

Translating Trials to Clinic: Understanding Treatment Options for your Patients

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Adjuvant Treatment When Used for Uterine-Confined Disease

Preferred Regimens

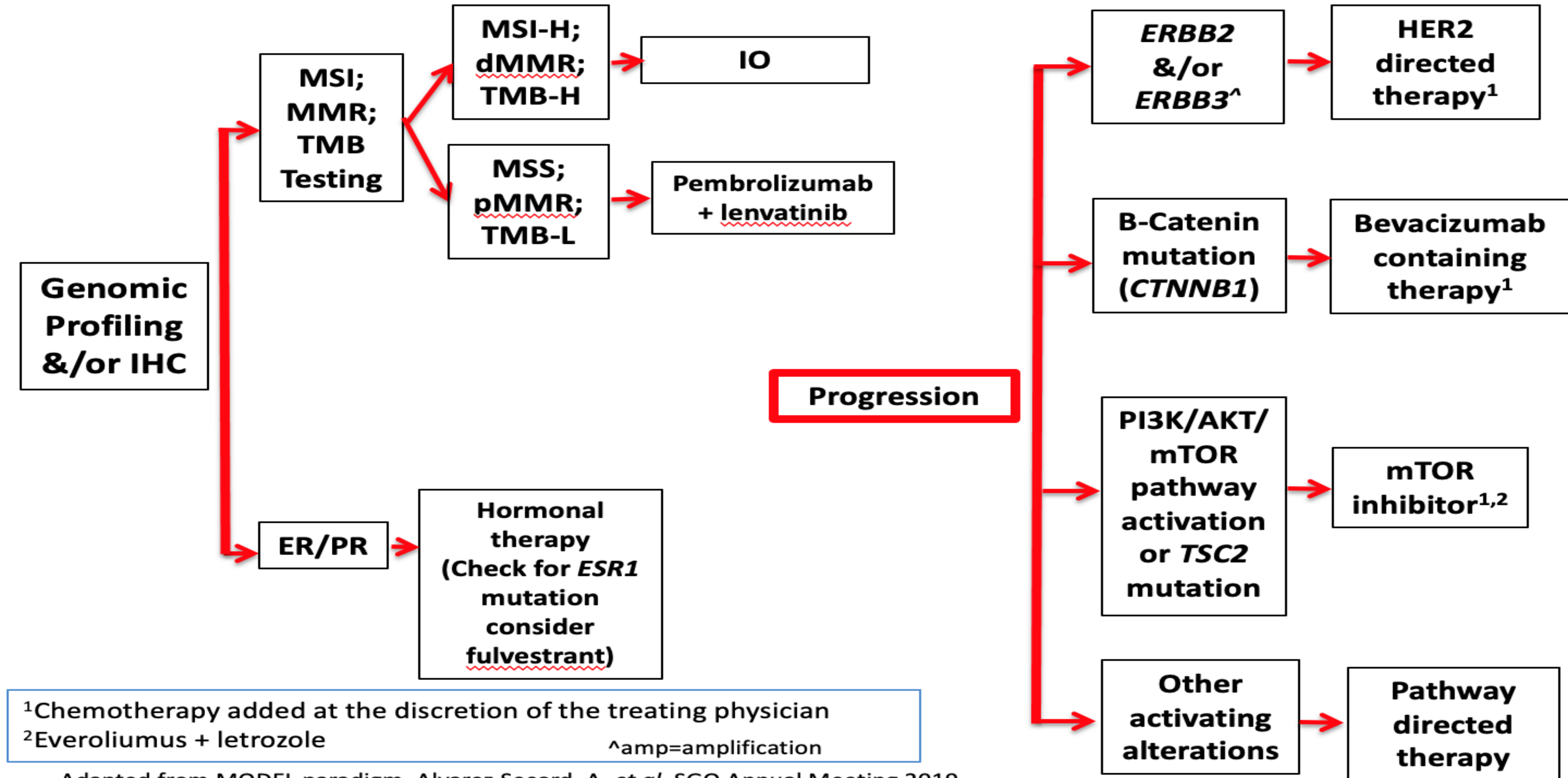
- Carboplatin/paclitaxel

Recurrent, Metastatic, Or High-Risk Disease^{a,b}

	Preferred Regimens	Other Recommended Regimens	Useful In Certain Circumstances
Systemic therapies^{a,b}	<ul style="list-style-type: none"> • Carboplatin/paclitaxel (category 1 for carcinosarcoma)¹ • Carboplatin/paclitaxel/trastuzumab^c (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)² 	<ul style="list-style-type: none"> • Carboplatin/docetaxel^d • Cisplatin/doxorubicin³ • Cisplatin/doxorubicin/paclitaxel^{e,f,3} • Carboplatin/paclitaxel/bevacizumab^{e,g,4} • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel⁵ • Albumin-bound paclitaxel^h • Topotecan • Bevacizumab^{g,i,6} • Temsirolimus⁷ • Docetaxel^d (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)⁸ • Cisplatin/ifosfamide (for carcinosarcoma) 	N/A
Biomarker-directed systemic therapy for second-line treatment	N/A	N/A	<ul style="list-style-type: none"> • Lenvatinib/pembrolizumab^{j,k,9} • Pembrolizumab^l (for TMB-H¹⁰ or MSI-high [MSI-H]/MMR deficient [dMMR] tumors^{m,11}) • Nivolumab^{n,12} • Dostarlimab-gxly^{o,13} • Larotrectinib or entrectinib for <i>NTRK</i> gene fusion-positive tumors (category 2B)^e

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MODEL: MOlecular Driven Endometrial Cancer Therapy for Recurrent Disease – Post Pem/Len



Adapted from MODEL paradigm. Alvarez Secord, A. et al, SGO Annual Meeting 2019

Case 1

- Postmenopausal Black female with Stage IVB grade 2 endometrioid endometrial cancer diagnosed in 2013 s/p surgical debulking and paclitaxel/carboplatin.
- **11/2015:** New groin mass. Biopsy: adenocarcinoma.
Immunostains: ER+, PR+, weak p53 staining
- PET/CT: Bilateral inguinal adenopathy left 9.3 x 7.0 cm with right 4.1 x 2.0 cm, avid bilateral iliac lymph nodes, and hypermetabolic soft sacral tissue mass 2.3 x 3.4.
- **Declined chemotherapy.**
- Completed BL groin and whole pelvic radiation.
- 9/2016: Started on megestrol acetate and aromatase inhibitor

Groin Recurrence Pre-Radiation



Post-Radiation



Case 1

- **9/2016:** Started on megestrol acetate and aromatase inhibitor
 - Exam partial response and imaging demonstrated stable disease.

Response rates to hormonal therapy vary based on ER/PR receptor status and grade.

Progestin only regimens: 2.4-40% response rates

van Weelden *et al.* conducted systematic review reported response rates tamoxifen (10 to 53%), other SERMs and SERDs (9–31%), aromatase inhibitors (8 to 9%), and combined tamoxifen/progestin treatment (19–58%).

Hormonal Therapy Efficacy		
Agent	RR (%)	PFS months
Megestrol acetate ¹	24	2.5
Tamoxifen ¹	10	1.9
MA alt Tamoxifen ¹	22-38	2.7
Letrozole ^{1,2}	9	3.9 ²
Anastrozole ¹	9	1
Letrozole + Everolimus ^{1,3}	24-32	3-6.3

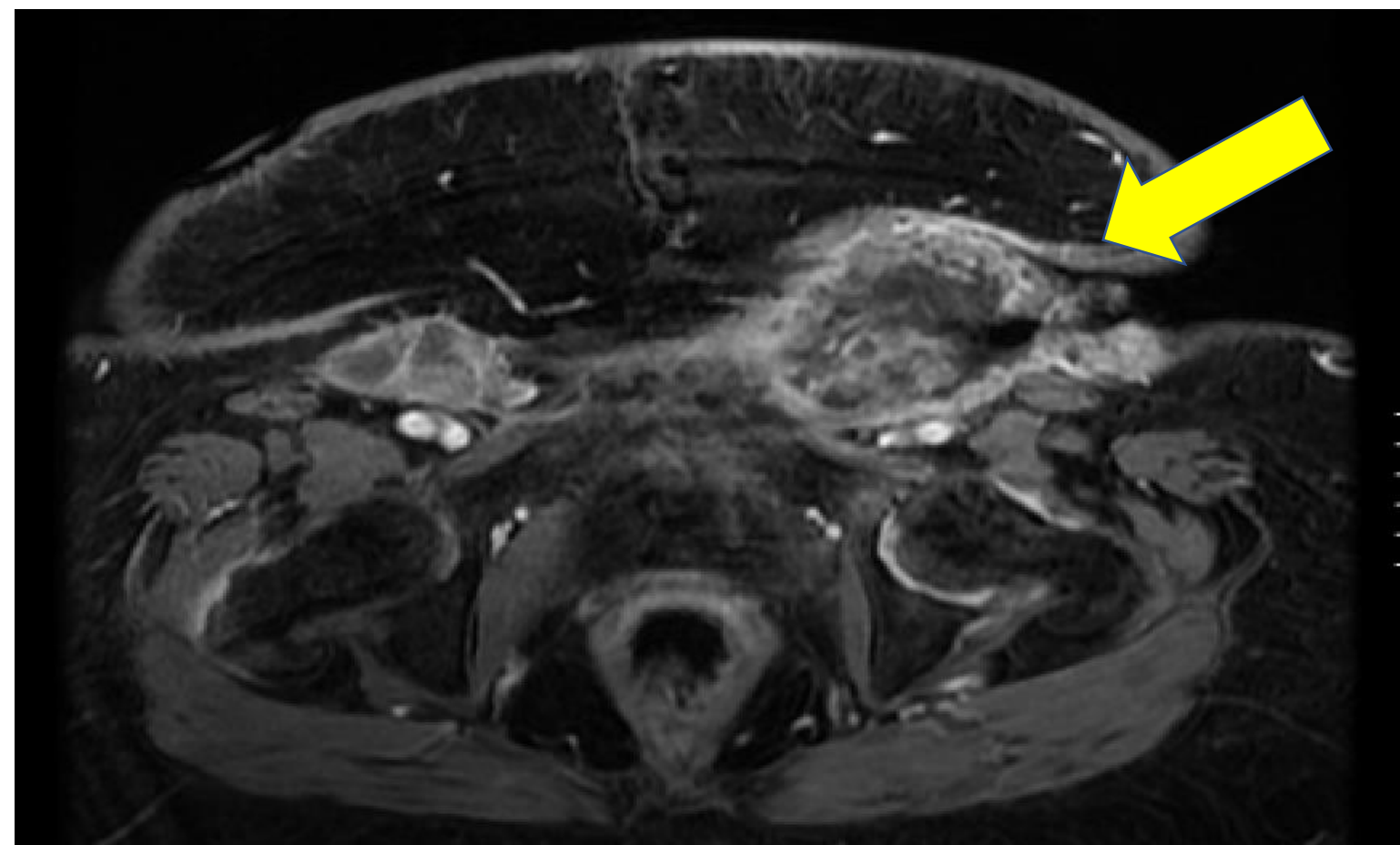
Grade	%	Progestin vs MA/Tam RR (%) ¹
1	84	37-40 / 38
2	50	17.5 / 24
3	25	2.4 / 22

¹UpToDate.com Accessed 3/4/2021; ²Ma BBY *IJGC* 2004;

³Slomovitz B *SGO Annual Meeting* 2018; ⁴van Weeden WJ *Frontier Oncol* 2019

Case 1

- 10/2017: Symptomatic progressive disease.
- MRI demonstrated 12 cm left groin mass;



Tumor testing: MSI-H, MMR-D with loss of MLH1 and PMS2, methylated MLH1 alleles

May 23, 2017

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

April 22, 2021

FDA grants accelerated approval for dostarlimab-gxly for women with recurrent or advanced dMMR endometrial cancer

11/2017: Initiated pembrolizumab 200 mg IV q3 wk
Pre-Pembrolizumab Treatment



One Month Post-Pembrolizumab Treatment



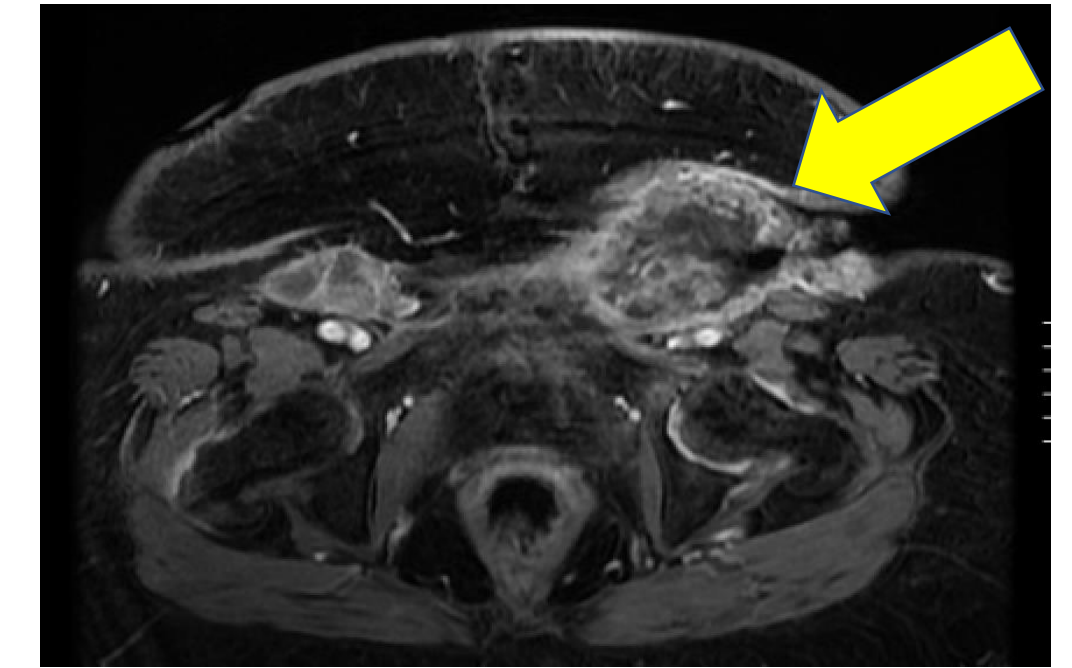
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Case 1

- Rapid evidence of clinical partial response confirmed on imaging with sustained response.
- **5/2018:** Pembrolizumab discontinued due to CHF and acute on chronic renal failure possibly related to IO therapy. Etiology uncertain.



Pre-Pembrolizumab Treatment



Five Months Post-Pembrolizumab Treatment



3.5 years Post-Pembrolizumab Treatment Initiation



MSI-H and dMMR Endometrial Cancers

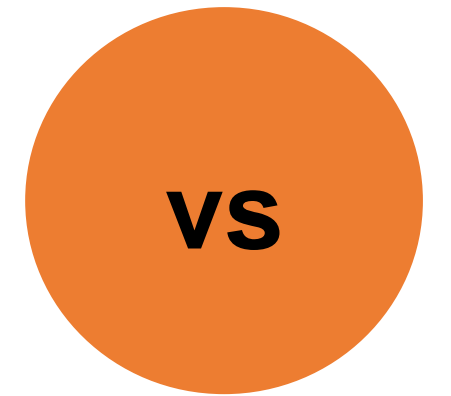
Pembrolizumab vs Pembrolizumab + Lenvatinib

- Is there any role to adding lenvatinib to pembrolizumab in patients with recurrent endometrial cancer?
- Single agent therapy
 - Pembrolizumab 57%
 - Dostarlimab 44.7%
- Combination therapy
 - Pembrolizumab/lenvatinib 63.6%

**Important question that hopefully will be addressed in RCT:
Need to determine if combination therapy adds clinically meaningful improvement in response rate and survival outcomes without negatively impacting QoL compared to IO monotherapy.**



“Less is More”



“More is better”



Case 2

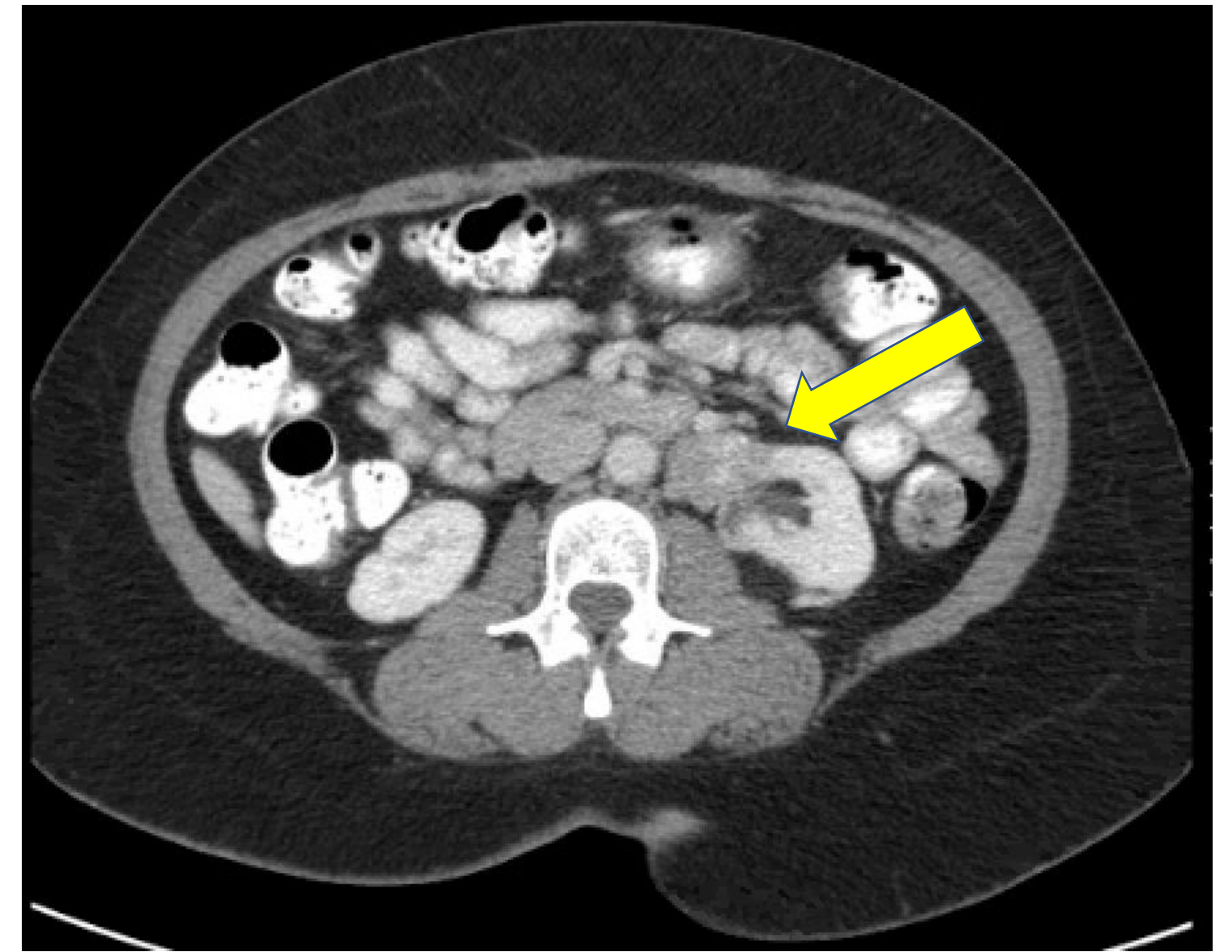
- Postmenopausal Black female with Stage IIIB uterine serous cancer diagnosed in 2015 s/p TLH/USO/LND s/p WPRT with VCB and paclitaxel/carboplatin .
- **1/2018:** symptomatic recurrence 2.7 cm periaortic mass with mild left hydronephrosis; and pulmonary metastases largest 1.3 cm.
- Treated with paclitaxel/carboplatin x 6 cycles with evidence of PR. Stopped due to side effects

Tumor testing:

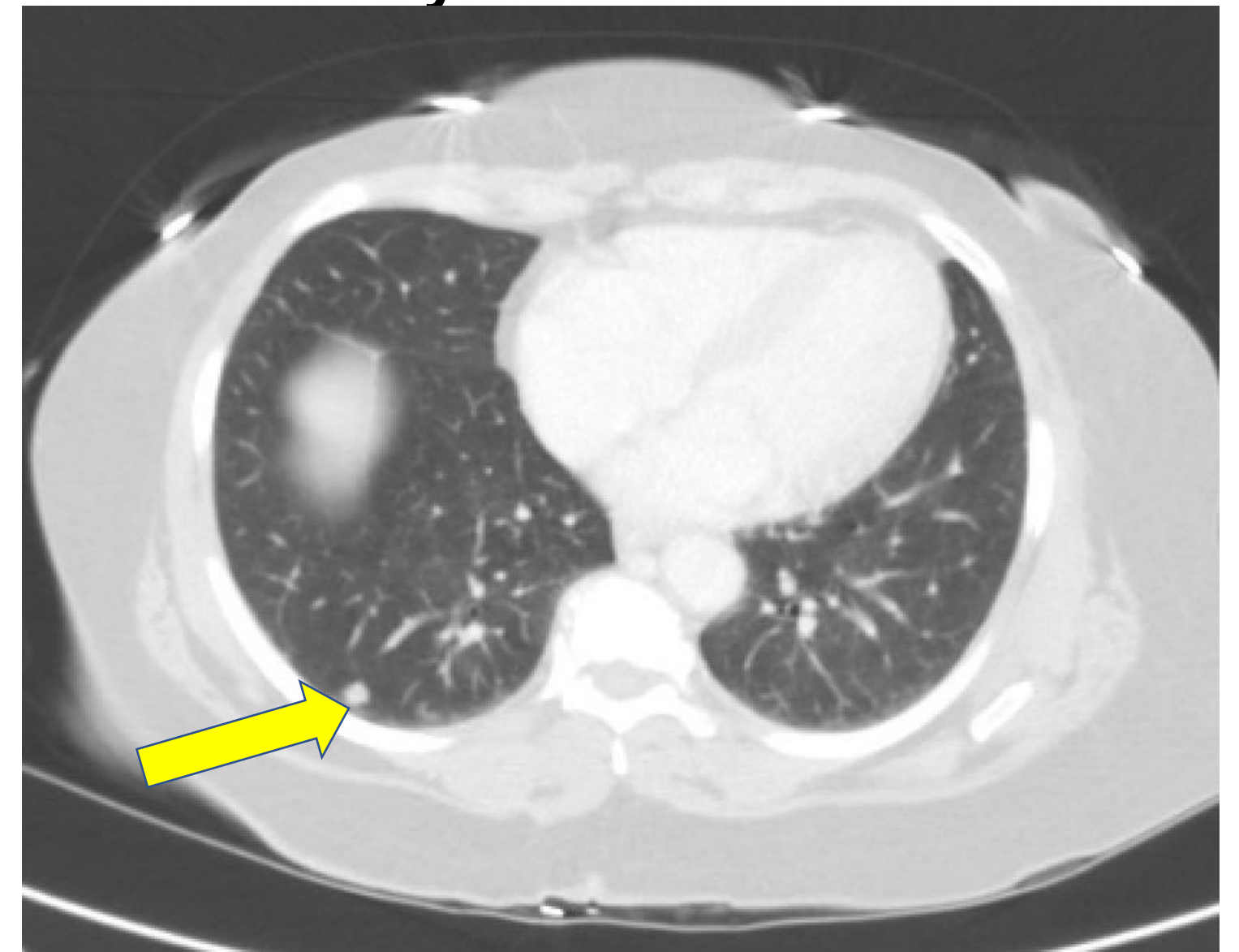
Foundation One: unable to be completed due to insufficient tissue

Molecular testing: MSS; MMR-P; ER+(ALLRED SCORE = 8); PR+(ALLRED SCORE = 5); HER2/neu NEGATIVE (1+)

PA Node Recurrence



Pulmonary Nodule Recurrence



Pre-Pembrolizumab/Lenvatinib Treatment



- ### Case 2
- Initiation megestrol acetate alternating with tamoxifen with stable disease on CT imaging. X 6 months then progressed.
 - 8/2019 Offered KEYNOTE-775 but she declined opted for treatment holiday given asymptomatic state.
 - Follow-up CT scan demonstrated significant progression retroperitoneal, pulmonary, and pericardial mets.
 - Treatment options reviewed.
 - Medical issues notable for BP 156/94, creatinine 1.2, negative proteinuria, and normal TSH. Started amlodipine 5 mg daily.
 - **5/8/2020** pembrolizumab started; followed later by 10 mg lenvatinib on **May 19th, 2020** (delayed start due to HTN).
 - Counseled about BP control, diarrhea management, and precautions.

September 17, 2019 Accelerated Approval

FDA Approval Summary: Pembrolizumab plus Lenvatinib for Endometrial Carcinoma, a Collaborative International Review under Project Orbis

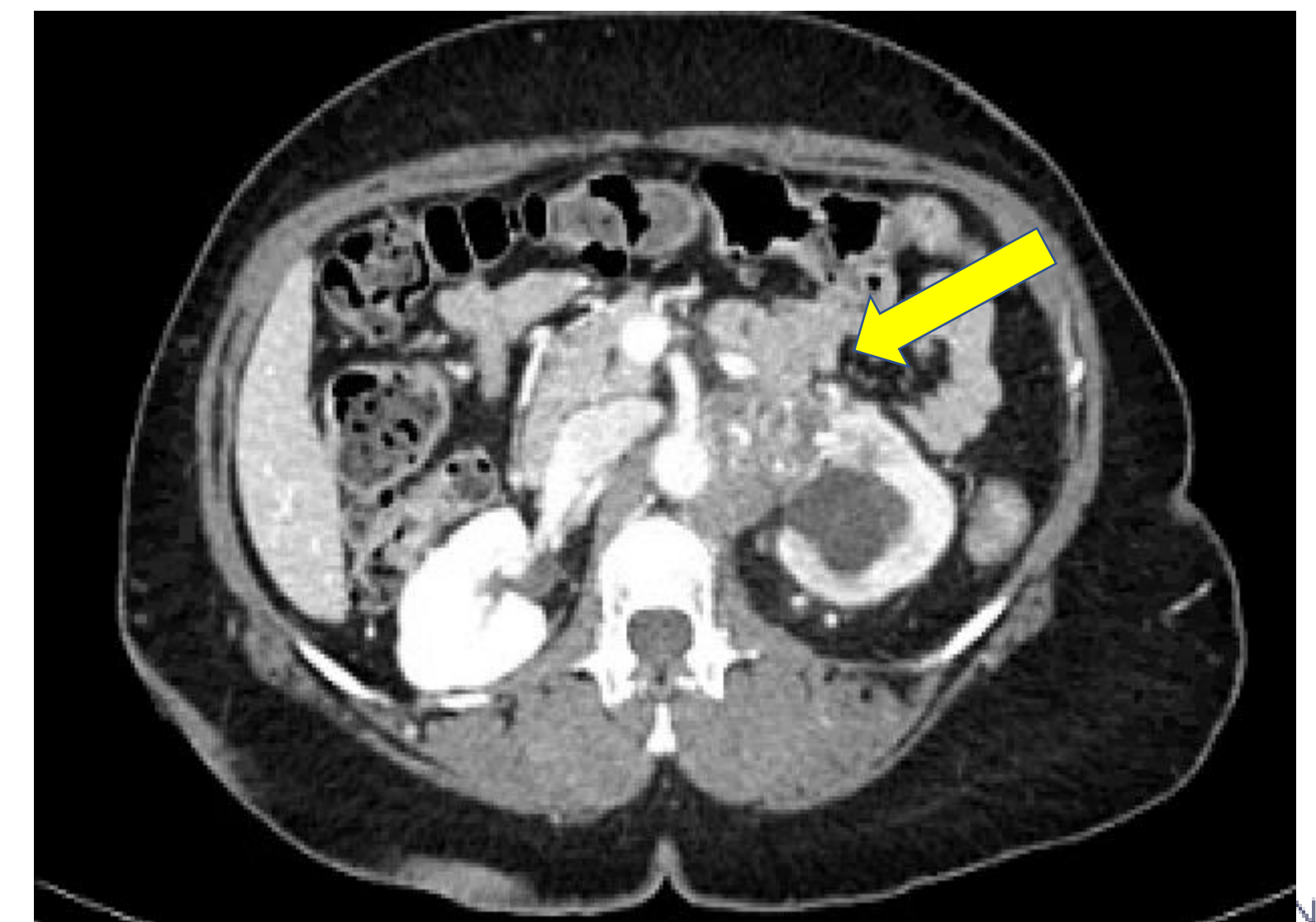
July 22, 2021 Full Approval

FDA Grants Full Approval for lenvatinib and pembrolizumab combination for advanced endometrial cancer that is not MSI-H or MMR-D with disease progression after systemic therapy

Pre-Pembrolizumab/Lenvatinib
Treatment



3 months Post-
Pembrolizumab/Lenvatinib Treatment



Case 2

- Pembrolizumab/lenvatinib
 - Partial response with 34% decrease in disease at first imaging
 - BP 121-135/80-94; increased amlodipine to 10 mg daily with adequate DBPs in the 70-80's
 - Diarrhea controlled with imodium and BRAT diet
 - TSH normal until cycle #6 increased to 7.23: T3/FT4 normal. Remained stable and never required thyroid replacement.

Thyroid screening questions:

Increased sensitivity to cold. - no

Constipation. no

Dry skin. - yes

Weight gain. yes

Puffy face. no

Hoarseness. no

Muscle weakness. no

Elevated blood cholesterol level. **Checked 3/2021 normal**

Muscle aches, tenderness and stiffness. no

- **17 cycles of therapy until new pulmonary nodule and pleural effusion**

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Thank You



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