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A National Cancer Institute-designated Comprehensive Cancer Center

Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

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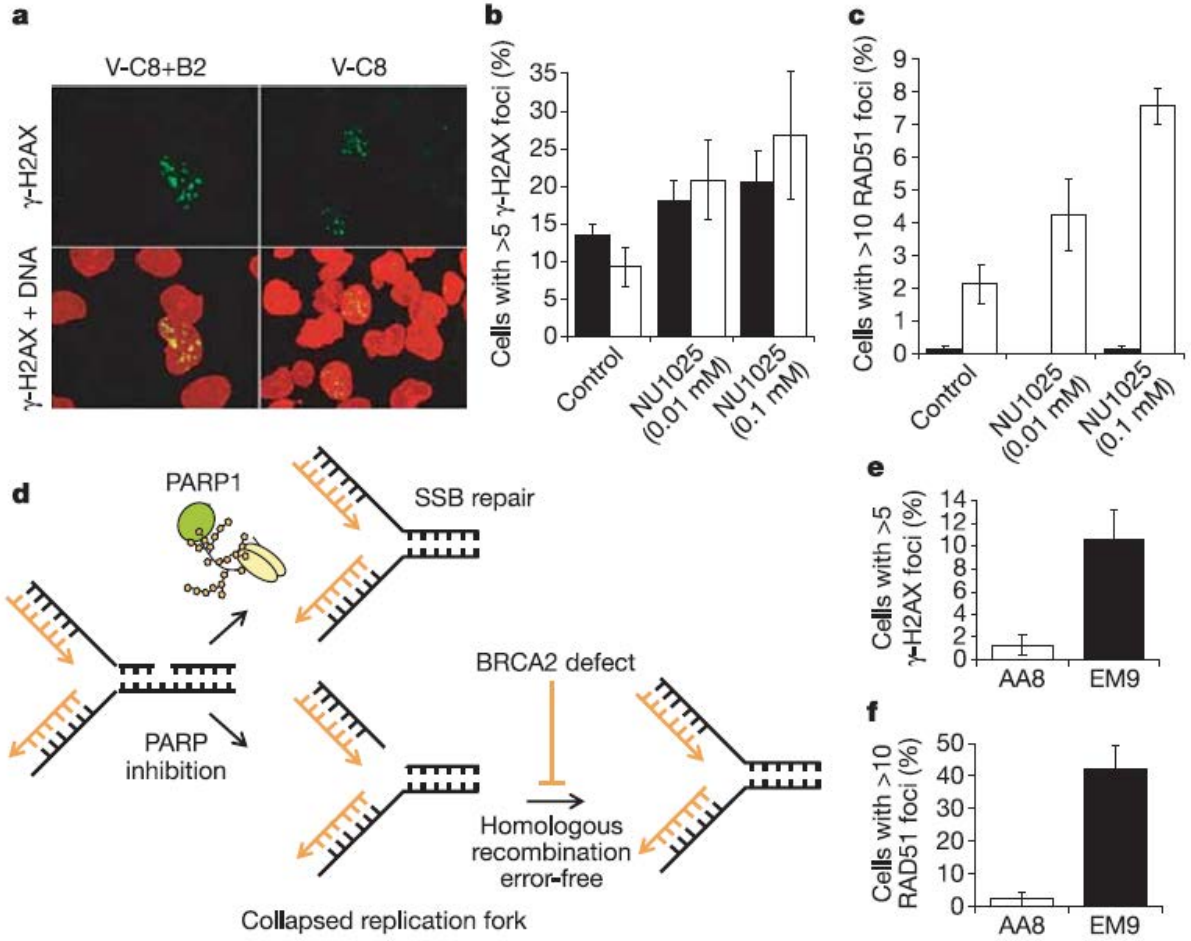
DukeMedicine

Discovery of PARP Inhibition

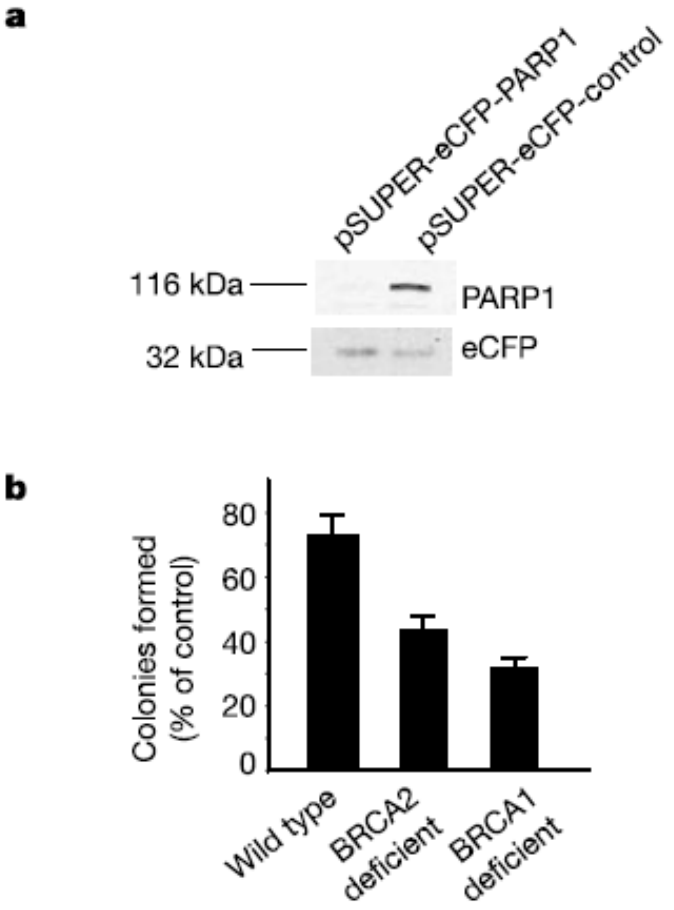
Discovery of PARP as a Target

Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005; 434: 913–17.

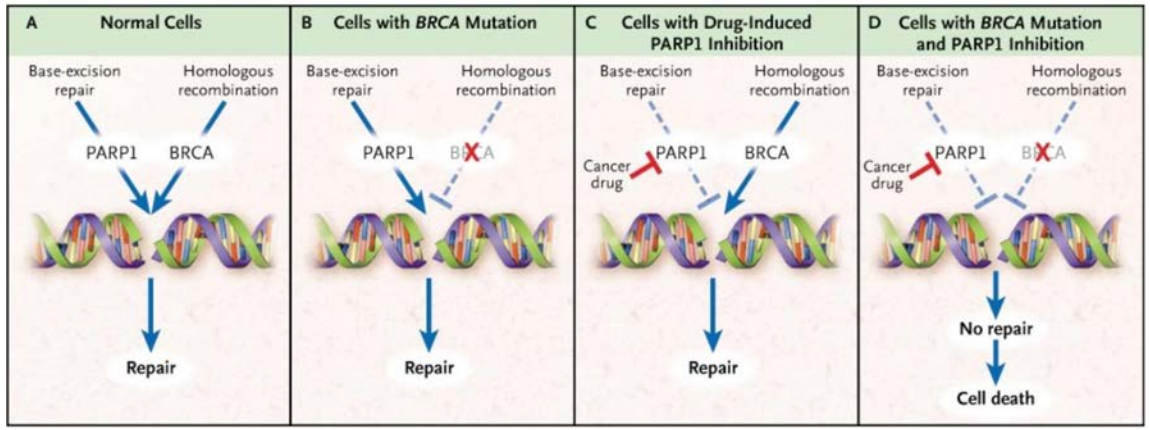


Courtesy of P Kelly Marcom, MD

Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434: 917–21.



PARPi MOA Trapping vs. not and potency



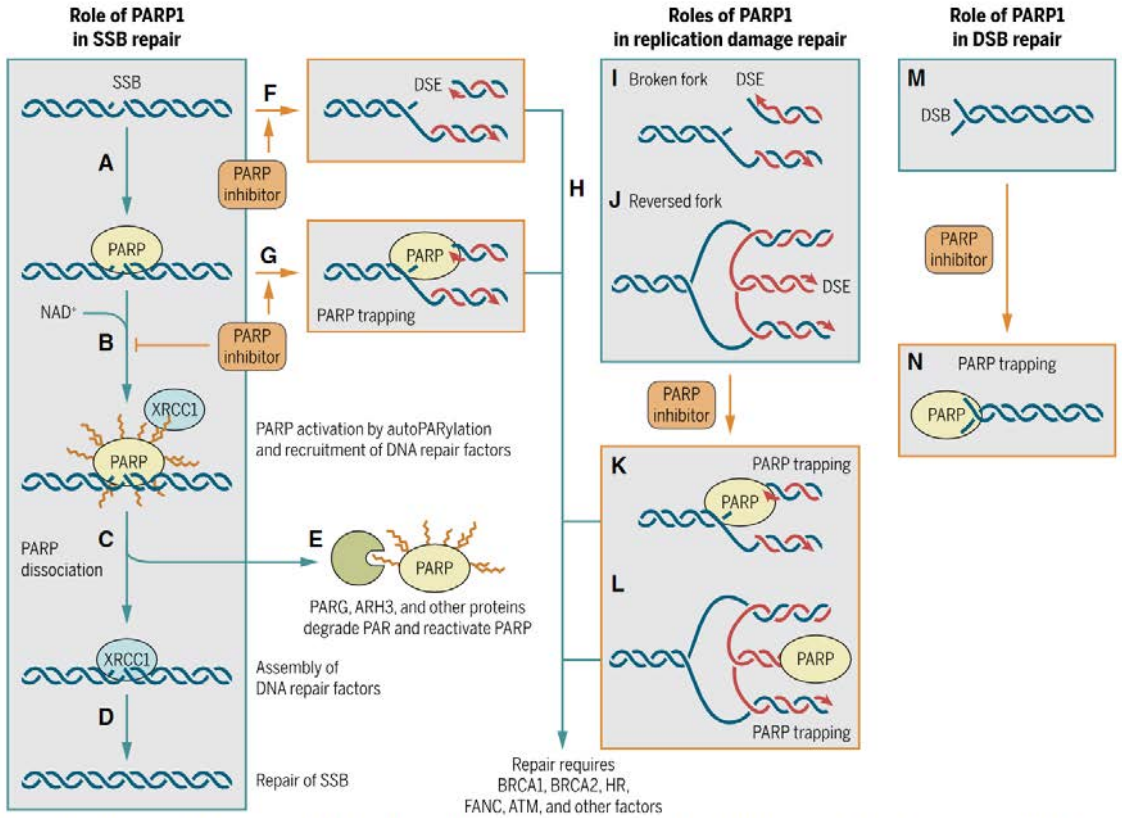


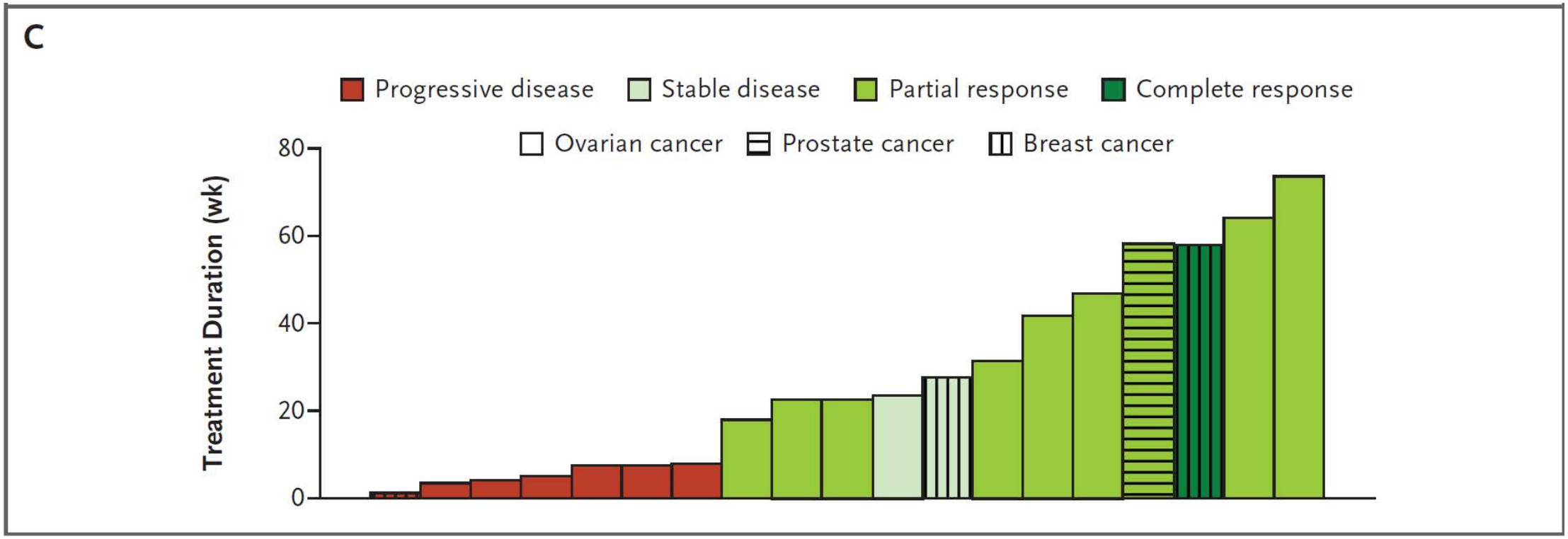
Fig. 1. DNA repair by PARP1 and the effects of PARP inhibitors. Upon the generation of an SSB, PARP1 binds to the break (**A**) and uses NAD^+ (**B**) to generate PAR polymers on itself (auto-PARylation), as well as on histones and chromatin-associated proteins. This serves the purpose of relaxing chromatin and recruiting repair proteins. Cumulative auto-PARylation causes the dissociation of PARP1 from DNA (**C**), allowing access to other repair factors scaffolded by XRCC1 (**D**). PARylation is removed by PARG (**E**), a glycohydrolase, which allows PARP1 reactivation. PARP inhibitors block NAD^+ binding and PARylation for as long as the inhibitor is bound to the NAD^+ site (B), thereby preventing PARP dissociation from the SSB, resulting in both accumulation of unrepaired SSBs (**F**) and PARP trapping (**G**). Repairing the ensuing DSB and PARP trapping will require BRCA1, BRCA2, and other HRR factors, as well as ATM, Fanconi, and replication bypass pathways for cell survival (**H**). PARP1 is also involved in the repair of "collapsed forks" with DSEs (**I**), in the retraction and restart of stalled replication forks (**J**), and in the repair of DSBs (**M**). PARP inhibitors trap PARP at DSEs (**K** and **L**) and DSBs (**N**).

Iglehart, J.D., Silver, D.P., 2009. Synthetic Lethality — A New Direction in Cancer-Drug Development. New England Journal of Medicine.. doi:10.1056/nejme0903044

Courtesy of P Kelly Marcom, MD

Pommier, O'Connor, de Bono, Sci. Transl. Med. 8, 362ps17 (2016) 26 October 2016

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers



Olaparib monotherapy at 200mg PO twice daily

Courtesy of P Kelly Marcom, MD

Fong, N Engl J Med 2009;361:123-34.

Currently Approved PARP Inhibitors in Select Settings

Inhibitor	Ovarian	Prostate	Breast	Pancreatic	Lung
Olaparib	Maintenance in platinum-sensitive (Dec 2014); 1st-line Maintenance Therapy (Dec 2018); 1st-line maintenance in combination with bevacizumab (May 2020)	Metastatic CRPC with germline or somatic HRR mutations (including BRCA and ATM) (May, 2020)	Metastatic HER2-negative BRCA mutated breast cancer (Jan 2018)	1st-line Maintenance in BRCA mutated pancreatic adenocarcinoma (Dec 2019)	
Rucaparib	Platinum sensitive ovarian cancer (Dec 2016) without companion diagnostic	Metastatic CRPC post taxane (BRCA mutation) (May 2020)			
Niraparib	Recurrent ovarian cancer maintenance (March 2017); After 3 or more prior chemo lines for HRD-pos ovarian cancer (Oct 2019); 1st-line maintenance for advanced ovarian cancer (April 2020)				
Talazoparib			Metastatic BRCA-mutated HER2-negative breast cancer (Oct 2018)		
Veliparib					Orphan drug status (Nov 2016)

Courtesy of P Kelly Marcom, MD

Phase III Clinical Data

Breast Cancer Approvals for Single Agent

Phase III Trial Designs:

OlympiAD Schema

- gBRCA mutation by BRACAnalysis
- HER2-negative (ER/PR +/-)
- Prior anthracycline and taxane
- ≤ 2 prior chemo lines in metastatic setting
- HR+ at least one line endocrine therapy
- Prior platinum allowed if: No progression in advanced setting or ≥ 12 months from (neo)adjuvant treatment.

2:1

- Olaparib 300 mg BID
- PC Chemo:
  - Capecitabine
  - Eribulin
  - Vinorelbine

Treatment Until RECIST Progression

Primary Endpoint:
- Progression Free Survival

Secondary Endpoints:
- Time to 2nd Progression
- Overall Survival
- Objective Response Rate
- Safety/Tolerability

Robson, N Engl J Med 2017;377:523-33.

EMBRACA Schema

- gBRCA mutation by BRACAnalysis
- HER2-negative (ER/PR +/-)
- Prior anthracycline and taxane
- ≤ 3 prior chemo lines in metastatic setting
- No limit on prior endocrine but not required
- Prior platinum allowed if: No progression in advanced setting or ≥ 6 months from (neo)adjuvant treatment.

2:1

- Talazoparib 1 mg daily
- PC Chemo:
  - Capecitabine
  - Eribulin
  - Vinorelbine
  - Gemcitabine

Treatment Until RECIST Progression

Primary Endpoint:
- Progression Free Survival

Secondary Endpoints:
- Overall Survival
- Objective Response Rate by investigator
- Safety/Tolerability

Litton, N Engl J Med 2018;379:753-63

Courtesy of P Kelly Marcom, MD

Phase III Trials: Patient characteristics

OlympiAD

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Olaparib Group (N=205)	Standard-Therapy Group (N=97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

Courtesy of P Kelly Marcom, MD

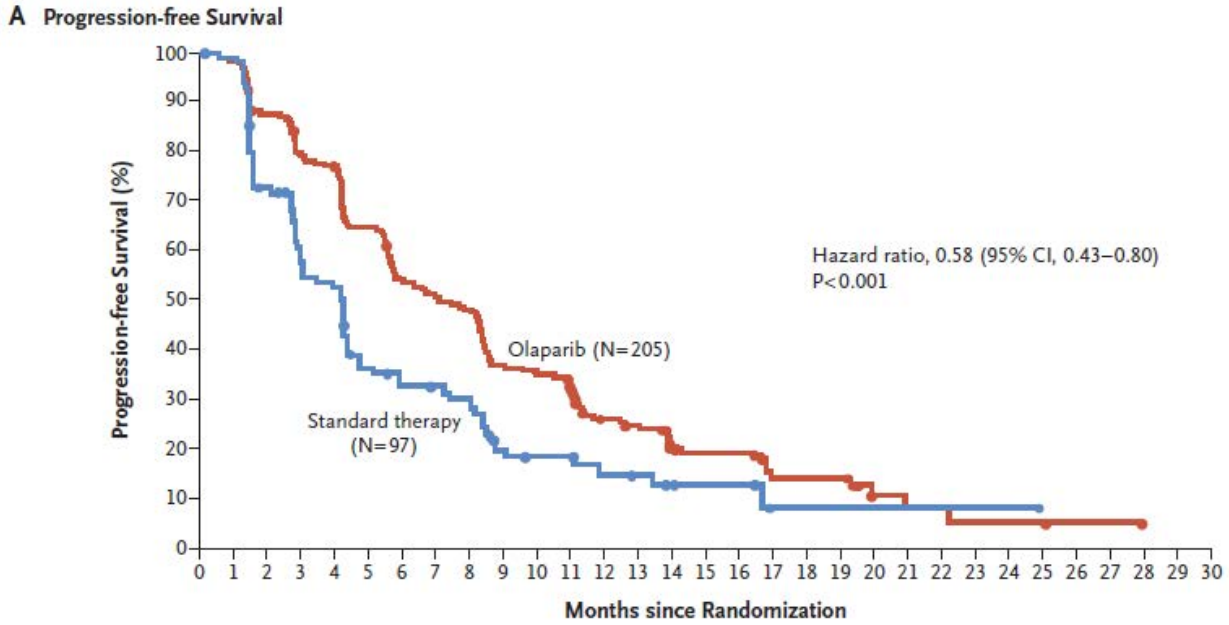
EMBRACA

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

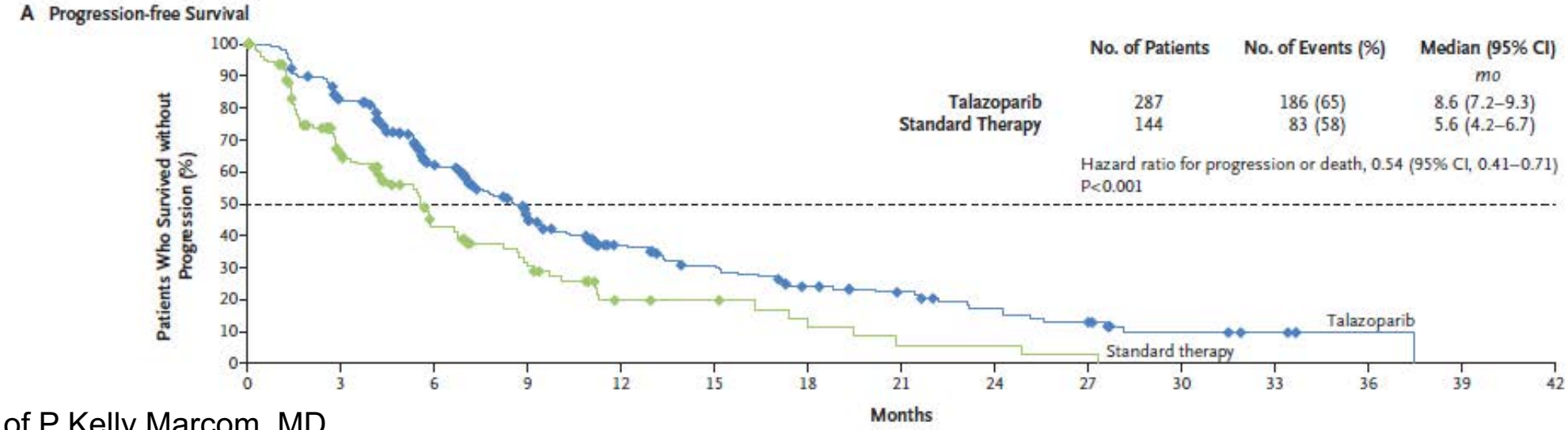
Characteristic	Talazoparib Group (N=287)	Standard-Therapy Group (N=144)
Age — yr		
Median	45	50
Range	27.0–84.0	24.0–88.0
Age <50 yr — no. (%)	182 (63.4)	67 (46.5)
Female sex — %	98.6	97.9
ECOG performance status score — %†		
0	53.3	58.3
1	44.3	39.6
2	2.1	1.4
Breast cancer stage — no. (%)‡		
Locally advanced	15 (5.2)	9 (6.2)
Metastatic	271 (94.4)	135 (93.8)
Measurable disease assessed by investigator — no. (%)	219 (76.3)	114 (79.2)
History of CNS metastases — no. (%)	43 (15.0)	20 (13.9)
Visceral disease — no. (%)	200 (69.7)	103 (71.5)
Hormone-receptor status — no. (%)		
Triple-negative	130 (45.3)	60 (41.7)
Hormone-receptor–positive	157 (54.7)	84 (58.3)
BRCA status — no. (%)§		
BRCA1-positive	133 (46.3)	63 (43.8)
BRCA2-positive	154 (53.7)	81 (56.2)
<12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%)	108 (37.6)	42 (29.2)
Previous adjuvant or neoadjuvant therapy — no. (%)	238 (82.9)	121 (84.0)
No. of previous hormone-therapy–based regimens for hormone-receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients)		
Median	2.0	2.0
Range	0–6	0–6
Previous platinum therapy — no. (%)	46 (16.0)	30 (20.8)
Previous cytotoxic regimens for advanced breast cancer — no. (%)		
0	111 (38.7)	54 (37.5)
1	107 (37.3)	54 (37.5)
2	57 (19.9)	28 (19.4)
3	12 (4.2)	8 (5.6)

Phase III Trials: Progression-Free Survival

OlympiAD



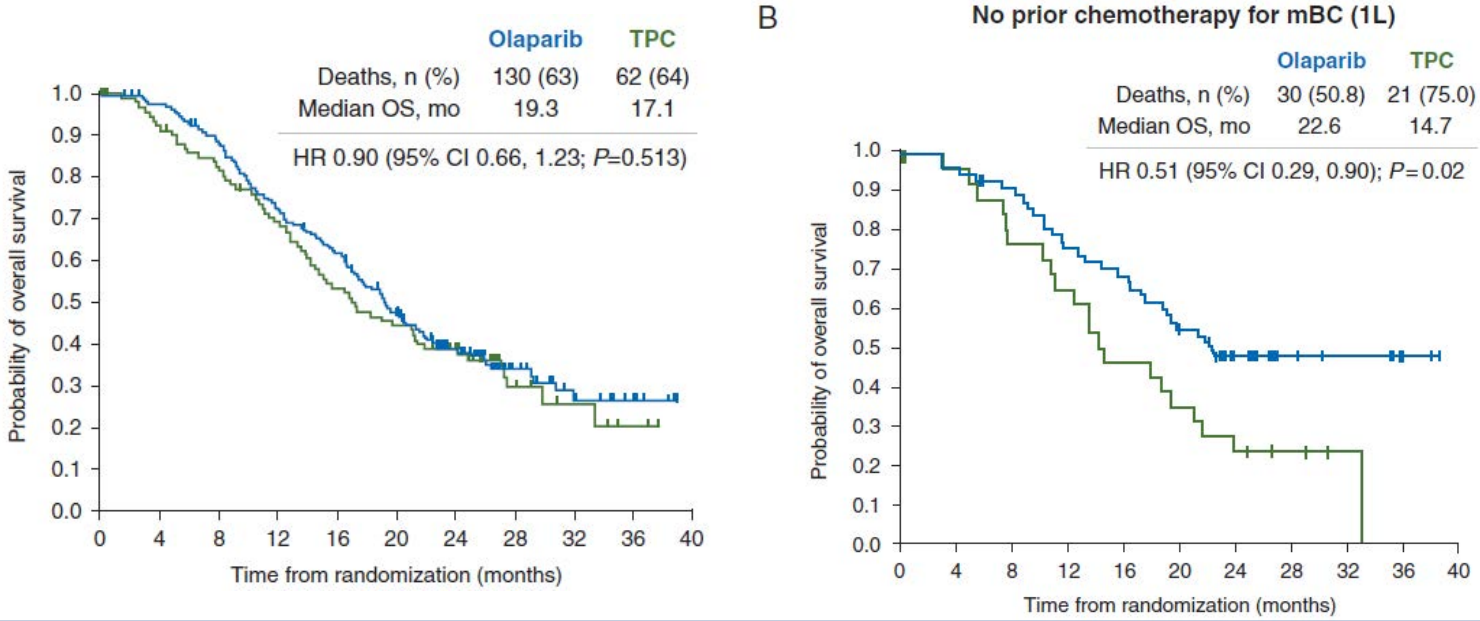
EMBRACA



Courtesy of P Kelly Marcom, MD

Phase III Trials: Final Overall Survival Data

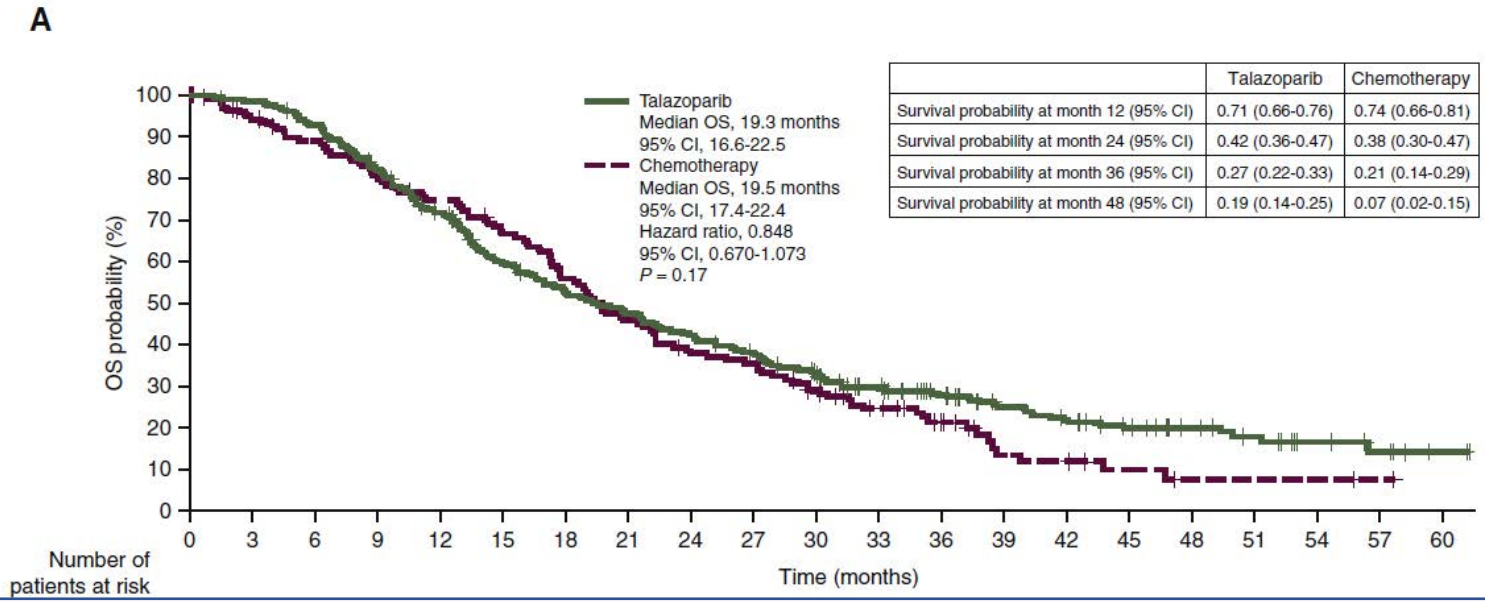
OlympiAD



- No crossover
- No approved PARPi available at progression.

Robson, Annals of Oncology 30: 558–566, 2019

EMBRACA



	Talazoparib	Chemotherapy
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

- 25% of chemo received olaparib in subsequent lines v. 2.8% of talazoparib.
- CDK4/6i: 13.6% talazoparib v. 10.4% chemotherapy

Litton, Annals of Oncology, 31: 1526-1535, 2020

Courtesy of P Kelly Marcom, MD

Veliparib

- A different PARP inhibitor; Inhibits PARP1 and PARP2
- No “PARP trapping”. More limited MOA allows combining with chemotherapy
- Results of I-SPY2 indicated high probability of improving pCR in TNBC (not genetically selected)
- In the BrighTNess preoperative trial, the addition of veliparib did NOT increase pCR rate, although was tolerated.
- The BROCADE2 Phase II trial investigated addition of veliparib to carboplatin/paclitaxel in gBRCA mutated metastatic breast cancer; a statistically non-significant improvement in PFS was seen.

Courtesy of P Kelly Marcom, MD

Loibl, BrighTNess, Lancet Oncol 2018; 19: 497–509

Han, BROCADE2, Annals of Oncology 29: 154–161, 2018

Study Design: BROCADE3 (NCT02163694)

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

2:1 Randomization
N=513

Veliparib + Carboplatin/paclitaxel

Placebo + Carboplatin/paclitaxel

Treat to progression:
If carboplatin and paclitaxel were discontinued prior to progression, dosing of veliparib/placebo increased to 300mg BID continuous, and then 400mg BID if tolerated

Optional open-label crossover to veliparib

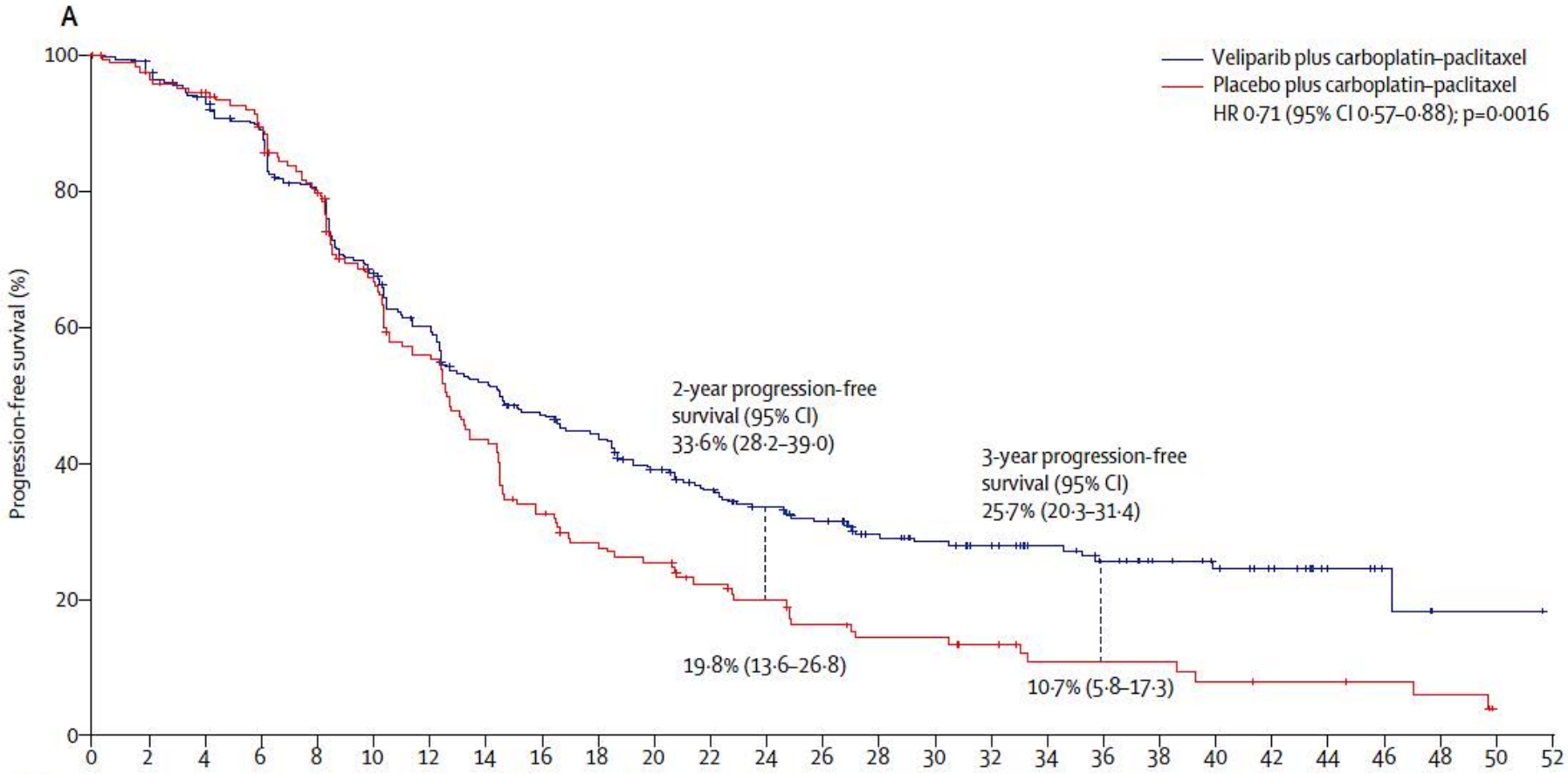
Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

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

BARCELONA 2019 ESMO congress

Courtesy of P Kelly Marcom, MD

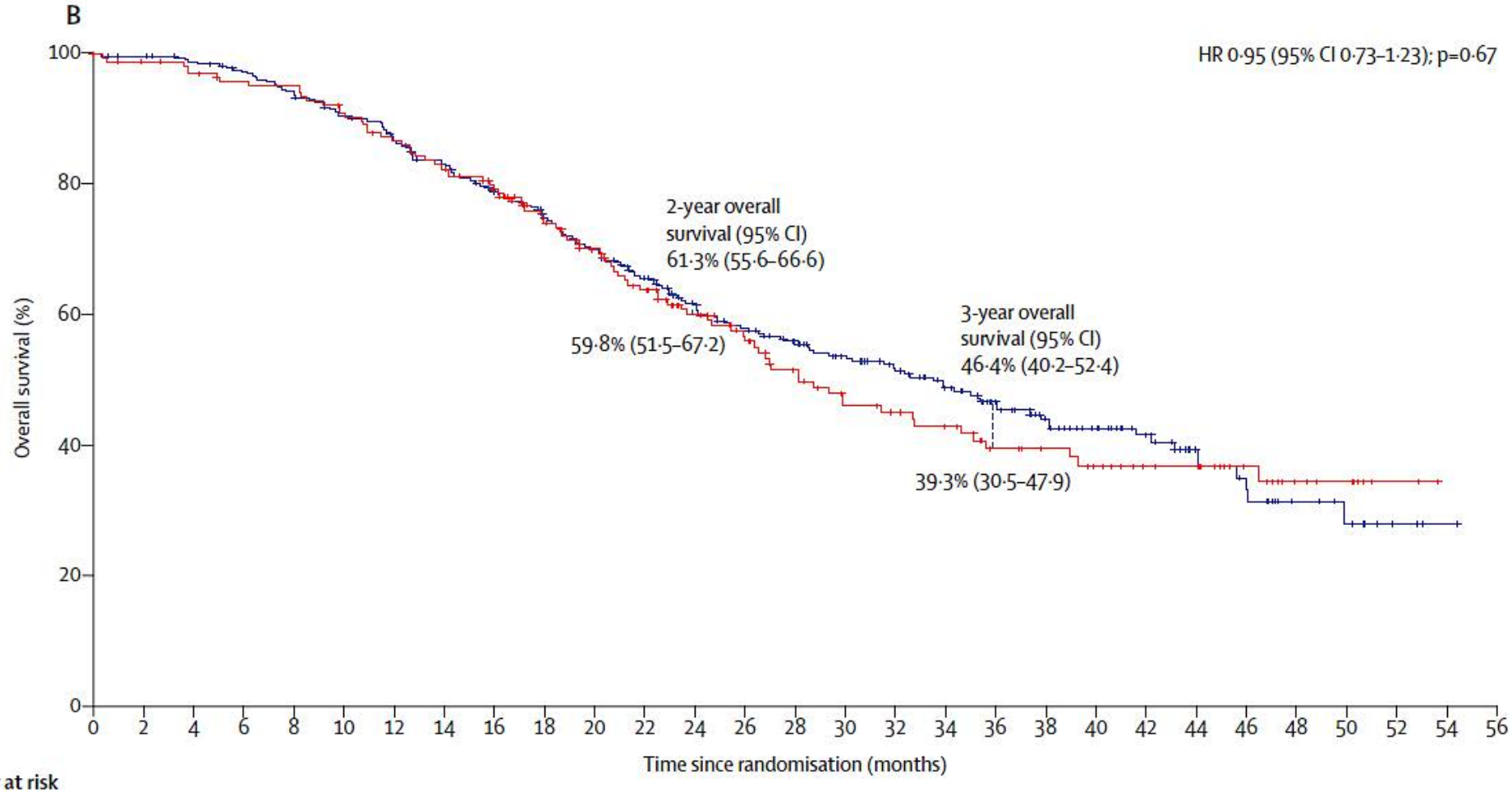
BROCADE3: Progression-Free Survival



Number at risk (number censored)																											
Veliparib plus carboplatin–paclitaxel	337 (0)	316 (13)	301 (16)	282 (21)	250 (24)	207 (29)	181 (32)	154 (43)	137 (37)	126 (40)	107 (44)	92 (51)	81 (56)	72 (60)	60 (68)	51 (75)	45 (80)	38 (87)	32 (90)	25 (97)	20 (101)	16 (105)	8 (113)	4 (117)	1 (119)	1 (119)	0 (120)
Placebo plus carboplatin–paclitaxel	172 (0)	160 (8)	153 (10)	140 (15)	123 (17)	99 (21)	82 (22)	64 (22)	47 (23)	39 (25)	35 (25)	27 (29)	23 (30)	18 (31)	15 (32)	15 (32)	12 (34)	8 (36)	8 (36)	8 (36)	6 (36)	5 (37)	5 (37)	4 (38)	3 (38)	0 (40)	.. ..

Courtesy of P Kelly Marcom, MD

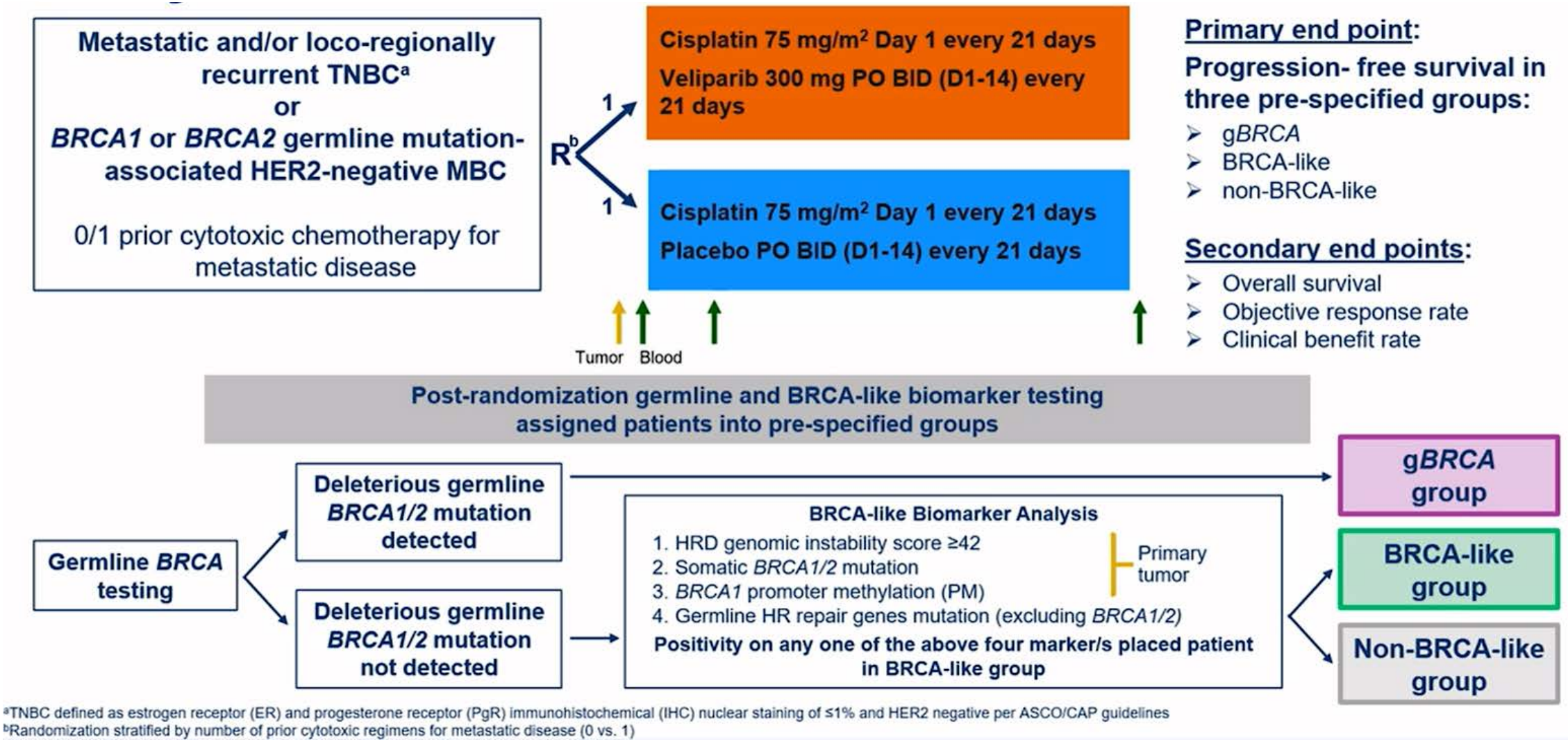
BROCADE3: Overall Survival



Number at risk (number censored)																													
Veliparib plus carboplatin–paclitaxel	337 (0)	332 (4)	326 (7)	318 (10)	307 (10)	294 (12)	281 (14)	265 (17)	247 (22)	223 (34)	203 (39)	185 (44)	161 (57)	145 (64)	132 (72)	117 (82)	106 (89)	90 (99)	76 (109)	62 (119)	50 (129)	41 (137)	30 (146)	18 (154)	11 (160)	8 (162)	3 (167)	1 (169)	0 (170)
Placebo plus carboplatin–paclitaxel	172 (0)	166 (4)	162 (5)	158 (7)	157 (7)	149 (8)	141 (9)	134 (9)	125 (14)	111 (19)	102 (22)	90 (25)	75 (35)	68 (38)	57 (43)	47 (47)	44 (49)	40 (51)	32 (56)	29 (59)	25 (61)	19 (67)	18 (68)	15 (71)	9 (76)	7 (78)	2 (83)	0 (85)	.. ..

Courtesy of P Kelly Marcom, MD

SWOG-S1416 A phase II randomized trial of cisplatin +/- veliparib in metastatic triple-negative breast cancer (TNBC) and/or germline BRCA-associated breast cancer

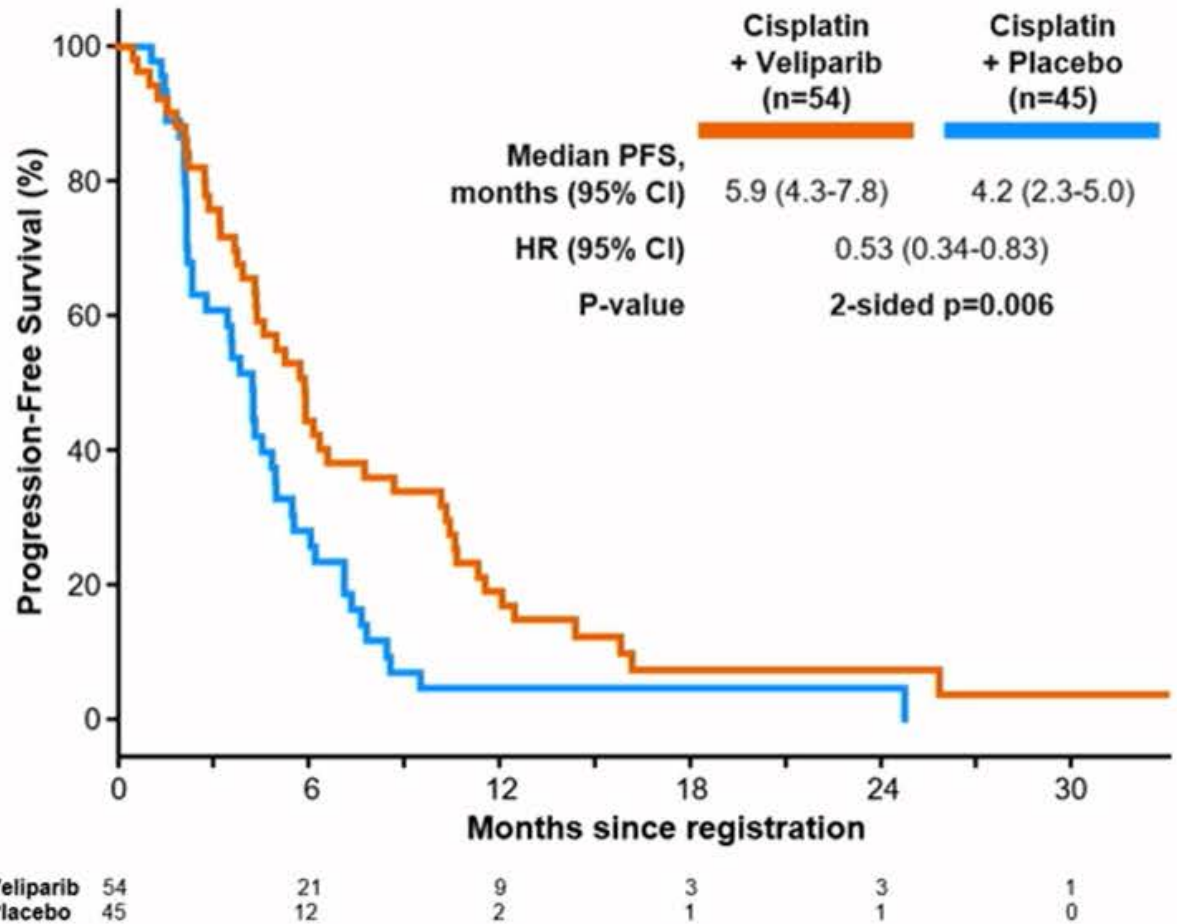


Sharma P et al. ASCO 2020;Abstract 1001.

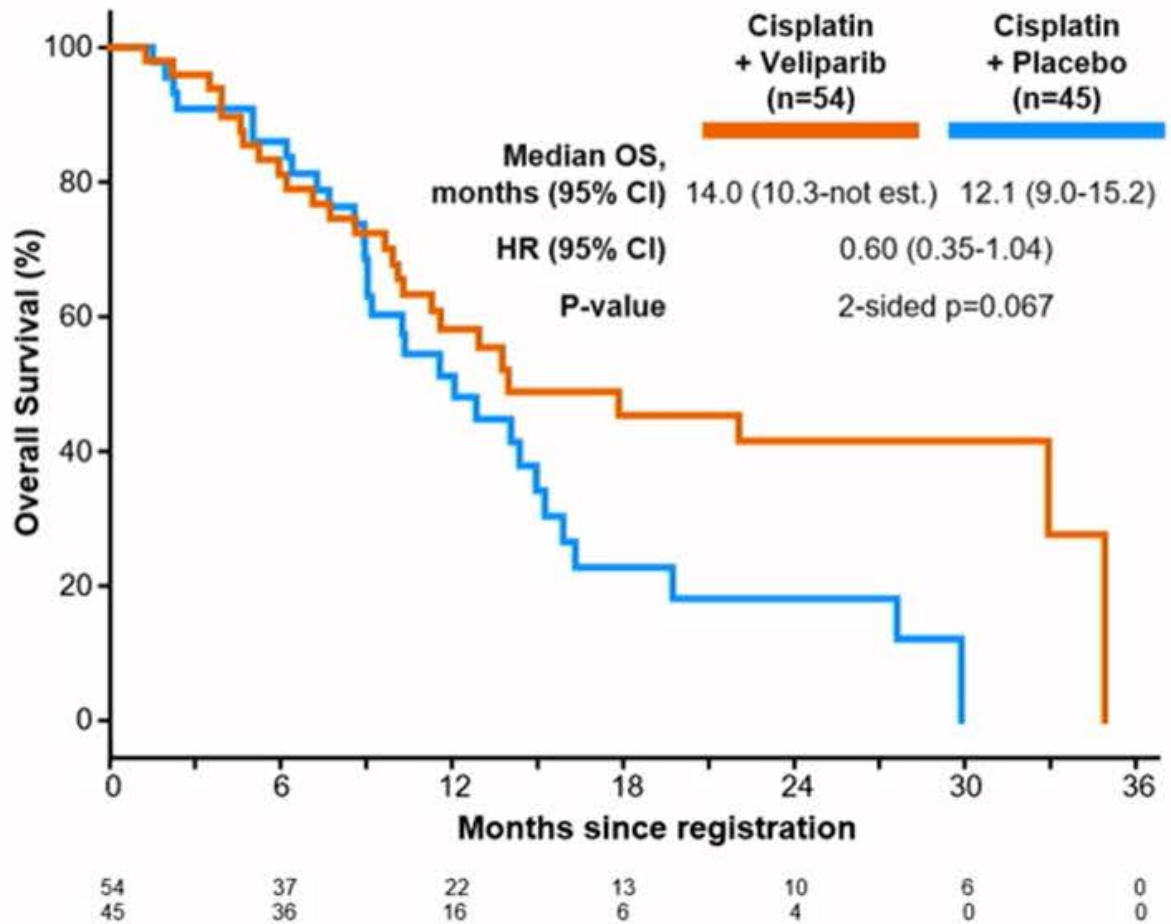
Courtesy of P Kelly Marcom, MD

BRCA-like group

Progression-free survival



Overall survival



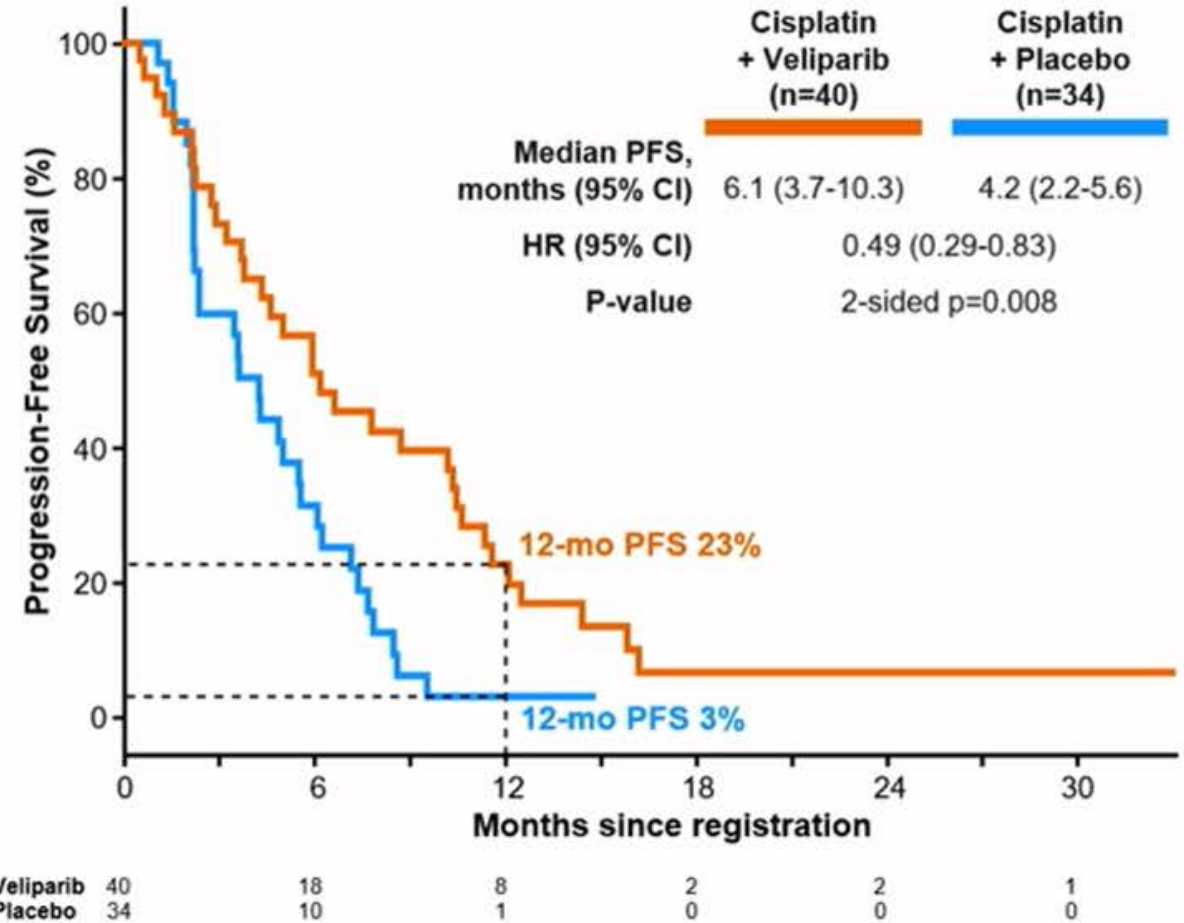
ORR (n=83): 45% vs 33%

Sharma P et al. ASCO 2020;Abstract 1001.

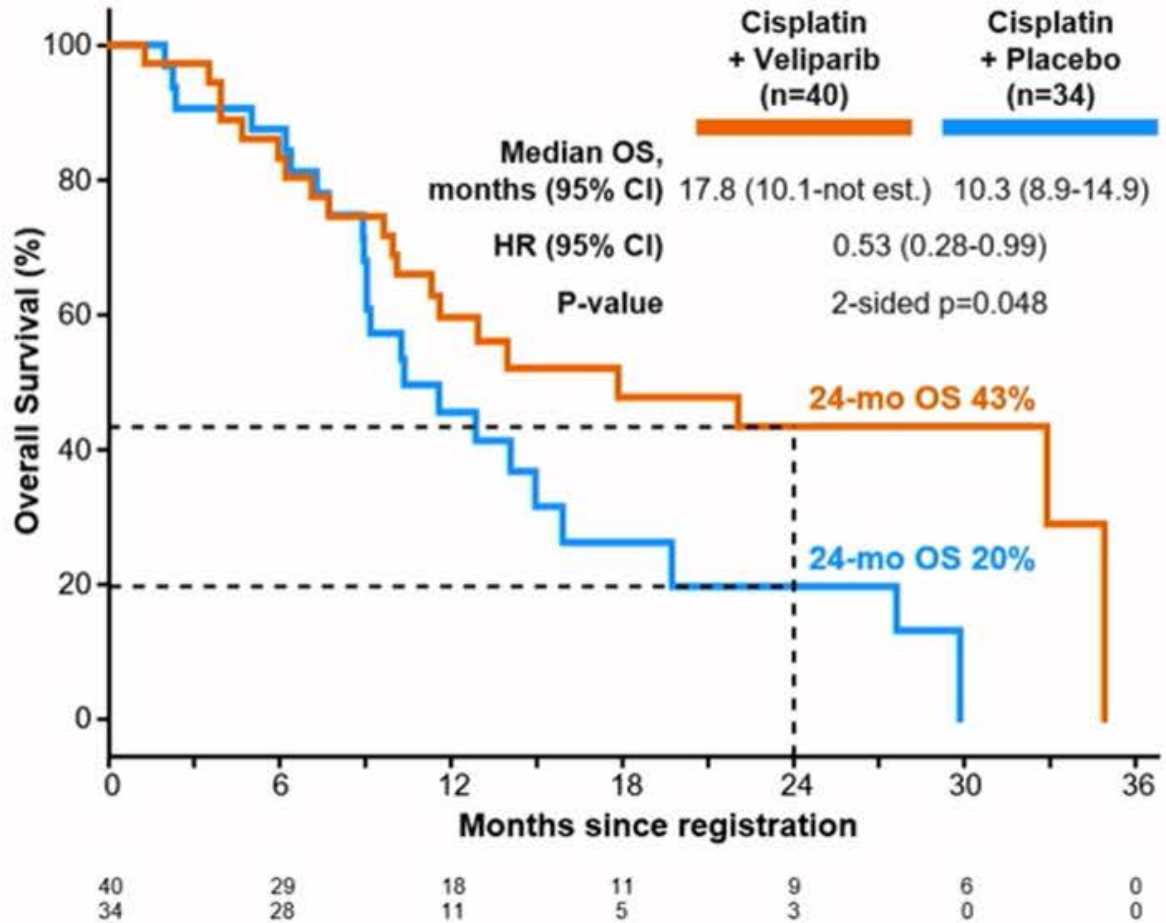
Courtesy of P Kelly Marcom, MD

BRCA-like group: 1st line

Progression-free survival



Overall survival



Sharma P et al. ASCO 2020;Abstract 1001.

Courtesy of P Kelly Marcom, MD

Safety and Toxicity: PARPi Associated ≥ Grade 3

PARPi	Any ≥ Gr3	Hematologic	Gastrointestinal	General	Treatment Change for Any AE	Alopecia (Any)
Olaparib	37%	Anemia: 16% Neutropenia: 9%	N/V: 0% Diarrhea: 1% LFTs: 3%	Fatigue: 3% Headache: 1%	Dose Reduction: 25% Delay: 35% Stop: 5%	3.4%
Talazoparib	26%	Anemia: 39% Neutropenia: 21%	N/V: 3% Diarrhea: 0.7%	Fatigue: 2% Headache: 2% Pleural Eff: 1.7%	Dose Reduction: 33% Dose interruption: 37% (At 7-12 months) Stop: 6%	25%
Veliparib+Chemo (BROCADE3)	95%	Anemia: 42% Neutropenia: 82% Thrombocytopenia: 40%	N/V: 7% Diarrhea: 5%	Fatigue: 4% Headache: 2%		54%

- Transfusions in OlympiAD were high at 20% but driven per protocol for Gr1/2 anemia. No leukemias or MDS.
- Transfusions in EMBRACA (at least one) were 39%. One leukemia case.

Courtesy of P Kelly Marcom, MD

PARPi with other HRD mutations

- Activity in high-grade serous carcinoma in non-gBRCA mutated cancer and in somatic BRCA1/2 mutated ovarian cancer
- Question of activity in ATM mutated CRPC
- What about breast cancer?

Courtesy of P Kelly Marcom, MD

TBCRC 048 Study: A Phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in homologous recombination (HR) pathway genes (Olaparib Expanded) (Nadine Tung, PI)

Hypothesis: Olaparib will have an overall response rate ≥ 20% in breast cancer patients with a germline or somatic mutation in DNA damage response (DDR) pathway genes associated with HR other than BRCA1/2 or with a somatic BRCA1/2 mutation.

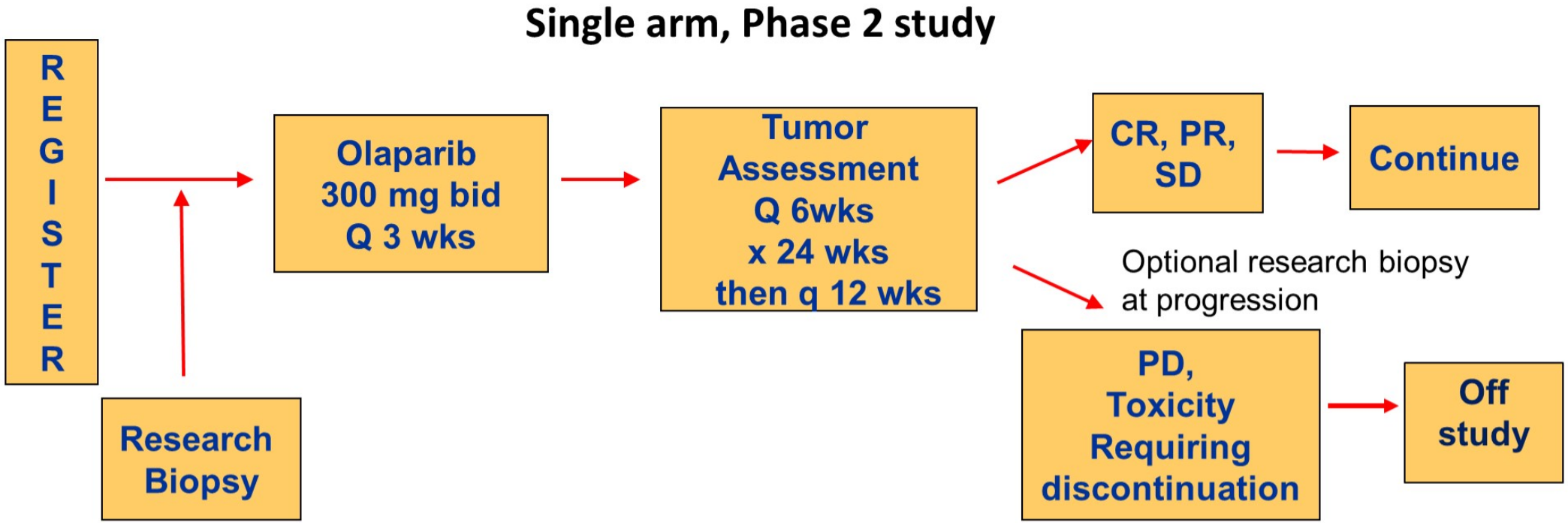
- Primary Aim: ORR (CR + PR by RECIST 1.1)
- Secondary Aim: CBR (CR + PR + SD ≥ 18 weeks), Duration of Response, Progression-Free Survival, Toxicity.

Eligibility: Measurable metastatic disease; no prior PARPi; No more than 2 prior chemotherapy regimens; Not platinum refractory.

Courtesy of P Kelly Marcom, MD

Tung, Journal of Clinical Oncology, Oct 29, 2020 https://dx.doi.org/10.1200/jco.20.02151

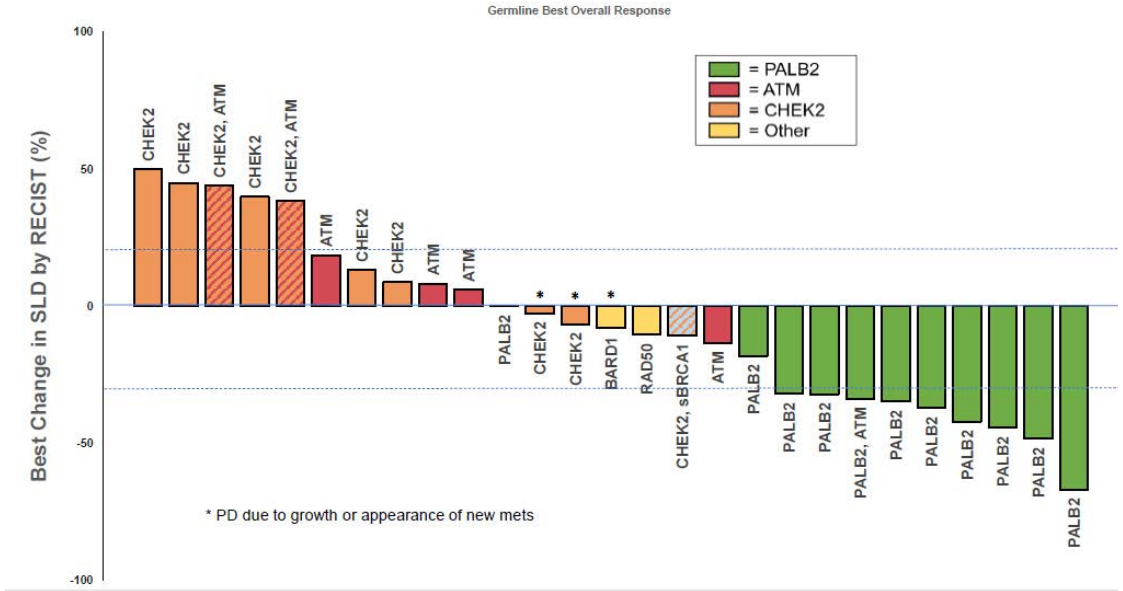
TBCRC 048 Trial Schema: Olaparib Expanded

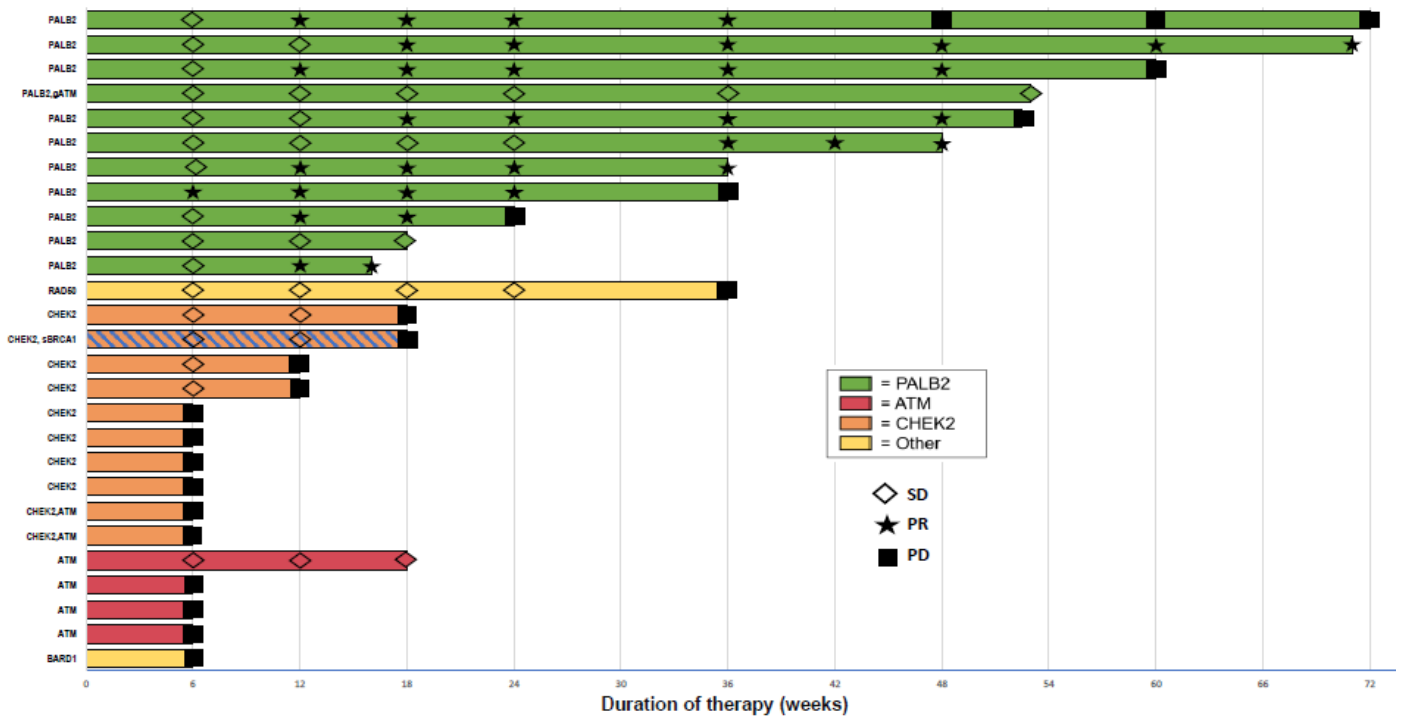


Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD

TBCRC 048 Trial Germline Cohort: Best Response and DOR

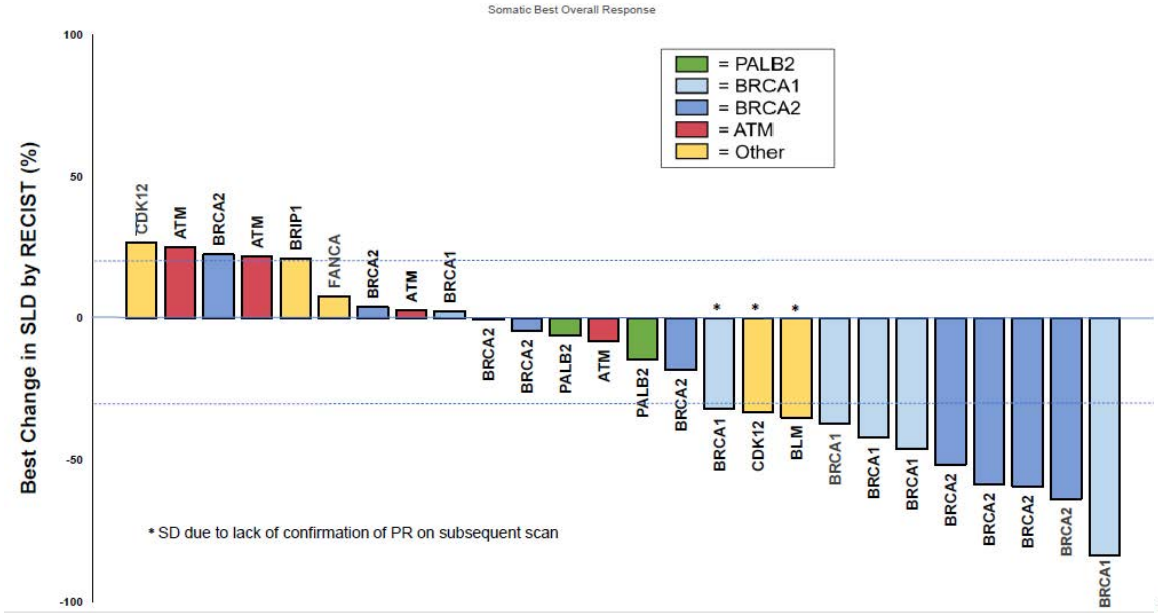


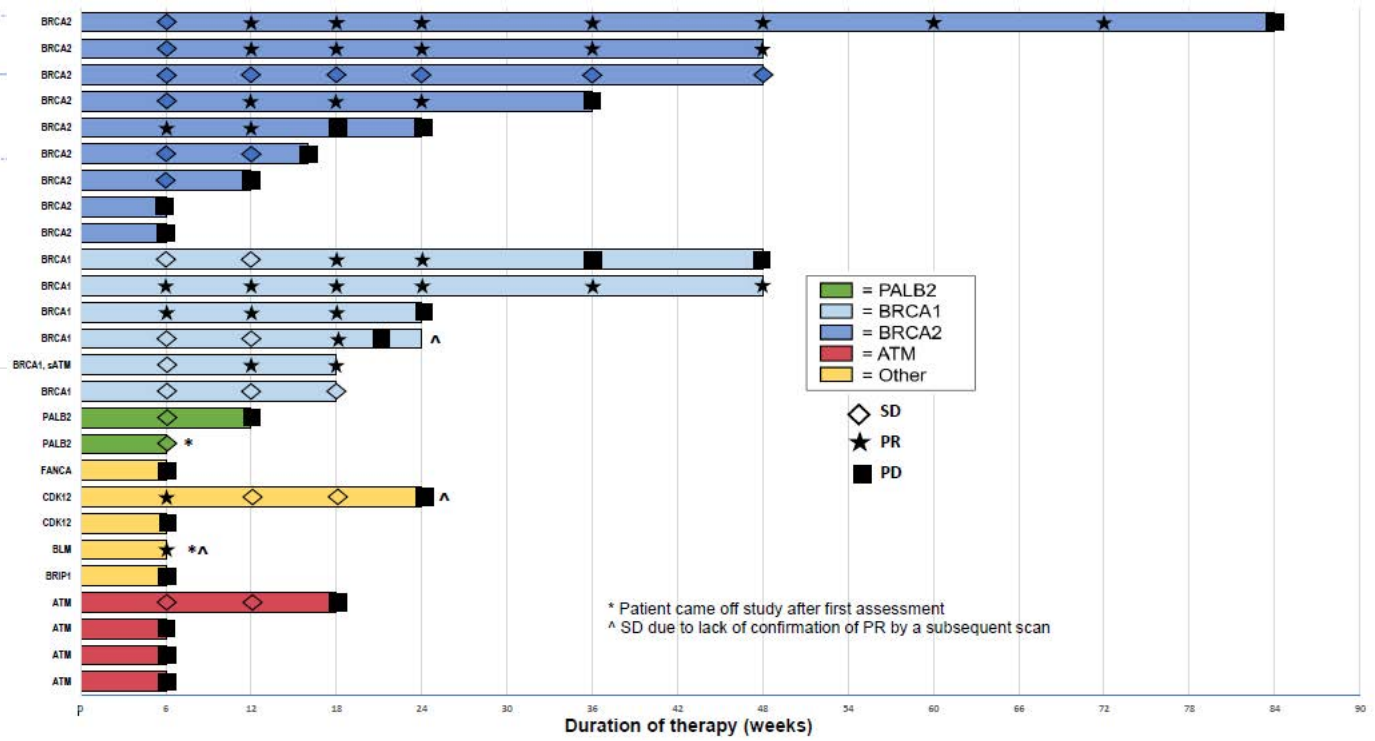


Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD

TBCRC 048 Trial Somatic Cohort: Best Response and DOR



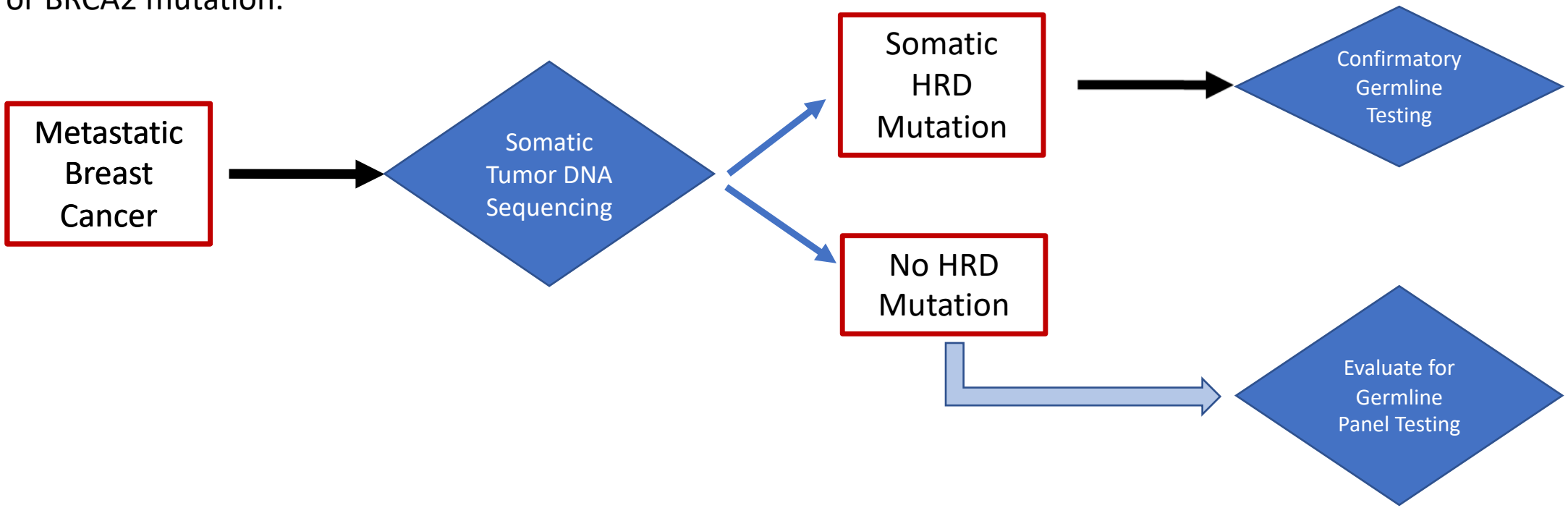


Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD

Identifying PARPi Candidates

- FDA Approved Companion Diagnostic: BRACAnalysis CDx for olaparib and talazoparib
- Somatic tumor sequencing has altered prior evaluation pathways
- NCCN Guidelines (BINV-R Footnote a): Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline or BRCA2 mutation.



Courtesy of P Kelly Marcom, MD

PARPi (Neo) Adjuvant Trials

Preoperative Talazoparib Study:
Single Agent for 6 months gBRCA+

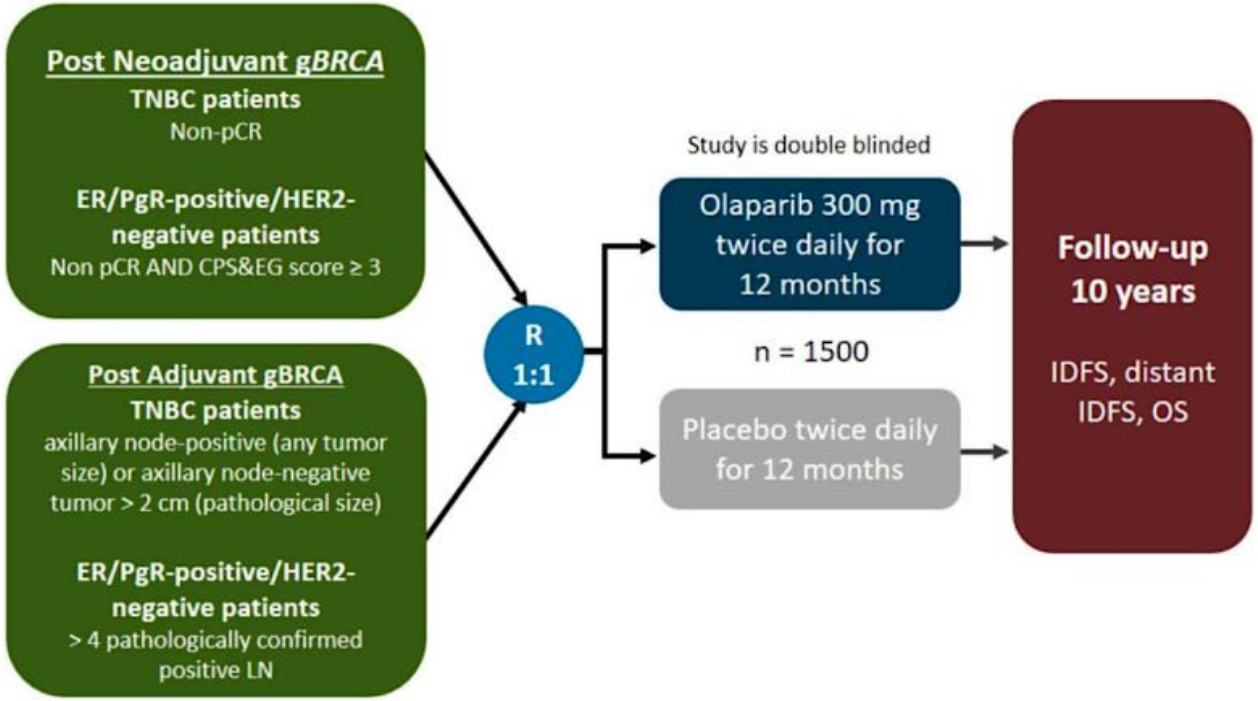
TABLE 1. Patient Characteristics

Characteristic	No. of Patients
Age, years	20
Median (range)	38 (23-58)
Race	
White	7
Black	5
Hispanic	5
Asian	3
BRCA	
1	16
2	4
Clinical stage	
I	5
II	12
III	3
Histology	
Ductal	18
Lobular	1
Metaplastic chondrosarcomatous	1
Tissue receptor subtype	
TNBC (ER and PR < 10%)	15
Hormone receptor positive (≥ 10%)	5

pCR 53%

OlympiA: Adjuvant Olaparib gBRCA+/HER2-

(NSABP B55/BIG 6-13)



Estimated primary completion date: November 18, 2020

Courtesy of P Kelly Marcom, MD

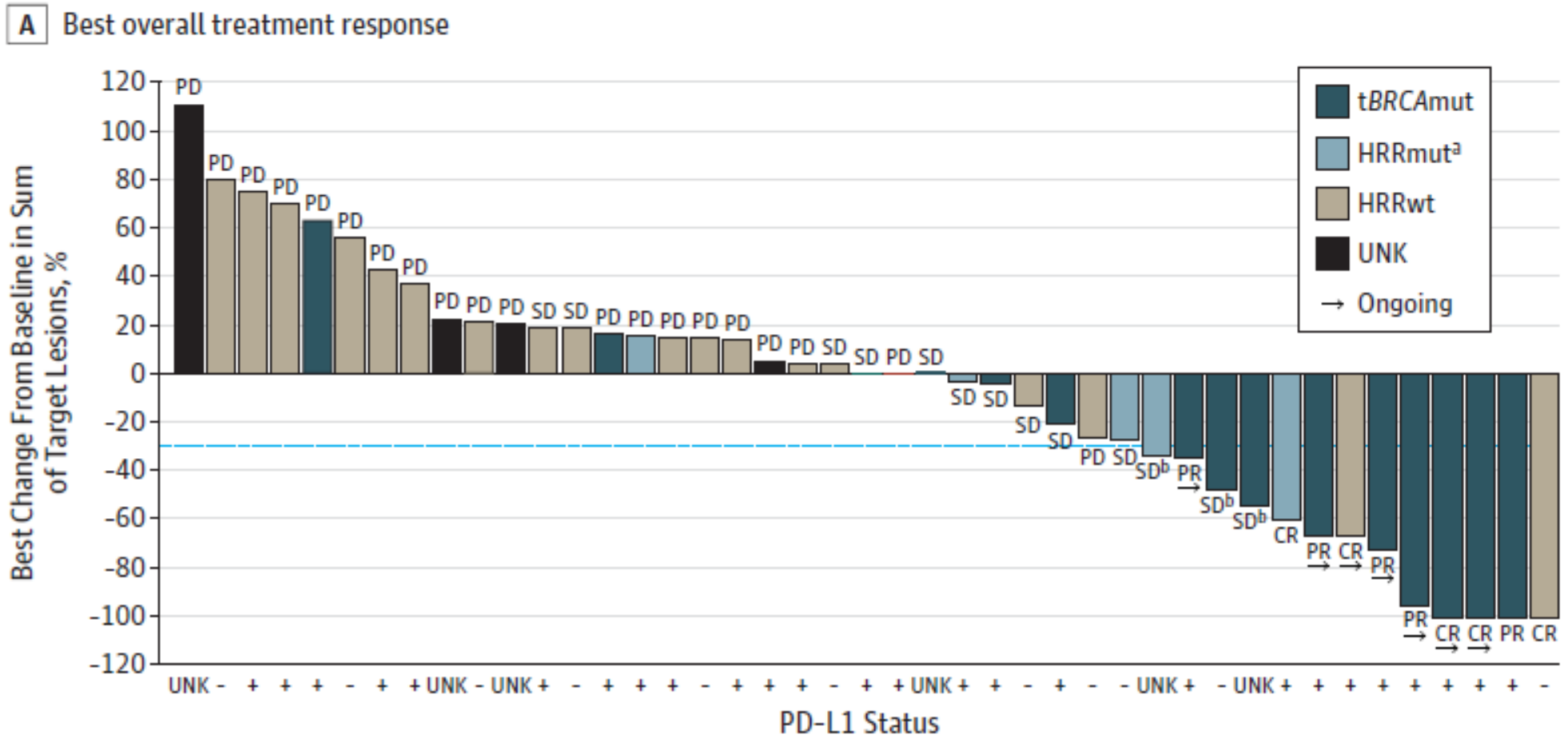
Novel Combinations: PARPi and Immune Checkpoints

- RATIONALE: PARPi activates intratumoral STING/c-GAS pathway causing CD8+ T-cell recruitment. IC might act synergistically with this activation.(Pantelidou, Cancer Discovery, 9: 722, 2019)

Trial	BRCA1/2 Status	Drugs	Eligibility	Cohort Size	Overall Response Rate
TOPACIO	Any BRCA or PD-L1 status	Niraparib Pembrolizumab	≤ 2 chemo	55	21%
MEDIOLA	gBRCA	Olaparib Durvalumab	≤ 2 chemo	30	63%

Courtesy of P Kelly Marcom, MD

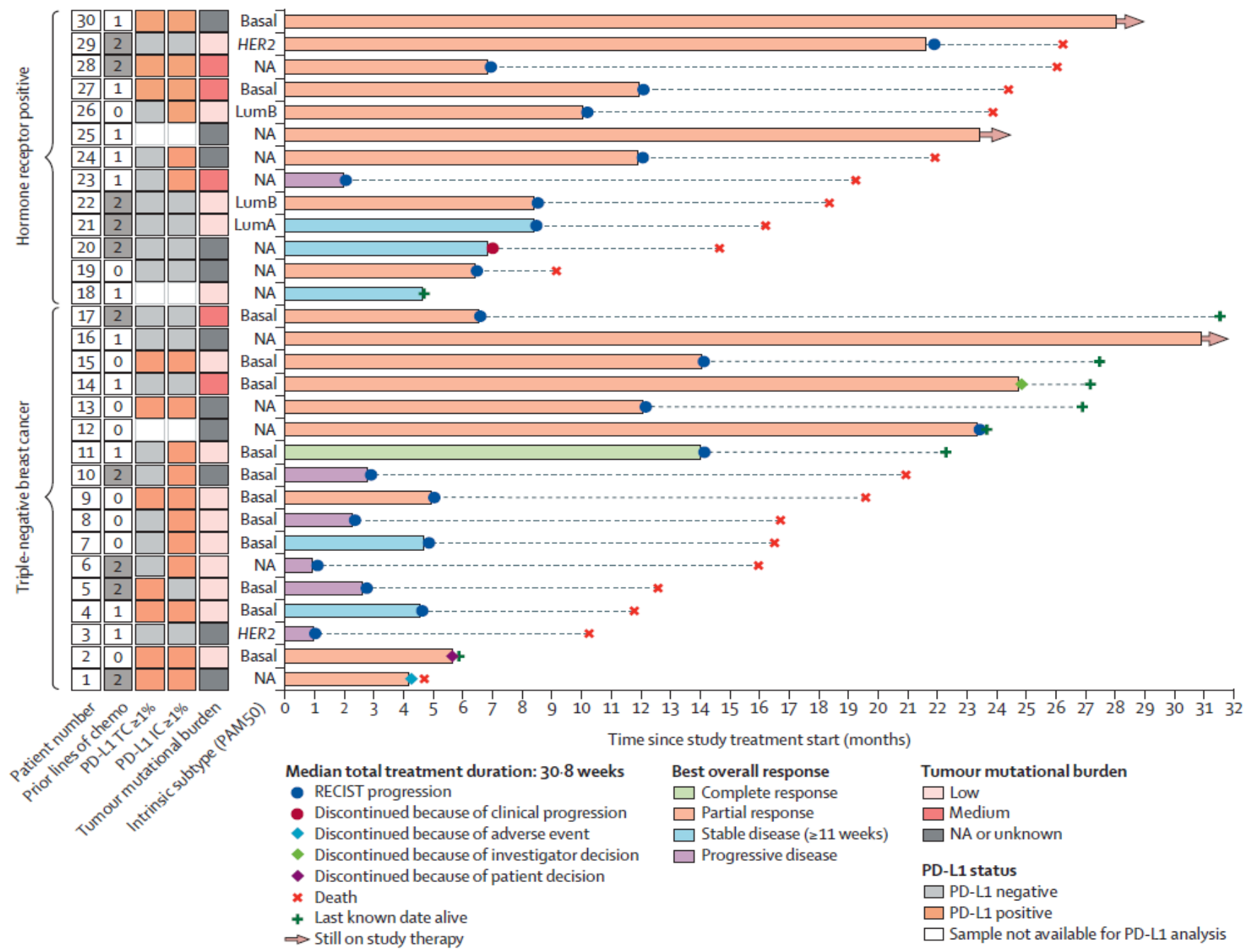
TOPACIO: Best Overall Response



Courtesy of P Kelly Marcom, MD

Vinayak, JAMA Oncol. 2019;5(8):1132-1140

MEDIOLA Trial



Courtesy of P Kelly Marcom, MD

Domchek, Lancet Oncol 2020; 21: 1155–64

Open PARPi/IO Trials

Olaparib:

- DORA- Durvalumab (consolidation of platinum responsive TNBC)
- OHSU-Durvalumab with multi-omics analysis
- KEYLYNK-009-Consolidation with olaparib/pembro v. chemo/pembro after chemo/pembro induction

Talazoparib:

- Avelumab

Niraparib:

- Dostarlimab (TSR042) - PD-1i (early-stage preop)
- HX008 (PD-1i)

Courtesy of P Kelly Marcom, MD

ClinicalTrials.gov Active/Recruiting November 2020

Novel Combinations: PARPi/Other Therapies

Olaparib:

- Radiation (IBC),
- Sapacitabine (nucleoside analogue)
- trastuzumab in BRCA+/HER2+ disease
- ceralasertib (ATRi) or adavosertib (WEE1i)
- hyperthermia
- palbociclib/fulvestrant in BRCA+/ER+
- Selumetinib (MEKi)
- CYH33 (alpha-PIK3CAi)

Talazoparib:

- Sacituzumab
- Decitabine & cedazuridine (ASTX727) - DNMTi
- ZEN003694 (BETi)
- Gedatolisib (PI3K/mTORi)

Niraparib:

- Radiation (TNBC post-op)
- AI in ER+/HRD+
- Everolimus

Veliparib:

- Radiation (Preop)

Courtesy of P Kelly Marcom, MD

ClinicalTrials.gov Active/Recruiting November 2020

Conclusions:

- PARPi therapy establishes an important new therapeutic approach (synthetic lethality) allowing “targeting” of loss of a tumor suppressor
- PARPi is an important treatment option for patients with metastatic breast cancer with germline and somatic mutations in homologous recombination genes (BRCA1/BRCA2/PALB2/To be defined)
- Justifies aggressive genetic testing (somatic→germline) for MBC
- Multiple agents with a spectrum of activity
- Generally well-tolerated: Primary hemoglobin suppression manageable with appropriate dose adjustments
- Promising combinations with Immune Checkpoint Inhibitors
- Promising preoperative data; adjuvant olaparib data available soon
- Potential as a prevention agent (but need long-term toxicity data)

Courtesy of P Kelly Marcom, MD

Patient #1: Single agent olaparib

The patient is a 63-year-old white woman initially diagnosed with right breast cancer in February, 2018. She underwent a right lumpectomy and sentinel node mapping for a grade 3 2.6cm invasive ductal breast cancer. The sentinel node had a 3mm metastasis. The cancer was estrogen, progesterone, and HER2 receptor negative.

On staging PET scan done following surgery, she had multiple pulmonary nodules. Biopsy confirmed metastatic breast cancer.

She was started on weekly paclitaxel in June 2018. Germline genetic testing with a 28 gene panel was done given the metastatic TNBC; the family history showed minimal cancer (father with bladder cancer at a young age and a paternal cousin with breast cancer at 50). Only an incidental MUTYH mutation was found.

On Next-Generation Sequencing of her tumor in July 2018, however, somatic mutations in BRCA1 (p.K739*; c. 2215A>T; estimated variant allele frequency 43%) and TP53 (p.E298*; c.892G>T; estimated variant allele frequency 43%) were found.

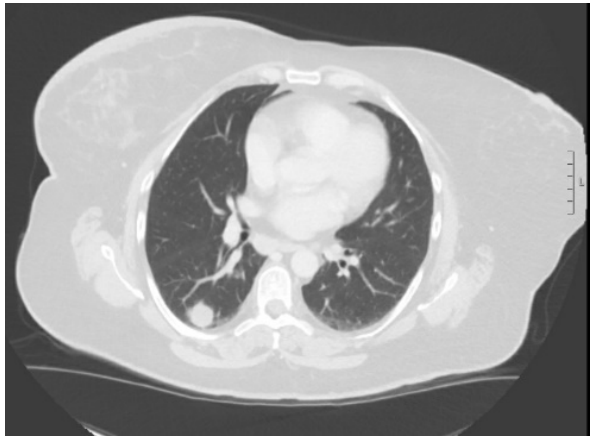


Figure 1: Baseline lung nodule

Courtesy of P Kelly Marcom, MD

Patient #1 (continued)

Restaging PET scan in October 2018 showed improvement in the lung lesions. However, a new lesion in the right cerebellum was noted; a brain MRI confirmed a 1.4 cm cerebellar lesion and a 4 mm left inferior temporal lobe lesion. Both lesions were treated by CyberKnife radiation to 18 Gy and 20 Gy, respectively. Paclitaxel was continued.

In February 2019, staging showed progression in the lung nodules.
She was treated with capecitabine, but it was discontinued for side effects.
Restaging in April 2019 showed progression in the lung lesions again and a new brain lesion in the left parietal cortex. The brain lesion was treated with stereotactic radiosurgery and systemic treatment was changed to weekly carboplatin.

She received weekly carboplatin through July, with continued response in the lungs and no brain progression; however, she developed carboplatin hypersensitivity requiring treatment change.

Given the somatic BRCA1 mutation, she was enrolled in a clinical trial evaluating olaparib activity in mutations in homologous repair deficiency genes other than BRCA1/2 as well as somatic BRCA1/2 mutations.

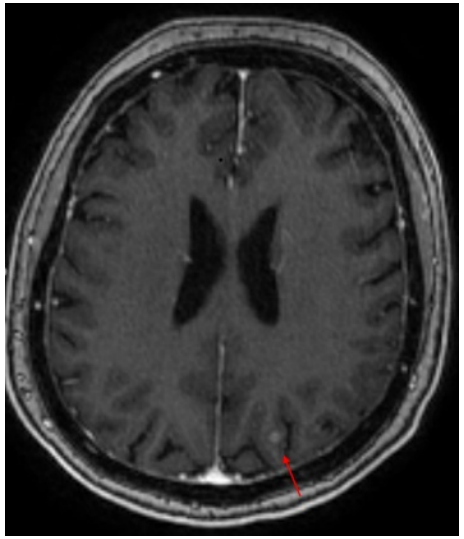


Figure 2: Recurrent left parietal lesion April 2019

Courtesy of P Kelly Marcom, MD

Patient #1 (continued)

She initiated single-agent olaparib at 300 mg PO BID in August 2019. She had resection of the cerebellar area for progression concerns in August 2020 that showed only radiation necrosis. She required one transfusion after 15 months of treatment at full dose olaparib, but has otherwise tolerated treatment well and remains in a complete clinical remission.

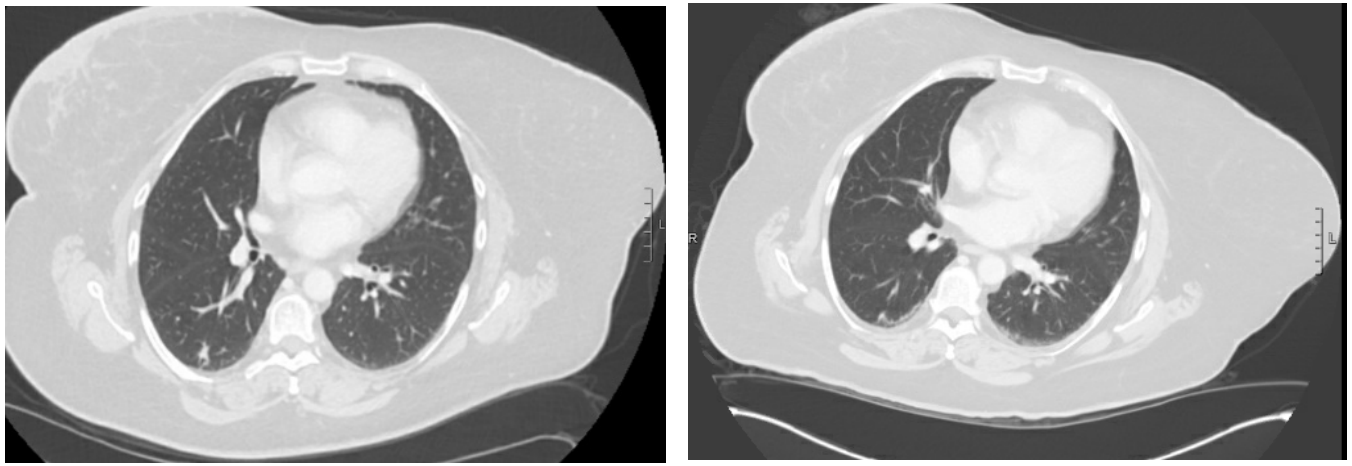


Figure 3 Lung lesion at baseline and 15 months on olaparib

Courtesy of P Kelly Marcom, MD

Patient #2: Metastatic TNBC recurrence associated with germline BRCA1 mutation

The patient is a 62-year-old white woman who originally presented with a locally advanced right breast cancer in December, 2015. Upon complete clinical evaluation, she had a right multifocal grade 3 3.5 cm ER Allred 3/PR Allred 0/HER2 IHC 0 invasive pleomorphic lobular breast cancer with matted axillary lymph nodes, as well as a left 4.8 cm ER/PR/HER2- invasive ductal breast cancer with clinically negative lymph nodes. Staging CT/PET showed the bilateral breast masses and local regional adenopathy as well as bilateral ovarian masses concerning for ovarian neoplasms. She underwent bilateral salpingo-oophorectomy showing bilateral high-grade serous adenocarcinoma with papillary morphology distinct from either breast lesion and a serous tubal intraepithelial carcinoma. Omental biopsies were negative (pathologic Stage II)

Germline genetic testing found a mutation in BRCA1 (c.1175_1214del40; L345fs).

She received preoperative Carboplatin and paclitaxel from January 2016 to June 2016 with an excellent clinical response. Bilateral mastectomies and axillary dissection showed: left breast with 6 mm residual focus with 10% cellularity and 2 of 39 lymph nodes with micrometastatic disease; and right breast with a pathologic complete response including 2 negative sentinel nodes. Treatment was completed with dose-dense AC for 4 cycles and post mastectomy chest wall and nodal radiation on the right, completed in December 2016.

Courtesy of P Kelly Marcom, MD

Patient #2 (continued)

She did well until June 2020, when the surveillance CA-125 increased to 52. CT of the chest/abdomen/pelvis showed metastases in the liver, left subpectoral/supraclavicular lymph nodes, and pulmonary nodules. She was asymptomatic. Biopsy of the left subpectoral lymph node was consistent with breast cancer with repeat receptors confirming triple-negative breast cancer. She had a normal CBC/diff, CMP; CA27.29 was elevated at 91.

Next-Gen Sequencing of the metastatic sample showed the germline BRCA1 mutation, AURKA amplification, GNAS amplification, RAF1 amplification, ZNF217 amplification, STK11 rearrangement, and TP53 A159P missense mutation. Tumor mutational burden was 8 Muts/Mb. PD-L1 staining was 1% in Tumor-infiltrating lymphocytes/0% on tumor cells.

She initiated treatment with single-agent cisplatin every 3 weeks as induction therapy in July 2018. After 3 cycles, the CA27.29 decreased to 52. On repeat scans, the liver lesions resolved and lymph nodes were stable. In October 2020, She enrolled in a clinical trial consolidating treatment to olaparib with or without durvalumab and was randomized to receive both. She tolerated cycle one of therapy well and treatment is ongoing.

Courtesy of P Kelly Marcom, MD

Patient #3: BRCA2 carrier with metastatic breast cancer, conversion to ER/PR-, treated with a PARP inhibitor

The patient is a 52-year-old white woman who was initially diagnosed with early stage left breast ER+/PR+/HER2 IHC 2+ FISH ratio 1.7 invasive lobular breast cancer in June 2012. Genetic testing showed a germline BRCA2 mutation (Y1894x05910 c>g). She underwent therapeutic left mastectomy and right prophylactic mastectomy. Pathology showed a left T1cN2a (8 positive lymph nodes) cancer. Adjuvant chemotherapy with dose-dense AC and paclitaxel followed by radiation was completed in February 2013. Prophylactic bilateral salpingo-oophorectomy was performed, but she did not take adjuvant endocrine therapy.

She developed metastatic breast cancer in September 2017, presenting with a left pleural effusion. Cytology was consistent with metastatic lobular breast cancer (E-cadherin negative). Biomarkers showed ER 50%/PR50%. HER2 was called as positive based on IHC 2+ and FISH ratio 2.1. On PET scan, she also had multiple osseous metastases. CA27.29 was informative at 190 and other labs normal.

Treatment was initiated with letrozole, palbociclib, and denosumab. She had a good response, with resolution of the pleural effusion and CA27.29 nadir to 52, but by June 2018 developed symptomatic liver lesions and CA27.29 to 2096. A repeat liver biopsy in June 2018 showed metastatic disease now ER/PR negative, and HER2 amplified at 2.1.

Courtesy of P Kelly Marcom, MD

Patient #3 (continued)

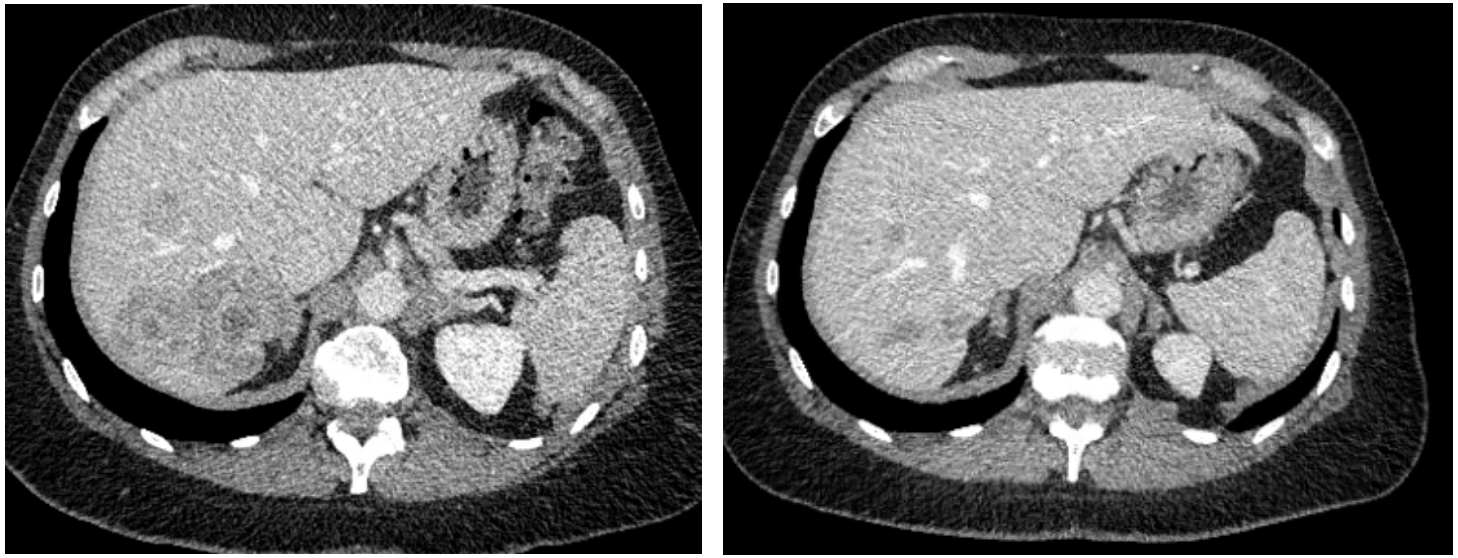
Treatment was changed to Paclitaxel/Trastuzumab/Pertuzumab from July 2018 to March 2019 with improvement in liver and CA27.29 to 157. In March 2019, treatment was changed to T-DM1 after progression in the liver. Restaging after 3 cycles showed progression in the liver, CA27.29 increase to 318, and worsening abdominal and back pain.

She was seen at Duke Cancer Institute in May 2019. Given the BRCA2 mutation, she was screened for a clinical trial of olaparib with or without atezolizumab for BRCA1/2 carriers. However, since HER2 positivity was an exclusion criterion for the trial, HER2 was repeated on the June 2018 liver biopsy and still called amplified with a ratio of 2.36 (copy number 4.6). She was therefore ineligible for the trial. Her primary oncologist was reluctant to treat with a PARP inhibitor since the label only indicates use in HER2-negative disease.

She was started on single-agent talazoparib 1 mg a day in July 2019. At that time, she was quite symptomatic with abdominal pain and early satiety. Within 2 weeks of starting, her symptoms resolved. Serial CTs after 3 months of therapy are shown and the marker trend by treatment shown. She did require a dose reduction for anemia.

Courtesy of P Kelly Marcom, MD

Patient #3 (continued)



Baseline liver after 3 months on talazoparib

In February 2020, she developed recurrent abdominal pain and early satiety. Repeat CAP CT showed liver progression. A repeat liver biopsy was performed for markers and NGS. ER/PR receptors continued to be negative; HER2 continued to be “amplified” at a ratio of 2.08 (copy number 5.2). On NGS she was found to have both a reversion mutation in BRCA2 (A1588_F2083del) and an activating mutation in HER2 (S310F). Additional events were: BCL2L1 amplification; CCND1 amplification; TP53 loss; JAK2 amplification; and FGF3/4/19 amplification. Tumor mutational burden was 14 Muts/Mb.

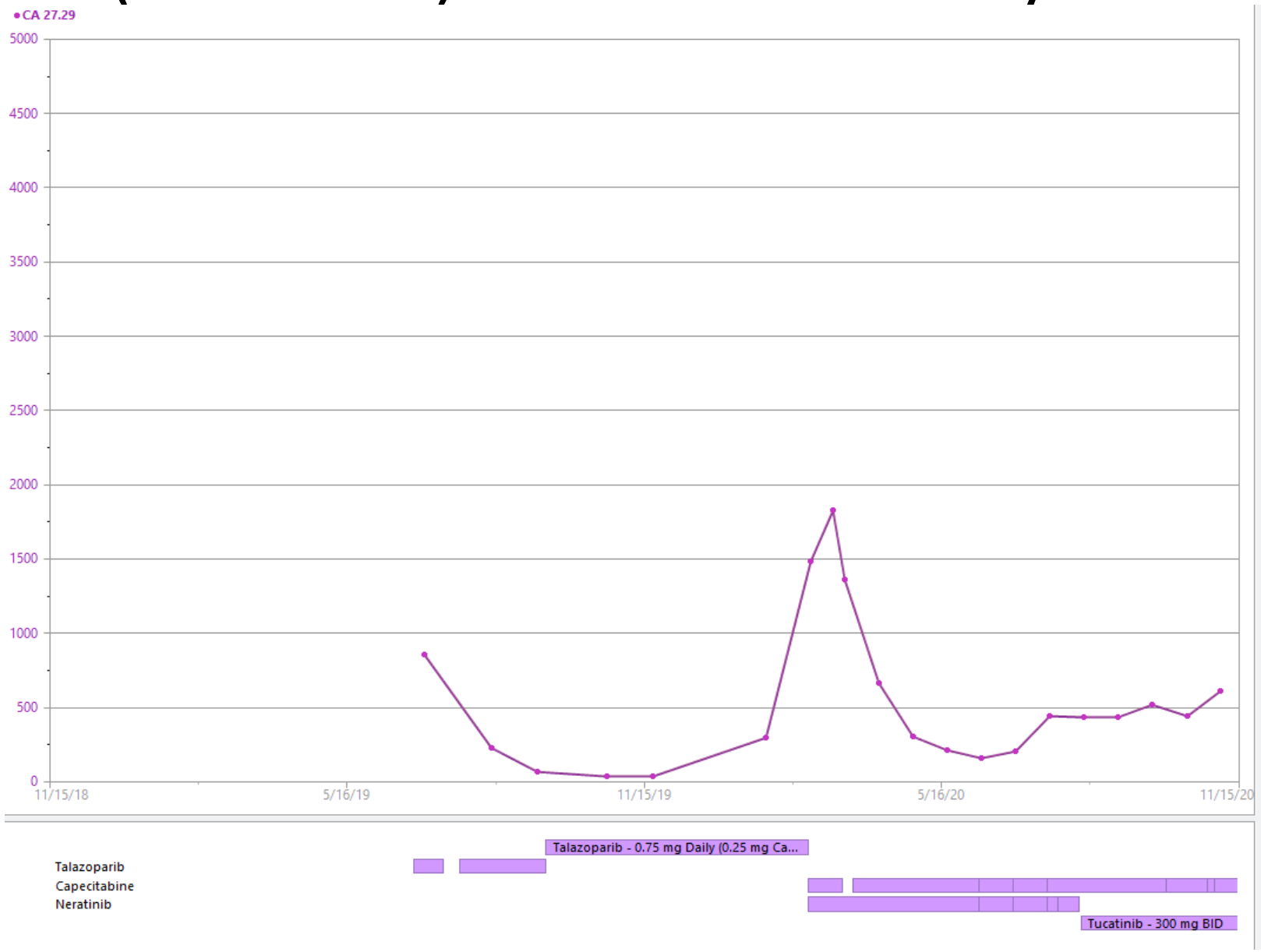
Courtesy of P Kelly Marcom, MD

Patient #3 (continued)

Given these molecular changes, the PARP inhibitor was held and the HER2 mutation targeted. Treatment was changed to neratinib, capecitabine, and trastuzumab. She again had quick relief in her abdominal pain. Her marker trend is shown along with the treatments. She had capecitabine toxicity requiring dose adjustment. As well, she had persistent gastrointestinal side effects on neratinib; when her marker began to trend up, treatment was changed to tucatinib with stabilization of marker and good symptom relief. More recently, she has re-developed a left pleural effusion and repeat staging is pending. Per the TMB score and recent approval, she will be eligible for pembrolizumab treatment on progression, but repeat NGS will also be performed to reassess the BRCA2 reversion mutation.

Courtesy of P Kelly Marcom, MD

Patient #3 (continued) — Marker Trend by Treatment



Course of treatment at DCI

Courtesy of P Kelly Marcom, MD