Project ECHO®

Med Learning Group - Endometrial Cancer

Immuno-oncology Therapies for the Treatment of ADVANCED ENDOMETRIAL CANCER:

Which of Your Patients May Benefit from Their Use?

FACULTY

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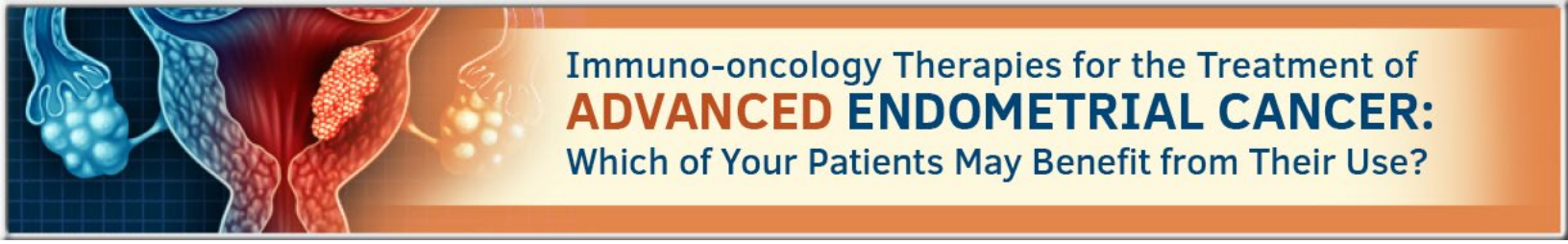
MEETING INFO

Tuesday, February 15, 2022

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This educational activity is supported by an independent medical education grant from Eisai and Merck & Co. Inc.



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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NURSING CREDIT INFORMATION
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
Ultimate Medical Academy/CCM is accredited as a provider of nursing continuing professional education development by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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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

The reviewer of this activity has nothing to disclose

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Douglas Cox, MSN, MHA, RN, UMA/CCM – LNP, has nothing to disclose.

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2. Participate in the web-based live activity.
3. Submit the evaluation form to Med Learning Group.

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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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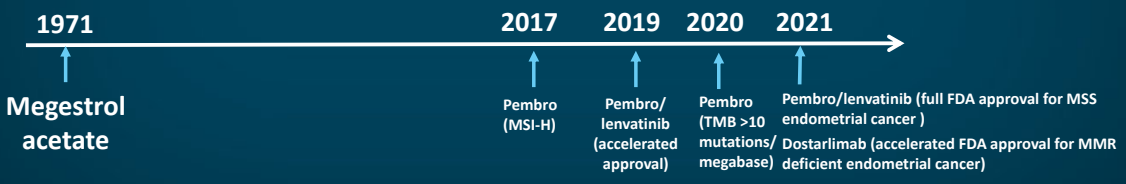
Endometrial Cancer (EC)

- 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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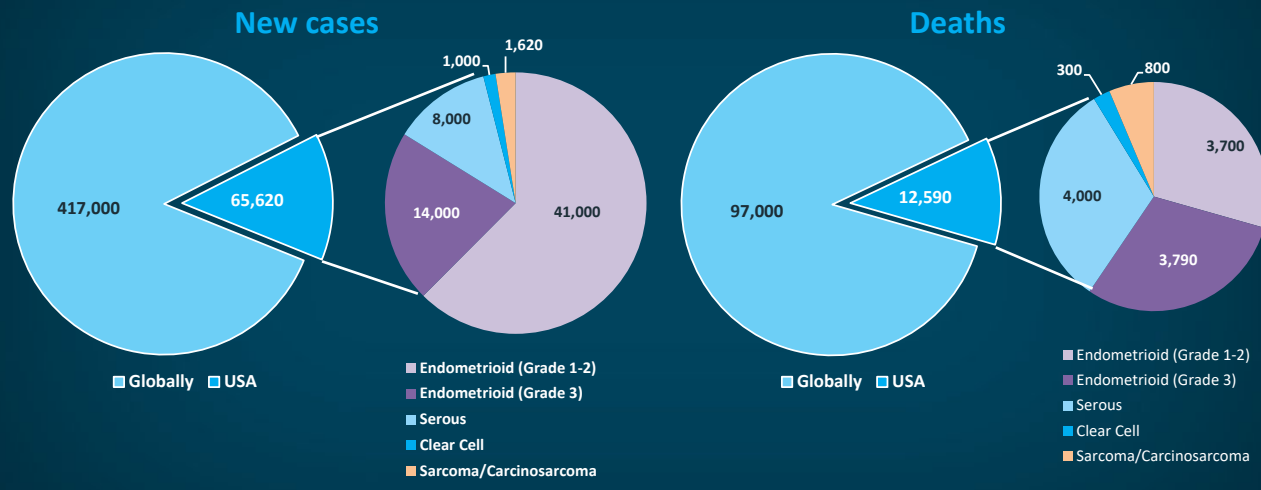
EC Cancer Statistics in the US and Globally in 2020



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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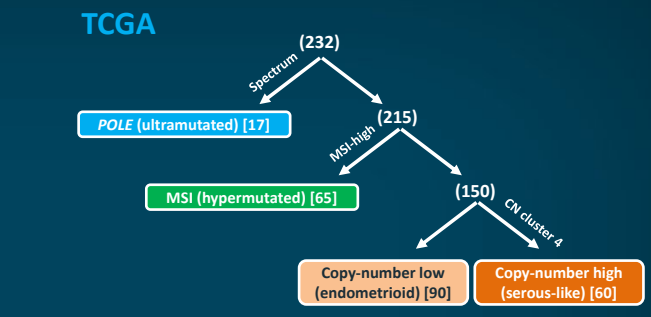
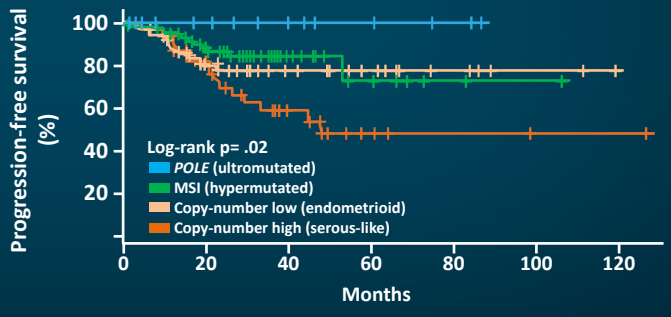
Molecular Classification of EC

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/m^2 on Day 1

TAP cycles 1 to 7
Doxorubicin 45 mg/m^2 IV on Day 1
Cisplatin 50 mg/m^2 on Day 1
Paclitaxel 3-hour 160 mg/m^2 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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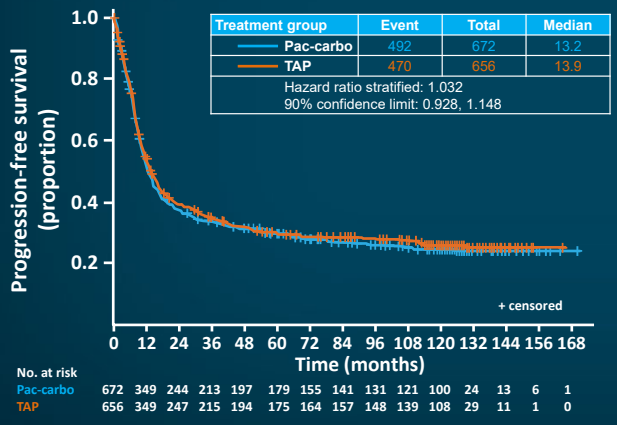
GOG 209: Efficacy Summary
Carboplatin and Paclitaxel for Advanced EC

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

Progression-free survival

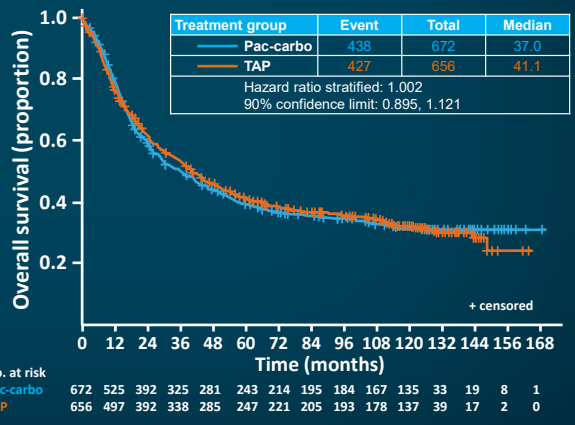


Treatment group	Event	Total	Median
Pac-carbo	492	672	13.2
TAP	470	656	13.9

Hazard ratio stratified: 1.032
90% confidence limit: 0.928, 1.148

No. at risk														
Pac-carbo	672	349	244	213	197	179	155	141	131	121	100	24	13	6	1
TAP	656	349	247	215	194	175	164	157	148	139	108	29	11	1	0

Overall survival



Treatment group	Event	Total	Median
Pac-carbo	438	672	37.0
TAP	427	656	41.1

Hazard ratio stratified: 1.002
90% confidence limit: 0.895, 1.121

No. at risk														
Pac-carbo	672	525	392	325	281	243	214	195	184	167	135	33	19	8	1
TAP	656	497	392	338	285	247	221	205	193	178	137	39	17	2	0

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), megace/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;38(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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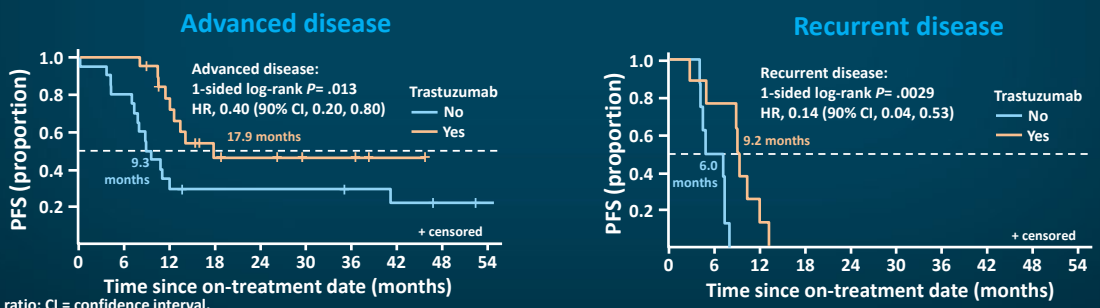
Benefit of Adding Trastuzumab in HER2+ Uterine Serous Carcinoma at Diagnosis with Carboplatin/Paclitaxel

- ~25% to 30% of patients with uterine serous carcinoma have HER2 amplification[1]
- Single agent trastuzumab in advanced/recurrent HER2+ uterine cancer has limited activity[2]
- Randomized phase 2 study of carboplatin/paclitaxel/trastuzumab vs carboplatin/paclitaxel showed increased PFS in HER2+ uterine serous cancer[3]
  - 58 evaluable patients (41 advanced, 17 recurrent) ; eligibility included 3+ IHC for HER2 or 2+ IHC plus FISH+



HR = hazard ratio; CI = confidence interval.

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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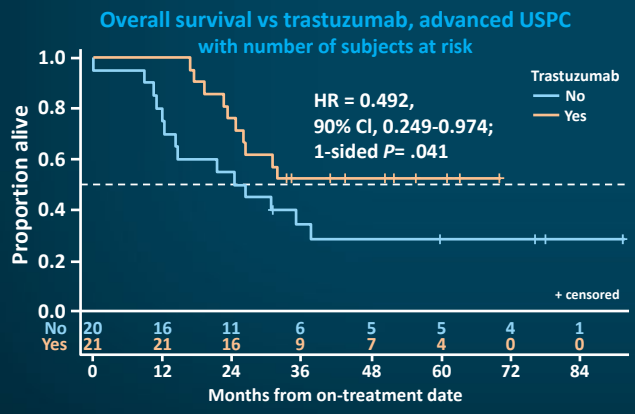
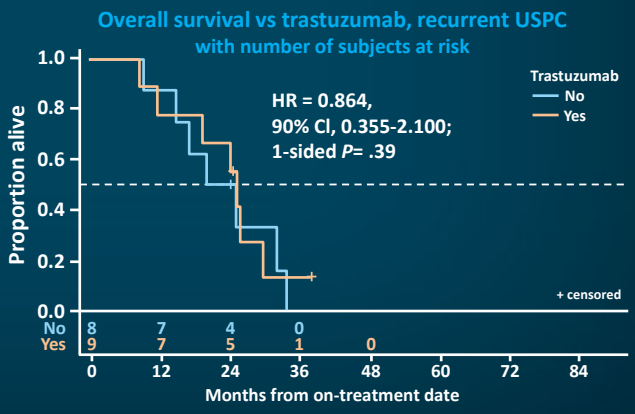
Trastuzumab in HER2+ Uterine Serous Carcinoma with Carboplatin/Paclitaxel

- 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)

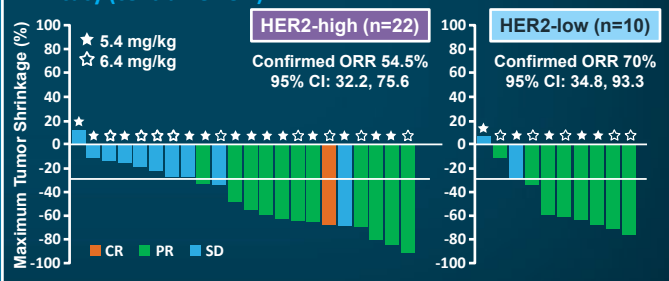
Key inclusion criteria

- 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)



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

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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 (Lenvatnib®) 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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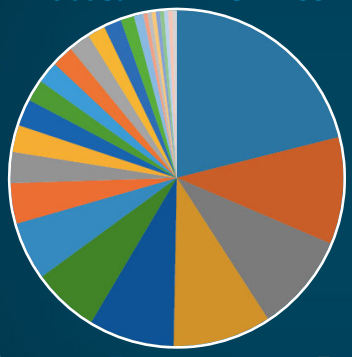
Keynote-158: Pembrolizumab for Non-Colorectal dMMR Recurrent Cancer

Distribution of tumor cohorts included in KEYNOTE-158



Antitumor activity for tumor types with greatest enrollment

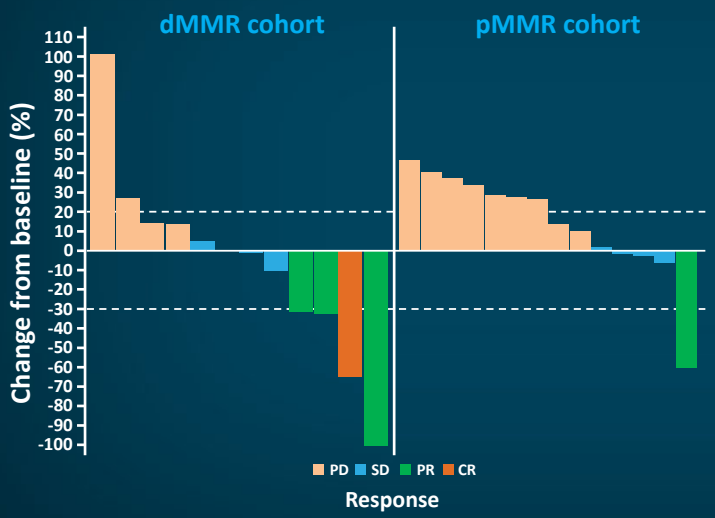
Tumor type	No.	CR, No.	PR, No.	ORR, % (95% CI)
Endometrial	49	8	20	57.1 (42.2 to 71.2)

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.

19

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



Response	Number of patients: dMMR cohort (n = 15)	Number of patients: 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..

20

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.

21

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

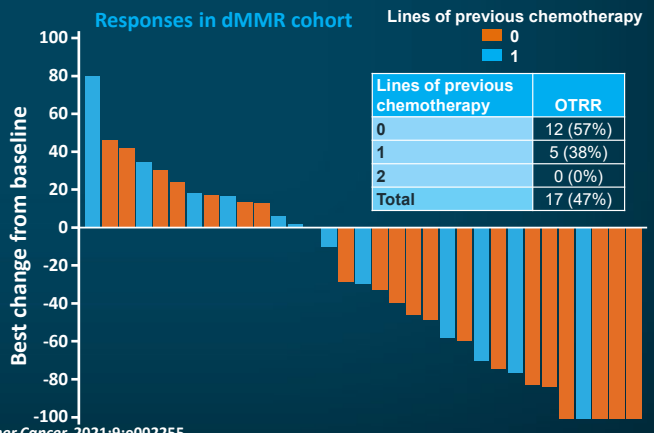
Key eligibility criteria
- Eastern Cooperative Oncology Group (ECOG): 0-2
- Advanced/recurrent endometrial cancer with not amenable to curative therapy
- Measurable disease by RECIST v1.1
- Known MMR status tumor tissue by IHC

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%)



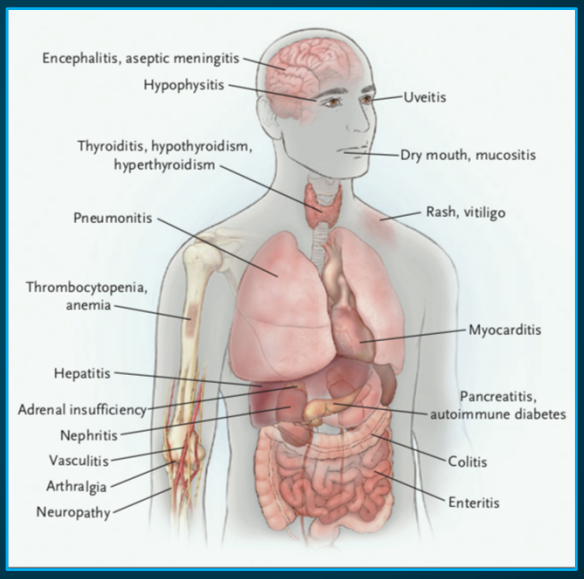
DCR = disease control rate; OTRR = objective tumor response rate. Antill Y, et al. *J Immunother Cancer.* 2021;9:e002255.

22

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.

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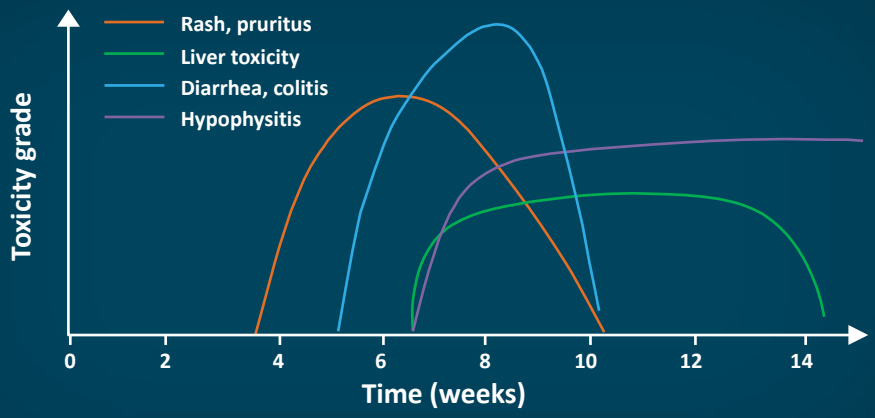
Managing Immune-Related AEs (cont)

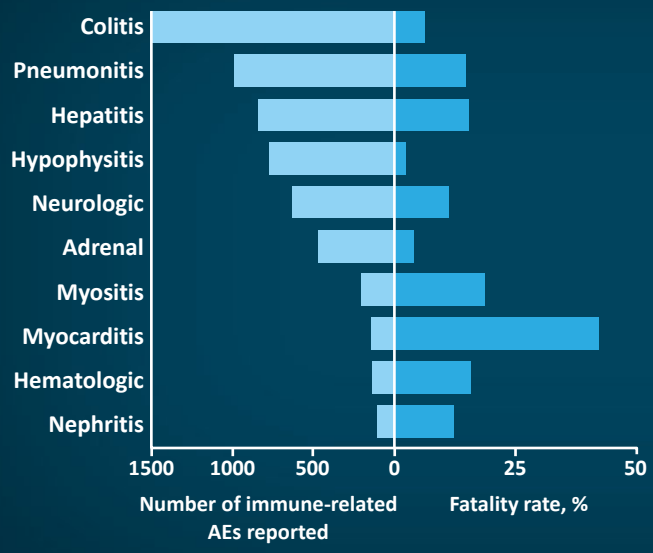


- Most immune-related AEs (irAEs) occur within first 6 months of treatment.
- Maintain high level of suspicion that new symptoms are treatment related.
- Use multidisciplinary care.

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 ≤ 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.

25

Single Agent IO Efficacy Is Low in pMMR EC

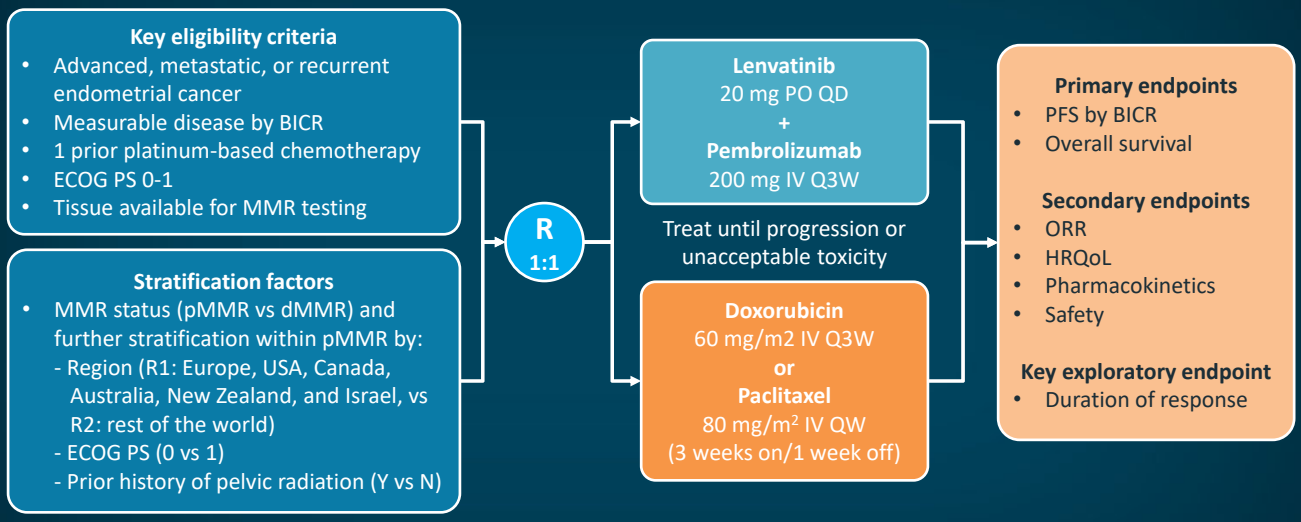
Study	Drug	N	Patient selection	ORR (%)
KEYNOTE-28[1]	Pembrolizumab	24	Advanced/metastatic PD-L1+	13%
Garnet[2]	Dostarlimab	142	Previously treated recurrent/advanced pMMR	13.4%
PHAEDRA[3]	Durvalumab	36	Advanced/metastatic pMMR	3%
Konstantinopoulos et al[4]	Avelumab	16	Advanced/metastatic pMMR	6%

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 Serous carcinoma Clear cell carcinoma Mixed	 22.9 / 14.4 / 21.9 25.1 7.3 5.4	 21.6 / 13.0 / 26.4 27.6 4.1 3.8
Prior lines of systemic treatment: 1 / ≥2, % Prior lines of platinum-based treatment: 1 / 2, % Prior neoadjuvant and/or adjuvant treatment, %	72.3 / 27.7 79.3 / 20.2 54.5	66.6 / 33.4 75.7 / 24.3 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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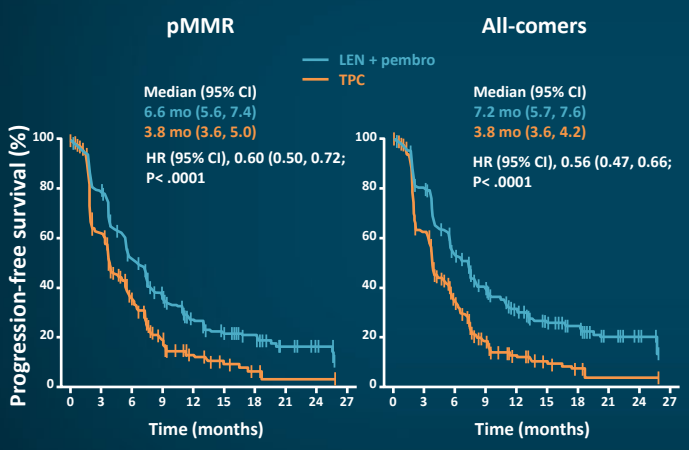
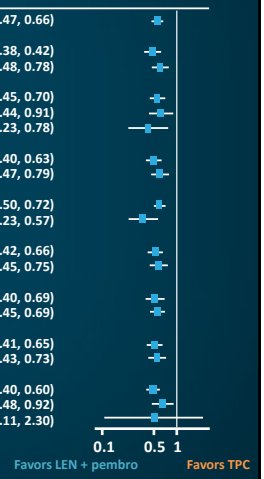
KEYNOTE-775: Progression-Free Survival

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



	No. of events/N	HR	95% CI
Overall	567/827	0.56	(0.47, 0.66)
Age group			
<65 years	284/410	0.49	(0.38, 0.42)
≥65 years	283/417	0.61	(0.48, 0.78)
Race			
White	340/507	0.56	(0.45, 0.70)
Asian	121/177	0.63	(0.44, 0.91)
Other	48/63	0.42	(0.23, 0.78)
Region			
Region 1	329/474	0.50	(0.40, 0.63)
Region 2	238/353	0.61	(0.47, 0.79)
MMR status			
pMMR	485/697	0.60	(0.50, 0.72)
dMMR	82/130	0.36	(0.23, 0.57)
ECOG status			
0	328/487	0.53	(0.42, 0.66)
1	239/339	0.58	(0.45, 0.75)
Prior history of pelvic radiation			
Yes	225/341	0.52	(0.40, 0.69)
No	342/486	0.56	(0.45, 0.69)
Histology			
Endometrioid	323/497	0.52	(0.41, 0.65)
Non-endometrioid	244/330	0.56	(0.43, 0.73)
Prior lines of therapy			
1	410/574	0.49	(0.40, 0.60)
2	150/229	0.66	(0.48, 0.92)
≥3	7/24	0.51	(0.11, 2.30)

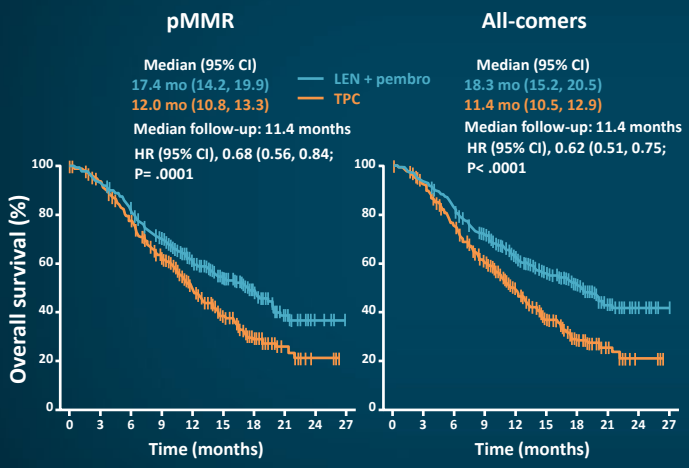


Makker V, et al. *N Engl J Med.* 2022;Epub ahead of print. Makker V, et al. SGO 2021; Abstract 0008/#785.

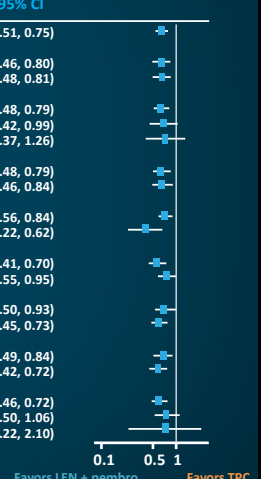
29

KEYNOTE-775: Overall Survival

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



	No. of events/N	HR	95% CI
Overall	433/827	0.62	(0.51, 0.75)
Age group			
<65 years	205/410	0.61	(0.46, 0.80)
≥65 years	228/417	0.62	(0.48, 0.81)
Race			
White	258/507	0.61	(0.48, 0.79)
Asian	87/177	0.65	(0.42, 0.99)
Other	44/63	0.68	(0.37, 1.26)
Region			
Region 1	255/474	0.61	(0.48, 0.79)
Region 2	178/353	0.62	(0.46, 0.84)
MMR status			
pMMR	368/697	0.68	(0.56, 0.84)
dMMR	65/130	0.37	(0.22, 0.62)
ECOG status			
0	222/487	0.53	(0.41, 0.70)
1	210/339	0.73	(0.55, 0.95)
Prior history of pelvic radiation			
Yes	169/341	0.68	(0.50, 0.93)
No	264/486	0.57	(0.45, 0.73)
Histology			
Endometrioid	222/497	0.65	(0.49, 0.84)
Non-endometrioid	211/330	0.55	(0.42, 0.72)
Prior lines of therapy			
1	308/574	0.57	(0.46, 0.72)
2	112/229	0.72	(0.50, 1.06)
≥3	13/24	0.69	(0.22, 2.10)



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

[a]In 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%). [b]Adverse 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, % Grade ≥3	99.8 88.9	99.5 72.7
Patients with any TEAEs leading to dose reductions, %	66.5	12.9
Patients with any-grade TEAEs leading to interruption, % LEN Pembro LEN + pembro	69.2 58.6 50.0 30.8	27.1 – – –
Patients with any-grade TEAEs leading to discontinuation, % LEN Pembro LEN + pembro	33.0 30.8 18.7 14.0	8.0 – – –

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.

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Emerging Therapies

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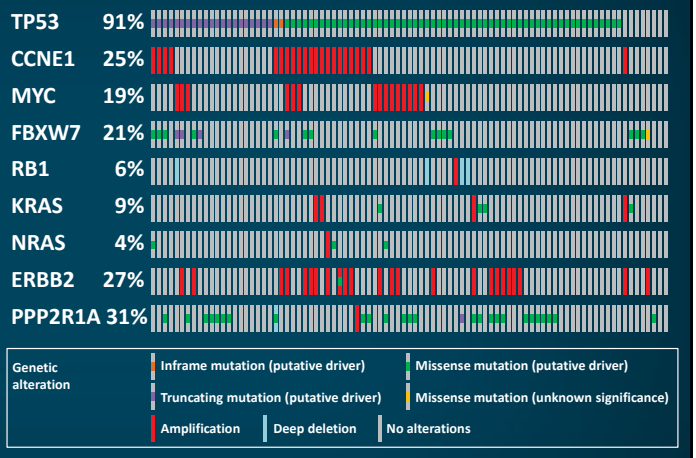
Targeting WEE1 in Uterine Serous or p53-Mutated Uterine Cancers

- 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

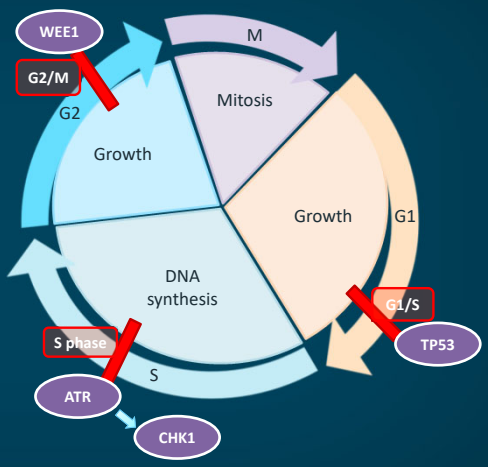


From cBioPortal query; combined TCGA and MSK-IMPACT datasets.

35

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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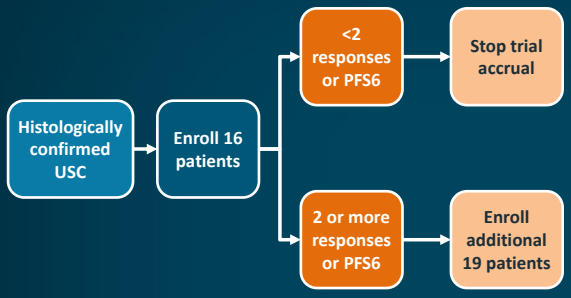
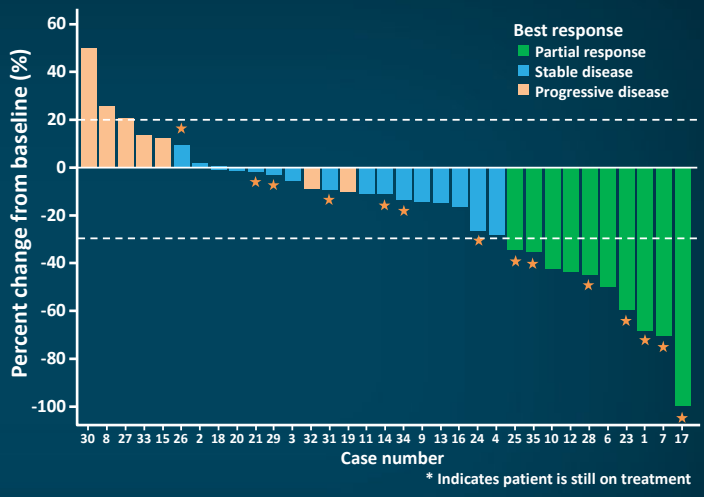
WEE1 Inhibition: Adavosertib in Uterine Serous Carcinoma





- **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.

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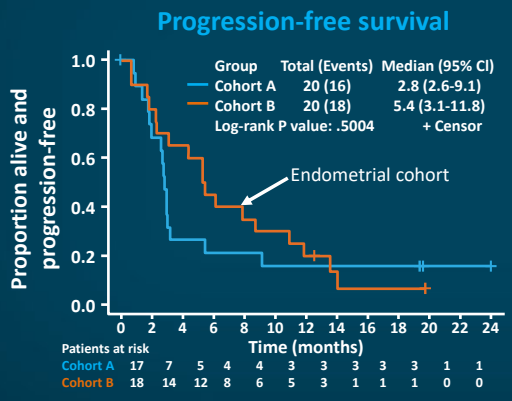
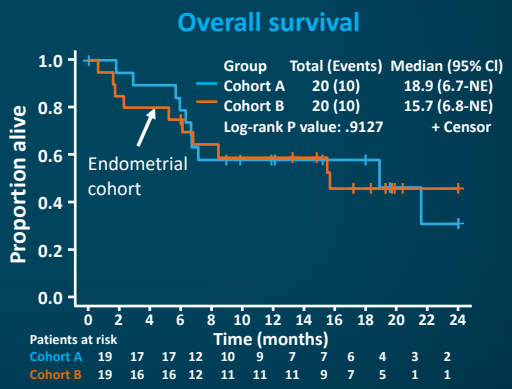
CDK4/6 Inhibitors

- 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+ (≥10%) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

Palbociclib 125 mg Days 1-21
Letrozole 2.5 mg Days 1-28

R 1:1

Repeated every 28 days until progression

Placebo 125 mg Days 1-21
Letrozole 2.5 mg Days 1-28

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.

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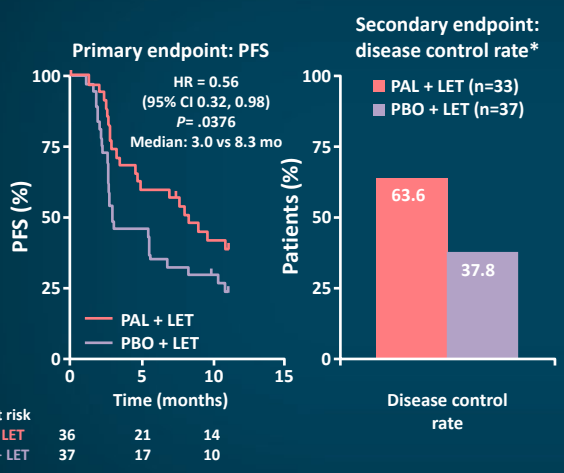
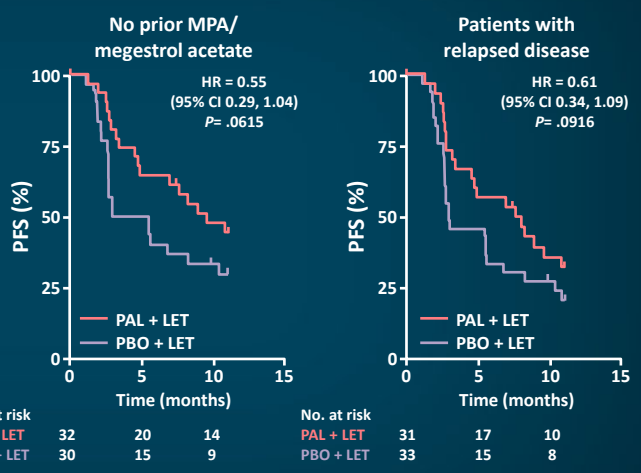
PALEO Results

Efficacy (intention-to-treat population)



No. at risk				
PAL + LET	36	21	14	
PBO + LET	37	17	10	

PFS by stratification factors



No. at risk				
PAL + LET	32	20	14	
PBO + LET	30	15	9	

No. at risk				
PAL + LET	31	17	10	
PBO + LET	33	15	8	

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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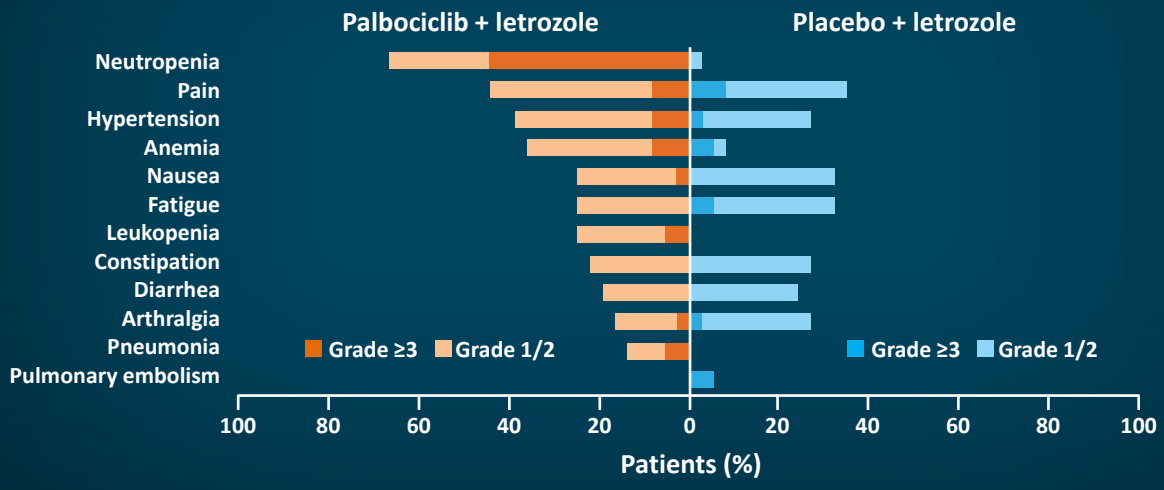
PALEO Toxicities: Summary of Adverse Events

Any grade in ≥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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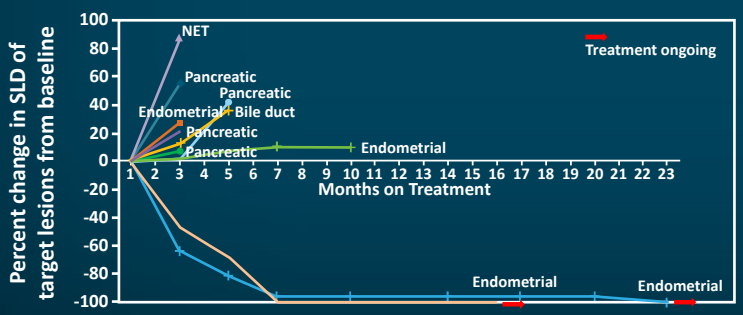
Other Targeted Therapies: ATR Inhibitors

- 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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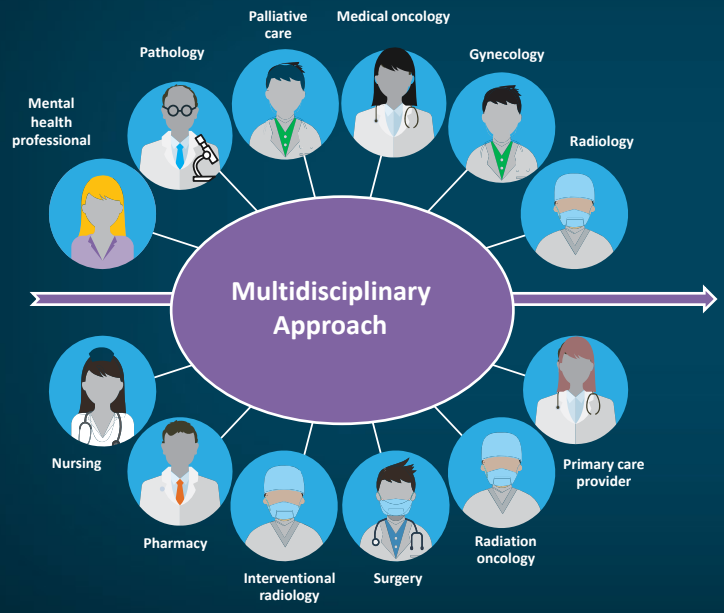
Managing Endometrial Cancer Requires a Multidisciplinary Approach



- 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

66-year-old nurse

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Case: 66-Year-Old Nurse

- Presented with postmenopausal bleeding
- CT scan showed 1 atrophic kidney
- 2020: Endometrial biopsy consistency with clear cell cancer
- Staging surgery: Diagnosed with advanced mixed clear cell (90%) and serous cancer (10%) of the endometrium with metastasis to the omentum, pelvic side wall, right and left ovaries; involved an endometrial polyp and the endometrium; no myometrial invasion. MMR was normal

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Case: 66-Year-Old Nurse

- NGS
  - Tumor mutational burden/megabase: 8.365
  - FGFR2 c.755C>G (p.S252W), exon 7
  - PIK3CA c.1034A>T (p.N345I), exon 5
  - PPP2R1A c.536C>G (p.P179R), exon 5
  - TP53 c.742C>T (p.R248W), exon 7
- Received 6 cycles of carboplatin and paclitaxel
  - CT at the completion of chemotherapy showed no evidence of disease
  - 4 months later, CT showed new peritoneal carcinomatosis and small volume ascites

How would you manage this patient?

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Case: 66-Year-Old Nurse (continued)

- Started on lenvatinib and pembrolizumab
  - 5 cycles of pembrolizumab from July 2021 to October 2021
  - Started lenvatinib 12 mg because of atrophic kidney
- After 3 cycles of pembrolizumab: Improvement in peritoneal carcinomatosis, with resolution of ascites
  - Grade 2 diarrhea started after Cycle 4

How would you manage this adverse event?

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Case: 66-Year-Old Nurse (continued)

- To manage diarrhea, lenvatinib held for 10 days
  - *C difficile* negative and CT unchanged
  - Restarted lenvatinib at 8 mg when diarrhea to Grade 1
- 1 month later CA125 rose >500/abdominal swelling, and CT scan showed increased peritoneal carcinomatosis and moderate ascites
- Started carboplatin/weekly paclitaxel on November 18, 2021

	November 2021	12/2/2021	12/9/2021	12/16/2021	12/23/2021
CA125 ***6 - 38 U/mL***	454 (H)	435 (H)	147 (H)	71 (H)	34

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Case Study

62-year-old woman

49

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; megace 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: 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
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