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Navigating New Waters for Advanced or Recurrent Endometrial Cancer

Supported by an educational grant from AstraZeneca Pharmaceuticals and Merck & Co., Inc., Rahway, New Jersey, USA

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Gynecologic Malignancies in Contrast

- Endometrial cancer is the only cancer for which survival has decreased over the past 4 decades
- In 2024, for the first time, the mortality rate for endometrial cancer exceeds that of ovarian cancer

Number of New Cases and Deaths for Gynecologic Cancers – 2024 US Data		
	Estimated New Cases	Estimated Deaths
Cervical	13,820	4,360
Endometrial	**67,880**	**13,250**
Ovarian	19,680	12,740

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Siegel RL, et al. *CA Cancer J Clin*. 2024;75(1):12-49. Forjaz G, et al. *Cancer Epidemiol Biomarkers Prev.* 2023;32(11):1508-1517.

Risk Factors for Endometrial Cancer

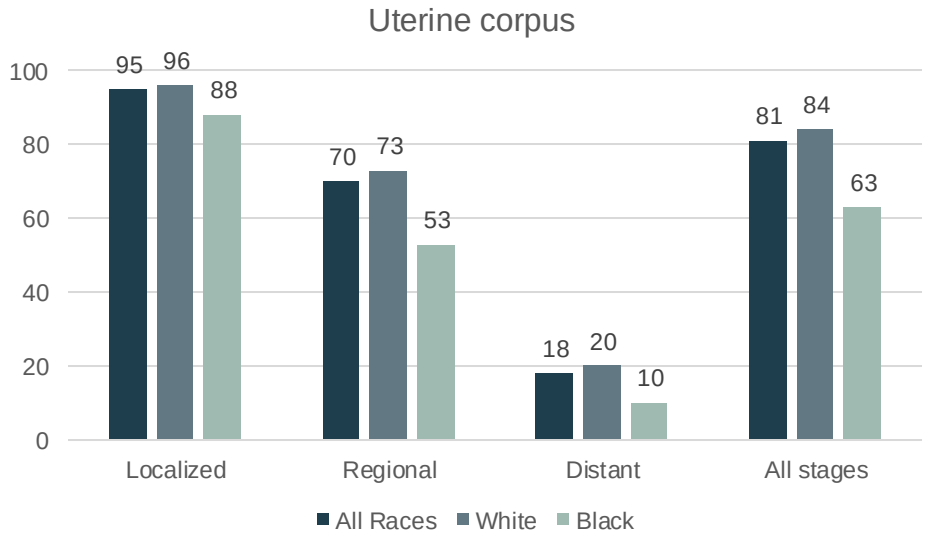
- Obesity
- Unopposed estrogen therapy for women with intact uterus (post-menopause)
- Tamoxifen
- Genetics: Lynch syndrome
- Early age menses, late age menopause
- Age 55-64
- Delay in accessing care

National Comprehensive Cancer Network [NCCN] Guidelines. *Uterine Neoplasms V2.* 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
National Cancer Institute. 2024. https://www.cancer.gov/types/uterine/hp/endometrial-prevention-pdq#_229_toc.

Disparities in Outcomes

- One of the largest Black/White disparities in cancer diagnosis and survival
- 56% of Black women diagnosed at a localized stage compared to 72% of White women

Five-year relative survival by race and stage at diagnosis



Siegel RL, et al. *CA Cancer J Clin.* 2024;75(1):12-49.

The Challenge of Treating Advanced/Recurrent Endometrial Cancer

Long-Term Outcomes Remain Poor

Advanced/recurrent endometrial cancer 5-year survival: **15-20%**

Carboplatin/paclitaxel (C/P): prior standard of care in GOG/NRG Oncology trials, but is **only moderately effective** in endometrial cancer

Disparities in Outcomes

Poor outcomes in higher-grade or measurable disease, tumors **with rare histology,** non-Hispanic **Black women**

Complex Molecular Mechanisms

Tumoral molecular/mutational profile is key

Median PFS rates of patients with biomarker unselected or mismatch repair proficient tumors: **~8-13 months**

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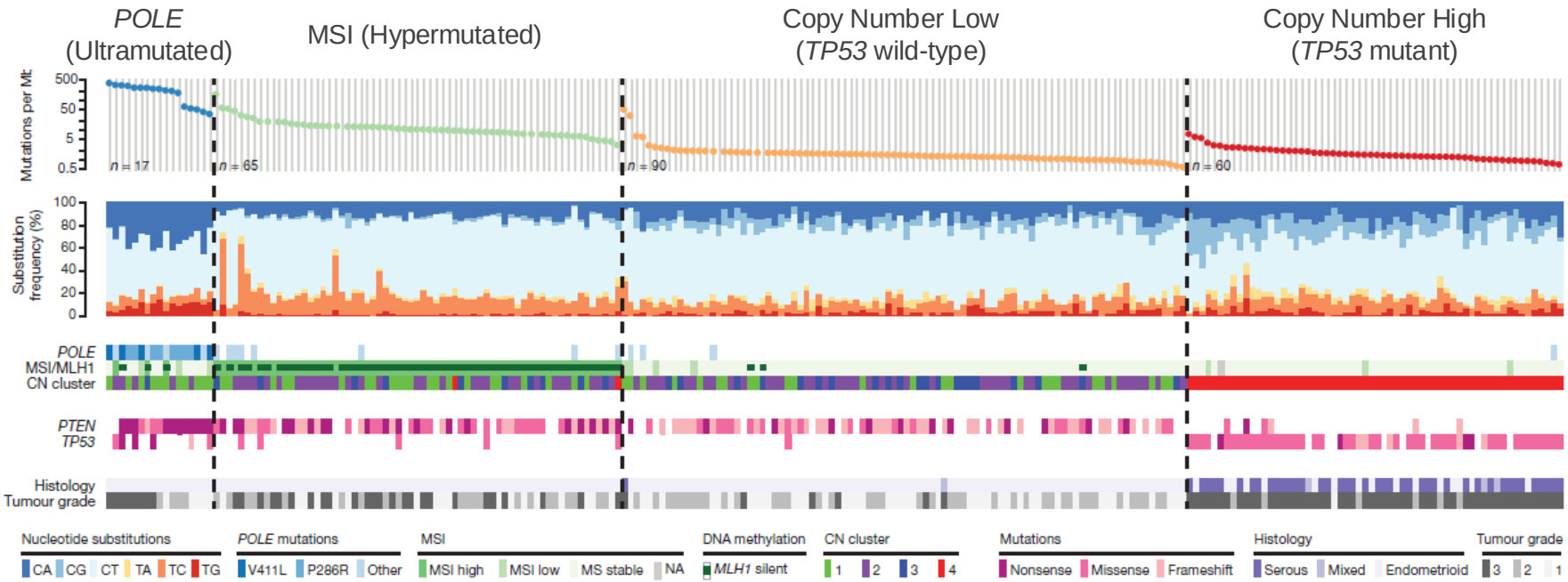
GOG = Gynecologic Oncology Group; PFS = progression-free survival.

Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. Brooks RA, et al. *CA Cancer J Clin.* 2019; 69(4):258-279. Siegel RL, et al. *CA Cancer J Clin.* 2024;75(1):12-49.

Integrate appropriate, guideline-directed molecular profiling strategies in the endometrial cancer (EC) risk assessment and treatment decision process.

LEARNING OBJECTIVE 1

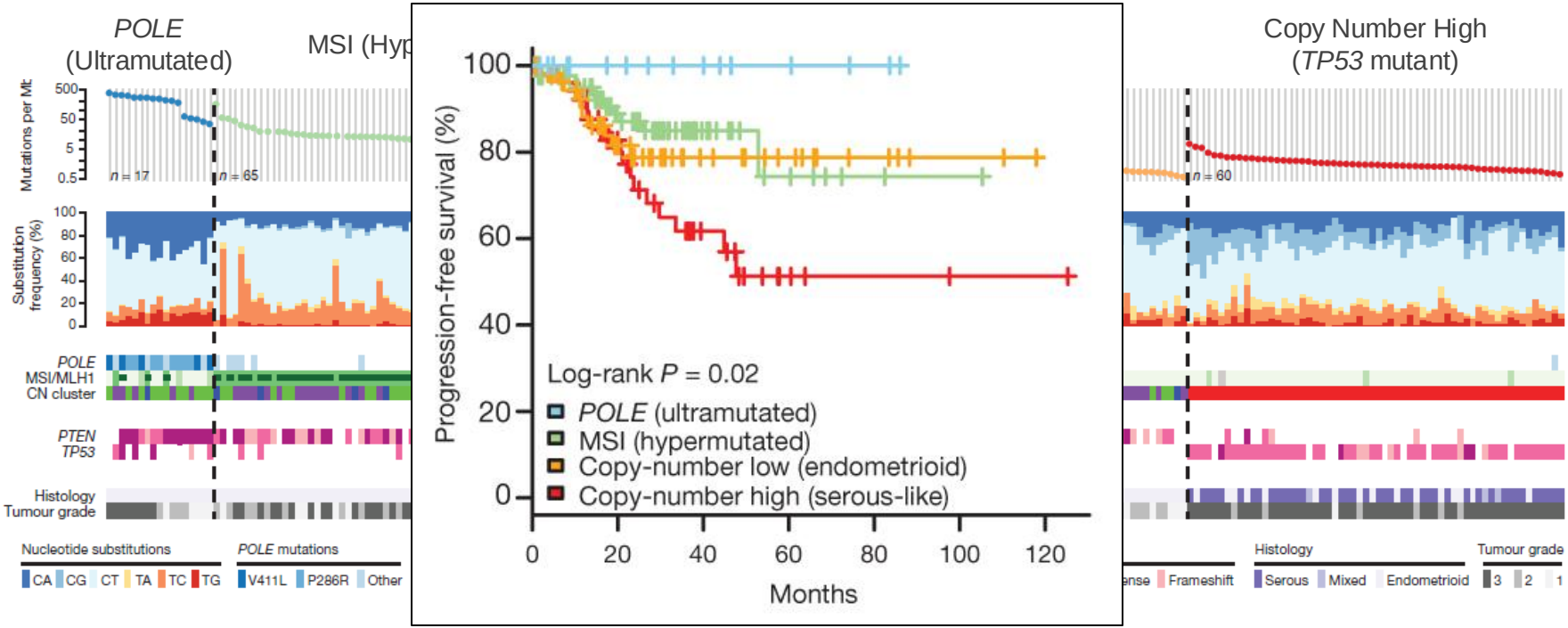
The Cancer Genome Atlas (TCGA) Integrated Genomic Characterization of Endometrial Carcinoma



MSI = microsatellite instability; CN = copy number.

Levine DA. *Nature*. 2013;497:67-73.

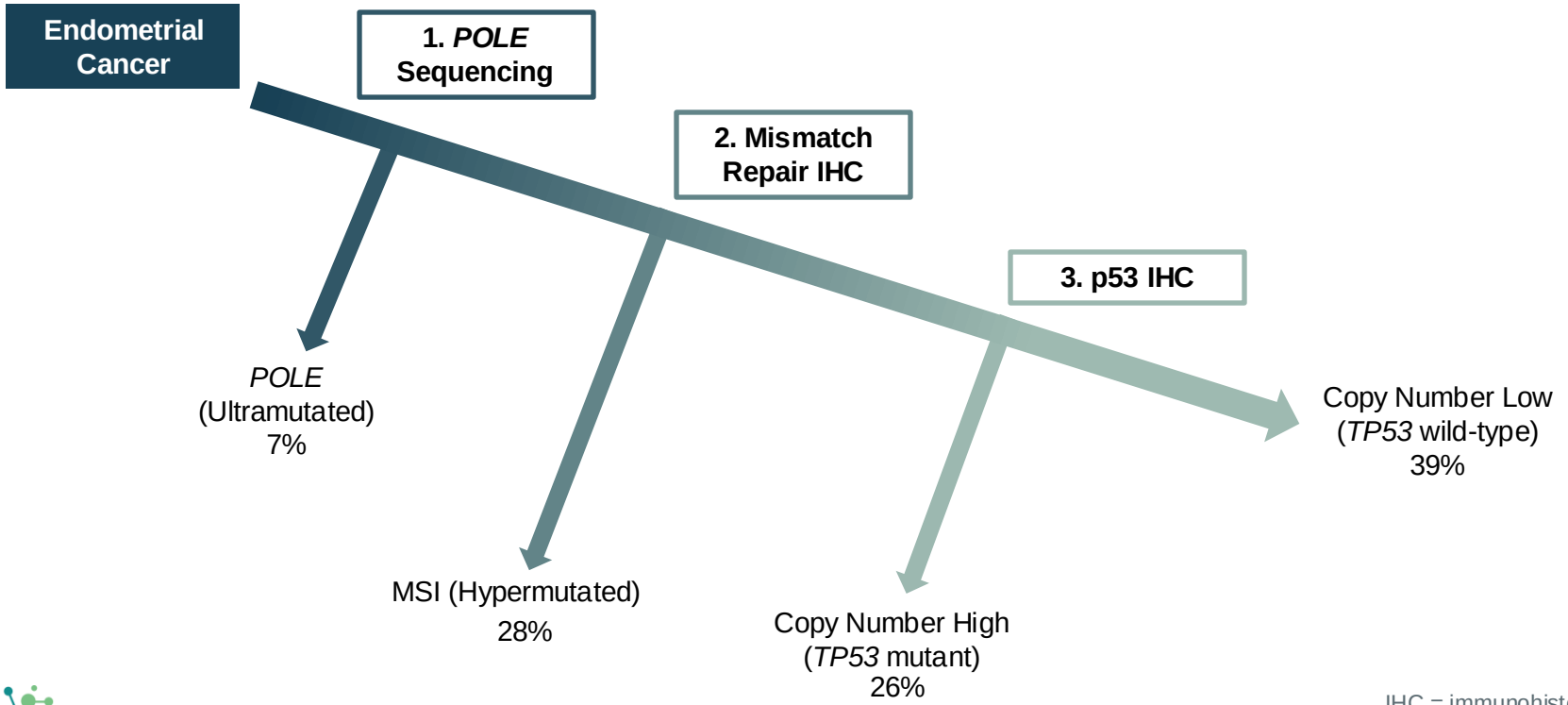
The Cancer Genome Atlas (TCGA) Integrated Genomic Characterization of Endometrial Carcinoma



MSI = microsatellite instability; CN = copy number.

Levine DA. *Nature*. 2013;497:67-73.

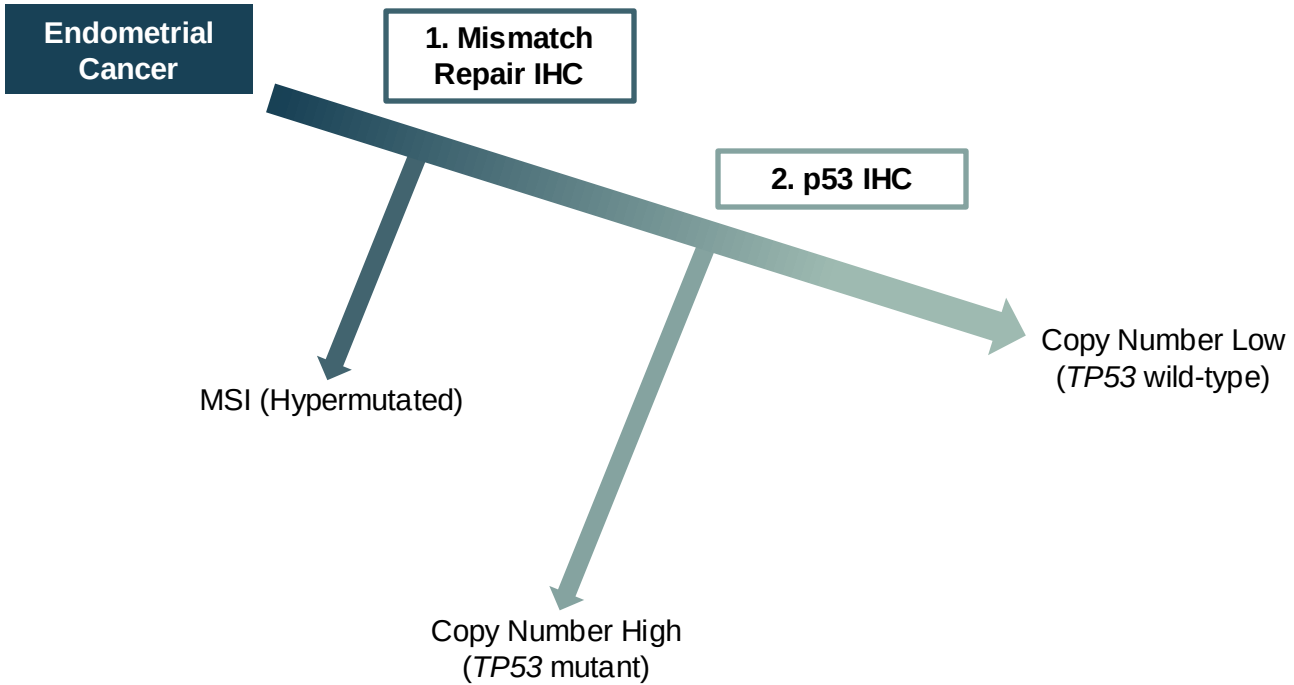
Ideal Sequence for TCGA Subgrouping



IHC = immunohistochemistry.

Levine DA. *Nature*. 2013;497:67-73. Walsh CS, et al. *Gynecol Oncol*. 2023;168:48-55.
NCCN Guidelines. *Uterine Neoplasms V2.* 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.

Practical Sequence for TCGA Subgrouping



Consider *POLE* Sequencing in Select Tumors

- Grade 2-3 stage I/II
- Associated histologic features
  - Ambiguous serous/endometrioid morphology
  - Intratumoral and peritumoral lymphocytic infiltrate
  - Frequent LVSI
  - Bizarre nuclear atypia

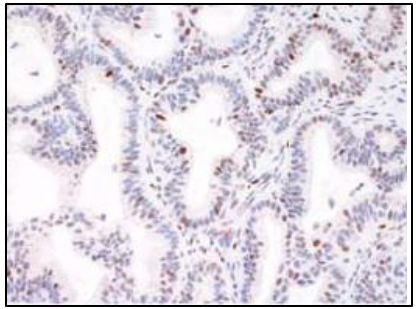
LVSI = lymphovascular space invasion.

Slide courtesy of Dr. Kyle M. Devins.

Levine DA. *Nature*. 2013;497:67-73. NCCN Guidelines. *Uterine Neoplasms V2*. 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Walsh CS, et al. *Gynecol Oncol*. 2023;168:48-55.

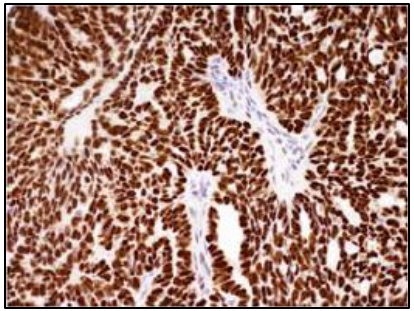
p53 Interpretation

Wild-Type Patterns

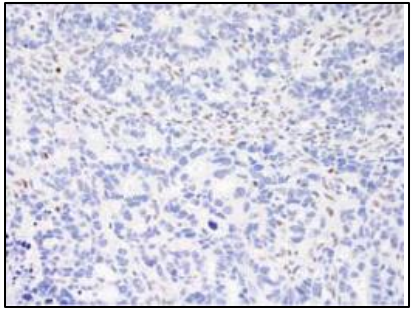


Wild-Type

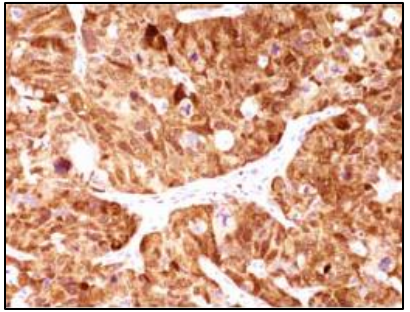
Mutant Patterns



Overexpression



Null



Cytoplasmic

Small percentage of tumors with truncating *TP53* mutations may appear wild-type by IHC

Overexpression (65-70%): nonsynonymous missense mutations
Null (25%): deletions, nonsense mutations
Cytoplasmic (5%): nuclear localization domain mutations

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Köbel M, et al. *J Path Clin Res*. 2016;2:247-258.

HER2 Testing

Uterine Serous Carcinomas and Carcinosarcomas[a]

- HER2 amplification in up to 30%
- Heterogeneous expression
  - Consider repeat testing in recurrent disease

IHC 2+ → Reflex ISH testing

High Stage and Recurrent Carcinomas of Any Type[b]

- For consideration of trastuzumab deruxtecan
- NOT dependent on gene amplification

IHC 2+ → No need for reflex ISH if IHC 2+

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[a]HER2 interpretation using uterine serous carcinoma criteria; [b]HER2 interpretation using gastric criteria.
HER2 = human epidermal growth factor receptor 2. ISH = in situ hybridization.
Buza N, Hui P. *Arch Pathol Lab Med.* 2022;146(5). Bartley AN, et al. *J Clin Oncol.* 2024;42(1):47-58.
NCCN Guidelines. *Uterine Neoplasms V2.* 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.

Testing Summary

All New Endometrial Cancers

- MMR proteins → MLH1 + PMS2 loss → *MLH1* promoter methylation
- p53
- ER/PR

Situational Options

- *POLE* sequencing
- ★ PD-L1
- ★ HER2
- ARID1A
- ★ Next Generation Sequencing

★ Special consideration in recurrent endometrial cancer

Walsh CS, et al. *Gynecol Oncol.* 2023;168:48-55. NCCN Guidelines. *Uterine Neoplasms V2.* 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.

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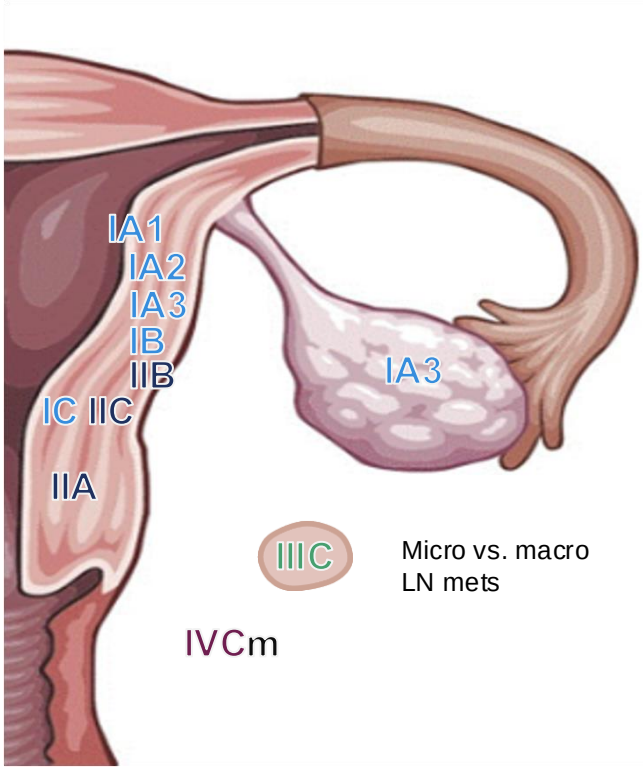
Endometrial Cancer - Updated 2023 FIGO Staging

	2009	2023
Stage I Early	A: Limited to endometrium B: < 50% myometrium involvement C. ≥ 50% myometrium involvement	**A1, IA2:** < 50% myometrium involvement **A3**: low-grade endometrioid carcinoma limited to uterus + ovary **B:** ≥ 50% myometrium involvement, no LVSI **C:** Aggressive histology limited to polyp or confined to endometrium
Stage II Cervix	A: Lining B: Stroma of cervix	**IIA**: Stroma of cervix **IIB**: Substantial LVSI **IIC:** Aggressive histology with any myometrium involvement
Stage III Locally Advanced	A: Serosa/adnexa B: Vaginal metastasis C: Pelvic/para-aortic nodes	**A:** Serosa/adnexa **B:** Vaginal metastasis **C:** Pelvic/para-aortic nodes • *Micro vs. macro LN mets*
Stage IV Advanced	A: Bowel or bladder B: Distant metastases; intra-abdominal and/or inguinal lymph nodes	**A:** Bowel or bladder **B:** Extrapelvic peritoneal **C:** Distant metastases

m = molecular subtype known (POLEmut, MMRd, NSMP, p53abn)



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Picture courtesy of Lauren Ritterhouse, MD, PhD. Pecorelli S, et al. *Int J Gynaecol Obstet.* 2009;105(2):103-104. Berek JS, et al. *Int J Gynaecol Obstet.* 2023;162(2):383-394.

Changes in Stage and Treatment

All staging in guideline is based on updated FIGO staging

Clinical Findings (Endometrioid Histology)

Surgically staged: Stage I →

Histologic Grade/Adjuvant Treatment

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if LVSI and/or age ≥ 60
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥ 70 or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age < 60 and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if age ≥ 60 and/or LVSI or Consider observation if age < 60 and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

EBRT = external beam radiotherapy; RT = radiotherapy.

NCCN Guidelines. *Uterine Neoplasms V2.* 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.

Assess the latest efficacy and safety data for the treatment of EC, factoring in updates to guidelines.

LEARNING OBJECTIVE 2

Biomarker-Driven Systemic Therapy for Endometrial Carcinoma

Systemic Therapy for Endometrial Carcinoma

Recurrent Disease

First-Line Therapy for Recurrent Diseases

Preferred
- Carboplatin/paclitaxel (category 1 for carcinosarcoma)
- Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma)
- Carboplatin/paclitaxel/dostarlimab-gxly (category 1)
- Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma)
- Carboplatin/paclitaxel/trastuzumab (for HER2-positive carcinosarcoma)

Other Recommended Regimens
- Carboplatin/docetaxel
- Carboplatin/paclitaxel/bevacizumab

Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)
- MMR-proficient (pMMR) tumors
  - Lenvatinib/pembrolizumab (category 1)
- TMB-H tumors
  - Pembrolizumab
- MSI-H/dMMR tumors
  - Pembrolizumab
  - Dostarlimab-gxly

Second-Line or Subsequent Therapy

Other Recommended Regimens
- Cisplatin/doxorubicin
- Cisplatin/doxorubicin/paclitaxel
- Cisplatin/gemcitabine
- Cisplatin
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Paclitaxel
- Albumin-bound paclitaxel
- Topotecan
- Bevacizumab
- Temsirolimus
- Cabozantinib
- Docetaxel (category 2B)
- Ifosfamide (for carcinosarcoma)
- Ifosfamide/paclitaxel (for carcinosarcoma)
- Cisplatin/ifosfamide (for carcinosarcoma)

Useful in Certain Circumstances (Biomarker-directed therapy)
- pMMR tumors
  - Lenvatinib/pembrolizumab (category 1)
- TMB-H tumors
  - Pembrolizumab
- MSI-H/dMMR tumors
  - Pembrolizumab
  - Dostarlimab-gxly
  - Avelumab
  - Nivolumab
- HER2-positive tumors (IHC 3+ or 2+)
  - Fam-trastuzumab deruxtecan-nxki*
- *NTRK* gene fusion-positive tumors
  - Larotrectinib
  - Entrectinib

*Fam-trastuzumab deruxtecan-nxki is not FDA approved for IHC 2+ tumors in this setting.

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NCCN Guidelines. *Uterine Neoplasms V2.* 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.

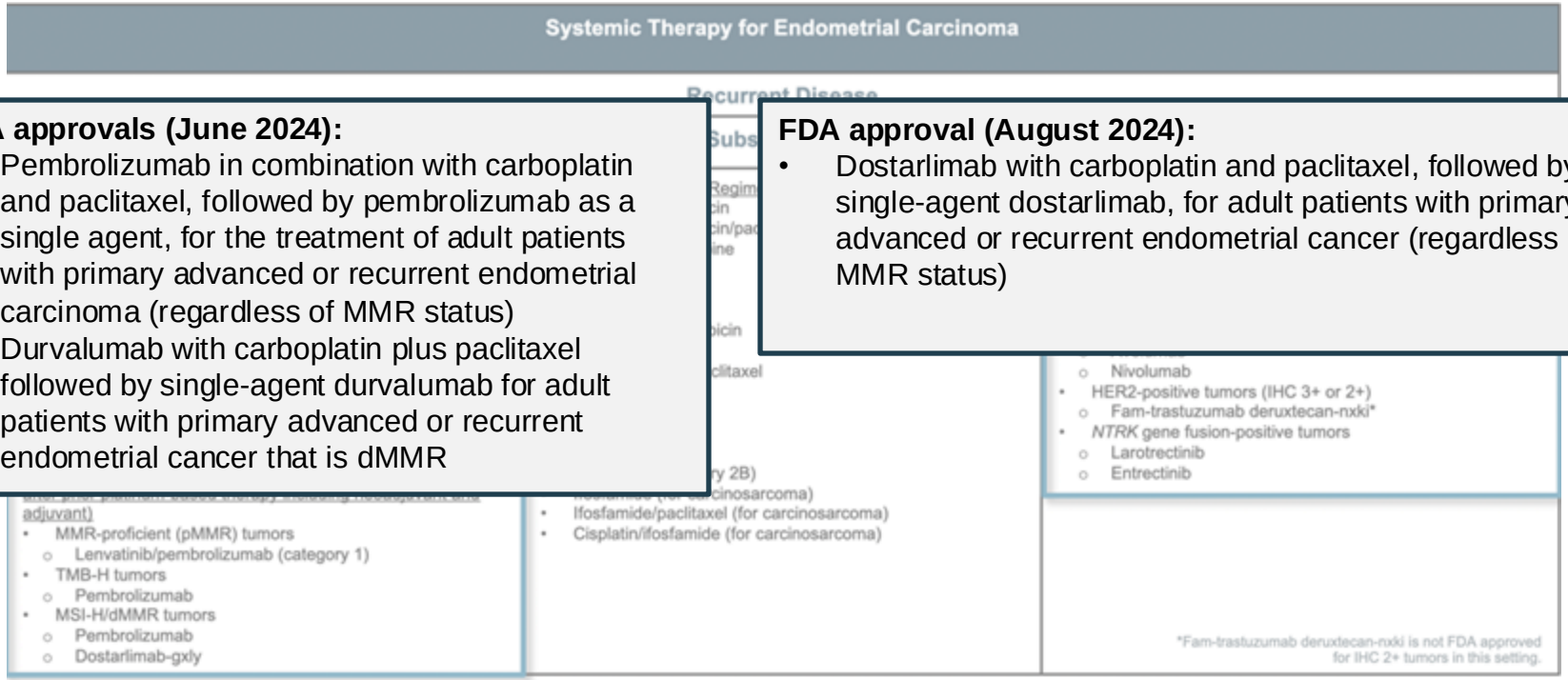
Biomarker-Driven Systemic Therapy for Endometrial Carcinoma

FDA approvals (June 2024):

- Pembrolizumab in combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma (regardless of MMR status)
- Durvalumab with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent endometrial cancer that is dMMR

FDA approval (August 2024):

- Dostarlimab with carboplatin and paclitaxel, followed by single-agent dostarlimab, for adult patients with primary advanced or recurrent endometrial cancer (regardless of MMR status)



NCCN Guidelines. Uterine Neoplasms V2. 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
Pembrolizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s155lbl.pdf.
Durvalumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761069s045lbl.pdf.
Dostarlimab-gxly [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf.
Fam-trastuzumab deruxtecan-nxki [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

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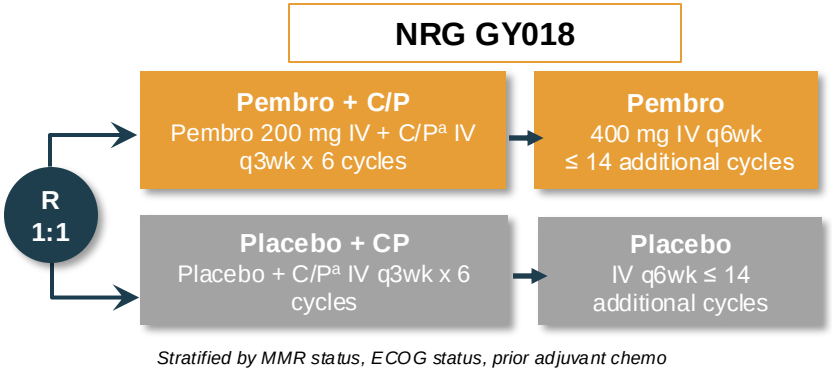
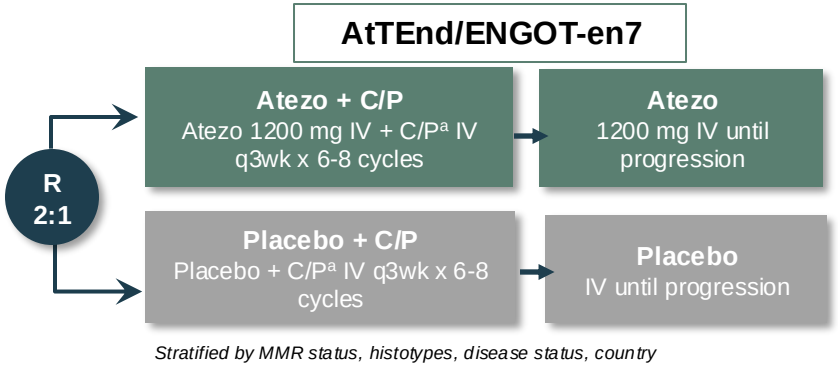
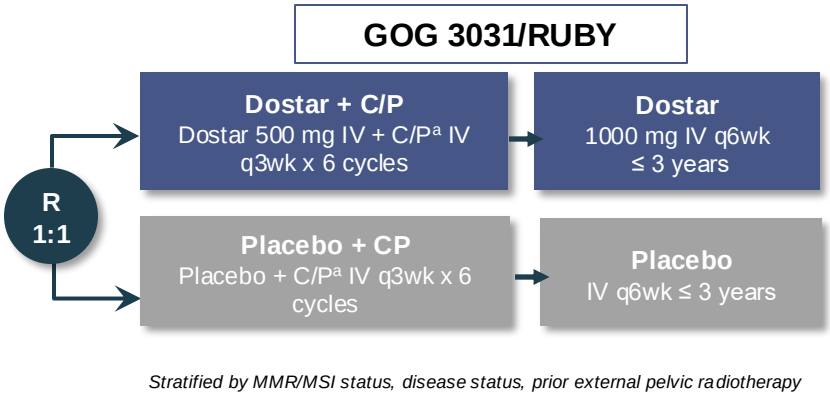
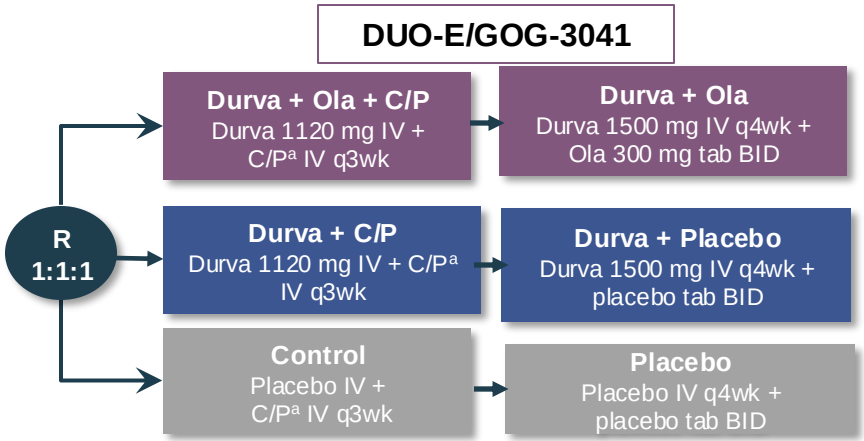
QUESTIONS & ANSWERS

Immunotherapy + Chemotherapy in EC: Phase III Trials









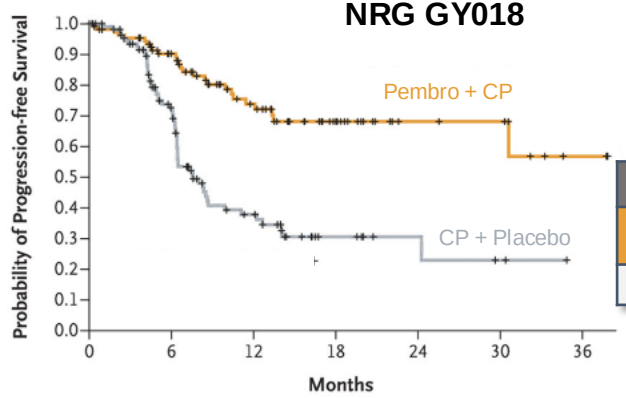
[a]Carboplatin AUC 5 IV + Paclitaxel 175 mg/m^2 IV. BID = twice daily.

This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with caution.

Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299.
Mirza MR, et al. European Society for Medical Oncology Congress [ESMO]; 2023. Abstract No. 740MO.

Immunotherapy + Chemotherapy for Advanced or Recurrent Endometrial Cancer: PFS in dMMR

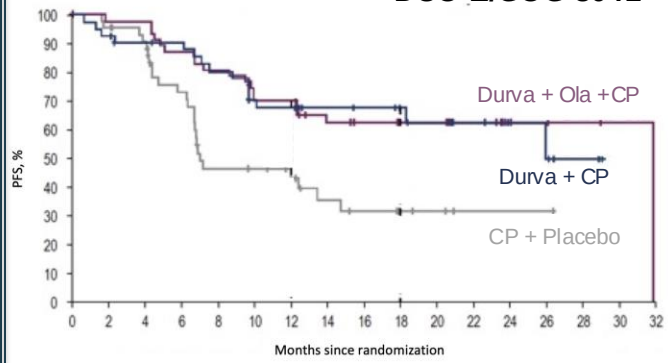
NRG GY018



HR, 0.30
(95% CI, 0.19-0.48)
p < 0.00001

mPFS, months	
Pembro + CP (n = 112)	CP (n = 113)
NR	7.6 mo

DUO-E/GOG-3041

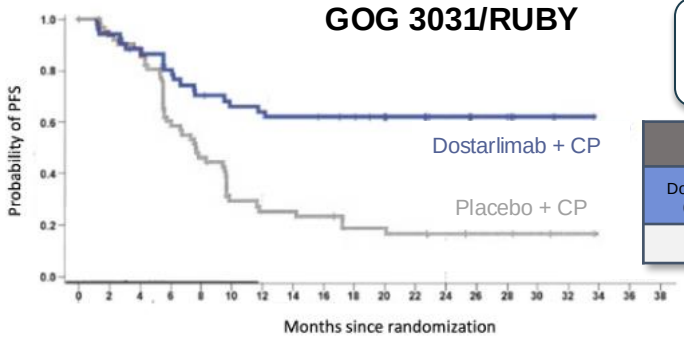


Durva + CT arm
HR, 0.42
(95% CI, 0.22-0.80)
No *p*-value given

mPFS, months		
D+O+CP (n = 48)	D+CP (n = 46)	CP (n = 49)
31.8 mo	NR	7.0 mo

Durvalumab in combination with olaparib is not FDA approved in endometrial cancer.

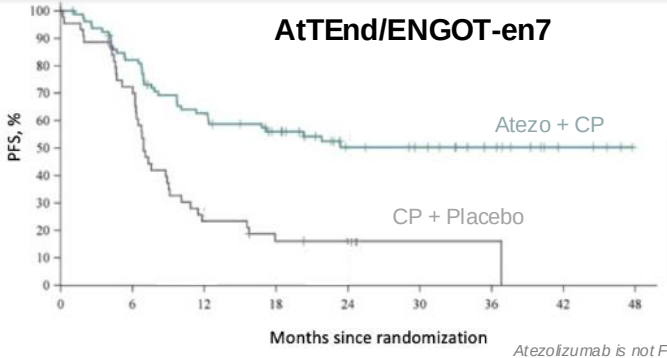
GOG 3031/RUBY



HR, 0.28
(95% CI, 0.16-0.50)
p < 0.0001

mPFS, months	
Dostar + CP (n = 53)	CP (n = 65)
NR	7.7 mo

AtTEnd/ENGOT-en7



HR, 0.36
(95% CI, 0.23-0.57)
p = 0.0005

mPFS, months	
Atezo + CP (n = 81)	CP (n = 41)
NR	6.9 mo

Atezolizumab is not FDA approved in endometrial cancer.

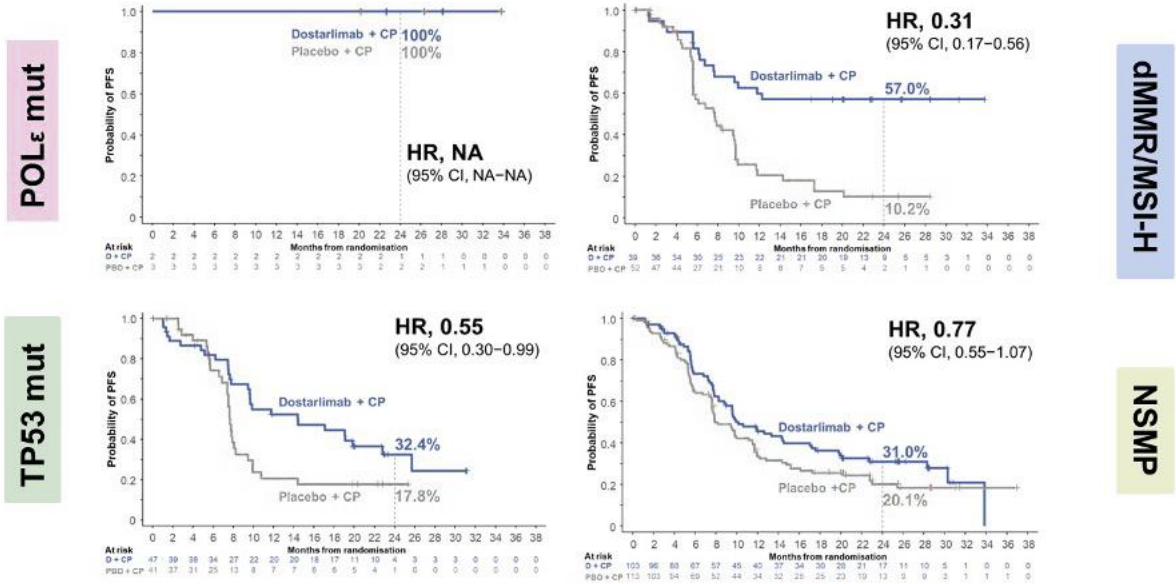
This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with caution.

Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. Westin SN, et al. ESMO; 2023. Abstract No. LBA41. Mirza MR, et al. *N Engl J Med.* 2023;388:2145-2158. Colombo N, et al. ESMO; 2023. Abstract LBA40.

GOG-3031/RUBY: PFS by Molecular Subgroup

PFS analyzed by 4 molecular subgroups in 400/494 patients enrolled in GOG-3031/RUBY who had whole-exome DNA sequencing results

- POLε mutation[a] (1.2%)
- dMMR/MSI-H (22.75%)
- *TP53* aberrant (22%)
- NSMP (54%)



[a]Patients showed no progression in either the treatment or placebo arm in the POLε mutation subgroup.
NSMP = no specific molecular profile.
Mirza MR, et al. ESMO; 2023. Abstract No. 740MO.

QUESTIONS & ANSWERS

Study 309/KEYNOTE-775

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

Stratification factors
MMR status (pMMR vs dMMR) and further stratification within pMMR by:
- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)

R
1:1

Lenvatinib
20 mg PO qd
+
Pembrolizumab[b]
200 mg IV q3wk

Treat until progression or unacceptable toxicity

Doxorubicin
60 mg/m^2 IV q3wk
or
Paclitaxel
80 mg/m^2 IV qwk
(3 weeks on/1 week off)

Primary endpoints
- PFS by BICR
- Overall survival

Secondary endpoints
- ORR
- HRQoL
- Pharmacokinetics
- Safety

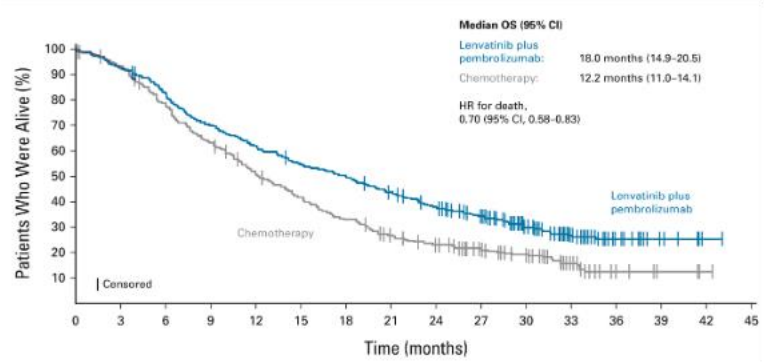
Key exploratory endpoint
- Duration of response

[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m^2.
BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQoL = health-related quality of life; IV = intravenous; ORR = objective response rate; PO = per os (by mouth).

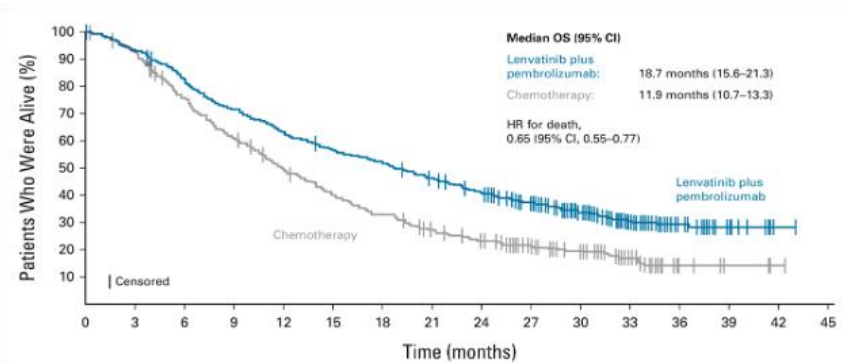
Adapted from Makker V, et al. SGO; 2021. Abstract No. 37/ID 11512. Makker V, et al. *N Engl J Med*. 2022;386(5):437-448.

KEYNOTE-775 Extended Follow-Up

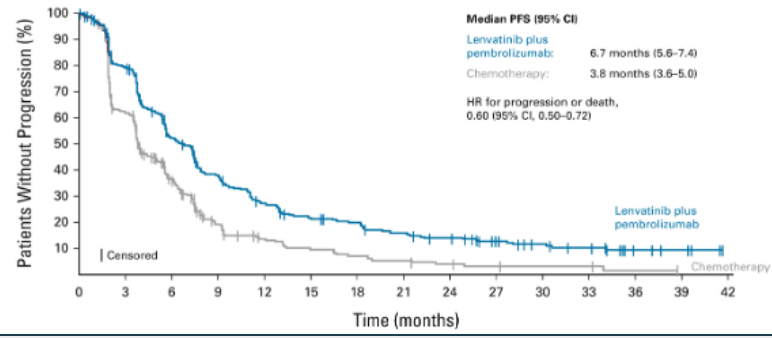
OS, pMMR Population (n = 697)



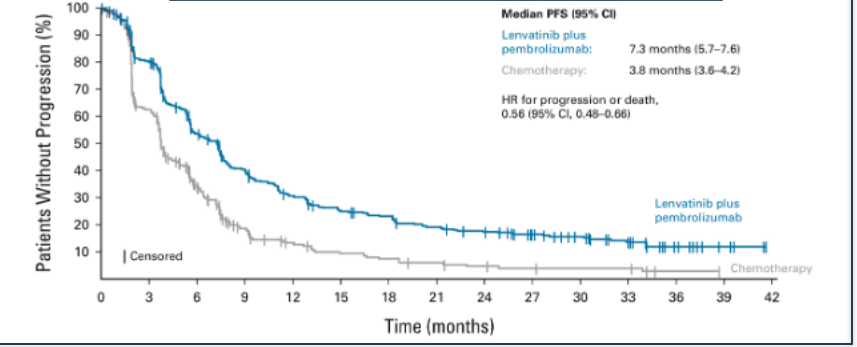
OS, All-Comer (n = 827)



PFS, pMMR Population (n = 697)



PFS, All-Comer (n = 827)



Makker V, et al. *N Engl J Med*. 2022;386(5):437-448. Makker V, et al. *J Clin Oncol*. 2023;41(16):2904-2910. Lorusso D, et al. *Eur J Cancer*. 2023; 186:172–184.

DUO-E Study Design

Patients

- Newly diagnosed FIGO 2009 stage III/IV or recurrent endometrial cancer (measurable disease if newly diagnosed stage III disease)
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥ 12 months from last treatment to relapse
- All histologies except sarcomas

N = 718

R
1:1:1

Stratified by:

- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs non-Asia)

	Chemotherapy phase (6 cycles)	Maintenance phase
CP arm	CP† (q3wk)	Placebos
CP+D arm	CP† (q3wk) + **Durvalumab** (1120 mg IV q3wk)	**Durvalumab** (1500 mg IV q4wk)
CP+D+O arm	CP† (q3wk) + **Durvalumab** (1120 mg IV q3wk)	**Durvalumab** (1500 mg IV q4wk) + **Olaparib** (300 mg tablets BID)

Patients without disease progression

Treatment until disease progression, unacceptable toxicity, or other discontinuation criteria were met

Endpoints

Primary

- PFS (RECIST per investigator) in:
  - CP+D arm vs CP arm
  - CP+D+O arm vs CP arm

Secondary

- OS (key secondary)
- ORR and DoR
- Safety

Exploratory

- PFS in CP+D+O arm vs CP+D arm
- Subpopulation analyses of PFS (prespecified) and ORR and DoR (post hoc) by MMR status

DUO-E is a placebo-controlled, double-blind study

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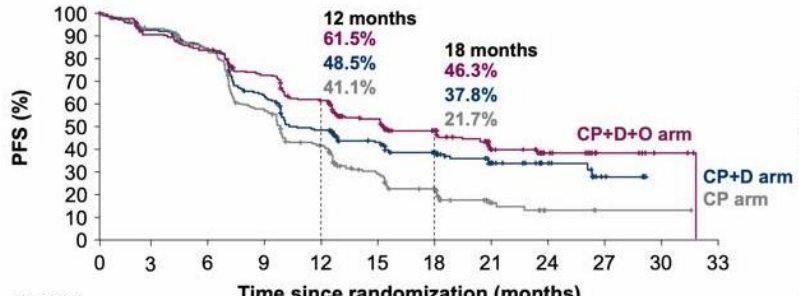
†Six cycles of carboplatin at an area under the concentration-time curve of 5 or 6 mg/mL/min at paclitaxel 175 mg/m^2.
D = durvalumab; DCO1 = data cut-off 1; FIGO = International Federation of Gynecology and Obstetrics; O = olaparib; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

Adapted from Chon HS, et al. SGO; 2021.

DUO-E PFS and OS in ITT Population

PFS: Primary endpoint



No. at risk

CP+D+O	239	214	198	169	139	95	51	30	16	7	3	0
CP+D	238	211	188	138	105	69	45	26	13	5	0	0
CP	241	213	184	125	86	45	26	10	3	1	1	0

	CP arm (N=241)	CP+D arm (N=238)	CP+D+O arm (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI), months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs CP arm*		**0.71 (0.57–0.89); *P*=0.003**	**0.55 (0.43–0.69); *P*<0.0001**
HR (95% CI) vs CP+D arm*			0.78 (0.61–0.99)

Overall data maturity: 61.0%

OS: Secondary endpoint; prespecified interim analysis

No. at risk

CP+D+O	239	233	227	208	202	152	109	77	38	18	8	2	0
CP+D	238	227	221	205	192	147	105	64	34	17	6	0	0
CP	241	229	215	201	185	136	104	69	35	15	4	0	0

	CP arm (N=241)	CP+D arm (N=238)	CP+D+O arm (N=239)
Events, n (%)	82 (34.0)	65 (27.3)	52 (21.8)
Median OS (95% CI), months	25.9 (23.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm†		**0.77 (0.56–1.07); *P*=0.120**	**0.59 (0.42–0.83); *P*=0.003**
HR (95% CI) vs CP+D arm†			0.77 (0.53–1.10)

Overall data maturity: 27.7%

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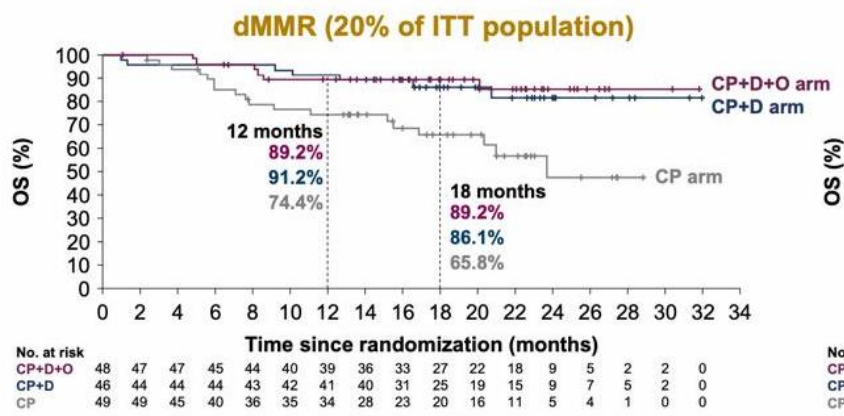
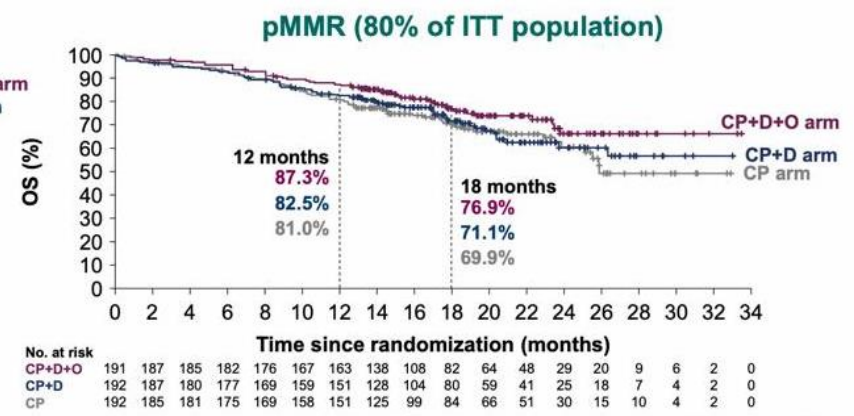
Westin SN, et al. *J Clin Oncol*. 2024;42(3):283-299. Baurain JF. SGO; 2024.

DUO-E OS by MMR Status (Post Hoc Exploratory Analysis)



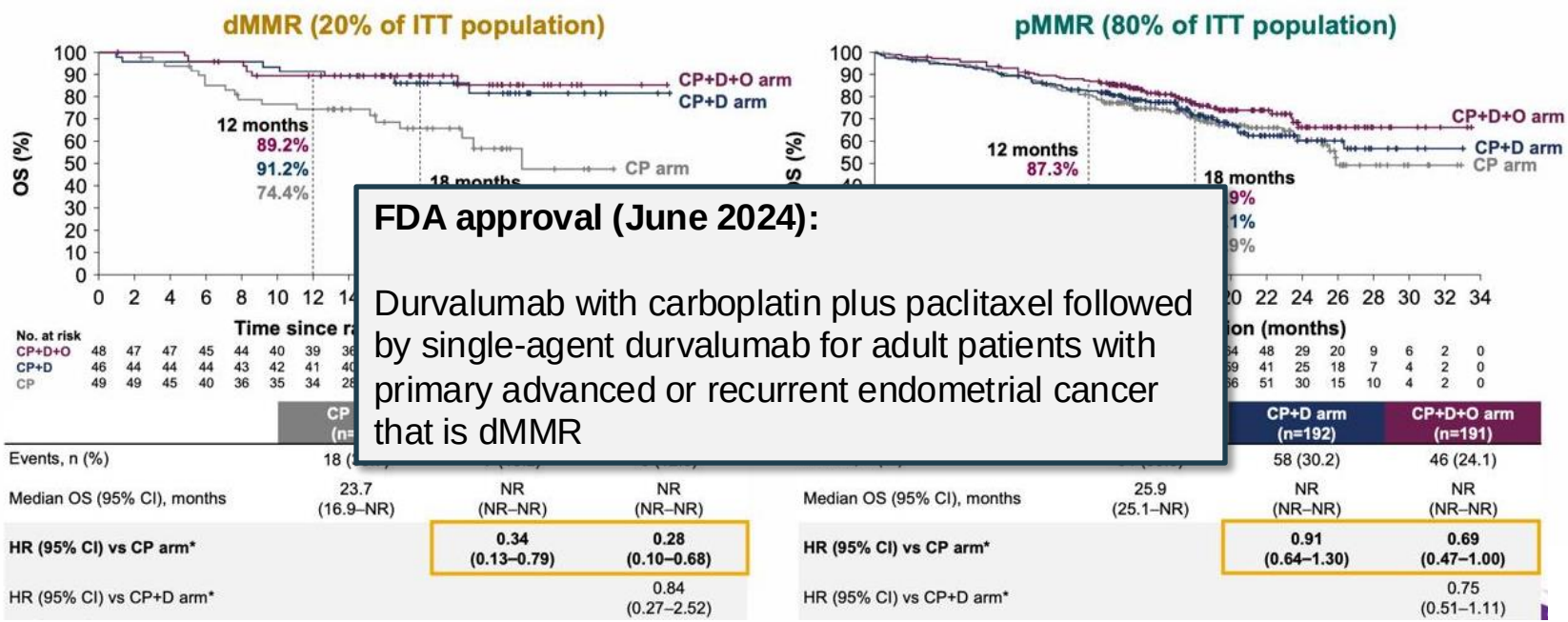


	CP arm (n=49)	CP+D arm (n=46)	CP+D+O arm (n=48)
Events, n (%)	18 (36.7)	7 (15.2)	6 (12.5)
Median OS (95% CI), months	23.7 (16.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.34 (0.13–0.79)**	**0.28 (0.10–0.68)**
HR (95% CI) vs CP+D arm*			0.84 (0.27–2.52)

	CP arm (n=192)	CP+D arm (n=192)	CP+D+O arm (n=191)
Events, n (%)	64 (33.3)	58 (30.2)	46 (24.1)
Median OS (95% CI), months	25.9 (25.1–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.91 (0.64–1.30)**	**0.69 (0.47–1.00)**
HR (95% CI) vs CP+D arm*			0.75 (0.51–1.11)

Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. Baurain JF. SGO; 2024. FDA. 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-chemotherapy-mismatch-repair-deficient-primary-advanced-or-recurrent.

DUO-E OS by MMR Status (Post Hoc Exploratory Analysis)



FDA approval (June 2024):

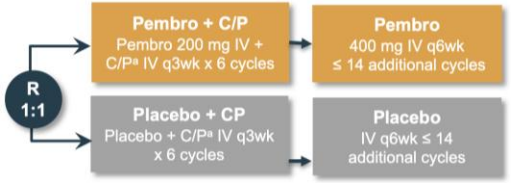
Durvalumab with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent endometrial cancer that is dMMR

	CP arm (n=49)	CP+D arm (n=192)	CP+D+O arm (n=191)
Events, n (%)	18 (36.7)	58 (30.2)	46 (24.1)
Median OS (95% CI), months	23.7 (16.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.34 (0.13–0.79)**	**0.28 (0.10–0.68)**
HR (95% CI) vs CP+D arm*		0.84 (0.27–2.52)	

	pMMR (80% of ITT population)		
	CP arm (n=566)	CP+D arm (n=192)	CP+D+O arm (n=191)
Events, n (%)	359 (63.4)	58 (30.2)	46 (24.1)
Median OS (95% CI), months	25.9 (25.1–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.91 (0.64–1.30)**	**0.69 (0.47–1.00)**
HR (95% CI) vs CP+D arm*			0.75 (0.51–1.11)

Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. Baurain JF. SGO; 2024. FDA. 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-chemotherapy-mismatch-repair-deficient-primary-advanced-or-recurrent.

NRG GY018: PFS, PFS by PD-L1 Status, and Interim OS



Endpoints
Primary Endpoint: PFS by investigator by MMR status
Select Secondary Endpoints:
- OS by MMR status
- PFS by PD-L1 status
- BICR vs investigator assessed outcomes by MMR status

pMMR Population

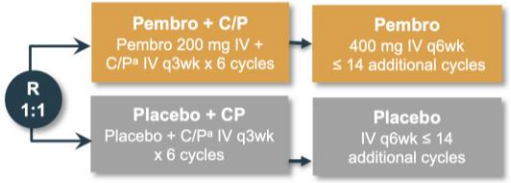
	Pembro (n = 288)	Placebo (n = 108)	
mPFS (investigator), months	13.1	8.7	HR, 0.57 (95% CI, 0.44-0.74) $p < 0.0001$
mPFS (BICR), months	19.5	11.0	HR, 0.64 (95% CI, 0.49-0.85) $p = 0.0008$
mPFS, months *PD-L1 CPS ≥ 1*	13.1	8.5	HR, 0.59 (95% CI, 0.43-0.80)
mPFS , months *PD-L1 CPS < 1*	15.1	11.0	HR, 0.44 (95% CI, 0.26-0.75)
mOS[a], months	27.96	27.37	HR, 0.79 (95% CI, 0.53-1.17) $p = 0.1157$

dMMR Population

	Pembro (n = 108)	Placebo (n = 111)	
mPFS (investigator), months	NR	8.3	HR, 0.34 (95% CI, 0.22-0.53) $p < 0.0001$
mPFS (BICR), months	NR	14.1	HR, 0.45 (95% CI, 0.27-0.73) $p = 0.0005$
mPFS, months *PD-L1 CPS ≥ 1*	NR	8.3	HR, 0.27 (95% CI, 0.16-0.47)
mPFS , months *PD-L1 CPS < 1*	12.0	4.9	HR, 0.30 (95% CI, 0.11-0.83)
mOS[a], months	NR	NR	HR, 0.55 (95% CI, 0.25-1.19) $p = 0.0617$

[a]Overall survival data not mature. At interim analysis, information fraction 22.2%% in pMMR and 18.0% in dMMR.
Eskander RN, et al. SGO; 2024.

NRG GY018: PFS, PFS by PD-L1 Status, and Interim OS



Endpoints
Primary Endpoint: PFS by investigator by MMR status
Select Secondary Endpoints:
- OS by MMR status
- PFS by PD-L1 status
- BICR vs investigator assessed outcomes by MMR status

pMMR Population

	Pembro (n = 288)	Placebo (n = 143)	
mPFS (investigator), months	13.1	8.7	HR, 0.59 (95% CI, 0.43-0.80)
mPFS (BICR), months	19.5	8.7	HR, 0.59 (95% CI, 0.43-0.80)
mPFS, months *PD-L1 CPS ≥ 1*	13.1	8.5	HR, 0.59 (95% CI, 0.43-0.80)
mPFS , months *PD-L1 CPS < 1*	15.1	11.0	HR, 0.44 (95% CI, 0.26-0.75)
mOS[a], months	27.96	27.37	HR, 0.79 (95% CI, 0.53-1.17) $p = 0.1157$

FDA approval (June 2024):

Pembrolizumab in combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma (regardless of MMR status)

dMMR Population

	Pembro (n = 111)	Placebo (n = 111)	
mPFS (investigator), months	13.1	8.3	HR, 0.34 (95% CI, 0.22-0.53) $p < 0.0001$
mPFS (BICR), months	19.5	14.1	HR, 0.45 (95% CI, 0.27-0.73) $p = 0.0005$
mPFS, months *PD-L1 CPS ≥ 1*	NR	8.3	HR, 0.27 (95% CI, 0.16-0.47)
mPFS , months *PD-L1 CPS < 1*	12.0	4.9	HR, 0.30 (95% CI, 0.11-0.83)
mOS[a], months	NR	NR	HR, 0.55 (95% CI, 0.25-1.19) $p = 0.0617$

aOverall survival data not mature. At interim analysis, information fraction 22.2%% in pMMR and 18.0% in dMMR.

Eskander RN, et al. SGO; 2024. Pembrolizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s155lbl.pdf.

Shifting Landscape: Frontline Immunotherapy Trials

ENGOT-en9/LEAP-001

R
1:1
(N = 842)

- Lenvatinib + Pembrolizumab
- Chemotherapy

Primary Endpoint(s):
PFS, OS

Key Secondary Endpoints:
ORR, QOL

dMMR and pMMR

GOG-3064/KEYNOTE-c93

R
1:1
(N = 280)

- Pembrolizumab
- Chemotherapy

Primary Endpoint(s):
PFS, OS

Key Secondary Endpoints:
ORR, DCR, DOR

dMMR

ENGOT-en13/DOMENICA

R
1:1
(N = 142)

- Dostarlimab
- Chemotherapy

Primary Endpoint(s):
PFS

Key Secondary Endpoints:
OS, QOL, ORR, DOR

dMMR

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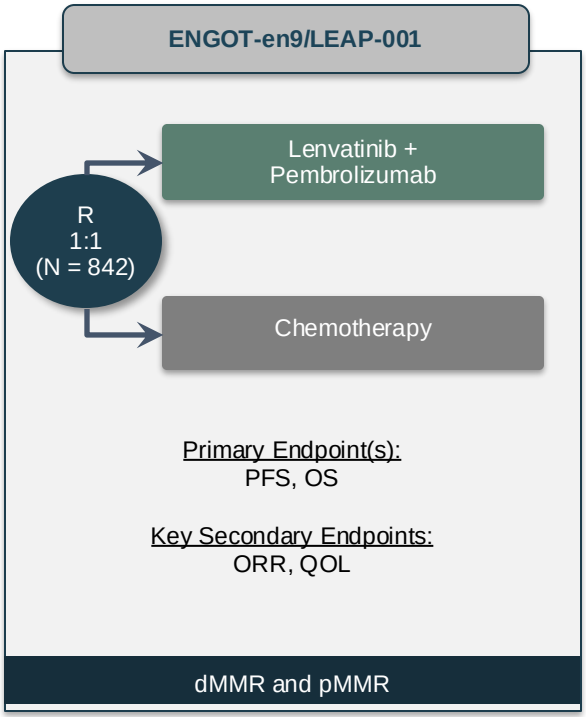
Marth C. American Society of Clinical Oncology Annual Meeting [ASCO]; 2020. Abstract No. 6106.
Slomovitz BM, et al. ASCO; 2022. Abstract No. TPS5623. Joly F, et al. ASCO; 2023. Abstract No. TPS5630.

ENGOT-en9/LEAP-001: Primary Results



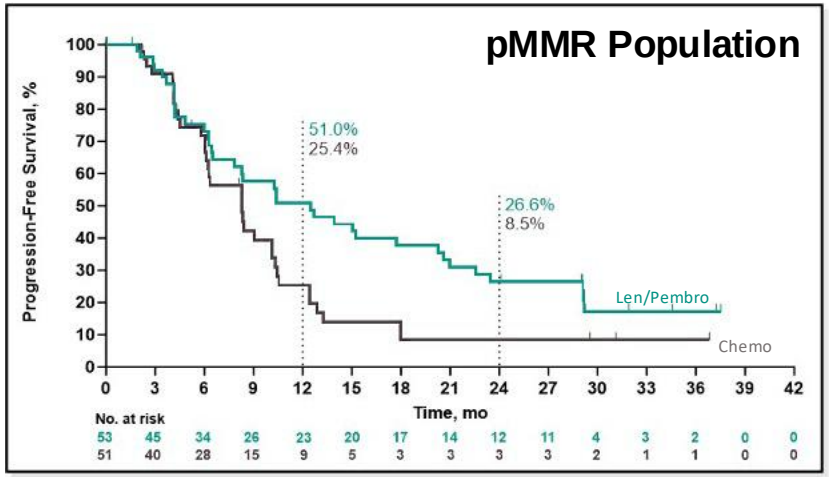
	pMMR (n = 642)	dMMR (n = 200)	All-Comers (n = 842)
mPFS, months	9.6 vs 10.2	31.8 vs 9.0	12.5 vs 10.2
HR (95% CI)	0.99 (0.82-1.21)	0.61(0.40-0.92)	0.91 (0.76-1.09)
mOS	30.9 vs 29.4	NR vs NR	37.7 vs 32.1
HR (95% CI)	1.02 (0.83-1.26)	0.57 (0.36-0.91)	0.93(0.77-1.12)

Lenvatinib + pembrolizumab is not FDA approved in the first-line setting in advanced or recurrent endometrial carcinoma.

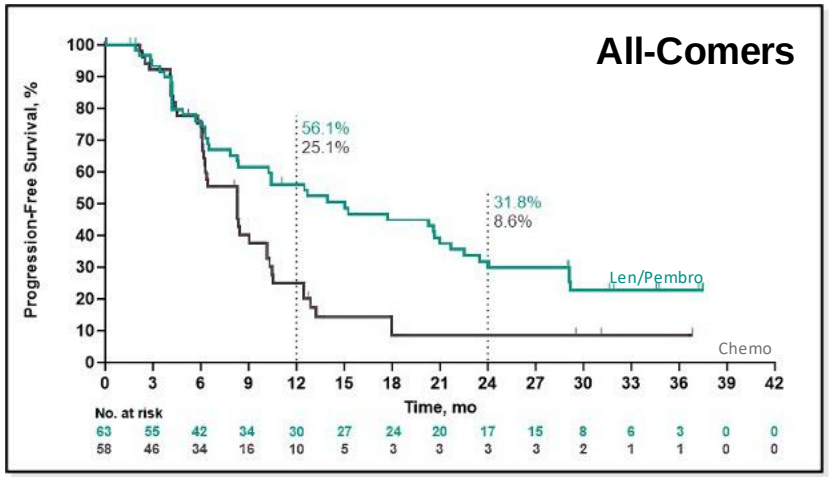
Marth C, et al. SGO; 2024. Abstract No. 88.

ENGOT-en9/LEAP-001: Subgroup Analysis

PFS improved with lenvatinib + pembrolizumab (len/pembro) vs chemotherapy in subgroup analysis of patients who received prior neoadjuvant or adjuvant chemotherapy



	mPFS, months	HR (95% CI)
Len/Pembro (n = 53)	12.5	0.60 (0.37-0.97)
Chemo (n = 51)	8.3	



	mPFS, months	HR (95% CI)
Len/Pembro (n = 63)	15.0	0.52 (0.33-0.82)
Chemo (n = 58)	8.3	

Lenvatinib + pembrolizumab is not FDA approved in the first-line setting in advanced or recurrent endometrial carcinoma.

Marth C, et al. SGO; 2024. Abstract No. 88.

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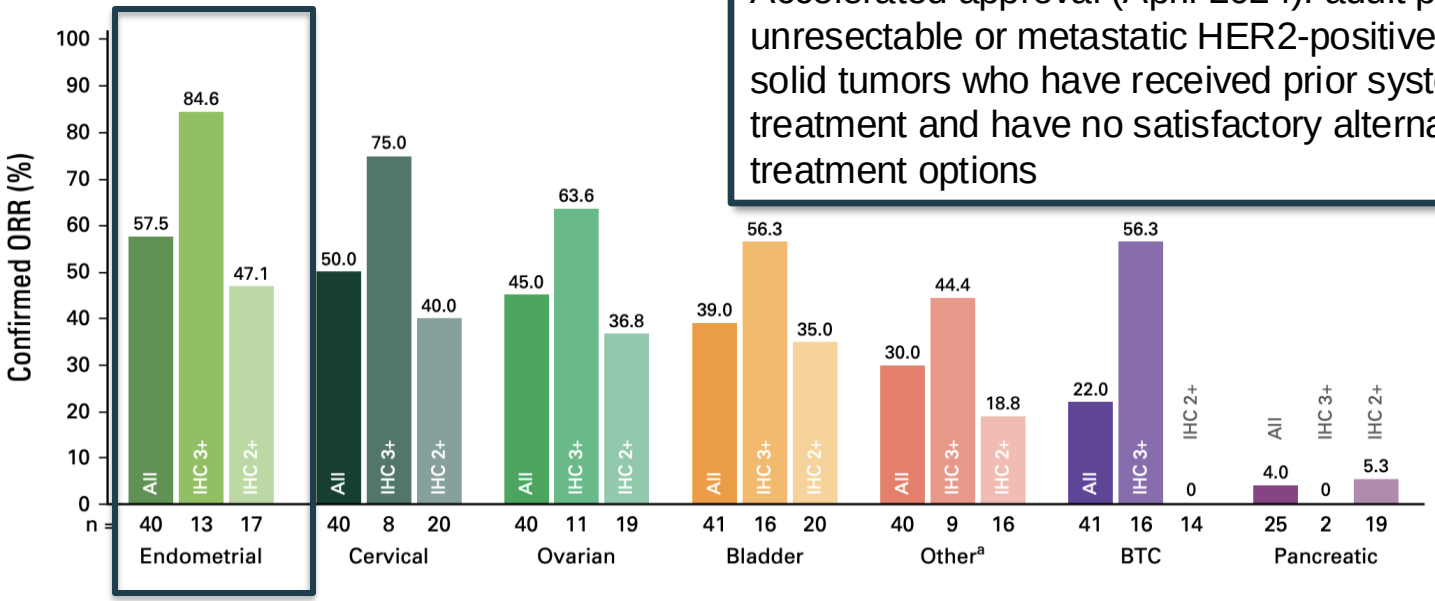
DESTINY-PanTumor02 Phase II Trial

- Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors (n = 40 with endometrial)

Accelerated approval (April 2024): adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options



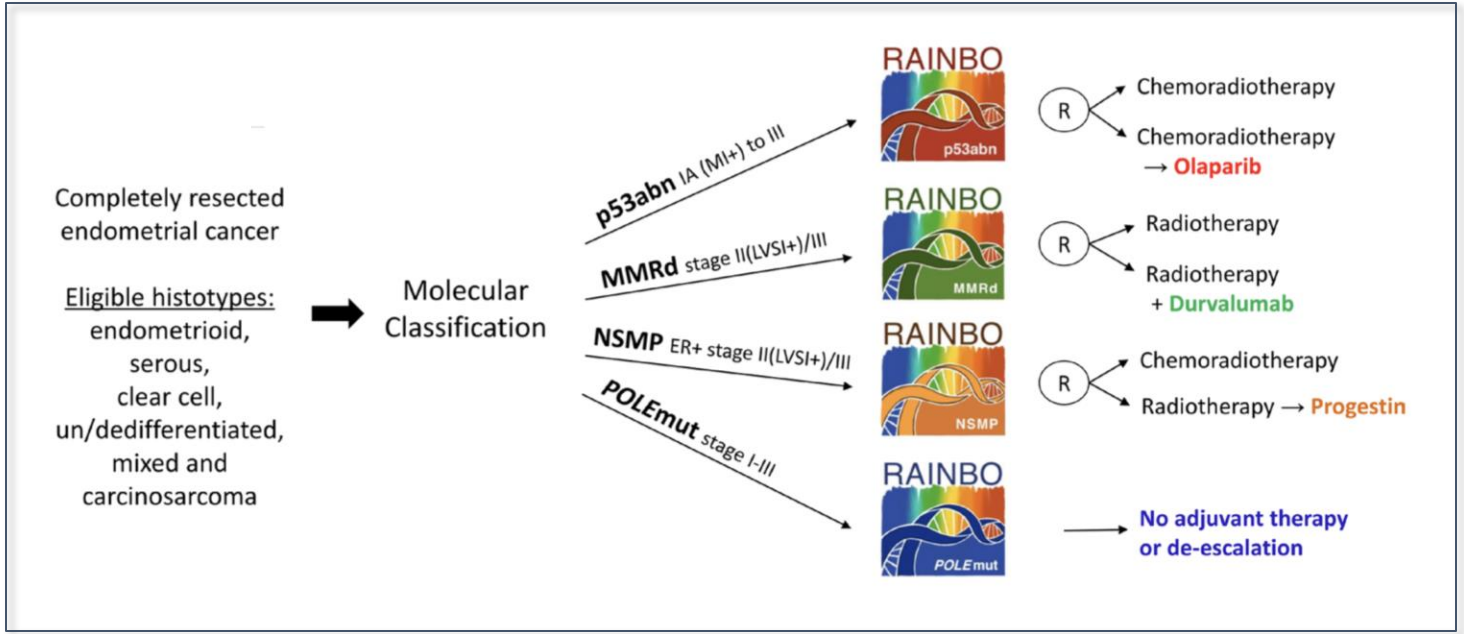
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58. FDA. 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2.

The RAINBO Clinical Trial Program

RAINBO

TransPORTEC

Refining adjuvant treatment in endometrial cancer based on molecular features



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RAINBO Research Consortium. *Int J Gynecol Cancer.* 2022;0:1-9.

Frontline Immunotherapy Trials: Outstanding Questions

- IO alone in POLEmut: **RAINBO**
- IO/IO combinations
- IO/PARPi combinations: **DUO-E, RUBY-2, RAINBO**
- Earlier stage disease: **RAINBO**, **NRG-GY020**
- Predictive biomarkers beyond MMR
- Integration of bevacizumab and selinexor
- Integration with ADCs and endocrine therapy

IO = immunotherapy; PARPi = poly (ADP-ribose) polymerase inhibitor; ADC = antibody-drug conjugate.

RAINBO Research Consortium. *Int J Gynecol Cancer.* 2022;0:1-9. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. Mirza MR, et al. ESMO; 2021. Abstract No. 820TiP. https://clinicaltrials.gov/study/NCT04214067.

Develop a guideline-concordant and patient-specific therapeutic plan for patients with newly diagnosed advanced or recurrent EC, utilizing MDT collaboration strategies.

LEARNING OBJECTIVE 3

Case #1

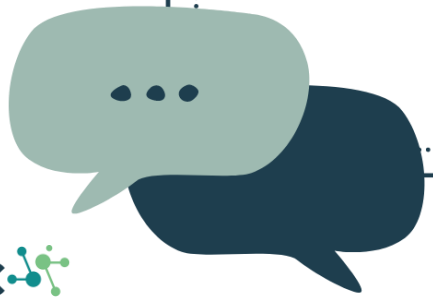
- MC (55 y/o female) presented with abnormal vaginal bleeding and pelvic pain. Upon further examination and imaging, a 5 cm deeply invasive endometrial mass was identified.
- Histology: Grade 2 endometrioid adenocarcinoma

Tumor Characteristics

- Size: 5 cm
- Deeply invasive (60% myometrial invasion)
- Prominent LVSI
- Lymph nodes: negative for metastasis

What additional information do you need?

A. HR
B. MMR IHC
C. p53 IHC
D. HER2 IHC/ISH
E. NGS with *POLE*
F. More than one of the above



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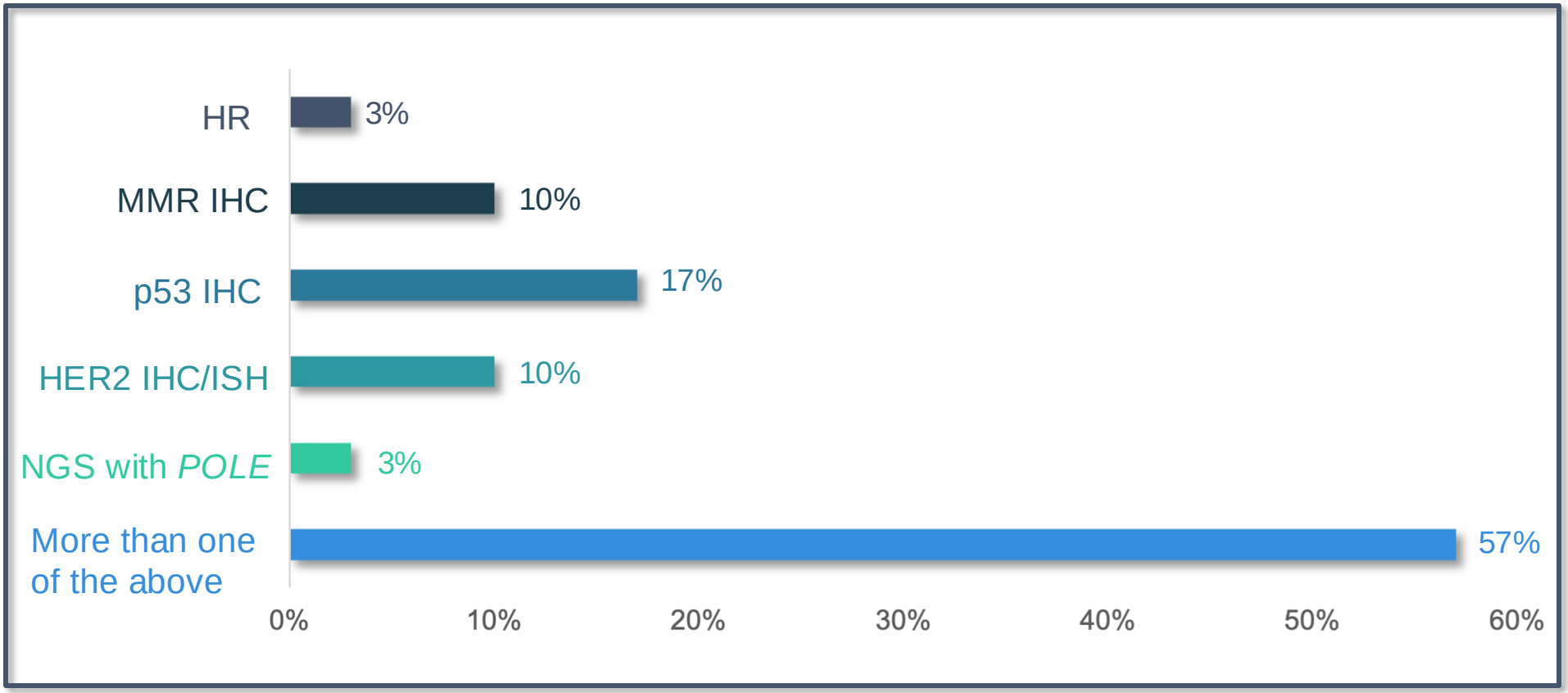
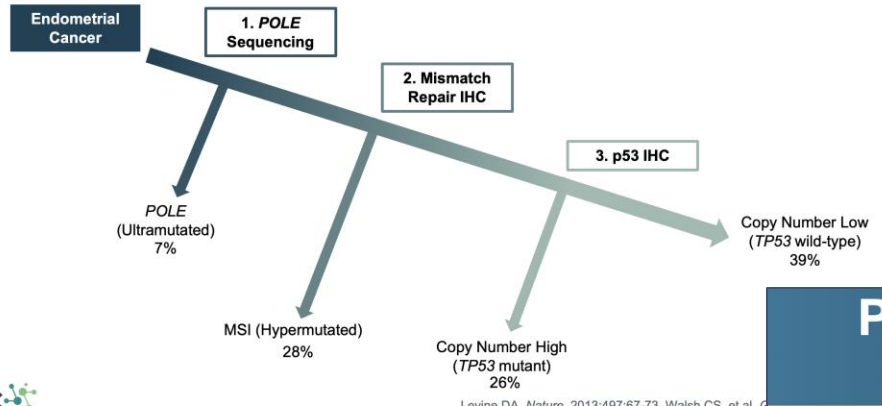
Case #1


HR
3%
MMR IHC
10%
p53 IHC
17%
HER2 IHC/ISH
10%
NGS with *POLE*
3%
More than one of the above
57%
0%
10%
20%
30%
40%
50%
60%

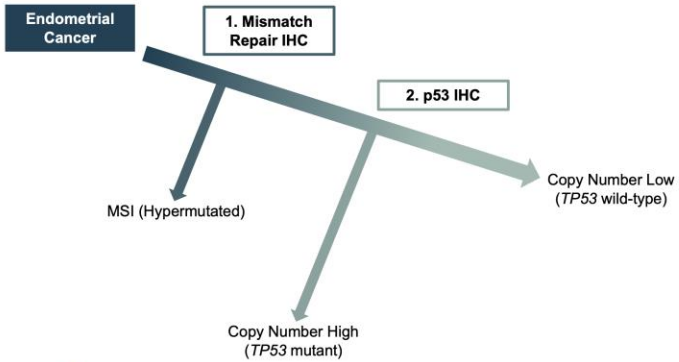
Ideal Sequence for TCGA Subgrouping



cec ONCOLOGY

Levine DA. *Nature*. 2013;497:67-73. Walsh CS, et al. G
NCCN Guidelines. *Uterine Neoplasms V2*. 2024. https://www.nccn.org/professiona

Practical Sequence for TCGA Subgrouping



Consider *POLE* Sequencing in Select Tumors

- Grade 2-3 stage I/II
- Associated histologic features
  - Ambiguous serous/endometrioid morphology
  - Intratumoral and peritumoral lymphocytic infiltrate
  - Frequent LVSI
  - Bizarre nuclear atypia

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LVSI = lymphovascular space invasion.
Slide courtesy of Dr. Kyle M. Devins.
Levine DA. *Nature*. 2013;497:67-73. NCCN Guidelines. *Uterine Neoplasms V2*. 2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Walsh CS, et al. *Gynecol Oncol*. 2023;168:48-55.

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Case #2

- MC (55 y/o female) presented with abnormal vaginal bleeding and pelvic pain. Upon further examination and imaging, a 5 cm deeply invasive endometrial mass was identified.
- Histology: Grade 2 endometrioid adenocarcinoma

Tumor Characteristics

- Size: 5 cm
- Deeply invasive (60% myometrial invasion)
- Prominent LVSI
- **1 of 3 LN+**
- **dMMR/MSI-H**

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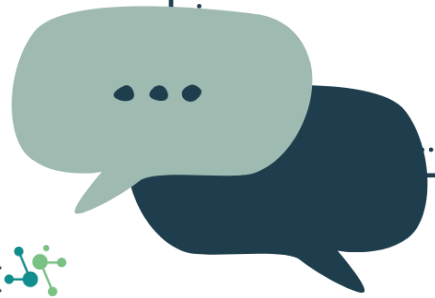
What would you recommend?

A. Chemotherapy
B. Chemotherapy and radiotherapy
C. Chemotherapy plus immunotherapy
D. Immunotherapy
E. Radiation



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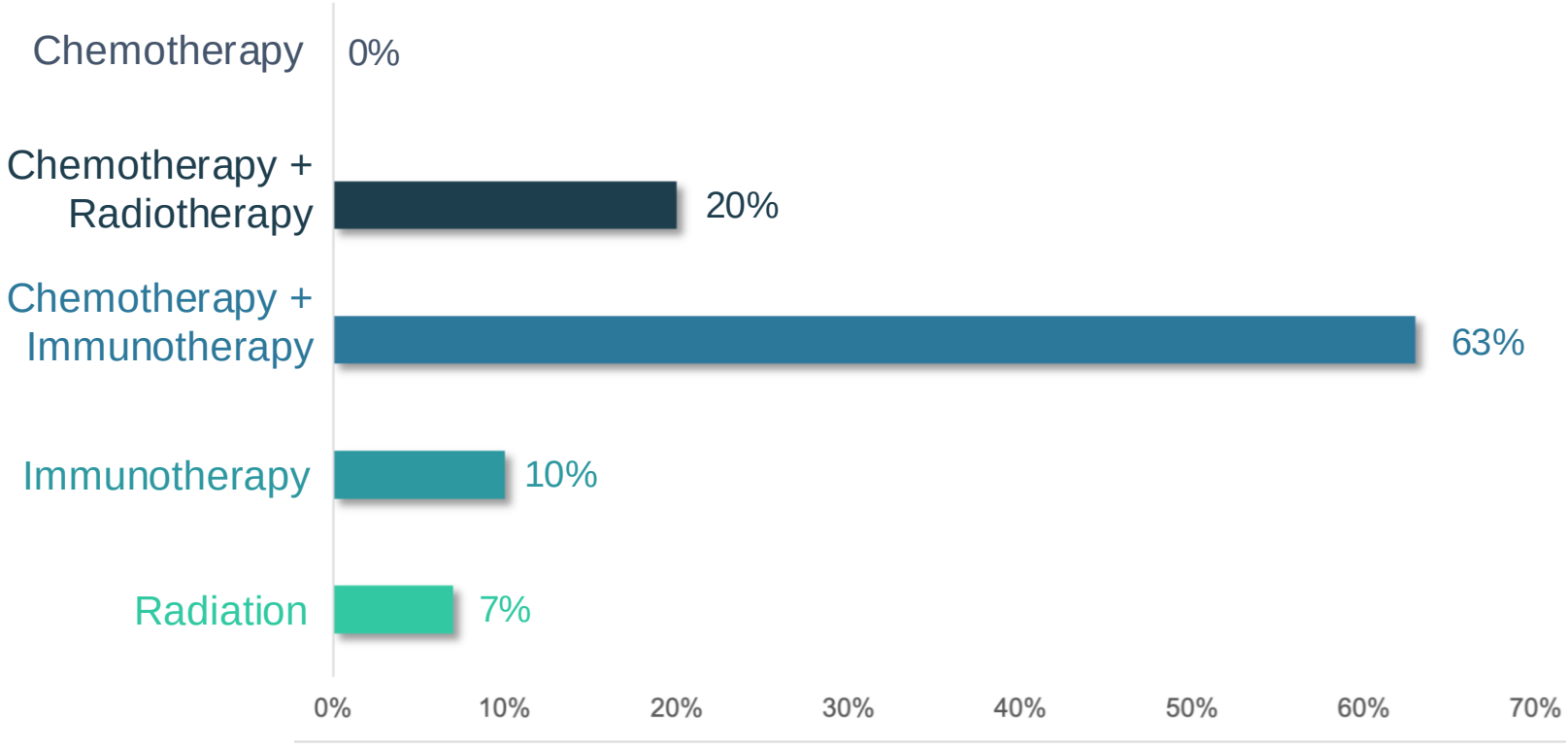
Case #2


Chemotherapy
0%
Chemotherapy + Radiotherapy
20%
Chemotherapy + Immunotherapy
63%
Immunotherapy
10%
Radiation
7%
0%
10%
20%
30%
40%
50%
60%
70%

Case #3

- MC (55 y/o female) presented with abnormal vaginal bleeding and pelvic pain. Upon further examination and imaging, a 5 cm deeply invasive endometrial mass was identified.
- Histology: Grade 2 endometrioid adenocarcinoma

Tumor Characteristics

- Size: 5 cm
- Deeply invasive (60% myometrial invasion)
- Prominent LVSI
- 1 of 3 LN+
- dMMR/MSI-H
- **Sadly, disease recurs 2 years post-C/P**

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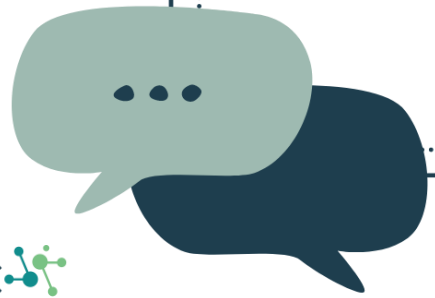
What would you recommend?

A. Repeat C/P
B. Immunotherapy
C. C/P + immunotherapy
D. Lenvatinib + pembrolizumab
E. Hormonal therapy



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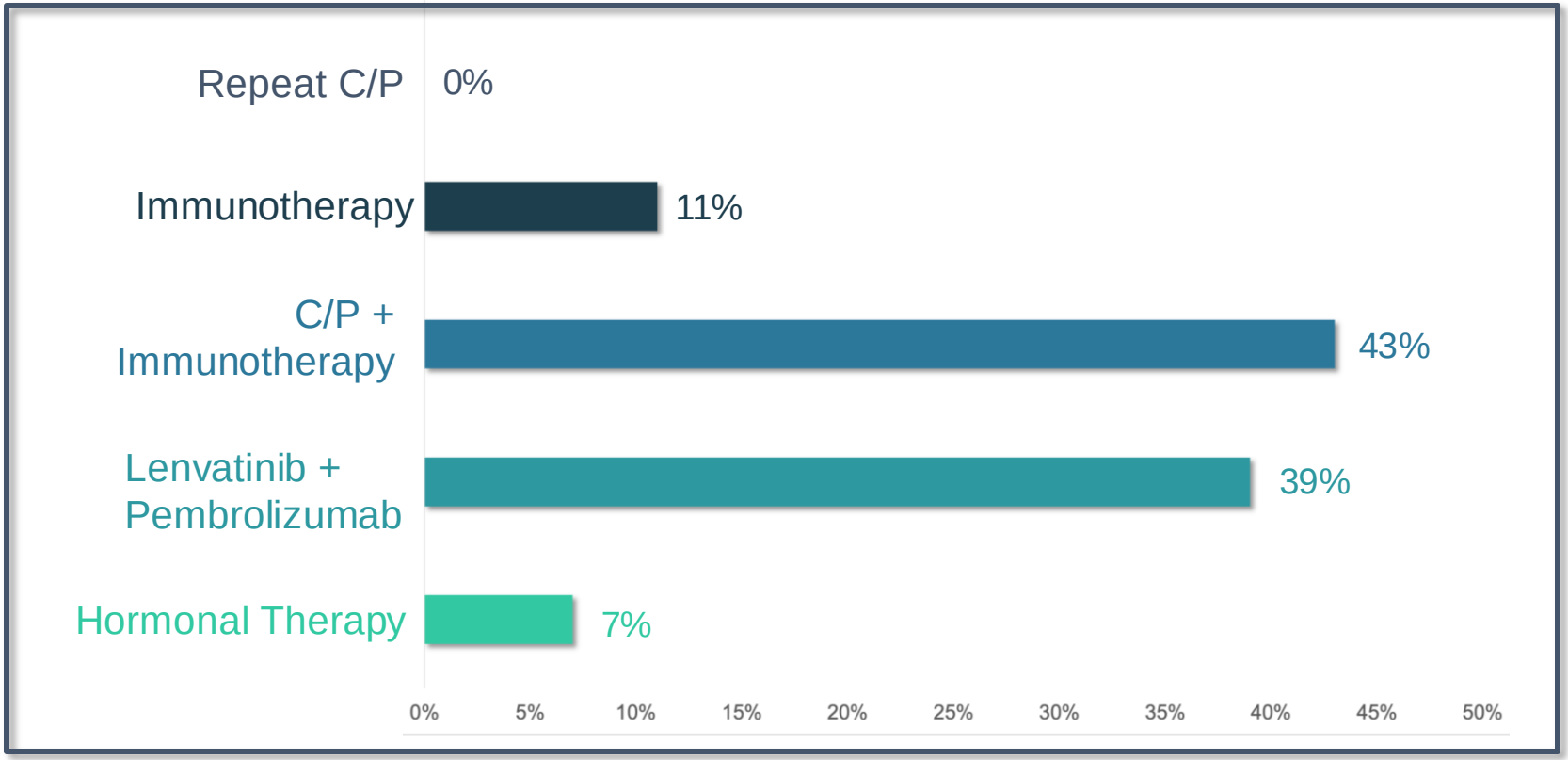
Case #3



Lenvatinib + pembrolizumab is not FDA approved in dMMR EC.

Case #4

- MC (55 y/o female) presented with abnormal vaginal bleeding and pelvic pain. Upon further examination and imaging, a 5 cm deeply invasive endometrial mass was identified.
- Histology: Grade 2 endometrioid adenocarcinoma

Tumor Characteristics

- Size: 5 cm
- Deeply invasive (60% myometrial invasion)
- Prominent LVSI
- 1 of 3 LN+
- dMMR/MSI-H
- Sadly, disease recurs 2 years post-C/P
- **Progressive disease at 8 months on C/P + pembrolizumab regimen**
- **Re-biopsy: HER2 2+**

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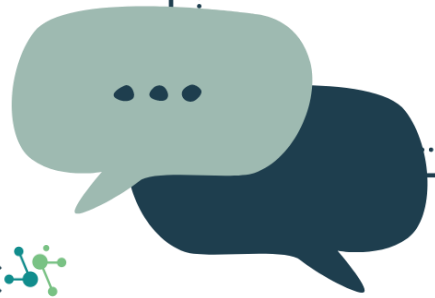
What would you recommend?

A. Add lenvatinib
B. Switch immunotherapy
C. Trastuzumab deruxtecan
D. Trastuzumab with weekly paclitaxel



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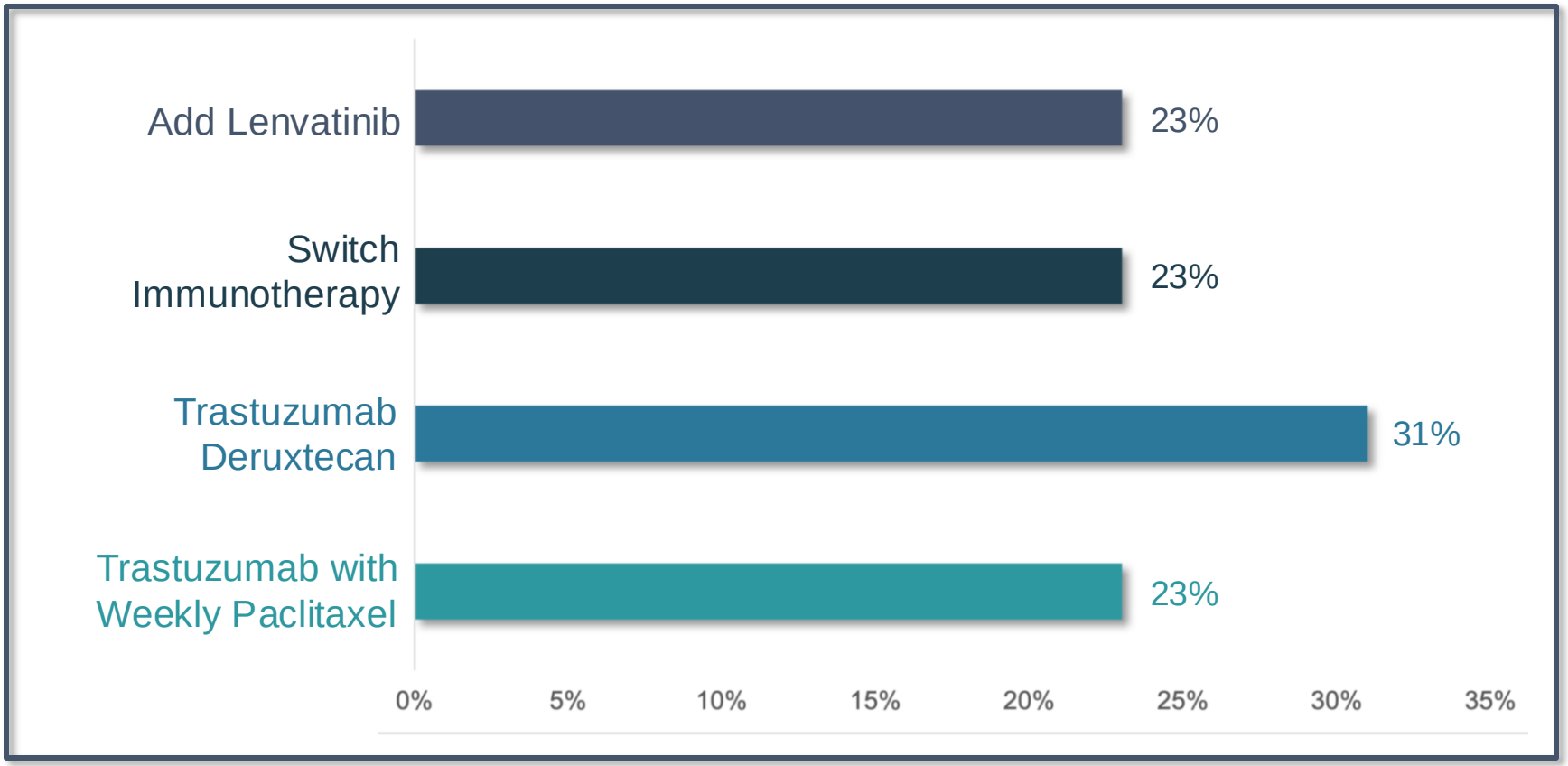
Case #4



Lenvatinib + pembrolizumab is not FDA approved in dMMR EC.
Trastuzumab deruxtecan is only FDA approved for HER2 IHC 3+ solid tumors.

Case #5

- MC (55 y/o female) presented with abnormal vaginal bleeding and pelvic pain. Upon further examination and imaging, a 5 cm deeply invasive endometrial mass was identified.
- Histology: Grade 2 endometrioid adenocarcinoma

Tumor Characteristics

- Size: 5 cm
- Deeply invasive (60% myometrial invasion)
- Prominent LVSI
- 1 of 3 LN+
- **pMMR**
- **Sadly, disease recurs 8 months post-C/P and pembrolizumab**

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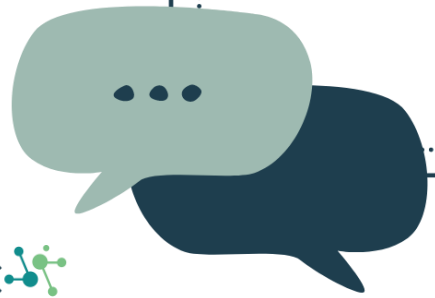
What would you recommend?

A. Repeat C/P
B. C/P + immunotherapy
C. Lenvatinib + pembrolizumab
D. Abemaciclib + letrozole
E. Hormonal therapy



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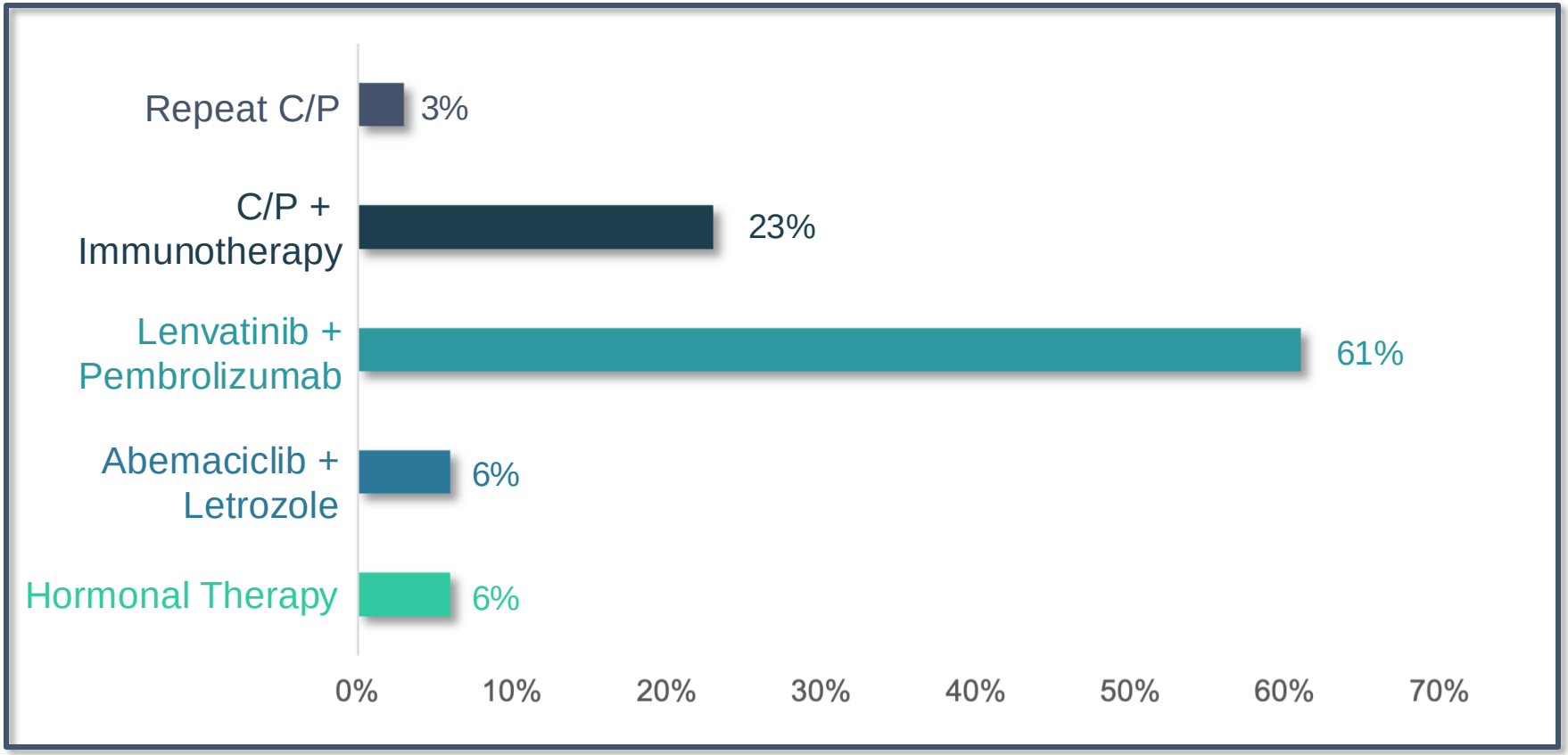
Case #5


Repeat C/P
3%
C/P + Immunotherapy
23%
Lenvatinib + Pembrolizumab
61%
Abemaciclib + Letrozole
6%
Hormonal Therapy
6%
0%
10%
20%
30%
40%
50%
60%
70%

Common Terminology Criteria for Adverse Events (CTCAE) Version 5: Grading of Severity of irAE

GRADE	Signs & Symptoms
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Criteria Apps

CTCAE v4.0

CTCAE plus

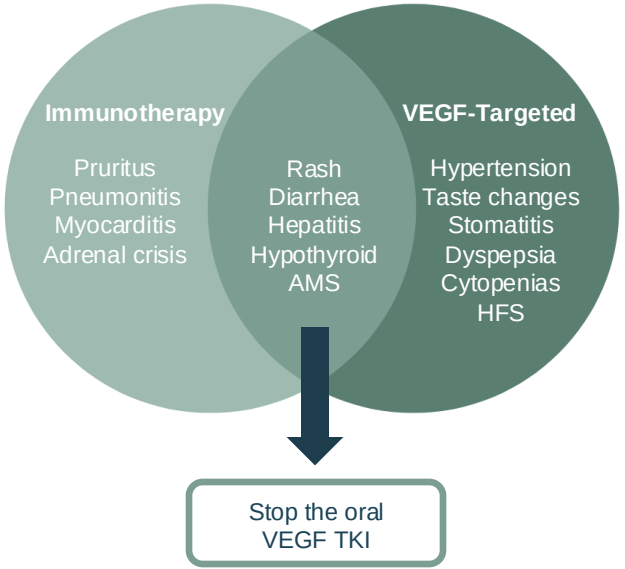
ADL = activities of daily living; AE = adverse event; irAE = immune-related adverse event.

Common Terminology Criteria for Adverse Events (CTCAE). Version 5. /https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

Lenvatinib + Pembrolizumab: Principles of Toxicity Management with Combination Therapy

Overlapping Toxicities

- What is the contribution of each drug?
  - Identify each medication's most common AE
  - VEGF-targeted therapy: diarrhea, HTN, mucositis, HFS
  - Immunotherapy: pruritus, colitis, pneumonitis, myocarditis
  - Identify if combination therapy overlapping adverse event
    - Rash, diarrhea, hypothyroidism
- Continue close monitoring
  - When to dose hold/dose reduce; which medication?
  - Consider corticosteroids if related to immunotherapy
  - Prednisone 1-2 mg/kg daily
  - Intravenous steroids



HFS = Hand Foot Syndrome; HTN = hypertension; AMS = altered mental state; TKI = tyrosine kinase inhibitor.

Diagram courtesy of Laura S. Wood, MSN, RN, OCN.

NCCN. *Management of Immunotherapy-Related Toxicities*. 2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Pembrolizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s155lbl.pdf.

Lenvatinib [package insert] . https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206947s031lbl.pdf.

Makker V, et al. *NEJM*. 2022;386(5):437-448.

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Common Q&A:
Managing Adverse Events and Comorbidities

Diarrhea	**1. How do you determine if diarrhea is from pembrolizumab or lenvatinib?** Recommend holding lenvatinib one week to assess if diarrhea decreases or resolves **2. How does that affect your management approach?** We ask patients their baseline bowel habits and identify risk factors. Start with full dose levantinb; dose hold at Grade 2. If resolves, restart dose reduction as needed. We do not dose reduce pembrolizumab. Recommend over-the-counter anti-diarrhea medications and hydration prior to dose reduction
Colitis	**How quickly do you use steroids to manage autoimmune colitis?** Ideally will hold levantinib if grade 2 diarrhea (< 4-6 over baseline). If no resolution, obtain abdominal CT and begin steroids
Hypertension	**How do you manage your patients with preexisting hypertension prior to administering lenvatinib?** Identify risk factors (preexisting history of HTN and history of anti-angiogenesis). Usually begin intervention when blood pressure > 140/80. Multidisciplinary collaboration with patients, primary care, or cardiologist
Hypothyroidism	**For an elevated TSH, what is your criteria for medical intervention?** Per ASCO and NCCN guidelines, we assess patient symptoms and usually begin intervention with thyroid medication when TSH > 10. Multidisciplinary intervention with endocrinologist

Colombo N, et al. *Oncologist*. 2024; 29(1):25-35. Schneider BJ, et al. J Clin Oncol. 2021;39(36):4073-4126.
NCCN. Management of Immunotherapy-Related Toxicities. 2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
Common Terminology Criteria for Adverse Events (CTCAE). Version 5. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

Common Q&A: Managing Adverse Events and Comorbidities

GI Disorder	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without changes in eating habits	Decreased oral intake without weight loss, dehydration, or malnutrition	Inadequate calorie or fluid intake, or tube feeding, TPN, or hospitalization indicated	—	—
Vomiting	No intervention indicated	Intervention needed—outpatient IV hydration or antiemetics	Tube feeding, TPN, or hospitalization needed	Life-threatening	Death
Diarrhea	Increase of 4 stools/day above baseline, or mild increase in ostomy output	Increase of 4-6 stools/ day above baseline, or moderate ostomy output, or limiting iADLs	Increase of ≥ 7 stools/day above baseline, or severe increase in ostomy output, or limiting self-care ADLs, or hospitalization indicated	Life-threatening, or urgent intervention needed	Death
Constipation	Occasional or intermittent, or occasional/intermittent use of laxatives, stool softeners, diet modification, or enema	Persistent symptoms, or regular use of laxatives or enema, or limiting iADLs	Obstipation with manual evacuation indicated, or limiting self-care ADL	Life-threatening, or urgent intervention required	Death

Hypothyroidism

Per ASCO and NCCN guidelines, we assess patient symptoms and usually begin intervention with thyroid medication when TSH > 10. Multidisciplinary intervention with endocrinologist

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NCCN. Management of Immunotherapy-Related Toxicities. 2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
Common Terminology Criteria for Adverse Events (CTCAE). Version 5. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

Common Q&A:
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Diarrhea	**1. How do you determine if diarrhea is from pembrolizumab or lenvatinib?** Recommend holding lenvatinib one week to assess if diarrhea decreases or resolves **2. How does that affect your management approach?** We ask patients their baseline bowel habits and identify risk factors. Start with full dose levantinb; dose hold at Grade 2. If resolves, restart dose reduction as needed. We do not dose reduce pembrolizumab. Recommend over-the-counter anti-diarrhea medications and hydration prior to dose reduction
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NCCN. Management of Immunotherapy-Related Toxicities. 2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
Common Terminology Criteria for Adverse Events (CTCAE). Version 5. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

Select AE Management T-DXd Interstitial Lung Disease

Monitor

- Inform patients to immediately report cough, dyspnea, fever, new/worsening respiratory symptoms
- Investigate evidence of ILD
- Consider consultation with pulmonologist
- Confirmation with high-res CT scan
- Blood culture and CBC
- Consider bronchoscopy
- PFTs and pulse oximetry

Dose Interruption/Discontinuation

Grade 1 (asymptomatic)

- Delay dose until recovery (grade 0)
- If resolved > 28 days, dose reduce

Grade ≥ 2 (symptomatic)

- Permanently discontinue

Corticosteroid Treatment

Grade 1 (asymptomatic)

- Consider corticosteroid treatment

If ILD is suspected

- E.g., ≥ 0.5 mg/kg prednisolone

Grade ≥ 2 (symptomatic)

- Promptly initiate corticosteroid treatment

If ILD/pneumonitis is suspected

- E.g., ≥ 1 mg/kg prednisolone

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T-DXd = Trastuzumab deruxtecan; ILD = interstitial lung disease; CBC = complete blood count; PFT = pulmonary function test

Tarantino P, et al. *JCO Oncol Pract*. 2023;19(8):536–527.

Considerations for Patient Education

- Patient-centered: explanation of treatment options (clinical trials), personalized therapy and biomarker-driven approaches
- Discuss differences between chemotherapy/targeted therapies and immunotherapy toxicities
- Unpredictable timing of long-term and late-onset irAEs
- Involve multidisciplinary team at start of new treatment
- Inform patient and caregiver whom to call and when to call regarding irAEs
  - How reliable is the patient's comprehension of "sense of urgency?"
  - Financial ability for support meds, blood pressure cuff, access to cancer center
  - Language, cognitive deficits, comorbidities, including psychosocial?

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Hickey M, Newton S. *Telephone Triage for Oncology Nurses.* 3rd ed. 2019. https://www.ons.org/books/telephone-triage-oncology-nurses-third-edition.
Rogers A, et al. *J Oncol*. 2019; 2019:526062.

Addressing Potential Health Care Disparities

Communication

- Improving patient-HCP communication
- Acknowledging patient beliefs and values
- Minimizing HCP bias
- Increasing representation of professionals (MDs, NPs, PAs) from underserved communities in the oncology workforce

Cost

- Reducing treatment costs with manufacturer grants, assistance programs
- Providing grants to cover transportation costs and dependent care
- Providing help in navigating insurance claims and financial assistance programs

Gaps in Outcomes Research

- Increasing representation of underserved racial and ethnic groups in clinical trials
- Including diverse populations in genetic/molecular surveys to better understand tumor biology

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HCP = health care professional.

Patel MI, et al. *J Clin Oncol*. 2020l 38(33):3976.

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Implement guideline-directed molecular profiling for **all patients** with endometrial cancer to **inform risk assessment** and **tailor treatment decisions**
- Collaborate with a multidisciplinary team (MDT) to **establish a streamlined process** for ordering, performing, and interpreting molecular profiling tests
- Ensure that treatment protocols **reflect the most current evidence-based practices**, improving patient outcomes and adherence to updated guidelines
- Establish regular MDT meetings, including oncologists, radiologists, pathologists, surgeons, and nursing staff, and **create standardized templates for therapeutic plans**

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