Nuove prospettive di trattamento del carcinoma endometriale

Michele Bartoletti

CRO Aviano

Conflict of interests

- GSK: advisory board, speaker fees
- MSD: advisory board, speaker fees
- Astrazeneca: advisory board, speaker fees
- EISAI: advisory board
- Roche: advisory board
- Abbvie: advisory board

Does endometrial cancer really exist?

Does endometrial cancer really exist?

NO

EC treatment must be guided by Clinico-pathologic and molecular characteristics

How a greater understanding of the molecular characteristics of endometrial carcinoma impacts its treatment

How a greater understanding of the molecular characteristics of endometrial carcinoma impacts its treatment

- New molecular targets and signatures, new targeted therapies

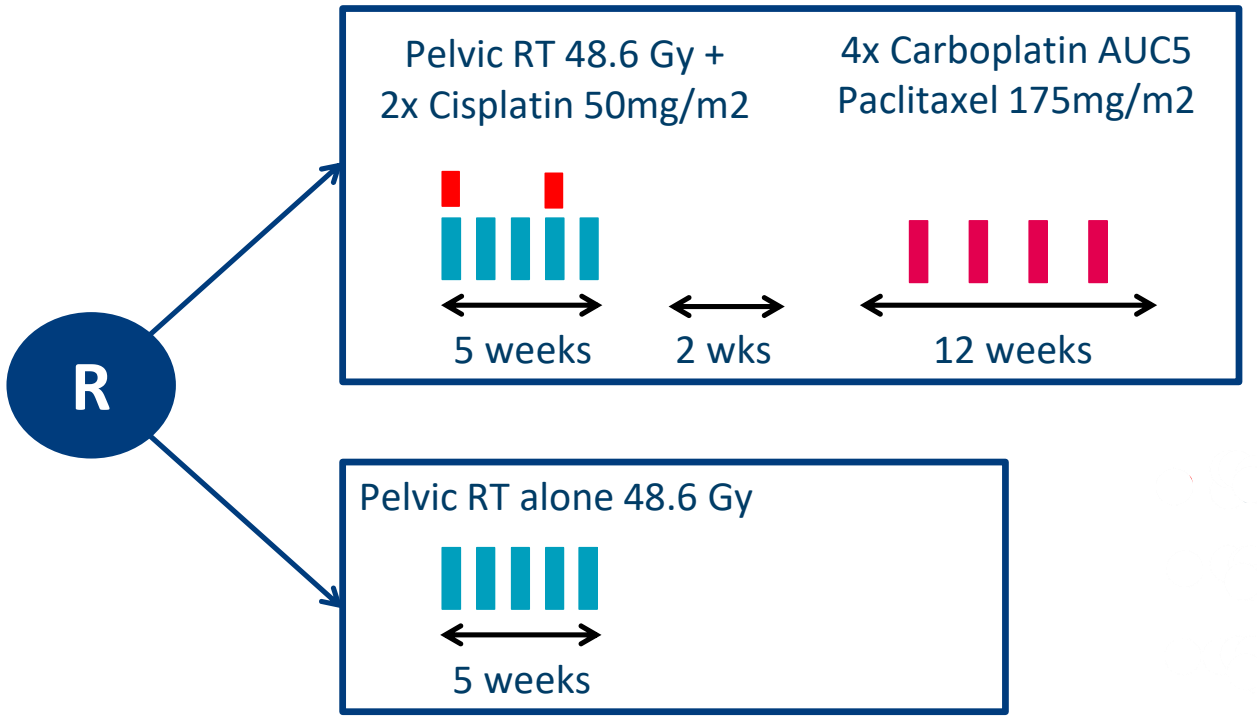
How a greater understanding of the molecular characteristics of endometrial carcinoma impacts its treatment

- New molecular targets and signatures, new targeted therapies
- Predictive and prognostic biomarkers to guide standard chemotherapy

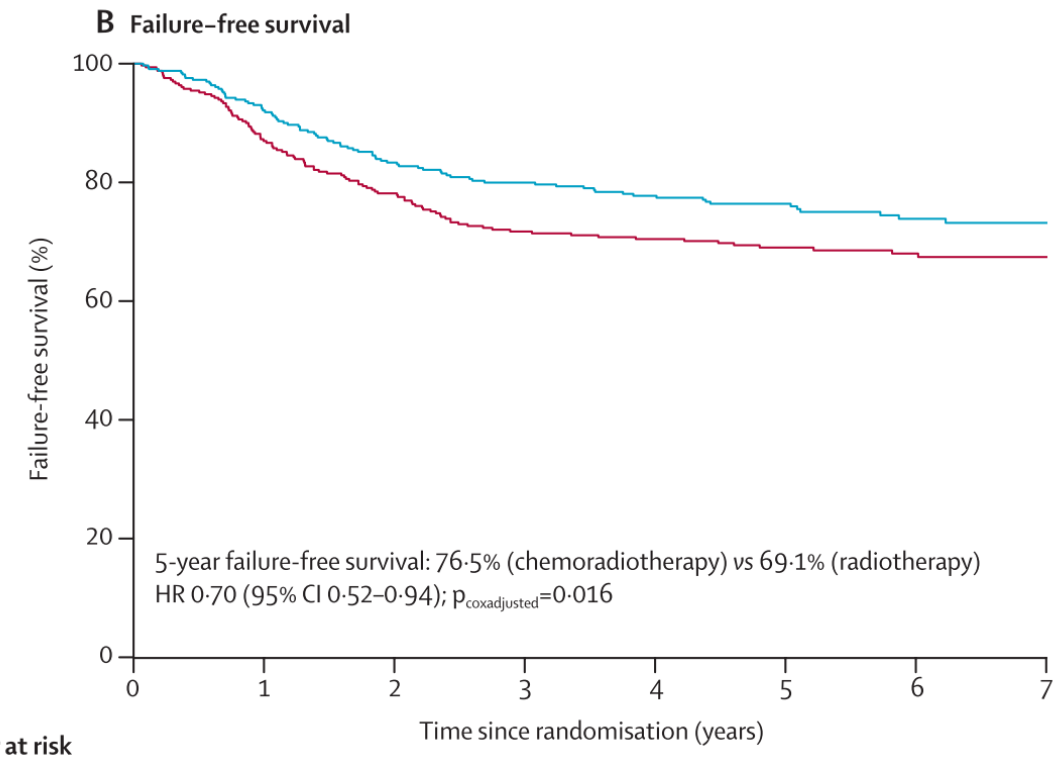
Adjuvant therapies in early stage endometrial cancer

PORTEC 3

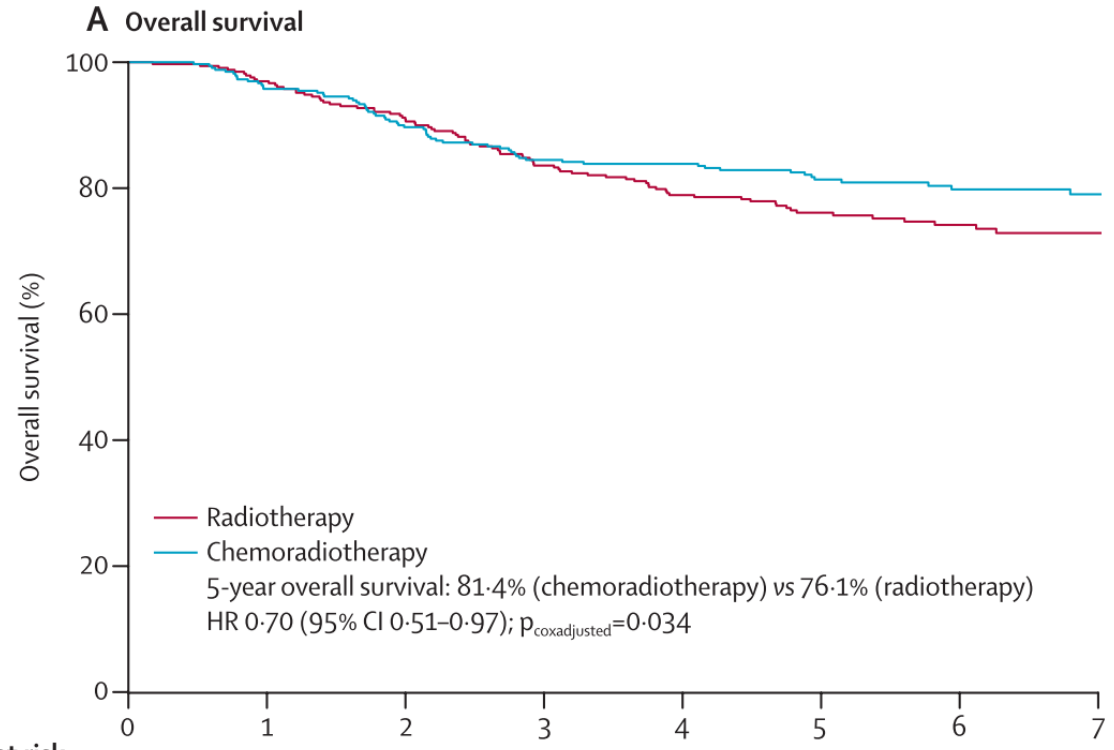
High risk Endometrial Cancer



PORTEC 3



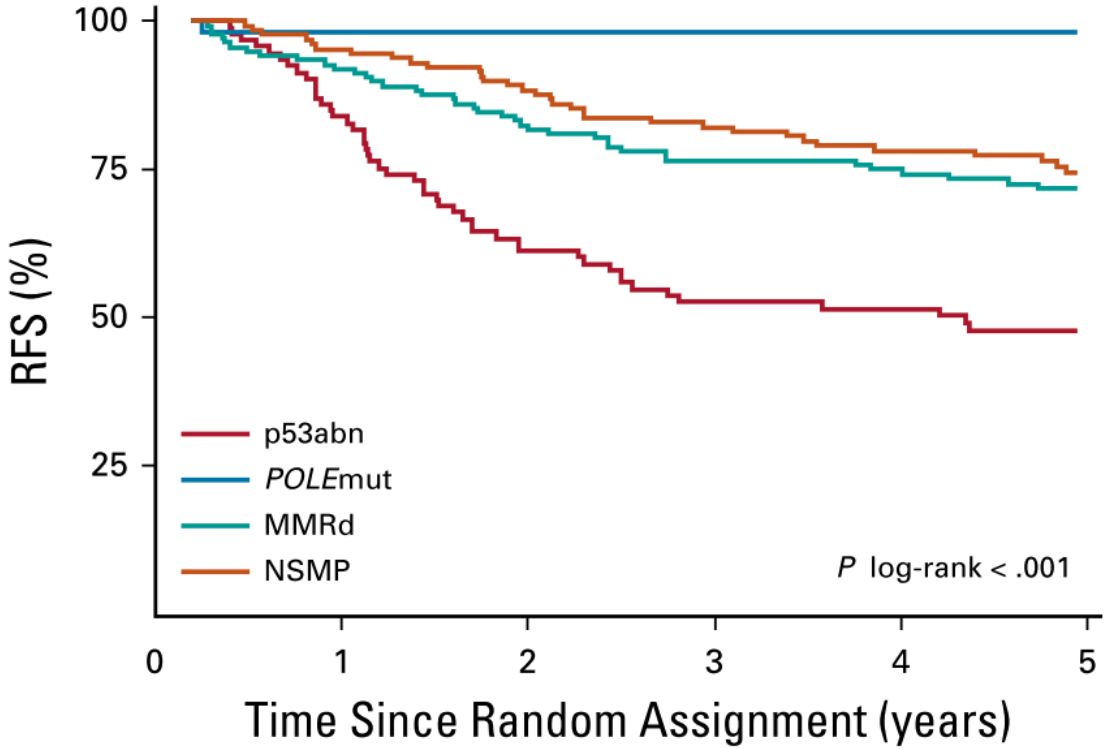
Number at risk (number censored)								
Radiotherapy	330 (0)	286 (1)	257 (1)	230 (3)	215 (13)	163 (61)	116 (106)	75 (146)
Chemoradiotherapy	330 (0)	304 (0)	275 (0)	256 (5)	237 (17)	182 (64)	120 (121)	78 (162)



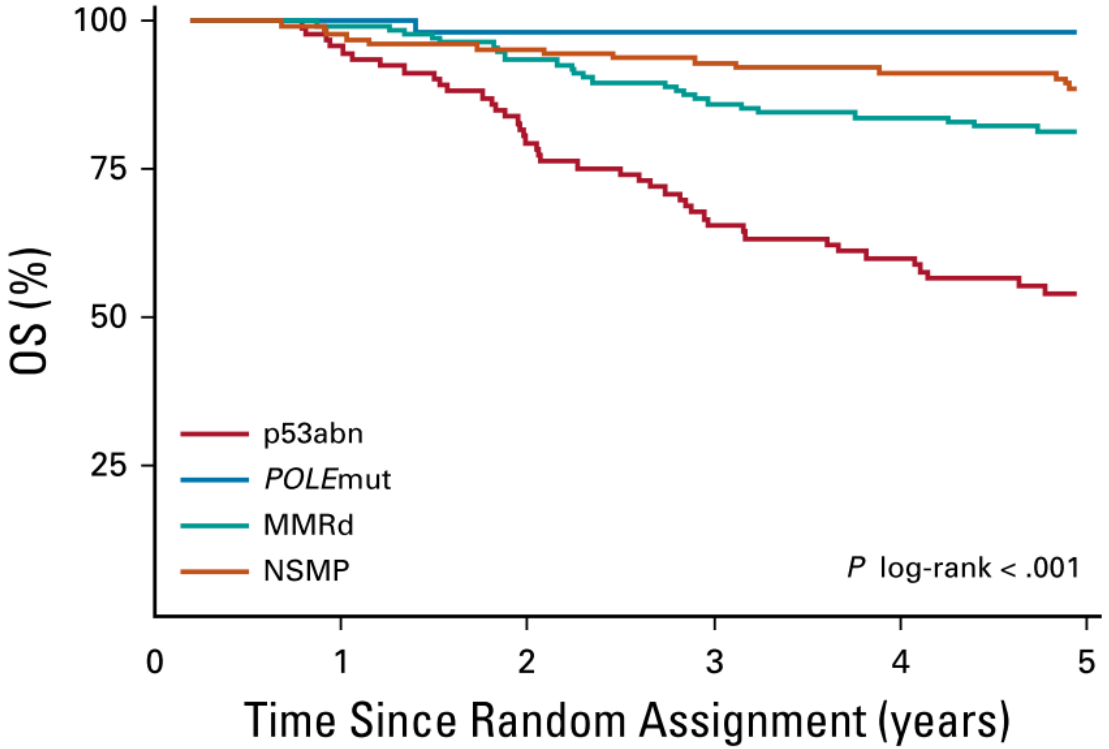
Number at risk (number censored)								
Radiotherapy	330 (0)	319 (1)	299 (1)	273 (3)	248 (13)	187 (66)	129 (120)	81 (166)
Chemoradiotherapy	330 (0)	316 (0)	295 (1)	272 (7)	258 (19)	201 (69)	137 (130)	89 (177)

Stephanie M de Boer Lancet Oncol 2019

PORTEC 3



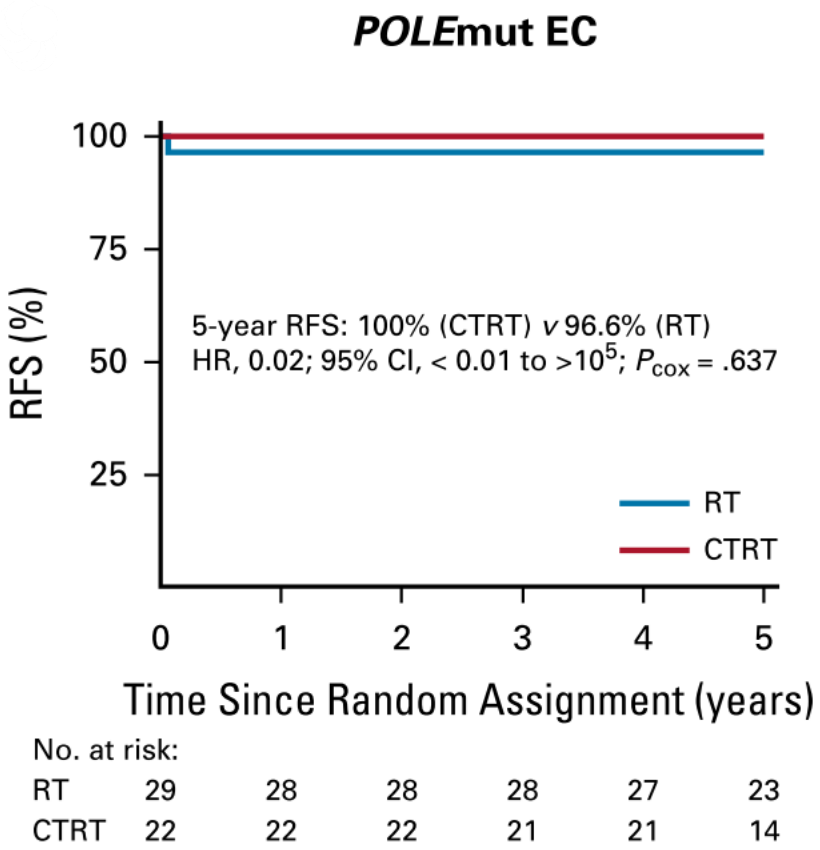
No. at risk:						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
MMRd	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

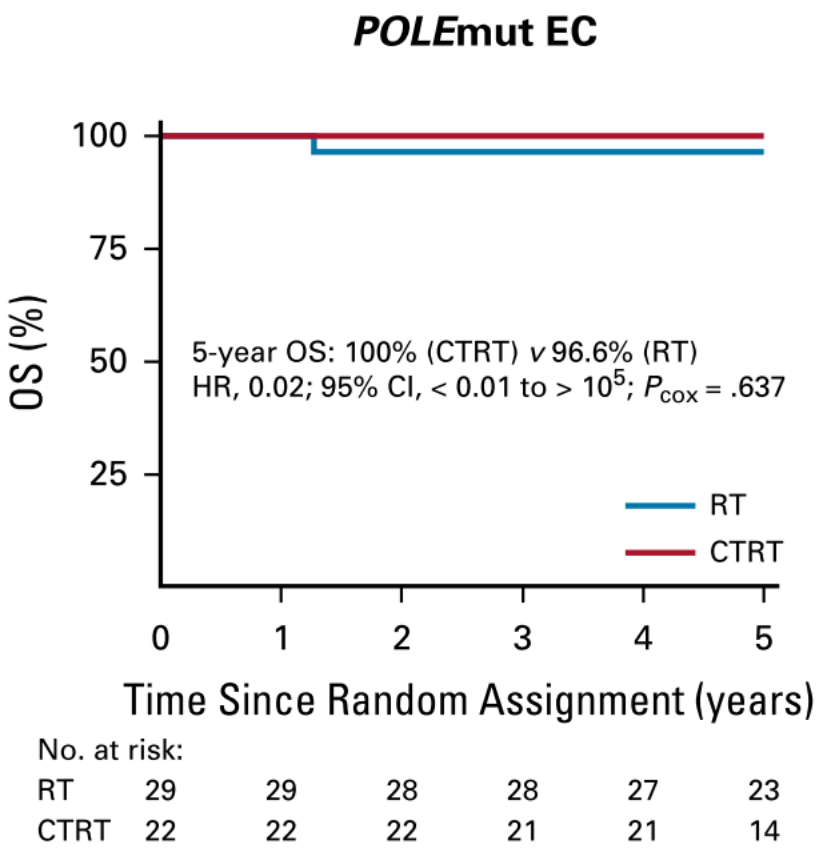


No. at risk:						
p53abn	93	87	71	61	52	37
*POLE*mut	51	51	50	49	48	37
MMRd	137	136	128	115	108	85
NSMP	129	125	122	118	110	85

Two new predictive categories

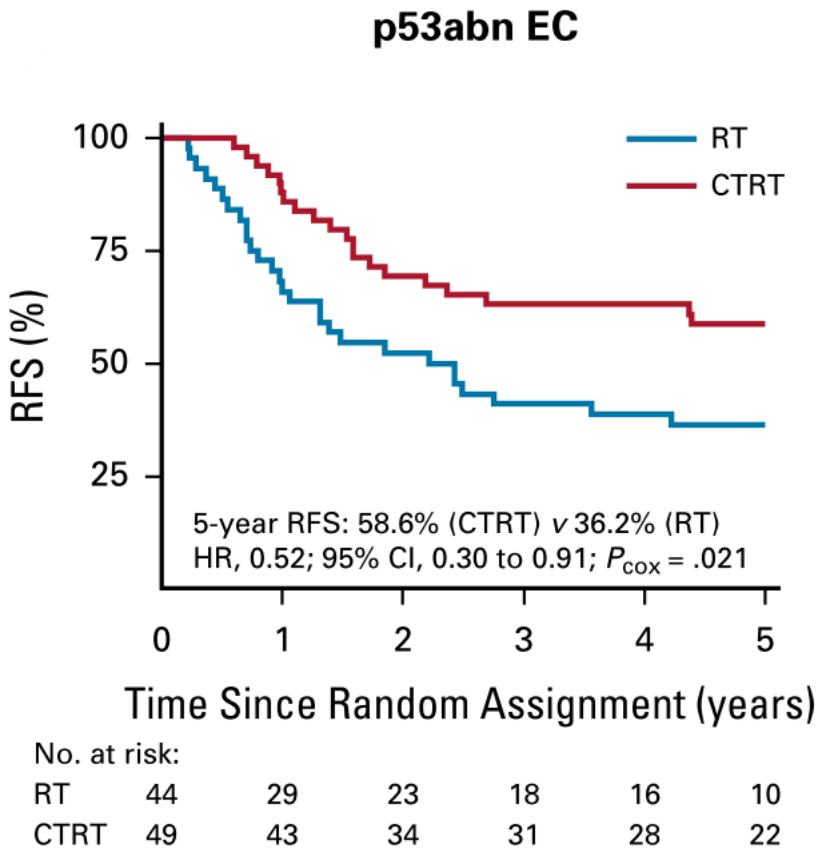
Molecular classification - predictive value

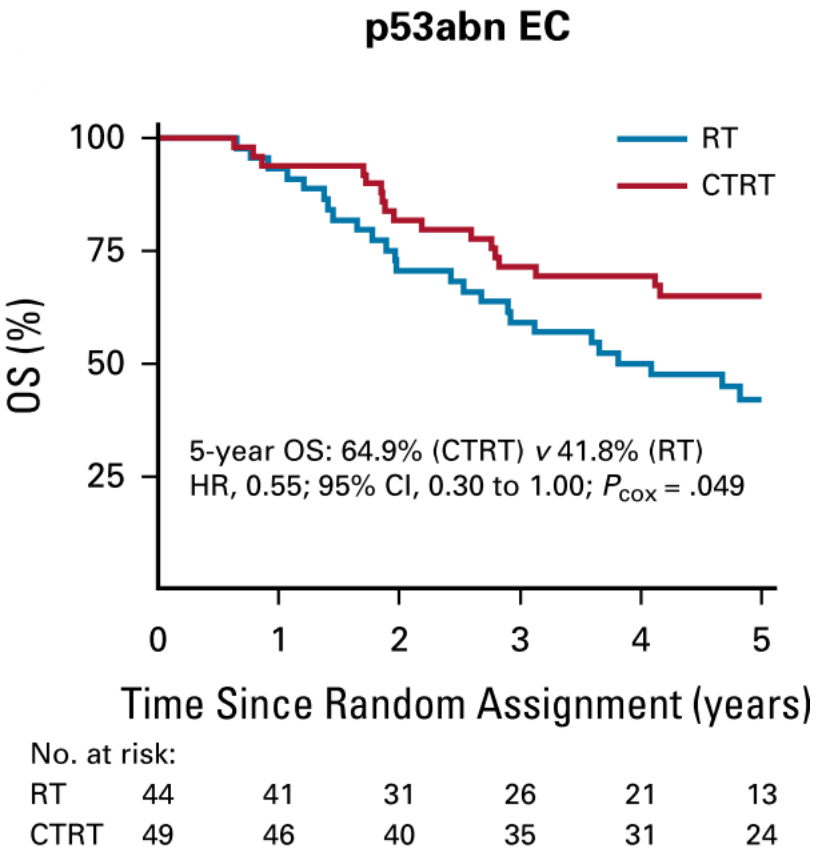




Leon- Castillo A, et al. JCO 2020

Molecular classification - predictive value



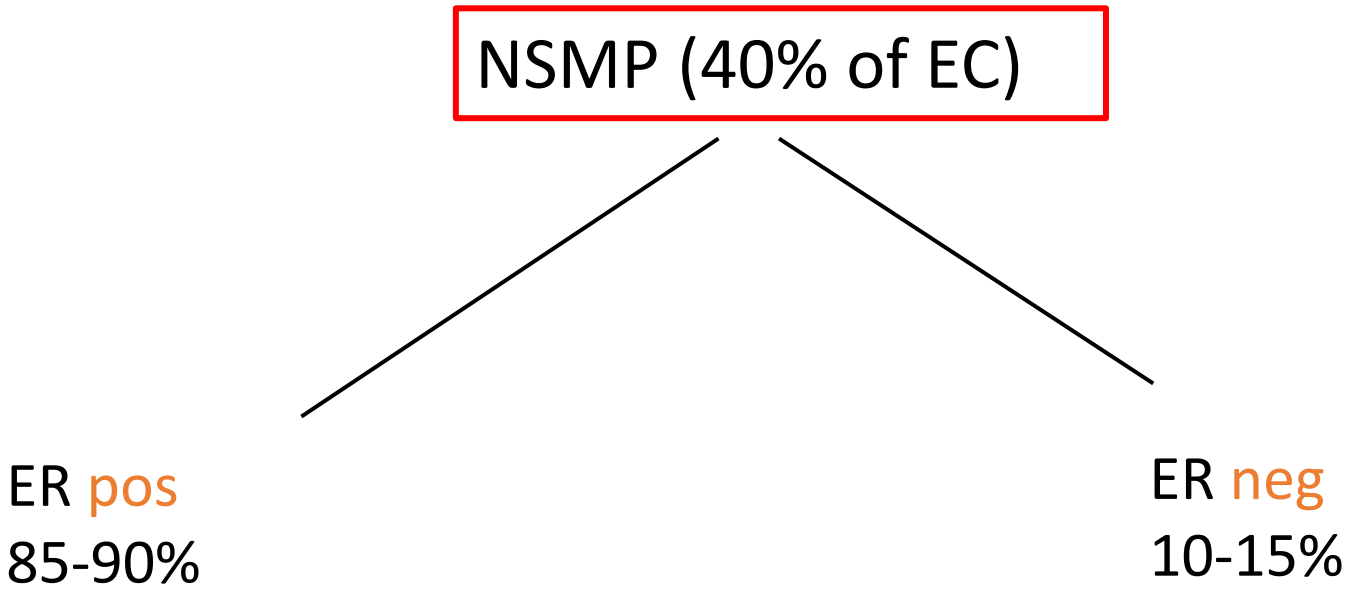


Leon- Castillo A, et al. JCO 2020

FIGO staging of endometrial cancer 2023

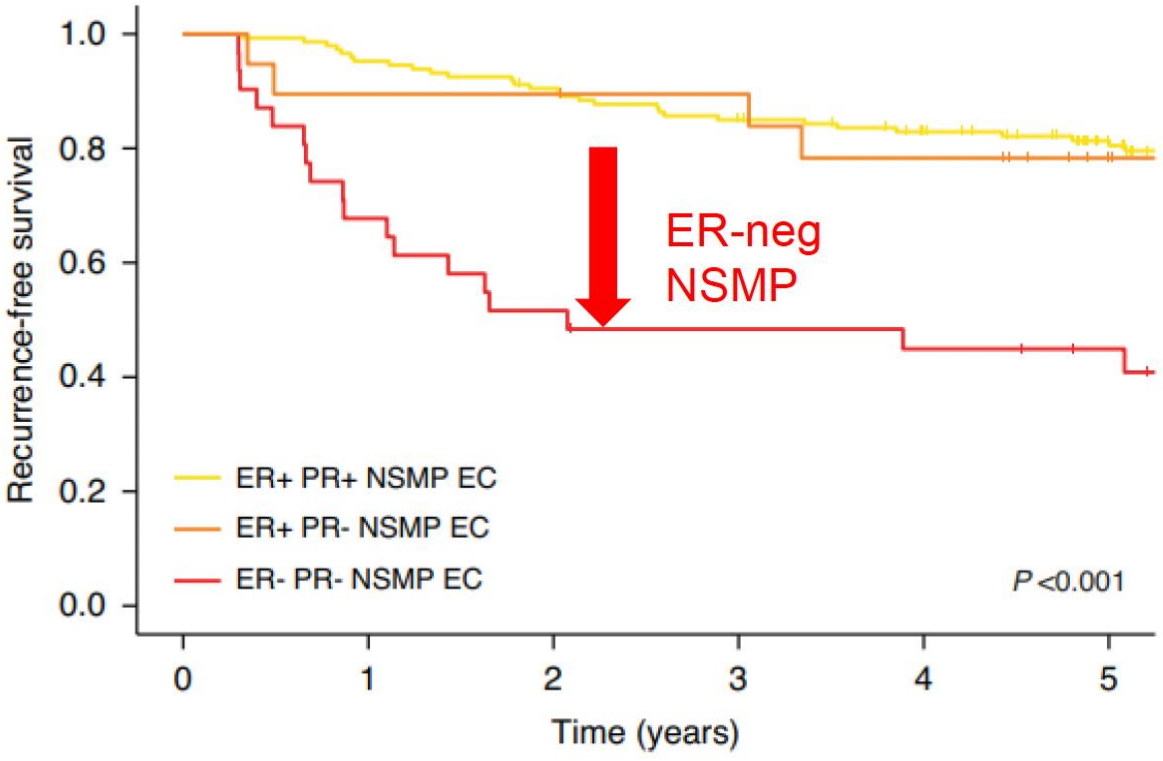
Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm$_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Berek et al Int J Gynecol Obstet. 2023

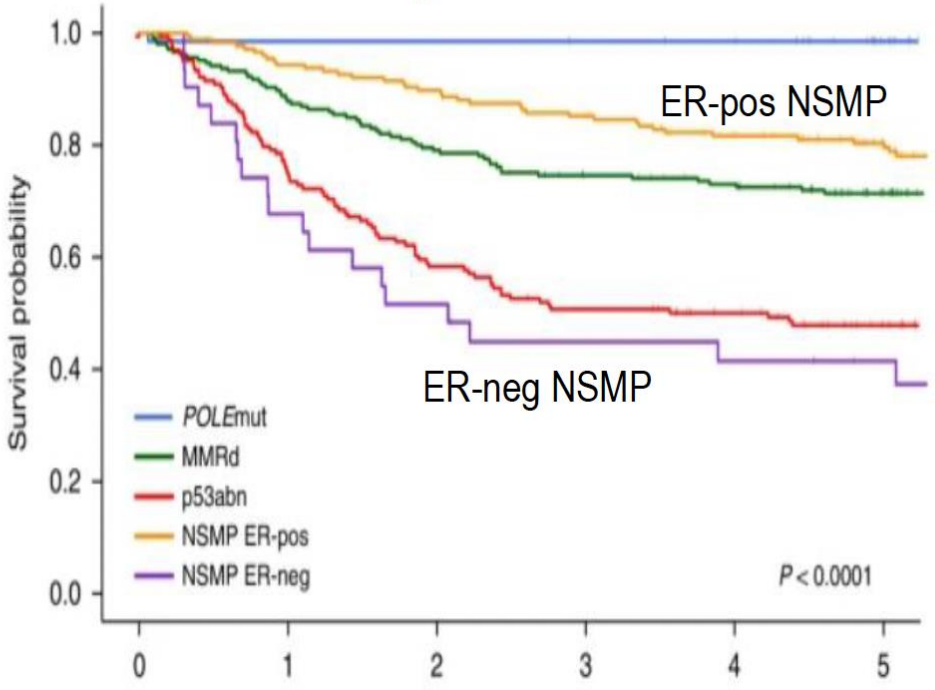

NSMP (40% of EC)
ER pos
85-90%
ER neg
10-15%

Further molecular stratification in NSMP category

Within the NSMP subclass, ER-neg stand out



Within molecular classified EC, ER-neg NSMP behave like p53abn…



Virmij Mol Diag 2023

DEFINITION OF RISK GROUPS

ESTRO European Society of Pathology

ESGO European Society of Gynaecological Oncology

Low | Intermediate | High-Intermediate | High | Uncertain

2023 FIGO staging[T]			Molecular classification*				
			***POLE*mut**	**MMRd**	**NSMP low-grade+ERpos**	**NSMP high-grade/ERneg****	**p53abn**
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	IAm *POLE*mut			**	
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#	IAm *POLE*mut			**	IICm p53abn
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	IAm *POLE*mut		n.a.		
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IAm *POLE*mut			**	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IAm *POLE*mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IAm *POLE*mut	Myoinvasion ≥50%, no/focal LVSI			
			IAm *POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IAm *POLE*mut	Substantial LVSI**			

ESTRO European Society of Pathology ESGO European Society of Gynaecological Oncology

DEFINITION OF RISK GROUPS

Prognostic risks in the respective groups are defined as estimated overall 5-year risk of recurrence:

- **low risk group**: risk less than 8%;
- **intermediate risk group**: risk between 8 and 15%;
- **high-intermediate risk group**: risk between 15 and 25%;
- **high risk group**: risk higher than 25%.

IO in early stage endometrial cancer

ENGOT-EN11/GOG-3053/KEYNOTE-B21 Study Design

Key Eligibility Criteria

- Newly diagnosed EC or carcinosarcoma
- Curative surgery with no residual disease
- At high risk for recurrence:
  - FIGO (2009) surgical stage I/II, non-endometrioid with myometrial invasion
  - FIGO (2009) surgical stage I/II of any histology with known aberrant p53 expression or *TP53* mutation with myometrial invasion
  - FIGO (2009) surgical stage III/IVA of any histology
- No prior radiation or systemic therapy (including neoadjuvant) for EC

R 1:1
N=1095

	Stage 1	Stage 2
	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m^2 (Q3W, 4 or 6 cycles)[a]	± radiotherapy ± cisplatin[b]
	Pembrolizumab 200 mg Q3W (6 cycles)	Pembrolizumab 400 mg Q6W (6 cycles)
	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m^2 (Q3W, 4 or 6 cycles)[a]	± radiotherapy ± cisplatin[b]
	Placebo Q3W (6 cycles)	Placebo Q6W (6 cycles)

Stratification Factors

- **MMR status (pMMR vs dMMR)**, and within pMMR stratum:
  - Planned radiation (chemo-EBRT vs EBRT vs no EBRT)
  - Histology (endometrioid vs non-endometrioid)
  - FIGO (2009) surgical stage (I/II vs III/IVA)

Dual primary endpoints

- DFS as assessed radiographically by the investigator or by histopathologic confirmation
- OS

[a]Chemotherapy was administered for 4 cycles in patients planned to receive chemoradiotherapy and 6 cycles for all other patients, including those planned for radiotherapy without radiosensitizing cisplatin. [b]Radiotherapy was optional at the discretion of the investigator, and cisplatin may have been given with EBRT as radiosensitizer; radiotherapy was started within 6 weeks after completion of carboplatin and paclitaxel (radiation may have been initiated during Stage 1 or Stage 2 depending on the number of cycles of chemotherapy that were administered).

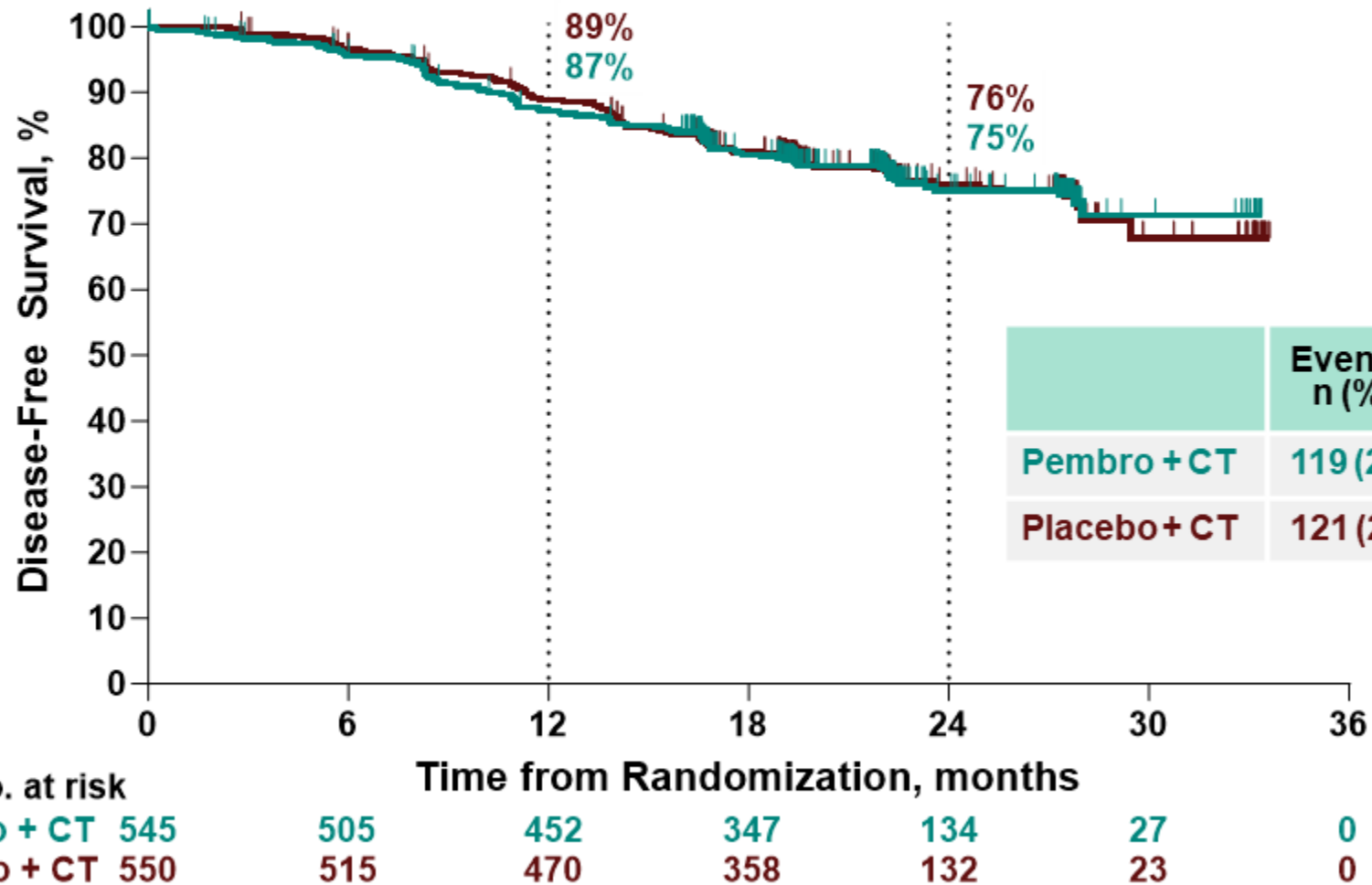
Baseline Characteristics: ITT Population

Characteristic	Pembro + Chemo (n = 545)	Placebo + Chemo (n = 550)
Age, median (range), y	62 (29–95)	62 (27–89)
ECOG PS 0	409 (75%)	416 (76%)
Race		
White	315 (58%)	362 (66%)
Asian	189 (35%)	157 (29%)
Multiple	23 (4%)	10 (2%)
Black or African American	11 (2%)	13 (2%)
American Indian or Alaska Native	2 (<1%)	3 (<1%)
Missing	5 (<1%)	5 (<1%)
Lymph node dissection	483 (89%)	502 (91%)
Lymph node status		
Lymph node involvement	223 (41%)	250 (45%)
No lymph node involvement	300 (55%)	284 (52%)
Not evaluable	22 (4%)	16 (3%)
MMR status at study entry		
dMMR	141 (26%)	140 (25%)
pMMR	404 (74%)	410 (75%)

Characteristic	Pembro + Chemo (n = 545)	Placebo + Chemo (n = 550)
FIGO 2009 stage at study entry		
IA/B	146 (27%)	144 (26%)
II	40 (7%)	41 (7%)
IIIA	109 (20%)	94 (17%)
IIIB	20 (4%)	19 (3%)
IIIC1	144 (26%)	169 (31%)
IIIC2	78 (14%)	81 (15%)
IVA/B[a]	8 (1%)	2 (<1%)
Planned radiation therapy at study entry		
EBRT[b] with cisplatin	94 (17%)	95 (17%)
EBRT[b] without cisplatin	256 (47%)	246 (45%)
Brachytherapy only	49 (9%)	52 (9%)
No EBRT or brachytherapy	146 (27%)	157 (29%)
Histology subtype		
Endometrioid	297 (54%)	297 (54%)
Non-endometrioid	248 (46%)	253 (46%)

[a]3 patients with stage IVB were randomized, including 2 in the pembro + chemo group and 1 in the placebo + chemo group. [b]With or without brachytherapy. Data cutoff date: March 4, 2024.

DFS[a] Similar Between Treatment Groups: ITT Population (Primary Endpoint)



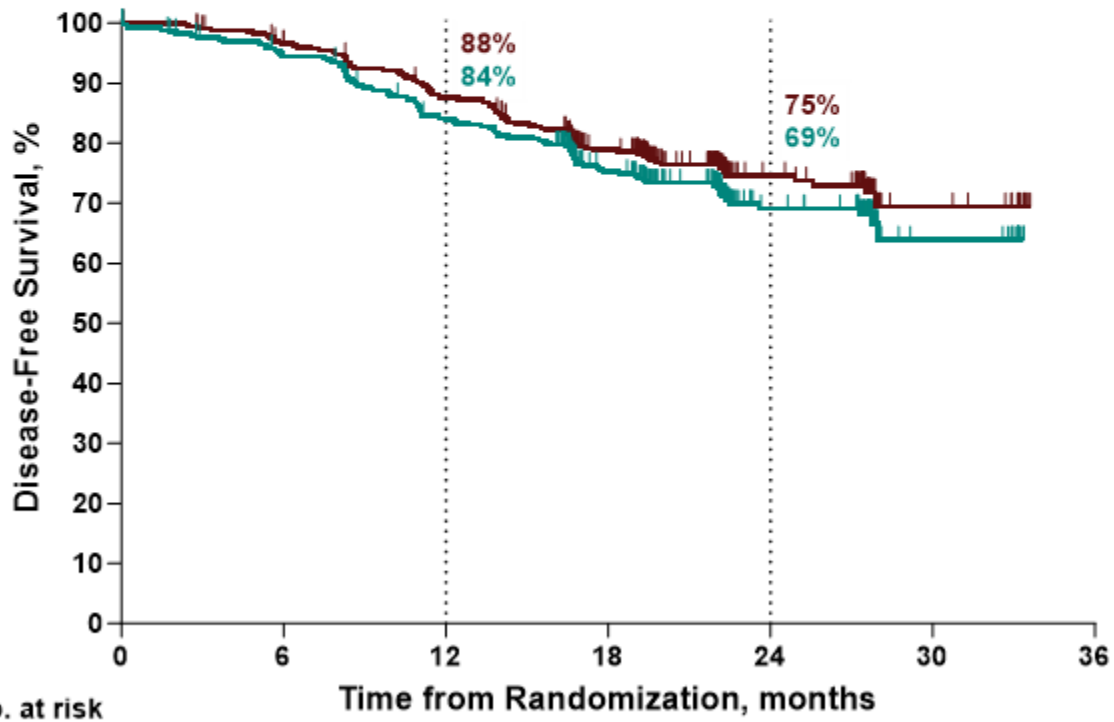
	Events, n (%)	Median (95% CI), mo	HR (95% CI)	*P* value
Pembro + CT	119 (22)	NR (NR–NR)	1.02 (0.79–1.32)	0.570
Placebo + CT	121 (22)	NR (NR–NR)		

[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause.
Data cutoff date: March 4, 2024.

Pembrolizumab Plus Chemotherapy Improved DFS[a] in dMMR Subgroup

pMMR Subgroup

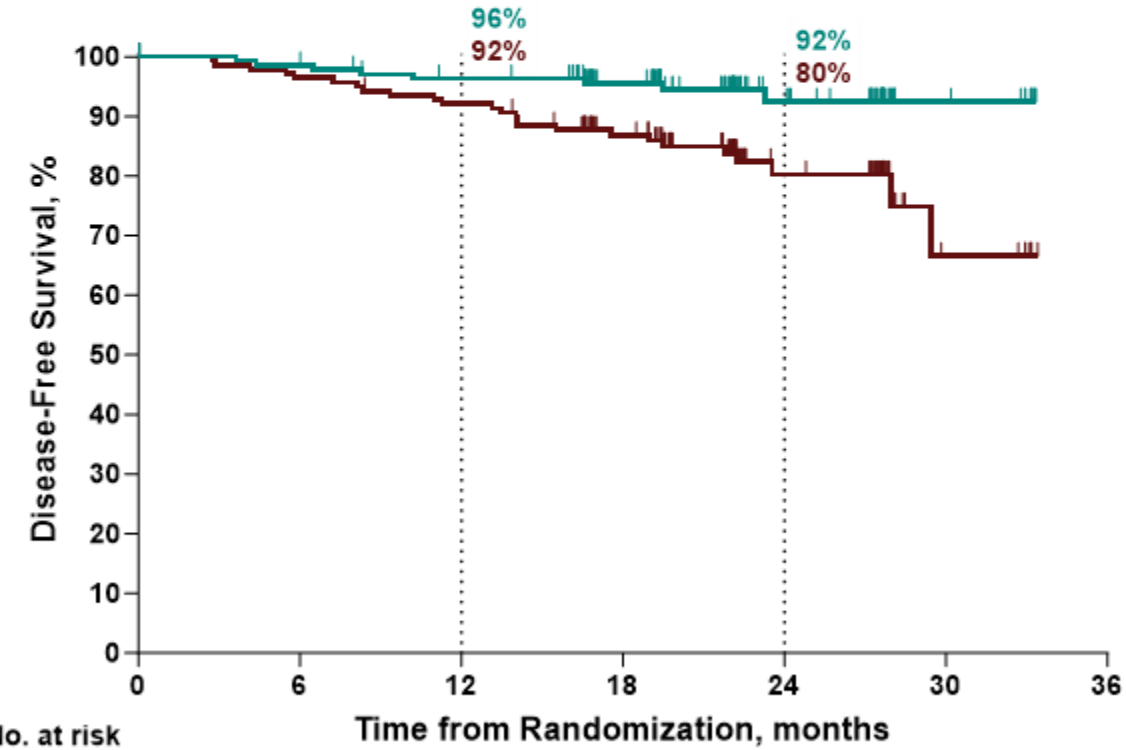
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	



No. at risk							
Pembro + CT	404	369	323	244	88	17	0
Placebo + CT	410	381	343	259	94	16	0

dMMR Subgroup

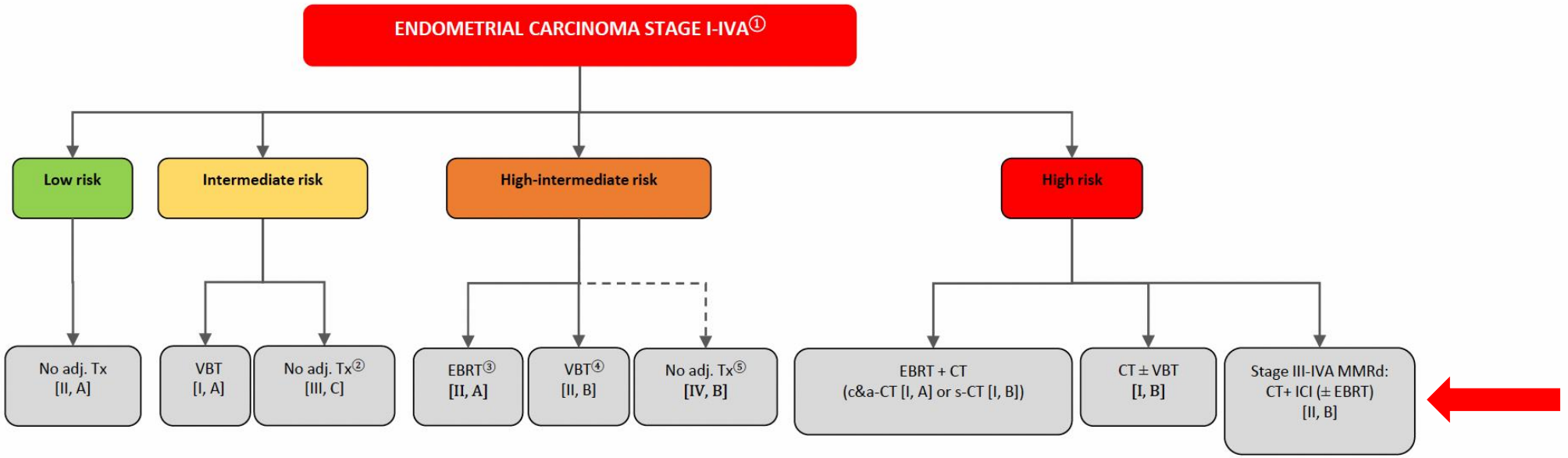
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	8 (6)	NR (NR–NR)	0.31 (0.14–0.69)
Placebo + CT	25 (18)	NR (29.5–NR)	



No. at risk							
	141	136	129	103	46	10	0
	140	134	127	99	38	7	0

[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause.
Data cutoff date: March 4, 2024.

Adjuvant therapy in endometrial carcinoma stage I-IVA



①for patients with FIGO 2023 stage IIIm *POLE*mut and IVAm *POLE*mut, no firm recommendation can be given, however de-descalation from high risk treatment can be considered.

②Especially for patients under 60 years of age and/or low-grade [II, A].

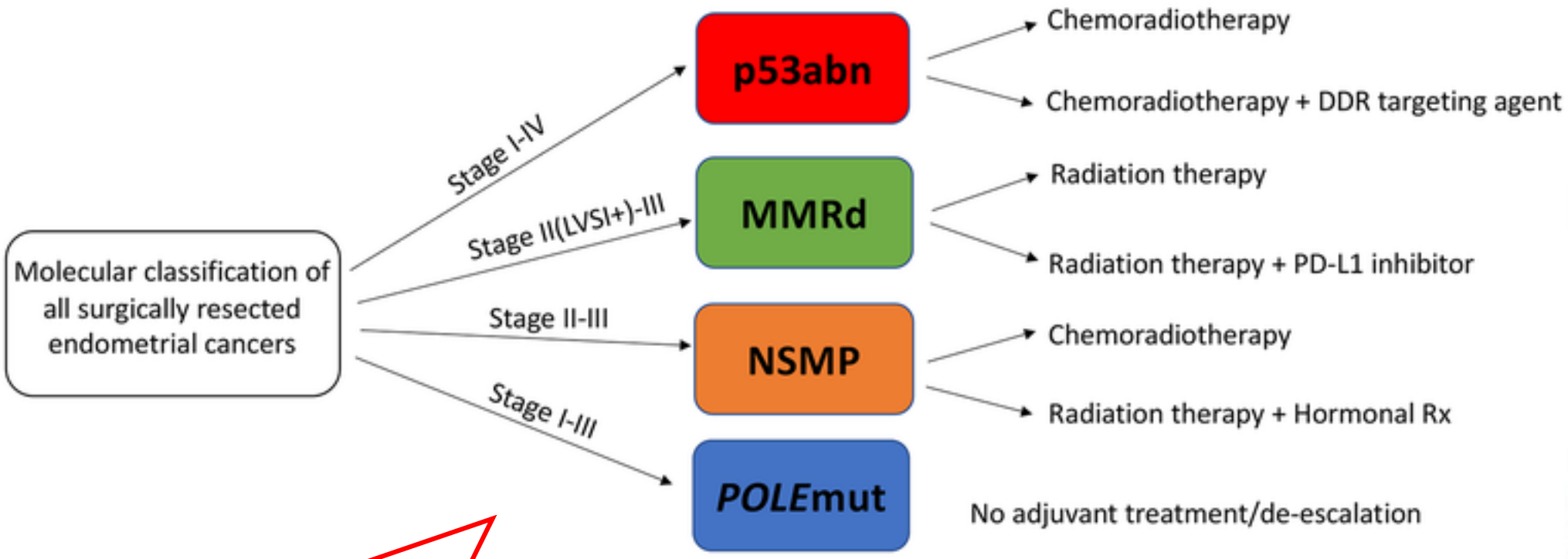
③EBRT is recommended for optimal pelvic control.

④VBT is an alternative option, especially for patients who underwent lymph node staging and are pN0.

⑤No adjuvant therapy can be considered, especially for patients who underwent lymph node staging and are pN0, without substantial LVSI and low-grade.

Adj. Tx adjuvant therapy; c&a-CT concurrent and adjuvant chemotherapy; CT chemotherapy; EBRT external beam radiotherapy; ICI immune checkpoint inhibitor; s-CT sequential chemotherapy; VBT vaginal brachytherapy.

TransPORTEC RAINBO Umbrella Trial

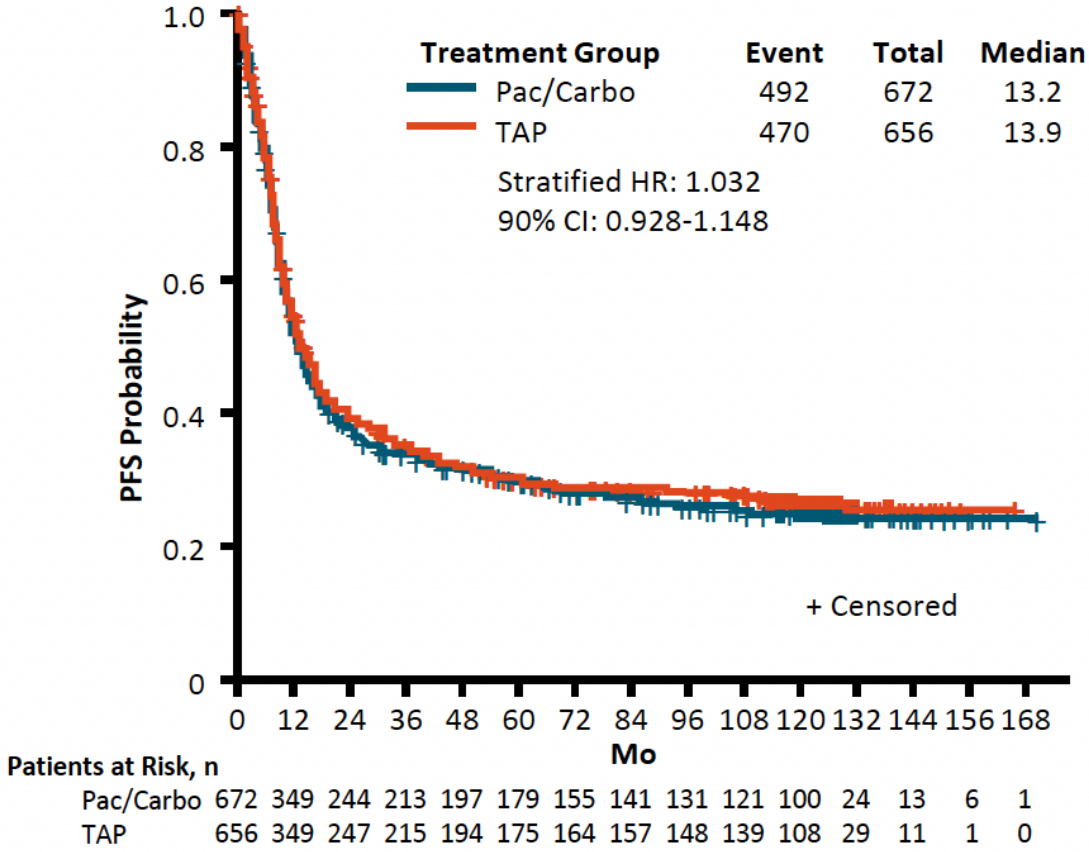


ER-neg NSMP are not eligible for orange NSMP, but will be followed as an independent observational cohort

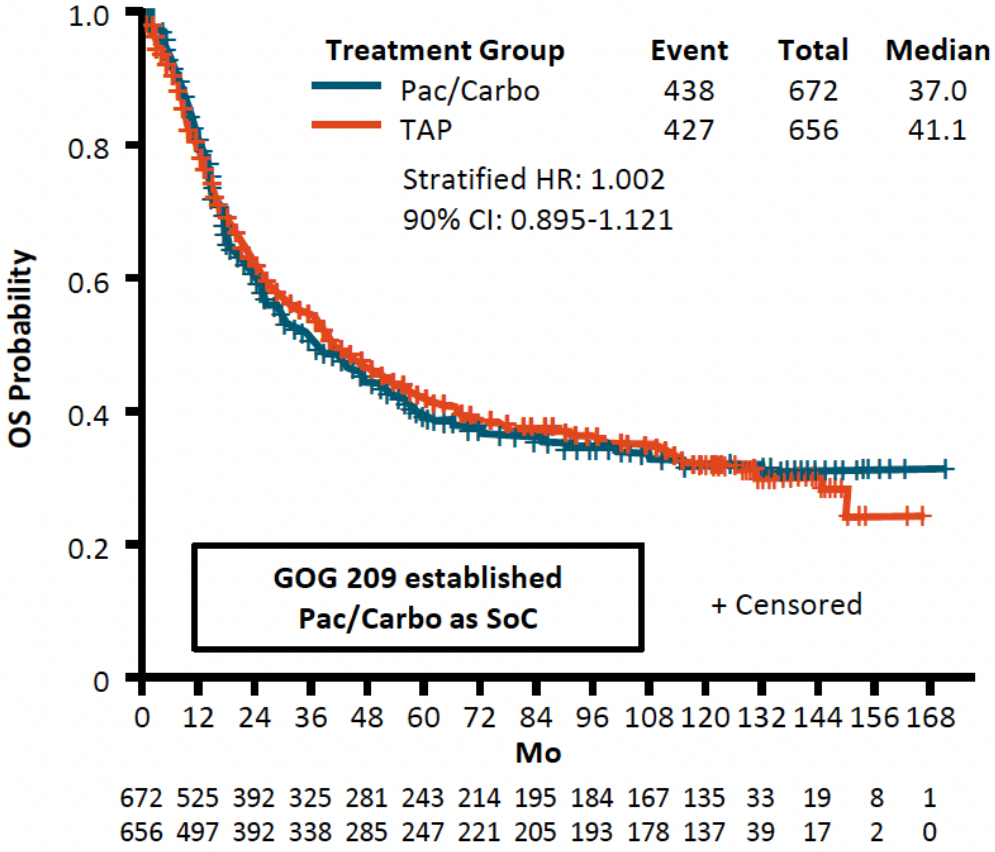
Advanced stage endometrial cancer

Advanced disease, 1st line

GOG 209: platinum paclitaxel +/- anthracyclines



PFS (median 13 vs 14 months)



OS (median 37 vs 41 months)

Miller et al. JCO 2020

ENGOT-en9/LEAP-001 Study Design (NCT03884101)

Key Eligibility Criteria

- Stage III, Stage IV or recurrent endometrial carcinoma[a]
- Radiographically apparent disease - either measurable or nonmeasurable
- No prior chemotherapy except in the neo/adjuvant setting[b]
- ECOG PS 0-1
- Tumor tissue sample for MMR testing

Stratification Factors

MMR status (pMMR vs dMMR),

- If pMMR
  - ECOG PS (0 vs 1)
  - Measurable disease (yes vs no)
  - Prior chemotherapy and/or chemoradiation (yes vs no)

R (1:1)
N = 842

Lenvatinib 20 mg orally QD until PD
+
Pembrolizumab 200 mg IV Q3W until PD or x35 cycles

Paclitaxel 175 mg/m² IV
+
Carboplatin AUC 6 IV Q3W up to 7 cycles[c]

Endpoints

- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DOR per RECIST v1.1 by BICR

AUC, area under the concentration-time curve; BICR, blinded independent central review; DOR, duration of response; HRQoL, health-related quality of life.
[a]Carcinosarcoma (malignant mixed Müllerian tumor), endometrial leiomyosarcoma or other high grade sarcomas, or endometrial stromal sarcomas excluded.
[b]1 prior line of neoadjuvant and/or adjuvant chemotherapy in the setting of curative-intent resection was permitted if recurrence occurred ≥6 months after last dose; prior radiotherapy with or without chemotherapy, or prior hormonal therapy were also permitted.
[c]Patients with ongoing clinical benefit could continue chemotherapy beyond 7 cycles if approved by sponsor.

Baseline Characteristics

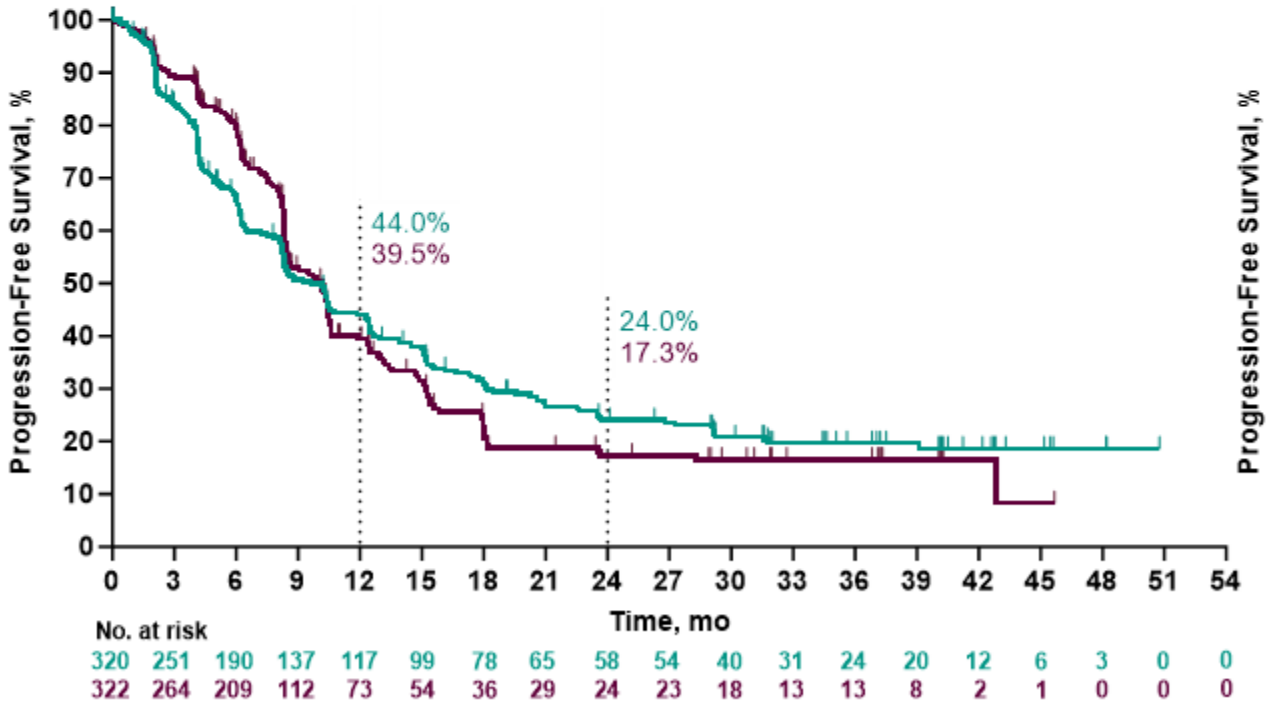
Characteristic	pMMR Population		All-comers	
	LEN/PEMBRO n = 320	TC n = 322	LEN/PEMBRO n = 420	TC n = 422
Age, median (range)	64 (22–87)	64 (32–88)	63 (22–93)	64 (32–88)
Geographic location				
North America	70 (21.9)	74 (23.0)	98 (23.3)	104 (24.6)
Western Europe	57 (17.8)	55 (17.1)	83 (19.8)	78 (18.5)
Asia	76 (23.8)	80 (24.8)	99 (23.6)	92 (21.8)
Rest of World	117 (36.6)	113 (35.1)	140 (33.3)	148 (35.1)
MMR Status, no. (%)				
pMMR	320 (100)	322 (100)	320 (76.2)	322 (76.3)
dMMR	–	–	100 (23.8)	100 (23.7)
ECOG PS 1, no. (%)	141 (44.1)	145 (45.0)	170 (40.5)	182 (43.1)
Measurable disease, no. (%)	318 (99.4)	317 (98.4)	418 (99.5)	416 (98.6)
Prior chemotherapy and/or chemoradiation, no. (%)	60 (18.8)	59 (18.3)	74 (17.6)	68 (16.1)
Chemoradiation alone	7 (2.2)	8 (2.5)	11 (2.6)	10 (2.4)
Neo/adjuvant chemotherapy alone	52 (16.3)	50 (15.5)	62 (14.8)	57 (13.5)
Neo/adjuvant chemotherapy and chemoradiation	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)
None	260 (81.3)	263 (81.7)	346 (82.4)	354 (83.9)
Histology, no. (%)				
Endometrioid	196 (61.3)	199 (61.8)	280 (66.7)	283 (67.1)
Non-endometrioid/adenocarcinoma/other[a]	124 (38.8)	123 (38.2)	140 (33.3)	139 (32.9)
FIGO Stage IVB at initial diagnosis, no. (%)	131 (40.9)	124 (38.5)	165 (39.3)	150 (35.5)

[a]Includes non-endometrioid, adenocarcinoma with no further information (17 patients in pMMR population; 22 patients among all-comers) and other (2 patients in pMMR population; 3 patients among all-comers).
Data cutoff date: October 2, 2023

Progression-Free Survival Similar Between LEN/PEMBRO and TC[a]

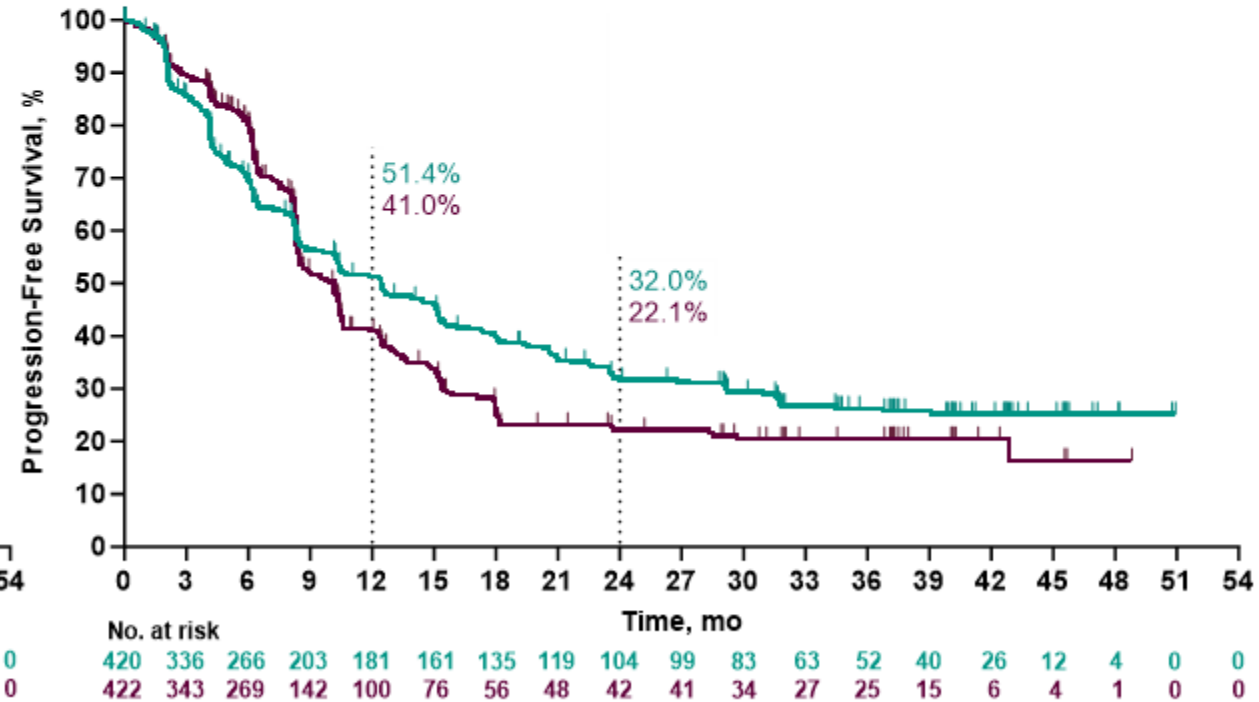
pMMR Population

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	224/320	9.6 (8.2–11.9)	0.99 (0.82–1.21)
TC	187/322	10.2 (8.4–10.5)	



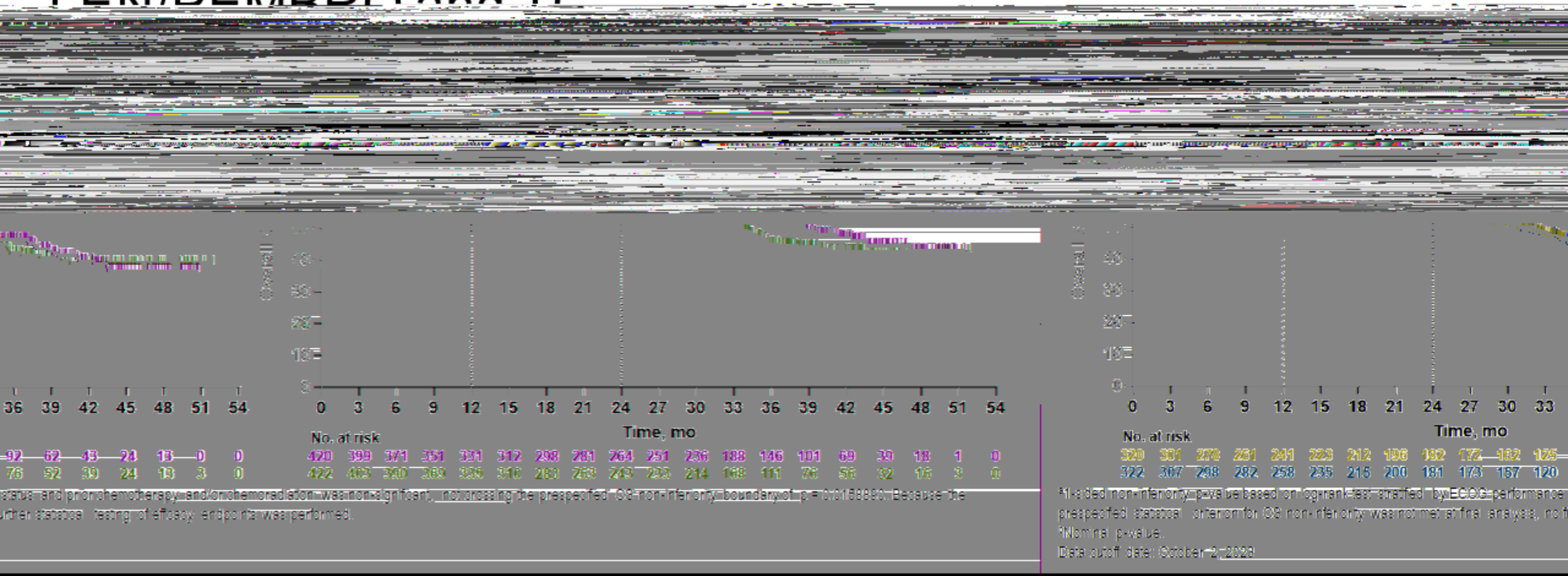
All-comers

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	271/420	12.5 (10.3–15.1)	0.91 (0.76–1.09)
TC	233/422	10.2 (8.4–10.4)	



[a]Based on RECIST v1.1 by blinded independent central review. No statistical testing was performed for PFS at the final analysis.
Data cutoff date: October 2, 2023

Overall Survival Similar Between LEN/PEMBRO and TC



status and pronochemotherapy and/or chemoradiation was not significant, not crossing the prespecified OS non-inferiority boundary of p = 0.0158980. Because the further statistical testing of efficacy endpoints was performed.

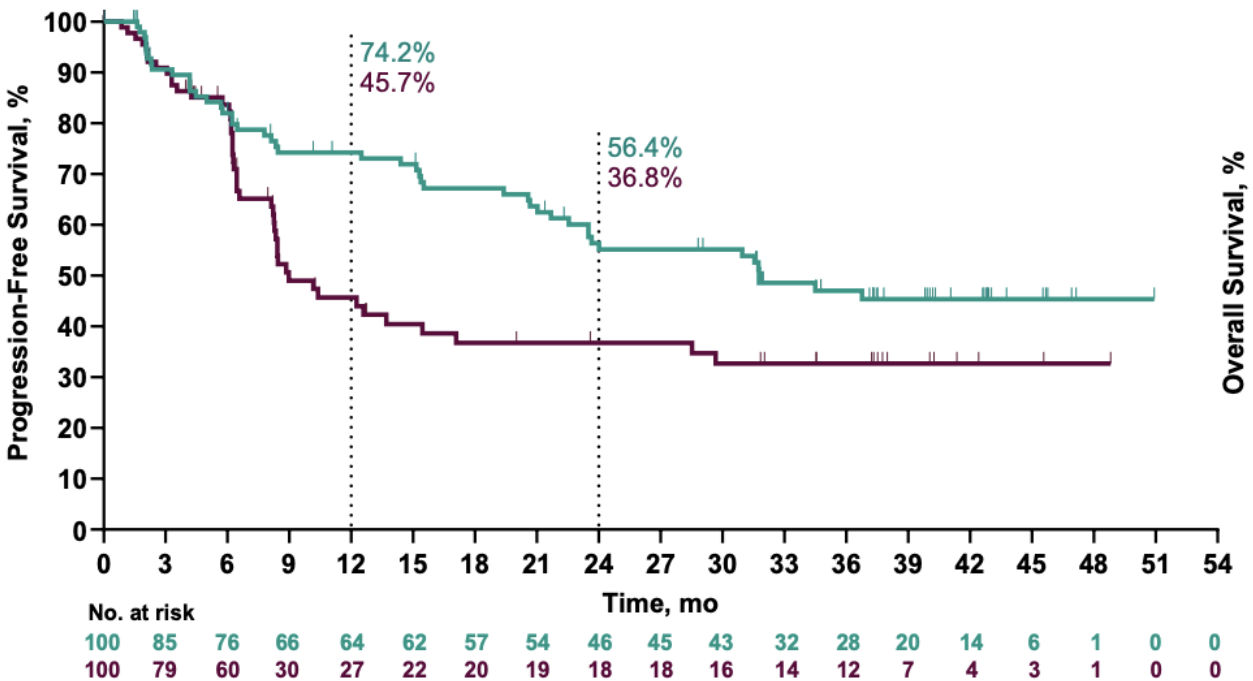
[1]1-sided non-inferiority p-value based on log-rank test stratified by ECOG performance prespecified statistical criterion for OS non-inferiority was not met at final analysis, not [2]Nominal p-value.

Data cutoff date: October 2, 2023

Exploratory Analysis(No analytical) PFS and OS in the dMMR Subgroup

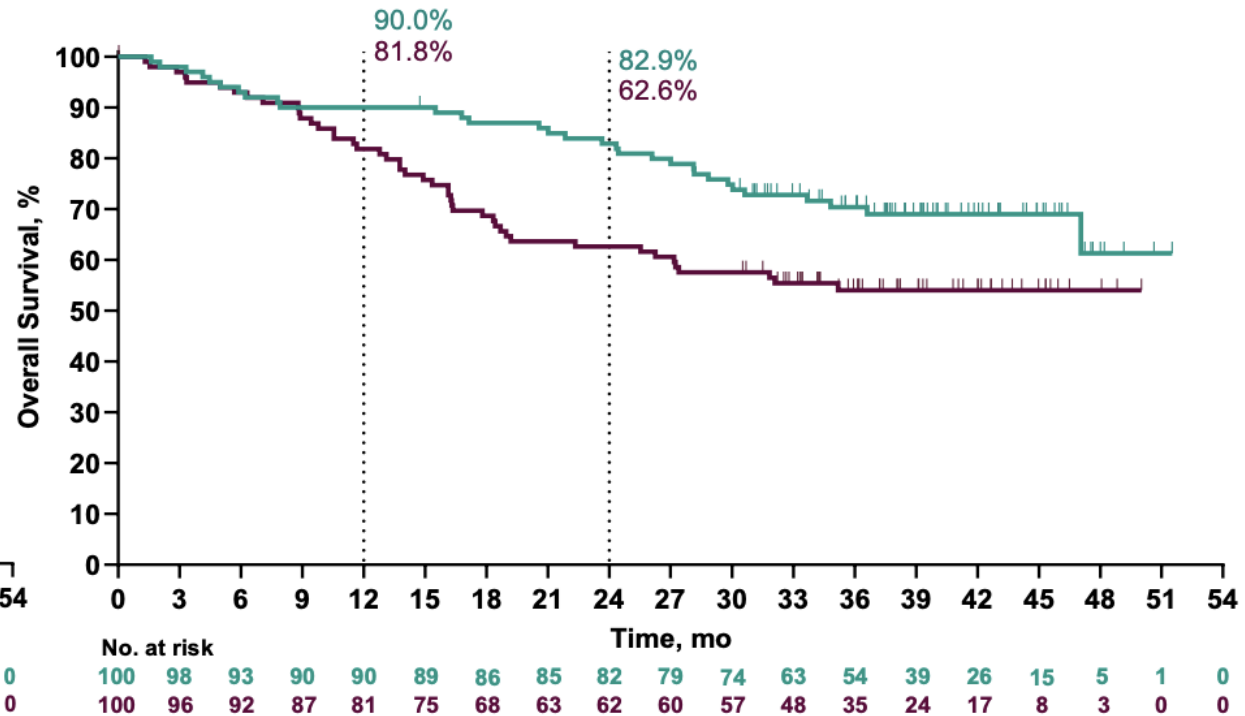
Progression-Free Survival

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	47/100	31.8 (22.5–NR)	0.61 (0.40–0.92)
TC	46/100	9.0 (8.2–17.1)	



Overall Survival

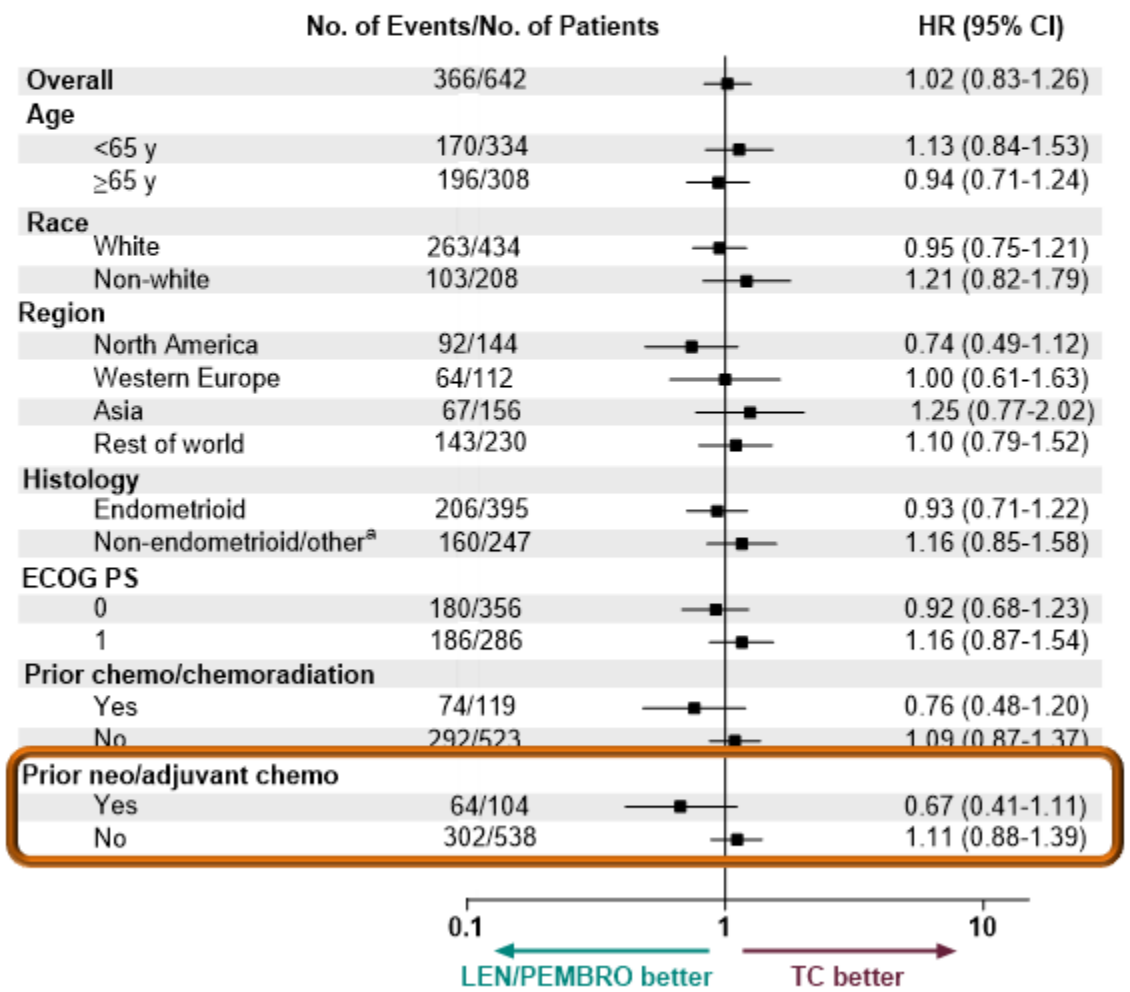
	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	31/100	NR (47.0–NR)	0.57 (0.36–0.91)
TC	45/100	NR (27.2–NR)	



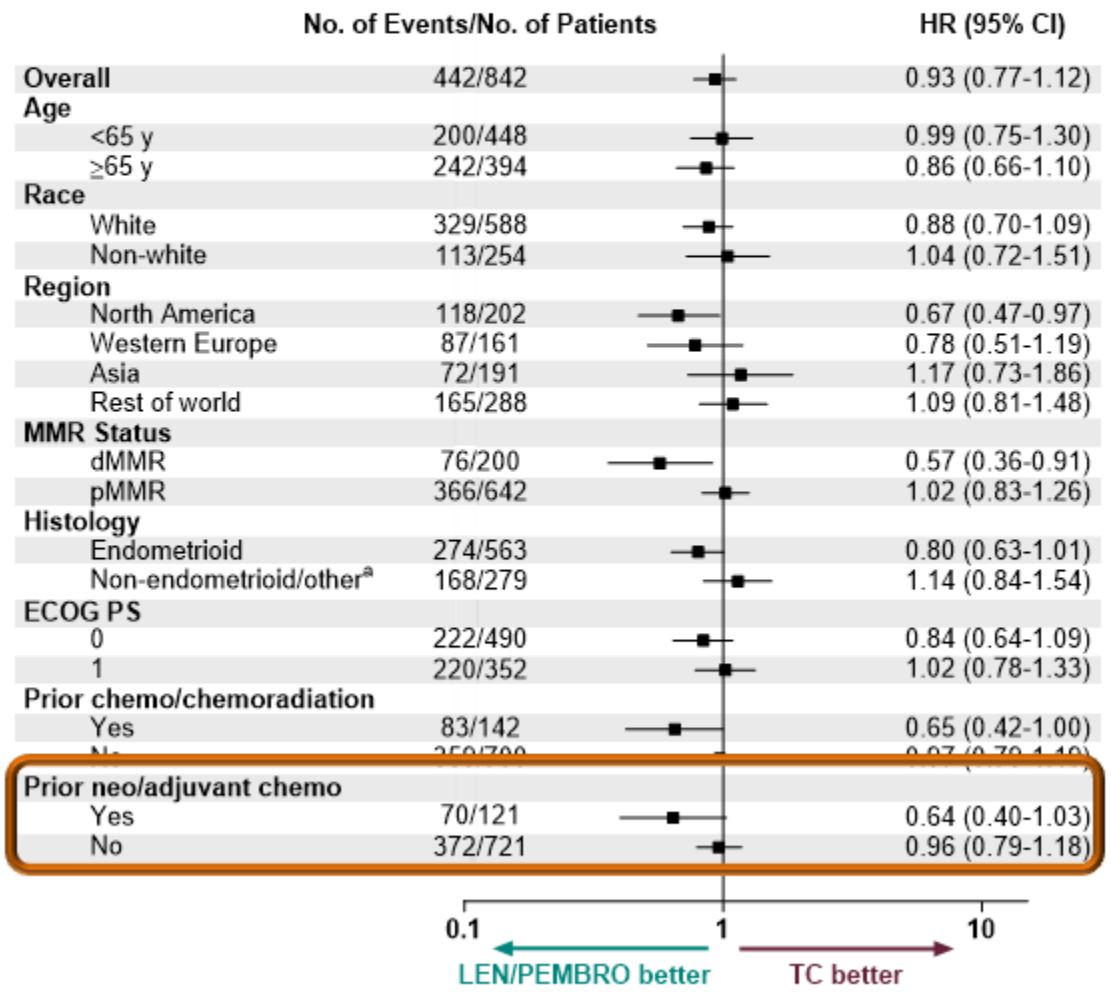
C. Marth et al. Presented at ESGO 2024 Meeting

Overall Survival Improved Following Progression on Prior Systemic Therapy

pMMR Population



All-comers



[a]Includes non-endometrioid, adenocarcinoma with no further information (17 patients in the pMMR population; 22 patients among all-comers) and other (2 patients in the pMMR population; 3 patients among all-comers).
Data cutoff date: October 2, 2023

First-line practice changing trials in advanced endometrial cancer

Studio	Fase	Terapia	Popolazione	Endpoint principale	PFI	Carcinosarcomi inclusi
RUBY	III	Dostarlimab + Carboplatino/Paclitaxel	dMMR e pMMR EC	PFS, OS	≥6 mesi	✅ Sì
KEYNOTE-868/NRG-GY018	III	Pembrolizumab + Carboplatino/Paclitaxel	dMMR e pMMR EC	**PFS**	>12 mesi	❌ No
AtTEnd	III	Atezolizumab + Carboplatino/Paclitaxel	dMMR e pMMR EC	PFS, OS	≥6 mesi	❌ No
DUO-E	III	Durvalumab ± Olaparib + Chemioterapia	dMMR e pMMR EC	**PFS**	>12 mesi	✅ Sì

Created using Chat GPT

Chemo-immunotherapy is the
NEW standard of care in 1° line dMMR patients

ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

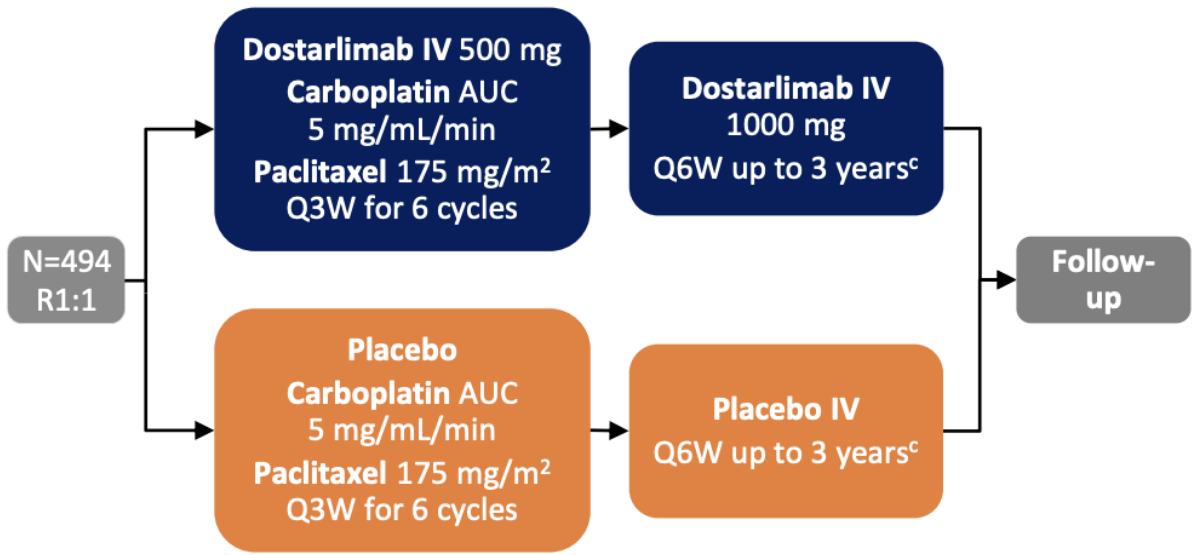
Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - **Carcinosarcoma, clear cell, serous, or mixed histology permitted**[a]
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD **≥6 months after completing treatment**
- ECOG PS 0-1
- Adequate organ function

Stratification

- MMR/MSI status[b]
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV
- OS

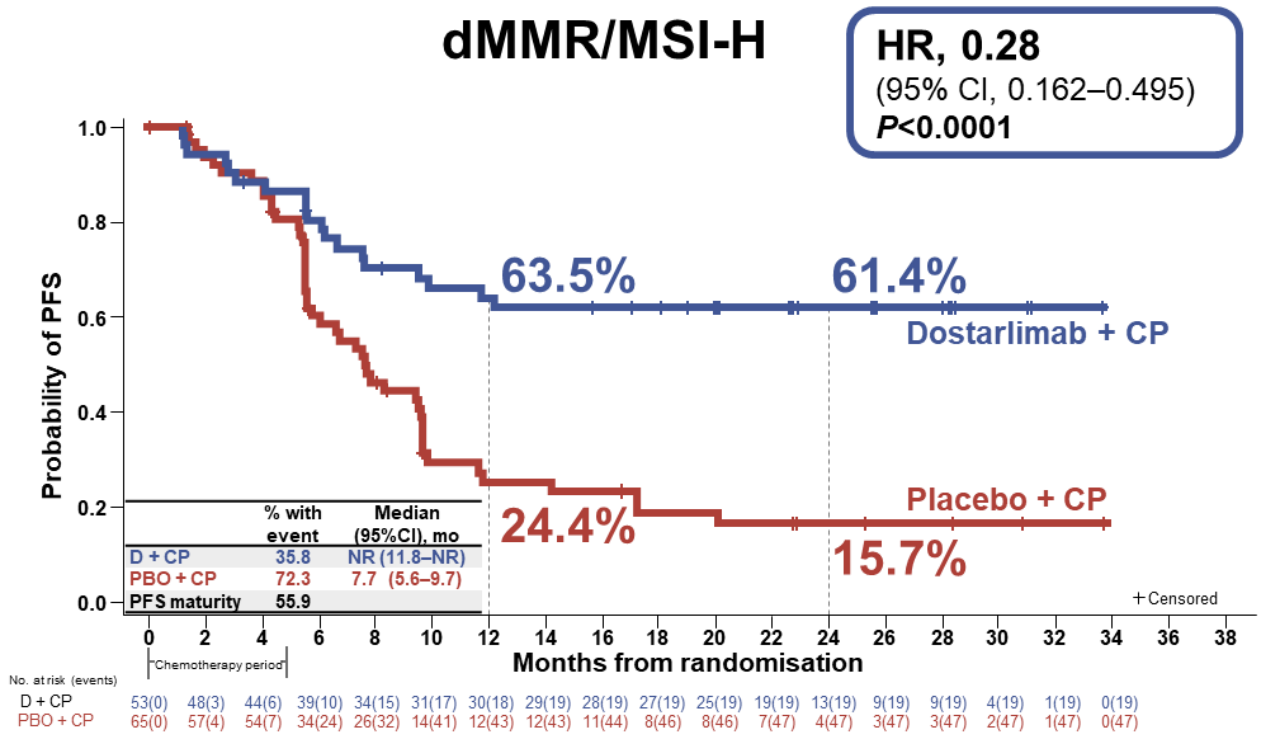
Secondary endpoints

- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

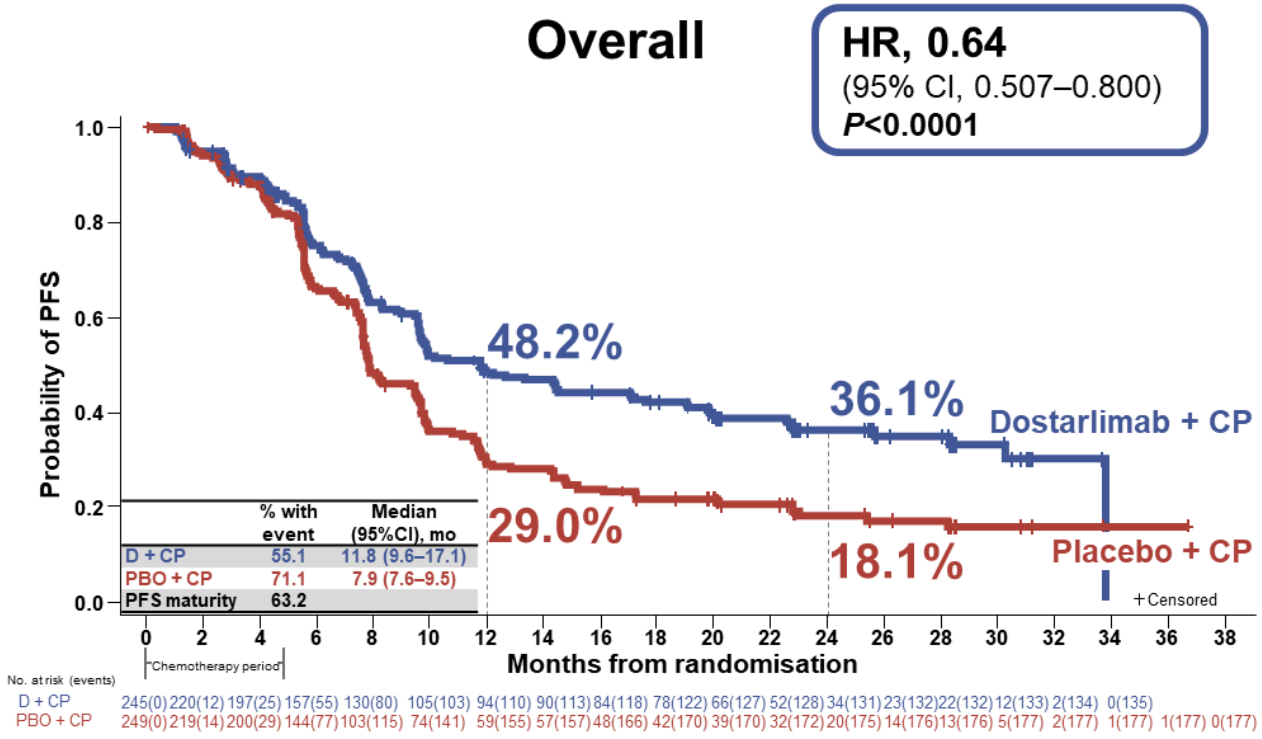
. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used.

Mirza MR. et al N Engl J Med. 2023 Jun 8;388(23):2145-2158.

Statistically Significant Improvements in PFS



Median duration of follow-up: 24.8 mo

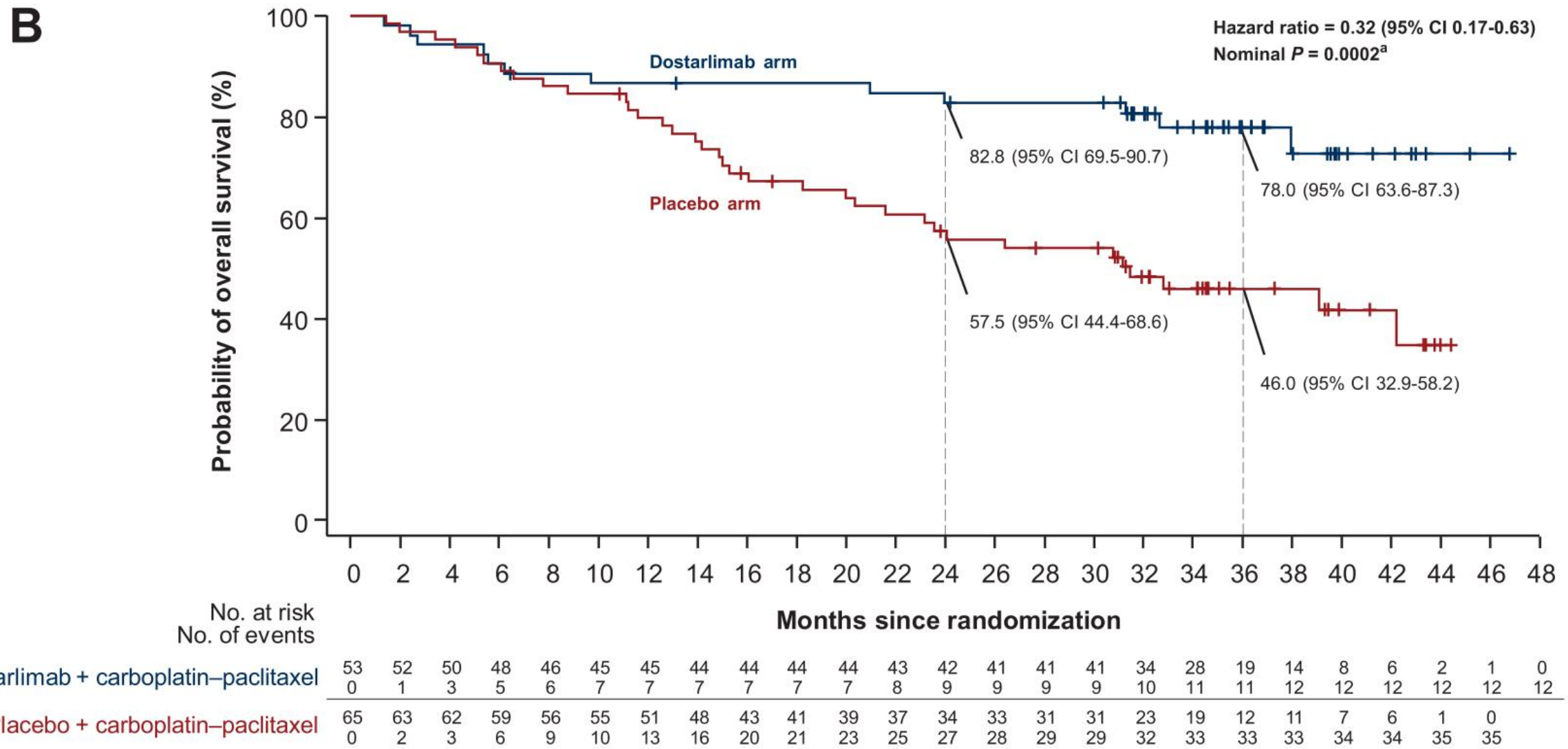


Median duration of follow-up: 25.4 mo

From *New England Journal of Medicine*, Mirza MR, Chase DM, Slomovitz MD, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. DOI: 10.1056/NEJMoa2216334. Copyright © 2023 Massachusetts Medical Society.

CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NR, not reached, PBO, placebo; PFS, progression-free survival.

OS data of Dostarlimab + CP in dMMR



M. A. Powell et al. Annal of Oncol 2024

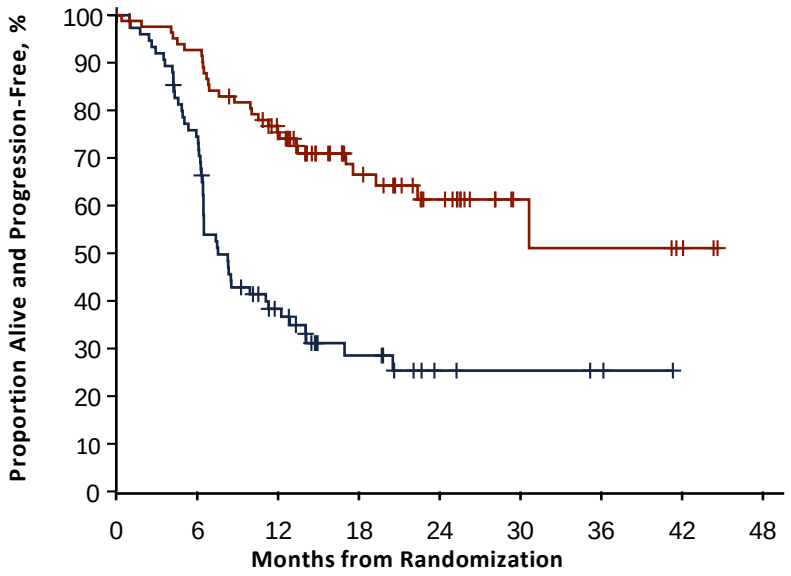
PFS by Methylation Status in dMMR Population

72%

Methylation

Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	51/77	7.5 (6.4–11.3)	0.307 (0.19–0.49) *P* <0.0001
Pembro + CP	28/83	NR (22.3–NR)	



Number at risk (Cumulative number censored)

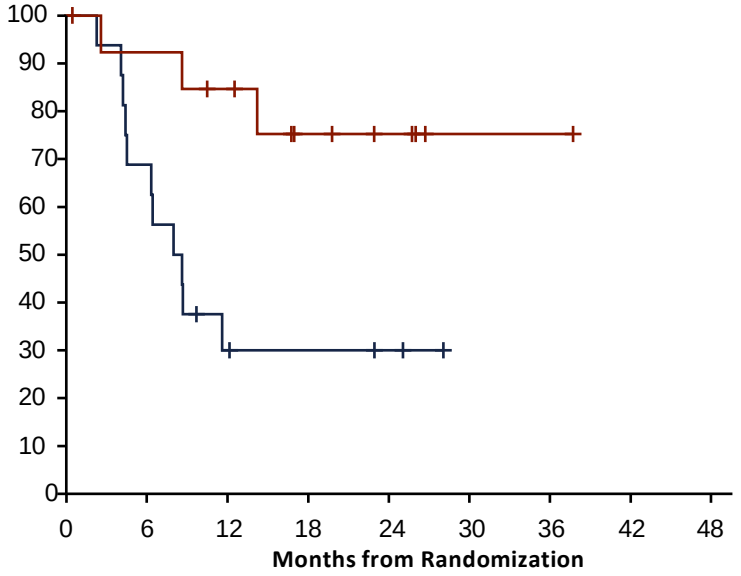
Placebo + CP	77 (2)	55 (3)	23 (9)	11 (16)	4 (22)	3 (23)	2 (24)	0 (26)	
Pembro + CP	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

13%

No Methylation

Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	11/17	8.3 (4.4–NR)	0.263 (0.07–0.99) *P* = 0.0172
Pembro + CP	3/13	NR (14.2–NR)	



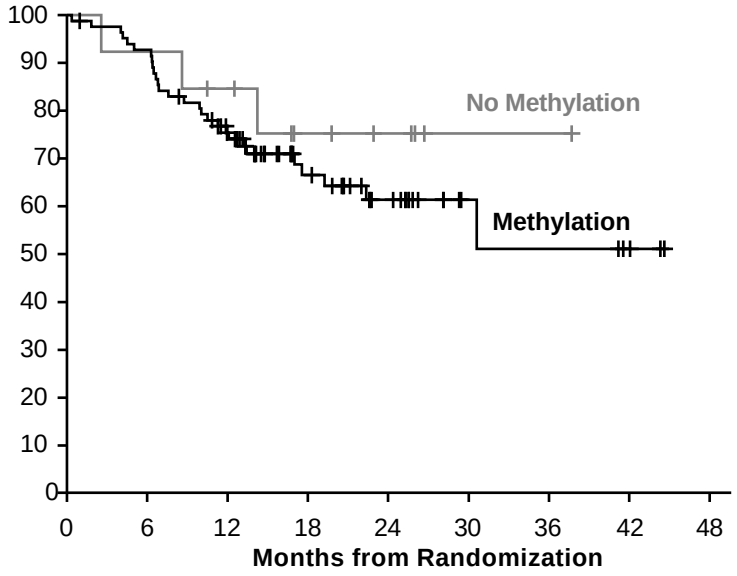
Number at risk (Cumulative number censored)

Placebo + CP	17 (0)	11 (1)	4 (2)	3 (3)	2 (4)	0 (6)		
Pembro + CP	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)

Methylation Status

Pembro + CP Arm

	Events n/N	Median (95% CI), mo
No Methylation	3/13	NR (14.2–NR)
Methylation	28/83	NR (22.3–NR)



Number at risk (Cumulative number censored)

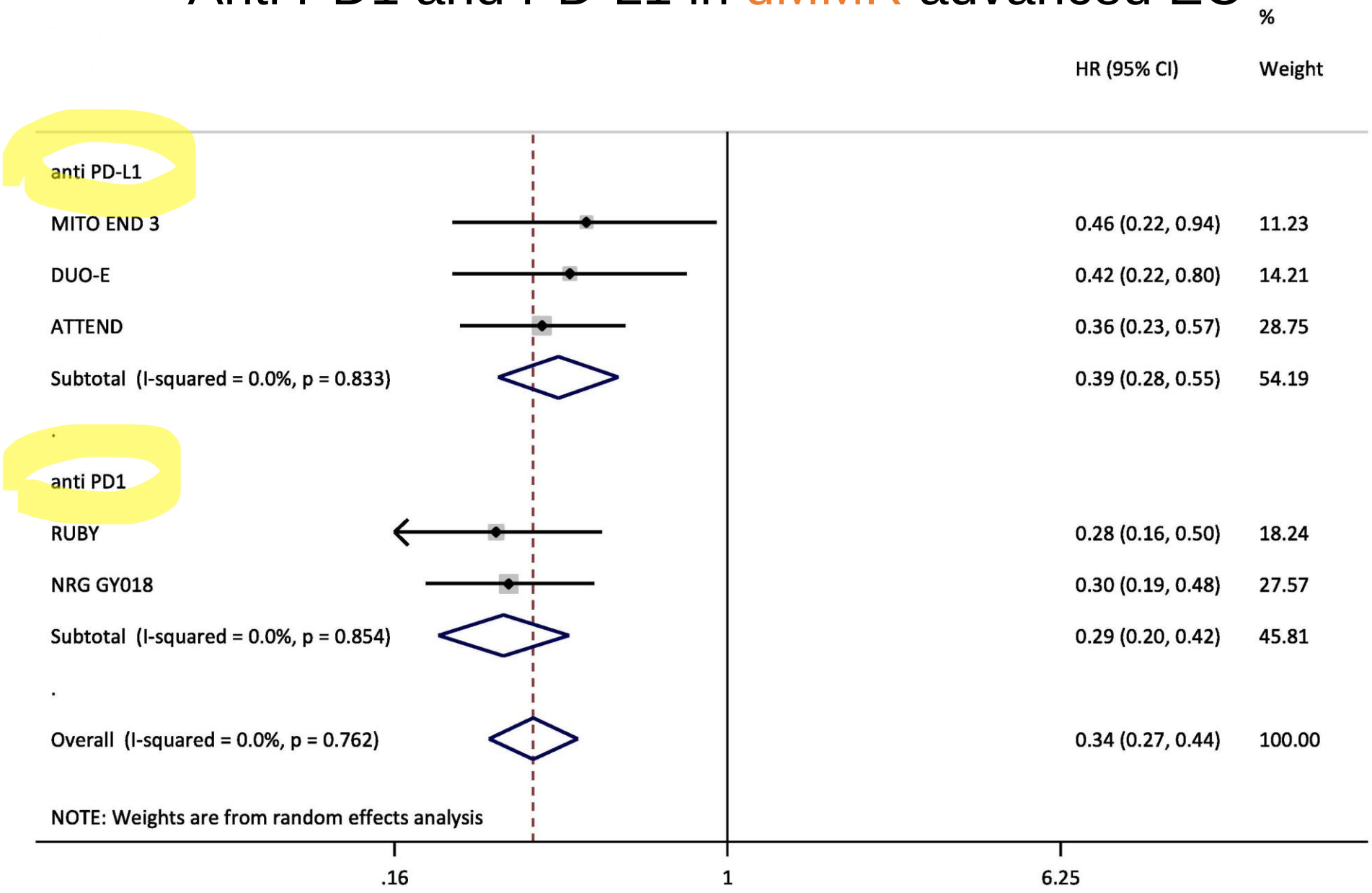
No Methylation	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)	
Methylation	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

MADRID 2023 ESMO congress

Ramez N. Eskander

Data cutoff date: August 18, 2023.

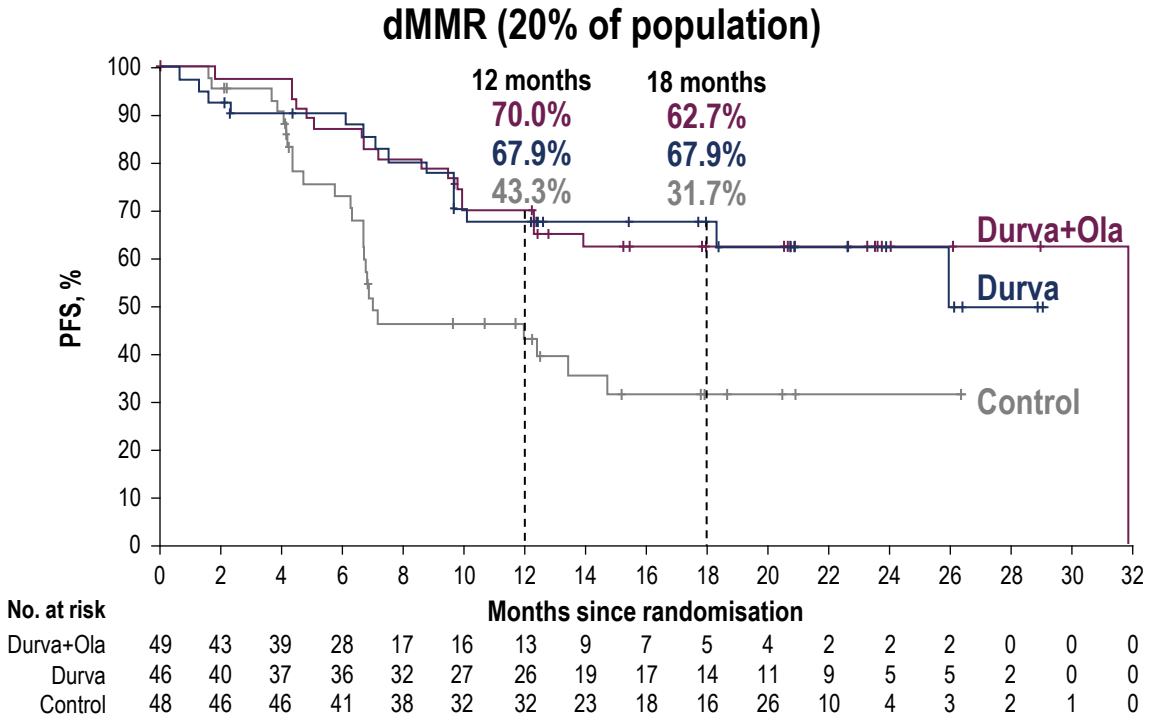
Anti PD1 and PD-L1 in dMMR advanced EC



Bartoletti et al. CTR 2024

DUO-E: Olaparib in maintenance in dMMR: Is it useful?

Prespecified exploratory analysis

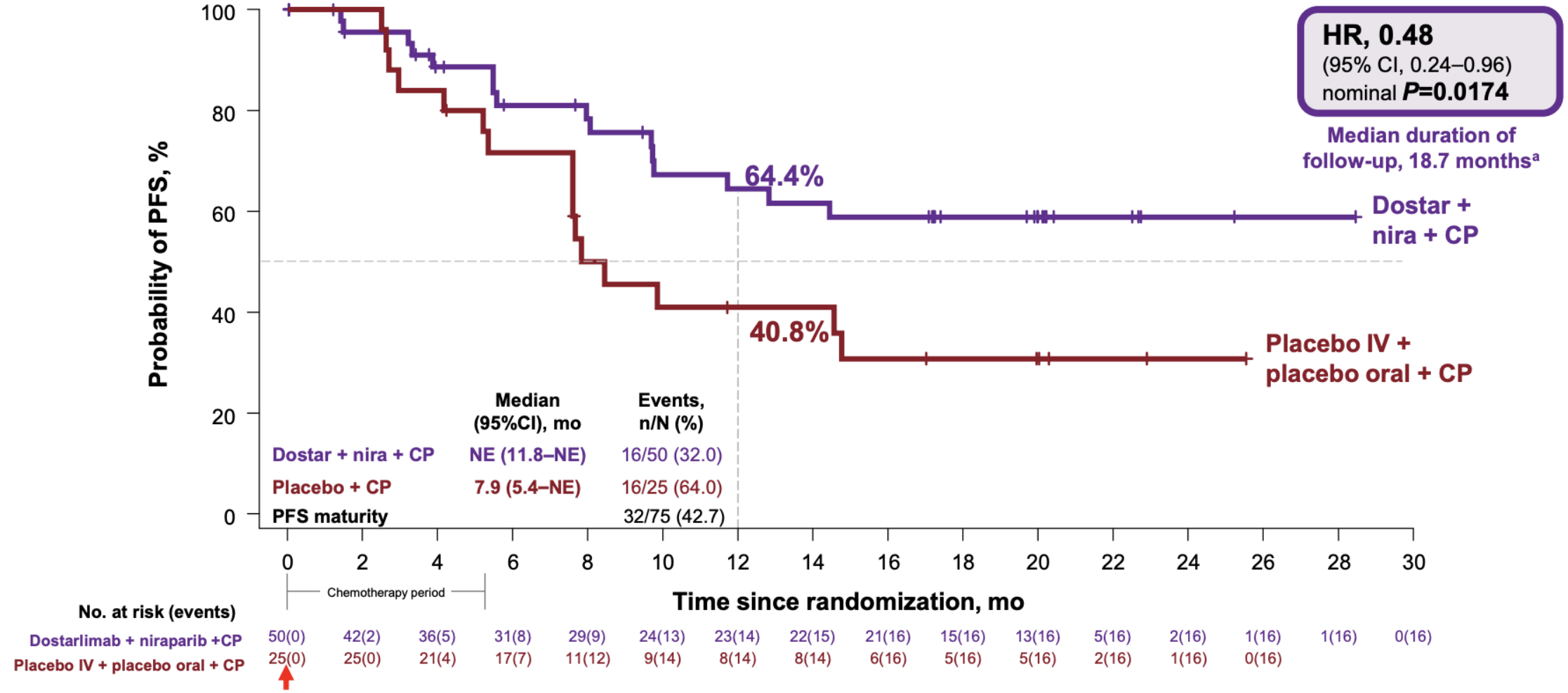


	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**

MADRID 2023 ESMO congress

Exploratory subgroup analysis. MMR status evaluated using the Ventana immunohistochemistry MMR panel. Rates were estimated by the KM method.
*CI for median PFS was derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from an unstratified Cox proportional hazards model.

RUBY part 2: PFS in dMMR



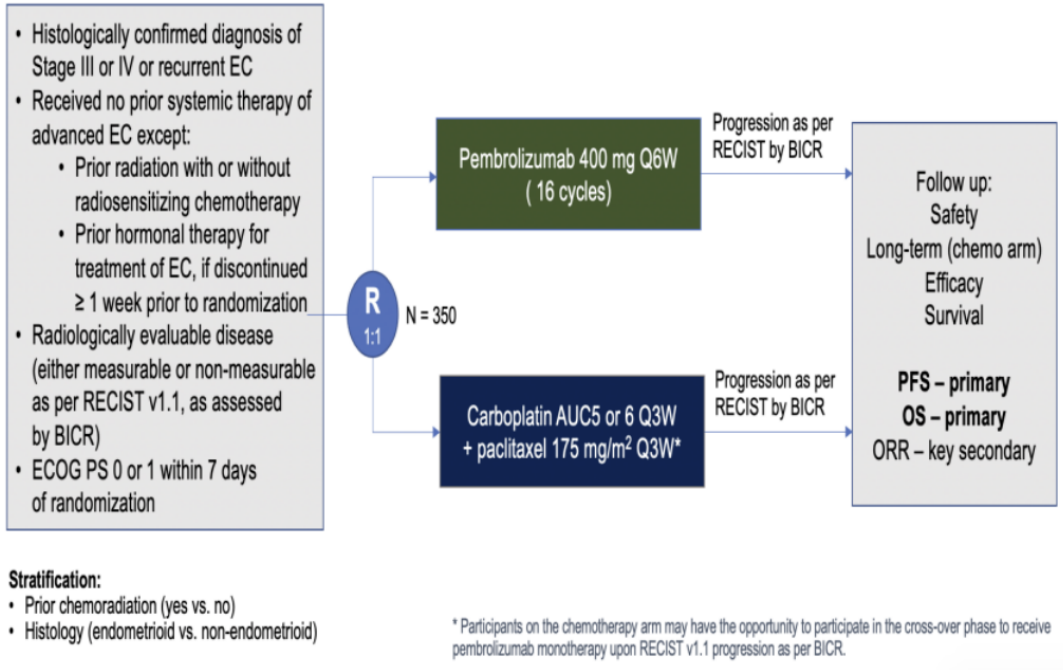
[a]Median expected duration of follow-up.
CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; HR, hazard ratio; MSI-H, microsatellite instability high; NE, not estimable; nira, niraparib; PFS, progression-free survival.

Mansoor MR et al. Presented at SGO Meeting 2024

The less the better?

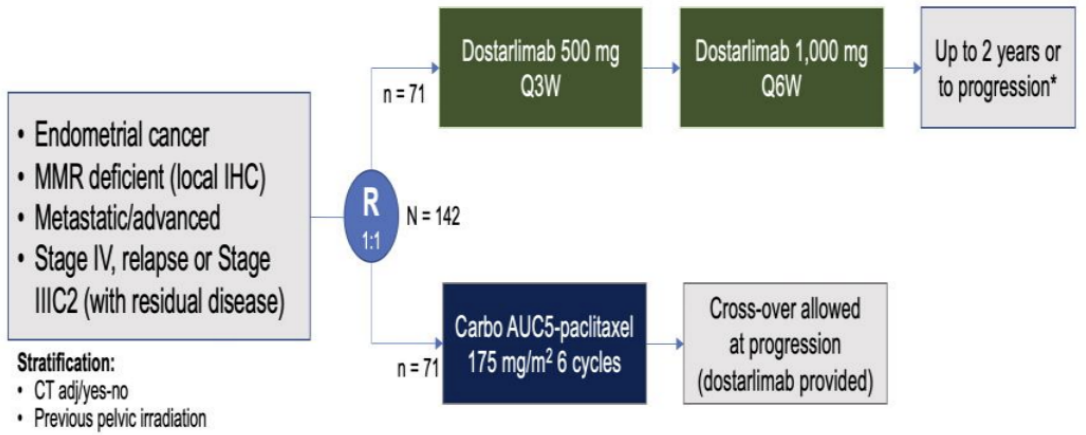
KEYNOTE-C93/GOG-3064/ENGOT-en 15
Study design

Phase III randomized trial of pembrolizumab vs. platinum doublet chemotherapy in first-line dMMR advanced or recurrent EC



ENGOT-en13/GINECO/DOMENICA
Study design

Phase III randomized trial comparing chemotherapy alone vs.dostarlimab in first-line dMMR EC advanced/metastatic



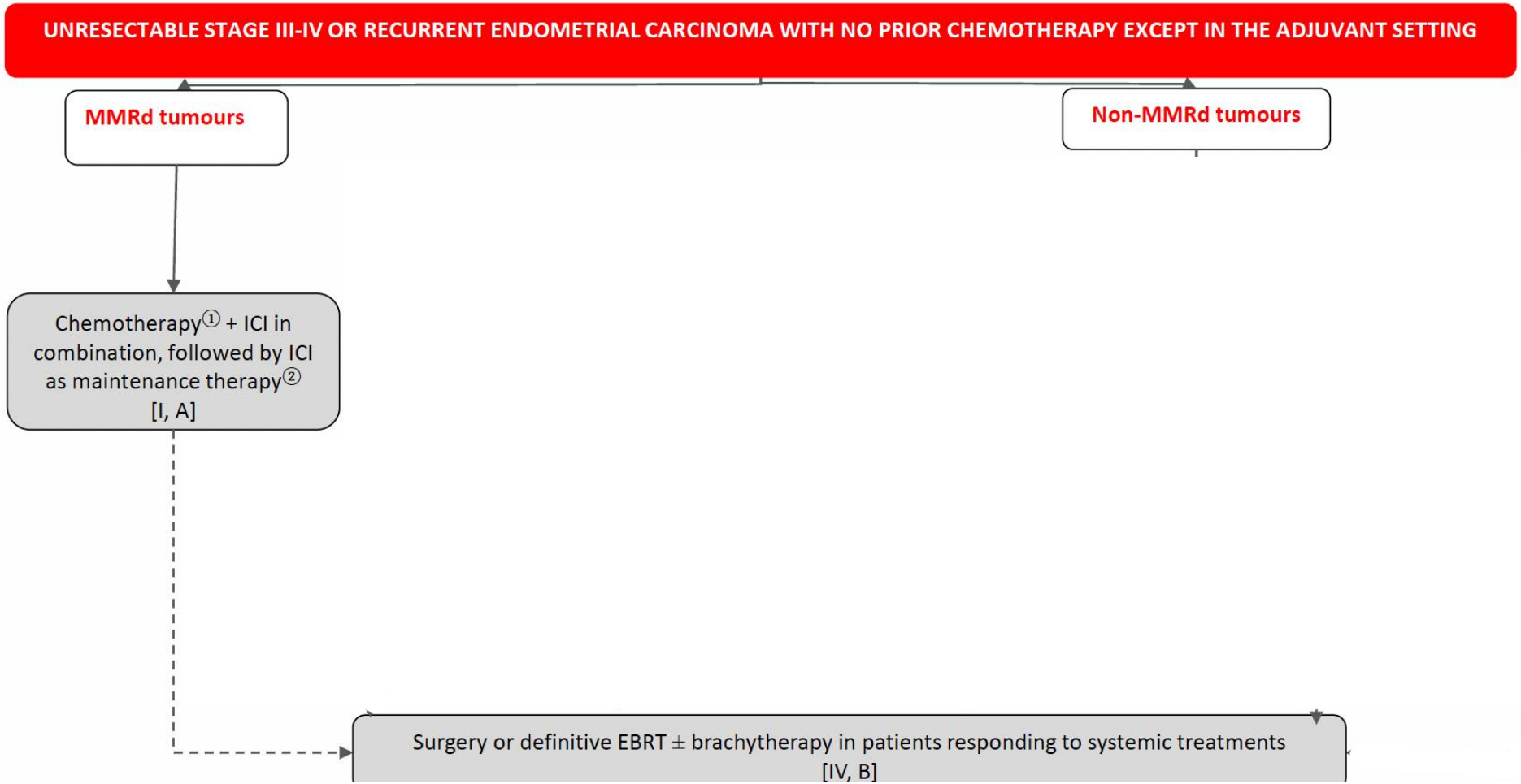
Primary endpoint: Investigator-assessed PFS by RECIST v1.1

Secondary endpoints: OS and PROs (key secondary endpoints), ORR, DoR, PFS2, TFST, safety and tolerability, central MMR

Exploratory endpoints: Translational (MSI, PD-1/-L1 status, immune signature); PFS according to iRECIST

clinicaltrials.gov:01244789; clinicaltrials.gov:05173987

NEW ESGO GUIDELINES 2025



70% of endometrial cancer are not dMMR

Should we use IO even in not dMMR advanced endometrial cancer?

YES

Study Design

Key Eligibility Criteria

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent endometrial cancer
- Pathology report showing results of institutional MMR IHC testing
- ECOG PS 0, 1, or 2
- No prior chemo except prior adjuvant chemo if completed ≥12 mo before study

Stratification Factors

- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

N = 816
(591 pMMR,
225 dMMR)

R
1:1

Arm 1
Placebo IV Q3W +
Paclitaxel 175 mg/m² IV Q3W +
Carboplatin AUC 5 IV Q3W

for 6 cycles

→ **Arm 1**
Placebo IV Q6W

for up to 14 additional cycles

Arm 2
Pembrolizumab 200 mg IV Q3W +
Paclitaxel 175 mg/m² IV Q3W +
Carboplatin AUC 5 IV Q3W

for 6 cycles

→ **Arm 2**
Pembrolizumab
400 mg IV Q6W

for up to 14 additional cycles

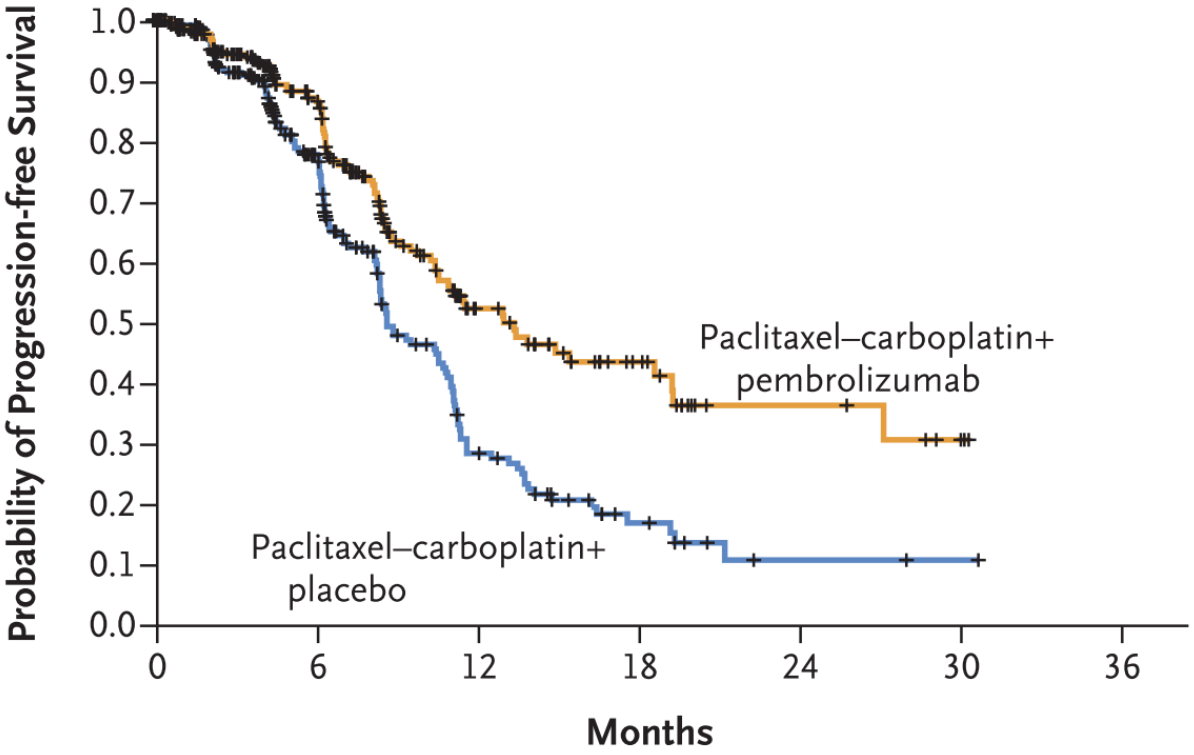
Endpoints

- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of MMR IHC testing at institution vs centralized

Median follow-up:

- IA1 data cutoff date of December 16, 2022: dMMR cohort, 12 months; pMMR cohort, 7.9 months
- **Current analysis data cutoff date of August 18, 2023**: dMMR cohort, 20.6 months; pMMR cohort, 15.8 months

pMMR Cohort



No. at Risk							
Paclitaxel–carboplatin+ pembrolizumab	290	150	45	20	7	3	0
Paclitaxel–carboplatin+ placebo	292	129	33	10	2	1	0

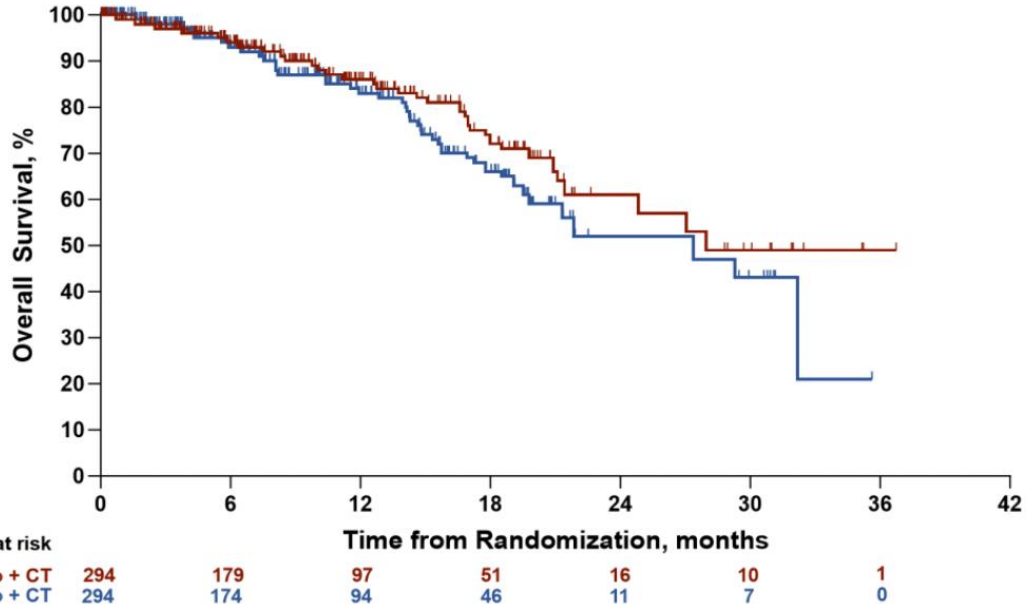
	No. of Events	No. of Patients	Median Progression-free Survival (95% CI)
			mo
Paclitaxel–Carboplatin+ Pembrolizumab	89	290	13.1 (10.5–18.8)
Paclitaxel–Carboplatin+ Placebo	133	292	8.7 (8.4–10.7)

Stratified hazard ratio for disease progression or death, 0.54 (95% CI, 0.41–0.71)

Eskander et al. NEJM 2023

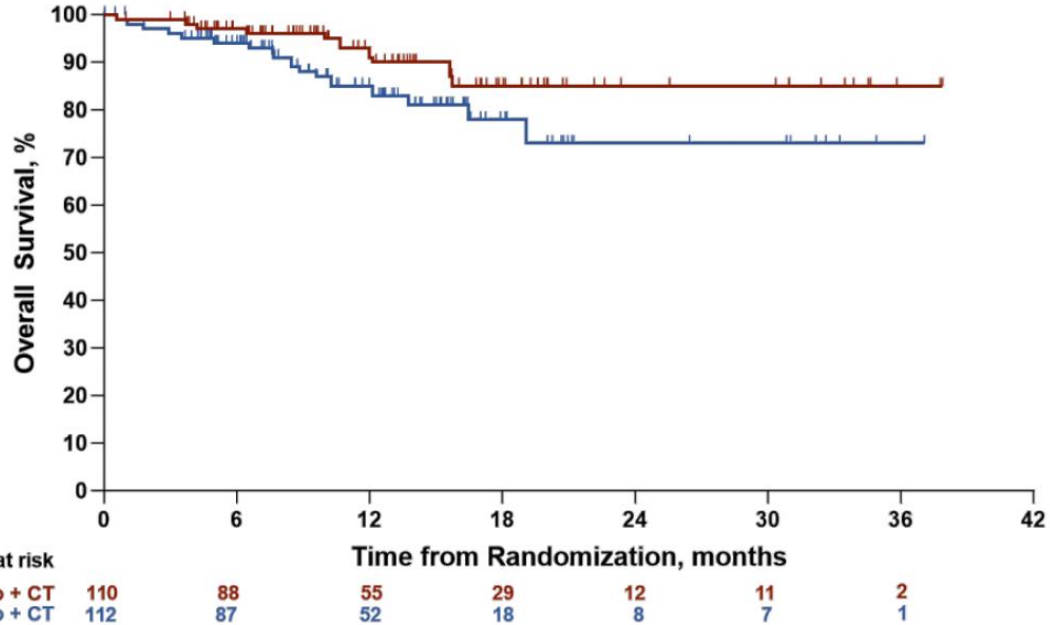
Still immature OS data for Pembrolizumab or placebo + carbopaclitaxel

pMMR



	Events, n/N	Follow-up Duration[a], median (range), mo	Median OS (95% CI), mo	HR (95% CI)[b], *P*-value[c]
Pembro + CT	45/294	8.8 (0.1–37.0)	27.96 (21.42–NR)	0.79 (0.53–1.17) *P* = 0.1157
Placebo + CT	54/294	8.4 (0.1–37.2)	27.37 (19.52–NR)	

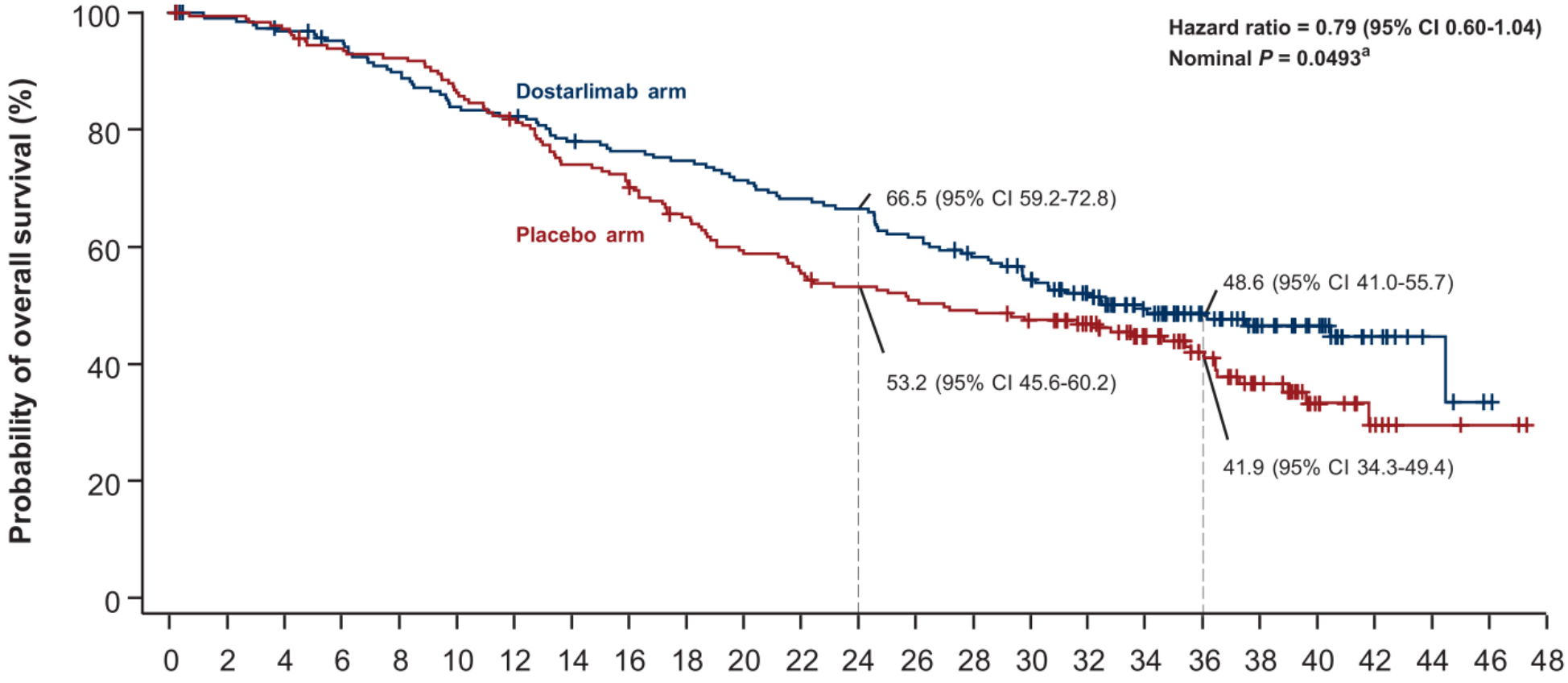
dMMR



	Events, n/N	Follow-up Duration[a], median (range), mo	Median OS (95% CI), mo	HR (95% CI)[b], *P*-value[c]
Pembro + CT	10/110	13.3 (0.6–39.4)	NR (NR–NR)	0.55 (0.25–1.19) *P* = 0.0617
Placebo + CT	17/112	13.7 (1.0–38.0)	NR (NR–NR)	

Eskander SGO 2024

OS data of Dostarlimab + CP in pMMR



No. at risk
No. of events

Dostarlimab + carboplatin–paclitaxel	192 0	187 2	182 6	175 11	165 21	156 30	153 33	144 41	140 44	137 47	131 53	125 59	122 62	113 71	105 77	96 84	84 88	67 91	51 93	38 95	29 95	11 96	4 96	1 97	0 97
Placebo + carboplatin–paclitaxel	184 0	181 1	177 5	169 12	167 14	155 26	146 34	133 47	125 54	115 63	104 74	98 80	93 84	89 88	86 91	81 94	73 95	59 98	41 101	28 106	15 108	7 109	3 109	2 109	0 109

M. A. Powell et al. Annal of Oncol 2024

RUBY part 1: subsequent immunotherapy use

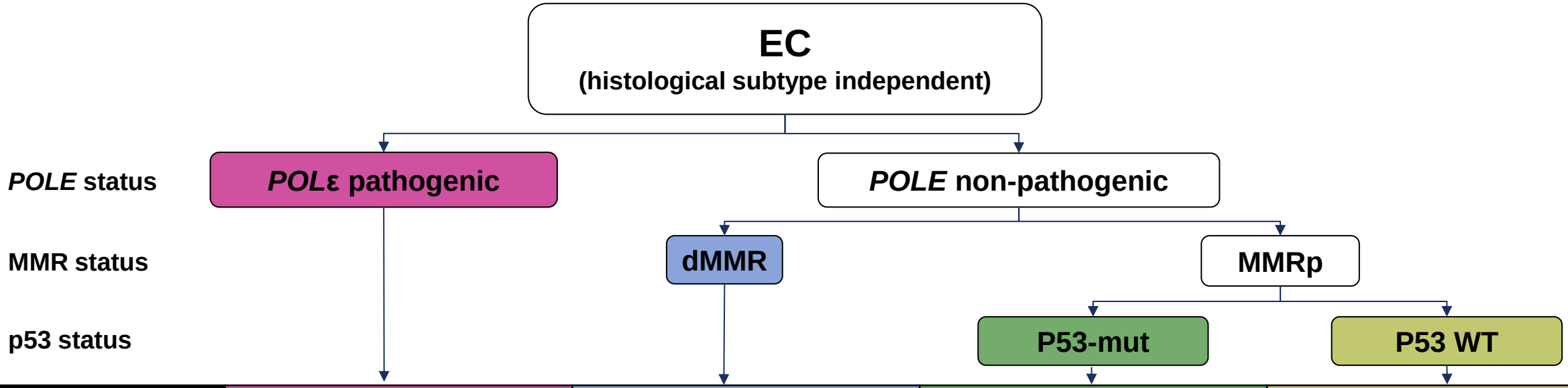
	dMMR/MSI-H		MMRp/MSS		Overall	
	Dostarlimab plus carboplatin–paclitaxel (n = 53)	Placebo plus carboplatin–paclitaxel (n = 65)	Dostarlimab plus carboplatin–paclitaxel (n = 192)	Placebo plus carboplatin–paclitaxel (n = 184)	Dostarlimab plus carboplatin–paclitaxel (n = 245)	Placebo plus carboplatin–paclitaxel (n = 249)
Any follow-up anticancer therapy, n (%)	15 (28.3)	39 (60.0)	105 (54.7)	134 (72.8)	120 (49.0)	173 (69.5)
Immunotherapy	8 (15.1)	27 (41.5)	34 (17.7)	68 (37.0)	42 (17.1)	95 (38.2)
Pembrolizumab	4 (7.5)	21 (32.3)	9 (4.7)	20 (10.9)	13 (5.3)	41 (16.5)
Pembrolizumab–lenvatinib	3 (5.7)	2 (3.1)	22 (11.5)	43 (23.4)	25 (10.2)	45 (18.1)
Dostarlimab	0	3 (4.6)	0	0	0	3 (1.2)
MK7694A	0	1 (1.5)	0	0	0	1 (0.4)
Pembrolizumab–tamoxifen	1 (1.9)	0	0	0	1 (0.4)	0
Retifanlimab–epacadostat	1 (1.9)	0	0	2 (1.1)	1 (0.4)	2 (0.8)
Investigational product	0	0	1 (0.5)	1 (0.5)	1 (0.4)	1 (0.4)
Atezolizumab–ipatasertib	0	0	0	1 (0.5)	0	1 (0.4)
Avelumab–axitinib	0	0	0	1 (0.5)	0	1 (0.4)
Bevacizumab–atezolizumab	0	0	0	1 (0.5)	0	1 (0.4)
Durvalumab–cediranib	0	0	0	2 (1.1)	0	2 (0.8)
Durvalumab–olaparib	0	0	2 (1.0)	0	2 (0.8)	0
Nivolumab–BMS986207–COM701	0	0	0	1 (0.5)	0	1 (0.4)
Nivolumab–lucitanib	0	0	0	1 (0.5)	0	1 (0.4)
SGN-ALPV	0	0	0	1 (0.5)	0	1 (0.4)

dMMR, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

M. A. Powell et al. Annal of Oncol 2024

RUBY Molecular Classification Algorithm

- In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients

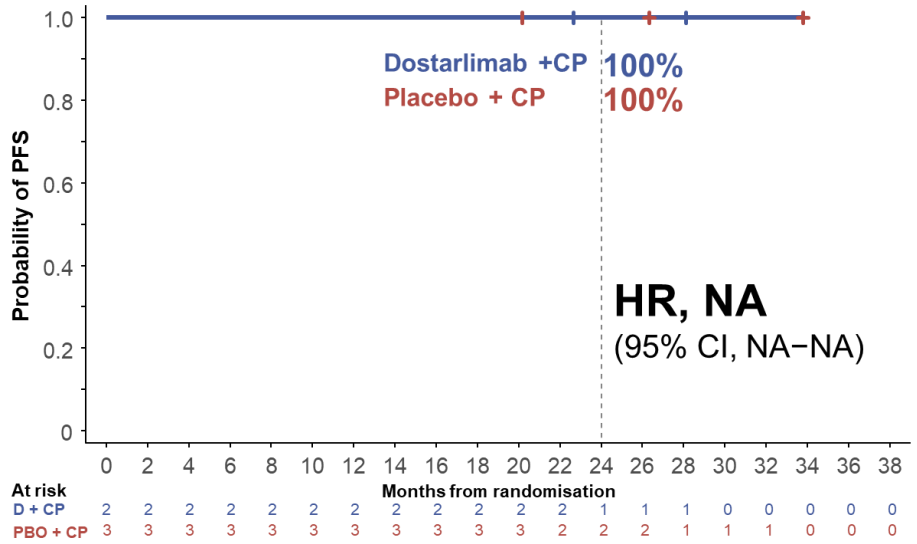


Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

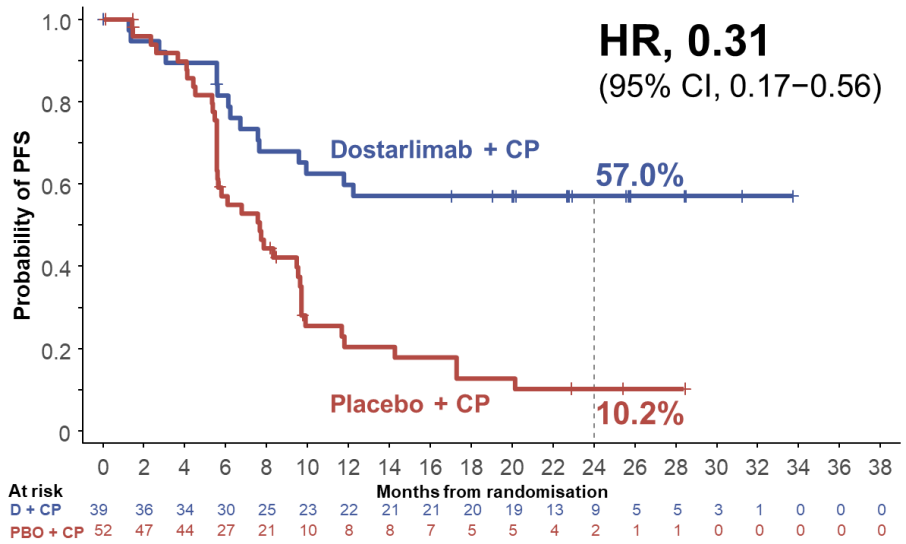
Efficacy per molecular classification was an exploratory analysis.
dMMR, mismatch repair deficient; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε , polymerase epsilon; SCNA, somatic copy number alterations; TIL, tumor-infiltrating lymphocytes; TLS, tertiary lymphoid structures; TP53, tumor protein 53; WES, whole exome DNA sequencing; WT, wild type.

PFS According to Molecular Subgroup

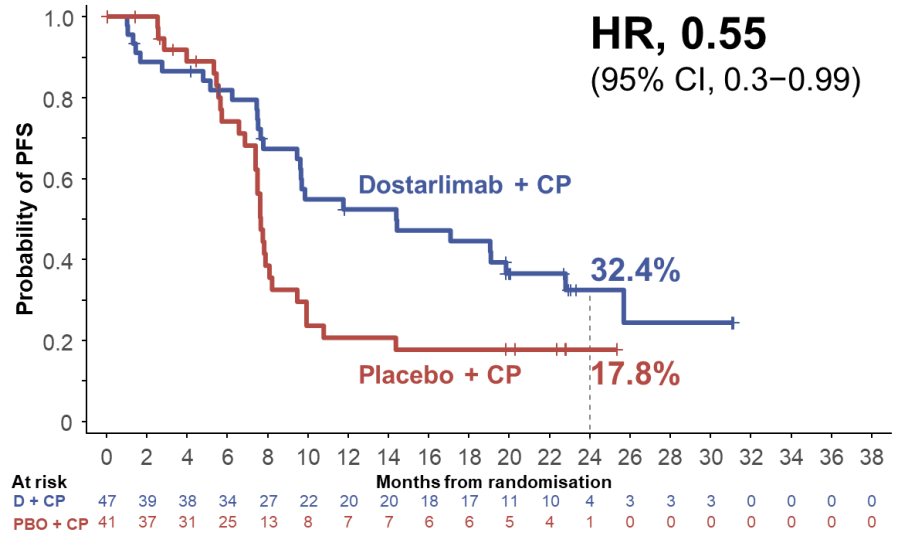
POLε mut



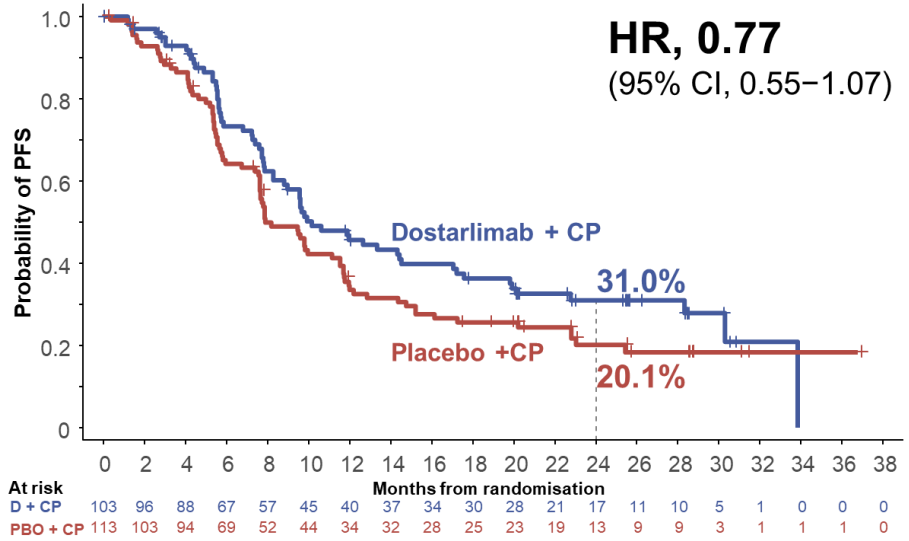
dMMR/MSI-H



TP53 mut



NSMP

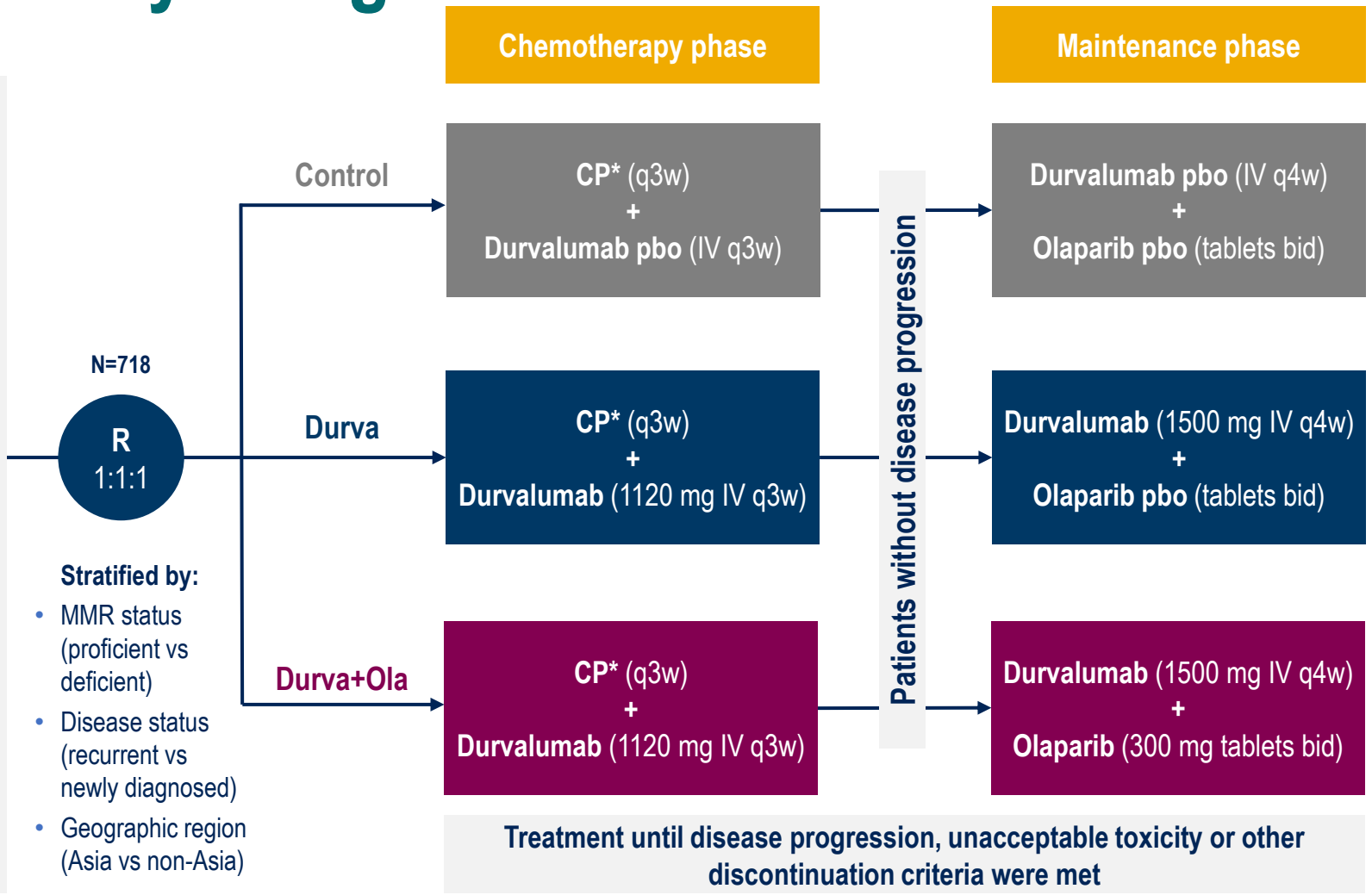


Data based on exploratory analysis based on 400 patients from the RUBY trial with known molecular classification with whole exome sequencing.
CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability–high; mut, mutated; NR, not reached; NSMP, no specific molecular profile; OS, overall survival; PBO, placebo; POLε , polymerase epsilon; TP53, tumor protein 53.

DUO-E study design

Patients

- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas



Endpoints

Primary

- PFS (RECIST per investigator) in:
  - Durva vs Control
  - Durva+Ola vs Control

Key secondary

- OS (analytical)
- Safety

Exploratory

- PFS in Durva+Ola vs durva
- Subgroup analyses of PFS
  - Including MMR, PD-L1, and HRRm

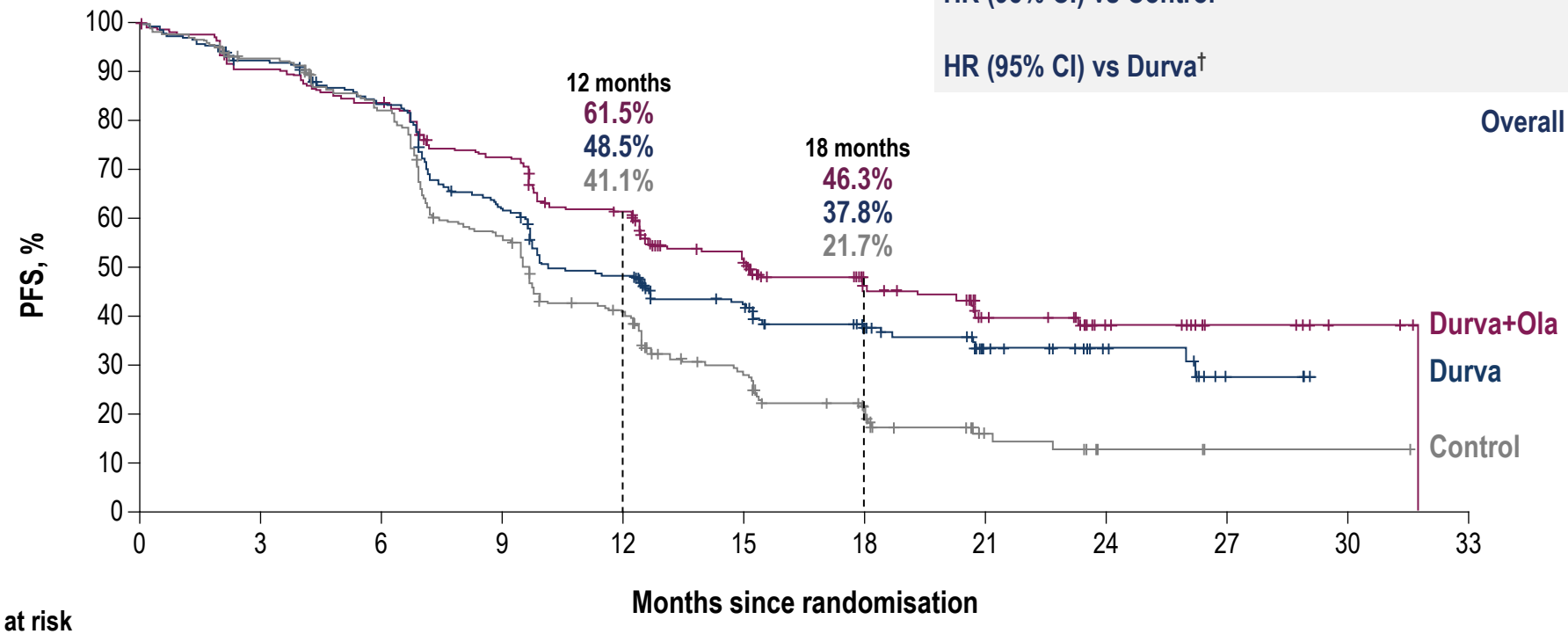
*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

PFS: ITT population

Primary endpoint

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk

Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

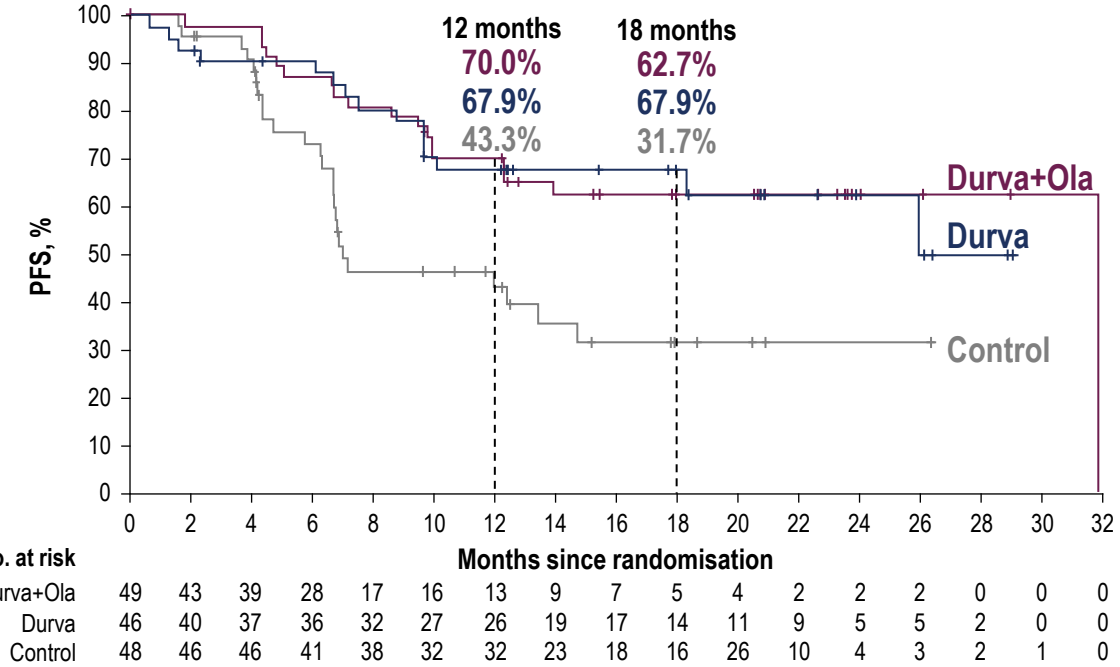
The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The *P* value was calculated using a log-rank test stratified by MMR and disease status. ITT, intent-to-treat; KM, Kaplan–Meier.

Shannon N. Westin

Subgroup analysis of PFS by MMR status

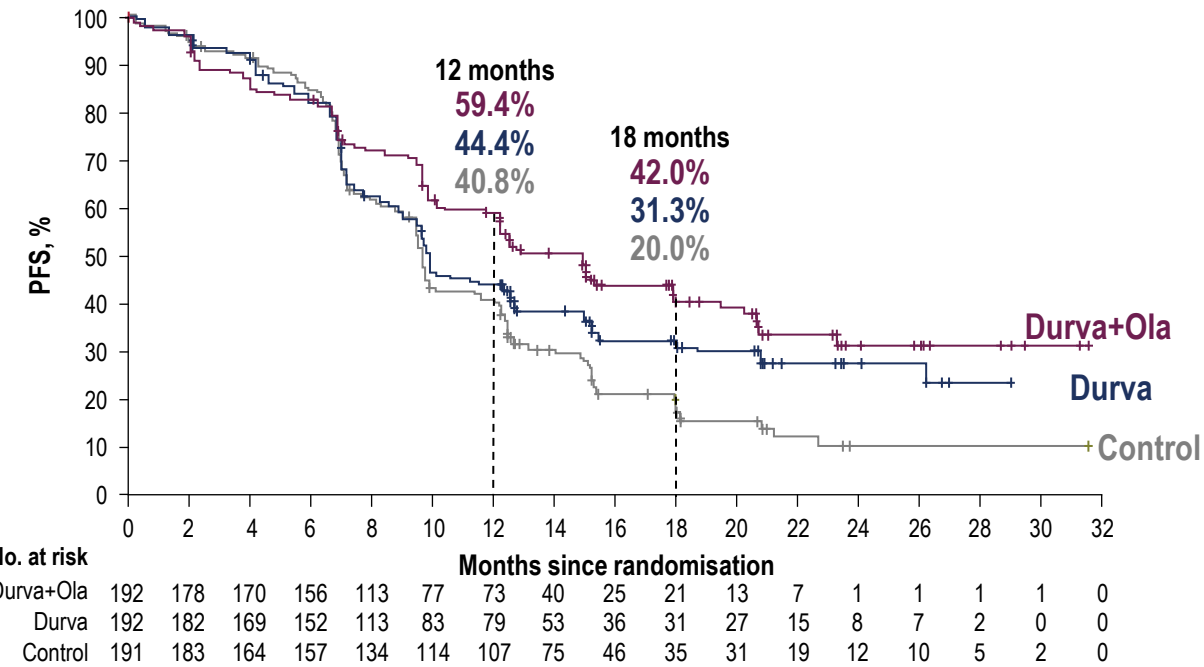
Prespecified exploratory analysis

dMMR (20% of population)



	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**

pMMR (80% of population)



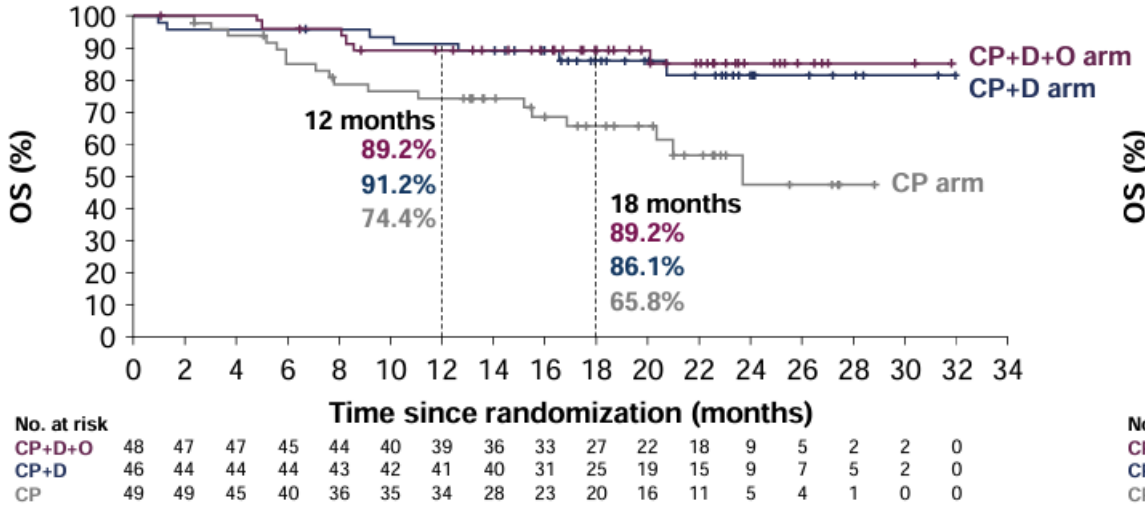
	Control (N=192)	Durva (N=192)	Durva+Ola (N=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs Durva†			**0.76 (0.59–0.99)**

MADRID 2023 ESMO congress

Exploratory subgroup analysis. MMR status evaluated using the Ventana immunohistochemistry MMR panel. Rates were estimated by the KM method.
*CI for median PFS was derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from an unstratified Cox proportional hazards model.

DUO-E immature OS data

dMMR (20% of ITT population)



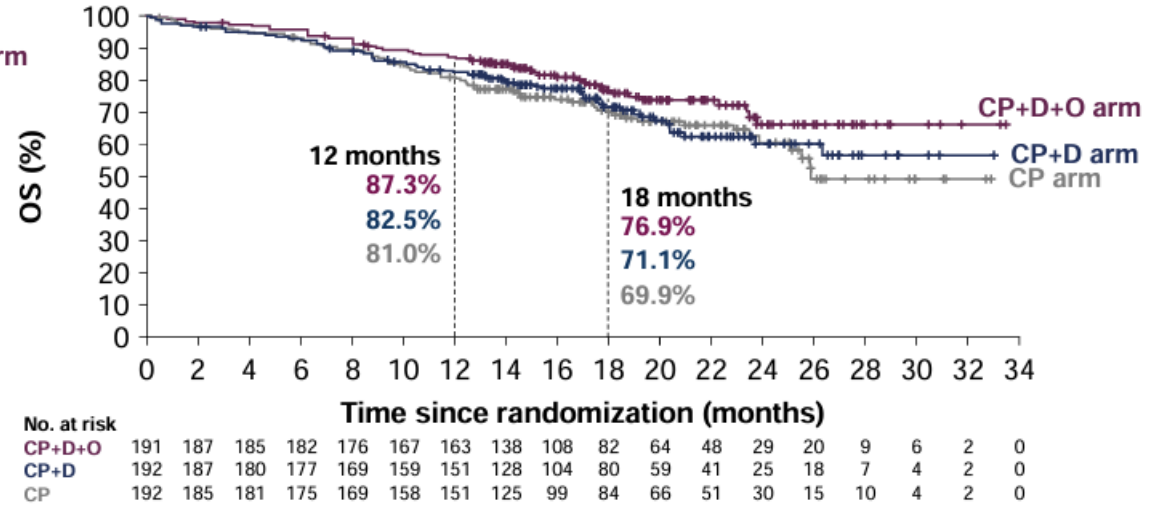
No. at risk

CP+D+O	48	47	47	45	44	40	39	36	33	27	22	18	9	5	2	2	0
CP+D	46	44	44	44	43	42	41	40	31	25	19	15	9	7	5	2	0
CP	49	49	45	40	36	35	34	28	23	20	16	11	5	4	1	0	0

	CP arm (n=49)	CP+D arm (n=46)	CP+D+O arm (n=48)
Events, n (%)	18 (36.7)	7 (15.2)	6 (12.5)
Median OS (95% CI), months	23.7 (16.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.34 (0.13–0.79)**	**0.28 (0.10–0.68)**
HR (95% CI) vs CP+D arm*			0.84 (0.27–2.52)

Overall data maturity: 21.7%

pMMR (80% of ITT population)



No. at risk

CP+D+O	191	187	185	182	176	167	163	138	108	82	64	48	29	20	9	6	2	0
CP+D	192	187	180	177	169	159	151	128	104	80	59	41	25	18	7	4	2	0
CP	192	185	181	175	169	158	151	125	99	84	66	51	30	15	10	4	2	0

	CP arm (n=192)	CP+D arm (n=192)	CP+D+O arm (n=191)
Events, n (%)	64 (33.3)	58 (30.2)	46 (24.1)
Median OS (95% CI), months	25.9 (25.1–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.91 (0.64–1.30)**	**0.69 (0.47–1.00)**
HR (95% CI) vs CP+D arm*			0.75 (0.51–1.11)

Overall data maturity: 29.2%

THE POWER OF SHARED PURPOSE:
Transforming Gynecologic Cancer Care

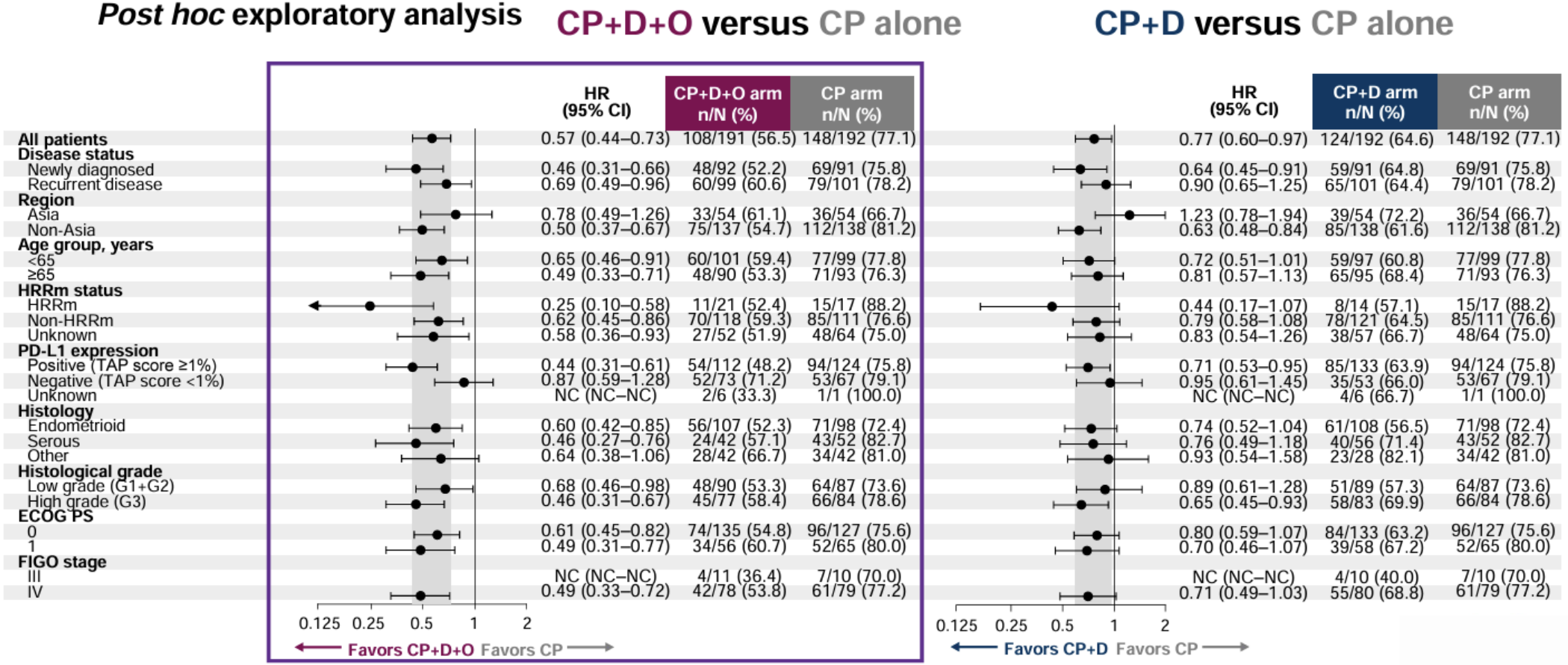
DCO: April 12, 2023. For the dMMR subpopulation, median duration of follow-up for OS was 18.4 (CP), 19.1 (CP+D) and 19.9 months (CP+D+O) in censored patients; for the pMMR subpopulation, median duration of follow-up was 18.6 (CP), 18.2 (CP+D) and 18.4 months (CP+D+O) in censored patients. MMR status was evaluated using the Ventana MMR immunohistochemistry panel. OS rates were estimated by the Kaplan–Meier method. *HRs and CIs were estimated from an unstratified Cox proportional hazards model.

SGO ANNUAL MEETING ON WOMEN'S CANCER San Diego, CA • 2024

DUO-E: who benefit the most?

pMMR subpopulation: PFS by subgroup

***Post hoc* exploratory analysis**



DCO: April 12, 2023. Stratification factors (disease status, MMR status, and geographic region) are per the randomization code. HRRm status was evaluated using the Foundation One CDx NGS assay and includes deleterious or suspected deleterious mutations in *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*. HRRm status unknown includes patients recruited in China, where HRR testing was not performed, and patients with samples that were unavailable for testing. PD-L1 status in baseline tumor tissue was determined centrally using Ventana SP263 assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumor area populated by tumor cells or immune cells with membranous PD-L1 staining. FIGO stage determined at the time of initial diagnosis of endometrial cancer under investigation.

IGCS 2024 Annual Global Meeting DUBLIN

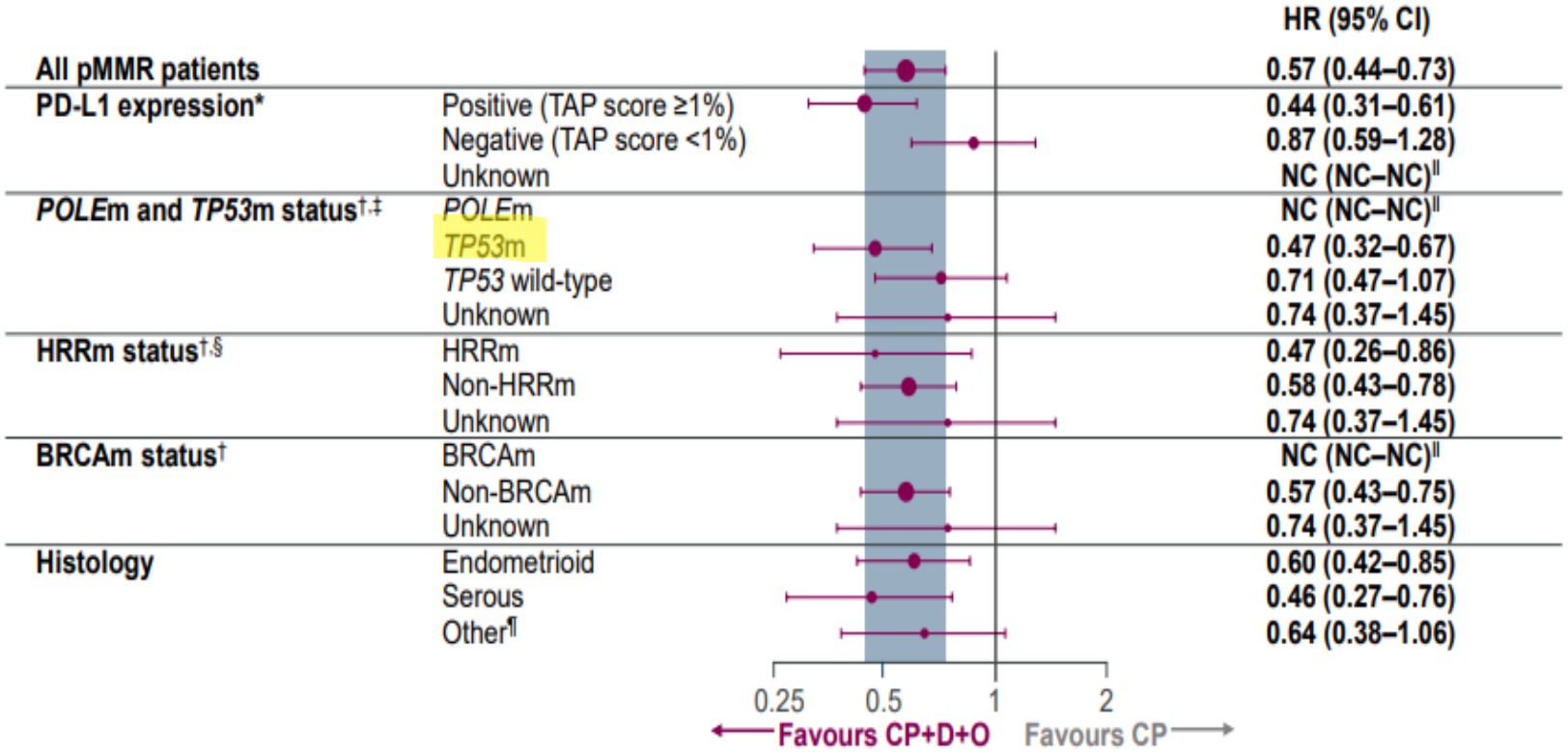
Durvalumab plus carboplatin/paclitaxel followed by durvalumab with/without olaparib in endometrial cancer: exploratory analyses of biomarker/histological heterogeneity and efficacy in the DUO-E mismatch repair proficient subpopulation

Shannon N. Westin,[1] Kathleen Moore,[2] Hye Sook Chon,[3] Jessica Thomes Pepin,[4] Erin Salinas,[5] David Starks,[6] Paul A. Disilvestro,[7] Brian Slomovitz,[8] Elen Vettus,[9] Fernando Gálvez,[10] Kofi Agyemang-Prempeh,[11] Flora Zagouri,[12] Jae-Weon Kim,[13] Qinglei Gao,[14] Fernando Contreras Mejia,[15] Andreia Cristina De Melo,[16] Tadaaki Nishikawa,[17] Matthew Kowgier,[18] Sonia Iyer,[19] Els Van Nieuwenhuysen[20]

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib versus CP

***Post hoc* exploratory analysis**

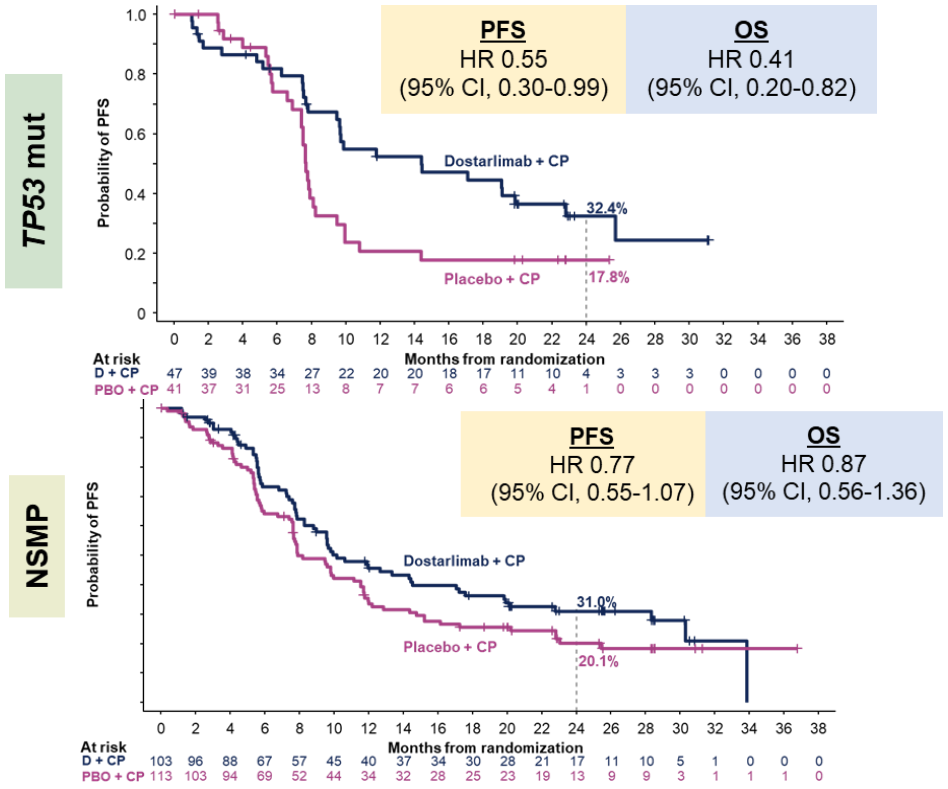


Potential benefit seen in TP53mut group, but we need to understand more about NSMP given the heterogenous nature of the group

Is TP53 a potential biomarker to predict benefit from ICI + chemotherapy (±) PARPi?

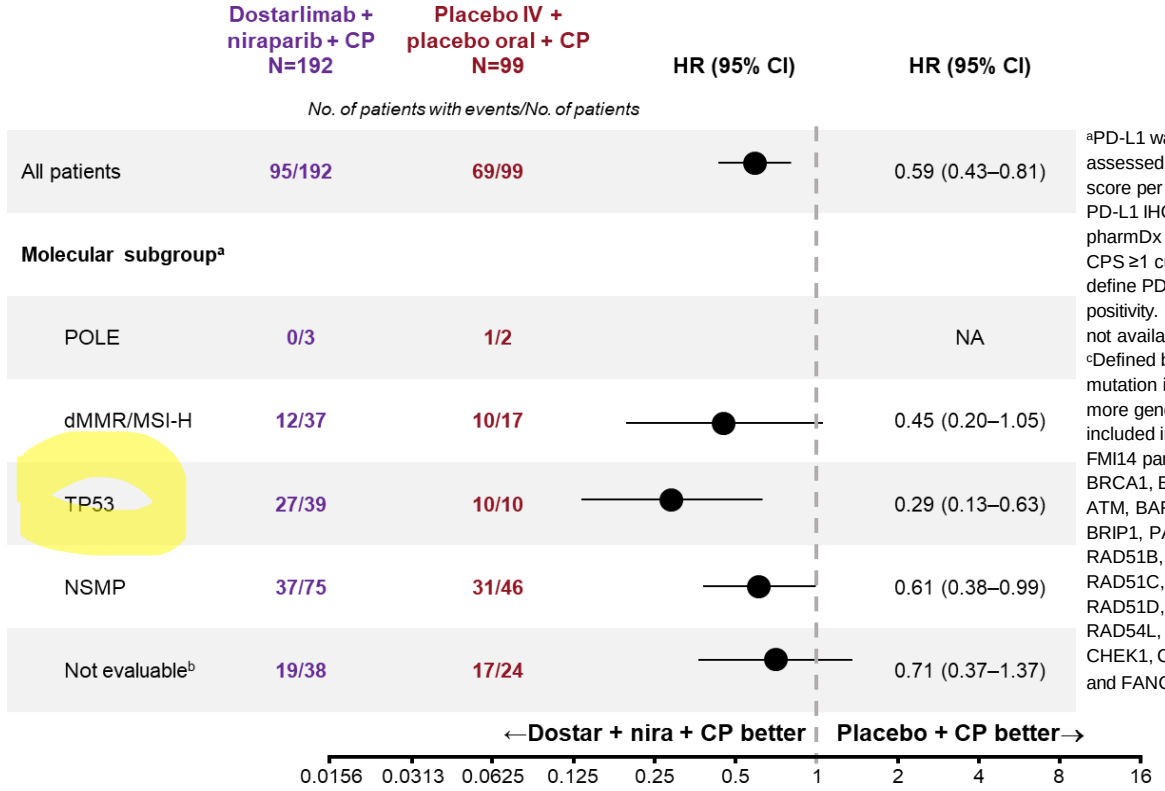
RUBY Part 1[1]

Molecular subgroup analysis based on 400/494 patients with known molecular classification per WES



RUBY Part 2[2]

Exploratory PFS molecular subgroup analyses in overall population



[a]PD-L1 was assessed by CPS score per Dako PD-L1 IHC 22C3 pharmDx with a CPS ≥1 cutoff to define PD-L1 positivity. [b]Sample not available. [c]Defined by a mutation in 1 or more genes included in the FMI14 panel: BRCA1, BRCA2, ATM, BARD1, BRIP1, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, CDK12, CHEK1, CHEK2, and FANCL

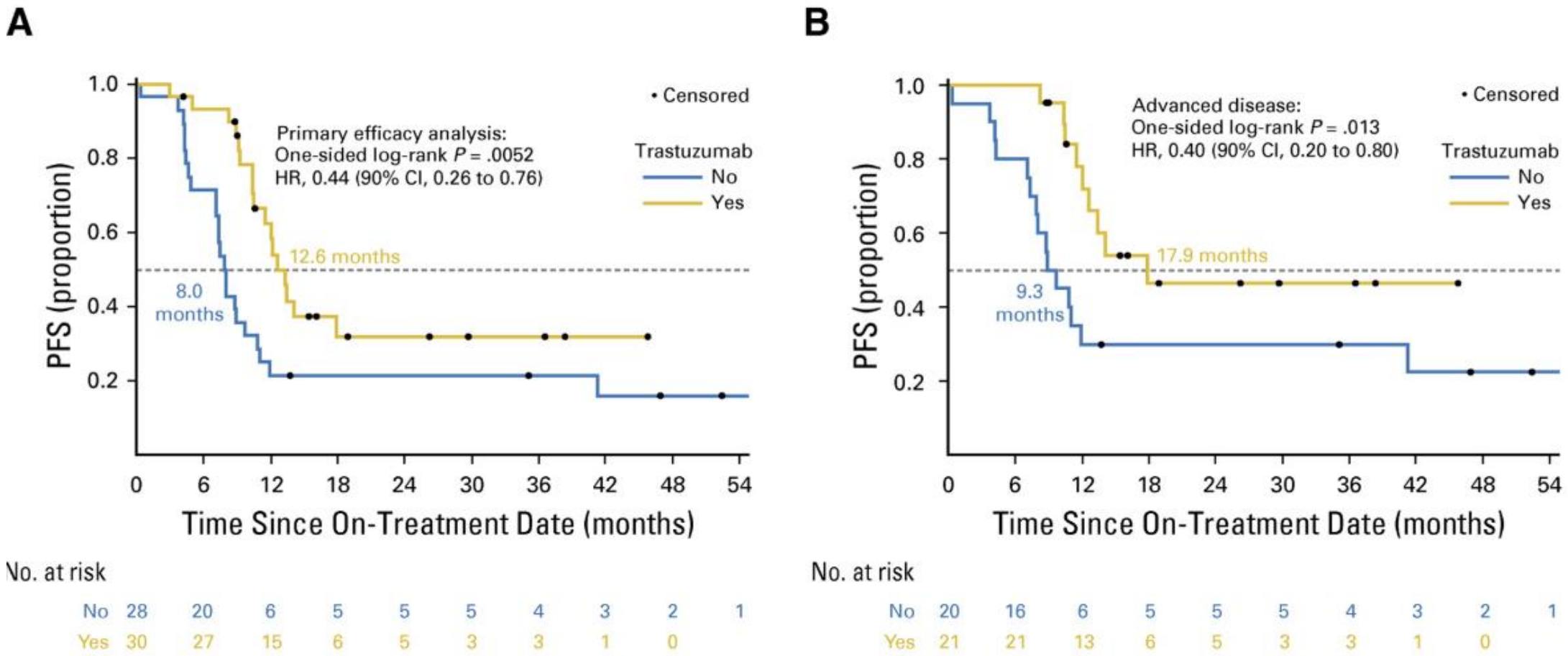
There are inherent limitations in cross-study comparisons and caution is needed when reviewing data across individual (non-comparative) trials.
This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; HR, hazard ratio; ICI, immune checkpoint inhibitor; MSI-H, microsatellite instability high; NA, not applicable; nira, niraparib; NSMP, no specific molecular profile; OS, overall survival; PARPi, Poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; TP53, tumour protein 53; WES, whole exome sequencing.

1. Mirza MR, et al. European Society for Medical Oncology (ESMO) Annual Meeting. 2023;Presentation #740MO. 2. Mirza MR, et al. Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer. 2024; Presentation LBA2.

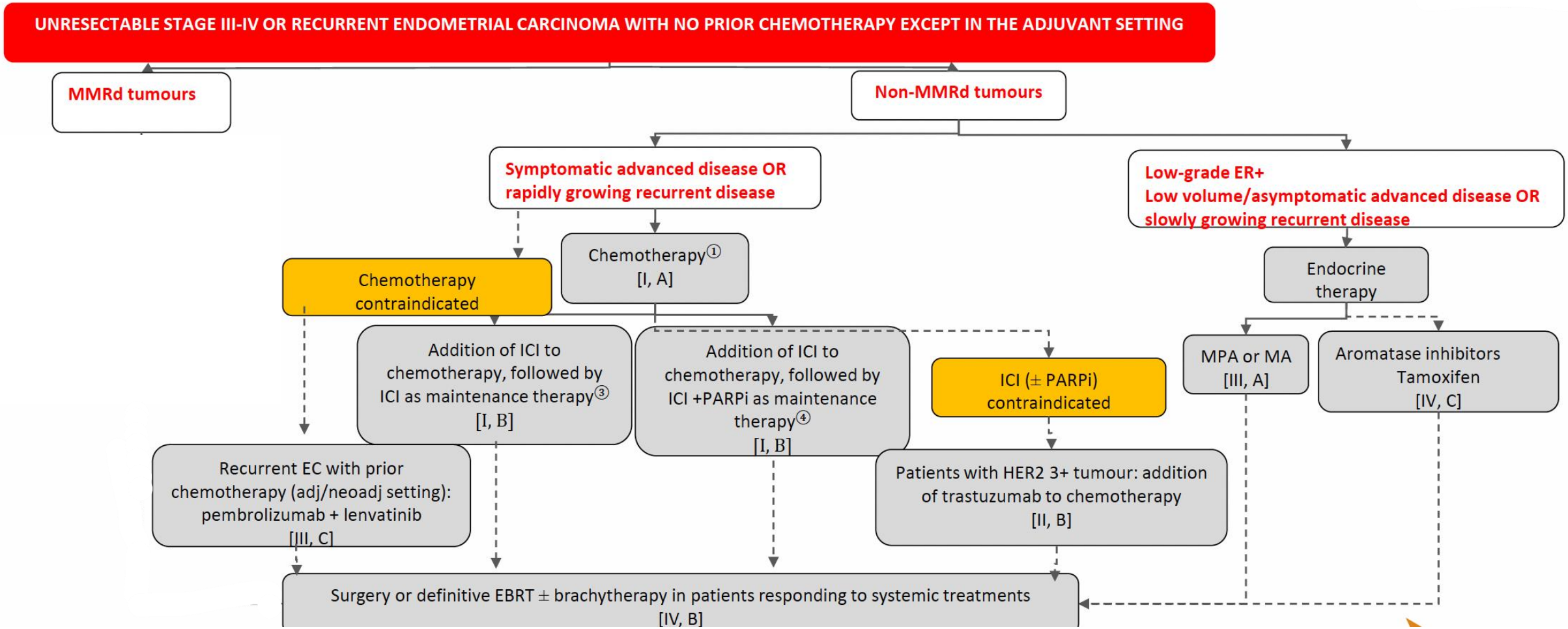
Targeting HER2

Randomized Phase II Trial of Carboplatin-Paclitaxel vs Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress HER2



Fader JCO 2018

NEW ESGO GUIDELINES 2025



After platinum chemotherapy

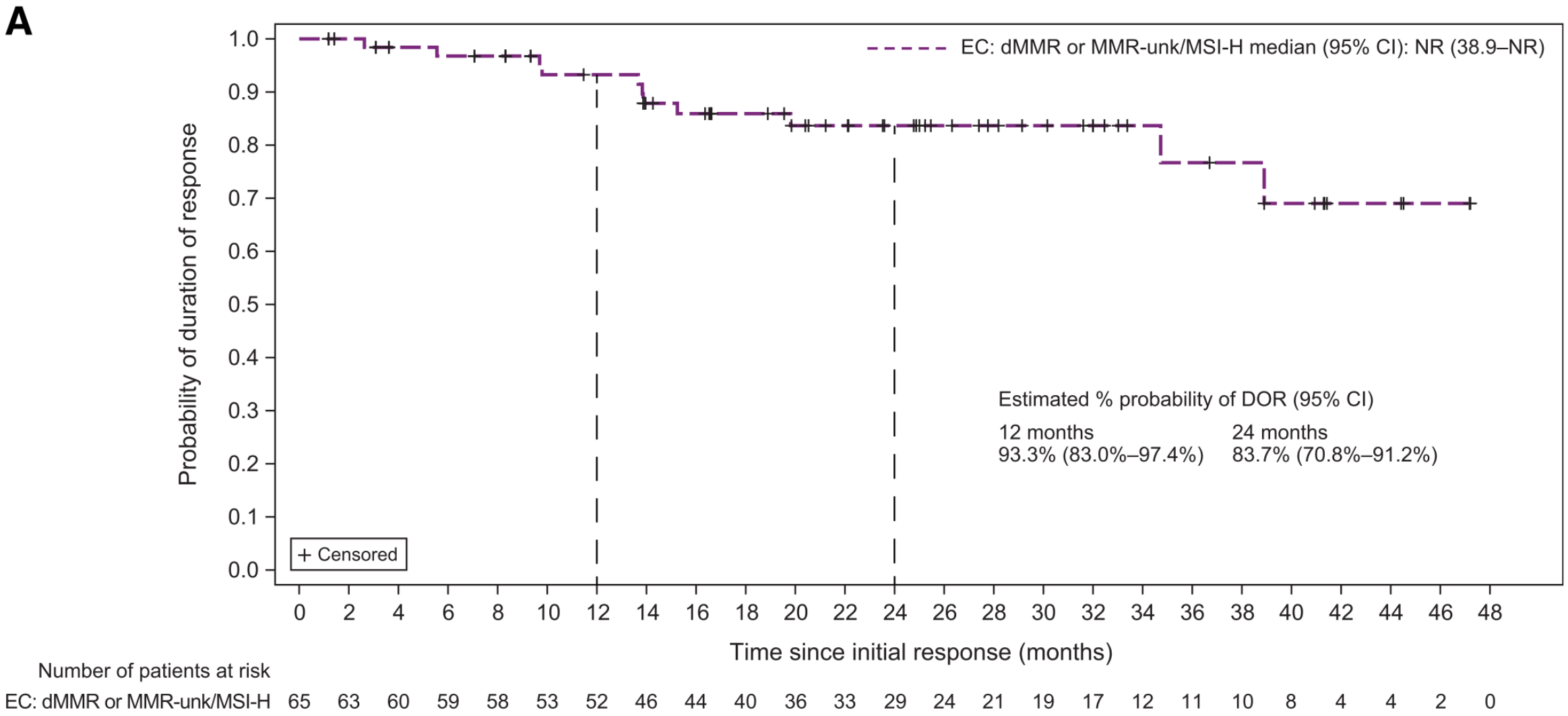
Is the patient dMMR or pMMR?

Single-Agent IO activity in dMMR Endometrial Cancer

Study	Drug	N	Patient selection	ORR
KEYNOTE158[a]	**Pembrolizumab**	49	Advanced/metastatic dMMR	**48%**
GARNET[b]	**Dostarlimab**	**103**	Previously treated Recurrent/advanced d-MMR	**45%**
PHAEDRA[c]	**Durvalumab**	35	Advanced/metastatic dMMR	**43%**
Konstantinopoulos[d]	**Avelumab**	15	Advanced/metastatic dMMR	**26.7%**

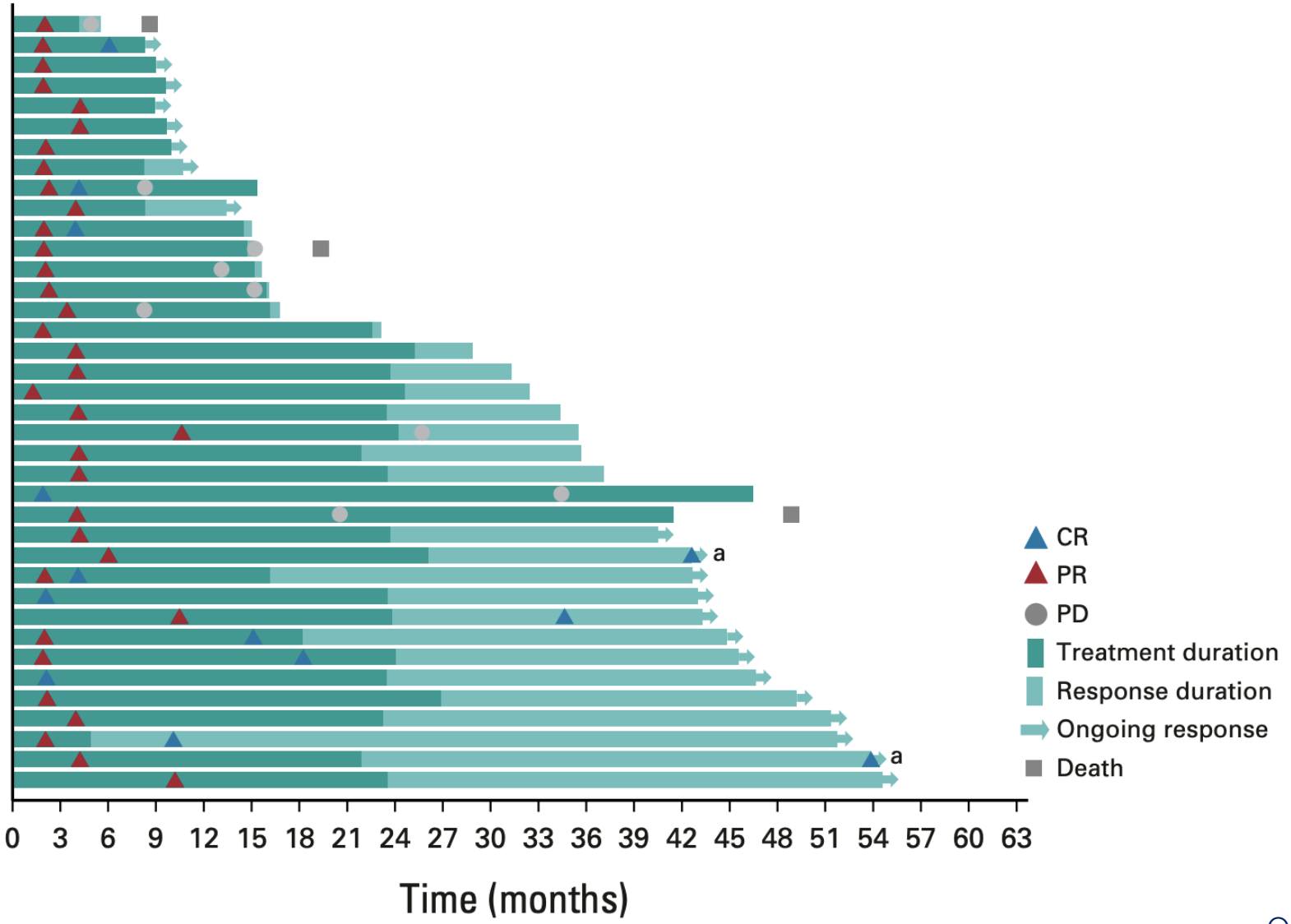
Marabelle et al. J Clin Oncol. 2020; b. Oaknin A, et al. Ann Oncol 2020; c. Antill Y, et al. ASCO®. 2019; d. Konstantinopoulos PA, et al. ASCO®. 2019;

GARNET – Last up date



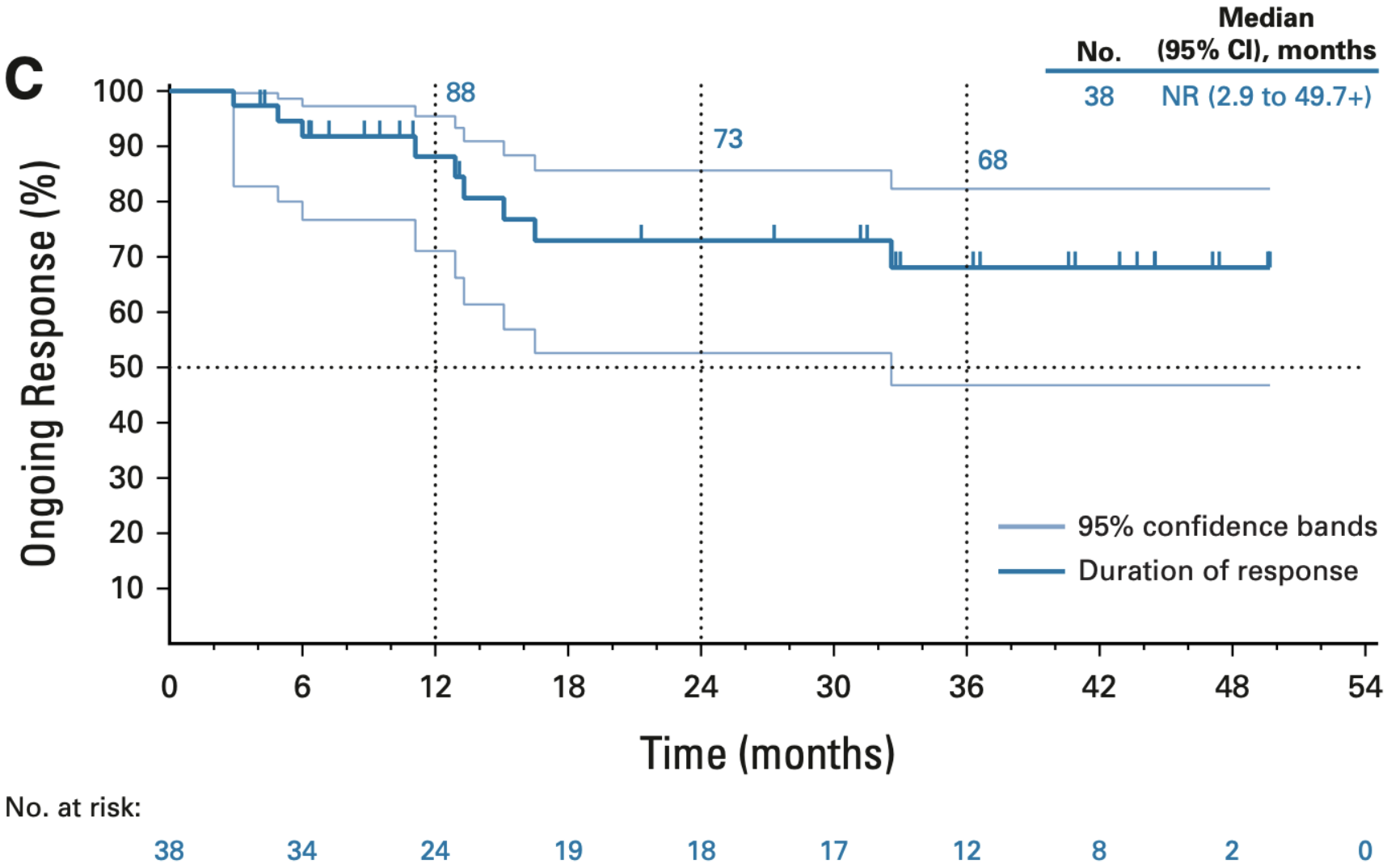
Oaknin et al Clin Can Research 2023

Keynote - 158



O'Malley et al. JCO 2021

Keynote - 158



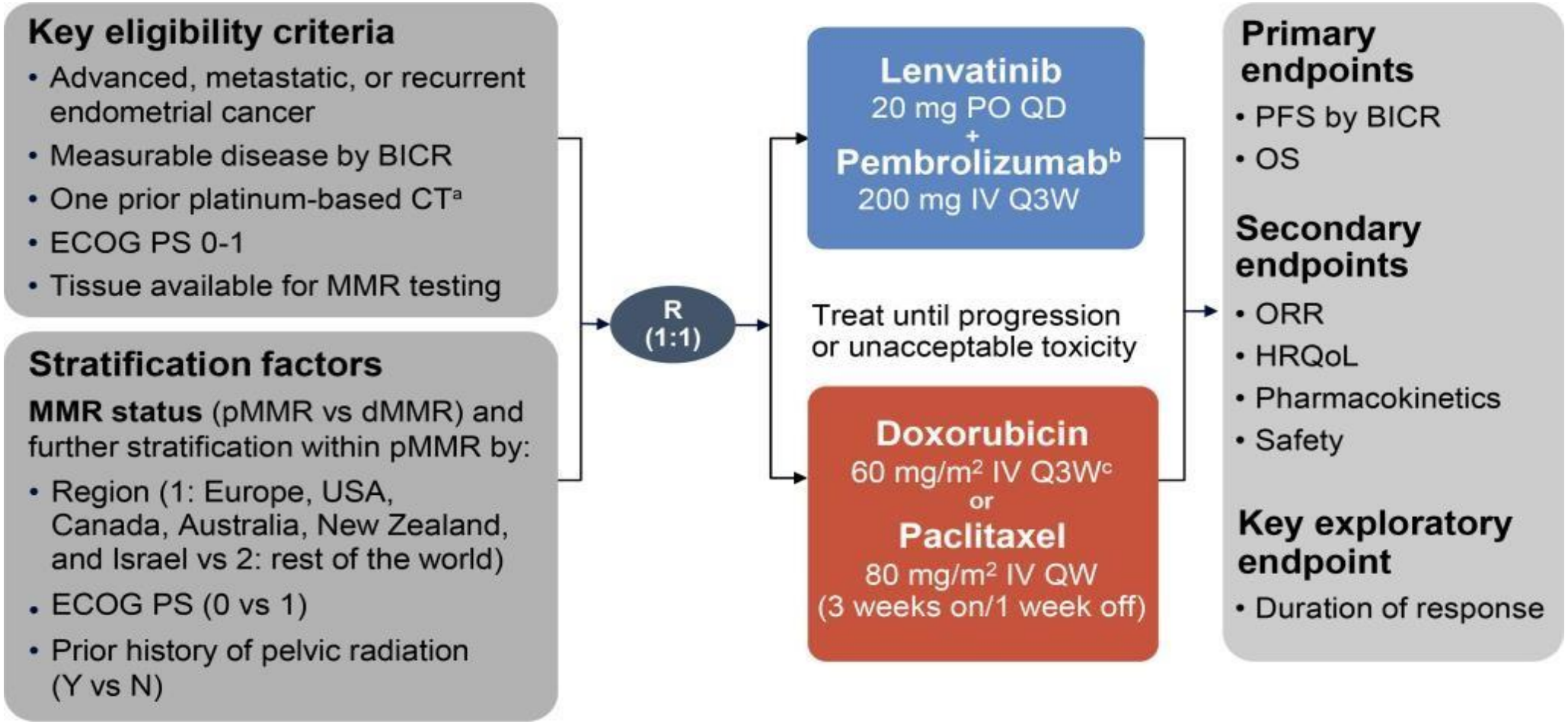
O'Malley et al. JCO 2021

Single-Agent IO activity in pMMR Endometrial Cancer

Study	Drug	N	Patient selection	ORR
KEYNOTE 28	**Pembrolizumab**	24	Advanced/metastatic PD-L1 pos	**13%**
GARNET[b]	**Dostarlimab**	**142**	Previously treated Recurrent/advanced pMMR	**13%**
PHAEDRA[c]	**Durvalumab**	36	Advanced/metastatic pMMR	**3%**
Konstantinopoulos[d]	**Avelumab**	13	Advanced/metastatic pMMR	**6%**

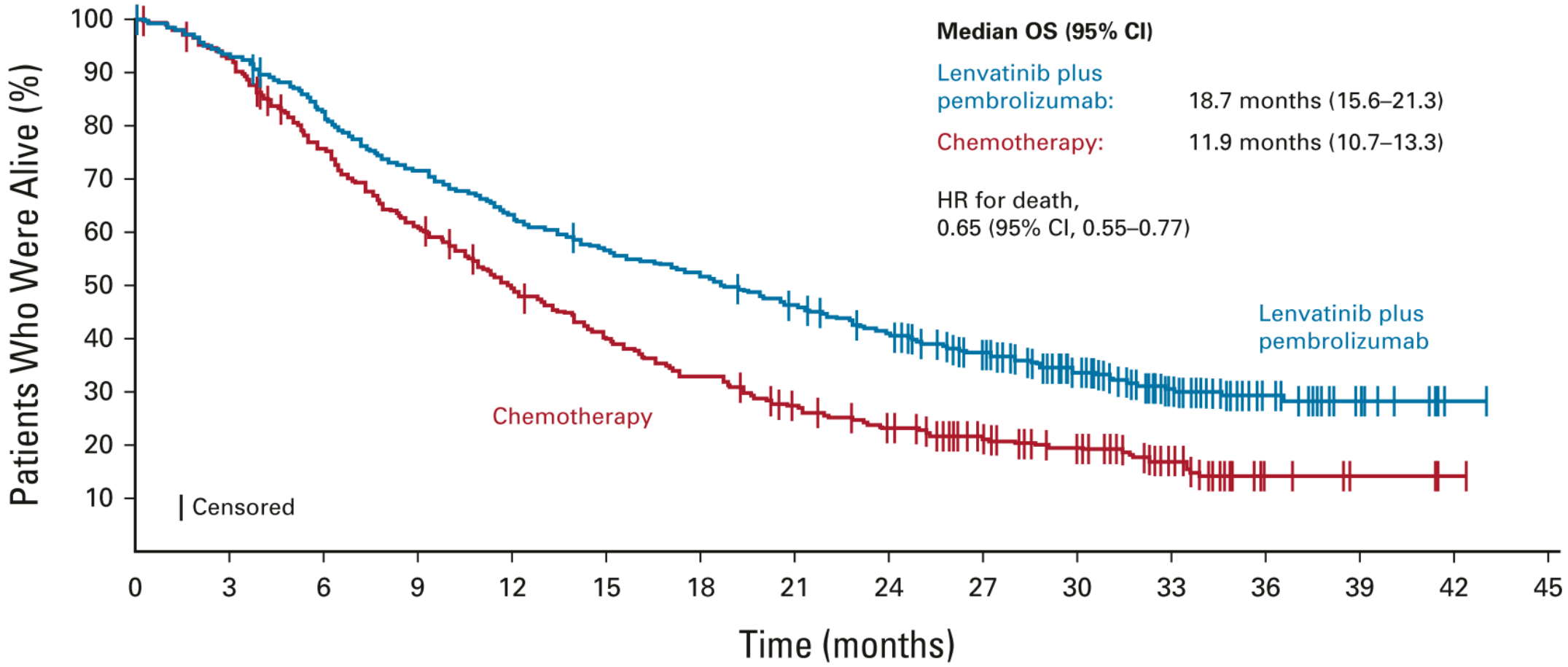
a. Marabelle et al. J Clin Oncol. 2020. b. Oaknin A, et al. Ann Oncol 2020; c. Antill Y, et al. ASCO®. 2019; d.Konstantinopoulos PA, et al. ASCO®. 2019

Phase III KEYNOTE-775: Second-line Pembrolizumab + Lenvatinib vs Chemotherapy in Advanced EC



NCT03517449.

All-comer (15% dMMR)

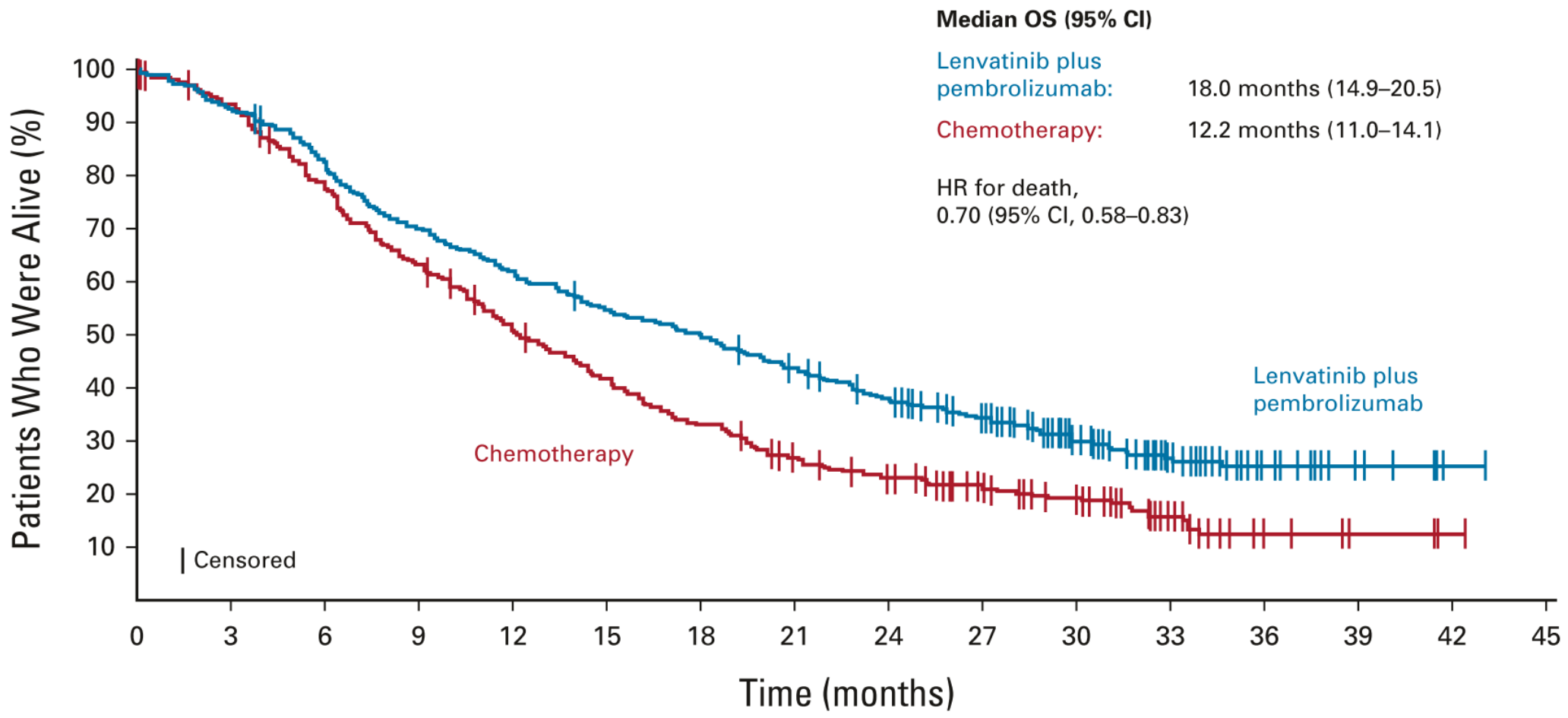


No. at risk:

Lenvatinib plus pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

Makker JCO 2023

pMMR (updated follow-up)



No. at risk:

Lenvatinib plus pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

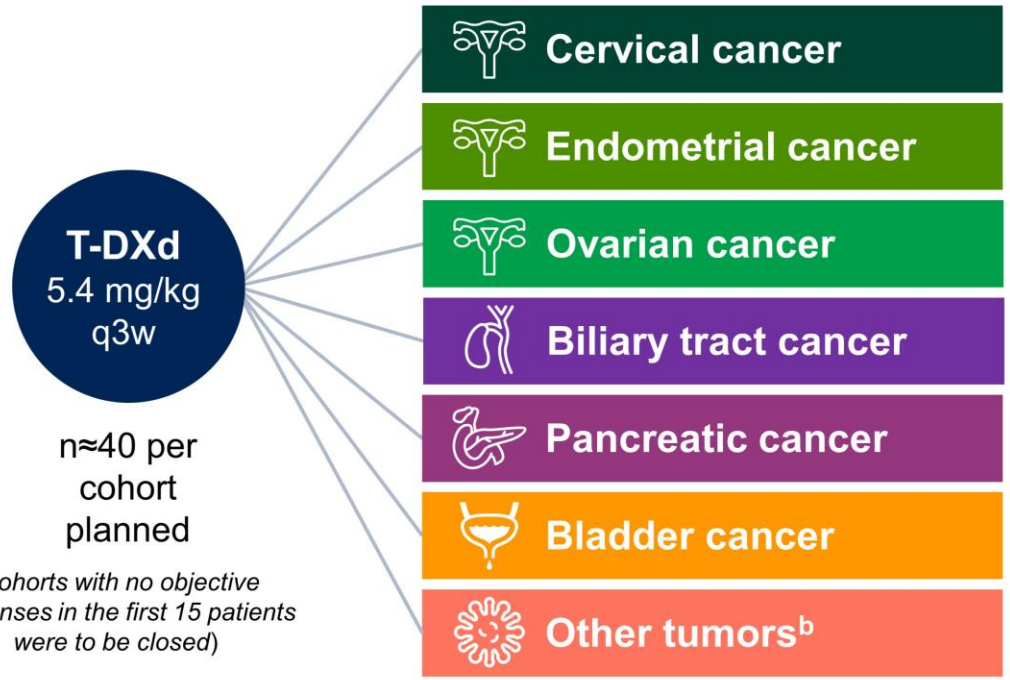
Makker JCO 2023

What’s next?

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

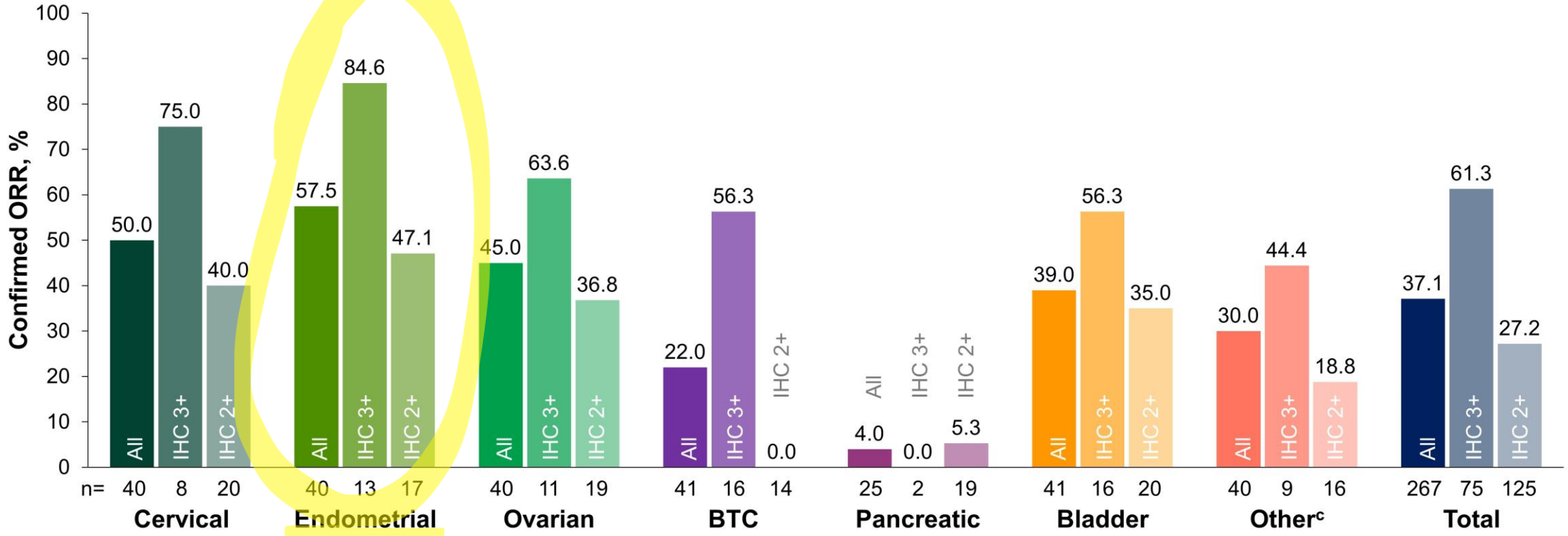
- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.
[c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

PRESENTED BY: Funda Meric-Bernstam, MD

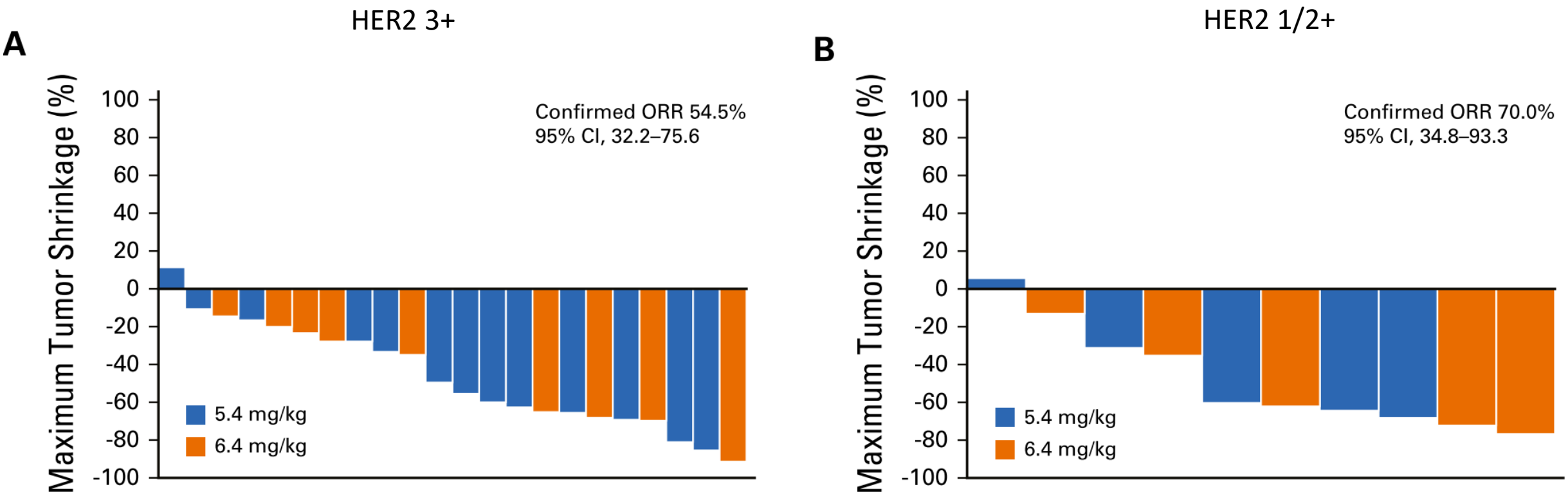
Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

PRESENTED BY: Funda Meric-Bernstam, MD



Nishikawa et al JCO 2023

ENGOT EN24

ENGOT
European Network of
Gynaecological Oncological Trial groups

Study: ENGOT-en24 / DESTINY-EC01

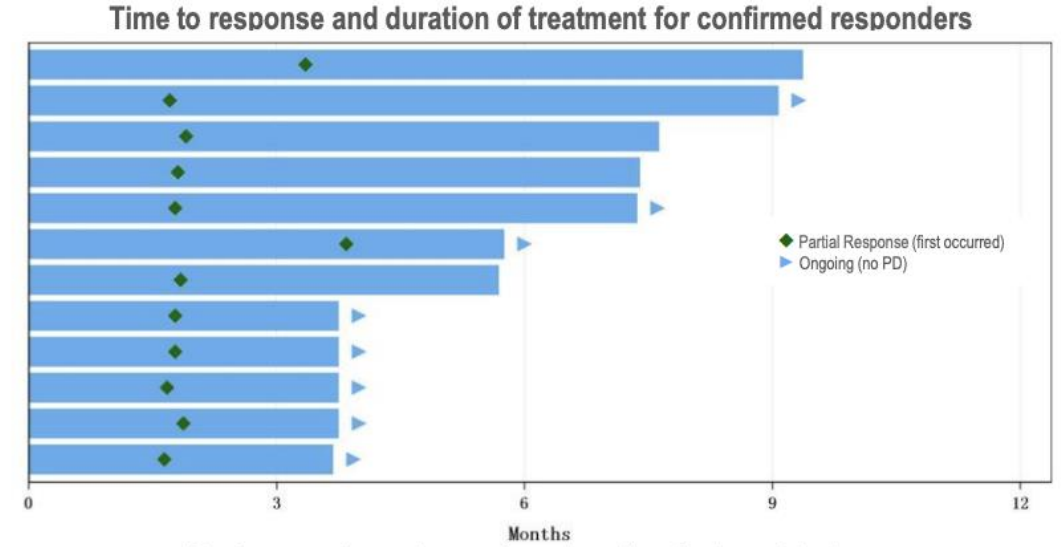
An Open label, Randomized, Multicenter, Controlled, Phase III Study of First-Line Trastuzumab Deruxtecan (T-DXd) Monotherapy versus Carboplatin and Paclitaxel with or without Pembrolizumab in Patients with HER2-expressing (IHC 3+/IHC2+) Mismatch Repair Proficient (pMMR) Primary Advanced or Recurrent Endometrial Cancer

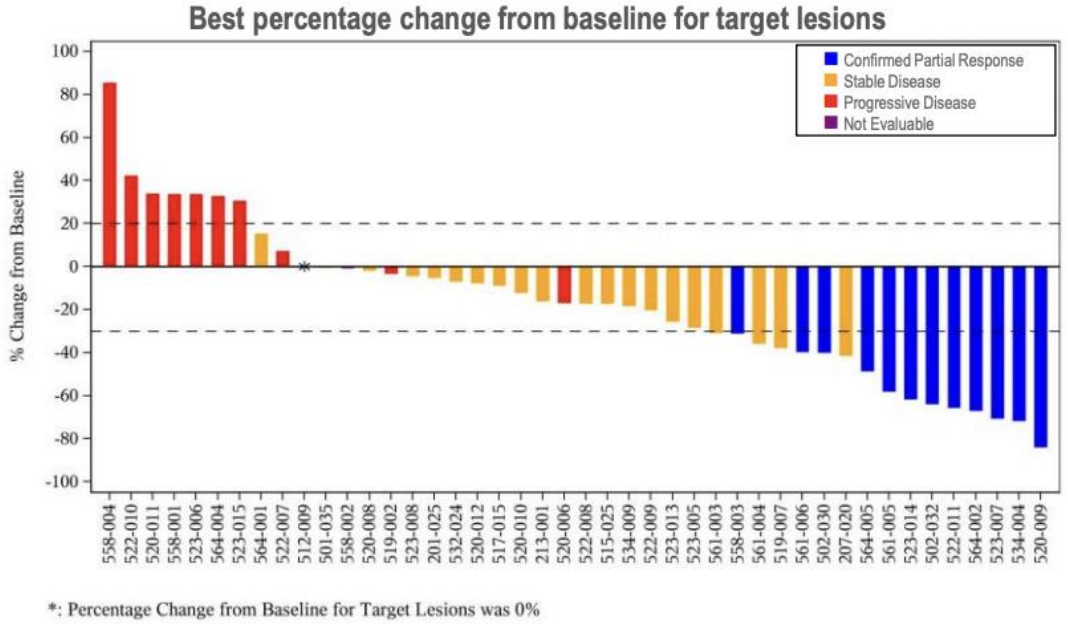
Sacituzumab – Tirumotecan (anti TROP2)

	EC (N = 44)[a]
ORR, % (n/N)	**34.1 (15/44)[b]**
Confirmed ORR	27.3 (12/44)
Subgroups	
TROP2 H-score >200	41.7 (5/12)
Prior IO	37.5 (6/16)
DCR, % (n/N)	**75.0 (33/44)**
PR	34.1 (15/44)
SD	40.9 (18/44)
DoR	
Median (range), months	5.7 (3.8, 7.4+)
PFS	
Median (95% CI), months	5.7 (3.7, 9.4)

a. Responses assessed per RECIST v1.1 by investigator.
b. Two patients with unconfirmed response were still receiving treatment at the data cutoff date.

CI, confidential interval; DCR, disease control rate; DoR, duration of response; EC, endometrial cancer; IO, immunotherapy; ORR, objective response rate; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TROP2, trophoblast cell surface antigen 2.





*: Percentage Change from Baseline for Target Lesions was 0%

Data cutoff: March 05, 2024.

ENGOT-cx20/MK-2870-020: Sacituzumab Tirumotecan

A Phase 3 Randomized, Active-Controlled, Open-Label, Multicenter Study

Key Eligibility Criteria:

Recurrent or metastatic cervical cancer that:

- ✓ Has progressed on or after 1 prior line of systemic platinum doublet treatment (with or without bevacizumab)
  AND
- ✓ Has received anti-PD-1/anti-PD-L1 therapy as part of prior cervical cancer regimens

Note: May have also received and progressed on or after 2nd line treatment with tisotumab vedotin (TV)

RAND
1:1
N=666

Arm 1: MK-2870 4 mg/kg by IV q2w

Treatment of Physician's Choice (TPC)
*(pemetrexed, topotecan, vinorelbine, gemcitabine, or irinotecan, **Tisotumab Vedotin**)*

PD by BICR

PD by BICR

Primary Endpoint

- OS

Secondary Endpoints

- PFS (BICR)
- ORR (BICR)
- DOR (BICR)
- QoL
- Safety/Tolerability

Stratification: 3 Factors

- ❖ Prior use of bevacizumab (yes vs. no)
- ❖ TROP2 expression (low vs. high)
- ❖ Selection of ICC (TV vs. other)

Toon Van Gorp

ENGOT EN26 (Sacituzumab Govitecan)

Key Eligibility Criteria

- Recurrent, advanced or metastatic endometrial carcinoma
- Histologically confirmed diagnosis of epithelial endometrial carcinoma, including carcinosarcoma
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy
  - These agents may have been received separately/ sequentially or in combination and in any setting
  - For pts who are ineligible for anti-PD-(L)1 therapy due to comorbidities, or if anti-PD-(L)1 agents are not available as standard of care in any line of treatment according to local standards, prior treatment with an anti-PD-(L)1 agent is not required
- Up to 3 prior lines of systemic therapy, with no more than 2 prior lines in the recurrent or advanced setting
  - Hormonal or hormonal-based therapies do not count as a line of therapy
- ECOG PS 0-1

N=520

R
1:1

Arm A: Sacituzumab Govitecan (SG)
10 mg/kg IV
Days 1 and 8, every 21 days

Arm B: Treatment of Physician's Choice (TPC)
Doxorubicin 60 mg/m^2 IV on Day 1, every 21 days, or
Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15, every 28 days

Stratification Factors

- # of Prior lines of systemic therapy in any setting (≤ 2 vs 3)
- Prior Anti-PD-(L)1 therapy (yes vs no)
- Histology (endometrioid vs non-endometrioid)

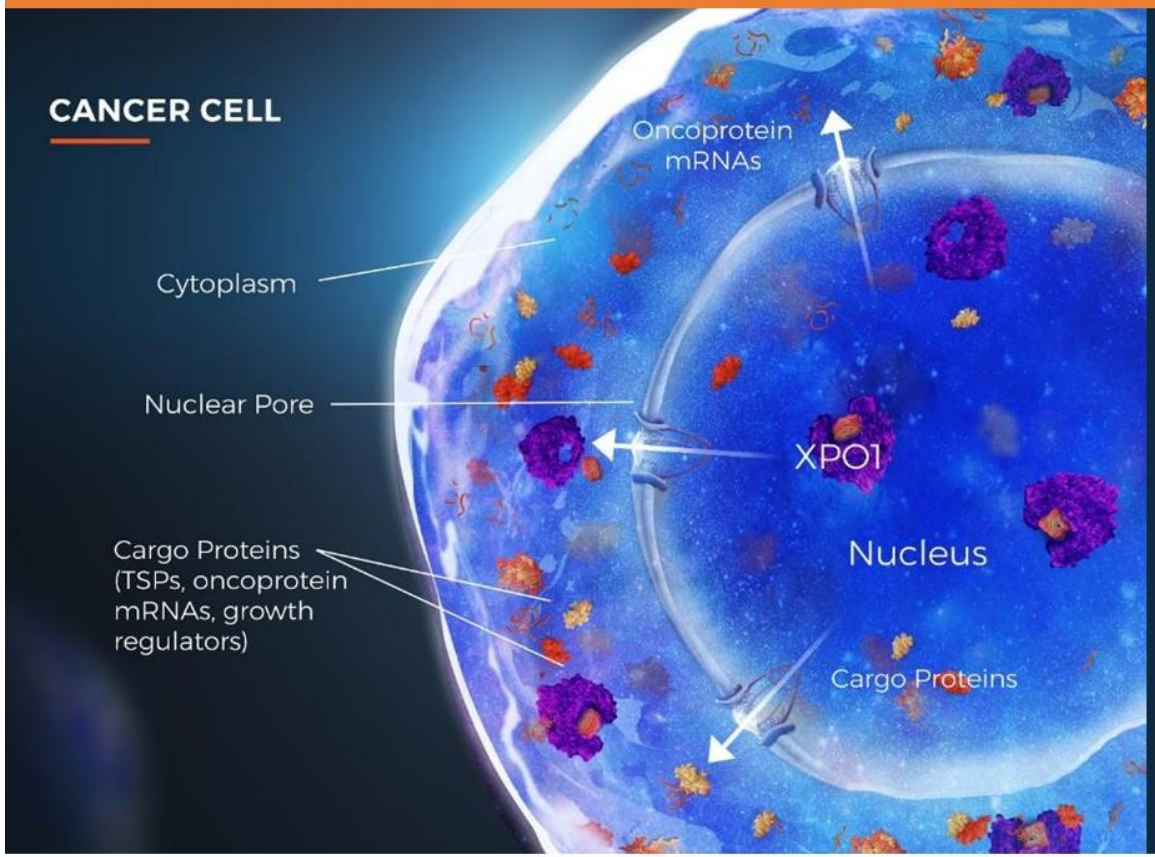
Key Study Endpoints

Primary Endpoint:
- PFS by BICR

Key Secondary Endpoints:
- OS
- ORR by BICR
- Change from baseline and TTdD in Physical Function as assessed by EORTC-QLQ-C30

Secondary Endpoints:
- PFS by INV
- ORR by INV
- DOR, CBR by BICR and INV
- Safety
- Change from baseline in GHS/QoL as assessed by EORTC-QLQ-C30

Selinexor: Oral XPO1 Inhibitor

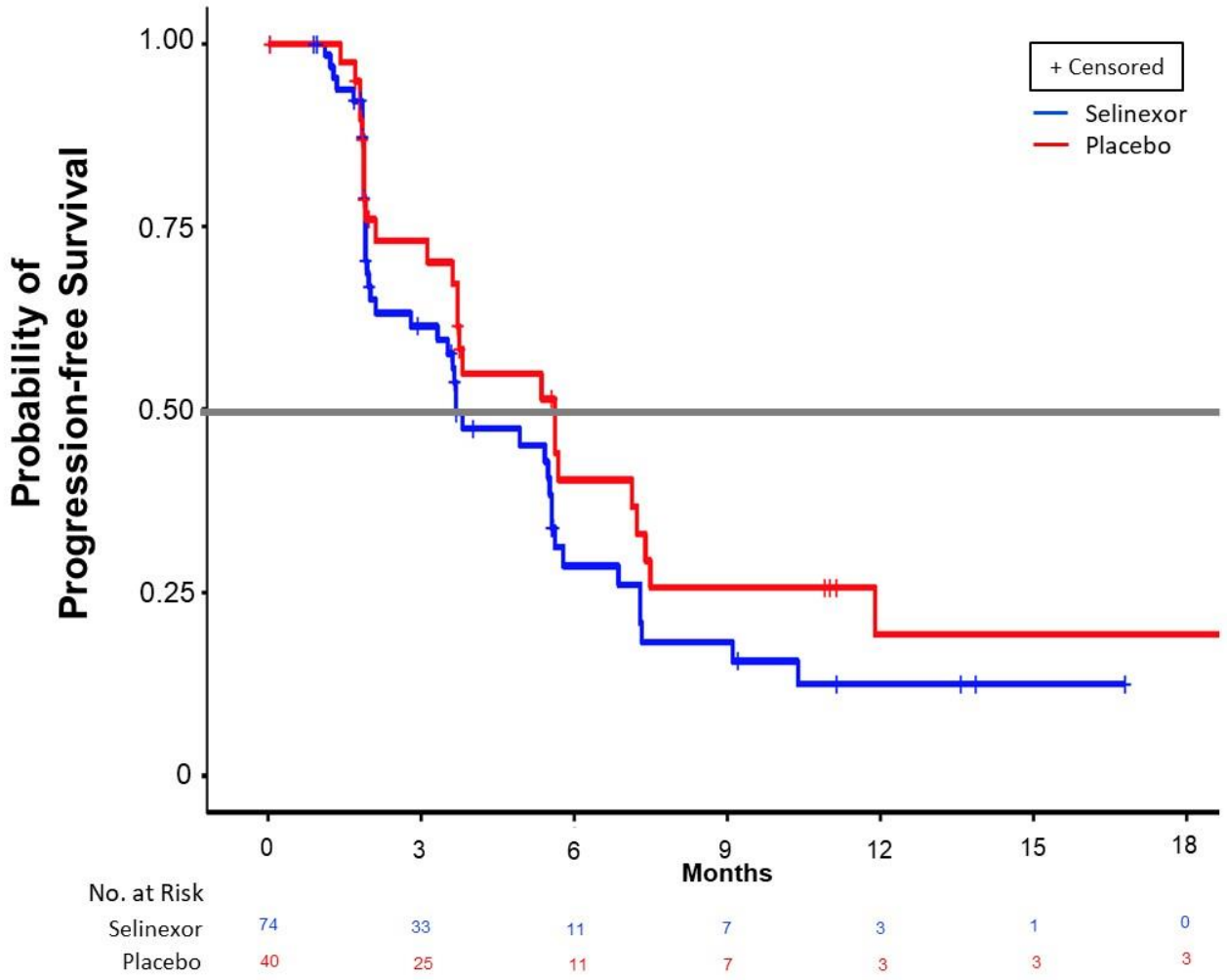


Selinexor is an oral selective inhibitor of XPO1-mediated nuclear export (SINE) compound

- XPO1 exports the major tumor suppressor proteins (TSPs) including p53 away from the nucleus, where TSPs carry out their function
- Tumor cells overexpress XPO1
- Tumor cells inactivate cytoplasmic *p53* through protein degradation
- Selinexor inhibits XPO1 nuclear export, leads to retention / reactivation of TSPs in the nucleus and stabilization of p53
- Retention of wild-type *p53* (p53wt) and other TSPs in the cell nucleus leads to selective killing of cancer cells, while largely sparing normal cells

[1]Fung HY, Chook YM. Semin Cancer Biol. 2014;27:52–61. [2]Tai YT, Landesman Y, Acharya C, et al. Leukemia. 2014;28(1):155–165.

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 Mutant/Aberrant EC



Median PFS

Selinexor (n=74): 3.7 mo (95% CI 3.32-5.55)

Placebo (n=40): 5.6 mo (95% CI 3.71-7.49)

Audited

HR = 1.306 (95% CI 0.795-2.145)

Nominal one-sided P value = 0.8530

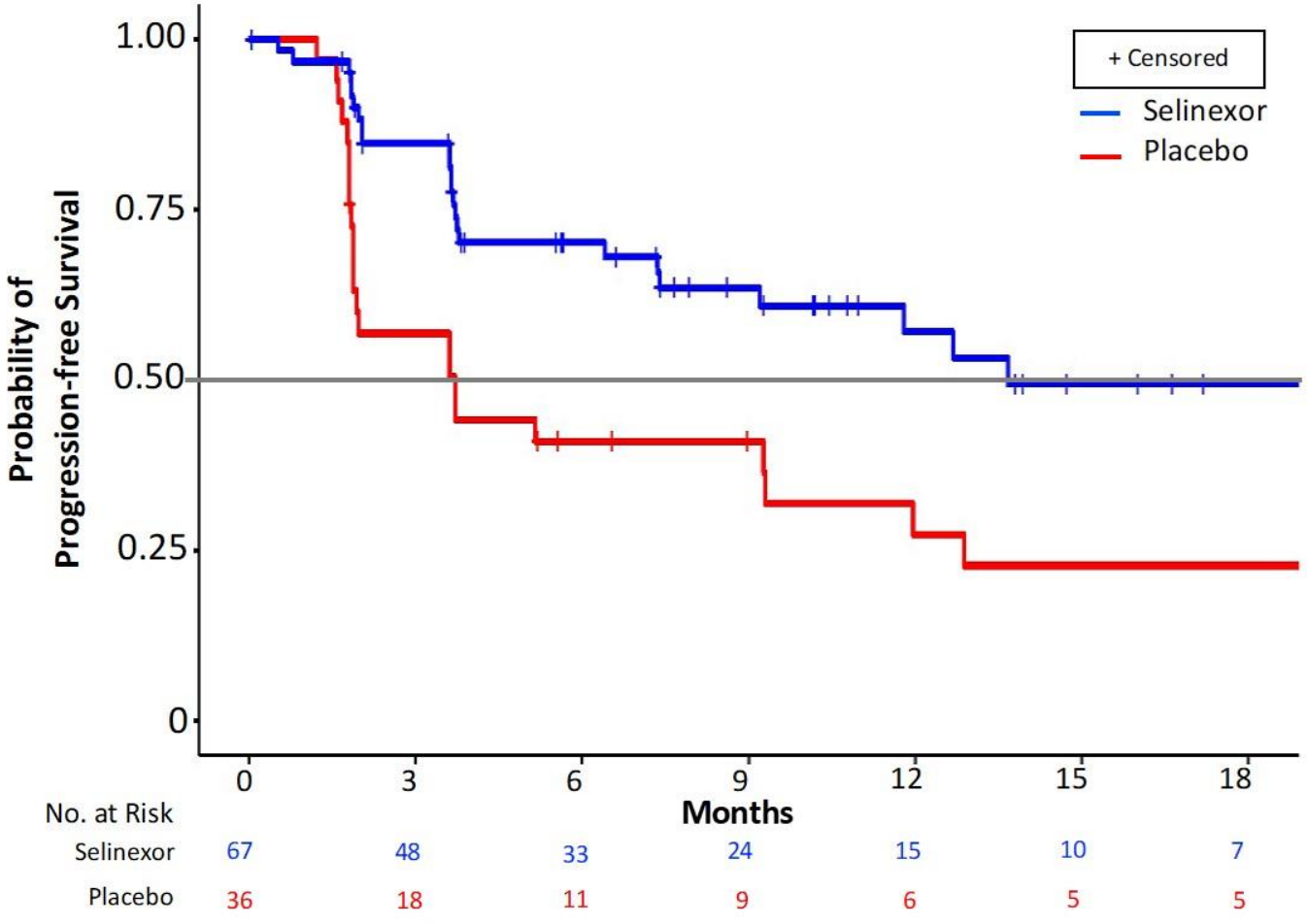
Unaudited

HR = 1.345 (95% CI 0.819-2.208)

Nominal one-sided P value = 0.8785

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 wild-type EC



Median PFS

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

Audited

HR = 0.375 (95% CI 0.210-0.670)

Nominal one-sided P value = 0.0003

Unaudited

HR = 0.407 (95% CI 0.229-0.724)

Nominal one-sided P value = 0.0008

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

ENGOT-EN3 / NSGO-PALEO

ENGOT model A, sponsor NSGO-CTU, NCT02730429

- Measurable/evaluable endometrial cancer
- Primary stage 4 or relapsed disease
- ≥1 prior systemic therapy
- ER+ (≥10%) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

1:1 randomisation

Placebo 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Repeated every 28 days until progression

Palbociclib 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Stratification:
- No. of prior lines (primary advanced disease vs 1st relapse vs ≥2 relapses)
- Measurable vs evaluable disease per RECIST
- Prior use of MPA/megestrol acetate

Primary endpoint: Investigator-assessed PFS (target HR 0.625, 80% power, 15% 1-sided α)
Secondary endpoints:
- PFS in subgroups
- Objective response rate, disease control rate, PFS2, overall survival
- PROs
- Safety and tolerability

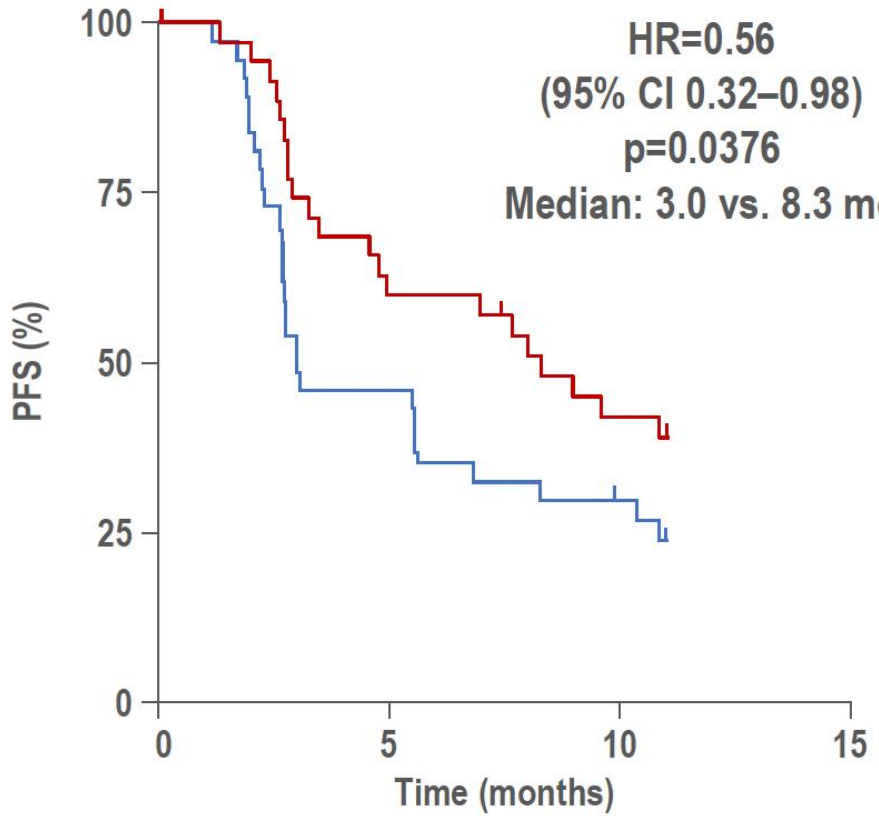
HR = hazard ratio; MPA = medroxyprogesterone acetate; PROs = patient-reported outcomes

Mirza, ESMO GYN 2023

ENGOT-EN3 / NSGO-PALEO

Efficacy (ITT population)

Primary endpoint: PFS

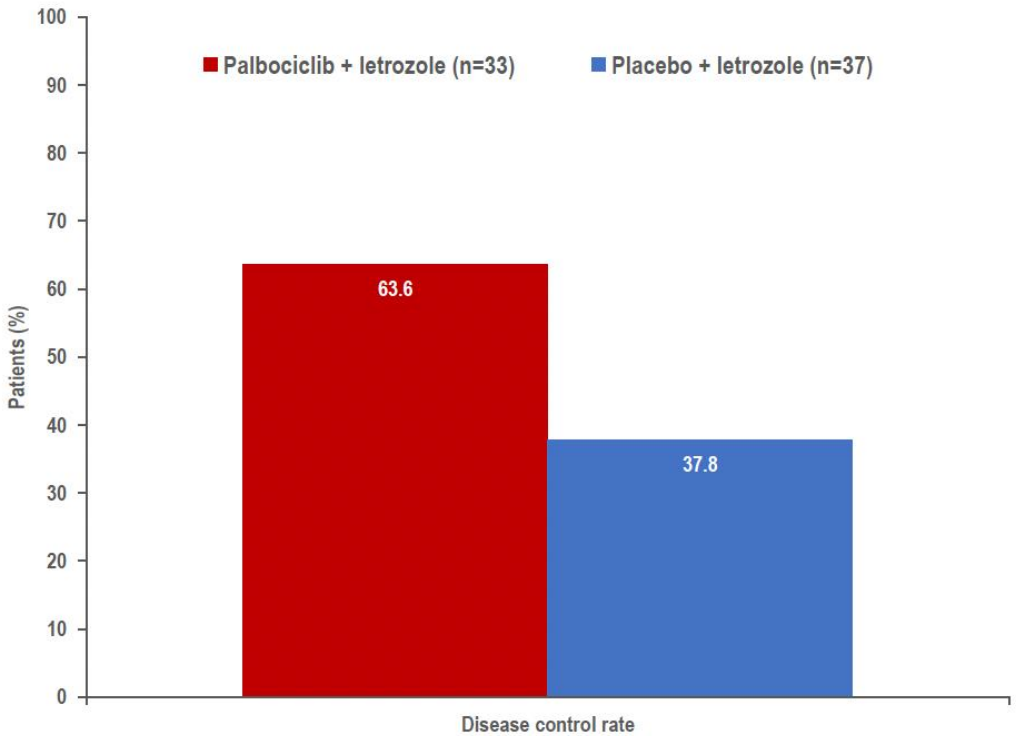


Number at risk			
Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	17	10

CI = confidence interval; HR = hazard ratio

Mirza et al. ESMO 2020

Secondary endpoint: Disease control rate*



* = at 24 weeks

Conclusions

- Molecular classification of EC is needed for a tailored approach in early and advanced setting

Conclusions

- Molecular classification of EC is needed for a tailored approach in early and advanced setting
- Some of the evidence guiding actual indications need to be reinforced and new biomarkers need further validation (p53, HRR/HRD)

Conclusions

- Molecular classification of EC is needed for a tailored approach in early and advanced setting
- Some of the evidence guiding actual indications need to be reinforced and new biomarkers need further validation (p53, HRR/HRD)
- Gray zones in treatment approach(POLE stage III/IV)

Conclusions

- Molecular classification of EC is needed for a tailored approach in early and advanced setting
- Some of the evidence guiding actual indications need to be reinforced and new biomarkers need further validation (p53, HRR/HRD)
- Gray zones in treatment approach(POLE stage III/IV)
- With the next coming new bullets (selinexor, CDK 4/6i, ADC) treatment's sequencing will increase importance

Grazie

michele.bartoletti@cro.it