Development of PARP Inhibitors as a new treatment option for Advanced Breast Cancer (ABC)

Karen A Gelmon
Professor of Medicine
University of British Columbia
Medical Oncologist
BC Cancer Agency

COI

- Boards
  - Susan G Komen Scientific Advisory Board
  - Breast International Group Executive Board
- Pharmaceutical Company Associations
  - Advisory Boards – AstraZeneca, Roche, Novartis, Pfizer, Oncotheryon, Nanostring, Merck
  - Research Funding – Pfizer, AstraZeneca, Novartis, BMS

Poly(ADP-ribose) polymerase (PARP)

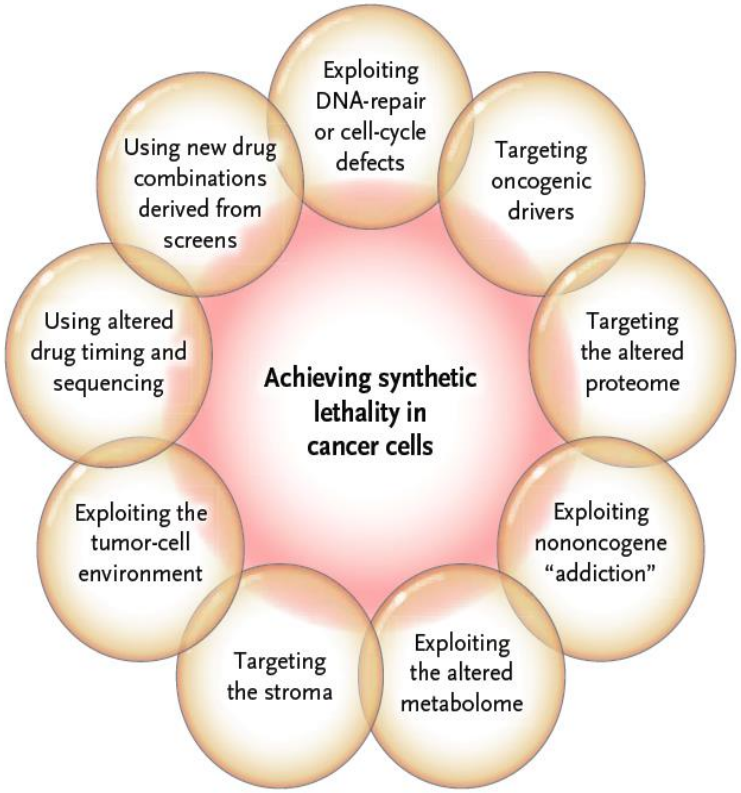
Family of 18 members. PARP1 and 2 are involved in cellular response to single-strand DNA breaks (SSB)

Inhibition of PARP results in catalytic enzyme effect, “trapping” of protein on DNA, inhibition of replication fork progression and increased dsDNA breaks

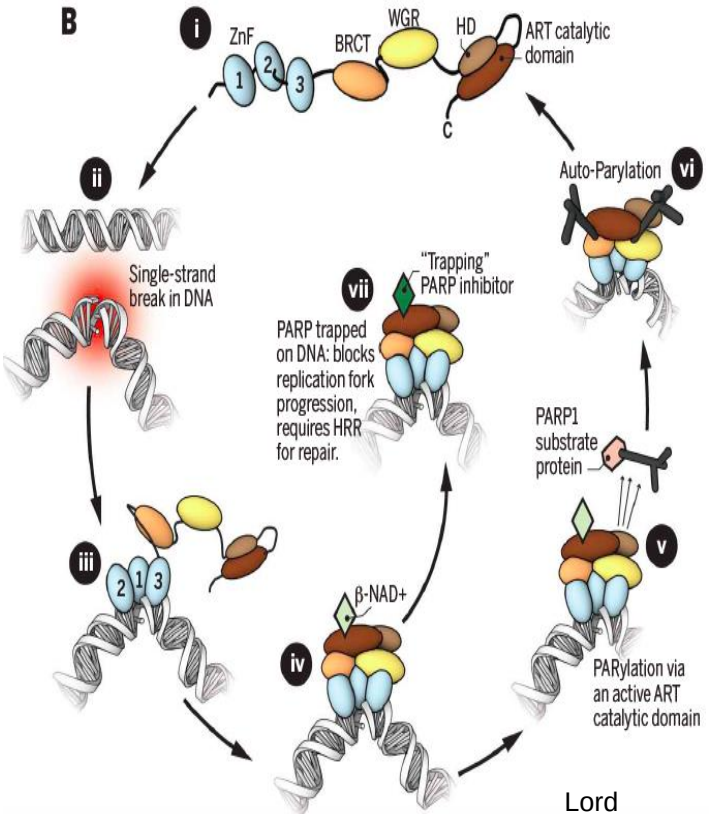
Resolution of lesions caused by PARP inhibition dependent on functioning homologous recombination

BRCA1 and *BRCA2* are components of homologous recombination pathway Cells lacking *BRCA1/2* are sensitive to PARP inhibition (“synthetic lethality”) *in vitro*

Synthetic Lethality



McLornan
NEJM 2014



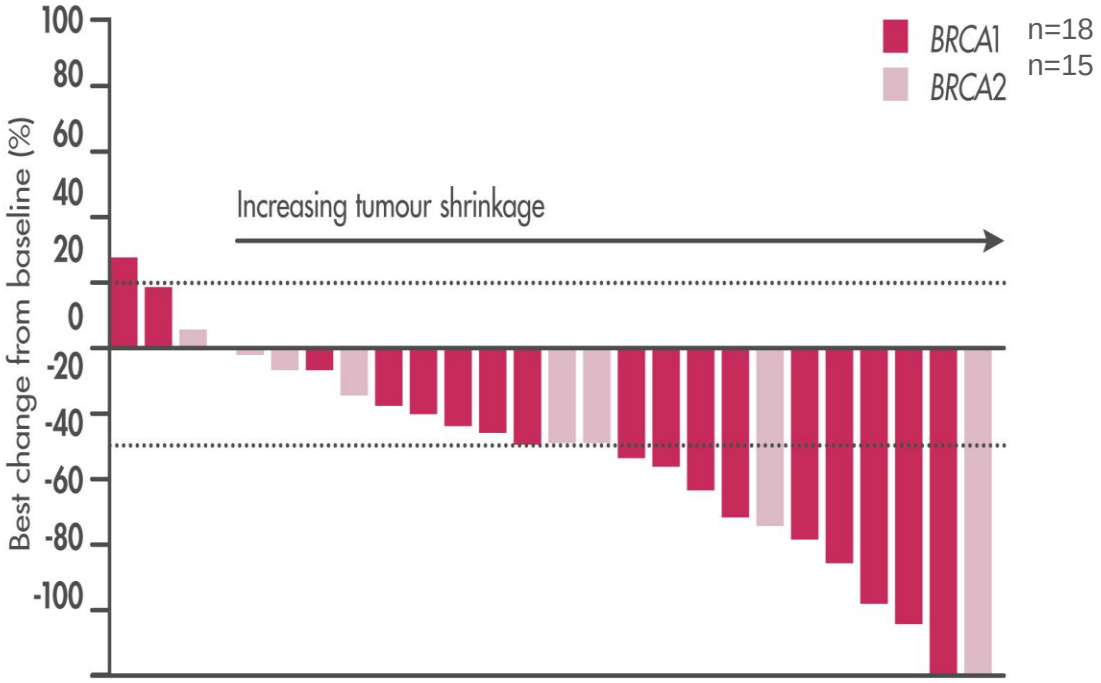
Lord
Science 2017

Clinical PARP inhibitors can be ranked by their ability to trap PARP (from the most to the least potent):

talazoparib >> niraparib > olaparib = rucaparib >> veliparib

Phase II study of Olaparib in g*BRCA* mutated breast cancer

- Rationale:
  - *BRCA1* loss = loss of *BRCA1*-dependent DNA damage repair
  - Become dependent on repair via PARP-dependent mechanisms
  - Proof of principle - Olaparib activity in *BRCA1/2+*

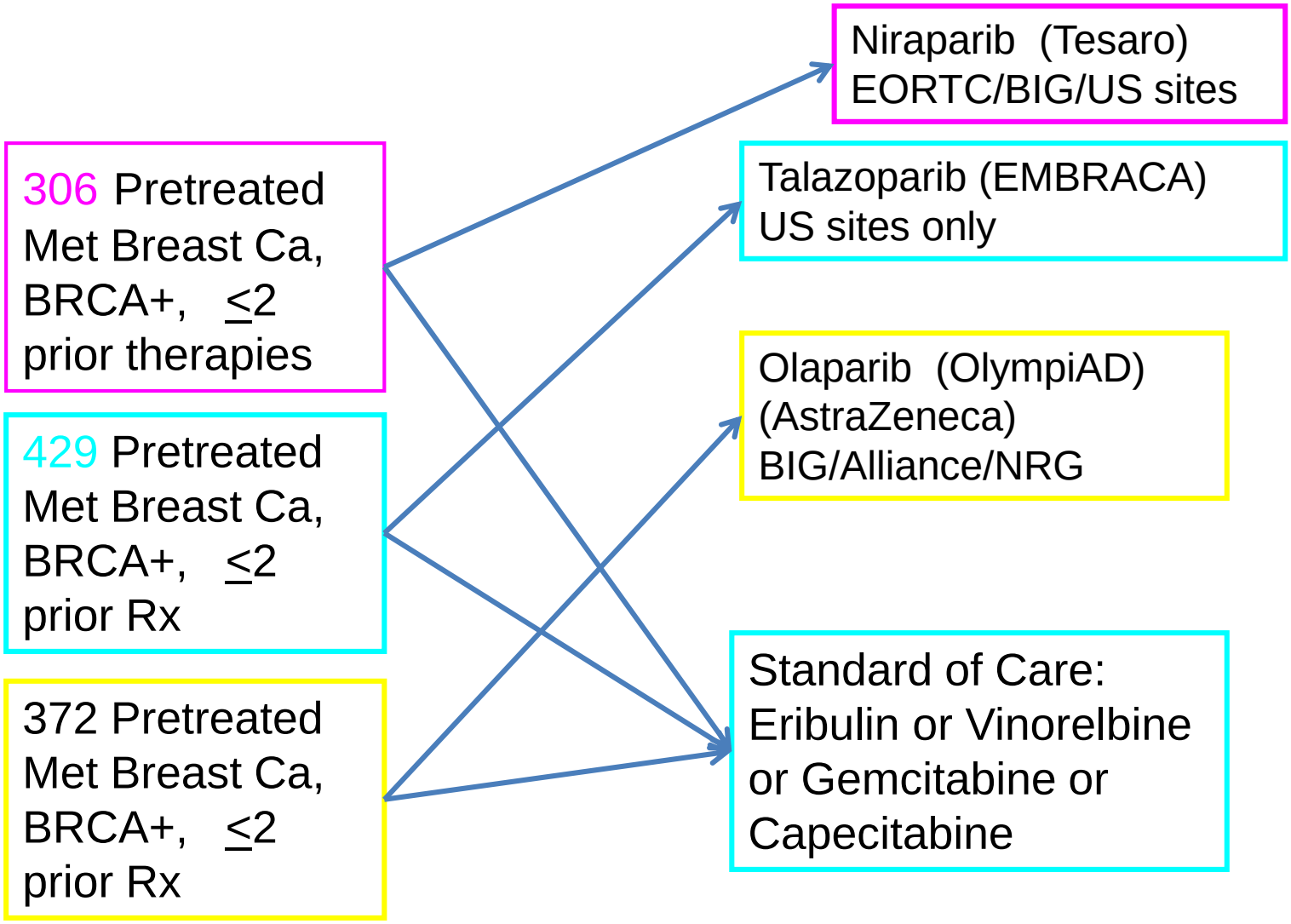


Tutt et al, Lancet 2010

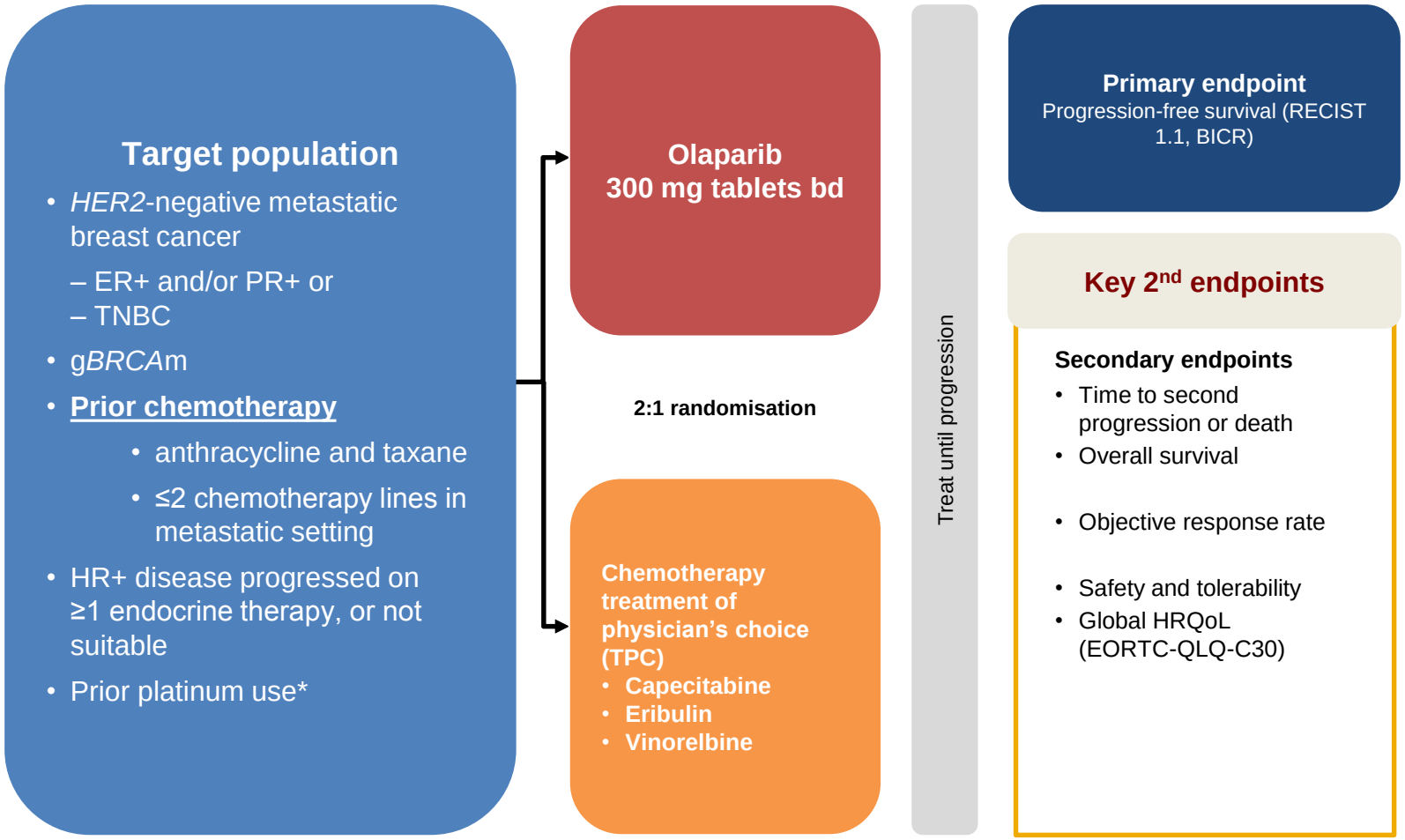
- Confirmed germline *BRCA1* or *BRCA 2* mutation[1]
- Pretreated with at least one chemotherapy regimen[1]
- Olaparib 400 mg bd[1]
- Objective response rate: 41%[1]

1. Tutt A et al, Lancet 2010; 376(9737): 235–244.

Registration Trials in Metastatic BRCA-Associated Breast Cancer



OlympiAD study design:



BICR, blinded independent central review; ER, oestrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criterial in solid tumours; TNBC, triple negative breast cancer
*No evidence of progression during treatment in the advanced setting or ≥12 months since (neo)adjuvant treatment

1. https://clinicaltrials.gov/ct2/show/NCT02000622

Patient characteristics:

	Olaparib (N=205)	Chemotherapy TPC (N=97)
Age, years (median, range)	44 (22–76)	45 (24–68)
Male, n (%)	5 (2)	2 (2)
White race, n (%)	134 (65)	63 (65)
BRCA mutation status, n (%) *BRCA1* *BRCA2* Both	 117 (57) 84 (41) 4 (2)	 51 (53) 46 (47) 0
Hormonal receptor status, n (%) ER and/or PgR positive TNBC	 103 (50) 102 (50)	 49 (51) 48 (49)
Prior chemotherapy for metastasis, n (%)	146 (71)	69 (71)
Prior platinum treatment, n (%)	60 (29)	26 (27)

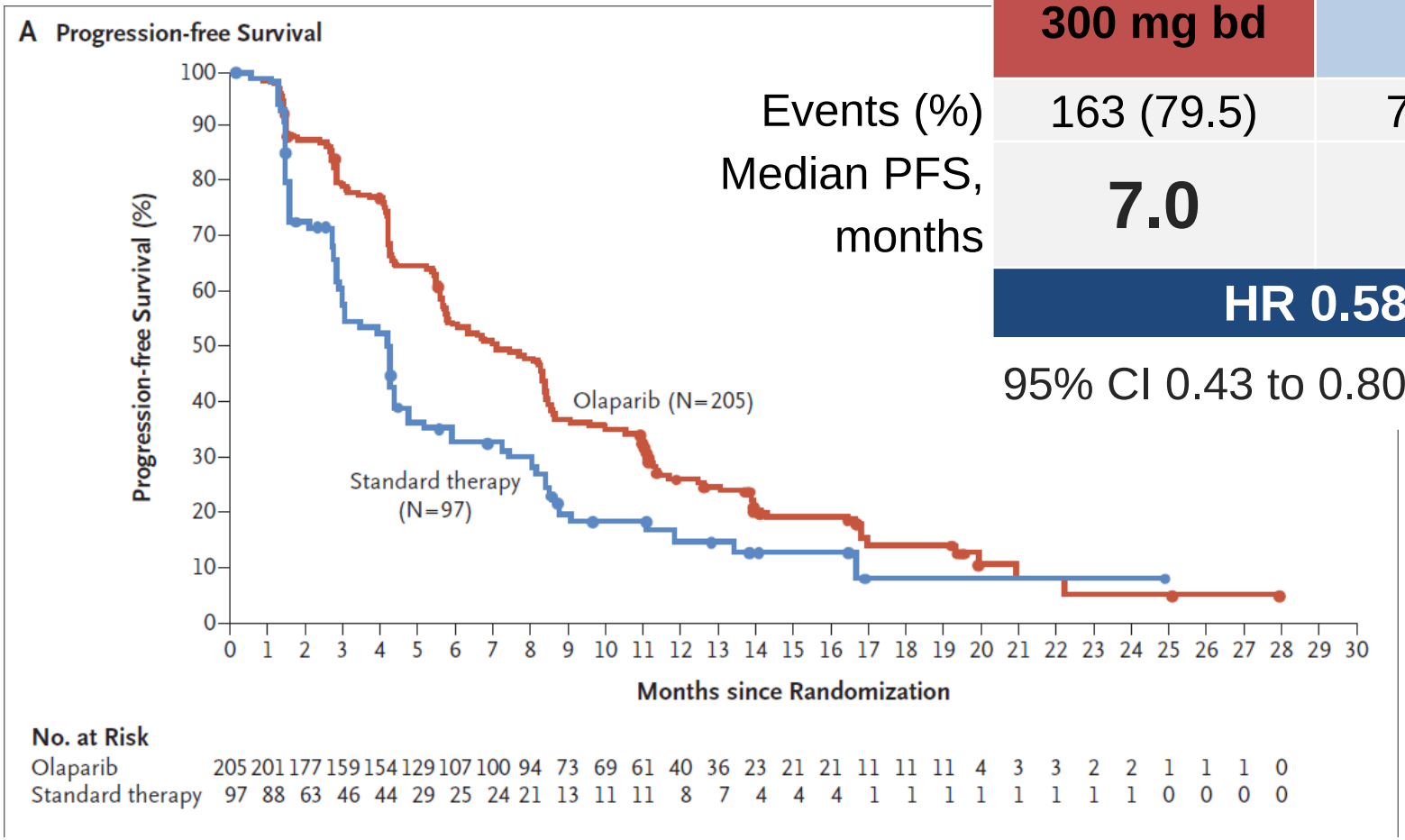
1. Robson M et al. N Engl J Med. 2017; 377(6): 523–533.

Olaparib versus physicians' choice: the phase III OLYMPIAD study

Primary end point: centrally-evaluated PFS

	Olaparib 300 mg bd	Chemotherapy TPC
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	**7.0**	**4.2**
HR 0.58		

95% CI 0.43 to 0.80; *P*=0.0009

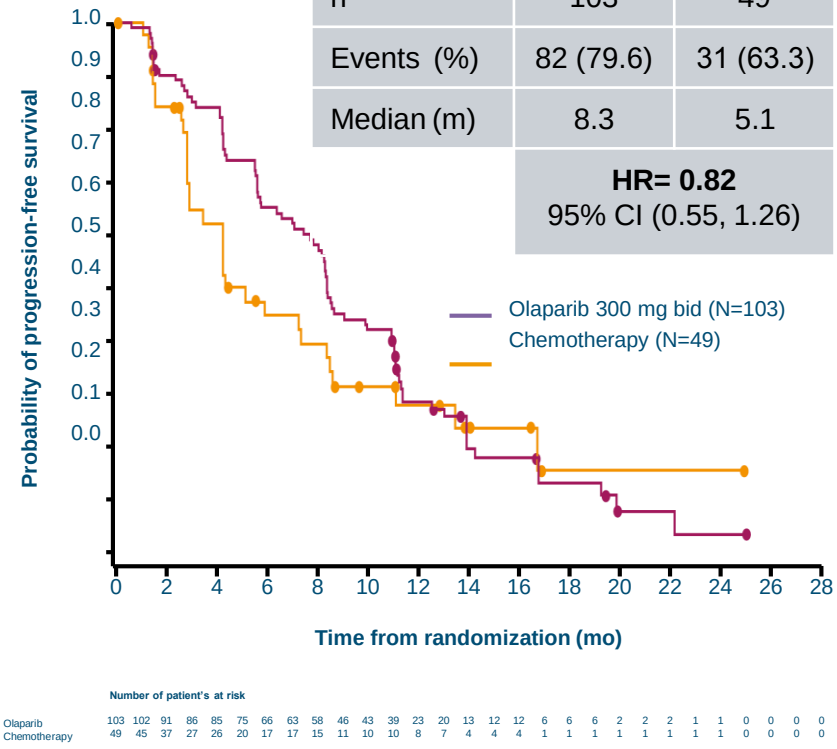


Robson et al, New Engl J Med 2017

OLYMPIAD: PFS IN HR+ BREAST CANCER AND TRIPLE-NEGATIVE BREAST CANCER

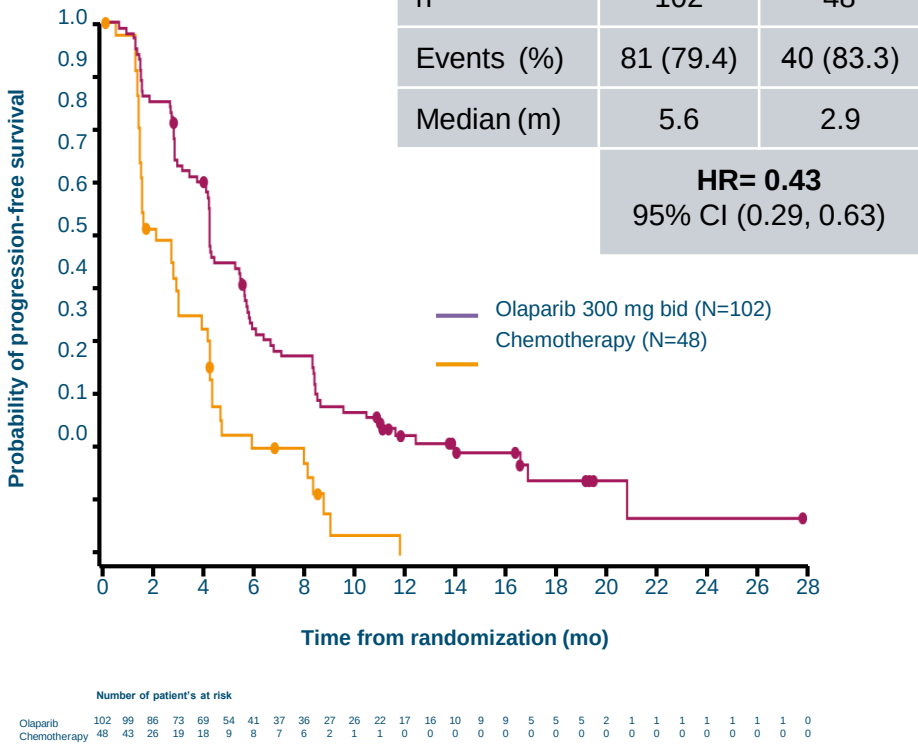
Patients with HR+ MBC[2]

	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)	



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)	

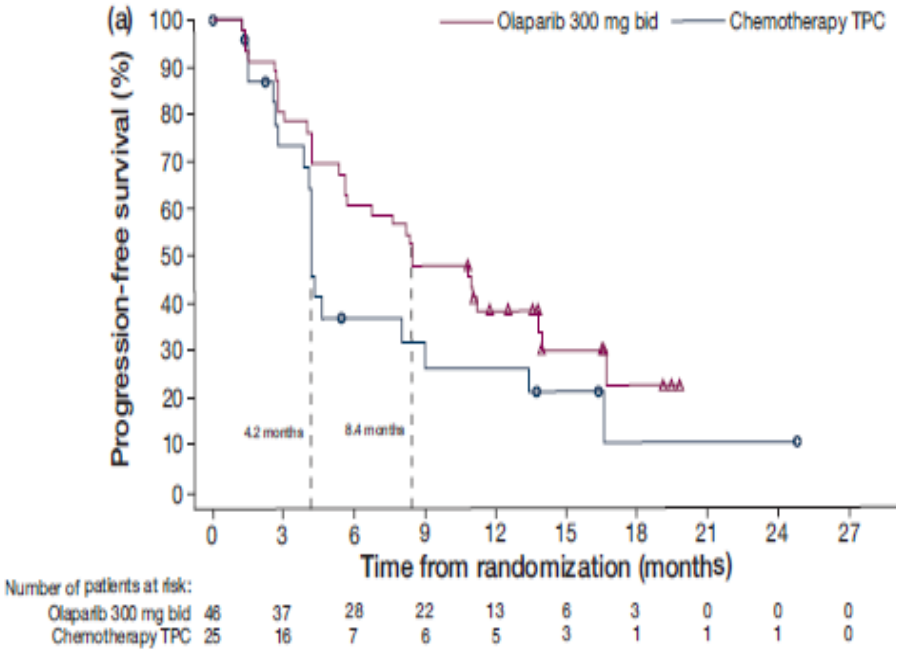


HR = hormone-receptor; PFS = progression-free survival; TNBC = triple-negative breast cancer TPC = treatment of physician's choice.

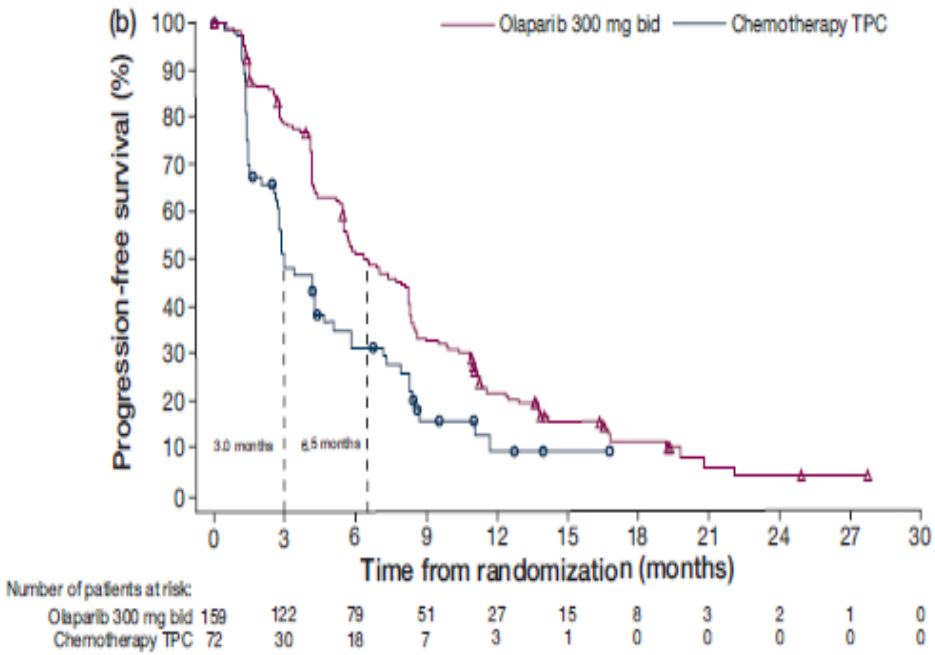
1. Robson M, et al. *N Engl J Med.* 2017;377(6):523–33.
2. Robson et al. *J Clin Oncol* 35, 2017 (presentation associated with abstr LBA4).

OLYMPIAD: PFS BY NUMBER OF METASTATIC SITES

PFS in patients with 1 metastatic site



PFS in patients with ≥2

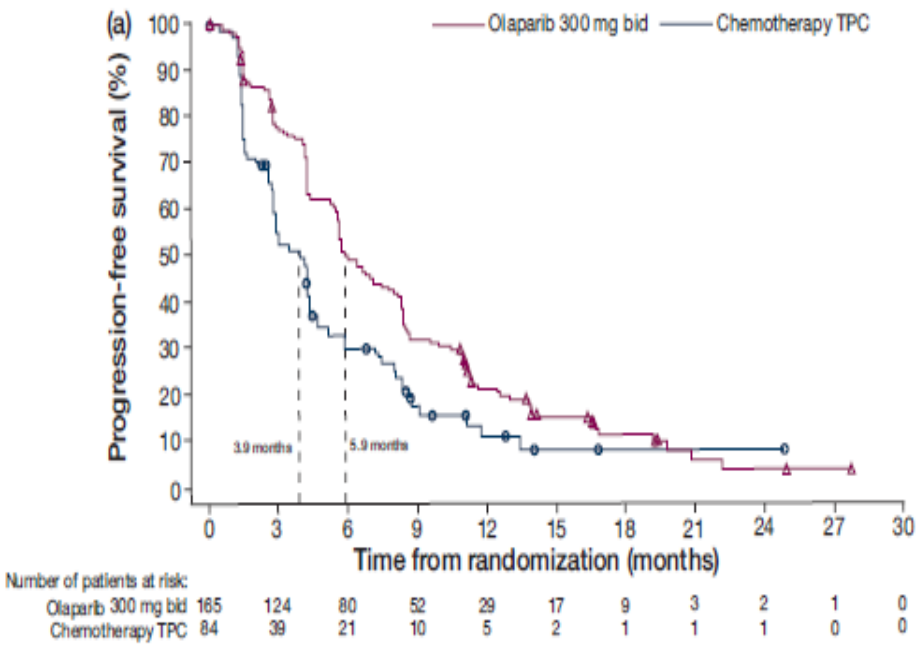


Dotted lines indicate median PFS.
PFS = progression-free survival; TPC = treatment of physician's choice.

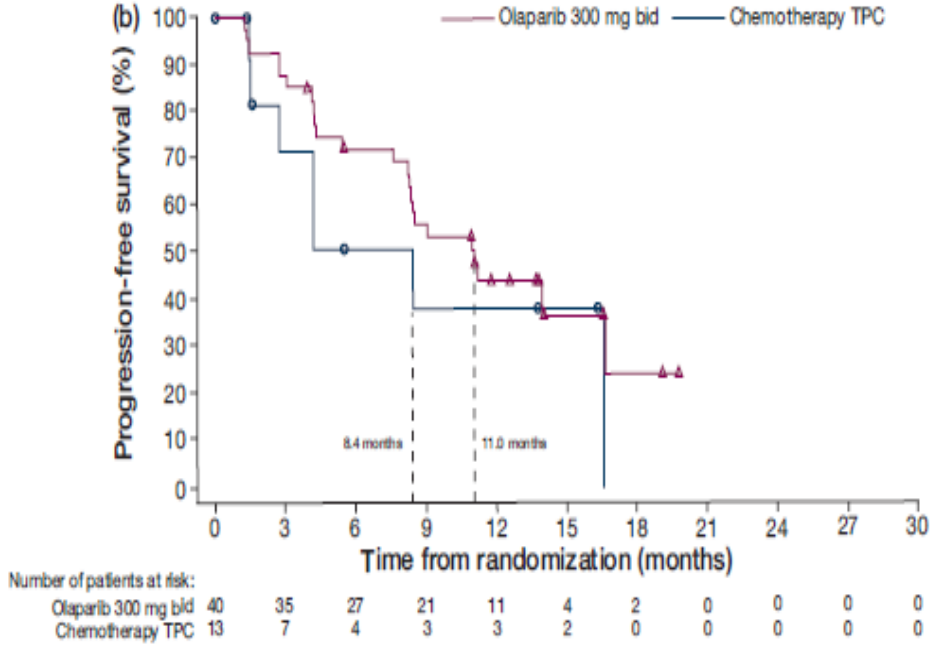
Delaloge S, et al. ESMO 2017; abst. 2434 (poster 243PD).

OLYMPIAD: PFS BY LOCATION OF METASTASES

PFS in patients with visceral metastases



PFS in patients with non-visceral* metastases

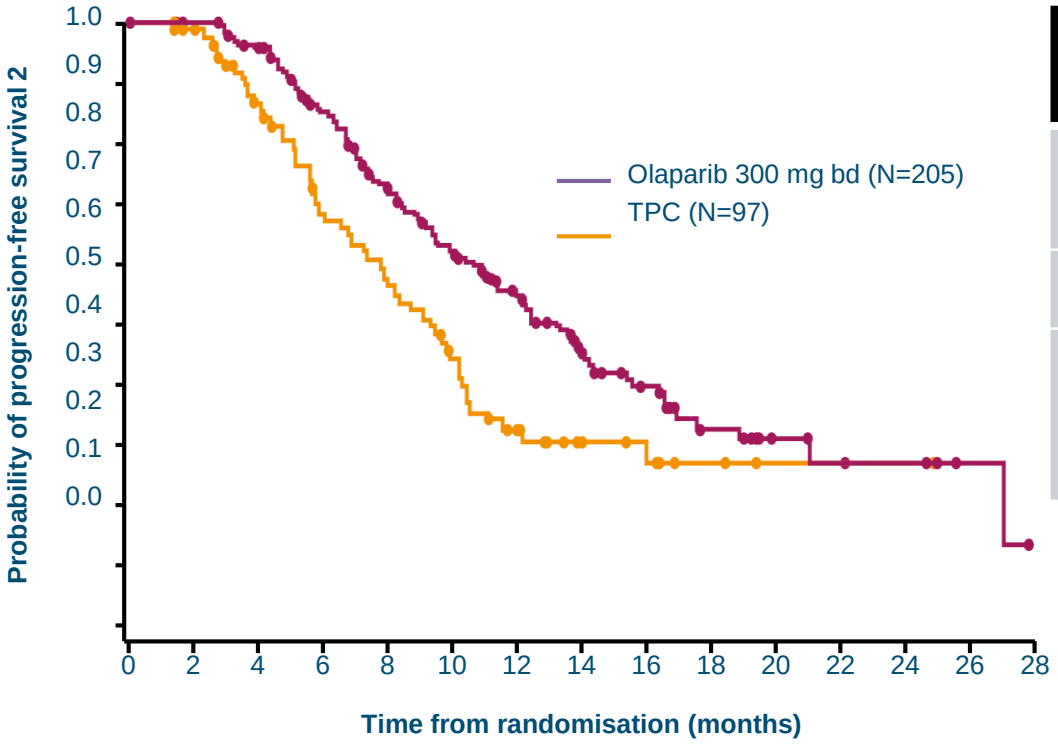


Dotted lines indicate median PFS. *Non-visceral disease includes lymph nodes, soft tissue, cutaneous and bone only.
PFS = progression-free survival; TPC = treatment of physician's choice.

Delaloge S, et al. ESMO 2017; abst. 2434 (poster 243PD).

OLYMPIAD: TIME TO SECOND PROGRESSION OR DEATH (PFS2)

- Risk of progression or death reduced by >40%



	Olaparib n=205	TPC n=97
Events (%)	104 (50.7%)	53 (54.6%)
Median (mo)	13.2	9.3
	HR = 0.57 95% CI (0.40, 0.83) P=0.0033	

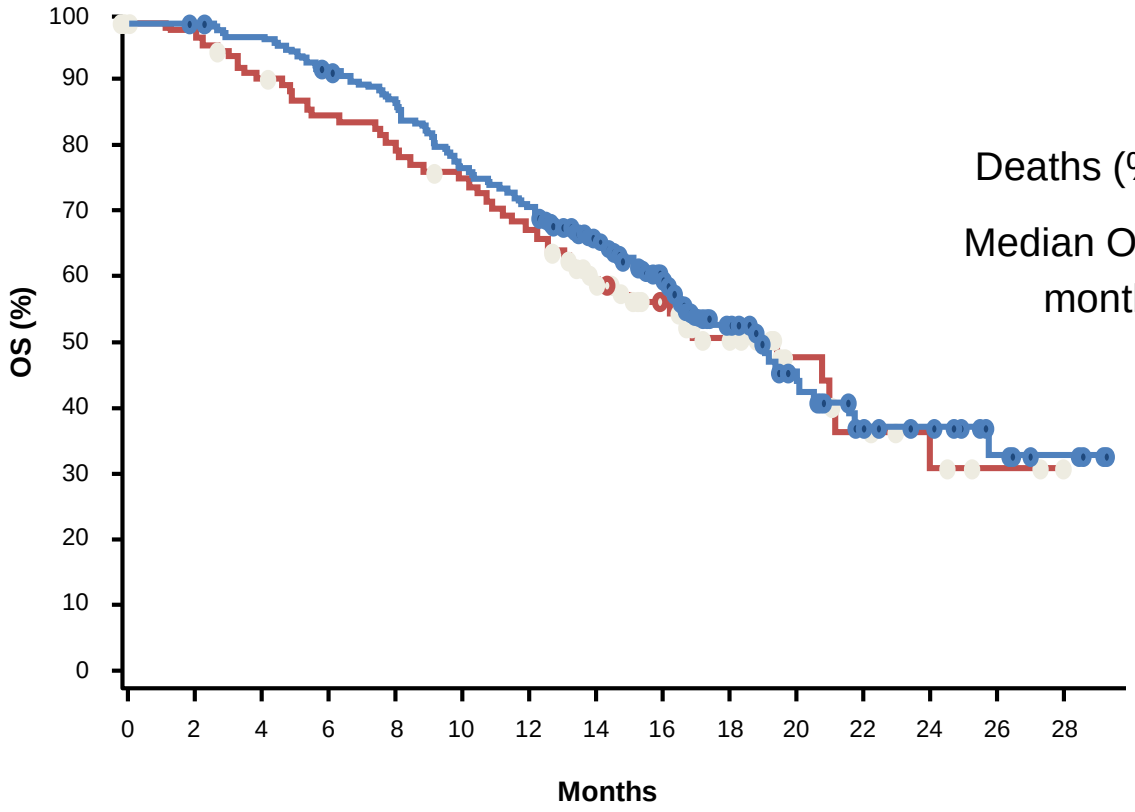
Number of patient's at risk

Olaparib	205	204	199	193	185	171	152	137	123	113	102	89	75	64	44	39	34	20	18	16	8	7	6	5	5	3	2	2	0
Chemotherapy	97	92	65	76	69	51	51	47	42	39	31	25	19	14	10	7	7	4	4	3	1	1	1	1	1	0	0	0	0

PFS2 = time from start of randomisation to second progression (or death); TPC = treatment of physician's choice.

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

Overall survival (interim analysis; 46% data maturity):[1]



	Olaparib 300 mg bd	Chemotherapy TPC
Deaths (%)	94 (45.9)	46 (47.4)
Median OS, months	19.3	19.6

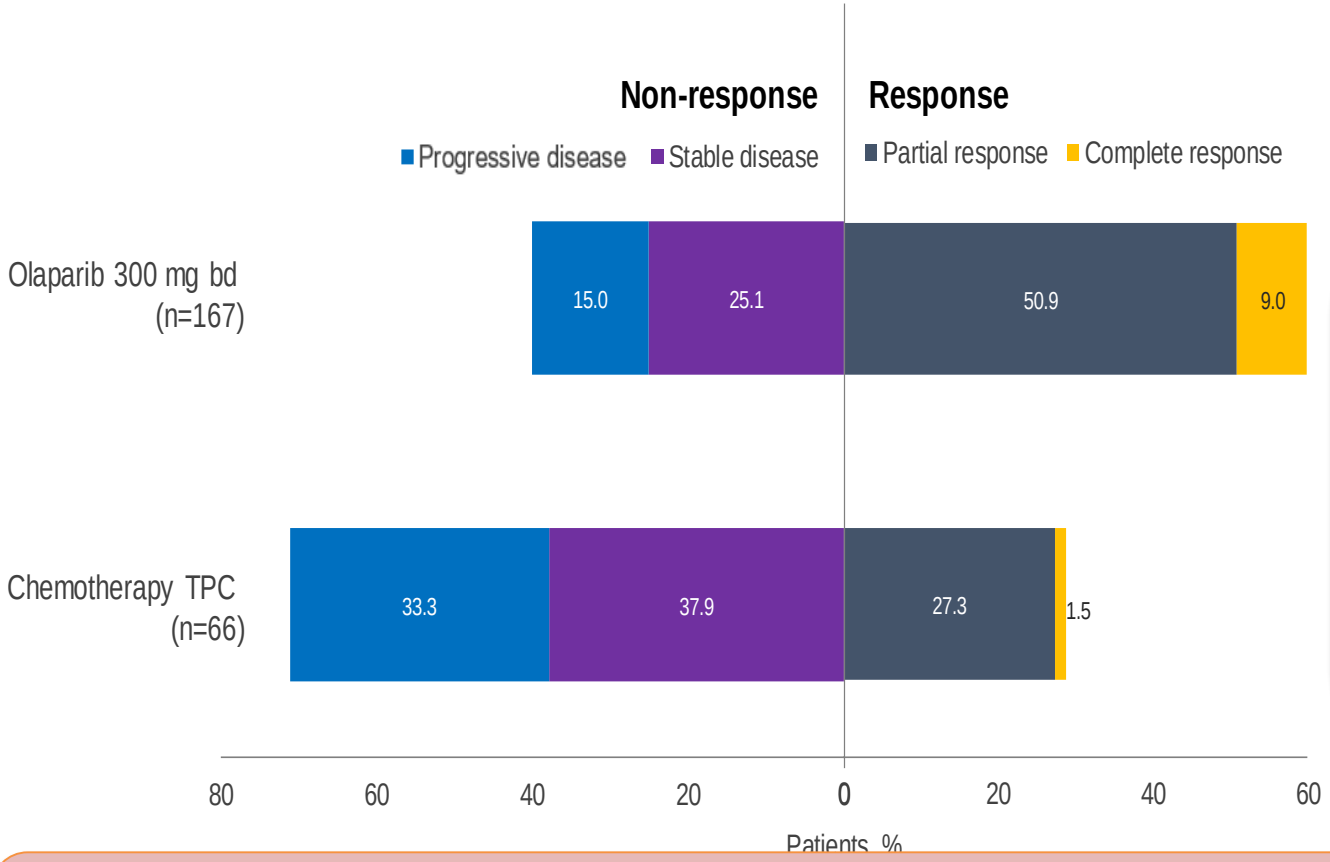
HR 0.90

95% CI 0.63, 1.29;
P=0.57

At risk, n																
Olaparib	205	205	199	189	178	159	146	109	78	46	30	18	14	8	4	0
TPC	97	92	85	78	74	69	62	50	34	24	13	9	7	4	2	0

1. Robson M et al. N Engl J Med. 2017; 377(6): 523–533.

OLYMPIAD : additional efficacy data



Median response onset

- **Olaparib: 47 days**
- **Chemotherapy TPC: 45 days**

Among patients with metastatic HER2-negative BC and a germline BRCA1/2 mutation in the OlympiAD study, the objective response rate with olaparib tablet monotherapy was double that seen with standard chemotherapy TPC

Delaloge et al, ESMO 2017 poster-discussion#243 PD

OLYMPIAD : PFS in relevant subgroups

Tumour burden

	Olaparib 300 mg bid	Chemotherapy TPC
1 metastatic site, n	46	25
Median PFS, months	**8.4**	**4.2**
HR (95% CI)	0.62 (0.35, 1.13)	
≥2 metastatic sites, n	159	72
Median PFS, months	6.5	3.0
HR (95% CI)	0.59 (0.43, 0.82)	

Tumour location

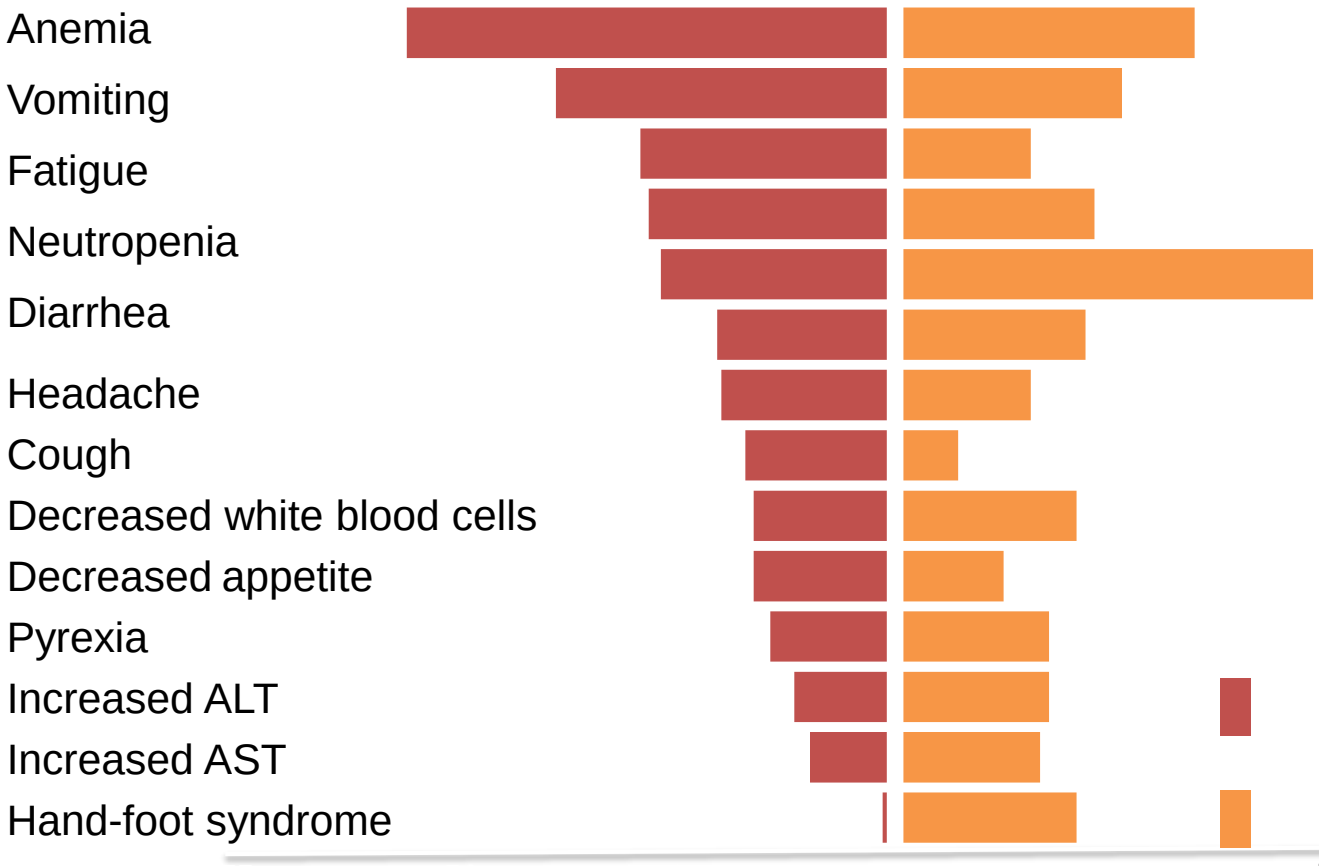
	Olaparib 300 mg bid	Chemotherapy TPC
Visceral, n	165	84
Median PFS, months	**5.9**	**3.9**
HR (95% CI)	0.64 (0.47,0.86)	
Non-visceral, n	40	13
Median PFS, months	11.0	8.4
HR (95% CI)	0.65 (0.30,1.65)	

HR, hazard ratio. Non-visceral disease includes lymph nodes, soft tissue, cutaneous and bone only.

1. Robson M *et al*. *N Engl J Med* 2017;377:523–533.

Delaloge et al, ESMO 2017 poster-discussion#243 PD

OLYMPIAD - Adverse events (any grade) in ≥15% of patients



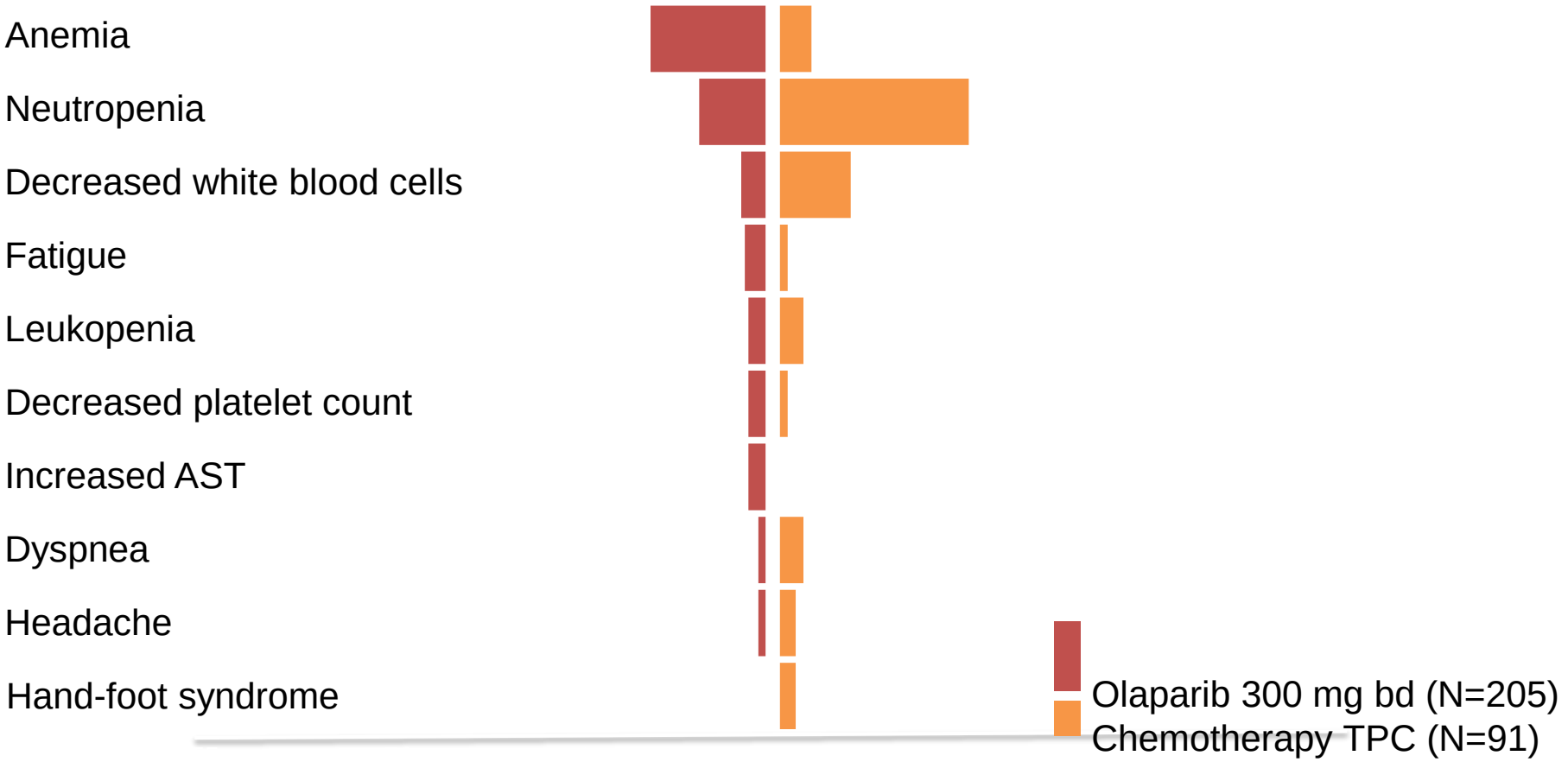
More anemia, Vomiting, nausea, Fatigue, headache And cough

Less of other toxicities

Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Robson, NEJM,2017

OLYMPIAD: Grade ≥3 adverse events in ≥2% patients in either arm



Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia

ALT, alanine aminotransferase; AST, aspartate aminotransferase

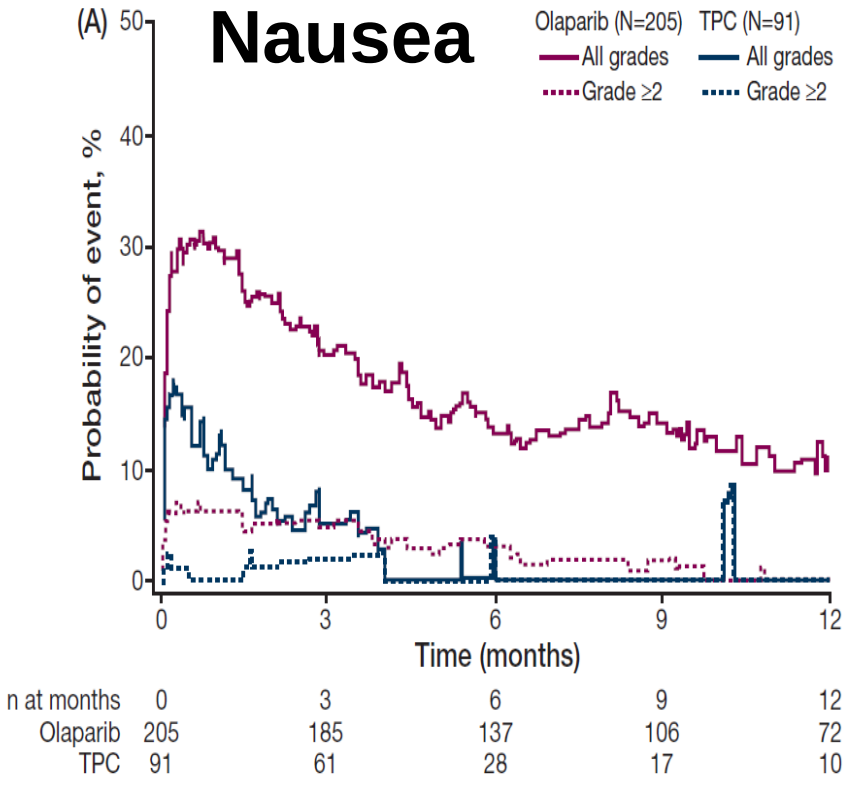
Robson, NEJM 2017

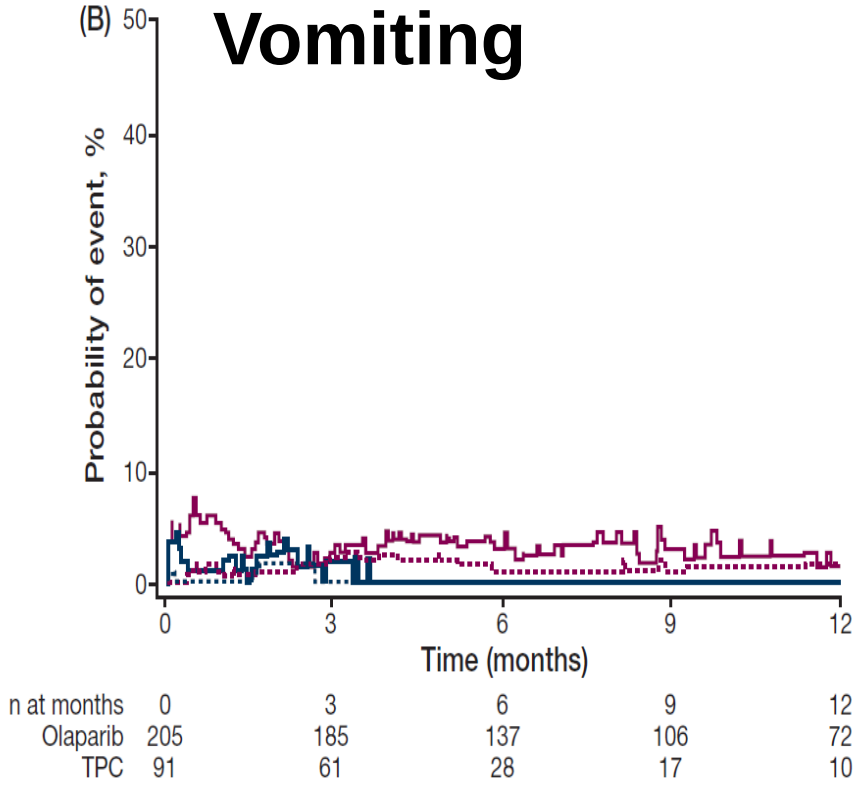
Olaparib versus chemo TPC (OLYMPIAD trial) Summary of adverse events, all causality

n patients (%)	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=91)
Grade 1–2	124 (60.5)	42 (46.2)
Grade ≥3	75 (36.6)	46 (50.5)
Death	1 (0.5)	1 (1.1)
Drug discontinuations	10 (4.9)	7 (7.7)
Dose reductions	52 (25.4)	28 (30.8)
Dose interruptions/delay	72 (35.1)	25 (27.5)

Robson et al, New Engl J Med 2017

OLYMPIAD: Time curve of adverse events: nausea and vomiting (olaparib)

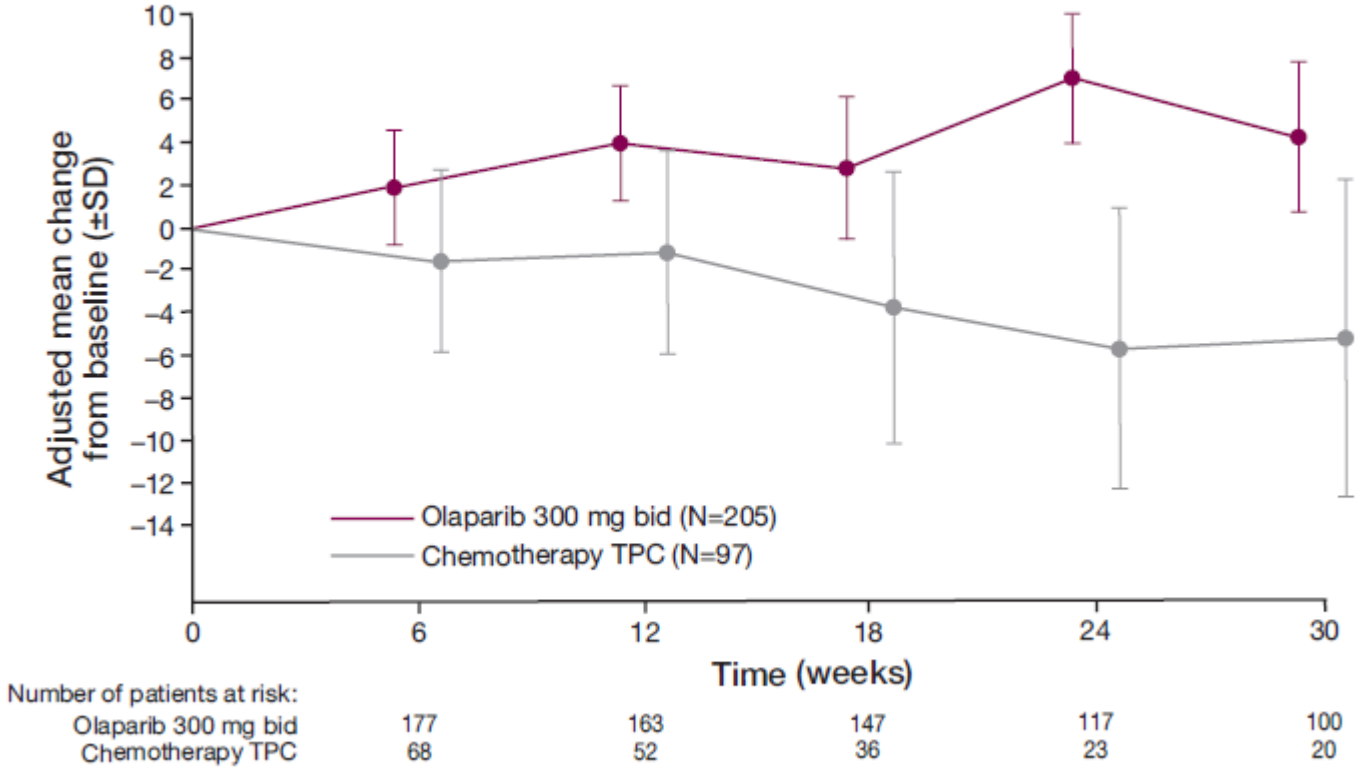




Domcheck et al, poster presentation, SABCS 2017

QoL in the OlympiaD trial

Figure 2. Adjusted mean (± SD) change from baseline in global health status/QoL score across time points in patients in the olaparib and chemotherapy TPC arms



A higher score represents better overall health-related quality of life

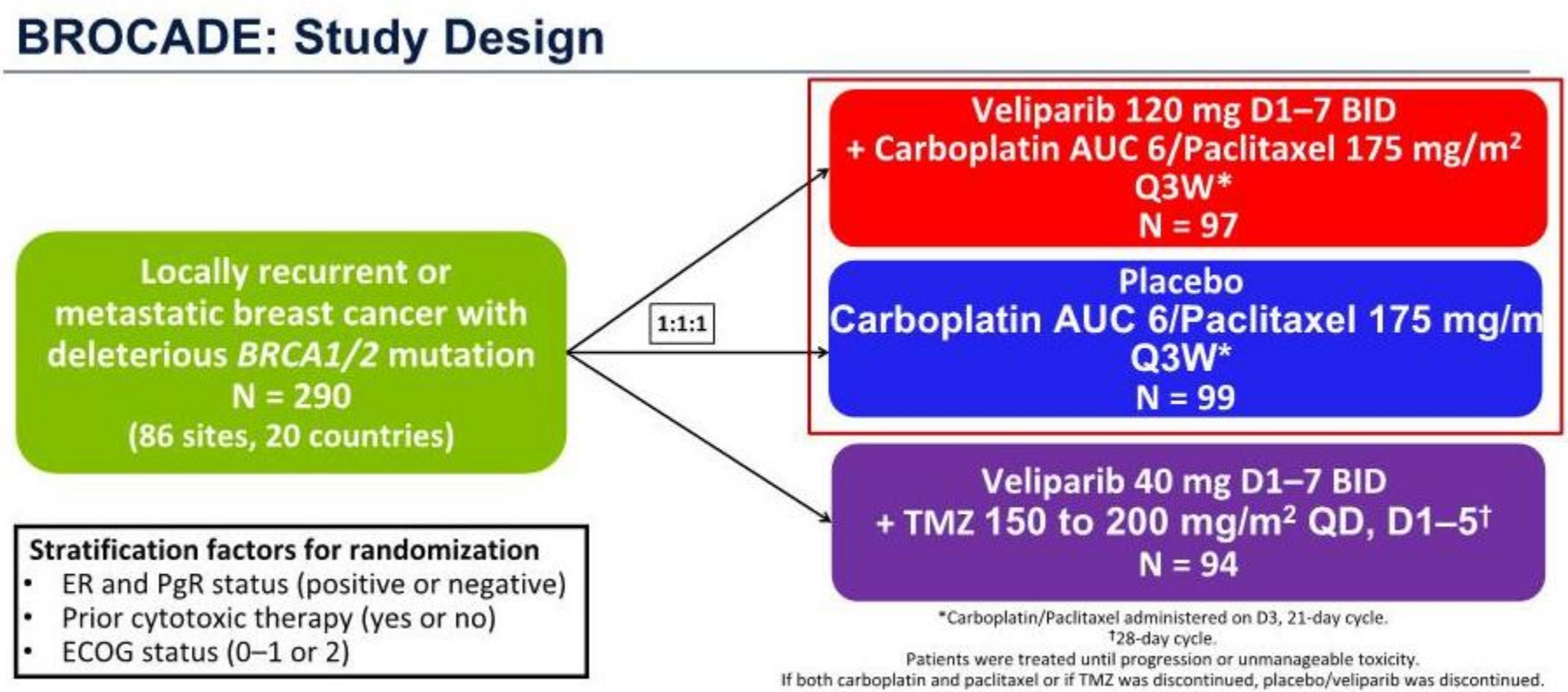
Adjusted mean (± standard error) change from baseline in global health status/QoL score across all visits of 3.9 (±1.2) versus –3.6 (±2.2; **difference 7.5; 95% CI 2.48–12.44; p=0.0035)**

Robson et al, ESMO 2017, Abstract 4542, Poster No. 290P

Olaparib for gBRCA mutated metastatic breast cancer Jan 11, 2018

Veliparib in a randomized phase II study: BROCADE 2

San Antonio Breast Cancer Symposium, December 6 - 10, 2016

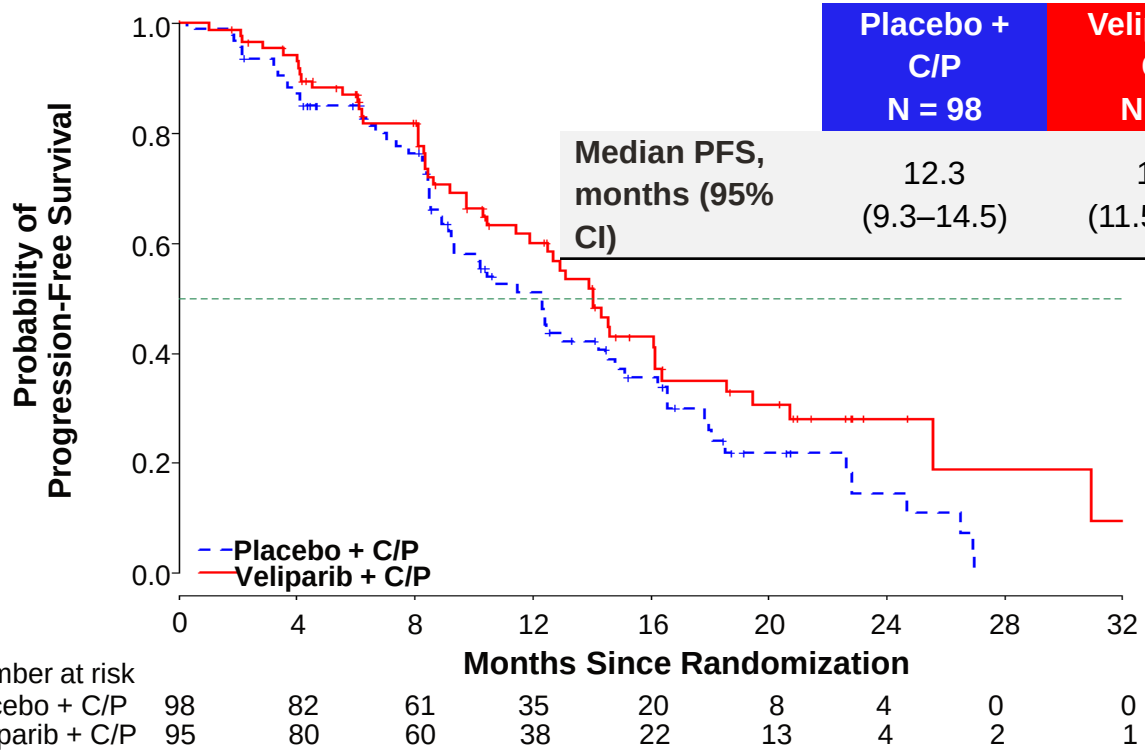


Veliparib + TMZ results will be presented separately; December 9, 2016, 7.30 am – 9.30 am
SABCS program number: P4-22-02

Han et al SABCS 2016

Veliparib in a randomized phase II study: BROCADE2

Progression-Free Survival



	Placebo + C/P N = 98	Veliparib + C/P N = 95	HR	P value*
Median PFS, months (95% CI)	12.3 (9.3–14.5)	14.1 (11.5–16.2)	0.789 (0.536–1.162)	0.231

Median (95% CI) PFS, Veliparib + TMZ: 7.4 (5.9–8.5) months; HR = 1.858 (1.278–2.702), P = 0.001. (SABCS program number: P4-22-02)

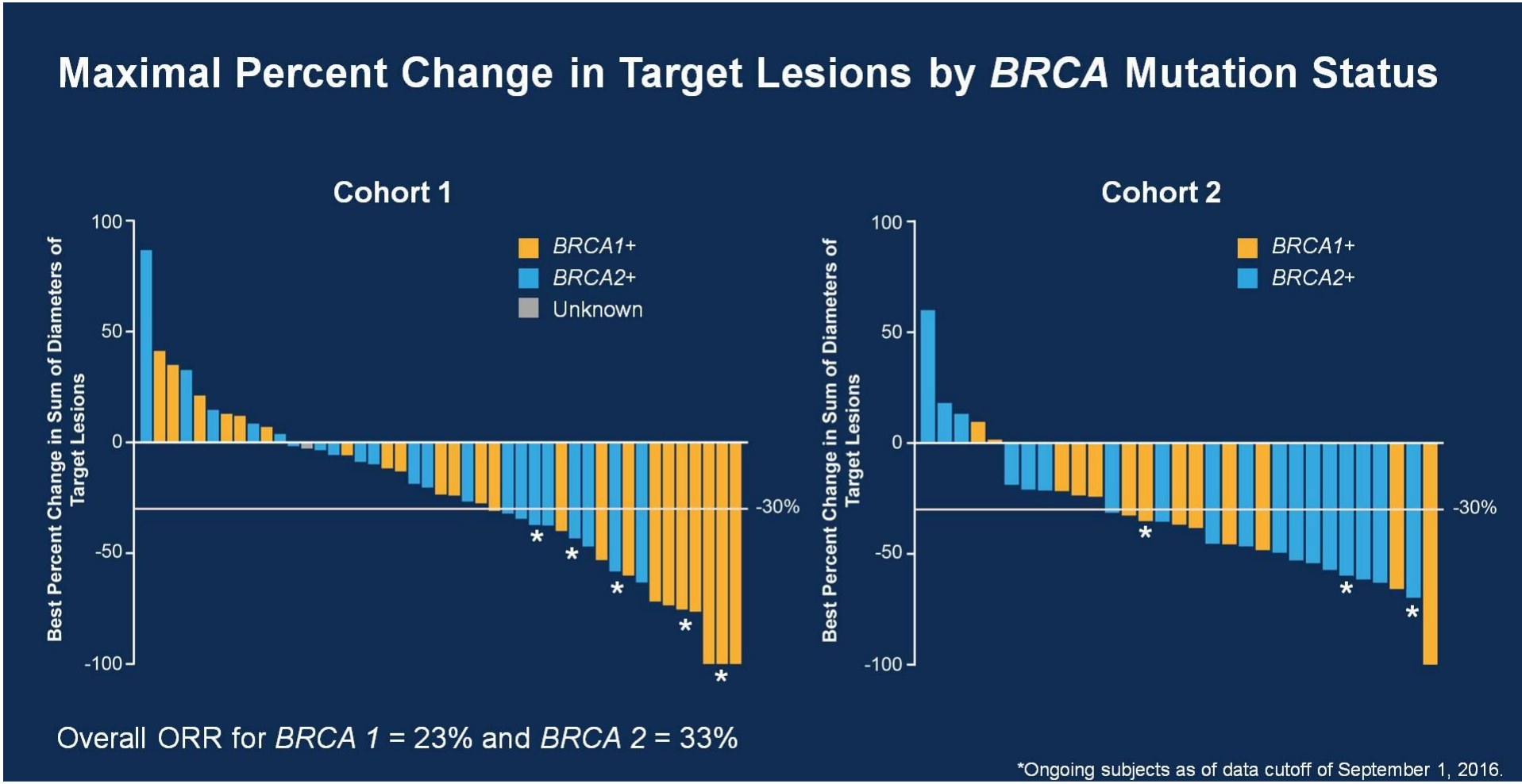
*From a proportional hazard model, stratified by ER/PgR status and prior cytotoxic therapy use.
Efficacy population includes all randomized patients who had a deleterious *BRCA1/2* mutation per the core lab.
CI, confidence interval; HR, hazard ratio.

Han et al SABCS 2016

Talazoparib in BRCA1/2 mutation carriers: ABRAZO trial

Prior platinum (sensitive)

3+ prior lines, no platinum



Turner et al ASCO 2017

Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (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

Primary endpoint

- **Progression-free survival by RECIST by blinded central review**

Key secondary efficacy endpoints

- **Overall survival (OS)**
- **ORR by investigator**
- **Safety**

Exploratory endpoints

- **Duration of response (DOR) for objective responders**
- **Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)**

Phase 3, international, open-label study randomized
431 patients in 16 countries and 145 sites

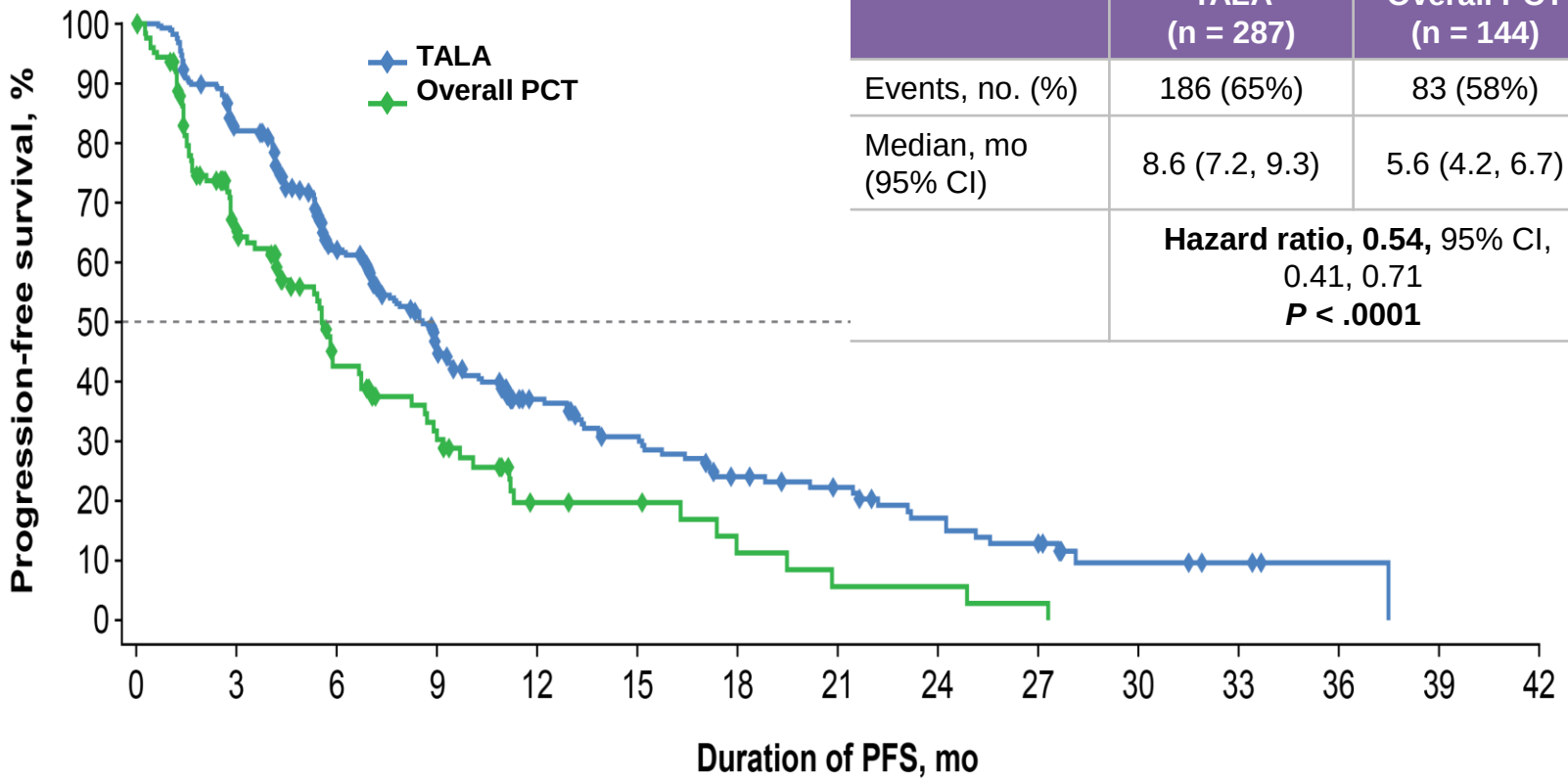
Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.

*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.

www.clinicaltrials.gov (NCT01945775)

EMBRACA Primary Endpoint: PFS by Blinded Central Review

	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**	

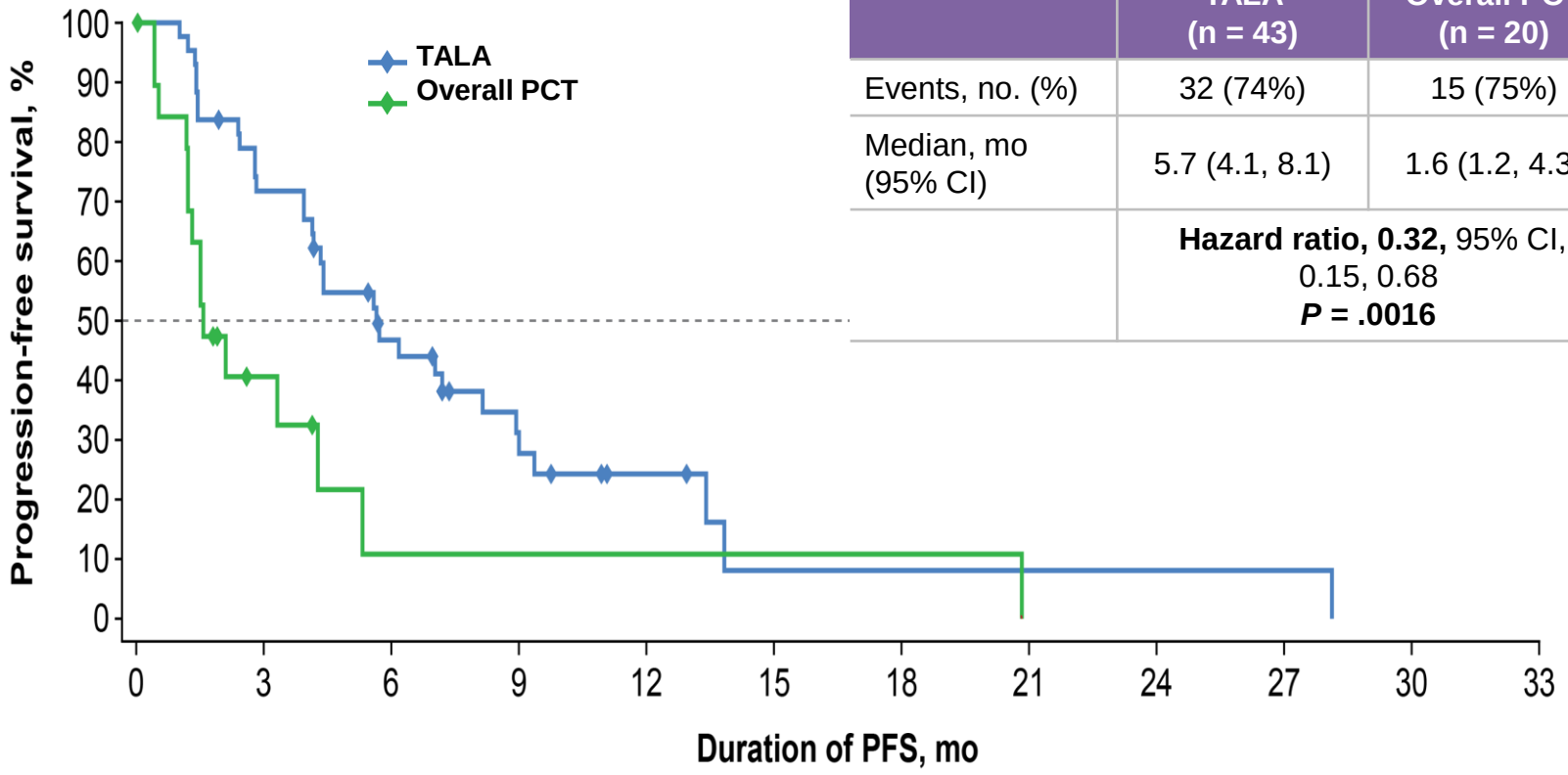


No. at risk (events/cumulative events)

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

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

EMBRACA PFS: CNS Metastases Subgroup

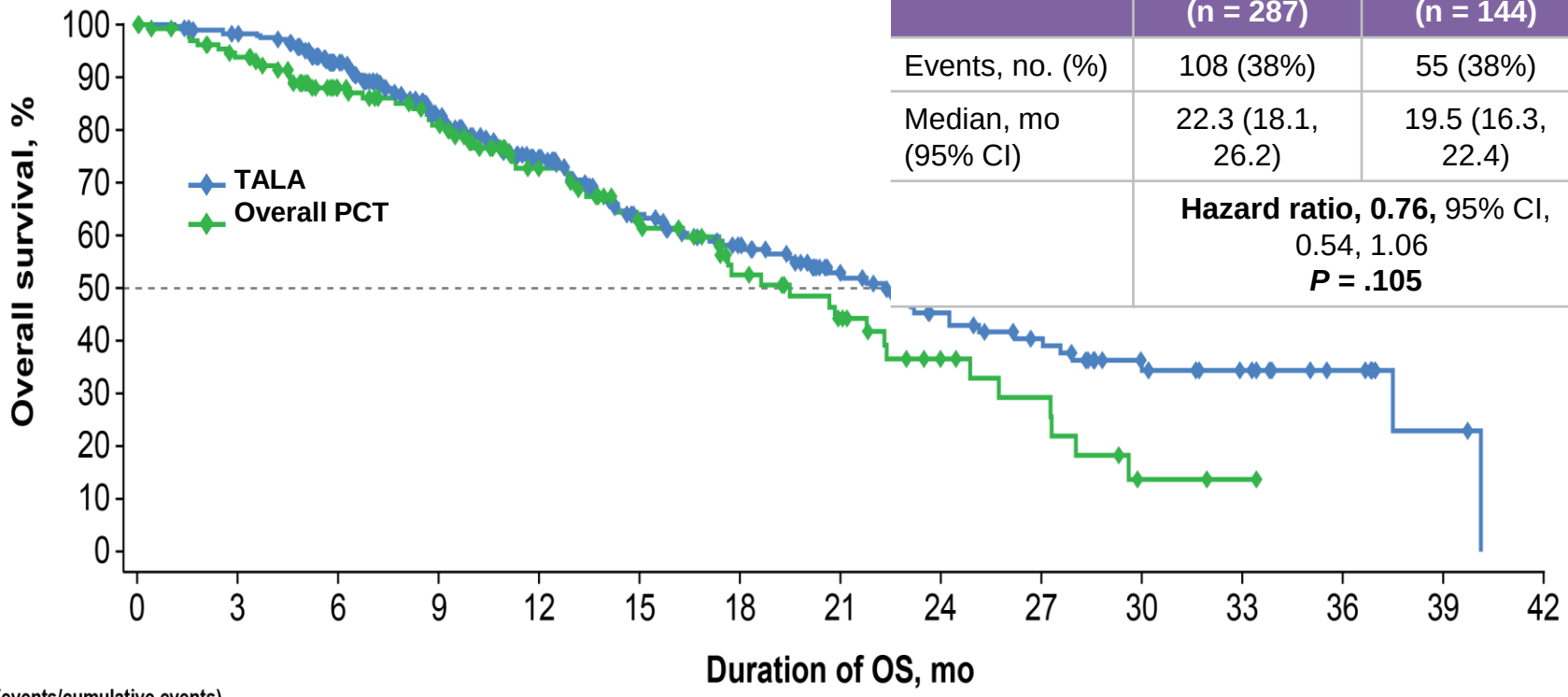


	TALA (n = 43)	Overall PCT (n = 20)
Events, no. (%)	32 (74%)	15 (75%)
Median, mo (95% CI)	5.7 (4.1, 8.1)	1.6 (1.2, 4.3)
	Hazard ratio, 0.32, 95% CI, 0.15, 0.68 ***P* = .0016**	

No. at risk (events/cumulative events)												
TALA	43 (0/0)	30 (12/12)	17 (10/22)	9 (5/27)	4 (2/29)	1 (2/31)	1 (0/31)	1 (0/31)	1 (0/31)	1 (0/31)	0 (1/32)	0 (0/32)
PCT	20 (0/0)	5 (11/11)	1 (3/14)	1 (0/14)	1 (0/14)	1 (0/14)	1 (0/14)	0 (1/15)	0 (0/15)	0 (0/15)	0 (0/15)	0 (0/15)

EMBRACA: Interim OS Analysis

	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**	



No. at risk (events/cumulative events)

TALA	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (8/85)	52 (6/91)	38 (7/98)	30 (4/102)	18 (4/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
PCT	144 (0/0)	119 (8/8)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (4/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

Survival Probability at:	TALA (n = 287)	Overall PCT (n = 144)
Month 24, % (95% CI)	45% (36.7-53.5)	37% (24.1-49.1)
Month 36, % (95% CI)	34% (25.3-43.7)	0%

Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	**Grade 3**	**Grade 4**	**All Grade**	**Grade 3**	**Grade 4**
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Long term safety of PARPi: hematological malignancies

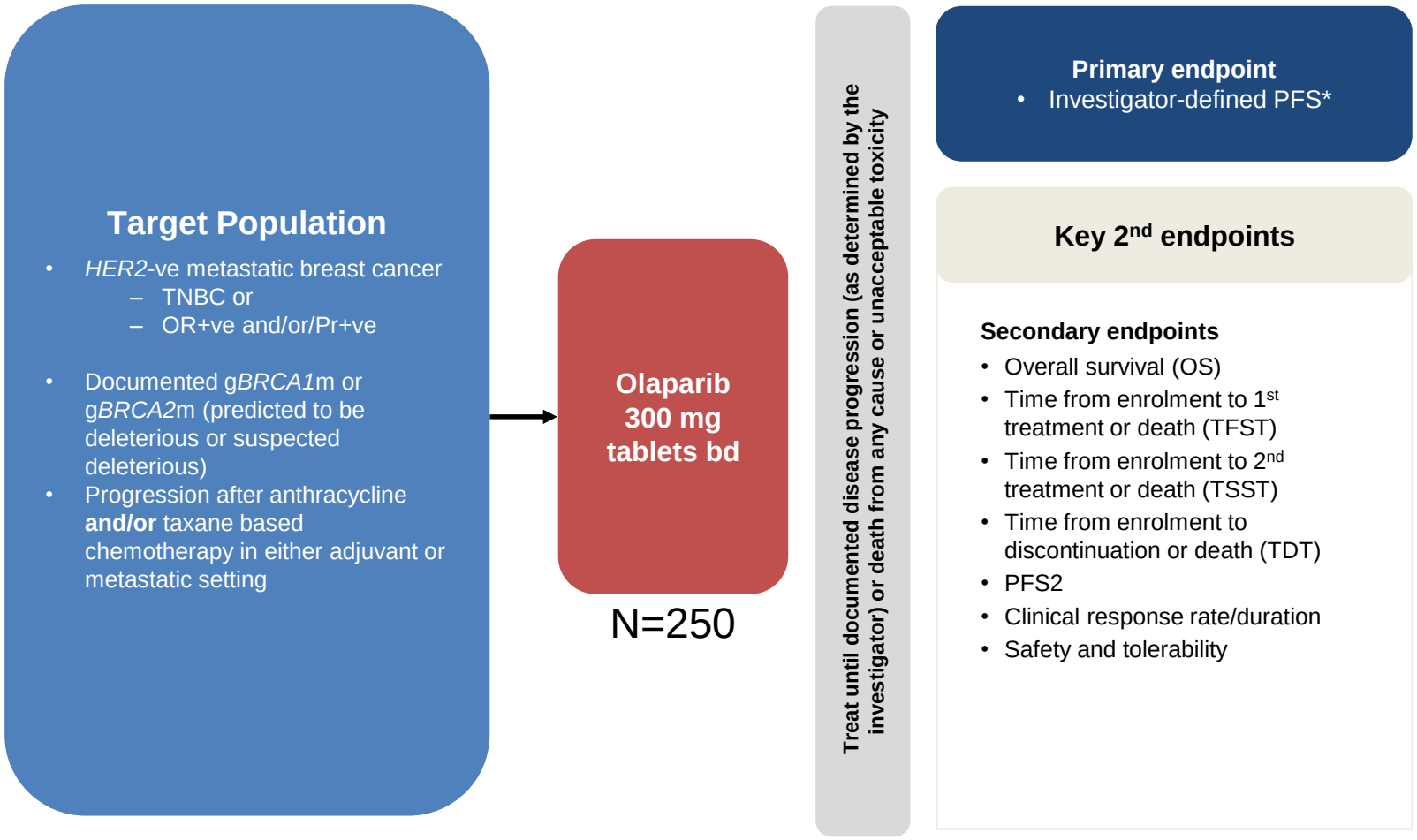
Long term incidence of AML, MDS, CMML in germline mutant carriers in phase III studies

Trial	Context	Treatment arm	Placebo arm
SOLO2	• Maintenance olaparib vs placebo, **ovarian** cancer • Germline BRCA1/2 mutation	2% (med FU 22.2 months, med treatment duration 19.1 months)	4% (med FU 22.1 months, med treatment duration 5.5 months)
NOVA	• Maintenance niraparib vs placebo, **ovarian** cancer • Both sporadic and Germline BRCA1/2 mutation	1,4% (med FU 16.9 months)	1,1% (med FU 16.9 months)
OLYMPIAD	• Olaparib vs placebo, **breast** cancer • Germline BRCA1/2 mutation	0% (med FU 14.5 months)	0% (med FU 14.1 months)

FU: follow-up, med: median; AML: acute myeloblastic leukaemia, MDS: myelodysplatic syndrome, CMML: chronic myelomonocytic leukaemia

Pujade Lauraine et al Lancet Oncol 2017, Mirza et al, New Engl J Med 2016, Robson et al New Engl J Med 2017

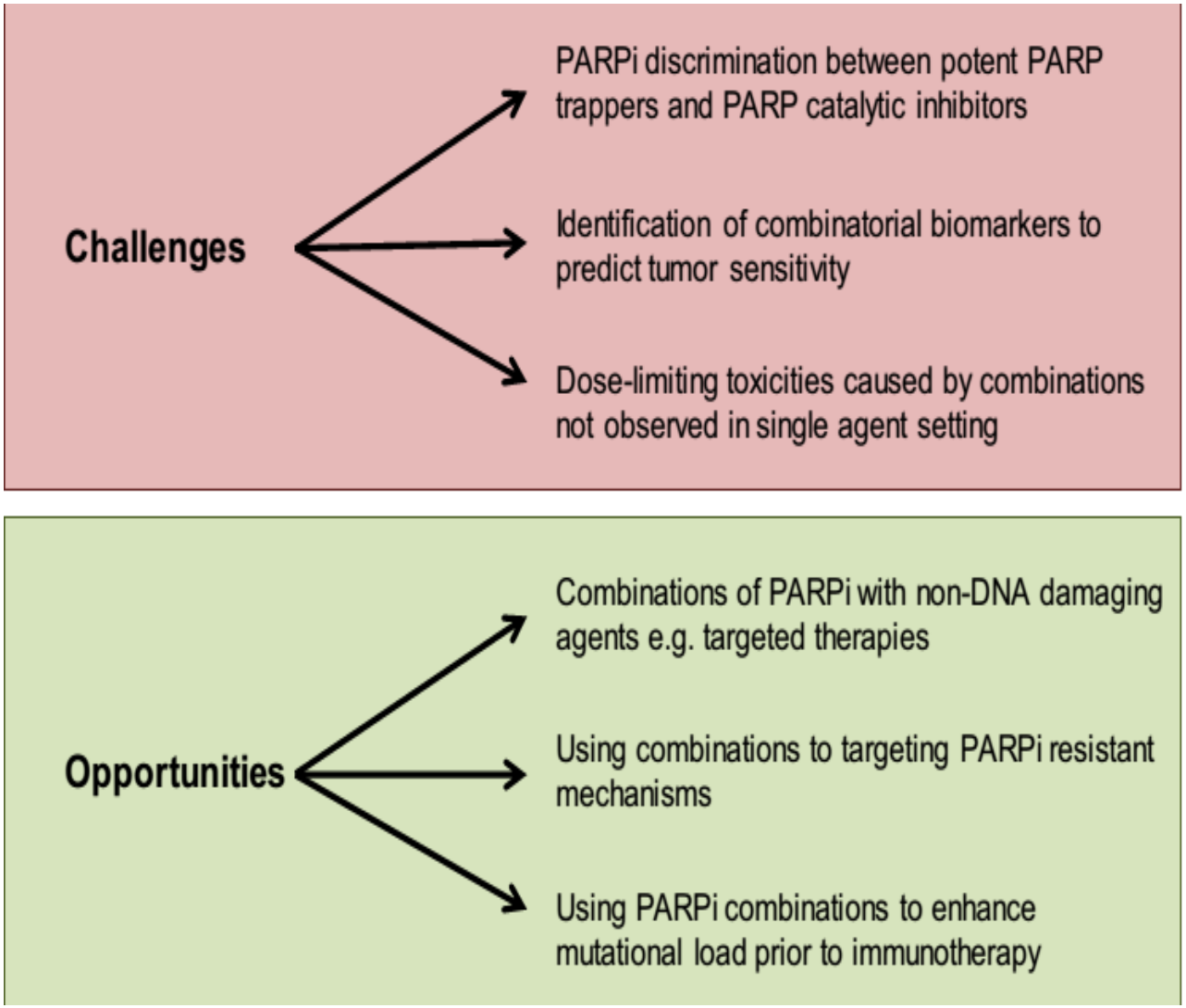
LUCY study design:[1]



*Investigator-defined PFS = the time from the date of first dose of olaparib to the date of progression as determined by the investigator (radiological or symptomatic) or death from any cause (in the absence of progression); OS = the time from the date of first dose of olaparib to the date of death from any cause; TFST= Time from enrolment to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment ; TSST= Time from enrolment to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment; TDT= Time from enrolment to study treatment discontinuation or death if this occurs before discontinuation of study treatment ; PFS2= Time from enrolment to the earliest of the progression event (subsequent to that used for the primary variable PFS) or death

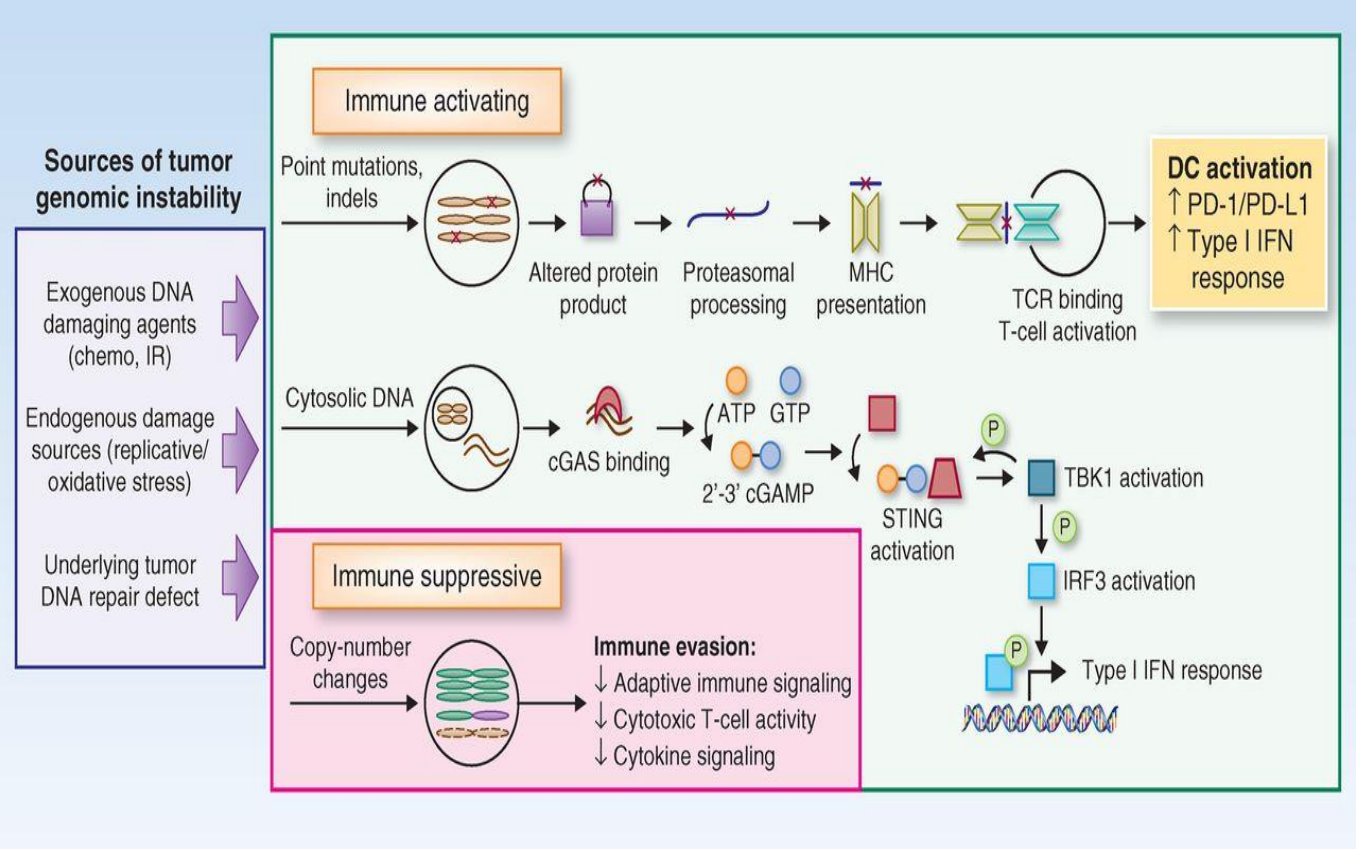
1. LUCY: Clinical Study Protocol

Challenges and Opportunities in PARPi Combinations



Drean A et al. Crit Rev Oncol/Hematol. 2016:108:73-85

DNA damage modulates tumour immunity



cGAS, cGAMP synthase; STING, Stimulator of Interferon Genes; TCR, T-cell receptor

Kent W. Mouw et al. Cancer Discov 2017;7:675-693

CHALLENGE – WHERE do PARPi fit in the Decision Tree for ABC

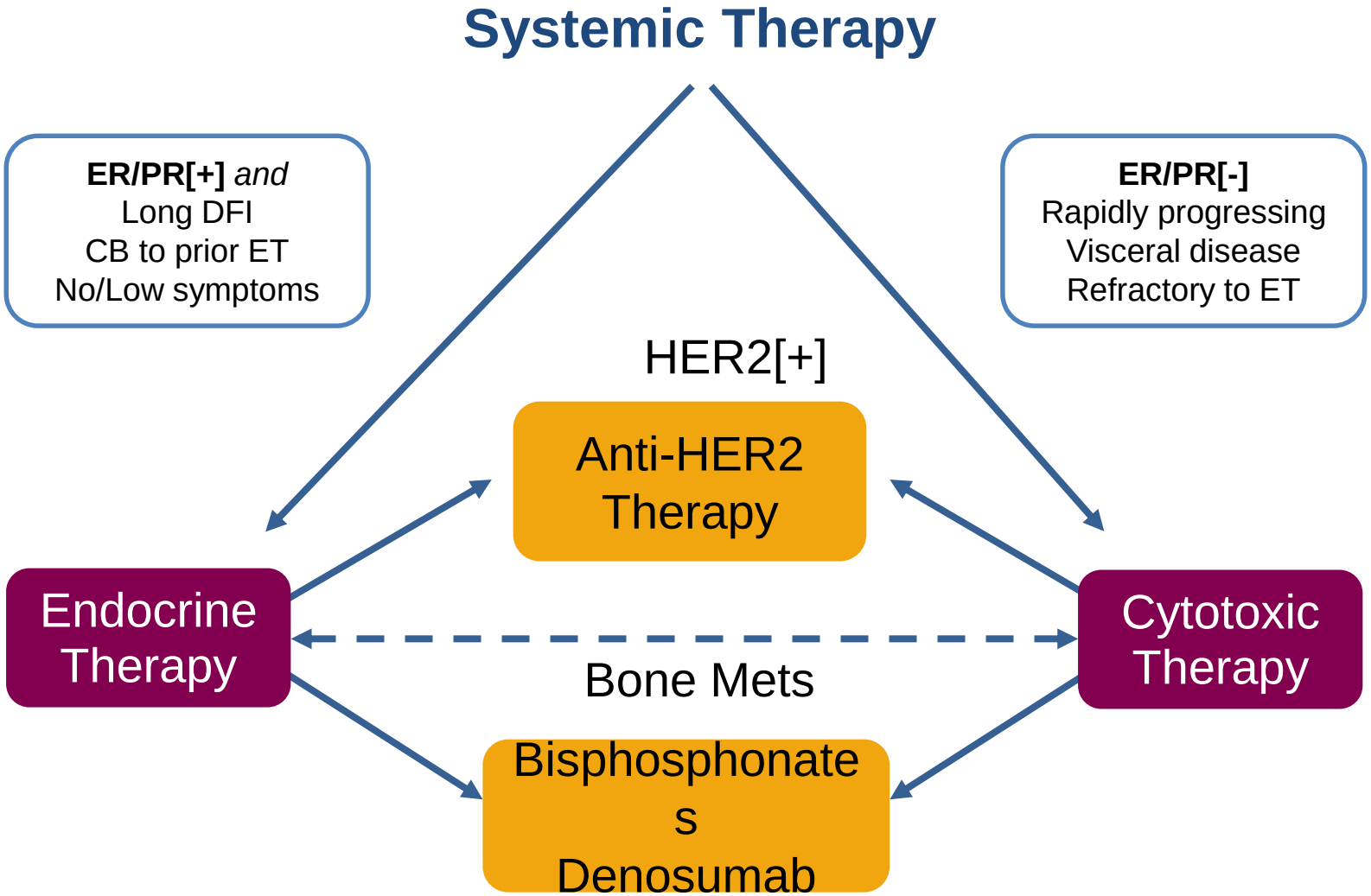
- TNBC

- Other options for treatment are chemo
- PARPi may be better tolerated then IV chemo and beneficial
- ? Compared to newer targeted therapies?
- Combo ? PARPi + IO? Or other

- LUMINAL BRCA+

- Better option than IV chemo but no data yet for sequencing
- ? CDK4/6 + ET vs PARPi
- ?PARPi + ET?
- Sequential single agent therapy?
- Duration of response

Treatment Algorithms for Advanced Breast Cancer



Treatment Algorithms for Advanced Breast Cancer

Conclusions

- For both ER+ and ER- gBRCAmutated advanced breast cancer PARPi is a new line of therapy
- The sequencing of treatments in ER+ vs ER- may vary
- Earlier treatment studies, including maintenance studies are underway
- A NEW and EXCITING TARGET!!!