SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena

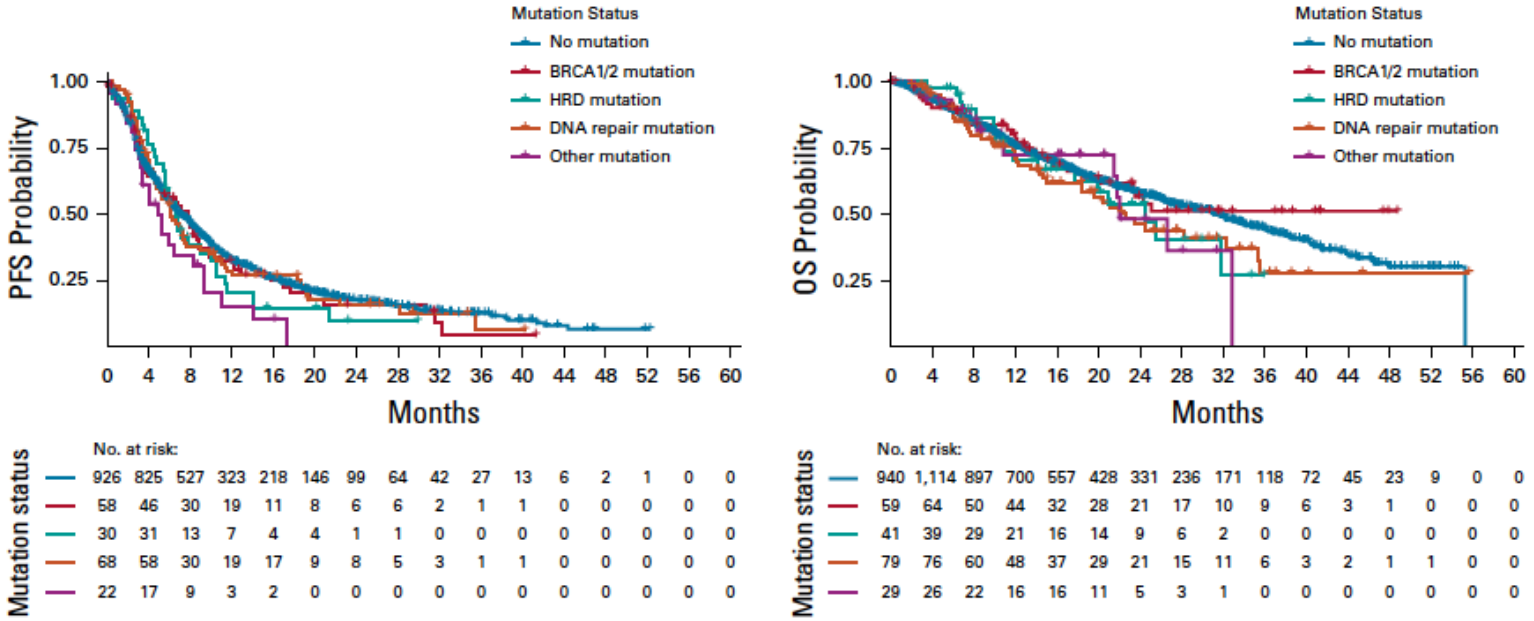
Università degli Studi di Modena e Reggio Emilia

Il carcinoma mammario metastatico in donne con VP gBRCA

Laura Cortesi

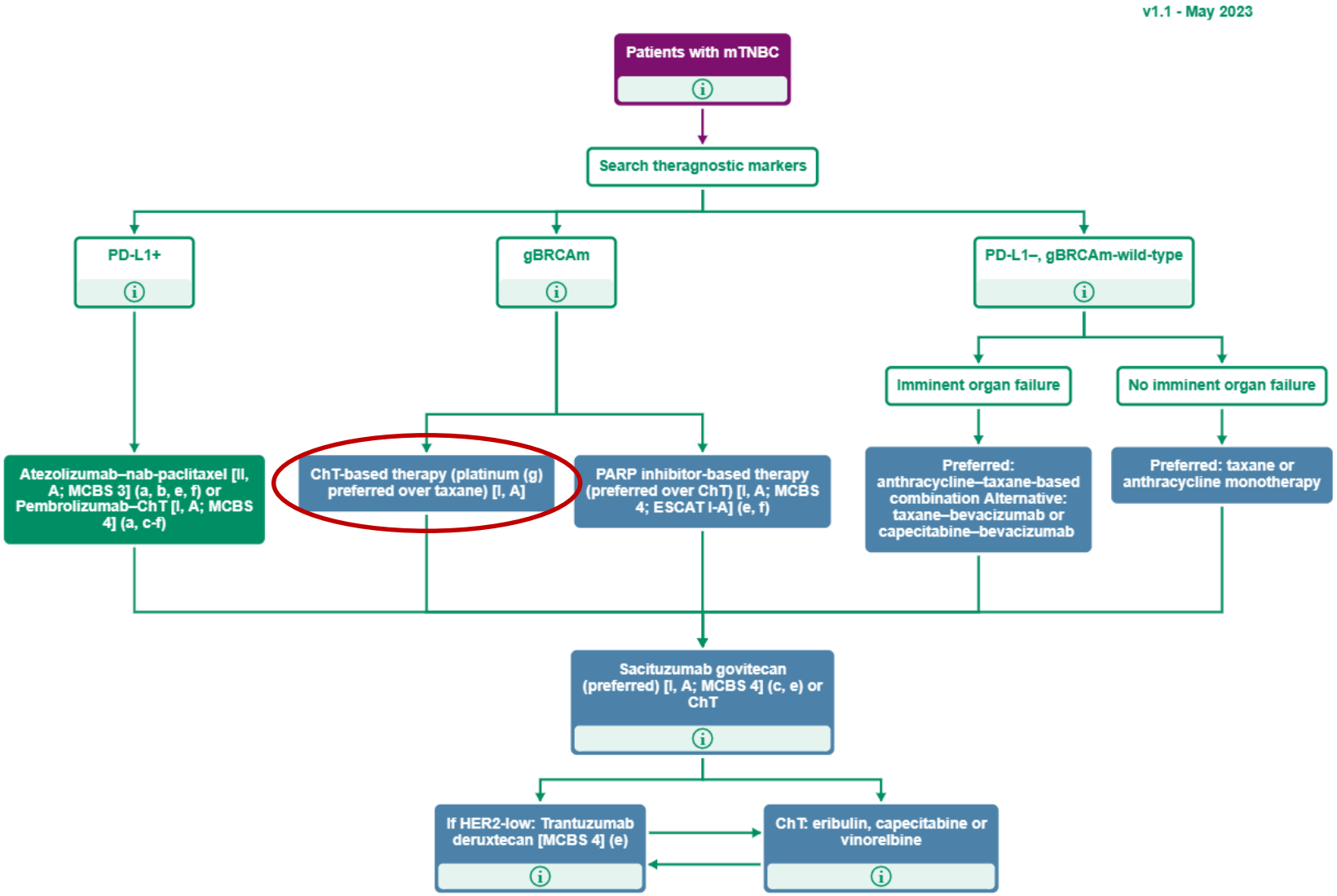
SS Genetica Oncologica-AOU Policlinico Modena

Mutations did not significantly modify PFS or OS for patients with mBC



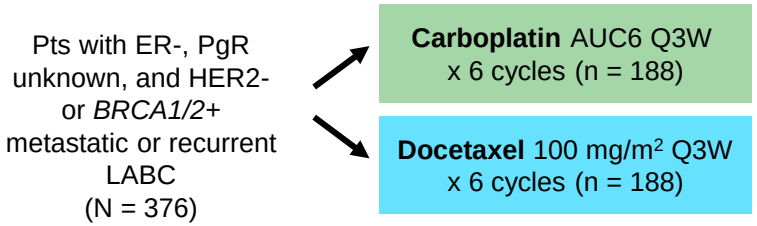
1. Peter A. Fasching, Siddhartha Yadav, Chunling Hu et al JCO 2021

ESMO GUIDELINES METASTATIC TNBC



TNT: Carboplatin vs Docetaxel in Advanced TNBC or *BRCA1/2* Positive Breast Cancer

Study Design



BRCA1/2 mut vs WT populations

	Carboplatin	Docetaxel	*P* value
ORR, %	31.4	35.6	.44
BRCA1/2 mutated	68	33	.03
BRCA1/2 nonmutated	28.1	36.6	.16
Median PFS, mo	3.1	4.5	
BRCA1/2 mutated	6.8	4.8	
BRCA1/2 nonmutated	3.1	4.6	

Primary endpoint: ORR in ITT population

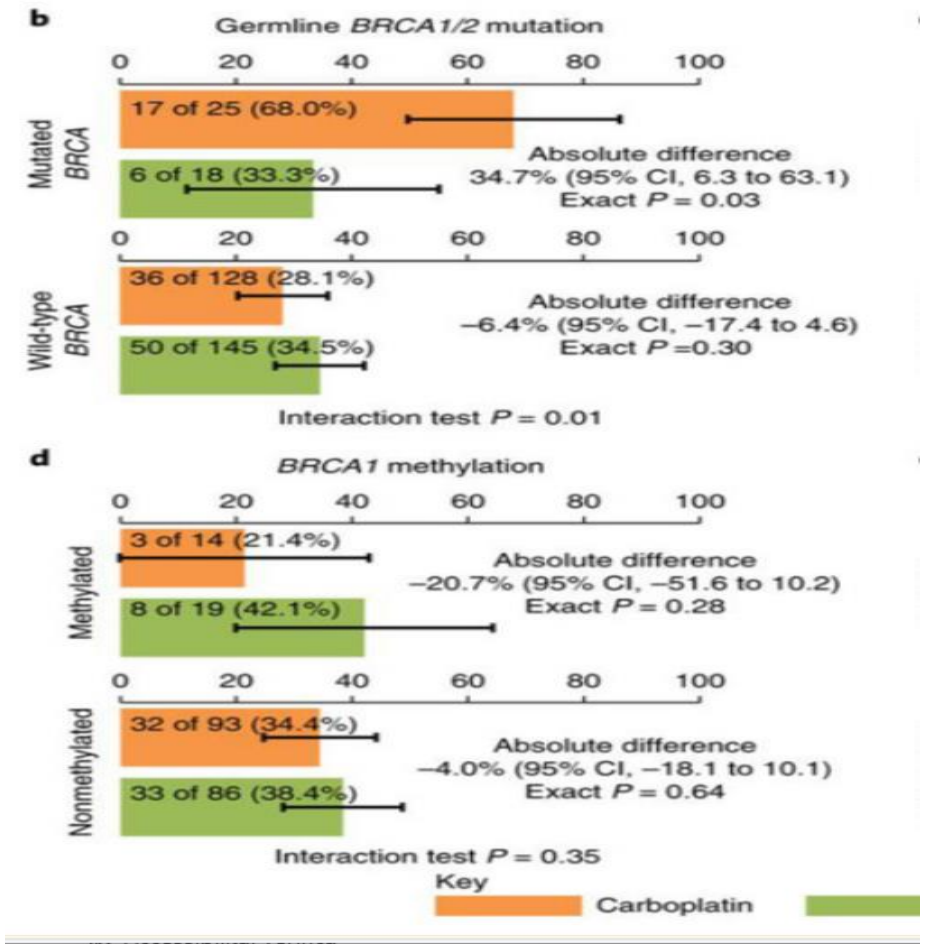
Secondary endpoints: PFS, OS, ORR (crossover), toxicity

Subgroup analyses: *BRCA*1/2 mutation, basallike subgroups, HRD biomarkers

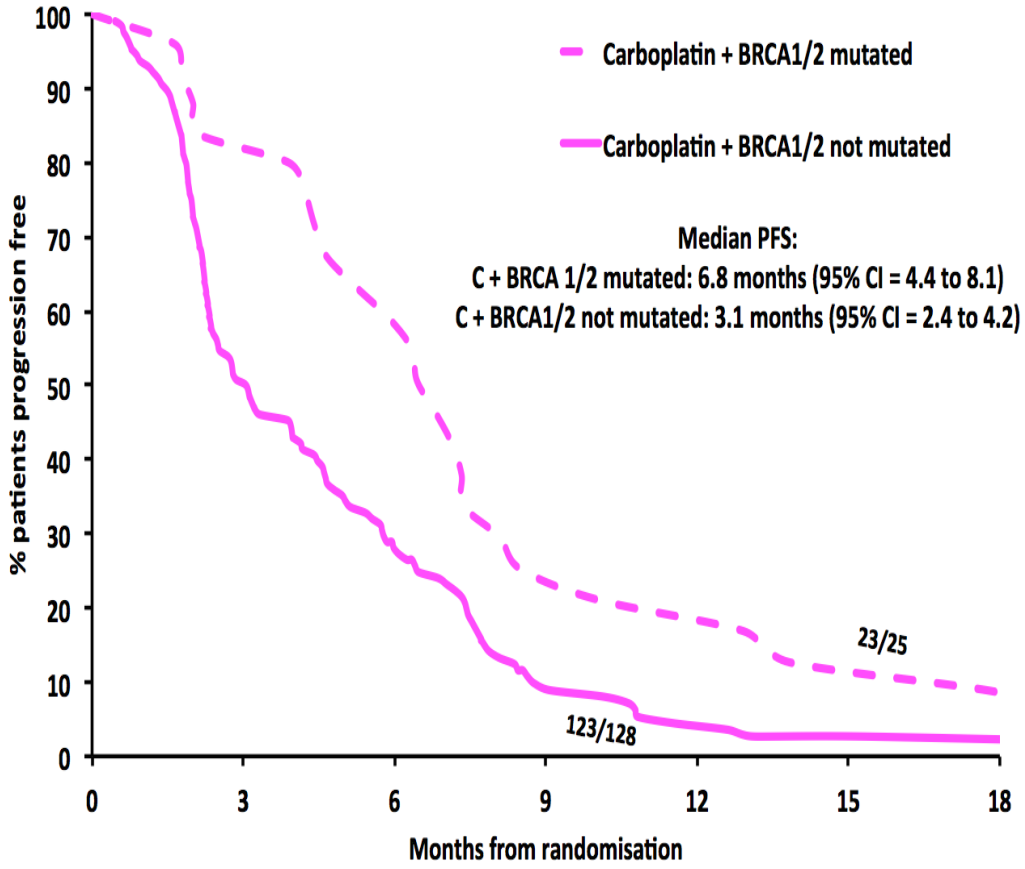
Tutt A, et al. Nat Medicine 2018

TNT: Carboplatin vs Docetaxel in Advanced TNBC or *BRCA1/2* Positive Breast Cancer

Objective Response Rate



Progression-Free Survival



Tutt A et al, Nat Med 2018;24(5):628-37

ESMO GUIDELINES METASTATIC TNBC

Germline BRCA Mutations (mTNBC)

- If *gBRCAm* and PD-L1 negative, the preferred options are olaparib or talazoparib [I, A; **ESMO-MCBS v1.1 score: 4**; ESCAT score: I-A] or ChT with carboplatin [II, A] (see text below).

Olaparib; **ESMO-MCBS (v1.1) score: 4**
Talazoparib; **ESMO-MCBS (v1.1) score: 4**

Context

Two randomised studies of patients with HER2-negative MBC and *gBRCAm* previously treated with anthracyclines and/or taxanes demonstrated that treatment with a PARP inhibitor (olaparib, talazoparib) resulted in statistically significant improvements in PFS compared with capecitabine, vinorelbine, eribulin or (in one study) gemcitabine. (Robson, 2017; Litton, 2018) OS was not improved but a *post hoc* subset analysis of one study suggested improved OS in patients receiving olaparib who had not received prior ChT for metastatic disease. (Robson, 2019)

Carboplatin may be considered as a superior treatment option to docetaxel, since median PFS was improved but only by 2.6 months without an OS benefit. (Tutt, 2018)

There are no studies directly comparing PARP inhibitors with a platinum agent. In the pivotal trials, health-related quality of life (HRQoL) was better with PARP inhibitors compared with ChT. (Robson, 2019; Ettl, 2018)

Hereditary breast cancer >

v1.1 - May 2023

Curigliano, 2023

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)

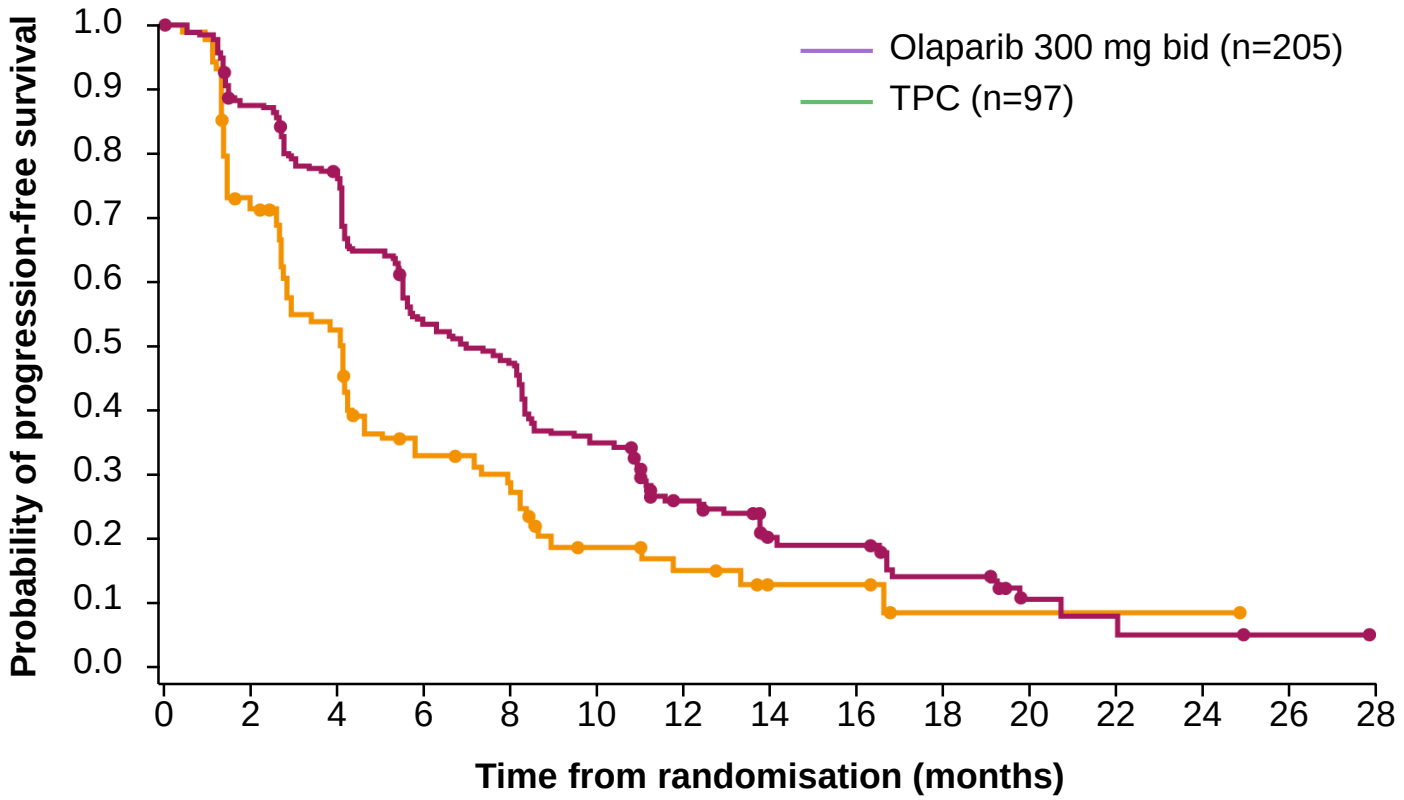
Primary endpoint
- PFS (RECIST 1.1, Independent Review)

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. https://clinicaltrials.gov/ct2/show/NCT02000622 [Accessed February 2019]; 2. Robson et al. Poster OT1-1-04, presented at SABCS 2014; 3. AZ data on file (2017); 4. Robson 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 (%)	163 (79.5%)	71 (73.2%)
Median (m)	7.0	4.2
	HR=0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

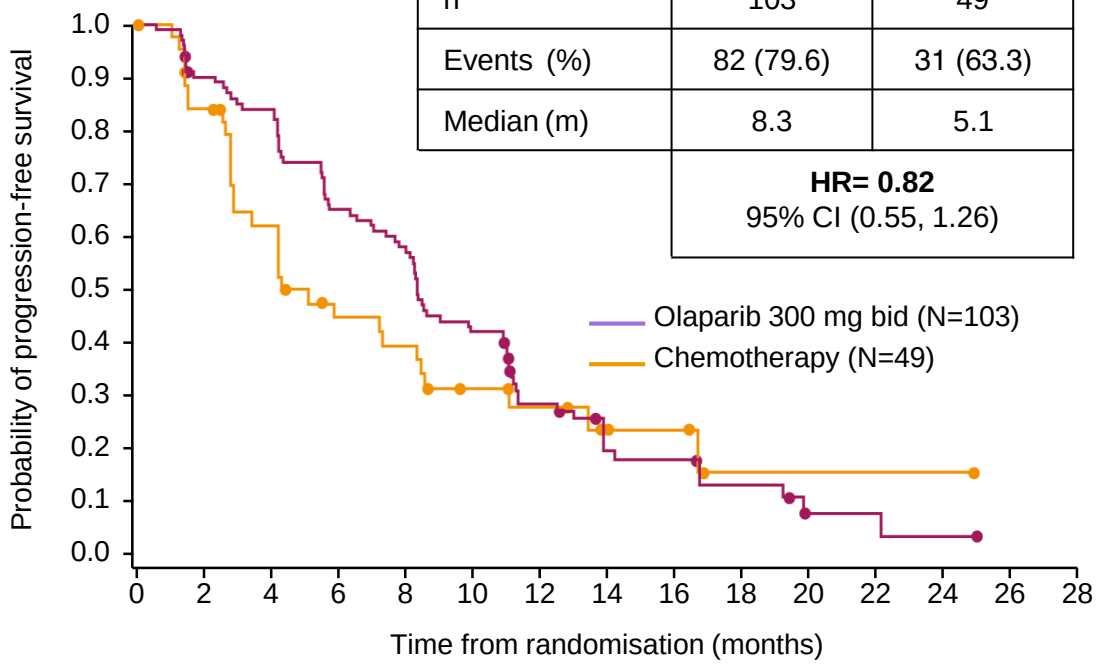
Median PFS was improved by 42% with olaparib treatment compared to standard of care chemotherapy

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

Risk of progression was reduced in olaparib-treated patients with HR+ disease and TNBC compared to TPC[1]

Patients with HR+ mBC[2]

	Olaparib	TPC
n	103	49
Events (%)	82 (79.6)	31 (63.3)
Median (m)	8.3	5.1
	HR= 0.82 95% CI (0.55, 1.26)	

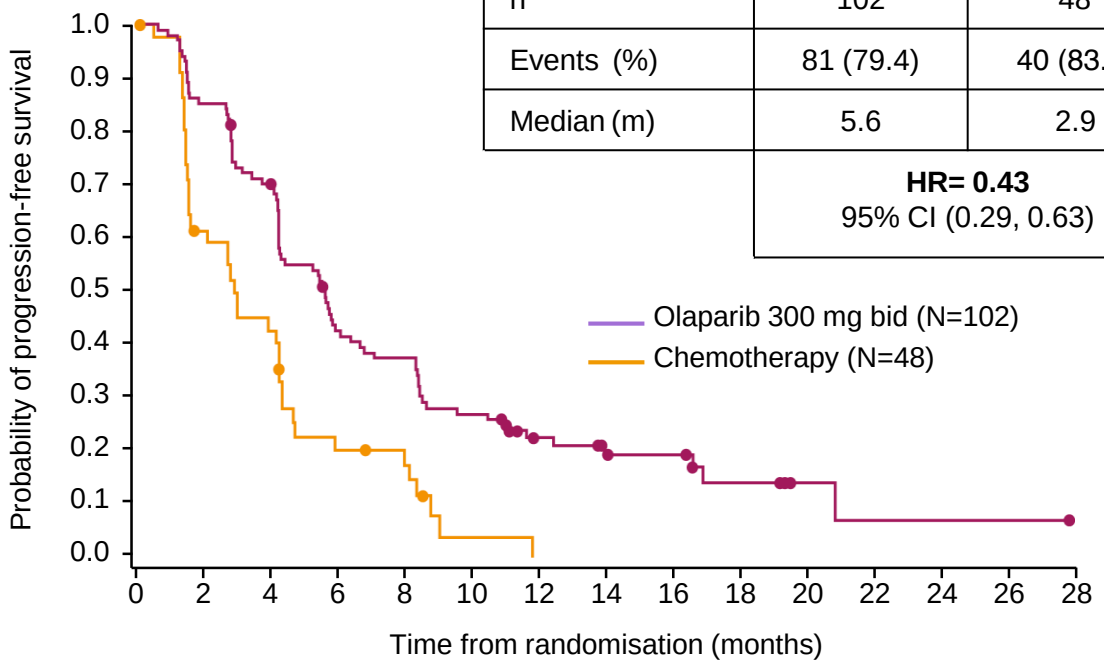


Number of patient's at risk

Olaparib	103	102	91	86	85	75	66	63	58	46	43	39	23	20	13	12	12	6	6	6	2	2	2	1	1	0	0	0	0
TPC	49	45	37	27	26	20	17	17	15	11	10	10	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Patients with TNBC[2]

	Olaparib	TPC
n	102	48
Events (%)	81 (79.4)	40 (83.3)
Median (m)	5.6	2.9
	HR= 0.43 95% CI (0.29, 0.63)	



Number of patient's at risk

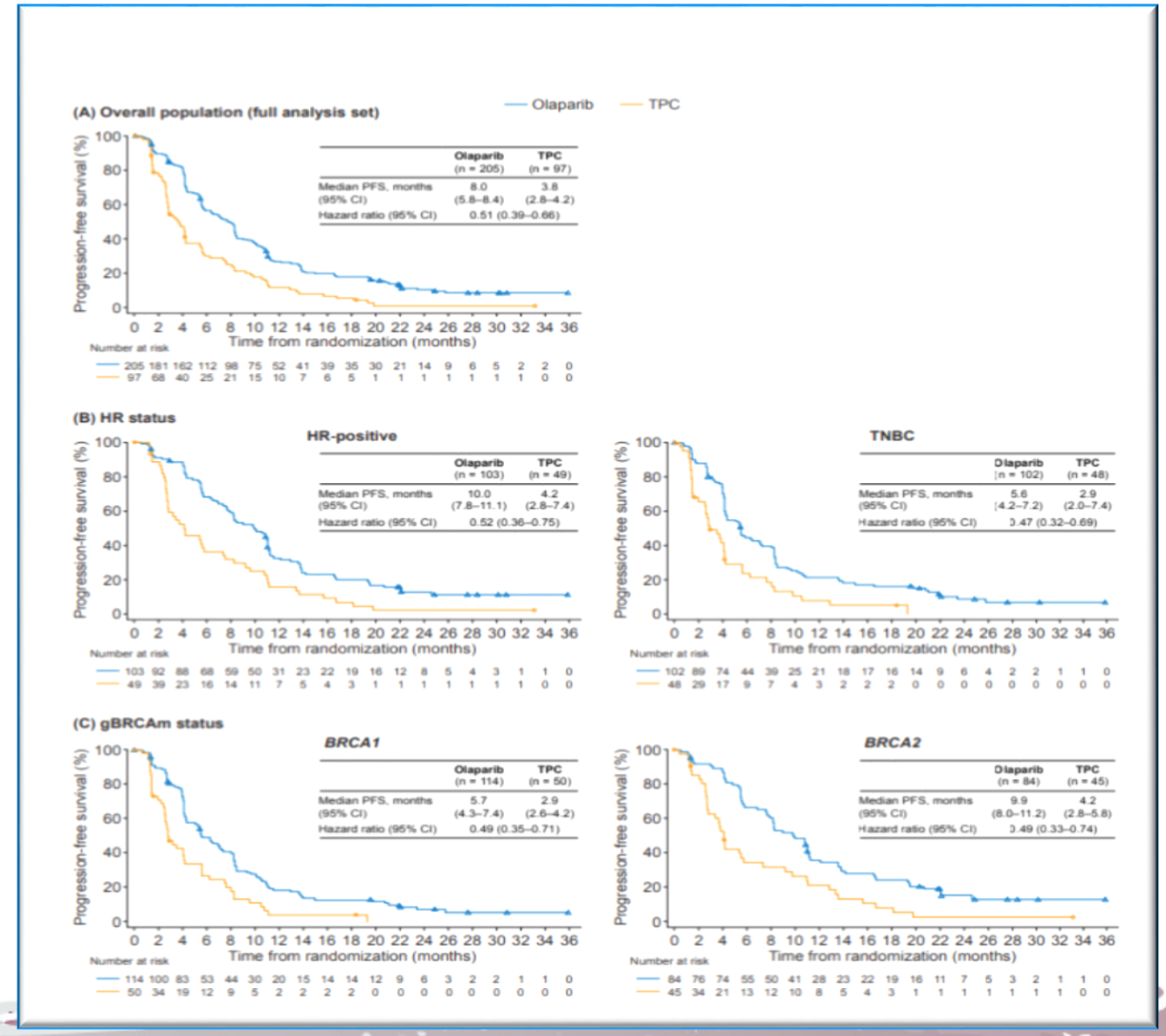
Olaparib	102	99	86	73	69	54	41	37	36	27	26	22	17	16	10	9	9	5	5	5	2	1	1	1	1	1	1	1	0
TPC	48	43	26	19	18	9	8	7	6	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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

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

2. Robson et al. J Clin Oncol 35, 2017 (presentation associated with abstr LBA4)

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

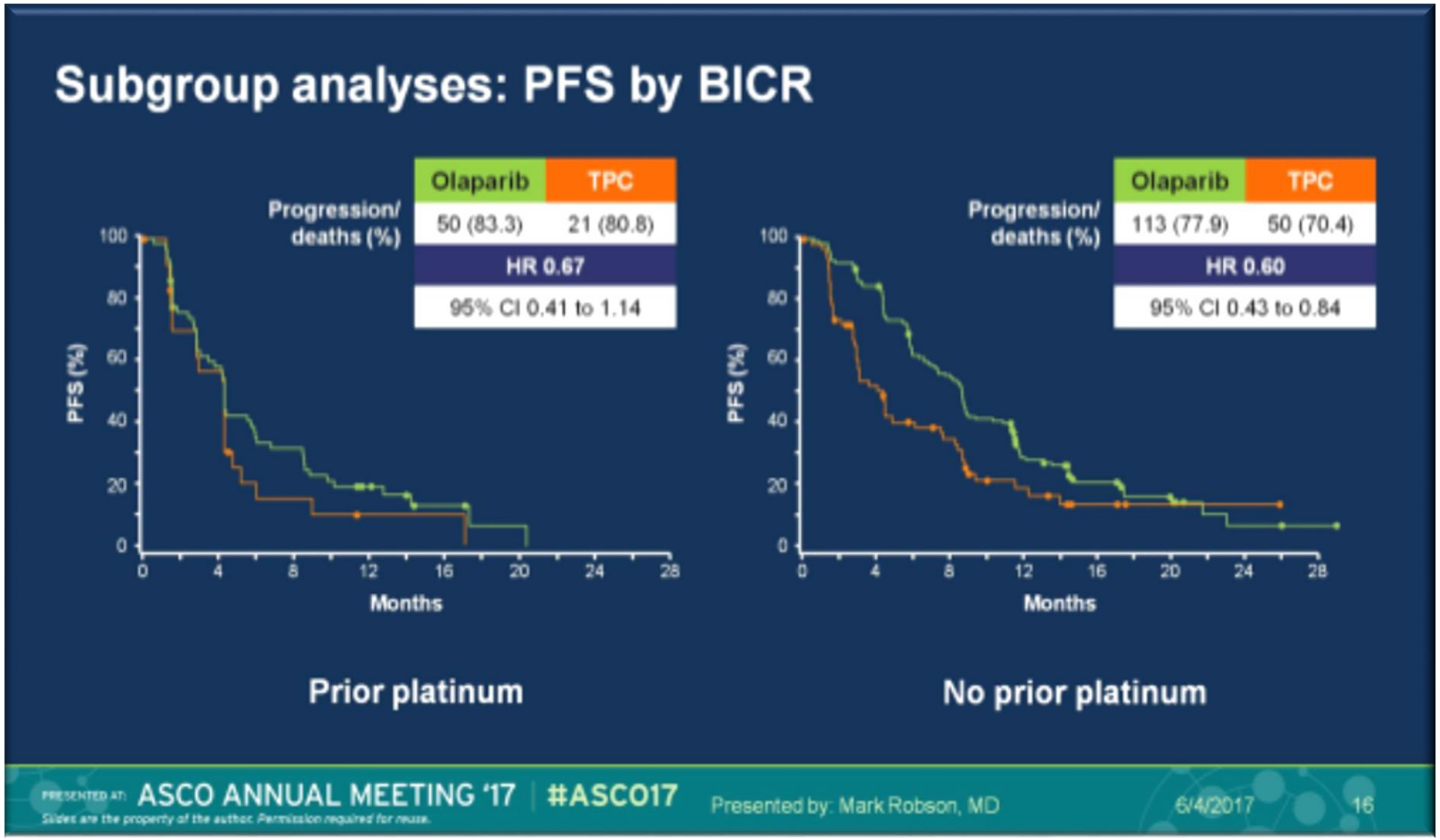
I pazienti con carcinoma mammario positivo ai recettori ormonali (HR) devono essere stati precedentemente trattati con terapia endocrina o ritenuti non idonei alla terapia endocrina.

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

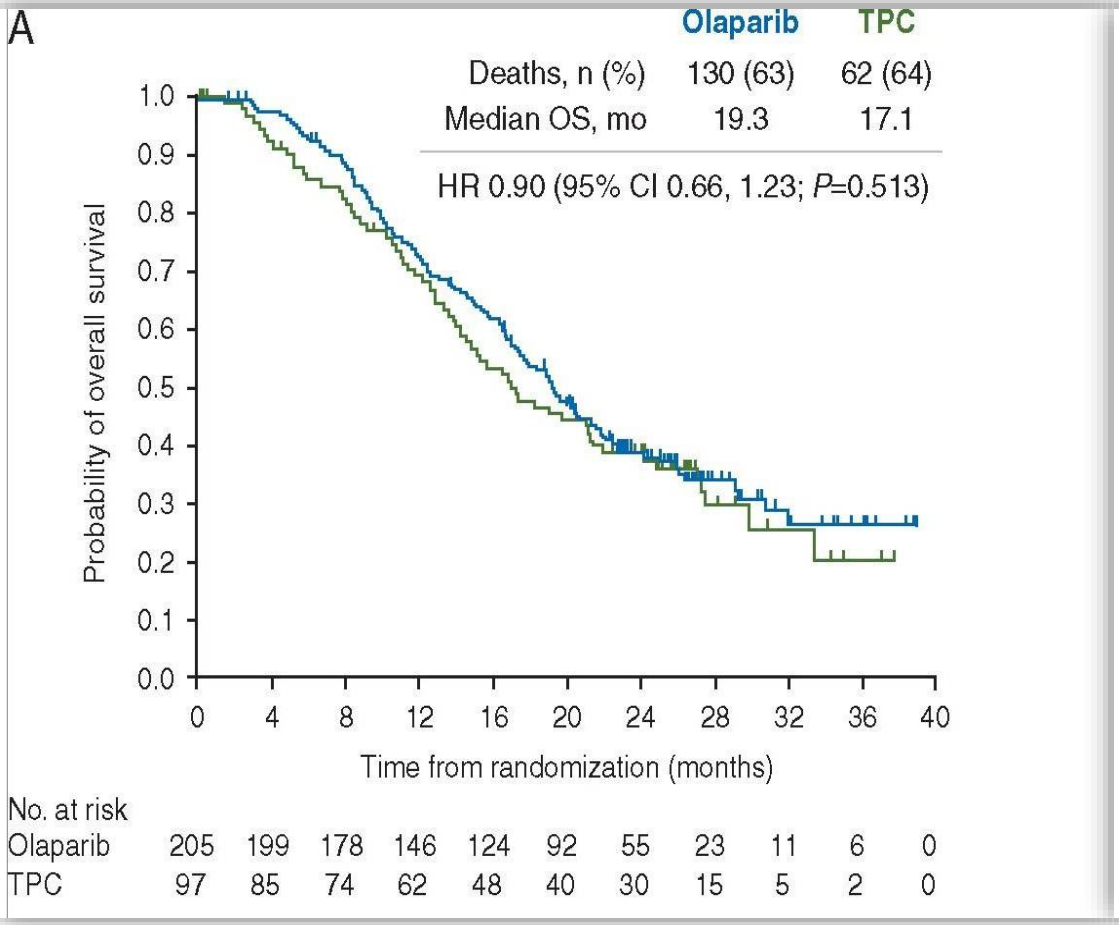
Scheda di monitoraggio AIFA

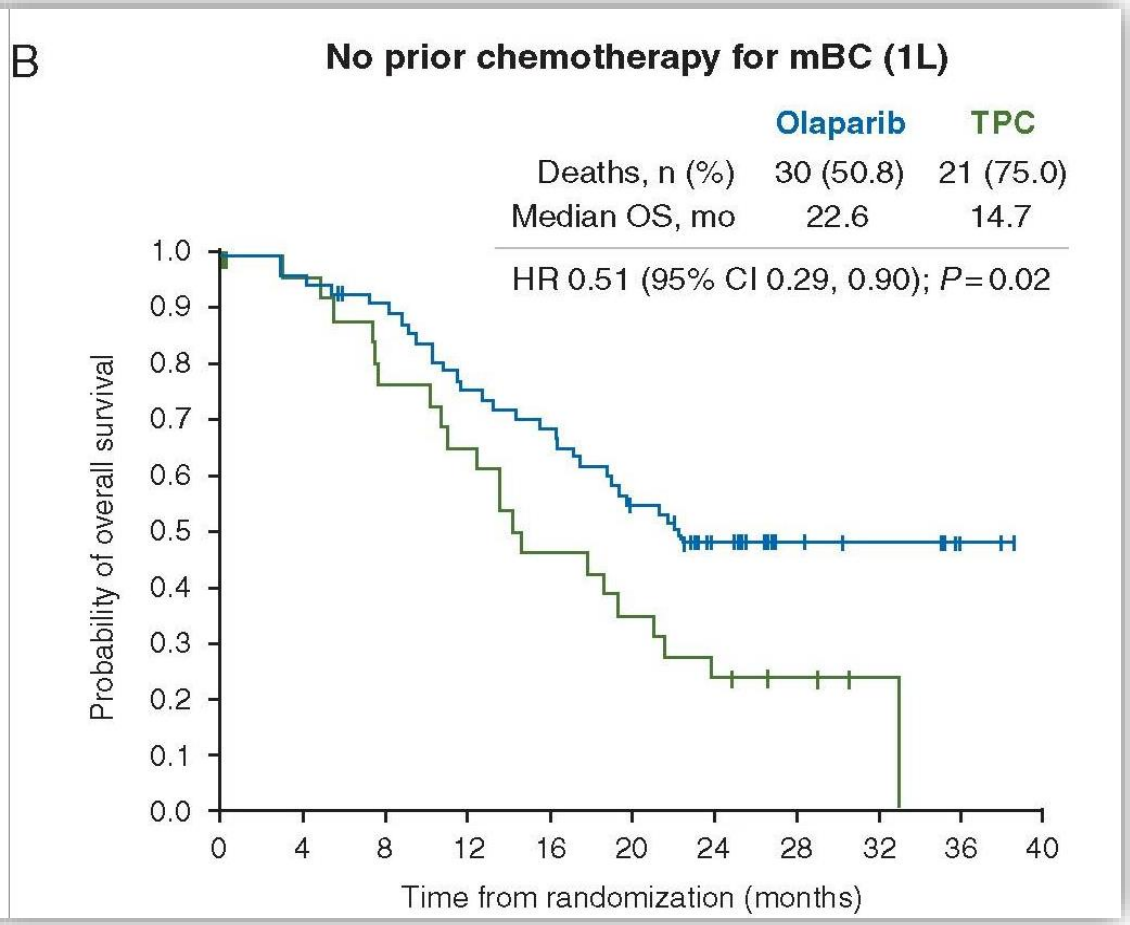
Subgroup analyses:PFS by BICR



Robson M. NEJM 2017

Overall Survival





Robson ME, Ann Oncol. 2019; 30(4): 558–566.

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

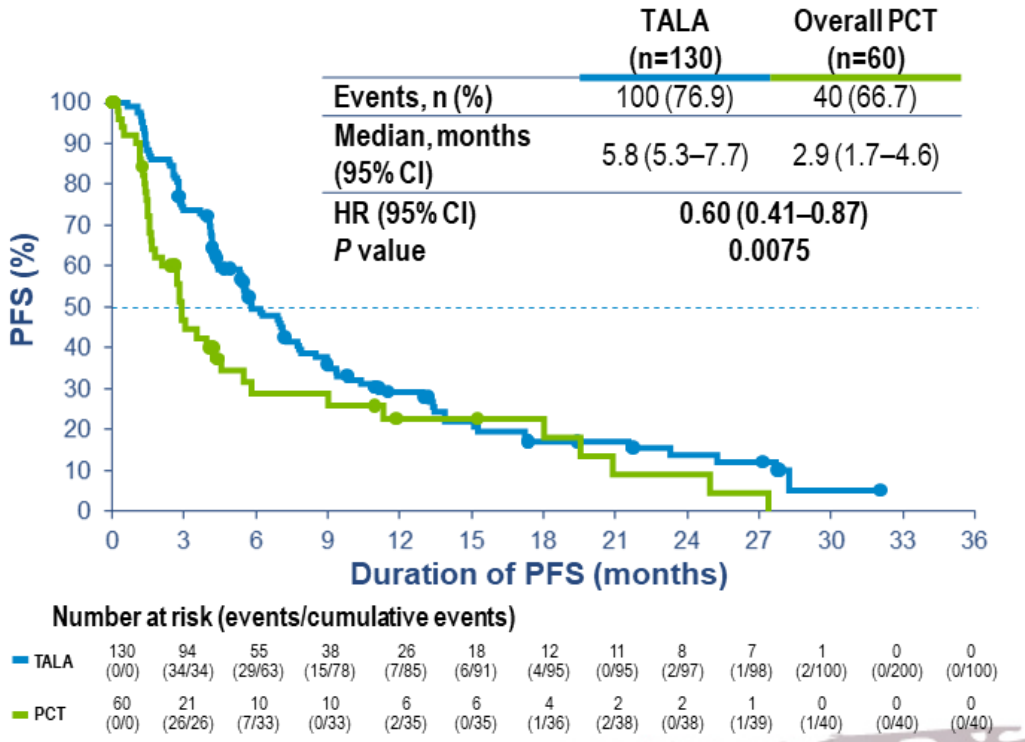
Patients stratified according to:
- *Number of prior chemotherapy regimens (0 vs. 1,2,3)*
- *Triple negative status (HR+ vs. TNBC)*
- *History of CNS metastasis (y/n)*

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

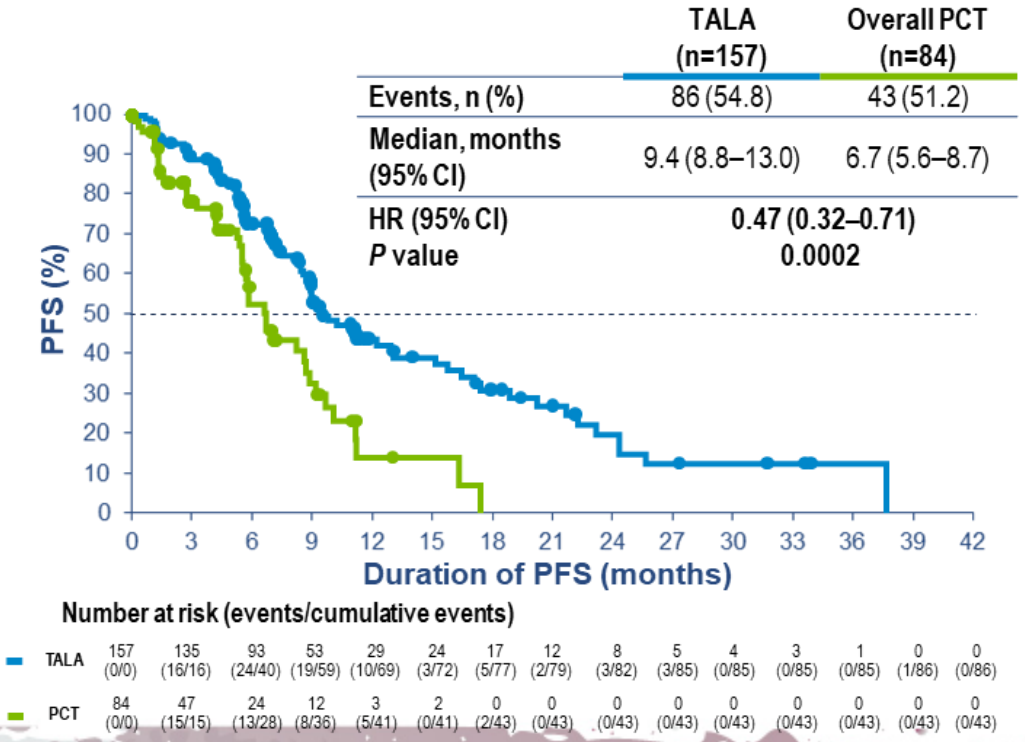
EMBRACA: PFS in base all'espressione dei recettori ormonali

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

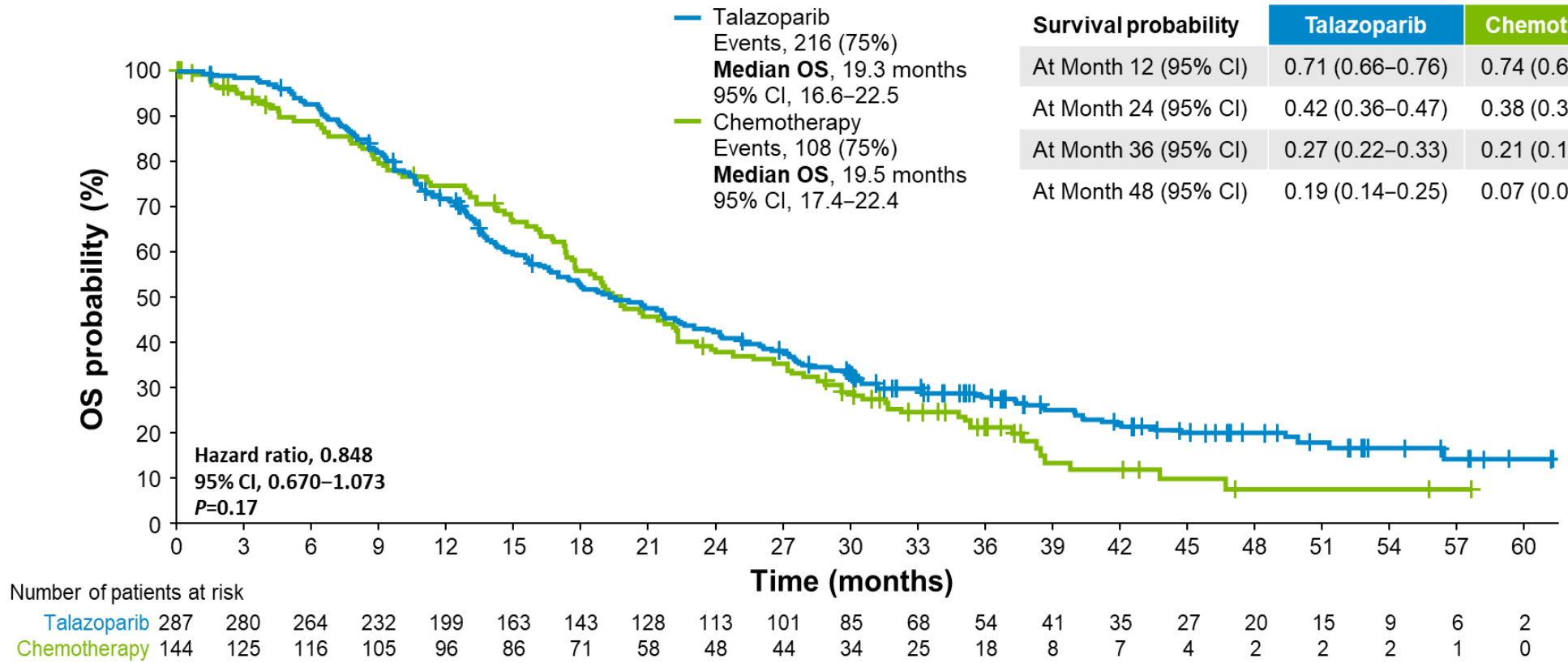


PFS nel sottogruppo HR+/HER2-



Rugo HS, et al. JNCI Cancer Spectr. 2020

EMBRACA: OS – analisi finale



Survival probability	Talazoparib	Chemotherapy
At Month 12 (95% CI)	0.71 (0.66–0.76)	0.74 (0.66–0.81)
At Month 24 (95% CI)	0.42 (0.36–0.47)	0.38 (0.30–0.47)
At Month 36 (95% CI)	0.27 (0.22–0.33)	0.21 (0.14–0.29)
At Month 48 (95% CI)	0.19 (0.14–0.25)	0.07 (0.02–0.15)

Data cutoff: September 30, 2019.
*ITT population.
ITT=intent-to-treat; OS=overall survival.

Litton JK, et al. *Ann Oncol*. 2020

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:

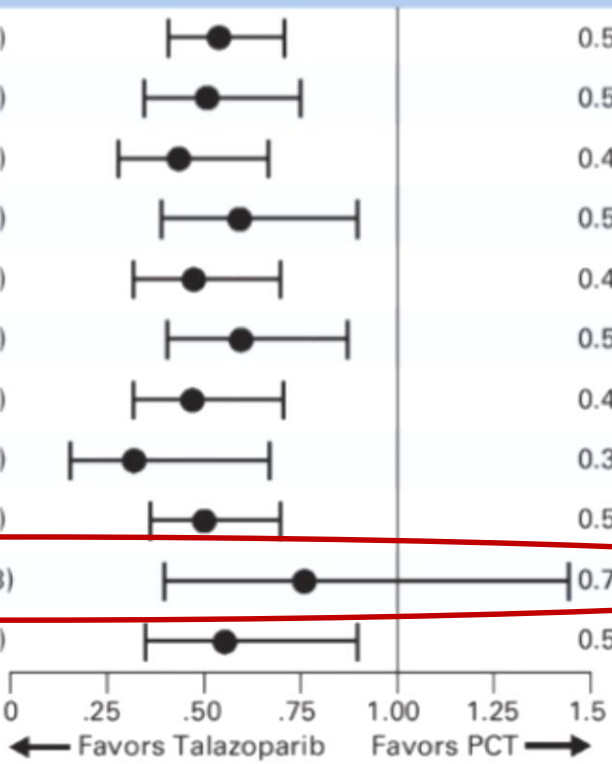
Talzenna è indicato come monoterapia per il trattamento di pazienti adulti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo localmente avanzato o metastatico. I pazienti devono essere stati precedentemente trattati con una antraciclina e/o un taxano nel contesto (neo)adiuvante,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

PFS Based on BICR for Specific Subgroups

PFS by subgroups	Talazoparib (N = 287) n	Talazoparib (N = 287) Median months (95% CI)	Overall PCT (N = 144) n	Overall PCT (N = 144) Median months (95% CI)	Treatment comparison (talazoparib vs overall PCT) Hazard ratio (95% CI)	*P* value
All randomized patients (ITT)	287	8.6 (7.2, 9.3)	144	5.6 (4.2, 6.7)	0.542 (0.413, 0.711)	<.0001
Age <50y	182	7.6 (5.8, 8.9)	67	4.2 (2.7, 6.7)	0.511 (0.348, 0.750)	.0005
ECOG PS >0	133	8.1 (5.8, 9.0)	59	5.5 (2.9, 7.1)	0.436 (0.284, 0.668)	<.0001
BRCA1	123	6.9 (5.3, 8.5)	60	3.5 (2.7, 6.7)	0.595 (0.393, 0.900)	.0130
BRCA2	147	9.8 (8.3, 13.0)	78	5.7 (4.6, 8.6)	0.474 (0.320, 0.702)	.0001
TNBC	130	5.8 (5.3, 7.7)	60	2.9 (1.7, 4.6)	0.596 (0.406, 0.874)	.0075
HR+	157	9.4 (8.8, 13.0)	84	6.7 (5.6, 8.7)	0.474 (0.318, 0.708)	.0002
CNS metastases	43	5.7 (4.1, 8.1)	20	1.6 (1.2, 4.3)	0.322 (0.154, 0.675)	.0016
Viceral disease	200	7.3 (6.8, 8.9)	103	5.3 (2.9, 6.7)	0.505 (0.366, 0.698)	<.0001
Prior platinum	46	7.0 (4.2, 12.9)	30	2.9 (1.5, 11.3)	0.762 (0.400, 1.451)	.4070
DFI <12 months	108	5.7 (5.2, 8.9)	42	3.5 (2.1, 5.9)	0.562 (0.352, 0.897)	.0145



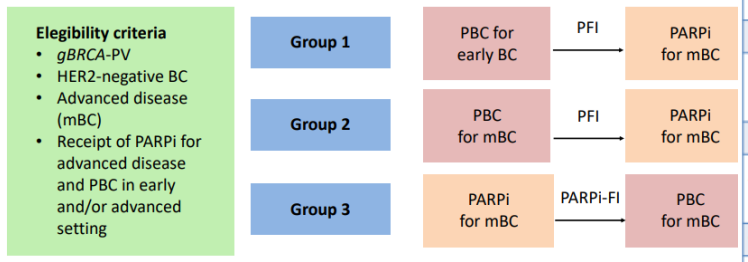
Abbreviations: *BRCA1*/*BRCA2*, breast cancer susceptibility gene 1 or 2; CI, confidence interval; CNS, central nervous system; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR+, hormone receptor positive; ITT, intent to treat; PCT, physician's choice of therapy; PFS, progression-free survival; TNBC, triple-negative breast cancer; y, years.

Litton JK, NEJM 2018

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)

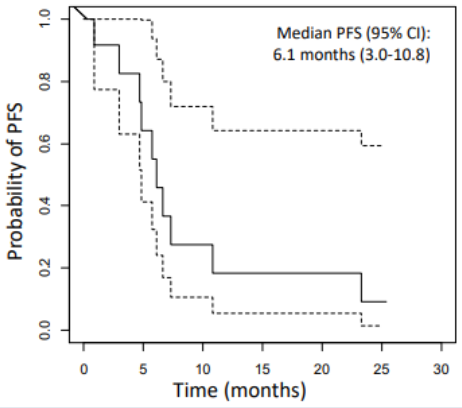


Figure 2. PFS of PARPi in metastatic setting post-PBC in metastatic setting (mFUP: 3.4 mo)

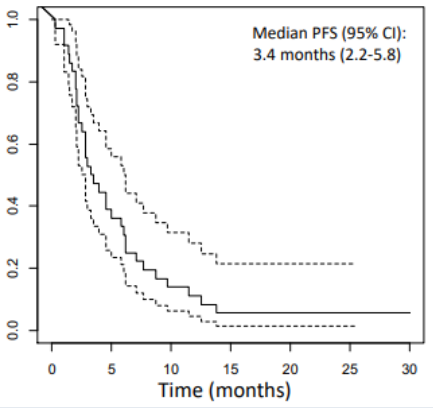
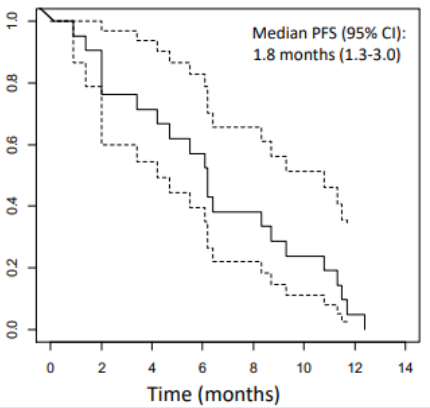


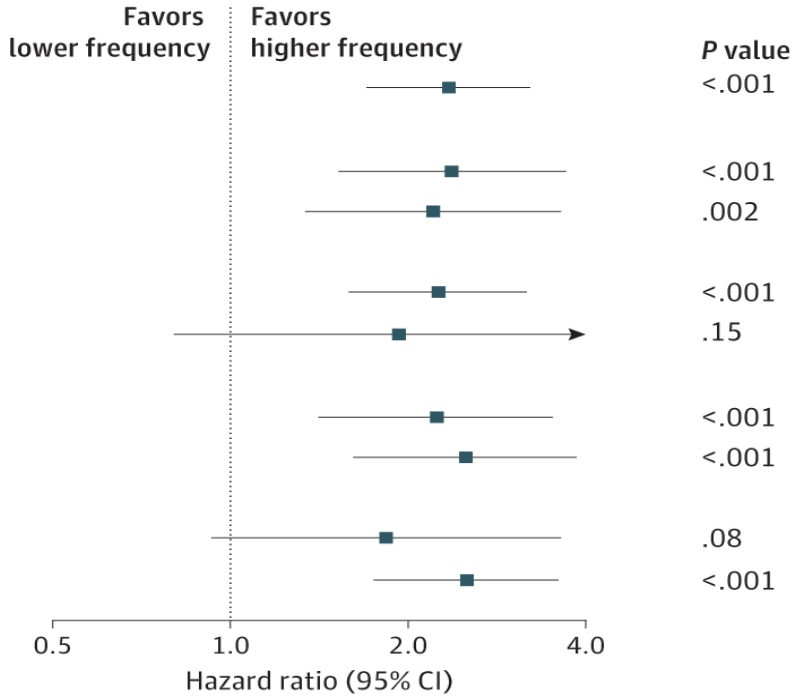
Figure 3. PFS of PBC in metastatic setting post-PARPi in metastatic setting



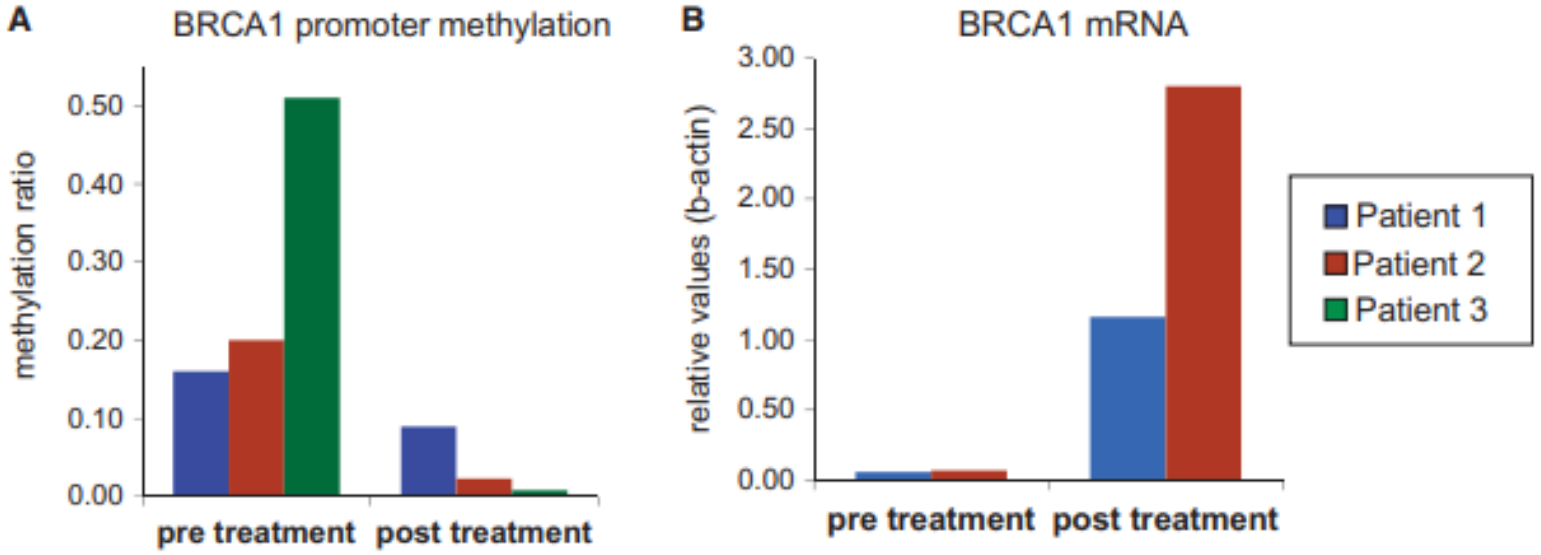
Valenza C., EJC 2023

Constitutional BRCA1 Methylation and Risk of Incident Triple-Negative Breast Cancer

Subgroup	Cases (M/U)	Controls (M/U)	Hazard ratio (95% CI)
Overall	79/557	104/1734	2.35 (1.70-3.23)
Age, y			
≤ Median	46/292	57/922	2.38 (1.53-3.72)
> Median	33/265	47/812	2.21 (1.34-3.64)
Race			
White	67/457	89/1429	2.25 (1.59-3.20)
Other[a]	12/100	15/305	1.93 (0.80-4.68)
Methylated epiallele frequency			
≤ Median	35/557	52/1734	2.23 (1.41-3.54)
> Median	44/557	52/1734	2.50 (1.61-3.89)
Years from screening to diagnosis			
≤ 5	16/124	104/1734	1.83 (0.92-3.64)
> 5	63/433	102/1715	2.52 (1.75-3.63)



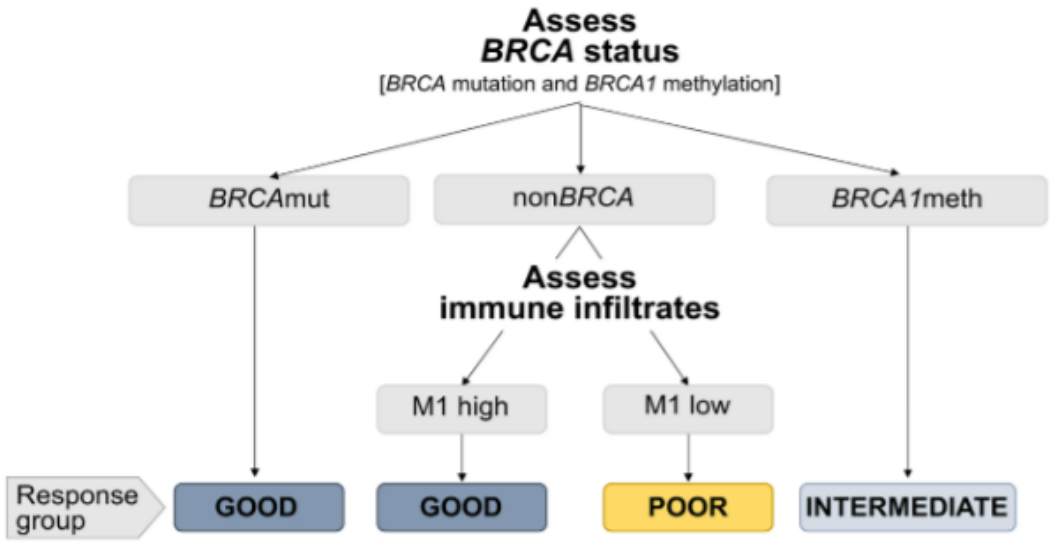
BRCA1 demethylation post-therapy



Brugge PT,, JNCI 2016

Genomic and epigenomic BRCA alterations predict adaptive resistance and response to platinum-based therapy in patients with TNBC and OC

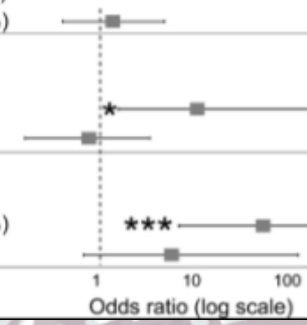
A



B

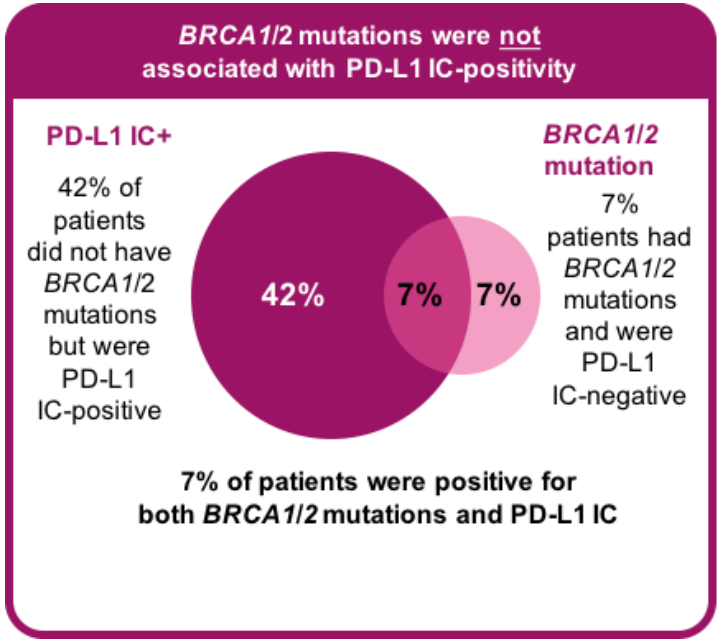
COH TNBC (n = 41 cancers with RNAseq data)

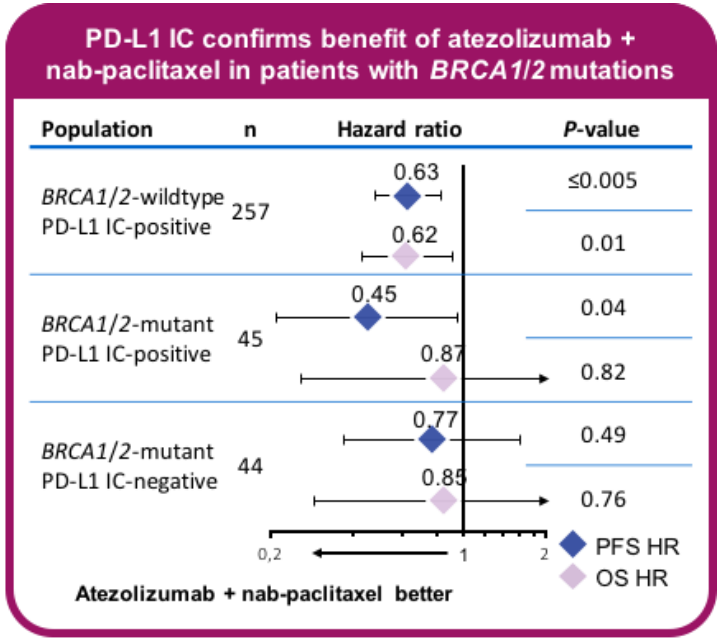
Variable	pCR (%)	Odds ratio (95% CI)	P-value	Accuracy
HRD (SBS3 contribution)				**53.7%**
Low	11/23 (47.8%)	1 (ref)		
High	10/18 (55.5%)	1.36 (0.40, 4.81)		
***BRCA* status**				**69%**
non*BRCA*	9/21 (42.9%)	1 (ref)		
*BRCA*mut	8/9 (88.9%)	10.7 (1.55, 217)	0.039	
*BRCA1*meth	4/11 (36.4%)	0.76 (0.16, 3.37)		
Combined response criteria				**81%**
Poor outcome	1/11 (9.1%)	1 (ref)		
Good outcome	16/19 (84.2%)	53.3 (6.83, 1200)	0.001	
Intermediate outcome	4/11 (36.4%)	5.71 (0.67, 125)		



- Menghi F, Sci Transl Med 2022

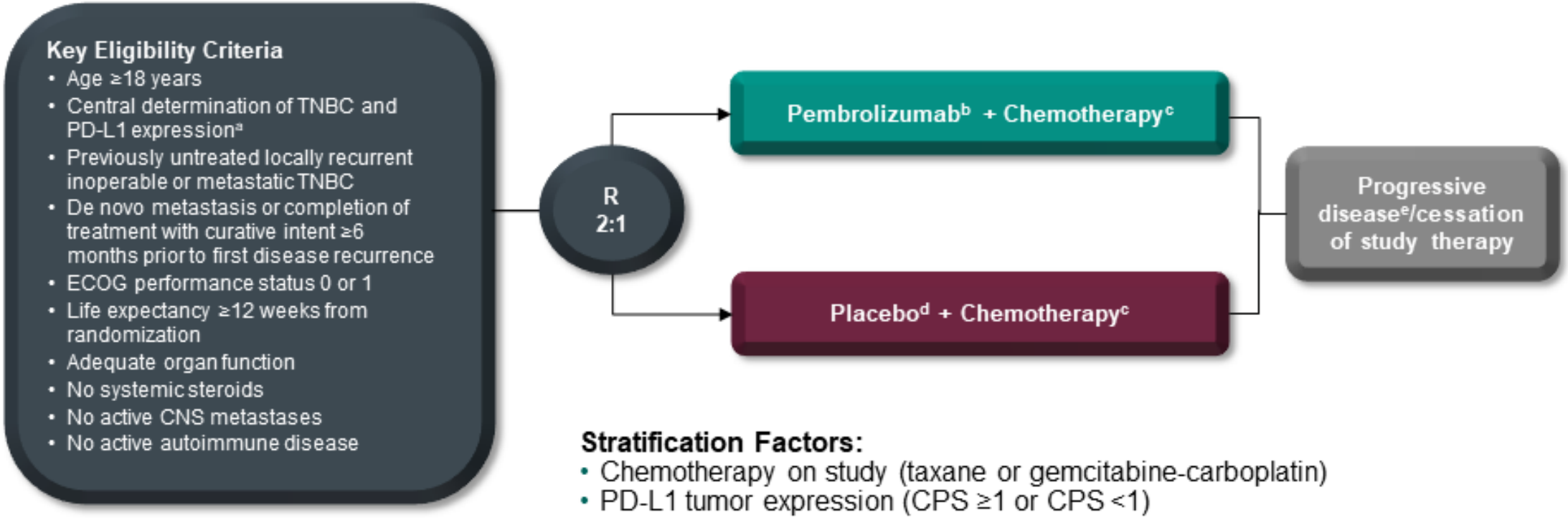
IMpassion130: clinical benefit of atezolizumab + nab-paclitaxel in the PD-L1 IC+ subgroup





Emens, et al. JNCI 2021

KEYNOTE-355 Study Design (NCT02819518)



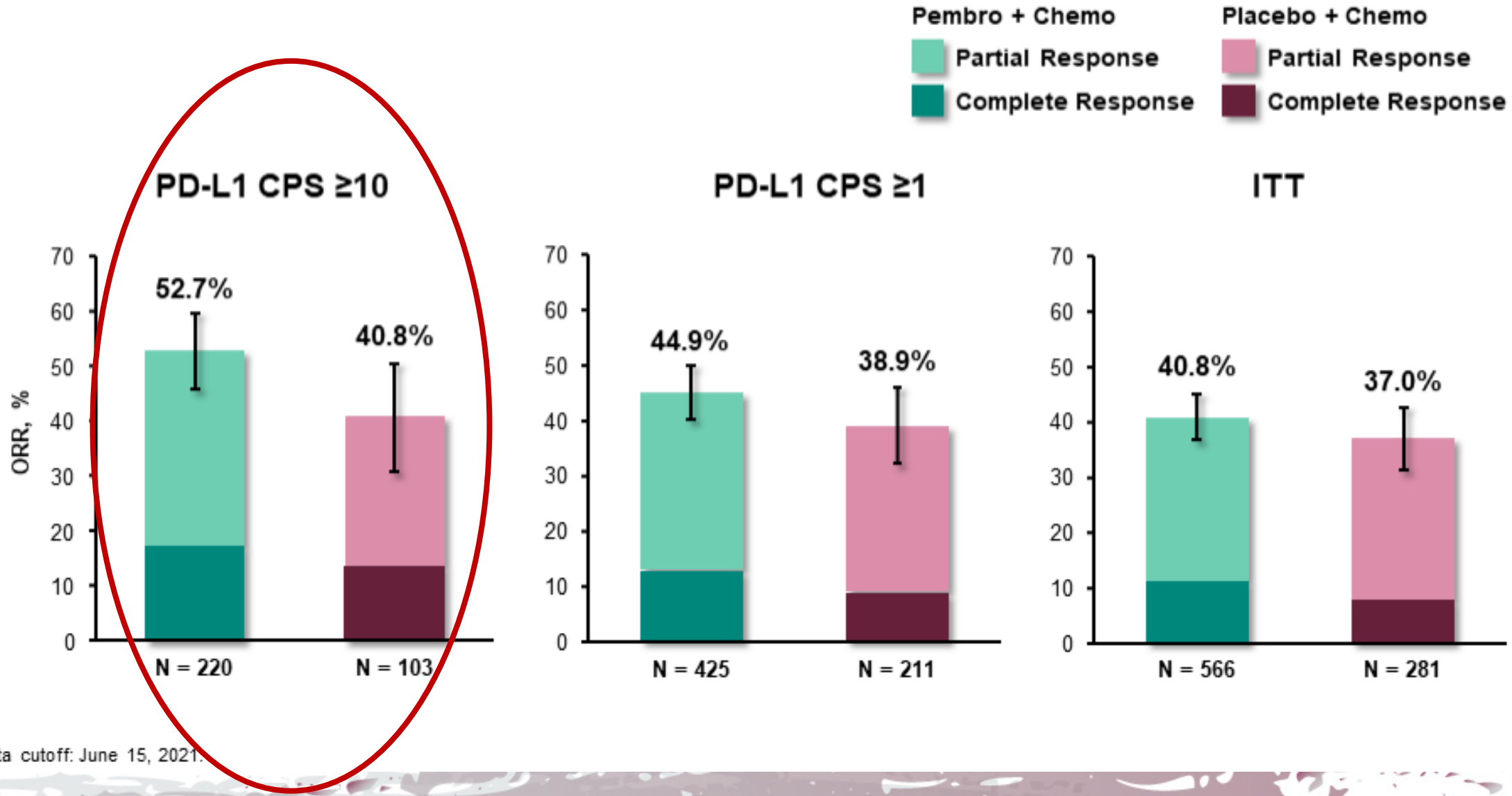
Stratification Factors:

- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

[a]Based on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumour sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). [b]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W). [c]Chemotherapy dosing regimens are as follows: Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days; Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days; Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days. [d]Normal saline. [e]Treatment may be continued until confirmation of progressive disease.

Cortes J, NEJM 2022

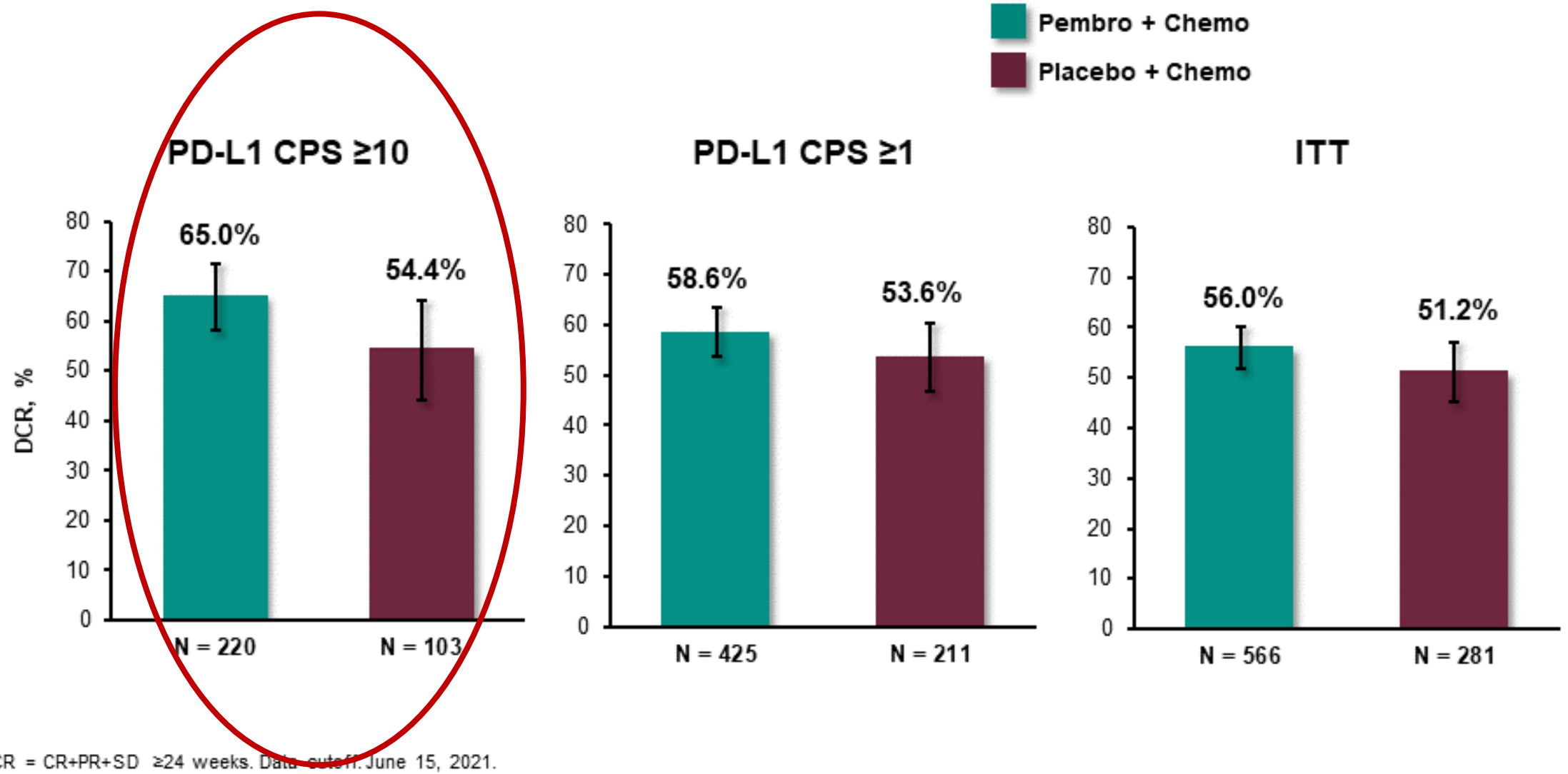
Objective Response Rate



Data cutoff: June 15, 2021.

Cortes J, NEJM 2022

Disease Control Rate



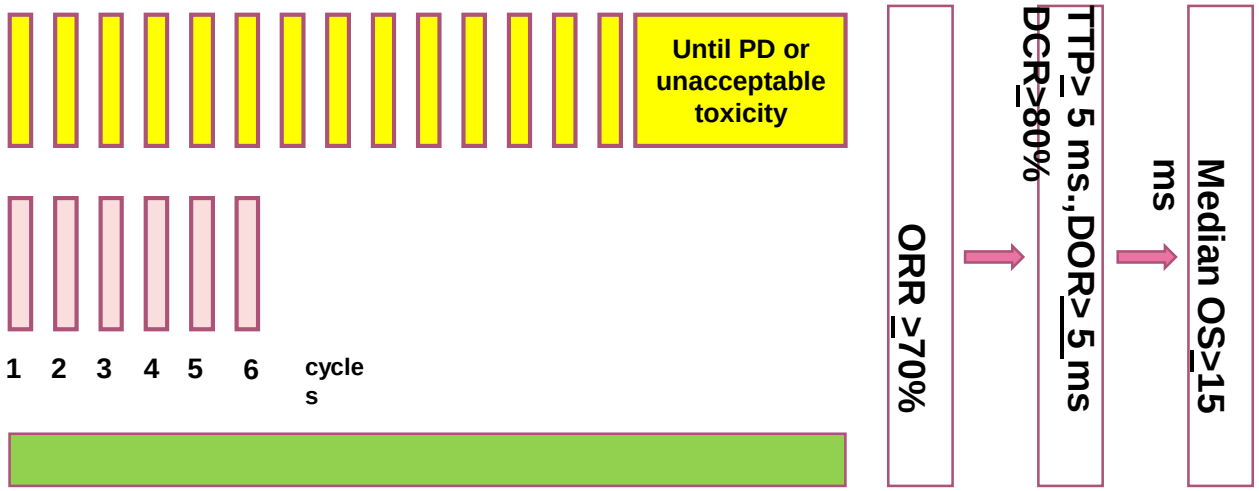
DCR = CR+PR+SD ≥24 weeks. Data cutoff: June 15, 2021.

Cortes J, NEJM 2022

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

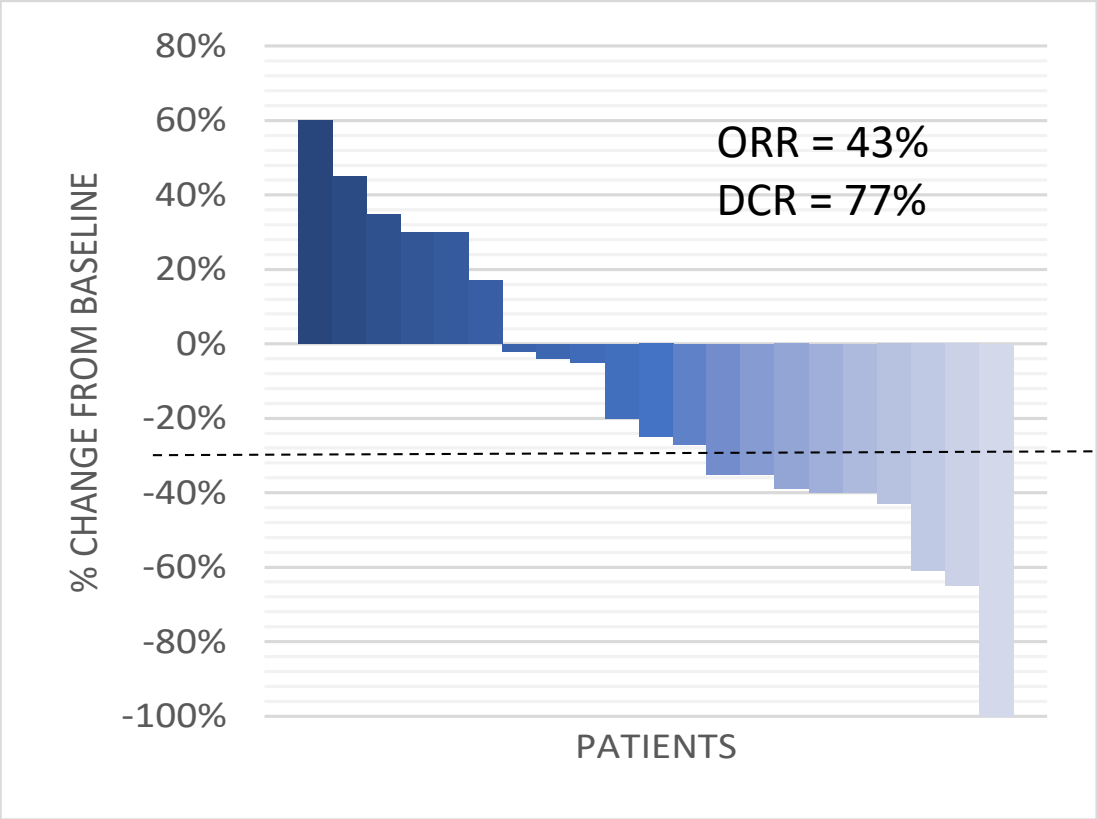


Pembrolizumab 200 mg ev q21
Carboplatin AUC6 ev q21x6

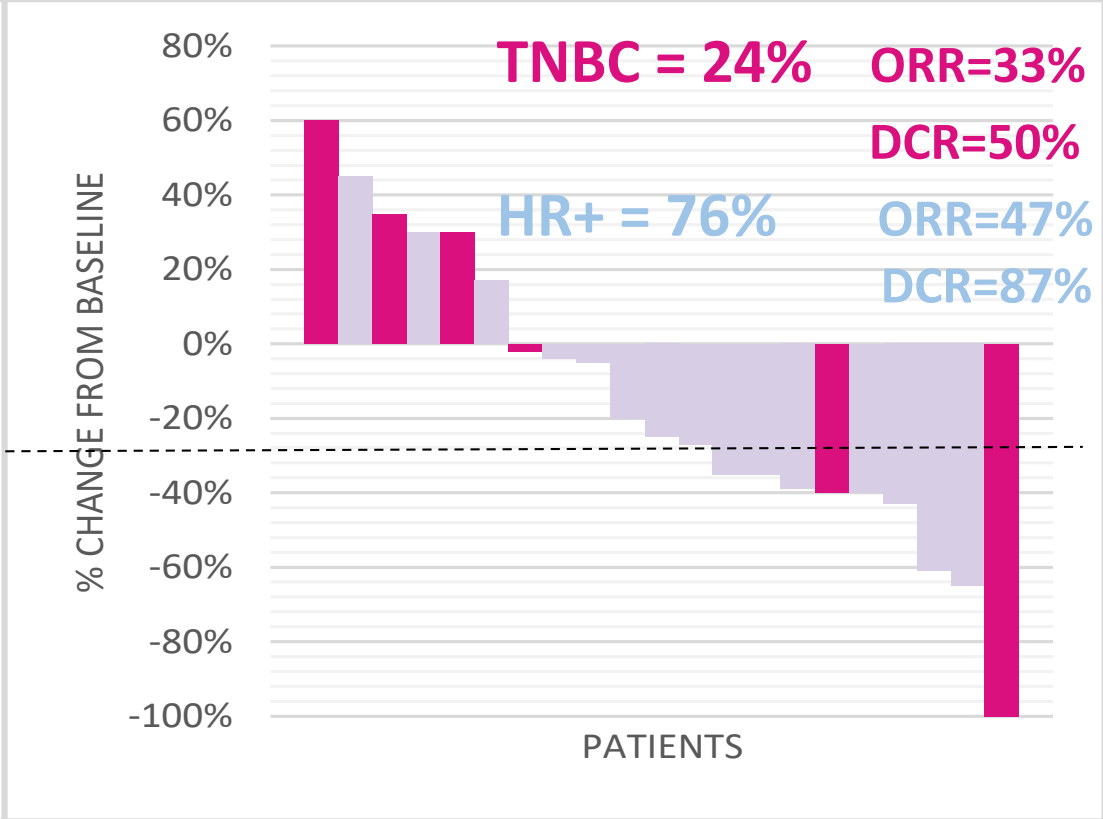
Cortesi L., Esmo Open 2023

ORR and DCR according to HR status

A

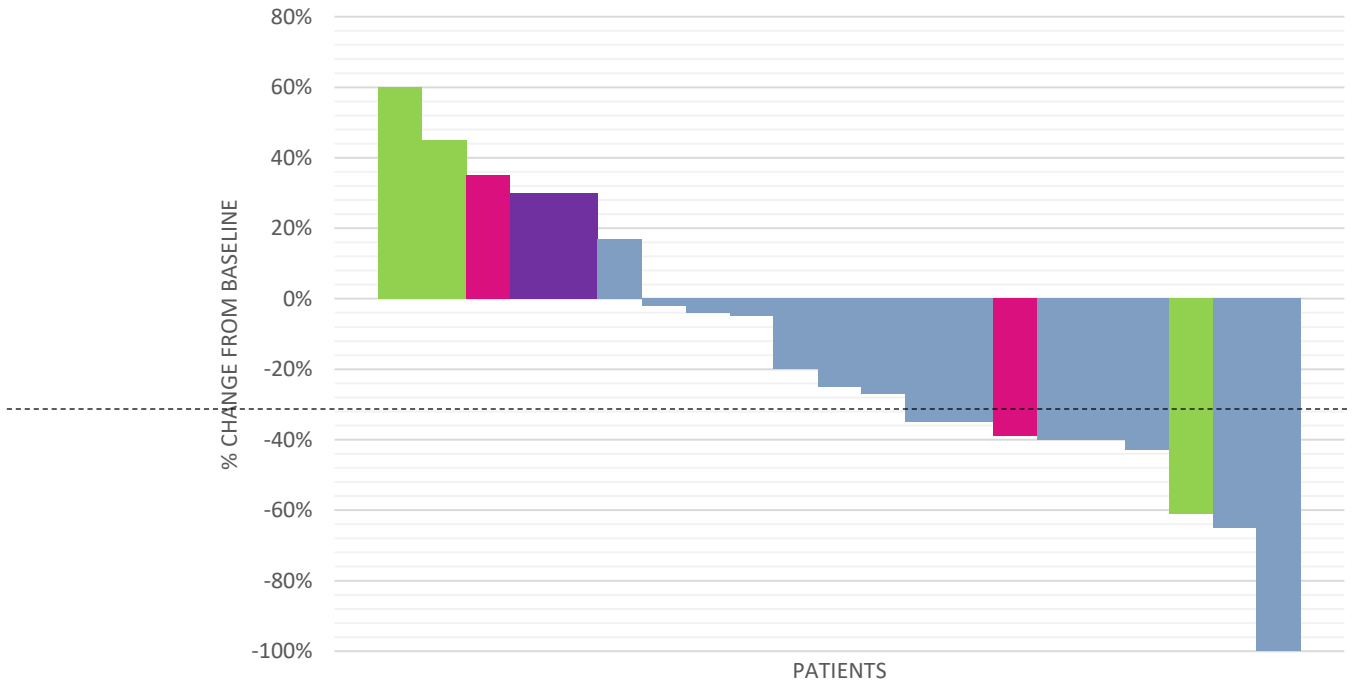


B



Cortesi L., Esmo Open 2023

RR according to the line of treatment for MBC



Tax

Anthra

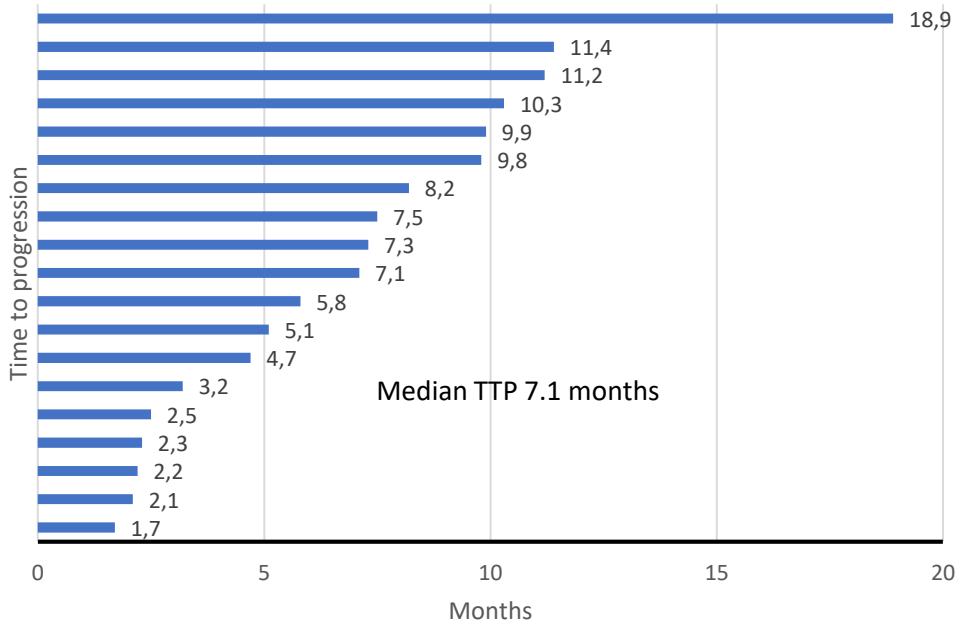
Other CT (cape)

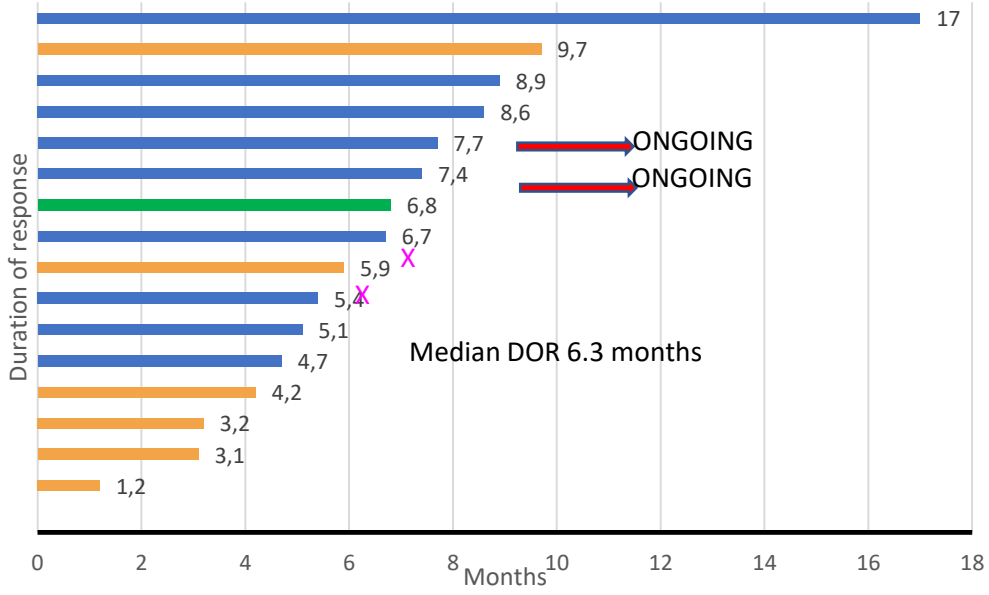
ORR=38%, DCR=38%

None ORR=46%, DCR=100%

Cortesi L., Esmo Open 2023

Median TTP and DOR

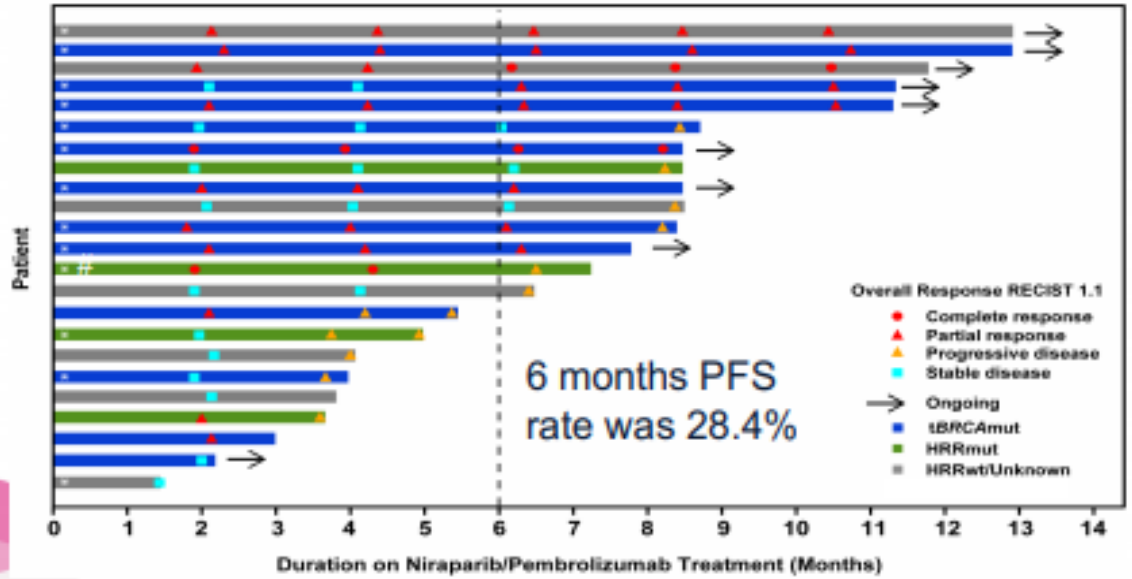




TOPACIO

Niraparib + Pembrolizumab in Pretreated mTNBC

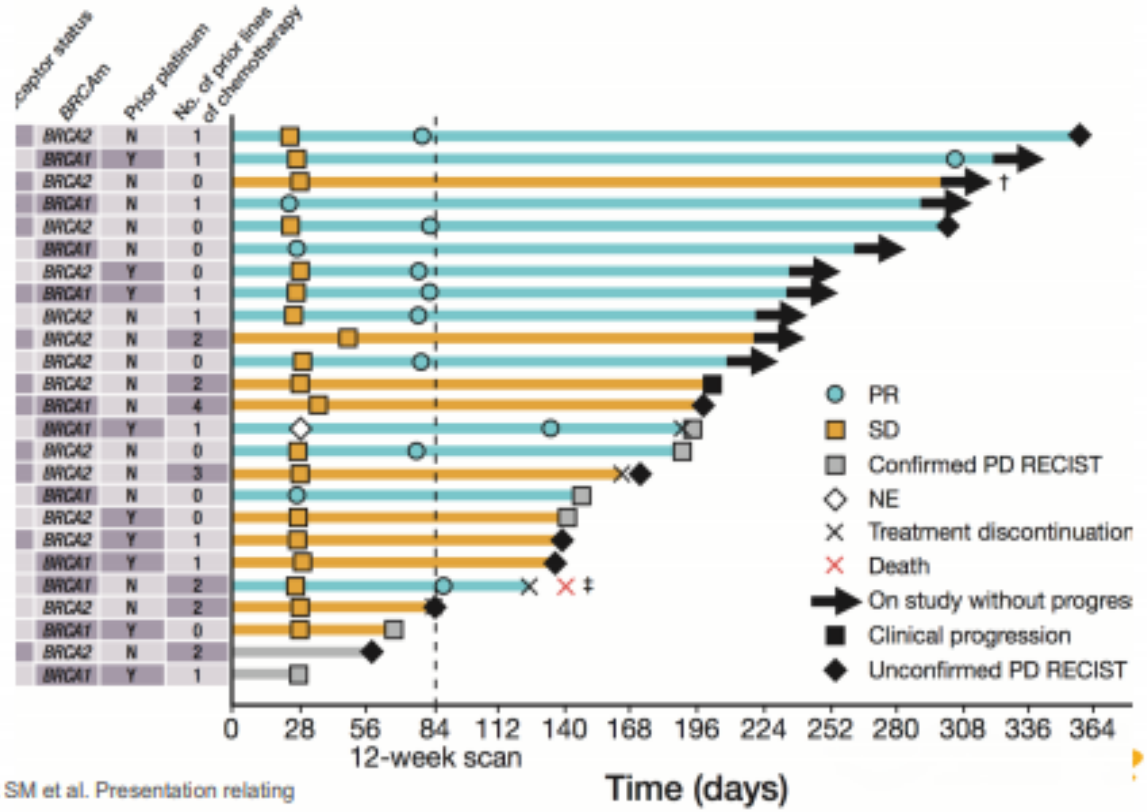
Response	Response Rate, n (%) Efficacy Evaluable (N=46)
CR	3 (7%)
PR**	10 (22%)
SD	10 (22%)
PD	23 (50%)
ORR (CR+PR)	13 (28%)
DCR (CR+PR+SD)	23 (50%)



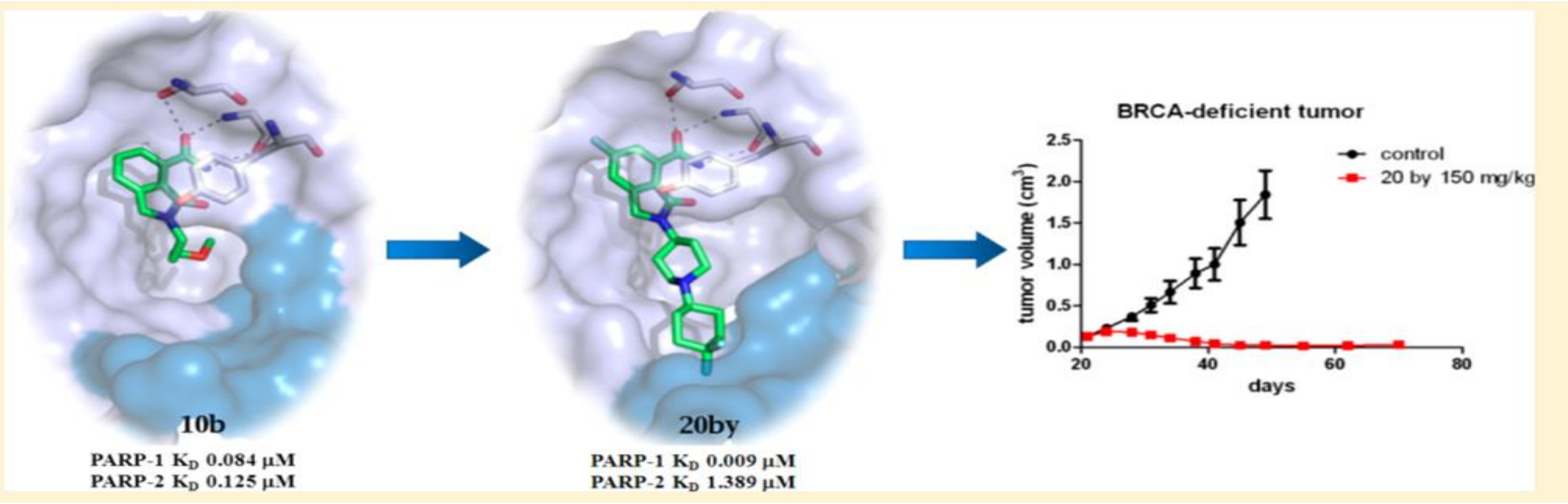
Mediola

Olaparib plus Durvalumab in MBC

12/25 (48%) had disease control at 28 weeks
Unconfirmed ORR 52% (13/25)
Median DOR/PFS/OS not yet reached

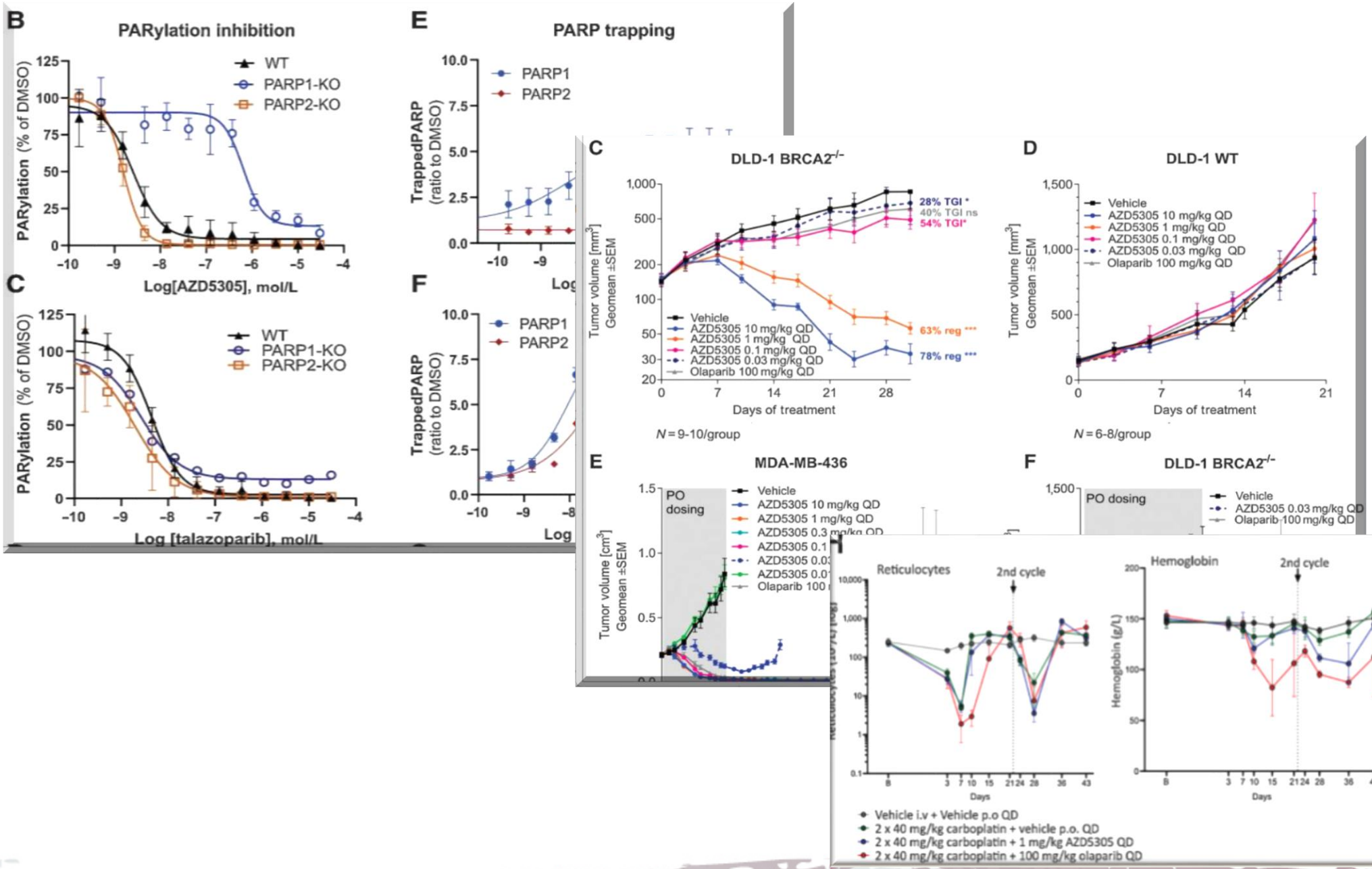


1. Vinayak S et al. Presentation relating to abstract 1011: Presented at; ASCO Annual Congress; June 1–5, 2018; Chicago, IL; 2. Domcheck SM et al. Presentation relating to abstract PD5-04: Presented at; SABCS Annual Meeting; 5–9 December, 2017; San Antonio, TX.



Recent literature reports suggest that only inhibition of PARP1 is required for anti-proliferative effects and that PARP2 plays a key role in the survival of haematopoietic stem progenitor cells in animal models (Farres et al, 2013; Farres et al, 2015). These observations suggest that the inhibition and trapping of PARP2, a feature shared by all the current clinical PARPi, is not needed for the anti-cancer effect, and may be the major driver of haematological toxicity observed in patients.

Papeo G et al., J. Med. Chem. 2015



Illuzzi G et al., CCR 2022

COLLOCAZIONE DEI PARP-INIBITORI NEL TUMORE DELLA MAMMELLA TNBC IN IV STADIO

PRIMA LINEA TNBC

Nei pazienti con tumore della mammella triplo negativo con variante patogenica di BRCA1/2, che non abbiano ricevuto CT con derivati del platino e siano PDL1 positive, carboplatino+/- gemcitabina + pembrolizumab potrebbe essere un trattamento di prima linea per la malattia avanzata.

COLLOCAZIONE DEI PARP-INIBITORI NEL TUMORE DELLA MAMMELLA TNBC IN IV STADIO

PRIMA LINEA TNBC

Nei pazienti con tumore della mammella triplo negativo con variante patogenica di BRCA1/2, già precedentemente trattati con chemioimmunoterapia secondo schema KEYNOTE-522 alla recidiva di malattia PDL1 positiva, sarebbe preferibile un trattamento di prima linea con PARP-inibitore rispetto alla chemio-immunoterapia per la malattia avanzata.

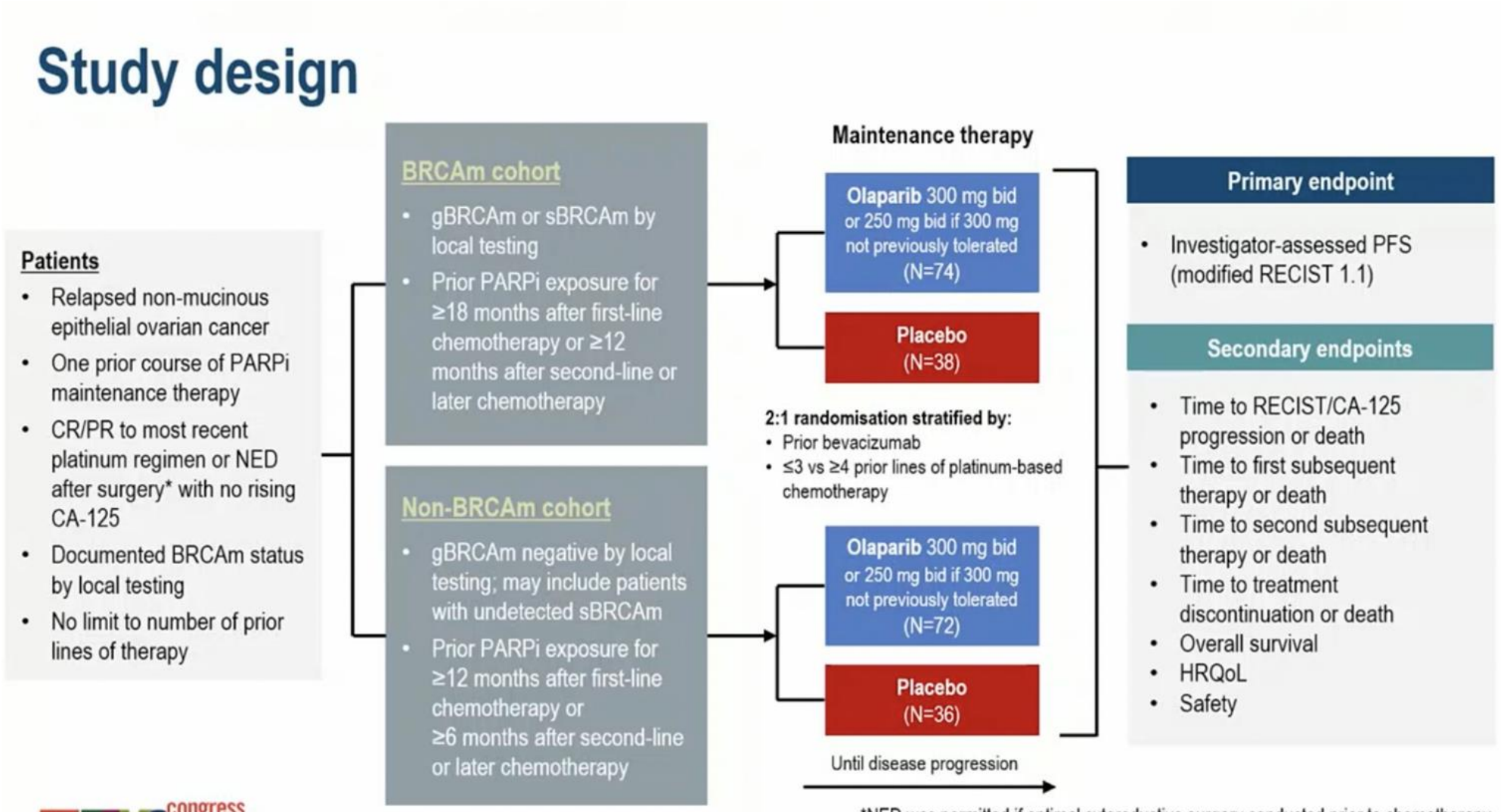
E se la paziente ha fatto olaparib in adiuvante (BRCA+)?

- Possiamo somministrare PARP dopo PARP?

  Non conosciamo i successivi trattamenti delle pazienti progredite ad Olympia

  Non abbiamo dati fondati sull’evidenza

OREO trial



2021 ESMO congress

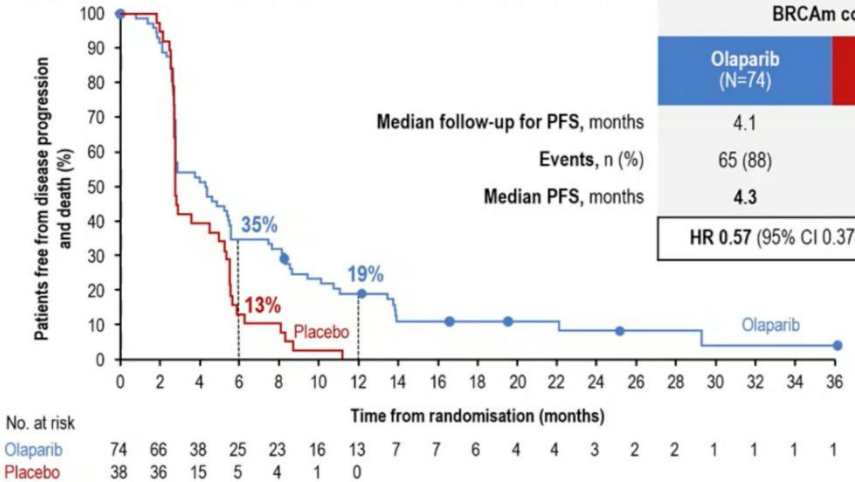
*NED was permitted if optimal cytoreductive surgery conducted prior to chemotherapy.

bid, twice daily; CA-125, cancer antigen 125; CR, complete response; gBRCAm, germline BRCA mutation; HRQoL, health-related quality of life; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; sBRCAm, somatic BRCA mutation.

OREO trial

A statistically significant PFS benefit was observed with olaparib in the BRCAm cohort

A proportion of patients derived clinically relevant long-term benefit



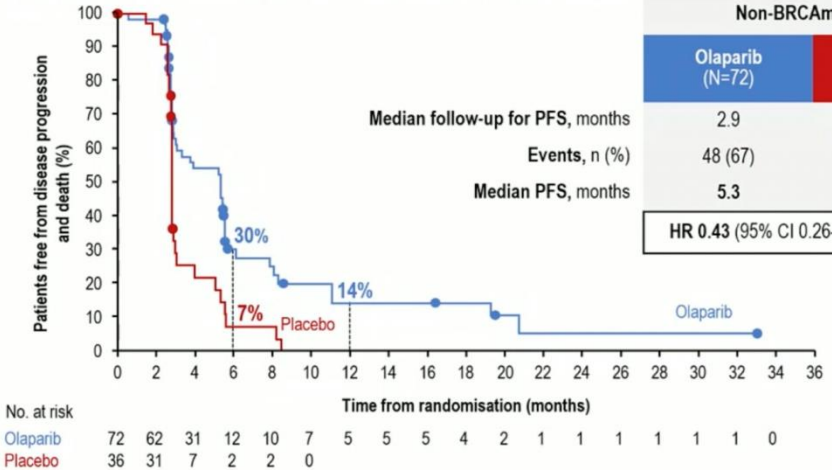
BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**
HR 0.57 (95% CI 0.37–0.87); *P*=0.022		

2021 ESMO congress

CI, confidence interval.

A statistically significant PFS benefit was observed with olaparib in the non-BRCAm cohort

A proportion of patients derived clinically relevant long-term benefit



Non-BRCAm cohort	Olaparib (N=72)	Placebo (N=36)
Median follow-up for PFS, months	2.9	2.8
Events, n (%)	48 (67)	30 (83)
Median PFS, months	**5.3**	**2.8**
HR 0.43 (95% CI 0.26–0.71); *P*=0.0023		

2021 ESMO congress

COLLOCAZIONE DEI PARP-INIBITORI NEL TUMORE DELLA MAMMELLA TNBC IN IV STADIO

OLTRE LA PRIMA LINEA TNBC

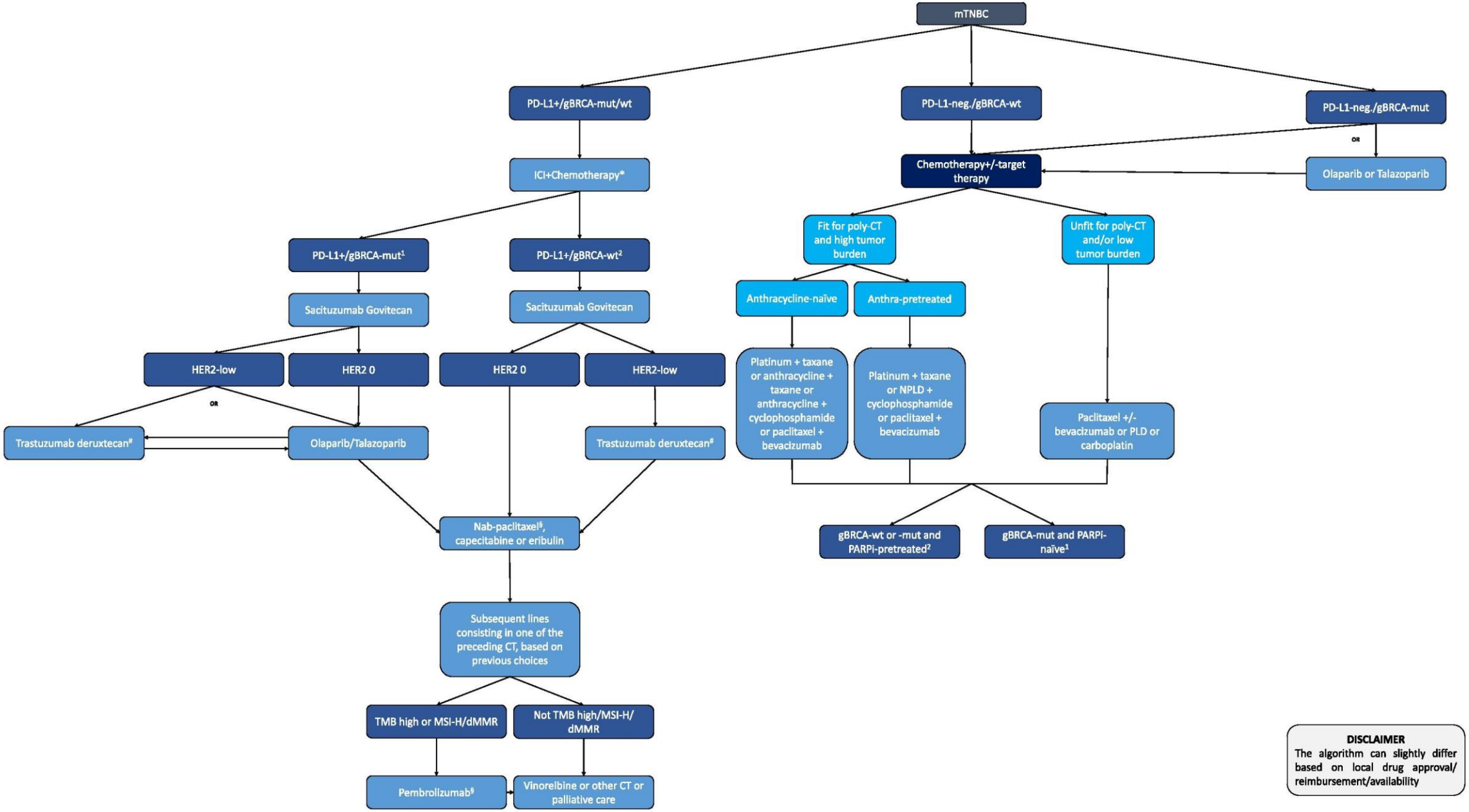
Nei pazienti con tumore della mammella triplo negativo con variante patogenica di BRCA1/2, che abbiano ricevuto una terapia in prima linea (CT o CT-IO), alla progressione sarebbe preferibile una terapia con PARP-inibitore rispetto a Sacituzumab Govitecan o altro ADC, qualora accessibile.

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.



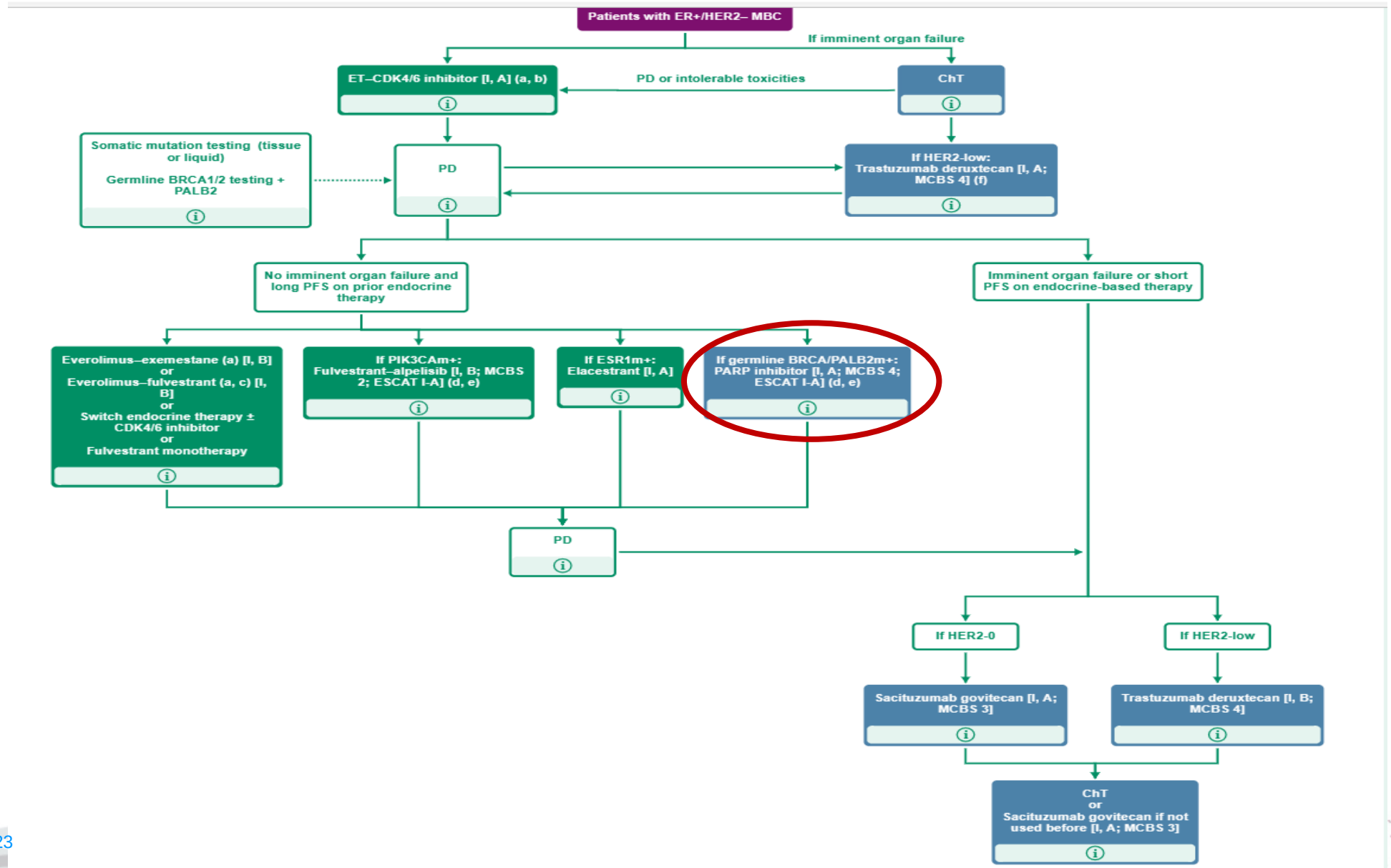
DISCLAIMER
The algorithm can slightly differ based on local drug approval/ reimbursement/availability

Schettini F et al., Cancer Treat Rev 2022

Dispute on mTNBC BRCA mutated

- Treat pts with platinum-derived drugs in early BC not at first relapse
  - Look at gBRCA mutation or BRCA methylation (poor response!!)
  - Olaparib in MBC first line → OS advantage
- If not platinum-derived in early setting and PDL-1+
  - Carbo+Pembro could provide a good compromise
- In second line post CT or CT-IO
  - Olaparib? Sacituzumab?

ESMO GUIDELINES FOR ER-positive HER2-negative Breast Cancer



Curigliano G, 2023

Germline Mutations

- PARP inhibitor monotherapy (olaparib or talazoparib) should be considered for patients with germline pathogenic *BRCA1/2* mutations [I, A; **ESMO-MCBS v1.1 score: 4**; ESCAT score: I-A] and as an option for those with somatic pathogenic or likely pathogenic *BRCA1/2* or germline *PALB2* mutations.

Olaparib; **ESMO-MCBS (v1.1) score: 4**
Talazoparib; **ESMO-MCBS (v1.1) score: 4**

Hereditary Breast Cancer >

v1.1 - May 2023

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 idone
trat

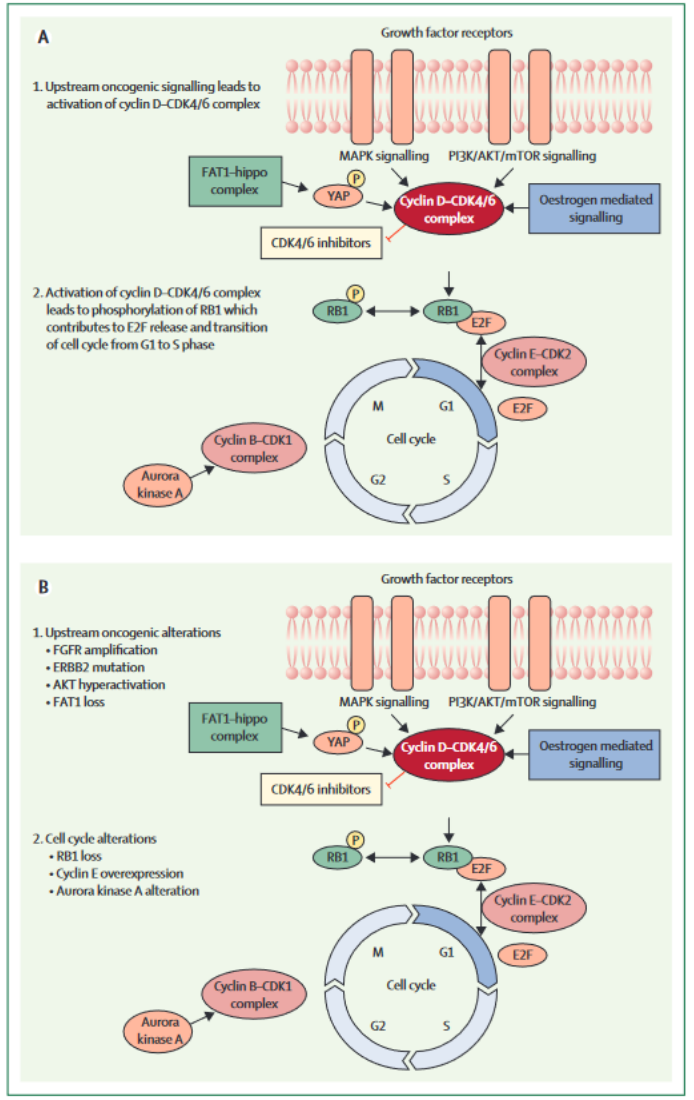
LINEE GUIDA AIOM ADDENDUM 2023

Pazienti senza caratteristiche cliniche associate a un'aumentata probabilità di VP BRCA, eleggibili a trattamenti specifici in caso di VP germinale:

- Paziente con carcinoma mammario in stadio iniziale a recettori ormonali positivi e ≥ 4 linfonodi positivi
- Paziente con carcinoma mammario a recettori ormonali positivi con precedente CT neoadiuvante, residuo di malattia e CPS/EG score≥3
- Paziente con carcinoma mammario metastatico recettori ormonali positivi/HER2-negativo già sottoposta a chemioterapia con antracicline/taxani e trattamento endocrino

CDK4/6 in Breast Cancer

- Resistance to endocrine therapy presents a major clinical challenge.
- The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER.
- Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle.[1]
- Cell line models of endocrine resistance remain dependent on Cyclin D1 and CDK4/6.[2,3]

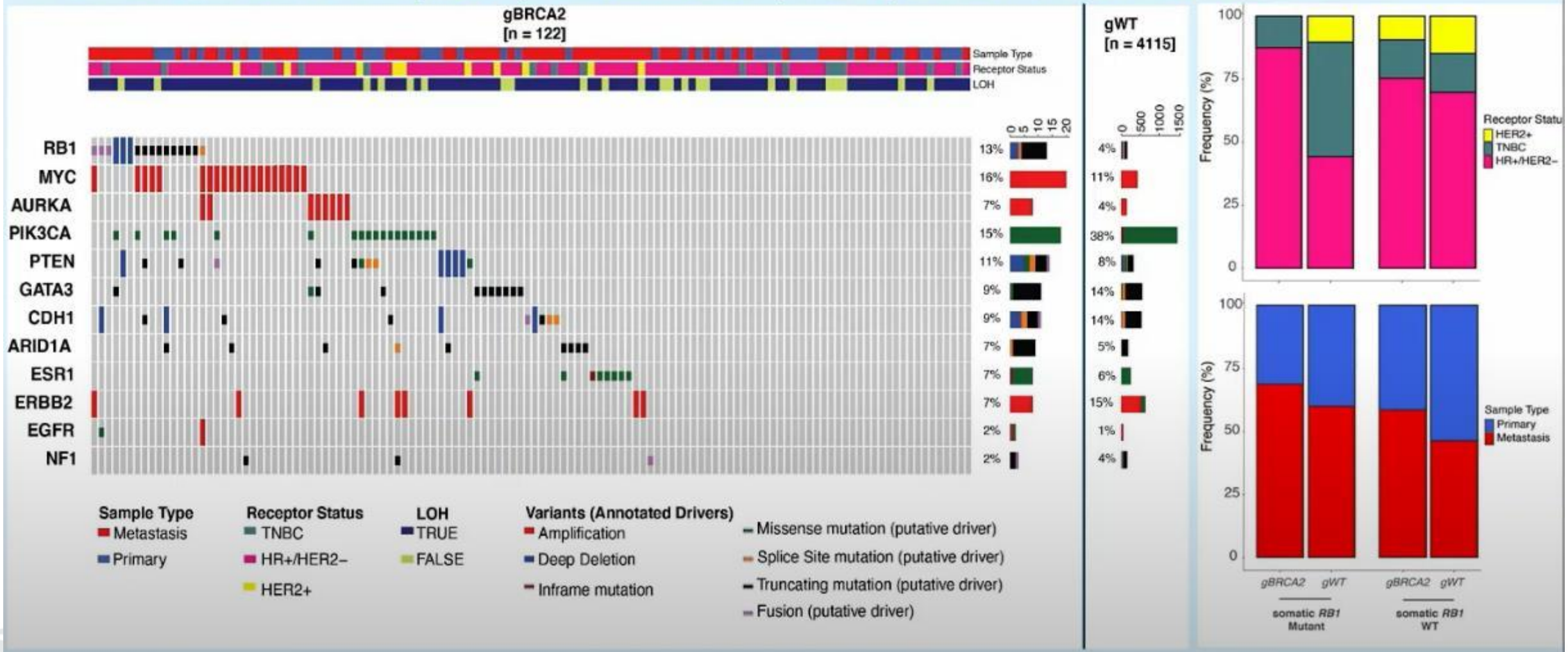


1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Miller T, et al. *Cancer Discov*. 2011; 1:338-51.
3. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive.

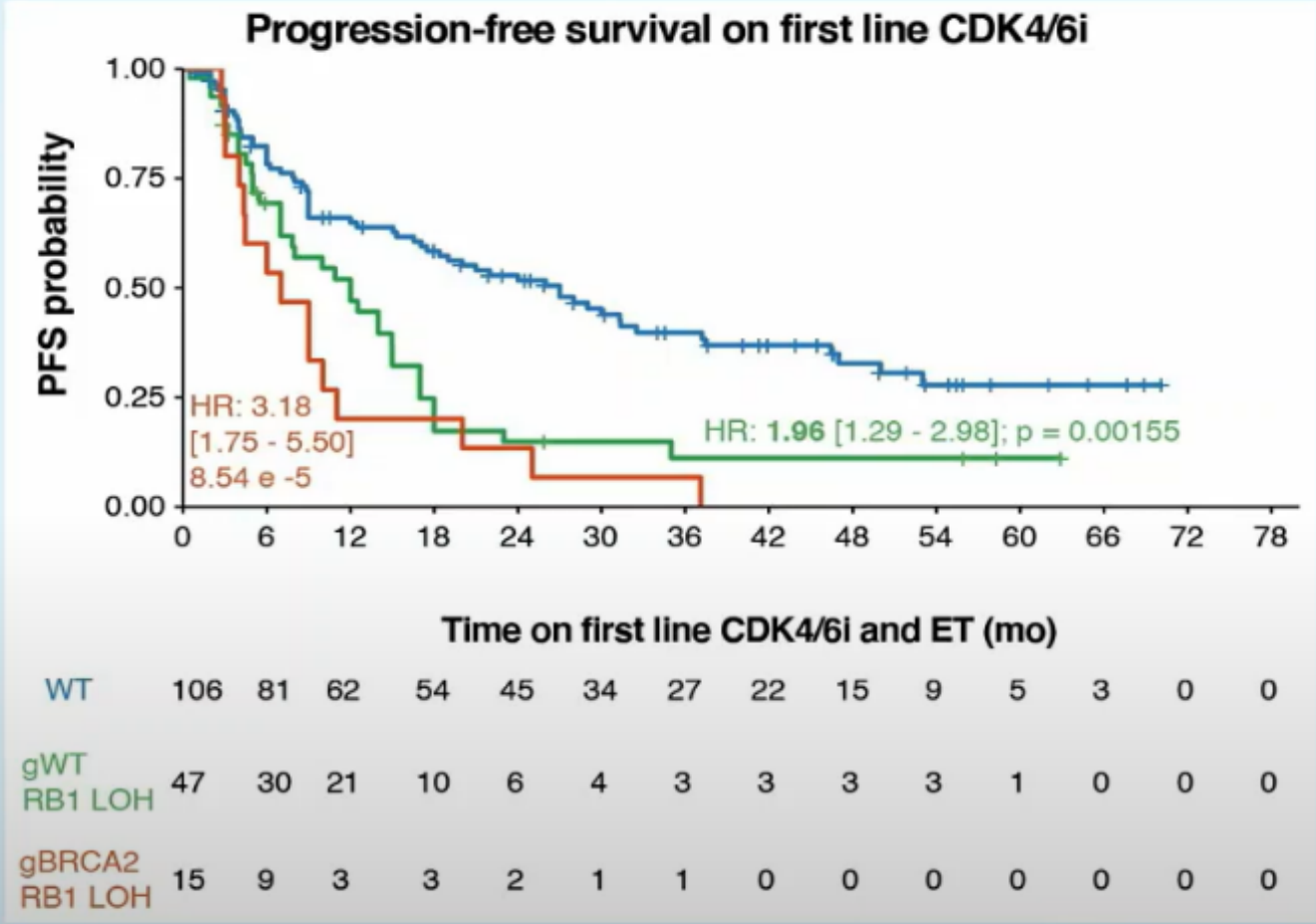
gBRCA2 is associated with a distinct somatic aberration profile, compared to WT

Most RB1 variants are in HR+/HER2- , metastatic disease, and in patients with bi-allelic *BRCA2* loss.



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

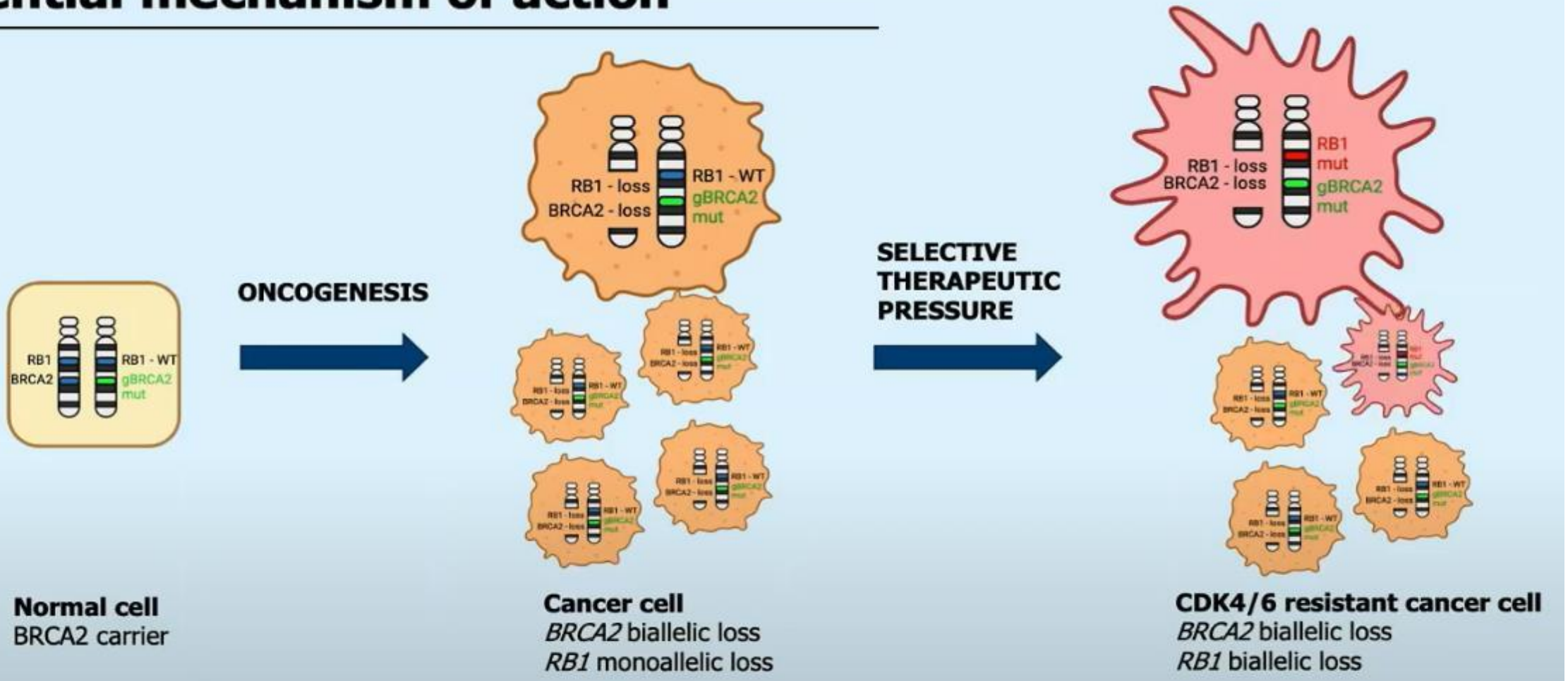
Concomitant *gBRCA2* pathogenic variant and *RB1* LOH confers particularly rapid progression in this setting



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

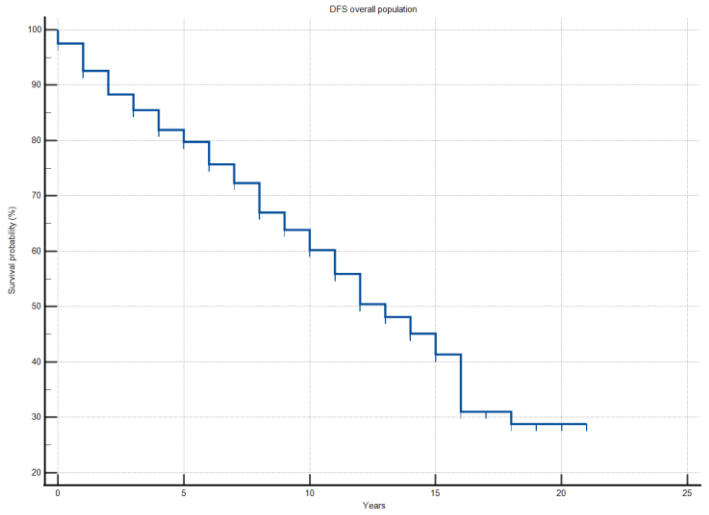
CDK4/6 resistant cancer cell
BRCA2 biallelic loss
RB1 biallelic loss

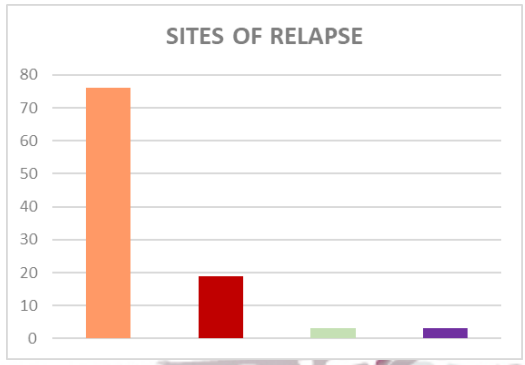
RESULTS: DFS

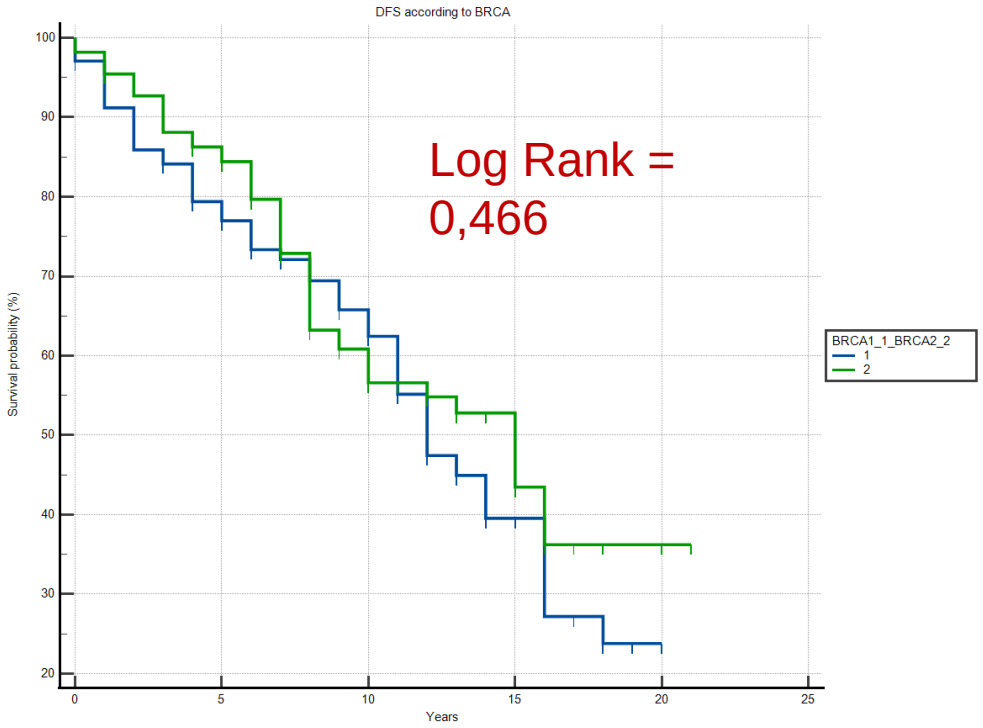
- 136 patients (**47,9%**) had **disease recurrence** during follow-up (ipsilateral local recurrence, contralateral second breast cancer or systemic recurrence)

- Median DFS in overall population was 13 years (95% CI from 11 to 15 years)

- More BRCA2 developed visceral disease (p= 0,013)



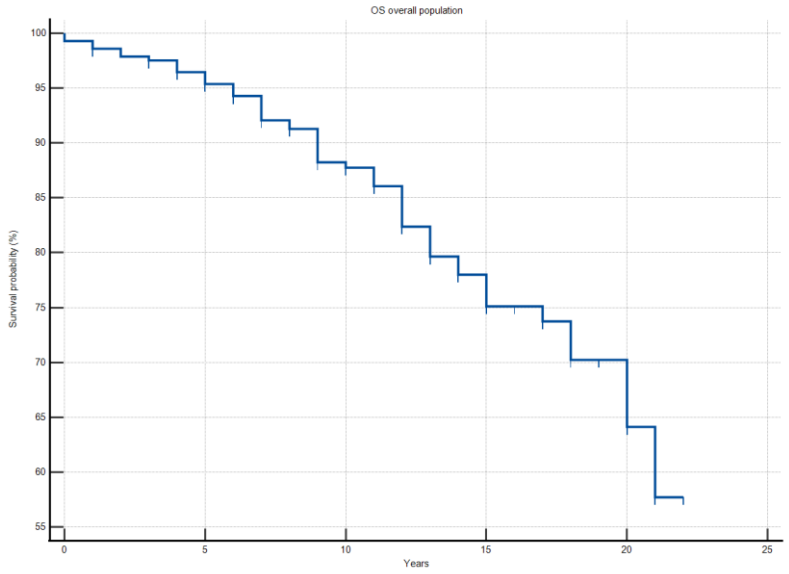


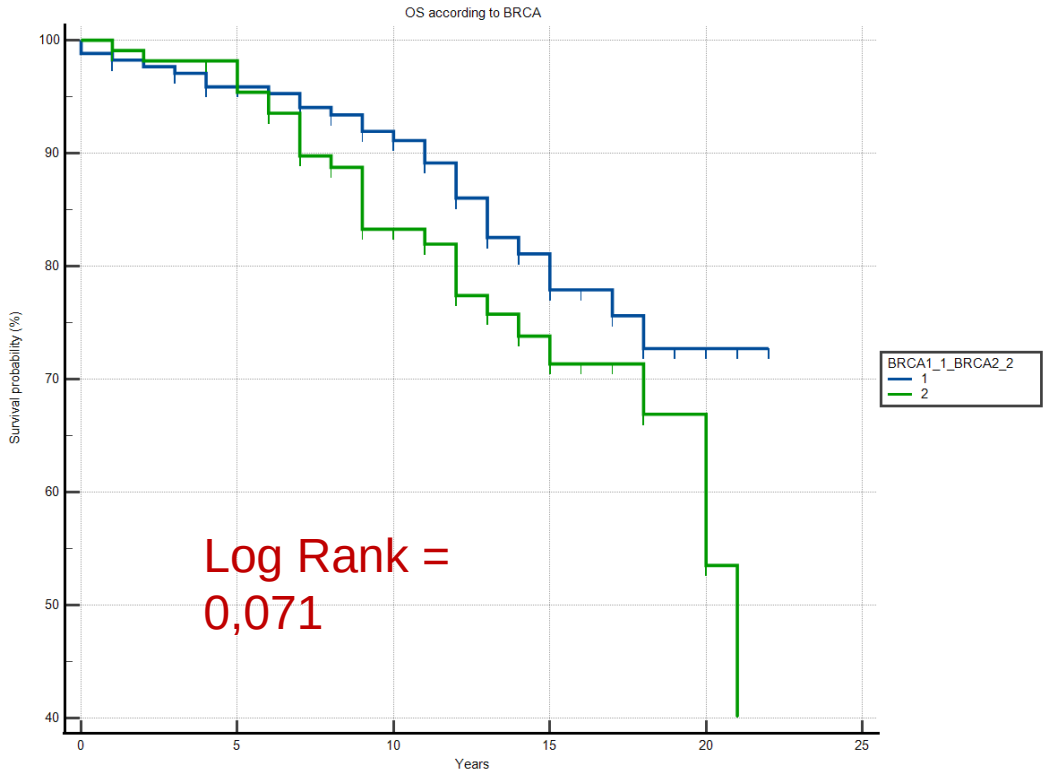


Loco-regional *Bone*
Visceral *SNC* ** Unknown*

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

Conclusions

- **Germline mutations better than epigenetic mutations**
- **In case of PDL-1 positive gBRCA: immunotherapy «plus» better than «before» PARPi?**
- **Is it right to offer PARPi after CDK4/6i in HR+ gBRCA2?**
- **More visceral recurrences in gBRCA2 than gBRCA1and worst OS**
- **What about the rechallenge of PARPi?**