foro debate oncología

Zaragoza 26-29 septiembre 2023

Inhibidores de PARP

Estado del arte y alternativas futuras en *Cáncer de mama*

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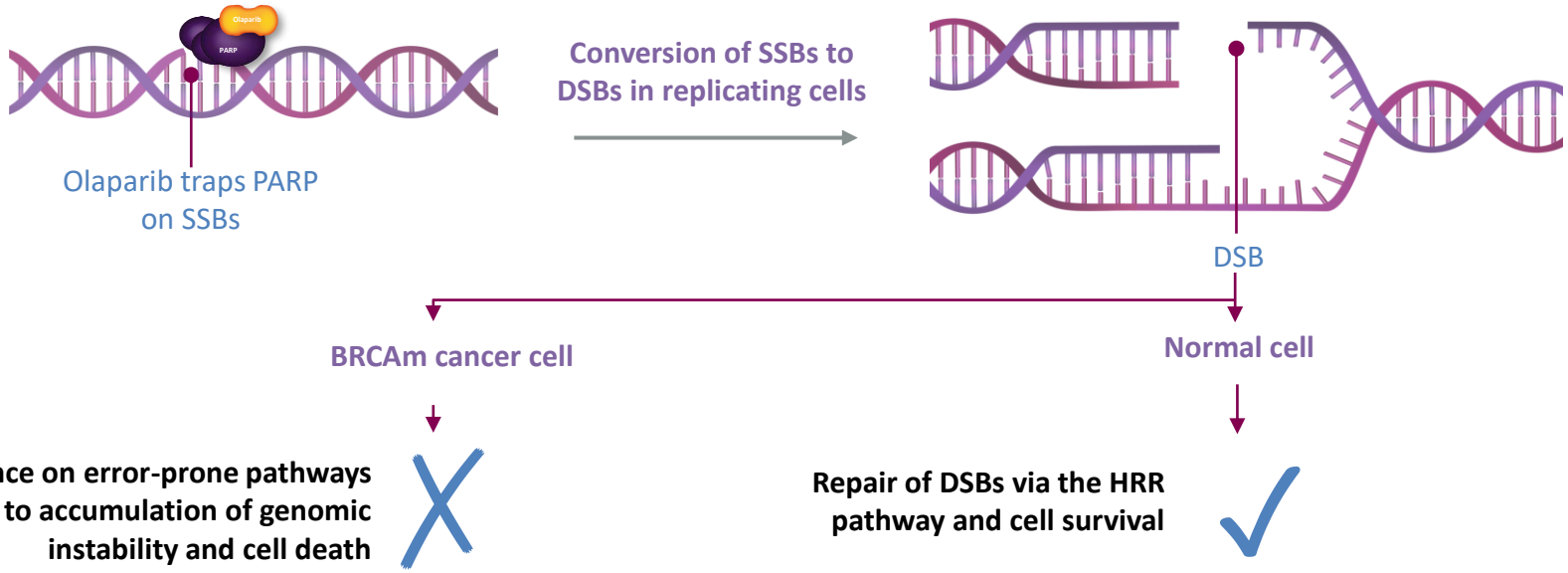
DISCLOSURE INFORMATION

- **Consultant or Advisory Role:** Astra-Zeneca, MSD, Novartis, Pfizer.
- **Speaking:** Astra-Zeneca, Lilly, Novartis, Pfizer.
- **Travel support:** Astra-Zeneca, Lilly, Novartis, Pfizer.

Approximately 5–35% of breast cancer patients have a BRCAm that may be targeted with PARPi therapy

Mutations in BRCA1 or BRCA2 render cells sensitive to treatment with PARPi agents[2,3]



The ability of the targeted agent olaparib to improve outcomes for those patients with a gBRCAm is being investigated.

BRCAm=BRCA mutation; DSB=double-strand break; gBRCAm=germline BRCA mutation; HRR=homologous recombination repair; PARPi=PARP inhibitor; SSB=single-strand break

1. Armstrong N, et al. *Clin Epidemiol.* 2019;11:543–561; 2. O'Connor MJ. *Mol Cell.* 2015;60:547–560; 3. Drew Y, et al. *Br J Cancer.* 2015;113(suppl 1):S3–S9;

Prevalence varies between key clinical and demographic subgroups

Prevalence in the 488 cases: 6.1% (4.2-8.7)

Prospective series of 488 women with invasive BC

Table 5. Deleterious Mutations by Breast Cancer Subtype (N = 488)

	Patients With TNBC Mutation (n = 87)		Patients With ER-Positive/ HER2-Negative Mutation (n = 301)		Patients With ER-Negative/HER2-Positive Mutation (n = 37)		Patients With ER-Positive/HER2-Positive Mutation (n = 63)	
Genes	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
Any deleterious mutation*	15	17.2 (10.0 to 26.8)	26	8.6 (5.7 to 12.4)	4	10.8 (3.0 to 25.4)	7	11.1 (4.6 to 21.6)
Genes related to breast cancer*	14	16.1 (9.1 to 25.5)	24	8.0 (5.2 to 11.6)	4	10.8 (3.0 to 25.4)	7	11.1 (4.6 to 21.6)
BRCA1 or *BRCA2*	12	13.8 (7.3 to 22.9)	15	5.0 (2.8 to 8.1)	2	5.4 (0.7 to 18.2)	1	1.6 (0.04 to 8.5)
*BRCA1**	11	12.6 (6.5 to 21.5)	5	1.7 (0.5 to 3.8)	2	5.4 (0.7 to 18.2)	0	0.0 (0.0 to 5.7)
*BRCA2**	1	1.1 (0.03 to 6.2)	10	3.3 (1.6 to 6.0)	0	0.0 (0.0 to 9.5)	1	1.6 (0.04 to 8.5)

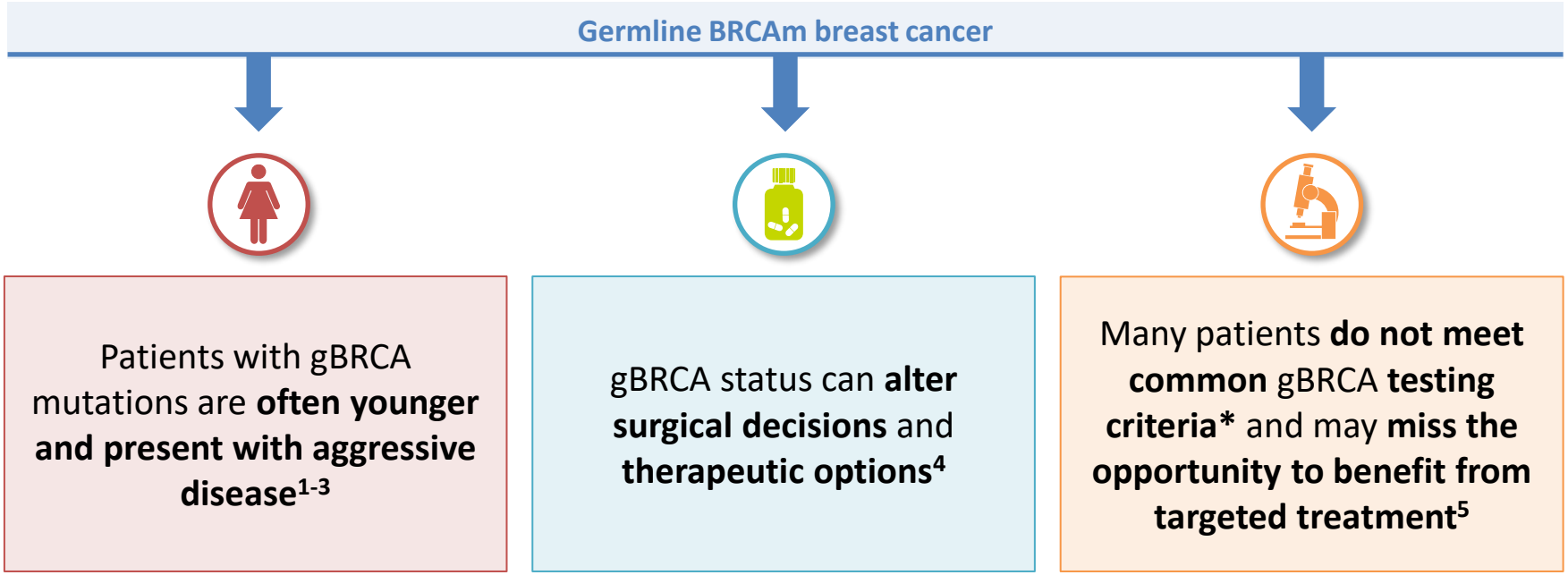
- **Dx BC < 46 yrs: 12.2% (7.8-17.9)**
- Dx BC 46-60 yrs: 3.0% (1.1-6.5)
- Dx BC >60 yrs: 1.8% (0.2 -6.5)

- **TNBC: 13.8% (7.3-22.9)**
- ER+, HER2 neg: 5.0% (2.8-8.1)
- HER2+, ER neg: *5.4% (0.7 -18.2)*
- HER2+, ER+ : 1.6% (0.04-8.5)

BRCAm are more prevalent in TNBC than ER-positive breast cancer[1]
PARPi can harness the deficiency in functional BRCAm, as demonstrated in metastatic breast cancer[2]

BRCAm=BRCA mutation; ER=hormone receptor; NR=not reported; PARPi=PARP inhibitors; TNBC=triple negative breast cancer;
1. Tung et al. J Clin Oncol, 2016 , 2. Armstrong N, et al. *Clin Epidemiol.* 2019;11:543–561; 3. Robson M, et al. *Ann Oncol*. 2019;30:558–566

Detection of a germline BRCAm significantly impacts a patient's care plan



*Such as family history or age of diagnosis

1. Baretta Z, et al. Medicine. 2016;95:e4975. 2. Aleskandarany M, et al. Breast Cancer Res Treat. 2015;150:81–90. 3. Becourt S, et al. J Clin Oncol. 2018;36(suppl; abstr e13522). 4. Tung N & Garber. Brit J Can. 2018;119:141–152.; 5. Rummel S, et al. Cancers. 2020;12:234.

Unmet needs in patients with gBRCA+ BC

In the absence of large prospective cohort studies, a consensus is unlikely to be reached

- Patients with a gBRCA+ are younger at diagnosis, have a higher tumour grade, more contralateral / ipsilateral disease, and a higher incidence of CNS metastases[2–6]
- Studies disagree on whether the risk of breast cancer recurrence is greater in patients with a gBRCA+ than in those with sporadic early breast cancer[7–9]
- There is an increased risk of second breast cancer and/or ovarian cancer in gBRCA+ vs. sporadic EBC patients[10]
- Studies have reported conflicting results for the impact of a gBRCA+ on OS[7,11–15]
- There are currently targeted treatments available for patients with gBRCA+ MBC, that are being investigated in the (neo) adjuvant setting of EBC

1. Holleczek B, et al. BMC Cancer. 2019;19:520; 2. Becourt et al. *J Clin Oncol.* 2018;36(suppl): abstract e13522; 3. Aleskandarany M, et al. *Breast Cancer Res Treat.* 2015;150:81–90; 4. Valachis A, et al. *Breast Cancer Res Treat.* 2014;144(3):443–455; 5. Kriege M, et al. *Cancer.* 2012;118:899–907; 6. Song Y, et al. *Cancer.* 2020;126(2):271–280; 7. Bordeleau L, et al. *Breast Cancer Res Treat.* 2010;119:13–24; 8. Quek R, et al. *J Clin Oncol.* 2018;36(suppl):abstract 12575; 9. Liu M and Wang S. Presented at SABCS 2019. 10–14 September. San Antonio, Texas. Poster #P3-08-51; 10. de Roodenbeke MD, et al. *Semin Oncol.* 2020;47:243–248; 11. Copson ER, et al. *Lancet Oncol*. 2018;19:169–180; 12. Klajer E, et al. *Ann Oncol.* 2018;29(suppl 8):viii68; 13. Quek R, et al. *J Clin Oncol.* 2018;36(suppl);abstr e12575; 14. Baretta Z, et al. *Medicine (Baltimore)*. 2016;95:e4975; 15. Zhu Y, et al. *Oncotarget*. 2016;7:70113–70127; 16. OlympiA. Available at: https://clinicaltrials.gov/ct2/show/NCT02032823. Accessed April 2021

STATE OF THE ART OF PARP INHIBITORS IN METASTATIC BREAST CANCER

HR+ HER2-neg MBC

Triple negative MBC

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
		Sacituzumab govitecan[f] (Category 1, preferred)
	Any	Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

OlympiAD
OLaparib in ADvanced BRCAm breast cancer

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

EMBRACA

A phase 3 trial comparing talazoparib to TPC in patients with MBC and a g*BRCA*-mutation

OlympiAD trial – Olaparib

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

R 2:1

Olaparib
300 mg tablets bd

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

EMBRACA trial – Talazoparib

Patients with locally advanced or metastatic HER2 negative BC and a germline BRCA1/2 mutation

Stratification factors
- Number of prior CT regimens (0 or ≥1)
- TNBC or HR+
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

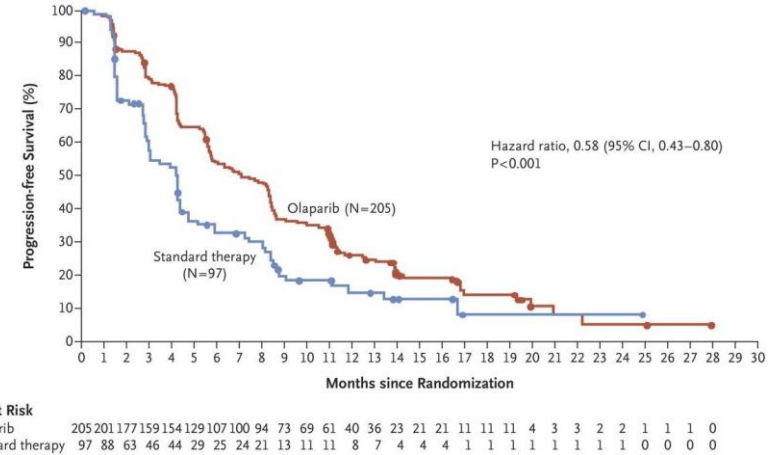
Physicians choice of therapy (PCT): capecitabine, eribulin, gemcitabine or vinorelbine

Robson M, *et al*. N Engl J Med 2017; Litton JK, *et al*. N Engl J Med 2018.

PFS RESULTS

OlympiAD
OLaparib in ADvanced BRCAm breast cancer

50% TN; A/T pretreated; 71% prior CT for MBC; TN: non-platinum resistant



No. at Risk

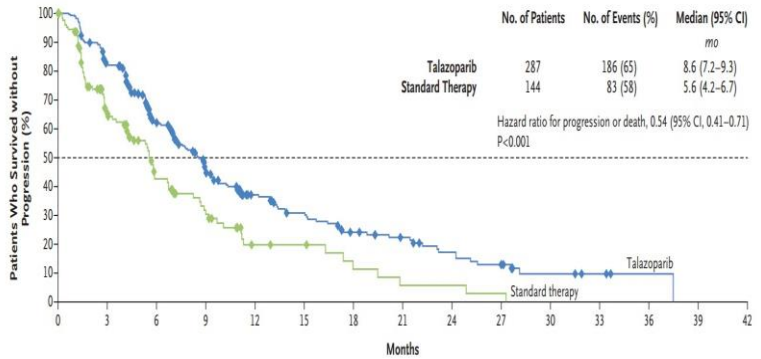
Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Median PFS **7.0 vs 4.8 months**
HR 0.58, 95% CI: 0.43, 0-80; P<0.001
TNBC: HR 0.43, 95% CI: 0.29, 0.63

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

EMBRACA

44% TN; A/T pretreated; 62% prior CT for MBC; TN: non-platinum resistant



No. at Risk (events/cumulative events)

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
Standard therapy	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

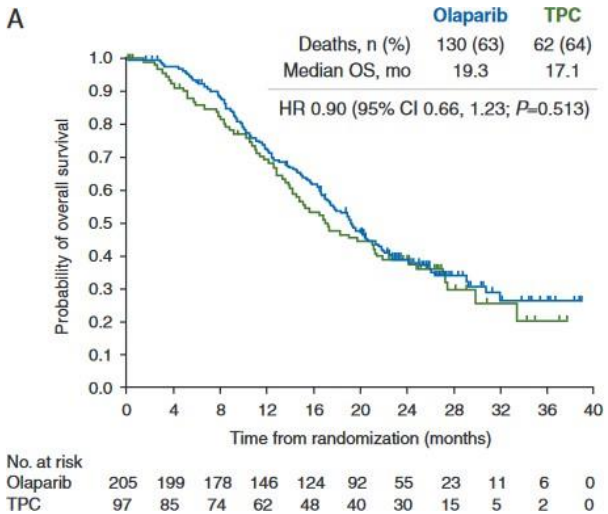
Median PFS **8.6 vs 5.6 months**
HR 0.54, 95% CI: 0.41.0, 71; P<0.001
TNBC: HR 0.60, 95% CI: 0.41, 0.87

1. From N Engl J Med 2017, Robson M, *et al.* Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation, 377:523-533. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 2. From N Engl J Med 2018, Litton JK, *et al.* Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation 379:753-763. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

OS RESULTS

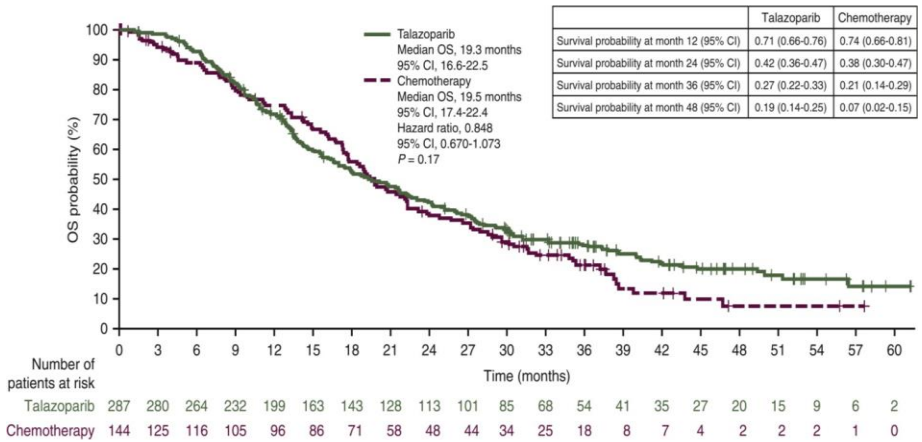
OlympiAD
OLaparib in ADvanced BRCAm breast cancer

OlympiAD was not powered to show an OS benefit[1]



- HR: 0.90 (95% CI: 0.66, 1.23; P=0.513)
- 1st line HR: 0.51 (95% CI: 0.29, 0.90; P=0.02)

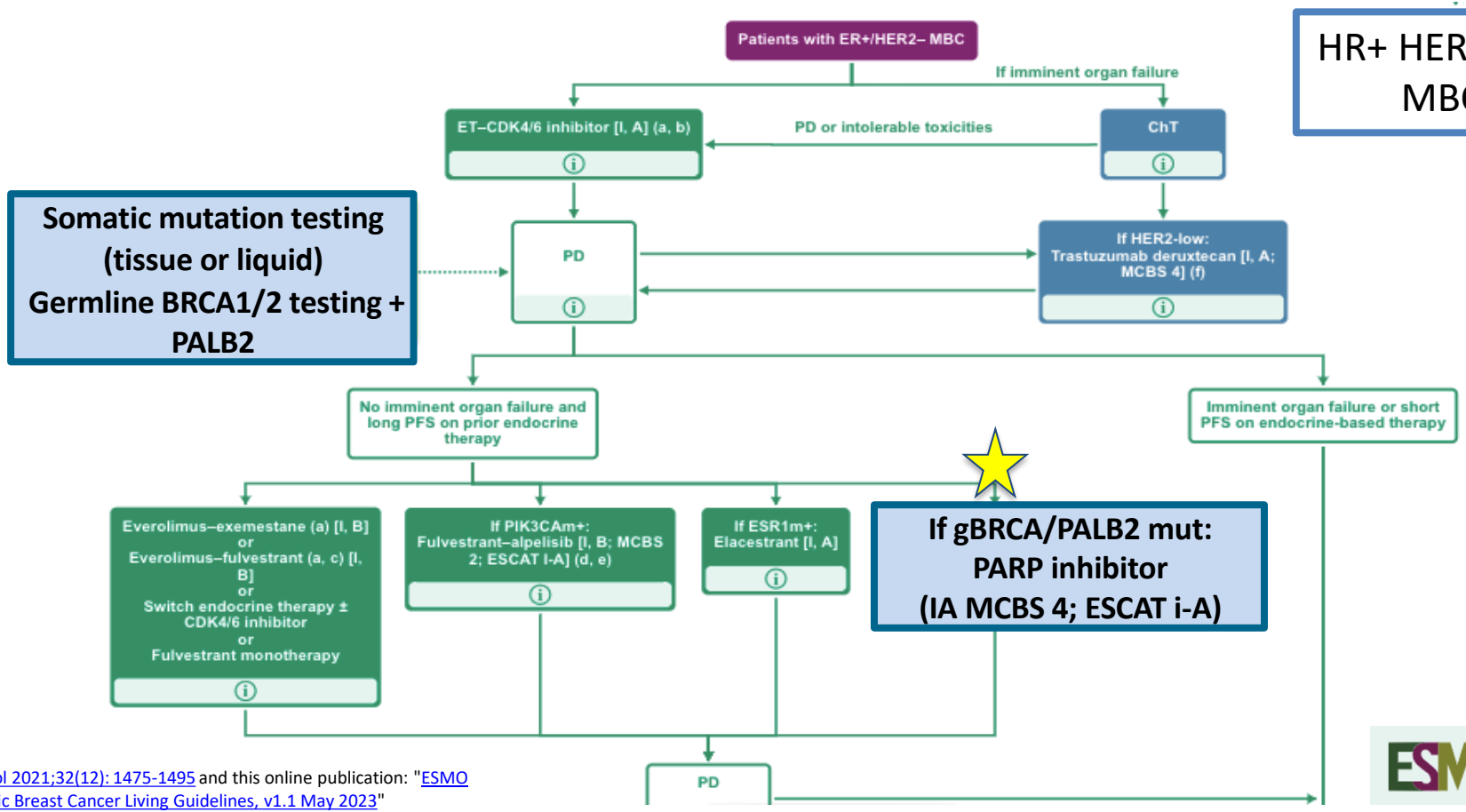
EMBRACA



- HR: 0.848 (95% CI: 0.670, 1.073; P=0.17)
- 33% of patients in CT arm received subsequent PARPi
  - Adjusted HR: 0.756 (95% CI: 0.503,1.029)

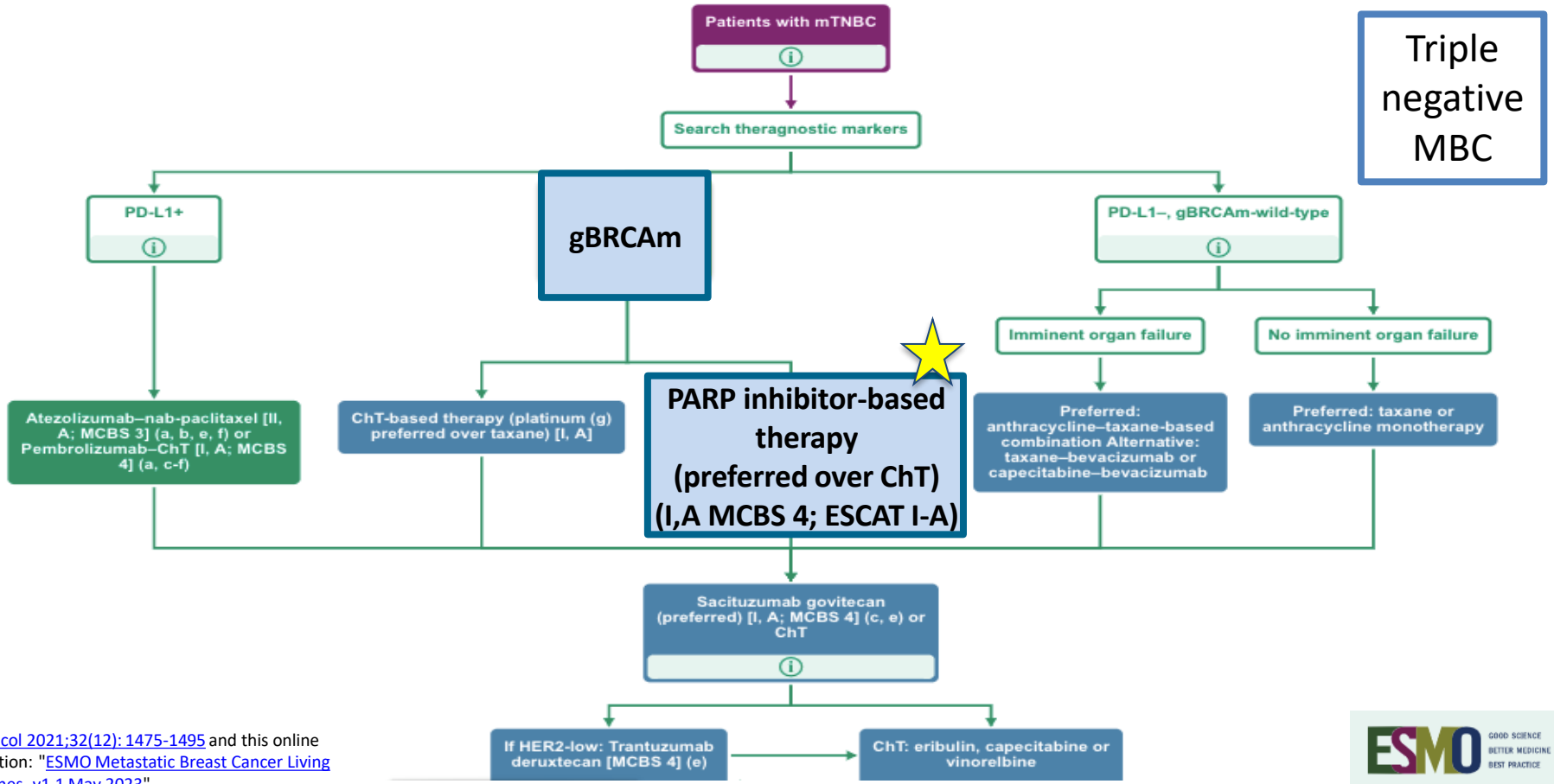
ESMO Metastatic Breast Cancer Living Guideline > ER-positive HER2-negative Breast Cancer

HR+ HER2-neg MBC



Ann Oncol 2021;32(12): 1475-1495 and this online publication: "ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023"

ESMO Metastatic Breast Cancer Living Guideline > Triple-negative Breast Cancer



Ann Oncol 2021;32(12): 1475-1495 and this online publication: "ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023"

PARP INHIBITORS MOVING TO THE ADJUVANT SETTING

Some EBC patients at high risk of recurrence may receive additional treatment beyond their (neo)adjuvant treatment

Post-neoadjuvant treatment:

- Adjuvant treatment for patients that **do not achieve a pCR** after neoadjuvant therapy[1]
- Currently available treatments for **high risk of recurrence:** chemotherapy (including capecitabine for TNBC), iCDK and ET (for ER+, HR2 neg EBC) [3,4,6]

In OlympiA, patients at high risk of recurrence received olaparib or placebo for up to 1 year following surgery and neoadjuvant or adjuvant chemotherapy[5]

Extended adjuvant treatment:

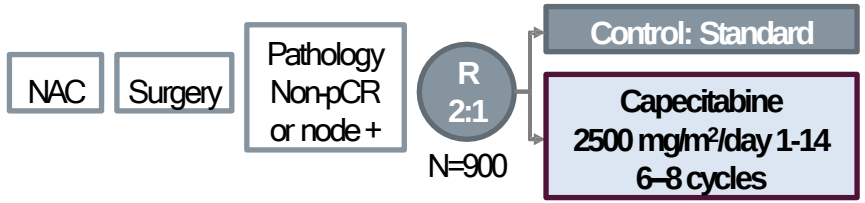
- Treatment given for **more than 5 years**[2]
- Currently available treatments: ASCO and ESMO guidelines now recommend that HR-positive HER2-negative patients receive ET for up to 10 years[3,4]*

*NCCN guidance to follow

ASCO=American Society of Clinical Oncology; ESMO=European Society for Medical Oncology; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; NCCN=National Comprehensive Cancer Network; pCR=pathologic complete response; TNBC=triple negative breast cancer

1. Caparica R, et al. *Ther Adv Med Oncol.* 2019;11:1758835919827714; 2. Vinayak S and Davidson NE. *Oncology (Williston Park).* 2019;33(6):243–246; 3. Burstein H, et al. *J Clin Onc*. 2019;37(5):423–438; 4. Cardoso F, et al. *Ann Oncol.* 2019;30:1194–1220; 5. OlympiA; 6. MONARCH-E; 7. NATALEE.

CREATE-X: Capecitabine may be offered to TN patients who do not achieve a pCR after optimal neoadjuvant ChT

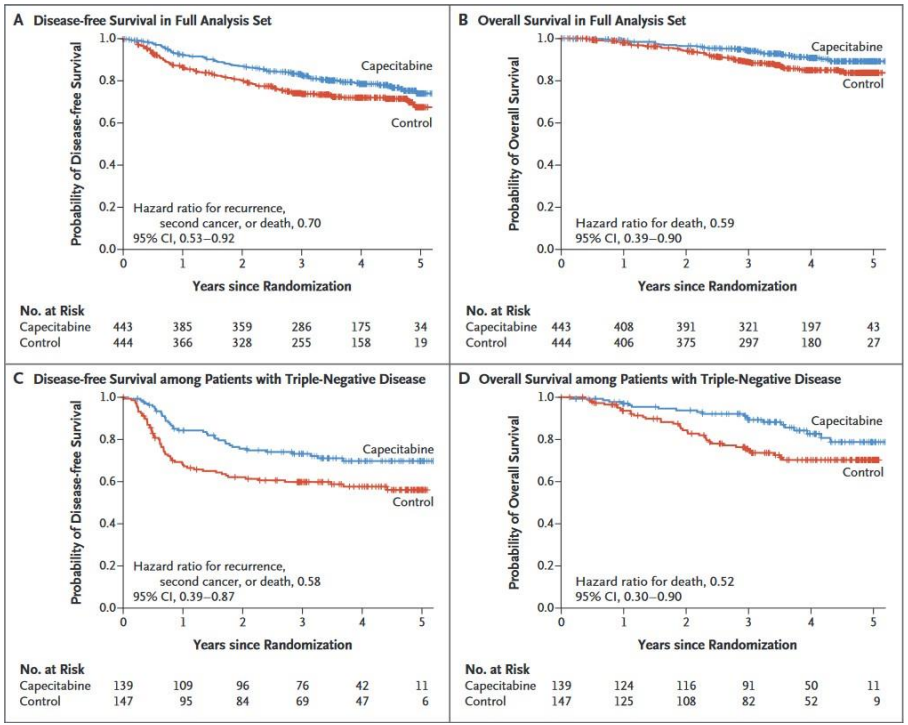


Stratification factors
- ER, age, NAC, ypN, 5FU and institution

Standard therapy
HR+: Hormone therapy
HR-: No further systemic treatment

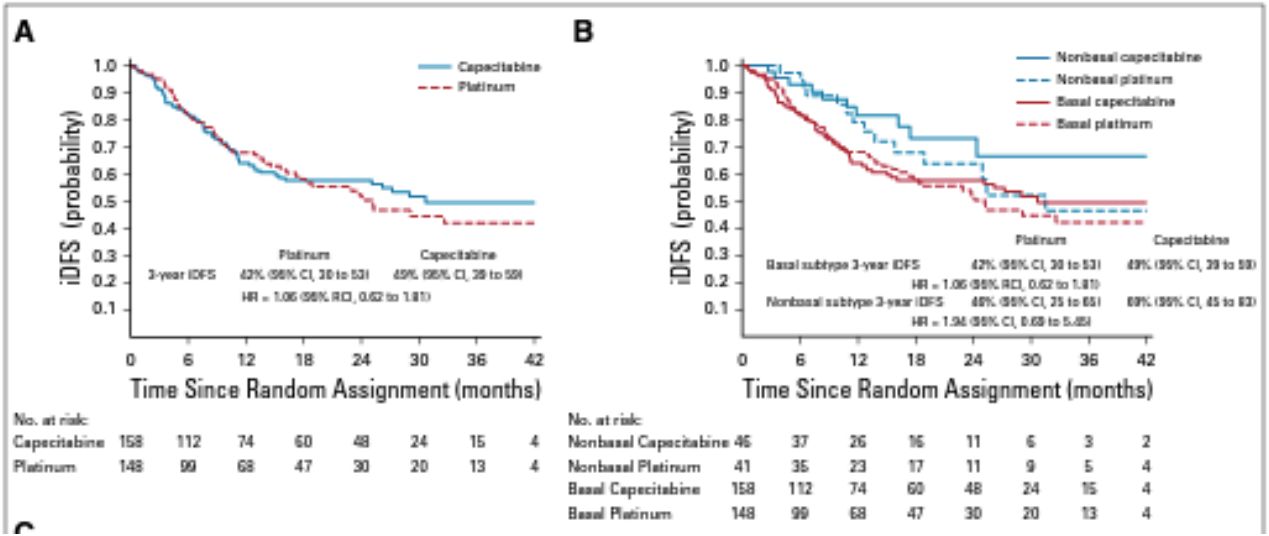
- Possible pharmacogenomic effect
- Amount of NACT received not specified
- Capecitabine use in adjuvant setting is off-label

ESMO 2019: This option may be offered to TN patients who do not achieve a pCR after optimal neoadjuvant ChT [I, B]



Lower capecitabine dose may be effective (data from Asian patients)*; 2000 mg/m²/day 1-14 commonly used in US ad EU.

ECOG-ACRIN EA1131:
Capecitabine vs Carboplatine in NON-PCR TNBC patients



N=308 clinical stage II or III basal-like TNBC with ≥1 cm RD in the breast post NACT[2]

100% taxane; 86% anthra; 40% other
~50% ypN+
~60% ≥ypT2

(ITT CREATE-X 60% ypN+, 42% marked treatment responses to NAC)

Kaplan-Meier estimates of iDFS

- Median follow-up of 20 months and 120 iDFS events
- Three-year iDFS in patients with basal subtype TNBC were similar across both treatment arms

Platinum agents do not improve outcomes in patients with basal subtype TNBCRD post-NAC and are associated with more severe toxicity when compared with capecitabine.

1. Mayer IA, *et al.* J Clin Oncol 2021;39(23):2539-2551; 2. Lluch A, *et al.* J Clin Oncol 2020.

KEYNOTE-522, PEMBROLIZUMAB + CT in previously untreated early TNBC[1–4]

KEYNOTE-522 study design[1–3]

- Age ≥18 years
- Early-stage TNBC
- cT1 N1–2 or T2–4 N0–2
- ECOG PS 0–1

N=1174
R 2:1

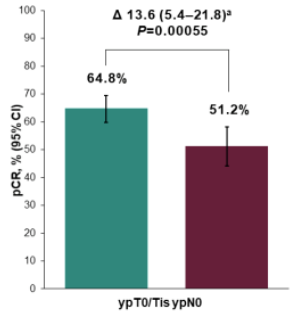
Neoadjuvant 4 cycles	Neoadjuvant 4 cycles		Adjuvant 9 cycles
Pembrolizumab + carboplatin + paclitaxel	Pembrolizumab + doxorubicin / epirubicin + cyclophosphamide	SURGERY	Pembrolizumab
Placebo + carboplatin + paclitaxel	Placebo + doxorubicin / epirubicin / + cyclophosphamide		Placebo

Primary endpoints:
- Locally assessed pCR (ypT0/Tis ypN0) in ITT
- Investigator-assessed EFS in ITT

Secondary endpoints:
- pCR (ypT0 ypN0 and ypT0/Tis) in ITT
- pCR in PD-L1–positive
- EFS in PD-L1–positive
- OS in ITT and PD-L1–positive

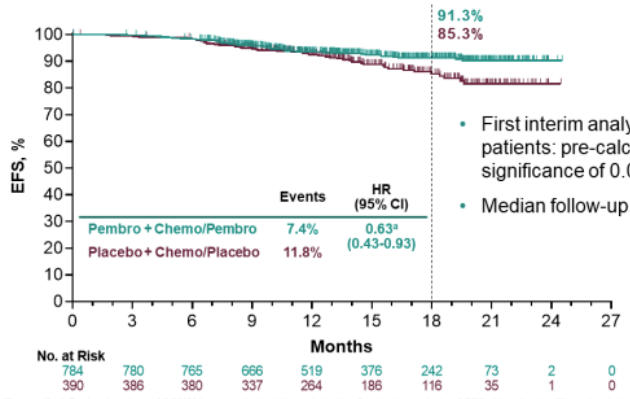
Stratified by:
- *Nodal status (+ vs. -)*
- *Tumour size (T1/T2 vs. T3/T4)*
- *Carboplatin schedule (QW vs. Q3W)*

Definitive pCR Analysis



- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

First Pre-planned Interim Analysis for EFS



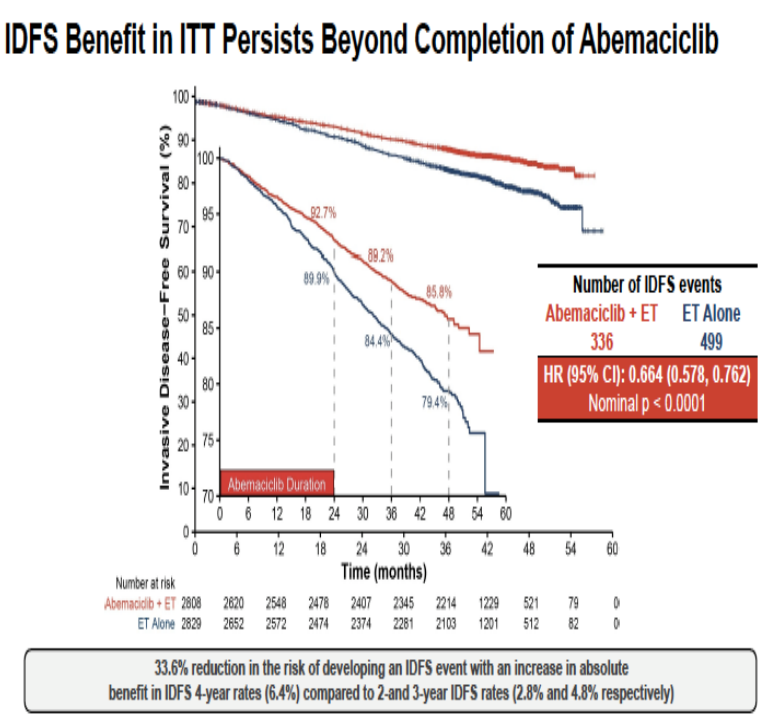
- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

[a]Pre-specified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

1. Schmid P, et al. *N Engl J Med*. 2020;382(9):810–821; 2. KEYNOTE-522. Available at: https://clinicaltrials.gov/ct2/show/NCT03036488. Accessed April 2021; 3. Schmid P, et al. Presented at ESMO Annual Congress 2019. 8–12 September. Barcelona, Spain. Presentation #LBA8_PR;

monarchE & NATALEE are investigating CDK4/6i agents in HR-positive HER2-negative EBC at high risk of recurrence[11–4]

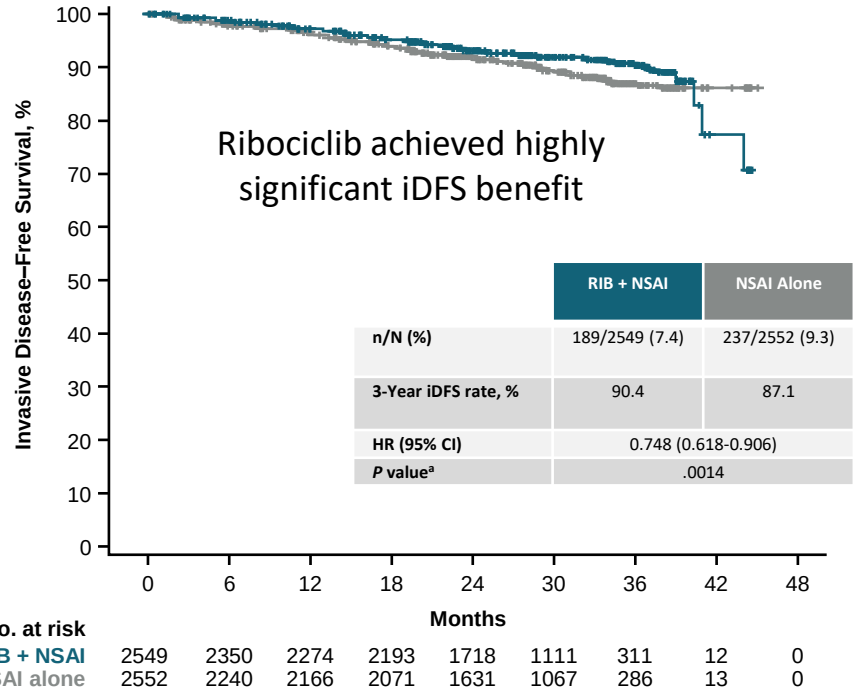
monarchE



Stephen Johnston, MD, PhD

NATALEE

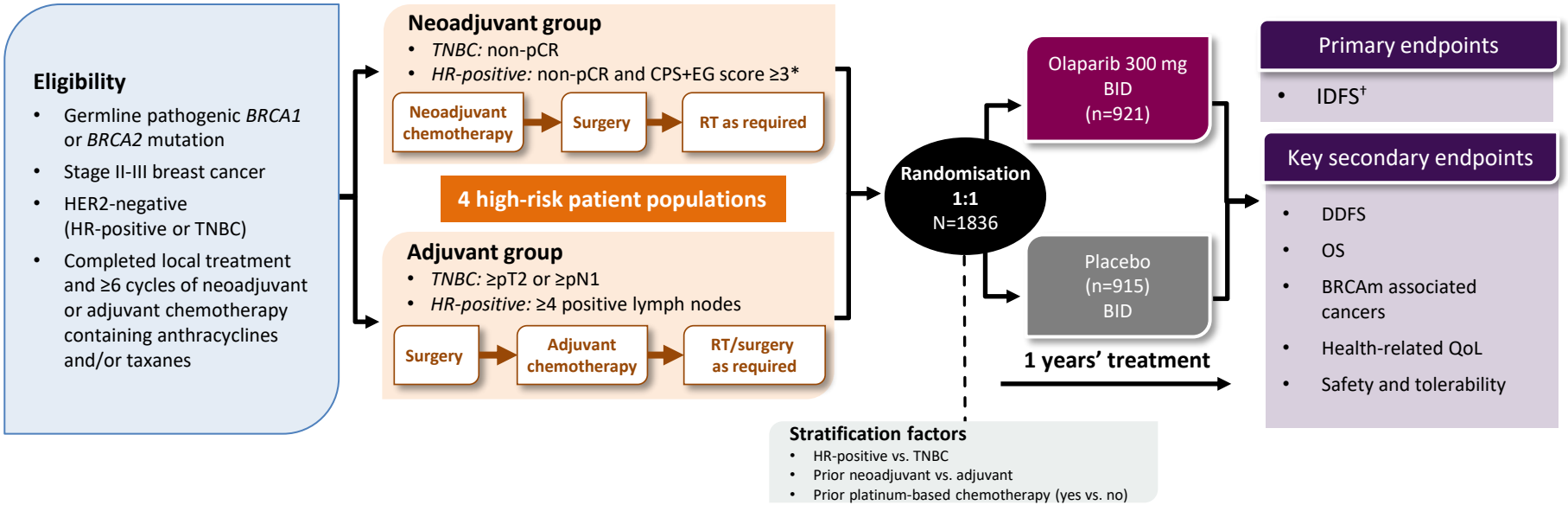
Median FUP for 27.7 m



	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

Dennis Slamon MD, PhD

OlympiA is a randomised Phase III study of olaparib vs. placebo as adjuvant treatment in patients with gBRCAm HER2-negative non-metastatic breast cancer at high risk of recurrence[1]



*CPS+EG score incorporates pretreatment clinical stage, oestrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy
†By STEEP system[2]
BID=twice a day; CPS+EG=clinical and pathological stage, oestrogen receptor, and nuclear grade; DDFS=distant disease-free survival; HR=hormone receptor; HER2=human epidermal growth factor receptor 2; gBRCAm=germline BRCA mutation; IDFS=invasive disease-free survival; OS=overall survival; pCR=pathologic complete response; QoL=quality of life; RT=radiotherapy; TNBC=triple negative breast cancer

1. Tutt A, et al. *N Engl J Med.* 2021. Epub ahead of print. DOI: 10.1056/NEJMoa2105215; 2. Hudis CA. *J Clin Oncol* 2007;25:2127–2132

A number of definitions are used to define a high-risk of recurrence in early breast cancer[1–5]

The OlympiA study enrolled gBRCAm patients at high risk of recurrence according to:[6]

OlympiA eligibility criteria[6]

Receipt of olaparib	HR-positive HER2-negative breast cancer	TNBC
Post-neoadjuvant (following NACT and surgery)	Did not achieve pCR and CPS&EG score ≥3	Did not achieve pCR
Adjuvant (following surgery and adjuvant chemotherapy)	≥4 positive lymph nodes	≥pN1 and any tumour size or pN0 with ≥pT2

✓ **Tumour staging[1]**

✓ **Presence of positive nodes[1]**

✓ **Failure to achieve a pCR after NACT[2]**

✓ **High CPS&EG score[3]**

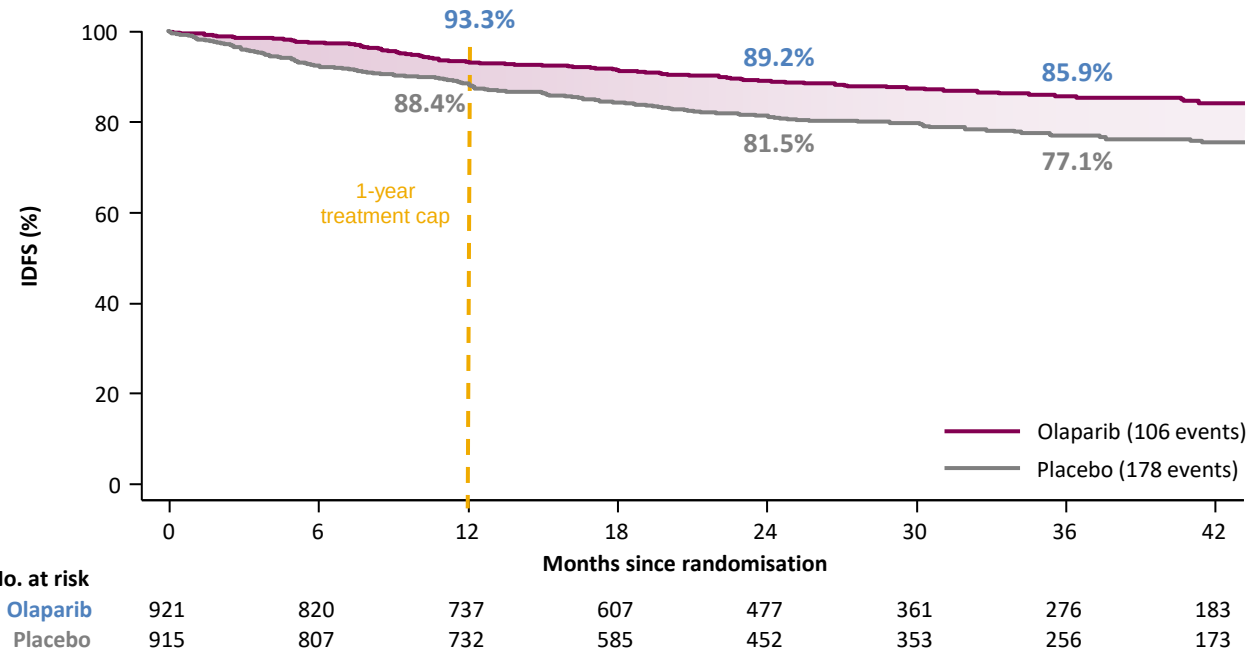
X **Molecular tests[4] and benefit-risk calculators[5]**

CPS&EG=clinical and post-treatment pathologic stage and oestrogen receptor and nuclear grade; gBRCAm=germline BRCA mutation; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; NACT=neoadjuvant chemotherapy; pCR=pathologic complete response; pN=pathological node status; pT=pathological tumour status TNBC=triple negative breast cancer

1. Urru SAM, et al. *BMC Cancer*. 2018;18:56; 2. Cortazar P, et al. *Lancet*. 2014;384:164–172; 3. Abdelsattar JM, et al. *Ann Surg Oncol*. 2016;23:3206–3211; 4. Cardoso F, et al. *Ann Oncol*. 2019;30:1194–1220; 5. Shachar S and Muss H. *NPJ Breast Cancer*. 2016;2:16011; 6. AstraZeneca 2018. OlympiA clinical study protocol, version 5 (18 May 2018)

Olaparib reduced the risk of invasive recurrence or death by 42% vs. placebo in OlympiA

Primary endpoint: IDFS in the ITT



No. at risk								
Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

IDFS

Hazard ratio 0.58†
99.5% CI 0.41–0.82
p<0.001

3-year IDFS rate*

Olaparib (n=921) **85.9%**

Placebo (n=915) **77.1%**

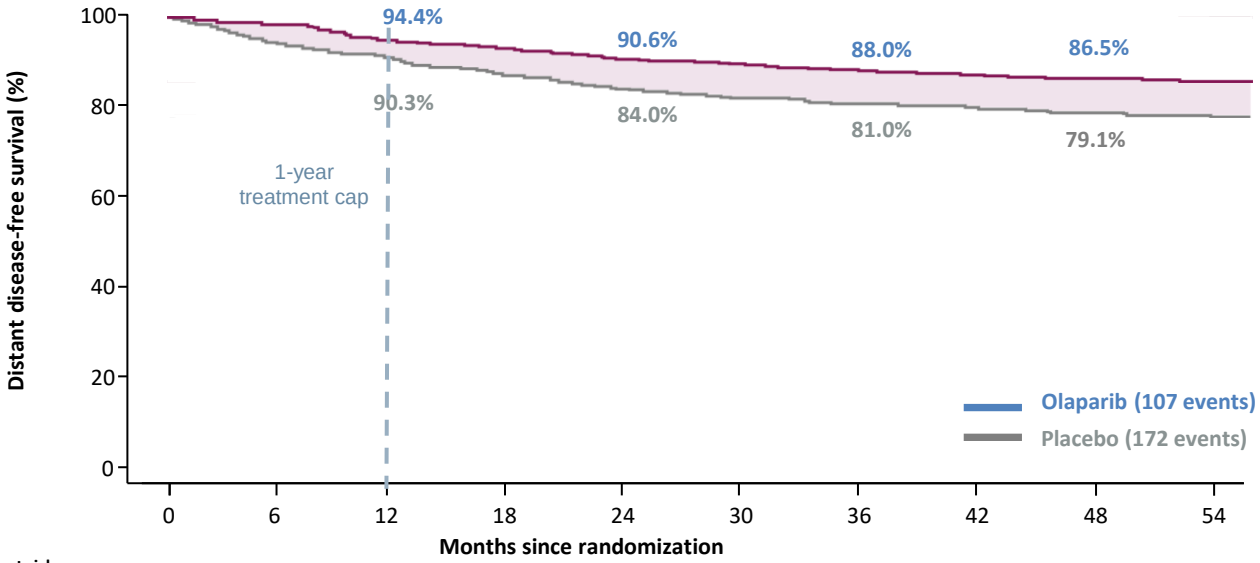
Difference 8.8%
95% CI 4.5–13.0

*Kaplan–Meier estimates
†Stratified Cox proportional hazards model; 99.5% CIs are shown for the HR because p<0.005 was required to indicate statistical significance for this endpoint
CI=confidence intervals; IDFS=invasive disease-free survival; ITT=intention-to-treat
Tutt A, et al. *N Engl J Med*. 2021. Epub ahead of print. DOI: 10.1056/NEJMoa2105215

ES-17534 marzo 2022

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

Exploratory Analysis



No. at risk										
Olaparib	921	828	784	746	698	609	501	391	302	209
Placebo	915	818	777	728	670	582	471	379	300	193

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%**

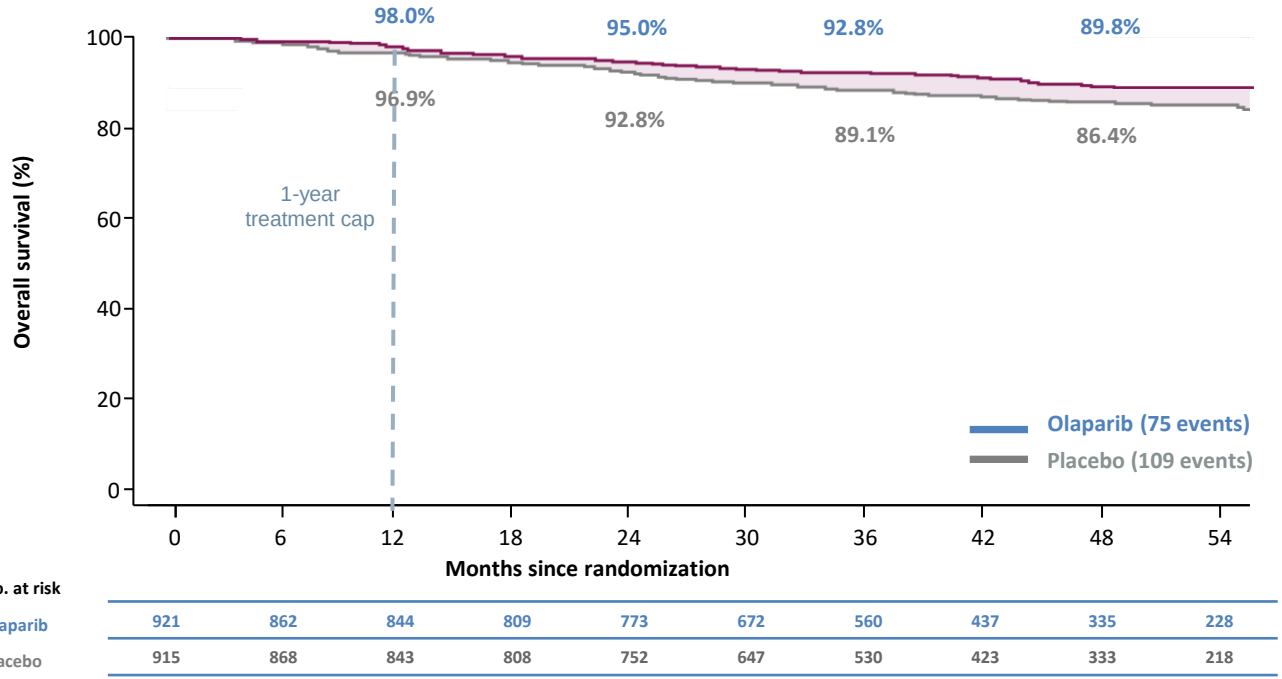
Difference 7.4%
95% CI, 3.6–11.3

ŧDDFS 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.

Olaparib demonstrated a significant OS benefit with 90% of patients alive at 4-years

Secondary endpoint: overall survival



No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

OS at DCO2

HR 0.68†
98.5% CI 0.47–0.97
p=0.009

4-year OS rate

Olaparib (n=921)	**89.8%**
Placebo (n=915)	**86.4%**

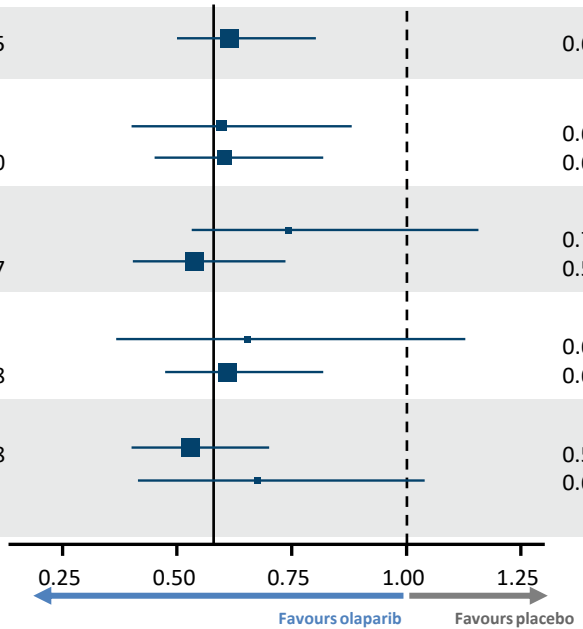
Difference 3.4%
95% CI -0.1–6.8

*Data from the pre-specified second interim analysis of OS (at ~330 IDFS events); cut-off date July 2021 (DCO2), data maturity 9%; †Non-proportional hazards; 98.5% CI is shown for the HR for OS because p<0.015 is required to indicate statistical significance for this endpoint

1. 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 2. In House Data, AstraZeneca. Data on file SD-2020-ALL-0088

A consistent benefit was seen across all IDFS subgroups

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	P value for heterogeneity
	No. of patients with an invasive-disease event/total no.			
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	

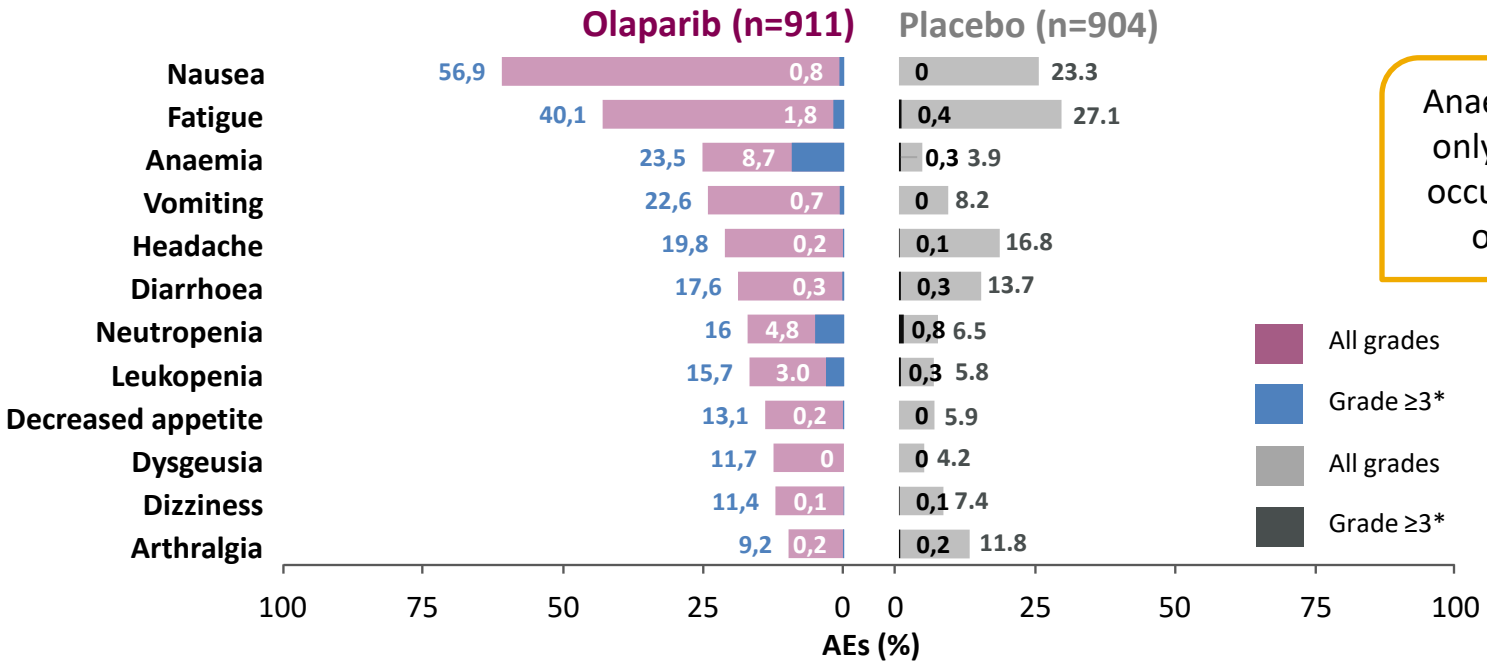


The size of the blue squares corresponds to the number of events contributing to the estimate of the treatment effect (i.e., proportional to square root of 1/variance of the estimated hazard ratio). There was no statistical evidence of heterogeneity between any subgroup and the ITT IDFS treatment effect. DCO2 12 July 2021

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.

No new safety signals were identified for olaparib in OlympiA

AEs of any grade occurring in ≥10% of patients in either arm



Anaemia was the only Grade 3 AE occurring in >5% of patients

*All listed AEs are Grade 3 except for 10 Grade 4 events in the olaparib arm: neutrophil count decreased, n=5; anaemia, n=4; fatigue, n=1

AE=adverse event

Tutt A, et al. *N Engl J Med.* 2021. Epub ahead of print. DOI: 10.1056/NEJMoa2105215

EMA Recommends Extension of Therapeutic Indications for Olaparib

Breast cancer

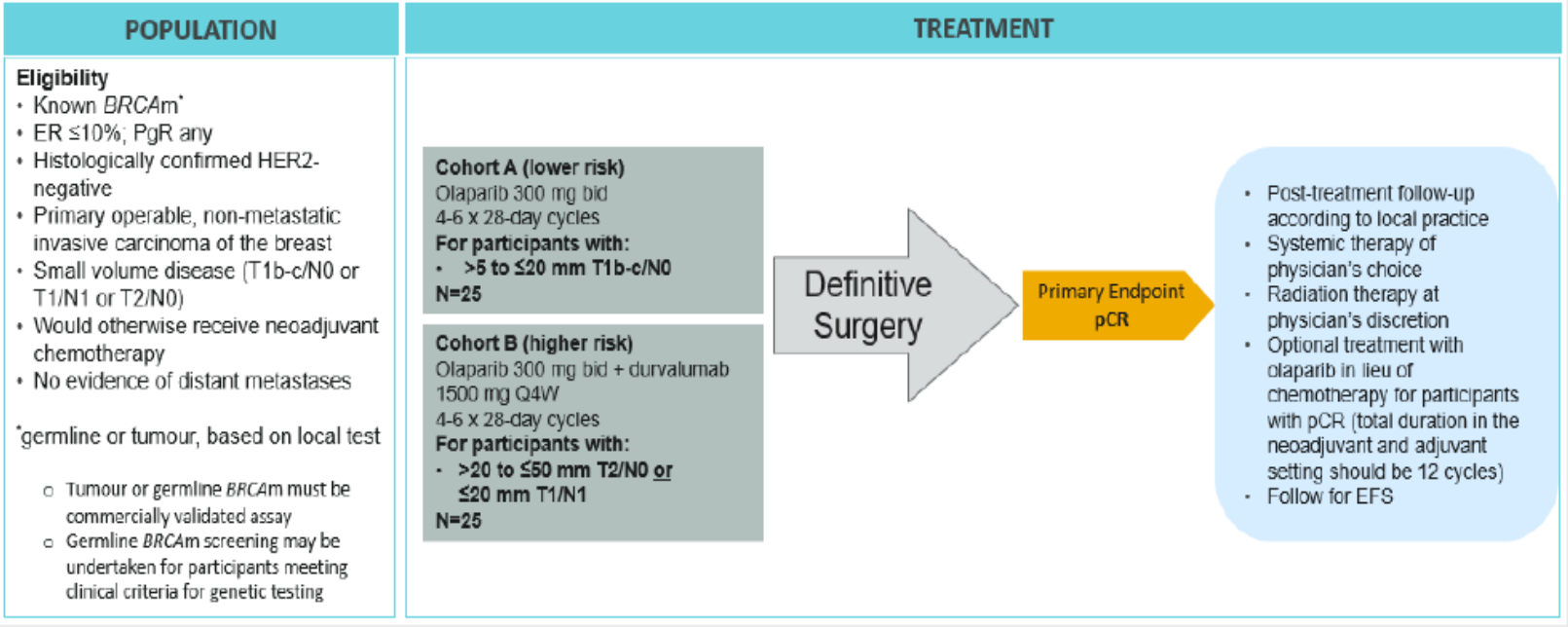
Lynparza is indicated as:

- **monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2* mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.**
- monotherapy for the treatment of adult patients with germline *BRCA1/2* mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

PARP INHIBITORS: ONGOING DEVELOPMENTS IN BC

ONGOING DEVELOPMENTS

OlympiaN Study Design

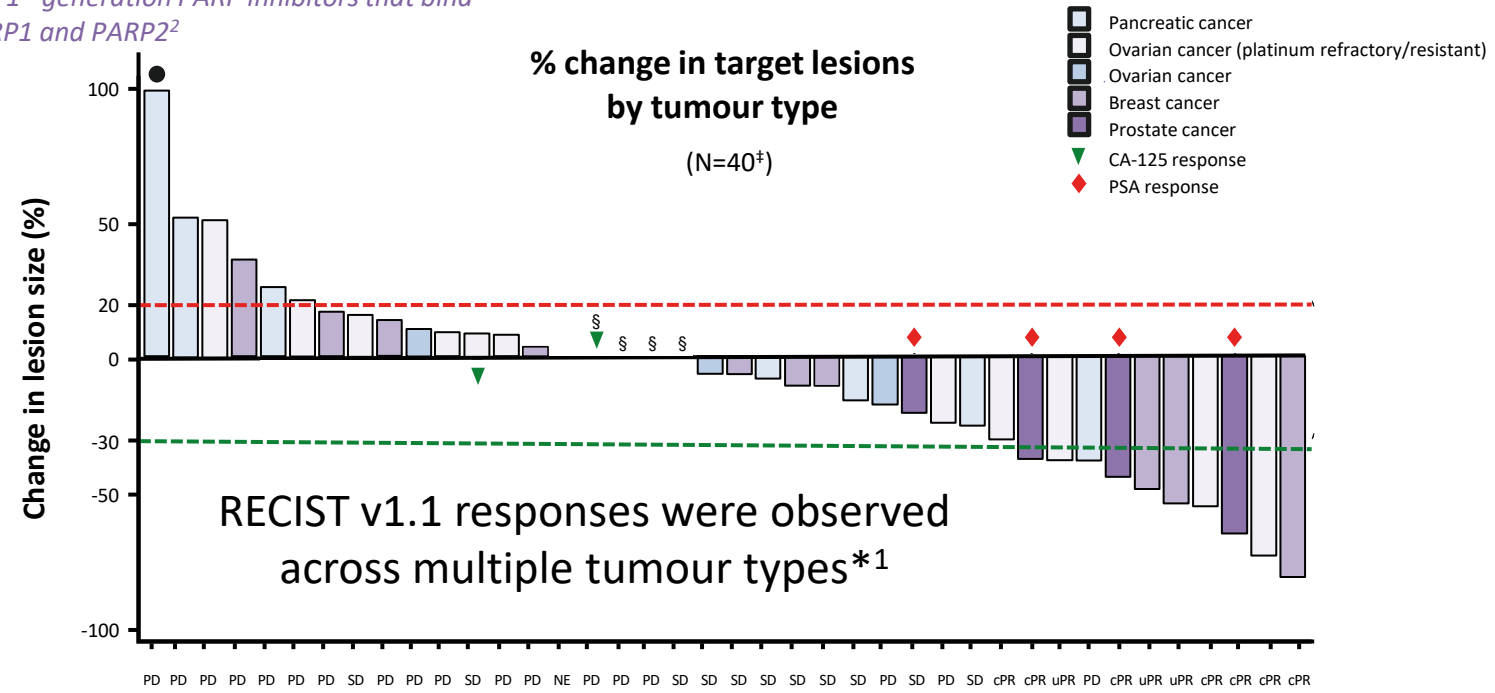


Abbreviations: BID = twice daily; EFS = event-free survival; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; pCR = pathological complete response; PgR = progesterone receptor; Q4W = every 4 weeks.

PETRA: First-in-class, first-in-human trial of AZD5305

AZD5305 selectively binds to and traps PARP1[1]

This is different from 1st generation PARP inhibitors that bind to and trap both PARP1 and PARP2[2]



Note: Included patients pre-treated with PARPi and patients eligible independently of platinum sensitivity

*Of the 40 patients evaluable for RECIST v1.1†, 10 had partial responses (7 confirmed; 3 unconfirmed) and 11 reported stable disease. †n=6 pts were Not evaluable: n=5 did not have a follow up scan and n=1 had SD <7 weeks.

‡n=6 patients did not have a post baseline assessment include n=1 patient with an early death. §Patients with 0% change from baseline; percent change >100 was cut at 100 and marked with black dot.

CA-125=cancer antigen 125; (c)PR=(confirmed) partial response; eCRF=electronic case report form; NE=not evaluable; PD=progressive disease; PSA=protein-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; (u)PR=(unconfirmed) partial response

1. Yap TM, et al. Presented at AACR 2022. 8–13 April. New Orleans, Louisiana. Abstract #CT007

foro debate oncología

Zaragoza 26-29 septiembre 2023

Dra. Vega Iranzo

Hospital General Universitario Valencia

"Que nunca te falte un abrazo"