Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress

Endometrial Cancer

Saturday, April 12, 2025

6:00 AM – 7:30 AM

Faculty

Kathryn M Lyle, MSN, WHNP-BC, AGNP-C
Ritu Salani, MD, MBA
Jaclyn Shaver, MS, APRN, CNP, WHNP
Brian M Slomovitz, MD

Moderator

Neil Love, MD

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Faculty

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Ms Lyle — Disclosures

No relevant conflicts of interest to disclose.

Dr Salani — Disclosures

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Ms Shaver — Disclosures

No relevant conflicts of interest to disclose.

Dr Slomovitz — Disclosures

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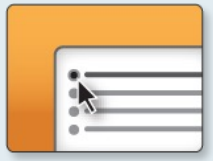
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

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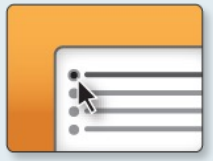

Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

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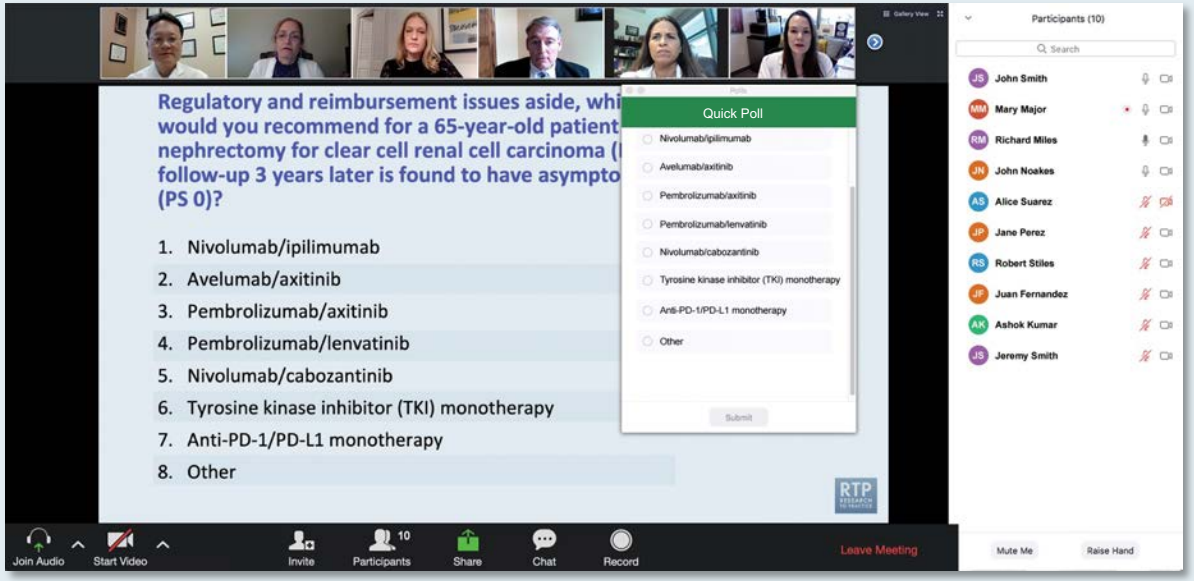
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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ONCOLOGY NURSING UPDATE WITH DR NEIL LOVE

Bispecific Antibodies in Lymphoma Part 1 — An Interview with Ms Robin Klebig for Oncology Nurses

MS ROBIN KLEBIG
MAYO CLINIC

Listen on Apple Podcasts

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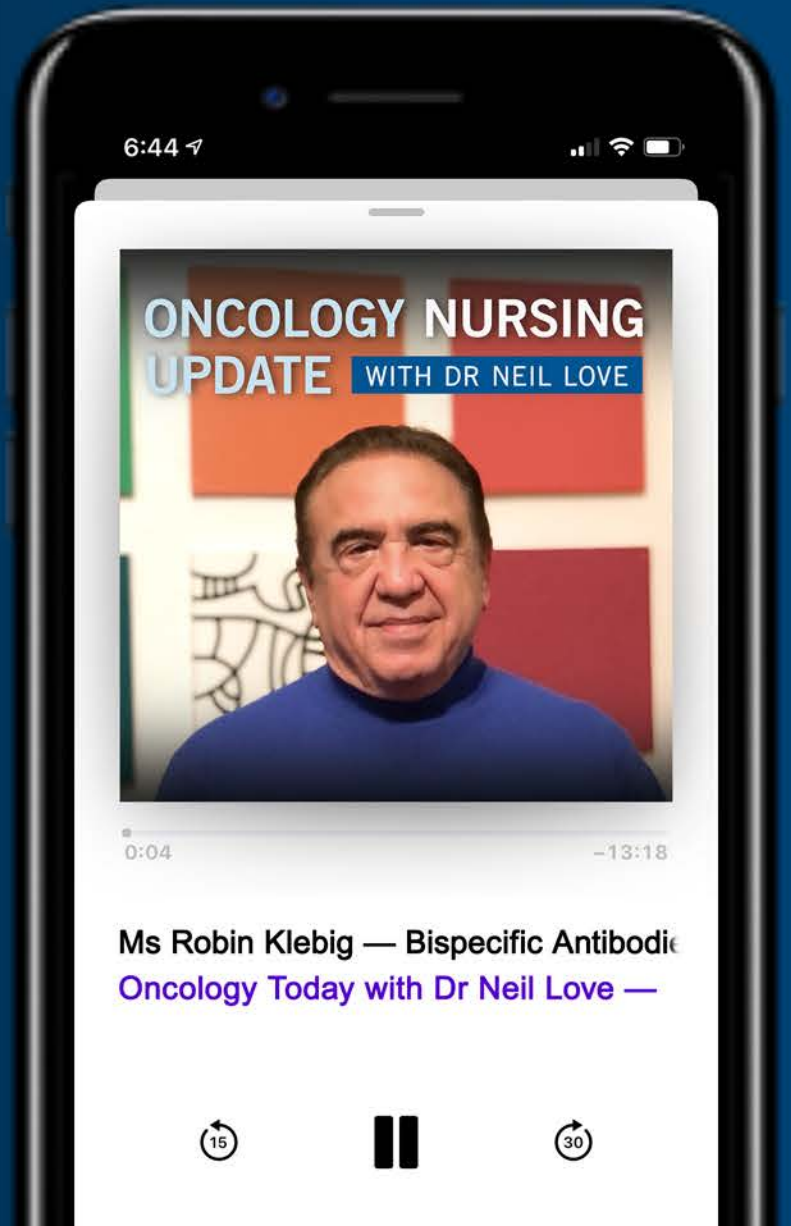
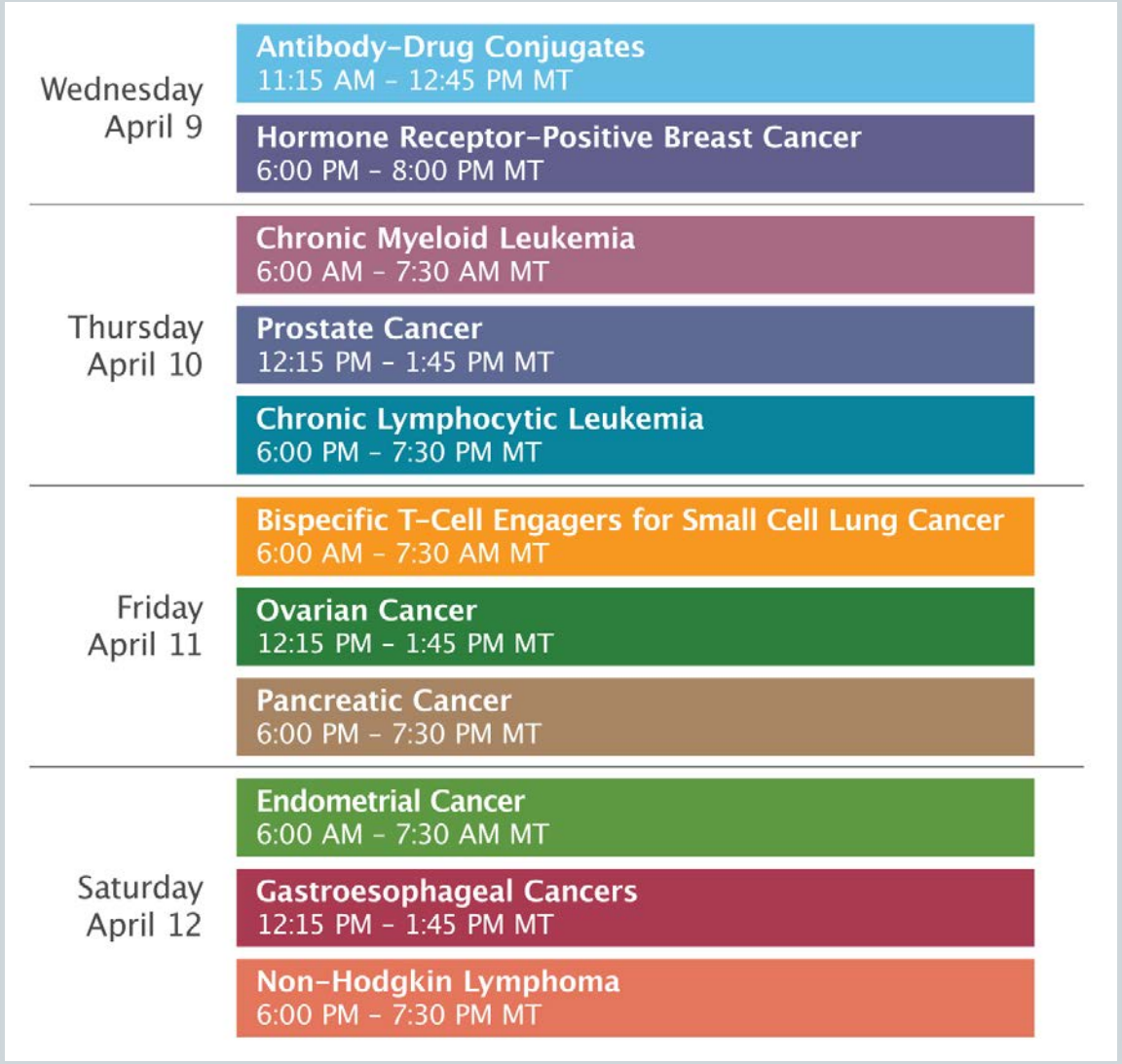


“Understanding the Current Paradigm and New Approaches”
Seventeenth Annual RTP-ONS NCPD Symposium Series



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Understanding the Current Paradigm and New Approaches
RTP Faculty at ONS 2025

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Agenda

Introduction: Overview of Endometrial Cancer (EC)

Module 1: First-Line Therapy for Advanced or Recurrent EC

Module 2: Role of Lenvatinib/Pembrolizumab in the Management of Progressive Advanced EC

Module 3: Novel Investigational Strategies for Newly Diagnosed Advanced EC

Module 4: Incidence and Management of HER2-Positive EC

Agenda

Introduction: Overview of Endometrial Cancer (EC)

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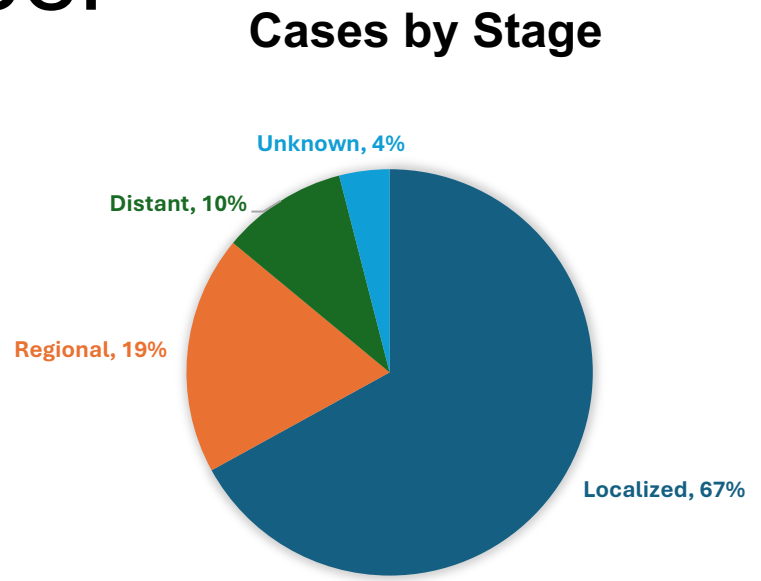
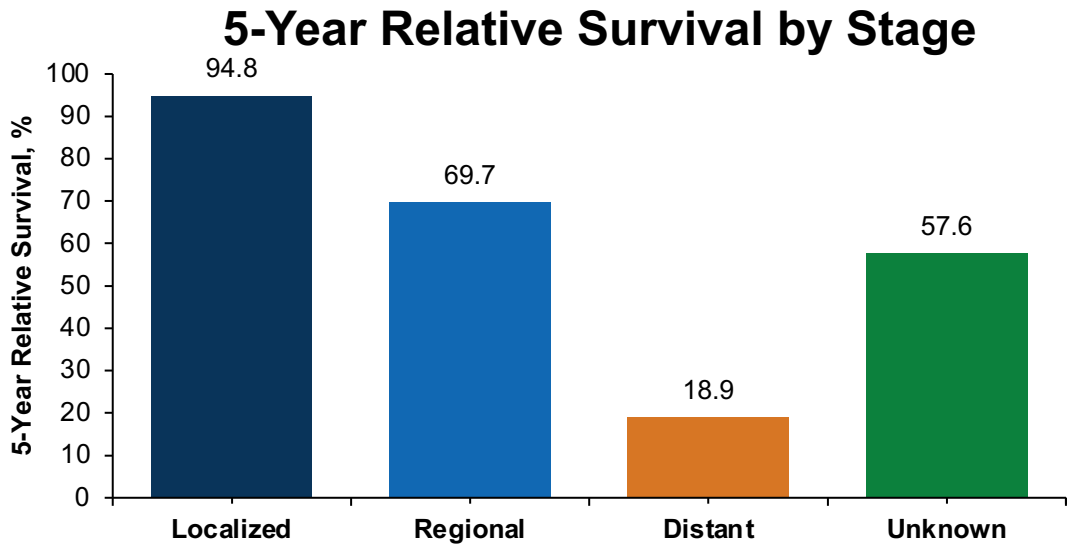
Overview of Endometrial Cancer

- Estimated 69,120 new cases
  - 3.4% of all cancers
- Estimated 13,860 deaths





Siegel RL, et al. *CA Cancer J Clin*. 2025;75. https://seer.cancer.gov/statfacts/html/corp.html?statfacts_page=corp

Agenda

Introduction: Overview of Endometrial Cancer (EC)

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Clinical Scenario

A patient with newly diagnosed mismatch repair-deficient metastatic EC is about to start treatment with chemotherapy in combination with an anti-PD-1/PD-L1 antibody

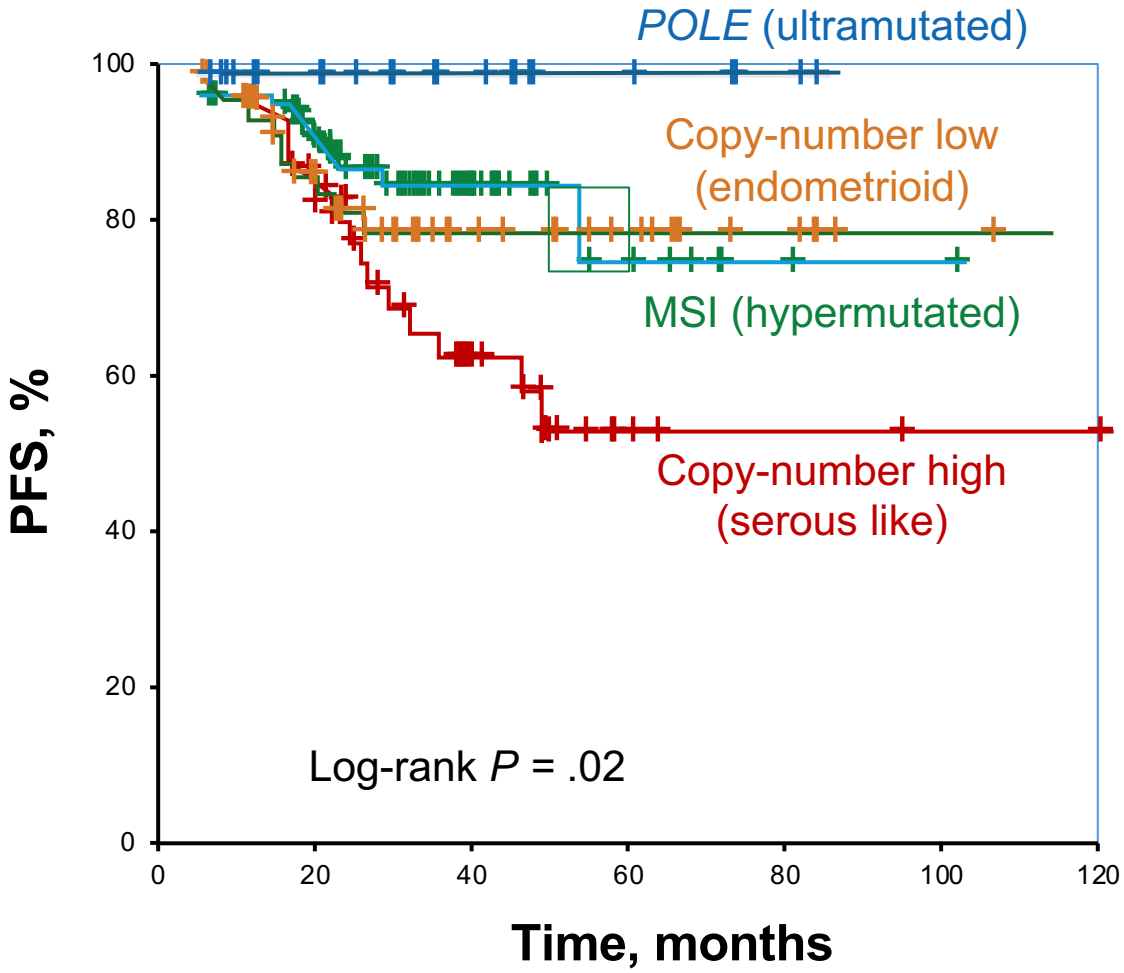
Endometrial Cancer First Line Therapy

Ritu Salani MD, MBA

Professor

UCLA

Molecular Profiling in Endometrial Cancer



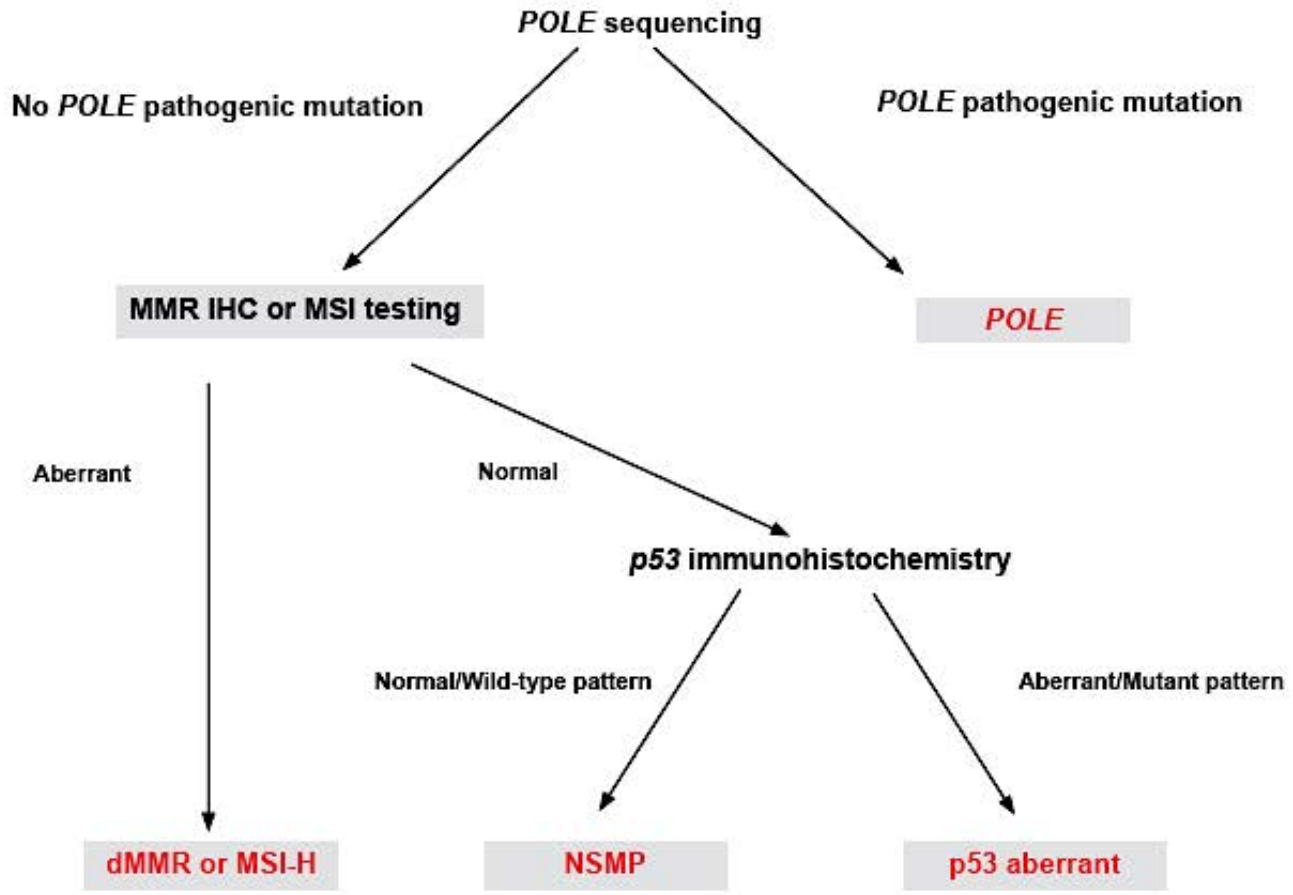
***POLE*: ultramutated, 100-500 mutations/Mb**	• 5%-10% of endometrial cancers • High mutation burden leads to better immune response, excessive mutations lead to inability to proliferate
dMMR/MSI-H: 10-20 mutations/Mb	• 20%-30% of endometrial cancers • Hereditary (Lynch syndrome) or somatic
CN low/NSMP/*TP53* WT/MSS: 2-3 mutations/Mb, endometrioid, G1	• Most common endometrial cancer • Low-grade tumors • Estrogen/progesterone positive • *PTEN, PIK3CA, ARID1A*, and *KRAS* mutations
CN high/*TP53* abn: 2-3 mutations/Mb, high grade	• Often serous or mixed histology • Poorest prognosis

1. The Cancer Genome Atlas Research Network. *Nature*. 2013;497:67-73.

ProMisE Tool Classification of Endometrial Cancer

PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center.)[f,g]



1. MMR deficiency evaluated by IHC (MSH6 and PMS2)
2. *POLE* sequencing (exons 9-14)
3. p53 expression determined by IHC

Biomarker testing

- MMR testing (IHC)
- P53 (IHC)
- HER2 (IHC)
- ER/PR (IHC)

- POLE testing (NGS)
  - Early stage, high risk factors
- TMB (NGS)
- MSI (NGS)

<u>Other considerations</u>

- Primary or recurrent
- Stage
  - Surgical resection status
- Comorbidities

Advanced Endometrial Cancer
Checkpoint inhibitors and Chemotherapy

Key Eligibility Criteria

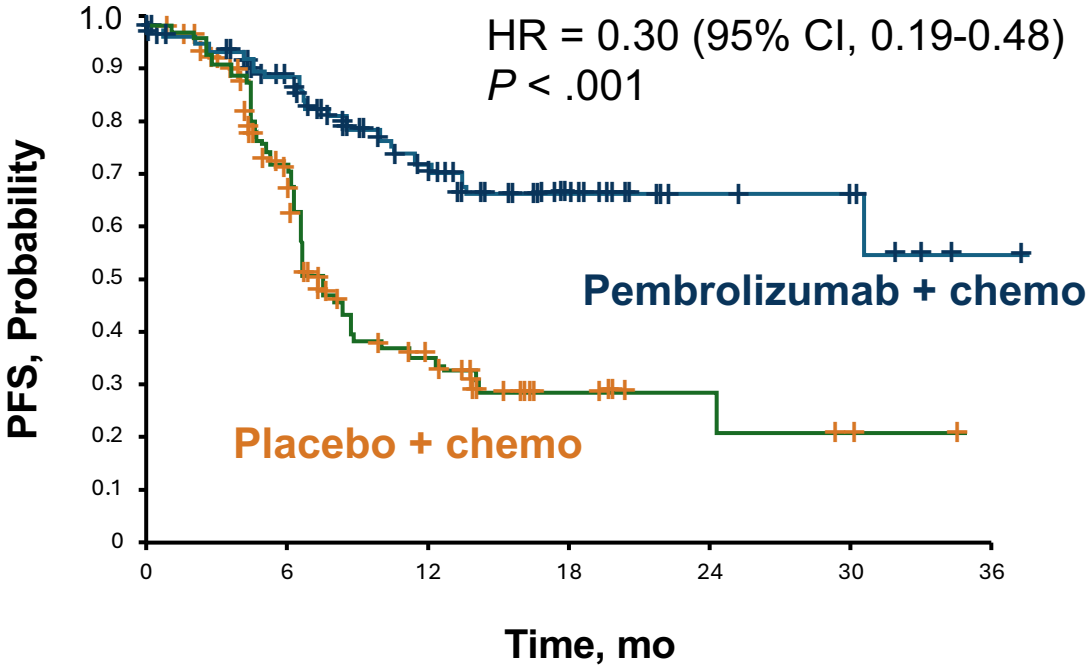
- Advanced (III-IV) or recurrent EC
- MMR status
- No previous chemotherapy for EC
- previous adjuvant chemotherapy allowed if completed ≥6-12 mo ago

R

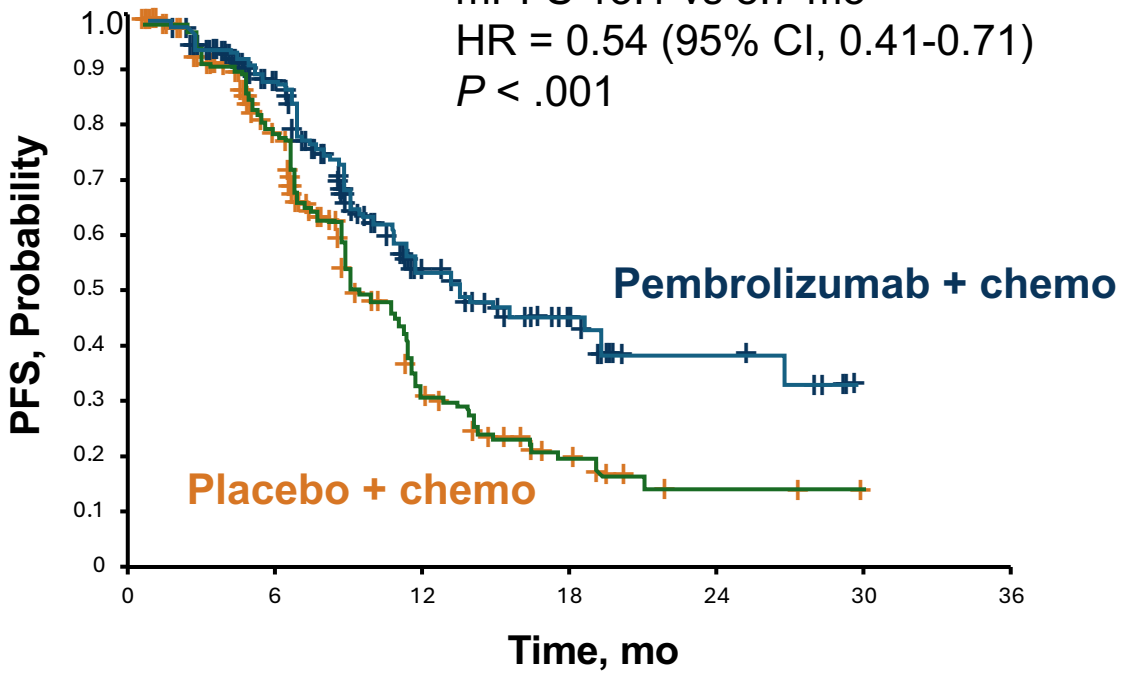
Pembrolizumab + carboplatin/paclitaxel Q3W for up to 6 cycles	**Pembrolizumab** Q6W for up to 14 cycles	**NRG-GY018**
Dostarlimab 500 mg + **carboplatin/paclitaxel** Q3W for up to 6 cycles	**Dostarlimab** 1,000 mg Q6W for up to 3 y	**RUBY**
Durvalumab 1120 mg + **carboplatin/paclitaxel** Q3W for up to 6 cycles	**Durvalumab** 1,500 mg Q4W +/- olaparib indefinitely	**DUO-E**
Placebo + carboplatin/paclitaxel Q3W for up to 6 cycles	**Placebo**	

NRG-GY018: PFS

dMMR Cohort



pMMR Cohort

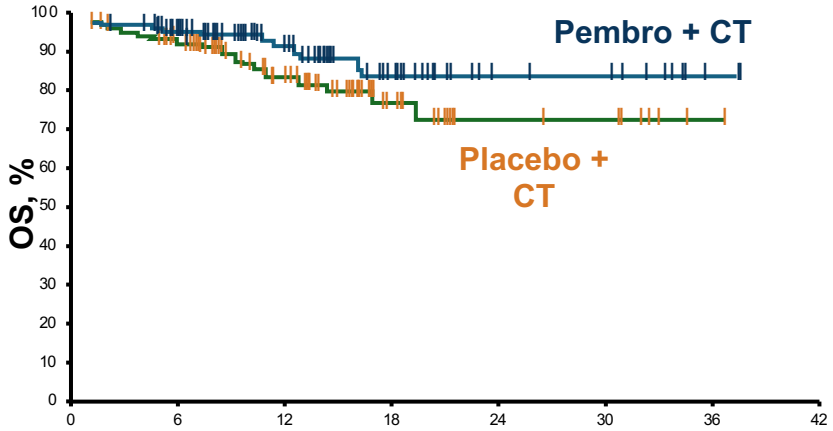


- Pembrolizumab improved INV PFS regardless of PD-L1 status for both the dMMR and pMMR populations

1. Eskander RN et al. *N Engl J Med*. 2023;388:2159-2170. 2. Eskander RN et al. SGO 2024. Abstract LBA.

NRG-GY018: OS

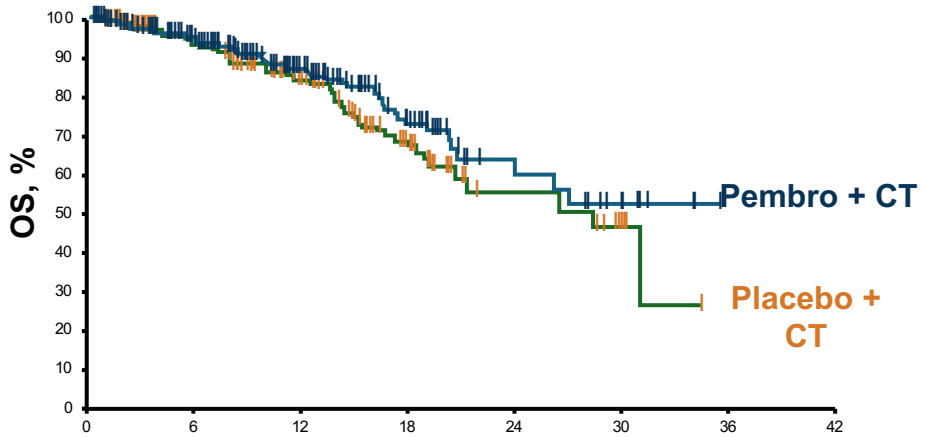
dMMR EC



	Events, n/N	Follow-Up Duration, Median (range), mo	Median OS (95% CI), mo	HR (95% CI), *P*
Pembro + CT	10/110	13.3 (0.6-39.4)	NR (NR-NR)	**0.55 (0.25-1.19)**
Placebo + CT	17/112	13.7 (1.0-38.0)	NR (NR-NR)	***P* = .0617**

Among those who discontinued treatment, more patients in the placebo + CT group vs the pembro + CT group received subsequent PD-1/PD-L1 inhibitors (54.5% vs 19.1%)

pMMR EC



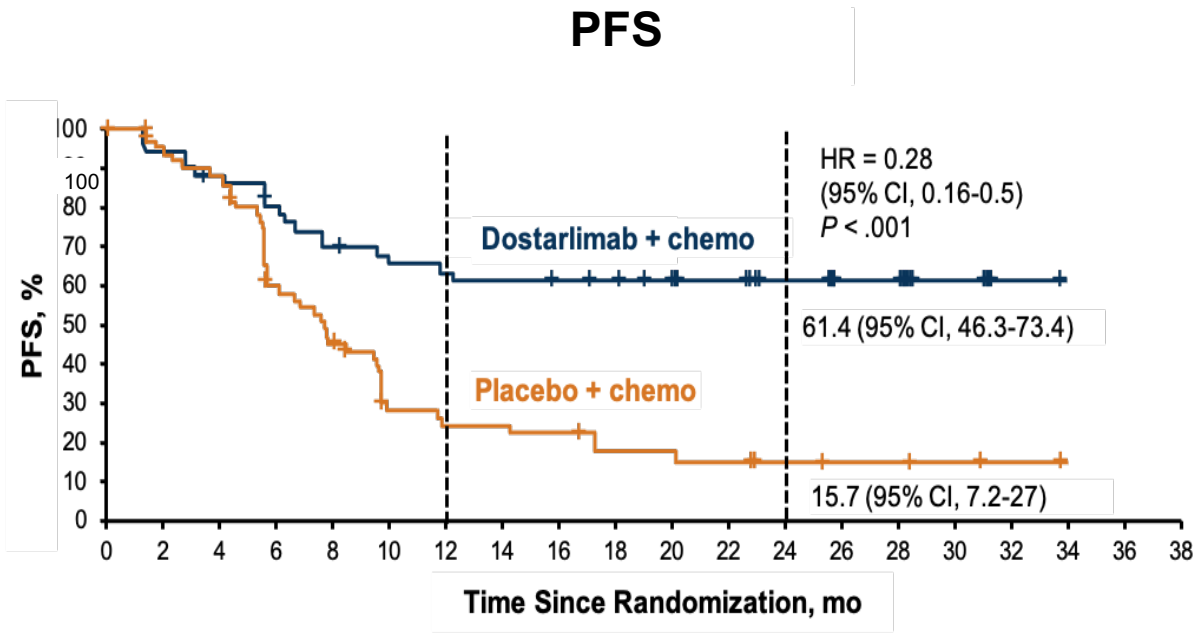
	Events, n/N	Follow-Up Duration, Median (range), mo	Median OS (95% CI), mo	HR (95% CI), *P*
Pembro + CT	45/294	8.8 (0.1-37.0)	27.96 (21.42-NR)	**0.79 (0.53-1.17)**
Placebo + CT	54/294	8.4 (1.0-37.2)	27.37 (19.52-NR)	***P* = .1157**

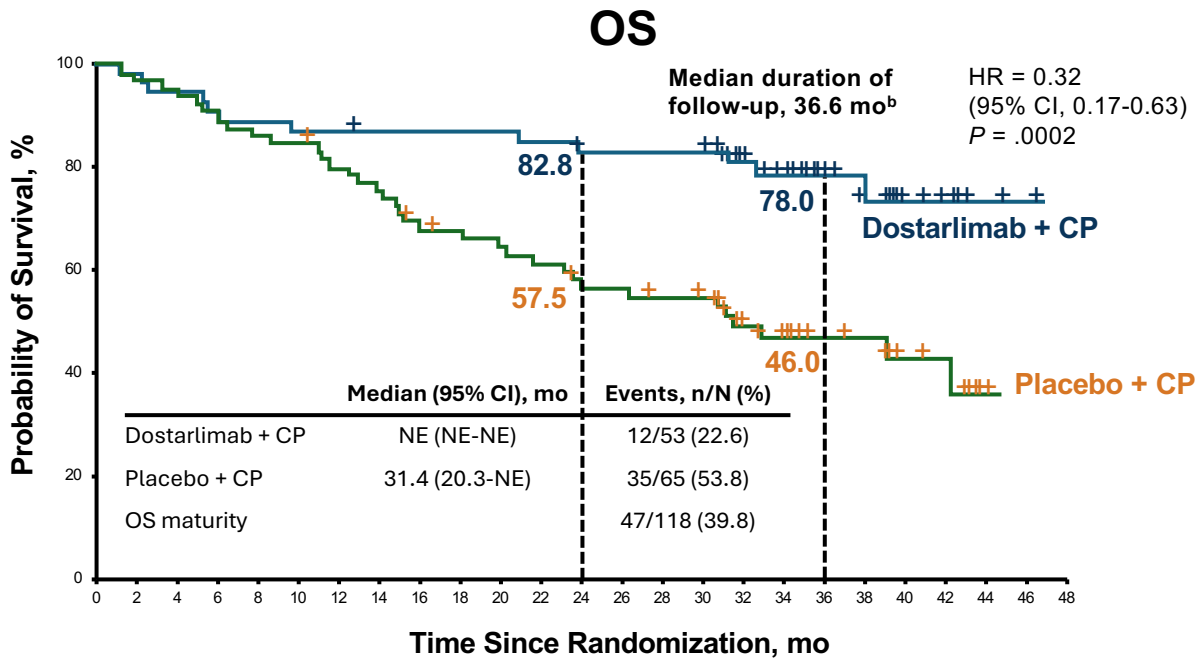
Among those who discontinued treatment, more patients in the placebo + CT group vs the pembro + CT group received subsequent PD-1/PD-L1 inhibitors (45.0% vs 19.3%)

June 17, 2024:
Pembrolizumab + chemotherapy followed by single-agent pembrolizumab approved by the FDA for patients with either dMMR or pMMR endometrial carcinoma

1. Eskander RN et al. SGO 2024 LBA. 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemotherapy-primary-advanced-or-recurrent-endometrial-carcinoma?utm_medium=email&utm_source=govdelivery.

RUBY: PFS and OS in dMMR



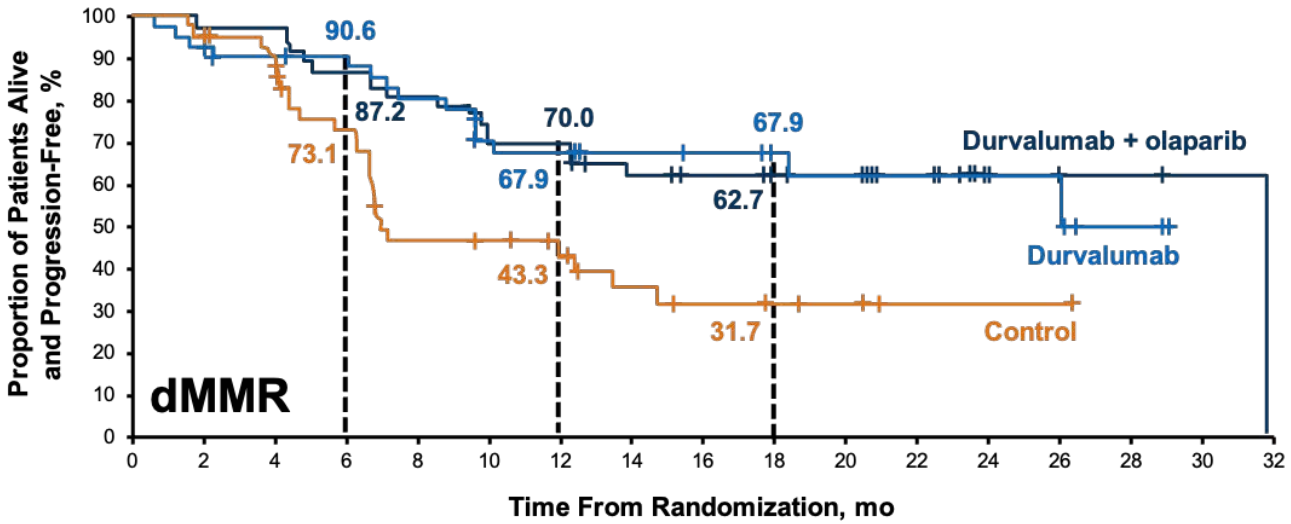


41.5% of patients in the placebo arm received subsequent immunotherapy

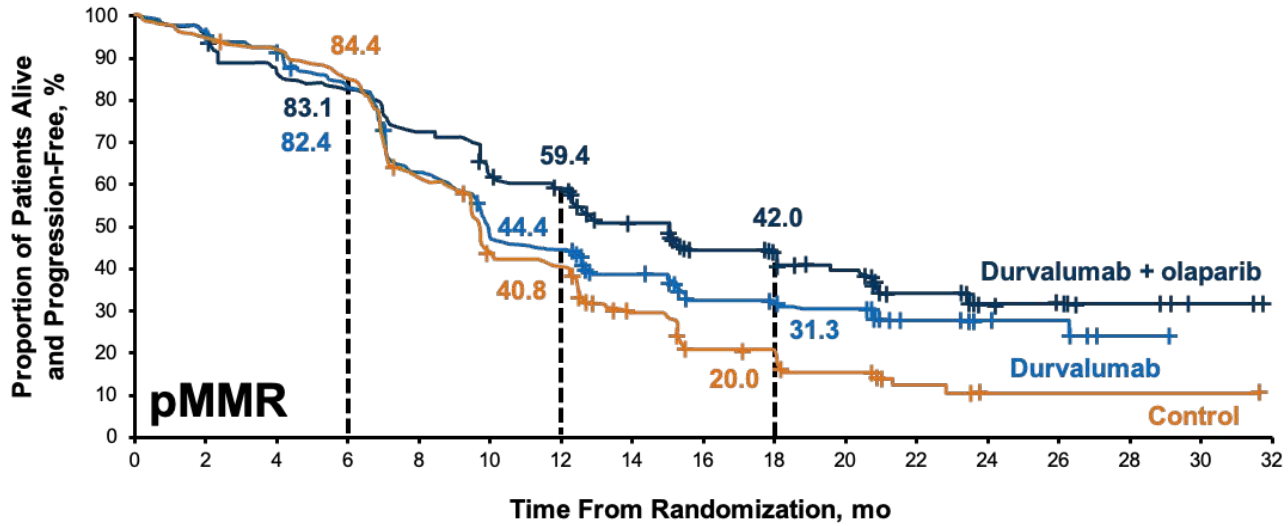
August 1, 2023
Expanded FDA approval of dostarlimab + chemotherapy followed by single-agent dostarlimab for patients with either dMMR or pMMR endometrial carcinoma

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

DUO-E: PFS by MMR Subgroups



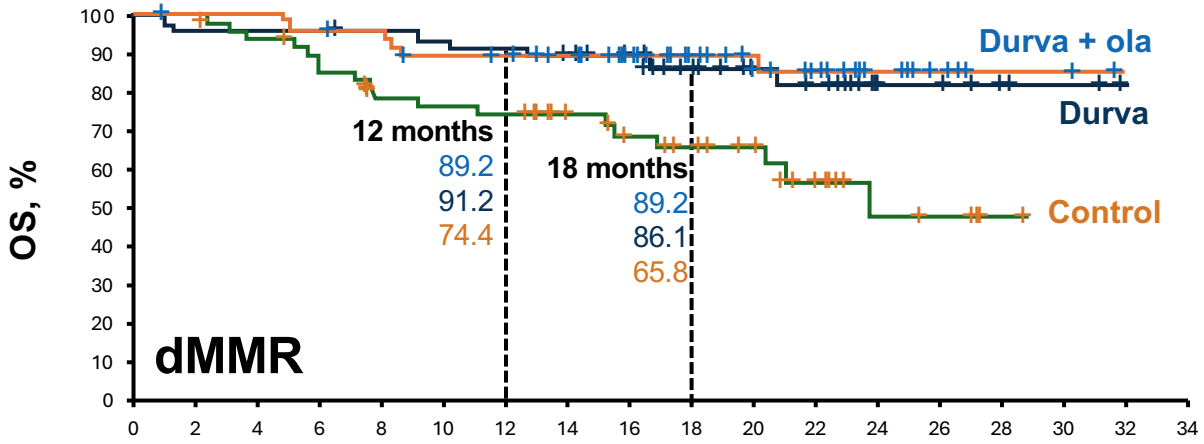
	Durvalumab + Olaparib Arm (n = 48)	Durvalumab Arm (n = 46)	Control Arm (n = 49)
Events, n (%)	18 (37.5)	15 (32.6)	25 (51.0)
Median PFS (95% CI), mo	31.8 (12.4-NR)	NR (NR-NR)	7.0 (6.7-14.8)
HR (95% CI) vs control	**0.41 (0.21-0.75)**	**0.42 (0.22-0.80)**	–



	Durvalumab + Olaparib Arm (n = 191)	Durvalumab Arm (n = 192)	Control Arm (n = 192)
Events, n (%)	108 (56.5)	124 (64.6)	148 (77.1)
Median PFS (95% CI), mo	15.0 (12.4-18.0)	9.9 (9.4-12.5)	9.7 (9.2-10.1)
HR (95% CI) vs control	**0.57 (0.44-0.73)**	**0.77 (0.60-0.97)**	–

1. Westin SN et al. ESMO 2023. Abstract LBA41. 2. Westin SN et al. *J Clin Oncol.* 2024;42:283-299.

DUO-E: OS

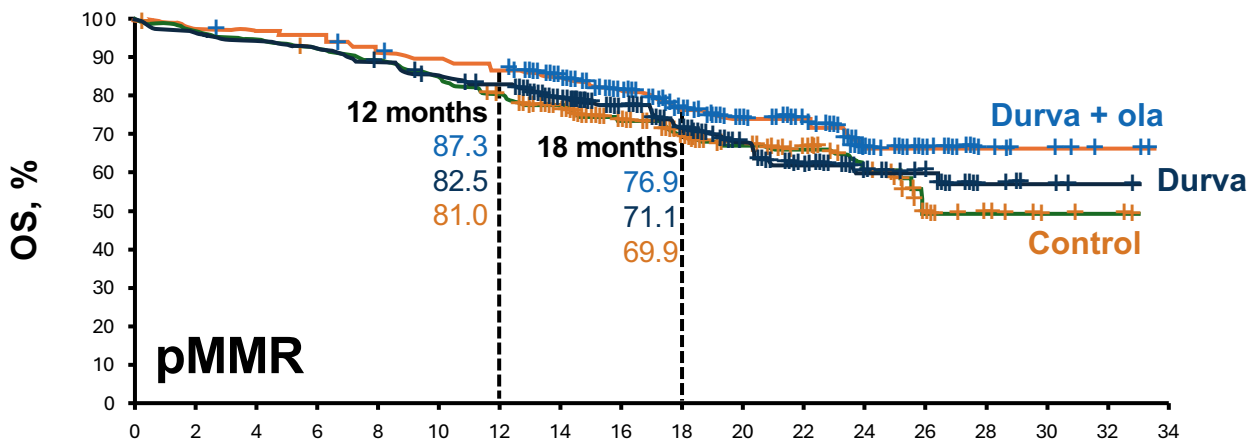


Time Since Randomization, mo

Durvalumab + C/P	15.2	NR (NR-NR)
Placebo + C/P	36.7	23.7 (16.9-NR)
OS data maturity	21.7%	

dMMR

HR = 0.28 (95% CI, 0.10-0.68); *Durva + Ola + C/P arm*
HR = 0.34 (95% CI, 0.13-0.79); *Durva + C/P arm*



Time Since Randomization, mo

Durvalumab + C/P	30.2	NR (NR-NR)
Placebo + C/P	33.3	25.9 (25.1-NR)
OS data maturity	29.2%	

pMMR

HR = 0.69 (95% CI, 0.47-1.00); *Durva + Ola + C/P arm*
HR = 0.91 (95% CI, 0.64-1.30); *Durva + C/P arm*

June 14, 2024: Durvalumab + chemotherapy followed by single-agent durvalumab approved by the FDA for patients with dMMR endometrial carcinoma

Westin SN et al. *J Clin Oncol.* 2024;42:283-299. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-chemotherapy-mismatch-repair-deficient-primary-advanced-or-recurrent

Conclusions

- Molecular testing is essential
  - Most testing can be done with IHC
- Endometrial Cancer with dMMR
  - Improved outcomes with chemotherapy and checkpoint inhibitor
  - FDA approval for pembrolizumab, dostarlimab and durvalumab
- NGS may identify candidates for immunotherapy outside of dMMR
  - POLE testing may allow for de-escalation of therapy

Roundtable Discussion

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Endometrial Cancer Symposium

Research To Practice | ONS 2025

Kathryn Lyle, MSN, WHNP-BC, AGNP-C

Division of Gynecologic Oncology

University of Alabama at Birmingham

Nursing Considerations for Patients Receiving an Anti-PD-1/PD-L1 Antibody

How does it work and why do we give it?

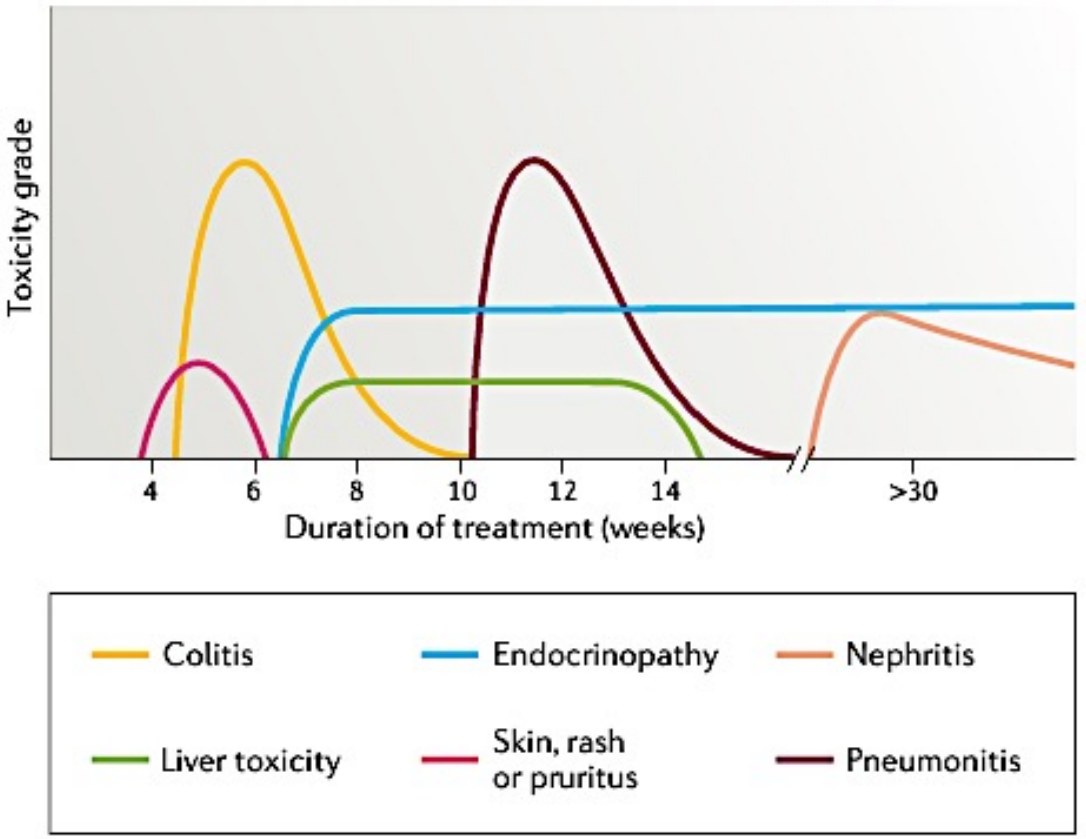
- Endometrial cancer cells can express PD-L1, which is why it's very important to order somatic testing on all patients with advanced or recurrent endometrial cancer.
- Tumor cells have PD-L1 receptors and T cells have PD-1 receptors. If you can block that interaction where they bind together (which prevents the T cell from killing cancer cells and puts the brakes on the immune system), you can rev up the immune system and allow T cells to kill the tumor cells.
- Immunotherapy can be used alone or in combination to treat endometrial cancer in certain circumstances.

How does it work and why do we give it?

- Mechanism of Action:
  - Immunotherapy uses the body's immune system to attack and kill cancer cells.
- Response time:
  - It can take longer to see an initial response to treatment with immunotherapy compared to traditional chemotherapy because it takes time for the immune response to occur.
  - Durable responses can occur even after discontinuation.
- Pseudoprogression

irAEs

- Non-specific activation of the immune system by checkpoint inhibitors causes immune-related adverse events (irAEs)
- The most common irAEs involve the skin, GI tract, endocrine system, and lungs (think *itis*)
- Timing of onset and duration varies
- Some toxicities can be reversible (GI, skin, pulmonary) while others may not be (endocrine)
- Monitoring:
  - Labs: TSH, FT4, LFTs (CBC, CMP, TSH)
  - CXR, CT scans
  - Closely monitor patients with pre-existing autoimmune disorders
- Management: Dose delay +/- steroid taper vs drug discontinuation



Martins, F., Sofiya, L., Sykiotis, G.P. *et al.* Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 16, 563–580 (2019).

irAEs

- Patient education is key to early recognition
- Consultation with other specialties may be needed (endocrinology, dermatology, etc)
- Utilize guidelines for patient management (i.e. ASCO Clinical Practice Guidelines, NCCN Guidelines: Management of Immunotherapy-Related Toxicities)
- Toxicity grading can vary some with each organ system, but in general:
  - Grade 1: Continue therapy and closely monitor patient.
  - Grade 2: Hold therapy. May consider steroid taper. Resume therapy once grade 1 or less.
  - Grade 3: Hold therapy and start high-dose corticosteroids with taper.
  - Grade 4: Typically permanently discontinue therapy.

Clinical Experience

- I have a 38yo Spanish speaking patient who was receiving single agent Pembrolizumab. 5 months into treatment, her normal TSH became low for one cycle, and then started increasing each cycle after that. She was started on Levothyroxine. She has significant financial toxicity and a challenging social situation (no car, moves from house to house with friends and family, inconsistent work as a roofer). She was non-compliant with taking her Levothyroxine. At one point, she wasn't tolerating the higher dose and self discontinued. Other times, she did not have the money to pay for her medication at her local pharmacy. She ultimately presented after missing multiple infusion/clinic appts with a hoarse voice, swollen face and extremities, and severe fatigue. TSH was >100. We admitted her to the hospital and had to urgently consult endocrinology. She ultimately was stabilized but could not go back on Pembrolizumab due to drug induced hypothyroidism with poor medication compliance. She is much better controlled today (TSH still abnormal but very much improved) and medication compliance remains an issue.

Roundtable Discussion

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Clinical Scenario

A patient with mismatch repair-proficient metastatic EC has experienced disease progression on first-line chemotherapy and is about to start treatment with lenvatinib/pembrolizumab

Endometrial Cancer Recurrence in pMMR EC

Ritu Salani MD, MBA

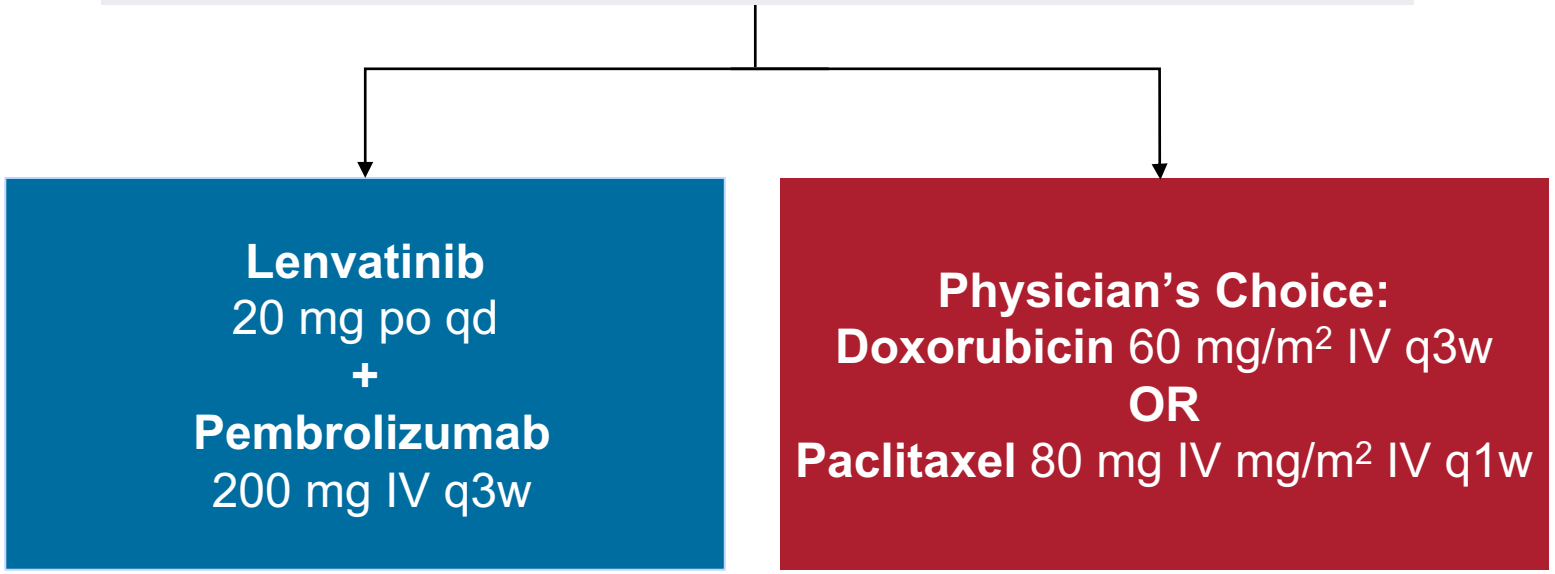
Professor

UCLA

KEYNOTE-775: Recurrent Endometrial Cancer

Key Eligibility Criteria

- Advanced, metastatic, or recurrent EC
- Measurable disease by BICR
- 1 prior platinum-based chemotherapy regimen
- ECOG PS 0–1



Stratification Factors

- MMR status (dMMR vs MMRp)
- ECOG PS
- Geographic region
- Prior pelvic radiation

Primary Endpoints

- PFS by BICR and OS

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

Study 309/KEYNOTE 775: Baseline Characteristics

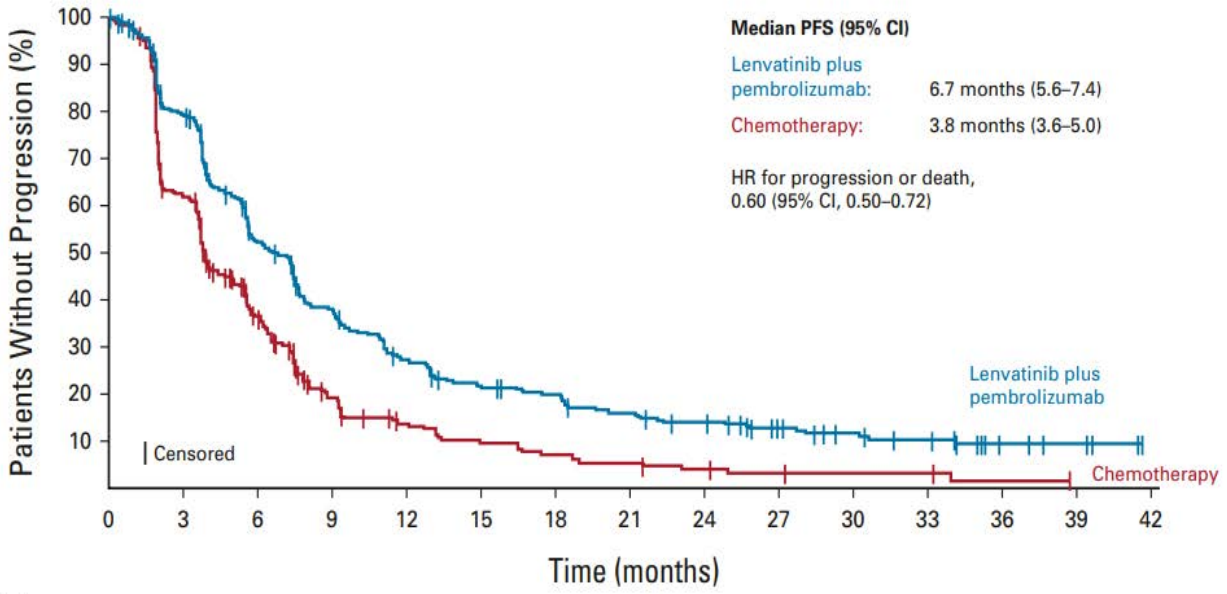
Characteristic	LEN + PEMBRO (N=411)	CT (N=416)
Median age (years)	64	65
Race, White/Black/Asian (%)†	63.5 / 4.1 / 20.7	59.1 / 3.4 / 22.1
MMR status, pMMR/dMMR (%)	84.2 / 15.8	84.4 / 15.6
ECOG PS, 0 or 1 (%)§	59.9 / 39.9	57.9 / 42.1
History of Pelvic Irradiation(%)	42.3	44.7
Histologic Features at Initial Diagnosis, n (%)¶		
Endometrioid carcinoma	243 (59.1)	254 (61.1)
High Grade	94 (22.9)	90 (21.6)
Low Grade	59 (14.4)	54 (13.0)
Not Specified ‖	90 (21.9)	110 (26.4)
Serous Carcinoma	103 (25.1)	115 (27.6)
Clear-cell Carcinoma	30 (7.3)	17 (4.1)
Mixed Features	22 (5.4)	16 (3.8)

* Percentages may not total 100 because of rounding. The term dMMR denotes mismatch repair–deficient, MMR mismatch repair, and pMMR mismatch repair–proficient.
† Race was reported by the patient. Data on race were missing for 36 patients (8.8%) in the lenvatinib–pembrolizumab group and for 44 (10.6%) in the chemotherapy group. Other races or ethnic groups (reported by 12 patients [2.9%] in the lenvatinib–pembrolizumab group and by 20 [4.8%] in the chemotherapy group) included American Indian or Alaska Native, Native Hawaiian, or Other Pacific Islander, and multiple.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability.
• One patient in the lenvatinib–pembrolizumab group had an ECOG performance status score of 3 (was enrolled in error).
¶ Information regarding histologic features at diagnosis for categories that included less than 5% of the patients is provided in Table S2.
‖ The "not specified" category included endometrioid carcinoma (grade not specified) and endometrioid carcinoma with squamous differentiation.

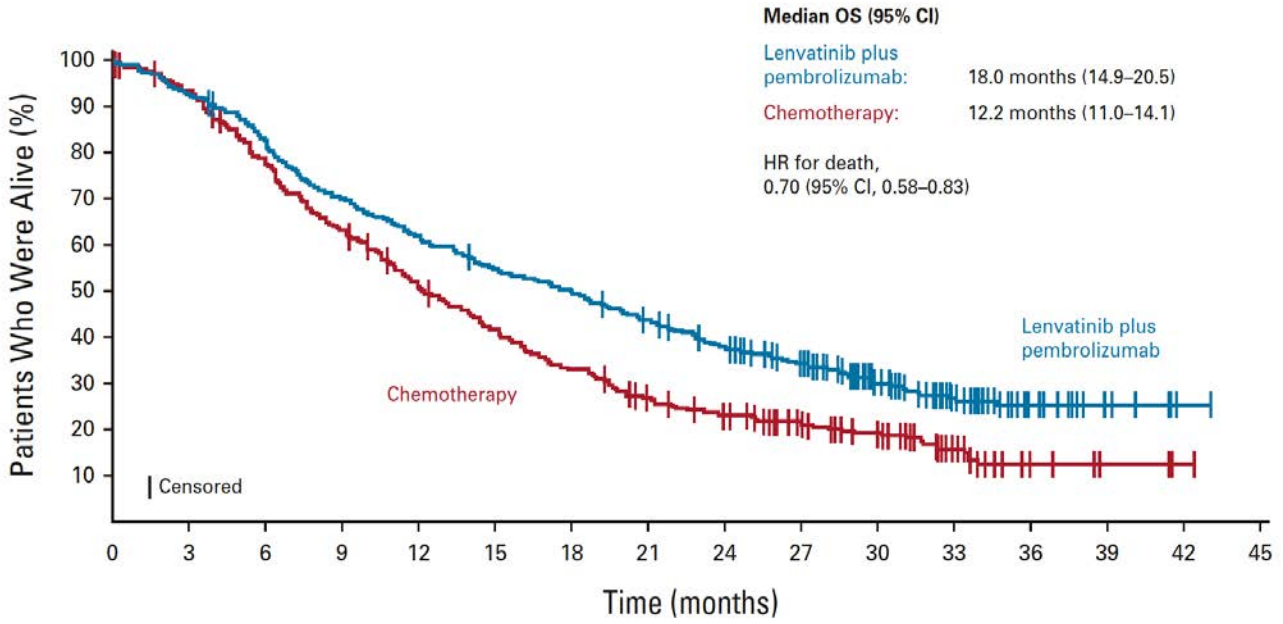
Adapted from: Makker V, et al. *N Engl J Med.* 2022;386:437-448.

KEYNOTE-775: Survival Outcomes-pMMR

Progression Free Survival



Overall Survival



pMMR Population	ORR, % (95% CI)	mDOR, mo (range)	mOS, mo (95% CI)	HR
Len + Pem	32.4 (27.5–37.6)	9.3 (1.6+ to 39.5+)	18.0 (14.2–19.9)	0.70 (0.56–0.83)
Chemotherapy	15.1 (11.5–19.3)	5.7 (0.0+ to 37.1+)	12.2 (11.0–14.1)	

Makker V. *J Clin Oncol*. 2023;41:2904-2910.

Study 309/KEYNOTE-775: Response

	pMMR Population		All Patients		dMMR Population	
	Lenvatinib + Pembrolizumab (N=346)	Chemotherapy (N=351)	Lenvatinib + Pembrolizumab (N=411)	Chemotherapy (N=416)	Lenvatinib + Pembrolizumab (N=65)	Chemotherapy (N=65)
Objective response, %	30.3	15.1	31.9	14.7	40	12
CR	5.2	2.6	6.6	2.6	14	3
PR	25.1	12.5	25.3	12.0	26	9
SD	48.6	39.6	47.0	40.1	38	43
PD	15.6	30.8	14.8	29.6	11	23
Median DOR, months §	9.2	5.7	14.4	5.7	NR	4.1
Median time to response, months	2.1	3.5	2.1	2.1	2.9	1.9
Disease control ¶, %	71.7	46.4	72	46.6	74	48

Subsequent Therapy

- ITT: 28% in lenvatinib + pembrolizumab, 48.1% in chemotherapy group
- pMMR: 9.1% in chemotherapy group received subsequent lenvatinib + pembrolizumab
- dMMR: 16.9% received PD-1 pathway–targeting monotherapy or combination regimens as subsequent therapies

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

KEYNOTE-775: Adverse Events

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 388)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypertension	65.0	39.2	5.2	2.6
Hypothyroidism	58.9	1.5	0.8	0
Diarrhea	55.7	8.1	20.4	2.1
Nausea	51.7	3.4	46.4	1.3
Decreased appetite	46.6	7.6	21.4	0.5
Vomiting	37.7	3.0	21.1	2.6
Weight decrease	35.5	10.8	5.9	0.3
Fatigue	34.0	5.4	27.6	3.1
Arthralgias	32.3	1.7	8.0	0

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 388)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Proteinuria	30.5	5.2	3.4	0.3
Constipation	28.3	0.7	24.5	0.5
Anemia	28.1	6.9	48.7	15.5
UTI	27.6	4.2	10.3	1.0
Headache	26.4	0.5	9.0	0.3
Neutropenia	9.1	2.0	34.0	26.0
Alopecia	5.9	0	30.9	0.3

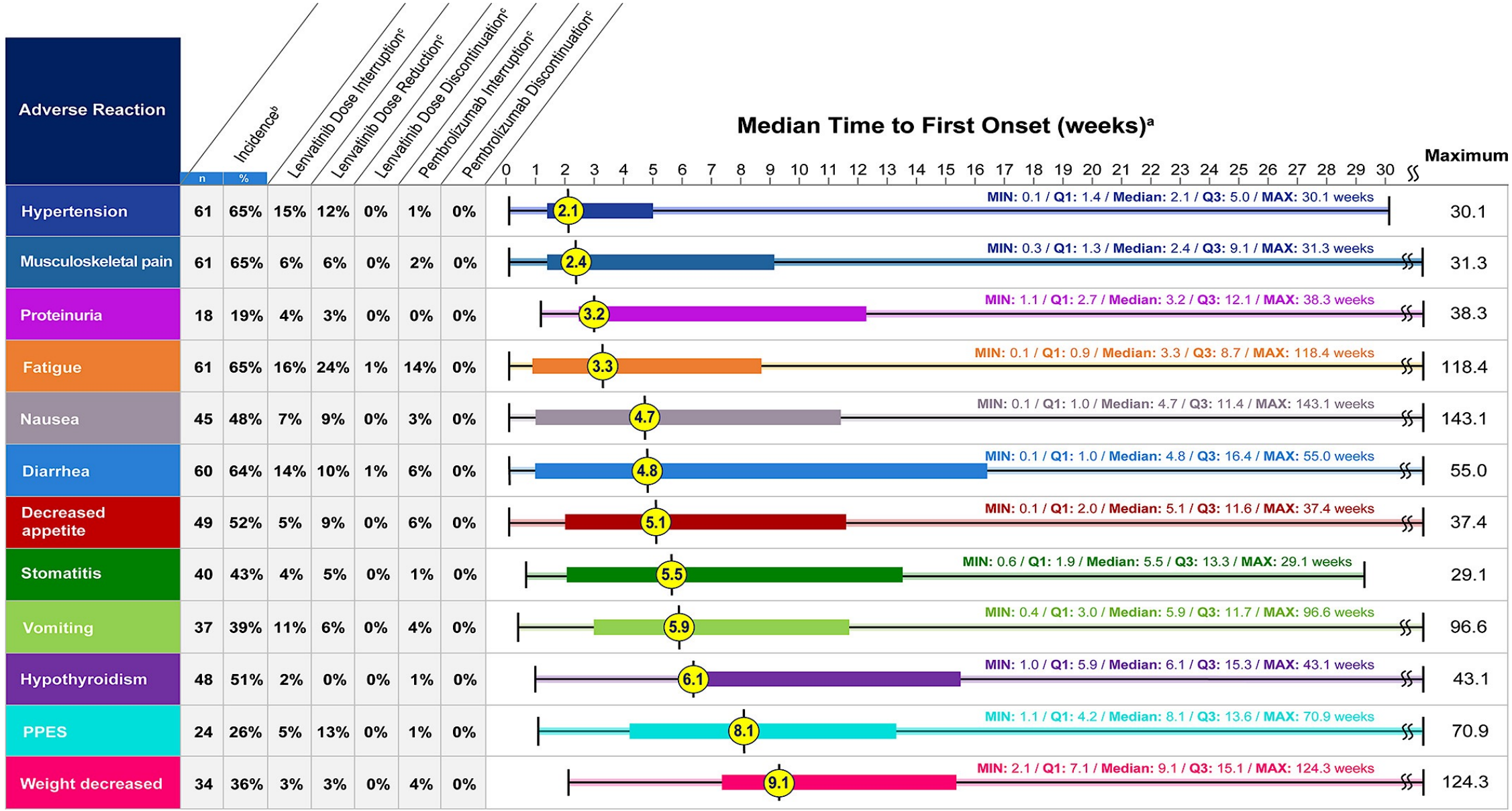
*In the lenvatinib and pembrolizumab arm, 6.4% of patients suffered grade 5 AEs, and 5.2% of patients in the TPC arm suffered grade 5 AEs.

Dose reductions 66.5%
Dose interruptions 69.2%
Discontinuation secondary to AE 33.0%

Makker V, et al. *N Engl J Med*. 2022;386:437-448;
Makker V, et al. *J Clin Oncol*. 2023;41:2904-2910.

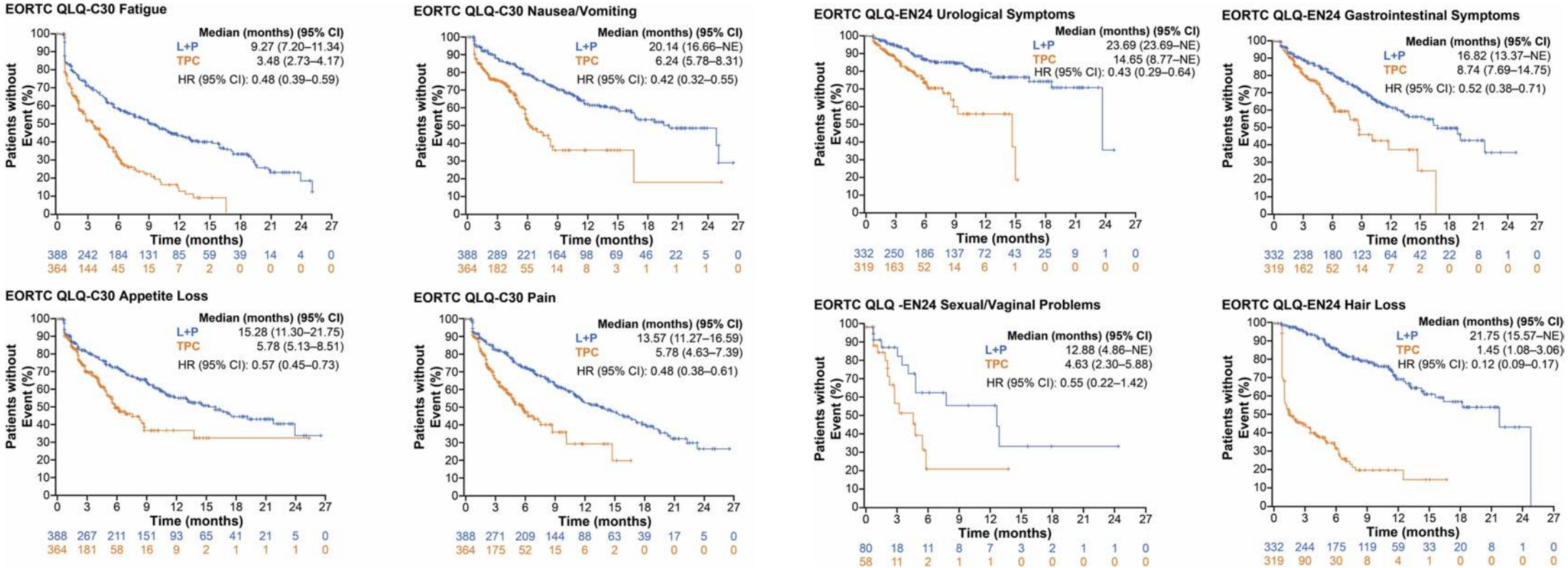
Lenvatinib and Pembrolizumab: Adverse Events

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



Makker V, et al. *Oncologist*. 2021;26:e1599-e1608.

Lenvatinib and Pembrolizumab: Quality of Life

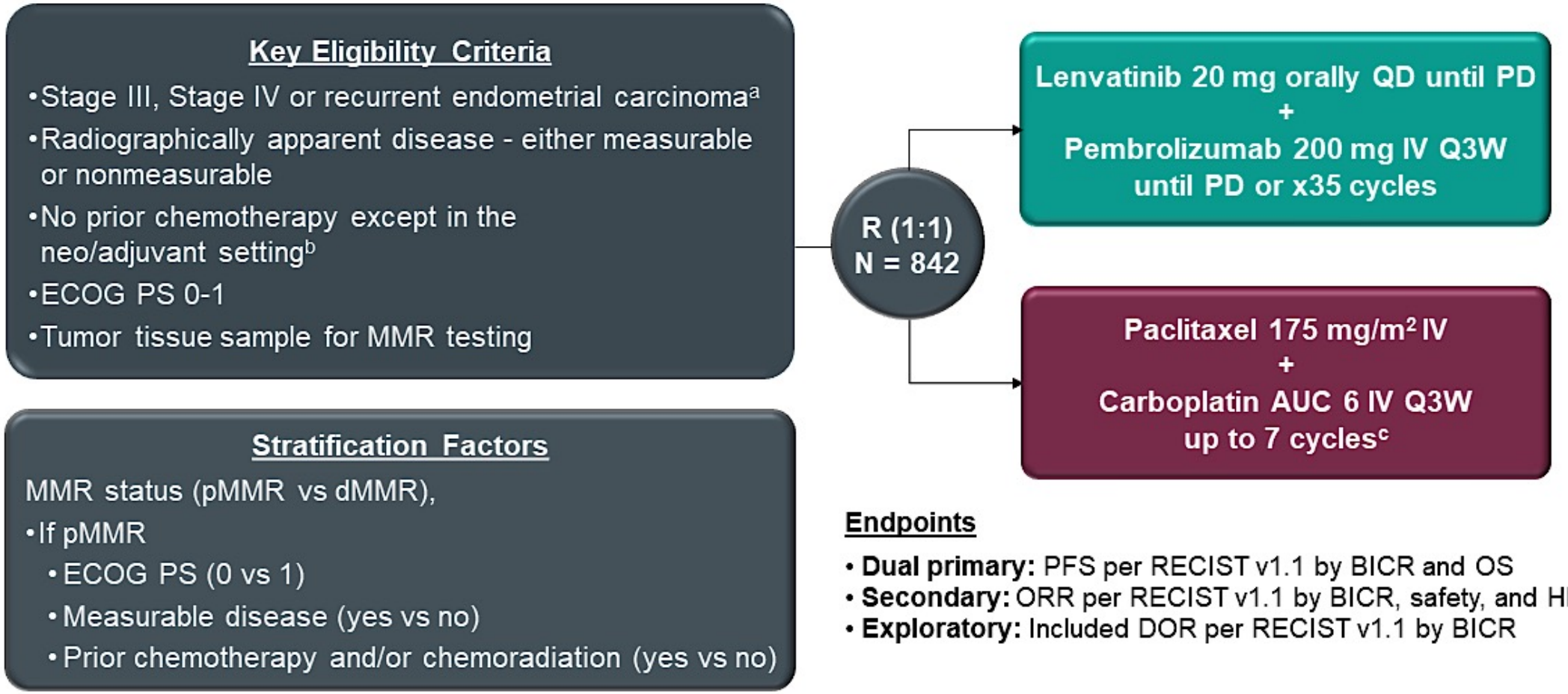


Len + Pem has survival and HRQOL benefit over TPC

Fig. 6 Time to Definitive Deterioration for Selected Scales of Interest in the All-Comer Population. CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire; EORTC QLQ-EN24, EORTC QLQ-Endometrial, 24 questions; HR, hazard ratio; L, lenvatinib; NE, not estimable; P, pembrolizumab; TPC, treatment of physician's choice.

Lorusso D, et al. *Eur J Cancer*. 2023;186:172-184.

ENGOT-en9/LEAP-001: Study Design

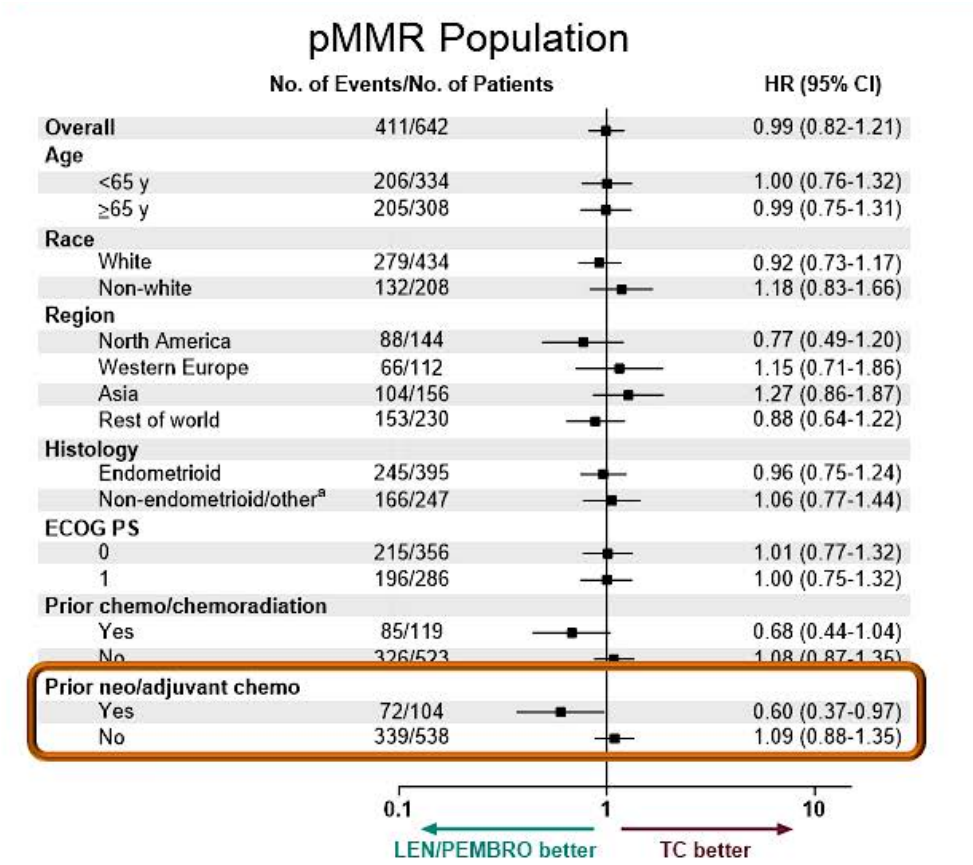


AUC, area under the concentration-time curve; BICR, blinded independent central review; DOR, duration of response; HRQoL, health-related quality of life.
[a]Carcinosarcoma (malignant mixed Müllerian tumor), endometrial leiomyosarcoma or other high grade sarcomas, or endometrial stromal sarcomas excluded.
[b]1 prior line of neoadjuvant and/or adjuvant chemotherapy in the setting of curative-intent resection was permitted if recurrence occurred ≥6 months after last dose; prior radiotherapy with or without chemotherapy, or prior hormonal therapy were also permitted.
[c]Patients with ongoing clinical benefit could continue chemotherapy beyond 7 cycles if approved by sponsor.

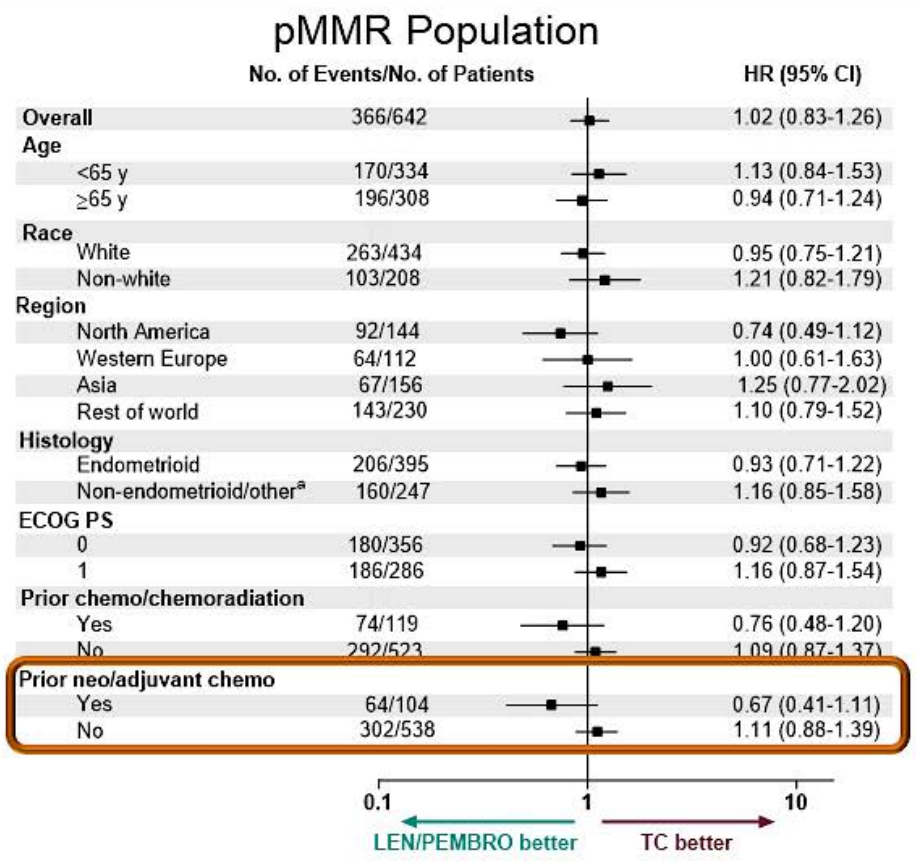
Marth C, et al. ESGO 2024. Abstract 88.

LEAP-001

Progression-Free Survival



Overall Survival



Marth C, et al. J Clin Oncol 2024.

Alternative options

- Clinical trials
- Targeted therapy
  - Trastuzumab deruxtecan if HER2 2 or 3+ expression
- Chemotherapy
  - Platinum rechallenge
  - Doxorubicin
  - Weekly paclitaxel
- Hormonal therapy

Conclusions

- Molecular testing should be integrated into routine practice
  - Prognostic and therapeutic implications in first line and recurrence
- Lenvatinib and pembrolizumab is standard second line therapy in pMMR (ICI naïve patient population)
  - Rechallenge with PD(L)-1 inhibitors has limited data
- HER2 status may identify candidates for trastuzumab deruxtecan
- Hormone therapy is an option
- Future studies continue to exploit new targets!

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Endometrial Cancer Symposium

Research To Practice | ONS 2025

Kathryn Lyle, MSN, WHNP-BC, AGNP-C

Division of Gynecologic Oncology

University of Alabama at Birmingham

Nursing Considerations for Patients Receiving Lenvatinib/Pembrolizumab

Lenvatinib/Pembrolizumab: Indication/Dosing

- **Indication:** Advanced or recurrent endometrial cancer that is not MSI-H or dMMR following prior systemic therapy and not suitable for curative surgery or radiation

- **Mechanism of Action:** Pembrolizumab and Lenvatinib have a synergistic effect. Lenvatinib is a tyrosine kinase inhibitor (prevents tumor growth and blood supply formation to the tumor). Pembrolizumab activates the body's own immune system to attack and kill the cancer

- **Dosing:**
  - FDA-approved label indication: Lenvatinib 20mg daily + Pembrolizumab 200mg q21 days
  - In practice, I start Lenvatinib at 12mg and dose reduce to 8mg if needed
  - Tablets come in blister packets that vary based on the dose

Lenvatinib/Pembrolizumab: Side Effects

- Lenvatinib AEs:
  - Most common: HTN, diarrhea, fatigue, N/V, arthralgias/myalgias, and weight loss
  - Other AEs include: PPE, stomatitis, proteinuria, decreased appetite, dry mouth, skin rash
- Lenvatinib side effect profile can overlap with Pembrolizumab irAEs
  - One strategy is to hold the Lenvatinib to see if the side effect improves
  - If yes, we often restart at a reduced dose
- Helpful medications to manage side effects:
  - Dexamethasone oral rinse or MMW (mucositis), Urea cream (PPE), Loperamide - OTC or Diphenoxylate/Atropine – Rx (diarrhea), antihypertensive agents, topical steroid creams

Lenvatinib/Pembrolizumab: Monitoring/Education

- Patient education:
  - Ask patients to report any new side effects at the initial occurrence
  - Keep loperamide on hand at home
  - Review the differences in types of therapy as it relates to the SE profile
  - Current therapy can exacerbate preexisting conditions
    - Make PCP aware of new treatment

- Monitoring:
  - Keep a BP log at home
  - Check urine protein levels monthly
  - Ask about side effects at every visit

Clinical Experience

- Multiple patients of mine have struggled with weight loss while on Len/Pem. We have worked with our nutritionists to try to increase protein intake. Oral mucositis and diarrhea can add to the weight loss.

- I had a patient on Len/Pem (14mg daily Lenvatinib at the time) who developed PPE on the soles of her feet bilaterally. The PPE significantly impacted her mobility and ability to walk, wear shoes, etc. We had to hold Lenvatinib for >4 weeks. We prescribed urea cream and waited until her PPE was back to a grade 1. She was able to restart at a reduced dose of 10mg daily and was able to remain on therapy.

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Agenda

Introduction: Overview of Endometrial Cancer (EC)

Module 1: First-Line Therapy for Advanced or Recurrent EC

Module 2: Role of Lenvatinib/Pembrolizumab in the Management of Progressive Advanced EC

Module 3: Novel Investigational Strategies for Newly Diagnosed Advanced EC

Module 4: Incidence and Management of HER2-Positive EC

Clinical Scenario

A patient with newly diagnosed metastatic EC is interested in learning about promising novel investigational strategies

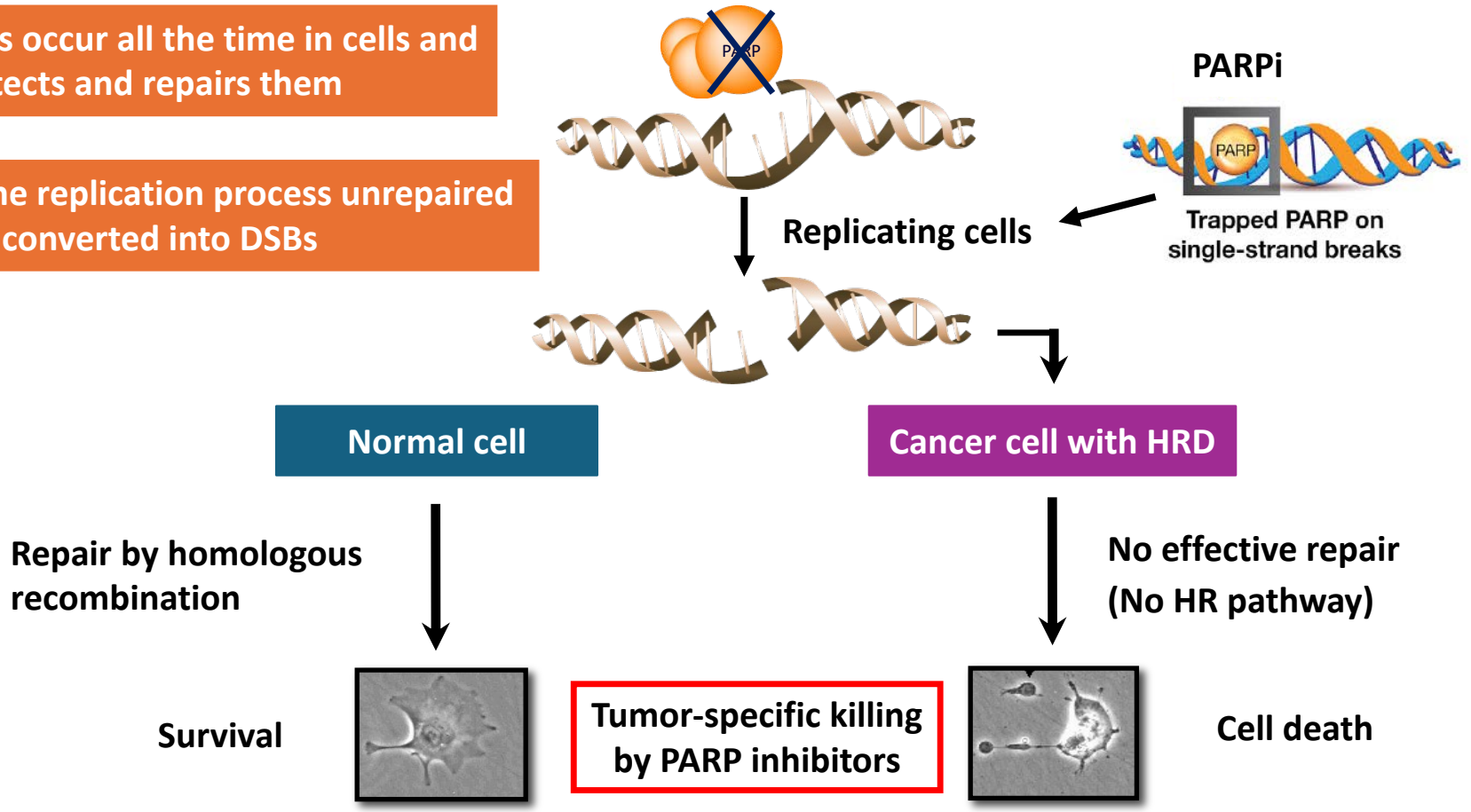
Novel Investigational Strategies for Newly Diagnosed Advanced EC

Brian M Slomovitz, MD
Professor, OB-GYN, Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

Mechanism of Action of PARP Inhibitors

DNA SSBs occur all the time in cells and PARP detects and repairs them

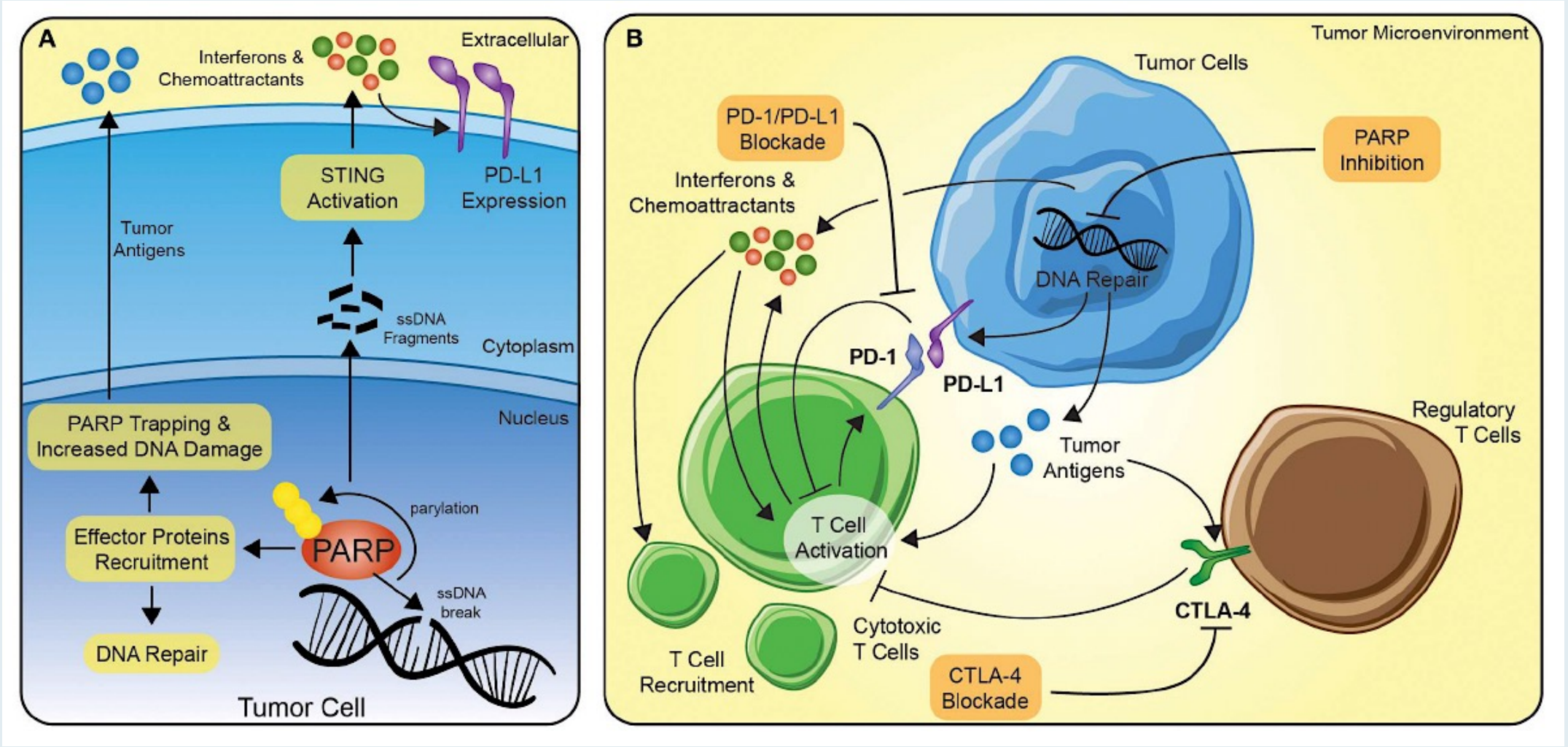
During the replication process unrepaired SSBs are converted into DSBs



DSB, double-strand break; HR, homologous recombination; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; SSB, single-strand break.

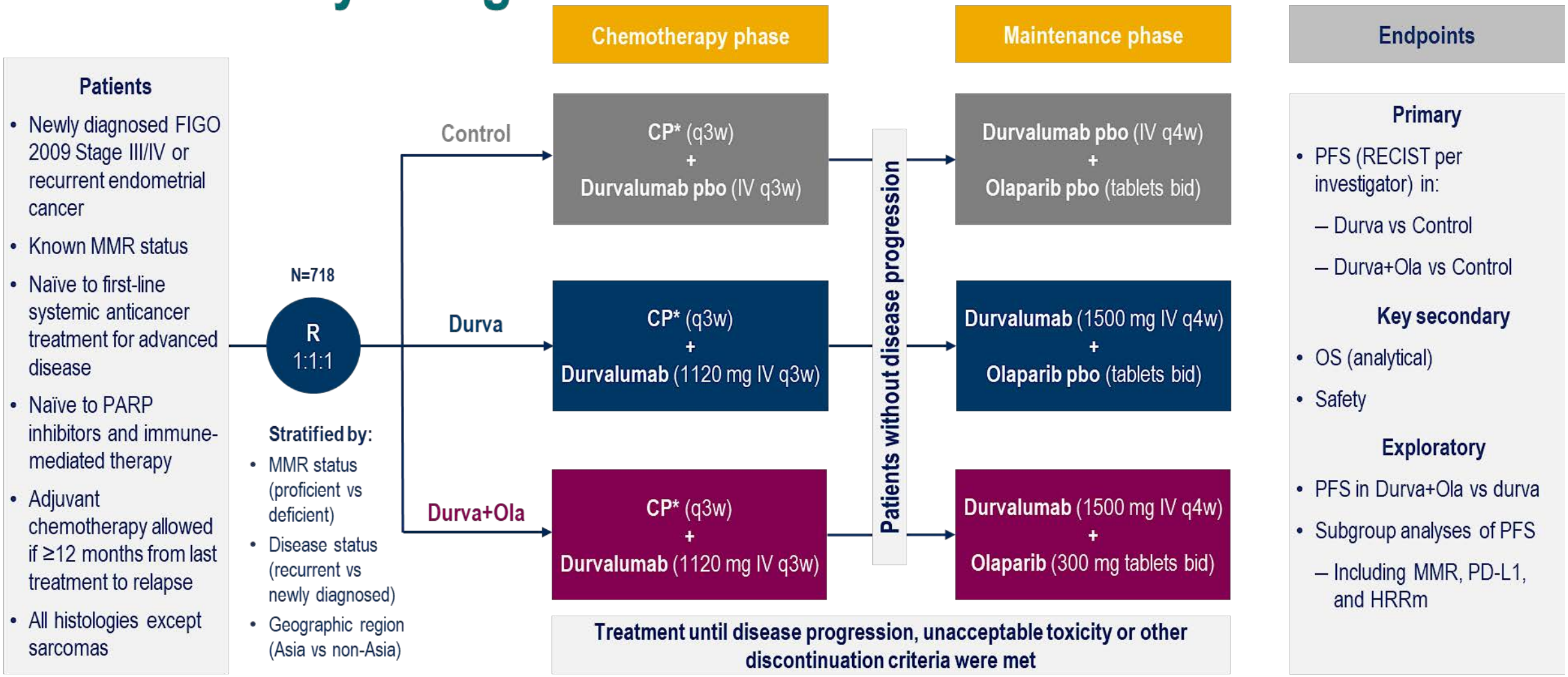
O'Connor MJ, et al. *Mol Cell*. 2015;60:547-560.

The Potential Synergy Between PARP Inhibition and Immune Checkpoint Blockade



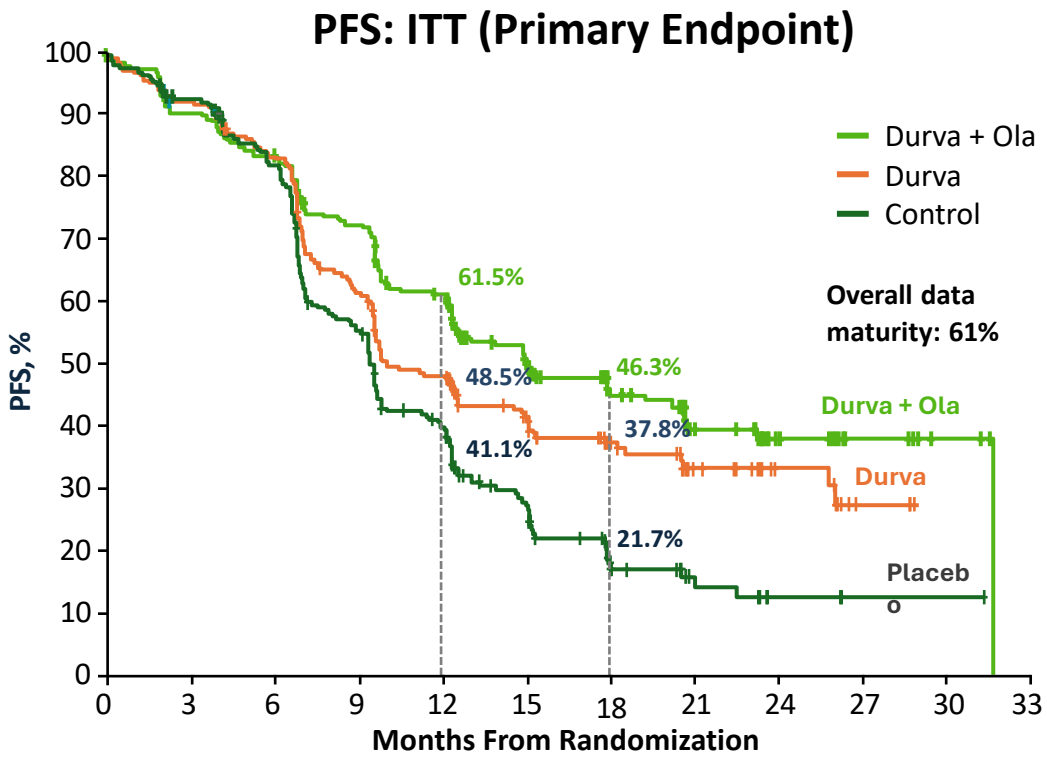
Vikas P et al. *Front Oncol* 2020;10:570.

DUO-E study design



*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

DUO-E: Maintenance Durvalumab ± Olaparib on PFS in ITT Population



	Control (n = 241)	Durva (n = 238)	Durva + Ola (n = 239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS, mo (95% CI)	9.6 (9.0-9.9)	10.2 (9.7-14.7)	15.1 (12.6-20.7)
HR (95% CI) vs control		**0.71 (0.57-0.89); *P* = .003**	**0.55 (0.43-0.69); *P* < .0001**
HR (95% CI) vs durva			**0.78 (0.61-0.99)**

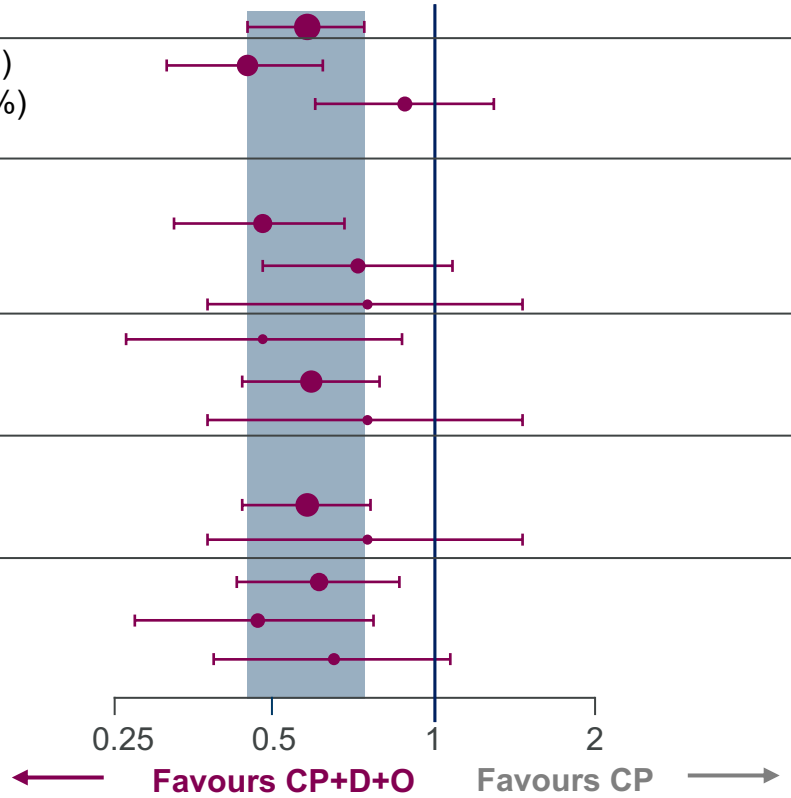
ITT, intention to treat; Ola, olaparib.

Westin SN, et al. *J Clin Oncol.* 2024;42:283-299.

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib versus CP

Post hoc exploratory analysis



		HR (95% CI)
All pMMR patients		**0.57 (0.44–0.73)**
PD-L1 expression*	Positive (TAP score ≥1%)	**0.44 (0.31–0.61)**
	Negative (TAP score <1%)	**0.87 (0.59–1.28)**
	Unknown	**NC (NC–NC)** [§]
***POLE*m and *TP53m* status**[†,‡]	*POLE*m	**NC (NC–NC)**[‖]
	*TP53*m	**0.47 (0.32–0.67)**
	TP53 wt	**0.71 (0.47–1.07)**
	Unknown	**0.74 (0.37–1.45)**
HRRm status[†, §]	HRRm	**0.47 (0.26–0.86)**
	Non-HRRm	**0.58 (0.43–0.78)**
	Unknown	**0.74 (0.37–1.45)**
BRCAm status[†]	BRCAm	**NC (NC–NC)**[‖]
	Non-BRCAm	**0.57 (0.43–0.75)**
	Unknown	**0.74 (0.37–1.45)**
Histology	Endometrioid	**0.60 (0.42–0.85)**
	Serous	**0.46 (0.27–0.76)**
	Other[¶]	**0.64 (0.38–1.06)**

DCO: 12 April 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%, and unknown included patients who withdrew consent or due to sample unavailability; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; *TP53* wt status defined as a sample with no deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; and unknown *TP53*m status included patients recruited in China, where *TP53* and/or *POLE* testing was not performed, patients who withdrew consent and patients for whom no sample was available; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; and unknown HRRm status included patients recruited in China, where HRR testing was not performed, patients who withdrew consent and patients for whom no sample was available; ‖Not calculated due to low event numbers; ¶'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other.
DCO, data cutoff; NC, not calculable.

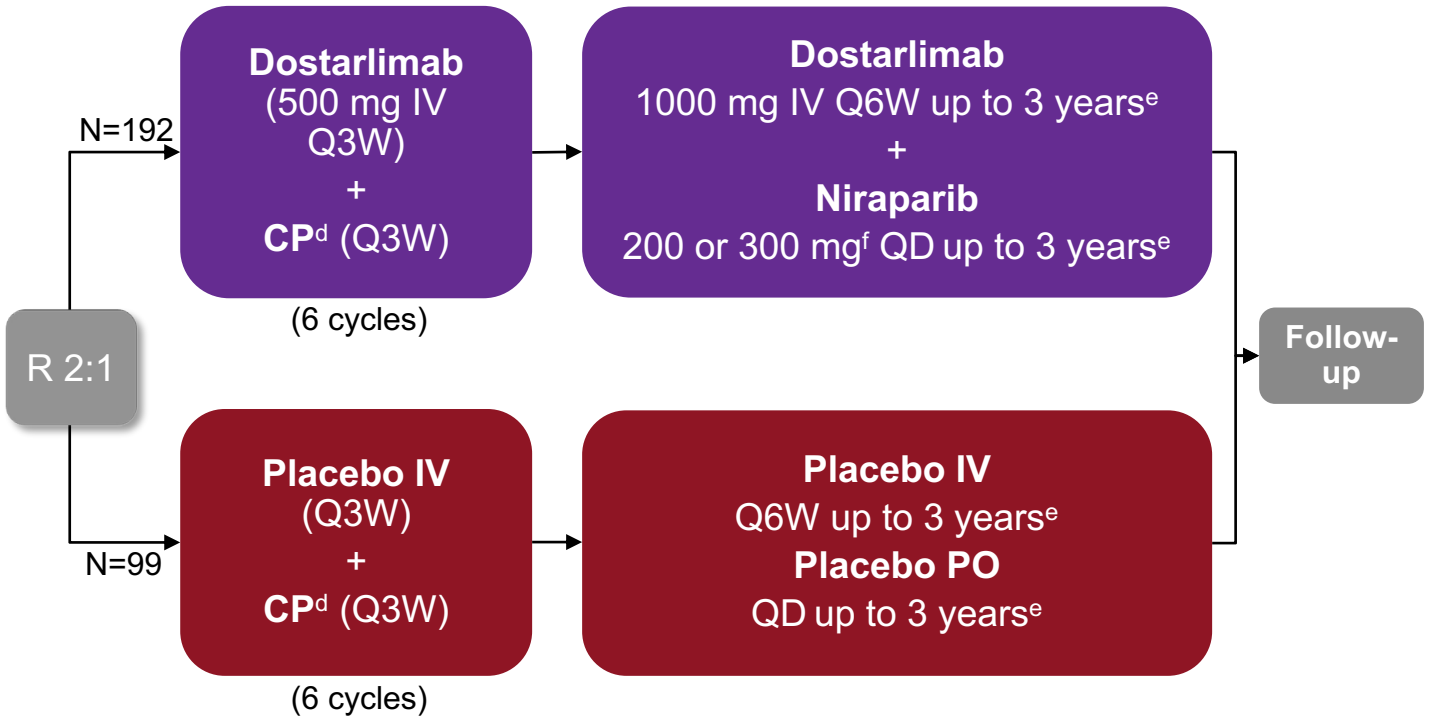
ENGOT-EN6-NSGO/GOG-3031/RUBY Part 2

Eligible patients

- Stage III/IV disease or first recurrent EC[a]
  - All histologies except sarcomas[b]
- Naive to systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- Naive to PARP inhibitor therapy

Stratification

- MMR/MSI status[c]
  - 25% dMMR/MSI-H
  - 75% MMRp/MSS
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV per RECIST v1.1
  - Overall
  - MMRp/MSS

Secondary endpoints

- OS
- PFS by BICR
- ORR
- DOR
- DCR (BOR of CR, PR, or SD)
- PFS2
- HRQOL/PRO
- PK
- Safety

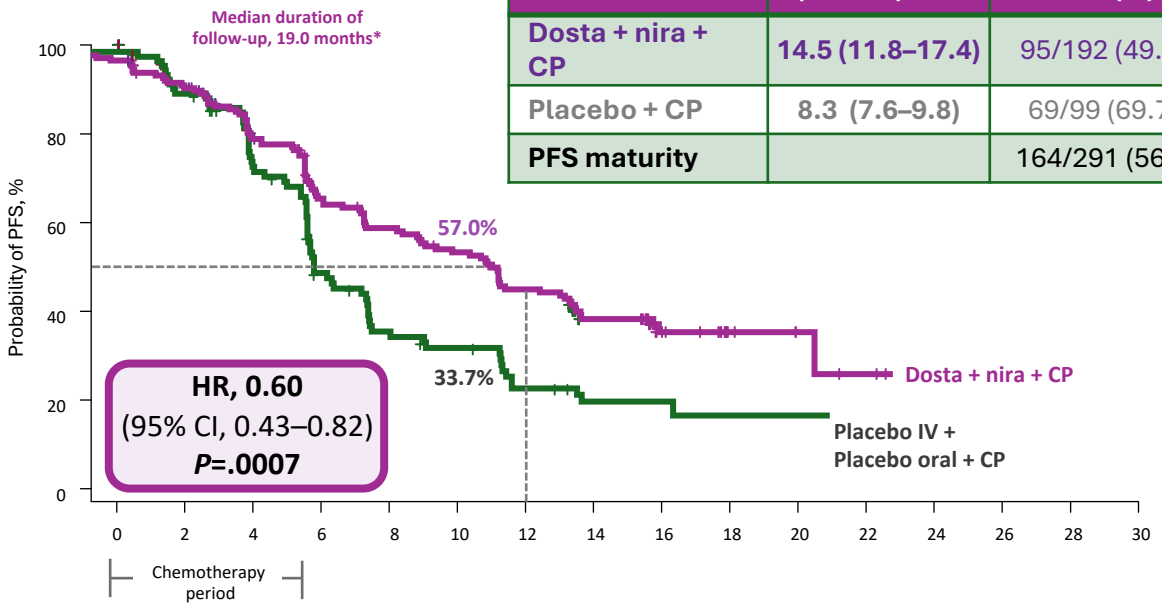
On-study imaging assessments were performed Q6W (±7 days) from the randomization date until week 25 (cycle 8), followed by Q9W (±7 days) until week 52. Subsequent tumor imaging was performed every 12 weeks (±7 days) until radiographic PD was documented by investigator assessment per RECIST v1.1 followed by 1 additional imaging 4–6 weeks later, or subsequent anticancer therapy was started, whichever occurred first. Thereafter, scans were performed per standard of care.
[a]Histologically/cytologically proven advanced or recurrent EC; stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination. [b]Carcinosarcoma, clear cell, serous, or mixed histology permitted (mixed histology containing ≥10% carcinosarcoma, clear cell, or serous histology). [c]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next-generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [d]Carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m^2. [e]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the sponsor and the investigator. [f]Dose of 300 mg in patients with body weight ≥77 kg and platelet count ≥150,000/µL and 200 mg in patients with body weight <77 kg or platelet count <150,000/µL or both. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; BOR, best overall response; CP, carboplatin-paclitaxel; CR, complete response; DCR, disease control rate; dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MMRp, MMR proficient; MSI, microsatellite instability; MSI-H, MSI high; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PO, by mouth; PR, partial response; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

1. Mirza M, et al. Presented at SGO 2024, San Diego, USA; 2. Westin SH, et al. Presented at ESMO 2023, Madrid, Spain

RUBY Part 2: Maintenance Dostarlimab ± Niraparib on PFS in Overall and pMMR Populations

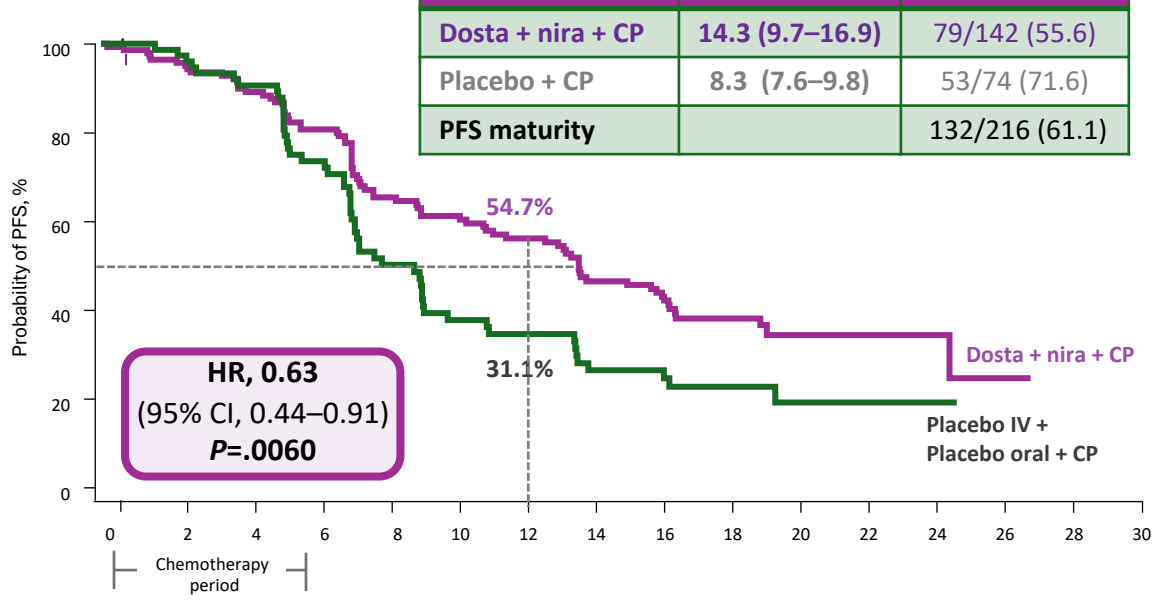
Overall

	Median (95% CI), mo	Events, n/N (%)
Dosta + nira + CP	14.5 (11.8–17.4)	95/192 (49.5)
Placebo + CP	8.3 (7.6–9.8)	69/99 (69.7)
PFS maturity		164/291 (56.4)



pMMR

	Median (95%CI), mo	Events, n/N (%)
Dosta + nira + CP	14.3 (9.7–16.9)	79/142 (55.6)
Placebo + CP	8.3 (7.6–9.8)	53/74 (71.6)
PFS maturity		132/216 (61.1)



Maintenance dostarlimab + niraparib resulted in a statistically significant improvement in PFS in the overall and pMMR populations

*Median expected duration of follow-up.

Nira, niraparib.

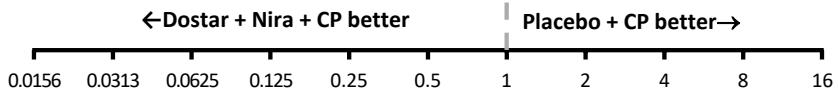
Mirza MR, et al. Presented at: 2024 ESMO Gynecological Cancers Congress; June 20-22, 2024; Florence, Italy. Oral abstract 38M0.

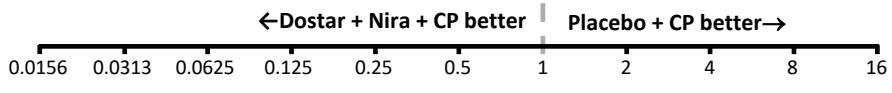
Selecting Which Patient May Benefit From Addition of PARPi

RUBY Part 2 ITT

	Dostarlimab + niraparib + CP N=192	Placebo IV + placebo oral + CP N=99	HR (95% CI)
All patients	95/192	69/99	0.59 (0.43–0.81)
PD-L1 status[a]			
PD-L1+	56/123	43/62	0.56 (0.37–0.83)
PD-L1-	37/64	24/31	0.67 (0.40–1.12)
Not evaluable[b]	2/5	2/6	NA
BRCA mutation status			
Positive	1/6	3/4	NA
Negative	75/148	49/71	0.61 (0.43–0.88)
Not evaluable[b]	19/38	17/24	0.71 (0.37–1.37)
HRR mutation status[c]			
Positive	3/20	10/14	NA
Negative	73/134	42/62	0.69 (0.47–1.01)
Not evaluable[b]	19/38	17/24	0.71 (0.37–1.37)

	Dostarlimab + niraparib + CP N=192	Placebo IV + placebo oral + CP N=99	HR (95% CI)
			No. of patients with events/No. of patients
All patients	95/192	69/99	0.59 (0.43–0.81)
Molecular subgroup[a]			
POLEmut	0/3	1/2	NA
dMMR/MSI-H	12/37	10/17	0.45 (0.20–1.05)
TP53mut	27/39	10/10	0.29 (0.13–0.63)
NSMP	37/75	31/46	0.61 (0.38–0.99)
Not evaluable[b]	19/38	17/24	0.71 (0.37–1.37)

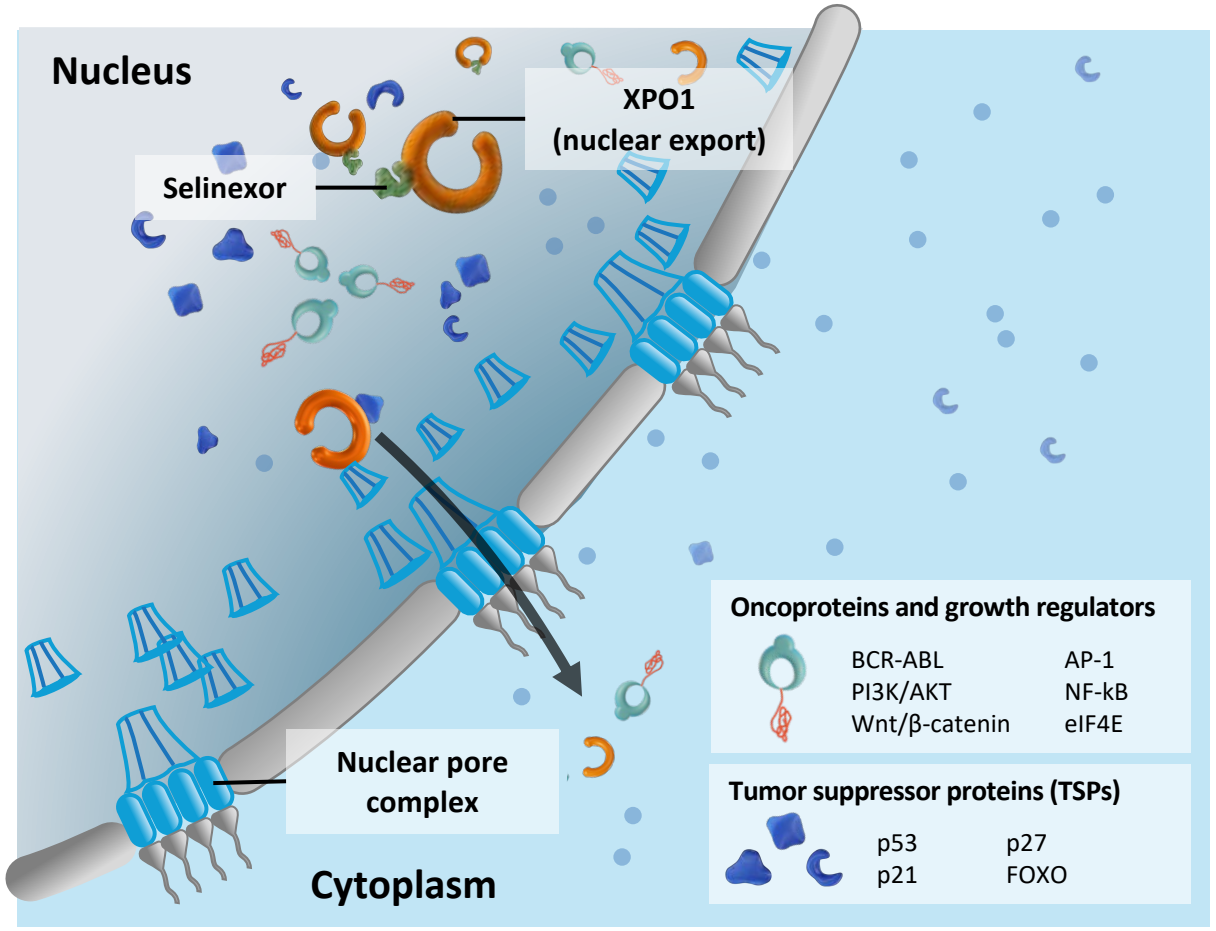




Results should be interpreted with caution as the study was not powered to detect a treatment difference in any subgroup, and there were small numbers and low data maturity in some subgroups. Where there were less than 20 events in the subgroup, the HR estimation and 95% CI were not analyzed as there were too few events ("not applicable"). [a]Based on available whole exome sequencing results; [b]Sample not available. [c]Defined by a mutation in 1 or more genes included in the FMI14 panel: BRCA1, BRCA2, ATM, BARD1, BRIP1, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, CDK12, CHEK1, CHEK2, and FANCL BRCA, breast cancer gene; CI, confidence interval; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; HR, hazard ratio; HRR, homologus recombination repair; ITT, intention to treat; IV, intravenous; MSI-H, microsatellite instability high; mut, mutation; nira, niraparib; NSMP, no specific molecular profile; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-L1, protein death ligand-1; POLE, polymerase epsilon.

Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Selinexor Is a Targeted Oral XPO1 Inhibitor

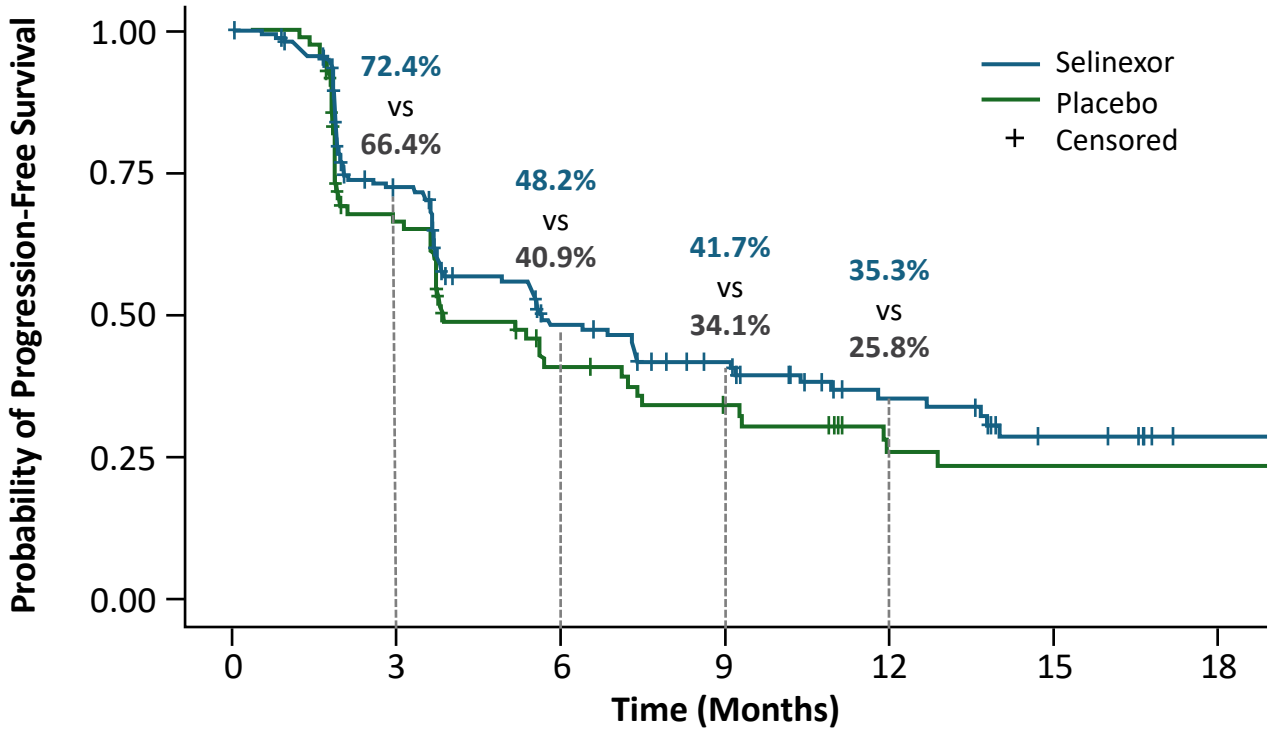


XPO1 inhibition by selinexor results in:

- Nuclear retention and functional reactivation of TSPs (eg, p53), which selectively kills cancer cells and largely spares normal cells
- Inhibition of mRNA export of select oncogenes, thus decreasing subsequent translation and synthesis of oncoproteins
- Simultaneous targeting of several oncogenic pathways involved in cancer development, maintenance, and progression

Tai Y-T, et al. *Leukemia*. 2014;28:155-165; Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:335-345; Sun Q, et al. *Signal Transduct Target Ther*. 2016;1:16010.

ENGOT-EN5/GOG-3055/SIENDO: PFS in ITT Population



Median follow-up: 10.2 months (95% CI 8.97, 13.57)

Median PFS

Selinexor (n = 174): 5.7 mo (95% CI, 3.81-9.20)

Placebo (n = 89): 3.8 mo (95% CI, 3.68-7.39)

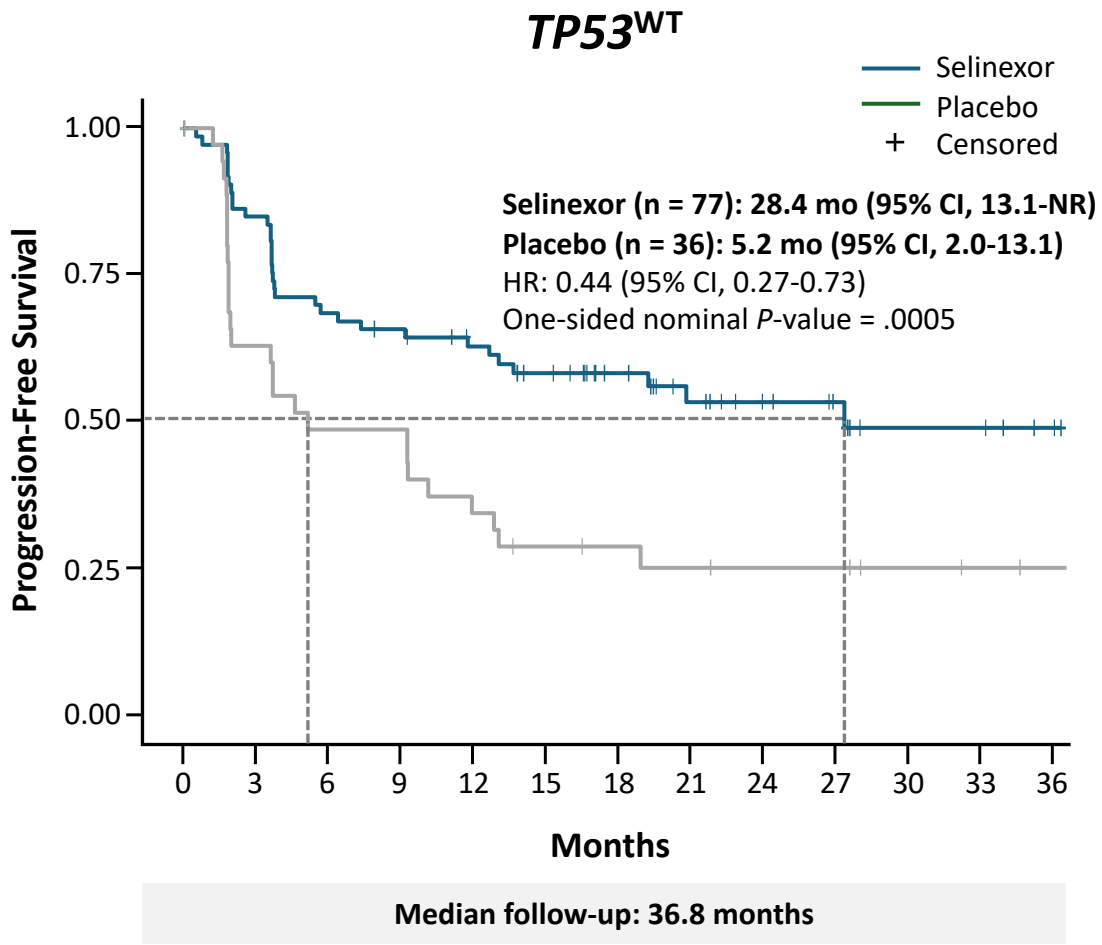
- Audited* (by electronic case report form)
  - HR = 0.71 (95% CI, 0.50-0.99)
  - Two-sided *P*-value = .05
- Unaudited* (by interactive response technology)
  - HR = 0.76 (95% CI, 0.54-1.08)
  - Two-sided *P*-value = .13

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

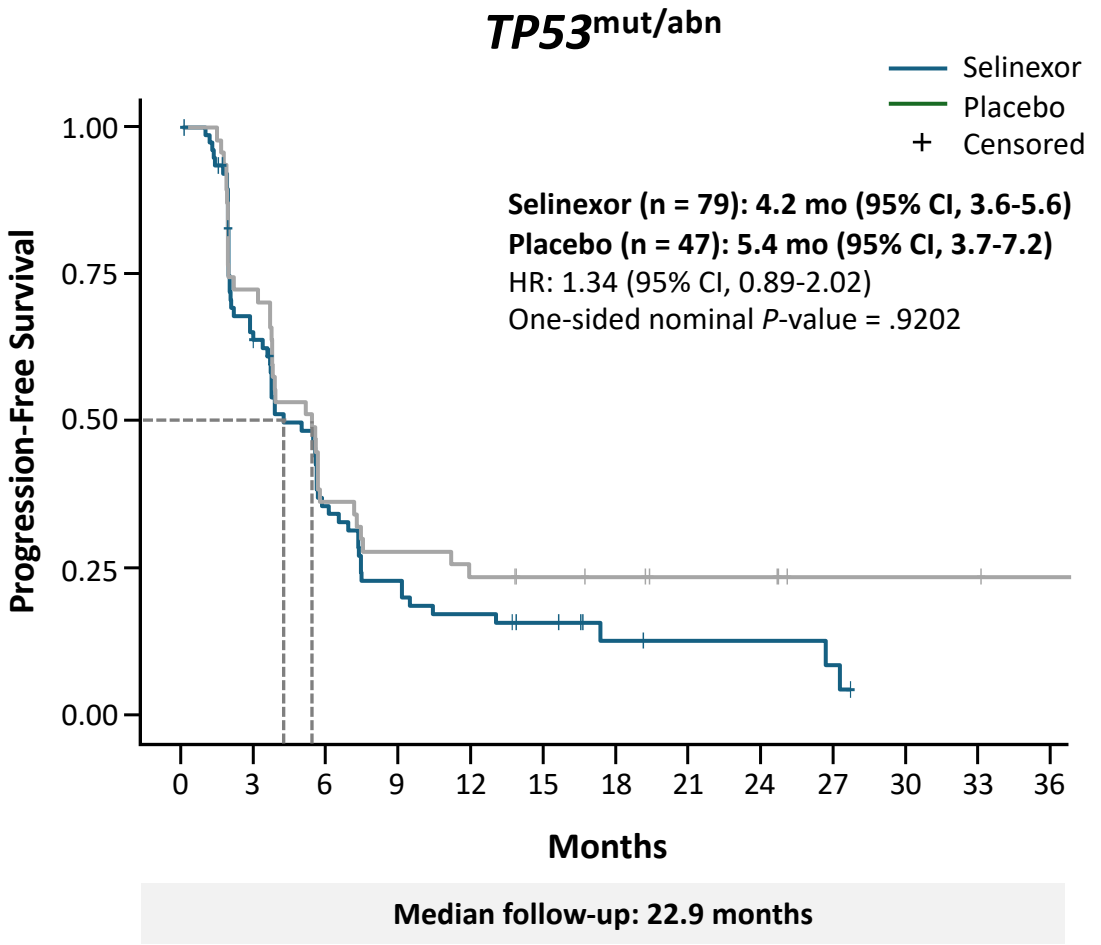
CR, complete response; IDMC, independent data safety monitoring committee; PR, partial response.

Vergote I, et al. *J Clin Oncol*. 2023;41:5400-5410.

ENGOT-EN5/GOG-3055/SIENDO: Long-Term Follow-Up of PFS in Prespecified Exploratory *TP53*^{WT} and *TP53*$^{mut/abn}$ Subgroups



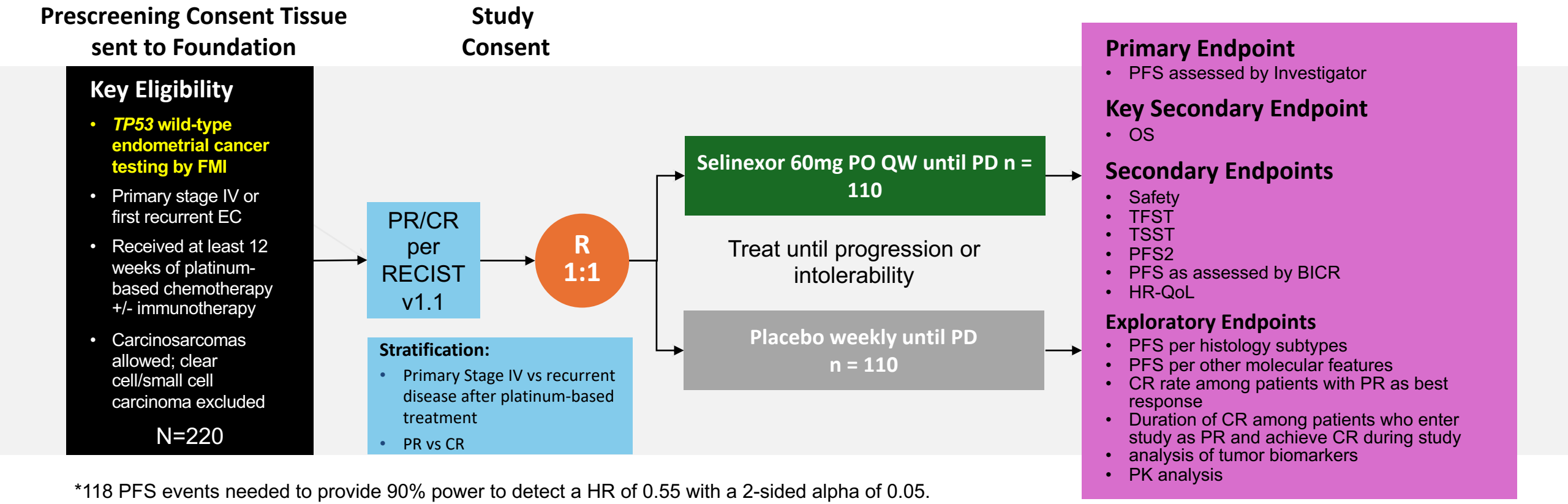
Median follow-up: 36.8 months



Median follow-up: 22.9 months

Makker V, et al. *Gynecol Oncol*. 2024;185:202-211; Slomovitz BM, et al. *J Clin Oncol*. 2023;41(suppl 36):427956.

XPORT-EC-042 (NCT05611931): A Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With *TP53* Wild-type, Advanced, or Recurrent EC



*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a 2-sided alpha of 0.05.

EC, endometrial cancer; FMI, Foundation Medicine; BICR, blinded independent central review; CR, complete response; DCR, disease control rate; EC, endometrial cancer; HR-QoL, health-related quality of life; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization until the second progression event; PD, progressive disease; PK, pharmacokinetics; PR, partial response; R, randomized; RECIST, Response Evaluation Criterial in Solid Tumors; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment; QW, every week.

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Nursing Considerations for Patients Receiving Selinexor

Jaclyn Shaver, MS, APRN, CNP, WHNP

Selinexor: TP53 Wild Type- What I tell my patients

- TP53 wild –type (Normal Functioning Gene)
  - Tumor suppressor gene – crucial role in maintaining genomic stability and preventing cancer
  - It detects DNA damage and triggers – repair, cell death of damage or cancerous cells, stop cell division
- Studies have shown Selinexor works better in patients with a normal functioning gene like yours.
  - Clinical Trial GOG-3083/XPORT- Phase 3 randomized placebo controlled double-blind multicenter trial of Selinexor in Maintenance Therapy after systemic therapy for patient with P53 wild type, advanced or recurrent endometrial carcinoma

Vergote I et al. *Int J Gynecol Cancer* 2024;34(8):1283-1289.

Selinexor: Common Side Effects

- GI
  - Nausea -#1, Vomiting, Constipation, Diarrhea, and Abdominal Pain
- Nutrition
  - Decreased Appetite/Weight loss -#1, Hyponatremia, Hypokalemia, Hyperglycemia
- Blood
  - Thrombocytopenia- #1, Anemia, Neutropenia, Leukopenia
- Nervous System
  - Altered Taste- #1, Dizziness, Headache
- Eye
  - Blurred Vision
- General
  - Fatigue-#1, Weakness, Feet/Ankle Swelling, Fever

Selinexor: Common Side Effects

- Respiratory
  - Cough -#1, Dyspnea, Pneumonia
- Musculoskeletal
  - Back Pain/Myalgias

Selinexor: Less Common Side Effects

- Cataract, Visual Disturbance, and Dry Eye
- Mucositis, Dry Mouth
- Low Blood Pressure
- Neuropathy
- URI/UTI, Sepsis
- Mental Status Changes- Confusion, Delirium
- Tumor Lysis Syndrome

Administration- GOG-3083/XPORT

- Oral Medication- with 4 oz of water, take whole- to avoid contact with skin
  - Same time each day, with or without food- No diet restrictions. Maintain adequate hydration and oral intake
- Weekly
- 28 day cycle
- Dosed at 60mg on D1, 8, 15, 22
- Dose missed – take next day
- 2 anti-nausea meds to prevent nausea at least first 2 cycles
  - Ondansetron and aprepitant, if needed can add olanzapine and dexamethasone

Vergote I et al. *Int J Gynecol Cancer* 2024;34(8):1283-1289.

Clinic Scenario

- 49 y/o stage IA grade 1, S/p RA-TLH, BSO with mini laparotomy on 6/13/19.
- No LVSI, No Myometrial Invasion- No adjuvant therapy
- Uncontrolled DM with baseline neuropathy, CHF, Afib, morbidly obese
- Recurrent disease to vaginal apex and mass with transmural colonic involvement (biopsy +5/18/20 of vaginal cuff and colonoscopy biopsies positive 6/30/20)
- S/p Carboplatin/Paclitaxel x 6 cycles (completed 11/11/20).
  - CT scan 9/24/20 with CR
- SIENDO/3055 maintenance study, enrolled 12/2020.
  - Discontinued after C1 due to intolerable side effects, primarily nausea.
  - Patient was noncompliant with anti-emetics
- Continues to be NED..? No showed her last surveillance visit on 4/1/25.

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Agenda

Introduction: Overview of Endometrial Cancer (EC)

Module 1: First-Line Therapy for Advanced or Recurrent EC

Module 2: Role of Lenvatinib/Pembrolizumab in the Management of Progressive Advanced EC

Module 3: Novel Investigational Strategies for Newly Diagnosed Advanced EC

Module 4: Incidence and Management of HER2-Positive EC

Clinical Scenario

A patient with HER2-positive advanced EC has experienced disease progression on first-line carboplatin/paclitaxel/trastuzumab and second-line lenvatinib/pembrolizumab and is about to start treatment with trastuzumab deruxtecan

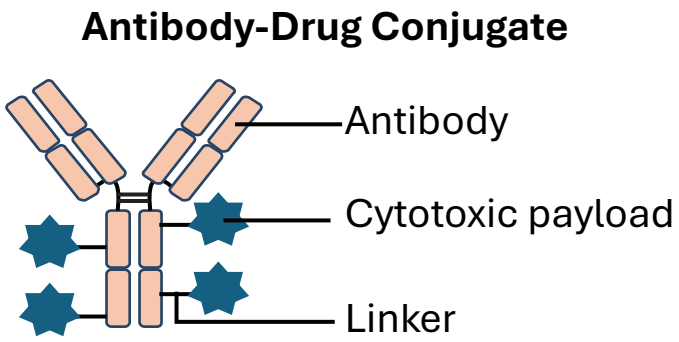
Incidence and Management of HER2-Positive EC

Brian M Slomovitz, MD
Professor, OB-GYN, Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

What is HER2?
(Human Epidermal Growth Factor Receptor 2)

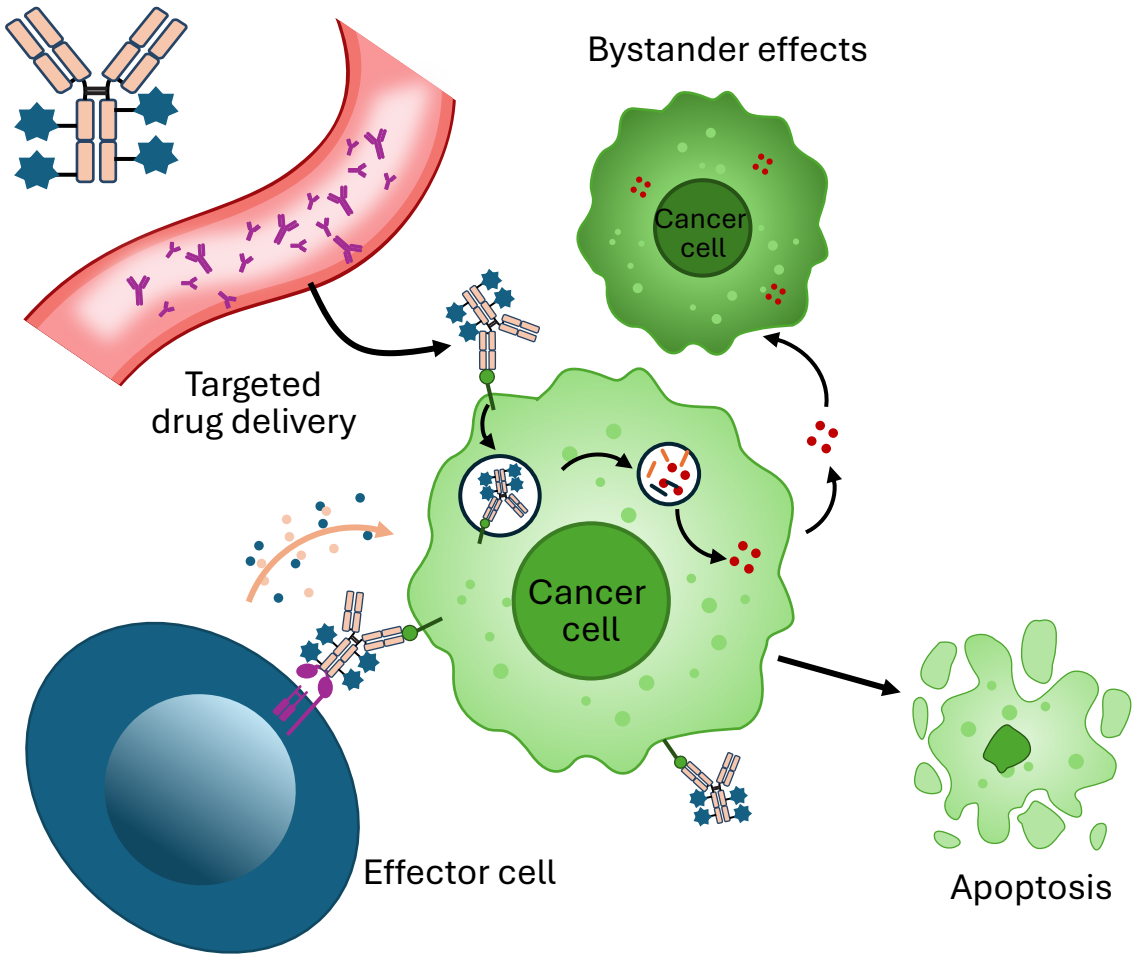
- Promotes cell growth and division
- Commonly overexpressed in breast and gastric cancers
- Endometrial Cancer
  - HER2 overexpression mainly in serous carcinoma (25-30%)
  - Rare in endometrioid (<5%) and other histologies (carcinosarcoma: 16%)
  - Associated with aggressive tumor behavior

Mechanism of ADC



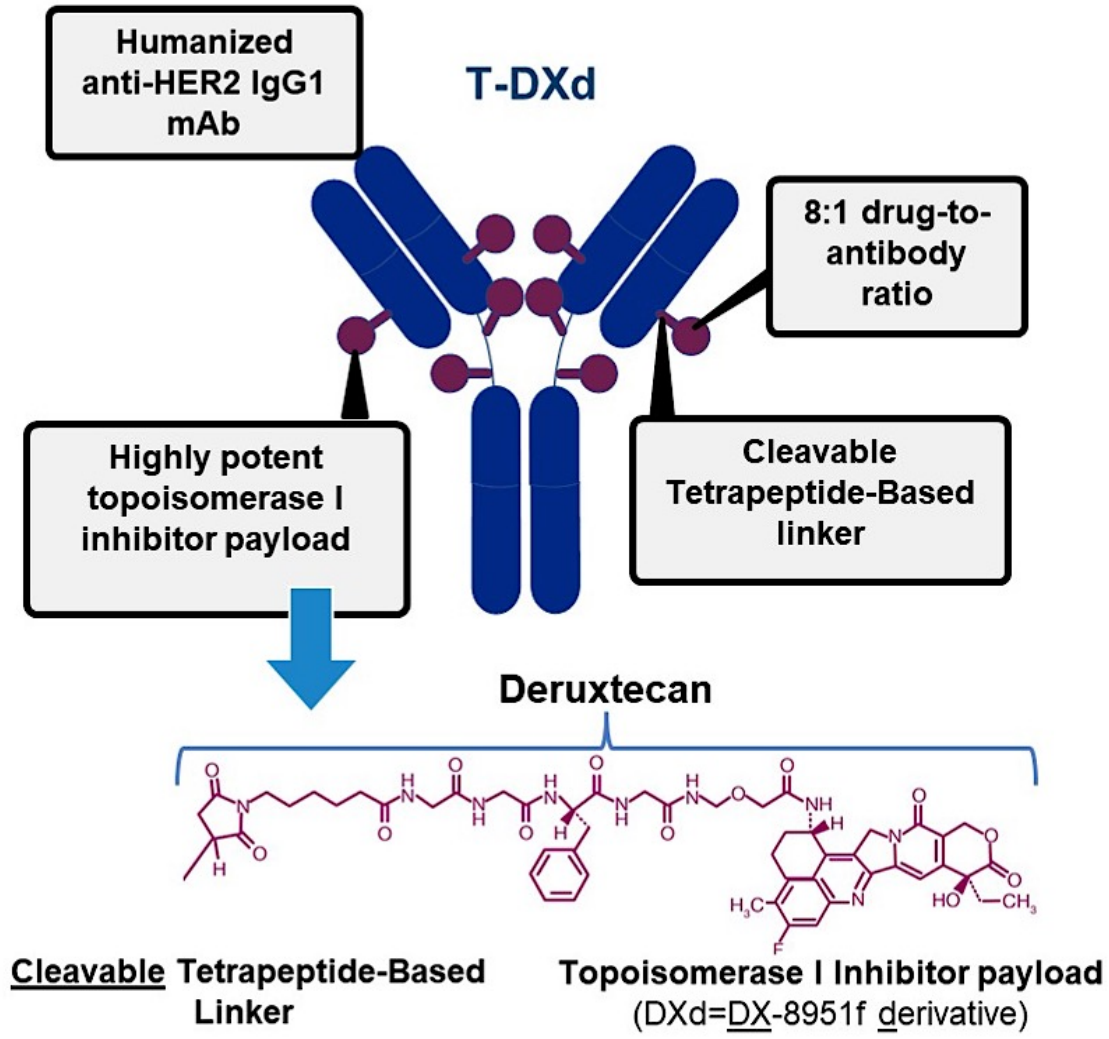
ADC Components

- **Antibody** specific for target antigen on cancer cells
- High potency **cytotoxic payload**
- Cleavable or non-cleavable **linker** between antibody and payload



Fu Z, et al. *Signal Transduct Target Ther*. 2022;7:93.

Trastuzumab Deruxtecan (T-DXd): an anti-Her2 ADC



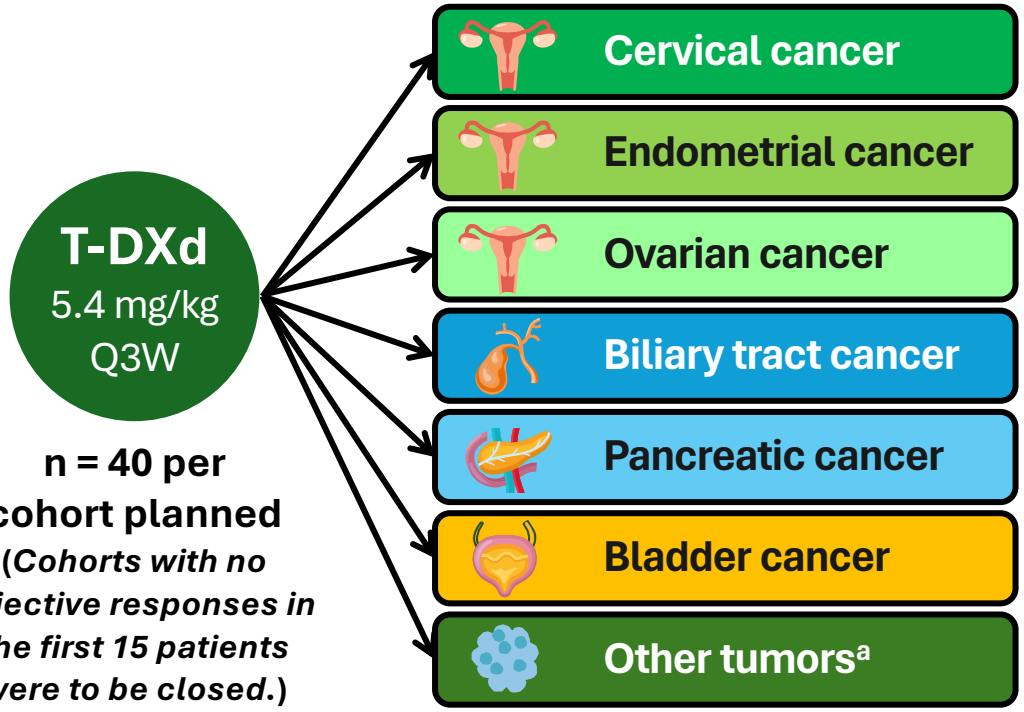
Seven Key Attributes[a,1–5]
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Bystander antitumor effect

Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126–142.
4. Okamoto H, et al. *Xenobiotica*. 2020;50(10):1242–1250. 5. Nagai Y, et al. *Xenobiotica*. 2019;49(9):1086–1096.

Open-Label, Phase 2 DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors

Tumor types were selected based on epidemiological frequency, prevalence of HER2 expression, and unmet medical need.

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep Test if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy
- ECOG/WHO PS 0–1 restricted in strenuous activity



n = 40 per cohort planned
(Cohorts with no objective responses in the first 15 patients were to be closed.)

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR
- DCR
- PFS
- OS
- Safety

Data cutoff for analysis

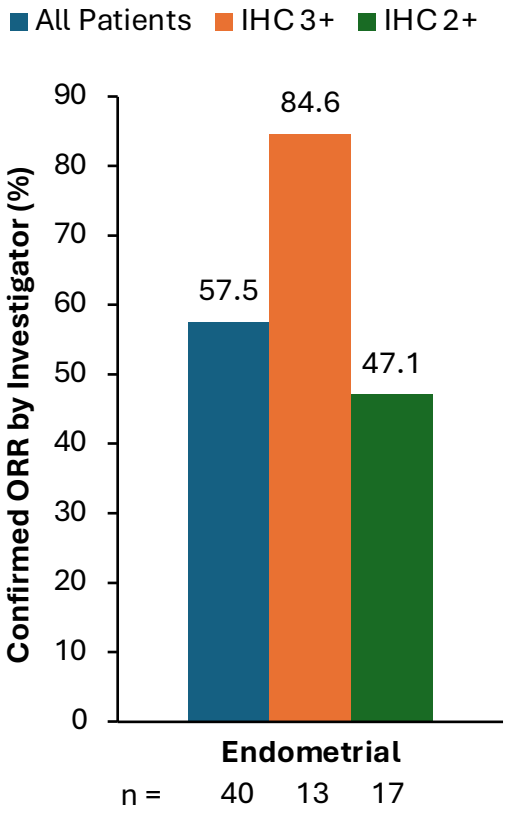
- June 8, 2023

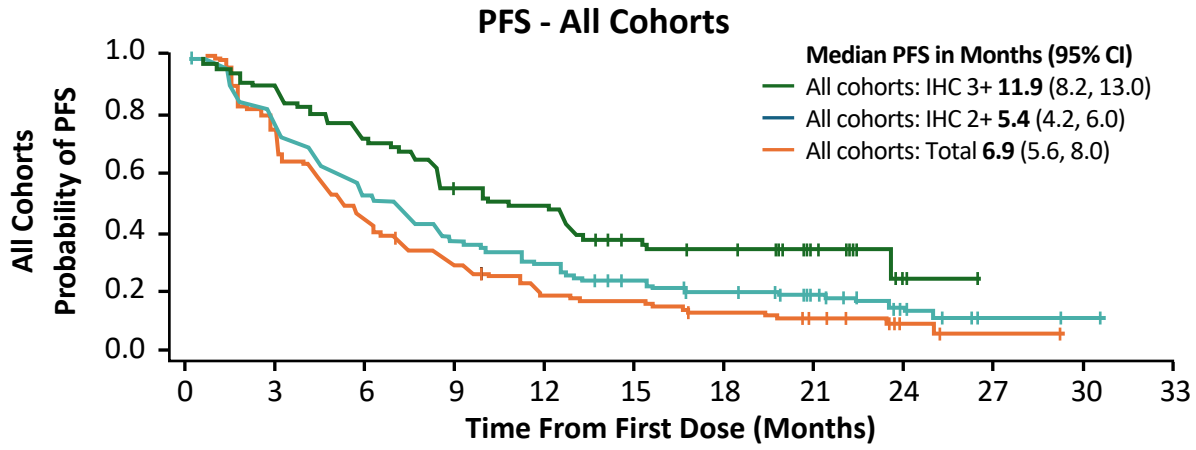
[a]Other tumors cohort: Salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 2), extramammary Paget disease (n = 2), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n = 1).

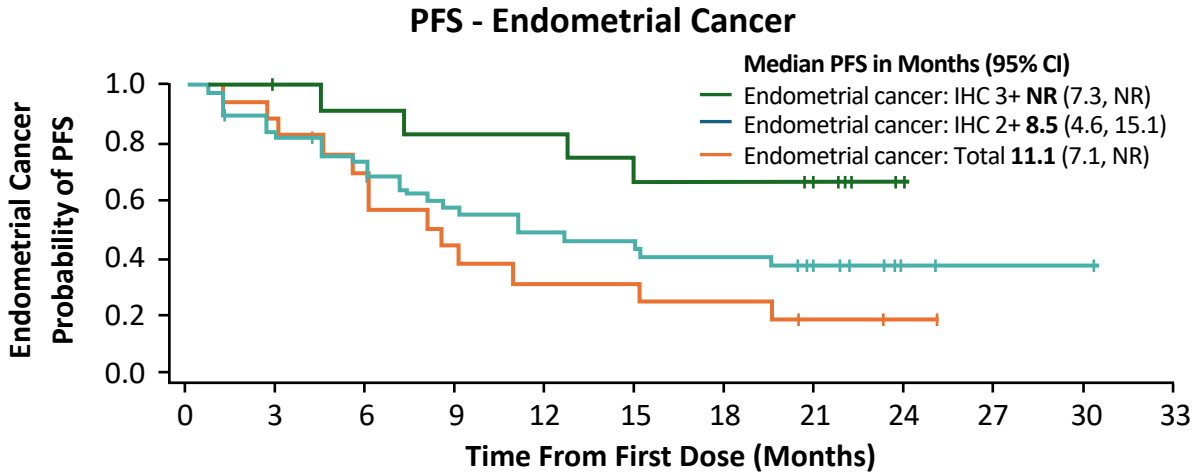
2L+ = second-line or beyond; ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; WHO = World Health Organization.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58. Clinicaltrials.gov. NCT04482309 (https://clinicaltrials.gov/study/NCT04482309). Accessed 11/8/2024.

DESTINY-PanTumor02: Trastuzumab Deruxtecan Efficacy by HER2 Expression







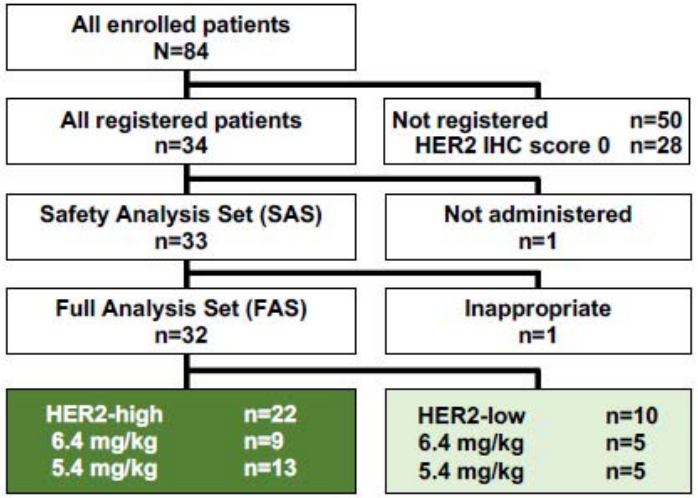
FDA granted accelerated approval to trastuzumab deruxtecan for unresectable or metastatic HER2-positive solid tumors in April 2024.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58;
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed September 23, 2024.

Clinical Data for Efficacy in HER2+ Uterine Carcinosarcoma

Patient Flow Diagram

- Patients were enrolled from February 2018 to June 2020 at 7 institutions in Japan
- Data cut-off was done in December 2020
- Twenty-eight patients (33.3%) were excluded from registration due to HER2 IHC score 0
- One patient did not receive T-DXd due to progression of UCS
- One patient was excluded from FAS due to central review with no measurable target lesion



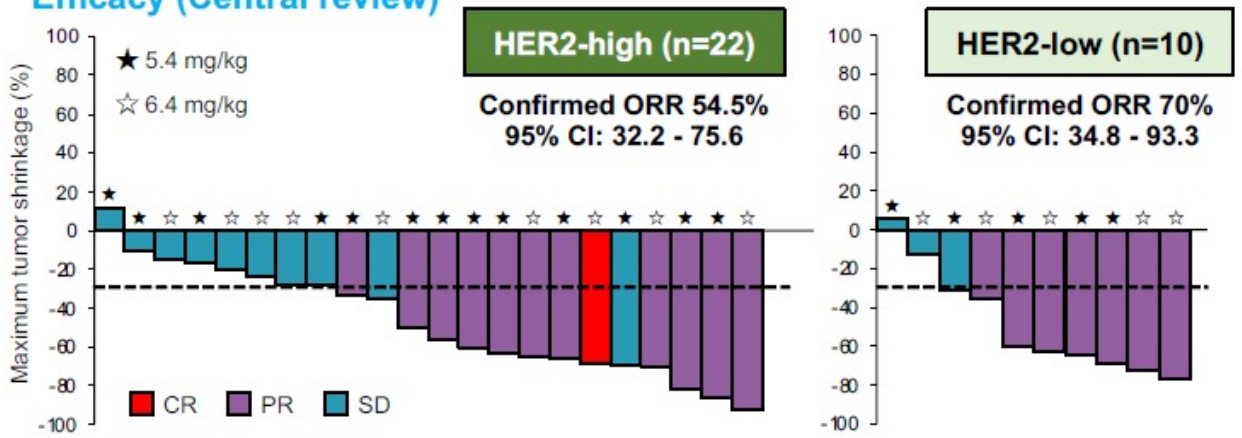
Patient Characteristics

HER2 IHC score (N=84)
0: 28 (33%), 1: 24 (29%)
2: 22 (26%), 3: 10 (12%)

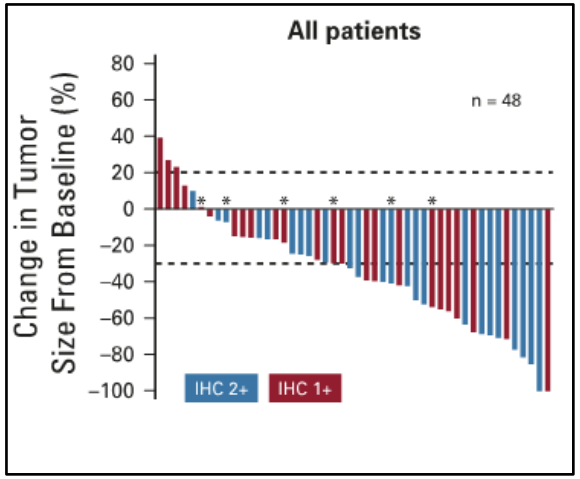
		All (n=34)	(%)	FAS (n=32)	(%)
Age (years)		45- 81	65.5 (median)	45-81	64.5 (median)
PS (ECOG)	0	25	(73.5)	24	(75)
	1	9	(26.5)	8	(25)
HER2 (IHC)	1	11	(32.4)	10	(31.3)
	2	16	(47.1)	15	(46.9)
	3	7	(20.6)	7	(21.9)
HER2 (FISH)	Negative	26	(76.5)	24	(75)
	Positive	8	(23.5)	8	(25)
Prior regimens	1			17	(53.1)
	2			9	(28.1)
	≥3			6	(18.8)

Hasegawa K et al. ESMO 2021 poster 813p.
Nishikawa T et al. J Clin Oncol 2023.

Efficacy (Central review)



Confirmed Response Rate	CR (n, %)		PR (n, %)		SD (n, %)		PD (n, %)		ORR (%)
HER2-high (n=22)	1	(4.5)	11	(50)	10	(45.5)	0	(0)	54.5
HER2-low (n=10)	0	(0)	7	(70)	3	(30)	0	(0)	70



T-DXd in heavily pretreated HER2-low MBC

- ORR = 37%
- mPFS = 11.1 months

Modi S et al JCO 2020

Clinical Case

A 62-year-old woman with HER2+ recurrent EC

Case: Presentation & Workup

- A 62 yo postmenopausal woman presents to her gyn/onc with vaginal bleeding in 2020
- **Pelvic US:** endometrial thickness 2 mm
- **CT CAP:** no evidence of metastatic disease
- **Endometrial biopsy** shows **high-grade serous adenocarcinoma**. IHC +p53, -ER, pMMR
- **Surgery**: Robotic hysterectomy, BSO, omental biopsy
- **Pathology:** endometrial serous carcinoma with **microscopic metastases to bilateral ovaries**, negative omentum, + pelvic nodes
- **Adjuvant therapy**: **Post-operative carboplatin + paclitaxel chemotherapy x 6 cycles**, along with vaginal cuff brachytherapy
- **Germline genetic testing**: no *BRCA*m, VUS in *ATM* gene

Case: (cont.)

- 1.5 years after completion of initial carboplatin and paclitaxel, she developed a recurrence with retroperitoneal adenopathy and mesenteric masses
- Treatment:
  - Lenvatinib/pembrolizumab, develops PD
- Molecular testing: HER2 IHC 3+

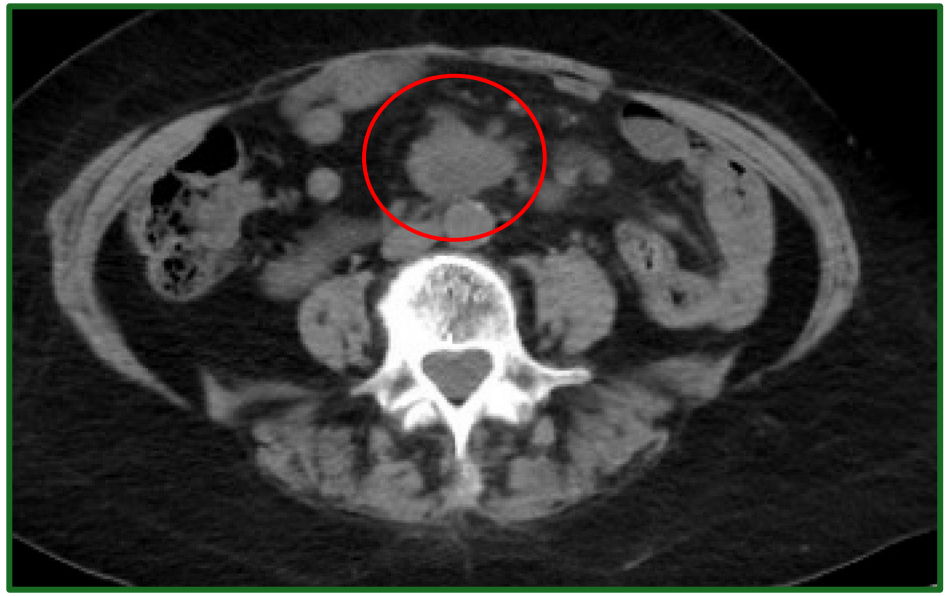
Case: (cont.)

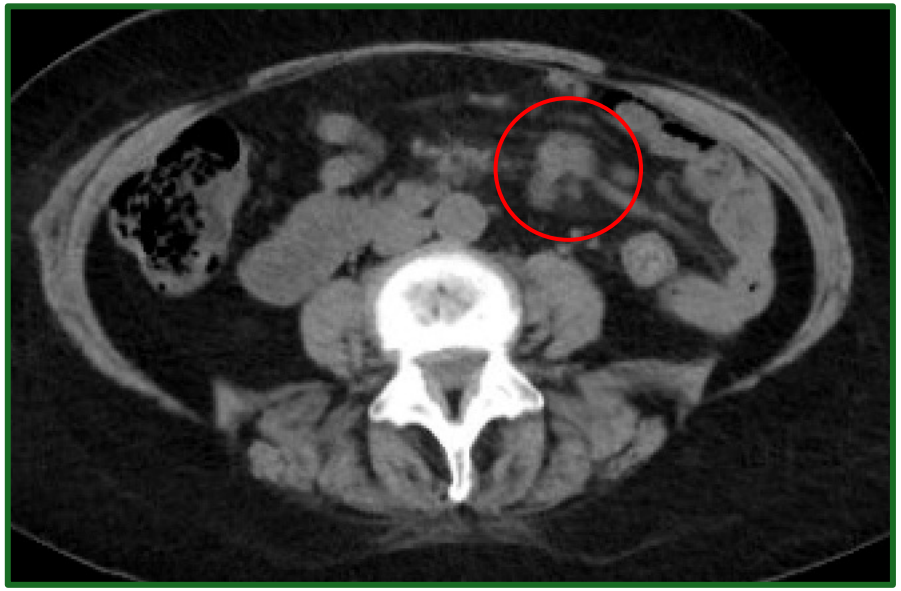
Trastuzumab deruxtecan 5.4 mg/kg was initiated

- LVEF 65% pre—T-DXd
- CAP CT scans were done every 2 cycles
- Improvement in measurable cancer after 2 cycles
- Because of grade 3 fatigue and grade 2 diarrhea, dose was dropped to 4.4 mg/kg and then again to 3.2 mg/kg because of persistent fatigue, diarrhea

Case: Radiology

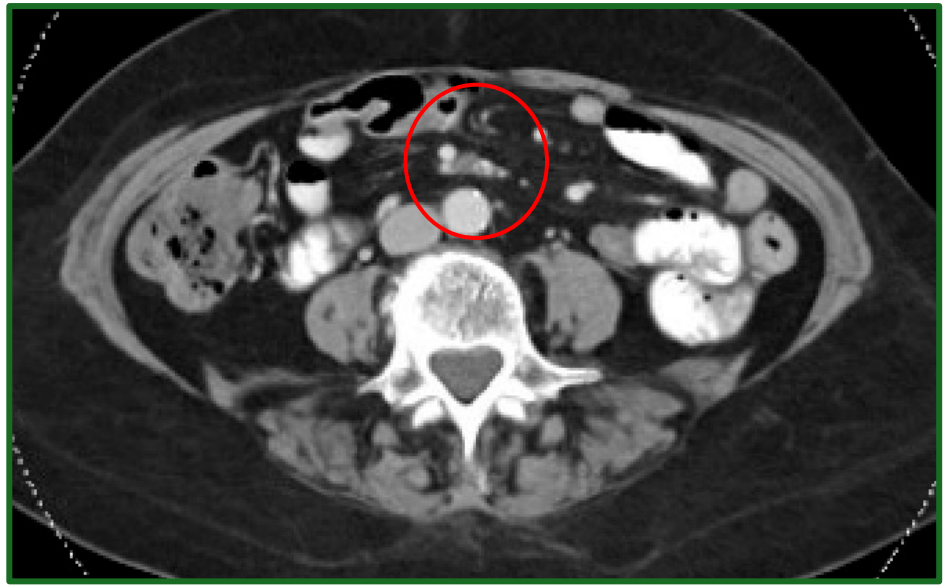
Start of T-DXd

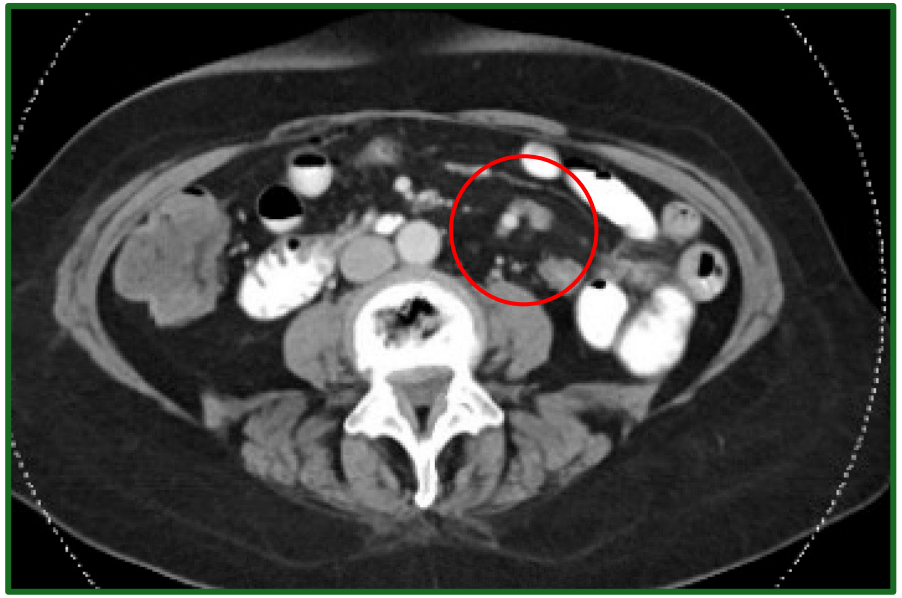




She remains on T-DXd

After 8 cycles





Roundtable Discussion

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Nursing Considerations for Patients Receiving HER2-Targeted Therapy

Jaclyn Shaver, MS, APRN, CNP, WHNP

Fam-Trastuzumab Deruxtecan (T-DXd)

- NCCN Guidelines – at least 2nd line therapy
  - HER2-positive tumors IHC 3+

T-DXd – Indications/Administration

- Unresectable or Metastatic HER2 – positive (IHC 3+) solid tumors who have received prior systemic therapy and have no satisfactory alternative treatment options.
- Administration – 5.4mg/kg every 3 weeks.
- First dose over 90 minutes, second and subsequent doses over 30 minutes
- Until disease progression or unacceptable toxicities.
- 1st dose reduction – 4.4mg/kg, 2nd dose reduction 3.2mg/kg

Trastuzumab deruxtecan package insert.

Boxed Warning

- ILD and pneumonitis, including fatal cases have been reported
- Using 5.4mg/kg
  - Overall Incidence - 12.3%. Median time to first onset of ILD - 5.5 months.
  - Death occurred in 0.9%
- Monitor for and promptly investigate signs and symptoms including, cough, dyspnea, fever, or other new or worsening respiratory symptoms.
- Permanently discontinue in all patients with Grade 2 or higher ILD/pneumonitis
- Advise patient of risk and the need to immediately report symptoms
  - Early detection is key, know patient baseline
- Higher incidence with patients who have moderate renal impairment
- CT at baseline and then at least every 12 weeks or 6-9 if baseline symptoms are present.

Trastuzumab deruxtecan package insert.

Suspect ILD/Pneumonitis

- Patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops acute onset of new or worsening respiratory symptoms.
  - High Resolution Chest CT
  - Pulmonology Referral- Bronchoscopy/PFT's
  - R/o other causes – viral panel, CBC, blood cultures, etc.
- Grade 1 – Interrupt until resolved and grade 0, consider starting systemic steroids 0.5mg/kg/day prednisone with gradual taper. Close follow up – 1-2 weeks
  - <28 days maintain dose
  - >28 days reduce dose 1 level
- Grade 2 – Discontinue, start systemic steroids 1mg/kg/day with gradual taper, close follow up 1-2 weeks
- Grade 3-4 – Hospitalization with IV high dose methylprednisolone

Trastuzumab deruxtecan package insert.

Cardiac Toxicity- Left Ventricular Dysfunction

- Overall Incidence - 4.6% --- Grade 3 or worse - 0.6%
- Assess LVEF prior to initiation of therapy and then every 3 months
- Interrupt and consult Cardiology if
  - IF LVEF 40%-45% and absolute decrease from 10-20%
  - LVEF <40%
  - Absolute decrease from baseline >20%

Trastuzumab deruxtecan package insert.

Common Side Effects

- GI – Nausea - #1, vomiting, diarrhea, constipation, stomatitis, abdominal pain, dyspepsia
- General – Fatigue - #1, fever, edema
- Metabolism/Nutrition - #1 Decreased appetite, loss of weight
- Skin – Alopecia #1, and rash
- Infections – URI- #1, and pneumonia
- Musculoskeletal – Musculoskeletal Pain
- Respiratory- Cough #1, ILD, Dyspnea
- Nervous System - Headache

Clinical Example

- 74 y/o Recurrent Stage IV Serous Carcinoma of the Uterus
  - s/p RATLH/BSO/right pelvic peritonectomy on 11/29/21
  - Residual Disease on small bowel mesentery <1cm
  - HER2 – 3+, P53 mutated, ER/ER+, pMMR, 100% invasion, + LVSI, + met to vagina
- Enrolled in DUO-E 6 cycles carboplatin/paclitaxel +/- durvalumab, followed by Durvalumab or placebo maintenance. CR after cycle #12
- 7/12/23- Mesenteric nodes started to increase in size, but not measurable.
  - 3/21/24- CT measurable at 1.8cm
- HER 2- 3+ -> ECHO- 55-65%→Started on fam-trastuzumab deruxtecan on 5/8/24
  - D1 – Aprepitant, Palonosetron, and Dexamethasone; Olanzapine D2-4
  - Now s/p cycle # 16 on 3/20/25, CT 3/14/25- node now 0.9cm.
- Tolerated well with no dose reductions, no signs of ILD/pneumonitis, ECHO remains 55-65% on 3/14/25

Roundtable Discussion

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Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress

Gastroesophageal Cancers

Saturday, April 12, 2025

12:15 PM – 1:45 PM

Faculty

Sunnie Kim, MD
Brooke Parker, MSN, FNP
Michal F Segal, BSN, RN, OCN
Manish A Shah, MD

Moderator

Neil Love, MD

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Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

To Claim NCPD Credit

In-person attendees: Please refer to the program syllabus for the NCPD credit link or QR code.

Virtual attendees: The NCPD credit link is posted in the chat room.

NCPD/ONCC credit information will be emailed to each participant within 1 to 2 business days.

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