A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA*-mutation

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Background

- Talazoparib (TALA) is a highly potent dual-mechanism PARP inhibitor[1-3]
  - Inhibits the PARP enzyme
  - Traps PARP on single-stranded DNA breaks[4]
  - Prevents repair of DNA damage, resulting in cell death
- Phase 1 trial established a tolerable dose of 1 mg/day for continuous dosing (fed or fasting)[5]
  - Single-agent activity in other tumor types (prostate, ovarian, SCLC)
- The phase 2 ABRAZO trial showed encouraging efficacy and safety in patients with germline *BRCA1/2* mutations and prior platinum therapy or at least 3 prior cytotoxic regimens[6]

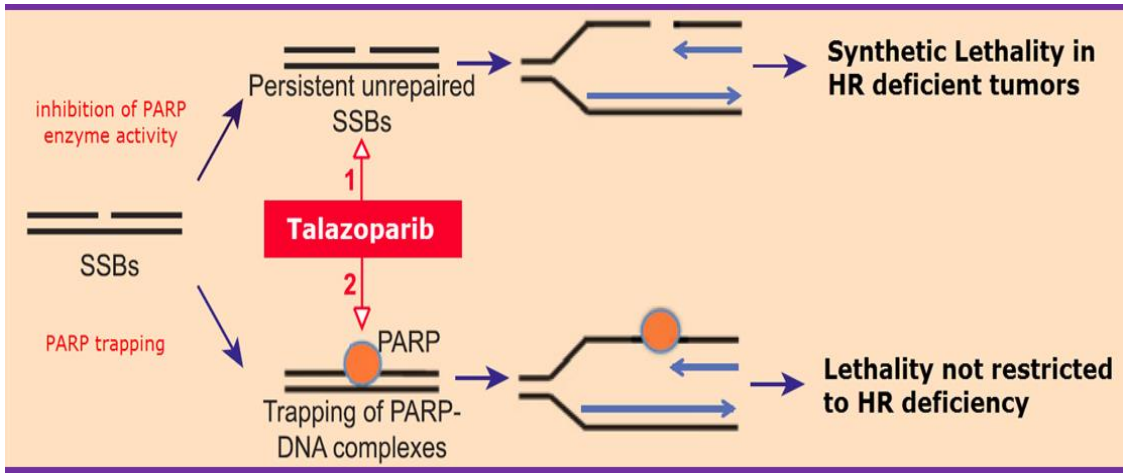


Figure adapted from Murai J et al. *Cancer Res*. 2012;72:5588-5599, with permission from AACR.

	ABRAZO		
	Phase 1 (n = 14)[a]	Prior Platinum (n = 48)	≥ 3 Lines, No Platinum (n = 35)
Confirmed ORR, % (95% CI)	50%	21% (10, 35)	37% (22, 55)
PFS, mo (95% CI)	7.5	4.0 (2.8, 5.4)	5.6 (5.5, 7.8)
CBR24, % (95% CI)	86%	38% (24, 53)	66% (48, 81)

[a]Data shown for the phase 1 study is only in breast cancer patients.

Abbreviations: CI, confidence interval; CBR24, clinical benefit rate at 24 weeks; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; ORR, objective response rate; PFS, progression-free survival; SCLC, small cell lung cancer; SSB, single-strand break.

1. Ashworth A. *J Clin Oncol*. 2008;26:3785-3790. 2. Jalve M, Curtin NJ. *Ther Adv Med Oncol*. 20113:257-267. 3. Helleday T. *Mol Oncol*. 2011;5:387-393. 4. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158. 5. de Bono J et al. *Cancer Discov.* 2017;7:620-629. 6. Turner NC et al. Presented at ASCO; June 3, 2017; Chicago, IL. Abstract 1007.

Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

Phase 3, international, open-label study randomized
431 patients in 16 countries and 145 sites

Primary endpoint

- **Progression-free survival by RECIST by blinded central review**

Key secondary efficacy endpoints

- **Overall survival (OS)**
- **ORR by investigator**
- **Safety**

Exploratory endpoints

- **Duration of response (DOR) for objective responders**
- **Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)**

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.
*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.
www.clinicaltrials.gov (NCT01945775)

Baseline Characteristics (ITT Population)

	TALA (n = 287)	Overall PCT (n = 144)
Age, median (range), y	45 (27.0-84.0)	50 (24.0-88.0)
<50 y, no. %	182 (63.4%)	67 (46.5%)
Gender, % female	98.6%	97.9%
ECOG = 0 / 1 / 2, %	53.0% / 44.0% / 2.0%	58.0% / 40.0% / 1.0%
Measurable disease by investigator, no. (%)	219 (76.3%)	114 (79.2%)
History of CNS metastasis, no. (%)	43 (15.0%)	20 (13.9%)
Visceral disease, no. (%)	200 (69.7%)	103 (71.5%)
Hormone receptor status, no. (%)		
TNBC	130 (45.3%)	60 (41.7%)
HR+	157 (54.7%)	84 (58.3%)
BRCA status, no. (%)		
BRCA1+	133 (46.3%)	63 (43.8%)
BRCA2+	154 (53.7%)	81 (56.3%)
Disease free interval (initial diagnosis to aBC) <12 months	108 (37.6%)	42 (29.2%)

Abbreviations: aBC, advanced breast cancer; ITT, intent to treat.

Prior Therapies for Advanced Breast Cancer

	TALA (n = 287)	Overall PCT (n = 144)
Prior adjuvant/neoadjuvant therapy, no. (%)	238 (82.9%)	121 (84.0%)
Prior hormonal therapy, no. (%)	161 (56.1%)	77 (53.5%)
Prior platinum therapy, no. (%)	46 (16.0%)	30 (21.0%)
No. of prior cytotoxic regimens for aBC, 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%)

Study Drug Exposure

	TALA (n = 286)	Overall PCT (n = 126)	Overall PCT (n = 126)			
			Capecitabine (n = 55)	Eribulin (n = 50)	Gemcitabine (n = 12)	Vinorelbine (n = 9)
Median duration of treatment, mo	6.1	3.9	4.1	2.9	5.5	4.2
Median relative dose intensity, %	87.2%		87.9%	96.4%	87.2%	64.3%

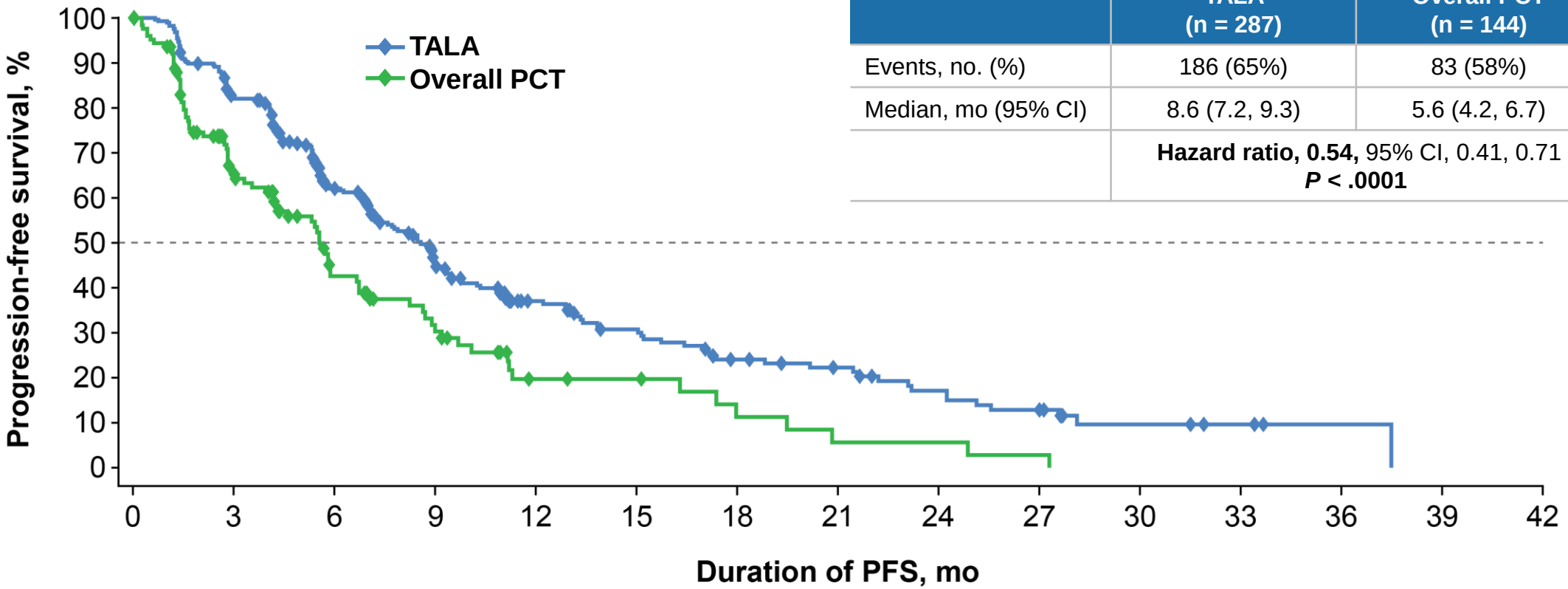
- The protocol-specific physician's choice was determined prior to randomization for each patient
- Choice of control arm drug (percentage of patients)*:
  - Capecitabine (44%); eribulin (40%); gemcitabine (10%); vinorelbine (7%)

*Percentages total >100% due to rounding up of values.

RESULTS

Primary Endpoint: PFS by Blinded Central Review

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

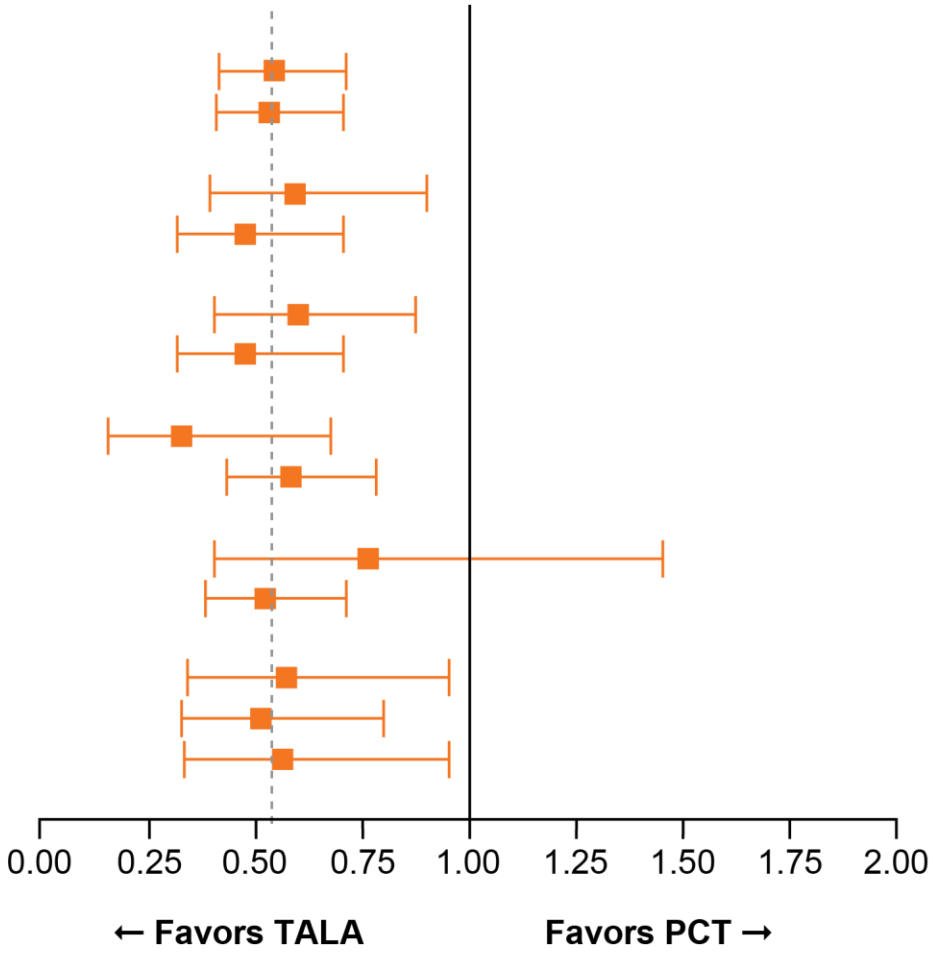


No. at risk (events/cumulative events)														
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

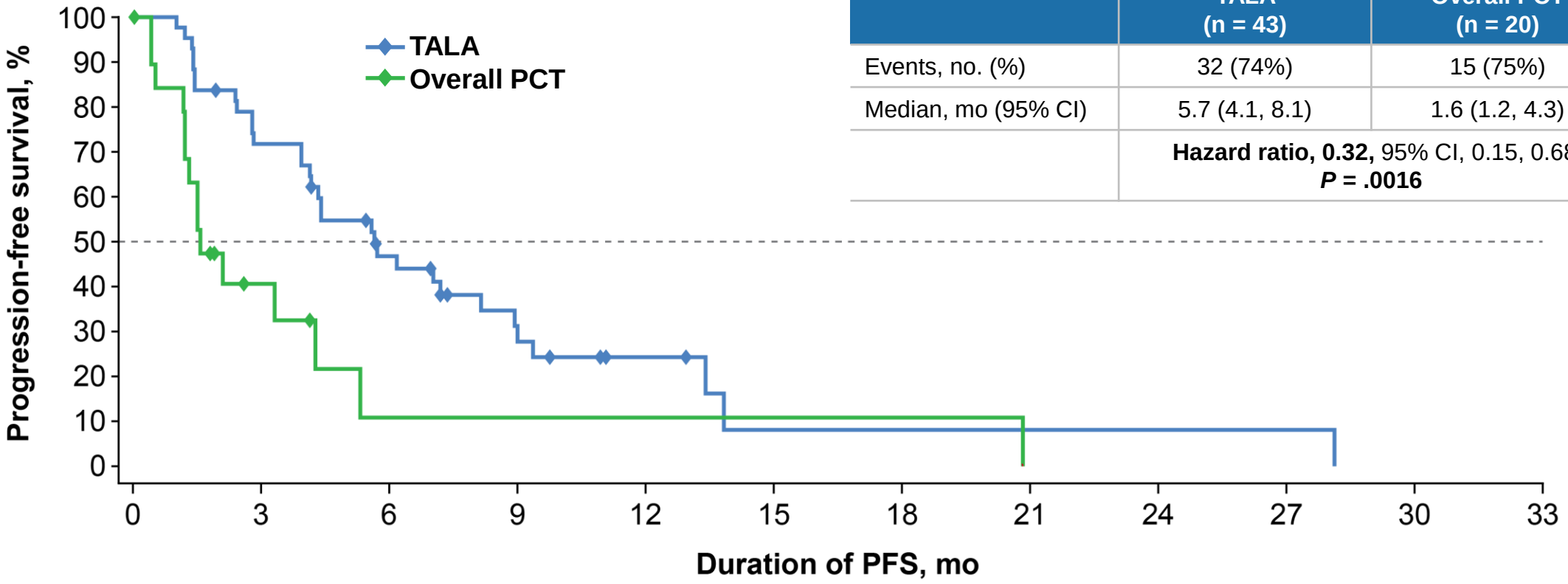
PFS: Subgroup Analysis

Subgroup	Patients, no. (%)	Hazard ratio (95% CI)
All randomized patients (ITT)	431 (100)	0.54 (0.41-0.71)
Patients with central testing available	408 (94.7)	0.53 (0.40-0.70)
BRCA status by 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		
TNBC based on most recent biopsy	190 (44.1)	0.60 (0.41-0.87)
HR+ based on most recent biopsy	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)
Prior platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Prior regimens of cytotoxic chemo for aBC		
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)



PFS: CNS Metastases Subgroup

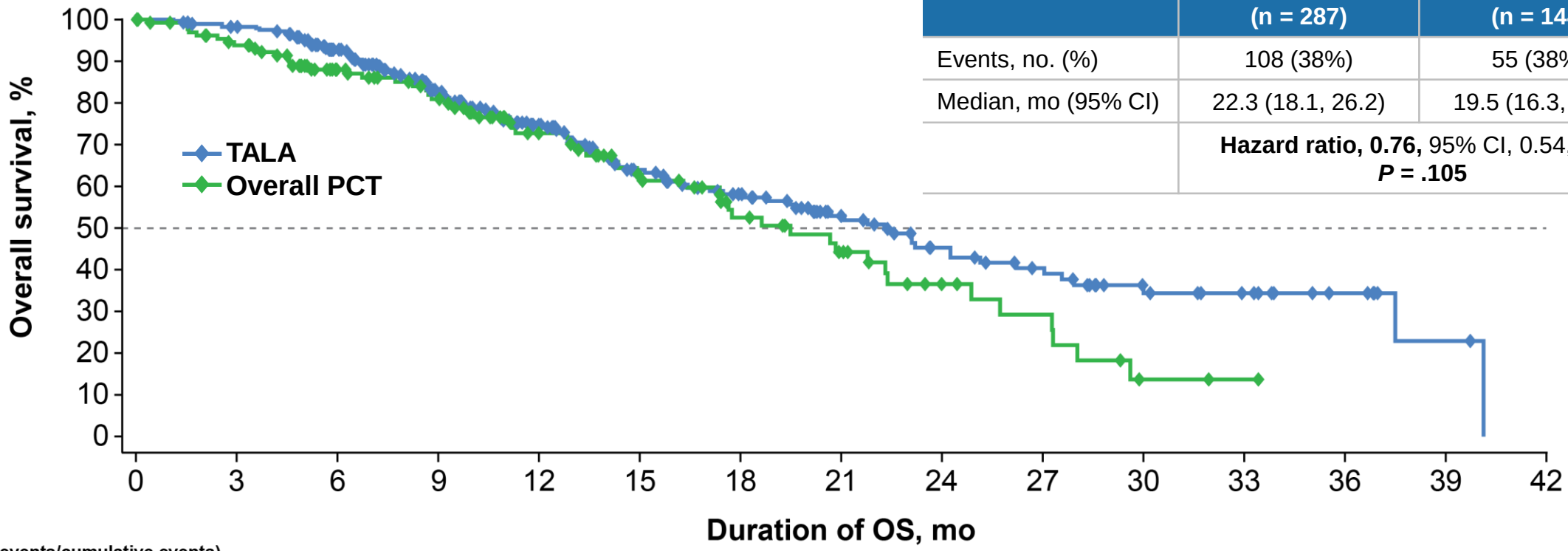
	TALA (n = 43)	Overall PCT (n = 20)
Events, no. (%)	32 (74%)	15 (75%)
Median, mo (95% CI)	5.7 (4.1, 8.1)	1.6 (1.2, 4.3)
	Hazard ratio, 0.32, 95% CI, 0.15, 0.68 ***P* = .0016**	



No. at risk (events/cumulative events)												
TALA	43 (0/0)	30 (12/12)	17 (10/22)	9 (5/27)	4 (2/29)	1 (2/31)	1 (0/31)	1 (0/31)	1 (0/31)	1 (0/31)	0 (1/32)	0 (0/32)
PCT	20 (0/0)	5 (11/11)	1 (3/14)	1 (0/14)	1 (0/14)	1 (0/14)	1 (0/14)	0 (1/15)	0 (0/15)	0 (0/15)	0 (0/15)	0 (0/15)

Interim OS Analysis: Secondary Endpoint

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	108 (38%)	55 (38%)
Median, mo (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
	Hazard ratio, 0.76, 95% CI, 0.54, 1.06 ***P* = .105**	



No. at risk (events/cumulative events)

TALA	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (8/85)	52 (6/91)	38 (7/98)	30 (4/102)	18 (4/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
PCT	144 (0/0)	119 (8/8)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (4/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

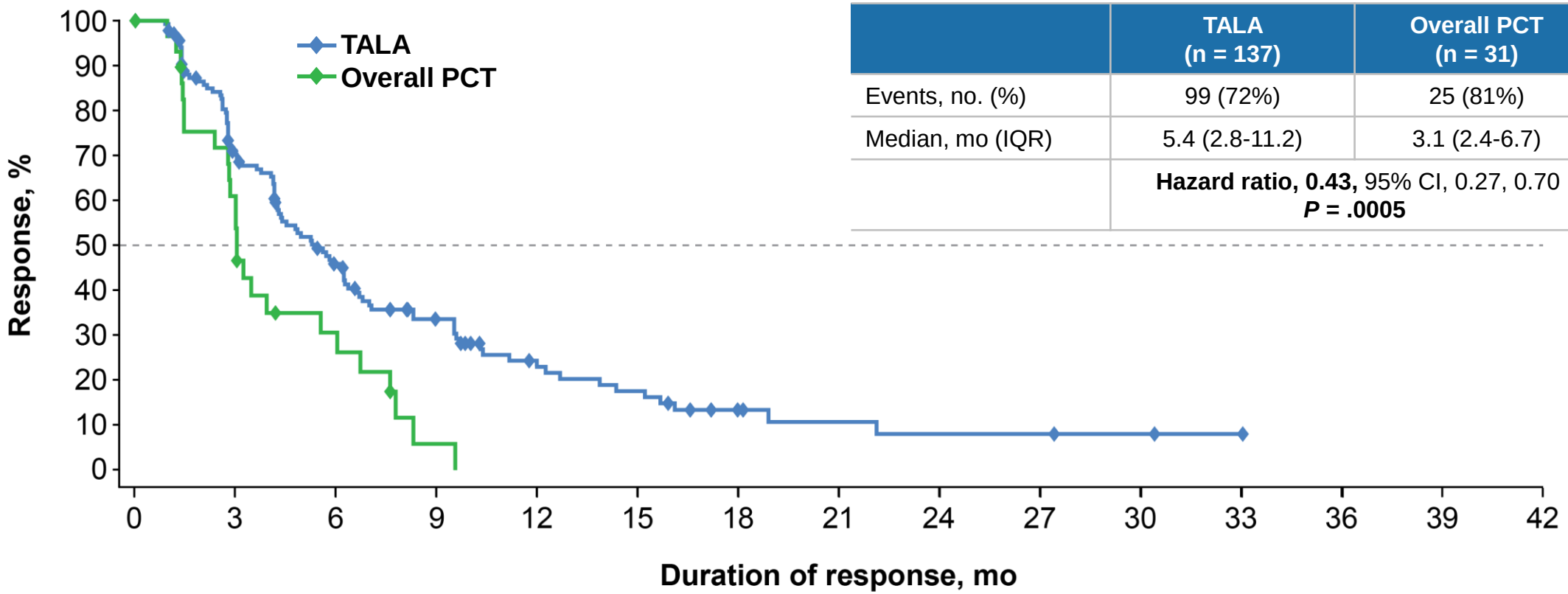
Survival Probability at:	TALA (n = 287)	Overall PCT (n = 144)
Month 24, % (95% CI)	45% (36.7-53.5)	37% (24.1-49.1)
Month 36, % (95% CI)	34% (25.3-43.7)	0%

Secondary/Exploratory Endpoints

	TALA	Overall PCT
Best overall response [measurable disease]*	**n = 219**	**n = 114**
Complete response, no. (%)	12 (5.5%)	0
Partial response, no. (%)	125 (57.1%)	31 (27.2%)
Stable disease, no. (%)	46 (21.0%)	36 (31.6%)
Non-evaluable, no. (%)	4 (1.8%)	19 (16.7%)
Objective response by investigator [measurable disease]*	**n = 219**	**n = 114**
ORR, % (95% CI)	62.6 (55.8-69.0)	27.2 (19.3-36.3)
Odds ratio (95% CI); 2-sided *P* value**	**4.99 (2.9-8.8); *P* < .0001**	
Clinical benefit rate at 24 weeks [ITT]	**n = 287**	**n = 144**
CBR24, % (95% CI)	68.6 (62.9-74.0)	36.1 (28.3-44.5)
Odds ratio (95% CI); 2-sided *P* value**	**4.28 (2.70-6.83); *P* < .0001**	
DOR by investigator [subgroup with objective response]	**n = 137**	**n = 31**
Median (IQR), mo	5.4 (2.8-11.2)	3.1 (2.4-6.7)

Abbreviation: IQR, interquartile range.
*Per RECIST version 1.1, confirmation of complete response or partial response was not required. **CMH=Cochran-Mantel-Haenszel.

DOR by Investigator Assessment

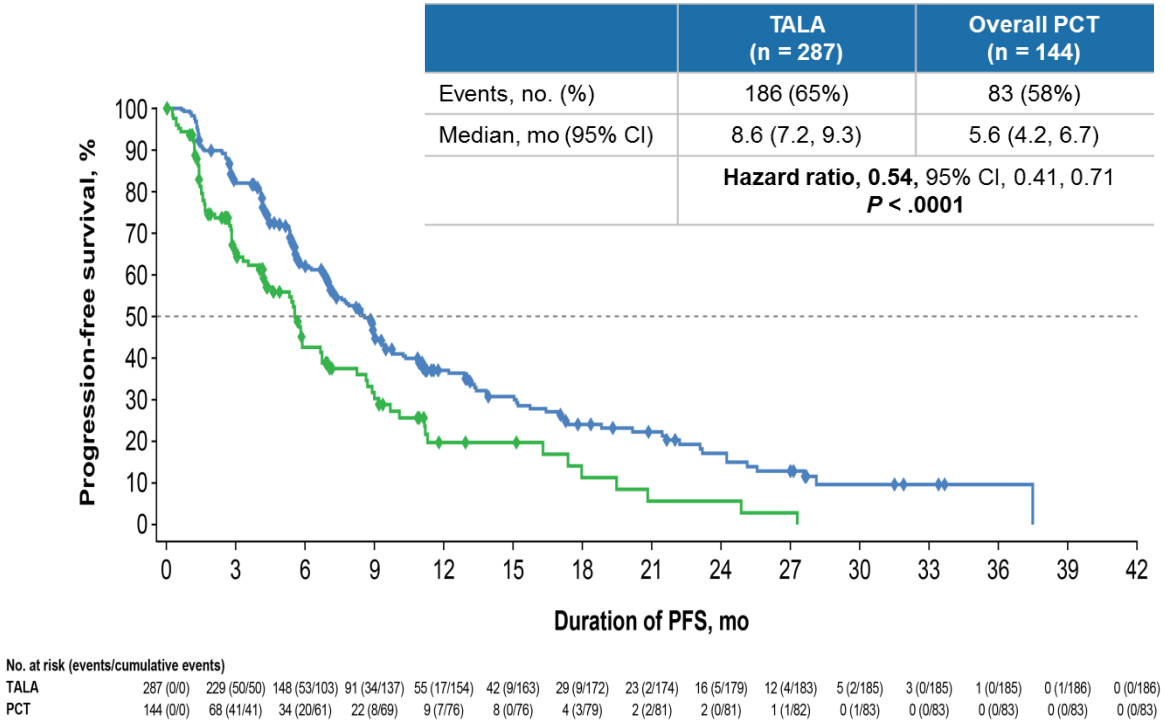


	TALA (n = 137)	Overall PCT (n = 31)
Events, no. (%)	99 (72%)	25 (81%)
Median, mo (IQR)	5.4 (2.8-11.2)	3.1 (2.4-6.7)
	Hazard ratio, 0.43, 95% CI, 0.27, 0.70 ***P* = .0005**	

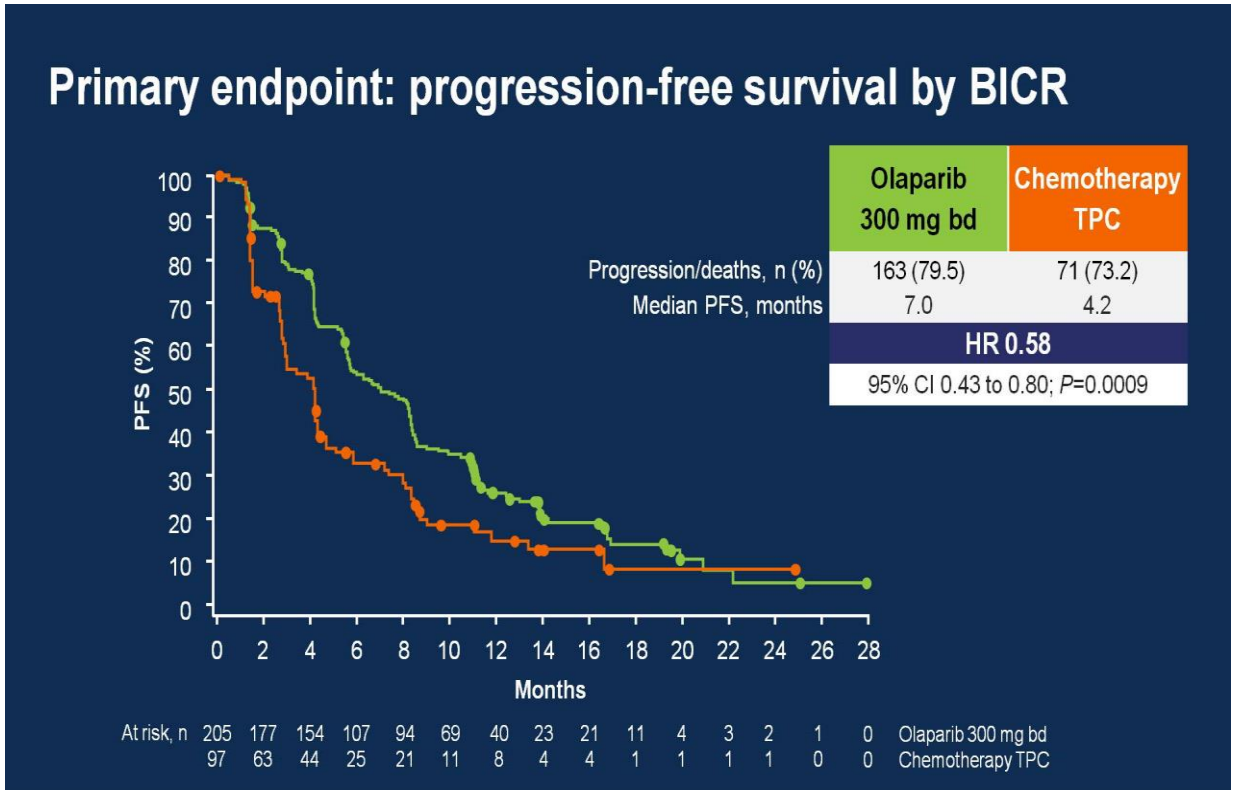
No. at risk (events/cumulative events)														
TALA	137 (0/0)	88 (38/38)	52 (30/68)	31 (13/81)	17 (9/90)	13 (4/94)	6 (3/97)	4 (1/98)	3 (1/99)	3 (0/99)	2 (0/99)	1 (0/99)	0 (0/99)	0 (0/99)	0 (0/99)
PCT	31 (0/0)	17 (11/11)	7 (8/19)	1 (5/24)	0 (1/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)

1-year probability of sustained response is 23% vs 0% with TALA and PCT, respectively

EMBRACA vs. OlympiAD



EMBRACA



OlympiAD

SAFETY

Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	**Grade 3**	**Grade 4**	**All Grade**	**Grade 3**	**Grade 4**
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	**Grade 3**	**Grade 4**	**All Grade**	**Grade 3**	**Grade 4**
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	**Grade 3**	**Grade 4**	**All Grade**	**Grade 3**	**Grade 4**
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

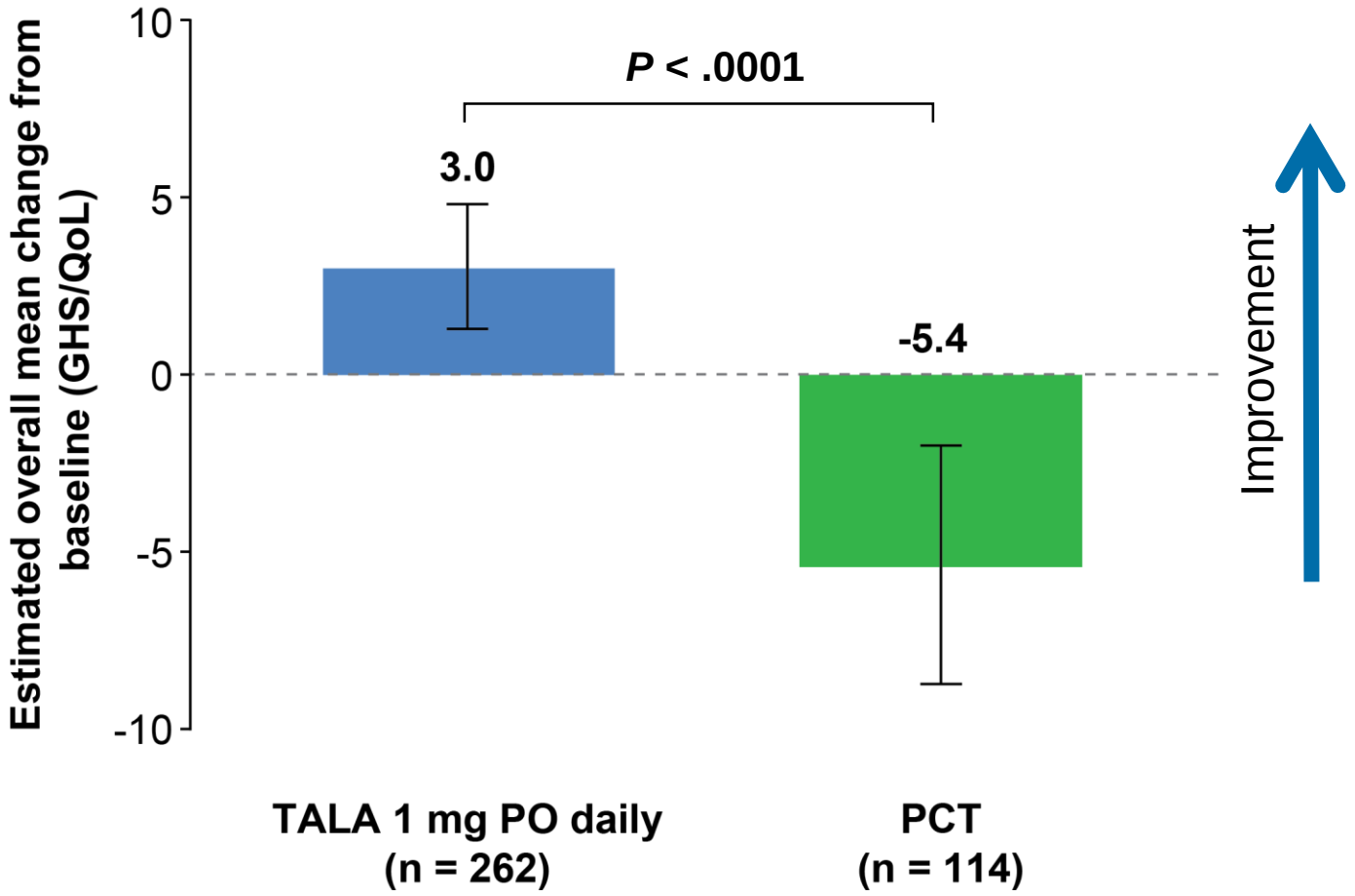
Adverse Events: Nonhematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	**Grade 3**	**Grade 4**	**All Grade**	**Grade 3**	**Grade 4**
No. of patients with ≥ 1 nonhematologic AE, no. (%)	282 (98.6%)	91 (31.8%)		123 (97.6%)	48 (38.1%)	
Fatigue	144 (50.3%)	5 (1.7%)	0	54 (42.9%)	4 (3.2%)	0
Nausea	139 (48.6%)	1 (0.3%)	0	59 (46.8%)	2 (1.6%)	0
Headache	93 (32.5%)	5 (1.7%)	0	28 (22.2%)	1 (0.8%)	0
Alopecia	72 (25.2%)	-	-	35 (27.8%)	-	-
Vomiting	71 (24.8%)	7 (2.4%)	0	29 (23.0%)	2 (1.6%)	0
Diarrhea	63 (22.0%)	2 (0.7%)	0	33 (26.2%)	7 (5.6%)	0
Constipation	63 (22.0%)	1 (0.3%)	0	27 (21.4%)	0	0
Decreased appetite	61 (21.3%)	1 (0.3%)	0	28 (22.2%)	1 (0.8%)	0
Back pain	60 (21.0%)	7 (2.4%)	0	20 (15.9%)	2 (1.6%)	0
Dyspnea	50 (17.5%)	7 (2.4%)	0	19 (15.1%)	3 (2.4%)	0
Palmar-plantar erythrodysesthesia syndrome	4 (1.4%)	1 (0.3%)	0	28 (22.2%)	3 (2.4%)	0
Pleural effusion	6 (2.1%)	5 (1.7%)	0	11 (8.7%)	5 (4.0%)	0

- All adverse events (AEs) in ≥ 20% of patients and grade 3-4 AEs in ≥ 2.4% of patients
- No clinically relevant cardiac or vascular toxicity observed in the TALA arm
- Alopecia: all grade 1 except 2.4% grade 2 in TALA; 7.9% grade 2 in PCT

EORTC QLQ-C30: Patient-Reported Global Health Status (GHS)/QoL

Statistically significant improvement in estimated overall mean change from baseline in GHS/QoL for TALA-treated patients [3.0 (95% CI, 1.2, 4.8)] compared to PCT-treated patients [-5.4 (-8.8, -2.0)]

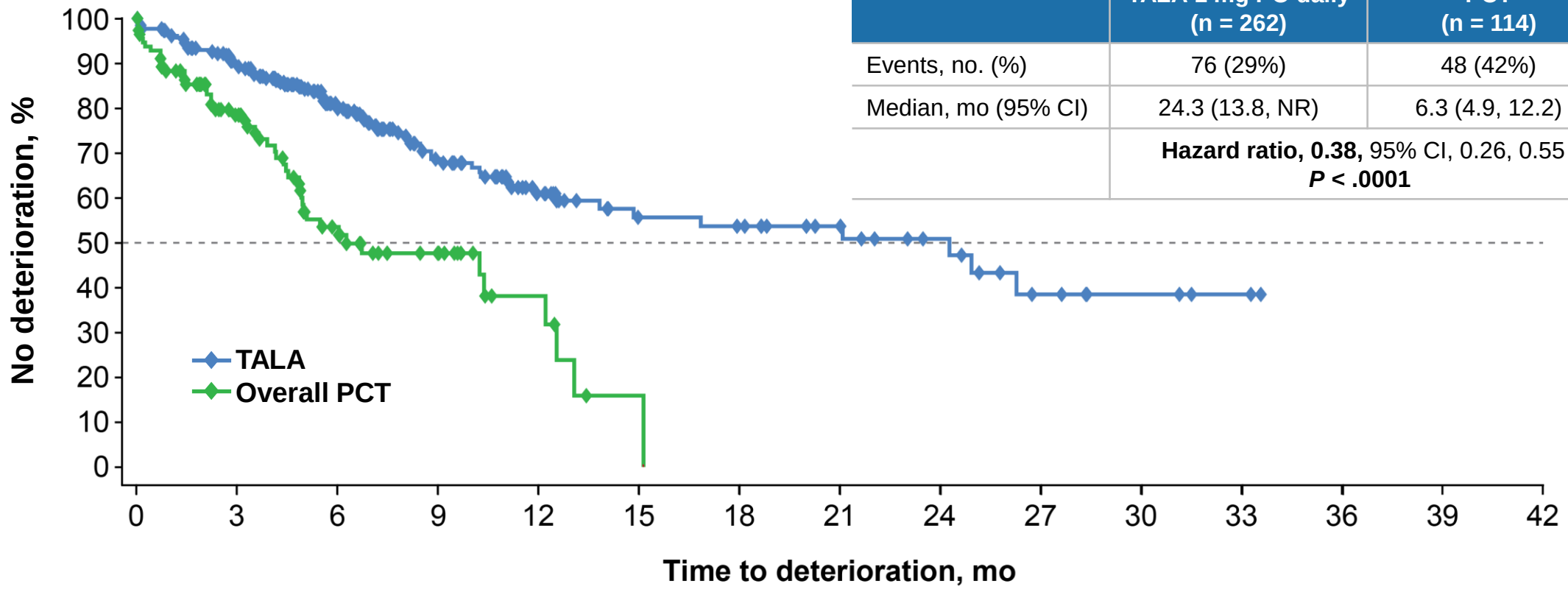


Note: Results from longitudinal repeated measures mixed effects model.

Time to Deterioration in EORTC QLQ-C30: GHS/QoL

Statistically significant delay in the time to clinically meaningful deterioration* in GHS/QoL favoring TALA

	TALA 1 mg PO daily (n = 262)	PCT (n = 114)
Events, no. (%)	76 (29%)	48 (42%)
Median, mo (95% CI)	24.3 (13.8, NR)	6.3 (4.9, 12.2)
	Hazard ratio, 0.38, 95% CI, 0.26, 0.55 ***P* < .0001**	



No. at risk (events/cumulative events)														
TALA	262 (0/0)	212 (26/26)	139 (18/44)	78 (17/61)	44 (7/68)	28 (3/71)	26 (1/72)	20 (0/72)	14 (1/73)	7 (3/76)	4 (0/76)	2 (0/76)	0 (0/76)	0 (0/76)	0 (0/76)
PCT	114 (0/0)	64 (22/22)	30 (17/39)	17 (3/42)	6 (2/44)	1 (3/47)	0 (1/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)

Abbreviation: NR, not reached. *≥ 10-point decrease and no subsequent observation with a < 10-point decrease from baseline.

EMBRACA Phase 3 Trial of Talazoparib: Conclusions

- EMBRACA is the largest randomized trial evaluating a PARP inhibitor in patients with advanced breast cancer and a germline *BRCA1/2* mutation
- Talazoparib resulted in prolonged progression-free survival vs physician's choice of therapy by blinded central review
  - HR: 0.54 (95% CI, 0.41, 0.71); $P < .0001$
- All key secondary efficacy endpoints demonstrated benefit with talazoparib
  - Overall survival is immature (51% of projected events); HR: 0.76 (95% CI, 0.54, 1.06); $P = .105$
- Global Health Status/Quality of Life showed overall improvement from baseline and a delay in the time to clinically meaningful deterioration in patients receiving talazoparib
  - HR: 0.38 (95% CI, 0.26, 0.55); $P < .0001$
- Talazoparib was generally well tolerated, with minimal nonhematologic toxicity and few adverse events resulting in treatment discontinuation