Quesito clinico 2 - Quale impatto nella pratica clinica?

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IOV - IRCCS

OlympiAD trial: implications for clinical practice

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

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Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves olaparib for germline BRCA-mutated metastatic breast cancer

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On January 12, 2018, the Food and Drug Administration granted regular approval to olaparib tablets (Lynparza, AstraZeneca Pharmaceuticals LP), a poly (ADP-ribose) polymerase (PARP) inhibitor, for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.

This is the first FDA-approved treatment for patients with gBRCAm HER2-negative metastatic breast cancer. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Patients must be selected for therapy based on an FDA-approved companion diagnostic for olaparib.

PATIENTS POPULATION

	Olaparib n=205	TPC n=97
Age (median)	44	45
BRCA1 BRCA2	117 (57) 84 (41)	51 (53) 46 (47)
HR+ TN	103 (50) 102 (50)	49 (51) 48 (49)
New MBC	26 (13)	12 (12)
Previous CT for MBC	146 (71)	69 (71)
Previous platinum	60 (29)	26 (27)
≥2 met sites	159 (78)	72 (74)
Bone only	16 (8)	6 (6)

A/T PRETREATED

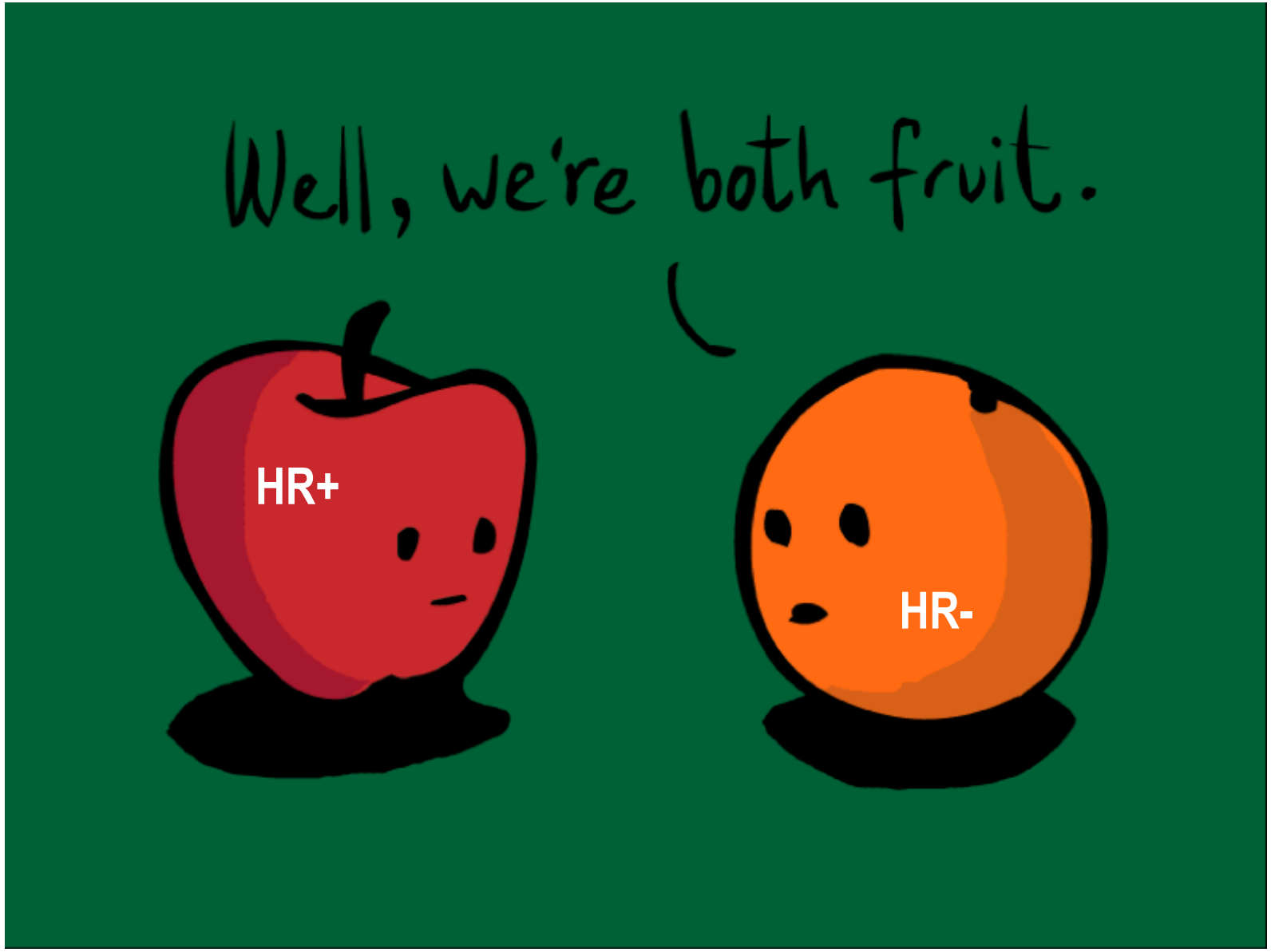
MOST pts RECEIVED CT FOR MBC

HR+: ENDOCRINE RESISTANT

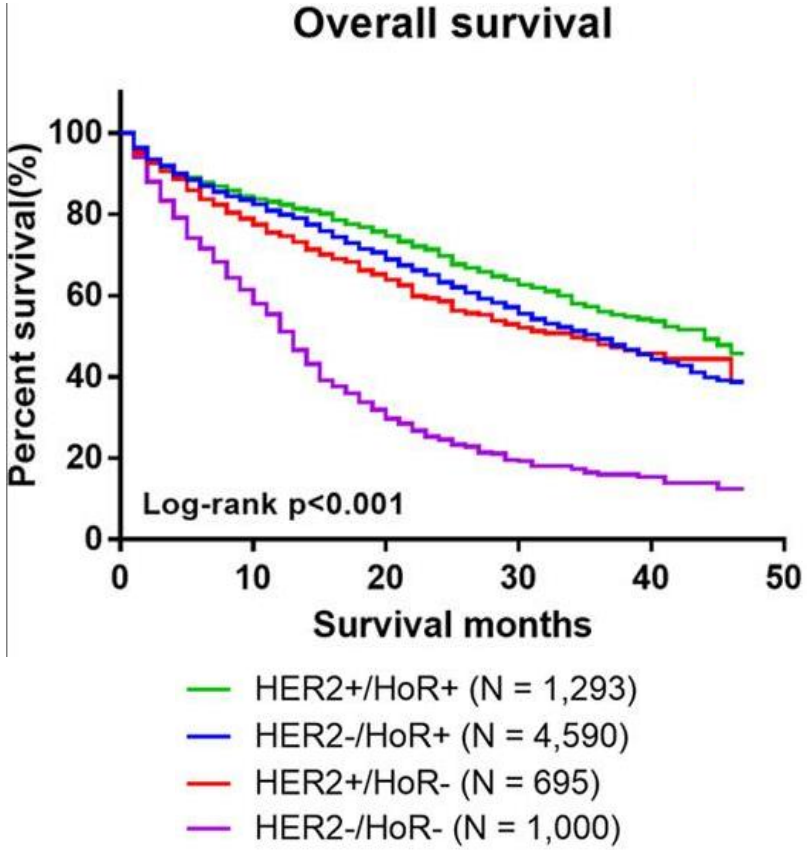
TN: NON-PLATINUM RESISTANT

Robson M, NEJM 2017

HER2- metastatic BRCA-mut BC



Metastatic BC according to molecular subtype

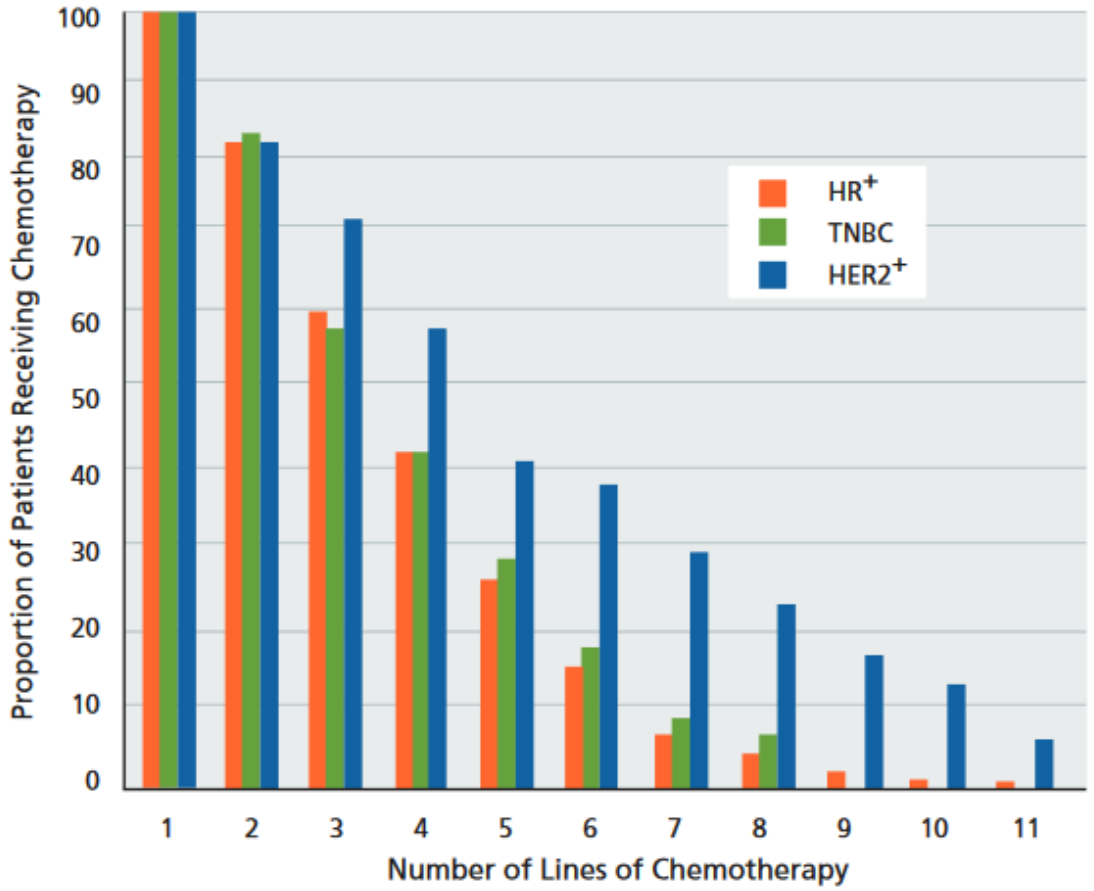


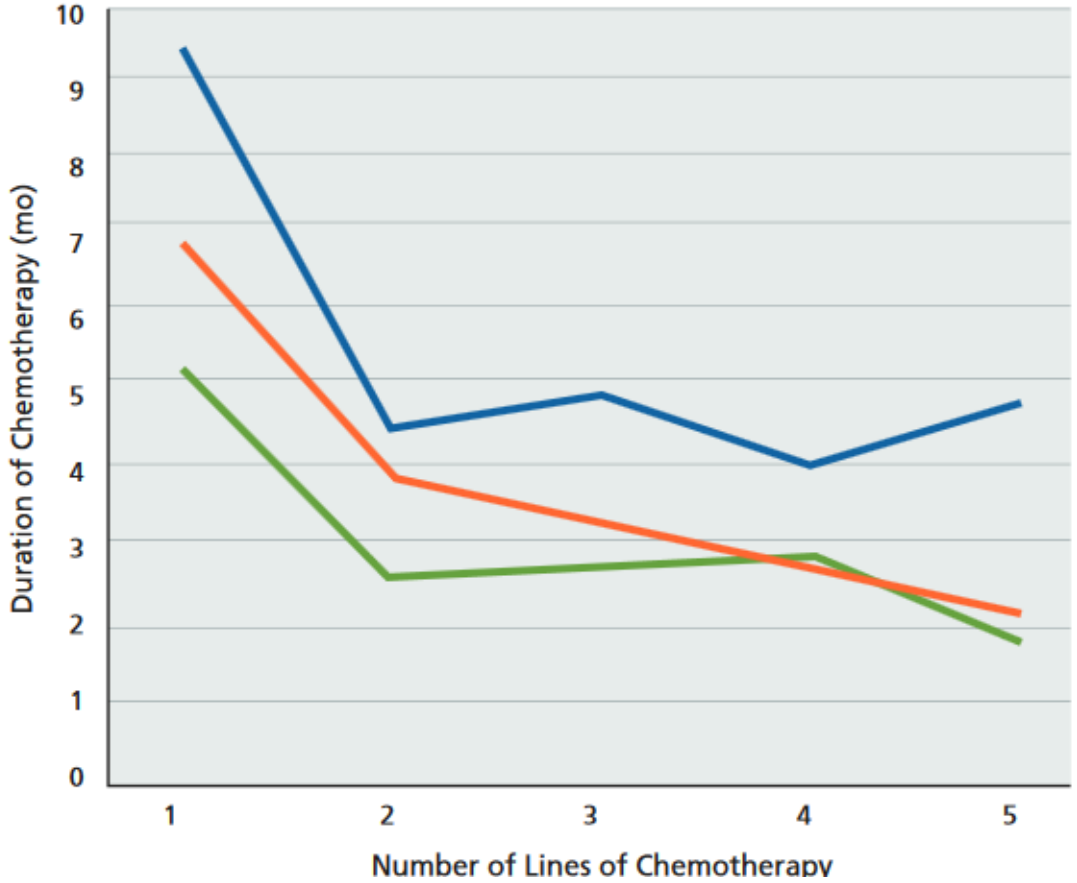
	n	Brain	Liver	Lung	Bone	Distant Nodal	Pleural/ peritoneal	Other
Luminal A	458	7.6	28.6	23.8	66.6	15.9	28.2	13.5
Luminal B	378	10.8	32.4	30.4	71.4	23.3	35.2	19.3
Luminal/HER2	117	15.4	4.4	36.8	65	22.2	34.2	13.7
HER2 enriched	136	28.7	45.6	47.1	59.6	25	31.6	16.9
Basal Like	159	25.2	21.4	42.8	39	39.6	29.6	23.9
TN non basal	109	22	32.1	35.8	43.1	35.8	28.4	25.7
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.32	0.006

Gong Y, Sci Rep 2017

Kennecke H, JCO 2010

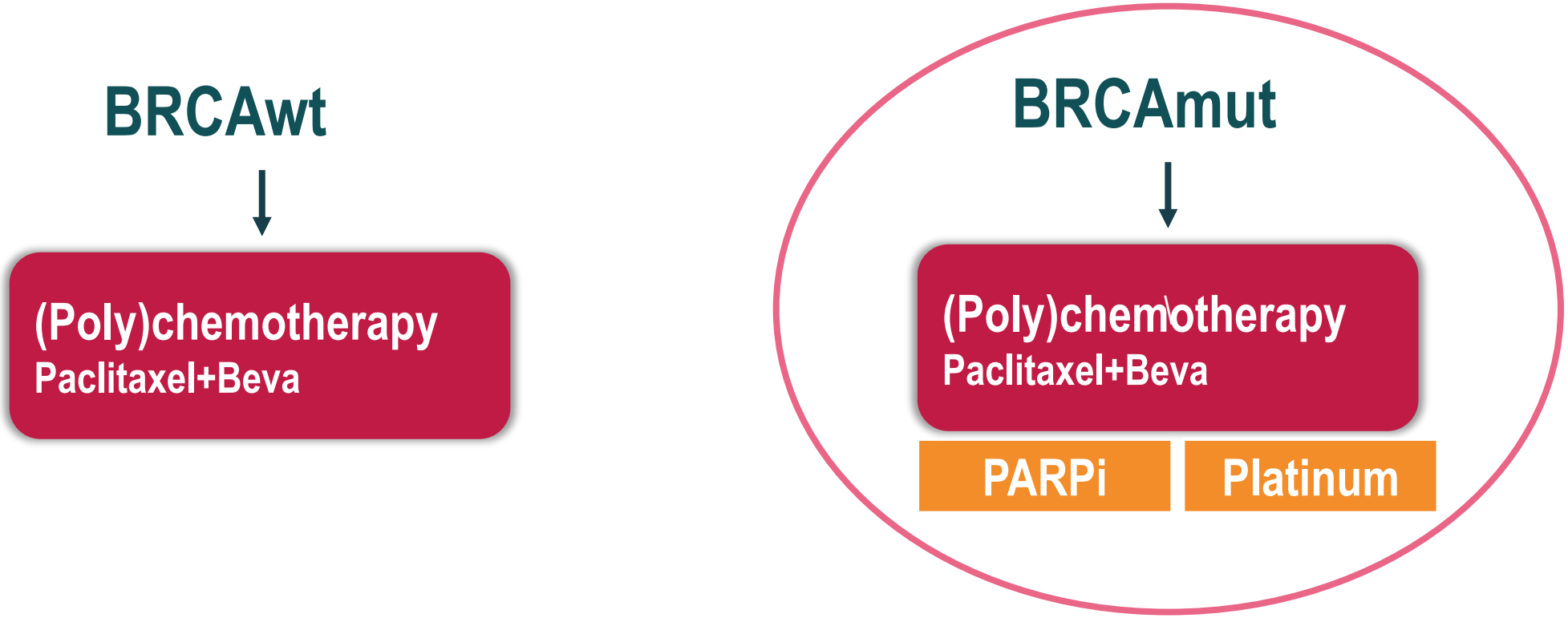
Lines of chemotherapy and duration according to BC subtype





Seah DSE, J Natl Compr Canc Netw 2014

Treatment of metastatic TNBC



Attempt to design a treatment algorithm for mTNBC: key considerations

- Metastatic TNBC pts
  - Most received A-T as adjuvant/neoadjuvant treatment
  - Visceral metastases
  - Poor survival from the onset of MBC
  - Limited options available with limited efficacy

→ Clinical trials!

→ A long-term treatment sequence is not possible (high attrition rate)

→ Best option first

Platinum-containing regimens for metastatic breast cancer (Review)

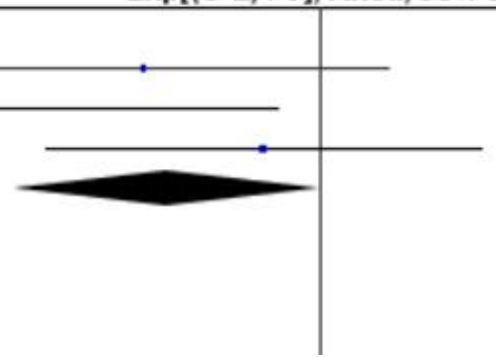
Cochrane Library
Cochrane Database of Systematic Reviews

Egger SJ, Willson ML, Morgan J, Walker HS, Carrick S, Ghersi D, Wilcken N

TNBC: OS

Study or Subgroup	platinum Events	Total	non-platinum Events	Total	O-E	Variance	Weight	HR Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Treatment-comparisons assessing patients with mTNBC								
Carey 2012	64	71	26	31	-6.18	19.08	4.3%	0.72 [0.46, 1.13]
Fan 2012	12	27	21	26	-5.15	5.77	1.3%	0.41 [0.18, 0.93]
Hu 2015	48	118	49	118	-2.49	24.12	5.5%	0.90 [0.61, 1.34]
Subtotal (95% CI)		**216**		**175**			**11.1%**	**0.75 [0.57, 1.00]**
Total events	124		96					

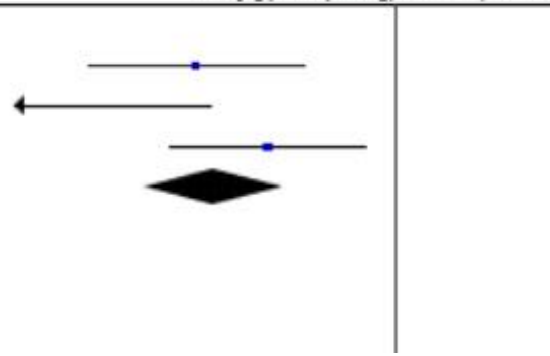
Heterogeneity: Chi² = 2.96, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.97 (P = 0.05)



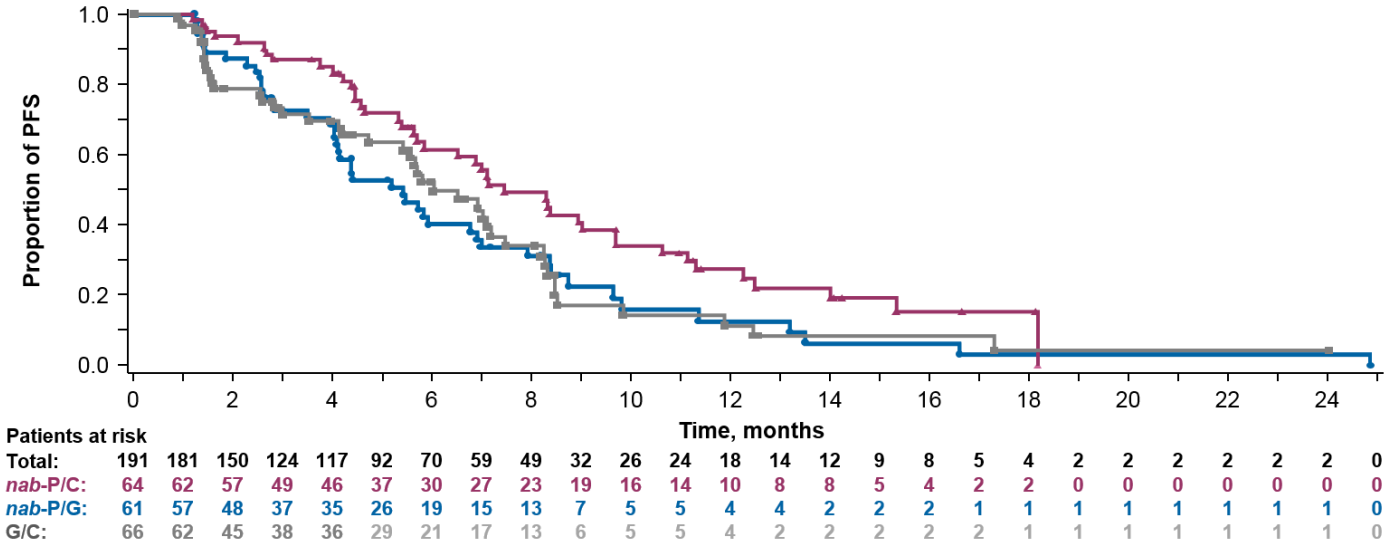
TNBC: PFS

Study or Subgroup	platinum Events	Total	non-platinum Events	Total	O-E	Variance	Weight	HR Exp[(O-E) / V], Fixed, 95% CI
1.2.1 Treatment-comparisons assessing patients with mTNBC								
Carey 2012	57	71	30	31	-22.86	39.79	7.4%	0.56 [0.41, 0.77]
Fan 2012	19	27	26	26	-9.65	7.8	1.5%	0.29 [0.14, 0.59]
Hu 2015	97	118	104	118	-18.08	49.12	9.2%	0.69 [0.52, 0.92]
Subtotal (95% CI)		**216**		**175**			**18.0%**	**0.59 [0.49, 0.72]**
Total events	173		160					

Heterogeneity: Chi² = 5.26, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 5.14 (P < 0.00001)

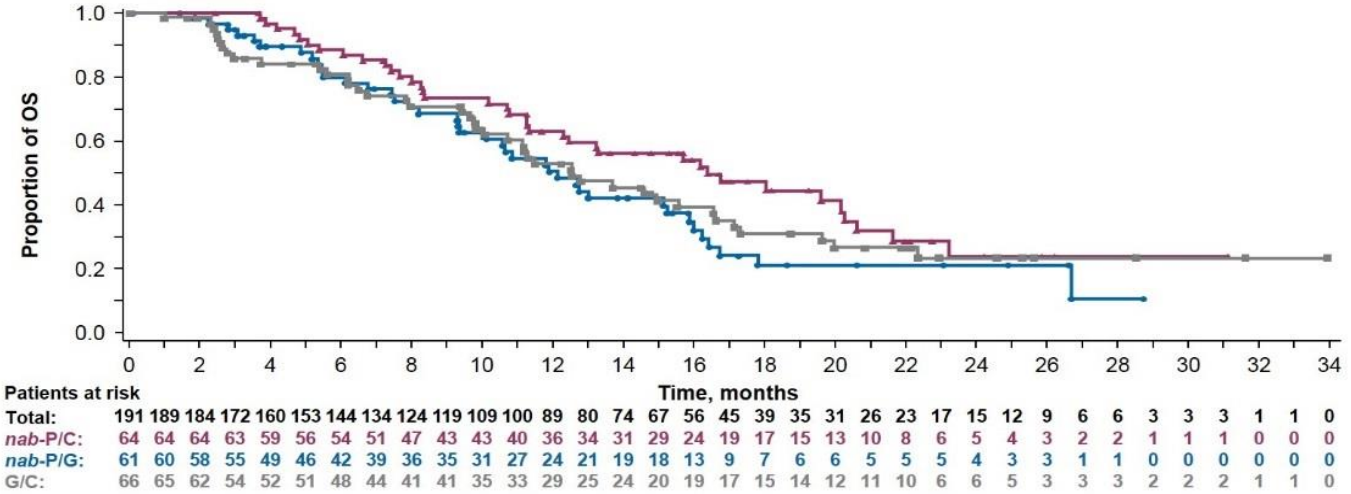


tnAcity Phase II



	nab-P/C	*nab*-P/G	G/C
Median PFS, months	7.4	5.4	6.0
HR (95% CI) *P* value	– –	0.60 (0.39 - 0.93) 0.02[a]	0.61 (0.39 - 0.94) 0.03[a]
12-month PFS rate, %	27	13	11

[a] Compared with *nab*-P/C.



	nab-P/C	*nab*-P/G	G/C
Median OS, months	**16.4**	**12.1**	**12.6**
HR (95% CI) ***P* value**	**–** **–**	**0.66 (0.42 - 1.04)** **0.07[a]**	**0.74 (0.48 - 1.16)** **0.18[a]**

[a] Compared with *nab*-P/C.

Yardley D et al, Poster at SABCS 2016 [abstract 874].

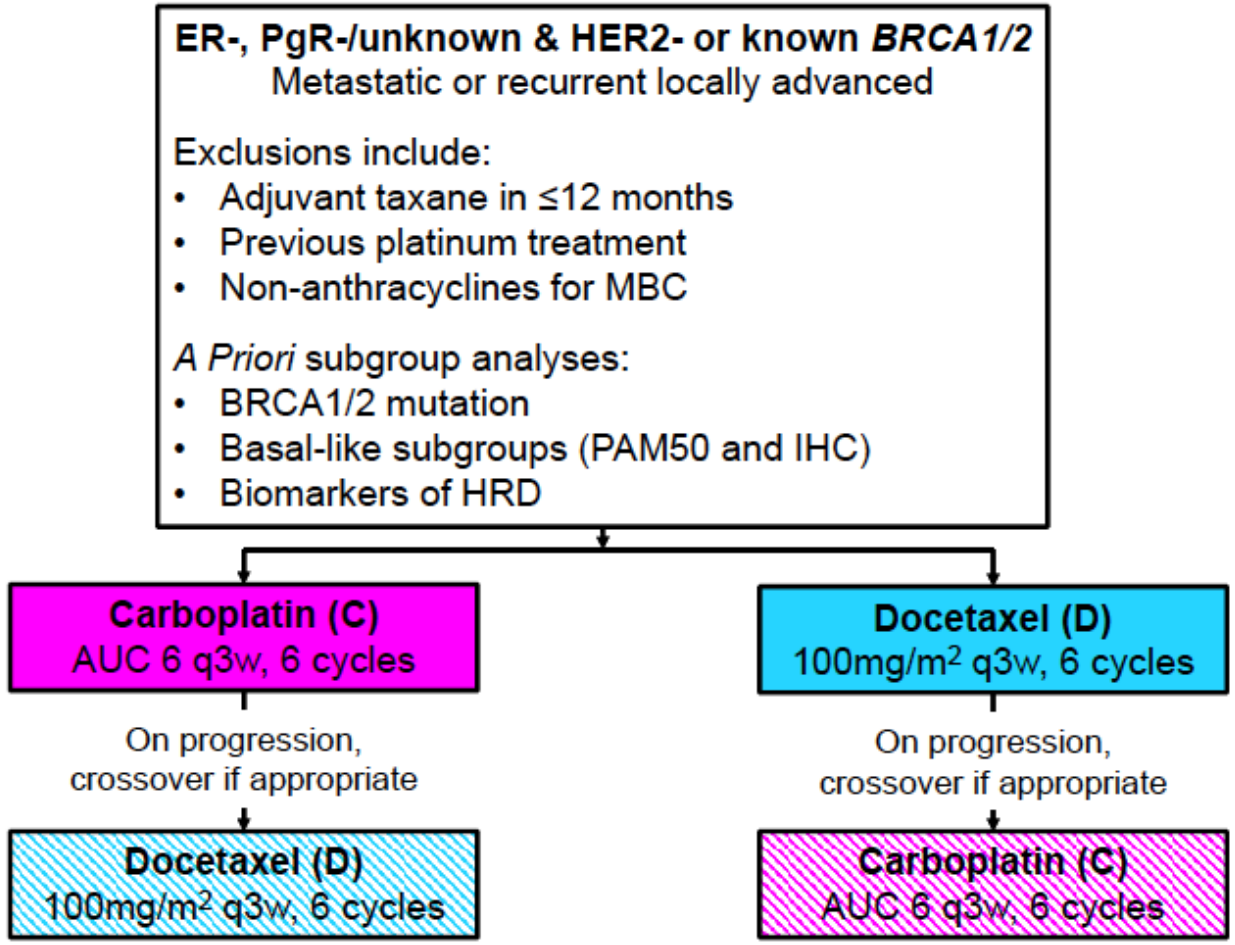
Platinum for gBRCAmut metastatic TNBC

Study	Drug	Setting	ORR		
			All/ Unselected	BRCA wt	BRCA mut
TBCR009[1]	Cisplatin or Carboplatin	1-2 line	26%	20%	54.5%
BALI[2]	Cisplatin	1-2 line	10%	--	--
Byrski[3]	Cisplatin	1-2 line	--	--	80%

1. Isakoff SJ, J Clin Oncol 2015; 2. Baselga J et al, J Clin Oncol 2013; 3. Byrski T et al, Breast Cancer Res 2012

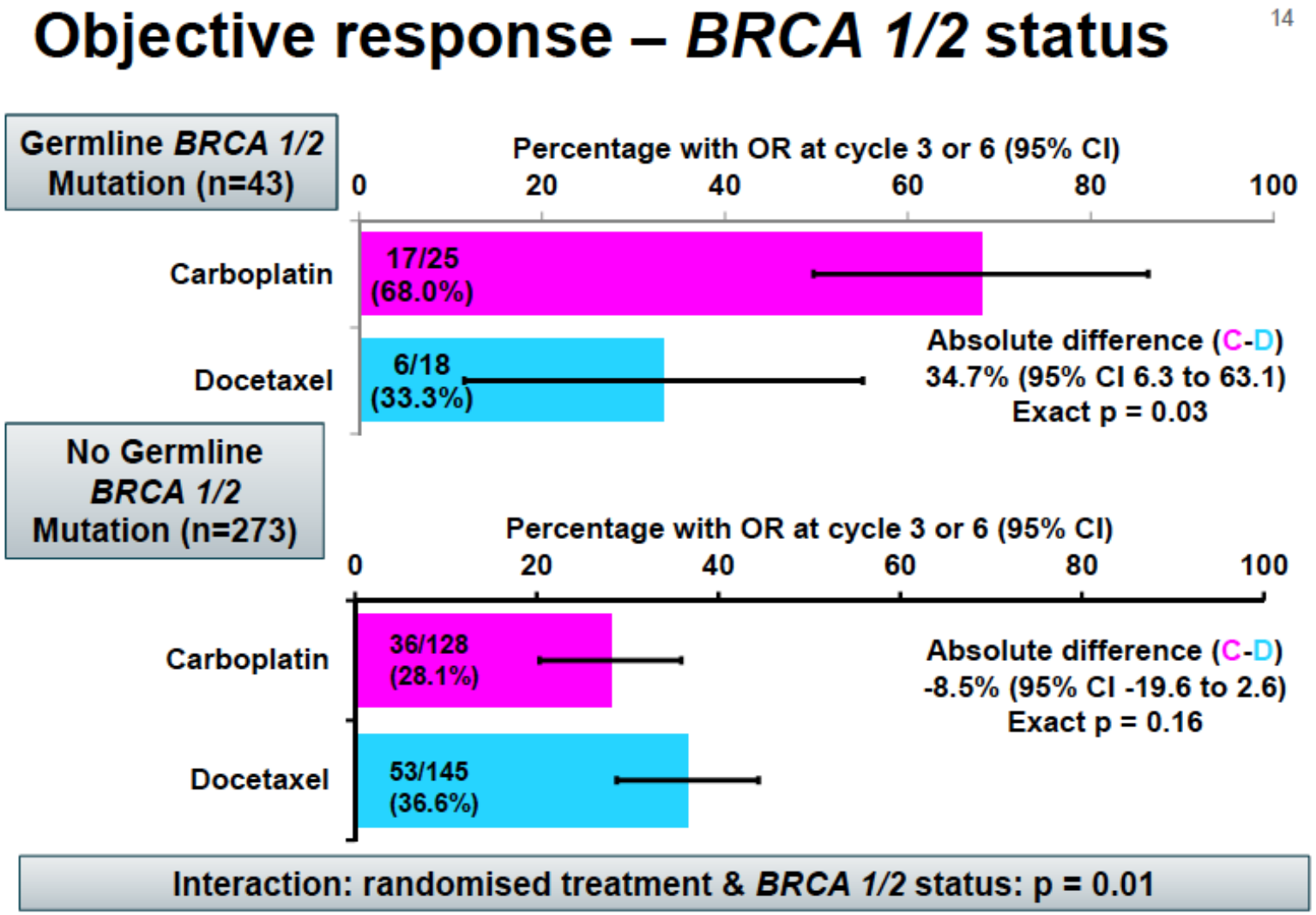
TNT phase III trial for TN metastatic BC

Trial design



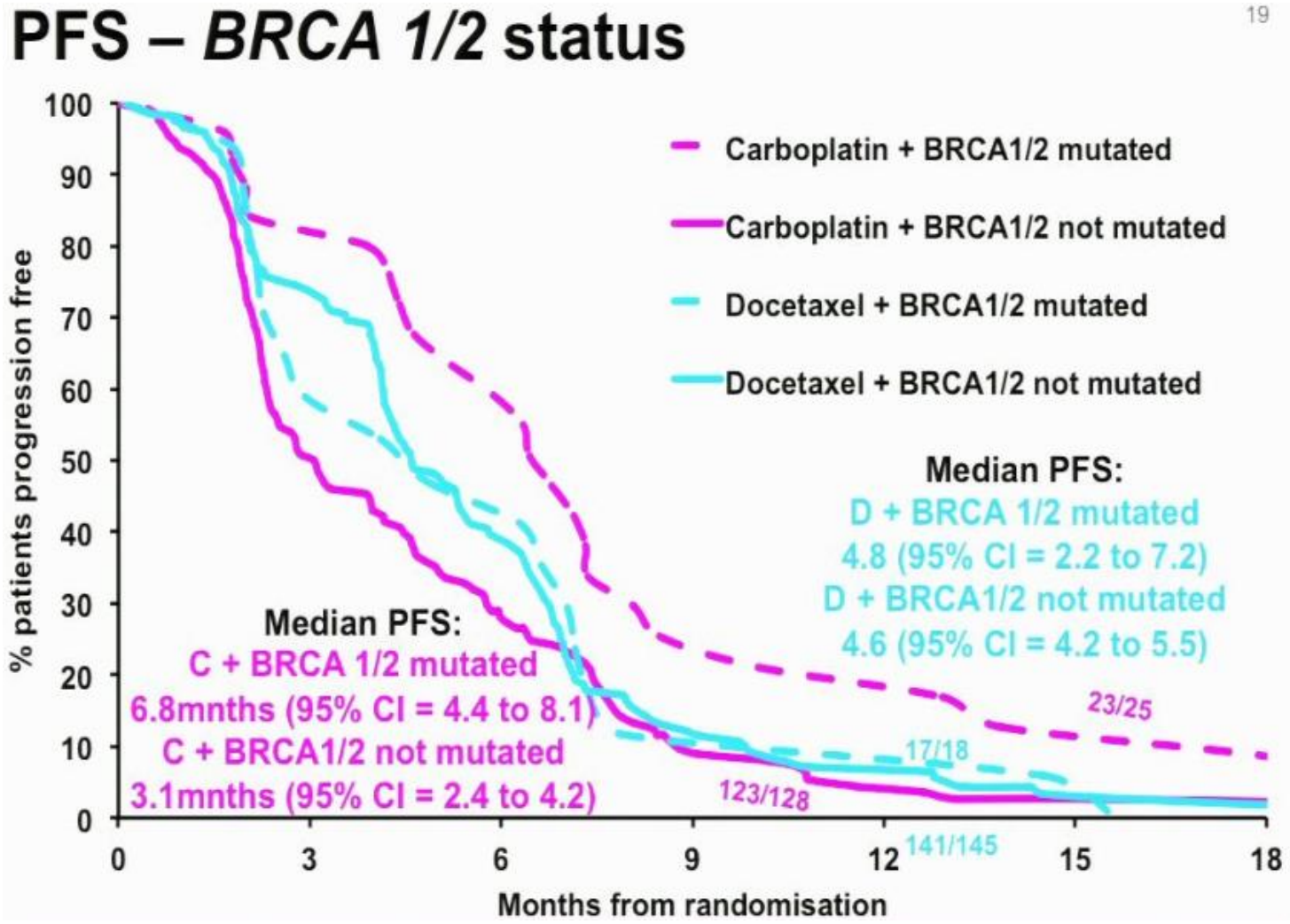
Tutt A et al, SABCS 2014

TNT phase III trial for TN metastatic BC



Tutt A et al, SABCS 2014

TNT phase III trial for TN metastatic BC



Tutt A et al, SABCS 2014

Attempt to design a treatment algorithm for gBRCAmut mTNBC: 1st line

- Based on available data it is reasonable to consider platinum-containing regimens as a valid option as 1st line treatment for BRCAmut mTNBC

- Is there any possible role for Olaparib in 1st line?
  - OlympiAD: mostly pre-treated with CT for MBC
  - Carboplatin inclusion in CT regimens for early disease will likely increase
  - No head to head comparison Olaparib vs Carboplatin

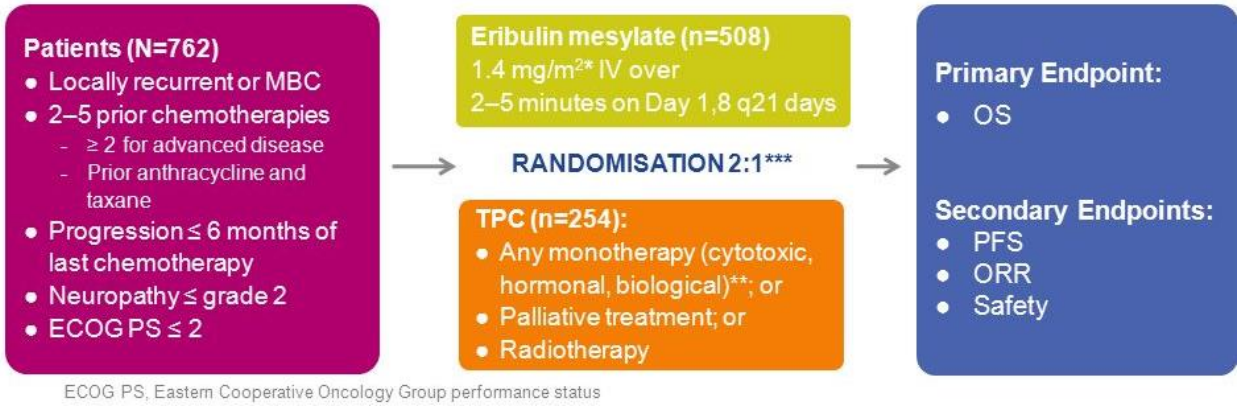
	Olympiad	TNT
ORR	55% (n=102)	68% (n=25)
PFS	6-7 mo	6.8 mo

Attempt to design a treatment algorithm for gBRCAmut mTNBC: 2nd line and further

- Unknown efficacy of Olaparib in pts progressing on previous platinum for MBC
- Eribulin prolongs OS over capecitabine or TPC in pretreated MBC patients, markedly in TNBC…

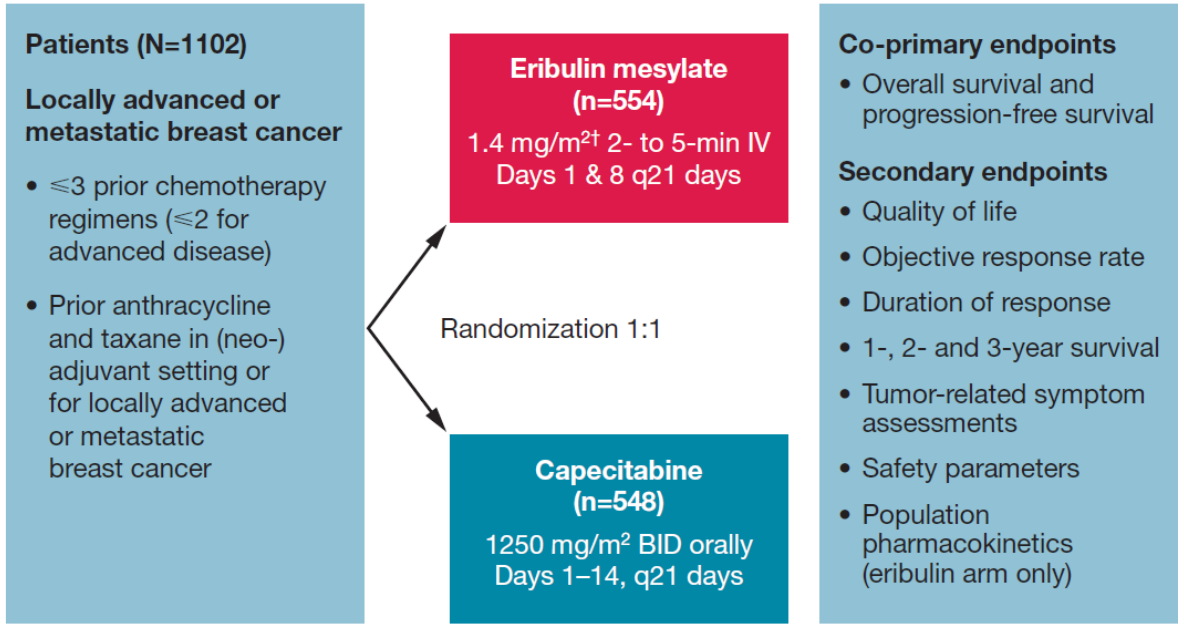
Eribulin in advanced breast cancer patients

EMBRACE



ECOG PS, Eastern Cooperative Oncology Group performance status

301 STUDY



†Equivalent to 1.23 mg/m² eribulin (expressed as free base)
BID, twice daily; IV, intravenous

Cortes J, Lancet 2011

Kaufman PA, J Clin Oncol 2015

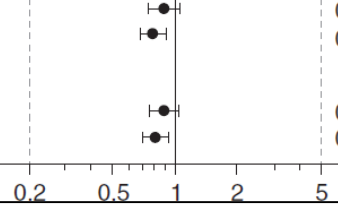
Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy

X. Pivot[1*], F. Marmé[2], R. Koenigsberg[3,4], M. Guo[5], E. Berrak[6] & A. Wolfer[7]

[1]Department of Oncology, Centre Hospitalier Universitaire de Besançon, Service d'Oncologie Médicale, Besançon cedex, France; [2]National Centre for Tumour Diseases, Heidelberg, Department of Gynecologic Oncology, University Hospital, Heidelberg, Germany; [3]3rd Medical Department—Centre for Oncology and Haematology, Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna)—LB Cluster Translational Oncology, Kaiser Franz Josef-Spital, Vienna; [4]3. Med. Abt.—Zentrum für Onkologie und Hämatologie, Ludwig Boltzmann Institut für angewandte Krebsforschung (LBI-ACR VIEnna), Kaiser Franz Josef-Spital, Wien, Austria; [5]Departments of Biostatistics, Oncology PCU; [6]Oncology, Eisai Inc., Woodcliff Lake, USA; [7]Department of Medical Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

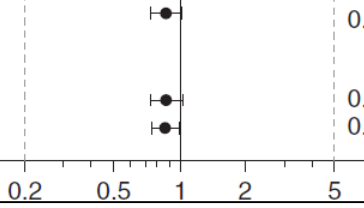
OS

Subgroup	Events/*n* – Eribulin	Events/*n* – Comparator	Median (months) – HR (95% CI) Eribulin/Comp	*P* value
Overall	844/946	621/698	0.85 (0.76, 0.94) 15.0/12.6	0.002
HER2 status				
Positive	136/150	97/104	0.75 (0.57, 1.00) 13.5/11.7	0.051
Negative	590/663	442/497	0.84 (0.74, 0.96) 15.1/12.0	0.008
Unknown	118/133	82/97	0.98 (0.73, 1.32) 16.5/16.9	0.894
ER status				
Positive	484/544	348/401	0.87 (0.75, 1.00) 15.7/13.5	0.058
Negative	285/319	225/237	0.72 (0.59, 0.86) 12.9/9.4	<0.001
Unknown	75/83	48/60	1.05 (0.70, 1.57) 17.1/20.4	0.816
Triple negative				
Yes	179/199	144/153	0.72 (0.57, 0.90) 12.4/8.1	0.005
No	665/747	477/545	0.86 (0.76, 0.97) 15.7/14.0	0.017
Site of disease				
Visceral disease	713/782	540/608	0.87 (0.78, 0.98) 14.3/12.0	0.025
Nonvisceral disease[b]	122/153	75/84	0.78 (0.57, 1.07) 18.6/16.2	0.128
Number of organs involved				
≤2	406/471	276/324	0.89 (0.76, 1.05) 16.2/15.5	0.168
>2	438/475	345/374	0.79 (0.68, 0.91) 13.1/10.4	0.002
HER2 negative and ER positive				
Yes	384/433	270/314	0.89 (0.75, 1.04) 15.7/14.3	0.152
No	460/513	351/384	0.80 (0.69, 0.92) 14.3/11.2	0.002



PFS

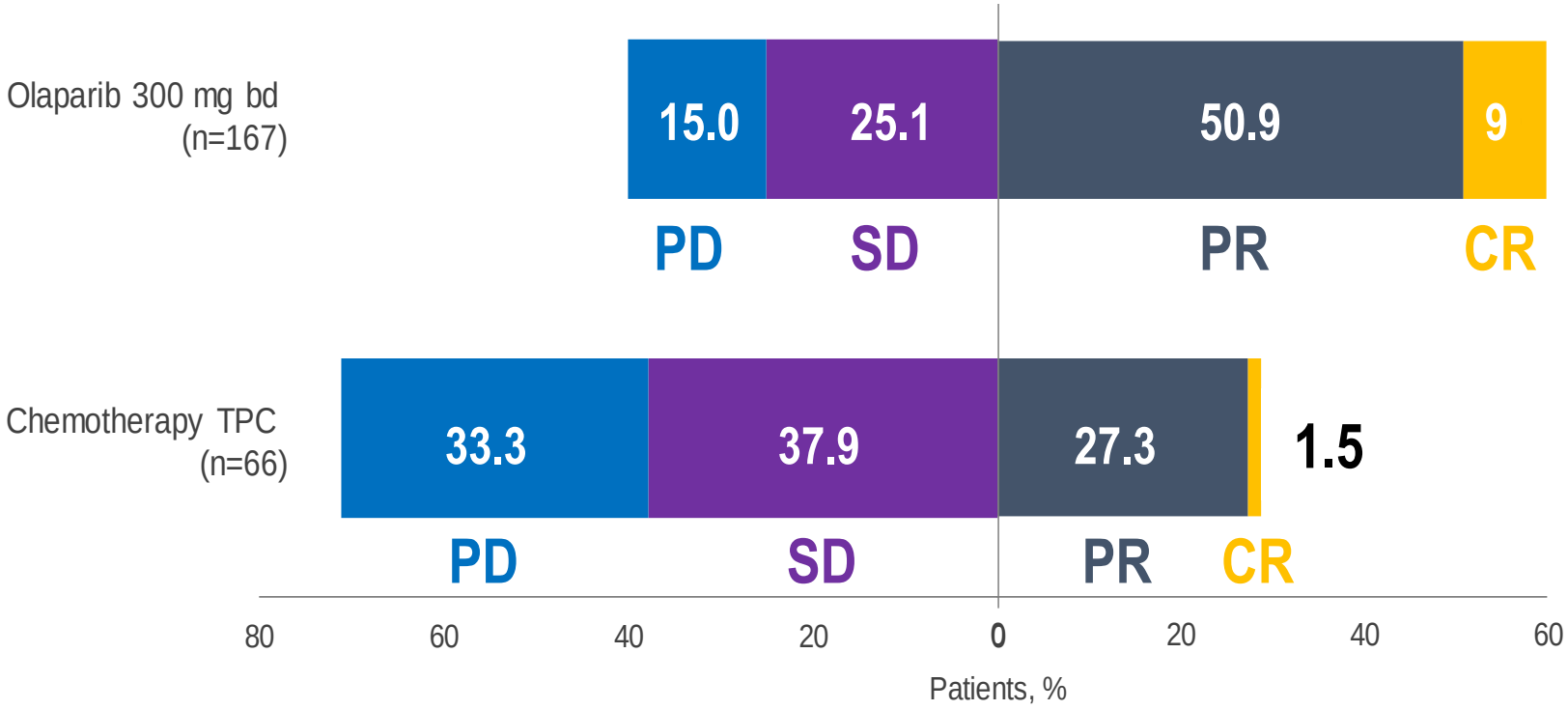
Subgroup	Events/*n* – Eribulin	Events/*n* – Comparator	Median (months) – HR (95% CI)	Eribulin/Comp	*P* value
Overall	826/946	592/698	0.87 (0.78, 0.97)	3.9/3.2	0.017
HER2 status					
Positive	131/150	86/104	1.00 (0.75, 1.35)	3.7/4.2	0.970
Negative	579/663	425/497	0.83 (0.73, 0.95)	3.7/2.9	0.007
ER status					
Positive[b]	467/544	322/401	0.84 (0.72, 0.98)	4.1/3.4	0.031
Negative	285/319	218/237	0.83 (0.68, 1.00)	3.2/2.8	0.061
Triple negative					
Yes	177/199	141/153	0.77 (0.60, 0.97)	2.8/2.5	0.028
No	649/747	451/545	0.90 (0.79, 1.02)	4.1/3.7	0.100
Site of disease					
Visceral disease	697/782	519/608	0.92 (0.81, 1.04)	3.7/3.1	0.176
Nonvisceral disease	121/153	68/84	0.68 (0.48, 0.95)	4.4/3.4	0.022
Number of organs involved					
≤2	400/471	273/324	0.87 (0.74, 1.03)	4.2/4.0	0.116
>2	426/475	319/374	0.86 (0.74, 1.01)	3.6/2.8	0.072
HER2 negative and ER positive					
Yes	375/433	258/314	0.87 (0.73, 1.03)	4.1/3.4	0.106
No	451/513	334/384	0.86 (0.74, 1.00)	3.7/3.0	0.045



Attempt to design a treatment algorithm for gBRCAmut mTNBC: 2nd line and further

- Unknown efficacy of Olaparib in pts progressing on previous platinum for MBC
- Eribulin prolongs OS vs capecitabine or TPC in pretreated MBC patients, markedly in TNBC …but PFS ~3 months and no specific data for gBRCAmut
- Olaparib prolongs PFS vs TPC including eribulin for gBRCAmut mTNBC, but no OS impact (immature data)
- Other critical endpoints for MBC: ORR, safety, HRQoL

OLYMPIAD: FURTHER EFFICACY OUTCOMES

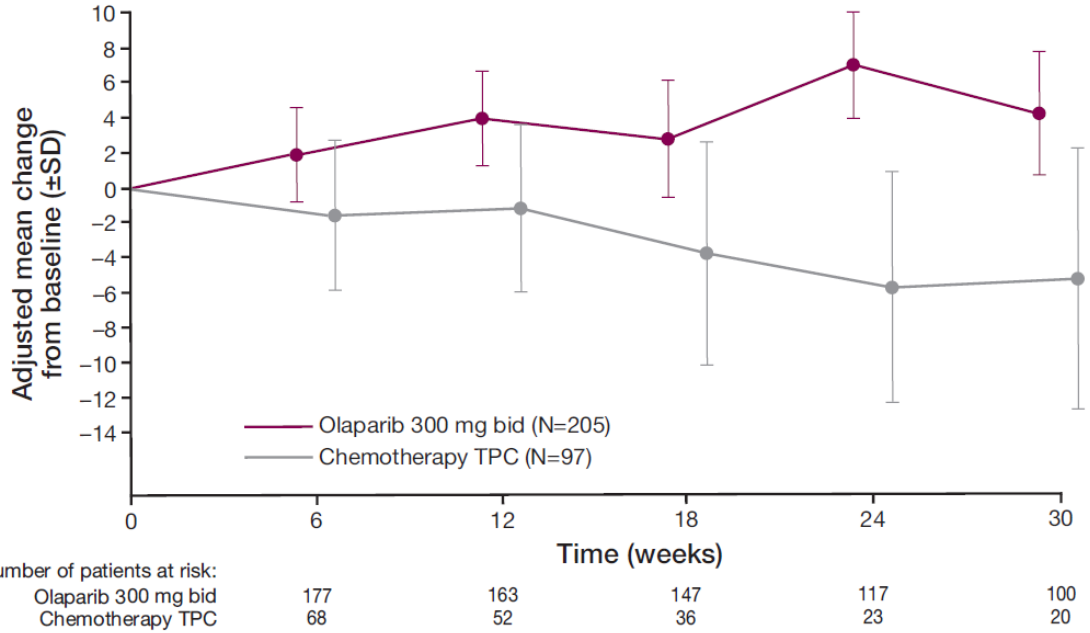


Median response onset
- Olaparib: 47 days
- TPC: 45 days

Median DOR
- Olaparib: 6.2 (4.6-7.2)
- TPC: 7.1 (2.8-12.2)

#243PD, Delaloge S, ESMO 2017

HRQoL in the OlympiAD trial



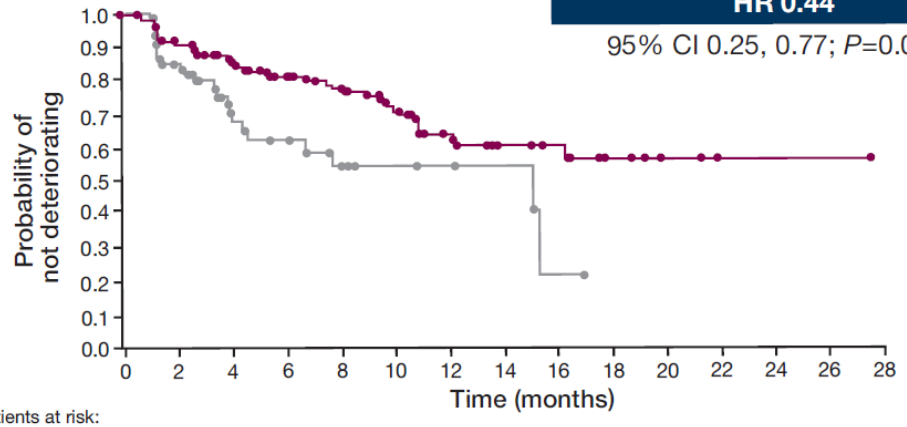
Number of patients at risk:

Olaparib 300 mg bid	177	163	147	117	100
Chemotherapy TPC	68	52	36	23	20

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

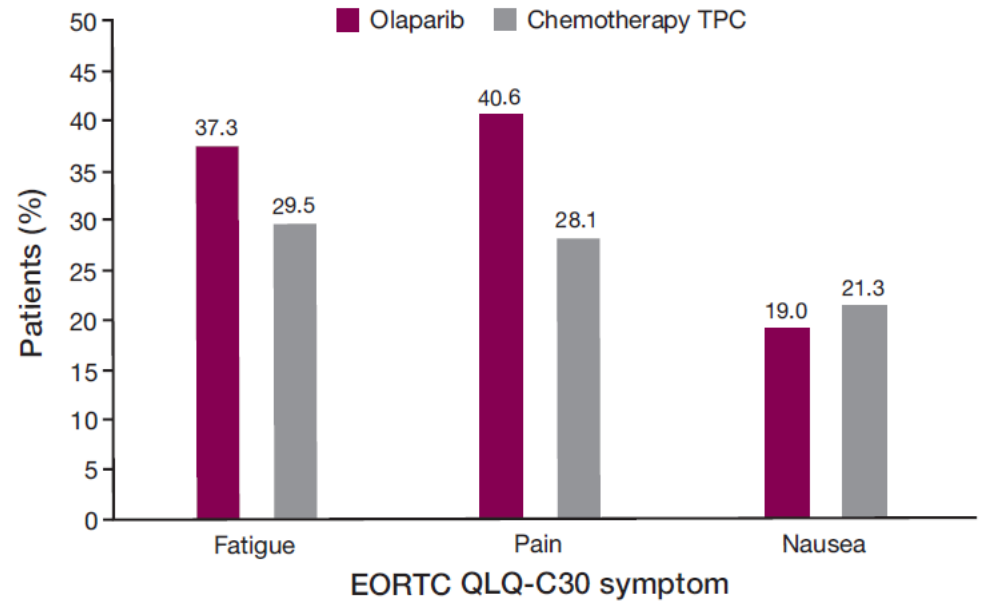
HR 0.44

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



Number of patients at risk:

Olaparib 300 mg bid	201	164	134	93	77	56	40	20	15	7	4	2	1	1	0
Chemotherapy TPC	93	54	30	19	13	8	7	4	1	0	0	0	0	0	0



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

Olaparib in the treatment algorithm for gBRCAmut HR+/HER2- MBC

- Crowded scenario dominated in first lines by endocrine Tx

- OlympiAD suggests more limited benefit of Olaparib vs TPC in HR+ disease

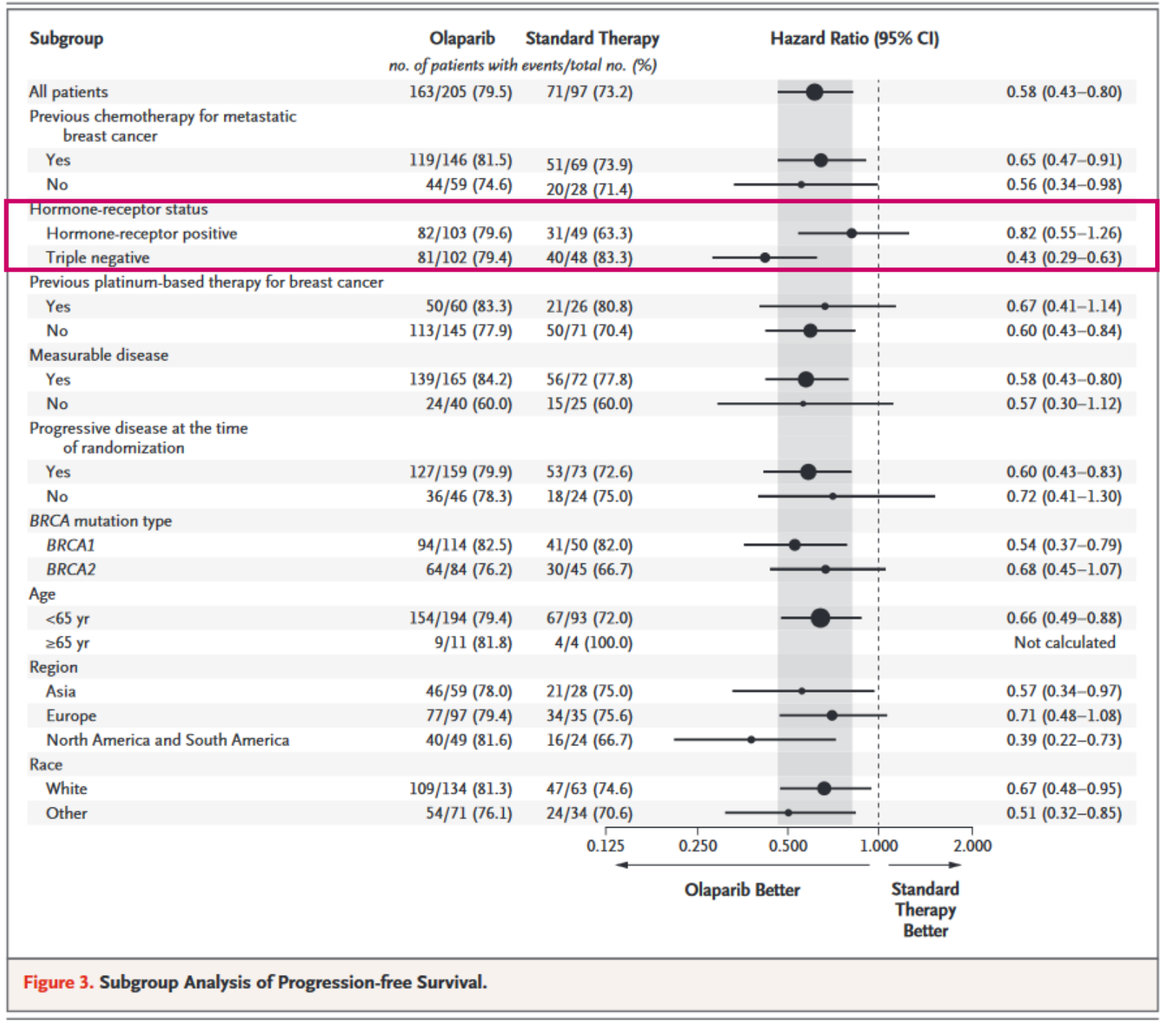


Figure 3. Subgroup Analysis of Progression-free Survival.

Robson M, NEJM 2017

EMBRACA trial: Talazoparib *vs* TPC in MBC with gBRCAmut

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

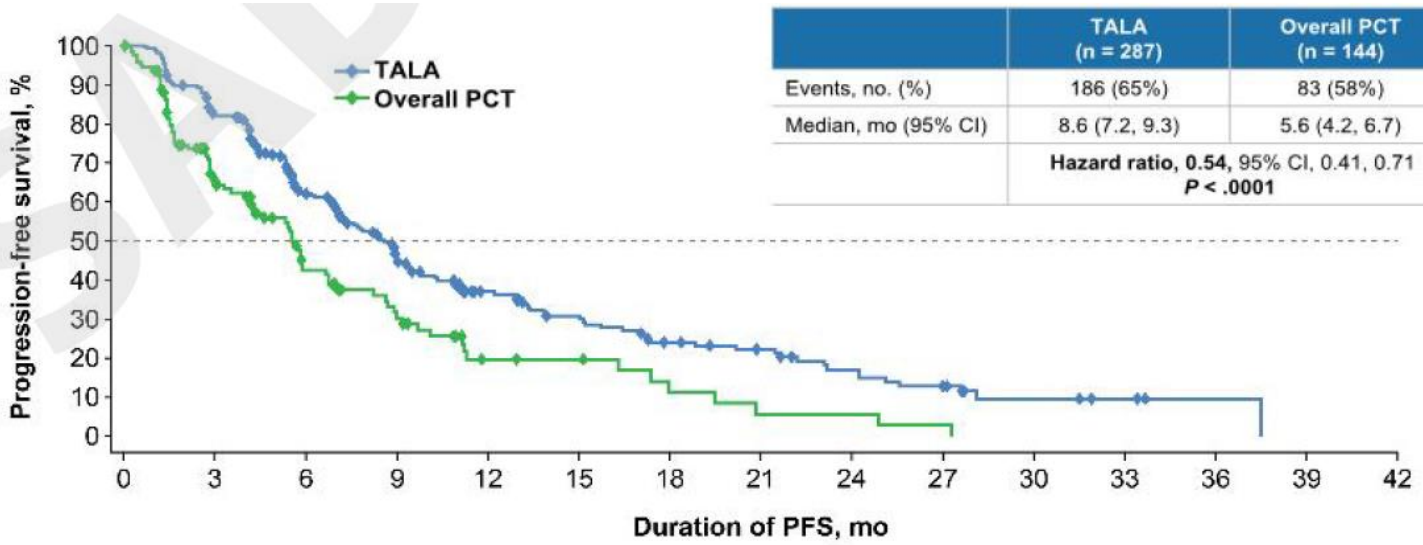
Stratification factors:
- Number of prior CT regimens (0 or ≥1)
- TNBC or HR+
- History of CNS mets or no CNS mets

R 2:1

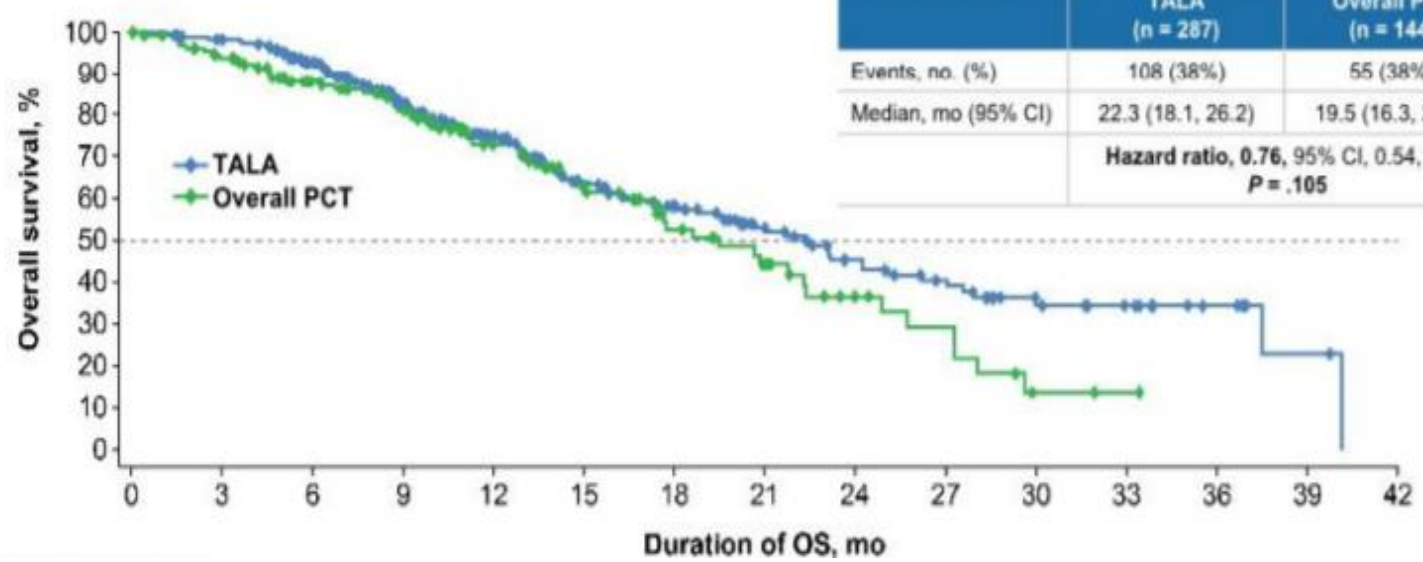
Talazoparib
1 mg PO daily

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

Physician's choice of therapy (PCT): capecitabine, eribulin, gemcitabine or vinorelbine



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

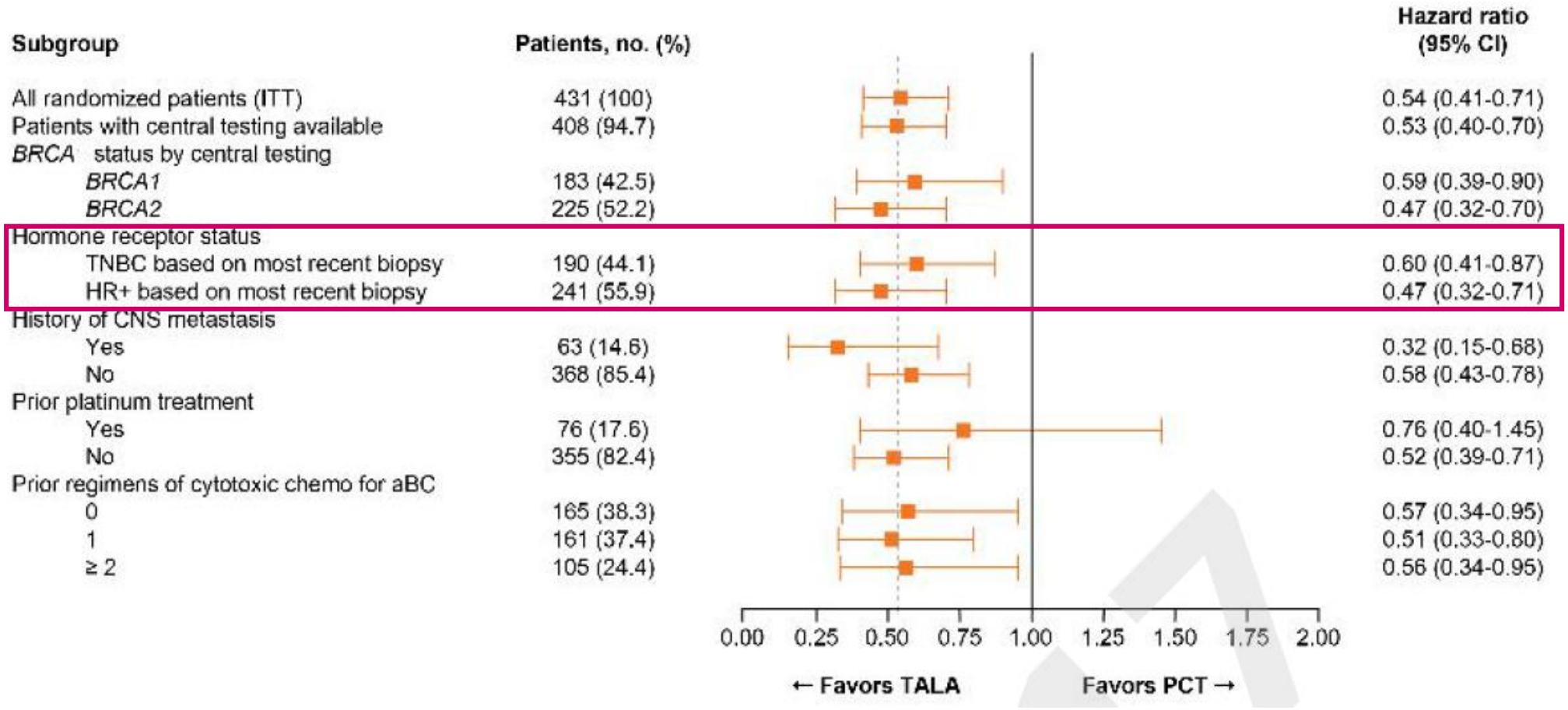


	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	108 (38%)	55 (38%)
Median, mo (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
	Hazard ratio, 0.76, 95% CI, 0.54, 1.06 ***P* = .105**	

Litton J, SABCS 2017

EMBRACA trial: Talazoparib *vs* TPC in MBC with gBRCAmut

Subgroup analysis for PFS



Litton J, SABCS 2017

Olaparib in the treatment algorithm for gBRCAmut HR+/HER2- MBC

- Crowded scenario dominated in first lines by endocrine Tx
- OlympiAD suggests more limited benefit of Olaparib vs TPC in HR+ disease
- OlympiAD shows better HRQoL with olaparib but TPC alltogether (vs capecitabine?)
- Disease course is longer than TNBC: a sequence strategy that includes olaparib among the options at some point as an additional line of therapy is feasible

Olaparib for gBRCAmut HER2- MBC

- Efficacy of PARPinh for BRCA mut BC demonstrated for the first time in a phase III trial (PFS benefit, OS immature)
- New drug with efficacy demonstrated in a genomic-defined subset of patients
- Especially attractive for TNBC, with limited options
- Comparison with platinum salts and efficacy in platinum refractory/resistant patients needs to be further assessed
- Correct positioning: maintenance, earlier lines (incl. delay of CT in HR+)

LUCY (expanded access) – Study Design

NCT 03286842

AstraZeneca

Multi-Center, Single Arm, Interventional Study

HER2-ve mBC
- Previous A and/orT (adj or mBC)
- ≤1 prior CT for mBC
- HR+: ≥ 1 prior ET (adj or mBC)

gBRCA Test

+ve

gBRCAm

N=250

Olaparib 300mg BD

Clinical outcomes:
- PFS (physician defined)
- OS
- Safety

Physician defined Progression

-ve

Wild Type

Not included in outcomes analysis

Target Accrual N=250

Completion date: April 29, 2020

Adapting genetic counselling to the new paradigm

- Until yesterday, the focus of *BRCA* testing was generally on risk assessment and the potential for preventive interventions

- Today, Ovarian and Breast cancer patients have different therapeutic priorities from genetic testing

- Some women will be adversely affected discussing the implication of BRCA testing at the time of cancer diagnosis. However, not having BRCA status takes away choice

- Need to rethink modalities of access to the test for patients with therapeutic priority