CHALLENGING CASES

Gynecologic Cancer

Prepared by: Cornerstone Specialty Network

Challenging Cases conducted: September 24, September 30, October 7, 2025

Participating Practices

Challenging Cases in…

Gynecologic Cancer

Program conducted:

September–October 2025

Note: Aggregated results and high-level summary based on 3 practices (22 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

- **Northwest Georgia Oncology Centers (n=9)** **September 24, 2025**
- **Singing River Cancer Center (n=6)** **September 30, 2025**
- **Ironwood Cancer & Research Centers (n=7)** **October 7, 2025**

Overall Program Impact and Future Considerations

Endometrial cancer frontline treatment of chemo-immunotherapy with IO choice guided by familiarity and perioperative considerations; HER2 IHC and NGS testing directs targeted therapy use and sequencing with a preference for T-DXd when applicable; selective use of hormonal therapies and CDK4/6 inhibitors, while chemotherapy re-treatment is based on platinum sensitivity and relapse timing, highlighting a need for streamlined biomarker testing and educational support to optimize therapy decisions in community practice

- **Front-line strategy:** Chemo-immunotherapy is widely used, with clinicians noting similar efficacy across regimens; choice of checkpoint inhibitor is often driven by familiarity (pembrolizumab often preferred) rather than efficacy, and perioperative considerations influence regimen selection
- **HER2 assessment:** HER2 testing is routinely done at diagnosis and progression, with tissue IHC and liquid biopsy NGS; repeat testing guides utilization of HER2-targeted therapies, particularly T-DXd in later-line (2L+) metastatic disease; NCCN Guidelines can support treatment decisions for use of T-DXd in HER2 IHC3+ or IHC 2+ tumors
- **Targeted therapy choice:** HER2-directed therapy is generally deferred to second or later lines, with hormonal therapy reserved for select ER/PR-positive, low-grade tumors; very limited, selective use of CDK4/6 inhibitors considered in ER-positive relapsed disease based on NCCN Guidelines and with no other options
- **Biomarker-driven sequencing:** MSI/MMR status guides early immunotherapy use, with MSI-H/MMR-deficient tumors prioritized for checkpoint inhibitors and HER2-positive, MMR-proficient tumors prioritized for HER2-targeted therapy; broad NGS panels help identify additional actionable mutations
- **Chemotherapy sequencing:** Platinum sensitivity and relapse interval inform re-treatment decisions, with chemotherapy reused after >6 months but alternative or targeted therapies preferred for earl relapse
- ***Recommended actions:*** *Educational initiatives and clinical discussions through CSN Challenging Cases to increase confidence in testing, prescribing, and sequencing behaviors in endometrial cancer among community physicians*

Challenging Cases in… Gynecologic Cancer

Endometrial cancer

Patient case: untreated metastatic disease

- *What is the optimal first line therapy? Second line therapy? Third line therapy?*
- *Challenges with biopsy and testing?*
- *Sequencing considerations to provide the best outcomes for patients?*

Audience Discussion

Do you regularly treat gynecologic patients in your practice?

Does your practice have providers that specialize in gynecological cancer?

How many endometrial cancer patients are you actively treating?

Patient History

59-year-old female, diagnosed May 2022

Post-menopausal

4-month history of unexplained bleeding

Tender, enlarged uterus

Otherwise, healthy

Diagnosis

Endometrial Biopsy and CT scan: confirmation

PET CT: lung mets and peritoneal mets

ER/PR+

dMMR/MSI positive

No *POLE* mutation

TP53 wild type

Stage IV Endometrial carcinosarcoma (de novo)

What first-line treatment do you recommend?

Is this representative of your typical patient?

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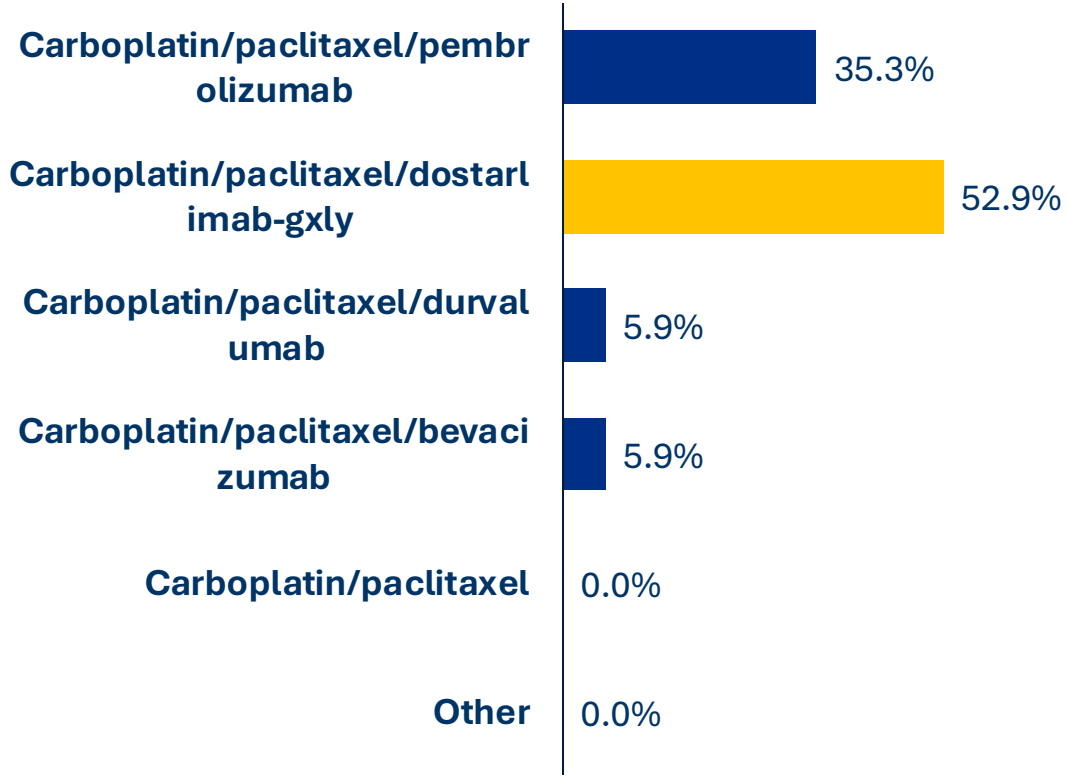
ARS Results from HCP Participants

What first-line systemic treatment do you recommend?



Answered: 17

FDA Approvals

June 14, 2024: **Durvalumab** with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR)

June 17, 2024: **Pembrolizumab** in combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma (EC).

August 1, 2024: **Dostarlimab-gxly** in combination with carboplatin and paclitaxel, followed by single-agent dostarlimab-gxly, for adult patients with primary advanced or recurrent endometrial cancer (EC)

NCCN Guidelines 1L setting
Version 3.2025 – March 7, 2025

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimen • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2] **Other Recommended Regimens (if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[3] (category 2B) • Gemcitabine[4] (category 2B) • Paclitaxel[5,6] (category 2B)	**Preferred Regimens** • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,7,8] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9] • Carboplatin/paclitaxel/durvalumab (for stage III–IV dMMR tumors only) (category 1)[c,d,f,10] • Carboplatin/paclitaxel/trastuzumab (for stage III–IV HER2-positive uterine serous carcinoma or carcinosarcoma)[d,g,11] • Carboplatin/paclitaxel/bevacizumab (stage III–IV with measurable disease)[d,12,13] • Carboplatin/paclitaxel[14]

When do you utilize chemoradiation therapy over IO systemic therapy combinations?

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] For stage III or IVA with measurable disease post surgery or stage IVB with or without measurable disease. For patients not meeting the eligibility criteria for NRG-GY018, carboplatin/paclitaxel + pembrolizumab should be considered for stage III–IV dMMR tumors (Van Gorp T, et al. Ann Oncol. Published online August 23, 2024).
[c] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[e] For adult patients with primary advanced endometrial carcinoma: stage IIIA, IIIB, or IIIC1 with measurable disease post surgery, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease, and stage IIIC2 or stage IV regardless of the presence of measurable disease.
[f] For stage III with measurable disease post surgery and stage IV with or without measurable disease.
[g] For patients who have not received prior trastuzumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

Comparison of IO therapy in the front-line metastatic setting

	RUBY JEMPERLI (dostarlimab-gxly)		KEYNOTE-868/NRG GY018 KEYTRUDA (pembrolizumab)		DUO-E IMFINZI (durvalumab)	
NCCN Guidelines	Preferred, category 1 (for stage III–IV tumors)		Preferred, category 1 (for stage III–IV tumors, **except for carcinosarcoma**)		Preferred, category 1 (for stage III–IV dMMR tumors only)	
Study Design	Dostarlimab + Chemotherapy, followed by dostarlimab	Placebo + Chemotherapy, followed by placebo	Pembrolizumab + Chemotherapy, followed by pembrolizumab	Placebo + Chemotherapy, followed by placebo	Durvalumab + chemotherapy, followed by durvalumab	Placebo + Chemotherapy, followed by placebo
Overall pt population	N=494		N=810		N=718	
dMMR/MSI-H	n=60	n=62	n=110	n=112	n=46	n=49
Median PFS	30.3 (11.8 – NE)	7.7 (5.6 – 9.7)	NR (30.7 – NR)	6.5 (6.4 – 8.7)	NR (NR – NR)	7 .0 (6.7 – 14.8)
PFS rate, %	HR: **0.29** *P<0.0001*		HR: **0.30** *P<0.001*		67.9% HR: **0.42** *P<0.001* 31.7%	
	Second interim analysis, 24 mos: *Immature*		Interim analysis: *Immature*		At 18 mos: *Immature*	
Median OS	NR (NR – NR)	31.4 (18.7 – NR) (HR, **0.32**; 95% CI, 0.17-0.63; P = 0.0002)	NR	NR (HR, **0.55**; 95% CI, 0.25-1.19; P = 0.0617)	NR (NR – NR)	23.7 (16.9 – NR)
OS rate, %	82.8%	57.5%	---	---	86.1%	65.8%
ORR	74%	62%	82%	71%	71.4%	40.5%
CR	26%	11%			28.6%	9.5%

ESMO Journals 2024, 35 8 p728-738
RUBY Efficacy & Study Design | JEMPERLI (dostarlimab-gxly) (jemperlihcp.com)

N Engl J Med 2023; 388:2159-2170
Nat Med . 2025 Mar 5. doi: 10.1038/s41591-025-03566-1. Online

https://www.imfinzihcp.com/dmmr-endometrial-cancer

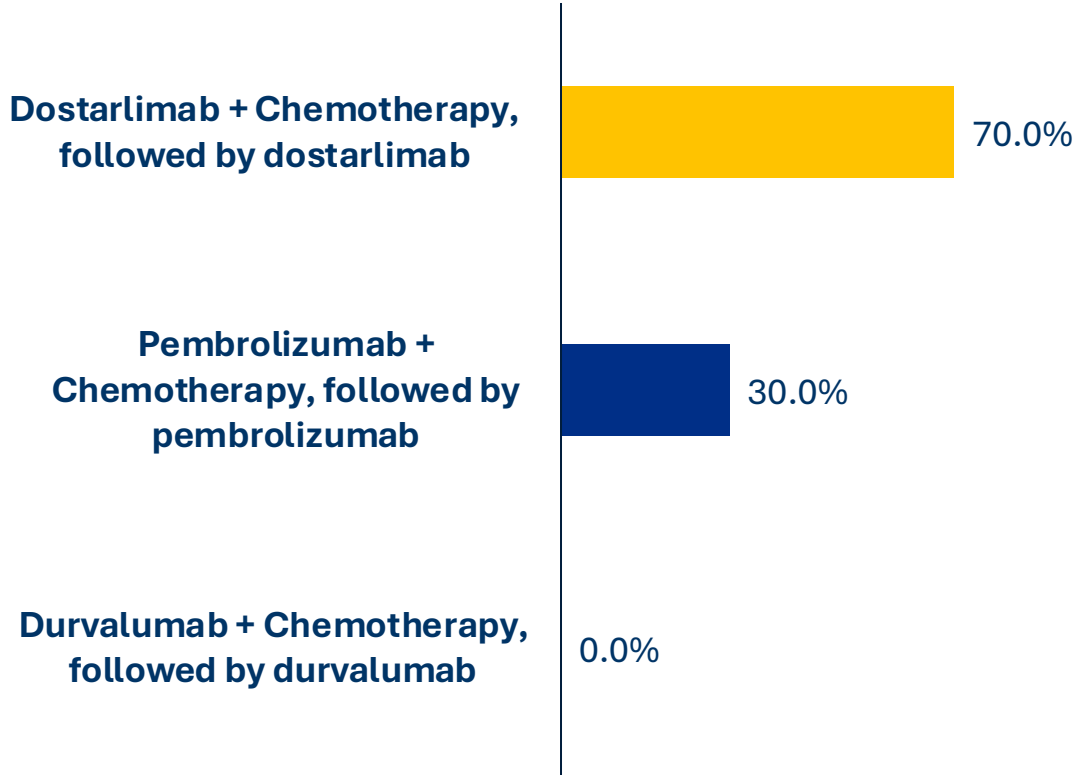
Highlights of Prescribing Information

How do adverse events influence your 1L treatment decision?

	JEMPERLI (dostarlimab-gxly)	KEYTRUDA (pembrolizumab)	IMFINZI (durvalumab)
Black box warnings	**None**	**None**	**None**
Contraindications	**None**	**None**	**None**
Warnings And Precautions	• Immune-Mediated Adverse Reactions • Infusion-related reactions • Complications of allogeneic HSCT • Embryo-Fetal toxicity	• Immune-Mediated Adverse Reactions • Infusion-related reactions • Complications of allogeneic HSCT • Embryo-Fetal toxicity	• Immune-Mediated Adverse Reactions • Infusion-Related Reactions • Complications of Allogeneic HSCT • Embryo-Fetal Toxicity
Adverse reactions	Most common adverse reactions (≥20) in combination with carboplatin and paclitaxel in patients with EC are: decreased hemoglobin, increased creatinine, peripheral neuropathy, decreased white blood cell count, fatigue, nausea, alopecia, decreased platelets, increased glucose, decreased lymphocytes, decreased magnesium, decreased neutrophils, increased aspartate aminotransferase (AST), arthralgia, rash, constipation, diarrhea, increased alanine aminotransferase (ALT), decreased potassium, decreased albumin, decreased sodium, increased alkaline phosphatase, abdominal pain, dyspnea, decreased appetite, increased amylase, decreased phosphate, urinary tract infection, and vomiting.	*Most common adverse reactions in combination with chemotherapy (reported in ≥20% of patients):* fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, and hypothyroidism	*Most common adverse reactions in combination with chemotherapy (≥ 20%) of patients with endometrial cancer):* peripheral neuropathy, musculoskeletal pain, nausea, alopecia, fatigue, abdominal pain, constipation, rash, decreased magnesium, increased ALT, increased AST, diarrhea, vomiting, cough, decreased potassium, dyspnea, headache, and increased alkaline phosphatase
Drug Interactions	---	---	---
Specific Populations	Lactation: Advise not to breastfeed.	Lactation: Advise not to breastfeed	Lactation: Advise not to breastfeed

ARS Results from HCP Participants

Based on the presented efficacy and safety data, what will be your preferred IO therapy with platinum chemotherapy in the 1L setting?



Answered: 20

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Does your treatment choice differ if 1L recurrent disease?

1L Preferred options for recurrent disease:

- Carboplatin/paclitaxel/pembrolizumab (*except for carcinosarcoma*) (category 1)
- Carboplatin/paclitaxel/dostarlimab-gxly (category 1)
- Carboplatin/paclitaxel/durvalumab (*for dMMR only*) (category 1)
- Carboplatin/paclitaxel/trastuzumab (*for HER2-positive uterine serous carcinoma or carcinosarcoma*)
- Carboplatin/paclitaxel (category 1 for carcinosarcoma)

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

RECURRENT DISEASE[h,i]

First-Line Therapy for Recurrent Disease[j]	Second-Line or Subsequent Therapy[j]
Preferred Regimens • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,k,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,k,9] • Carboplatin/paclitaxel/durvalumab (for dMMR only) (category 1)[c,d,k,10] • Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma or carcinosarcoma)[d,g,11] • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,14]	**Other Recommended Regimens** • Cisplatin/doxorubicin[20] • Cisplatin/doxorubicin/paclitaxel[p,20] • Cisplatin/gemcitabine[21] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[22] • Albumin-bound paclitaxel[q] • Topotecan • Bevacizumab[r,23] • Temsirolimus[24] • Cabozantinib • Lenvatinib[25] • Gemcitabine[26] • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[27] • Cisplatin/ifosfamide (for carcinosarcoma)
Other Recommended Regimens • Carboplatin/docetaxel[m] • Carboplatin/paclitaxel/bevacizumab[d,12,13]	
Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant) • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,15,16] • TMB-high (TMB-H) tumors[n] ▸ Pembrolizumab[c,17] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,18] ▸ Dostarlimab-gxly[c,19]	**Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,15,16] • TMB-H tumors[n] ▸ Pembrolizumab[c,17] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,18] ▸ Dostarlimab-gxly[c,19] ▸ Avelumab[c] ▸ Nivolumab[c,s,28] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[29] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[t,30]

Footnotes on ENDO-D 2A of 5

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References
ENDO-D
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Treatment

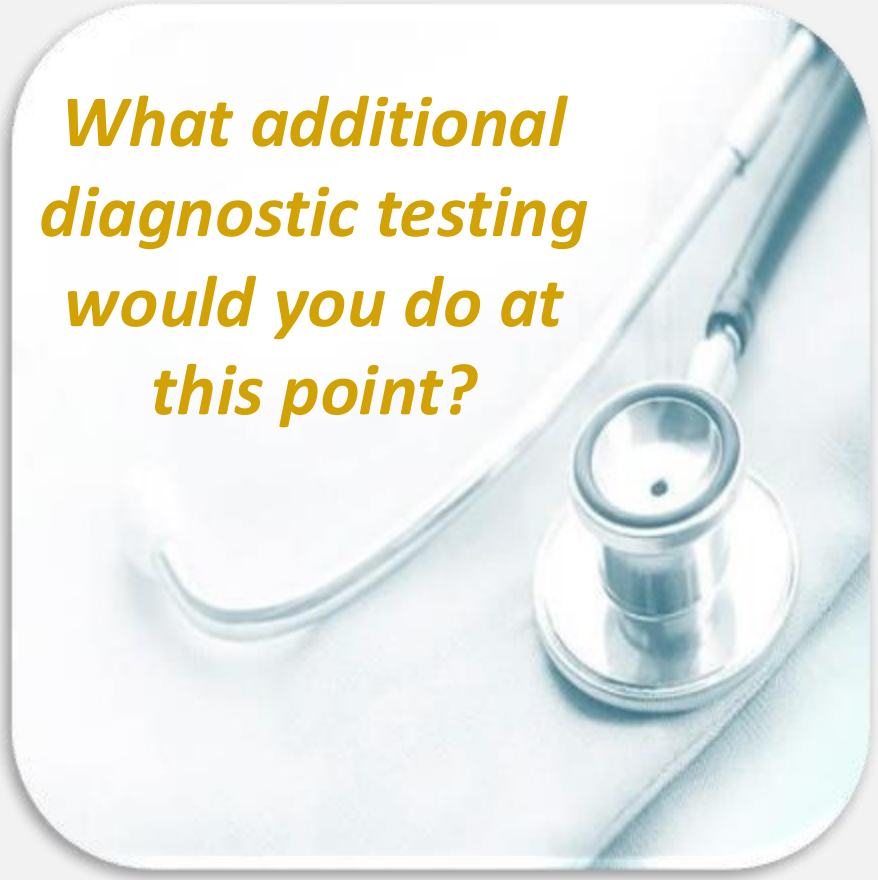
1L:

Patient receives Platinum-based chemotherapy and IO

Progression

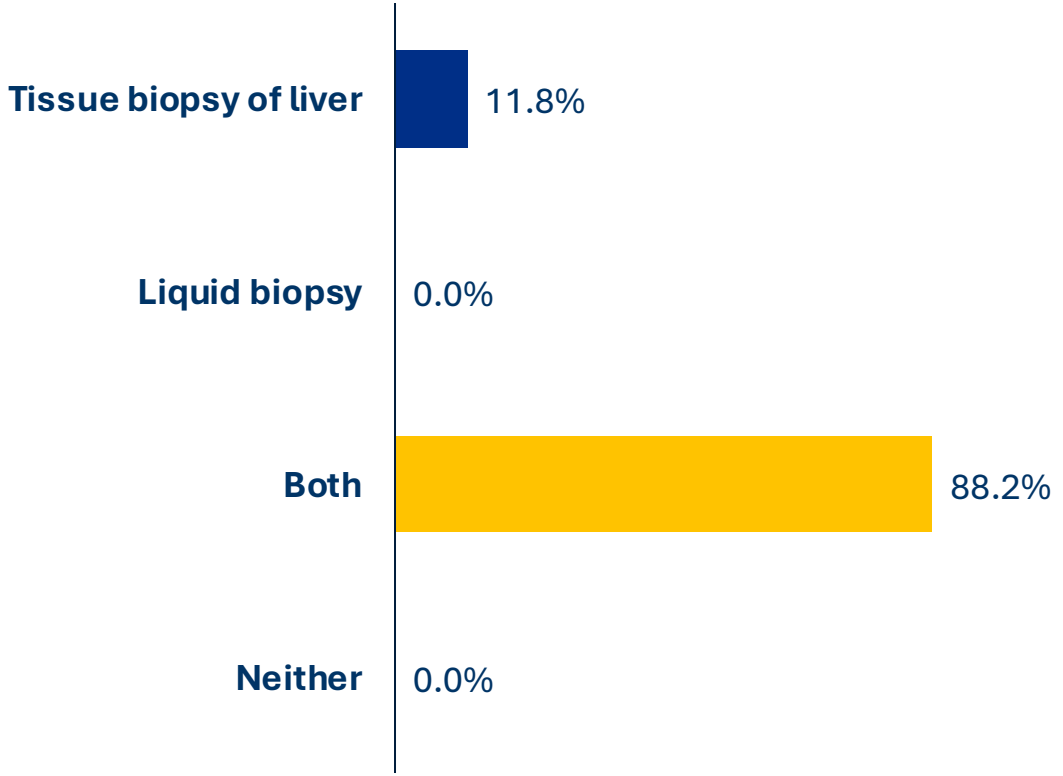
Patient has stable disease for 7 months, then progresses in liver

What additional diagnostic testing would you do at this point?



ARS Results from HCP Participants

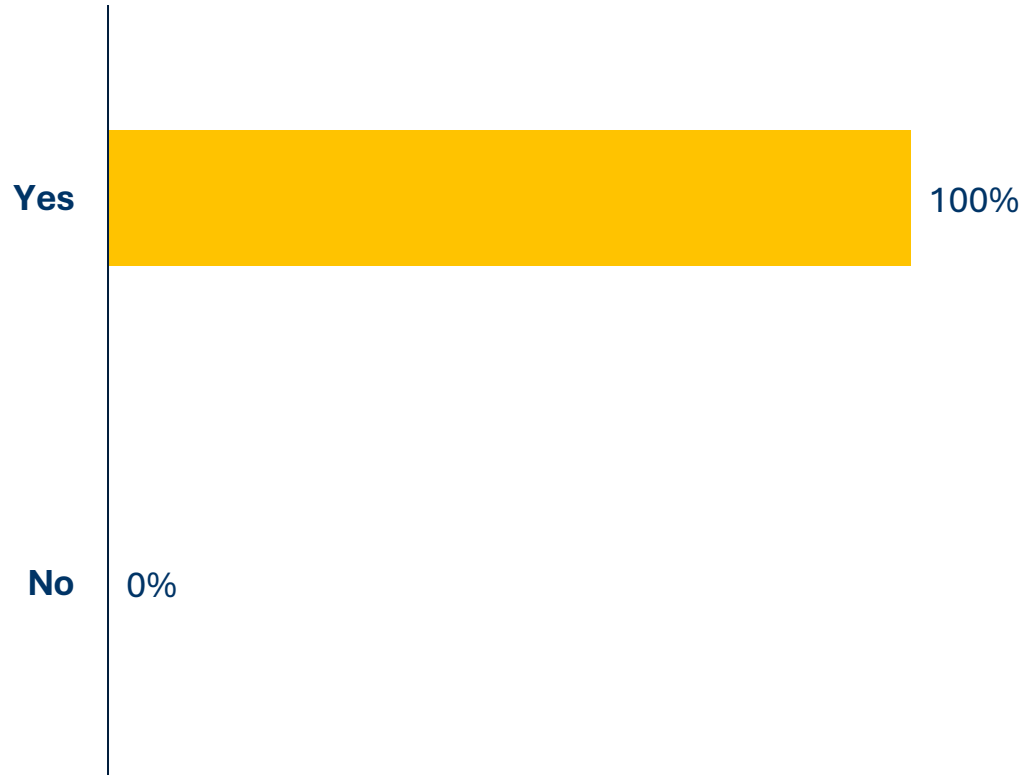
What additional diagnostic testing would you do at this point?



Answered: 17

ARS Results from HCP Participants

Are you currently testing or retesting for HER2?



Answered: 19

NCCN Guidelines

HER2 IHC testing (with or without reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for all p53 aberrant carcinomas regardless of histology

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PRINCIPLES OF MOLECULAR ANALYSIS

- Molecular analysis of endometrial carcinoma has identified four clinically significant molecular subgroups associated with differing clinical prognoses: *POLE* mutations, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), no specific molecular profile (NSMP), and p53 aberrant.[6,7]
- Retrospective analyses indicate that these four molecular subgroups may respond to therapy differently and therefore may require escalation or de-escalation of therapy compared to previous guidelines. Prospective randomized trials are ongoing to determine the role of a molecular profile–guided treatment strategy in the management of high-intermediate-risk and high-risk endometrial carcinomas.
- Ancillary studies for POLE mutations (pathogenic mutations in the exonuclease domain), immunohistochemical (IHC) staining for mismatch repair (MMR) or MSI testing, and p53 IHC are recommended to complement morphologic assessment regardless of histologic tumor type.[8] See Figure 1: Pathology and Genomics in Endometrial Carcinoma (ENDO-A 3 of 4).
- Comprehensive molecular profiling is strongly encouraged via an FDA-approved assay, or a validated test performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory, in the initial evaluation of uterine neoplasms.
- For tumors that are POLE-mutated, MSI-H, p53 aberrant, or NSMP, clinical trial enrollment is strongly encouraged.
- Molecular testing may be performed on the initial biopsy or D&C material or the final hysterectomy specimen.
- Evaluation for MMR status is commonly done using IHC. Molecular profiling via NGS panels or MSI PCR assay are acceptable alternatives.
  - MSI testing is recommended if IHC results are equivocal.
  - MLH1 loss should be further evaluated for promoter methylation to assess for an epigenetic mechanism.
  - Genetic counseling for any suspected germline mutation is strongly recommended.
  - For those who have a strong family history of endometrial and/or colorectal cancer, genetic counseling and testing are recommended regardless of MMR or MLH1 promoter methylation results [see Lynch Syndrome (LS-1) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric].
- HER2 IHC testing (with or without reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for all p53 aberrant carcinomas regardless of histology.[9-12]
- Estrogen receptor (ER) and progesterone receptor (PR) testing is recommended in the settings of stage III, stage IV, and recurrent disease.
- Consider *NTRK* gene fusion testing for metastatic or recurrent endometrial carcinoma.
- Consider tumor mutational burden (TMB) testing through an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory.[13]

Note: All recommendations are category 2A unless otherwise indicated.

References
Continued

Progression

Patient has stable disease for 7 months, then progresses in liver

Biopsy Results

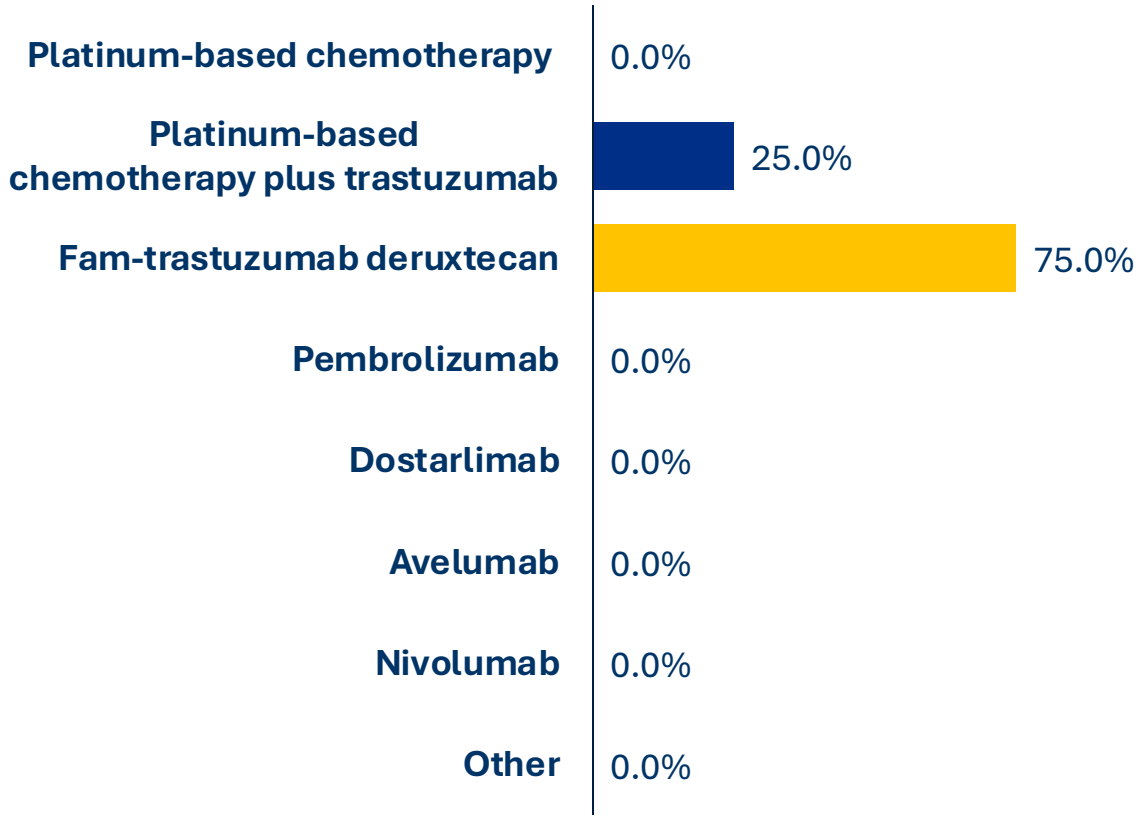
Liver biopsy:

HER2 positive (IHC 3+)

What is your choice of second line therapy?

ARS Results from HCP Participants

What is your choice of second line therapy?



Answered: 16

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1L Preferred options for recurrent disease:

- Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma or carcinosarcoma)

(Not FDA approved)

How does HER2 positivity impact your treatment decisions?

2L or subsequent therapy:

- HER2-positive tumors (IHC 3+ or 2+) Fam-trastuzumab deruxtecan-nxki

(FDA approved)

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

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Footnotes on ENDO-D 2A of 5

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

ENDO-D
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Phase II trial	Trastuzumab plus carboplatin-paclitaxel (C/P)	
NCCN Guidelines	• Primary or Adjuvant Therapy Preferred Regimen for stage III–IV **HER2-positive uterine serous carcinoma or carcinosarcoma** • **1L Preferred** option for recurrent disease	
Study Design	**C/P** for 6 cycles with **Trastuzumab** followed by maintenance Trastuzumab	C/P for 6 cycles
Overall pt population	61 patients, randomized 1:1	
Overall Median PFS	*median-follow-up of 25.9-months* 12.9 mos	8.0 mos
	HR 0.46, 90%CI 0.28–0.76; P=0.005	
mPFS Stage III – IV primary treatment	**17.7 mos**	9.3 mos
	HR 0.44, 90%CI 0.23–0.83; P=0.015; **n=41**	
mPFS with recurrent disease	9.2 mos	7.0 mos
	HR 0.12, 90%CI 0.03–0.48; P=0.004; **n=17**	
Overall Median OS	29.6 mos	24.4 mos
	HR 0.58; 90%CI 0.34–0.99; P=0.046	
References	J Clin Oncol . 2018 Jul 10;36(20):2044-2051 Clin Cancer Res. 2020 Jun 29;26(15):3928–3935	

Phase II trial	Fam-trastuzumab deruxtecan-nxki (DESTINY-PanTumor02)
NCCN Guidelines	• Endometrial Carcinoma: Useful in Certain Circumstances (Biomarker-directed therapy) for **HER2-positive tumors (IHC 3+ or 2+)**
Study Design	Single arm, open-label: **T-DXd** (5.4 mg/kg q3w) At least one prior therapy
Patient population	40 patients
ORR IHC 3+, n=16	56.3% (29.9 – 80.2)
mDOR IHC 3+, n=16	NE mos (5.8 – NE)
mPFS IHC 3+, n=16	NE mos (4.5 – NE)
mPFS IHC 2+, n=24	11.0 mos (6.0 – 19.5)
Median OS IHC 3+	26.0 mos (4.5 – NE)
Median OS IHC 2+	20.3 mos (8.1 – NE)
References	Adv Ther (2024) 41:4125–4139 ESMO 2023. Abstr LBA34; J Clin Oncol 2023 42:47-58

***April 5, 2024**: Fam-trastuzumab deruxtecan is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (**IHC 3+**) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options based on DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 phase II trials*

NE, not estimable

Treatment

2L: 2023

Patient **receives Platinum-based chemotherapy and trastuzumab**

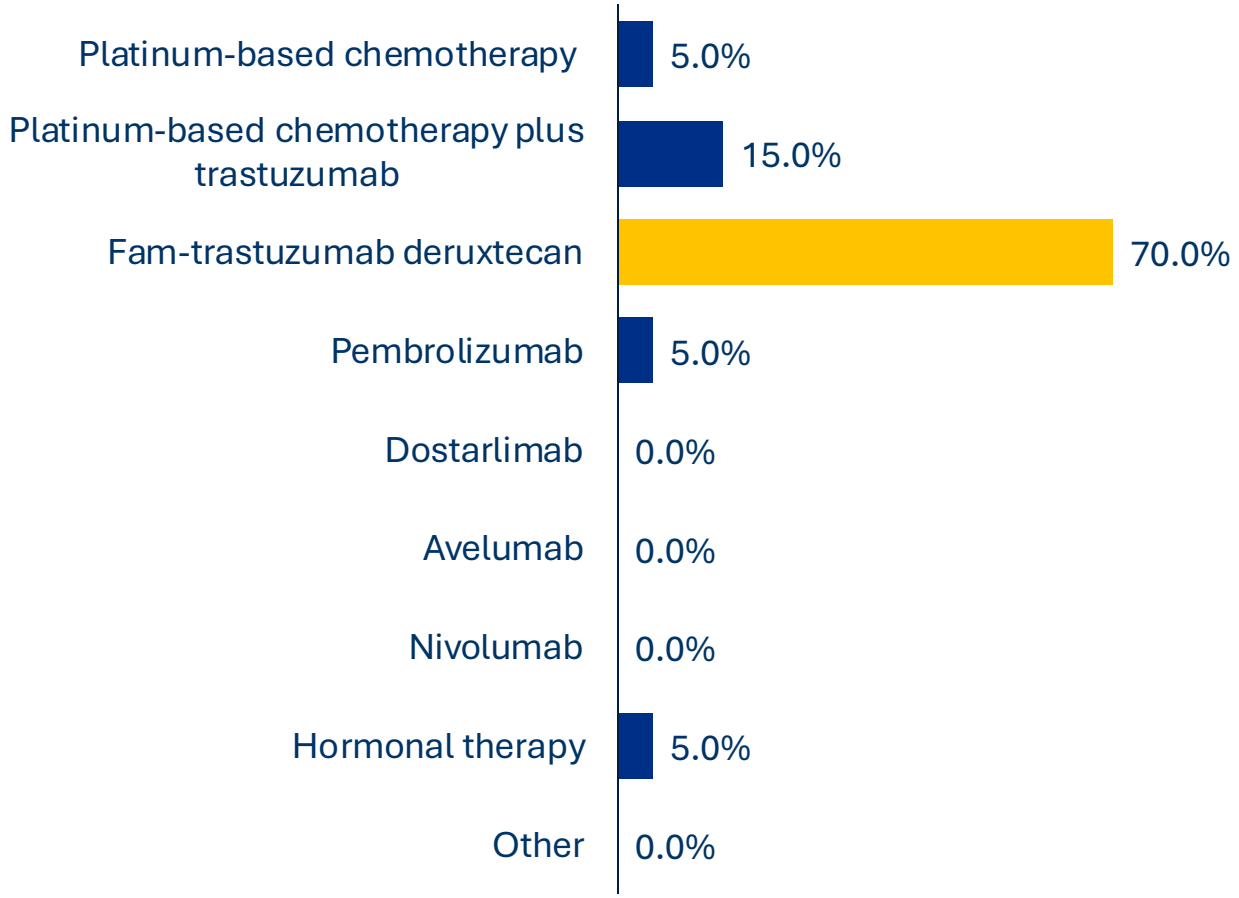
Progression

Patient has stable disease for 8 months, then progresses in liver and lung

What is your choice of third line therapy?

ARS Results from HCP Participants

What is your choice of third line therapy?



Answered: 20

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma[t]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Megestrol acetate/tamoxifen (alternating) • Everolimus/letrozole	• Medroxyprogesterone acetate/tamoxifen (alternating) • Progestational agents ▸ Medroxyprogesterone acetate ▸ Megestrol acetate • Aromatase inhibitors ▸ Anastrozole ▸ Letrozole ▸ Exemestane • Tamoxifen • Fulvestrant	• ER-positive tumors ▸ Letrozole/ribociclib ▸ Letrozole/abemaciclib

Hormonal Therapy for Uterine-Limited Disease Not Suitable for Primary Surgery or for Those Desiring Uterine Preservation for Fertility (ENDO-1)[t]

Preferred Regimen	Other Recommended Regimens
• Levonorgestrel IUD	• Progestational agents ▸ Megestrol acetate ▸ Medroxyprogesterone acetate • Dual progestin agents ▸ Megestrol acetate + levonorgestrel IUD ▸ Medroxyprogesterone acetate + levonorgestrel IUD

[t] Hormonal therapy is typically used for lower-grade endometrioid histologies, preferably in patients with small tumor volume or an indolent growth pace.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

For what patient and / or at what point in a patient's treatment journey would you consider utilizing hormonal therapy?

If used, what is your preferred hormonal therapy for recurrent of metastatic endometrial carcinoma?

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Key Takeaways

Endometrial Cancer

Patient case: untreated metastatic disease

- *Testing and retesting drives treatment strategies*
- *Awareness of clinical trial data provides new treatment options for patients*
- *New FDA approvals and NCCN Guidelines will play a pivotal role in directing treatment pathways*