
# Il carcinoma mammario metastatico in donne con VP gBRCA

Laura Cortesi

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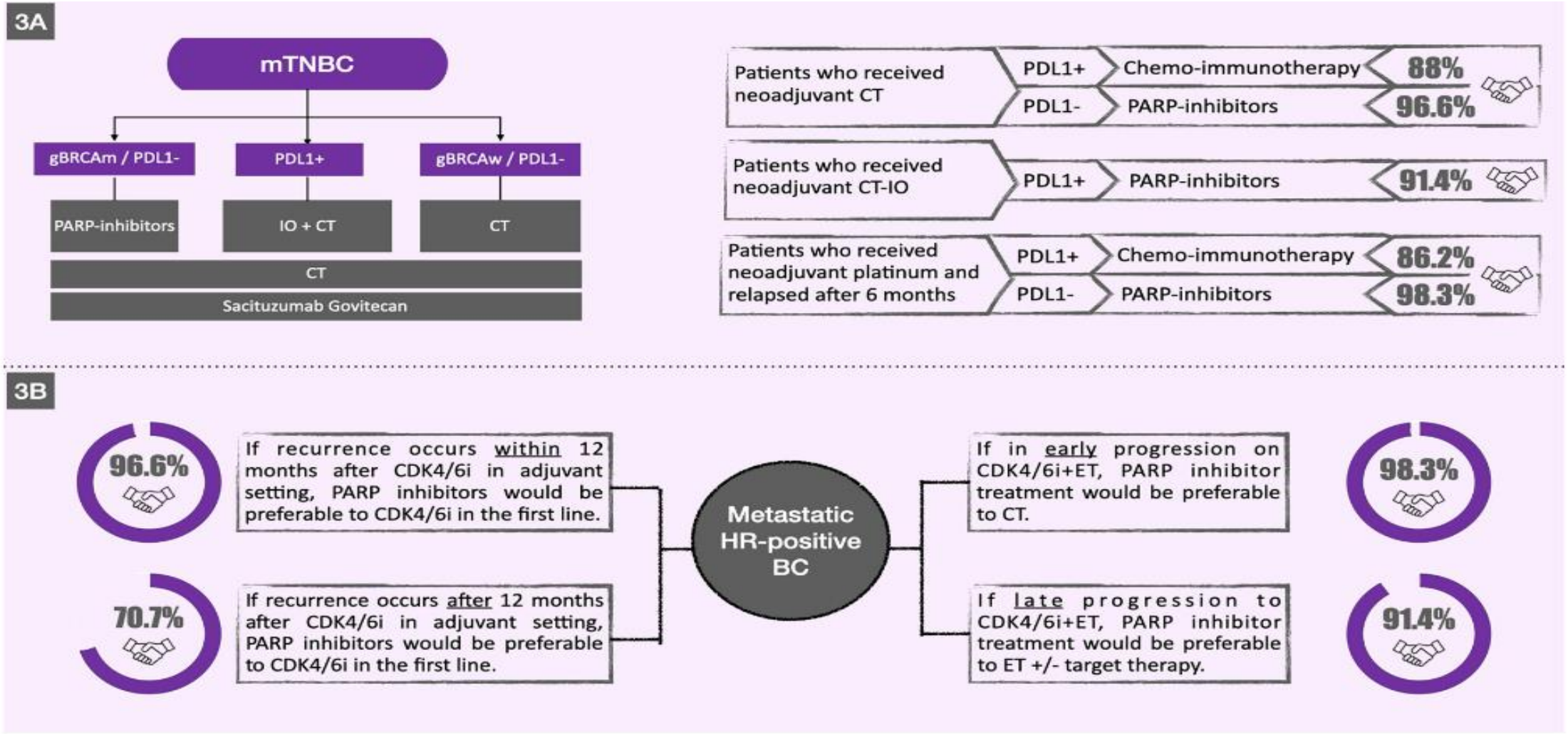
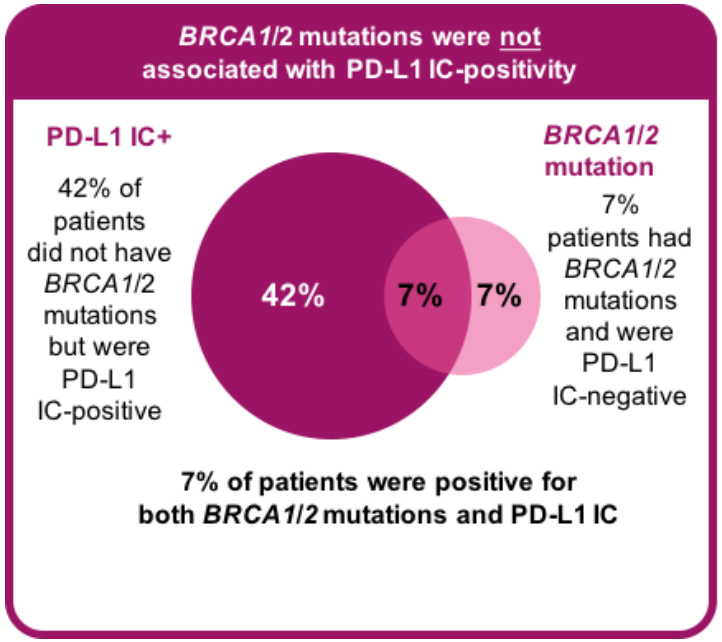
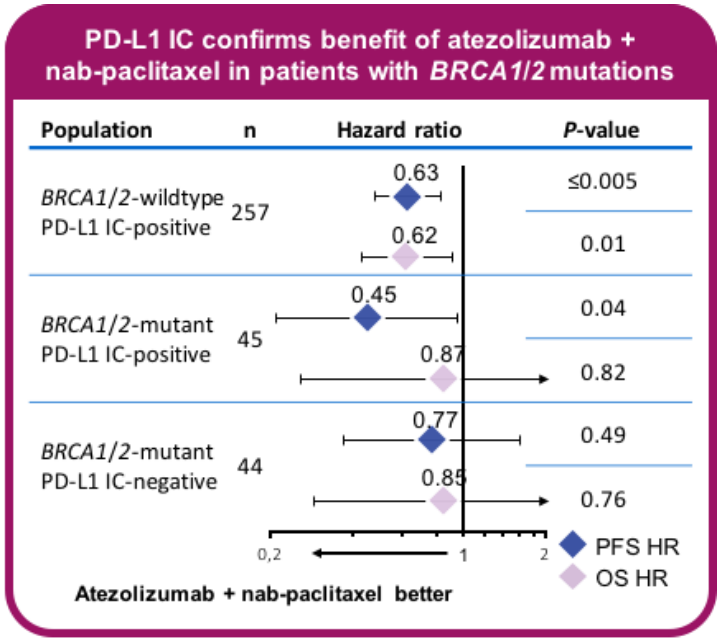



Zambelli A, Cortesi L*,Cancer Treatment Review 2024

* Co-first authors.

# IMPASSION130: CLINICAL BENEFIT OF ATEZOLIZUMAB + NAB-PACLITAXEL IN THE PD-L1 IC+ SUBGROUP




mPFS=9.1 ms

Emens, et al. JNCI 2021

# OLYMPIAD: PHASE III STUDY OF OLAPARIB VS. TPC IN gBRCAM HER2- MBC[1]

## Study design

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

*FSI May 2014:*[3]

*Global Study in 19 countries and approximately 141 sites*[1]

***Randomise 2:1***
*n=302*[4]

*Stratification by:*[2]

- *Prior chemotherapy regimens for metastatic breast cancer*
- *Hormonal receptor (HR) status*
- *Prior platinum therapy*

**Olaparib**
300mg**po* bid

**Treatment of Physician's Choice**
(TPC)

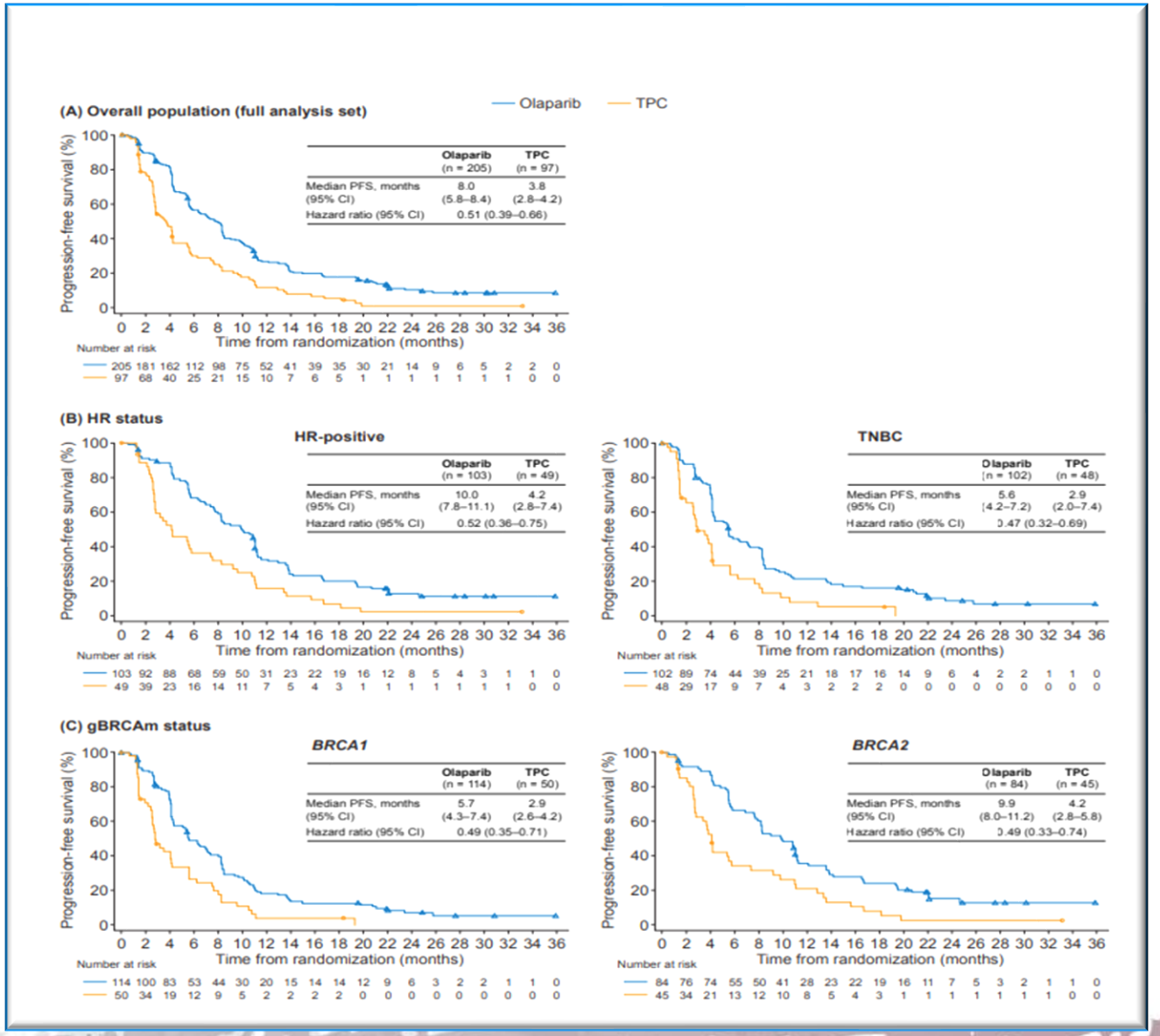
Primary endpoint
- PFS (RECIST 1.1, Independent Review)

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

* Tablet formulation (2 tablets twice daily)

[1]Robson et al. N Engl J Med. 2017; 377:523-533

# PFS at 18 months of median fullow-up




Senkus et al., IJC 2023

## INDICAZIONE APPROVATA:

Lymparza è indicato come monoterapia per il trattamento di pazienti adulti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo a recettori negativi metastatico. I pazienti devono essere stati precedentemente trattati con una antraciclina e un taxano nel contesto (neo)adiuvante, localmente avanzato o metastatico, ad eccezione dei pazienti non idonei per tali trattamenti

I pazienti con carcinoma mammario positivo ai recettori ormonali (HR) devono essere stati precedentemente trattati con terapia endocrina o ritenuti non idonei alla terapia endocrina.

## INDICAZIONE RIMBORSATA:

Lymparza è indicato come monoterapia per il trattamento di pazienti adulti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo, recettori ormonali negativi, localmente avanzato o metastatico. I pazienti devono essere stati precedentemente trattati con una antraciclina e un taxano e devono aver ricevuto una chemioterapia a base di platino nel contesto (neo)adiuvante, localmente avanzato o metastatico, ad eccezione dei pazienti non idonei per tali trattamenti

Scheda di monitoraggio AIFA

# EMBRACA: PHASE III STUDY OF TALAZOPARIB VS. TPC IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BREAST CANCER

## Study design

- Locally advanced breast cancer and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy
- gBRCAm
- ECOG 0-2
- ≤3 prior lines of chemotherapy for locally advanced/metastatic disease
- HER2-negative
- Prior platinum permitted if:
  - In (neo-)adjuvant setting: disease-free interval of ≥6 months after the last dose
  - In advanced setting: no objective disease progression while receiving platinum
- Previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated

***Randomise 2:1***

**Talazoparib (n=287)**
1 mg/day 21 day cycles *po*

**Therapy of physician's choice (TPC) (n=144)**
(capecitabine, eribulin, gemcitabine or vinorelbine)

**Primary endpoint:**
- PFS (BICR)

**Secondary endpoints include:**
- ORR
- OS
- Safety and tolerability
- PK

**Exploratory endpoint:**
- HRQoL

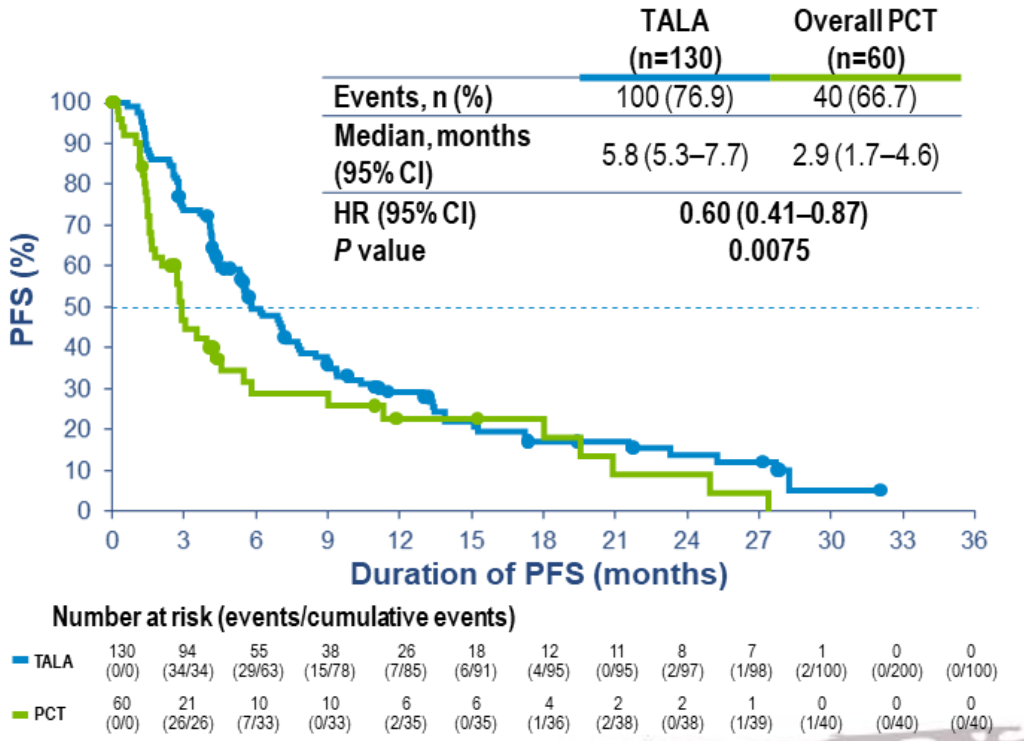
***Patients stratified according to:***
- *Number of prior chemotherapy regimens (0 vs. 1,2,3)*
- *Triple negative status (HR+ vs. TNBC)*
- *History of CNS metastasis (y/n)*

Litton J et al. N Engl J Med 2018; 379:753–763

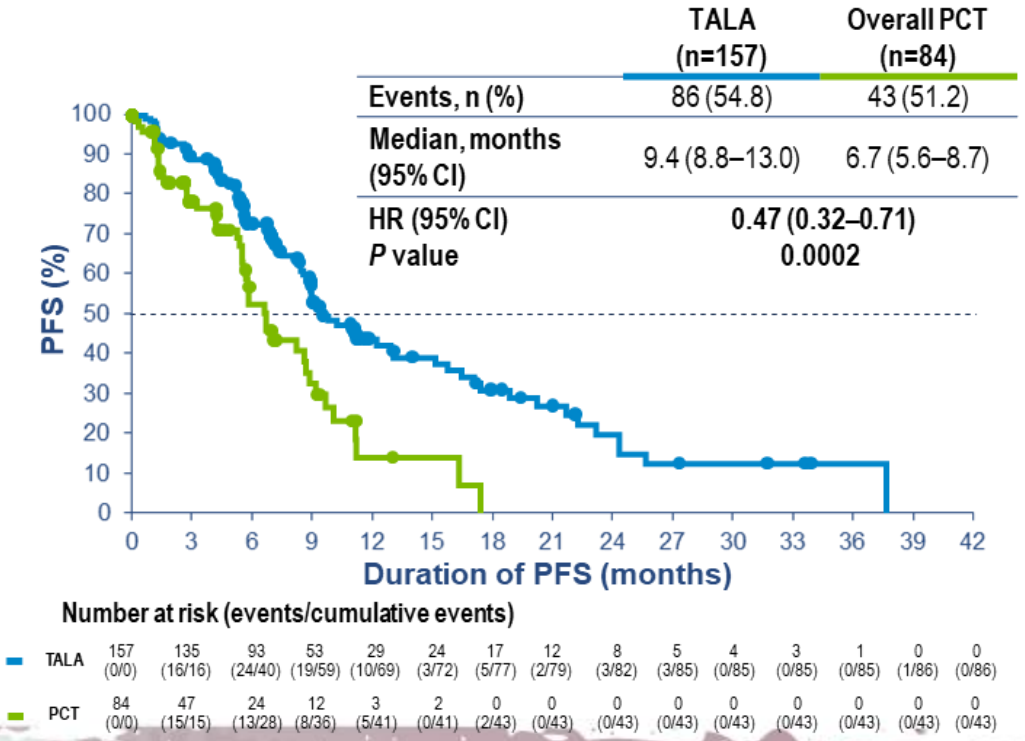
# EMBRACA: PFS IN BASE ALL'ESPRESSIONE DEI RECETTORI ORMONALI

| Characteristic | Talazoparib (N = 287) | Chemotherapy (N = 144) (capecitabine [44%], eribulin [40%], gemcitabine [10%], and vinorelbine [7%]) |
|---|---|---|
| Triple-negative BC, n (%) | 130 (45.3) | 60 (41.7) |
| Hormone receptor–positive BC, n (%) | 157 (54.7) | 84 (58.3) |

## PFS nel sottogruppo TNBC




## PFS nel sottogruppo HR+/HER2-




Rugo HS, et al. JNCI Cancer Spectr. 2020

## INDICAZIONE APPROVATA:

Talzenna è indicato come monoterapia per il trattamento di pazienti adulti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo localmente avanzato o metastatico. I pazienti devono essere stati precedentemente trattati con una antraciclina e/o un taxano nel contesto (neo)adiuvante, localmente avanzato o metastatico, ad eccezione dei pazienti non idonei per tali trattamenti (vedere paragrafo 5.1).

I pazienti con carcinoma mammario positivo ai recettori ormonali (HR) devono essere stati precedentemente trattati con terapia endocrina o ritenuti non idonei alla terapia endocrina.

## INDICAZIONE RIMBORSATA:

Talzenna è indicato come monoterapia per il trattamento di pazienti adulti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo localmente avanzato o metastatico. I pazienti devono essere stati precedentemente trattati con una antraciclina e/o un taxano nel contesto (neo)adiuvante, localmente avanzato o metastatico, ad eccezione dei pazienti non idonei per tali trattamenti (vedere paragrafo 5.1).

I pazienti con carcinoma mammario positivo ai recettori ormonali (HR) devono essere stati precedentemente trattati con terapia endocrina o ritenuti non idonei alla terapia endocrina e devono aver ricevuto una linea di trattamento con inibitori delle chinasi ciclina-dipendenti (CDK4/6).

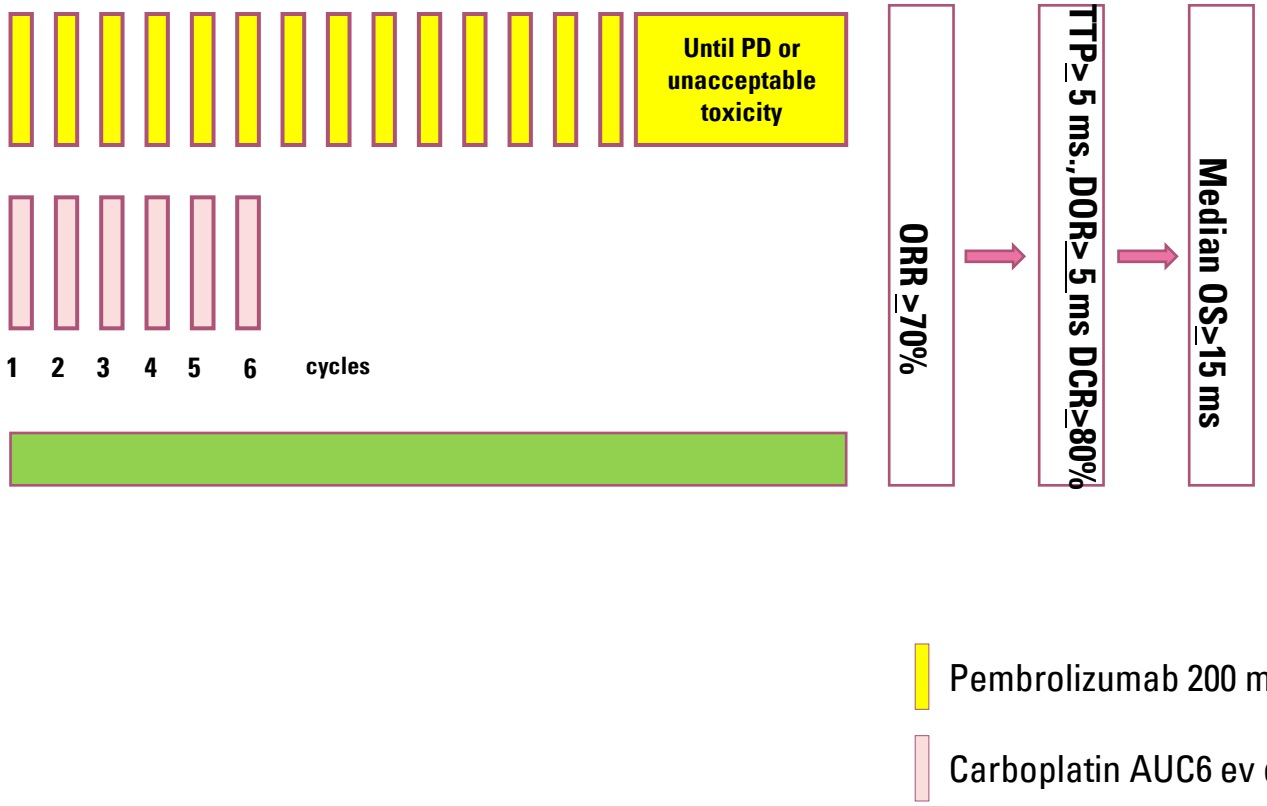
I pazienti con carcinoma mammario negativo ai recettori ormonali (HR) devono essere stati precedentemente trattati con chemioterapia a base di platino, ad eccezione dei pazienti non idonei per tale trattamento.

Scheda di monitoraggio AIFA

# PEMBRACA STUDY DESIGN

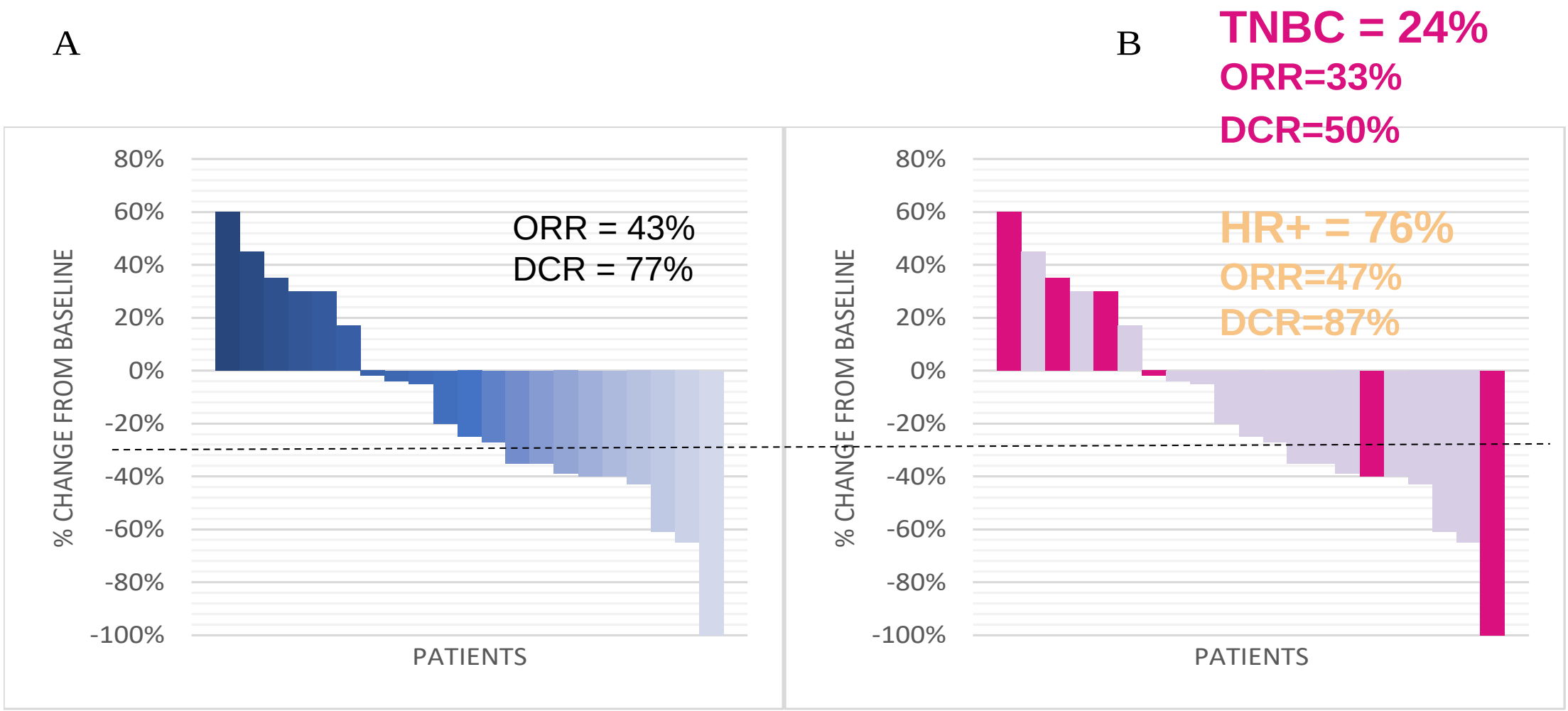
- Evidence of metastatic disease gBRCAm
- No more than one line of chemotherapy for mBC
- At least one measurable lesion according to RECIST 1.1
- ECOG 0-1
- Males or females age ≥ 18 years at the time of informed consent
- Adequate hematological, hepatic and renal function

Two step Simon design
N=20; if ORR≥12 → 53



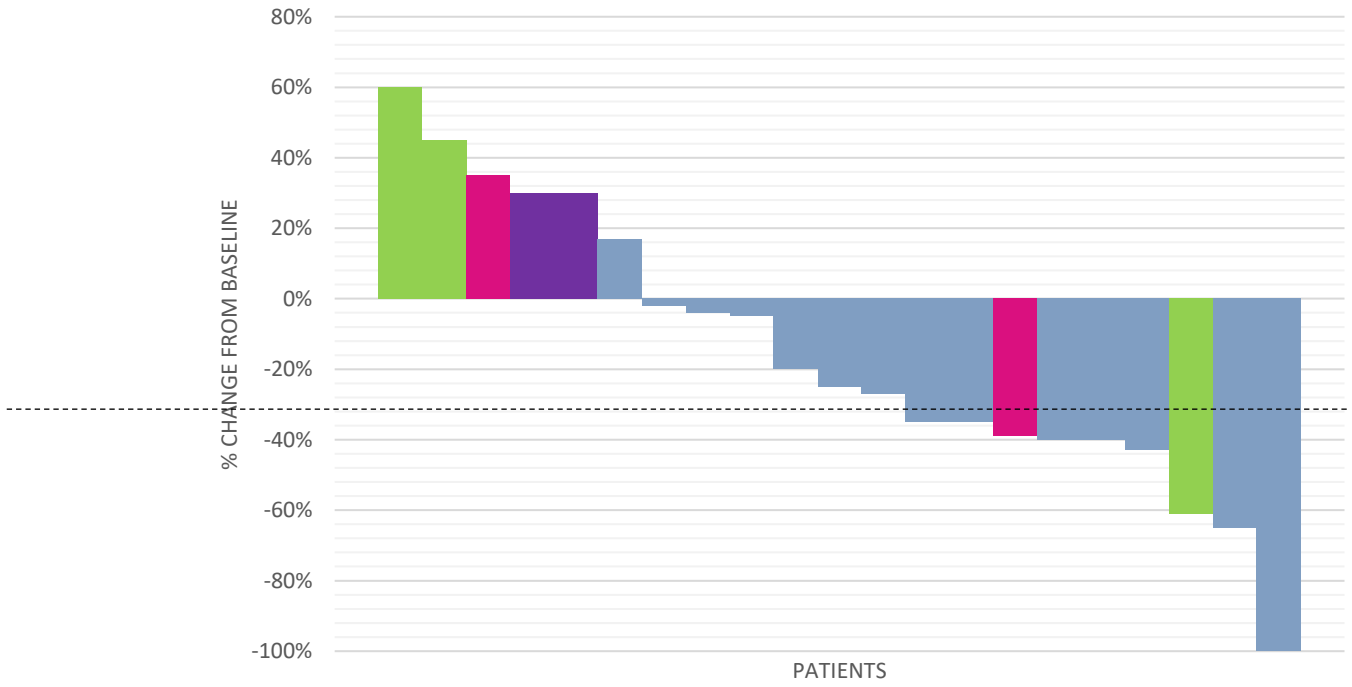

Cortesi L., Esmo Open 2023

# ORR AND DCR ACCORDING TO HR STATUS




Cortesi L., Esmo Open 2023

# RR ACCORDING TO THE LINE OF TREATMENT FOR MBC

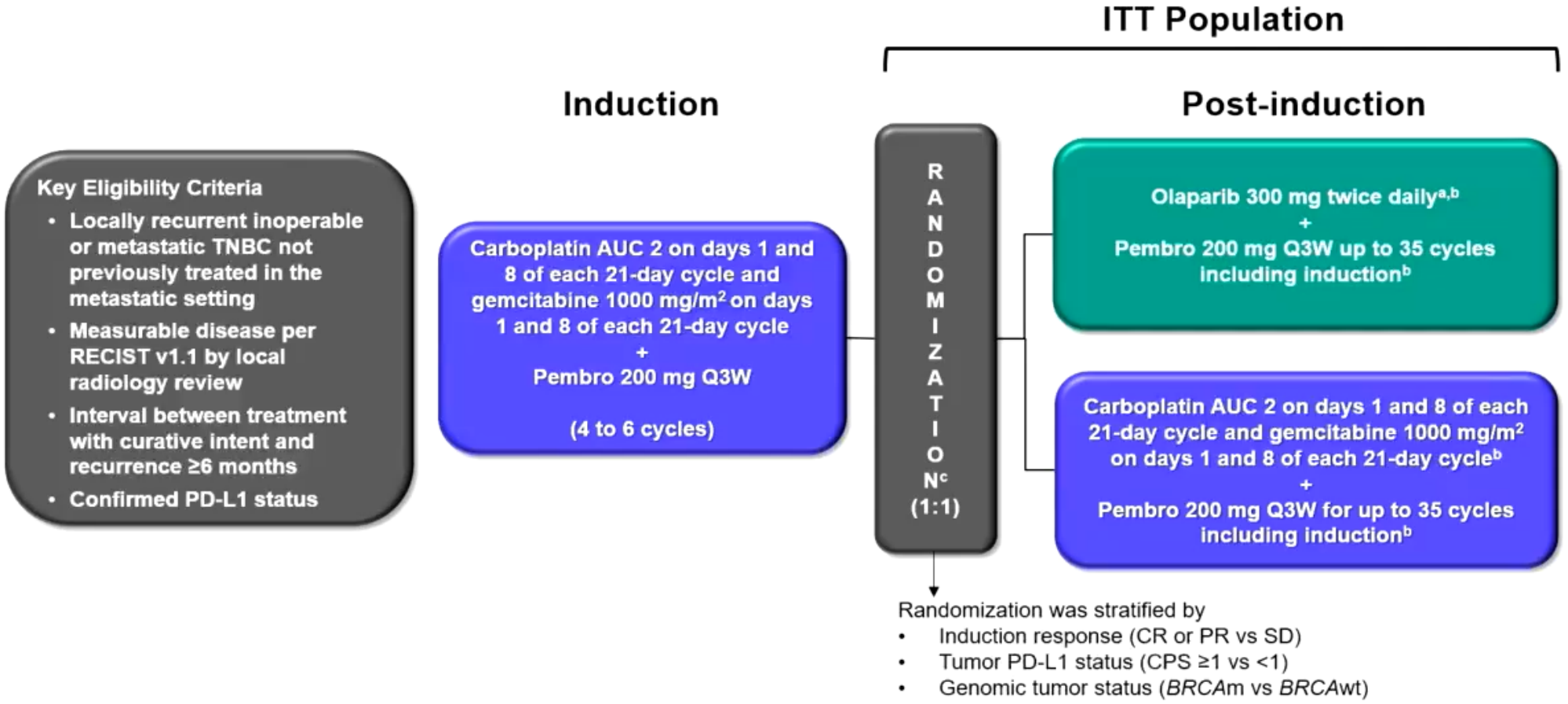



**Tax**
**Anthra**
**Other CT (cape)**
**ORR=38%, DCR=38%**

**None ORR=46%, DCR=100%**

Cortesi L., Esmo Open 2023

# KEYLYNK-009 (NCT04191135): Study Design

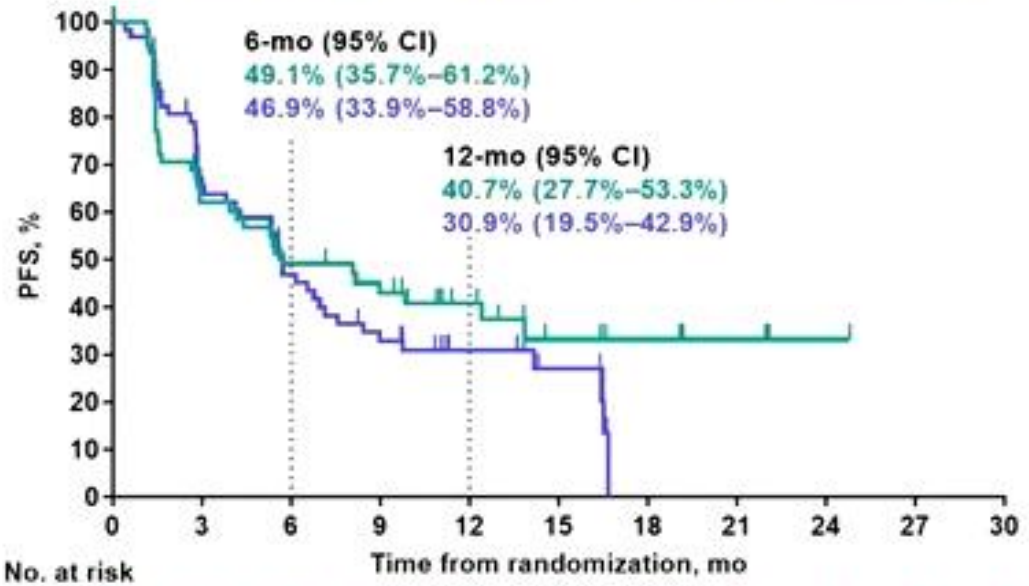



[a]Olaparib was administered postinduction and given concurrently with pembrolizumab. [b]Until disease progression or unacceptable toxicity. [c]ITT population was determined from randomization (not from the time of enrollment).

# PFS per RECIST v1.1 by BICR: PD-L1 CPS ≥10 and t*BRCA*m

## Tumor PD-L1 CPS ≥10 Population

| | Events, n (%) | Median, mo (95% CI) | HR[a] (95% CI) |
|---|---|---|---|
| Pembro + Olaparib | 36 (55.4) | 5.7 (2.9–13.9) | 0.92 (0.59–1.43) |
| Pembro + Chemo | 45 (69.2) | 5.7 (3.8–7.6) | |

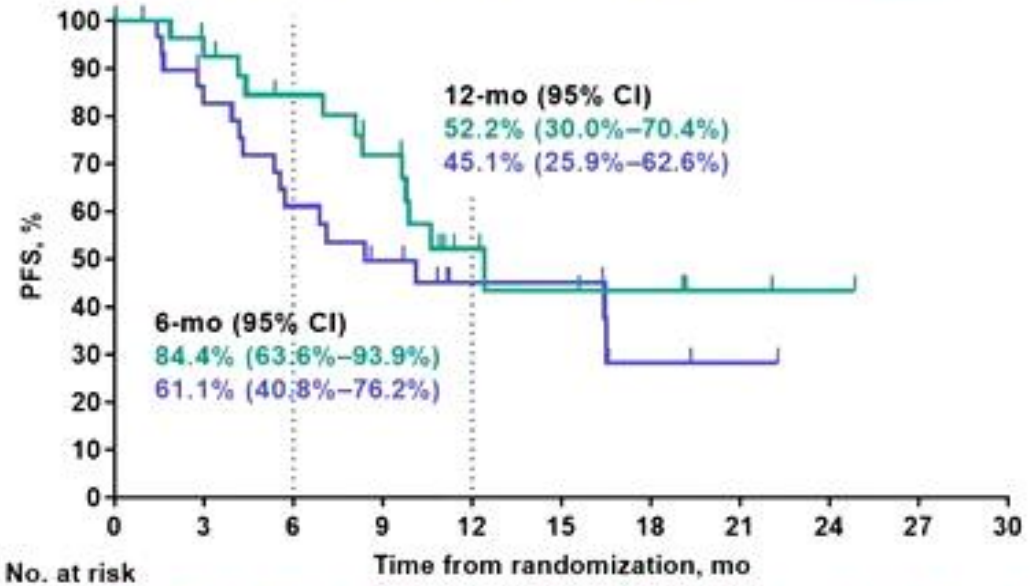



No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 65 | 35 | 25 | 21 | 13 | 7 | 5 | 3 | 1 | 0 | 0 |
| 65 | 39 | 27 | 18 | 11 | 6 | 0 | 0 | 0 | 0 | 0 |

## t*BRCA*m Population

| | Events, n (%) | Median, mo (95% CI) | HR[b] (95% CI) |
|---|---|---|---|
| Pembro + Olaparib | 12 (41.4) | 12.4 (8.3–NR) | 0.70 (0.33–1.48) |
| Pembro + Chemo | 17 (56.7) | 8.4 (5.4–NR) | |




No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 29 | 24 | 20 | 16 | 7 | 5 | 4 | 2 | 1 | 0 | 0 |
| 30 | 23 | 16 | 12 | 7 | 7 | 2 | 1 | 0 | 0 | 0 |

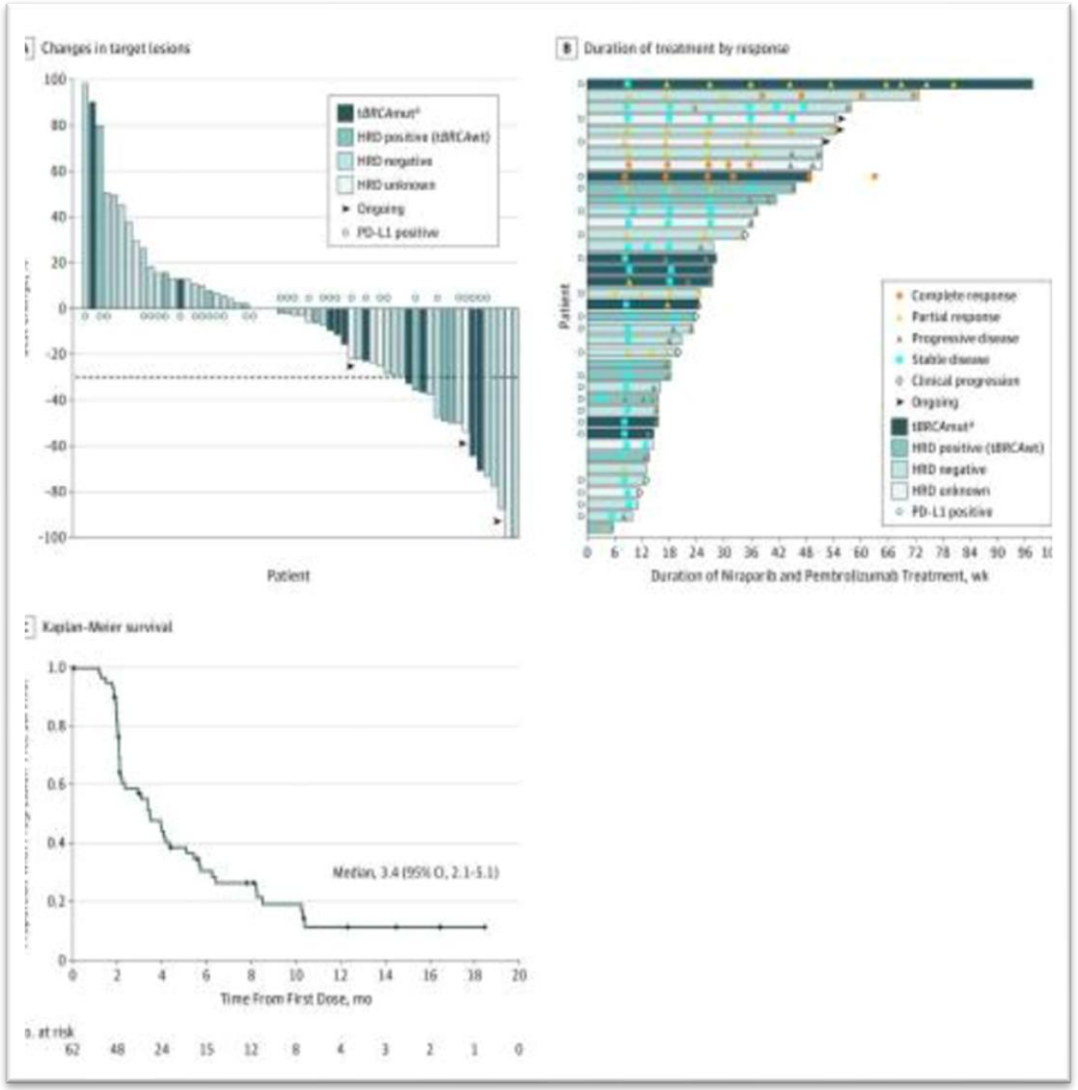
NR, not reached; t*BRCA*m, tumor *BRCA* mutation (includes germline and somatic mutations). [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and *BRCA* status. [b]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and tumor PD-L1 status.
Data cutoff date: December 15, 2022. 

# Adverse Events Summary (As-Treated Population)

| | Pembro + Olaparib n = 135 | Pembro + Chemo n = 133 |
|---|---|---|
| **Treatment-related AEs** | | |
| Any grade treatment-related AEs | 114 (84.4) | 128 (96.2) |
| Grade 3–5 treatment-related AEs | 44 (32.6)[a] | 91 (68.4)[b] |
| Treatment-related AEs leading to discontinuation of any treatment | 12 (8.9) | 26 (19.5) |
| **Immune-Mediated AEs and Infusion Reactions[c]** | | |
| Any grade | 26 (19.3) | 31 (23.3) |
| Grade 3/4[d] | 6 (4.4) | 6 (4.5) |
| Led to discontinuation of any treatment | 0 | 4 (3.0) |

Data are n (%) of patients.
[a]There were no grade 5 events in the pembro + olaparib group.
[b]2 patients had grade 5 events in the pembro + chemo group (gastrointestinal hemorrhage and thrombotic thrombocytopenic purpura, n = 1 each).
[c]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.
[d]There were no grade 5 events in either group.
Data cutoff date: December 15, 2022.

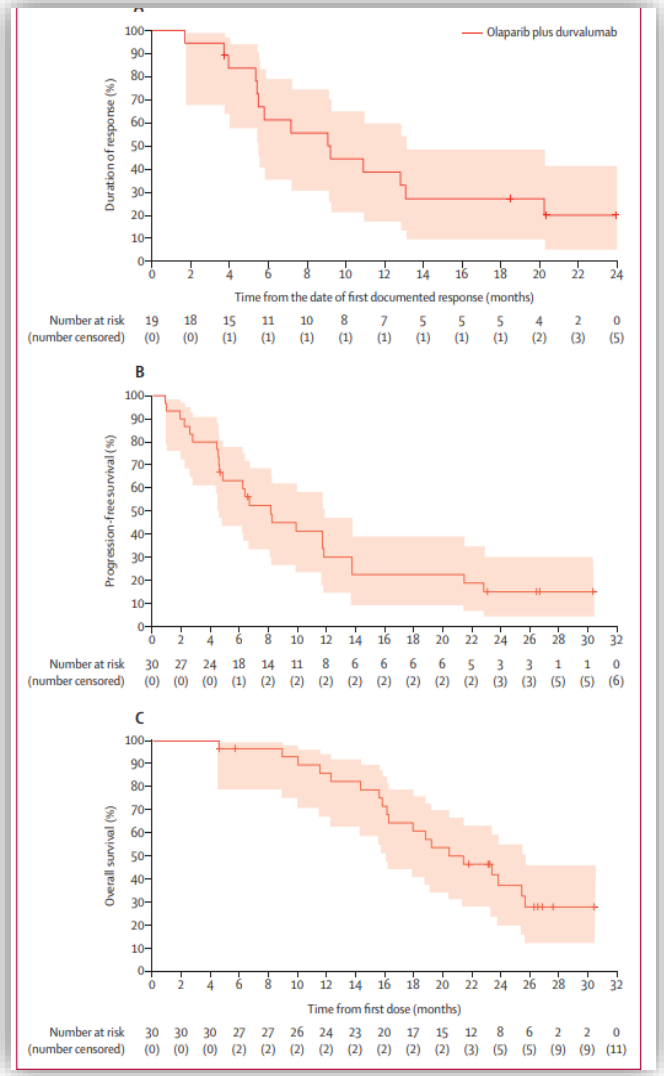
## TOPACIO:NIRAPARIB+PEMBROLIZUMAB




mPFS=3.4 ms

Konstantinopoulos P et al. Jama Oncol 2019

## MEDIOLA: OLAPARIB + DURVALUMAB



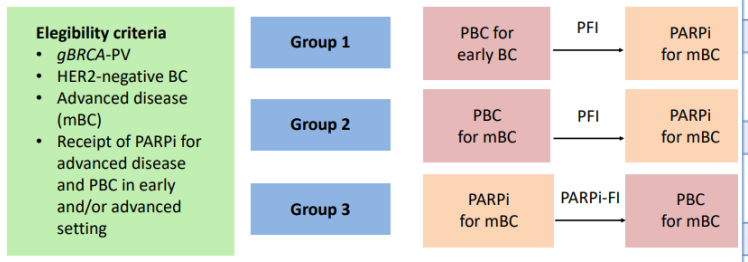

mPFS=8.2 ms

Domchek S et al. Lancet Oncol 2021

# PLATINUM-BASED CHEMOTHERAPY AND PARP INHIBITORS FOR BRCA MUTATED METASTATIC BREAST CANCER (LATER-BC): RETROSPECTIVE MULTICENTRE ANALYSIS OF POST-PROGRESSION TREATMENTS

## Methods

- Multicenter, observational, retrospective study in five Italian Institutions. Da
  18 years old or more, with eligibility criteria were collected (from March
  2023). Patients were divided into three groups.




- Primary endpoint was progression free survival (PFS), secondary endpoint
  rate (DCR). Time from last cycle of PBC/PARPi to first cycle of subsequ
  defined as platinum/PARPi-free interval (PFI or PARPi-FI).
- Survival was calculated using Kaplan–Meier method. The Cox proportional
  logistic-regression analysis were used to estimate the independent factors
  and disease control rate (DCR), respectively.

**Table 1**. Patient characteristics

| | Group 1 (N=12) PARPi post-PBC | Group 2 (N=36) PARPi post-PBC | Group 3 (N=21) PBC post-PARPi |
|---|---|---|---|
| **Age at diagnosis, median (range)** | 40 (26-72) | 40 (28-72) | 39 (28-62) |
| **De novo disease, n (%)** | 0 (0%) | 6 (17%) | 5 (24%) |
| **Mutational status** | | | |
| **BRCA1 mutation, n (%)** | 7 (58%) | 20 (56%) | 6 (29%) |
| **BRCA2 mutation, n (%)** | 5 (42%) | 12 (33%) | 13 (62%) |
| **Not available, n (%)** | 0 (0%) | 4 (11%) | 2 (10%) |
| **Subtype of disease** | | | |
| **Triple negative breast cancer, n (%)** | 8 (67%) | 18 (50%) | 4 (19%) |
| **HR+/HER2- BC, n (%)** | 4 (33%) | 18 (50%) | 17 (81%) |
| **Age at baseline of treatment, median (range)** | 42 (30-74) | 49 (31-79) | 53 (32-68) |
| **Visceral disease at baseline, n (%)** | 8 ( | | |
| **Metastatic burden at baseline** | | | |
| **0-1 metastatic site, n (%)** | 4 ( | | |
| **>1 metastatic site, n (%)** | 8 ( | | |
| **PBC line, median (range)** | | | |
| **1st-2nd line, n (%)** | | | |
| **>2nd line, n (%)** | | | |
| **PARPi line, median (range)** | 2 | | |
| **1st-2nd line, n (%)** | 9 ( | | |
| **>2nd line, n (%)** | 3 ( | | |
| **PARP inhibitor** | | | |
| **Olaparib, n (%)** | 8 ( | | |
| **Talazoparib, n (%)** | 4 ( | | |

**Figure 1**. PFS of PARPi in metastatic setting post-PBC in early setting (mFUP: 6.1 mo)

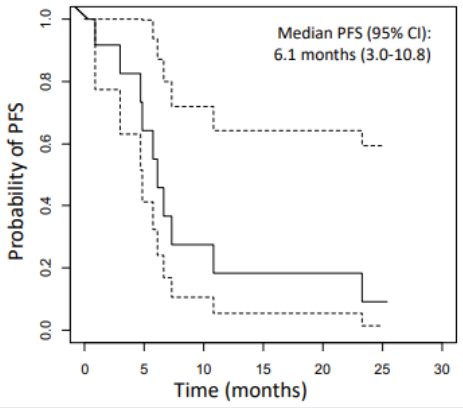



**Figure 2**. PFS of PARPi in metastatic setting post-PBC in metastatic setting (mFUP: 3.4 mo)

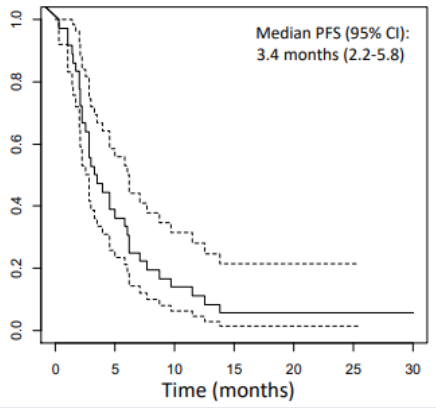
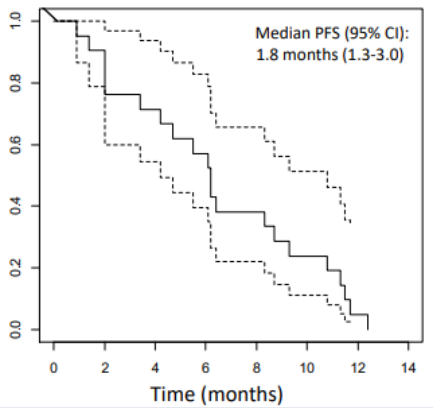
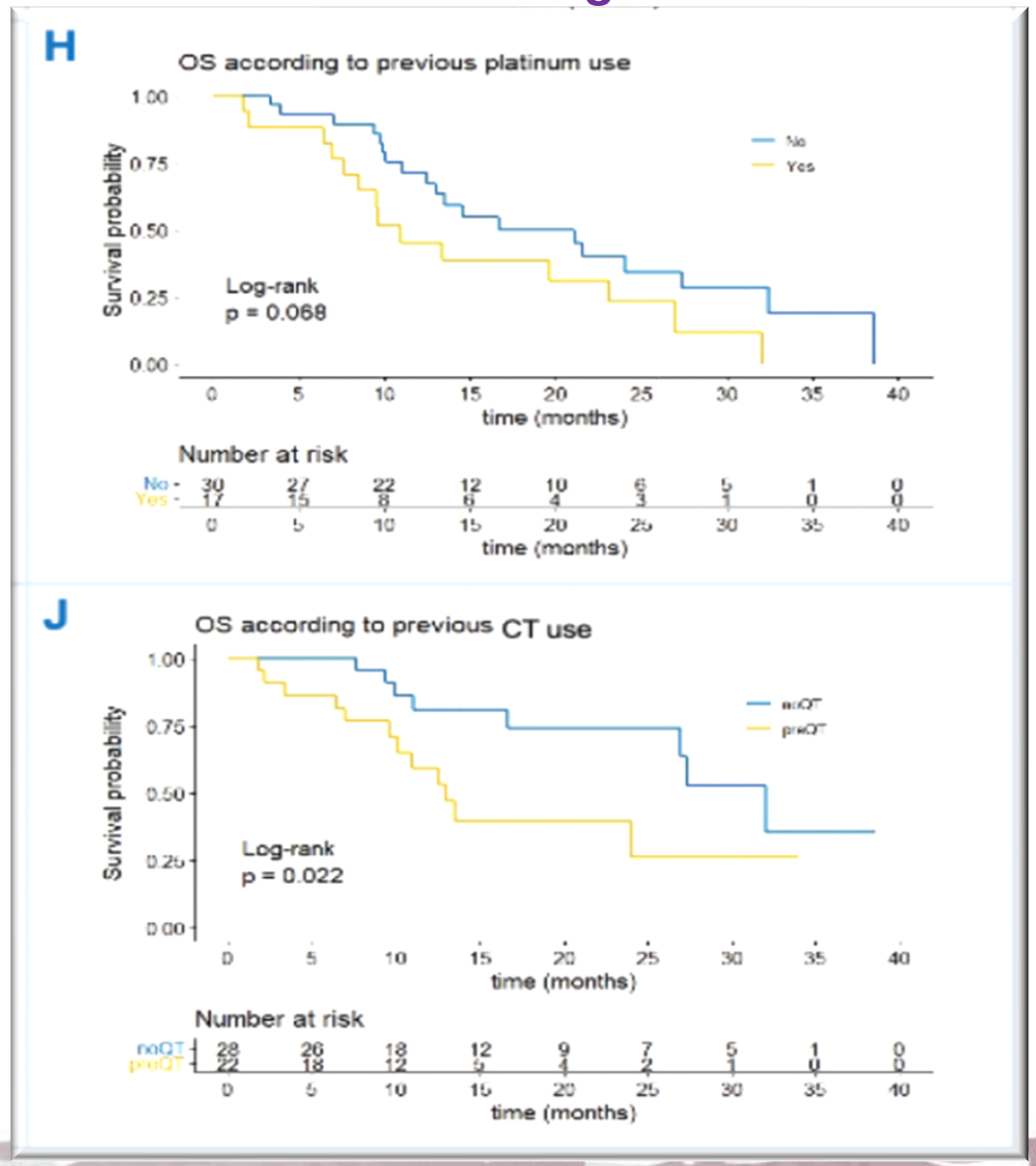



**Figure 3.** PFS of PBC in metastatic setting post-PARPi in metastatic setting




Valenza C., EJC 2023

# REAL WORLD DATA ON PARPi USING IN gBRCA and sBRCA




Petracci FA et al., Ecancermedicine 2024

# BIOMARKER ANALYSES IN THE PHASE III ASCENT STUDY OF SACITUZUMAB GOVITECAN VERSUS CHEMOTHERAPY IN PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER

**Table 2. ORR, PFS, and OS summary by germline *BRCA1/2* status**

| | Germline *BRCA1/2*-positive | | Germline *BRCA1/2*-negative | |
|---|---|---|---|---|
| | SG ($n = 16$) | TPC ($n = 18$) | SG ($n = 133$) | TPC ($n = 125$) |
| ORR, *n* (%) | 3 (19) | 1 (6) | 44 (33) | 7 (6) |
| Odds ratio (95% CI) | 3.9 (0.4-42.2) | | 8.3 (3.6-19.4) | |
| Median PFS, months (95% CI) | 4.6 (1.3-10.3) | 2.5 (0.8-5.5) | 4.9 (3.8-5.9) | 1.6 (1.5-2.5) |
| HR (95% CI) | 0.6 (0.2-1.6) | | 0.4 (0.3-0.6) | |
| Median OS, months (95% CI, months) | 15.6 (6.2-NE) | 4.4 (3.6-9.7) | 10.9 (9.6-13.4) | 7.0 (5.6-8.2) |
| HR (95% CI) | 0.4 (0.2-0.9) | | 0.5 (0.4-0.7) | |

*BRCA*, breast cancer gene; CI, confidence interval; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bardia A et al., Ann Oncol 2021

# CENTRAL NERVOUS SYSTEM METASTASES IN BREAST CANCER PATIENTS WITH GERMLINE BRCA PATHOGENIC VARIANTS COMPARED TO NON-CARRIERS: A MATCHED-PAIR ANALYSIS

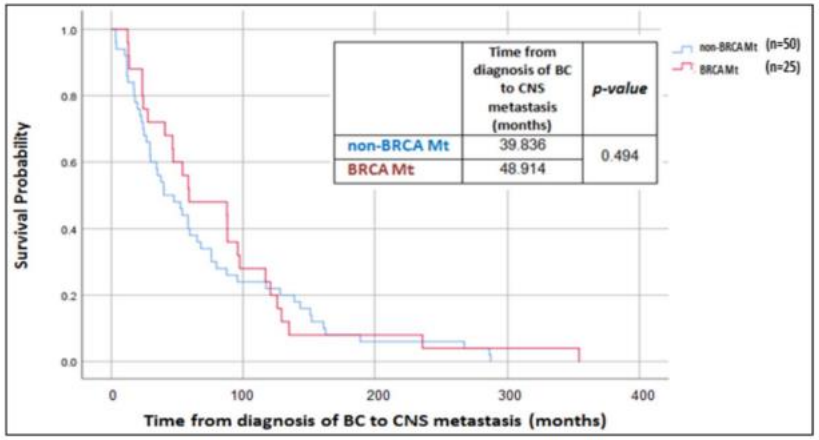



**Fig. 1** Time from breast cancer (BC) diagnosis to CNS metastasis

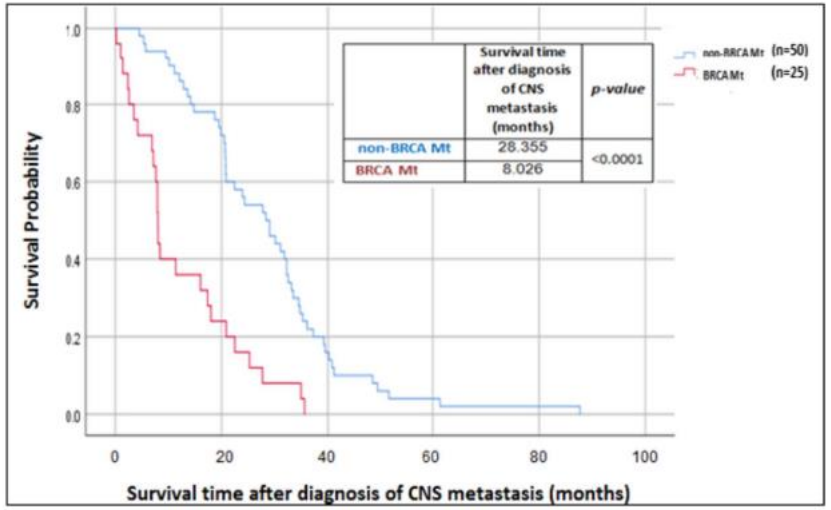



**Fig. 2** Survival time after diagnosis of CNS metastasis

Ben-Zion Berliner BMC Cancer 2024

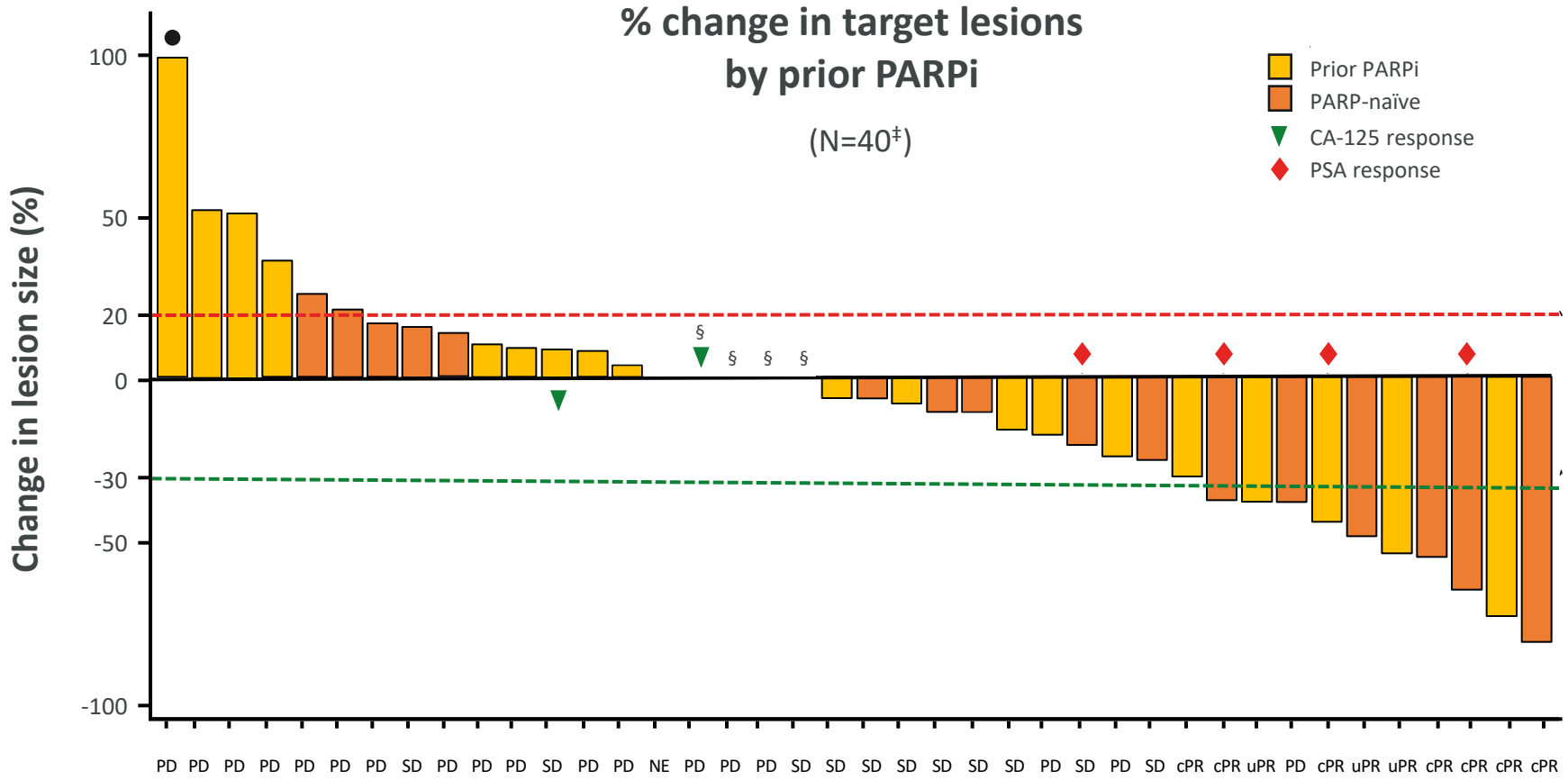
# E SE LA PAZIENTE HA FATTO OLAPARIB IN ADIUVANTE (BRCA+)?

- Possiamo somministrare PARP dopo PARP?

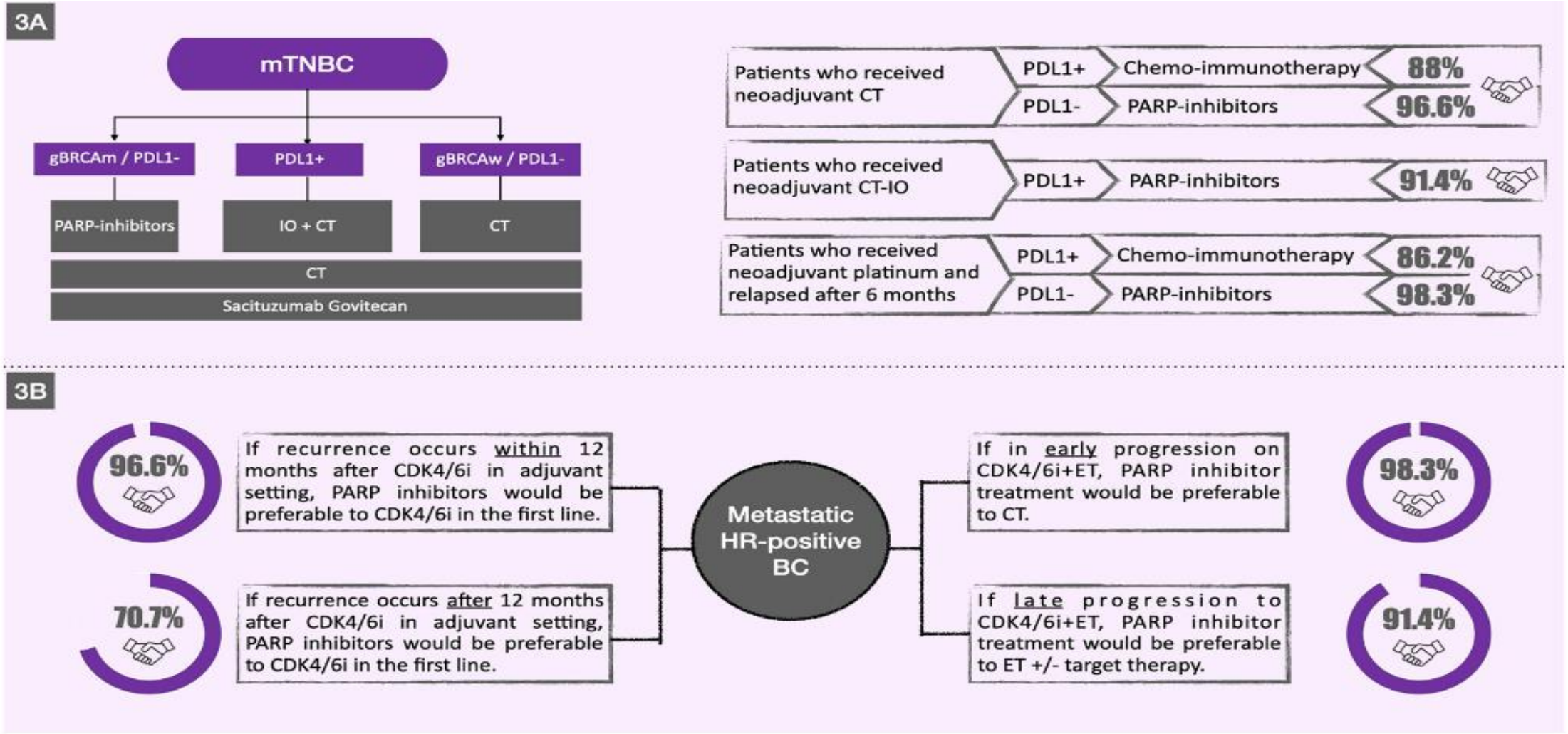
  Non conosciamo i successivi trattamenti delle pazienti progredite ad Olympia

  Non abbiamo dati fondati sull’evidenza

# RECIST V1.1 RESPONSES WERE OBSERVED WITH AZD5305 REGARDLESS OF PRIOR PARPI USE*[1]




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

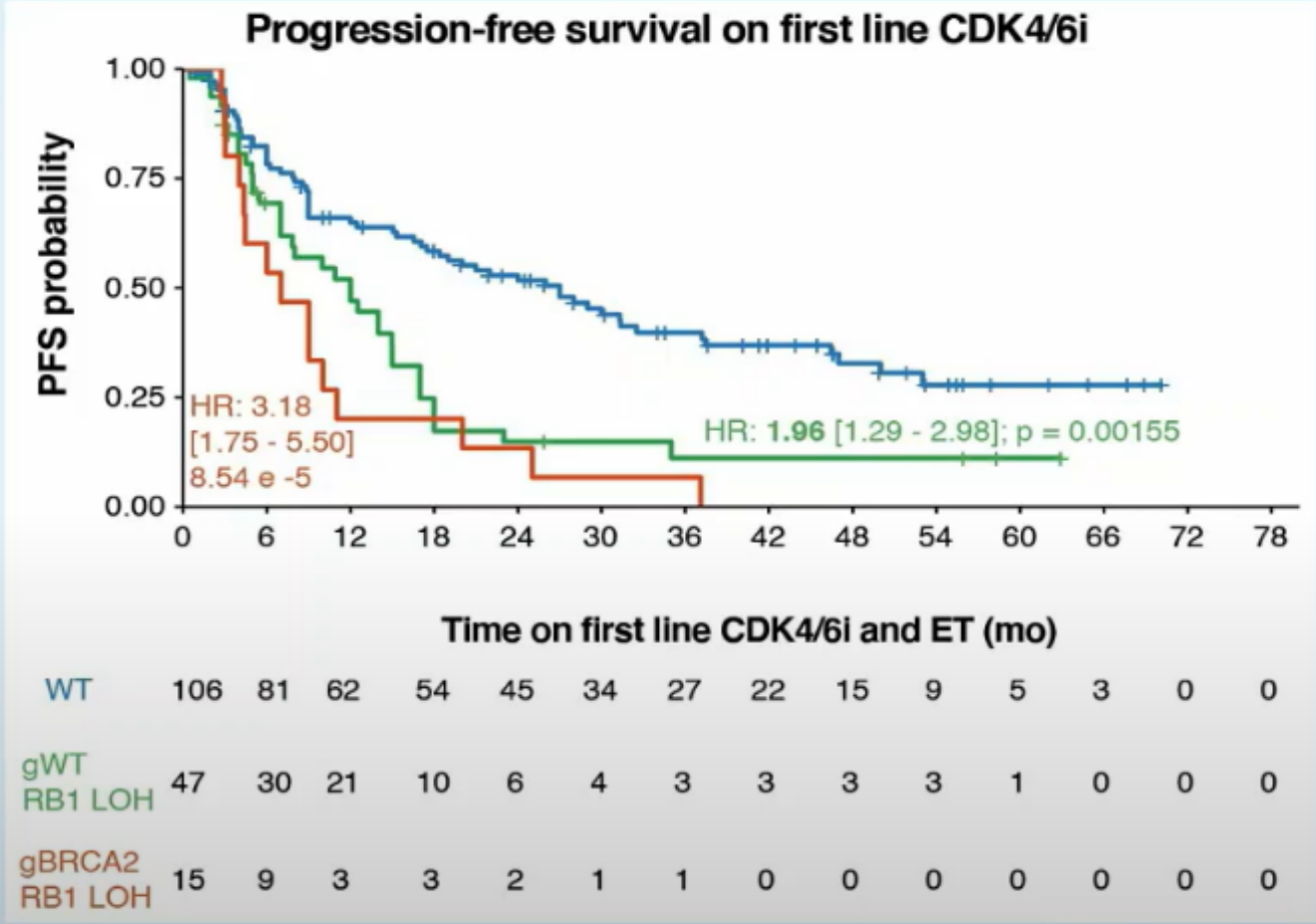



Zambelli A, Cortesi L*,Cancer Treatment Review 2024

* Co-first authors.

# RB1 loss of heterozygosity confers worse outcomes to first-line CDK4/6 + ET

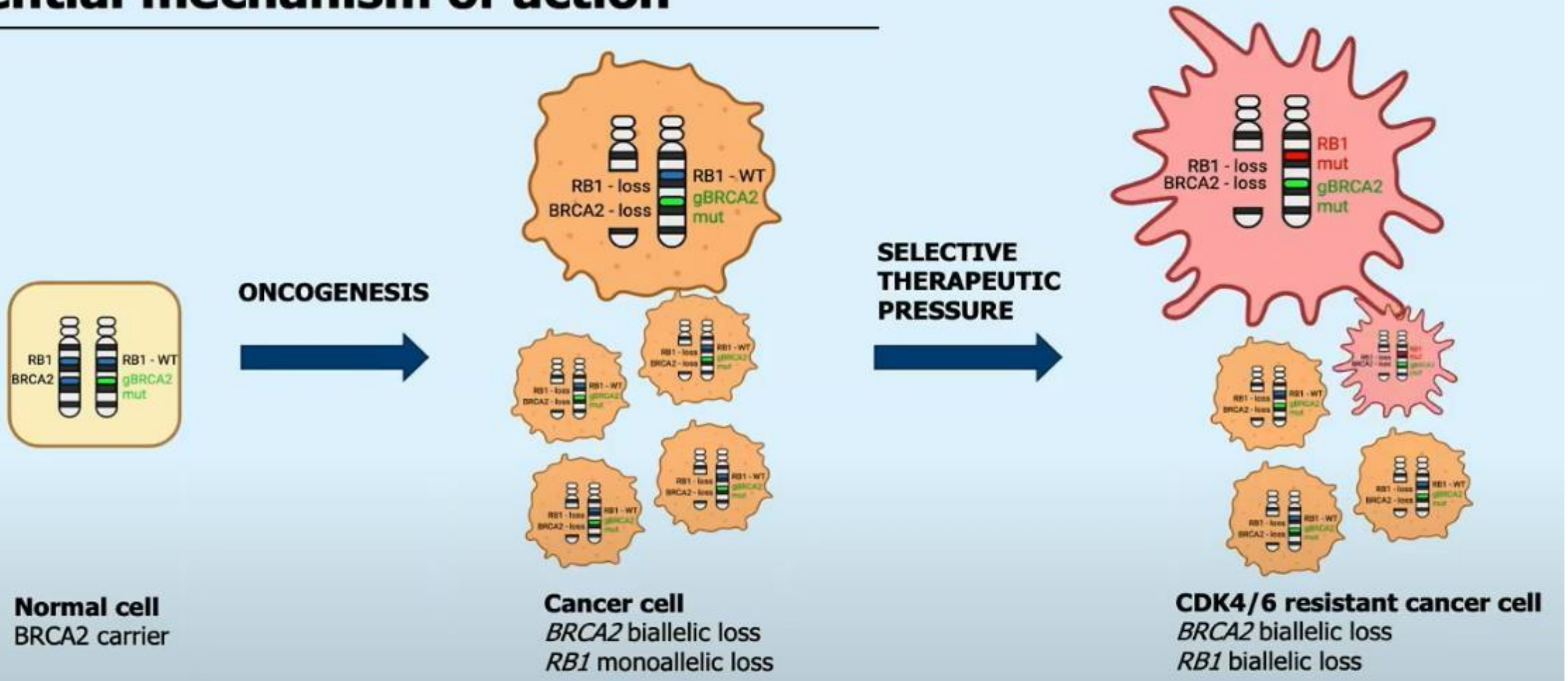
Concomitant *gBRCA2* pathogenic variant and *RB1* LOH confers particularly rapid progression in this setting




| BRCA2 status | Median PFS (mo) [95% CI] |
|---|---|
| gWT RB1 intact | 26.0 [15.3 – 31.4] |
| gWT RB1 LOH | 12.0 [7.5 – 15.0] |
| gBRCA2 RB1 LOH | 7.0 [3.2 – 10.0] |

**Analysis restricted to pre-treatment samples*

# Potential mechanism of action




**Normal cell**
BRCA2 carrier

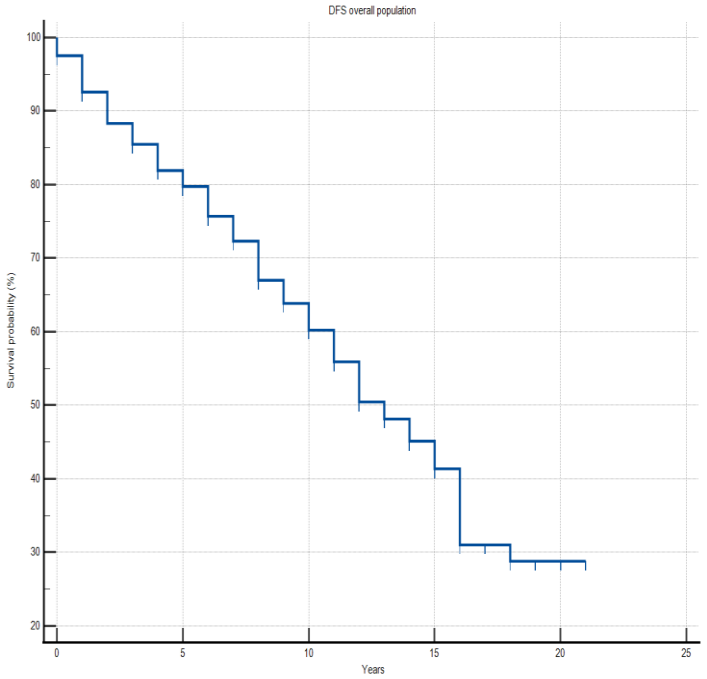
**Cancer cell**
*BRCA2* biallelic loss
*RB1* monoallelic loss

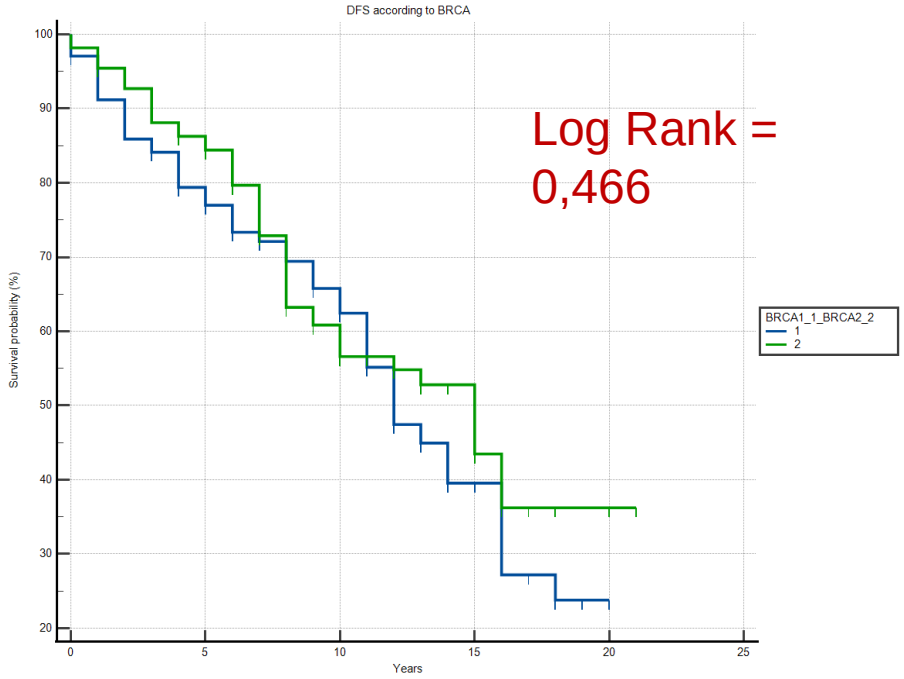
**CDK4/6 resistant cancer cell**
*BRCA2* biallelic loss
*RB1* biallelic loss

# MUTINA RESULTS: OS

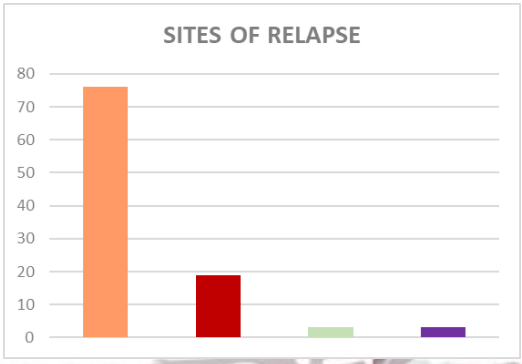
- 136 patients (**47,9%**) had **disease recurrence** during 20 ys. follow-up (ipsilateral local recurrence, contralateral second breast cancer or systemic recurrence)
- Median DFS in overall population was 13 years (95% CI from 11 to 15 ys)
- More BRCA2 developed visceral disease (p=0,013)

Cortesi L et al, ASCO 2023; EJSO *2024*




Log Rank = 0,466

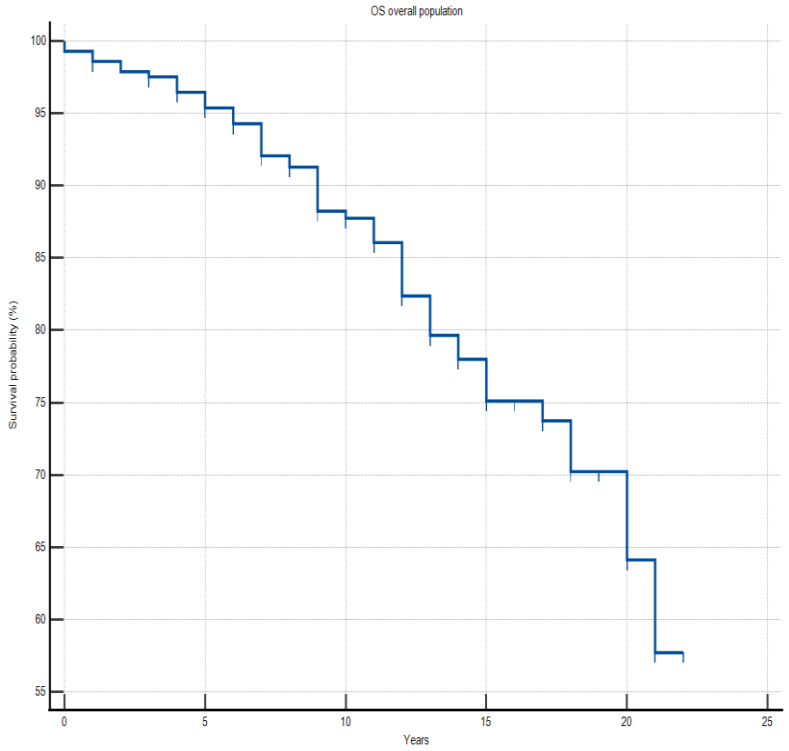


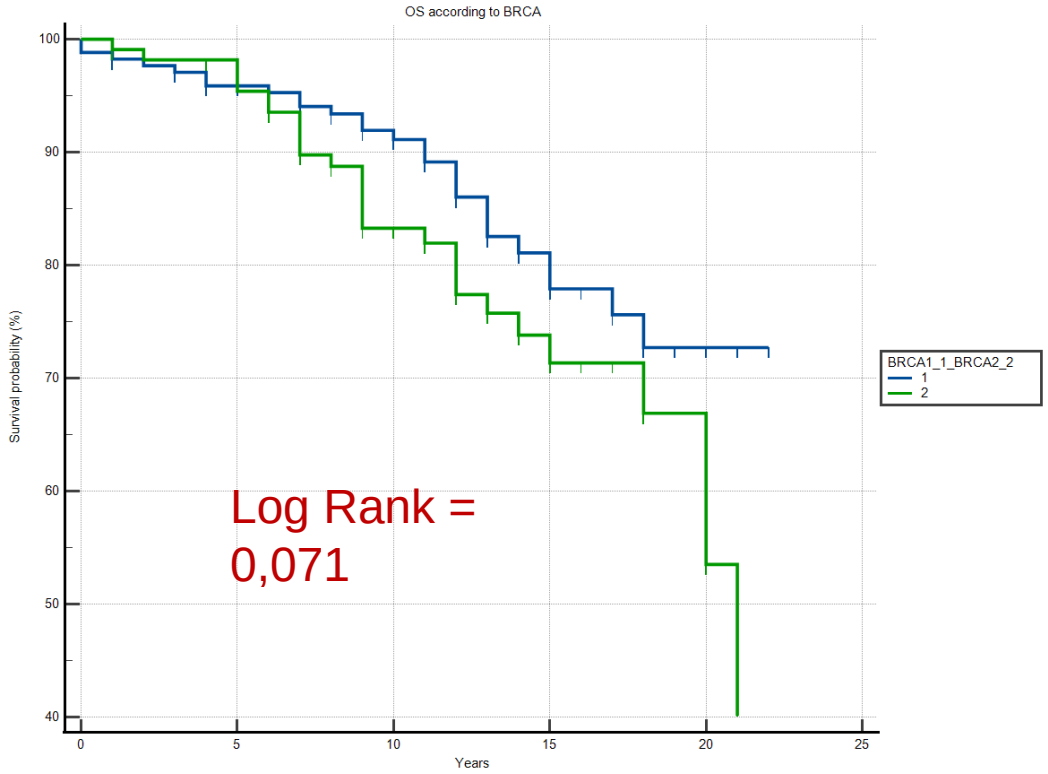

LRR: 83 SBC (42 CBC); 8 only N=91
DR: 45 (12 NVD; 33 VD)

*Loco-regional* *Bone*
*Visceral* *SNC*
* *Unknown*

# MUTINA RESULTS: OS

- Median OS not reached in the whole population
- At the time of analysis:
- **19,7%** died
- **80,3%** alive

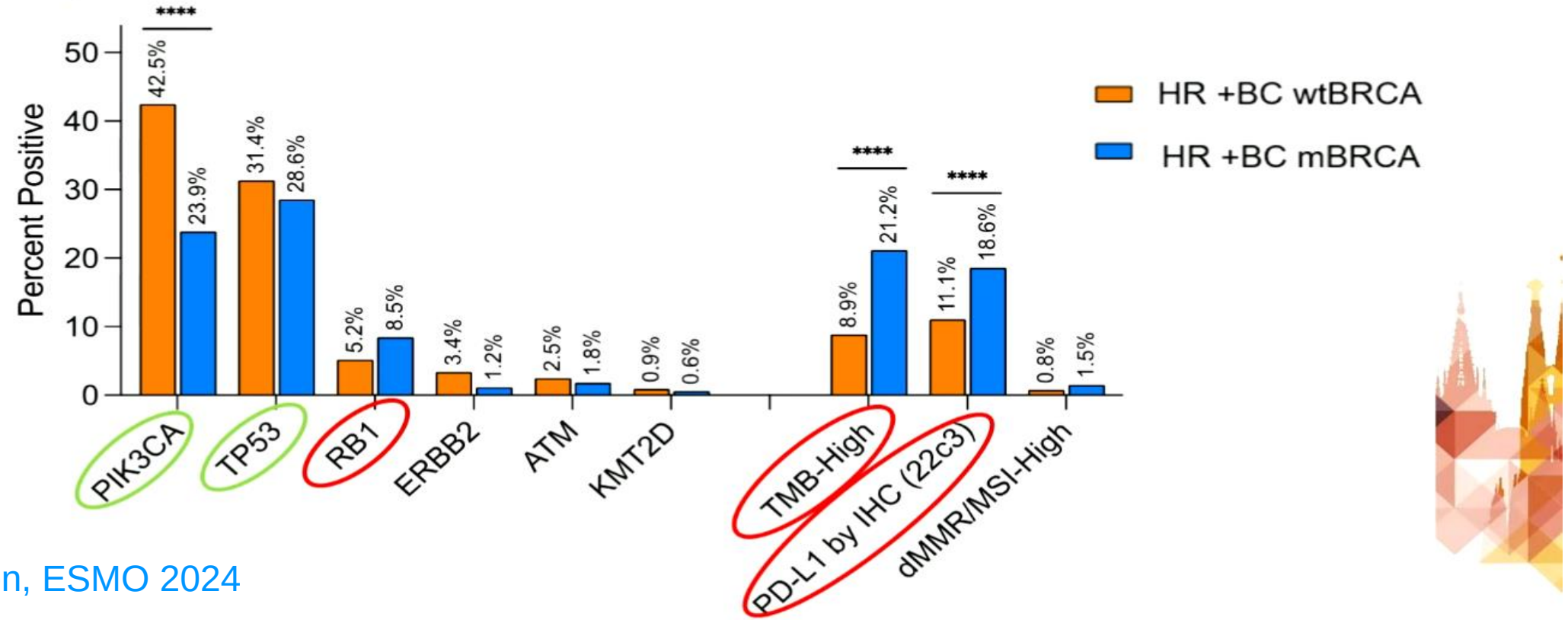



- Almost significant OS benefit in **BRCA1** vs BRCA2

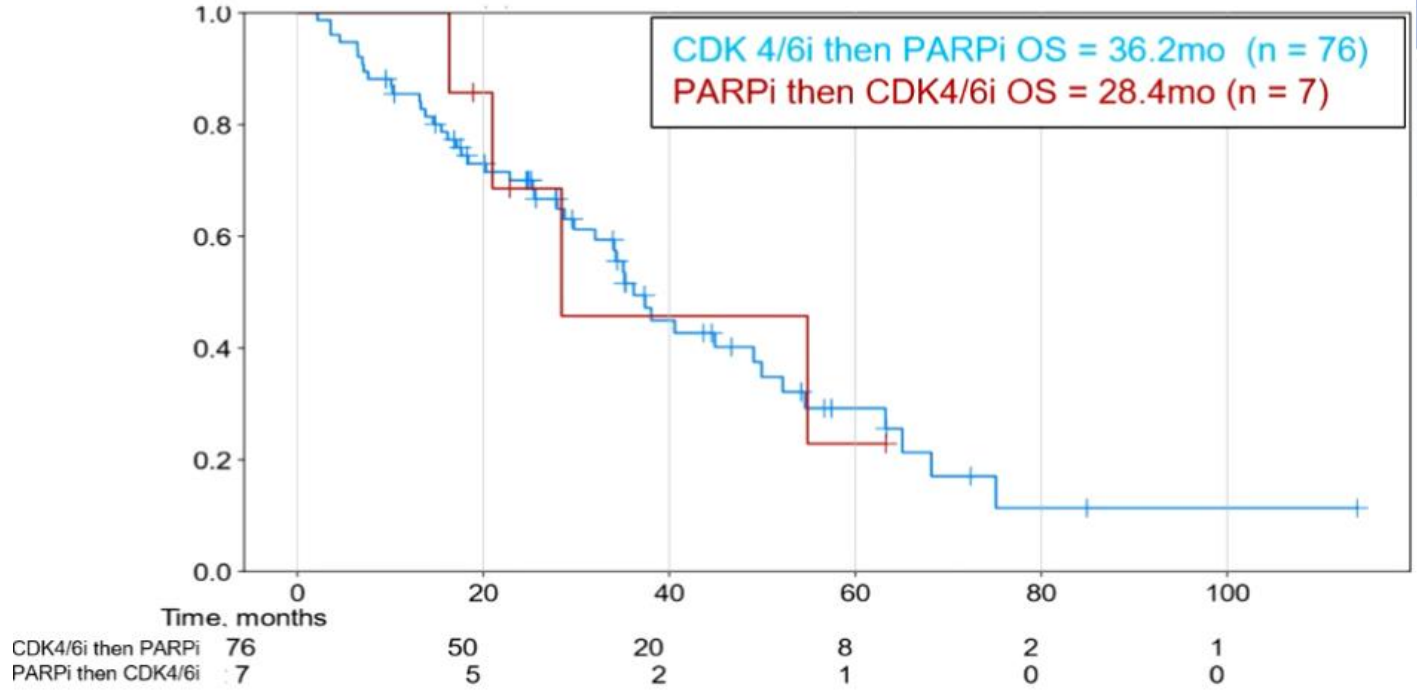
Cortesi L et al, ASCO 2023; EJSO *2024*

# Tumor Mutations associated with HR+BC mBRCA patients compared to HR+BC wtBRCA




G.Parkinson, ESMO 2024

# Overall survival when comparing the order of administration of CDK4/6i vs PARPi in HR+BC mBRCA patients




| | Median OS | 95% CI |
|---|---|---|
| **CDK4/6i then PARPi** | 36.19 mo | 29.77 mo-49.942 mo |
| **PARPi then CDK4/6i** | 28.42 mo | 16.35 mo-Inf |

HR = 1.072 (95% CI: 0.38 - 2.99), p = 0.895

**Median OS difference: 7.76mo**

G.Parkinson, ESMO 2024

TABLE 4 Overall survival and mortality among patients with germline *BRCA1/2*-mutated, HER2-negative advanced breast cancer.

| | TNBC (n = 194) | HR+/HER2– (n= 111) |
|---|---|---|
| **All-cause from index chemotherapy, mo** | | |
| **Kaplan-Meier estimate** | | |
| Mean (SE) | 36.0 (1.5) | 33.7 (1.8) |
| Median | NE | 45.9 |
| 95% CI | 32.5-NE | 29.1-NE |
| Censored, n (%) | 134 (69.1) | 79 (71.2) |
| **Survival rate, % (SE), mo** | | |
| 12 | 83.9 (2.6) | 88.2 (3.1) |
| 24 | 73.9 (3.4) | 77.0 (4.4) |
| 36 | 56.9 (5.1) | 51.6 (8.0) |
| 48 | 56.9 (5.1) | 44.2 (9.7) |
| 60 | 53.1 (6.0) | 44.2 (9.7) |

*BRCA*, germline breast cancer gene; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NE, not estimable; SE, standard error; TNBC, triple-negative breast cancer.

Obeid E., Front Oncol 2024

# Methods: Study Design and Participants

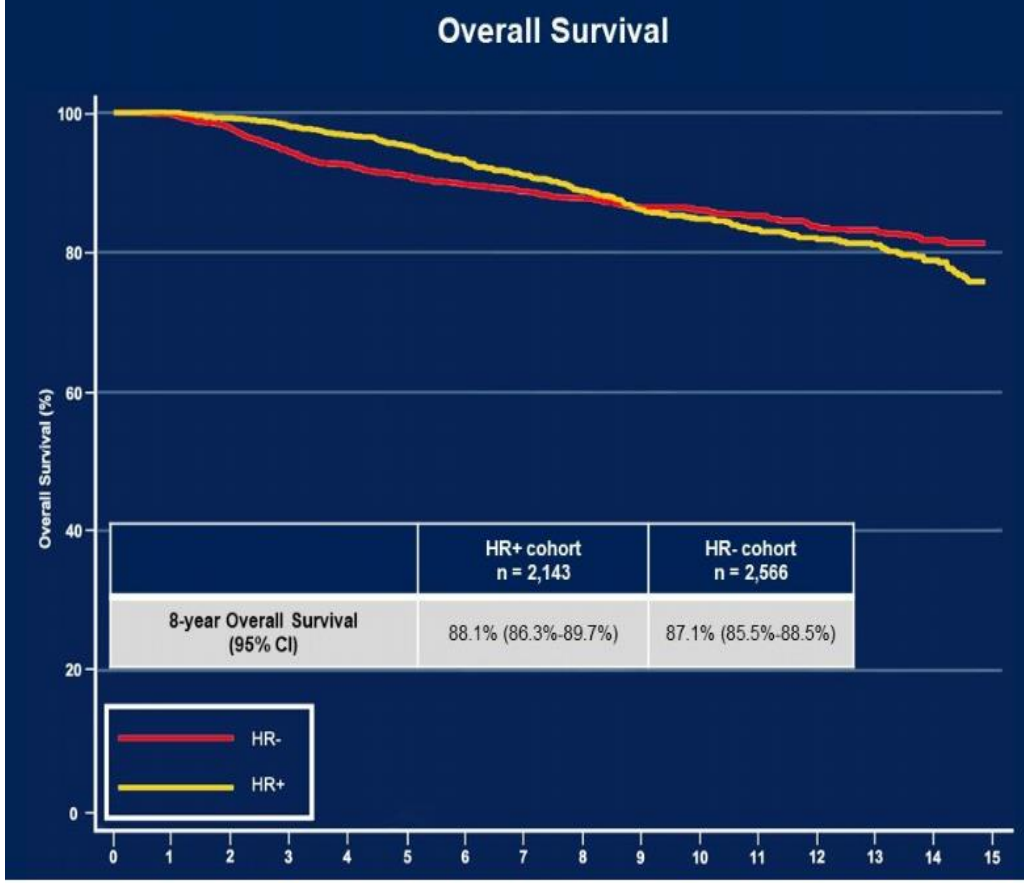
- The ***BRCA* BCY Collaboration** is an international, multicenter, hospital-based, retrospective cohort study (NCT03673306)[1]

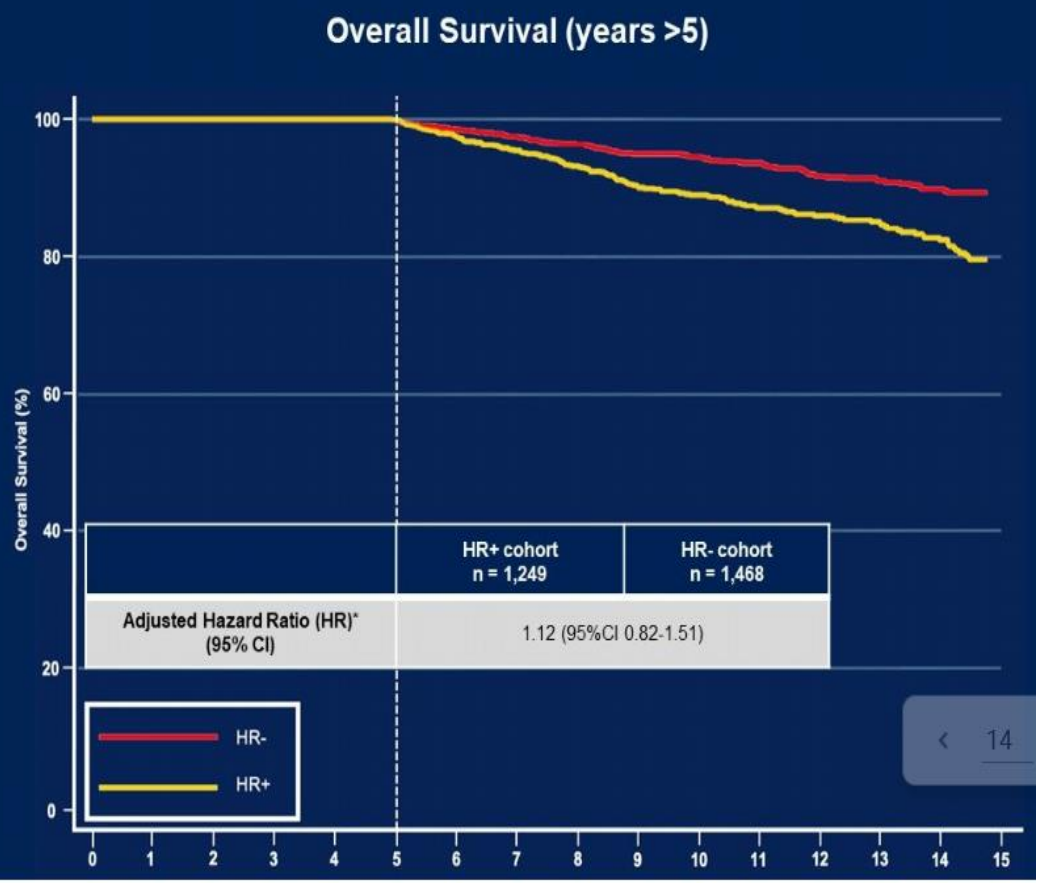
| Key inclusion criteria | Key exclusion criteria |
|---|---|
| Stage I - III invasive breast cancer | Stage IV *de novo* breast cancer |
| Age ≤ 40 years at diagnosis | History of malignancies other than breast cancer or *BRCA* healthy carriers |
| Diagnosis between January 2000 and December 2020 | Lack of data on follow-up |
| Known germline PV in the *BRCA1* and/or *BRCA2* genes | Unknown hormone receptor status |



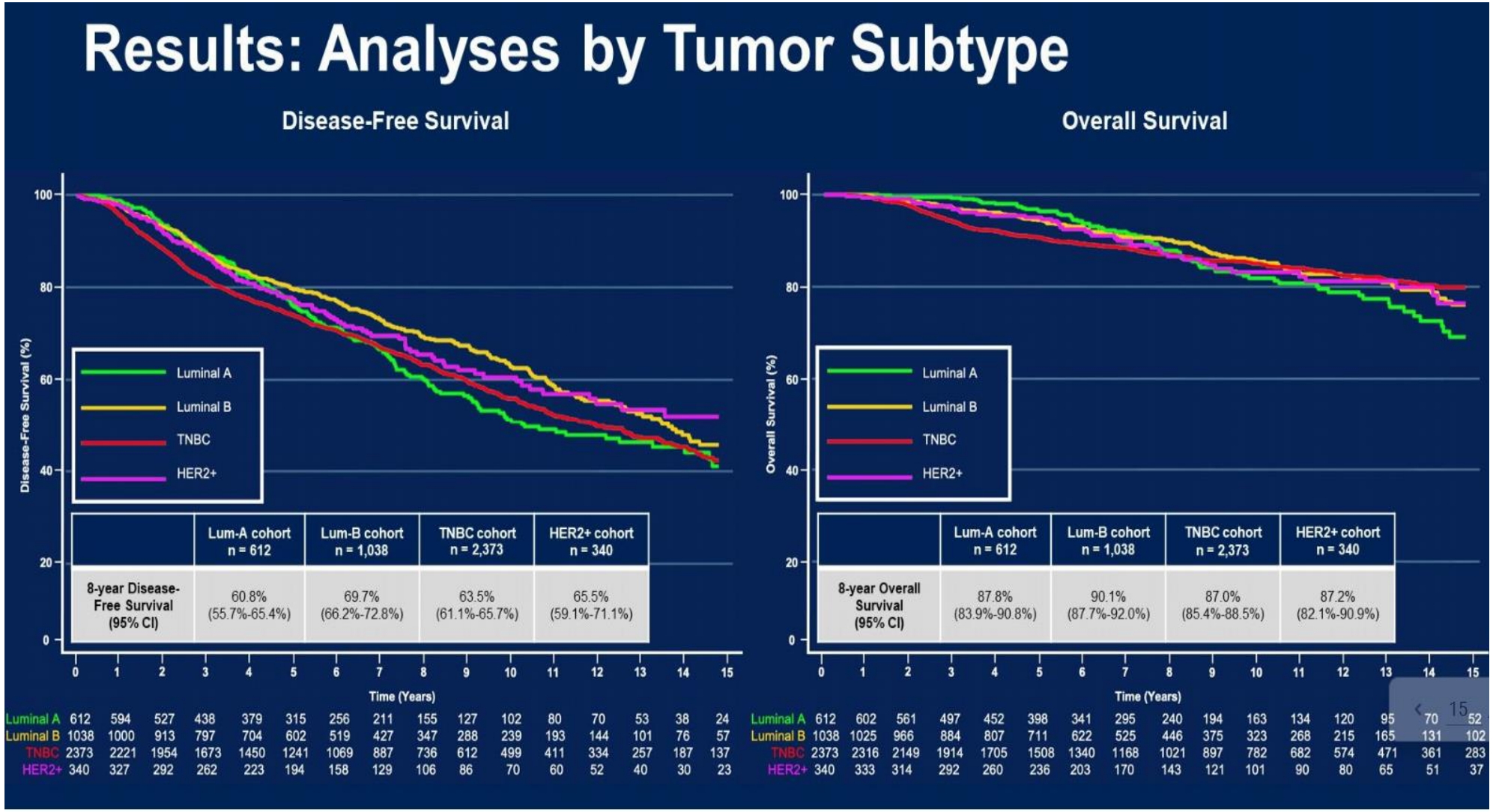
1. Lambertini M et al, *JAMA* 2024;331(1):49-59

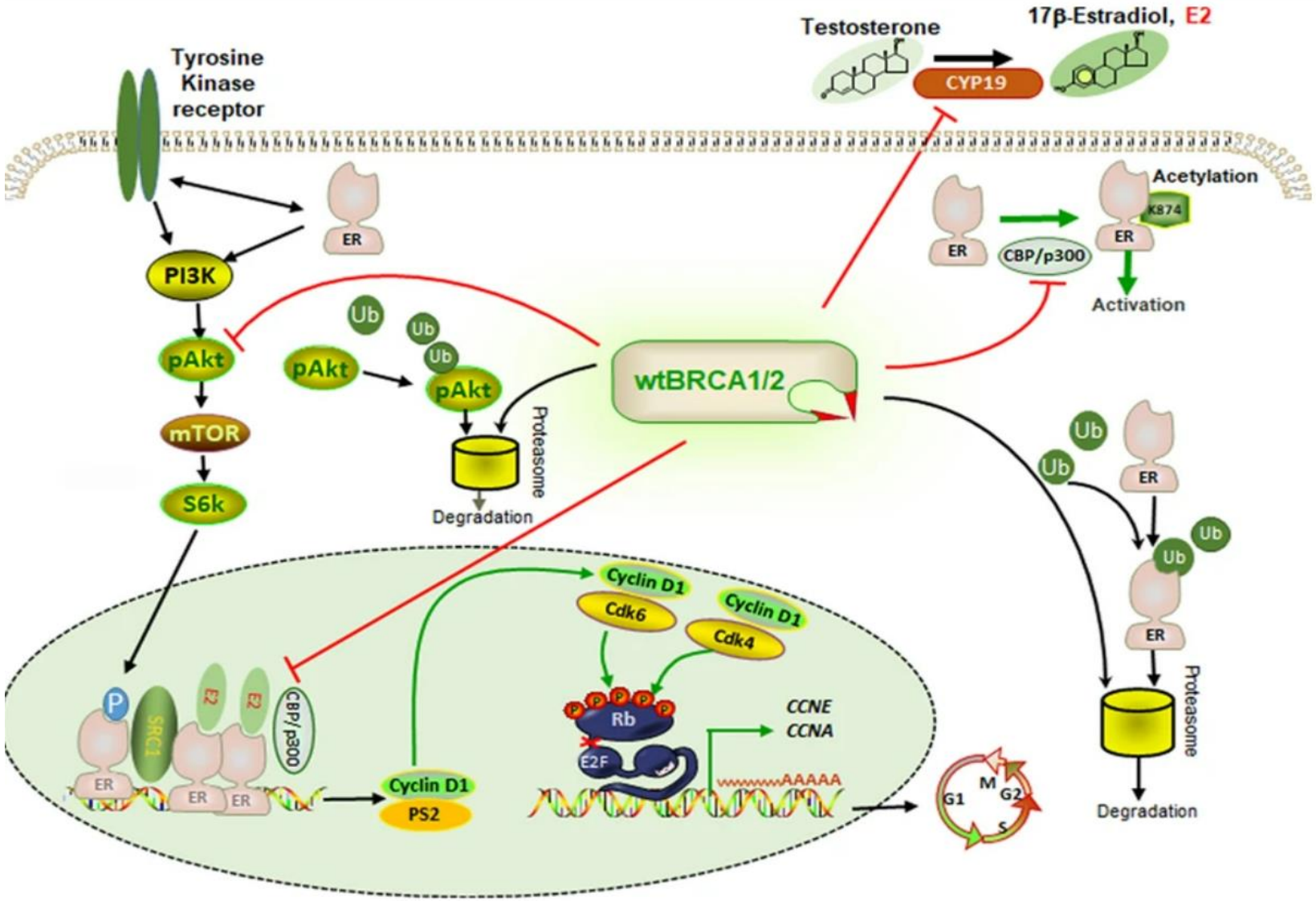
# Results: Analyses by Hormone Receptor Status



# Results: Analyses by Tumor Subtype



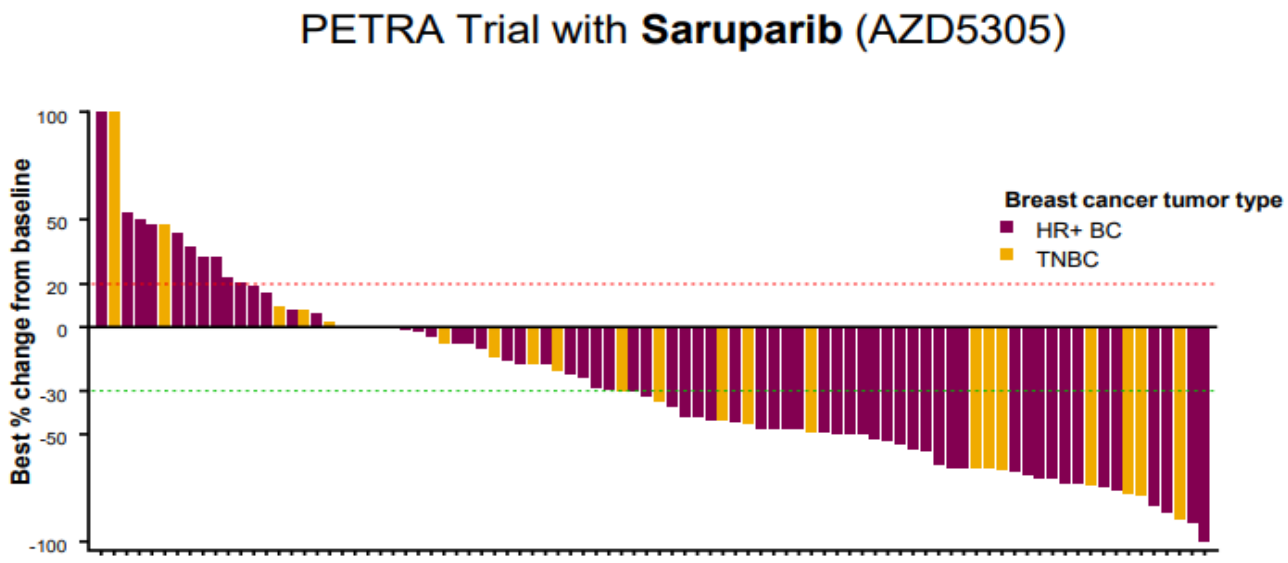



Yan S. Disc Oncol 2023

# PARP inhibitors in metastatic triple-negative breast cancer

## Next generation PARP1-selective inhibitors

- Saruparib is a first-in-class, potent new generation PARP inhibitor with high selectivity for PARP1.
- Wide therapeutic index, superior PK/PD properties and efficacy compared with approved PARP inhibitors
- Favorable safety profile and low rate of dose reduction compared with approved PARP inhibitors

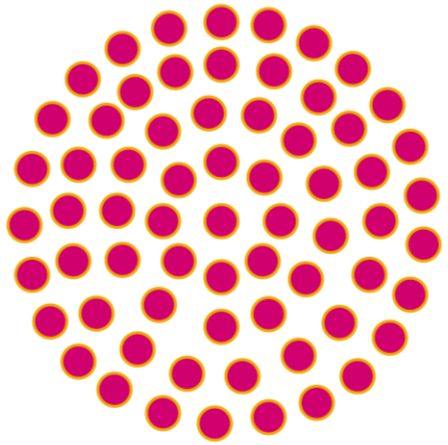



Yap, AACR 2024

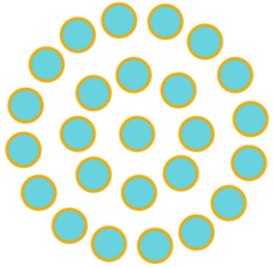


Giuseppe Curigliano, MD PhD

# HOW MANY gBRCAM BREAST CANCERS ARE HER2-POSITIVE?



**~66%**
of gBRCAm breast cancers are HR-positive HER2-negative



**~25%**
of gBRCAm breast cancers are TNBC

**~7%**
of gBRCAm breast cancers are HR-positive HER2-positive

**~2%**
of gBRCAm breast cancers are HR-negative HER2-positive

gBRCAm HR-positive HER2-negative

gBRCAm TNBC

gBRCAm HR-positive HER2-positive

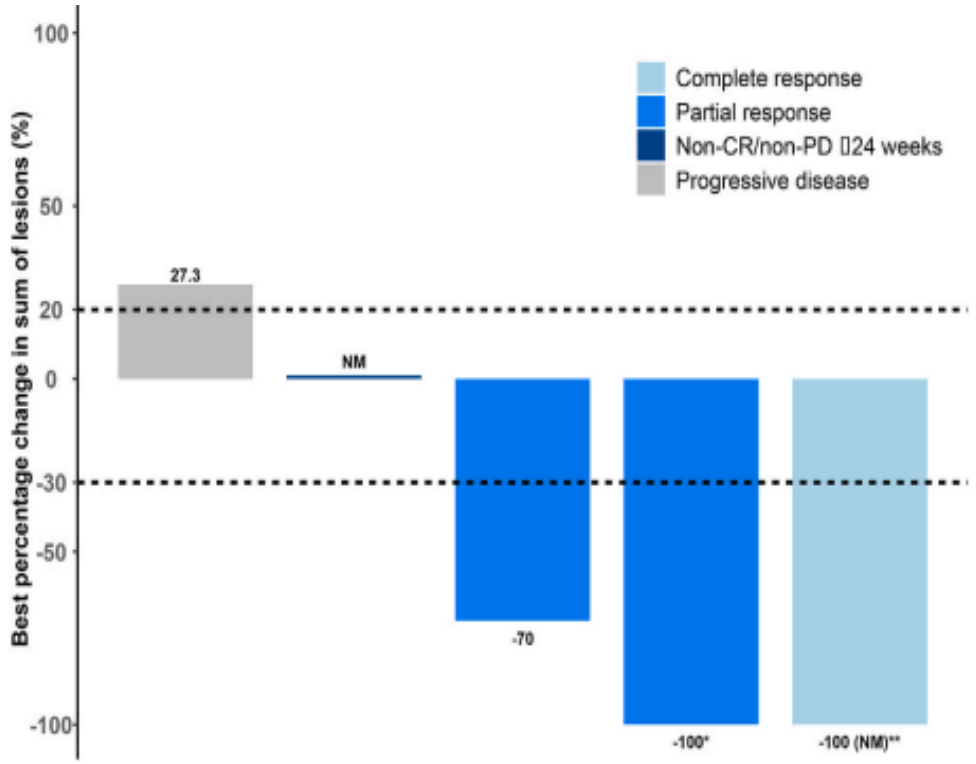
gBRCAm HR-negative HER2-positive

Mesa-Eguiagaray I, et al. Br J Cancer 2020;123:852-859; Winter C, et al. Ann Oncol 2016;27:1532–1538; Winter C, et al. Ann Oncol 2016;27:1532–1538 suppl;

# OLAPARIB PLUS TRASTUZUMAB IN HER2-POSITIVE ADVANCED BREAST CANCER PATIENTS WITH GERMLINE BRCA1/2 MUTATIONS: THE OPHELIA PHASE 2 STUDY

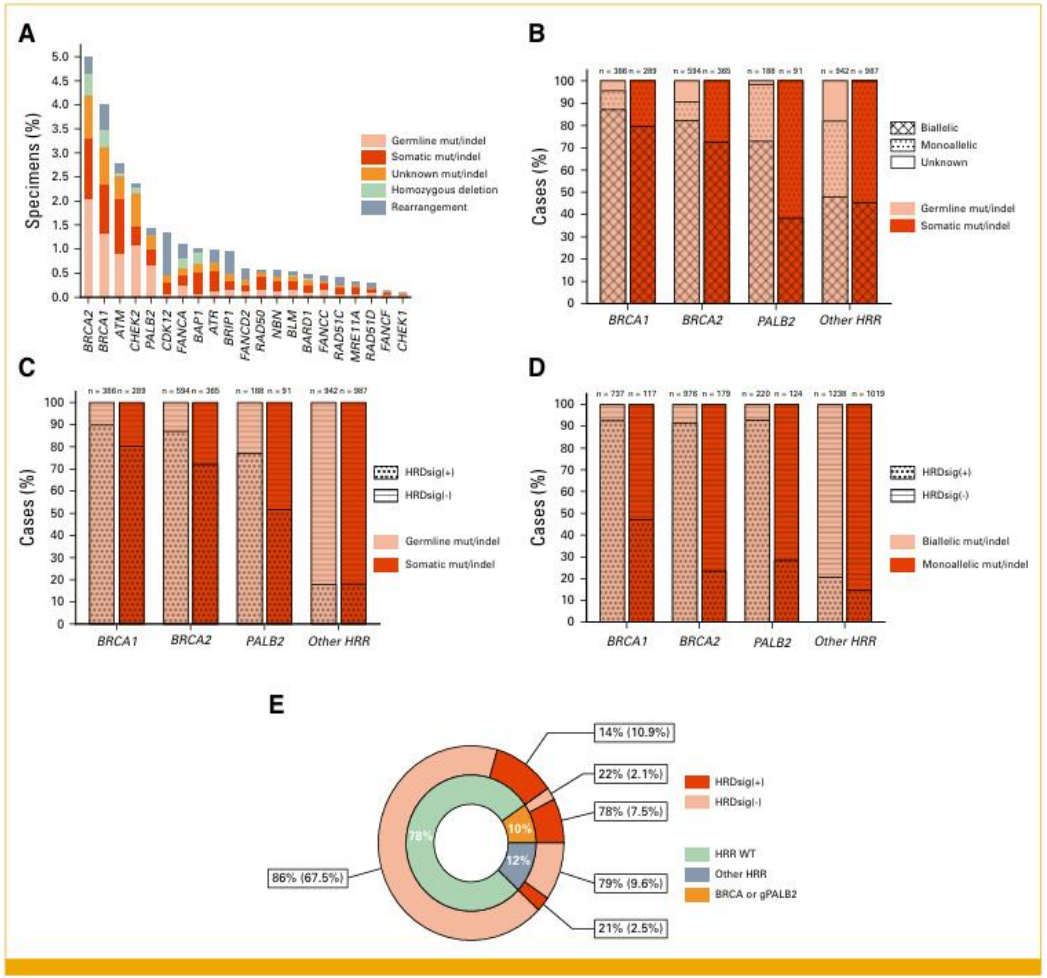
**Table 1**
Baseline patient characteristics.

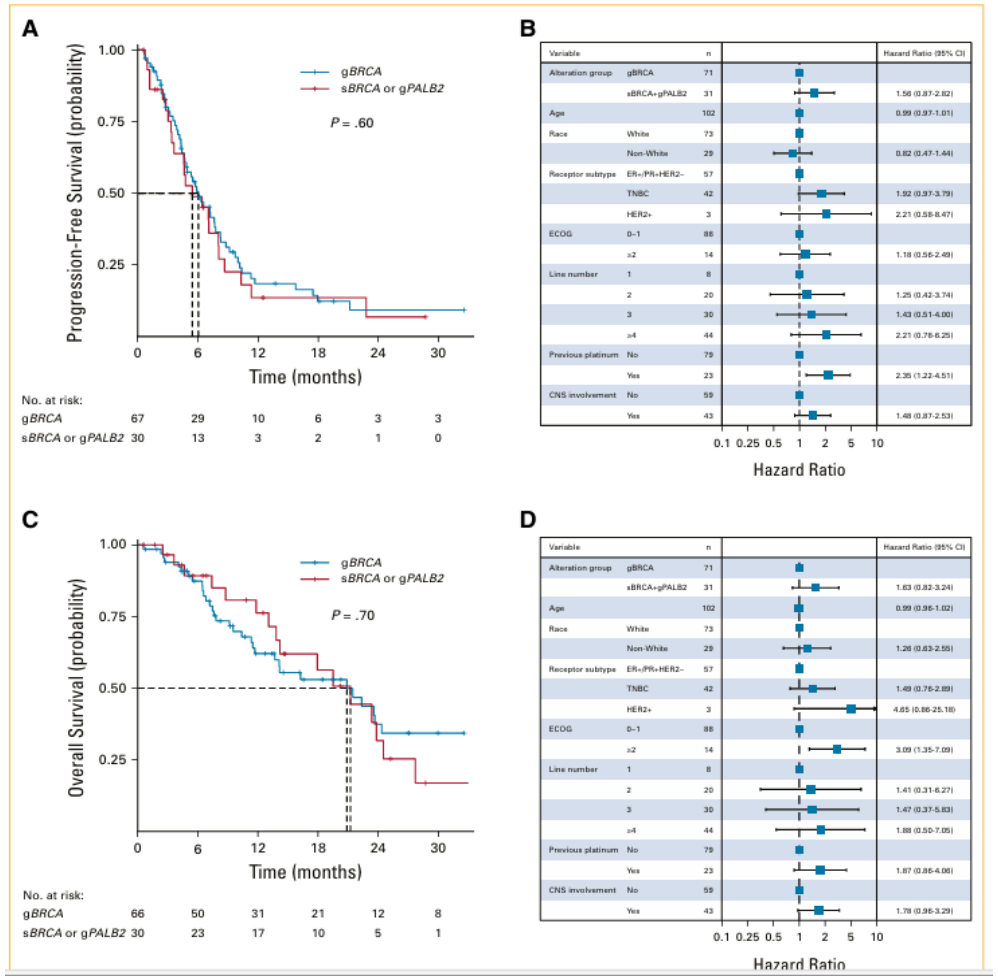
| Baseline characteristics | n (%)<br>N = 5 |
|---|---|
| **Age; median (min; max) (years)** | 37.0 (32.0; 54.0) |
| **Sex** | |
| Female | 4 (80.0) |
| Male | 1 (20.0) |
| **Premenopausal status** | |
| No | 2 (40.0) |
| Yes | 2 (40.0) |
| NA (male) | 1 (20.0) |
| **ECOG performance status** | |
| 0 | 3 (60.0) |
| 1 | 2 (40.0) |
| **Measurable lesions** | |
| Yes | 3 (60.0) |
| No | 2 (40.0) |
| **Disease sites** | |
| Bones | 3 (60.0) |
| Lung | 2 (40.0) |
| Brain | 1 (20.0) |
| Breast | 1 (20.0) |
| Liver | 1 (20.0) |
| Lymph nodes | 1 (20.0) |
| Mediastinum | 1 (20.0) |
| **Number of metastatic sites** | |
| 1 | 1 (20.0) |
| 2 | 3 (60.0) |
| 3 | 1 (20.0) |
| **HR status** | |
| Positive | 3 (60.0) |
| Negative | 2 (40.0) |
| ***BRCA* mutations** | |
| Germinal *BRCA1* mutation | 1 (20.0) |
| Germinal *BRCA2* mutation | 4 (80.0) |
| **Advanced disease at first diagnosis** | |
| Yes | 3 (60.0) |
| No | 2 (40.0) |
| **Number of previous lines of therapy for ABC** | |
| 1 | 1 (20.0) |
| 3 | 2 (40.0) |
| 4 | 2 (40.0) |
| **Previous treatment for ABC** | |
| Anti-HER2 agents | 5 (100.0) |
| Trastuzumab + pertuzumab | 5 (100.0) |
| T-DM1 | 2 (40.0) |
| Other | 1 (20.0) |
| Chemotherapy | 5 (100) |
| Therapeutic radiopharmaceuticals | 2 (40.0) |
| Endocrine therapy | 1 (20.0) |




Curigliano, Ales-Martinez Breast 2024

HRD Landscape and Biomarkers for PARP Inhibitors in Breast Cancer



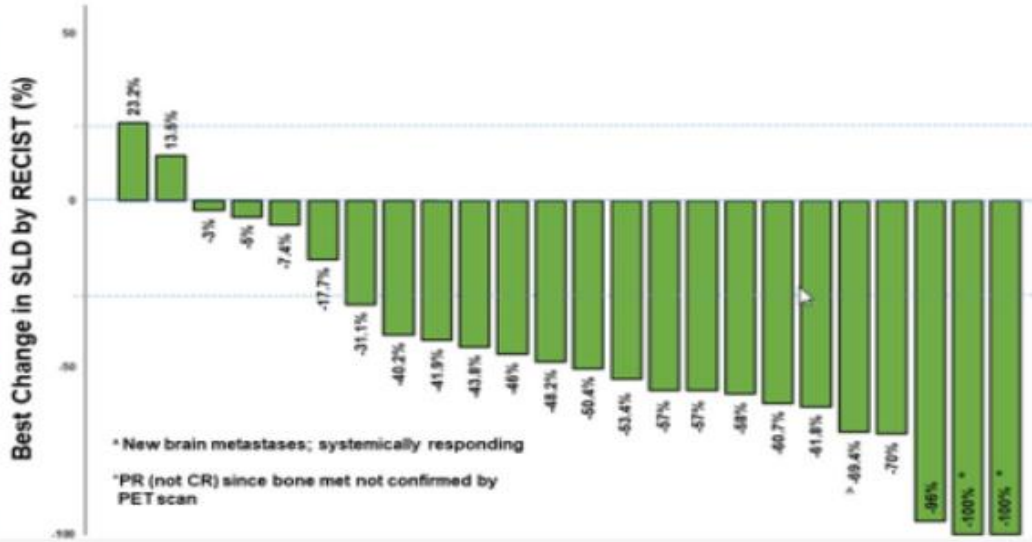




Batalini F., JCO Prec Oncol 2023

# Responses for g*PALB2*

| g*PALB2* N=24 | |
|---|---|
| **Best Response** | **Responses (rate, %)** |
| Complete Response (CR) | 1 (4%) |
| Partial Response (PR) | 17 (71%) |
| Stable Disease (SD) | 5 (21%) |
| Progressive Disease (PD) | 1 (4%) |
| ORR = 75% (18/24, 80%-CI: 60%-86%) | |
| CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%) | |

Datacut May 3, 2024




| Tumor subtype | Responses |
|---|---|
| TNBC | 2/2 |
| ER+/HER2-neg | 13/19 |
| HER2+ | 3/3 |

# (EVOPAR-BREAST01)

A randomized phase III study of first-line saruparib (AZD5305) plus camizestrant vs CDK4/6i plus physician's choice endocrine therapy or plus camizestrant in patients with BRCA1/BRCA2/PALB2 mutations and HR+/HER2− advanced breast cancer (EvoPAR-Breast01)

**Key Eligibility**

- De novo metastatic breast cancer, or localized disease with progression that is no longer amenable to treatment with curative intent
- First line HR-positive, HER2-negative advanced breast cancer
- *BRCA1* or *BRCA2* or *PALB2* mutation (germline or somatic)


**Stratification Factors:**

- Liver metastasis vs non-liver visceral metastasis vs non-visceral metastasis
- TFI <12 months vs TFI ≥12 months or de novo metastatic [c]
- Prior PARP inhibitor or platinum chemotherapy (yes vs no)

| Endpoint | Measure |
|---|---|
| Primary | PFS (BICR) [d] |
| Key Secondary | OS |

## CONCLUSIONS

- TNBC: early platinum-based therapy ⟶ PARPi
- TNBC PDL-1: CT+IO, PARPi if already treated as KN-522
- HR+/HER2-:always PARPi after CDK4/6i (early or advanced)
- More visceral recurrences in gBRCA2 than gBRCA1 and worst OS in Luminal A than Luminal B
- TNBC/HR+ after Olaparib: saruparib 25% ORR
- HER2+ gBRCA:Olaparib+Trastuzumab=60% ORR (a few patients)
- Olaparib in gPALB2: 75% ORR
- Saruparib in first line study: EvoPAR-Breast01