



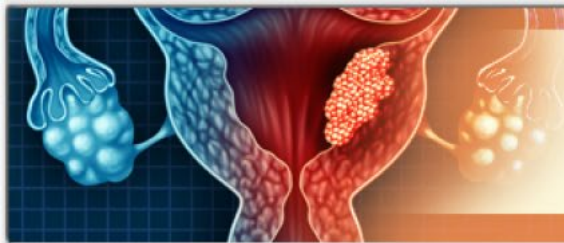
Immuno-oncology Therapies for the Treatment of **ADVANCED ENDOMETRIAL CANCER:** Which of Your Patients May Benefit from Their Use?

FACULTY

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MEETING INFO

Wednesday, March 2, 2022



Immuno-oncology Therapies for the Treatment of **ADVANCED ENDOMETRIAL CANCER:** Which of Your Patients May Benefit from Their Use?

I. Endometrial Cancer (EC): An Overview

- a. Epidemiology of endometrial cancer
- b. Molecular classification of endometrial cancer

II. Therapeutic Options for the Treatment of Advanced and/or Recurrent EC

- a. Guideline recommended care for EC
- b. Clinical trial data on the efficacy and safety of:
 - a. Monotherapy with immune checkpoint inhibitors
 - b. Immune checkpoint inhibitors in combination with tyrosine kinase inhibitors
 - c. Other emerging therapies

III. Individualizing the Care of Patients with Advanced EC

- a. Using molecular testing to select treatment options
- b. Managing adverse events
 - a. Recognizing and treating immune-related adverse events
 - b. Strategies to manage treatment-related adverse events
- c. Benefits of multidisciplinary care

IV. Interactive case studies

V. Questions and answers

VI. Adjournment

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PROGRAM CHAIR

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PROGRAM OVERVIEW

This TeleECHO series will explore the management of patients with advanced endometrial cancer through interactive case studies. Faculty will review strategies on personalizing the selection of treatment options based on molecular testing and discuss the management of adverse events with immune-oncology/tyrosine kinase inhibitor combination therapies.

TARGET AUDIENCE

This activity is intended for U.S.-based gynecologic oncologists, medical oncologists, obstetrician/gynecologists and other healthcare providers involved in the treatment of gynecologic cancers including endometrial cancer.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Critique the rationale supporting the biological features of endometrial cancer (EC) that make it an attractive candidate for the use of immuno-oncology (IO) therapies
- Evaluate evidence from clinical trials assessing available and emerging therapies for the treatment of patients with advanced EC
- Devise strategies to manage the immune-related adverse events (irAEs) and treatment-related adverse events (trAEs) associated IO/tyrosine kinase inhibitor (TKI) combination therapies in development for patients with advanced EC
- Support multidisciplinary care teams for the management of patients with EC

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Purpose: This program would be beneficial for nurses involved in the care of patients with advanced endometrial cancer.

CNE Credits: 1.0 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

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Faculty Member	Disclosures
Ursula A. Matulonis, M.D.	She has been a consultant for Astrazeneca, Merck, Novartis, Trillium, and Blueprint Med. She has also worked with DSMB for Symphogen, Alkermes, GSK, NextCure, Agenus and Imvax.

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN

Ultimate Medical Academy/CCM – Lead Nurse Planner

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Disclosures

- **Dr. Matulonis** has been a consultant for AstraZeneca, Merck, Novartis, GSK, Trillium, Agenus, and Blueprint Med. She serves on a scientific advisory board for NextCure, Rivkin Foundation, Ovarian Cancer Research Alliance and DSMB: Symphogen, Alkermes, Advaxis.
- During this lecture, faculty may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications
- This educational activity is supported by an independent medical education grant from Eisai and Merck & Co., Inc.

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Learning Objectives

- Critique the rationale supporting the biological features of endometrial cancer (EC) that make it an attractive candidate for the use of immuno-oncology (IO) therapies
- Evaluate evidence from clinical trials assessing available and emerging therapies for the treatment of patients with advanced EC
- Devise strategies to manage the immune-related adverse events (irAEs) and treatment-related adverse events (trAEs) associated with IO/tyrosine kinase inhibitor (TKI) combination therapies in development for patients with advanced EC
- Support multidisciplinary care teams for the management of patients with EC

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Endometrial Cancer (EC)

- 65,950 new cases per year with 793,846 women living with uterine cancer in the US
- Incidence and death rates are increasing in the US
 - ~1% increase in incidence per year (driven by non-endometrioid subtypes) AND death rates have been rising by ~1.9% per year
- 12,550 women will die of EC per year (2022 estimate)
- Black women are diagnosed at later stages than White women and have poorer 5-year survival rates

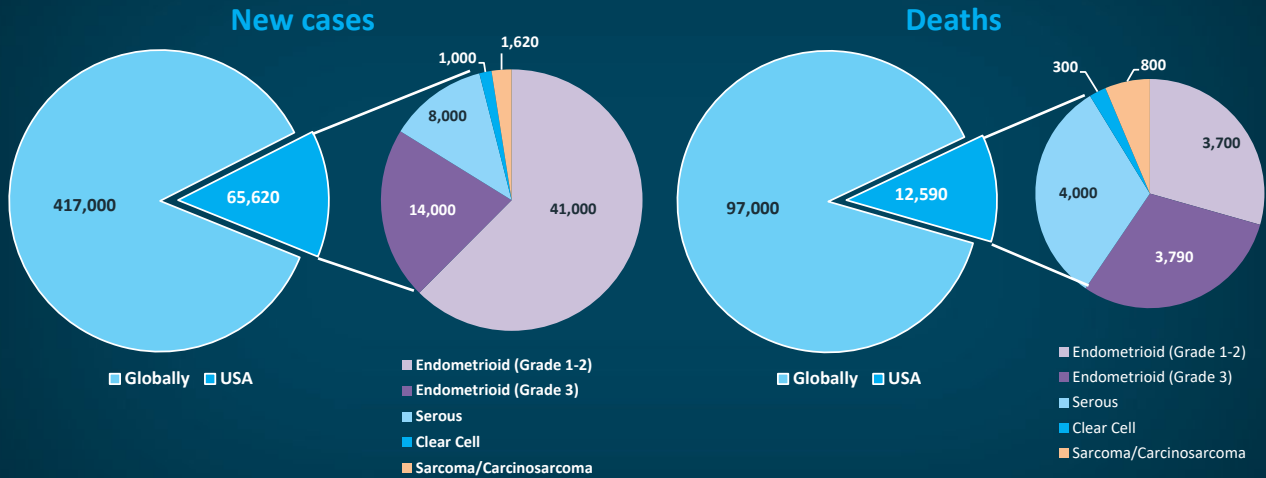
FDA-approved drugs for EC



US = United States; MSI-H = microsatellite instability-high; MSS = microsatellite stable; MMR = mismatch repair; Pembro = pembrolizumab; TMB = tumor mutational burden. Siegel RL, et al. *CA Cancer J Clin.* 2022;72:7-33. Clarke MA, et al. *J Clin Oncol.* 2019;37:1895-1908. McAlpine JN, et al. *Cancer.* 2016;122:2787-2798. Lortet-Tieulent J, et al. *J Natl Cancer Inst.* 2018;110:354-361. Oaknin A, et al. *JAMA Onc.* 2020. Makker V, et al. Society of Gynecologic Oncology (SGO) 2021; Abstract 0008/#785. Cancer Today. Cancer fact sheets: corpus uteri. 2018. (<https://gco.iarc.fr/today/fact-sheets-cancers>).

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EC Cancer Statistics in the US and Globally in 2020



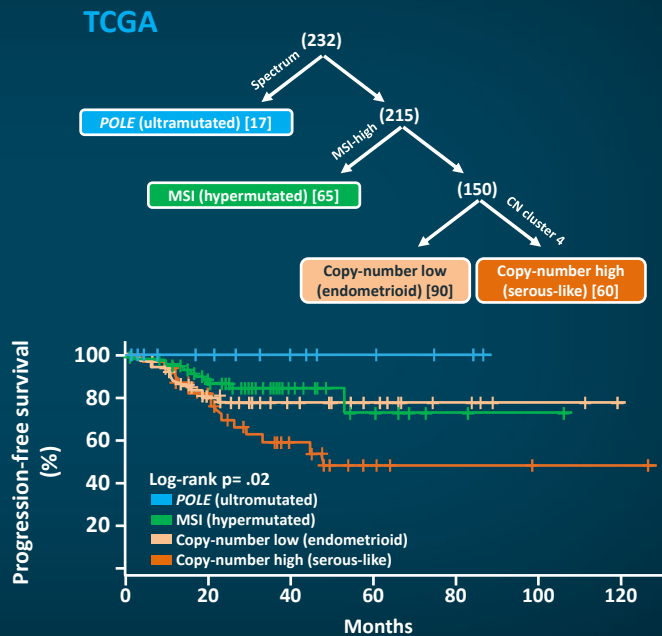
Sung H, et al. *CA Cancer J Clin.* 2021;71:209-249. Siegel RL, et al. *CA Cancer J Clin.* 2020;70:7-33.

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Molecular Classification of EC

TCGA molecularly classified EC into 4 groups

- *POLE* (DNA polymerase ϵ catalytic subunit) ultramutated
- Microsatellite instability (MSI) hypermutated
- Copy number low
- Copy number high (serous)



CN = copy number; TCGA = The Cancer Genome Atlas.
 Levine DA, et al. *Nature.* 2013;497:67-73.

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GOG 209: Study Design

Carboplatin and Paclitaxel for Advanced EC

- Established carboplatin and paclitaxel as the standard of care chemotherapy for patients with advanced stage or recurrent cancer

- Stage III, stage IV, or recurrent endometrial carcinoma
- No prior cytotoxic chemotherapy
- Estrogen and progesterone receptor assessed on primary tumor
- Known LVEF <50% within 6 months of study entry ineligible
- N = 1381

R

Paclitaxel-carboplatin cycles 1 to 7
Carboplatin AUC 6 IV on Day 1
Paclitaxel 3-hour 175 mg/m² on Day 1

TAP cycles 1 to 7
Doxorubicin 45 mg/m² IV on Day 1
Cisplatin 50 mg/m² on Day 1
Paclitaxel 3-hour 160 mg/m² on Day 2
Filgrastim 5 mcg/kg on Days 3-12 or
pegfilgrastim 6 mg on Day 3

AUC = area under the curve; GOG = Gynecologic Oncology Group; LVEF = left ventricular ejection fraction; R = randomized; TAP = paclitaxel/doxorubicin/cisplatin.
Miller DS, et al. *J Clin Oncol*. 2020;38:3841-3850.

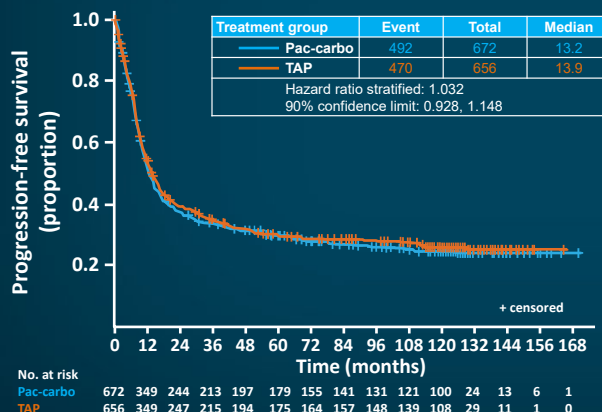
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GOG 209: Efficacy Summary

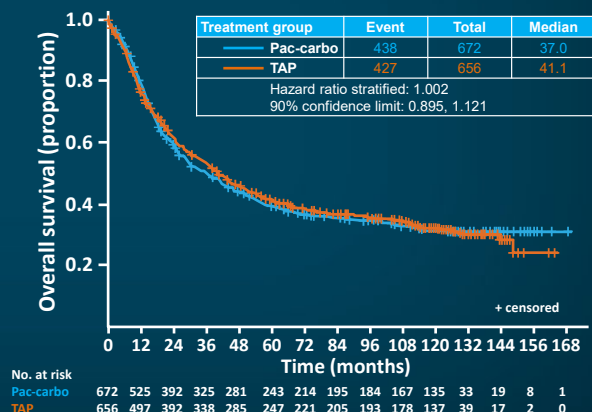
Carboplatin and Paclitaxel for Advanced EC

- Established carboplatin and paclitaxel as standard of care for patients with advanced stage or recurrent disease

Progression-free survival



Overall survival



Carbo = carboplatin; Pac = paclitaxel

Miller DS, et al. *J Clin Oncol*. 2020;38:3841-3850.

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Systemic Therapies for Recurrent/Newly Diagnosed Advanced EC

- **Standard of care: carboplatin and paclitaxel (GOG 209, GOG 261)**
 - Addition of trastuzumab in HER2+ uterine serous cancers in newly diagnosed advanced cancer: PFS and OS improvements in newly diagnosed patients
- **Beyond carboplatin/paclitaxel**
 - Pembrolizumab (mismatch repair [MMR] deficient or MSI-high tumors) (FDA-approved)
 - Pembrolizumab and lenvatinib (MMR proficient recurrent EC after standard therapies) (FDA-approved)
 - Hormonal therapy: progestins (11-55% ORR), megestrol/tamoxifen (33% ORR), aromatase inhibitors (~9% ORR)
 - Antiangiogenic agents/other TKIs: bevacizumab (13.5% ORR), cabozantinib (14% ORR)
 - Alternative chemotherapies and other targeted agents
 - Liposomal doxorubicin (9% ORR), paclitaxel (25% ORR), topotecan (9% ORR)
 - Combination letrozole and everolimus (24-32% response rate): *CTNNB1* mutation predictive of response; serous histology not predictive of response
 - WEE1 inhibitors
 - Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors
 - ATR inhibitors
 - Anti-HER2 antibody drug conjugates

ATR = ataxia telangiectasia and RAD3 related; HER2 = human epidermal growth factor receptor 2; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
 Miller D, et al. *Gyn Oncol.* 2012;125(3):771-773. FDA package inserts. Lentz SS, et al. *J Clin Oncol.* 1996;14(2):357-361. Aghajanian C, et al. *J Clin Oncol.* 2011;29:2259-2265. Thigpen JT, et al. *J Clin Oncol.* 1999;17(6):1736-1744. Fiorica JV, et al. *Gyn Oncol.* 2004;92(1):10-14. Whitney CW, et al. *Gyn Oncol.* 2004;92(1):4-9. Dhani S, et al. *Cancer Clin Res.* 2020;26(11):2477-2486. Bogliolo S, et al. *Arch Gyn Oncol.* 2016;293(4):701-708. Slomovitz BM, et al. *J Clin Oncol.* 2015;33(8):930-936. Slomovitz BM, et al. SGO 2018; Abstract 1. Miller et al, 2002
 GOG 261: Powell et al, JCO 2022

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National Comprehensive Cancer Network® (NCCN) Guidelines

Primary or adjuvant treatment when used for uterine-confined high-risk disease

Preferred regimens: Carboplatin/paclitaxel

Recurrent or metastatic disease

	Preferred regimens	Other recommended regimens
Systemic therapies	• Carboplatin/paclitaxel (category 1 for carcinosarcoma) • Carboplatin/paclitaxel/trastuzumab (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)	• Carboplatin/docetaxel • Cisplatin/doxorubicin • Cisplatin/doxorubicin/paclitaxel • Carboplatin/paclitaxel/bevacizumab • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel • Albumin-bound paclitaxel • Topotecan • Bevacizumab • Temsirolimus • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma) • Cisplatin/ifosfamide (for carcinosarcoma)
Biomarker-directed systemic therapy for second-line treatment	• Lenvatinib/pembrolizumab (category 1) for non-MSI-high [MSI-H]/non-MMR-deficient [dMMR] tumors • Pembrolizumab for tumor mutational burden-high (TMB-H) or MSI-H/dMMR tumors	• Nivolumab for dMMR/MSI-H tumors • Dostarlimab-gxly for dMMR/MSI-H tumors • Larotrectinib or entrectinib for neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive tumors (category 2B) • Avelumab for dMMR/MSI-H tumors • Cabozantinib

NCCN guidelines for uterine neoplasms v1 2022 (<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473>).

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NCCN Guidelines

Hormone therapy

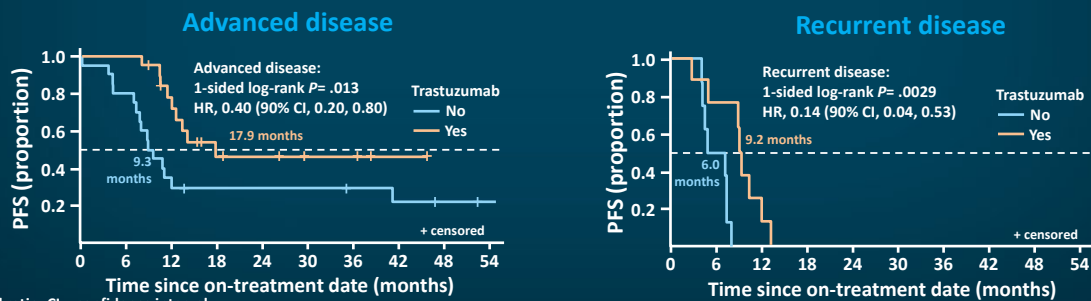
Preferred regimens	Other recommended regimens	Useful in certain circumstances
- Medroxyprogesterone acetate/tamoxifen (alternating) - Megestrol acetate/tamoxifen (alternating) - Progestational agents - Medroxyprogesterone acetate - Megestrol acetate - Levonorgestrel intrauterine device (IUD) (for select fertility-sparing cases) - Aromatase inhibitors - Tamoxifen - Fulvestrant	Everolimus/letrozole (for endometrioid histology)	N/A

NCCN guidelines for uterine neoplasms v1 2022 (<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473>).

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Benefit of Adding Trastuzumab in HER2+ Uterine Serous Carcinoma at Diagnosis with Carboplatin/Paclitaxel

- ~25% to 30% of patients with uterine serous carcinoma have HER2 amplification¹
- Single agent trastuzumab in advanced/recurrent HER2+ uterine cancer has limited activity²
- Randomized phase 2 study of carboplatin/paclitaxel/trastuzumab vs carboplatin/paclitaxel showed increased PFS in HER2+ uterine serous cancer³
 - 58 evaluable patients (41 advanced, 17 recurrent) ; eligibility included 3+ IHC for HER2 or 2+ IHC plus FISH+

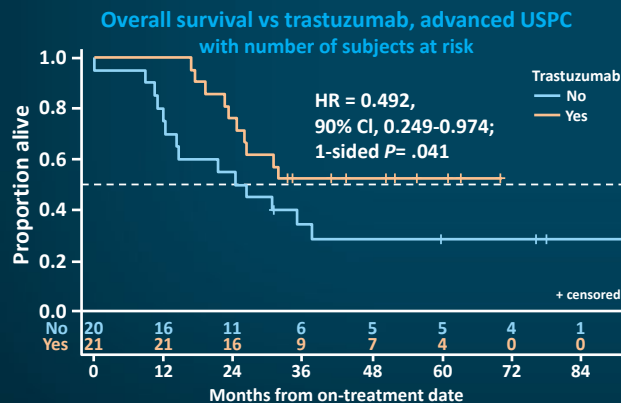


1. Levine DA, et al. *Nature*. 2013;497:67-73. 2. Fleming GF, et al. *Gyn Oncol*. 2010;116(1):15-20. 3. Fader AN, et al. *J Clin Oncol*. 2018;36(20):2044-2051.

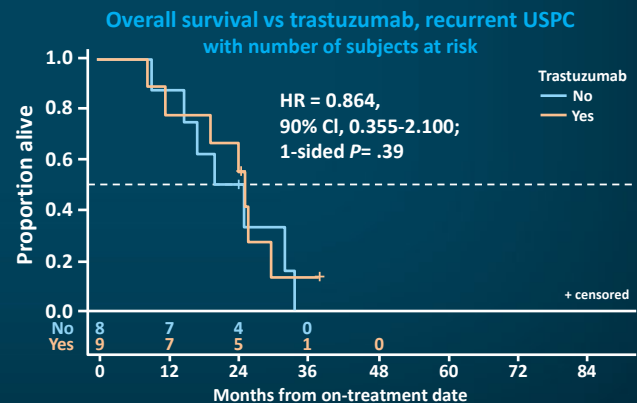
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Trastuzumab in HER2+ Uterine Serous Carcinoma with Carboplatin/Paclitaxel

- OS benefit observed in women with newly diagnosed stage III or IV serous cancer
- No OS benefit using trastuzumab in recurrent serous cancer



Fader AN, et al. *Clin Cancer Res.* 2020;26:3928-3935.



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Other HER2 Targeted Agents; DS8201a

- DS8201A: anti-HER2 antibody, tetrapeptide-based linker, and cytotoxic topoisomerase I inhibitor
- Examples of ongoing studies that allow recurrent endometrial cancer:
 - DS8201a + olaparib (NCT04585958) (focused on serous histology)
 - DESTINY-PanTumor02: Basket study, HER2+, multiple gynecologic cancers eligible (NCT04482309)
 - DS8201a + ceralasertib (AZD6738) (NCT04704661), phase 1
 - ESMO 2021: single agent DS8201A in HER2+ uterine carcinosarcomas, + results (below)

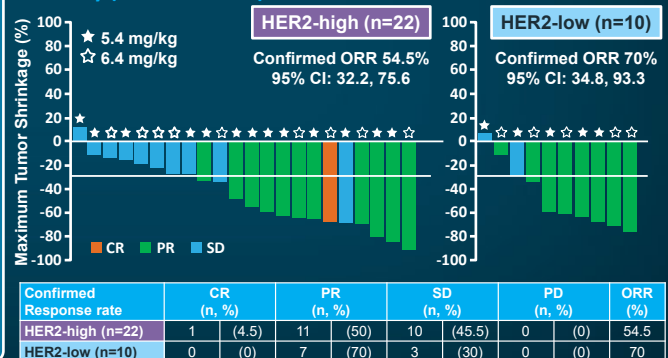
Key inclusion criteria

- Unresectable uterine carcinosarcoma histologically confirmed by the pathologist of each trial site
- Progression after 1 or more lines of prior chemotherapy
- HER2-positive (IHC score 1+ or higher) by central pathological review
- HER2 low = 1+ and HER2 high = 2 or 3+
- Age ≥20 years
- Performance status (ECOG) 0 or 1
- ≥1 measurable disease (RECIST version 1.1)

Key exclusion criteria

- Active concurrent malignancy (except for carcinoma in situ)
- History of interstitial lung disease
- Symptomatic congestive heart failure (New York Heart Association Classification II-IV)
- Cancerous meningitis/symptomatic brain metastasis/spinal metastasis requiring surgery

Efficacy (central review)



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Current FDA Approvals for EC Based on MS Status

Patients with MSI-high, dMMR deficient, or TMB-high cancer

Pembrolizumab

Patients with MSS or MMR proficient cancers

Lenvatinib/Pembrolizumab

Patients with dMMR recurrent or advanced EC

Dostarlimab (accelerated FDA approval)

Lenvima (Lenvatinib®) PI 2021 (<https://www.lenvima.com/-/media/Project/EISAI/Lenvima/PDF/prescribing-information.pdf>). Dostarlimab (Jemperli) PI 2021 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761174s000lbl.pdf).

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Microsatellites

- Microsatellites are repetitive DNA sequences that are distributed across the genome
- DNA mismatch repair is a process used to restore DNA integrity after mismatch errors occur
 - 4 genes that play a critical role are *MLH1*, *MSH2*, *MSH6*, and *PMS2*
- Microsatellite instability is a condition of genetic hypermutation resulting from defective DNA mismatch repair

Luchini C, et al. *Ann Oncol*. 2019;30:1232-1243.

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Molecular Testing and Mismatch Repair Assessment

- The presence of MMR deficiency, or MSI, is detected clinically by
 - 1) MMR protein immunohistochemistry (IHC) to detect loss of MMR protein expression (usually for 4 proteins: *MLH1*, *PMS2*, *MSH2*, and *MSH6*)
 - 2) Polymerase chain reaction (PCR) at a panel of microsatellite loci in the genome to detect repetitions
 - 3) Observation of an MMR mutational signature in next generation sequencing tests
- NCCN guidelines recommend universal testing of ECs for MMR proteins/MSI
- Testing can be done on initial endometrial biopsy or the final hysterectomy specimen
- *MLH1* loss should be further evaluated for promoter methylation to assess for an epigenetic process
- 30% of ECs are MMR deficient at diagnosis

NCCN guidelines for uterine neoplasms v1 2022 (<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473>). Bonneville R, et al. *JCO Precis Oncol.* 2017;1-15.

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Single Agent Immune Checkpoint for Recurrent MMR Deficient (MSI-high) EC

- Pembrolizumab was FDA-approved in 2017 for any solid tumor that is MMR deficient or MSI-high
- Dostarlimab was FDA-approved in 2021 for MSI-high recurrent EC
- Up to 30% of ECs are dMMR/MSI-high

	Number of patients with EC (MMR deficient)	Response rate (RR)	Duration of response range
Pembrolizumab	49	57.1%	2.9 to 27+ months
Avelumab	15	27%	Not reported
Dostarlimab	104	42.3%	Not reached
Durvalumab	35	40%	Not reported

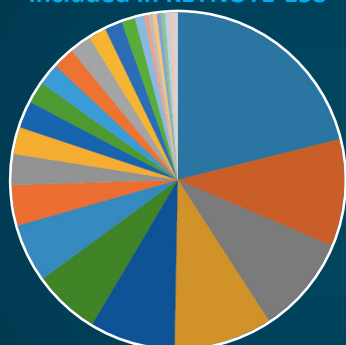
Response rates are much lower in MMR proficient cancers; not FDA-approved for microsatellite stable (MSS) tumors.

Marabelle A, et al. *J Clin Oncol.* 2020;38:1-10. Antill YC, et al. American Society of Clinical Oncology (ASCO) 2019; Abstract 5501. Pembrolizumab (Keytruda®) PI 2021 (https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf). Konstantinopoulos PA, et al. *J Clin Oncol.* 2019;38(11):1222-1245. Oaknin A, et al. *JAMA Oncol.* 2020;6:1766-1772.

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Keynote-158: Pembrolizumab for Non-Colorectal dMMR Recurrent Cancer

Distribution of tumor cohorts included in KEYNOTE-158



Endometrial	Prostate	Anal
Gastric	Adrenocortical	Head and neck squamous cell carcinoma
Cholangiocarcinoma	Breast	Nasopharyngeal
Pancreatic	Thyroid	Retroperitoneal
Small intestine	Urothelial	Testicular
Ovarian	Mesothelioma	Tonsil
Brain	Small-cell lung cancer	Vaginal
Sarcoma	Renal	Vulvar
Neuroendocrine tumor	Salivary	
Cervical		

Antitumor activity for tumor types with greatest enrollment

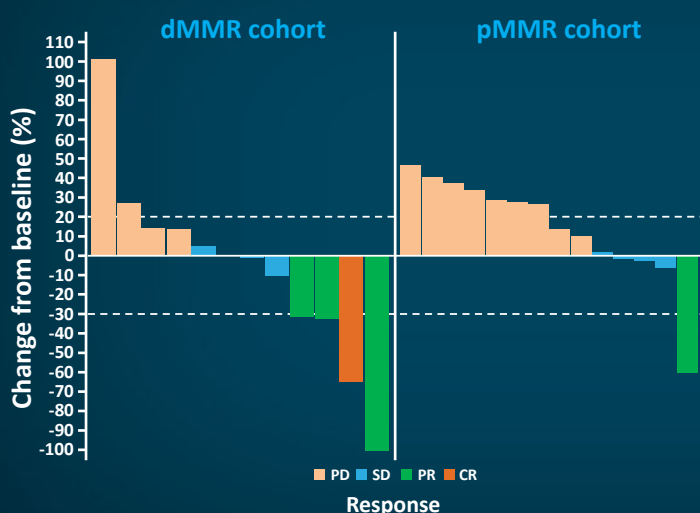
Tumor type	No.	CR, No.	PR, No.	ORR, % (95% CI)
Endometrial	49	8	20	57.1 (42.2 to 71.2)

Tumor type	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)

CR = complete response; PR = partial response; NR = not reached; DOR = duration of response. Marabelle A, et al. *J Clin Oncol*. 2019;38:1-10.

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Phase 2 Study of Avelumab in Patients With dMMR and Proficient MMR (pMMR) Recurrent/Persistent EC



Response	Number of patients	
	dMMR cohort (n = 15)	pMMR/non-POLE cohort (n = 16)
Best overall response		
Complete response	1	0
Partial response	3	1
Stable disease (SD)	4	4
Progressive disease (PD)	4	9
Not evaluable	3	2
ORR, % (95% CI)	26.7 (7.8 to 55.1)	6.25 (0.16 to 30.2)
PFS6		
Yes	6	1
No	9	15
PFS6, % (95% CI)	40 (16.3 to 66.7)	6.25 (0.16 to 30.2)

PFS6 = progression-free survival of at least 6 months
Konstantinopoulos PA, et al. *J Clin Oncol*. 2019;37:2786-2794..

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GARNET Study: Single Agent Dostarlimab (anti PD-1 antibody) for Recurrent dMMR EC

Tumor response by RECIST v1.1

Characteristic	dMMR EC cohort Number (%) (n = 71)
Best overall response	
Complete response	9 (12.7)
Partial response	21 (29.6)
Stable disease	11 (15.5)
Progressive disease	27 (38.0)
Not evaluable	3 (4.2)
Confirmed ORR	
Number (%) [95% CI]	30 (42.3) [30.6-54.6]
Response ongoing	25/30 (83.3)
Disease control rate, number (%) [95% CI]	41 (57.7) [45.4-69.4]
Duration of response, median (95% CI), months	Not reached

FDA-approved in April 2021 under accelerated approval for recurrent mismatch repair deficient EC that has progressed on or following prior treatment with a platinum-containing regimen

dMMR = deficient mismatch mutation repair; ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
Oaknin A, et al. *JAMA Oncol.* 2020;6:1766-1772. ClinicalTrials.gov NCT02715284.

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PHAEDRA Study: Phase 2, 2-Cohort Study of Durvalumab in Patients With Advanced/Recurrent EC

Key eligibility criteria

- Eastern Cooperative Oncology Group (ECOG): 0-2
- Advanced/recurrent endometrial cancer with not amenable to curative therapy
- Measurable disease by RECIST v1.1
- Known MMR status tumor tissue by IHC

Main demographics and disease characteristics

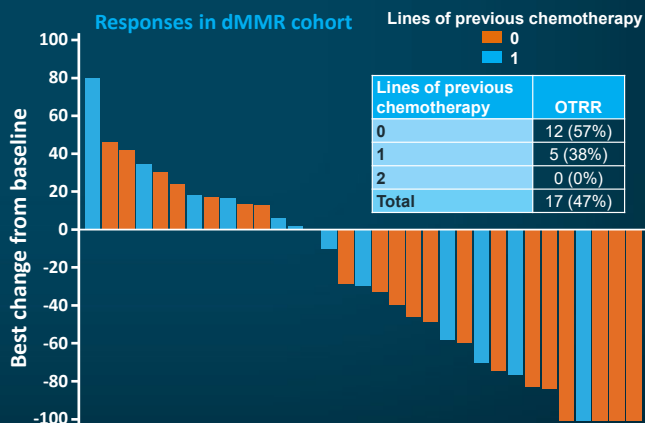
- N=35 pMMR cohort (1-3 prior lines of therapy [LOT])
 - ✓ 31% serous histology; 72% Grade 3
- N=36 dMMR cohort (0-3 prior LOT)
 - ✓ 94% endometrioid histology; 47% Grade 2

Treatment: durvalumab 1500 mg once every 4 weeks (Q4W) until disease progression

Primary endpoint

- ORR by iRECIST

Response	dMMR cohort (n=36)	pMMR cohort (n=35)
ORR, n (%)	17 (47%)	1 (3%)
DCR, n (%)	21 (58%)	8 (23%)



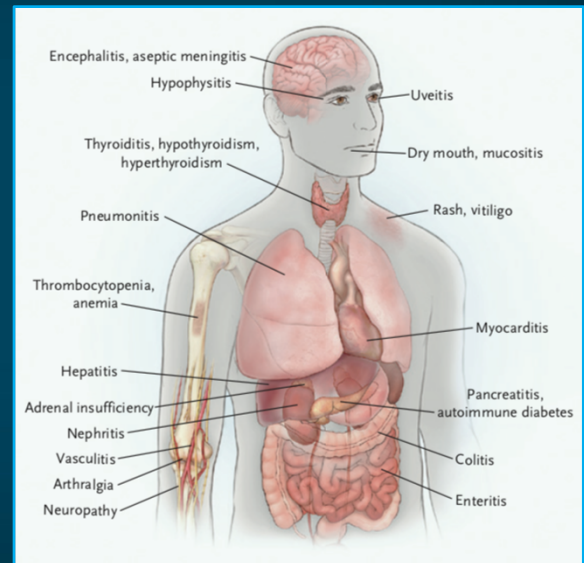
DCR = disease control rate; OTRR = objective tumor response rate. Antill Y, et al. *J Immunother Cancer.* 2021;9:e002255.

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Managing Immune-Related Adverse Events (AEs)

- Immune checkpoint blockade can result in inflammation of any organ
- Patient selection
- Treatment settings
- Clinical trial access
- Team education and communication
- Patient education and expectation setting
- Multidisciplinary care

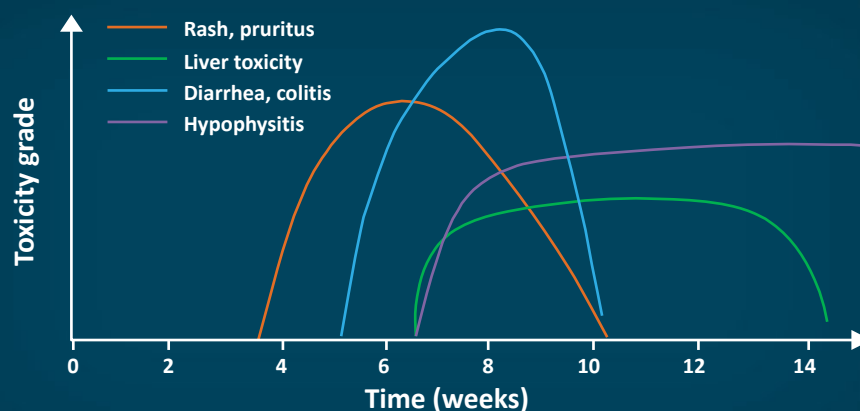
Organs affected by checkpoint blockade



Postow MA, et al. *N Engl J Med*. 2018;378:158-168. Menderes G, et al. *Expert Opin Biol*. 2016;16:989-1004. Minion LE, Tewari KS. *Gynecol Oncol*. 2018;148:609-621.

23

Managing Immune-Related AEs (cont)

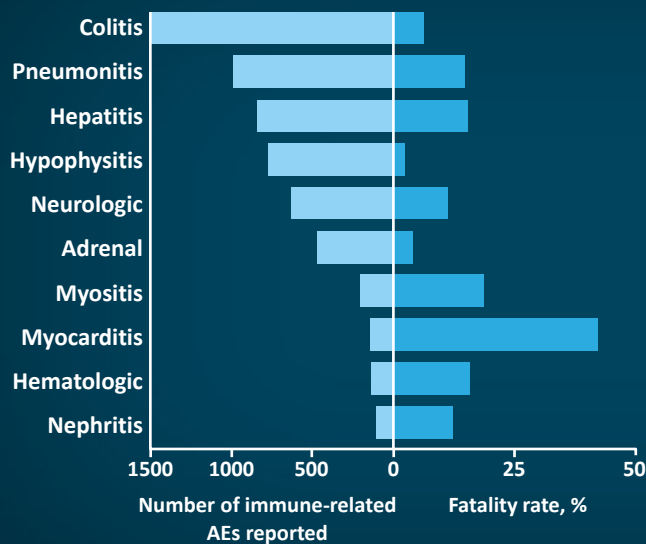


- Most immune-related AEs (irAEs) occur within first 6 months of treatment.
- Maintain high level of suspicion that new symptoms are treatment related.
- Use multidisciplinary care.

Weber JS, et al. *J Clin Oncol*. 2015;33:2092-2099. Schneider BJ, et al. *J Clin Oncol*. 2021;39:4073-4126.

24

Cases and Fatality Rates for Immune-Related AEs



General recommendations

- **Grade 1:** continue therapy with close monitoring, except for some neurologic, hematologic and cardiac toxicities.
- **Grade 2:** consider holding therapy and resume when symptoms revert to $\leq$ grade 1. Corticosteroids may be administered.
- **Grade 3:** Hold therapy and initiate high-dose corticosteroids. Taper steroids over at least 4-6 weeks. If no improvement after 48-72 hours, infliximab may be an option for some toxicities.
- **Grade 4:** Permanently discontinue therapy, except for controlled endocrinopathies.

Wang DY, et al. *JAMA Oncol.* 2018;4:1721-1728. Schneider BJ, et al. *J Clin Oncol.* 2021;39:4073-4126.

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Single Agent IO Efficacy Is Low in pMMR EC

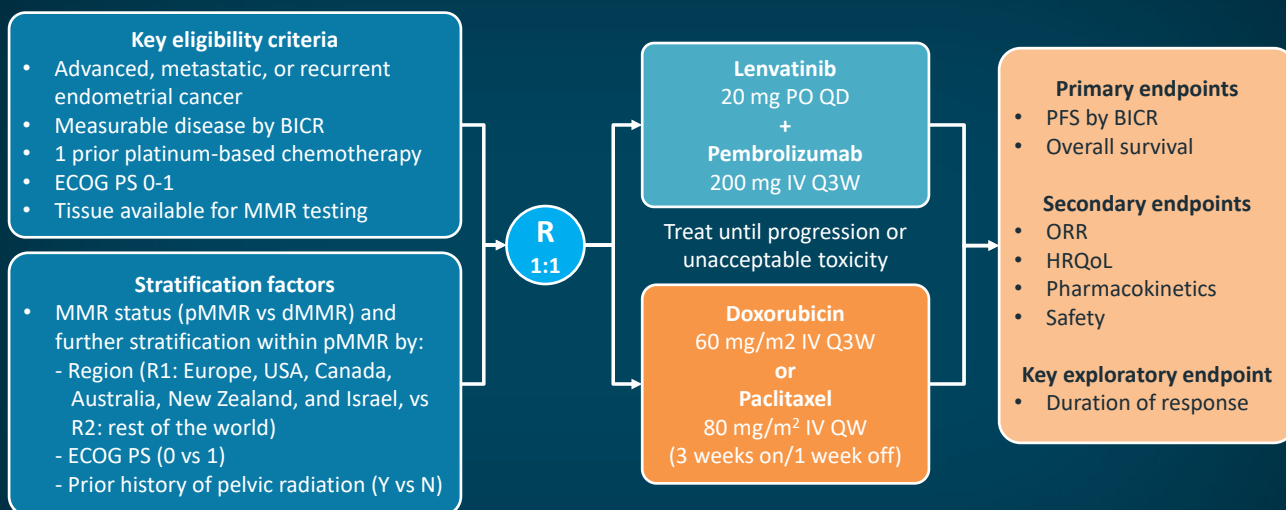
Study	Drug	N	Patient selection	ORR (%)
KEYNOTE-28 ¹	Pembrolizumab	24	Advanced/metastatic PD-L1+	13%
Garnet ²	Dostarlimab	142	Previously treated recurrent/advanced pMMR	13.4%
PHAEDRA ³	Durvalumab	36	Advanced/metastatic pMMR	3%
Konstantinopoulos et al ⁴	Avelumab	16	Advanced/metastatic pMMR	6%

PD-L1+ = programmed cell-death ligand 1 positive.

1. Ott PA, et al. *J Clin Oncol.* 2017;35(22):2535-2541. 2. Oaknin A, et al. *JAMA Oncol.* 2020;6:1766-1772. 3. Antill Y, et al. *J Immunother Cancer.* 2021;9:e002255. 4. Konstantinopoulos PA, et al. *J Clin Oncol.* 2019;37(30):2786-2794.

26

KEYNOTE-775 Study Design



BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQoL = health-related quality of life; IV = intravenous; PFS = progression-free survival; pMMR = mismatch repair-proficient; ORR = objective response rate; PO = per os (by mouth); QD = once daily, Q3W = every 3 weeks; QW = once weekly. Makker V, et al. *N Engl J Med.* 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

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KEYNOTE-775: Baseline Characteristics

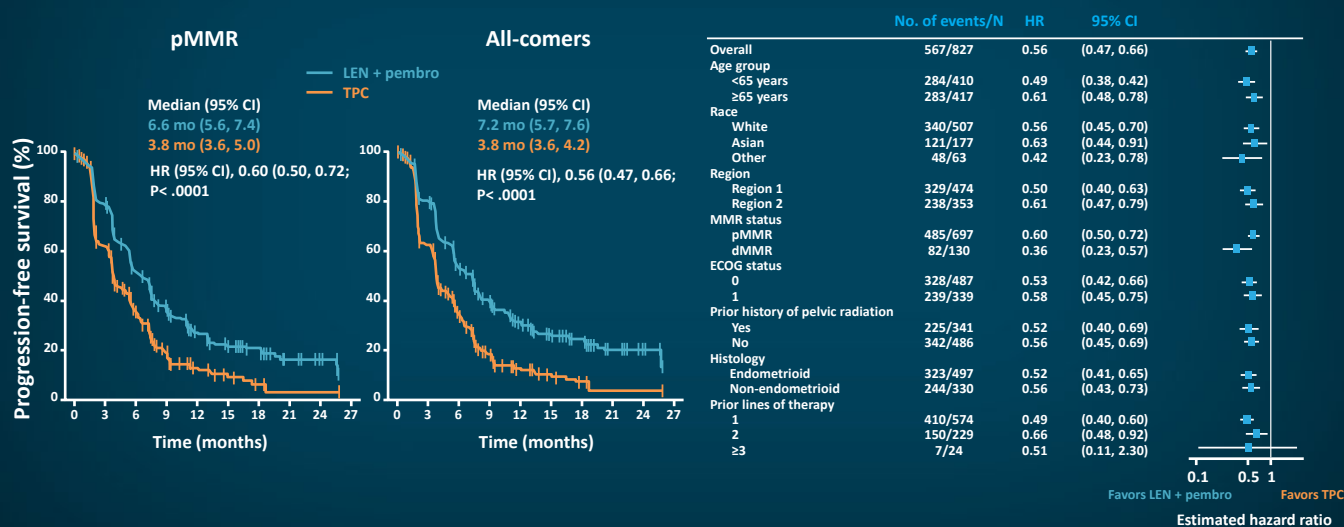
	LEN + pembro (n = 411)	TPC (n = 416)
Median age (range), years	64 (30-82)	65 (35-86)
MMR status: pMMR/dMMR, %	84.2 / 15.8	84.4 / 15.6
Prior history of pelvic radiation, %	40.9	41.6
ECOG 0/1, %	59.9 / 39.9	57.9 / 42.1
Race: White/Black/Asian/other, %	63.5 / 4.1 / 20.7 / 2.9	59.1 / 3.4 / 22.1 / 4.8
Histology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

LEN = Lenvatinib; pembro = pembrolizumab; TPC = treatment of physician's choice. Makker V, et al. *N Engl J Med.* 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

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KEYNOTE-775: Progression-Free Survival

Top-line results: Coprimary endpoints of PFS and OS were met and in favor of the pembrolizumab/lenvatinib arm.

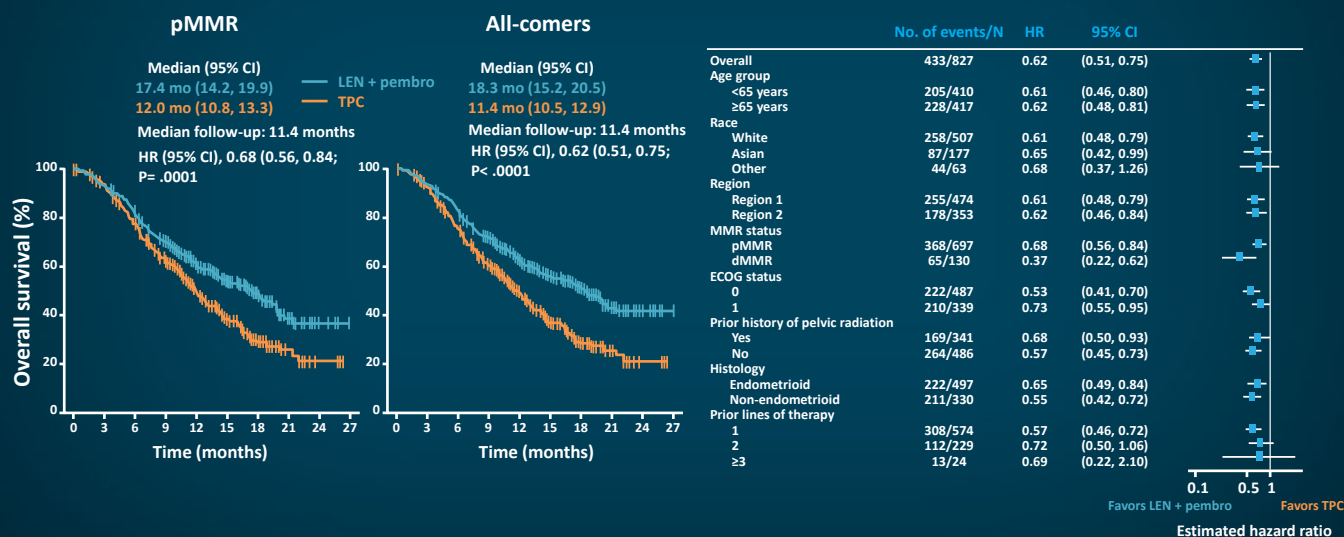


Makker V, et al. *N Engl J Med*. 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

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KEYNOTE-775: Overall Survival

Top-line results: Coprimary endpoints of PFS and OS were met and in favor of the pembrolizumab/lenvatinib arm.



Makker V, et al. *N Engl J Med*. 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

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KEYNOTE-775: Additional Results

	pMMR		All-comers	
	LEN + pembro	TPC	LEN + pembro	TPC
Patients, n	346	351	411	416
Objective response rate, % (95% CI)	30.3 (25.5-35.5)	15.1 (11.5-19.3)	31.9 (27.4-36.6)	14.7 (11.4-18.4)
Difference vs TPC, %	15.2	—	17.2	—
P-value	< 0.0001	—	< 0.0001	—
Best overall response, %				
Complete response	5.2	2.6	6.6	2.6
Partial response	25.1	12.5	25.3	12.0
Stable disease	48.6	39.6	47.0	40.1
Progressive disease	15.6	30.8	14.8	29.6
Not evaluable/assessed	0.6 / 4.9	2.0 / 12.5	1.2 / 5.1	1.9 / 13.7
Median duration of response (range), months	9.2 (1.6-23.7)	5.7 (0.0-24.2)	14.4 (1.6-23.7)	5.7 (0.0-24.2)
Median time to response (range), months	2.1 (1.5-9.4)	3.5 (1.0-7.4)	2.1 (1.5-16.3)	2.1 (1.0-7.4)

Makker V, et al. *N Engl J Med*. 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

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KEYNOTE-775: TEAEs With Frequency ≥25% in All-Comers

	LEN + pembro (n = 406)		TPC (n = 388)	
	Any Grade	Grade ≥3 ^a	Any Grade	Grade ≥3 ^a
Patients with any TEAEs, %	99.8	88.9	99.5	72.7
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism ^b	57.4	1.2	0.8	0.0
Diarrhea	54.2	7.6	20.1	2.1
Nausea	49.5	3.4	46.1	1.3
Decreased appetite	44.8	7.9	21.1	0.5
Vomiting	36.7	2.7	20.9	2.3
Weight decrease	34.0	10.3	5.7	0.3
Fatigue	33.0	5.2	27.6	3.1
Arthralgia	30.5	1.7	8.0	0.0
Proteinuria	28.8	5.4	2.8	0.3
Anemia	26.1	6.2	48.7	14.7
Constipation	25.9	0.7	24.7	0.5
Urinary tract infection	25.6	3.9	10.1	1.0
Headache	24.9	0.5	8.8	0.3
Asthenia	23.6	5.9	24.5	3.9
Neutropenia	7.4	1.7	33.8	25.8
Alopecia	5.4	0.0	30.9	0.5

^aIn the LEN + pembro arm, 5.7% of patients died due to grade 5 events (gastrointestinal disorders: 1.2%, cardiac disorders: 0.5%, general disorders: 1.5%, infections: 0.7%, decreased appetite: 0.2%, neoplasms, nervous system, psychiatric, renal, reproductive, or respiratory disorders: 0.2% each). In the TPC arm, 4.9% of patients died due to grade 5 events (cardiac disorders: 1%, general disorders: 1.3%, infections: 1.5%, subdural hematoma: 0.3%, respiratory disorders: 0.8%). ^bAdverse event of interest for pembrolizumab.

Makker V, et al. *N Engl J Med*. 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

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KEYNOTE-775: Treatment Exposure, Safety, and Discontinuation in All-Comers

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

Median dose intensity of lenvatinib was 13.8 mg per day

Makker V, et al. *N Engl J Med.* 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

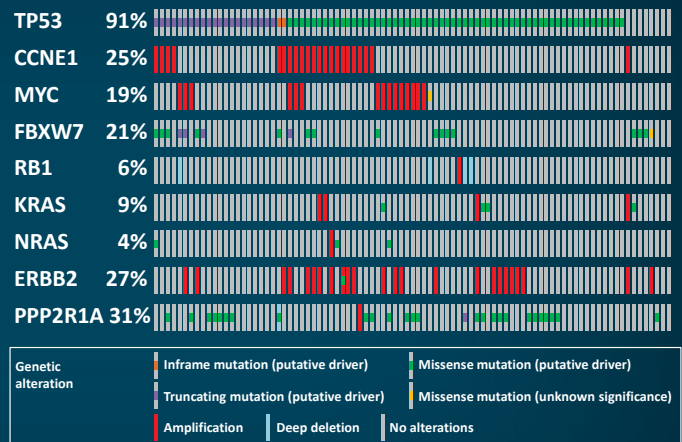
33

Emerging Therapies

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Targeting WEE1 in Uterine Serous or p53-Mutated Uterine Cancers

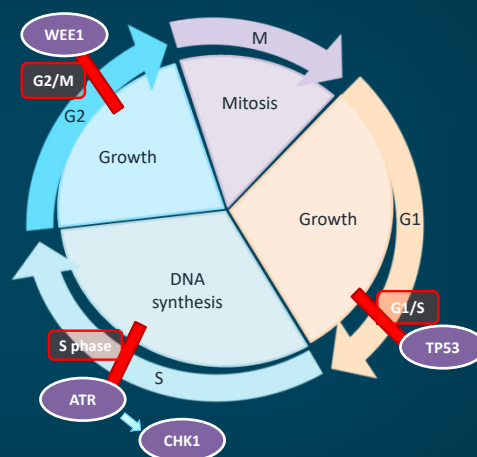
- Uterine serous cancer (USC)/serous-like cancers are a subtype of EC with aggressive features, accounting for up to 40% of uterine cancer mortality
- Beyond carboplatin/paclitaxel and pembrolizumab/lenvatinib, there is limited activity of standard therapies in USC
- Molecular characterization of USC demonstrates multiple molecular characteristics suggestive of **high replication stress**
 - CCNE1 amplification, MYC amplification, KRAS mutation, RB1 loss, ERBB2 amplification



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p53 Mutation and WEE1 Inhibition

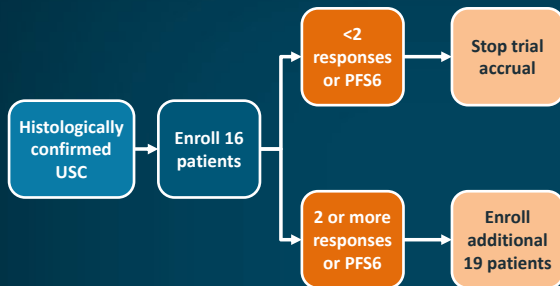
- WEE1 regulates the G2/M checkpoint: the Gatekeeper
- Cells with p53 aberrant expression/mutation or loss lose G1/S checkpoint
- Increases replication stress
- Increases dependence on G2/M checkpoint
- Synthetic lethality



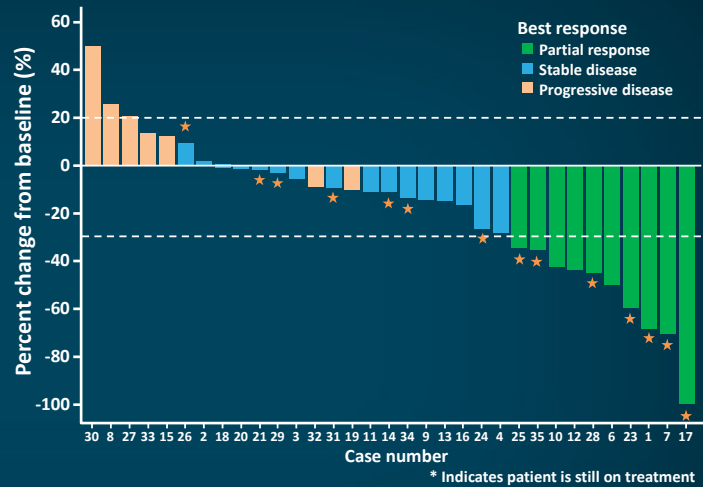
Liu JF, et al. *J Clin Oncol*. 2021;39(14):1531-1539.

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WEE1 Inhibition: Adavosertib in Uterine Serous Carcinoma



- 29.4% ORR
- 38.2% Clinical benefit response (CBR)
- DOR: 6.2 months
- PFS6: 55.6%



Open studies:

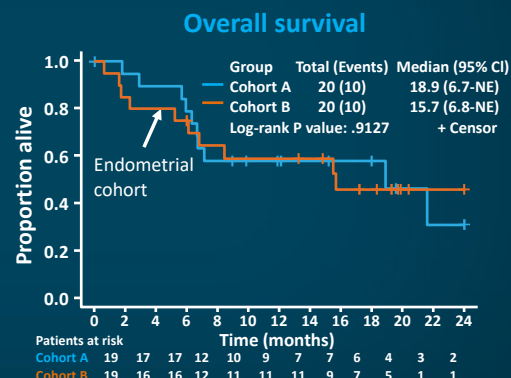
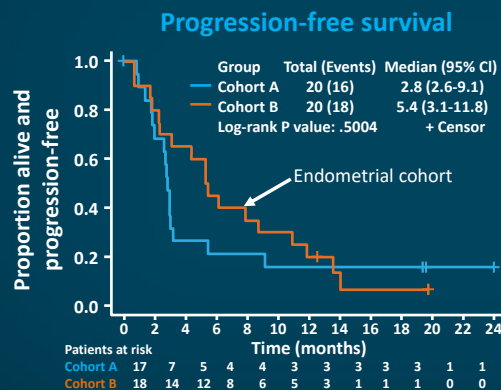
NCT04590248: Phase 2 of adavosertib in recurrent endometrial serous cancer
 NCT04814108: Phase 2 of ZN-c3 in recurrent endometrial serous cancer

Liu et al. *J Clin Oncol*. 2021;39(14):1531-1539.

37

CDK4/6 Inhibitors

- Phase 2 trial of ribociclib and letrozole in patients with relapsed estrogen receptor-positive ovarian or endometrial cancers
- 20 patients with EC enrolled; PFS12 was primary endpoint
- 2 confirmed responses in EC



Cohort A is the ovarian cancer cohort, and cohort B is the endometrial cancer cohort.
 Other phase 2 studies testing abemaciclib: NCT03675893 (DFCI), NCT04393285 (GOG)

NCT02657928

Colon-Otero G, et al. *ESMO Open*. 2020;5:e000926.

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PALEO Study (ESMO 2020)

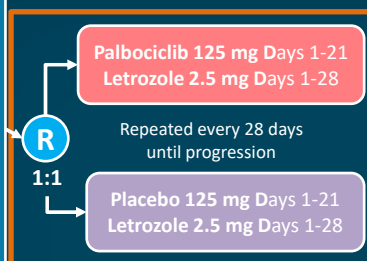
ENGOT-EN3/NDGO-PALEO trial design

Key inclusion criteria

- Measurable/evaluable endometrial cancer
- Primary Stage 4 or relapsed disease
- ≥ 1 prior systemic therapy
- ER+ ($\geq 10\%$) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

Stratification

- Number of prior lines (primary advanced disease vs 1st relapse vs ≥ 2 relapses)
- Measurable vs evaluable disease per RECIST
- Prior use of MPA/megestrol acetate



Primary endpoint: Investigator-assessed PFS (target HR 0.625, 80% power, 15% 1-sided α)

Secondary endpoints

- PFS in subgroups
- Objective response rate, disease control rate, PFS2, overall survival
- PROs

Baseline characteristics

Characteristics, n (%)		Palbociclib + Letrozole (n=35)	Placebo + Letrozole (n=37)
Median age, years (range)		68.5 (36-82)	67 (29-83)
Previous cancer		3 (8)	4 (11)
Diabetes		6 (17)	3 (8)
Hypertension		17 (47)	13 (35)
Other comorbidities		3 (8)	4 (11)
RECIST status	Measurable	32 (89)	31 (84)
	Evaluable	4 (11)	6 (16)
Prior use of megestrol acetate/MPA		4 (11)	7 (19)
Prior lines of therapy	0	5 (14)	4 (11)
	1	19 (53)	17 (46)
	≥ 2	12 (33)	16 (43)

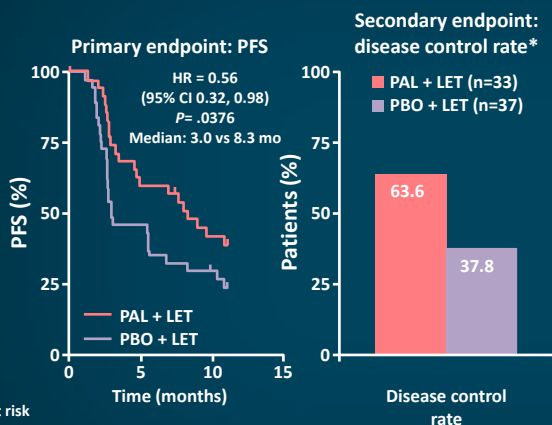
HR = hazard ratio; MPA = medroxyprogesterone acetate; CDK = cyclin-dependent kinase; PROs = patient-reported outcomes.

Mirza MR, et al. European Society of Medical Oncology (ESMO) 2020; Abstract LBA28.

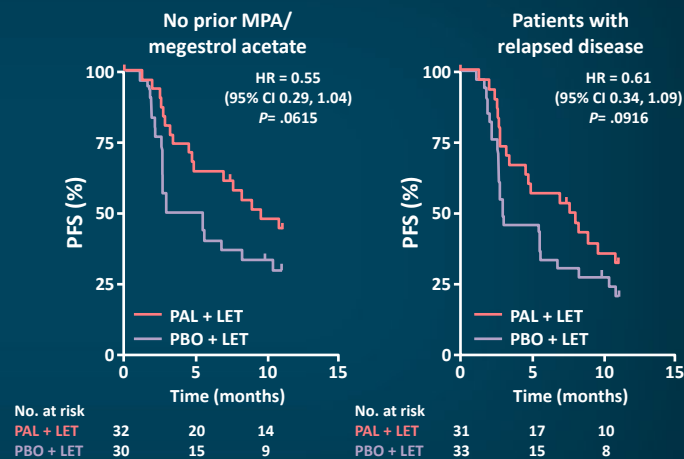
39

PALEO Results

Efficacy (intention-to-treat population)



PFS by stratification factors



CI = confidence interval; HR = hazard ratio; PAL = palbociclib; LET = letrozole.

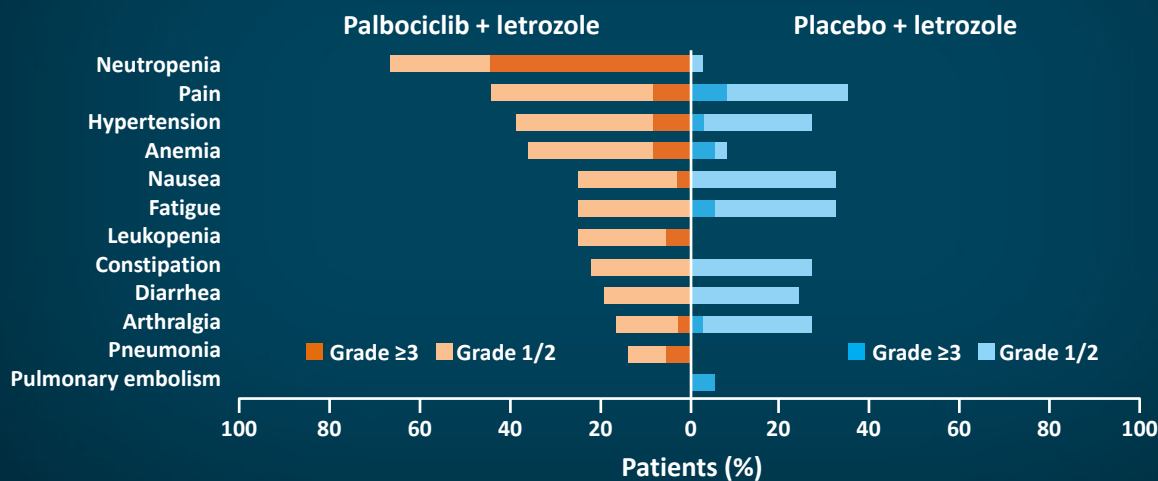
* At 24 weeks.

Mirza MR, et al, ESMO 2020; Abstract LBA28.

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PALEO Toxicities: Summary of Adverse Events

Any grade in $\geq 20\%$ of patients and/or >1 patient with Grade ≥ 3 in either arm

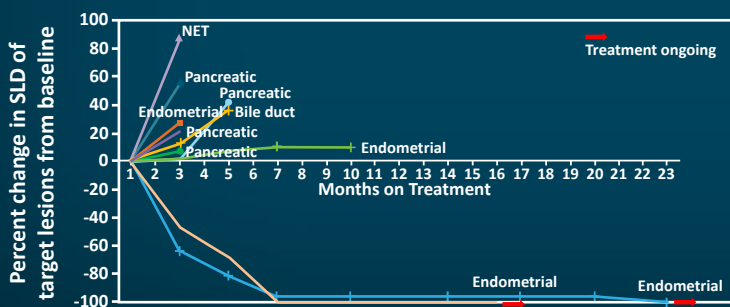


Mirza MR, et al. ESMO 2020; Abstract LBA28.

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Other Targeted Therapies: ATR Inhibitors

- Phase 2 study of the ATR inhibitor ceralasertib, alone and in combination with olaparib, in patients with ARID1A-deficient and ARID1A-intact solid tumors
- Rationale: Loss of ARID1A leads to increased reliance on ATR kinase
- 2 cohorts enrolled: ARID1A deficient (cohort 1, ceralasertib monotherapy) and ARID1A intact (cohort 2, ceralasertib combined with olaparib)
- In cohort 1, the ORR was 20% with 2 complete responses (CRs) observed; both patients were patients with EC who remained on treatment for 21.3+ and 16.3+ months, respectively. No responses in cohort 2

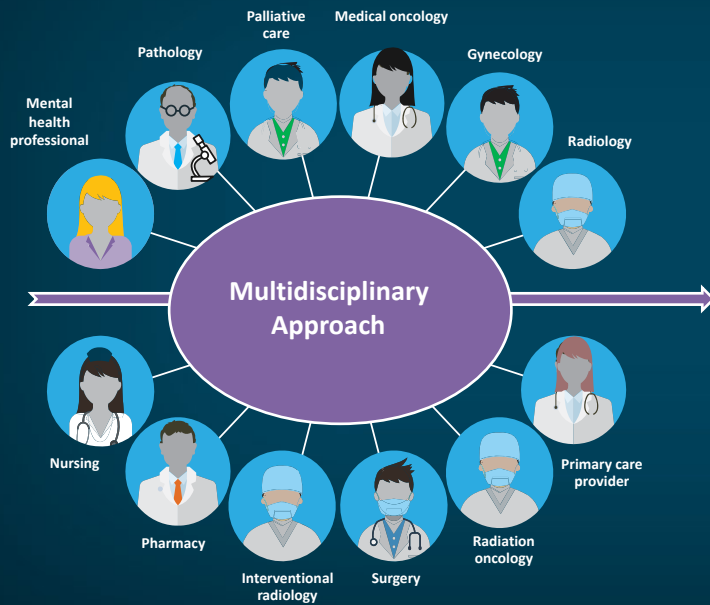


ATARI trial: Ceralasertib inhibitor in combination with olaparib in gynecological cancers with ARID1A loss or no loss (ENGOT/GYN1/NCRI) (NCT04065269): currently open

SLD = sum of the longest diameters. ESMO 2021 (<https://www.esmo.org/oncology-news/antitumour-activity-of-ceralasertib-in-arid1a-deficient-solid-tumours>).

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Managing Endometrial Cancer Requires a Multidisciplinary Approach



- Improved outcomes
- Early identification of irAEs
- Better QoL
- Provides individualized care
- Optimized treatment
- Management of comorbidities
- Enables shared decision-making

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Case Study

49-year-old woman

44

Case: 49-Year-Old White Female

- Initially presented with intermenstrual bleeding; endometrial biopsy showed EC, Grade 2
- Staging surgery showed a FIGO IVB Grade 2 endometrioid adenocarcinoma (wild type p53). 75% myometrial invasion, positive cervical stromal invasion, and lymphovascular invasion were present. The tumor was metastatic to the right ovary, omentum, and pelvic lymph nodes contained micrometastases. No evidence of disease at end of surgery
- MMR was normal and intact via IHC
- She was treated with adjuvant carboplatin and paclitaxel for 6 cycles
- Approximately 2 years later she presented with nausea and vomiting
- Found to have recurrent cancer with peritoneal metastasis; biopsy consistent with recurrent cancer

How would you manage this patient?

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Case: 49-Year-Old White Female (continued)

- Re-treated with carboplatin and paclitaxel with some decrease in tumor burden; 1 month later had cancer progression
- Underwent a secondary cytoreductive surgery; 3 months later had progression of cancer
- NGS of initial cancer and secondary cytoreduction sent

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Case: Histologic and pathologic characteristics

Pathological features	Primary tumor	Recurrence
Histology	Grade 2 endometrioid carcinoma	Metastatic high grade Mullerian carcinoma
Other features	- Centered in lower endometrial cavity and lower uterine segment - Deep myometrial and cervical stroma involvement - LVSI+	
MSI/MMR (IHC)	- MMR intact (<i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, <i>PMS2</i>)	- MMR intact (<i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, <i>PMS2</i>)
MSI (PCR)	No MSI by PCR (0/5 loci)	n/d
Hormone status (IHC)	- ER 18% (1+) - PR 17% (1+)	n/d
P53 (IHC)	Wild type	Wild type
TMB (NGS)	231.165 (98th %ile of endometrial, 100th %ile for all DFCI OncoPanel cases)	305.685 (98th %ile endometrial, 100th %ile for all DFCI OncoPanel cases)
Mutational signature (NGS)	- POLE signature - MMR deficiency signature	- POLE signature - MMR deficiency signature
Selected variants (NGS)	<i>POLE</i> c.1231G>T (V411L), exon 13 hotspot mutation <i>POLE</i> c.6391C>T (p.R2131C), VUS <i>POLE</i> c.5378+2T>G, VUS <i>IDH1</i> c.394C>T (p.R132C) <i>MSH6</i> c.3202C>T (R1068*) <i>PIK3CA</i> c.263G>A (p.R88Q)	<i>POLE</i> c.1231G>T (V411L), exon 13 hotspot mutation <i>POLE</i> c.6391C>T (p.R2131C), VUS <i>POLE</i> c.5378+2T>G, VUS <i>IDH1</i> c.394C>T (p.R132C) <i>MSH6</i> c.3202C>T (R1068*) <i>PIK3CA</i> c.263G>A (p.R88Q)

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How would you manage this patient given the NGS results?

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POLE Mutated Cancers

- The *POLE* gene encodes the major catalytic subunit of DNA polymerase-ε, which, along with polymerase-δ, synthesizes the leading and lagging strands during DNA replication in eukaryotes
- Mutations in *POLE* may compromise the 3' to 5' proofreading function, leading to loss of replication fidelity, development of genomic instability, and consequently an ultramutated phenotype
- Majority of cases of *POLE* mutated cancers are classified as microsatellite stable (76%)
- Certain mutations in exon 13 (our patient had this), which harbors the exonuclease domain, can generate more than 8000 neoepitopes, leading to a highly immunogenic microenvironment demonstrated by
 - 1) Increased numbers of peritumoral and tumor-infiltrating lymphocytes (TILs)
 - 2) Elevated PD-1 or PD-L1 expression

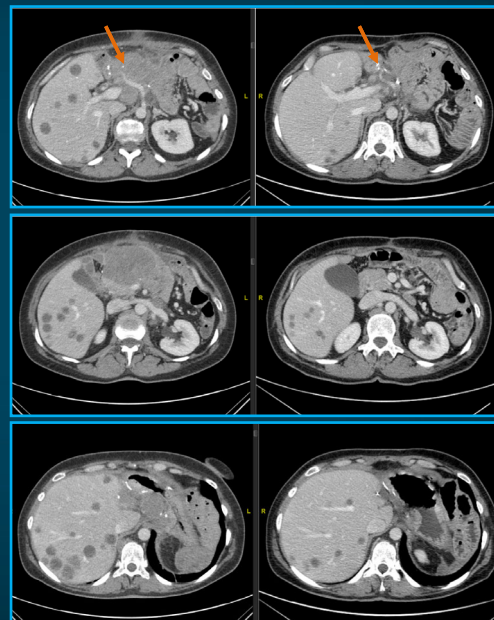
Veneris JT, et al. *Gyn Oncol.* 2020;156:488-497.

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POLE Mutated Cancers

- Started on pembrolizumab as a single agent
- Significant anti-cancer response occurred after 3 cycles
- This case supports the use of immune checkpoint inhibitors (ICIs) in the setting of
 - 1) High TMB
 - 2) *POLE* mutation
 - 3) Genomic *POLE* mutational signature as markers to predict response to ICI beyond MSI status

Before pembrolizumab After 3 cycles of pembrolizumab



Veneris JT, et al. *Gyn Oncol.* 2020;156:488-497.

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Case Study

62-year-old woman

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Case: 62-Year-Old White Female

- 2010: Vaginal spotting; endometrial biopsy showed a Grade I EC
- Staging surgery showed an endometrial adenocarcinoma, endometrioid mucinous type, Grade I. MMR testing: *MSH2*, *MSH6* (normal); *MLH1*, *PMS2* (abnormal)
- Stage IA Grade 1 endometrioid endometrial cancer; the cancer was minimally invasive of the myometrium. No further treatment recommended
- 1 year later she self-palpated a right inguinal lymph node. Positron emission tomography (PET) showed lymphadenopathy in the right pelvis and inguinal regions with no other sites of cancer in the upper abdomen. Biopsy was positive for malignant cells
- She started carboplatin/paclitaxel, then followed by involved field radiotherapy and 3 additional courses of carboplatin/paclitaxel; megestrol started as maintenance
- She was followed by every 6 months with CT scans
- 3 years later, there was documented recurrent cancer with enlarged RTP nodes and pelvic side wall disease

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How would you manage this patient?

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Case: 62-Year-Old White Female (continued)

- Patient was started on pembrolizumab in 2018, and after 5 months of treatment (7 doses) she was hospitalized for severe watery diarrhea. At that time flexible sigmoidoscopy with biopsy showed no colitis. She was treated with steroids and had rapid improvement. Pembrolizumab was held during steroid treatment and tapered
- 2 months later after resolution of diarrhea and completion of steroid course, she was rechallenged with pembrolizumab, and again developed severe watery diarrhea.

How would you manage this adverse event?

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Case 6: 62-Year-Old White Female (continued)

- Patient was again hospitalized for severe diarrhea
- She was started on 1 mg/kg methylprednisolone, which was increased to 2 mg/kg because of lack of improvement
- Colon biopsy was positive for checkpoint inhibitor induced colitis. She was unable to taper below 50 mg of prednisone and received 3 doses of infliximab over the next 3 months.
- No further pembrolizumab given. Diarrhea eventually completely resolved and steroids stopped
- CT scans x 3 years have shown no evidence of disease

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Thank You

Q & A

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**Immuno-Oncology Therapies for the Treatment of Advanced Endometrial Cancer:
Which of Your Patients May Benefit from Their Use?**

Resource	Address
Henley SJ, Miller JW, Dowling NF, Benard VB, Richardson LC. Uterine cancer incidence and mortality - United States, 1999-2016. <i>MMWR Morb Mortal Wkly Rep.</i> 2018;67:1333-1338.	https://pubmed.ncbi.nlm.nih.gov/30521505/
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