NOVEL ADVANCES IN OVARIAN AND UTERINE CANCERS

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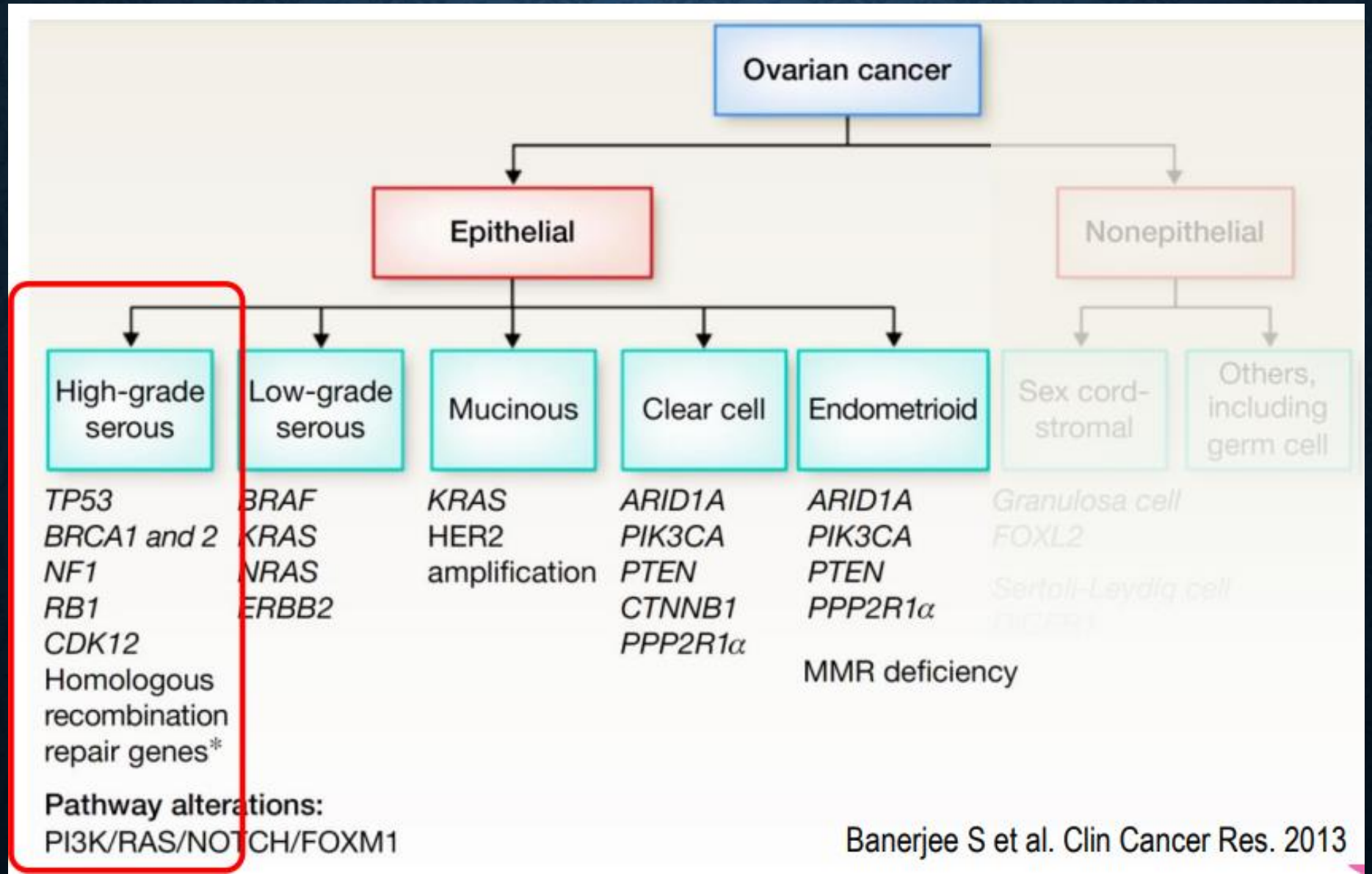
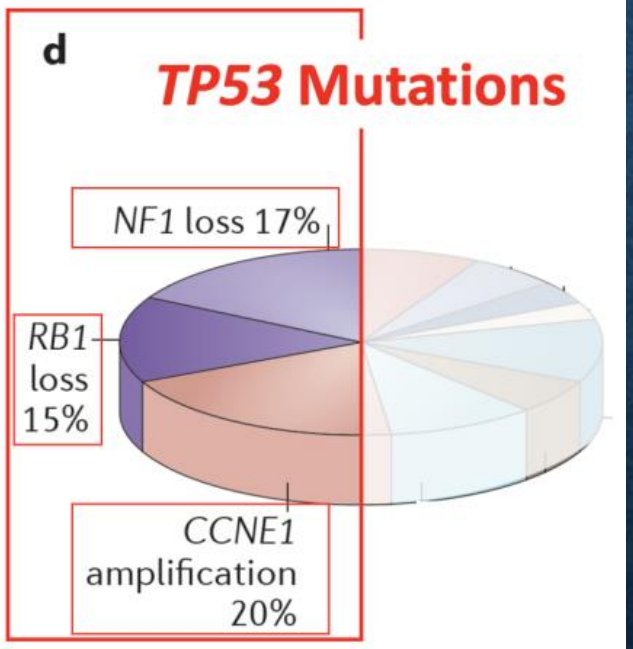
OVARY CANCER HETEROGENEITY

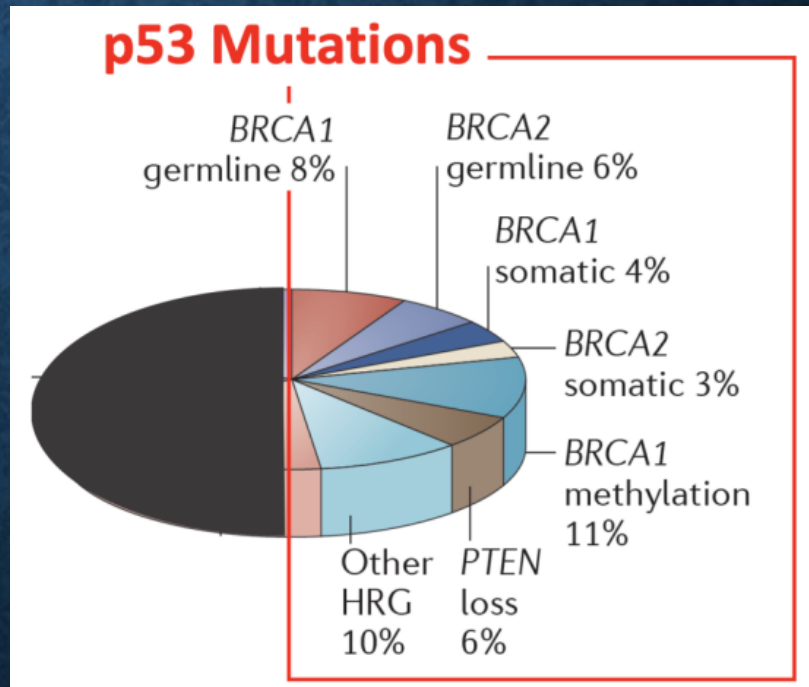


HRD-

Platinum-resistant ←

PARPi-resistant ←

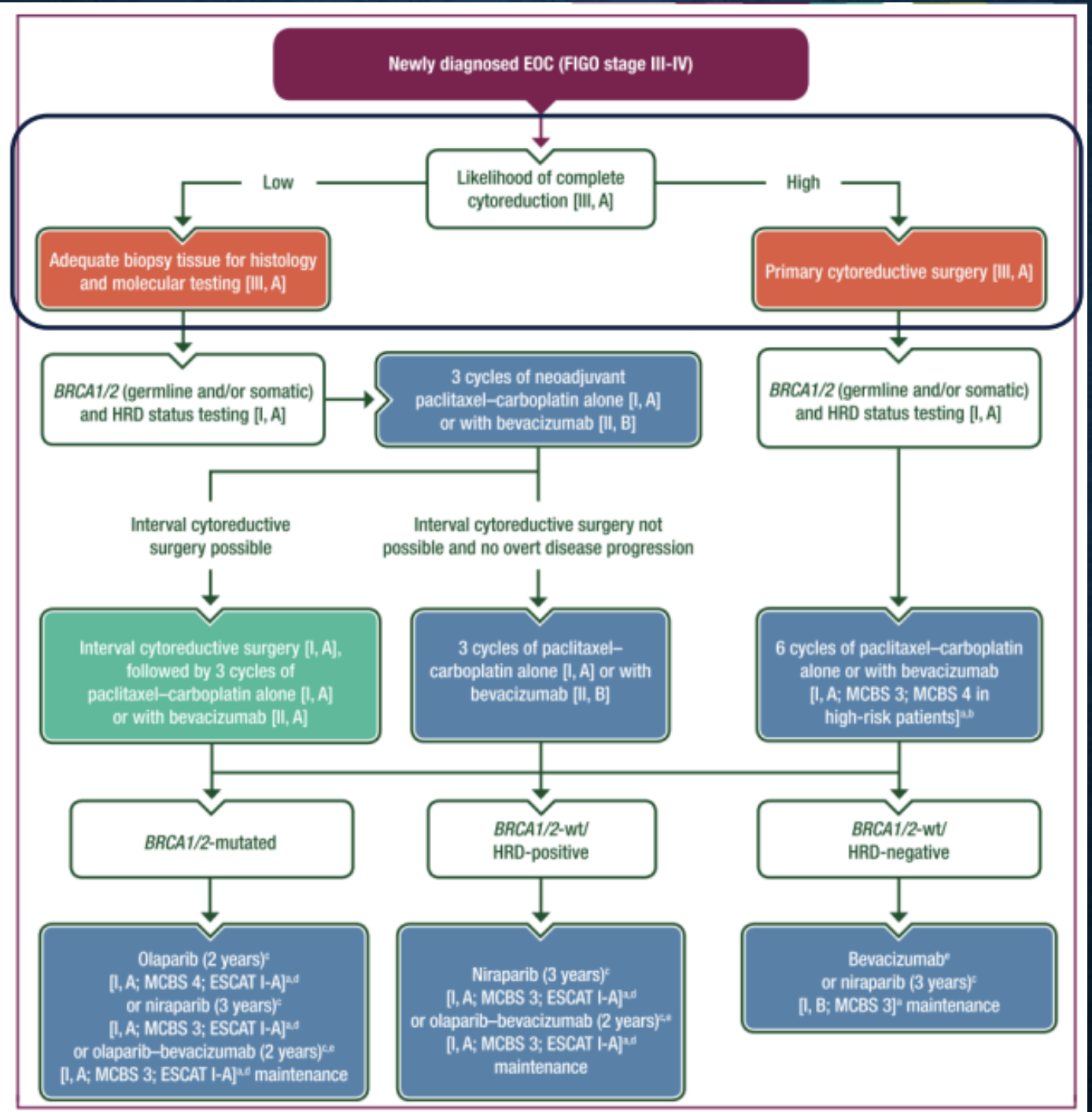




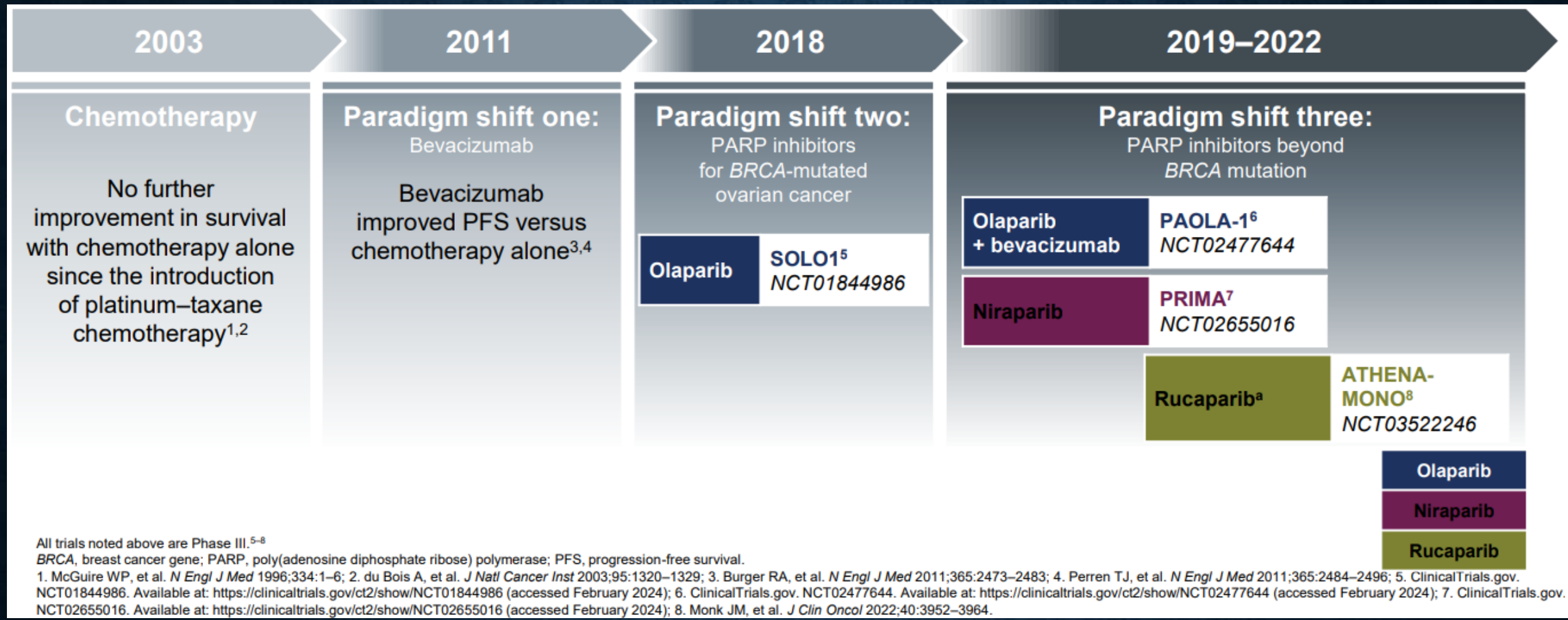
HRD+

→ Platinum

→ PARPi


Newly diagnosed EOC (FIGO stage III-IV)
Likelihood of complete cytoreduction [III, A]
Low
High
Adequate biopsy tissue for histology and molecular testing [III, A]
Primary cytoreductive surgery [III, A]
BRCA1/2 (germline and/or somatic) and HRD status testing [I, A]
3 cycles of neoadjuvant paclitaxel–carboplatin alone [I, A] or with bevacizumab [II, B]
BRCA1/2 (germline and/or somatic) and HRD status testing [I, A]
Interval cytoreductive surgery possible
Interval cytoreductive surgery not possible and no overt disease progression
Interval cytoreductive surgery [I, A], followed by 3 cycles of paclitaxel–carboplatin alone [I, A] or with bevacizumab [II, A]
3 cycles of paclitaxel–carboplatin alone [I, A] or with bevacizumab [II, B]
6 cycles of paclitaxel–carboplatin alone or with bevacizumab [I, A; MCBS 3; MCBS 4 in high-risk patients][a,b]
BRCA1/2-mutated
BRCA1/2-wt/ HRD-positive
BRCA1/2-wt/ HRD-negative
Olaparib (2 years)[c] [I, A; MCBS 4; ESCAT I-A][a,d] or niraparib (3 years)[c] [I, A; MCBS 3; ESCAT I-A][a,d] or olaparib–bevacizumab (2 years)[c,e] [I, A; MCBS 3; ESCAT I-A][a,d] maintenance
Niraparib (3 years)[c] [I, A; MCBS 3; ESCAT I-A][a,d] or olaparib–bevacizumab (2 years)[c,e] [I, A; MCBS 3; ESCAT I-A][a,d] maintenance
Bevacizumab[e] or niraparib (3 years)[c] [I, B; MCBS 3][a] maintenance

- Patients with advanced EOC should be evaluated for PCS by a **specialised team**, with the aim of achieving **complete cytoreduction** (absence of all visible residual disease) [III, A].
- **When complete cytoreductive surgery is feasible, PCS is recommended** [III, A]; otherwise, obtaining adequate biopsy tissue for histology and molecular testing is recommended [III, A].
- **When complete cytoreductive surgery is not feasible, NACT for three cycles followed by ICS** and three cycles of paclitaxel carboplatin are recommended [I, A]. Bevacizumab in the neoadjuvant setting, before ICS, can be considered [II, B].
- When ICS is not possible, and in the absence of overt disease progression, three additional cycles of paclitaxel carboplatin alone [I, A] or with bevacizumab [II, B] are recommended.



SIGNIFICANT PROGRESS IN OVARY CANCER

	SOLO-1[1]	PRIMA[2]	PAOLA-1[3]	ATHENA-MONO[4]	PRIME[5]
PARPi	Olaparib	Niraparib	Olaparib	Rucaparib	Niraparib
Bevacizumab	No	No	Yes	No	No
Population	BRCAmut	All comers	All comers	All comers	All comers (Chinese)
HRD test	NA	MyChoice	MyChoice	Foundation-One	BGI
BRCAmut	0.33 (0.25–0.43)	0.40* (0.27–0.62)	0.31* (0.20–0.47)	0.31* (0.20–0.47)	0.40* (0.23-0.68)
BRCAwt/HRD+	-	0.50* (0.31-0.83)	0.43* (0.28-0.66)	0.58* (0.33-1.01)	0.58* (0.36-0.93)
BRCAwt/HRD-	-	0.68* (0.49-0.94)	1.0* (0.75-1.36)	0.65* (0.45-0.95)	0.41* (0.25-0.65)

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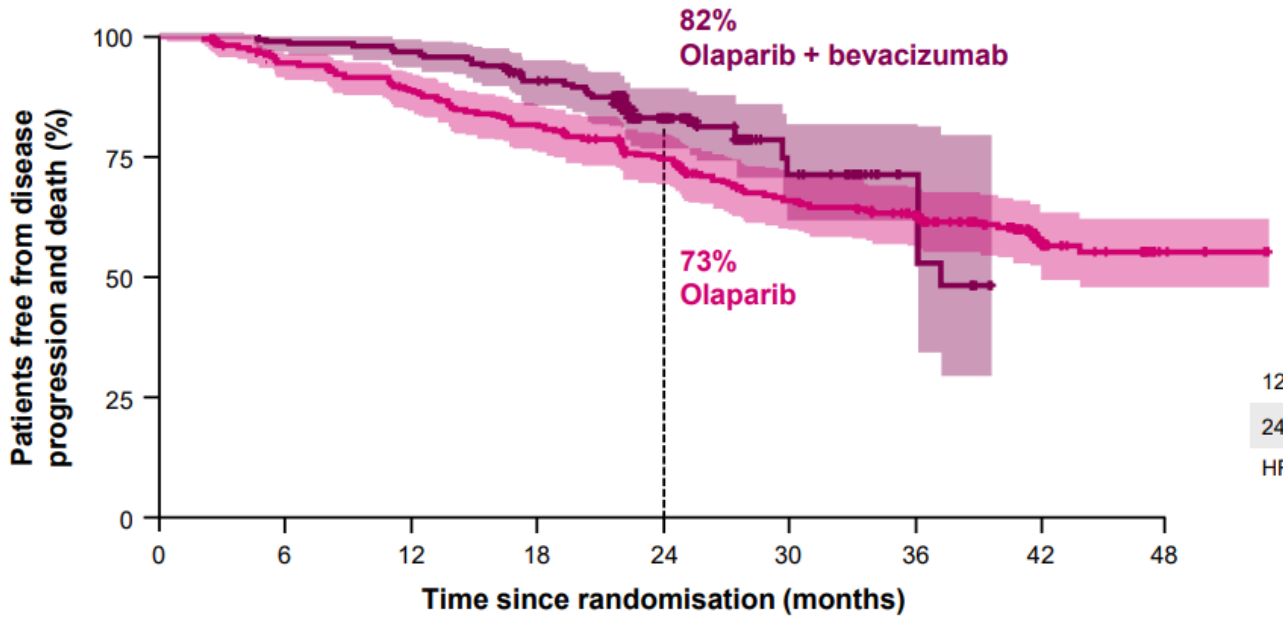
BIOMARKERS AND PARP-I

Patients with BRCAm

Should we add bevacizumab?

ADDITIVE BENEFIT FROM BEVACIZUMAB: PAOLA-1 V SOLO-1



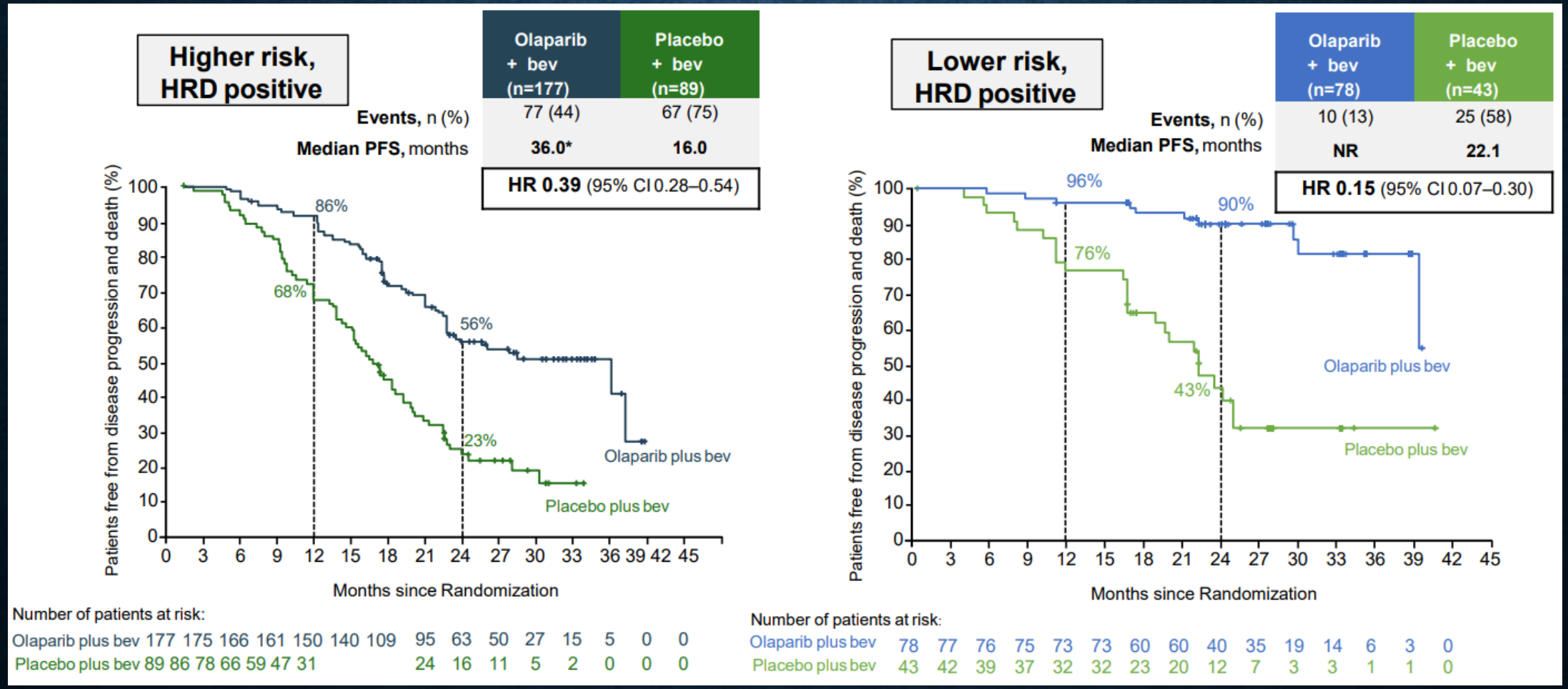
Kaplan-Meier estimate of % of patients progression-free

	PAOLA-1 tumour *BRCA*m	SOLO1
	Olaparib + bevacizumab* n=151	Olaparib n=254
12 months	96	88
24 months	82	73
HR (95% CI)	0.71 (0.45-1.09)†	

In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. Shaded region represents 95% CI.
In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm.
*These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (PDS vs IDS), residual disease status after surgery, response to first-line treatment and age to SOLO1. †CIs generated by bootstrapping. *BRCA*, breast cancer susceptibility gene; *BRCA*m, *BRCA* mutation; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IDS, interval debulking surgery; PDS, primary debulking surgery.
Vergote I, et al. *Eur J Cancer*. 2021;157:415-423.

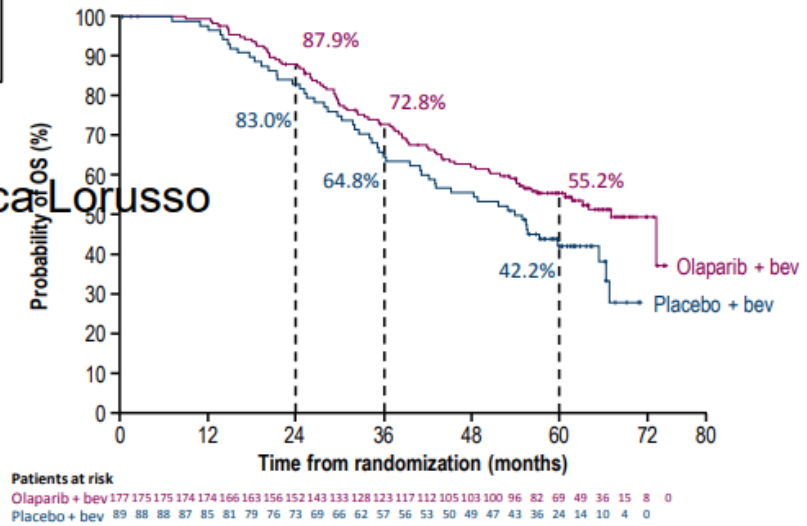
Patients with HRD positive tumor

Should we add bevacizumab?



5-year OS by clinical risk in HRD-positive patients

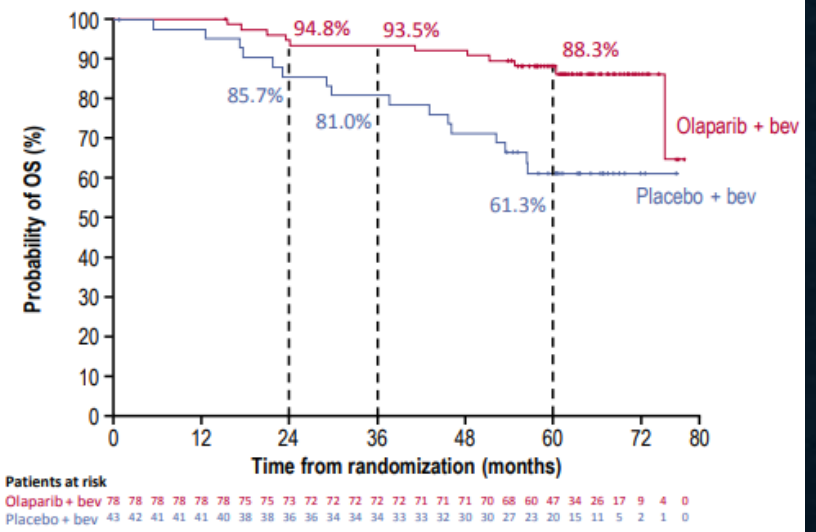
Higher risk



Domenica Lorusso

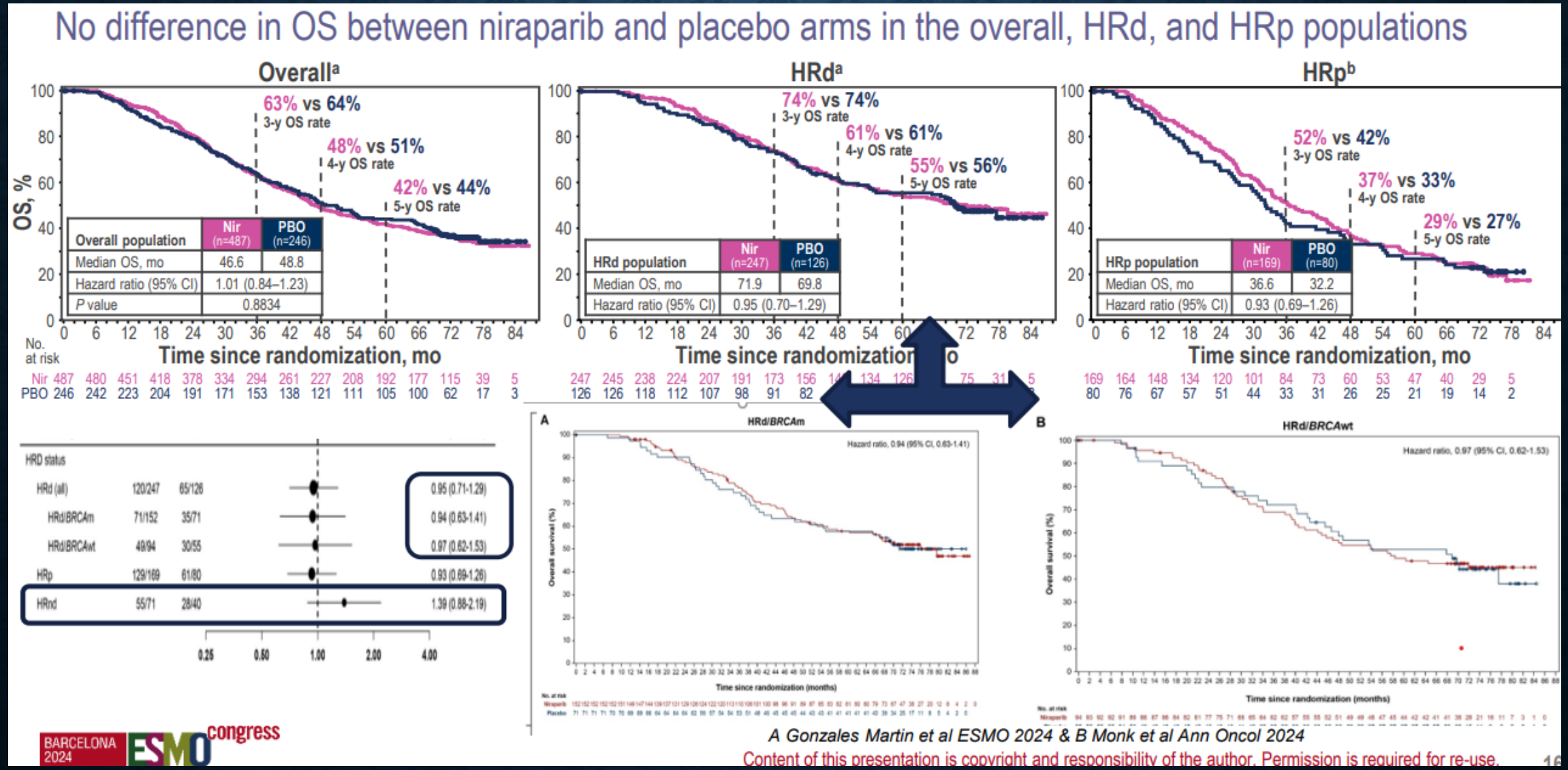
	Olaparib + bevacizumab (n=177)	Placebo + bevacizumab (n=89)
Events, n (%)	82 (46.3)	53 (59.6)
Median OS, months	67.0*	54.0
5-year OS rate, %	55.2	42.2
	HR 0.70 (95% CI 0.50–1.00)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	18.6	56.2

Lower risk



	Olaparib + bevacizumab (n=78)	Placebo + bevacizumab (n=43)
Events, n (%)	11 (14.1)	16 (37.2)
Median OS, months	NE	NE
5-year OS rate, %	88.3	61.3
	HR 0.31 (95% CI 0.14–0.66)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	14.1	39.5

PRIMA: NO OVERALL SURVIVAL BENEFIT



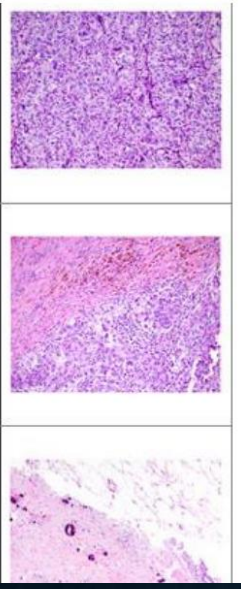
A Gonzales Martin et al ESMO 2024 & B Monk et al Ann Oncol 2024

WHY DID PRIMA SHOW NO BENEFIT IN 1ST LINE OVARY CA MAINTENANCE?

Hypotheses to explore

- Different clinical trial (population, sensitivity to platinum based CT…), no direct comparison
- Combination with bevacizumab (before randomisation and during maintenance Parpi) versus monotherapy
- Safety and dose intensity
- Progression during Parpi maintenance alone (more than 90% in PRIMA) or in combination with Bevacizumab (35% in PAOLA-1)
- Role of subsequent therapies
  - Surgery post progression 15.8% in PRIMA
  - Bevacizumab 35.8% PRIMA and 14.8% PAOLA-1
- Role of upfront surgery and no residual disease

The chemotherapy response score (CRS)



CRS score 1: No or minimal tumour response (mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci)

CRS score 2: Appreciable tumour response with residual tumour, (ranging from multifocal or diffuse fibro-inflammatory regressive changes, with tumour in sheets, streaks or nodules, to extensive regression associated fibro-inflammatory changes with multifocal residual tumour which is **regularly** distributed and easily identifiable)

CRS score 3: Complete or near-complete response (mainly regression associated fibro-inflammatory changes with minimal i.e. very few, **irregularly** scattered individual tumour cells or cell groups or nodules up to 2mm OR no residual tumour identified)

Pathological chemotherapy response score is prognostic in HGSC: A systematic review and meta-analysis of individual patient data

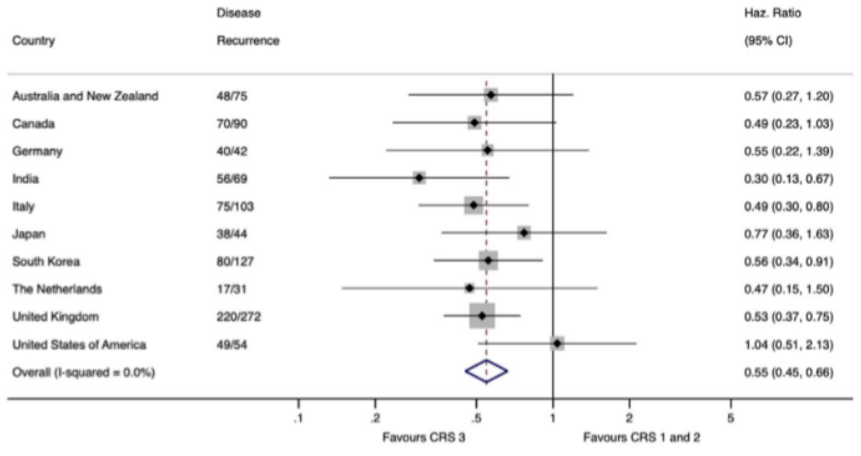
CRS After NACT

Individual data of 877 patients

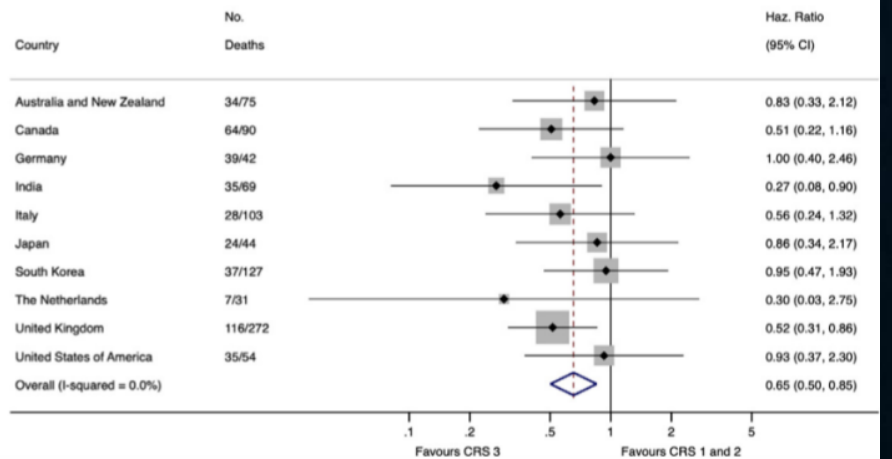
28% achieved CRS-3

Patients with NACT were not included In ICON-7 / GOG-218
Lack of data about the correlation of CRS and PARPi benefit

a) PFS adjusted Forest plot.



b) OS adjusted Forest plot.



SAFETY PROFILE OF PARP-I IN 1ST LINE TRIALS

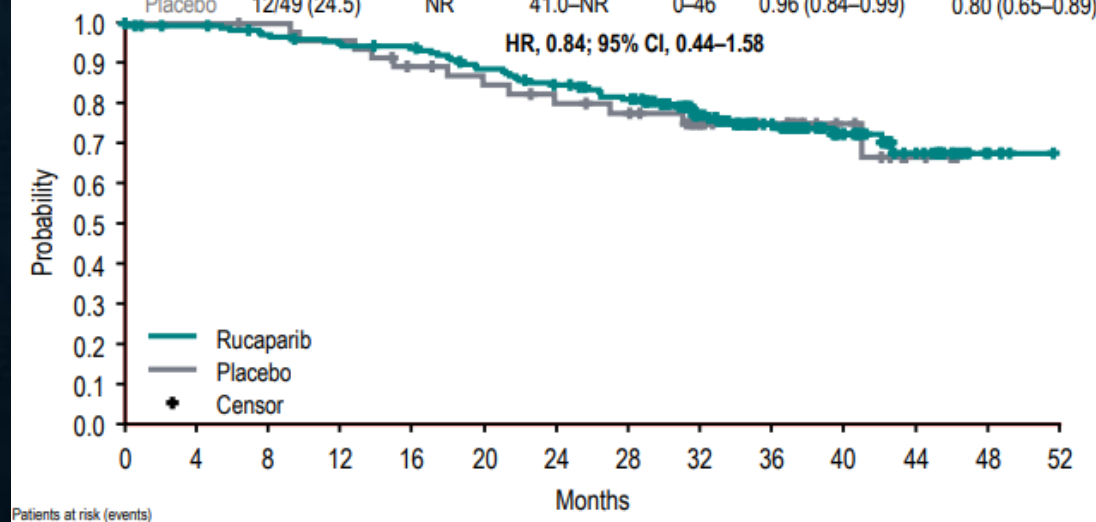
	SOLO1[1]		PRIMA[2]		ATHENA-MONO[3]		PAOLA-1[4]	
	Olaparib	Placebo	Niraparib	Placebo	Rucaparib	Placebo	Bevacizumab + olaparib	Bevacizumab + placebo
n	260	130	484	244	185	49	535	267
AE leading to								
Dose reduction	28.8%	3.1%	71.7%	10.2%	49.4%	8.2%	41%	7%
Dose interruption	**52.7**%	16.9%	**80.8**%	23.0%	**60.7**%	20.0%	**54**%	24%
Discontinuation	11.9%	3.1%	16.0%	3.7%	11.8%	5.5%	20%	6%
Grade ≥3 AEs	39.6%	20%	70.5%	18.9%	60.5%	22.7%	57%	51%

ATHENA MONO OS RESULTS

Primary Analysis Populations

HRD (25% Maturity)

	Events/N (%)	Median	95% CI	Range	12-mo Est	24-mo Est
Rucaparib	46/185 (24.9)	NR	NR–NR	0–52	0.95 (0.91–0.97)	0.85 (0.78–0.89)
Placebo	12/49 (24.5)	NR	41.0–NR	0–46	0.96 (0.84–0.99)	0.80 (0.65–0.89)

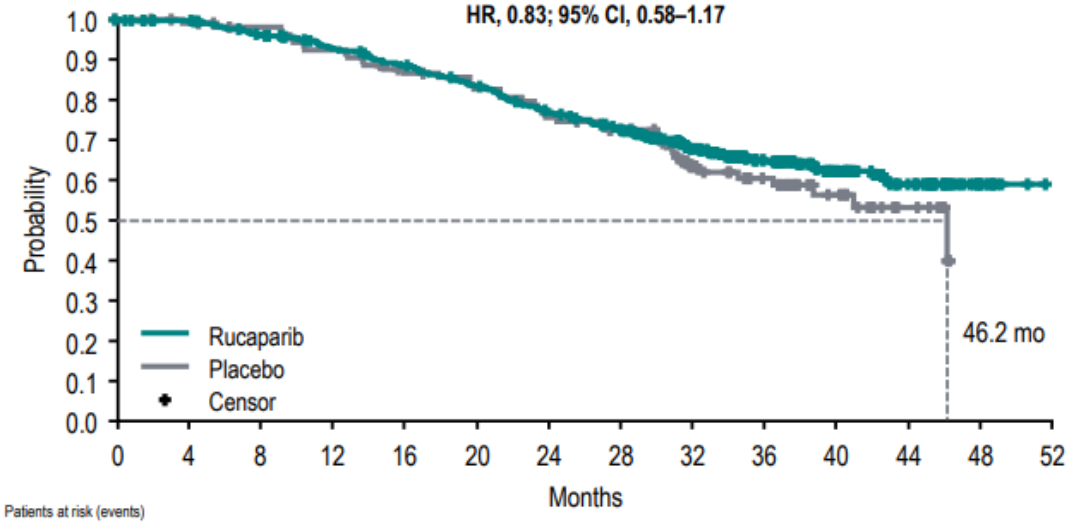


Patients at risk (events)

Rucaparib	185 (0)	180 (1)	174 (5)	169 (9)	166 (11)	155 (20)	146 (27)	137 (33)	106 (39)	79 (42)	43 (44)	23 (46)	5 (46)	0 (46)
Placebo	49 (0)	48 (0)	47 (0)	45 (2)	40 (5)	37 (7)	34 (9)	32 (10)	23 (11)	18 (11)	10 (11)	4 (12)	0 (12)	

ITT (35% Maturity)

	Events/N (%)	Median	95% CI	Range	12-mo Est	24-mo Est
Rucaparib	144/427 (33.7)	NR	NR–NR	0–52	0.93 (0.90–0.95)	0.77 (0.73–0.81)
Placebo	42/111 (37.8)	46.2	34.6–NR	0–46	0.92 (0.85–0.96)	0.76 (0.66–0.83)



Patients at risk (events)

Rucaparib	427 (0)	419 (1)	399 (16)	379 (29)	359 (47)	337 (67)	308 (93)	284 (111)	217 (128)	156 (136)	89 (141)	45 (144)	11 (144)	0 (144)
Placebo	111 (0)	107 (1)	103 (2)	97 (8)	89 (13)	83 (18)	75 (25)	69 (28)	49 (36)	36 (38)	22 (40)	9 (41)	0 (42)	

Data cutoff date: March 9, 2023.

CI, confidence interval; Est., estimate; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; mo, months; NR, not reached; OS, overall survival.

Risk factor for progression of disease[1,a]	PRIMA[2] (niraparib)	PAOLA-1[3] (olaparib)	ATHENA-MONO[4] (rucaparib)	GOG-0218[5] (bevacizumab)
Stage IV disease	35%	31%	25%	26%
*BRCA*wt	70%	71%	79%	70%
Upfront primary surgery		50%	48.9%	100%
Neoadjuvant chemotherapy	67%	49%	51%	0%
Partial response to chemotherapy	31%	27%	18%	N/A
Visible residual disease	47%	40%	25%	>75%

CROSS TRIALS COMPARISON IS DIFFICULT!

?

Patients with HRD negative tumor

Should we use PARP-I or bevacizumab?

Survival Data?

Clinical characteristics (stage and residual tumor)?

Response to chemotherapy?

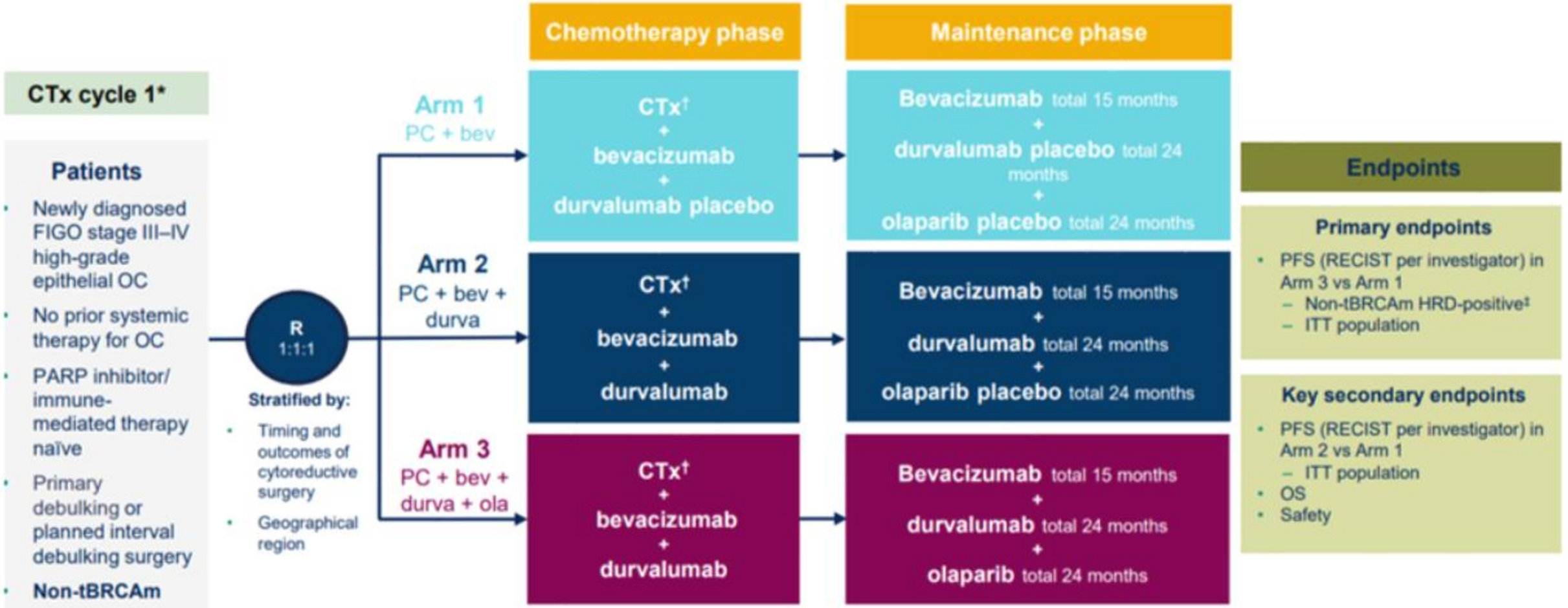
Toxicity and quality of life/patient preference ?

PARP-I IN COMBINATION WITH ICI

- **DUO-O**
- **ATHENA Combo**
- **Keylynk**
- **FIRST**

DUO-O/ENGOT-ov46/GOG-3025

Adding CPI and Bevacizumab to Parpi maintenance



Endpoints

Primary endpoints

- PFS (RECIST per investigator) in Arm 3 vs Arm 1
  - Non-tBRCAm HRD-positive‡
  - ITT population

Key secondary endpoints

- PFS (RECIST per investigator) in Arm 2 vs Arm 1
  - ITT population
- OS
- Safety

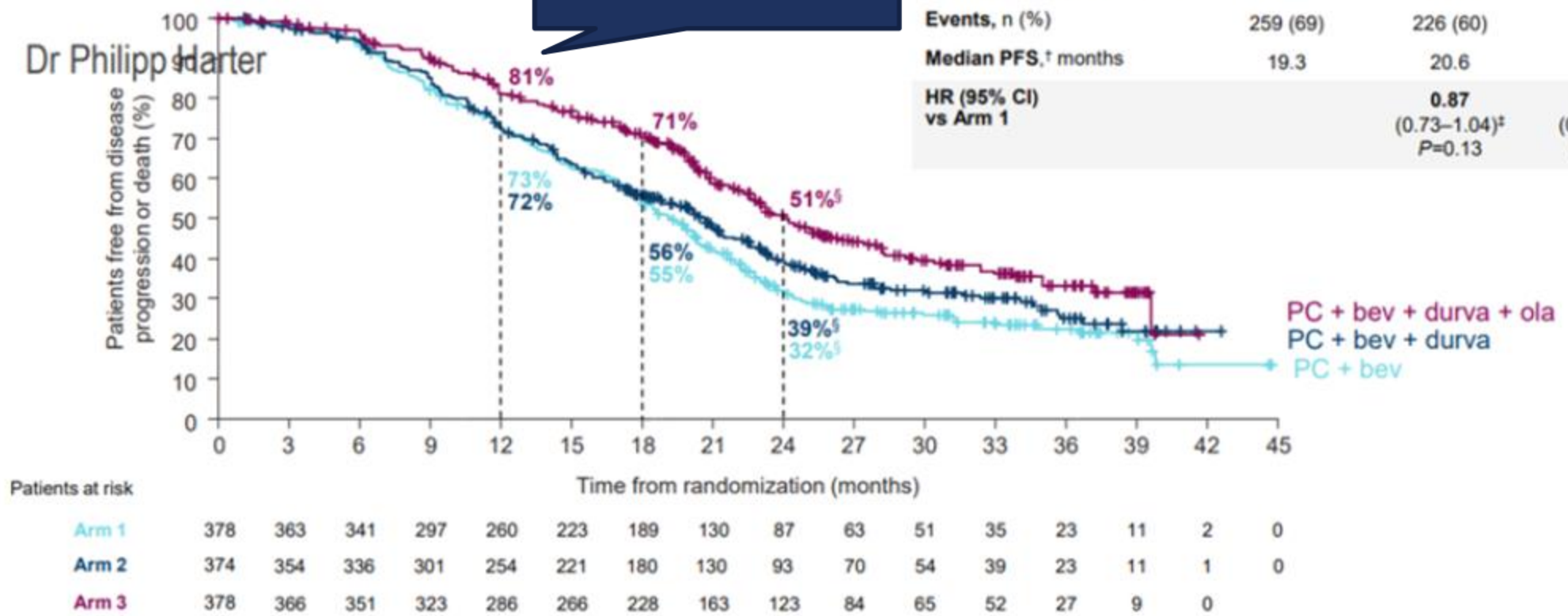
Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m² IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022

DUO-O PFS: ITT population

What is the contribution of durvalumab?
Is this another Paola 1 ?

Dr Philipp Harter

	Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.1	23.3
Events, n (%)	259 (69)	226 (60)	193 (51)
Median PFS,† months	19.3	20.6	24.2
HR (95% CI) vs Arm 1		**0.87** (0.73–1.04)‡ *P*=0.13	**0.63** (0.52–0.76)‡ *P*<0.0001

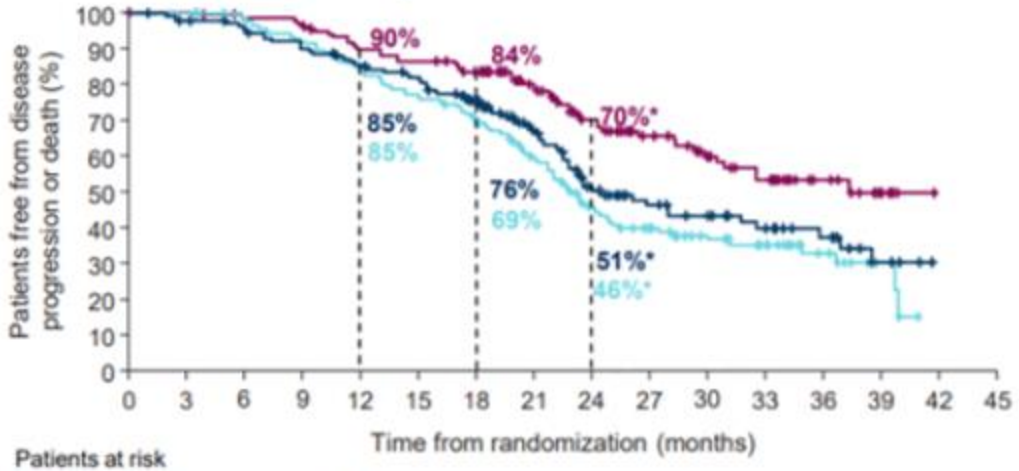


Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 2	374	354	336	301	254	221	180	130	93	70	54	39	23	11	1	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

DUO-O Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

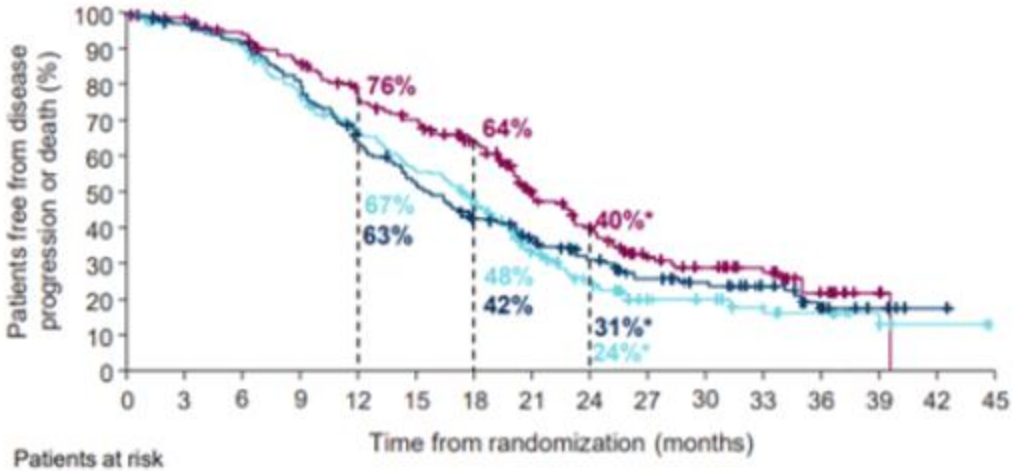


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

ATHENA STUDY

Key Patient Eligibility

- Newly diagnosed, stage III–IV, advanced, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; complete resection permitted)
- ECOG PS 0 or 1
- No prior frontline maintenance treatment for ovarian cancer

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

- Tumor HRD test status[a]
- Disease status post-chemotherapy
- Timing of surgery

Treatment for 24 months,[b] with a 4-week lead-in of rucaparib; study drugs could be discontinued independently

Study Analyses

ATHENA-COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

ATHENA-MONO

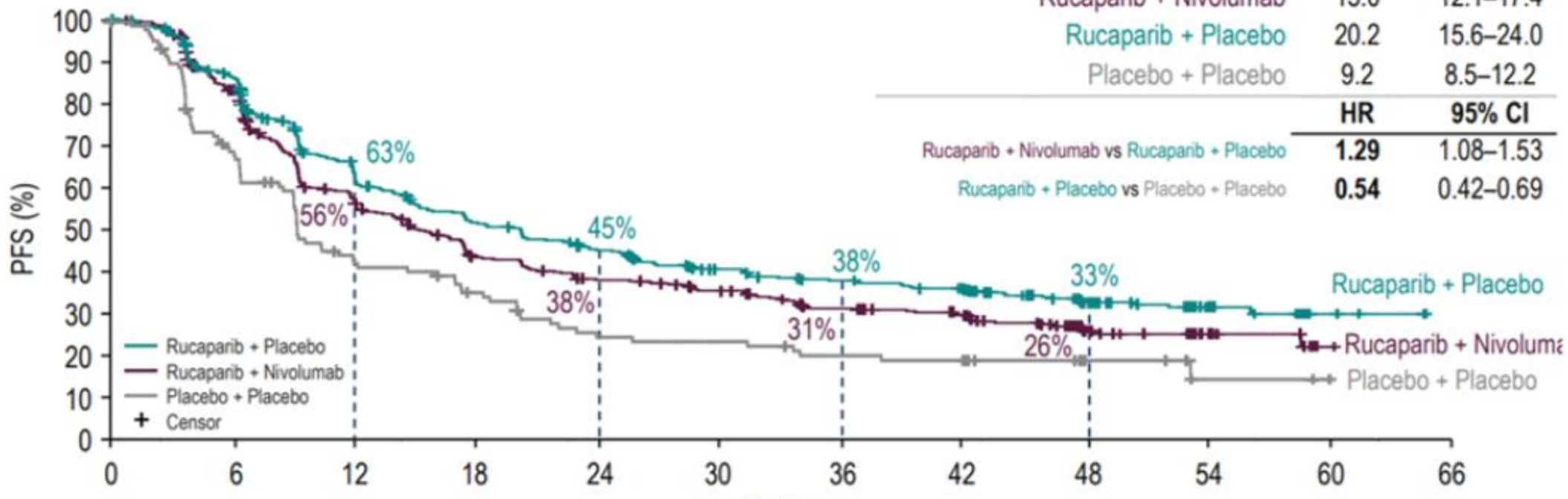
Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

Primary endpoint: Investigator-assessed PFS in the ITT population

ATHENA-COMBO: INVESTIGATOR-ASSESSED PFS (ITT)

	Median	95% CI
Rucaparib + Nivolumab	15.0	12.1–17.4
Rucaparib + Placebo	20.2	15.6–24.0
Placebo + Placebo	9.2	8.5–12.2
	HR	**95% CI**
Rucaparib + Nivolumab vs Rucaparib + Placebo	**1.29**	1.08–1.53
Rucaparib + Placebo vs Placebo + Placebo	**0.54**	0.42–0.69



Patients at risk (events)

Ruca+Nivo	436 (0)	333 (69)	218 (174)	159 (224)	136 (244)	122 (253)	98 (267)	87 (272)	44 (280)	14 (282)	1 (283)	0 (283)
Ruca+Plac	427 (0)	352 (57)	246 (149)	197 (193)	166 (218)	136 (234)	123 (243)	113 (249)	68 (258)	24 (260)	4 (261)	0 (261)
Plac+Plac	111 (0)	73 (34)	43 (61)	33 (69)	23 (78)	21 (80)	17 (83)	16 (84)	8 (84)	2 (85)	1 (85)	0 (85)

SGO2025 LATE BREAKING ABSTRCTS NEWSFLASH

December 9, 2024 6:45 am ET

(pembrolizumab) plus chemotherapy followed by maintenance with (olaparib), with or without bevacizumab, demonstrated a statistically significant and clinically meaningful improvement in PFS compared to chemotherapy alone

The study did not reach its secondary endpoint of overall survival

Issued: 20 December 2024, London UK

announces FIRST trial met its primary endpoint of progression free survival in first line advanced ovarian cancer

- Addition of (dostarlimab) to both platinum-based chemotherapy and (niraparib) maintenance, with or without bevacizumab, demonstrated a statistically significant effect on progression free survival (PFS) versus active comparator arm

OVARY CANCER SUBTYPES: GENETIC ALTERATIONS

Table 1. Most common genetic alterations by OC subtypes

Genomic alteration	HGSOC	LGSOC	Clear cell	Mucinous	Endometrioid
TP53	96.2%	2.0%	21.6%	26.8%	28.0%
KRAS	–	23.7%	8.0%	53.7%	28.0%
BRCA1	12.0%	–	3.0%	–	–
BRCA2	5%	–	–	–	–
PTEN	7.3%	–	5.6%	–	28.0%
CDKN2A	2.2%	1.6%	–	15.9%	–
ARID1A	–	–	51.2%	8.3%	38.0%
PIK3CA	–	1.3%	52.8%	–	43.0%
CCNE1	22%	-	14%	–	10.7%
ERBB2	–	-	16.7%	26.0%	17.8%

LOW GRADE SEROUS CARCINOMA OF OVARY

MEKi & Co

. GOG 0281:	**Trametinib** vs Soc	unselected	HR_{PFS} 0.48	✓
. ENGOT-ov11:	**Binimetinib** vs CHT	unselected	HR_{PFS} 1.21	✗
. ENGOT-gyn2:	**Cobimtinib**	MAPK alt.	33% ORR	✓
. ENGOT-ov60:	**Avumetinib/Defactinib**	RASwt	29% ORR	✓
		RASmut	60% ORR	✓

→ **ENGOT-ov81 RAMP 301 Randomized Phase III**

Endocrine +/- CDK4/6:

. GOG 0281:	**Letrozol**	13% ORR
. PARAGON	**Anastrozol**	14% ORR
. GOG 3026:	**Letrozol** + **Ribociclib**	23% ORR, DOR 19 mo
. Neoadjuvant	**Fulvestrant** + **Abemaciclib**	60% ORR

OVARIAN CLEAR CELL CA

Gene	Changes	Pathways affected
ARID1A	Mutation in approximately 50%	SWI/SNF chromatin remodeling complex
ARID1B	Mutation in 6%–18%	SWI/SNF chromatin remodeling complex
SMARCA4	Mutation in 5%–18%	SWI/SNF chromatin remodeling complex
PIK3CA	Mutation in approximately 50%	PI3K/AKT
PIK3R1	Mutation 7%–10%	PI3K/AKT
AKT2	Amplification in 8%–26%	PI3K/AKT
PTEN	Mutation in 2%–13%	PI3K/AKT
KRAS	Mutation in 4.7%–20%	MAPK
PPP2R1A	Mutation in 4.1%–20%	MAPK
ERBB2	Mutation and amplification in 2%–13%	MAPK
MET	Amplification in 24%–37%	MAPK
TP53	Mutation in 8.5%–21.6%	DNA repair
TERT promoter	Mutation in 5%–16%	TERT
ZNF217	Amplification in 20%–36%	ZNF217

⇨ HER2-ADCs

NOVEL STRATEGIES IN OVARY CLEAR CELL CA

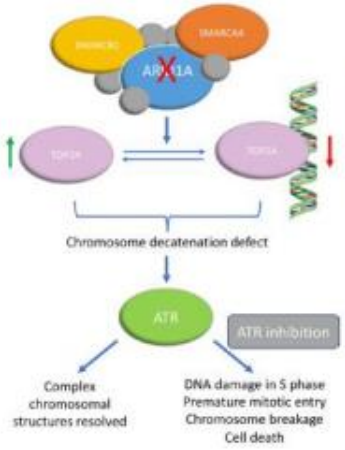
Ovarian Clear Cell Carcinoma

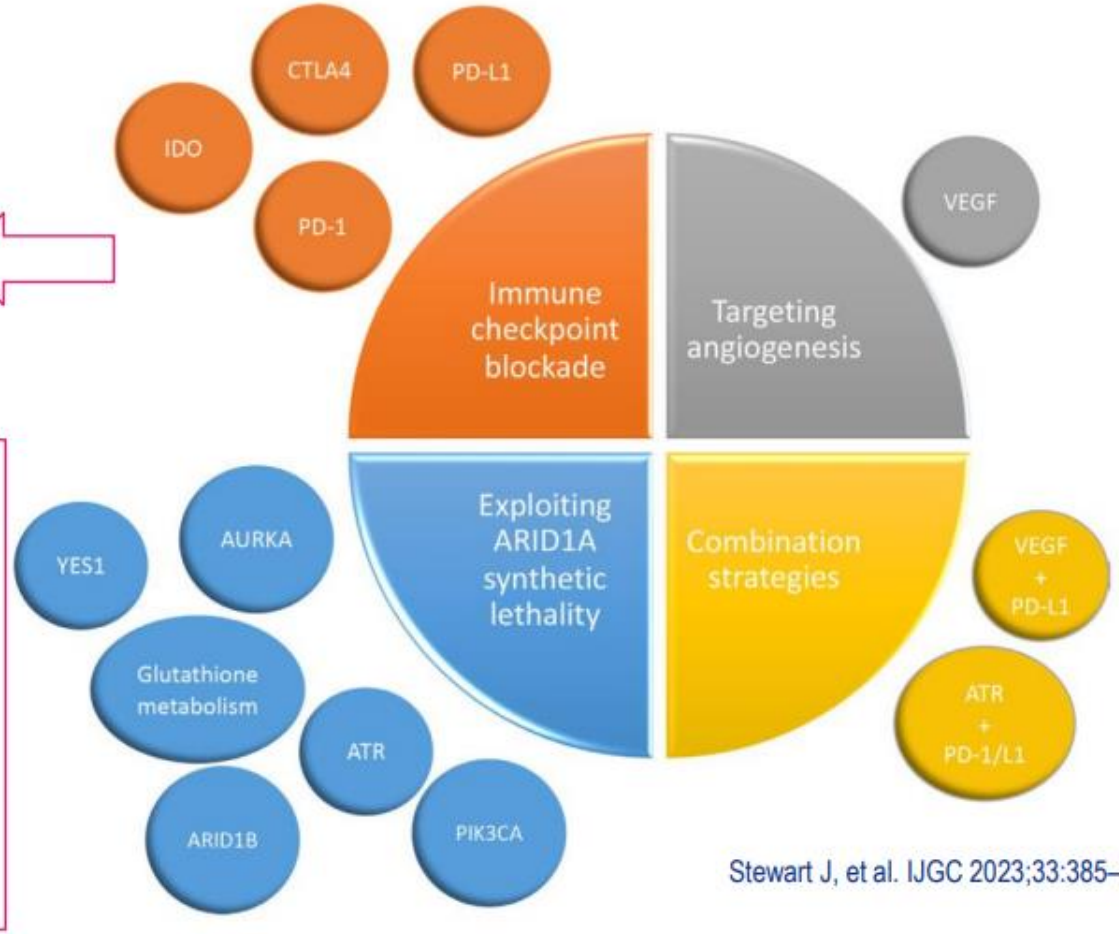
ARID1A loss associated with:
↑PD-L1, ↑TMB, ↑MSI

NRG-GY016:	Pembro + IDOi	**ORR 21%**
PEACOCC:	Pembro	**ORR 25%**
INAVO:	Sintili + Bev	**ORR 38%**
BrUOG-354:	IPI + Nivo	**ORR 33%**

ATARI trial: ATR inhibitor in combination with olaparib in gynecological cancers with ARID1A loss or no loss (ENGOT/GYN1/NCRI)

OCCC	ARID1A loss	Celarasertib	**ORR 14%**
OCCC	ARID1A no loss	Cela/Ola	**ORR 14%**



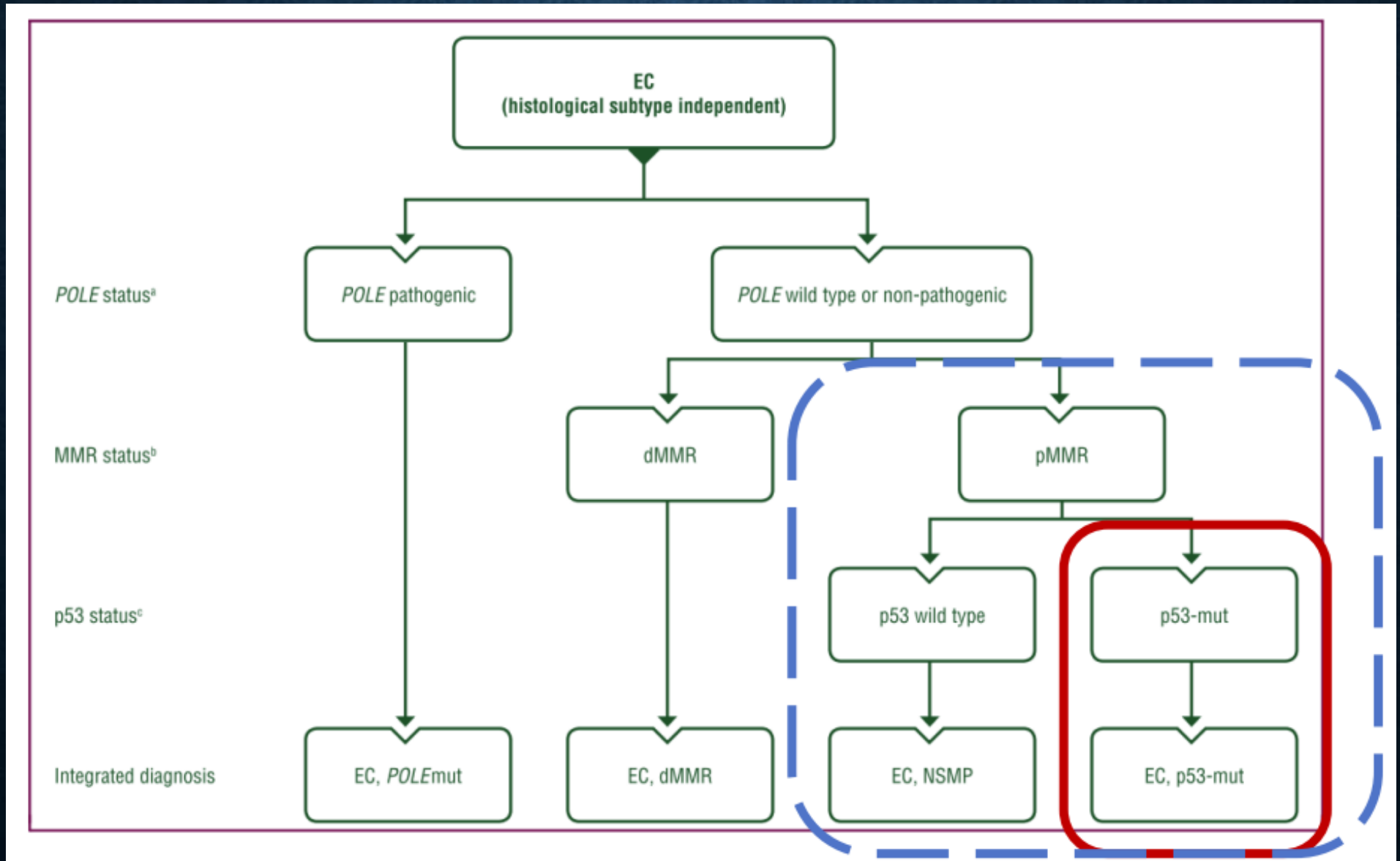


Stewart J, et al. IJGC 2023;33:385–393

ENDOMETRIAL CANCER: FIGO 2023 STAGING

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

ENDOMETRIAL CA: SUBTYPES



FIRST LINE CLINICAL TRIALS WITH IO IN EC

NRG-GY018

Key Eligibility Criteria

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent EC
- No prior Chemo except prior adjuvant Chemo if completed ≥12 months before study
- ECOG PS 0-1 or 2

Randomization 1:1

Pembrolizumab 200 mg IV q3w **Paclitaxel** 175 mg/m² IV q3w **Carboplatin** AUC 5 IV q3w for 6 cycles	**Pembrolizumab** 400 mg IV q6w for up to 14 additional cycles
Placebo IV q3w **Paclitaxel** 175 mg/m² IV q3w **Carboplatin** AUC 5 IV q3w for 6 cycles	**Placebo** IV q6w for up to 14 additional cycles

Stratification Factors

- MMR/MSI status
- ECOG PS (0-1 vs 2)
- Prior adjuvant Chemo

Primary Endpoints

- PFS per RECIST v1.1 by investigator in MMRp and dMMR populations

Secondary Endpoints

- Safety, ORR/DOR, OS (MMRp and dMMR), QOL (MMRp)

GOG-3031/RUBY Part 1

Key Eligible Patients

- Histologically/cytologically proven advanced or recurrent EC
- Measurable Stage III/IVA disease, non measurable Stage IVB, or first recurrent EC
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted (also if IIIC2-IVA non measurable)
- Naive to systemic therapy or systemic anticancer therapy and recurrence/PD ≥6 months after completing treatment
- ECOG PS 0-1

Randomization 1:1

Dostarlimab IV 500 mg **Carboplatin** AUC 5 mg/mL/min **Paclitaxel** 175 mg/m² q3w for 6 cycles	**Dostarlimab IV** 1000 mg q6w up to 3 years
Placebo **Carboplatin** AUC 5 mg/mL/min **Paclitaxel** 175 mg/m² q3w for 6 cycles	**Placebo IV** q6w up to 3 years

Stratification Factors

- MMR/MSI status
- Prior pelvic RT
- Disease status

Primary Endpoints

- PFS by INV
- OS

Secondary Endpoints

- PFS by BICR, PFS2, ORR, DOR, DCR , HRQoL/PRO, safety

RESEARCH SUMMARY

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Eskander RN et al. DOI: 10.1056/NEJMoa2302312

CLINICAL PROBLEM

Standard first-line therapy for advanced endometrial cancer is chemotherapy with paclitaxel plus carboplatin. Whether the addition of pembrolizumab would improve patient outcomes is unclear.

CLINICAL TRIAL

Design: A phase 3, double-blind, randomized, controlled trial evaluated the efficacy and safety of standard chemotherapy combined with pembrolizumab in patients with advanced or recurrent endometrial cancer.

Intervention: 816 women with newly diagnosed measurable disease (stage III or IVA) or stage IVB or recurrent endometrial cancer were randomly assigned to receive pembrolizumab or placebo (in 6 cycles every 3 weeks, followed by up to 14 maintenance cycles every 6 weeks) in addition to combination therapy with paclitaxel plus carboplatin. Patients were stratified into two cohorts according to whether they had mismatch repair–deficient (dMMR) or mismatch repair–proficient (pMMR) disease. The primary outcome was progression-free survival.

RESULTS

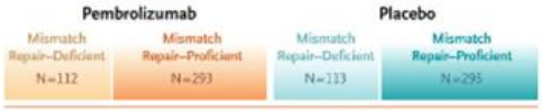
Efficacy: In both cohorts, the addition of pembrolizumab significantly improved progression-free survival.

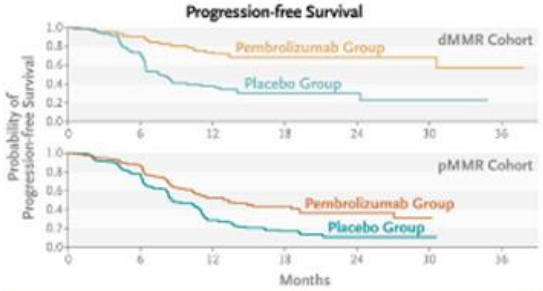
Safety: The frequency of grade ≥3 adverse events was higher with the addition of pembrolizumab to combination chemotherapy. No unexpected adverse events occurred.

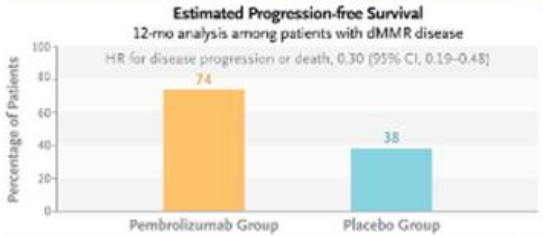
LIMITATIONS AND REMAINING QUESTIONS

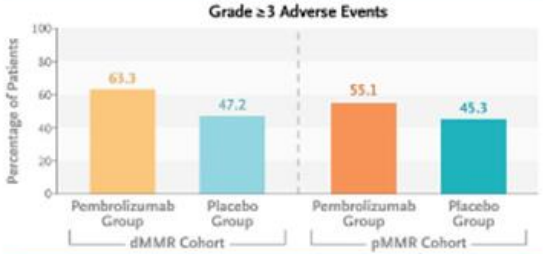
- Follow-up duration was relatively short.
- Whether pembrolizumab monotherapy is more efficacious than pembrolizumab plus chemotherapy in this patient population warrants additional study.

Links: Full Article | NEJM Quick Take









CONCLUSIONS

In patients with advanced or recurrent endometrial cancer, progression-free survival was significantly improved with the addition of pembrolizumab to standard chemotherapy, regardless of the mismatch-repair status of the tumor.

RESEARCH SUMMARY

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

Mirza MR et al. DOI: 10.1056/NEJMoa2216334

CLINICAL PROBLEM

Standard first-line treatment for primary advanced or recurrent endometrial cancer entails chemotherapy with carboplatin and paclitaxel. However, long-term outcomes are poor. Whether combining chemotherapy with immunotherapy could improve outcomes is uncertain; of particular interest is the potential benefit in patients with mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumors, which account for 25 to 30% of endometrial tumors.

CLINICAL TRIAL

Design: A global, phase 3, double-blind, randomized, controlled trial assessed the efficacy and safety of the immune-checkpoint inhibitor dostarlimab combined with chemotherapy, as compared with placebo plus chemotherapy, in patients with primary stage III or IV or recurrent endometrial cancer.

Intervention: 494 patients were assigned to receive dostarlimab (500 mg) or placebo combined with carboplatin and paclitaxel administered intravenously every 3 weeks for six cycles, followed by dostarlimab (1000 mg) or placebo administered intravenously every 6 weeks for up to 3 years. The primary end points were progression-free survival both among patients with dMMR–MSI-H tumors and in the overall trial population and overall survival in the overall trial population. Safety was also assessed.

RESULTS

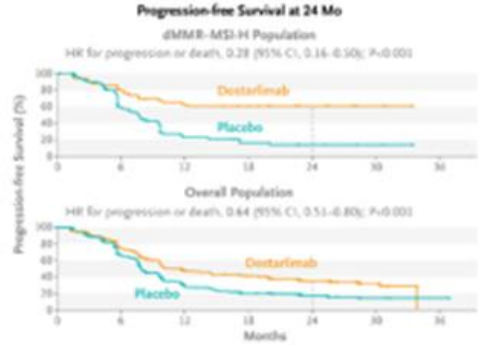
Efficacy: Dostarlimab significantly improved progression-free survival outcomes at 24 months, both in the dMMR–MSI-H population and in the overall population. Overall survival was also improved with dostarlimab.

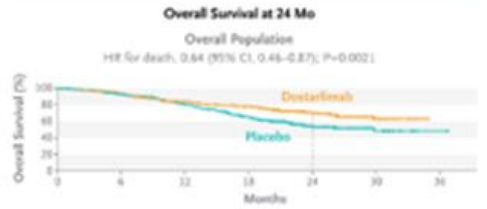
Safety: Both severe (grade ≥3) adverse events and serious adverse events were more common with dostarlimab than with placebo. The most common events were nausea, alopecia, and fatigue.

LIMITATIONS AND REMAINING QUESTIONS

- Subgroup analyses were limited owing to the relatively small sample size and short duration of follow-up.
- Longer-term survival outcomes are unknown and will be assessed as follow-up time increases.

Links: Full Article | NEJM Quick Take

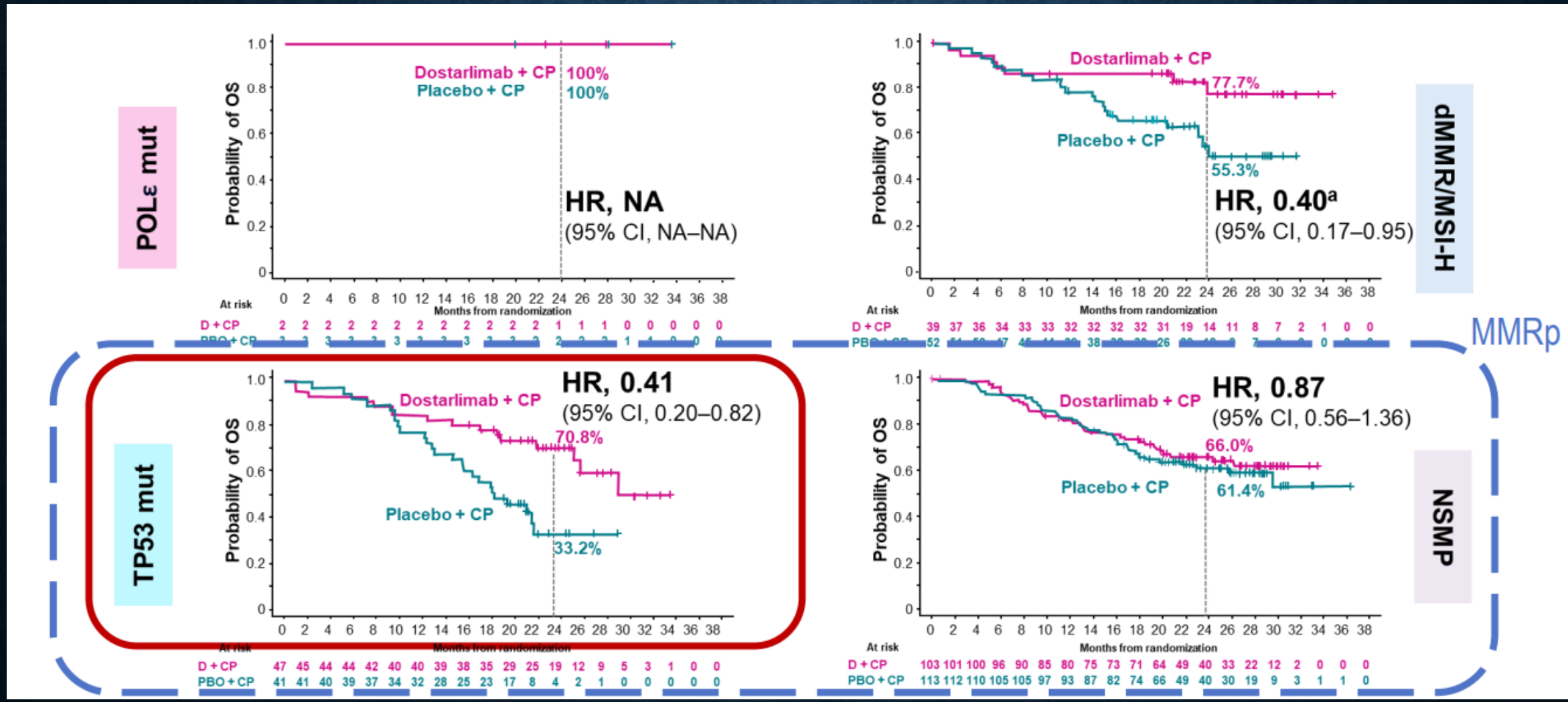




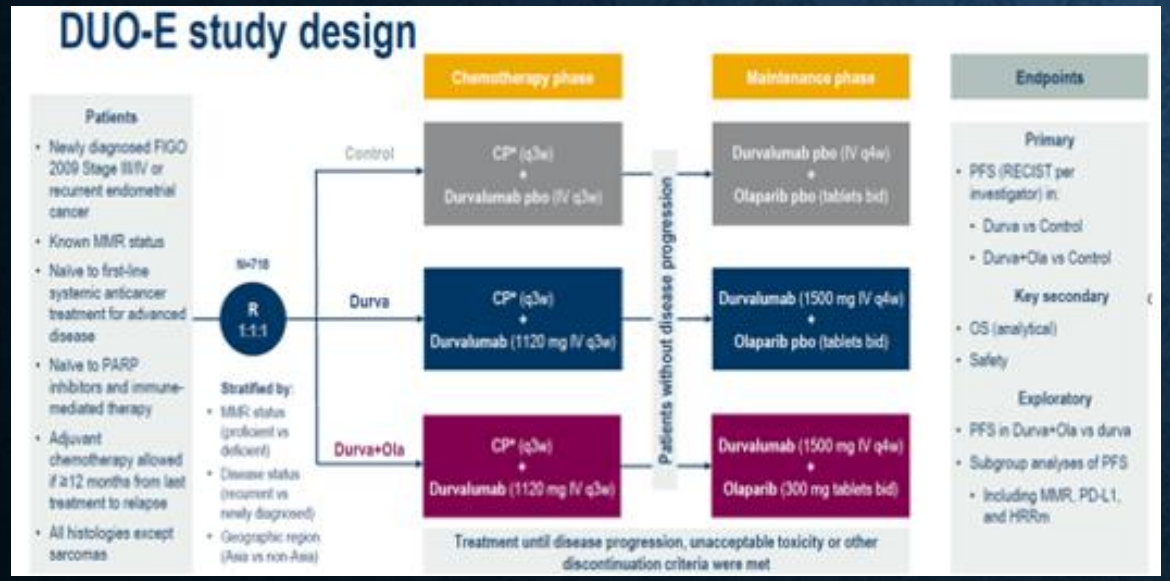
CONCLUSIONS

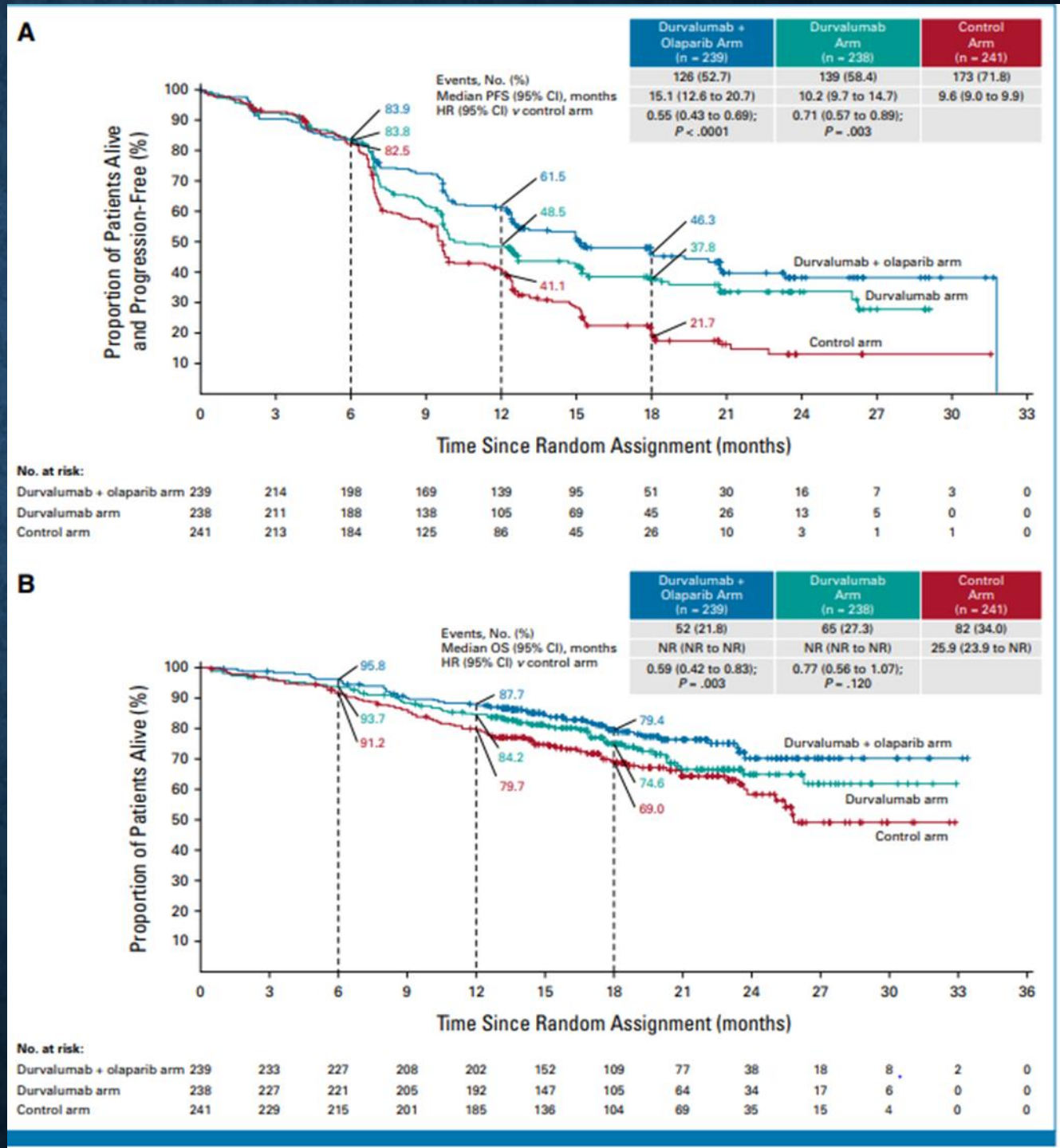
In patients with primary advanced or recurrent endometrial cancer, the combination of dostarlimab plus chemotherapy significantly increased progression-free survival as compared with placebo plus chemotherapy, with particular benefit observed in those with dMMR–MSI-H tumors.

RUBY OS BASED ON MOLECULAR CLASSIFICATION



IO +PARP IN EC: DUO-E TRIAL





IO + PARP IN EC: RUBY PART 2

Eligible patients
- Stage III/IV disease or first recurrent EC[a]
  - All histologies except sarcomas[b]
- Naive to systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- Naive to PARP inhibitor therapy

Stratification:
- MMR/MSI status[c]
  - 25% dMMR/MSI-H
  - 75% MMRp/MSS
- Prior external pelvic radiotherapy
- Disease status

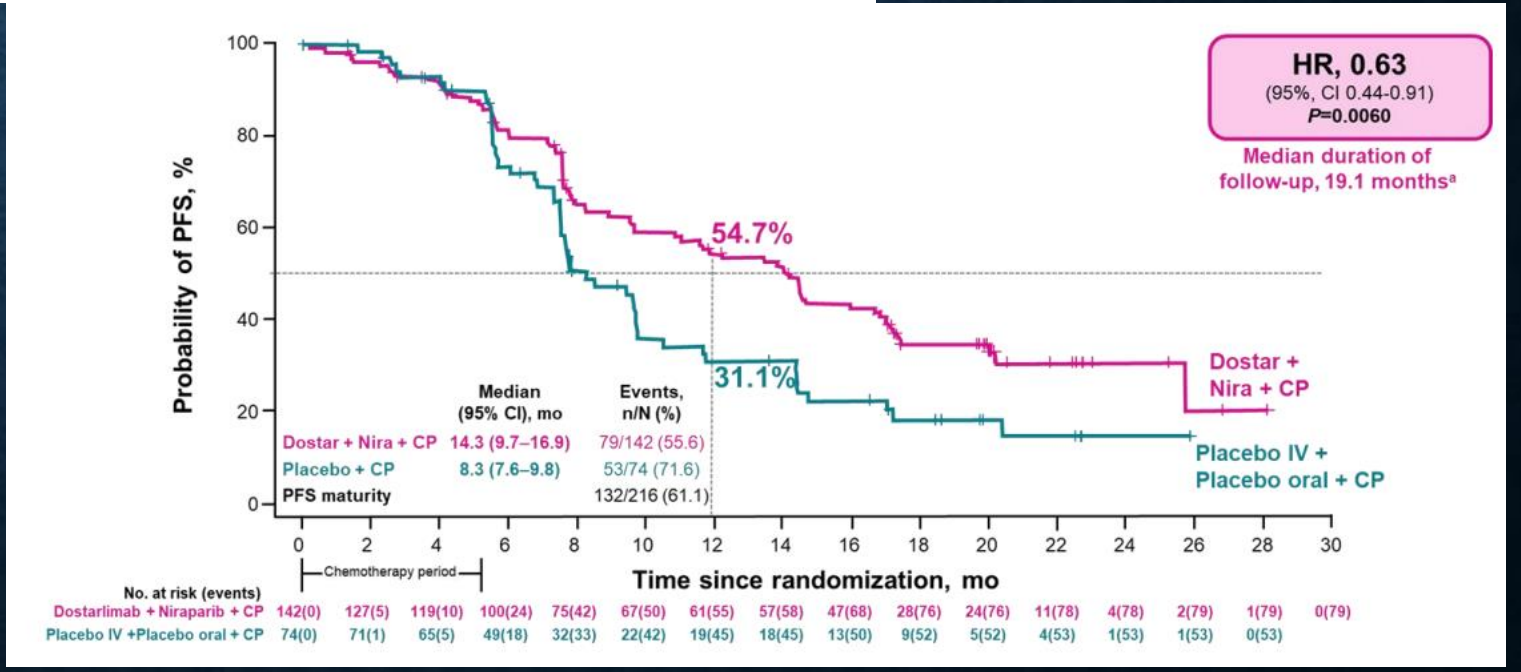
R 2:1

N=192
- **Dostarlimab** (500 mg IV Q3W) + **CP**[d] (Q3W) (6 cycles)
- **Dostarlimab** 1000 mg IV Q6W up to 3 years[e] + **Niraparib** 200 or 300 mg[f] QD up to 3

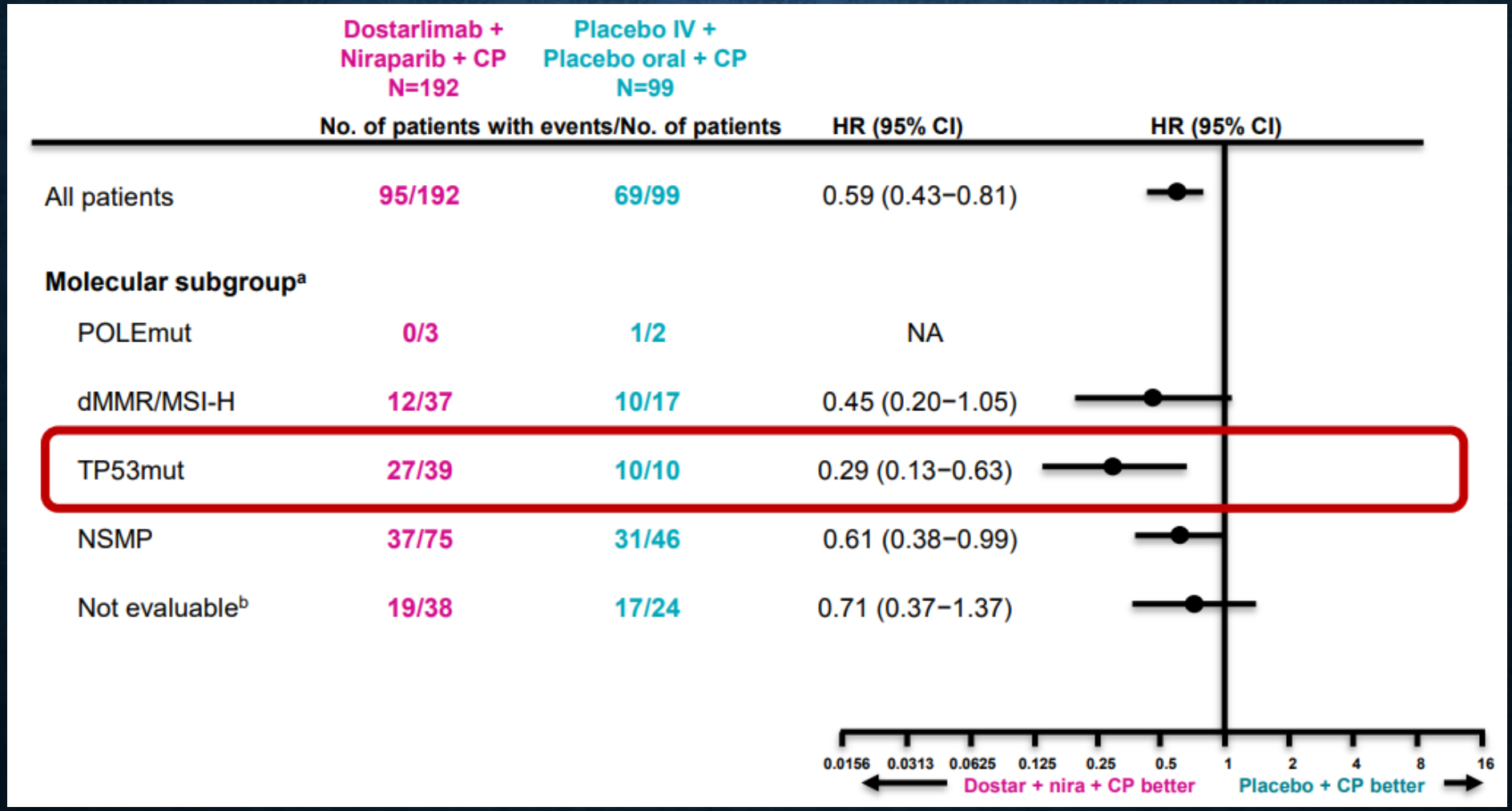
N=99
- **Placebo IV** (Q3W) + **CP**[d] (Q3W) (6 cycles)
- **Placebo IV** Q6W up to 3 years[e] **Placebo PO** QD up to 3 years[e]

Primary endpoint
- PFS by INV per RECIST v1.1
  - Overall
  - MMRp/MSS

Secondary endpoints
- OS
- PFS by BICR
- ORR
- DOR
- DCR (BOR of CR, PR, or SD)
- PFS2
- HRQOL/PRO
- PK
- Safety



RUBY 2: EXPLORATORY PFS MOLECULAR SUBGROUP



- ICI have durale activity in MMRd/MSI-H and some MMRp/MSS EC
- Clinical trials sub analysis show higher response in MMRd/MSI and p53 mut tumors
- There is a subset of MMRd/MSItumors that do not respond to ICI
- MMRd/MSI endometrial ca are heterogeneous regarding mechanism of mismatch repair, TMB, secondary alterations, microenvironmental features and clonal /sub clonal status
- This heterogeneity may have an impact in the response to ICI
- It is not clear why p53mut tumors may respond to immunotherapy

ENGOT-en9/LEAP-001: Lenvatinib + pembrolizumab vs chemo

Study Design

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

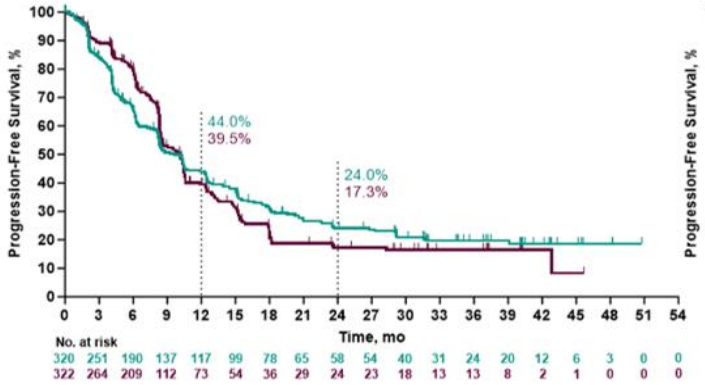
- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DOR per RECIST v1.1 by BICR

ENGOT-en9/LEAP-001: Lenvatinib + Pembrolizumab vs Chemo

PFS in pMMR and All-Comers Populations

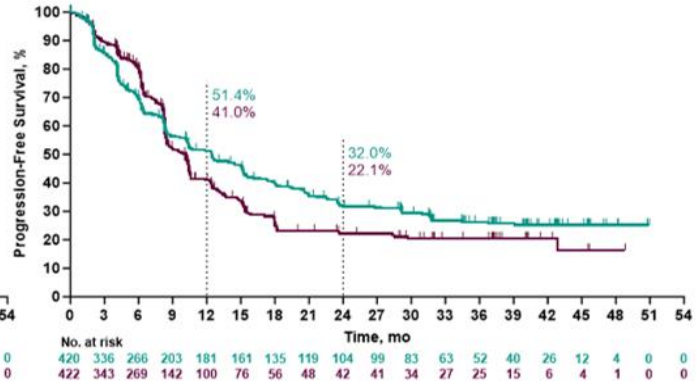
pMMR Population

	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)	

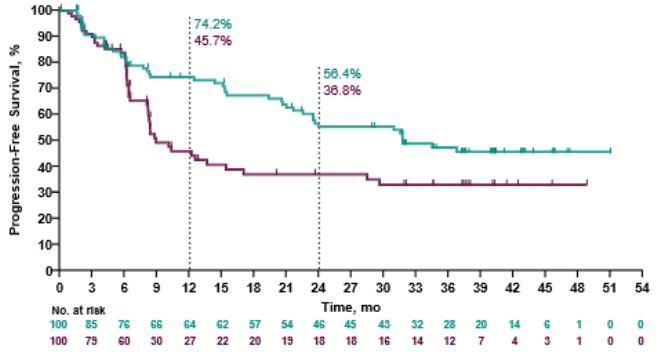


ENGOT-en9/LEAP-001: Lenvatinib + pembrolizumab vs chemo

PFS and OS in the dMMR Subgroup

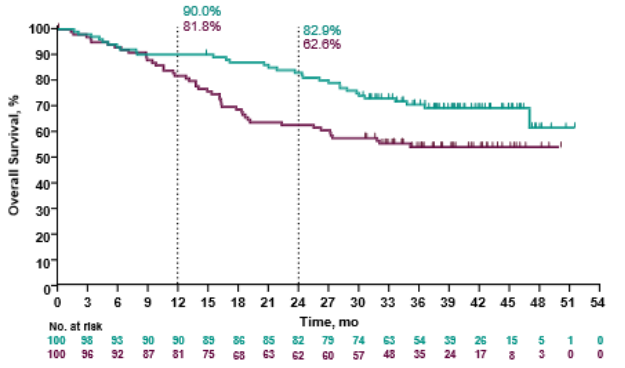
Progression-Free Survival

	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)	

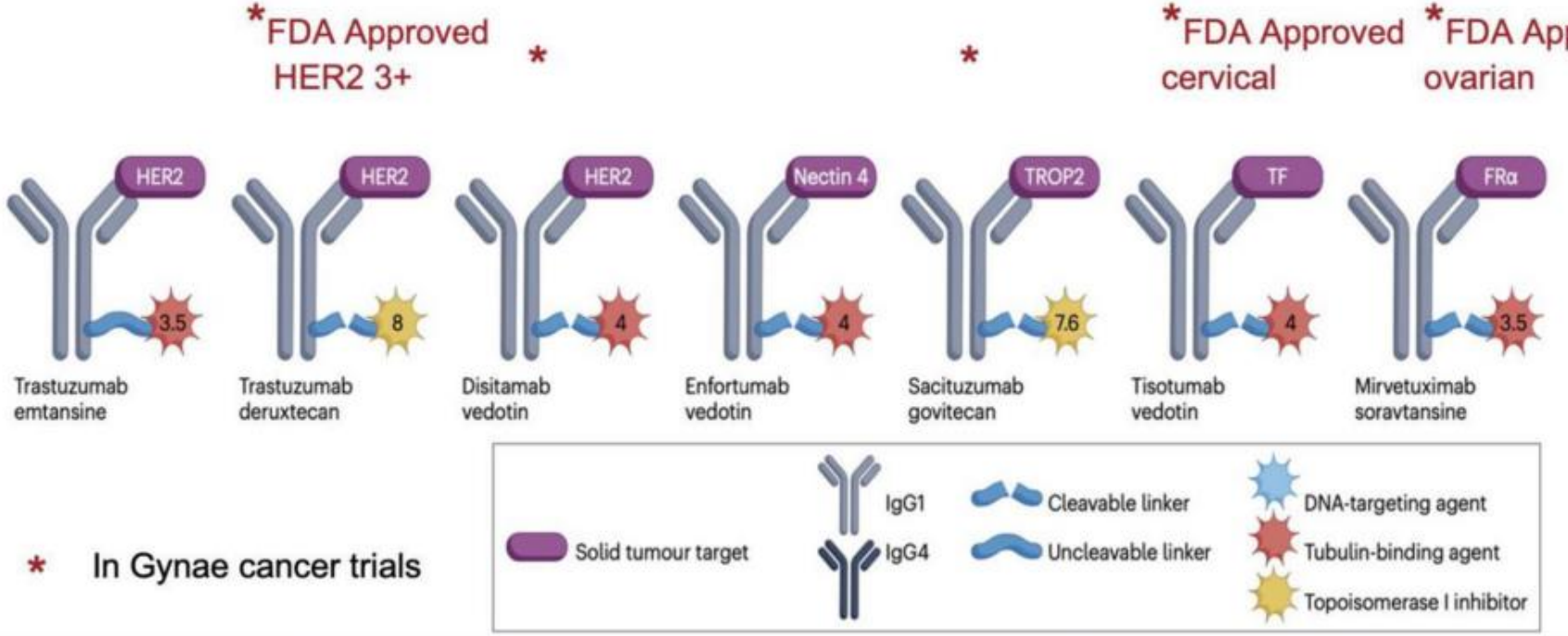


Overall Survival

	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)	



APPROVED ADCS IN SOLID TUMORS



Trastuzumab deruxtecan	Anti-HER2 antibody with a DXd (exatecan derivative) payload and a cleavable glycine–glycine–phenylalanine–glycine linker conjugated using full homogeneous cysteine alkylation with an average DAR of 7.7	HER2⁺ breast cancer (2019), HER2⁺ gastric cancer (2021), HER2^{low} breast cancer (2022) HER2 3+ solid tumours (2024)
Sacituzumab govitecan	Anti-TROP2 antibody with an SN-38 payload and a cleavable lysine–PAB and carbonate linker conjugated using full homogeneous cysteine alkylation with an average DAR of 7.6	TNBC (2020), urothelial carcinoma (2021), HR⁺, HER2⁻ breast cancer (2023)
Tisotumab vedotin	Anti-TF antibody with an MMAE payload and a cleavable valine–citrulline linker conjugated using cysteine alkylation (partial) with an average DAR of 4	Cervical cancer (2021)
Mirvetuximab soravtansine	Anti-FRα antibody with a DM4 (maytansine derivative) payload and a cleavable disulfide linker conjugated using lysine–amide coupling with an average DAR of 3.5	FRα⁺ ovarian, fallopian tube and peritoneal cancers (2022)

FR ALPHA TARGETING ADC IN GYN CANCERS

Drug/Antibody	Payload	Linker	DAR	ORR	Patient population	Ongoing/to open Trials
Mirvetuximab Soravantansine	DM4 (MTI)	Disulfide	3.4	42% (n=227)[1]	Approved PROC (FDA, EMA pending)	GLORIOSA (NCT05445778) Phase III 2L maintenance PSOC
Luveltamab tazevilbulin (STRO-002)	SC209 (MTI)	Dipeptide	4.0	OC 38% (n=38)[2] EC 38%)n=16)[3]	Phase III PROC	REFRαME-01(NCT05870748) Phase III PROC
Farletuzumab ecteribulin (MORAB-202)	Eribulin (MTI)	Dipeptide	4.0	38% (n=45)[4]	PROC	Phase II randomised PROC (CA116-001)
Rinatabart sesutecan (Rina-S, PRO1184)	Exatecan (TOPO1i)	Dipeptide	8.0	38% (n=36) 67% (OC and EC)[5]	PROC, EC	RAINFOL-ov2 (not yet recruiting) Phase III PROC
BAT8006	Exatecan (TOPO1i)	Dipeptide	8.0	37% (n=54)[6]	PROC	Phase I (NCT05378737)
AZD-5335	AZ14170132 (TOPO1i)	Dipeptide	8.0	Not available	PROC	Phase I (NCT05797168)
IMGN-151	DM21 (MTI)	Tripeptide	3.5	Not available	EC and PROC	Phase I (NCT05527184)
ZW191	ZD06519 (TOPO1i)	Tetrapeptide	8.0	Not available	PROC, EC	Phase I (NCT06555744) (not yet recruiting)

Examples of FRα- targeting ADCs in development (Sept 2024).

MTI: microtubule inhibitor; TOPO1i: topoisomerase inhibitor 1; DAR: drug-antibody ratio; PROC: platinum-resistant ovarian cancer PSOC: platinum-sensitive ovarian cancer; EC: Endometrial Cancer

1. Moore KN, et a;. N Engl J Med. 2023 2. Oaknin et al ASCO 2023 3. Pothuri B, et al. ESMO 2023 4. Nishio S, et al. ASCO 2022 5. Call J et al SITC 2023 6. Jia H et al ASCO 2024

OTHER ADC TARGETS IN GYN TRIALS

Drug/Antibody	Target	Payload	Clinical trial status
XMT-1536	Napi2b	MTI	Stopped
TUB-040	Napi2b	TOPO1i	Phase I/II NCT06303505
ZW220	Napi2b	TOPO1i	Phase I (not yet recruiting)
Sacituzumab govitecan	TROP2	TOPO1i (SN-38)	Phase III EC post IO NCT06486441
Sacituzumab tiromotecan (MK2970)	TROP2	TOPO1i	Phase III EC post IO NCT06132958 Phase III cervical cancer NCT06459180
Disitamab Vedotin	HER2	MMAE	Phase 2 Basket (OC and EC included) NCT06003231
BNT323/DB-1303	HER2	TOPO1i	Phase III EC NCT06340568 (not yet recruiting)
Raludotatug Deruxtecan (R-DXd)	CDH6	TOPO1i (DXd)	Phase II/III PROC NCT06161025
TORL-1-23 (TORL	CLDN6	MMAE	Phase II PROC

Other target examples:
B7-H4
Mesothelin