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Combos are Complicated! Navigating the Balance of Efficacy and Safety in Advanced Endometrial Cancer

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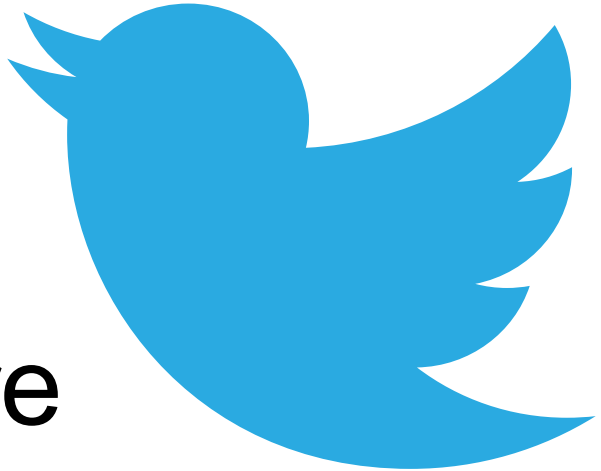

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Learning Objective 1

Examine the rationale and data leading to the approval of combination regimens in advanced EC

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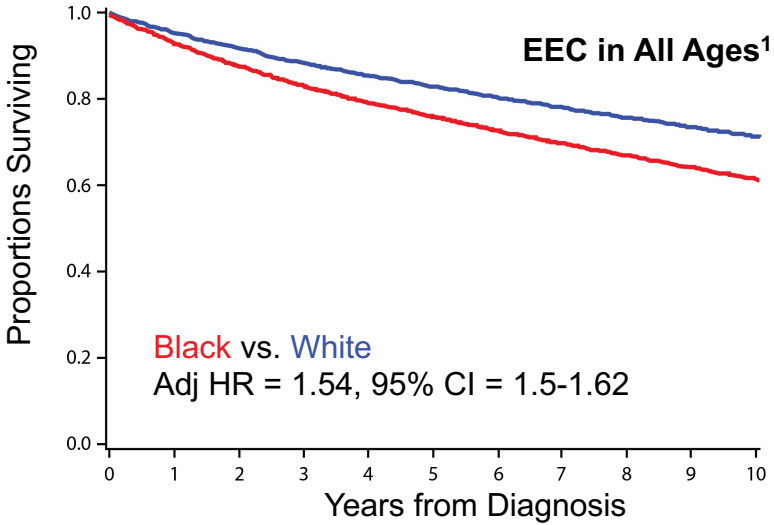
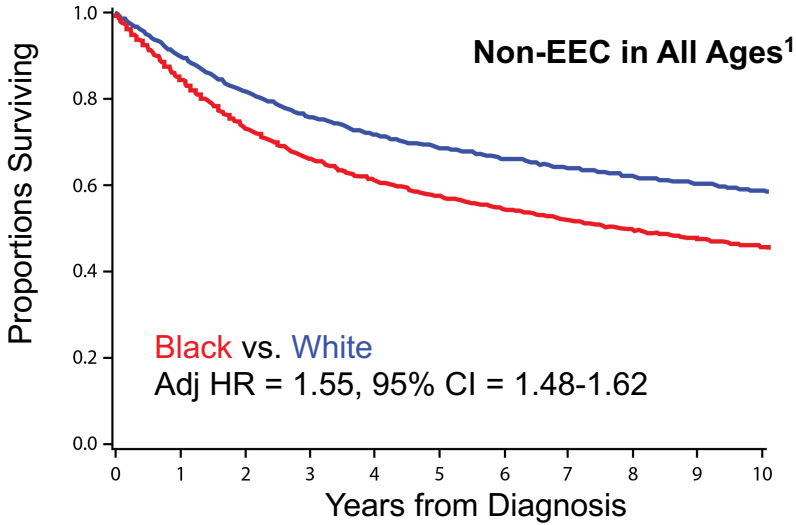
Learning Objective 2

Apply best practices to address treatment challenges related to combination therapy in advanced EC

Racial Disparities in Survival



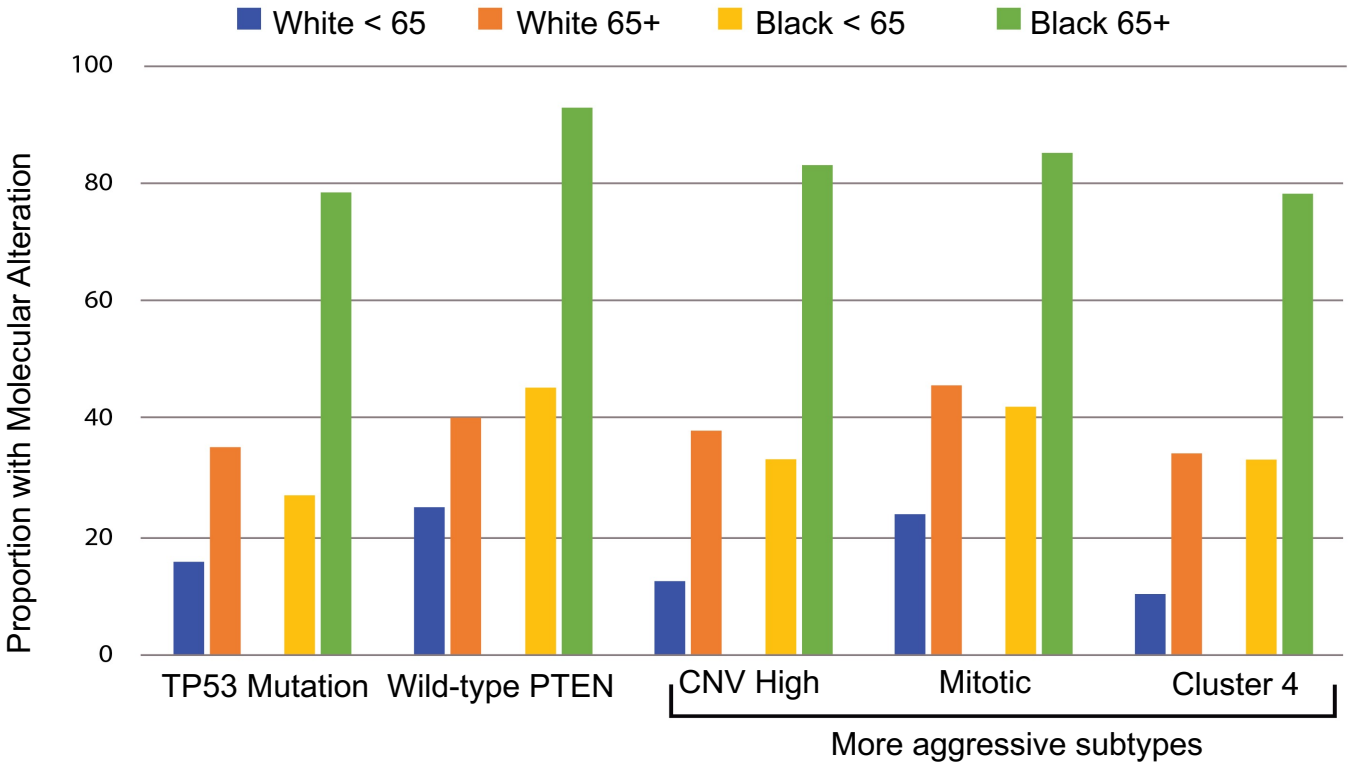


- In 2021: 66,570 new cases of endometrial cancer diagnosed and 12,940 endometrial cancer-related deaths in United States[2]
- Limited effective treatment options in women with advanced or recurrent disease

CI = Confidence interval. EEC, endometrioid endometrial cancer; non-EEC includes serous, mixed, clear cell, and carcinosarcoma. HR = Hazard ratio.

1. Tarney CM, et al. *Gynecol Oncol*. 2018;149(1):12-21. 2. Siegel RL, et al. *CA Cancer J Clin*. 2021;71(1):7-33.

Racial and Age Disparities in Mutation Burden



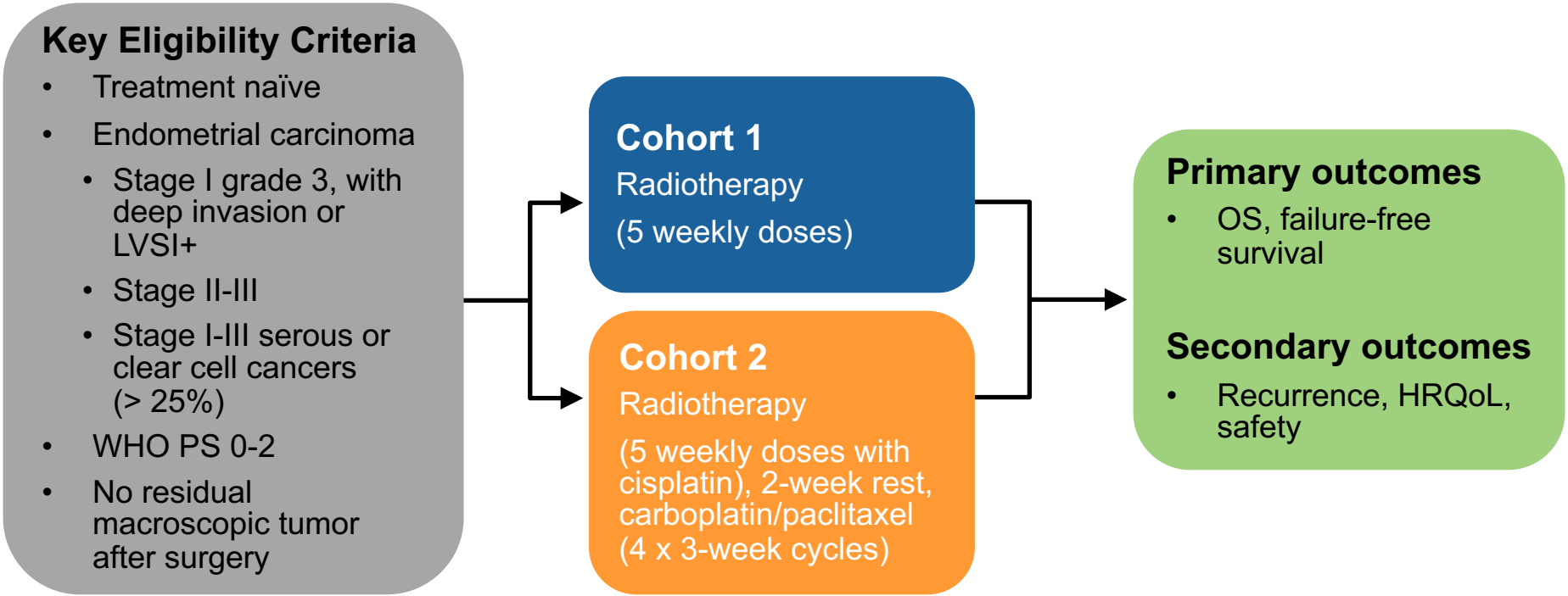
Aggressive molecular subtypes including the integrative copy number (CNV) high subtype, transcript-based mitotic subtype, and somatic copy number alteration (SCNA)-based cluster 4 subtype; for all comparisons, $p < .05$. PTEN = Phosphatase and tensin homolog gene. TP53 = Tumor protein p53 gene.
Tarney CM, et al. *Gynecol Oncol*. 2018;149(1):12-21.

Case Study 1: Mary

- 63-year-old Black woman
- Heavy vaginal bleeding, with clots
- Stage IIIC1 endometrial adenocarcinoma
- Hysterectomy, lysis of adhesions
- Bilateral sentinel lymph node biopsy, 2 of 3 pelvic nodes positive

- What would you recommend for this patient?

PORTEC-3 Trial Design

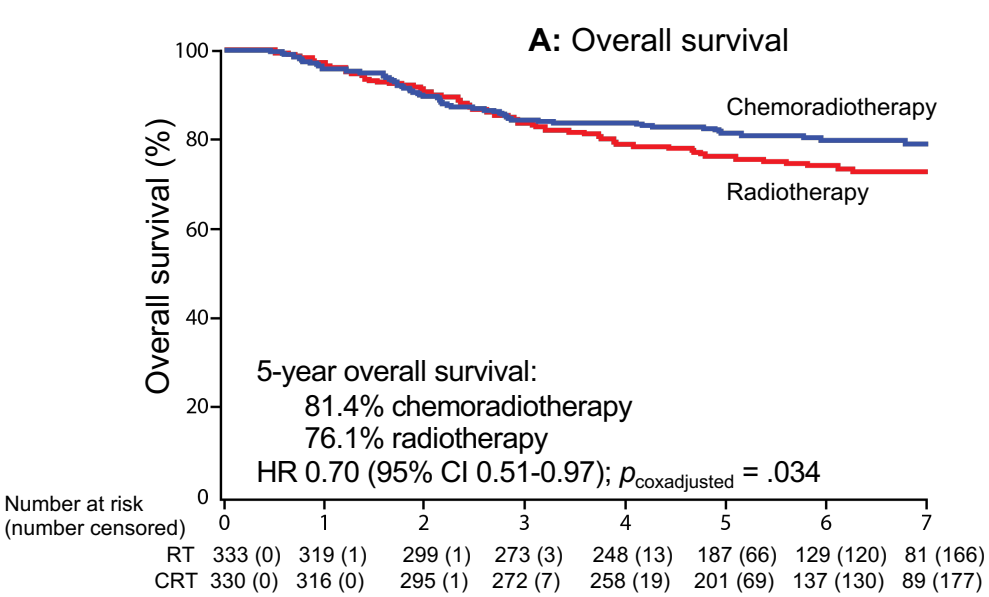


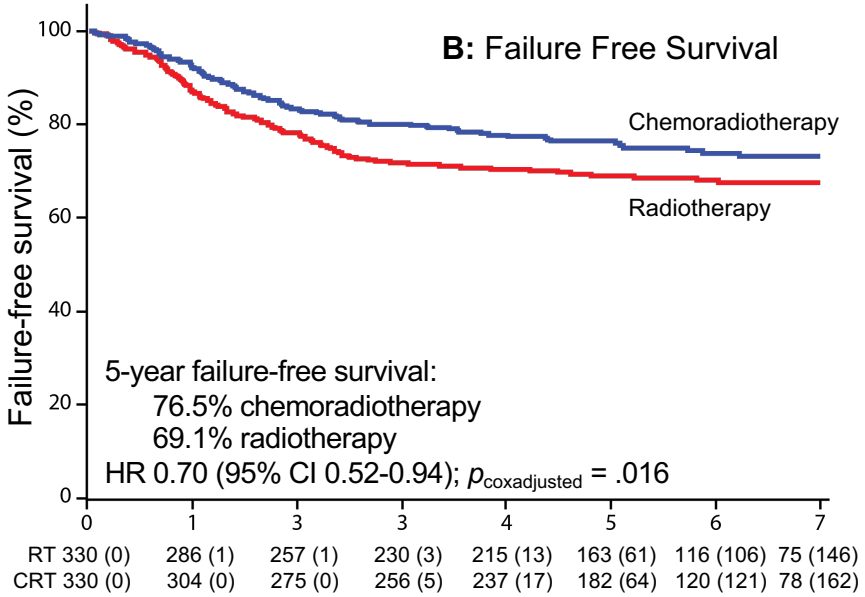
HRQoL = Health-related quality of life. LVSI+ = Lymphatic vessel invasion positive. OS = Overall survival. PS = Performance status. WHO = World Health Organization.

de Boer SM, et al. *Lancet Oncol.* 2019;20(9):1273-1285.

PORTEC-3 Efficacy

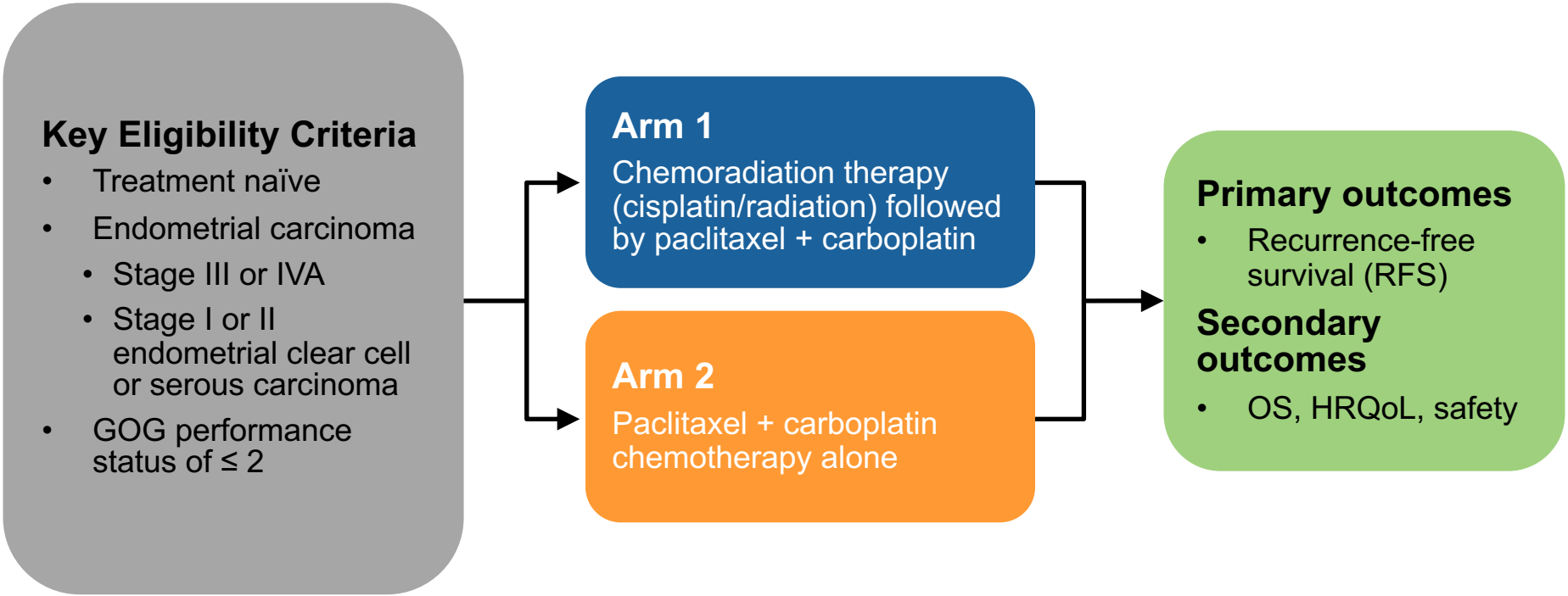
- Improved 5-year FFS and OS with CRT





CRT = Chemoradiotherapy. RT = Radiotherapy. FFS = Failure Free survival.
de Boer SM, et al. *Lancet Oncol*. 2019;20(9):1273-1285.

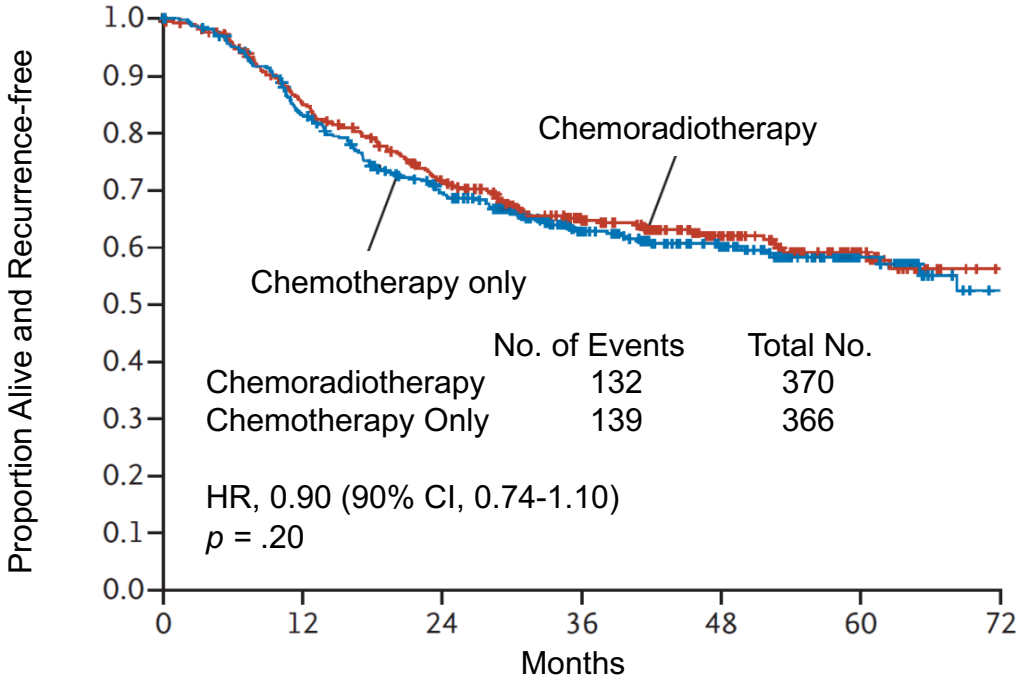
GOG-0258 Trial Design



GOG = Gynecologic Oncology Group.

Matei D, et al. *N Engl J Med*. 2019;380(24):2317-2326.

GOG-0258 Relapse-Free Survival



No. at Risk						
Chemoradiotherapy 370	295	235	164	103	45	19
Chemotherapy only 366	293	230	159	113	55	17

Chemotherapy + radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma

Matei D, et al. *N Engl J Med*. 2019;380(24):2317-2326.

Case Study 1: Mary

- She receives chemoradiation therapy
- Cancer recurs 24 months later with multiple < 1 cm peritoneal lesions
- Results of DNA mismatch repair analysis in a tumor specimen reveals dMMR/MSI-H

cm = Centimeters. dMMR = Deficient mismatch repair.

Single-Agent Immune Checkpoint Inhibitor Therapy

Study	Drug	N (dMMR/MMRp)	Patient Selection	ORR	
				dMMR	MMRp
KEYNOTE−158[1] KEYNOTE-028[5]	Pembrolizumab	49/24	Advanced/metastatic	57%	13%
GARNET[2]	Dostarlimab	103/142	Previously-treated recurrent/advanced	45%	13%
PHAEDRA[3]	Durvalumab	35/36	Advanced /metastatic	47%	3%
Konstantinopoulos[4]	Avelumab	15/16	Advanced /metastatic	27%	6%

- dMMR cancers produce relatively large amounts of neoantigens
- Release of immune checkpoint blockade with anti-PD-1/PD-L1 antibodies allows for immune recognition of neoantigens
- Single-agent nivolumab trial NCT04106414 is still recruiting

dMMR = Deficient mismatch repair. MMRp = Mismatch repair proficient. ORR = Overall response rate. PD-1 = Programmed cell death protein 1. PD-L1 = Programed death-ligand 1.

1. Marabelle A, et al. *J Clin Oncol*. 2020;38(1):1-10. 2. Oaknin A, et al. *Ann Oncol*. 2020;31(suppl_4):S645. 3. Antill Y, et al. *J Immunother Cancer*. 2021;9(6). 4. Konstantinopoulos PA, et al. *J Clin Oncol*. 2019;37(30):2786-2794. 5. Ott PA, et al. *J Clin Oncol*. 2017;35(22):2535-2541.

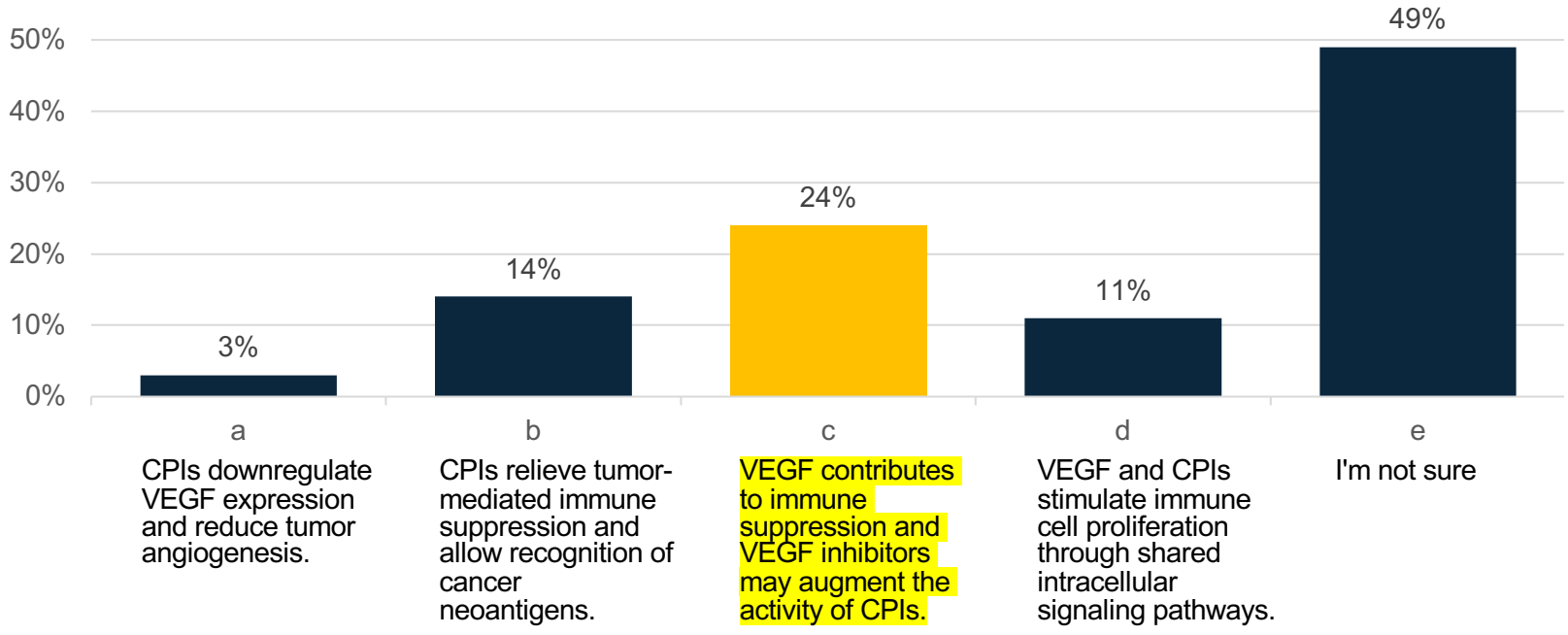
Polling Question

What is the rationale for combining immune checkpoint inhibitors (CPIs) and VEGF inhibitors in the treatment of endometrial cancer?

A. CPIs downregulate VEGF expression and reduce tumor angiogenesis.
B. CPIs relieve tumor-mediated immune suppression and allow recognition of cancer neoantigens.
C. VEGF contributes to immune suppression and VEGF inhibitors may augment the activity of CPIs.
D. VEGF and CPIs stimulate immune cell proliferation through shared intracellular signaling pathways.
E. I'm not sure

Audience Responses

What is the rationale for combining immune checkpoint inhibitors (CPIs) and VEGF inhibitors in the treatment of endometrial cancer?



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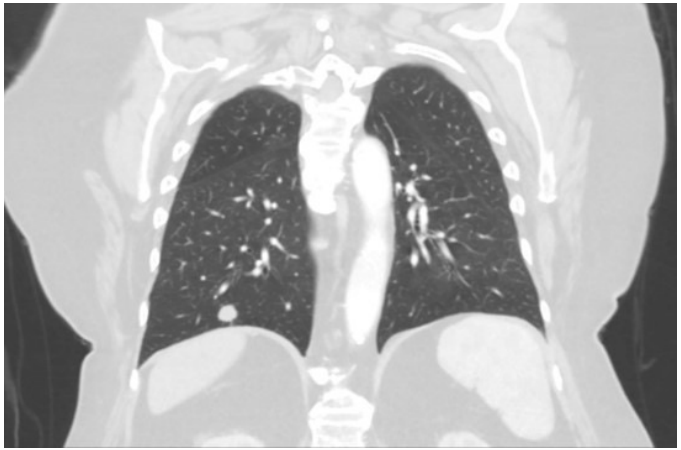
Case Study 2: Susan

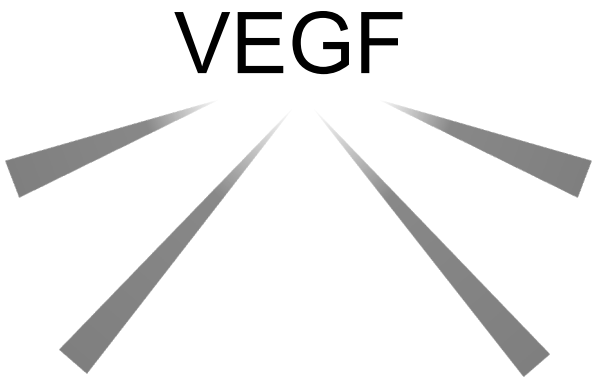
- 72-year-old White woman
- Stage IA MSS Grade 1 EEC.
- Cancer recurs at 4 years with lung, peritoneal, and nodal metastases
- Rx: Tamoxifen/Megestrol, letrozole
- Mutations in *PTEN*, *CTNB1*, *ESR1*, *ARID1A* and *PIK3R1* with tumor mutational burden of 9



- What would you recommend for this patient?

EEC = endometrioid endometrial cancer. MSS = Microsatellite stable.

VEGF Reduces Anti-Tumor Immune Response



Induces abnormal tumor vasculature that reduces T-cell trafficking and infiltration[4-6]

Inhibits T-cell function by binding to VEGFR2 on T cells[1]

Stimulates immunosuppressive regulatory T cells[2]

Inhibits dendritic cell function driving them into an immature state[3]

VEGF = Vascular endothelial growth factor. VEGFR2 = VEGF receptor 2.

1. Gavalas NG, et al. *Br J Cancer.* 2012;107(11):1869-1875. 2. Terme M, et al. *Cancer Res.* 2013;73(2):539-549. 3. Coukos G, et al. *Br J Cancer.* 2005;92(7):1182-1187. 4. Bouzin C, et al. *J Immunol.* 2007;178(3):1505-1511. 5. Shrimali RK, et al. *Cancer Res.* 2010;70(15):6171-6180. 6. Chen DS, et al. *Immunity.* 2013;39(1):1-10.

Mechanistic Reasoning for Synergism Between VEGFR and Immune Checkpoint Inhibitors

- VEGF supports an immunosuppressive tumor microenvironment
  - Lenvatinib, a small-molecule tyrosine kinase inhibitor, targets VEGFR1-3, FGFR-1–4, RET, c-kit, and PDGFRα[1]
- CPIs block several targets, such as CTLA-4, PD-1, and PD-L1, which in turn disinhibit proliferation of antitumor T cells
  - Pembrolizumab has efficacy in patients with endometrial cancers that are MSI-H, dMMR, or have high TMB[3]
- Inhibition of VEGF-mediated immune suppression may augment the activity of CPIs[4]
- Presence of intratumoral T cells independently correlated with delayed recurrence or delayed death and increased expression of interferon-γ, interleukin-2, and lymphocyte-attracting chemokines within the tumor[5]

C-kit = Receptor tyrosine kinase. CTLA-4 = Cytotoxic T lymphocyte antigen 4. FGFR-1-4 = Fibroblast growth factor receptors 1-4. CPI = Immune checkpoint inhibitor. MSI-H = Microsatellite instability–high. dMMR = Mismatch repair deficient. PD-1 = Programmed death 1. PD-L1 = Programmed death ligand 1.PFGFRα = Platelet-derived growth factor receptor-alpha. RET = Rearranged during transfection. TMB = Tumor mutational burden.

1. Capozzi M, et al. *Cancer Manag Res*. 2019;11:3847-3860. 2. Ellithi M, et al. *Cureus*. 2020;12(2):e6935. 3. Marabelle A, et al. *J Clin Oncol*. 2020;38(1):1-10. 4. Taylor MH, et al. *J Clin Oncol*. 2020;38(11):1154-1163. 5. Zhang, et al. N Engl J Med. 2003;348(3):203-13

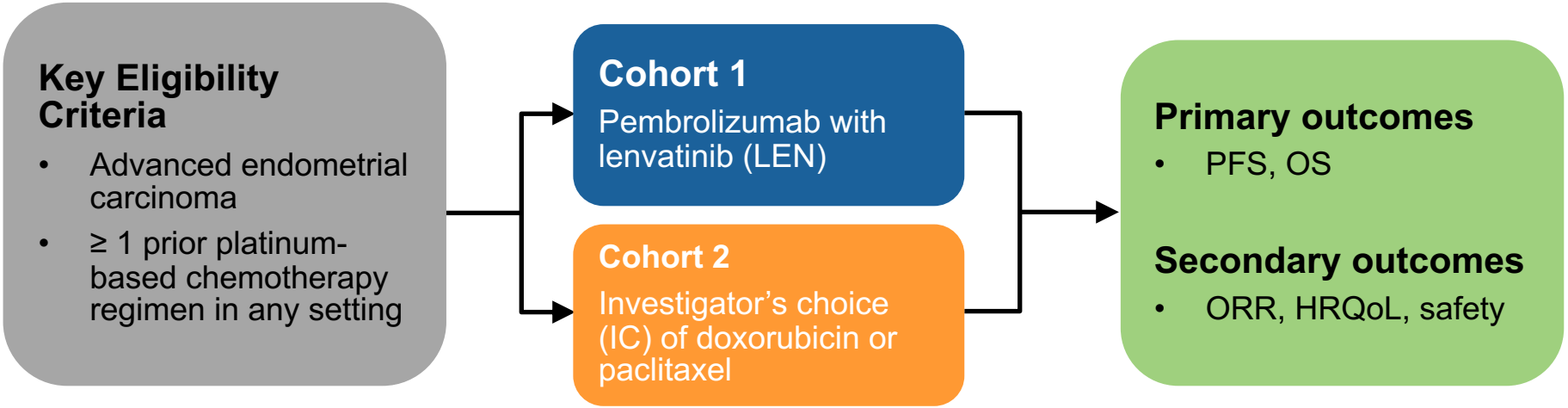
Mechanistic Reasoning for Synergism Between VEGFR and Immune Checkpoint Inhibitors

- Pembrolizumab + lenvatinib have efficacy in patients with endometrial cancers[1]
  - KEYNOTE-146
  - Overall: ORR (24 week), 38%; DOR, 21 months; median PFS, 7.4 months; median; OS, 17 months
    - MSI-H tumors: 64% ORR
    - Microsatellite stable tumors: 36% ORR
- Nivolumab + cabozantinib[3]
  - Phase 2 study
  - ORR: 25% nivolumab + cabozantinib vs. 17% nivolumab alone
- Atezolizumab + bevacizumab
  - Phase 2 (NCT03694262), no results

DOR = Duration of response. PFS = Progression-free survival.

1. Makker V, et al. *J Clin Oncol*. 2020;38(26):2981-2992. 2. U.S. Food and Drug Administration Website. 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-pembrolizumab-and-lenvatinib-advanced-endometrial-carcinoma. Accessed October 21, 2021. 3. Lheureux S, et al. *J Clin Oncol*. 2020;38(15_suppl):6010-6010.

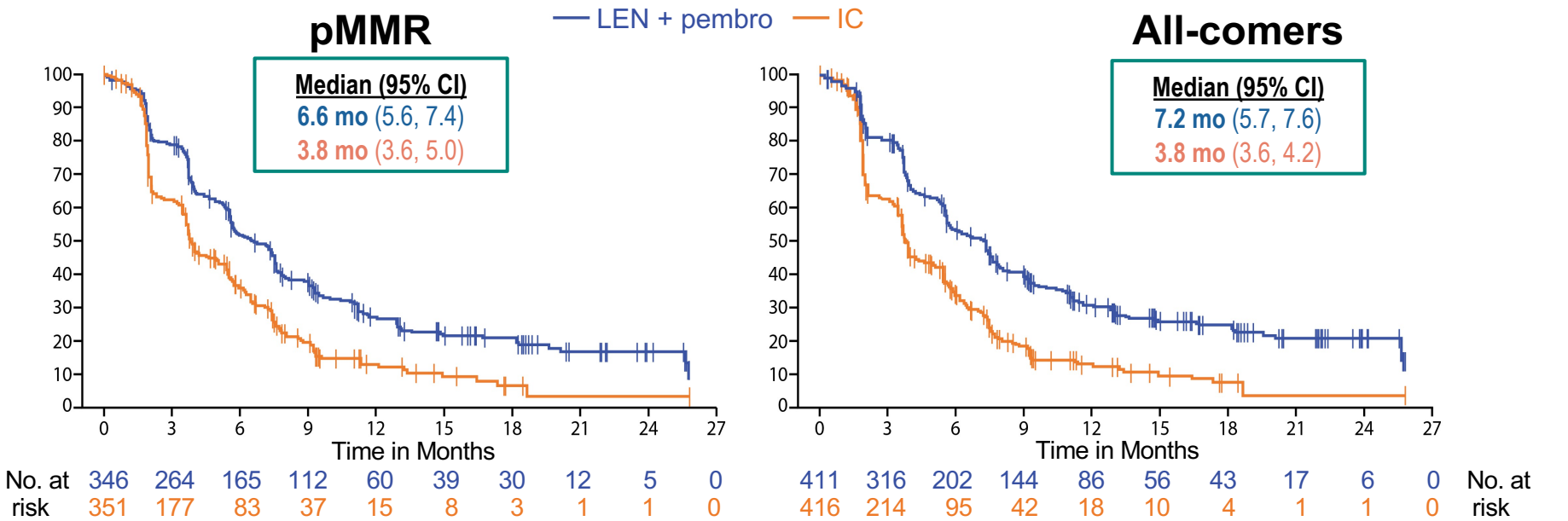
KEYNOTE-775 Study: Pembrolizumab and Lenvatinib



IC = Investigator's choice

1. Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021. 2. Makker V, et al. *Gynecol Oncol*. 2021;162:S4.

Progression-Free Survival



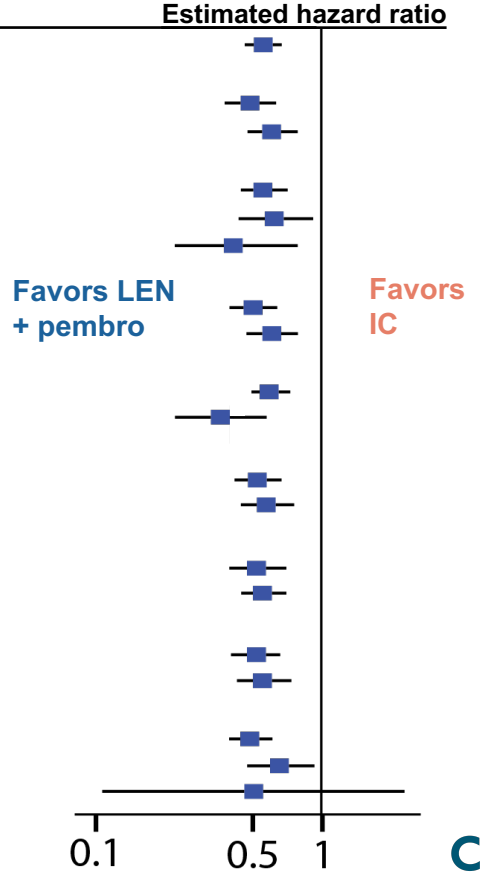
	Events	HR (95% CI)	*p* - value
LEN + pembro	247	**0.60** (0.50, 0.72)	< .0001
IC	238		

	Events	HR (95% CI)	*p* - value
LEN + pembro	281	**0.56** (0.47, 0.66)	< .0001
IC	286		

Mo = months.
Blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1.
Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

PFS Subgroup Analyses: All-Comers

	No. of Events/N	HR	95% CI
Overall	567/827	.056	(0.47, 0.66)
Age Group			
< 65 years	284/410	0.49	(0.38, 0.62)
≥ 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)

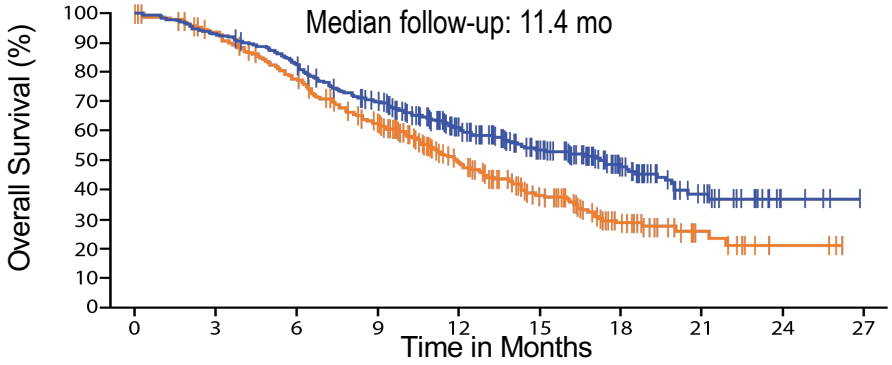


Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

Overall Survival

pMMR

Median (95% CI)
17.4 mo (14.2, 19.9)
12.0 mo (10.8, 13.3)

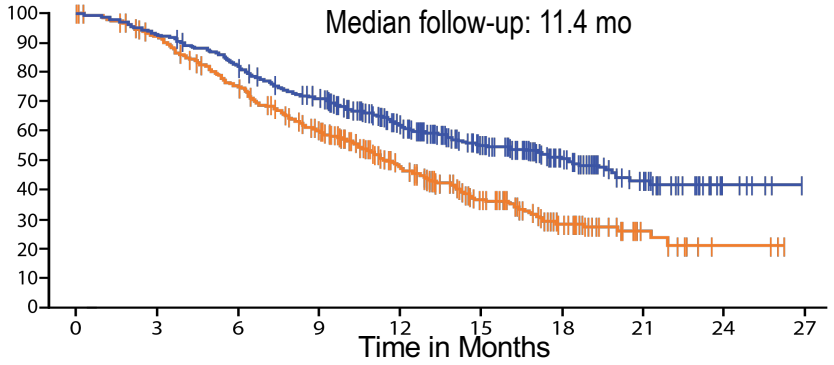


No. at risk										
LEN + pembro	346	322	285	232	160	109	62	28	5	0
IC	351	319	262	201	120	70	33	11	3	0

	Events	HR (95% CI)	*p* - value
LEN + pembro	165	**0.68** (0.56, 0.84)	.0001
IC	203		

All-comers

Median (95% CI)
18.3 mo (15.2, 20.5)
11.4 mo (10.5, 12.9)



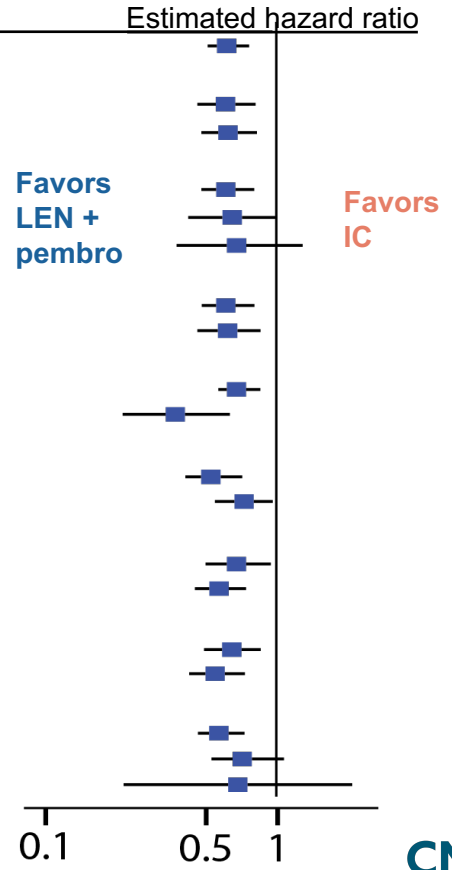
No. at risk											
LEN + pembro	411	383	337	282	198	136	81	40	7	0	No. at risk
IC	416	373	300	228	138	80	40	11	3	0	

	Events	HR (95% CI)	*p* - value
LEN + pembro	188	**0.62** (0.51, 0.75)	< .0001
IC	245		

Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

OS Subgroup Analyses: All-Comers

	No. of Events/N	HR	95% CI
Overall	433/827	.062	(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	0.61	(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)

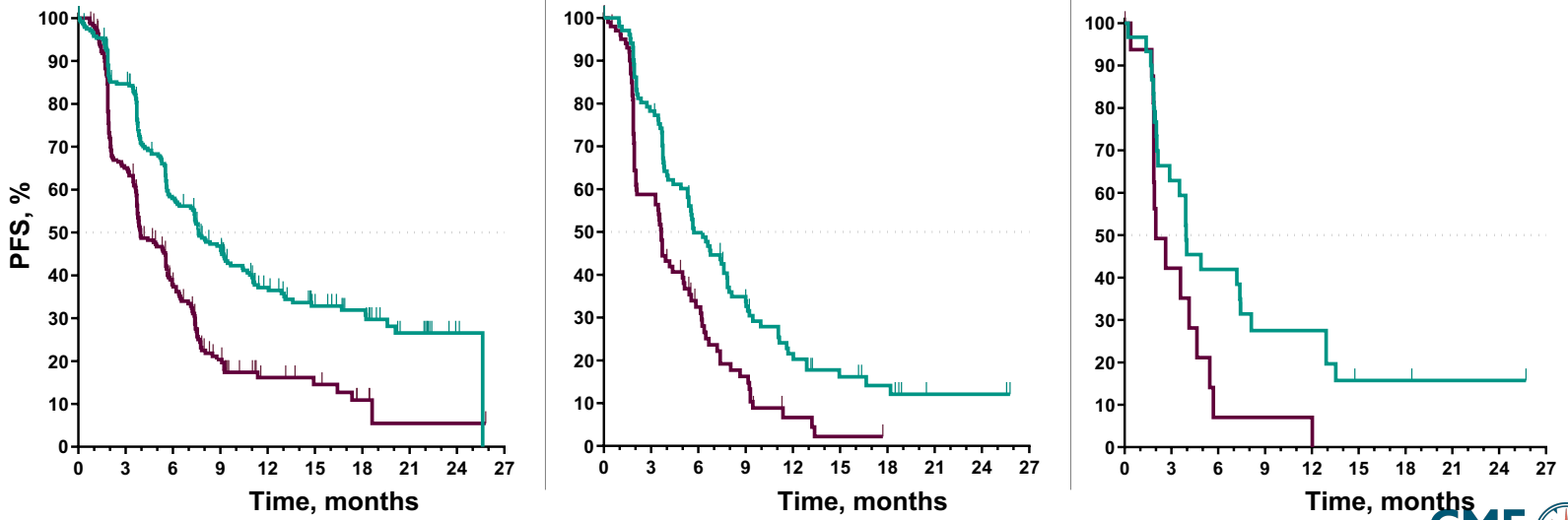


Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

Progression-Free Survival by Histology

		Endometrioid			Serous			Clear cell		
		N	Events, n (%)	Median PFS (mo)	N	Events, n (%)	Median PFS (mo)	N	Events, n (%)	Median PFS (mo)
All-comers	Len + pembro	243	150 (61.7)	7.6	103	81 (78.6)	5.7	30	24 (80.0)	3.9
	TPC	254	173 (68.1)	3.9	115	80 (69.6)	3.6	17	15 (88.2)	2
	HR (95% CI)		0.52 (0.41-0.65)			0.53 (0.38-0.72)			0.47 (0.24-0.92)	
pMMR	Len + pembro	243	150 (61.7)	7.6	103	81 (78.6)	5.7	30	24 (80.0)	3.9
	TPC	254	173 (68.1)	5	115	80 (69.6)	3.6	17	15 (88.2)	2
	HR (95% CI)		0.52 (0.41-0.65)			0.53 (0.38-0.72)			0.47 (0.24-0.92)	

All-comers
LEN + pembro
TPC



Colombo N, et al. *Ann Oncol*. 2021;32(suppl_5):S725.

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Progression-Free Survival by Histology (All-Comers)

Subgroup	Events/N	HR for PFS (95% CI)
1 prior line of platinum		
pMMR	370/526	0.54 (0.44–0.67)
All-comer	446/641	0.50 (0.41–0.61)
> 1 prior line of platinum		
pMMR	114/170	0.75 (0.52–1.09)
All-comer	120/185	0.69 (0.48–0.99)
Received (neo)adjuvant therapy		
pMMR	190/258	0.58 (0.43–0.78)
All-comer	217/303	0.55 (0.42–0.73)
No (neo)adjuvant therapy		
pMMR	295/439	0.60 (0.47–0.76)
All-comer	350/524	0.54 (0.44–0.67)

Subgroup	Events/N	HR for PFS (95% CI)
PFI ≥ 6 months		
pMMR	158/240	0.59 (0.43–0.81)
All-comer	173/270	0.55 (0.41–0.75)
PFI < 6 months		
pMMR	323/451	0.57 (0.45–0.71)
All-comer	390/550	0.51 (0.42–0.63)
PFI ≥ 12 months		
pMMR	67/99	0.74 (0.45–1.20)
All-comer	70/111	0.72 (0.45–1.16)
PFI < 12 months		
pMMR	414/592	0.56 (0.46–0.68)
All-comer	493/709	0.50 (0.42–0.60)

Colombo N, et al. *Ann Oncol*. 2021;32(suppl_5):S725.

Overall Survival by Histology

		Endometrioid			Serous			Clear cell		
		N	Events, n (%)	Median OS (mo)	N	Events, n (%)	Median OS (mo)	N	Events, n (%)	Median OS (mo)
All-comers	Len + pembro	243	95 (39.1)	NR	103	62 (60.2)	12	30	13 (43.3)	19.9
	TPC	254	127 (50.0)	13.4	115	81 (70.4)	9.3	17	13 (76.5)	8.7
	HR (95% CI)		0.65 (0.49-0.84)			0.68 (0.48-0.94)			0.33 (0.15-0.74)	
pMMR	Len + pembro	243	95 (39.1)	NR	103	62 (60.2)	12	30	13 (43.3)	19.9
	TPC	254	127 (50.0)	13.4	115	81 (70.4)	9.3	17	13 (76.5)	8.7
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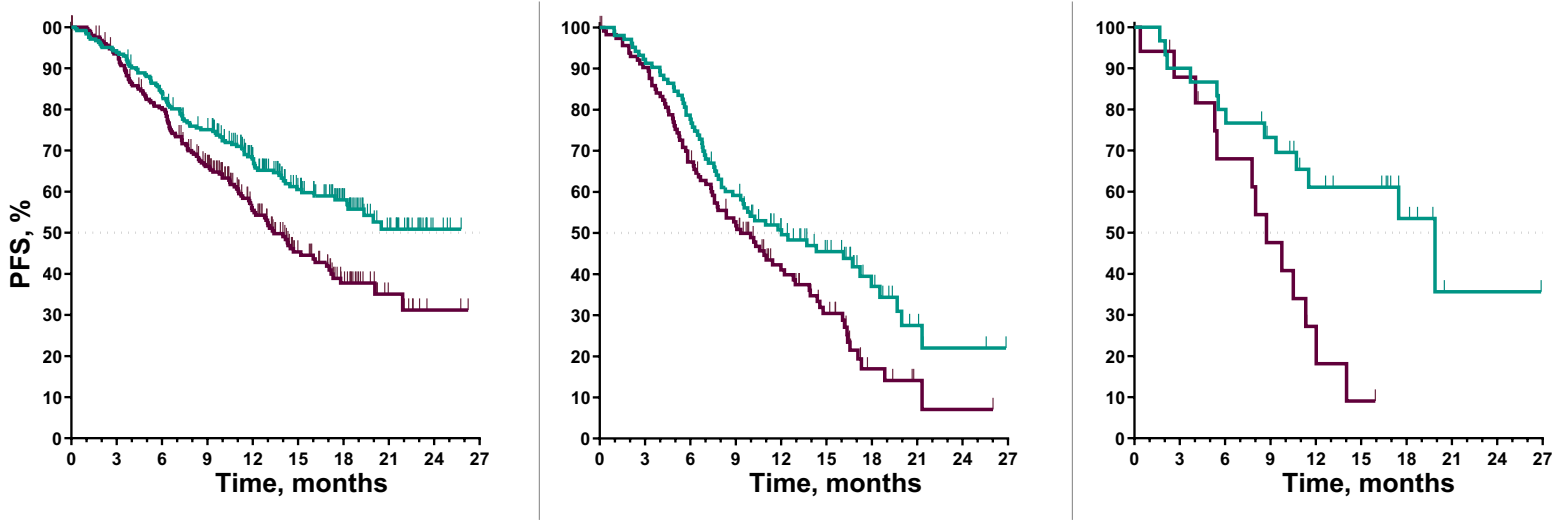
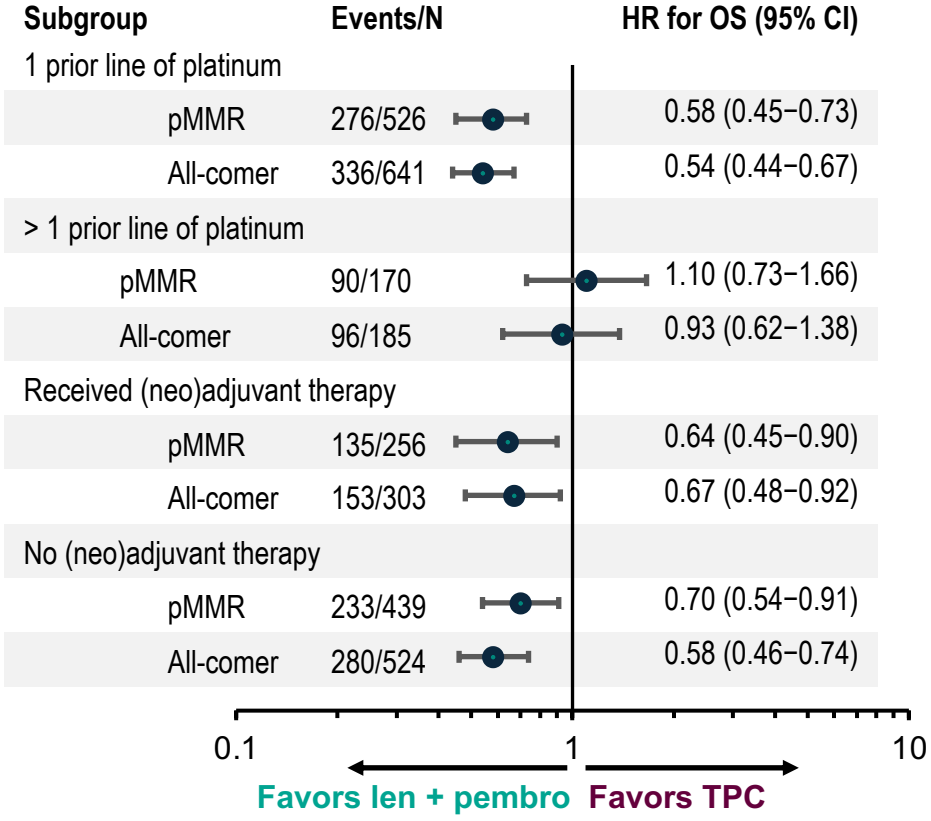
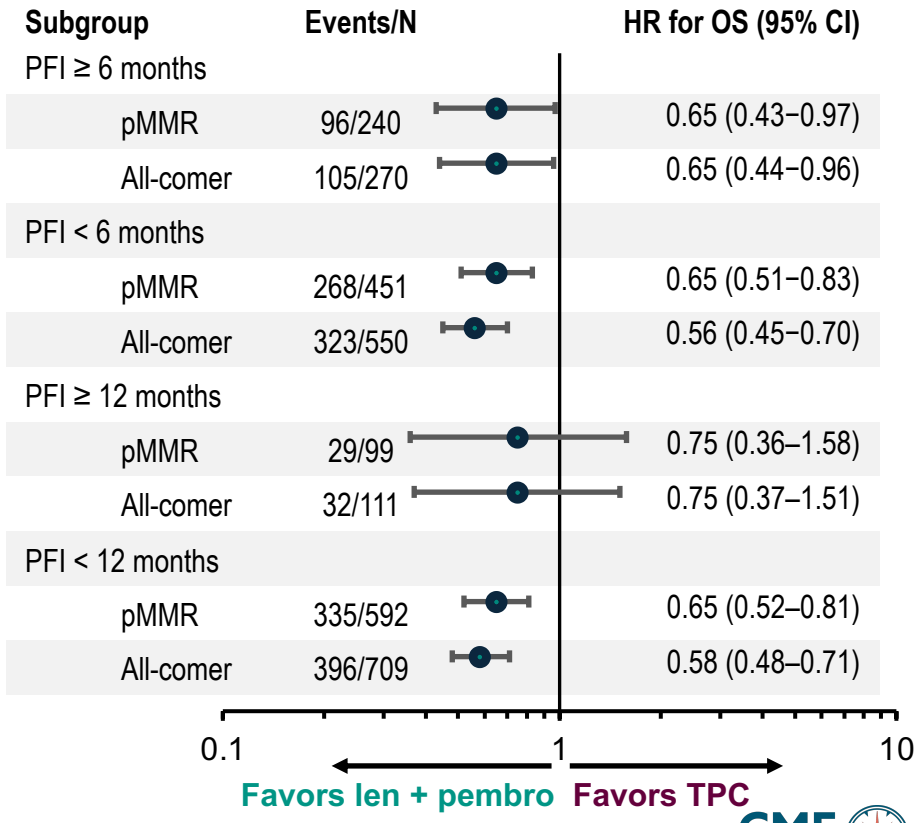
All-comers
LEN + pembro
TPC



Colombo N, et al. *Ann Oncol*. 2021;32(suppl_5):S725.

Overall Survival by Histology (All-Comers)





Colombo N, et al. *Ann Oncol*. 2021;32(suppl_5):S725.

Objective Response Rate

	pMMR		All-comers	
	LEN + pembro	IC	LEN + pembro	IC
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. IC, % *p* - value	15.2 < .0001	--	17.2 < .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. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

Pembrolizumab and Lenvatinib

- Based on KEYNOTE-775, pembrolizumab + lenvatinib is FDA approved for patients:
  - With advanced endometrial carcinoma that is not MSI-H or dMMR
  - Who have disease progression following prior systemic therapy in any setting
  - Who are not candidates for curative surgery or radiation

U.S. Food and Drug Administration Website. 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-pembrolizumab-and-lenvatinib-advanced-endometrial-carcinoma. Accessed October 21, 2021.

NCCN Recommended Systemic Regimens for Recurrent, Metastatic, or High-Risk Endometrial Cancer

Systemic therapies	Preferred Carboplatin/paclitaxel Carboplatin/paclitaxel/trastuzumab (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)		
	Other single or combination agents		
	Albumin-bound paclitaxel Bevacizumab Cisplatin Carboplatin	Doxorubicin Docetaxel Ifosfamide Liposomal doxorubicin	Paclitaxel Topotecan Temsirolimus
Biomarker-directed systemic therapy for second-line treatment	Preferred Lenvatinib/pembrolizumab for non–MSI-H/dMMR tumors Pembrolizumab for TMB-H or MSI-H/dMMR tumors	Other options Nivolumab for dMMR/MSI-H tumors Dostarlimab-gxly for dMMR/MSI-H tumors Larotrectinib or entrectinib for NTRK gene fusion-positive tumors Avelumab for dMMR/MSI-H tumors* Cabozantinib*	

HER-2 = Human epidermal growth factor receptor 2. NTRK = Neurotrophic tyrosine receptor kinase. TMB-H = Tumor mutational burden-high.
* Not specifically approved for endometrial cancers.

National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Uterine Neoplasms, Version 4.2021*. NCCN Website. 2021. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed October 28, 2021.

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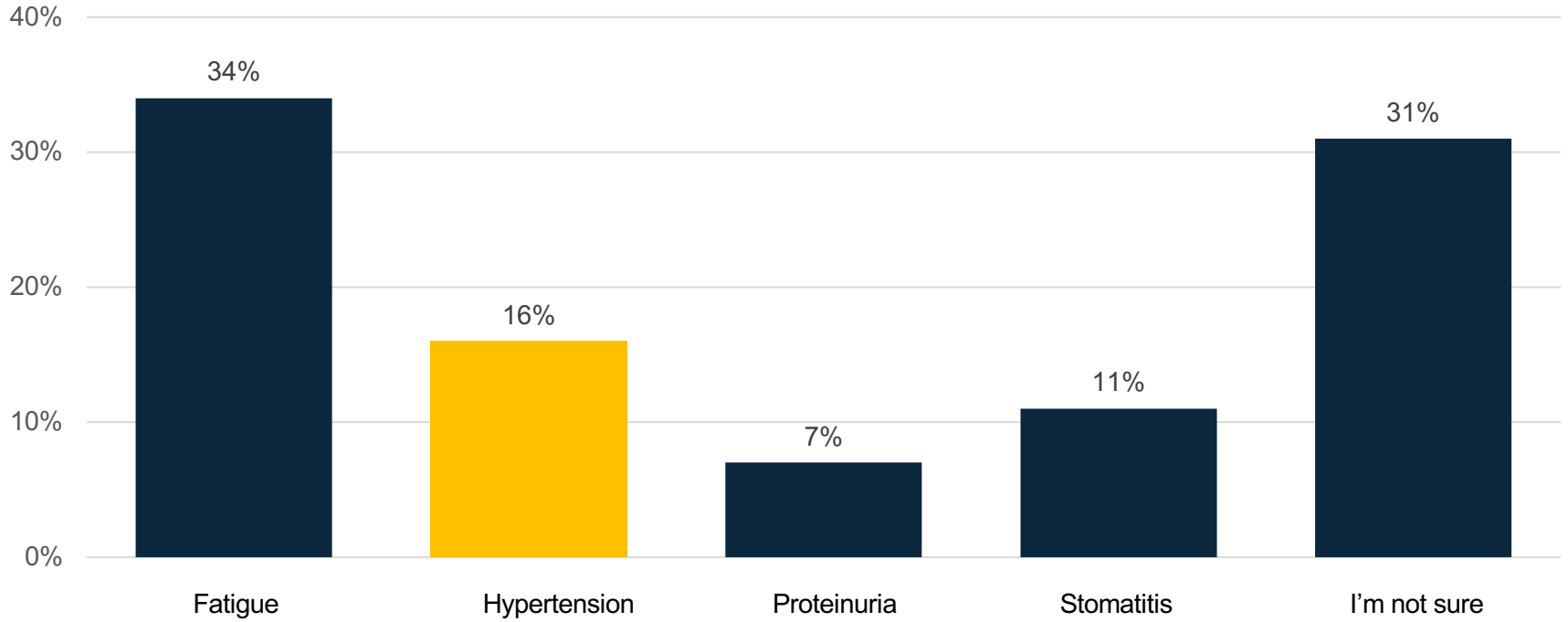
Polling Question

Which of the following was the most common adverse event (any grade) in the pembrolizumab/lenvatinib arm of the KEYNOTE-775 trial?

A. Fatigue
B. Hypertension
C. Proteinuria
D. Stomatitis
E. I'm not sure

Audience Responses

Which of the following was the most common adverse event (any grade) in the pembrolizumab/lenvatinib arm of the KEYNOTE-775 trial?



CME OUTFITTERS

Case Study 2: Susan

- Receives pembrolizumab + lenvatinib
- 4-6 weeks into therapy, she complains of nausea, significant fatigue, constipation, cough, and cold

Treatment Exposure, Safety, and Discontinuation

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

[a] Includes LEN only or IC. [b]Includes LEN or pembro or LEN + pembro or IC. [c]Regardless of action taken with the other drug in the combination arm.
TEAE, treatment-emergent adverse event.

Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

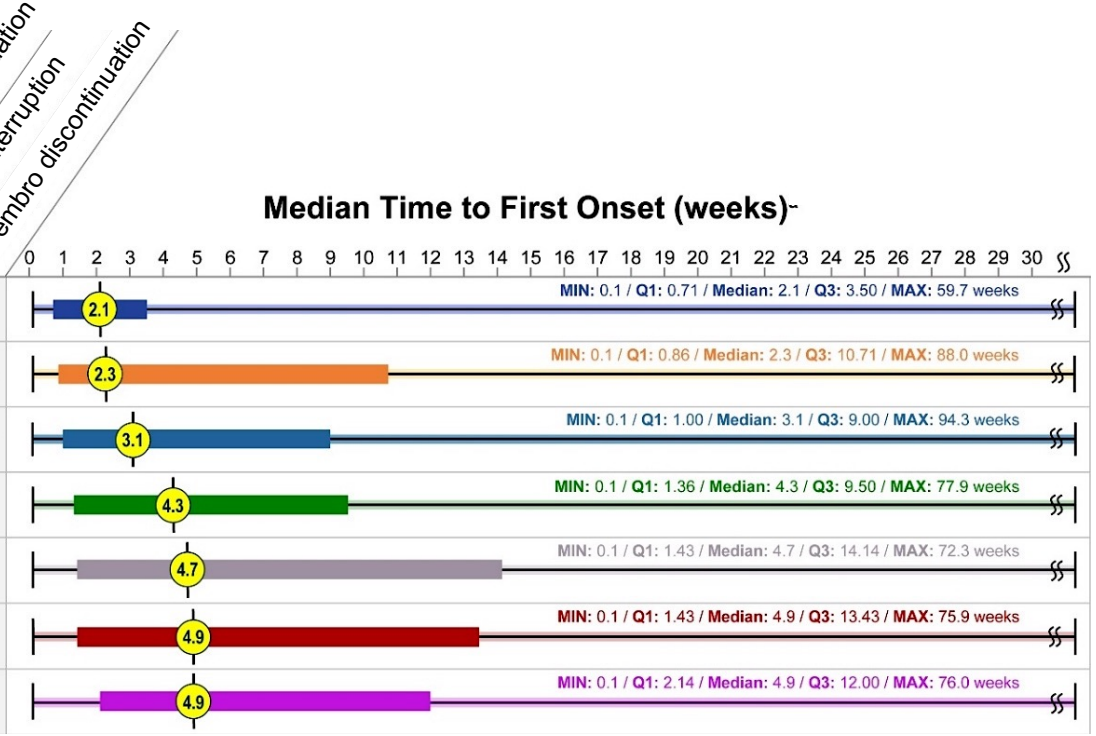
Adverse Events

	LEN + pembro (n = 406)		IC (n = 388)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with any TEAEs, %	99.8	88.9	99.5	72.7
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism	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

Makker V, et al. 2021 IGCS Annual Global Meeting; 2021. Plenary 1 Abstract 43. IGCS21_Orals__withoutLB_.pdf. Accessed November 2, 2021.

Time to First Onset of AEs in All-comers from KEYNOTE-775

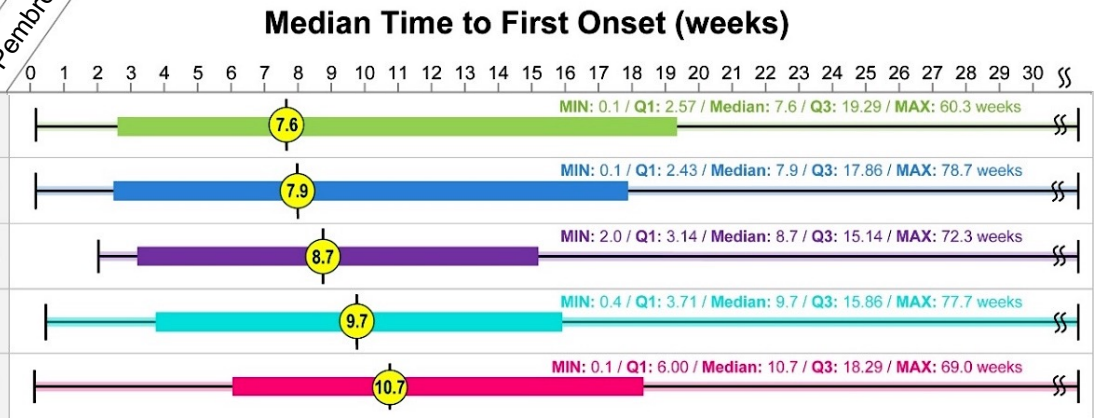
Adverse reaction	Incidence n	Incidence %	LEN dose interruption	LEN dose reduction	LEN dose discontinuation	Pembro interruption	Pembro discontinuation
Hypertension	264	65.0%	11.8%	17.7%	2.0%	3.4%	0%
Fatigue	238	58.6%	6.4%	11.8%	2.0%	4.2%	0.2%
Musculoskeletal pain	213	52.5%	3.4%	4.9%	0.7%	3.4%	0.2%
Stomatitis	144	35.5%	2.2%	4.2%	0.5%	0.5%	0.2%
Nausea	201	49.5%	3.4%	4.9%	0.5%	1.7%	0%
Decreased appetite	183	45.1%	4.9%	6.2%	1.7%	2.2%	0.7%
Proteinuria	120	29.6%	6.2%	7.9%	1.2%	2.0%	0%



Max = Maximum. Min = Minimum. Q1 = First quartile. Q3 = Third quartile.
Colombo N, et al. *Int J Gynecol Cancer.* 2021;31(Suppl 3):A78

Time to First Onset of AEs in All-comers from KEYNOTE-775

Adverse reaction	Incidence n	Incidence %	LEN dose interruption	LEN dose reduction	LEN dose discontinuation	Pembro interruption	Pembro discontinuation
Vomiting	149	36.7%	5.4%	3.2%	1.0%	1.7%	0%
Diarrhea	221	54.4%	10.8%	11.3%	1.2%	8.1%	1.0%
Hypothyroidism	279	68.7%	2.2%	0.7%	0%	1.7%	0.2%
PPES	89	21.9%	1.7%	8.1%	0.5%	1.7%	0%
Weight decrease	138	34.0%	2.5%	5.4%	1.5%	1.5%	0.2%



AEs best managed with combination of supportive care medications and judicious lenvatinib dose modifications

PPES = Palmar-plantar erythrodysesthesia syndrome.

Colombo N, et al. *Int J Gynecol Cancer.* 2021;31(Suppl 3):A78.

Case Study 2: Susan

- TSH, 8.4 mU/L; free-T4, 1.1 µg/dL

- How would you manage this patient?
- What supportive care does she need?
- Does she need dose modifications?

mU/L = Milliunits per liter. T4 = Thyroxine. µg/dL = Micrograms per deciliter.

Immune-Related Adverse Events (irAEs)

- irAEs are rare side effects of relaxing control over a patient's immune system[1,2]
  - The most common irAEs are rash and pruritus, pneumonitis, diarrhea and/or immune-mediated colitis, hepatitis, nephritis, and endocrine disorders (e.g., hypothyroidism, hypophysitis, adrenal insufficiency, diabetes)
  - However, other very rare disorders are possible (e.g., myocarditis, uveitis, pancreatitis, arthritis, and many others)
- Management of irAEs[1,2]
  - Generally, CPI therapy can be continued for grade 1 irAEs, interrupted until resolution for grade 2/3 irAEs, and permanently discontinued with grade 4 irAEs
    - Hypothyroidism: supplement with levothyroxine, no treatment interruption
  - Medications include corticosteroids, immunomodulators, vedolizumab, mycophenolate

1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Management of Immunotherapy-Related Toxicities Version 4.2021*. 2021. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed October 28, 2021. 2. Ellithi M, et al. *Cureus*. 2020;12(2):e6935.

Dosing Modifications for Lenvatinib and Pembrolizumab In KEYNOTE-775

- Dosing modifications and interruptions for lenvatinib and pembrolizumab
  - Dose reductions for lenvatinib
  - Dose modifications according to package insert
- Use optimal medical management when available (e.g., nausea, vomiting, hypertension, diarrhea, and hypothyroidism)
- For most AEs
  - The protocol for Study 309/KEYNOTE-775 recommended that patients resume lenvatinib treatment upon resolution of AEs to tolerable grade 2 or grade ≤ 1 severity
  - Lenvatinib package insert recommends withholding lenvatinib treatment for persistent or intolerable grade 2 or grade 3 severity; upon resolution to grade ≤ 1 or baseline, lenvatinib can be resumed at a lower dose

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

Concomitant Medications for the Management of AEs

Adverse Reaction Medications received, n (%)	pMMR Population LEN + Pembro (n = 342)	All-Comer Population LEN + Pembro (n = 406)
Hypertension	**186 (54.4)**	**216 (53.2)**
Amlodipine	70 (20.5)	80 (19.7)
Amlodipine besylate	41 (12.0)	49 (12.1)
Losartan	24 (7.0)	28 (6.9)
Ramipril	19 (5.6)	20 (4.9)
Captopril	16 (4.7)	21 (5.2)
Fatigue	**10 (2.9)**	**12 (3.0)**
Nausea	**111 (32.5)**	**131 (32.3)**
Ondansetron	39 (11.4)	41 (10.1)
Metoclopramide hydrochloride	31 (9.1)	36 (8.9)
Metoclopramide	24 (7.0)	31 (7.6)
Vomiting	**45 (13.2)**	**52 (12.8)**
Diarrhea	**121 (35.4)**	**141 (34.7)**
Loperamide hydrochloride	51 (14.9)	61 (15.0)
Loperamide	50 (14.6)	58 (14.3)

Colombo N, et al. *Int J Gynecol Cancer.* 2021;31(Suppl 3):A78.

Concomitant Medications for the Management of AEs

Adverse Reaction Medications received[a], n[b] (%)	pMMR Population LEN + Pembro (n = 342)	All-Comer Population LEN + Pembro (n = 406)
Decreased appetite	**36 (10.5)**	**42 (10.3)**
Weight decreased	**12 (3.5)**	**17 (4.2)**
Hypothyroidism Levothyroxine sodium	**180 (52.6)** 177 (51.8)	**216 (53.2)** 213 (52.2)
Palmar-plantar erythrodysesthesia syndrome	**53 (15.5)**	**62 (15.3)**
Musculoskeletal disorders Paracetamol Ibuprofen	**105 (30.7)** 50 (14.6) 23 (6.7)	**125 (30.8)** 59 (14.5) 23 (5.7)
Stomatitis	**76 (22.2)**	**91 (22.4)**
Proteinuria	**5 (1.5)**	**5 (1.2)**

Colombo N, et al. *Int J Gynecol Cancer.* 2021;31(Suppl 3):A78.

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Colombo N, et al. *Int J Gynecol Cancer.* 2021;31(Suppl 3):A78.

Ongoing Trials of CPIs Plus Targeted Agents

Emerging agents, not yet approved by the FDA for the treatment of endometrial cancer

- Atezolizumab +
  - Bevacizumab, ipatasertib (AKTi), talazoparib (PARPi), or cytotoxic chemotherapy
- Nivolumab +
  - Rucaparib (PARPi), cabozantinib (MET/VEGF inhibitor), or ipilimumab
- Durvalumab + olaparib (PARPi)
- Dostarlimab + cytotoxic chemotherapy
- Combinations are being explored in the first-line setting as well.

AKTi = Protein kinase B inhibitor. MET = Mesenchymal-epithelial transition proto-oncogene. PARPi = Poly (ADP-ribose) polymerase inhibitor.

Considerations for Combining TKI and CPI Therapies

- Dual therapy with TKIs and CPI therapies have potential to be synergistic and improve patient outcomes
  - However, side effects are more common and potentially more severe
- Managing side effects may be challenging
  - What are early symptoms of important side effects?
  - Which agent is responsible for the side effect?
  - Which agent should be held, or dosage reduced?
  - Can patients be rechallenged with the withheld agent?

Przybylski DJ, et al. *J Oncol Pharm Pract*. 2021;27(4):930-938

Summary

- VEGF and immune checkpoint inhibitor combinations are reasonable combinations for the treatment of endometrial cancer based on mechanisms of action
- Lenvatinib + pembrolizumab are efficacious in the treatment of endometrial cancer
- TKI and CPI combination therapy presents challenges to providing maximum efficacy, while minimizing safety concerns
- Early monitoring for AEs and proactive management are critical to maintaining patients on therapy

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Clinicians should closely monitor and proactively manage emergent AEs, particularly in the first 2 months of treatment
- Clinicians should consider consulting with specialists early about symptoms that are resistant to management
- Clinicians should continue monitoring women receiving pembrolizumab/lenvatinib combination for late appearing AEs

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