ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

Patient Advocacy Seminar

Sept 29 - Oct 1, 2023, Istanbul, Türkiye

A year gone by……..

Progress in the treatment of Gynaecological Cancers 2022-2023

Jonathan A Ledermann
UCL Cancer Institute, London, UK

Declaration of Interests

Advisory Boards: AstraZeneca, Clovis Oncology, GSK, Artios Pharma, Merck/MSD, VBL Therapeutics, Bristol Myers Squibb, Nuvation, Ellipses, Immagene

Speaker Fees: AstraZeneca; MSD/Merck; GSK; Eisai; Neopharm

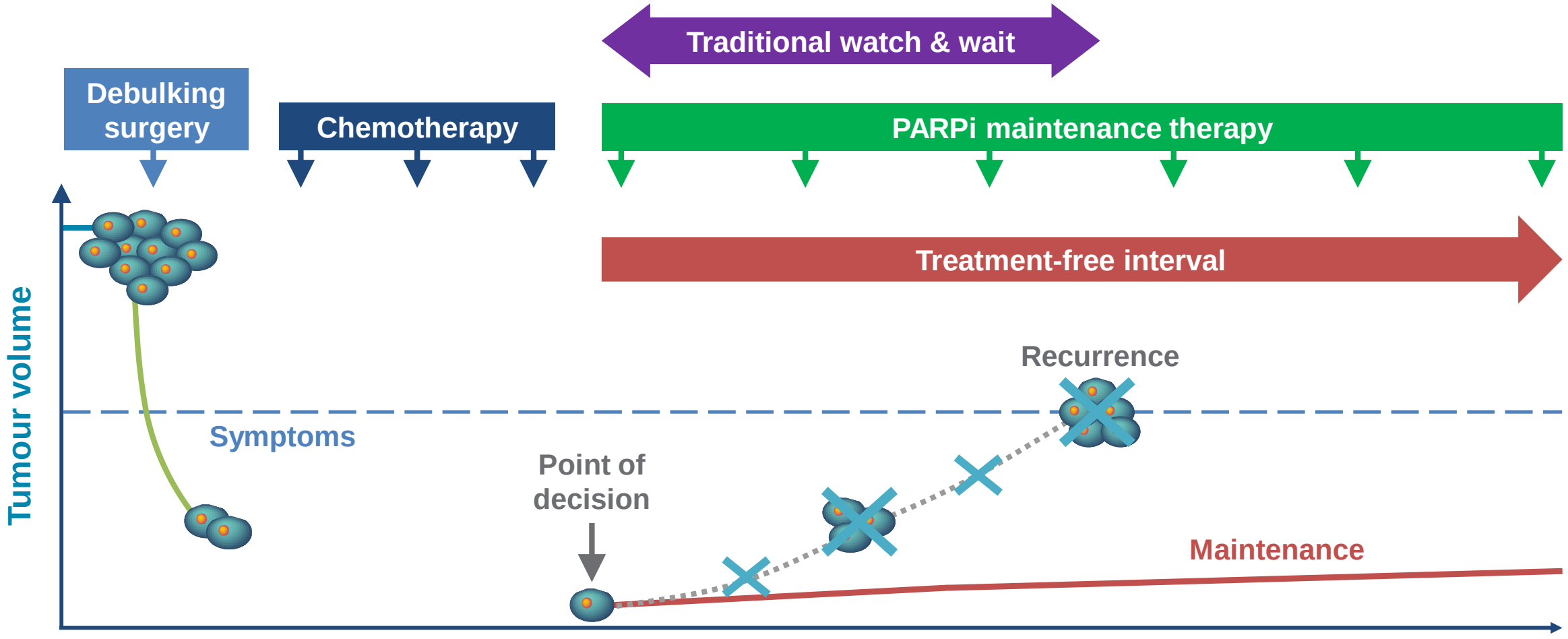
Independent Data Monitoring Committee Mersana; Sutro Bio

Clinical Research Grants: AstraZeneca, MSD/Merck Research

ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

Ovarian Cancer

A paradigm shift with the introduction of PARP inhibitor maintenance therapy



PARP, poly ADP ribose polymerase

Trials of PARP inhibitor maintenance in front line treatment of ovarian cancer

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

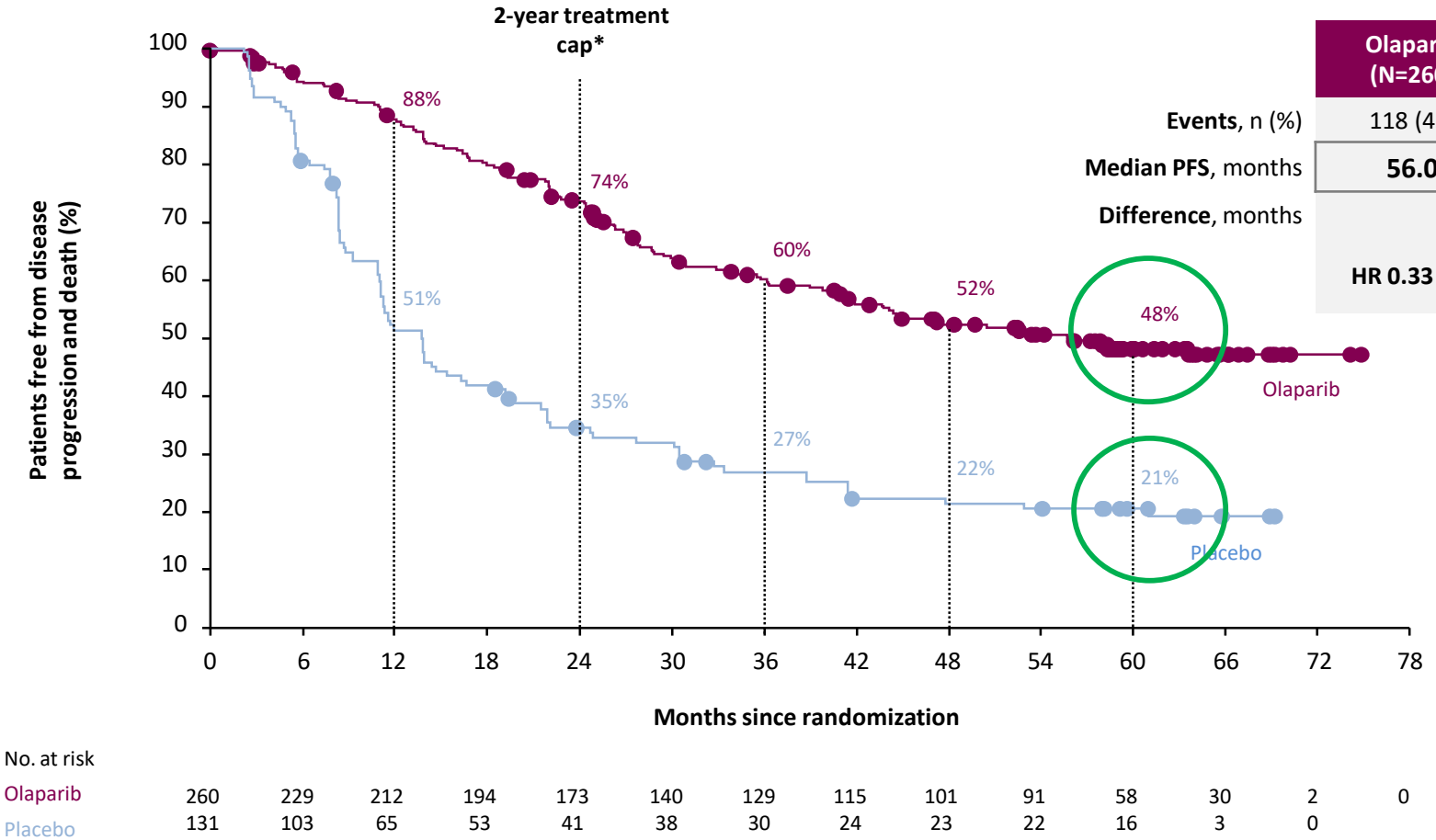
Overall Survival results now available

	SOLO1	PAOLA-1	PRIMA	PRIME	ATHENA	VELIA
Entry	BRCA mutation	All comers	All comers ('high risk')	All comers	All comers	All comers
Drug/Placebo	Olaparib	Bevacizumab + Olaparib	Niraparib	Niraparib	Rucaparib	Veliparib + Chemo followed by maintenance
Duration	24 months	15 months bevacizumab 24 months olaparib	36 months or to progression	36 months or to progression	24 months	24 months maintenance

All improve Progression-Free Survival !

Moore et al NEJM 2018; Ray-Coquard et al NEJM 2019; Gonzalez-Martin et al NEJM 2019; Li et al SGO 2022; Monk et al J Clin Oncol 2022; Coleman et al NEJM 2019

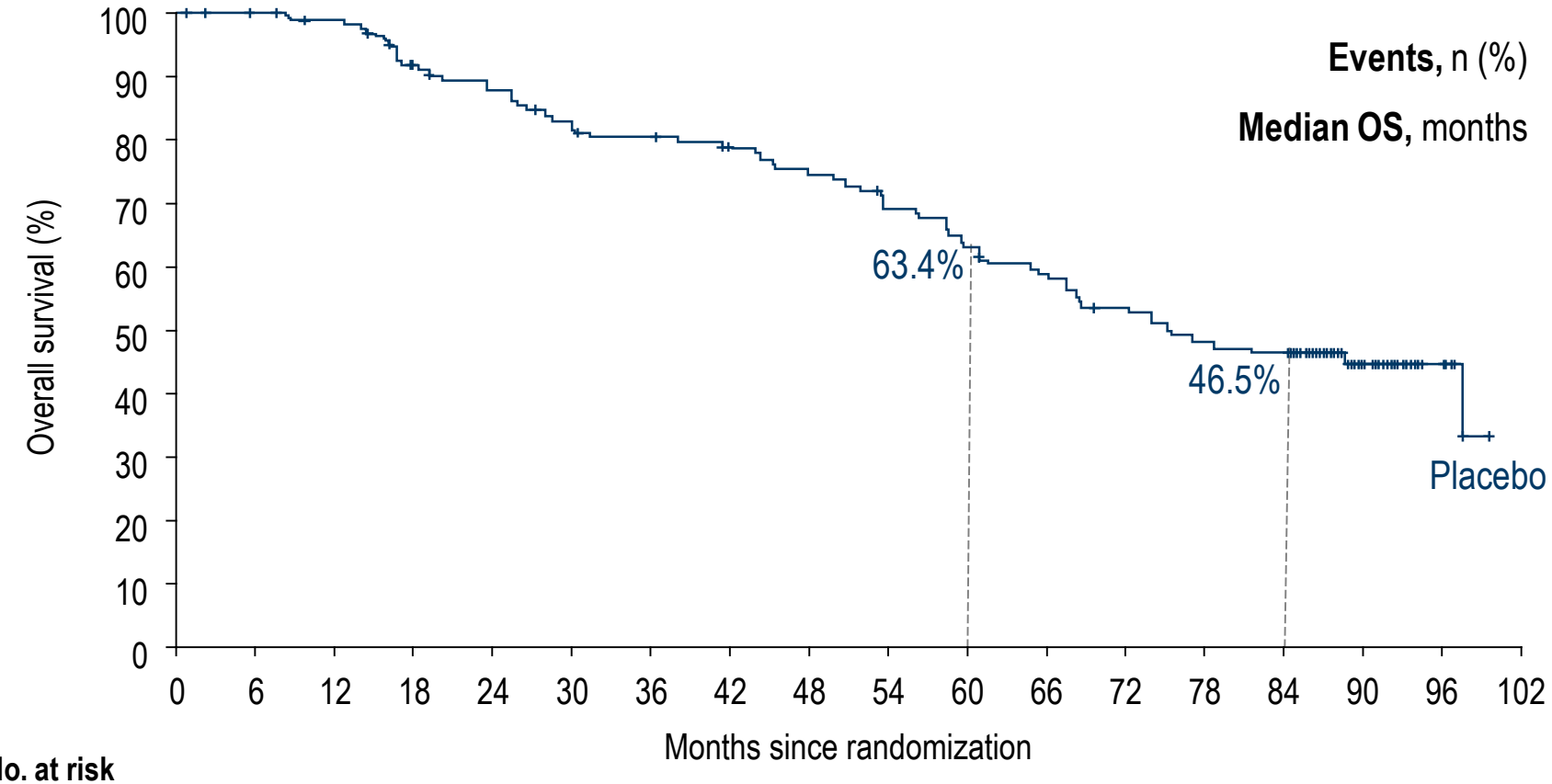
SOLO1: ovarian cancer and a BRCA mutation
Progression-Free survival of maintenance olaparib



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
	HR 0.33 (95% CI 0.25–0.43)	

Olaparib (N=260)	Placebo (N=131)
Median-follow up for PFS	
4.8 years	**5.0** years

7-Year descriptive survival analysis of SOLO1- BRCA mutated ovarian cancer

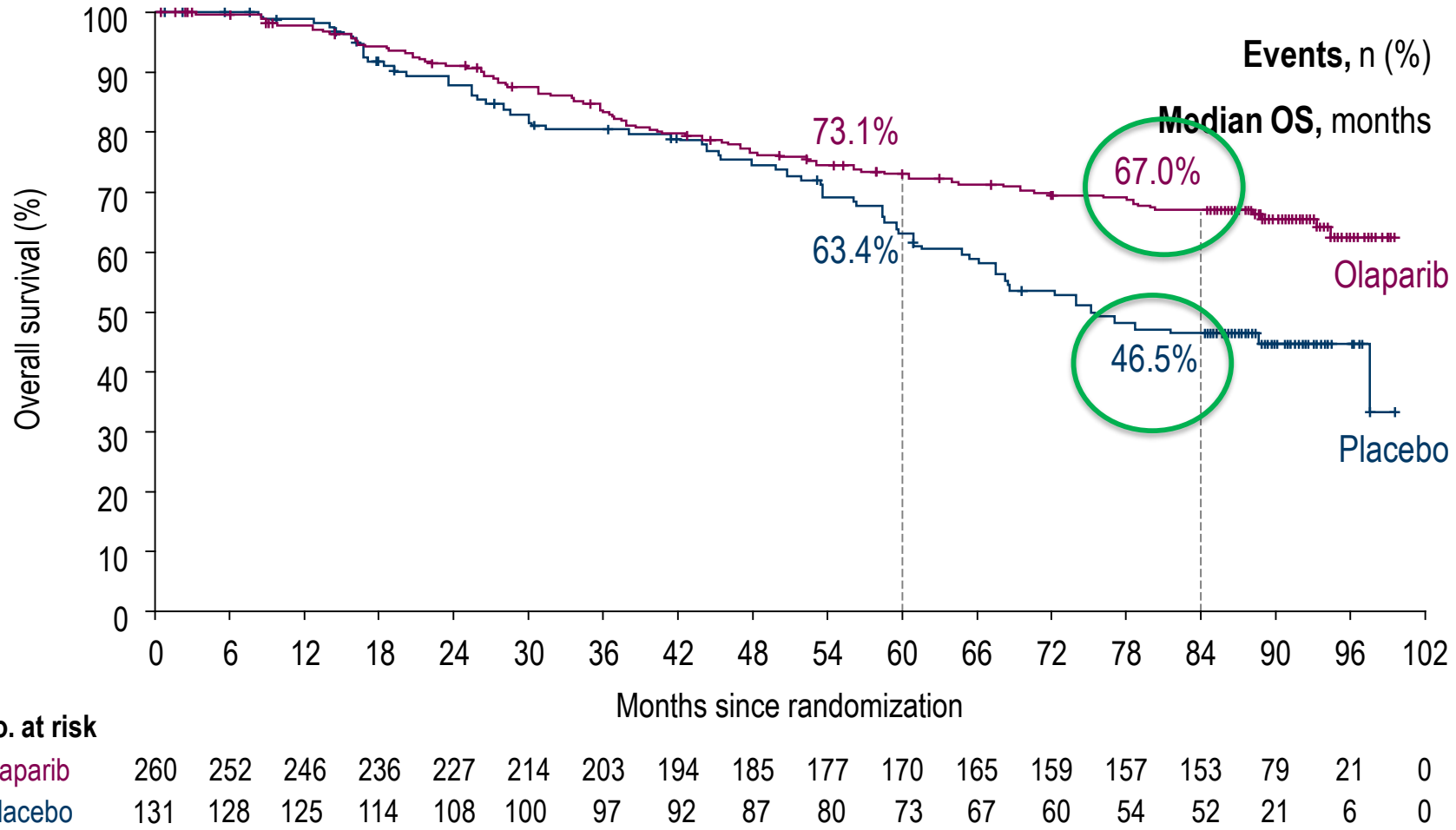


	Olaparib (N=260)	Placebo (N=131)
Events, n (%)		65 (49.6)
Median OS, months		**75.2**

No. at risk

Placebo	131	128	125	114	108	100	97	92	87	80	73	67	60	54	52	21	6	0

7-Year descriptive survival analysis of SOLO1- BRCA mutated ovarian cancer



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**

HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

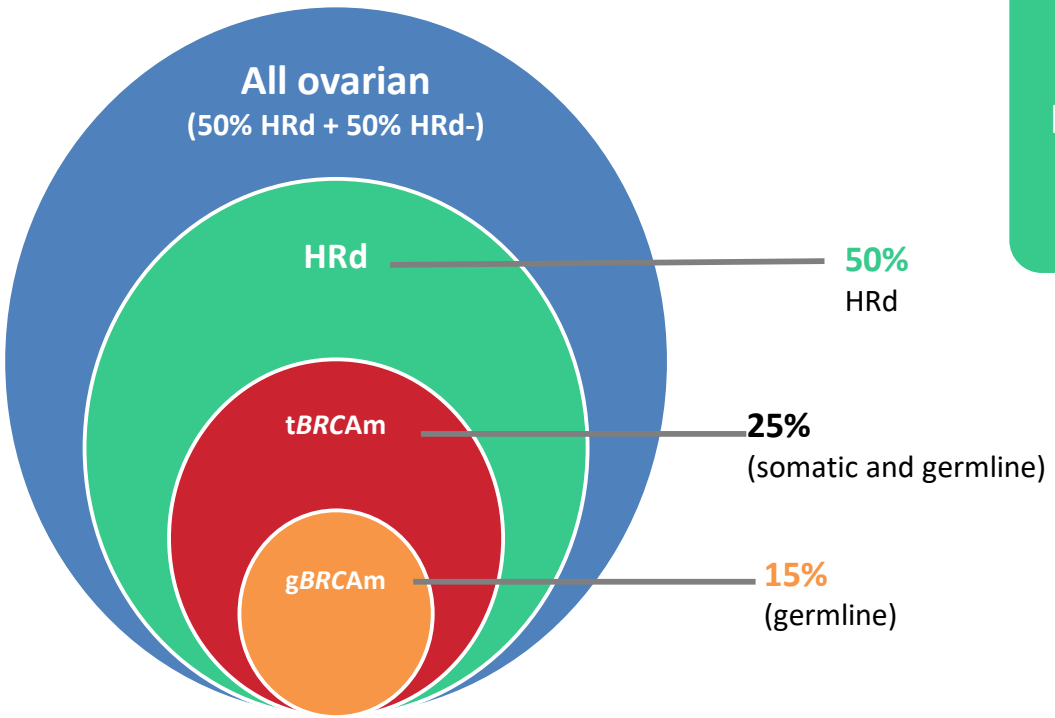
44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

**P*<0.0001 required to declare statistical significance

Exploiting Biomarker subgroups in high-grade serous ovarian cancer to optimise treatment

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

Half of high-grade serous ovarian cancer exhibit a high degree of genomic instability due to deficiencies in homologous recombination



50% are HRd including *BRCA*m, *BRCA*1/2 and RAD51 promoter methylation, BRIP1, and other genes involved in homologous recombination

25% are t*BRCA*m at diagnosis

15% are g*BRCA*m at diagnosis

BRCA, breast cancer gene; BRIP1, *BRCA*1-interacting protein; g*BRCA*, germline *BRCA* mutant; HR, homologous recombination deficient; OC, ovarian cancer; t*BRCA*m, tumour *BRCA* mutant.

The Cancer Genome Atlas Research Network, Nature 2011;474:609–15; Konstantinopoulos PA, et al. Cancer Discov 2015;11:1137–54.

PAOLA-1: 'All comer' Design

Key inclusion criteria

- Newly diagnosed, FIGO Stage III–IV HGSOC and HGEOC*
- PDS or IDS
- ≥2 cycles of bevacizumab†
- NED/CR/PR

Stratification

- Tumour BRCA status‡
- First-line treatment outcome §

Olaparib 300 mg BID

Bevacizumab

2:1 randomisation

Placebo

Bevacizumab

2 years treatment

Primary objective

- Progression-Free survival

Secondary efficacy objectives

- Overall Survival

Safety and tolerability

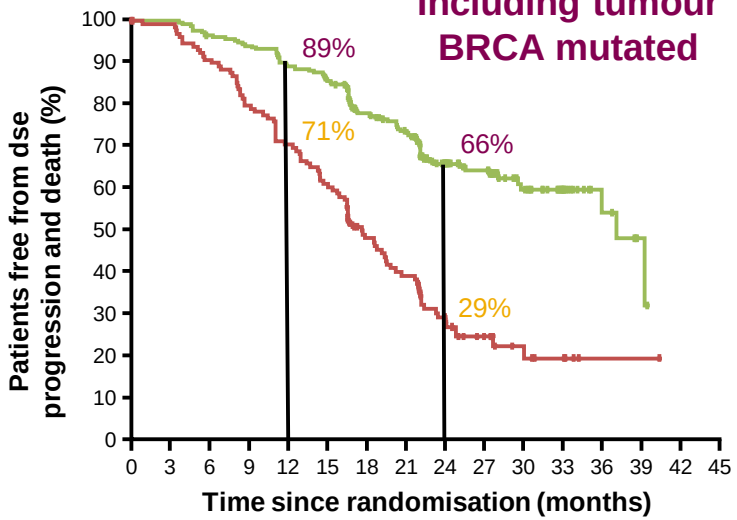
Tumours were tested for HRD (**H**omologous **R**ecombination **D**eficiency) and tumour BRCA using Myriad myChoice assay

HRD is a marker for sensitivity to PARP innhibitors

PAOLA-1: PFS by HRD status

HRD-positive

Including tumour BRCA mutated

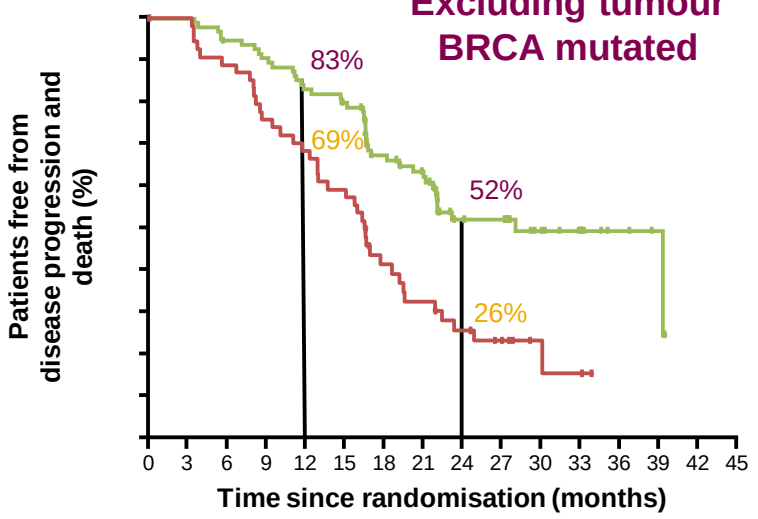


No. at risk

Olaparib	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	**87** (34)	**92** (70)
Median PFS, months	**37.2***	**17.7**
Δ Median PFS, months	**19.5**	
HR (95% CI)	**0.33** (0.25–0.45)	

Excluding tumour BRCA mutated



No. at risk

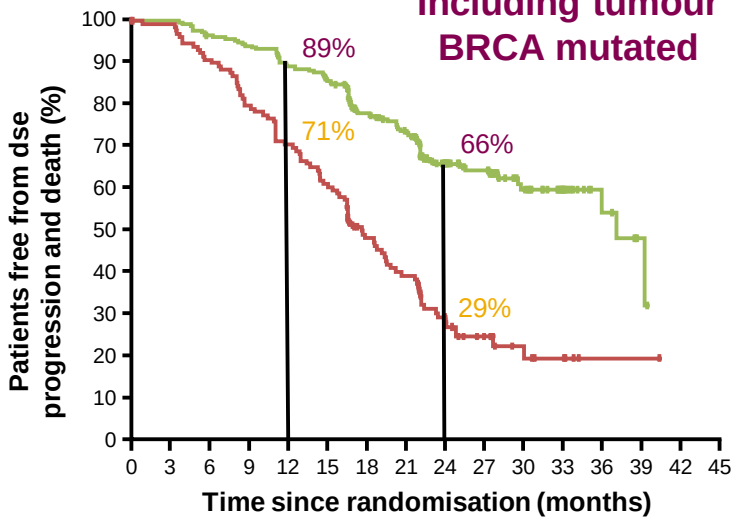
Olaparib	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo	55	54	48	41	37	32	19	15	11	8	3	2	0		

	Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
Events, n (%)	**43** (44)	**40** (73)
Median PFS, months	**28.1***	**16.6**
Δ Median PFS, months	**11.5**	
HR (95% CI)	**0.43** (0.28–0.66)	

PAOLA-1: PFS by HRD status

HRD-positive

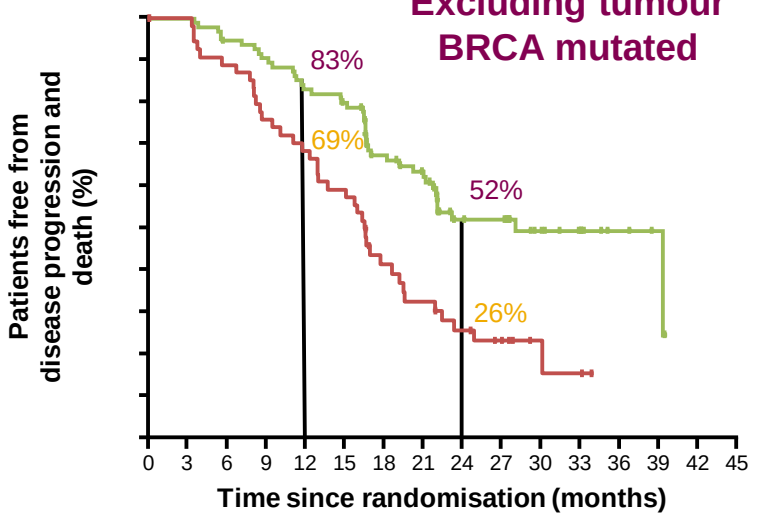
Including tumour BRCA mutated



No. at risk															
Olaparib	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	**87** (34)	**92** (70)
Median PFS, months	**37.2***	**17.7**
Δ Median PFS, months	**19.5**	
HR (95% CI)	**0.33** (0.25–0.45)	

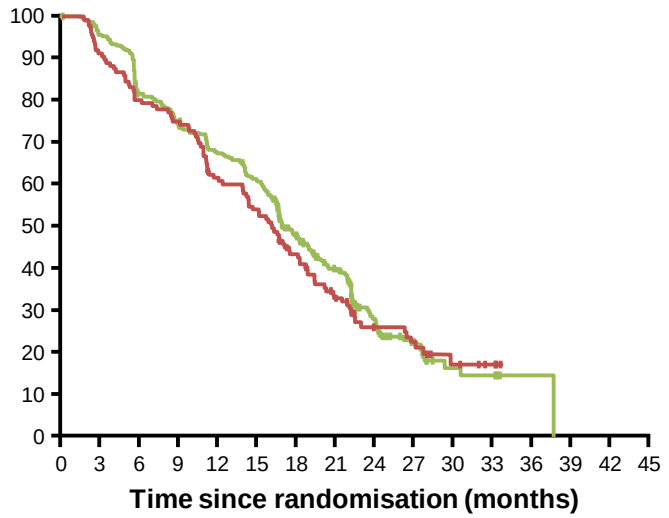
Excluding tumour BRCA mutated



No. at risk															
Olaparib	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo	55	54	48	41	37	32	19	15	11	8	3	2	0		

	Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
Events, n (%)	**43** (44)	**40** (73)
Median PFS, months	**28.1***	**16.6**
Δ Median PFS, months	**11.5**	
HR (95% CI)	**0.43** (0.28–0.66)	

HRD-negative/unknown



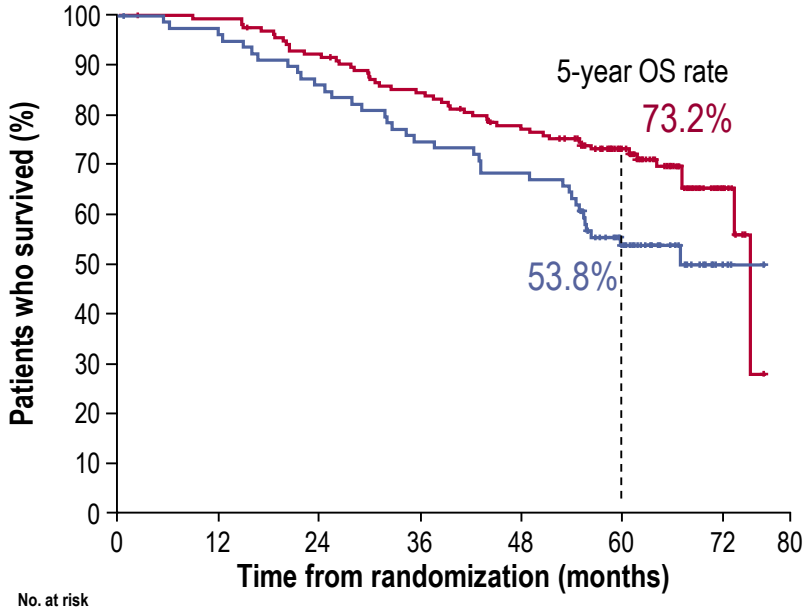
No. at risk															
Olaparib	282	261	219	197	180	161	110	85	38	27	9	8	1	0	
Placebo	137	124	109	102	81	72	55	39	22	17	7	4	1		

	Olaparib + bevacizumab (n=282)	Placebo + bevacizumab (n=137)
Events, n (%)	**193** (68)	**102** (74)
Median PFS, months	**16.9**	**16.0**
Δ Median PFS, months	**0.9**	
HR (95% CI)	**0.92** (0.72–1.17)	

Overall Survival subgroup analysis by BRCAm and HRD status

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

BRCAm*



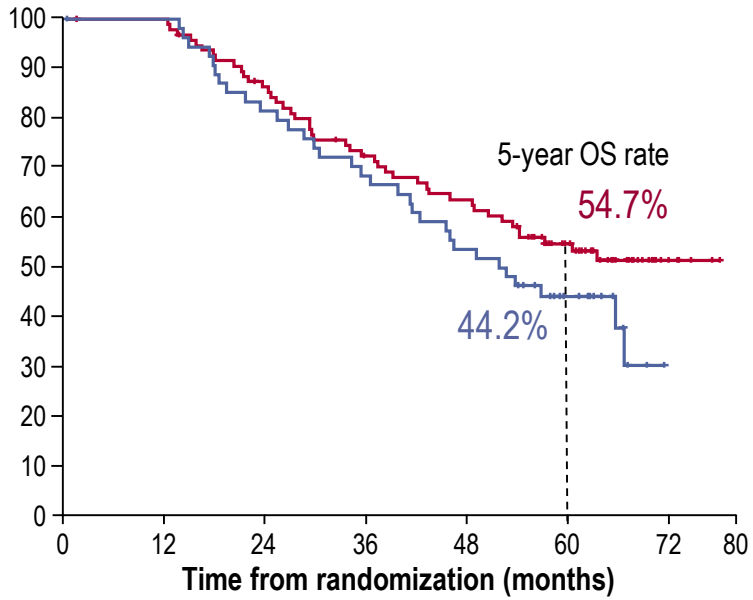
No. at risk

Olaparib + bevacizumab	157	156	156	155	155	152	150	144	143	139	134	131	130	127	123	118	117	115	112	99	80	55	42	21	11	2	0
Placebo + bevacizumab	80	79	78	77	76	74	72	71	68	66	64	61	59	58	58	54	54	53	50	40	33	22	17	10	3	1	0

	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)

HR 0.60 (95% CI 0.39–0.93)

HRD positive‡ excluding BRCAm

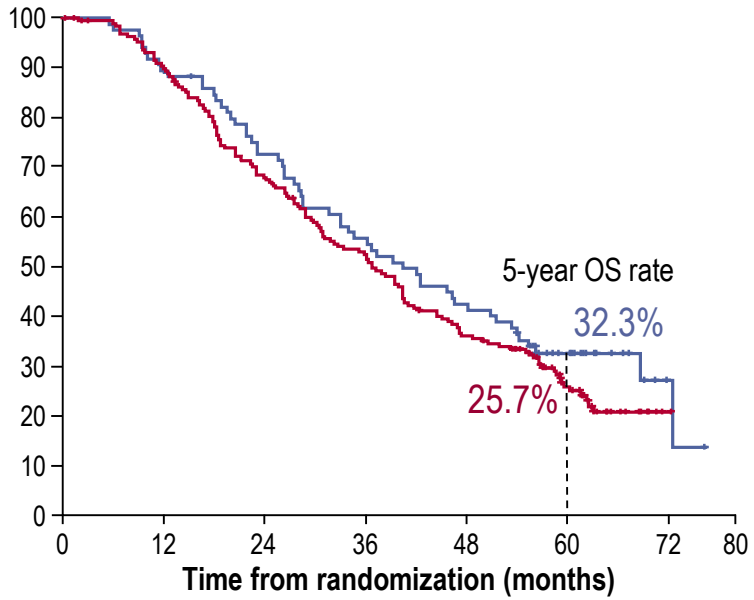


Olaparib + bevacizumab	97	96	96	96	96	91	87	86	81	76	71	70	66	63	61	59	58	55	52	45	37	29	22	12	5	2	0
Placebo + bevacizumab	55	54	54	54	54	51	48	46	44	42	40	39	37	36	33	32	29	28	24	21	15	9	6	2	0		

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	**44.2**
	9 (9.3)	23 (41.8)

HR 0.71 (95% CI 0.45–1.13)

HRD negative†



Olaparib + bevacizumab	192	187	186	179	169	157	146	135	126	119	109	100	97	89	77	72	66	62	57	43	30	16	11	5	1	0	
Placebo + bevacizumab	85	85	84	83	76	74	71	65	60	56	51	48	46	43	41	38	35	33	31	21	17	11	8	5	2	1	0

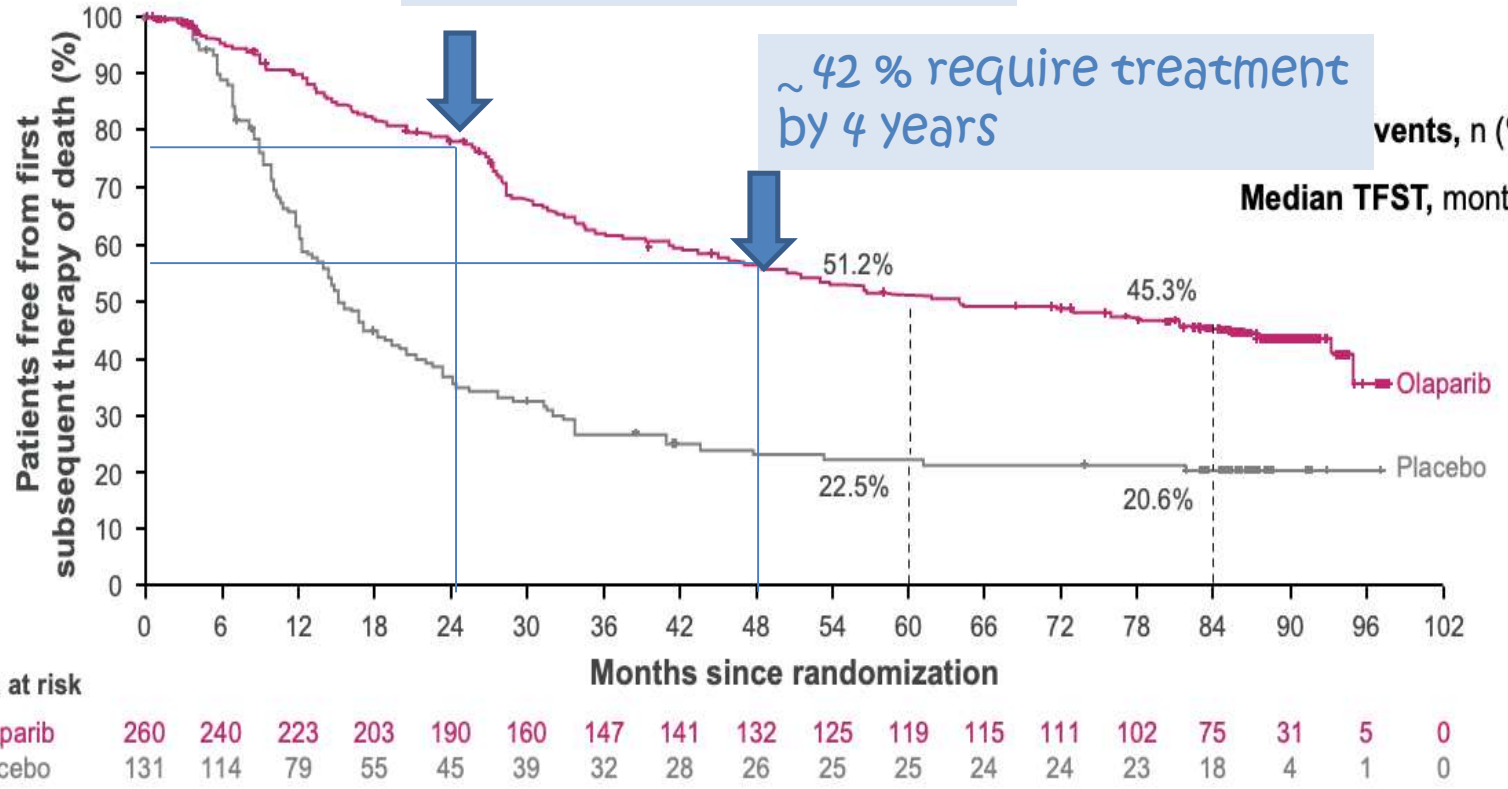
	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
	140 (72.9)	58 (68.2)
	36.8	40.4
	25.7	**32.3**
	46 (24.0)	34 (40.0)

HR 1.19 (95% CI 0.88–1.63)

Time to first subsequent therapy (for recurrence) in patients with BRCA mutation treated with olaparib [SOLO-1]

~22 % require treatment by 2 years

~42 % require treatment by 4 years



	Olaparib (N=260)	Placebo (N=131)
vents, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	**64.0**	**15.1**
HR 0.37 (95% CI 0.28–0.48)		

In the olaparib arm **45%** of patients who were still alive at 7 years had **yet to receive any subsequent treatment**

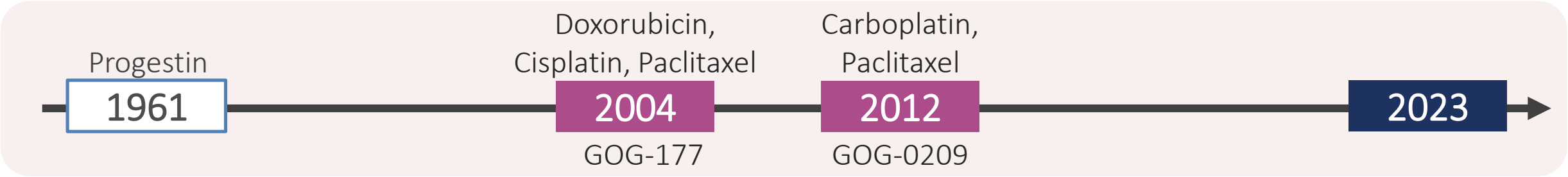
ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

Endometrial Cancer

History

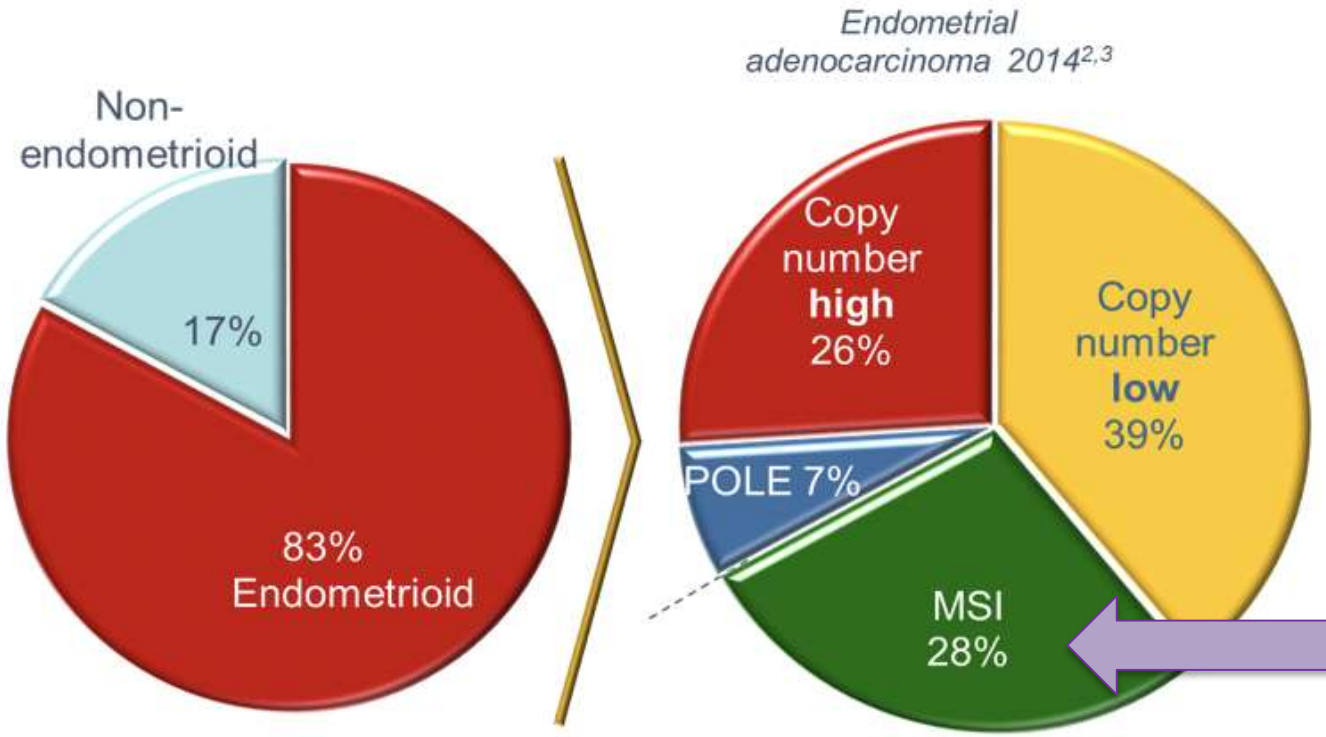
- Endometrial cancer (EC) remains the only gynaecologic malignancy with a rising incidence and mortality.

- While patients diagnosed at an early-stage (low-risk) have an excellent prognosis, those diagnosed at a late stage have a 5-year survival rate of only 17%.



Sung, H. et al.CA CancerJ. Clin. 71, 209–249 (2021); Colombo N, *et al*. *Ann Oncol* 2016; 27: 16–41; Bestvina CM & Fleming GF. *Oncologist* 2016; 21: 1250–1259; Concin N, *et al*. *Int J Gyn Cancer* 2021; 31: 12–39; Yang S, et al. *Discov Med.* 2011;12:205-212; Fleming GF, et al. *J Clin Oncol*. 2004;22:2159-2166; O'Malley DM, et al. *J Clin Oncol.* 2022;40(7):752-761; Miller DS, et al., *Gynecol Oncol*. 2012;125:771–773; Miller DS, et al., *J Clin Oncol*. 2020;38:3841-3850.

Molecular Subtype of Endometrial Cancer



MSI-H- microsatellite Instability- High

MMRd– DNA mis-matched repair deficiency

Poor repair of DNA

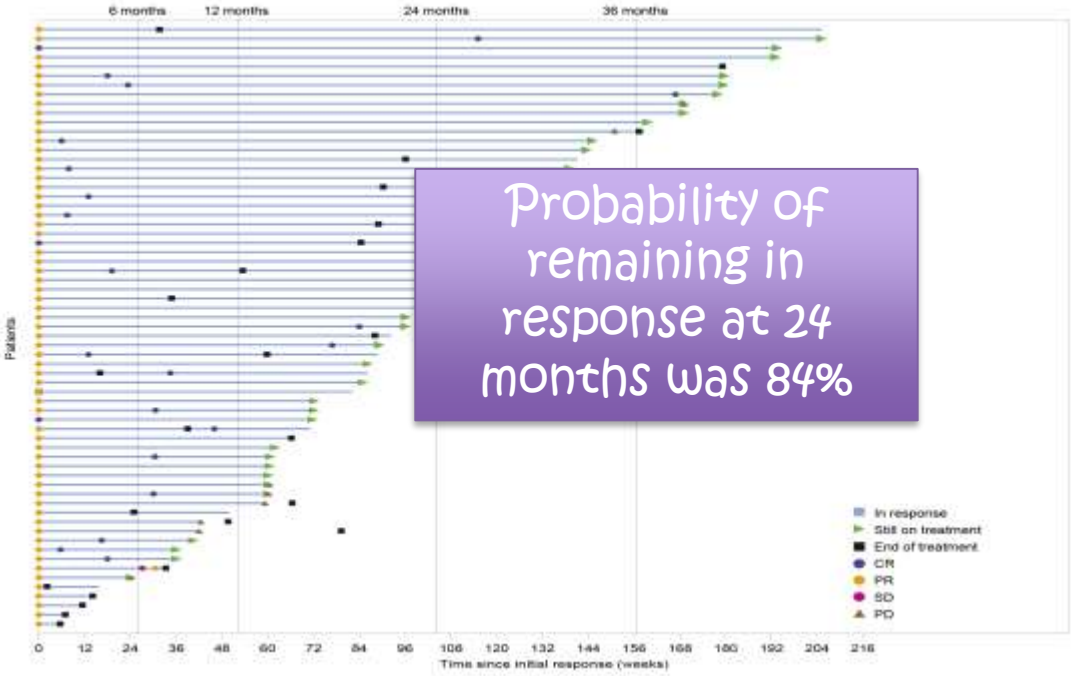
Talhouk A, *et al. Cancer* 2017; 123: 802–813;Luchini C, *et al. Ann Oncol* 2019; 30: 1232–1243; Bonneville R, *et al. JCO Precis Oncol* 2017; 1: PO.17.00073.

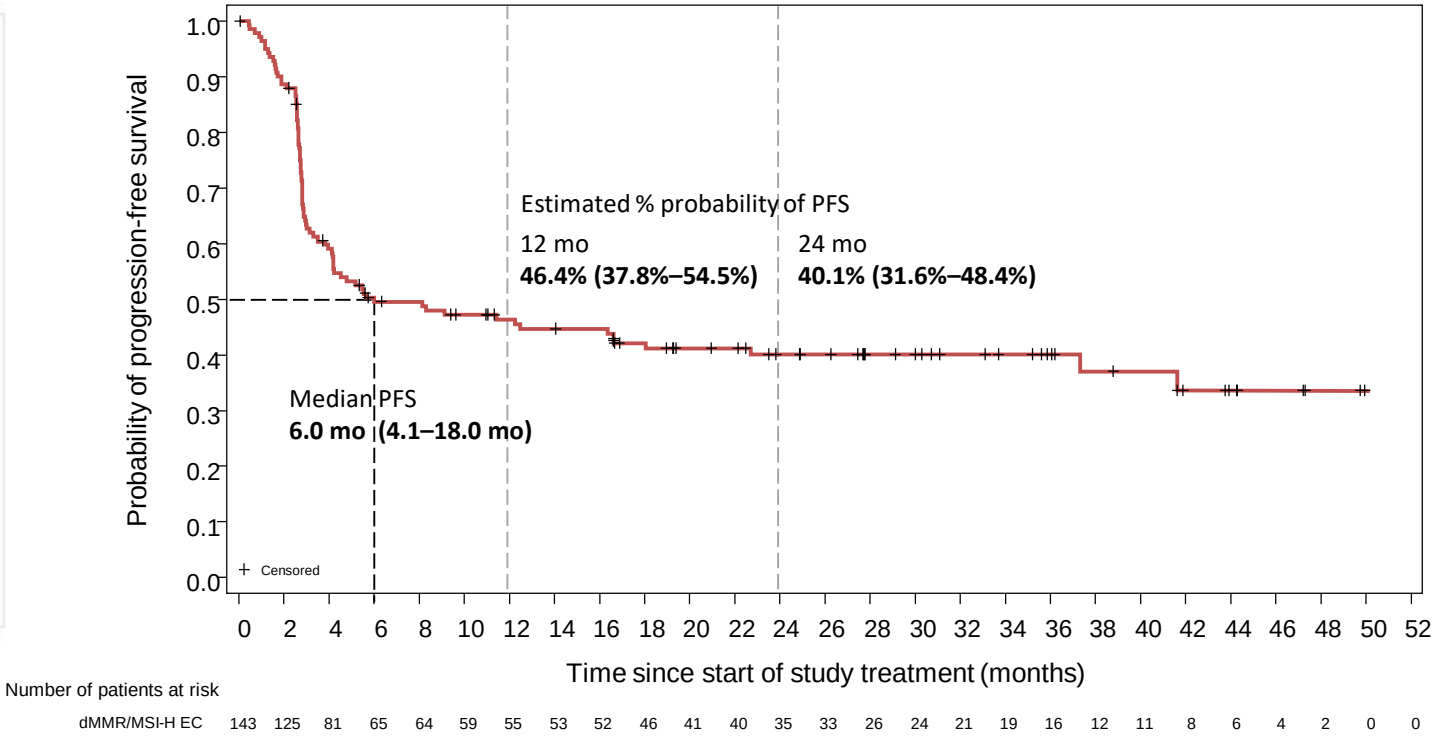
Immune Checkpoint Inhibitors Endometrial Cancer

		MMR-d		MMR-p	
Study	Drug	N	ORR(%)	N	ORR(%)
KEYNOTE 158: O'Malley (2019+22)	Pembrolizumab	79	48%	107	11%
GARNET: Oaknin (2022)	Dostarlimab	143	46%	156	15%
PHAEDRA: Antill (2019)	Durvalumab	35	43%	36	3%
Konstantinopoulos (2019)	Avelumab	15	27%	16	6%
KEYNOTE 775 Makker (2022)	Pembrolizumab + Lenvatinib	65	42%	346	32%

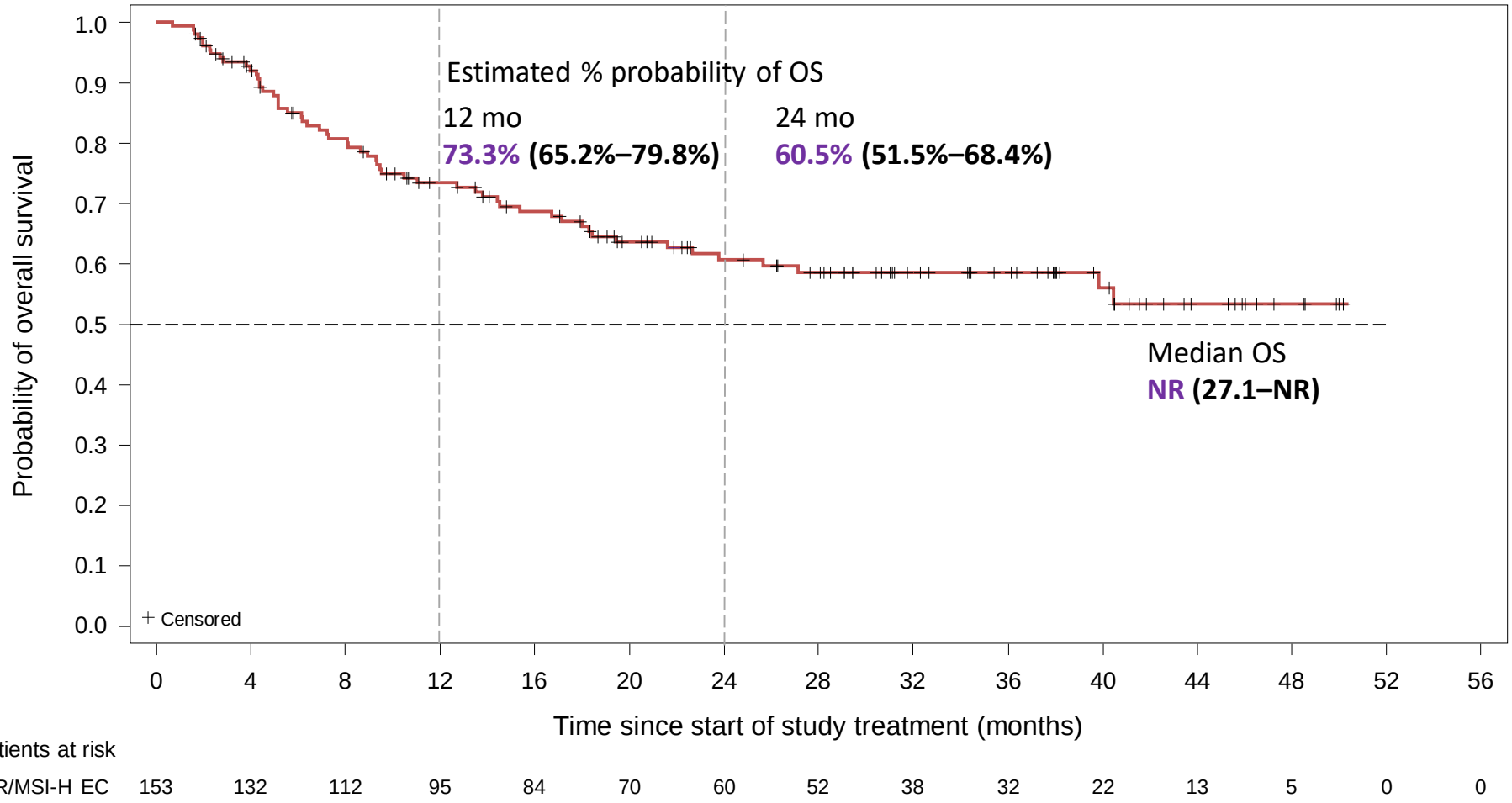
O'Malley et al. ESMO 2019. JCO2022; Oaknin, ASCO 2022; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019, Makker NEJM 2022

Garnet Trial: Dostarlimab in MSI-High Endometrial Cancer after progression on platinum-based therapy





Dostarlimab Probability of Overall Survival: dMMR/MSI-H

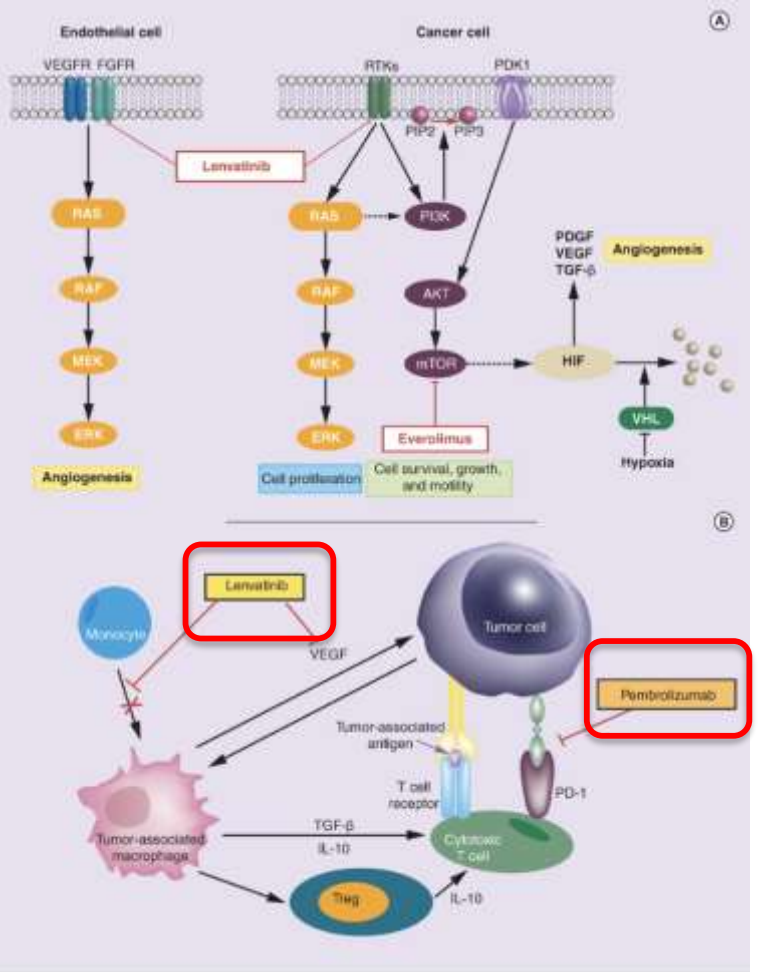


Number of patients at risk

dMMR/MSI-H EC	153	132	112	95	84	70	60	52	38	32	22	13	5	0	0

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; NR, not reached; OS, overall survival.

KEYNOTE 775: Combining Lenvatinib and pembrolizumab in Endometrial Cancer after platinum failure



Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- One prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:

- Region (1: Europe, USA, Canada, Australia, New Zealand, and Israel vs 2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)

R (1:1)

Lenvatinib
20 mg PO QD
+
Pembrolizumab[b]
200 mg IV Q3W

Treat until progression or unacceptable toxicity

Doxorubicin
60 mg/m² IV Q3W[c]
or
Paclitaxel
80 mg/m² IV QW
(3 weeks on/1 week off)

Primary endpoints

- PFS by BICR
- OS

Secondary endpoints

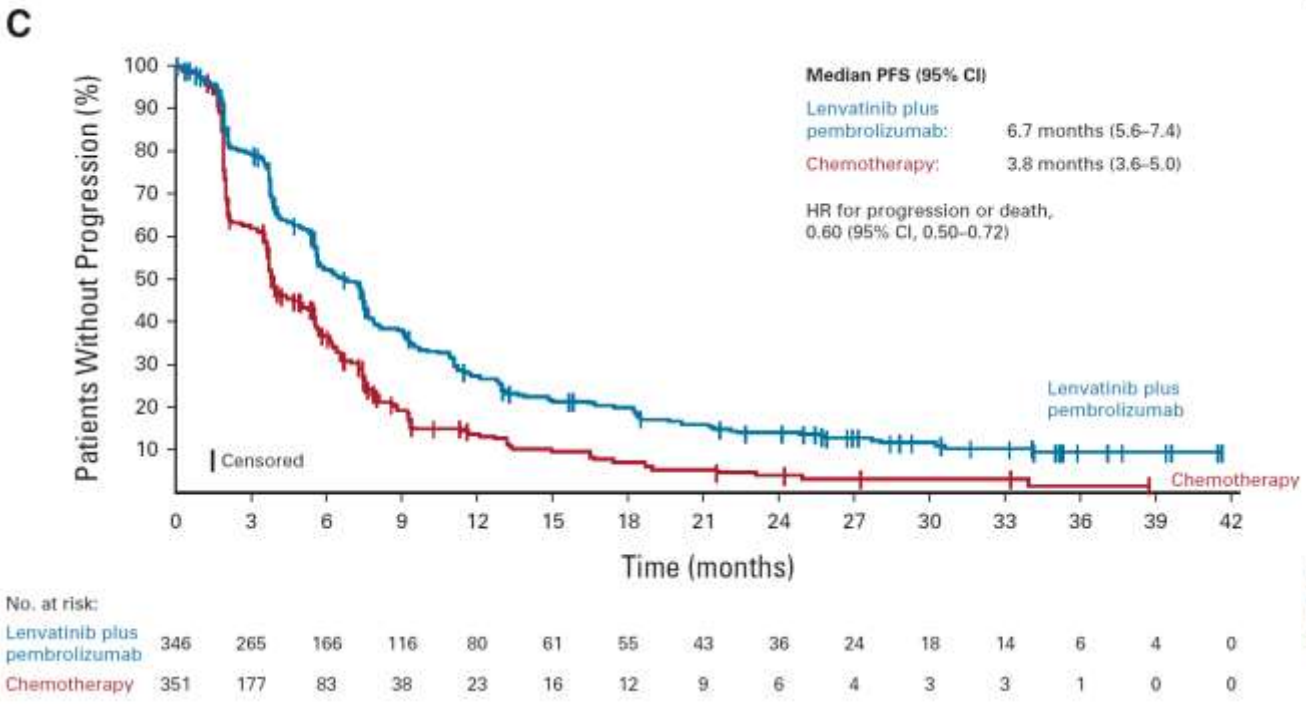
- ORR
- HRQoL
- Pharmacokinetics
- Safety

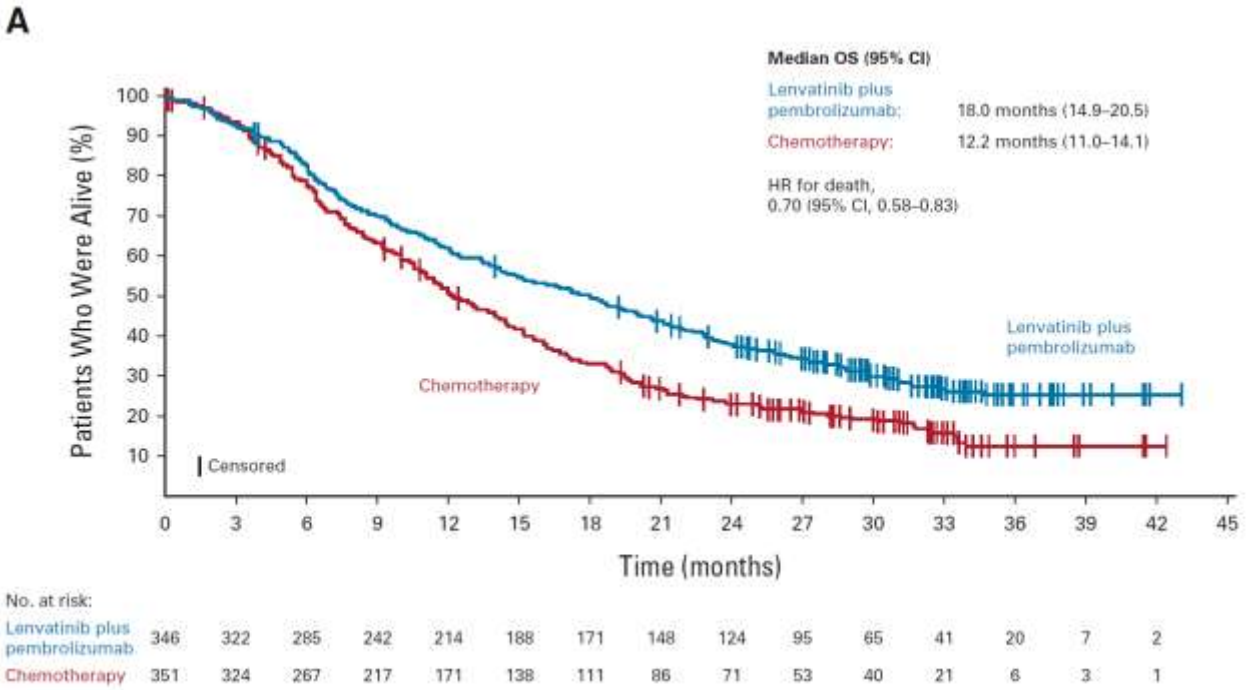
Key exploratory endpoint

- Duration of response

[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 was given in the neoadjuvant or adjuvant treatment setting; [b]maximum of 35 doses; [c]maximum cumulative dose of 500 mg/m².

Final Results of Lenvatinib and pembrolizumab without mis-matched repair deficiency (MMRp)





Progression-Free Survival

HR for progression or death
0.60 (95% CI 0.50-0.72)

Overall Survival

HR for death 0.70 (95% CI 0.58-0.83)

ENGOT-EN6-NSGO/GOG-3031/RUBY

Phase 3, randomized, double-blind, multicentre study of
dostarlimab plus carboplatin-paclitaxel ***versus*** **placebo plus carboplatin/paclitaxel**
in patients with primary advanced or recurrent Endometrial Cancer

Eligible patients

- 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

Stratification

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

R1:1

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

Dostarlimab IV 1000 mg Q6W up to 3 years[c]

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

Placebo IV Q6W up to 3 years[c]

Follow-up

Primary endpoint

- PFS by INV
- OS

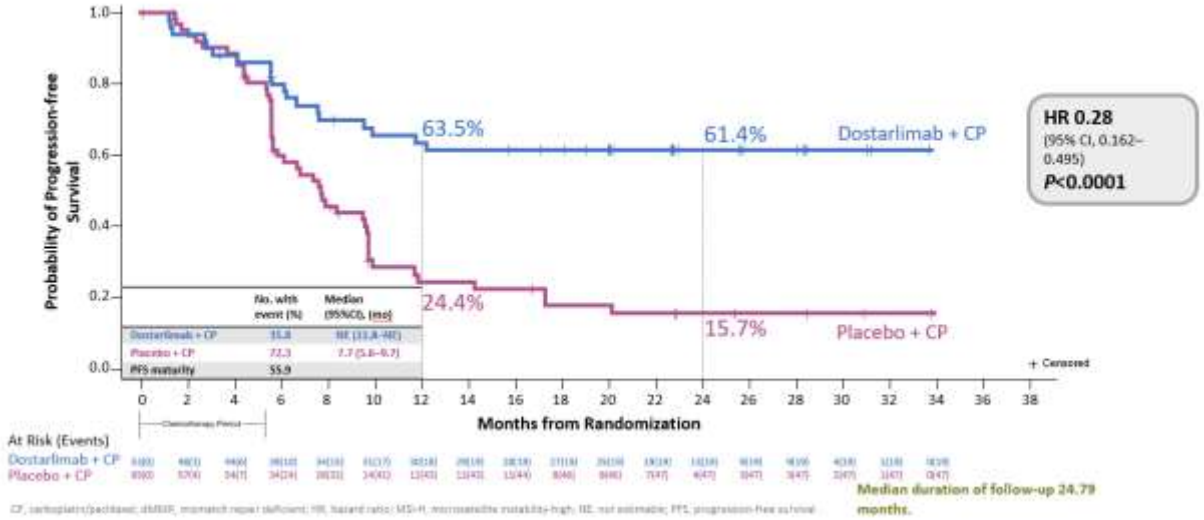
Secondary endpoints

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

Progression-Free and Overall Survival in dMMR/MSI-H Population

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

PRIMARY ENDPOINT: PFS IN dMMR-MSI-H POPULATION



OS IN dMMR-MSI-H POPULATION

26.3% MATURITY

Progression-Free and Overall Survival in MMRp/MSS Population

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

PFS IN MMR$_P$/MSS POPULATION

OS IN MMR$_P$/MSS POPULATION

33% MATURITY

Progress in the treatment of advanced endometrial Cancer- the last decade

GOG 209

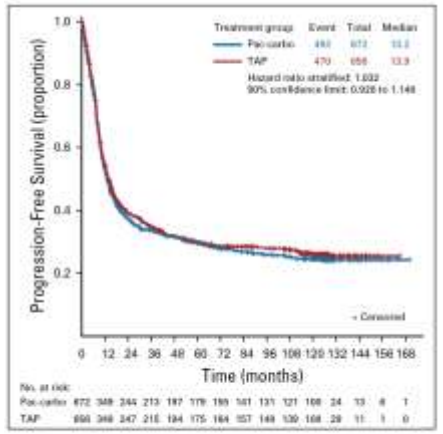


FIG 2. Updated progression-free survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

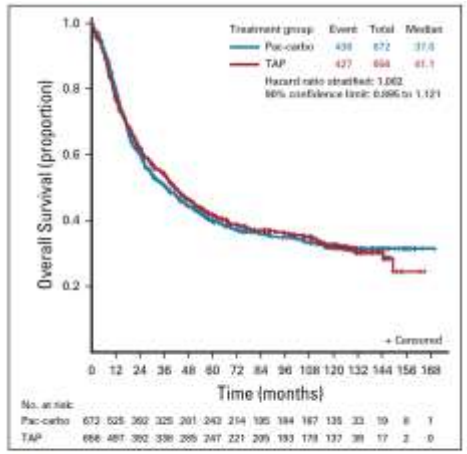


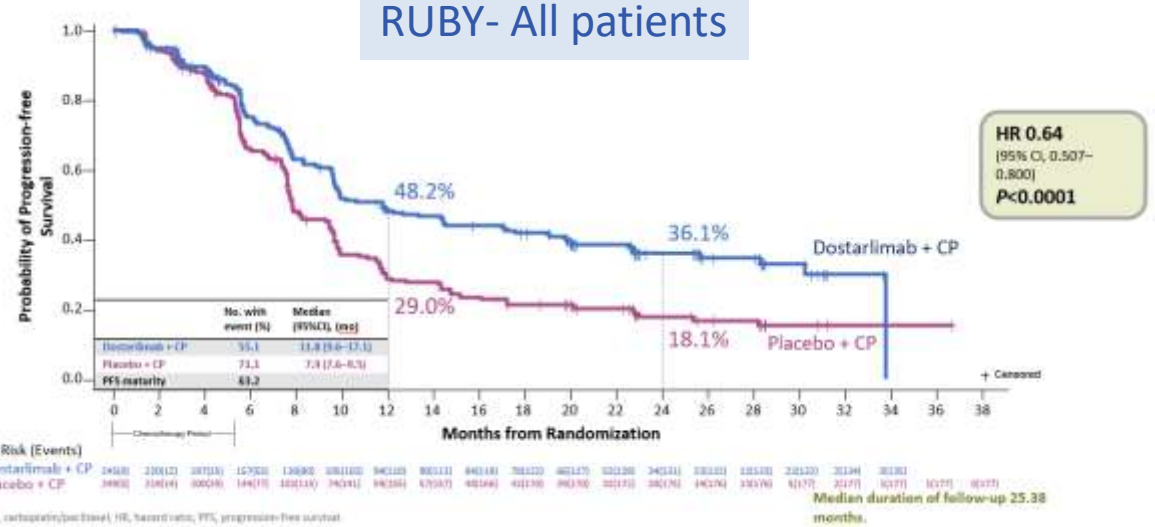
FIG 3. Updated overall survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

2009 → **2021**

PFS

OS

RUBY- All patients



Miller DS et al. *J Clin Oncol.* 2020; 38(33): 3841-3850

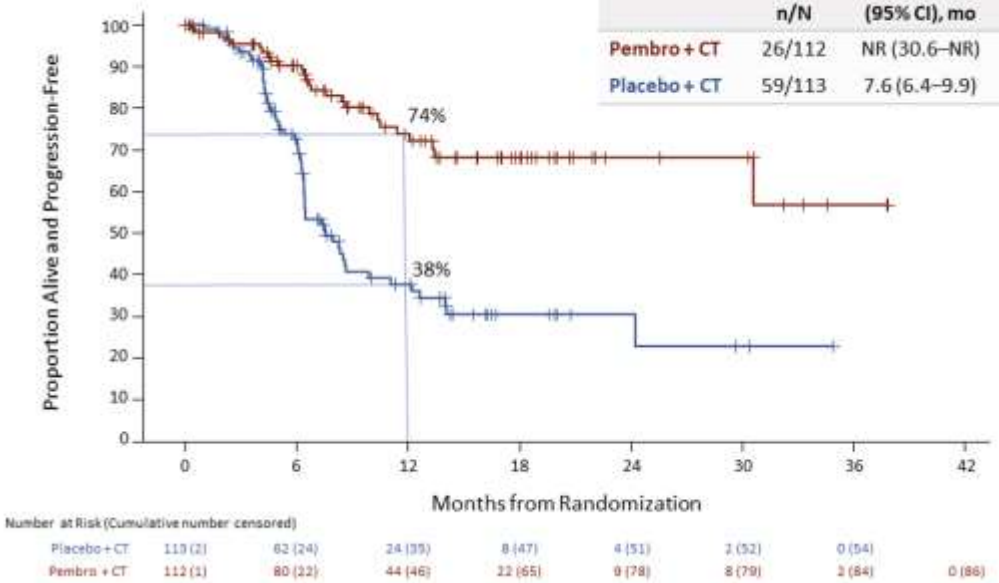
Mirza MR, *et al. N Engl J Med 2023; 388:2145-2158*

Pembrolizumab and carboplatin/paclitaxel NRG GY018

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

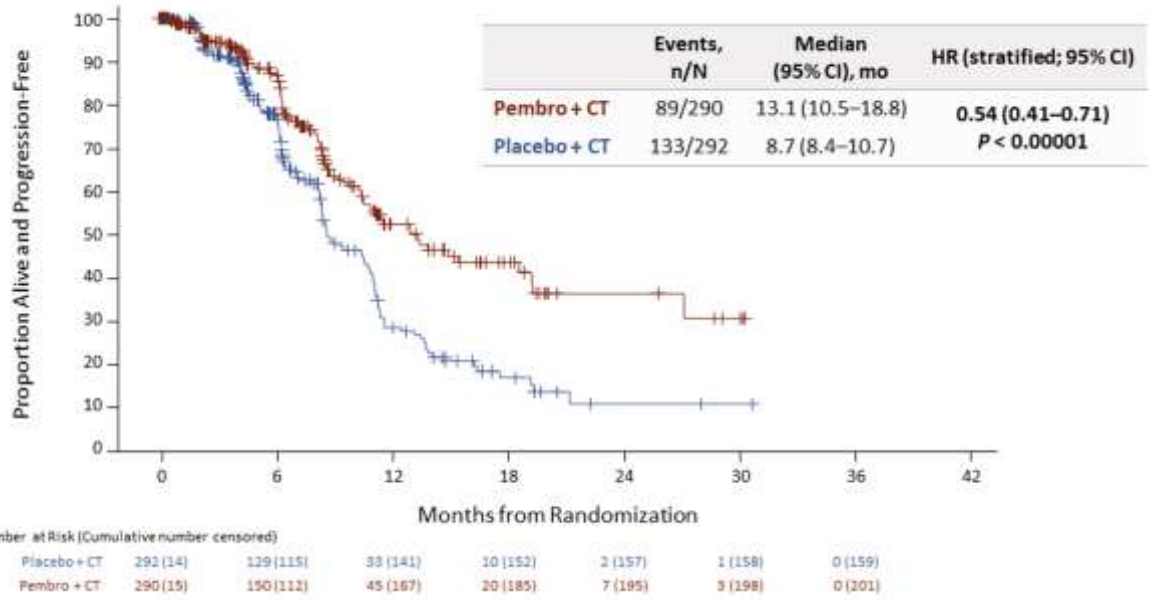
PFS in dMMR population

	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	26/112	NR (30.6–NR)	0.30 (0.19–0.48)
Placebo + CT	59/113	7.6 (6.4–9.9)	*P* = <0.00001



PFS in the pMMR population

	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	89/290	13.1 (10.5–18.8)	0.54 (0.41–0.71)
Placebo + CT	133/292	8.7 (8.4–10.7)	*P* < 0.00001



Questions for the future

ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

Will Immunotherapy replace chemotherapy as front-line treatment for advanced or high-risk endometrial cancer ?

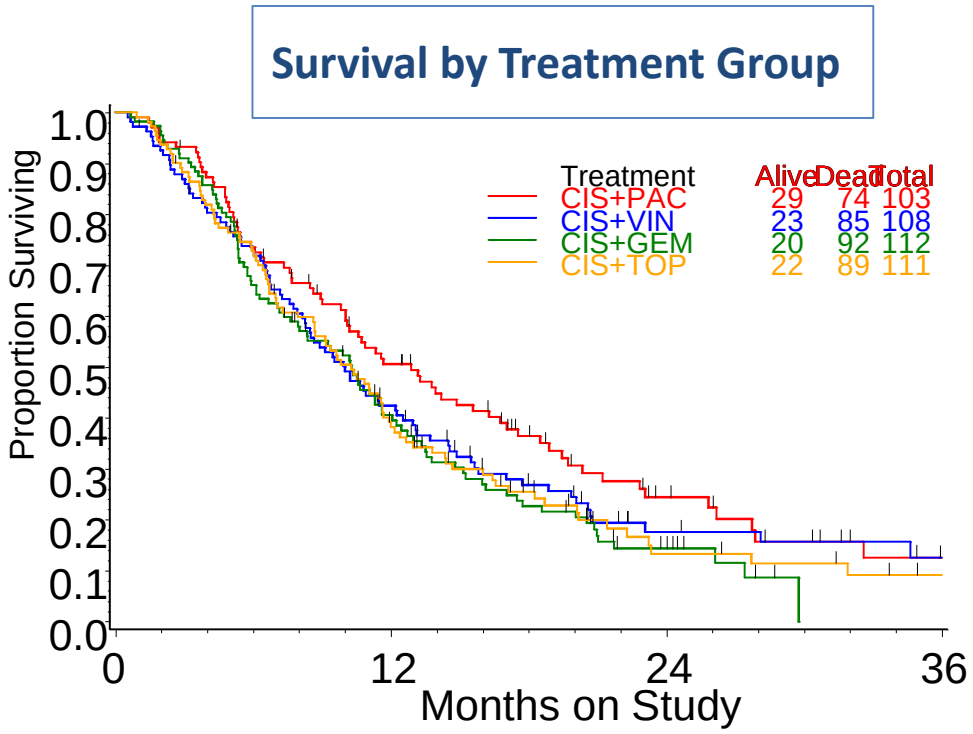
ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

Cervical Cancer

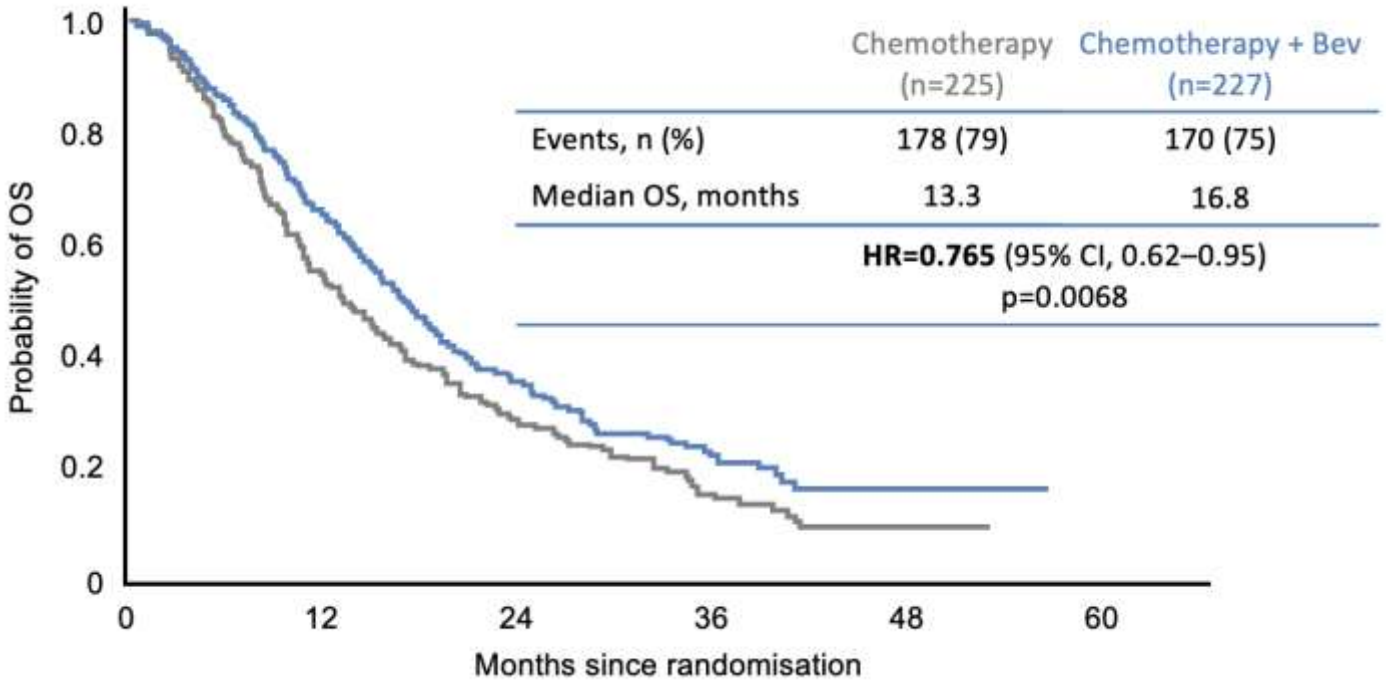
History - chemotherapy for recurrent cervical cancer

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

GOG-204
Combination chemotherapy



GOG–240
Adding bevacizumab to chemotherapy



Monk BJ, et al. *J Clin Oncol* 2009; 27(28):4649-4655;

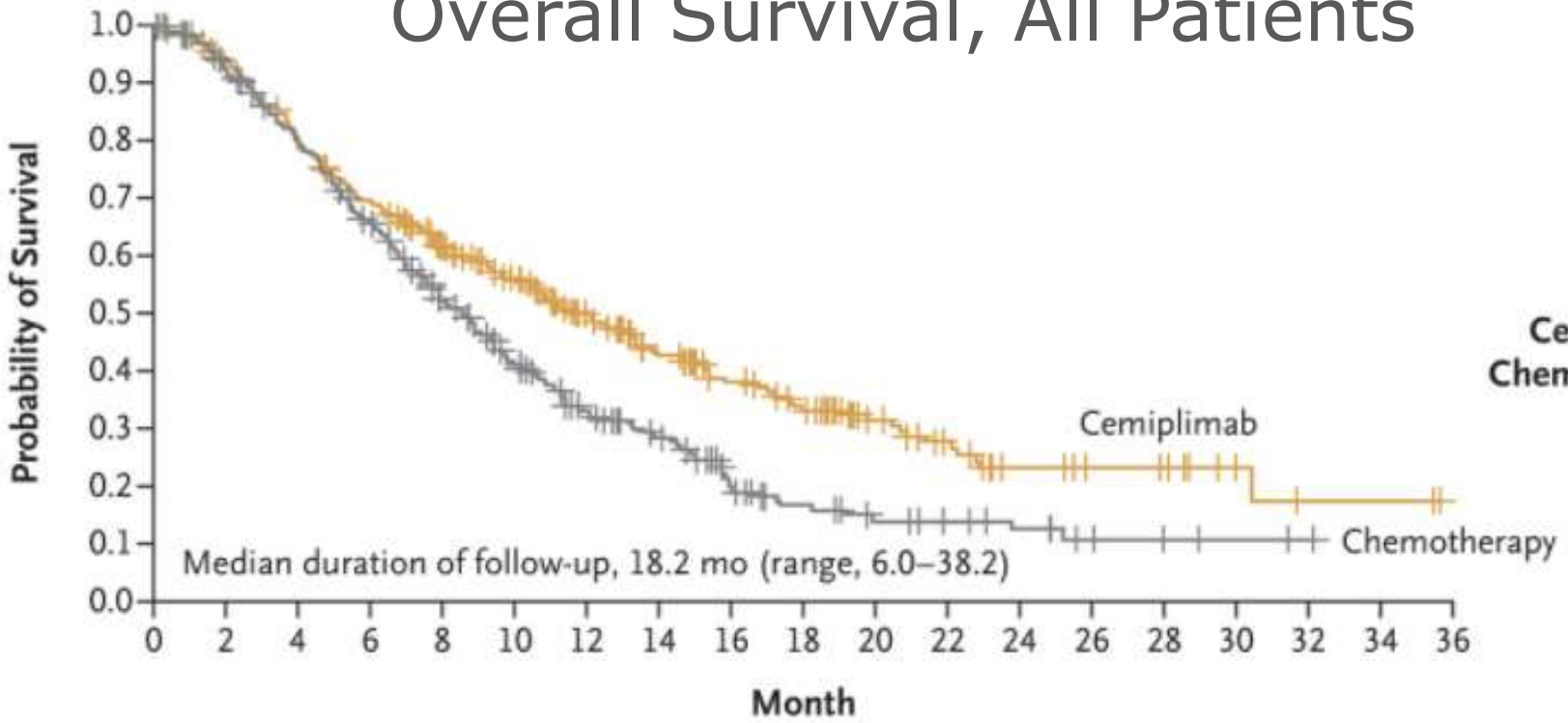
Tewari et al Lancet. 2017

Immunotherapy with Cemiplimab for Recurrent Cervical Cancer Resistant/failed platinum therapy

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 (NCT03257267) Trial

Overall Survival, All Patients



	No. of Patients	Median Overall Survival (95% CI)
		mo
Cemiplimab	304	12.0 (10.3–13.5)
Chemotherapy	304	8.5 (7.5–9.6)

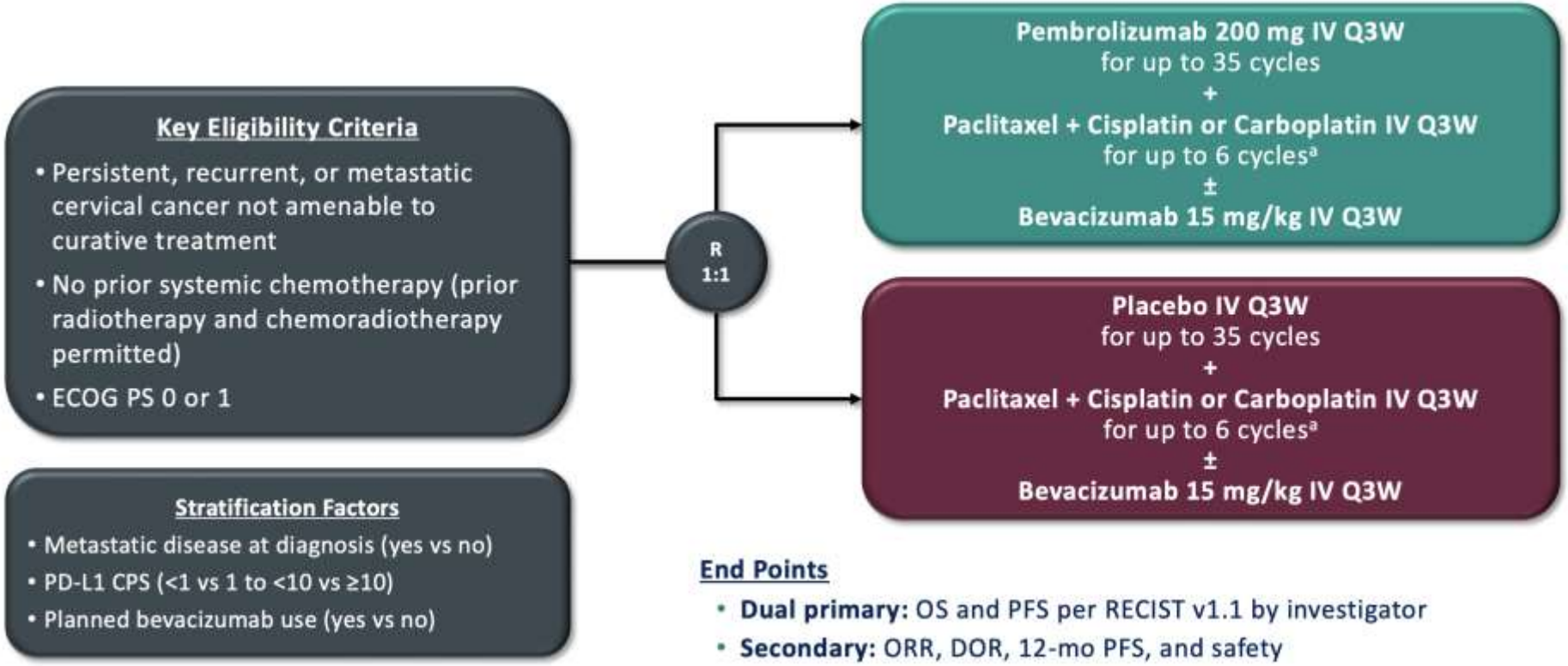
Hazard ratio for death, 0.69 (95% CI, 0.56–0.84)
Two-sided P<0.001

No. at Risk

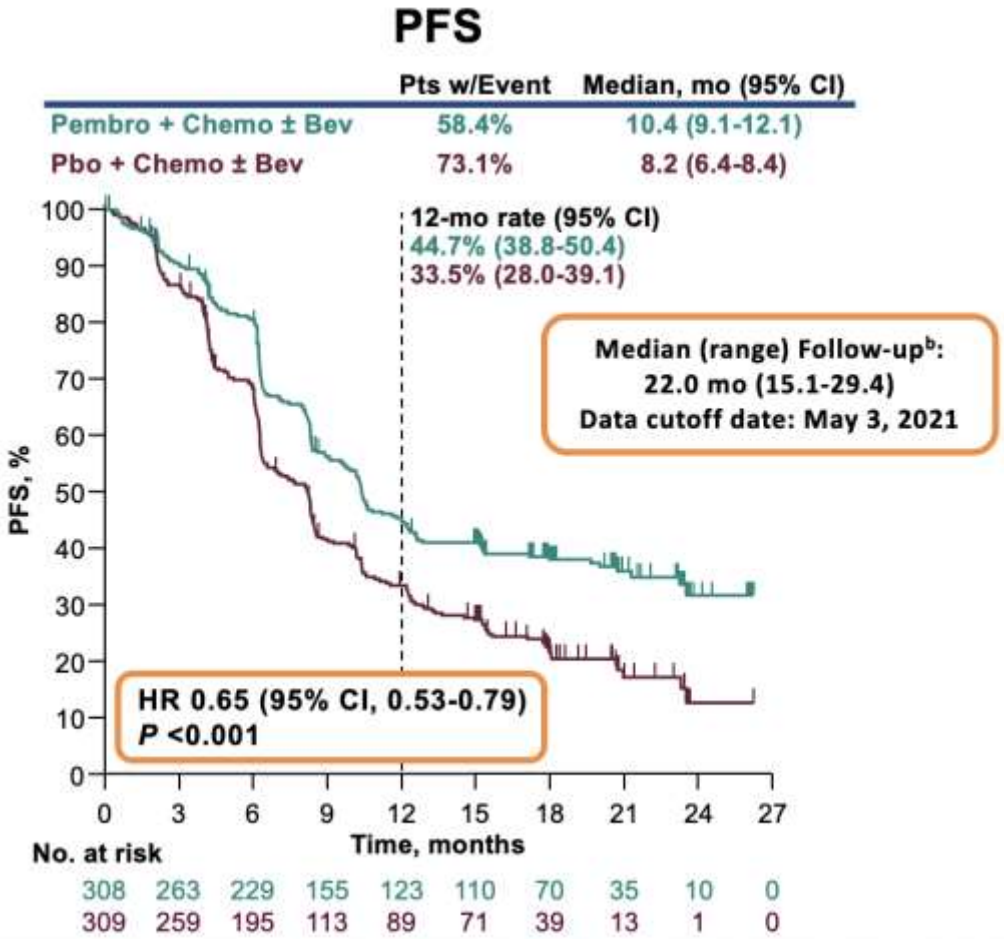
Cemiplimab	304	281	236	206	167	139	110	83	65	52	35	26	13	10	9	4	2	2	0
Chemotherapy	304	264	224	183	132	99	70	54	32	22	15	12	9	5	3	2	1	0	0

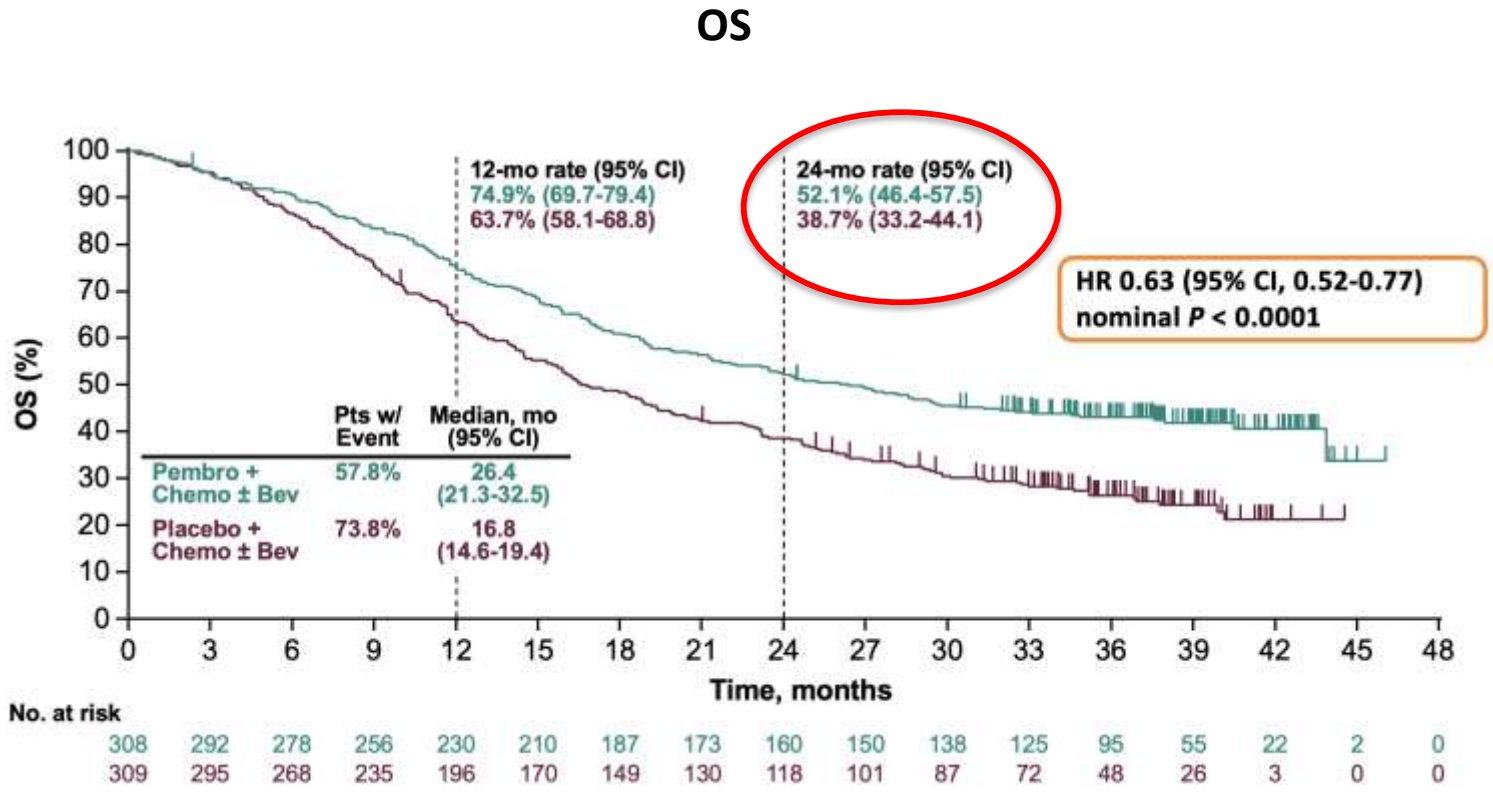
KEYNOTE-826: Randomized, Double-Blind Phase 3 Study

Combining immune Checkpoint inhibitor Pembrolizumab with chemotherapy



Keynote – 826: Final Results Overall Survival

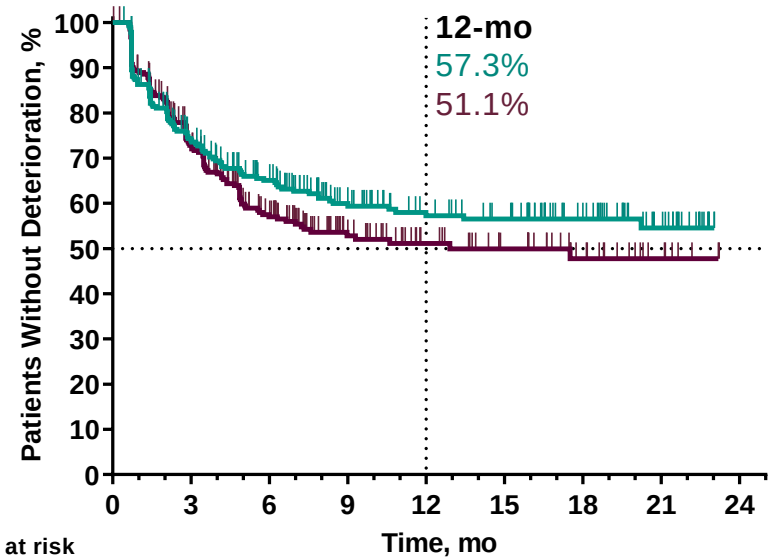




Time to True Deterioration[a] of Quality of Life

QLQ-C30 GHS/QoL

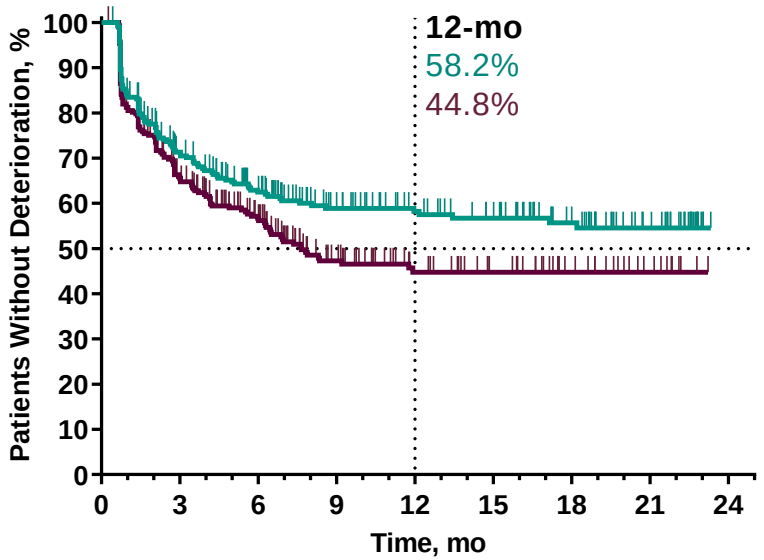
	Median, mo (95% CI)	HR (95% CI) *P* Value
Pembrolizumab group	NR (13.4–NR)	0.84 (0.65–1.09)
Placebo group	12.9 (6.6–NR)	*P*=0.1851



No. at risk									
Pembrolizumab group	279	182	141	102	80	71	46	23	0
Placebo group	283	187	117	69	46	34	18	7	0

EQ-5D-5L VAS

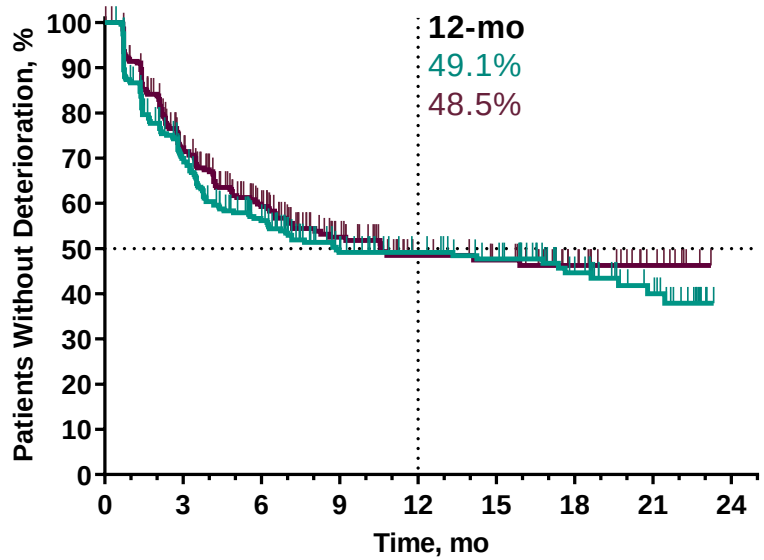
	Median, mo (95% CI)	HR (95% CI) *P* Value
Pembrolizumab group	NR (17.2–NR)	0.75 (0.58–0.97)
Placebo group	7.7 (6.0–NR)	*P*=0.0273



	281	177	138	101	83	72	49	26	0
	285	168	118	72	48	36	20	9	0

QLQ-C30 Physical Functioning

	Median, mo (95% CI)	HR (95% CI) *P* Value
Pembrolizumab group	8.9 (6.0–19.7)	1.11 (0.87–1.42)
Placebo group	10.6 (7.0–NR)	*P*=0.3937



	279	177	126	86	73	64	41	22	0
	283	182	120	75	49	43	23	9	0

NR, not reached; TTD, time to true deterioration.

[a]TTD: time from baseline to the first ≥10-point deterioration in PRO score with confirmation by a second adjacent ≥10-point deterioration or death. TTD was estimated using the Kaplan-Meier method.

Data cutoff date: May 3, 2021.

Incremental **Improvements in Survival (OS) in Treating Metastatic and Recurrent Cervical Cancer with Combinations and Biomarkers**

ENGAGe ESGO European Network of Gynaecological Cancer Advocacy Groups

Chemotherapy backbone (platinum + taxane) 2009

GOG 204 established the global standard with a median OS of 12.9 months[1]

Adding bevacizumab 2014

GOG 240 added bevacizumab in eligible patients with a median OS of 17.5 months[2]

Adding pembrolizumab if biomarker positive (PD-L1 22c3)

KN-826 added pembrolizumab in PD-L1 positive (CPS ≥1%). Median OS not recached (24.4 months in all comers) [3]

J Clin Oncol. 2009 Oct 1;27(28):4649-55; Lancet. 2017 Oct 7;390(10103):1654-1663; N Engl J Med. 2021 Nov 11;385(20):1856-1867.

Thank you!

engage@esgo.org
engage.esgo.org

ENGAGe
ESGO | European Network of Gynaecological Cancer Advocacy Groups