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January 27, 2018

40 YEAR ANNIVERSARY
SAN ANTONIO BREAST CANCER SYMPOSIUM®

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San Francisco, CA
USA
January 27, 2018

Novel Therapeutics for Advanced Breast Cancer

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Financial Disclosure

MELINDA L. TELLI, M.D.

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Advisory Panel/Consultant:	**Celldex, Pfizer, PharmaMar, Tesaro, Vertex**
Stock/Shareholder:	**NA**
Employee:	**NA**

Triple-Negative & Hereditary Breast Cancer

Abstract	Presenter	Title
GS6-07	Litton	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
GS1-07	Bardia	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
PD3-14	Modi	Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative metastatic breast cancer

Role of PARP inhibition in 1st-4th line BRCA1/2 mutant MBC?

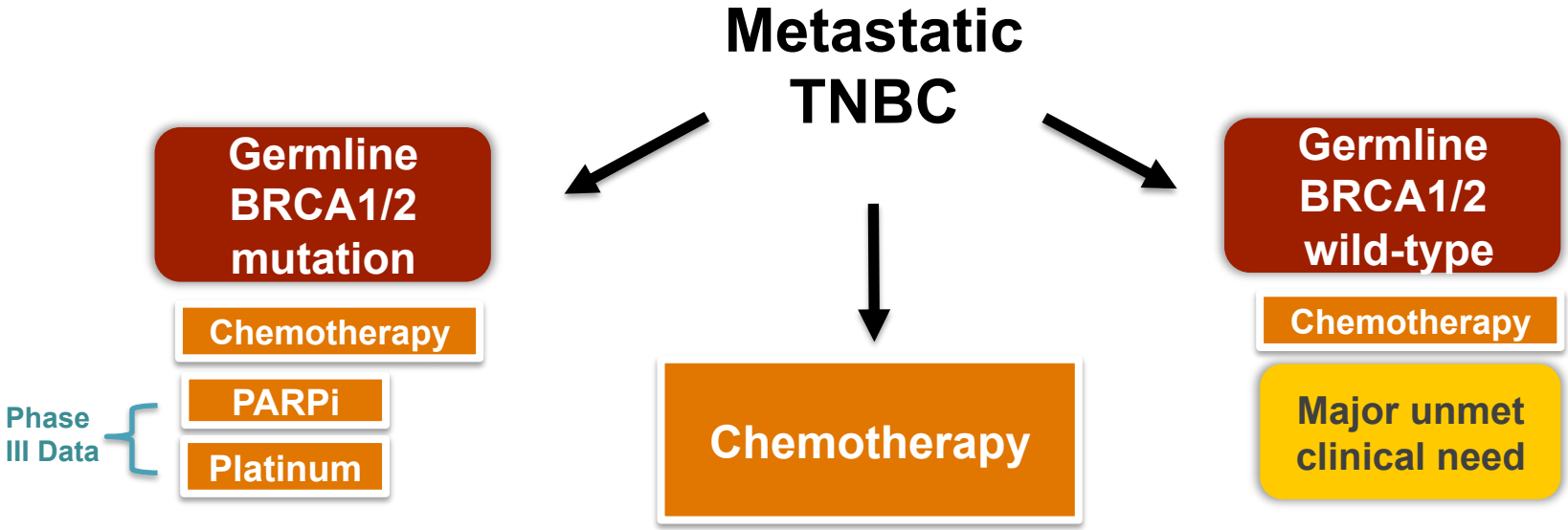
Role of ADCs in metastatic TNBC?

Metastatic HR-Positive Breast Cancer

Abstract	Presenter	Title
GS2-05	Tripathy	First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial
P5-21-03	Rugo	Palbociclib + letrozole as first-line therapy in estrogen receptor–positive /HER2–negative advanced breast cancer (ABC): Efficacy and safety updates with longer follow-up across patient subgroups

Role of CDK4-6 inhibition in 1st line treatment of HR+/HER2- MBC?

Defining the road map in mTNBC



TNT: Higher response rate in BRCA1/2 mutant mTNBC

Trial design

ER-, PgR-/unknown & HER2- or known *BRCA1/2*
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

A Priori subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

Carboplatin (C)
AUC 6 q3w, 6 cycles

On progression, crossover if appropriate

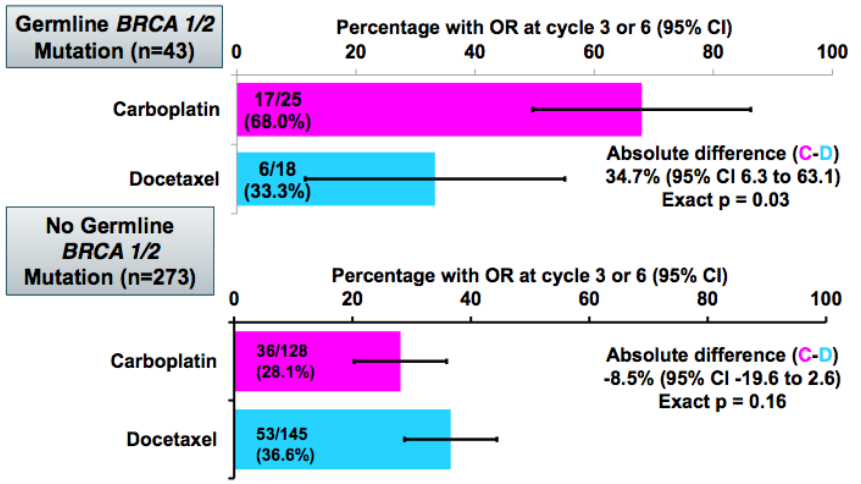
Docetaxel (D)
100mg/m² q3w, 6 cycles

Docetaxel (D)
100mg/m² q3w, 6 cycles

On progression, crossover if appropriate

Carboplatin (C)
AUC 6 q3w, 6 cycles

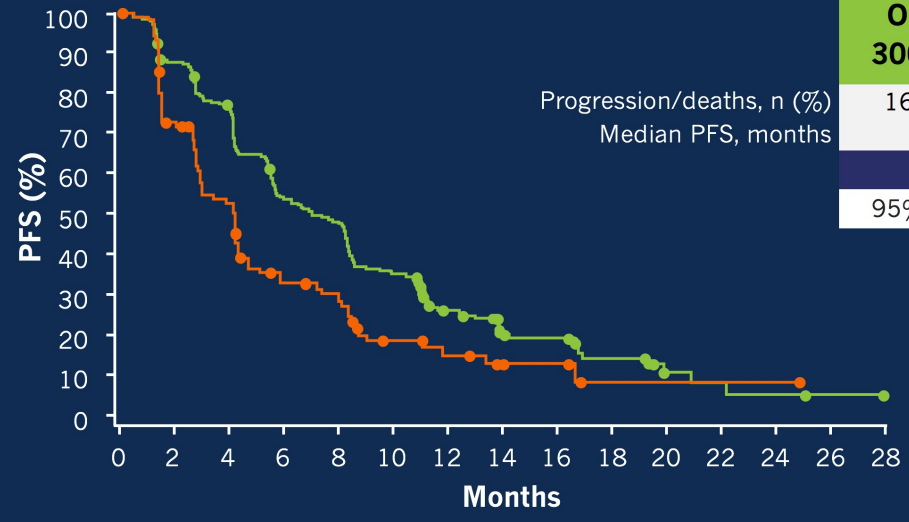
Objective response – *BRCA 1/2* status



Tutt A, et al. SABCS 2014

OlympiAD: Olaparib in metastatic BRCA1/2 mutant breast cancer

Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

Chemotherapy treatment of physician's choice (TPC)

- Capecitabine
- Eribulin
- Vinorelbine

- **1st – 3rd line metastatic disease**
- **~50% TNBC**
- **ORR**
  - **Olaparib: 60%**
  - **TPC: 29%**
- **PFS HR**
  - **TNBC: 0.43**
  - **HR+: 0.82**

Robson M, et al. ASCO 2017

Talazoparib in BRCA1/2 mutant MBC patients following platinum or multiple cytotoxic regimens: ABRAZO

	Cohort 1 Prior Platinum (n = 48)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 83)
Objective response rate, % (95% CI)	21 (10-35)	37 (22-55)	28 (18-39)
Best overall response, % (No.)			
Complete response	4 (2)	0	2 (2)
Partial response	17 (8)	37 (13)	25 (21)
Stable disease	38 (18)	51 (18)	43 (36)
Progressive disease	38 (18)	11 (4)	27 (22)
Not evaluable	4 (2)	0	2 (2)

- **Cohort 1: Prior response to platinum with no progression on or within 8 weeks of last dose**
- **~35% TNBC**
  - **ORR 26%**

Turner N, et al. ASCO 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

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

- 0-3 prior chemotherapy lines
- Prior taxane and/or anthracycline
- No progression on platinum

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.

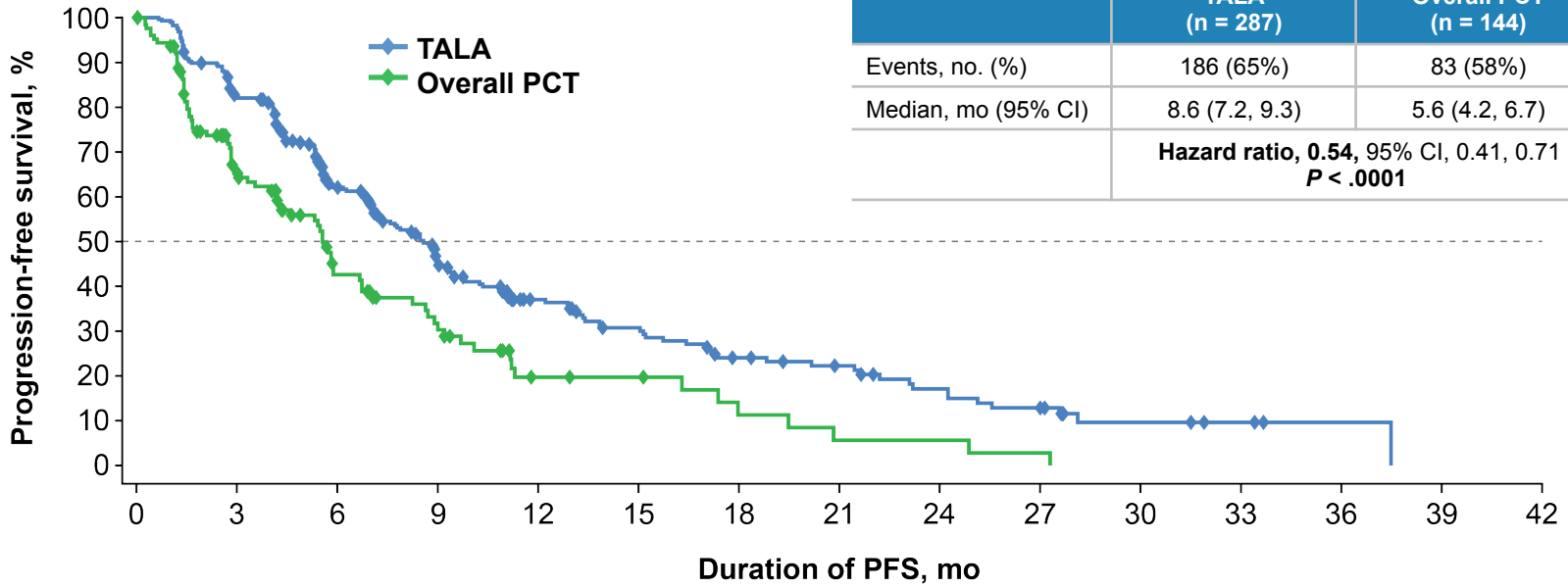
Prior Therapies for Advanced Breast Cancer

	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%)

- **No progression on platinum for metastatic disease**
- **No relapse within 6 months of neoadjuvant/adjuvant platinum**

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**	

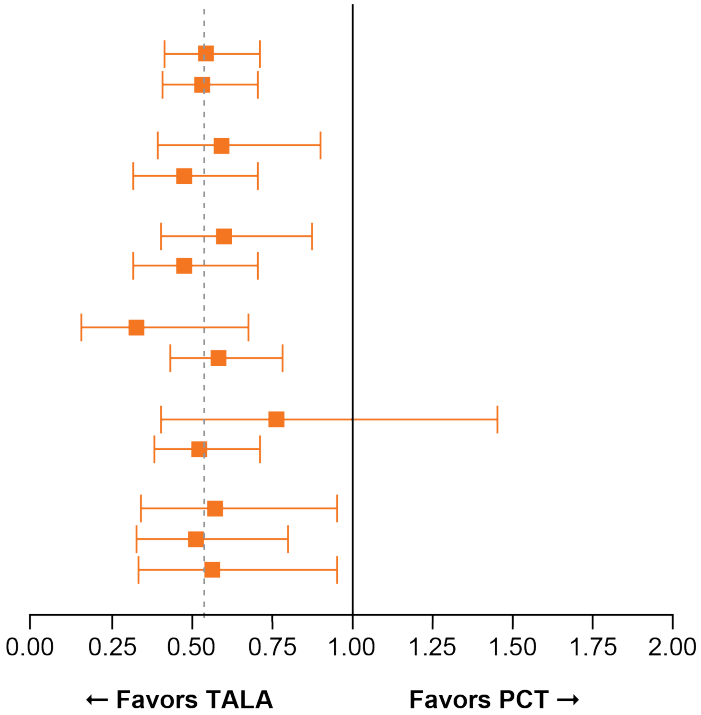


No. at risk (events/cumulative events)														
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)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



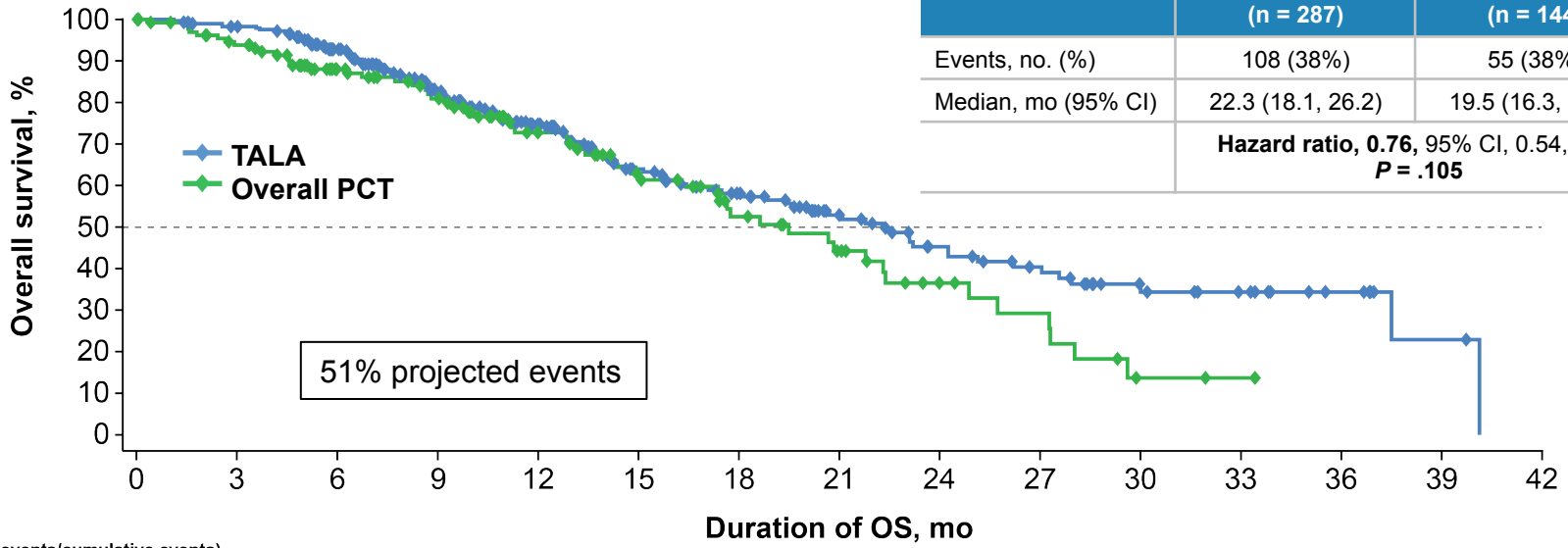
Secondary/Exploratory Endpoints

	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.

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%

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

2.4% G2 →

- 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

Take Home Message

- **Talazoparib active and overall well tolerated in BRCA1/2 mutation-associated MBC**
  - **PFS 8.6 months, ORR 63%**
  - **No OS advantage as yet**
- **Control arm of EMBRACA (& OlympiAD) evaluated non-DNA damaging chemotherapeutics**
  - **How PARPi performs compared to platinum is unknown**
  - **Patients with platinum resistance not evaluated in EMBRACA, OlympiAD or ABRAZO**
  - **Cross resistance to platinum & PARPi expected**
  - **What do we do following progression on platinum/PARPi?**

Antibody-Drug Conjugates in mTNBC

	Glembatumumab vedotin	Ladiratuzumab vedotin	Sacituzumab govitecan
Other name:	CDX-011	SGN-LIV1A	IMMU-132
Target:	gpNMB ~40%	LIV-1 71%	Trop-2 88%
Cytotoxic:	MMAE	MMAE	SN-38
Single agent activity:	ORR = 28%	ORR=37%	ORR= 30%
Registrational Trials:	METRIC 1st-3rd line		ASCENT 3rd line & beyond

Yardley D, et al. JCO 2015, Forero A, et al SABCS 2016, Bardia A, et al. JCO 2017.

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.

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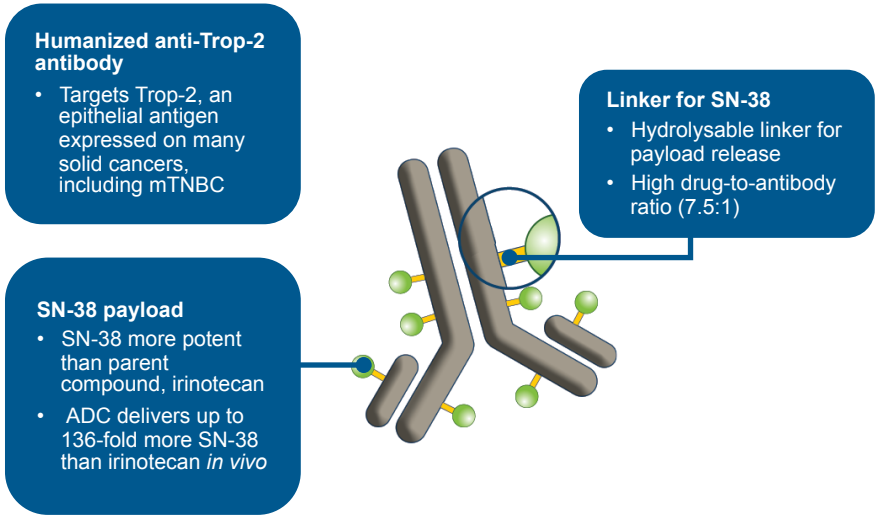
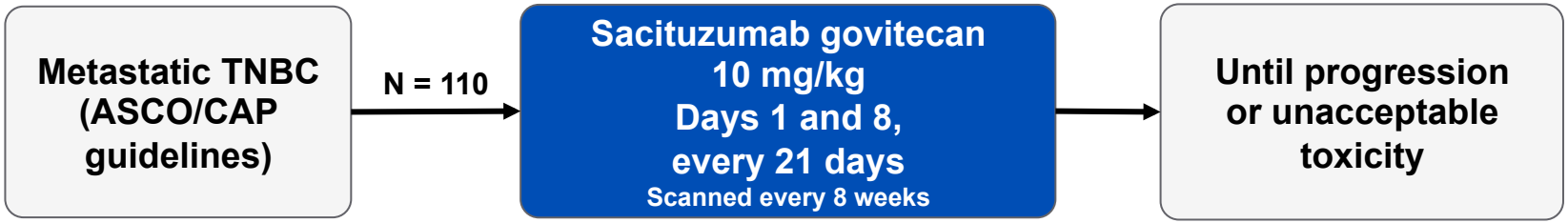
Clinical Trial Experience

- **Preliminary results in 69 patients with mTNBC showed an objective response rate of 30%, which was published earlier this year in the *Journal of Clinical Oncology*[1]**
- **In 2016, sacituzumab govitecan was awarded breakthrough therapy designation by the FDA, and enrollment was resumed in a more defined population in ≥3rd-line setting**
- **110 mTNBC patients were treated with sacituzumab govitecan 10 mg/kg on days 1 and 8 every 21 days until progression or unacceptable toxicity**
  - Includes 53 of 69 patients who received ≥2 prior therapies from previously reported study



1. Bardia et al. *J Clin Oncol.* 2017;35:2141-2148.

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

Immunomedics

SAN ANTONIO BREAST CANCER SYMPOSIUM

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)

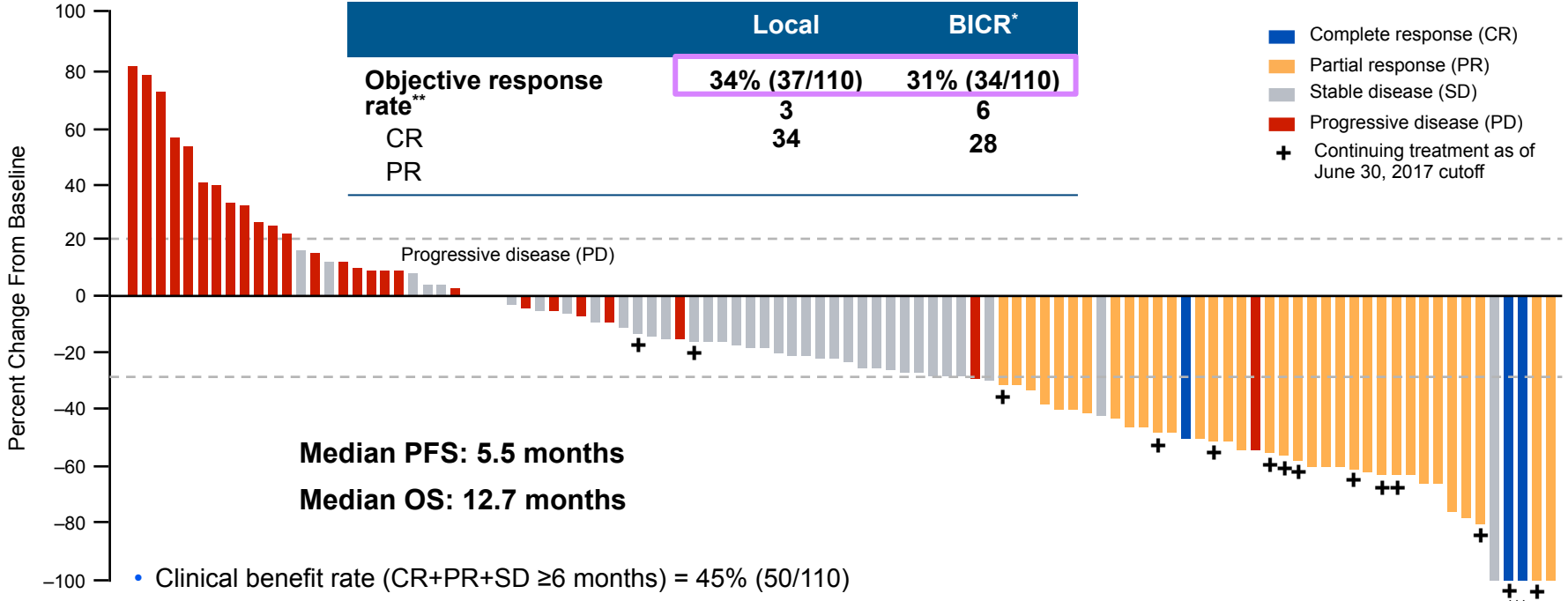
- AEs were managed with supportive medication or dose modifications
  - 25% of patients had dose modifications, predominantly to 7.5 mg/kg
- Two patients (1.8%) discontinued due to AEs (grade 3 transient infusion reaction/ grade 2 fatigue)
- There were no treatment-related deaths

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%	NA
	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 based on local assessment; BICR = Blinded Independent Adjudicated Central Review.

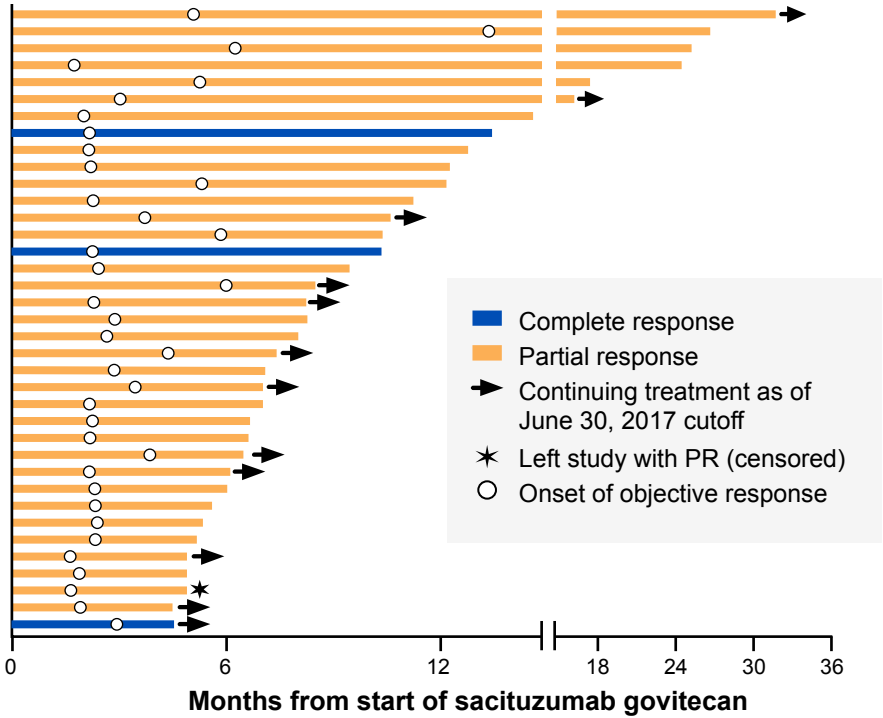
Immunomedics

SAN ANTONIO BREAST CANCER SYMPOSIUM

Response Onset and Durability (n = 37)

	Local	BICR*
Median duration of response, months (95% CI)	**7.6** (4.8, 11.3)	**9.1** (4.1, 14.3)

- Median time to onset of response: 2.0 months (range: 1.5-13.4)
- 9 long-term responders were progression free for >1 year from start of treatment (4 responders >2 years)
- 12 responders were still receiving sacituzumab govitecan at time of data cutoff, June 30, 2017



*Patients with at least 20% tumor reduction (n = 56) were reviewed; BICR = Blinded Independent Adjudicated Central Review. 1 patient left study with PR due to clinical progression.

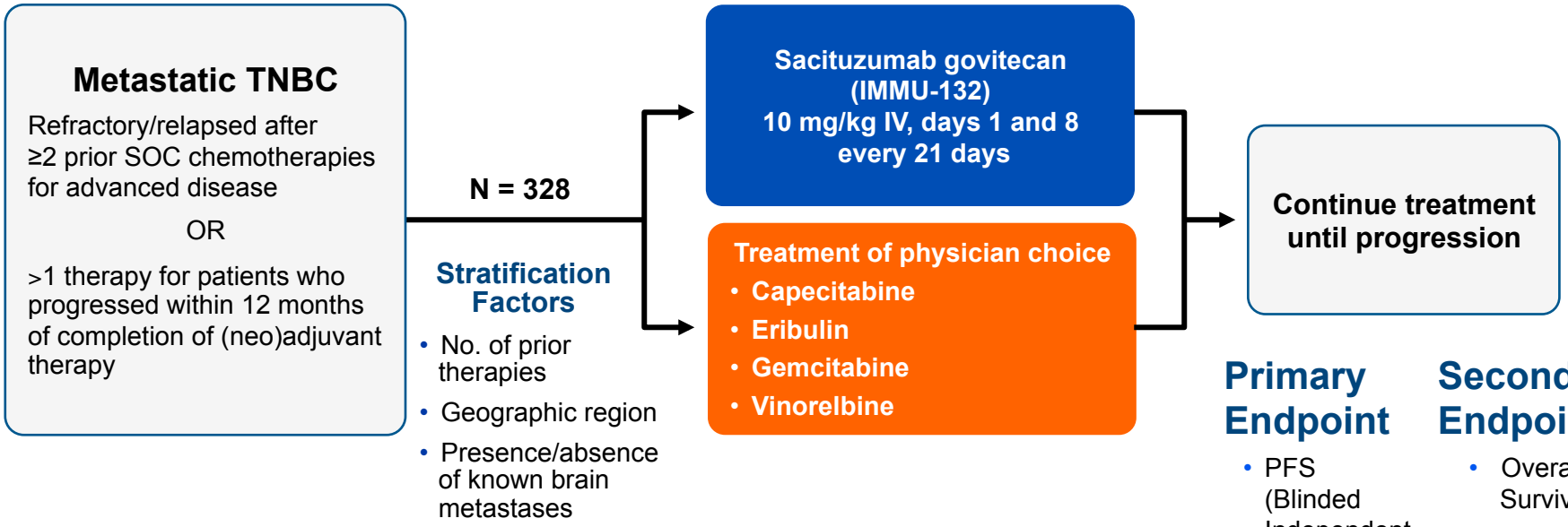
Response to Sacituzumab Govitecan in Subgroups

	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

ASCENT Phase III Trial is Recruiting



- Now enrolling in the US; European enrollment to begin in first half of 2018
- Clinical trials number: NCT02574455

Take Home Message

- **Single agent sacituzumab govitecan demonstrated clear clinical activity as ≥3rd-line therapy in patients with mTNBC**
  - **Confirmed ORR: 34%; median PFS 5.5 months**
  - **Responses durable**
- **Toxicity not inconsequential**
  - **Grade 3/4 neutropenia in 41%**
  - **Febrile neutropenia 7%**
  - **GI toxicity common: Nausea, vomiting, diarrhea**
  - **Alopecia in 36%**
- **Has definite potential to gain regulatory approval in late line mTNBC**

Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative MBC

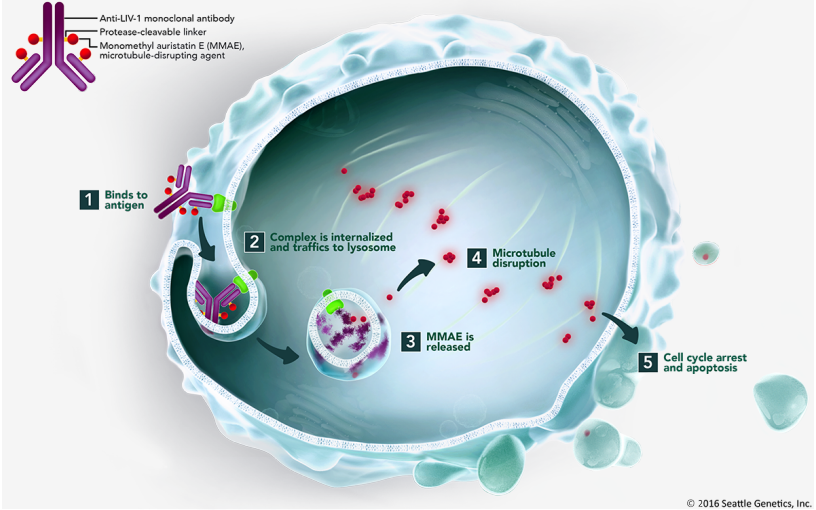
Modi S, et al.

SGN-LIV1A is an antibody-drug conjugate composed of:

- Humanized IgG1 anti-LIV-1 monoclonal antibody
  - Targets the LIV-1 zinc transporter
- Microtubule-disrupting agent, MMAE

<u>Phase I Study Key Eligibility Criteria</u>

- ≥2 prior metastatic cytotoxic regimens
- LIV-1 expression (H-score ≥100) by central pathology review



614 archived/fresh MBC tumor samples screened to date

- 90% positive for LIV-1 expression
- Moderate-to-high LIV-1 expression (H-score ≥100) is present in 68% of mTNBC

Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative MBC

Modi S, et al.

Dose escalation =

0.5–2.8 mg/kg IV q3wk

Recommended Phase 2 Dose =

2.5 mg/kg IV q3 weeks

Adverse Events (n=81)

	Dose (mg/kg)						
			2.5 mg/kg				
Preferred Term	0.5–1.5 N=11	2.0 N=36	≤200 mg N=20	>200 mg N=11	Total N=31	2.8 N=3	Total N=81
Alopecia	2 (40.0)	16 (44.4)	9 (45.0)	4 (36.4)	13 (41.9)	2 (66.7)	33 (40.7)
Neutropenia	1 (20.0)	6 (16.7)	6 (30.0)	6 (54.5)	12 (38.7)	1 (33.3)	20 (24.7)
Vomiting	4 (36.4)	7 (19.4)	4 (20.0)	2 (18.2)	6 (19.4)	2 (66.7)	19 (23.5)
Anemia	1 (20.0)	10 (27.8)	4 (20.0)	1 (9.1)	5 (16.1)	1 (33.3)	17 (21.0)
Neuropathy peripheral	6 (54.5)	5 (13.9)	1 (5.0)	2 (18.2)	3 (9.7)	2 (66.7)	16 (19.8)
Peripheral sensory neuropathy	1 (20.0)	4 (11.1)	6 (30.0)	3 (27.3)	9 (29.0)	0 (0.0)	14 (17.3)
Sepsis	0 (0.0)	2 (5.6)	0 (0.0)	2 (18.2)	2 (6.5)	0 (0.0)	4 (4.9)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	2 (6.5)	0 (0.0)	2 (2.5)

Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative MBC

Modi S, et al.

Efficacy

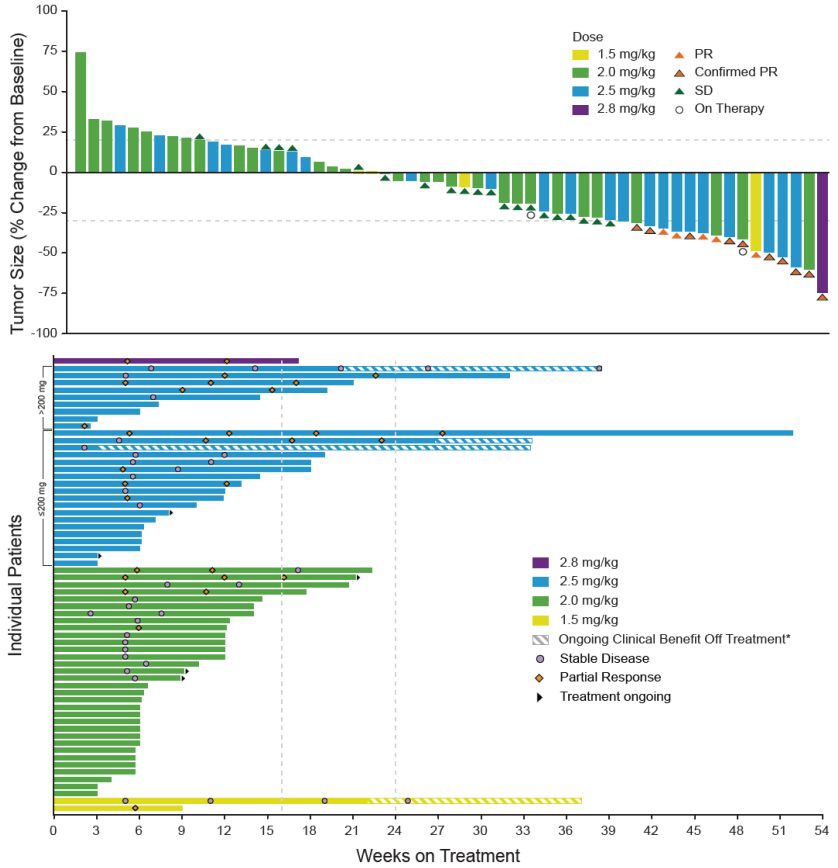
All patients (n=60)

ORR = 25%

RP2D of 2.5 mg/kg IV q3 weeks(n=26)

ORR = 34.6%

PFS = 2.9 months



Metastatic HR-Positive Breast Cancer

Abstract	Presenter	Title
GS2-05	Tripathy	First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial
P5-21-03	Rugo	Palbociclib + letrozole as first-line therapy in estrogen receptor–positive /HER2–negative advanced breast cancer (ABC): Efficacy and safety updates with longer follow-up across patient subgroups

Role of CDK4-6 inhibition in 1st line treatment of HR+/HER2- MBC?

CDK4-6 Inhibitors: A new paradigm in HR+ MBC

	Palbociclib	Ribociclib	Abemaciclib
1st line studies:	**Paloma-2**	**Monaleesa-2**	**Monarch-3**
Endocrine Partner:	Letrozole	Letrozole	Letrozole Anastrazole
PFS (months):	24.8 vs 14.5 HR = 0.58	25.3 vs 16.0 HR = 0.556	NR vs 14.7 HR = 0.53
Prior endocrine tx:	**Paloma-3**	**Monaleesa-3**	**Monarch-2**
Endocrine Partner:	Fulvestrant	Fulvestrant	Fulvestrant
PFS (months):	11.2 vs 4.6 HR = 0.5	Pending	16.4 vs 9.3 HR = 0.55

Finn NEJM 2016, Hortobagyi NEJM 2016, Di Leo ESMO 2017, Turner NEJM 2015, Sledge JCO 2017.

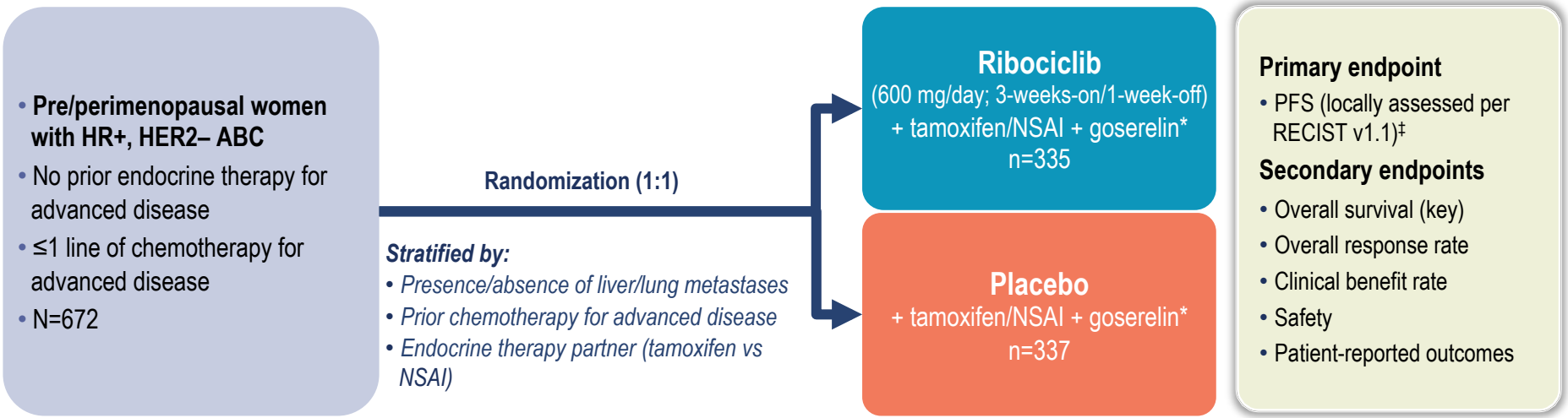
First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial

Debu Tripathy,[1] Joohyuk Sohn,[2] Seock-Ah Im,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Sara Hurvitz,[8] Louis Chow,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Gary Carlson,[14] Gareth Hughes,[15] Ivan Diaz-Padilla,[15] Caroline Germa,[14] Samit Hirawat,[14] Yen-Shen Lu[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Severance Hospital of Yonsei University Health System, Seoul, Republic of Korea; [3]Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Unità di Ricerca in Senologia Medica – Istituto Europeo di Oncologia, Milan, Italy; [5]Hospital de Caridade de Ijuí, CACON, Ijuí, Brazil; [6]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [7]Breast Center, University of Munich (LMU), Munich, Germany; [8]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [9]Organisation for Oncology and Translational Research, Hong Kong; [10]Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea; [11]Centro Oncológico Estatal, Instituto de Seguridad Social del Estado de México y Municipios, Toluca, Mexico; [12]Institut Català d'Oncologia, Hospital Moisès Broggi, Barcelona, Spain; [13]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [15]Novartis Pharma AG, Basel, Switzerland; [16]National Taiwan University Hospital, Taipei, Taiwan

GS2-05

MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), and a sample size of 660 patients

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
*Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.
1. Klijn JG, *et al*. *J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al*. *J Clin Oncol* 2001;19:2596–2606.

Key enrollment criteria

Key inclusion criteria

- Pre/perimenopausal women (per NCCN guidelines)
- ≥1 measurable lesion (RECIST 1.1) or ≥1 predominantly lytic bone lesion
- ECOG performance status of ≤1
- ≤1 line of chemotherapy for ABC
- Prior (neo)adjuvant therapy was allowed:
  - If no prior endocrine therapy OR if ≥12 months since the last dose, patient was eligible for tamoxifen or an NSAI, per investigator/patient choice
  - If last dose of tamoxifen was <12 months prior to randomization, patient was eligible for an NSAI
  - If last dose of AI/NSAI was <12 months prior to randomization, patient was eligible for tamoxifen

Key exclusion criteria

- Any prior endocrine therapy for ABC
- Inflammatory breast cancer
- Active cardiac disease or history of cardiac dysfunction, including QTcF >450 msec
- CNS metastases
- Symptomatic visceral disease

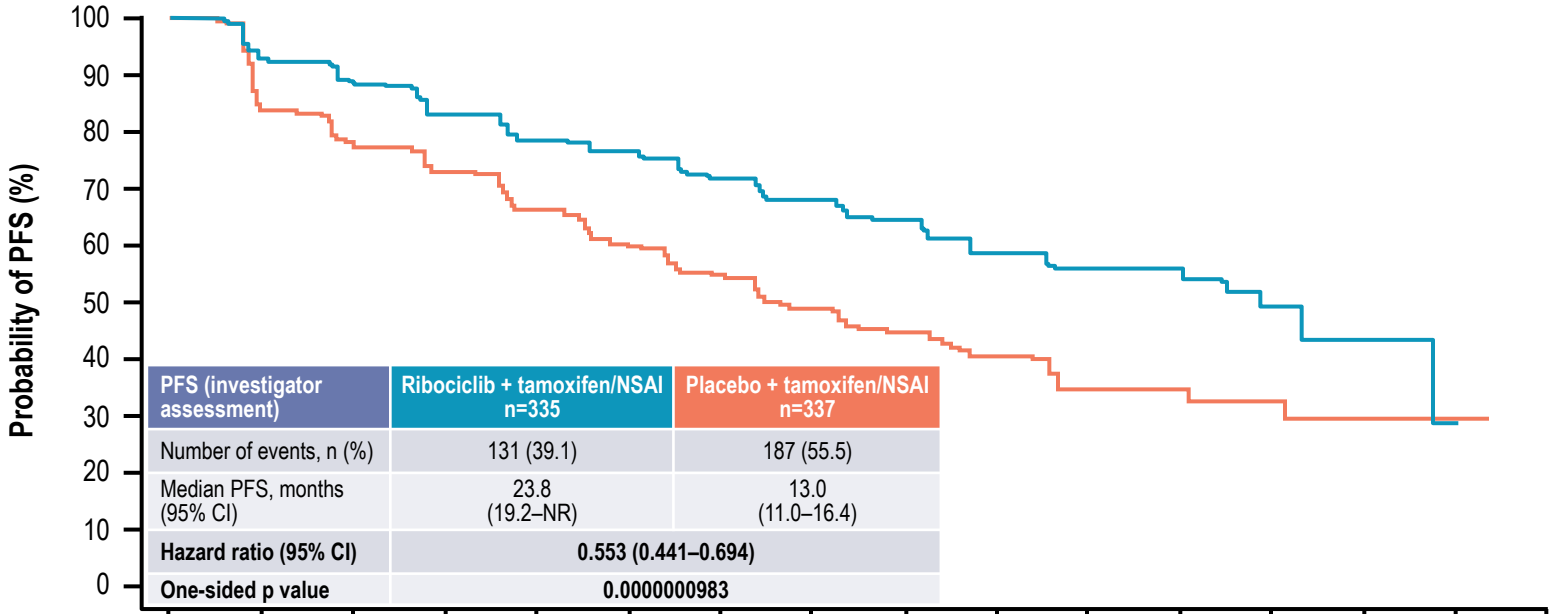
AI, aromatase inhibitor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network; QTcF, Fridericia's corrected QT interval.
Perimenopausal defined as neither premenopausal nor postmenopausal per NCCN guidelines.
Goserelin included in all combinations.

Patient demographics and baseline characteristics

Characteristic*	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Median age, years (range)	43 (25–58)	45 (29–58)
Race		
Caucasian	187 (55.8)	201 (59.6)
Asian	99 (29.6)	99 (29.4)
Other‡	29 (8.7)	19 (5.6)
Unknown	20 (6.0)	18 (5.3)
ECOG performance status§		
0	245 (73.1)	255 (75.7)
1	87 (26.0)	78 (23.1)
Missing	3 (0.9)	3 (0.9)
Metastatic sites		
Visceral disease	193 (57.6)	188 (55.8)
Bone-only disease	81 (24.2)	78 (23.1)
***De novo* metastatic disease**	136 (40.6)	134 (39.8)
Non-*de novo* metastatic disease	199 (59.4)	203 (60.2)
Disease-free interval		
≤12 months	23 (6.9)	13 (3.9)
>12 months	176 (52.5)	190 (56.4)
Prior (neo)adjuvant endocrine therapy	127 (37.9)	141 (41.8)
Prior chemotherapy		
For advanced disease	47 (14.0)	47 (13.9)
(Neo)adjuvant only	138 (41.2)	138 (40.9)
None	150 (44.8)	152 (45.1)

*All values are n (%), unless stated otherwise; ‡'Other' includes Black, Native American, and other; §One patient in the placebo arm had an ECOG performance status of 2. Goserelin included in all combinations.

Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

No. at risk

Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

CI, confidence interval; NR, not reached.
Goserelin included in all combinations.

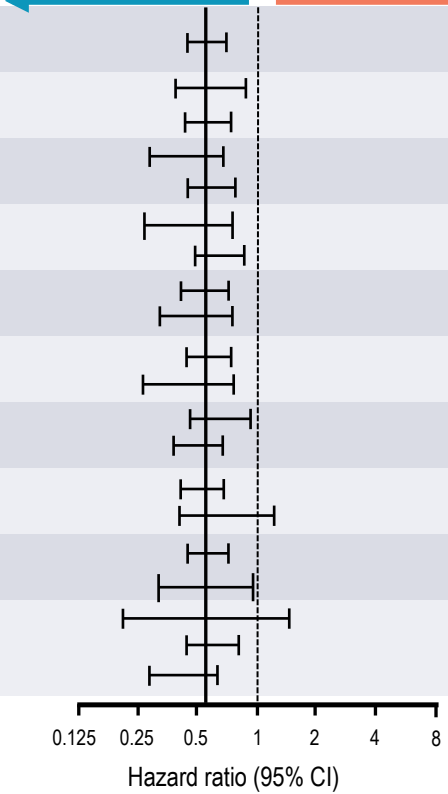
PFS by endocrine therapy partner (investigator-assessed)

PFS (investigator assessment)	Tamoxifen		NSAI	
	Ribociclib arm n=87	Placebo arm n=90	Ribociclib arm n=248	Placebo arm n=247
Number of events, n	39	55	92	132
Median PFS, months (95% CI)	22.1 (16.6–24.7)	11.0 (9.1–16.4)	27.5 (19.1–NR)	13.8 (12.6–17.4)
Hazard ratio (95% CI)	**0.585 (0.387–0.884)**		**0.569 (0.436–0.743)**	

Goserelin included in all combinations.

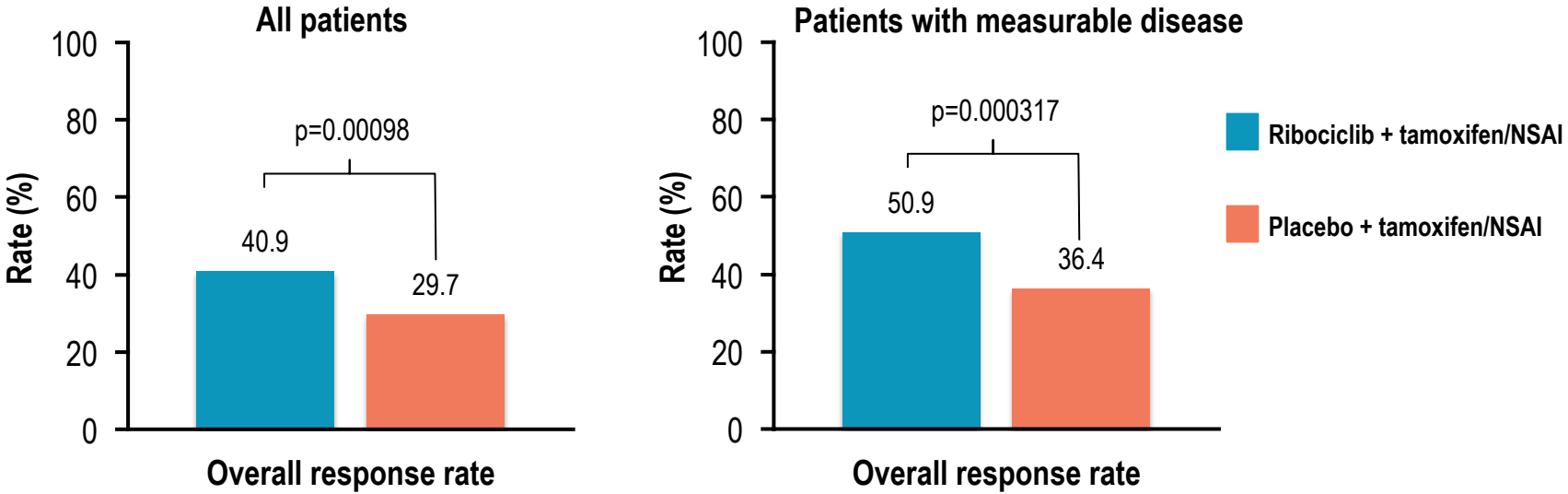
PFS subgroup analysis*

Subgroup		n (%)	Hazard ratio	95% CI
All patients		672 (100)	0.553	0.441–0.694
Endocrine therapy partner	Tamoxifen	177 (26)	0.585	0.387–0.884
	NSAI	495 (74)	0.569	0.436–0.743
Age	<40 years	186 (28)	0.443	0.293–0.671
	≥40 years	486 (72)	0.590	0.449–0.777
Race‡	Asian	198 (29)	0.401	0.258–0.625
	Non-Asian	413 (61)	0.657	0.492–0.877
ECOG performance status§	0	500 (74)	0.549	0.417–0.721
	≥1	166 (25)	0.495	0.320–0.765
ER/PgR status	ER+ and PgR+	572 (85)	0.574	0.446–0.739
	Other	100 (15)	0.444	0.258–0.765
Liver and/or lung involvement	No	329 (49)	0.642	0.454–0.907
	Yes	343 (51)	0.503	0.375–0.677
Bone-only disease	No	513 (76)	0.533	0.415–0.686
	Yes	159 (24)	0.703	0.414–1.194
Prior chemotherapy for advanced disease	No	578 (86)	0.566	0.443–0.724
	Yes	94 (14)	0.547	0.314–0.954
Disease-free interval	≤12 months	36 (5)	0.560	0.210–1.490
	>12 months	366 (54)	0.615	0.455–0.832
	De novo	270 (40)	0.428	0.287–0.640



ER, estrogen receptor; PgR, progesterone receptor.
*Locally assessed PFS; ‡Non-Asian race includes Caucasian, Black, and Native American; §ECOG performance status missing for n=6; 1 patient had an ECOG performance status of 2.

Secondary endpoints



- The CBR in patients with measurable disease was 79.9% for ribociclib + tamoxifen/NSAI vs 67.3% for placebo + tamoxifen/NSAI (p=0.000340)
- Overall survival data were immature at the cut-off date

CBR, clinical benefit rate.
CBR = complete response + partial response + (stable disease + non-complete response/non-progressive disease ≥24 weeks).
Goserelin included in all combinations.

Hematologic adverse events

Regardless of study treatment relationship

AEs ≥5% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	75.8	50.7	9.9	7.7	3.0	0.6
Leukopenia	31.3	13.1	1.2	5.6	1.2	0
Anemia	20.9	3.0	0	10.1	2.1	0
Thrombocytopenia	8.7	0.6	0.3	2.1	0.3	0.3

- Febrile neutropenia occurred in 2.1% of patients in the ribociclib arm vs 0.6% of patients in the placebo arm

Goserelin included in all combinations.

Non-hematologic adverse events

Regardless of study treatment relationship

AEs ≥20% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Hot flush	34.0	0.3	0	33.5	0	0
Nausea	31.6	0.6	0	19.6	0.3	0
Arthralgia	29.9	0.9	0	27.3	0.9	0
Fatigue	23.6	1.2	0	24.6	0	0
Headache	23.0	0	0	24.3	0.9	0
Diarrhea	20.3	1.5	0	18.7	0.3	0

- Post-baseline QTcF >480 msec, based on ECG data, occurred in 23 patients (6.9%) in the ribociclib arm vs 4 patients (1.2%) in the placebo arm
  - Post-baseline QTcF >500 msec occurred in 5 patients (1.5%) vs 1 patient (0.3%)
- Treatment discontinuation due to QT prolongation AEs occurred in 1 patient (0.3%) in the ribociclib arm vs 2 patients (0.6%) in the placebo arm
- QT prolongation events were not associated with clinical symptoms or arrhythmia

ECG, electrocardiogram.
Goserelin included in all combinations.

Take Home Message

- **MONALEESA-7 represents the first Phase III trial dedicated to the evaluation of a CDK4/6 inhibitor-based regimen as 1st line treatment for premenopausal women with HR+, HER2– MBC**

- **PFS was significantly prolonged with the addition of ribociclib to tamoxifen/NSAI + goserelin**
  - **Median PFS = 23.8 months vs 13.0 months**

- **Ribociclib plus tamoxifen/NSAI + goserelin is a potential new option for premenopausal women with HR+, HER2– MBC**

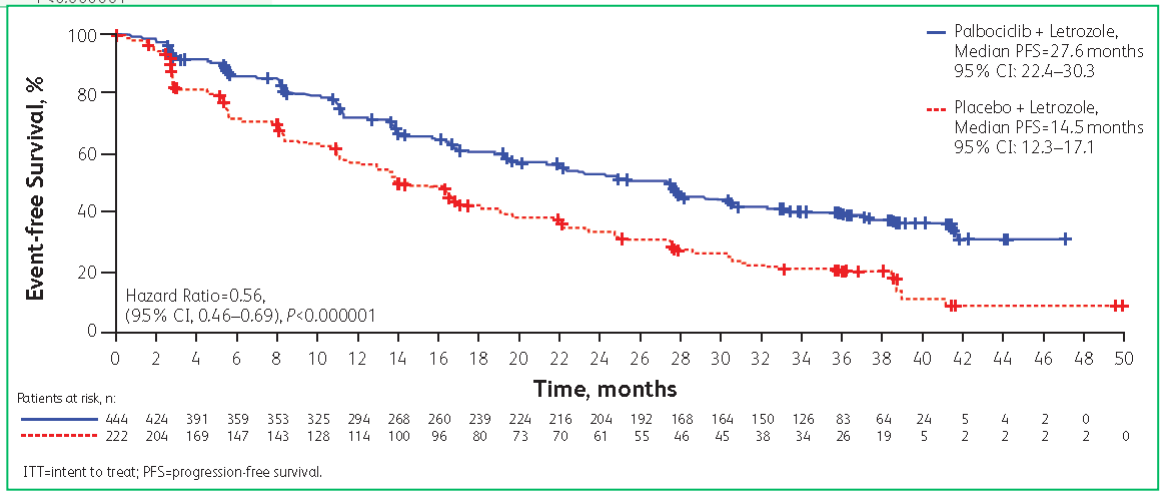
PALOMA-2: Updated PFS at 37 months (Investigator Assessed, ITT Population)

- **Median PFS for palbociclib plus letrozole was 27.6 months (95% CI, 22.4–30.3) vs 14.5 months (95% CI, 12.3–17.1) for placebo plus letrozole; HR=0.563 (95% CI, 0.461–0.687; *p*<0.000001)**

Table 1. Investigator-Assessed PFS

	Data Cutoff Date: February 26, 2016[a]		Data Cutoff Date: May 31, 2017[b]	
	Palbociclib + Letrozole	Placebo + Letrozole	Palbociclib + Letrozole	Placebo + Letrozole
Median PFS, mo (95% CI)	24.8 (22.1–NE)	14.5 (12.9–17.1)	27.6 (22.4–30.3)	14.5 (12.3–17.1)
PFS HR (95% CI); 1-sided *P* value	0.576 (0.463–0.718); *P*<0.000001		0.563 (0.461–0.687); *P*<0.000001	

HR=hazard ratio; NE=not estimable; PFS=progression-free survival
[a]Median follow-up duration was 23.0 months in the palbociclib + letrozole arm and 22.3 months in the placebo + letrozole arm.
[b]Median follow-up duration was 37.6 months in the palbociclib + letrozole arm and 37.3 months in the placebo + letrozole arm.

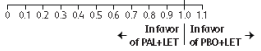


ITT=intent to treat; PFS=progression-free survival.

Progression-Free Survival Overall and Subgroup Analysis

- **Median PFS was consistently longer among all subgroups of patients treated with palbociclib plus letrozole vs placebo plus letrozole**
- **Substantial PFS benefit across subgroups was noted for patients with a low disease burden**
  - **DFI >5 years**
  - **Non-measurable disease**
  - **Bone-only disease**
  - **Single disease site**
  - **No prior endocrine therapy**
  - **No prior endocrine therapy with non-visceral disease**

Baseline Factors	PAL+LET Patients, n (%)	PBO+LET Patients, n (%)	PAL+LET mPFS (95% CI)	PBO+LET mPFS (95% CI)	PAL+LET vs PBO+LET HR (95% CI)	P*
All randomized patients, IA	444 (100)	222 (100)	27.6 (22.4–30.3)	14.5 (12.3–17.1)	0.56 (0.46–0.69)	<0.0001
All randomized patients, BICR	444 (100)	222 (100)	35.7 (27.7–38.9)	19.5 (16.6–26.6)	0.61 (0.49–0.77)	<0.0001
Visceral disease	214 (48.2)	110 (49.5)	19.3 (16.4–24.2)	12.3 (8.4–16.4)	0.62 (0.47–0.81)	<0.0005
Nonvisceral disease	230 (51.8)	112 (50.5)	35.9 (27.7–NE)	17.0 (13.8–24.8)	0.50 (0.37–0.67)	<0.0001
Bone-only disease	103 (23.2)	48 (21.6)	36.2 (27.6–NE)	11.2 (8.2–22.0)	0.41 (0.26–0.63)	<0.0001
No bone-only disease†	341 (76.8)	174 (78.4)	24.2 (19.4–27.7)	14.5 (12.9–18.5)	0.62 (0.50–0.78)	<0.0001
DFI‡ >12 mo	179 (40.3)	93 (41.9)	30.3 (24.8–NE)	13.8 (8.8–18.2)	0.55 (0.40–0.76)	<0.0005
DFI‡ ≤12 mo	98 (22.1)	48 (21.6)	16.6 (13.9–24.2)	11.0 (5.6–12.9)	0.48 (0.32–0.72)	<0.0005
DFI‡ >2 y	154 (34.7)	77 (34.7)	38.5 (27.5–NE)	16.6 (13.7–23.5)	0.52 (0.36–0.75)	<0.0005
DFI‡ >5 y	90 (20.3)	46 (20.7)	38.6 (27.6–NE)	23.5 (16.3–32.2)	0.60 (0.36–1.00)	<0.05
DFI‡ >10 y	32 (7.2)	23 (10.4)	NR (30.4–NE)	23.5 (16.6–NE)	0.44 (0.19–1.03)	<0.05
De novo metastatic	167 (37.6)	81 (36.5)	27.9 (22.1–33.4)	22.0 (13.9–27.4)	0.61 (0.44–0.85)	<0.005
DFI from prior ET >12 mo	156 (35.1)	78 (35.1)	27.6 (22.2–38.6)	13.8 (8.2–16.6)	0.58 (0.41–0.82)	<0.001
DFI from prior ET ≤12 mo	94 (21.2)	48 (21.6)	16.6 (13.9–24.2)	11.0 (5.6–12.9)	0.49 (0.33–0.73)	<0.0005
Measurable disease	338 (76.1)	171 (77.0)	23.7 (19.3–27.6)	14.5 (12.3–18.5)	0.63 (0.50–0.79)	<0.0001
Nonmeasurable disease§	106 (23.9)	51 (23.0)	36.2 (27.6–NE)	16.5 (8.3–19.6)	0.39 (0.25–0.60)	<0.0001
No prior ET with visceral disease	86 (19.4)	47 (21.2)	23.7 (16.8–30.3)	13.9 (10.2–22.2)	0.55 (0.36–0.85)	<0.005
No prior ET without visceral disease	108 (24.3)	49 (22.1)	36.2 (27.9–NE)	27.6 (19.1–35.6)	0.59 (0.38–0.92)	<0.01
Prior ET	250 (56.3)	126 (56.8)	24.2 (18.8–27.6)	11.2 (8.4–14.5)	0.54 (0.42–0.71)	<0.0001
No prior ET	194 (43.7)	96 (43.2)	30.3 (24.5–35.7)	21.9 (15.9–27.4)	0.59 (0.43–0.80)	<0.0005
Prior chemotherapy	213 (48.0)	109 (49.1)	24.8 (19.3–27.9)	12.9 (9.6–16.5)	0.53 (0.40–0.71)	<0.0001
No prior chemotherapy	231 (52.0)	113 (50.9)	27.9 (23.2–33.4)	18.5 (13.6–24.8)	0.59 (0.45–0.79)	<0.0005
Disease site, 1	138 (31.1)	66 (29.7)	30.4 (24.8–NE)	16.5 (11.0–22.1)	0.52 (0.36–0.75)	<0.0005
Disease sites, 2	117 (26.4)	52 (23.4)	28.1 (19.4–NE)	16.3 (11.0–27.4)	0.57 (0.37–0.89)	<0.01
Disease sites, ≥3	189 (42.6)	104 (46.8)	23.7 (19.2–27.6)	13.8 (8.8–17.0)	0.61 (0.46–0.82)	<0.0005
ECOG PS 0	257 (57.9)	102 (45.9)	27.9 (24.9–36.2)	19.3 (14.5–24.9)	0.65 (0.48–0.87)	<0.005
ECOG PS 1/2	187 (42.1)	120 (54.1)	22.2 (16.6–27.7)	11.8 (8.3–16.5)	0.51 (0.39–0.68)	<0.0001
Age <65 y	263 (59.2)	141 (63.5)	23.2 (19.3–27.6)	13.7 (11.0–16.6)	0.55 (0.43–0.70)	<0.0001
Age ≥65 y	181 (40.8)	81 (36.5)	30.6 (27.6–NE)	19.1 (11.0–30.4)	0.60 (0.43–0.86)	<0.005



BICR=blinded independent central review; DFI=disease-free interval; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; HR=hazard ratio; IA=investigator assessed; ITT=intent to treat; LET=letrozole; mPFS=median progression-free survival; NE=not estimable; NR=not reached; PAL=palbociclib; PBO=placebo.
*1-sided *P* value from the log-rank test.
†Per tumor site.
‡Protocol-defined DFI refers to DFI since completion of prior (neo)adjuvant therapy and onset of metastatic disease or disease recurrence.
§A few patients initially enrolled as having measurable disease were later found to have nonmeasurable disease beyond bone-only disease.

Any-Grade Treatment-Emergent AEs* Clustered by PT† and Occurring in >1% of Patients (All Cycles, All Causalities)

- No new safety signals were observed for palbociclib plus letrozole (PAL+L) with an extended follow-up
- Neutropenia was the most frequent any-grade AE in PAL+L (81.8%) vs PBO+L (6.3%)
  - Most events were grade 3 (57.4%) and rarely associated with permanent study discontinuation
- Other common AEs (PAL+L vs PBO+L) included:
  - Infections (62.6% vs 45.0%)
  - Leukopenia (40.3% vs 2.3%)
  - Fatigue (39.6% vs 28.4%),
  - Arthralgia (37.6% vs 36.0%)
  - Nausea (37.2% vs 27.0%)
  - Pulmonary embolism (1.6% vs 1.4%)
  - Febrile neutropenia (2.0%) in PAL+L

	Palbociclib + Letrozole n=444				Placebo + Letrozole n=222			
Clustered PTs	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
All AEs, %‡	99.1	64.0	15.3	2.7	95.9	25.7	2.7	1.8
Hematologic AEs†								
Neutropenia	81.8	57.4	11.7	0	6.3	0.9	0.5	0
Leukopenia	40.3	24.3	0.9	0	2.3	0	0	0
Anemia	26.4	5.6	0.2	0	9.5	1.8	0	0
Thrombocytopenia	19.6	1.4	0.2	0	1.4	0	0	0
Nonhematologic AEs†								
Infection	62.6	6.5	0.9	0.2	45.0	3.2	0	1.4
Stomatitis	31.5	1.1	0	0	14.9	0	0	0
Rash	19.8	0.9	0	0	12.6	0.5	0	0
Hyperglycemia	3.6	0.7	0	0	7.7	0.9	0	0
Pulmonary embolism	1.6	1.1	0.2	0.2	2.3	1.4	0.5	0.5

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.
*MedDRA (version 20.0) coding dictionary applied.
†Clustered PT (any event having a PT that is equal to those listed): anemia (anemia or hematocrit decreased or hemoglobin decreased); infections includes any event with a PT that is part of the system organ class infections and infestations; hyperglycemia (blood glucose increased or diabetes mellitus or diabetes mellitus inadequate control or glycosylated hemoglobin increased or hyperglycemia or type 1 diabetes mellitus or type 2 diabetes mellitus); leukopenia (leukopenia or white blood cell count decreased); neutropenia (neutropenia or neutrophil count decreased); pulmonary embolism (pulmonary artery thrombosis or pulmonary embolism or pulmonary thrombosis); rash (dermatitis or dermatitis acneiform or rash or rash erythematous or rash maculopapular or rash papular or rash pruritic or toxic skin eruption); stomatitis (aphthous stomatitis or cheilitis or glossitis or glossodynia or mouth ulceration or mucosal inflammation or oral pain or oropharyngeal discomfort or oropharyngeal pain or stomatitis); thrombocytopenia (platelet count decreased or thrombocytopenia).
‡All observed or volunteered AEs regardless of suspected causal relationship to the study medication.

- The majority of infections were grade 1/2; any-grade infections were reported in 62.6% of patients receiving palbociclib plus letrozole and 45.0% of patients receiving placebo plus letrozole

Thank you