Current and Future Role of PARP Inhibitors in Metastatic Triple-Negative Breast Cancer

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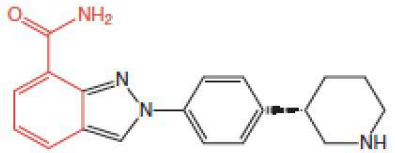
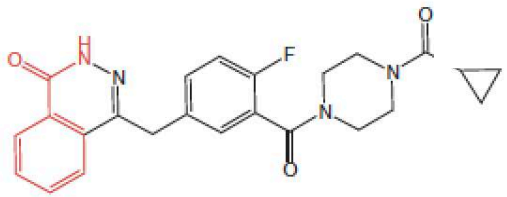
PARP Inhibitors

Veliparib
ABT - 888

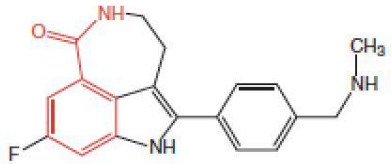
4-AN



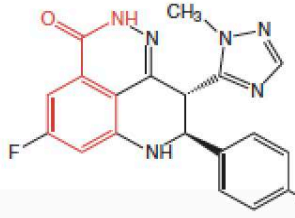
Niraparib
MK-4827



Olaparib
AZD-2281
KU-0059436



Rucaparib
AG-014699



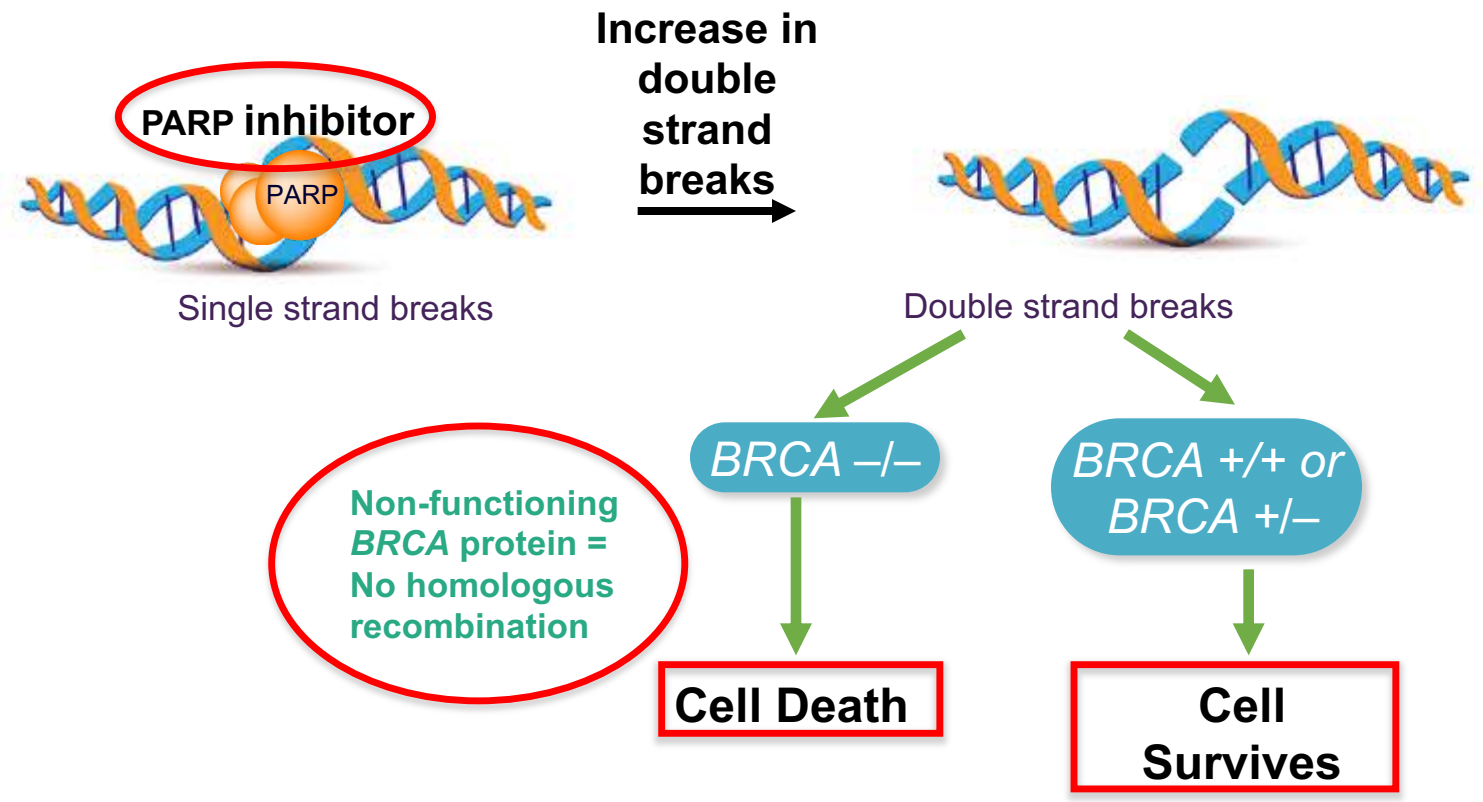
Talazoparib
BMN-673

- Veliparib – Phase III data
- Niraparib
- Olaparib - Approved 1/12/2018
- Rucaparib
- Talazoparib - Approved 10/16/2018

★ NCCN guidelines endorse germline BRCA1/2 mutation testing for all metastatic breast cancer patients

Murai J, Pommier Y. Classification of PARP Inhibitors Based on PARP Trapping and Catalytic Inhibition, and Rationale for Combinations with Topoisomerase I Inhibitors and Alkylating Agents. In: Curtin NJ, Sharma RA, eds. *PARP Inhibitors for Cancer Therapy*. New York: Springer International Publishing;2015:261-274.

PARP inhibitors active in BRCA1/2 mutated cancers



Adapted from O'Connor, et al. Mol Cell. 2015

RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE

WORKUP[a]

Stage IV (M1) or Recurrent →

- History and physical exam
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Imaging for systemic staging:
  - Chest diagnostic CT with contrast
  - Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
  - Brain MRI with contrast if suspicious CNS symptoms
  - Spine MRI with contrast if back pain or symptoms of cord compression
  - Bone scan or sodium fluoride PET/CT[ss] (category 2B)
  - FDG PET/CT[tt] (optional)
  - X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Biomarker testing:
  - Biopsy of first recurrence of disease
  - Evaluation of ER/PR and HER2 status to differentiate recurrent disease from new primary[d,ccc,ddd]
  - Comprehensive germline and somatic profiling to identify candidates for additional targeted therapies, see Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R)
- Genetic counseling if patient is at risk[e] for hereditary breast cancer
- Assess for distress[g]

→ See Treatment of Local and Regional Recurrence (BINV-19) and Supportive care[eee]

→ See Systemic Treatment of Recurrent Unresectable (local or regional) or Stage IV (M1) (BINV-20)[fff] and Supportive care[eee]

Initial biomarkers at recurrent/metastatic presentation

[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.

[d] See Principles of Biomarker Testing (BINV-A).

[e] For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[g] See NCCN Guidelines for Distress Management.

[ss] Bone scan or sodium fluoride PET/CT may not be needed if FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component.

[tt] FDG PET/CT can be performed at the same time as diagnostic CT. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies.

[ccc] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

[ddd] In clinical situations where a biopsy cannot safely be obtained but the clinical evidence is strongly supportive of recurrence, treatment may commence based on the ER/PR/HER2 status of the primary tumor.

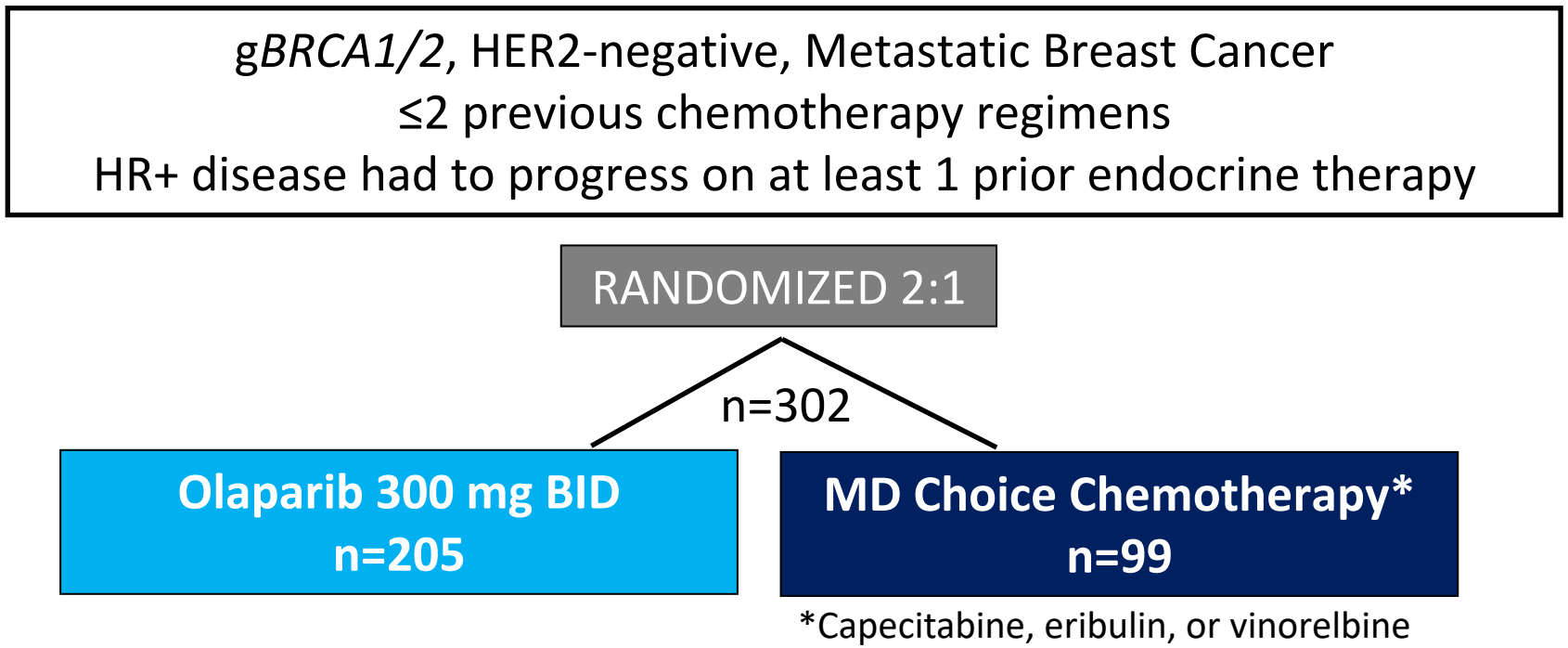
[eee] See NCCN Guidelines for Palliative Care and NCCN Guidelines for Supportive Care.

[fff] For the treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Phase III OlympiAD Trial

Olaparib in gBRCA1/2 Mutant Advanced Breast Cancer



- ~50% TNBC
- 27-29% Prior platinum
- Platinum resistant excluded

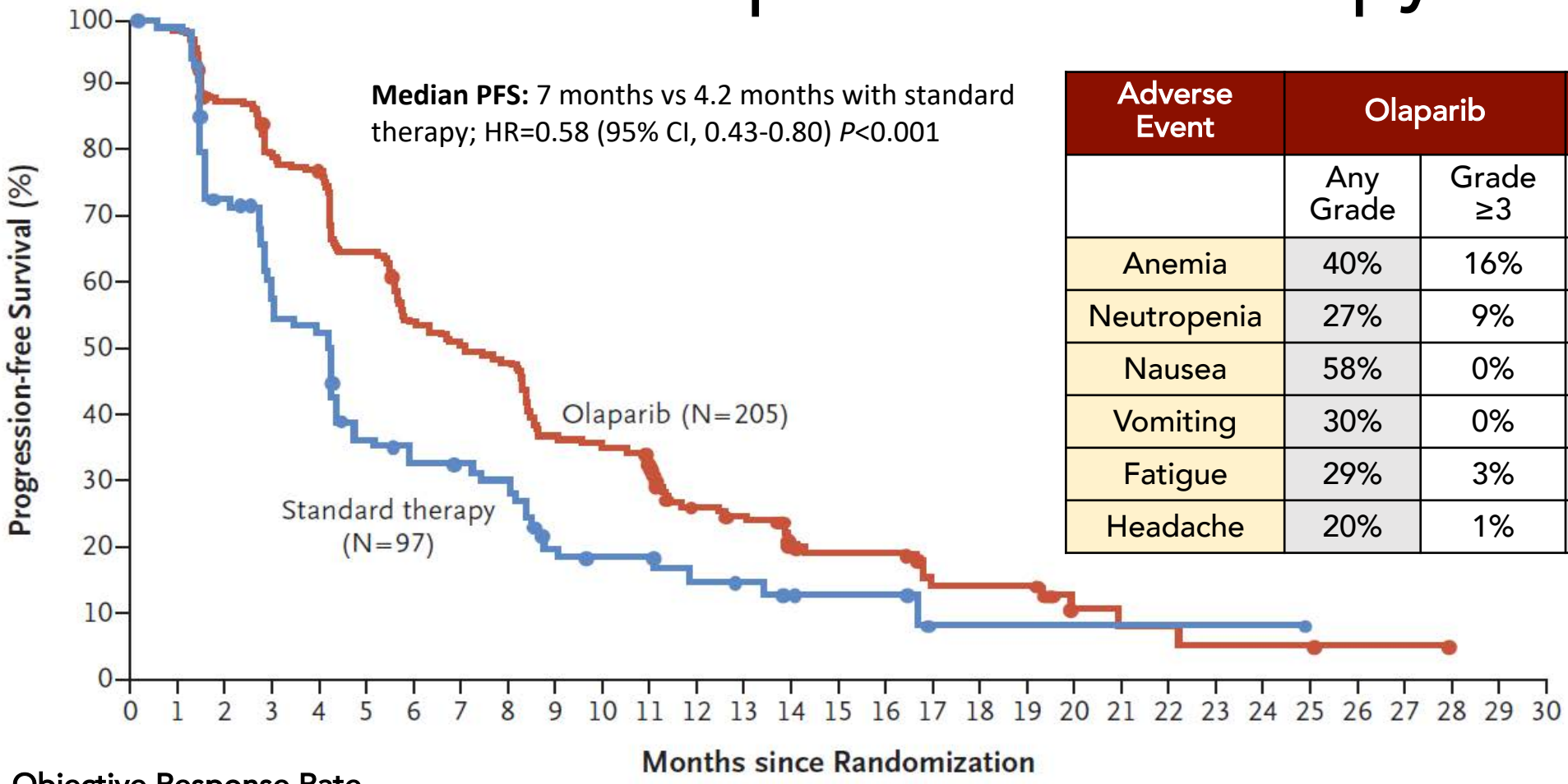
Primary endpoint: PFS (blinded central review)

Secondary endpoints: Safety, OS, ORR, and health-related QOL scores

Robson M, et al. NEJM. 2017

Phase III OlympiAD Trial

PFS with Olaparib Monotherapy



Median PFS: 7 months vs 4.2 months with standard therapy; HR=0.58 (95% CI, 0.43-0.80) *P*<0.001

Adverse Event	Olaparib		Standard Therapy	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	40%	16%	26%	4%
Neutropenia	27%	9%	50%	26%
Nausea	58%	0%	35%	1%
Vomiting	30%	0%	15%	1%
Fatigue	29%	3%	23%	1%
Headache	20%	1%	15%	2%

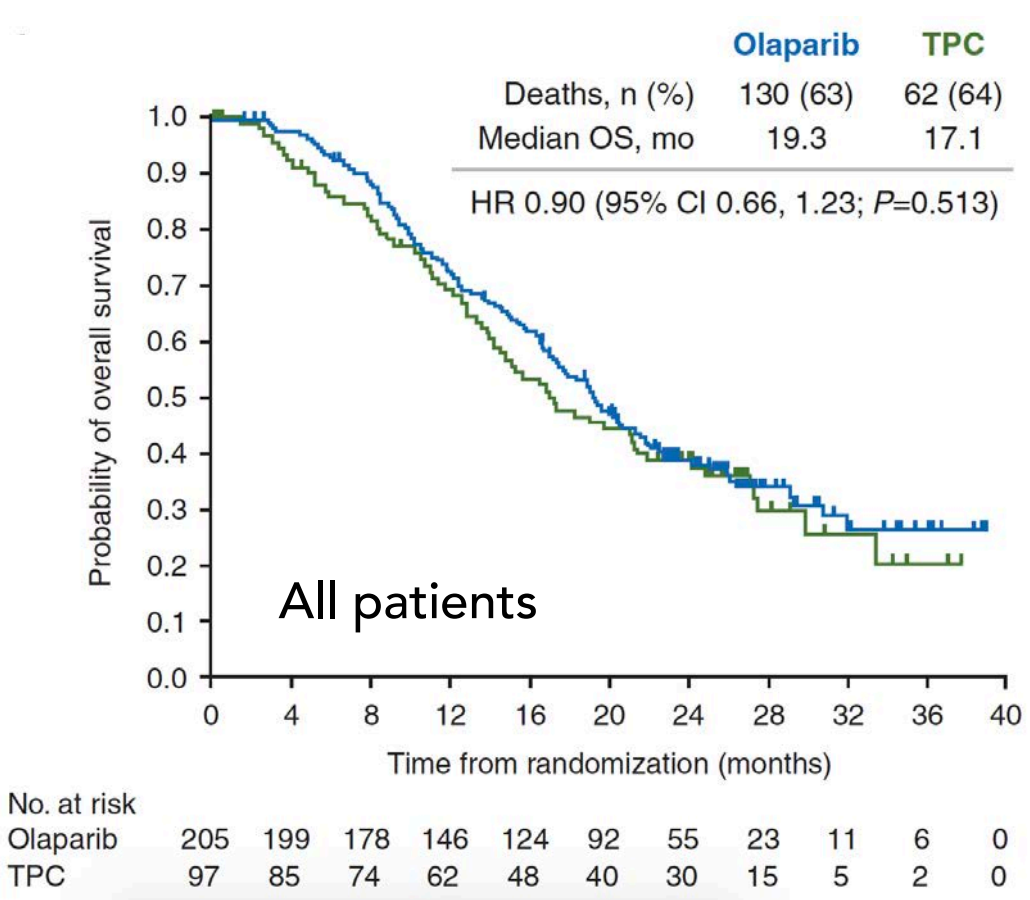
Objective Response Rate

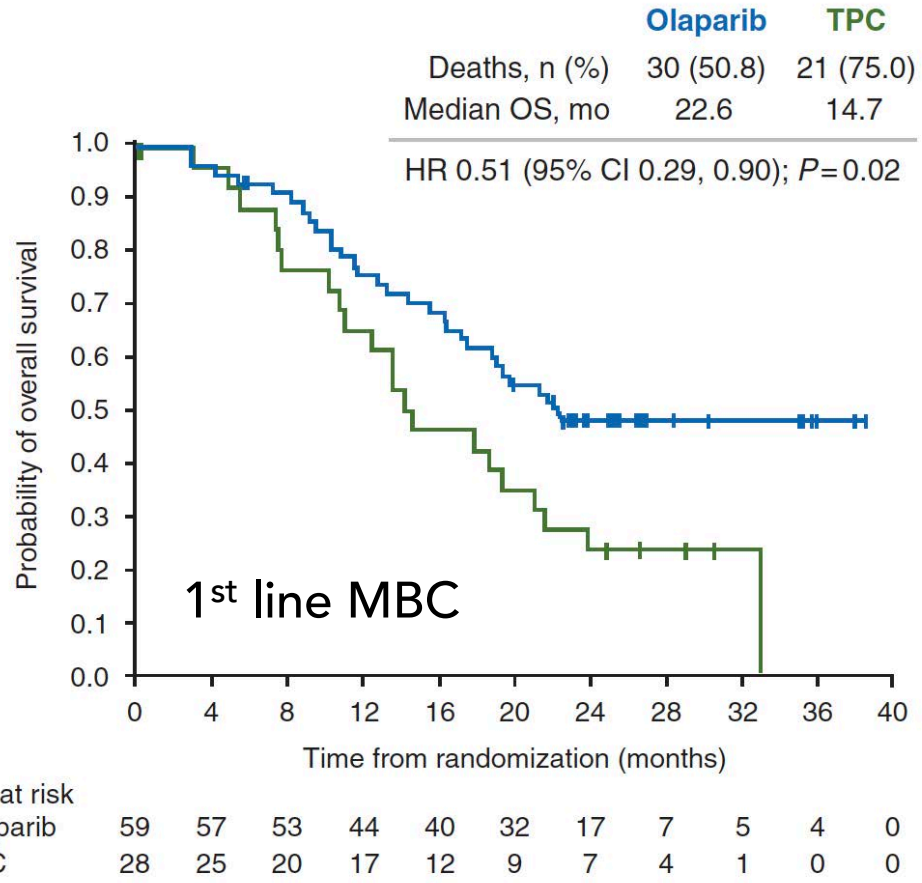
- 59.9% Olaparib
- 28.8% Chemotherapy

Robson M, et al. NEJM, 2017

Phase III OlympiAD Trial

Final OS with Olaparib Monotherapy





Robson, M et al. Ann Oncol, 2019

Phase III EMBRACA Trial

Talazoparib in gBRCA1/2 Mutant Advanced Breast Cancer

g*BRCA1/2*, HER2-negative, Locally Advanced or Metastatic breast cancer
≤3 previous chemotherapy regimens
No limit on number of prior endocrine therapies

RANDOMIZED 2:1

N=431

Talazoparib 1 mg daily
n=287

MD Choice Chemotherapy**
n=144

**Capecitabine, eribulin, vinorelbine, or gemcitabine

- ~45% TNBC
- 16-21% prior platinum
- Platinum resistant excluded

Primary Endpoint: PFS (blinded central review)

Secondary Endpoints: OS, ORR, CBR24, Safety

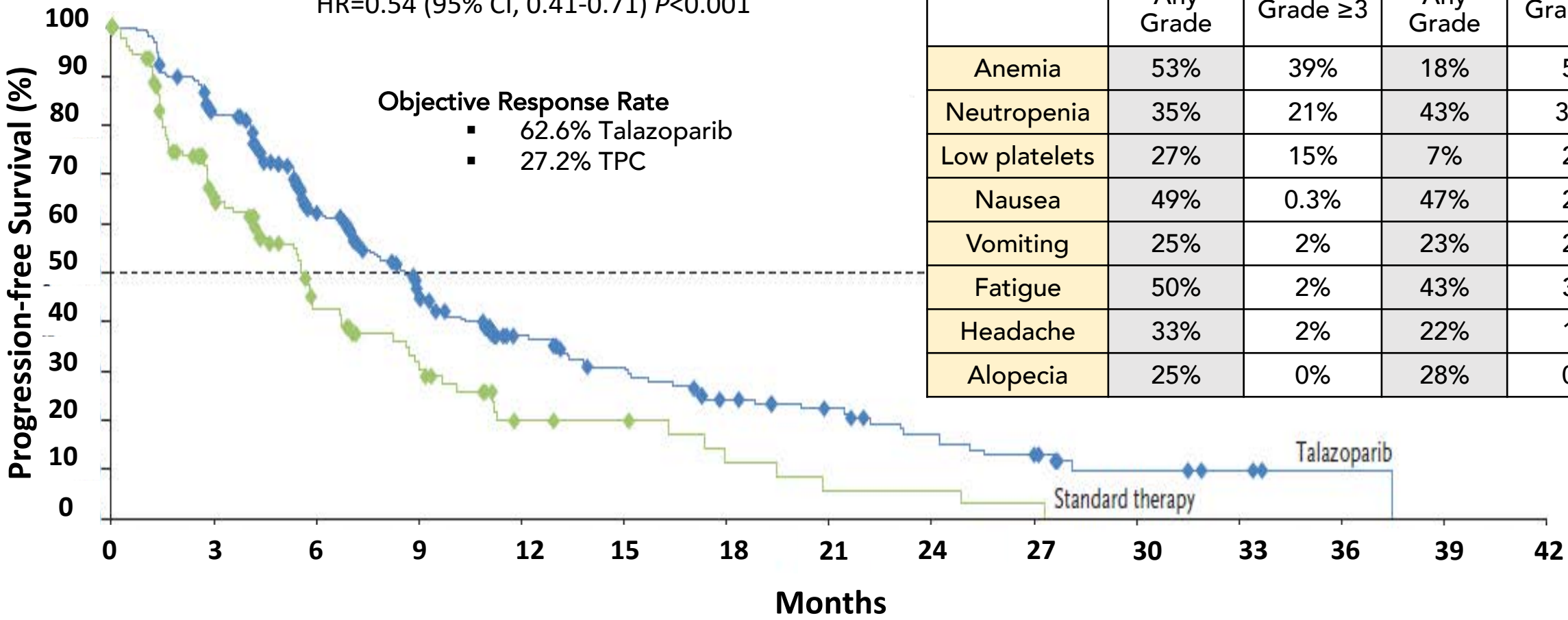
Litton J, et al. NEJM, 2018

Phase III EMBRACA Trial

PFS with Talazoparib Monotherapy

Median PFS: 8.6 months vs **5.6 months** with standard therapy
HR=0.54 (95% CI, 0.41-0.71) *P*<0.001

Objective Response Rate
- 62.6% Talazoparib
- 27.2% TPC

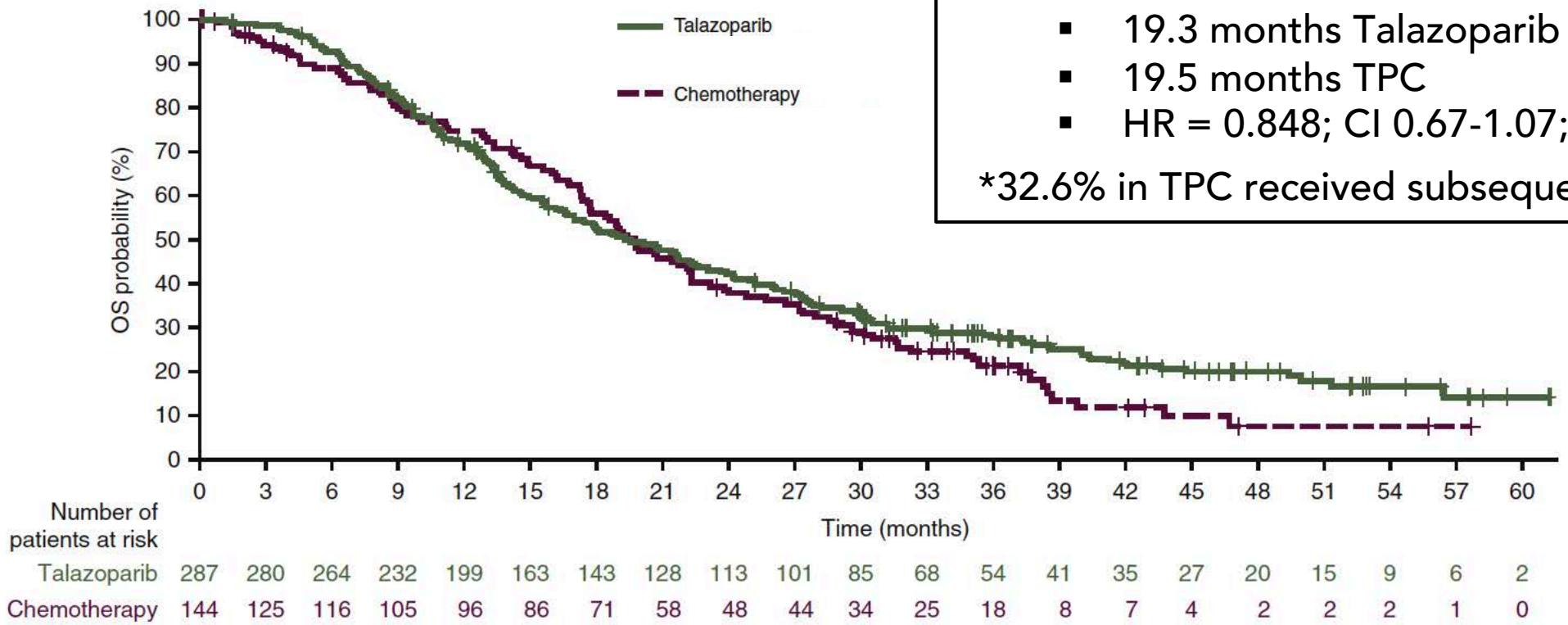


Adverse Event	Talazoparib		Standard Therapy	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	53%	39%	18%	5%
Neutropenia	35%	21%	43%	35%
Low platelets	27%	15%	7%	2%
Nausea	49%	0.3%	47%	2%
Vomiting	25%	2%	23%	2%
Fatigue	50%	2%	43%	3%
Headache	33%	2%	22%	1%
Alopecia	25%	0%	28%	0%

Litton JK, et al. NEJM, 2018

Phase III EMBRACA Trial

Final OS with Talazoparib Monotherapy



Final Overall Survival

- 19.3 months Talazoparib
- 19.5 months TPC
- HR = 0.848; CI 0.67-1.07; p=0.17

*32.6% in TPC received subsequent PARPi

Litton JK, et al. Annals Oncol, 2020

Phase III BROCADE 3 Trial

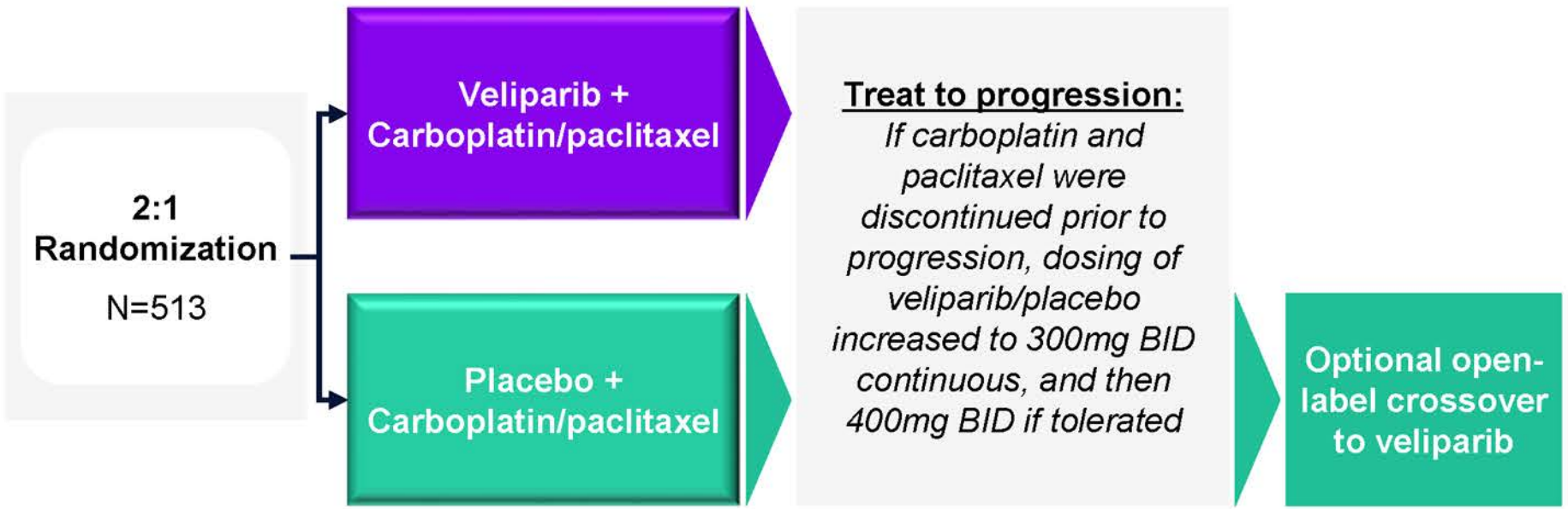
Carboplatin + Paclitaxel +/- Veliparib

Patient Population

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

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis



Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:

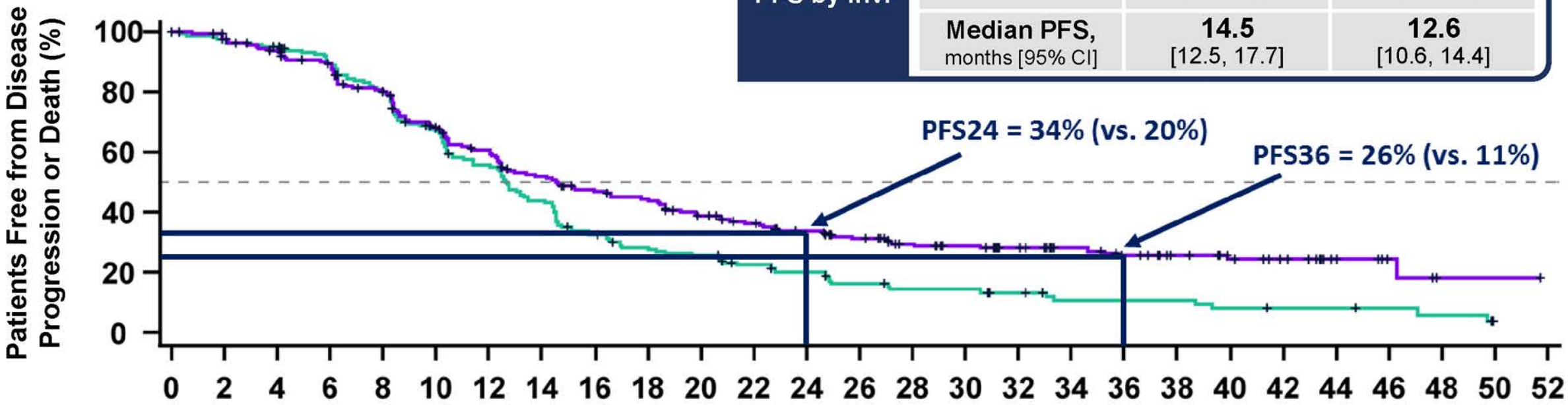
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m^2 on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

Dieras V, et al. *Lancet Oncol*, 2020

Primary Endpoint: PFS by Investigator Assessment

HR 0.705
[95% CI 0.566-0.877], p = 0.002

PFS by Inv.		Veliparib + C/P	Placebo + C/P
	PFS Events, n/N	217/337	132/172
	Median PFS, months [95% CI]	**14.5** [12.5, 17.7]	**12.6** [10.6, 14.4]



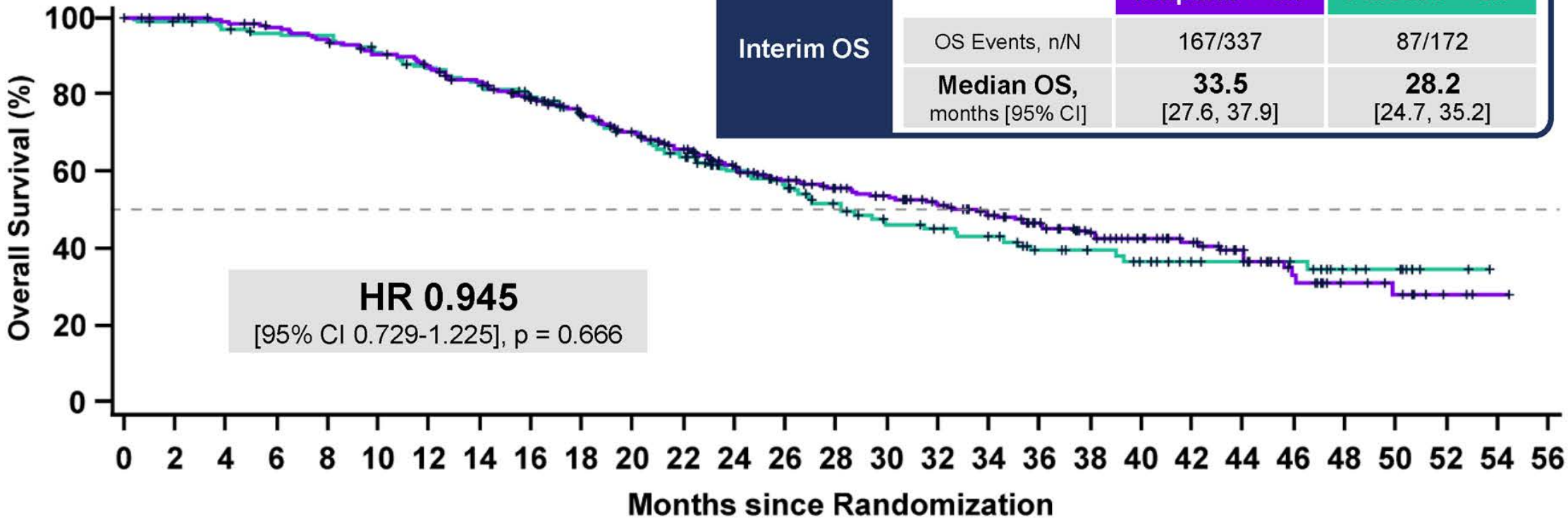
Induction chemotherapy followed by maintenance PARPi may be superior to PARPi monotherapy

No. at Risk

Control	172	160	153	140	123	99	82	64	47	39	35	27	23	18	15	15	12	8	8	8	6	5	5	4	3	0
Veliparib	337	316	301	282	250	207	181	154	137	126	107	92	81	72	60	51	45	38	32	25	20	16	8	4	1	1	0

Dieras V, et al. *Lancet Oncol*, 2020

Secondary Endpoint: Overall Survival (Interim Analysis)



Interim OS	Veliparib + C/P	Placebo + C/P
OS Events, n/N	167/337	87/172
Median OS, months [95% CI]	**33.5** [27.6, 37.9]	**28.2** [24.7, 35.2]

No. at Risk

Control	172	166	162	158	157	149	141	134	125	111	102	90	75	68	57	47	44	40	32	29	25	19	18	15	9	7	2	0	
Veliparib	337	332	326	318	307	294	281	265	247	223	203	185	161	145	132	117	106	90	76	62	50	41	30	18	11	8	3	1	0

BARCELONA 2019 ESMO congress

C/P: Carboplatin and Paclitaxel

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

Dieras V, et al. *Lancet Oncol*, 2020

Talazoparib Beyond BRCA (TBB)

COHORT B: HER2-Negative Breast or Other Solid Tumor

↓

No mutation in BRCA1 or BRCA2

↓

Germline or somatic HR pathway gene mutation

↓

Accrue 10 patients

↓

Accrue 10 additional pts if ≥ 2 responses in stage 1

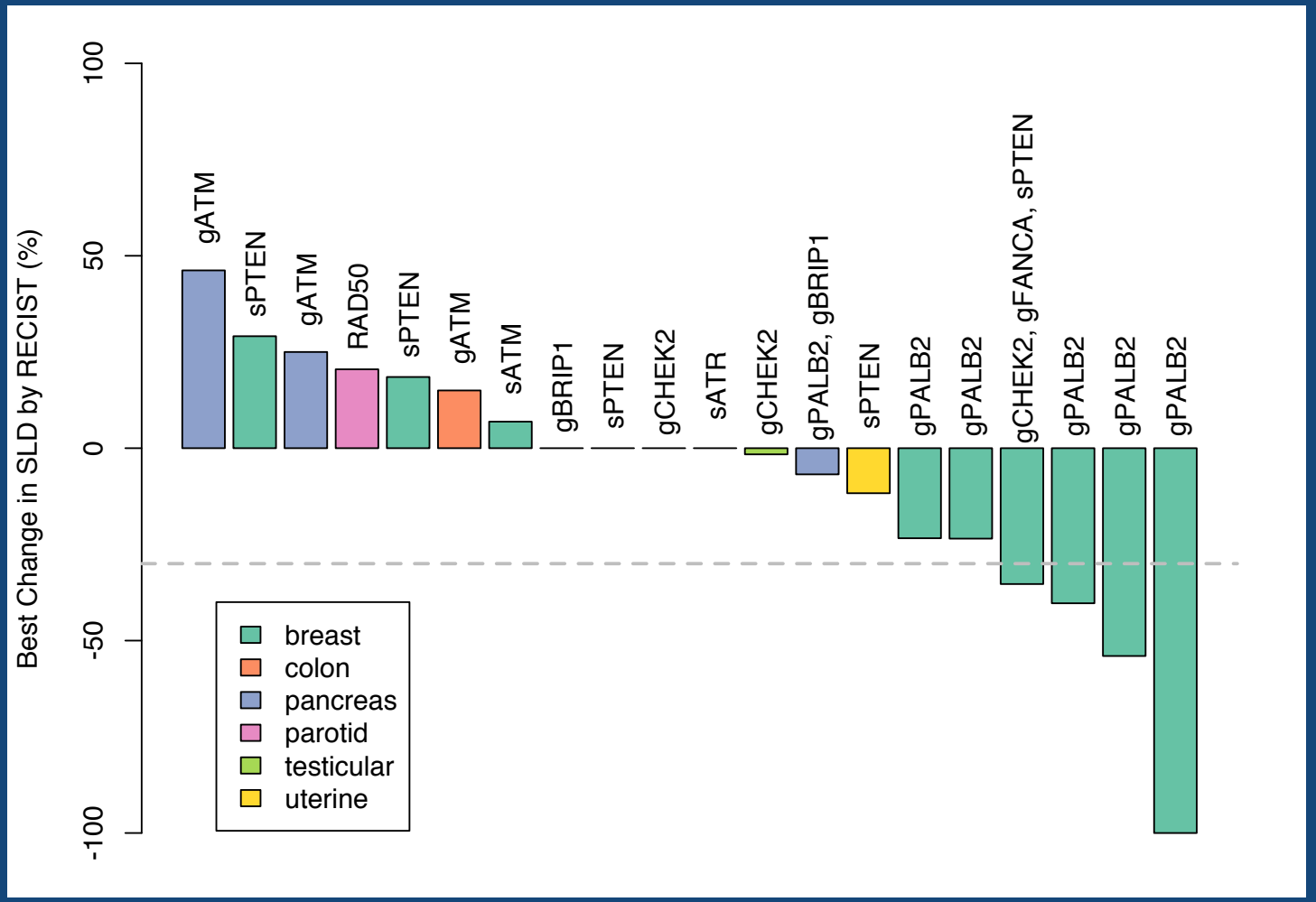
Cohort B mutations:

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

Talazoparib Beyond BRCA cohort B

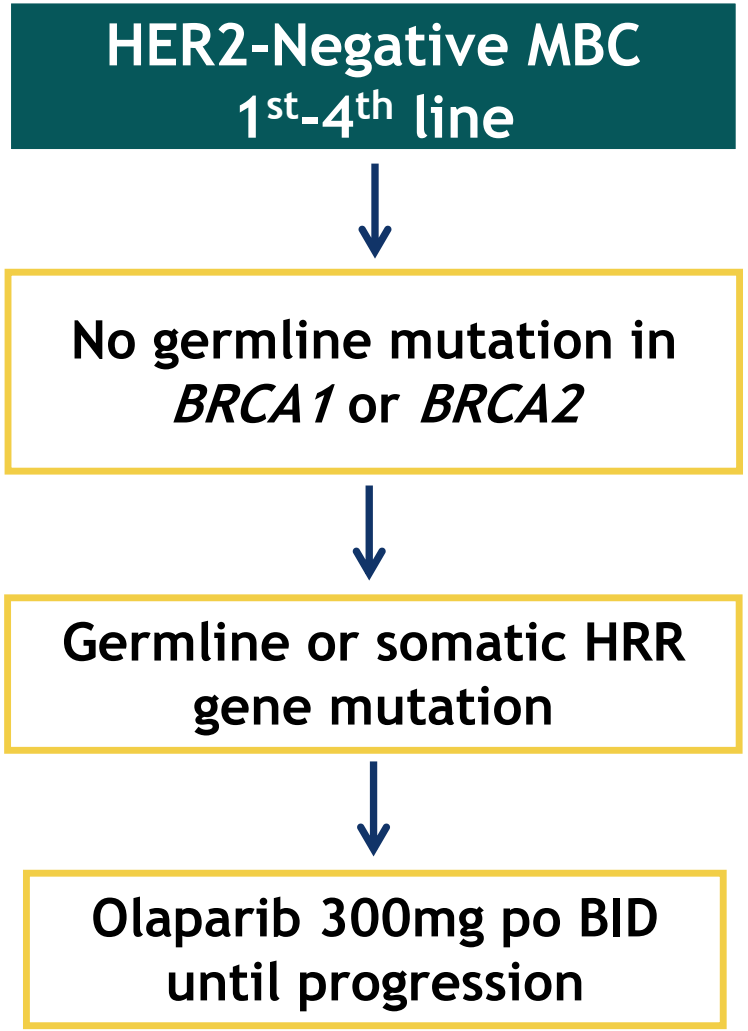
Best Overall Responses

All Patients



Gruber JJ, et al. ASCO 2019

TBCRC-048: Olaparib Expanded



Eligible mutations:

Germline or Somatic

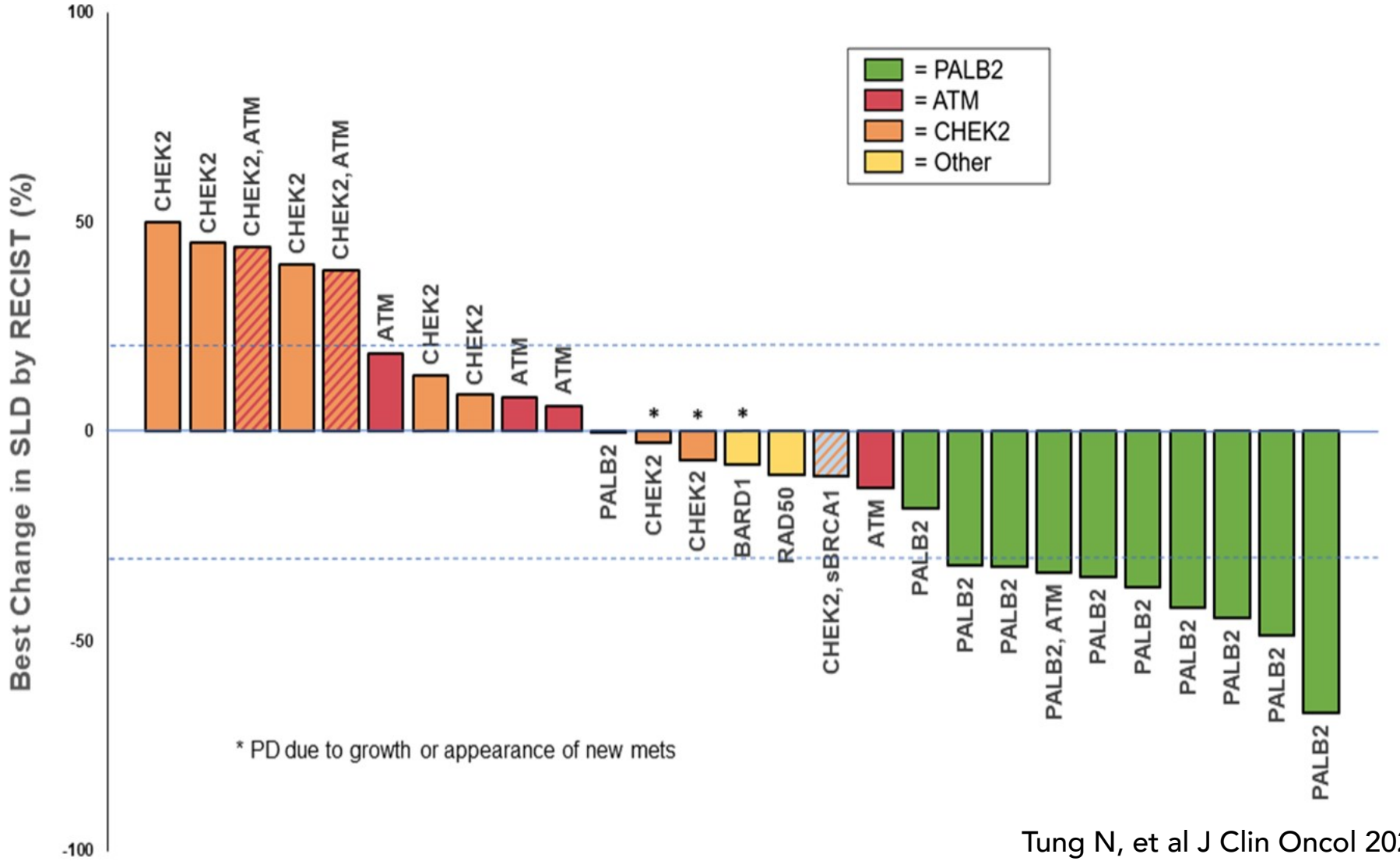
PALB2	RAD51C
CHEK2	RAD51D
ATM	FANCA
NBN	FANCC
BARD1	FANCD2
BRIP1	FANCE
MRE11A	FANCF
ATR	FANCM
RAD50	

Somatic

BRCA1
BRCA2

Tung N, et al J Clin Oncol 2020

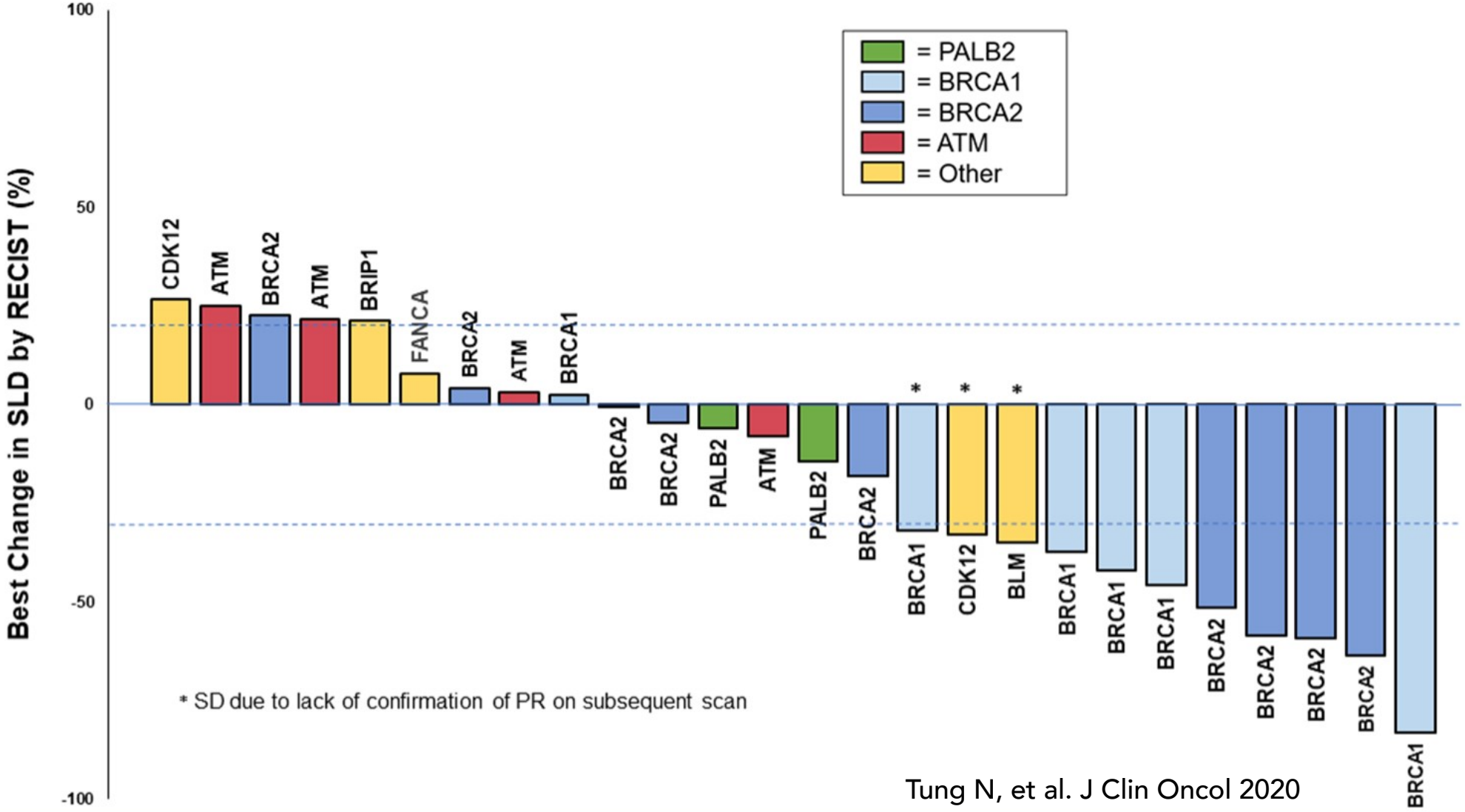
Best Overall Responses: Cohort 1 (Germline)



Datacut May 4, 2020

Tung N, et al J Clin Oncol 2020

Best Overall Responses: Cohort 2 (Somatic)



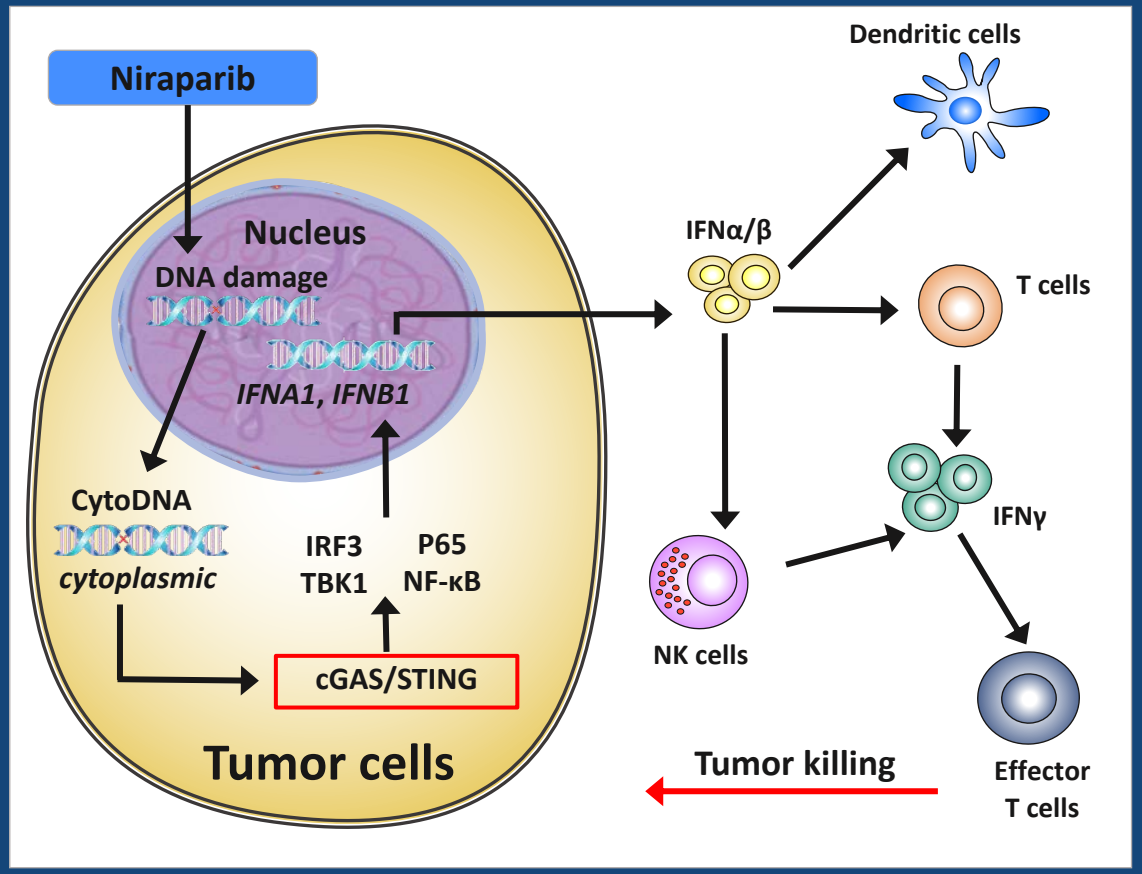
Datacut May 4, 2020

Tung N, et al. J Clin Oncol 2020

TOPACIO: Niraparib + Pembrolizumab in mTNBC

Preclinical studies demonstrated synergistic activity of PARPi + anti-PD-1, regardless of *BRCA* mutational status or PD-1 sensitivity

- Potential Mechanism of Action
  - Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, activating Stimulator of Interferon Genes (STING) pathway
  - Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T-cells



1. Huang J et al. Biochem Biophys Res Commun. 2015 Aug 7;463(4):551-6; 2. Jiao SP et al. Clin Cancer Res. 2017 Jul 15;23(14):3711-3720; 3. Sato H et al. Nat Commun. 2017 Nov 24;8(1):1751

JAMA Oncology | Original Investigation

Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer

Shaveta Vinayak, MD, MS; Sara M. Tolaney, MD, MPH; Lee Schwartzberg, MD; Monica Mita, MD; Georgia McCann, MD; Antoinette R. Tan, MD; Andrea E. Wahner-Hendrickson, MD; Andres Forero, MD; Carey Anders, MD; Gerburg M. Wulf, MD, PhD; Patrick Dillon, MD; Filipa Lynce, MD; Corrine Zarwan, MD; John K. Erban, MD; Yinghui Zhou, PhD; Nathan Buerstatte, BS, MPH; Julie R. Graham, PhD; Sujata Arora, MS; Bruce J. Dezube, MD; Melinda L. Telli, MD

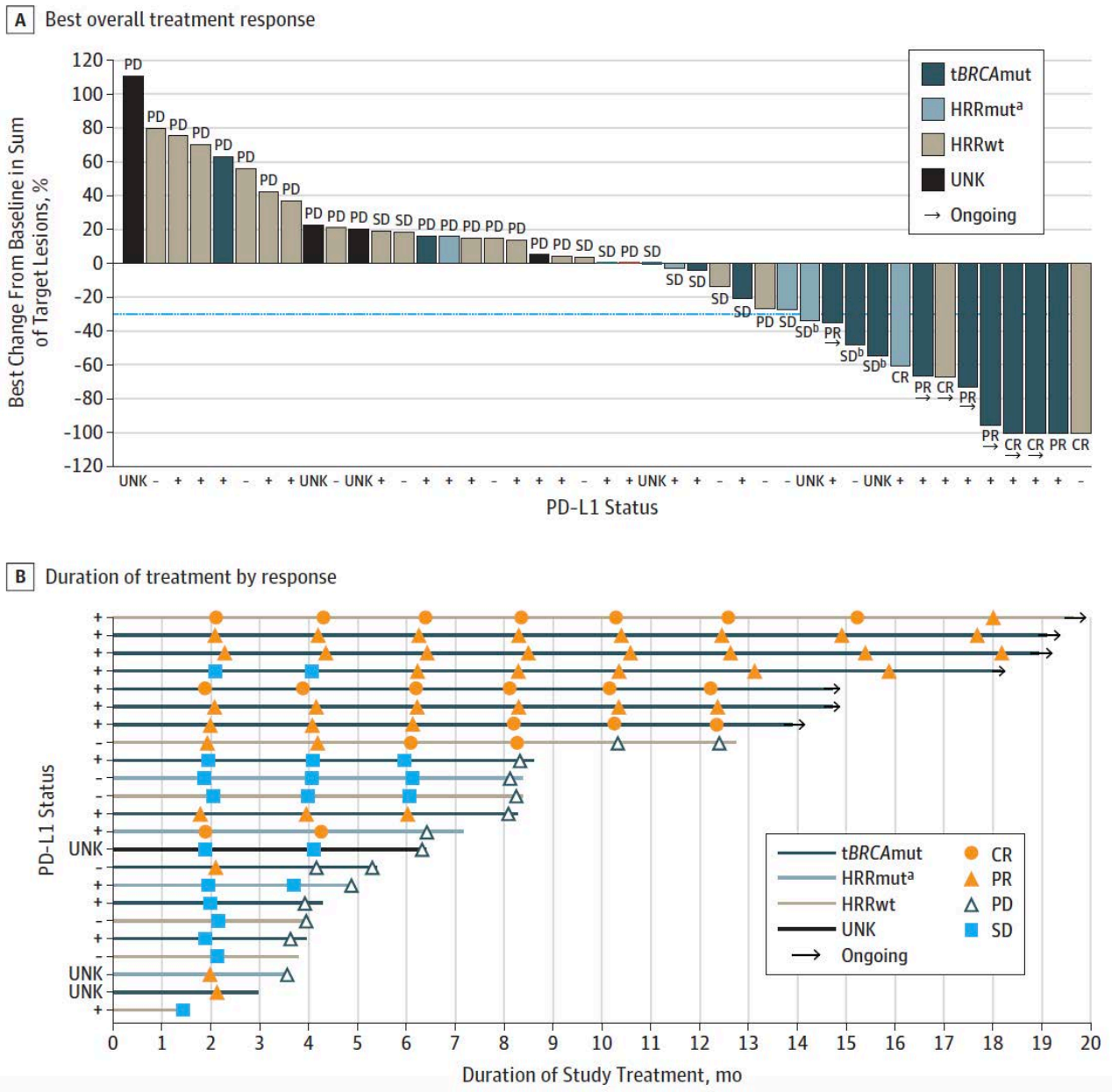
- 47 evaluable patients with mTNBC
- 1st-3rd line
- Included patients with platinum resistant disease

- **ORR = 21%**

TOPACIO CLINICAL TRIAL

Vinayak S, et al. JAMA Oncology 2019

Figure 2. Antitumor Activity of Niraparib in Combination With Pembrolizumab by Biomarker Status



Select PARP inhibitor & PD-1/PD-L1 Inhibitor Trials

Trial	Phase	Treatment Arms	Inclusion	Primary Outcomes
DORA NCT03167619	II	• Olaparib • Olaparib/durvalumab	• TNBC 1st / 2nd line with CR/PR/SD after 4 cycles of platinum induction therapy	PFS
MEDIOLA NCT02734004	I/II	• Olaparib/durvalumab	• HER2-, *gBRCA+* 1st / 2nd line • HER2-, mHRR+ 1st / 2nd line	ORR/DCR
TOPACIO/ KEYNOTE-162 NCT02657889	II	• Niraparib/pembrolizumab	• TNBC, 1st – 3rd line	ORR
JAVELIN PARP MEDLEY NCT03330405	II	• Talazoparib/avelumab	• TNBC, 1st – 3rd line • HR+, DDR+, 1st – 3rd line	ORR
KEYLYNK-009 NCT04191135	II/III	• Olaparib/pembrolizumab • GC/pembrolizumab	• TNBC 1st line with CR/PR/SD after 4-6 cycles of gem/carbo + pembrolizumab	PFS/OS

Thank you