CLUBE DA MAMA

Novidades SABCS 2017

Câncer de Mama – Doença avançada

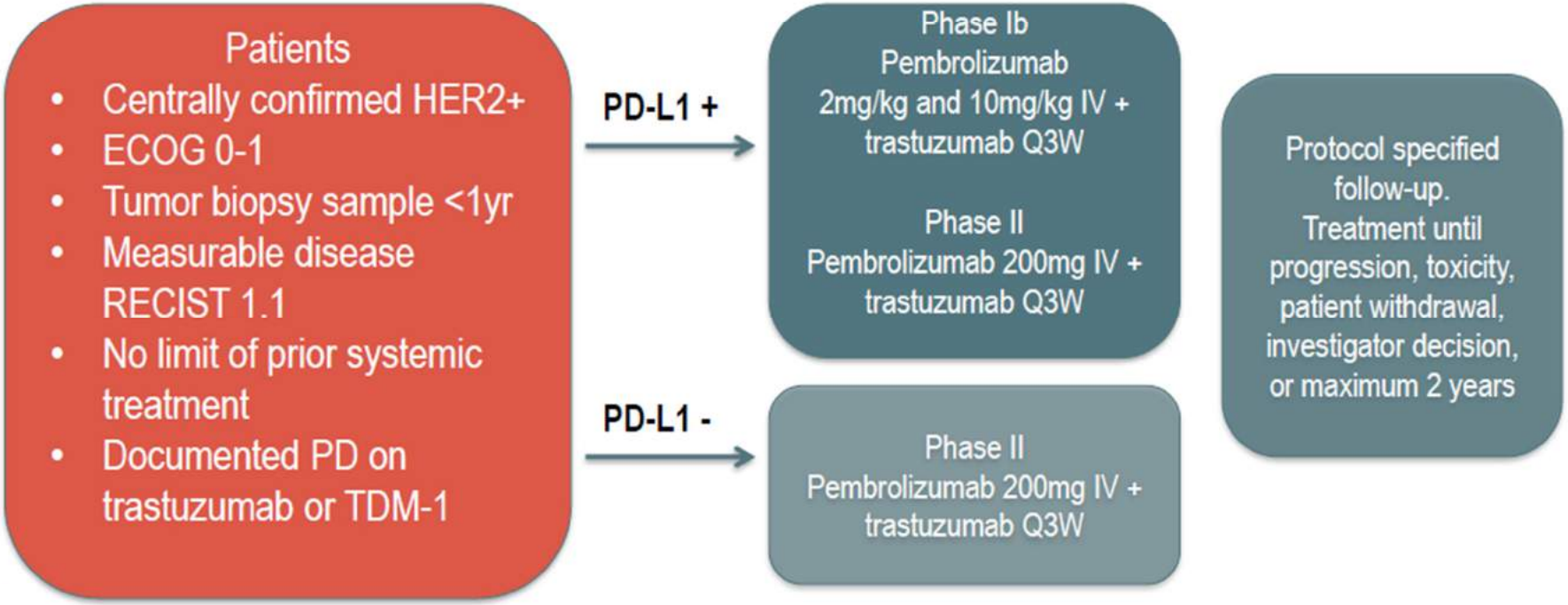
Dra. Danielle Laperche

Phase Ib/II Study Evaluating Safety and Efficacy of Pembrolizumab and Trastuzumab in Patients with Trastuzumab-Resistant HER2-positive Advanced Breast Cancer: Results from the PANACEA Study (IBCSG 45-13/BIG 4-13/KEYNOTE-014)

Sherene Loi, Anita Giobbie-Hurder, Andrea Gombos, Thomas Bachelot, Rina Hui, Giuseppe Curigliano, Mario Campone, Laura Biganzoli, Herve Bonnefoi, Guy Jerusalem, Rupert Bartsch, Manuela Rabaglio-Poretti, Rosita Kammler, Rudolf Maibach, Mark J. Smyth, Angelo Di Leo, Marco Colleoni, Giuseppe Viale, Meredith M. Regan, Fabrice André

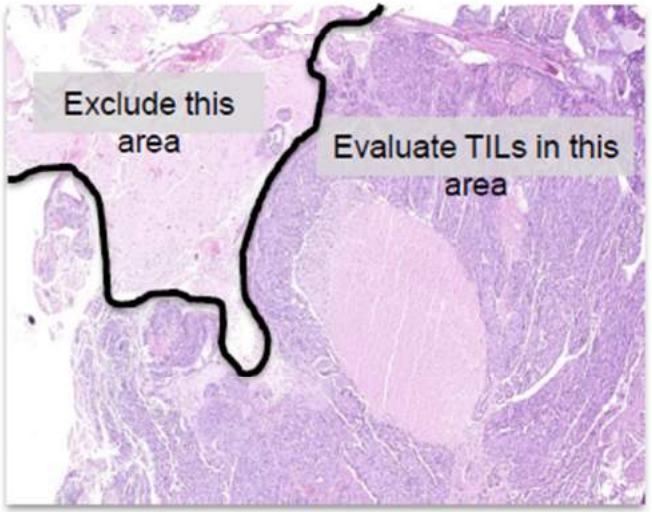
On behalf of the International Breast Cancer Study Group and Breast International Group

Study Design: PANACEA
IBCSG 45-13/BIG 4-13/KEYNOTE-014



Stromal TIL Method of Evaluation

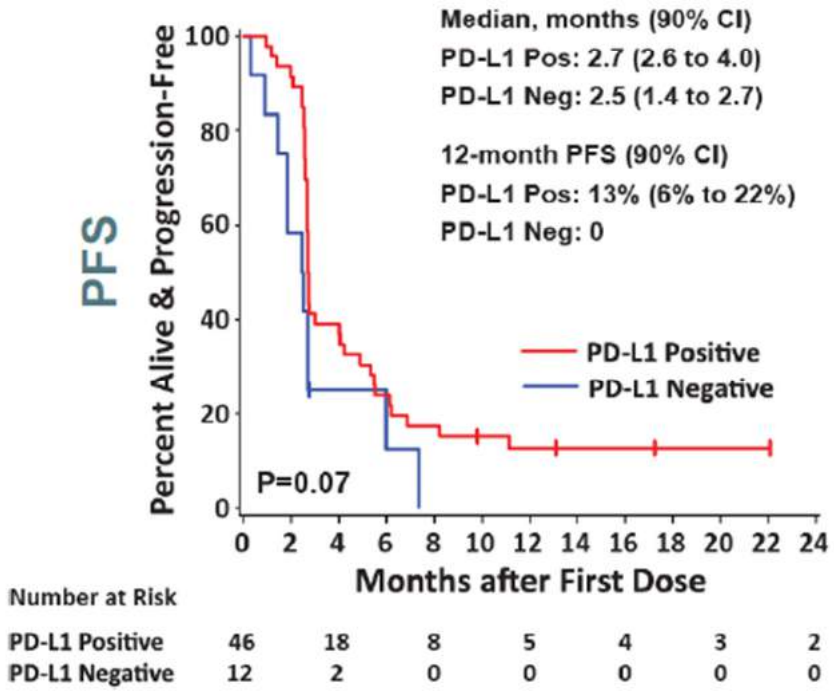
- Pre-defined method[1,2]: using light microscopy of H&E stained slides of tissue obtained from non-irradiated metastatic sites up to maximum one year prior to enrollment
- Quantification: single pathologist blinded to clinical data
- Measurement: percentage of stromal area showing dense mononuclear infiltrate

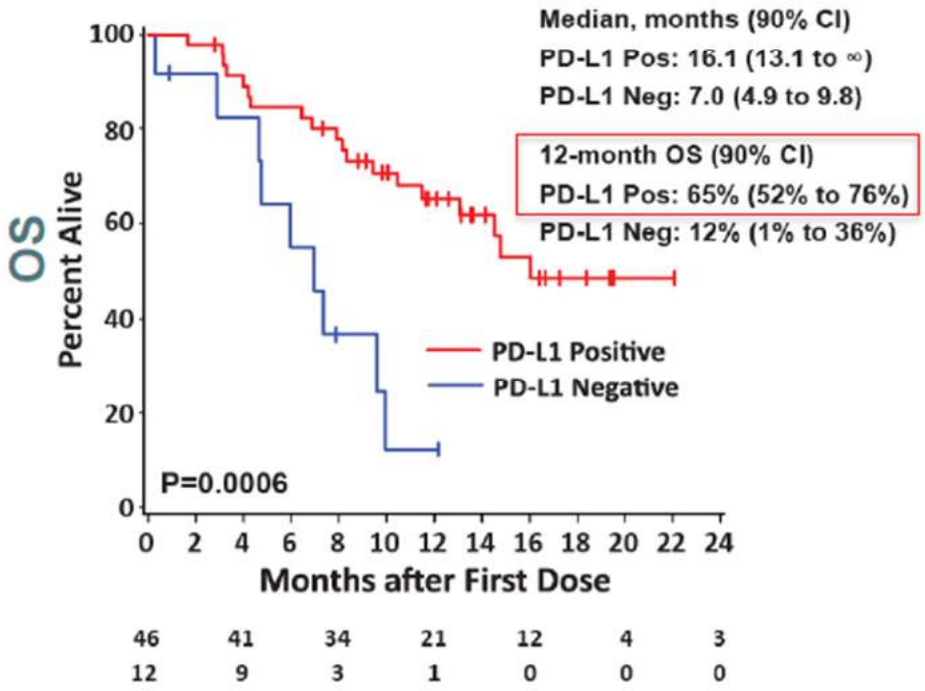


Breast Cancer Brain Metastasis

[1]Salgado R et al, Ann of Oncol 2015; [2]Hendry S et al, Adv Anat Pathol 2017

PFS and OS by PD-L1 Status





Summary and Conclusions

- PANACEA study of pembrolizumab with trastuzumab in trastuzumab-resistant mHER2+ patients met its primary endpoint in the PD-L1 positive cohort (ORR 15%, DCR 25%)
  - No responses observed in PD-L1 negative patients
  - Stromal TIL levels associated with responses: sTILs ≥ 5% patients (ORR 39%, DCR 47%)
  - For responders: combination offers durable control without chemotherapy
- Metastatic HER2+ disease in the heavily pretreated setting is poorly immunogenic (majority of patients had low TILs in their metastatic lesions)
- Future directions in IO in mHER2+ should focus on combinations with effective anti-HER2 therapy, especially in low TIL patients

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

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

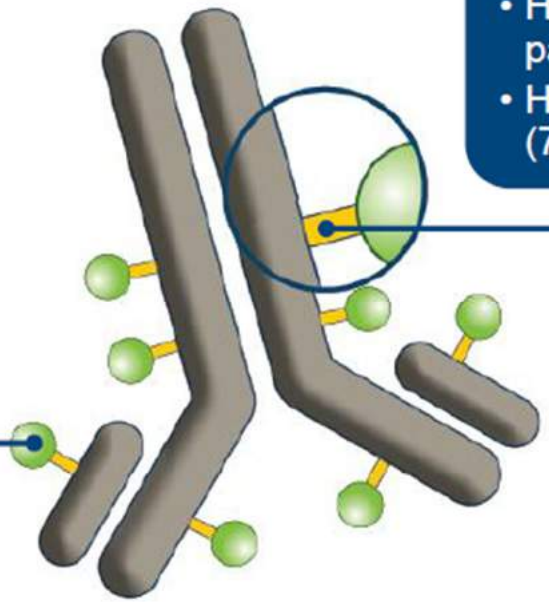
Sacituzumab Govitecan Antibody-Drug Conjugate (ADC)

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*

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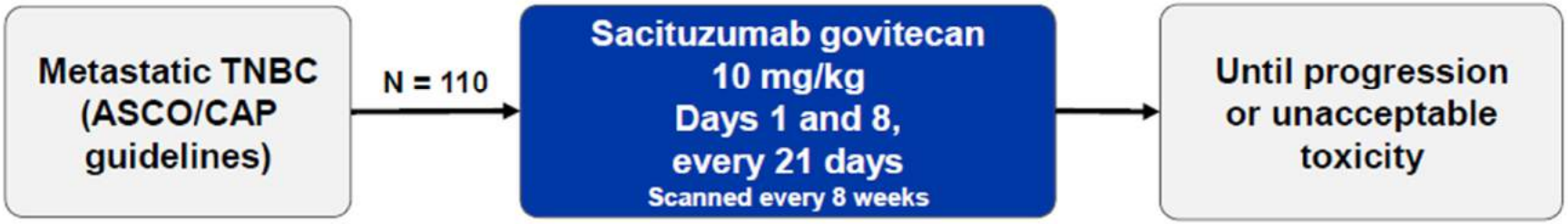
Single-Arm, Open-Label Study Design



Key Eligibility Criteria

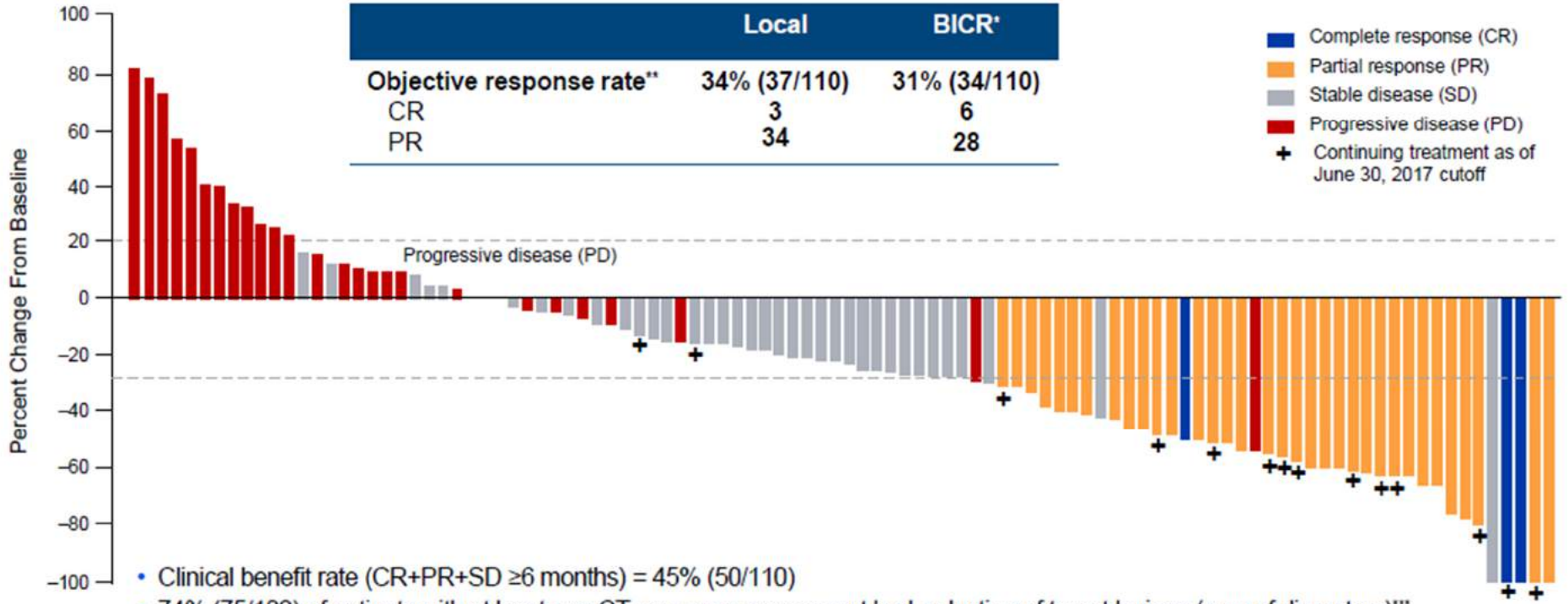
- Adults, ≥18 years of age
- ECOG 0-1
- ≥2 prior therapies in metastatic setting or >1 therapy if progressed within 12 months of (neo)adjuvant therapy
- Prior taxane therapy
- Measurable disease

Evaluations

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

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.

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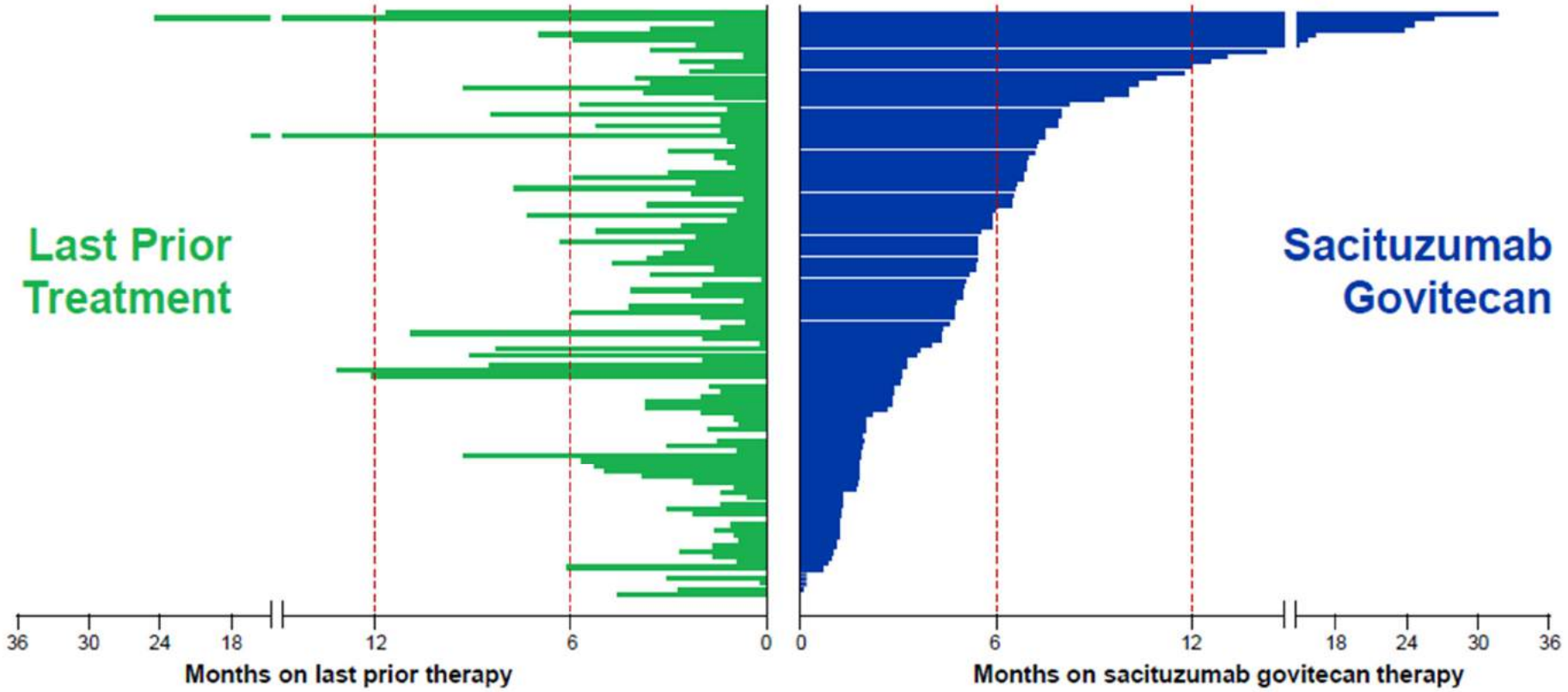
Time on Treatment for All Patients (N = 110)



Last prior time on treatment calculated as last dose date – first dose date. Sacituzumab govitecan time on treatment calculated as (date off study or data cut off date) – first dose date. If more than 1 agent is given in the last prior regimen, the time of treatment is taken as the longest time for any one of the agents used

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SAN ANTONIO BREAST CANCER SYMPOSIUM

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

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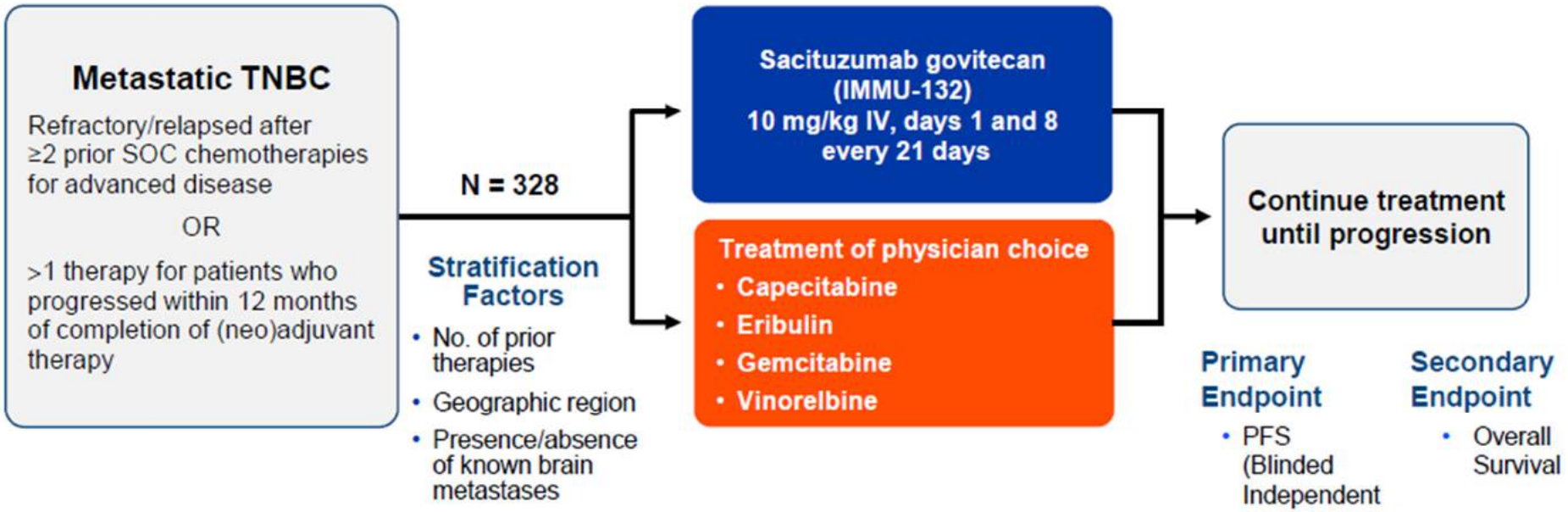
SAN ANTONIO BREAST CANCER SYMPOSIUM

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

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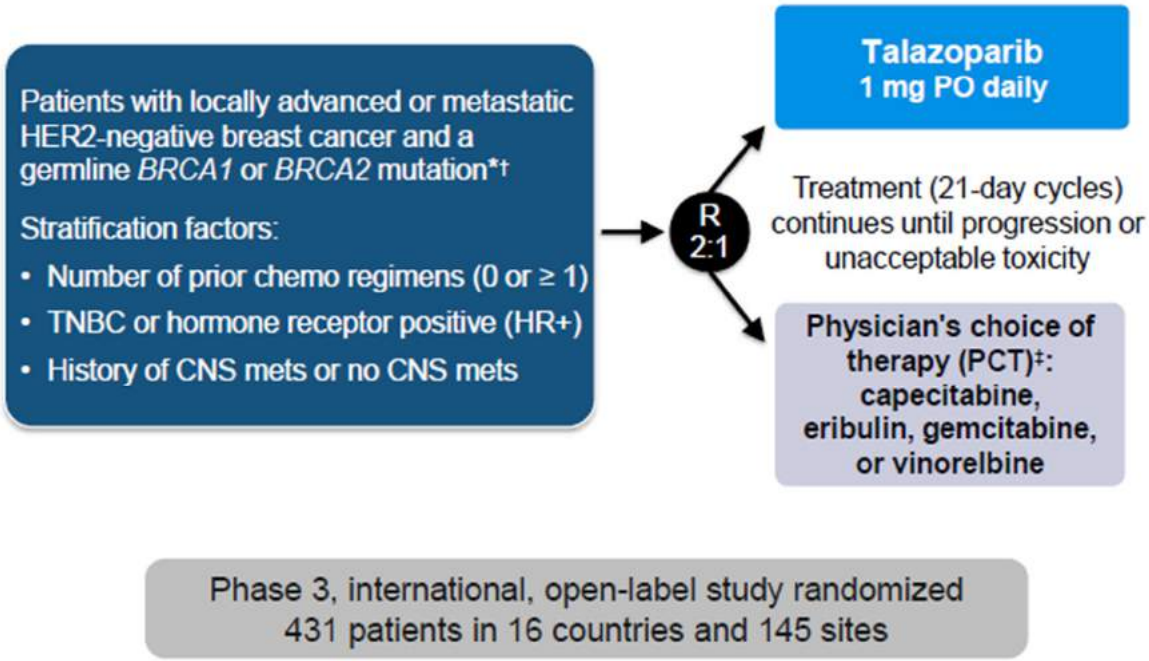
EMBRACA

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



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

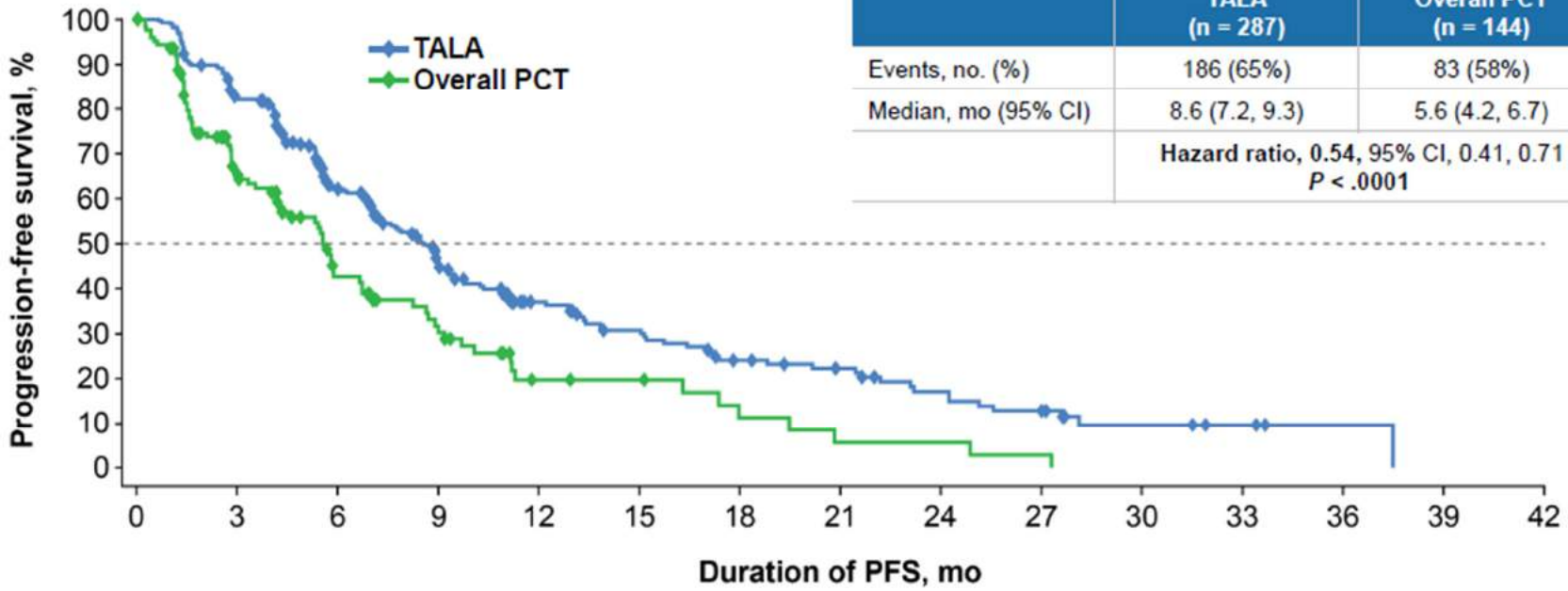
- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints

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

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**	



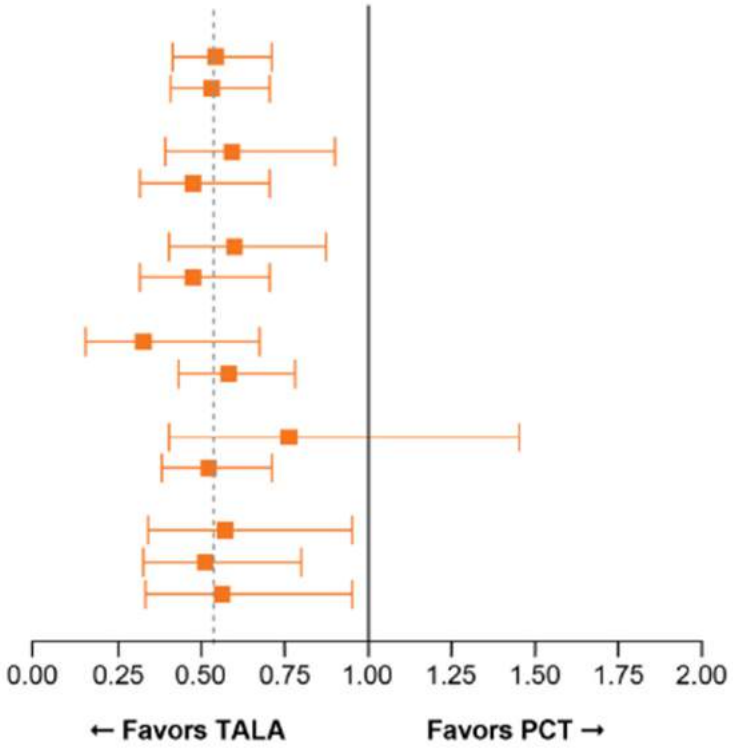
No. at risk (events/cumulative events)

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)



EMBRACA Phase 3 Trial of Talazoparib: Conclusions

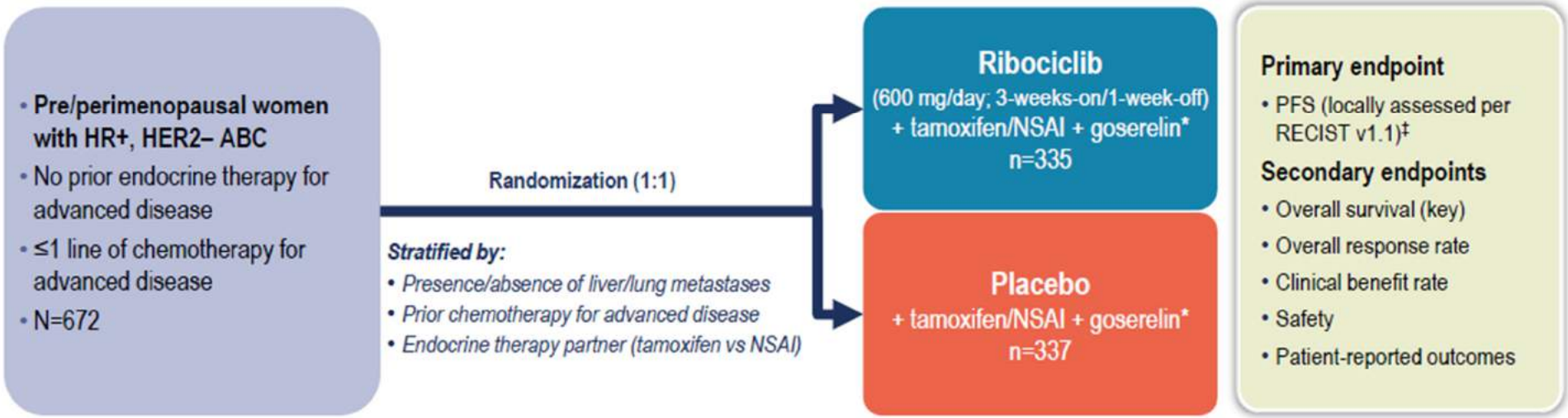
- EMBRACA is the largest randomized trial evaluating a PARP inhibitor in patients with advanced breast cancer and a germline *BRCA1/2* mutation
- Talazoparib resulted in prolonged progression-free survival vs physician's choice of therapy by blinded central review
  - HR: 0.54 (95% CI, 0.41, 0.71); $P < .0001$
- 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

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

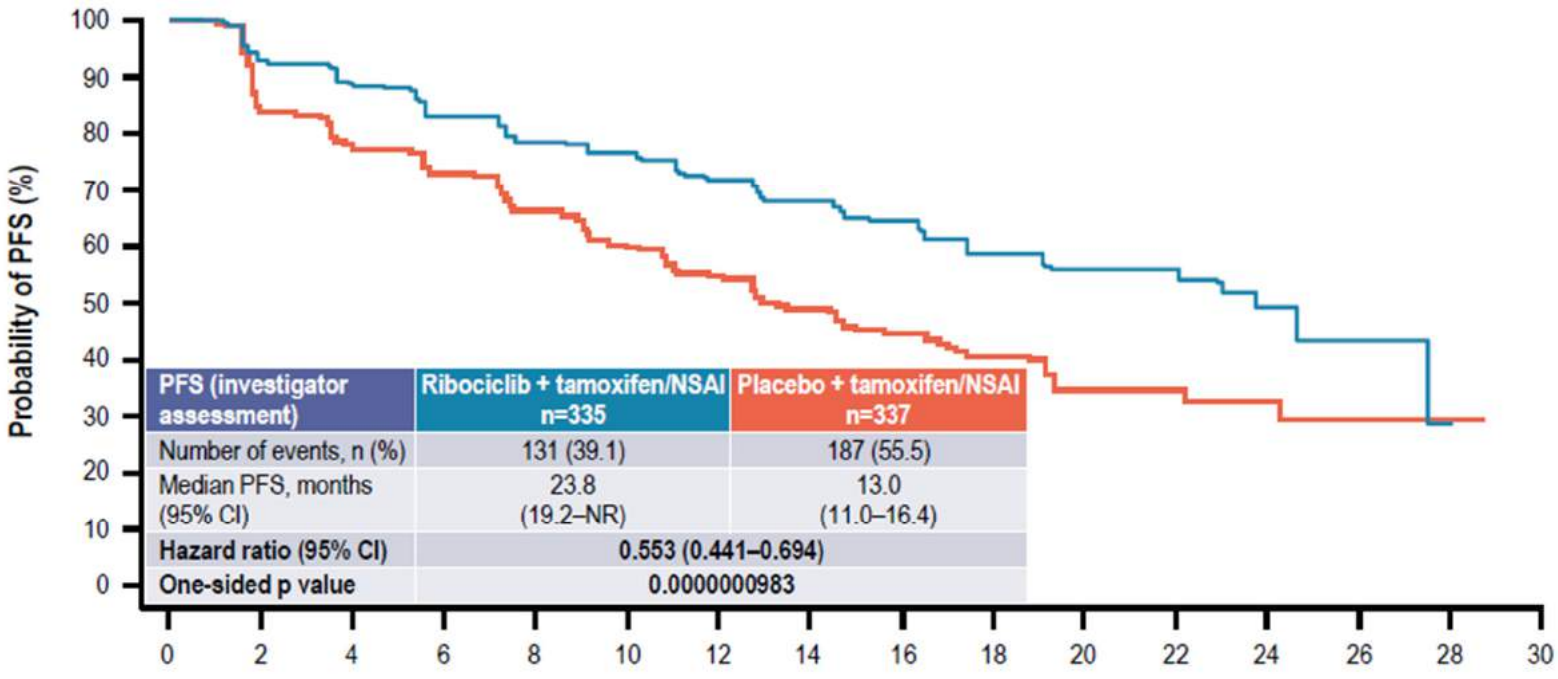
MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin



- 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

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

Primary endpoint: PFS (investigator-assessed)

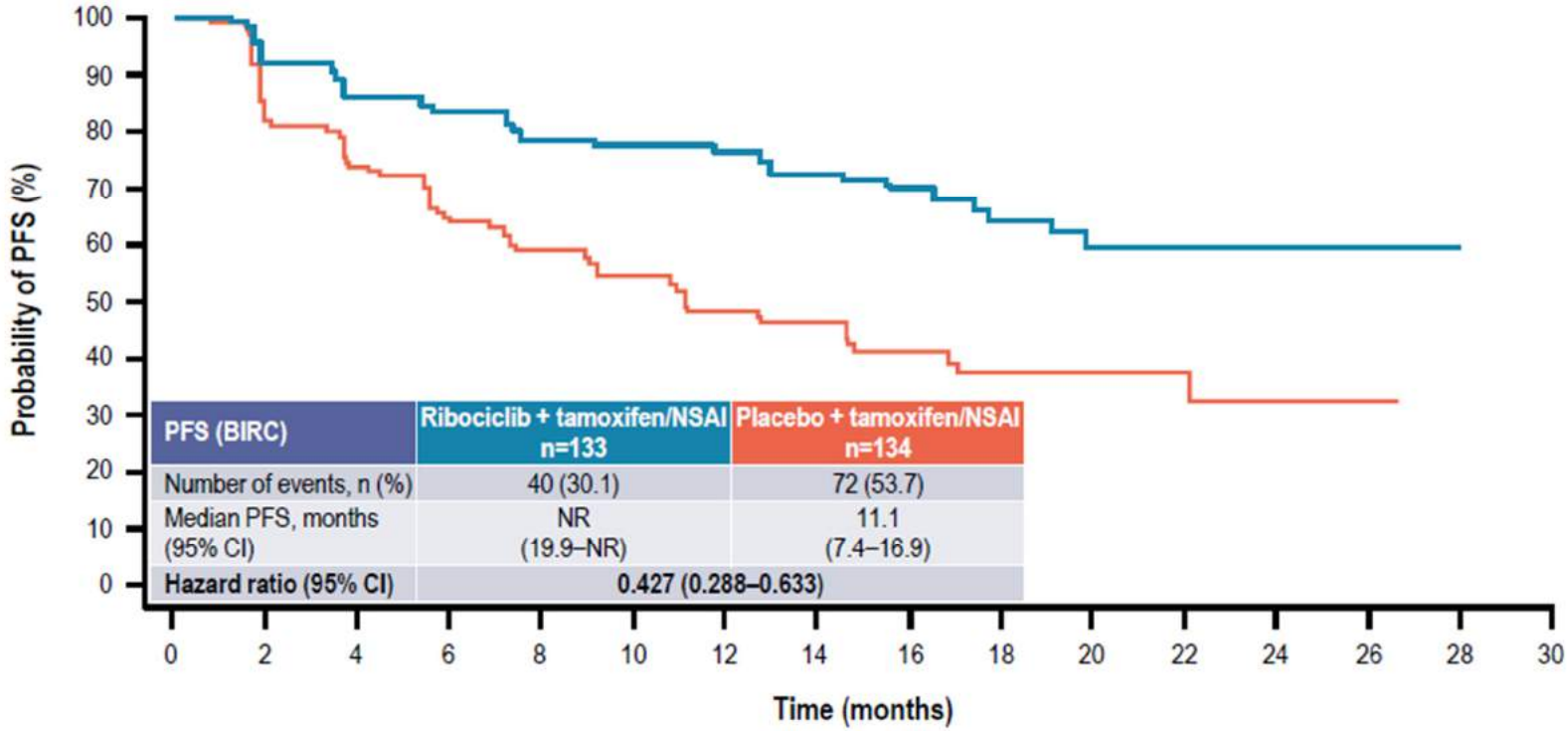


PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

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

Supportive analysis: PFS (Blinded Independent Review Committee*)



PFS (BIRC)	Ribociclib + tamoxifen/NSAI n=133	Placebo + tamoxifen/NSAI n=134
Number of events, n (%)	40 (30.1)	72 (53.7)
Median PFS, months (95% CI)	NR (19.9–NR)	11.1 (7.4–16.9)
Hazard ratio (95% CI)	**0.427 (0.288–0.633)**	

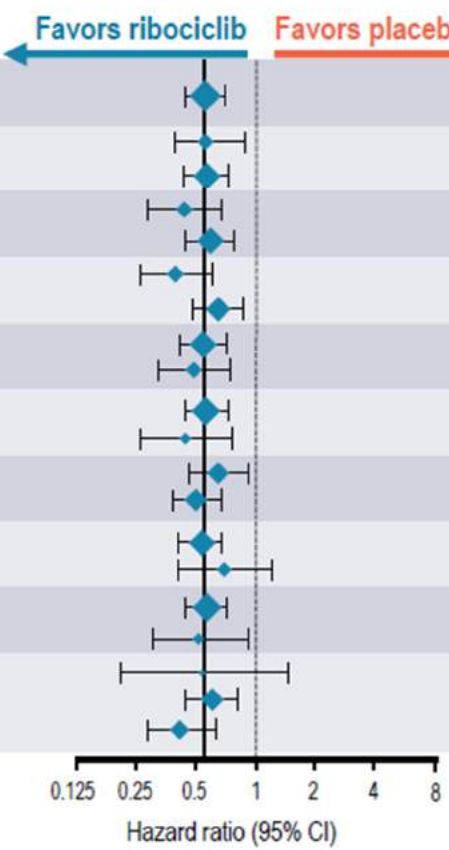
No. at risk

Ribociclib + tamoxifen/NSAI	133	115	105	100	90	87	85	64	46	32	23	16	9	2	1	0
Placebo + tamoxifen/NSAI	134	103	91	76	69	61	52	38	29	21	11	7	5	1	0	0

BIRC, Blinded Independent Review Committee.
*Audit-based review of 40% of randomized patients.

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



Conclusions

- MONALEESA-7 represents the first Phase III trial dedicated to the evaluation of a CDK4/6 inhibitor-based regimen as front-line treatment for premenopausal women with HR+, HER2– advanced breast cancer
- PFS was significantly prolonged with the addition of ribociclib to tamoxifen/NSAI + goserelin vs placebo + tamoxifen/NSAI + goserelin
  - Median PFS = 23.8 months vs 13.0 months; hazard ratio = 0.553; p=0.0000000983
- Treatment benefit was consistent across patient subgroups and regardless of endocrine partner
- Ribociclib-based combinations demonstrated a predictable and manageable safety profile
- A clinically meaningful improvement in time to deterioration of QoL and improvement in pain score were observed for patients in the ribociclib arm
- Ribociclib combined with tamoxifen/NSAI + goserelin is a potential new treatment option for premenopausal women with HR+, HER2– advanced breast cancer, regardless of disease-free interval or endocrine partner

San Antonio Breast Cancer Symposium
December 5-9, 2017

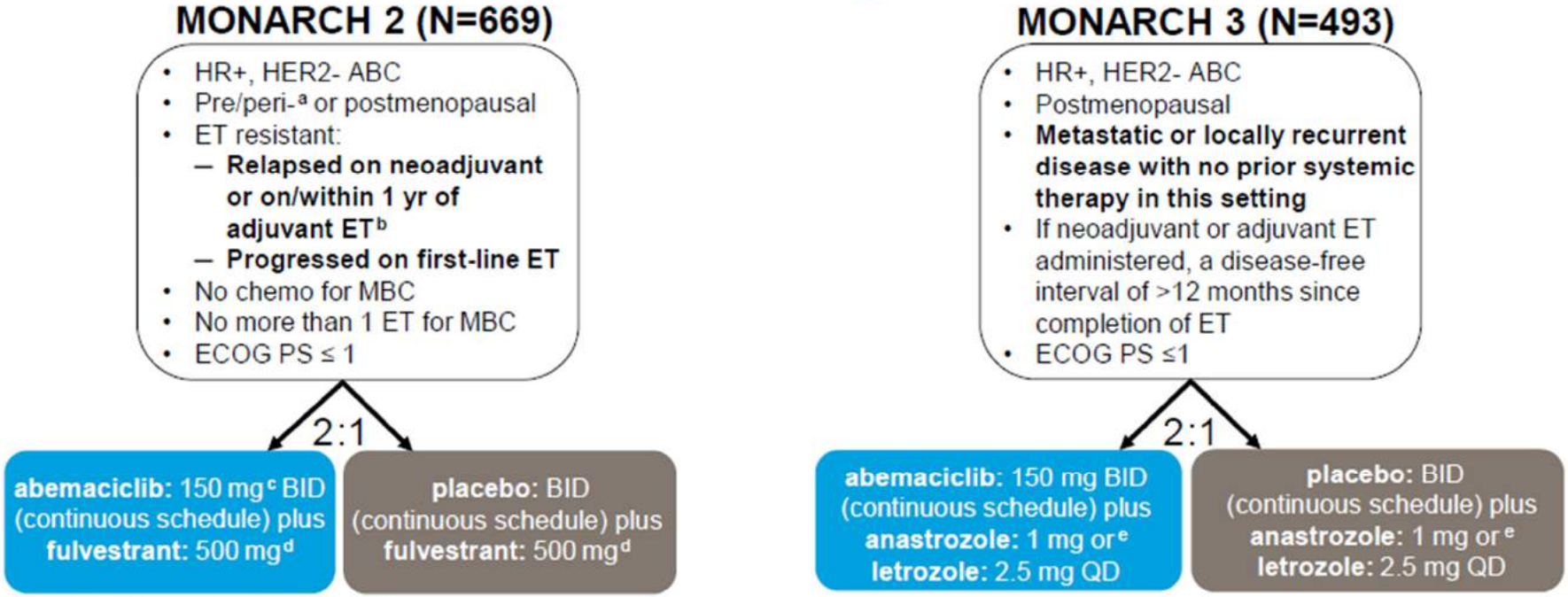
The benefit of abemaciclib in prognostic subgroups: An exploratory analysis of combined data from the MONARCH 2 and 3 studies

Matthew P. Goetz[1], Joyce O'Shaughnessy[2], George W. Sledge Jr.[3], Miguel Martin[4], Yong Lin[5], Tammy Forrester[5], Colleen Mockbee[5], Ian C. Smith[5], Angelo Di Leo[6], Stephen Johnston[7]

[1]Mayo Clinic, Rochester, MN; [2]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas TX; [3]Stanford University, Stanford, CA; [4]Instituto De Investigacion Sanitaria Gregorio Marañon, Ciberonc, Geicam; Universidad Complutense, Madrid, Spain; [5]Eli Lilly and Company, Indianapolis, IN; [6]Hospital of Prato, Istituto Toscano Tumori, Prato, Italy; [7]The Royal Marsden NHS Foundation Trust, London, UK

San Antonio Breast Cancer Symposium
December 5-9, 2017

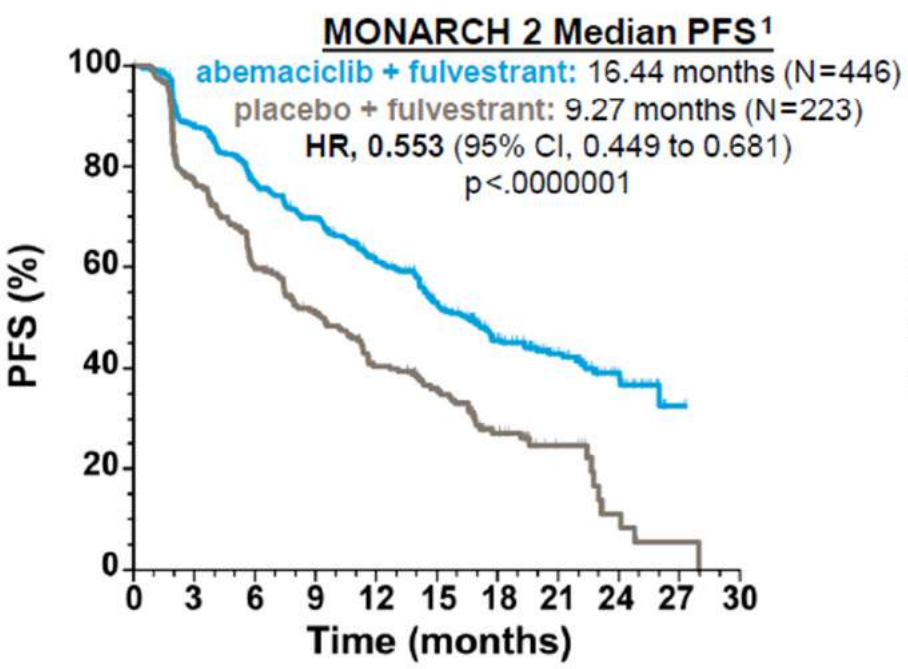
MONARCH 2 and 3 Study Design

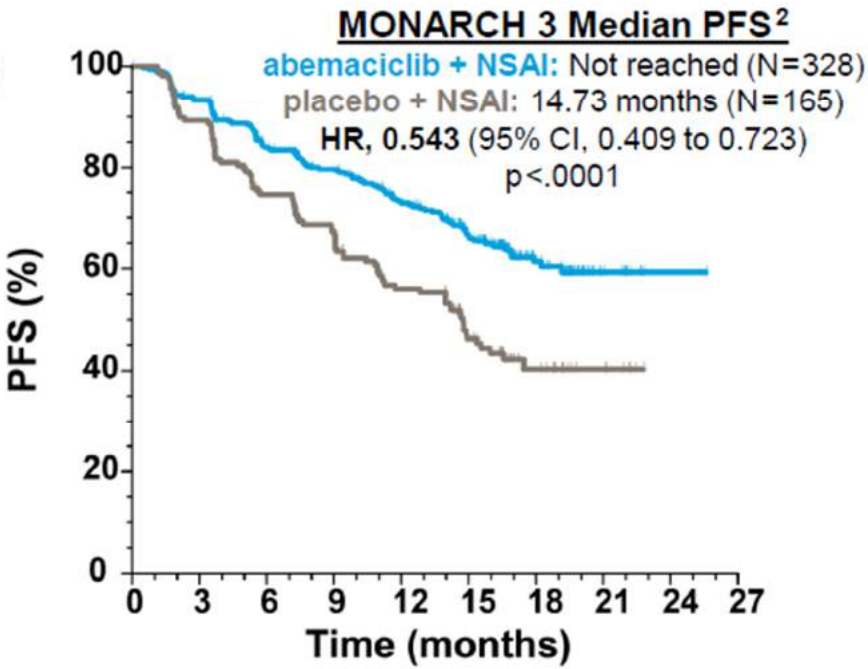


[a] *Required to receive GnRH agonist*
[b] *Most patients entered after progressing while receiving prior ET, with only 8.8% who had disease that progressed within 1 year after completing adjuvant therapy*
[c] *Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled*
[d] *Fulvestrant administered per label*
[e] *Per physician's choice: 79.1% received letrozole, 19.9% received anastrozole*

MONARCH 2 and 3 PFS (ITT)

San Antonio Breast Cancer Symposium
December 5-9, 2017





Liver Metastases

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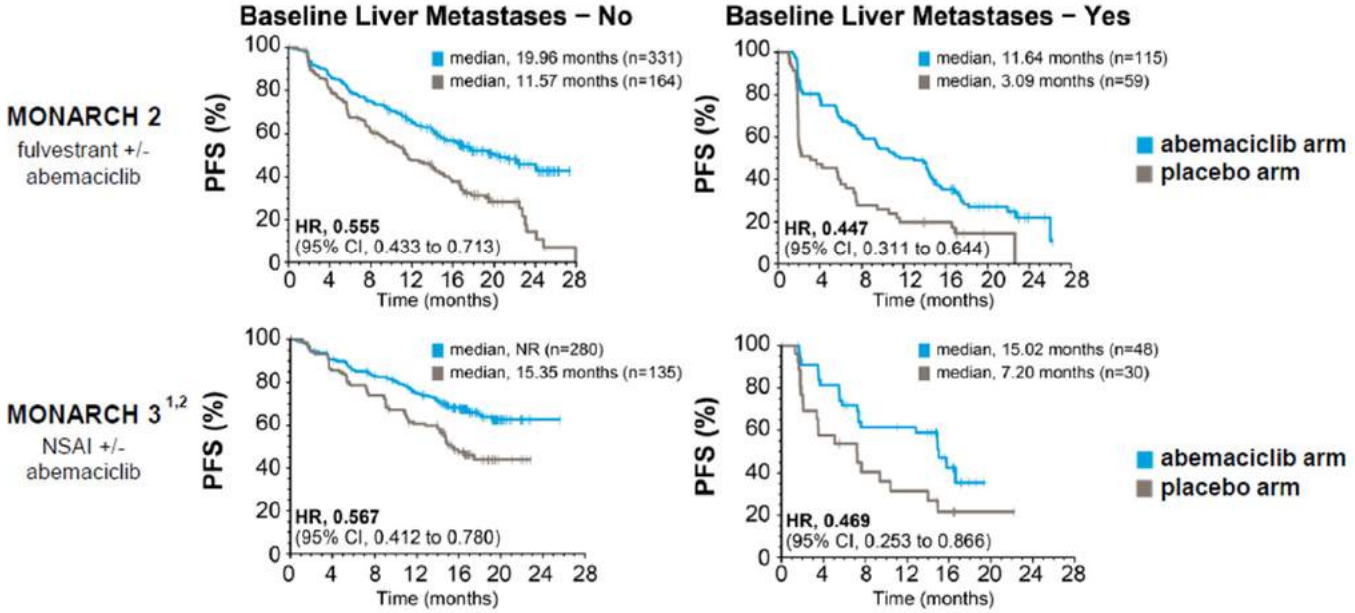

Progesterone Receptor Status

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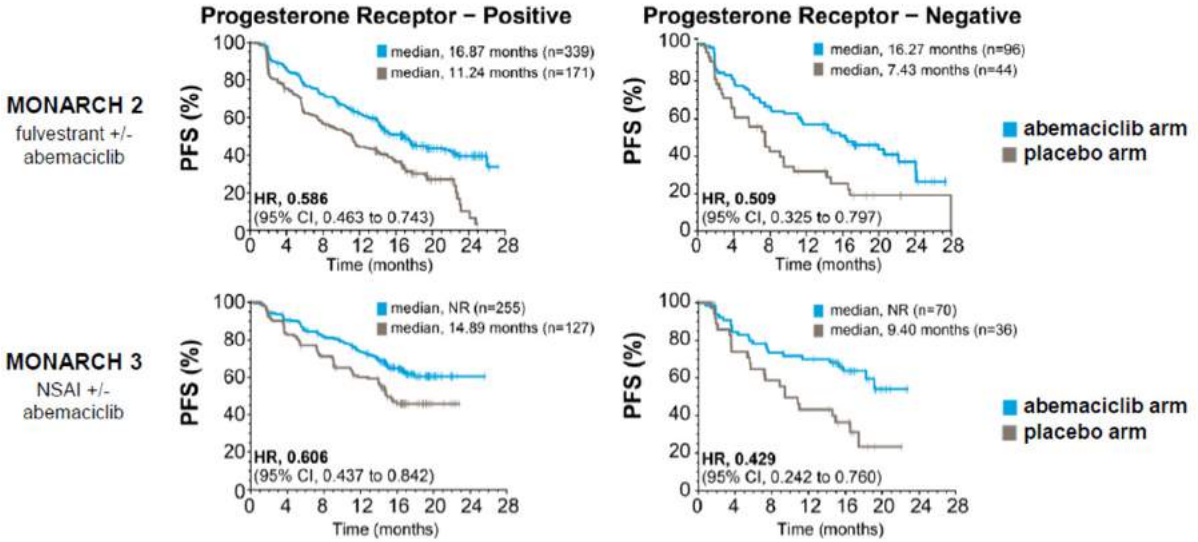

Tumor Grade

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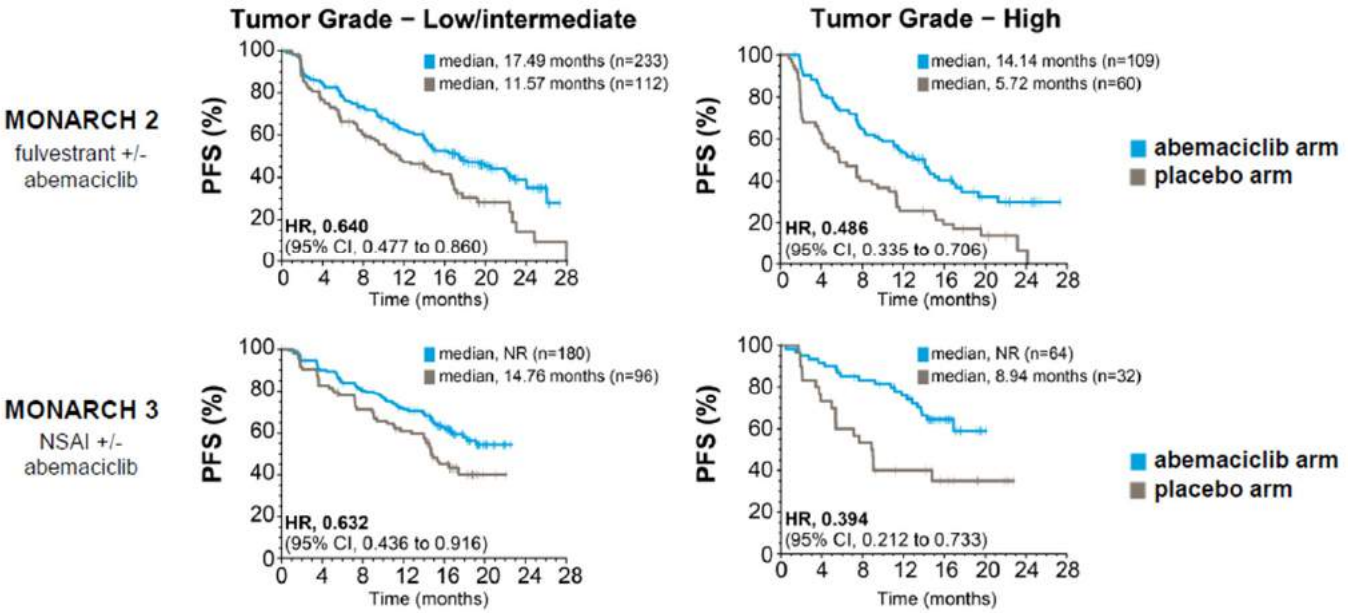
MONARCH 2
fulvestrant +/- abemaciclib

MONARCH 3
NSAI +/- abemaciclib



Bone-only Metastases

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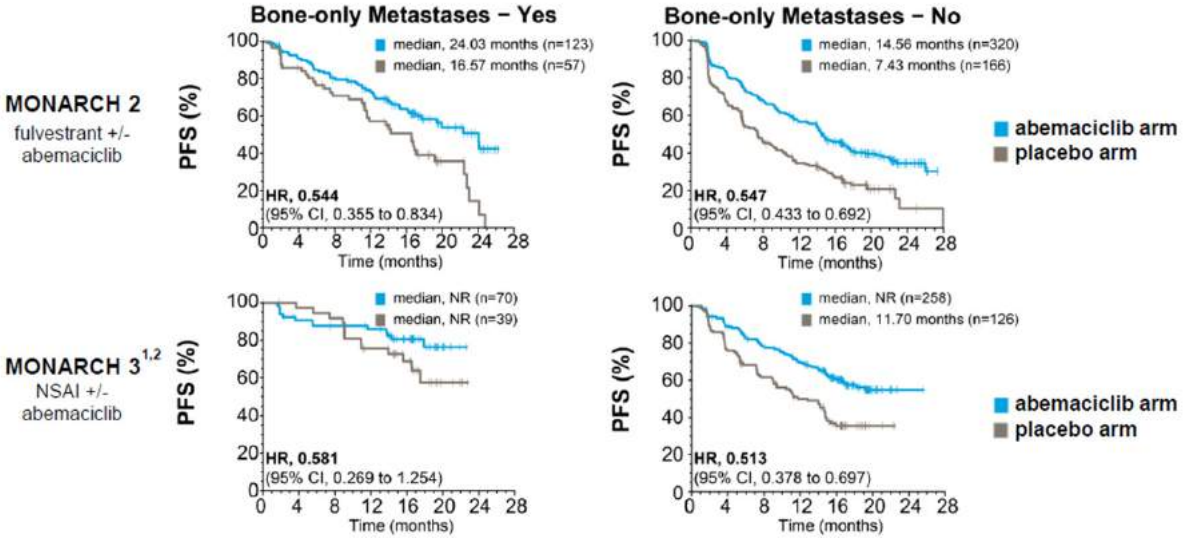
MONARCH 2
fulvestrant +/- abemaciclib

MONARCH 3[1,2]
NSAI +/- abemaciclib



ECOG Performance Status

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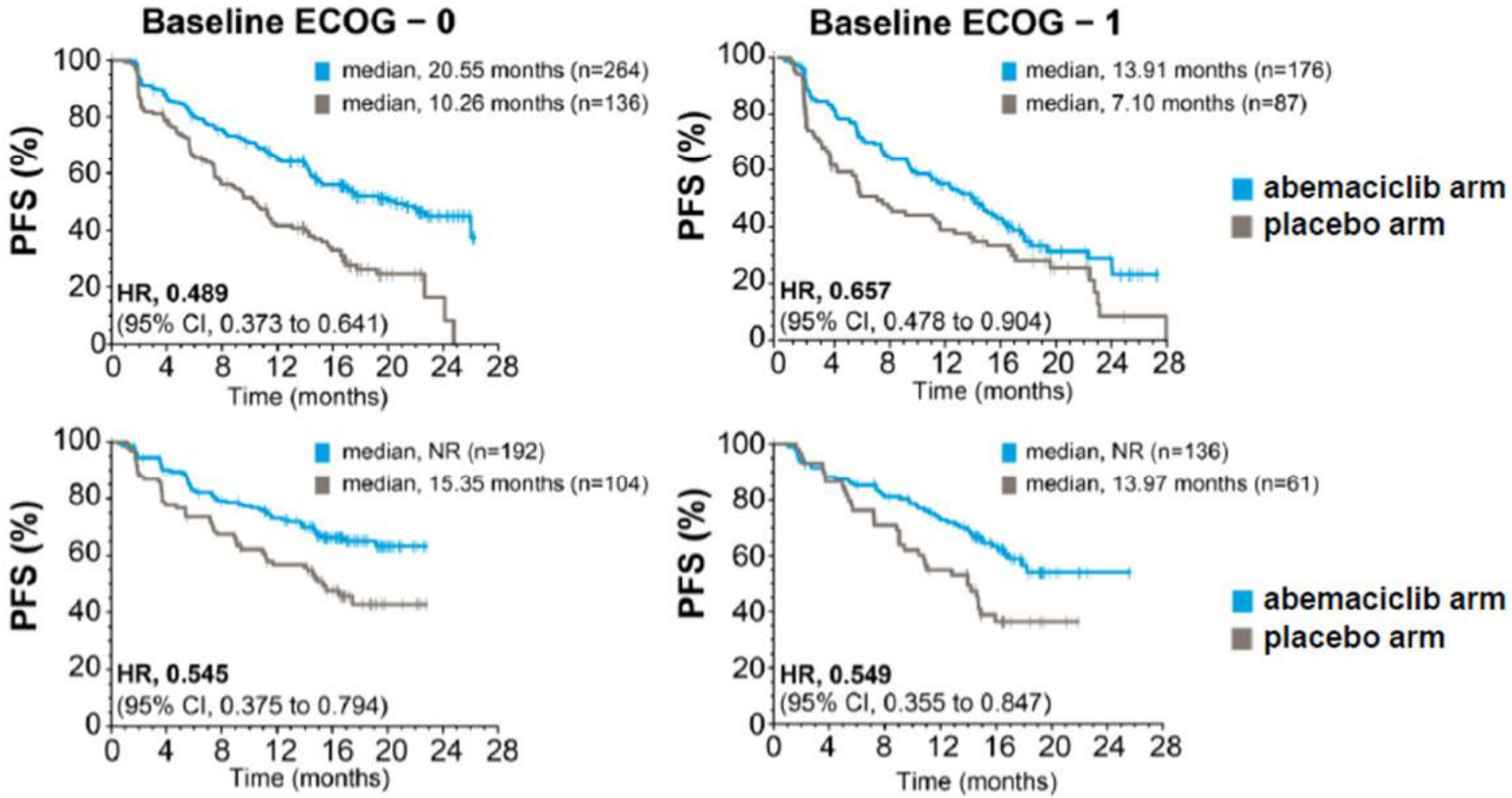
MONARCH 2
fulvestrant +/-
abemaciclib

MONARCH 3
NSAI +/-
abemaciclib



Conclusions

- These exploratory analyses from over 1000 patients treated in MONARCH 2 and MONARCH 3 demonstrated that all subgroups benefited from the addition of abemaciclib to endocrine therapy
- Abemaciclib in combination with endocrine therapy offered the largest benefit (PFS and ORR) in patients with clinical characteristics that make the prognosis more concerning
  - The largest improvements were in patients with liver metastases, PgR-negative tumors, or high grade tumors
- In the first-line setting, for patients with a short TFI, a substantial improvement from the addition of abemaciclib to endocrine therapy was observed
- Further data are needed to inform treatment strategies for patients with more favorable baseline prognostic factors (e.g., bone-only, long TFI)