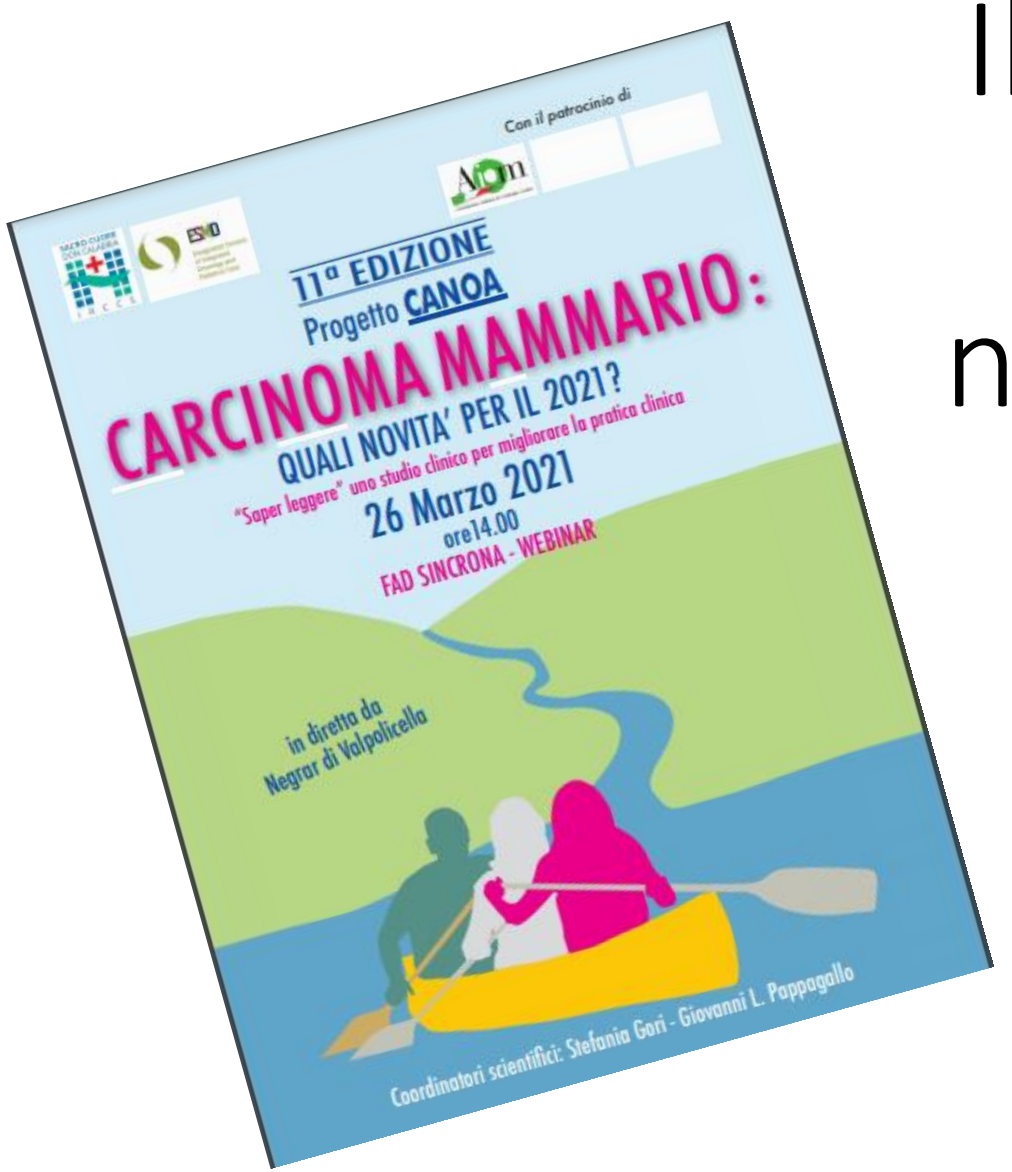
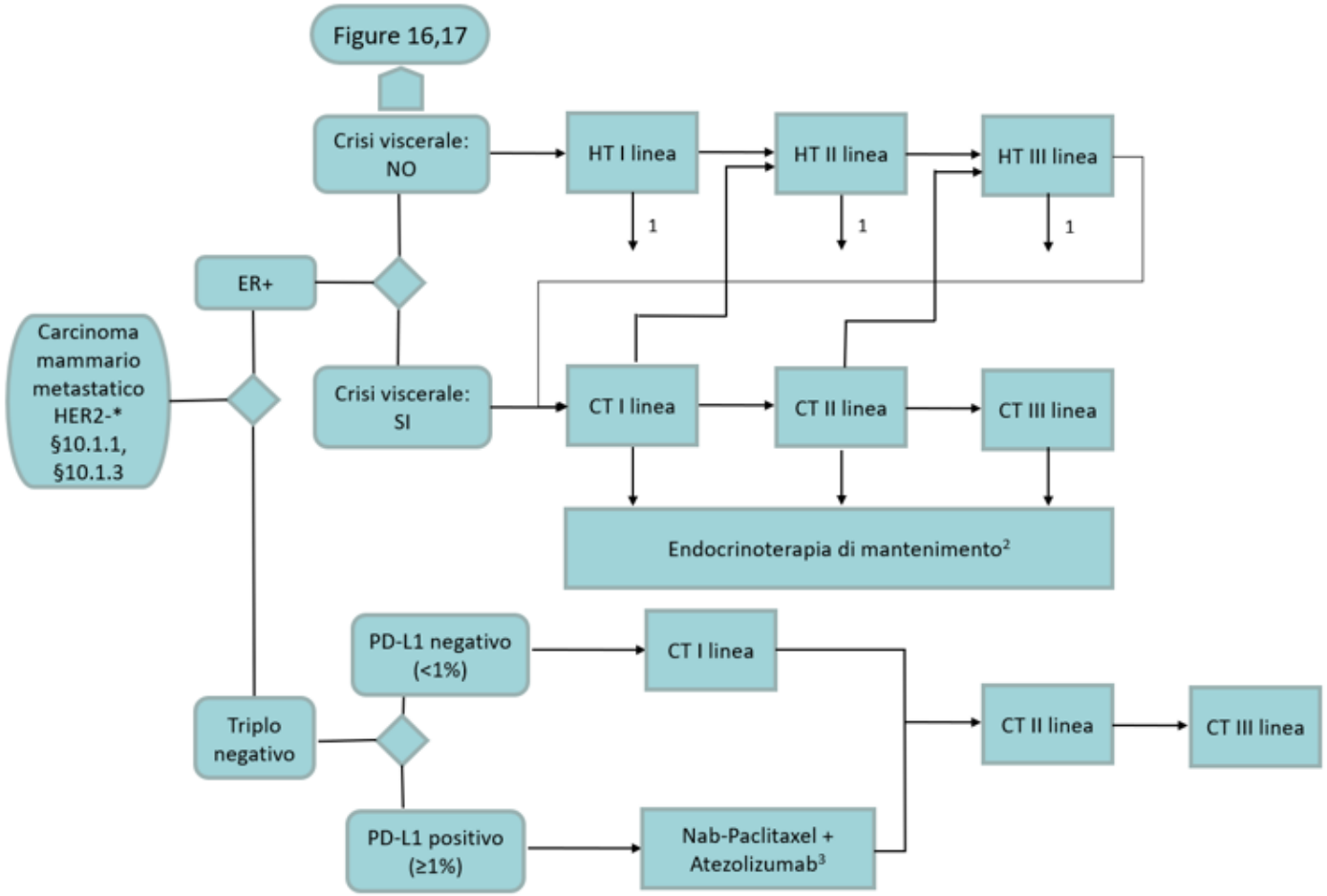


Il carcinoma mammario metastatico nella paziente portatrice di VP germline BRCA: I tumori TN

Laura Cortesi

AOU Policlinico Modena

Figura 12 – CARCINOMA MAMMARIO METASTATICO HER2-NEGATIVO: Terapia medica in base alle caratteristiche patologiche e cliniche



QUESITO GRADE PARP-I NEL CARCINOMA METASTATICO TN BRCA+

NEOPLASIE DELLA MAMMELLA

LINEE GUIDA 2020

GRADE Quesito 29: Dovrebbe un trattamento con PARP-I vs una chemioterapia standard essere utilizzato per pazienti portatrici di VP gBRCA con carcinoma mammario metastatico TN, che abbiamo ricevuto precedente chemioterapia con A/T e non già resistenti al platino?
RACCOMANDAZIONE: Un trattamento con PARP-I vs una chemioterapia standard può essere preso in considerazione come prima opzione per pazienti portatrici di VP gBRCA con carcinoma mammario metastatico TN, che abbiano ricevuto precedente chemioterapia con A/T e non già resistenti al platino
Forza della raccomandazione: POSITIVA DEBOLE
Qualità delle evidenze: Outcome di beneficio: Bassa; Outcome di danno: Bassa

Votazione rapporto Beneficio/danno			
Favorevole	**Incerto (Favorevole)**	**Incerto (sfavorevole)**	**Sfavorevole**
0	**9**	**0**	**0**
Votazione forza della Raccomandazione			
Positiva forte	**Positiva debole**	**Negativa debole**	**Negativa forte**
0	**9**	**0**	**0**

INDICAZIONE RIMBORSABILITA’ AIFA OLAPARIB

Olaparib per le pazienti con carcinoma mammario metastatico triplo-negativo con mutazione (VP) BRCA germline, precedentemente trattate con antracicline e taxani e platino nel setting (neo)adiuvante o metastatico a meno che i pazienti non fossero elegibili per questi trattamenti

Linee Guida AIOM 2020

USO COMPASSIONEVOLE PARP INIBITORI

Talazoparib per il trattamento di pazienti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo localmente avanzato o metastatico, indipendentemente dallo stato dei recettori ormonali

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)
(capecitabina, vinorelbine, eribulina)

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

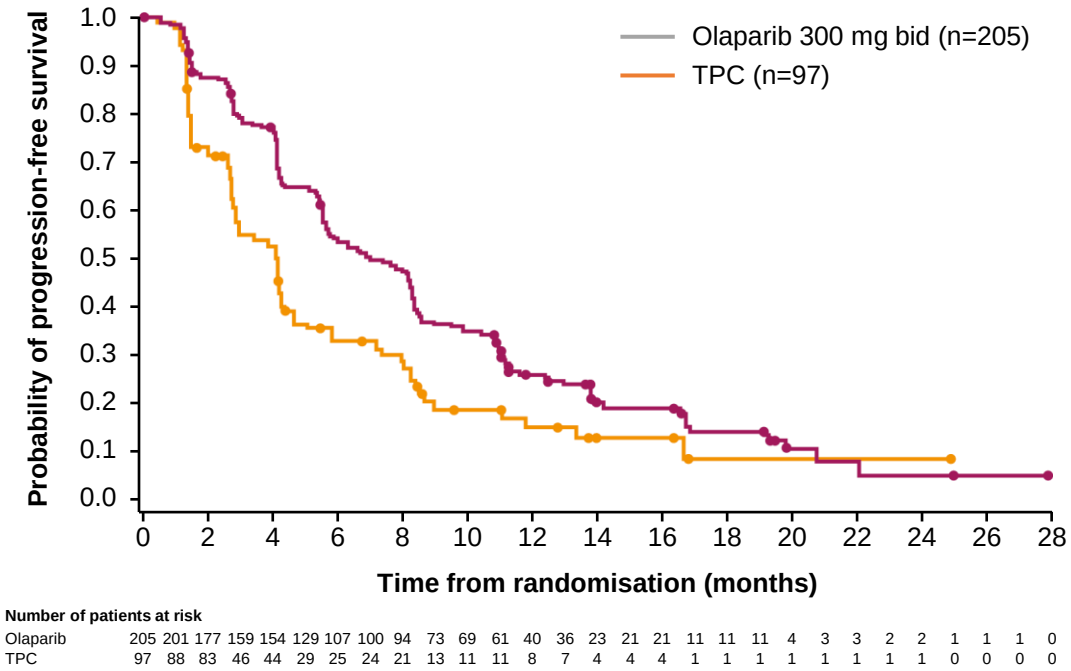
- * Tablet formulation (2 tablets twice daily)
- 1. https://clinicaltrials.gov/ct2/show/NCT02000622 [Accessed February 2019]; 2. Robson et al. Poster OT1-1-04, presented at SABCS 2014; 3. AZ data on file (2017); 4. Robson et al. N Engl J Med. 2017; 377:523-533

50% of patients in OlympiAD were TNBC[1]

	Olaparib n=102 n (%)	TPC n=49 n (%)
Number of prior chemotherapy lines 0 1 2	 40 (39.2) 37 (36.3) 25 (24.5)	 17 (35.4) 25 (52.1) 6 (12.5)
Received previous chemotherapy for mBC	66 (64.7)	32 (66.7)
Received prior platinum therapy for breast cancer	36 (35.3)	15 (31.3)

- Data Cutoff: 9 December 2016
- 1. Robson et al. N Engl J Med. 2017; 377:523-533

Primary endpoint: Olaparib treatment significantly improved PFS assessed by BICR compared to TPC[1]

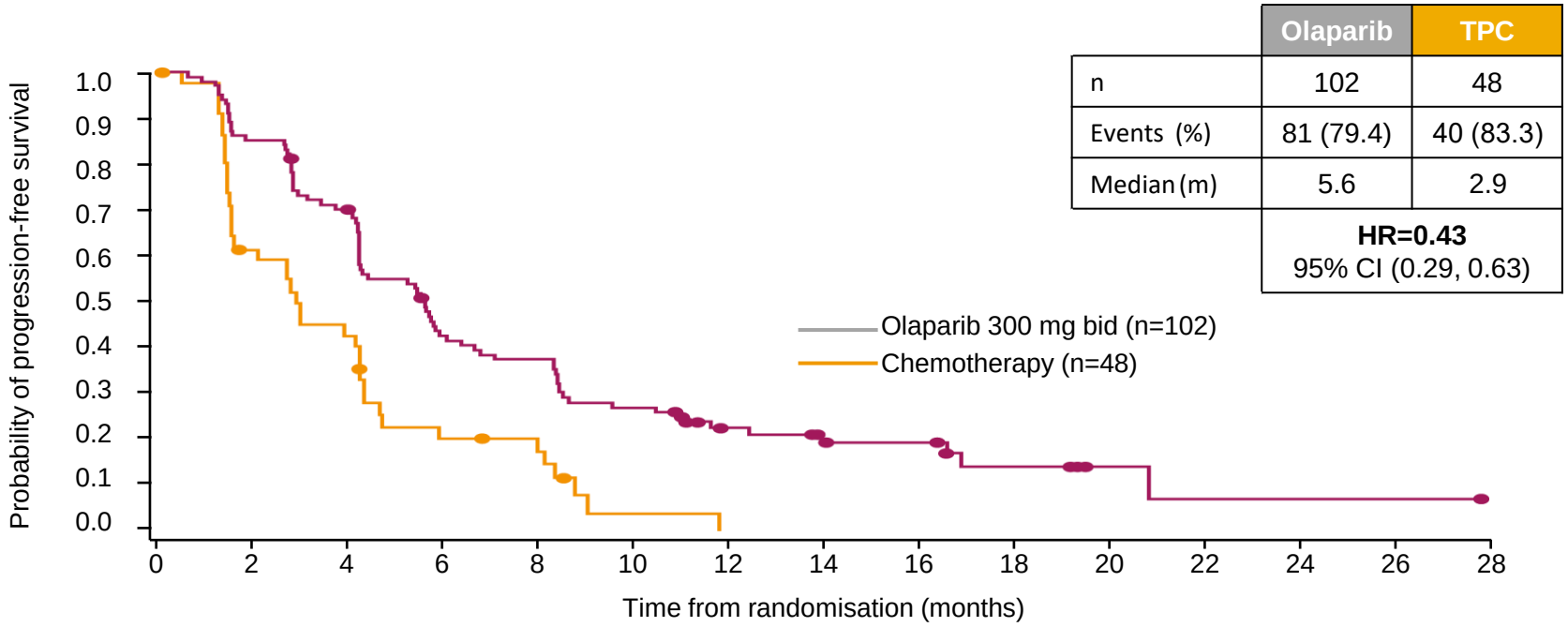


	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	7.0	4.2
	HR=0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

Median PFS was improved by 42% with olaparib treatment compared to standard of care chemotherapy[2]

- Stratified log rank test, stratified by previous chemotherapy for mBC (yes/no) and HR+ versus TNBC
- FAS; Maturity rate: 234/302=77%; 2 sided p value; figure adapted with permission[1]
- Data cutoff: 9 December 2016
- 1. Robson et al. N Engl J Med. 2017; 377:523-533; 2. AZ data on file (2017)

In TNBC, olaparib reduced the risk of progression compared to TPC by 57%[1]



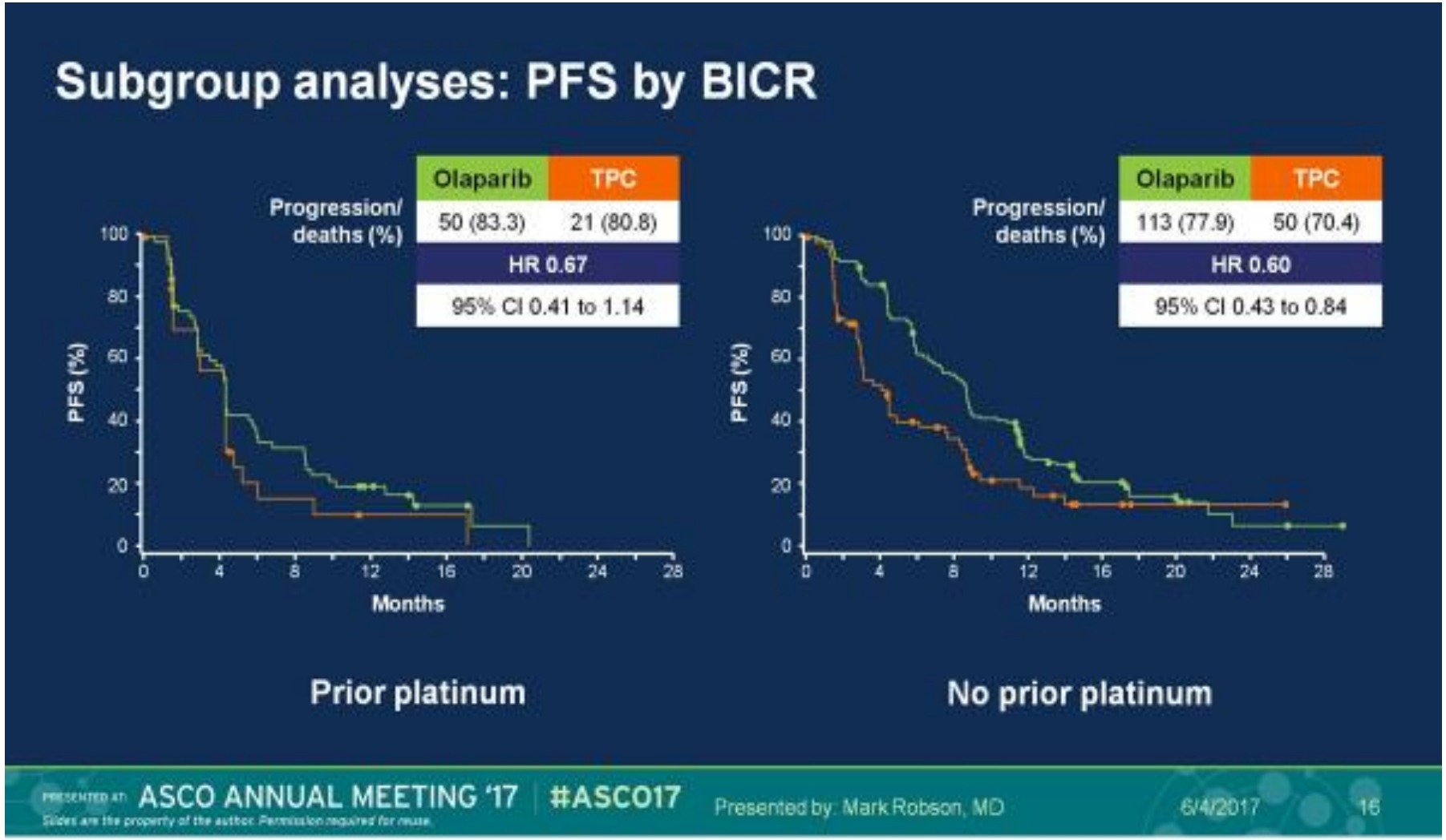
	Olaparib	TPC
n	102	48
Events (%)	81 (79.4)	40 (83.3)
Median (m)	5.6	2.9
	HR=0.43 95% CI (0.29, 0.63)	

Number of patients 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	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

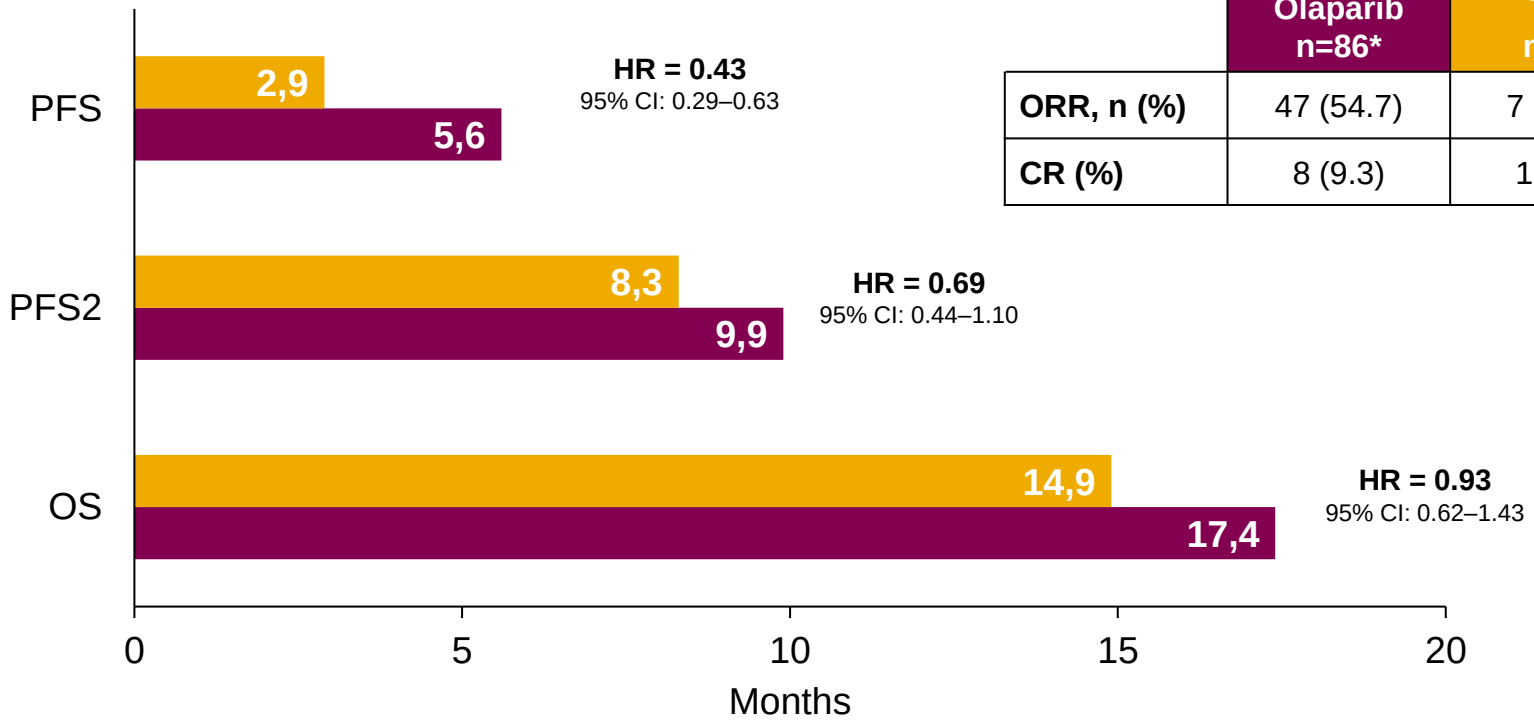
- The OlympiAD study was not powered to identify differences in treatment effect between subgroups, and any differences observed here are hypothesis-generating
- Data Cutoff : 9 December 2016
- 1. Robson et al. N Engl J Med. 2017; 377:523-533, 2. Robson et al. J Clin Oncol 35, 2017 (presentation associated with abstr LBA4); 3. Senkus et al., Poster PB-002, presented at EBCC 2018

Subgroup analyses: PFS by Platinum Exposure



Robson M. NEJM 2017

Secondary Endpoints in TNBC

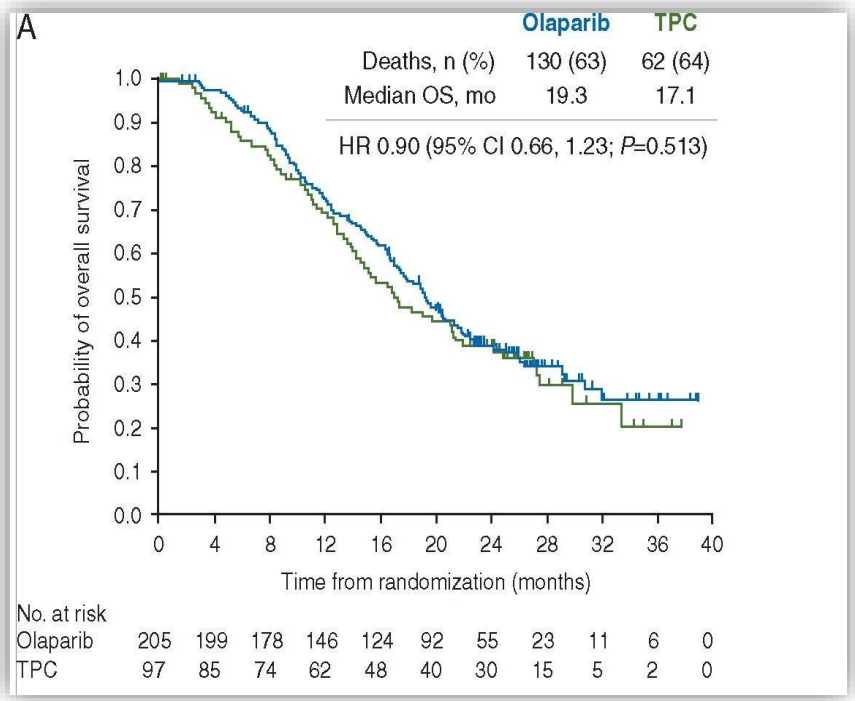


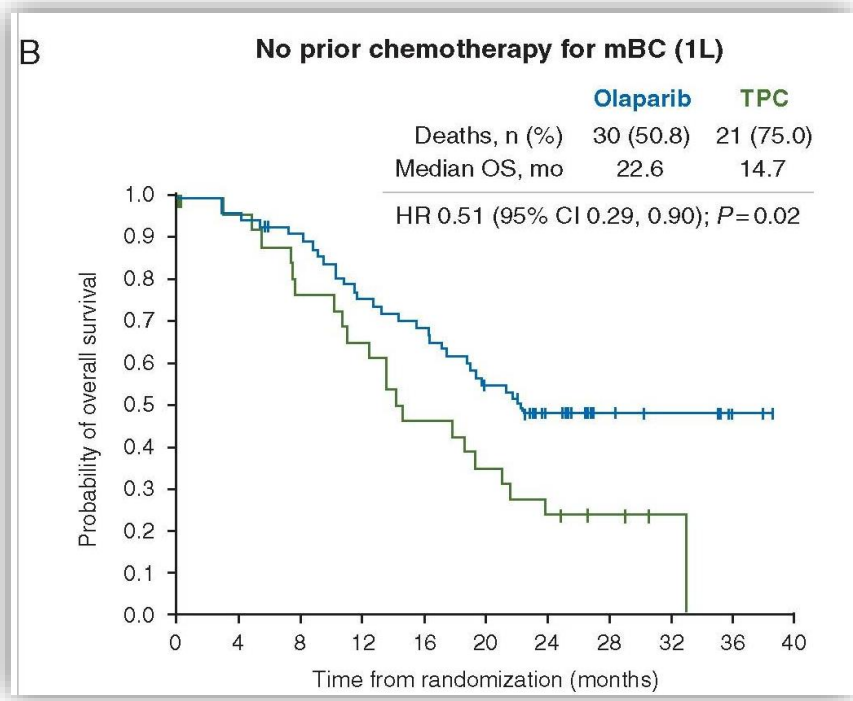
	Olaparib n=86*	TPC n=33*
ORR, n (%)	47 (54.7)	7 (21.2)
CR (%)	8 (9.3)	1 (3.0)

*In patients with measurable disease
The OlympiAD study was not powered to identify differences in treatment effect between subgroups, and any differences observed here are hypothesis-generating
Data cutoff PFS, PFS2: 9 December 2016; Data cutoff OS: 25 September 2017

1. Senkus et al., Poster PB-002, presented at EBCC 2018, 2. Robson M et al. Annals of Oncology 2019. ePub before print

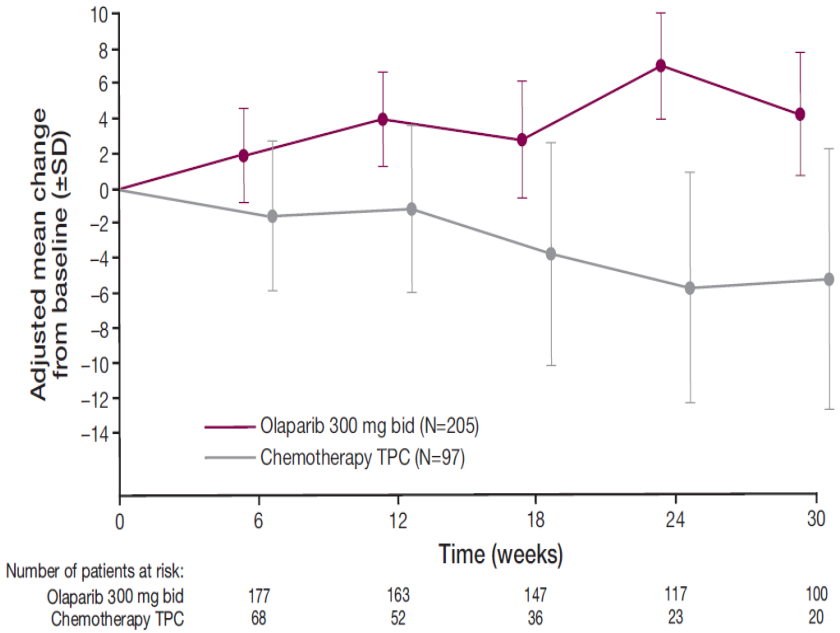
Overall Survival





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

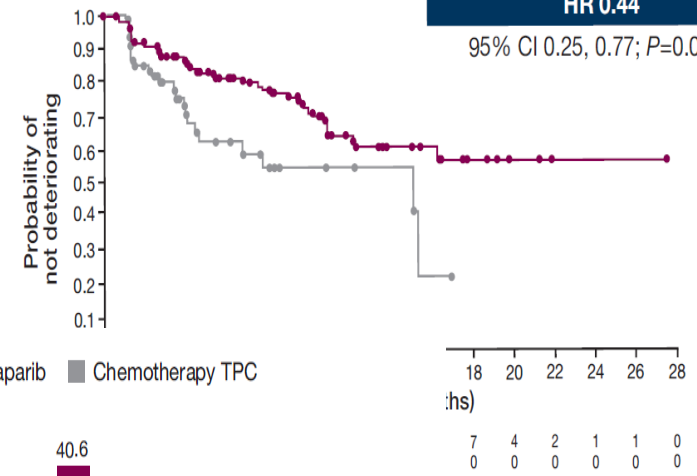
HRQoL in the OlympiAD trial

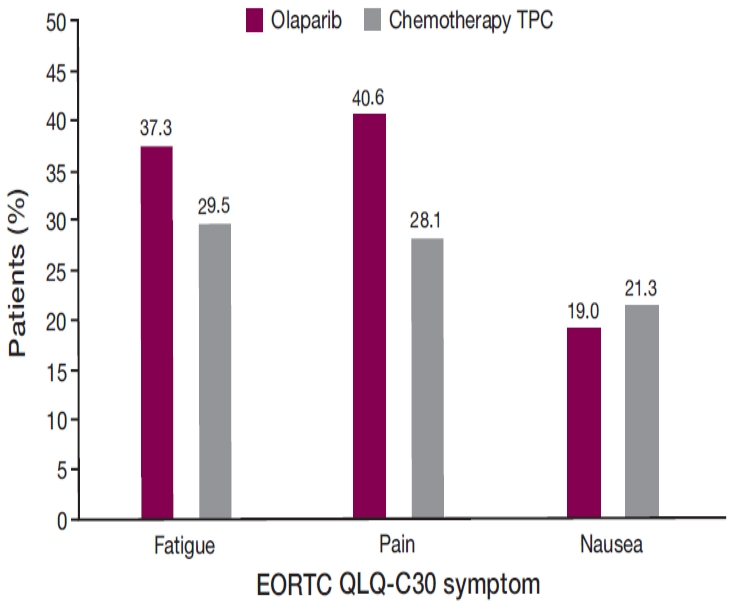


	Olaparib 300 mg bid (n=201)	Chemotherapy TPC (n=93)
Deterioration, n (%)	49 (24)	25 (27)
Median time to deterioration, months	NC	15.3

HR 0.44

95% CI 0.25, 0.77; *P*=0.0043





Odds ratio	1.46	1.76	0.85
95% CI	(0.78, 2.81)	(0.93, 3.45)	(0.42, 1.81)

Robson M, ESMO 2017

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)*

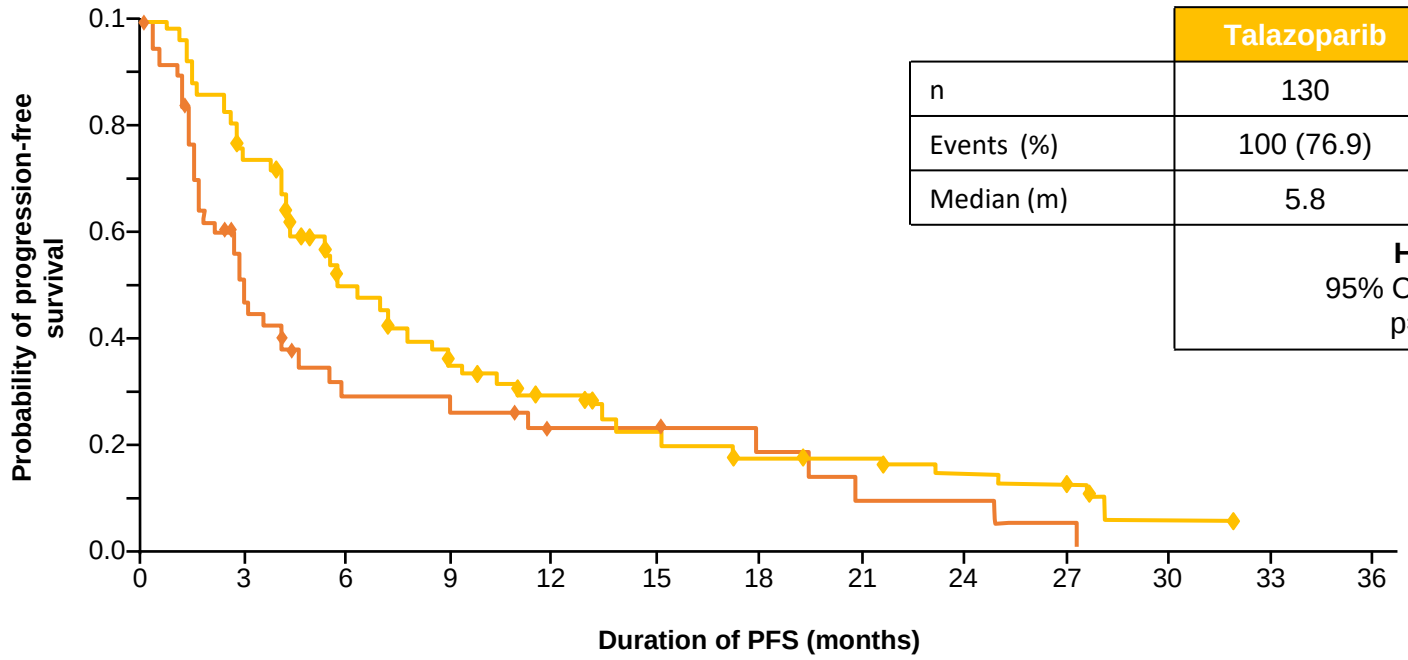
- Litton J et al. N Engl J Med 2018; 379:753–763

45% of patients in EMBRACA had TNBC

	Talazoparib n=130 n (%)	TPC n=60 n (%)
Number of prior chemotherapy lines 0 1 2 3 ≥4	 52 (40.0) 50 (38.5) 21 (16.2) 6 (4.6) 1 (0.8)	 26 (43.3) 21 (35.0) 9 (15.0) 4 (6.7) 0 (0)
Number of prior cytotoxic chemotherapy regimens, median (min, max)	1 (0, 10)	1 (0, 3)
Received prior platinum therapy for breast cancer	31 (23.8)	18 (31.7)

- Eiermann W. et al., Poster 1070, presented at ASCO 2018

Talazoparib reduced the risk of progression or death by 40% vs. chemotherapy in TNBC patients



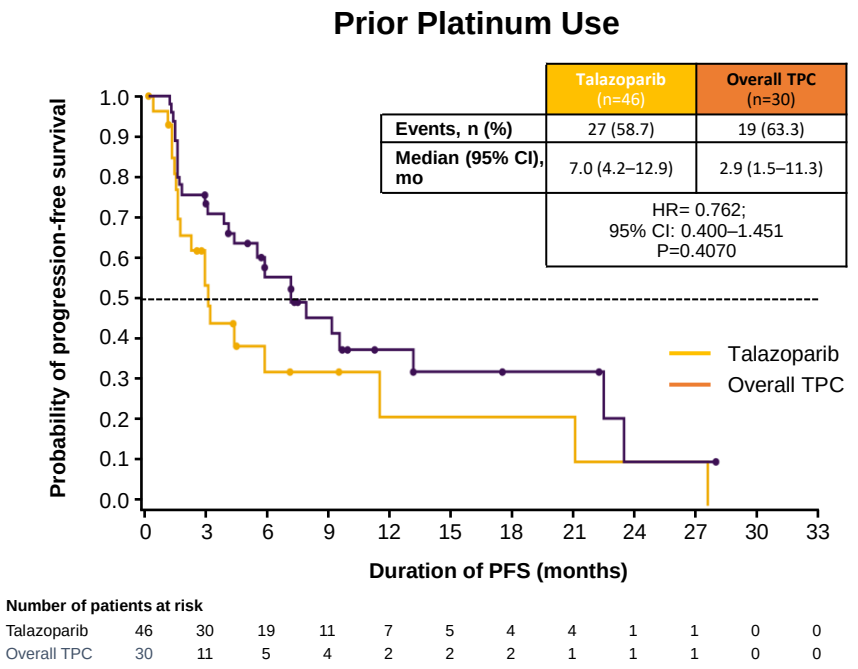
	Talazoparib	Overall TPC
n	130	60
Events (%)	100 (76.9)	40 (66.7)
Median (m)	5.8	2.9
	HR=0.60 95% CI (0.41, 0.87) p=0.0075	

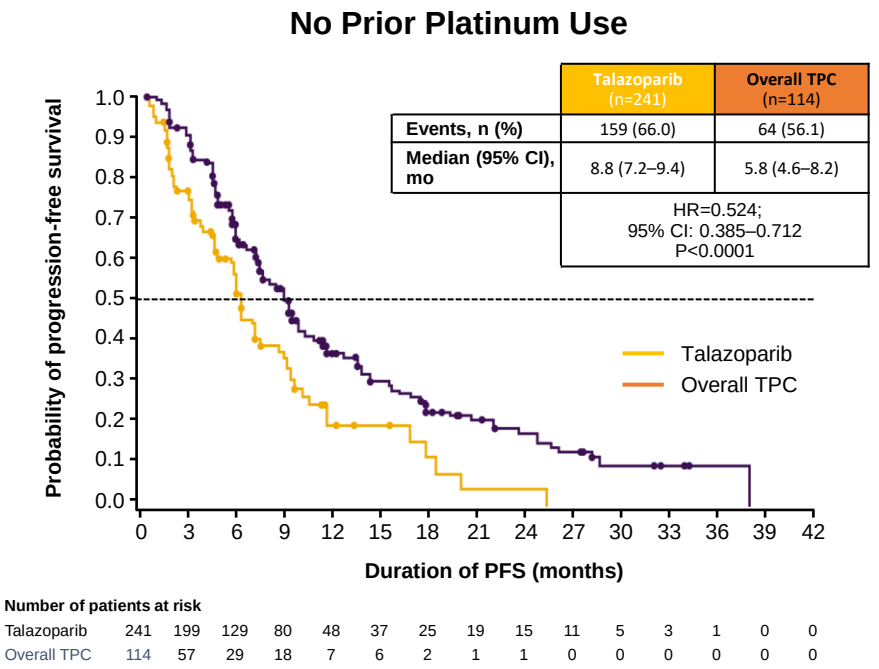
Number at risk (events/cumulative events)

Talazoparib	130 (0/0)	94 (34/34)	55 (29/63)	38 (15/78)	26 (7/85)	18 (6/91)	12 (4/95)	11 (0/95)	8 (2/97)	7 (1/98)	1 (2/100)	0 (0/200)	0 (0/100)
Overall TPC	60 (0/0)	21 (26/26)	10 (7/33)	10 (0/33)	6 (2/35)	6 (0/35)	4 (1/36)	2 (2/38)	2 (0/38)	1 (1/39)	0 (1/40)	0 (0/40)	0 (0/40)

- Eiermann W. et al., Poster 1070, presented at ASCO 2018

EMBRACA: Prior vs. no prior platinum subgroup analysis
PFS based on prior platinum use (assessed by BICR)

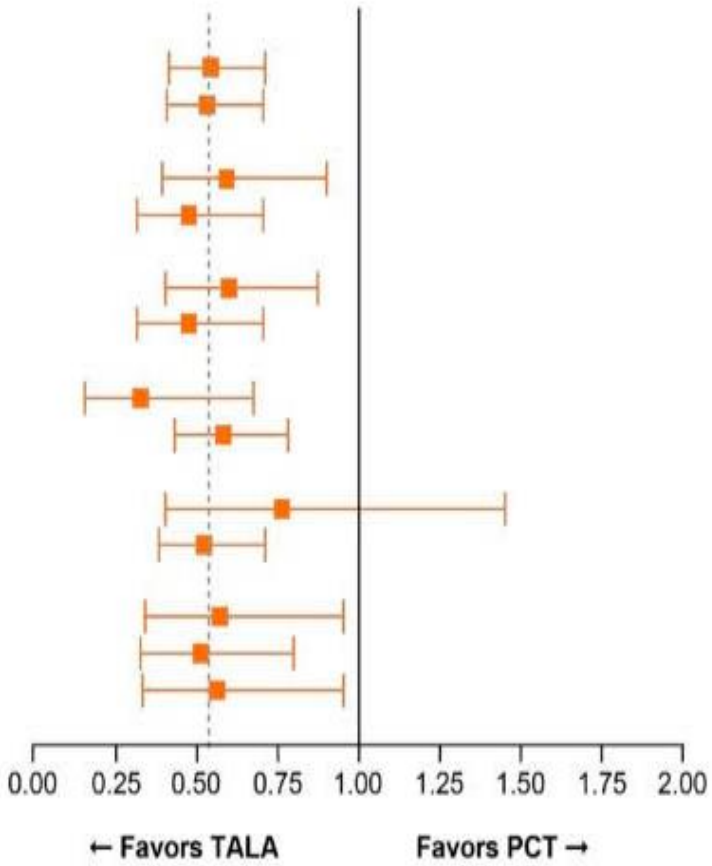




- Martin M, et al. Poster 303P. ESMO 2018.

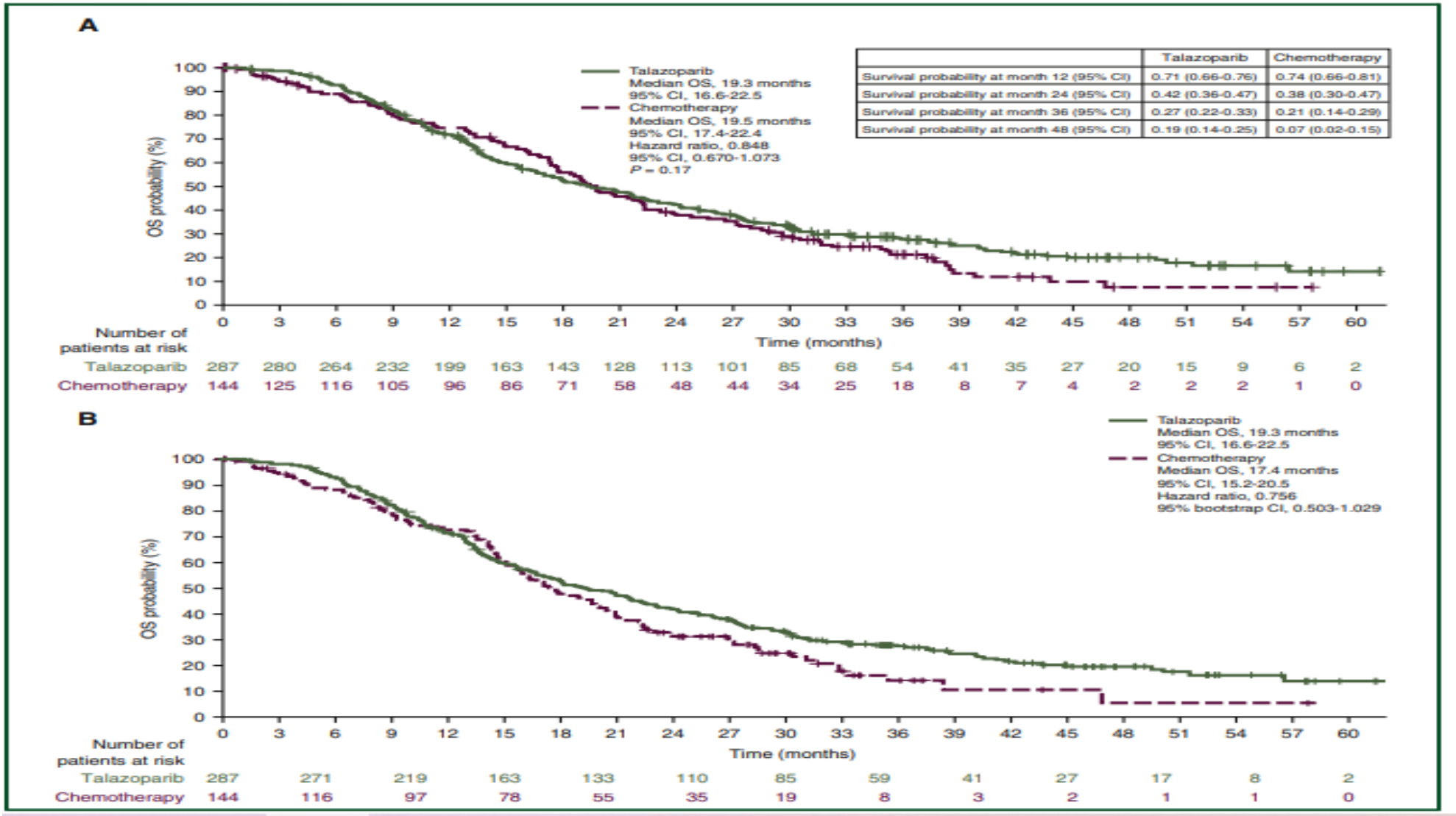
PFS: Subgroup Analysis

Subgroup	Patients, no. (%)	Hazard ratio (95% CI)
All randomized patients (ITT)	431 (100)	0.54 (0.41-0.71)
Patients with central testing available	408 (94.7)	0.53 (0.40-0.70)
BRCA status by central testing		
BRCA1	183 (42.5)	0.59 (0.39-0.90)
BRCA2	225 (52.2)	0.47 (0.32-0.70)
Hormone receptor status		
TNBC based on most recent biopsy	190 (44.1)	0.60 (0.41-0.87)
HR+ based on most recent biopsy	241 (55.9)	0.47 (0.32-0.71)
History of CNS metastasis		
Yes	63 (14.6)	0.32 (0.15-0.68)
No	368 (85.4)	0.58 (0.43-0.78)
Prior platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Prior regimens of cytotoxic chemo for aBC		
0	165 (38.3)	0.57 (0.34-0.95)
1	161 (37.4)	0.51 (0.33-0.80)
≥ 2	105 (24.4)	0.56 (0.34-0.95)



Litton JK NEJM 2018

FINAL OS

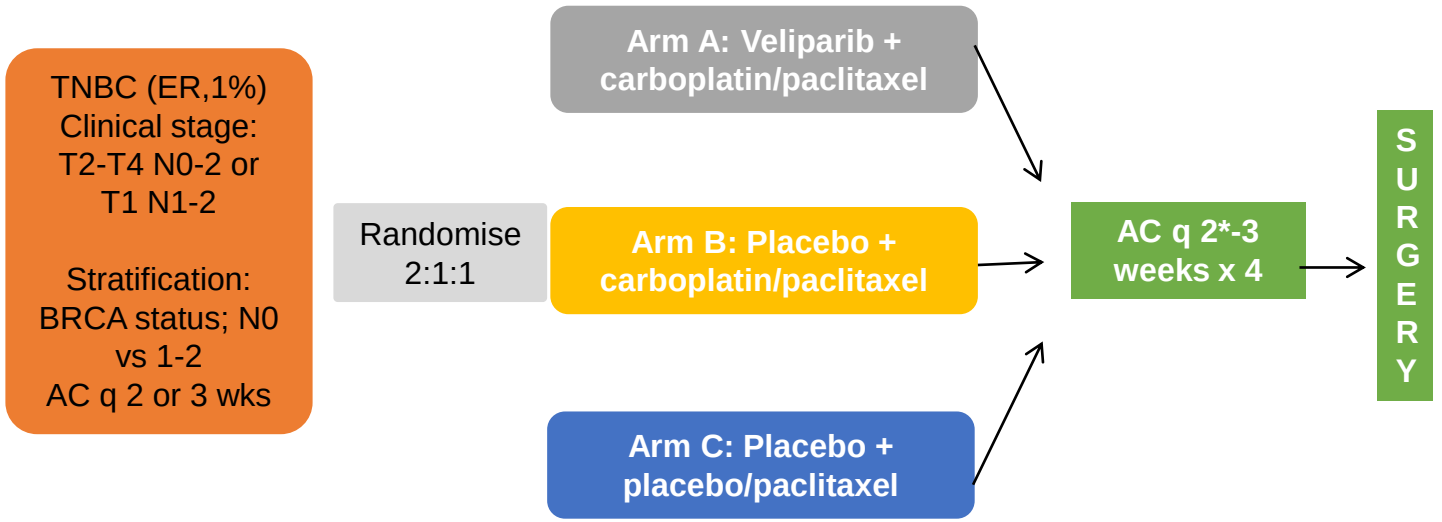


	Talazoparib	Chemotherapy
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)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

Litton JK Annals Oncol 2020

BrighTNess: A randomised Phase III neoadjuvant trial in TNBC

N=624; primary endpoint pCR breast/axilla



15% with gBRCA mutations (45/25/23)

Veliparib: 50 mg PO BID x 12 weeks; *carboplatin*: AUC 6 IV q 3 weeks x 4; *paclitaxel:* 80 mg/m^2 IV weekly x 12; AC: *doxorubicin:* 60 mg/m^2/cyclosphosphamide 600 mg/m^2

Loibl S et al. Lancet Oncol. 2018 Apr;19(4):497-509

Differential benefit in gBRCA carriers?

pCR rates by germline mutation and treatment arm

pCR	gBRCAm	gBRCAwt
Placebo + placebo/paclitaxel	41% (9/22)	29% (40/136)
Veliparib + carboplatin/paclitaxel	57% (26/46)	53% (142/270)
Placebo + carboplatin/paclitaxel	50% (12/24)	59% (80/136)

Loibl S et al. Lancet Oncol. 2018 Apr;19(4):497-509

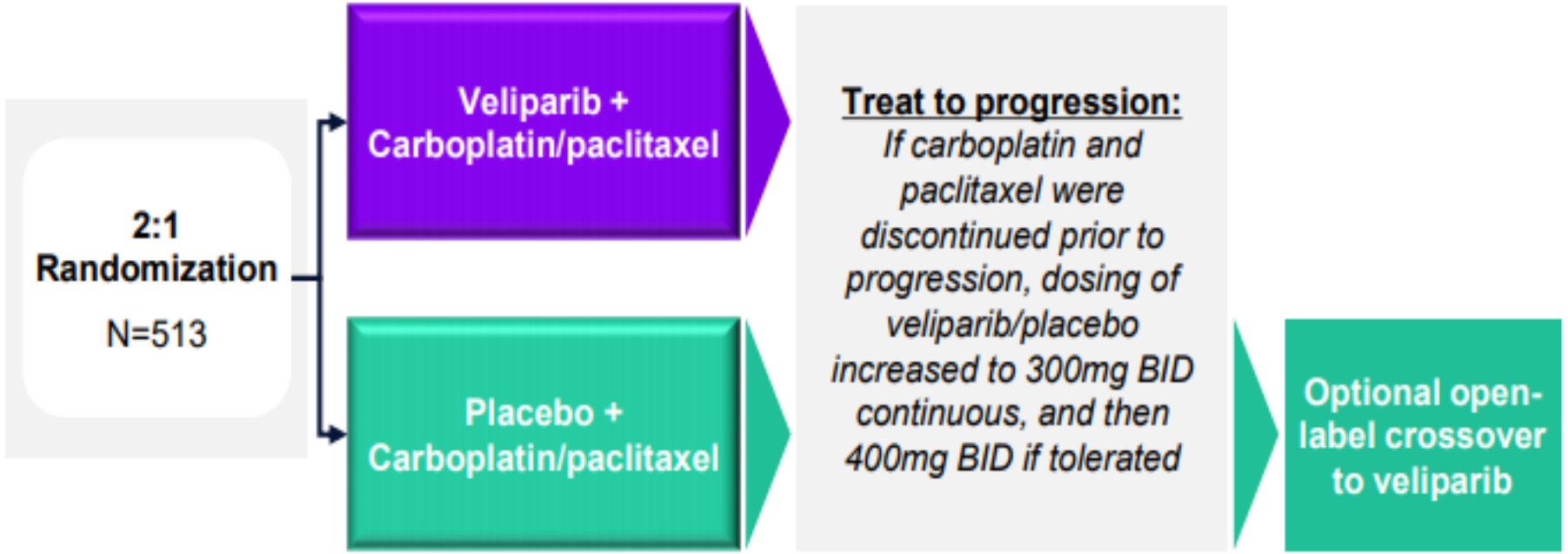
Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3)

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis

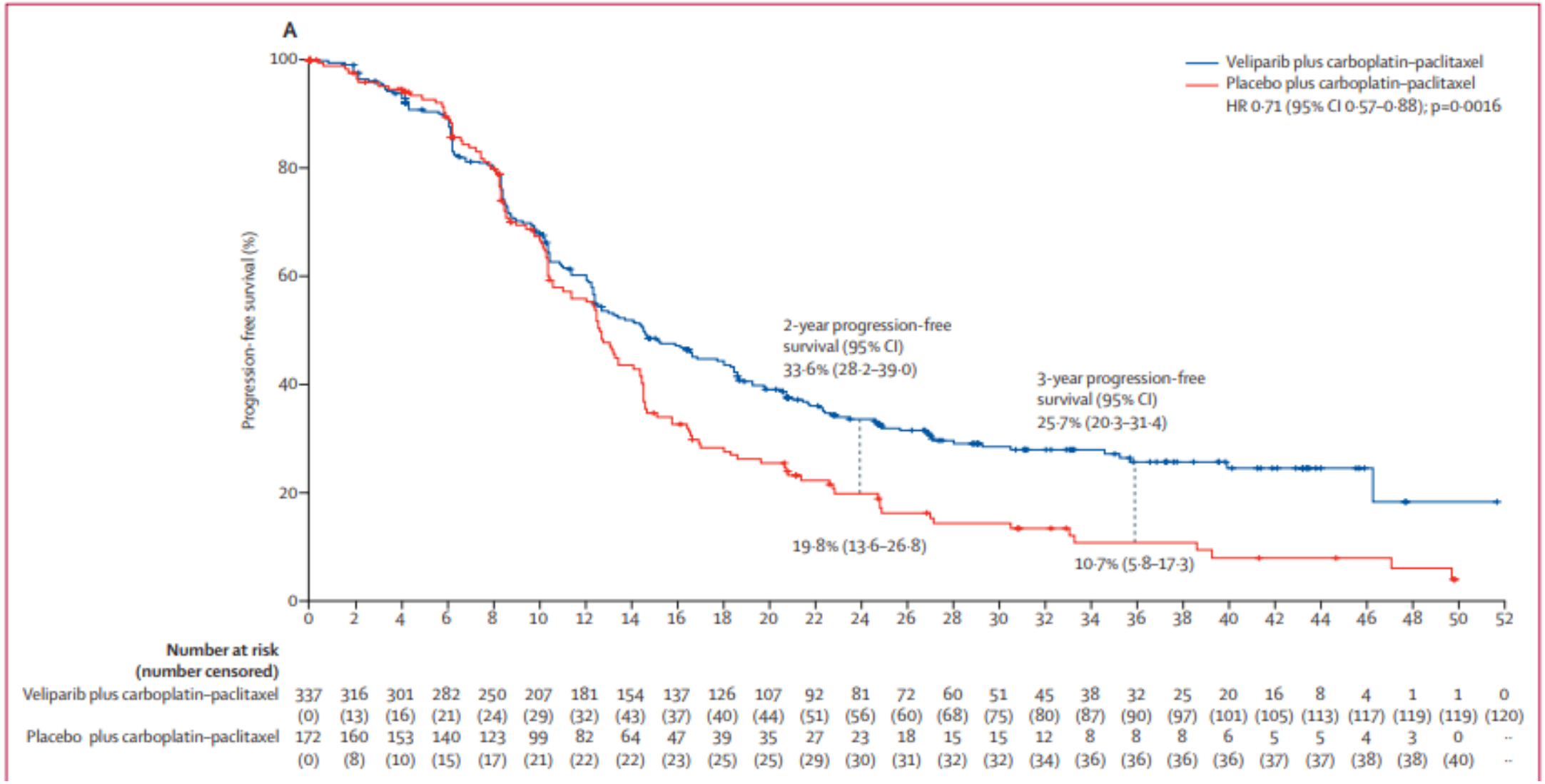


Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:

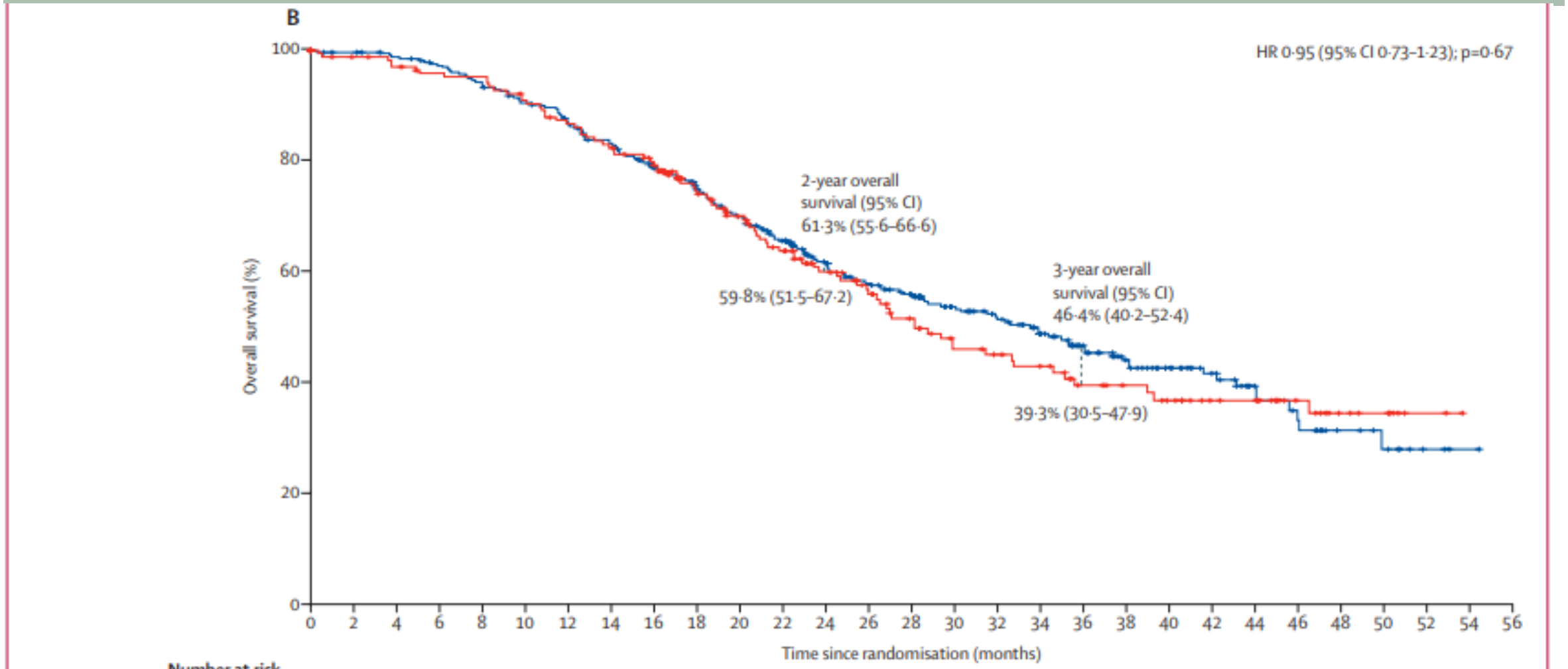
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m^2 on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3)



- Vieras D et al., Lancet Oncol 2020

Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3)



Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3)

	Veliparib plus carboplatin–paclitaxel		Placebo plus carboplatin–paclitaxel		Hazard ratio (95% CI)
	Events/patients	Median progression-free survival (95% CI)	Events/patients	Median progression-free survival (95% CI)	
Hormone receptor status					
ER positive or PgR positive	124/174	13·0 (12·1–16·6)	74/92	12·5 (10·2–13·2)	0·69 (0·52–0·92)
ER negative and PgR negative (TNBC)	93/163	16·6 (12·3–22·7)	58/80	14·1 (11·0–15·8)	0·72 (0·52–1·01)
***BRCA* status**					
BRCA1 mutation	113/177	14·5 (12·1–17·7)	68/89	13·1 (10·3–14·5)	0·72 (0·53–0·97)
BRCA2 mutation	106/167	14·7 (12·4–19·3)	67/86	12·6 (10·4–14·5)	0·66 (0·48–0·89)
Previous platinum therapy					
Previous platinum therapy	19/27	10·9 (8·4–20·7)	14/16	12·5 (6·6–14·6)	0·70 (0·34–1·44)
No previous platinum therapy	198/310	14·6 (12·5–18·0)	118/156	12·7 (10·6–14·5)	0·71 (0·56–0·89)
Previous cytotoxic therapy for metastatic disease					
Previous chemotherapy in metastatic setting	46/63	9·5 (8·3–12·5)	29/33	10·3 (8·3–14·5)	0·80 (0·50–1·27)
No previous chemotherapy in metastatic setting	171/274	16·6 (13·4–18·7)	103/139	13·1 (11·4–14·5)	0·69 (0·54–0·88)
History of CNS metastases					
Yes	14/16	8·3 (6·1–8·6)	8/10	12·5 (5·5–38·7)	2·08 (0·78–5·52)
No	203/320	14·8 (12·7–18·5)	124/161	12·7 (10·6–14·4)	0·66 (0·53–0·83)
All patients	**217/337**	**14·5 (12·5–17·7)**	**132/172**	**12·6 (10·6–14·4)**	**0·70 (0·57–0·87)**

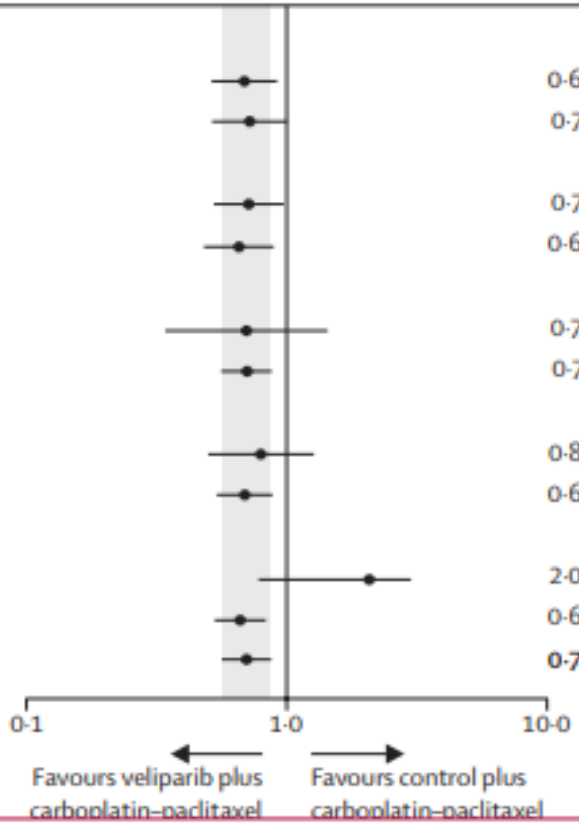
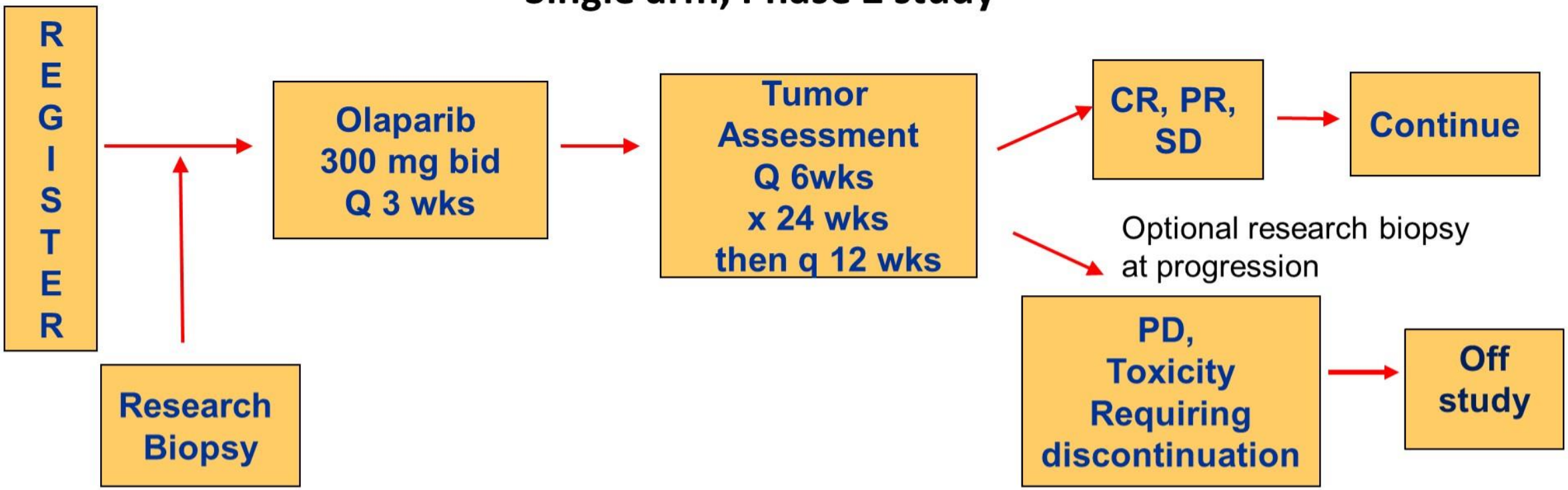


***Figure 3*: Subgroup analysis of progression-free survival**

Hazard ratios presented for subgroups other than hormone receptor status are from a Cox model stratified by hormone receptor status only. The hormone receptor status subgroup hazard ratios are from an unstratified model. ER=oestrogen receptor. PgR=progesterone receptor. TNBC=triple-negative breast cancer.

Schema: Olaparib Expanded

Single arm, Phase 2 study

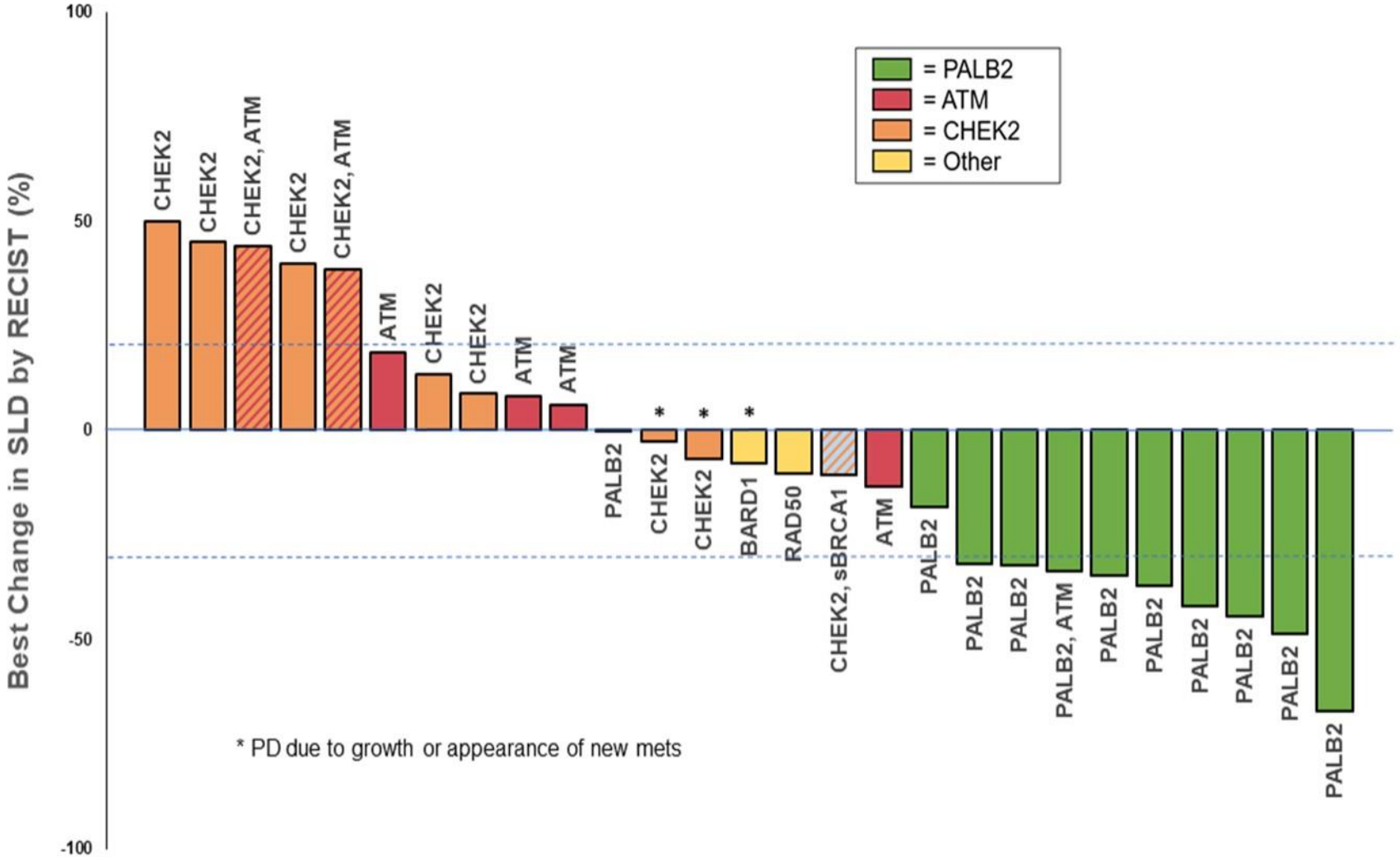


Cohort 1: Germline Mutation
Cohort 2: Somatic Mutation

s*BRCA1/2* allowed if g*BRCA* negative

ATM, ATR, BAP1, BARD1, BLM, BRIP1 (FANCJ), CHK1 (CHEK1), CHEK2 , CDK12, FANCA, FANCC, FANCD2, FANCF, MRE11A, NBN (NBS1), PALB2, RAD50, RAD51C, RAD51D, WRN

Best Overall Responses: Cohort 1 (Germline)



Datacut May 4, 2020

Presented By Nadine Tung at TBD

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Talazoparib Beyond BRCA (TBB)

Joshua J. Gruber, Anosheh Afghahi, Alyssa Hatton[1], Danika Scott, Alex McMillan, James M. Ford, Melinda L. Telli

2019 ASCO Annual Meeting, Abstract 3006

COHORT A: Advanced Triple Negative Breast Cancer

No gBRCA1 or gBRCA2 mutation

↓

HRD Assay - Tumor

HRD score < 42 → Excluded

HRD score ≥ 42 → Accrue 10 patients

↓

Accrue 10 additional pts if ≥ 2 responses in stage 1

COHORT B: HER2-Negative Breast or Other Solid Tumor

No mutation in BRCA1 or BRCA2

↓

Germline or somatic HR pathway gene mutation

↓

Accrue 10 patients

↓

Accrue 10 additional pts if ≥ 2 responses in stage 1

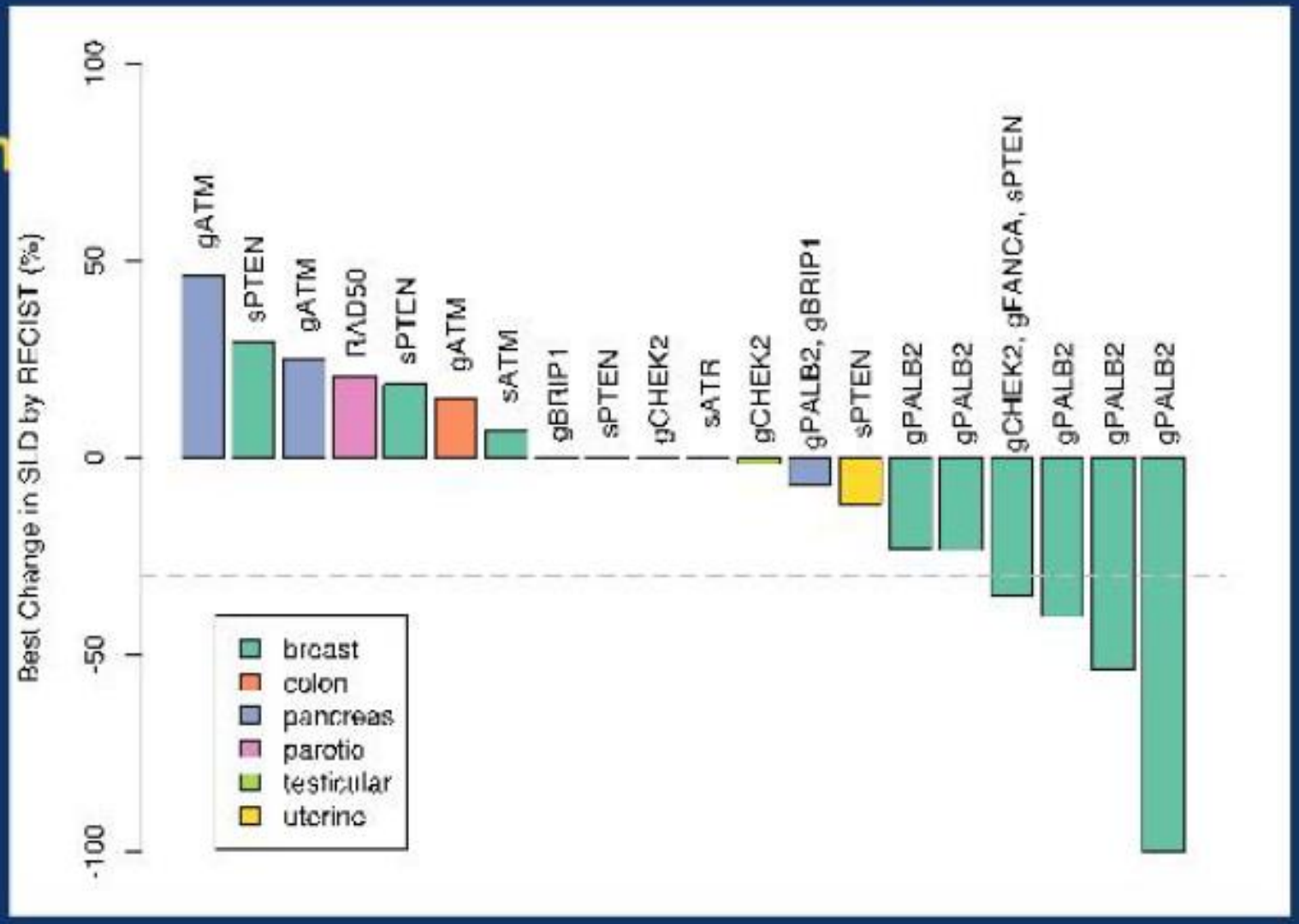
Cohort B mutations:

PALB2	RAD51C
CHEK2	RAD51D
ATM	FANCA
NBN	FANCC
BARD1	FANCD2
BRIP1	FANCE
PTEN	FANCF
MRE11	FANCG
ATR	FANCL
RAD50	

Talazoparib Beyon
BRCA
cohort B

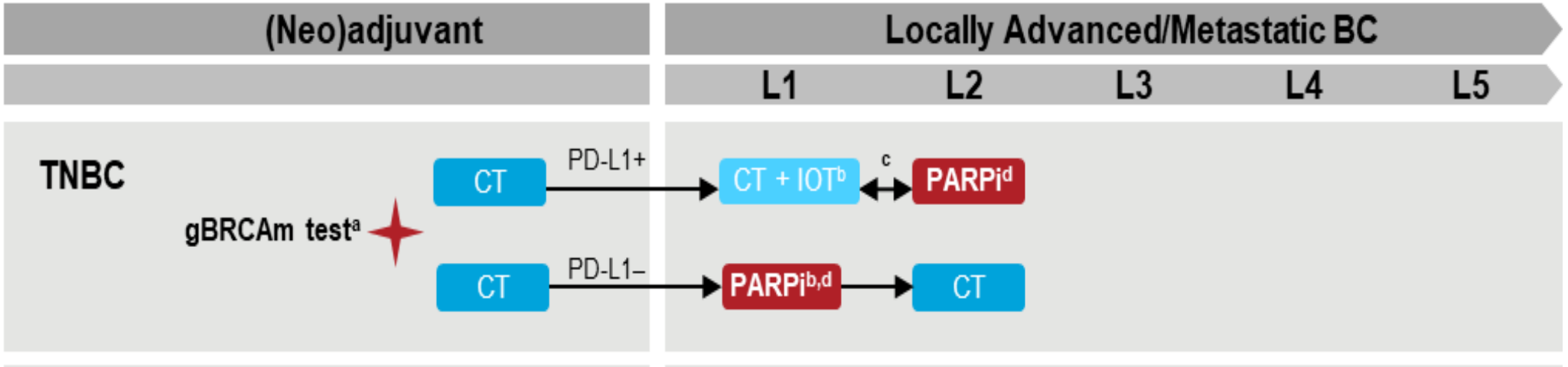
Best Overall Responses

All Patients



Gruber JJ, et al. ASCO 2019

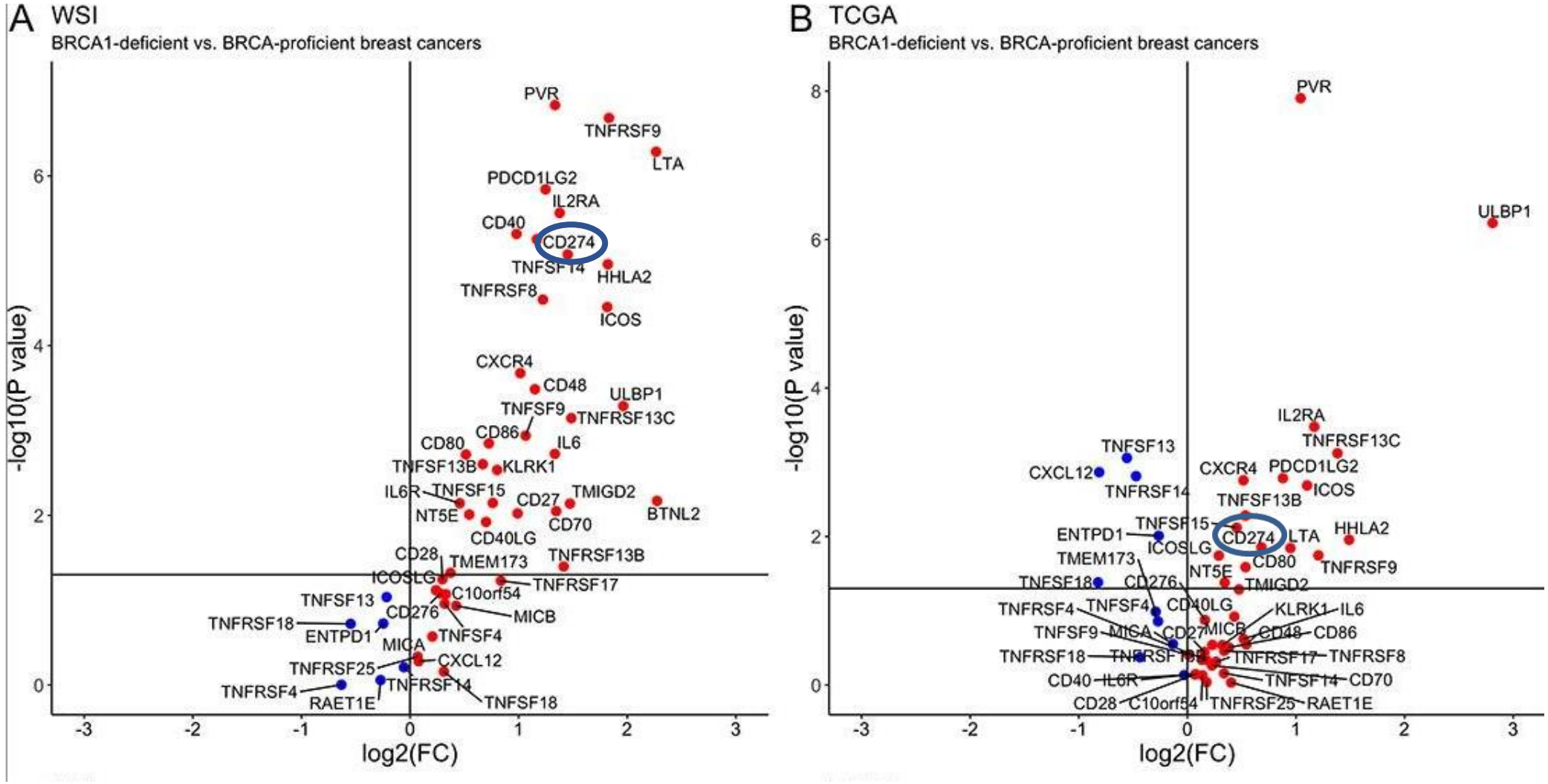
Possible treatment pathways for TNBC gBRCA-mutated, HER2-negative breast cancer and proposed positions of gBRCA mutation testing



A Red star denotes potential positions of gBRCA mutation testing in the treatment pathways.
B The PD-L1 inhibitor atezolizumab plus albumin-bound paclitaxel. For patients with visceral crisis (organ dysfunction) and PD-L1+, first-line treatment could be CT or PARPi. For patients with visceral crisis (organ dysfunction) and PD-L1–, first-line CT may be appropriate.
C Double-headed arrows show that therapies can be provided in either sequence.
D Olaparib and talazoparib are PARPi monotherapies approved for deleterious/suspected deleterious gBRCA-mutated, HER2-negative BC. Olaparib is approved in the USA for metastatic BC and in Europe for locally advanced/metastatic BC; talazoparib is approved for locally advanced/metastatic BC in the USA and Europe.

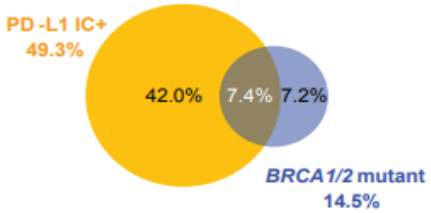
L. Cortesi, H.S. Rugo, C.Jackisch, Targeted Oncology 2021

Association of BRCA1- and BRCA2-deficiency with mutation burden, expression of PD-L1/PD-1, immune infiltrates, and T cell-inflamed signature in breast cancer



Wei Xiong Wen, Plos One 2019

Atezolizumab and nab-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study



PD-L1 status	BRCA1/2 status	Arm	Events/ patients	Median PFS, mo	HR (95% CI)	Events/ patients	Median OS, mo	HR (95% CI)
IC+	Any	A + nP	124/158	7.5	0.62 (0.49 to 0.80)	79/158	25.0	0.71 (0.52 to 0.97)
		P + nP	127/144	4.7		85/143	18.2	
IC–	Any	A + nP	141/165	5.6	0.84 (0.66 to 1.06)	99/164	20.2	0.98 (0.74 to 1.31)
		P + nP	134/145	5.5		89/144	20.0	
Any	Mutant	A + nP	27/39	7.4	0.69 (0.42 to 1.12)	18/39	28.9	0.71 (0.39 to 1.29)
		P + nP	43/50	5.5		27/48	20.1	
	Wild type	A + nP	238/284	7.2	0.72 (0.60 to 0.86)	160/283	20.8	0.85 (0.68 to 1.07)
		P + nP	218/239	5.4		147/239	19.2	
IC+	Mutant	A + nP	11/19	9.1	0.44 (0.21 to 0.93)	7/19	NE	0.55 (0.21 to 1.41)
		P + nP	22/26	3.8		13/25	20.1	
	Wild type	A + nP	113/139	7.4	0.65 (0.50 to 0.85)	72/139	23.4	0.72 (0.52 to 0.99)
		P + nP	105/118	4.7		72/118	17.9	
IC–	Mutant	A + nP	16/20	6.3	1.04 (0.52 to 2.06)	11/20	21.1	0.78 (0.34 to 1.77)
		P + nP	21/24	6.3		14/23	20.1	
	Wild Type	A + nP	125/145	5.6	0.80 (0.62 to 1.04)	88/144	19.7	1.01 (0.74 to 1.37)
		P + nP	113/121	5.5		75/121	20.0	
BRCA BEP		A + nP	265/323	7.2	0.72 (0.61 to 0.85)	178/322	21.1	0.84 (0.68 to 1.03)
		P + nP	261/289	5.4		174/287	19.4	

Emens LA et al , JNCI 2021

CONCLUSIONI

1) **Olaparib** è il solo PARP-i **rimborsato** in scheda AIFA per pazienti TNBC già trattati con **antracicline/taxani e platino** in qualunque setting, a menochè unfit per queste terapie

2) Nessun vantaggio di Olaparib in OS, anche se pazienti **non pretrattati con CT per malattia avanzata** sembrano avere una **riduzione del 49% di rischio di morte** rispetto alla CT

3) Data la necessità di effettuare un trattamento a base di platino e considerata la migliore OS in pazienti non pretrattati con CT per la malattia avanzata, la **chemioterapia a base di platino** andrebbe proposta in **neoadiuvante**

4) Comunque i vantaggi del **platino in neoadiuvante** nelle pazienti **BRCA+ sono controversi**

5) Dallo studio IMPASSION130 risulta un 15% circa di pazienti TNBC con mutazione BRCA1/2 e circa un 7% di questi risulta PDL-1 positivo

6) Pazienti **PDL-1/BRCA+** devono effettuare in **prima linea Nab/Atezo**, anche se i dati **non** sembrerebbero dimostrare un **vantaggio in PFS** in questa popolazione