MOONSHOT FROM SAN ANTONIO

12/6/2022 THROUGH 12/10/2022

SABCS 45

TACOS 4/22/23

Disclosures/Acknowledgements

I am an employed physician at Dignity Health
I am have been volunteer at Casting for Recovery

Thank you to Ann Partridge for permission to use her slide set from the POSITIVE trial
Thank you Sudeep Gupta for use of slides
Thank you Ruth O'Regan for use of slides

Thanks to Neil Love for his dedication to education of medical oncologistsand **hematologists caring for cancer patients**

Thank you, Siddhartha Yadav use of slides

Others have not responded to requests

SABCS UPDATE 2022

- Historical bloviation
- SABCS 2022
  - Adjuvant
    - ER positive
    - Her 2 neu positive
    - TNBC--carboplatin
  - Metastatic
    - ER positive
    - Her 2 neu positive (her 2 low)
    - TNBC

HISTORICAL BLOVIATION

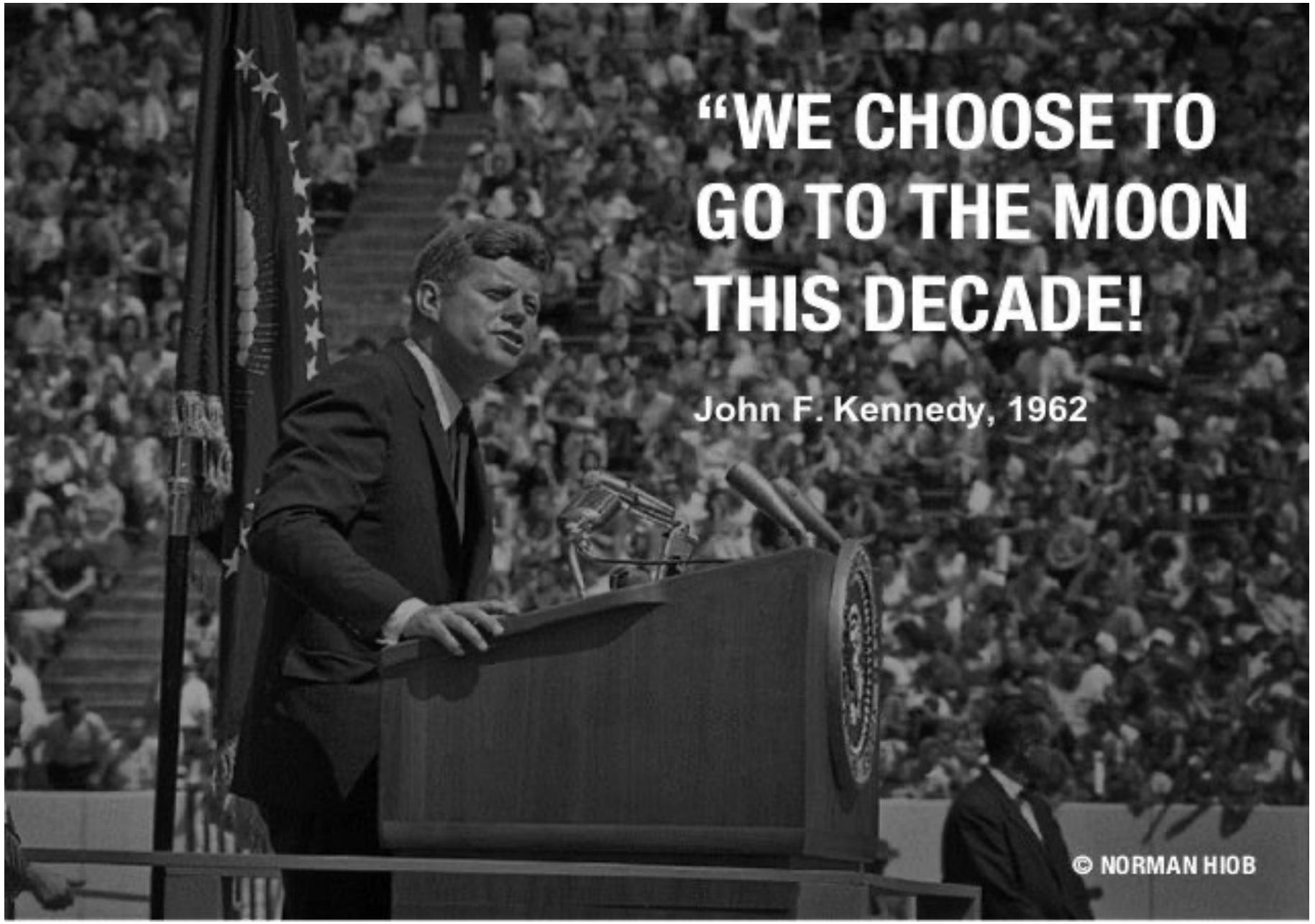
- War on cancer 1971
- 1972 board exam in medical oncology offered for 1st time
- 1978 1st SABCS

- Before that, JFK, 9/12/1962 “We choose to go to the moon”

President Richard Nixon signs the war on cancer bill, 12/23/1971, committing 1.5 billon dollars to curing cancer

What is moon shot cancer care?

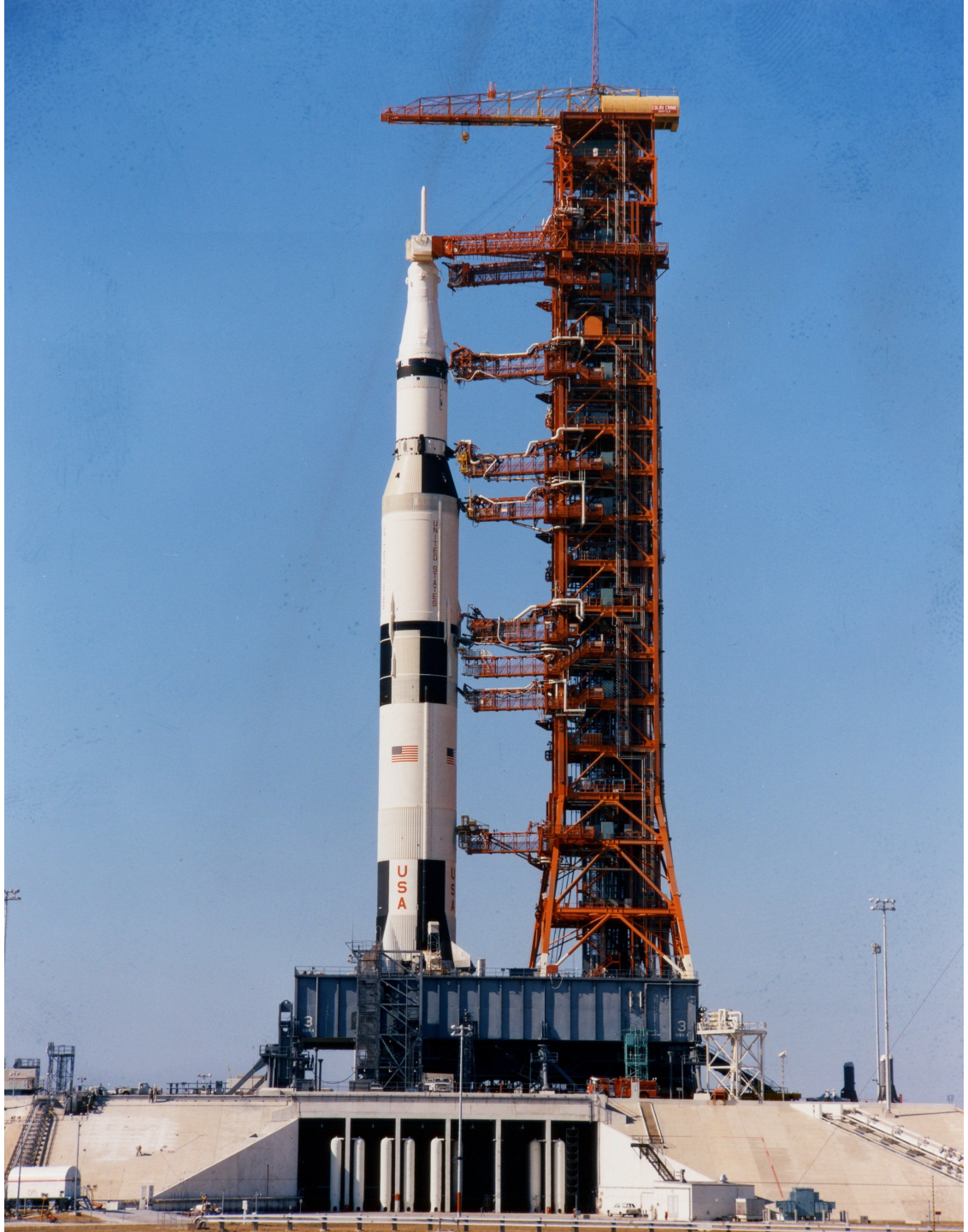
- How did this term get coined?



“We choose to go to the moon. We choose to go to the moon and to do the other things; not because they are easy but because they are hard.”

FROM THE EARTH TO THE MOON

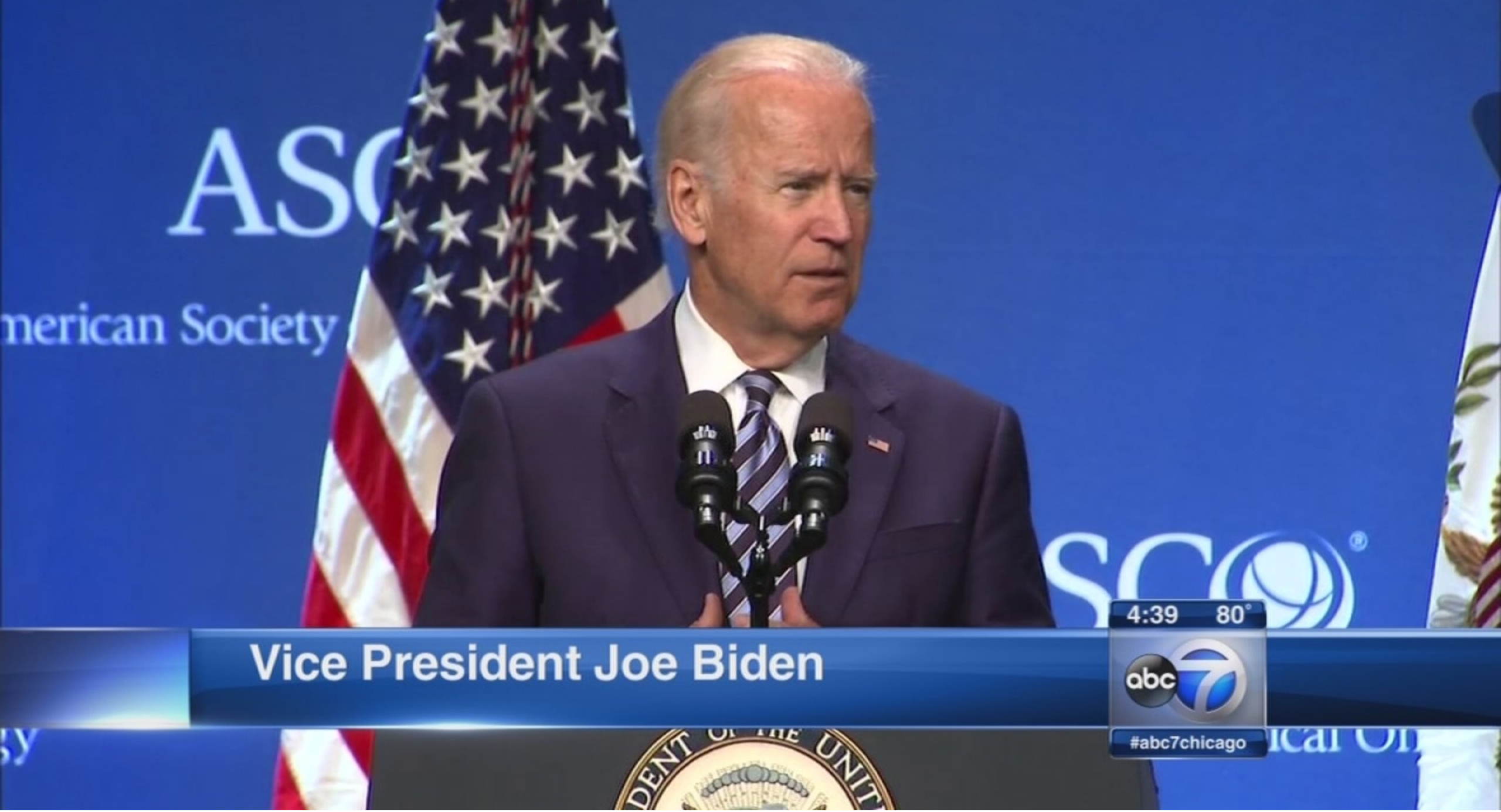
Jules Verne



Launchpad, July, 1969
Apollo 11

“One small step for man; one giant leap for mankind.” 7/20/1969

- JFK’S vision and the fact it was fulfilled has been the envy of politicians ever since but so far not duplicated


merican Society
Vice President Joe Biden
4:39 80°
abc 7
#abc7chicago

IS THE MOON THE LIMIT?

HOW FAR CAN WE GO?

https://media.techeblog.com/images/nasa-osiris-rex-spacecraft-asteroid-101955-bennu-landing.jpg

Osiris Rex mission timeline
“Origins Spectral Resource Security Identification Regolith Explorer”

- 9/8/2016 launch
- 9/22/2017 Earth flyby
- 12/3/2018 arrival at Asteroid Bennu
- 10/20/2020 Touch and go (TAG) sample collection
- 4/17/2021 Osiris Rex completes its last flyover of Bennu
- 5/10/2021 Osiris Rex began its return journey back to earth-2.91 million miles from earth
- 9/24/2023 Sample capsule expected to be delivered to earth
- $1.16 billion, 7 years from launch, 27,700 mph,


HOUSE BILL 2144

SABCS 45

Did we hit the moon? Asteroid Bennu? Or somewhere in between?
Are we still on the launching pad? Or did we just get shot down?

SABCS UPDATE 2022

Adjuvant

- ER positive
- Her 2 neu positive
- TNBC--carboplatin

Metastatic

- ER positive
- Her 2 neu positive
- TNBC

SABCS 45 Adjuvant Treatment ER Positive

MONARCHE update

POSITIVE TRIAL {Pregnancy Outcomes and Safety of Interrupting Therapy for women with endocrine responsive breast cancer} (IBCSG 48-14/BIG 8-13)

RXsponder update (TAILORx)

Baby TAM

SOFT/TEXT update

MonarchE

monarchE Study Design (NCT03155997) (4y efficacy)

HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

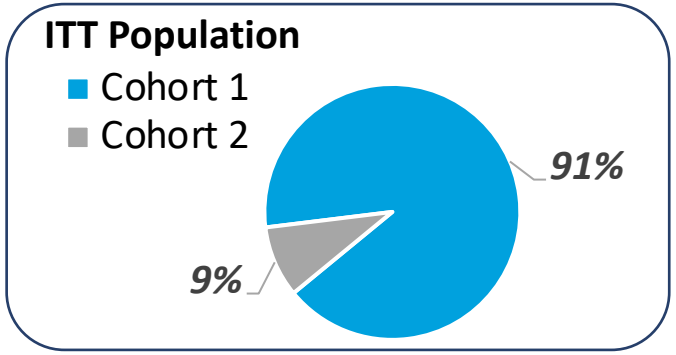
On-study treatment period
2 years

Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

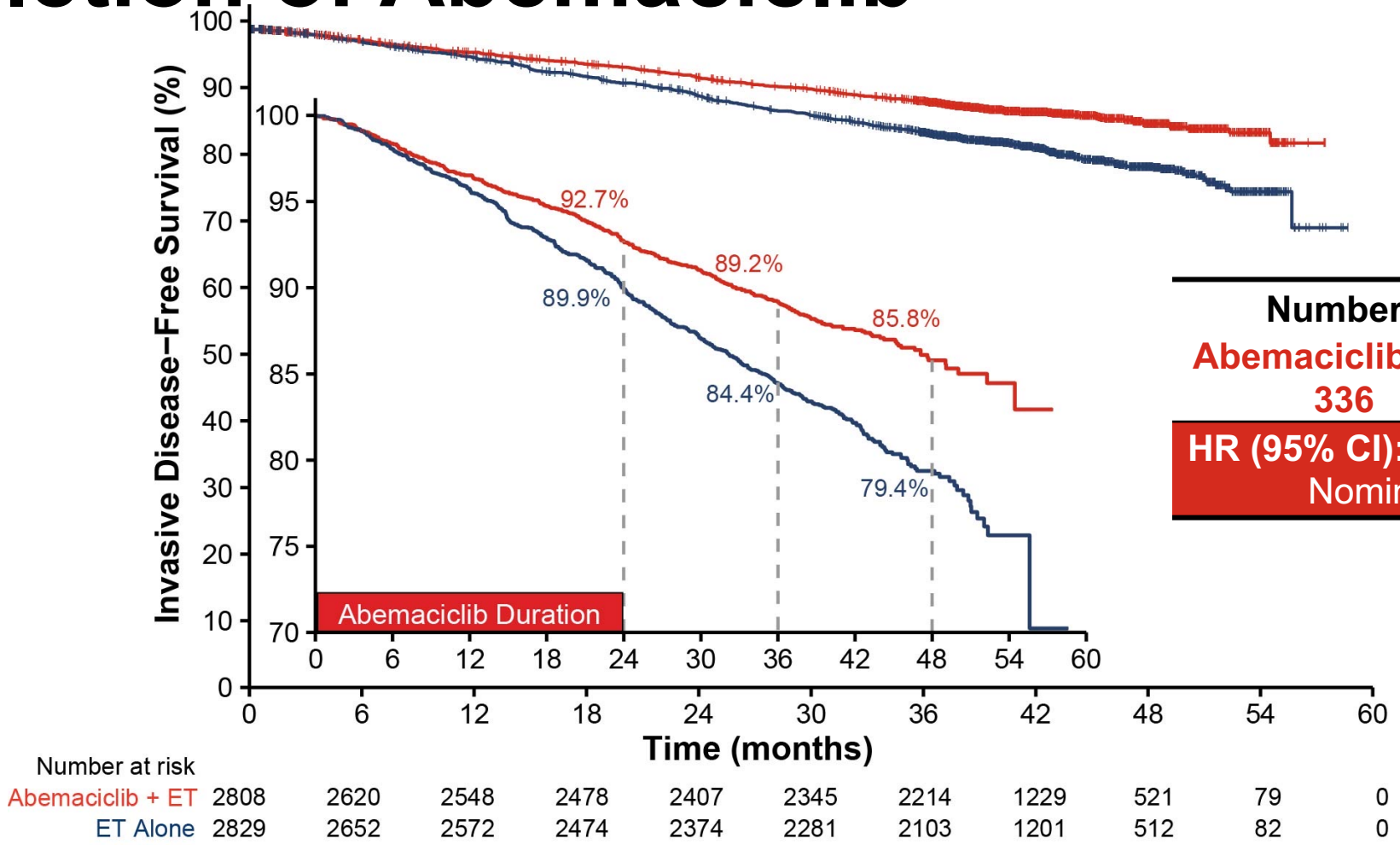
Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO



IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



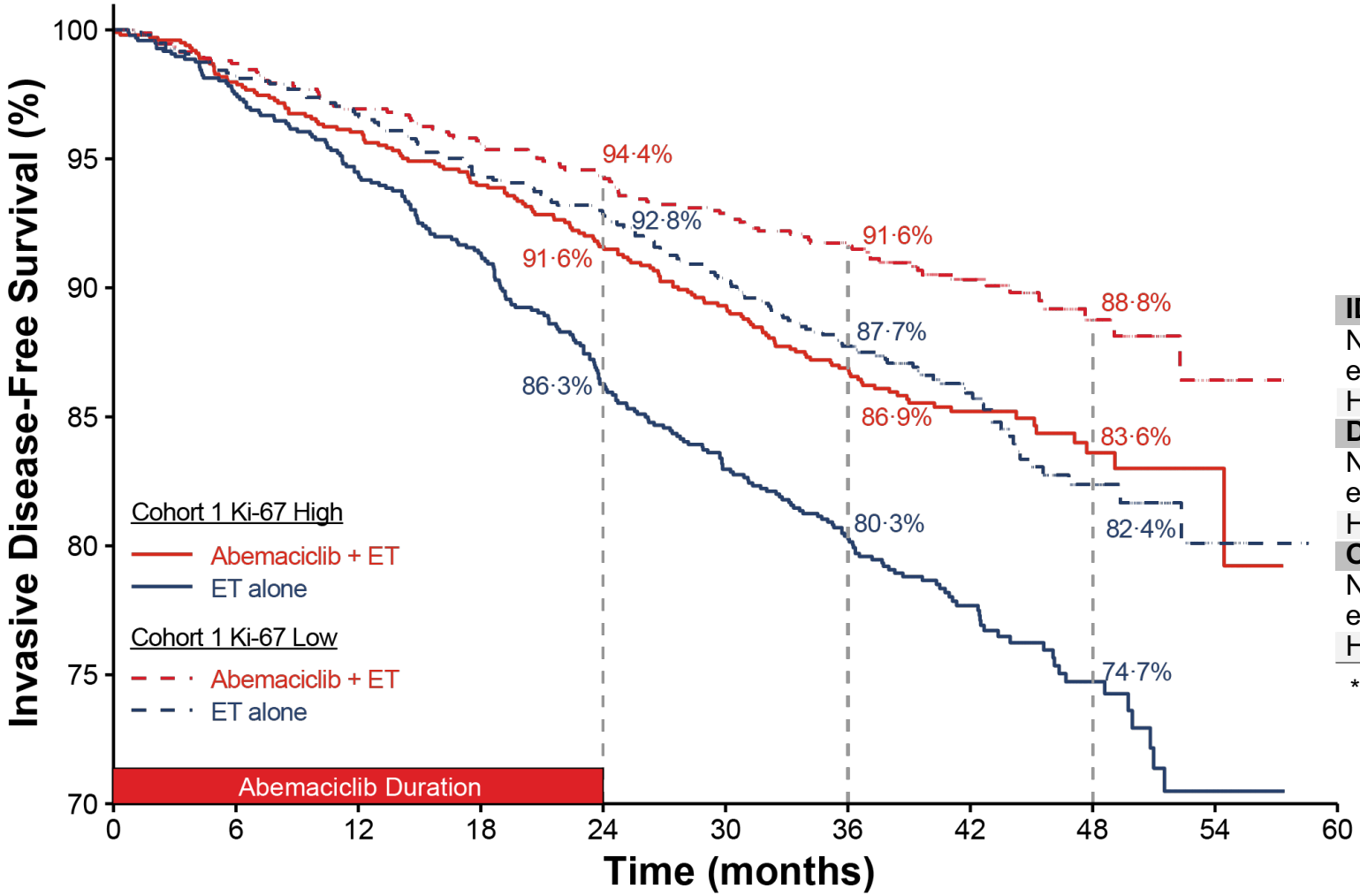
Number of IDFS events

Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit



	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Abemaciclib approved in the adjuvant setting 2021 BUT with KI67 > 20%

3/3/2023 FDA no longer requires KI67 > 20%

SABCS 45 adjuvant ER positive

- POSITIVE trial

San Antonio Breast Cancer Symposium – December 6-10, 2022

Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer

Initial Results from the **POSITIVE Trial**
(IBCSG 48-14 / BIG 8-13 / Alliance A221405)

Ann Partridge on behalf of the POSITIVE Consortium

A H Partridge, S M Niman, M Ruggeri, F A Peccatori, H A Azim Jr, M Colleoni, C Saura, C Shimizu, A Barbro Sætersdal, J R Kroep, A Mailliez, E Warner, V F Borges, F Amant, A Gombos, A Kataoka, C Rousset-Jablonski, S Borstnar, J Takei, J Eon Lee, J M Walshe, M Ruíz Borrego, H CF Moore, C Saunders, V Bjelic-Radisic, S Susnjar, F Cardoso, K L Smith, T Ferreiro, K Ribi, K J Ruddy, S El-Abed, M Piccart, L A Korde, A Goldhirsch†, R D Gelber, O Pagani

BACKGROUND

IBCSG

- Many young breast cancer (BC) survivors desire pregnancy[1,2]
- Retrospective evidence shows pregnancy after BC does not worsen disease outcomes, regardless of hormone receptor (HR) status[3]
- Standard 5-10 years of adjuvant endocrine therapy (ET) compromises conception in women with (HR+) disease[4]
- **Pregnancy after BC and interruption of ET to attempt pregnancy have not been studied prospectively**

1 Ruddy KJ et al. J Clin Oncol 2014;32(11):1151-6. DOI: 10.1200/JCO.2013.52.8877
2 Ruggeri M et al. Breast 2019;47:85-92. DOI: 10.1016/j.breast.2019.07.001
3 Lambertini M et al. J Clin Oncol 2021;39(29):3293-3305. DOI: 10.1200/JCO.21.00535
4 Paluch-Shimon S et al. Ann Oncol. 2022 Aug 4:S0923-7534(22)01858-0

ELIGIBILITY

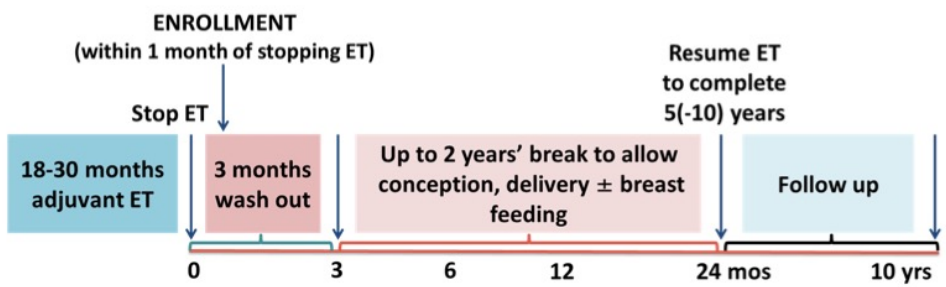
IBCSG

- Premenopausal women wishing to become pregnant
- Age ≤42 years at study entry
- At least 18 months and no more than 30 months of prior adjuvant ET for stage I-III HR+ BC
  - Prior neo/adjuvant chemotherapy ± fertility preservation allowed
- No clinical evidence of recurrence

TRIAL PROCEDURES

IBCSG

- Planned ET interruption (within 1 month of trial enrollment):
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including 3-months washout period
  - If no pregnancy by 1 year, fertility assessment strongly recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs
- Long-term follow-up



ENDPOINTS

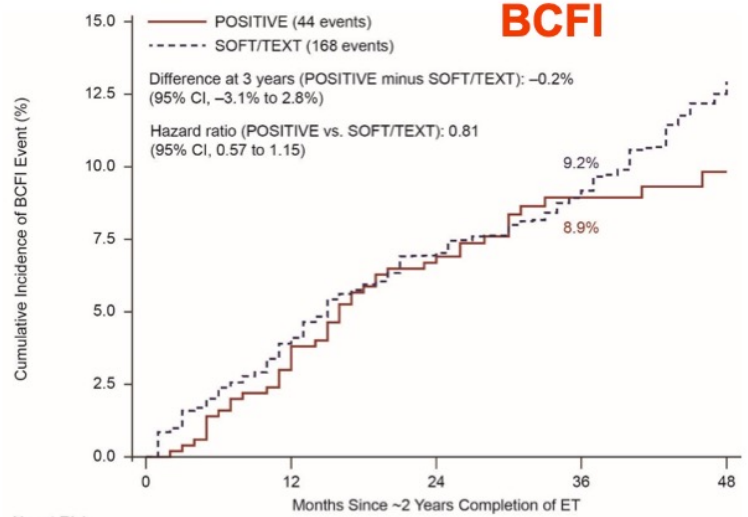
IBCSG

- **Primary**
  - **Breast cancer-free interval (BCFI)** = time from enrollment (after 18-30 months of ET) to the first ipsilateral / locoregional / contralateral invasive disease or distant recurrence
- **Secondary**
  - Pregnancy outcomes
  - Offspring outcomes
  - Breastfeeding
  - Use of assisted reproductive technology (ART)
  - Adherence to endocrine treatment
  - Distant recurrence-free interval (DRFI) = time from enrollment to the first BC distant recurrence

BREAST CANCER OUTCOMES – POSITIVE & SOFT/TEXT

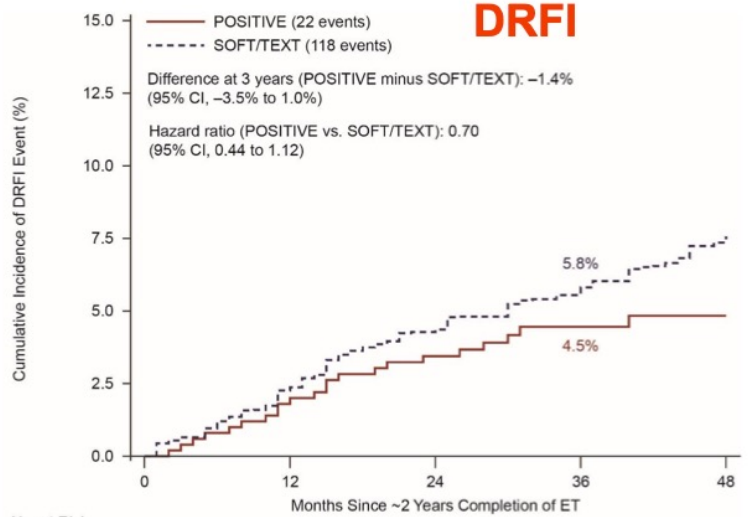
IBCSG

BCFI



No. at Risk					
POSITIVE	516	470	412	270	144
SOFT/TEXT	1499	1336	1159	943	646

DRFI

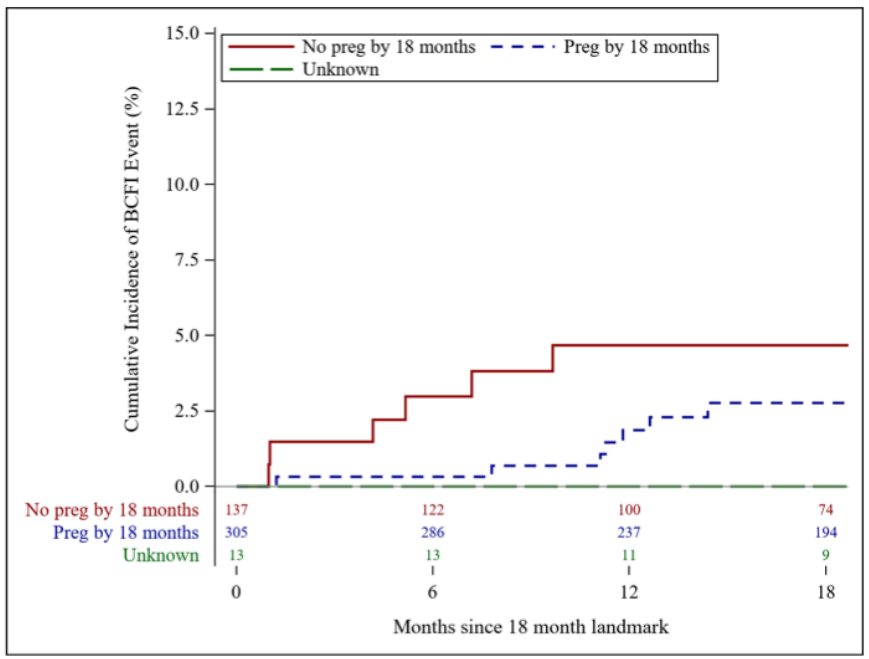


No. at Risk					
POSITIVE	516	479	428	285	153
SOFT/TEXT	1499	1349	1179	969	668

BCFI FOR PREGNANT vs NON PREGNANT PATIENTS

IBCSG

18-month Landmark Analysis



Time-dependent Cox Models

BCFI hazard ratios

(pregnant vs. not pregnant):

0.55 (95% CI: 0.28 to 1.06) – univariable

0.53 (95% CI: 0.27 to 1.04) – multivariable*

* including age, BMI, lymph node status, prior chemo, and prior AI

PREGNANCY OUTCOMES

IBCSG

- 368 (74%) of the 497 women in the secondary endpoint population had at least one pregnancy (70% within 2 years) for a total of 507 pregnancies
- 317 had at least one live birth (64% of all women, 86% of those who became pregnant)

	N	% of 497	% of 368
Secondary endpoint population	497	100%	
At least one on trial pregnancy	368	**74%**	100%
At least one live birth (full-term or preterm)	317	**64%**	**86%**
At least one miscarriage	93	19%	25%
At least one elective abortion	16	3%	4%
At least one stillbirth/neonatal death	1/1	0.2% / 0.2%	0.3% / 0.3%

Note: 110 women had more than one pregnancy, and may contribute information to more than one row

- **Delivery**
  - Vaginal 66%
  - Cesarean section 34%
- **Pregnancy complications**
  - 11% of pregnancies
  - Most common: Hypertension/preeclampsia 3% Diabetes 2%

OFFSPRING OUTCOMES

IBCSG

- 350 live births for the 317 women who had at least 1 live birth
- 335 singleton births and 15 sets of twins (365 offspring)
- 62% of 317 women reported breastfeeding

	N	%
Total offspring	365	100%
Low birth weight (<2500g)		
Yes	29	8%
No	**334**	**92%**
Missing/Unknown	2	0.5%
Birth defects		
Yes	8	2%
No	**350**	**96%**
Missing/Unknown	7	2%

CONCLUSIONS

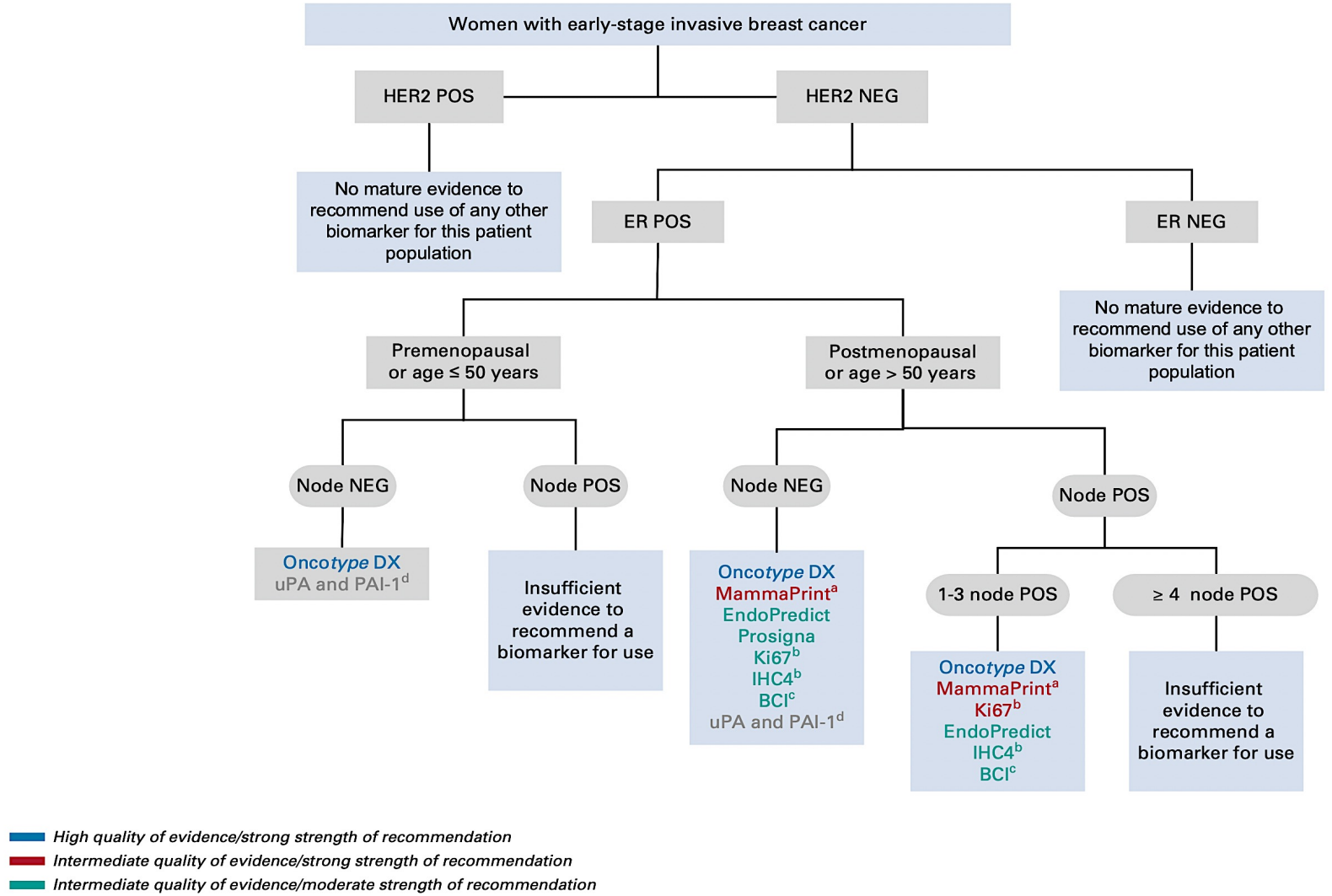
IBCSG

- In POSITIVE, temporary interruption of ET to attempt pregnancy among women who desire pregnancy does not impact short-term disease outcomes
- 74% of women had at least one pregnancy, most (70%) within 2 years
- Birth defects were low (2%), not clearly associated with treatment exposure
- Follow-up to 2029 planned to monitor ET resumption and disease outcomes
- **These data stress the need to incorporate patient-centered reproductive healthcare in the treatment and follow-up of young women with breast cancer**

SABCS 45 Adjuvant Treatment ER positive

- RXsponder

Biomarkers for Adjuvant Endocrine and Chemotherapy in Localized Breast Cancer: ASCO Guideline Update



Andre F et al. *J Clin Oncol* 2022;40(16):1816-37.

San Antonio Breast Cancer Symposium®, December 7-10, 2021

RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007

Kevin Kalinsky, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Miguel Martin, Catherine M Kelly, Manuel Ruiz-Borrego, Miguel Gil Gil, Claudia Arce-Salinas, Etienne G.C. Brain, Eun Sook Lee, Jean-Yves Pierga, Begoña Bermejo, Manuel Ramos-Vazquez, Kyung Hae Jung, Jean-Marc Ferrero, Anne F. Schott, Steven Shak, Priyanka Sharma, Danika L. Lew, Jieling Miao, Debasish Tripathy, Lajos Pusztai, Gabriel N. Hortobagyi

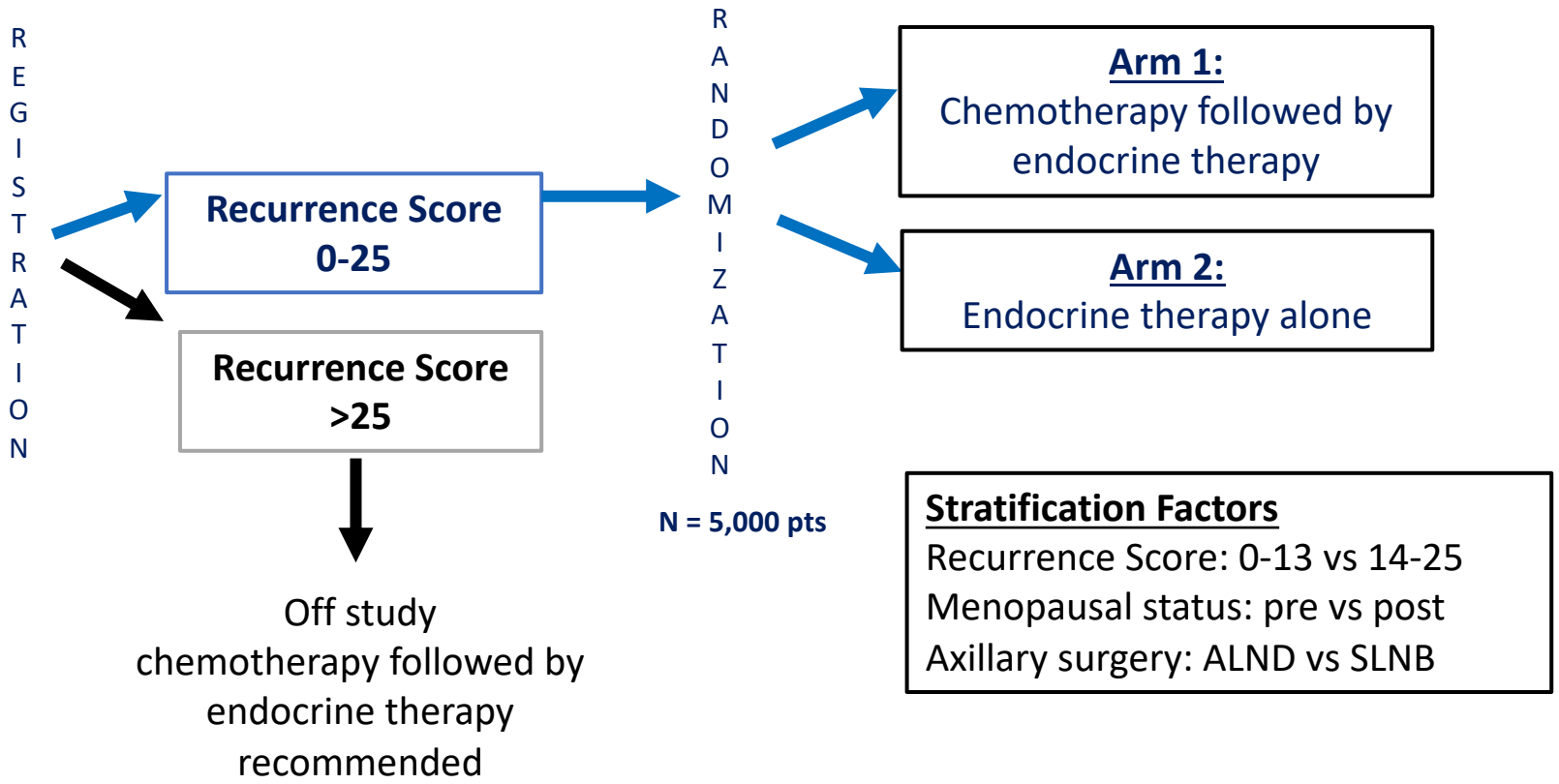
On Behalf of the RxPonder Investigators

SABCS 2021;Abstract GS2-07.

RxPONDER Trial Schema

Key Entry Criteria

- Women age ≥18
- ER and/or PR ≥1%, HER2-negative breast cancer with 1*-3 positive LN without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy†
- Axillary staging by SLNB or ALND



* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

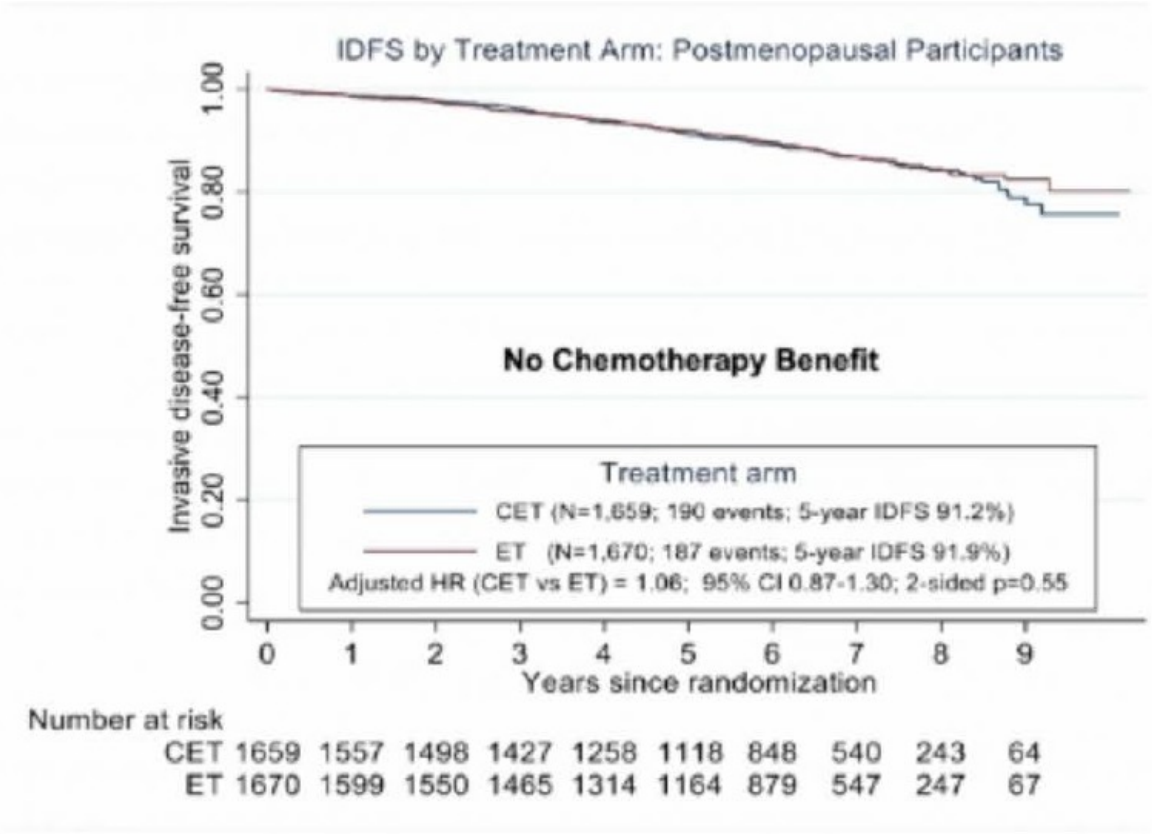
† Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

LN = lymph node; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; pts = patients

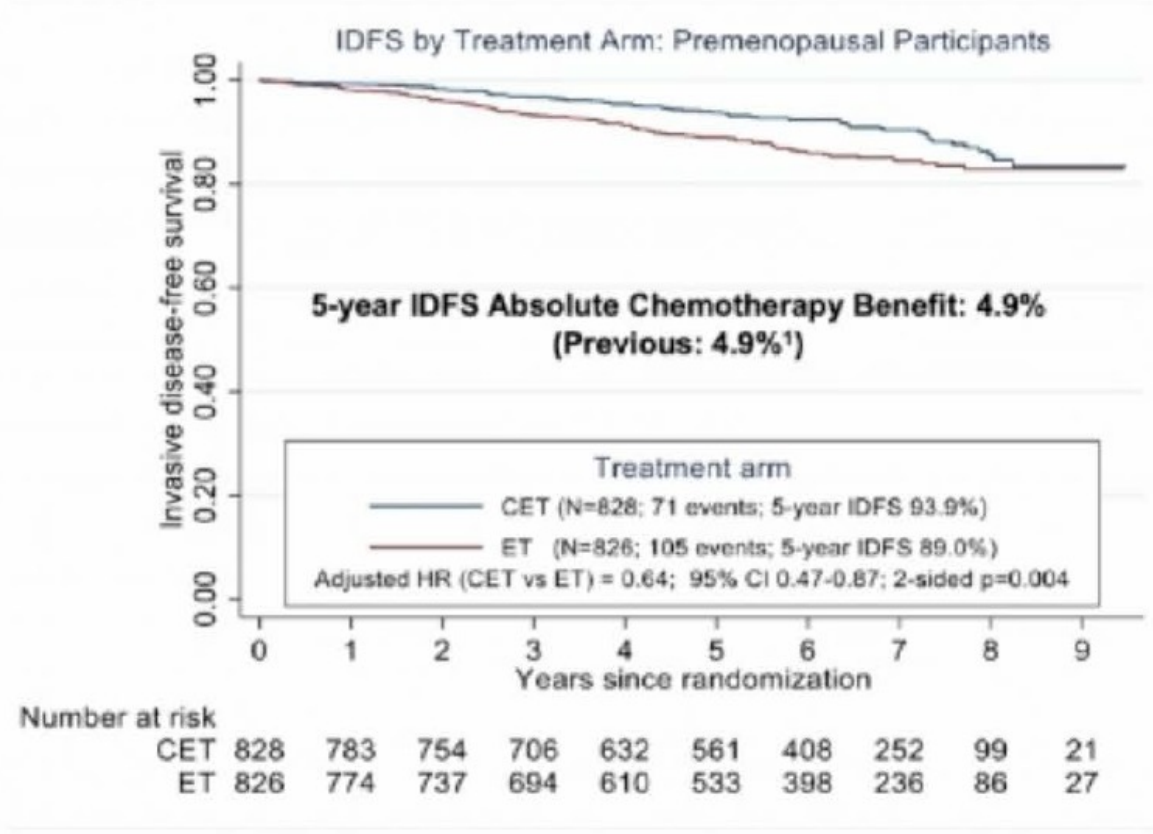
Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RxPONDER Updated Analysis: IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal

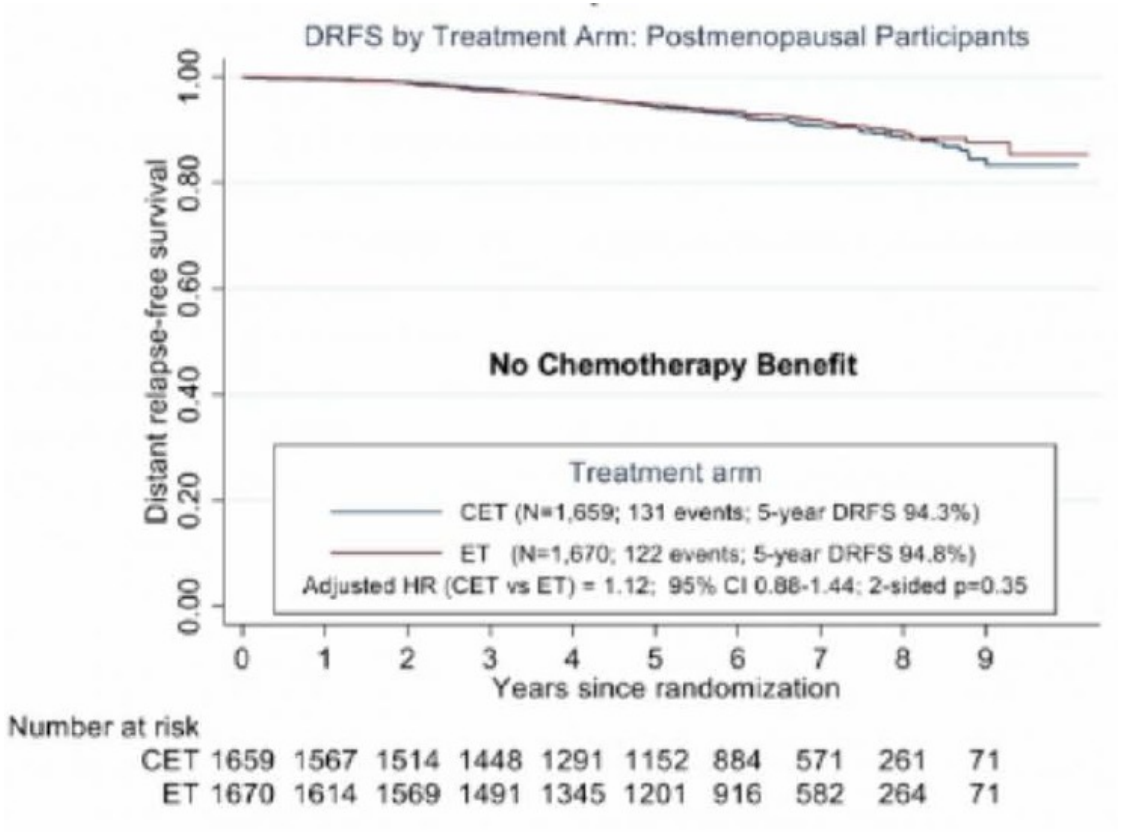


IDFS = invasive disease-free survival

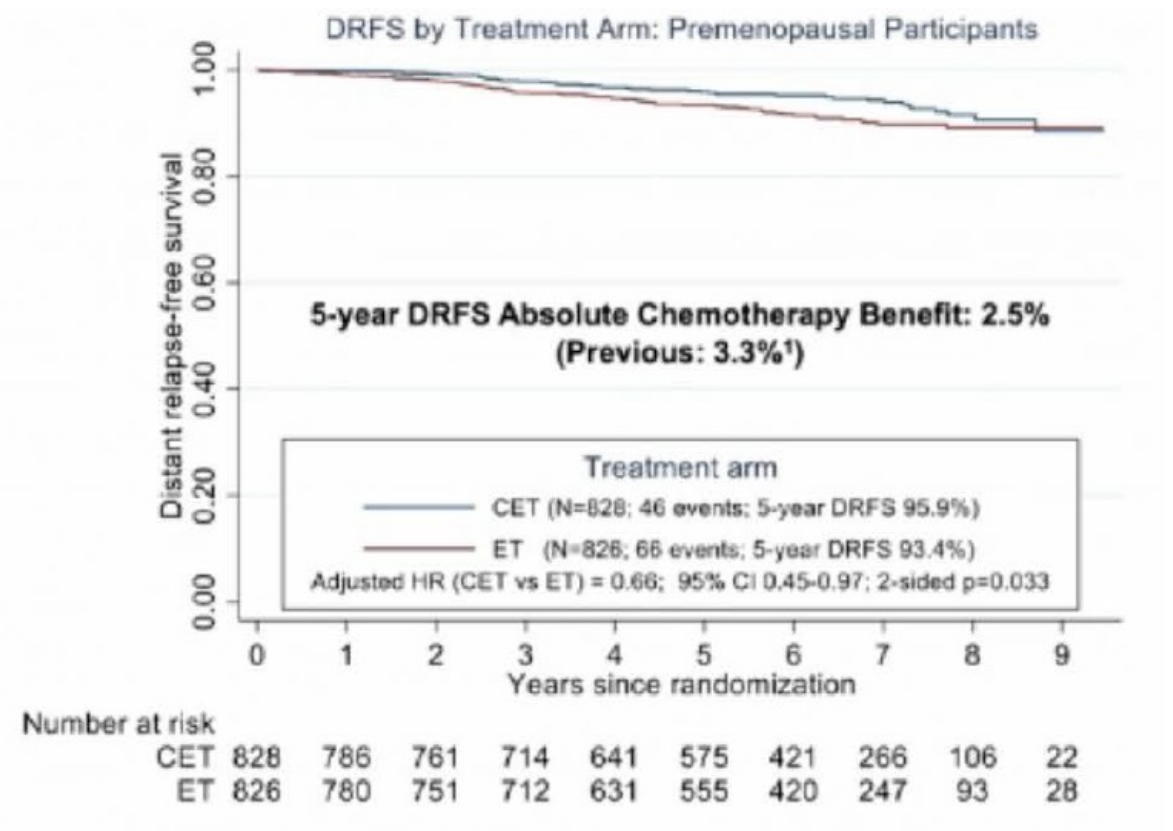
Kalinsky K et al. SABCS 2021;Abstract GS2-07.

RxPONDER Updated Analysis: DRFS Stratified by Menopausal Status

Postmenopausal



Premenopausal

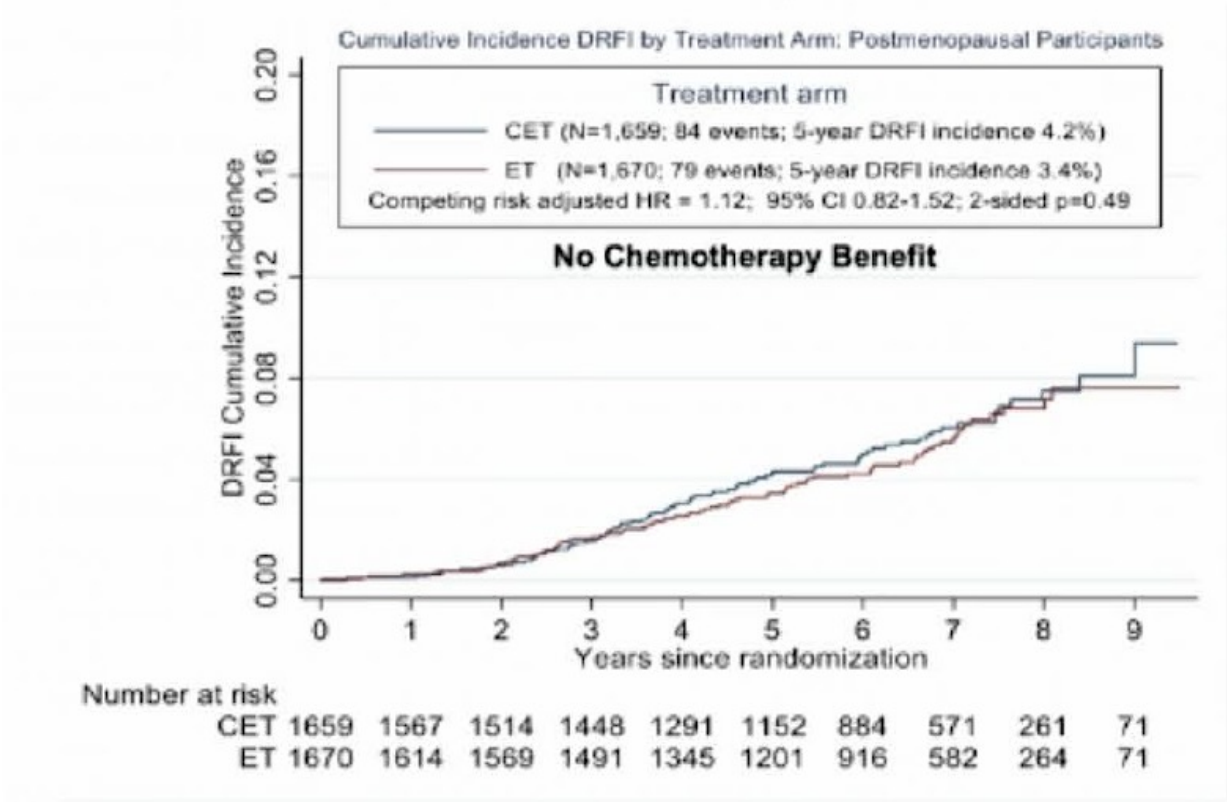


DRFS = distant recurrence-free survival

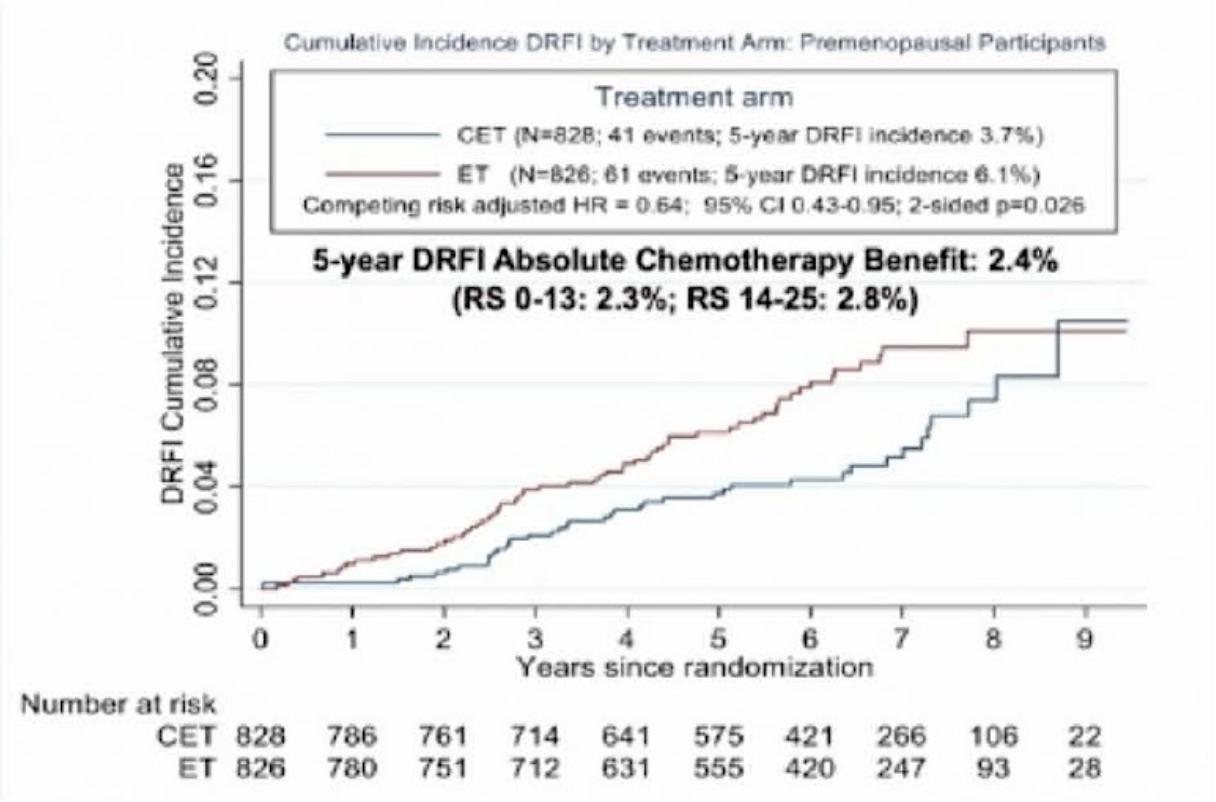
Kalinsky K et al. SABCS 2021;Abstract GS2-07.

RxPONDER New Analysis: DRFI Stratified by Menopausal Status

Postmenopausal



Premenopausal



Time from randomization assignment to date of first invasive recurrence (distant) or death from breast cancer

In multivariate analysis, higher RS (continuous) and larger tumor size remained independently prognostic in both treatment arms

DRFI = distant recurrence-free interval

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

TAILORx update

Trial Assigning IndividuaLized Options for TReatment (TAILORx): An Update Including 12-Year Event Rates

Joseph A. Sparano, Robert J. Gray, Della F. Makower, Kathy S. Albain, Daniel F. Hayes, Charles E. Geyer, Elizabeth Claire Dees, Matthew P. Goetz, John A. Olson, Jr., Tracy G. Lively, Sunil Badve, Thomas J. Saphner, Timothy J. Whelan, Virginia Kaklamani, & George W. Sledge, Jr.

on behalf of the TAILORx Investigators

Funding: U.S. NIH/NCI U10CA180820, U10CA180794, UG1CA189859, UG1CA190140, UG1CA233160, UG1CA23337, UG1CA189869; U.S. Postal Service Breast Cancer Stamp Fund; Canadian Cancer Society Research Institute grants 015469, 021039; Breast Cancer Research Foundation, Komen Foundation.

TAILORx Study Design: Treatment Assignment & Randomization

Accrued Between April 2006 – October 2010

Key Eligibility Criteria

- **Node-negative**
- **ER-pos, HER2-neg**
- **T1c-T2 (high-risk T1b)**

Preregister – Oncotype DX RS (N=11,232)

Register (N=10,273)

Statistical Design

- **Non-inferiority - IDFS**
- **HR 1.332 (90 vs. 87% 5-yr DFS)**
- **Type I 10%, type II 5%**
- **Full info– 835 IDFS events**

ARM A: Low RS 0-10
(N=1619 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors:
Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

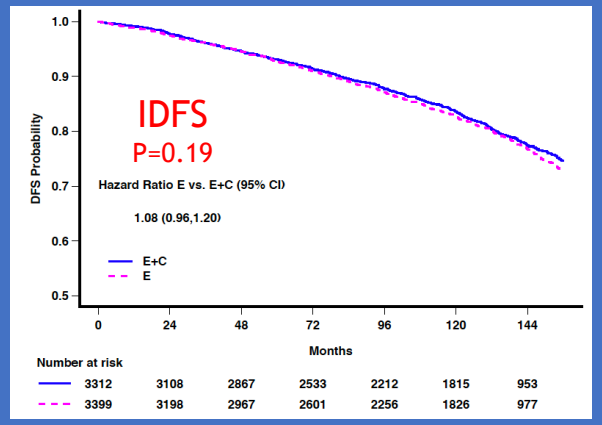
ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

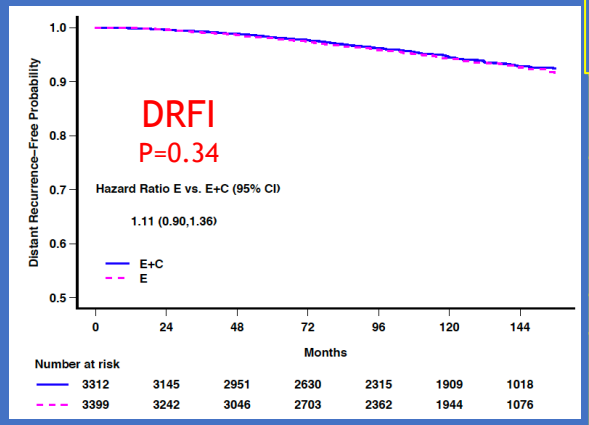
ARM B: Experimental Arm
(N=3399)
ET Alone

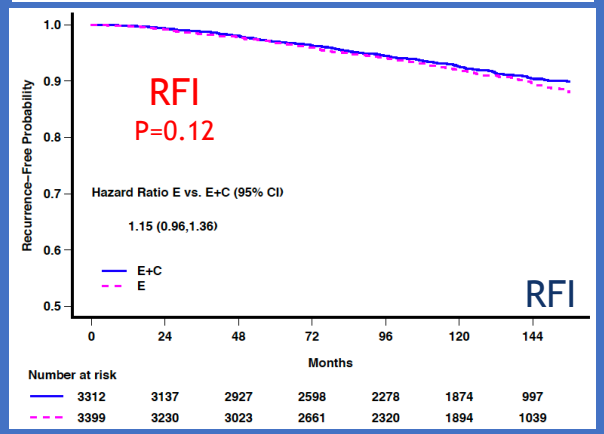
ARM C: Standard Arm
(N=3312)
ET + Chemo

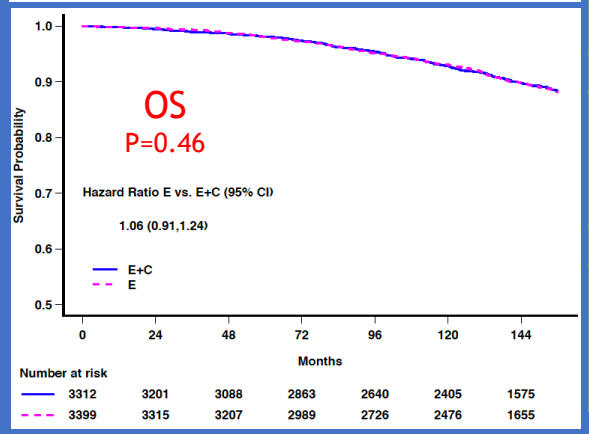
Sparano et al. NEJM 2018
(PMID: 31157962)

TAILORx: Updated Analysis - Kaplan-Meier Curves in RS 11-25 Arms (ITT population)





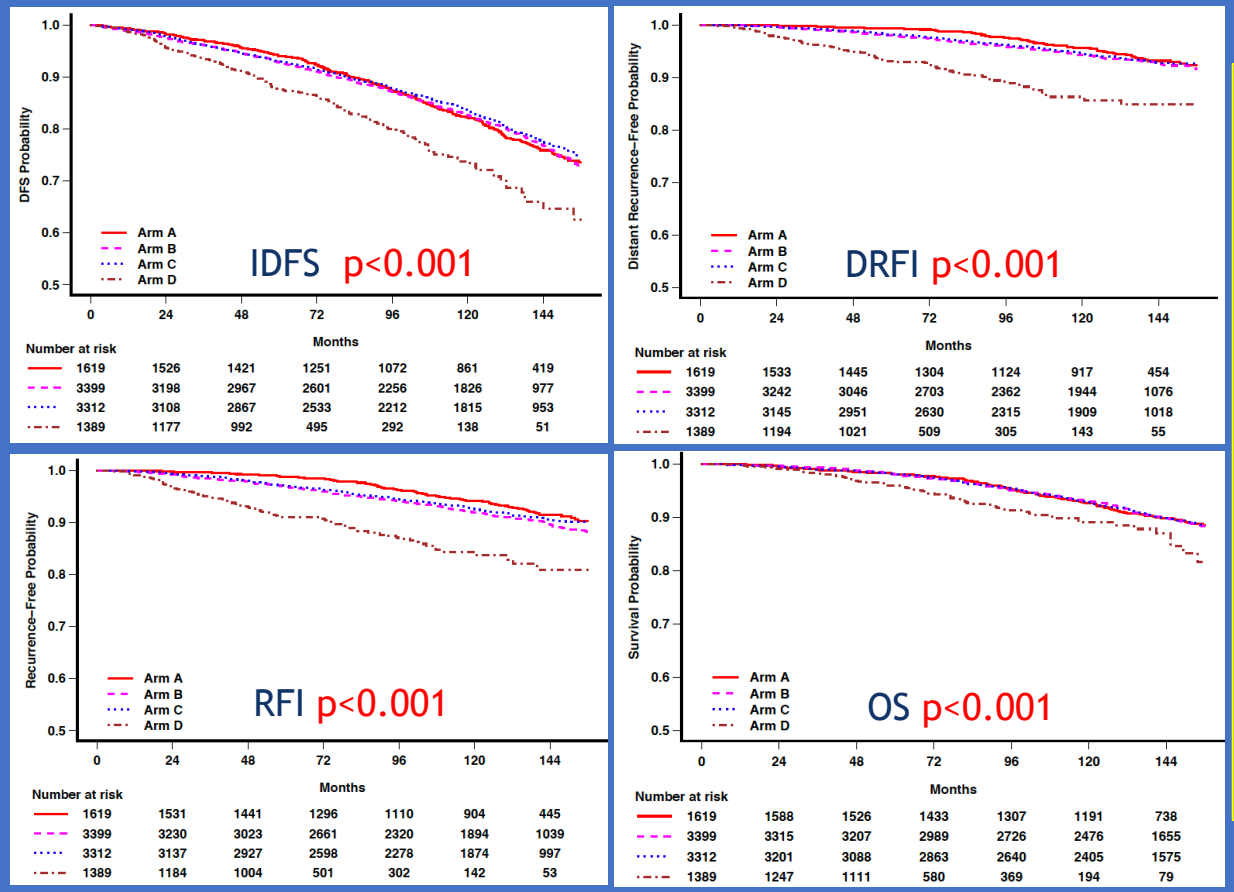




Primary trial conclusions unchanged:
ET non-inferior to CET (N=6711)

Event	Hazard Ratio: Arm B vs. C (95% CI)
IDFS	Primary analysis: 1.08 (0.94, 1.24, p=0.26)
	Updated analysis: 1.08 (0.96, 1.20)
DRFI	Primary analysis: 1.10 (0.85,1.41, p=0.48)
	Updated analysis: 1.11 (0.90, 1.36)
RFI	Primary analysis: 1.11 (0.90, 1.37, p=0.33)
	Updated analysis: 1.15 (0.96, 1.36)
OS	Primary analysis: 0.99 (0.79, 1.22, p=0.89)
	Updated analysis: 1.06 (0.91, 1.24)

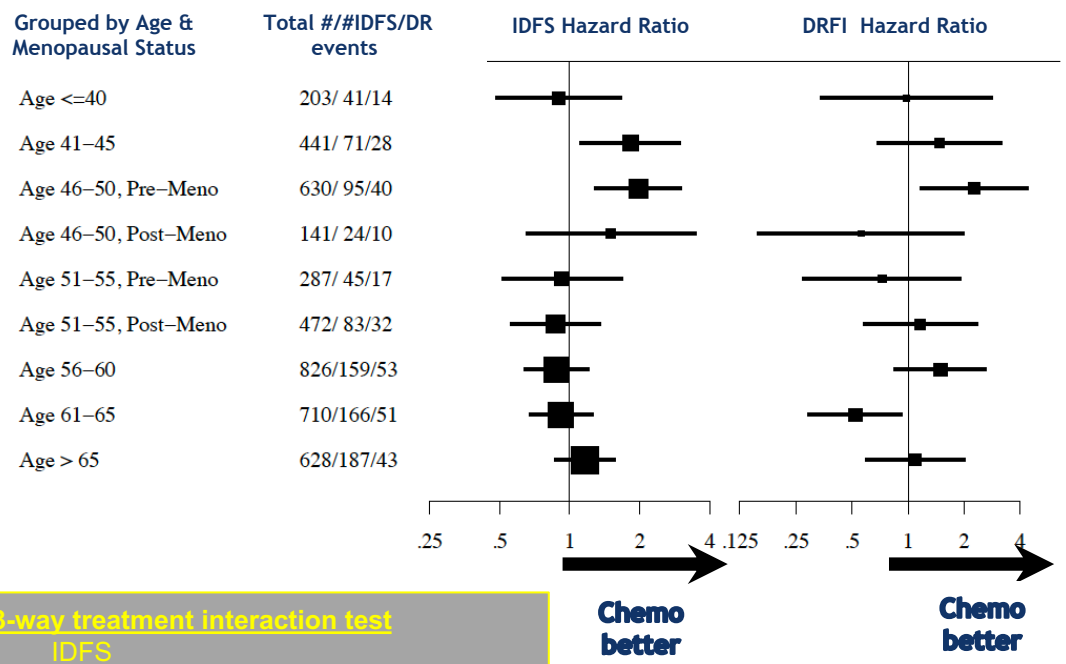
TAILORx: Updated Analysis- Kaplan-Meier Curves in All Arms (ITT population)



12-Year Event Rates (N=9719)

- **RS prognostic for all endpoints**
- **RS 0-10 (Arm A) – ET Alone**
  - DFRI rate: 93.2% (SE 0.8)
  - RFI rate: 91.4% (SE 0.9)
- **RS 11-25 (Arms B & C) – ET vs. CET**
  - < 1 % difference for all endpoints
    - IDFS: 76.8 vs. 77.4%
    - DRFI: 92.6 vs. 92.8%
    - RFI: 89.6 vs. 90.4%
    - OS: 89.8 vs. 89.8%
- **RS 26-100 (Arm D) – CET**
  - DFRI rate: 84.8% (SE 1.8)
  - RFI rate: 80.9 (SE 2.2)

TAILORx: Updated Analysis - Effect of Age, RS, and Clinical Risk on Chemotherapy Benefit (ITT Population)



3-way treatment interaction test

- IDFS
  - Chemo-Age-RS (p=0.007)
  - Chemo-Menopause-RS (p=0.06)
- DRFI
  - Chemo-Age-RS (p=0.43)
  - Chemo-Menopause-RS (p=0.26)

12-Year DRFI Rates in Age ≤ 50 Years & RS 16-25

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

Conclusion

- Adjuvant chemotherapy provides no benefit in postmenopausal ER+/HER2- node negative patients (RS 11-25) and postmenopausal ER+/HER2-, 1-3 + LN (RS 0-25).

- Why did chemotherapy provide benefit in TailoRx and RxPonder premenopausal patients?
  - Endocrine Hypothesis:
    - Endocrine only arm: Inadequate endocrine therapy delivered (mostly tamoxifen and without OFS)
    - Chemotherapy treatment resulted in ovarian suppression not measured adequately
  - Cytotoxic hypothesis: chemotherapy eliminates micro-metastatic disease, independent of endocrine effects[1]

1.Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

Conclusion

- TAILORx and RxPONDER have provided prospective evidence for lack of adjuvant chemotherapy benefit in postmenopausal patients with RS <25
- In contrast, the RS may not be predictive of chemotherapy benefit in age <50 patients
  - NRG BR009 will provide the definitive answer to this question
- The RS is poorly correlated with the proliferation module but highly correlated with ER
- Additional clinical and pathological biomarkers may provide additional insight into those patients that derive benefit from chemotherapy.

1.Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

SABCS 45 adjuvant ER positive (DCIS)

- Baby TAM

San Antonio Breast Cancer Symposium®, December 6-10, 2022

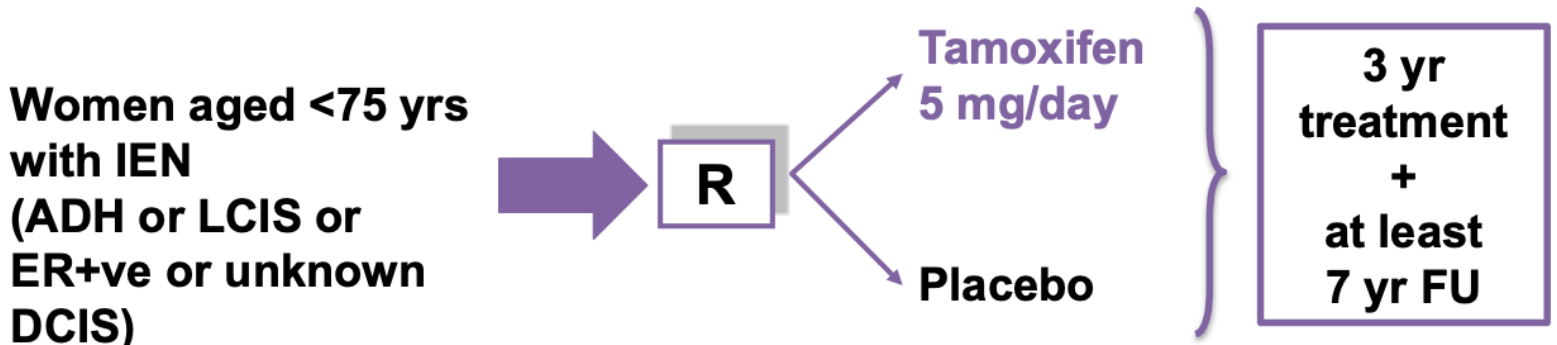
GS408

10 YEAR RESULTS OF A PHASE 3 TRIAL OF LOW-DOSE TAMOXIFEN IN NONINVASIVE BREAST CANCER

Andrea De Censi[1], Matteo Lazzeroni[2], Matteo Puntoni[3], Luca Boni[4], Aliana Guerrieri Gonzaga[2], Tania Buttiron Webber[1], Marianna Fava[1], Irene Maria Briata[1], Livia Giordano[5], Maria Digennaro[6], Laura Cortesi[7], Katia Cagossi[8], Elisa Gallerani[9], Alessia De Simone[10], Anna Cariello[11], Giuseppe Aprile[12], Maria Renne[13], Bernardo Bonanni[2]

(1) E.O. Ospedali Galliera, Genova, Italy; (2) IEO - European Institute of Oncology IRCCS, Milan; (3) Clinical & Epidemiological Research Unit, University Hospital of Parma; (4) IRCCS Ospedale Policlinico San Martino, Genoa; (5)Azienda Ospedaliera-Universitaria Città della Salute e della Scienza di Torino; (6) IRCCS Istituto Tumori Giovanni Paolo II, Bari; (7) Azienda Ospedaliera-Universitaria Policlinico di Modena; (8) Ospedale Bernardino Ramazzini, Carpi; (9) ASST Settelaghi Varese; (10) ICS Maugeri -Centro Medico di Pavia; (11) Ospedale Santa Maria delle Croci, Ravenna; (12) Azienda ULSS8 Berica- Ospedale di Vicenza; (13) Chirurgia Generale Azienda Ospedaliera Mater Domini Catanzaro.

TAM 01- Study Design



Primary endpoint:
Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months for 3 yrs, Mx every year for 10 yrs

Main subject and tumor characteristics (n=500)

	Babytam N=253	Placebo N=247
Age, mean (SD)	54 (9.6)	54 (9.1)
Pre-menopausal, %	43	40
BMI, mean (SD)	25.7 (4.8)	25.3 (4.2)
ADH, %	20	20
LCIS, %	11	10
DCIS, %	69	70
ER/PR+ve/unk DCIS, %	66 / 34	67 / 33
Radiotherapy for DCIS, %	61	61

DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019

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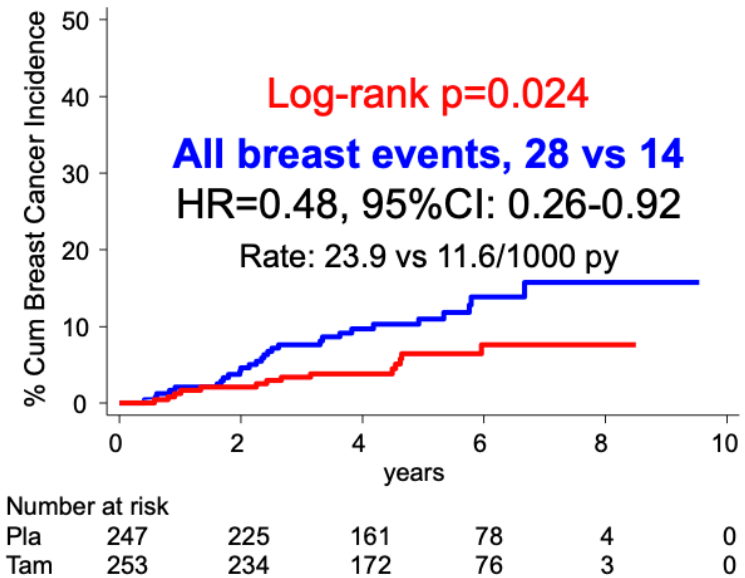
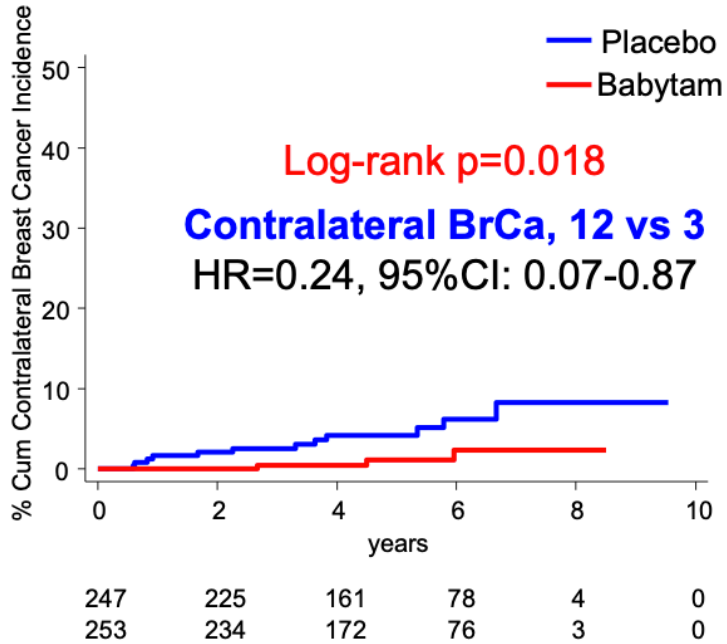
Babytam decreased breast cancer events (n=42) after a median of 5 years (SABCS 2018)





DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019

What happened after SABCS 2018[1]

- ASCO and USPSTF guidelines included babytam for preventive therapy in high risk lesions[2,3]
- NCCN recommends babytam after DCIS if patient is symptomatic or unwilling/unable to take full dose[4]
- Babytam most popular choice in women with high risk lesions in the US, with lower discontinuation rates at 1 year vs 20 mg/d and raloxifene or AIs[5,6]

1. DeCensi et al, *JCO* 37; 2019; 2. Visvanathan et al, *JCO* 2019; 3. Pace et al, *Jama* 322; 2019;
4. NCCN v.4.2022; 5. Bychkovski et al, *BCRT* 193:417, 2022; 6. Patel et al, *JCO* 40(16), e12537. 2022

Follow-up after 5 years

- Annual follow-up with mammography and clinical visit or telephone contact
- All breast cancer events (n=66) centrally adjudicated
- The primary endpoint was invasive breast cancer or DCIS
- Analysis based on a median of 9.7 years (range, 8.3-10.9)

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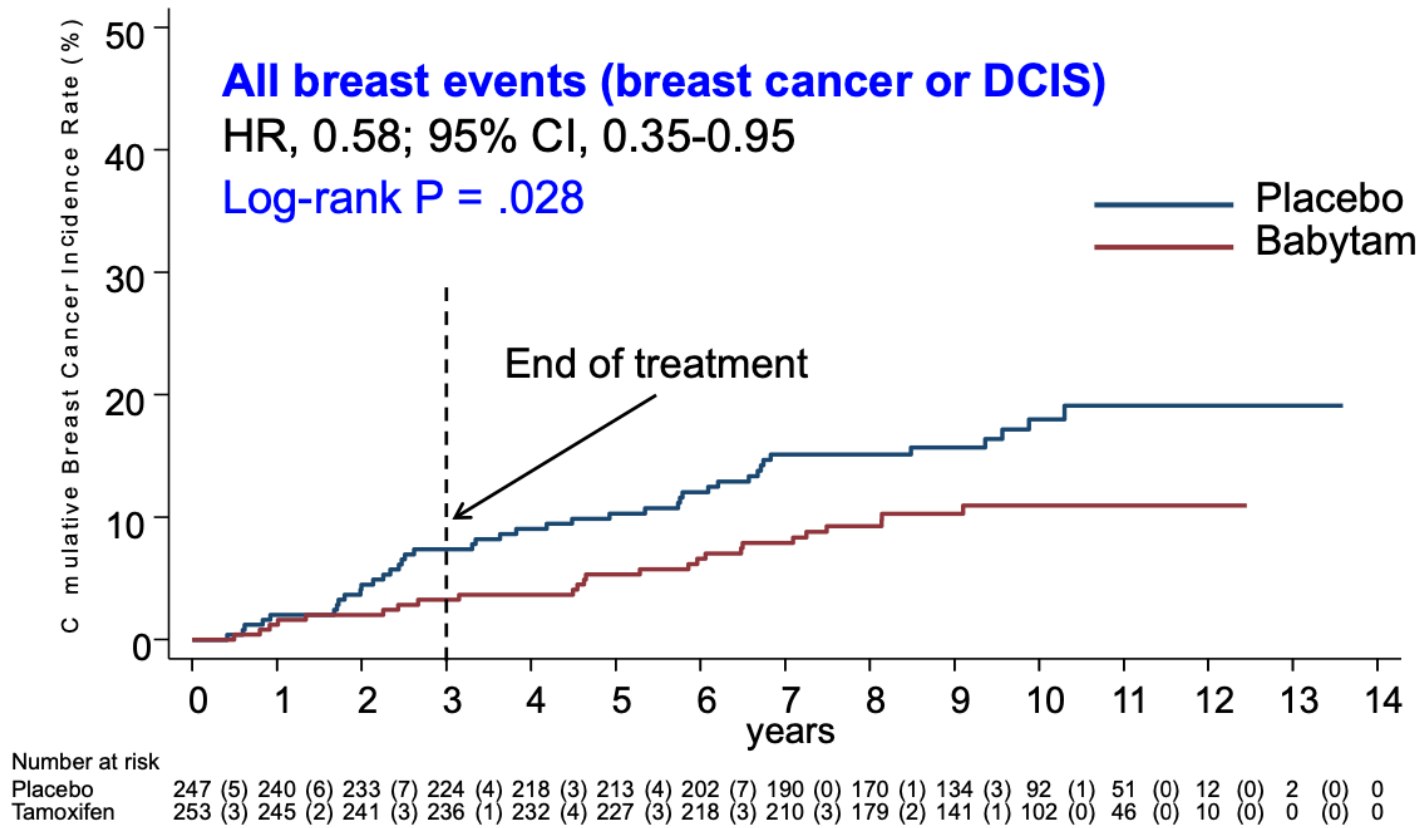
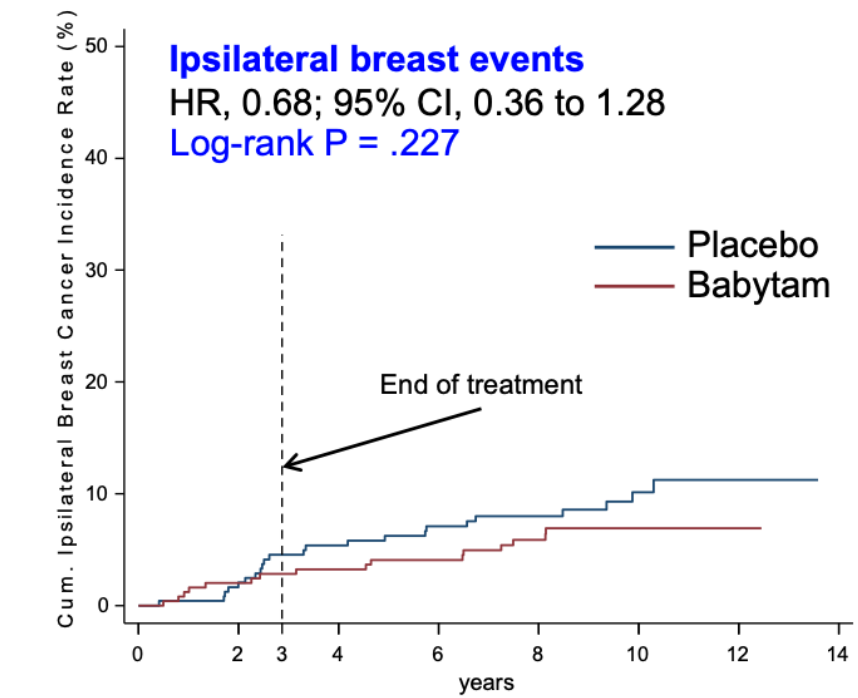
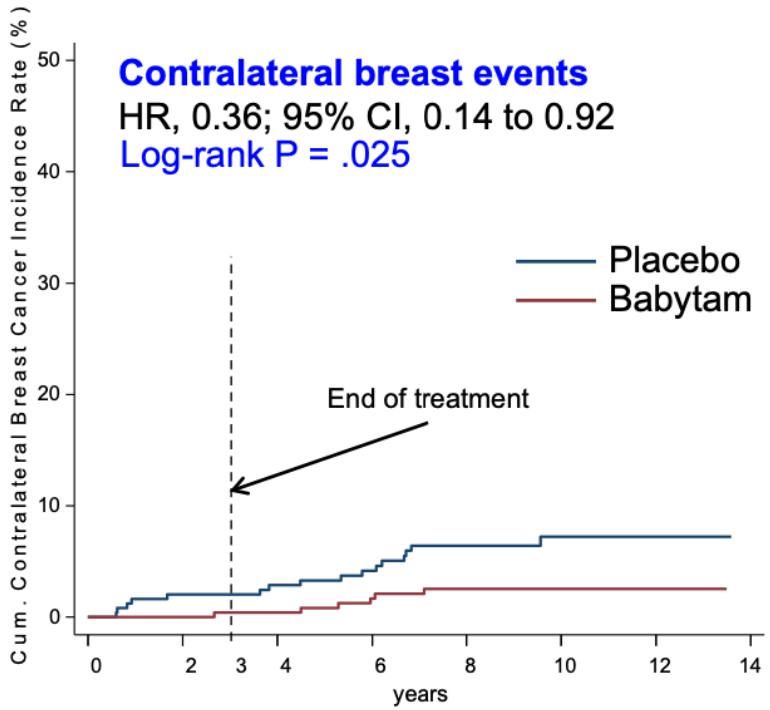


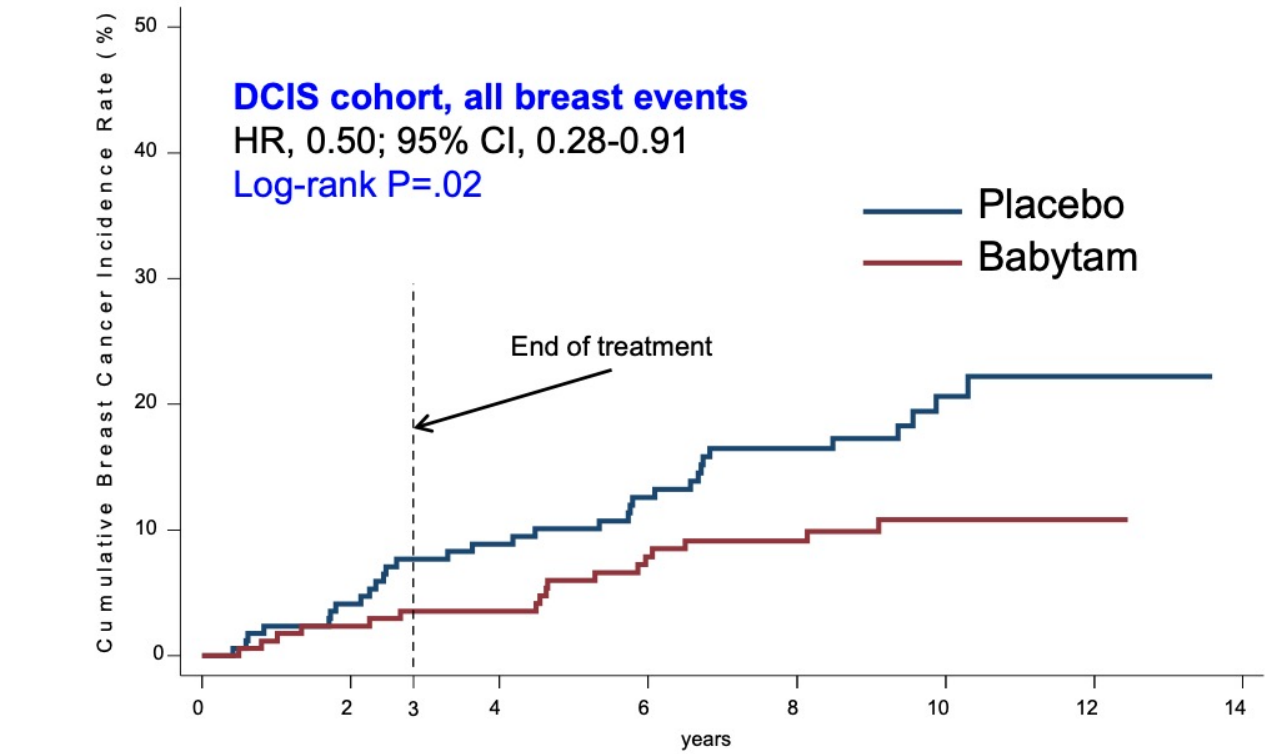


Number at risk

Placebo	247	(5)	238	(8)	225	(4)	212	(2)	182	(3)	100	(1)	12	(0)	0
Tamoxifen	253	(5)	241	(3)	233	(2)	223	(4)	183	(2)	105	(0)	10	(0)	0



247	(5)	239	(2)	230	(3)	218	(5)	185	(1)	102	(0)	12	(0)	0
253	(0)	246	(1)	240	(3)	229	(2)	192	(0)	109	(0)	12	(0)	0



Number at risk															
Placebo	172	(7)	162	(8)	151	(6)	139	(6)	116	(4)	61	(1)	4	(0)	0
Tamoxifen	174	(4)	165	(2)	159	(7)	146	(2)	124	(2)	77	(0)	6	(0)	0

Main characteristics of breast neoplastic events, by arm

	Tamoxifen (N=25)	Placebo (N=41)	p-value
Invasiveness, *n*			0.38
Invasive	21	30	
DCIS	4	11	
Site of recurrence, *n*			0.35
Ipsilateral	16	23	
Contralateral	6	16	
Distant	3	2	
Tumor stage, *n*			0.19
Tis	4	11	
T1	15	23	
T2-4	2	6	
Tx	4	1	
Nodes, *n*			0.89
Node-negative	21	33	
Node-positive	2	5	
Molecular phenotype, *n*			
Luminal	6	12	0.78
HER2+	15	22	0.80
Triple negative	0	3	0.28
Ki-67 %, *median (IQR)*	17 (11-30)	20 (13-30)	0.57

Adverse events by allocated arm

	Tamoxifen N=249	Placebo N=246	P Value
Adverse Events, n			
Endometrial cancer	1	0	1.0
Other neoplasms	16	9	0.22
Deep vein thrombosis or pulmonary embolism	1	1	1.0
Superficial phlebitis	2	0	0.50
Coronary heart disease	2	2	1.0
Bone fracture	4	2	0.69
Cataract	5	5	1.00
Endometrial polyps	20	13	0.28
Death from other causes	5	2	0.45
Death from breast cancer	1	2	0.62
Other serious adverse events	3	6	0.34

Limitations

- Limited power for subgroup analysis and interactions
- Lack of a vis-a-vis comparison with 20 mg/d. A non-inferiority trial would be poorly accepted due to the toxicity of the standard dose
- Lack of 5 mg tablet in the market. Using 10 mg on alternate days is reasonable due to its long half-life[1]

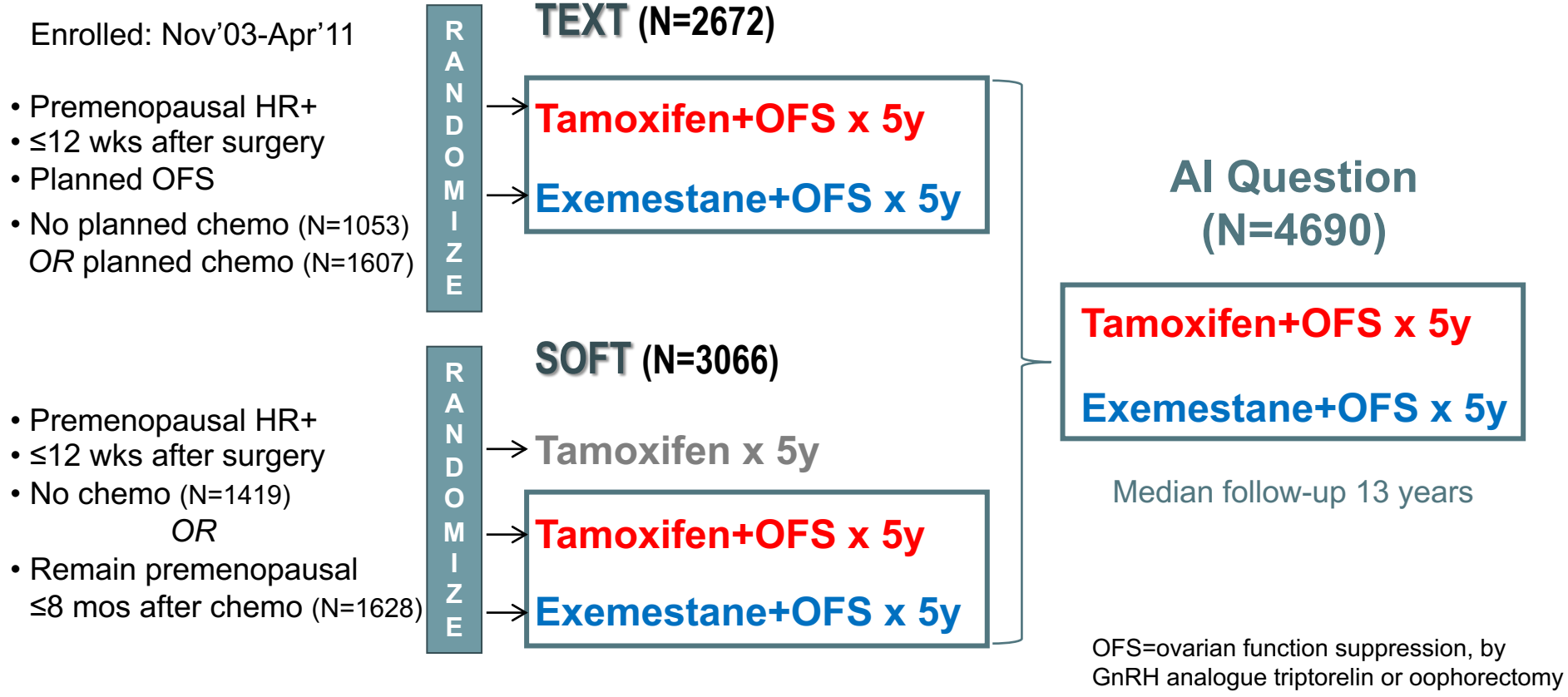
1. Guerrieri-Gonzaga A, et al. *Int J Cancer* 2016;139:2127

SABCS 45 ER positive Adjuvant

TEXT/SOFT update

SOFT and TEXT

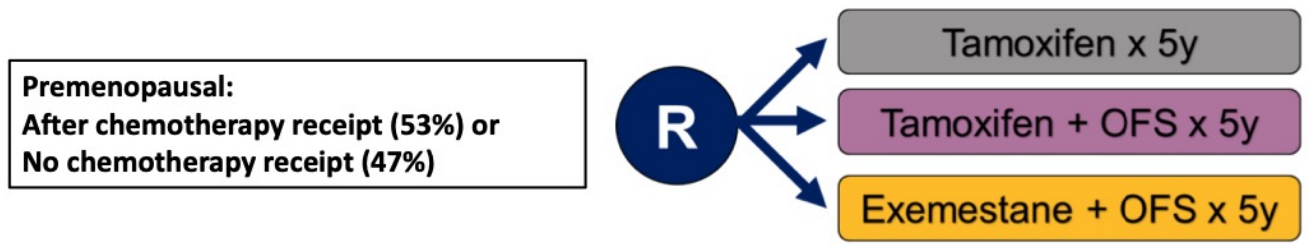
TEXT and SOFT Designs



Pagani et al. NEJM 2014; Francis et al. NEJM 2014, Regan SABCS 2021

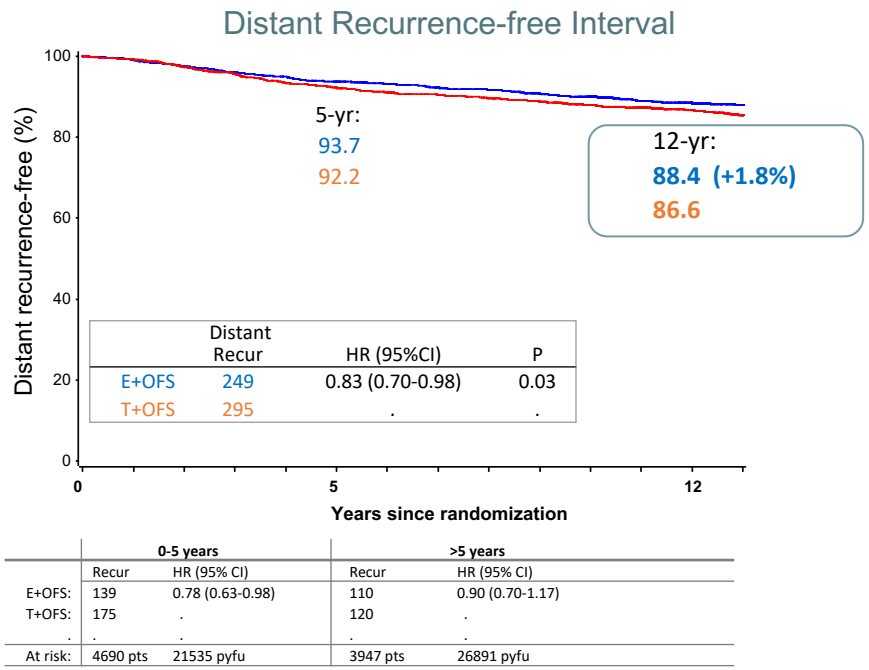
SOFT: Suppression of Ovarian Function Trial

- 3066 patients with HR+ invasive early BC, premenopausal after chemotherapy or premenopausal and did not receive chemotherapy (per investigator/patient decision), were randomized in 1:1:1 ratio

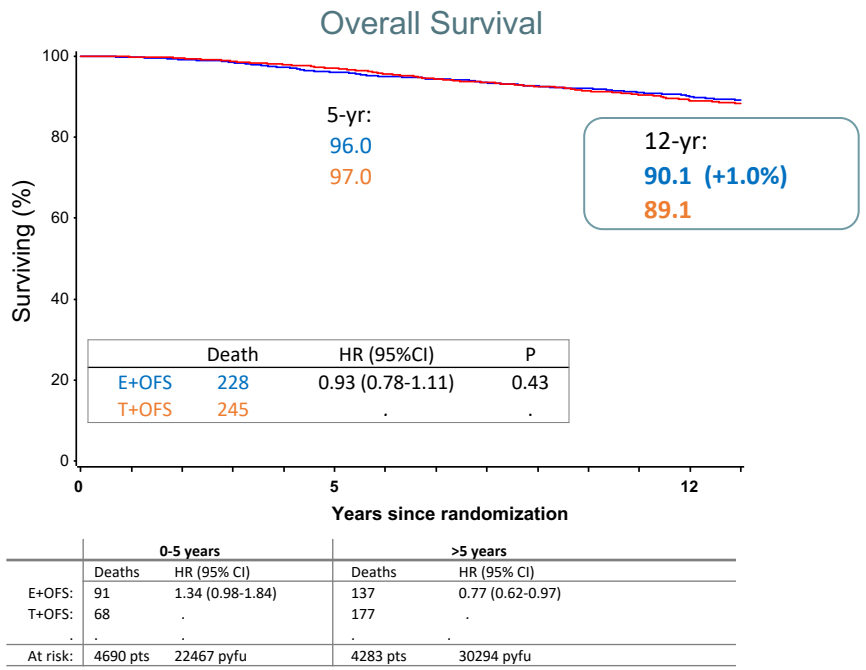


- With 12-year median follow-up:
  - 3% improvement 12-year freedom from distant recurrence with EXE+OFS vs TAM alone (HR: 0.75, 95% CI: 0.59-0.97)
  - DRFI benefit for EXE+OFS (3%) greater than for TAM+OFS (1.4%)

AI Question: SOFT+TEXT Overall Populations
13 years median follow-up



	0-5 years		>5 years	
	Recur	HR (95% CI)	Recur	HR (95% CI)
E+OFS:	139	0.78 (0.63-0.98)	110	0.90 (0.70-1.17)
T+OFS:	175	.	120	.
.	.	.	.	.
At risk:	4690 pts	21535 pyfu	3947 pts	26891 pyfu



	0-5 years		>5 years	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
E+OFS:	91	1.34 (0.98-1.84)	137	0.77 (0.62-0.97)
T+OFS:	68	.	177	.
.	.	.	.	.
At risk:	4690 pts	22467 pyfu	4283 pts	30294 pyfu

E+OFS vs T+OFS: absolute reduction in distant recurrence, 1.8% at 12 years
absolute reduction in death, 1.0% at 12 years

pyfu=person-years follow-up

Regan SABCS 2021 and J Clin Oncol (in press)

SABCS UPDATE 2022

Adjuvant

- ER positive
- Her 2 neu positive
- TNBC--carboplatin

Metastatic

- ER positive
- Her 2 neu positive
- TNBC

SABCS 45 Adjuvant Treatment Her 2 neu Pos

APT 10 year results

(PD18-02) Adjuvant Paclitaxel and Trastuzumab Trial (APT) for Node-Negative, Human Epidermal Growth Factor Receptor 2–Positive (HER2+) Breast Cancer: final 10-year analysis

Friday, December 9, 2022 7:00 AM – 8:15 AM CT

APT Trial overview

- 406 patients ITT (410 enrolled)
- Median age 55 (24 to 85)
- Her 2 positive
- 3 cm or less, node negative {51% 1 cm or smaller, 9% 2-3 cm}
- 1.1 cm mean tumor size
- Treatment 12 weekly doses of paclitaxel given concurrent with trastuzumab and trastuzumab continued for a total of 1 year
- 67% were hormone receptor positive-endocrine therapy indicated

Reference: Annals of Oncology, vol 25, issue 3, March 2014, pages 623-628

APT results

- 10 year overall survival 94.2%
- 10 year BCSS 99.1%
- 36 iDFS events
  - 6 non breast cancer death
  - 9 contralateral breast cancers (8 her 2 neg)
  - 7 distant recurrences (1 T2, 3 T1c, 3T1b){6HR+, 1 HR-}
    - 5 of 7 her 2+, 1 her 2- and 1 unknown
  - 8 local regional recurrences

Conclusion: After 10 years of follow-up, adjuvant TH confirmed excellent long-term outcomes for small, node-negative HER2+ breast cancer, with a 10-year RFI of 96.8% and a 10-year BCSS of 99.1%.

Table 1

iDFS events with adjuvant paclitaxel plus trastuzumab after 10.2 years of follow up

	ER-negative at baseline		ER-positive at baseline	
DFS EVENT	**N**	**Time to event (months)**	**N**	**Time to event (months)**
Local/regional recurrence	3		2	
- ipsilateral axilla (HER2+*)	1	20	0	
- ipsilateral breast	2	12, 153	2	37, 65
HER2+*	1		1	
HER2-*	1		1	
Contralateral breast events	4	36**, 59**, 84, 90	5	12, 56, 88, 106, 130
- HER2+*	0		1	
- HER2-*	4		4	
Distant recurrence	1	63**	6	27, 46, 54, 59, 81, 86
Death	6	42, 45, 52, 62, 62, 119	9	14, 21, 48, 61, 62, 63
- Breast-cancer related	0		0	79, 106, 107
- Non-breast cancer related	6		9	
Any recurrence or death	13		23	

*HER2 status locally determined on a biopsy of the recurrent or contralateral tumor tissue
**Patient had subsequent breast cancer-related death, which was counted toward the calculation of breast cancer-specific survival

Conclusion: After 10 years of follow-up, adjuvant TH confirmed excellent long-term outcomes for small, node-negative HER2+ breast cancer, with a 10-year RFI of 96.8% and a 10-year BCSS of 99.1%.

SABCS UPDATE 2022

Adjuvant

- ER positive
- Her 2 neu positive
- TNBC--carboplatin

Metastatic

- ER positive
- Her 2 neu positive
- TNBC

Session: General Session 5

GS5-01 Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial

Friday, December 9, 2022 12:00 PM – 12:15 PM CT Location: Hall 3 CME 0.25 Credit Hours

Session Type: Oral Presentation
Submission Sub-Category: Therapeutic Strategies: 613. Neoadjuvant Chemotherapy

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial

Sudeep Gupta, M.D., D.M.; on behalf of

Nita S Nair, Rohini W Hawaldar, Vaibhav Vanmali, Vani Parmar, Seema Gulia, Jaya Ghosh, Shalaka Joshi, Rajiv Sarin, Tabassum Wadasadawala, Tejal Panhale, Sangeeta Desai, Tanuja Shet, Asawari Patil, Garvit Chitkara, Sushmita Rath, Jyoti Bajpai, Meenakshi Thakur, and Rajendra A Badwe.

Breast Cancer Working Group, Tata Memorial Centre, Mumbai

Funded by Tata Memorial Centre, Mumbai

Background

- Randomized phase II trials and meta-analyses have shown that addition of platinum to anthracycline-taxane neoadjuvant therapy increases pathological response. [1]
- Studies of neoadjuvant platinum have been underpowered to detect survival outcomes.
- The GeparSixto & BrighTNess studies showed increase in EFS with the addition of carboplatin to taxane-anthracycline regimens, but CALGB 40603 did not. [2, 3, 4]

[1] Poggio F, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018 Jul 1;29(7):1497-1508..
[2] Loibl S, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347.
[3] Geyer CE, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384-394..
[4] Shepherd JH, et al. CALGB 40603 (Alliance): Long-Term Outcomes and Genomic Correlates of Response and Survival After Neoadjuvant Chemotherapy With or Without Carboplatin and Bevacizumab in Triple-Negative Breast Cancer. J Clin Oncol. 2022 Apr 20;40(12):1323-1334..

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TMC Neoadjuvant Platinum TNBC Study

- TNBC (1% cutoff for ER & PR)
- No evidence of M1
- Fit for anthracycline
- T1-T4, N0-3

R

Platinum
Pacli+Carbo → AC/EC

Control
Pacli → AC/EC

Surgery → Radiotherapy

Stratification

Menopausal Status
(Pre+Peri, Post)

Clinical Stage
OBC (cT_{1-3},N_{0-1}, M_0)
LABC (cT_4/N_{2-3}, M_0)

Breast conserving surgery
OR
Mastectomy

Platinum Arm:
Paclitaxel 100/m2 + Carboplatin (AUC-2) once per week X 8w*
followed by
[Doxorubicin (60/m2) or Epirubicin (90/m2)] + Cyclo (600/m2) every 2 weeks or 3 weeks X 4 cycles

Control Arm: Same as above, without carboplatin

*Gupta S, et al. Single agent weekly paclitaxel as neoadjuvant chemotherapy in locally advanced breast cancer: a feasibility study. Clin Oncol (R Coll Radiol). 2012 Nov;24(9):604-9

Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Receptor Status			
TNBC	356 (100%)	361 (100%)	717 (100%)
Other	0 (0%)	0 (0%)	0 (0%)
Pathological Subtype			
Invasive Duct Carcinoma	310 (87.1%)	331 (91.7%)	641 (89.4%)
Metaplastic	33 (9.3%)	22 (6.1%)	55 (7.7%)
Others	13 (3.7%)	8 (2.2%)	21 (2.9%)
Grade			
II	2 (0.6%)	3 (0.8%)	5 (0.7%)
III	354 (99.4%)	358 (99.2%)	712 (99.3%)

Toxicity

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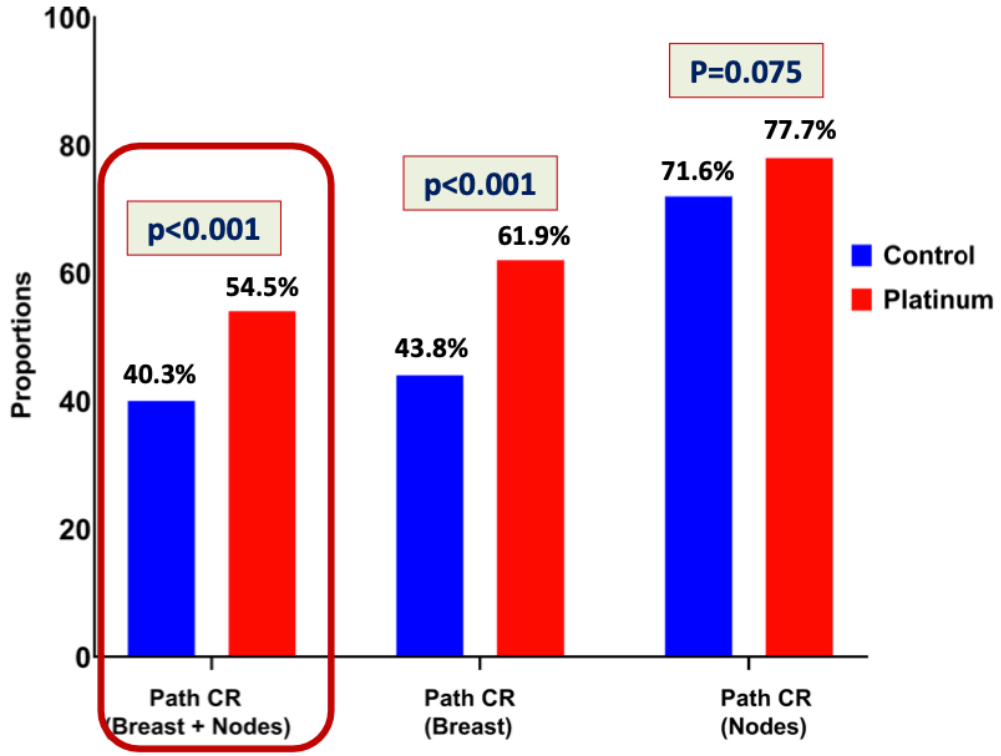
Toxicity	Platinum (N=361)	Control (N=356)		Platinum (N=361)	Control (N=356)
	Any Grade			Grade III or Worse	
Neutropenia	56 (15.5%)	18 (5.1%)		31 (8.6%)	7 (2.0%)
Anemia	23 (6.4%)	9 (2.5%)		7 (1.9%)	1 (0.3%)
Thrombocytopenia	21 (5.8%)	4 (1.1%)		7 (1.9%)	0 (0%)
Neutropenic Fever	-	-		16 (4.4%)	10 (2.8%)
Nausea	24 (6.6%)	26 (7.3%)		0 (0%)	1 (0.3%)
Vomiting	37 (10.2%)	34 (9.6%)		1 (0.3%)	1 (0.3%)
Diarrhea	22 (6.1%)	16 (4.5%)		4 (1.1%)	3 (0.8%)
Mucositis	21 (5.8%)	21 (5.9%)		1 (0.3%)	3 (0.8%)
Peripheral Neuropathy	65 (18.0%)	65 (18.3%)		3 (0.8%)	3 (0.8%)
Skin	10 (2.8%)	15 (4.2%)		3 (0.8%)	3 (0.8%)
Cardiac	3 (0.8%)	0 (0%)		0 (0%)	0 (0%)
Hepatic	1 (0.3%)	2 (0.6%)		0 (0%)	0 (0%)
Renal	0 (0%)	0 (0%)		0 (0%)	0 (0%)
Any SAE	53 (14.7%)	46 (12.9%)			

Results

- **Study accrual period:** April 2010 to January 2020
- N = 720
- Eligibility violations in 3 patients.
- **Modified ITT = 717**
- **Data cutoff:** June 15, 2022
- Median follow-up of 67.6 (18.9-142.2) months

ITT: Pathological Response to NACT by Rx-Arm



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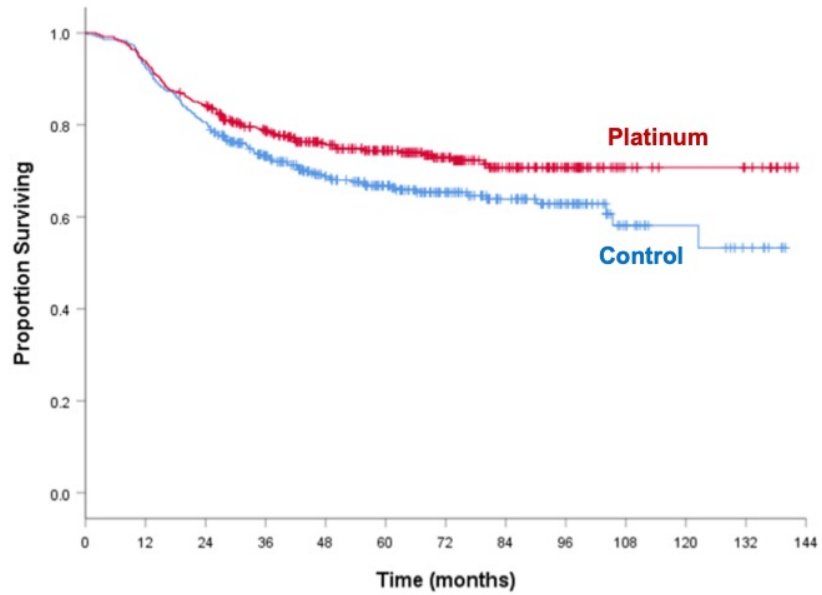
Overall Survival in ITT (N=717)



Control	356	330	287	229	179	147	106	74	48	20	12	7
Platinum	361	339	303	252	201	168	122	83	51	19	14	12

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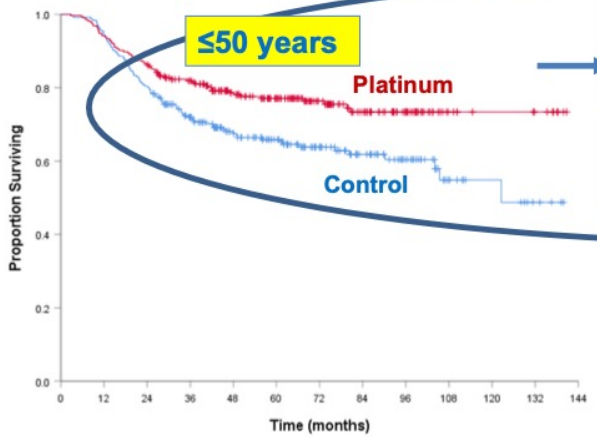
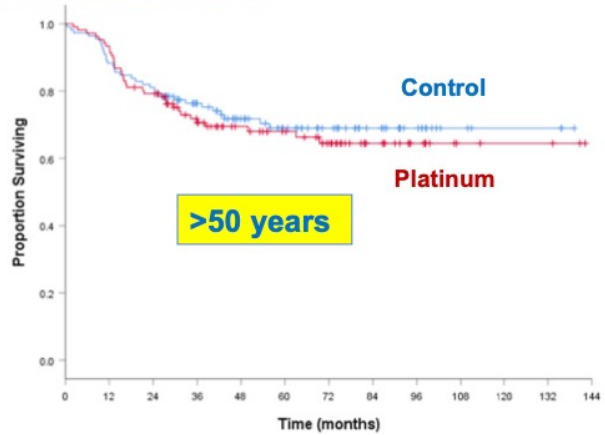
Overall Survival in Younger and Older Patients



	Platinum	Control
5-year OS (95% CI)	77.1% (71.81 - 82.39%)	65.9% (59.82 - 71.98%)
HR (95% CI)	0.611 (0.440 - 0.848)	
'p'	0.003	

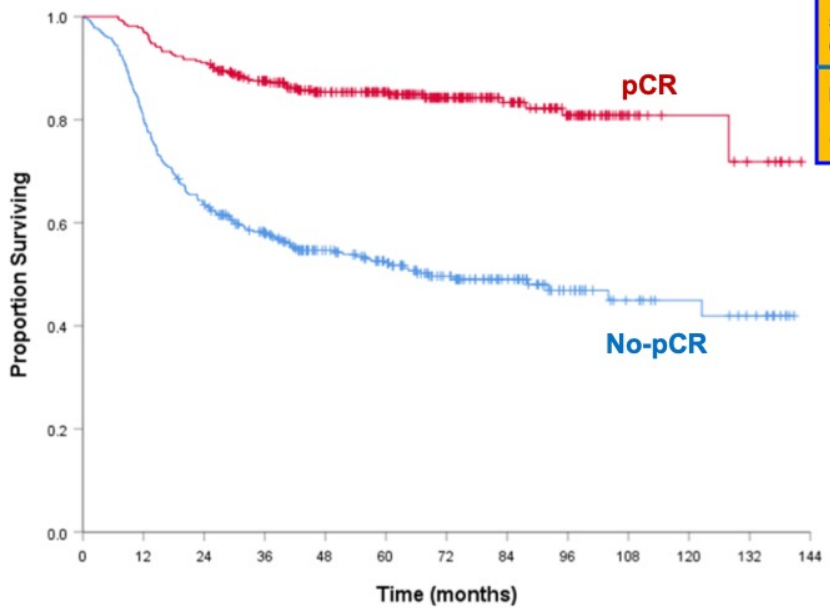
Control	245	232	197	160	125	104	74	53	35	15	9	4
Platinum	255	240	220	190	153	127	91	64	40	15	11	9



	Platinum	Control
5-year OS (95% CI)	68.0% (58.79 - 77.21%)	68.9% (59.69 - 78.11%)
HR (95% CI)	1.132 (0.698 - 1.835)	
'p'	0.615	

Control	111	98	90	69	54	43	32	21	13	5	3	3
Platinum	106	99	83	62	48	41	31	19	11	4	3	3

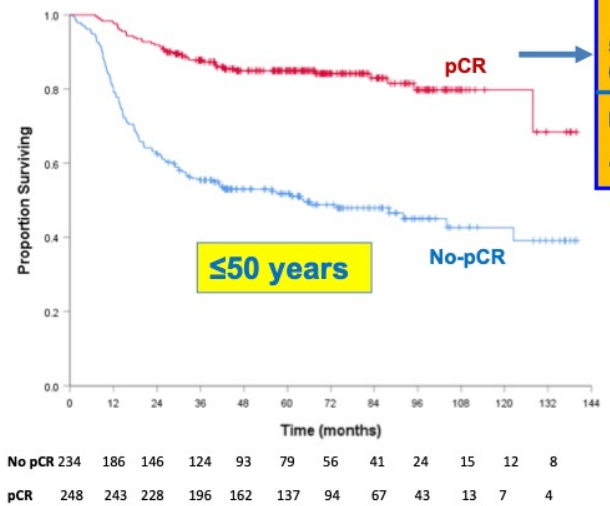
EFS (Full Population): Prognostic Impact of Pathological Response



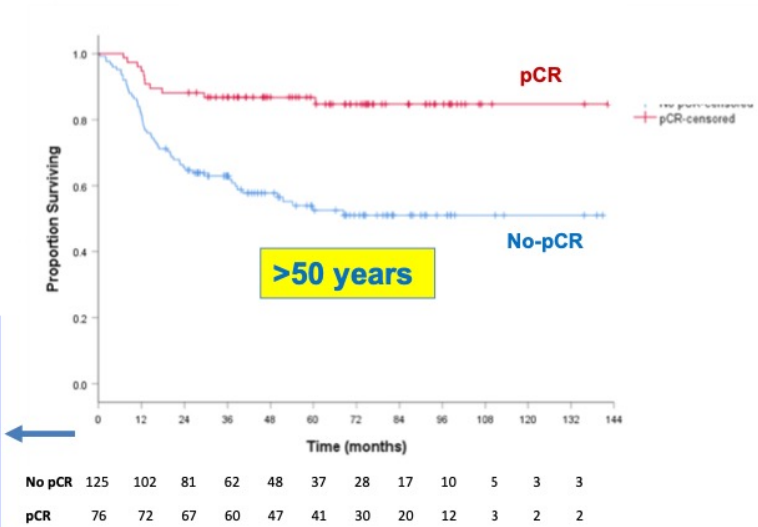
No pCR	359	288	227	186	141	116	84	58	34	20	15	11
pCR	324	315	295	256	209	178	124	87	55	16	9	6

	pCR (ypT0/is ypN0)	No-pCR
5-year EFS (95% CI)	85.3% (81.38 - 89.22%)	52.2% (46.91 - 57.49%)
HR (95% CI)	0.253 (0.186 - 0.345)	
'p'	<0.001	

EFS: Prognostic Impact of Pathological Response in Younger and Older Patients



	pCR (ypT0/is ypN0)	No-pCR
5-year EFS (95% CI)	84.9% (80.39 - 89.41%)	51.8% (45.33 - 58.27%)
HR (95% CI)	0.248 (0.174 - 0.353)	
'p'	<0.001	



	pCR (ypT0/is ypN0)	No-pCR
5-year EFS (95% CI)	86.8% (79.16 - 94.44%)	52.6% (43.19 - 62.01%)
HR (95% CI)	0.258 (0.135 - 0.493)	
'p'	<0.001	

CONCLUSIONS

- Addition of carboplatin to sequential taxane-anthracycline neoadjuvant chemotherapy significantly improves overall survival and tends to improve event-free survival among patients with operable and locally-advanced TNBC.
  - The benefit seems confined to younger or premenopausal patients in whom there is substantial and significant improvement in EFS and OS.
- Increased pCR with carboplatin is predictive of EFS and OS benefit in younger patients ***AND*** lack of improvement in pCR is predictive of lack of EFS and OS benefit in older patients.

CONCLUSIONS

- The precise reasons for interaction between age/menopausal status and carboplatin are unclear.
- Our survival results are concordant with GeparSixto and BrighTNess studies but discordant with CALGB 40603.
  - We used weekly carboplatin in all patients in the platinum arm (like GeparSixto) which likely increased compliance and reduced toxicity.
  - We used the standard chemotherapy backbone of taxane, anthracycline and cyclophosphamide.
  - We did not use bevacizumab or PARP inhibitors.

CONCLUSIONS

- **Addition of carboplatin to taxane-anthracycline neoadjuvant chemotherapy should be the standard treatment in patients with TNBC who are ≤50 years or who are pre-menopausal.**

THINGS CHANGE

SABCS UPDATE 2022
Metastatic BC

Metastatic

- ER positive
- Her 2 low
- Her 2 neu positive
- AKT pathway

SABCS 45 Metastatic BC ER positive

- CDK 4/6i overview
- SERDS
- AKT pathway

Results for Pivotal CDK 4/6 Inhibitor Trials

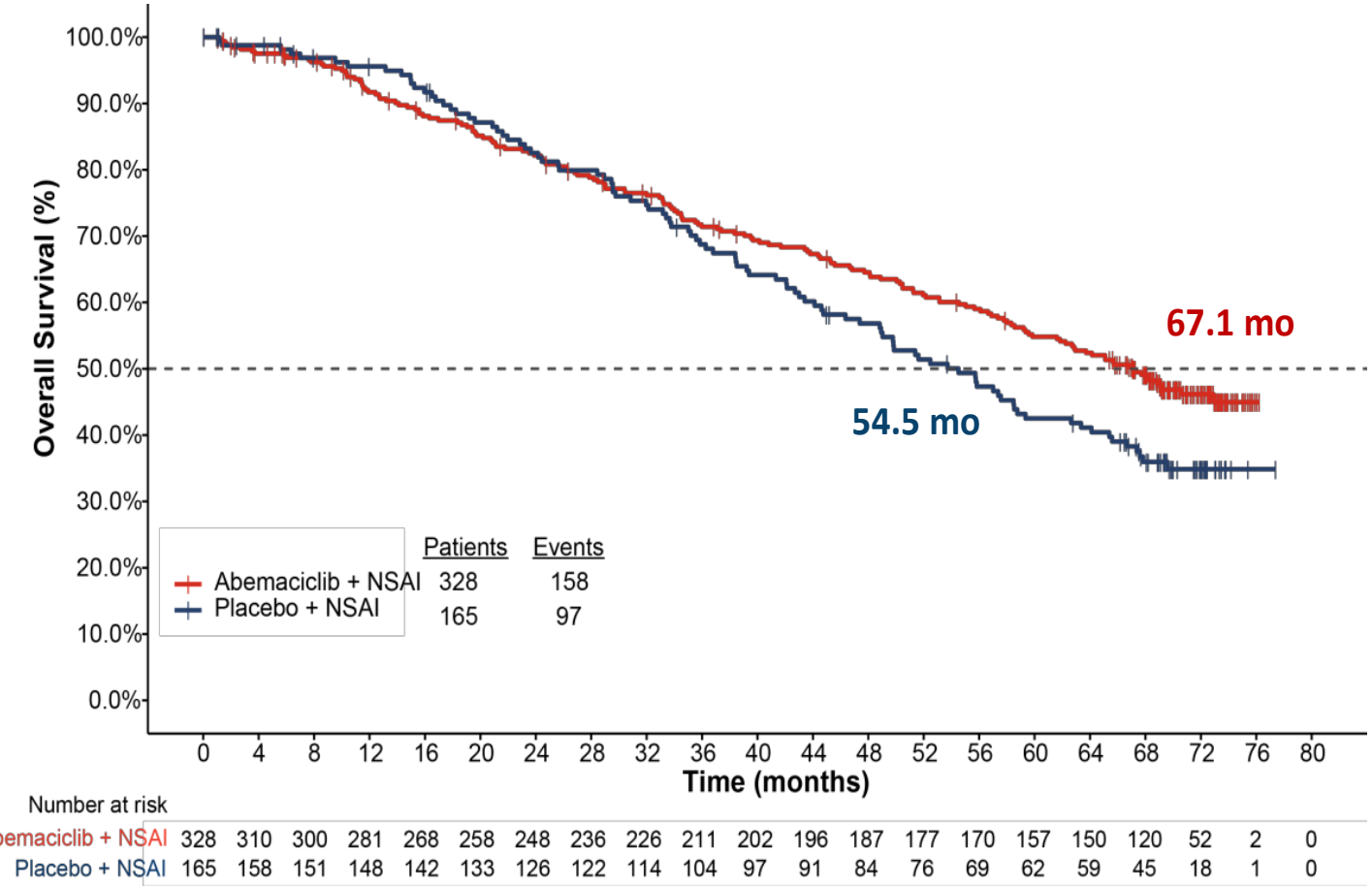
Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3a]	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3[4]	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (@IA2)
PALOMA-3[5]	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2[6]	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3[7]	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

a. Missing survival data (ie, pts who withdrew consent or were lost to follow-up) and were censored (assumed to be alive) at time of analysis: 13% in palbo+AI arm vs 21% in control arm.
b. 27% of patients in control arm went on to receive a CDK4/6i (24% received palbociclib).
c. PFS/OS data reported for approved AI subset.

AI indicates aromatase inhibitor; Fulv, fulvestrant; IA2, interim analysis 2; NR, not reported; Rx, therapy.

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936; Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719-729. Finn R, et al. ASCO 2022. LBA1003. **2.** MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR. **3.** MONALEESA-7: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; Im S-A, et al. *New Engl J Med*. 2019;381:307-316. **4.** MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5*. Goetz MP, et al. ESMO 2022. Abstract LBA 15. **5.** PALOMA-3: Turner NC, et al. *New Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *New Engl J Med*. 2015;373:1672-1673. **6.** MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol*. 2020;6:116-124**. 7.** MONALEESA-3: Slamon D, et al. *J Clin Oncol*. 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524.

MONARCH-3: NSAI ± Abemaciclib – Overall Survival



	abemaciclib + NSAI	placebo + NSAI
Median OS, (months)	67.1	54.5
HR (95% CI; *P* value)	0.754 (0.584-0.974) p-value 0.0301*	
Pre-planned OS IA2 Analysis Data cut: 02 Jul 2021		

*p-value did not reach threshold for statistical significance at this interim

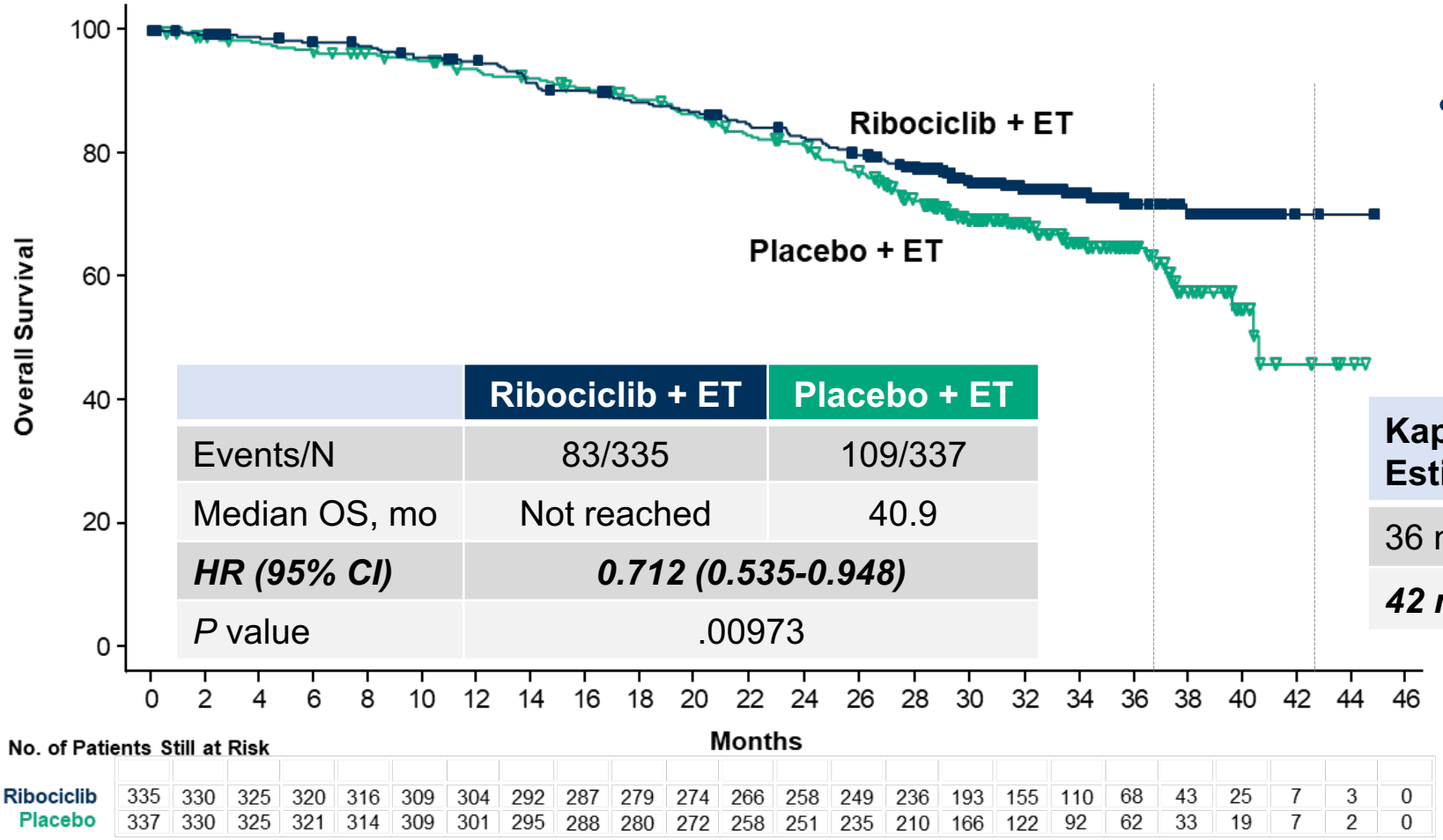
31.5% of patients in the control arm and 10.1% in the abemaciclib arm received a subsequent CDK4 & 6 inhibitor

At this interim analysis, statistical significance was not reached but data are maturing favorably (HR 0.754, 95% CI: 0.584-0.974) and follow up continues. The observed difference in median OS was 12.6 months.

Key secondary end point.

Goetz M. et al. ESMO 2022. Abstract LBA15

MONALEESA-7: Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

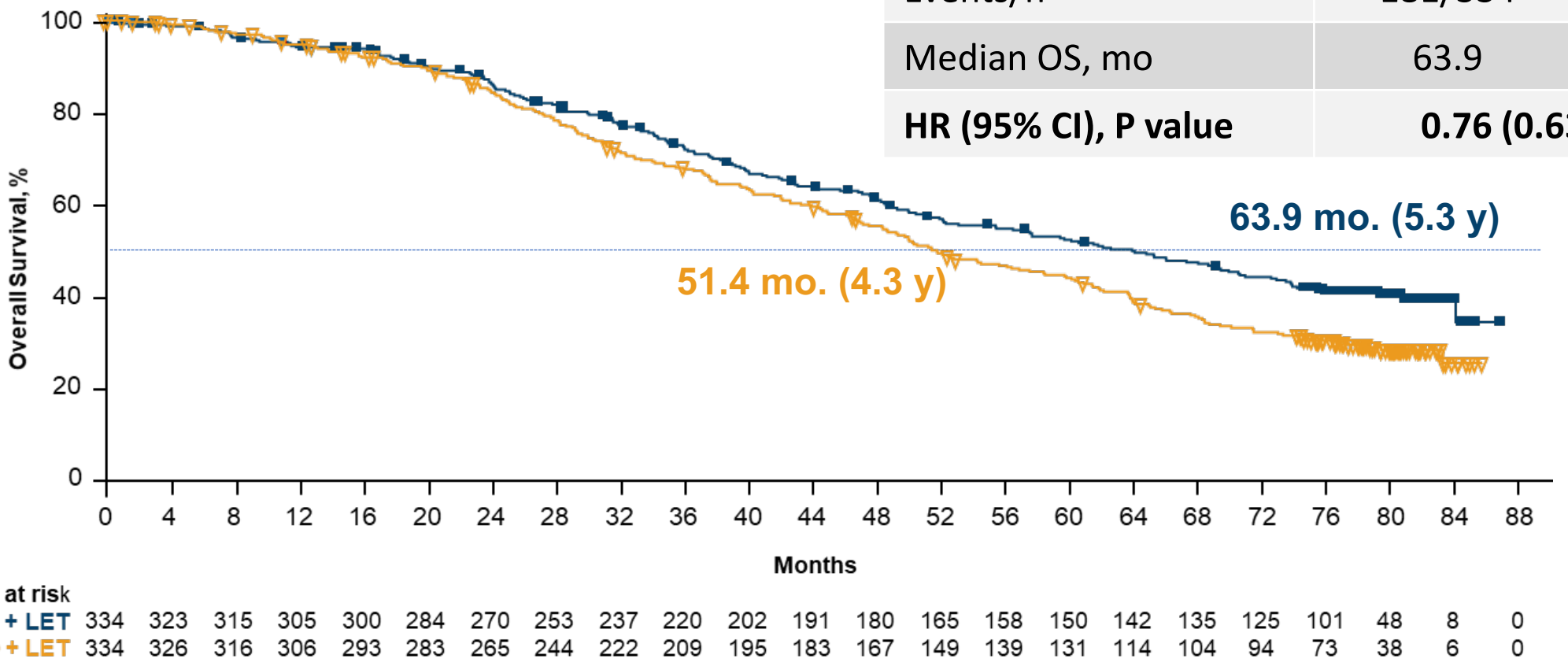
Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 mo	71.9%	64.9%
42 mo	***70.2%***	***46.0%***

Protocol-specified key secondary end point.
Im S-A, et al. *New Engl J Med*. 2019;381:307-316.

MONALEESA-2: Letrozole ± Ribociclib – Overall Survival

Final Analysis at 400 death events: Improvement in median OS of 12.5 mo

	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI), P value	**0.76 (0.63-0.93), .004**	



Key secondary end point.

Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR.

DIFFERENCES IN CDK4/6i?

PALOMA-3 Trial failed to show survival advantage

MONALEESA-7 Trial showed substantial survival advantage

Key differences between trials:

PALOMA-3 included pre and post menopausal patients who were more heavily treated

MONALESSA-7 patients were all pre or perimenopausal and were receiving initial endocrine treatment

"chemotherapy in the setting of advanced disease—a possible indication of a higher risk population". 14% In MONALEESA-7 vs 34% in PALOMA 3

"These differences may limit cross-trial comparisons."
NEJM July 25, 2019 vol 381 No. 4

SABCS 45 Metastatic BC ER positive

Right Choice Trial

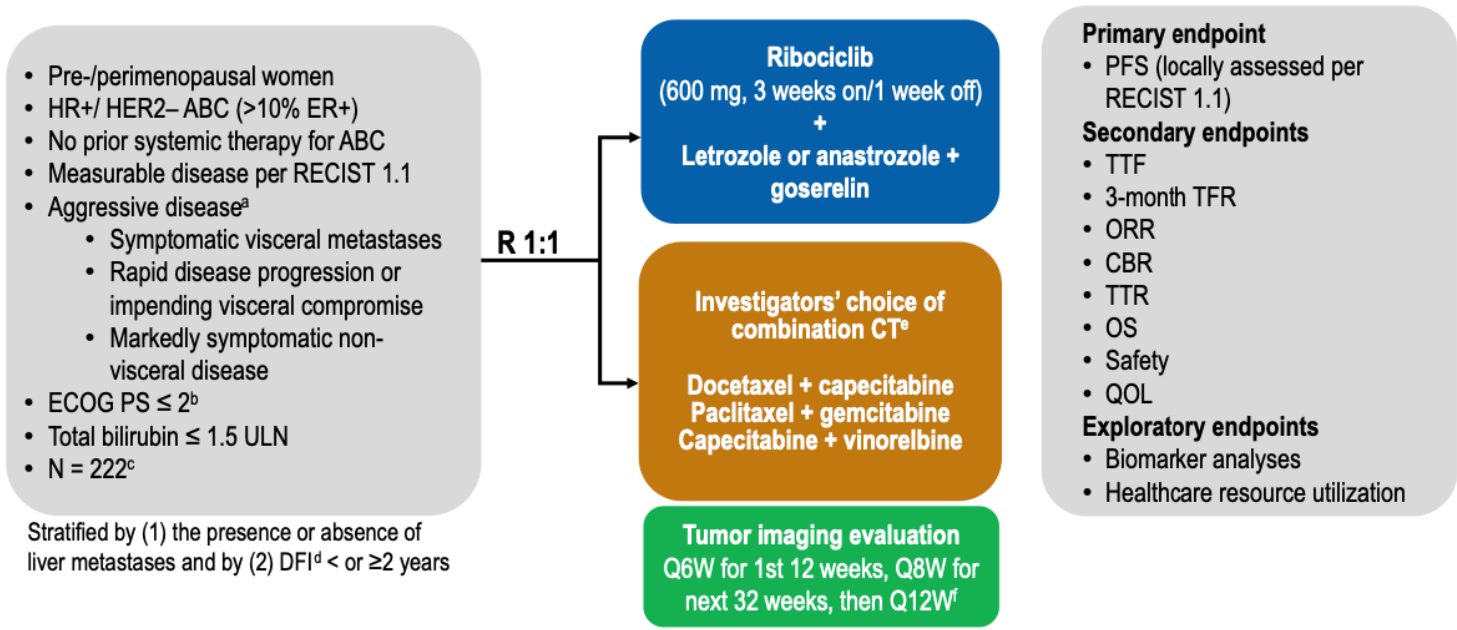
San Antonio Breast Cancer Symposium®, December 6-10, 2022

Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy

Yen-Shen Lu,[1] Eznal Izwadi Bin Mohd Mahidin,[2] Hamdy Azim,[3] Yesim Eralp,[4] Yoon-Sim Yap,[5] Seock-Ah Im,[6] Julie Rihani,[7] James Bowles,[8] Teresa Delgar Alfaro,[8] Jiwen Wu,[9] Melissa Gao,[8] Khemaies Slimane,[8] Nagi El Saghir[10]

[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [3]School of Medicine, Cairo University, Cairo, Egypt; [4]Acibadem Research Institute of Senology, Acibadem University, Istanbul, Turkey; [5]National Cancer Centre Singapore, Singapore; [6]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [7]King Hussein Cancer Center, Amman, Jordan; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]American University of Beirut Medical Center, Beirut, Lebanon.

RIGHT Choice study design



ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

Background

- Chemotherapy (CT) is the standard of care in ABC with clinically aggressive disease features that include rapidly progressing or highly symptomatic disease and life-threatening visceral crisis, which requires rapid disease control[1]
- Combination CT is associated with a higher ORR and longer PFS than single-agent CT and may be preferred for those who have a critical disease condition and may tolerate potentially toxic treatment[2]
- Ribociclib (RIB) + endocrine therapy (ET) demonstrated statistically significant PFS and OS benefits over ET alone in 3 Phase III clinical trials (MONALEESA-2, -3, and -7) in patients with HR+/HER2− ABC, including patients with visceral metastases and a high tumor burden[3-11]
- No data on a head-to-head comparison of CDK4/6 inhibitor + ET vs combination CT in the patient population with aggressive HR+/HER2− disease have been published
- Here we report the prespecified primary analysis of PFS and key secondary endpoints from the randomized, open-label, multinational, Phase II RIGHT Choice trial

ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinases 4 and 6; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Cardoso F, et al. *Ann Oncol.* 2020;31:1623-1649. 2. O'Shaughnessy J. *Oncologist.* 2005;10 Suppl 3:20-9. 3. Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915. 4. Slamon DJ, et al. *J Clin Oncol.* 2018;36:2465-2472. 5. Hortobagyi GN, et al. *N Engl J Med.* 2016;375:1738-1748. 6. Im SA, et al. *N Engl J Med.* 2019;381:307-316. 7. Slamon DJ, et al. *N Engl J Med.* 2020;382:514-524. 8. Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950. 9. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR. 10. Tripathy D, et al. SABCS 2020. Poster PD2-04. 11. Slamon DJ, et al. ASCO 2021. Oral 1001.

Baseline characteristics were well balanced

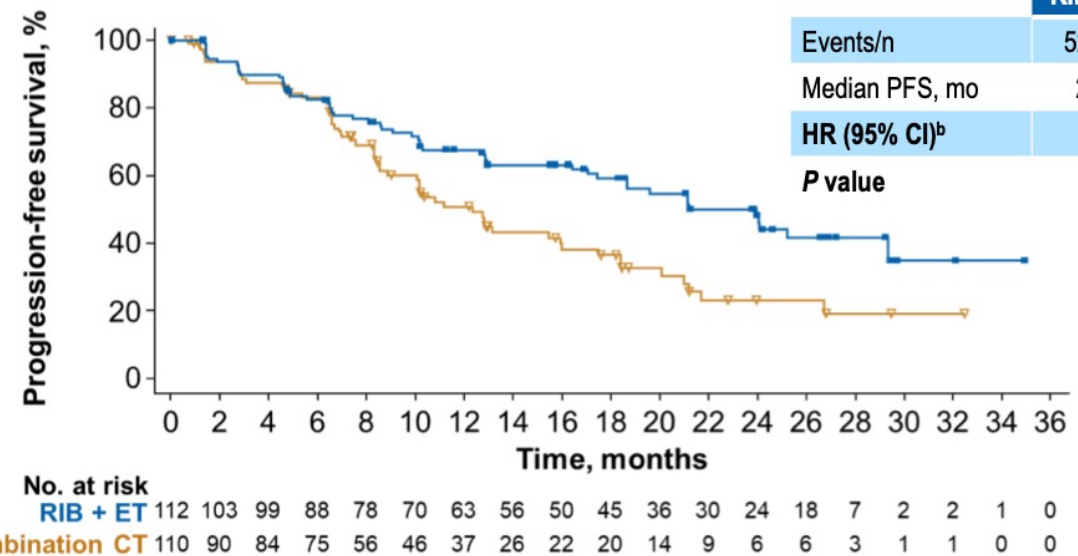
Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

Combo CT, combination chemotherapy; ER+, estrogen receptor positive; ET, endocrine therapy; RIB, ribociclib.
[a] One patient (0.9%) in the RIB arm was African American; [b] The same patient may have multiple visceral metastatic sites. [c] Based on PI's judgment, which followed ABC3 and NCCN guidelines, which were available at the time of study design.

San Antonio Breast Cancer Symposium®, December 6-10, 2022

First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2− ABC

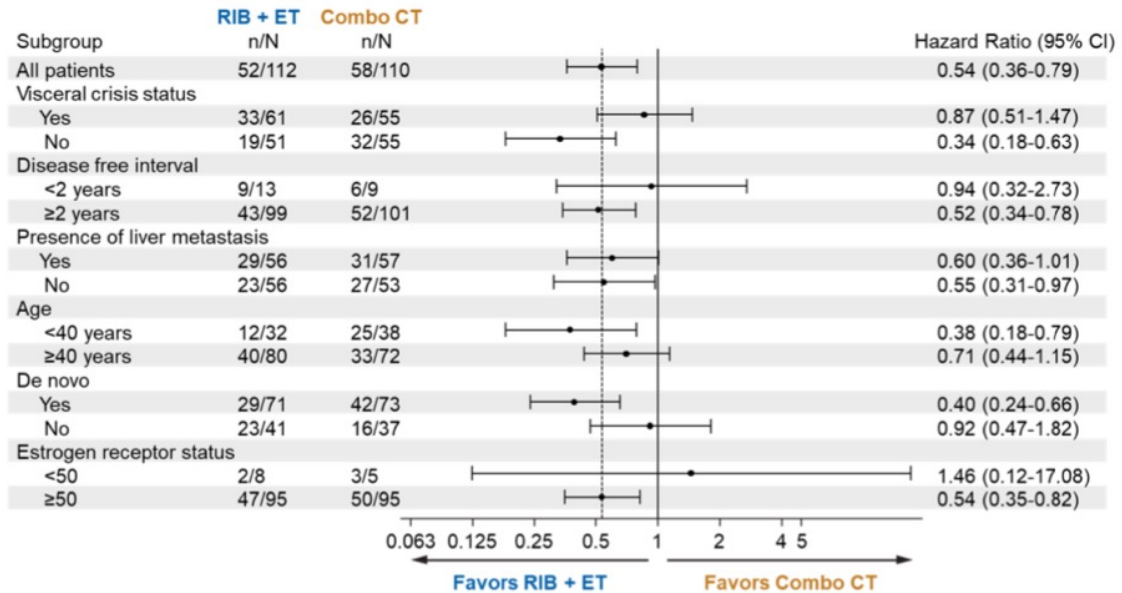


	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; IRT, interactive response technology; PFS, progression-free survival; RIB, ribociclib.

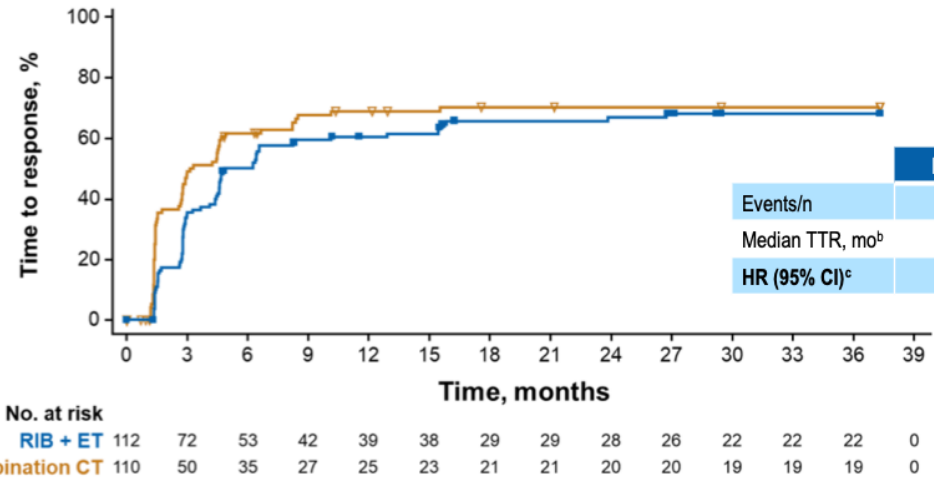
[a] Ten patients in CT arm did not receive any treatment; [b] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT.

PFS benefit with RIB + ET over combination CT was consistent across most subgroups of patients with aggressive HR+/HER2− ABC



ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival; RIB, ribociclib.

Time to onset of response (TTR) for RIB + ET was similar to combination CT

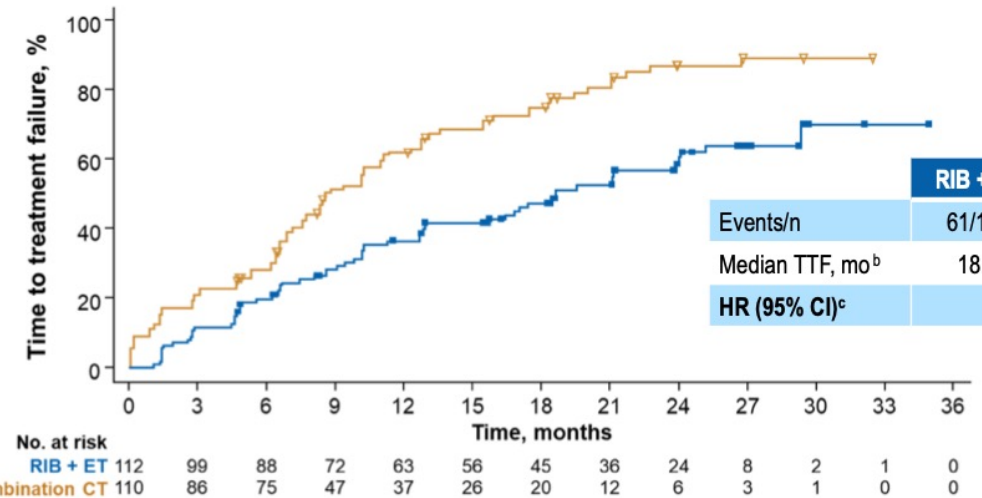


	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	**0.78 (0.56-1.09)**	

- A sensitivity analysis[d] confirmed the TTR findings in the safety set

Combo CT, combination chemotherapy; CR, complete response, ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; PR, partial response; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] TTR is defined as the time from the date of randomization to the first documented response of either CR or PR without confirmation (confirmation imaging was not required according to study protocol); [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment and were removed from the denominator for the CT arm.

Median time to treatment failure (TTF) was longer with RIB + ET vs combination CT



	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	**0.45 (0.32-0.63)**	

- A sensitivity analysis[d] confirmed the TTF findings in the safety set
- The 3-month treatment failure rate[e] in the RIB arm was approximately half (n = 13; 11.6%; 95% CI, 6.3%-19.0%) that in the combination CT arm (n = 24; 21.8%; 95% CI, 14.5%-30.7%)

Combo CT, combination chemotherapy; ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] Defined as the time from randomization to progression, death, change to other anticancer therapy, or discontinuation; [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment; [e] The proportion of patients who discontinued study treatment due to progressive disease, death, change to other anticancer therapy, or discontinuation due to reasons other than protocol violation.

Conclusions

- RIGHT Choice is the first prospective study comparing a CDK4/6 inhibitor + ET with combination CT and demonstrating the PFS superiority of RIB + ET over combination CT in patients with HR+/HER2− ABC with aggressive clinical features of rapidly progressing or highly symptomatic disease, including visceral crisis
  - First-line RIB + ET demonstrated a statistically significant PFS benefit (≈1 year longer) vs combination CT (24.0 vs 12.3 months; HR, 0.54) in pre/perimenopausal patients with aggressive HR+/HER2− ABC
- RIB + ET also showed longer TTF than combination CT with similar TTR and ORR between the two treatment groups, matching the high tumor response rate seen with combination CT
- No new safety signals were observed with RIB + ET
  - Compared with RIB +ET, combination CT was associated with higher rates of treatment-related AEs, many that impact QOL
- First-line RIB + ET offers an efficacious, clinically meaningful treatment option for patients with aggressive HR+/HER2− ABC, obviating the need for combination CT and related toxicities

ABC, advanced breast cancer; AE, adverse event; CDK4/6, cyclin-dependent kinases 4 and 6; CT, chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; QOL, quality of life; RIB, ribociclib; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response.

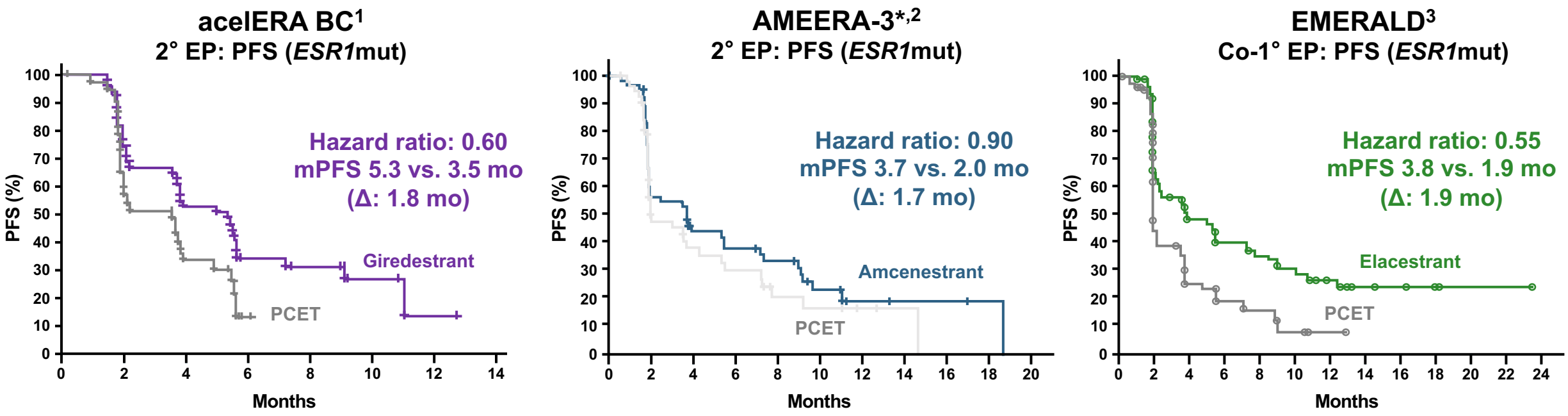
SABCS 45 Metastatic BC ER positive

-SERDS

Oral SERDS: Randomized Trials in the Post-CDK4/6 Inhibitor Setting

	EMERALD (NCT03778931)	AMEERA-3 (NCT04059484)	acelERA (NCT04576455)	SERENA-2 (NCT04214288)	EMBER-3 (NCT04975348)
N	477	282	303	288	830
Patient Population	ER+/HER2- ABC	ER+/HER2- ABC (ET sensitivity required)	ER+/HER2- ABC Measurable disease	ER+/HER2- MBC	ER+/HER2- MBC
Number of Prior Therapies	1-2	0-2	0-2	0-2	1 (AI + CDK4/6i)
Prior Chemotherapy	20% had 1 line	Allowed (≤1) or CDK	Allowed (≤1)	Allowed (≤1)	Not allowed
Prior Fulvestrant	30%	Allowed	Allowed	Not allowed	Not allowed
Prior CDK 4/6i	100%	80%	Allowed	Allowed	Allowed
Treatment Arms	Elacestrant vs ET (AI or Fulvestrant)	Amcenestrant vs ET (AI, Tamoxifen or Fulvestrant)	Giredestrant vs ET (AI or Fulvestrant)	Camizestrant (various doses) vs Fulvestrant	Imlunestrant (N~370) vs ET (AI or Fulv) (N=280) vs Imlunestrant + Abemaciclib (N= 180)
Primary Endpoint	PFS in ITT and *ESR1* mutant	PFS	PFS	PFS	PFS
Results	**Positive** **IIT: 2.79 vs 1.891** **HR 0.7** ***ESR1*m: 3.78 vs 1.87** **HR 0.55**	**Did not meet primary EP**	**Did not meet primary EP**	**Positive (SABCS 2022)** **3.7 vs 7.2 (75mg)** **HR 0.58** **3.7 vs 7.7(150mg)** **HR 0.67**	Not yet reported Modified from Jhaveri

A significant PFS benefit was seen in the *ESR1*-mutated population of EMERALD; a benefit trend was observed in acelERA BC and AMEERA-3



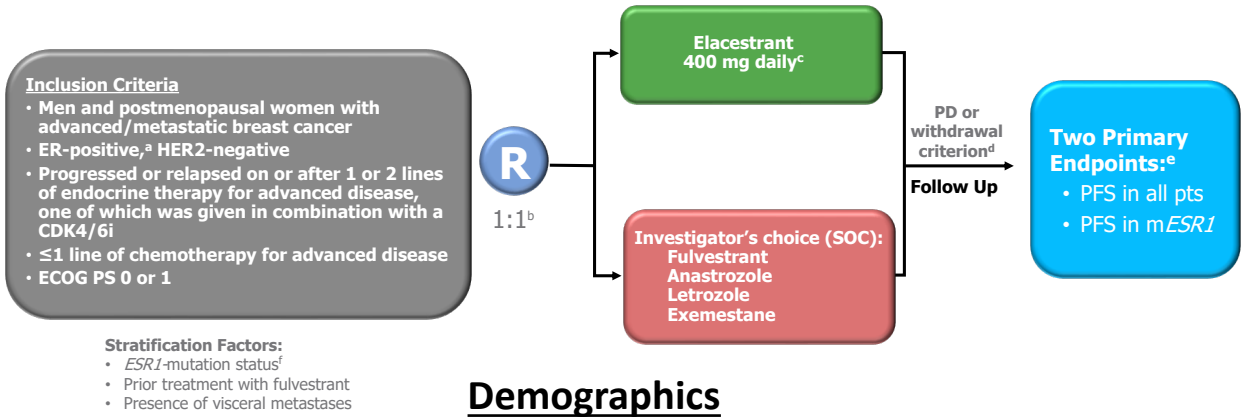
Giredestrant and elacestrant had comparable PFS hazard ratios vs. PCET in *ESR1*-mutated subpopulations; the HR for amcenestrant was notably higher

- It was announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[4]

1° primary; 2°, secondary; BC, breast cancer; EP, endpoint; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.

1. Martin M, *et al*. ESMO 2022 (Abstract 211MO; mini oral presentation); 2. Tolaney SM, *et al*. ESMO 2022 (Abstract 212MO; mini oral presentation); 3. Bidard F-C, *et al. J Clin Oncol* 2022; 4. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022).

EMERALD Phase 3 Trial: Elacestrant vs SOC ET



Demographics

- ~70% visceral mets
- ~40% 2 lines prior ET for MBC
- ~24% one line of chemotherapy
- 100% prior CDK4/6i

Conclusions

- Hazard ratios are relatively similar in pts who received >6 months prior CDK4/6i or longer
- Pts with endocrine sensitive disease had remarkable PFS with elacestrant alone
- Benefit was more marked in the ESR1 mutant population
- Next steps: combinations with targeted agents (ELEVATE)

Bardia, Bidard …… and **Kaklamani;** SABCS 2022

PFS by Duration of CDK4/6i: All Patients

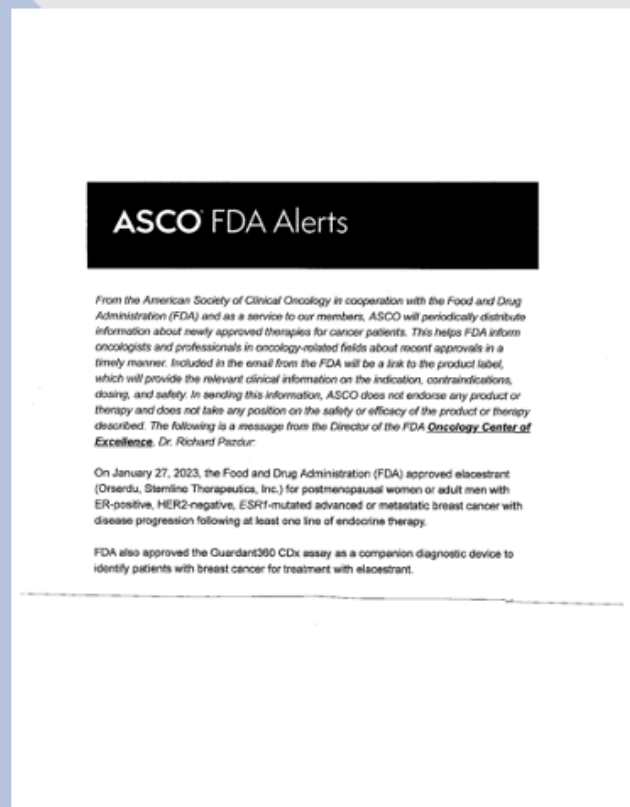
Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=202)	SOC (n=205)	Elacestrant (n=150)	SOC (n=160)	Elacestrant (n=98)	SOC (n=119)
Median PFS Months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

PFS by Duration of CDK4/6i: ESR1 mutant

Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=103)	SOC (n=102)	Elacestrant (n=78)	SOC (n=81)	Elacestrant (n=55)	SOC (n=56)
Median PFS Months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	



ASCO® FDA Alerts

From the American Society of Clinical Oncology in cooperation with the Food and Drug Administration (FDA) and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA inform oncologists and professionals in oncology-related fields about recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the Director of the FDA ***Oncology Center of Excellence****, Dr. Richard Pazdur:*

On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

Elacestrant approved 1/27/23 as 1st oral SERD

Additional Phase III SERD Trials for MBC: Examples

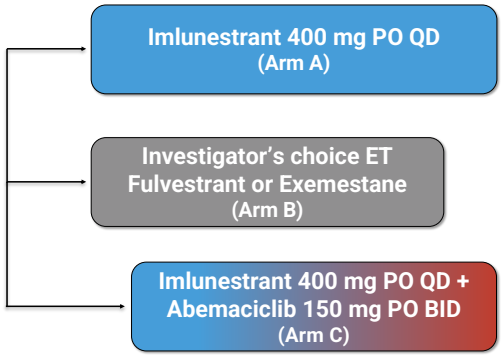
EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

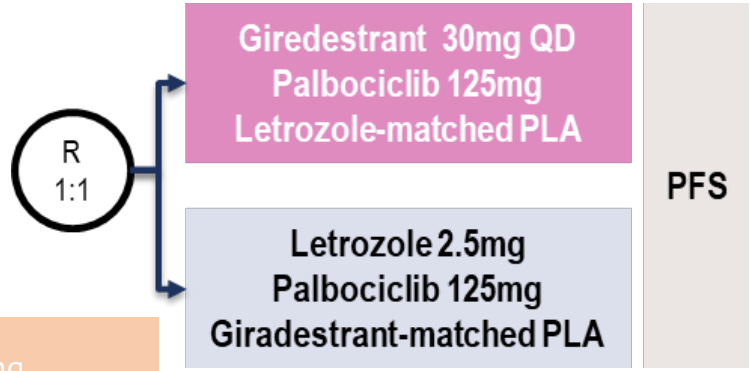


Primary Objective:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

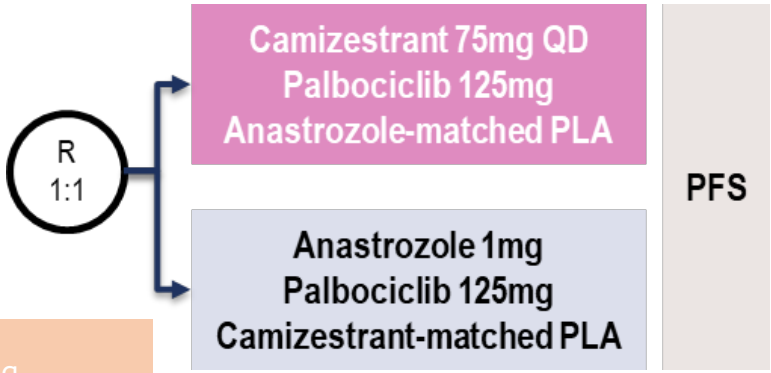


Recruiting

NCT04546009

SERENA-4

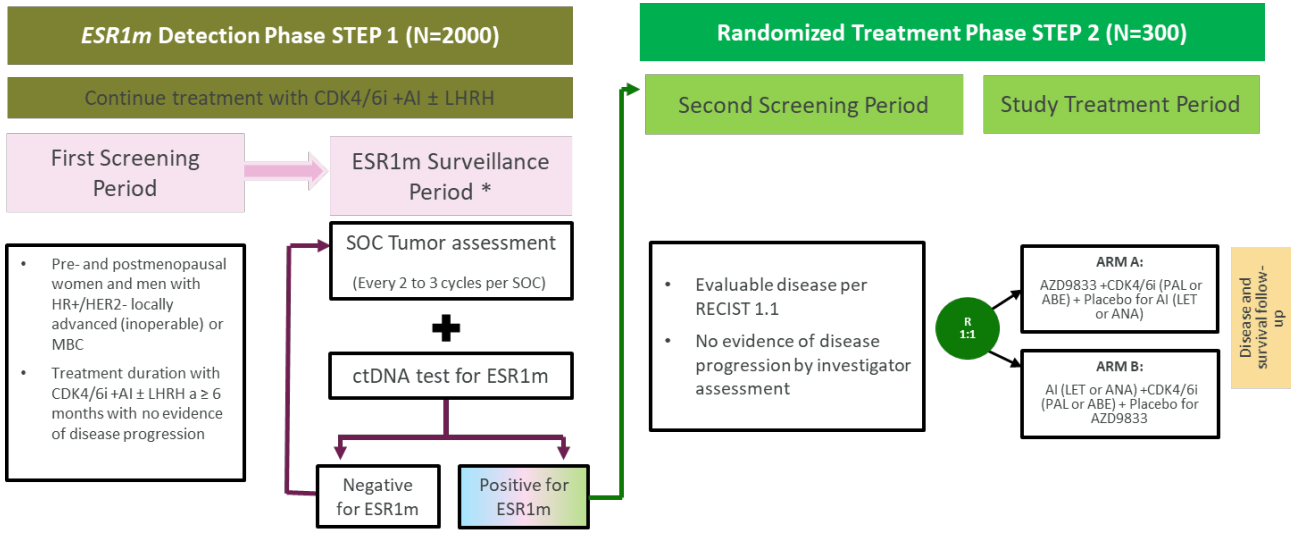
N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



Recruiting

NCT04711252

SERENA-6



SABCS 45 ER Positive metastatic BC

- AKT pathway
  - CAPItello-291 phase III trial

Session: General Session 3

GS3-04 Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial

Thursday, December 8, 2022 9:15 AM – 9:30 AM CT Location: Hall 3 CME 0.25 Credit Hours

Session Type: Oral Presentation
Submission Sub-Category: LB - 607. Advanced Therapy – Targeted

San Antonio Breast Cancer Symposium®, December 6–10, 2022

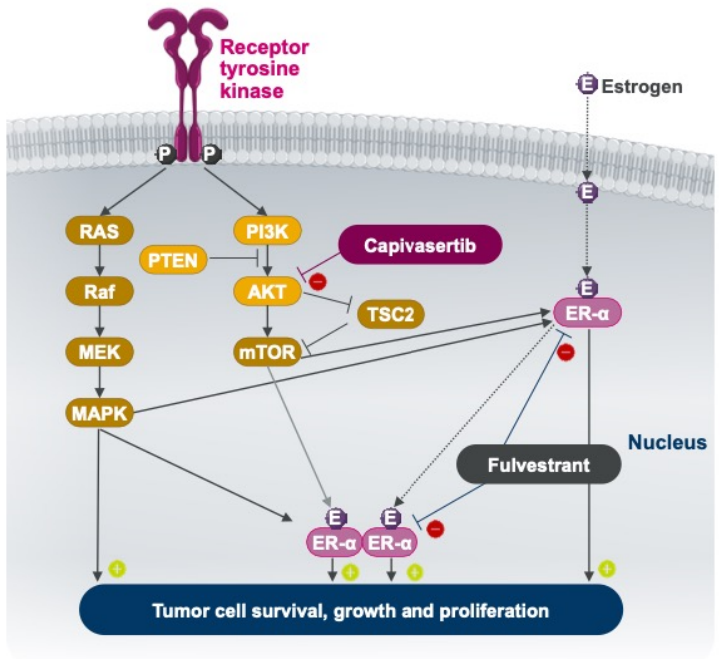
Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the Phase III CAPItello-291 trial

Nicholas C Turner,[1] Mafalda Oliveira,[2] Sacha Howell,[3] Florence Dalenc,[4] Javier Cortes,[5] Henry Gomez,[6] Xichun Hu,[7] Komal Jhaveri,[8] Sibylle Loibl,[9] Serafin Morales Murillo,[10] Zbigniew Nowecki,[11] Meena Okera,[12] Yeon Hee Park,[13] Masakazu Toi,[14] Lyudmila Zhukova,[15] Chris Yan,[16] Gaia Schiavon,[16] Andrew Foxley,[16] and Hope S Rugo[17]

[1]Institute of Cancer Research, Royal Marsden Hospital, London, UK; [2]Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [3]The Christie NHS Foundation Trust, Manchester, UK; [4]Institut Claudius Regaud, l'Institut Universitaire du Cancer de Toulouse Oncopole – IUCT Oncopole, Toulouse, France; [5]International Breast Cancer Center (IBCC), Barcelona, Spain; [6]Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru; [7]Shanghai Cancer Center, Fudan University, Shanghai, China; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]GBG Forschungs GmbH, Neu-Isenburg, Germany; [10]Institut de Recerca Biomèdica, Barcelona, Spain; [11]The Maria Skłodowska Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [12]ICON Cancer Centre, Adelaide, Australia; [13]Sungkyunkwan University School of Medicine, Samsung Medical Centre, Seoul, Republic of Korea; [14]Kyoto University Hospital, Kyoto, Japan; [15]Loginov Moscow Clinical Scientific Center, Moscow, Russia; [16]Oncology R&D, AstraZeneca, Cambridge, UK; [17]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

Background and overview of capivasertib

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*, but may also occur in cancers without those genetic alterations.[1,2] AKT signalling is also implicated in the development of resistance to endocrine therapy[2]
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- In the Phase II, placebo-controlled FAKTION trial[3]:
  - The addition of capivasertib to fulvestrant significantly improved PFS and OS in postmenopausal women with AI-resistant HR+/HER2– ABC in the overall population, with a more pronounced benefit in pathway altered tumours
  - No patients had received prior CDK4/6 inhibitors



1. Millis et al. *JAMA Oncol* 2016;2:1565-1573; 2. Toss et al. *Oncotarget*. 2018;9:31606-31619; 3. Howell et al. *Lancet Oncol* 2022;23:851–64. ABC, advanced breast cancer.

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

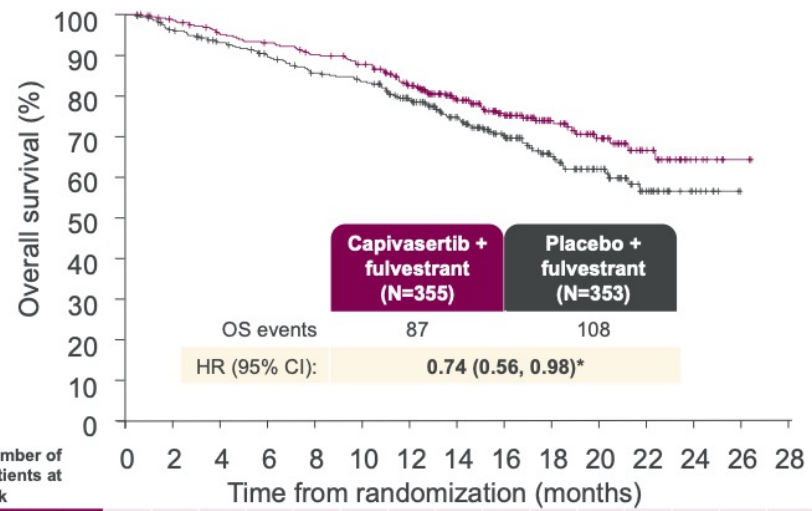
AKT pathway alterations

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

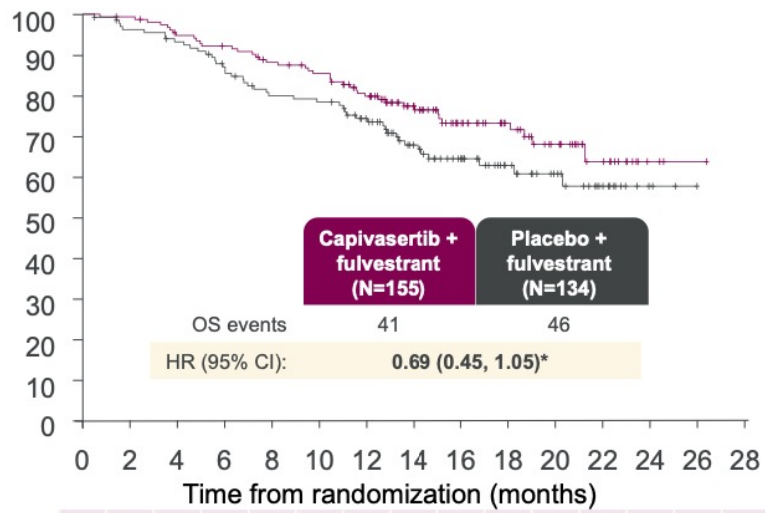
Overall survival at 28% maturity overall

Overall population



Number of patients at risk															
Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

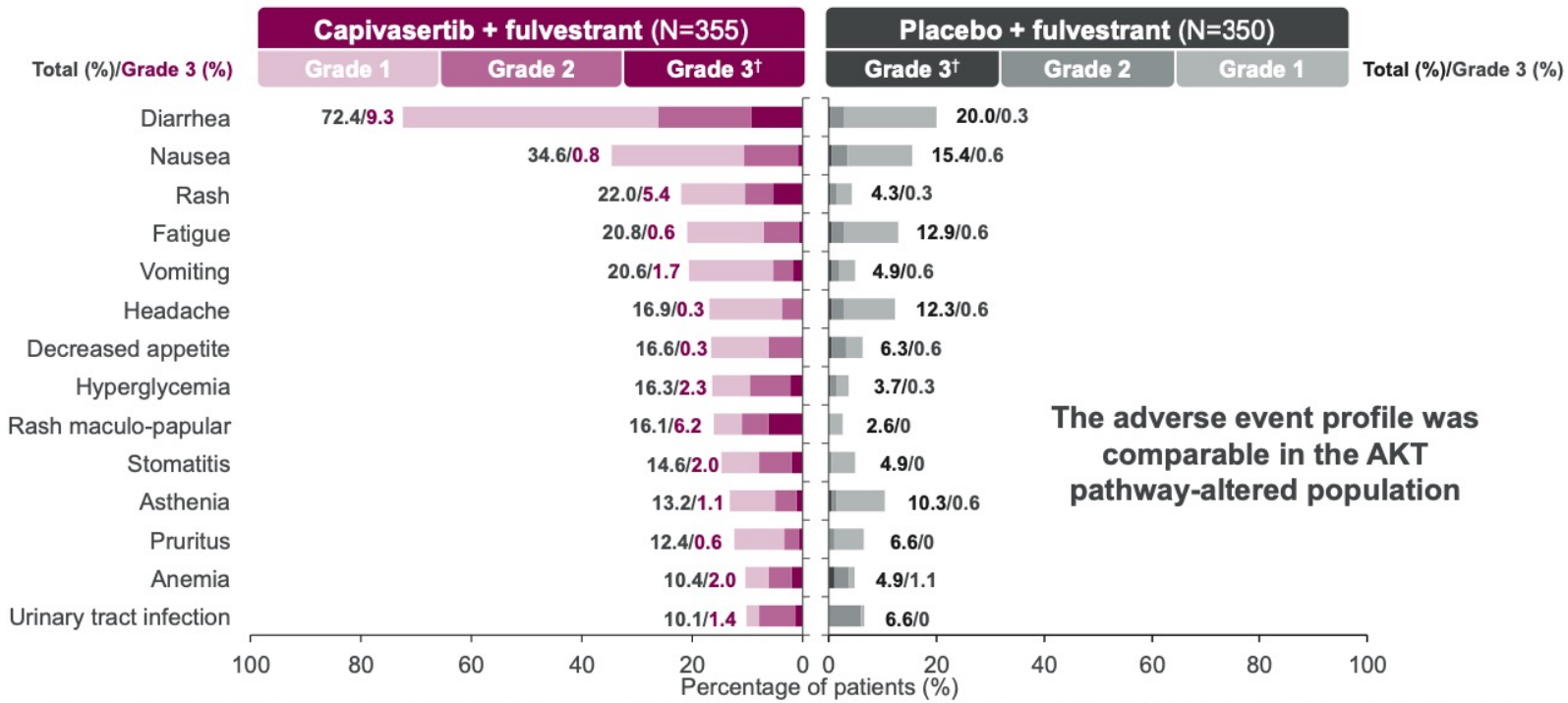
AKT pathway-altered population



Capivasertib + fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo + fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (overall population only) and prior use of CDK4/6 inhibitor.

Adverse events (>10% of patients) – overall population



The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

CAPItello-291: Conclusions

- Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered population (dual primary)
- Benefit from capivasertib was consistent across clinically relevant subgroups, including in:
  - patients previously treated with a CDK4/6 inhibitor
  - patients with liver metastases
- Overall survival follow-up is ongoing
- Capivasertib plus fulvestrant safety profile appears consistent with that previously reported, with a relatively low discontinuation rate due to adverse events

Capivasertib plus fulvestrant has the potential to be a future treatment option for patients with HR+ ABC who have progressed on an endocrine-based regimen

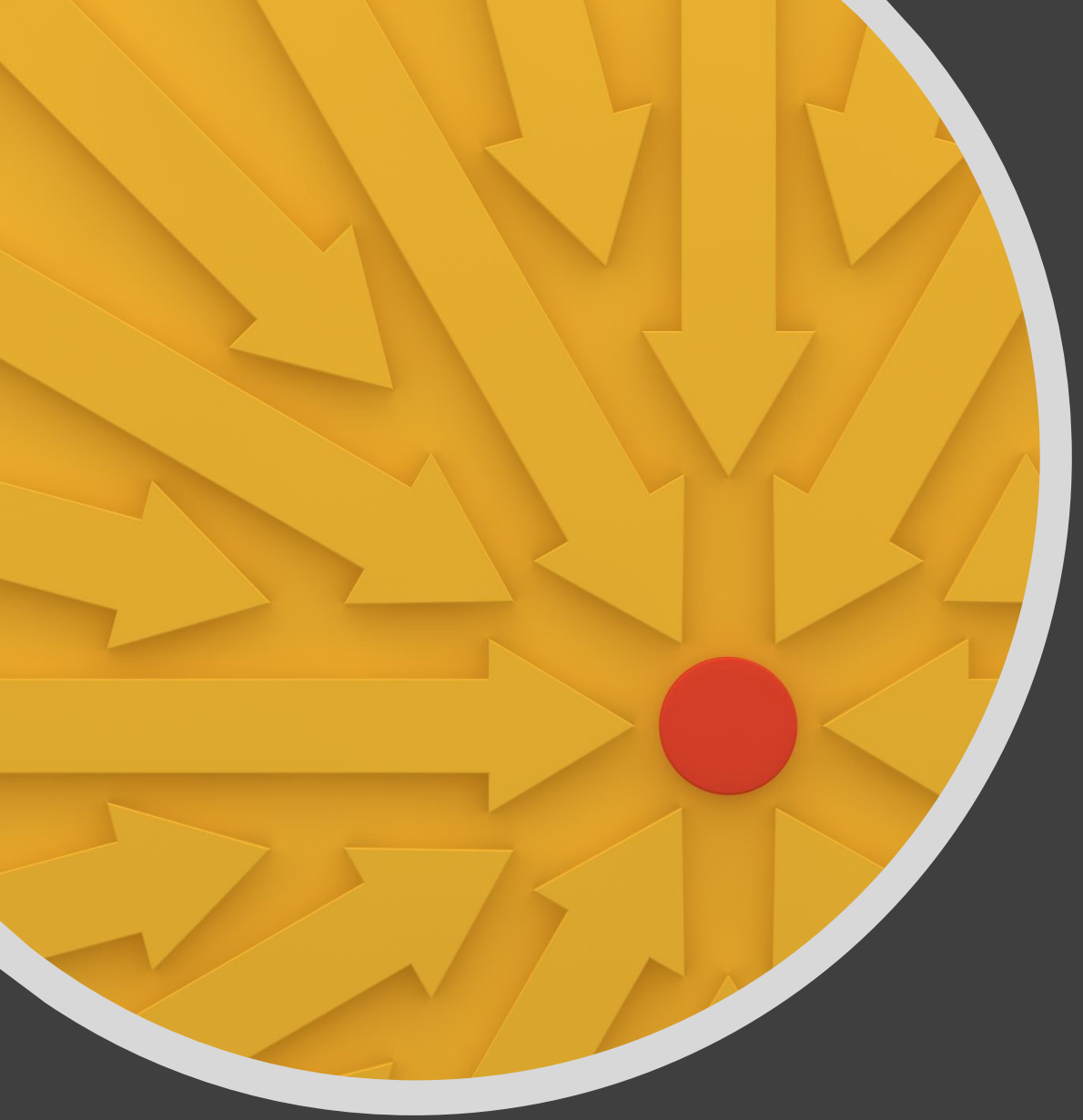
SABCS UPDATE 2022
Metastatic BC

Metastatic

- ER positive
- Her 2 low
- Her 2 neu positive

SABCS 45 Metastatic BC Treatment

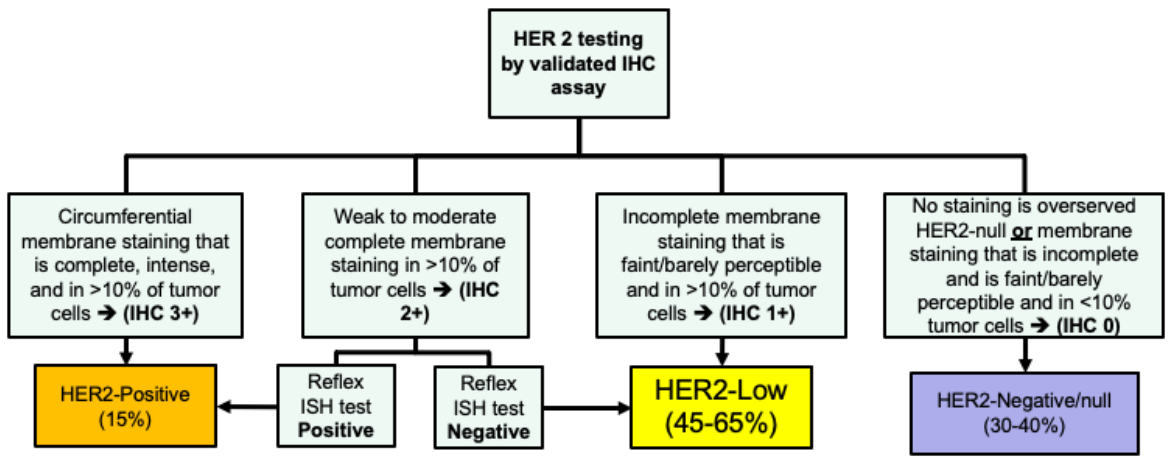
- Her 2 low
  - T-DXd
  - Sacituzumab govitecan-hzly



T-DXd

- Destiny-B04

HER2-Low Breast Cancer: Current Definition

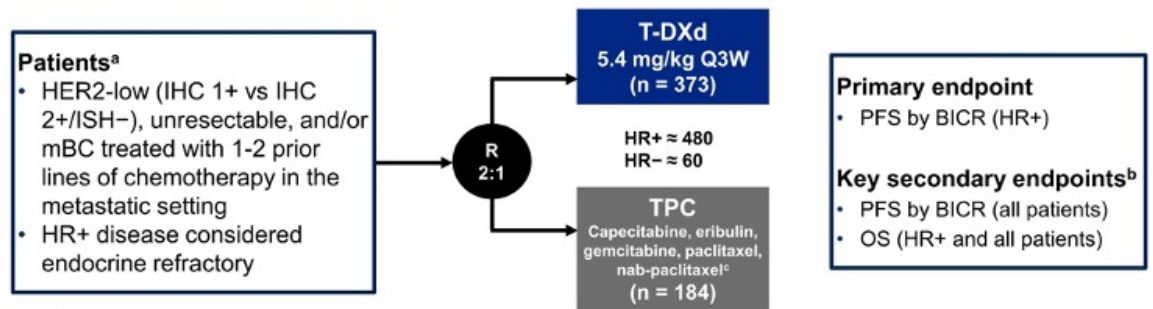


Trastuzumab Deruxtecan vs TPC: Study Design (DESTINY-B04)

DESTINY-Breast04

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



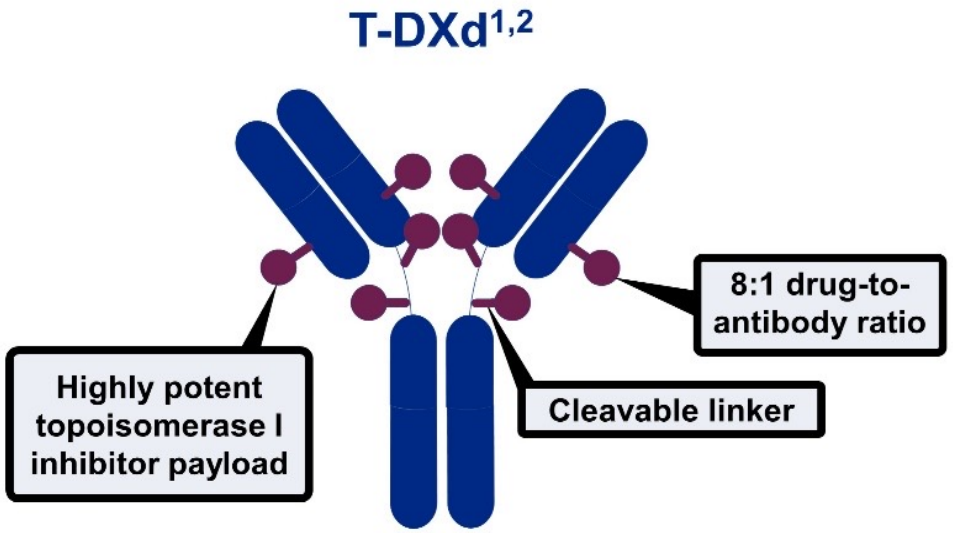
Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

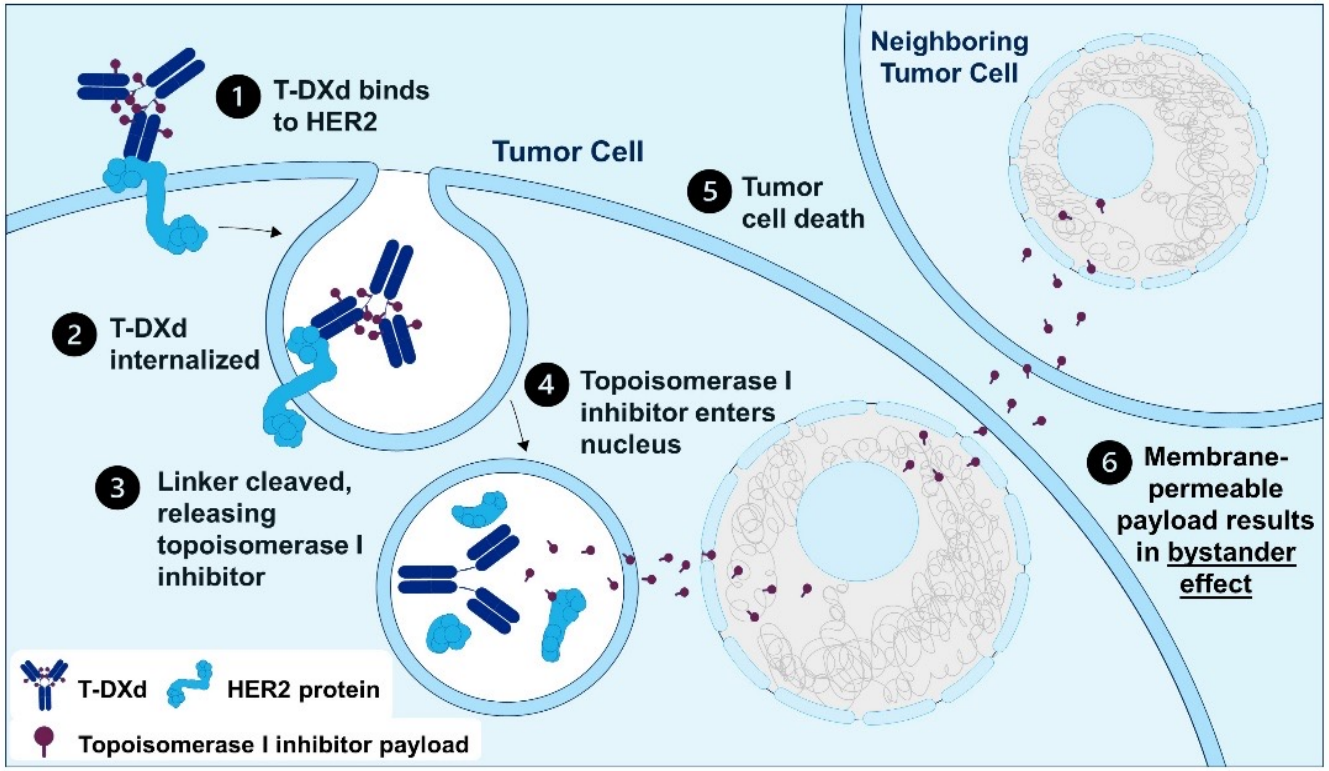
Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]All patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only (IUO) Assay system.

Trastuzumab Deruxtecan (T-DXd): Selective delivery of toxic payload



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

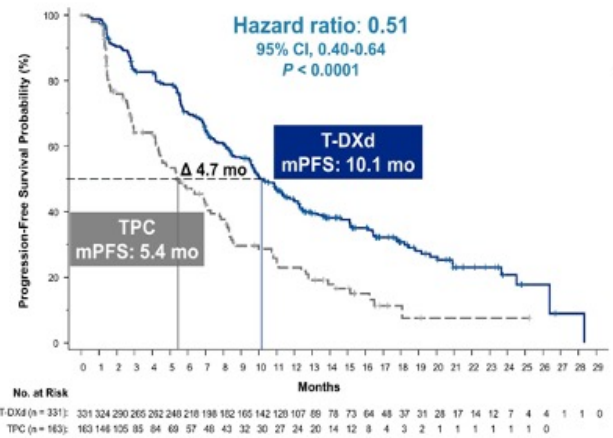
Nagayama, A, et al. Target Oncol. 2017

Modi S, et al. ASCO 2022.

Trastuzumab Deruxtecan vs TPC: PFS (HR+/HER2 Low BC)

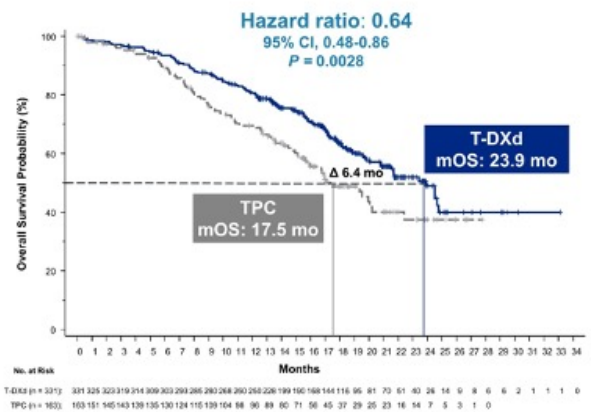
Progression-Free Survival

Hormone receptor–positive



Overall Survival

Hormone receptor–positive



PFS by blinded independent central review.

HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan;

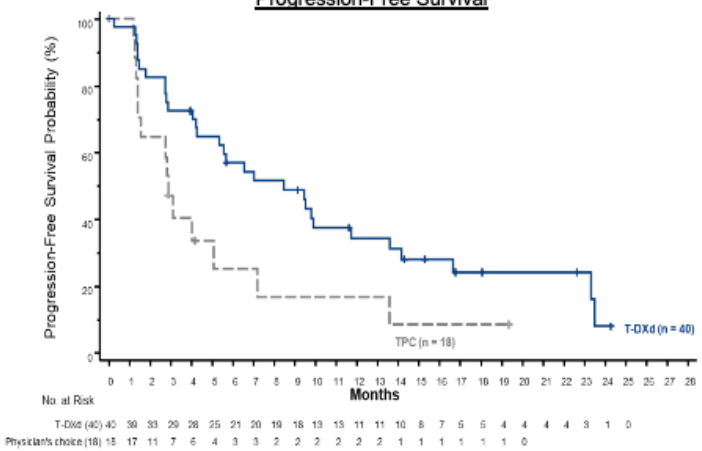
2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY:
Shanu Modi, MD

Trastuzumab Deruxtecan: Efficacy in HER2-low mTNBC

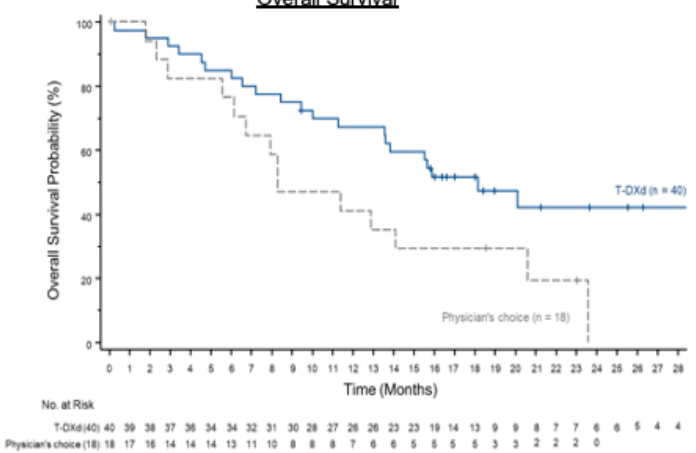
Exploratory Endpoint

Progression-Free Survival



	T-DXd (n=40)	TPC (n=18)
Median PFS (95% CI)	8.5 (4.3-11.7)	2.9 (1.4-5.1)
HR (95% CI), *P*-value	**0.46** (0.24-0.89)	

Overall Survival



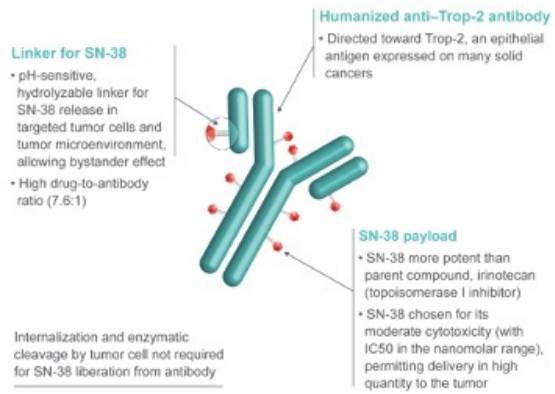
	T-DXd (n=40)	TPC (n=18)
Median OS (95% CI)	18.2 (13.6-NE)	8.3 (5.6-20.6)
HR (95% CI), *P*-value	**0.48** (0.24-0.95)	

Modi S et al. *NEJM*. 2022.

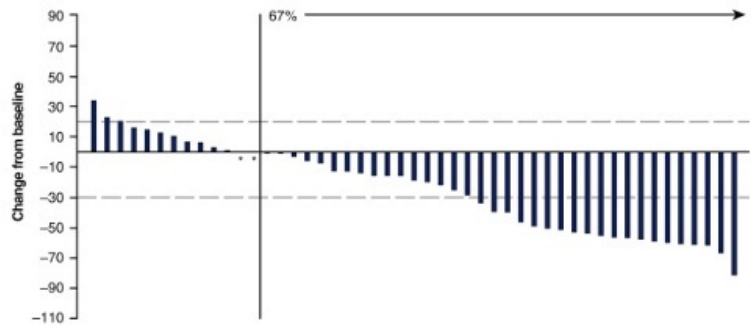
Sacituzumab govitecan-hzly

- TROPiCS-02
- ASCENT

Trop2 ADC for HR+ MBC: Sacituzumab Govitecan



Confirmed ORR = 31.5%



Phase I/II Basket Trial

≥3rd Line HR+/HER2- MBC N=54[a]

Other Advanced Epithelial Cancers

- Adults, ≥18 y
- Patients with metastatic epithelial cancers who progressed ≥1 standard therapeutic regimen for their disease
- ECOG performance status 0/1
- Measurable disease by CT/MRI

Sacituzumab govitecan 10 mg/kg IV

Days 1 and 8 every 21 days (restaging scans every 8 weeks)

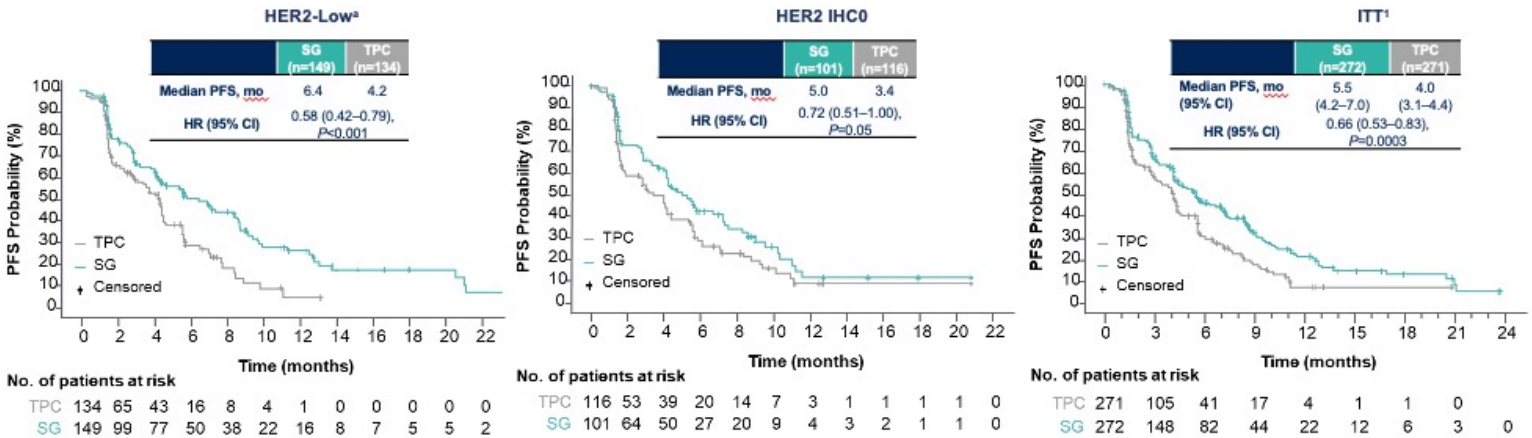
Until progression or unacceptable toxicity

Endpoints:

- Response evaluation by investigators according to RECIST 1.1
- Duration of response
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety

Kalinsky K et al. Ann Oncol. 2020

Sacituzumab Govitecan vs TPC: Efficacy by HER2 status (TROPiCS-02)



- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

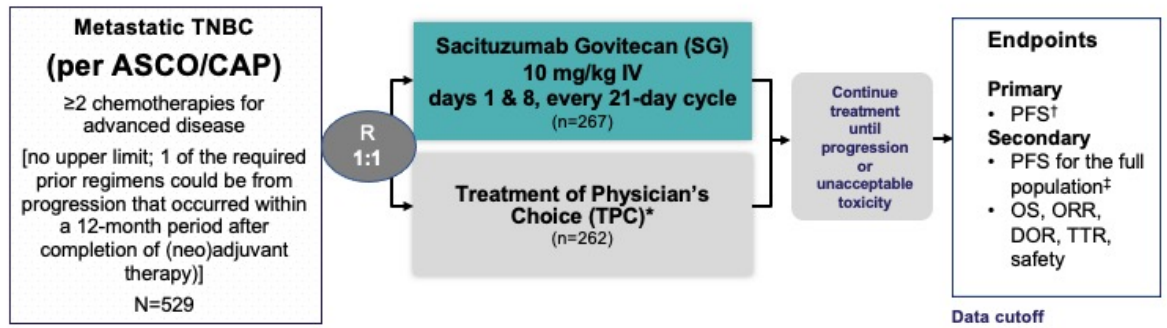
[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01032. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01032. Reprinted with permission from American Society of Clinical Oncology.

PARIS 2022 ESMO congress

Presented by: Dr. Frederik Marmé

Slide Number

Phase III Study of Sacituzumab Govitecan vs TPC: ASCENT



ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

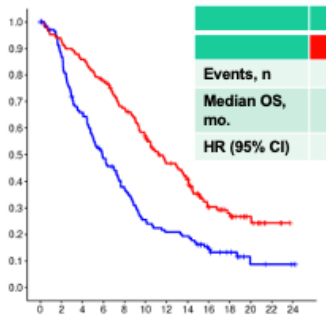
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia A et al. *NEJM*. 2021

Sacituzumab Govitecan vs TPC: Efficacy in HER2 low mTNBC (ASCENT)

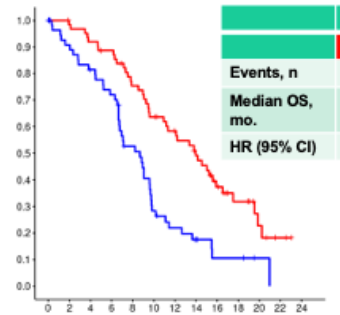
A **HER2 IHC0**



	HER2 IHC0	
	SG	TPC
Events, n	149	144
Median OS, mo.	11.3	5.9
HR (95% CI)	0.51 (0.39-0.66), *P*<0.001	

SG, HER2 IHC0	149	139	128	115	98	80	62	52	29	22	11	4	0
TPC, HER2 IHC0	144	118	88	64	48	33	27	25	15	9	3	2	1

B **HER-Low**



	HER2-Low*	
	SG	TPC
Events, n	63	60
Median OS, mo.	14.0	8.7
HR (95% CI)	0.43 (0.28-0.67), *P*<0.001	

SG, HER2 IHC0	63	61	57	54	45	38	32	26	17	10	5	2	0
TPC, HER2 IHC0	60	49	43	38	26	14	10	7	3	3	1	0	0

*HER2-Low defined as IHC1+ or ICH2+ and ISH-negative.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Hurvitz S et al. ESMO Breast. 2022

Sacituzumab govitecan-hzly Approved 2/3/23

ASCO FDA Alerts

From the American Society of Clinical Oncology in cooperation with the Food and Drug Administration (FDA) and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA inform oncologists and professionals in oncology-related fields about recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the Director of the FDA ***Oncology Center of Excellence****, Dr. Richard Pazdur:*

On February 3, 2023, the Food and Drug Administration (FDA) approved sacituzumab govitecan-hziy (Trodelvy, Gilead Sciences, Inc.) for unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

SABCS UPDATE 2022
Metastatic BC

Metastatic

- ER positive
- Her 2 low
- Her 2 neu positive

TDXd vs TDM1

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Cortés J et al. DOI: 10.1056/NEJMoa2115022

ORIGINAL ARTICLE

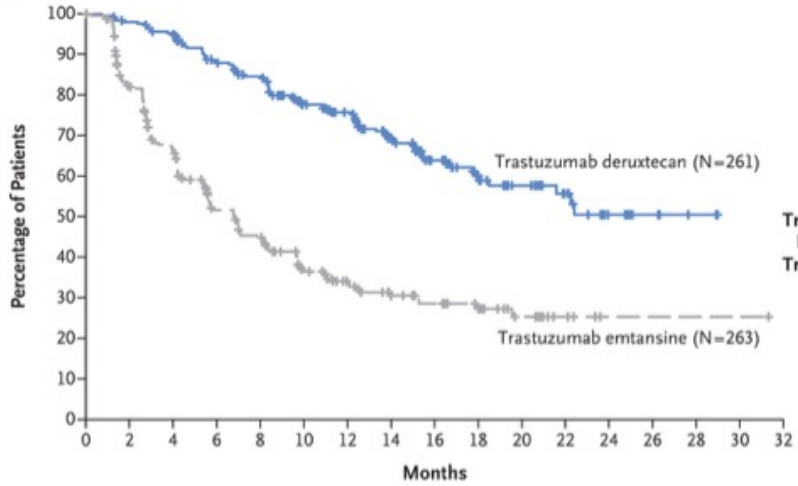
Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Javier Cortés, M.D., Ph.D., Sung-Bae Kim, M.D., Ph.D., Wei-Pang Chung, M.D., Seock-Ah Im, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Roberto Hegg, M.D., Ph.D., Min Hwan Kim, M.D., Ph.D., Ling-Ming Tseng, M.D., Vanessa Petry, M.D., Chi-Feng Chung, M.D., Hiroji Iwata, M.D., Ph.D., Erika Hamilton, M.D., et al., for the DESTINY-Breast03 Trial Investigators*

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Median age (range) — yr	54.3 (27.9–83.1)	54.2 (20.2–83.0)
Geographic region — no. (%)		
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Europe	54 (20.7)	50 (19.0)
Rest of world	41 (15.7)	36 (13.7)
Race — no. (%)†		
White	71 (27.2)	72 (27.4)
Black	10 (3.8)	9 (3.4)
Asian	152 (58.2)	162 (61.6)
Multiple	2 (0.8)	0
Other	26 (10.0)	20 (7.6)
Hispanic or Latinx ethnic group — no. (%)†		
Yes	29 (11.1)	29 (11.0)
No	203 (77.8)	209 (79.5)
Unknown	5 (1.9)	6 (2.3)
Data not collected	24 (9.2)	19 (7.2)
HER2 status — no. (%)‡		
3+	234 (89.7)	232 (88.2)

A Progression-free Survival



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

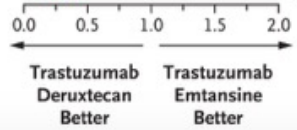
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

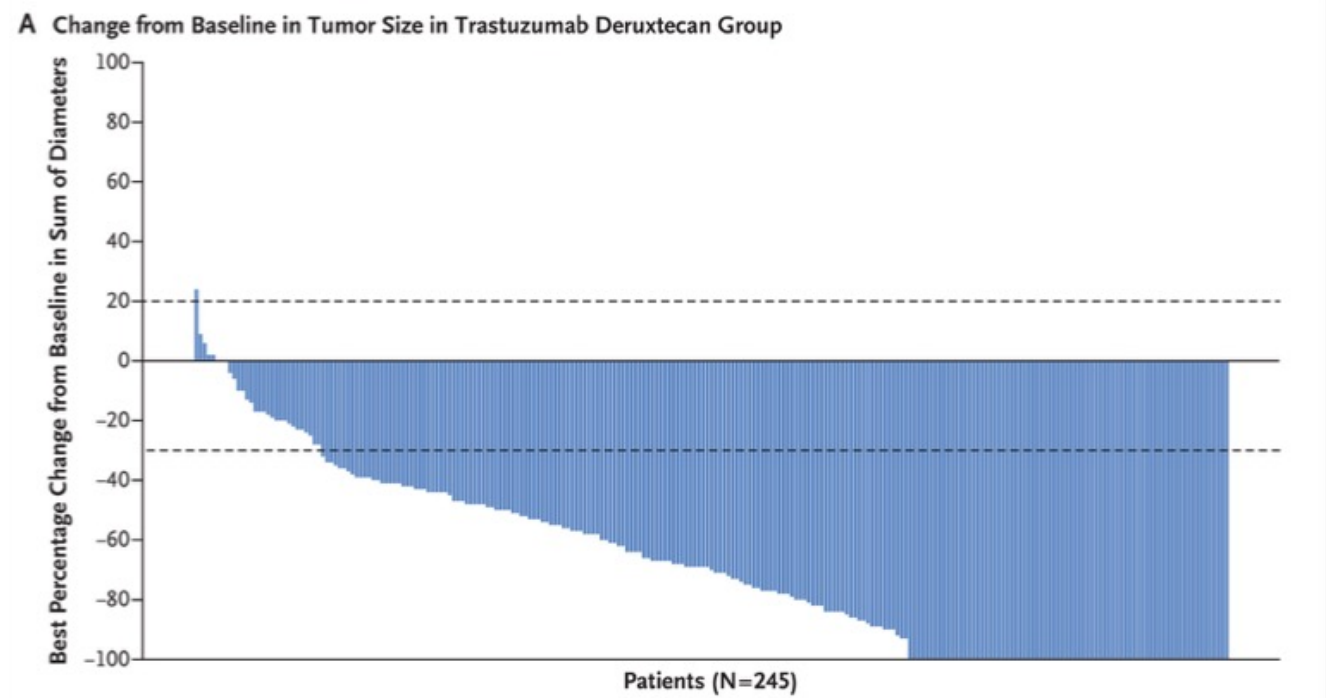
No. at Risk

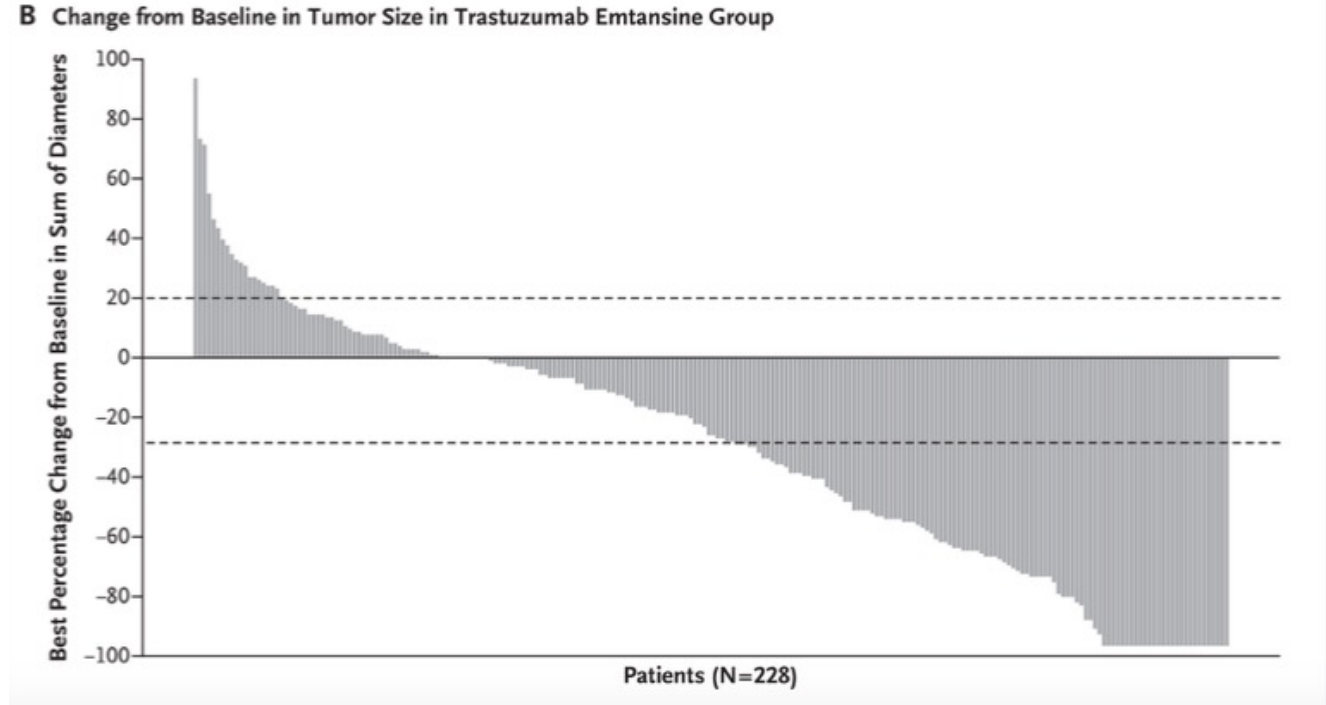
Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2		
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	1	0

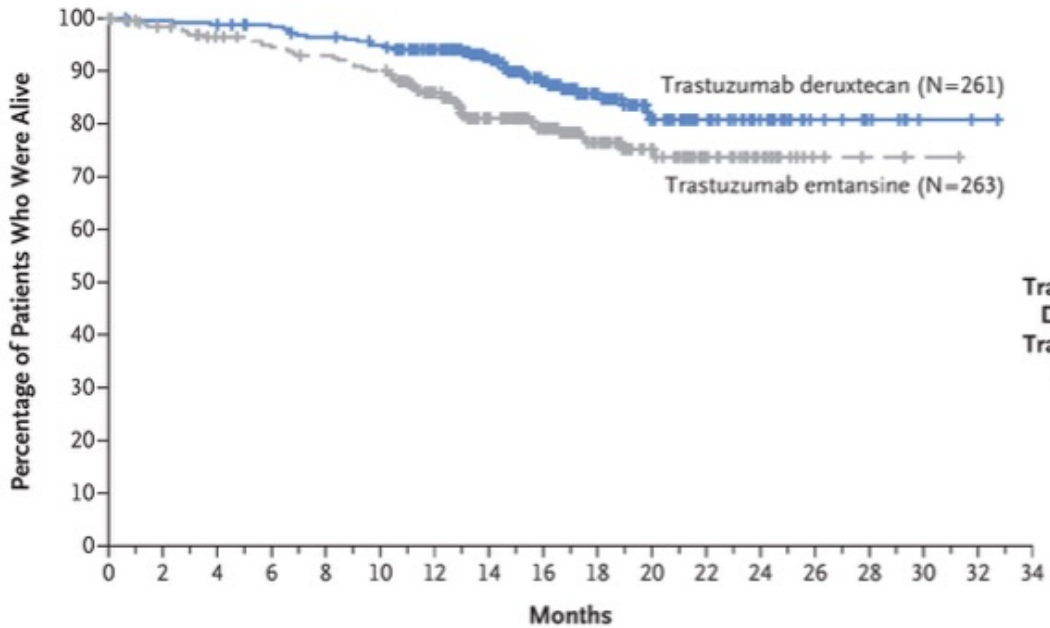
B Progression-free Survival in Prespecified Subgroups

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI) *mo*		Hazard Ratio for Disease Progression or Death (95% CI)
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)




A Change from Baseline in Tumor Size in Trastuzumab Deruxtecan Group
Best Percentage Change from Baseline in Sum of Diameters
100
80
60
40
20
0
−20
−40
−60
−80
−100
Patients (N=245)


B Change from Baseline in Tumor Size in Trastuzumab Emtansine Group
Best Percentage Change from Baseline in Sum of Diameters
100
80
60
40
20
0
−20
−40
−60
−80
−100
Patients (N=228)



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

RESEARCH SUMMARY

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Cortés J et al. DOI: 10.1056/NEJMoa2115022

CLINICAL PROBLEM

The antibody–drug conjugate trastuzumab deruxtecan is approved in the United States to treat patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have received at least two previous anti-HER2 regimens in the context of metastatic disease. The benefits of trastuzumab deruxtecan as second-line therapy are unknown.

CLINICAL TRIAL

Design: A phase 3, multicenter, open-label, randomized, controlled trial compared trastuzumab deruxtecan with standard second-line treatment, trastuzumab emtansine, in patients with HER2-positive metastatic breast cancer.

Intervention: 524 patients with metastatic cancer that had progressed during or after treatment with trastuzumab and a taxane or that had progressed within 6 months after neoadjuvant or adjuvant treatment with trastuzumab or a taxane were assigned to receive either trastuzumab deruxtecan or trastuzumab emtansine intravenously every 3 weeks. The primary end point was progression-free survival.

RESULTS

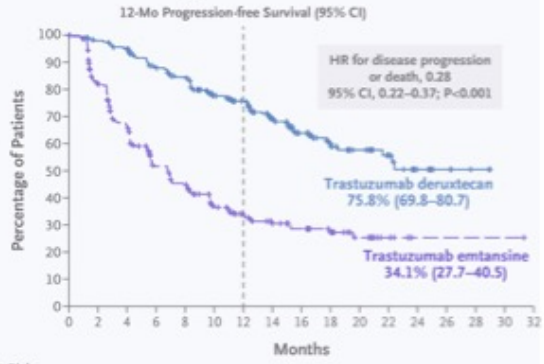
Efficacy: During a median follow-up of approximately 15 or 16 months, progression-free survival was significantly longer with trastuzumab deruxtecan than with trastuzumab emtansine.

Safety: The incidence of drug-related adverse events was higher with trastuzumab deruxtecan than with trastuzumab emtansine. In particular, drug-related interstitial lung disease or pneumonitis was more common with trastuzumab deruxtecan; all such events in both groups were of grade 3 or lower.

LIMITATIONS AND REMAINING QUESTIONS

- Longer follow-up is needed to assess the effect of trastuzumab deruxtecan on overall survival.
- Whether trastuzumab deruxtecan is associated with late toxic effects is unknown.

Progression-free Survival



Drug-Related Adverse Events

Adverse Event	Trastuzumab deruxtecan (N=257)	Trastuzumab emtansine (N=261)
Drug-related events, any grade — %	98.1	86.6
Drug-related events, grade ≥3 — %	45.1	39.8
Interstitial lung disease or pneumonitis, any grade — no. (%)	27 (10.5)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	18 (7.0)	1 (0.4)
Grade 3	2 (0.8)	0

CONCLUSIONS

In patients with HER2-positive metastatic breast cancer and disease progression after treatment with trastuzumab and a taxane, trastuzumab deruxtecan showed a progression-free survival benefit over standard second-line treatment with

- https://youtube.com/watch?v=5F-BhY4q3wo&feature=shares

SABCS 45 Tidbits

Genetics

Duration of adjuvant endocrine therapy

San Antonio Breast Cancer Symposium®, December 6-10, 2022

MAYO CLINIC

Population-based Estimates of Contralateral Breast Cancer Risk among Carriers of Germline Pathogenic Variants in *ATM, BRCA1, BRCA2, CHEK2* and *PALB2*

Siddhartha Yadav, MD, FACP
On behalf of
CARRIERS CONSORTIUM
PI: Fergus J. Couch, PhD

Introduction

- *ATM, CHEK2* and *PALB2:* Contralateral breast cancer risk is not well-defined.

- *BRCA1* and *BRCA2:* Contralateral breast cancer risk has primarily been investigated among women qualifying for genetic testing.

- The effects of several important other factors on contralateral breast cancer risk in germline PV carriers are not known:
  - Age and menopausal status at initial breast cancer diagnosis
  - Race/ethnicity
  - Adjuvant endocrine therapy (in ER+ initial breast cancer)

Introduction

- Precise estimates of contralateral breast cancer in PV carriers can inform:
  - Surveillance strategies (e.g. Supplemental MRI)
  - Risk-reducing strategies (e.g. contralateral prophylactic mastectomy)
  - Personalized approach to risk management

San Antonio Breast Cancer Symposium®, December 6-10, 2022

The CARRIERS Study

- Population-based case-control study

Gene	Odds Ratio	95% CI	P Value
ATM	1.8	1.5 – 2.3	<0.001
BRCA1	7.6	5.3 – 11.3	<0.001
BRCA2	5.2	4.1 – 6.8	<0.001
CHEK2	2.5	2.0 – 3.0	<0.001
PALB2	3.8	2.7 – 5.6	<0.001

Hu et. al. N Engl J Med 2021;384:440-451

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Investigating Contralateral Breast Cancer in the CARRIERS study

15,104 women with unilateral invasive breast cancer from 10 prospective epidemiological studies in the United States

Inclusion:
-Preserved contralateral breast
-At least one year of follow up

Exclusion:
- DCIS at initial diagnosis

Results of germline sequencing for 5 genes using a QIAseq custom panel

- Time-to-event analysis comparing contralateral breast ca risk between carriers in each gene vs. non-carriers
  - Multivariate proportional hazard regression analysis accounting for competing risk of death[1]
    - Censoring at last follow-up or contralateral prophylactic mastectomy
- Adjusting for contributing study, race/ethnicity, age at diagnosis, menopausal status, histology and ER status of the first breast cancer and the use of endocrine therapy

1. Fine JP and Gray RJ. Journal of the American Statistical Association 1999; 94:496-509

Patient Characteristics

	N=15,104 (%)
Median age at diagnosis	62 years
Race/ethnicity:	
Non-Hispanic White	9,513 (63%)
Black	2,249 (15%)
Post-menopausal status*	11,050 (73%)
ER-positive breast cancer*	11,406 (75%)
Ductal histology*	11,882 (79%)
Adjuvant endocrine therapy use*	7,004 (46%)

*: At first breast cancer diagnosis

Contralateral Breast Cancer Events

- Median follow-up duration: 11 Years

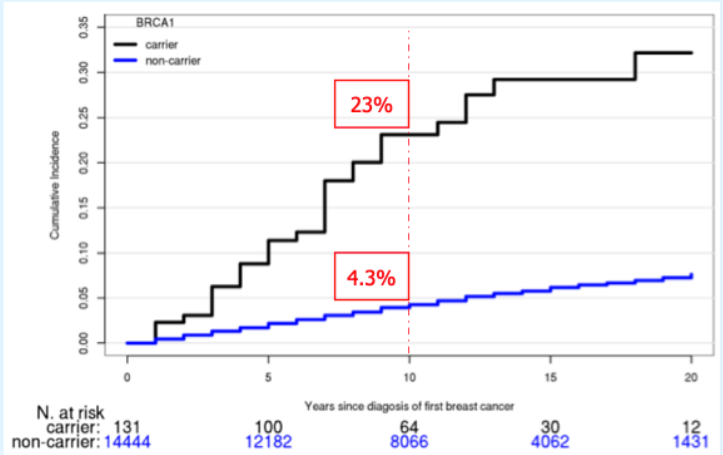
Gene	Total (n)	CBC Events (n)
Non-carriers	14,444	711
ATM	116 (0.7%)	7
BRCA1	132 (0.9%)	31
BRCA2	170 (1.1%)	33
CHEK2	140 (0.9%)	12
PALB2	97 (0.6%)	7
Total		**801**

CBC: Contralateral Breast Cancer

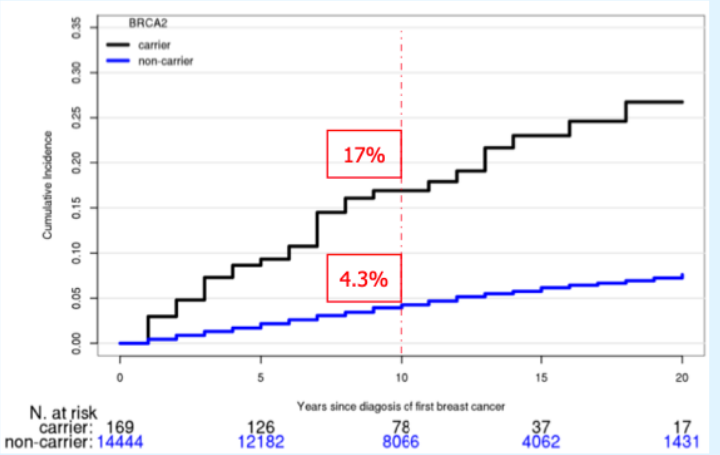
San Antonio Breast Cancer Symposium®, December 6-10, 2022

Unadjusted Cumulative Incidence of CBC from the First Breast Cancer Diagnosis

BRCA1



BRCA2



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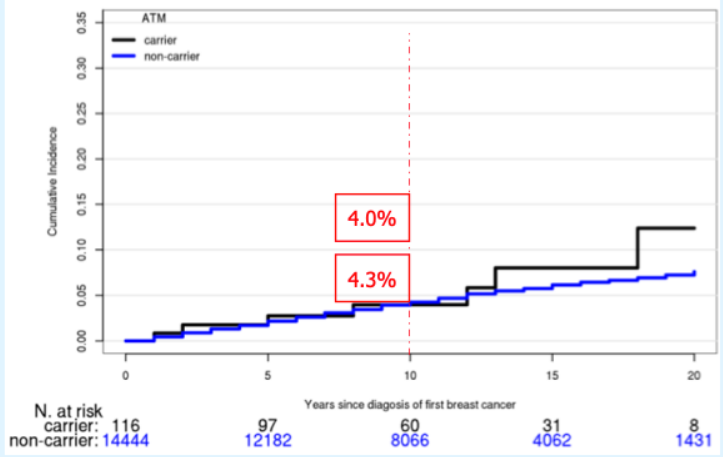
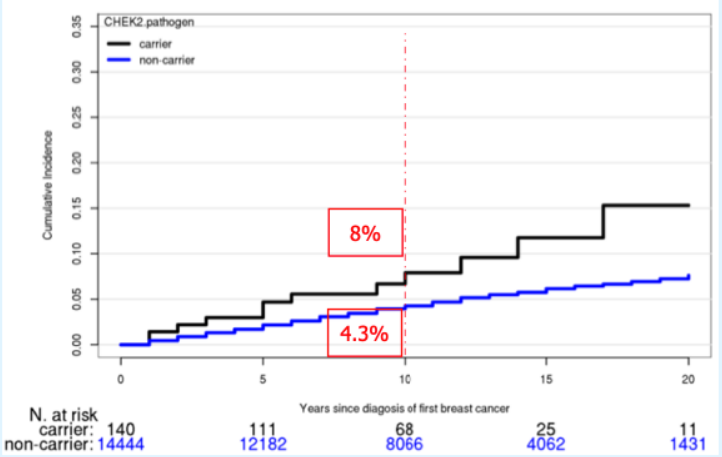
Unadjusted Cumulative Incidence of CBC from the First Breast Cancer Diagnosis

ATM



CHEK2



Unadjusted Cumulative Incidence of CBC from the First Breast Cancer Diagnosis

	10-year Cumulative Incidence of CBC (Overall)	10-year Cumulative Incidence of CBC in ER-negative first BC
Non-carriers	4.3%	5.4%
PALB2	7.9%	19.7%

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Contralateral Breast Cancer Risk in **women over the age of 65** at first breast ca diagnosis

- Total, **N=6010**
- PV carriers in *ATM, BRCA1, BRCA2, CHEK2* and *PALB2=* **153 (2.6%)**
- Median follow-up duration: **10 years**
- Number of contralateral breast cancer events in PV carriers: **3**

Discussion – Key Points

- Largest study of contralateral breast cancer risk from population-based prospective studies

- Contralateral breast cancer (CBC) risk in germline PV carriers:
  - *BRCA1, BRCA2* and *CHEK2*: > 2-fold increased risk
  - *ATM:* CBC risk not increased
  - *PALB2:* Only PV carriers with ER-negative breast cancer were at an increased risk
    - Effect of adjuvant endocrine therapy?

- Black women with *BRCA1* or *BRCA2* PVs have a similarly elevated risk of CBC as non-Hispanic White women.
  - Risk-management strategies should be similar

- https://youtube.com/watch?v=5F-BhY4q3wo&feature=shares

SABCS 45 Tidbits

- Duration of adjuvant endocrine therapy

SABCS 45 Tidbits

Duration of adjuvant endocrine therapy

SABCS 45 Tidbits

Duration of adjuvant endocrine therapy

SOFT cohort, translational data

Evaluation of the Breast Cancer Index in premenopausal women with early-stage HR+ breast cancer in the SOFT trial

Ruth O'Regan[1], Yi Zhang[2], Gini F Fleming[3], Prudence Francis[4,5], Roswitha Kammler[6], Giuseppe Viale[7,8], Istvan Lang[9], Meritxell Bellet[10,11], Herve Bonnefoi[12], Sherene Loi[4], Marco Colleoni[13], Cathy Schnabel[2], Kai Treuner[2], Meredith M Regan[14,15]

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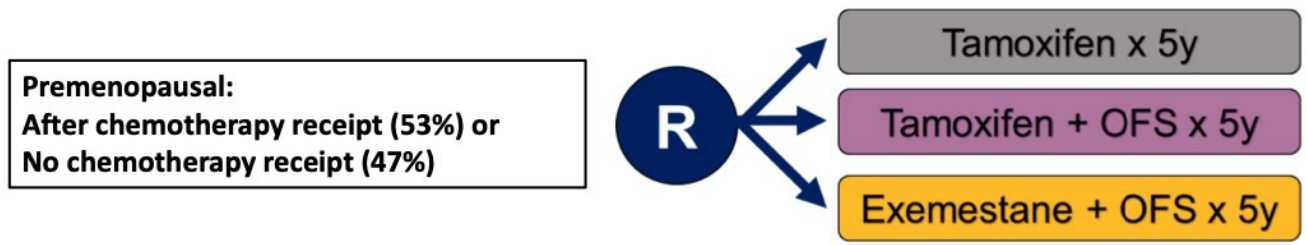
SOFT: Suppression of Ovarian Function Trial

- 3066 patients with HR+ invasive early BC, premenopausal after chemotherapy or premenopausal and did not receive chemotherapy (per investigator/patient decision), were randomized in 1:1:1 ratio



- With 12-year median follow-up:
  - 3% improvement 12-year freedom from distant recurrence with EXE+OFS vs TAM alone (HR: 0.75, 95% CI: 0.59-0.97)
  - DRFI benefit for EXE+OFS (3%) greater than for TAM+OFS (1.4%)

Hypotheses to be Tested in SOFT Population

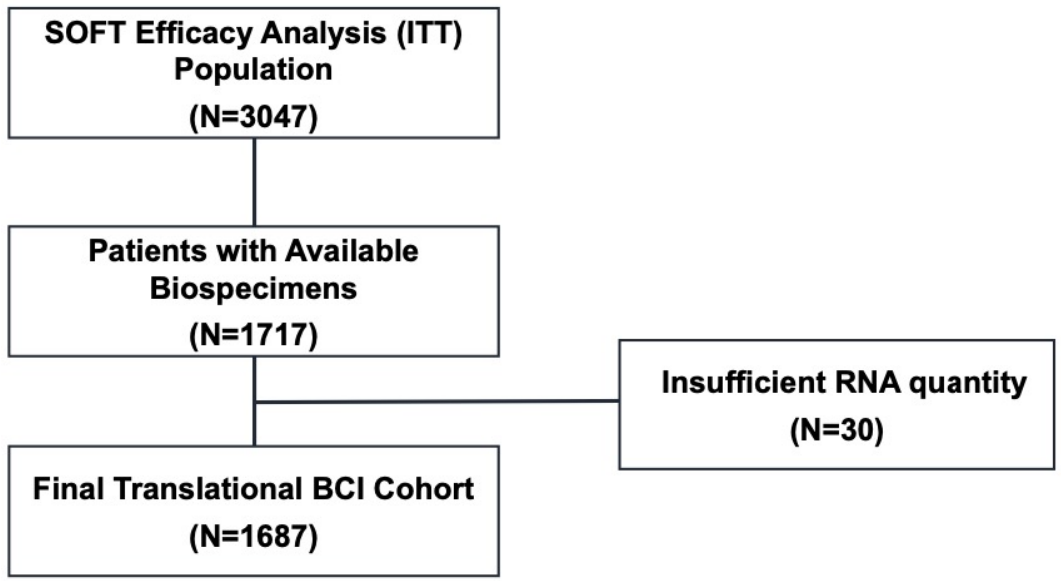
- BCI and BCIN+ are prognostic in patients with N0 and N1 disease, respectively, who received endocrine therapy with/without chemotherapy
- BCI (H/I)-High status is predictive of OFS benefit whereas BCI (H/I)-Low status is not
  - Hypothesis based on previous BCI data in adjuvant (extended) endocrine therapy[1-4]

[1]Sgroi et al. JNCI 2013 (105):1036; [2]Barlett et al. CCR 2022 (28):1872; [3]Noordhoek et al. CCR 2021(27):311; [4]Mamounas et al. JCO 2021 (39:15_suppl):S501

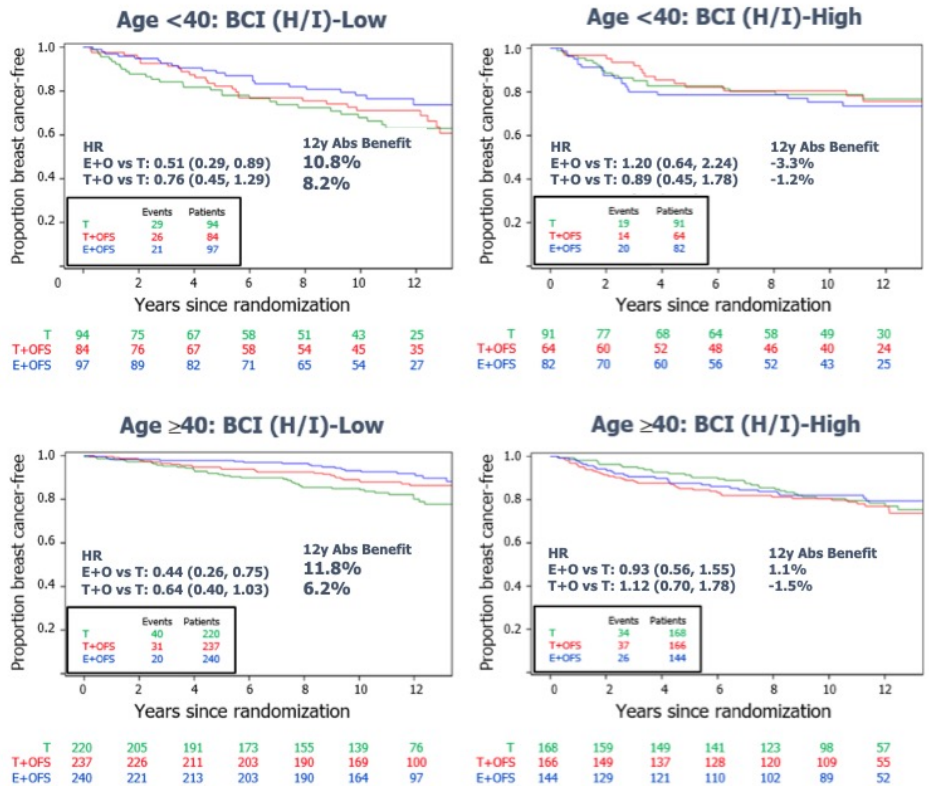
Study Objectives and Endpoints

- **Study objectives**
  - **Primary**: Evaluate if BCI (H/I) predicts benefit from EXE+OFS vs TAM
  - **Secondary**:
    - Evaluate if BCI and BCIN+ are prognostic in premenopausal women with N0 and N1 breast cancer, respectively
    - Evaluate if BCI (H/I) predicts benefit from TAM+OFS vs TAM
- **Study endpoints**:
  - Breast Cancer-Free Interval (BCFI: invasive local, regional, distant, contralateral) for predictive analysis
  - Distant Recurrence-Free Interval (DRFI) for prognostic analysis
- **Statistical considerations:**
  - Cox regression and log-rank test stratified on nodal status and prior chemotherapy use, adjusted for treatment, age, tumor size, grade and HER2 status
  - Clinical and outcome data were based on 2021 database lock after 12 years median follow-up

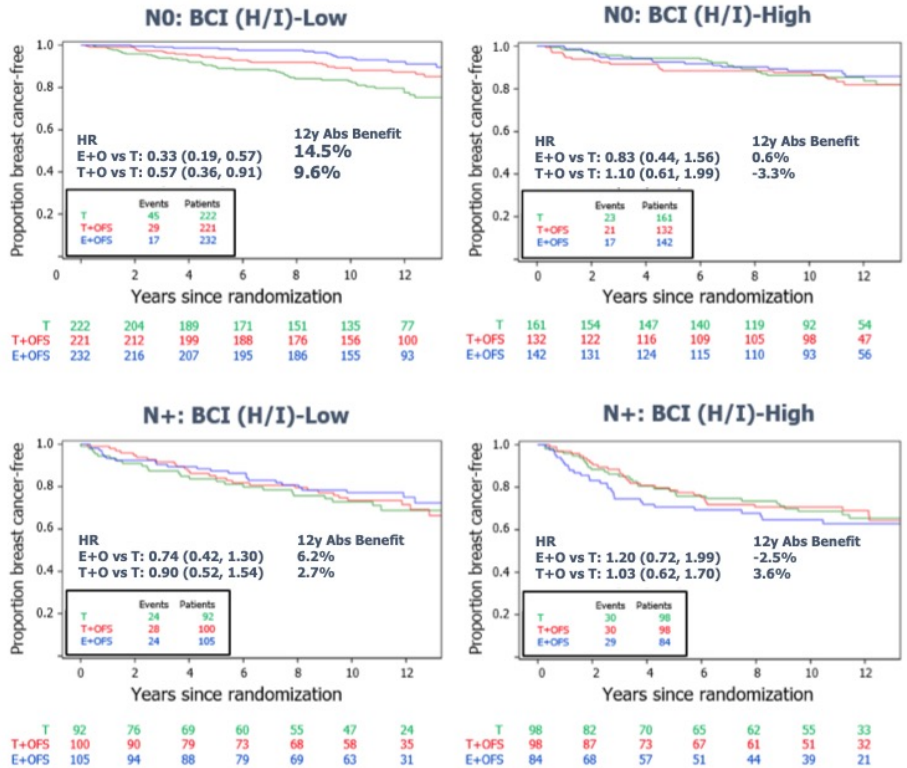
SOFT Translational Cohort Case Flow



BCI (H/I) Predictive Results for BCFI – Age

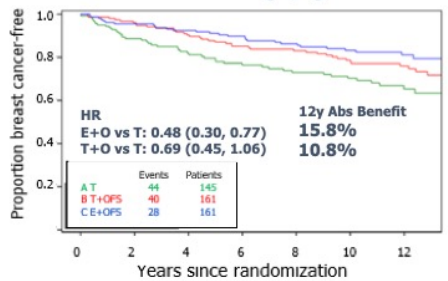


BCI (H/I) Predictive Results for BCFI – Nodal Status



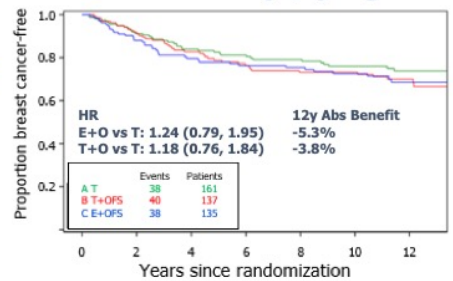
BCI (H/I) Predictive Results for BCFI – Prior Chemo or No Chemo

Chemo: BCI (H/I)-Low



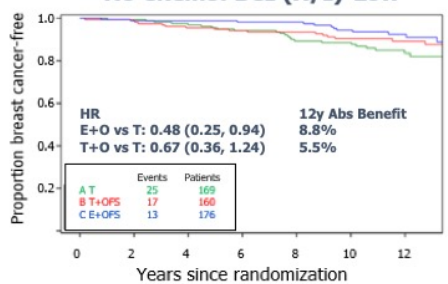
A T	145	122	108	93	84	71	41
B T+OFS	161	150	137	125	119	103	69
C E+OFS	161	151	142	128	119	102	60

Chemo: BCI (H/I)-High



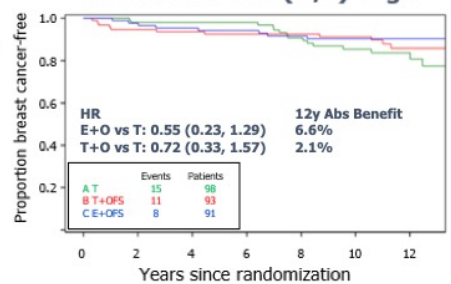
A T	161	142	125	117	110	92	57
B T+OFS	137	123	107	96	90	78	45
C E+OFS	135	116	102	93	84	72	39

No Chemo: BCI (H/I)-Low



A T	169	158	150	138	122	111	60
B T+OFS	160	152	141	136	125	111	66
C E+OFS	176	159	153	146	136	116	64

No Chemo: BCI (H/I)-High



A T	98	94	92	88	71	55	30
B T+OFS	93	86	82	80	76	71	34
C E+OFS	91	83	79	73	70	60	38

Summary & Conclusions

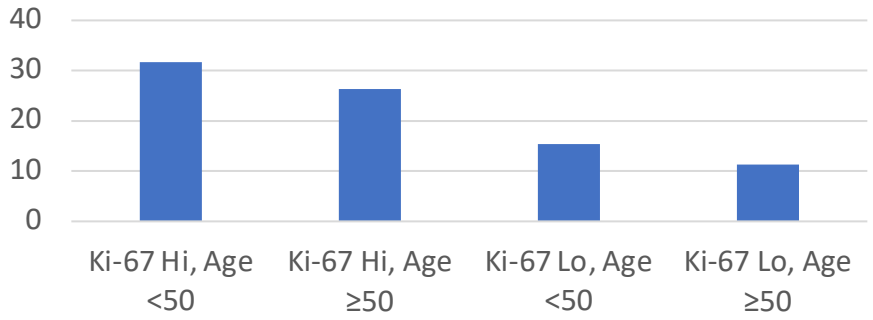
- BCI translational cohort was representative of SOFT parent trial
- BCI risk scores were prognostic in premenopausal women with HR+ tumors receiving adjuvant endocrine therapy
  - Higher risk scores associated with worse outcome
- BCI (H/I) was predictive of OFS benefit
  - Contrary to study hypothesis, BCI (H/I)-Low group consistently derived clinically meaningful benefit while BCI (H/I)-High group did not
- Results point to potential differences in the tumor biology underlying the OFS response
- First genomic assay to demonstrate benefit from OFS supporting additional clinical utility of BCI in premenopausal women

- https://youtube.com/watch?v=5F-BhY4q3wo&feature=shares

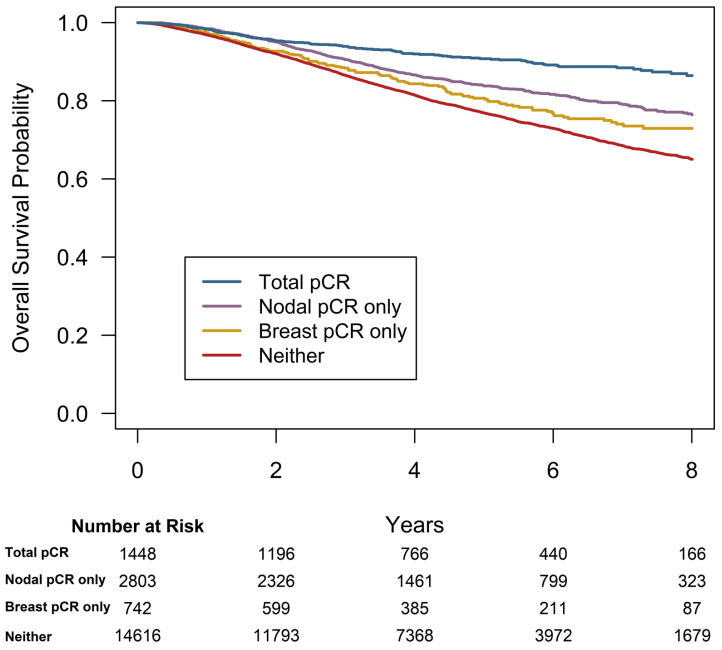
ER+/HER2- Breast Cancer Treated with Neoadjvuant Chemotherapy: Total pCR vs nodal pCR

NCDB: 2010-2018, 20,084 cN+ ER+/HER2- BC pts treated with NAC.

- 7.4% had total pCR
- **14.3% had nodal-only pCR**



Nodal pCR is highly prognostic for survival in ER+/HER2- Breast Cancer



Number at Risk

Total pCR	1448	1196	766	440	166
Nodal pCR only	2803	2326	1461	799	323
Breast pCR only	742	599	385	211	87
Neither	14616	11793	7368	3972	1679

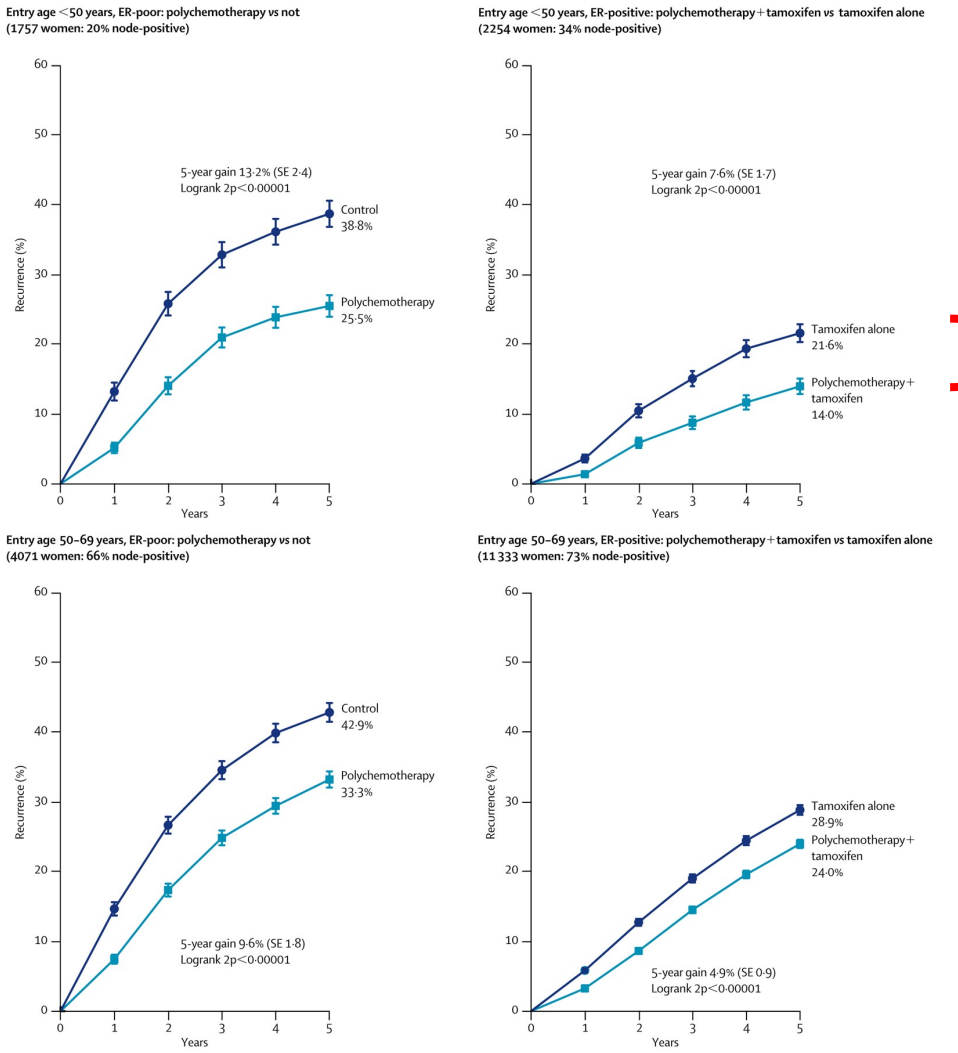
NCDB: Nodal pCR more likely in a) premenopausal pts and b) high Ki-67.

RxPONDER inclusion criteria (cT1-3, N1, Grade I or II, ER+/PR+/Her2-)

- Nodal pCR varied by age: 17.5% in age < 50 vs 13.6% in age ≥ 50, p<0.001
- Nodal pCR also varied by Ki-67: 16.8% in Ki-67 ≥ 20% vs 7.9% in Ki-67 < 20%, p<0.001

Moldovenau et al. SABCS 2022

Polychemotherapy versus not, by entry age <50 or 50-69 years and ER status (Oxford Overview)



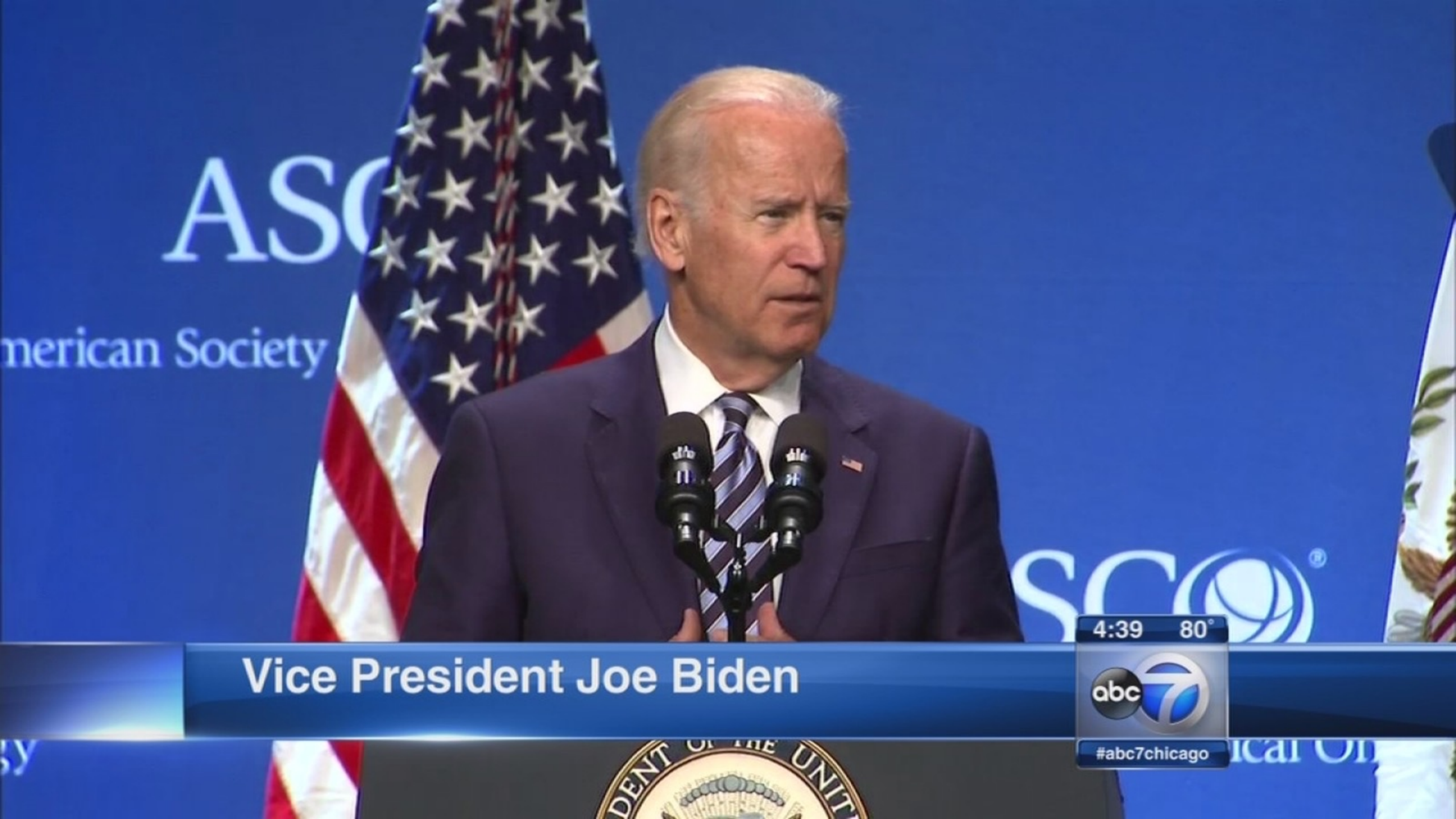
Age < 50: Enriched with tumors that harbor deficiencies in DNA repair?

Proportional risk reductions are a bit smaller, but clearly still evident

Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2005

FROM THE EARTH TO THE MOON

Jules Verne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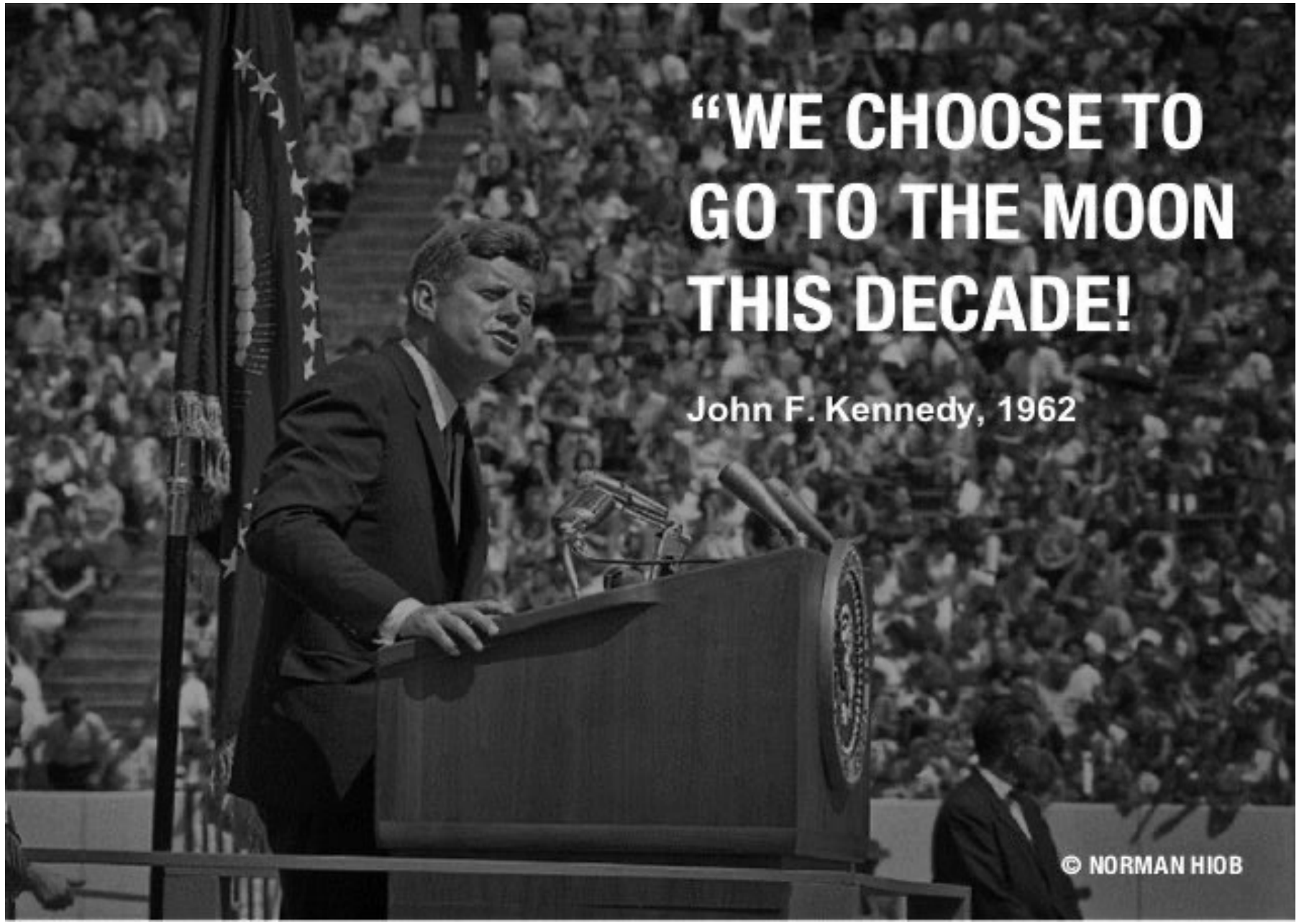
"WE CHOOSE TO GO TO THE MOON THIS DECADE!
John F. Kennedy, 1962
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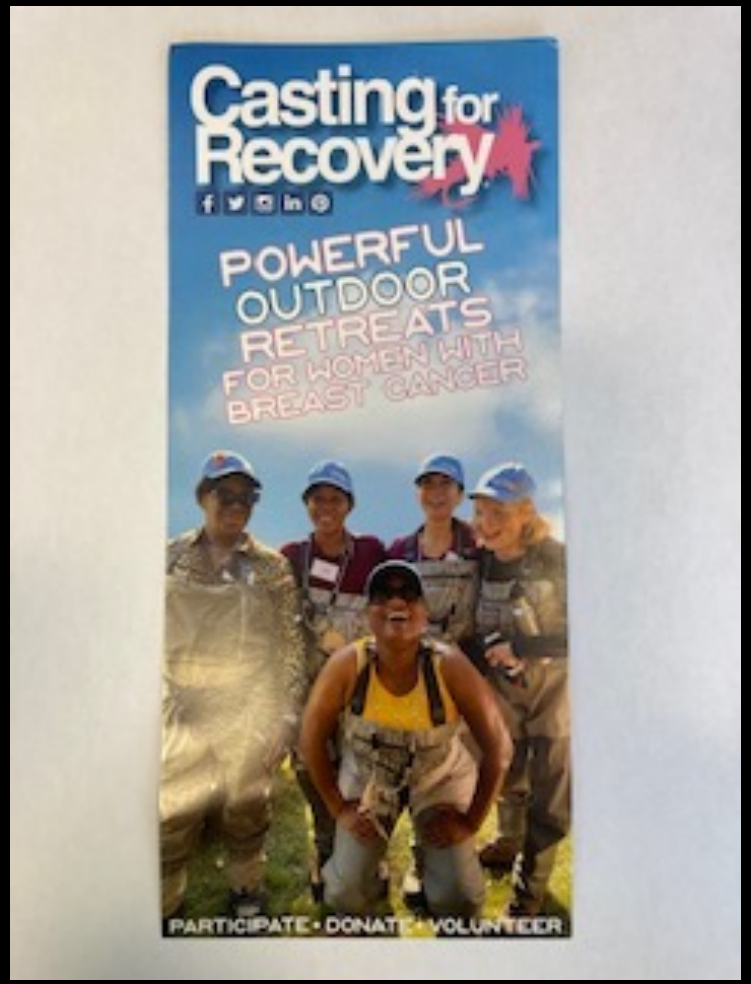
The James Webb Space Telescope has released another image of the magnificent Pillars of Creation, combining Near-Infrared Camera (NIRCam) and Mid-Infrared Instrument (MIRI) footage.

ARIZONA CANCER CENTER PHOENIX

Dignity Health



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THINGS CHANGE