Precision oncology and target therapies: gynaecological cancers

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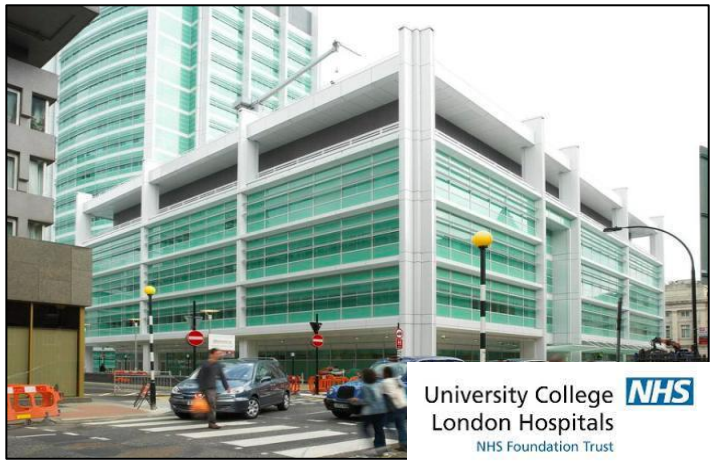
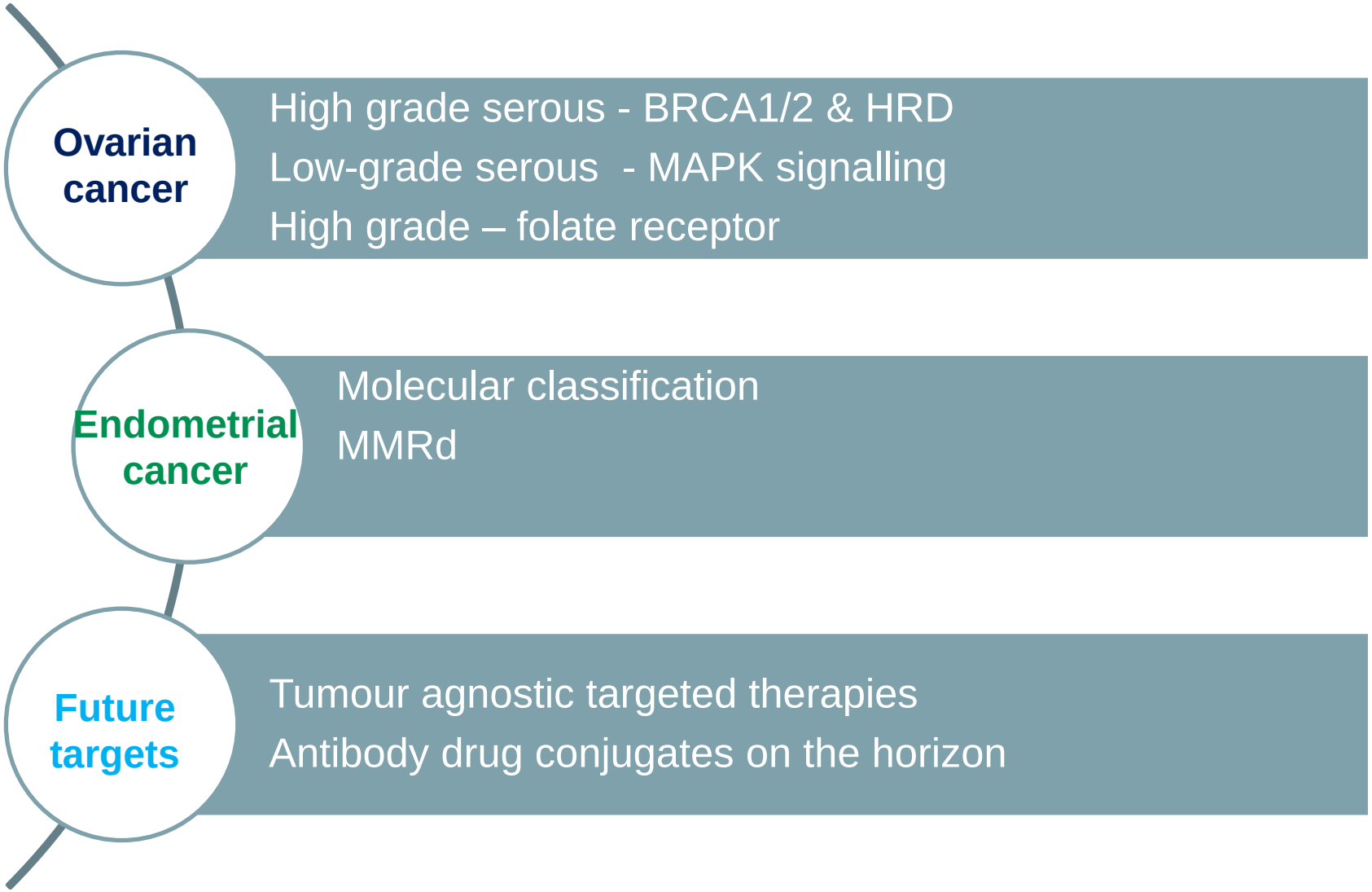



Ovarian cancer
High grade serous - BRCA1/2 & HRD
Low-grade serous - MAPK signalling
High grade – folate receptor
Endometrial cancer
Molecular classification
MMRd
Future targets
Tumour agnostic targeted therapies
Antibody drug conjugates on the horizon

Ovarian cancer

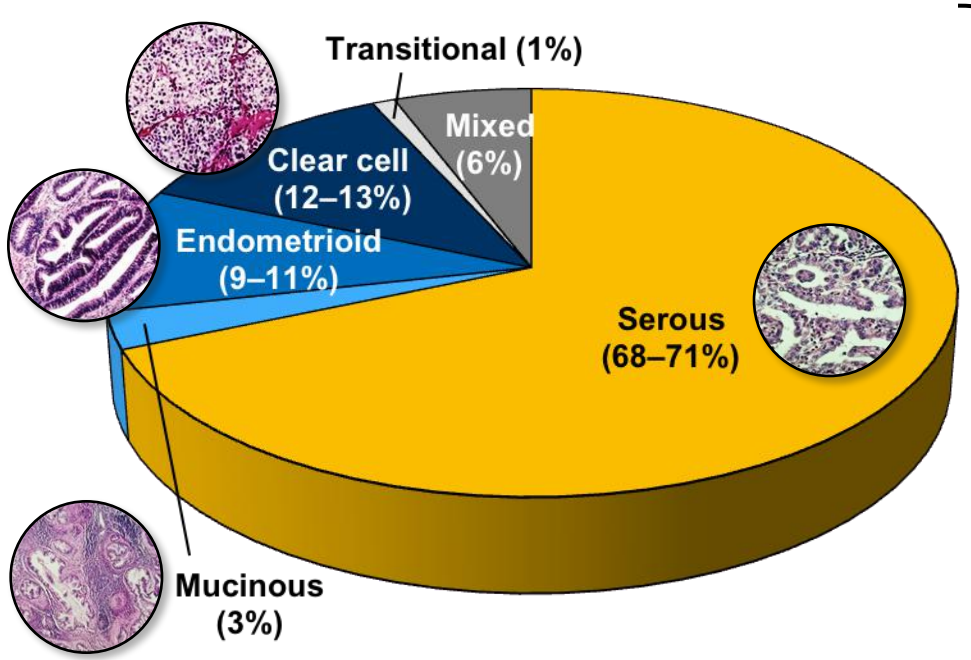
High grade serous - BRCA1/2 & HRD

Low-grade serous - MAPK signalling

High grade – folate receptor

Histological Subtypes of Ovarian Cancer

- **Epithelial ovarian cancer** accounts for 90% of ovarian tumours



	Stage I/II	Stage III/IV
Serous	36%	88%
Clear cell	26%	5%
Endometrioid	27%	3%
Mucinous	8%	1%

Serous ovarian cancer is the most common subtype of epithelial ovarian cancer, and accounts for the majority of advanced cases

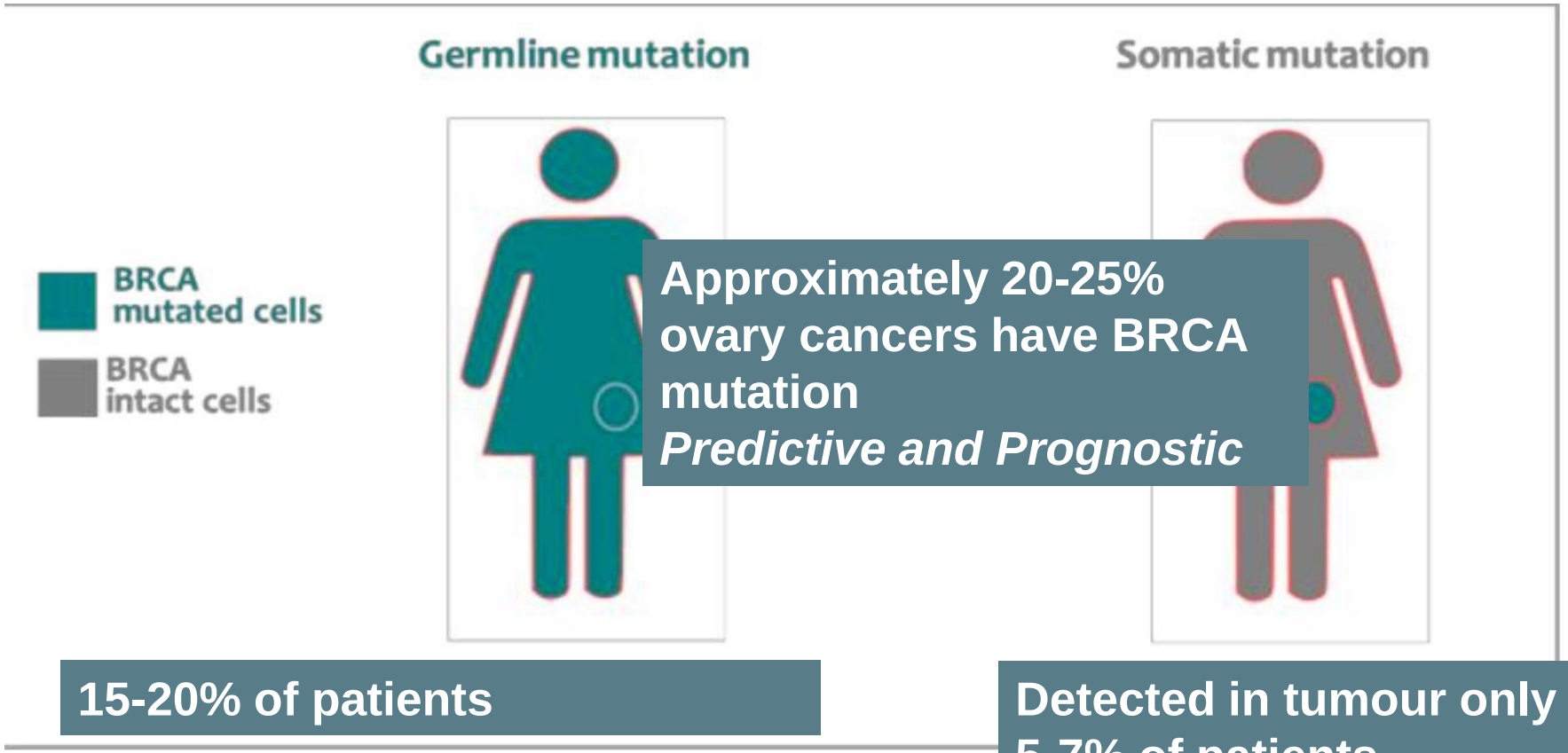
McCluggage WG. *Pathology.* 2011;43:420–32; Kim J et al. *Proc Natl Acad Sci USA.* 2012;109:3921–6.

Potential targets

	High-Grade Serous	Endometrioid	Clear Cell	Mucinous	Low-Grade Serous
Molecular drivers	*TP53* (96%), ***BRCA*** (<20%), *CCNE1* (14%)	*ARID1A* (30%), *CTNNB1* (25-60%), *KRAS/BRAF* (20%), *PIK3CA* (12%), *TP53* (25%)	*ARID1A* (50%), *PIK3CA* (50%), *ARID1B* (6-18%), *SMARCA4* (5-18%), *PIK3R1* (7-10%), *AKT2* (8-26%), *PTEN* (2-13%), *KRAS* (5-20%), *TP53* (8-22%), *MET* (24-37%), HER2 (14%)	*KRAS* (66%), *TP53* (26-55%), *PIK3CA* (8%), *PTEN* (4%), *BRAF* (0-9%), *CTNNB1* (5%), *HER2* (18-35%)	*BRAF* (0-33%), *KRAS* (35%), *NRAS* (8-26%), *PIK3CA (0-60%), USP9X (11%), EIF1AX* (15%)
Major pathways affected	**Homologous Recombination Deficiency (HRD)**	MAPK, β-catenin signaling, PI3K/PTEN	PI3K/PTEN/AKT, MAPK	MAPK, Wnt signaling, PI3K/PTEN/AKT	**MAPK**, PI3K, mTOR

Hollis & Gourley 2017, Ledermann et a 2013, babaier & Ghataget 2020, Tan et al 2011, Lida et al 2011, Mackenzie et al 2015, Gorringe et al 2020, Singer et al 2003

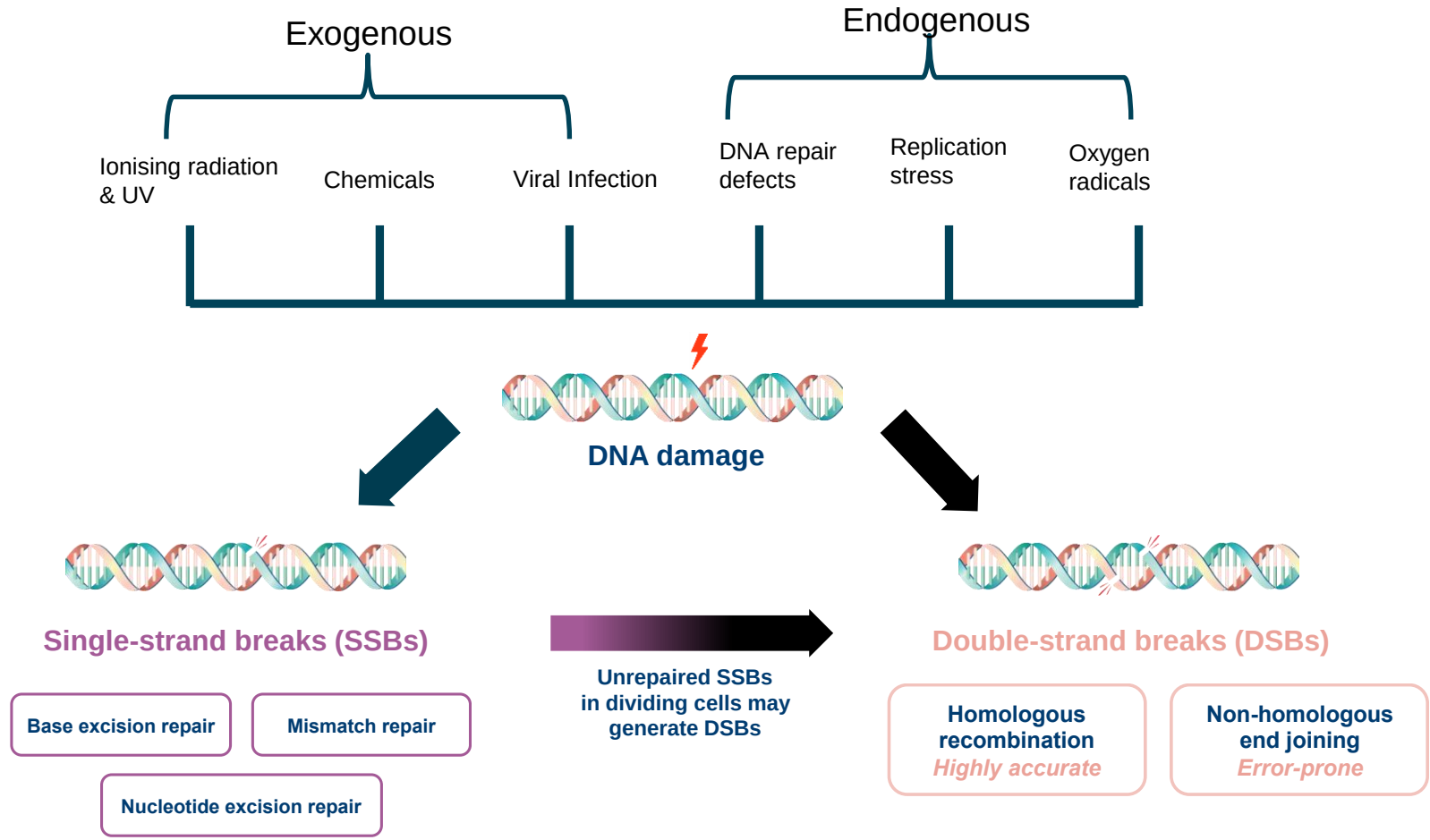
BRCA1/2 mutations



All patients with high grade ovarian cancer have parallel germline and tumour BRCA testing

Why BRCA is important to cells? DNA is constantly under attack

DNA repair protects the genome from deleterious mutations



Konecny GE *et al. Br J Cancer* 2016; Jones P *et al. J Med Chem* 2015

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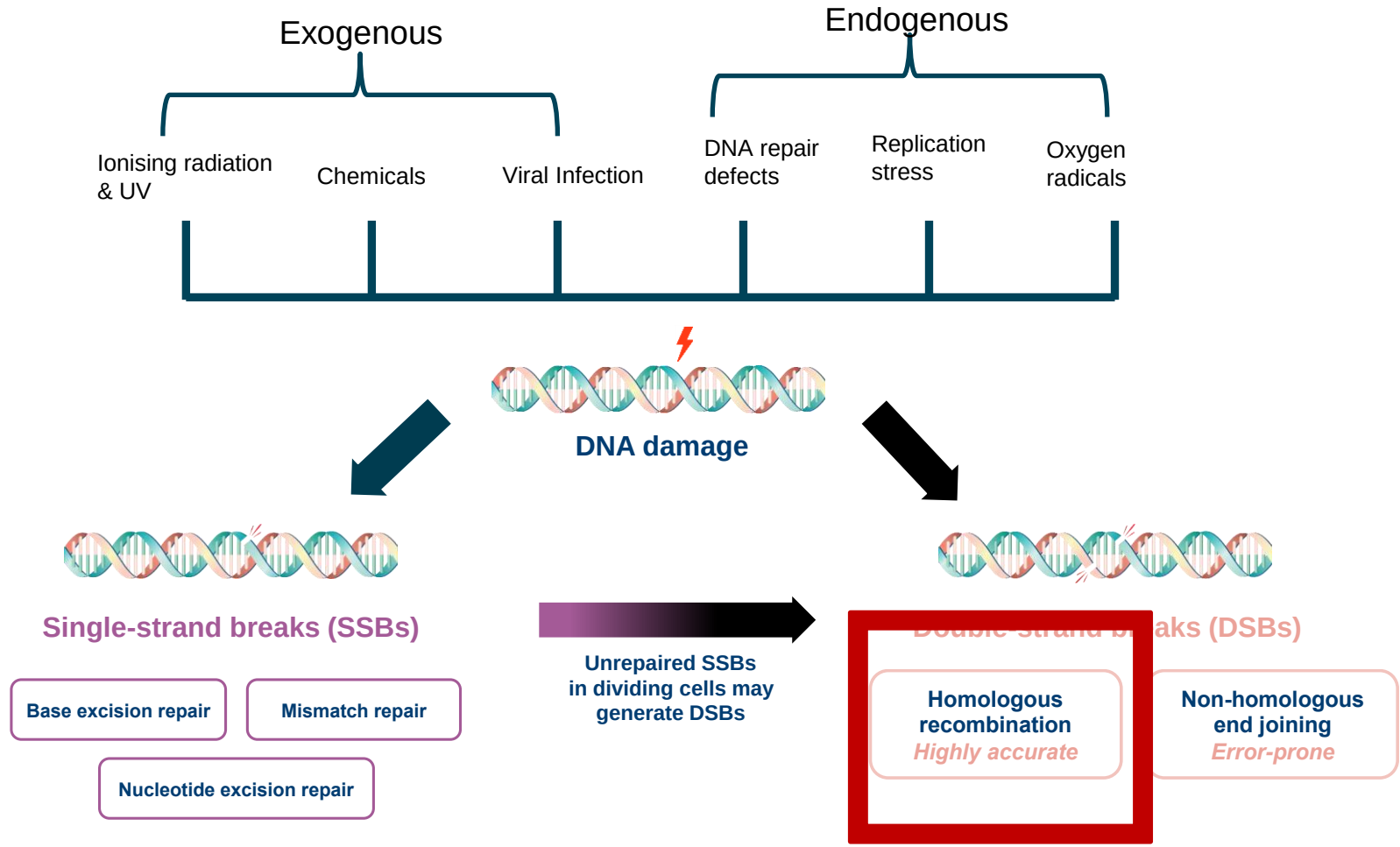

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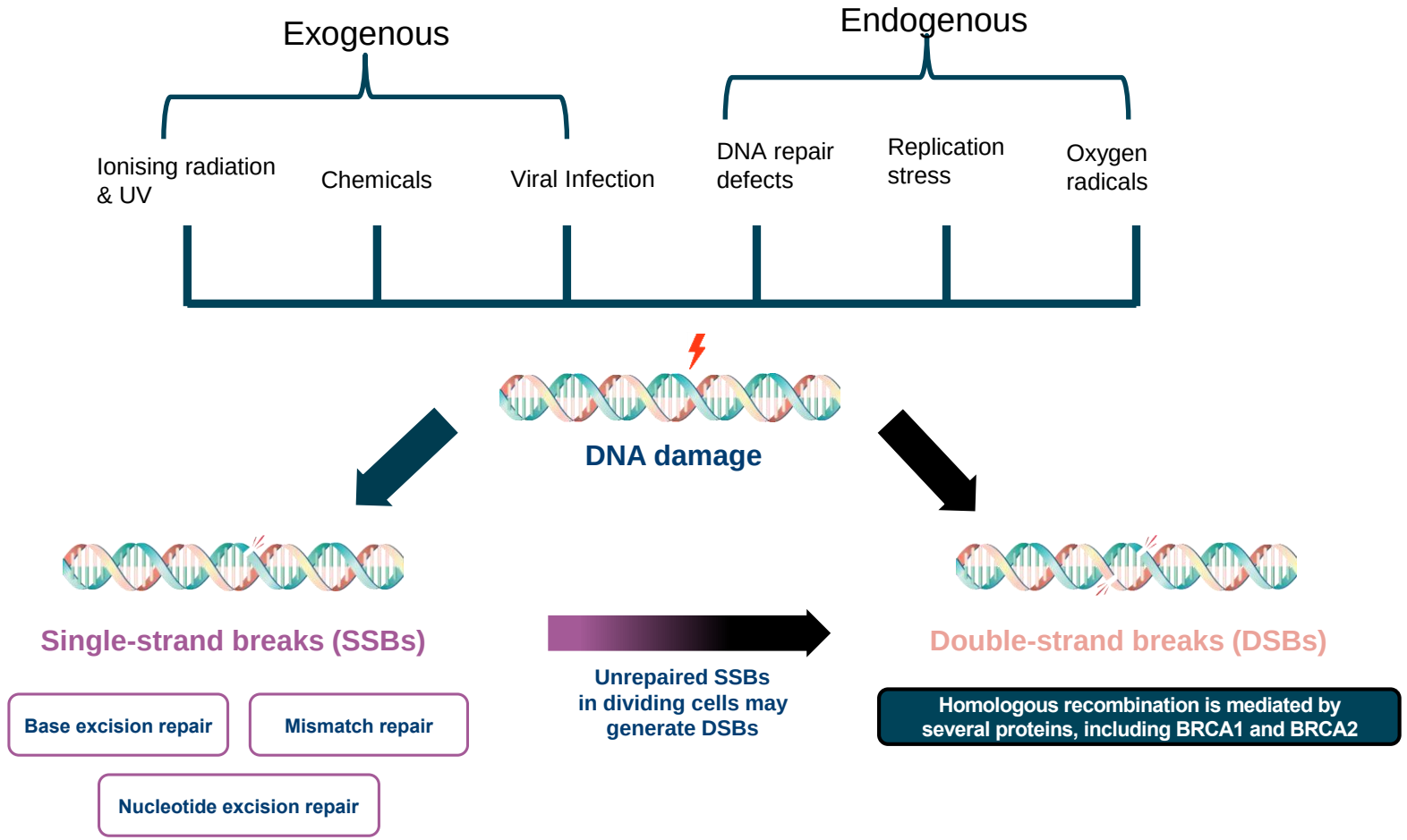

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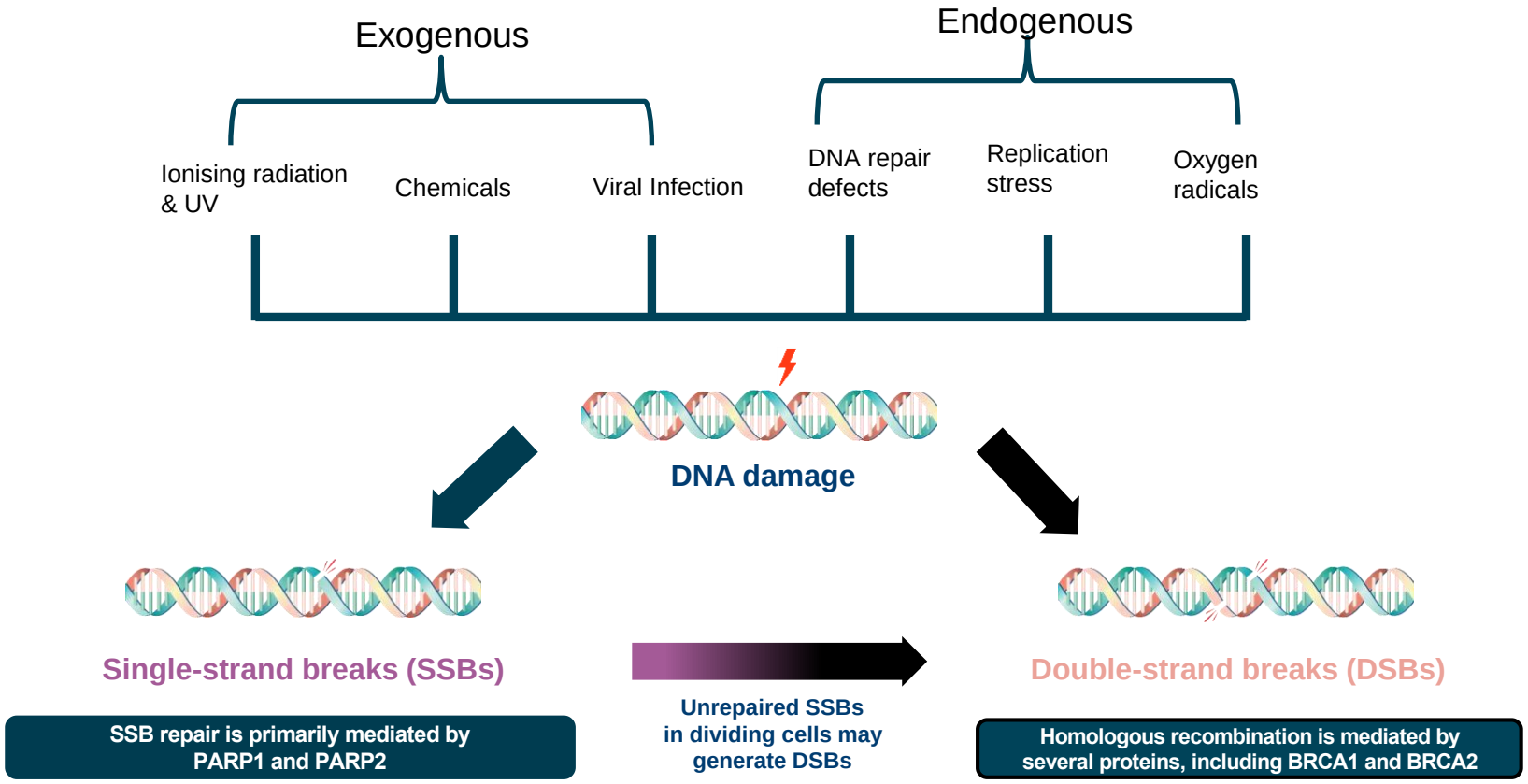

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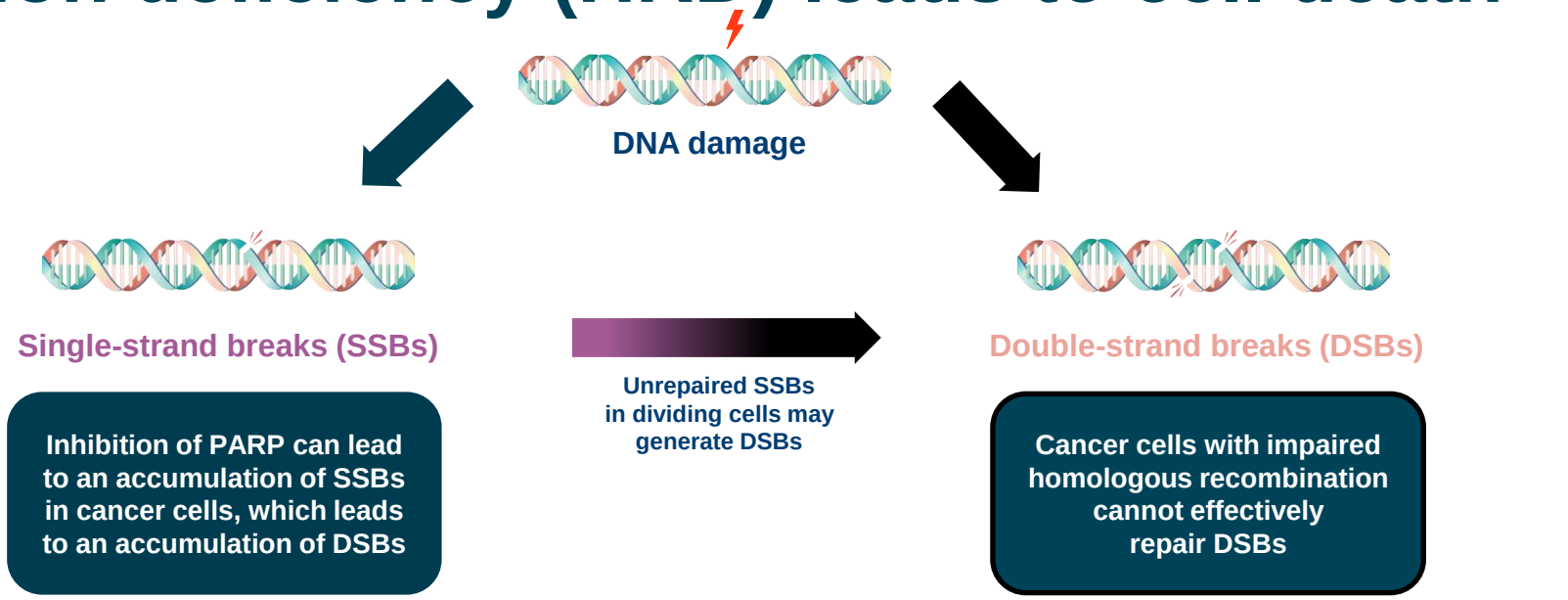
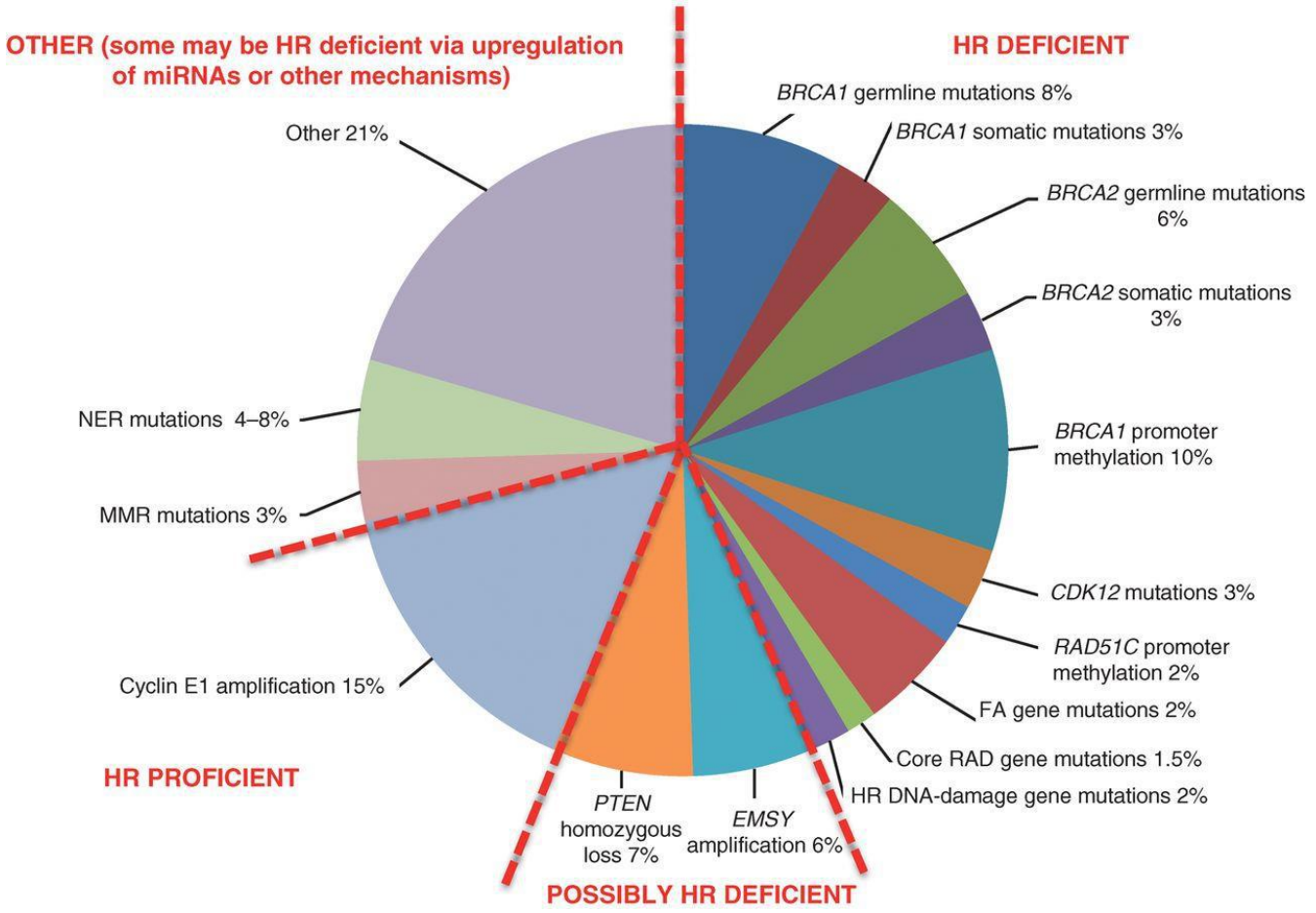
Inhibiting PARP in cancer cells with homologous recombination deficiency (HRD) leads to cell death



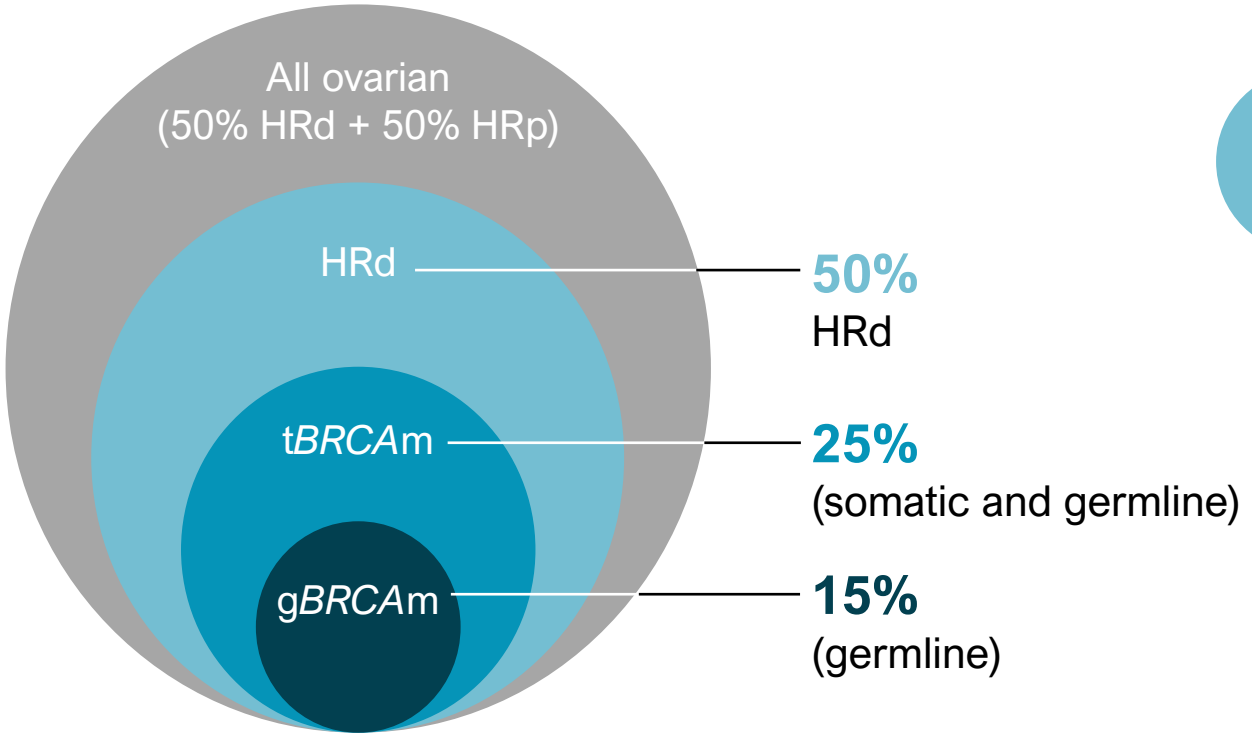
Konecny GE *et al. Br J Cancer* 2016; Jones P *et al. J Med Chem* 2015

Importance of HRD in high-grade serous ovarian cancer



Konstantinopoulos et al. Cancer Discov 2015
Levine D. TCGA Nature 2011

Biomarkers play an important role in diagnosing and defining patient populations in ovarian cancer



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

25% are t*BRCA*m at diagnosis[1,2]

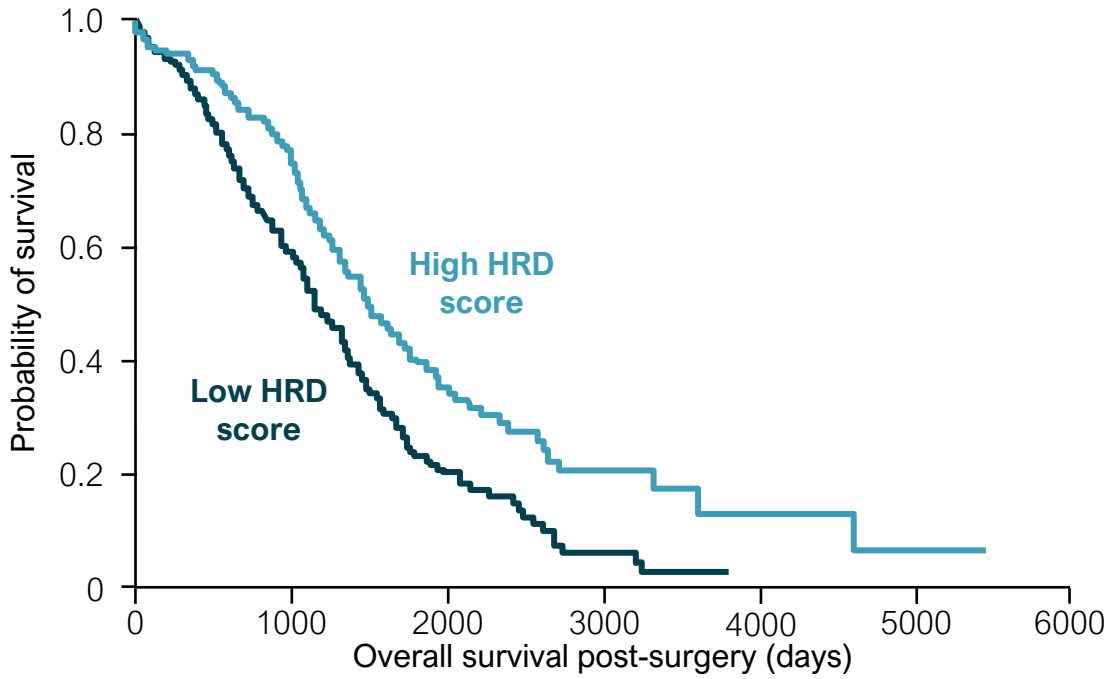
15% are g*BRCA*m at diagnosis[1,2]

BRCA, breast cancer gene; BRIP1, BRCA1-interacting protein; gBRCAm, germline BRCA mutant; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OC, ovarian cancer; tBRCAm, tumour BRCA mutant.

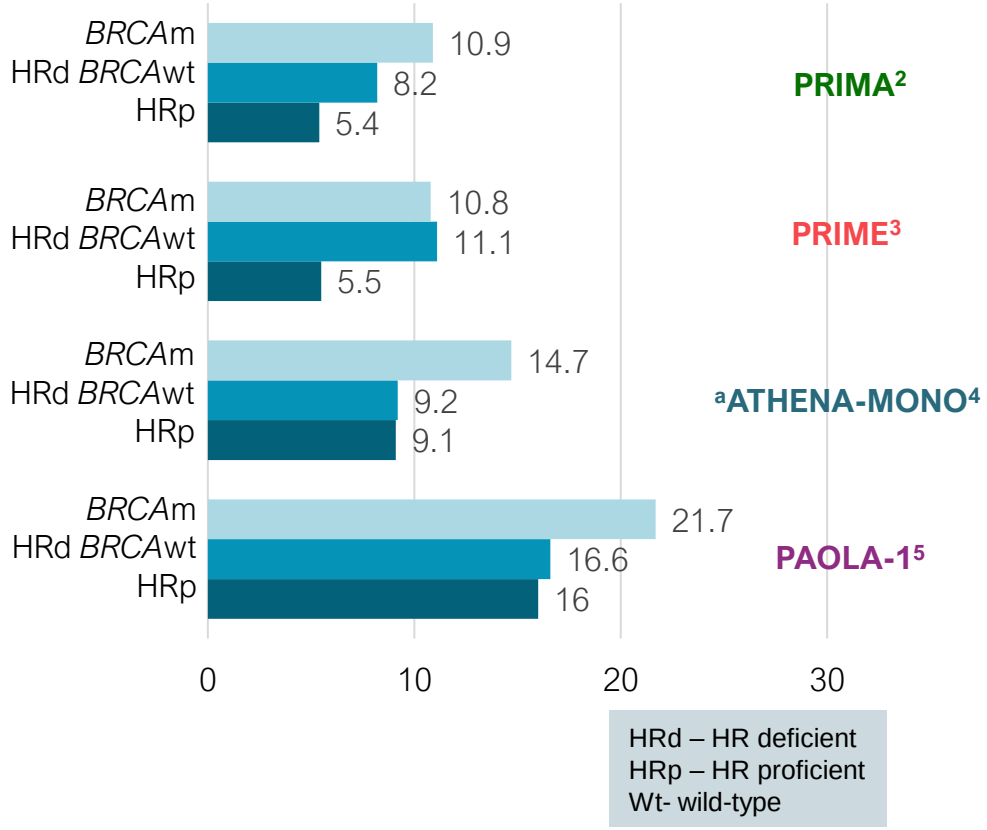
1. Abkevich V, et al. Br J Cancer 2012;107:1776–82; 2. The Cancer Genome Atlas Research Network. Nature 2011;474:609–15.

HRD status is important – prognostic and predictive

HRD test analysis from the TCGA data set for data and survival information were available



Median PFS with placebo 1st line PARPi trials (pts treated with carboplatin/paclitaxel)



There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

.1. Abkevich V, et al. Br J Cancer 2012;107:1776–1782; 2. González Martín A, et al. N Engl J Med 2019;381:2391–402; 3. Li N, et al. Presented at SGO 2022, 18–21 Mar, Phoenix, AZ. 4, Monk BJ, et al. J Clin Oncol 2022: https://doi.org/10.1200/JCO.22.01003; 5. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–28.

How to we detect HRD?

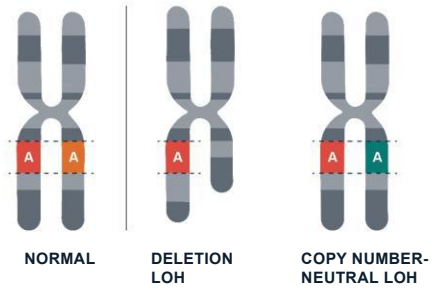
Cause or Effect?

- Driver mutation
- HRD ‘phenotype’
  - Accumulation of associated HRD damage

- Current HRD status
  - Functional status

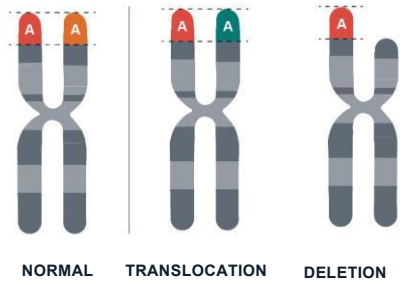
How can we identify HRD tumours?
-Phenotype - Genomic scar based assays

Loss of heterozygosity
Presence of a single allele



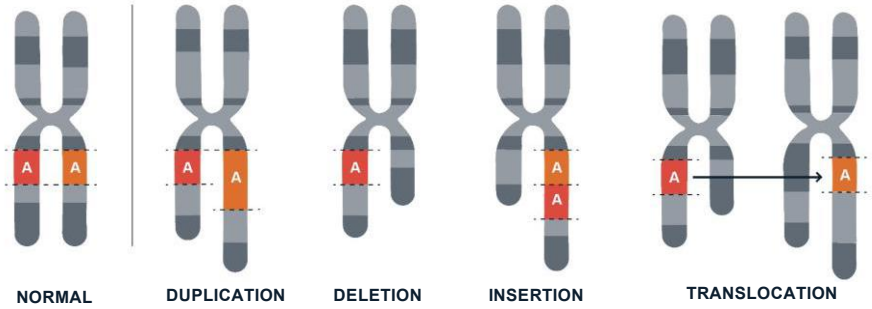
LOH score is the total number of LOH regions across the entire genome that are **larger than 15 Mb** but do not cover whole chromosomes

Telomeric allelic imbalance
A discrepancy in the 1:1 allele ratio at the end of the chromosome (telomere)



The number of telomeric imbalances is the number of allelic imbalances (the unequal contribution of parental allele sequences with or without changes in the overall copy number of the region) **that extend to the telomeric end of a chromosome**

Large-scale state transitions
Transition points between regions of abnormal and normal DNA or between two different regions of abnormality



LST is defined as a chromosomal break between adjacent regions of at least 10 Mb

Due to the reliance on error-prone DNA repair, tumours with HRD have a characteristic mutational signature, resulting in a 'mutational scar'

Genomic Instability Score (GIS) SCORE
- myChoice CDx (Myriad Genetics)
- Composite score LOH/TAI/LST and BRCA status

LOH score
FoundationOne®CDx (Foundation Medicine)

Myriad myChoice Technical Information. Available at: https://myriadweb.s3.amazonaws.com/myChoiceCDx/downloads/myChoiceCDxTech.pdf. Accessed August 2020;

HRD Testing - Imperfect test!

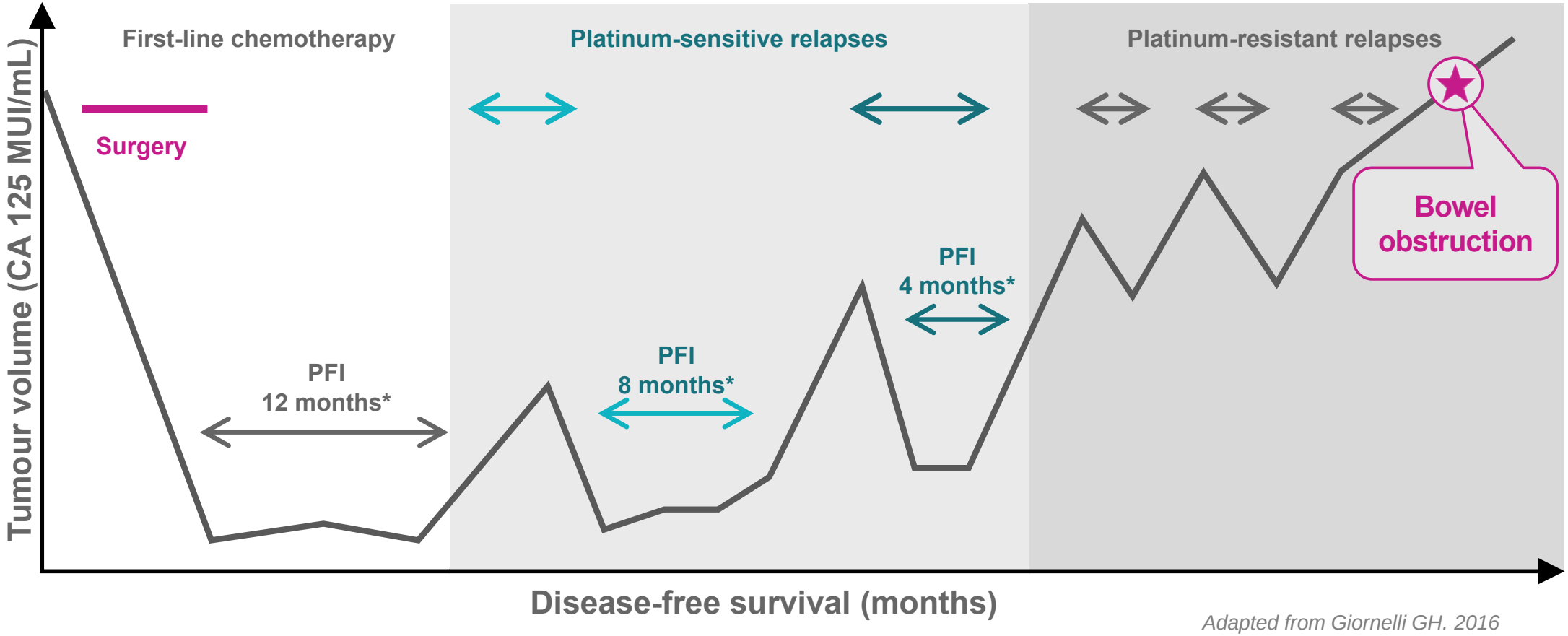
- Current commercial tests don’t always agree with HRD status
- Not all BRCA patients are HRD+ve on assays
- Fail to reliable identify patients who will not benefit
- Historic read of of genomic damage
- Many other assays in development

Timms et al ASCO 2020, Gourley et al ESMO 2019, Miller et al 2020

BRCA/ HRD and treatment implications

- Role in 1L maintenance therapy

Natural history of advanced epithelial ovarian cancer prior to introduction of maintenance therapy



Adapted from Giornelli GH. 2016

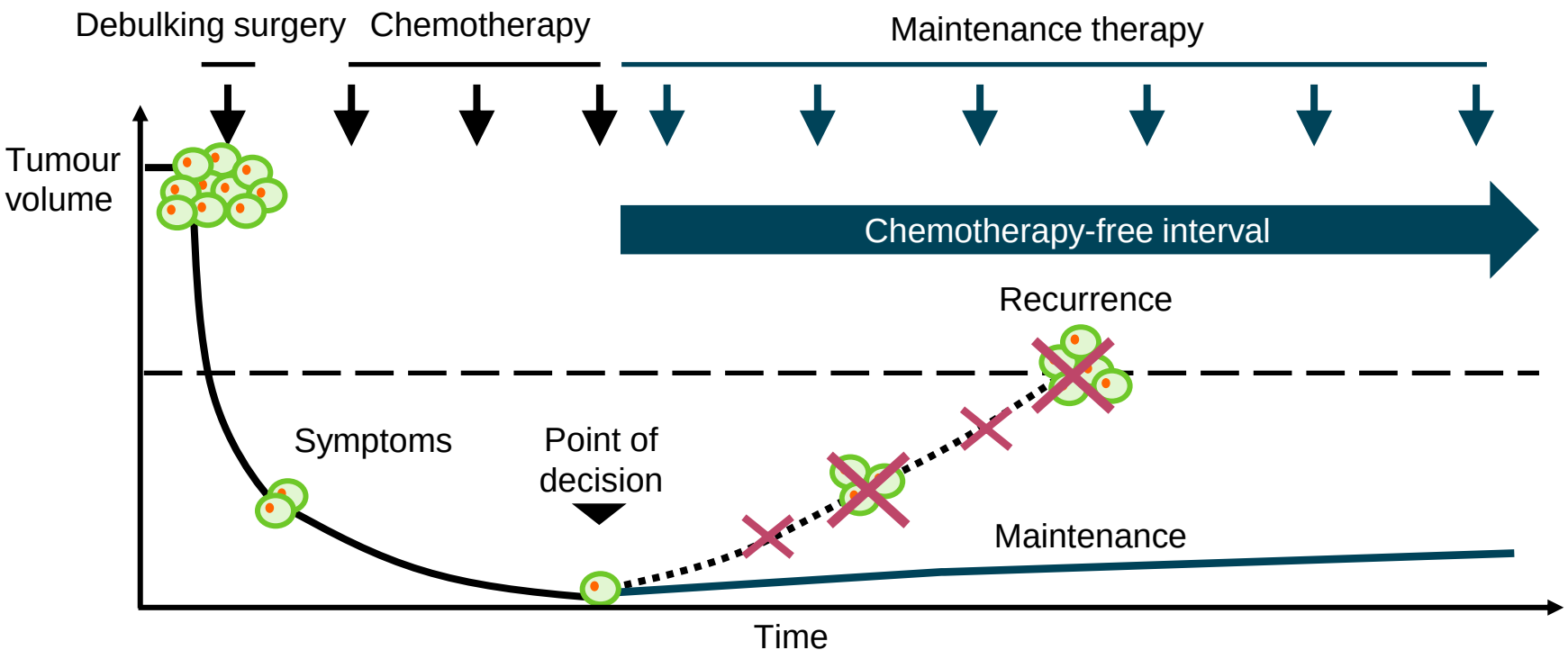
*Estimate.

PFI=platinum-free interval.

Giornelli GH. *Springerplus*. 2016;5(1):1197.

First-line maintenance a paradigm shift, altering the natural course of disease in ovarian cancer by extending progression free survival (PFS)

Management of OC:[1]



Goals of maintenance therapy

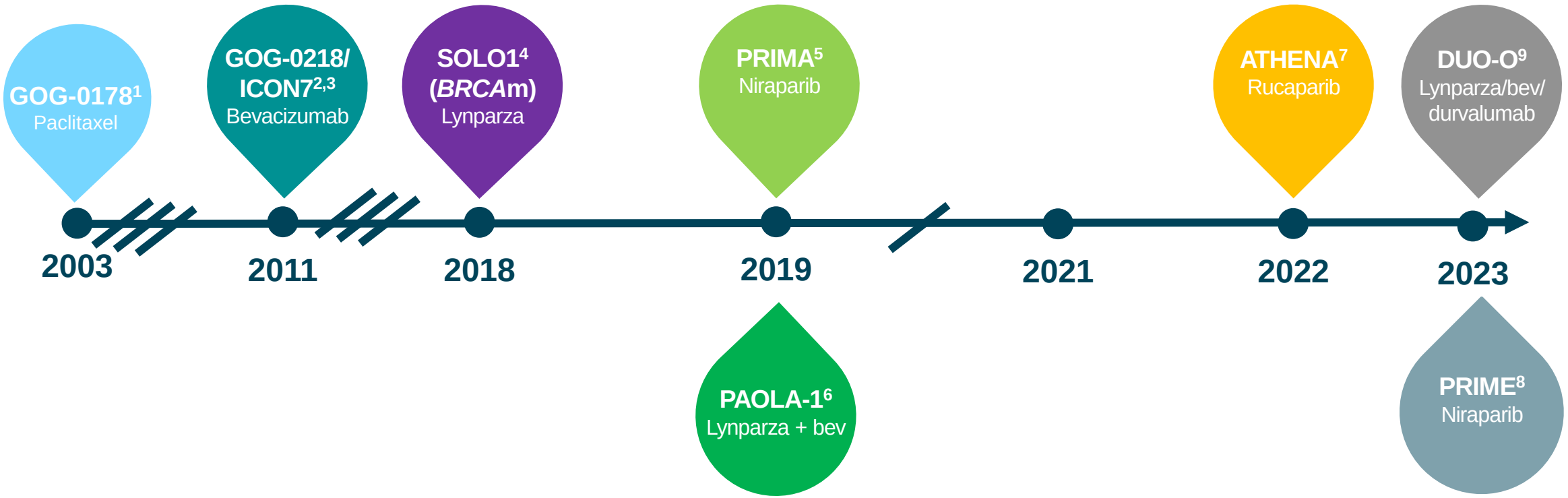
1. Prolong benefit following surgery and chemotherapy
2. Improve survival (PFS and hopefully OS)
3. Manageable toxicity and no negative effects on QoL

Figure is for illustrative purposes only.

OC, ovarian cancer; OS, overall survival; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival; QoL, quality of life.

1. DiSilvestro P, Alvarez Secord A. Cancer Treat Rev 2018;69:53-65.

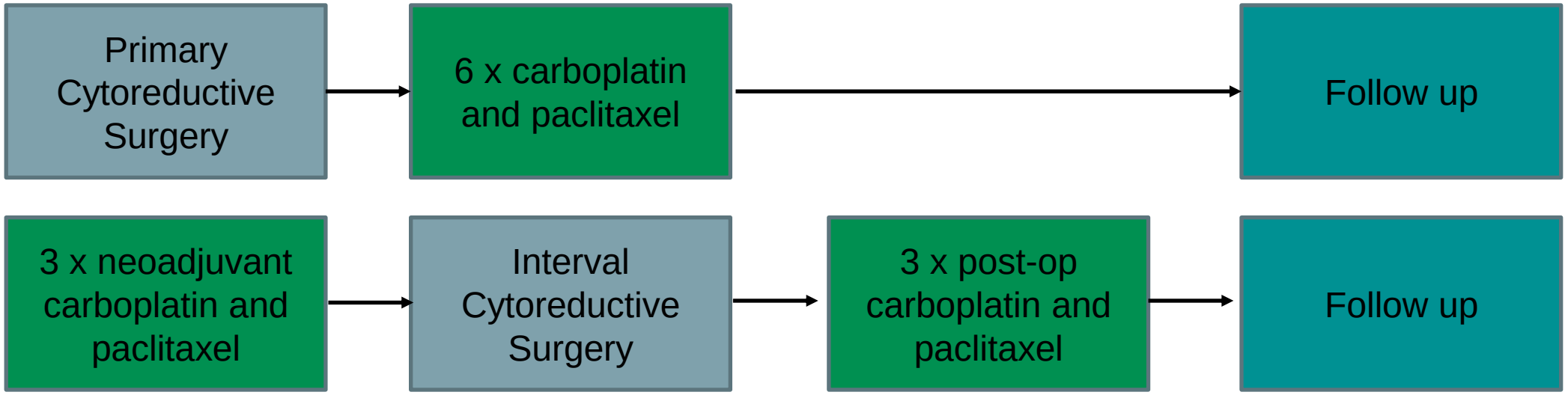
Pivotal first line maintenance trials



1Lm, first-line maintenance; bev, bevacizumab; *BRCA*m, breast cancer gene mutant.

1. Markman M, et al. *J Clin Oncol* 2003;21:2460–5; 2. Burger RA, et al. *N Engl J Med* 2011;365:2473–83; 3. Perren TJ, et al. *N Engl J Med* 2011;365:2484–96; 4. Moore K, et al. *N Engl J Med* 2018;379:2495–505; 5. González-Martín A, et al. *N Engl J Med* 2019;381:2391–402; 6. Ray-Coquard I, et al. *N Engl J Med* 2019;381:2416–28; 7. Li N, et al. presented at SGO 2022, 18–21 Mar, Phoenix, AZ; 8. Monk BJ, et al. *J Clin Oncol* 2022; https://doi:10.1200/JCO.22.01003.8. Monk et al NEJM 2022

Management of advanced (FIGO III/IV) EOC pre-2019

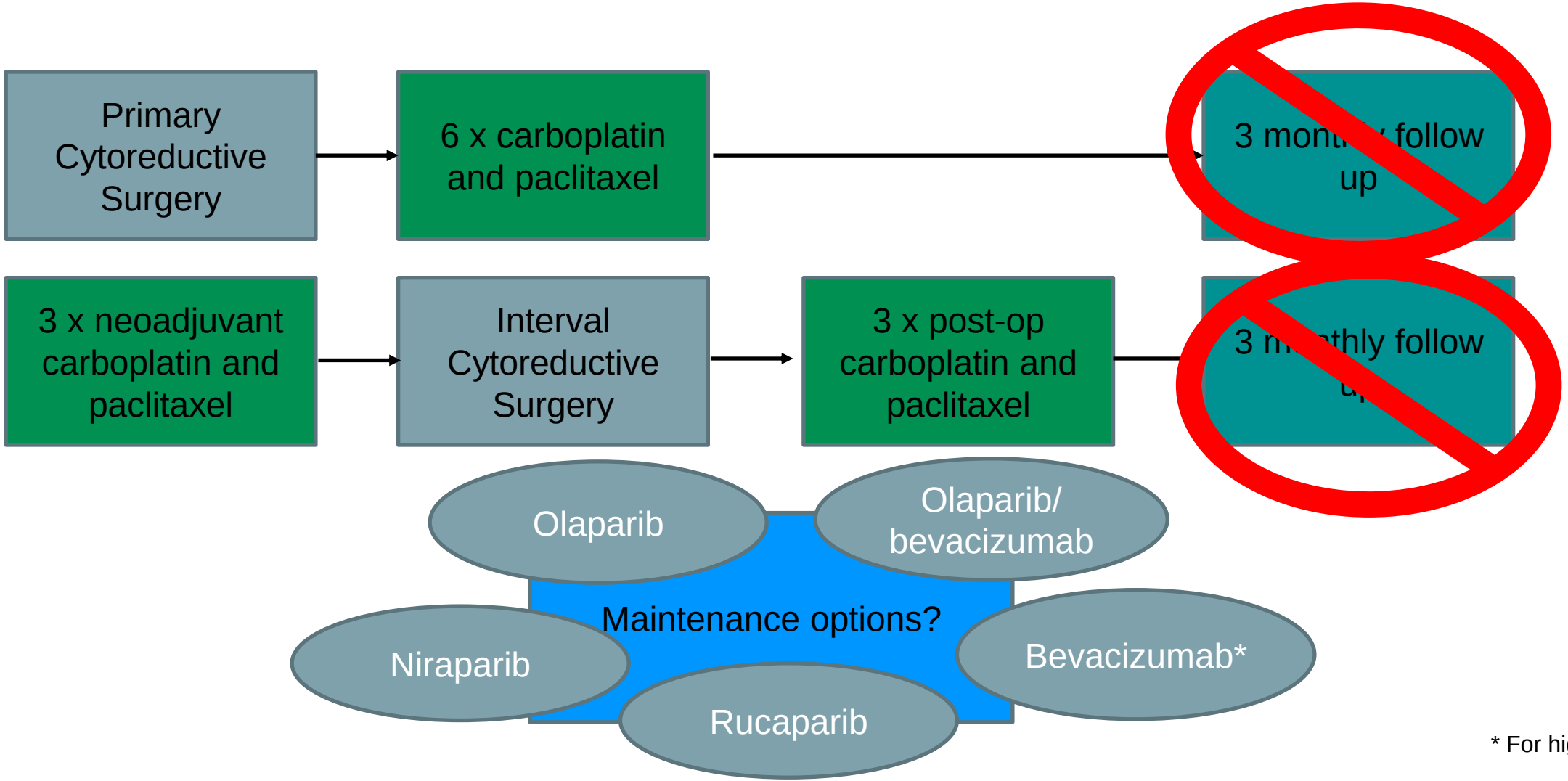


? + Bevacizumab

High risk patients only

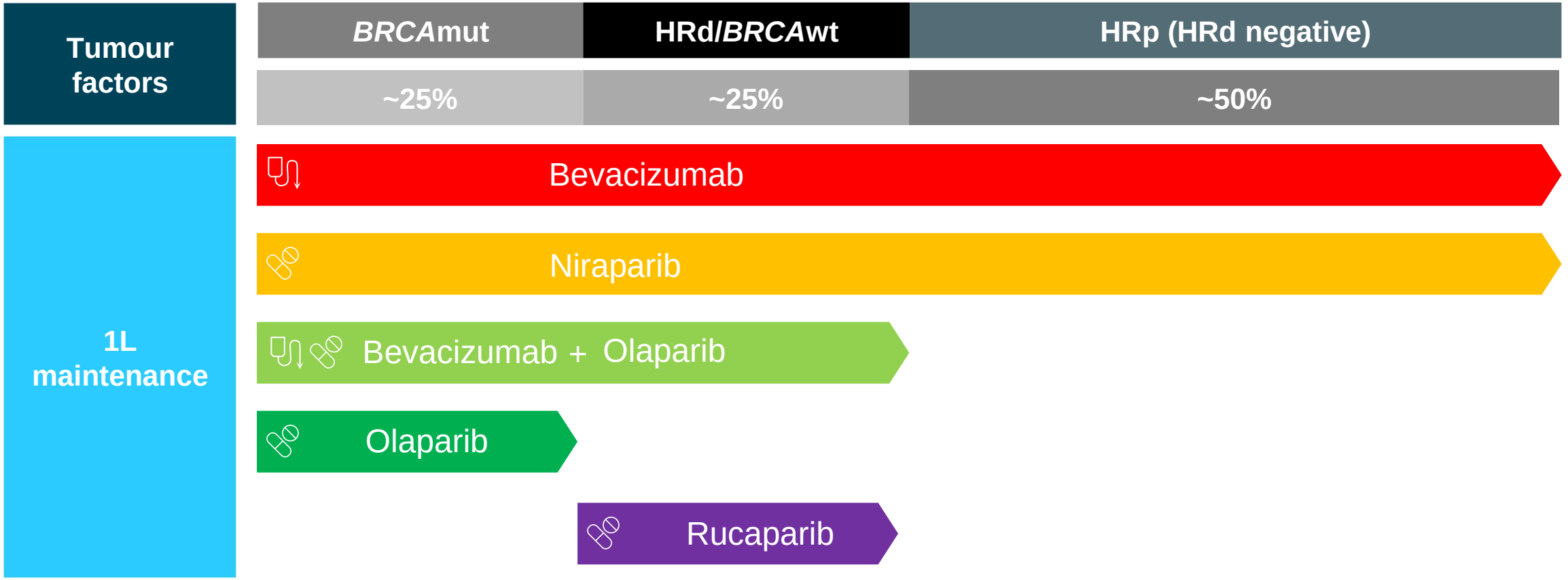
- Inoperable
- Residual disease
- Stage 4

Management of advanced (FIGO III/IV) EOC 2024



* For high-risk groups

1st line maintenance options for advanced high-grade epithelial ovarian cancer – BIOMARKER DEPENDENT



mut = mutant, HRd = homologous recombination repair deificient, wt = wild-type, HRp = homologous recombination repair proficient

First Line PARPi Maintenance Trials

HRD – homologous recombination deficient, HRP - homologous recombination proficient
UK – unknown, NACT – neoadjuvant chemo
PFS – progression free survival , PCS – primary cytoreductive surgery
CR/PR – complete/partial response

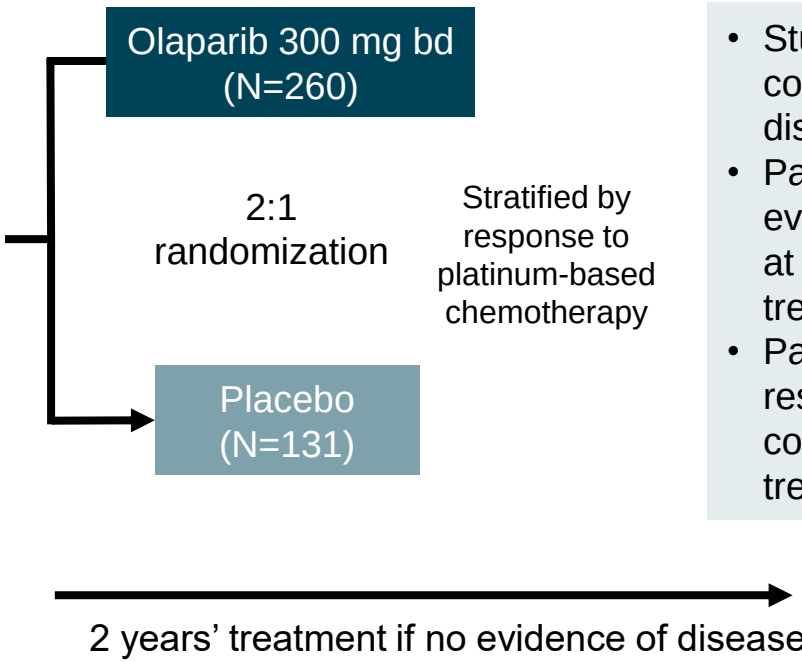
TRIAL	Patients enrolled	Stratification	PARPi (duration months)	Control Arm	Primary end point
SOLO1	FIGO III/IV *BRCA1/2*	Chemo response (CR/PR)	Olaparib (24)	Placebo	PFS
PAOLA1	FIGO III/IV ≥ 3 cycles bevacizumab	Tumour *BRCA1/2* Chemo response	Olaparib (24) /Bevacizumab (15)	Placebo/ Bevacizumab	PFS
PRIMA	FIGO III/IV (Stage III with disease post PCS or Stage III/IV NACT)	Chemo response NACT (yes/no) HRD vs HRP/UK	Niraparib (36)	Placebo	PFS
ATHENA	FIGO III/IV All HG histology	Chemo response Timing of surgery HRD vs HRP/UK	Rucaparib (24)*	Placebo	PFS
PRIME	FIGO III/IV Surgical attempt as minimum Chinese population	Chemo response NACT (yes/no) HRD vs HRP/UK g*BRCA1/2*	Niraparib (36)	Placebo	PFS

* also include nivolumab - data not reported

Moore et al NEJM 2018, Gonzalez Martin et al NEJM 2019, RayCoquard et al NEJM 2019, Monk JCO 2022, Li et al SGO 2022

SOLO1 Study design

- Newly diagnosed, FIGO **stage III–IV**, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- **Germline or somatic *BRCA1/2*m**
- ECOG performance status 0–1
- **Cytoreductive surgery***
- In clinical complete response or partial response after platinum-based chemotherapy



- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

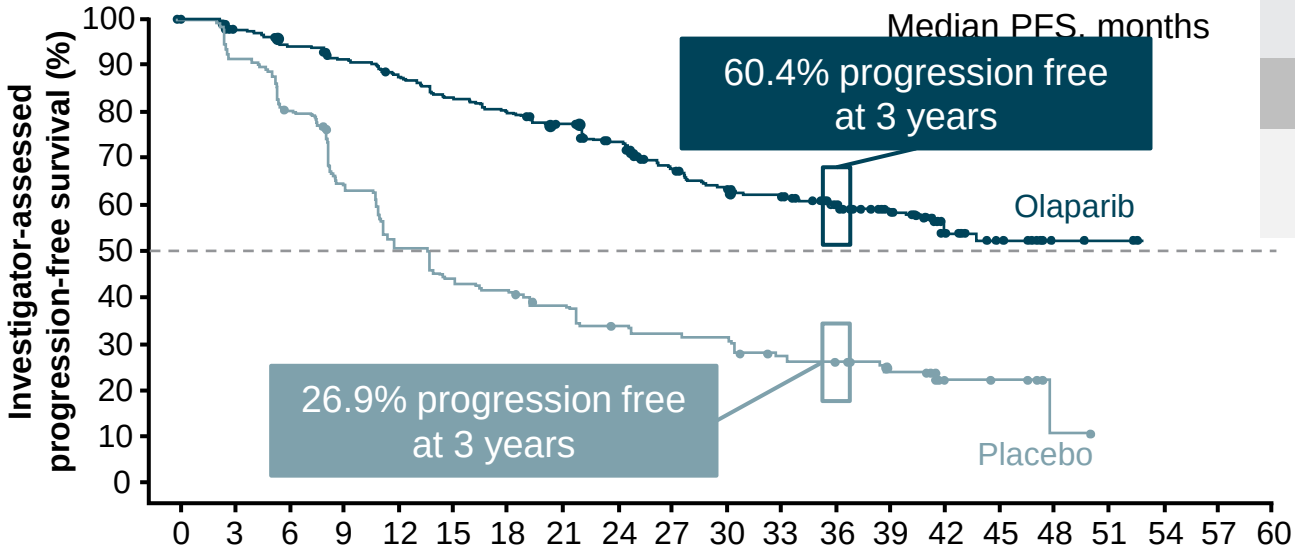
- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease. BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index

Moore et al. NEJM 2018

Progression Free Survival

	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

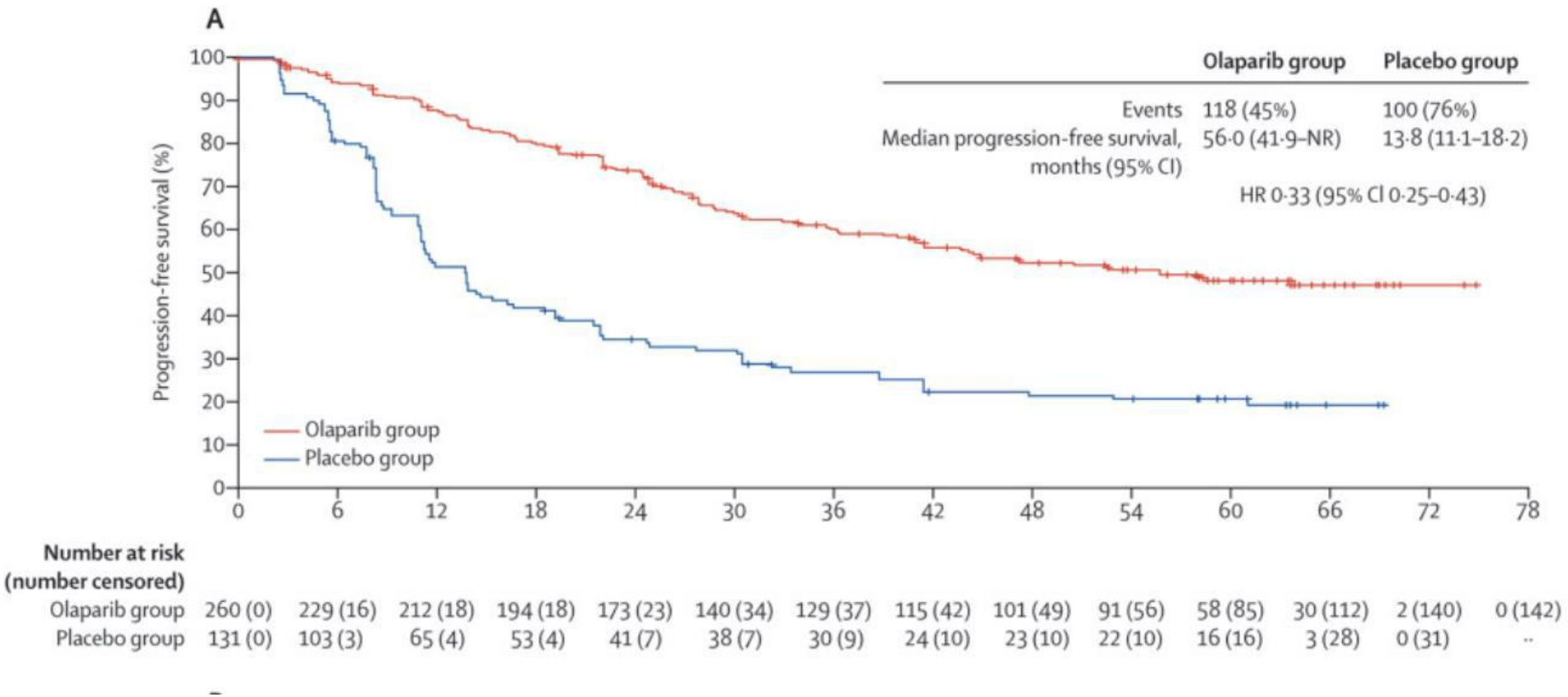


No. at risk																					
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

CI, confidence interval; NR, not reached

Moore et al. NEJM 2018

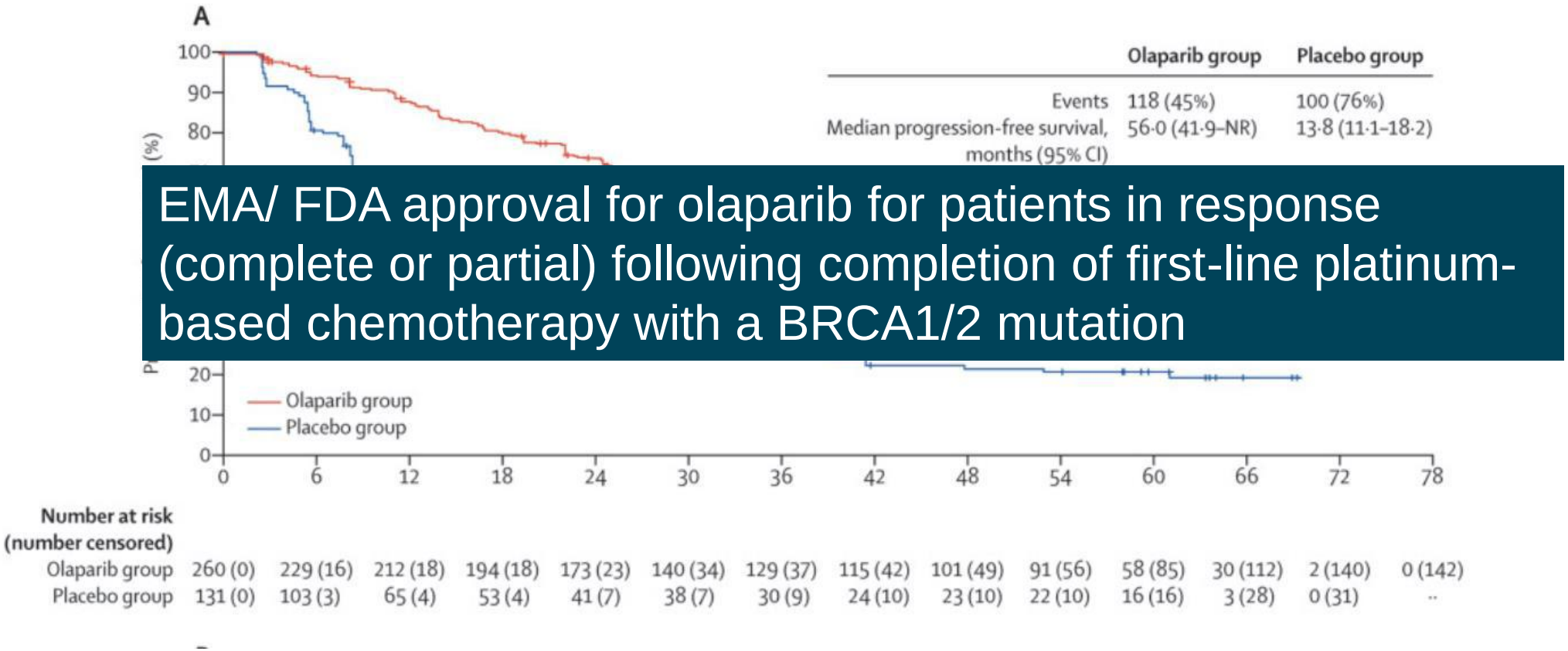
Progression Free Survival – updated analysis



Banerjee et al Lancet Oncology 2021

SOLO 1 Trial

Progression Free Survival – updated analysis

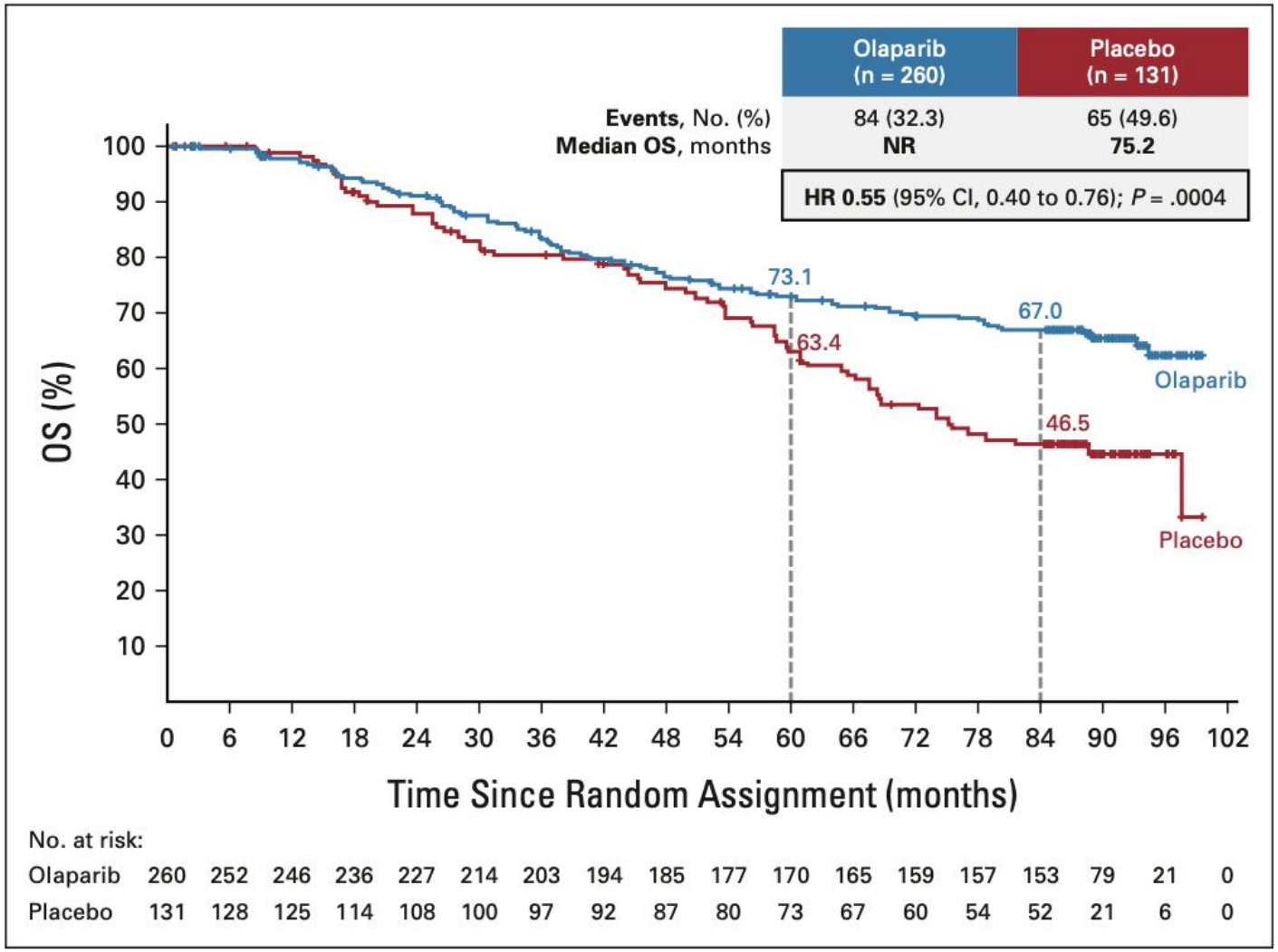


	Olaparib group	Placebo group
Events	118 (45%)	100 (76%)
Median progression-free survival, months (95% CI)	56·0 (41·9–NR)	13·8 (11·1–18·2)

EMA/ FDA approval for olaparib for patients in response (complete or partial) following completion of first-line platinum-based chemotherapy with a BRCA1/2 mutation

Banerjee et al Lancet Oncology 2021

Overall Survival – updated analysis



DiSilvestro et al JCO 2022

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PAOLA-1 study design

- *FIGO stage **III–IV high-grade** ovarian cancer (**serous or endometrioid**) or BRCAmut non-mucinous ovarian, primary peritoneal or fallopian-tube cancer*
- ***Surgery (upfront or interval)***
- *Platinum-taxane based Chemotherapy*
- ***≥3 cycles of bevacizumab*†***

NED/CR/PR

N=806
2:1

Maximum of 24 months maintenance treatment

Experimental arm: n=537

Olaparib (300 mg BD) x 2 years
+
Bevacizumab (15 mg/kg Q3W)
*Up to **15 months** as maintenance*†

Stratification by t*BRCA1/2* status and first-line treatment outcome

Active control arm: n=269

PLACEBO (300 mg BD) x 2 years
+
Bevacizumab (15 mg/kg Q3W)
*Up to **15 months** as maintenance*†

Primary endpoint:
Investigator assessed PFS

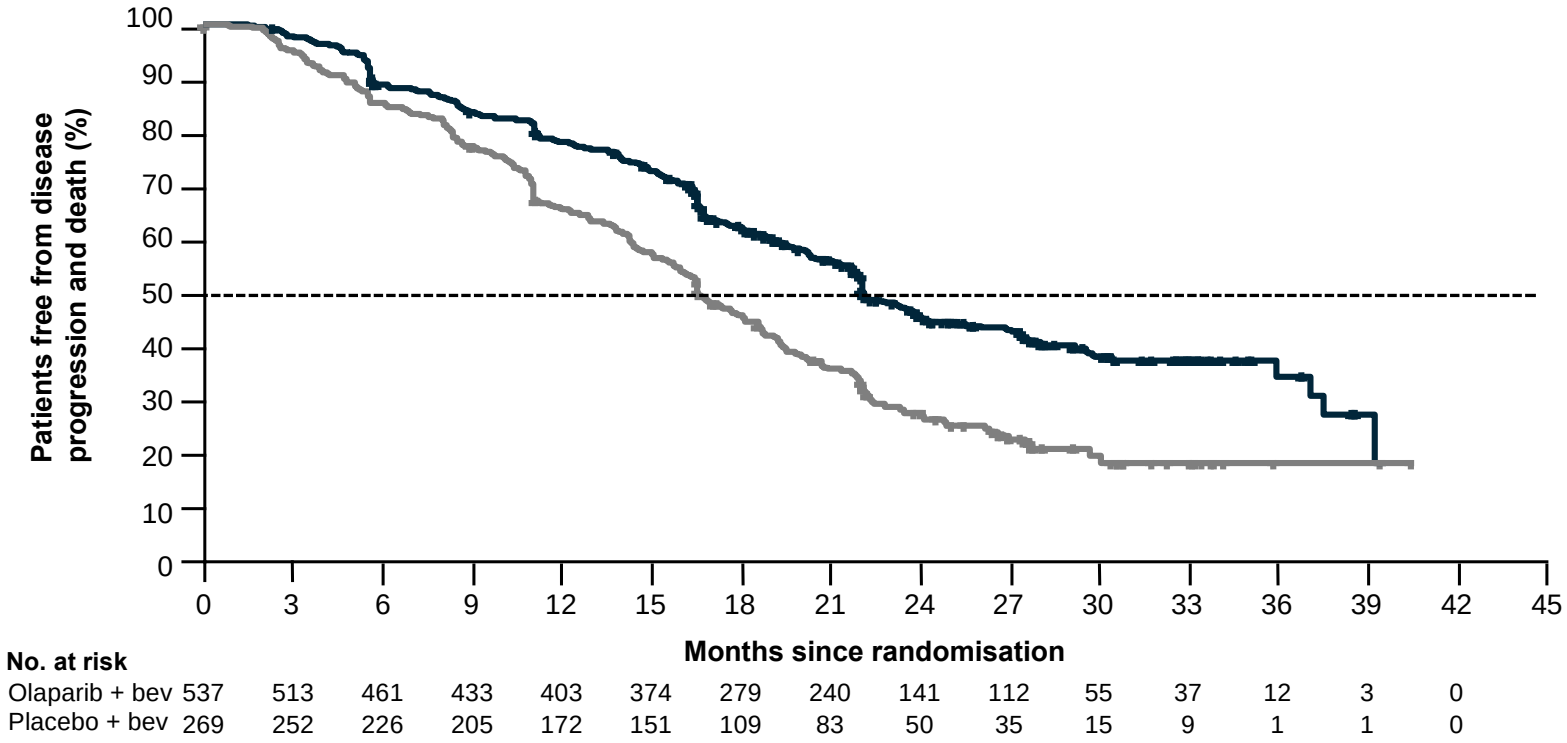
Key secondary endpoints
included PFS2, OS and QoL

Pre-specified exploratory endpoints
included PFS in tBRCA status, first-line treatment outcome, tumour characteristics as assessed by Myriad myChoice® HRD Plus assay[3]

BRCAm=BRCA mutation; CR=complete response; HRD=homologous recombination deficiency; ITT=intention to treat; NED=no evidence of disease; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2; PR=partial response; Q3W=every 3 weeks; QoL=quality of life; tBRCAm=tumour BRCA mutation.

RayCoquard et al NEJM 2019. RayCoquard et al ESMO 2019

PAOLA-1:Primary endpoint of investigator-assessed PFS in the ITT population



	Olaparib + bevacizumab n=537	Placebo + bevacizumab n=269
Events, n (%)	280 (52)	194 (72)
Median PFS, months (inv)	22.1	16.6
	HR 0.59 95% CI 0.49–0.72 p<0.001	

Primary endpoint:
investigator-assessed PFS

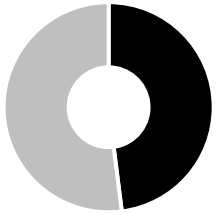
PFS by investigator assessment. Analysis per eCRF. Data maturity=59%. Median duration of follow-up for primary analysis: Lynparza, 22.7 months; placebo, 24.0 months. Data cut-off: 22 March 2019
Bev=bevacizumab; CI=confidence interval; eCRF=electronic case report file; HR=hazard ratio; inv=investigator-assessed; ITT=intention to treat; PFS=progression-free survival.

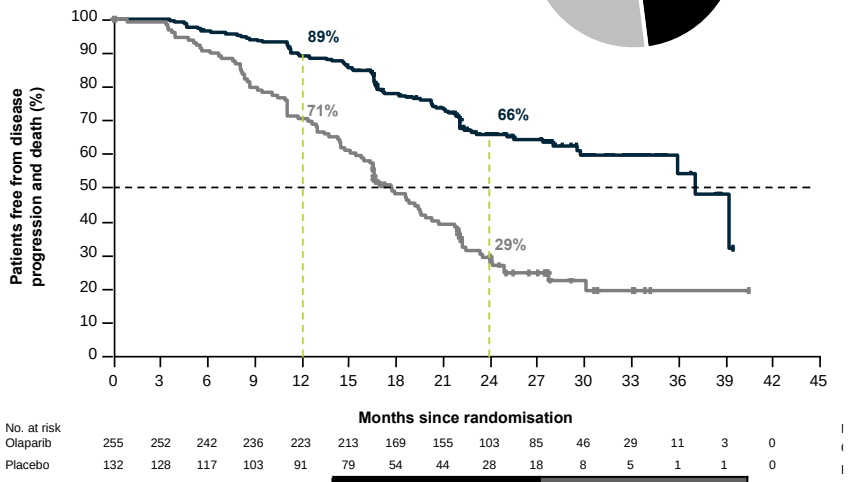
RayCoquard et al NEJM 2019. RayCoquard et al ESMO 2019

PAOLA-1 by HRD status

Pre-specified exploratory subgroup analyses of PFS by HRD status in PAOLA-1

HRD-positive (incl. t*BRCA1/2*m)





	Olaparib + bevacizumab n=255	Placebo + bevacizumab n=132
Median PFS, months (inv)	37.2†	17.7
	HR 0.33 95% CI 0.25–0.45	

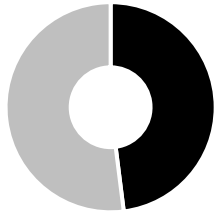
Data maturity=46%. The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. *HRD-positive determined by tBRCAm or Myriad myChoice® HRD Plus assay with a genomic instability score ≥42. †This median is unstable due to a lack of events – less than 50% maturity. CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; inv=investigator-assessed; (m)PFS=(median) progression-free survival; tBRCAm=mutation in tumour BRCA.

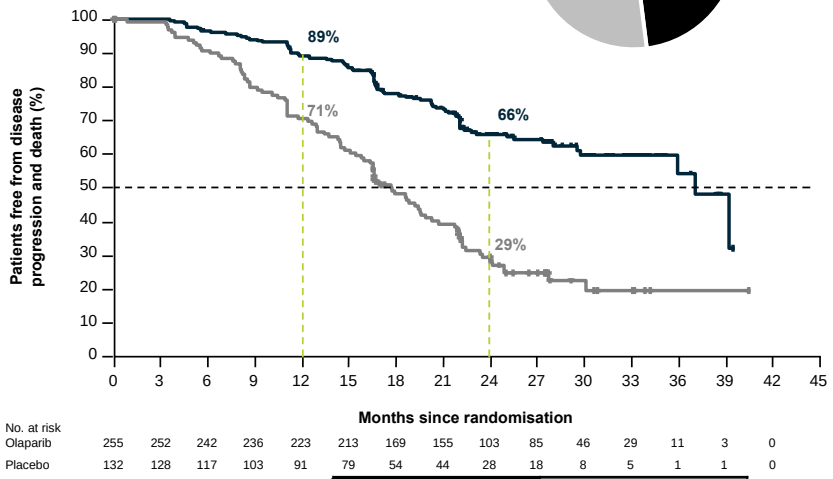
RayCoquard et al NEJM 2019. RayCoquard et al ESMO 2019

PAOLA-1 by HRD status

Pre-specified exploratory subgroup analyses of PFS by HRD status in PAOLA-1

HRD-positive (incl. t*BRCA1/2*m)





	Olaparib + bevacizumab n=255	Placebo + bevacizumab n=132
Median PFS, months (inv)	37.2†	17.7
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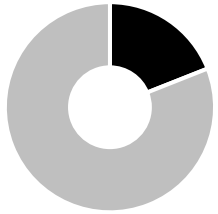
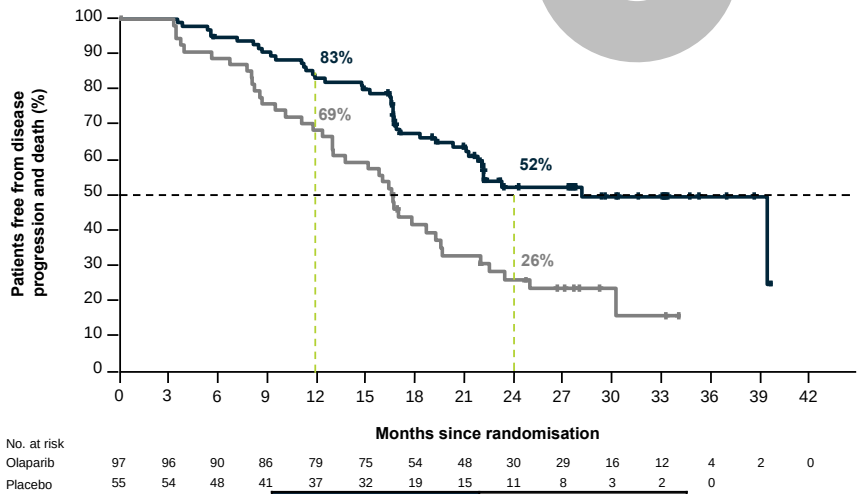
HRD-positive (exl. t*BRCA1/2*m)





	Olaparib + bevacizumab n=97	Placebo + bevacizumab n=55
	28.1†	16.6
	HR 0.43 95% CI 0.28–0.66	

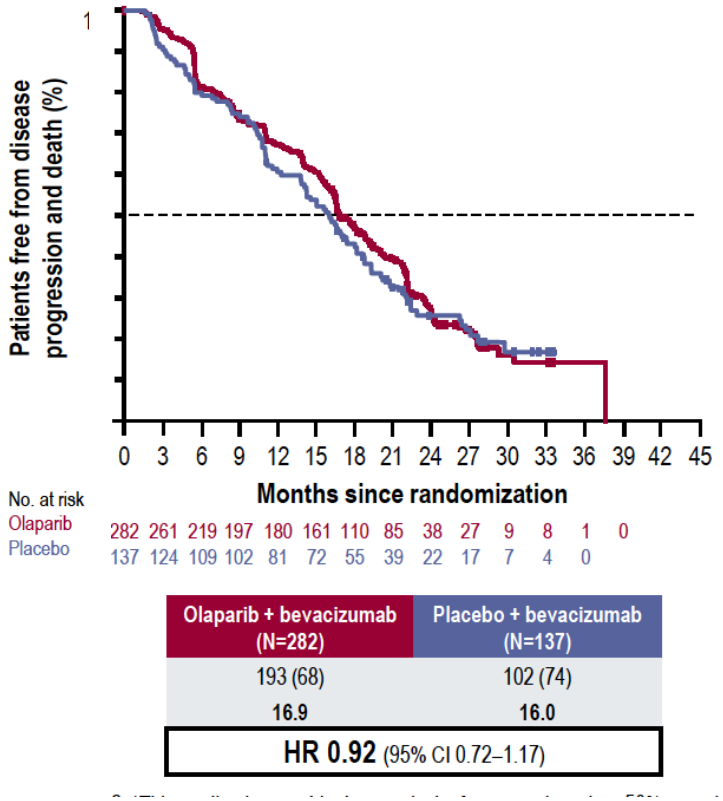
Data maturity=46%. The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. *HRD-positive determined by tBRCAm or Myriad myChoice® HRD Plus assay with a genomic instability score ≥42. †This median is unstable due to a lack of events – less than 50% maturity. CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; inv=investigator-assessed; (m)PFS=(median) progression-free survival; tBRCAm=mutation in tumour BRCA.

RayCoquard et al NEJM 2019. RayCoquard et al ESMO 2019

PAOLA-1 by HRD status

Pre-specified exploratory subgroup analyses of PFS by HRD status in PAOLA-1

HRD negative/ unknown



Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
193 (68)	102 (74)
16.9	**16.0**
HR 0.92 (95% CI 0.72–1.17)	

No benefit in the HRD negative (HRP) sub-group

RayCoquard et al NEJM 2019. RayCoquard et al ESMO 2019

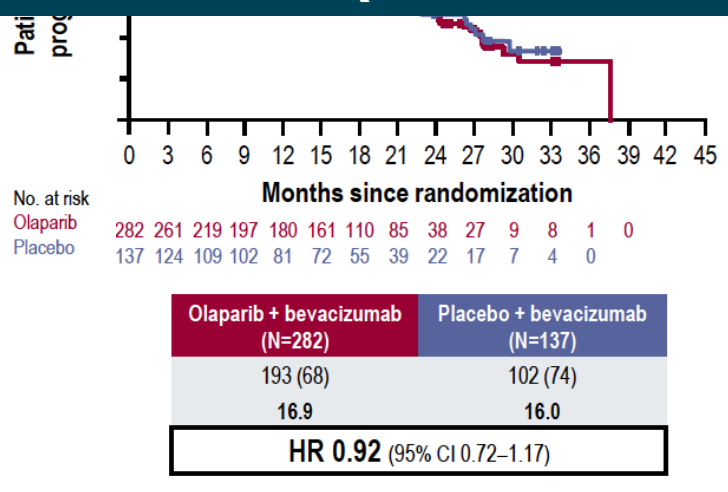
PAOLA-1 by HRD status

Pre-specified exploratory subgroup analyses of PFS by HRD status in PAOLA-1

HRD negative/ unknown

No benefit in the HRD negative

EMA/ FDA approval for Olaparib/ bevacizumab combination for patients in response (complete or partial) following completion of first-line platinum-based chemotherapy whose cancer is associated with **HRD (GIS+ and/or *BRCA1/2* mutation)**



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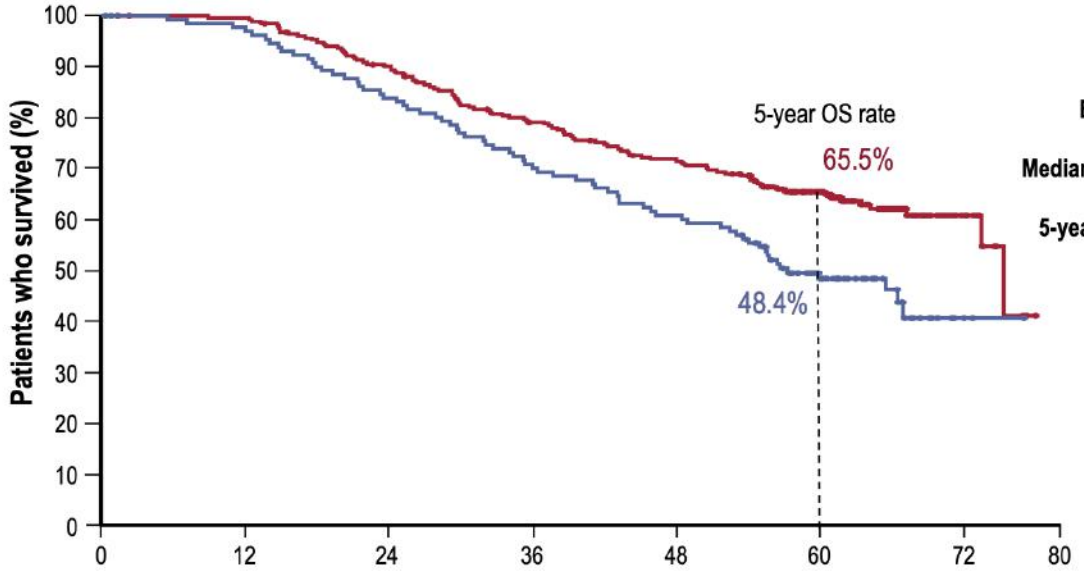
HR 0.92 (95% CI 0.72–1.17)	

RayCoquard et al NEJM 2019. RayCoquard et al ESMO 2019

PAOLA-1 Overall Survival



No. at risk

Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

PARIS 2022 ESMO congress

Isabelle Ray-Coquard

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

First Line PARPi Maintenance Trials

HRD – homologous recombination deficient, HRP - homologous recombination proficient
UK – unknown, NACT – neoadjuvant chemo
PFS – progression free survival , PCS – primary cytoreductive surgery
CR/PR – complete/partial response

TRIAL	Patients enrolled	Stratification	PARPi (duration months)	Control Arm	Primary end point
SOLO1	FIGO III/IV *BRCA1/2*	Chemo response (CR/PR)	Olaparib (24)	Placebo	PFS
PAOLA1	FIGO III/IV ≥ 3 cycles bevacizumab	Tumour *BRCA1/2* Chemo response	Olaparib (24) /Bevacizumab (15)	Placebo/ Bevacizumab	PFS
PRIMA	FIGO III/IV (Stage III with disease post PCS or Stage III/IV NACT)	Chemo response NACT (yes/no) HRD vs HRP/UK	Niraparib (36)	Placebo	PFS
ATHENA	FIGO III/IV All HG histology	Chemo response Timing of surgery HRD vs HRP/UK	Rucaparib (24)*	Placebo	PFS
PRIME	FIGO III/IV Surgical attempt as minimum Chinese population	Chemo response NACT (yes/no) HRD vs HRP/UK g*BRCA1/2*	Niraparib (36)	Placebo	PFS

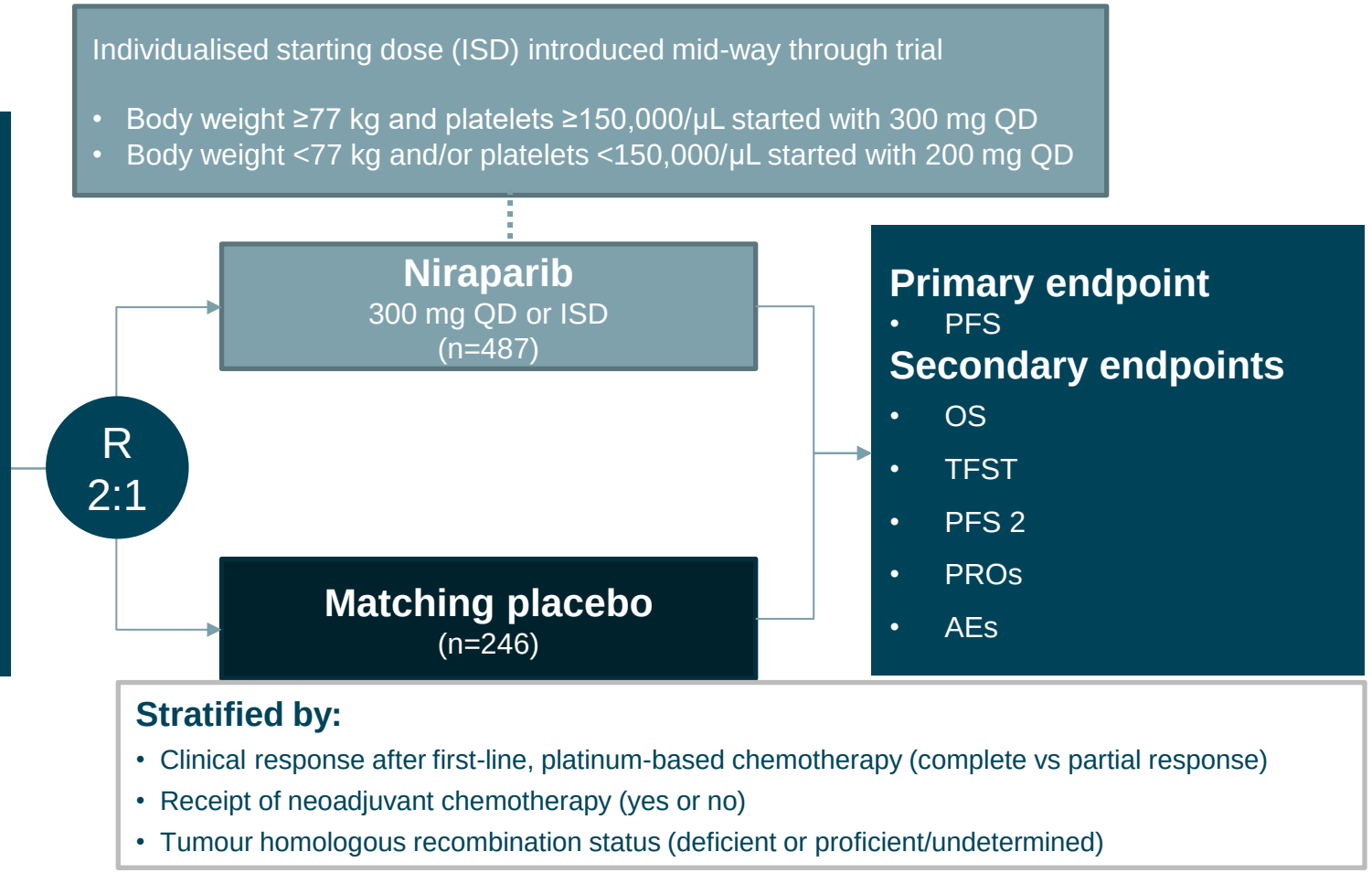
* also include nivolumab - data not reported

Moore et al NEJM 2018, Gonzalez Martin et al NEJM 2019, RayCoquard et al NEJM 2019, Monk JCO 2022, Li et al SGO 2022

PRIMA study design

Patient population

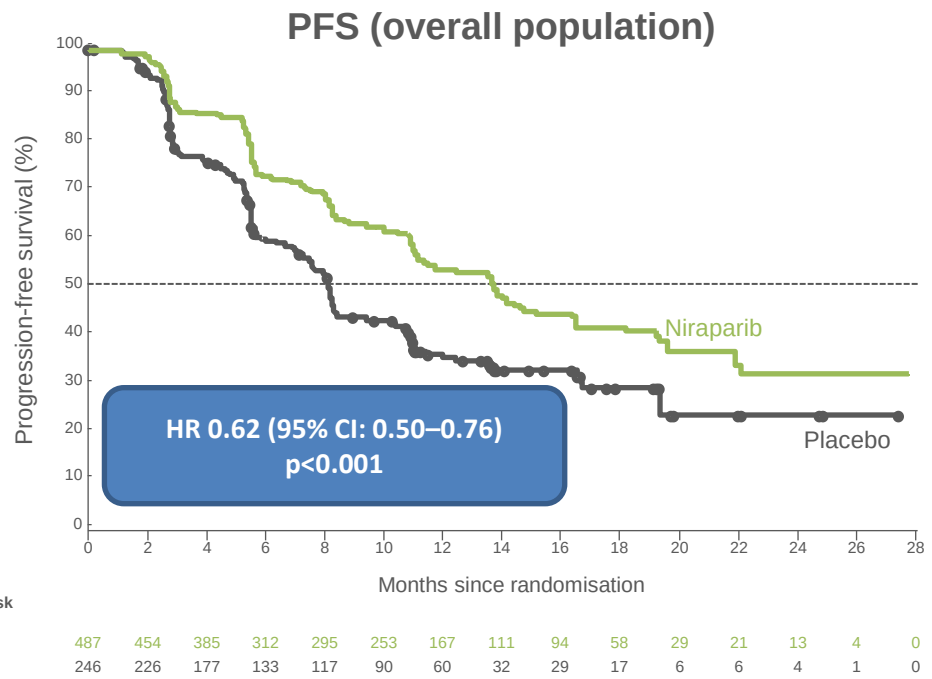
- N=733
- ≥18 years of age
- Newly diagnosed, histologically confirmed advanced ovarian cancer
- High-grade, predominantly serous or endometrioid histological features*
- Complete or partial response to first-line platinum-based chemotherapy
- **Stage III patients with visible residual disease after primary debulking surgery**
- **Stage III and IV* patients with inoperable disease**
- Tumour sample testing for *BRCA* mutations or HRd



AE, adverse event; *BRCA*, breast cancer susceptibility gene; HRd, homologous recombination deficient; ISD, individualised starting dose; OS, overall survival; QD, once daily; PFS, progression-free survival; PRO, patient-reported outcome; R, randomised; TFST, time to first subsequent therapy.

González-Martín A et al. *N Engl J Med* 2019

Primary End-point PFS



Median PFS for overall population

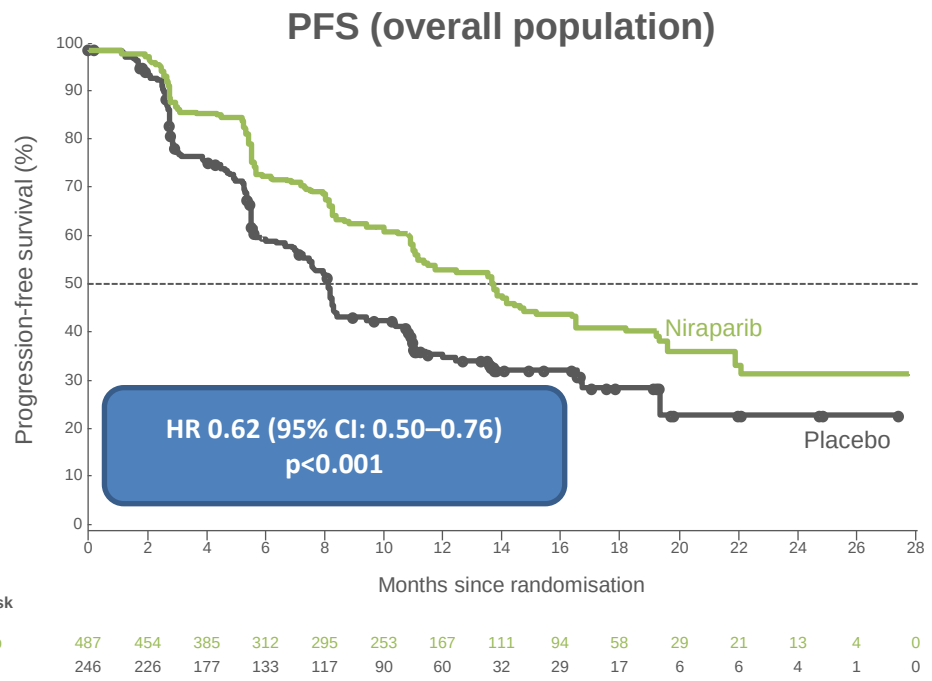
13.8 months for niraparib

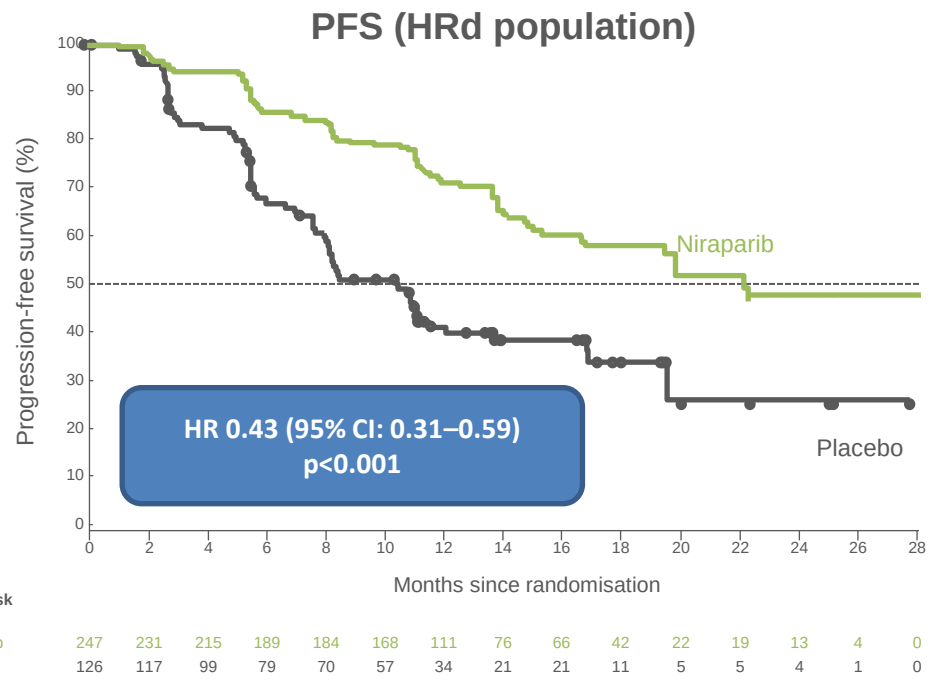
8.2 months for placebo

Median duration of follow-up at time of data cut-off: **13.8 months**

González-Martín A et al. *N Engl J Med* 2019;381:2391–2402.

Primary End-point PFS





Median PFS for overall population

13.8 months for niraparib

8.2 months for placebo

Median duration of follow-up at time of data cut-off: **13.8 months**

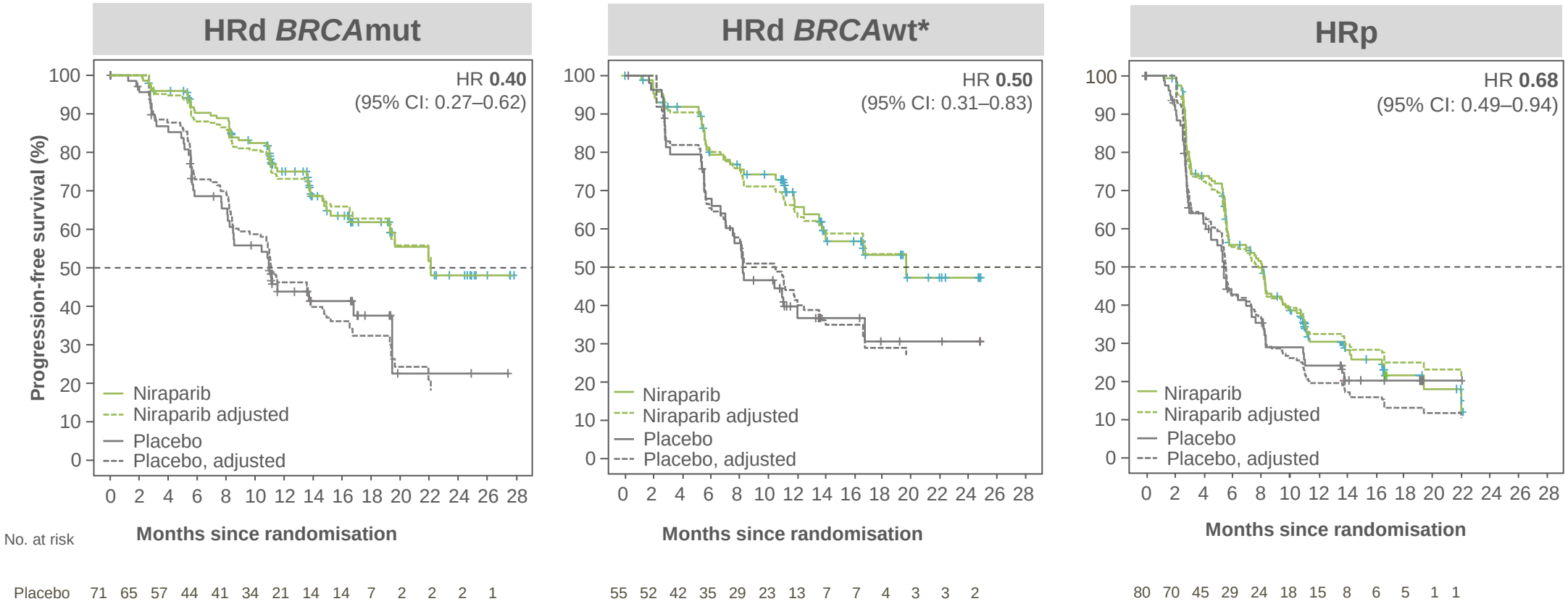
Median PFS for HRd patients

21.9 months for Niraparib

10.4 months for placebo

González-Martín A et al. *N Engl J Med* 2019;381:2391–2402.

PFS benefit in HRD subgroups

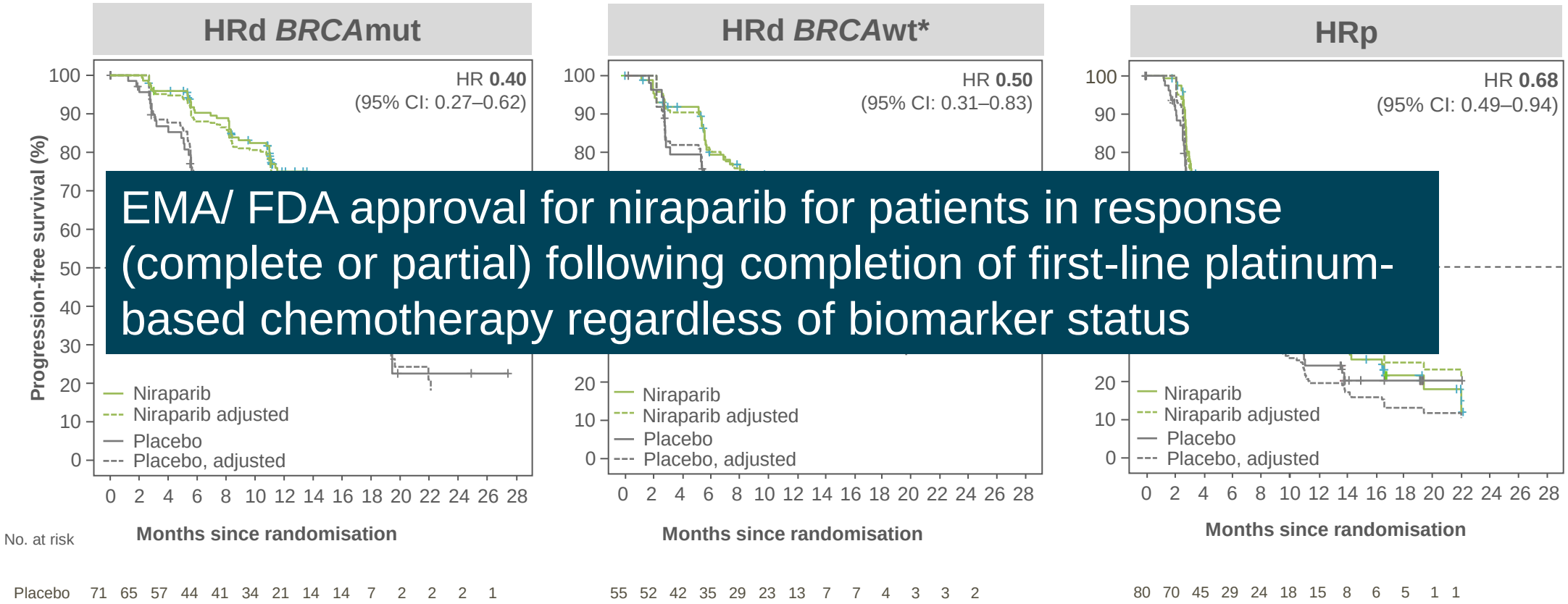


These prespecified subgroup analyses were not powered to detect a statistically significant treatment effect; therefore, results should be interpreted with caution.

Monk BJ et al. SGO 2020

González-Martín A et al. *N Engl J Med* 2019;381:2391–2402.

PFS benefit in HRD subgroups



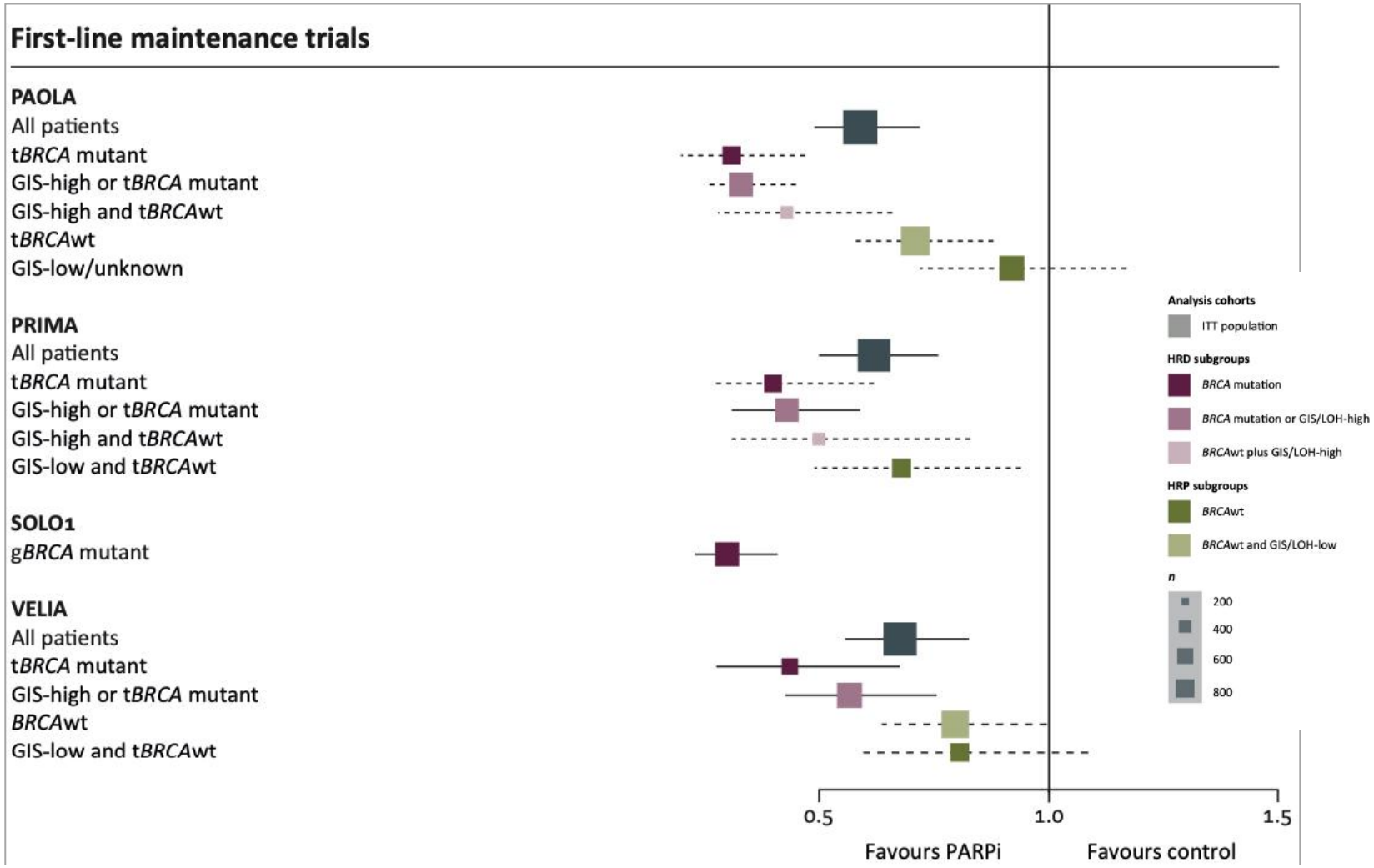
EMA/ FDA approval for niraparib for patients in response (complete or partial) following completion of first-line platinum-based chemotherapy regardless of biomarker status

These prespecified subgroup analyses were not powered to detect a statistically significant treatment effect; therefore, results should be interpreted with caution.

Monk BJ et al. SGO 2020

González-Martín A et al. *N Engl J Med* 2019;381:2391–2402.

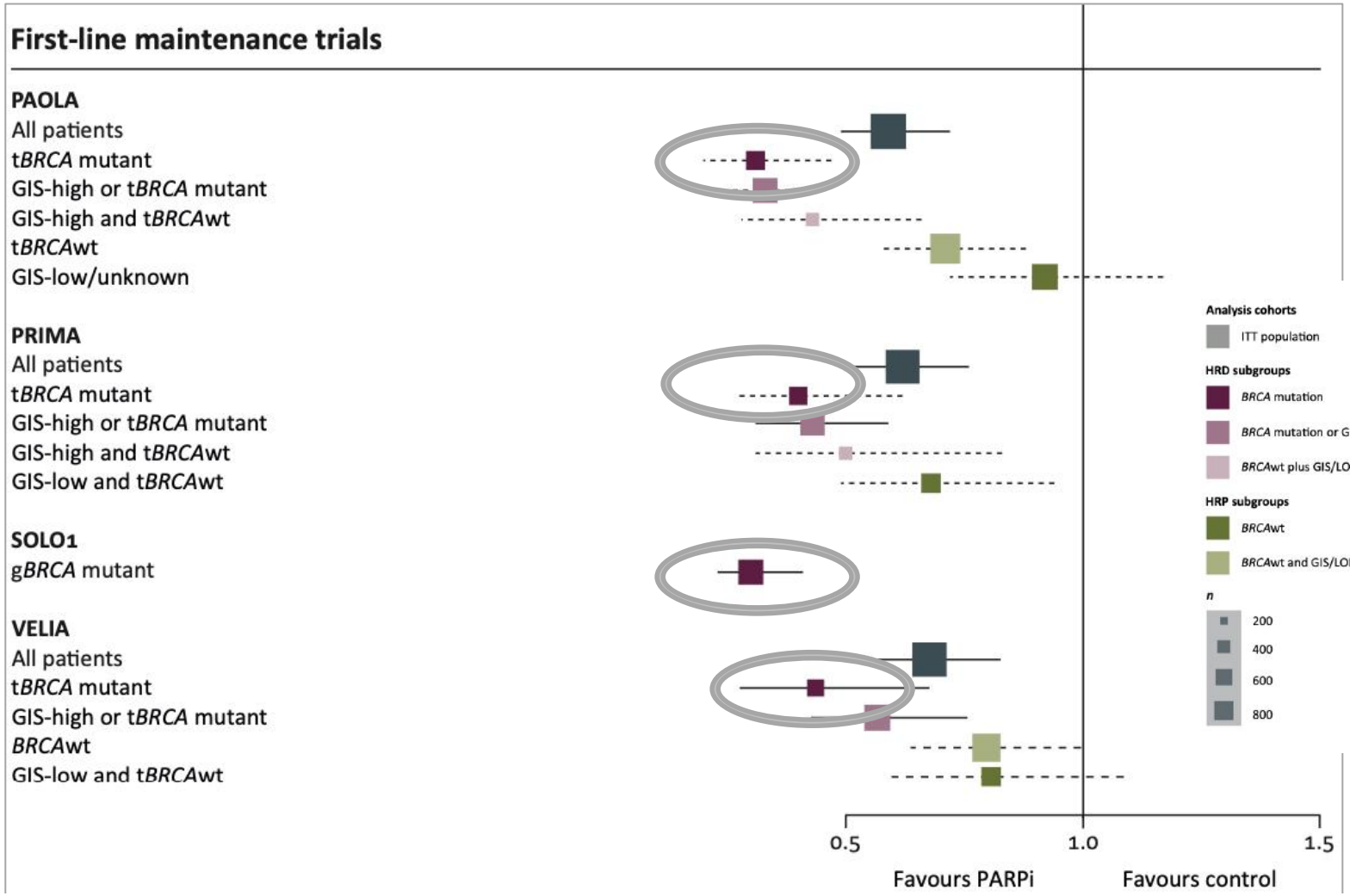
HRD status as predictor for magnitude of PARP inhibitor response in first line maintenance

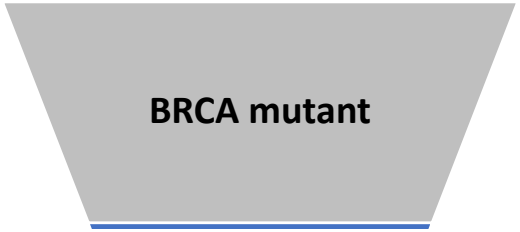


tBRCA – tumour BRCA, gBRCA – germline BRCA, GIS – genomic instability score, wt- wildtype, PARPi – PARP inhibitor, ITT – intention to treat

Miller et al 2020. Annals of Oncology, RayCoquard et al NEJM 2019, Coleman et al NEJM 2019, Gonzalez Martin et al NEJM 2019 , Moore et al NEJM 2018

HRD status as predictor for magnitude of PARP inhibitor response in first line maintenance

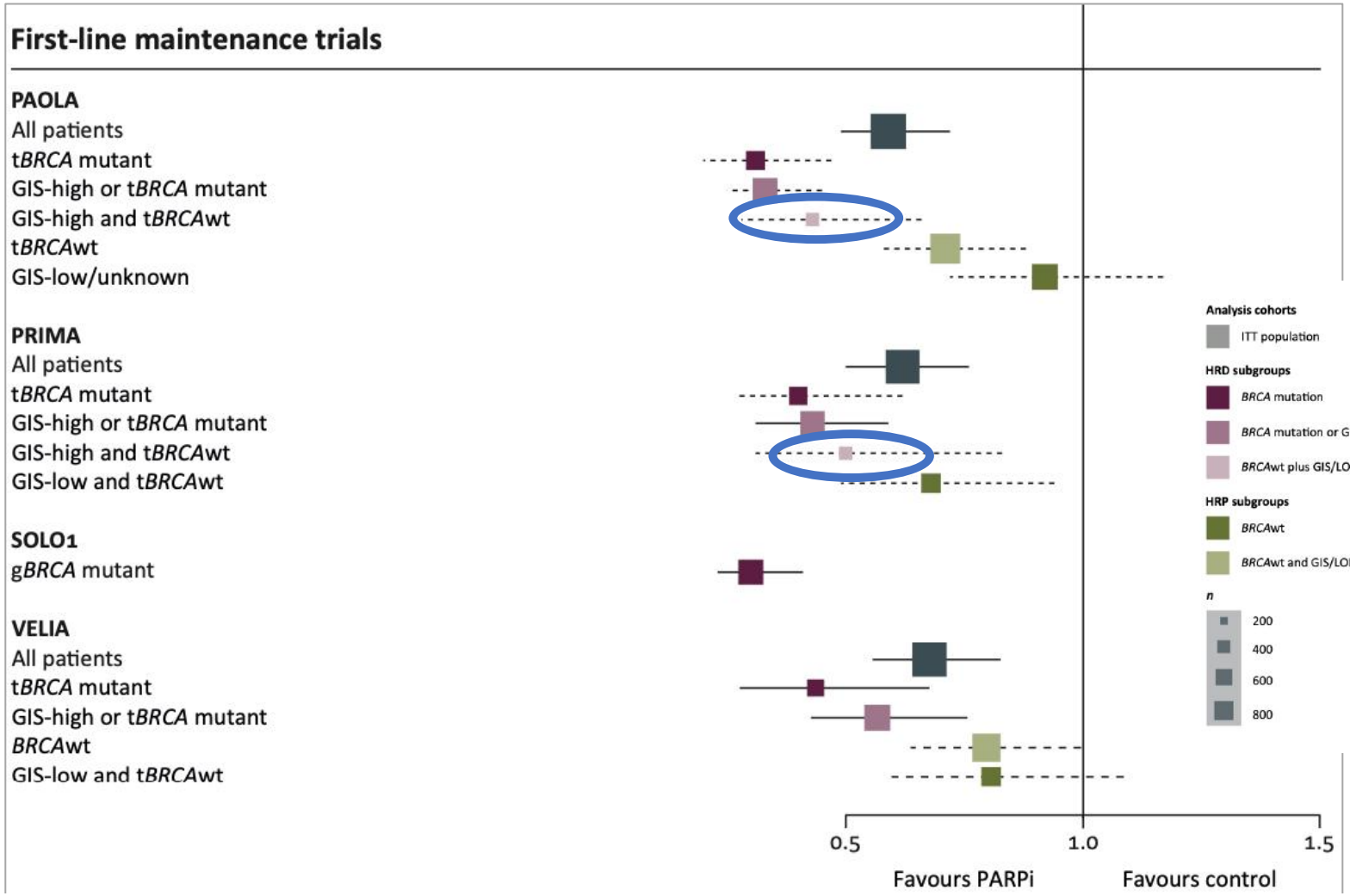


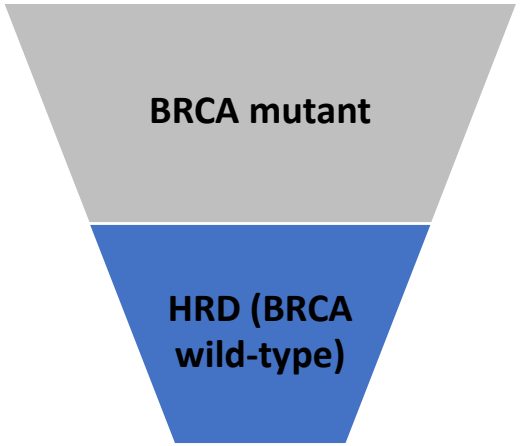


tBRCA – tumour BRCA, gBRCA – germline BRCA, GIS – genomic instability score, wt- wildtype, PARPi – PARP inhibitor, ITT – intention to treat

Miller et al 2020. Annals of Oncology, RayCoquard et al NEJM 2019, Coleman et al NEJM 2019, Gonzalez Martin et al NEJM 2019 , Moore et al NEJM 2018

HRD status as predictor for magnitude of PARP inhibitor response in first line maintenance





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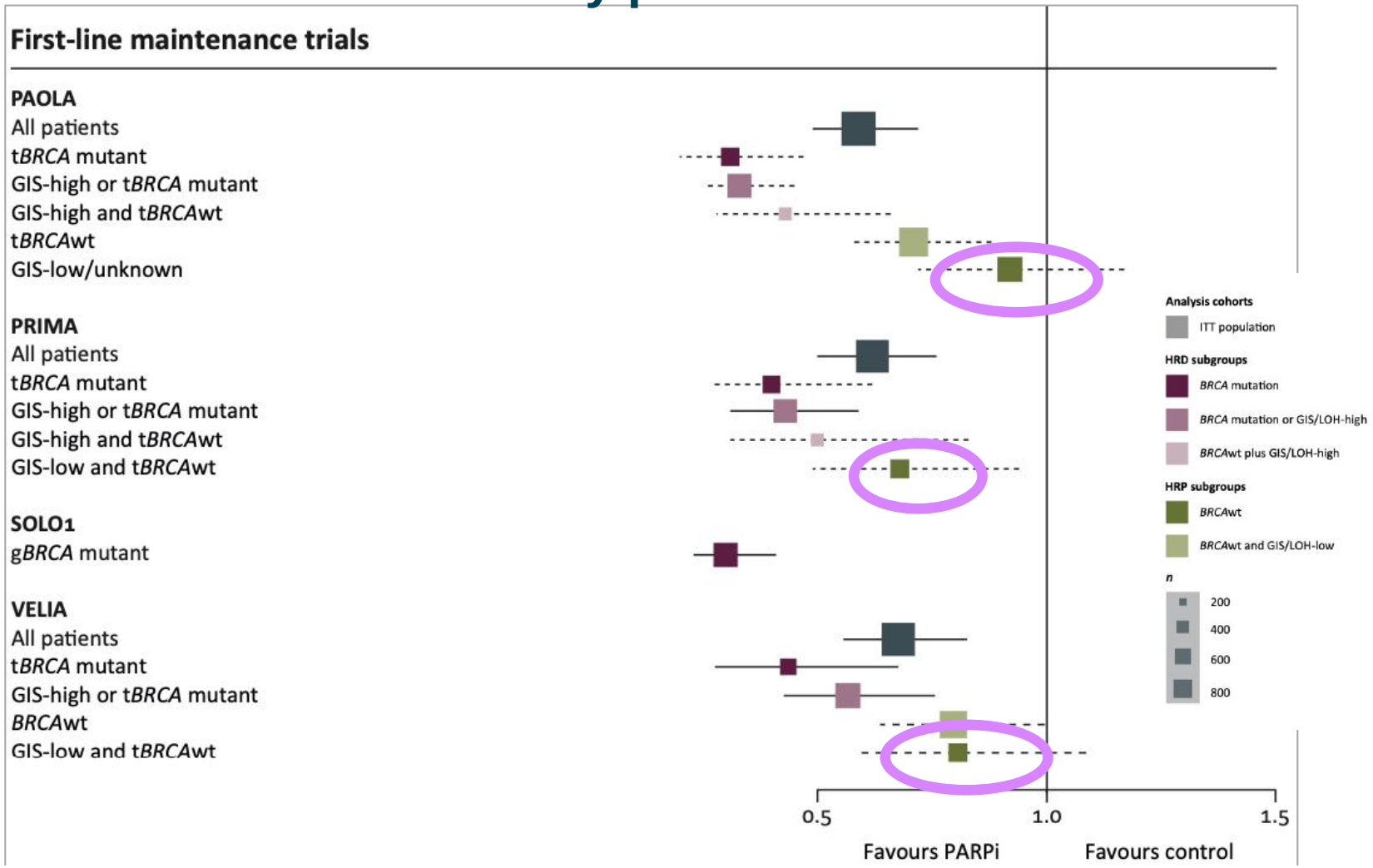
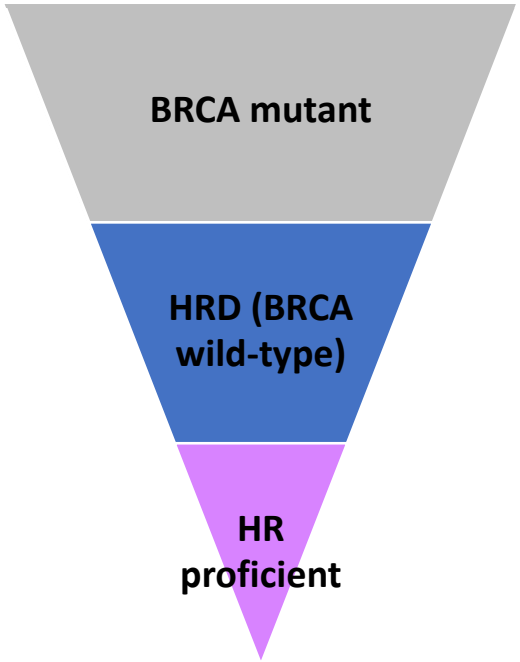
Miller et al 2020. Annals of Oncology, RayCoquard et al NEJM 2019, Coleman et al NEJM 2019, Gonzalez Martin et al NEJM 2019 , Moore et al NEJM 2018

HRD status as predictor for magnitude of PARP inhibitor response in first line maintenance - but do they predict those who done benefit?





tBRCA – tumour BRCA, gBRCA – germline BRCA, GIS – genomic instability score, wt- wildtype, PARPi – PARP inhibitor, ITT – intention to treat

Miller et al 2020. Annals of Oncology, RayCoquard et al NEJM 2019, Coleman et al NEJM 2019, Gonzalez Martin et al NEJM 2019 , Moore et al NEJM 2018

All this data….
How do we decide what is best for our patients ?

- Clinical characteristics (symptoms, residual tumour)
- Molecular characteristics (biomarker status)
- Histology (low/high grade)
- Platinum sensitivity

- Safety and efficacy
- Ease of administration
- Individualised dosing
- Drug interactions

- Genetic *BRCA* and HRD testing
- Approvals and indications
- Reimbursement/cost

- Overall treatment plan
- Comorbidities
- Patient preference (IV vs PO)
- Quality of life/ patient-reported outcomes
- General/functional status

1. Buechel M, et al. *Ann Oncol* 2019;30:721–32; 2. Mirza MR, et al. *Ann Oncol* 2020;31:1148–59; 3. O'Cearbhaill RE. Oncology (Williston Park) 2018;32:339–43; 4. Havrilesky LJ, et al. *Gynecol Oncol* 2020;156:561–67. 5. Miller RE, et al. *Ann Oncol* 2020;31:1606–22.

Ovarian cancer

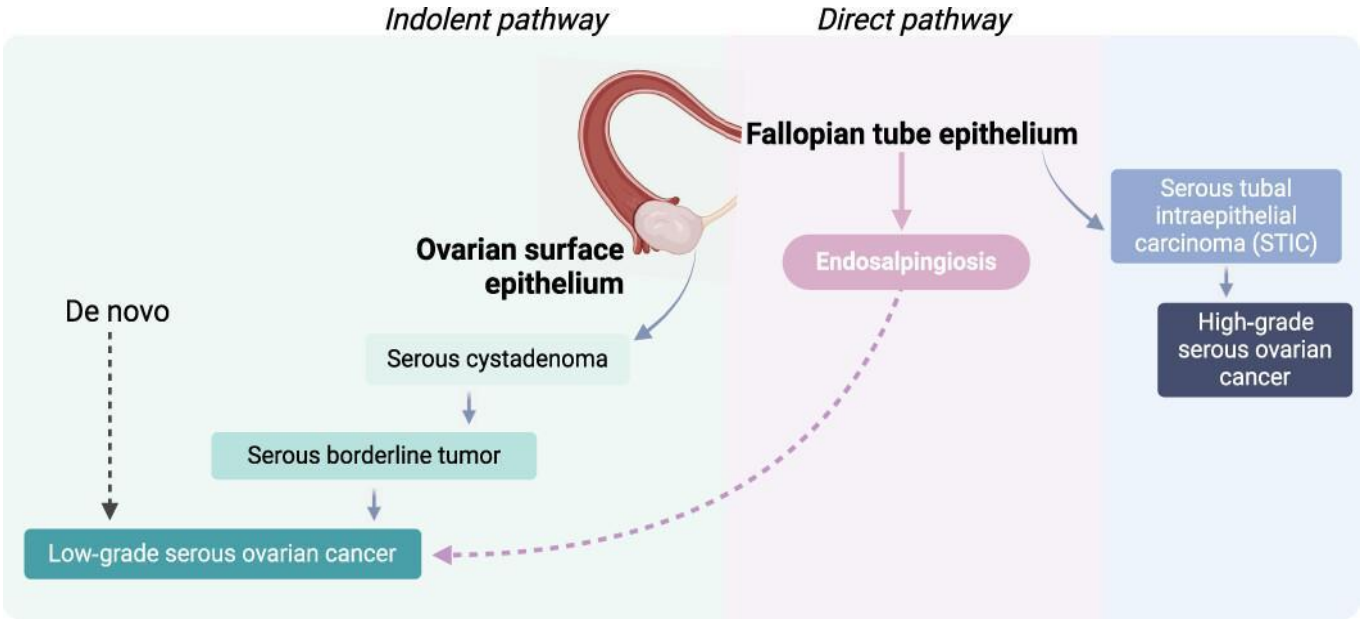
High grade serous - BRCA1/2 & HRD

Low-grade serous - MAPK signalling

High grade – folate receptor

Low grade serous ovarian cancer

- LGSOC 5-10% of all serous tumours
- Rare histologically subtype
- Biologically distinct from HGSOC
- Young age presentation: med 43-54 yrs
- Median survival 91 mo vs 67 mo for HGSOC
- Arise de novo or stepwise progression from serous cystadenoma
- Likely origin in fallopian tube



1.Schmeler Gyn Oncol 2008; 2. Granowski Gyn Oncol 2016; 3 Monk JCO 2020; Gershenson 2022;

LGSOC: First Line management

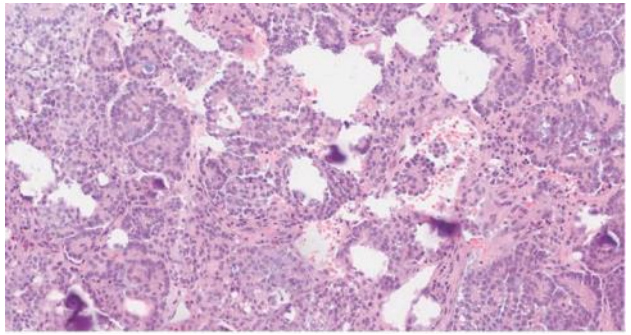
Although LGSOC distinct entity management has been similar to HGSOC

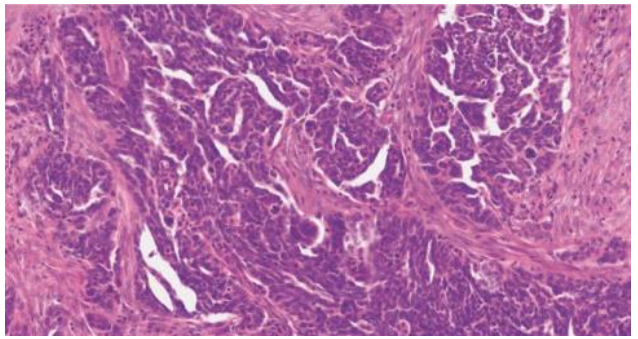
- Mainstay of treatment is surgery: first line/recurrent disease
- First line: maximal cytoreduction followed by chemotherapy
- Slow growing disease with relative chemo - insensitivity
    - 4-23% RR to first line treatment (retrospective data) [1,2]
    - Approx 5% RR –relapse (Milo/ GOG281) [3,4]
- Limited role for neoadjuvant chemo in advanced disease
- Role of: adjuvant chemotherapy - unclear
    - bevacizumab - improved response rates
    - PARP inhibitors –Platinum insensitive; only BRCAm 1-5%; ltd evidence for benefit
    - NCCN/ASCO- still recommend germline BRCA testing in this population

- Significant unmet need

1.Schmeler Gyn Oncol 2008; 2. Granowski Gyn Oncol 2016; 3 Monk JCO 2020; Gershenson 2022;

Variable	LGSOC	HGSOC
Nuclear Atypia	Uniform round to oval/ min variation	+++ Marked variation
Mitotic Index	<12 mitosis/ 10hpf	>12 mitosis/ 10hpf
Chromatin+ nuclear variation	Little	Marked (nuclear size ratio ≥ 3
Mutation	**ER/PR +++** **KRAS ++ (19-55%)** **BRAF + (5%)** PAX2 +	P53 +++ BRCA 1/2
Major Pathway Affected	**MAPK, PI3K, mTOR**	Homologous Recombination
Precursor	Serous borderline tumour	Tubal intraepithelial neoplasia





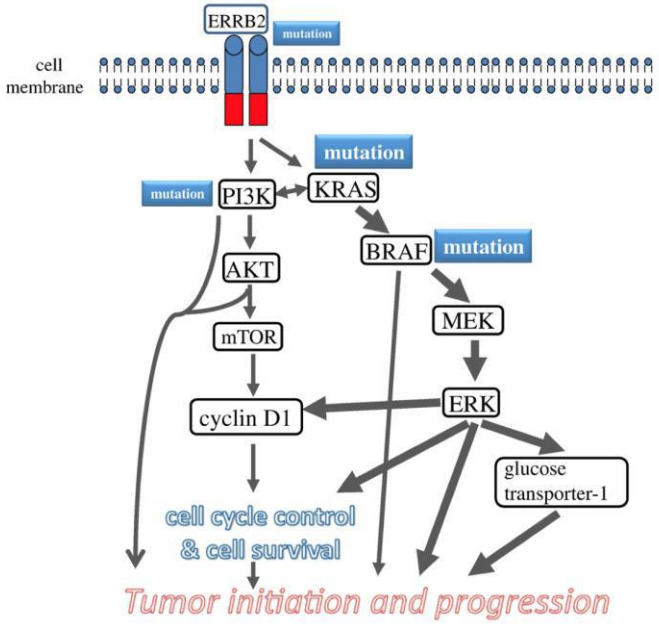
Kurman et al Am J path 2007; Malpica et al Am J path 2007

Recurrent LGSOC – MEK inhibitors

Low-grade serous

BRAF
KRAS
NRAS
ERBB2

Binimetinib (MILO/ENGOT Ov-11) and Trametinib (LOGS/ GOG-281) trials



Kurman & Shih 2011 Grisham et al J Clin Oncol 2020; Gershenson et al Lancet 2022

Recurrent LGSOC – MEK inhibitors

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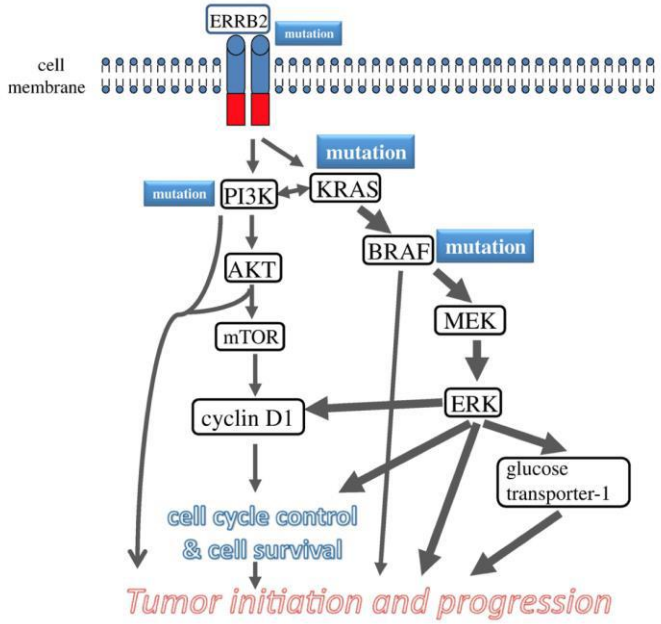
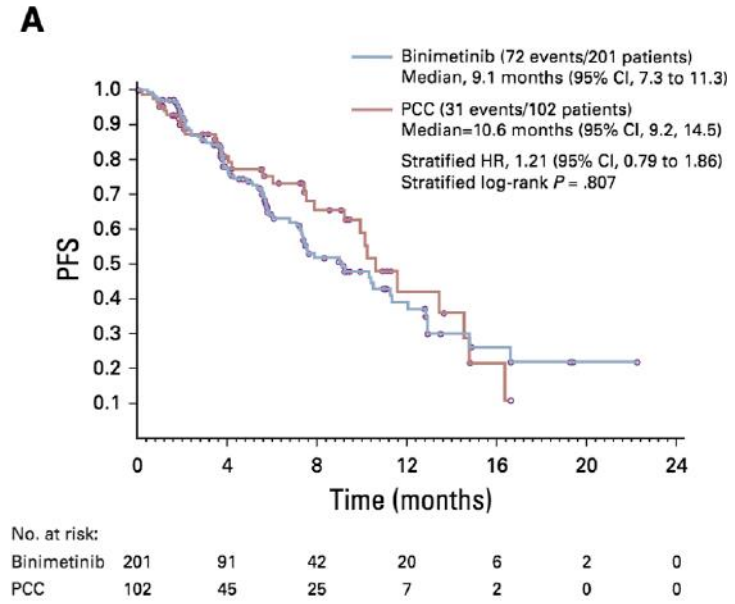
ERBB2

Binimetinib (MILO/ENGOT Ov-11) and Trametinib (LOGS/ GOG-281) trials

Binimetinib





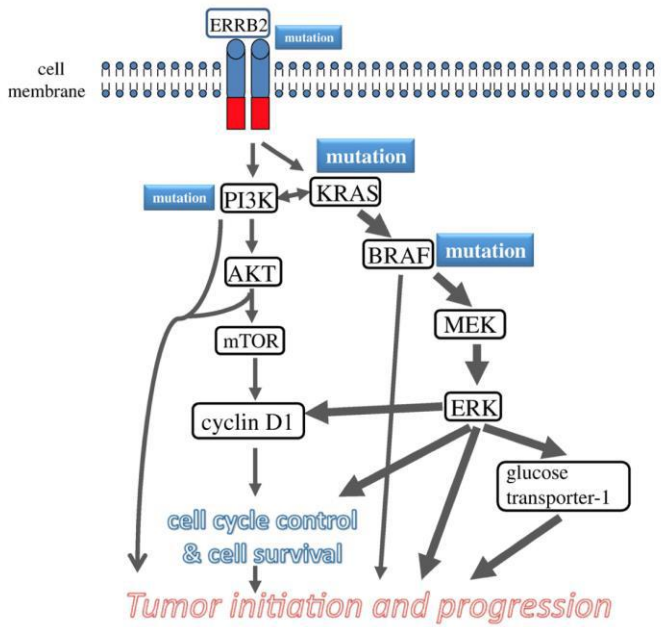
Kurman & Shih 2011 Grisham et al J Clin Oncol 2020; Gershenson et al Lancet 2022

Recurrent LGSOC – MEK inhibitors

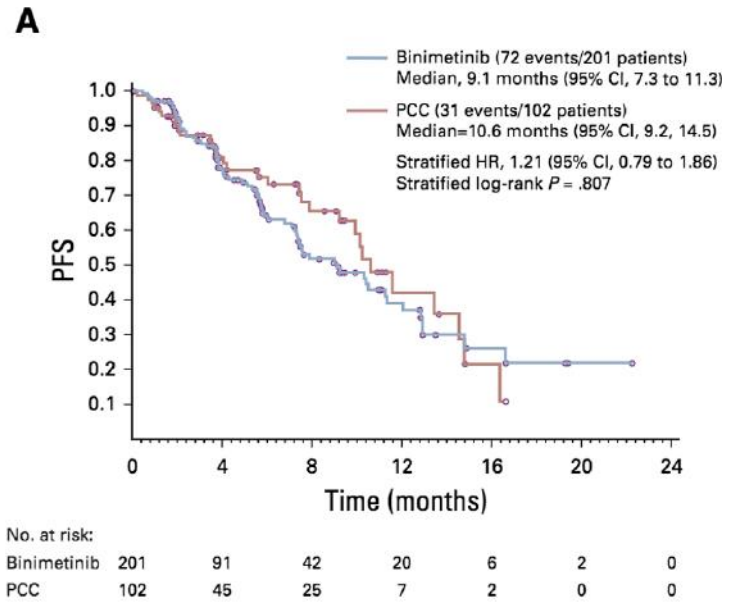
Low-grade serous

BRAF
KRAS
NRAS
ERBB2

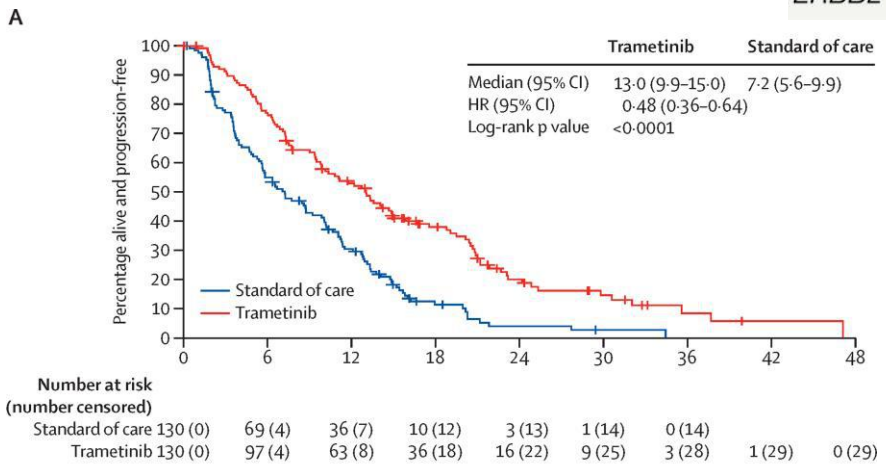
Binimetinib (MILO/ENGOT Ov-11) and Trametinib (LOGS/ GOG-281) trials

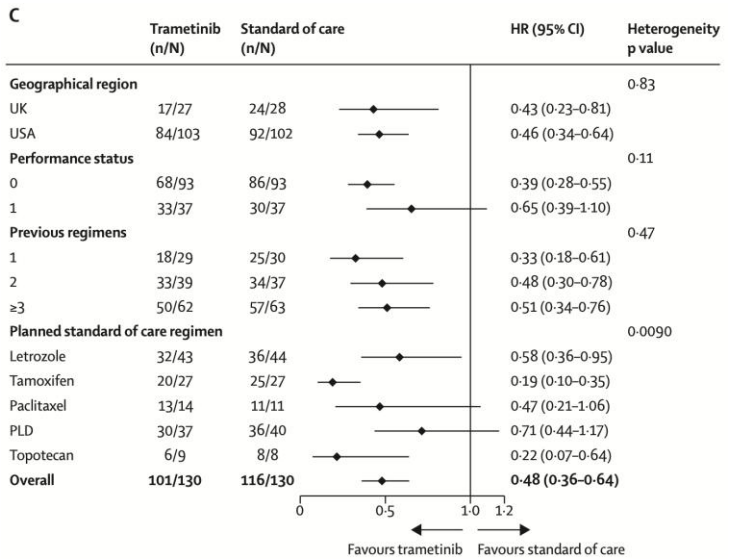


Binimetinib



Trametinib





Kurman & Shih 2011 Grisham et al J Clin Oncol 2020; Gershenson et al Lancet 2022

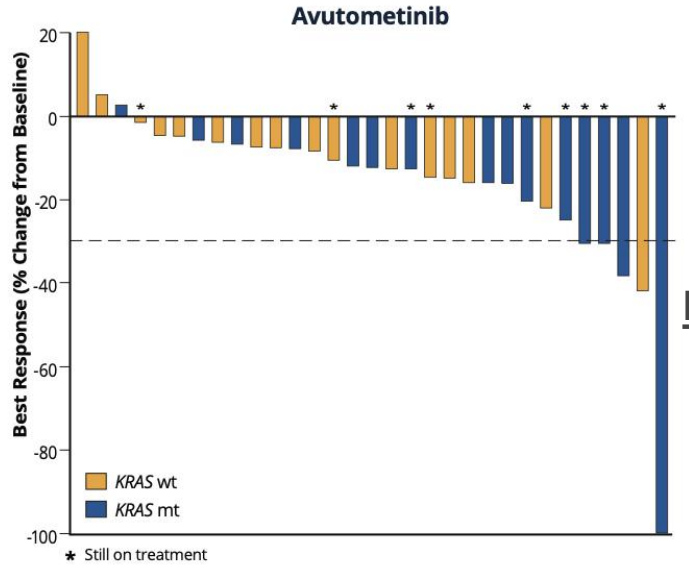
Combination therapy in recurrent LGSOC
RAMP 201 Study

- Recurrent LGSOC*
- KRAS agnostic**
- Measurable disease (RECIST 1.1)
- Prior MEKi allowed
- Approximately 32 subjects

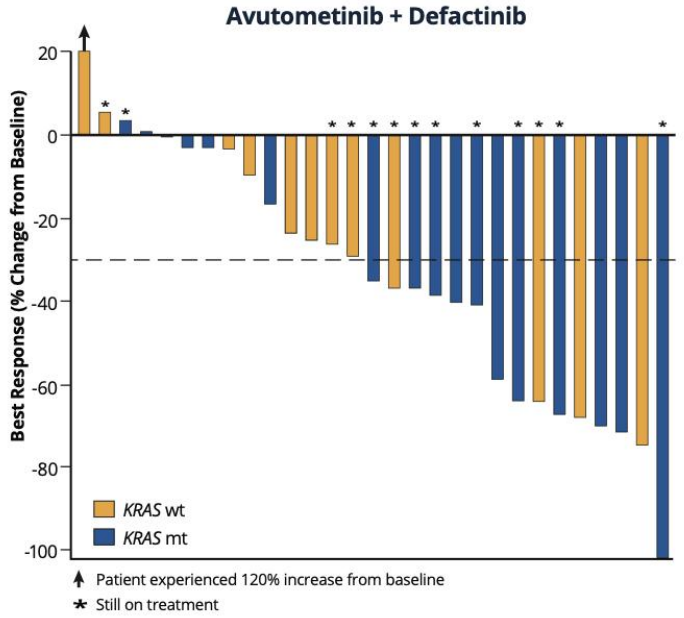
Randomize 1:1
Stratified on KRAS status

Defactinib+Avutometinib
Defactinib 200 mg PO BID
21/28 days + VS-6766 3.2 mg PO 2x/wk
21/28 days

Avutometinib Mono
VS-6766 3.2 mg PO 2x/wk
21/28 days
PD to cross over to combo
PD to be assessed by single independent reviewer



Monotherapy (30)
- **ORR 10%**
- **DCR 93%**



Combination (29)
- **ORR 45%**
- **DCR 90%**

Avutometinib :RAK/MEK inhibitor
Defactinib: FAK inhibitor (focal Adhesion Kinase)

*LGSOC: To include low grade serous ovarian carcinoma;
**KRAS WT to be included on per KOL feedback

Banerjee et al ASCO 2023

Combination therapy in recurrent LGSOC
RAMP 201 Study

- Recurrent LG
- KRAS agnos
- Measurable d (RECIST 1.1)
- Prior MEKi al
- Approximatel

FDA Awards Orphan Drug Designation to Avutometinib Alone or With Defactinib for Recurrent Low-Grade Serous Ovarian Cancer

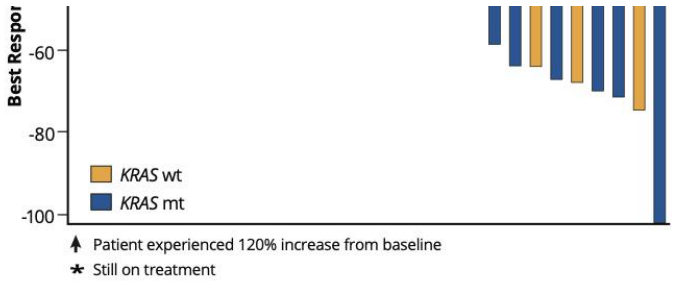
March 6, 2024
Chris Ryan

News *Article*

Avutometinib alone or in combination with defactinib has received an orphan drug from the FDA for recurrent low-grade serous ovarian cancer.

The FDA has granted an orphan drug designation to avutometinib (VS-6766) alone or in combination with defactinib (VS-6063) for the treatment of patients with recurrent low-grade serous ovarian cancer.[1]

Avutometinib : RAF/MEK inhibitor
Defactinib: FAK inhibitor (focal Adhesion Kinase)

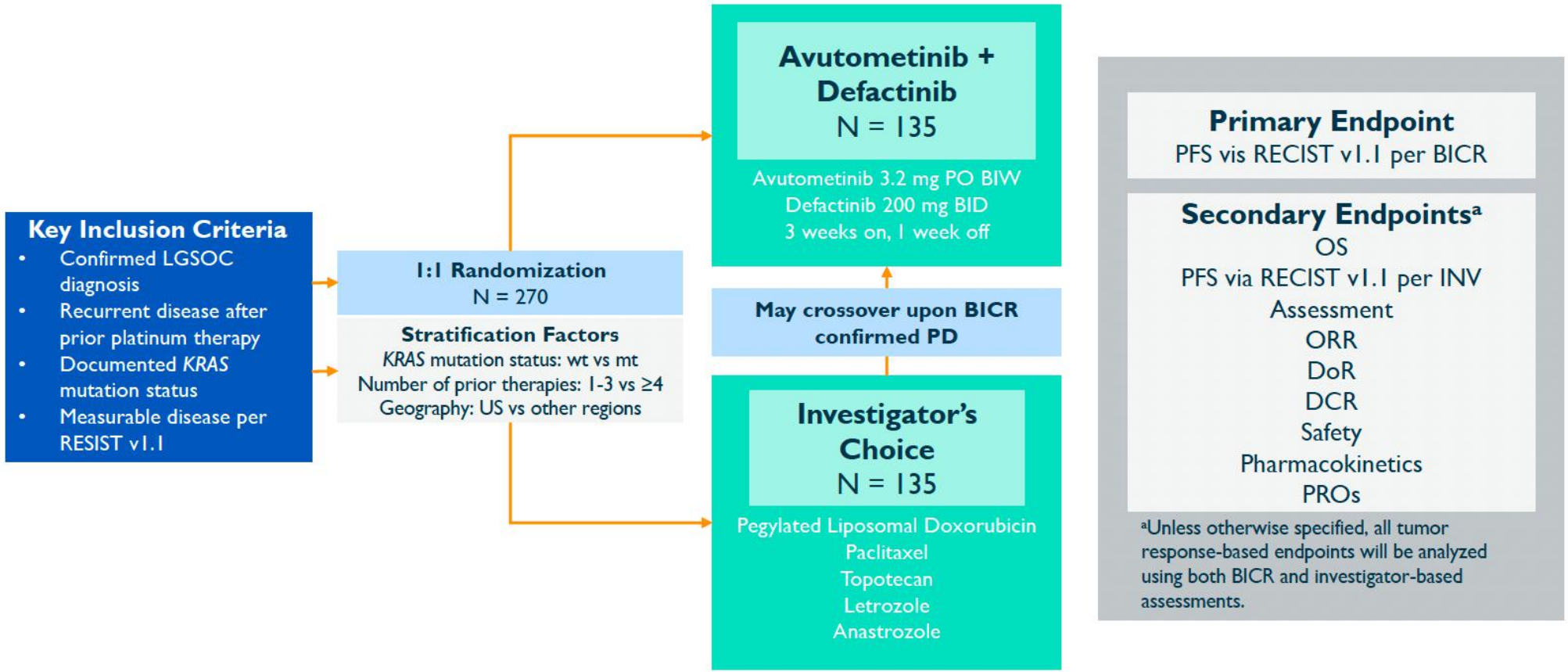


- ORR 45%
- DCR 90%

*LGSOC: To include low grade serous ovarian carcinoma;
**KRAS WT to be included on per KOL feedback

Banerjee et al ASCO 2023

GOG-3097/ENGOT-ov81/NCRI/RAMP 301: A Phase 3, Randomized, Open-Label Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator's Choice of Treatment in Patients with Recurrent Low-Grade Serous Ovarian Cancer (LGSOC)



LGSOC, low-grade serous ovarian cancer; RECIST, response evaluation criteria in solid tumors; BICR, blinded independent central review; BID, twice a day; BIW, twice a week; INV, investigator; mt, mutant; wt, wild-type; PFS, progression free survival; ORR, objective response rate; OS, overall survival; PD, progressive disease; US, United States.

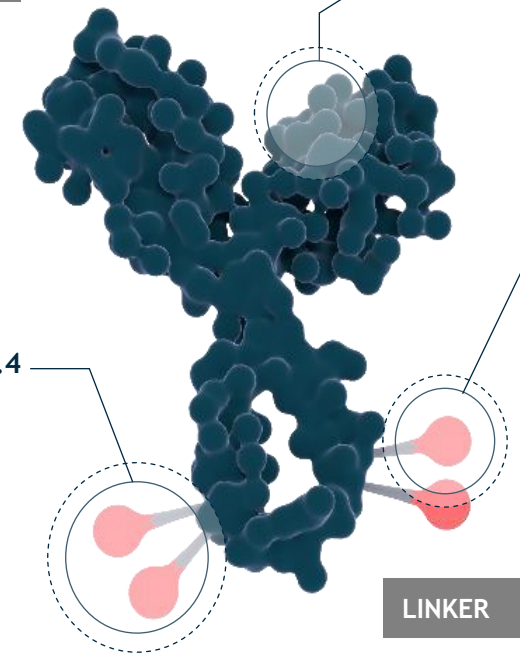
Ovarian cancer

High grade serous - BRCA1/2 & HRD

Low-grade serous - MAPK signalling

High grade – folate receptor

Mirvetuximab soravtansine (MIRV)

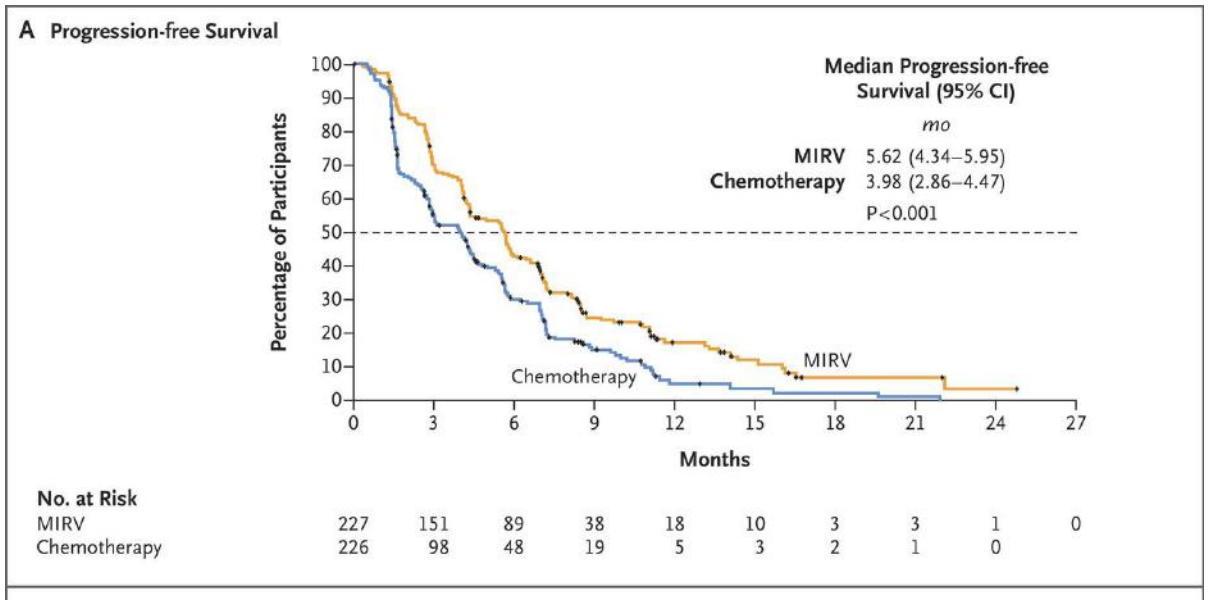


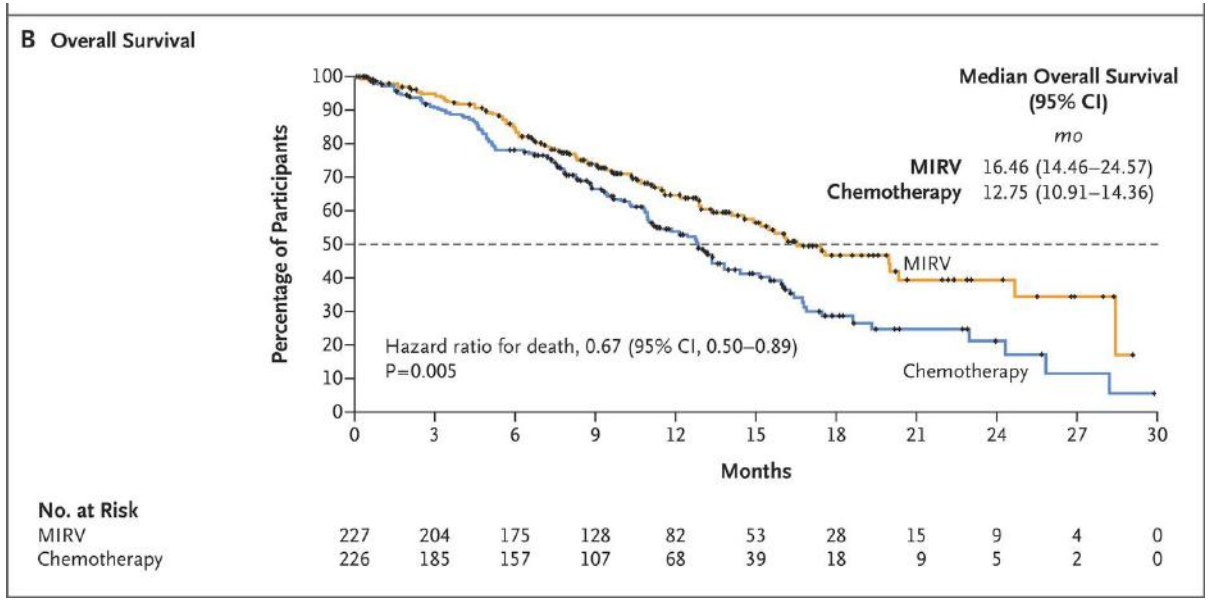
- **MIRV** is an **antibody-drug conjugate (ADC)** comprising:[1,2]
  - **FRα-binding antibody**
    expressed in ~80% of ovarian carcinomas[3]. ~35% of PROC tumours exhibit high FRα expression (≥75% of tumour cells positive with ≥2+ intensity)[4,5]
  - **Cleavable linker**
  - **Maytansinoid DM4 payload**

Folate Receptor
Mirasol Study: Randomised phase III trial

- High FRα expression*
- Platinum resistant (1-3 prior lines of therapy)
- Randomised to mirvetuximab or physician's choice chemotherapy

First drug to demonstrate OS benefit in platinum resistant disease





Moore et al NEJM 2024

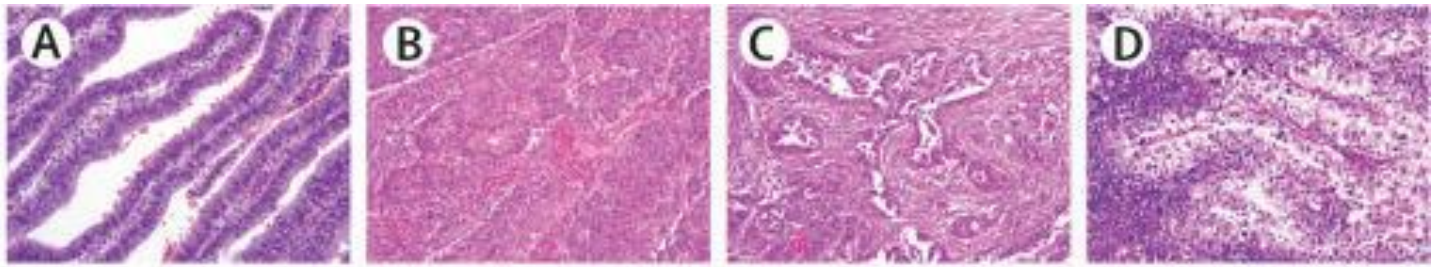
*Ventana FOLR1 assay 75% viable tumour cells with 2+ IHC

Endometrial cancer

Molecular classification

MMRd

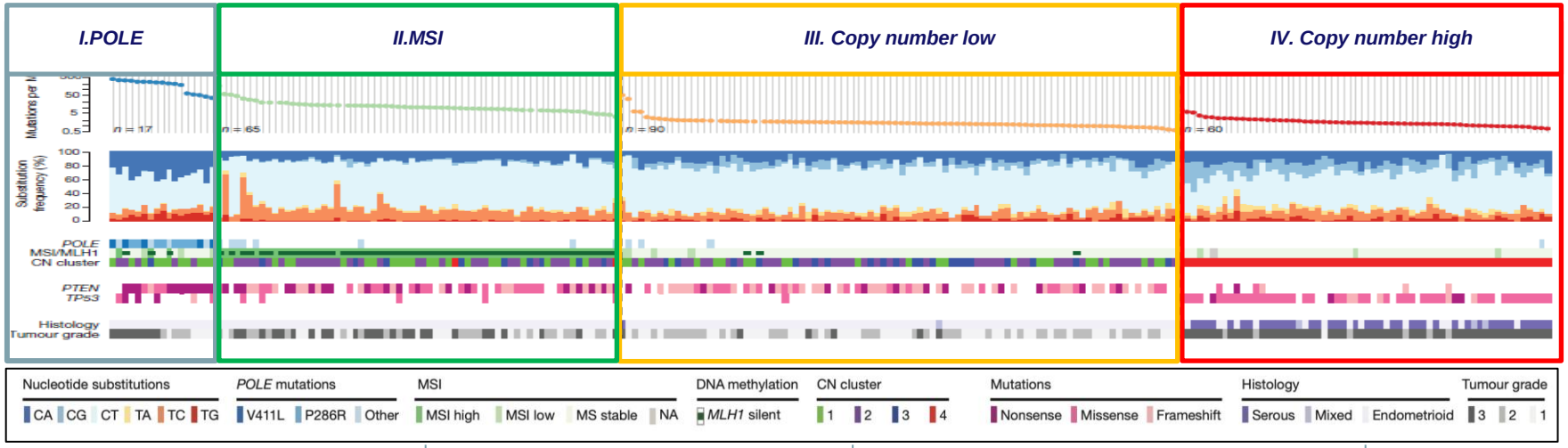
Endometrial Cancer: Histological classification - old



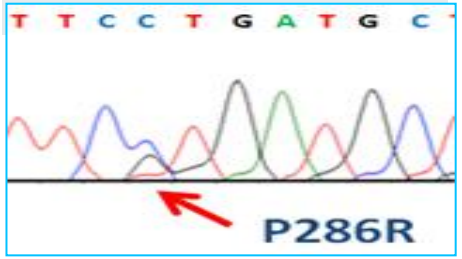
Histological type	Endometrioid	Endometrioid	Serous	Clear cell
Histological grade	Low	High	High	High
Metastasis	Uncommon	Lymph nodes Distant organs	Lymph nodes Peritoneal Distant organs	Lymph nodes Peritoneal –/+
Prognosis	Favourable	Poor	Poor*	Poor*†
Molecular markers[18–21]				
ER/PR expression	+	+/–	–/+	–
PTEN expression	–/+	–/+	+	+
DNA MMR loss	–/+	–/+	–	–/+
Aberrant P53	–	–/+	+	–/+
Ki-67/MIB-1	Low	High	High	Low or high

Murali et al Lancet 2014

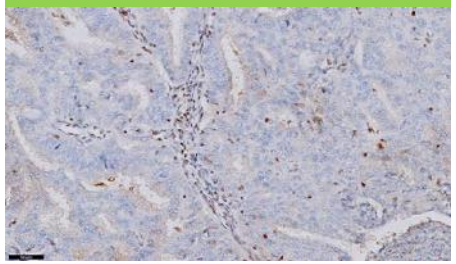
Molecular Classification



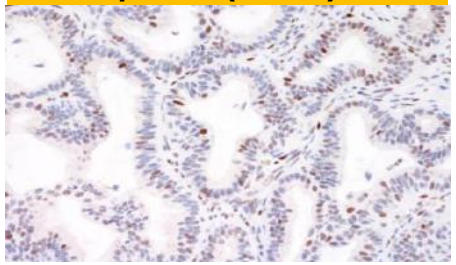
Ultramutated
***POLE* mutant** ~5%



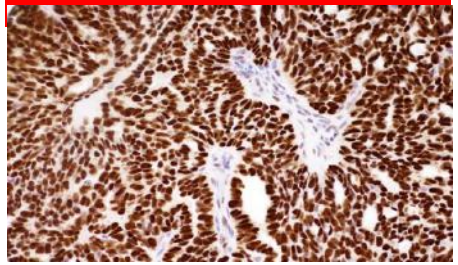
Hypermutated
MMRd ~25%



Copy number low/
No specific molecular profile (NSMP) ~40%

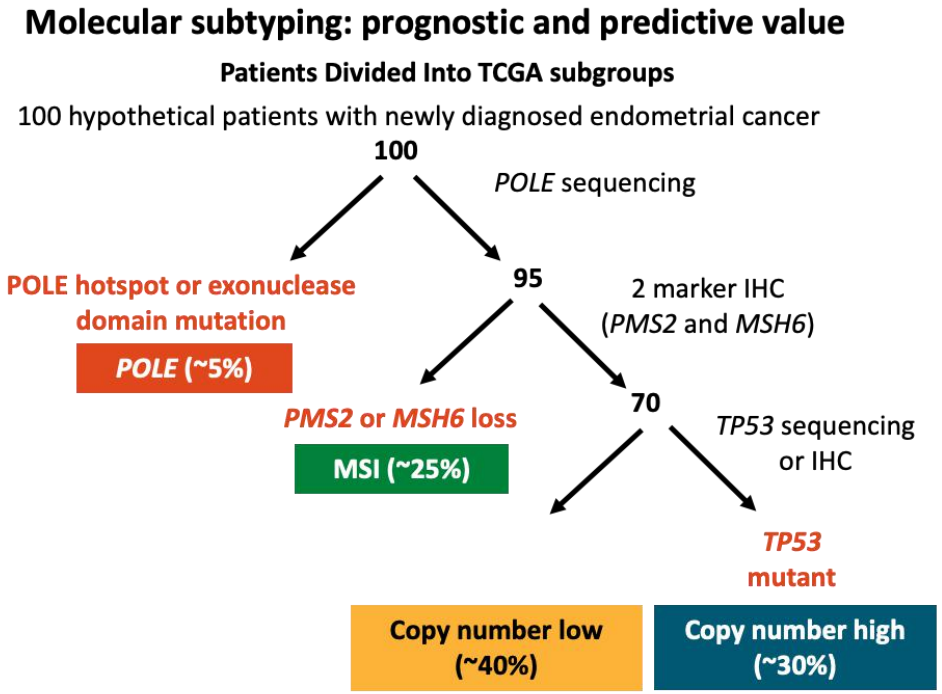


Copy number high / *TP53* mutant/ Serous-like ~30%

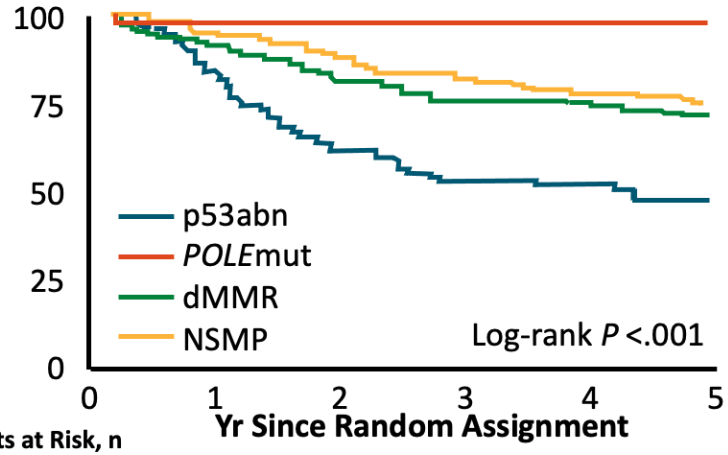


TCGA, Kandoth et al, Nature 2013

Molecular Classification and Outcomes



- Prognostic value of molecular classification of high-risk endometrial cancer for benefit from chemotherapy
- 83% and 17% of endometrial cancer can be classified as endometrioid and non endometrioid, respectively



Patients at Risk, n						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
dMMR	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

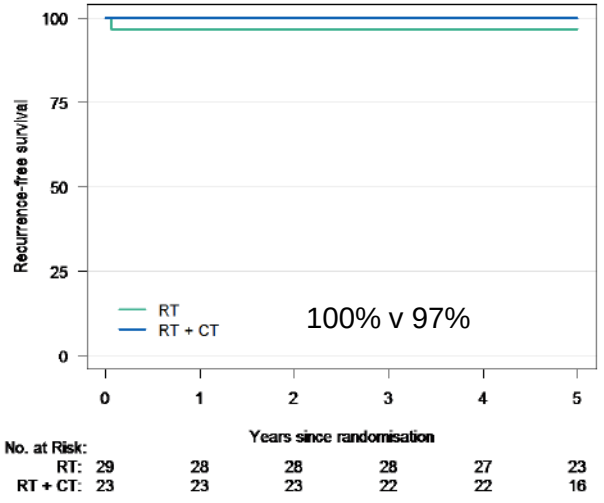
- 410 patients with successful molecular testing
  - **23%** *p53*abn: *p53* abnormal
  - **12%** *POLE*mut: *POLE* ultramutated
  - **33%** dMMR: mismatch repair deficient
  - **32%** NSMP: no specific molecular profile

MacKay. Oncotarget. 2017;8:84579. León-Castillo. JCO. 2020;38:3388.

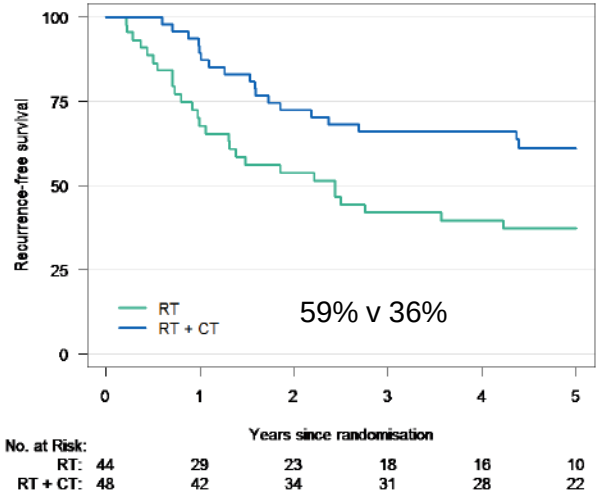
PORTEC-3

Benefit of Chemotherapy on Recurrence Free Survival by molecular group

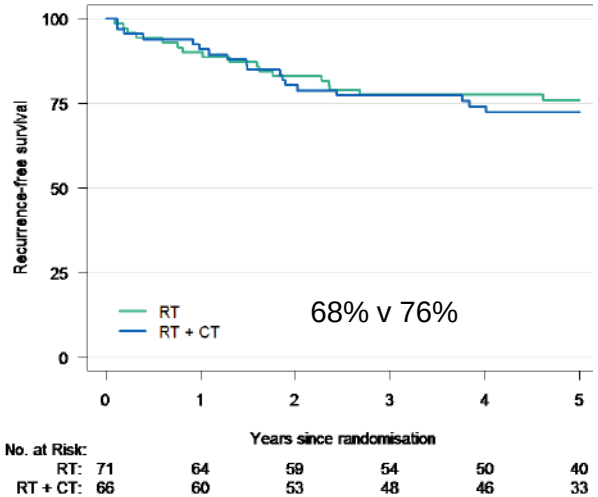
*POLE*mut



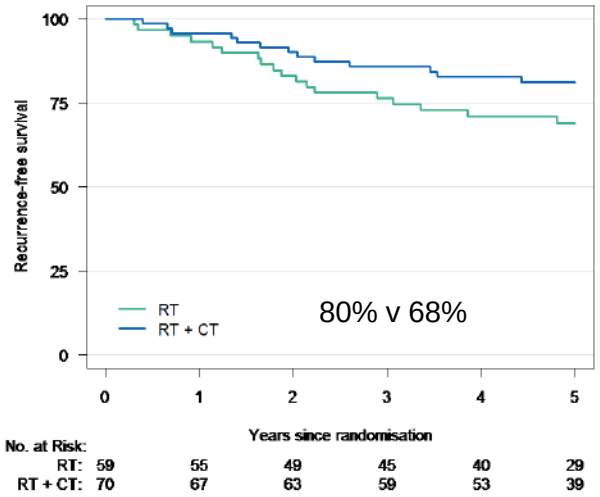
p53abn



MMRd



NSMP



Leon-Castillo et al, JCO 2020

EC: High rates of micro-satellite instability and defective DNA Mismatch Repair (dMMR)

- EC highest rates of **micro-satellite instability (MSI) of any solid tumour** – up to 30% of EC
- Major cause of MSI is a defect in the DNA Mismatch repair (dMMR) pathway:
  - Loss of expression of one or more of the MMR proteins MLH1, MSH2, MSH6, and PMS2
  - Due to **genetic mutation or epigenetic silencing** results in accumulation of DNA replication errors at microsatellite regions

- Can we improve outcome by targeting MMRd/ MSI-H with immunotherapy ?

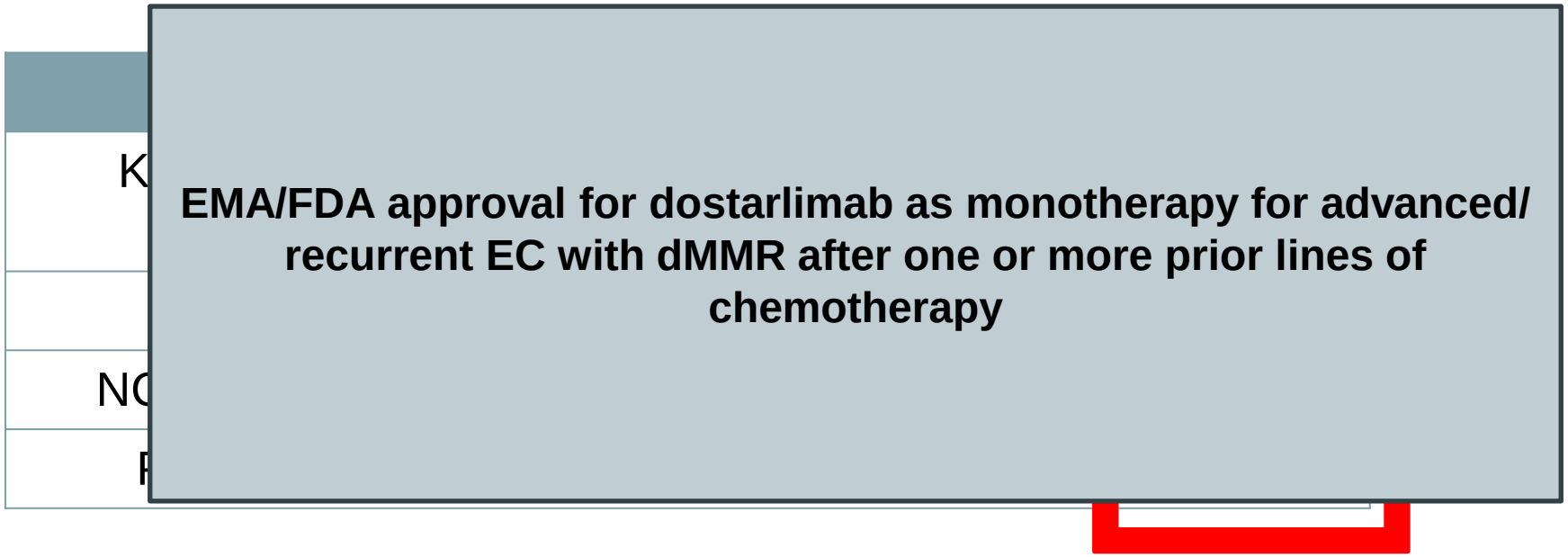
Single Agent Immunotherapy in Biomarker Selected Populations –dMMR
Second line +

Study	Drug	N	ORR
Keynote 158	Pembrolizumab	79	48%
Garnet	Dostarlimab	143	45.5%
NCT02912572	Avelumab	15	27%
PHAEDRA	Durvalumab	35	43%

Response rate in dMMR/MSI-H population

ORR – overall response rate. O'Malley et al, JCO 2022,Oaknin et al J Immunotherapy Cancer 2022, Oaknin et al ASCO 2022, Konstantinopoulos et al JCO 2019, Antill et al JCO 2019

Single Agent Immunotherapy in Biomarker Selected Populations –dMMR
Second line +



Response rate in dMMR/MSI-H population

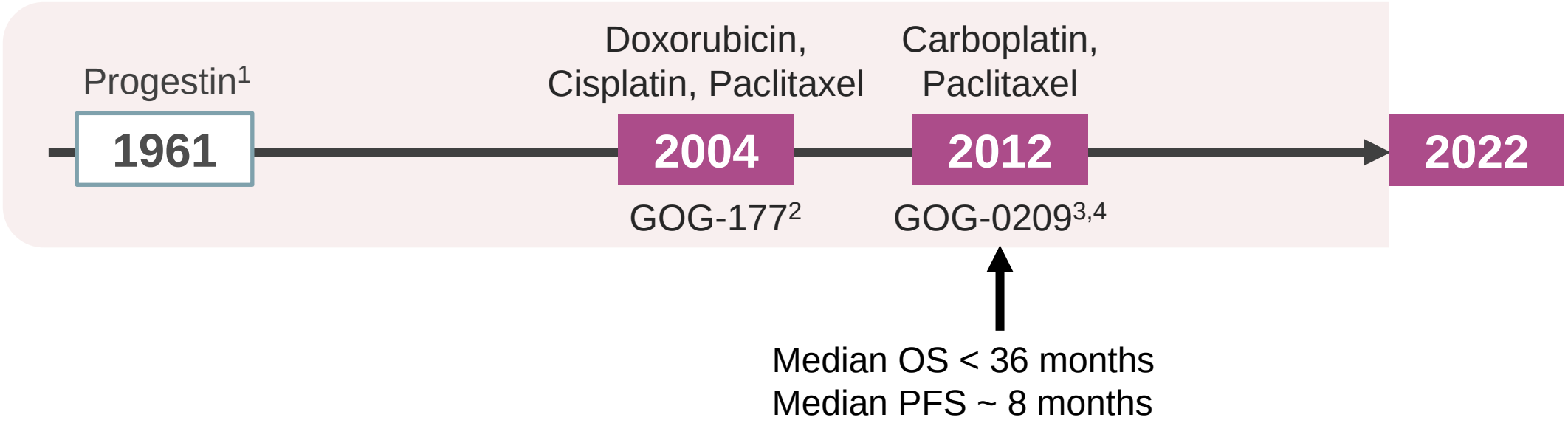
ORR – overall response rate. O'Malley et al, JCO 2022,Oaknin et al J Immunotherapy Cancer 2022, Oaknin et al ASCO 2022, Konstantinopoulos et al JCO 2019, Antill et al JCO 2019

Single Agent Immunotherapy in NON-Biomarker Selected Populations –pMMR
Second line +

Study	Drug	Phase	Cohort	N	ORR
Garnet	Dostarlimab	I/II	Previously tx recurrent/advanced pMMR	156	15.4%
Phaedra	Durvalumab	II	Recurrent pMMR	35	3%
NCT02912572	Avelumab	II	Recurrent pMMR	16	6%

Oaknin et al ASCO 2022, Konstantinopoulos et al JCO 2019, Antil et al ASCO 2019

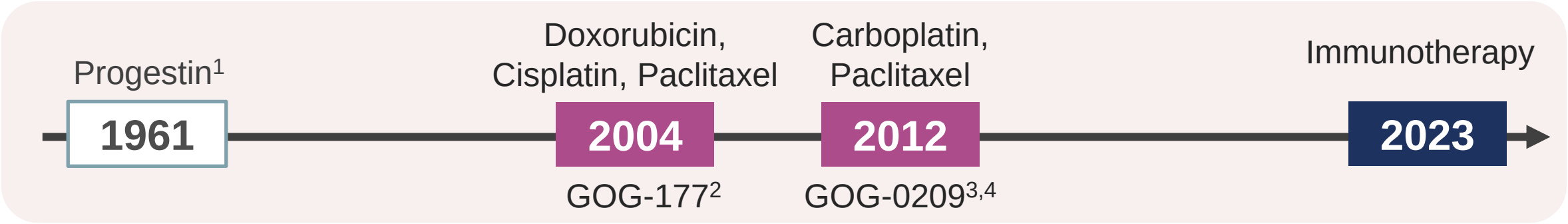
What about 1st line treatment?



dMMR, mismatch repair deficient; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI-H – microsatellite high, RT – radiotherapy ITT – intention to treat, PFS – progression free survival, OS – overall survival

Mirza et al NEJM 2023,Eskander R et al NEJM 2023, Colombo N et al ESMO 2023 , Westin et al JCO 2023 , 1. Yang S, et al. *Discov Med.* 2011;12:205-212. 2. Fleming GF, et al. *J Clin Oncol*. 2004;22:2159-2166. 3. Miller DS, et al., *Gynecol Oncol*. 2012;125:771–773. 4. Miller DS, et al., *J Clin Oncol*. 2020;38:3841-3850.

What about 1st line treatment?



RUBY
GY018
AtTEnd
DUO-E

dMMR, mismatch repair deficient; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI-H – microsatellite high, RT – radiotherapy ITT – intention to treat, PFS – progression free survival, OS – overall survival

Mirza et al NEJM 2023,Eskander R et al NEJM 2023, Colombo N et al ESMO 2023 , Westin et al JCO 2023 , 1. Yang S, et al. *Discov Med.* 2011;12:205-212. 2. Fleming GF, et al. *J Clin Oncol*. 2004;22:2159-2166. 3. Miller DS, et al., *Gynecol Oncol*. 2012;125:771–773. 4. Miller DS, et al., *J Clin Oncol*. 2020;38:3841-3850.

2023 - Exciting time for Endometrial Cancer

ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

RUBY
ENGOT-EN6
GOG-3031

MADRID 2023 ESMO congress

AtTEND
ENGOT-EN7
MaNGO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

Mansoor R. Mirza, M.D., Dana M. Chase, M.D., Brian M. Slomovitz, M.D., René dePont Christensen, Ph.D., Zoltán Novák, Ph.D., Destin Black, M.D., Lucy Gilbert, M.D., Sudarshan Sharma, M.D., Giorgio Valabrega, M.D., Lisa M. Landrum, M.D., Ph.D., Lars C. Hanker, M.D., Ashley Stuckey, M.D., Ingrid Boere, M.D., Ph.D., Michael A. Gold, M.D., Annika Auranen, M.D., Bhavana Pothuri, M.D., David Cibula, M.D., Carolyn McCourt, M.D., Francesco Raspagliesi, M.D., Mark S. Shahin, M.D., Sarah E. Gill, M.D.

MADRID 2023 ESMO congress

Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma: ENGOT-en7/MaNGO/AtTEnd study

Nicoletta Colombo, Milan, Italy

On behalf of K. Harano (JGOG, Japan), E. Hudson (NCRI, United Kingdom), F. Galli (MaNGO, Italy), Y. Antill (ANZGOG, Australia-New Zealand), C. H. Choi (KGOG, Korea), M. Rabaglio (SAKK, Switzerland), F. Marmé (AGO, Germany), E. Petru (AGO-A, Austria), C.-H. Lai (TGOG, Taiwan), E. Biagioli (MaNGO, Italy), L. Fariñas-Madrid (GEICO, Spain), K. Takehara (JGOG, Japan), K. Allan (NCRI, United Kingdom), Y. C. Lee (ANZGOG, Australia-New Zealand), E. Piovano (MaNGO, Italy), C. Zamagni (MaNGO, Italy), G. Tasca (MaNGO, Italy), A. Ferrero (MaNGO, Italy), M.-P. Barretina-Ginesta (GEICO, Spain)

NRG-GY018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cea, Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Th, Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

ABSTRACT

SGO ANNUAL MEETING ON WOMEN'S CANCER TAMPA, FL • 2023 PATIENTS • PURPOSE • PROGRESS

MADRID 2023 ESMO congress

MADRID 2023 ESMO congress

Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab ± olaparib as a first-line treatment for newly diagnosed advanced or recurrent endometrial cancer: results from the Phase III DUO-E/GOG-3041/ENGOT-EN10 trial

Shannon N. Westin,[1] Kathleen N. Moore,[2] Hye Sook Chon,[3] Jung-Yun Lee,[4] Jessica Thomes Pepin,[5] Michael Sundborg,[6] Joseph de la Garza,[7] Shin Nishio,[8] Ke Wang,[9] Kristi McIntyre,[10] Todd D. Tillmanns,[11] Fernando Contreras Mejia,[12] Andreia Cristina De Melo,[13] Dagmara Klasa-Mazurkiewicz,[14] Christos Papadimitriou,[15] Marta Gil-Martin,[16] Birute Brasiuniene,[17] Conor Donnelly,[18] Xiaochun Liu,[19] Els Van Nieuwenhuysen[20]

DUO-E
GOG-3041/
ENGIT-EN10

Key First Line Studies for Advanced/Recurrent EC

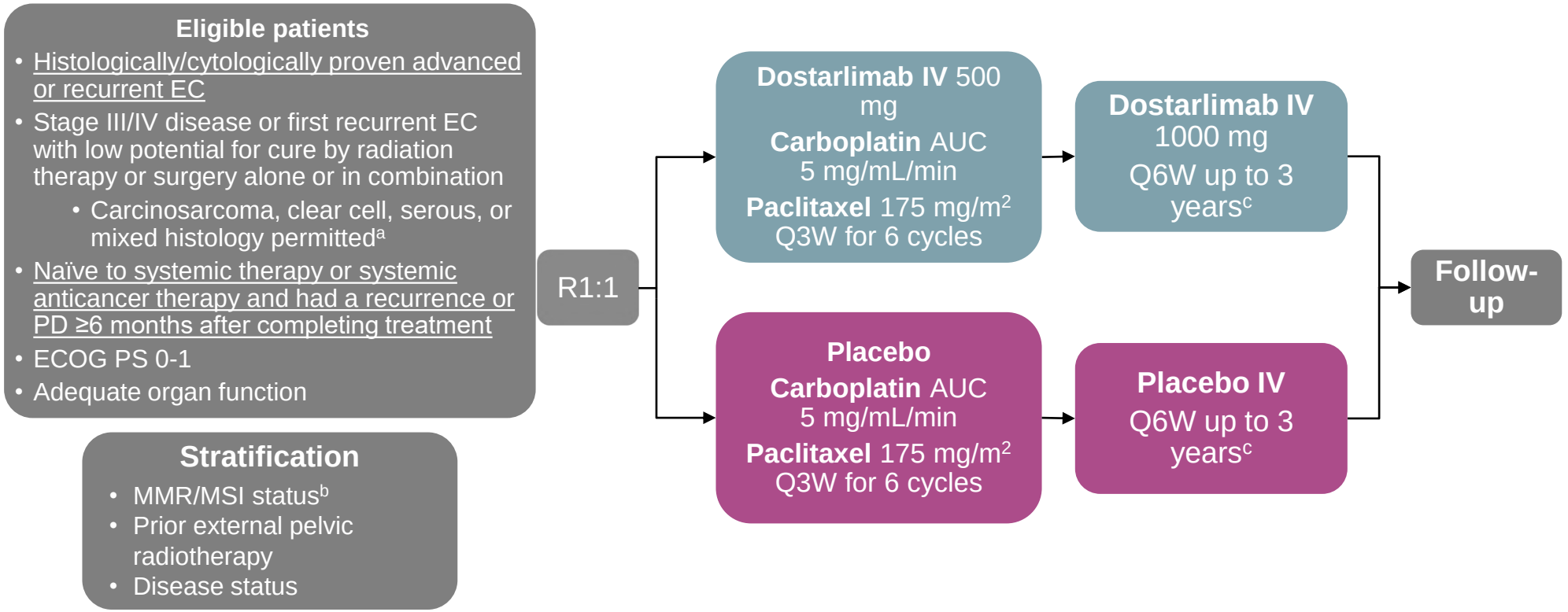
TRIAL	Reference	N	Treatment (CP – Carboplatin/Paclitaxel chemotherapy)	Treatment duration	Primary end points
RUBY	Mirza M et al NEJM 2023	494	CP/Dostarlimab vs CP/placebo (1:1)	36 months	PFS dMMR PFS ITT OS ITT
GY018	Eskander R et al NEJM 2023	816	CP/Pembrolizumab vs CP/placebo (1:1)	14 cycles	PFS dMMR PFS pMMR
AtTEnd	Colombo N et al ESMO 2023	549	CP/Atezolizumab vs CP/placebo (2:1)	Until disease progression	PFS dMMR PFS ITT OS ITT
DUO-E	Westin S et al JCO 2023	718	CP/Placebo/placebo vs CP/Durvalumab/placebo vs CPDurvalumab/olaparib (1:1:1)	Until disease progression	PFS Durva vs control ITT PFS Durva/olap vs control ITT

dMMR, mismatch repair deficient; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI-H – microsatellite high, RT – radiotherapy ITT – intention to treat, PFS – progression free survival, OS – overall survival

Mirza et al NEJM 2023,Eskander R et al NEJM 2023, Colombo N et al ESMO 2023 , Westin et al JCO 2023

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

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



Primary endpoint
- **PFS by INV**
  - **dMMR**
  - **ITT**
- OS ITT

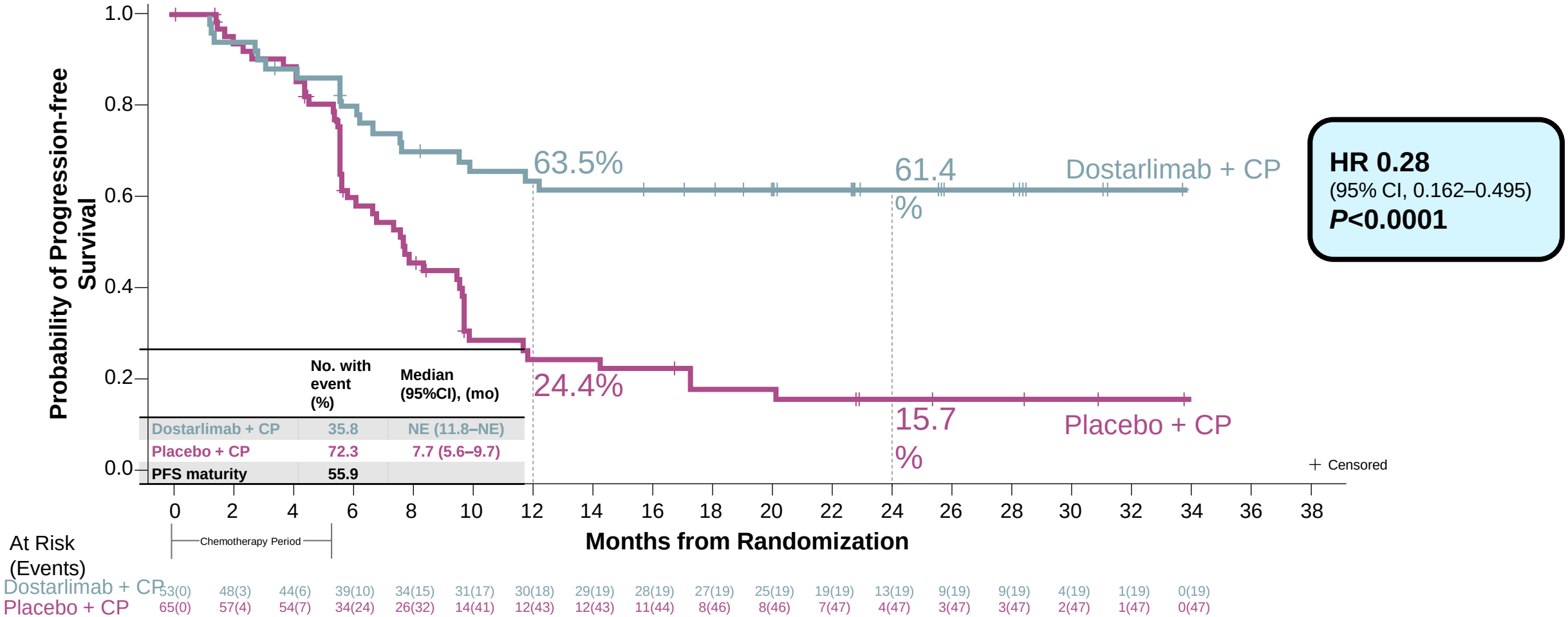
Secondary endpoints
- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later,or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.

[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; IV, administered intravenously; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

M Mirza ESMO Virtual Plenary 2023, Mira et al NEJM 2023

Primary Endpoint: PFS in dMMR/MSI-H Population



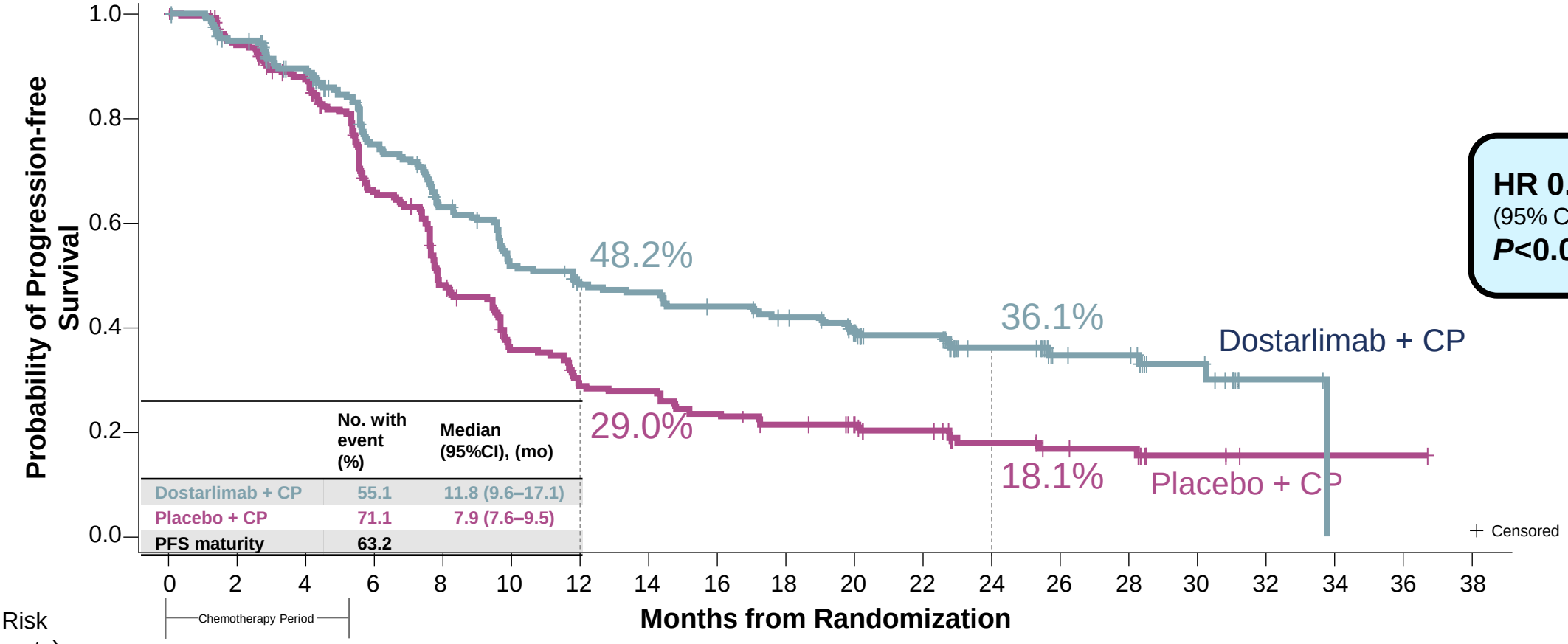
HR 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

Median duration of follow-up 24.79 months.

M Mirza ESMO Virtual Plenary 2023, Mira et al NEJM 2023

Primary Endpoint: PFS in Overall Population



HR 0.64
(95% CI, 0.507–0.800)
***P*<0.0001**

At Risk (Events)

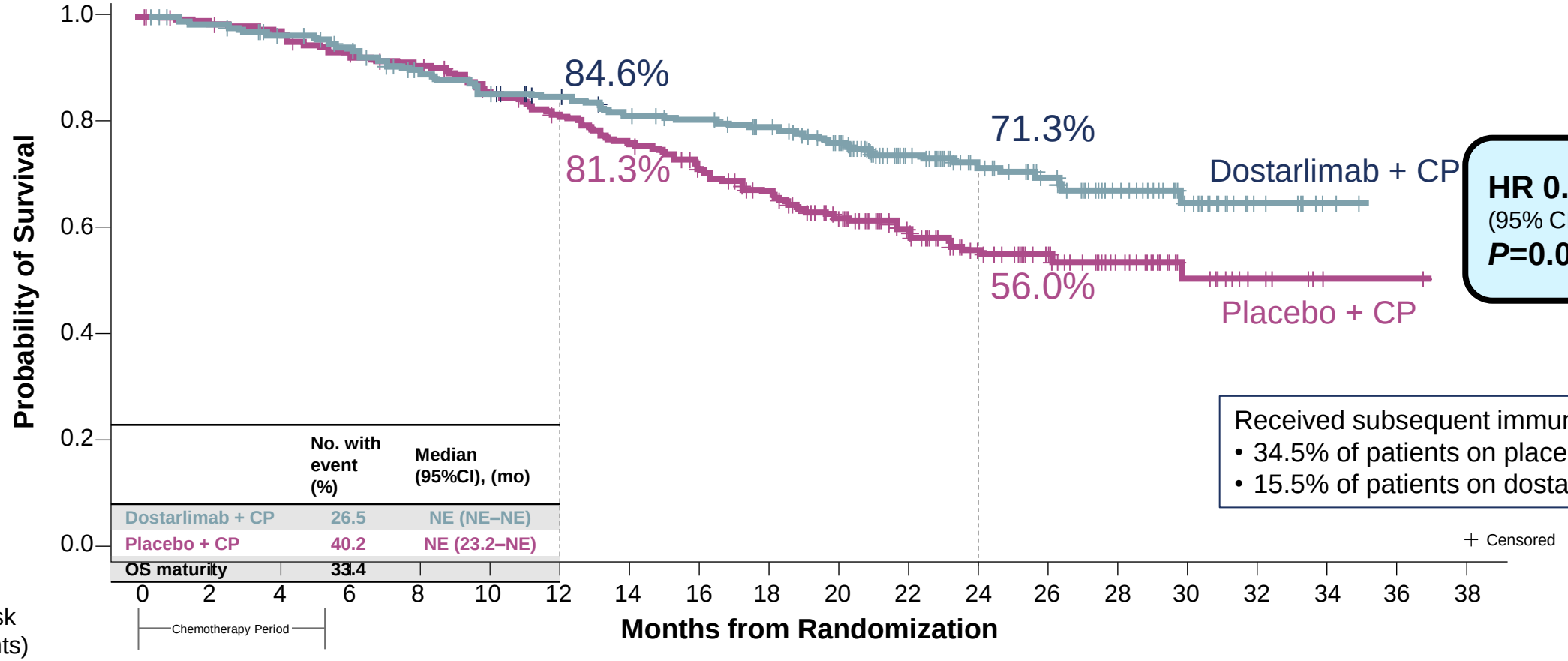
Dostarlimab + CP	245(0)	220(12)	197(25)	157(55)	130(80)	105(103)	94(110)	90(113)	84(118)	78(122)	66(127)	52(128)	34(131)	23(132)	12(133)	22(132)	2(134)	0(135)	
Placebo + CP	249(0)	219(14)	200(29)	144(77)	103(115)	74(141)	59(155)	57(157)	48(166)	42(170)	39(170)	32(172)	20(175)	14(176)	13(176)	5(177)	2(177)	1(177)	1(177)	0(177)

CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

Median duration of follow-up 25.38 months.

M Mirza ESMO Virtual Plenary 2023, Mira et al NEJM 2023

Primary Endpoint: OS in Overall Population (33% maturity)



HR 0.64
(95% CI, 0.464–0.870)
***P*=0.0021[a]**

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

At Risk (Events)

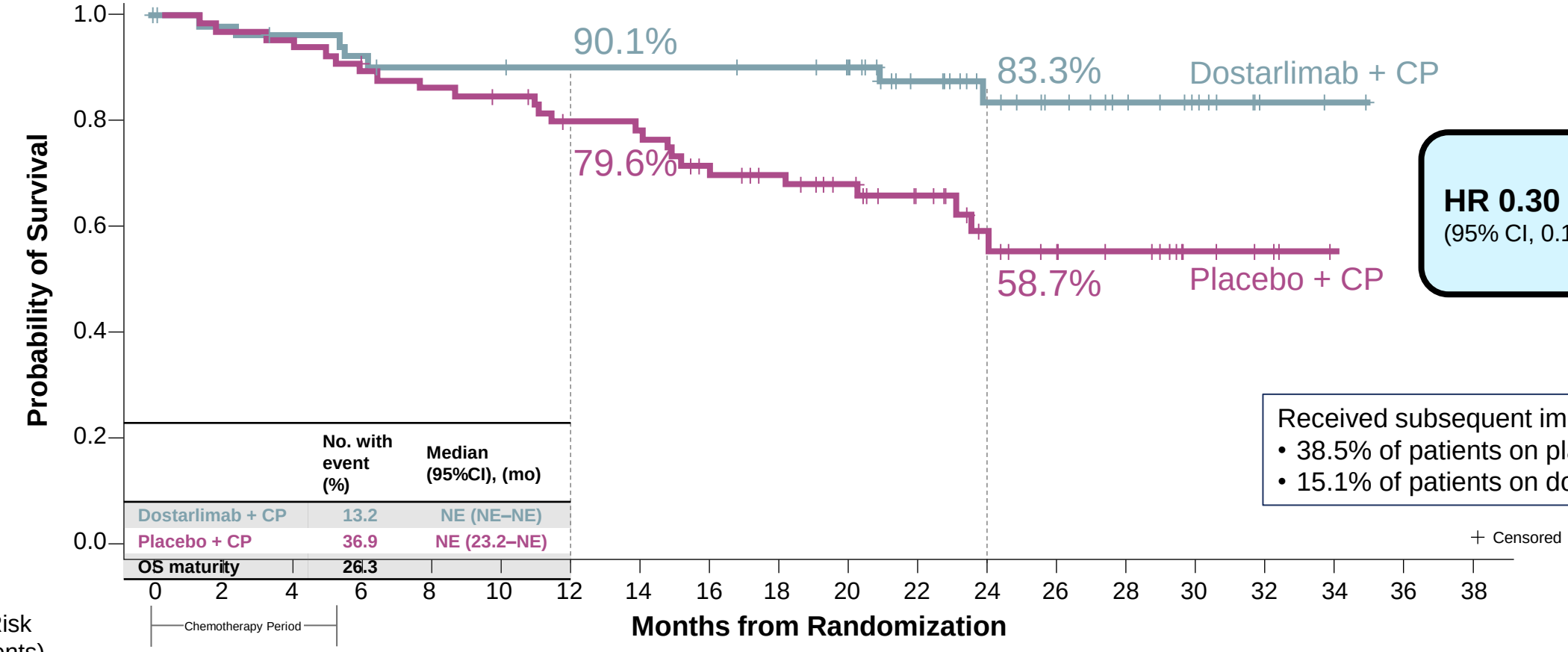
Dostarlimab + CP	245(0)	235(5)	224(8)	214(15)	198(25)	190(33)	183(35)	174(42)	169(44)	162(47)	145(53)	110(57)	83(60)	64(62)	45(64)	25(65)	7(65)	2(65)	0(65)	
Placebo + CP	249(0)	242(3)	237(7)	226(17)	219(22)	203(35)	189(45)	177(57)	162(68)	147(78)	125(88)	88(93)	65(97)	48(98)	33(99)	15(100)	6(100)	1(100)	1(100)	0(100)

[a]P≤0.00177 required to declare statistical significance at first interim analysis.
CP, carboplatin/paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival.

Median duration of follow-up 25.38 months.

M Mirza ESMO Virtual Plenary 2023, Mira et al NEJM 2023

OS in dMMR/MSI-H population



HR 0.30
(95% CI, 0.127–0.699)

Received subsequent immunotherapy:
- 38.5% of patients on placebo arm
- 15.1% of patients on dostarlimab arm

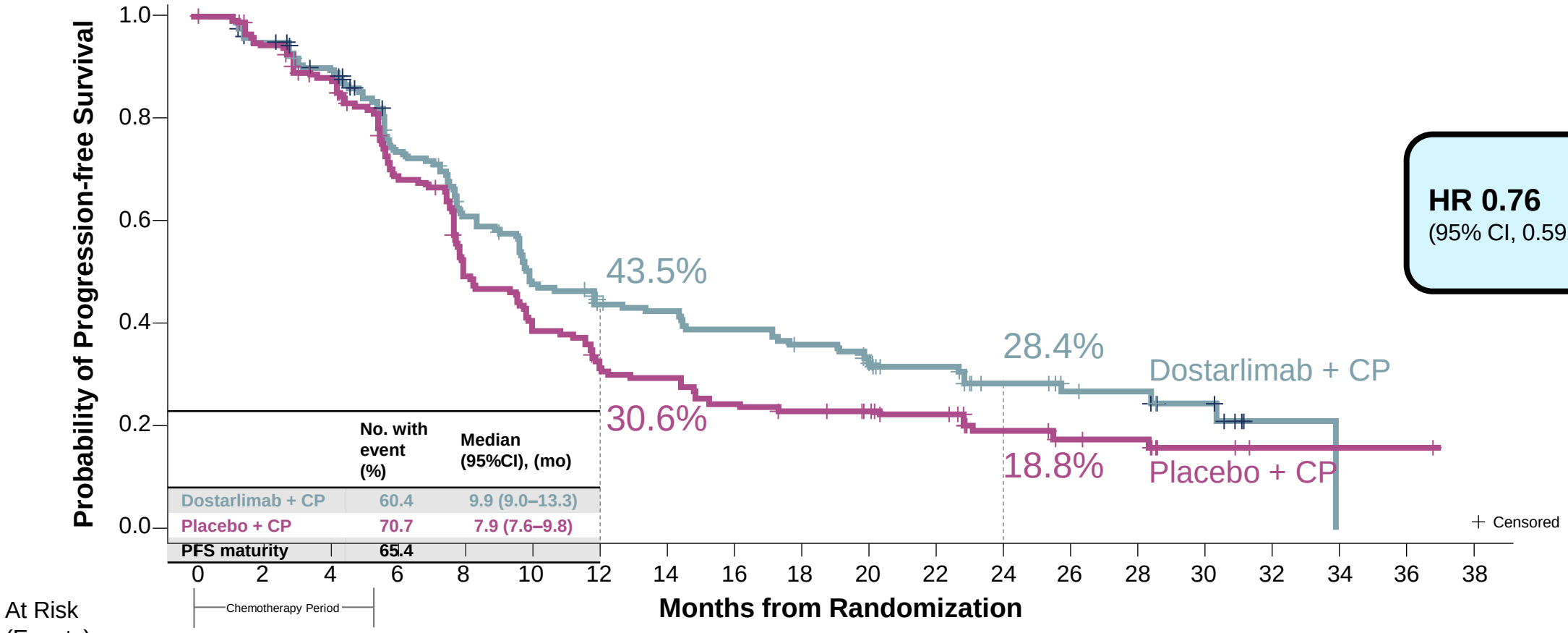
At Risk (Events)

Dostarlimab + CP	53(0)	50(1)	48(2)	46(4)	44(5)	44(5)	43(5)	43(5)	43(5)	42(5)	41(5)	29(6)	20(7)	16(7)	12(7)	8(7)	2(7)	1(7)	0(7)
Placebo + CP	65(0)	63(2)	62(3)	59(6)	55(9)	53(10)	49(13)	47(14)	41(18)	37(19)	32(20)	25(21)	16(23)	12(24)	10(24)	5(24)	3(24)	0(24)	

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

M Mirza ESMO Virtual Plenary 2023, Mira et al NEJM 2023

PFS in pMMR/MSS population



HR 0.76
(95% CI, 0.592–0.981)

CP, carboplatin/paclitaxel; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-free survival.

M Mirza ESMO Virtual Plenary 2023, Mira et al NEJM 2023

RUBY Conclusions

- Dostarlimab + carboplatin and paclitaxel (CP) demonstrated statistically significant and clinically meaningful PFS benefit with an early OS trend
    - Substantial, unprecedented benefit in dMMR/MSI-H patients
    - Clinically meaningful long-term benefit observed in pMMR/MSS patients
- Safety profile for dostarlimab + CP was manageable and generally consistent with that of the individual drugs
- **Dostarlimab plus carboplatin/paclitaxel represents a new standard of care for patients with primary advanced or recurrent dMMR endometrial cancer**
- **Regulatory approval**
    - **FDA July 23**
    - **EMA – CHMP approval Oct 23**
    - **NICE approved March 2024 for patients with primary advanced or recurrent dMMR endometrial cancer**

Non-IO Molecularly Directed Therapy in Endometrial Cancer

TP 53

- **GOG-86P: Bev + CP vs CP**
- PFS HR 0.48 vs 0.87 in mutant TP53 vs. wt TP53 Bev better TP53 mutant
- **ENGOT-EN5/GOG-3055/SIENDO trial** – Selinexor maintenance
- PFS HR 0.71, P53 wild type PFS of 13.7 vs 3.7 mths

Anti-HER2

- Evolution of anti-HER2 treatments
- **Fader et al. 2018**: Trastuzumab + C/P **PFS HR** 0.44 **OS HR** 0.58
- **DESTINY-Pan Tumor02**: ORR 57.5%; Median DOR: NR
- **Nishikawa et al. 2023: ORR** 54.5% & 70%
- **NRG GY026**

DNA Damage Repair/ Replication Stress

- HRD more prevalent in p53 mutant EC
- **ADAGIO:** Adavosertib (WEE1 inhibitor) single agent – all p53 mut Median prior LOT = 3 **BICR ORR 26%** **Median PFS 2.8mo**
- **RUBY 2**
- **UTOLA ESMO 2023**

Hormonal Therapies

- ? Role in the copy number low wt TP53 population
- **PALEO Study:** Letrozole vs Palbocilcib + letrozole **HR 0.56** **Median PFS** 8.3 vs 3 mo
- **Letrozole + Abemaciclib:** ORR 30%

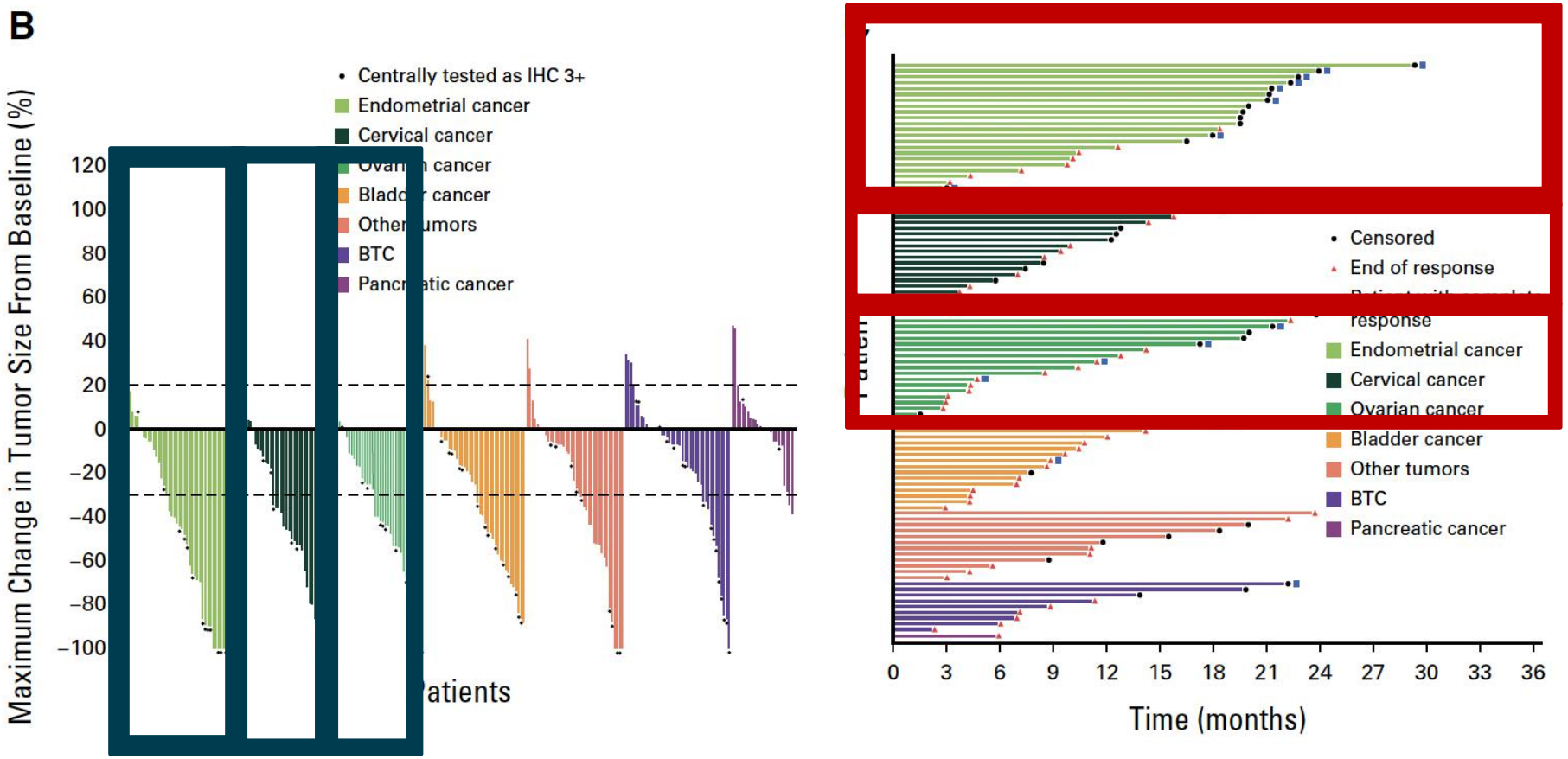
Aghajanian et al. J Clin Oncol. 2011; Leslie K. et al. Gyncol Oncol 2021; Nickles-Fader J Clin Oncol 2018; Nickles-Fader Clin Cancer Research 2020; Nishikawa et al. J Clin Oncol. 2023; de Jonge MM CCR 2019, Liu JF, et al. SGO 2023. Abstract 219; Mirza et al. ESMO 2020; P Konstantinopoulos et al. J Clin Oncol 2022; Funda Meric-Bernstam, MD et al. ASCO 2023

Future targets

Tumour agnostic targeted therapies

Antibody drug conjugates on the horizon

Trastuzumab deruxtecan (T-DXd) - HER2/Topoisomerase I inhibitor ADC
DESTINY-PanTumor02 Phase II Trial



Meric-Bernstam et al JCO 2023

• Expanding the Biomarker Approach in Ovarian Cancer

Examples of antigens exploited for ADC development in OC[1]

Reported expression in OC	60–100%	70%	5–60%	55–100%	80–90%	95%	25–100%	70–90%

Note: Some ADCs may only demonstrate efficacy in higher expression levels of the target antigen.[2,3]

- ADC, antibody-drug conjugate; CDH6, cadherin 6; FRα, folate receptor-α; HER-2, human epidermal growth factor receptor-2; HGSOC, high-grade serous ovarian cancer; MSLN, mesothelin; MUC-16, mucin-16, also known as CA 125; NaPi2b, sodium-dependent phosphate transport protein 2B; OC, ovarian cancer; TF, tissue factor; Trop2, tumour-associated calcium signal transducer 2.Figure adapted from reference 1.
- **1.** Chelariu-Raicu A, et al. Int J Gynecol Cancer. 2023;33(3):420-429. **2.** Moore KN, et al. European Society for Medical Oncology (ESMO) Annual Meeting. 2019; Presentation 992O. **3.** Meric-Bernstam F, et al. J Clin Oncol. 2024;42(1):47-58.

Thank you

Questions?

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