PARP inhibitors and chemotherapy in breast cancer

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MEMORIAL
BREAST CANCER CENTER

Mechanisms of DNA Repair

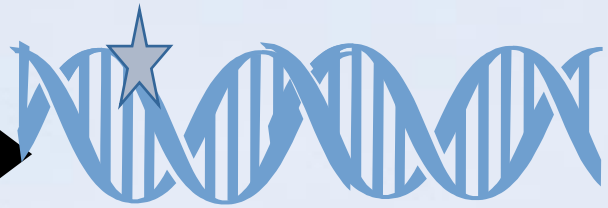
Environmental factors
(UV, radiation, chemicals)

Normal physiology
(DNA replication)

Chemotherapy
(alkylating agents, antimetabolites))

Radiotherapy

DNA DAMAGE



Cell Death

MAJOR DNA REPAIR PATHWAYS

Single Strand Breaks
- Nucleotide excision repair
- Base excision repair
  - PARP1

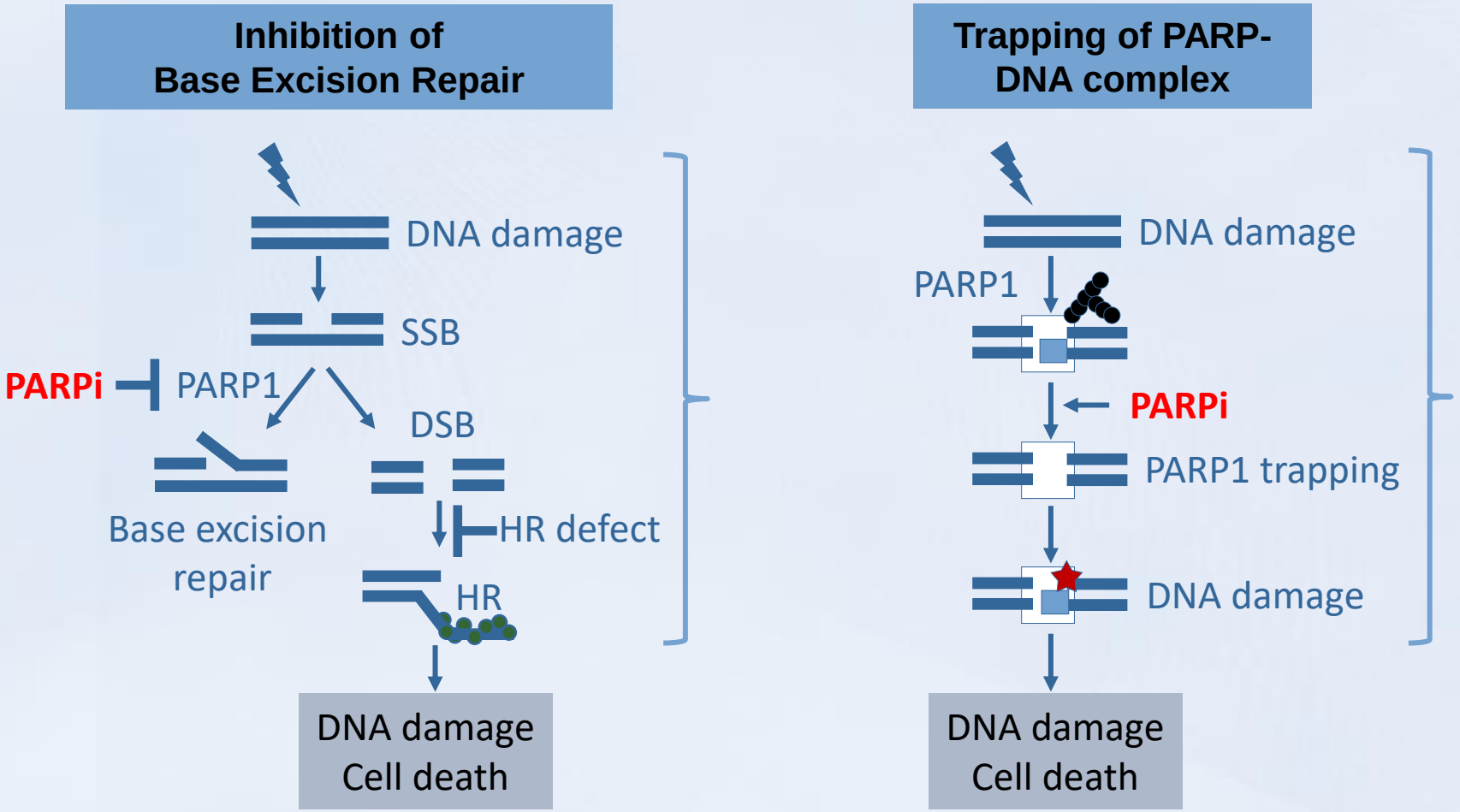
Double Strand Breaks
- Nonhomologous end-joining
- Homologous recombination
  - BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

Replication Lesions
- Base excision repair
  - PARP1

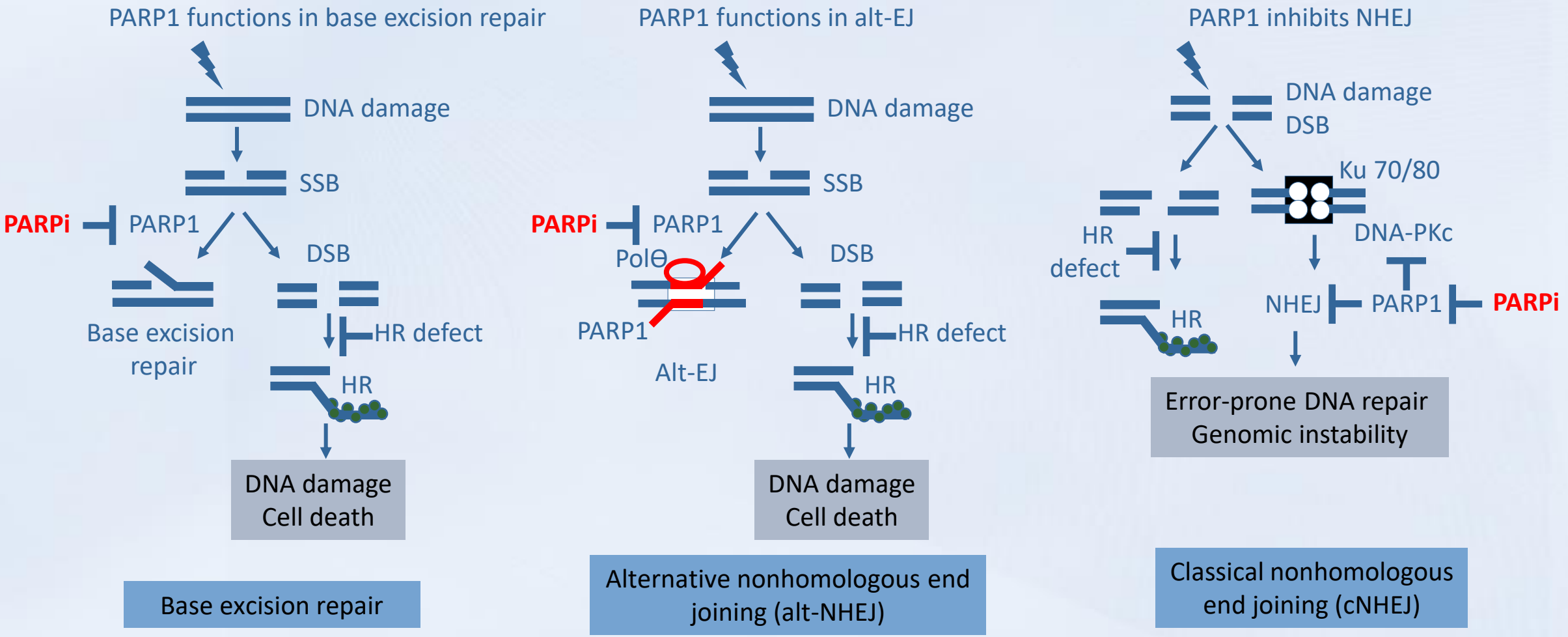
DNA Adducts/Base Damage
- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
  - PARP1

Helleday. Nat Rev Cancer. 2008;8:193

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

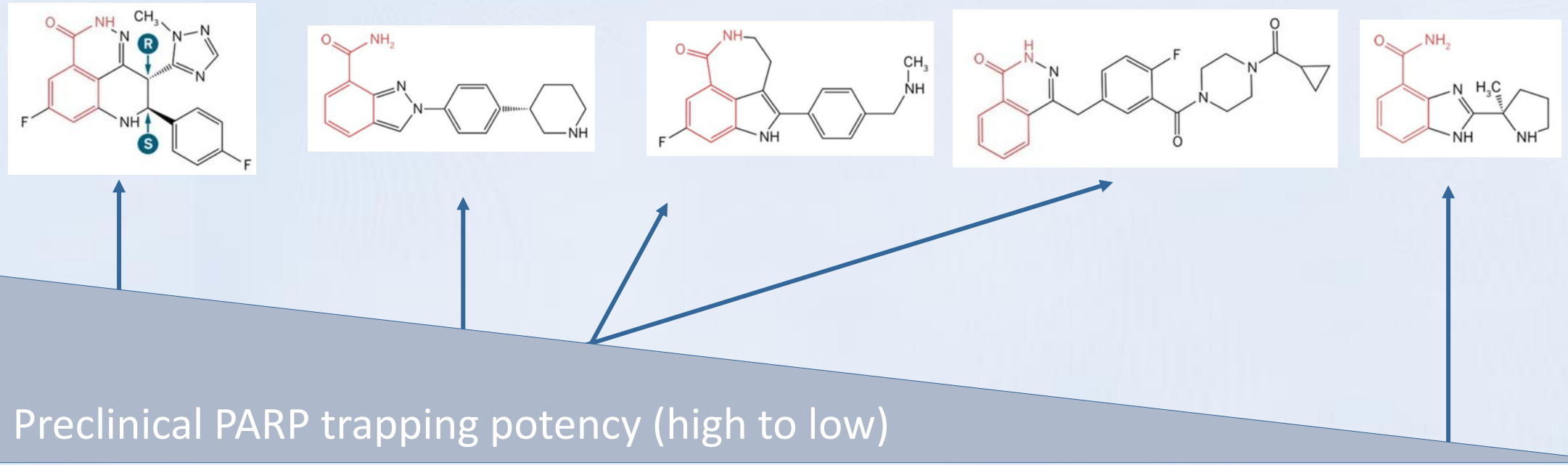


Mechanisms of Synthetic Lethality Based on Catalytic Inhibition of PARP1



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.

OlympiAD: Study Design

- Randomized, open-label phase III study

Stratified by HR status (ER+ and/or PgR+ vs TNBC), prior CT for metastases (yes vs no), prior platinum tx (yes vs no)

Patients with HER2-negative MBC with deleterious or suspected deleterious g*BRCA* mutation; previous anthracycline and taxane, **≤ 2 previous lines of CT* for metastatic disease**; if HR+, not suitable for ET or progressed on ≥ 1 ET (N = 302)

→ **Olaparib**† 300 mg PO BID (n = 205)

→ **CT**‡ on 21-day cycles (n = 97 §)

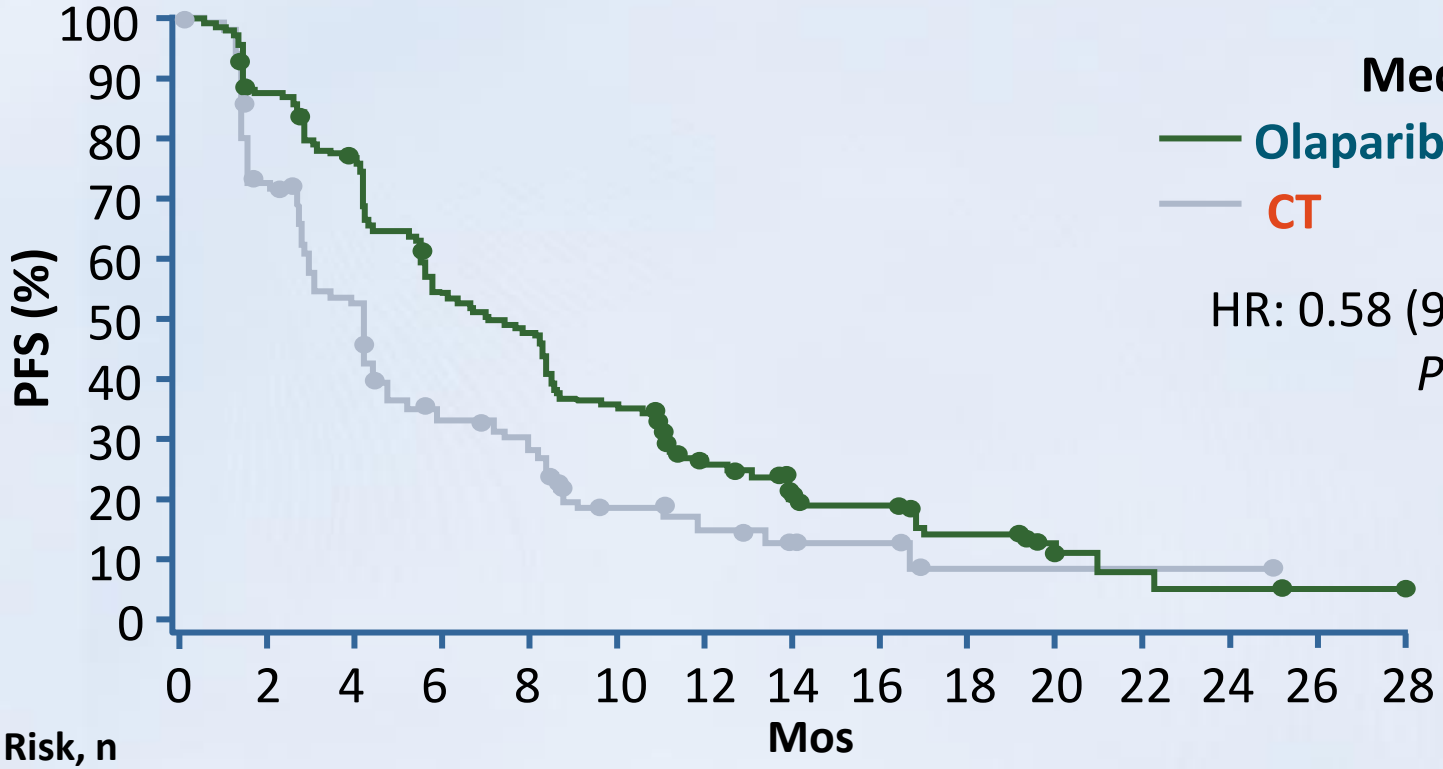
→ ***Until PD or unacceptable AEs***

*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 ME, et al. N Engl J Med. 2017;377:523-533. Robson ME, et al. AACR 2018. Abstract CT038.

OlympiAD: PFS by BICR (Primary Endpoint)



Median PFS, Mos

Olaparib	7.0
CT	4.2

HR: 0.58 (95% CI: 0.43-0.80; *P* < .001)

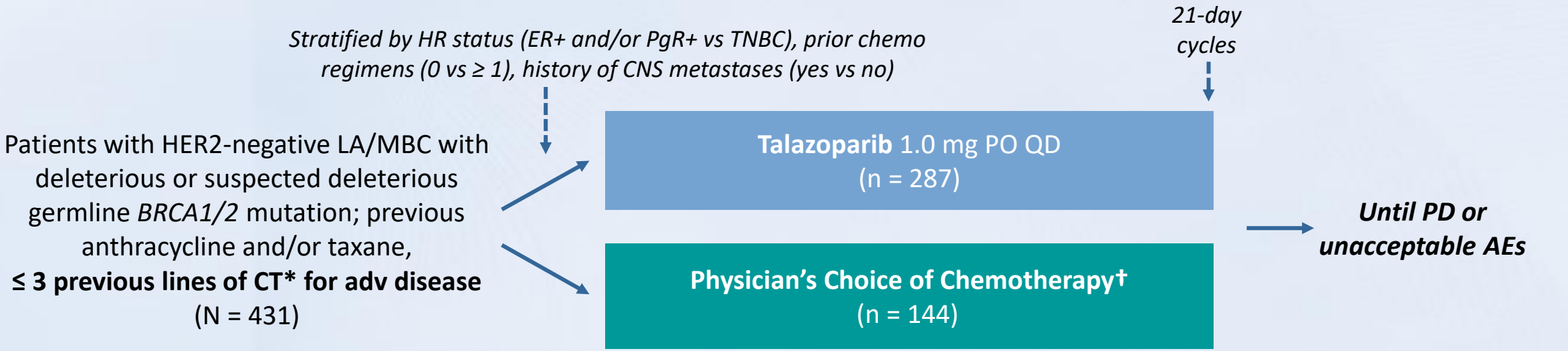
Patients at Risk, n

Olaparib	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
CT	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0

- Extended, exploratory follow-up analysis at SABCS 2019 showed a mOS of 19.3 mos with olaparib vs 17.1 mos with CT (HR: 0.84; 95% CI: 0.63-1.12); 4-yr OS rates were 18.9% vs 14.2%, respectively

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



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

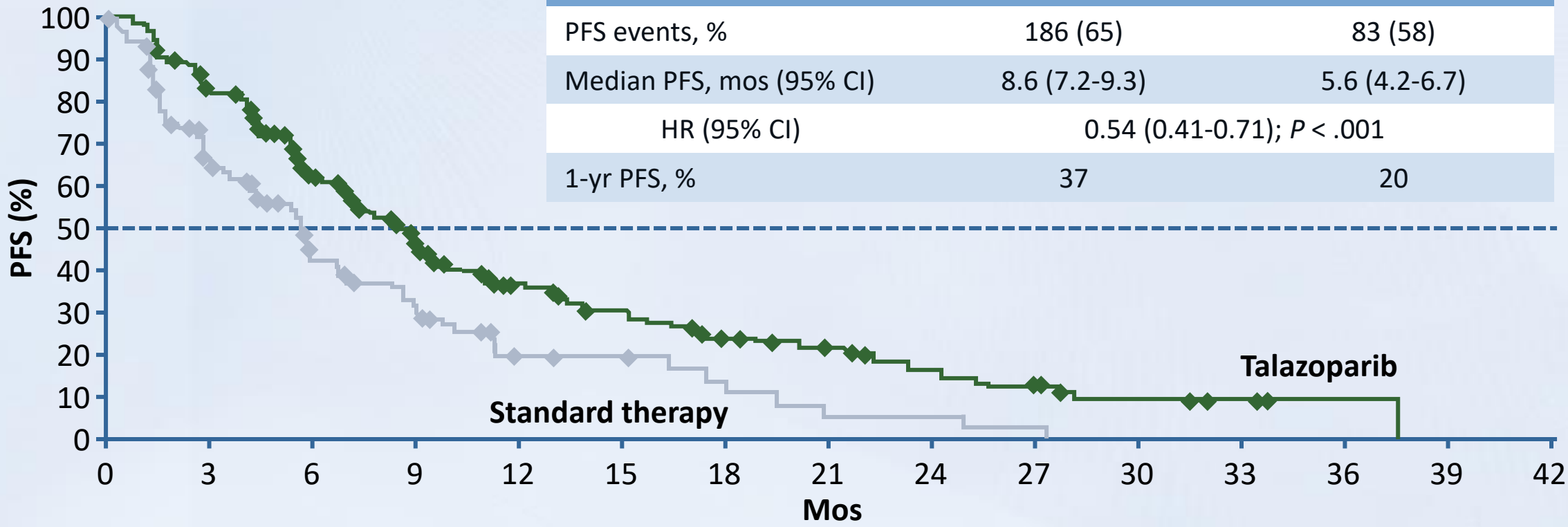
*Previous platinum-based therapy for EBC permitted if DFI ≥ 6 mos
†Physician's choice of: capecitabine 1250 mg/m^2 PO BID Days 1-14; eribulin 1.4 mg/m^2 IV Days 1, 8; gemcitabine 1250 mg/m^2 IV Days 1, 8; or vinorelbine 30 mg/m^2 IV Days 1, 8, and 15.

Litton. NEJM. 2018;379:753.

EMBRACA: PFS by BICR (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



- No OS advantage for talazoparib vs CT; findings consistent across all prespecified subgroups

PARP Inhibitors: Tolerance Profiles of Olaparib and Talazoparib

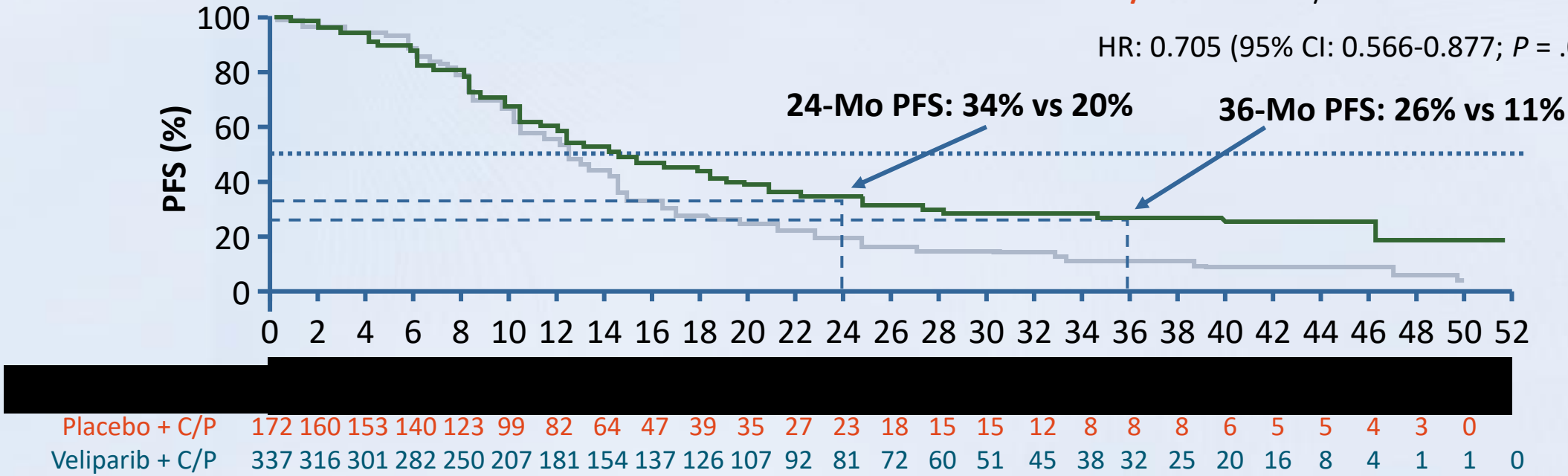
Adverse Event, %	Olaparib (OlympiAD)[1]	Talazoparib (EMBRACA)[2]
Grade ≥ 3 serious AE	38 (vs 50 TPC)	25.5 (vs 25.4 TPC)
▪ Anemia	16.1	39.2
▪ Neutropenia	9.3	20.9
▪ Thrombocytopenia	2.4	14.7
MDS/AML	0	0
Nausea (all grades)	58.0	48.6
Alopecia	3.4	25.2

1. Robson. Ann Oncol. 2019;30:558. 2. Litton. NEJM. 2018;379:753.

BROCADE3: Veliparib + Carboplatin/Paclitaxel for HER2- ABC With gBRCA1/2 Mutations

	PFS Events, n/N	Median PFS, Mos
Veliparib + C/P	217/337	14.5
Placebo + C/P	132/172	12.6

HR: 0.705 (95% CI: 0.566-0.877; *P* = .002)



- Primary endpoint met with investigator-assessed PFS significantly improved with veliparib vs placebo (*P* = .002)
- PFS assessed by independent central review also significantly improved with veliparib vs placebo (median PFS: 19.3 vs 13.5 mos, respectively; HR: 0.695; 95% CI: 0.537-0.899; *P* = .005)

Diéras. ESMO 2019. Abstr LBA9. Reproduced with permission.

PARP AND IO

MEDIOLA: Study Design

- Open-label, phase I/II multicenter study

Adults with g*BRCA* mutant/HER2-negative MBC; platinum-sensitive, relapsed SCLC; g*BRCA*-mutant ovarian cancer; or metastatic/relapsed gastric cancer
(N = 34)

→ **Olaparib** 300 mg BID + **Durvalumab** 1.5 g IV q4w (starting on Wk 5) →

Until PD or intolerance

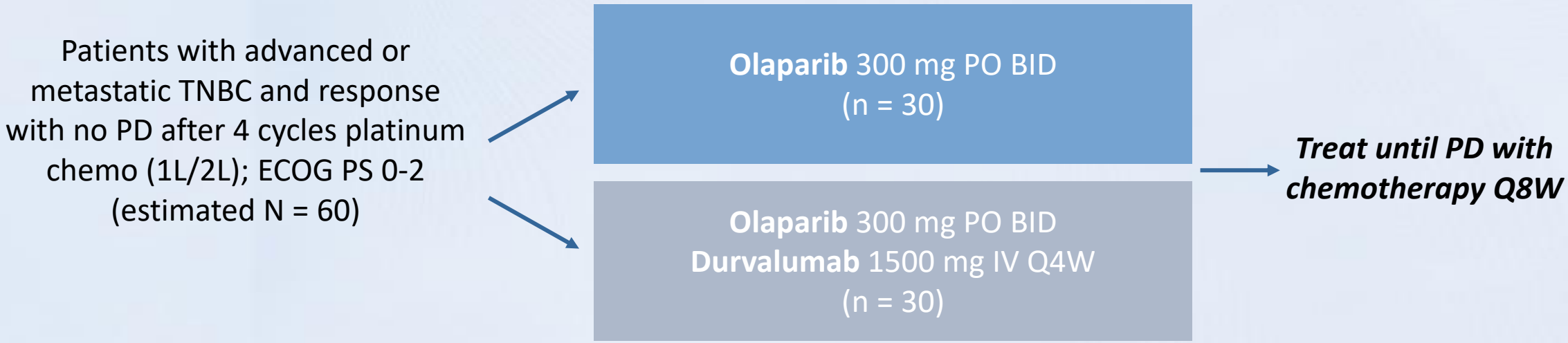
- Primary endpoints: 12-wk DCR; safety and tolerability
- Secondary endpoints: DCR; time to study discontinuation; OS; percent change from baseline in tumor size, ORR
- 24 (80%; 90% CI 64.3-90.9)of 30 patients had DCR at 12-wk

Adverse Event, n (%)	Olaparib + Durvalumab
Grade ≥ 3 serious AE	11 (32)
▪ Anemia	4 (12)
▪ Neutropenia	3 (9)
▪ Pancreatitis	2 (6)
Discontinued due to AE	3 (9)
Total of 6 serious AEs	4 (12)
Treatment-related deaths	0

Domchek. SABCS 2018. Abstr PD5-04. Domchek. Lancet Oncol. 2020;21:1155

DORA: Maintenance Durvalumab Plus Olaparib vs Olaparib Alone in Platinum-Treated Metastatic TNBC

- Randomized, multicenter phase II trial

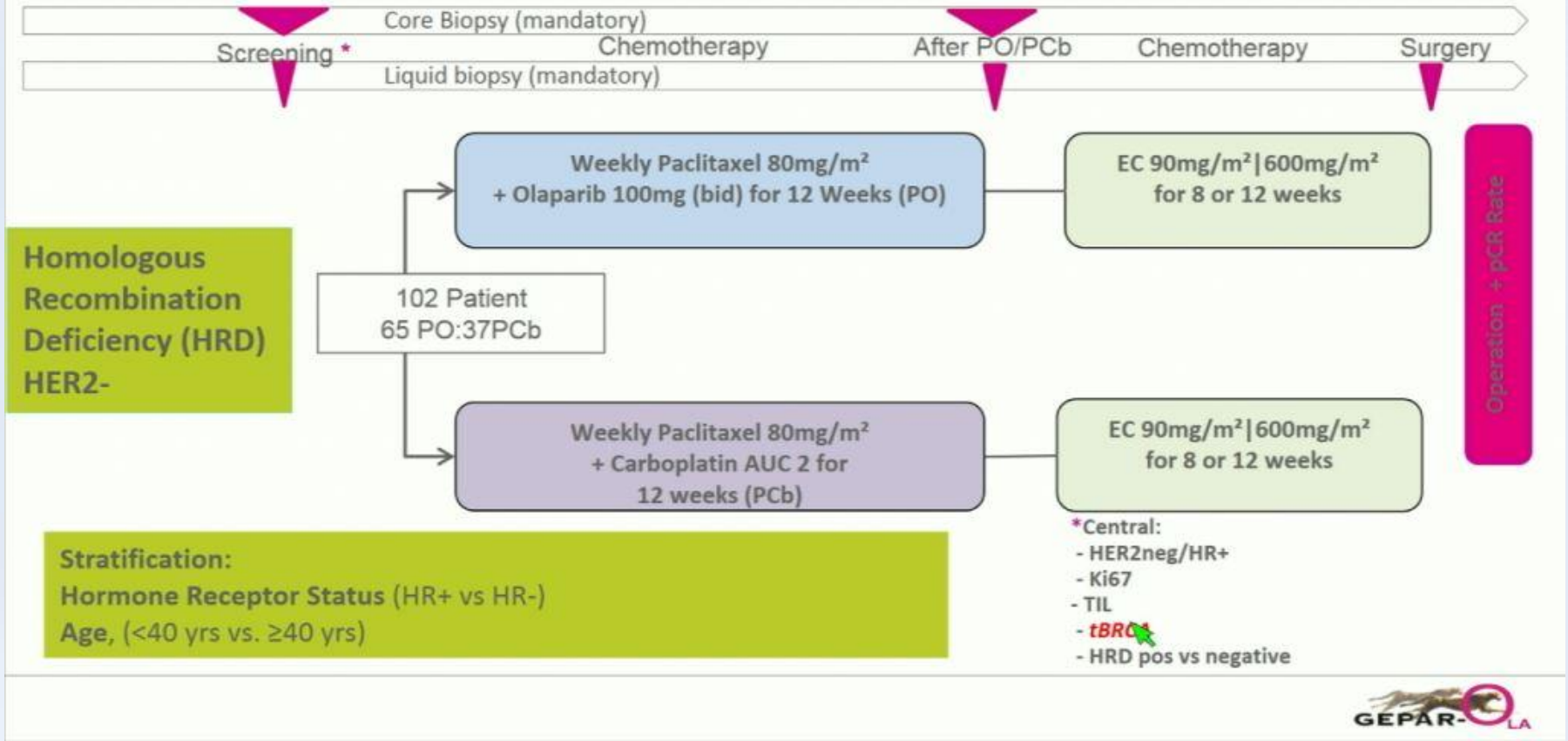


- Primary endpoint: PFS
- Secondary endpoints: OS, toxicity, ORR
- Exploratory endpoints: biomarker analyses

NCT03167619.

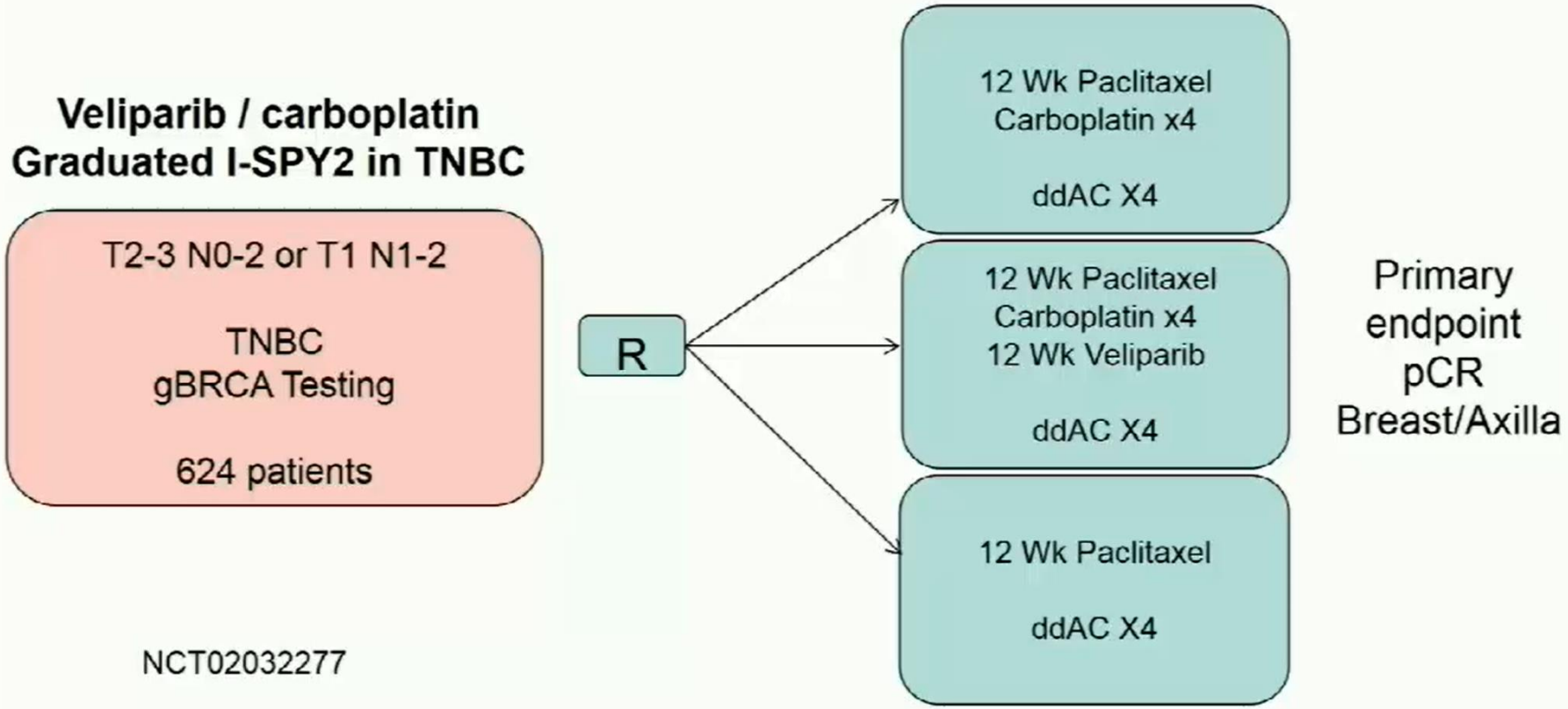
PARP IN EARLY STAGE BREAST CA

GEPARO$_{LA}$ Study – tests PARPi vs Carboplatin



BRIGHTNESS Neo-adjuvant Trial

Veliparib / carboplatin
Graduated I-SPY2 in TNBC

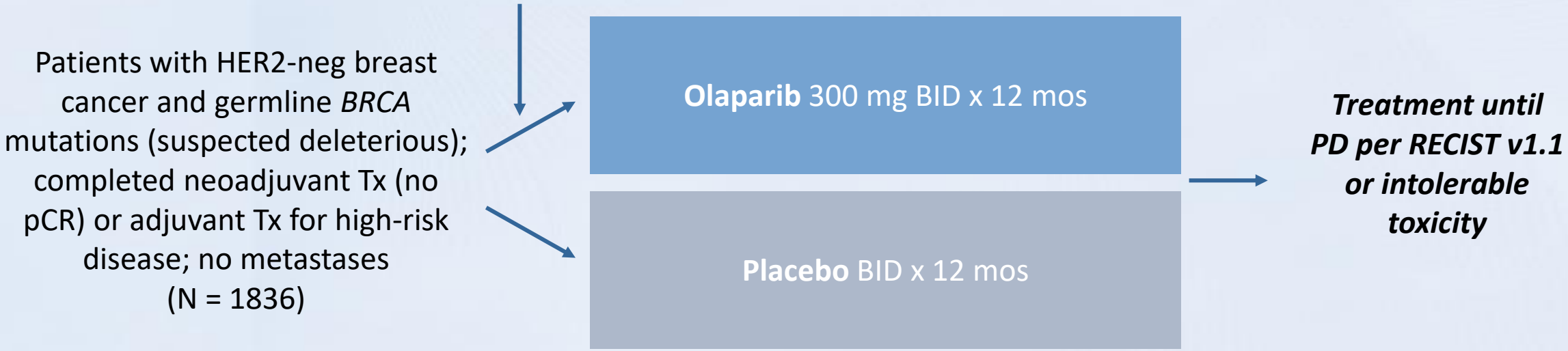


NCT02032277

OlympiA: Adjuvant Olaparib in *BRCA*-Mutated, HER2-Negative Breast Cancer

- Randomized, double-blind phase III trial

Stratified by HR status (ER and/or PR pos/HER2 neg vs TNBC), prior chemotherapy (neoadjuvant vs adjuvant), prior platinum for breast cancer (yes vs no)

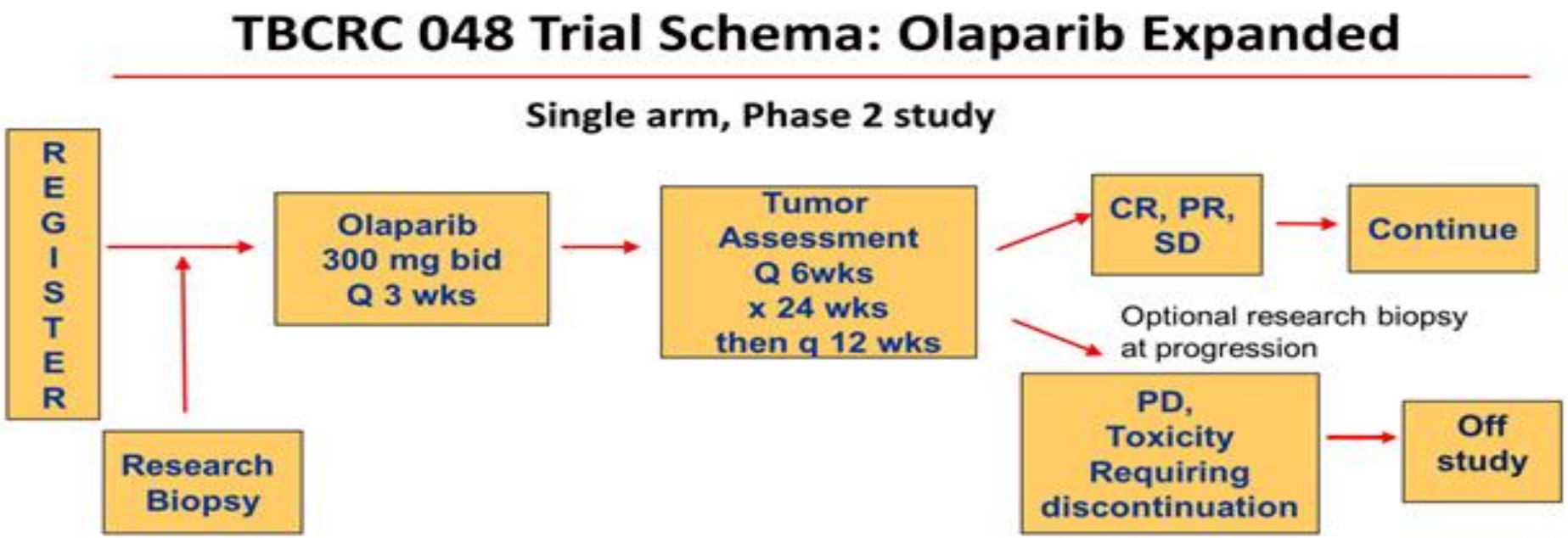


- Primary endpoint: invasive DFS
- Secondary endpoints: OS, distant DFS, incidence of new cancers, QoL

NCT02032823.

EXPANDING THE USE OF PARPI

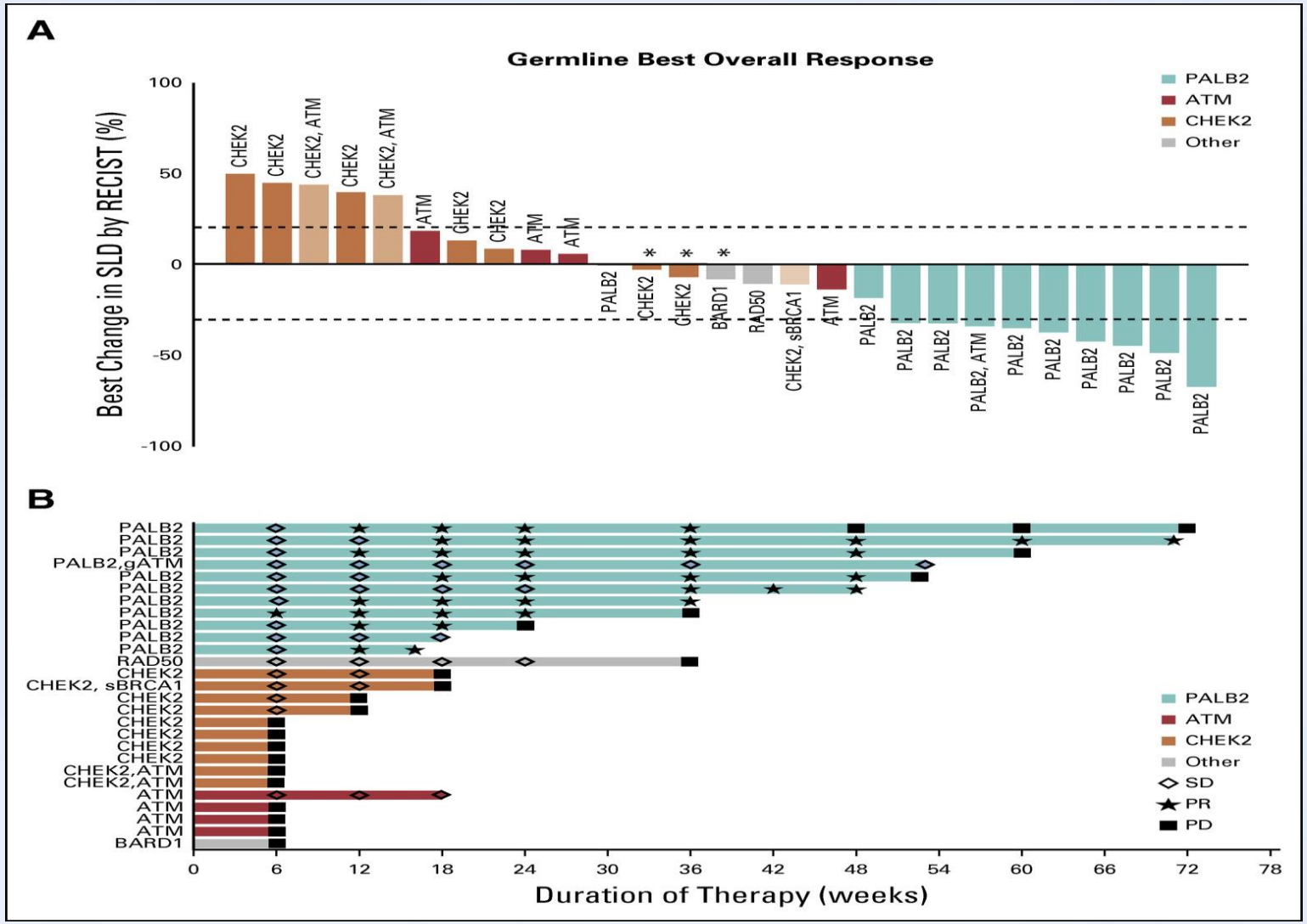
TBCRC 048: Olaparib for MTBC and mutations in Homologous Recombination-Related Genes



Tung NM et al. ASCO 2020;Abstract 1002.

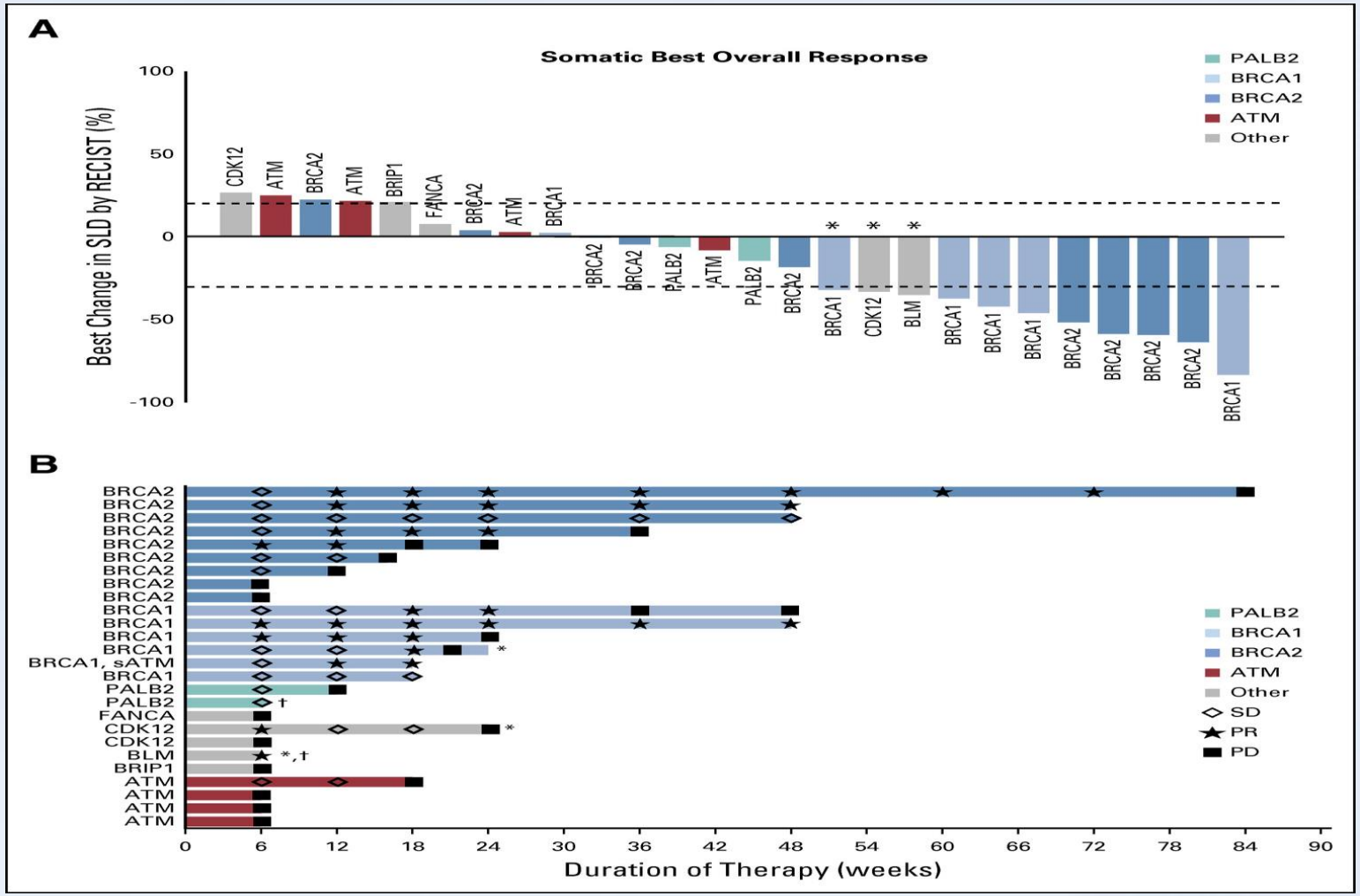
Courtesy of P Kelly Marcom, MD

TBCRC 048: Olaparib for MTBC and mutations in Homologous Recombination-Related Genes



Tung. JCO 2020 38:36, 4274-4282

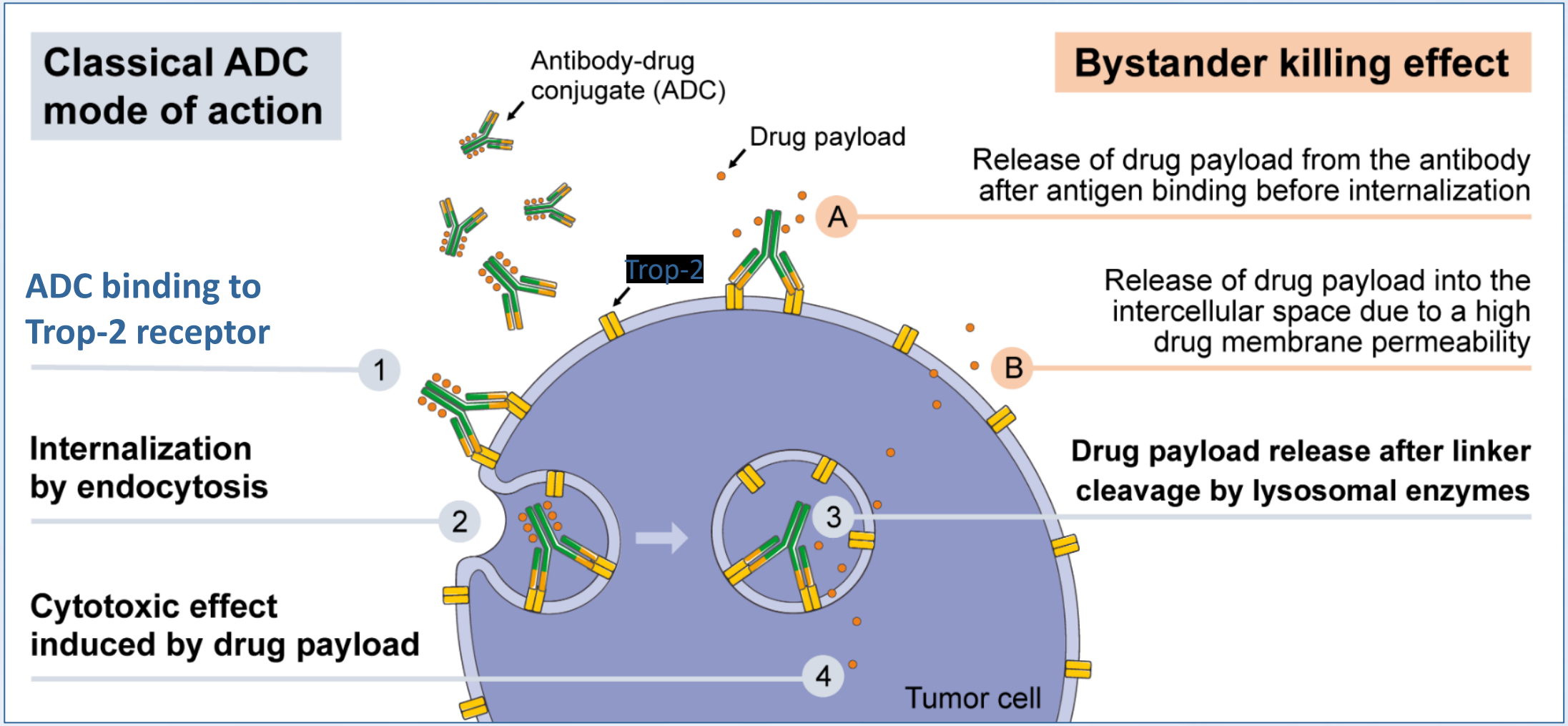
TBCRC 048: Olaparib for MTBC and mutations in Homologous Recombination-Related Genes



Tung. JCO 2020 38:36, 4274-4282

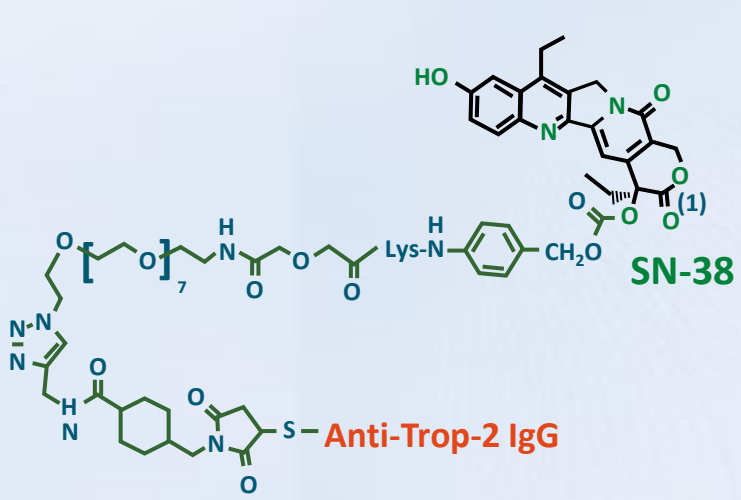
CHEMOTHERAPY IN BREAST CA

Selective Delivery of Toxic Payload



Nagayama. Target Oncol. 2017;12:719. Image adapted from Rinnerthaler. Int J Mol Sc 2019;20:1115. HER2 directed antibody-drug-conjugates beyond T-DM1 in breast cancer. Licensed

Sacituzumab Govitecan (IMMU-132): Trop-2–Targeted Antibody-Drug Conjugate

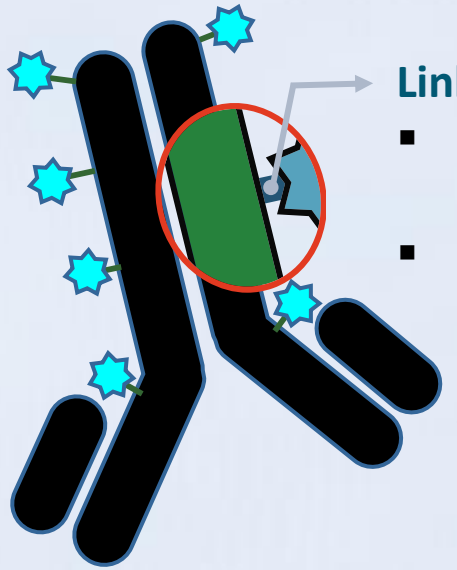


SN-38 Payload

- Targets 136-fold more than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor

Humanized RS7 Antibody

- Targets Trop-2, an antigen expressed in many epithelial cancers, including mTNBC (88%)
- Antibody type: h-IgG1

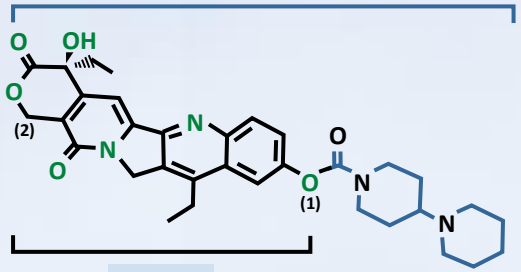


Linker for SN-38

- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Irinotecan (Topoisomerase Inhibitor)

Irinotecan



SN-38

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti–Trop-2 antibody, diffuses into neighboring Trop-2–negative cells

Sacituzumab Govitecan for Patients With Heavily Treated Metastatic TNBC

- Analysis of metastatic TNBC subgroup from multicenter, single-arm, open-label phase I/II trial evaluating sacituzumab govitecan in patients with advanced epithelial cancers

Patients with metastatic TNBC previously treated with ≥ 2 therapies for metastatic disease; expected survival ≥ 6 mos; prior CNS metastasis allowed if treated/stable; ECOG PS 0/1
(N = 108)

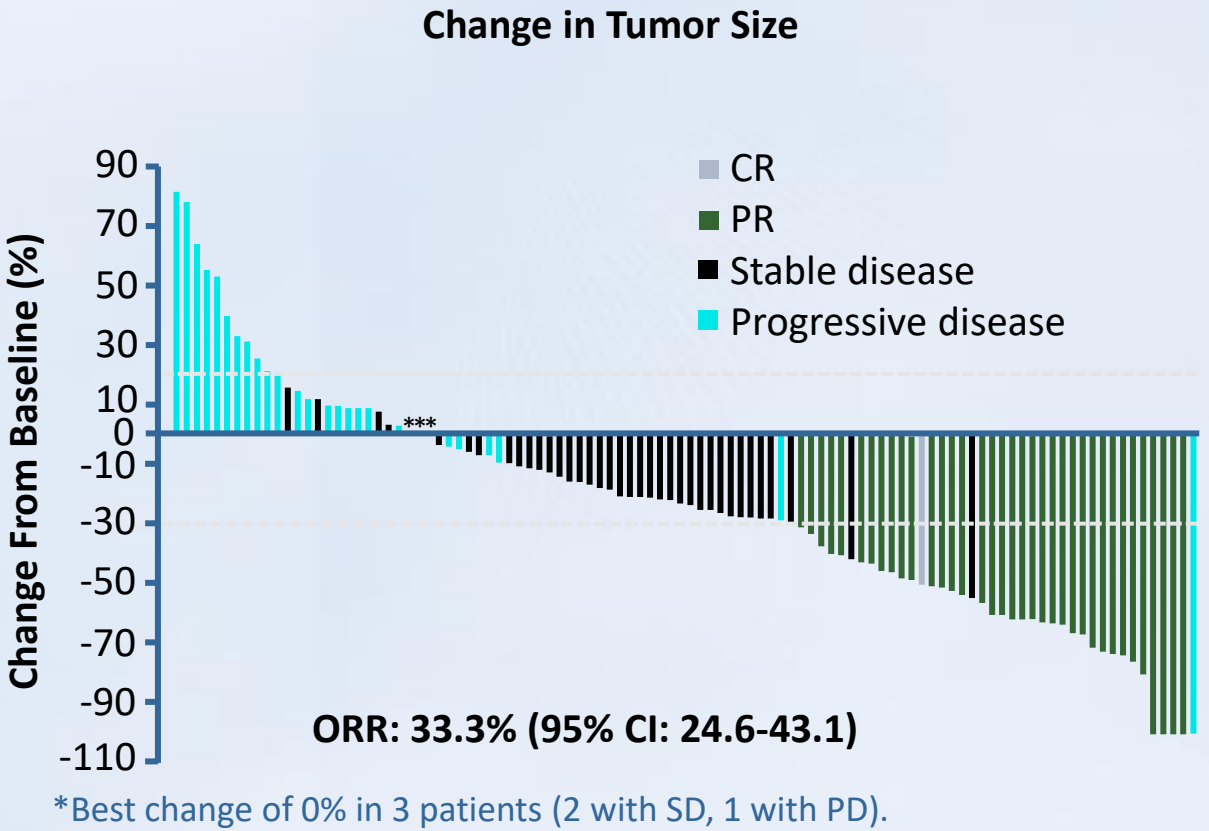
→ **Sacituzumab govitecan-hziy** 10 mg/kg IV on Days 1, 8 of 21-day cycles →

Until PD or unacceptable toxicity

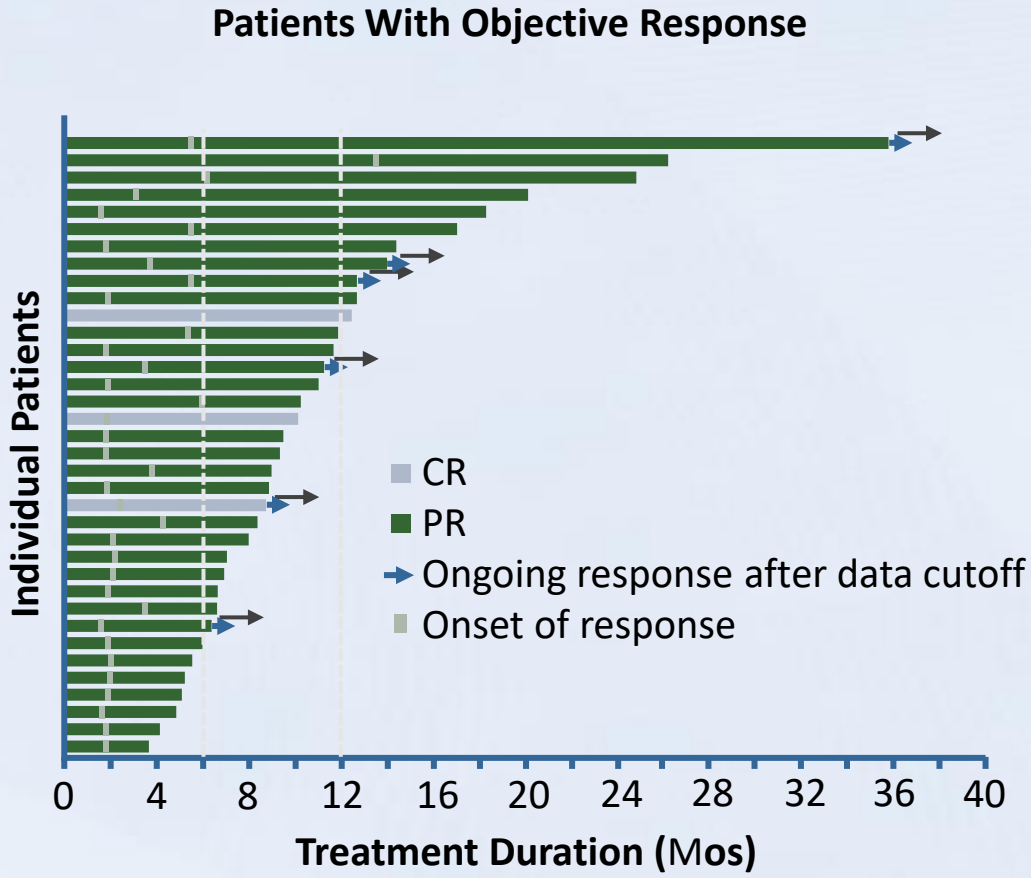
- Primary endpoint: ORR (RECIST v 1.1 per local assessment); other endpoints: TTR, DoR, clinical benefit rate, PFS, OS
- Baseline: median no. prior therapies in metastatic setting: 3 (range: 2-10); prior therapies: ICI, 17%; taxanes, 98.1%; anthracyclines, 86.1%

Bardia. NEJM. 2019;380:741. NCT01631552.

Sacituzumab Govitecan in Refractory Metastatic TNBC: Response



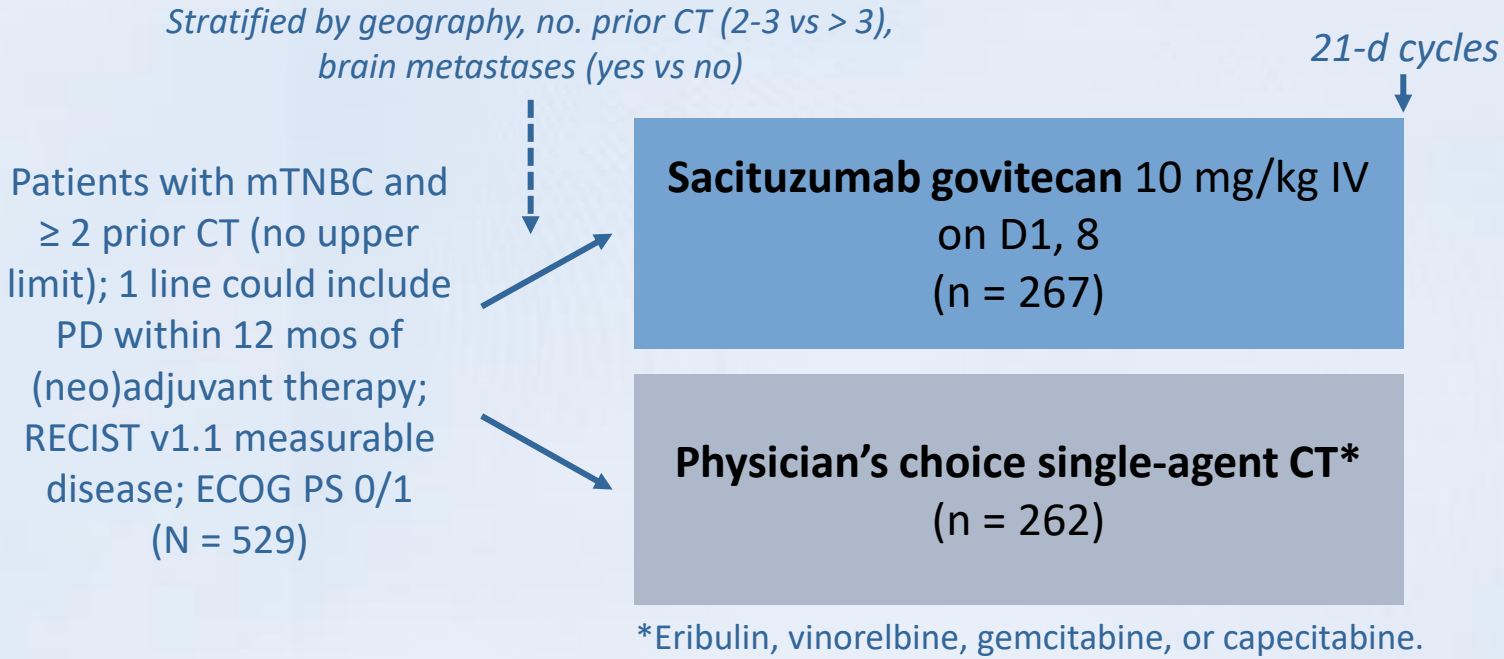
*Best change of 0% in 3 patients (2 with SD, 1 with PD).



- Clinical benefit rate (CR + PR + SD ≥ 6 mos): 45.4% (49/108 patients)

ASCENT: Sacituzumab Govitecan vs Single-Agent CT in Metastatic TNBC After ≥ 2 Previous CT Regimens

- Randomized, open-label phase III trial



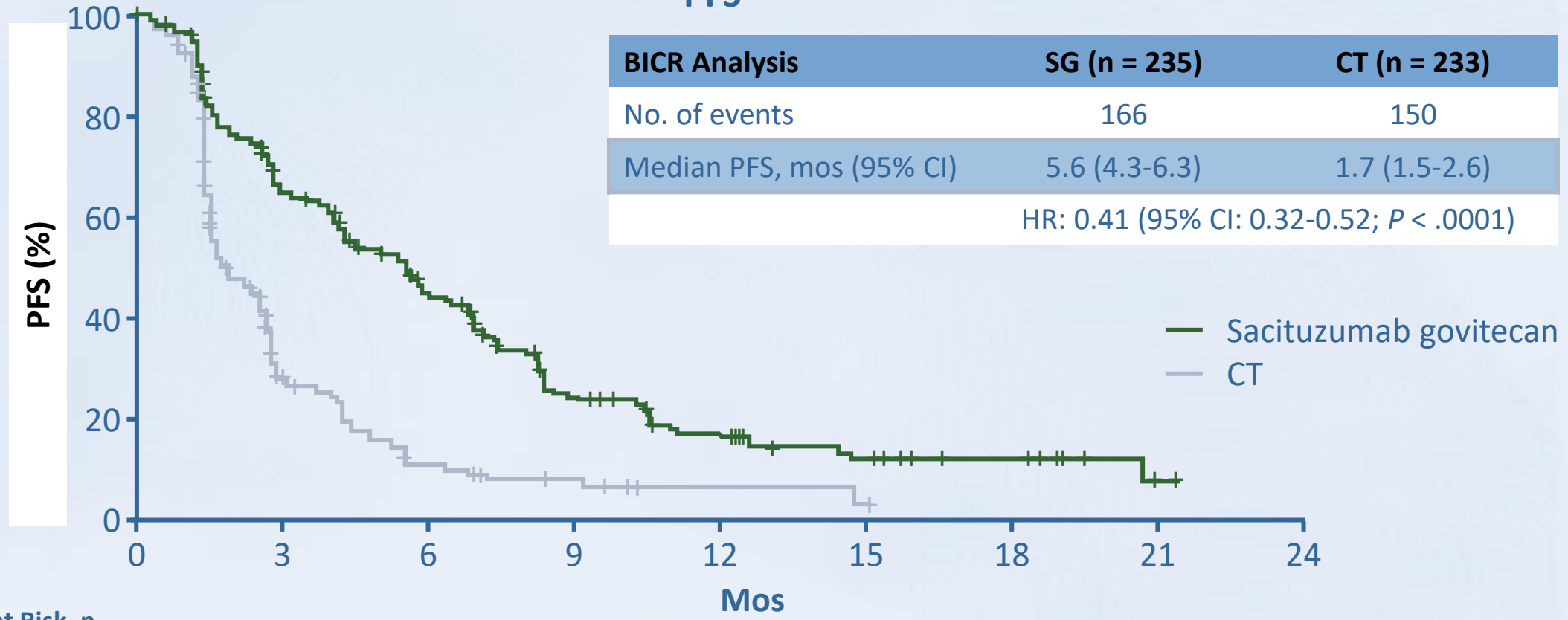
- Primary endpoint: PFS by IRC in patients without brain metastases
- Secondary endpoints: PFS (full population), OS, ORR, DoR, TTR, safety

- **Trial halted early based on efficacy** per unanimous independent DSMC recommendation

ASCENT: PFS by BICR (Primary Outcome)

PFS

BICR Analysis	SG (n = 235)	CT (n = 233)
No. of events	166	150
Median PFS, mos (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
	HR: 0.41 (95% CI: 0.32-0.52; *P* < .0001)	

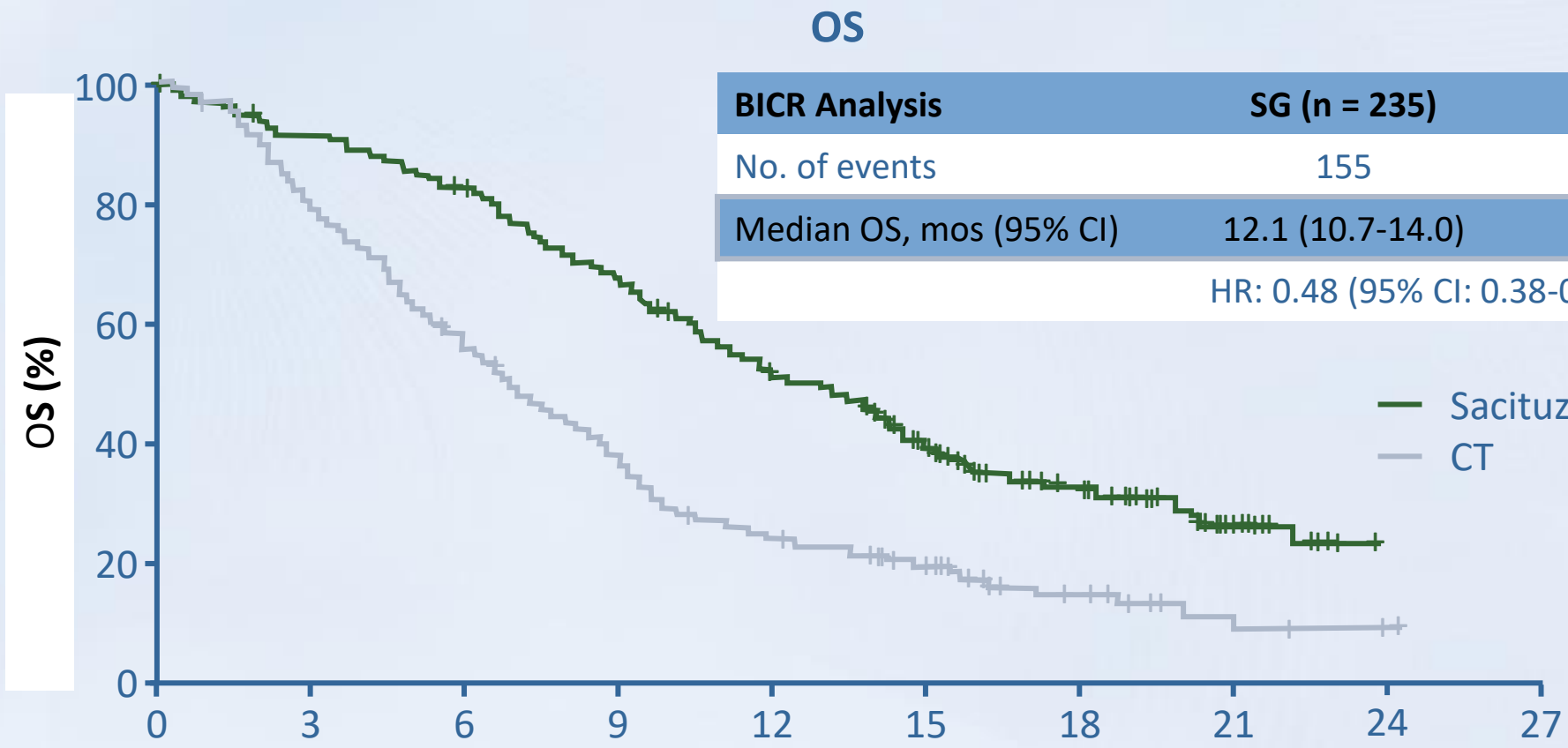


Patients at Risk, n

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
CT	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Bardia. ESMO 2020. Abstr LBA17.

ASCENT: OS



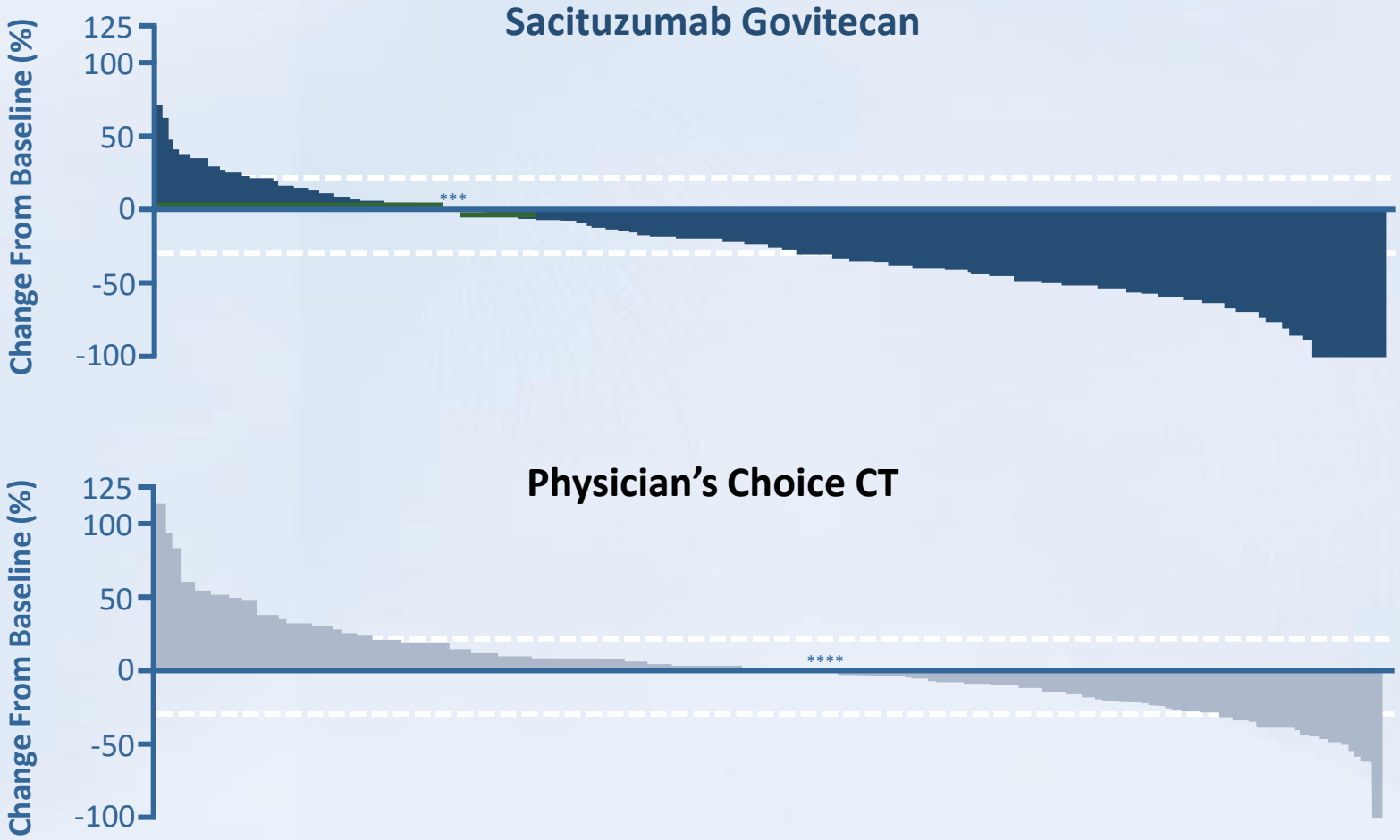
BICR Analysis	SG (n = 235)	CT (n = 233)
No. of events	155	185
Median OS, mos (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
	HR: 0.48 (95% CI: 0.38-0.59; *P* < .0001)	

Patients at Risk, n

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
CT	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Bardia. ESMO 2020. Abstr LBA17.

ASCENT: Response



Outcome	Sacituzumab Govitecan (n = 235)	Physician's Choice CT (n = 233)
ORR, n (%)	82 (35)*	11 (5)*
▪ CR	10 (4)	2 (1)
▪ PR	72 (31)	9 (4)
CBR, n (%)	105 (45)*	20 (9)*
Median DoR, mos	6.3†	3.6†

*$P < .0001$
†$P = .057$

Bardia. ESMO 2020. Abstr LBA17.

ASCENT: Safety

	TRAEs, %	Sacituzumab Govitecan (n = 258)			Physician's Choice CT (n = 224)		
		All	Grade 3	Grade 4	All	Grade 3	Grade 4
Hematologic	Neutropenia	63	46	17	43	27	13
Hematologic	Anemia	34	8	0	24	5	0
Hematologic	Leukopenia	16	10	1	11	5	1
Hematologic	Febrile neutropenia	6	5	1	2	2	< 1
GI	Diarrhea	59	10	0	12	< 1	0
GI	Nausea	57	2	< 1	26	< 1	0
GI	Vomiting	29	1	< 1	10	< 1	0
Other	Fatigue	45	3	0	30	5	0
Other	Alopecia	46	0	0	16	0	0

- No treatment-related deaths, severe cardiovascular toxicity, grade ≥ 3 neuropathy, or grade ≥ 4 ILD with sacituzumab govitecan; 1 treatment-related death (neutropenic sepsis) with physician's choice CT
- AEs leading to discontinuation: sacituzumab govitecan, 4.7%; physician's choice CT, 5.4%

Bardia. ESMO 2020. Abstr LBA17.