Updates in Gynecologic Malignancies

Ritu Salani MD, MBA
University of California Los Angeles
Professor, Obstetrics & Gynecology
Division Director, Gynecologic Oncology

UCLA Health

Objectives

- Review updates in gynecologic malignancies
  - Ovarian cancer
  - Cervical cancer
  - Endometrial cancer
- Focus on targeted therapy and immunotherapy
- Explore future studies

Ovarian Cancer Updates

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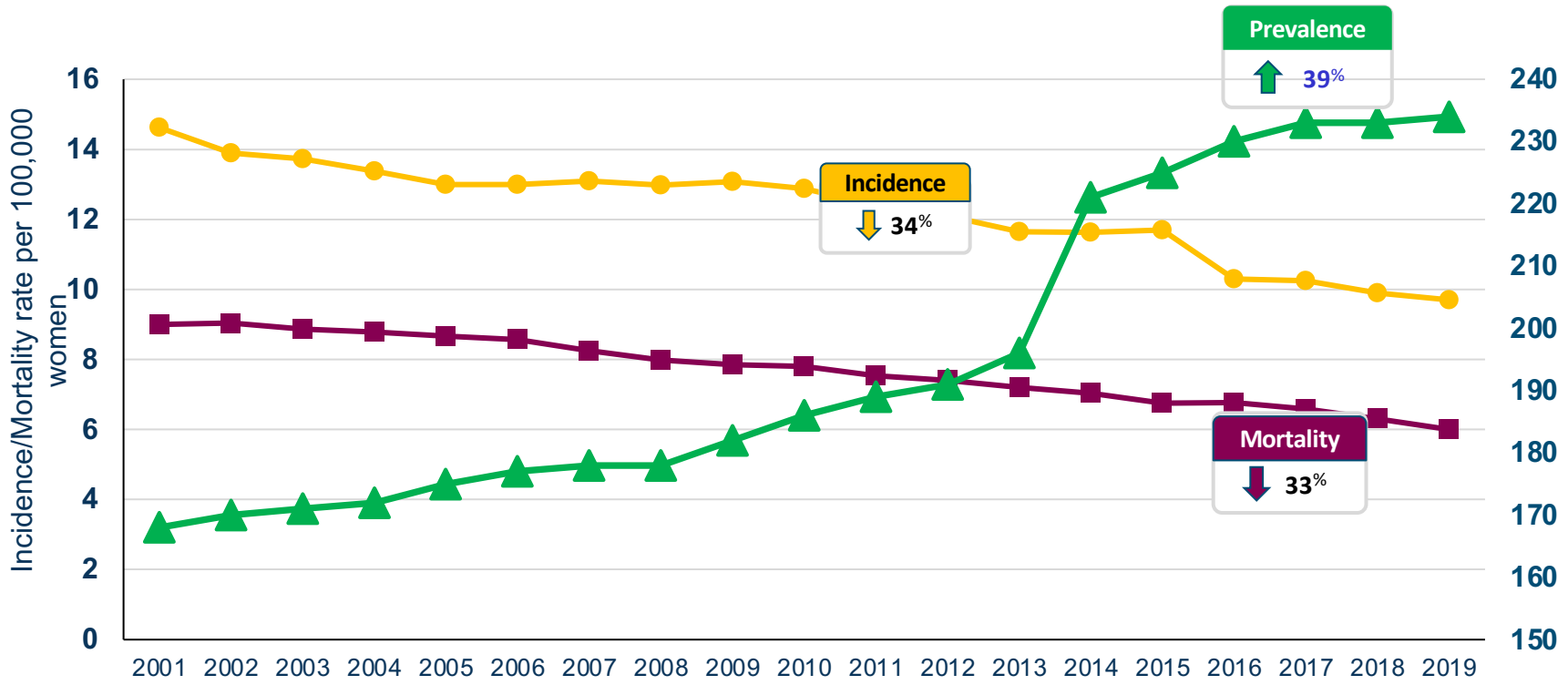
Ovarian Cancer Overview

- In 2023, estimated 19,710 cases and 13,270 deaths
  - 75% diagnosed in advanced stages



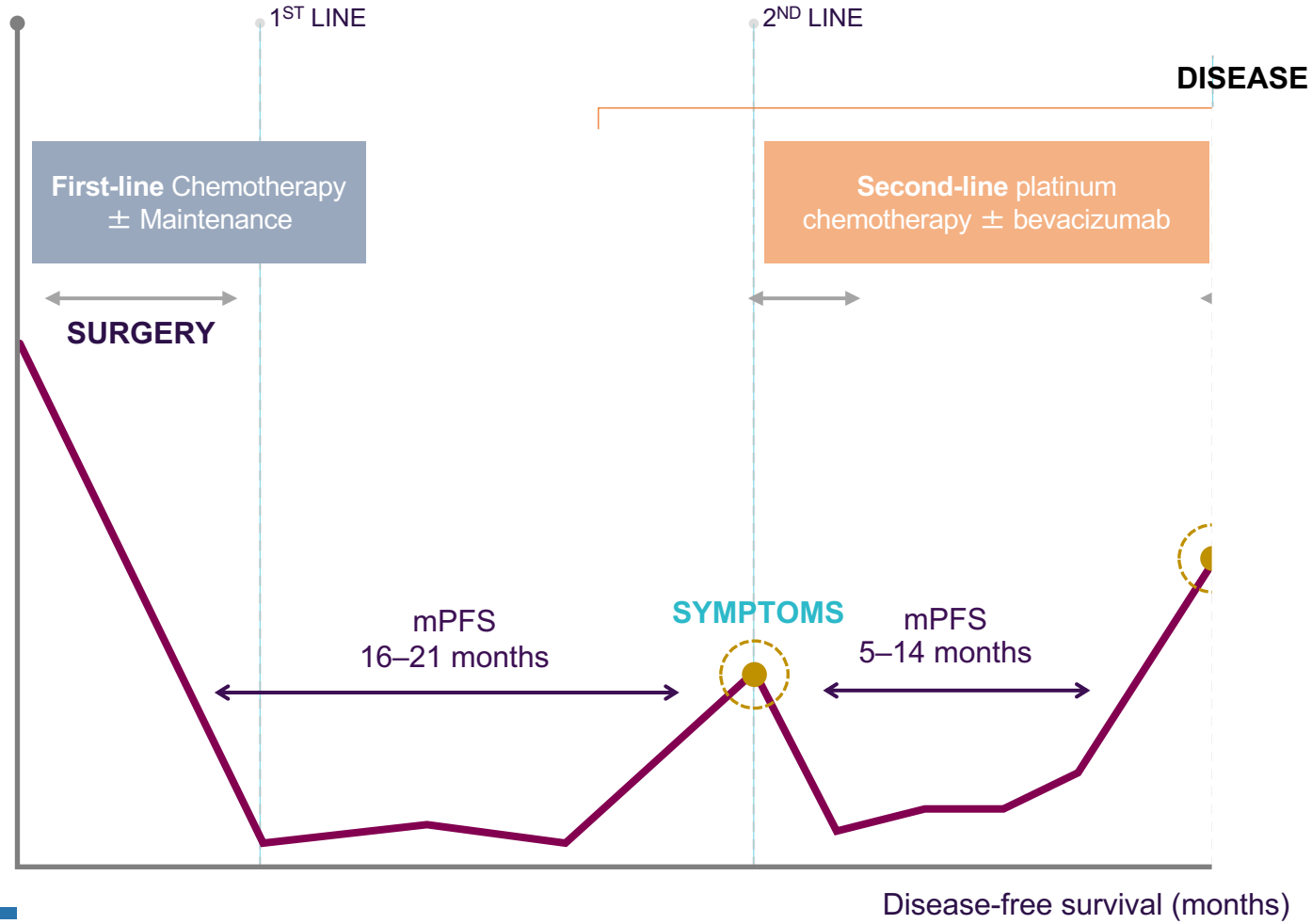
5-Year Relative Survival

50.8%

2013–2019

https://seer.cancer.gov/statistics-network/explorer/application.html

Ovarian Cancer Course



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Platinum Resistant Ovarian Cancer

Trial	Agent	Result
OVAL study (VB-111)	Ofranergene obadenovec (TNFR1)	Negative
AXLerate-OC	Batiraxcept	Negative
UPLIFT	Upifitamab rilsodotin (NaPi2b)	Negative
INNOVATE-3	Tumor testing fields	Negative
ARTISTRY 7	Nemvaleukin and Pembrolizumab	Ongoing

MIRASOL: Mirvetuximab Soravtansine

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility
Platinum-resistant disease
(PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

High-grade serous histology

1º platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors
IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint

PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints

1) ORR by INV
2) OS
3) PROs[a]

Secondary Endpoints

Safety and tolerability
DOR
CA-125 response[b]
PFS2

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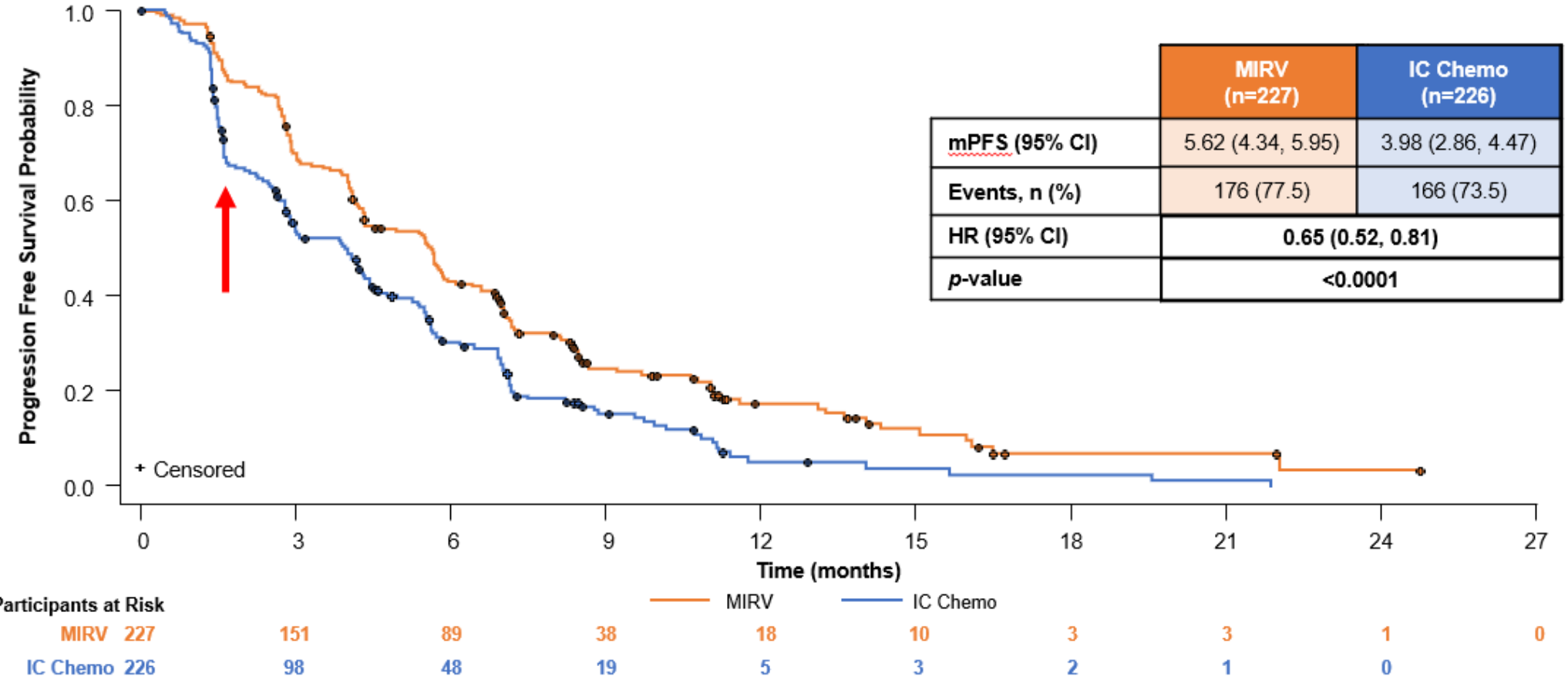
11/14/22: FDA accelerated approval in high FRα PROC

Moore KN. ASCO 2023

MIRASOL: PFS



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

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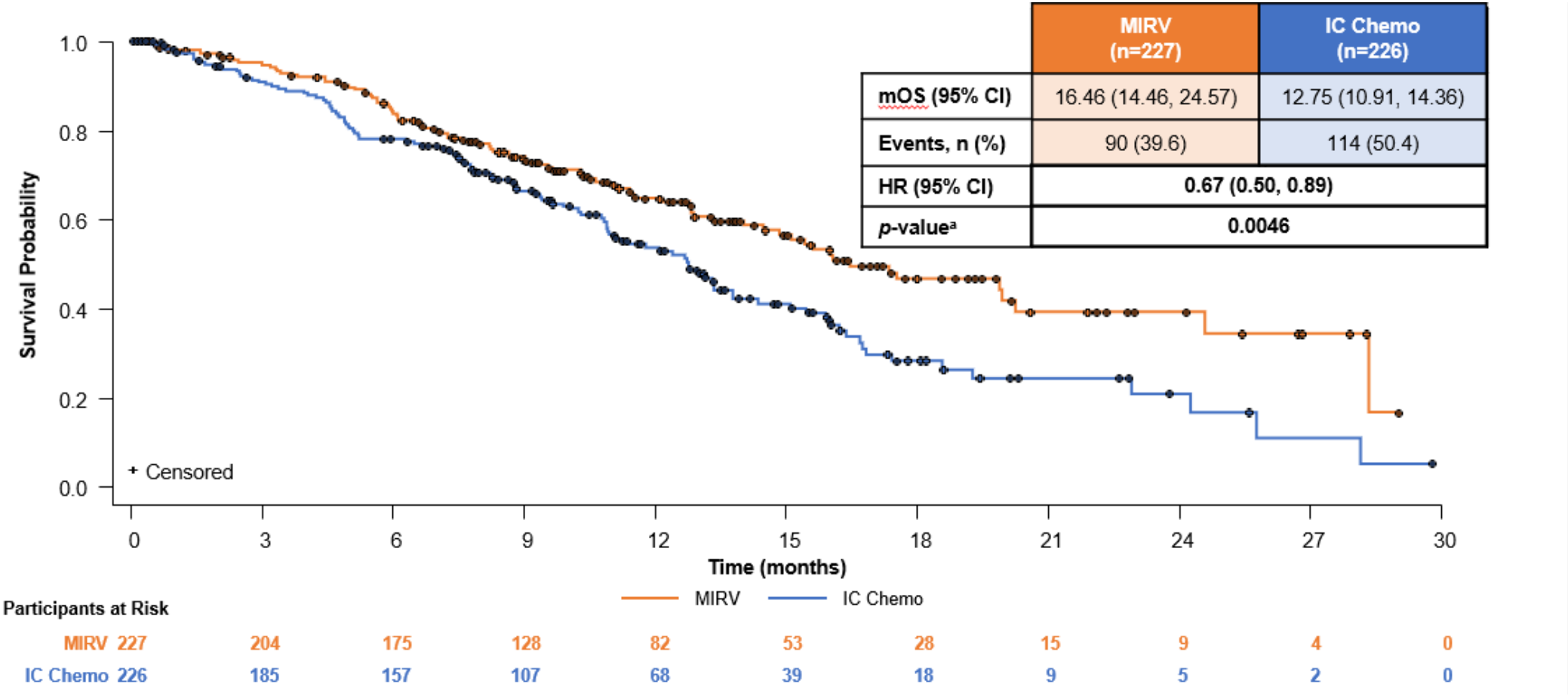
Moore KN. ASCO 2023

MIRASOL: OS



	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50, 0.89)	
p-value[a]	0.0046	

No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

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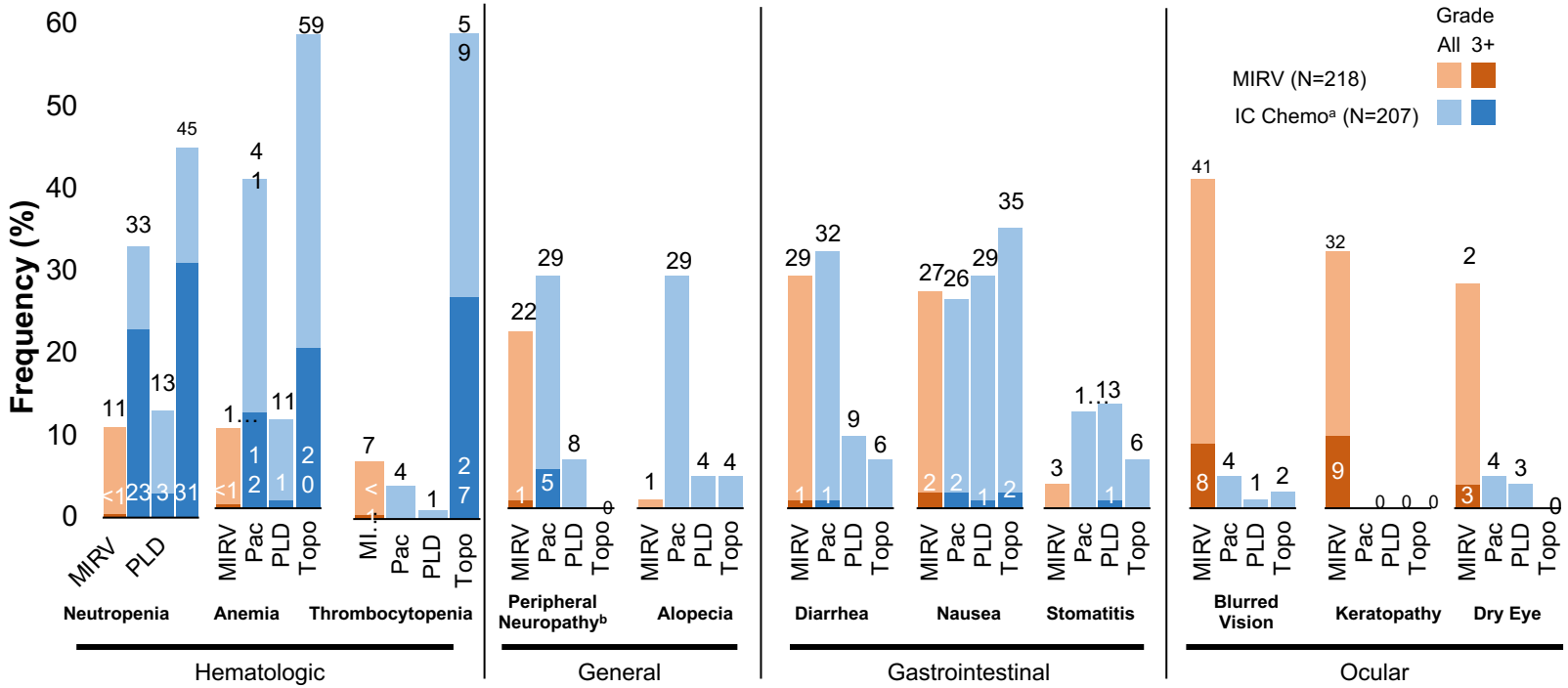
Moore KN. ASCO 2023

MIRASOL: Outcomes

	MIRV	IC Chemo
ORR	42%	16%
CR	5%	0%
PR	37%	16%
SD	38%	40%
PD	14%	27%

ORR difference 26.4%
OR 3.81
P<0.0001

Treatment related adverse events



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Moore KN. ASCO 2023

Cervical Cancer Updates

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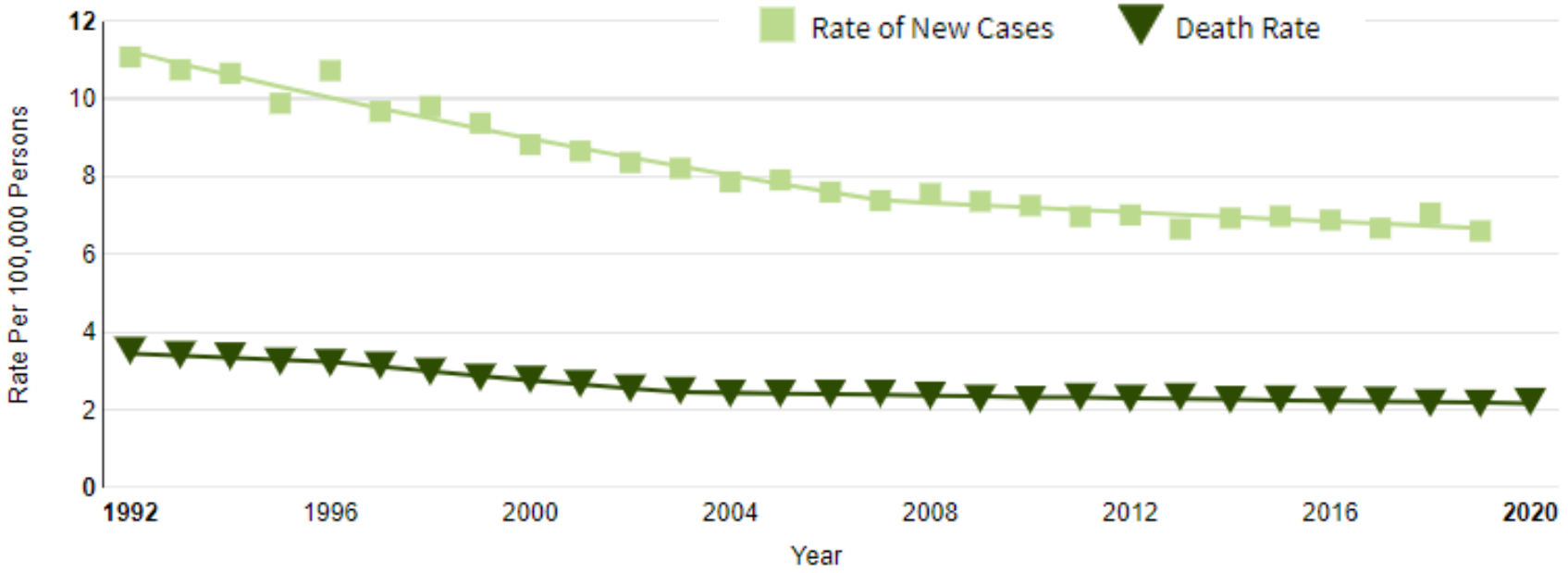
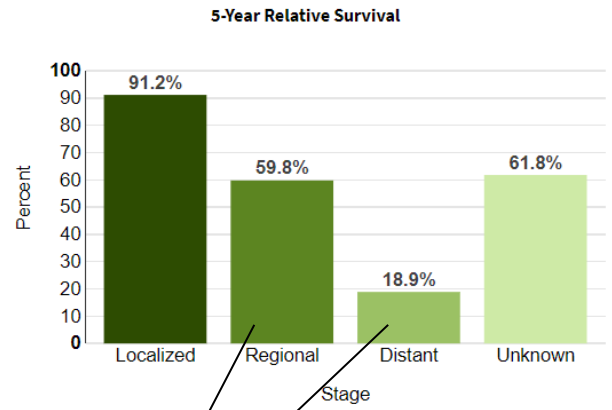
Cervical Cancer Overview

- 13,960 new cases and 4,310 deaths





Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	68.1%	68.0%	66.4%	72.1%	74.9%	72.2%	67.5%	69.4%

2013-2019
67.2%

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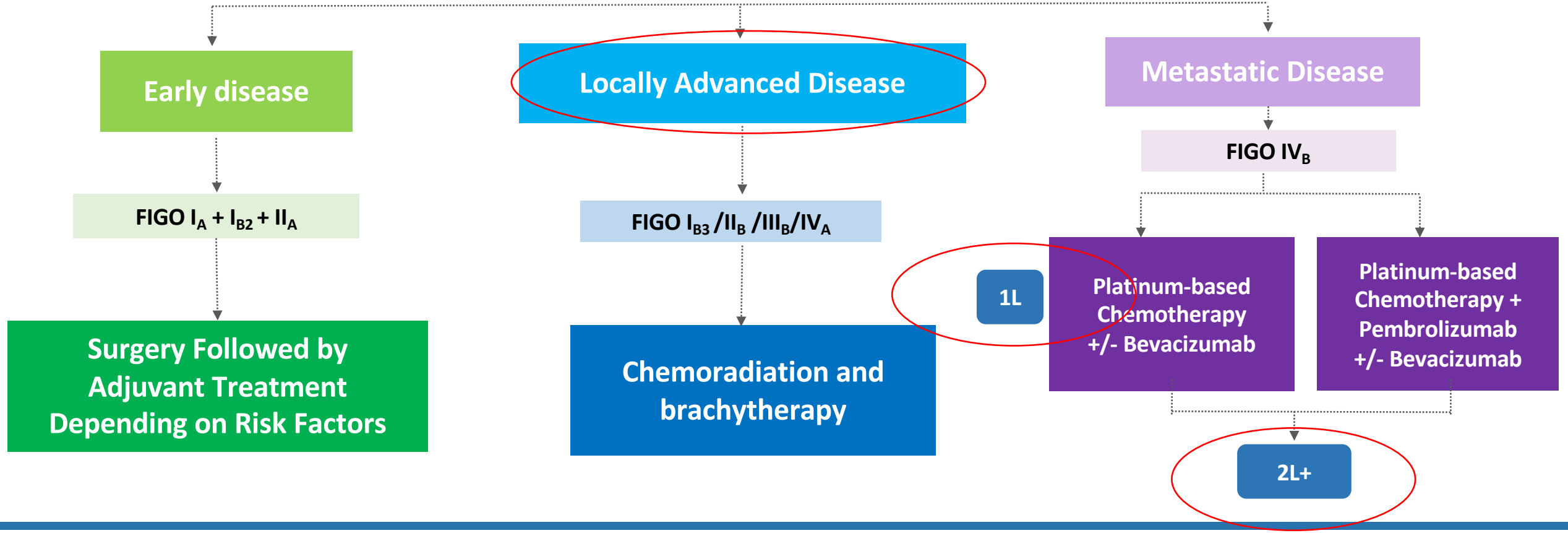
SEER Cancer Stat Facts: Cervical Cancer.

Cervical Cancer: Treatment Overview



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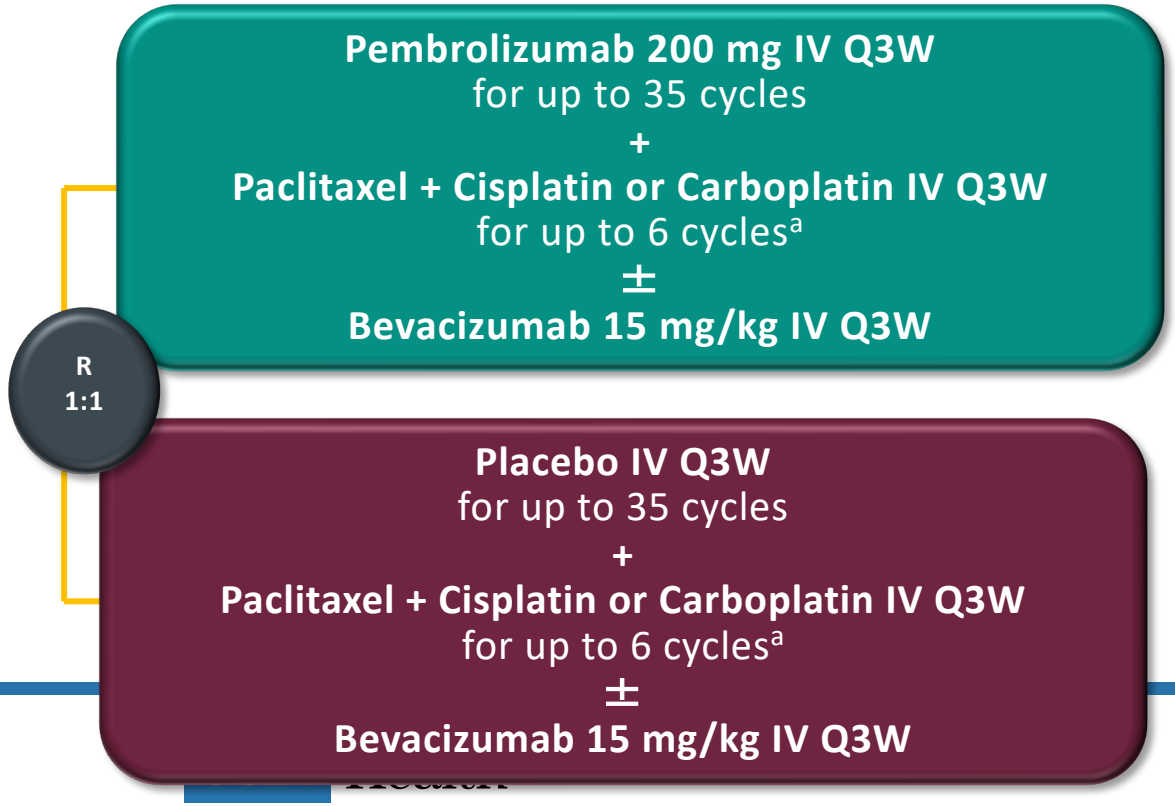
NCCN Cervical Cancer Guidelines v2.2019. SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD.

KEYNOTE 826: Pembrolizumab

- Persistent, recurrent or metastatic cervical cancer
- No prior chemotherapy (prior chemoradiation permitted)



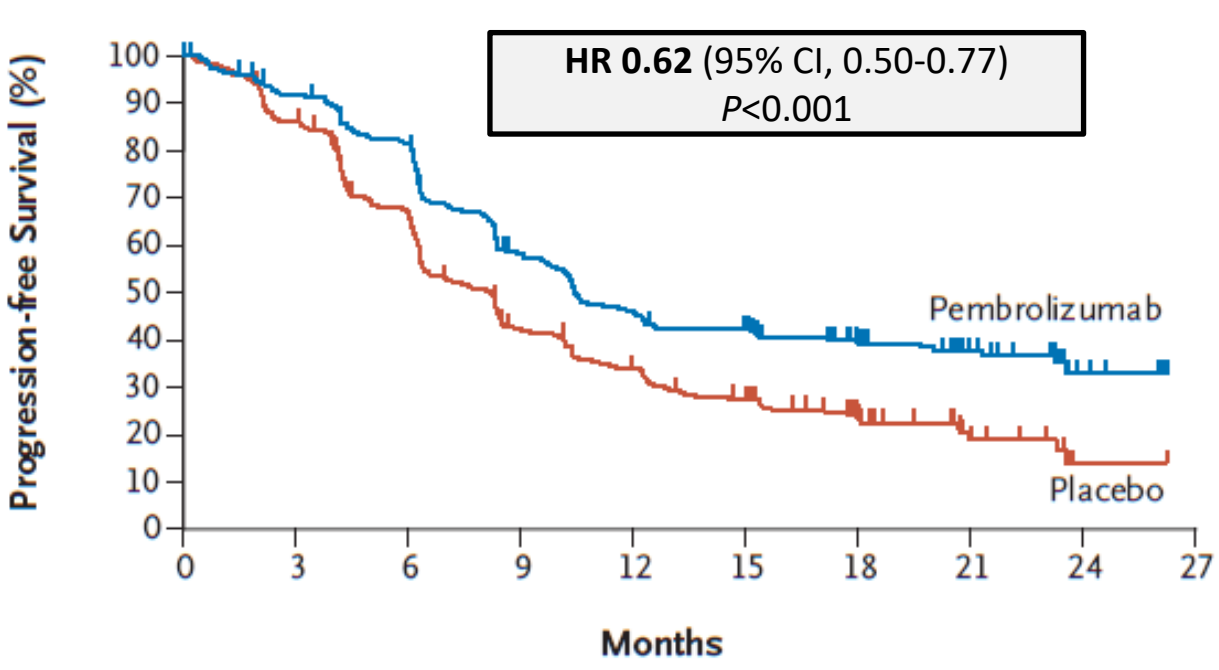
	Pembrolizumab group (n=308)	Placebo group (n=309)
Age, median (range), y	51 (25-82)	50 (22-79)
ECOG PS 1, No. (%)	128 (42)	139 (45)
SCC, No. (%)	235 (76)	211 (68)
PD-L1 CPS, No. (%)		
<1	35 (11)	34 (11)
1 to <10	115 (37)	116 (38)
≥10	158 (51)	159 (51)
Bevacizumab use during trial, No. (%)	196 (64)	193 (62)

Colombo N. N Engl J Med. 2021.

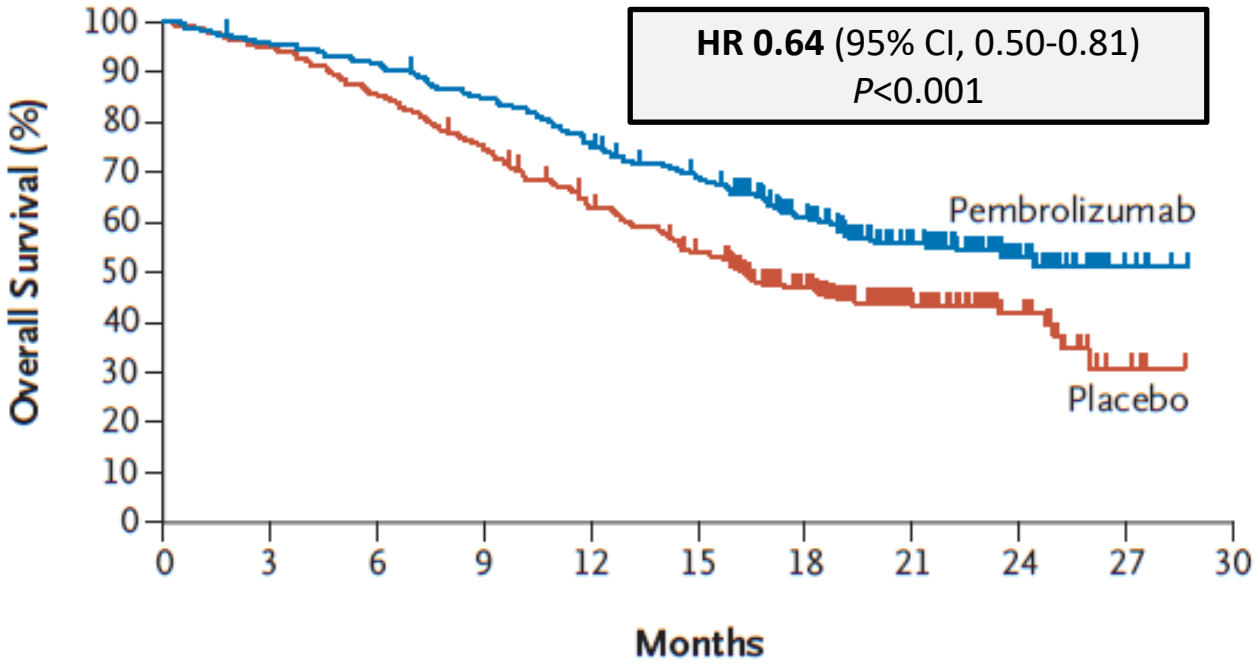
KEYNOTE 826: Outcomes (CPS ≥1)

- FDA approval on 10/31/21

Progression free survival



Overall survival



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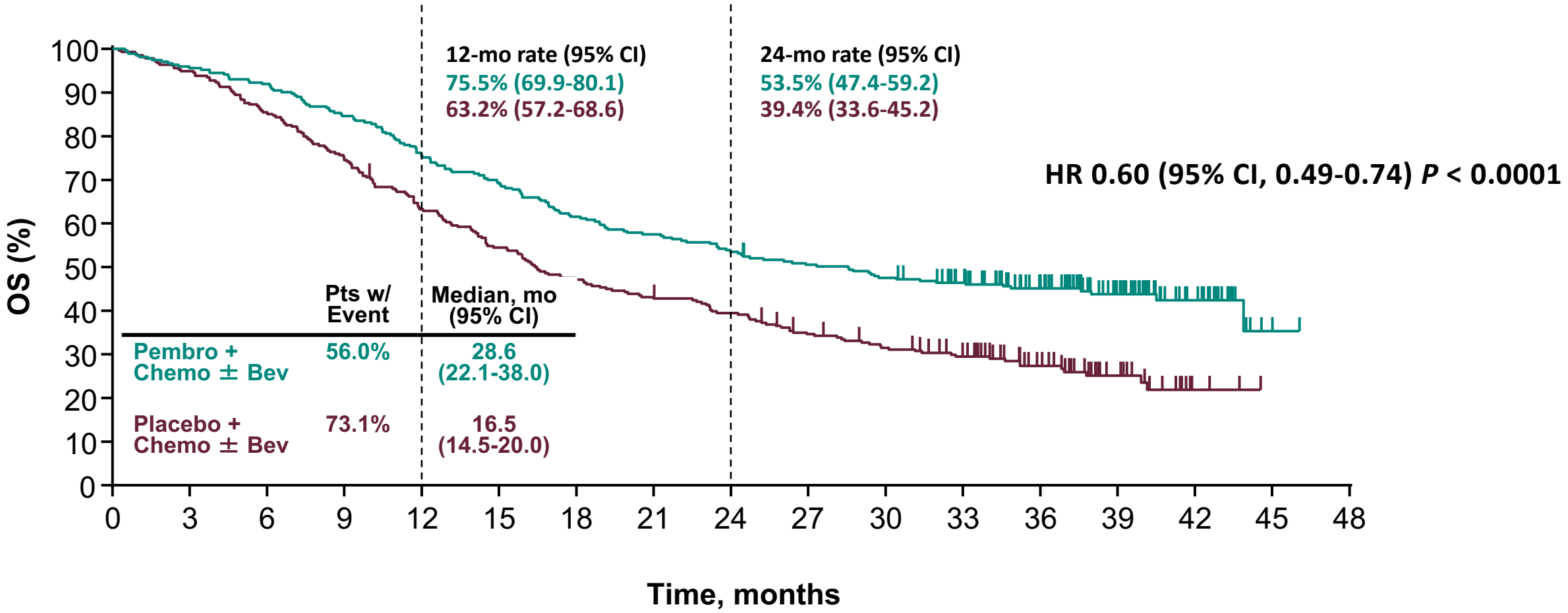
Colombo N. N Engl J Med. 2021.

KEYNOTE 826: Final Survival Analysis (CPS ≥1)



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Monk BJ. ASCO 2023

BEATcc: Atezolizumab

- Metastatic, persistent or recurrent cervical cancer not amenable to curative therapy
- GOG/ECOG PS ≤1
- No prior systemic anti-cancer therapy for R/M CC
- In patients with pelvic disease, no bladder or rectal mucosa involvement
- Available archival or fresh tumour sample for PD-L1 expression

Stratification factors:

- Prior concurrent chemoradiation (yes vs no)
- Histology (squamous cell carcinoma vs adenocarcinoma[b] including adenosquamous carcinoma)
- Chemotherapy backbone (cisplatin vs carboplatin)

R
1:1

N=410

Atezolizumab 1200 mg + bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

Bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

- Continued until disease progression/unacceptable toxicity
- Patients with CR after ≥6 cycles could stop chemotherapy and continue biological therapy alone
- Crossover from standard arm at progression not permitted

Dual primary endpoints

- Investigator-assessed PFS (RECIST 1.1)
- OS

Key secondary endpoints

- ORR (RECIST v1.1)
- DoR (RECIST v1.1)
- TFST
- PFS2
- Safety

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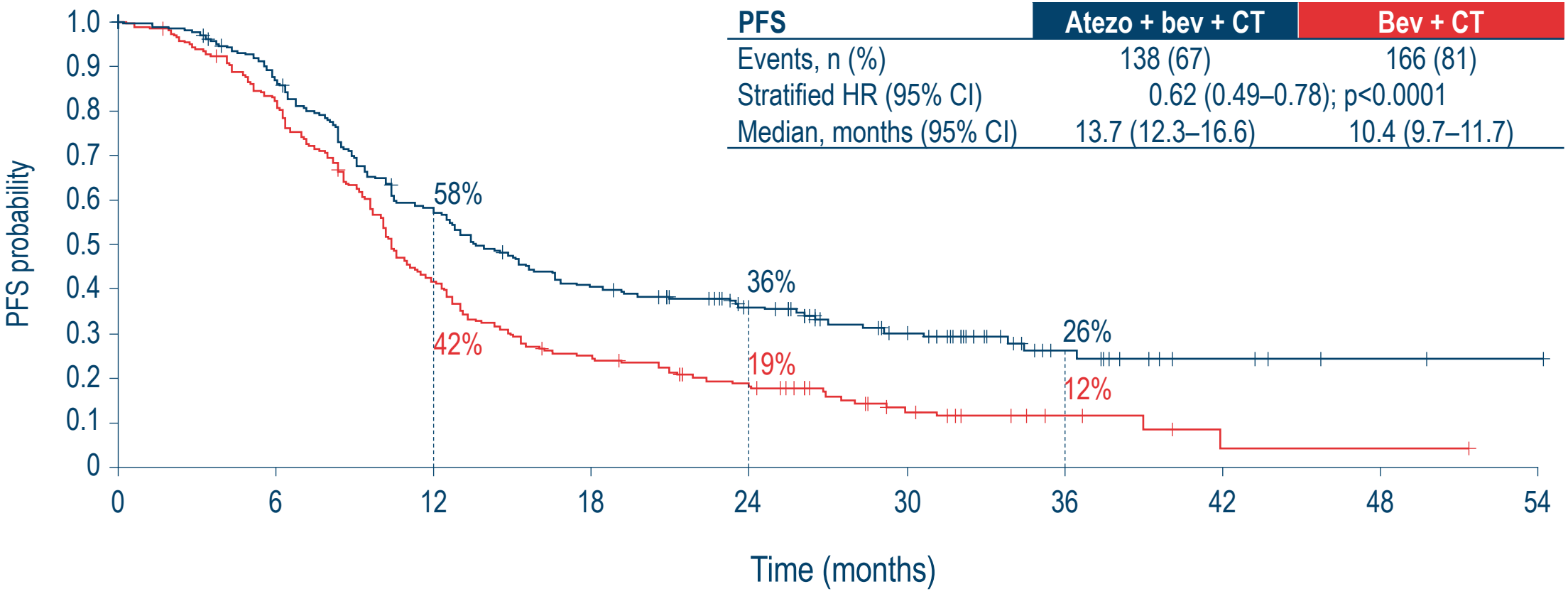
Oaknin A. ESMO 2023.

BEATcc: PFS

PFS	Atezo + bev + CT	Bev + CT
Events, n (%)	138 (67)	166 (81)
Stratified HR (95% CI)	0.62 (0.49–0.78); p<0.0001	
Median, months (95% CI)	13.7 (12.3–16.6)	10.4 (9.7–11.7)



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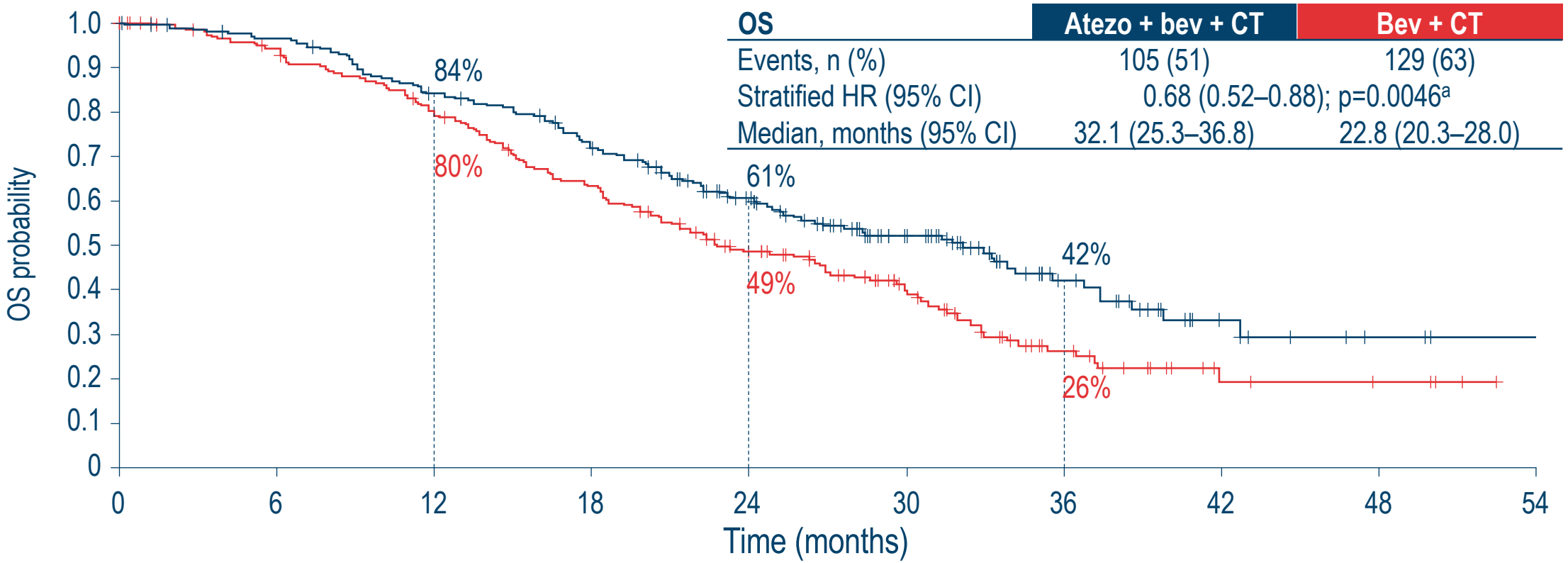
Oaknin A. ESMO 2023.

BEATcc: OS (Interim Analysis)



OS	Atezo + bev + CT	Bev + CT
Events, n (%)	105 (51)	129 (63)
Stratified HR (95% CI)	0.68 (0.52–0.88); p=0.0046[a]	
Median, months (95% CI)	32.1 (25.3–36.8)	22.8 (20.3–28.0)

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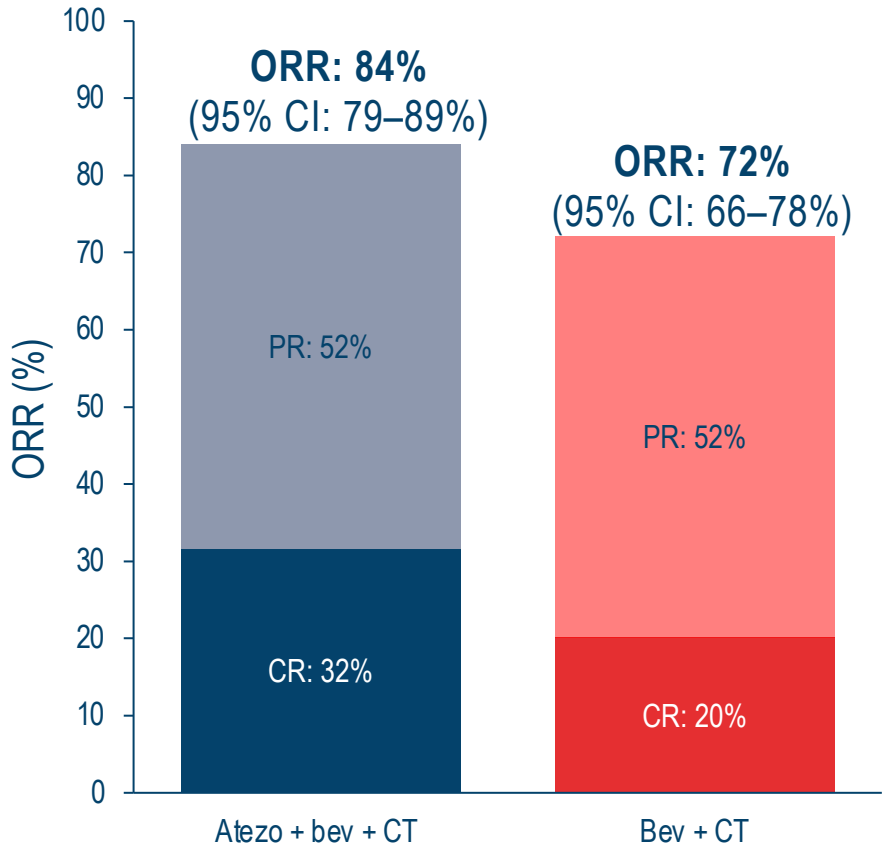
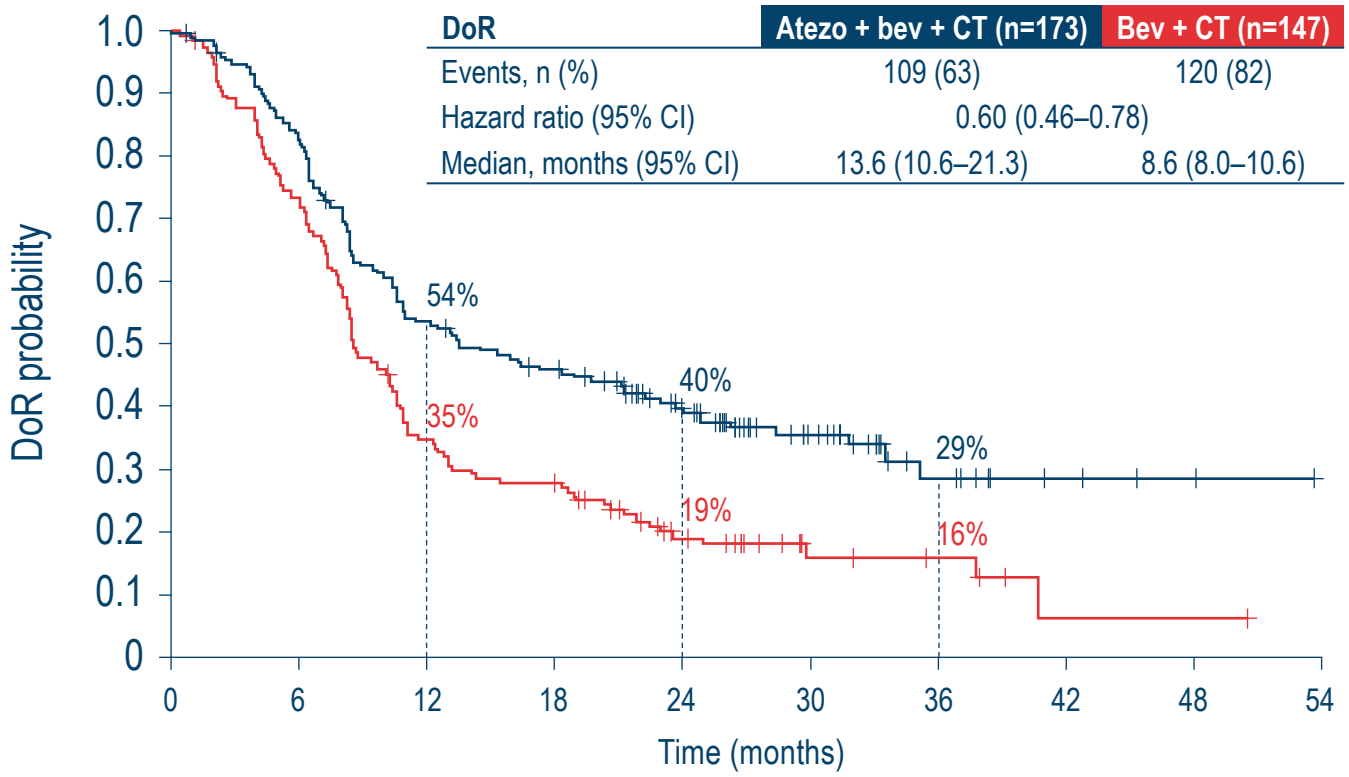
Oaknin A. ESMO 2023.

BEATcc: ORR and DoR





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Oaknin A. ESMO 2023.

Locally Advanced Cervical Cancer

- Radiation with cisplatin has been the standard for 20+ years!
- Progression free survival: 60-80%

TRIAL	INTERVENTION	OUTCOME
GOG 109	Adjuvant RT vs CDDP-based RT	Superiority of Adjuvant ChemoRT
GOG 85	CDDP-based vs HU-based RT	Superiority of ChemoRT
GOG 120	CDDP-based vs HU-based RT	Superiority of ChemoRT
GOG 123	CDDP-based RT vs RT alone	Superiority of ChemoRT
RTOG 9001	CDDP+5FU-based RT vs RT alone	Superiority of ChemoRT
GOG 191	ChemoRT ± Erythropoietin	TERMINATED EARLY
GOG 219	ChemoRT ± Tirapazimine	TERMINATED EARLY
AIM2CERV	ChemoRT ± Axalimogene Filolisbac	TERMINATED EARLY
OUTBACK	ChemoRT ± consolidation ChemoRx	NEGATIVE (OS)
CALLA	ChemoRT ± anti-PD-L1 Durvalumab	NEGATIVE (PFS)
NRG-GY006	ChemoRT ± Triapine	NEGATIVE (OS)

Morris M. N Engl J Med 1999. Rose PG. N Engl J Med 1999. Keys HM. N Engl J Med 1999. Whitney CW. J Clin Oncol 1999. Peters III WA. J Clin Oncol 2000. Mileshkin, LR. Lancet Oncol 2023. Leath CA. ASCO 2023.

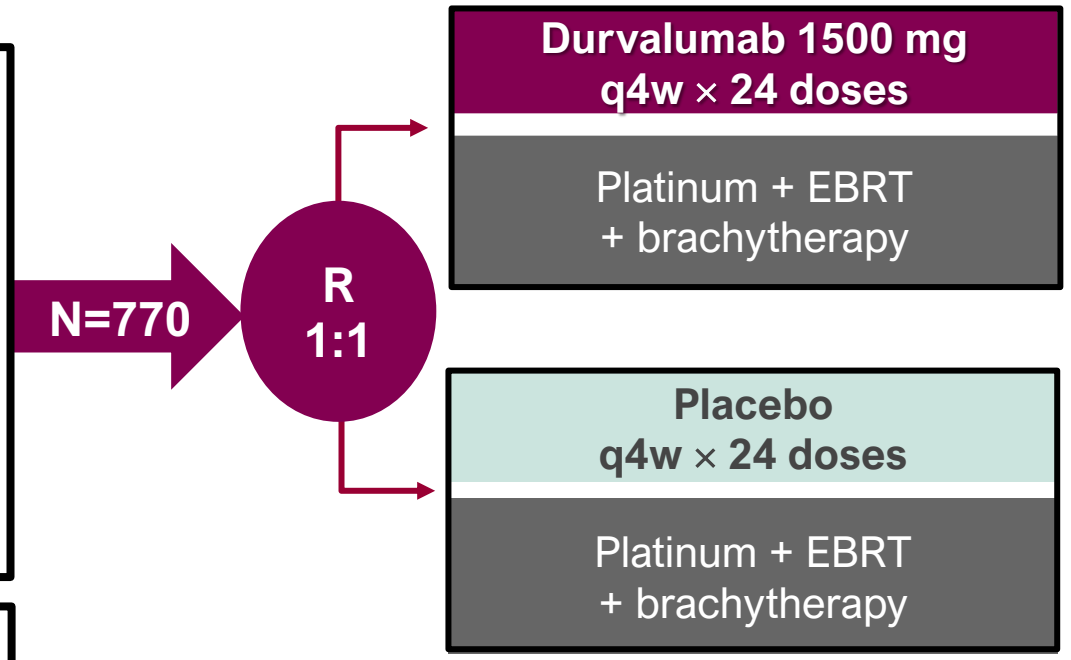
CALLA: Durvalumab

Eligible population

- Women aged ≥18 years
- Histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma
- High-risk LACC (FIGO 2009)
  - Stages IB2 to IIB, node positive (N≥1)
  - Stages IIIA to IVA with any node (N≥0)
- WHO ECOG performance status of 0 or 1

Stratification factors

- Disease stage
  - FIGO Stage IB2–IIB and LN+
  - FIGO Stage ≥III and LN–
  - FIGO Stage ≥III and LN+
- Region of world



Primary Endpoint:

Progression-Free Survival[a] (Investigator-assessed)

Key Secondary Endpoints:

- Overall survival
- Objective response rate
- Duration of response
- Incidence of local or distant progression / 2° malignancy
- Safety and tolerability

Chemoradiotherapy Regimen

Platinum agent	Cisplatin 40 mg/m^2 or carboplatin AUC2 q1w × 5 weeks
EBRT	45 Gy in 25 fractions at 1.8 Gy/fraction, 5 fractions per week
Brachytherapy	High-dose rate: 27.5–30 Gy; Low/pulsed-dose rate: 35–40 Gy

15 countries, **120** sites

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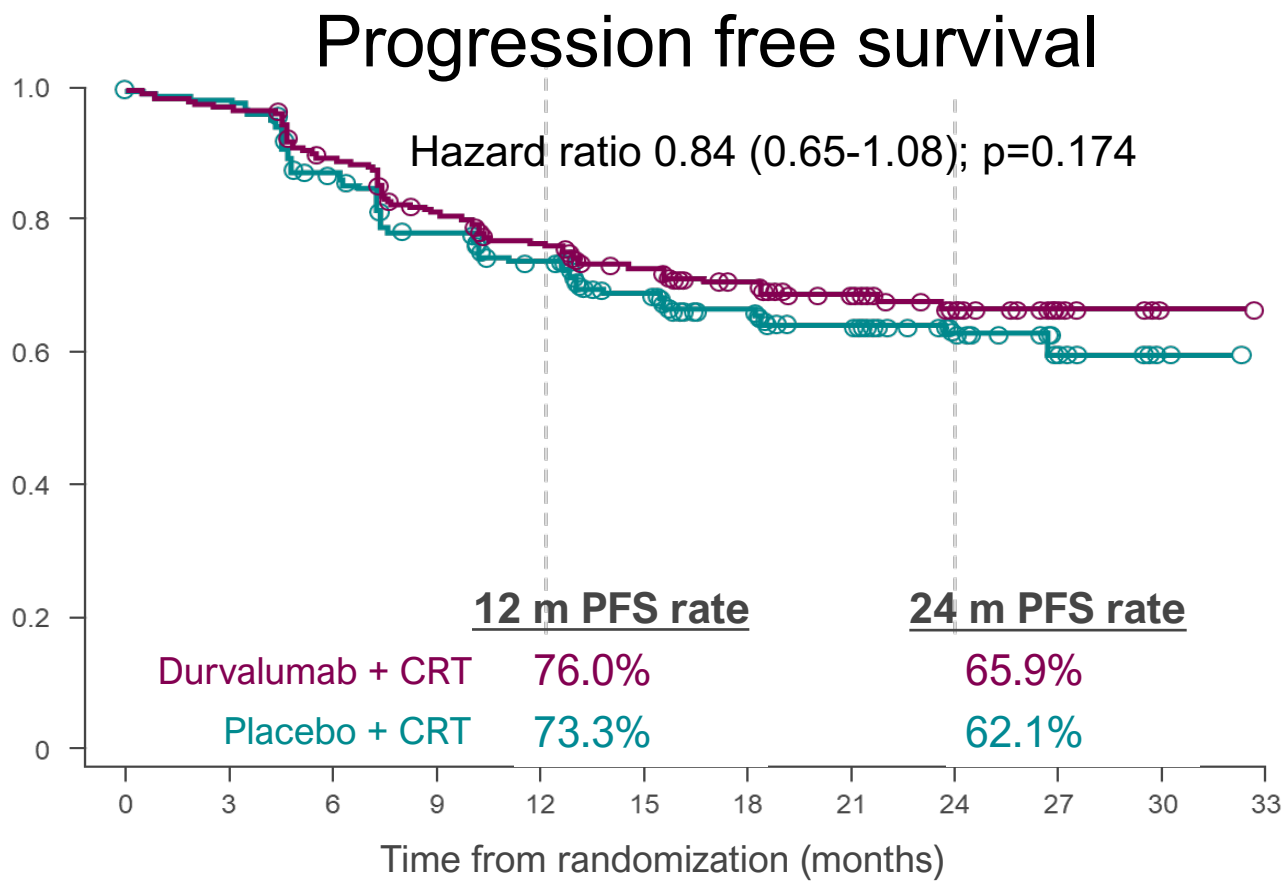
Monk BJ. IGCS 2022.

CALLA: Outcomes

	Durvalumab + CRT (N=385)	Placebo + CRT (N=385)
Histology, n (%)		
Squamous	**322 (83.6)**	**320 (83.1)**
Adeno	**55 (14.3)**	**58 (15.1)**
Stage n (%)		
IB2–IIB	**135 (35.1)**	**130 (33.8)**
III	**225 (58.4)**	**236 (61.3)**
IVA	**25 (6.5)**	**19 (4.9)**
LN, n (%)		
Pelvic	**246 (63.9)**	**268 (69.6)**
Para-aortic	**47 (12.2)**	**38 (9.9)**
PD-L1 status, n (%)		
TAP ≥1%	**356 (92.5)**	**352(91.4)**
TAP ≥5%	**311 (80.8)**	**300 (77.9)**
Missing	**14 (3.6)**	**21 (5.5)**



Overall survival: HR 0.78 (0.55-1.10)

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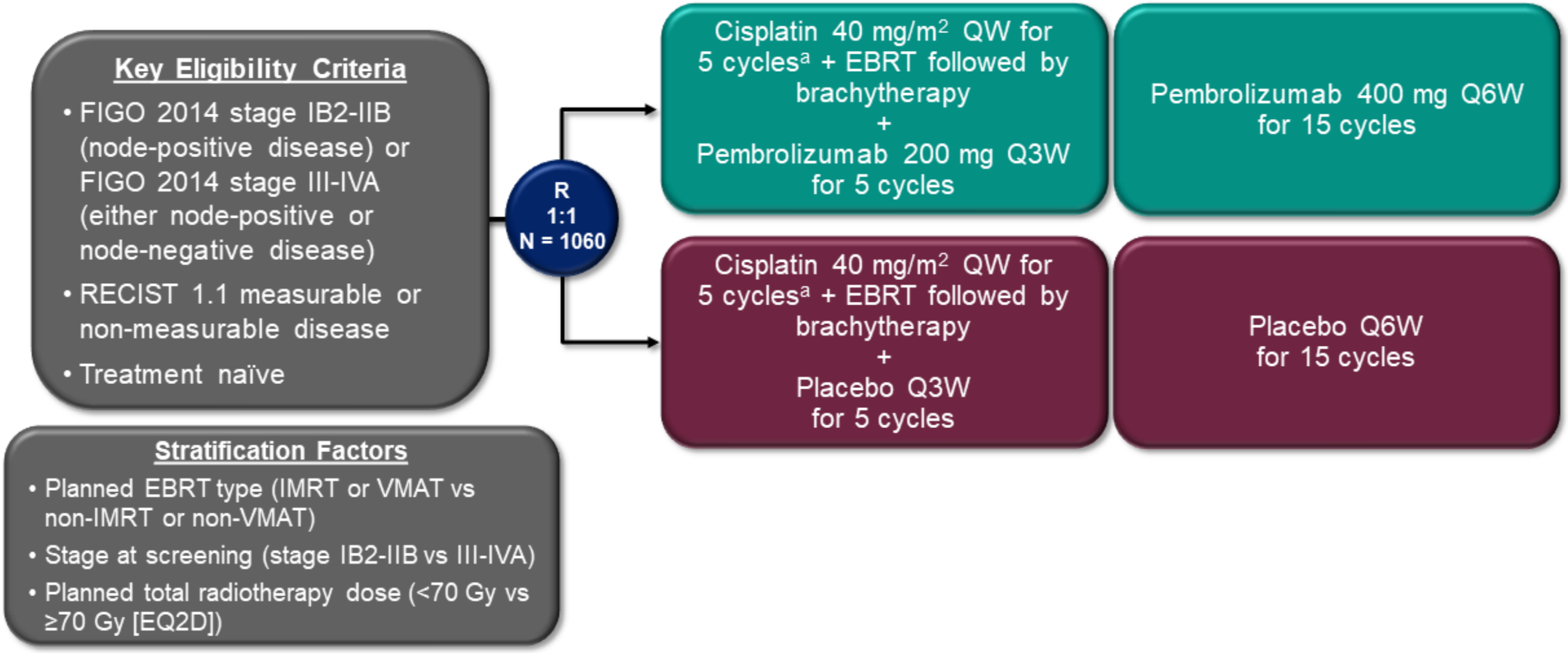
Monk BS. IGCS 2022.

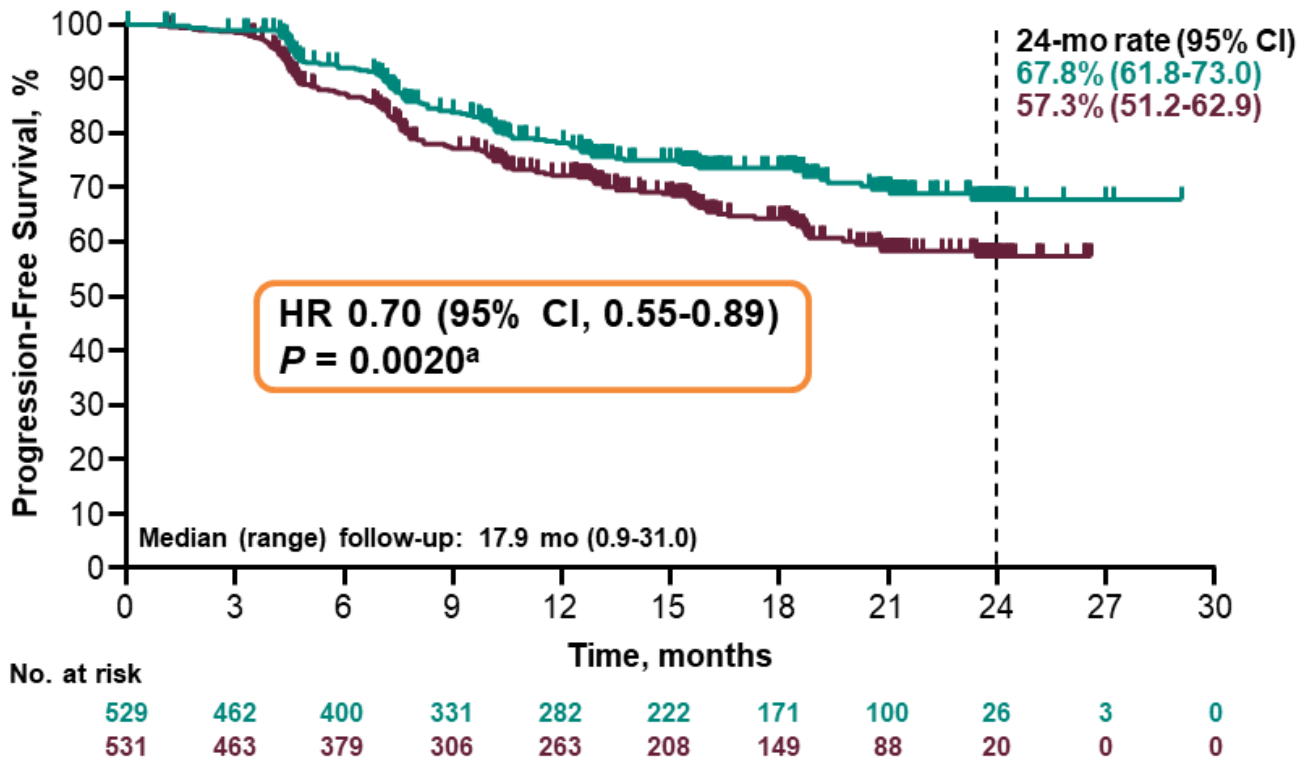
KEYNOTE A18: Pembrolizumab



Lorusso D. ESMO 2023.

KEYNOTE A18: PFS

	Pembro (n=529)	Placebo (n=531)
Age	49 (22-87)	50 (22-78)
PDL1 CPS>1	94.9%	93.8%
Stage IB2-I	44.4%	42.7%
Stage III-IVA	55.6%	57.3%
Positive lymph nodes	84.1%	82.5%
IMRT or VMAT	88.7%	88.5%
Radiation dose ≥70 Gy	91.1%	91.3%
Radiation within 56 days	74.5%	74.7%



Overall survival: HR 0.73 (0.49-1.07)

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Lorusso D. ESMO 2023.

INTERLACE Trial: Induction chemotherapy

Newly diagnosed FIGO (2008) stage IB1 node+,IB2, II, IIIB, IVa cervical cancer

- Site
- Stage
- Nodal status
- 3D v IMRT EBRT
- 2D v 3D BT
- Tumour size
- SCC v other

Randomised (n=500)

Induction chemotherapy (n=250)

Carboplatin (AUC2) & paclitaxel (80mg/m^2) given weekly for **6 weeks**

Week 7

Standard CRT (n=250)

Chemotherapy: cisplatin (40mg/m^2) weekly for 5 weeks
Radiotherapy: EBRT (40-50.4Gy in 20-28 fractions) & brachytherapy

Follow-up

3-monthly for 2 years then 6-monthly for 5 years

Primary endpoints

- PFS
- OS

Secondary endpoints

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment

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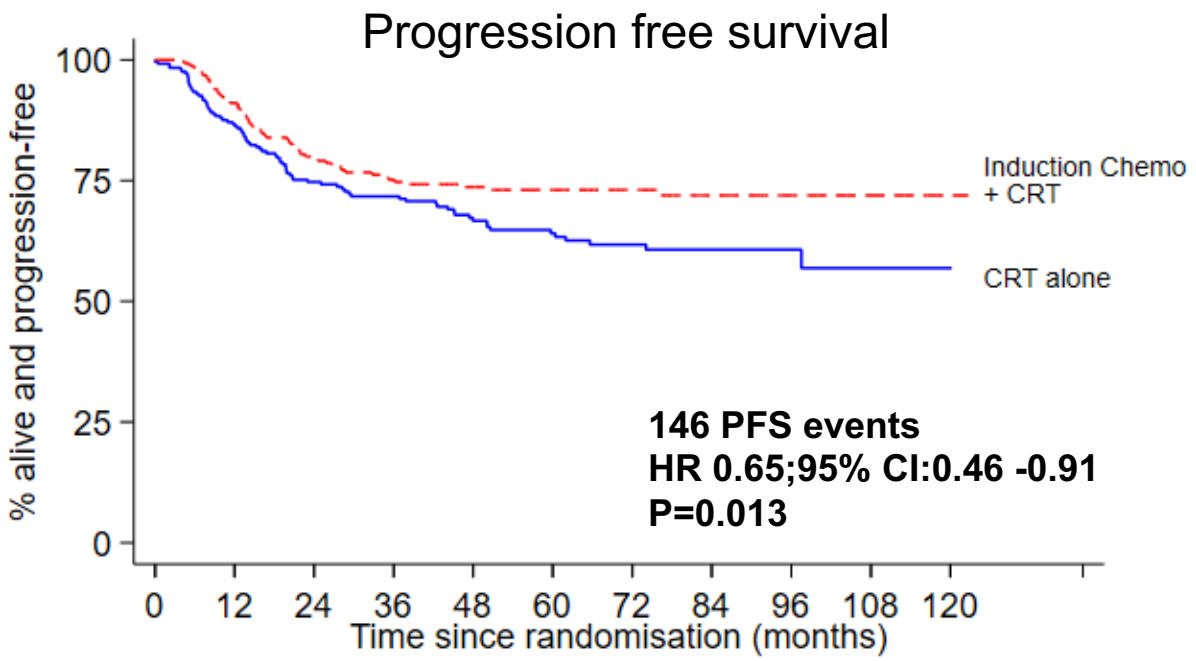
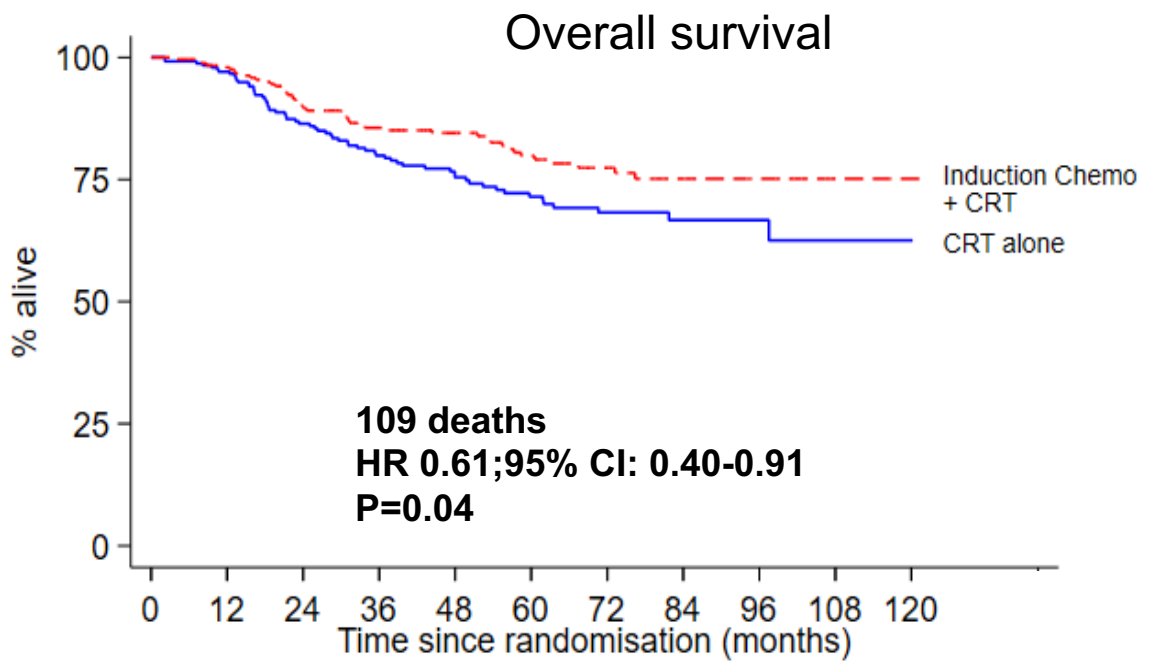
McCormack M. ESMO 2022.

INTERLACE Trial: Induction chemotherapy





	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

McCormack M. ESMO 2022.

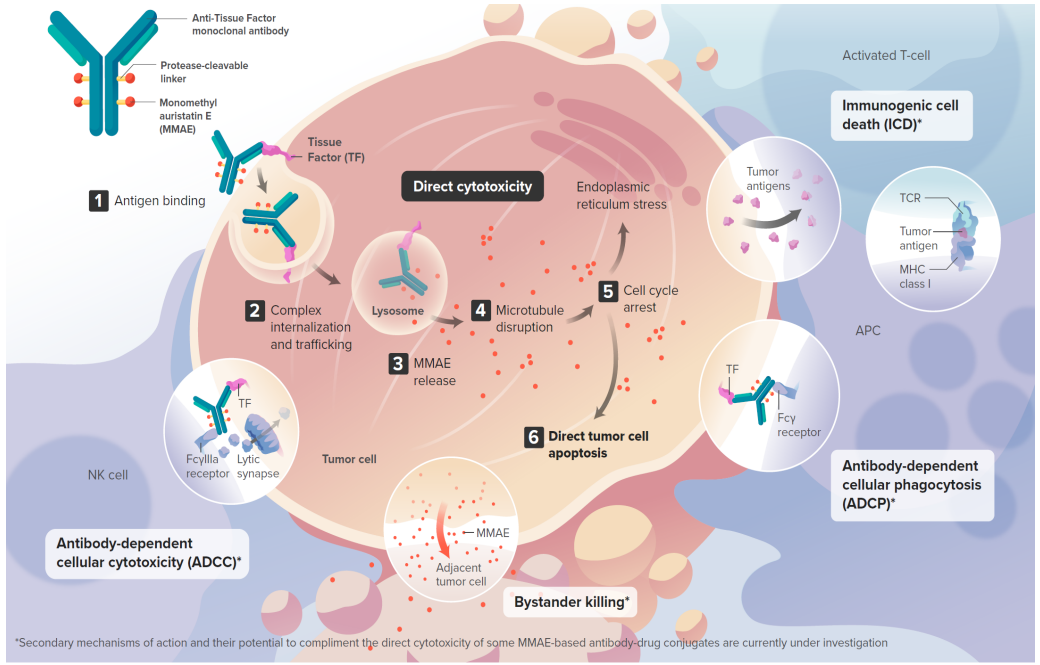
Recurrent Cervical Cancer: Tisotumab Vedotin (TV)

- Tissue factor ADC
  - Highly expressed in cervix cancer
  - Involved in progression and metastases

Linker
Protease-cleavable val-citrulline maleimidocaproyl linker
Conjugated to monoclonal antibody via cysteine residues

Fully human mAb
Targets tissue factor

Cytotoxic payload
Monomethyl auristatin E (MMAE), a microtubule-disrupting agent
Drug-to-antibody ratio of approximately 4:1



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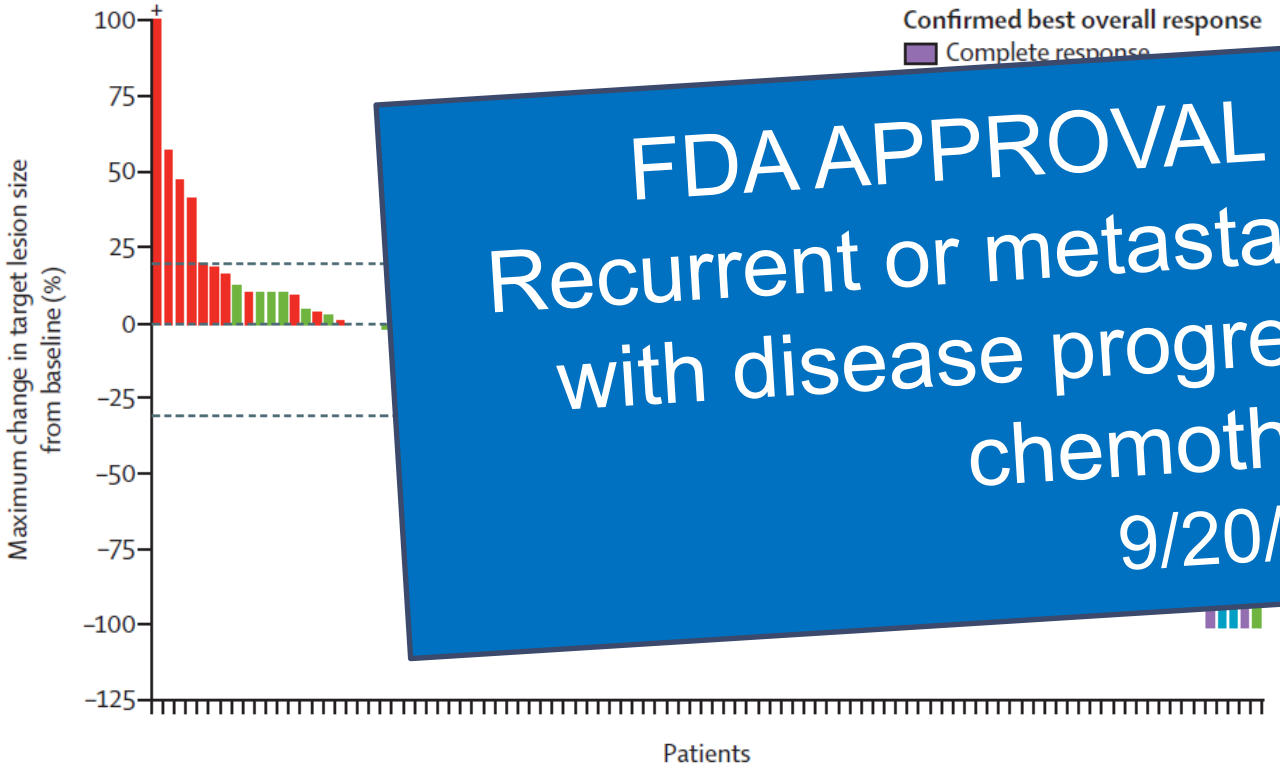
Cocco E. BMC Cancer 2011. Coleman R. Lancet Oncol 2021.

TV: Phase 2 study

- Recurrent (2L+) cervical cancer



FDA APPROVAL (accelerated): Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy 9/20/21

Response rates (IRC)	(N=101)
ORR (95% CI), %	**24 (16-33)**
CR, No. (%)	7 (7)
	17 (17)
	49 (49)
	24 (24)
	4 (4)
	72 (63-81)
	8.3 (4.2-NR)
Median time to response (IQR), mo	1.4 (1.3-1.5)
Median PFS (95% CI), mo	4.2 (3.0-4.4)
Median OS (95% CI), mo	12.1 (9.6-13.9)

UCLA Health

Coleman R. Lancet Oncol 2021.

InnovaTV301: Tisotumab vedotin

Key Eligibility Criteria

- Recurrent or metastatic cervical cancer
- Disease progression on or after chemotherapy doublet ± bevacizumab and an anti-PD-(L)1 agent, if eligible and available
- ≤2 prior lines
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

Stratified by:

- **ECOG PS (0 vs 1)**
- **Prior bevacizumab (yes vs no)**
- **Prior anti-PD-(L)1 therapy (yes vs no)**
- **Geographic region (US, Europe, Other)**

Treatment

1:1

N=502

Tisotumab Vedotin (n=253)

2.0 mg/kg IV Q3W

IC Chemotherapy (n=249)

- Topotecan
- Vinorelbine
- Gemcitabine
- Irinotecan
- Pemetrexed

Outcomes/Endpoints

Primary Endpoint

- OS

Key Secondary Endpoints

- PFS
- ORR
- Safety

Patient Characteristics	Tisotumab	IC Chemo
Squamous cell carcinoma	63.2%	63.1%
1 prior regimen	62.8%	59.8%
Prior bevacizumab	64.8%	63.1%
Prior anti PD(L)1	28.1%	26.9%

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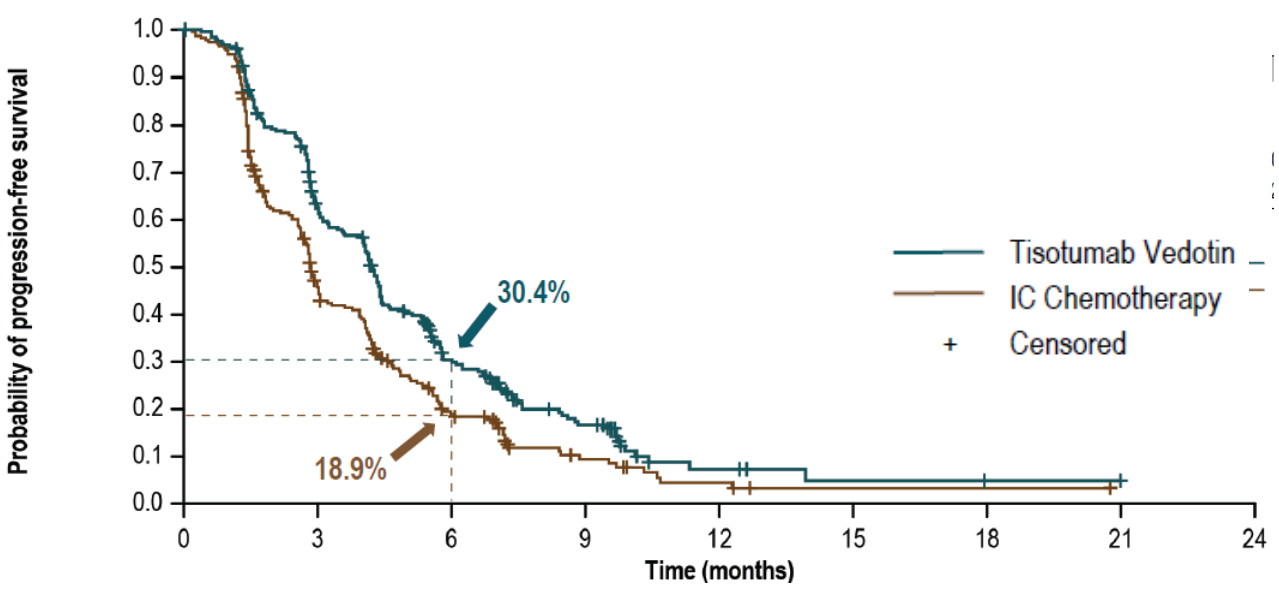
Vergote I. ESMO 2023.

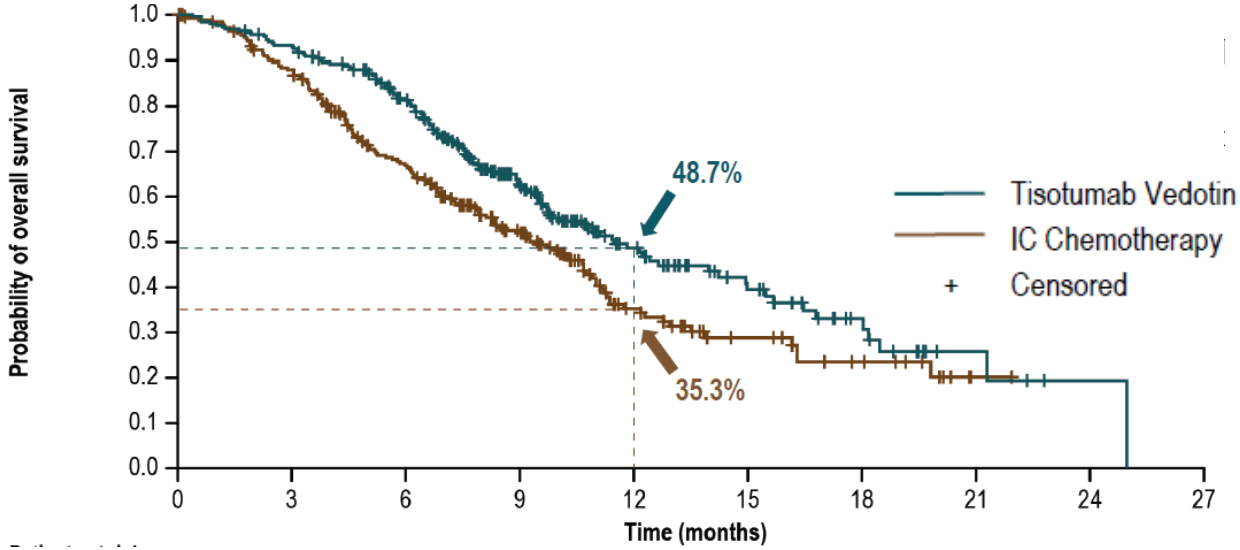
InnovaTV301: Survival Outcomes

Progression Free Survival



	mPFS (95% CI)	HR (95% CI)	P value
TV	**4.2** (4.0-4.4)	**0.67** (0.54-0.82)	<0.0001
Chemo	**2.9** (2.6-3.1)		

Overall Survival



	mOS (95% CI)	HR (95% CI)	P value
TV	**11.5** (9.8-14.9)	**0.70** (0.54-0.89)	0.0038
Chemo	**9.5** (7.9-10.7)		

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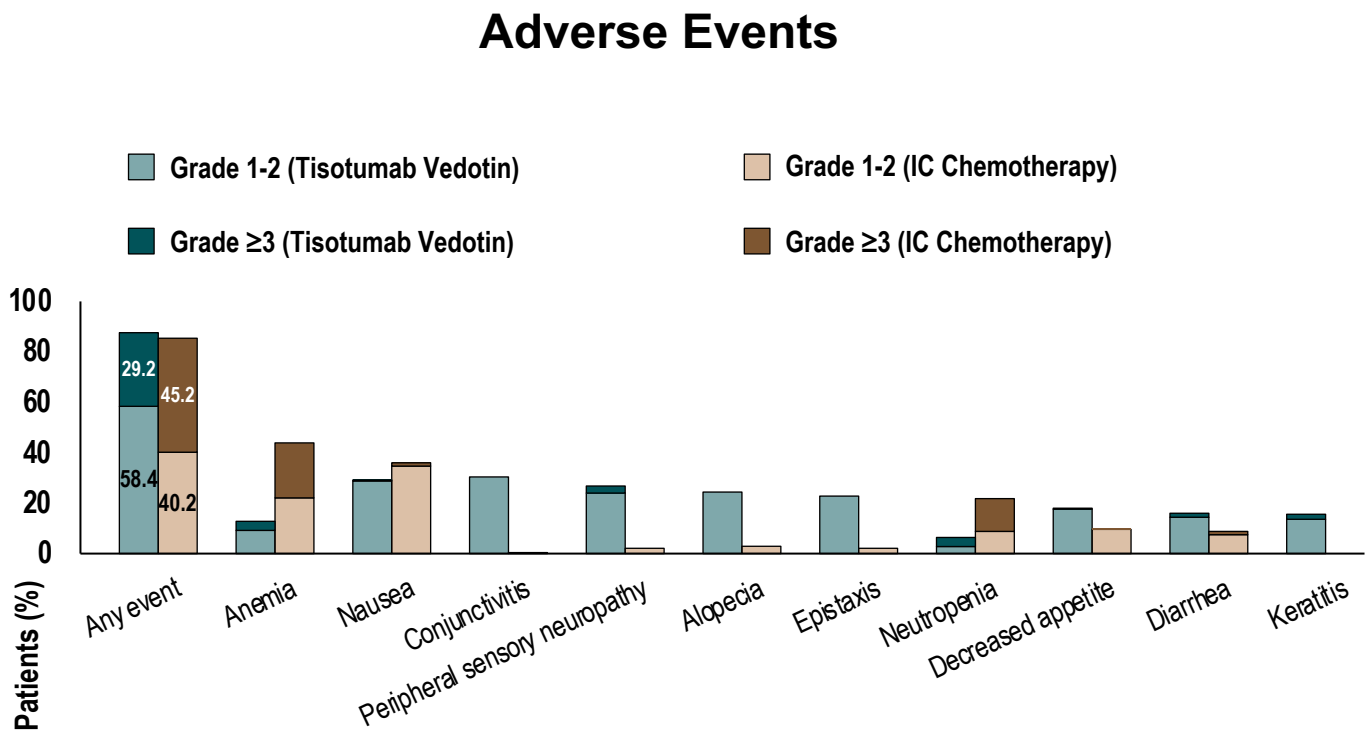
Vergote I. ESMO 2023.

InnovaTV301: Outcomes

	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI) P value	4.0 (2.1-7.6) p<0.0001	
Best Response, n (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
DCR, % (95% CI)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
Median DOR (95% CI)	5.3 (4.2-8.3)	5.7 (2.8-NR)



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Ongoing Trials

Immunotherapy Combinations
Tisotumab + Pembrolizumab
TILs (LN-145)**
DNA Vaccines
GX-188E + Pembrolizumab
VB10.16 + Atezolizumab**

**Prior checkpoint inhibitor therapy

Endometrial Cancer

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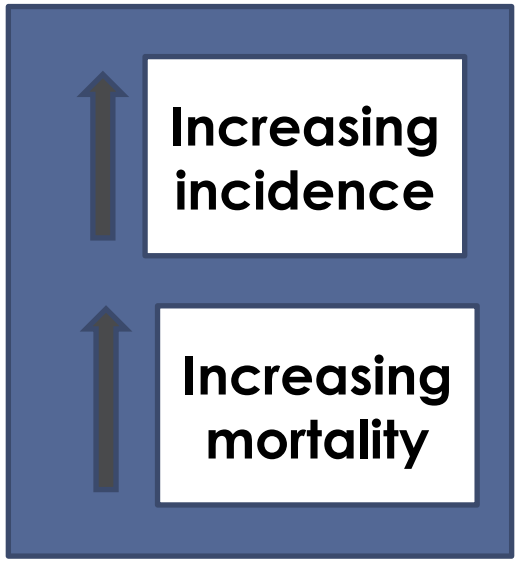
Overview of Endometrial Cancer

- Estimated 66,200 new cases (3.4% of all cancers)
  - ~70% are diagnosed in early stages
  - ~1/3 are diagnosed with high grade or advanced disease
    - This is the population of interest
- Estimated 13,030 deaths

Only gynecologic malignancy with an increasing incidence and mortality



Siegel et al, 2023.

Biomarkers in Endometrial Cancer

Immunologically responsive

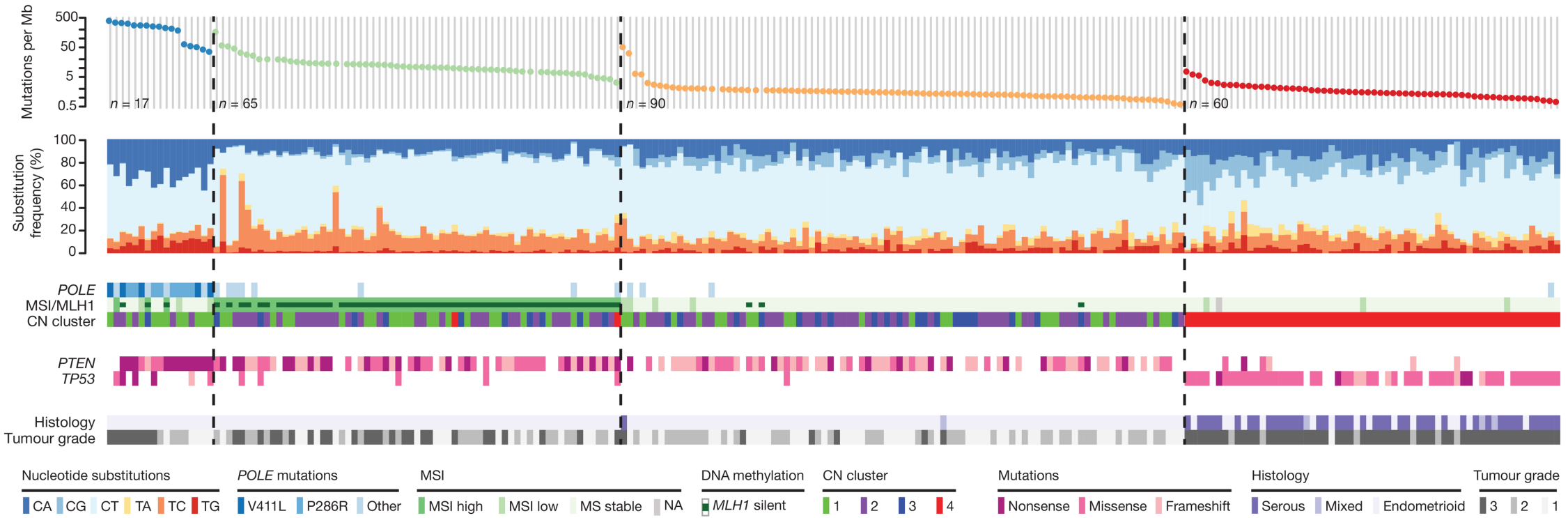
Immunologically non-responsive

1. *POLE* **(ultramutated)**

2. MSI **(hypermutated)**

3. Copy-number low **(endometrioid)**

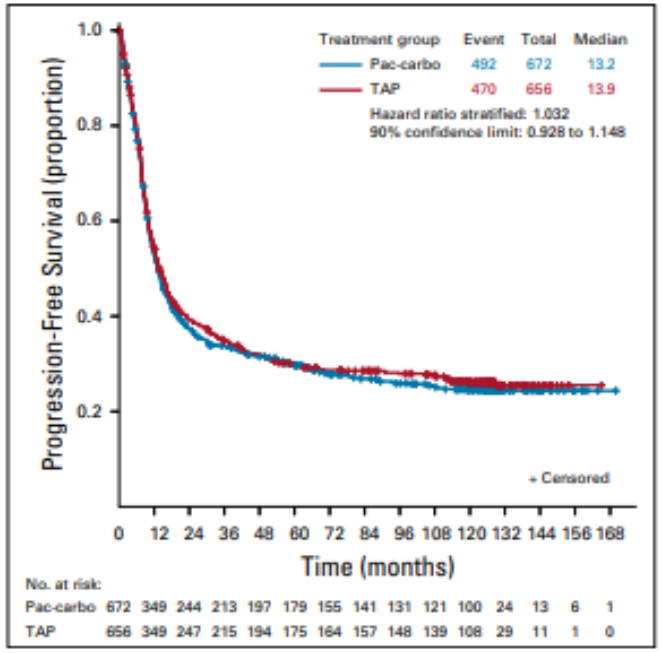
4. Copy-number high **(serous-like)**

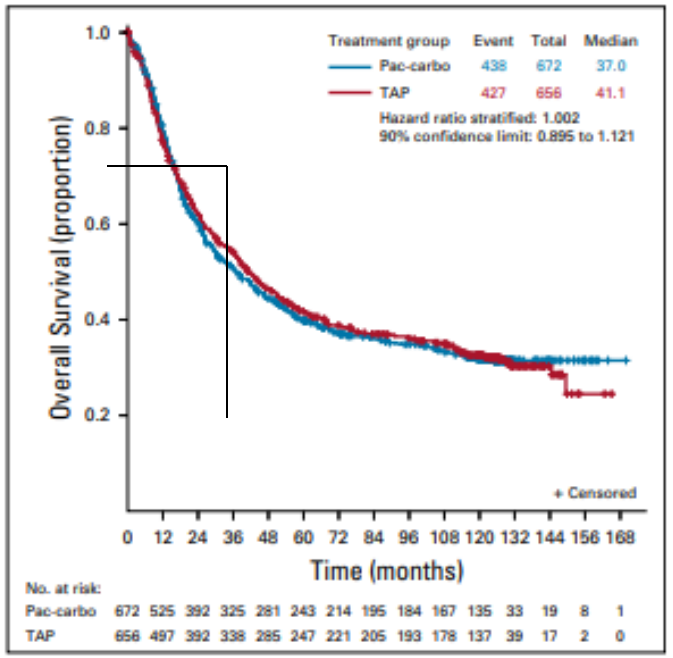


MSI, microsatellite instability. Levine et al, 2013.

Advanced/Recurrent Endometrial Cancer

- 2000's: Chemotherapy has been standard of care
- 2010: Carboplatin and paclitaxel became the preferred regimen
  - Recurrence rates and median PFS ~8 months





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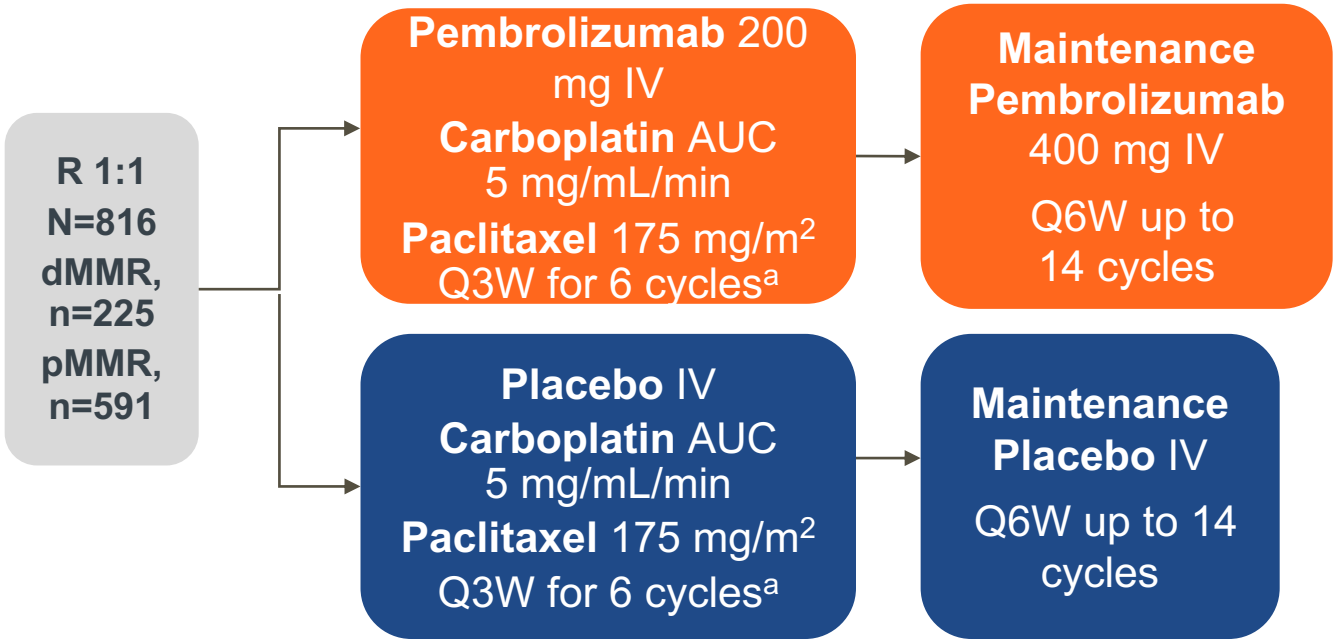
Miller DS J Clin Oncol 2020.

GY018 (KEYNOTE 868): Study Schema

Eligible patients

- Histologically confirmed recurrent or advanced (stage III, IVA, or IVB) EC
- ECOG PS of 0-2
- Results of institutional MMR IHC testing
- Submission of tumor specimens for centralized MMR IHC testing
- No prior chemotherapy treatment for EC
- Prior adjuvant chemotherapy allowed if completed ≥12 months before enrollment



Primary end point: PFS (IA)

Secondary end points: AEs, ORR, DOR, OS, QOL, concordance between institutional MMR IHC and centralized MMR IHC

Stratification

- MMR status
- ECOG PS (0, 1 or 2)
- Prior chemotherapy (yes/no)

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Eskander RN. N Engl J Med. 2023.

GY018: Patient Characteristics

Patient Characteristics, n (%)		dMMR (n=225)		pMMR (n=588)	
		Pembro + CT (n=112)	Placebo + CT (n=113)	Pembro + CT (n=293)	Placebo + CT (n=295)
Median age (range), years		67 (38-81)	66 (37-85)	66 (31-93)	65 (29-90)
ECOG PS	0	72 (64.3)	73 (64.6)	196 (66.9)	198 (67.1)
	1	39 (34.8)	35 (31.0)	88 (30.0)	88 (29.8)
	2	1 (0.9)	5 (4.4)	9 (3.1)	9 (3.1)
Histology					
Clear cell		1 (0.9)	0	17 (5.8)	20 (6.8)
Endometrioid, G1		21 (18.8)	35 (31.0)	54 (18.4)	46 (15.6)
Endometrioid, G2		52 (46.4)	41 (36.3)	51 (17.4)	58 (19.7)
Endometrioid, G3		15 (13.4)	16 (14.2)	53 (18.1)	42 (14.2)
Serous		4 (3.6)	1 (0.9)	78 (26.6)	72 (24.4)
No prior chemotherapy		107 (95.5)	105 (92.9)	221 (75.4)	218 (73.9)

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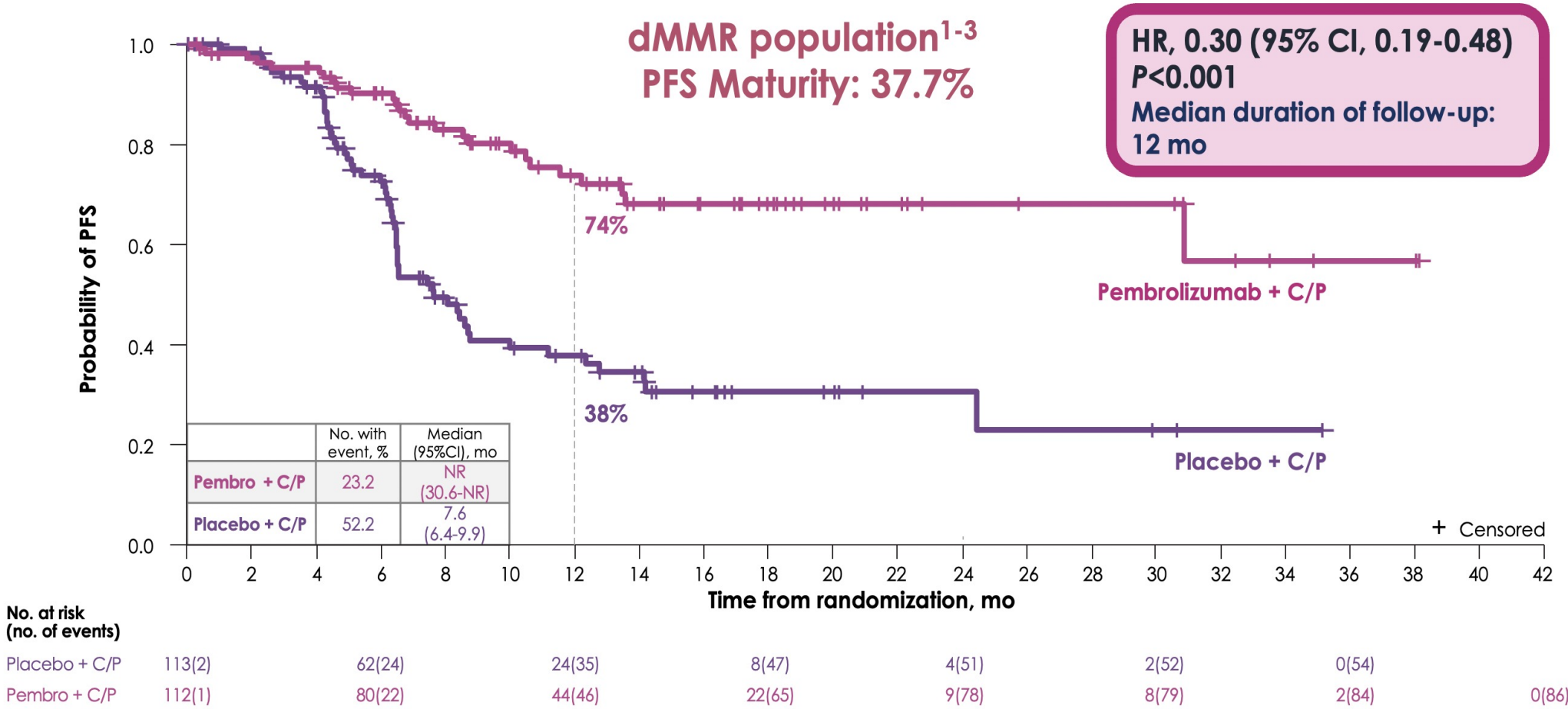
Eskander RN. N Engl J Med. 2023.

GY018 PFS dMMR



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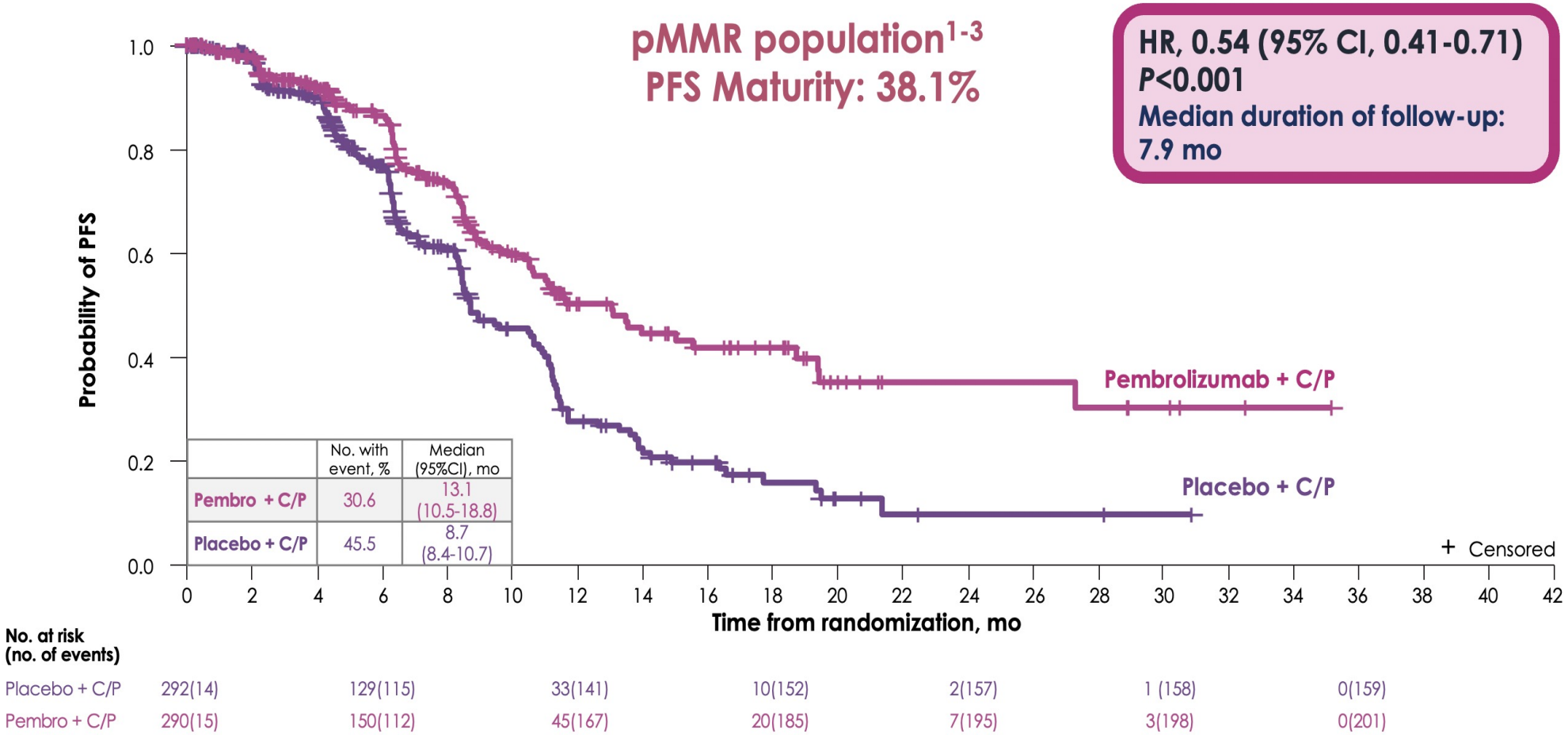
Eskander RN. N Engl J Med. 2023.

GY018: PFS pMMR



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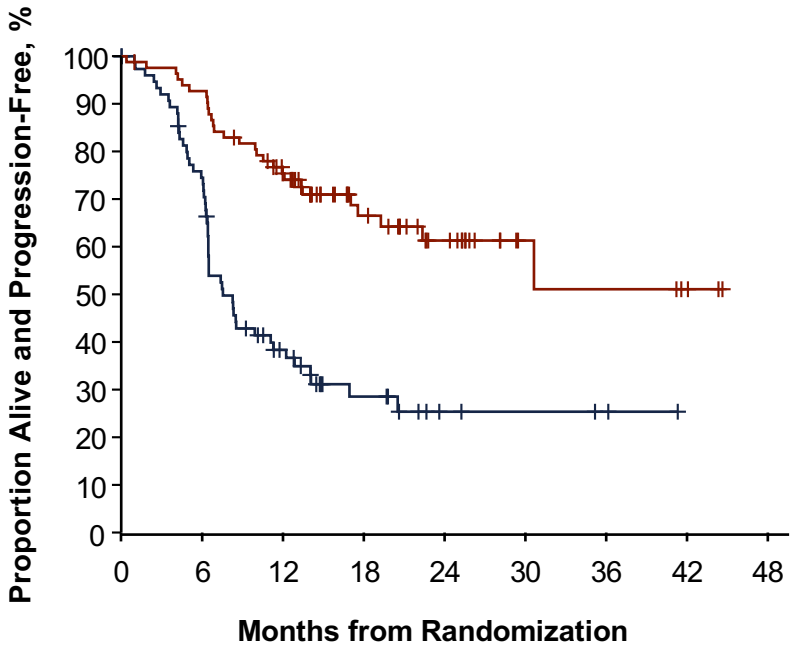
Eskander RN. N Engl J Med. 2023.

GY018: PFS by Methylation Status

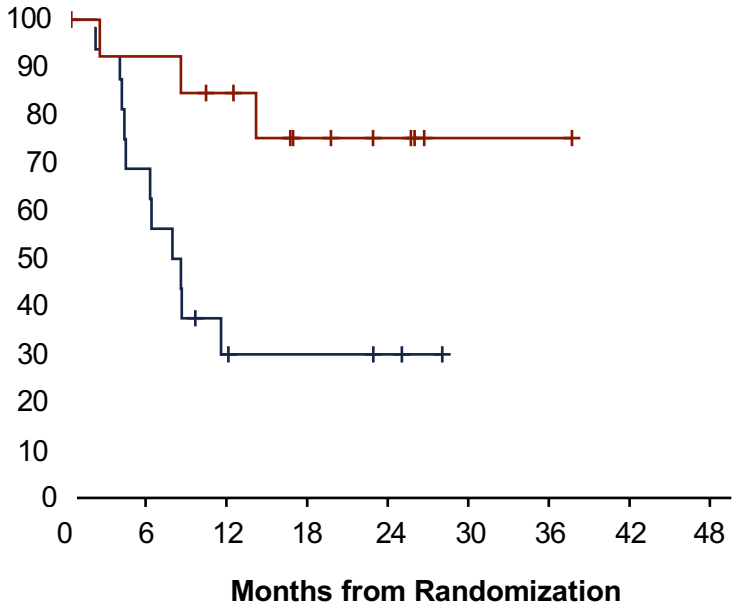
Methylation

	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)	



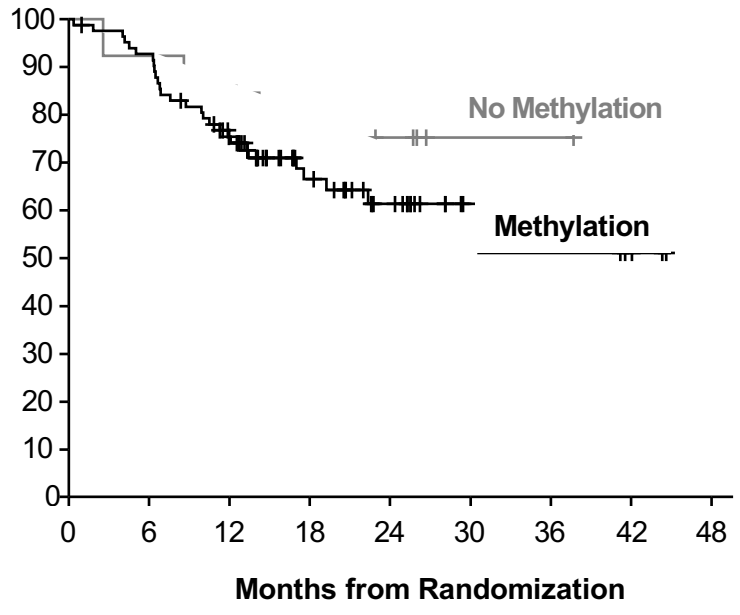
No Methylation

	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)	



Methylation Status

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



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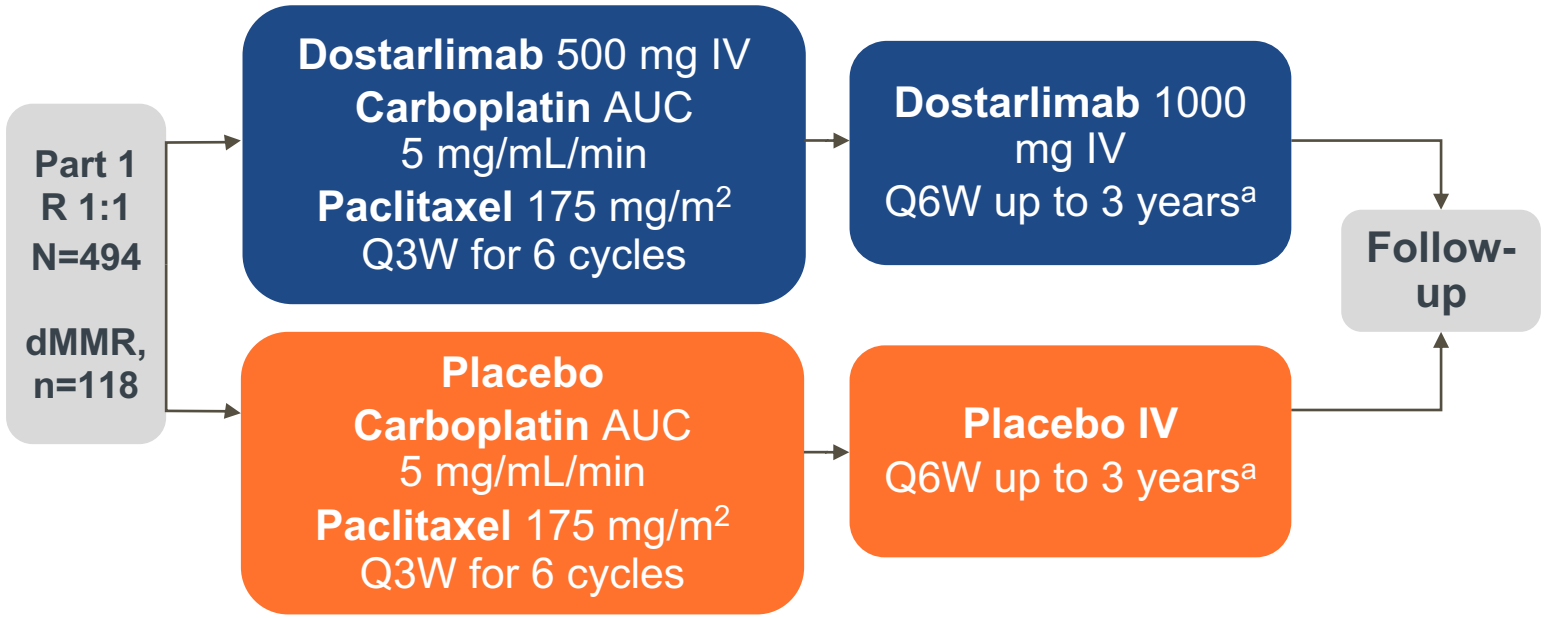
Eskander RN. ESMO 2023.

RUBY: ENGOT-en6/GOG 3031

Eligible patients

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



Primary end points: PFS (IA), OS

Secondary end points: PFS (BICR), PFS2, ORR/DOR/DCR, QOL, PK and immunogenicity, safety

Stratification

- MMR/MSI status
- Prior radiotherapy
- Disease status

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Mirza M. NEJM 2023.

RUBY: Patient Characteristics

Patient Characteristics n(%)		dMMR/MSI-H		Overall	
		Dostarlimab + CP (n=53)	Placebo + CP (n=65)	Dostarlimab + CP (n=245)	Placebo + CP (n=249)
Median age (range), years		61 (45-81)	66 (39-85)	64 (41-81)	65 (28-85)
ECOG PS	0	28 (53.8)	39 (60.0)	145 (60.2)	160 (65.0)
	1	24 (46.2)	26 (40.0)	96 (39.8)	86 (35.0)
Histology					
Clear cell		0	0	8 (3.3)	9 (3.6)
Carcinosarcoma		4 (7.5)	1 (1.5)	25 (10.2)	19 (7.6)
Endometrioid		44 (83.0)	56 (86.2)	134 (54.7)	136 (54.6)
Prior systemic therapy		7 (13.2)	10 (15.4)	48 (19.6)	52 (20.9)
Carboplatin/paclitaxel		4 (7.5)	6 (9.2)	36 (14.7)	39 (15.7)
Measurable disease at baseline		49 (92.5)	58 (89.2)	212 (86.5)	219 (88.0)

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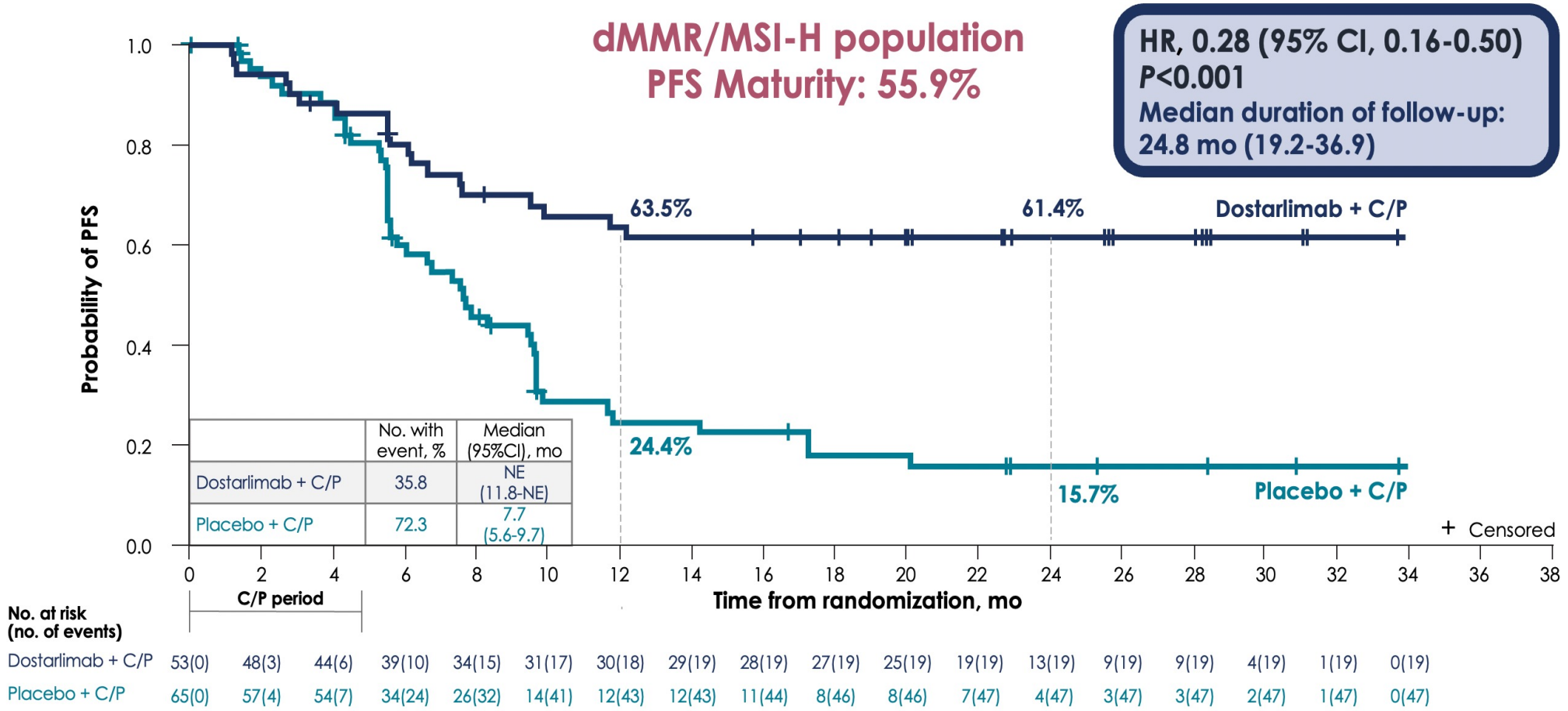
Mirza M. NEJM 2023.

RUBY: PFS dMMR



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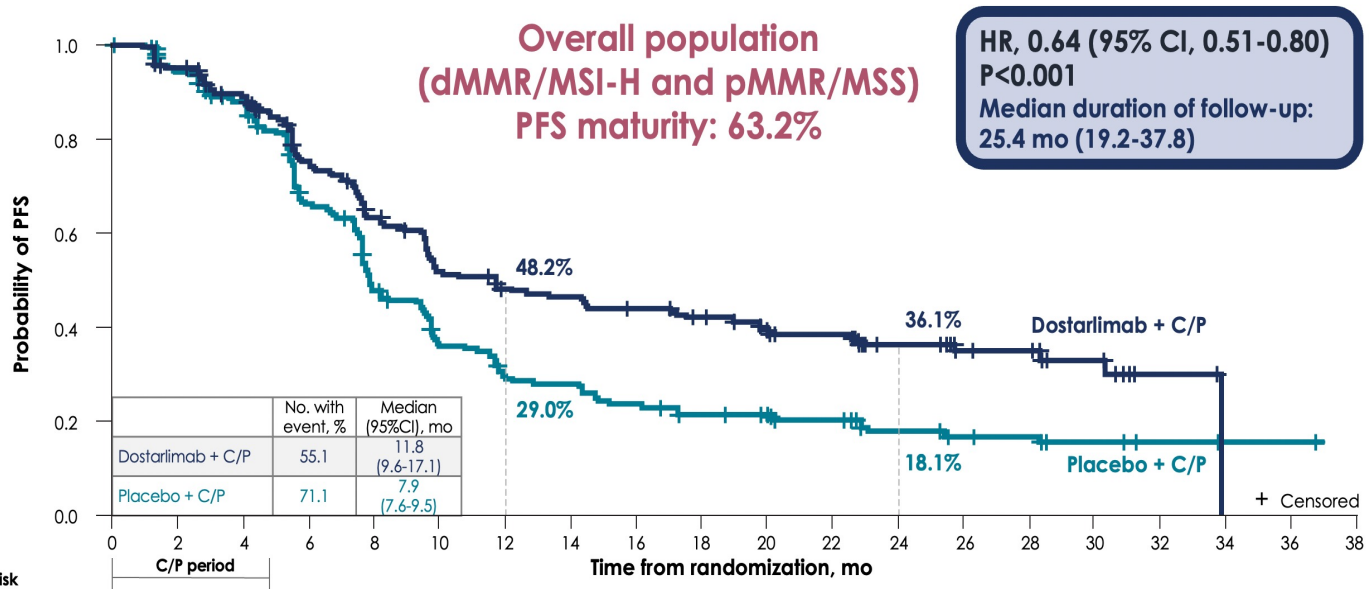
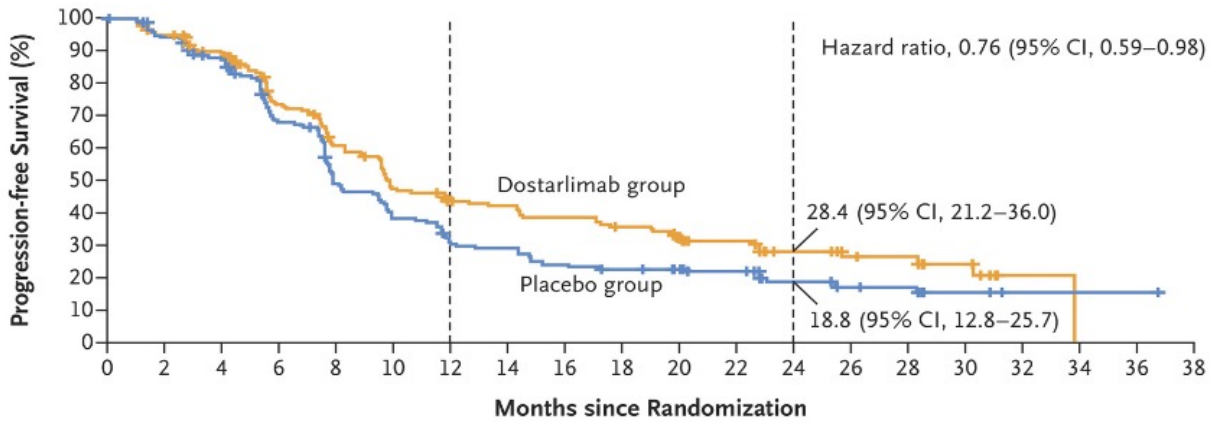
Mirza M. NEJM 2023.

RUBY: PFS ITT and pMMR



PFS pMMR



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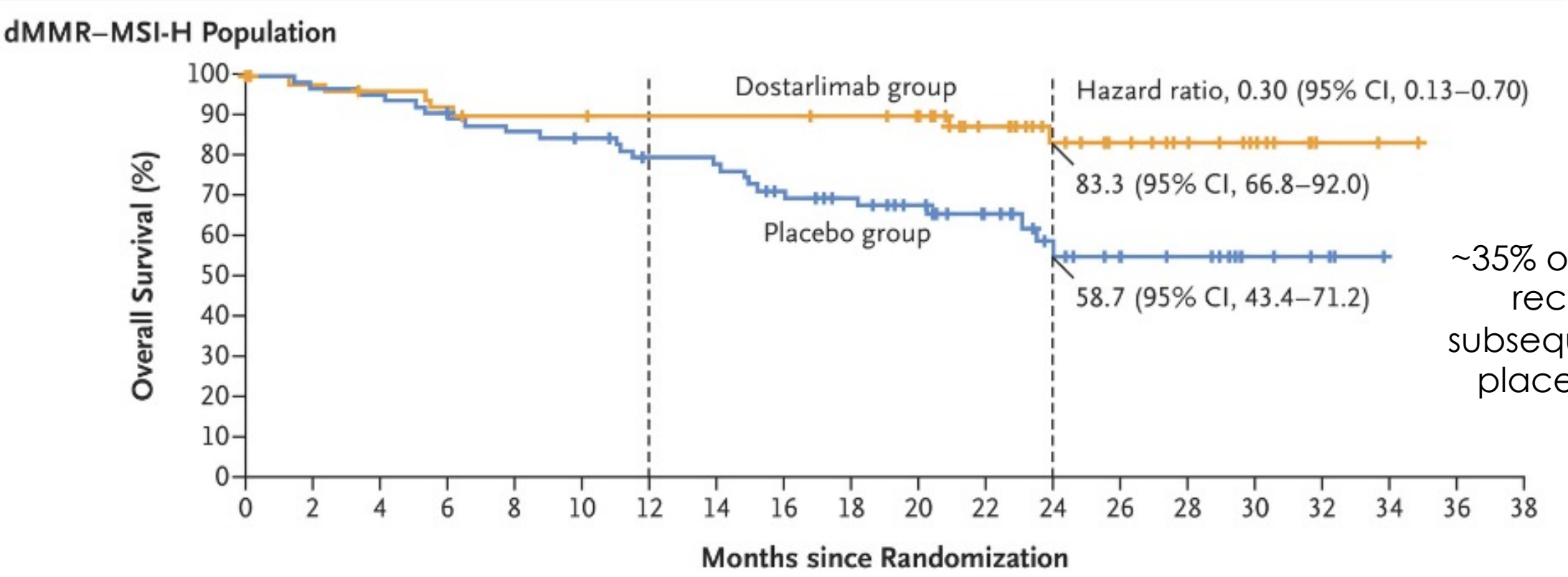
Mirza M. NEJM 2023.

RUBY Trial: OS dMMR

FDA approval in dMMR population on 7/31/2023



~35% of patients received subsequent IO in placebo arm

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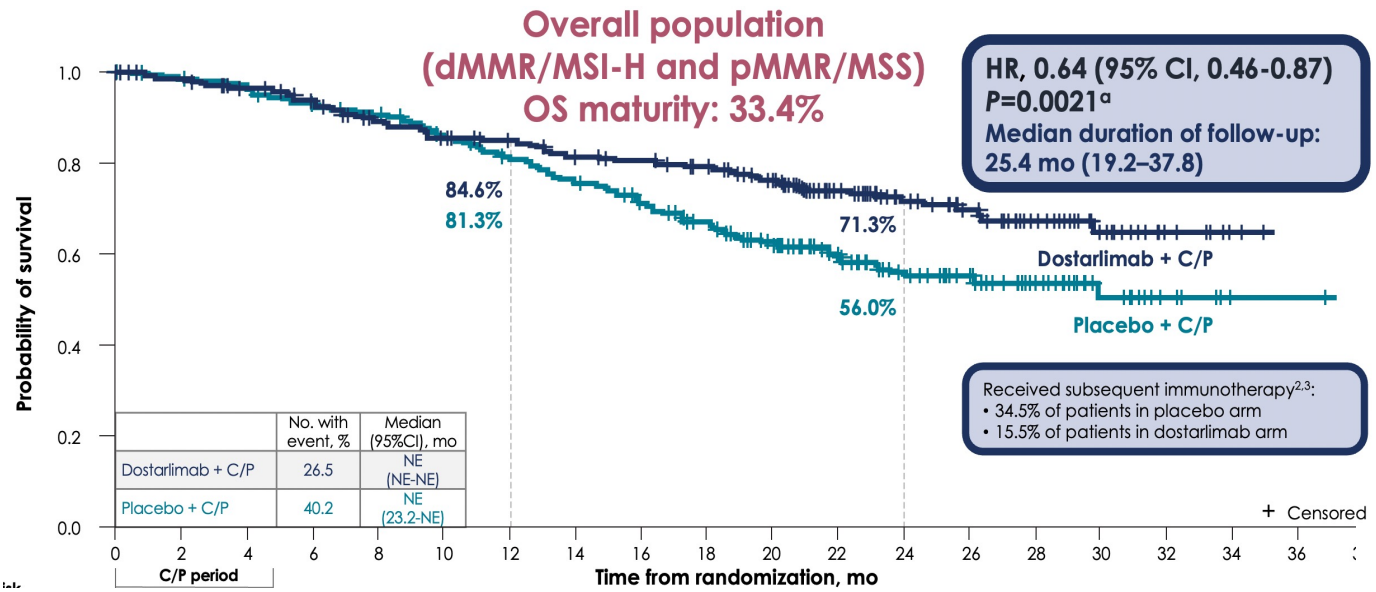
RUBY OS ITT and pMMR

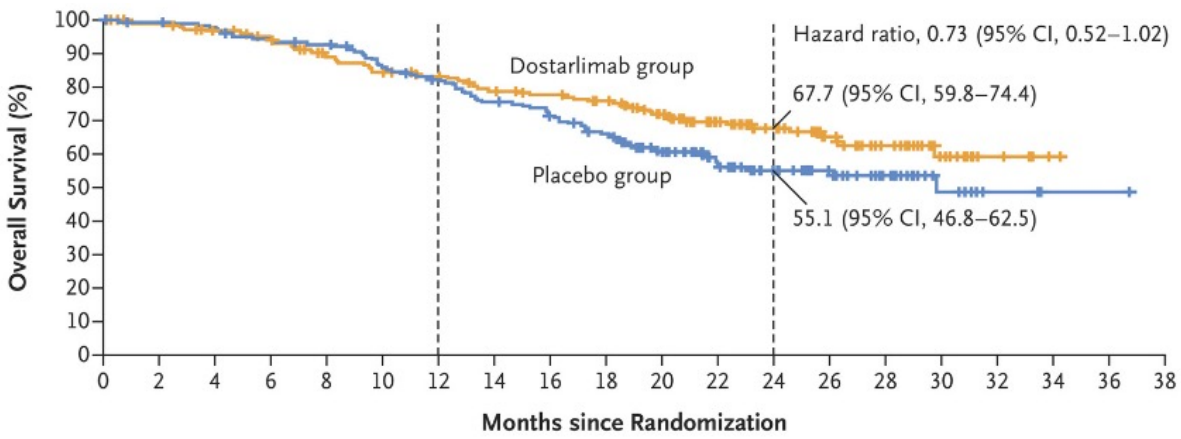


Issued: 30 October 2023, London UK

Phase III RUBY trial of *Jemperli* (dostarlimab) plus chemotherapy meets endpoint of overall survival in patients with primary advanced or recurrent endometrial cancer

- Statistically significant and clinically meaningful overall survival benefit observed in the overall population in the trial
- Dostarlimab plus chemotherapy is the only immuno-oncology combination regimen to show an overall survival benefit in this patient population

pMMR overall survival



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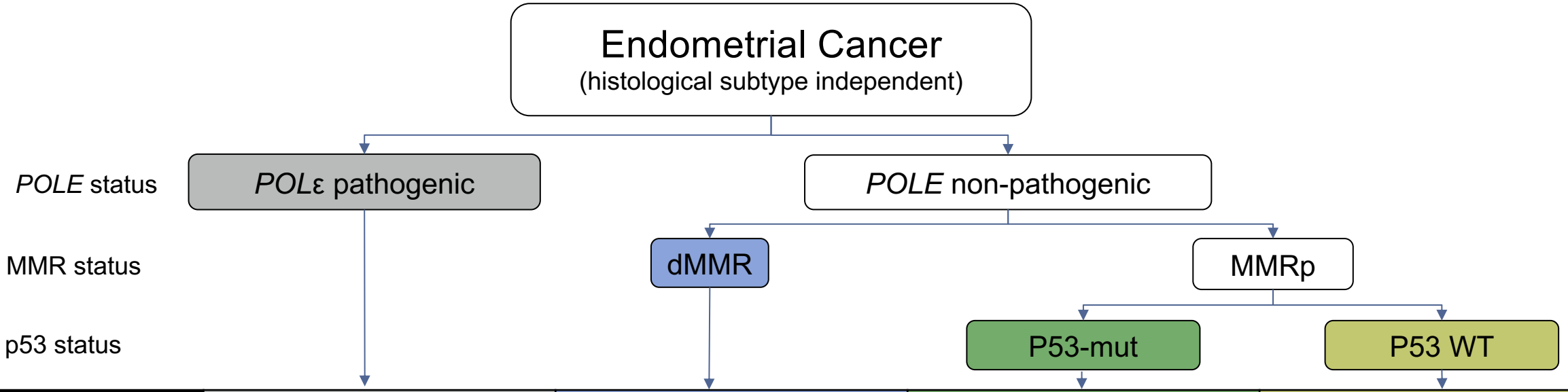
RUBY: Molecular Subgroups

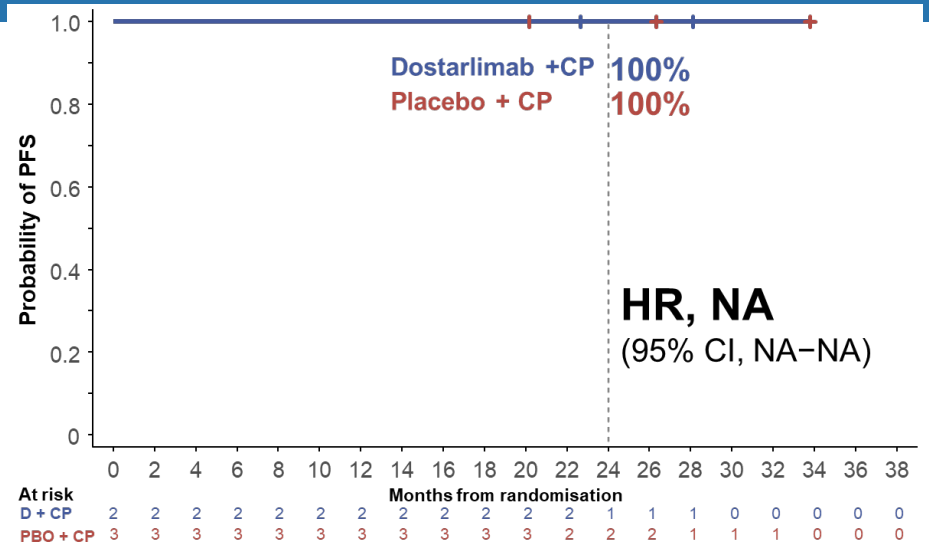


Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

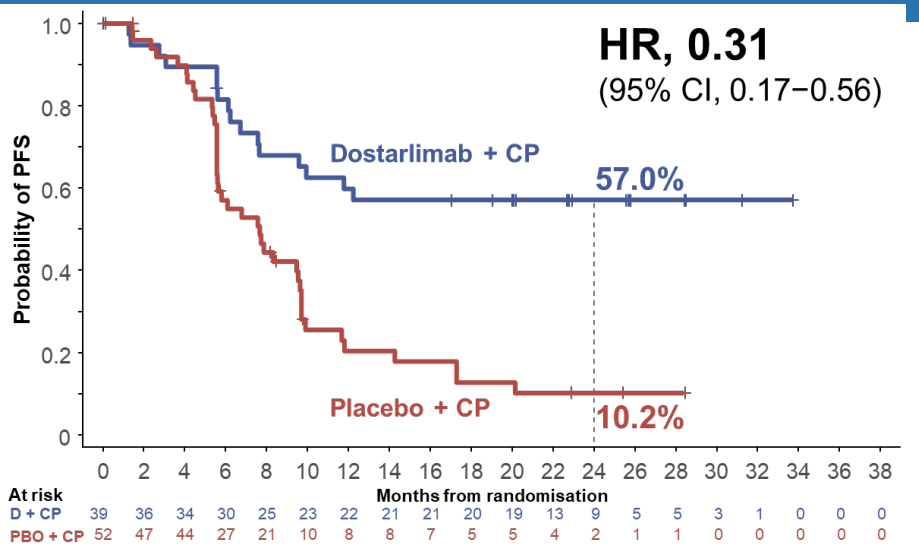
Mirza M. ESMO 2023.

RUBY: PFS Molecular Subgroups

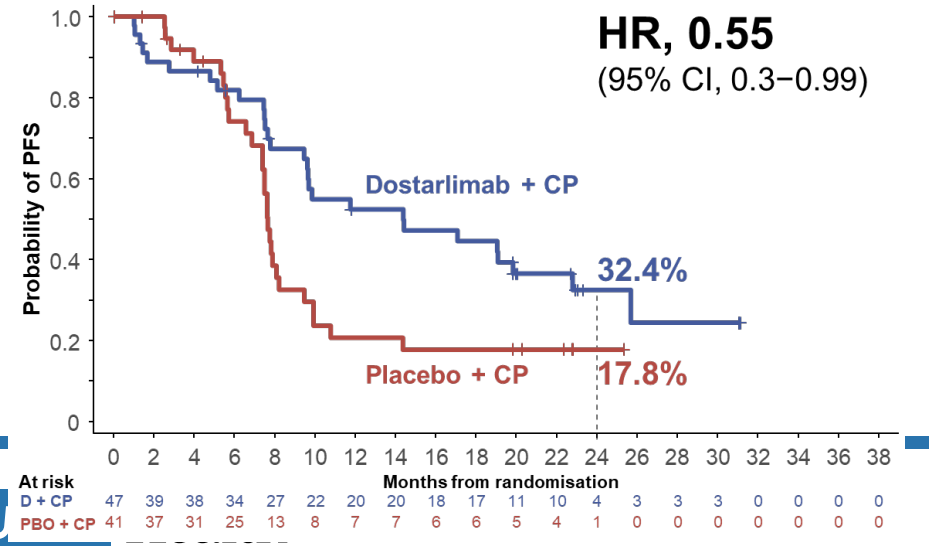
POLε mut



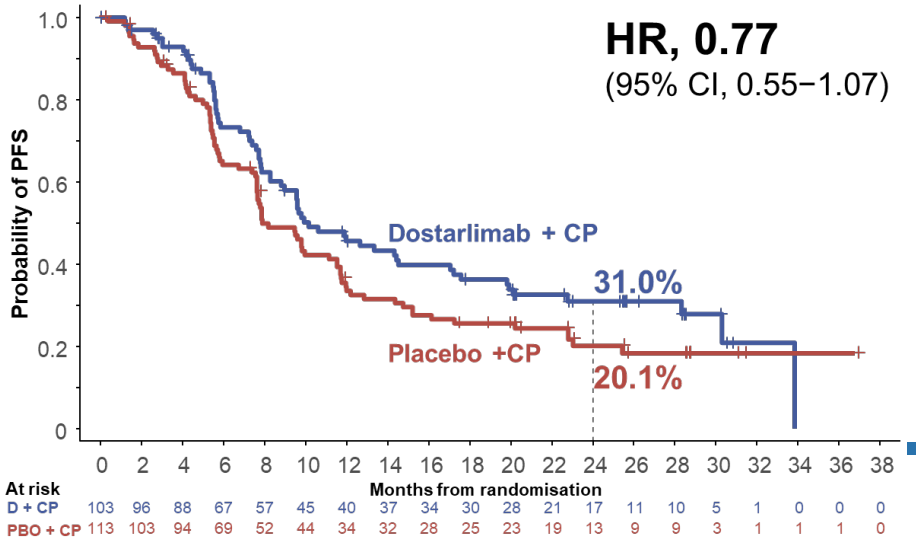
dMMR/MSI-H



TP53 mut



NSMP



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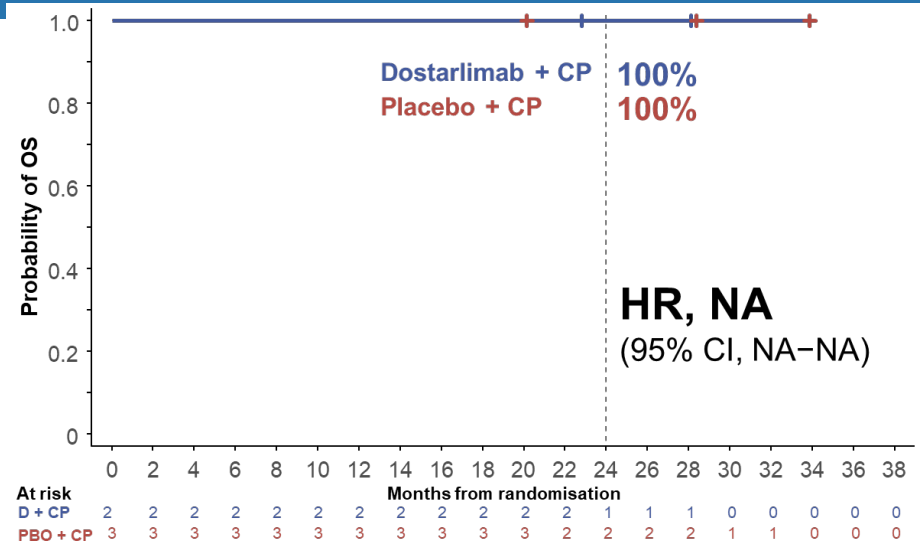
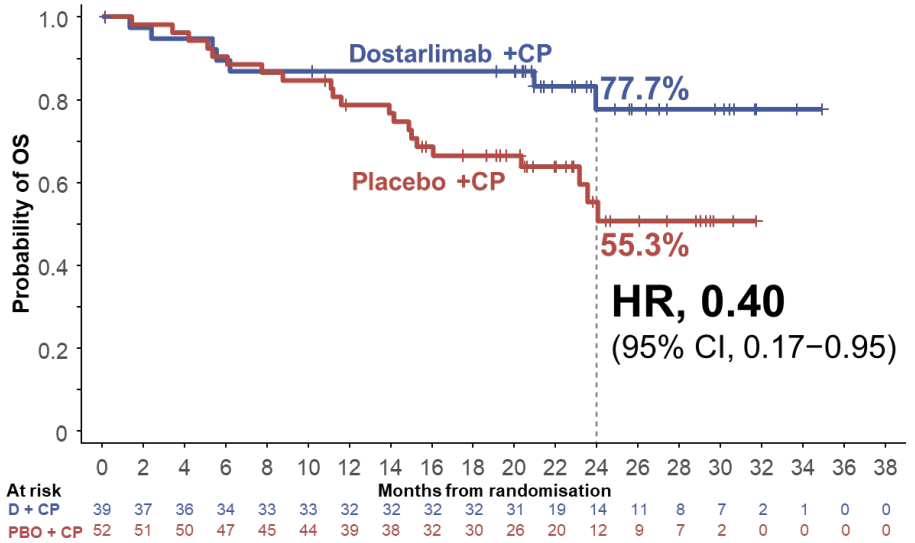
RUBY: OS Molecular Subgroups

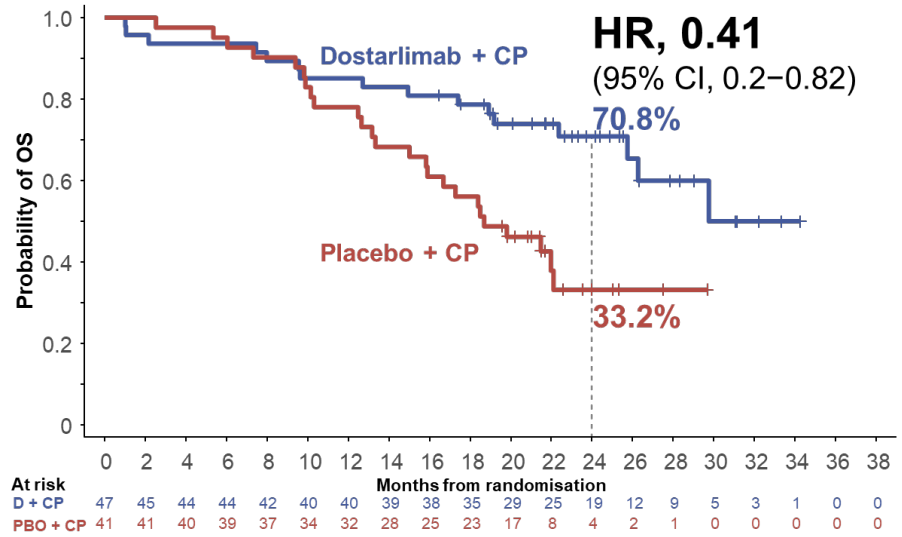
POLε mut



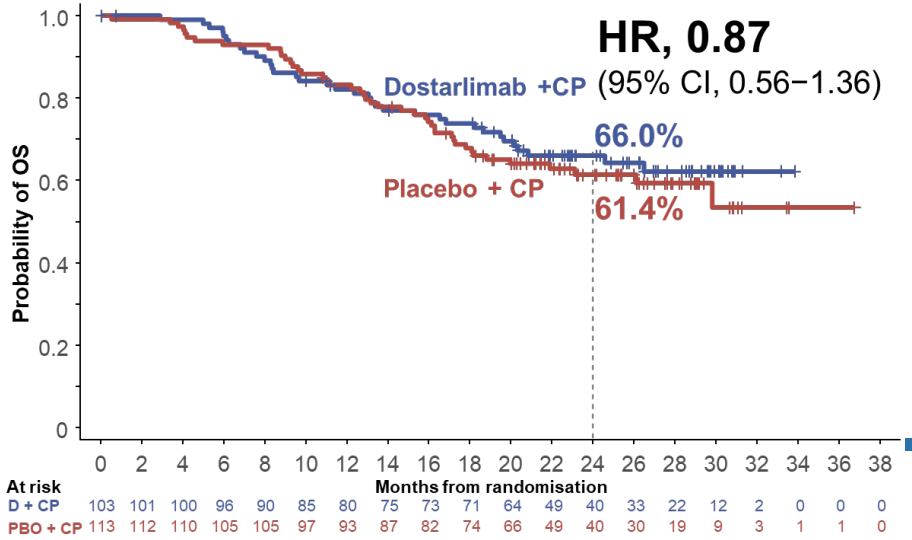
dMMR/MSI-H



TP53 mut



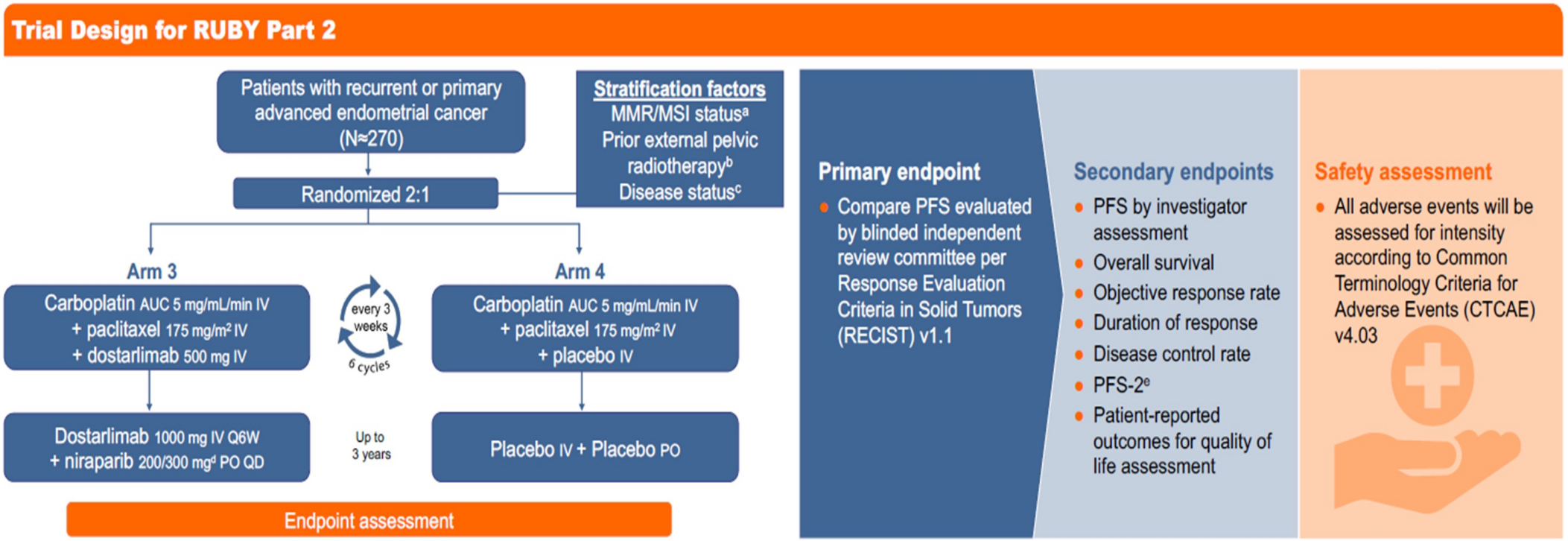
NSMP



Mirza M. ESMO 2023.

The Role of PARPi: RUBY Part 2

Multi-center Phase 3 study that will evaluate the efficacy and safety of DOSTARLIMAB + carboplatin-paclitaxel followed by DOSTARLIMAB + NIRAPARIB



[a]MMR/MSI status: dMMR/MSI-H or MMRp/MSS; [b]Prior external pelvic radiotherapy: yes or no; [c]Disease status: recurrent, primary stage III, or primary stage IV; [d]Niraparib dosing is 200 mg PO QD for patients with baseline BW <77 kg or PC <150,000/μL or 300 mg QD for patients with baseline BW ≥77 kg and PC ≥150,000/μL; [e]PFS-2 is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever is earlier.

AUC, area under the curve; BW, body weight; dMMR, mismatch repair deficient; IV, intravenously; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatelite stable; PC, platelet count; PFS, progression-free survival; PO, by mouth; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily.

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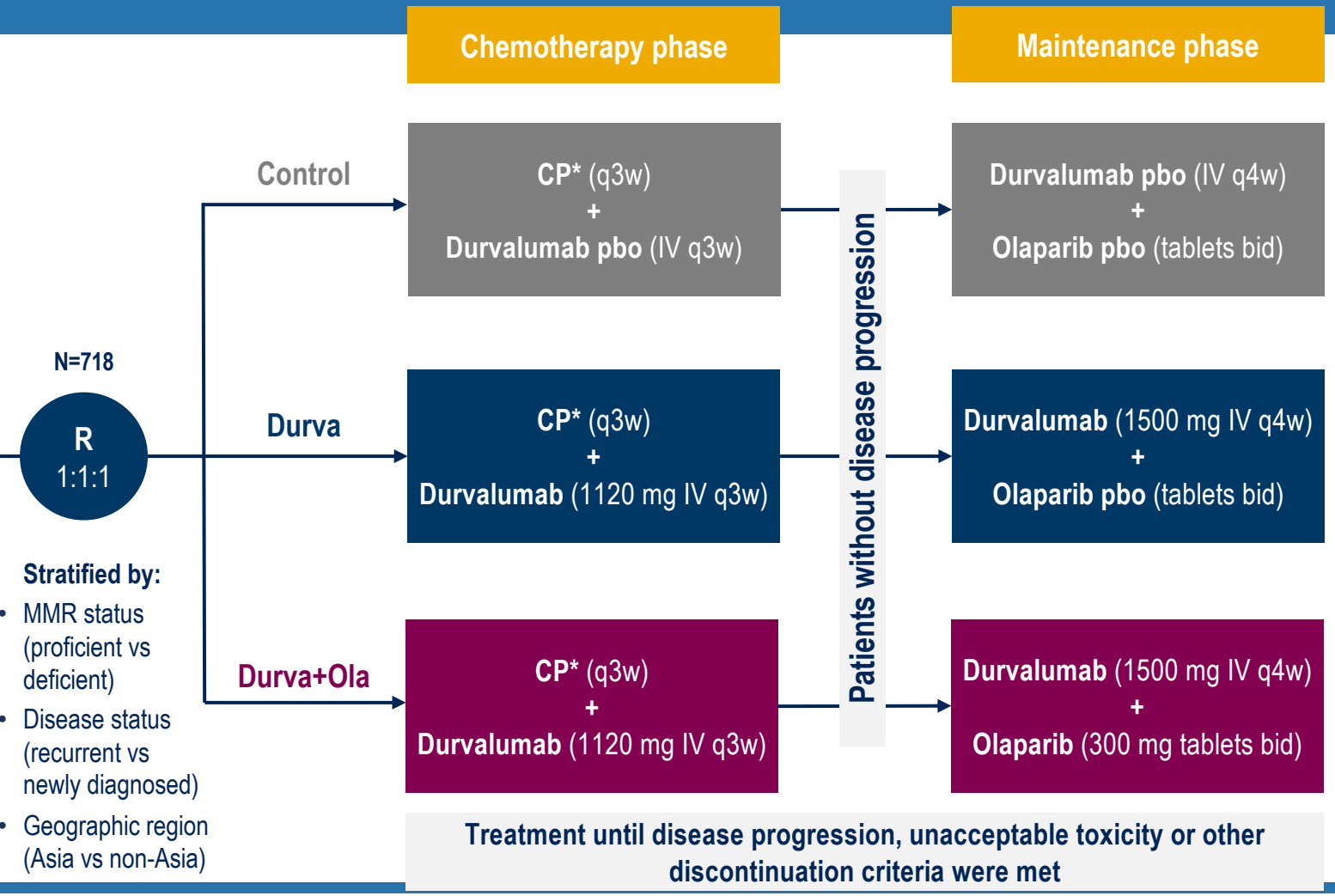
clinicaltrials.gov:01244789.

DUO-E: Study Schema

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, HRRm

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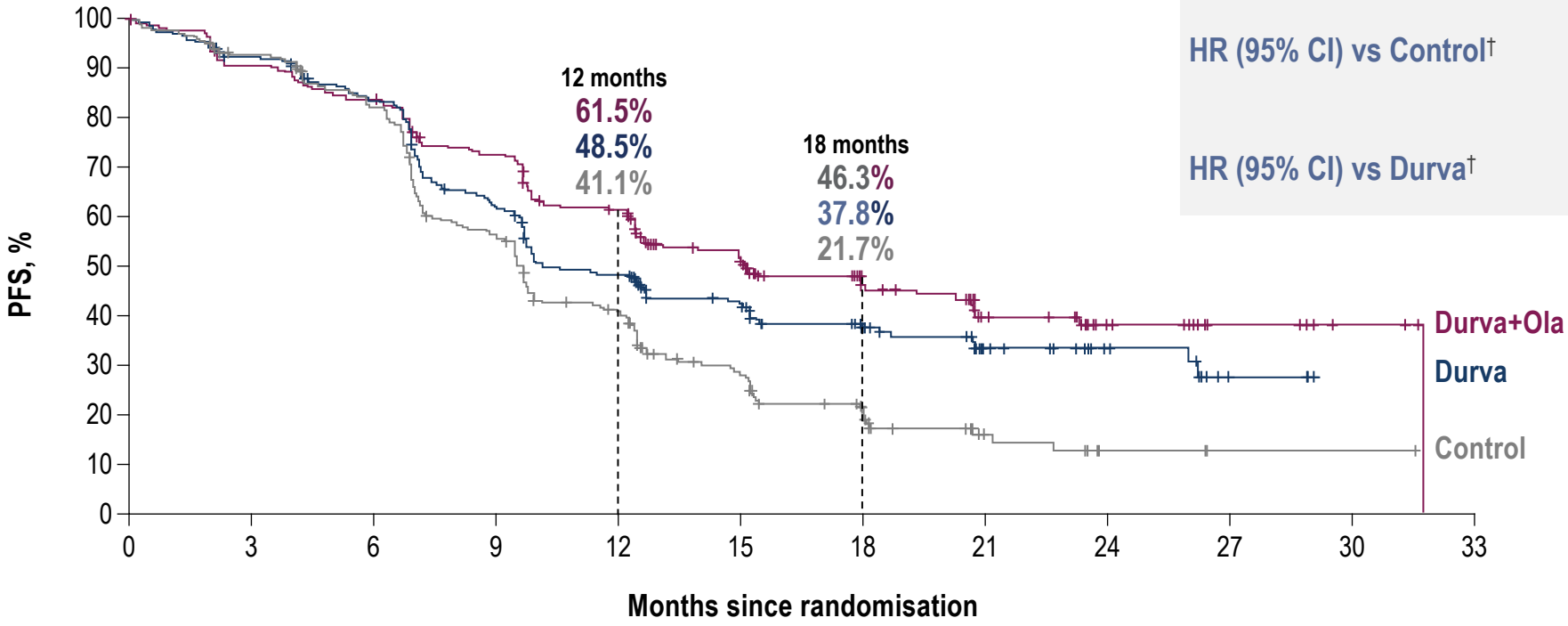
Westin S. ESMO 2023.

DUO-E: 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%

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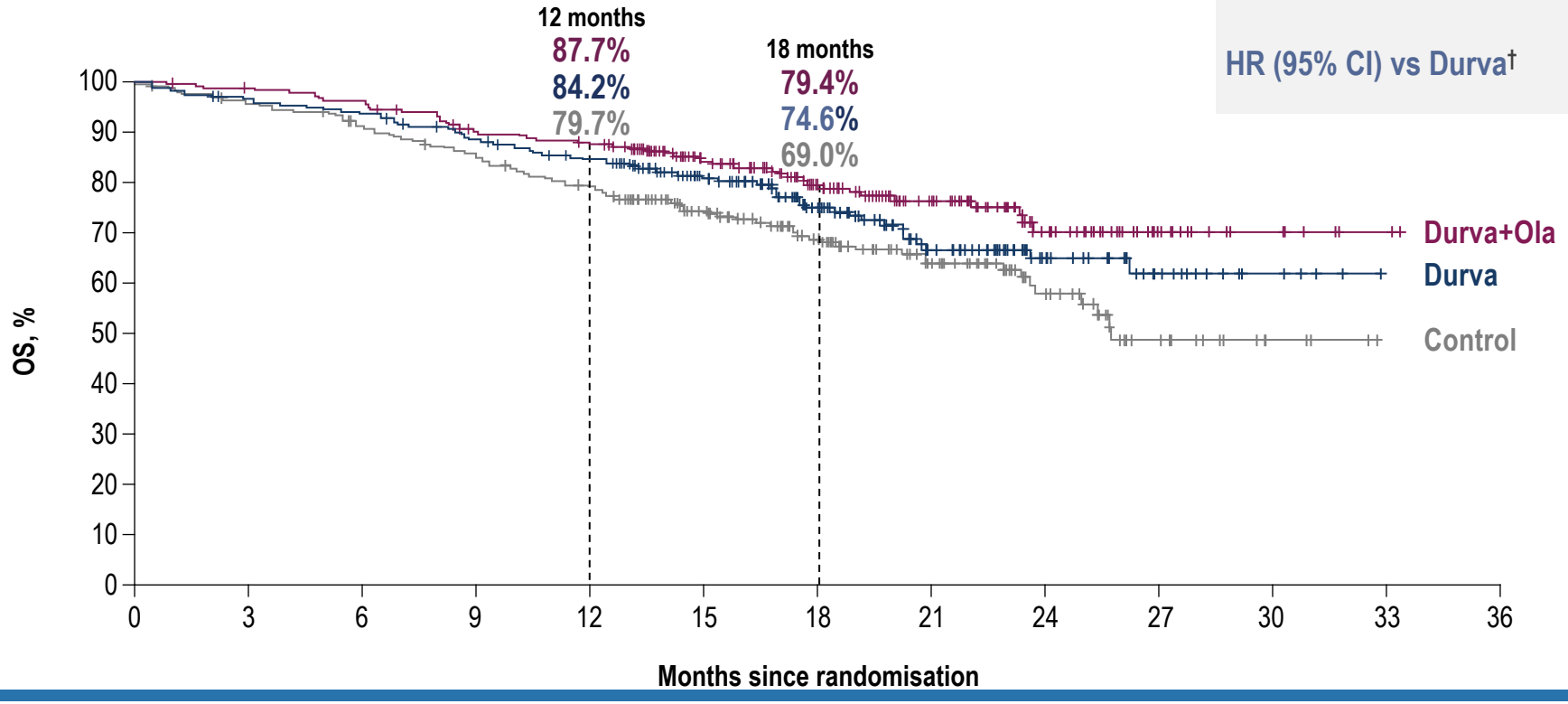
Westin S. ESMO 2023.

DUO-E OS: ITT Population

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	82 (34.0)	65 (27.3)	52 (21.8)
Median OS (95% CI),* months	25.9 (23.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs Control†		**0.77** (0.56–1.07); *P*=0.120	**0.59** (0.42–0.83); *P*=0.003
HR (95% CI) vs Durva†			**0.77** (0.53–1.10)

Overall data maturity 27.7%



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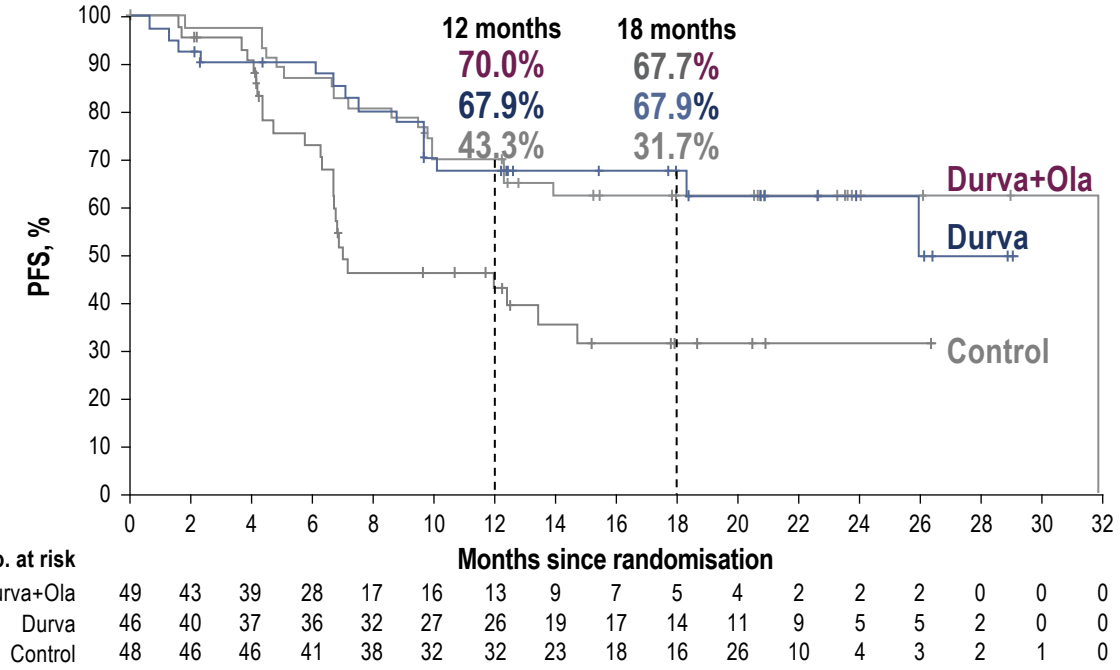
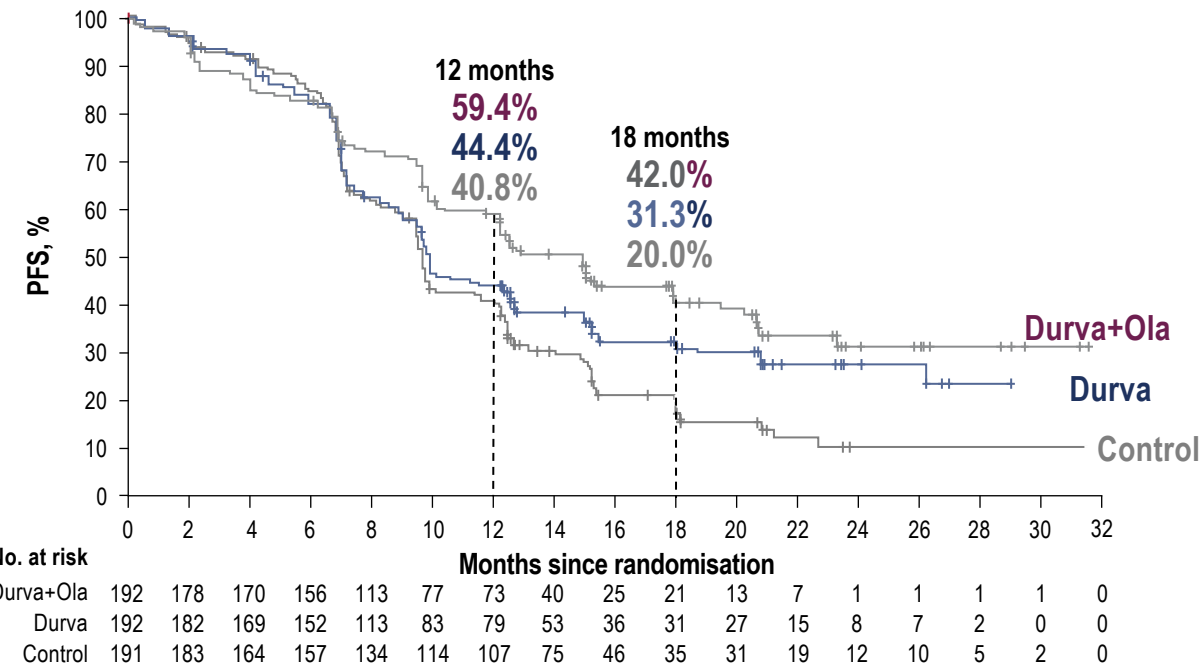
DUO-E: Subgroup Analysis of PFS by MMR Status

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)**

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Ongoing Trials: Is Chemotherapy Necessary?

	Pembrolizumab KEYNOTE-C93	Dostarlimab DOMENICA	Lenvatinib/Pembrolizumab LEAP-001
Study treatment	▪ Pembrolizumab 400 mg IV q6w for 18 cycles (2 years) ▪ Carboplatin AUC 5 or 6 mg/mL/min IV q3w + paclitaxel 175 mg/m^2 IV q3w for 6 cycles (with option for >6 cycles)	▪ Dostarlimab 500 mg q3w (cycles 1-4) then dostarlimab 1000 mg q6w (for up to 2 years) ▪ Carboplatin AUC 5-6 + paclitaxel 175 mg/m² q3w (for 6 cycles)	▪ Lenvatinib 20 mg orally qd + pembrolizumab 200 mg IV q3w ▪ Carboplatin AUC 6 IV q3w + paclitaxel 175 mg/m^2 IV q3w
Key eligibility criteria	▪ dMMR status ▪ Stage III/IV or recurrent EC including carcinosarcoma Radiographically evaluable disease (measurable or nonmeasurable per RECIST v1.1) ▪ No prior systemic therapy ▪ ECOG PS 0-1	▪ dMMR/MSI-H status ▪ Stage IIIC2/IV disease or first recurrence ▪ Prior neo/adjuvant chemotherapy allowed if ≥6 months from last treatment to relapse ▪ All histologic subtypes of endometrial adenocarcinoma included ▪ ECOG PS 0-1	▪ Stage III-IV or recurrent EC ▪ Prior adjuvant Chemo ≥6 months before study ▪ ECOG 0-1

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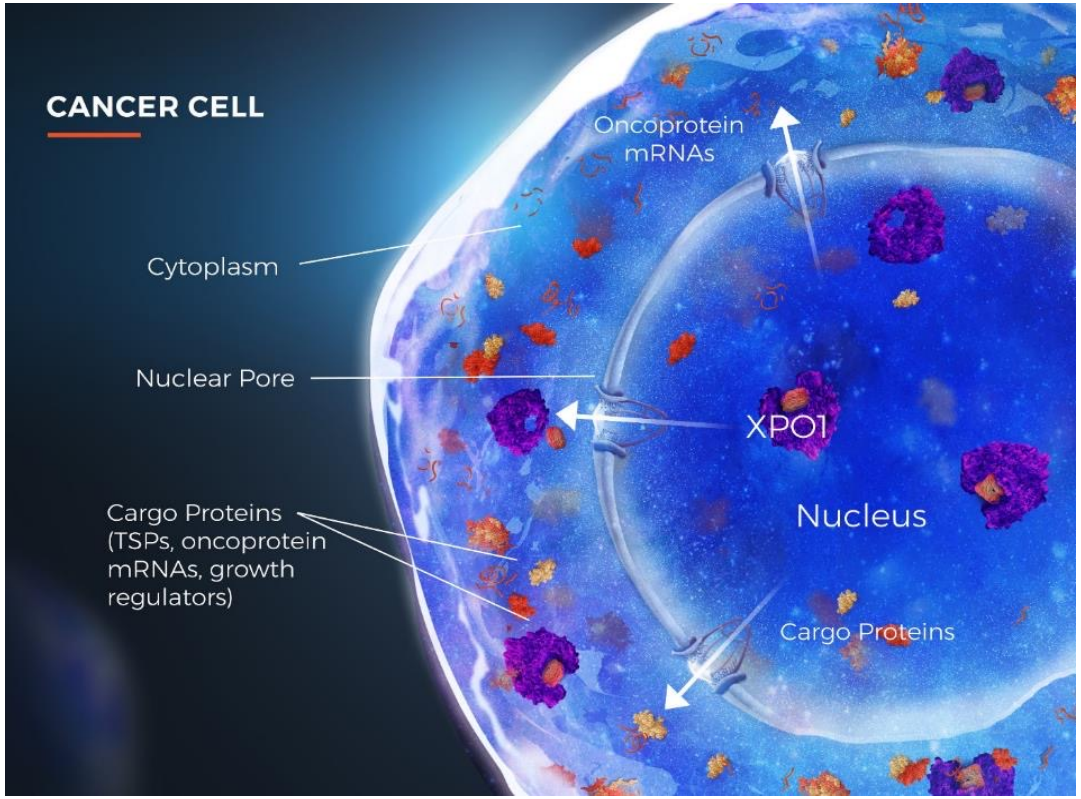
ClinicalTrials.gov.

Maintenance Therapy?

- XPO1 exports major tumor suppressor proteins away from nucleus
  - Overexpressed in caner cells
- Selinexor
  - Stabilizes p53 in nucleus
  - Results in selective killing of cancer cells



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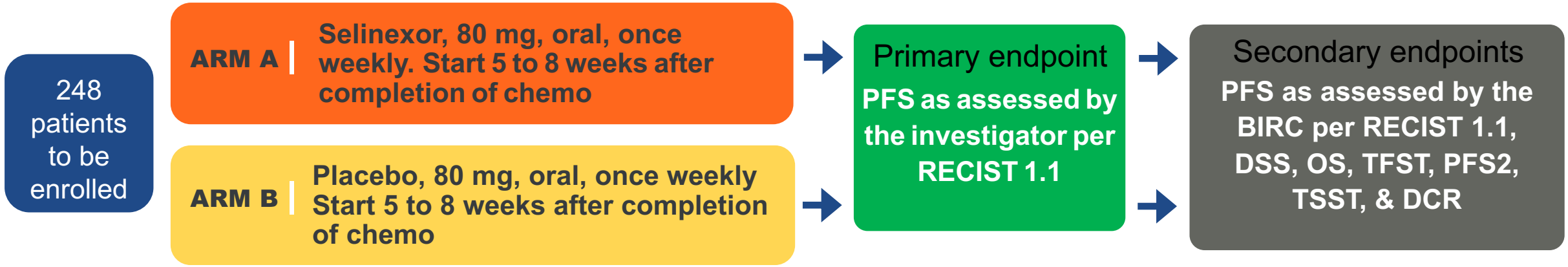
Vergote I. J Clin Oncol 2023.

SIENDO Trial: Selinexor

Randomized, Double-blinded, Phase 3 Trial of Maintenance with Selinexor/Placebo After Combination Chemotherapy for Participants with Advanced or Recurrent EC



KEY INCLUSION CRITERIA:

- Histological confirmed endometrial cancer of the endometrioid, serous, or undifferentiated type. Carcinosarcoma of the uterus is also allowed.
- Completed a single line of at least 12 weeks of taxane-platinum combination therapy (not including adjuvant or neoadjuvant therapy), and achieved partial or complete remission (PR or CR) according to RECIST version 1.1 for:
  - Primary Stage IV disease, OR
  - At first relapse (i.e., relapse after primary therapy including surgery and/or chemotherapy therapy for Stage I-IV disease).
- Must be able to initiate study drug 5 to 8 weeks after completion of their final dose of chemotherapy.

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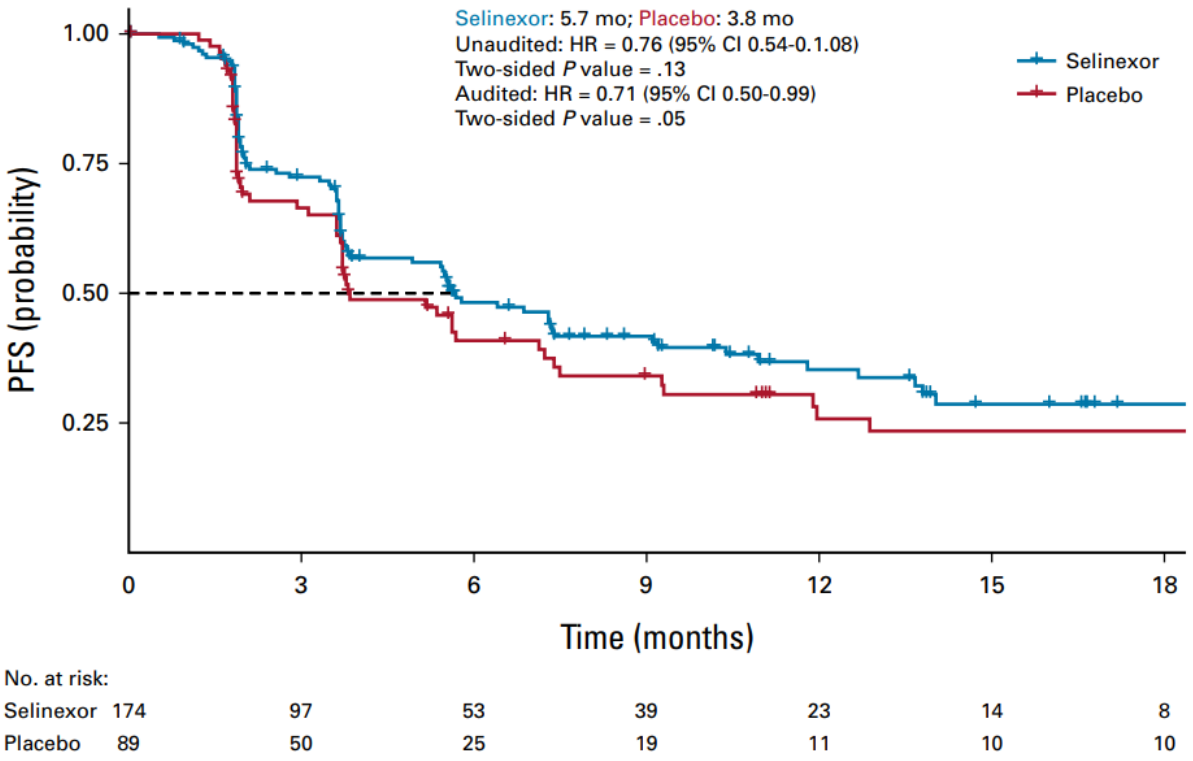
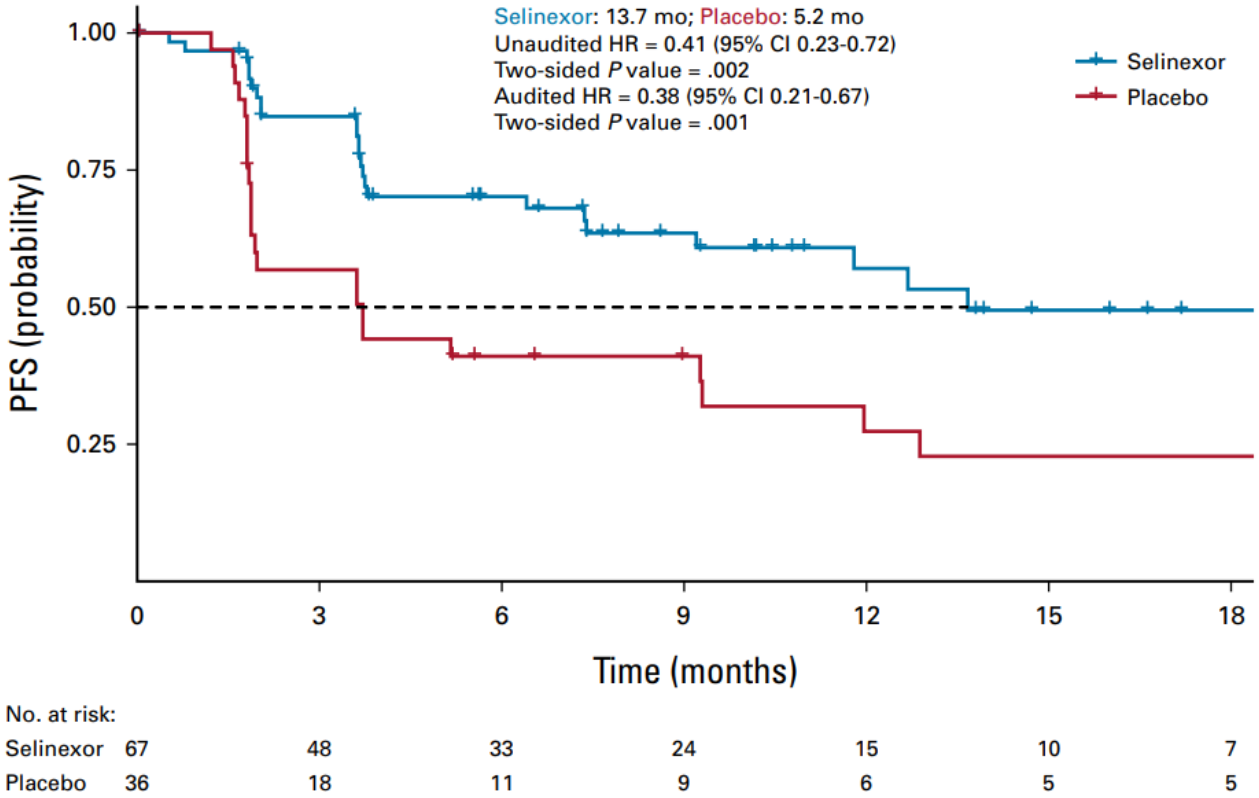
Vergote I. J Clin Oncol 2023.

SIENDO: PFS ITT: Primary Endpoint





Pre-specified cohort: p53wt

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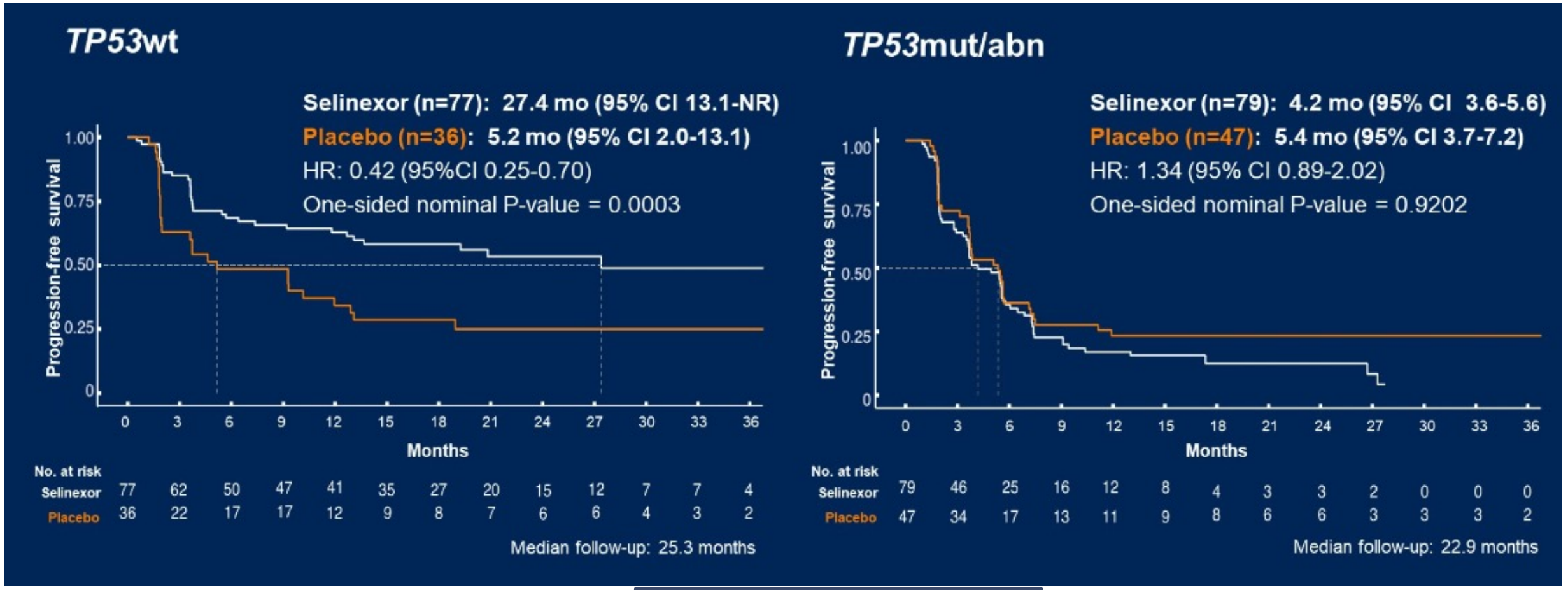
SIENDO: Long-term PFS, *TP53*



Pre-specified subgroups

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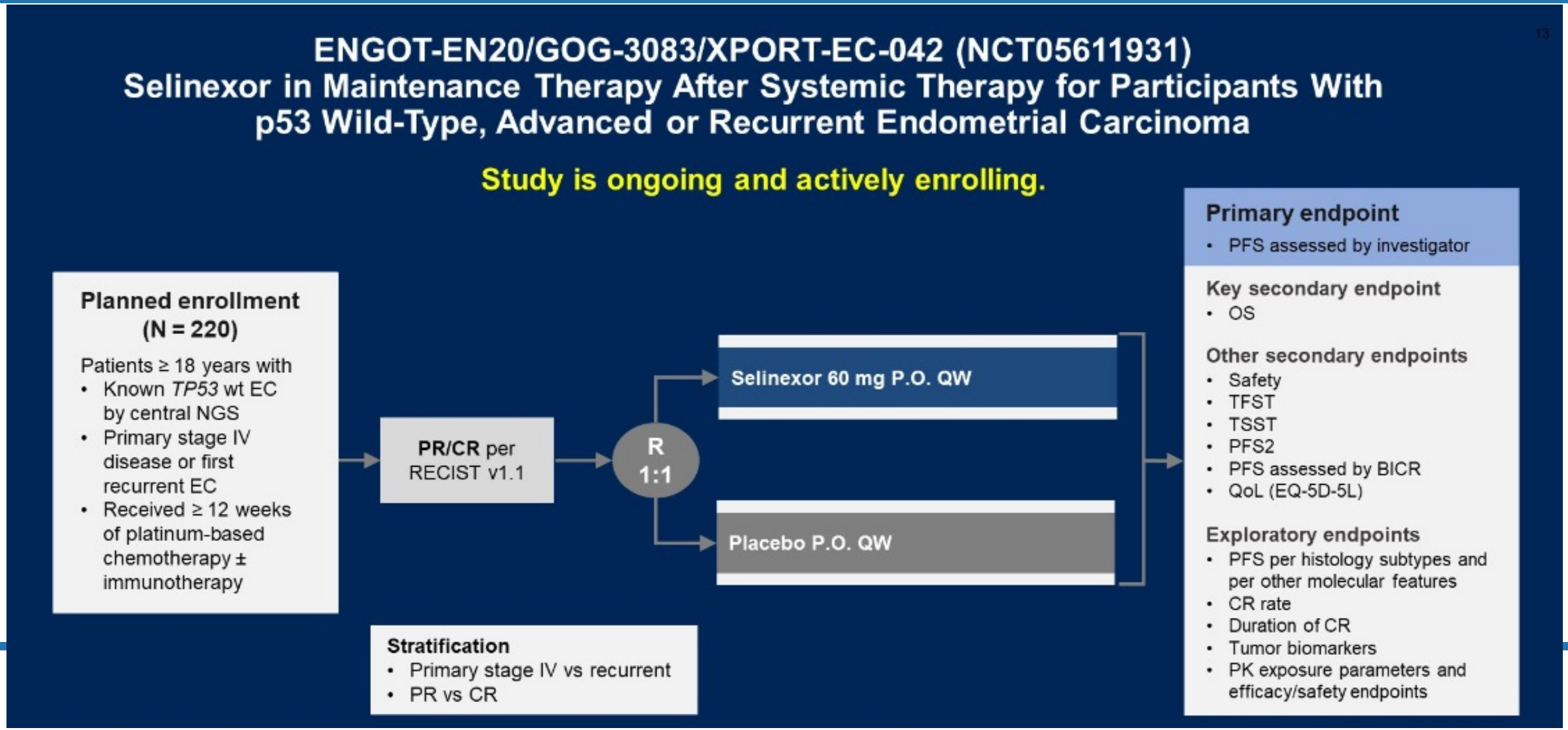
Slomovitz B. ASCO 2023.

ENGOT-EN20/GOG 3083/XPORT-EC-042



Gynecologic Malignancies

Targeting HER2: Phase 2 DESTINY-PanTumor02

- Key eligibility criteria

  Advanced solid tumors

  Second line + population

  HEr2 expression (IHC 3 or 2+)

    ASCO/CAP gastric cancer scoring

  Prior HER2-targeting therapy allowed

- Baseline characteristics

  267 patients (75 patients 3+ based on central testing)

  Median age 62 years

  109 patients received ≥3 lines of therapy

T-DXd
5.4 mg/kg Q3W

40 per cohort[b]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[c]
- Biliary tract cancer
- Pancreatic cancer

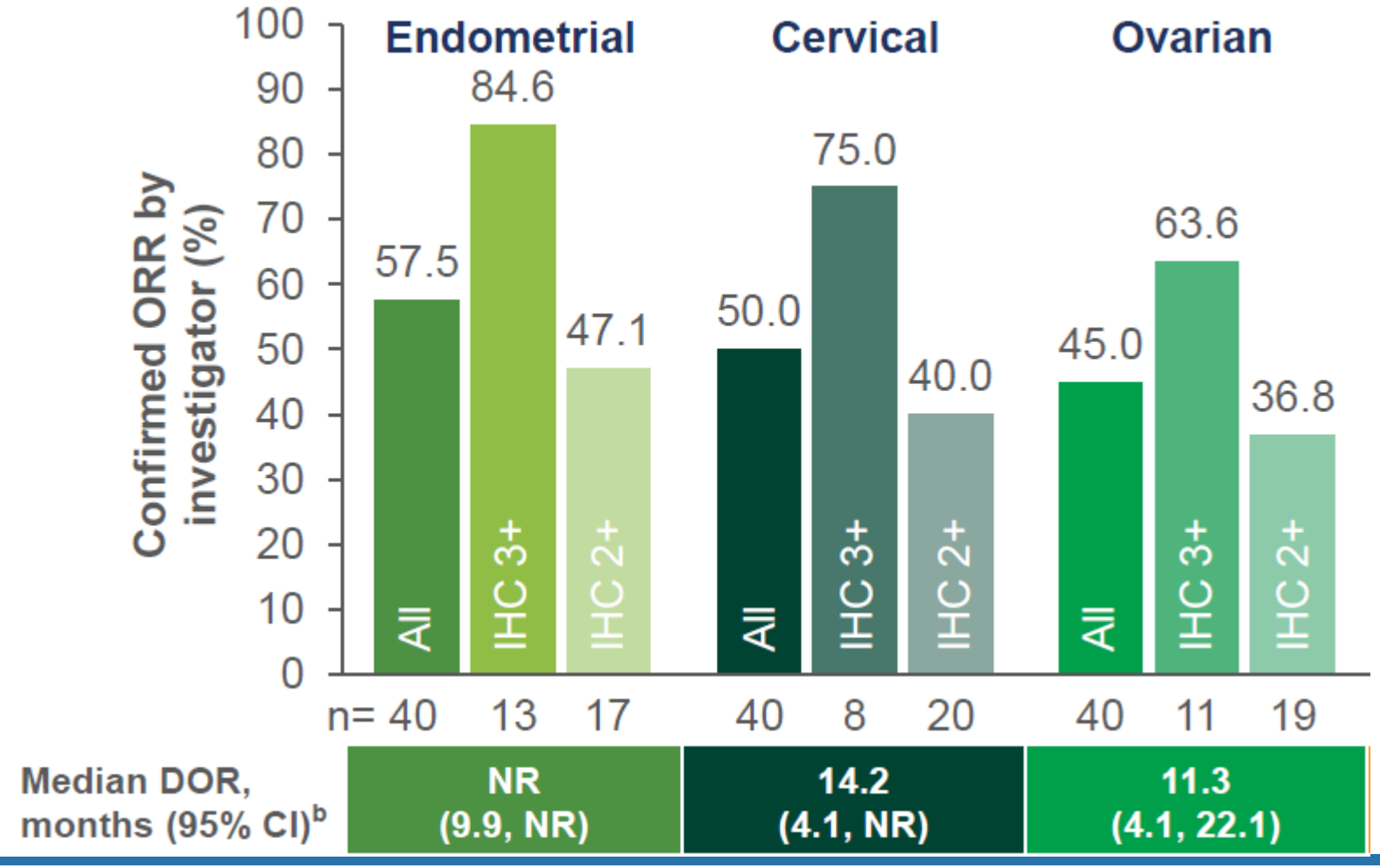
Primary endpoint
- Confirmed ORR (investigator)

Secondary endpoints
- DOR, DCR, PFS, OS
- Safety

Exploratory analysis
- Subgroup analyses by HER2 status

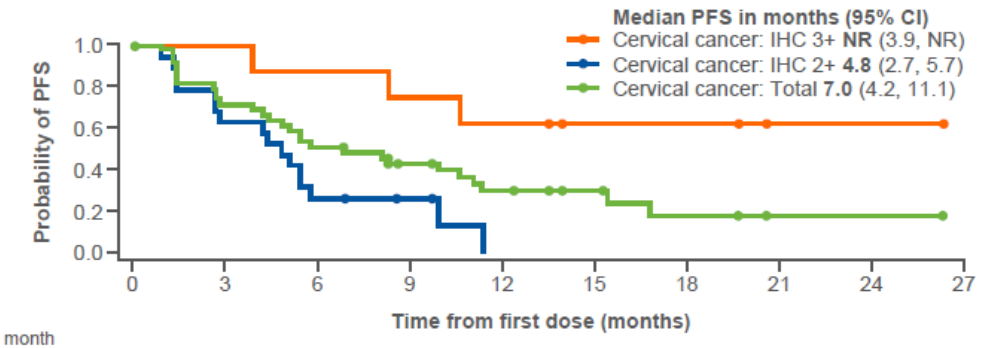
Primary analysis
data cutoff: Jun 8, 2023
Median follow up: 12.75 mo

Objective Response Rate



PFS by HER2 status

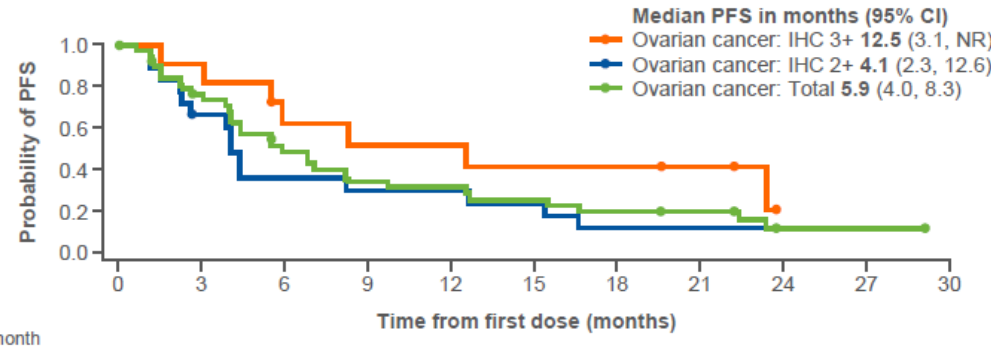
Cervical cancer



Number at risk, month

Cervical cancer: IHC 3+	8	8	7	6	5	3	3	1	1	0
Cervical cancer: IHC 2+	20	12	5	3	0					
Cervical cancer: Total	40	28	20	14	9	6	3	1	1	0

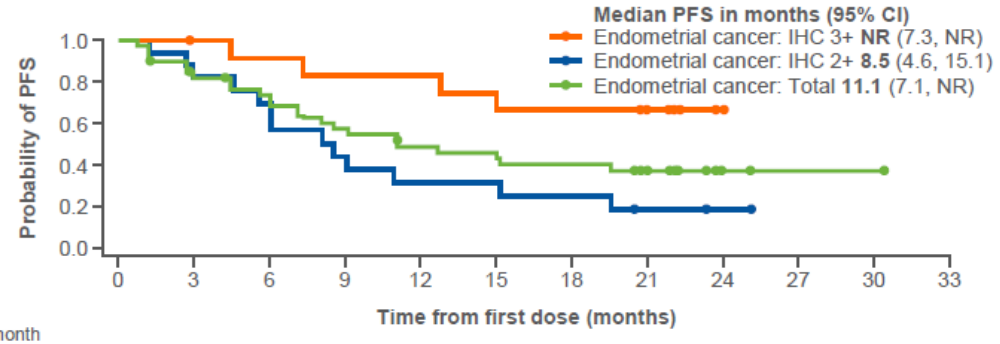
Ovarian cancer



Number at risk, month

Ovarian cancer: IHC 3+	11	10	6	5	5	4	4	3	0		
Ovarian cancer: IHC 2+	19	11	6	5	5	4	2	2	1	1	0
Ovarian cancer: Total	40	28	17	12	11	9	7	6	1	1	0

Endometrial cancer



Number at risk, month

Endometrial cancer: IHC 3+	13	12	11	10	10	9	8	5	0		
Endometrial cancer: IHC 2+	17	14	11	7	5	5	4	2	1	0	
Endometrial cancer: Total	40	31	27	21	17	16	14	8	2	1	1	0

- Potential tumor agnostic therapy for HER2 expressing tumors
- NCCN listed as an option for HER2 2 and 3+

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Conclusions

- Despite improvements, challenge remain
  - Platinum resistant disease remains a challenge
  - pMMR endometrial cancer
- Checkpoint inhibitors are moving to earlier lines of therapy in cervix and endometrial cancer
  - Creates a new needs gap which are being addressed
- Ongoing studies exploring new targets/approaches are needed

Thank you

rsalani@mednet.ucla.edu

"It's always Sit, Stay, Heel - never Think, Innovate, Be yourself."