Enhancing Endometrial Cancer Management: Highlights of Molecular Insights, Treatment Approaches, and Toxicity Management

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Educational Objectives

After completion of this activity, participants will be able to:

- Apply molecular testing insights into patient evaluations to improve the timing and choice of therapies for those diagnosed with endometrial cancer
- Ensure appropriate use of checkpoint inhibitor-based treatment strategies in advanced or recurrent endometrial cancer based on patient- and disease-specific characteristics
- Construct strategies to manage and mitigate toxicities of systemic endometrial cancer therapies, including dose adjustments, supportive care, and patient education

Pretest Questions

Pretest Question 1

Based on the molecular profile listed below, which patient with endometrial cancer would be most likely to respond to immunotherapy?

A. *CDKN2A* mutation
B. Microsatellite instability-high
C. Programmed death-ligand 1 positive
D. Proficient mismatch repair

Pretest Question 2

BB is a 65-year-old woman with a history of endometrial cancer (stage II, grade 2) who received primary therapy with surgery, radiation therapy, and 6 cycles of adjuvant paclitaxel + carboplatin. She now has recurrent disease 2 years after her initial diagnosis. Her tumor is HER2-negative, microsatellite instability-high, mismatch repair deficient (MSI-H/dMMR). What would be the most appropriate second-line option for treatment?

A. Dostarlimab
B. Docetaxel + bevacizumab
C. Lenvatinib + pembrolizumab
D. Paclitaxel + carboplatin + trastuzumab

Pretest Question 3

Which are common overlapping toxicities of immune checkpoint inhibitor therapy and targeted agents?

A. Diarrhea, fatigue, rash
B. Myalgia, electrocardiogram abnormalities, dyspnea
C. Fatigue, hypertension, headache
D. Rash, cough, proteinuria

Pretest Question 4

Before participating in this activity, how confident are you with the management of targeted therapies for endometrial cancer?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Endometrial Cancer

Endometrial Cancer Overview

- Incidence: 67,880 estimated new cases and 13,250 estimated deaths in 2024
  - Diagnosis median age: 64 years
  - Death median age: 71 years
- Risk factors: increased levels of estrogen, early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age, tamoxifen use

≈3.1% of women will be diagnosed with uterine cancer at some point during their lifetime

5-year OS: 80.8%

OS, overall survival.

Cancer stat facts: uterine cancer. National Cancer Institute. Accessed September 30, 2024. seer.cancer.gov/statfacts/html/corp.html; NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024.

Advanced Endometrial Cancer

15%-20%
of patients with endometrial cancer are diagnosed with advanced disease at time of diagnosis

≈13% of endometrial cancers are recurrent

<1 year OS for advanced/recurrent endometrial cancer failing first-line systemic treatment

There are **limited treatment options** for patients diagnosed with advanced endometrial cancer.

Colombo N et al; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. *Ann Oncol*. 2016;27(1);16-41; Siegel RL et al. *CA Cancer J Clin*. 2022;72(1):7-33; Oaknin A et al. *JAMA Oncol.* 2020;6(11):1766-1772; Huijgens AN, Mertens HJ. *Facts Views Vis Obgyn.* 2013;5(3):179-186.

International Federation of Gynecology and Obstetrics Stage

Stage I	Limited to the uterus
Stage II	Spread to the cervix
Stage III	Spread to vagina, ovaries, and/or lymph nodes
Stage IV	Spread to bladder, rectum, or distant organs such as lungs or bones

NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024.

International Federation of Gynecology and Obstetrics Staging: Molecular Classifications

- When feasible, the addition of molecular subtypes to staging criteria allows a better prediction of prognosis in a staging/prognosis scheme
- The performance of complete molecular classification (polymerase epsilon mutation [*POLE*mut], mismatch repair deficient [dMMR], no specific molecular profile [NSMP], p53abn) is encouraged in all endometrial cancer cases for prognostic risk stratification

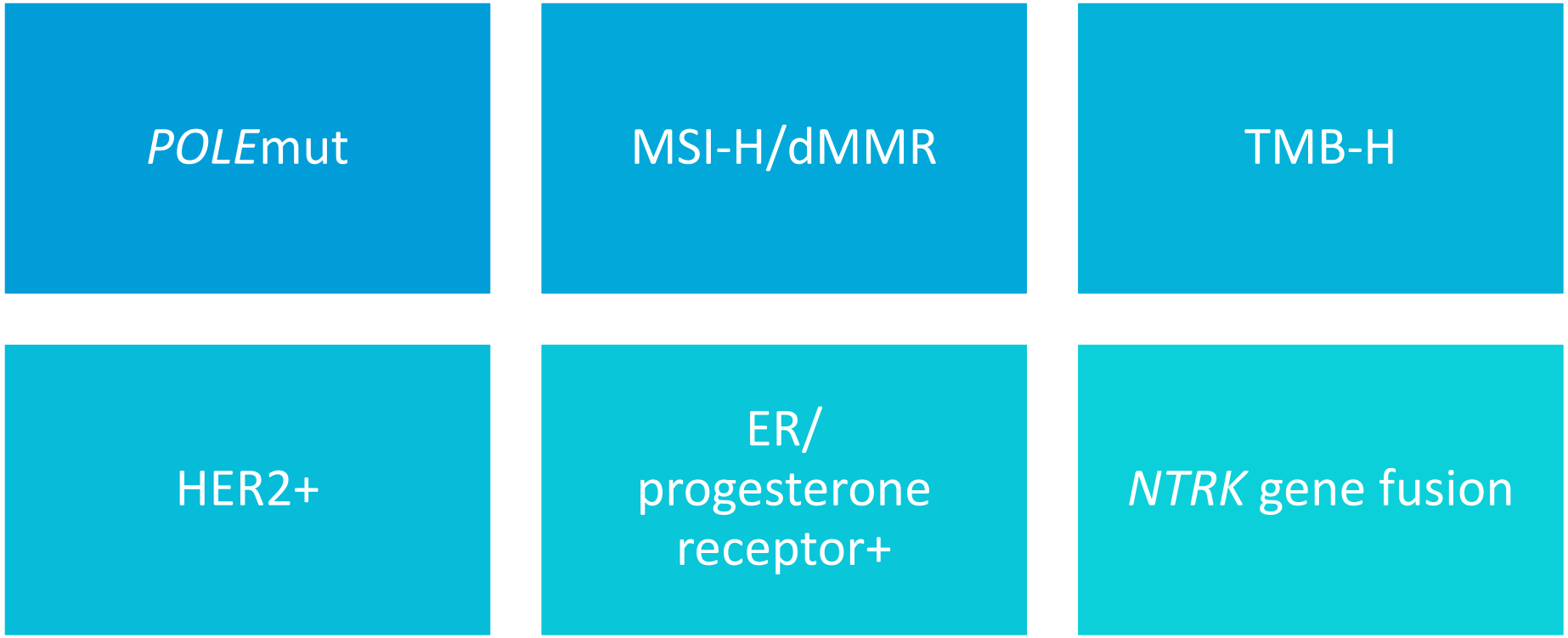
Prognosis	Molecular subgroup
Good prognosis	Pathologic *POLE*mut
Intermediate prognosis	dMMR/MSI-H and no NSMP
Poor prognosis	p53abn

MSI-H, microsatellite instability-high.

Zheng W. *Cancers (Basel).* 2023;15(16):4101.

Biomarker Testing

- 67%-91% of patients with advanced or recurrent endometrial cancer have ≥1 therapeutically actionable genomic alteration(s)



ER, estrogen receptor; TMB-H, high tumor mutation burden.

Green AK et al. *Am Soc Clin Oncol Educ Book*. 2020;40:1-7; NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024.

MSI-H/dMMR

- MSI-H, MSI-low, or microsatellite stable (MSS)
- dMMR or proficient MMR (pMMR)
- Endometrial cancer has the highest prevalence of MSI across cancer types
  - ≈30% of primary endometrial cancers are MSI-H/dMMR
  - 16%-31% of recurrent endometrial cancers are MSI-H/dMMR
- Majority of MSI caused by defects in DNA MMR genes
  - Mainly *MLH1*, *MSH2*, *MSH6*, and *PMS2*
- Appears to have better responses to immunotherapy

Microsatellite: short segment of DNA (1-6 base pairs) that is repeated multiple times at a genomic location

Kurnit KC et al. *Cancer*. 2019;125(13):2154-2163; NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024; Kanopiene D et al. *Medicina (Kaunas)*. 2014;50(4):216-221; Dio C et al. *Gynecol Oncol*. 2023;169:27-33.

POLE Mutation

- 7%-12%% of endometrial cancers have this mutation
- 17% of *POLE*mut cases developed recurrences
- Presence of high number of tumor-infiltrating T cells, which predict to be neoantigen rich
- Harbor high densities of programmed cell death protein 1 (PD-1)- and programmed death-ligand 1 (PD-L1)-expressing immune cells

Eggink FA et al. *Oncoimmunology*. 2017;6(2):e1264565; Veneris J et al. *Gynecol Oncol*. 2019;153(3):471-478; Stasenko M et al. *Gynecol Oncol*. 2020;156(1):194-202.

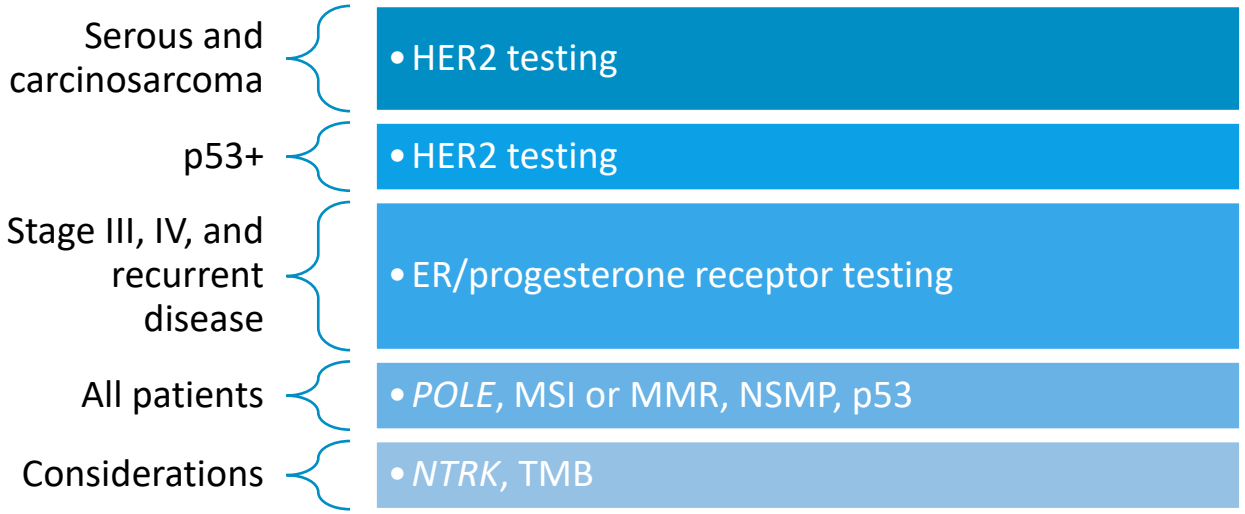
TMB

- Number of genetic changes in a cancer cell
- TMB-H (≥10 mutations/megabase) more likely to respond to immunotherapy

Fusco MJ et al. *JAMA Oncol*. 2021;7(2):316.

Summary of Biomarkers

- Consider comprehensive genomic profiling in the initial evaluation of endometrial cancer
- Results of molecular testing guide treatment decisions and are correlated with outcomes



NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024; Murali R et al. *J Natl Compr Canc Netw*. 2018;16(2):201-209.

Treatment of Metastatic or Recurrent Disease

Treatment Guidelines

Newly diagnosed metastatic or first-line recurrent disease (no prior platinum)
Category 1: • C/T/dostarlimab • C/T/pembrolizumab (except for carcinosarcoma) • C/T/durvalumab (for dMMR tumors only)
C/T (category 1 for carcinosarcoma)
HER2+ uterine serous or carcinosarcoma: • C/T/trastuzumab
Hormone therapy: • Megestrol/tamoxifen (alternating), everolimus/letrozole, aromatase inhibitor (eg, letrozole), tamoxifen, fulvestrant **Useful in certain circumstances:** • ER+ tumors → letrozole/ribociclib or letrozole/abemaciclib

Recurrent disease, second line or more, biomarker directed (prior platinum therapy)	
pMMR tumors	Lenvatinib/pembrolizumab (category 1)
TMB-H tumors	Pembrolizumab
MSI-H/dMMR tumors	Pembrolizumab, dostarlimab, avelumab, or nivolumab
HER2+ tumors (IHC 3+ or 2+)	Fam-trastuzumab deruxtecan
***NTRK* gene fusion+ tumors**	Larotrectinib or entrectinib

C/T, carboplatin/paclitaxel; IHC, immunohistochemistry.

NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024.

KEYNOTE-868/NRG-GY018: Pembrolizumab + Chemotherapy

Phase 3, multicenter, randomized, double blind, placebo controlled	
Population	Stage III or IVA endometrial carcinoma with measurable disease or stage IVB or recurrent disease of **any histologic subtype (except carcinosarcoma)**
Intervention	• C/T + placebo (n = 113 in dMMR; n = 295 in pMMR) • C/T + pembrolizumab x 6 cycles followed by pembrolizumab up to 14 cycles every 6 weeks (maximum of 2 years) (n = 112 in dMMR; n = 293 in pMMR)
Outcomes	• mPFS **(dMMR, MSI-H):** NR (pembrolizumab) vs 6.5 months (placebo) • mPFS **(pMMR, MSS):** 13.1 months (pembrolizumab) vs 8.7 months (placebo)
Safety	• Fatigue (66% vs 59%), sensory neuropathy (58% vs 59%), anemia (56% vs 53%), nausea (46% vs 42%) • Grade ≥3: 57% vs 46%; AEs of interest (possible immune etiology): 35% vs 22%; infusion reaction, thyroid disorders, colitis, pneumonitis

Pembrolizumab is FDA approved in combination with chemotherapy in patients with advanced stage III-IV disease or recurrent endometrial cancer.

AE, adverse effects.

Eskander RN et al. *N Engl J Med*. 2023;388(23):2159-2170.

RUBY: Dostarlimab + Chemotherapy

Phase 3, global, double blind, randomized, placebo controlled	
Population	Stage III or IV primary or recurrent disease, including **all histologies**
Intervention	• C/T + dostarlimab x 6 cycles followed by dostarlimab every 6 weeks maintenance (maximum 3 years) (n = 245) • C/T + placebo followed by placebo maintenance (n = 249)
Outcomes	• mPFS (overall population): 11.8 months (dostarlimab) vs 7.9 months (placebo) • mPFS (dMMR, MSI-H) at 2 years: 61.4% (dostarlimab) vs 15.7% (placebo) • PFS (pMMR, MSS) at 2 years: 28.4% (dostarlimab) vs 18.8% (placebo) • mOS (overall population): 44.6 months (dostarlimab) vs 28.2 months (placebo)
Safety	• Nausea (54% vs 46%), alopecia (53.5% vs 50%), fatigue (52% vs 54.5%), rash (23% vs 14%), maculopapular rash (14% vs 4%) • Grade ≥3: 70.5% vs 60%; serious AEs: 38% vs 28% • irAEs: hypothyroidism, rash, increase in ALT, arthralgia

Dostarlimab is FDA approved in combination with chemotherapy in patients with advanced stage III-IV disease or recurrent endometrial cancer due to statistically significant and clinically meaningful OS improvement regardless of MMR status.

ALT, alanine aminotransferase; ir, immune related; m, median; PFS, median progression-free survival.

Mirza MR et al; RUBY Investigators. *N Engl J Med*. 2023;388(23):2145-2158.

DUO-E: Durvalumab + Olaparib + Chemotherapy

Phase 3, global, randomized, double blind, placebo controlled	
Population	• Stage III/IV endometrial cancer • Recurrent endometrial cancer **IF** >12 months from last carboplatin treatment • Known MMR status (stratified by status)
Intervention	• C/T + placebo (n = 241) • C/T + durvalumab x 6 cycles followed by durvalumab every 4 weeks maintenance (n = 238) • C/T + durvalumab + olaparib followed by maintenance (n = 239)
Outcomes	• mPFS (dMMR): 31.8 months (durvalumab + olaparib) vs NR (durvalumab) vs 7 months (placebo) • mPFS (pMMR): 15 months (durvalumab + olaparib) vs 9.9 months (durvalumab) vs 9.7 months (placebo) • mPFS (overall): 15.1 months (durvalumab + olaparib) vs 10.2 months (durvalumab) vs 9.6 months (placebo) • mOS: NR (durvalumab + olaparib) vs NR (durvalumab) vs 25.9 months (placebo)

Durvalumab is FDA approved in combination with C/T followed by maintenance durvalumab due to PFS benefit in patients with dMMR advanced or recurrent endometrial cancer.

Westin SN et al; DUO-E Investigators. *J Clin Oncol*. 2024;42(3):283-299.

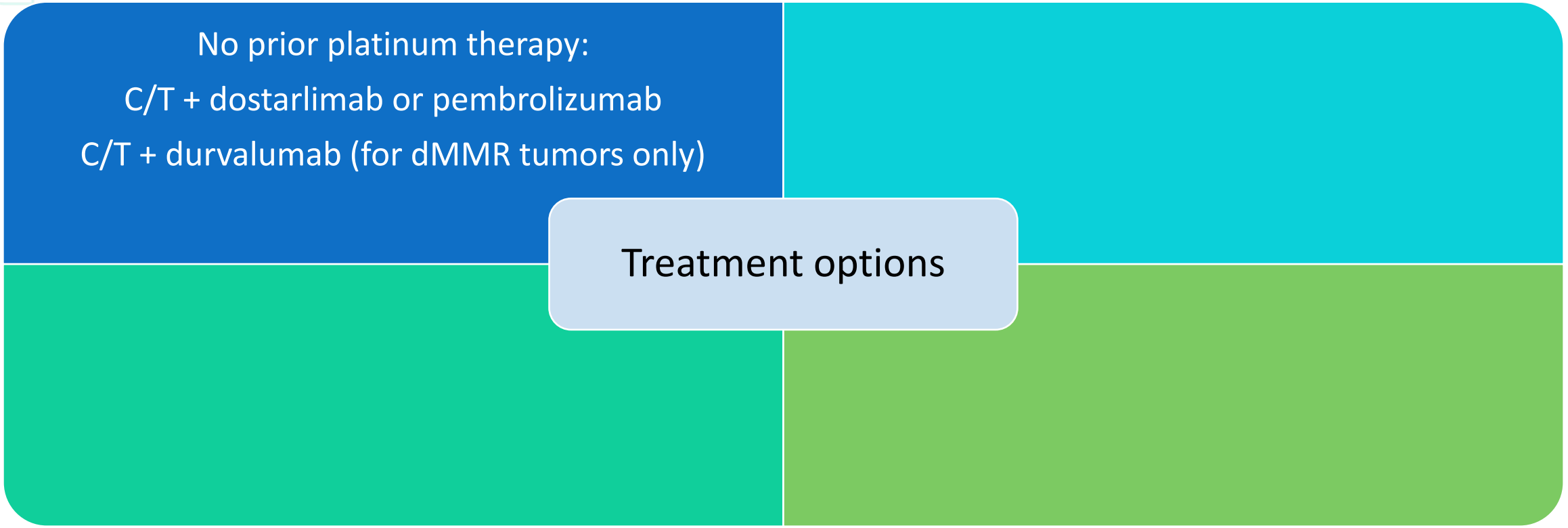
AtTEnd: Atezolizumab + Chemotherapy

Double-blind, randomized, phase 3 trial	
Population	• Advanced or recurrent endometrial cancer • Known MMR status (stratified by status)
Intervention	• C/T + placebo (n = 189) • C/T + atezolizumab x 6-8 cycles followed by maintenance (n = 362)
Outcomes	• mPFS (dMMR): not estimable (atezolizumab) vs 6.9 months (placebo) • mPFS (overall population): 10.1 months (atezolizumab) vs 8.9 months (placebo) • mOS (overall population): 38.7 months (atezolizumab) vs 30.2 months (placebo)

Atezolizumab plus chemotherapy increased PFS in patients with advanced or recurrent endometrial carcinoma, particularly in those with dMMR carcinomas.

Colombo N et al; AtTEnd study group. *Lancet Oncol*. 2024;25(9):1135-1146.

Navigating Immune Checkpoint Inhibitor Treatment Selection



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KEYNOTE-158: Pembrolizumab

Phase 2, multi-cohort, open label, non-randomized	
Population	• Patients with advanced non-colorectal **MSI-H/dMMR** tumors • Progressed on or following prior treatment with a platinum-containing regimen in any setting including neoadjuvant or adjuvant therapy • N = 233 (n = 49 for endometrial cancer)
Intervention	Pembrolizumab 200 mg IV every 3 weeks for 2 years or until disease progression or unacceptable toxicity
Outcomes	• ORR: 48% (95% CI, 37-60) • Median PFS: 13.1 months (95% CI, 4.3-34.4) • Median OS: NR (95% CI, 27.2-NR)

Pembrolizumab monotherapy demonstrated a durable clinical benefit in patients with advanced MSI-H/dMMR endometrial cancer.

IV, intravenous; ORR, objective response rate.

Marabelle A et al. *J Clin Oncol*. 2020;38(1):1-10; Musacchio L et al. *J Clin Med*. 2020;9(6):1721; O'Malley D et al. *J Clin Oncol*. 2022;40(7):752-761.

GARNET: Dostarlimab

Phase 1, non-randomized	
Population	• Patients with dMMR/MSI-H recurrent endometrial cancer • N = 245 (n = 103 in dMMR; n = 142 in pMMR)
Intervention	Dostarlimab 500 mg IV every 3 weeks for 4 doses, then 1000 mg every 6 weeks until disease progression or treatment discontinuation

Outcomes	• ORR: 45.5% in dMMR vs 13.9% in pMMR
	  • dMMR: 7 CRs, 43 PRs
	  • pMMR: 3 CRs, 17 PRs
	• Median DOR: NR in both groups
	• Median PFS: 8.1 months

Dostarlimab is associated with clinically meaningful and durable antitumor activity in patients with dMMR recurrent endometrial cancer.

CR, complete response; DOR, duration of response; PR, partial response.

Oaknin A et al. *JAMA Oncol*. 2020;6(11):1766-1772; Oaknin A et al. Interim analysis of the immune-related endpoints of the mismatch repair deficient (dMMR) and proficient (MMRp) endometrial cancer cohorts from the GARNET Study. SGO 2021 Annual Meeting; March 19-25, 2021; Virtual.

NCI-MATCH (EAY131) – Z1D subprotocol: Nivolumab

Phase 2, open label, single arm	
Population	• Relapsed or refractory tumors with **dMMR** • N = 42 (13 patients had endometrial adenocarcinoma)
Intervention	Nivolumab 3 mg/kg IV every 2 weeks x 8 doses followed by 480 mg IV every 4 weeks
Outcomes	• Overall population ORR: 36% • 2 patients with endometrial adenocarcinoma achieved CR • 18-month PFS: 31.4% • Median OS: 17.3 months

Nivolumab demonstrated promising results as monotherapy in the treatment of a variety of tumors with dMMR.

Azad NS et al. *J Clin Oncol*. 2019;38(3):214-222.

Avelumab

Phase 2, single arm, 2 cohort	
Population	2 cohorts (N = 33): 1. Patients with dMMR or *POLE*mut 2. pMMR
Intervention	Avelumab 10 mg/kg IV every 2 weeks until progression or unacceptable toxicity
Outcomes	• ORR (dMMR): 26.7% • ORR (pMMR/non-*POLE*): 6.25% • 6-month PFS (dMMR): 40% • 6-month PFS (pMMR/non-*POLE*): 1 of 16 patients (6.25%)

Avelumab demonstrated activity in dMMR endometrial cancer.
Activity of avelumab in pMMR patients with endometrial cancer was low.

Konstantinopoulos PA et al. *J Clin Oncol*. 2019;37(30):2786-2794.

Immunotherapy Monotherapy Efficacy in Biomarker-Selected Endometrial Cancer

- MSI-H or dMMR advanced endometrial cancers

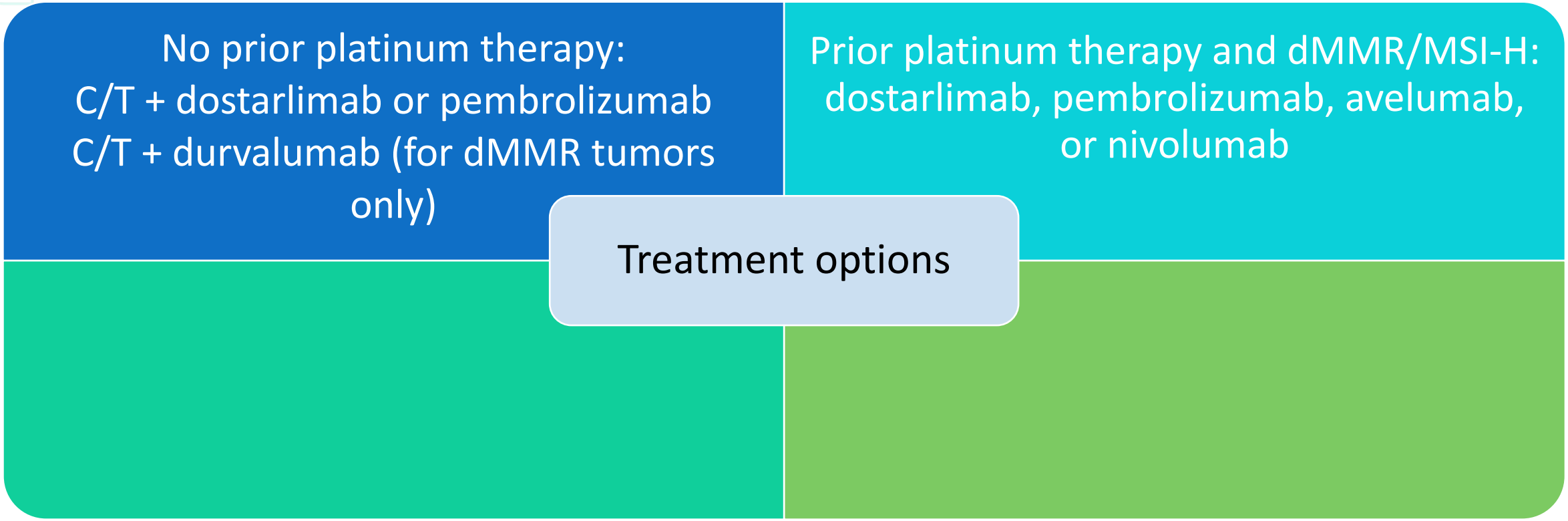
PD-1 inhibitor	Response rate
Dostarlimab	45%
Nivolumab	36%
Pembrolizumab	57%

PD-L1 inhibitor	Response rate
Avelumab	27%
Durvalumab	43%

- pMMR advanced endometrial cancers
  - Single-agent immune checkpoint inhibitor (ICI) efficacy response rates range from 3%-23%

Green AK et al. *Am Soc Clin Oncol Educ Book*. 2020;40:238-244; Azad NS et al. *J Clin Oncol*. 2019;38(3):214-222.

Navigating Immune Checkpoint Inhibitor Treatment Selection



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KEYNOTE-146/Study 111: Pembrolizumab + Lenvatinib

Phase 2, open label, single arm	
Population	• Advanced or recurrent endometrial cancer • N = 108 (MSS/pMMR, n = 94; MSI-H/dMMR, n = 11; unknown, n = 3)
Intervention	Lenvatinib 20 mg orally daily + 200 mg pembrolizumab IV every 3 weeks for a maximum of 35 pembrolizumab treatments

Outcomes	• ORR: 38% at week 24 (10 CRs, 26 PRs)
	  • ORR of **MSS/pMMR**: 36%
	  • ORR of **MSI-H/dMMR**: 64%
	• Median PFS: 7.5 months
	• 25 patients (69% of responders) had response durations ≥6 months
	• Median DOR: 21.2 months
	• Median OS: 16.7 months

Overall responses with lenvatinib + pembrolizumab were observed regardless of MSI status, PD-L1 status, or histology.

Makker V et al. *J Clin Oncol*. 2020;38(26):2981-2992.

KEYNOTE-775/Study 309: Pembrolizumab + Lenvatinib

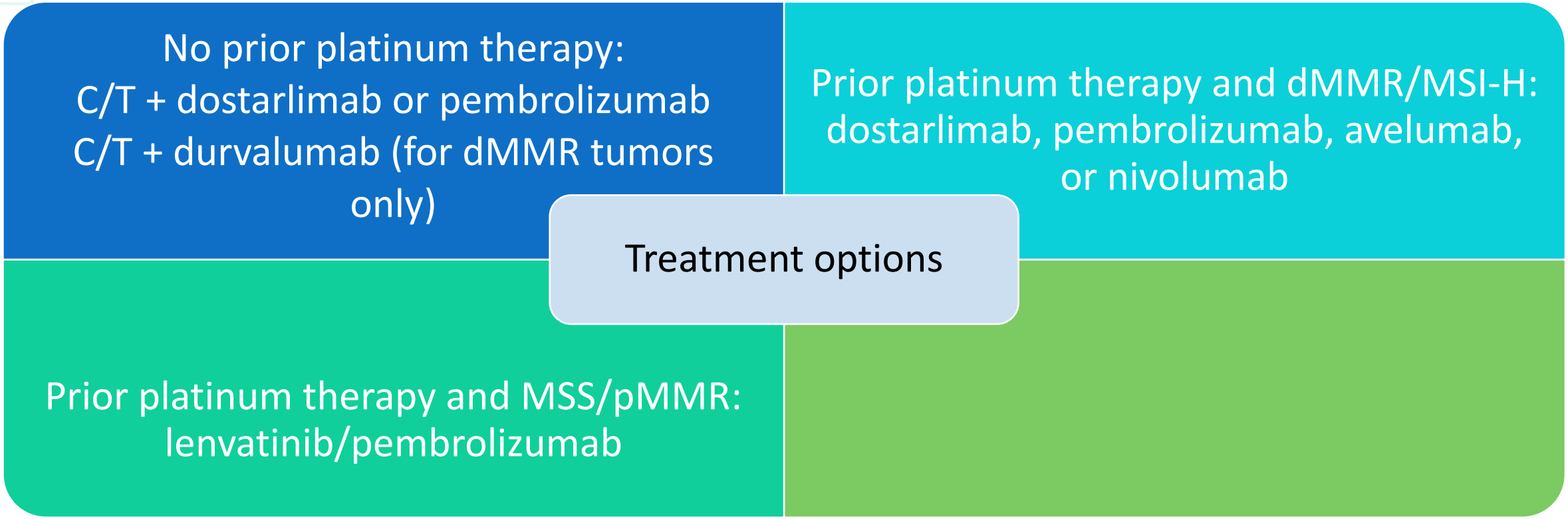
Phase 3, randomized, open label	
Population	• Patients who progressed after 1 prior platinum-based therapy • N = 827 (n = 697 in pMMR; n = 130 in dMMR)
Intervention	• Lenvatinib 20 mg orally daily + pembrolizumab 200 mg IV every 3 weeks for maximum 2 years vs treatment of physician's choice • Treatment of physician's choice: doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly (3 weeks on, 1 week off)

Outcomes	• Overall population mPFS: 6.7 vs 3.8 months
	  • pMMR population mPFS: 6.6 vs 3.8 months
	• Overall population mOS: 18 vs 12.2 months
	  • pMMR population mOS: 17.4 vs 12 months
	• Overall ORR: 31.9% vs 14.7%
	  • pMMR population ORR: 30.3% vs 15.1%

Pembrolizumab + lenvatinib is FDA approved for patients with advanced endometrial with pMMR/MSS in the second line setting after 1 prior platinum-based therapy.

Makker V et al. *Int J Gynecol Cancer*. 2021;31(suppl 4):785; Makker V et al. *J Clin Oncol*. 2023;41(16):2904-2910.

Navigating Immune Checkpoint Inhibitor Treatment Selection



NCCN. Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2024.

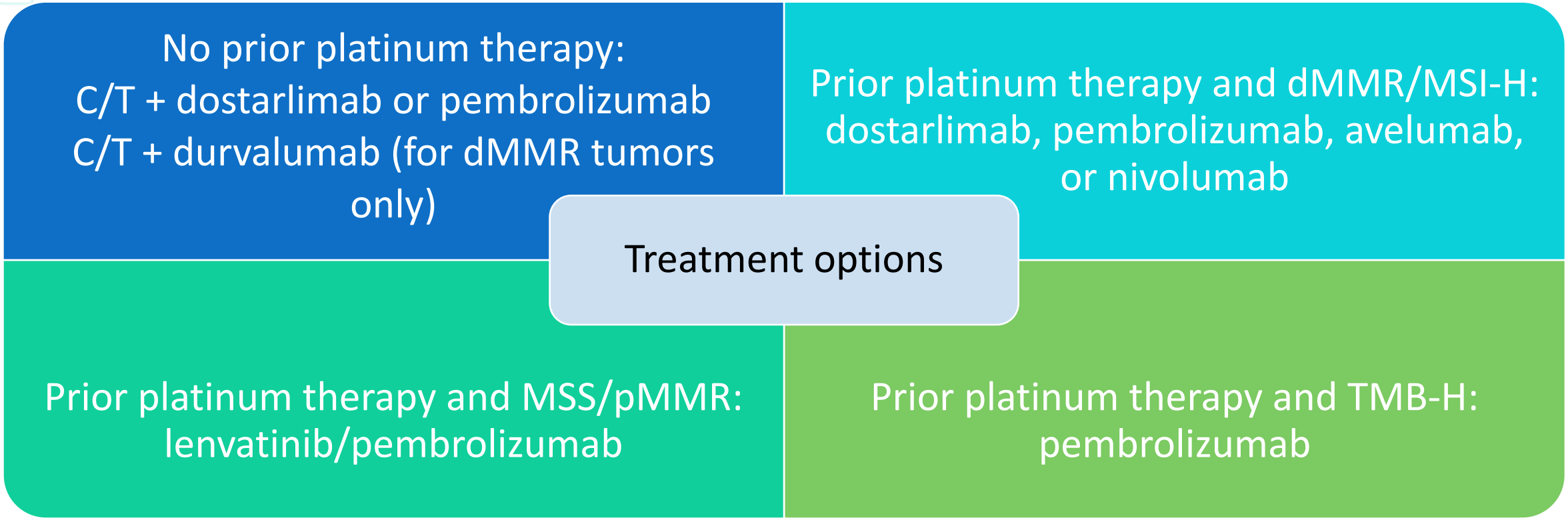
KEYNOTE-158: Pembrolizumab for TMB-H

Phase 2, multi-cohort, open label, non-randomized	
Population	• Patients with advanced non-colorectal MSI-H/dMMR tumors • Progressed on or following prior treatment with a platinum-containing regimen in any setting including neoadjuvant or adjuvant therapy
Intervention	Pembrolizumab 200 mg IV every 3 weeks for 2 years or until disease progression or unacceptable toxicity
Outcomes	• 790 patients were evaluable for TMB • 102 (13%) had TMB-H • ORR (TMB-H): 29% • ORR (non-TMB-H): 6%

TMB-H status identifies a subgroup of patients who could have a robust tumor response to pembrolizumab monotherapy.

Marabelle A et al. *Lancet Oncol*. 2020;21(10):1353-1365.

Navigating Immune Checkpoint Inhibitor Treatment Selection



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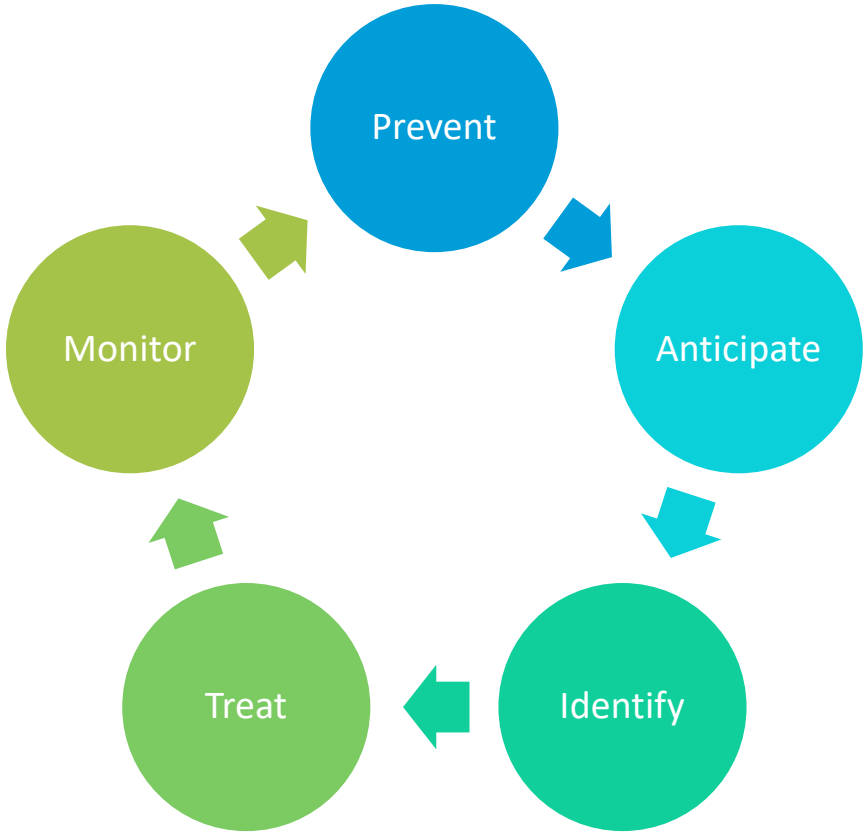
Toxicity Management

The Pharmacist's Role in Managing irAEs



- Higher odds of treatment discontinuation due to irAEs in patients who did not receive dedicated pharmacist follow-up

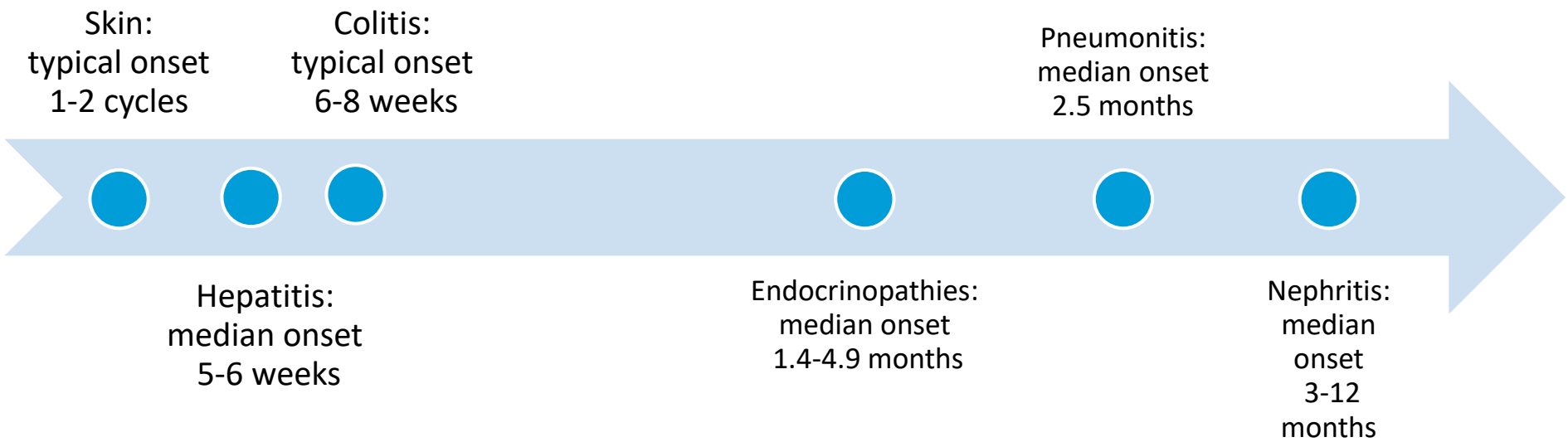
Medina P et al. *J Pharm Practice*. 2020;33(3):338-349; Myers G et al. *J Oncol Pharm Pract*. 2023;29(1):145-154.

Educating Patients About Treatment

- Educate patients and caregivers on irAE signs and symptoms
  - Most irAEs can be managed, particularly when they are identified early
- Stress the need to complete prespecified laboratory tests
  - General blood work (complete blood count and complete metabolic panel) should be completed every 4 weeks during immunotherapy, then in 6-12 weeks or as indicated
- Ask patients to promptly report new symptoms or health changes
  - Even minor changes in how the patient feels may constitute an early sign of irAE onset

NCCN. Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities, version 1.2024.

Onset of irAEs

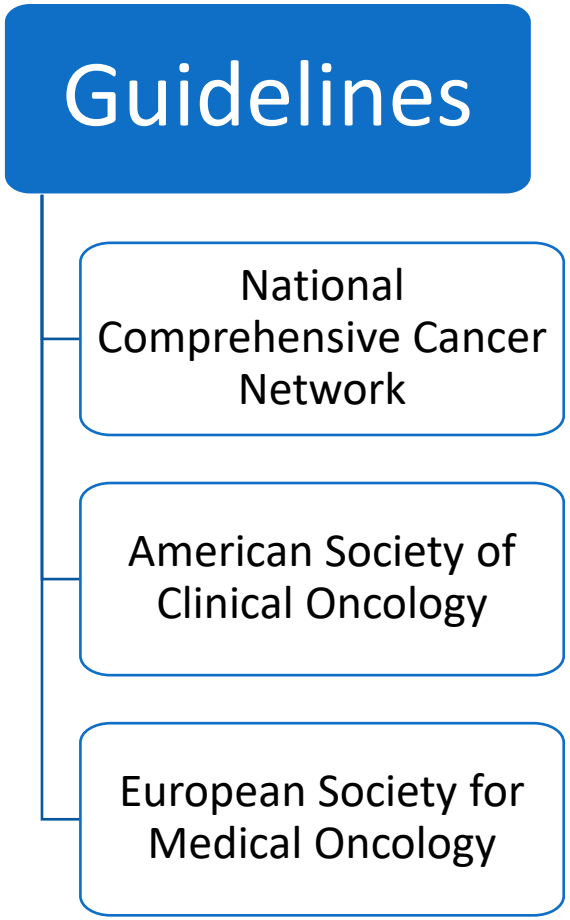


- irAEs can occur up to a year after treatment completion or discontinuation
- Considerations for combination therapy:
  - Chemotherapy: onset of AEs generally occurs earlier, and AEs are more dose dependent than ICIs
  - Consider overlapping AEs (eg, diarrhea, endocrine, skin, liver)

Medina P et al. *J Pharm Practice*. 2020;33(3):338-349; Puzanov I et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. *J Immunother Cancer.* 2017;5(1):95.

irAEs Management

- Provide counseling for prompt identification of moderate or severe irAEs
- General management strategies
  - Withhold treatment and do not resume until toxicity returns to grade ≤1
  - irAEs management options
    - Initiate corticosteroids
      - 0.5-2.0 mg/kg/day of prednisone equivalent
    - Infliximab
    - Mycophenolate mofetil
    - Cyclophosphamide
  - Supportive care and symptom management



NCCN. Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities, version 1.2024; Schneider B et al. *J Clin Oncol*. 2021;39(36):4073-4126.

irAEs With ICI

Trial	Treatment arm	Thyroid changes	Skin reaction	Hepatic toxicity	Other irAEs (all grades)
RUBY	Carboplatin + paclitaxel + dostarlimab, followed by dostarlimab maintenance	11.2%	6.6%	5.8%	Arthralgia 5.8%
NRG-GY018	Carboplatin + paclitaxel + pembrolizumab, followed by pembrolizumab maintenance	• dMMR: 22% • pMMR: 19.2%	• dMMR: 6.4% • pMMR: 20.7%	• dMMR: 0.9% • pMMR: 0%	• Colitis: 6.4% in dMMR; 1.4% in pMMR • Pneumonitis: 2.8% in dMMR; 0.7% in pMMR
DUO-E	Carboplatin + paclitaxel + durvalumab, followed by dostarlimab maintenance ± olaparib or placebo maintenance	13.5%	6.3%	2.1%	• Colitis: 1.7% • Pneumonitis: 2.1%

Mirza MR et al; RUBY Investigators. *N Engl J Med*. 2023;388(23):2145-2158; Eskander RN et al. *N Engl J Med*. 2023;388(23):2159-2170; Westin SN et al; DUO-E Investigators. *J Clin Oncol*. 2024;42(3):283-299; Imfinzi. Prescribing information. AstraZenca; August 2024.

KEYNOTE-146/Study 111: Pembrolizumab + Lenvatinib Safety Data

Grade 3 or 4 treatment-related AEs

- 66.9% of patients

Drug discontinuation due to toxicity

- 22 of 124 patients (nearly 1 in 5)
- Of the 22, 19 discontinued because of lenvatinib toxicity

Treatment interruptions

- 70.2% of patients

Lenvatinib dose reductions

- 62.9% of patients

- Despite a starting dosage of lenvatinib of 20 mg orally daily, the mean dose intensity was 14.4 mg/day, and only 8.9% of patients remained on lenvatinib for ≥6 months without any dose reductions

Makker V et al. *J Clin Oncol*. 2020;38(26):2981-2992.

Pembrolizumab + Lenvatinib: Real-World Use

- Median time to first onset of AE was within first 10 weeks
- Grade ≥3 fatigue, hypertension, and nausea occurred in ≥5%
  - Overall hypothyroidism incidence: 51%
- Toxicities managed with supportive medications, dose interruptions, and/or lenvatinib dose reductions
- Due to the multikinase mechanism of action, most patients do not tolerate full-dose lenvatinib
  - Can consider starting at lower dose for patients with baseline comorbidities and/or history of overlapping toxicities

Makker V et al. *Oncologist*. 2021;26(9):e1599-e1608.

Pembrolizumab + Lenvatinib: Real-World Use

Starting dosage of lenvatinib

- 16 patients (22.9%) started 20 mg daily (recommended dosage)
- 54 patients (77.1%) started at a reduced dosage

Overall median number of treatment cycles: 5 (range 1-15)

- Median numbers of treatment cycles for the recommended dose: 4.5 (range 1-12)
- Median numbers of treatment cycles for reduced dose cohorts: 6 (range 1-15)

Hospitalization

- 54.3% experienced at least 1 hospitalization while on treatment
- 32.9% due to treatment-related toxicity

Rates of treatment discontinuation due to toxicity

38.6%

Lenvatinib dose interruption

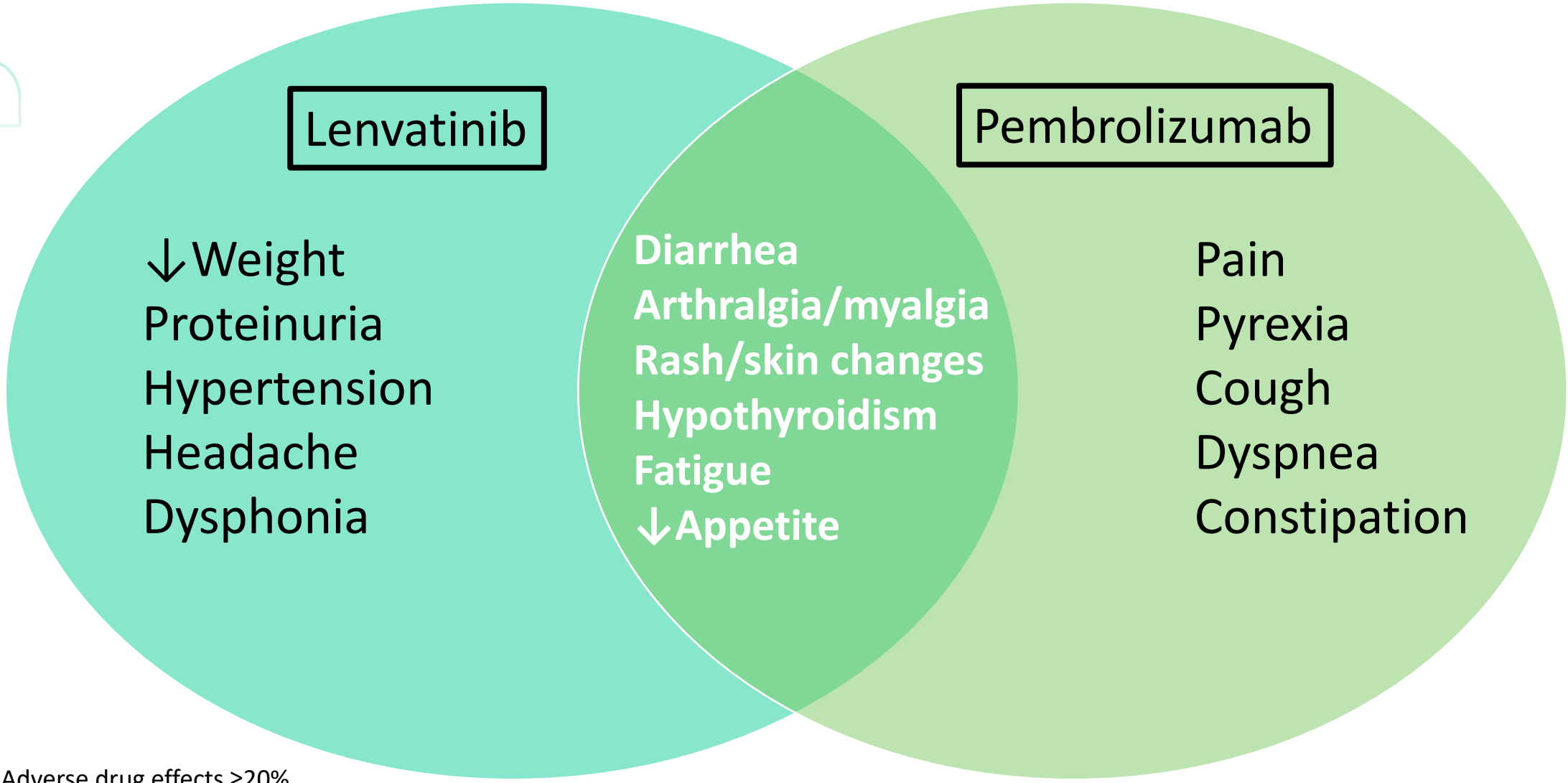
82.9%

Recommended dose cohort vs reduced dose cohort

- Dose reductions (1.1 vs 0.4)
- Indications for lenvatinib dose reductions
  - Intolerable fatigue (37.5% vs 14.8%)
  - Anorexia (25.0% vs 5.6%)
  - Gastrointestinal toxicity (43.8% vs 11.1%)
  - Hematologic toxicity (18.8% vs 1.9%)

How J et al. *Gynecol Oncol*. 2021;162(1):24-31.

Overlapping AE Combination Therapy



*Adverse drug effects ≥20%.

Lenvima. Prescribing information. Eisai Inc; June 2024; Keytruda. Prescribing information. Merck Sharp & Dohme LLC; August 2024.

Conclusion

- Molecular profiling of this disease has completely transformed the therapeutic approach for advanced endometrial cancer
- C/T + immunotherapy represents the new standard of care for newly diagnosed advanced or recurrent endometrial cancer
- ICIs and targeted therapies have an important place in the treatment of advanced endometrial cancer
- Prompt identification and management of endocrine effects from immunotherapy can minimize impact on patient experience and mortality

Additional Resources

Resource	Website
NCCN Guidelines – Uterine Neoplasms	https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473
NCCN Guidelines – Management of Immunotherapy-Related Toxicities	https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1486
ASCO irAE from ICI Guidelines	https://ascopubs.org/doi/10.1200/JCO.21.01440

Posttest Questions

Posttest Question 1

Based on the molecular profile listed below, which patient with endometrial cancer would be most likely to respond to immunotherapy?

A. *CDKN2A* mutation
B. Microsatellite instability-high
C. Programmed death-ligand 1 positive
D. Proficient mismatch repair

Posttest Question 2

BB is a 65-year-old woman with a history of endometrial cancer (stage II, grade 2) who received primary therapy with surgery, radiation therapy, and 6 cycles of adjuvant paclitaxel + carboplatin. She now has recurrent disease 2 years after her initial diagnosis. Her tumor is HER2-negative, microsatellite instability-high, mismatch repair deficient (MSI-H/dMMR). What would be the most appropriate second-line option for treatment?

A. Dostarlimab
B. Docetaxel + bevacizumab
C. Lenvatinib + pembrolizumab
D. Paclitaxel + carboplatin + trastuzumab

Posttest Question 3

Which are common overlapping toxicities of immune checkpoint inhibitor therapy and targeted agents?

A. Diarrhea, fatigue, rash
B. Myalgia, electrocardiogram abnormalities, dyspnea
C. Fatigue, hypertension, headache
D. Rash, cough, proteinuria

Posttest Question 4

After participating in this activity, how confident are you with the management of targeted therapies for endometrial cancer?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Thank you!