un evento promosso da

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI DINO AMADORI

SCHOOL OF NGS

Nuove frontiere del Next Generation Sequencing nella diagnostica oncologica ed ematologica

04 Novembre 2022

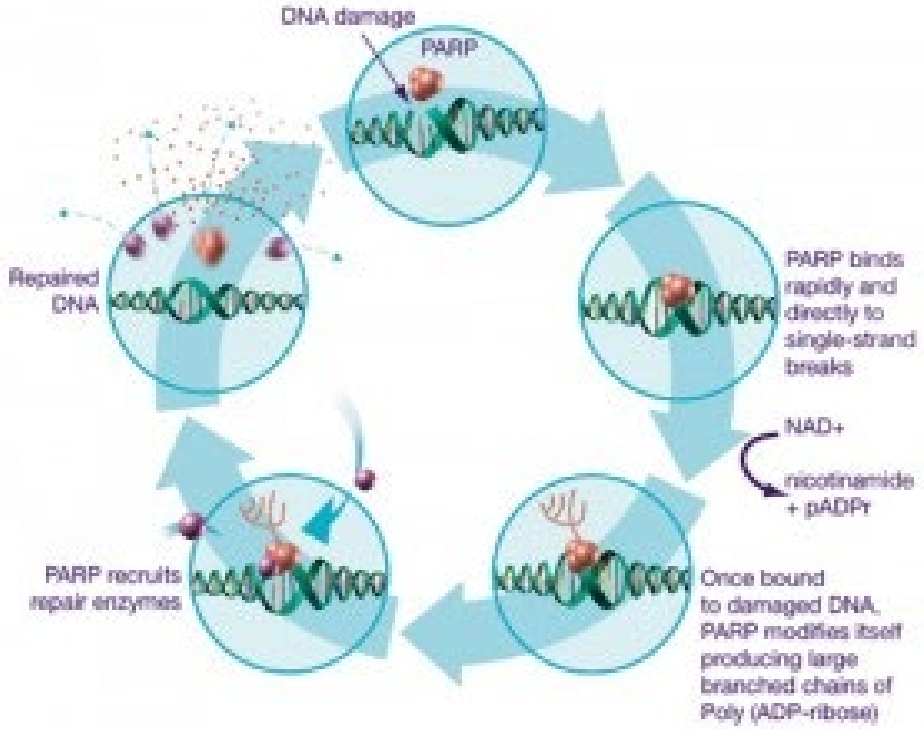
Centro Congressi FEDERICO II Napoli

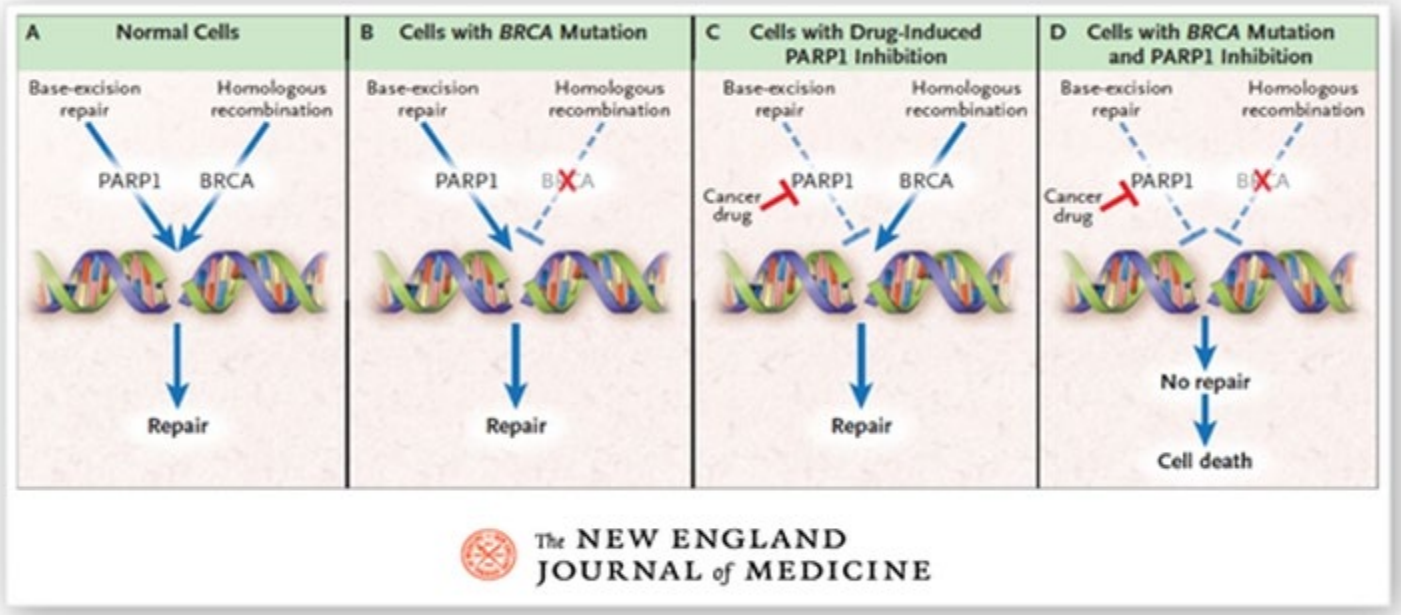
Dr. Alberto Farolfi

IRCCS IRST

Il ruolo dei PARP inibitori nel trattamento terapeutico

I PARPi e la teoria del tavolo

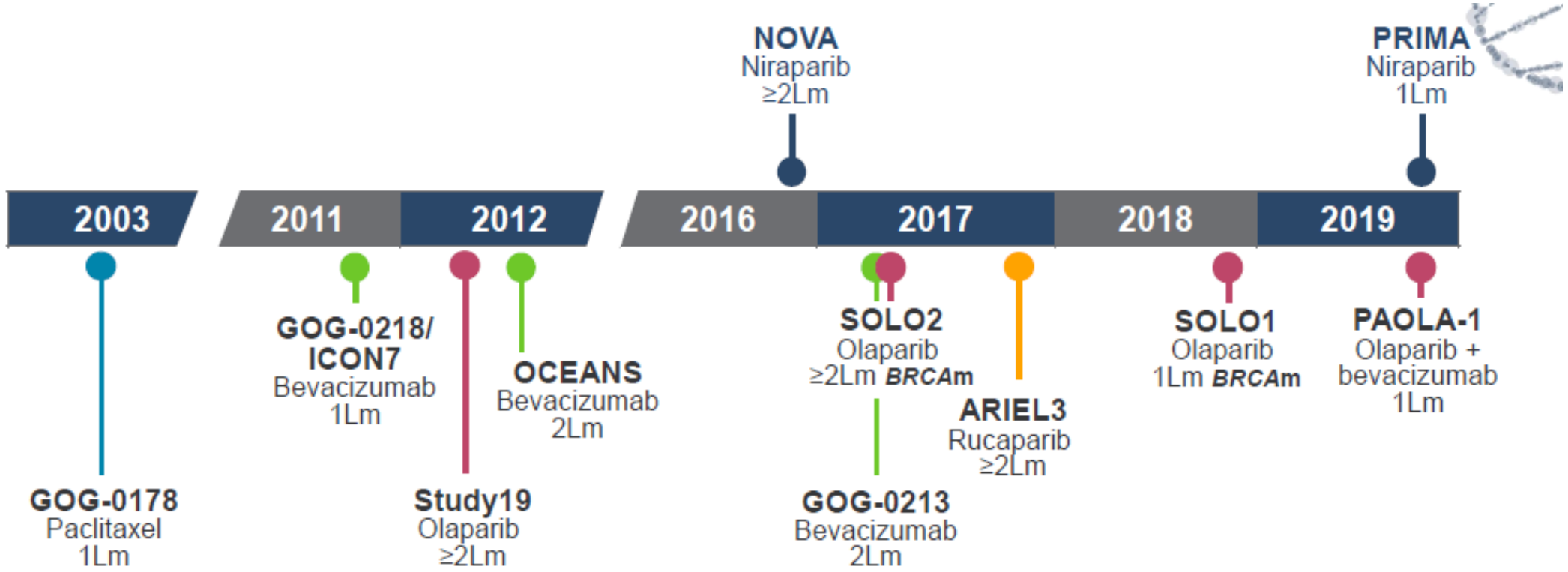




My Agenda

- ✓ Ovarian Cancer
- ✓ Breast Cancer
- ✓ Prostate Cancer
- **X** Pancreatic Cancer

Maintenance's therapy in Ovarian Cancer



Dates shown indicate the year of the publication of the pivotal studies. 1Lm, first-line maintenance; 2Lm, second-line maintenance; *BRCA*m, breast cancer gene mutant; OC, ovarian cancer.

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. Ledermann J, et al. N Engl J Med 2012;366:1382–92; 5. Aghajanian C, et al. J Clin Oncol 2012;30:2039–45; 6. Mirza MR, et al. N Engl J Med 2016;375:2154–64; 7. Coleman R, et al. Lancet Oncol 2017;18:779–91; 8. Pujade-Lauraine E, et al. Lancet Oncol 2017;18:1274–84; 9. Coleman R, et al. Lancet 2017;390:1949–61; 10. Moore K, et al. N Engl J Med 2018;379:2495–505; 11. González Martín A, et al. N Engl J Med 2019;381:2391–402; 12. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–28.

PARP Inhibitors in Patients With Recurrent or Relapsed Ovarian Cancer: Maintenance Therapy

Outcome Measure	ENGOT-OV16/NOVA[1,2]		SOLO2[3,4]	ARIEL3[5]		
Study regimen	Niraparib vs placebo (N = 553*)		Olaparib vs placebo (N = 295)	Rucaparib vs placebo (N = 564)		
Study phase	III		III	III		
Median f/u, mo	16.9[1] to 67[2]		65.7 vs 64.5	--		
	gBRCAm	**non-gBRCAm**	**gBRCAm**	**BRCAm**	**HRD**	**ITT**
ORR, % ▪ *CR*	--	--		38% vs 9% 18% vs 0%	27% vs 7% 12% vs 0%	18% vs 8% 7% vs 2%
Median PFS, mo	21.0 vs 5.5 (HR: 0.27)	9.3 vs 3.9 (HR: 0.45)	19.1 vs 5.5[†] (HR: 0.30; P <.0001)	16.6 vs 5.4 (HR: 0.23; P <.0001)	13.6 vs 5.4 (HR: 0.32; P <.0001)	10.8 vs 5.4 (HR: 0.36; P <.0001)
Median OS, mo	43.6 vs 41.6 (HR: 0.93)	31.1 vs 36.5 (HR: 1.10)	51.7 vs 38.8[‡] (HR: 0.74)	--		

*Germline BRCAm: niraparib, n = 138; placebo, n = 65. Non-germline *BRCA*m: niraparib, n = 234; placebo, n = 116. [†]Investigator assessed. [‡]Unadjusted OS.

1. Mirza. NEJM. 2016;375:2154. 2. Matulonis. SGO 2021. Abstr 37. 3. Poveda. Lancet Oncol. 2021;22:620.
4. Pujade-Lauraine. Lancet Oncol. 2017;18:1274. 5. Coleman. Lancet. 2017;390:1949.

SOLO-1 was the first Phase III trial to investigate maintenance PARP inhibitor treatment in newly diagnosed advanced ovarian cancer

- Newly diagnosed, FIGO Stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic BRCAm
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical CR or PR 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 NED at 2 years stopped treatment
- Patients with a PR at 2 years could continue treatment

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- OS
- TFST
- TSST
- HRQoL (FACT-O TOI score)

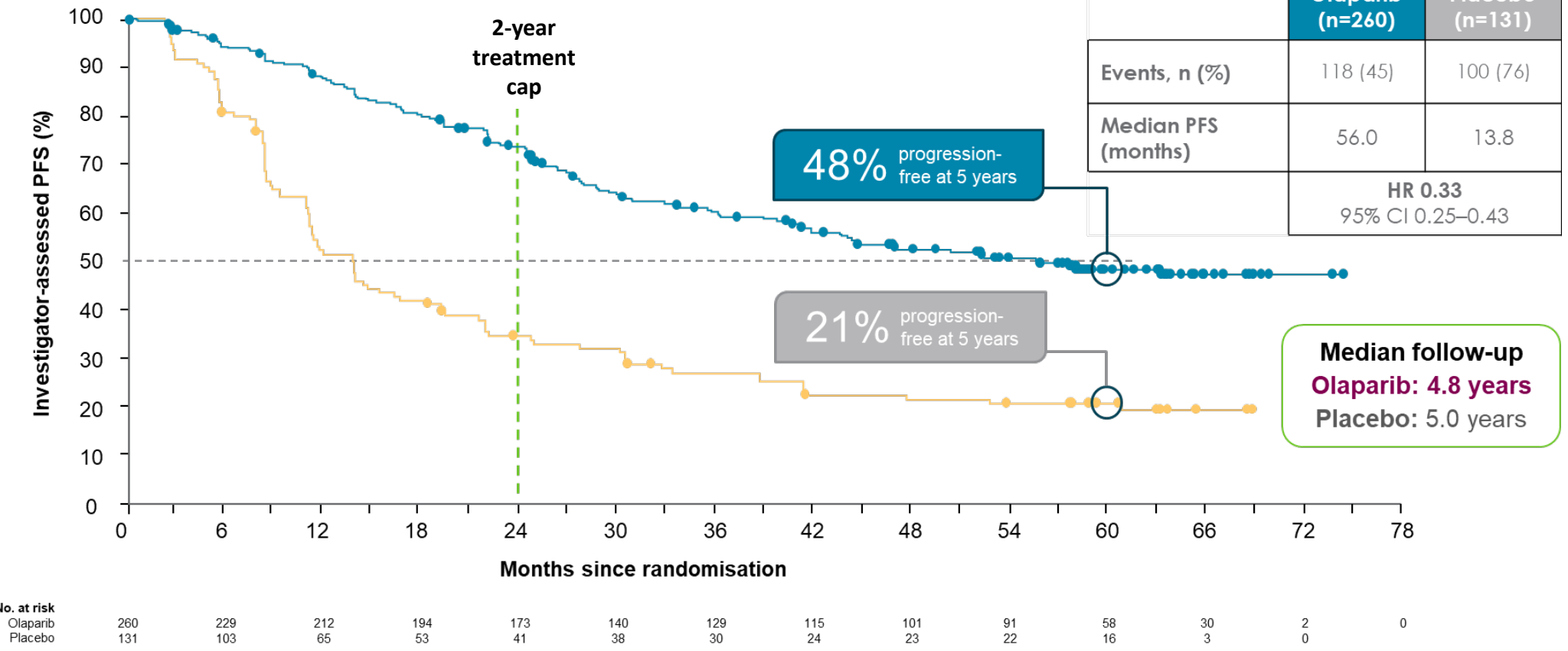
2 years' treatment if NED

*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; BID=twice daily; BRCAm=BRCA mutation; CR=complete response; 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; NED=no evidence of disease; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; TFST=time from randomisation to first subsequent therapy or death; TSST=time from randomisation to second subsequent therapy or death; TOI=Trial Outcome Index

1. Moore K, et al. N Engl J Med. 2018;379:Clinical Study Protocol; 2. Moore K, et al. N Engl J Med. 2018;379:2495–2505

After 5 years' follow-up, the PFS benefit derived from maintenance olaparib was sustained substantially beyond the end of treatment

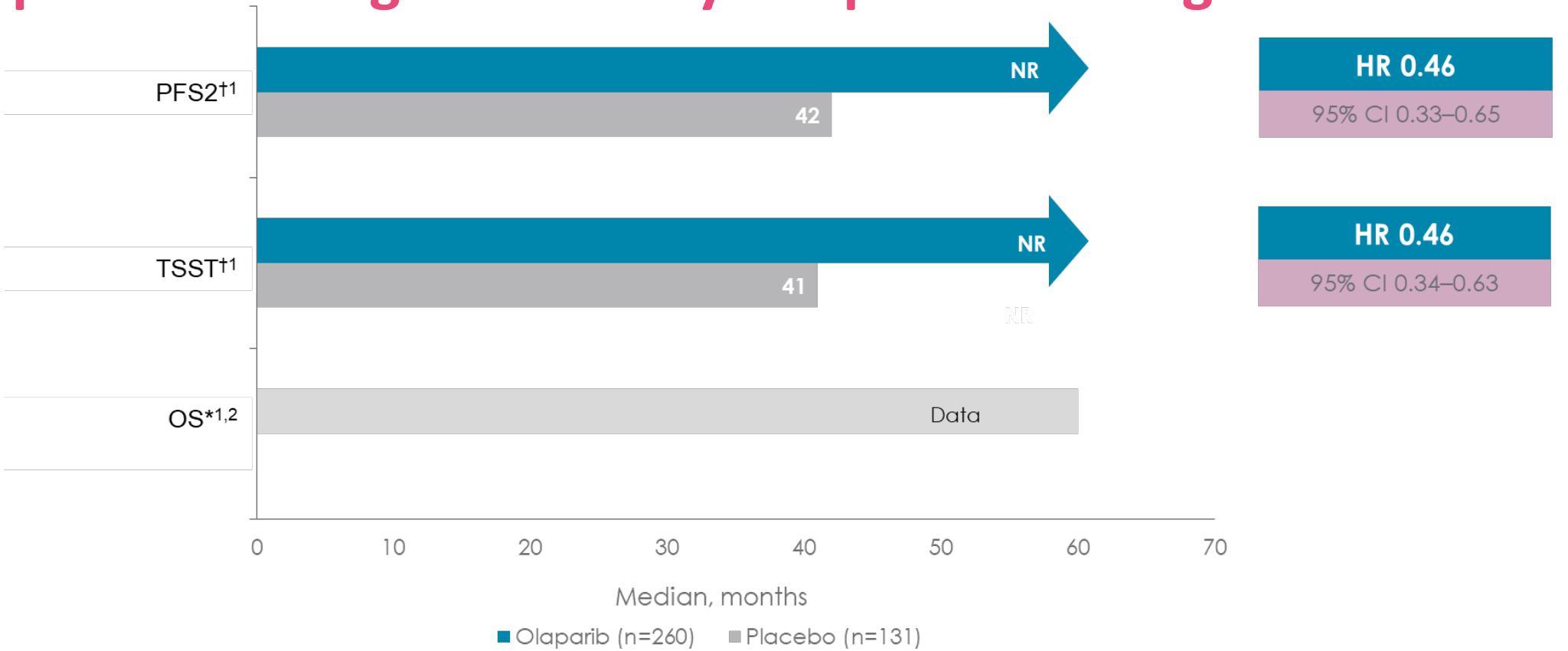


	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS (months)	56.0	13.8
	HR 0.33 95% CI 0.25–0.43	

Median follow-up
Olaparib: 4.8 years
Placebo: 5.0 years

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

After 5 years' follow-up, patients continued to derive benefit from olaparib in a range of efficacy endpoints at long-term follow-up



*TFST data from the primary DCO of May 2018. Median follow-up: olaparib 40.7 months, placebo 41.2 months

†Data are from the 5-year follow-up DCO of March 2020. Median follow-up: olaparib 4.8 years, placebo 5.0 years

1. Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19–21 September. Abstract #811MO; 2. Moore K, et al. N Engl J Med. 2018;379:2495–2505

PRIMA Trial

Patients with newly-diagnosed OC at Stage III with residual disease or stage IV after response to 1L platinum-based chemotherapy

2:1 Randomization

Niraparib 3 years — **Placebo**

- Body weight ≥77 kg and platelets ≥150,000/µL started with 300 mg QD
- Body weight <77 kg and/or platelets <150,000/µL started with 200 mg QD

Stratification Factors

- Neoadjuvant chemotherapy administered: Yes or no
- Best response to first platinum therapy: CR or PR
- Tissue homologous recombination test status: deficient or proficient/not-determined

Endpoint assessment

Primary Endpoint: Progression-free survival by BICR

Key Secondary Endpoint: Overall Survival

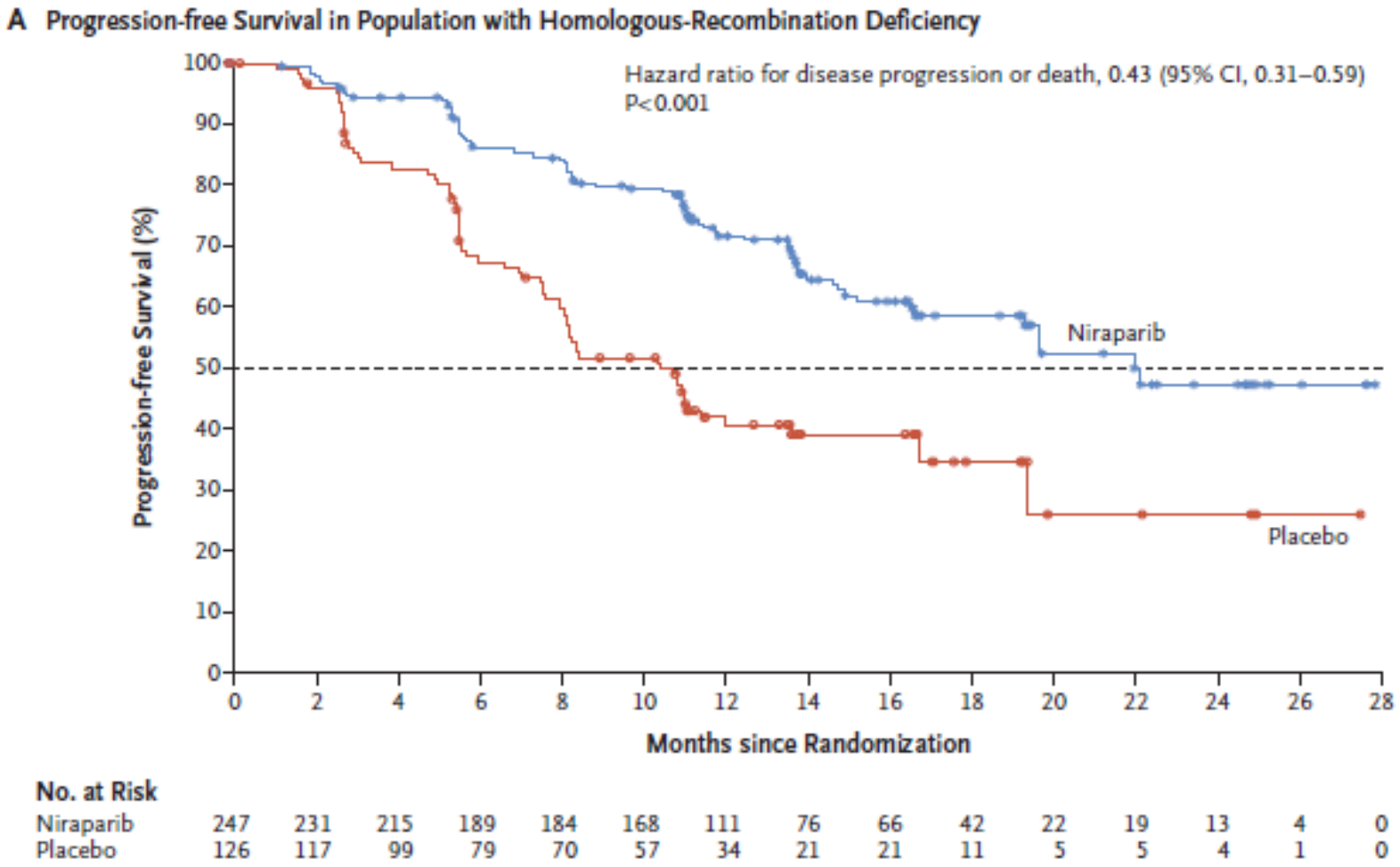
Secondary Endpoints: PFS2, TFST, PRO, Safety

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

Hierarchical PFS Testing

- **Patients with homologous recombination deficient tumors**, followed by the **overall population**.
- Statistical assumption: a hazard ratio benefit in PFS of
  - 0.5 in homologous recombination deficient patients
  - 0.65 in the overall population
- >90% statistical power and one-sided type I error of 0.025

The PFS benefit derived from maintenance niraparib was confirmed in the ITT population, irrespective of HRD status

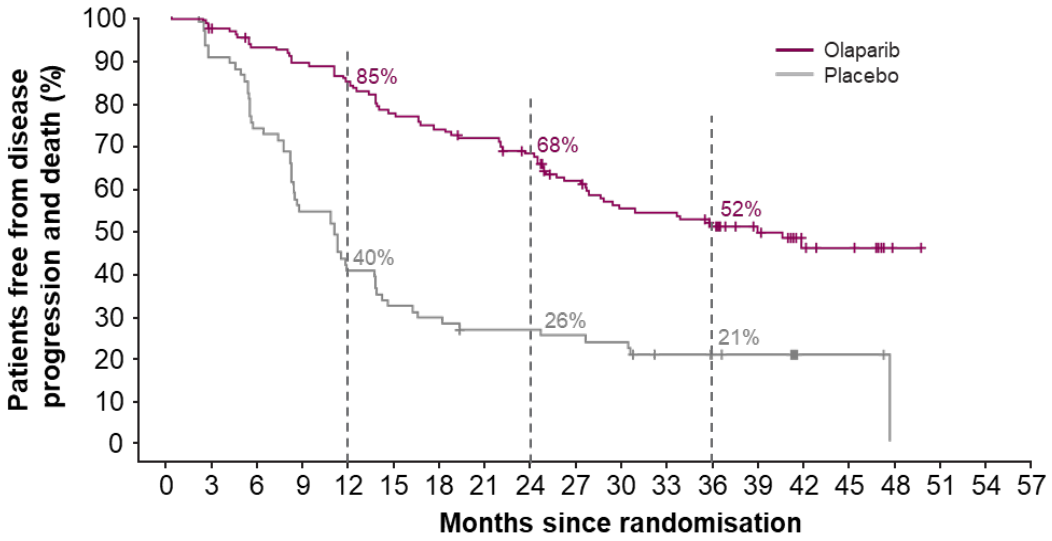


PFS benefit derived from maintenance PARPi in BRCA mutated, higher risk population (NON-PRESPICIFIED SUBGROUP ANALYSIS)

Higher risk

Stage III patients with PDS and residual disease, patients who received NACT, inoperable patients, Stage IV patients

	Olaparib n=146	Placebo n=73
Median PFS, months	39.0	11.1
	HR 0.34 95% CI 0.24–0.48	



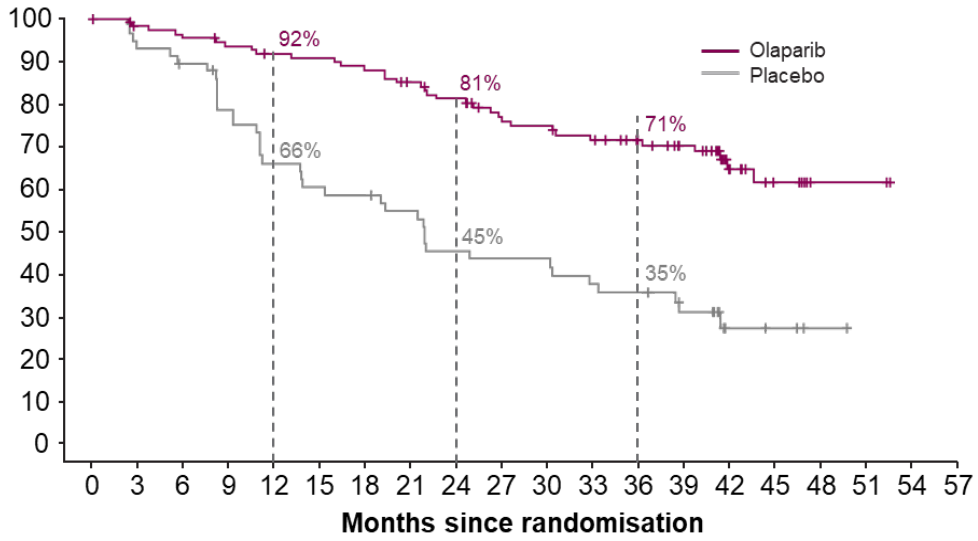
No. at risk:

Olaparib	146	135	127	122	116	106	101	97	90	77	68	67	54	40	20	18	1	0	0	0
Placebo	73	65	53	39	29	23	21	18	18	17	16	12	10	9	2	2	0	0	0	0

Lower risk

Stage III patents with PDS and no residual disease

	Olaparib n=114	Placebo n=58
Median PFS, months	NR	21.9
	HR 0.33 95% CI 0.20–0.52	



No. at risk:

Olaparib	114	105	102	99	96	95	93	87	82	72	70	66	57	48	25	18	3	3	0	0
Placebo	58	53	50	43	36	33	32	29	23	22	22	19	18	13	4	3	1	0	0	0

PFS benefit derived from maintenance PARPi in BRCA mutated, higher risk population (NON-PRESPICIFIED SUBGROUP ANALYSIS)

SOLO-1

Higher risk

Stage III patients with PDS and residual disease, patients who received NACT, inoperable patients, Stage IV patients

	Olaparib n=146	Placebo n=73
Median PFS, months	39.0	11.1
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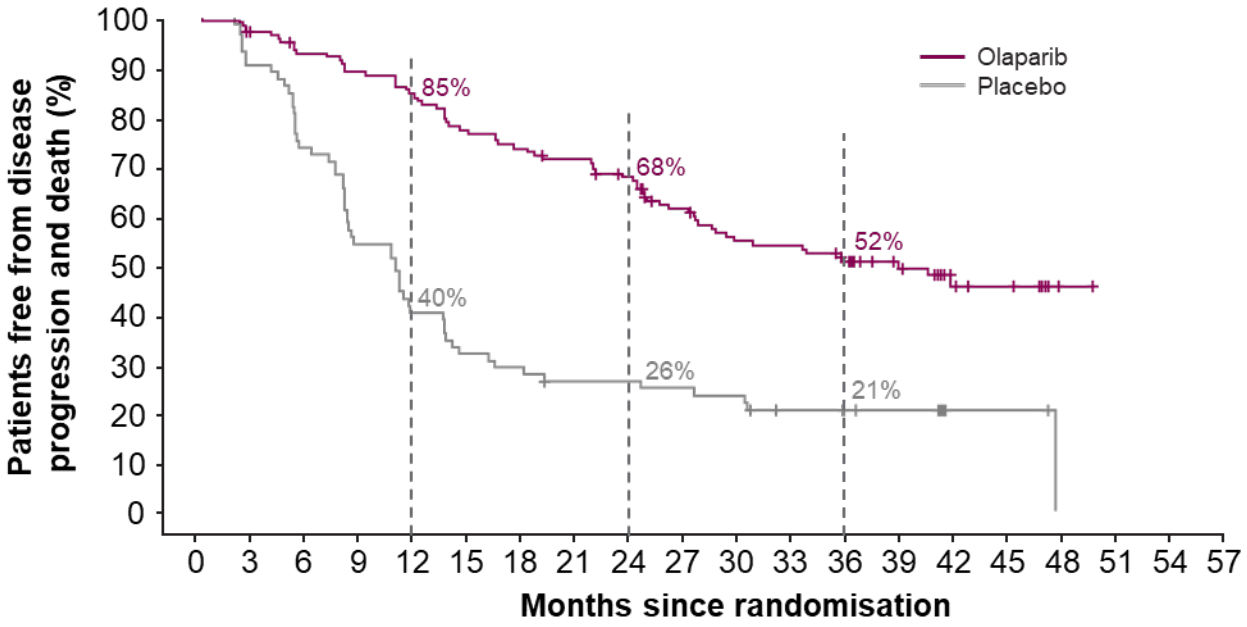
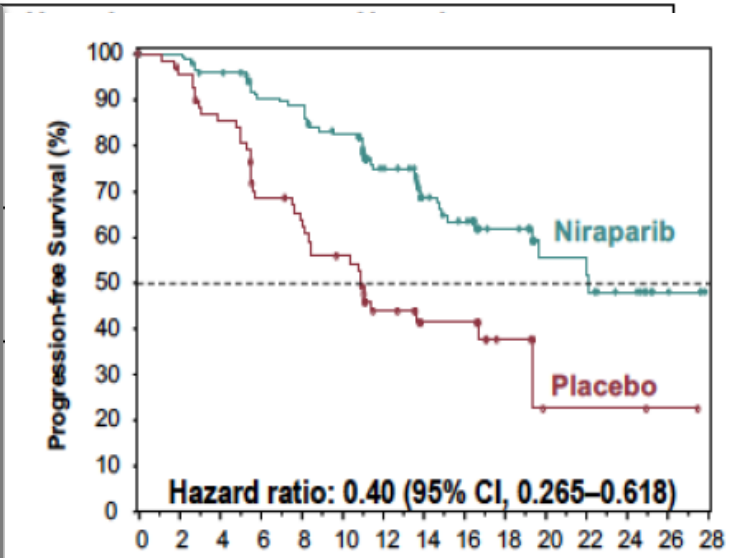


PRIMA

PFS	Homologous recombination deficient, *BRCA*mut	
	Niraparib (n=152)	Placebo (n=71)
Median	22.1	10.9
(95% CI) — mo	(19.3–NE)	(8.0–19.4)
HR (95% CI)	0.40 (0.27–0.62)	
P value	<0.001	



CI, confidence interval; HR, hazard ratio; mut, mutated; NE, not estimable; PFS, progression-free survival; wt, wild type.

First Line Maintenance Therapy

Maintenance olaparib provided a clinically meaningful OS benefit

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
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)

ToGlieTemi TuTTo, ma NoN il mio PARPi

Placebo 246 226 191 151 125 103 92 78 77 66 57 55 51 46 43 43 40 40 37 37 36 18 15 10 7 3 3 2 1 0

mPFS, median progression-free survival; PFS, progression-free survival.

PAOLA-1: Olaparib maintenance in newly diagnosed advanced ovarian cancer patients treated with chemotherapy and bevacizumab

- FIGO stage III–IV high-grade ovarian cancer (serous or endometrioid)* or non mucinous BRCAm
- Surgery (upfront or interval)
- Platinum taxane-based chemotherapy
- ≥3 cycles of bevacizumab†

NED/ CR/PR

Olaparib (300 mg BID) x 2 years
+ bevacizumab†

2:1 randomisation; **N=806**

Stratification by tBRCA status‡ and 1L treatment outcome

Placebo x 2 years
+ bevacizumab†

2 years' maintenance treatment

Primary endpoint

- Investigator-assessed PFS (RECIST 1.1)
  Sensitivity analysis by BICR

Secondary endpoints

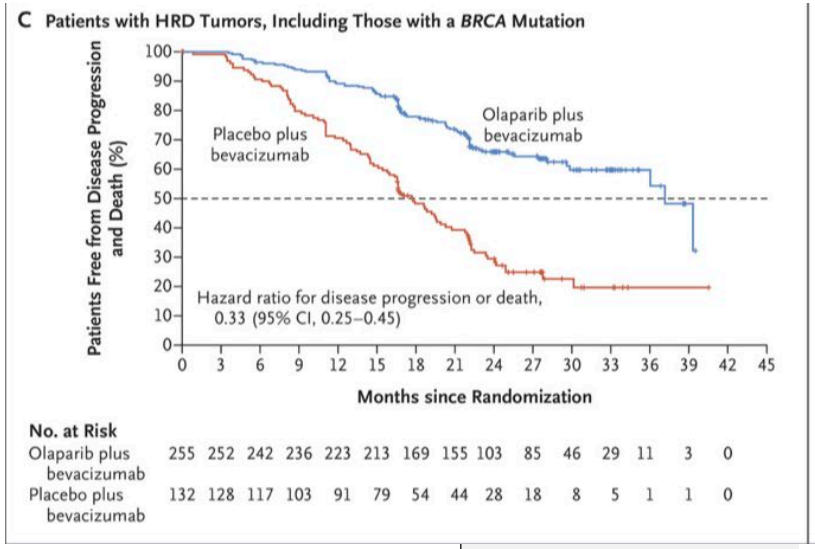
- TFST
- PFS2
- TSST
- OS
- Safety
- PRO/HRQoL

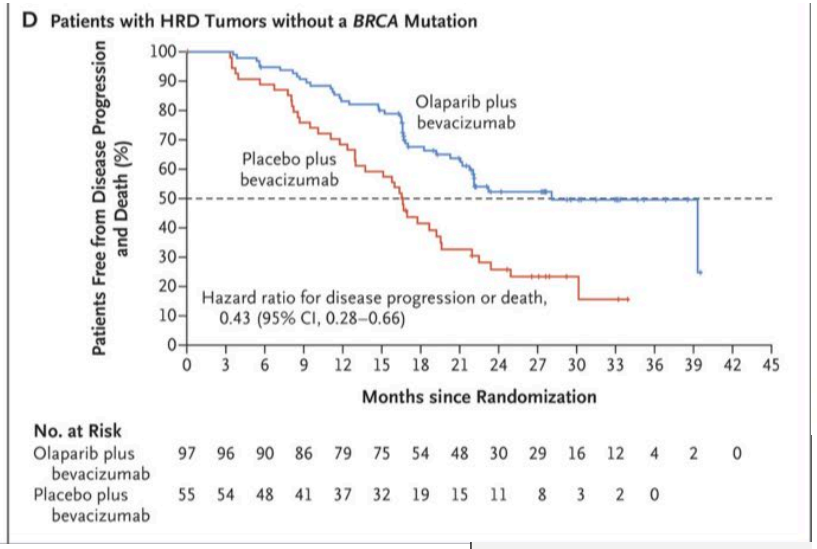
Pre-specified exploratory endpoints

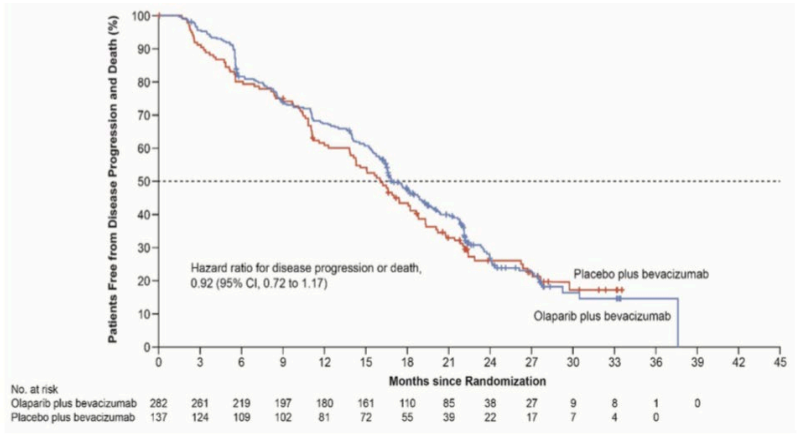
- PFS in pre-defined subgroups including tBRCAm and Myriad myChoice® CDx

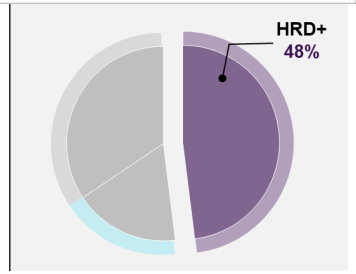
L'associazione bevacizumab + olaparib si e' dimostrata efficace solo nelle pazienti HRD positive

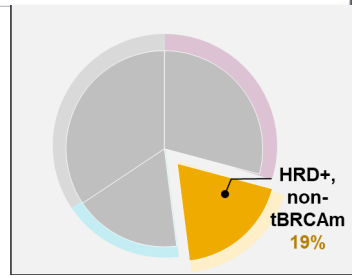
The clinically meaningful improvement in mPFS (20 months) may increase with longer follow-up

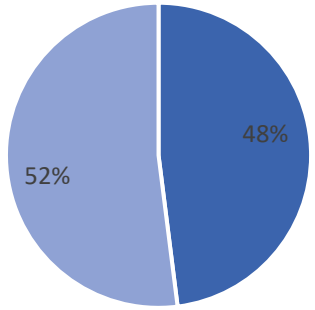






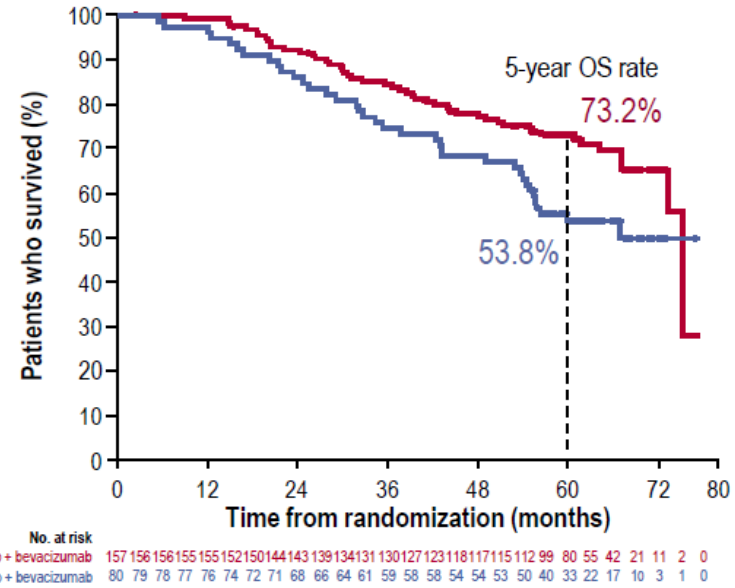






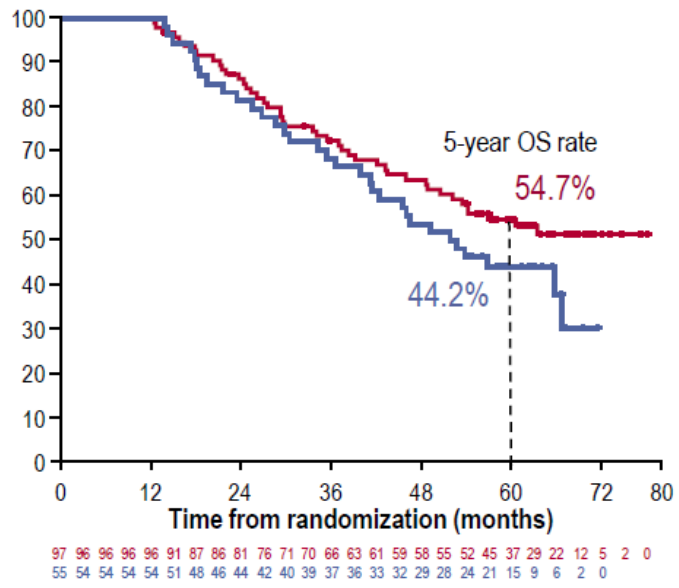
OS subgroup analysis by BRCAm and HRD status

BRCAm*



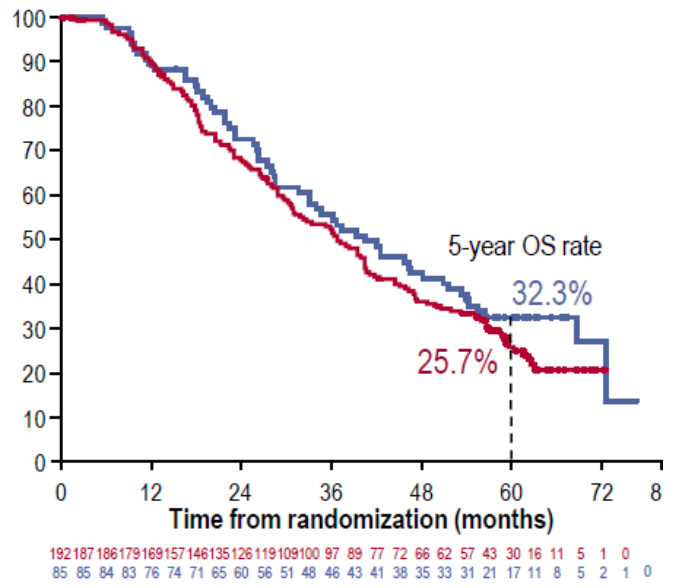
	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
HR 0.60 (95% CI 0.39–0.93)		

HRD positive‡ excluding BRCAm



	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	**44.2**
	9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)		

HRD negative†



	Olaparib + bevacizumab (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; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

Incidence of PARPi-related MDS/AML

Clinical trials

Overall: 0.2-8%

First-line setting

SOLO1 (OLA vs PBO)	PRIMA (NIRA vs PBO)	ATHENA-MONO (RUCA vs PBO)	PAOLA1 (OLA+BEVA vs PBO+BEVA)
1% vs 0%	0.2% vs 0%	0.5% vs 0%	1.1% vs 0.4%
7-yr FU: 1.5% vs 0.8%			5-yr FU: 1.7% vs 2.2%
Moore, 2018 *Banerjee, 2022*	*González-Martín, 2019*	*Monk, 2022*	*Ray-Coquard, 2019* *Ray-Coquard, 2022*

Recurrent setting

SOLO2 (*OLA vs PBO*)	NOVA (*NIRA vs PBO*)	ARIEL3 (*RUCA vs PBO*)	OReO trial (*OLA rechallenge vs PBO*)
2.1% vs 4%	1.4% vs 1.1%	1% vs 0%	Awaited…
6-yr FU: 8% vs 4%	4-yr FU: 2.2% vs 1.1%	2-yr FU: 1% vs 0%	
Pujade-Lauraine, 2017 *Poveda, 2021*	*Mirza, 2016* *Mirza, 2020*	*Coleman, 2017* *Ledermann, 2020*	*Pujade-Lauraine*

DEO

Breast Cancer

gBRCAm prevalence in unselected breast cancer is ~3%, with a higher prevalence found in patients with TNBC

~17%

of **TNBC** patients have BRCA mutations[1,2]

~6%

of **HR-positive** patients have BRCA mutations[1,2]

gBRCA testing offers the opportunity to personalise care for the patients and their family

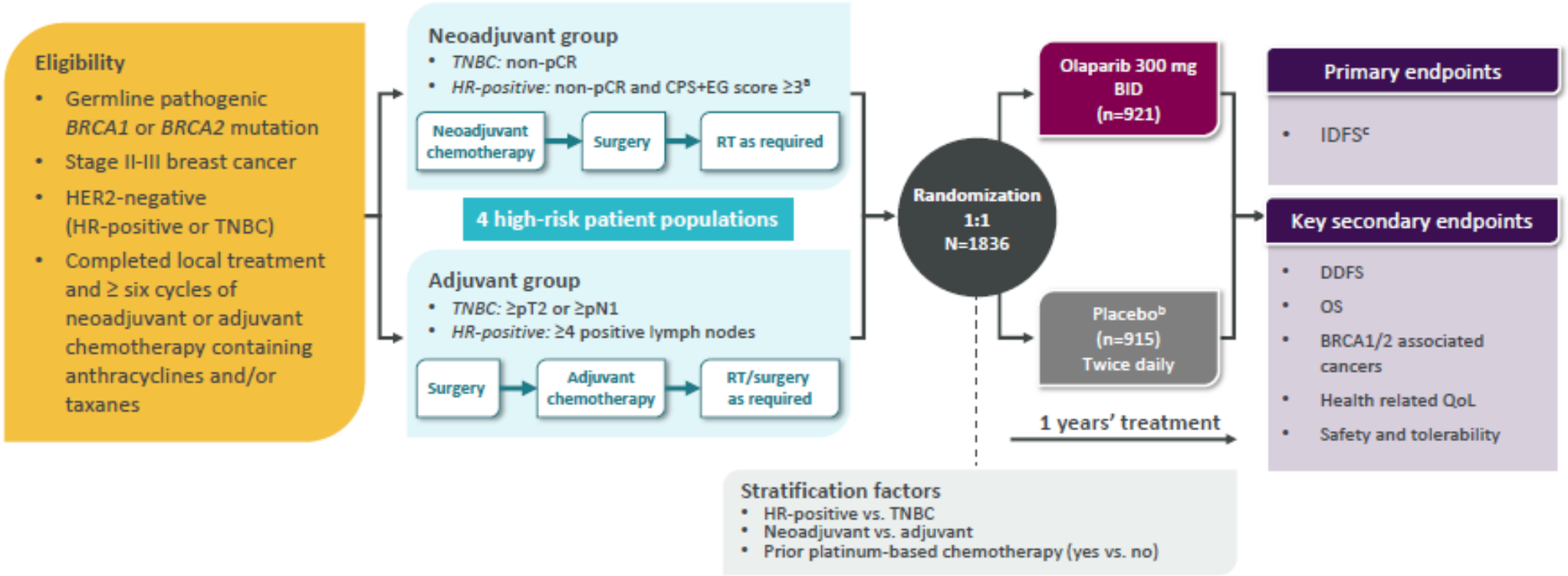
Germline BRCAm breast cancer

Patients with gBRCA mutations are **often younger and present with aggressive disease**[1-3]

gBRCA status can **alter surgical decisions** and **therapeutic options**[4]

Many patients **do not meet common** gBRCA **testing criteria*** and may **miss the opportunity to benefit from targeted treatment**[5]

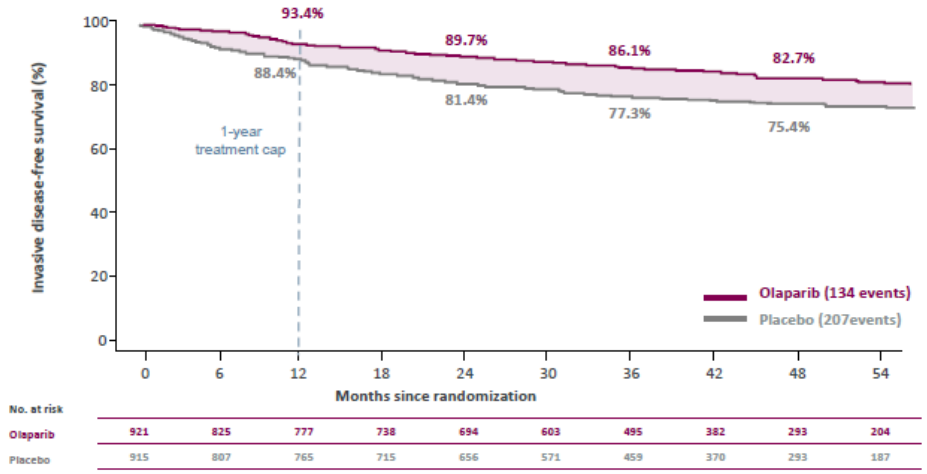
OlympiA: phase III study of olaparib versus placebo as adjuvant treatment for high risk gBRCA-mutated, HER2-negative BC



[a] CPS+EG score incorporates pretreatment clinical stage, oestrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy
[b] Data to support adjuvant capecitabine was not available when the OlympiA study was initiated in 2014
[c] by STEEP system[1]
1. NEJM OlympiA; 2.Hudis CA. J Clin Oncol 2007;25:2127–32

IDFS benefit associated with olaparib was maintained with 1-year additional follow-up†

Exploratory Analysis



IDFS at DCO2‡

HR 0.63
95% CI 0.50–0.78

4-year IDFS rate

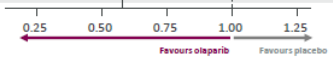
Olaparib (n=921)	82.7%
Placebo (n=915)	75.4%

Difference 7.3%
95% CI 3.0–11.5

†IDFS analysis is descriptive at OS IA2; ‡DCO2 12 July 2021 (at 330 IDFS events, 25% data maturity)

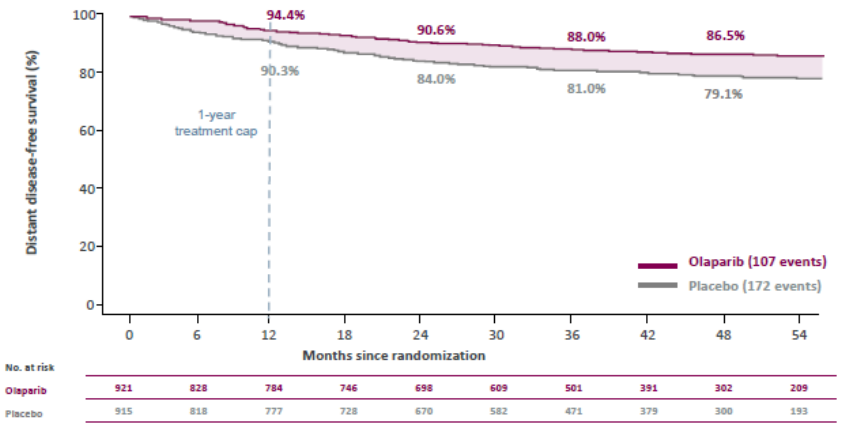
Tutt J, Garber J, Gelber R, et al. Pre-specified event driven analysis of Overall Survival in the OlympiA Phase III trial of adjuvant olaparib in germline BRCA1/2 mutation associated breast cancer. [Presentation]. Presented at ESMO Virtual Plenary; March 16-18, 2022.

Subgroup	Olaparib (No. of patients with an invasive-disease event/total no.)	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	P value for heterogeneity
All patients	134 / 921	207 / 915	0.628 (0.504, 0.779)	NA
Prior chemo				
Adjuvant	46 / 461	75 / 455	0.618 (0.425, 0.888)	0.977
Neoadjuvant	88 / 460	132 / 460	0.622 (0.473, 0.813)	
Prior platinum				
Yes	42 / 247	51 / 238	0.791 (0.523, 1.187)	0.197
No	92 / 674	156 / 677	0.575 (0.443, 0.742)	
HR status				
HR-positive/HER2-negative	25 / 168	34 / 157	0.680 (0.402, 1.134)	0.754
TNBC	109 / 751	173 / 758	0.620 (0.487, 0.787)	
BRCA				
BRCA1	83 / 579	149 / 588	0.533 (0.406, 0.695)	0.615
BRCA2	34 / 235	44 / 216	0.693 (0.440, 1.082)	
BRCA1 and *BRCA2*	0 / 2	0 / 3	NC	



Longer follow-up confirms DDFS benefit of adjuvant olaparib vs placebo with over 7% more patients free of distant recurrence at 4 years

Exploratory Analysis



DDFS at DCO2‡

HR 0.61
95% CI, 0.48–0.77

4-year DDFS rate

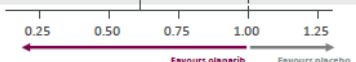
Olaparib (n=921)	86.5%
Placebo (n=915)	79.1%

Difference 7.4%
95% CI, 3.6–11.3

†DDFS analysis is descriptive at second OS interim analysis; ‡DCO2 12 July 2021 (at 330 IDFS events, 15% maturity)

Tutt A, Garber J, Gelber R, et al. Pre-specified event driven analysis of Overall Survival in the OlympiA Phase III trial of adjuvant olaparib in germline BRCA1/2 mutation associated breast cancer. [Presentation]. Presented at ESMO Virtual Plenary; March 16-18, 2022.

Subgroup	Olaparib (No. of patients with an distant-disease event/total no.)	Placebo	Stratified hazard ratio for distant disease-free survival (95% CI)	P value for heterogeneity
All patients	107 / 921	172 / 915	0.607 (0.476, 0.771)	NA
Prior chemo				
Adjuvant	33 / 461	59 / 455	0.562 (0.363, 0.855)	0.698
Neoadjuvant	74 / 460	113 / 460	0.623 (0.463, 0.832)	
Prior platinum				
Yes	36 / 247	43 / 238	0.812 (0.519, 1.263)	0.132
No	71 / 674	129 / 677	0.540 (0.403, 0.719)	
HR status				
HR-positive/HER2-negative	23 / 168	31 / 157	0.692 (0.399, 1.182)	0.608
TNBC	84 / 751	141 / 758	0.591 (0.450, 0.772)	
BRCA				
BRCA1	66 / 579	118 / 588	0.544 (0.400, 0.732)	0.927
BRCA2	28 / 235	41 / 216	0.609 (0.373, 0.979)	
BRCA1 and *BRCA2*	0 / 2	0 / 3	NC	



OlympiAD is a Phase III study investigating olaparib vs. TPC in gBRCAm HER2-negative metastatic breast cancer

- gBRCAm mBC
- TNBC or HER2-, HR+
- ≤2 prior chemotherapy lines for mBC
- Previous treatment with anthracycline and taxane in either the adjuvant or metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If patients have received platinum therapy there should be:
  - No evidence of disease progression during treatment in the advanced setting
  - At least 12 months since neoadjuvant or adjuvant treatment and randomisation
- ECOG PS 0-1
- At least one lesion that can be assessed by RECIST v1.1

FSI April 2014:[3]
Global Study in 19 countries and approximately 172 sites[1]

Randomise 2:1
N=302[3]

Stratification by:[2]
- *Prior chemotherapy regimens for mBC*
- *Hormonal receptor status*
- *Prior platinum therapy*

Olaparib
300 mg* *po* bid

TPC

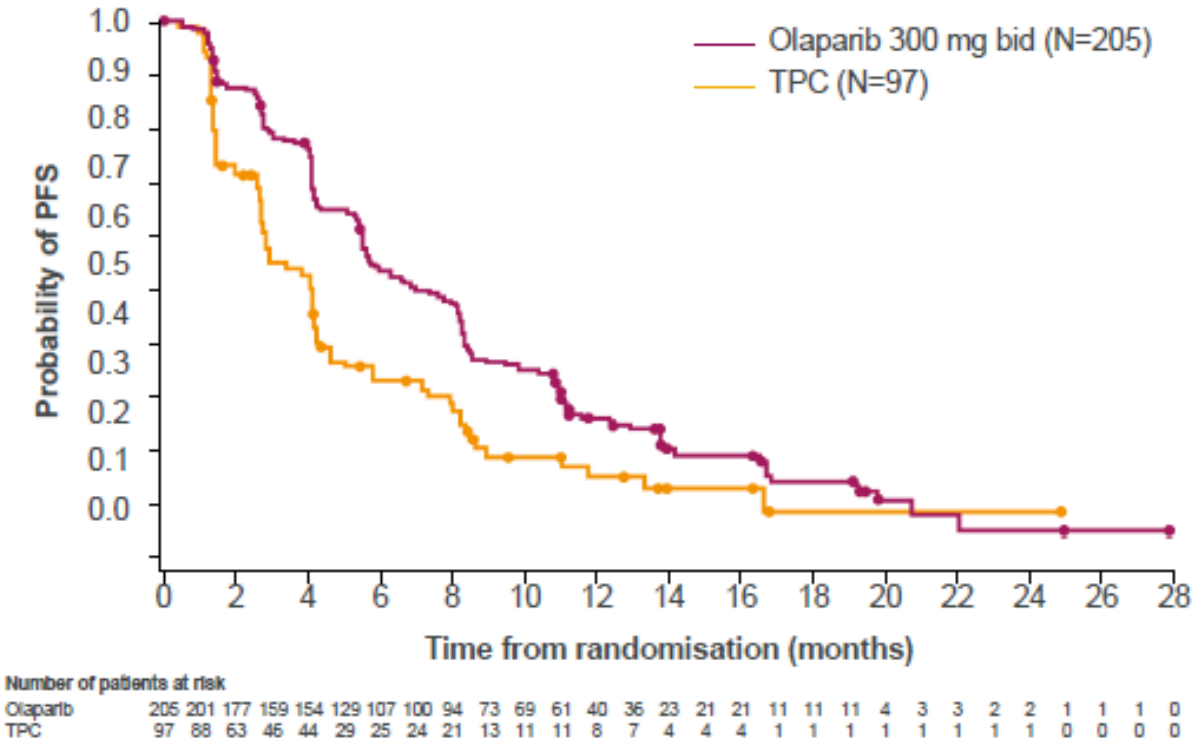
Primary endpoint
- PFS (BICR)

Secondary endpoints
- OS
- PFS2
- ORR
- PFS (INV), PFS2 and OS based on Myriad gBRCAm status
- HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

* Tablet formulation (2 tablets twice daily)
ECOG PS= Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FSI=first subject in; gBRCAm=germline BRCA mutation; HER2= human epidermal growth factor receptor 2; HR+=hormone receptor positive; HRQoL=health related quality of life; mBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PFS2=time to second progression; po=oral; RECIST=response evaluation criteria in solid tumours; TNBC=triple negative breast cancer; TPC=treatment of physician's choice

1. Study NCT02000622. ClinicalTrials.gov website; 2. Robson M et al. Poster OTI-1-1-04 presented at: SABCS; December 9-13, 2014; San Antonio, Texas; 3. Robson M et al. N Engl J Med. 2017;377:523-533

Primary endpoint: Olaparib treatment significantly improved PFS assessed by BICR compared to TPC



	Olaparib	TPC
N	205	97
Events, n (%)	163 (79.5)	71 (73.2)
mPFS, months	7.0	4.2
	HR = 0.58 95% CI (0.43–0.80) P<0.001	
PFS free at 6m,%	54.1	32.9
PFS free at 12m,%	25.9	15.0

Median PFS was improved by 69% with olaparib treatment compared to standard of care chemotherapy[2]

Stratified log rank test, stratified by previous chemotherapy for mBC (yes/no) and HR+ vs. TNBC
FAS; Maturity rate: 234/302=77.5%; two-sided p value; figure adapted with permission[1]
Data cut-off: 9 December 2016
BICR=blinded independent central review; HR+=hormone receptor positive; PFS=progression free survival; TPC=treatment of physician's choice

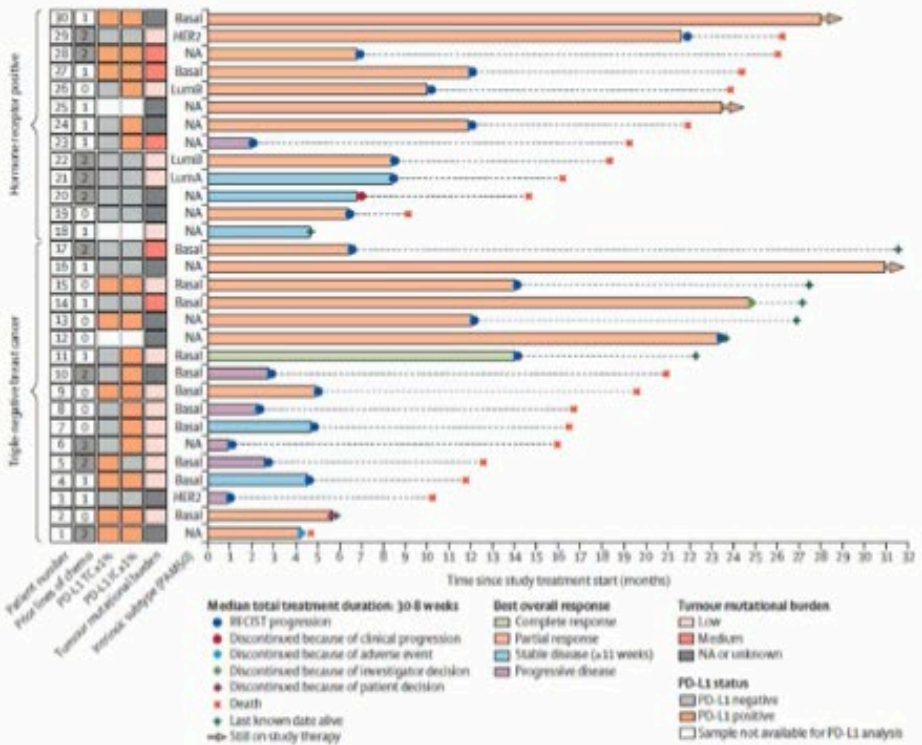
1. Robson M et al. *N Engl J Med*. 2017;377:523-533; 2. Tung NM et al. Poster 1052 presented at: ASCO; June 2, 2018; Chicago, IL

PARP Inhibitors in *BRCAm BC*

The future of PARPi is likely combination strategies

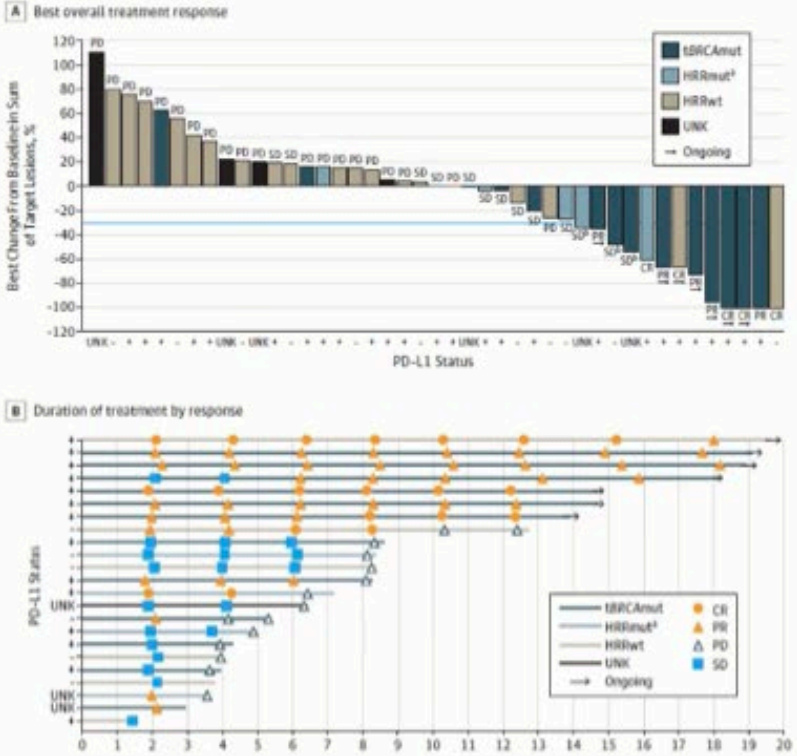
MEDIOLA Trial

Olaparib + Durvalumab



TOPACIO Trial

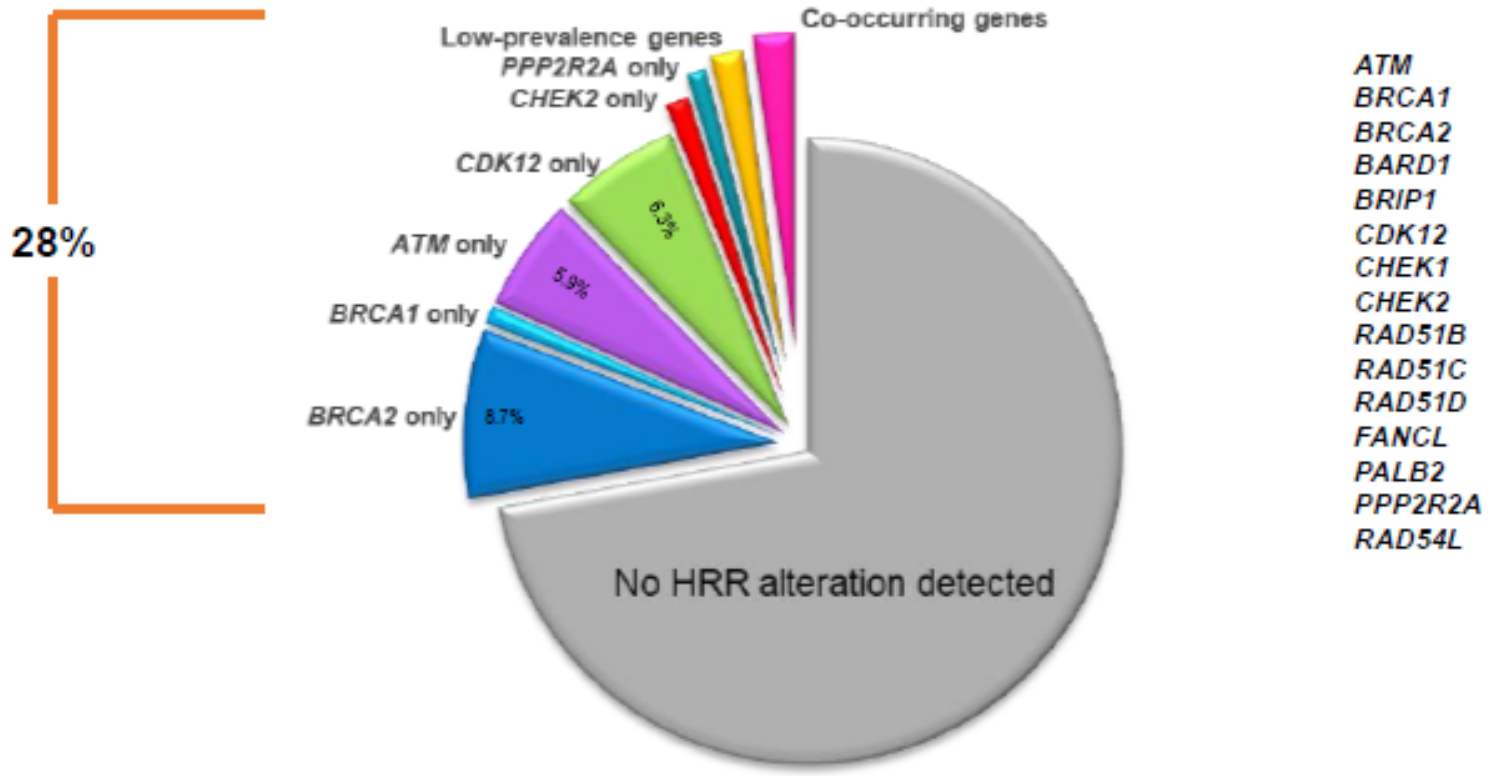
Niraparib + Pembrolizumab



Prostate Cancer

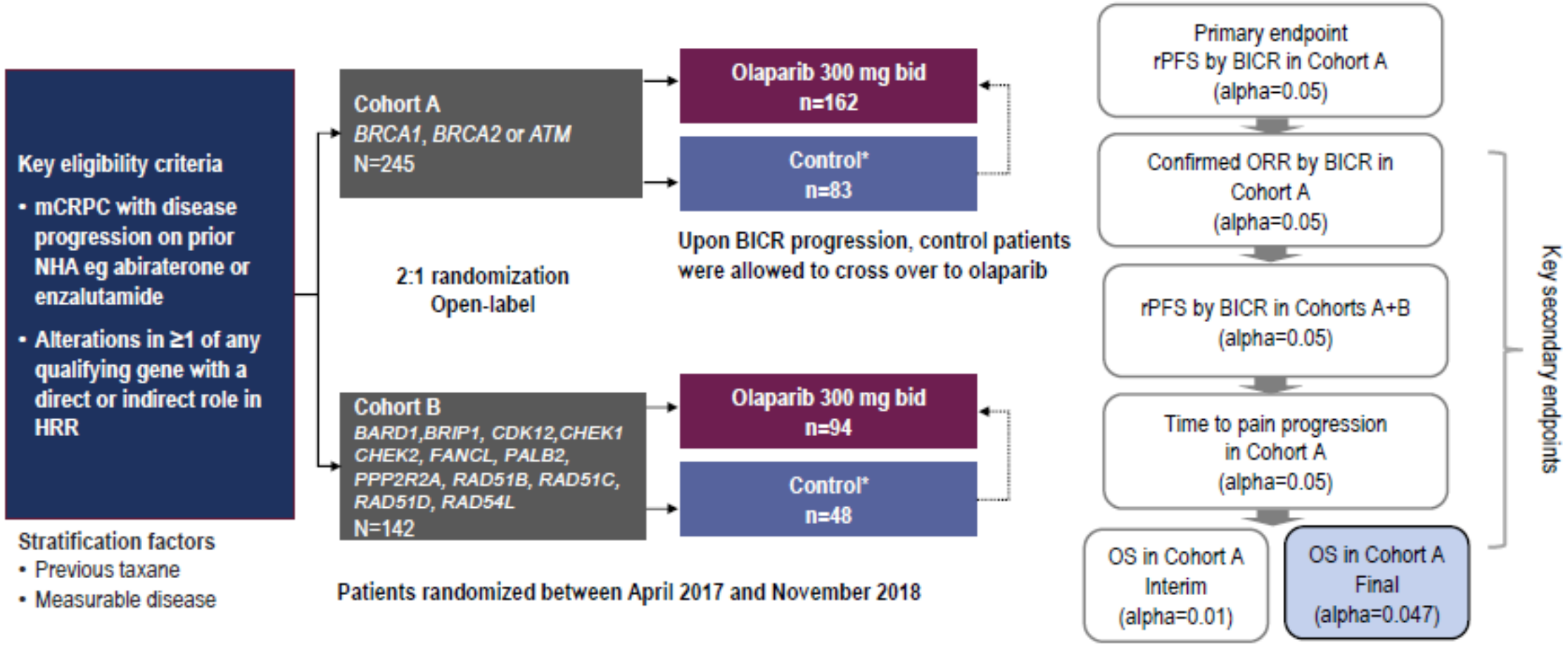
Alterations in Homologous Recombination Repair (HRR) genes

(PROFOUND ≃ 2800 samples)

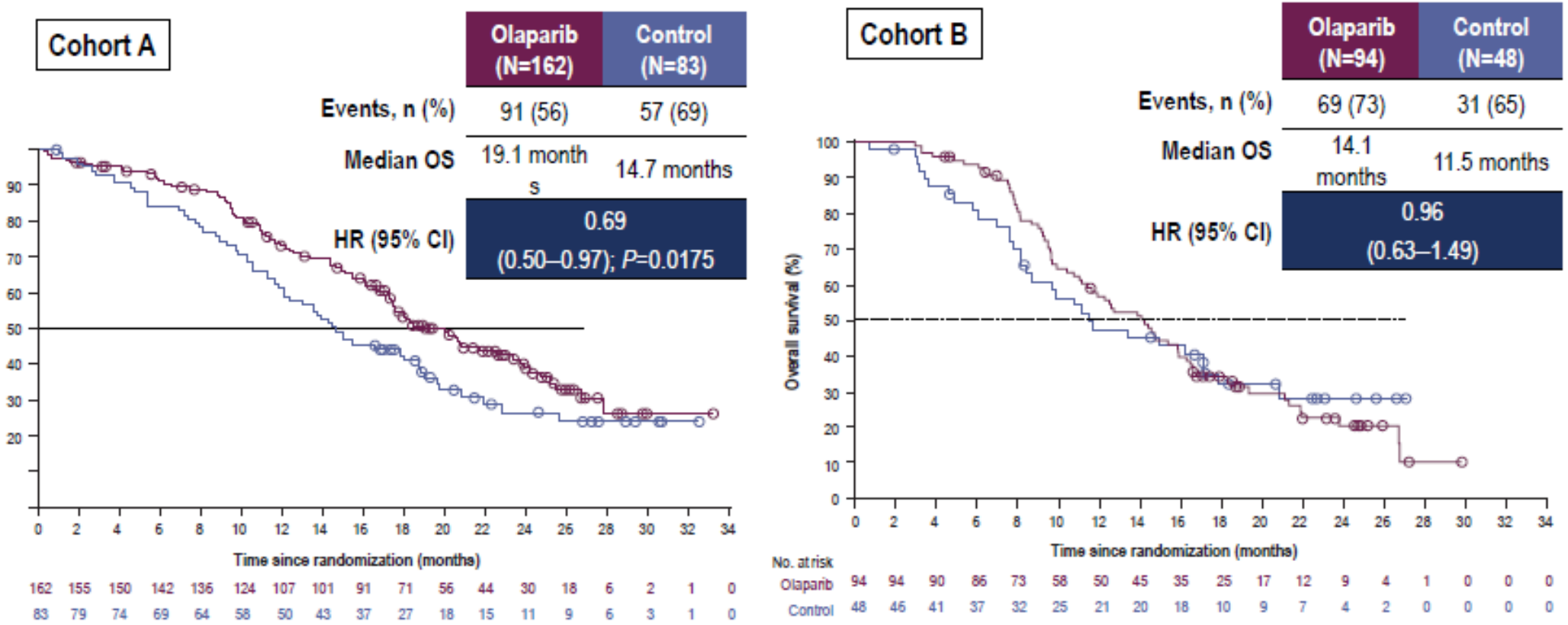


Presented by Dr de Bono at ESMO 2019; De Bono NEJM, 2020

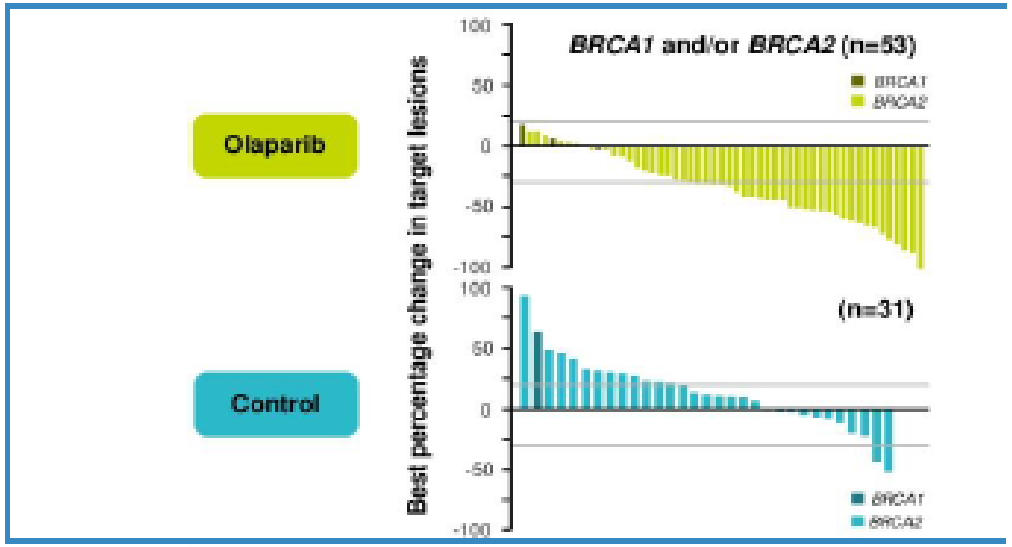
PROfound Stuy design

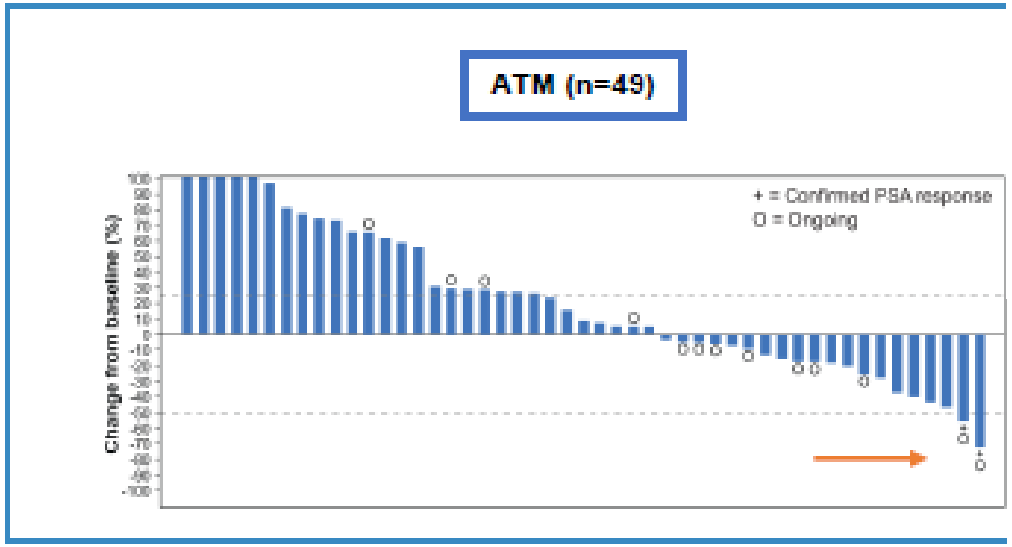


PROfound study



Hussain et al, NEJM, 2020





EMA

- OLAPARIB is indicated as monotherapy for the treatment of adult patients with mCRPC and ***BRCA1/BRCA2*** mutations (**germline and/or somatic**) who have progressed following prior therapy that included **an androgen receptor-directed therapy**

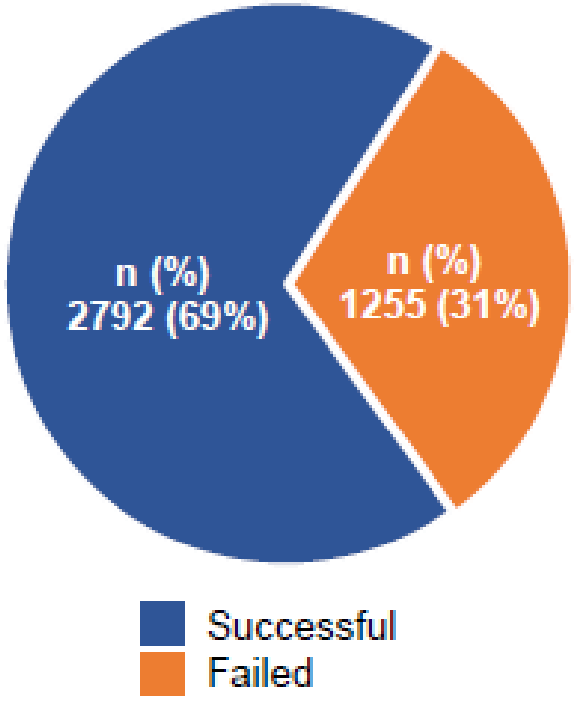
FDA

- OLAPARIB is a treatment option for patients with **mCRPC** and a pathogenic mutation (germline and/or somatic) in a HRR gene (***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51C, RAD51D or RAD54L***) who have been treated previously with **androgen receptor-directed therapy**.

- RUCAPARIB is a treatment option of patients with mCRPC and a pathogenic ***BRCA1/BRCA2*** mutation (germline and/or somatic) who have been treated with **androgen receptor-directed therapy and a taxane based chemotherapy.** If the patients is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

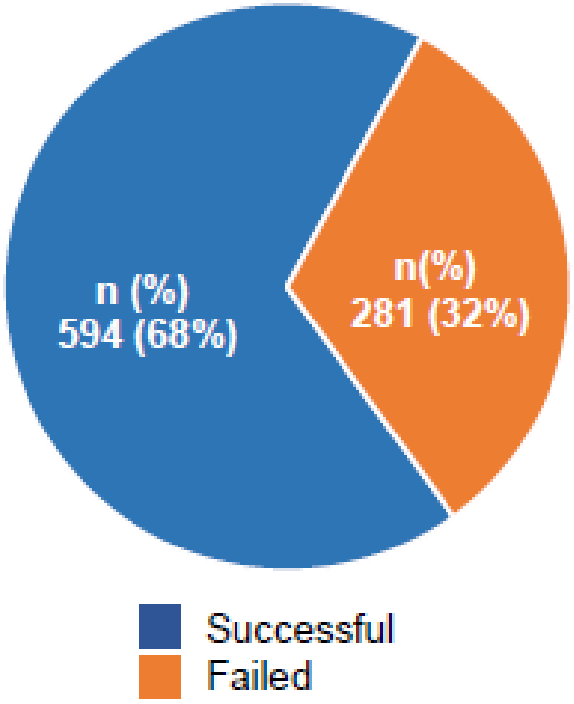
PROfound[1]

N = 4047 samples



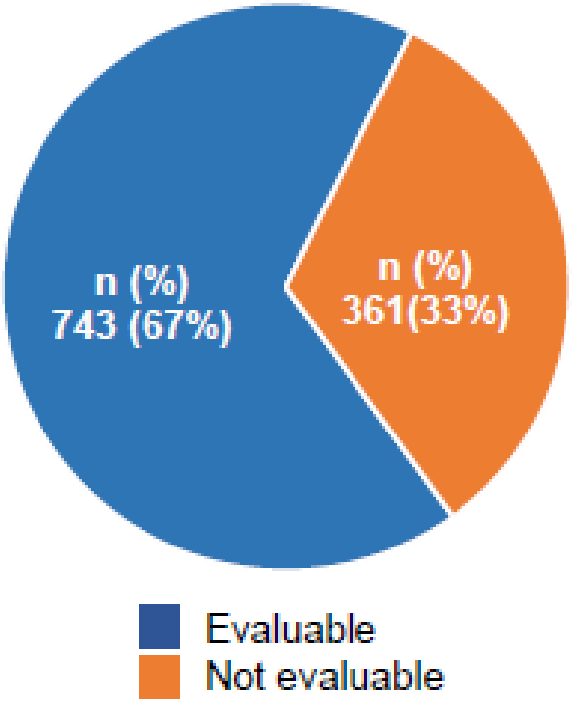
TRITON2[2*]

N = 875 samples

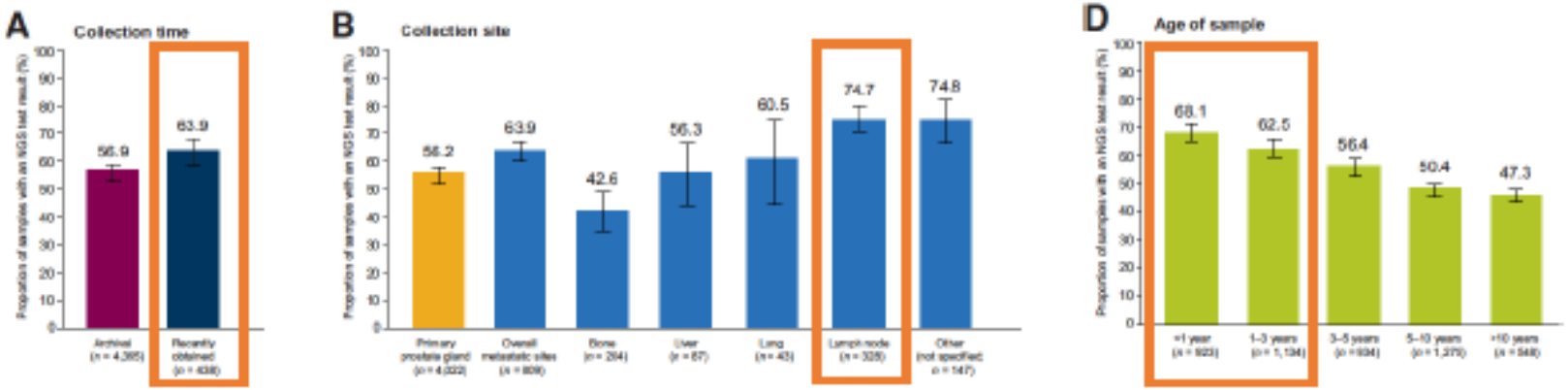


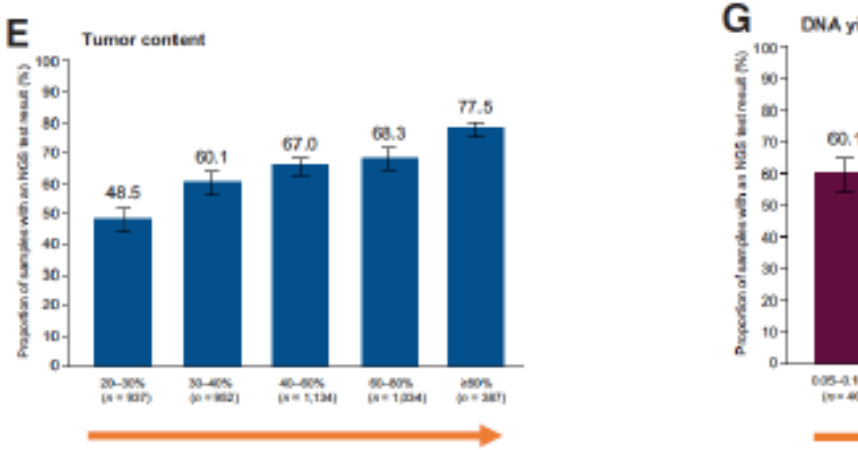
IPATential150[3]

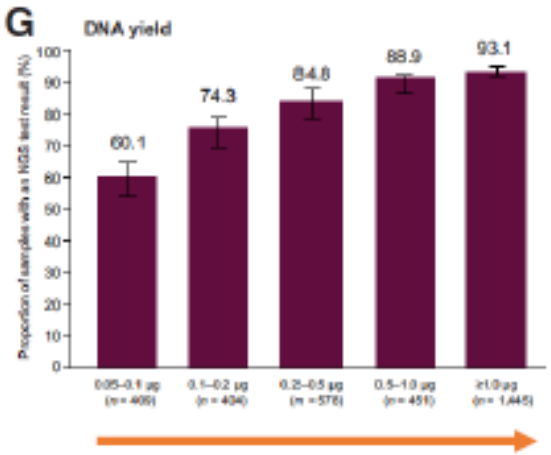
N = 1104 samples



Sample selection and optimisation of tissue collection is critical, since 30–50% of prostate cancer samples fail NGS[1–3]







- If multiple samples available, consider using the **younger samples if the tumor content is similar.**

-For samples >5 years: use the ones with **higher tumor content** and high DNA yield (i.e. Lymph nodes)

-For **newly collected samples**: optimize formalin fixation and preservation and avoid decalfcification

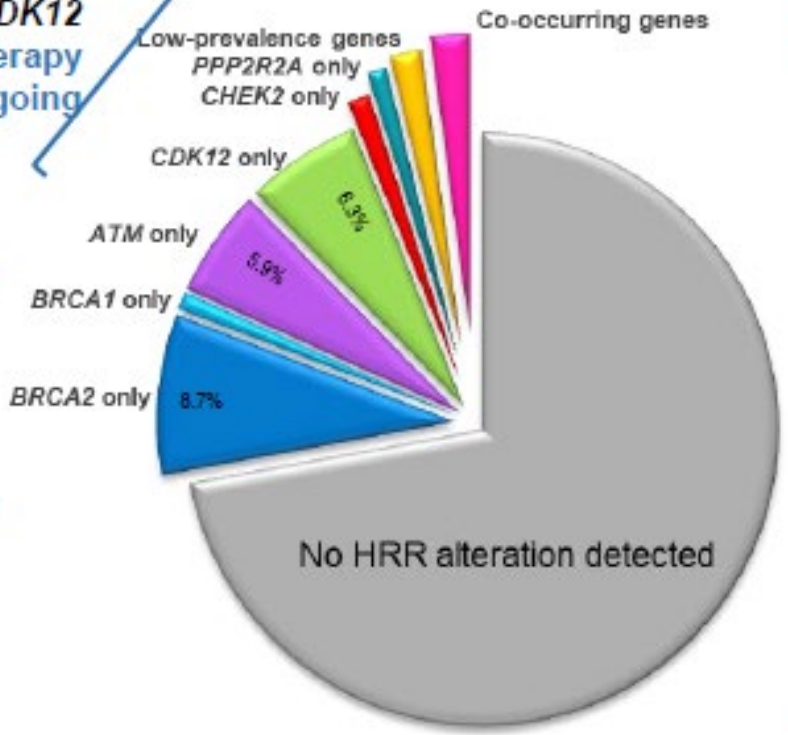
Hussain et al, Clin Cancer Res, 2022

Current scenario of iPARP by HRR alterations in mCRPC

≈ 5% Unfrequent HRR alterations
Further evidence needed

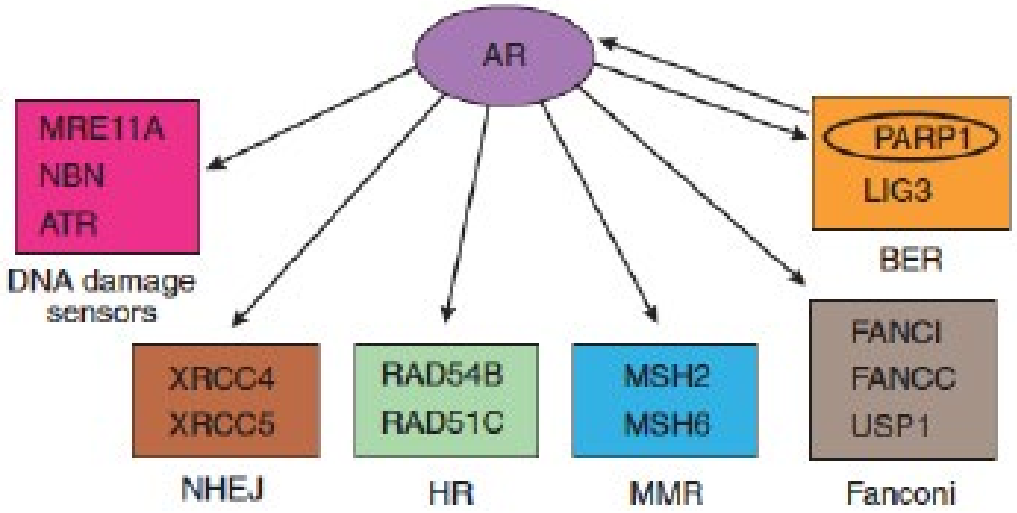
≈ 12% *ATM, CDK12*
No PARPi in monotherapy
Several combination studies ongoing

≈ 9% *BRCA1/2*
iPARP

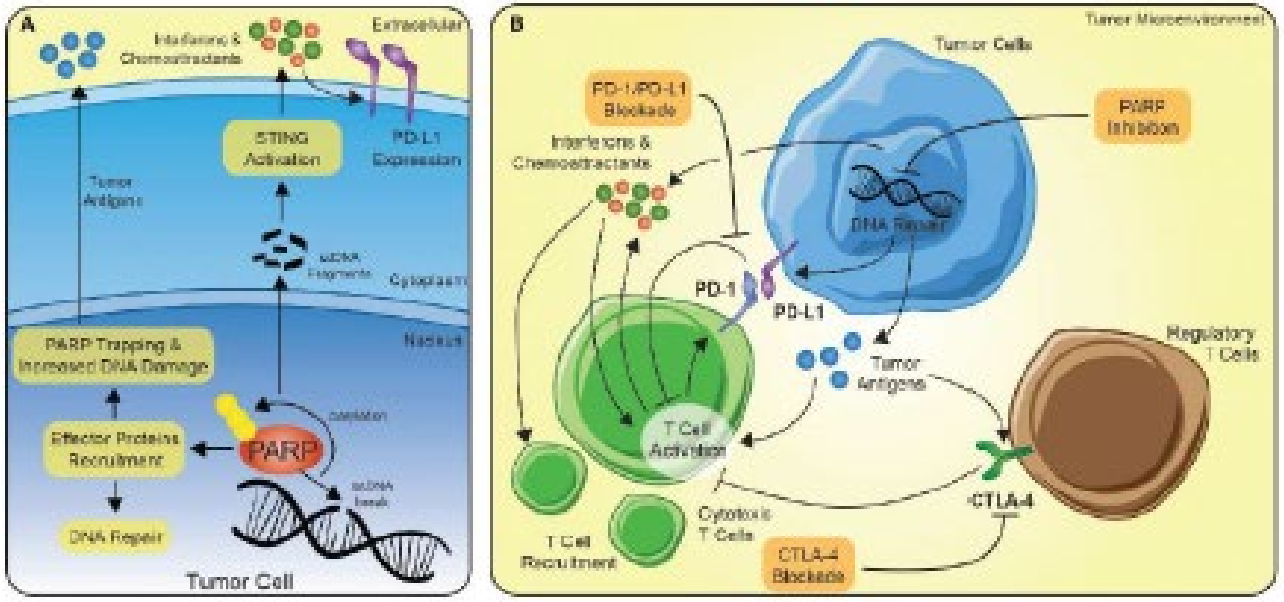


≈ 70% No HRR detected
No PARPi in monotherapy
Several combination studies ongoing

with ARSi

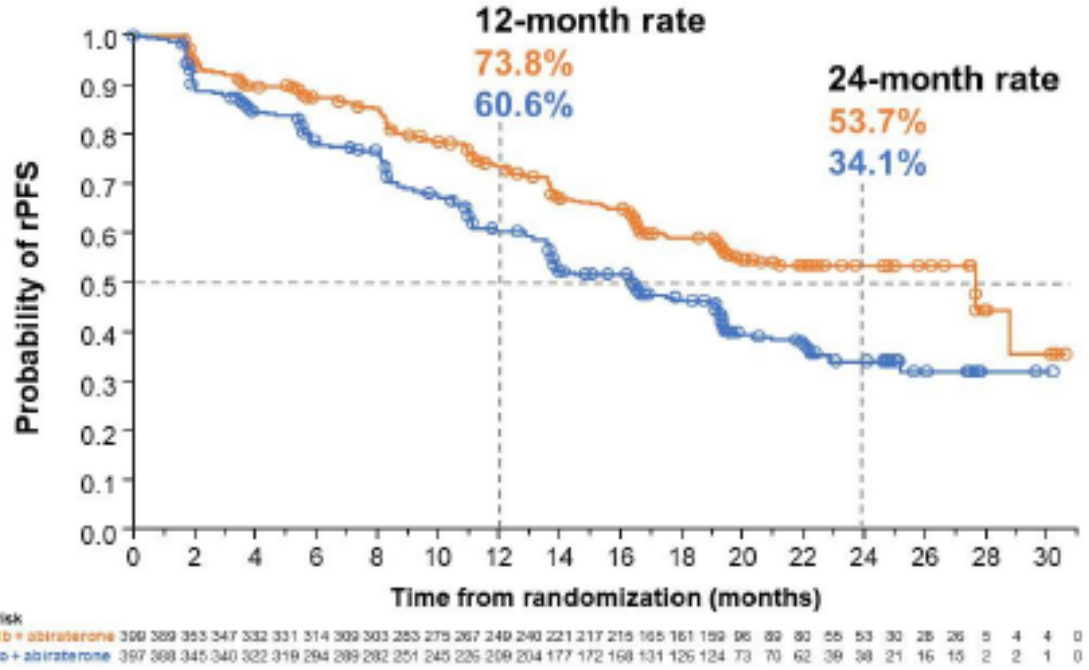


with Inmunotherapy



PROpel: rPFS by blinded independent central review*

39% risk reduction of progression or death with olaparib + abiraterone
Highly consistent with the primary analysis



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

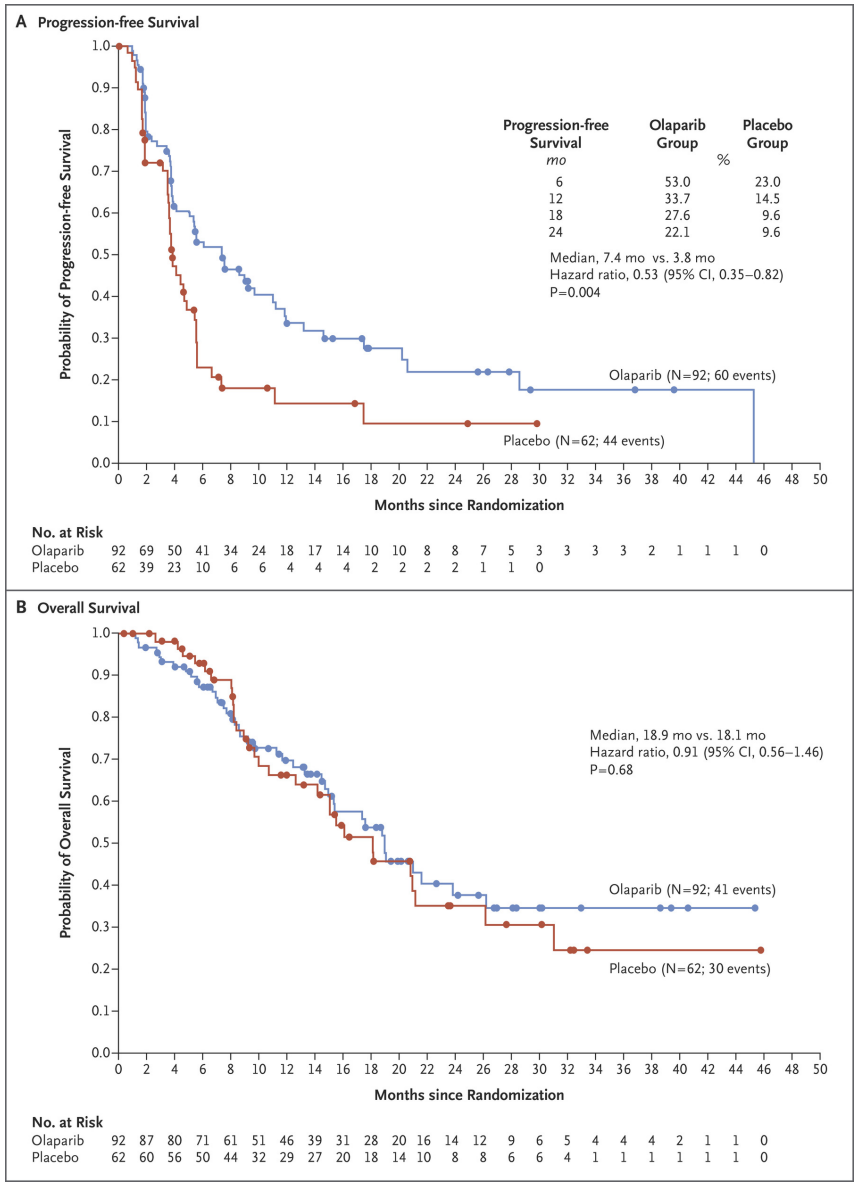
Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

*Predefined sensitivity analysis. †Nominal. ‡In combination with prednisone or prednisolone

TAKE HOME MESSAGE

- **A significant proportion of mCRPC patients (≈30%) have DDR alterations**
  - Some predict response to targeted therapies (i.e. PARPi)
  - Some may impact prognosis and response to other therapies
  - 50% of altrations in BRCA1/2 found in tumor are germline
- **Tumor profiling** will be required to select the most appropriate therapy for patients with advanced PC
  - Optimization of tissue collection
  - Metastatic biopsy is the preferred method for testing, but some early events could be detected in the primary tumors.
  - Liquid biopsy may help overcome some limitations of tissue testing
- **Investigate germline origin of alterations in cancer-predisposition genes found in tumor**
  - Although germline testing is recommended in all patients with metastatic disease
- **Potential sinergy of ARSi and PARPi** in mCRPC regardless HRR status

Pancreatic Cancer



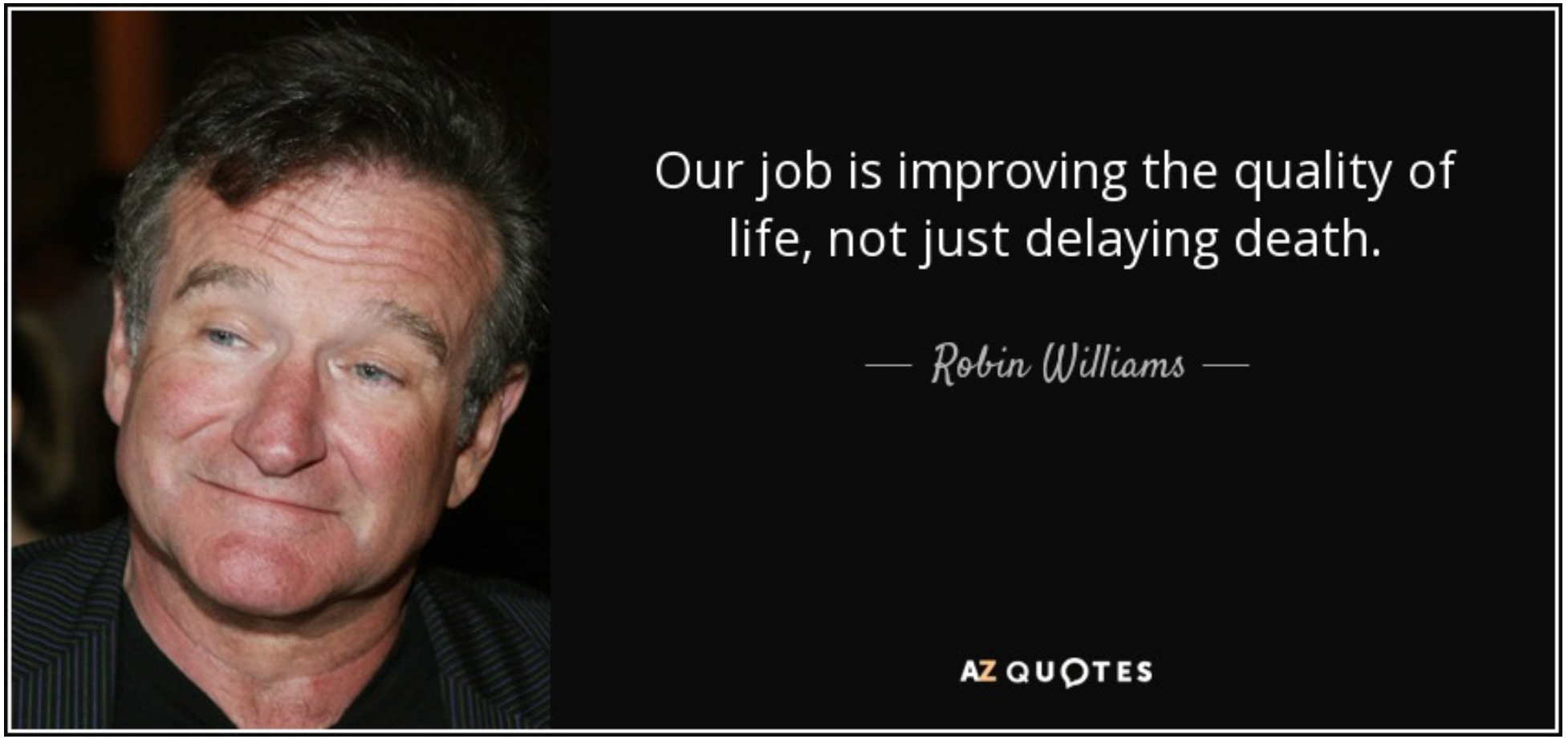
In conclusion, the POLO trial showed that maintenance olaparib provided a significant progression-free survival benefit to patients with a germline BRCA mutation and metastatic pancreatic cancer that had not progressed during platinum-based chemotherapy.

No dell'Aifa alla rimborsabilità del farmaco per cancro al pancreas

Take Home Message

- I PARPi sono una classe di farmaci che ha dimostrato un'efficacia in diversi tumori solidi, con una sorta di effetto di classe sia per attività sia per profilo di tollerabilità
- Ad oggi l'unico fattore predittivo di risposta è «off-target»
- Pur potendo determinare l'insorgenza di MSD/AML, tale evento rimane raro anche nel lungo termine
- Si stanno studiando associazioni per valutare un aumento dell'attività e dell'efficacia dei PARPi

Questions?


Our job is improving the quality of life, not just delaying death.
— Robin Williams —
AZ QUOTES