INIBITORI DEI CHECK-POINT IMMUNITARI NEL CARCINOMA DELL'ENDOMETRIO E DELLA CERVICE

ANGIOLO GADDUCCI (PISA)

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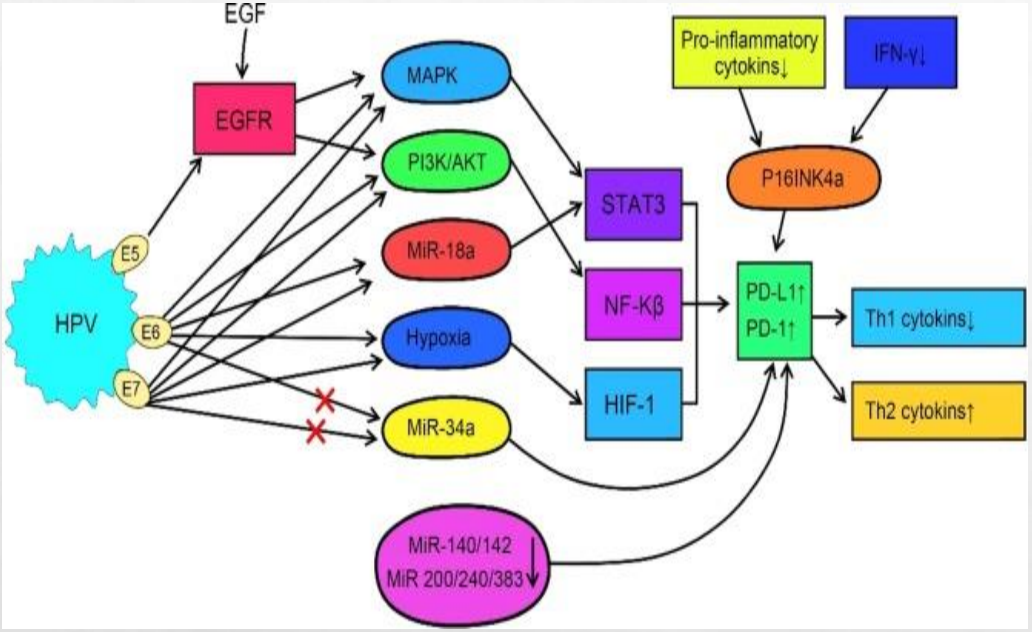
PD-L1: Can it be a biomarker for the prognosis or a promising therapeutic target in CC?



- ✓ E5, E6 and E7 activate signaling pathways (HIF-1, MAPK-STAT3,PI3K/AKT-NF-Kb,HIF-1), thus up-regulating PD-1 and PD-L1 expression
- ✓ Down-regulation of miR-140/142/200/340/383 increases PD-1 and PD-L1 expression

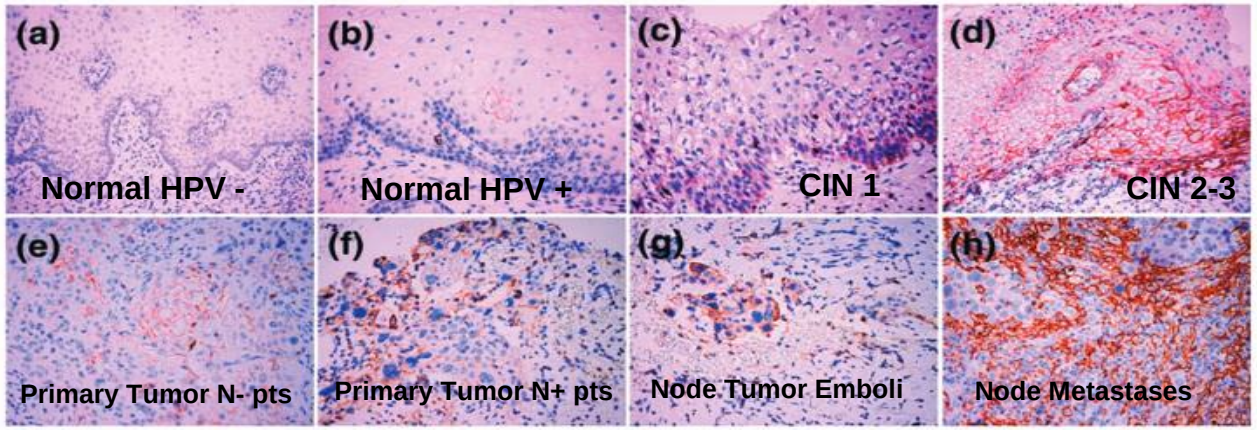
Wang W et al. 2022

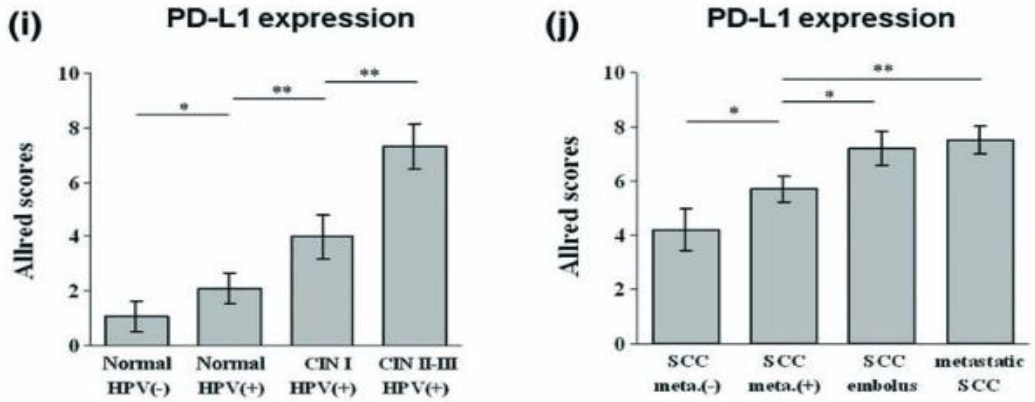
Expressions of PD-1 and PD-L1 in CIN and SCC have a prognostic value and are associated with HPV status

Cohort I: CIN samples from 40 pts tested positive or negative for HR-HPV

Cohort II: paired primary/metastatic tumor samples from 20 SCC pts

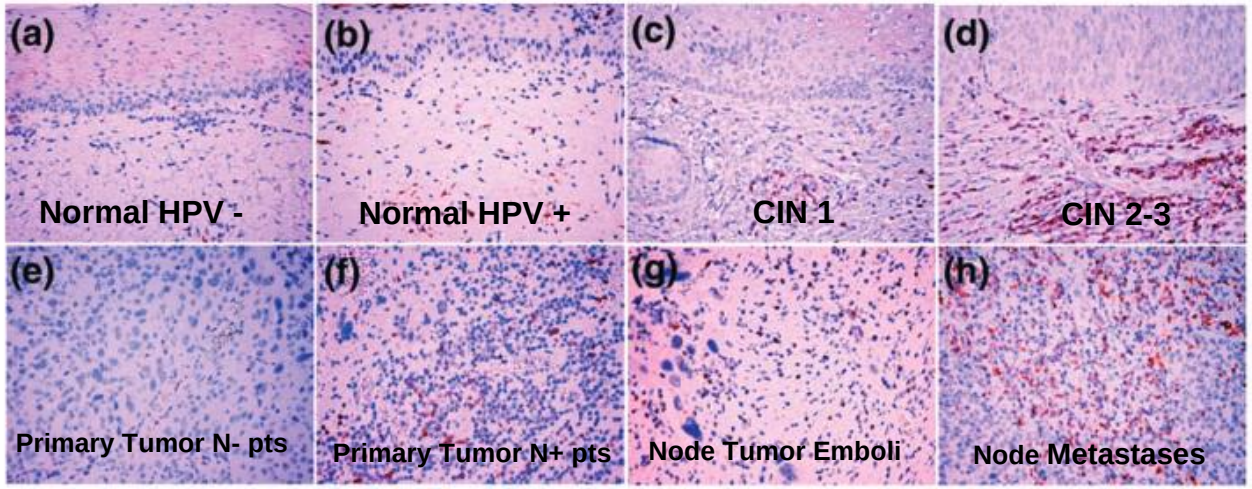
IHC used to detect PD-L1 in tumor cells and PD-1 in TAM and TIL

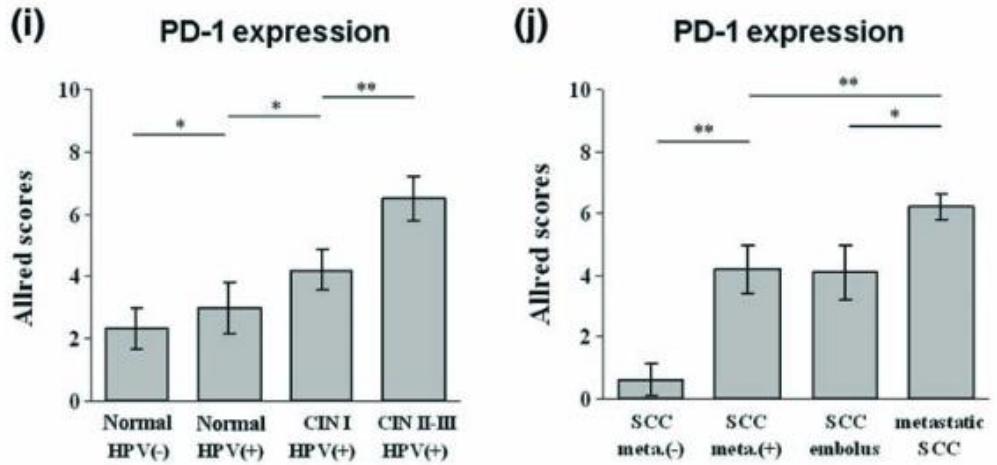




PD-L1 expression was increased in lymphatic tumor emboli ($p<0.05$) and N metastases ($p<0.01$) compared to primary lesions

Yang W et al. 2017





PD-1 expression in N MTS higher than in primary lesion ($p<0.01$) and metastatic emboli ($p<0.05$)

>Increased PD-L1/D-1 expression correlates with HPV-positivity, increase in CIN grade, and tumor MTS

>PD-L1/PD-1 expression could be a prognostic markers of CIN and CC, and therapies that inhibit PD-L1/PD-1 could be effective in CC

Immune checkpoint inhibitors (ICI)s in persistent, recurrent or metastatic cervical cancer

Authors	ICI	pts (n)	OR	DOR (months)
Neumann (2019)	Nivolumab	19	26.3%	NR
Tamura (2019)	Nivolumab	20	25.0%	5.6
Chung (2019)	Pembrolizumab	99	12.2%	NR
Lan (2020)	Canrelizumab+ Apatinib	45	55.6%	NR
O'Malley (2021)	Balstilimab	140	15.0%	15.4
Tawari (2022)	Cemiplimab	304	16.4%	16.4

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Efficacy and safety of PEMBRO in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study (NCT02628067).

- Basket study investigating PEMBRO (200 mg iv Q3W up to 2 years in multiple, advanced solid tumor types that have progressed with standard-of-care systemic therapy)
- Interim results from pts with previously treated advanced cervical cancer
- 98 pts included. 82 pts (83.7%): PD-L1+ tumors (CPS ≥ 1), 77 having previously received one or more CT lines for recurrent /metastatic disease. Median follow-up: 10.2 months (range, 0.6 to 22.7)
- ORR: 12.2% (95% CI, 6.5% - 20.4%) (CR, 3; PR, 9)
- All 12 responses were in pts with PD-L1+ tumors, for an ORR of 14.6% (95% CI, 7.8% - 24.2%)
- Median DOR: NR (range, ≥ 3.7 to ≥ 18.6 months)

FDA granted accelerated approval of PEMBRO for pts with advanced PD-L1+ cervical cancer who experienced progression during or after chemotherapy

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Pembrolizumab (PEMBRO) for persistent, recurrent, metastatic cervical cancer: KEYNOTE-826. Double-blind phase 3 trial

Eligibility criteria:

- ✓ Pts ≥ 18 years with persistent, recurrent, or metastatic AD, ASC or SCC not pre-treated with systemic CT and not amenable to curative treatment.
- ✓ Previous RT or CT/RT permitted if completed ≥ 2 weeks before randomization
- ✓ ECOG PS= 0, 1
- ✓ Measurable disease according to RECIST, version 1.1
- ✓ Available tumor-tissue sample from a nonirradiated lesion for PD-L1 status.

CPS: $\frac{\text{number of PD-L1-staining cells}}{\text{total number of viable tumor cells}} \times 100$

Colombo N et al, N Engl J Med 2021

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PEMBRO for persistent, recurrent, metastatic cervical cancer: KEYNOTE-826

RANDOM stratified by
- Metastatic Disease (yes vs not)
- BEV (yes vs not)
- CPS (<1 vs 1-<10 vs ≥10)

PEMBRO	Placebo
200 mg Q3W up to 35 cycles +	Q3W up to 35 months +
CDDP 50 mg/m^2 or CBDCA AUC5+	CDDP 50 mg/m^2 or CBDCA AUC5+
PTX 175 mg/m^2 Q3W +	PTX 175 mg/m^2 Q3W +
BEV 15 mg/kg Q3W *	BEV 15 mg/kg Q3W*

*according to local practice at the investigator's discretion

Dual primary endpoints: PFS and OS tested sequentially in pts with CPS ≥ 1, ITT population , and pts with CPS ≥10 (investigator review)

Protocol amendment (June 2019) limited CT to 6 cycles (pts with ongoing clinical benefit without AEs could continue >6 cycles after consultation with sponsor)

Colombo N et al, N Engl J Med 2021

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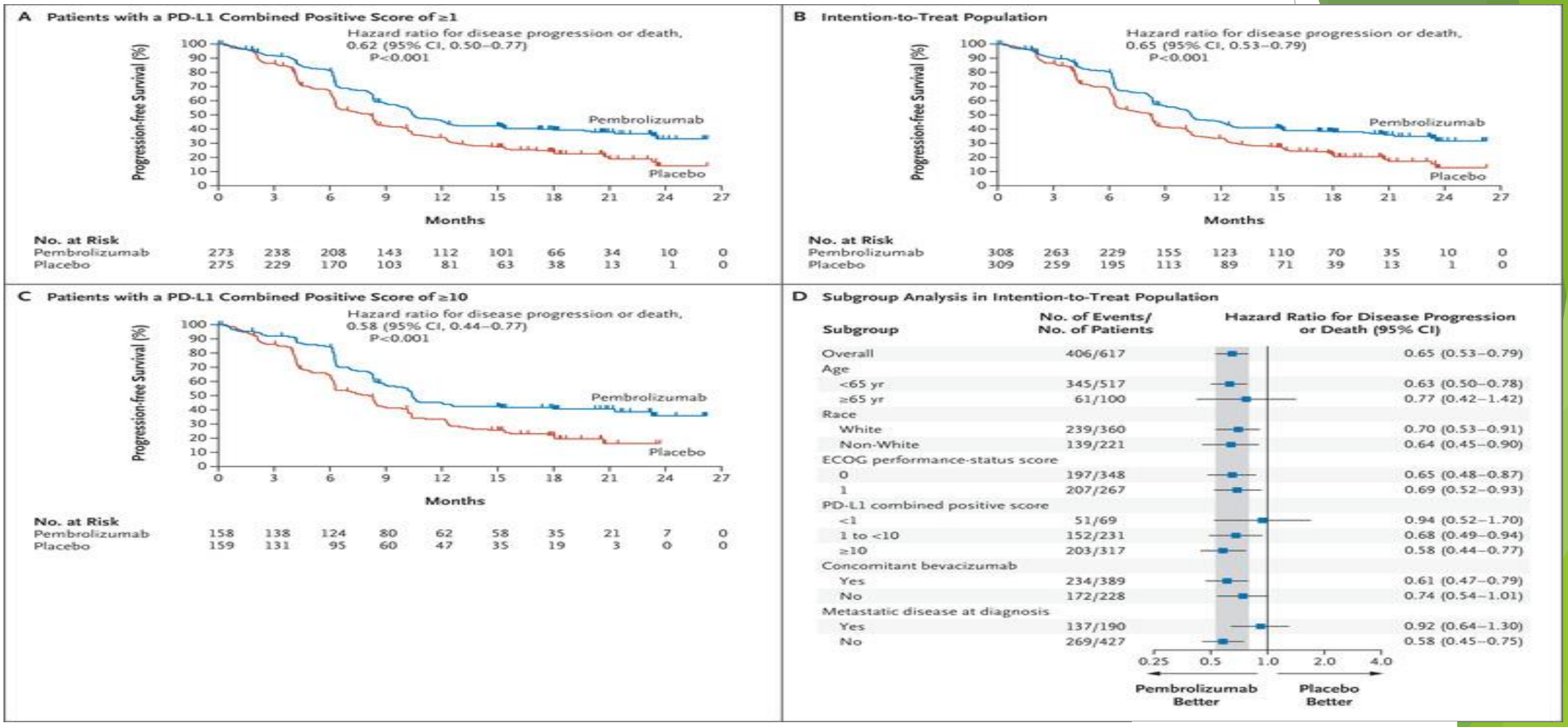
PEMBRO for persistent, recurrent, metastatic cervical cancer: KEYNOTE-826

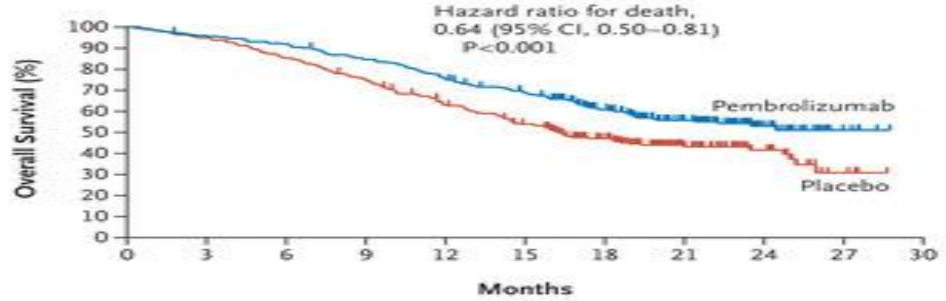
Kaplan–Meier Estimates of PFS



PEMBRO for persistent, recurrent, metastatic cervical cancer: KEYNOTE-826

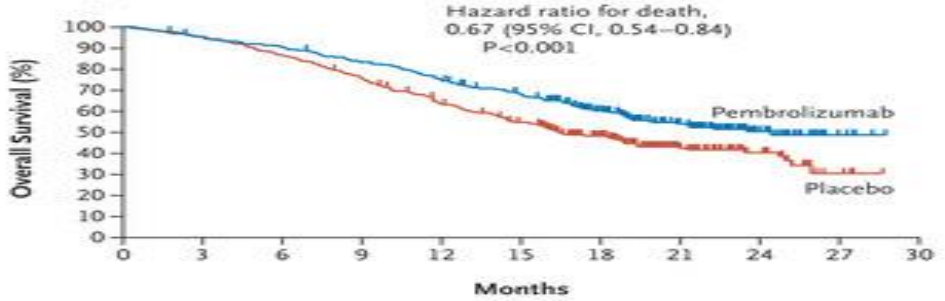
Kaplan-Meier Estimates of OS

A Patients with a PD-L1 Combined Positive Score of ≥1



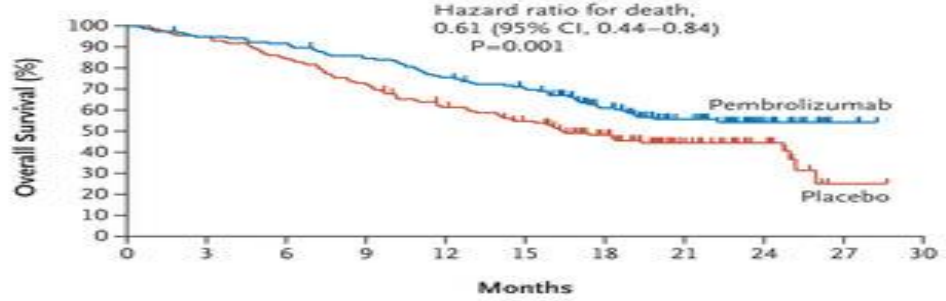
No. at Risk											
Pembrolizumab	273	260	250	229	204	181	132	82	34	6	0
Placebo	275	261	235	206	168	140	100	55	25	4	0

B Intention-to-Treat Population



No. at Risk											
Pembrolizumab	308	291	277	254	228	201	145	89	36	6	0
Placebo	309	295	268	234	191	160	116	60	28	4	0

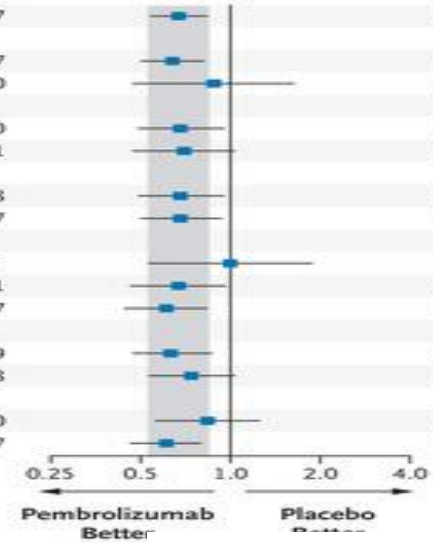
C Patients with a PD-L1 Combined Positive Score of ≥10



No. at Risk											
Pembrolizumab	158	149	144	132	118	106	76	46	21	3	0
Placebo	159	151	135	116	95	81	56	31	15	1	0

D Subgroup Analysis in Intention-to-Treat Population

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	312/617	0.67 (0.54–0.84)
Age		
<65 yr	265/517	0.64 (0.50–0.82)
≥65 yr	47/100	0.88 (0.47–1.64)
Race		
White	189/360	0.68 (0.50–0.91)
Non-White	107/221	0.70 (0.47–1.04)
ECOG performance-status score		
0	141/348	0.68 (0.49–0.96)
1	169/267	0.68 (0.50–0.94)
PD-L1 combined positive score		
<1	40/69	1.00 (0.53–1.89)
1 to <10	118/231	0.67 (0.46–0.97)
≥10	154/317	0.61 (0.44–0.84)
Concomitant bevacizumab		
Yes	166/389	0.63 (0.47–0.87)
No	146/228	0.74 (0.53–1.04)
Metastatic disease at diagnosis		
Yes	104/190	0.84 (0.56–1.26)
No	208/427	0.61 (0.46–0.80)



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PEMBRO for persistent, recurrent, metastatic cervical cancer: KEYNOTE-826

Response	Pts with PDL1 CPS >1		Intention to treat population		Pts with PDL1 CPS >10	
	PEMBRO n. 273	Placebo N 275	PEMBRO N 308	Placebo N 309	PEMBRO N 158	Placebo n 159
OR (95% CI)	68,1 (62.2-73.6)	50,2 (44,1-56.2)	65,9 (60,3-71.2)	50,8 (45,1-56,5)	69,6 (61,8-76.7)	49,1 (41,1-57,1)
CR, n %	62 (22.7%)	36 (13,1%)	66 (21.4%)	40 (12.9%)	35 (22.2%)	18 (11,3%)
PR, n %	124 (45.4%)	102 (37,1%)	137 (44,5%)	117 (37,9%)	75 (47.5%)	60 (37.7%)
SD, n %	58 (21.2%)	88 (32,0%)	69 (22.4%)	99 (32.0%)	29 (18,4%)	53 (33,3%)
PD , n %	9 (3.3%)	29 (10,5%)	15 (4,9%)	33 (10,7%)	4 (2,5%)	16 (10,1%)
Not evaluable	1 (0.4%)	2 (0.7%)	1 (0.3%)	2 (0.6%)	1 (0.6%)	12 (1,3%)
Not assessed	19 (7.0%)	18 (6,5%)	20 (6,5%)	18 (5,8%)	14 (8,9%)	10 (6,3%)
Median DOR	18.0 months	10.4 months	18.0 months	10.4 months	21.1 months	9.4 months

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Table S12. Potentially Immune-Mediated Adverse Events (As-Treated Population).*

Event	Pembrolizumab Group (N=307)†		Placebo Group (N=309)†	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
	number of patients (percent)			
Any event	104 (33.9)	35 (11.4)‡	47 (15.2)	9 (2.9)§
Hypothyroidism	56 (18.2)	4 (1.3)	28 (9.1)	1 (0.3)
Hyperthyroidism	23 (7.5)	0	9 (2.9)	1 (0.3)
Colitis	16 (5.2)	5 (1.6)	5 (1.6)	5 (1.6)
Severe skin reactions	14 (4.6)	12 (3.9)	1 (0.3)	1 (0.3)
Thyroiditis	11 (3.6)	2 (0.7)	1 (0.3)	0
Pneumonitis	6 (2.0)	1 (0.3)	1 (0.3)	0
Hepatitis	5 (1.6)	4 (1.3)	1 (0.3)	1 (0.3)
Adrenal insufficiency	4 (1.3)	3 (1.0)	0	0
Pancreatitis	3 (1.0)	2 (0.7)	1 (0.3)	0
Myositis	2 (0.7)	1 (0.3)	0	0
Type 1 diabetes mellitus	2 (0.7)	2 (0.7)	0	0
Vasculitis	2 (0.7)	0	0	0
Cholangitis sclerosing	1 (0.3)	1 (0.3)	0	0
Encephalitis	1 (0.3)	1 (0.3)	0	0
Hypophysitis	1 (0.3)	1 (0.3)	1 (0.3)	0
Myocarditis	1 (0.3)	1 (0.3)		
Nephritis	1 (0.3)	0		

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KEYNOTE-826: Final OS results from a randomized, phase 3 study of pembrolizumab+CT vs placebo+ CT for first-line treatment of persistent, recurrent, or metastatic cervical cancer.

	PDL1 CPS >1		Intention to treat population		PDL1 CPS >10	
	PEMBRO+CT	PL+CT	PEMBRO+CT	PL+CT	PEMBRO+CT	PL+CT
OS, median, mo	28.6	16.5	26.4	16.8	29.6	17.4
24-mo OS rate, %	53.5	39.4	52.1	38.7	54.4	42.5
OS, HR (95% CI)	0.60 (0.49-0.74); *P*< 0.0001		0.63 (0.52-0.77); *P*< 0.0001		0.58 (0.44-0.78); *P*< 0.0001	
PFS, median, mo	10.5	8.2	10.4	8.2	10.4	8.1
12-mo PFS rate, %	45.6	33.7	44.7	33.1	44.7	33.5
PFS, HR (95% CI)	0.58 (0.47-0.71); *P*< 0.0001		0.61 (0.50-0.74); *P*< 0.0001		0.52 (0.40-0.68); *P*< 0.0001	

These data provide further support for PEMBRO+ CT ± BEV as a new standard of care for first-line treatment of persistent, recurrent, or metastatic cervical cancer.

MONK BL et al. ASCO 2023

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Randomized Phase III Trial of Platinum + PTX + BEV + Atezolizumab vs Platinum + PTX + BEV in Metastatic (Stage IVB), Persistent, or Recurrent Carcinoma of the Cervix (NCT03556839, BEATcc)

- ✓ No prior systemic therapy for metastatic or recurrent disease
- ✓ Measurable disease by RECIST v1.1 criteria
- ✓ A tumor specimen mandatory at study entry

RANDOM

CDDP 50 mg/m^2 or CBDCA AUC5 +
PTX 175 mg/m2+ BEV 15 mg/kg Q3W

CDDP 50 mg/m^2 or CBDCA AUC5 +
PTX 175 mg/m2+ BEV 15 mg/kg +
Atezolizumab 1200 mg Q3W

- ✓ Responders after ≥6 cycles may continue on biologic therapy
- ✓ Primary ENDPOINTS : OS

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Survival with Cemiplimab in Recurrent CC

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9

✓ Phase 3 on 608 cervical cancer pts* who progressed after 1st-line platinum-containing CT regardless of PD-L1 status

Pts were required to have measurable disease.

Stratified by
- Histologic type
- Geographic region
- Prior BEV
- ECOG PS

Random

Cemiplimab (350 mg iv Q3W)

Single-agent CT**

Pemetrexed, Topotecan, Irinotecan, Gemcitabine, Vinorelbine

* Candidates for pelvic exenteration excluded

**investigator's choice chemotherapy

Primary end point= OS

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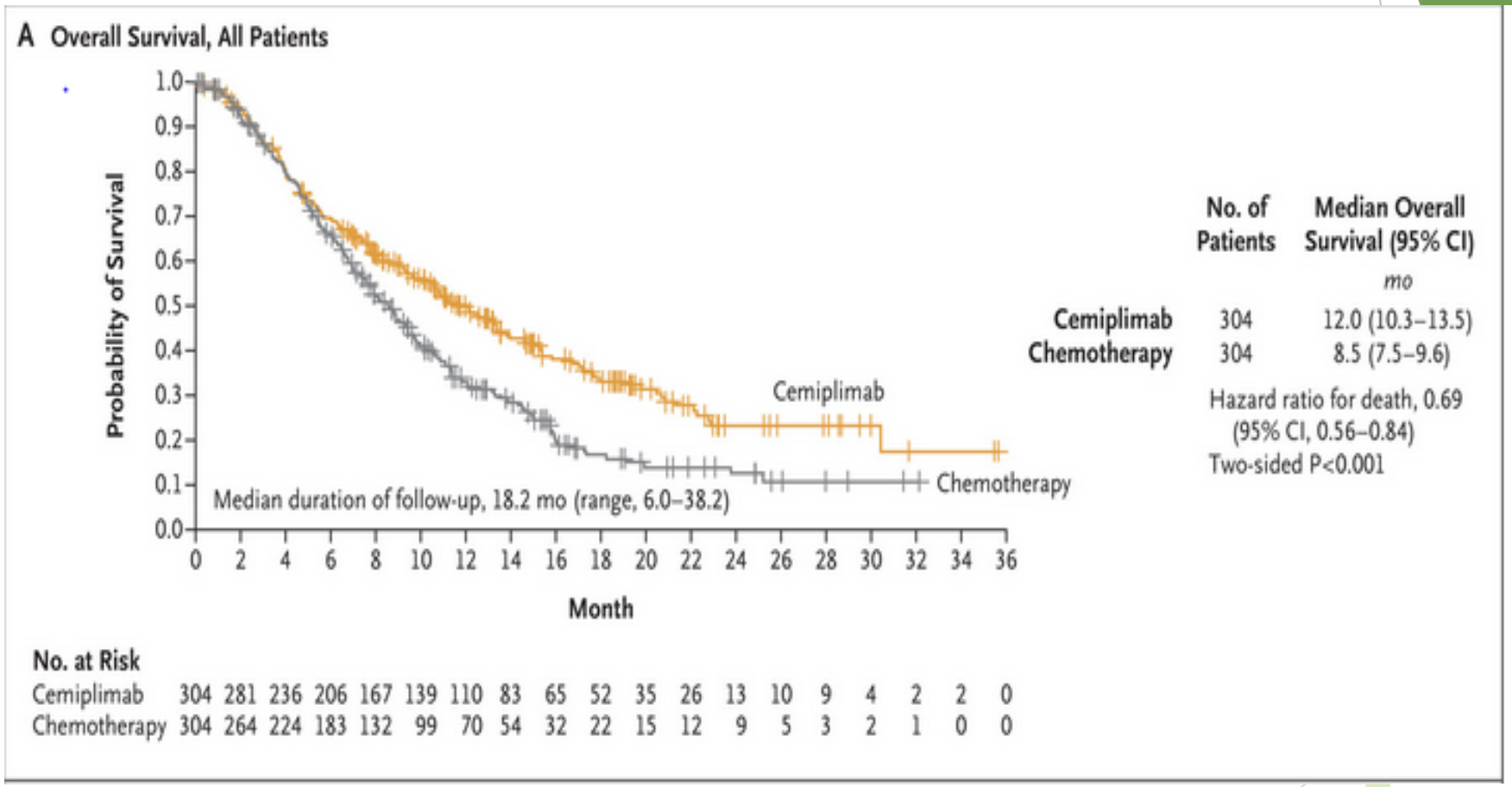
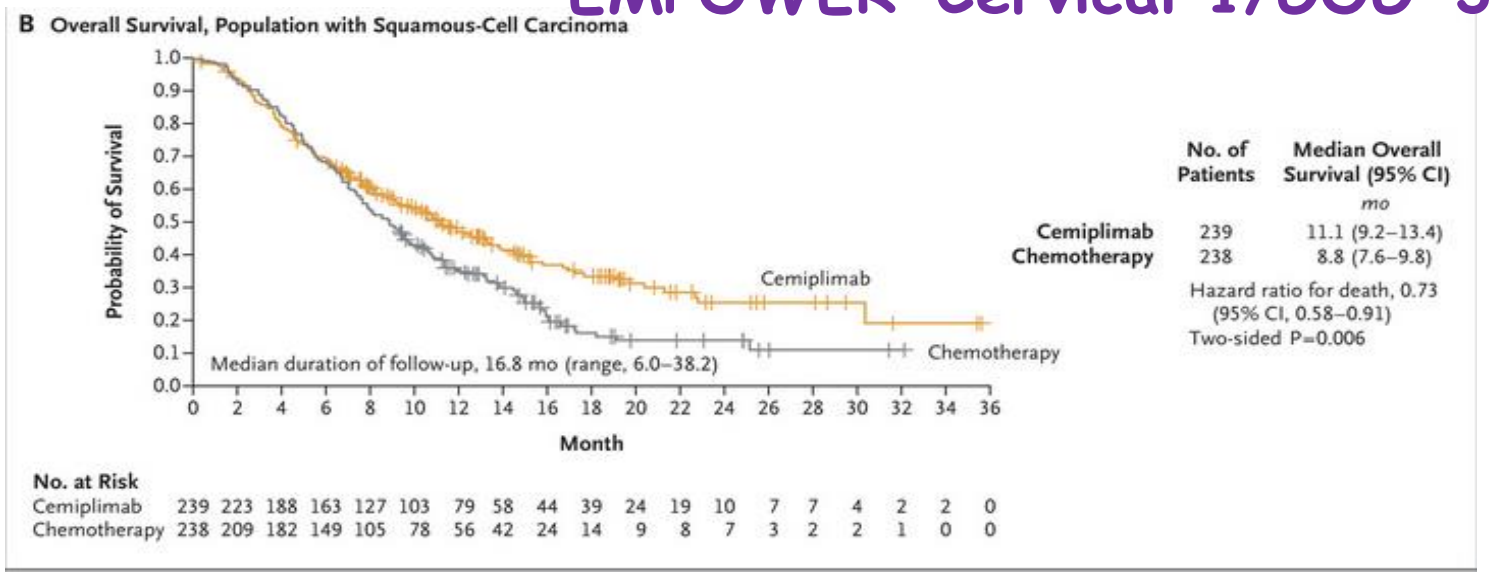
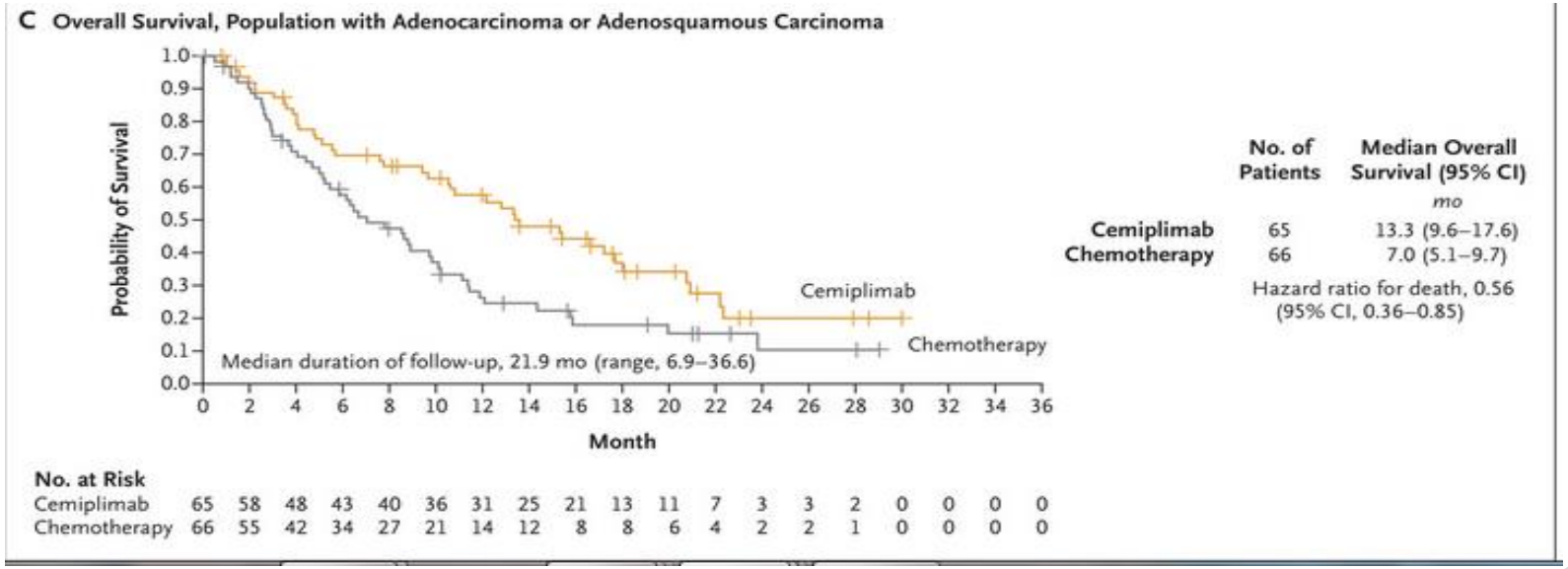
Tewari KS et al 2022

Survival with Cemiplimab in Recurrent Cervical Cancer
EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9



Survival with Cemiplimab in Recurrent Cervical Cancer
EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9





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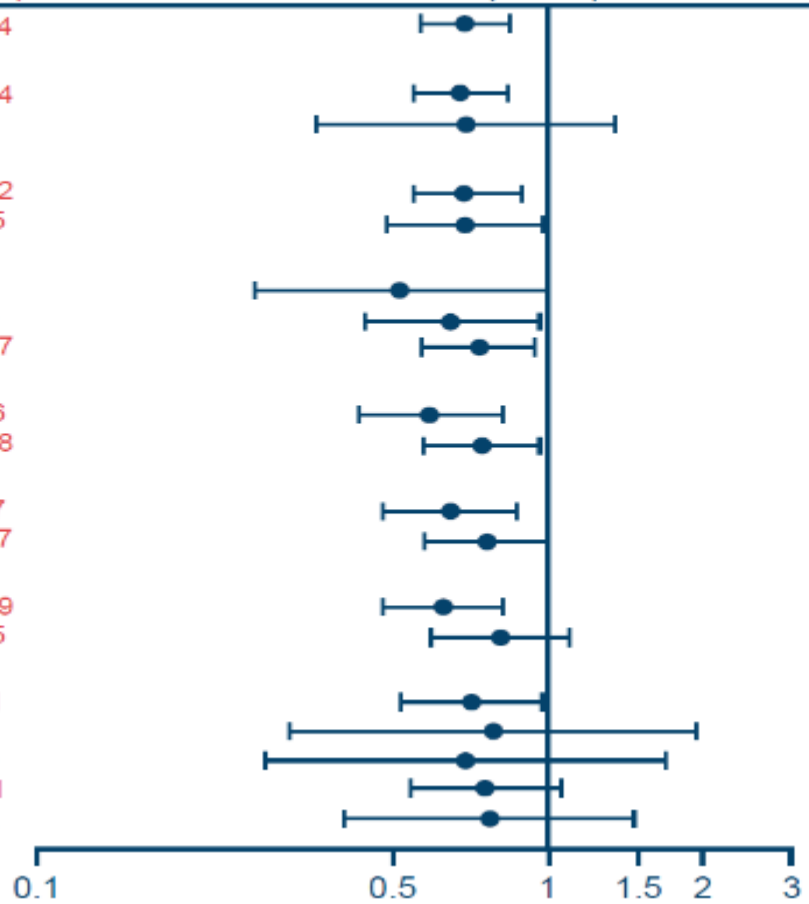
Survival with Cemiplimab in Recurrent cervical cancer

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9

	Cemiplimab (events/total)	Chemotherapy (events/total)	HR (95% CI)*
All patients	184/304	211/304	0.69 (0.56–0.84)
Age group			
<65 years	166/269	186/264	0.67 (0.54–0.84)
≥65 years	18/35	25/40	0.69 (0.35–1.36)
Race			
White	115/193	135/192	0.69 (0.54–0.89)
Non-White	67/107	71/105	0.69 (0.48–0.98)
Geographic region, group 1			
North America	16/32	22/34	0.52 (0.27–1.00)
Asia	54/83	54/83	0.65 (0.44–0.96)
Rest of World	114/189	135/187	0.73 (0.57–0.94)
ECOG status per IWRS			
0	73/146	88/146	0.59 (0.43–0.82)
1	111/158	123/158	0.74 (0.57–0.96)
Prior bevacizumab use per IWRS			
Yes	85/149	97/147	0.64 (0.48–0.86)
No	99/155	114/157	0.76 (0.58–1.00)
Number of prior lines of systemic therapy for R/M disease			
1 line	103/177	120/169	0.62 (0.48–0.82)
>1 line	80/124	91/135	0.81 (0.59–1.10)
IC of chemotherapy prior to randomization			
Pemetrexed	73/119	84/111	0.71 (0.52–0.98)
Topotecan	14/20	11/21	0.78 (0.31–1.96)
Irinotecan	12/26	12/19	0.69 (0.28–1.70)
Gemcitabine	65/108	80/121	0.76 (0.54–1.06)
Vinorelbine	20/31	24/32	0.77 (0.40–1.48)



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Ongoing trials of ICI for locally advanced CC using CCRT as a backbone

Trial name/ identification	Investigational therapy	Concurrent CCRT	Phase
	Immune checkpoint inhibitors		
CALLA NCT03830866	Durvalumab vs placebo •Concurrent with CCRT and adjuvant	Weekly platinum-based CT + EBRT->, BCT	III
KEYNOTE-A18 NCT04221945	Pembrolizumab vs placebo •Concurrent with CCRT and adjuvant	Weekly CDDP + EBRT ->BCT	III
ATEZOLACC NCT03612791	Atezolizumab vs standard of care •Concurrent with CCRT and adjuvant	Weekly CDDP + EBRT >BCT	II
BrUOG 355 NCT03527264	Nivolumab •Concurrent with CCRT •Adjuvant to CCRT •Concurrent with CCRT and adjuvant	Weekly CDDP + EBRT (BCT not specified)	II
NCT02635360	Pembrolizumab •Concurrent with CCRT •Adjuvant to CCRT	Weekly CDDP, then BCT only	II
NCT03738228	Atezolizumab •NACT and concurrent with CCRT •Concurrent with CCRT	Weekly CDDP + EBRT ->BCT	I

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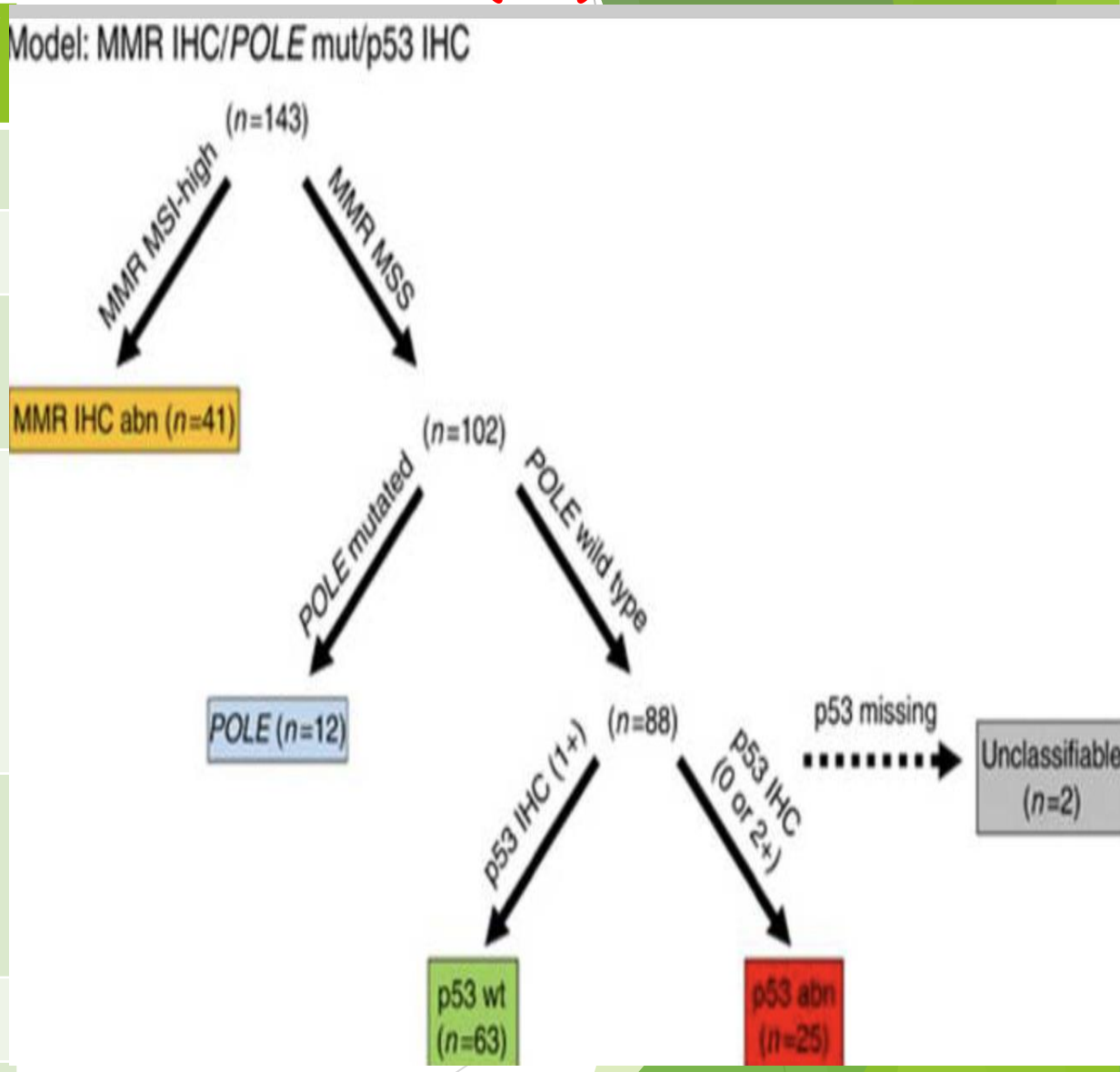
Molecular classification of endometrial cancer (EC)

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometrioid)	Copy-number high (serous-like)
Copy-number aberrations	Low	Low	Low	High
MSI/MLH1 methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232 × 10^{-6}mutations/Mb)	High (18 × 10^{-6}mutations/Mb)	Low (2·9 × 10^{-6}mutations/Mb)	Low (2·3 × 10^{-6}mutations/Mb)
Genes commonly mutated (prevalence)	POLE (100%) PTEN (94%) PIK3CA (71%) PIK3R1 (65%) FBXW7 (82%) ARID1A (76%) KRAS (53%) ARID5B (47%)	PTEN (88%) RPL22 (37%) KRAS (35%) PIK3CA (54%) PIK3R1 (40%) ARID1A (37%)	PTEN (77%) CTNNB1 (52%) PIK3CA (53%) PIK3R1 (33%) ARID1A (42%)	TP53 (92%) PPP2R1A (22%) PIK3CA (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumour grade	Mixed (grades 1-3)	Mixed (grades 1-3)	Grades 1 and 2	Grade 3
Progression-free survival	Good	Intermediate	Intermediate	Poor



PEMBRO in MSI-H advanced EC: KEYNOTE-158 study (NCT02628067)

- ✓ Nonrandomized, multicohort, phase II study of pembrolizumab in multiple types of advanced (unresectable and/or metastatic) cancers
- ✓ 90 pts with MSI-H/dMMR EC (2/2016-9/2020) with disease progression on standard therapy
- ✓ As cutoff date (October 5, 2020), 79 pts receiving ≥ 1 dose of PEMBRO were enrolled ≥ 26 weeks before data cut-off, and included in efficacy analysis.

✓ ORR:	48%	(95%CI, 37 – 60%)
✓ Median DOR:	NR	(range,2.9-49.7+ months)
✓ Median PFS:	13.1 months	(range,4.3 - 34.4 months
✓ Median OS:	NR	(range, 27.2 months – NR)

Among all treated pts, No fatal AEs

IR-AEs or infusion reactions: 28% (G3-4= 7%)

(O'Malley DM et al. 2022)

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Safety and antitumor activity of dostarlimab advanced/ recurrent (dMMR/MSI-H) or MMRp/MSS EC : interim results from GARNET—phase I, single-arm study

- Single-arm, open-label, phase I trial of dostarlimab in advanced/recurrent tumors (123 sites)
- Two cohorts of pts with EC were recruited: those with dMMR/MSI-H (cohort A1) and those with proficient/stable (MMRp/MSS) (cohort A2).
- Dostarlimab 500 mg Q3W for 4 cycles then 1000 mg Q6W until progression
- Primary endpoints= ORR and DOR (RECIST 1.1) by blinded independent central review.

Oaknin A et al. 2022

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Results: primary endpoint analysis

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	**27.6**	**33.0**
ORR, % (95% CI; n/N)	**45.5** (37.1–54.0; 65/143)	**15.4** (10.1–22.0; 24/156)
CR, n (%)	23 (16.1)	4 (2.6)
PR, n (%)	42 (29.4)	20 (12.8)
SD, n (%)	21 (14.7)	29 (18.6)
PD, n (%)	51 (35.7)	88 (56.4)
NE, n (%)	6 (4.2)	15 (9.6)
Median duration of response (range), months	**NR** (1.18+ to 47.21+)	**19.4** (2.8 to 47.18+)
Probability of remaining in response, %		
6 months	96.8	82.6
12 months	93.3	60.3
24 months	83.7	44.2

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	**27.6**	**33.0**
PFS events observed, n (%)	**83** (58.0)	**136** (87.2)
Median PFS (95% CI), months	**6.0** (4.1–18.0)	**2.7** (2.6–2.8)
Estimated probability of PFS, % (95% CI)		
6 months	**49.5** (41.0–57.5)	**22.9** (16.5–30.0)
12 months	**46.4** (37.8–54.5)	**13.3** (8.3–19.5)
24 months	**40.1** (31.6–48.4)	**9.4** (5.2–15.0)
36 months	**40.1** (31.6–48.4)	**6.8** (3.3–12.0)

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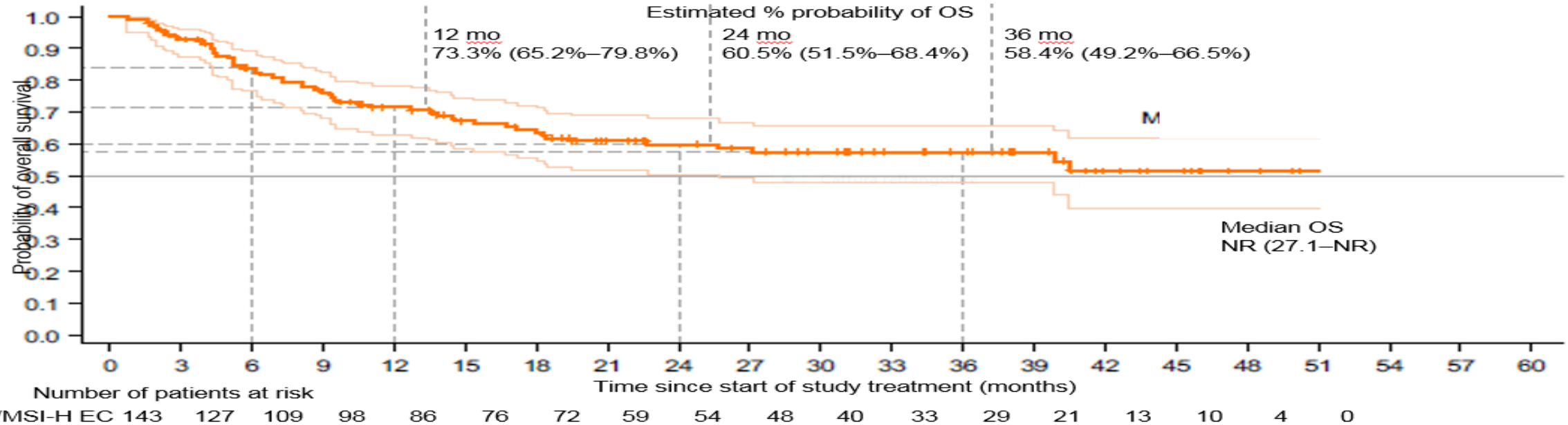
European Society for Medical Oncology Congress (poster). September 9-13, 2022; Paris, France

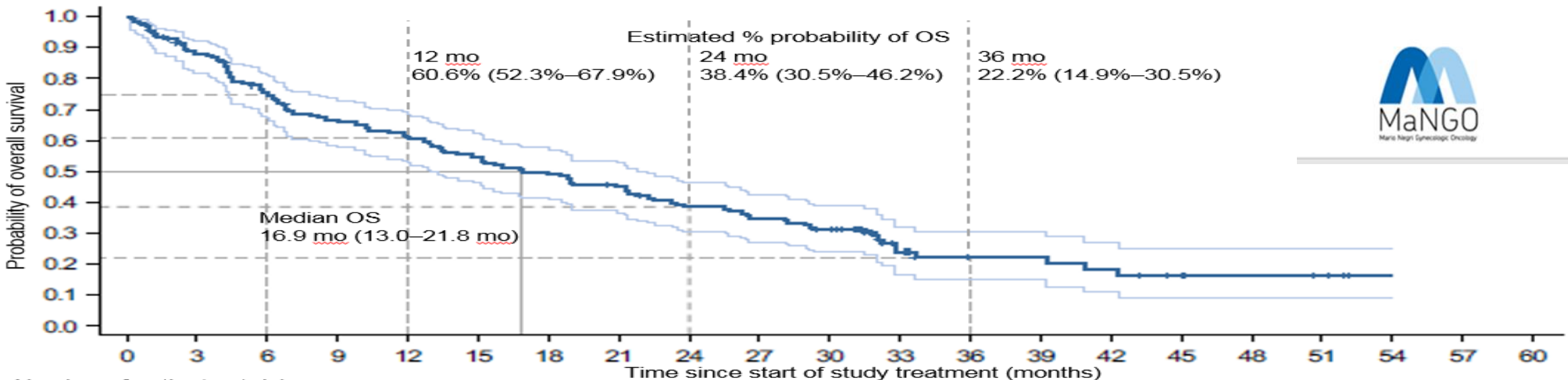
Probability of overall survival – dMMR/MSI-H EC[1]



Number of patients at risk

dMMR/MSI-H EC	143	127	109	98	86	76	72	59	54	48	40	33	29	21	13	10	4	0

Probability of overall survival – MMRp/MSS EC



Number of patients at risk

MMRp/MSS EC	156	129	108	95	87	78	71	63	53	48	42	17	11	11	9	6	4	3	0

Phase 3 randomized, double-blind, multicenter study of dostarlimab plus CBDCA + PTX vs placebo plus CBDCA + PTX in pts with recurrent or primary advanced EC (RUBY TRIAL)

Eligible patients:

- Histologically or cytologically proven EC with recurrent or primary advanced disease
- Stage III or IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment

Stratification:

- [illegible]

- MMR/MSI status
- Prior radiotherapy
- Disease status

Randomized
- 1:1
(N = 494)

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2 Q3W for 6 cycles

→ **Dostarlimab IV** 1000 mg Q6W up to 3 years[a]

Placebo
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2 Q3W for 6 cycles

→ **Placebo IV** Q6W up to 3 years[a]

→ **Follow-up**

Endpoints[2]

Primary endpoint: PFS, OS

Secondary end points: PFS,[d] PFS2, ORR, DOR, DCR, QoL, pharmacokinetics and safety

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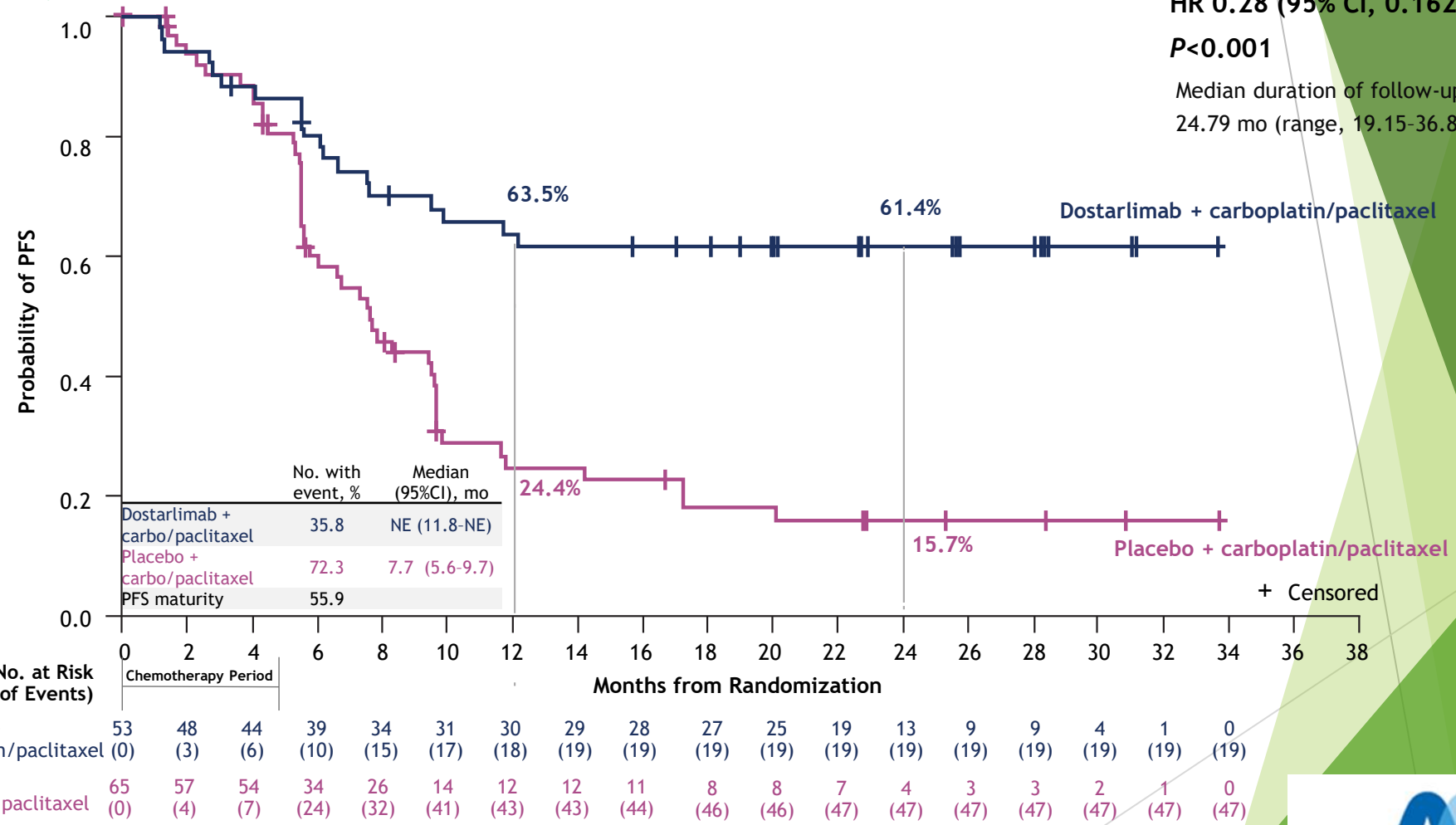
PFS per Investigator Assessment – Primary Endpoint

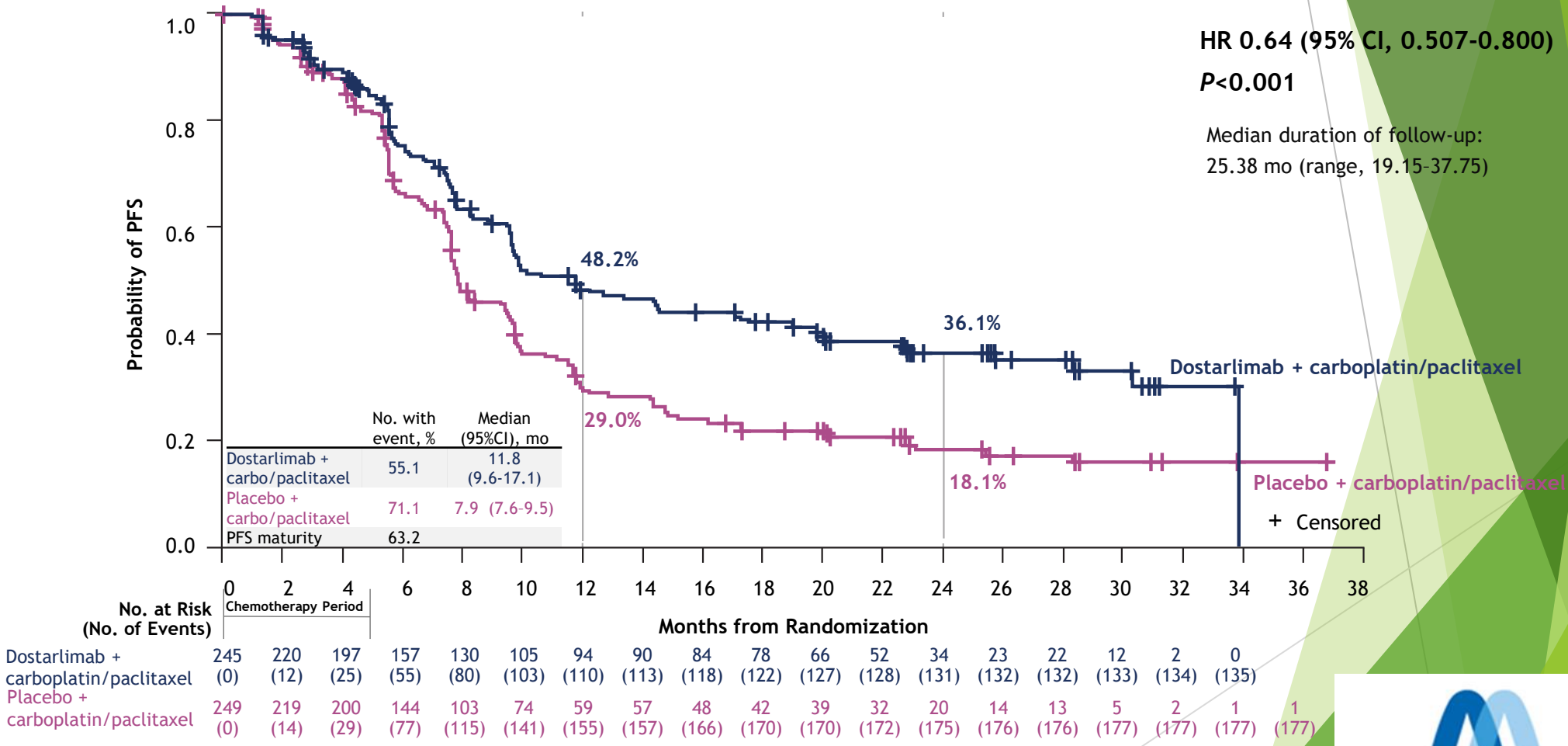
dMMR/MSI-H Population



Link to sensitivity analysis results

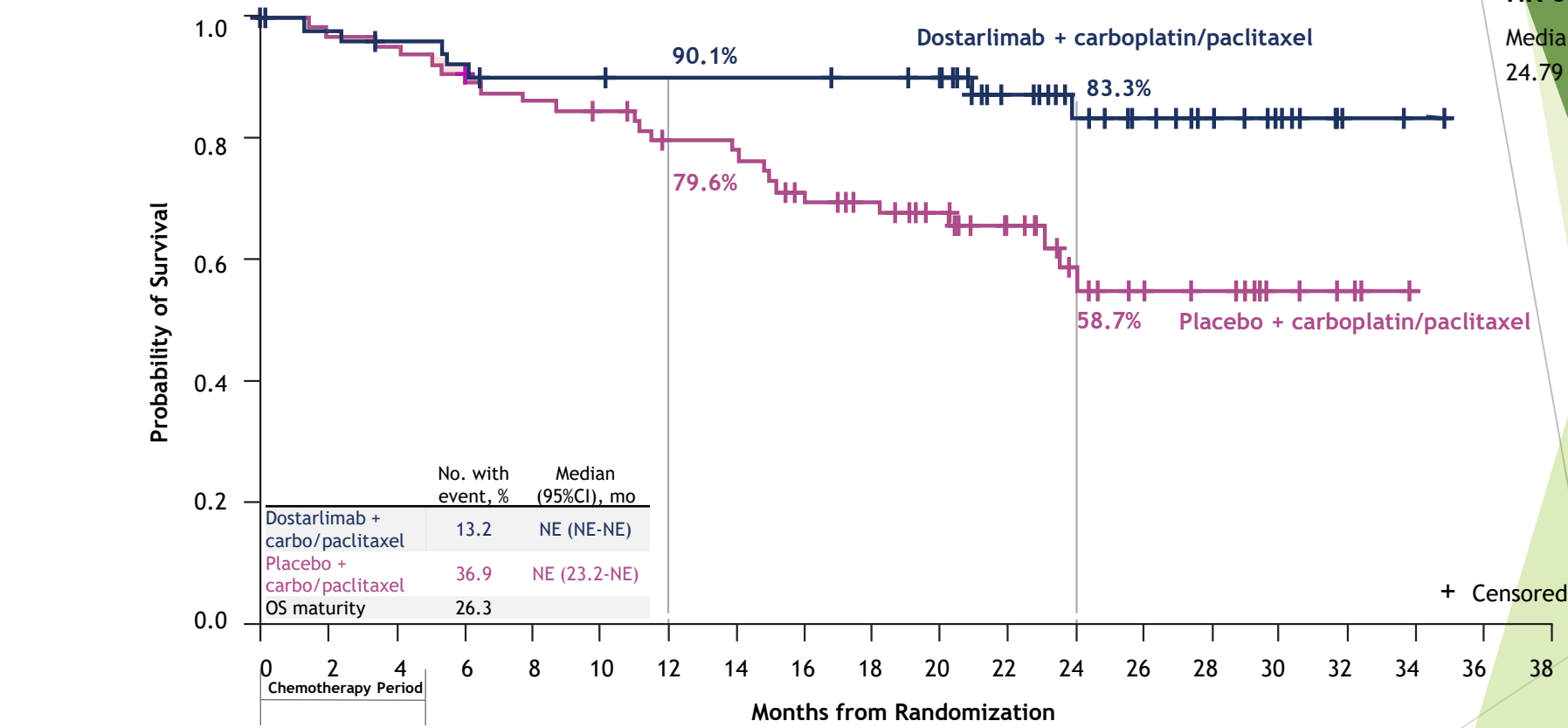
PFS per Investigator Assessment – Primary Endpoint

Overall Population (dMMR/MSI-H and MMRp/MSS)



Overall Survival – Primary Endpoint

dMMR/MSI-H Population



HR 0.30 (95% CI, 0.127-0.699)

Median duration of follow-up: 24.79 mo (range, 19.15-36.86)

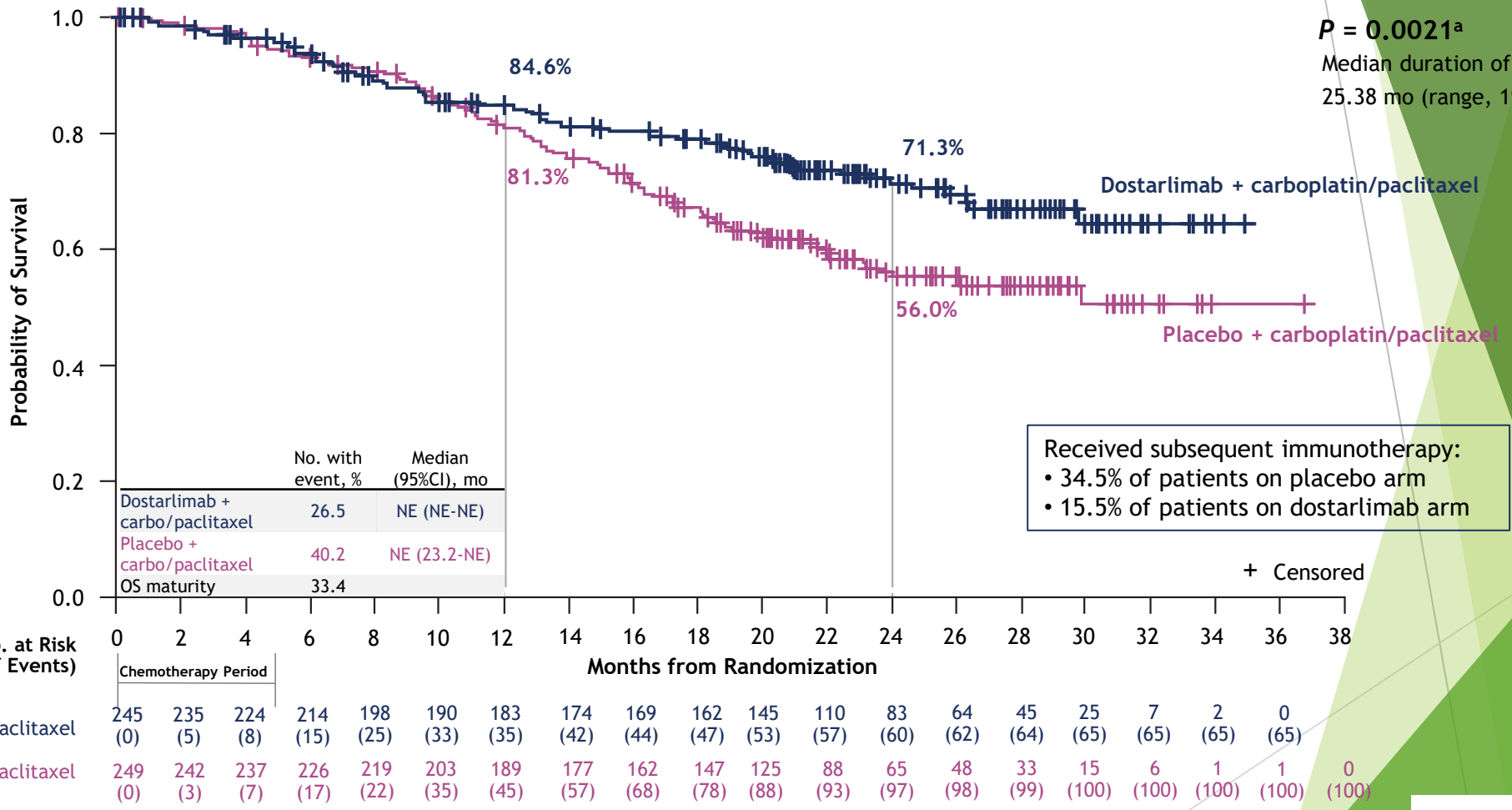
Overall Survival – Primary Endpoint

Overall Population (dMMR/MSI-H and MMRp/MSS)

HR 0.64 (95% CI, 0.464-0870)

***P* = 0.0021[a]**

Median duration of follow-up:
25.38 mo (range, 19.15-37.75)

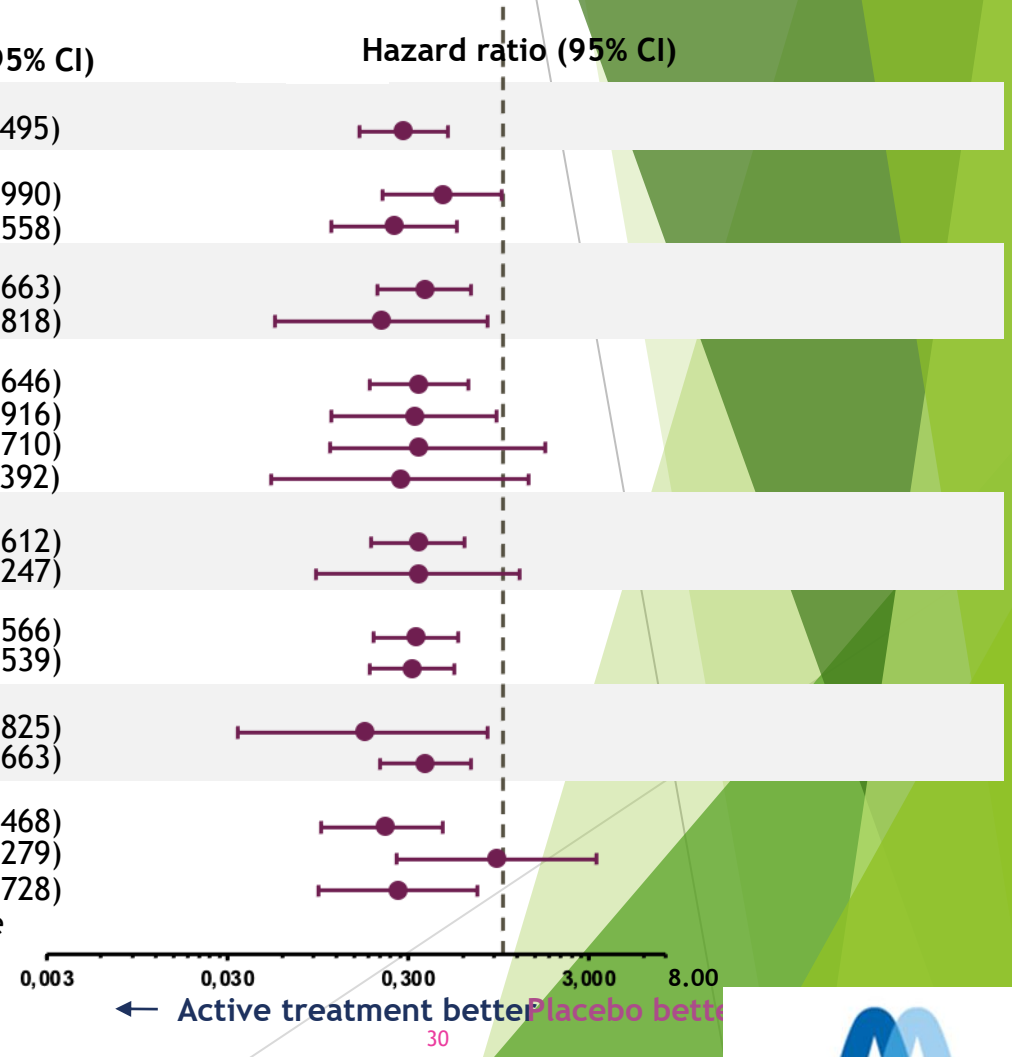


Received subsequent immunotherapy:
- 34.5% of patients on placebo arm
- 15.5% of patients on dostarlimab arm

PFS per Investigator Assessment – Prespecified Subgroups

dMMR/MSI-H Population

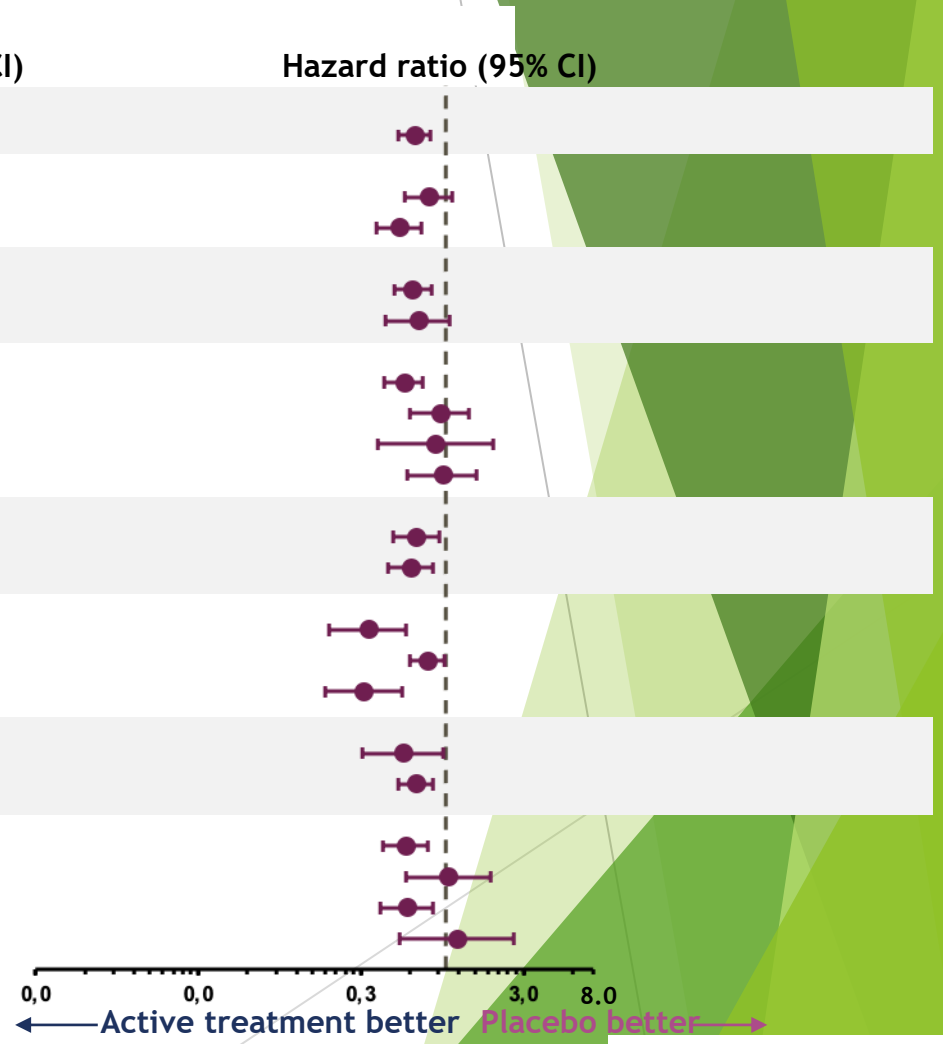
Category	Dostarlimab plus carboplatin/paclitaxel (no. events/ no. patients)	Placebo plus carboplatin/paclitaxel (no. events/ no. patients)	Hazard ratio (95% CI)
All patients	19/53	47/65	0.28 (0.162-0.495)
Age			
<65 years	11/30	18/30	0.46 (0.217-0.990)
≥65 years	8/23	29/35	0.25 (0.113-0.558)
Race			
White	16/44	38/56	0.37 (0.203-0.663)
Other	3/9	9/9	0.21 (0.055-0.818)
Region			
North America	14/36	35/50	0.34 (0.182-0.646)
Europe	5/17	12/15	0.32 (0.112-0.916)
Eastern Europe	3/7	7/7	0.43 (0.111-1.710)
Western Europe	2/1	5/8	0.27 (0.052-1.392)
Histology category	0		
Endometroid carcinoma	16/45	37/54	0.34 (0.186-0.612)
Other	3/8	10/11	0.34 (0.092-1.247)
MMR/MSI status			
dMMR/MSI-H	19/53	47/65	0.33 (0.192-0.566)
dMMR status (derived)	19/53	47/63	0.31 (0.182-0.539)
Prior external pelvic RT			
Yes	2/8	8/13	0.17 (0.034-0.825)
No	17/45	39/52	0.37 (0.209-0.663)
Disease status			
Recurrent	10/27	25/32	0.22 (0.099-0.468)
Primary stage III	4/10	6/14	0.92 (0.260-3.279)
Primary stage IV	5/16	16/19	0.26 (0.095-0.728)
No disease at baseline	0/4	4/7	Not applicable



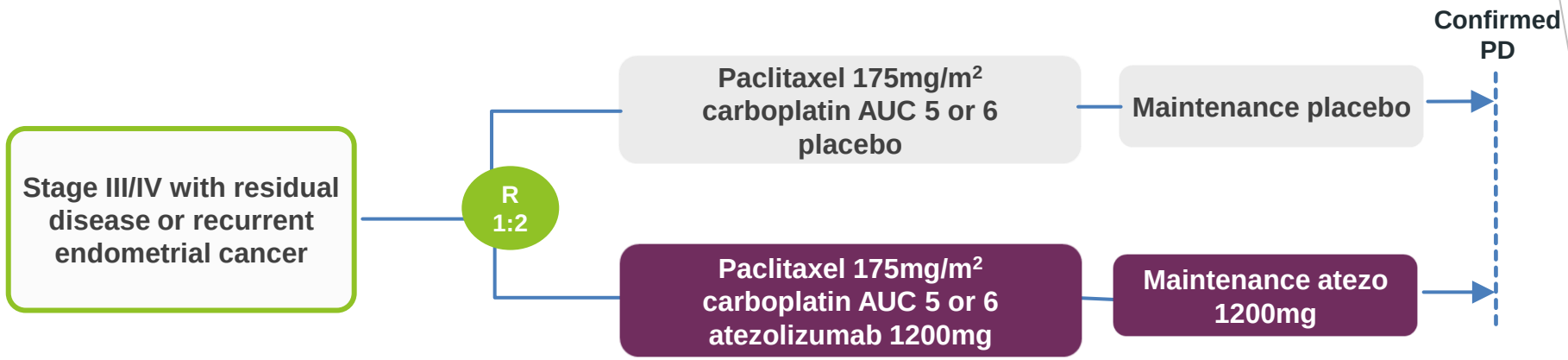
PFS per Investigator Assessment – Prespecified Subgroups

Overall population (dMMR/MSI-H and MMRp/MSS)

Category	Dostarlimab plus carboplatin/paclitaxel (no. events / no. patients)	Placebo plus carboplatin/paclitaxel (no. events / no. patients)	Hazard ratio (95% CI)
All patients	135/245	177/249	0.64 (0.507-0.800)
Age			
<65 years	69/127	72/144	0.78 (0.559-1.083)
≥65 years	66/118	105/135	0.51 (0.376-0.704)
Race			
White	101/189	135/191	0.62 (0.481-0.808)
Other	34/56	42/58	0.67 (0.422-1.050)
Region			
North America	91/171	133/187	0.55 (0.419-0.718)
Europe	44/74	44/62	0.91 (0.602-1.390)
Eastern Europe	11/1	12/1	0.86 (0.377-1.959)
Western Europe	33/58	32/48	0.95 (0.581-1.539)
Histology category			
Endometroid carcinoma	64/130	89/136	0.65 (0.473-0.902)
Other	71/115	88/113	0.60 (0.439-0.823)
MMR/MSI status			
dMMR/MSI-H	19/53	47/65	0.33 (0.192-0.566)
MMRp/MSS	116/192	130/184	0.76 (0.595-0.982)
dMMR status (derived)	19/53	47/63	0.31 (0.182-0.539)
Prior external pelvic RT			
Yes	21/41	31/45	0.54 (0.303-0.956)
No	114/204	146/204	0.65 (0.508-0.831)
Disease status			
Recurrent	68/117	89/119	0.56 (0.408-0.775)
Primary stage III	21/45	21/47	1.03 (0.563-1.891)
Primary stage IV	46/83	67/83	0.57 (0.392-0.836)
No disease at baseline	12/33	12/30	1.16 (0.520-2.590)



Phase III double-blind randomized placebo trial of ATEZOLIZUMAB in combination with PTX+CBDCA in pts with advanced/recurrent EC (AtTEnd) NCT03603184



Stratified by:

- Country of the experimental center
- Histological type (endometrioid vs. other types)
- Disease (recurrent disease vs advanced disease at primary diagnosis)
- MS status (MSS vs MSI vs non-evaluable)

Primary Endpoints:

- **PFS in the MSI population and overall (hierarchical approach)**
- **OS**

- The first efficacy analysis is expected for July 2023 with one year of delay respect to the orginal plan (mostly due to the activation/accrual timelines)

Lenvatinib (LEN) Plus PEMBRO in pts With Advanced EC. KEYNOTE-146/Study 111

- Multinational, phase Ib-II open-label, single-arm study (NCT02501096) of LEN+PEMBRO in pts with selected solid tumors (ie, NSCLC, renal cell carcinoma, EC, urothelial carcinoma, HN-SCC, melanoma) that have progressed after treatment with approved therapies
- LEN (20 mg one daily orally) + Pembro (200 mg iv Q3w)
- 108 pts with EC who had previously received systemic therapy

	ORR at 24 weeks (95%CI)
All pts	38.0% (28.8%-47.8%).
Pts with MSH-I (n=11)	63.6% (30.8%-89.1%)
Pts with MSS (n.94)	36.2% (26.5%-46.7%)

(Makker 2020)

LEN + PEMBRO in Advanced EC. Study 309-KEYNOTE-775

827 pts with prior platinum-based CT (697 pMMR, 130 dMMR)

RANDOM

LEN (20 mg/d) +
PEMBRO (200 mg q21)

CT of physician's choice
a) DOX (60 mg/m^2)
b) weekly PTX (80 mg/m^2)

Primary end points: PFS and OS evaluated in pts with mismatch repair-proficient (pMMR) disease and in all pts

(Makker 2022)

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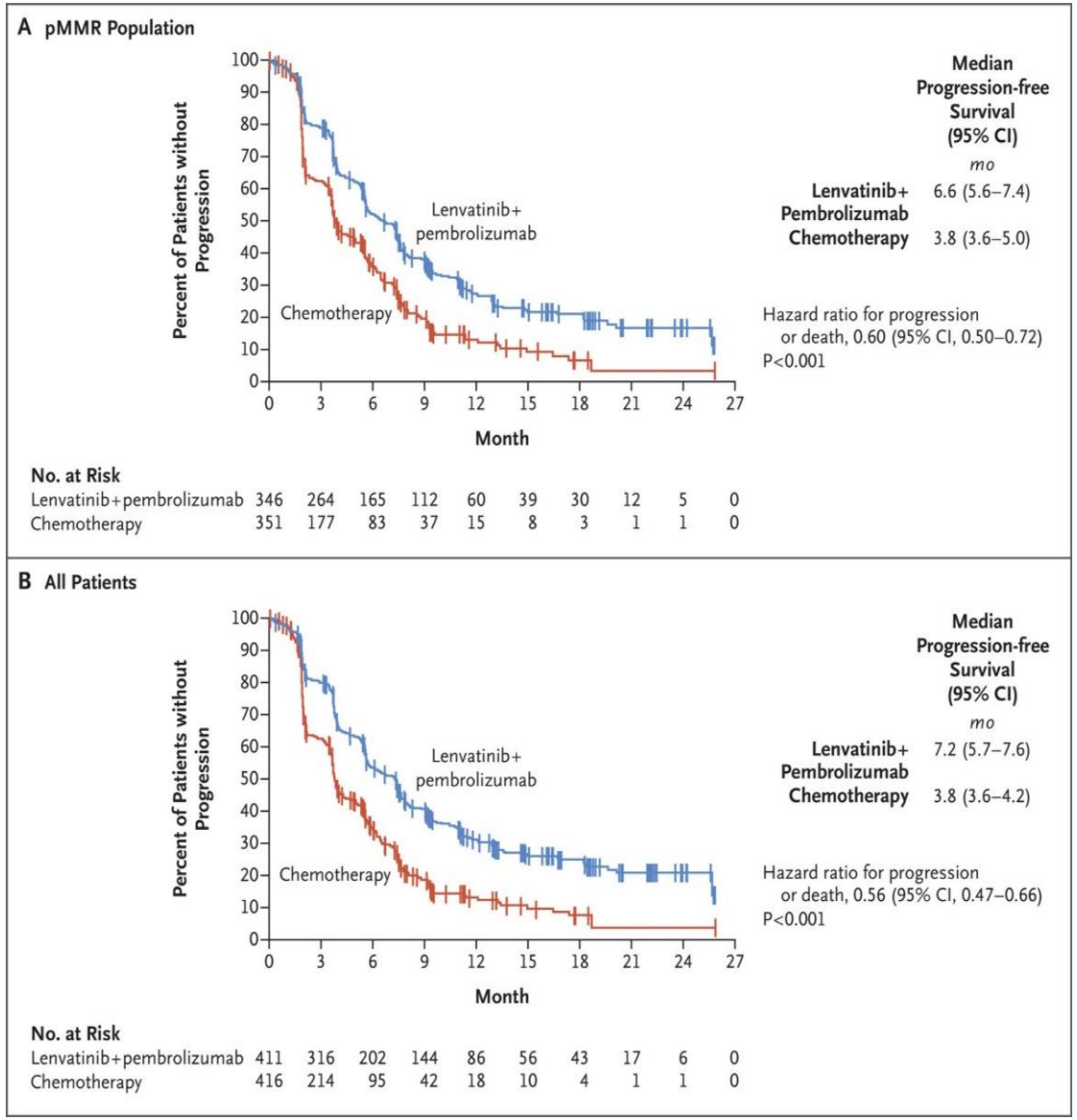
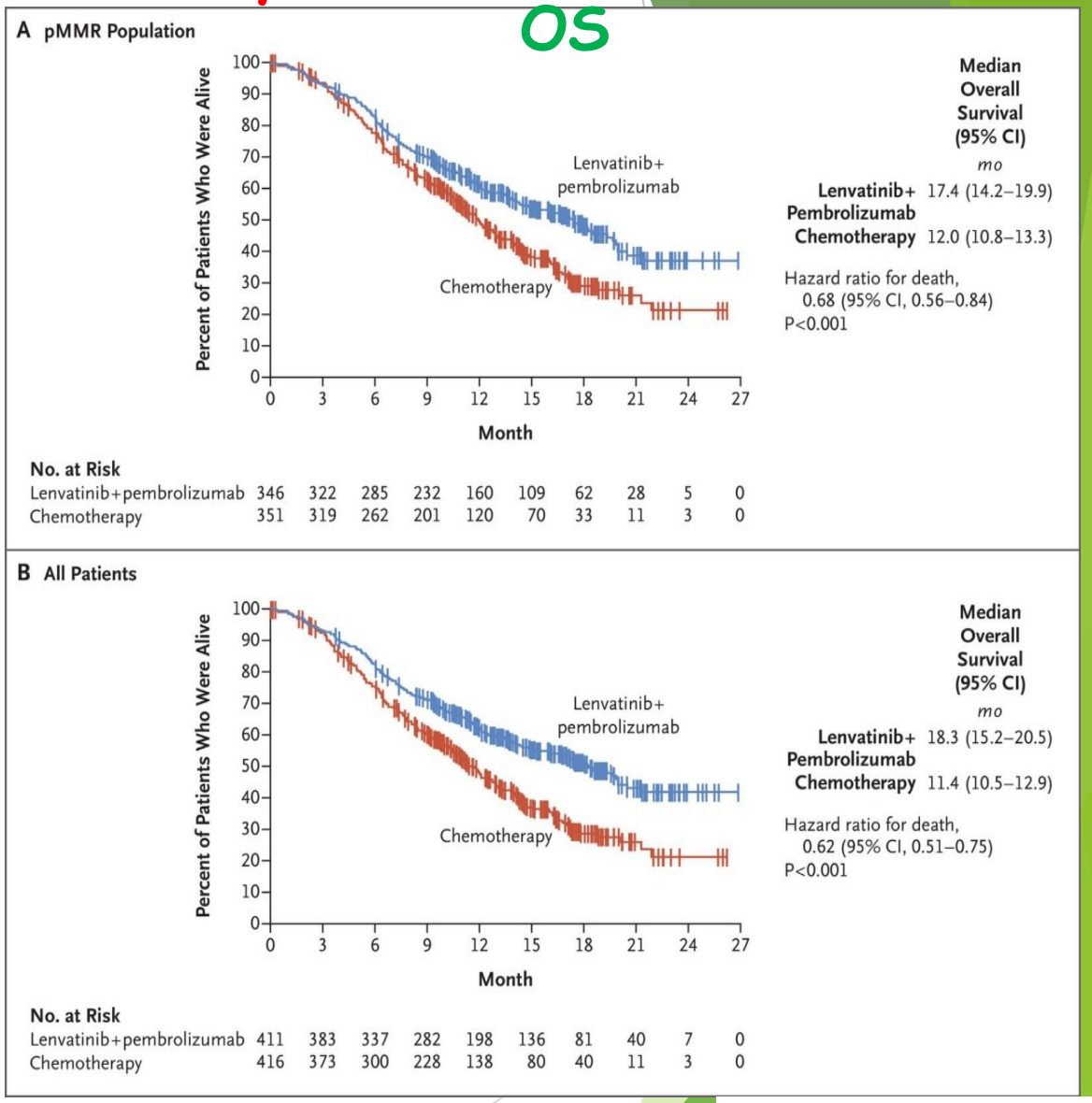
LEN + PEMBRO in Advanced EC. Study 309-KEYNOTE-775

PFS



OS



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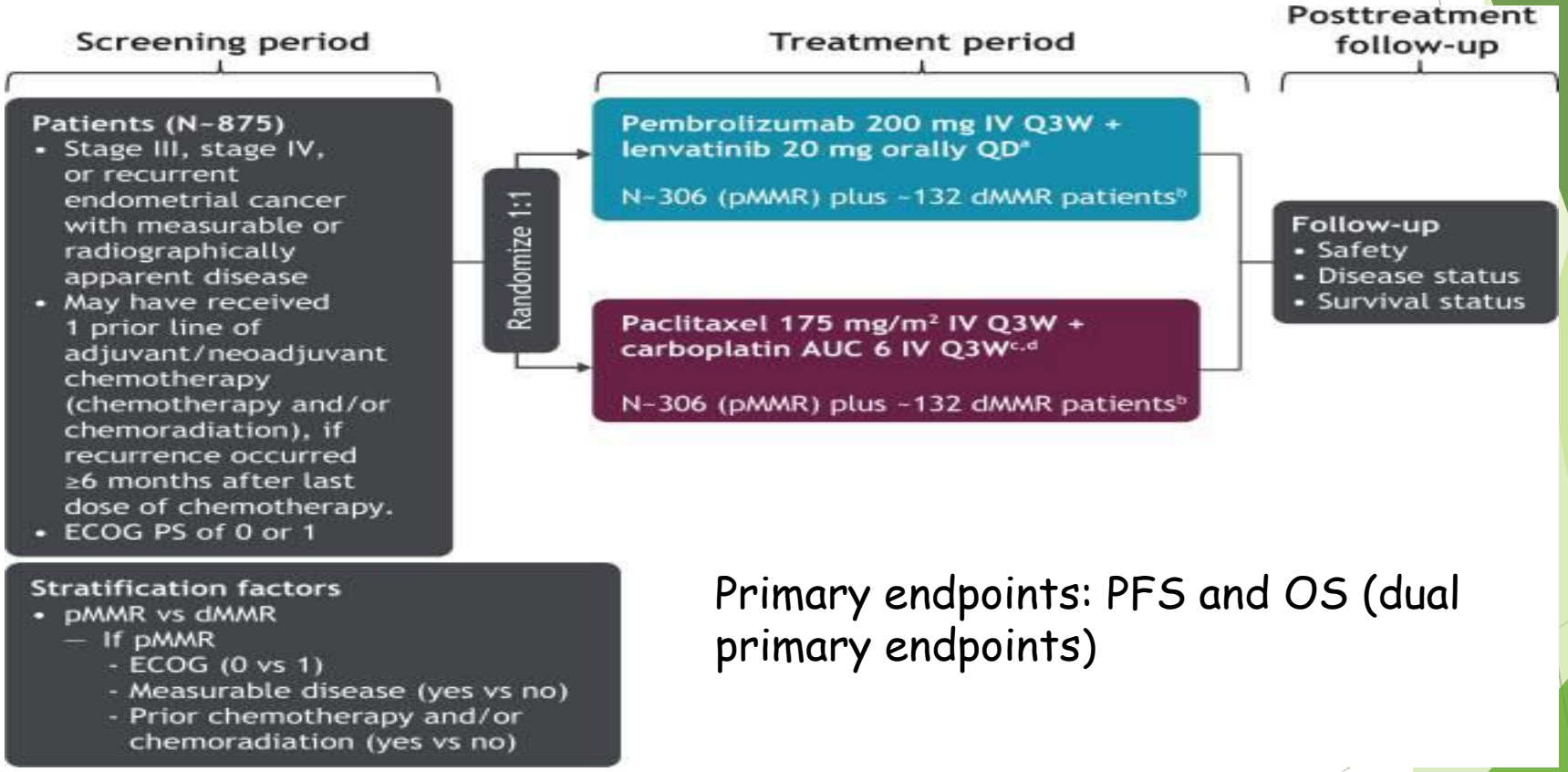
Phase 3, randomized, open-label study of Pembro + LEN VS CT for first-line treatment of advanced or recurrent EC : ENGOT-en9/LEAP-001.



Primary endpoints: PFS and OS (dual primary endpoints)

(Marth C Int J Gynecol Cancer 2022)

Conclusions : Cervical cancer

- ✓ PEMBRO significantly improves PFS and OS of pts with persistent, recurrent, or metastatic cervical cancer receiving platinum-based CT ± BEV
- ✓ PEMBRO available in addition to CT ± BEV within Early Access Program (EAP)
- ✓ Ongoing study of CCRT ± PEMBRO for Locally Advanced Cervical Cancer (MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047)
- ✓ Cemiplimab : significant and clinically meaningful advantage in terms of OS in pts with recurrent cervical cancer who progressed after platinum-containing therapy,

Study	Population	Treatment	Status	Competitive Countries	Sample size	Primary endpoint	Primary analysis results
ENGOT-En6 (Ruby)	Same population	Pac/carbo+Dostarlimab/Dostarlimab maintenance vs Pac/carbo/placebo/placebo maintenance	Start July 2019	Europe	470	PFS; PFS in MSI-H	Published on April 2023
NRG-GY018	Same population	Pac/carbo+Pembro/Pembro maintenance vs Pac/carbo/placebo/placebo maintenance	Start July 2019	No competitive countries	810	PFS	Published on April 2023
KEYNOTE-775	Advanced, recurrent, or metastatic EC; **after 1 prior platinum chemo**	Lenvatinib+ Pembro vs Treatment Physician's Choice (doxorubicin or paclitaxel)	Start June 2018	AU/NZ; Japan; Europe	780	PFS & OS	Published on Feb 2022
ENGOT-en9/ A-AGO (LEAP-001)	Advanced or recurrent endometrial carcinoma, **No prior chemotherapy** (except chemoradiation)	Pembro/lenvatinib vs Carboplatin/paclitaxel	Start Apr 2019	Europe; Japan	720	PFS & OS	Expected for Apr 2023
DUO-E	Newly diagnosed stage III-IV, or recurrent endometrial cancer	Pac/carbo+Durvalumab/Durvalumab+Olaparib maintenance vs Pac/carbo+Durvalumab/Durvalumab+placebo maintenance vs Pac/carbo+placebo/placebo+placebo maintenance	Start May 2020	Europe; Japan	699	PFS	Press release 26 May 2023

Among these competitive trials, AtTEnd was the only Academic