The role of PARP inhibitors in management of breast cancer

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No relevant disclosures

Learning Objectives

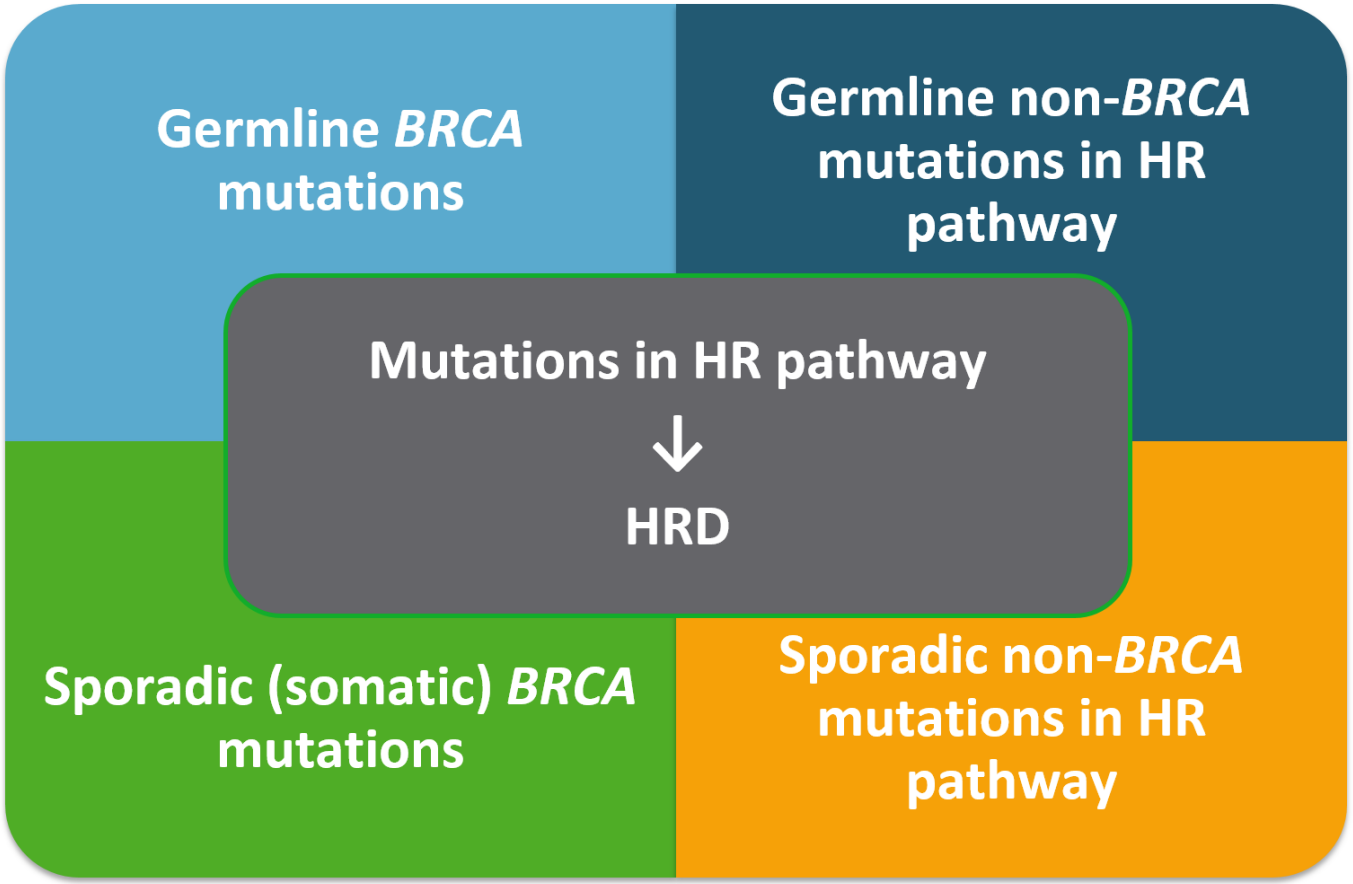
- Identify role of PARP inhibitors in management of metastatic breast cancer
- Discuss ongoing clinical trials with PARP inhibitors in early stage breast cancer and combination with other classes of drugs

How Common Are *BRCA* Mutations?

- General population (not AJ): ~ 1 in 400 (~ 0.25%)
  - Women with breast cancer (any age): 1 in 50 (2%)
  - Women with breast cancer (younger than 40 yrs): 1 in 10 (10%)
  - Men with breast cancer (any age): 1 in 20 (5%)
  - Women with ovarian cancer (any age): 1 in 8 to 1 in 10 (10% to 15%)
- General AJ population: 1 in 40 (2.5%)
  - AJ women with breast cancer (any age) 1 in 10 (10%)

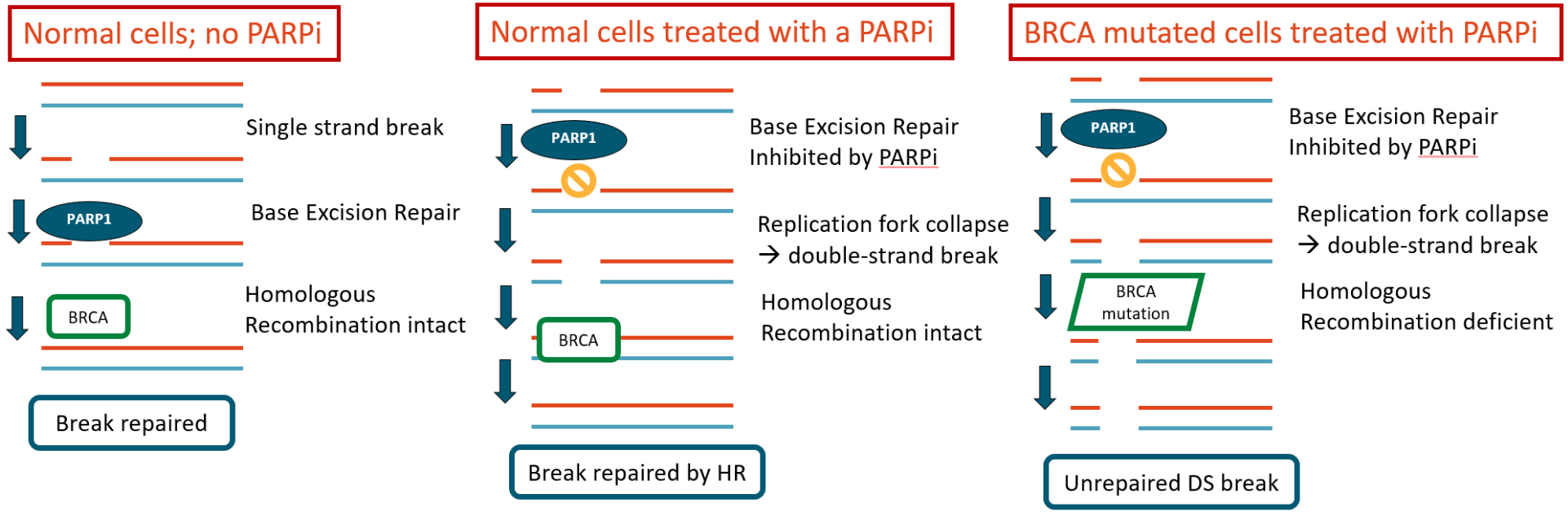
www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

HRD and *BRCA* Mutations



HR-Deficient Cells Are More Susceptible to PARP Inhibition

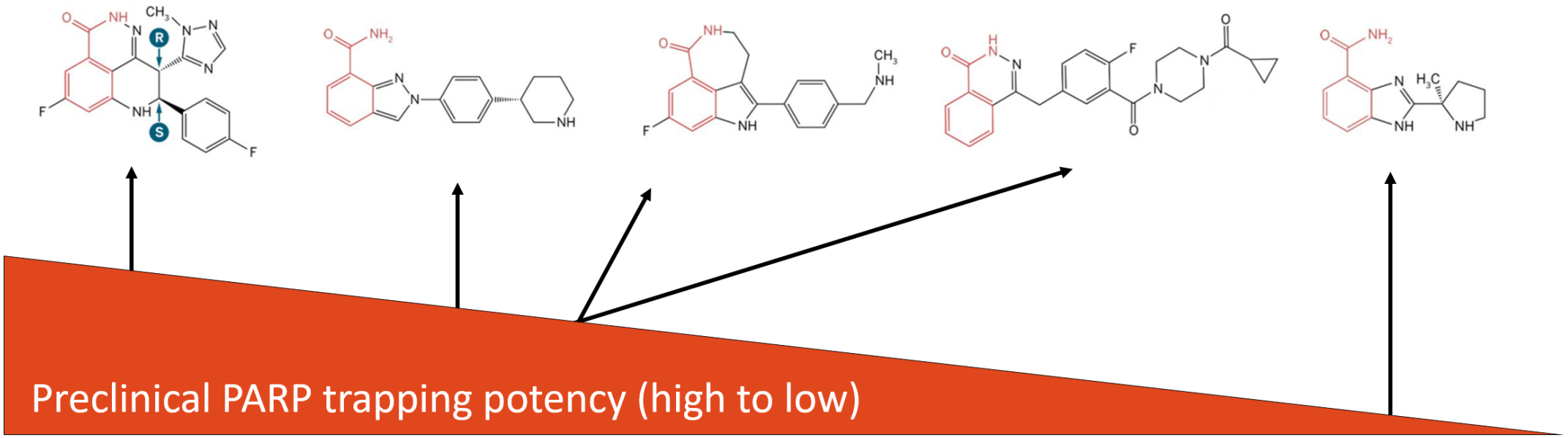
- PARP inhibition prevents repair of SS DNA breaks → DS DNA breaks
- *BRCA1/2* critical for DNA repair of DS DNA breaks via homologous recombination
- Cells defective in *BRCA1/2* are more sensitive to PARP inhibition
  - Cancer cells unable to repair double-stranded breaks die through apoptosis



Rowe. Breast Cancer Res. 2010;12:203.

PARP Inhibitors Target Tumors With Defects in Homologous Recombination

Talazoparib > Niraparib > Rucaparib ≈ Olaparib > Veliparib



- PARP trapped on DNA by PARPi; more trapping ≈ more potent

Lord. Science. 2017;355:1152.

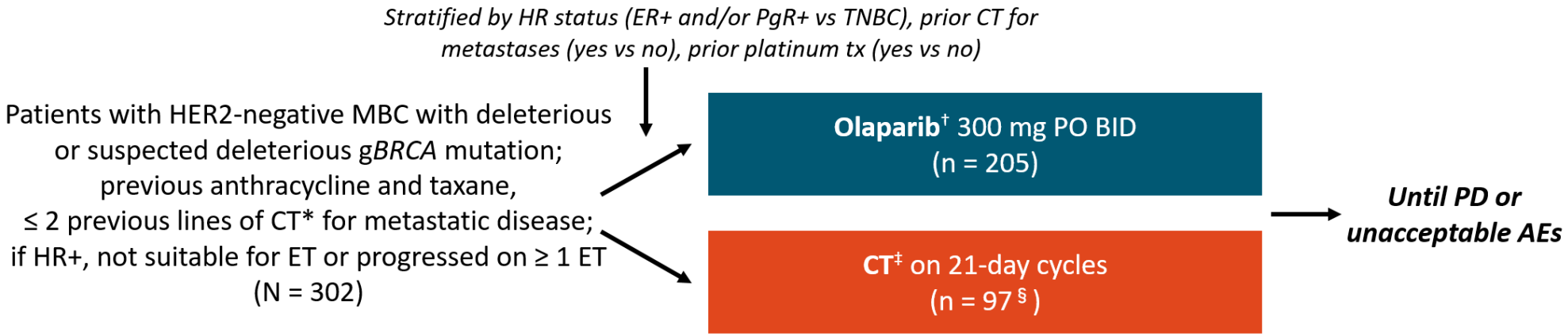
FDA-Approved PARP inhibitors for Metastatic Breast Cancer with germline BRCA

- Olaparib—approved in 1/2018 as a single agent for gBRCA-mutated HER2-negative metastatic breast cancer (ER+ or TNBC)

- Talazoparib—approved in 10/2018 as a single agent for gBRCA-mutated HER2-negative metastatic breast cancer (ER+ or TNBC)

OlympiAD: Olaparib vs Chemotherapy in HER2-Negative MBC

- Randomized, open-label phase III study

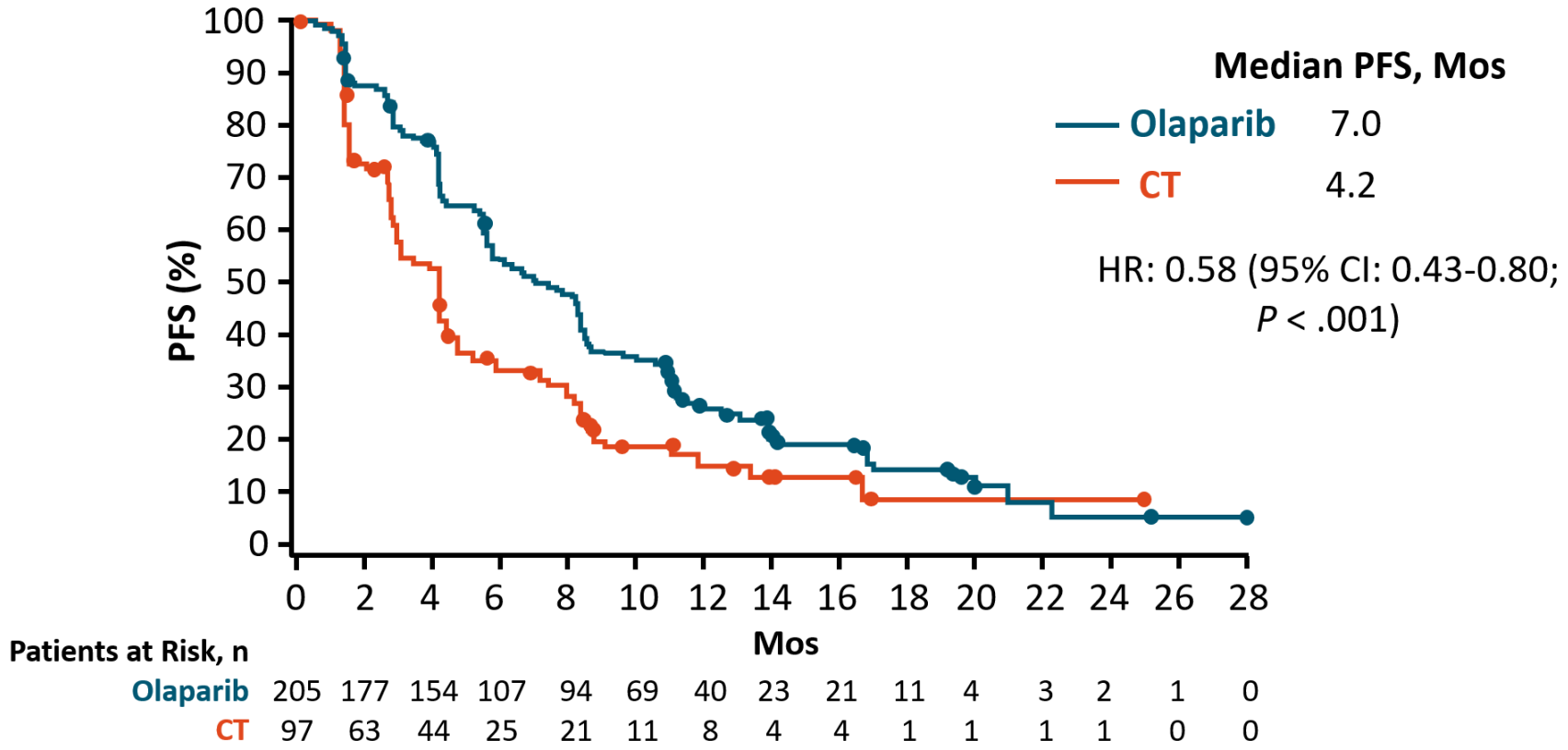


*If platinum-based therapy, patient could not have experienced progression on tx in advanced setting or ≥ 12 mos since (neo)adjuvant tx.
†Tablet. ‡Physician's choice of: capecitabine 2500 mg/m^2 PO Days 1-14; vinorelbine 30 mg/m^2 IV Days 1, 8; or eribulin 1.4 mg/m^2 IV Days 1, 8.
§ n = 6 patients declined treatment.

- Primary endpoint: PFS per modified RECIST 1.1 (BICR)
- Secondary endpoints: time to second progression/death, OS, ORR, safety, tolerability, global HRQoL

Robson. NEJM. 2017;377:523. Robson. AACR 2018. Abstr CT038.

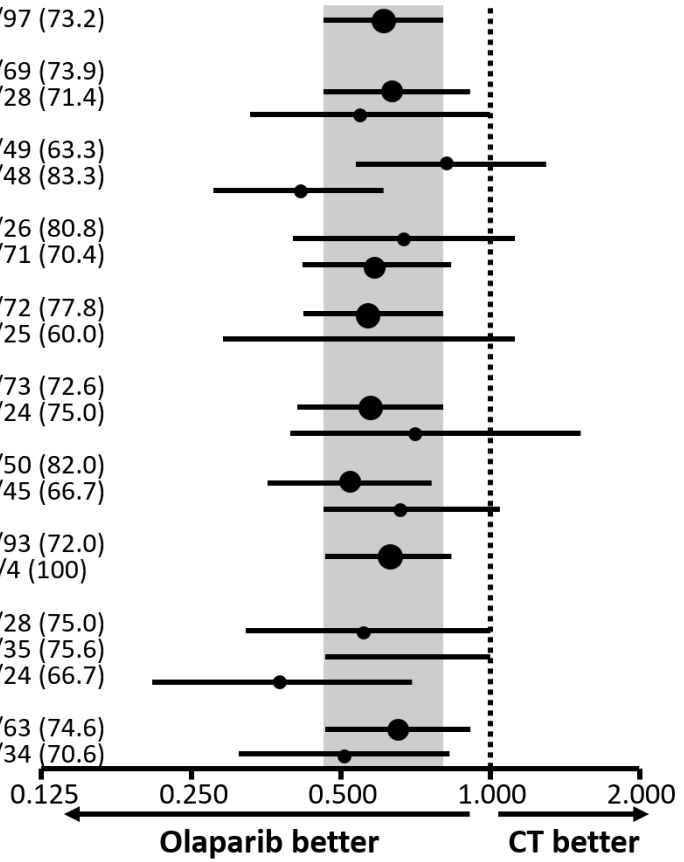
OlympiAD: PFS (Primary Endpoint)



Robson. NEJM. 2017;377:523.

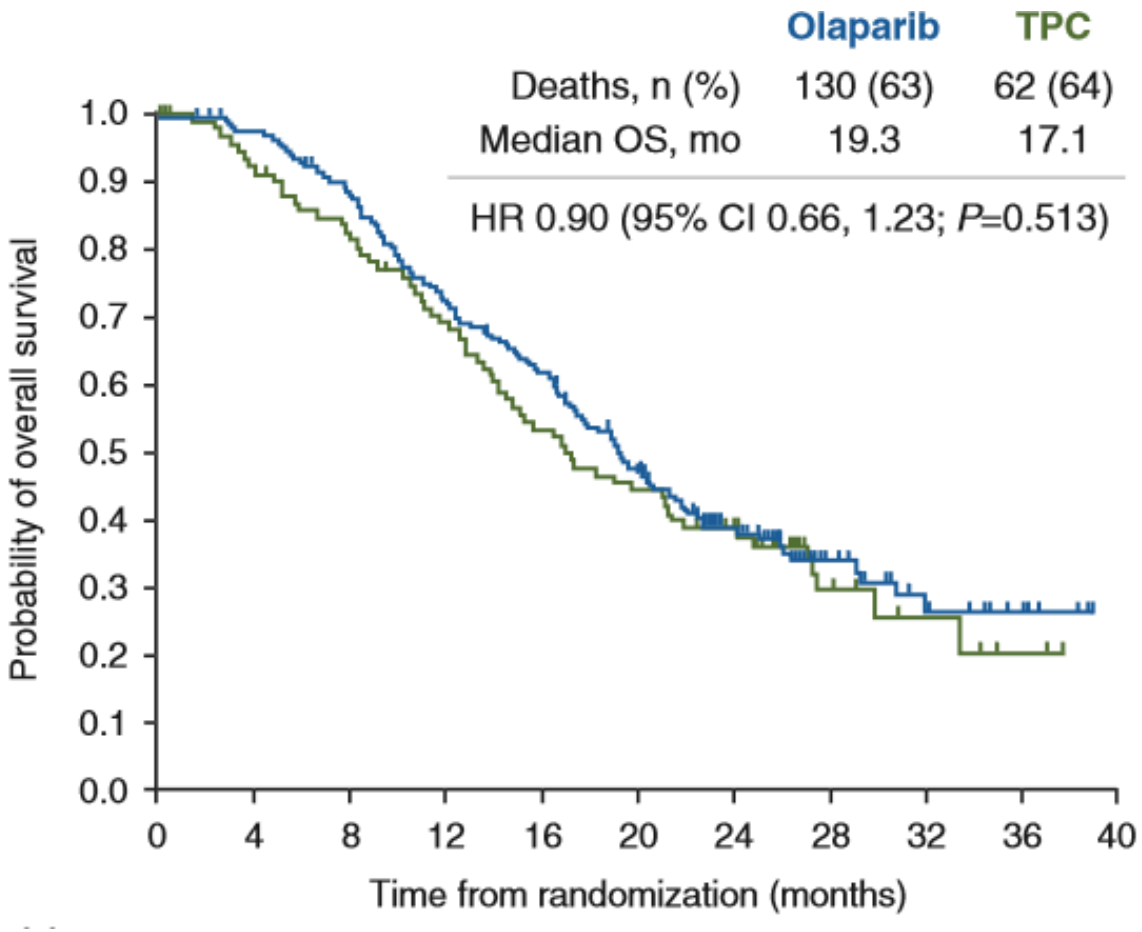
OlympiAD: PFS Subset Analysis

Subgroup	Olaparib	Standard Therapy	HR (95% CI)
	No. of Patients With Events/Total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43-0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47-0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34-0.98)
Hormone receptor status			
Hormone receptor positive	82/103 (79.6)	31/49 (63.3)	0.82 (0.55-1.26)
Triple negative	81/102 (79.4)	40/48 (83.3)	0.43 (0.29-0.63)
Previous platinum-based therapy for breast cancer			
Yes	50/60 (83.3)	21/26 (80.8)	0.67 (0.41-1.14)
No	113/145 (77.9)	50/71 (70.4)	0.60 (0.43-0.84)
Measurable disease			
Yes	139/165 (84.2)	56/72 (77.8)	0.58 (0.43-0.80)
No	24/40 (60.0)	15/25 (60.0)	0.57 (0.30-1.12)
Progressive disease at the time of randomization			
Yes	127/159 (79.9)	53/73 (72.6)	0.60 (0.43-0.83)
No	36/46 (78.3)	18/24 (75.0)	0.72 (0.41-1.30)
BRCA mutation type			
BRCA1	94/114 (82.5)	41/50 (82.0)	0.54 (0.37-0.79)
BRCA2	64/84 (76.2)	30/45 (66.7)	0.68 (0.45-1.07)
Age			
< 65 yrs	154/194 (79.4)	67/93 (72.0)	0.66 (0.49-0.88)
≥ 65 yrs	9/11 (81.8)	4/4 (100)	Not calculated
Region			
Asia	46/59 (78.0)	21/28 (75.0)	0.57 (0.34-0.97)
Europe	77/97 (79.4)	34/35 (75.6)	0.71 (0.48-1.08)
North America and South America	40/49 (81.6)	16/24 (66.7)	0.39 (0.22-0.73)
Race			
White	109/134 (81.3)	47/63 (74.6)	0.67 (0.48-0.95)
Other	54/71 (76.1)	24/34 (70.6)	0.51 (0.32-0.85)



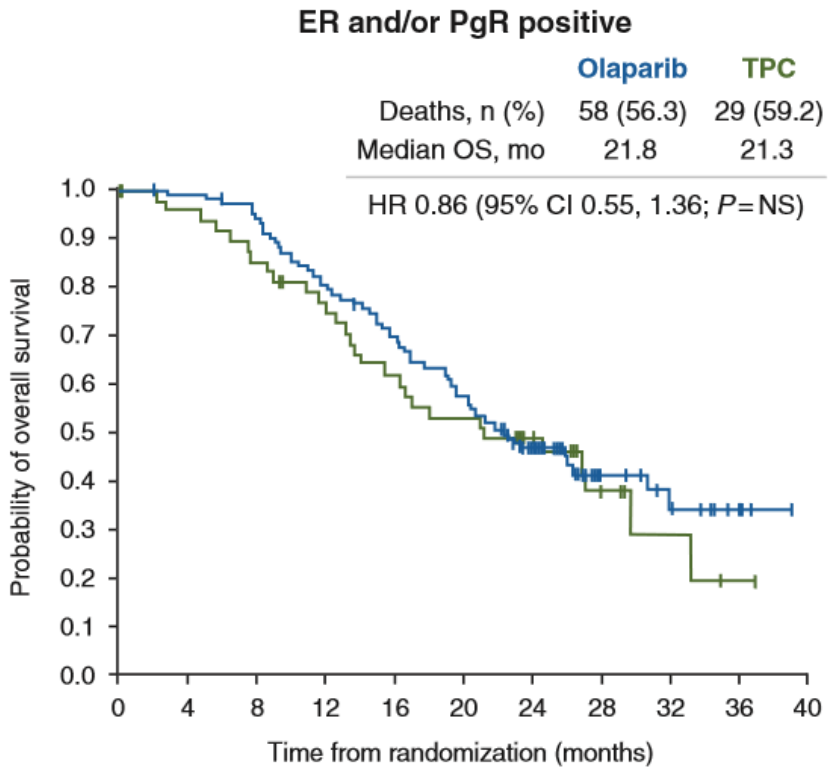
Robson. NEJM. 2017;377:523.

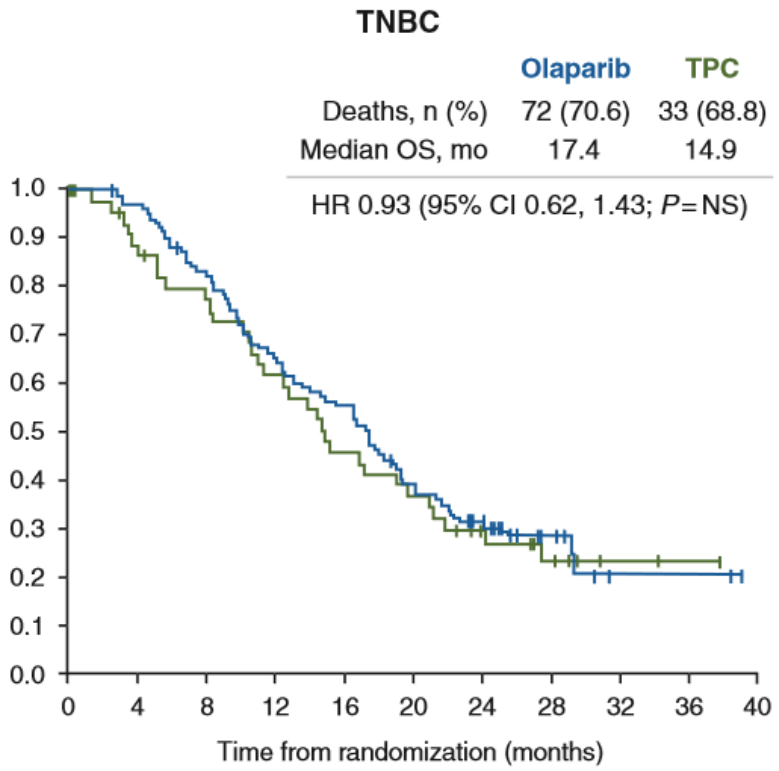
OlympiAD: OS Analysis



Robson. Ann Oncol 2019:30: 558-566.

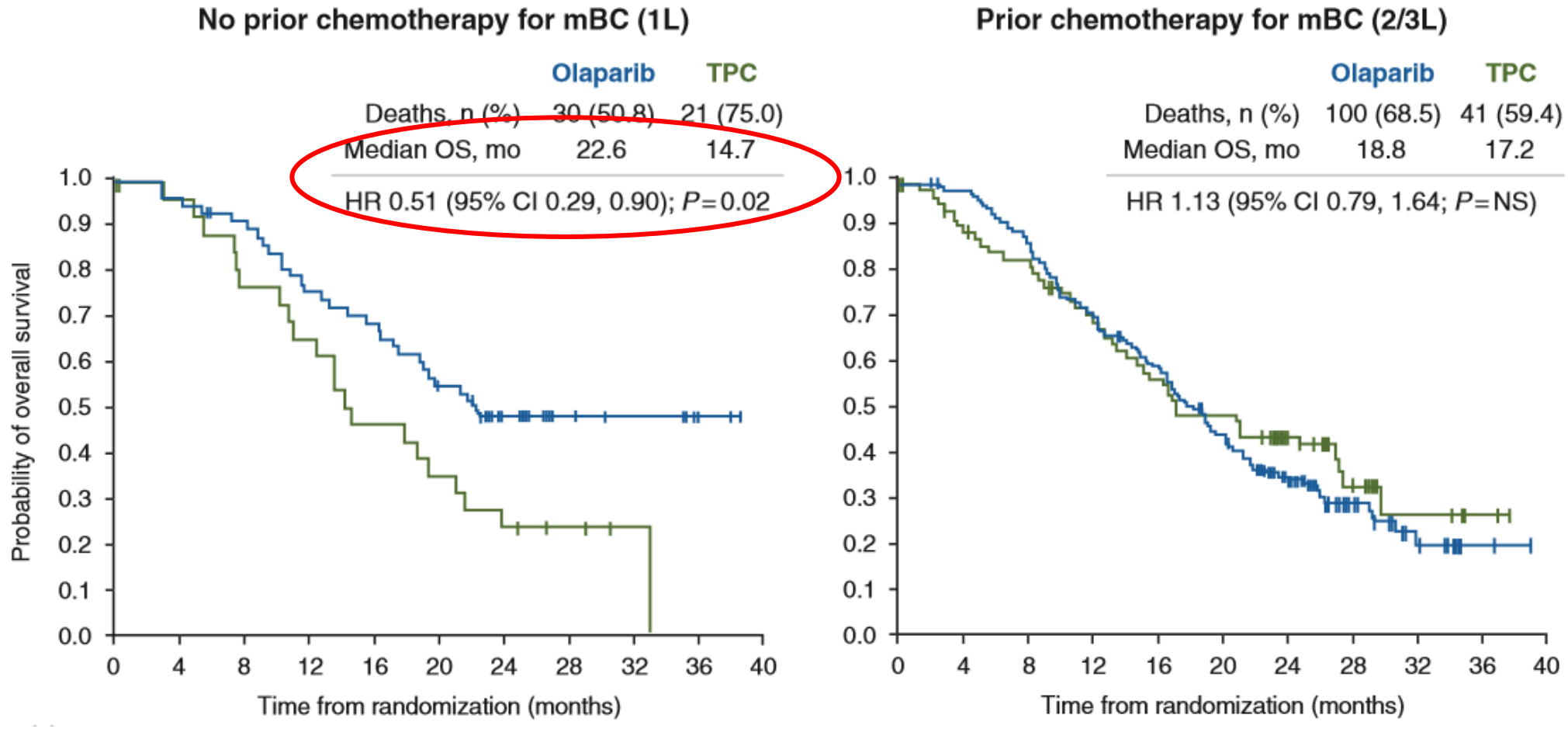
OlympiAD: OS for ER/PR and TNBC





Robson. Ann Oncol 2019:30: 558-566.

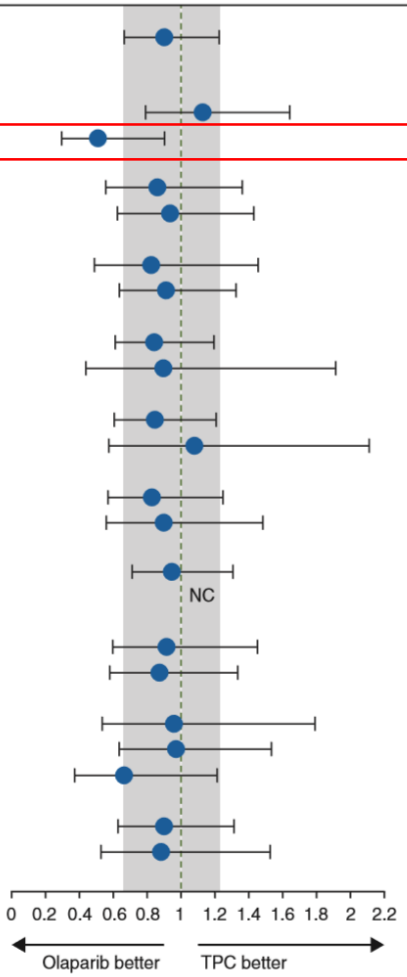
OlympiAD: OS by Prior Chemotherapy With Olaparib vs CT in HER2-Negative MBC With g*BRCA* Mutation



Robson. Ann Oncol 2019:30: 558-566.

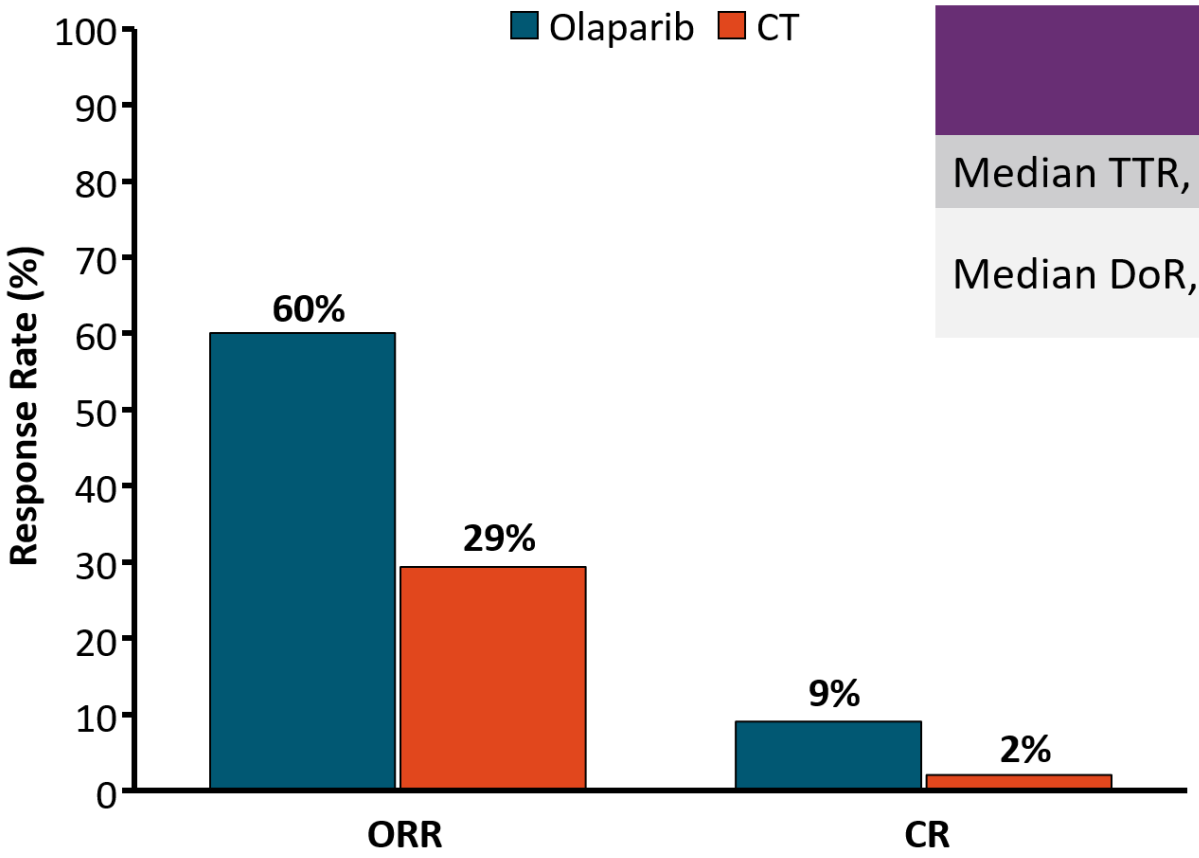
OlympiAD: OS Subset Analysis

Subgroup	Olaparib	TPC	HR (95% CI)
	No of patients with events/total no (%)		
All patients	130/205 (63%)	62/97 (64%)	0.90 (0.66, 1.23)
Received previous chemotherapy for metastatic breast cancer			
Yes (2nd-/3rd-line)	100/146 (69%)	41/69 (59%)	1.13 (0.79, 1.64)
No (1st-line)	30/59 (51%)	21/28 (75%)	0.51 (0.29, 0.90)
Receptor status			
ER and/or PgR positive	58/103 (56%)	29/49 (59%)	0.86 (0.55, 1.36)
ER and PgR negative	72/102 (71%)	33/48 (69%)	0.93 (0.62, 1.43)
Prior platinum for BC			
Yes	42/60 (70%)	19/26 (73%)	0.83 (0.49, 1.45)
No	88/145 (61%)	43/71 (61%)	0.91 (0.64, 1.33)
Measurable vs non measurable disease			
Measurable	112/165 (68%)	50/72 (69%)	0.85 (0.61, 1.19)
Non-measurable	18/40 (45%)	12/25 (48%)	0.90 (0.44, 1.91)
Progressive disease at randomization			
Yes	102/159 (64%)	48/73 (66%)	0.85 (0.61, 1.20)
No	28/46 (61%)	14/24 (58%)	1.08 (0.58, 2.11)
BRCA mutation type			
BRCA1	78/114 (68%)	37/50 (74%)	0.83 (0.57, 1.25)
BRCA2	47/84 (56%)	25/45 (56%)	0.90 (0.56, 1.48)
Age, years			
<65	126/194 (65%)	59/93 (63%)	0.95 (0.70, 1.31)
≥65	4/11 (36%)	3/4 (75%)	NC
Age, years			
< median 44	64/99 (65%)	28/39 (72%)	0.92 (0.60, 1.46)
≥ median 44	66/106 (62%)	34/58 (59%)	0.87 (0.58, 1.34)
Region			
Asia	33/59 (56%)	16/28 (57%)	0.96 (0.54, 1.79)
Europe	63/97 (65%)	29/45 (64%)	0.97 (0.63, 1.53)
North and South America	34/49 (69%)	17/24 (71%)	0.66 (0.38, 1.21)
Race			
White	89/134 (66%)	41/63 (65%)	0.90 (0.63, 1.32)
Other	41/71 (58%)	21/34 (62%)	0.89 (0.53, 1.53)



Robson. Ann Oncol 2019:30: 558-566.

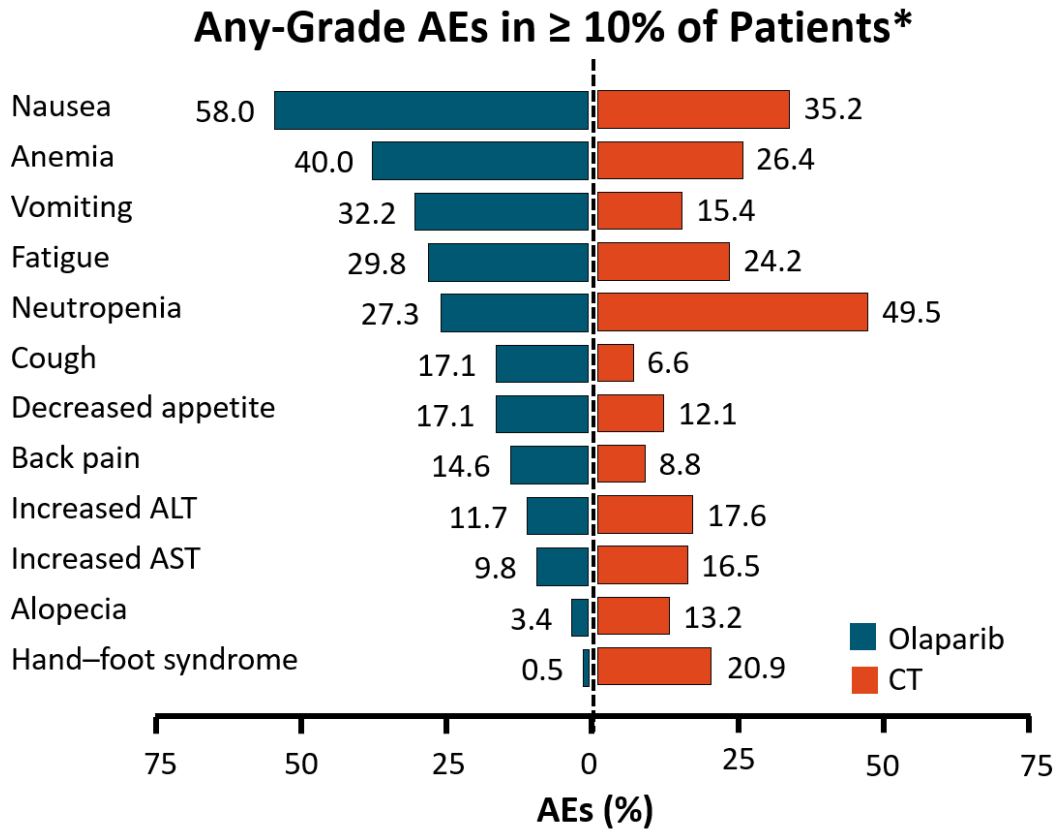
OlympiAD: Overall Response

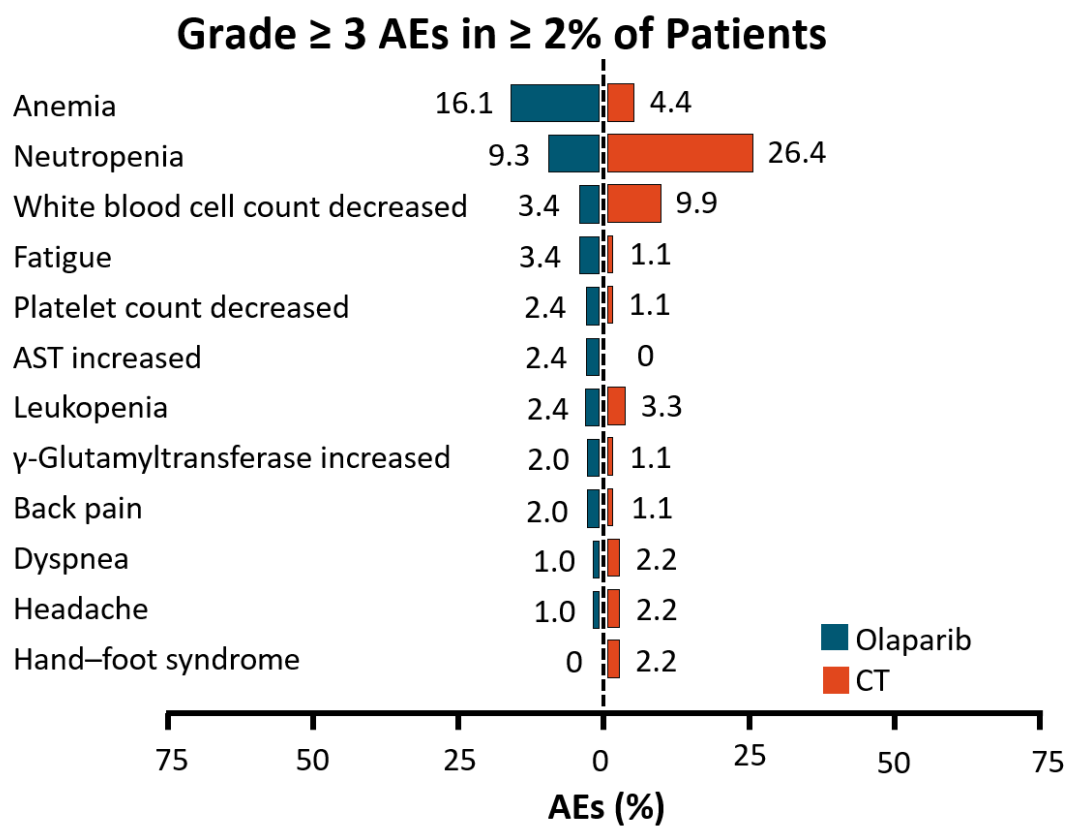


	Olaparib (n = 167)	CT (n = 66)
Median TTR, days	47	45
Median DoR, mos (IQR)	6.4 (2.8-9.7)	7.1 (3.2-12.2)

Robson. NEJM. 2017;377:523.

OlympiAD: Adverse Events

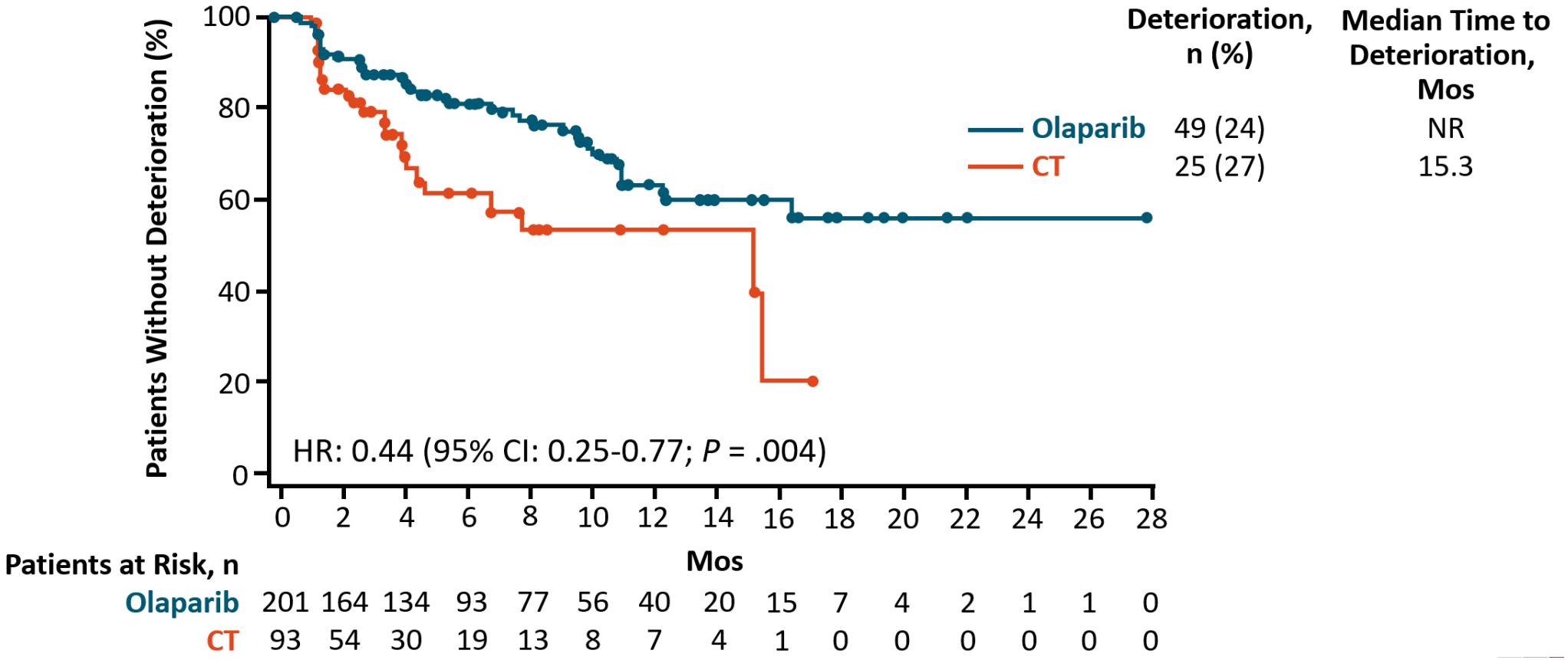




*AEs with ≥ 5% difference in frequency between arms.

Robson. AACR 2018. Abstr CT038.

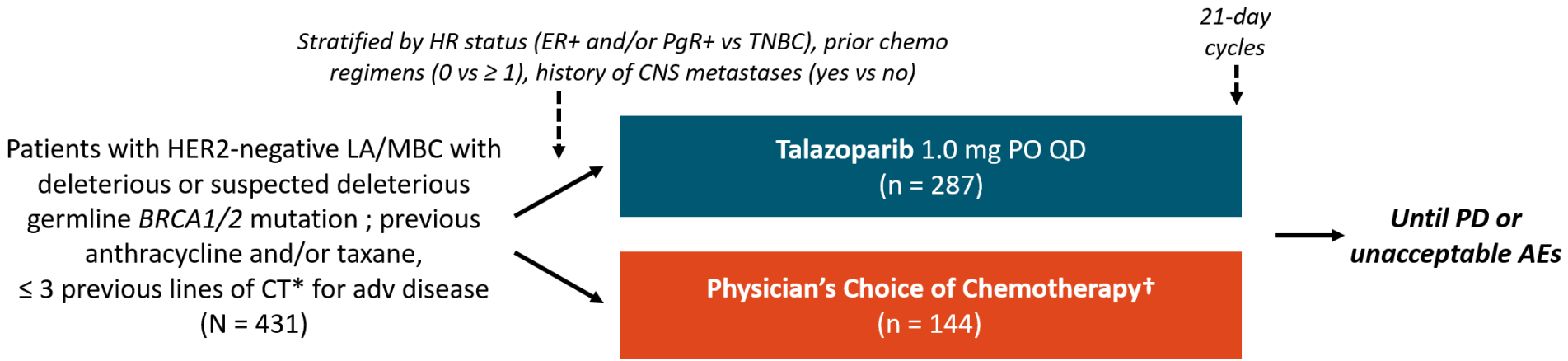
OlympiAD: Time to Deterioration of Global HRQoL



Robson. ESMO 2017. Abstr 290P. Robson. NEJM. 2017;377:523.

EMBRACA: Talazoparib vs Chemotherapy in Advanced *BRCA1/2*-Positive, HER2-Negative Breast Cancer

- Randomized, open-label phase III study conducted at 145 sites in 16 countries



*Previous platinum-based therapy for EBC permitted if DFI ≥ 6 mos
†Physician's choice of: capecitabine 1250 mg/m^2 PO BID Days 1-14; eribulin 1.4 mg/m^2 IV Days 1, 8; gemcitabine 1250 mg/m^2 IV Days 1, 8; or vinorelbine 30 mg/m^2 IV Days 1, 8, and 15.

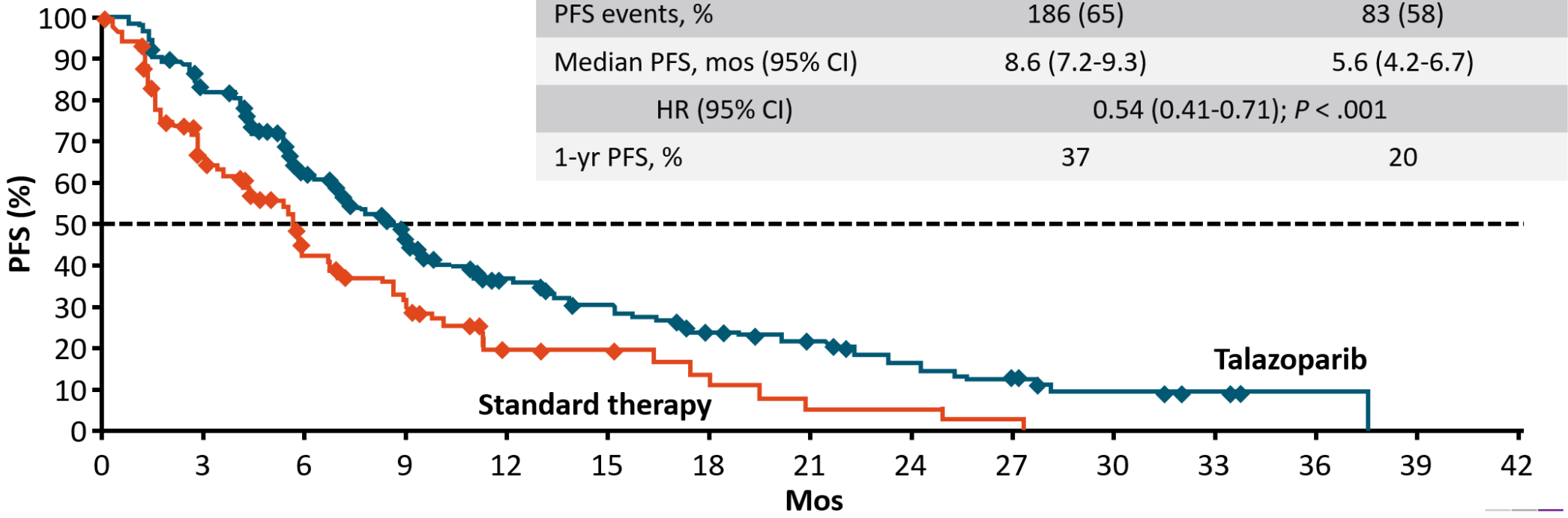
- Primary endpoint: PFS by BICR
- Secondary endpoints: ORR, OS, safety,
- Investigational endpoints: DoR, QoL

Litton. NEJM. 2018;379:753.

EMBRACA: PFS (Primary Endpoint)

- Median follow-up time: 11.2 mos

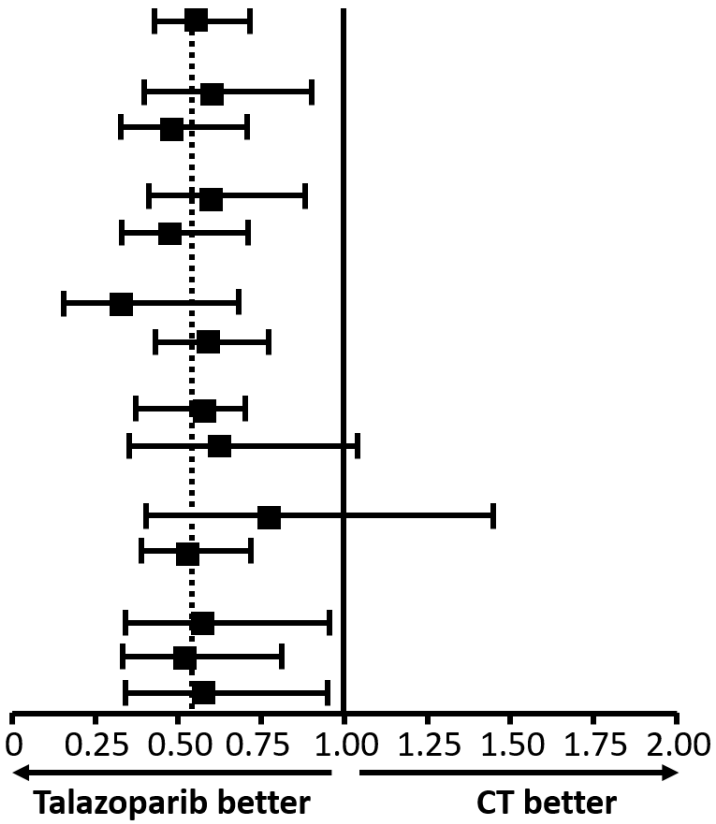
PFS Outcome	Talazoparib (n = 287)	Standard CT (n = 144)
PFS events, %	186 (65)	83 (58)
Median PFS, mos (95% CI)	8.6 (7.2-9.3)	5.6 (4.2-6.7)
HR (95% CI)	0.54 (0.41-0.71); *P* < .001	
1-yr PFS, %	37	20



Litton. NEJM. 2018;379:753.

EMBRACA: PFS by Patient Subgroup

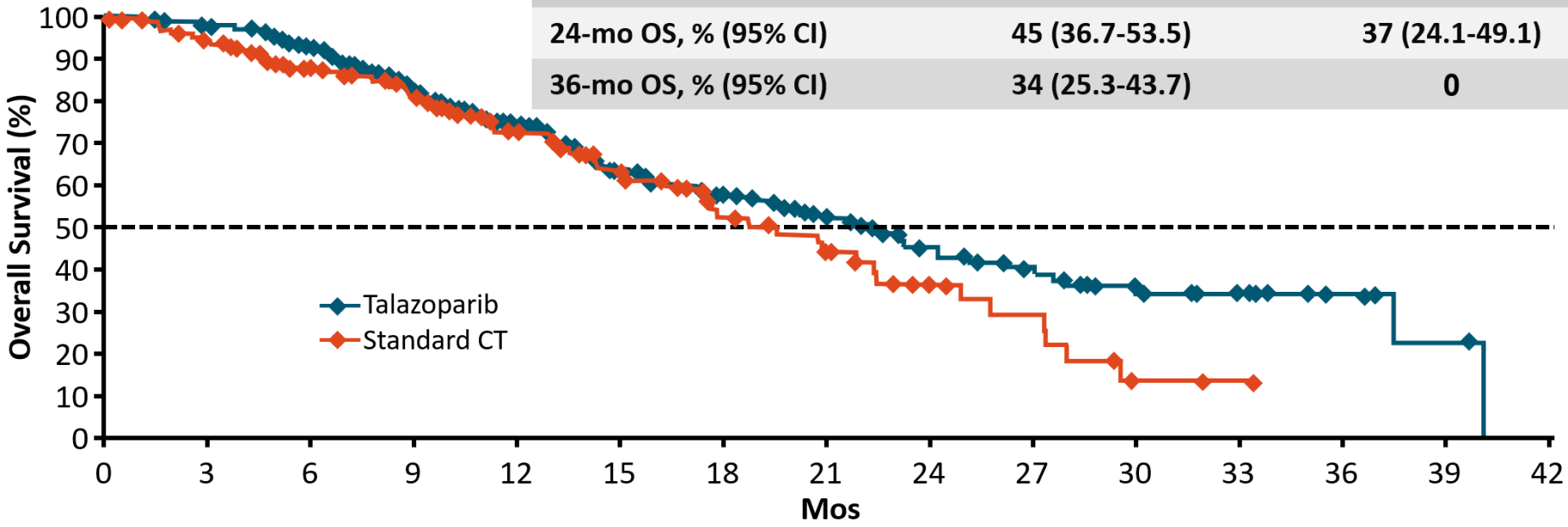
Subgroup	No. of Patients (%)	HR for Disease Progression or Death (95% CI)
All patients	431 (100)	0.54 (0.41-0.71)
BRCA1 mutation type, according to central testing		
BRCA1	183 (42.5)	0.59 (0.39-0.90)
BRCA2	225 (52.2)	0.47 (0.32-0.70)
Hormone receptor status according to most recent biopsy		
Triple-negative breast cancer	190 (44.1)	0.60 (0.41-0.87)
Hormone receptor positive	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)
Visceral disease assessed by investigator		
Yes	303 (70.3)	0.51 (0.37-0.70)
No	128 (29.7)	0.59 (0.34-1.02)
Previous platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Previous regimens of cytotoxic chemotherapy for advanced breast cancer		
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. NEJM. 2018;379:753.

EMBRACA: OS Analysis

OS Outcome	Talazoparib (n = 287)	Standard CT (n = 144)
OS events, n (%)	108 (38)	55 (38)
Median OS, mos (95% CI)	22.3 (18.1-26.2)	19.5 (16.3-22.4)
HR (95% CI)	**0.76** (0.54-1.06); ***P* = .105**	
24-mo OS, % (95% CI)	45 (36.7-53.5)	37 (24.1-49.1)
36-mo OS, % (95% CI)	34 (25.3-43.7)	0



Litton. NEJM. 2018;379:753.

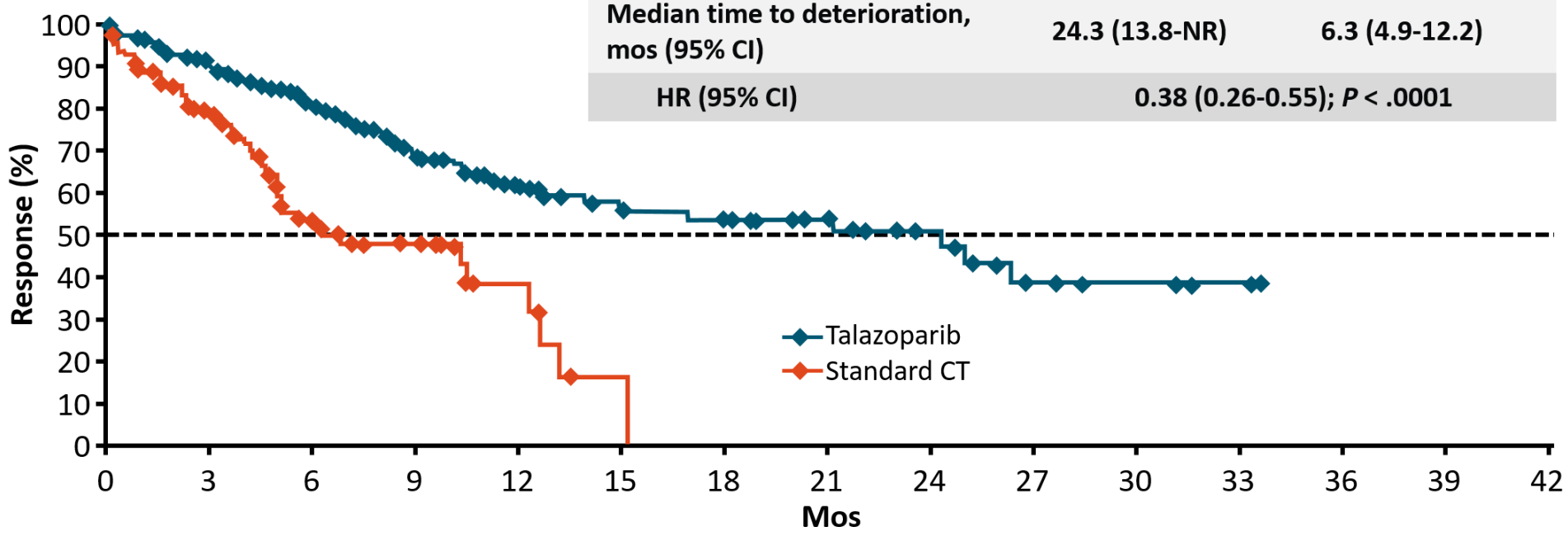
EMBRACA: Adverse Events

Adverse Event, n (%)	Talazoparib (n = 286)		Standard CT (n = 126)	
	Any	Grade 3/4	Any	Grade 3/4
Hematologic	**194 (67.8)**	**157 (54.9)**	**63 (50.0)**	**48 (38.1)**
Anemia	151 (52.8)	112 (39.2)	23 (18.3)	6 (4.8)
Neutropenia	99 (34.6)	60 (21.0)	54 (42.9)	44 (34.9)
Thrombocytopenia	77 (26.9)	42 (14.7)	9 (7.1)	2 (1.6)
Leukopenia	49 (17.1)	19 (6.6)	17 (13.5)	11 (8.7)
Nonhematologic	**282 (98.6)**	**91 (31.8)**	**123 (97.6)**	**48 (38.1)**
Fatigue	144 (50.3)	5 (1.7)	54 (42.9)	4 (3.2)
Nausea	139 (48.6)	1 (0.3)	59 (46.8)	2 (1.6)
Headache	93 (32.5)	5 (1.7)	28 (22.2)	1 (0.8)
Vomiting	71 (24.8)	7 (2.4)	29 (23.0)	2 (1.6)
Diarrhea	63 (22.0)	2 (0.7)	33 (26.2)	7 (5.6)
Back pain	60 (21.0)	7 (2.4)	20 (15.9)	2 (1.6)
PPE	4 (1.4)	5 (1.7)	28 (22.2)	3 (2.4)

Litton. NEJM. 2018;379:753.

EMBRACA: Time to Deterioration of Global HRQoL

HRQoL Outcome	Talazoparib (n = 287)	Standard CT (n = 144)
QoL events, n (%)	76 (29.0)	48 (42.1)
Median time to deterioration, mos (95% CI)	24.3 (13.8-NR)	6.3 (4.9-12.2)
HR (95% CI)	0.38 (0.26-0.55); *P* < .0001	



Ettl. Ann Oncol. 2018;29:1939.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b]

HER2-Negative

Preferred regimens

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors (options for patients with HER2-negative tumors and germline *BRCA1/2* mutation)[d]
  - Olaparib[d] (category 1)
  - Talazoparib[d] (category 1)
- Platinum (option for patients with triple-negative tumors and germline *BRCA1/2* mutation)[d]
  - Carboplatin
  - Cisplatin
- Atezolizumab + albumin-bound paclitaxel (option for patients with PD-L1-positive TNBC)[e]

Other recommended regimens[c]

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

Useful in certain circumstances[c]

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[f]

HER2-Positive[g]

Preferred regimens

- Pertuzumab + trastuzumab + docetaxel (category 1)[h]
- Pertuzumab + trastuzumab + paclitaxel[g]

Other recommended regimens:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel[h] ± carboplatin
- Trastuzumab + docetaxel[h]
- Trastuzumab + vinorelbine[h]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[h,i,j]

Future Directions of PARP Inhibitors in Management Of Breast Cancer

- Early stage breast cancer
  - Neoadjuvant (MDACC, NEOTALA, PARTNER)
  - Adjuvant (OlimpiaA)
- Combination therapy
  - With chemotherapy (BROCADE3)
  - With checkpoint inhibitors (TOPACIO, MEDIOLA)
  - With other agents
- Expanding beyond germline *BRCA* mutation (LUCY, RUBY)

Neoadjuvant PARP Inhibitor Trials in Breast Cancer

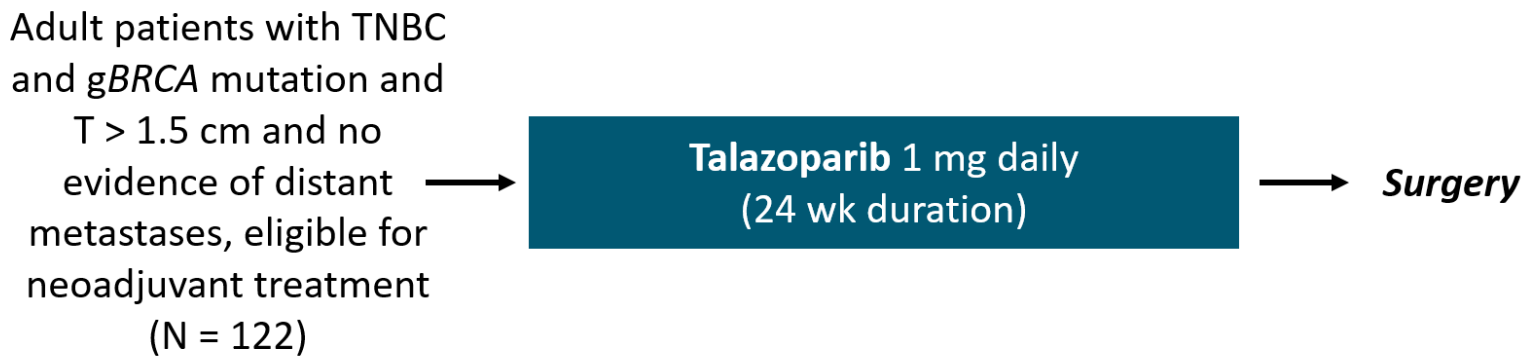
PARP Inhibitor (Dose)	Trial	Patient Population	Treatment Arms	Sample Size, n	Results
Veliparib (50 mg BID)[1]	I-SPY 2 (phase II)*	Stage II-III TNBC	▪ Veliparib + Q3 IV carboplatin (AUC dose = 6) + QW IV 80 mg/m^2 paclitaxel ▪ QW IV 80 mg/m^2 paclitaxel	39 21	pCR: 51% pCR: 26%
Veliparib (50 mg BID)[2]	BrighTNess (phase III)*	Stage II-III TNBC (15% *gBRCA* +)	▪ Veliparib + Q3 IV carboplatin (AUC dose = 6) + QW IV 80 mg/m^2 paclitaxel ▪ Placebo + Q3 IV carboplatin (AUC dose = 6) + QW IV 80 mg/m^2 paclitaxel ▪ QW IV 80 mg/m^2 paclitaxel	316 160 158	pCR: 53% pCR: 58% pCR: 31%
Talazoparib (1 mg daily)[3]	MDACC (pilot)	Stage I-III *gBRCA* + (69% TNBC)	Talazoparib x 2 mos followed by standard NAC	13	88% decrease in tumor volume pCR: 54% after NAC
Talazoparib (1 mg daily)[4]	MDACC (pilot phase II)	Stage I-III *gBRCA* + (74% TNBC)	Talazoparib x 6 mos followed by surgery (adjuvant therapy as per physician's choice)	19†	pCR: 53% RCB 0+I: 63% (pCR in pts with lobular, metaplastic and IBC)

*All patients in I-SPY2 and BrighTNess additionally received doxorubicin and cyclophosphamide every 2-3 wks for 4 cycles before surgery.
†20 patients enrolled; 19 completed study.

1. Rugo. NEJM. 2016;375:23. 2. Loibl. Lancet Oncol. 2018;19:497. 3. Litton. NPJ BC. 2017;3:49. 4. Litton. ASCO 2018. Abstr 508.

Talazoparib as Neoadjuvant Treatment for g*BRCA* Mutation-Positive Early TNBC (NEOTALA)

- Open-label, multicenter phase II study

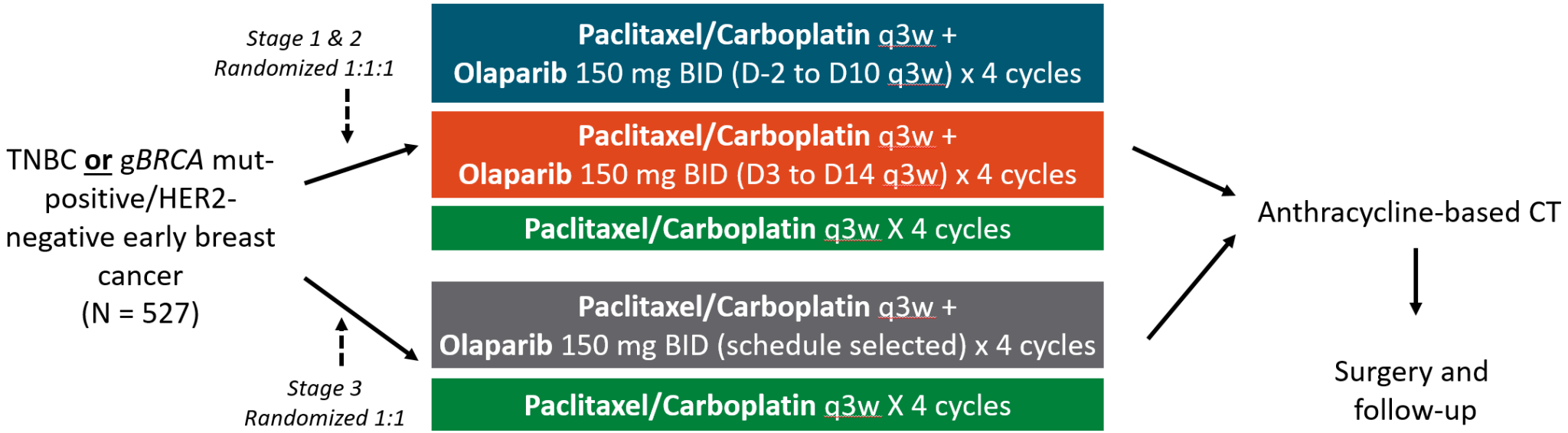


- Primary endpoint: pCR by independent central review
- Secondary endpoints: pCR by investigator, RCB, pCR in breast by independent reviewer, EFS, OS, safety, PROs, pharmacokinetics

NCT03499353.

Neoadjuvant Platinum-based CT + Olaparib in TNBC and/or g*BRCA* Mutation–Positive EBC (PARTNER)

- Open-label, randomized, 3-stage phase II/III study

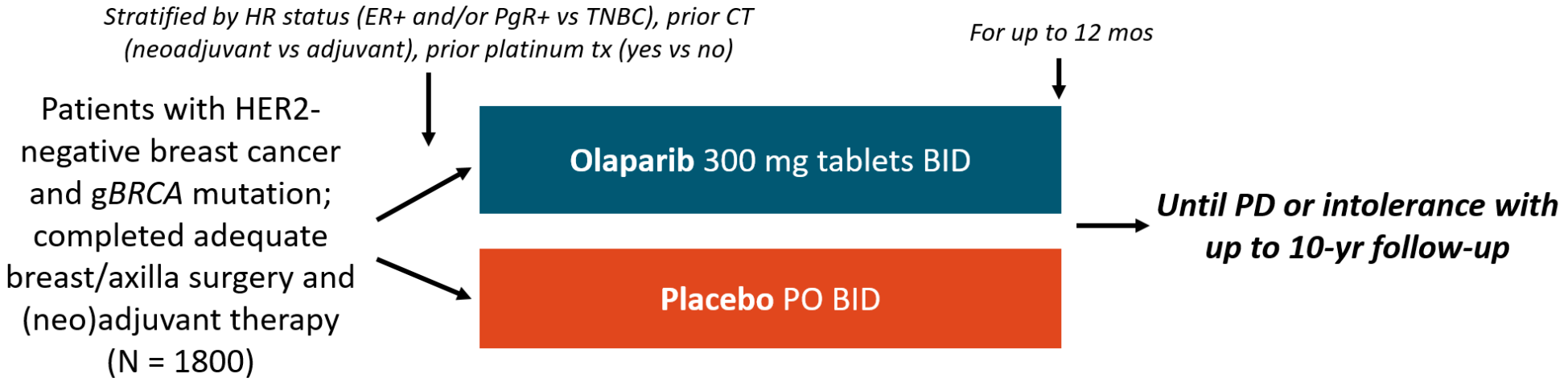


- Stage 1 primary endpoint: safety
- Stage2 primary endpoint: pCR and completion rate of olaparib
- Stage 3 primary endpoint: pCR by central review

NCT03150576.

Olaparib vs Placebo as Adjuvant Therapy in HER2-/g*BRCA* Mutation-Positive EBC (OlympiA)

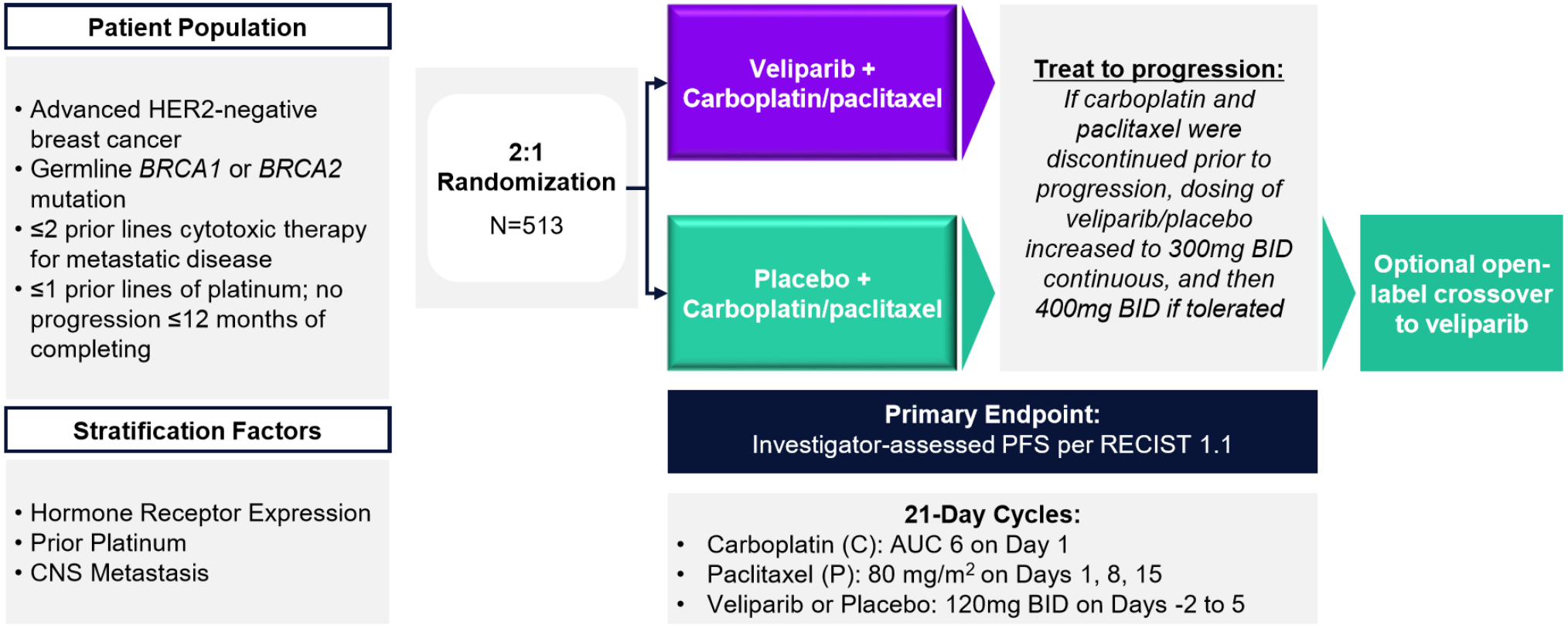
- Randomized, double-blind, placebo-controlled, multicenter phase III study



- Primary endpoint: invasive DFS
- Secondary endpoints: distant DFS, OS, safety, QoL
- Fully accrued: results expected in 2020

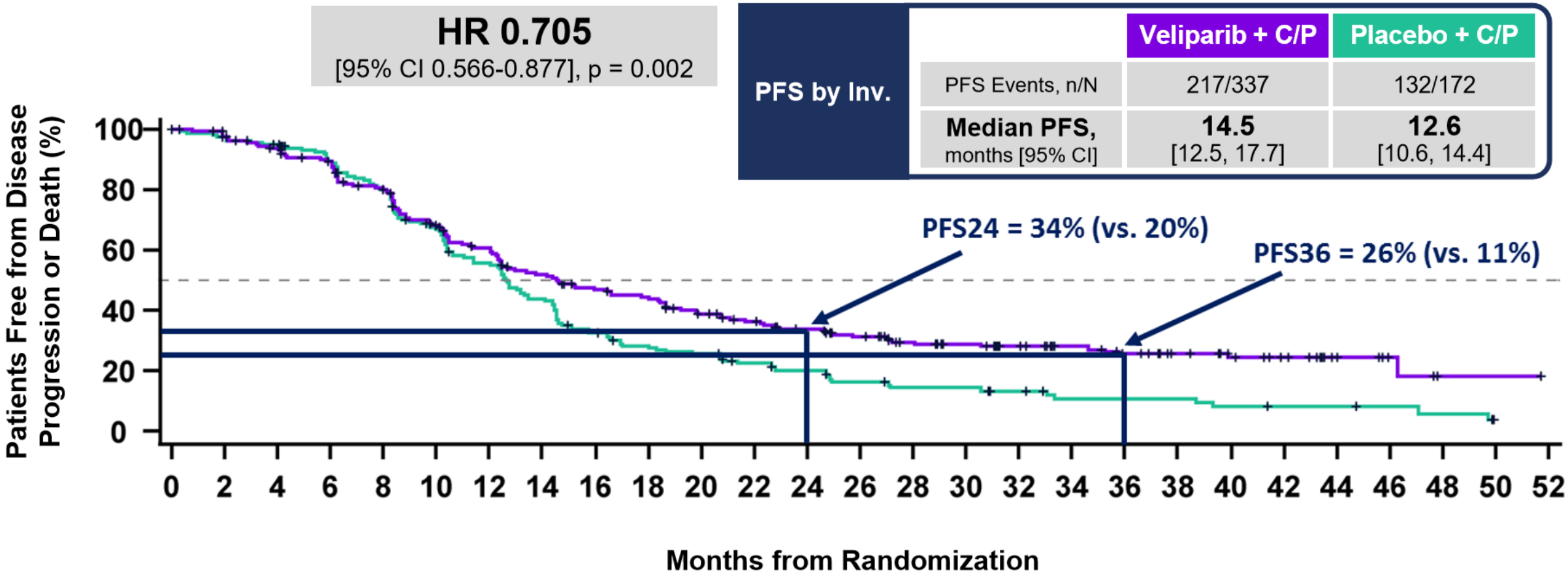
NCT02032823.

Carboplatin/Paclitaxel ± Veliparib in HER2-Negative Metastatic/Locally Adv *BRCA*-Associated BC (BROCADE-3)



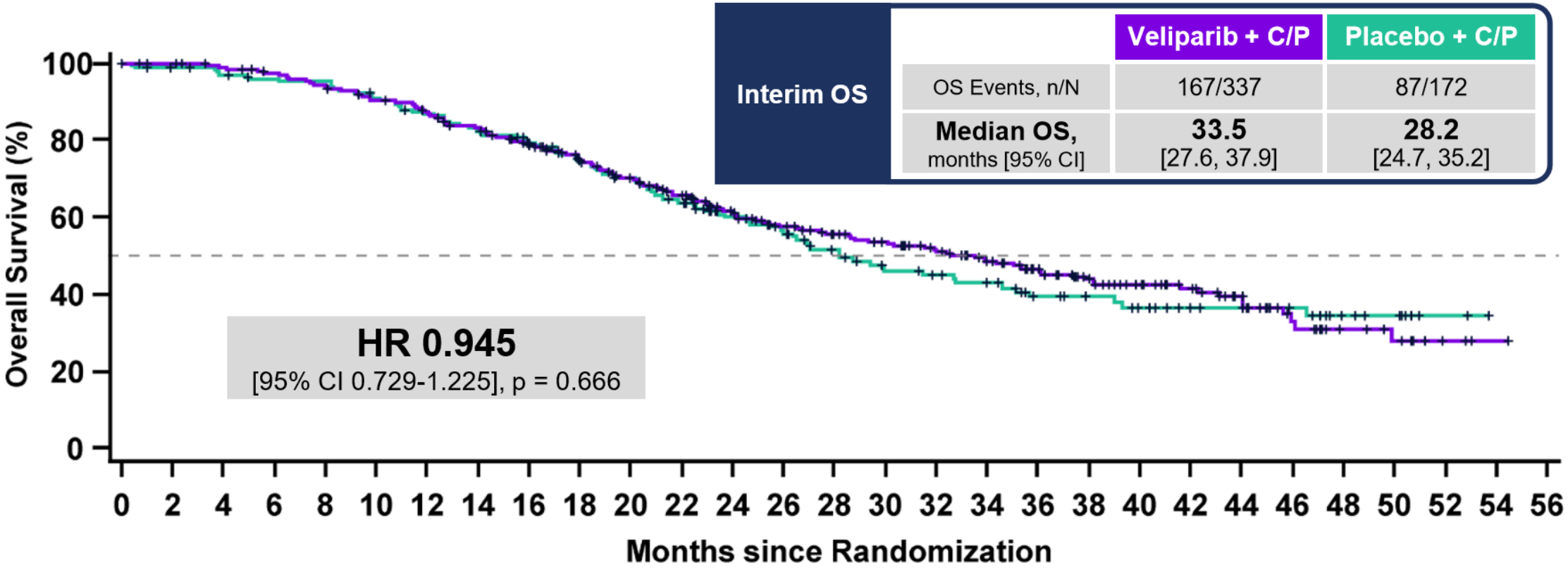
Dieras V. Presented at ESMO 2019.

BROCADE-3: PFS (Primary Endpoint)



Dieras V. Presented at ESMO 2019.

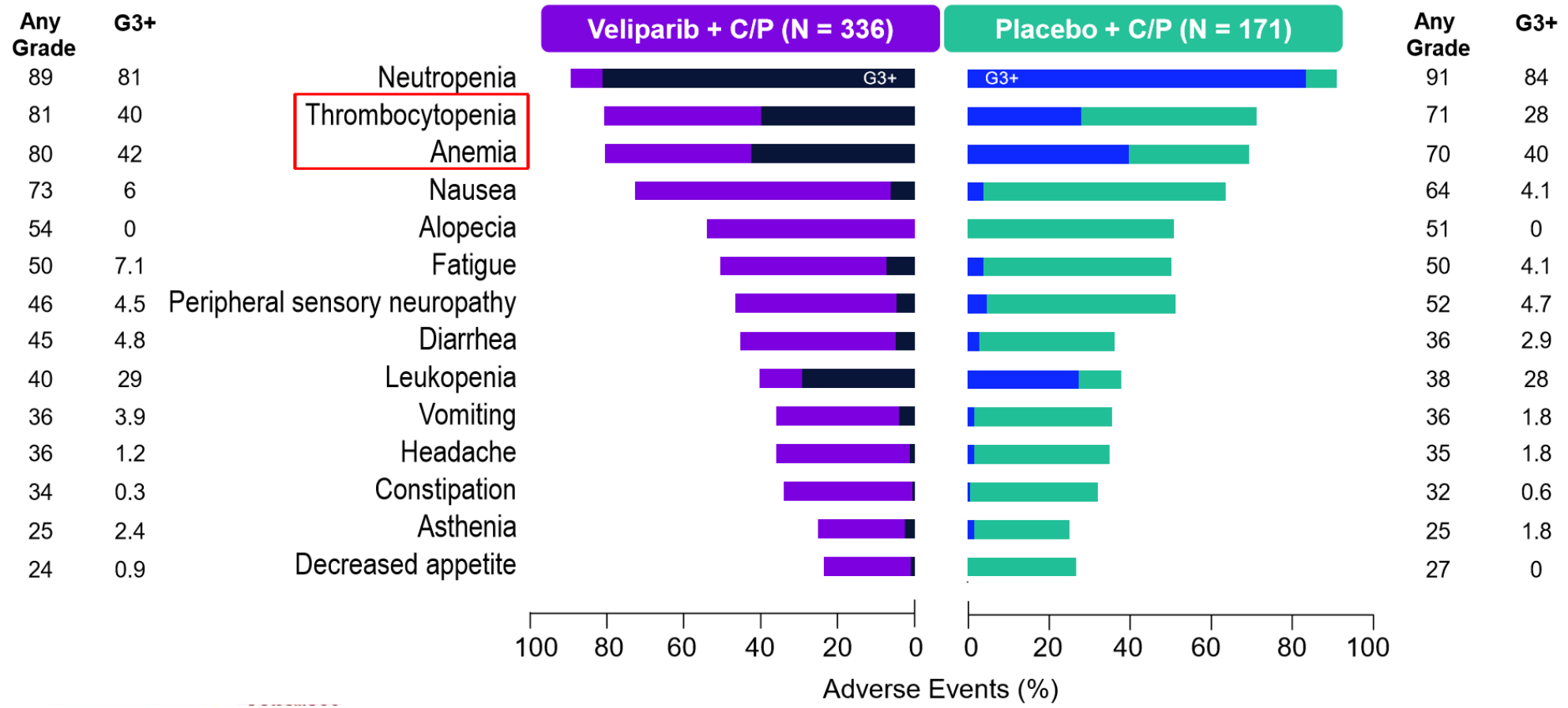
BROCADE-3: OS (Interim Analysis)



Crossover: 44% of ITT subjects randomized to placebo + C/P elected open-label veliparib as 1st subsequent therapy

Dieras V. Presented at ESMO 2019.

BROCADE-3: Adverse events

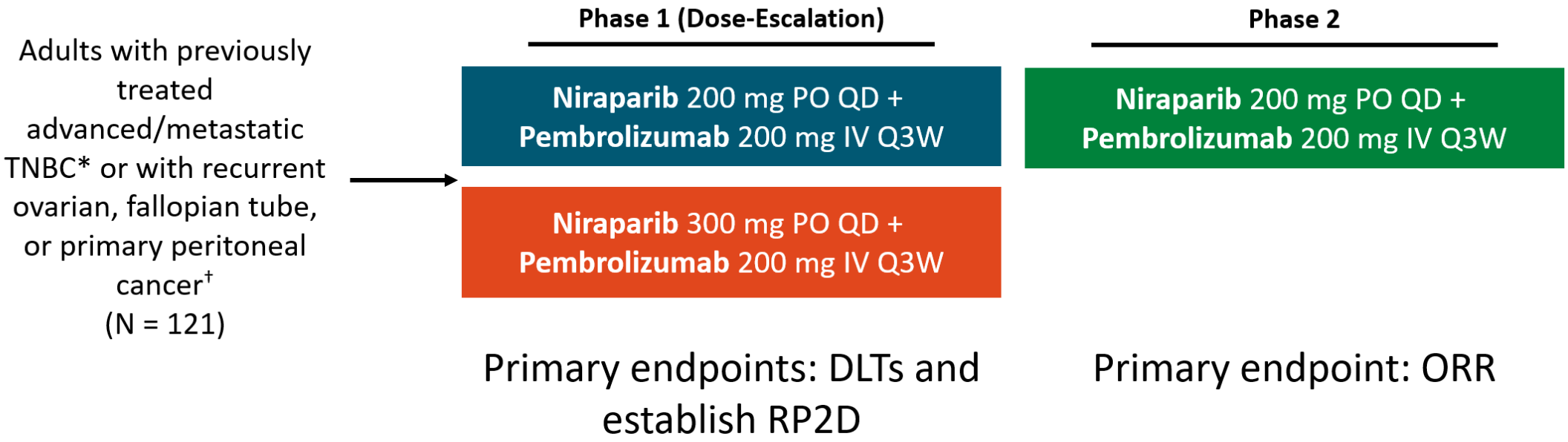


Dieras V. Presented at ESMO 2019.

Ongoing clinical trials evaluating PARPi in combination with Immune checkpoint inhibitors in HER2 negative BC.

Clinicaltrials.gov identifier	Phase	Treatment	Tumor type	Outcome measures
NCT03167619	II	Olaparib + Durvalumab (anti-PD-L1)	Metastatic TNBC	PFS
NCT03544125	I	Olaparib + Durvalumab	Metastatic TNBC	Proportion of completion of clinical laboratory improvement amendments analytics, Safety, ORR, CBR, DOR
NCT02484404	I/II	Olaparib and/or Cediranib + Durvalumab (anti-PD-L1)	Advanced solid tumors and advanced or recurrent ovarian, TNBC, lung, prostate and colorectal cancers	Phase I: RP2D, safety Phase-II: ORR
NCT02734004	I/II	Olaparib + Durvalumab (anti-PD-L1)	Advanced or metastatic solid tumors (ovarian, breast, SCLC, gastric cancer)	DCR, safety and tolerability
NCT02657889	I/II	Niraparib + Pembrolizumab (anti-PD-1)	Advanced or metastatic TNBC or recurrent ovarian cancer	Phase I: RP2D, DLTs Phase-II: ORR
NCT02849496	II	Veliparib + Atezolizumab (anti-PD-L1)	TNBC (stage III/IV)	PFS

Niraparib + Pembrolizumab in Platinum-Resistant OC and Advanced TNBC (TOPACIO)



*Up to 4 prior lines of CT in phase 1 or ≤ 2 prior lines of CT in phase 2; previous platinum agent allowed if no progression on or within 8 wks of last treatment.

†Up to 5 prior lines of CT in phase 1 or ≤ 4 prior lines of CT in phase 2.

Vinayak. ASCO 2018. Abstr 1101.

TOPACIO: Best Overall Tumor Responses in Patients With Advanced TNBC

Best Overall Response	Study Population	
	Full Analysis (N = 55)	Efficacy Evaluable (n = 47)
Complete response, No. (%)	5 (9)	5 (11)
Partial response, No. (%)	5 (9)	5 (11)
Stable disease, No. (%)	13 (24)	13 (28)
Progressive disease, No. (%)	24 (44)	24 (51)
Not performed or not evaluable, No. (%)	8 (15)	NA
ORR, No. (%) [90% CI][a]	10 (18) [10-29]	10 (21) [12-33]
DCR, No. (%) [90% CI][b]	23 (42) [31-54]	23 (49) [36-62]

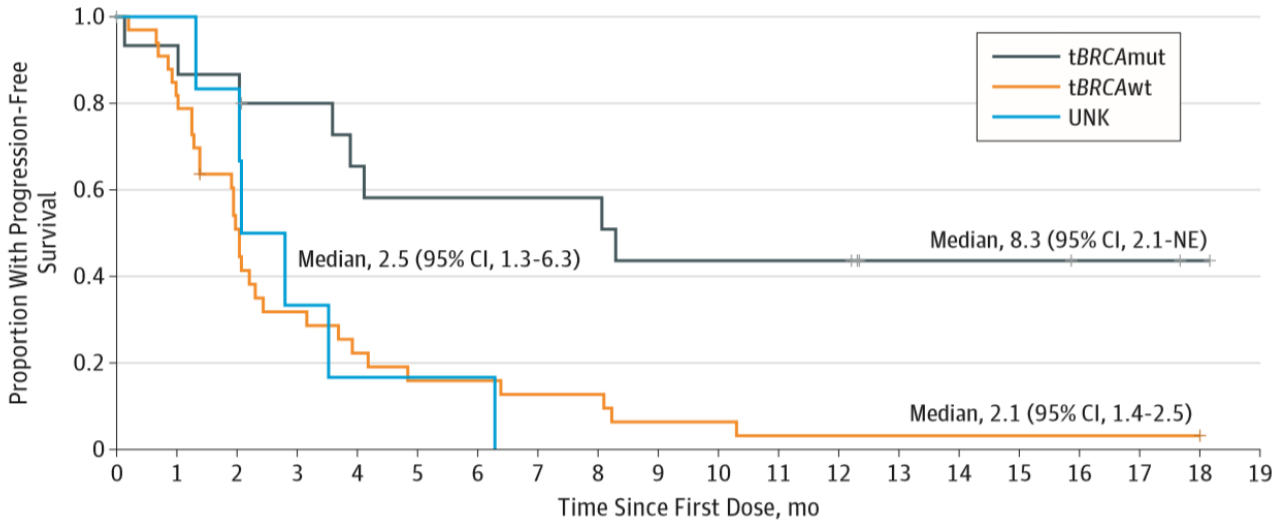
Abbreviations: DCR, disease control rate; NA, not applicable; ORR, objective response rate.

[a] Includes complete and partial responses.

[b] Includes complete and partial responses and stable disease.

Vinayak S. JAMA Oncology August 2019. 5: 1332-1140.

TOPACIO: Response Rates in Biomarker-Defined, Efficacy-Evaluable Population



Biomarker Status	No.	ORR, No. (%) [90% CI]	DCR, No. (%) [90% CI]
BRCA			
t*BRCA*mut	15	7 (47) [24-70]	12 (80) [56-94]
t*BRCA*wt	27	3 (11) [3-26]	9 (33) [19-51]
t*BRCA* unknown	5	0 (0) [0-45]	2 (40) [8-81]
HRR[a]			
HRRmut	20	8 (40) [22-61]	16 (80) [60-93]
HRRwt	22	2 (9) [2-26]	6 (27) [13-47]
HRR unknown	5	0 (0) [0-45]	1 (20) [1-66]
PD-L1			
Positive	28	9 (32) [18-49]	14 (50) [33-67]
Negative	13	1 (8) [0.4-32]	6 (46) [22-71]
Unknown	6	0 (0) [0-39]	3 (50) [15-85]

Vinayak S. JAMA Oncology August 2019. 5: 1332-1140.

TOPACIO: Adverse Events

Adverse Event	No. (%) of Patients by Adverse Event	
	Any Grade (N = 55)	Grade ≥3 (N = 55)
Any treatment-related	51 (93)	32 (58)
Treatment-related occurring in >10% of patients		
Nausea	30 (55)	0
Fatigue	24 (44)	4 (7)
Anemia	19 (35)	10 (18)
Thrombocytopenia	14 (25)	8 (15)
Constipation	13 (24)	0
Diarrhea	10 (18)	0
Decreased appetite	9 (16)	0
Vomiting	8 (15)	0
Prespecified treatment-related and immune-related		
Any	8 (15)	2 (4)
Adrenal insufficiency	1 (2)	1 (2)
Hyperglycemia	1 (2)	0
Hyperthyroidism	1 (2)	0
Hypothyroidism	4 (7)	0
Pneumonitis	1 (2)	0
Polymyalgia rheumatica	1 (2)	1 (2)

Vinayak S. JAMA Oncology August 2019. 5: 1332-1140.

Combination Therapy: PARP Inhibition Plus Other Targeted Agents

Inhibitor Class	Trial	Pt Population	N (planned)	Treatment Arms	Primary Endpoint
VEGFR	Phase I/II (NCT01116648)	Previously treated TNBC or platinum-sensitive high-grade ovarian cancer	162	Olaparib + Cediranib vs Olaparib	DLT, MTD, PFS
PI3K	Phase I (NCT01623349)	Previously treated TNBC or high-grade serous ovarian cancer	118	Olaparib + Buparlisib or Olaparib + Alpelisib	MTD, RP2D

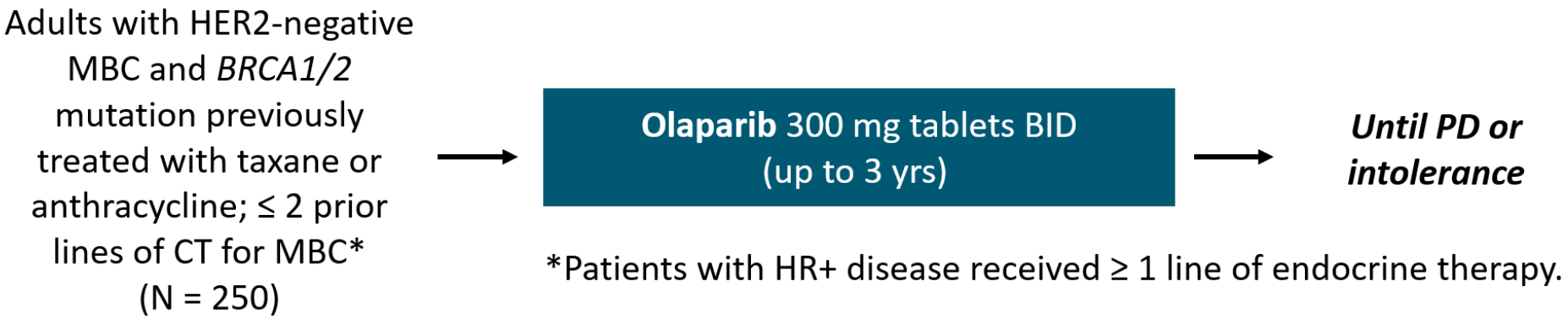
Ongoing clinical trials evaluating PARPi in combination with targeted agents in HER2 negative BC

PARP inhibitor	Phase	Study population/ tumor type	Treatment	NCT
Olaparib	I/II	Recurrent ovarian, fallopian tube, peritoneal or TNBC patients with gBRCA mutation	Olaparib+ Cediranib Maleate	NCT01116648
Olaparib	II	Metastatic or unresectable solid tumors (TNBC, NSCLC, SCLC and pancreatic adenocarcinoma)	Olaparib+ Cediranib Maleate	NCT02498613
Fluzoparib	I	Recurrent ovarian or TNBC patients and subjects with deleterious BRCA mutation	Fluzoparib + Apatanib	NCT03075462
Olaparib	I	Recurrent TNBC or HGSOC	Olaparib + PI3K inhibitor (BKM 120 or BYL719)	NCT01623349
Olaparib	I/II	Recurrent endometrial, TNBC, and ovarian, primary peritoneal, or fallopian tube cancer	Olaparib + mTORC1/2 inhibitor (AZD2014) & AKT inhibitor (AZD5363)	NCT02208375
Olaparib	I	Metastatic, unresectable or recurrent solid tumors (ovarian, fallopian tube, or primary peritoneal and TNBC)	Olaparib + Onalespib (HSP90 inhibitor)	NCT02898207

Liu JF. Ann Oncol. 2019 Apr 1;30(4):551-557.

Olaparib for HER2-Negative MBC With Deleterious Germline or Somatic *BRCA*1/2 Mutations (LUCY)

- Open-label, phase IIIb multicenter study

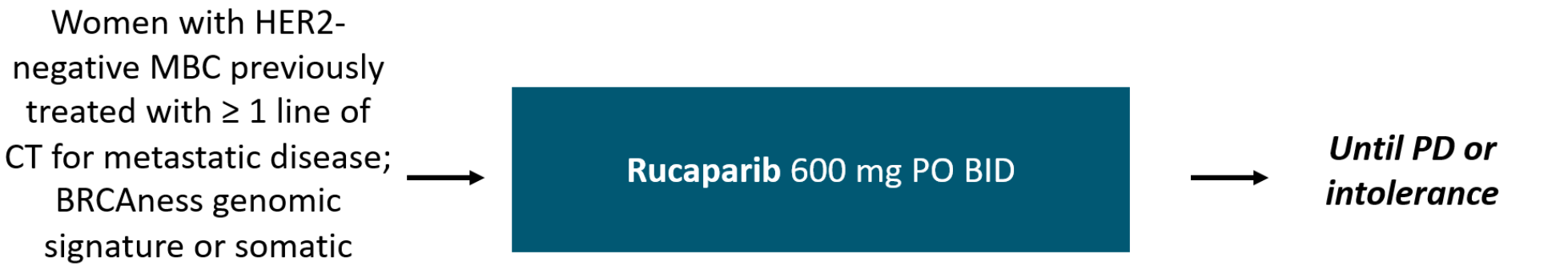


- Primary endpoint: PFS (real-world setting)
- Key secondary endpoints: time to first subsequent treatment or death, time to second subsequent treatment or death, time to second progression or death, OS, time to study treatment discontinuation or death, clinical response rate, duration of clinical response

NCT03286842. Gelmon. ESMO 2018. Abstr 367TiP.

Rucaparib in MBC Patients With BRCAness Genomic Signature (RUBY)

- Open-label, phase II multicenter study



*Patients with known germline *BRCA* mutations are excluded.

- Primary endpoint: CBR (response or stable disease) lasting for ≥ 16 wks
- Secondary endpoints: response, PFS, OS, safety

NCT02505048.

Ongoing clinical trials evaluating PARPi in combination with chemo-and radio-therapy in HER2 negative BC

PARP inhibitor	Phase	Study population/ tumor type	Treatment	NCT
Olaparib	II/III	TNBC and/or gBRCA BC	Olaparib + paclitaxel + carboplatin	NCT03150576
Olaparib	I	TNBC and advanced ovarian cancer	Olaparib + paclitaxel + carboplatin	NCT00516724
Olaparib	I	Advanced HER2 negative BRCA1/2 mutated BC	Olaparib+carboplatin followed by Olaparib monotherapy vs Capecitabine	NCT02418624
Olaparib	I	Inflammatory, loco-regionally advanced or metastatic TNBC or patient with operated TNBC with residual disease	Olaparib+ radiation therapy	NCT03109080
Olparib	I	Locally Advanced Malignant Neoplasm, Inflammatory BC, TNBC	Olaparib+ radiation therapy	NCT02227082
Veliparib	III	Metastatic HER2 negative or locally advanced unresectable BRCA-associated BC	Veliparib+ carboplatin+ paclitaxel	NCT02163694
Veliparib	I	BC	Veliparib+radiation therapy	NCT01618357
Rucaparib	II	Patients with invasive TNBC or ER/PR+, HER2 negative with known BRCA1/2 mutations	Rucaparib+ cisplatin	NCT01074970

Conclusions

- PARP inhibitors Olaparib and Talazoparib are approved for metastatic germline *BRCA*-mutated, HER2-negative breast cancer.

    - Olaparib and Talazoparib have meaningful clinical benefit with overall less toxicity and improved QOL compared to standard single agent chemotherapy

    - Patients without prior exposure to chemotherapy in metastatic setting have the highest benefit.

- Clinical trials using PARP inhibitors in neoadjuvant and adjuvant setting, as well as combination with chemotherapy, targeted agents and immune checkpoint inhibitors are ongoing.

Thank you

Summary of completed trials with PARPi, mono and combination therapy

Clinicaltrials.gov identifier	Phase	Treatment	Tumor type	Outcome measures
NCT02000622	III	Olaparib vs chemotherapy (capacitabine, eribulin or vinorelbine)	HER2- BC	Median PFS: 7.0 vs 4.2 months Response rate: 59.9% vs 28.8%
NCT00494234	II	Olaparib: 400mg bid vs 100 mg bid	Advanced BC with BRCA1 or BRCA2 mutations	ORR: 41% vs 22% Median PFS: 5.7 months vs 3.8 months
NCT01078662	II	Olaparib	Ovarian, breast, pancreatic and prostate cancers	ORR: 31.1%, 13% 21.7% and 50.0%
NCT01945775	III	Talazoparib vs Chemotherapy	Advanced or HER2- BC with BRCA1 or 2 mutations	PFS: 8.6 months vs 5.6 months ORR: 62.6% vs 27.2% Median DoR: 5.4 Vs 3.2 months
NCT01042379	II	Veliparib-carboplatin vs standard therapy alone	TNBC	Pathological complete response rate: 51% vs 26%
NCT01149083	I/II	Veliparib vs veliparib with carboplatin	Metastatic BC with BRCA1/2 mutations	PFS: 8.7 vs 18.8 months
NCT01506609	II	Veliparib to temozolomide or carboplatin/paclitaxel Vs carboplatin/paclitaxel with placebo	Metastatic BC with BRCA1/2 mutations	PFS: 14.1 vs 12.3 months OS: 28.3 Vs 25.9 months ORR: 77.8% vs 61.3%
NCT02484404	I/II	Durvalumab plus olaparib or cediranib	Women's cancer	Disease control rate: 83% vs 75%

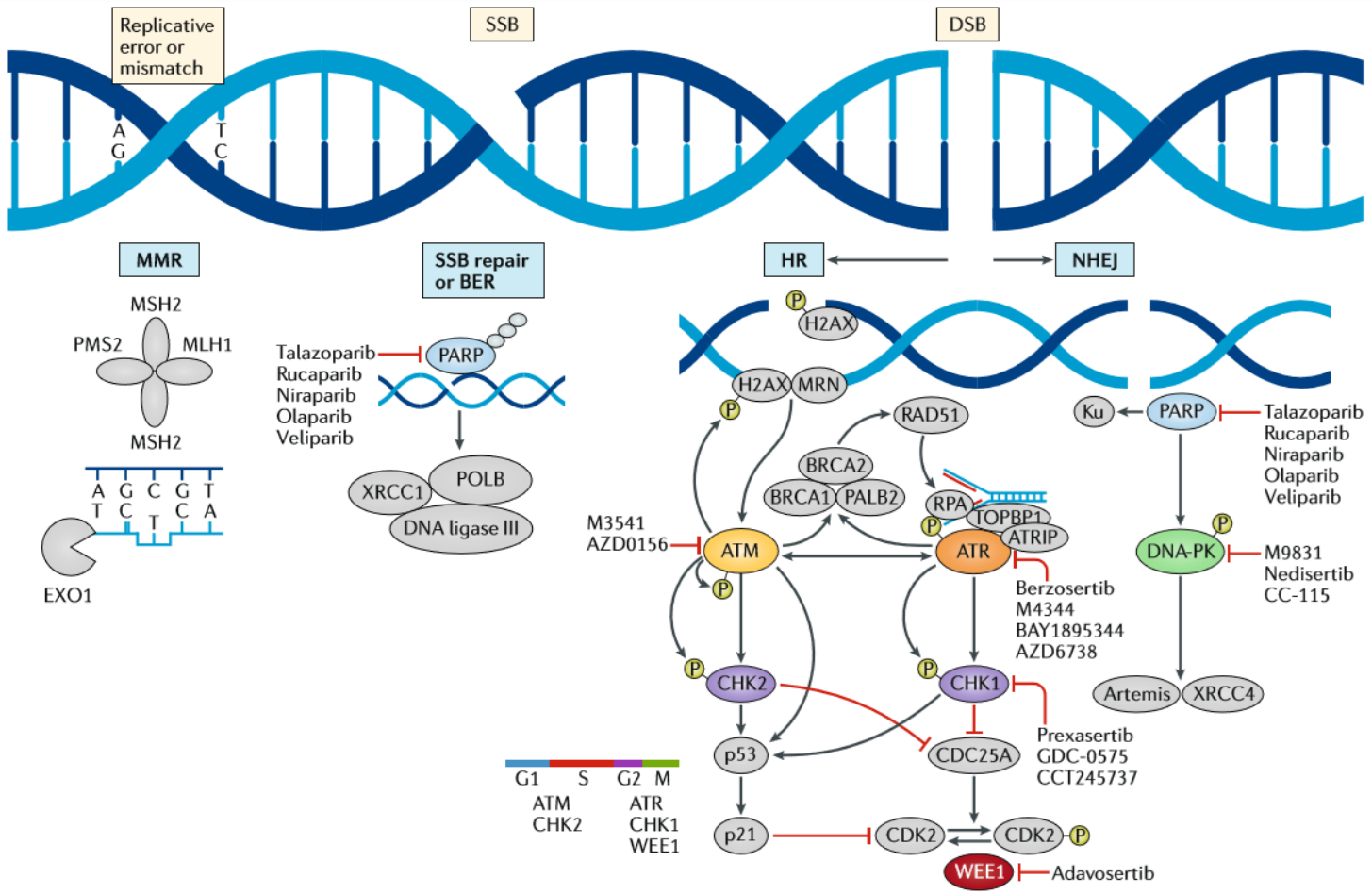
BRE09–146 trial: Rucaparib

- N=135
- Randomized patients with TNBC with residual disease after NACT to Cisplatin or Cisplatin and Rucaparib.
- 2-year DFS was 67% for the combination and 60% for Cisplatin alone, not statistically significant

Early PARP Inhibitor Trials in Breast Cancer

Study	Treatment	N	*BRCA1/2* Mutation Status	TNBC, %	Response
Fong[1]	Olaparib (phase I; multiple tumor types)	60	*BRCA1/2*: 37%	N/A	CBR: 63% (in 19 patients with *BRCA*-associated cancers)
ICEBERG 1[2]	Olaparib 400 mg PO BID	27	*BRCA1/2: 67%/33%*	50	41%
Isakoff[3]	Veliparib + temozolomide	41	*BRCA1/2: 7.3%/12.0%*	56	*BRCA1/2*: 37.5% **WT *BRCA*: 0%**
Kaufman[4]	Olaparib 400 mg PO BID	62	*BRCA1/2: 60%/40%*	48	**Tumor response: 12.9%**
Gelmon[5]	Olaparib 400 MG PO BID	26	TNBC: 16 g*BRCA*: 10	g*BRCA*: 50% WT *BRCA*: 100%	**WT *BRCA*: 0%**

1. Fong. NEJM. 2009;361:123. 2. Tutt. Lancet. 2010;376:235. 3. Isakoff. ASCO 2010. Abstr 1019.
4. Kaufman. JCO. 2015;33:244. 5. Gelmon. Lancet Oncol. 2011;12:852.



- DNA damage response pathways being targeted in the clinic. Specific types of DNA damage — mismatches due to replication, single- strand DNA breaks (SSBs) or double- strand DNA breaks (DSBs) — result in the activation of specific signalling and repair cascades. DNA damage response (DDR) pathways mitigate replication stress and repair DNA ; thus, deficiencies in these pathways result in the accumulation of SSBs and DSBs and increased immunogenicity owing to the generation of neoantigens from mutant proteins. Poly(ADP- ribose) polymerase (PARP) enzymes are key to activating a host of downstream repair mechanisms and are primary proteins involved in SSB repair or base- excision repair (BER). The repair of DSBs occurs predominately through the rapid, error- prone non- homologous end joining (NHEJ) repair pathway in conjunction with the much slower higher- fidelity , error- free homologous recombination (HR) repair pathway. DNA replication is a necessary component of DNA repair and thus cell cycle regulation and replication stress responses are intertwined with DDR pathways. The kinases ATR and ATM have crucial roles in DDR signalling and in maintaining replication fork stability , while also working together via their downstream targets, CHK1 and CHK2, respectively , to regulate cell cycle control checkpoints. The kinase activity of DNA- PK is essential for NHEJ and V(D)J recombination. WEE1 is a distinct nuclear kinase that regulates mitotic entry and nucleotide pools in coordination with DDR . Drugs targeting these key components of the DDR pathways that are undergoing clinical testing are indicated. ATRIP, ATR- interacting protein; EXO1, exonuclease 1; H2AX, histone H2AX; MRN, MRE11, RAD50 and NBS1 complex; POLB, DNA polymerase- β; RPA , replication protein A ; TOPBP1, DNA topoisomerase 2-binding protein.

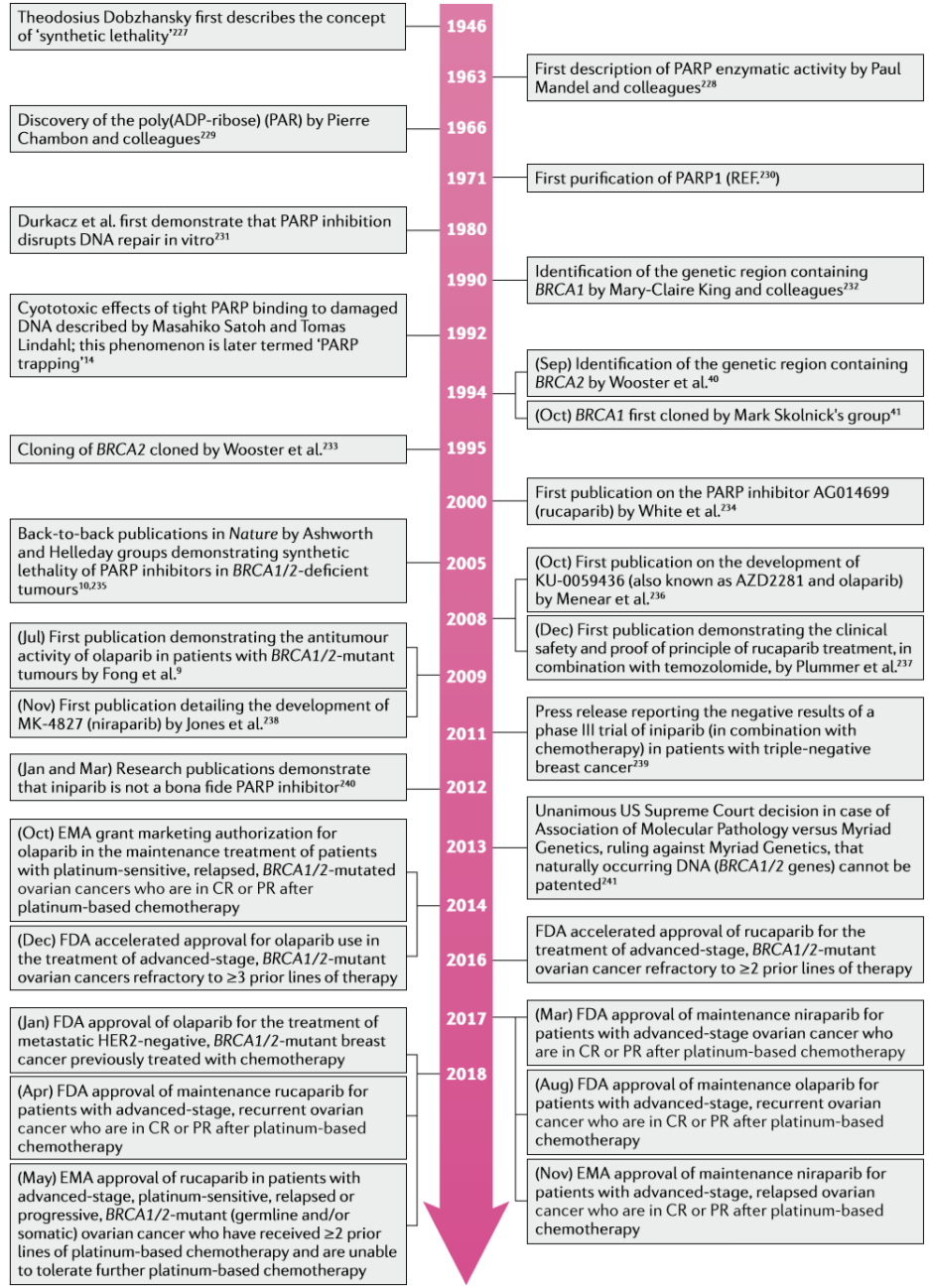
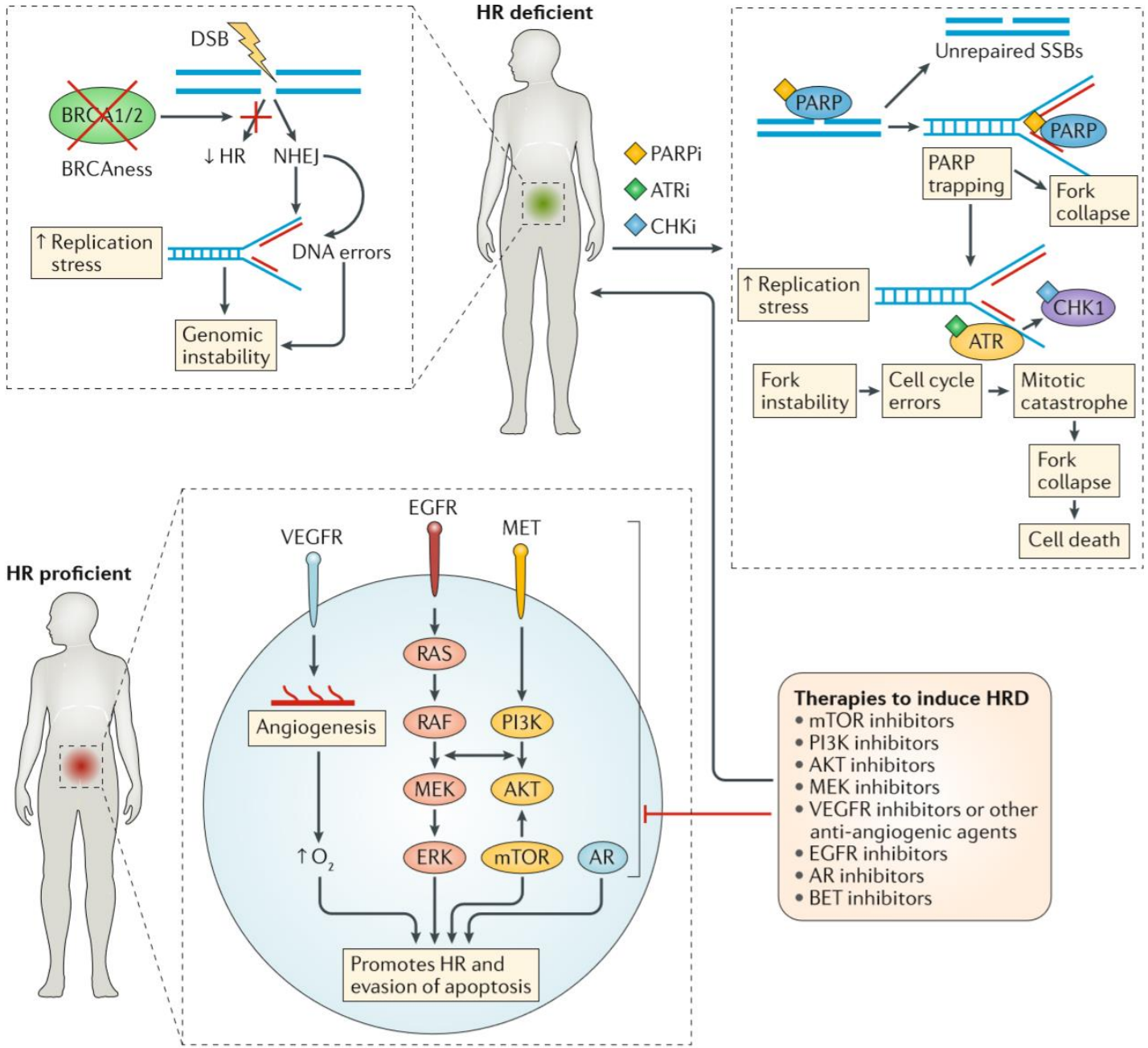


Fig. 2 | **Timeline of key events leading to FDA approvals of PARP inhibitors in cancer medicine.** Landmark discoveries and advances in the development of poly(ADP-ribose) polymerase (PARP) inhibitors are indicated[10,14,40,41,227–235], together with the current approved indications for these agents in the USA and the EU. CR, complete remission; PR, partial remission.


HR deficient
DSB
BRCA1/2
BRCAness
↓ HR
NHEJ
↑ Replication stress
DNA errors
Genomic instability
PARPi
ATRi
CHKi
Unrepaired SSBs
PARP
PARP
PARP trapping
Fork collapse
↑ Replication stress
CHK1
ATR
Fork instability
Cell cycle errors
Mitotic catastrophe
Fork collapse
Cell death
HR proficient
VEGFR
EGFR
MET
RAS
RAF
PI3K
MEK
AKT
ERK
mTOR
AR
Angiogenesis
↑ O_2
Promotes HR and evasion of apoptosis
Therapies to induce HRD
• mTOR inhibitors
• PI3K inhibitors
• AKT inhibitors
• MEK inhibitors
• VEGFR inhibitors or other anti-angiogenic agents
• EGFR inhibitors
• AR inhibitors
• BET inhibitors

PARP Inhibitors: Most Common Grade 3/4 Toxicities

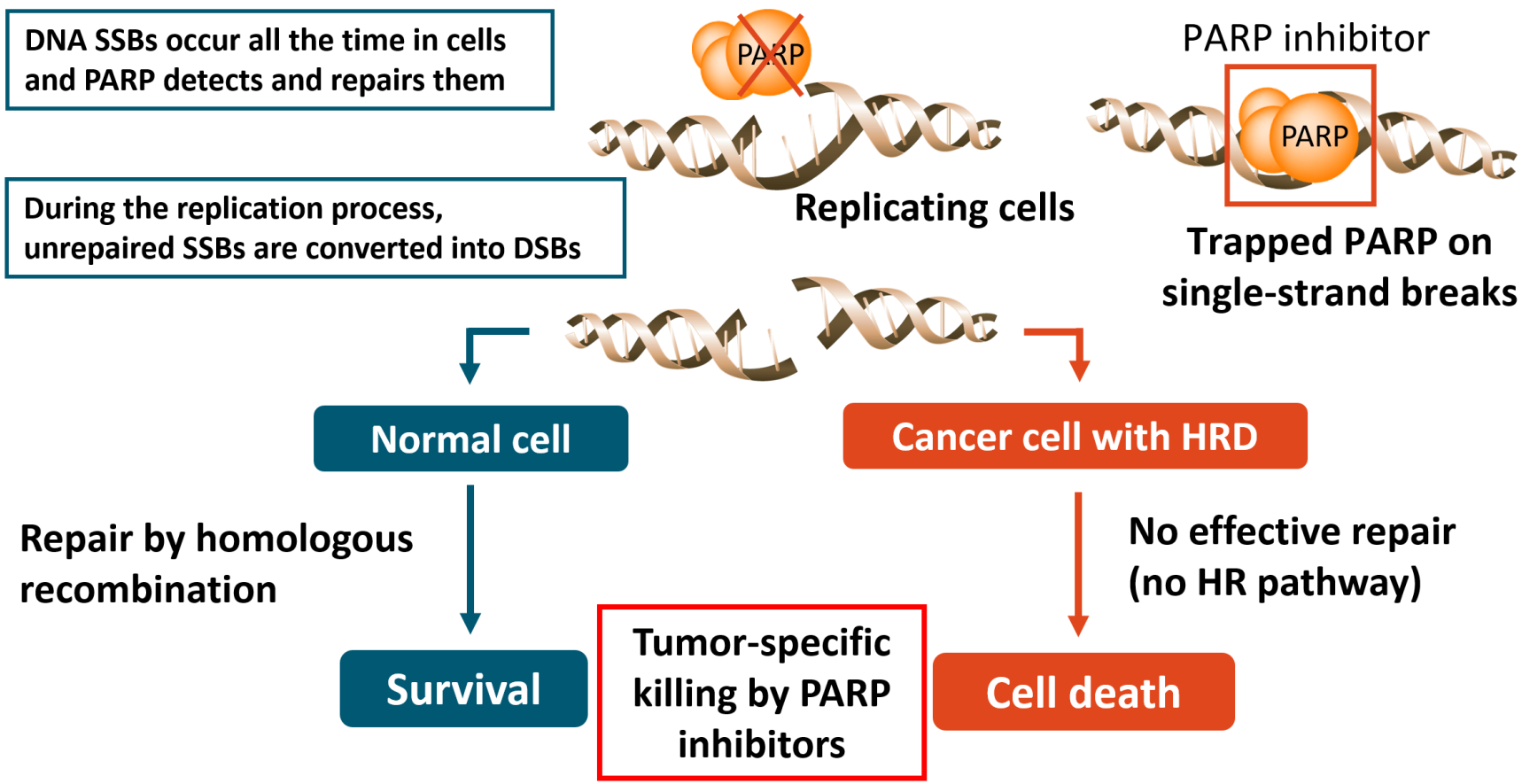
Trial (Agent)	Setting	Thrombocytopenia, %	Anemia, %	Neutropenia, %	HTN, %	Fatigue, %	ALT/AST Increased, %
NOVA (Niraparib)[1]	Maintenance plt-sensitive, recurrent OC	33.8	25.3	19.6	8.2	8.2	NR
EMBRACA (Talazoparib)[2]	g*BRCA* mut MBC	14.7	39.2	20.9	NR	1.7	NR
SOLO-2 (Olaparib)[3]	Maintenance plt sensitive relapsed OC	1	19	5	NR	4	NR
OlympiAD (Olaparib)[4]	g*BRCA* mut MBC	2	16	9	NR	3	2

1. Mirza. NEJM. 2016;375:2154. 2. Litton. NEJM. 2018;379:753. 3. Pujade-Lauraine. Lancet Oncol. 2017;18:1274. 4. Le. Expert Rev Clin Pharmacol. 2018;11:833.

Where are we going next?

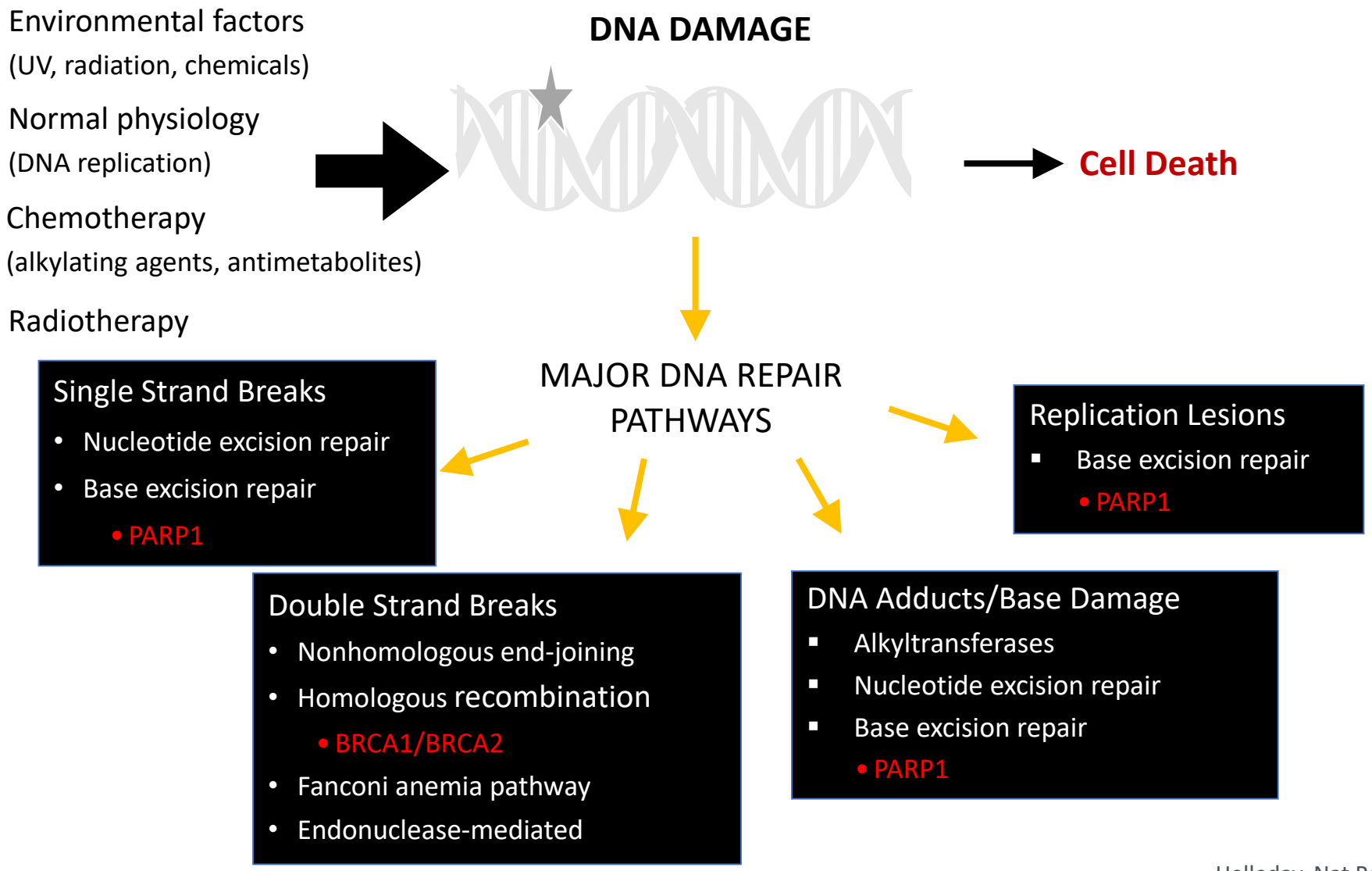
- With PARP inhibitors now approved, there's a lot of interest in expanding the reach of PARP inhibitors outside of patients with germline *BRCA* mutations and also improving the response in patients with *BRCA* mutations. The OLYMPIA adjuvant trial completed accrual this year, so we will be looking for that. There's really intriguing data in the neoadjuvant setting with single-agent talazoparib in patients with germline *BRCA* mutations, and a phase II trial is now going on with high pCR rates with talazoparib alone. OLYMPIA, of course, is looking at adjuvant olaparib in patients with germline *BRCA* mutations, which is a much larger trial. It is really exciting to see that complete accrual now.
- Combining PARP inhibitors with chemotherapy was presented at ESMO this year, showing improvement in PFS in the second progression after randomization with the addition of the fairly less potent PARP inhibitor veliparib to carboplatin and paclitaxel. I think the reason they could add it was because it doesn't cause as much bone marrow toxicity. There was a marked increase in the rate of grade 3 thrombocytopenia with the addition of veliparib, but otherwise, the toxicities were relatively similar. What happens in terms of long-term data will really determine how we use that combination, but what's intriguing to me is the concept of getting an induction with chemotherapy plus or minus a checkpoint inhibitor, then maybe using the PARP inhibitor combined with immunotherapy as maintenance. This is actually similar to what's being done in ovarian cancer, and there are very interesting data from the laboratory suggesting that the combination of PARP inhibitors and checkpoint inhibitors will enhance the efficacy of checkpoint inhibitors. PARP inhibitors increase the immune responsiveness of the tumor microenvironment by a variety of mechanisms, so there are actually a number of studies going on looking at those combinations as well with some early encouraging data.
- There's also a lot interest in PARP inhibitors, as I mentioned, looking at homologous recombination defect type testing to see whether or not that can help determine the benefit of combining a PARP with immunotherapy, but these are all approaches for the future.
-

PARP Inhibitor and Homologous Recombination



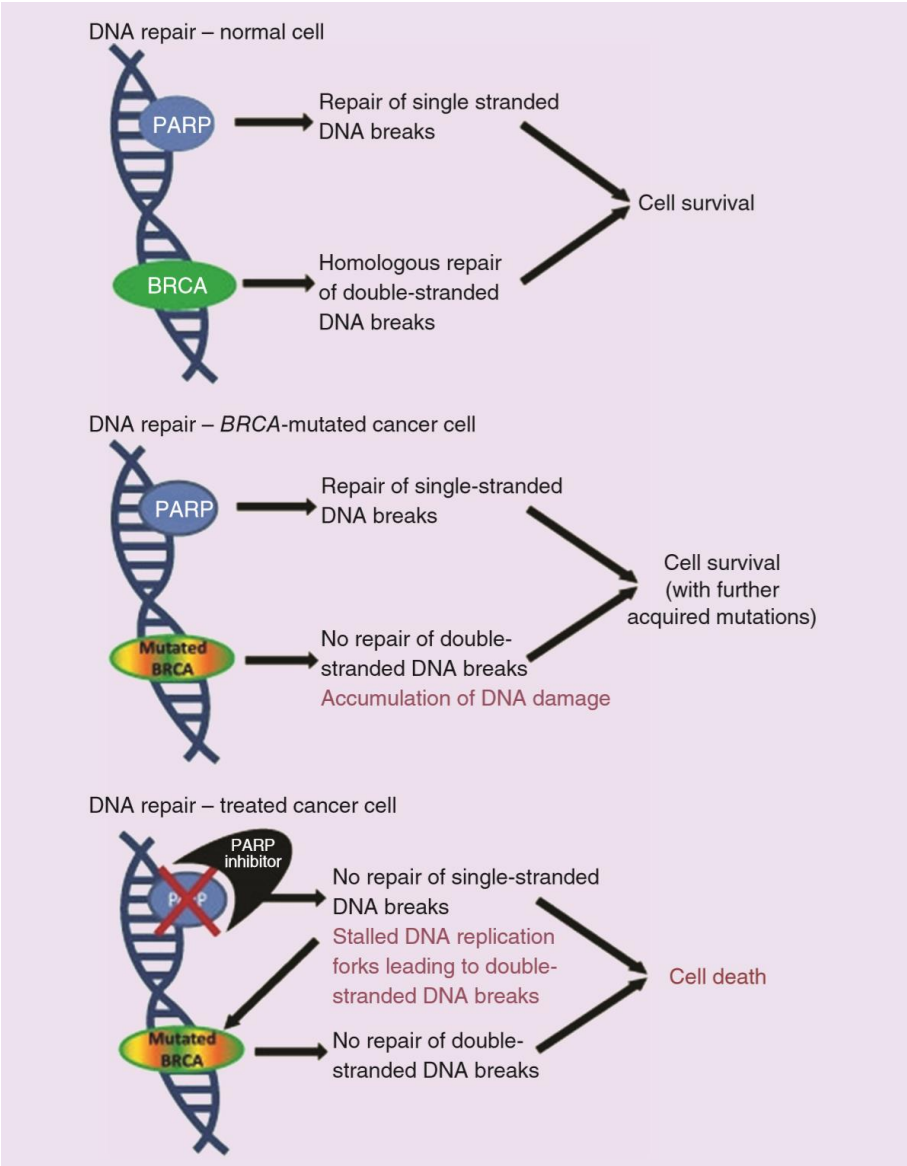
O'Connor. Mol Cell. 2015;60:547.

Mechanisms of DNA Repair



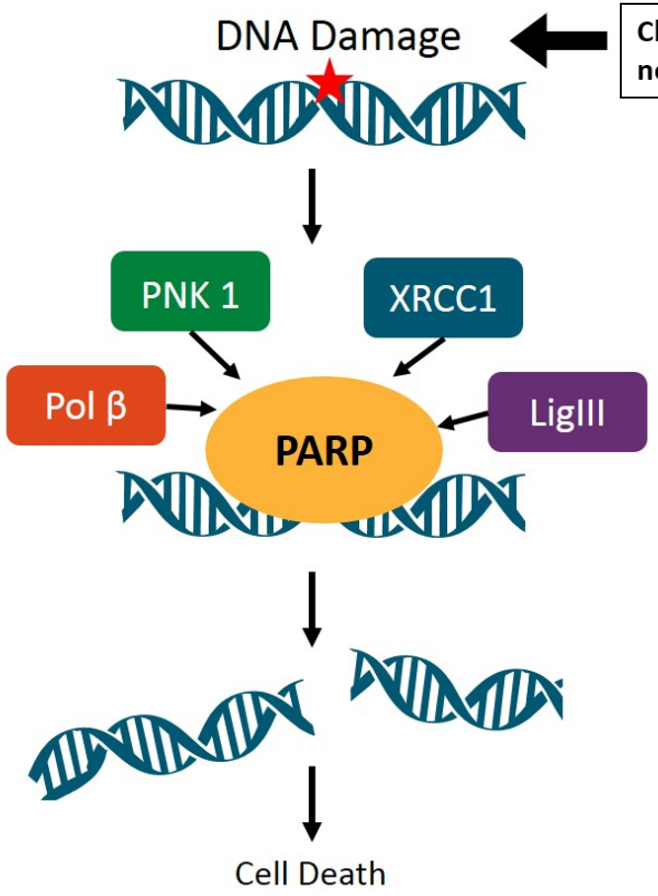
Helleday. Nat Rev Cancer. 2008;8:193.

PARP inhibitors: Mechanisms of Action



Armstrong AC. Future Oncol. (2019)15(20),2327–2335.

Inhibition of PARP Catalytic Activity

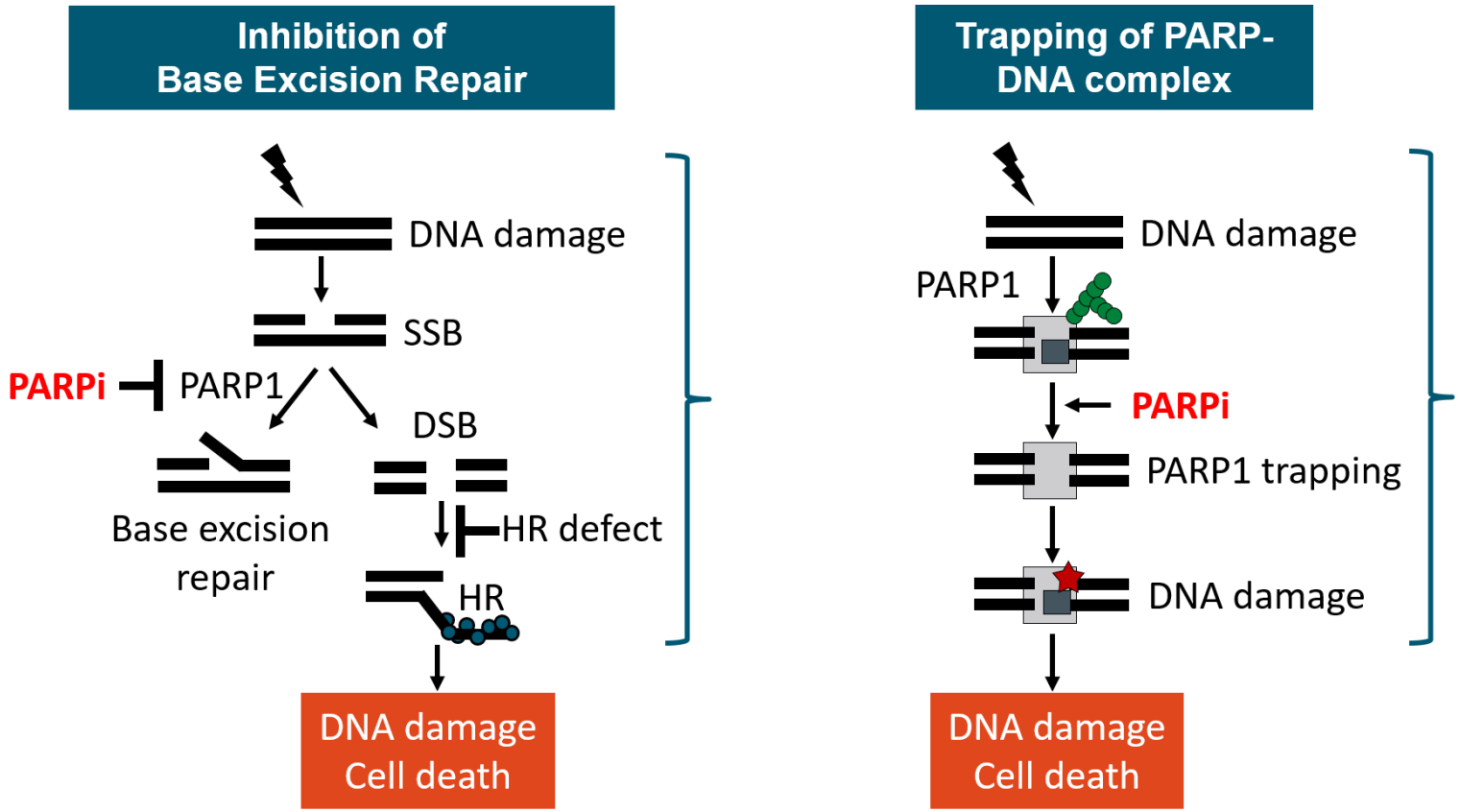


Chemotherapy (eg, alkylating agents), radiotherapy, environmental factors (UV, radiation, chemicals), normal physiology (DNA replication, ROS)

- PARP
  - Critical DNA repair enzyme (SSB, BER)
  - Often overexpressed in cancer cells
  - Confers resistance to chemotherapy and radiation
- PARP Inhibition
  - Prevents recruitment of DNA repair enzymes
  - Leads to failure of single strand break repair
- Unrepaired break site → replication fork arrest
  - Leads to degeneration into double-strand breaks
  - Ultimately leads to chromosomal catastrophe and cell death

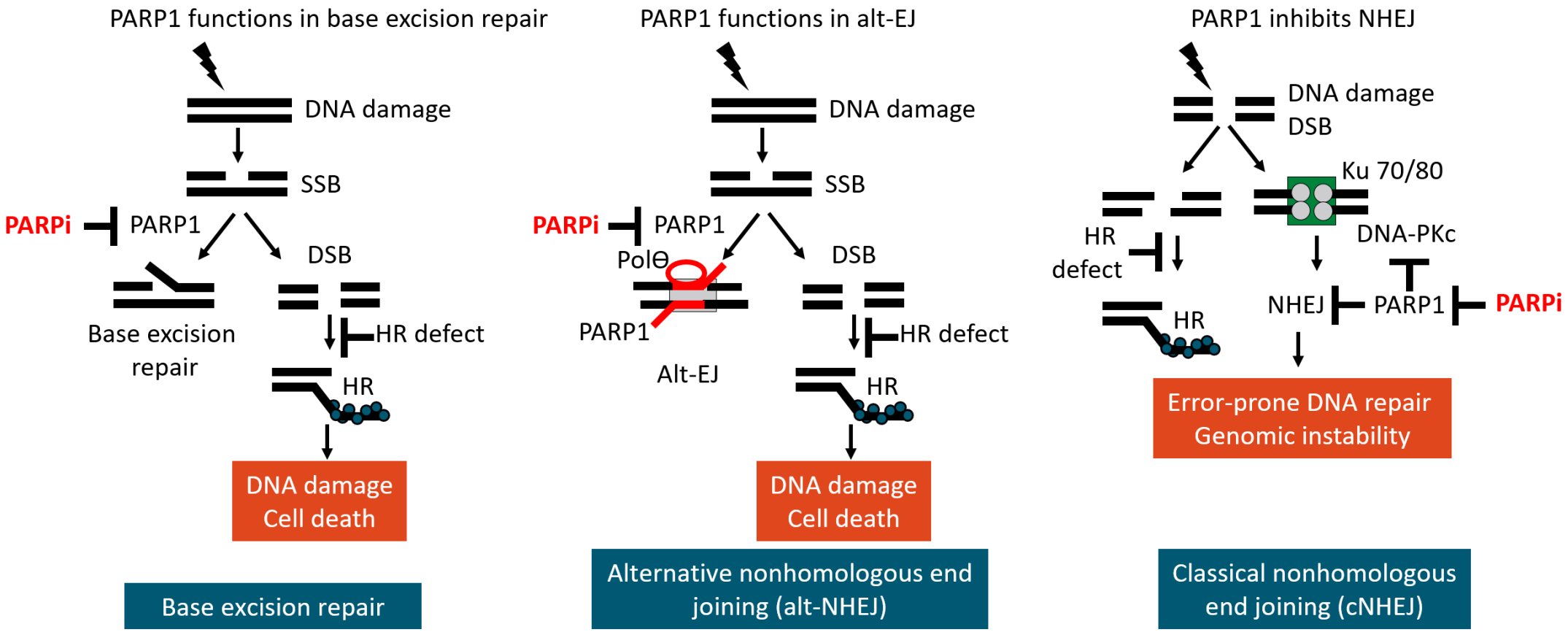
Helleday. Nat Rev Cancer. 2008;8:193.

How Do PARP Inhibitors Kill Tumor Cells With Homologous Recombination Deficiency?



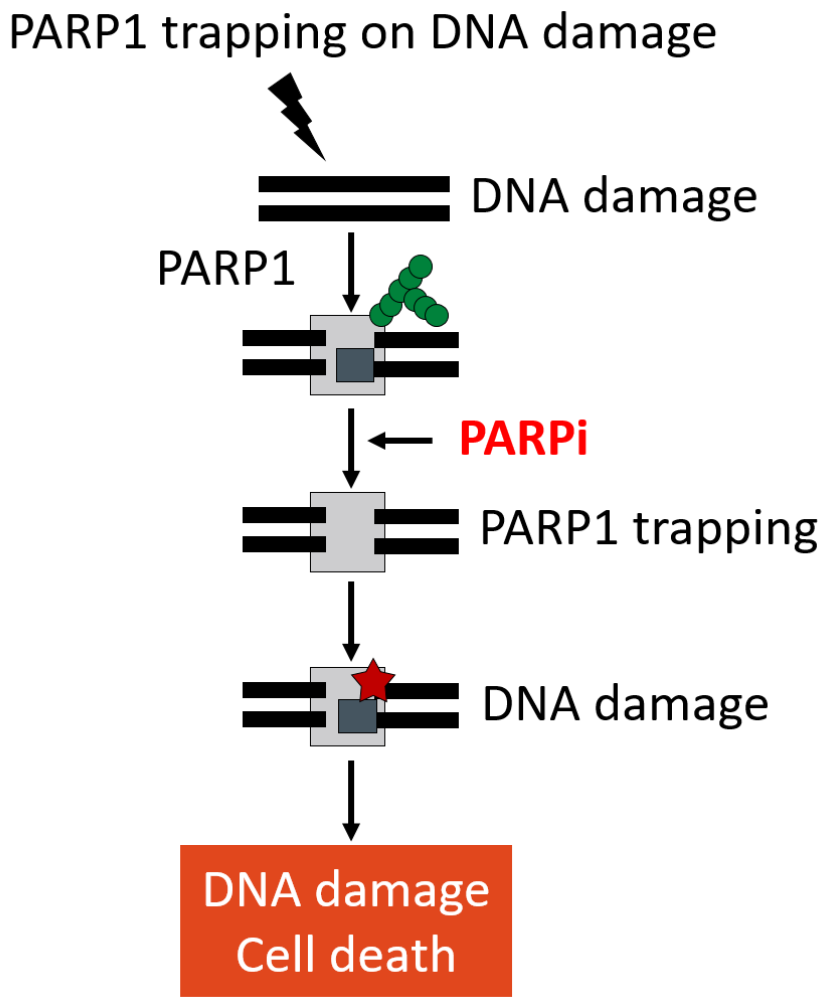
Konstantinopoulos. Cancer Discov. 2015;5:1137.

Mechanisms of Synthetic Lethality Based on Catalytic Inhibition of PARP1



Konstantinopoulos. Cancer Discov. 2015;5:1137.

PARP-DNA Trapping by PARP Inhibitors



- PARP inhibitor traps PARP1 on DNA
- Homologous recombination required to bypass lesion
  - In HR-deficient cell, trapped PARP causes DNA damage and cell death
  - Mechanism is reminiscent of conversion of topoisomerase I into a poison by topoisomerase I inhibitors

Konstantinopoulos. Cancer Discov. 2015;5:1137.