Test BRCA – HRD
in Regione Emilia-Romagna
Carcinoma dell'ovaio

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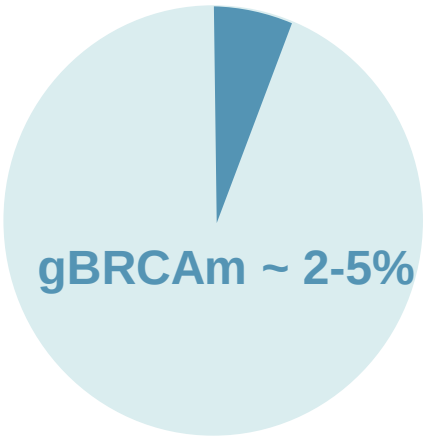
I numeri del cancro dell'ovaio in Italia

nuovi casi/anno	5.200
decessi/anno	3.200
sopravvivenza a 5 anni	43%
prevalenza	49.800

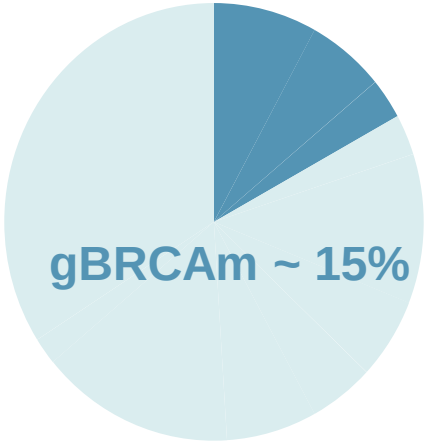
AIRTUM/AIOM 2022

Varianti patogenetiche di BRCA1/2 e rischio di carcinoma della mammella e dell'ovaio

	Popolazione generale	gBRCA1	gBRCA2
Carcinoma mammella	**12.5%**	**55-72%**	**45-69%**
Carcinoma ovaio	**1.2%**	**39-44%**	**11-17%**

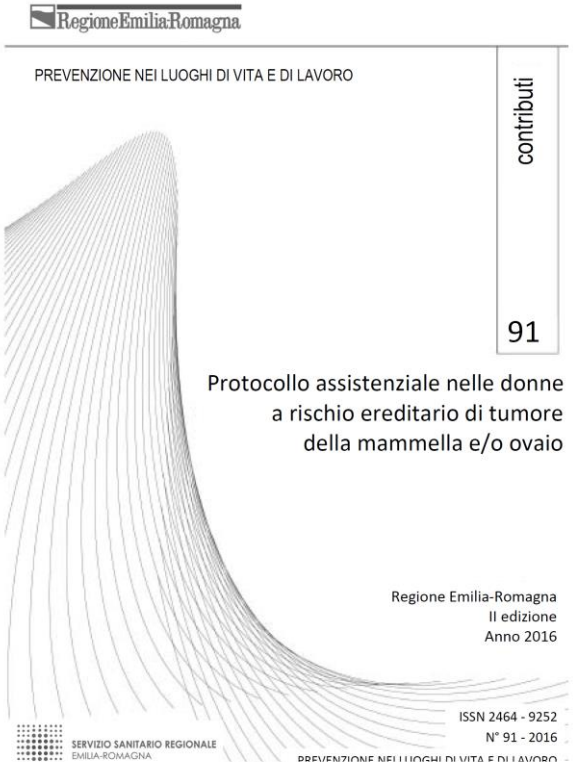


mammella



ovaio

NCI Official Website 2023
Kuchenbaecher KB el JAMA 2017
Antoniou A et al AM J Hum Genetics 2003
Chen S et al J Clin Oncol 2007



5.1.2 Sorveglianza ovarica

Pur in assenza di chiare evidenze scientifiche in proposito, per quanto riguarda l'efficacia delle seguenti proposte in termini di diagnosi precoce, per le donne portatrici di mutazione Brca1/2, la sorveglianza intensiva dell'apparato genitale prevede:

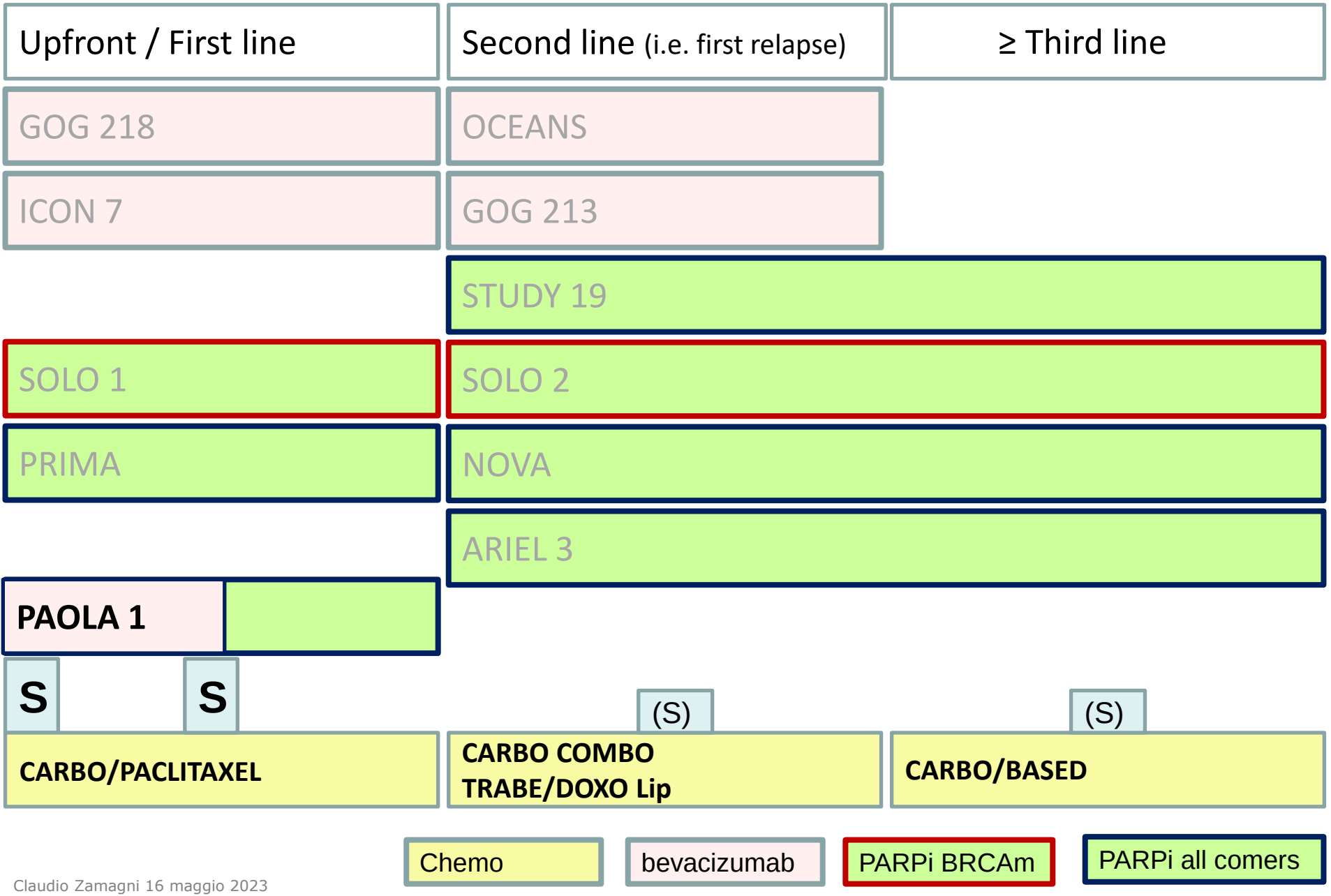
a) Visita ginecologica bimanuale ogni 6 mesi
b) Ecografia pelvica transvaginale ogni 6 mesi [3]
c) Dosaggio ematico CA125 ogni 6 mesi.

Qualunque lesione ovarica sospetta deve essere caratterizzata secondo i criteri IOTA (1).

5.3.2. Salpingo-Ovariectomia di riduzione del rischio (RRSO)

La procedura deve essere proposta a tutte le donne BRCA mutate a partire da 35-40 anni (secondo la storia familiare oncologica della donna) che abbiano completato il percorso riproduttivo. L'intervento va particolarmente incoraggiato

Most relevant RCT for Clinical Practice in AOC
(beyond chemo in P sensitive disease)



SOLO-1 is the first Phase III trial to investigate maintenance therapy with a PARP inhibitor in newly diagnosed ovarian cancer

SOLO-1 is a global randomised multicentre placebo controlled Phase III study

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

Olaparib 300 mg bid (N=260)

2:1 randomisation

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- 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

2 years' treatment if no evidence of disease

Primary endpoint

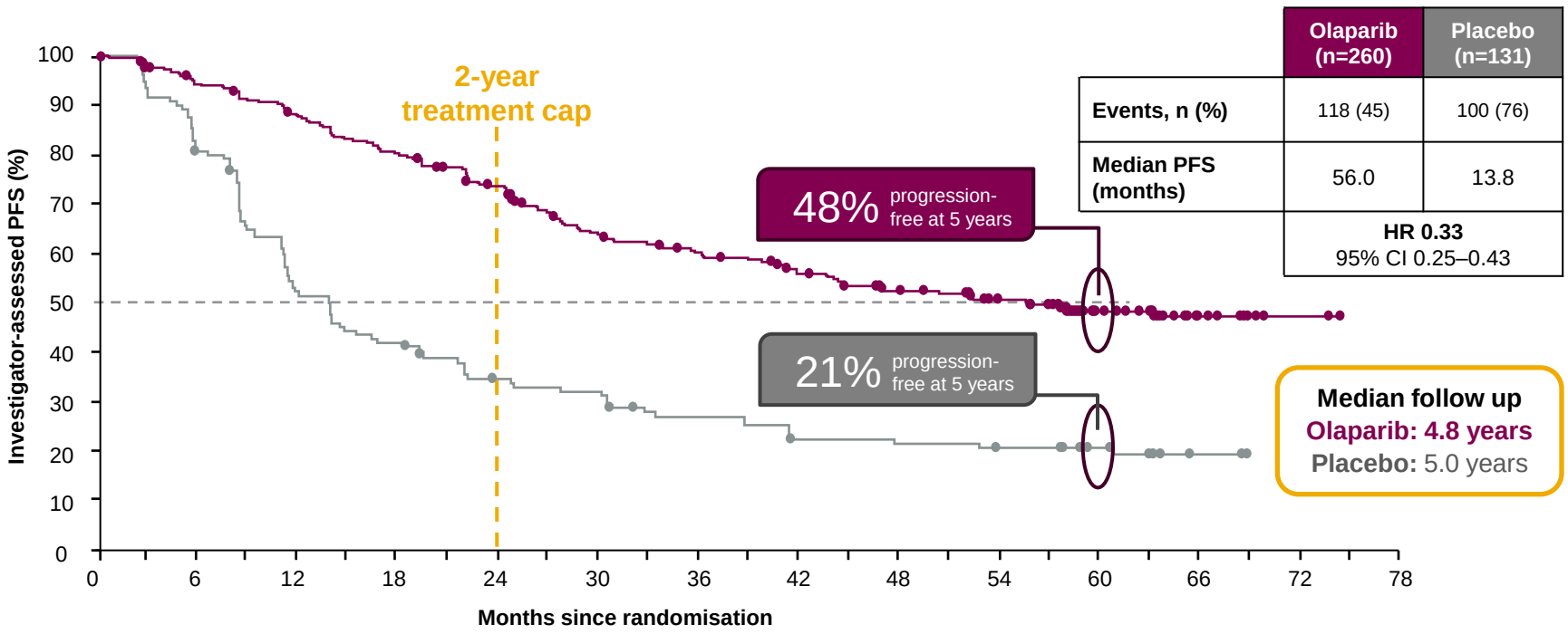
- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomisation to first subsequent therapy or death
- Time from randomisation 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; PARP = poly (ADP-ribose) polymerase; *BRCA*m = *BRCA* gene mutation
https://clinicaltrials.gov/ct2/show/NCT01844986 (accessed October 2018)

Investigator-assessed Progression-free Survival



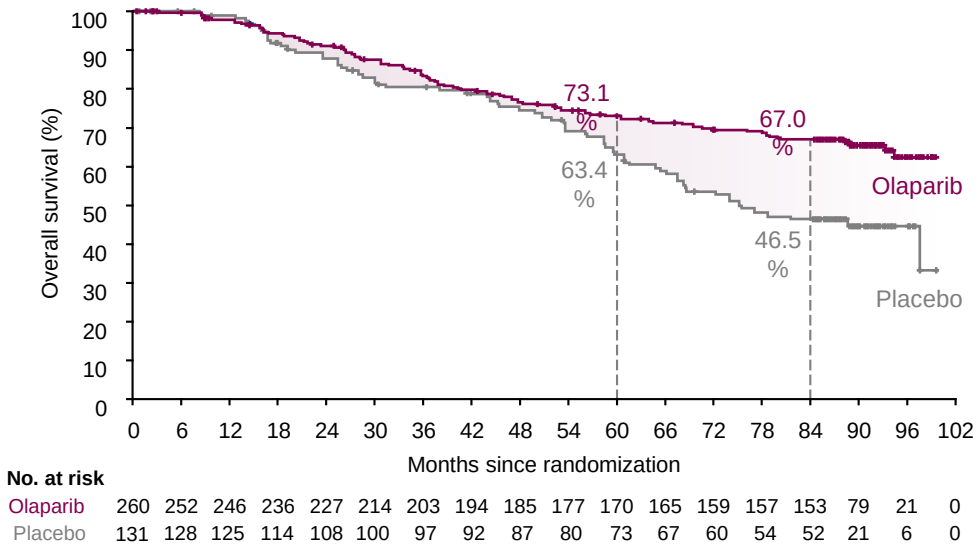
	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS (months)	56.0	13.8
	HR 0.33 95% CI 0.25–0.43	

Investigator-assessed PFS
DCO: March 2020; Median follow-up: olaparib, 4.8 years, placebo, 5.0 years
CI=confidence interval; HR=hazard ratio; PFS=progression-free survival

Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19-21 September. Abstract #811MO

At the 7-year data cut-off, clinically meaningful OS benefit was observed with olaparib vs. placebo

67% of olaparib patients were alive at 7 years vs 47% of placebo patients



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

HR 0.55
(95% CI, 0.40–0.76)
P=0.0004*

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

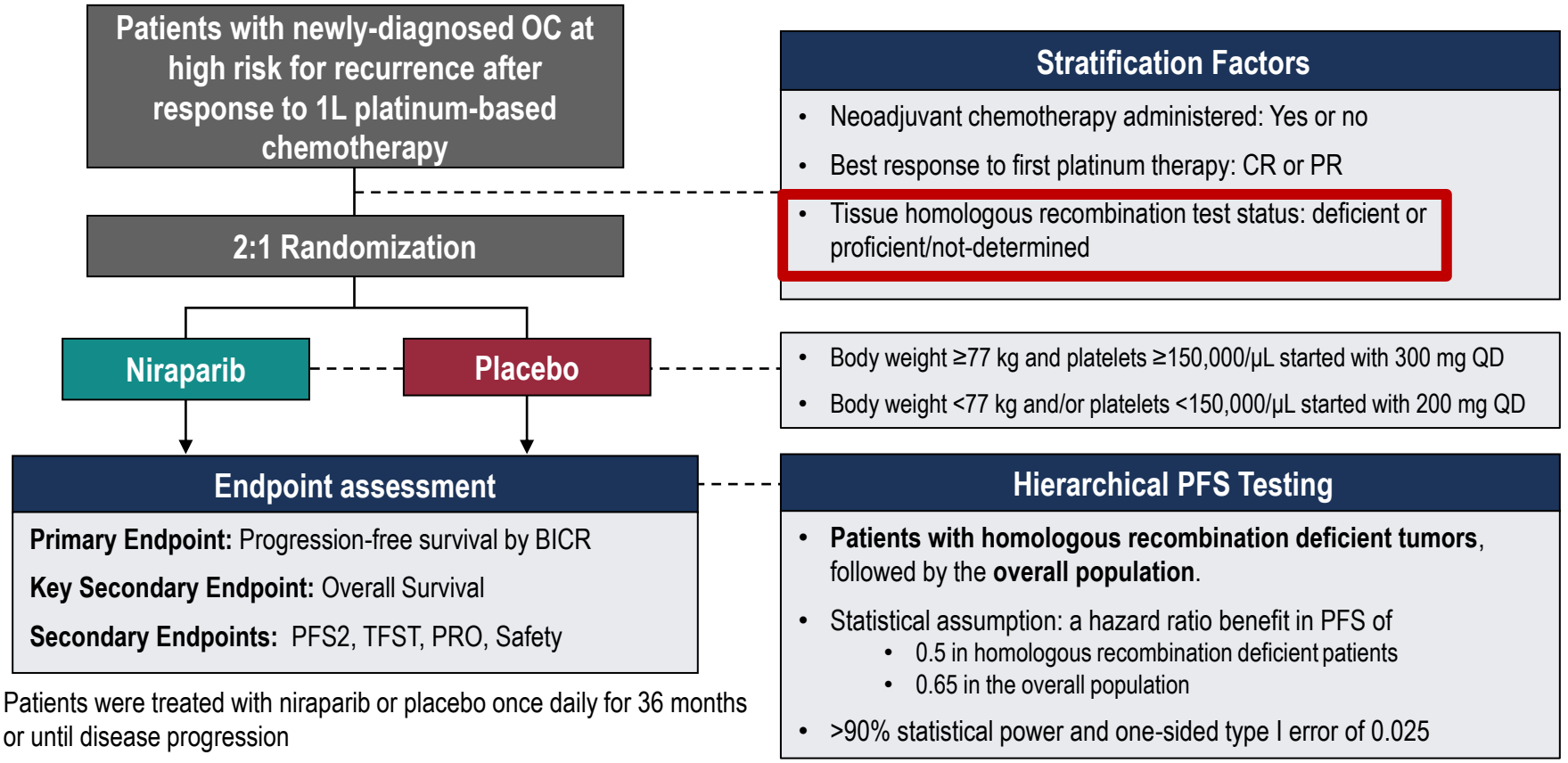
Data cut-off for the 7-year descriptive OS analysis: 07 March 2022.

Median follow-up of approximately 88 months.

**P*<0.0001 required to declare statistical significance

DiSilvestro P, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France.

PRIMA Trial Design

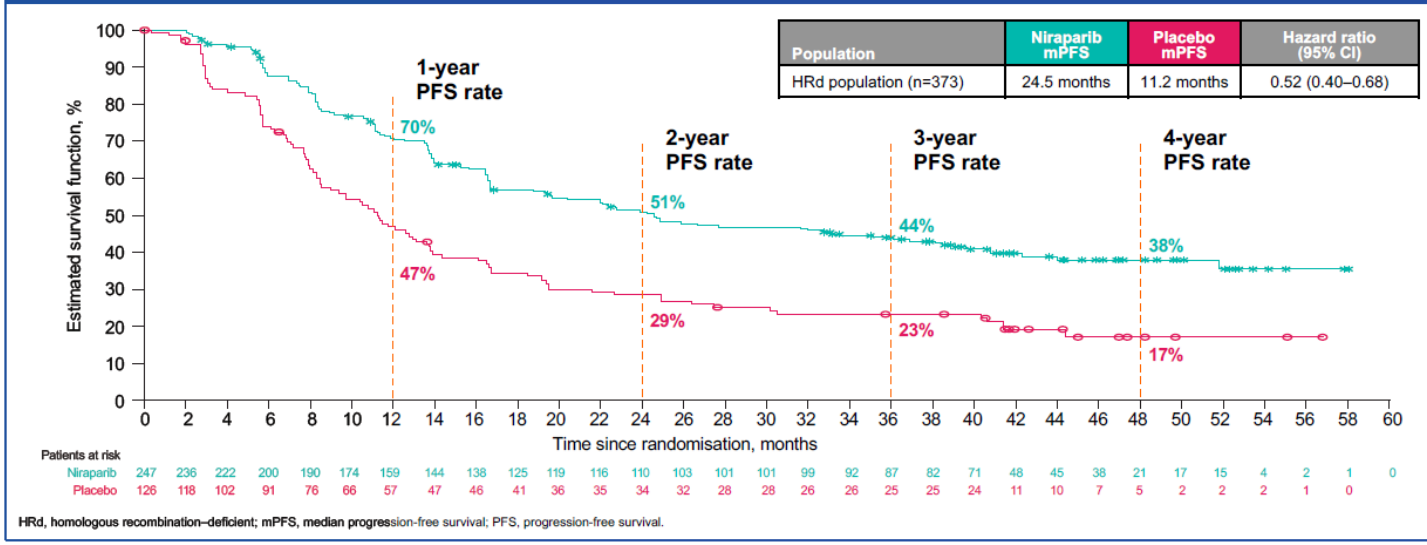


Patients were treated with niraparib or placebo once daily for 36 months or until disease progression

1L, first-line; BICR, blinded independent central review; CR, complete response; OC, ovarian cancer; PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy.

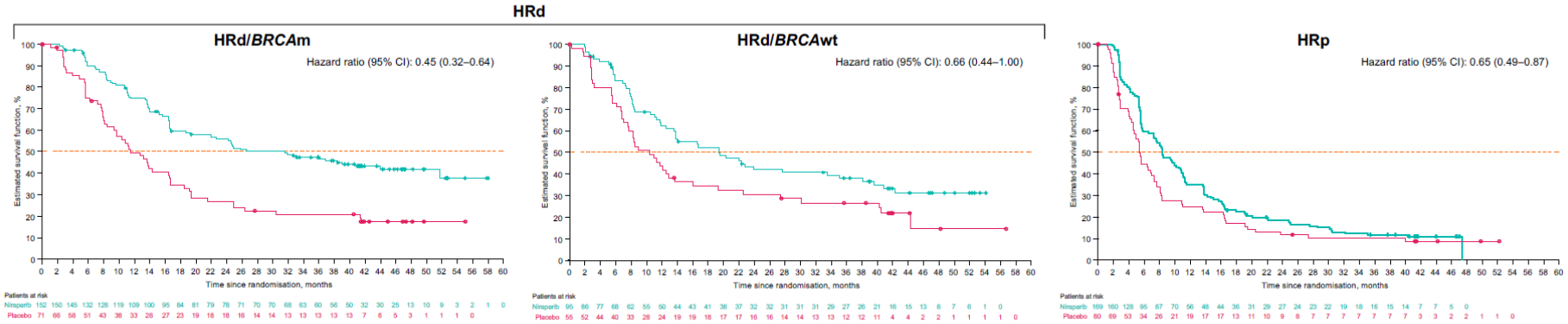
PRIMA trial: Updated Long-term PFS
(median FU 3.5 y)

Figure 2. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment in the HRd Population, 17 November 2021 Clinical Cutoff Date



HRd, homologous recombination–deficient; mPFS, median progression-free survival; PFS, progression-free survival.

Figure 4. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment Across Biomarker Subgroups, 17 November 2021 Clinical Cutoff Date



*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild-type; HRd, homologous recombination–deficient; HRp, homologous recombination–proficient.

Gonzales-Martin A et al ESMO 2022 #530P

Study design

Newly diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer*

FIRST LINE
- Surgery (upfront or interval)
- Platinum–taxane based chemotherapy
- ≥3 cycles of bevacizumab†

NED/CR/PR

N=806

Randomization

2:1

Maintenance therapy

Olaparib (300 mg BID) x2 years
+ bevacizumab†

Placebo x2 years
+ bevacizumab†

Stratification
- Tumour *BRCA*m status‡
- First-line treatment outcome¶

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)

Sensitivity analysis
PFS by BICR

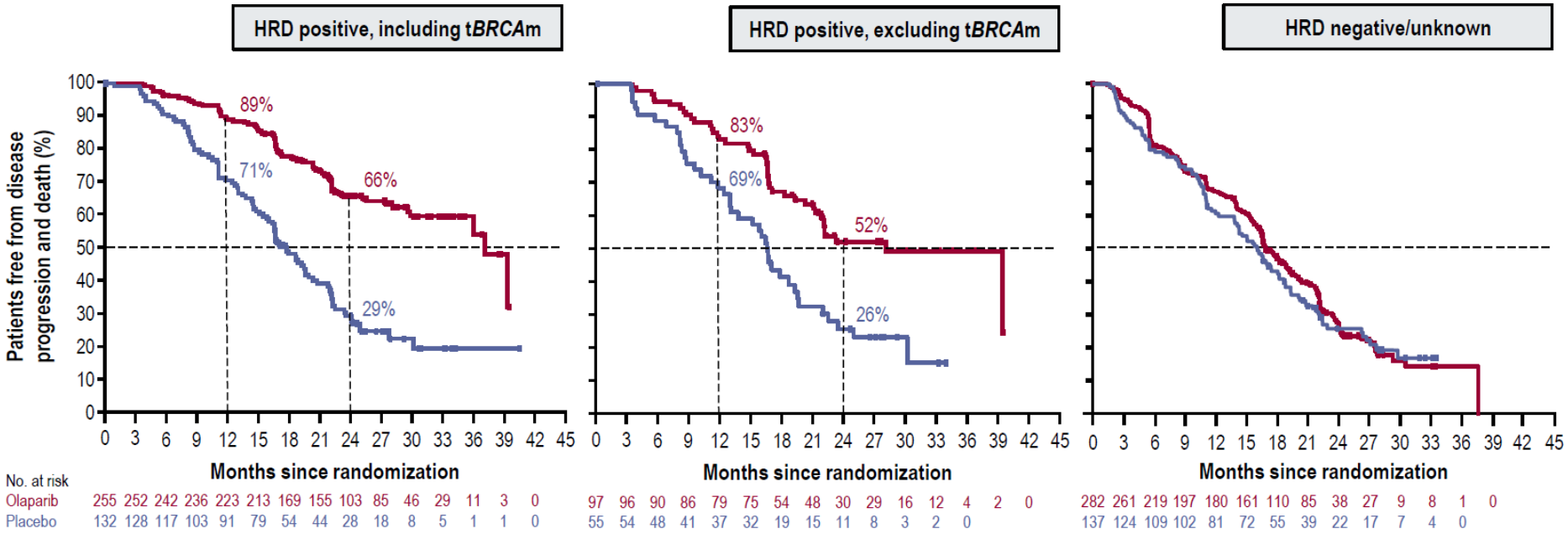
Secondary endpoints
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

BARCELONA 2019 ESMO congress

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Ray-Coquard I et al ESMO 2019

PFS by HRD status



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

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	43 (44)	40 (73)
	28.1*	**16.6**
	HR 0.43 (95% CI 0.28–0.66)	

	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)	

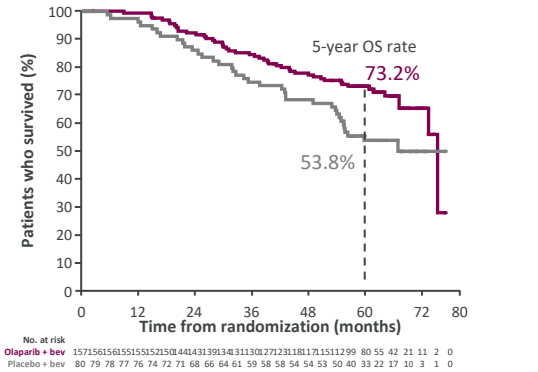
The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less than 50% maturity

Ray-Coquard I et al ESMO 2019

PAOLA-1
OS subgroup analysis by BRCAm and HRD status

The addition of olaparib to bevacizumab prolonged OS in HRD+ patients regardless of BRCA status, no OS difference was observed in the HRD- subgroup

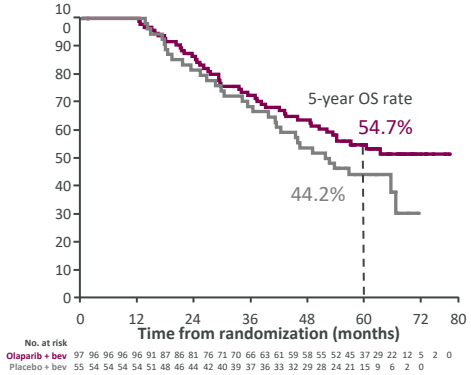
BRCAm*



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

HR 0.60 (95% CI, 0.39–0.93)

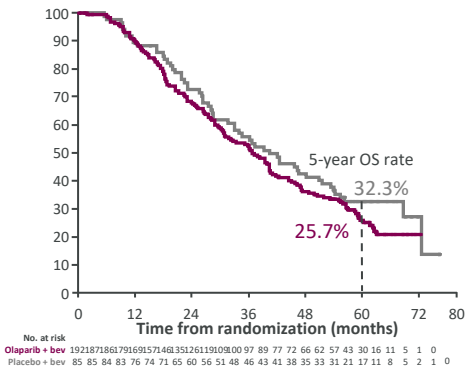
HRD-positive,† excluding tBRCAm



	Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
	44 (45.4)	32 (58.2)
	NR	**52.0**
	54.7	**44.2**
	9 (9.3)	23.0 (41.8)

HR 0.71 (95% CI, 0.45–1.13)

HRD-negative†



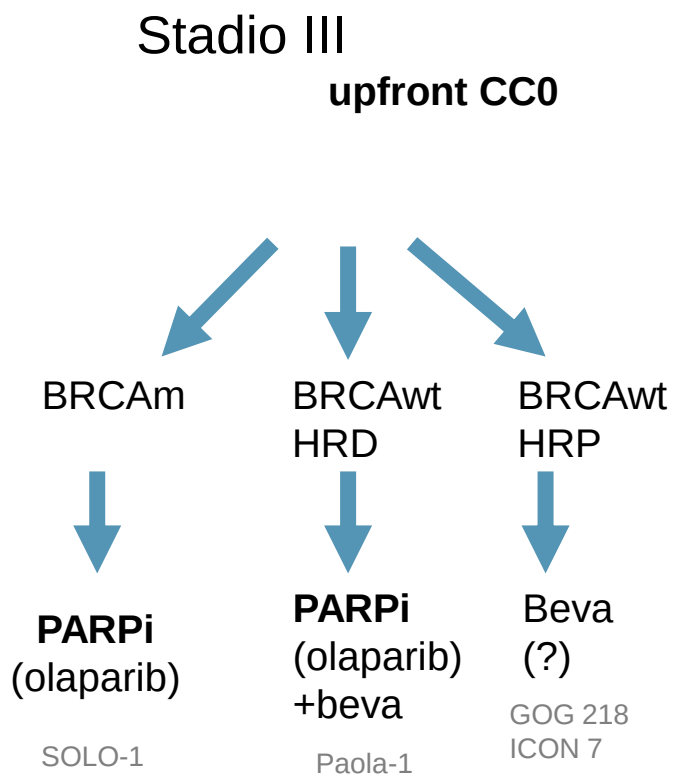
	Olaparib + bevacizumab (n=192)	Placebo + bevacizumab (n=85)
	140 (72.9)	58 (68.2)
	36.8	**40.4**
	25.7	**32.3**
	46 (24.0)	34 (40.0)

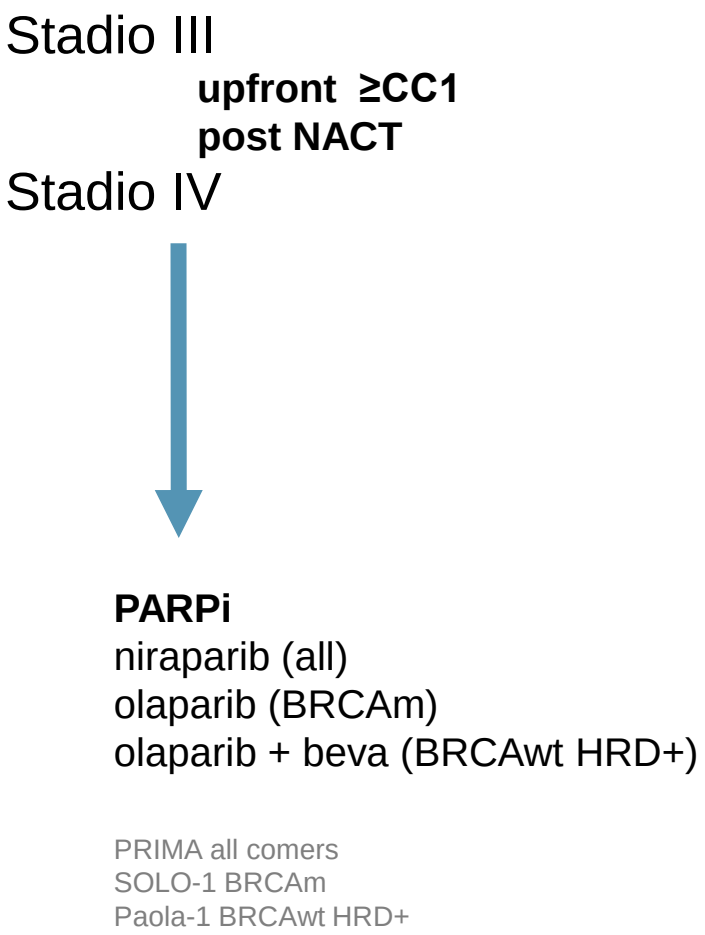
HR 1.19 (95% CI, 0.88–1.63)

*By central labs; †By Myriad myChoice® HRD Plus; ‡Unstable median; <50% data maturity

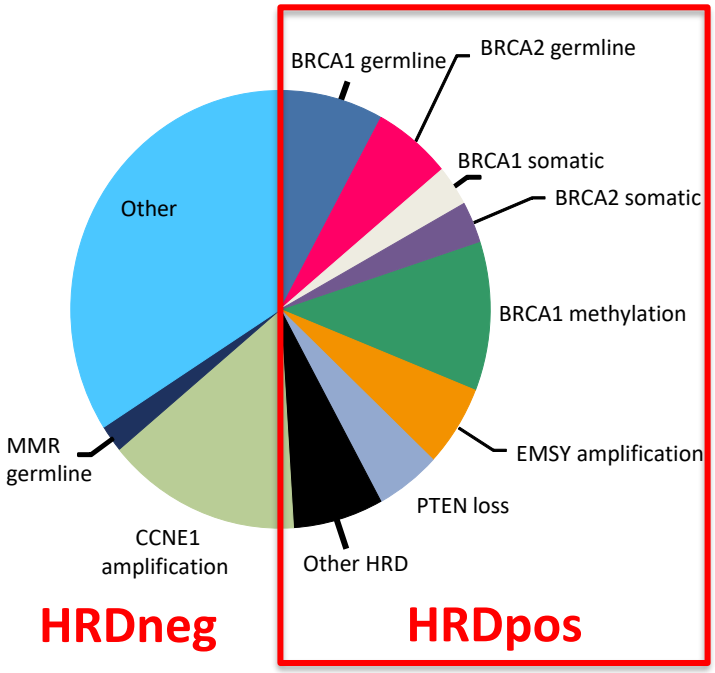
Ray-Coquard I, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France

Carcinoma ovarico alto grado 1L
Algoritmo terapia di mantenimento





HRD nel carcinoma ovarico



Levine D. The Cancer Genome Atlas, 2011

BRCA mutated
BRCAwt, HRD positive

PARPi +++ Beva ?

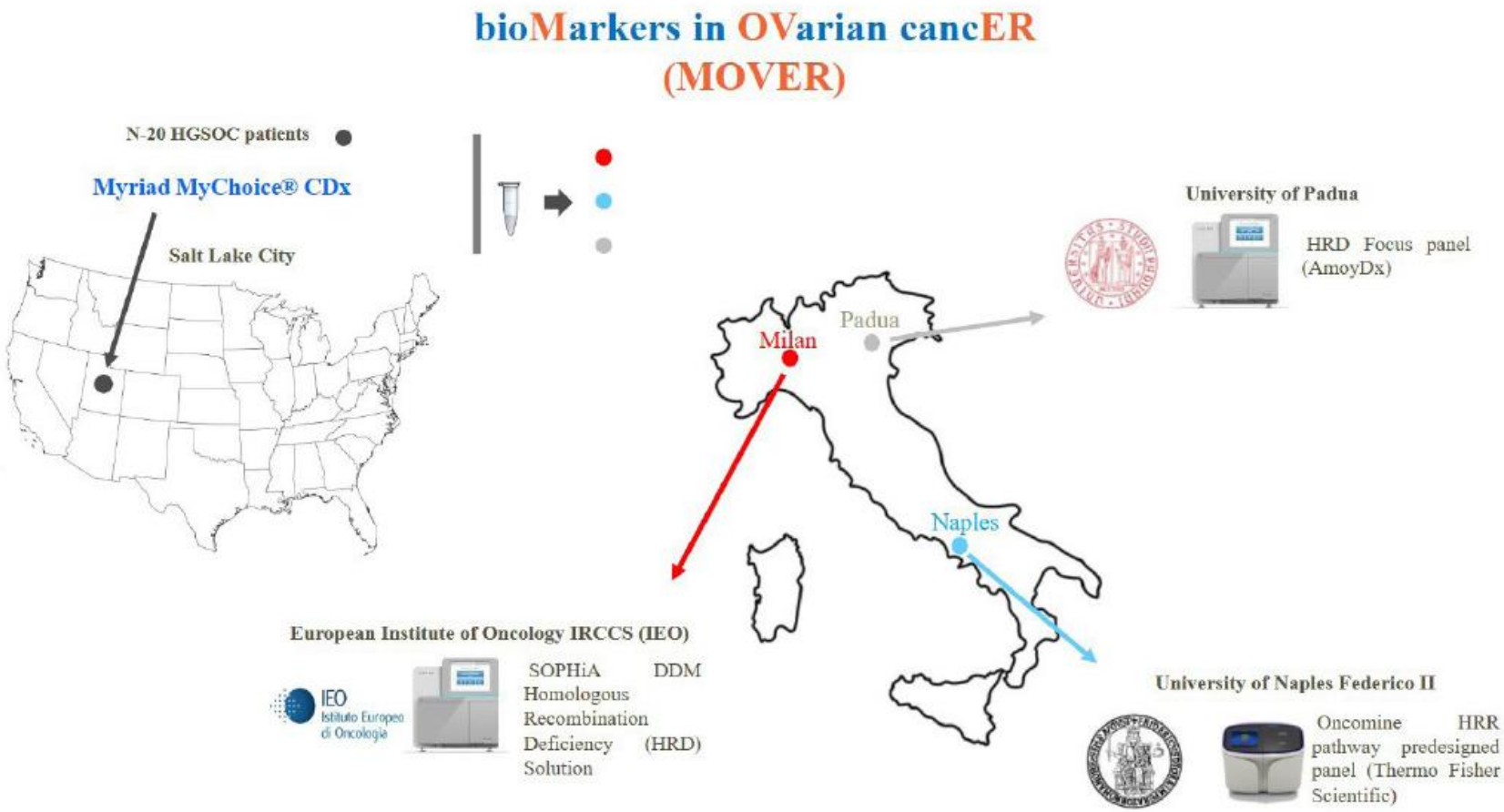
HRD negative

PARPi vs Beva

Myriad myChoice

BRCA1 and *BRCA2* variants
(sequencing and large rearrangement)

Genomic instability: loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions



Study design. HGSOC, high-grade serous ovarian cancer; HRR, homologous recombination repair.

In-house homologous recombination deficiency testing in ovarian cancer: a multi-institutional Italian pilot study

Francesco Pepe,[1] Elena Guerini-Rocco,[2,3] Matteo Fassan,[4,5] Nicola Fusco ,[2,3] Davide Vacirca,[2] Alberto Ranghiero,[2] Konstantinos Venetis,[2] Alessandra Rappa,[2] Sergio Vincenzo Taormina,[2] Gianluca Russo ,[1] Elena Rebellato,[4] Giada Munari,[5] Andrea Moreno-Manuel ,[6,7,8] Carmine De Angelis,[9] Claudio Zamagni,[10] Giorgio Valabrega,[11] Umberto Malapelle ,[1] Giancarlo Troncone ,[1] Massimo Barberis ,[2] Antonino Iaccarino[1]

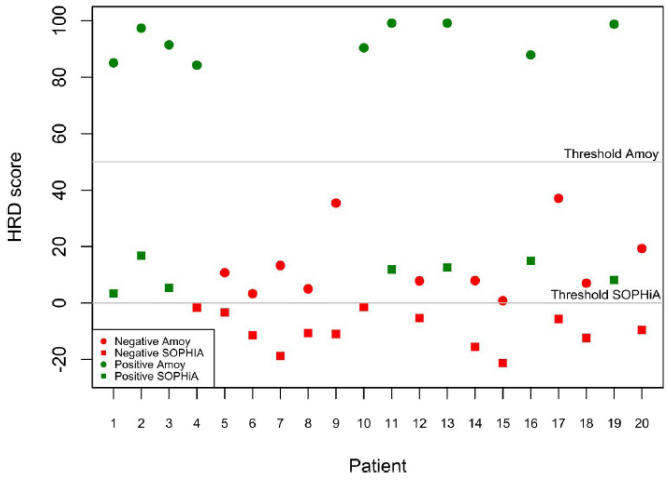


Figure 3 Concordance rate of center #1 by using SOPHiA DDM HRD Solution assay and Amoy HRD focus assay. HRD, homologous recombination deficiency.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Homologous recombination deficiency (HRD) status has revolutionised the clinical management of patients with high-grade serous ovarian cancer.

WHAT THIS STUDY ADDS

⇒ In-house harmonised next-generation sequencing (NGS) procedures may represent a valid testing strategy for HRD evaluation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In-house harmonised NGS procedures for HRD testing lead an improvement of successful testing rate.

Pepe F, *et al*. *J Clin Pathol* 2023;**0**:1–8. doi:10.1136/jcp-2023-208852