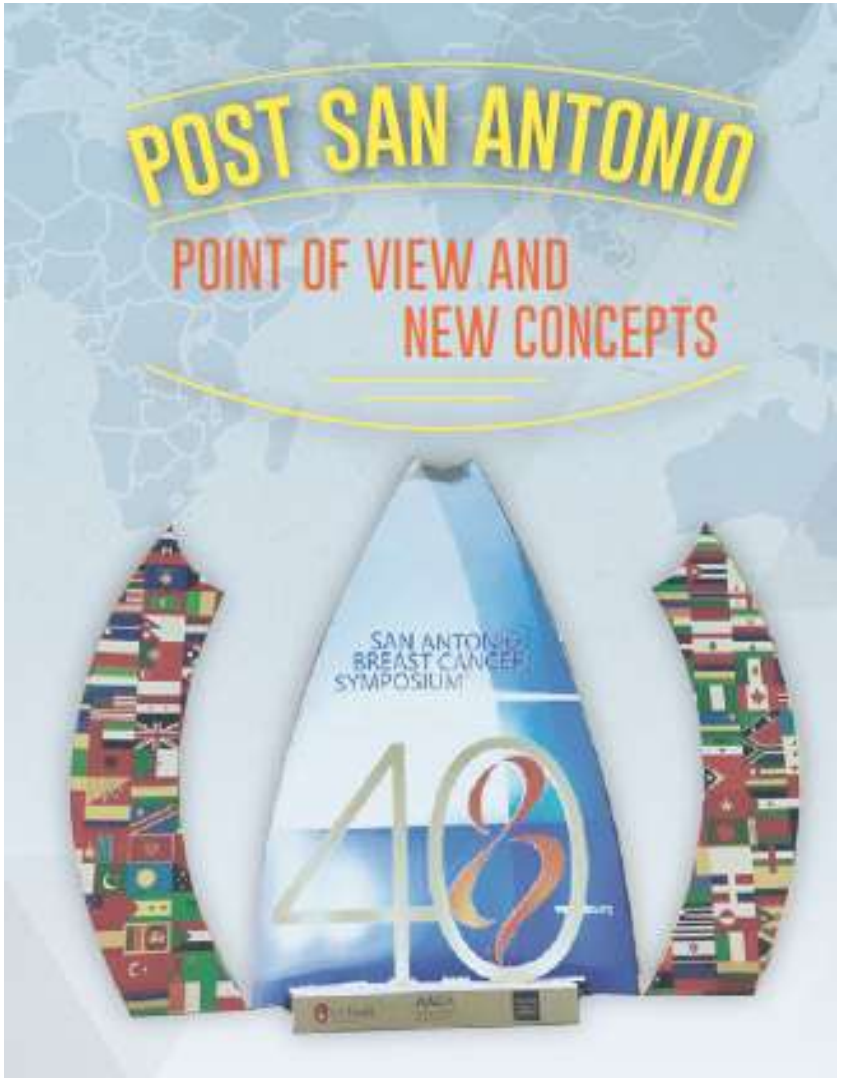


Point of View on Triple Negative: Metastatic setting

Dott.ssa llaria Portarena MD, PhD

UOSD Oncologia Medica

Policlinico Tor Vergata

Roma, 29 Gennaio 2018

PTV
FONDAZIONE PTV
POLICLINICO TOR VERGATA

Background

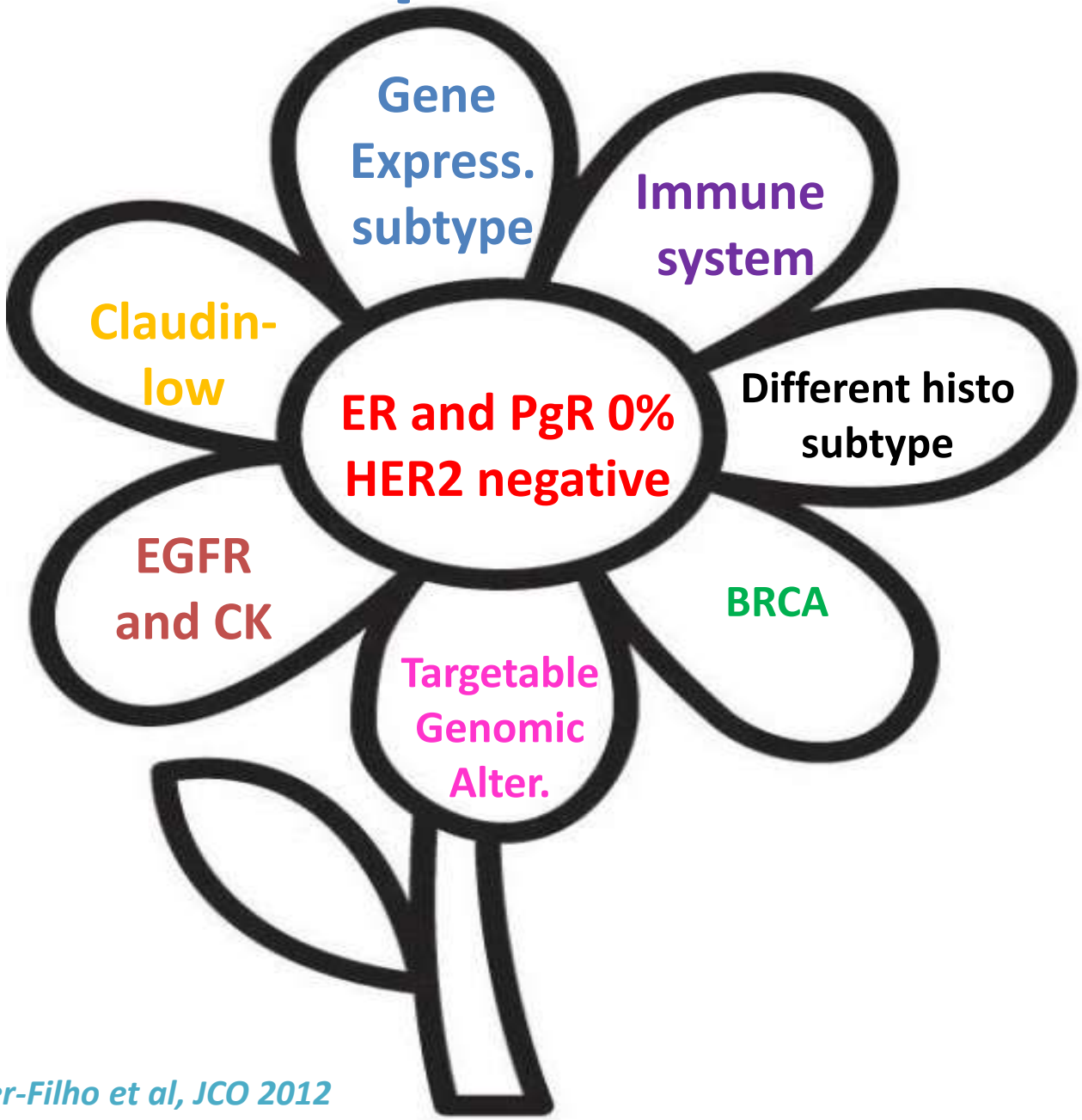
- Metastatic triple-negative breast cancer (mTNBC) is an aggressive disease with poor prognosis that disproportionally affects young women
  - Visceral and brain metastases are very common
- No single standard chemotherapy available for relapsed/refractory mTNBC
  - Response rates with standard chemotherapy are low (~10-15%)
  - Median progression-free survival (PFS) is ~2-3 months with standard therapies (capecitabine, cisplatin or carboplatin, eribulin, nab-paclitaxel)
- Currently, there is a large unmet need in the breast cancer community

Low Response Rates in Pretreated mTNBC

Drug	Phase	N	Population	ORR, %	PFS, months	OS, months	Source
1st-line treatment							
Carboplatin	III	188	1st line	31	3.1	12.4	Tutt A, SABCS 2014
Docetaxel	III	188	1st line	36	4.5	12.3	Tutt A, SABCS 2014
Cisplatin/ Carboplatin	II	86	1st line (80.2%)	26	2.9	11.0	Isakoff SJ, J Clin Oncol, 2015
≥1st-line treatment							
Ixabepilone	II (pooled analysis)	60	Resist to AC-T or just to T	6-17	1.6-2.7	--	Perez EA, Breast Cancer Res Treat 2010
Capecitabine	III (pooled analysis)	208	Prior A, T or resist to A, T	15	1.7	--	Perez EA, Breast Cancer Res Treat 2010
Eribulin	III (pooled analysis)	199	≥1 prior chemo	11	2.8	12.4	Pivot X, Ann Oncol 2016

Includes breast cancer drugs with data from Phase II/III trials with minimum mTNBC sample size ≥60; ORR and PFS data

The flower of hope



Modified by Metzger-Filho et al, JCO 2012

…From San Antonio

1. New drugs in mTNBC

2. Immunotherapy

3. BRCA-mutated mTNBC

San Antonio Breast Cancer Symposium, December 5-9, 2017

Long-term Follow-up of CALGB 40502/NCCTG N063H (Alliance): A Randomized Phase III Trial of Weekly Paclitaxel Compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel or Ixabepilone +/- Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

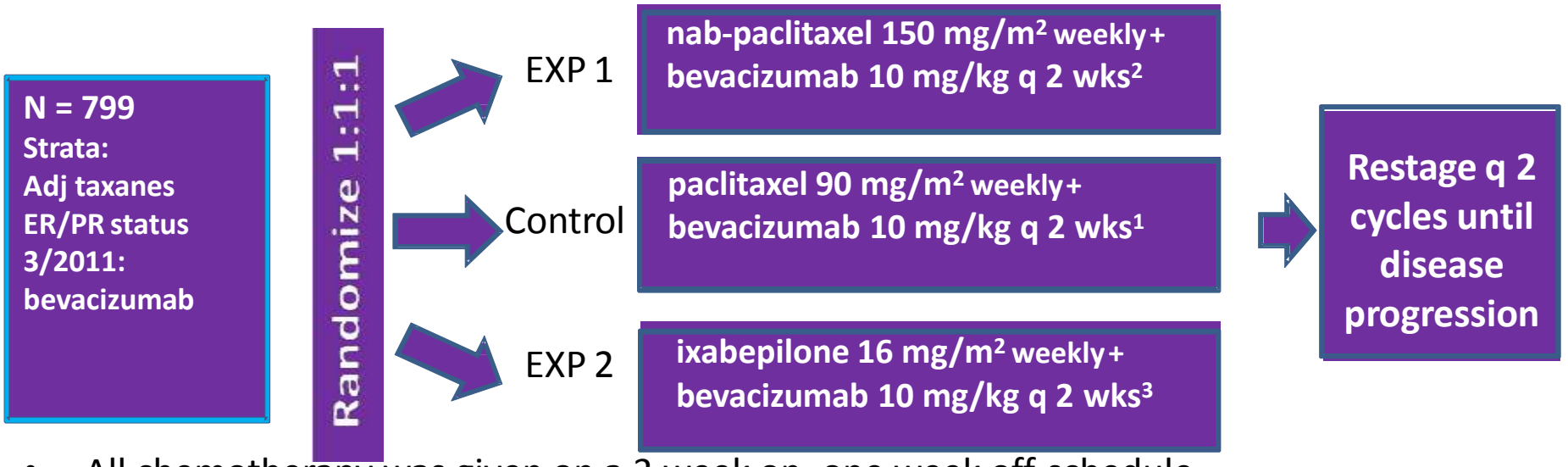
HS Rugo, WT Barry, A Moreno-Aspitia, A Lyss, L Huebner, EL Mayer, M Naughton, RM Layman, LA Carey, RA Somer, D Toppmeyer, M Velasco, EA Perez, CA Hudis, E Winer

Support: U10CA180820, U10CA180821, U10CA180882, U10CA180888
ClinicalTrials.gov Identifier: NCT00785291

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 40502 - NCCTG N063H - CTSU 40502

An Open Label Phase III Trial of First-line Therapy for Locally Recurrent or Metastatic Breast Cancer



- All chemotherapy was given on a 3 week on, one week off schedule
- Patients could discontinue chemotherapy and continue bevacizumab alone after 6 cycles if stable or responding disease
  - 98% of patients received bevacizumab
- Primary objective: to compare PFS between EXP 1 or EXP 2 and paclitaxel

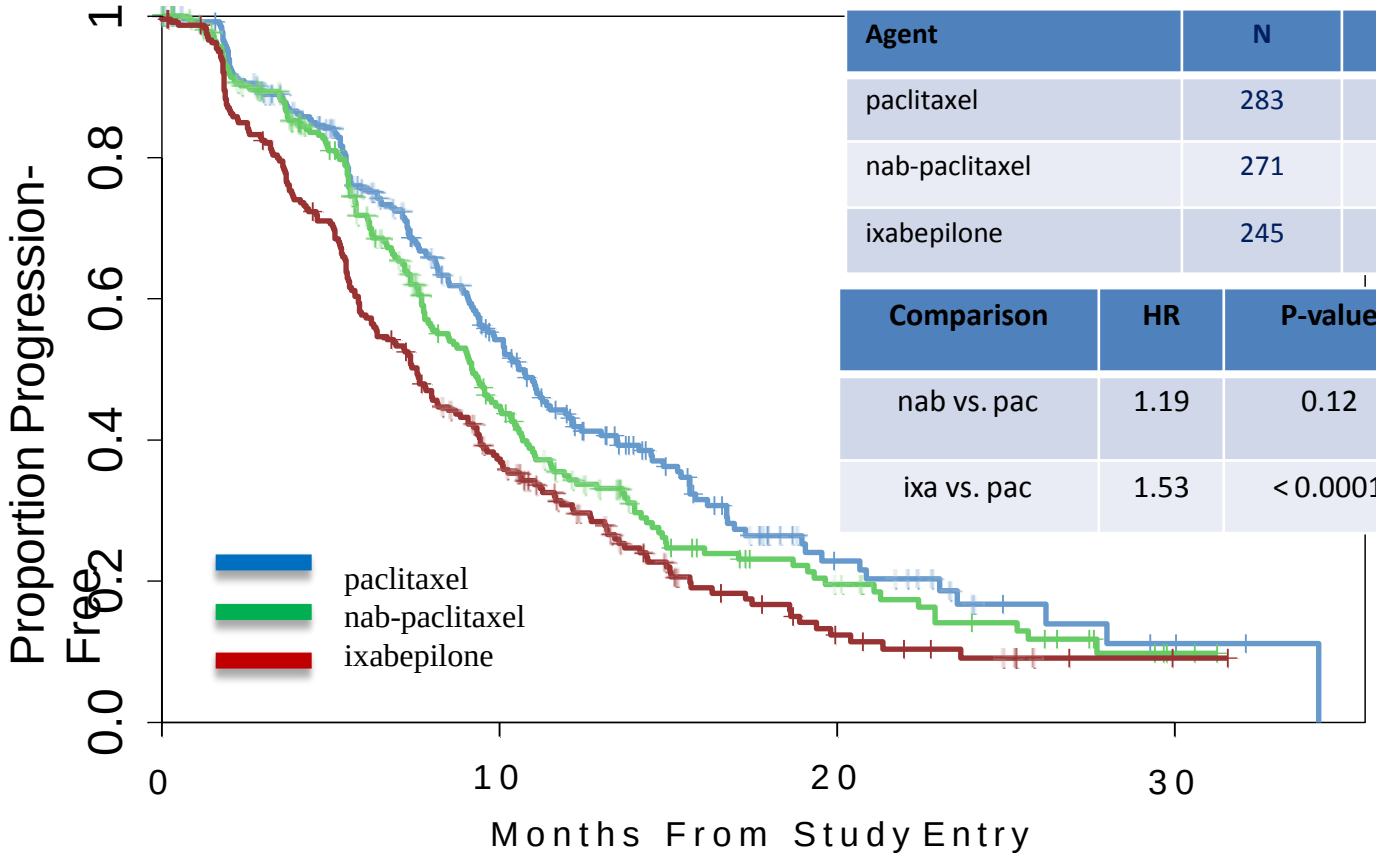
1. Miller et al, NEJM, 2007 2. Gradishar et al, JCO, 2009. 3. Dickson et al, Proc ASCO 2006.

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Study Design

- Eligibility
  - No prior chemotherapy for advanced disease and at least 12 months from adjuvant taxane
  - Measurable disease and adequate organ function
  - Peripheral neuropathy $\leq$ grade 1; ECOG PS $\leq$ 1
- Statistical considerations
  - Separate log-rank tests of superiority to paclitaxel (control)
  - Hypothesis:
    - Median PFS 11 mos in control vs 15 mos in experimental arms (HR = 0.73)
  - Planned sample size of 900 (300 per arm) to have 88% power
  - Interim analyses: allow early stopping for superiority or futility (separate for each experimental agent)

CALGB 40502: Primary Analysis in 2013 Progression-Free Survival By Treatment Arm



Agent	N	Median PFS
paclitaxel	283	10.6
nab-paclitaxel	271	9.2
ixabepilone	245	7.6

Comparison	HR	P-value	95% CI
nab vs. pac	1.19	0.12	0.96-1.49
ixa vs. pac	1.53	< 0.0001	1.24-1.90

Rugo et al, JCO 2015

Objectives of the Current Analysis

- Aim of the present analysis
  - Update PFS and OS with 4 years of additional follow-up
  - Retrospective subset analysis in TN and HR+/HER2-
  - Association of treatment outcomes with early discontinuation
- Relative to primary analysis (6/2013 to May 3, 2017)
  - 70 additional PFS events (732 total)
  - 191 new deaths (628 total)
  - Median follow-up for survival is 5.5 years.

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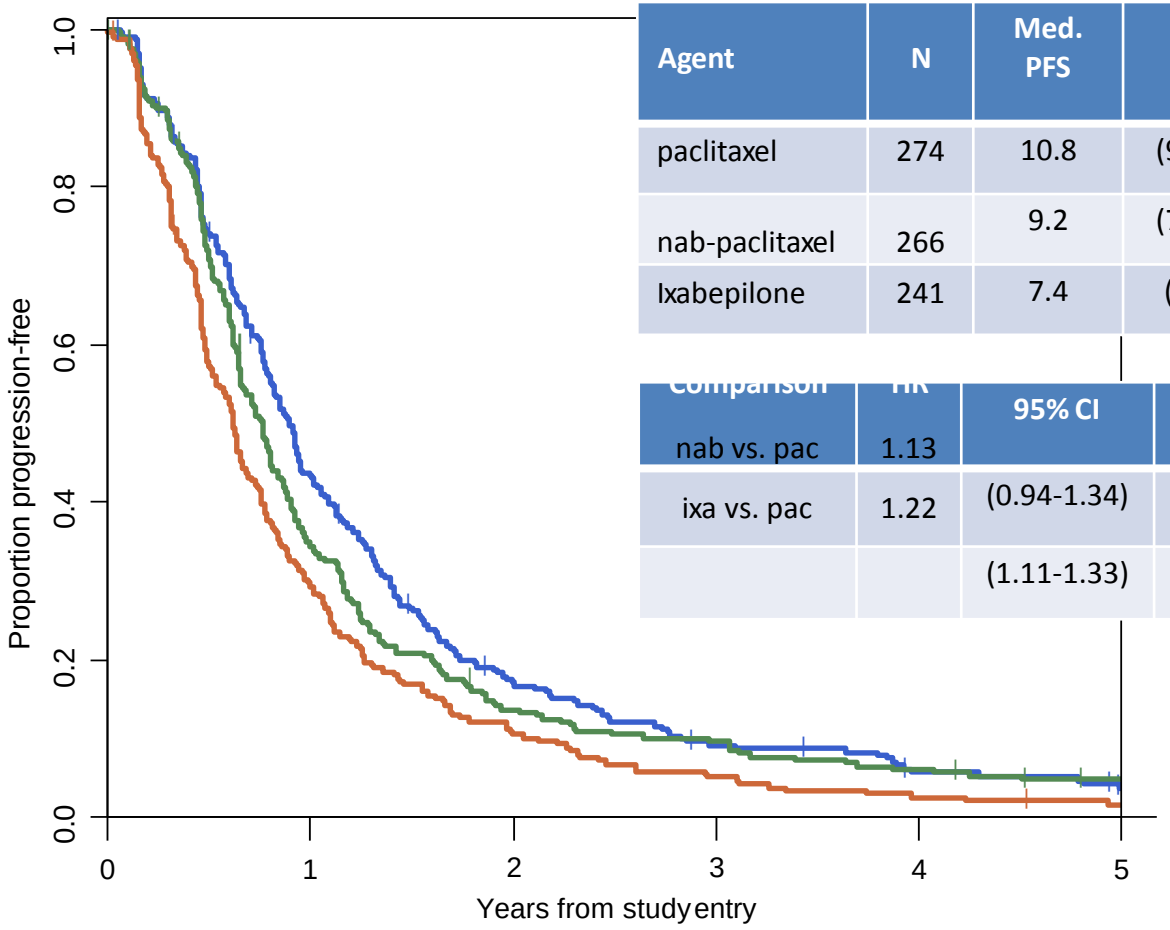
Updated Progression Free Survival

Agent	N	Med. PFS	95% CI
paclitaxel	274	10.8	(9.6-12.0)
nab-paclitaxel	266	9.2	(7.9-10.1)
Ixabepilone	241	7.4	(6.3-8.3)

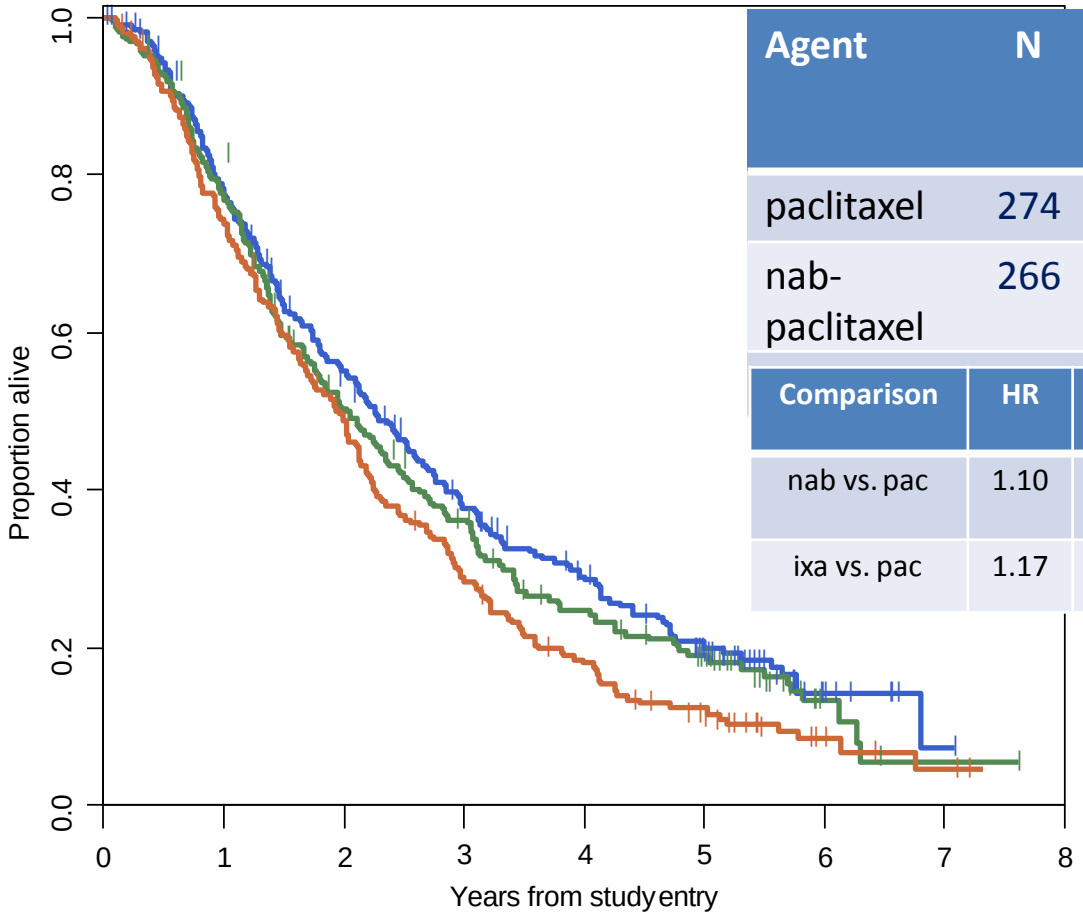
Comparison	HR	95% CI	P-value
nab vs. pac	1.13		
ixa vs. pac	1.22	(0.94-1.34)	0.16
		(1.11-1.33)	<0.0001



Number at risk

Paclitaxel	274	114	43	22	12	6
Nab-paclitaxel	266	88	34	24	15	9
Ixabepilone	241	70	25	12	6	3

Updated Overall Survival



Agent	N	Med. OS	95% CI
paclitaxel	274	27.1	(23.5-31.8)
nab-paclitaxel	266	24.2	(21.0-28.3)

Comparison	HR	95% CI	P-value
nab vs. pac	1.10	(0.91-1.33)	0.33
ixa vs. pac	1.17	(1.06-1.29)	0.0024

Number at risk

Paclitaxel	274	206	141	90	63	37	7	1	0
Nab-paclitaxel	266	198	123	86	55	39	5	1	0
Ixabepilone	241	176	113	65	39	24	6	2	0

SUBSET ANALYSES FOR PFS AND OS

San Antonio Breast Cancer Symposium, December 5-9, 2017

Multivariate Model for PFS

	Comparison of nab-paclitaxel to paclitaxel			Comparison of ixabepilone to paclitaxel		
	HR	95% CI	p-value	HR	95% CI	p-value
Univariate model						
Treatment Arm (Exp : Ctrl)	1.13	0.94-1.34	0.16	1.22	1.11-1.33	<0.0001
Multivariate model [1, 2]						
Treatment Arm in HR+ (Exp : Ctrl)	1.35	1.09-1.66	0.0047	1.22	1.10-1.36	0.0003
Treatment Arm in HR- (Exp : Ctrl)	0.71	0.51-1.00	0.052	1.22	1.02-1.45	0.030
Prior taxane (No : Yes)	0.64	0.51-0.79	<0.0001	0.71	0.57-0.88	0.012
Disease-free interval (>2yr : ≤2yr)	0.97	0.88 – 1.06	0.46	0.97	0.88-1.07	0.49
Visceral metastases (Any : None)	1.46	1.17-1.82	0.0010	1.21	0.95-1.54	0.12

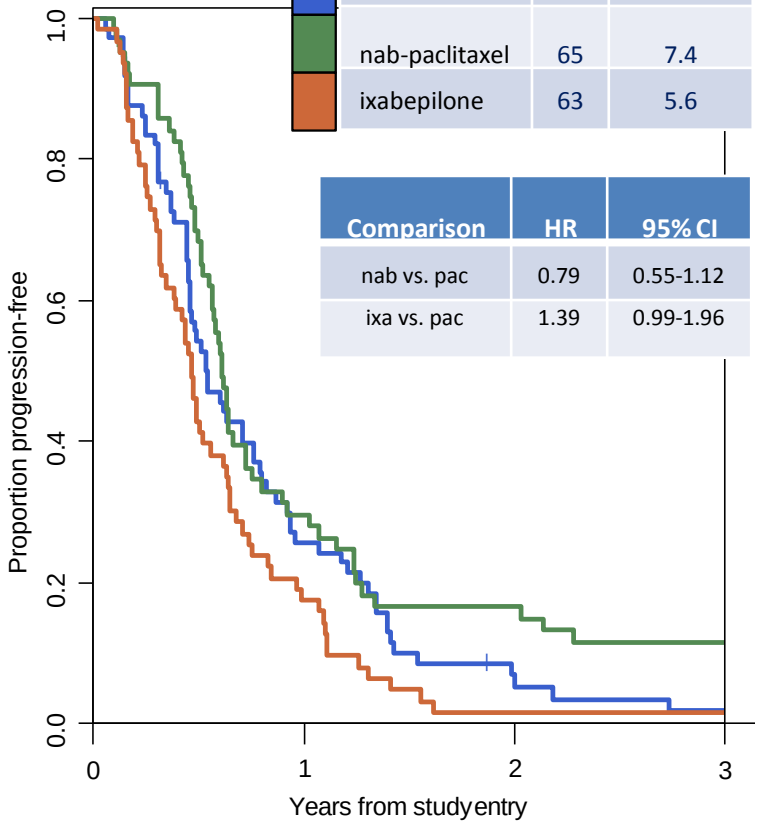
- Test of interaction between nab vs. pac and hormone receptor status was significant (p-value = 0.0018), so treatment effects are summarized within subgroups
- Test of interaction with ixabepilone was not significant (p = 0.96)

Progression Free Survival: TN and HR+

Triple Negative (n=201)

Agent	N	PFS
paclitaxel	73	6.4
nab-paclitaxel	65	7.4
ixabepilone	63	5.6

Comparison	HR	95% CI
nab vs. pac	0.79	0.55-1.12
ixa vs. pac	1.39	0.99-1.96



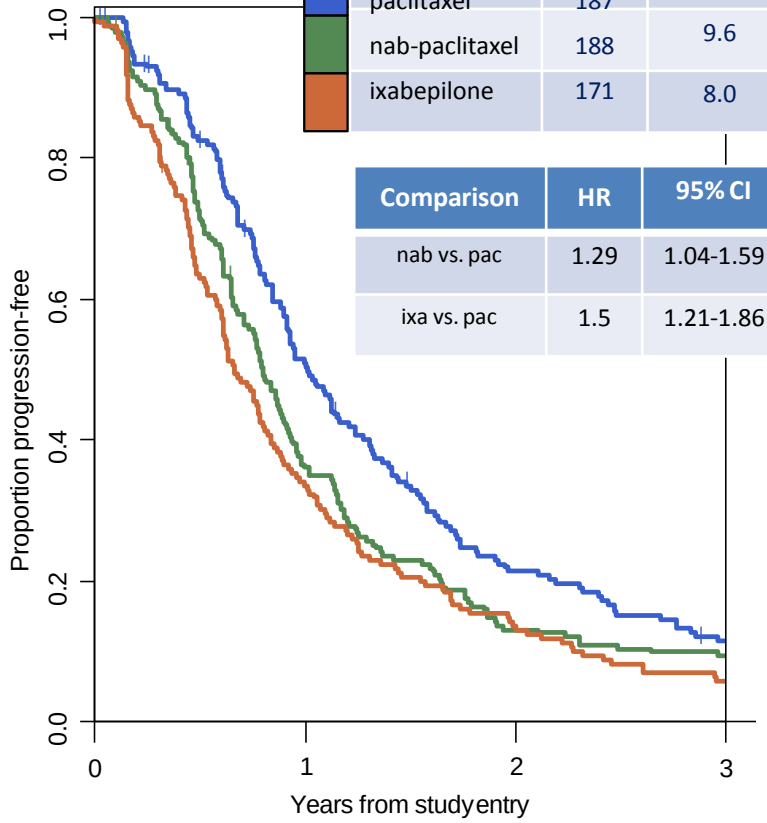
Number at risk

73	18	4	1
65	18	10	7
63	11	1	1

HR positive / HER2- (n=546)

Agent	N	PFS
paclitaxel	187	12.2
nab-paclitaxel	188	9.6
ixabepilone	171	8.0

Comparison	HR	95% CI
nab vs. pac	1.29	1.04-1.59
ixa vs. pac	1.5	1.21-1.86



Number at risk

187	91	37	19
188	66	24	17
171	57	22	10

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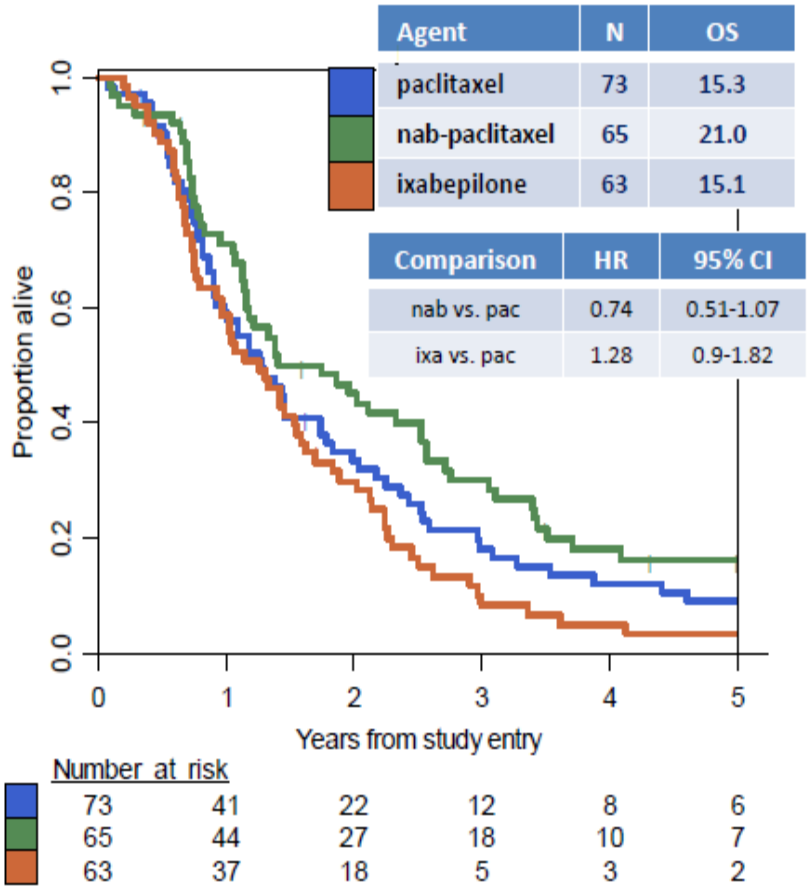
Multivariate Model for Overall Survival

	Comparison of nab-paclitaxel to paclitaxel			Comparison of ixabepilone to paclitaxel		
	HR	95% CI	p-value	HR	95% CI	p-value
Univariate model						
Treatment Arm (Exp : Ctrl)	1.10	0.91-1.33	0.33	1.17	1.06-1.29	0.0024
Multivariate model [1, 2]						
Treatment Arm in HR+ (Exp : Ctrl)	1.30	1.03-1.63	0.027	1.16	1.03-1.30	0.016
Treatment Arm in HR- (Exp : Ctrl)	0.73	0.51-1.04	0.078	1.15	0.95-1.37	0.14
Prior taxane (No : Yes)	0.68	0.54-0.85	0.0009	0.73	0.58-0.92	0.0067
Disease-free interval (>2yr : ≤2yr)	0.95	0.86 – 1.05	0.32	0.96	0.87-1.07	0.47
Visceral metastases (Any : None)	1.71	1.33-2.20	<0.0001	1.61	1.23-2.11	0.0006

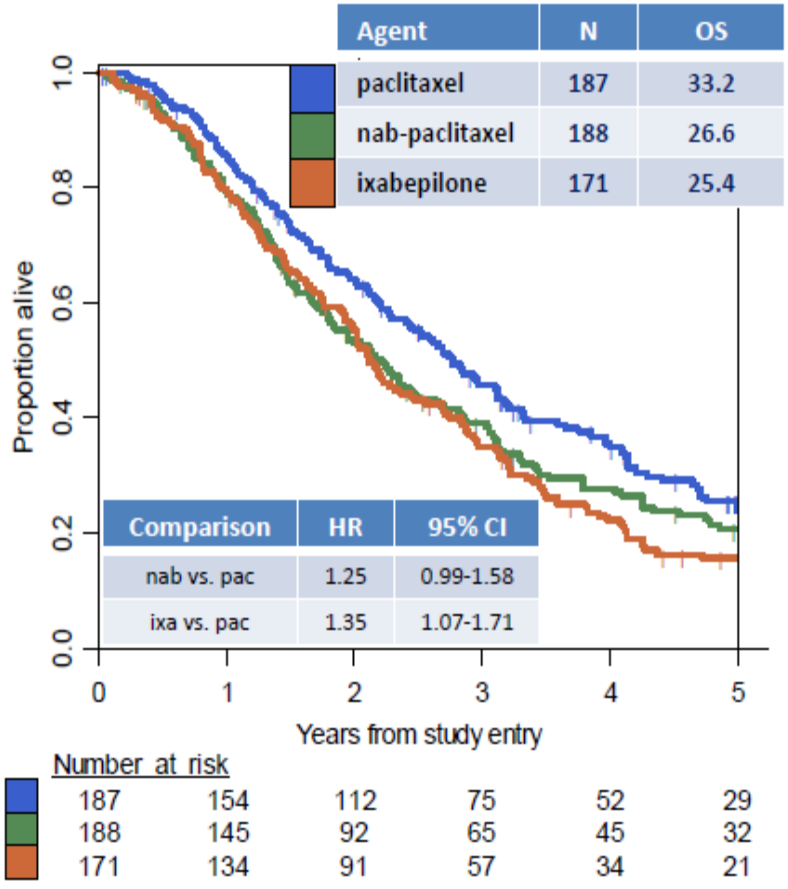
- Test of interaction between nab vs. pac and hormone receptor status was significant (p-value = 0.0073), so treatment effects are summarized within subgroups
- Test of interaction with ixabepilone was not significant (p = 0.92)

Overall Survival: TN and HR+

Triple Negative (n=201)



HR Positive (n=546)



Adverse Events (Grade 3+)

Toxicity (Grade 3+)	Paclitaxel (n=272)	nab-Paclitaxel (n=263)	Ixabepilone (n=239)
Any hematologic AE	60 (22%)	**144 (55%)**	29 (12%)
Neutropenia	50 (18%)	134 (51%)	16 (7%)
Any nonhematologic AE	183 (66%)	163 (60%)	154 (63%)
Sensory neuropathy	48 (18%)	**70 (27%)**	60 (25%)
Fatigue	27 (10%)	43 (16%)	35 (15%)
Hypertension	25 (9%)	20 (8%)	28 (12%)
Motor neuropathy	9 (3%)	**26 (10%)**	17 (7%)
Pain	12 (4%)	25 (10%)	10 (4%)
Nausea	0 (0%)	13 (5%)	14 (6%)
All Grade 3+ AEs	**162 (60%)**	**221 (84%)**	**151 (61%)**

Conclusions (1)

- In this updated analysis of weekly chemotherapy in patients with chemotherapy-naive MBC, ixabepilone continued to be inferior to paclitaxel for PFS
  - Now also inferior for OS
- *Post-hoc* subset analysis - significant interaction with receptor status between nab-paclitaxel and paclitaxel for PFS and OS
  - In HR+ disease, ixabepilone and nab-paclitaxel were inferior to paclitaxel
  - In TNBC, suggestion of improved PFS and OS with nab-paclitaxel compared to paclitaxel

Conclusions (2)

- Adverse events, discontinuation and dose reductions were more frequent with weekly nab-paclitaxel dosed at 150 mg/m^2
- GeparSepto also suggests improved efficacy in TNBC with less toxicity and similar pCR rates with 125 mg/m^2
- Further investigation is required to explain and validate the subtype specificity seen in this exploratory analysis.

SABCS 2017, Dec 5 -9, 2017: "Spotlight on Novel Drugs"

New Drugs and Treatment Strategies

- Phase 1 study of CB-839, a first-in-class oral inhibitor of glutaminase, in combination with paclitaxel in patients with advanced triple negative breast cancer: Kalinsky et al.

- Phase 1 Study of the Antibody-Drug Conjugate SGN-LIV1A in Patients with Heavily Pretreated Triple-Negative Metastatic Breast Cancer: Modi et al.

Advanced Therapy – Targeted:

- Clinical safety and efficacy of the Aurora and angiogenic kinase inhibitor ENMD-2076 in previously treated, locally advanced or metastatic triple-negative breast cancer. Diamond, et al

Stem/Progenitor Cells:

- Novel cFlip Inhibitor (OH14) Suppresses Chemotherapy-Induced Breast Cancer Stem Cell Activity Through Blocking HIF1-α: Robinson et al

Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, as ≥3rd-line Therapeutic Option for Patients With Relapsed/Refractory Metastatic Triple-Negative Breast Cancer (mTNBC): Efficacy Results

Aditya Bardia,[1] Linda T. Vahdat,[2,†] Jennifer R. Diamond,[3] Kevin Kalinsky,[4] Joyce O'Shaughnessy,[5] Rebecca L. Moroose,[6] Steven J. Isakoff,[1] Sara M. Tolaney,[7] Alessandro D. Santin,[8] Vandana Abramson,[9] Nikita C. Shah,[6] Serengulam V. Govindan,[10] Pius Maliakal,[10] Robert M. Sharkey,[10] William A. Wegener,[10] David M. Goldenberg,[10] Ingrid A. Mayer[9]

[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [2]Weill Cornell Medicine, New York, NY; [3]University of Colorado Cancer Center, Aurora, CO; [4]Columbia University-Herbert Irving Comprehensive Cancer Center, New York, NY; [5]Texas Oncology, Baylor University Medical Center, US Oncology, Dallas, TX; [6]UF Health Cancer Center, Orlando, FL; [7]The Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [8]Yale University School of Medicine, New Haven, CT; [9]Vanderbilt-Ingram Cancer Center, Nashville, TN; [10]Immunomedics, Inc., Morris Plains, NJ; †Current affiliation: Memorial Sloan Kettering Cancer Center, New York, NY.

Immunomedics

40 YEAR ANNIVERSARY SAN ANTONIO BREAST CANCER SYMPOSIUM®

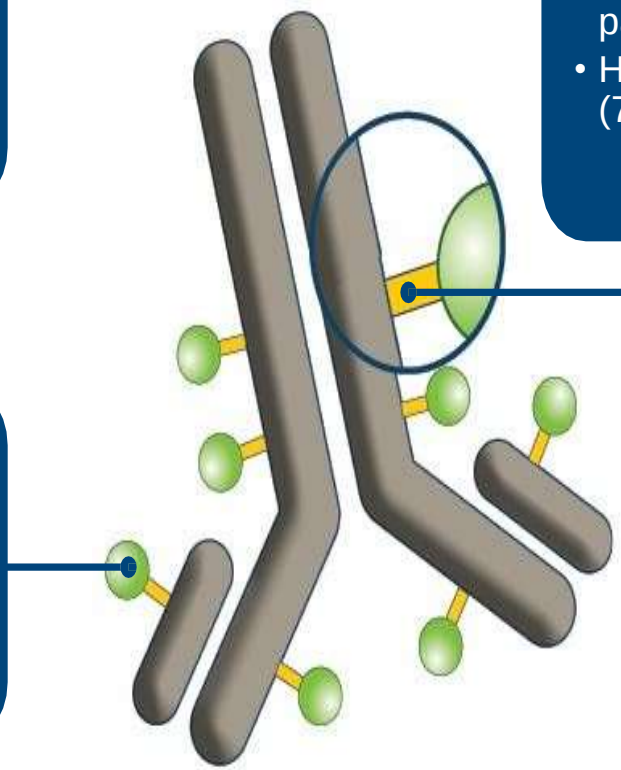
Sacituzumab Govitecan Antibody-Drug Conjugate (ADC)

Humanized anti-Trop-2 antibody

- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Linker for SN-38

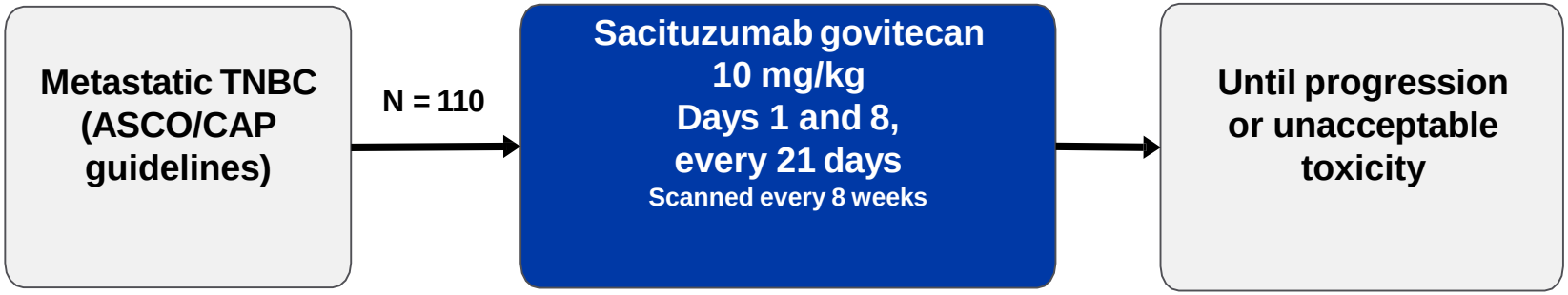
- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.5:1)



SN-38 payload

- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

Single-Arm, Open-Label Study Design



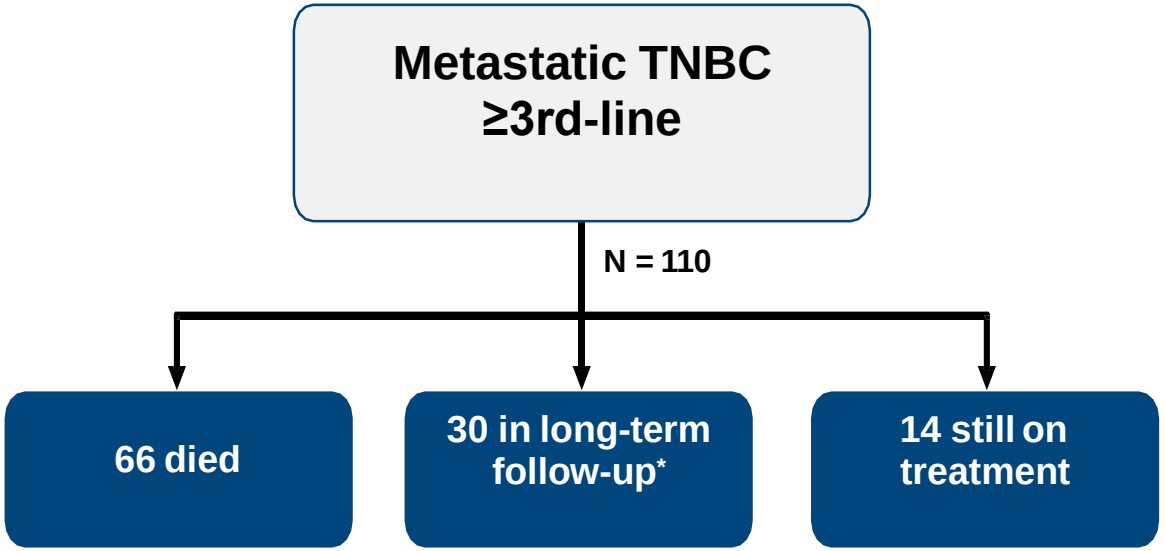
Key Eligibility Criteria

- Adults, ≥18 years of age
- ECOG 0-1
- ≥2 prior therapies in metastatic setting or >1 therapy if progressed within 12 months of (neo)adjuvant therapy
- Prior taxane therapy
- Measurable disease

Evaluations

- Response evaluation by investigators
- Blinded independent central review of all CRs, PRs, and ≥20% tumor reductions
- Other evaluations: safety, immunogenicity, Trop-2 expression

Patient Disposition and Treatment



- Enrollment between Jul 2013 and Feb 2017. Data cutoff date of June 30, 2017.
- Patients received a median of 14.5 doses (range: 1-88) over a median duration of 4.9 months (range: 0.2-32.1)

*Includes 2 patients who were lost to follow up

Demographics and Patient Characteristics

	N = 110
Female/male, n	109/1
Median age, years (range)	55 (31-81)
Race	
White	75%
Black	7%
Asian	4%
Other	4%
Not specified	10%
ECOG performance status	
0	30%
1	70%
Median time from metastatic disease to study entry, years (range)	1.5 (0.2-9.8)
≥3rd line for metastatic disease	100%
3rd line*	41%
≥4th line	59%

	N = 110
Prior chemotherapy drugs**	
Taxanes	98%
Anthracyclines	86%
Cyclophosphamide	85%
Platinum agents	75%
Gemcitabine	57%
Fluoropyrimidine agents	51%
Eribulin	45%
Vinorelbine	15%
Prior checkpoint inhibitors	17%
Sites of metastatic disease at study entry***	
Lung/mediastinum	58%
Liver	46%
Bone	45%
Chest wall	24%

*2 patients who progressed within 12 months of (neo)adjuvant therapy only received one line in the metastatic setting;
**Used in >10% patients; ***Metastatic sites reported in >20% patients

Adverse Events (Regardless of Causality)

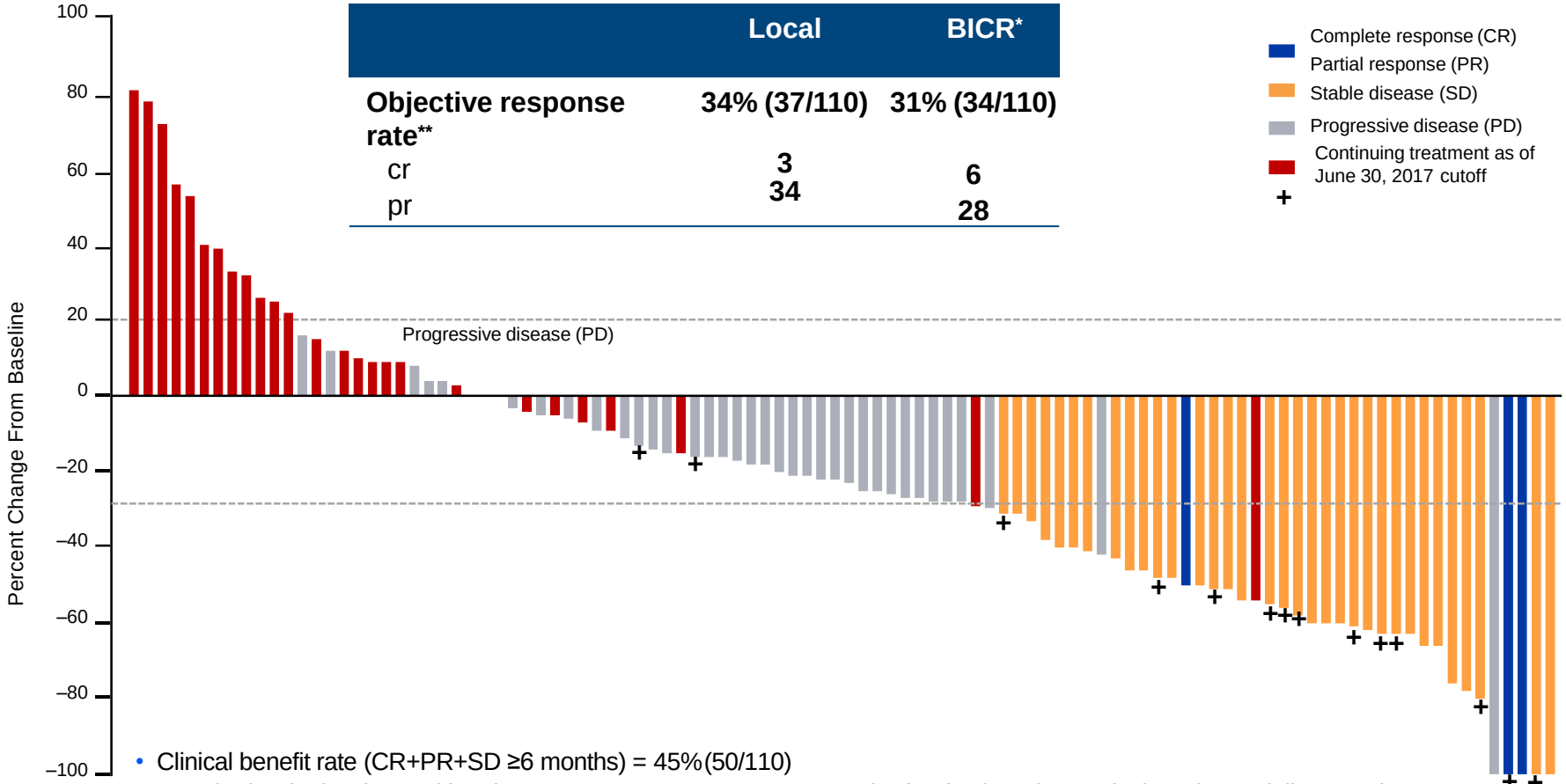
- AEs were managed with supportive medication or dose modifications
  - 25% of patients had dose modifications, predominantly to 7.5 mg/kg
- Two patients (1.8%) discontinued due to AEs (grade 3 transient infusion reaction/ grade 2 fatigue)
- There were no treatment-related deaths

Body system	Adverse event (AE)	All grades	Grade 3 or 4
Hematologic	Neutropenia	63%	41%
	Febrile neutropenia	8%	7%
	Anemia	52%	10%
	Leukopenia	24%	14%
Gastrointestinal	Nausea	63%	5%
	Diarrhea	56%	8%
	Vomiting	46%	5%
	Constipation	32%	1%
Other	Fatigue	50%	7
	Alopecia	36%	0
	Decreased appetite	30%	0
	Hyperglycemia	23%	4%
	Hypomagnesemia	21%	1%
	Hypophosphatemia	15%	8%

Includes all events >20% (all grades) or >5% (grade 3 or 4); NA = not applicable.

Tumor Response to Treatment

	Local	BICR*
Objective response rate**	**34% (37/110)**	**31% (34/110)**
cr	**3**	**6**
pr	**34**	**28**

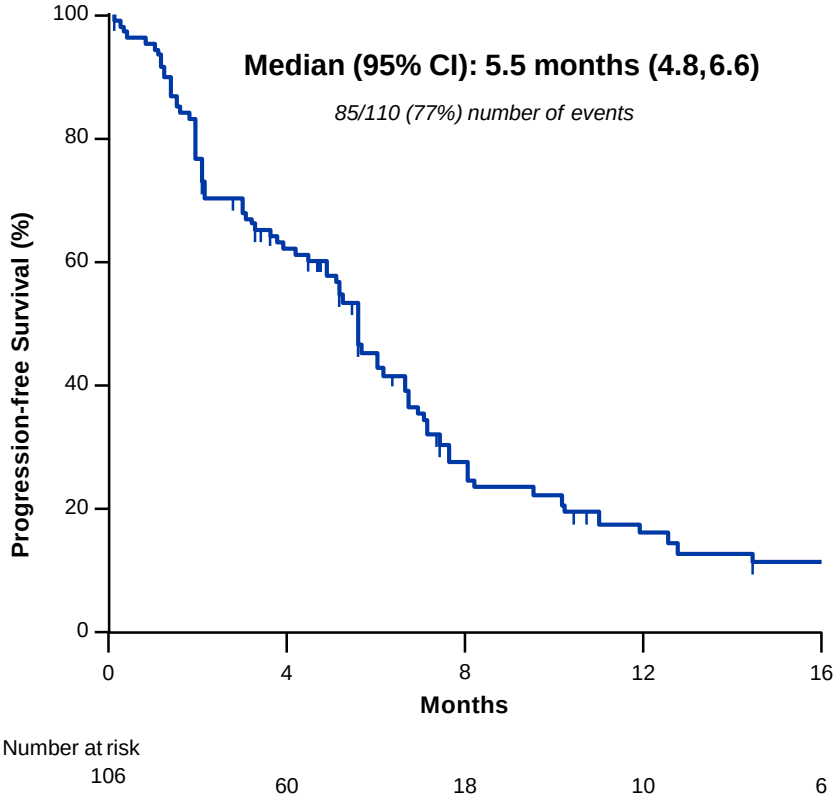


- Clinical benefit rate (CR+PR+SD ≥6 months) = 45%(50/110)
- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)***
- 102 patients had ≥1 scheduled CT response assessment. 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases)

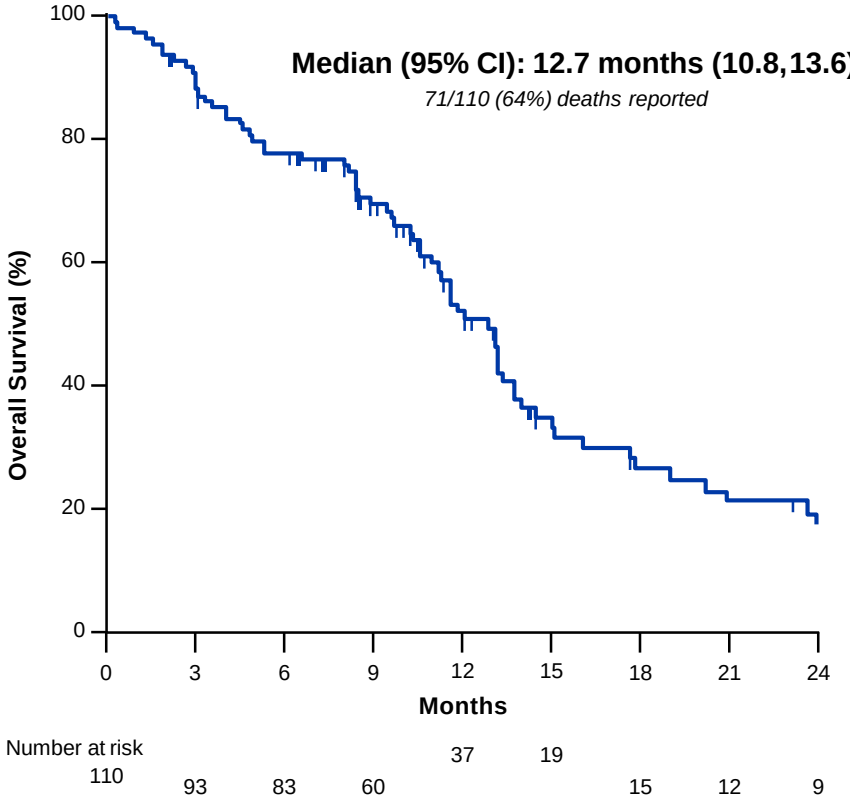
*Patients with at least 20% tumor reduction (n = 56) were reviewed; **Confirmed objective response rate per RECIST; ***Waterfall is

Progression-Free and Overall Survival

Progression-free survival



Overall survival



Based on local assessment

Response to Sacituzumab Govitecan in Subgroups

	ORR, % (n/N)
Overall	34% (37/110)
Age	
<55	37% (20/54)
≥55	30% (17/56)
Onset of metastatic disease	
<1.5 years	29% (16/55)
≥1.5 years	38% (21/55)
Prior regimens for metastatic disease	
3rd line	36% (16/45)
≥4th line	32% (21/65)

	ORR, % (n/N)
Visceral involvement at study entry	
Yes	30% (26/88)
No	50% (11/22)
Trop-2 IHC (n = 62)	
0-1 (weak, absent)	0% (0/5)
2-3 (moderate, strong)	40% (23/57)
No Trop-2 IHC	29% (14/48)
Prior checkpoint inhibitors	47% (9/19)

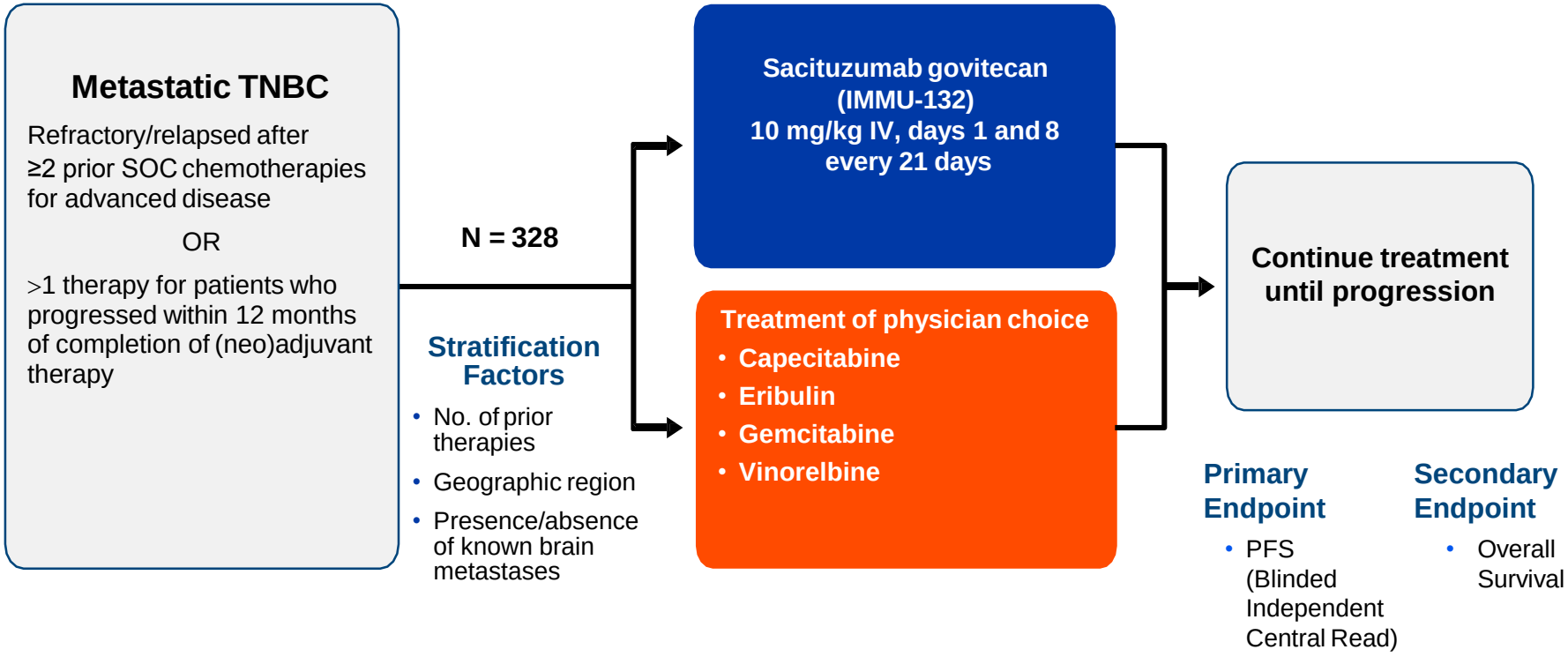
Based on local assessment

Conclusions

- Sacituzumab govitecan as a single agent demonstrated significant clinical activity as ≥3rd-line therapy in patients with relapsed/refractory mTNBC
  - Confirmed ORR*: 34%
  - Clinical benefit rate (6 months)*: 45%
  - The responses were durable (estimated median duration of response was 7.6 months based on local assessment)
  - All data consistent with central review
- Results suggest that sacituzumab govitecan has a predictable and manageable safety profile
- Additional studies including rational combinations are currently being evaluated for mTNBC and other breast cancer subsets

*Based on local assessment

ASCENT Phase III Trial is Recruiting



- Now enrolling in the US; European enrollment to begin in first half of 2018
- Clinical trials number: NCT02574455
- Presented at: New Agents and Strategies; December 7, 2017; 5:00-7:00 PM,

  Hall 1 (abstract# 733), SABCS

IMMUNOTHERAPY AND TNBC 1

PDL1 is a rational target for TNBC treatment due to:

- Increased PD-L1 expression in TNBC, which was shown to decrease T-cell proliferation and increase apoptosis
- High levels of TILs, which have been correlated with improved outcomes.
- Results from Phase I clinical trials with immuno-checkpoint inhibitors showed that they are well tolerated in patients with mTNBCs, alongside promising and durable clinical activity

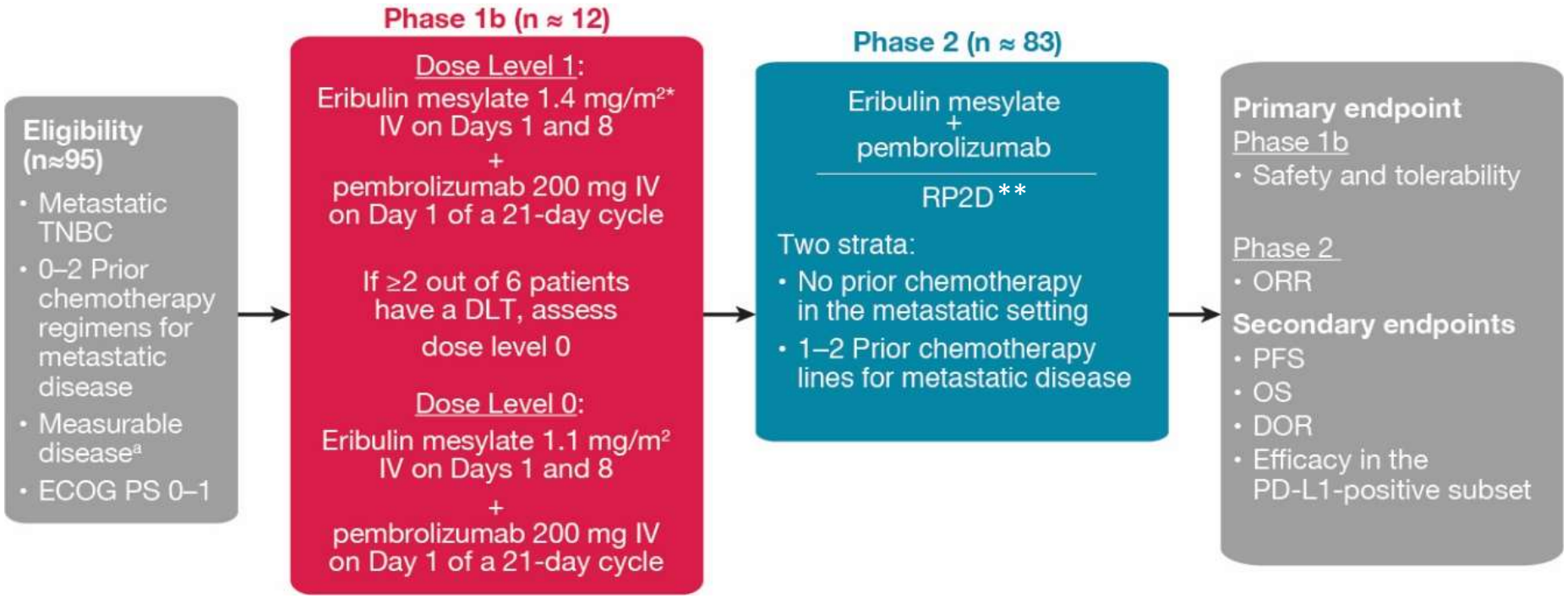
IMMUNOTHERAPY AND TNBC 2

….Not only single agent immunotherapy but different combinations:

CARBOPLATIN (+PEMBROLIZUMAB, ONGOING)
GEMCITABINE (+PEMBROLIZUMAB, ONGOING)
PACLITAXEL (+ ATEZOLIZUMAB, ONGOING)
BGB324 (+PEMBROLIZUMAB, ONGOING)
Imprime PGG (+PEMBROLIZUMAB, ONGOING)
Olaparib (+DURVALUMAB, ONGOING)

Study Design

Phase 1b/2, open-label, single-arm, multicenter study



*equivalent to 1.23 mg/m^2 eribulin (expressed as free base)
**RP2D, recommended phase 2 dose

Study Endpoints

- The primary endpoint for phase 1b is safety and tolerability
- The primary endpoint for phase 2 is investigator-assessed ORR
- The secondary endpoints for phase 2 are:
  - Progression-free survival
  - Overall survival
  - Duration of response
  - Efficacy in a subset of patients with PD-L1 positive tumors

Patient Demographics

Parameter	Phase 1b (n = 7) n (%)[a]	Phase 2 (n = 32) n (%)[a]	Total (n = 39) n (%)[a]
Age (years)			
Mean (SD)	53.9 (7.7)	52.7 (10.4)	52.9 (9.9)
Median	54.0	52.0	53.0
Minimum, maximum	44, 65	32, 80	32, 80
Age group			
< 50 years	2 (28.6)	9 (28.1)	11 (28.2)
≥ 50 years	5 (71.4)	23 (71.9)	28 (71.8)
Sex			
Female	7 (100)	32 (100)	39 (100)
Race			
White	7 (100)	28 (87.5)	35 (89.7)
Black or African American	0	3 (9.4)	3 (7.7)
Other	0	1 (3.1)	1 (2.6)
Ethnicity			
Hispanic or Latino	0	2 (6.3)	2 (5.1)
Not Hispanic or Latino	7 (100)	30 (93.8)	37 (94.9)

[a]Unless otherwise denoted.

Patient Disease Characteristics

Parameter	Phase 1b (n = 7) n (%)[a]	Phase 2 (n = 32) n (%)[a]	Total (n = 39) n (%)[a]
Enrollment strata			
No prior chemotherapy in the metastatic setting	3 (42.9)	14 (43.8)	17 (43.6)
Previously treated with 1 to 2 lines of chemotherapy in the metastatic setting	4 (57.1)	18 (56.3)	22 (56.4)
Tumor PD-L1 status[†]			
Negative	1 (14.3)	17 (53.1)	18 (46.2)
Positive	3 (42.9)	14 (43.8)	17 (43.6)
Not available	3 (42.9)	1 (3.1)	4 (10.3)
ECOG status			
0	4 (57.1)	18 (56.3)	22 (56.4)
1	3 (42.9)	14 (43.8)	17 (43.6)
Sites of metastases			
Liver	1 (14.3)	15 (46.9)	16 (41.0)
Lung	3 (42.9)	20 (62.5)	23 (59.0)
Brain	1 (14.3)	5 (15.6)	6 (15.4)
Bone	2 (28.6)	15 (46.9)	17 (43.6)
Skin	0	5 (15.6)	5 (12.8)
Other	7 (100)	14 (43.8)	21 (53.8)

[a]Unless otherwise denoted; [†]PD-L1 positivity is defined as staining in the stroma or ≥1% tumor cells; The threshold is 1% combined positive score (CPS).

Safety

- No DLTs were observed in phase 1b
- The recommended phase 2 dose was defined as:
  - Eribulin mesylate 1.4 mg/m^2* IV on Day 1 and Day 8 of a 21-day cycle, and
  - Pembrolizumab 200 mg IV on Day 1 of a 21-day cycle

DLT, dose limiting toxicity
*equivalent to 1.23 mg/m^2 eribulin (expressed as free base)

Safety: Summary

- 66.7% Of patients had treatment-emergent adverse events (TEAEs) of grade 3 or 4
  - The most common TEAEs of grade 3/4 were neutropenia (30.8%) and fatigue (7.7%)

	Phase 1b (n = 7) n (%)	Phase 2 (n = 32) n (%)	Total (n = 39) n (%)
TEAEs	7 (100)	32 (100)	39 (100)
Treatment-related TEAEs	7 (100)	31 (96.9)	38 (97.4)
TEAEs with CTCAE grade 3 and 4	4 (57.1)	22 (68.8)	26 (66.7)
Deaths	0	1 (3.1)	1 (2.6)[a]
Other SAEs			
Important medical events	2 (28.6)	7 (21.9)	9 (23.1)
Life-threatening	0	3 (9.4)	3 (7.7)
Requires inpatient hospitalization or prolongation of existing hospitalization	1 (14.3)	10 (31.3)	11 (28.2)
TEAEs leading to study drug dose adjustment[b]	4 (57.1)	23 (71.9)	27 (69.2)
TEAEs leading to study drug withdrawal	2 (28.6)	5 (15.6)	7 (17.9)
TEAEs leading to study drug dose reduction	0	11 (34.4)	11 (28.2)
TEAEs leading to study drug interruption	4 (57.1)	15 (46.9)	19 (48.7)

[a]respiratory failure (n=1), not treatment related
[b]refers to either eribulin, pembrolizumab, or both

Safety: Most Common TEAEs (>10%)

Parameter	All Grades (n = 39) n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any	39 (100)	20 (51.3)	5 (12.8)	1 (2.6)
Fatigue	29 (74.4)	3 (7.7)	0	0
Nausea	20 (51.3)	1 (2.6)	0	0
Peripheral neuropathy[a]	17(43.6)	2 (5.1)	0	0
Neutropenia[b]	15 (38.5)	8 (20.5)	4 (10.3)	0
Alopecia	14 (35.9)	0	0	0
Pyrexia	13 (33.3)	0	1 (2.6)	0
Cough	13 (33.3)	0	0	0
Decreased appetite	12 (30.8)	2 (5.1)	0	0
Hypothyroidism	12 (30.8)	0	0	0
Arthralgia	11 (28.2)	0	0	0
Constipation	11 (28.2)	0	0	0
Diarrhea	9 (23.1)	2 (5.1)	0	0
Headache	9 (23.1)	0	0	0
Rash	9 (23.1)	2 (5.1)	0	0
Vomiting	9 (23.1)	0	0	0
Dyspnea	7 (17.9)	1 (2.6)	0	0
Dysgeusia	7 (17.9)	0	0	0
Dyspepsia	7 (17.9)	0	0	0
Hyperglycemia	7 (17.9)	1 (2.6)	0	0
Anemia	6 (15.4)	0	0	0
Dry mouth	6 (15.4)	0	0	0
Rash maculopapular	6 (15.4)	0	0	0
Stomatitis	6 (15.4)	1 (2.6)	0	0
Urinary tract infection	6 (15.4)	0	0	0
Back pain	5 (12.8)	1 (2.6)	0	0
Dehydration	5 (12.8)	1 (2.6)	0	0
Myalgia	5 (12.8)	0	0	0

[a]pooled term includes peripheral sensory neuropathy and peripheral motor neuropathy ; [b]pooled term includes neutropenia and neutrophil count decreased

Safety: Full Analysis Set (n = 89)

- At the time of data cutoff (July 12, 2016) a total of 3 (3.4%) patients had fatal events due to TEAEs, all occurring in phase 2 and none of which were related to study drug (respiratory failure, n = 1; pleural effusion, n = 1; multiple organ dysfunction syndrome, n = 1)
- A total of 10 (11.2%) patients had TEAEs leading to study drug withdrawal (2 patients in phase 1b, 8 patients in phase 2)

Treatment Duration

	Eribulin	Pembrolizumab
Number of cycles, n		
Median	6	6
Range*	2-12	2-14
Duration of treatment, month		
Median	3.9	3.7
Range*	1.0-8.3	0.8-9.0

*patients ongoing

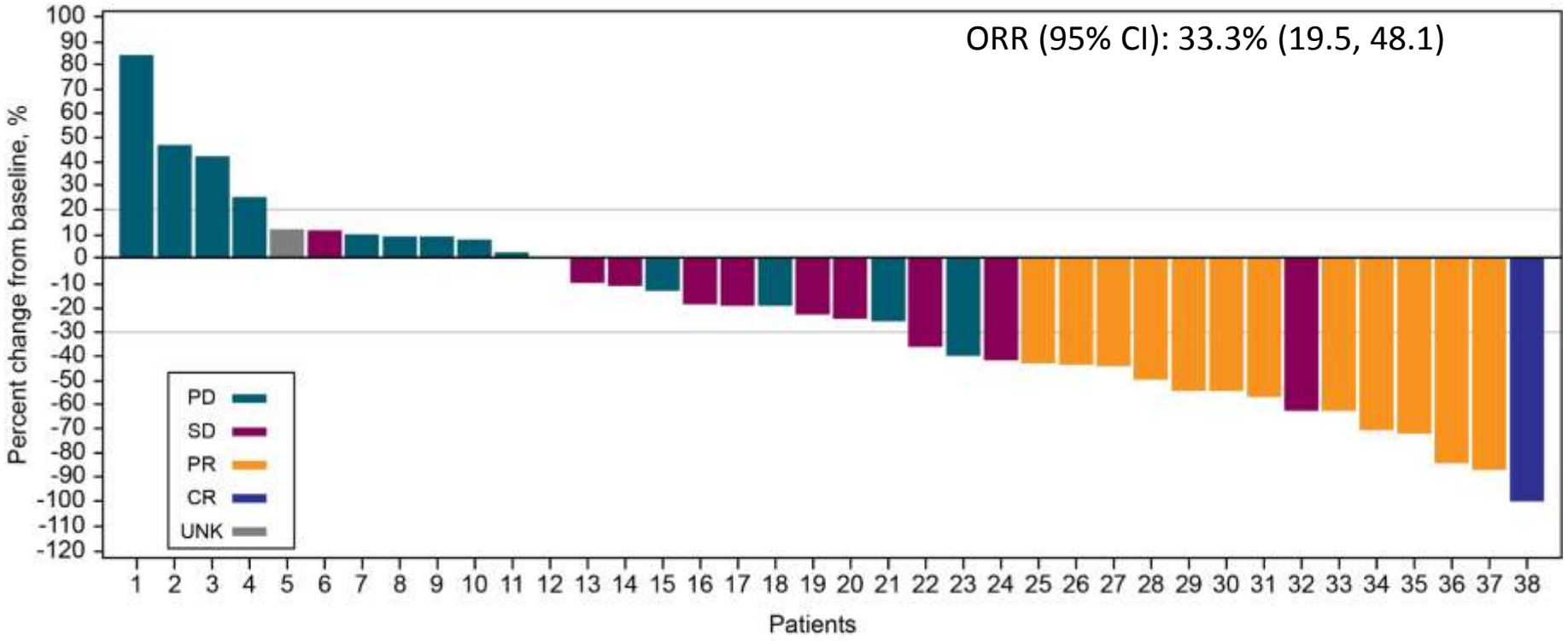
Efficacy: Summary of Tumor Response

Parameter, n (%)	Phase 1b (n = 7)	Phase 2 (n = 32)	Total (n = 39)
Responses			
Complete response (CR)—confirmed	1 (14.3)	0	1 (2.6)
Partial response (PR)—confirmed	1 (14.3)	11 (34.4)	12 (30.8)
Stable disease (SD)	2 (28.6)	9 (28.1)	11 (28.2)
Progressive disease (PD)	3 (42.9)	11 (34.4)	14 (35.9)
Unknown	0	1 (3.1)	1 (2.6)
Objective response rate (ORR)[1]	2 (28.6)	11 (34.4)	13 (33.3)
95% credible interval	--	--	(19.5, 48.1)
Clinical benefit rate (CBR)[2]	3 (42.9)	13 (40.6)	16 (41.0)
Durable SD rate	1 (14.3)	2 (6.3)	3 (7.7)

*based on Investigator assessment

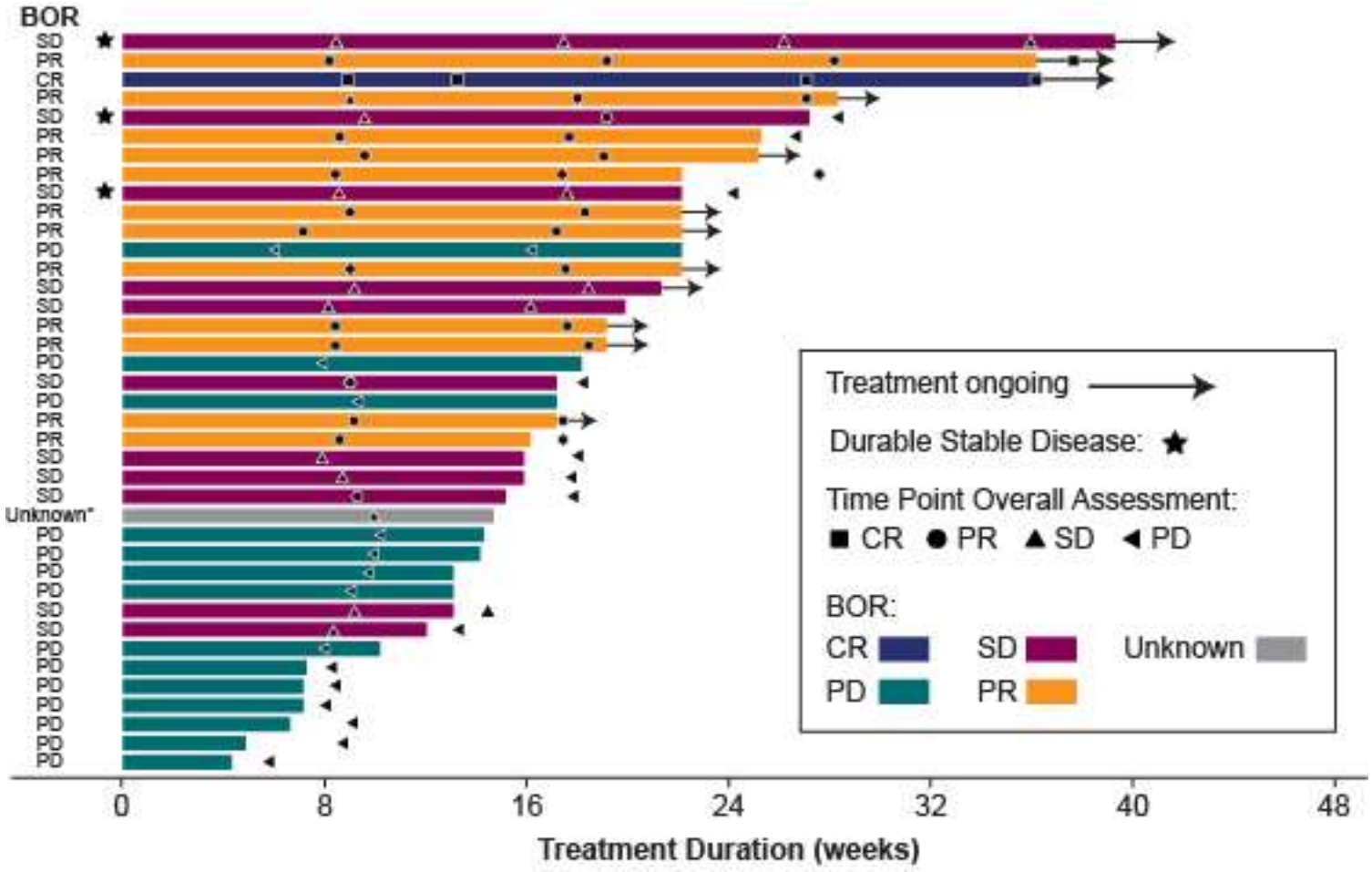
1 Objective response = confirmed CR + confirmed PR.
2 Clinical benefit response = confirmed CR + confirmed PR + durable SD.
Stable disease (SD) must be >=8 weeks after first dose date. Durable stable disease is a subset of SD with a duration of ≥24 weeks after first dose date

Efficacy: Percentage Change in Total Sum of Target Lesion Diameters From Baseline



1 patients had missing sum of target lesion

Efficacy: Duration of Treatment and Overall Time Point Assessments

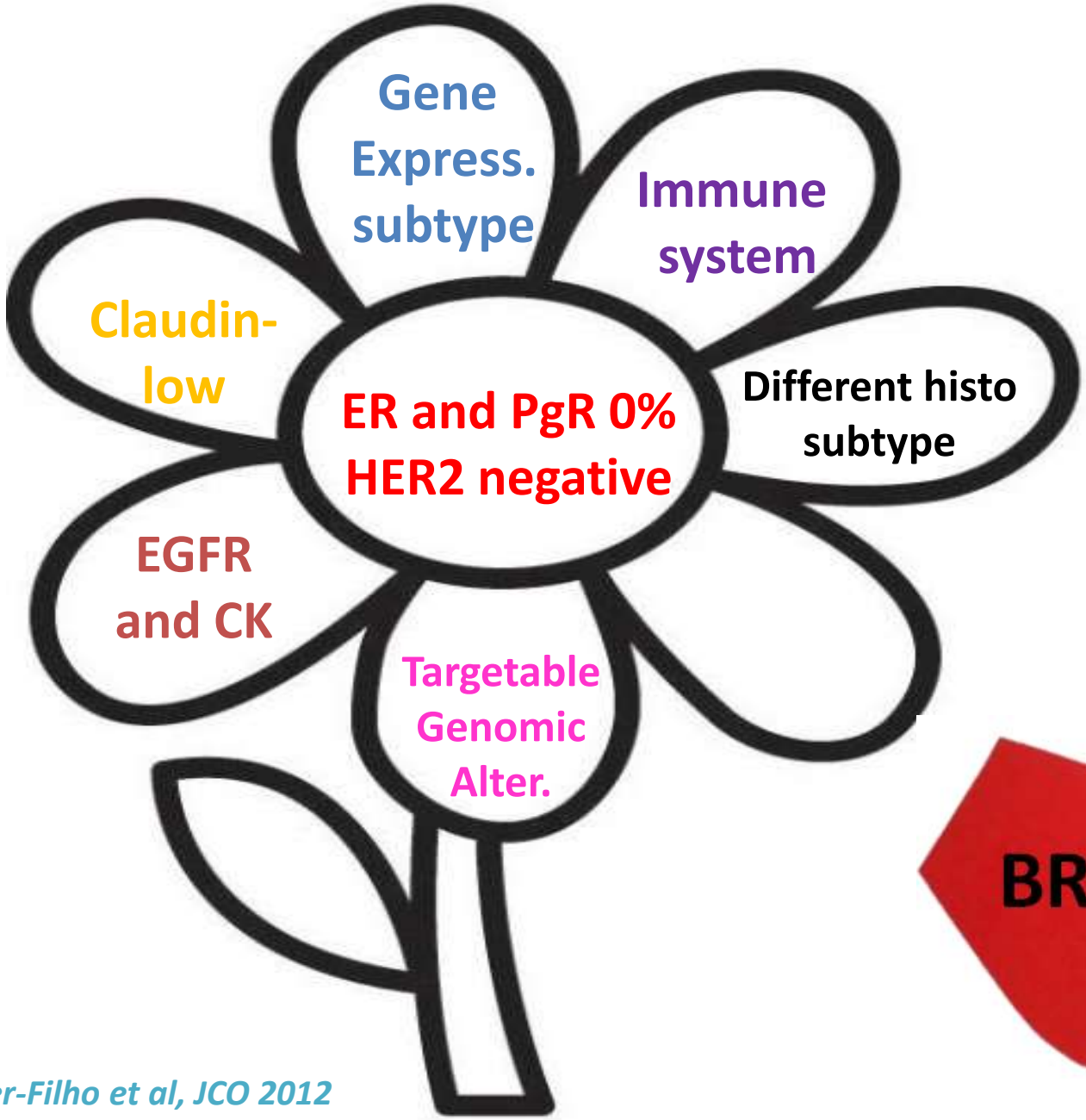


*patient started palliative radiotherapy in week 4
Durable stable disease is a subset of SD with a duration of ≥24 weeks after first dose date

Conclusions

- The combination of eribulin plus pembrolizumab demonstrated activity in patients with metastatic TNBC
- AEs observed with the combination were comparable to those observed historically with either treatment as monotherapy
- Objective responses, including a complete response, were observed during this interim analysis:
  - In this study, PD-L1 positivity did not seem to predict response to treatment

The flower of hope



Modified by Metzger-Filho et al, JCO 2012

San Antonio Breast Cancer Symposium,
December 5-9, 2017

EMBRACA

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

Jennifer K. Litton, Hope S. Rugo, Johannes Ettl, Sara Hurvitz, Anthony Gonçalves, Kyung-Hun Lee, Louis Fehrenbacher, Rinat Yerushalmi, Lida A. Mina, Miguel Martin, Henri Roché, Young-Hyuck Im, Ruben G. W. Quek, Iulia Cristina Tudor, Alison L. Hannah, Wolfgang Eiermann, Joanne L. Blum

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]

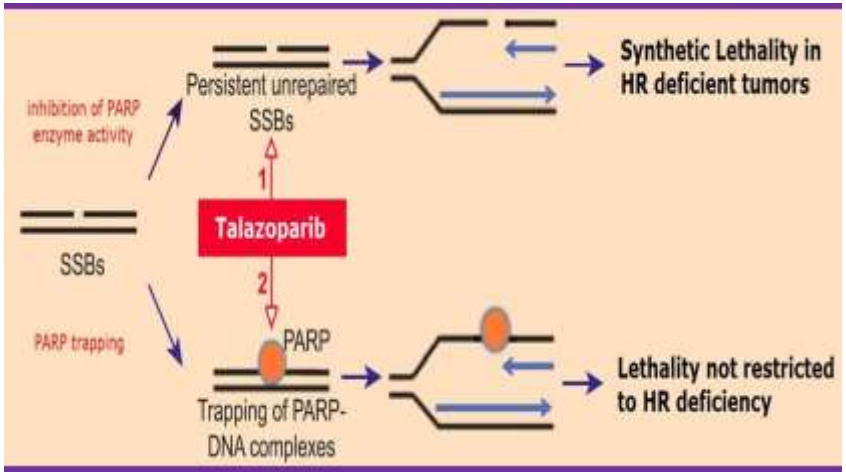


Figure adapted from Murai J et al. *Cancer Res*. 2012;72:5588-5599, with permission from AACR.

		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

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.

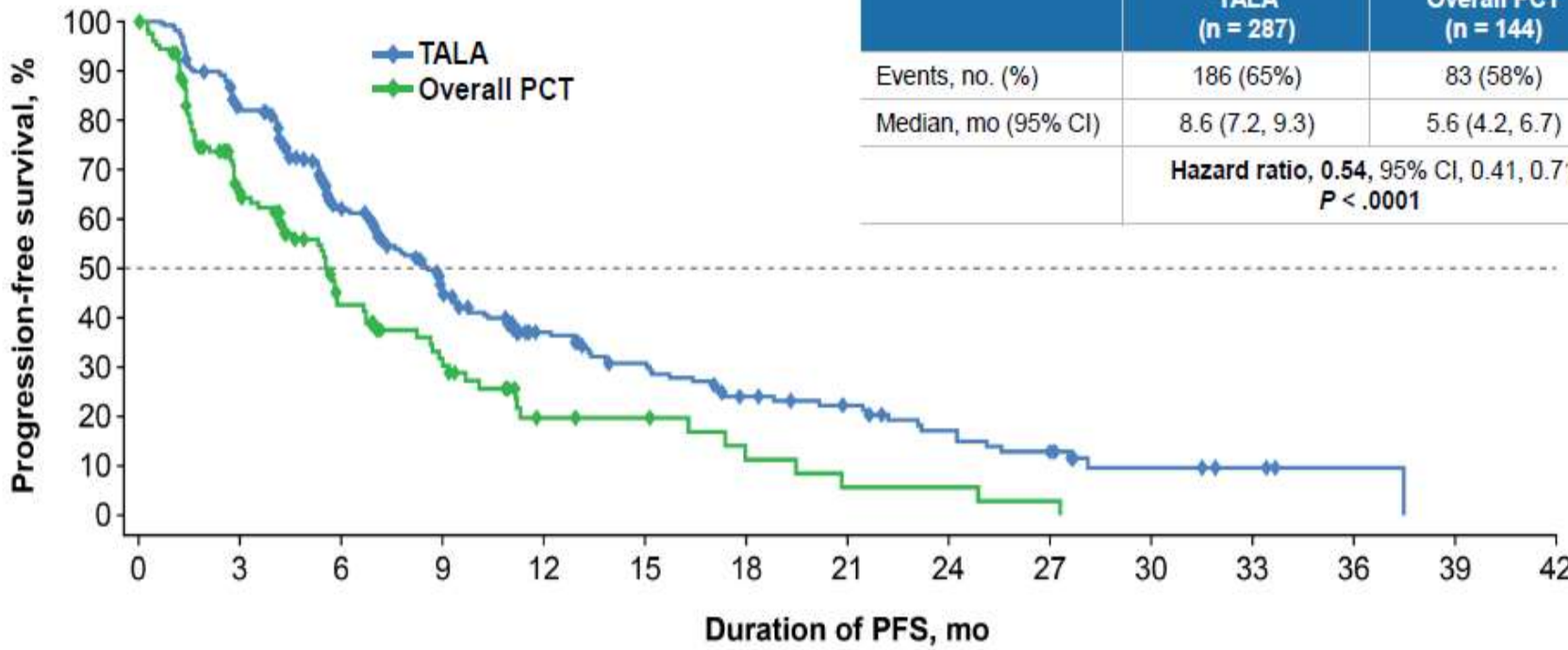
Prior Therapies for Advanced Breast Cancer

	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%)

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**	

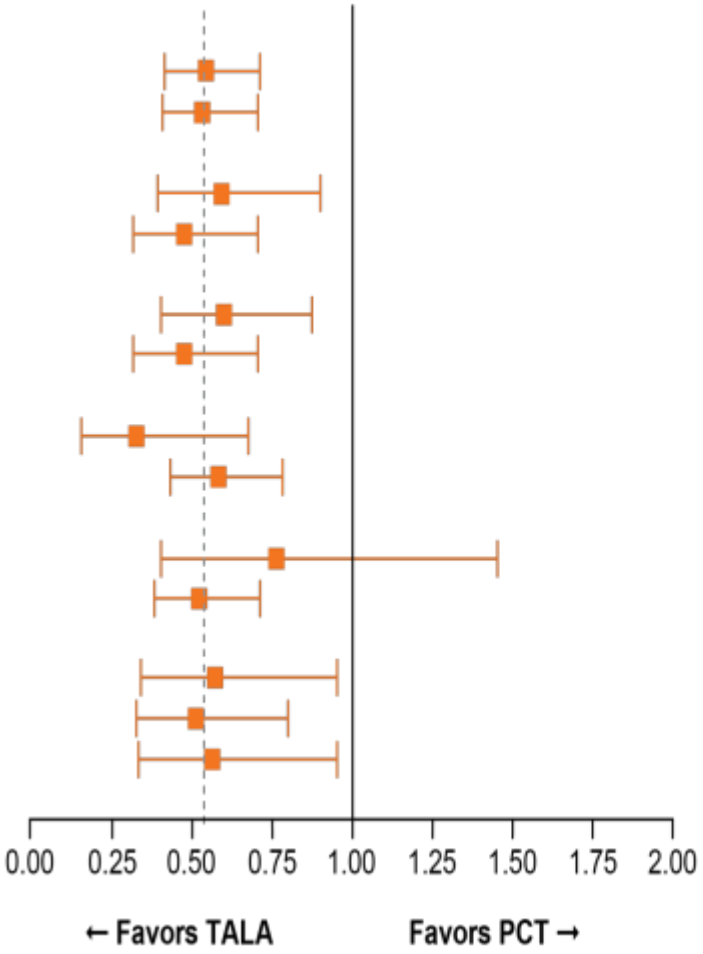


No. at risk (events/cumulative events)														
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)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

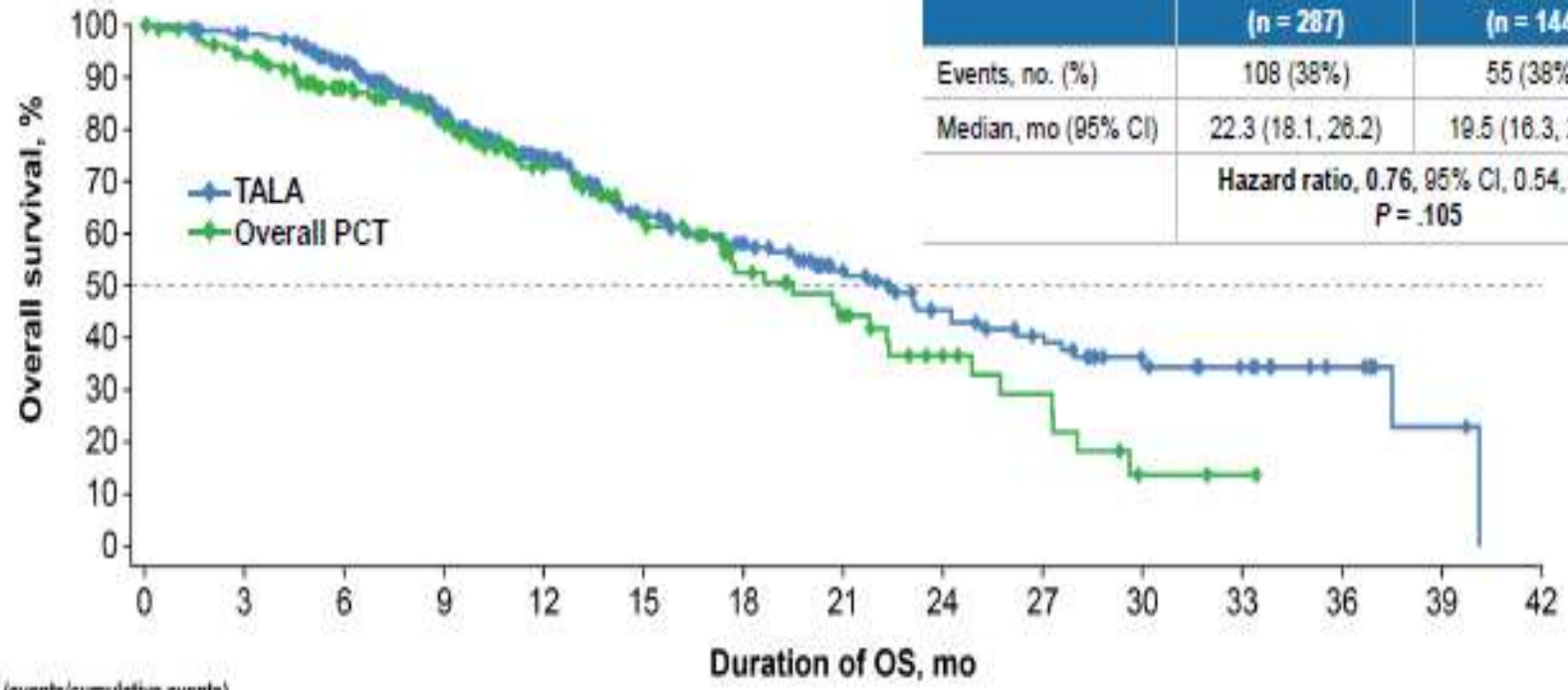
PFS: Subgroup Analysis

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)
BRCA1 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)



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.

SAFETY

Adverse Events: Hematologic

	TALA (N=286)			OVERALL (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 (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%)

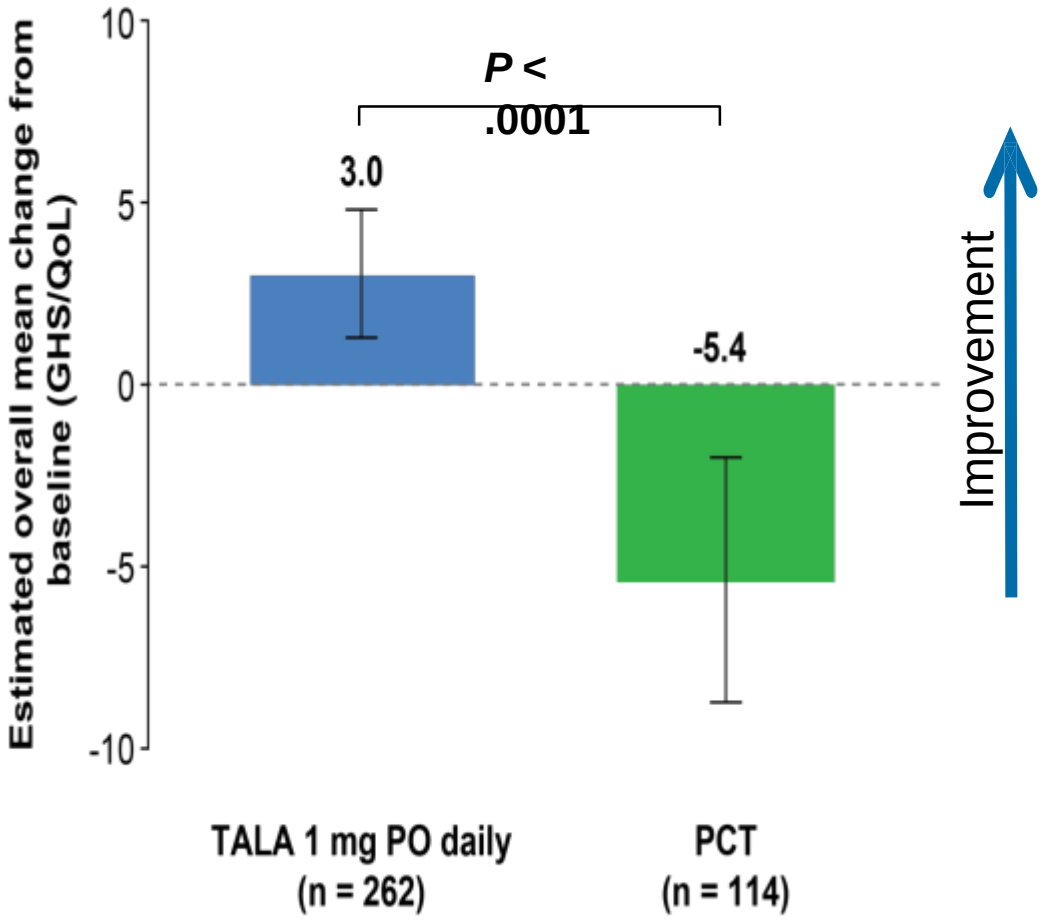
Adverse Events: Nonhematologic

	TALA (N=286)			OVERALL (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.

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

Thanks for your attention

And see you on ….