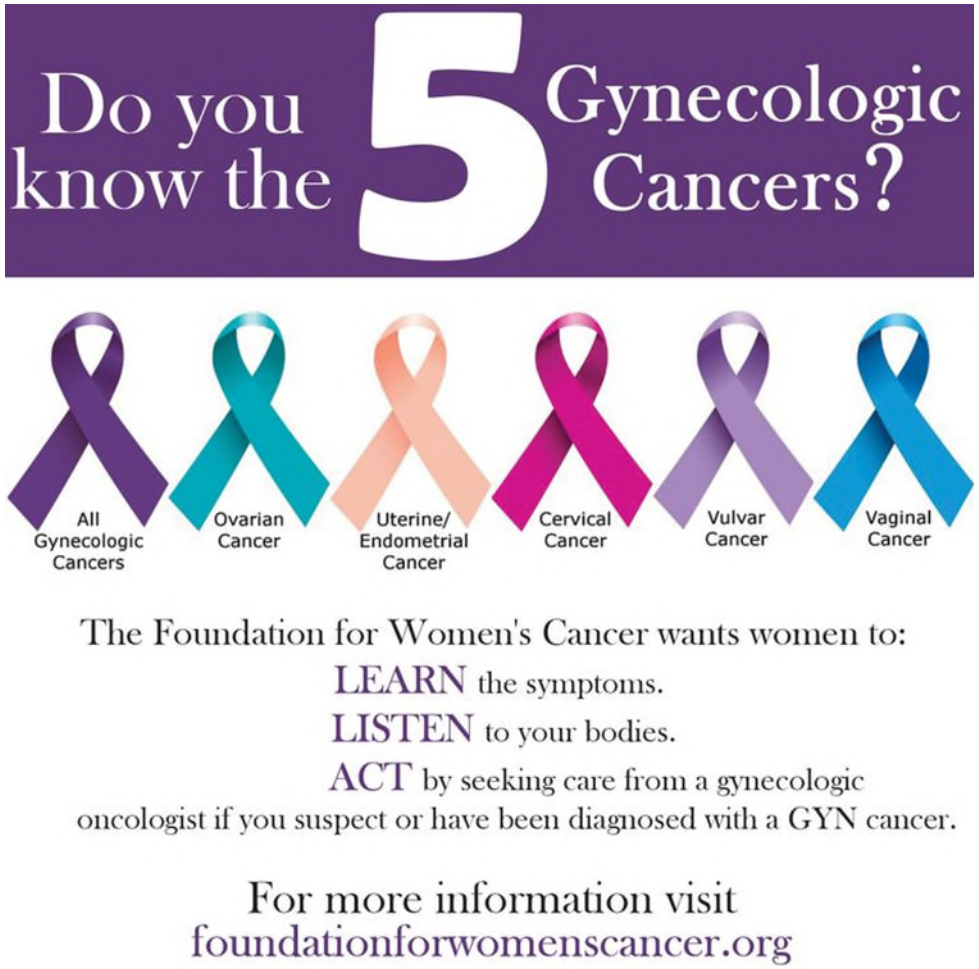
***EXEMPTION:***

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

***The following CLC & IB components will be addressed in this presentation:***

- *Access and barriers to care.*
- *Factors that determine the type and level of care a populations receives.*

# September was Gynecologic Cancer Awareness Month




98,000 women will be diagnosed with a gynecologic cancer this year

30,000 women will die from gynecologic cancer this year

# Cancer Impact in the United States

Estimated Deaths

| Male | | | Female | | |
|---|---|---|---|---|---|
| Lung & bronchus | 69,410 | 22% | Lung & bronchus | 62,470 | 22% |
| Prostate | 34,130 | 11% | Breast | 43,600 | 15% |
| Colon & rectum | 28,520 | 9% | Colon & rectum | 24,460 | 8% |
| Pancreas | 25,270 | 8% | Pancreas | 22,950 | 8% |
| Liver & intrahepatic bile duct | 20,300 | 6% | Ovary | 13,770 | 5% |
| Leukemia | 13,900 | 4% | Uterine corpus | 12,940 | 4% |
| Esophagus | 12,410 | 4% | Liver & intrahepatic bile duct | 9,930 | 3% |
| Urinary bladder | 12,260 | 4% | Leukemia | 9,760 | 3% |
| Non-Hodgkin lymphoma | 12,170 | 4% | Non-Hodgkin lymphoma | 8,550 | 3% |
| Brain & other nervous system | 10,500 | 3% | Brain & other nervous system | 8,100 | 3% |
| **All sites** | **319,420** | | **All sites** | **289,150** | |

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.



https://www.cancer.org/content

# Alarming Trends with Disparities in High-Risk Endometrial Cancer

- Rising incidence of uterine cancer in the United States – 65,950 new cases in 2022
- Mortality among black women with uterine cancer is 1.6-fold higher than ovarian cancer (9.3 vs 5.7 per 100,000) and nearly two-fold higher compared to white women
- High risk histologic subtypes of endometrial cancer disproportionately impact black people
  - Black women are two to four times more likely to present with aggressive, non-endometrioid tumors compared to white women
  - Black women are more likely to present with advanced stage disease and are 21% more likely to die of disease than both Hispanic and non-Hispanic white women

Eakin, et al, 2023

# The Journey of PARP Inhibitors in Ovarian Cancer

- Began with monotherapy treatment for ovarian cancer recurrence in 2014
  - 12/2014 – olaparib – germline BRCAm
  - 12/2016 – rucaparib – germline/somatic BRCAm
  - 10/2019 – niraparib – HRD positive

# The Journey of PARP Inhibitors in Ovarian Cancer

- Then came maintenance strategy after chemotherapy for platinum sensitive recurrence
  - 3/2017 – niraparib – biomarker agnostic
  - 8/2017 – olaparib – biomarker agnostic
  - 4/2018 – niraparib – biomarker agnostic

# The Journey of PARP Inhibitors in Ovarian Cancer

- Then PARP inhibitors were moved to front-line as maintenance after chemotherapy
  - 12/2018 – olaparib – germline/somatic BRCAm
  - 4/2020 – niraparib – biomarker agnostic
  - 5/2020 – olaparib/bevacizumab – germline/somatic BRCAm or HRD positive

# Dear Healthcare Provider Letters

- From 5/2022 to 12/2022 a series of letters sent regarding withdrawal of indications for PARP inhibitor use

- **Maintenance Indication Withdrawals**
  - ENGOT-OV16/NOVA – niraparib restricted to patients with germline BRCAm for maintenance after treatment of platinum sensitive recurrent ovarian cancer
  - ARIEL3 – rucaparib restricted to patients with tumor BRCAm for maintenance after treatment of platinum sensitive recurrent ovarian cancer

- **Single Agent Indication Withdrawals**
  - ARIEL4 – rucaparib withdrawal for treatment of germline/somatic BRCAm recurrent ovarian cancer (2 or more prior lines of chemotherapy)
  - SOLO3 – Olaparib withdrawal for treatment of germline BRCAm recurrent ovarian cancer (3 or more prior lines of chemotherapy)
  - QUADRA – niraparib withdrawal for treatment of HRD positive recurrent ovarian cancer (3 or more prior lines of chemotherapy)

# Caveats with Interpretation of Overall Survival Data

- Patients with ovarian cancer often receive numerous lines of subsequent therapy prior to overall survival calculation (can we attribute OS to PARP inhibitor alone?)

- Impact of cross-over (ie significant cross-over to PARP inhibitor was noted in SOLO3 and ARIEL4 for germline patients)

# Now where are we? (FDA approved)

- Indications withdrawn for olaparib, rucaparib, and niraparib monotherapy for recurrence

- Maintenance treatment in platinum sensitive recurrent setting

  - niraparib – 11/2022 restricted to germline BRCAm or suspected germline BRCAm

  - olaparib – had been available (Study 19, SOLO-2) – **As of September 2023 – now restricted to BRCA-mutated (germline or somatic) patient population only**

  - rucaparib – 12/2022 restricted to tumor BRCAm

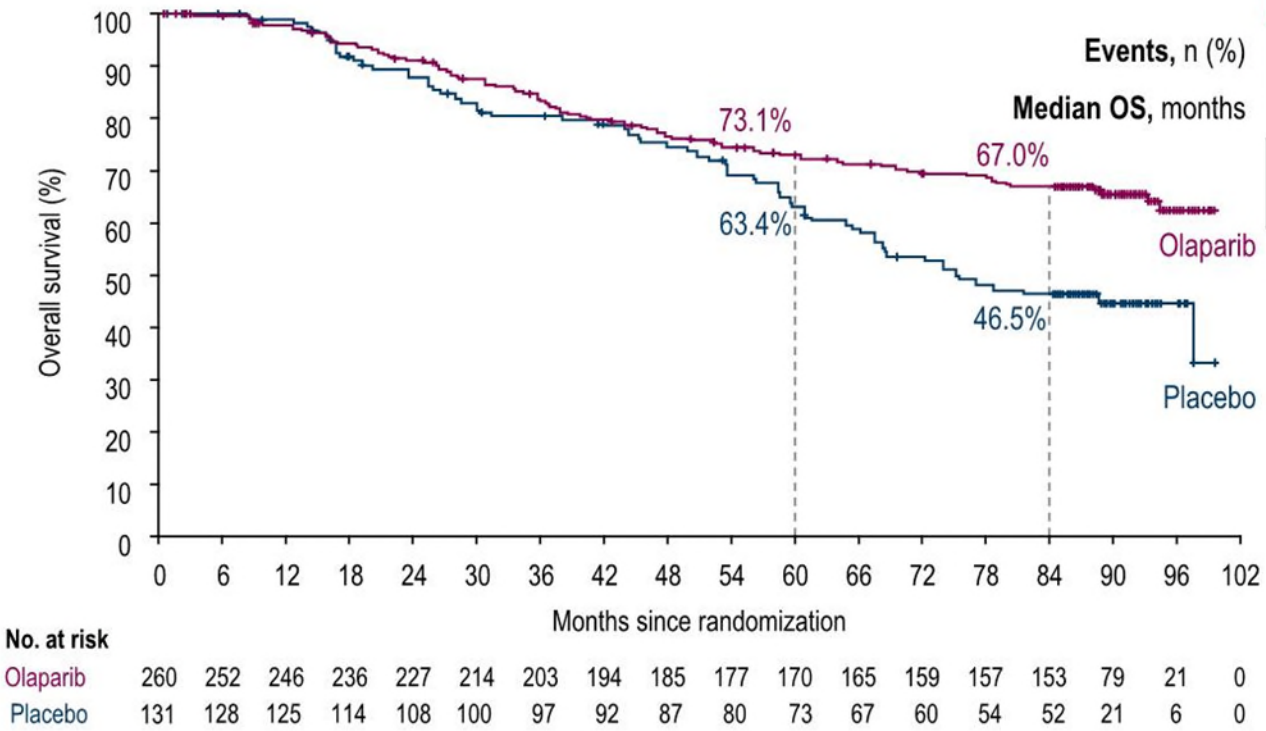
# Now where are we? (FDA approved)

- Maintenance therapy with upfront treatment
  - 12/2018 – olaparib – germline/somatic BRCAm
  - 4/2020 – niraparib – biomarker agnostic
  - 5/2020 – olaparib/bevacizumab – germline/somatic BRCAm or HRD positive

  - *3/2022 – niraparib/bevacuzimab (OVARIO) – single arm study – combination is safe to use – no FDA approval*
  - *6/2022 – rucaparib (ATHENA-MONO) – response seen irrespective of HRD status – no FDA approval*

# SOLO-1/GOG 3004 Final OS Presented at ESMO 2022

## Maintenance olaparib provided a clinically meaningful OS benefit




| | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| Events, n (%) | 84 (32.3) | 65 (49.6) |
| Median OS, months | NR | 75.2 |
| HR 0.55 (95% CI 0.40–0.76); *P*=0.0004* | | |

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

*$P<0.0001$ required to declare statistical significance

- **67.0% of olaparib patients vs 46.5% of patients in the placebo group were alive at 7 years**
- **OS benefit seen despite over 40% of patients in the placebo group receiving subsequent PARP inhibitor therapy**
- **Benefit extends well beyond 2-year treatment cap**

Dr. DiSilvestro, et al, ESMO, 2022

# Phase III PRIMA/ENGOT-OV26/GOG-3012: Updated Long-Term PFS (INV) at ESMO 2022

This double-blind, placebo (PBO)-controlled phase 3 trial evaluated nir in pts with newly diagnosed advanced high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer (OC) with a complete or partial response (CR or PR) to 1L platinum-based CT. Primary endpoint PFS. 733 patients in study.

Niraprib maintained clinically significant improvement in PFS with 3.5 y of follow-up in pts with newly diagnosed advanced OC at high risk of progression irrespective of HRD status. No new safety signals were identified.

| | Primary efficacy analysis 17 May 2019 | | Updated efficacy analysis (INV) 17 Nov 2021 |
|---|---|---|---|
| | BICR | INV | |
| **Median PFS, mo** | | | |
| **Overall** | 13.8 vs 8.2 | 13.8 vs 8.2 | 13.8 vs 8.2 |
| Nir vs PBO HR (95% CI) *p* | 0.62 (0.50–0.76) <0.0001 | 0.63 (0.51–0.76) <0.0001 | 0.66 (0.56–0.79) <0.0001 |
| **HRd** | 21.9 vs 10.4 | 21.9 vs 11.2 | 24.5 vs 11.2 |
| Nir vs PBO HR (95% CI) *p* | 0.43 (0.31–0.59) <0.0001 | 0.46 (0.34–0.63) <0.0001 | 0.52 (0.40–0.68) <0.0001 |
| **HRp** | 8.1 vs 5.4 | 8.3 vs 5.4 | 8.4 vs 5.4 |
| Nir vs PBO HR (95% CI) *p* | 0.68 (0.49–0.94) 0.0203 | 0.62 (0.45–0.85) 0.0025 | 0.65 (0.49–0.87) 0.0038 |
| Estimated probability of no progressive disease or death for ≥4 | | | **Overall** Nir: 23% PBO: 14% **HRd** Nir: 38% PBO: 17% |

As of 17 Nov 2021, median PFS follow-up time was 3.5 y.
González-Martín A, et al. ESMO 2022. Abstract 530P.

# PAOLA-1 Final OS Presented at IGCS 2022

| | Olaparib + bevacizumab (N=255) | Placebo + bevacizumab (N=132) |
|---|---|---|
| **Events,** n (%) | 93 (36.5) | 69 (52.3) |
| **Median OS,** months | **75.2** (unstable)* | **57.3** |
| **5-year OS rate**, % | **65.5** | **48.4** |
| | **HR 0.62** (95% CI 0.45–0.85) | |

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

**Patients receiving a PARP inhibitor during any subsequent treatment**

Olaparib + bevacizumab: **17.3%** (44/255)

Placebo + bevacizumab: **50.8%** (67/132)

- No OS difference was observed in the HRD-negative subgroup
- No new safety signals were observed with longer-term follow-up
- Incidence of MDS/AML and new primary malignancies remained low and balanced between both arms

Dr. Ray-Coquard, et al, ICGS 2022

# Long Term Toxicity

- Therapy Related Myelodysplastic Syndrome or Acute Myeloid Leukemia
  - ARIEL 3 – 11.4% (9/79) with 24 months on PARPi vs 0/4 in placebo group
  - SOLO 2 – BRCAm population – 8% on PARPi vs 4% of controls
  - PAOLA-1 – 1.7% on PARPi/Bev and 2.2% on placebo/Bev
  - SOLO-1 – 7 year follow up – 1.5% on PARPi and 1% on placebo
    - For other new primary malignancies (not MDS) – 5.4% and 6.2% respectively

- The longer someone is on a PARP inhibitor, there is a likely increased risk of MDS – but given ovarian cancer, shared decision making is key

# When to use PARP inhibitors

- Key to find those patients at initial diagnosis who will benefit from PARP inhibitor use in the initial treatment plan
  - Approximately 50% of epithelial ovarian cancer patients will benefit from a PARP inhibitor based on HRD pathways

- If you encounter a patient who has not received a PARP inhibitor in the initial management of ovarian cancer, and she has platinum sensitive disease, there is still an opportunity for her to benefit from a PARP inhibitor

- Ask yourself if it would make sense for your patient to use combination strategy for maintenance with PARP inhibitor and bevacizumab

# NCCN Guidelines Version 2.2023
# Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
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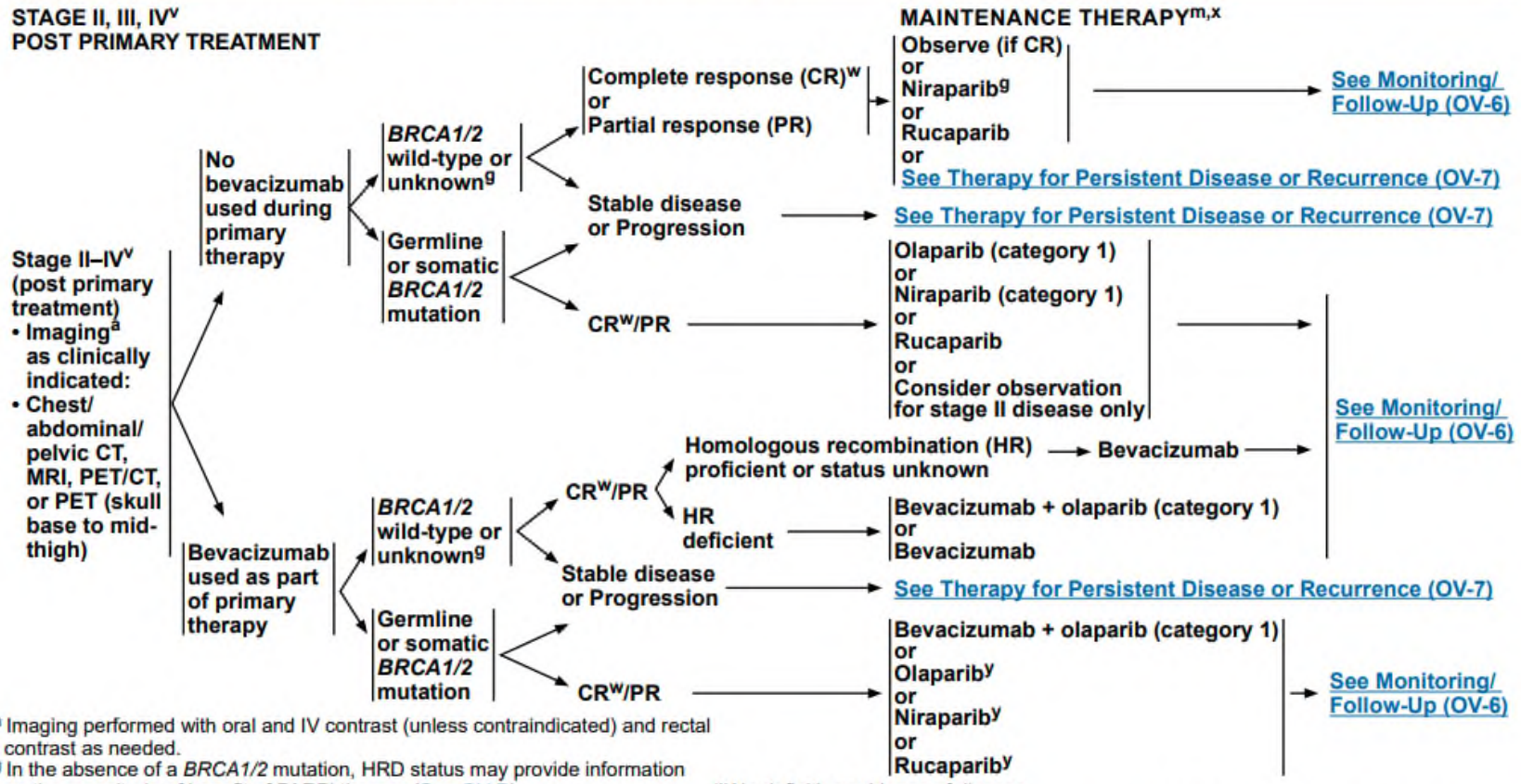
Discussion




[a] Imaging performed with oral and IV contrast (unless contraindicated) and rectal contrast as needed.

[g] In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARPi therapy (See OV-B).

[m] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

[v] Post primary treatment recommendations for stage II–IV high-grade serous or grade 2/3 endometrioid carcinoma; consider for clear cell carcinoma or carcinosarcoma with a *BRCA1/2* mutation.

[w] No definitive evidence of disease.

[x] Data are limited for maintenance therapy with a PARPi for patients with stage II disease.

[y] After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARPi (olaparib, niraparib, or rucaparib) for patients with a germline or somatic *BRCA1/2* mutation. However, based on the magnitude of benefit of PARPi maintenance therapy for other subgroups, single-agent PARPi can be considered.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# Future of PARP Inhibitors

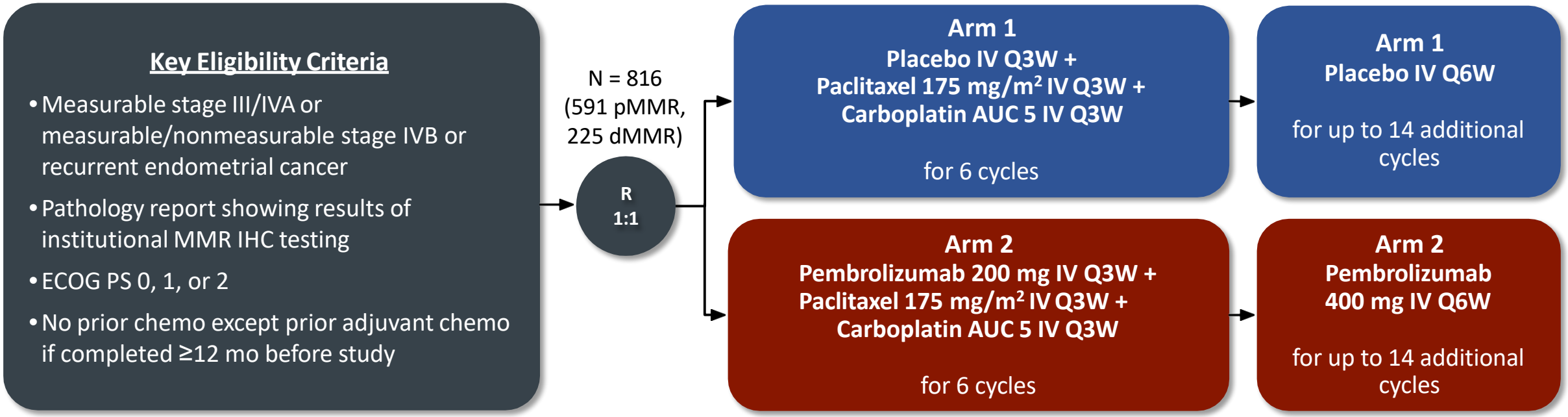
- What is the optimal duration in upfront maintenance?
- PARPi after PARPi?
- PARPi and I/O?
- Neoadjuvant PARPi for advanced stage disease?

- Dr. Shannon Westin presented the NOW (neoadjuvant Olaparib window) trial –a  single arm, open-label polit study presented at 2023 SGO Annual Meeting
- Patients received two 28-day cycles of Olaparib, all 15 women completed the 2 cycles, 86.6% of patients were able to proceed with surgery of which 85.7% had complete gross resection.
- This trial showed neoadjuvant PARPi treatment is feasible in patients with germline mutations in (BRCA1/2, PALB2, RAD51C).

# Endometrial Cancer

- GOG study 209 established paclitaxel and carboplatin (PC) as standard first-line chemotherapy for the treatment of patients with advanced-stage or recurrent endometrial cancer
- Immune checkpoint inhibitor monotherapy has established efficacy in the second-line and beyond settings in dMMR/MSI-H endometrial cancer (pembrolizumab, dostarlimab-gxly)
- Pembrolizumab in combination with Lenvatinib has proven efficacy in pMMR/microsatellite-stable (MSS), recurrent endometrial cancer
- In 2023, new standard of care with metastatic/advanced stage endometrial cancer incorporating immunotherapy in the initial systemic management

# NRG-GY018/KEYNOTE-868 (NCT03914612)




**Stratification Factors**

- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

**Endpoints**

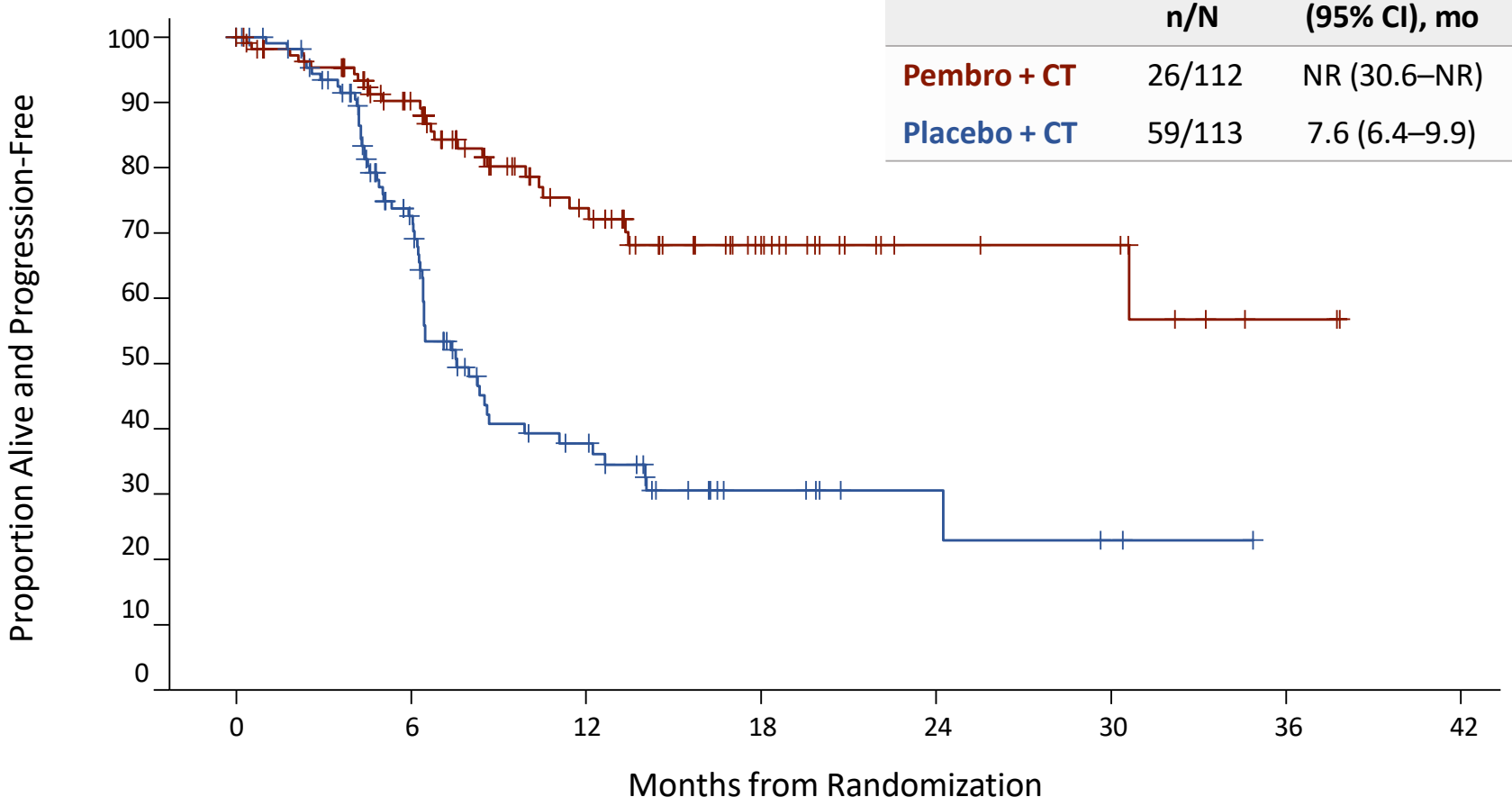
- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of institutional vs central MMR IHC testing results

BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; PRO, patient-reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

Eskander et al, NEJM, 2023

# PFS per RECIST v1.1: dMMR Population

| | Events, n/N | Median (95% CI), mo | HR (stratified; 95% CI) |
|---|---|---|---|
| Pembro + CT | 26/112 | NR (30.6–NR) | **0.30 (0.19–0.48)** |
| Placebo + CT | 59/113 | 7.6 (6.4–9.9) | ***P* = <0.00001** |



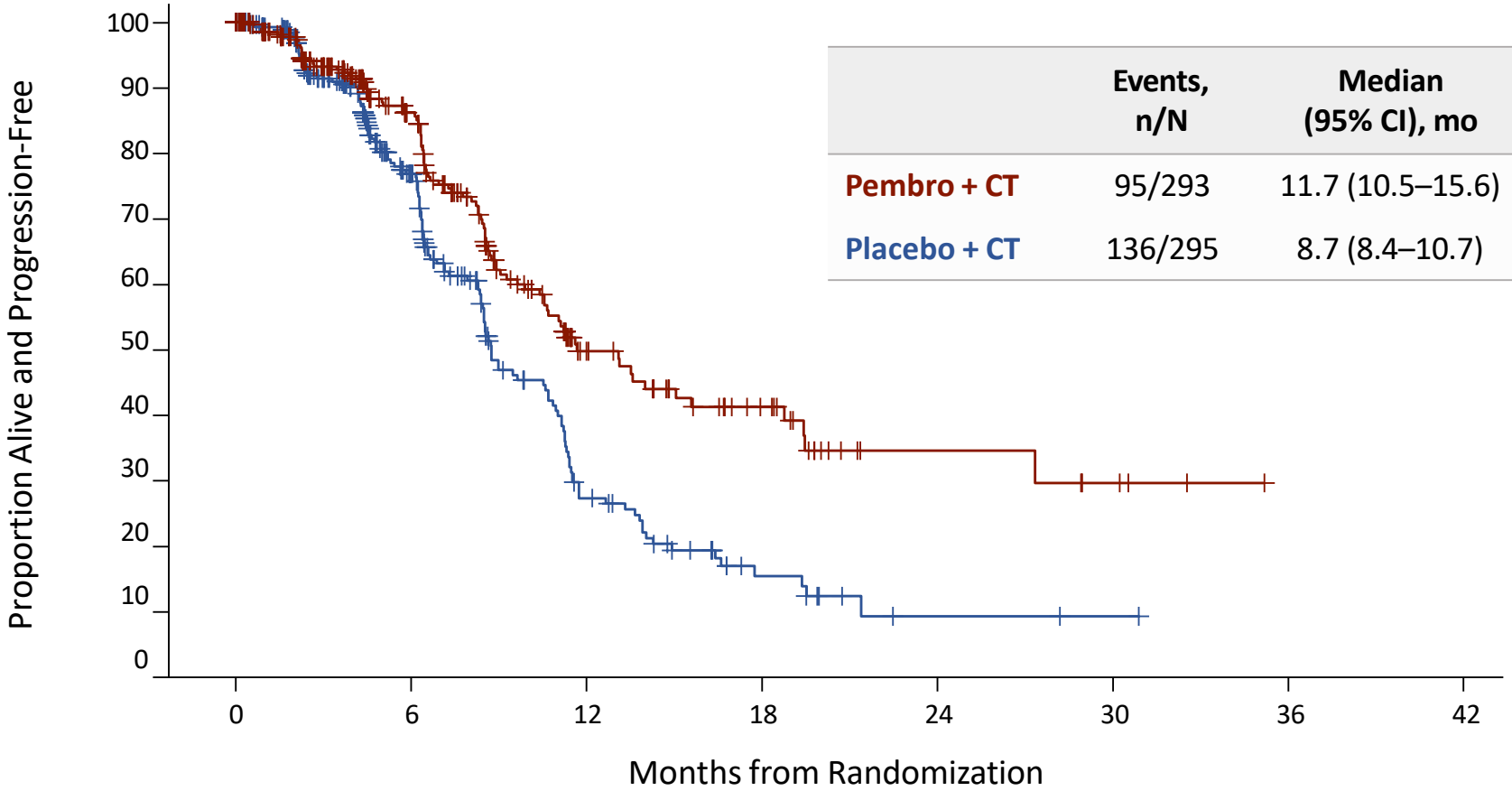

Number at Risk (Cumulative number censored)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo + CT | 113 (2) | 62 (24) | 24 (35) | 8 (47) | 4 (51) | 2 (52) | 0 (54) | |
| Pembro + CT | 112 (1) | 80 (22) | 44 (46) | 22 (65) | 9 (78) | 8 (79) | 2 (84) | 0 (86) |

Data cutoff date: December 16, 2022.

Eskander et al, NEJM, 2023

# PFS per RECIST v1.1: pMMR Population




| | Events, n/N | Median (95% CI), mo | HR (stratified; 95% CI) |
|---|---|---|---|
| **Pembro + CT** | 95/293 | 11.7 (10.5–15.6) | **0.57 (0.44–0.74)** |
| **Placebo + CT** | 136/295 | 8.7 (8.4–10.7) | ***P* = <0.0001** |

Number at Risk (Cumulative number censored)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo + CT | 295 (14) | 133 (112) | 34 (140) | 10 (152) | 2 (157) | 1 (158) | 0 (159) |
| Pembro + CT | 293 (11) | 152 (110) | 45 (164) | 23 (179) | 7 (192) | 4 (194) | 0 (198) |

Eskander et al, NEJM, 2023

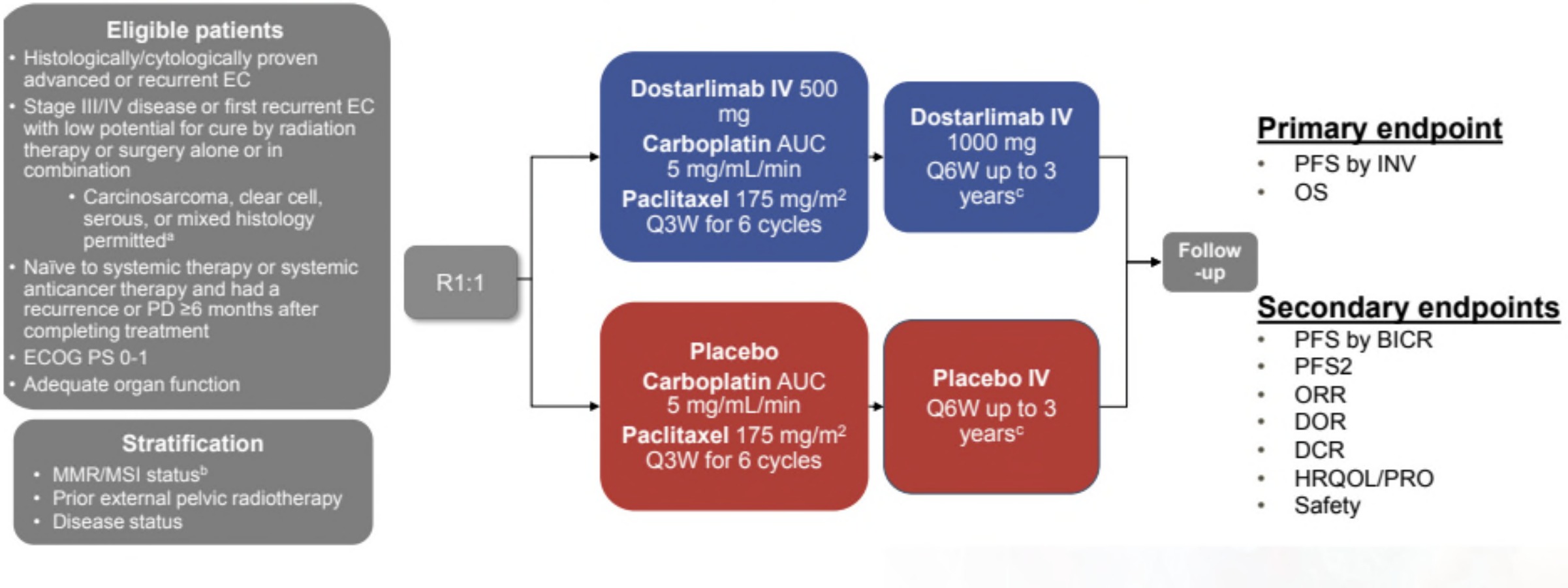
# Summary of Adverse Events

| Adverse Event | dMMR Population | | pMMR Population | |
|---|---|---|---|---|
| | Pembro + CT (N = 109) | Placebo + CT (N = 106) | Pembro + CT (N = 276) | Placebo + CT (N = 274) |
| Any adverse event (all-cause), no. (%) | 107 (98.2) | 105 (99.1) | 258 (93.5) | 256 (93.4) |
| Grade 3-5 | 69 (63.3) | 50 (47.2) | 152 (55.1) | 124 (45.3) |
| Event leading to death | 1 (0.9)[a] | 2 (1.9)[a] | 6 (2.2)[b] | 2 (0.7)[b] |
| Adverse events of interest, no. (%)[c] | | | | |
| Any[d] | 42 (38.5) | 28 (26.4) | 92 (33.3) | 54 (19.7) |
| Grade 3-5 | 9 (8.3) | 6 (5.7) | 10 (3.6) | 7 (2.6) |

[a]These events included one each of: cardiac arrest, sepsis, and lower gastrointestinal hemorrhage.
[b]These event included sepsis in 4 patients, cardiac arrest in 2 patients; and small intestinal obstruction, sudden death not otherwise specified in 1 patient each.
[c]The events of interest are those with a possible immune-related cause and are considered regardless of attribution to a trial drug by the investigator.
[d]Total number of patients who experienced an immune-related AE. Some patients experienced multiple immune-related adverse events.

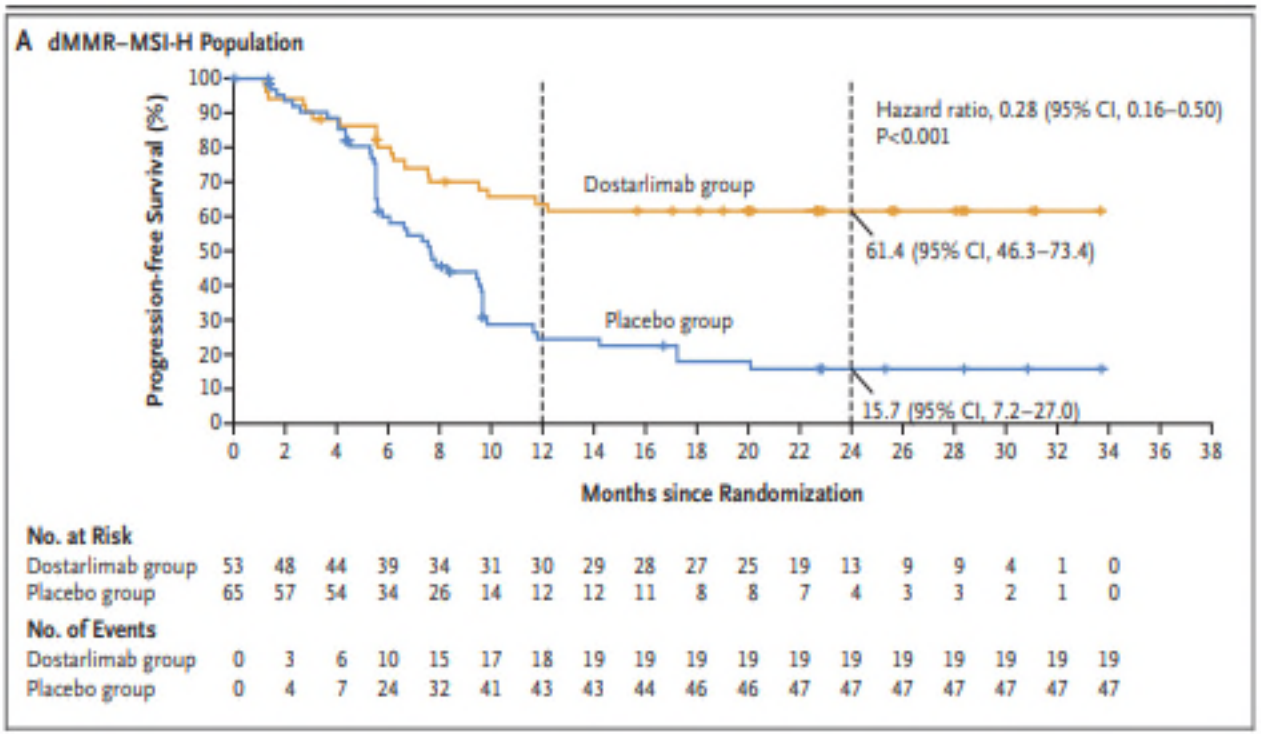
Eskander et al, NEJM, 2023

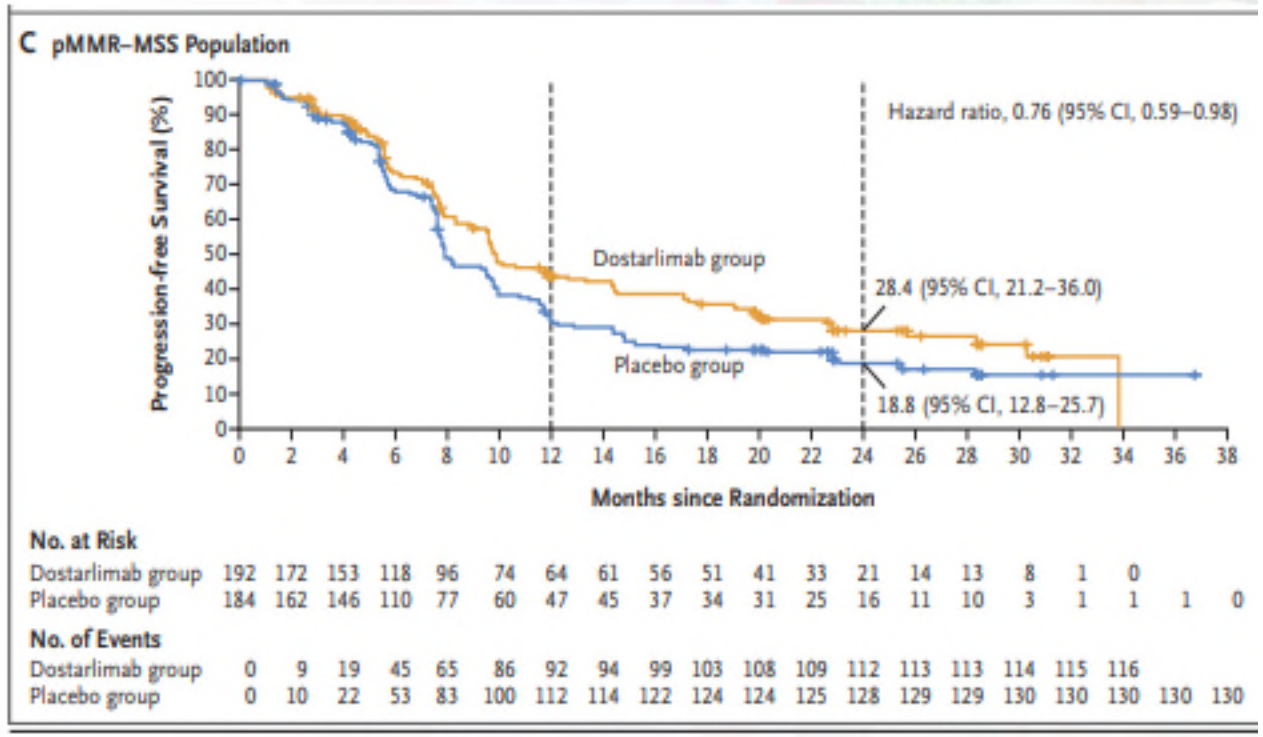
# ENGOT-EN6-NSGO/GOG-3031/RUBY




Mirza et al, NEJM, 2023

# PFS Results




Mirza et al, NEJM, 2023

# Endometrial Cancer

- The addition of pembrolizumab or dostarlimab to standard of care chemotherapy (PC), followed by immunotherapy maintenance, resulted in reduction in the risk of disease progression or death in patients with dMMR and pMMR endometrial cancer, respectively
- This benefit was identified in all evaluable subgroups, including patients who received prior adjuvant chemotherapy, prior radiation, and in less common histologic subtypes.
- The addition of pembrolizumab or dostarlimab did not appear to increase the frequency of adverse events commonly associated with PC combination chemotherapy.
- The incidence of immune-mediated adverse events was not greater than that observed in prior endometrial cancer studies examining pembrolizumab or dostarlimab monotherapy
- This is a new standard of care for patients with endometrial cancer with advanced stage disease or who have recurred greater than 6 months from their first systemic treatment

## SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

| Primary or Adjuvant Therapy (Stage I–IV) | |
|---|---|
| **Chemoradiation Therapy** | **Systemic Therapy** |
| **Preferred Regimens**<br>• Cisplatin plus RT followed by carboplatin/paclitaxel[1,2]<br><br>**Other Recommended Regimens[a]**<br>**(if cisplatin and carboplatin are unavailable)**<br>• Capecitabine/mitomycin[3]<br>• Gemcitabine[4]<br>• Paclitaxel[5,6] | **Preferred Regimens**<br>• Carboplatin/paclitaxel[7]<br>• Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8]<br>• Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9]<br>• Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,f,g,10]<br>• Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,f,g,10] |

[a] These agents may be considered when cisplatin and carboplatin are unavailable.
[b] For stage III or IVA with measurable disease or stage IVB with or without measurable disease.
[c] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[e] For stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV regardless of the presence of measurable disease.
[f] For patients who have not received prior trastuzumab therapy.
[g] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

References
Continued

# Platinum Resistant Ovarian Cancer

- 80% of patients with epithelial ovarian cancer present with advanced stage disease, and of these patients approximately 80% will relapse and require additional treatment
- Those who recur within the first 6 months of completing platinum- based therapy have the worst prognosis and are considered “platinum resistant”
- This includes women who progress during their initial platinum-based therapy, “platinum refractory”
- Treatment options in this setting are far less effective than for those with a longer platinum-free interval
- Limited effective treatment options for these patients
- Consider clinical trial as best option, otherwise chemotherapy with bevacizumab or chemotherapy alone
- With platinum resistant disease, quality of life paramount and treatment decisions should include side effect profile and tolerability

# Platinum Resistant Ovarian Cancer – Anti-Folate Receptor Alpha Based Antibody Drug Conjugates

- Folate receptor alpha (FRalpha) is anchored cell surface glycoprotein that mediates folate uptake into cells, which is needed for DNA synthesis, cellular metabolism, and proliferation, and it is marginally expressed in normal cells.

- It is overexpressed in up to 90–95% of epithelial ovarian carcinomas, mainly in serous and endometrioid subtypes.

    - Mirvetuximab soravtansine is an anti-FR ADC conjugated with the tubulin-targeting DM4 through a cleavable linker, with promising activity in epithelial ovarian carcinoma.

# Phase III MIRASOL (GOG 3045/ENGOT-ov55) Study: Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers with High Folate Receptor-Alpha (FRalpha) Expression

Key Inclusion Criteria:

- Advanced platinum-resistant high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers
- Received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy is appropriate as the next line of treatment
- Progressed on or after most recent line of therapy
- Tumor demonstrated FRα-high membrane staining with IHC PS2 scoring
- ≥75% of cells staining positive with ≥2+ staining intensity
- Prior bevacizumab and PARPi

Key Exclusion Criteria:

• Primary platinum-refractory disease, defined as disease that did not respond to or has progressed within 3 months of the last dose of first line platinum containing chemotherapy

Mirv vs Investigators Choice – weekly taxol, liposomal doxorubucin, or topotecan

Moore et al, ASCO 2023

**Phase III MIRASOL (GOG 3045/ENGOT-ov55)**

- Compared to IC chemo, MIRV:
  - 35% improvement in PFS with HR of 0.65, p<0.0001
  - More than doubled the ORR, 42%  vs 16%, p<0.0001 with 12 CRs compared to zero in the IC chemo group
  - Provided 33% improvement in OS with HR of 0.67, p=0.0046

- BICR PFS and ORR results are concordant with investigator assessment

- Results from both BEV-naïve and BEV-pretreated subgroups demonstrated a consistent benefit with MIRV in patients with platinum resistant disease

Moore et al, ASCO 2023

## Phase III MIRASOL (GOG 3045/ENGOT-ov55)

- MIRV is the first novel treatment to demonstrate an overall survival benefit in platinum resistant ovarian cancer in a phase 3 trial
- MIRV is the first ADC for ovarian with proven efficacy and is the only FDA-approved biomarker-directed therapy for platinum resistant ovarian cancer
- New standard of care for patients with FRalpha-positive platinum resistant ovarian cancer

Moore et al, ASCO 2023

# Mirvetuximab soravtansine plus bevacizumab

- Phase 1b/2 Study evaluating safety and tolerability of mirvetuximab soravtansine in combination with bevacizumab
- Other arms including mirv plus carbo, PDL, pembro, bev/carbo still pending (FORWARD II)
- FOLR1 expression levels of >=25% were included
- Dosing mirv 6 mg/kg adjusted ideal  body weight followed by bev 15 mg/kg IV q 3 weeks
- Range of FOLR1 expression: 47% >=75%, 42% 50-74%, 12% 25-49%
- > 50% of patients had 3 priors, 59% had prior bev, 27% had prior PARPs

Gilbert, et al, Gyn Oncology, 2023

# Mirvetuximab soravtansine plus bevacizumab

- ORR 44% (5 CR, 36 PR), mDOR 9.7 months, median PFS 8.2 months
- Activity  noted across all expression levels (longest PFS in highest expressors and bev-naive)
- Benchmark:
  - bev-naive platinum resistant patients in AURELIA - ORR 27%, mDOR 9.4 months, mPFS 6.7 months
  - bev-naive patients in this trial - ORR 56%, DOR 10.4 months, PFS 10.6 months irrespective of tumor FOLR1 expression level

Gilbert, et al, Gyn Oncology, 2023

# Management of Toxicity – Mirasol Protocol

**Table 7: Mirvetuximab Soravtansine Dose Reduction Dose Levels**

| If the patient was receiving MIRV at: | Dose should be reduced to: |
|---|---|
| 6.0 mg/kg AIBW | 5.0 mg/kg AIBW |
| 5.0 mg/kg AIBW | 4.0 mg/kg AIBW |
| 4.0 mg/kg AIBW | Permanently discontinue |
| *Reduction of MIRV below 4.0 mg/kg will not be permitted. Dose re-escalation is not permitted.* | |

Abbreviations: AIBW = adjusted ideal body weight; MIRV = mirvetuximab soravtansine.

# Toxicities with mirvetuximab soravtansine

- Ocular events:
  - 49% some form of vision impairment, 61% had any ocular AE
  - 9% grade 3, 0.2% grade 4 = 1 patient
  - 0.6% patients permanently discontinued drug
  - Median time to onset between C2-3, 1.2 months
  - NO PATIENTS had permanent sequelae
- Peripheral neuropathy: 33%, 1.9% grade 3
- Fatigue: 49%, 2.8% grade 3
- Pneumonitis: 10% (0.8% grade 3, 0.2% grade 4 = 1 patient)
- Infusion reactions: 9%
- GI toxicities, generally mild, few cases of grade 3-4 abdominal pain, diarrhea, constipation
- Decreased appetite, arthralgia, myalgia, dyspnea 10-18%, mostly grade 1-2

## PRINCIPLES OF SYSTEMIC THERAPY

### Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[n]/Fallopian Tube/Primary Peritoneal Cancer[o]

**Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)**

| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| Cytotoxic Therapy<br>Cyclophosphamide (oral)/ bevacizumab[i,35]<br>Docetaxel[36]<br>Etoposide, oral[37]<br>Gemcitabine[38,39]<br>Liposomal doxorubicin[38,39]<br>Liposomal doxorubicin/ bevacizumab[i,q,40]<br>Paclitaxel (weekly)[f,41]<br>Paclitaxel (weekly)/ bevacizumab[f,i,q,40]<br>Topotecan[42,43]<br>Topotecan/bevacizumab[i,q,40]<br><br>Targeted Therapy (single agents)<br>Bevacizumab[i,q,17,18]<br>Mirvetuximab soravtansine-gynx (for FRα-expressing tumors)[x,44] | Cytotoxic Therapy[s]<br>Capecitabine<br>Carboplatin[*]<br>Carboplatin/docetaxel[*]<br>Carboplatin/paclitaxel (weekly)[f,*]<br>Carboplatin/gemcitabine[10] ± bevacizumab[i,q,r,11,*]<br>Carboplatin/liposomal doxorubicin[12] ± bevacizumab[i,q,13,*]<br>Carboplatin/paclitaxel[f,14] ± bevacizumab[i,q,r,15,*]<br>Cyclophosphamide<br>Doxorubicin<br>Gemcitabine/bevacizumab[i,46]<br>Gemcitabine/cisplatin[16,*]<br>Ifosfamide<br>Irinotecan<br>Ixabepilone/bevacizumab (category 2B)[i,y,47]<br>Melphalan<br>Oxaliplatin<br>Paclitaxel<br>Paclitaxel, albumin bound<br>Pemetrexed<br>Sorafenib/topotecan[45]<br>Vinorelbine<br><br>Targeted Therapy (single agents)<br>Niraparib (category 3)[u,23]<br>Olaparib (category 3)[v,24]<br>Pazopanib (category 2B)[25]<br>Rucaparib (category 3)[w,26]<br><br>Hormone Therapy<br>Aromatase inhibitors (anastrozole, exemestane, letrozole)<br>Leuprolide acetate<br>Megestrol acetate<br>Tamoxifen | Carboplatin/paclitaxel (for age >70)[f,t,*]<br>Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*]<br>Immunotherapy<br>Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[x,32]<br>Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/ megabase)[x,33]<br><br>Hormone Therapy<br>Fulvestrant (for low-grade serous carcinoma)<br><br>Targeted Therapy<br>Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[x,28]<br>Entrectinib or larotrectinib (for *NTRK* gene fusion positive tumors)[x]<br>Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors) (category 2B)[i,x,48,49]<br>Selpercatinib (for *RET* gene fusion-positive tumors)[x,29]<br>For low-grade serous carcinoma:<br>• Trametinib[30]<br>• Binimetinib (category 2B)[31,32] |

* Do not use in platinum-refractory disease.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

Continued

# Antibody Drug Conjugates Targeting Her2-Expressing Solid Tumors

**DESTINY-PanTumor-02 – tumor agnostic study including range of HER2-expressing solid tumors**

- antibody-drug conjugate (ADC) T-DXd consists of the humanized monoclonal antibody trastuzumab covalently linked to the TOP1 inhibitor deruxtecan
- international, phase II, open-label study that involved 267 patients across 7 different cohorts, including 6 tumor-specific cohorts (urothelial bladder, biliary tract, cervical, endometrial, ovarian, and pancreatic cancers) as well as a rare tumor cohort that included a range of tumor types for which T-DXd is currently either not available or not being investigated (including head and neck cancers and intestinal adenocarcinoma)
- Efficacy and safety of trastuzumab deruxtecan presented at ASCO 2023 with interim results
- T-DXd is approved by the U.S. Food and Drug Administration for use in unresectable or metastatic HER2-positive breast cancer, HER2-low breast cancer, HER2-mutant non–small cell lung cancer, and locally advanced or metastatic HER2-positive gastric cancer

Meric-Bernstam et al, ASCO 2023

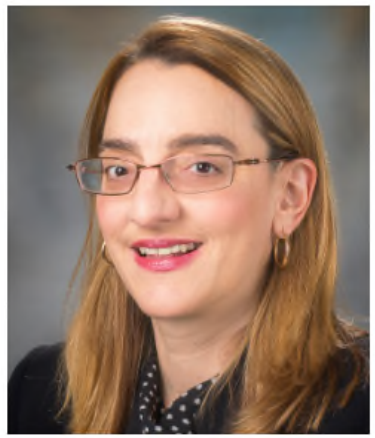
2023 ASCO ANNUAL MEETING

# DESTINY-PanTumor-02: Trastuzumab Deruxtecan Has Activity Against a Range of HER2-Expressing Solid Tumors

June 5, 2023 | Updated June 7, 2023

**Key Points:**

- Interim results of the phase 2 trial DESTINY-PanTumor-02 show that T-DXd has broad activity across tumor types and a toxicity profile consistent with previous studies.
- T-DXd had the lowest activity in pancreatic cancer, and this cohort was stopped early.
- Responses were especially high among patients who had cervical, endometrial, and ovarian cancers.



Dr. Funda Meric-Bernstam

The interim results of the phase 2 trial DESTINY-PanTumor-02, a tumor-agnostic study including a range of HER2-expressing solid tumors, show that trastuzumab deruxtecan (T-DXd) has broad activity across tumor types and a

Meric-Bernstam et al, ASCO 2023

# Antibody Drug Conjugates Targeting Her2-Expressing Solid Tumors

**DESTINY-PanTumor-02 – tumor agnostic study including range of HER2-expressing solid tumors**

- Endometrial cancer patients (n=40) – 57.5% ORR, median DOR not reached
- Cervical cancer patients (n=40) – 50% ORR, median DOR 9.8 months
- Ovarian cancer patients (n=40) – 45% ORR, median DOR 11.3 months

- Endometrial cancer patients – if HER2 IHC 3+ 84.6% ORR, if HER2 IHC 2+ 47.1% ORR
- Cervical cancer patients - if HER2 IHC 3+ 75% ORR, if HER2 IHC 2+ 40% ORR
- Ovarian cancer patients - if HER2 IHC 3+ 63.6% ORR, if HER2 IHC 2+ 36.8% ORR

- T-DXd demonstrated clinically meaningful activity across a large arrange of HER-2 expressing solid tumors
  - ORR 37.1% in all patients and 61.3% in patients with IHC 3+
  - Durable response rates: median ORR 11.8 months in all patients and 22.1 months in patients with IHC 3+
  - Safety of T-DXd was consistent with known profile

Meric-Bernstam et al, ASCO 2023

# Antibody Drug Conjugates Targeting Her2-Expressing Solid Tumors

- Where are these drugs best used?
- Should we be testing all recurrent ovarian, endometrial, and cervical cancers for HER2
- Is IHC scoring reproducible, what scoring system should be used?
- Need to be familiar with the toxicity profile
- The trial DESTINY-PanTumor-02 trial is ongoing, OS and PFS will be analyzed with additional follow up

Cervical cancer – additional of pembrolizumab in first-line treatment for persistent, recurrent, or metastatic disease

**KEYNOTE-826: Final overall survival results from a randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of persistent, recurrent, or metastatic cervical cancer**

- Pembrolizumab added to chemotherapy with or without bevacizumab was evaluated as a first-line treatment for patients with persistent, recurrent, or metastatic cervical cancer
- Has persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has not been treated with systemic chemotherapy and is not amenable to curative treatment (such as with surgery and/or radiation).
- Trial arm participants receive an intravenous (IV) infusion of pembrolizumab 200 mg for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin Area Under the Curve (AUC) 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label).

Monk et al, ASCO 2023

dailynews.ascopubs.org/do/keynote-826-update-confirms-survival-benefit-addition-pembrolizumab-first-line

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2023 ASCO ANNUAL MEETING

# KEYNOTE-826 Update Confirms Survival Benefit With Addition of Pembrolizumab to First-Line Chemotherapy in Cervical Cancer

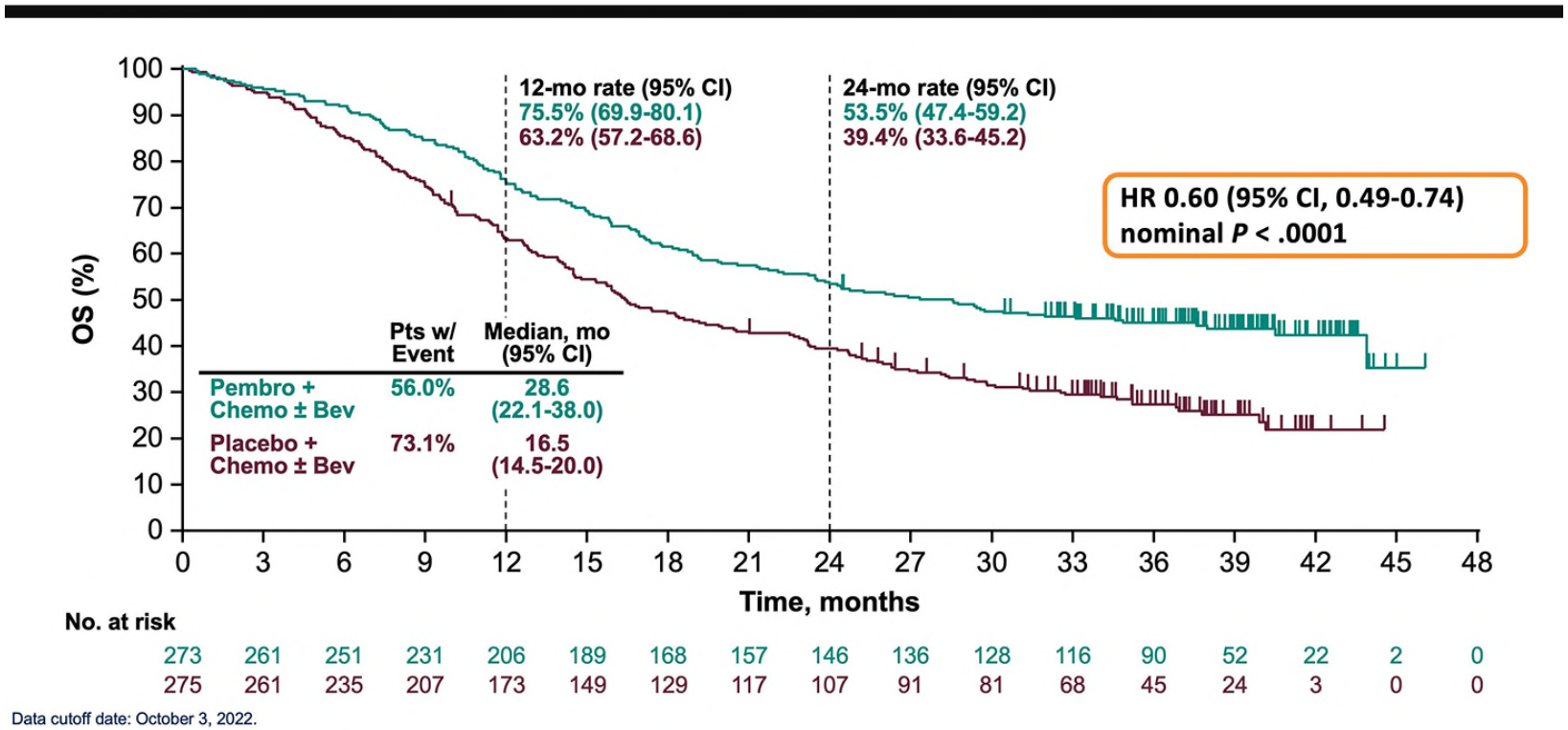
June 3, 2023

**Key Points:**

- KEYNOTE-826 data continues to show a significant OS and PFS benefit with the addition of pembrolizumab to chemotherapy with or without bevacizumab in the first-line treatment of patients with persistent, recurrent, or metastatic cervical cancer.
- No new safety findings were noted after more than 3 years of follow up.
- Investigators concluded that the

Dr. Bradley J. Monk

## Overall Survival Data




Data cutoff date: October 3, 2022.

Monk et al, ASCO 2023

Cervical cancer – additional of pembrolizumab in first-line treatment for persistent, recurrent, or metastatic disease

**KEYNOTE-826: Final overall survival results from a randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of persistent, recurrent, or metastatic cervical cancer**

- After more than 3 years of follow up, KEYNOTE-826 (median follow up 39.1 months) continues to show a significant OS and PFS benefit with the addition of pembrolizumab to chemotherapy with or without bevacizumab in the first-line treatment of patients with persistent, recurrent, or metastatic cervical cancer.
- Pembro + chemo significantly improved OS and PFS in the CPS ≥1, all-comer, and CPS ≥10 populations
- Addition of pembro to chemo ± bev significantly reduced the risk of death by 40% in the PD-L1 CPS ≥1 population, by 37% in the all-comer population, and by 42% in the CPS ≥10 population, and had a manageable safety profile.
- No new safety findings were noted after more than 3 years of follow up
- Findings support use of pembrolizumab plus chemotherapy with or without bevacizumab as a new standard of care for patients with persistent, recurrent, or metastatic cervical cancer

Monk et al, ASCO 2023

## SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

| Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma | | |
|---|---|---|
| **Chemoradiation[b]** | **Recurrent or Metastatic Disease** | |
| | **First-line Therapy[b,d]** | **Second-line or Subsequent Therapy[i]** |
| **Preferred Regimens**<br>• Cisplatin<br>• Carboplatin if patient is cisplatin intolerant<br><br>**Other Recommended Regimens[c] (if cisplatin and carboplatin are unavailable)**<br>• Capecitabine/mitomycin[1]<br>• Gemcitabine[2]<br>• Paclitaxel[3,4] | **Preferred Regimens**<br>• PD-L1–positive tumors<br>▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[e,f,g,h,5]<br>▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[e,f,g,h,5]<br>• Cisplatin/paclitaxel/bevacizumab[e,h,6] (category 1)<br>• Carboplatin/paclitaxel/bevacizumab[e,h]<br><br>**Other Recommended Regimens**<br>• Cisplatin/paclitaxel (category 1)[7,8]<br>• Carboplatin/paclitaxel[9,10] (category 1 for patients who have received prior cisplatin therapy)<br>• Topotecan/paclitaxel/bevacizumab[e,h,6,11] (category 1)<br>• Topotecan/paclitaxel[11]<br>• Cisplatin/topotecan[11]<br>• Cisplatin[8]<br>• Carboplatin[12,13] | **Preferred Regimens**<br>• Pembrolizumab for TMB-H tumors[f,j] or PD-L1–positive[g] or MSI-H/dMMR tumors[f,14]<br>• Tisotumab vedotin-tftv[15]<br>• Cemiplimab[f,16]<br><br>**Other Recommended Regimens**<br>• Bevacizumab[e]<br>• Paclitaxel[13,17]<br>• Albumin-bound paclitaxel<br>• Docetaxel<br>• Fluorouracil<br>• Gemcitabine<br>• Pemetrexed<br>• Topotecan<br>• Vinorelbine<br>• Irinotecan<br><br>**Useful in Certain Circumstances**<br>• PD-L1–positive tumors<br>▸ Nivolumab[f,g,18]<br>• HER2-positive tumors (IHC 3+ or 2+)<br>▸ Fam-trastuzumab deruxtecan-nxki[19]<br>• RET gene fusion-positive tumors<br>▸ Selpercatinib<br>• *NTRK* gene fusion-positive tumors<br>▸ Larotrectinib<br>▸ Entrectinib |

Footnotes on CERV-F 1A of 3

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

Continued
References

# Summary

- Significant changes to indications for PARP inhibitors in the management of recurrent ovarian cancer – find those patients that will benefit as it can be life changing for them
- PARP inhibitor maintenance is an important consideration for all epithelial ovarian cancer patients, consider combination with bevacizumab if clinically indicated
    - Every patient who is being treated initially with epithelial ovarian cancer, ask yourself if she will benefit from a PARP inhibitor
- New standard of care for metastatic or platinum sensitive recurrent endometrial cancer with the addition of immunotherapy to chemotherapy  discuss indications for use of immunotherapy in cervical cancer
- Antibody drug conjugates targeting alpha folate receptor are effective in platinum resistant ovarian cancer
- Antibody drug conjugates targeting HER2 expressing tumors appear to have efficacy in gynecologic cancers
- The addition of pembrolizumab to chemotherapy with or without bevacizumab in the management of recurrent, metastatic, or persistent cervical cancer demonstrates overall survival benefit

# Thank you!

- PLEASE ENROLL YOUR PATIENTS ON CLINICAL TRIALS
- REACH OUT WITH QUESTIONS

Email: jgcohen@coh.org