Memorial Sloan Kettering Cancer Center

Available Data with and Practical Integration of PARP Inhibition into the Care of Patients with mTNBC

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https://openpaymentsdata.cms.gov/physician/612669/payment-information

Case Presentation: Dr Rugo

A 32-year-old woman was seen in clinic for a new diagnosis of inflammatory left breast cancer. Core biopsy confirmed triple negative high-grade disease with dermal invasion, with clear axillary node involvement. Staging was negative for metastatic disease. Due to her age at diagnosis and without significant family history, she had genetic testing which revealed a pathologic mutation in BRCA1.

She was treated with neoadjuvant paclitaxel combined with carboplatin, but developed an anaphylactic reaction to carboplatin during treatment. She had an excellent clinical response and continued on to dose dense AC. At the last dose of AC, the erythema on her left breast was again noted. At the time of surgery with bilateral mastectomy she had extensive residual disease with persistent dermal invasion, and multiple positive axillary nodes.

She underwent radiation therapy, but shortly after completing therapy a new erythematous patch was noted just inferior to her reconstructed breast. A biopsy was positive for dermal invasion with TNBC. A PET/CT showed no evidence of distant mets. NGS revealed no targetable mutations and PD-L1 testing was not available at the time of her diagnosis.

Case Presentation: Dr Rugo (continued)

What would you do now?

1. Start gemcitabine and carboplatin
2. Radiate the new area of skin involvement
3. Start a PARP inhibitor
4. Resect the area of involved skin

If she had evidence of asymptomatic visceral disease would you take a different approach?

She started on olaparib with complete resolution of her skin disease, but developed nausea which was controlled by a low dose of bedtime olanzapine. She also experienced thrombocytopenia (platelets of 70K), which improved with one dose reduction of olaparib.

Unfortunately her disease progressed with lymphangitic spread to lung and extensive skin disease after 5 months, requiring IV chemotherapy.

CASE PRESENTATION: DR HAMILTON

A 61-year-old woman with ER-/PR-/HER2- MBC was referred to my clinic last year after having received gemcitabine/carboplatin in the 1st line setting.

- I ordered germline genetic testing and NGS profiling of her tumor, neither of which had been done.
- Germline genetic testing showed a BRCA2 alteration.
- NGS showed a p53 mutation, CCNE1 amplification, AKT2 amplification, NF1 mutation, and the BRCA2 alteration.
- I started her on PARP inhibitor therapy.
- She did need a dose reduction of olaparib from 300 mg po BID to 200 mg po BID for GI side effects and cytopenias. She now tolerates it well.

Questions for panel:

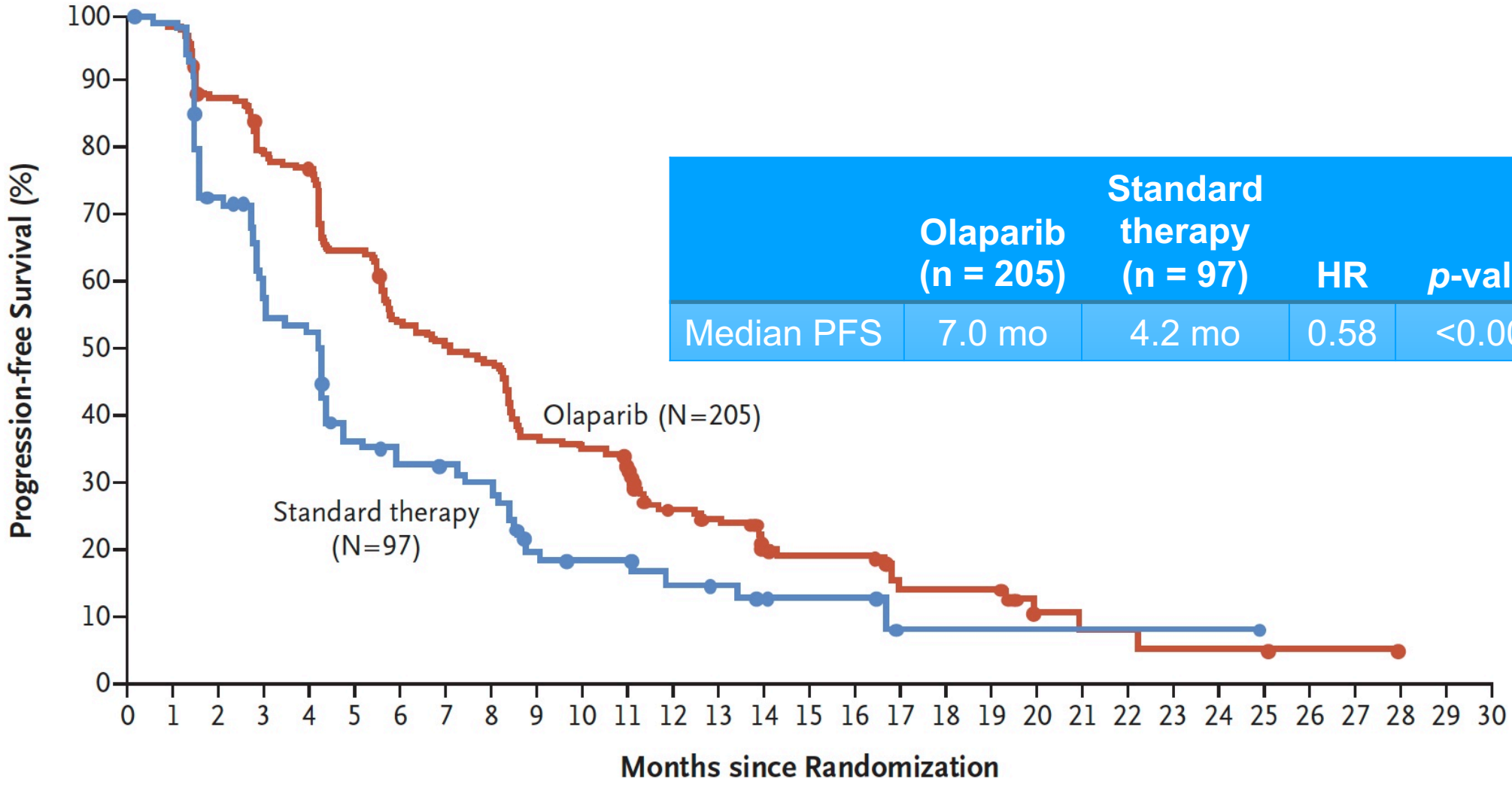
1. How do you decide which PARP inhibitor to use for your patients?
2. If a patient does not tolerate one PARP inhibitor, do you switch to another one? If no, why?
3. Are there any situations where you may use PARP inhibitors off label? For example, HRD-high?

Pivotal Phase III Trials Supporting the FDA Approvals of Olaparib and Talazoparib for mBC with a Germline BRCA Mutation

Trial	Eligibility	Randomization	Primary endpoint
OlympiAD[1] (n = 302)	• HER2-negative mBC – ER+ and/or PR+ or TNBC • Deleterious or suspected deleterious gBRCA mutation • Prior anthracycline and taxane • ≤2 prior chemotherapy lines in metastatic setting	• Olaparib • Physician's choice – Capecitabine – Eribulin – Vinorelbine	• PFS by blinded independent central review
EMBRACA[2] (n = 431)	• HER2-negative locally advanced or metastatic BC • Germline BRCA1 or BRCA2 mutation • ≤3 prior cytotoxic chemotherapy regimens • Prior treatment with a taxane and/or anthracycline unless medically contraindicated	• Talazoparib • Physician's choice – Capecitabine – Eribulin – Gemcitabine – Vinorelbine	• PFS by blinded independent central review

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07; www.clinicaltrials.gov. Accessed December 2019.

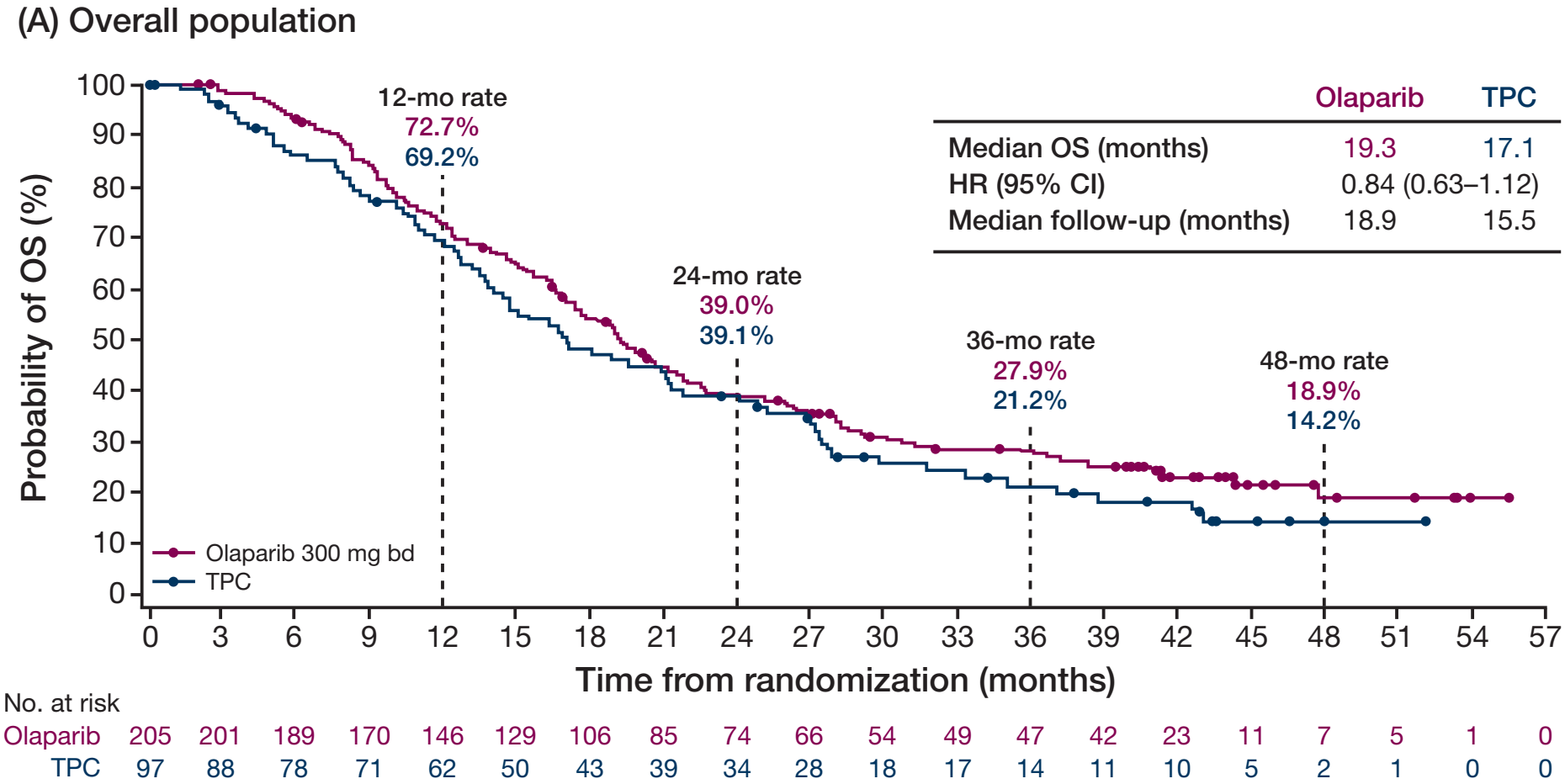
OlympiAD: Olaparib for HER2-Negative Metastatic Breast Cancer in Patients with Germline BRCA Mutations



	Olaparib (n = 205)	Standard therapy (n = 97)	HR	*p*-value
Median PFS	7.0 mo	4.2 mo	0.58	<0.001

Robson M et al. *N Engl J Med* 2017;377(6):523-33.

OlympiAD: Updated OS Data (Poster PD4-03)

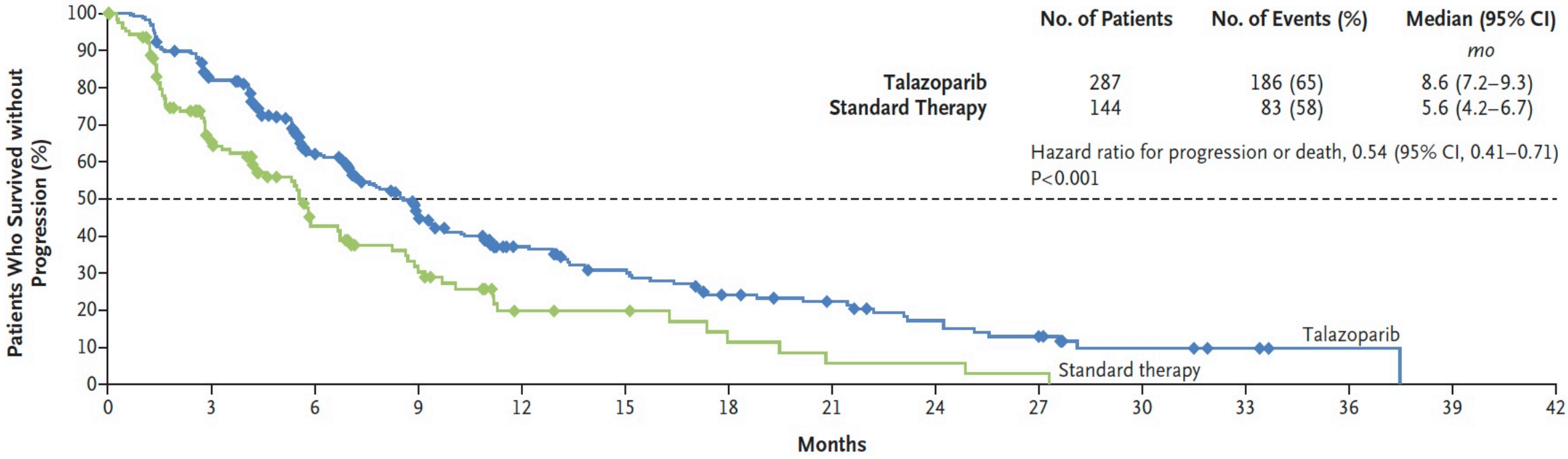


	Olaparib	TPC
Median OS (months)	19.3	17.1
HR (95% CI)	0.84 (0.63–1.12)	
Median follow-up (months)	18.9	15.5

Median FU 18.9 mo in olaparib arm, 15.5 mo in TPC arm

Robson M et al. SABCS 2019;Abstract PD4-03.

EMBRACA: Progression-Free Survival Analyses



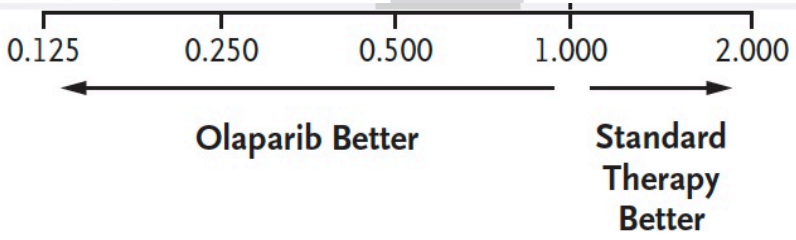
Interim HR for OS 0.76 (95% CI 0.55-1.06)

P = 0.11

Litton JK et al. *N Engl J Med* 2018;379:753-63.

OlympiAD: Subgroup Analyses for PFS

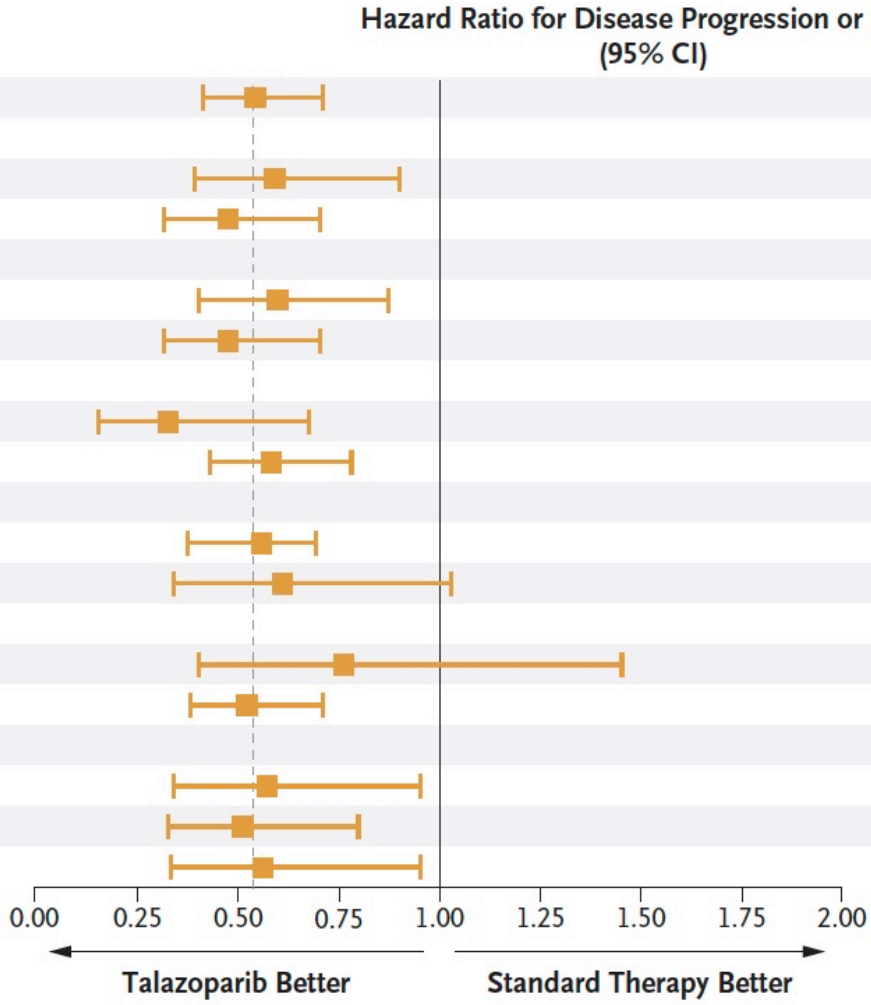
Subgroup	Olaparib	Standard Therapy	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43–0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47–0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34–0.98)
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)



Robson M et al. *N Engl J Med* 2017;377(6):523-33.

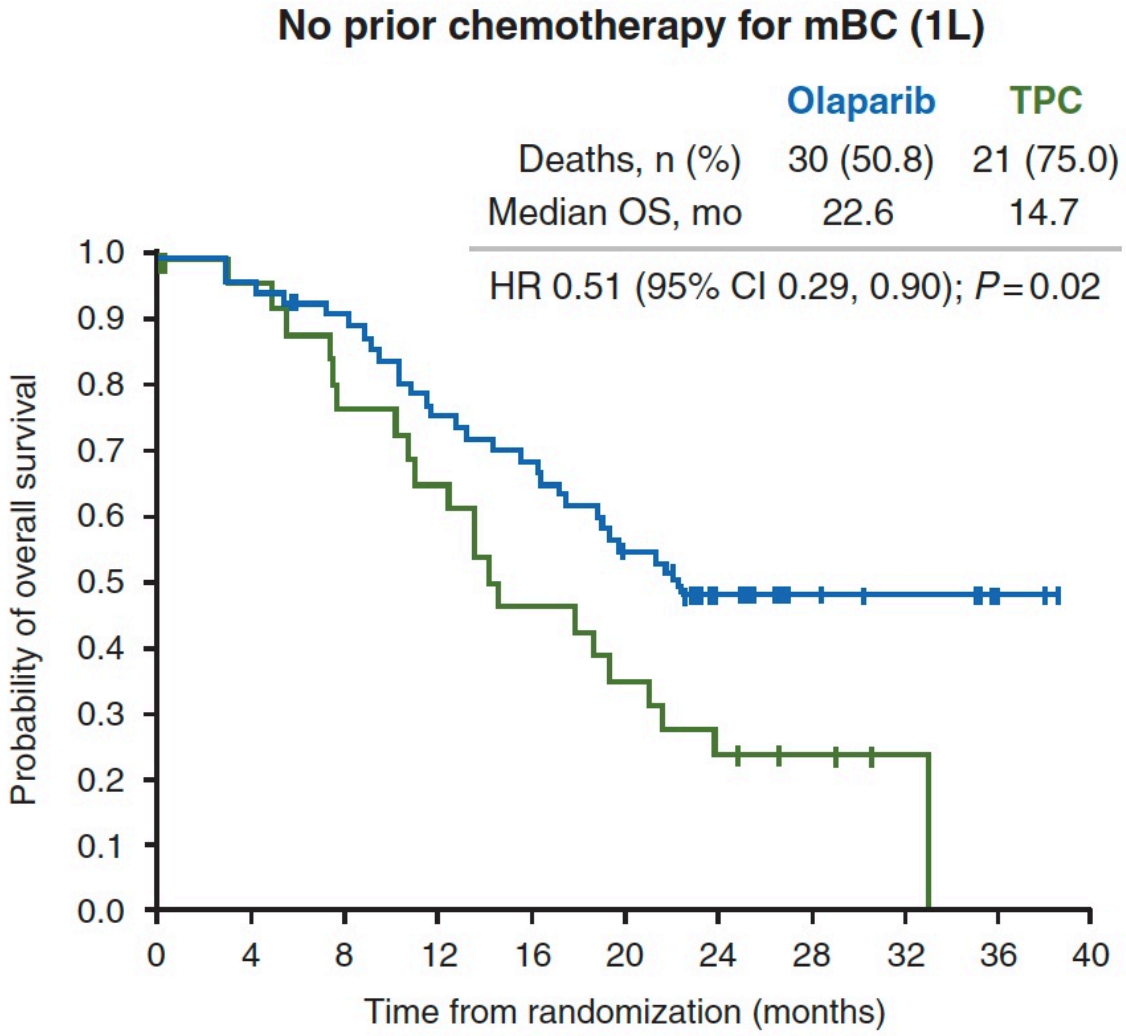
EMBRACA: Subgroup Analyses for PFS

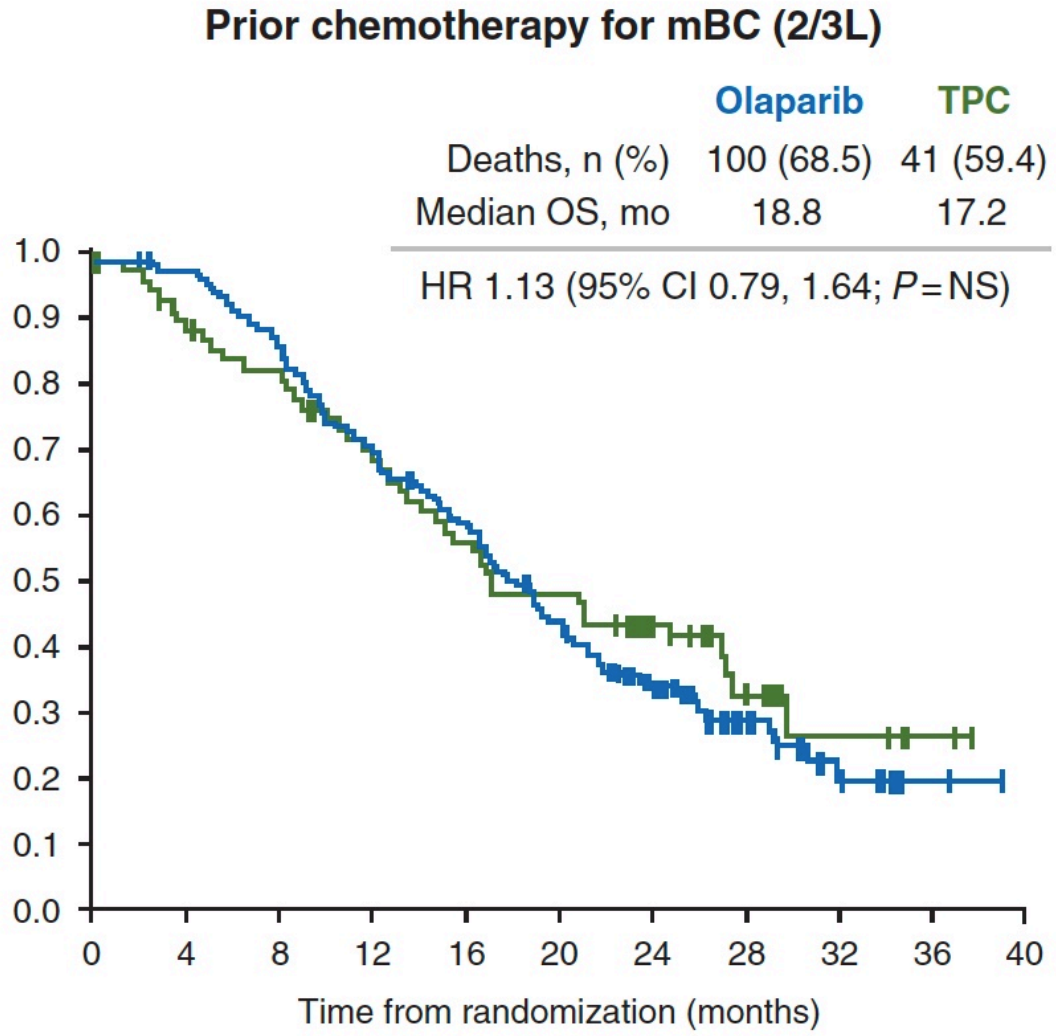
Subgroup	No. of Patients (%)	Hazard Ratio for Disease Progression or Death (95% CI)
All patients	431 (100)	0.54 (0.41–0.71)
BRCA1 mutation type, according to central testing		
BRCA1	183 (42.5)	0.59 (0.39–0.90)
BRCA2	225 (52.2)	0.47 (0.32–0.70)
Hormone-receptor status according to most recent biopsy		
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 JK et al. *N Engl J Med* 2018;379:753-63.

OlympiAD: OS by Prior Chemo (hypothesis generating)





Robson M et al. *Ann Oncol* 2019;30(4):558-66.

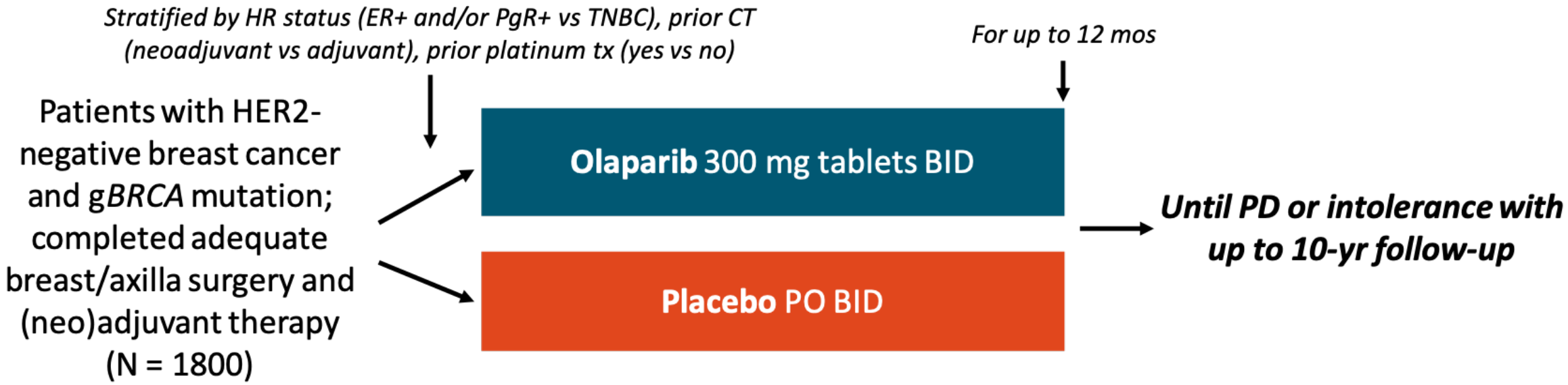
OlympiAD and EMBRACA: Safety

	Olaparib	Talazoparib
Nausea (any grade)	58.0%	48.6%
Fatigue ≥ Grade 2	10.2%	27.2%
Alopecia (any grade)	3.4%	25.1%
Anemia ≥ Grade 3	16.1%	39.2%
Neutropenia ≥ Grade 3	9.3%	20.9%
Thrombocytopenia ≥ Grade 3	2.4%	14.7%
MDS/AML	0	0

Hurvitz et al, The Oncologist 2019; Robson et al, Ann Oncol 2019

Approaches to Increasing Benefit – Early Stage

Olaparib vs Placebo as Adjuvant Therapy in HER2-/g*BRCA* Mutation-Positive EBC (OlympiA; NCT02032823)



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

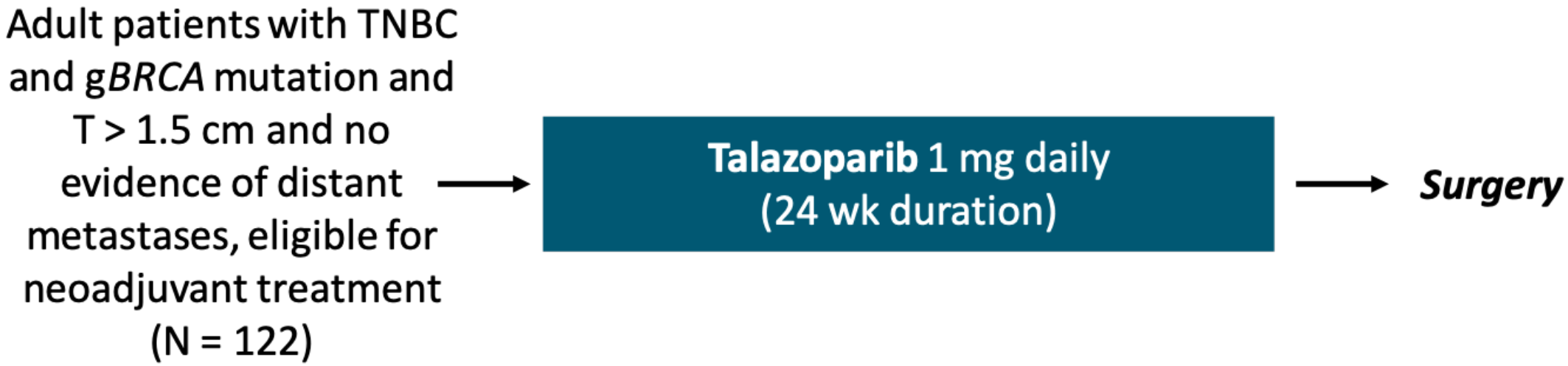
Neoadjuvant PARP Inhibitor Trials in Breast Cancer

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 + Q3W 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 + Q3W IV carboplatin (AUC dose = 6) + QW IV 80 mg/m^2 paclitaxel ▪ Placebo + Q3W 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; NCT03499353)



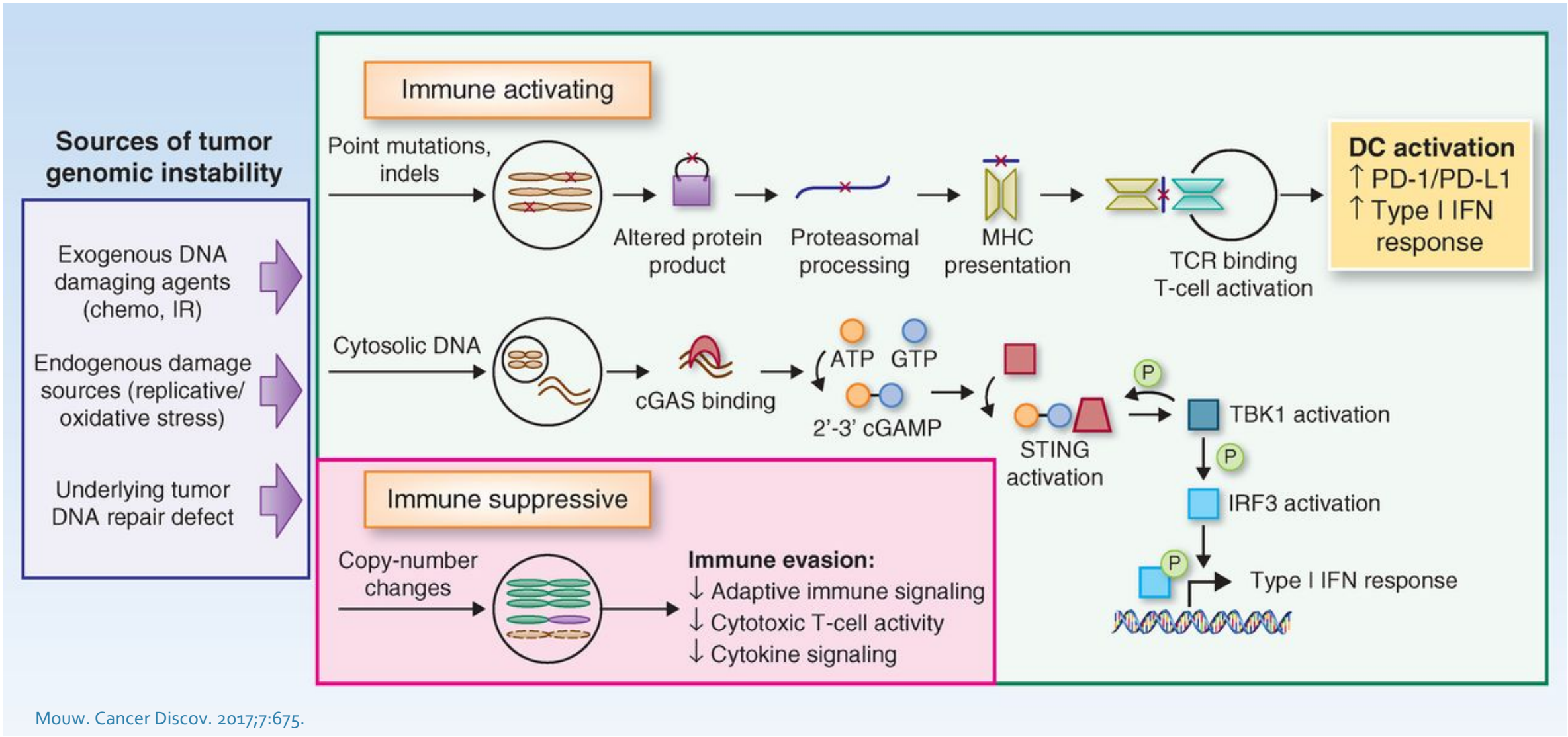
Primary endpoint: pCR by independent central review

Secondary endpoints: pCR by investigator, RCB, pCR in breast by independent reviewer, EFS, OS, safety, PROs, pharmacokinetics

Improving outcomes and extending benefits
Combination therapies

- PI3K-alpha inhibitor (alpelisib)
- VEGFi (cediranib)
- WEE1, ATR, ATM inhibitors (increase replication stress)
- BET inhibitors
- SERD and CDK4/6i
- ADC with TOPO1i payloads
- Checkpoint inhibitors

IO combinations (rationale)



Mouw. Cancer Discov. 2017;7:675.

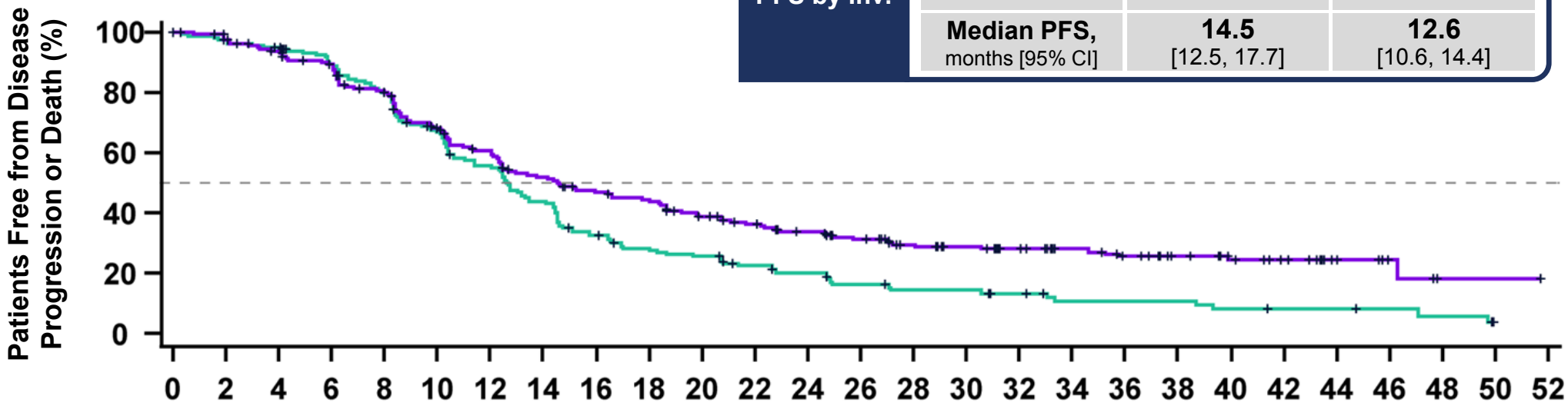
BROCADE3
Carbo/Paclitaxel +/- Veliparib

- 81% first line
- 30% no adjuvant
- Treated to POD

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]

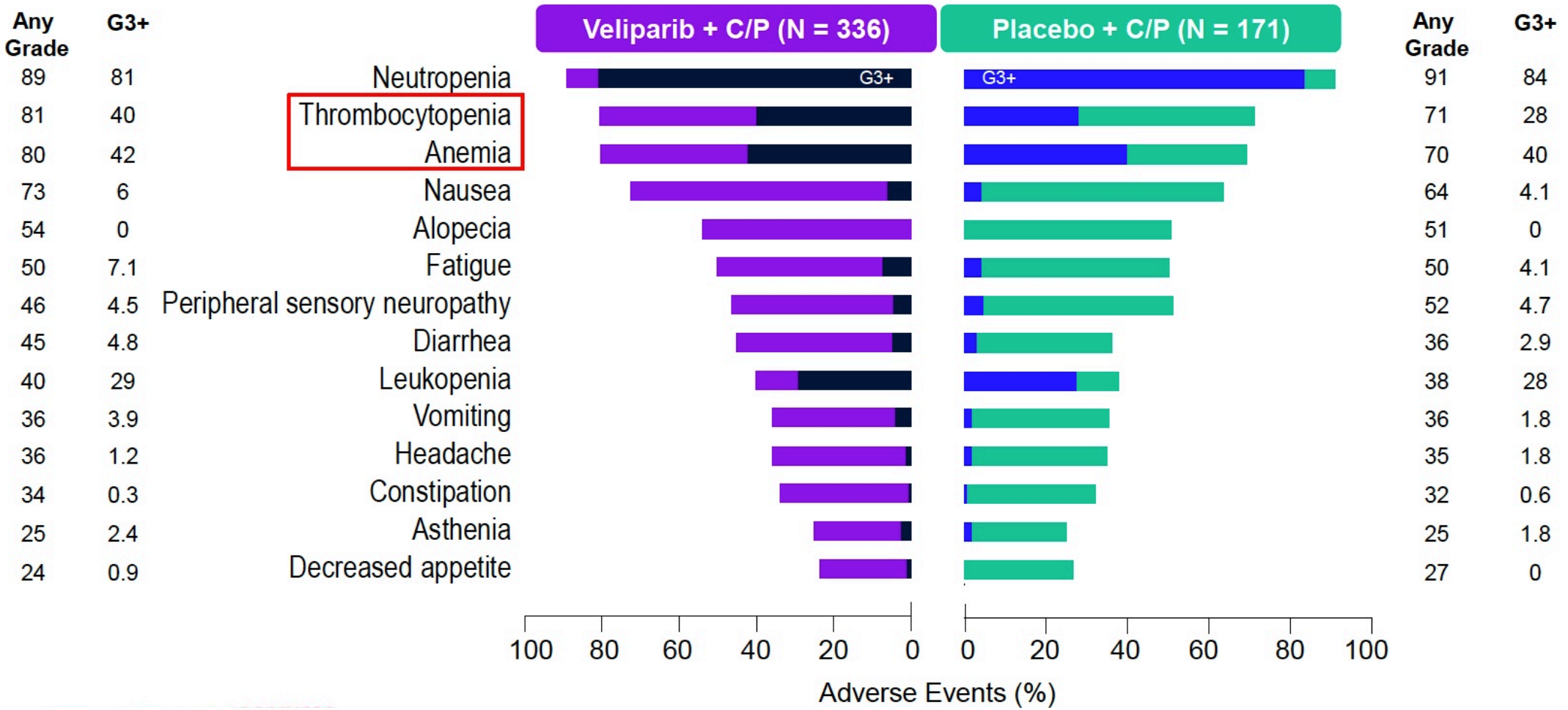


No. at Risk

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 VC et al. *Proc ESMO* 2019;Abstract LBA9.

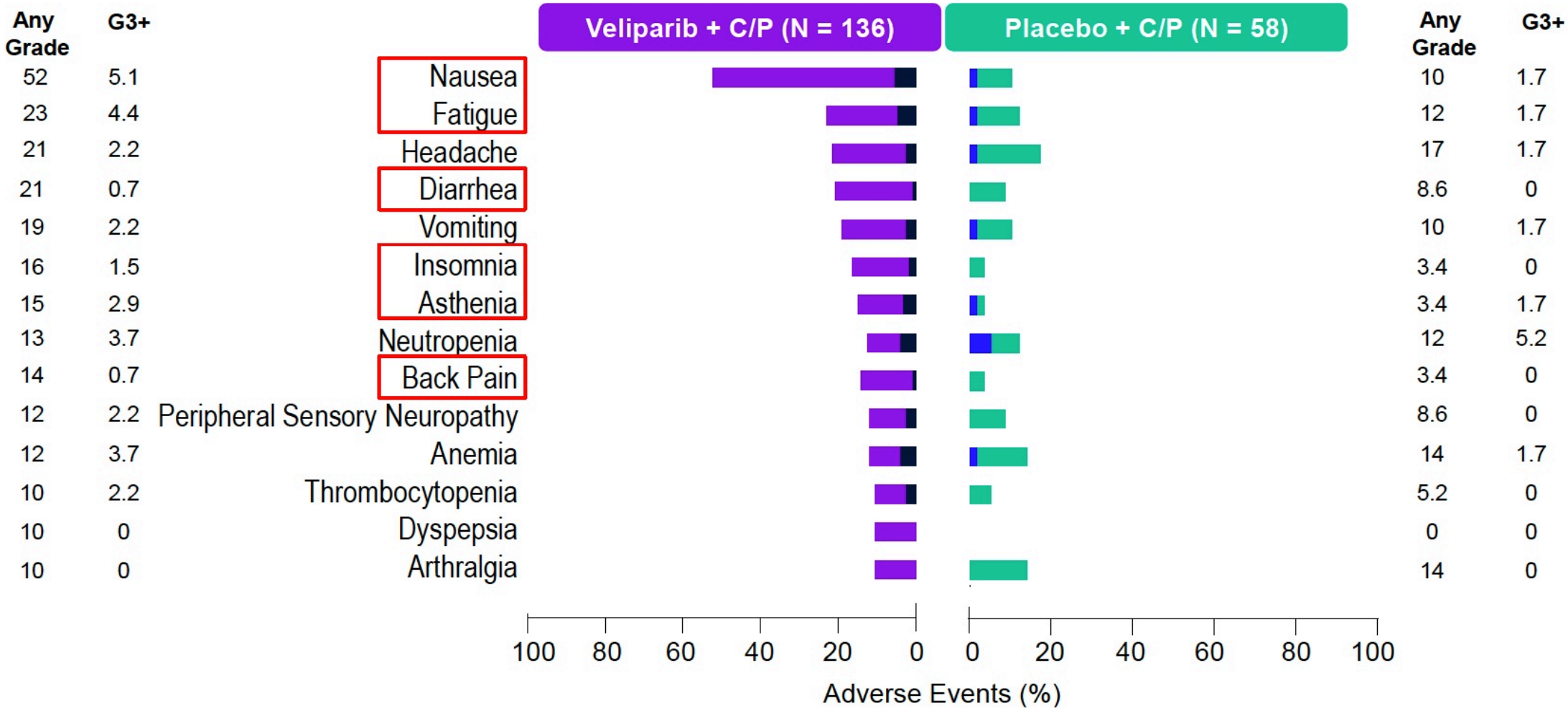
BROCADE3: Common Adverse Events (Entire Treatment Period)



All-grade AEs in ≥25% of patients. Red boxes indicate differences ≥10% in any grade AEs between arms.
G3+: Grade 3 or Higher. C/P: Carboplatin and Paclitaxel

Dieras VC et al. *Proc ESMO* 2019;Abstract LBA9.

BROCADE3: Common Adverse Events (Blinded Monotherapy)



All-grade AEs in ≥25% of patients. Red boxes indicate differences ≥10% in any grade AEs between arms.
G3+: Grade 3 or Higher. C/P: Carboplatin and Paclitaxel

Dieras VC et al. *Proc ESMO* 2019;Abstract LBA9.