Master Lecture Series: Hormone Receptor+ BC

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Young Women's Breast Cancer Translational Program

Objectives

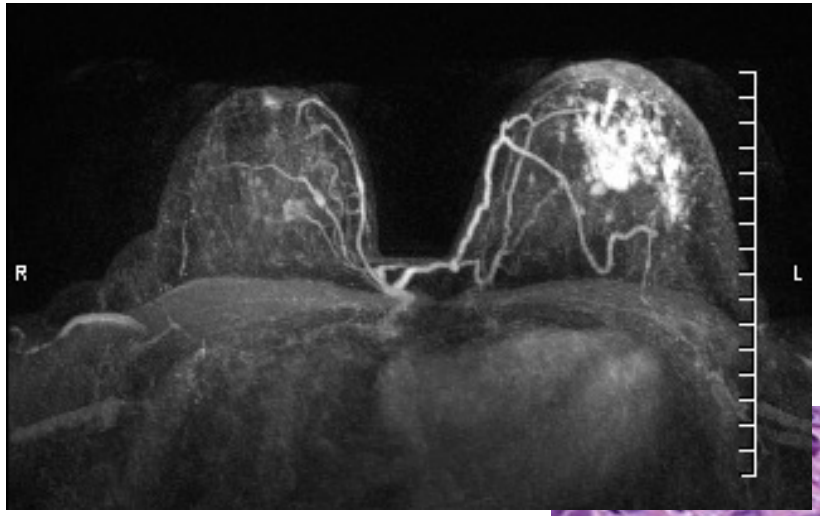
- Understand the current controversies for HR+, Her2- young women's breast cancer in the early stage
- Identify the current algorithm of treating HR+ MBC
- Review recent update on current standard of care and emerging novel therapies
- Identify how to incorporate the latest updates into your clinic

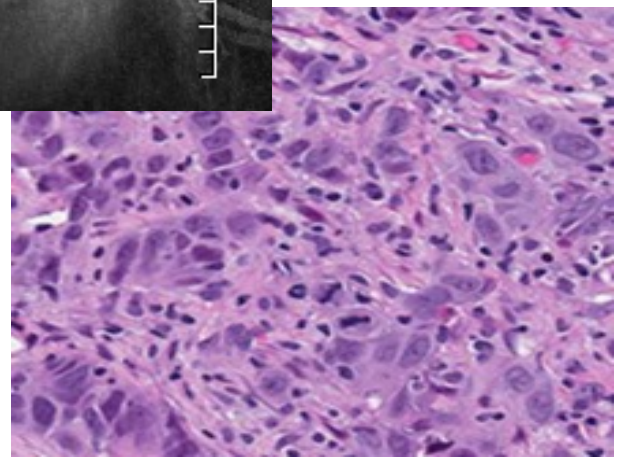
Friday afternoon in clinic….

35-year-old woman presents for consultation for her breast cancer

<u>Breast Cancer History:</u>

2 weeks ago, presented with L breast mass
Stage II/prognostic stage I [T2N1M0]
Grade 2, Ki-67 20%
ER 60%, PR 20%, Her 2 IHC 0%
No identified gene mutation





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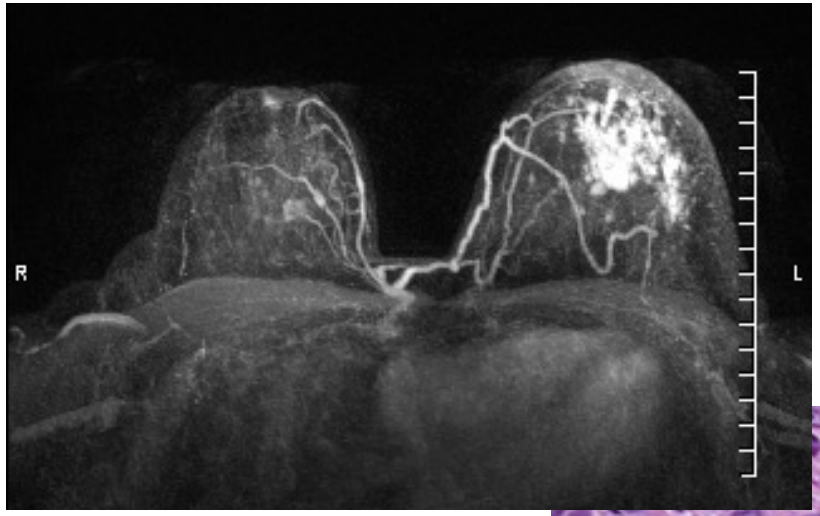
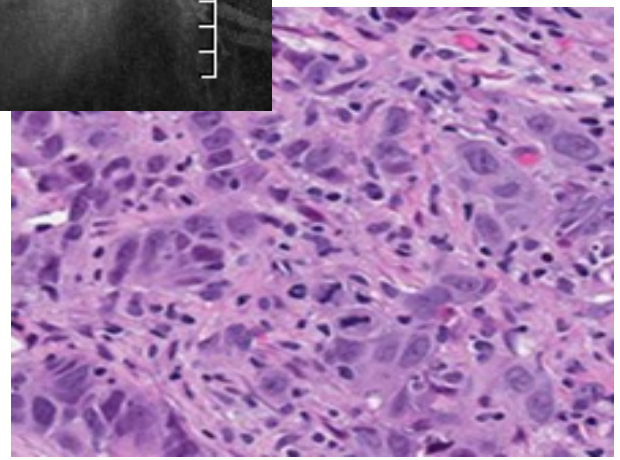




Surgery first?
Genomic test?
Neoadjuvant or adjuvant chemo?
Other things to remember?

Fertility Issues

- If a women has never been pregnant, her fertility status is an unknown
  - Fertility declines after age 35, normally
- Modern chemotherapy regimens less frequently alter fertility than older ones
  - Delay of therapy for egg harvesting
  - Oocytes/ovarian tissue if NO Acceptable Sperm on hand.
- *Post treatment pregnancy does NOT increase breast cancer recurrence risk [POSITIVE trial data, NEJM 2023]*
- Right now, is a REALLY BAD TIME for pregnancy, so fertility must be controlled in a definitive manner.

EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

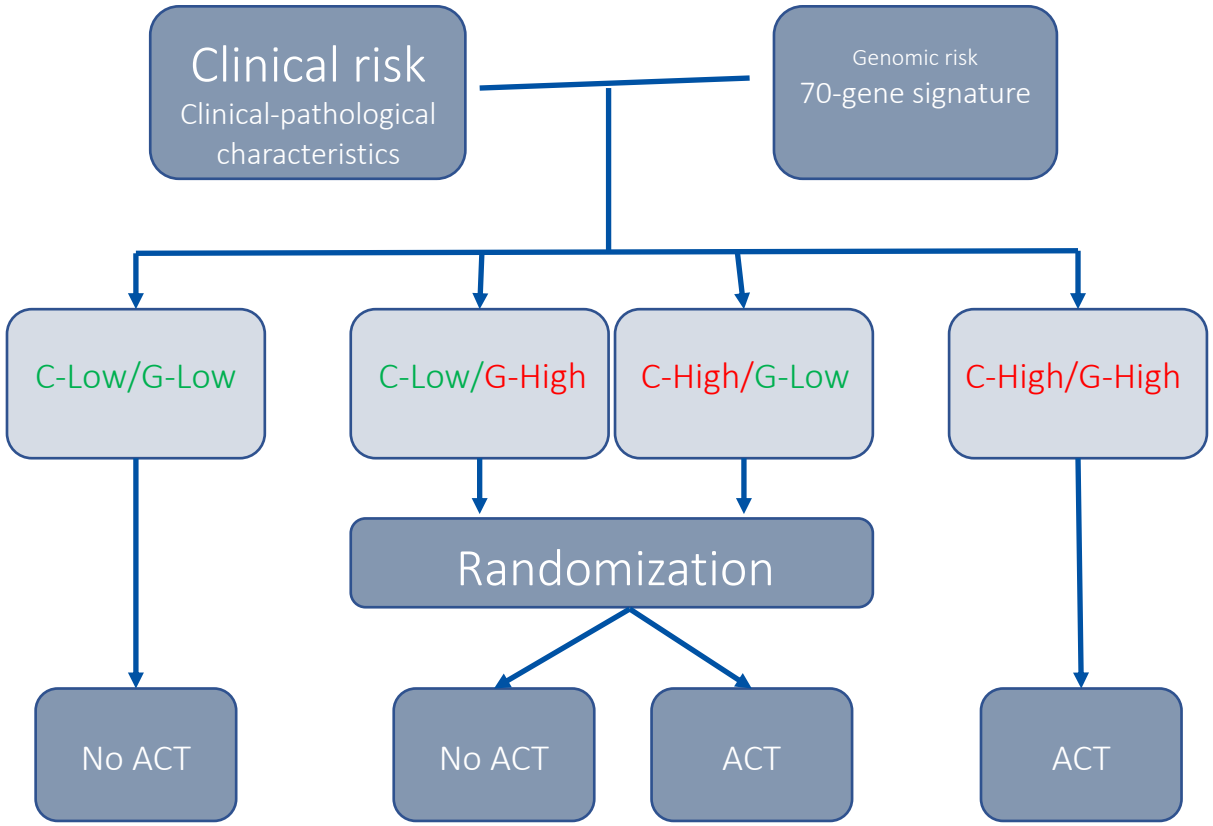
MINDACT

NETHERLANDS CANCER INSTITUTE ANTONI VAN LEEUWENHOEK

Inclusion criteria

- Women aged 18-70
- Operable invasive breast cancer
- Tumor size max 5 cm
- 0-3 positive lymph nodes
- No distant metastasis

MINDACT trial design



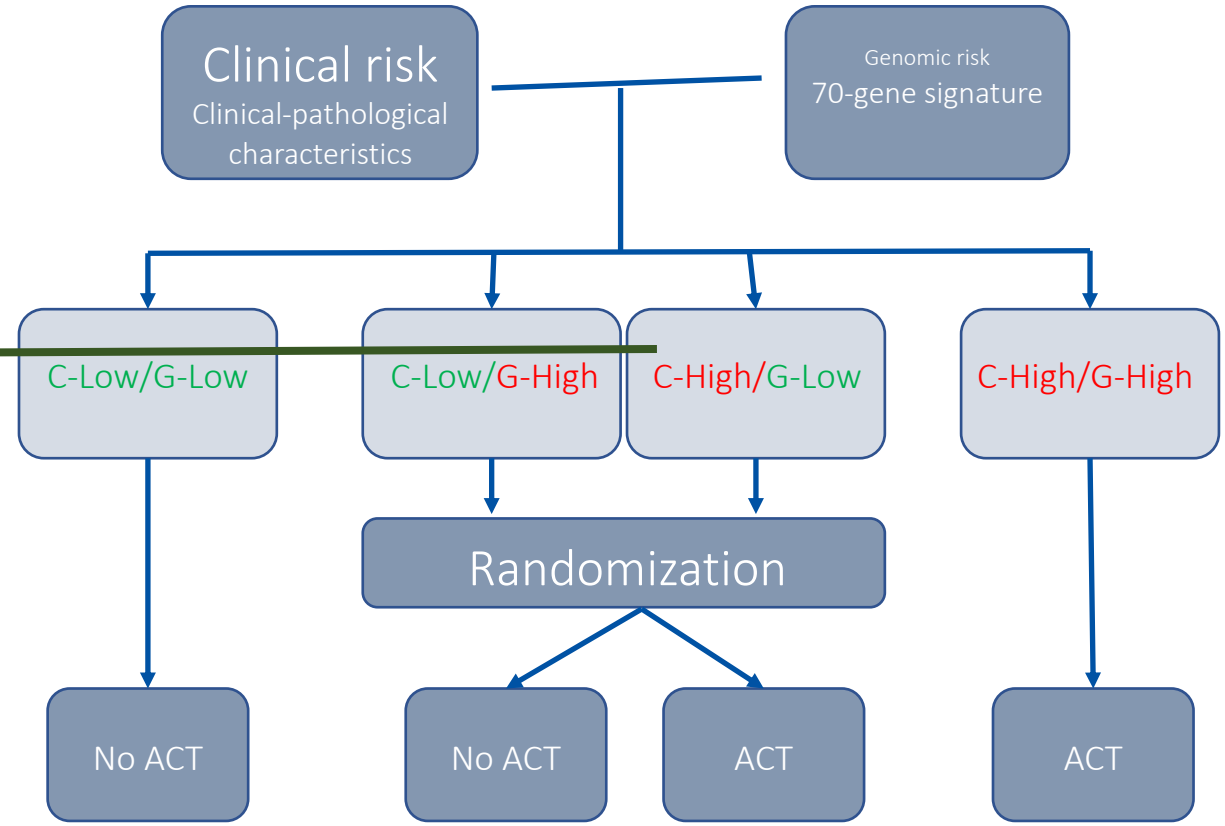
Cardoso (2016) NEJM;375:717-729. ; Piccart (2021) Lancet Oncol. 2021; 22:476–488

Josephine Lopes Cardozo
j.lopes.cardozo@nki.nl

MINDACT

- Women under 50 chemo/no chemo
  - 93.6% v 88.6% [5% gain for chemo]

MINDACT trial design



Cardoso (2016) NEJM;375:717-729. ; Piccart (2021) Lancet Oncol. 2021; 22:476–488

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

Key Entry Criteria
- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION

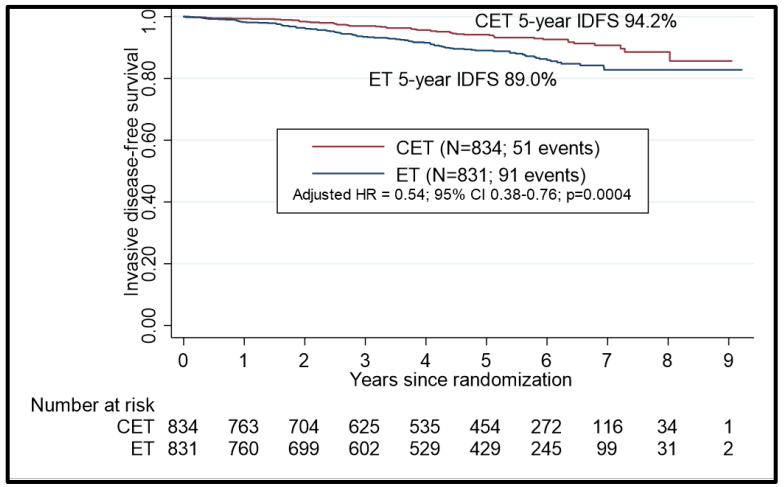
Arm 1:
Chemotherapy Followed by Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

N = 5,000 pts

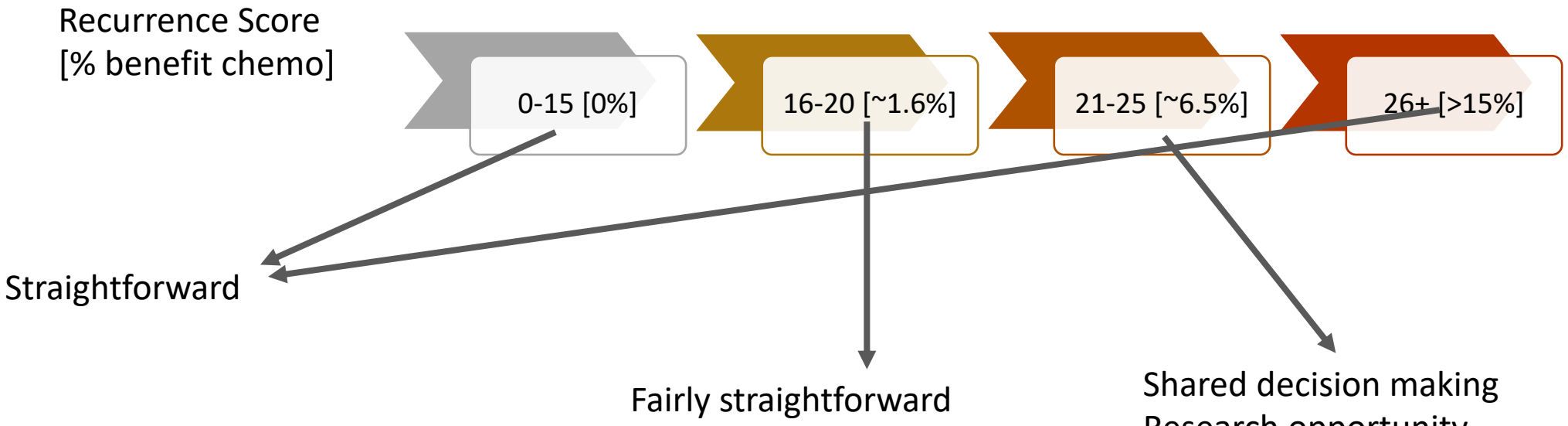
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

IDFS premenopausal women



- Premenopausal women with RS 0-25 had benefit from the addition of chemotherapy to endocrine therapy
- 46% decrease in IDFS events; benefit was observed across premenopausal subgroups
- 53% decrease in deaths, leading to a 5-year OS absolute improvement of 1.3%
- 1 node v 2-3 nodes – equal benefit at ~5% benefit

Chemotherapy Benefits for Node Negative Premenopausal Women: TailorRX Results Overview



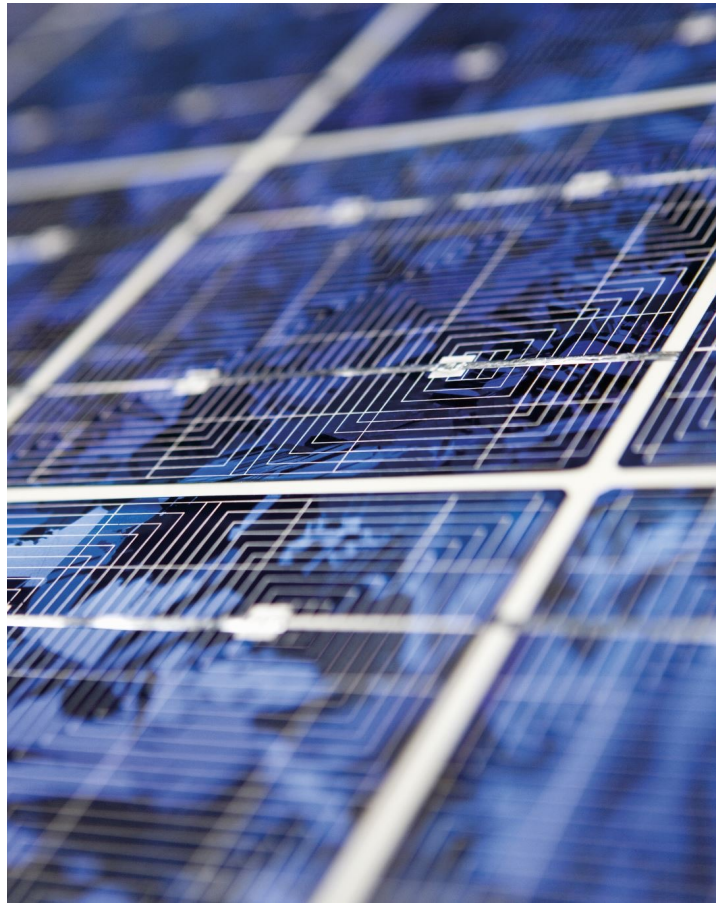
-13% had OFS combination anti-HR therapy

-If all of the appropriate patients had optimized antiendocrine therapy, would the benefit be the same?

J Sporano, et al. N Engl J Med 2018;379:111-21. DOI: 10.1056/NEJMoa1804710

Considerations of Adjuvant Chemo for HR+ Cancer

- Chemotherapy offers benefit for node positive patients
- Further refinement of who truly needs chemo is warranted
- Where do we go next to better define the mechanisms of metastasis and improve therapy?



THE LANCET

Articles

Ovarian ablation in early breast cancer: overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group**

- **Early review of trials randomizing ovarian ablation/suppression vs none (N=2012)**
- **~13% absolute benefit for DFS**

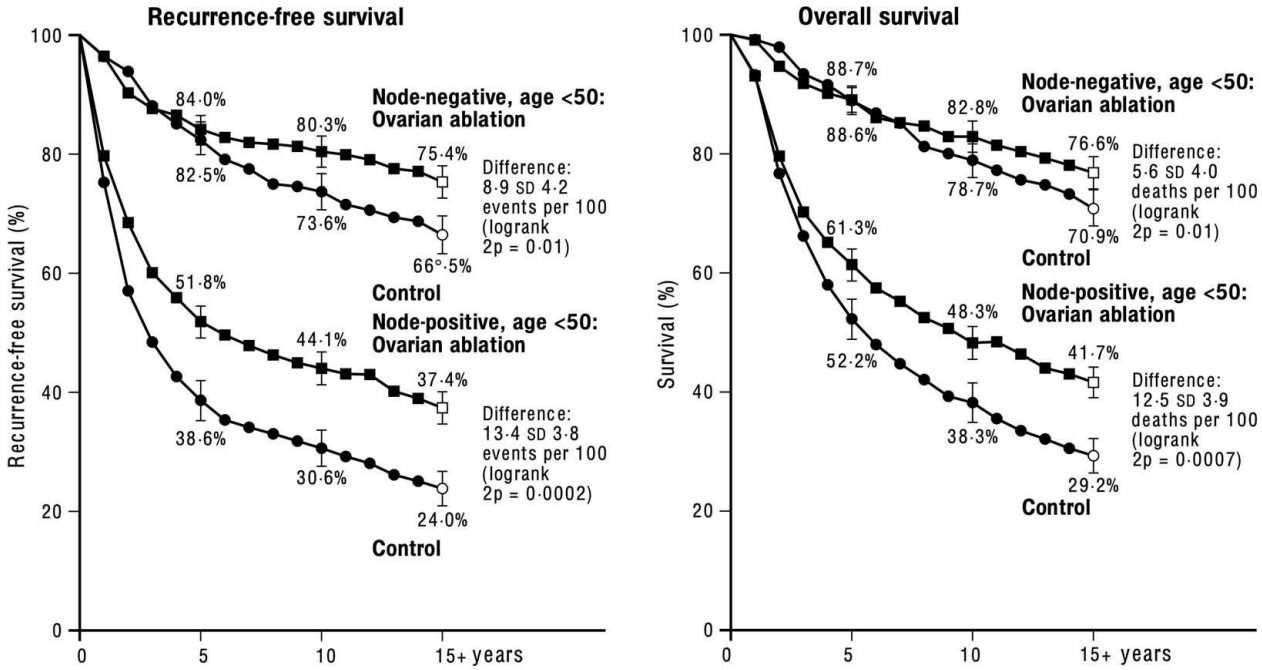
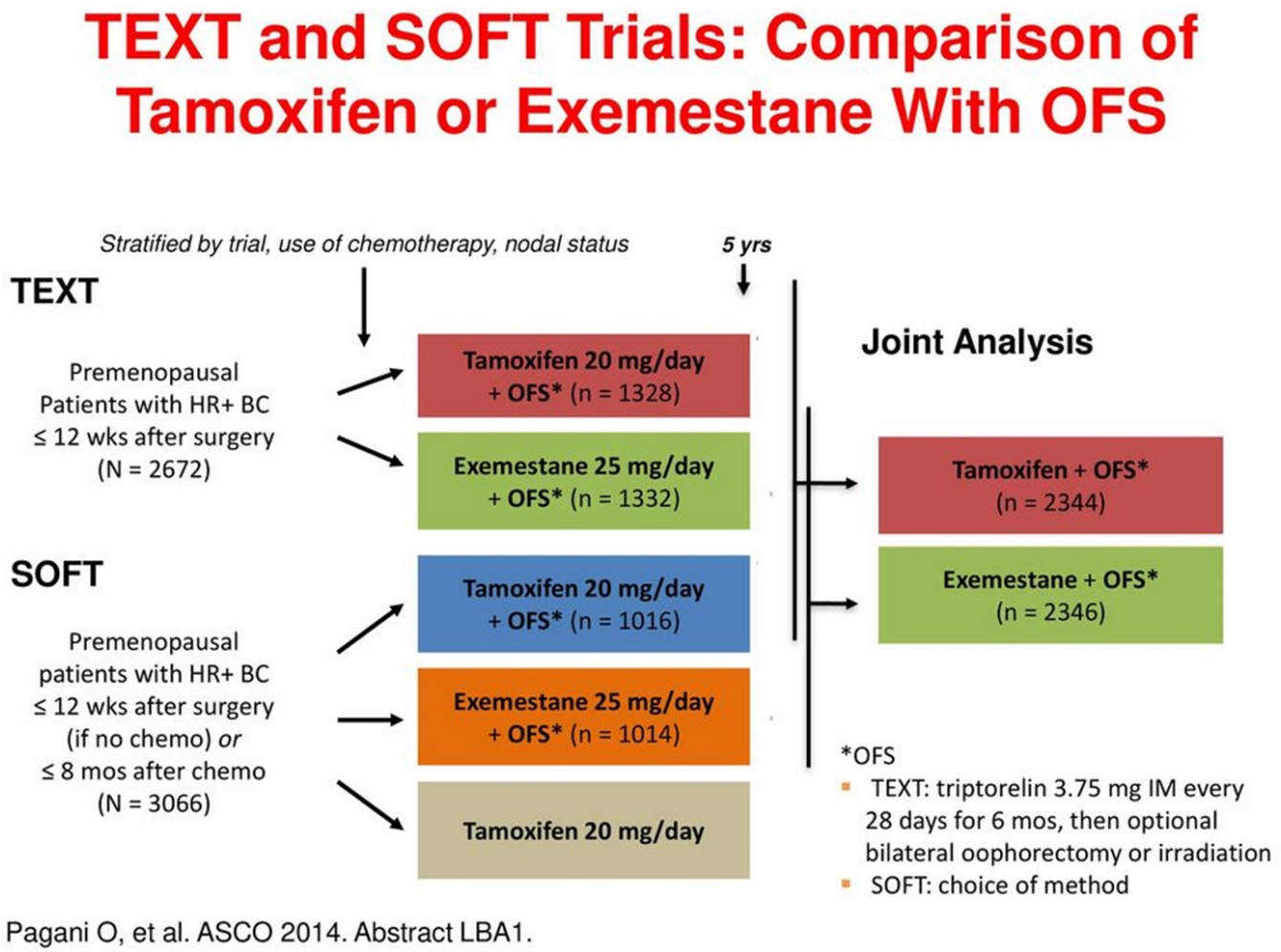


Figure 3: **Absolute effects of ovarian ablation in absence of routine chemotherapy in all trials combined among women aged under 50 at entry**

EBCTCG, Lancet 1996

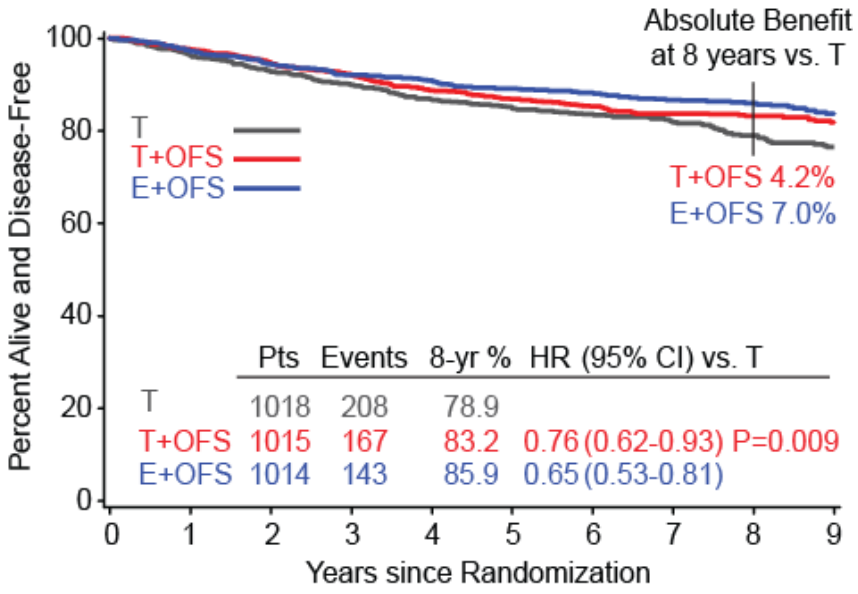
Optimized antiendocrine therapy

- Hormone blocking therapy is the best treatment for HR+ BC
- Combination therapy has shown improved outcomes, especially for very young women, node + disease and ‘high-risk’



Pagani O, et al. ASCO 2014. Abstract LBA1.

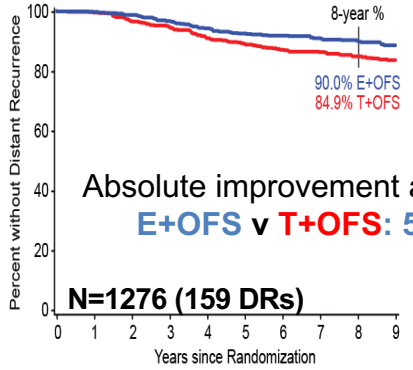
SOFT and TEXT data: 8-Year Update: T+AI Significantly Improves DFS



TEXT

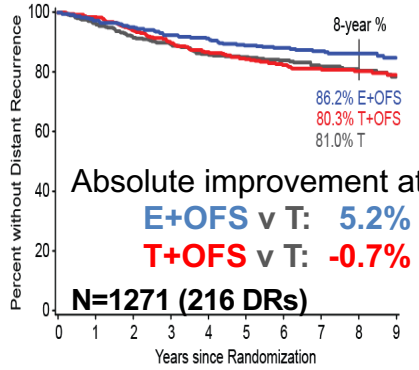
SOFT

CHEMO



Absolute improvement at 8 yrs:
E+OFS v T+OFS: 5.1%

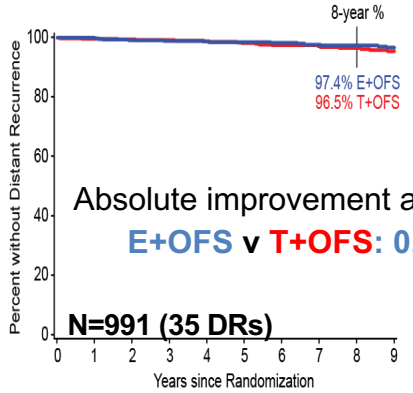
N=1276 (159 DRs)



Absolute improvement at 8 yrs:
E+OFS v T: 5.2%
T+OFS v T: -0.7%

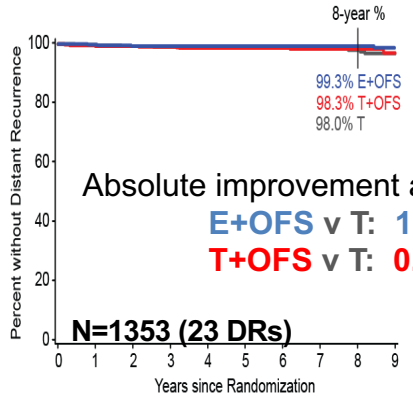
N=1271 (216 DRs)

NO CHEMO



Absolute improvement at 8 yrs:
E+OFS v T+OFS: 0.9%

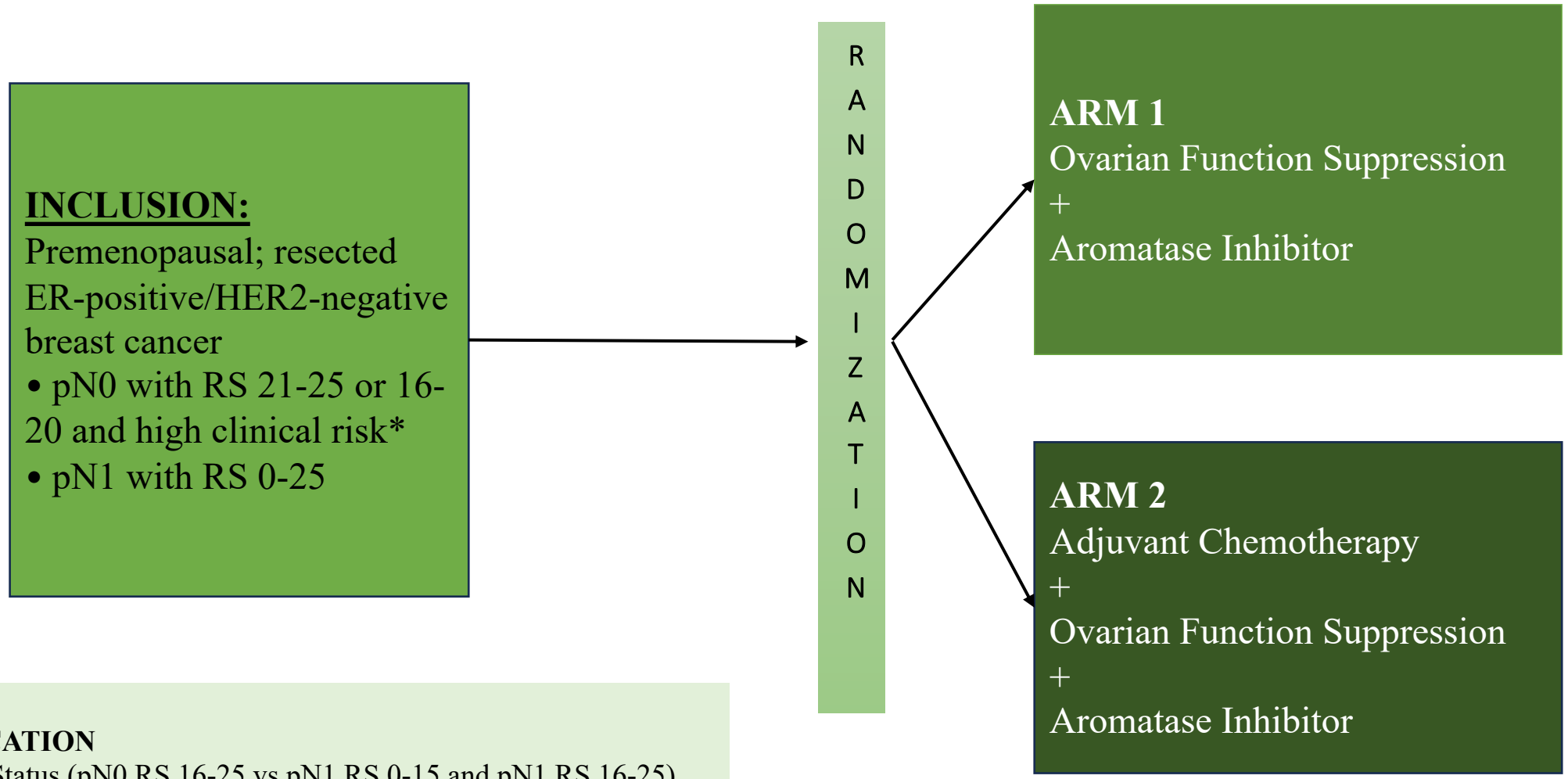
N=991 (35 DRs)



Absolute improvement at 8 yrs:
E+OFS v T: 1.3%
T+OFS v T: 0.3%

N=1353 (23 DRs)

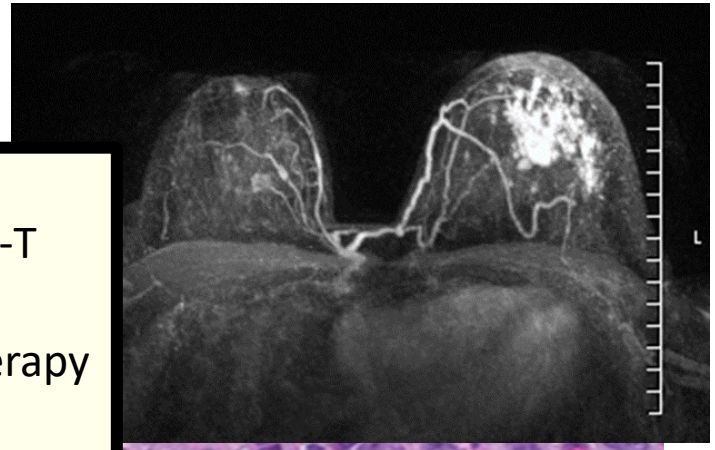
NRG-BR009: OFSET trial



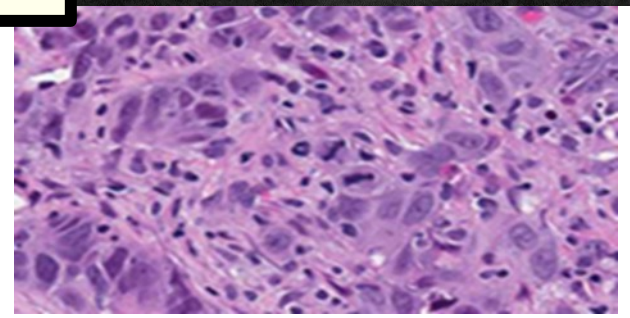
STRATIFICATION
- Nodal/RS Status (pN0 RS 16-25 vs pN1 RS 0-15 and pN1 RS 16-25)
- Intent) to receive CDK4/6 inhibitor (yes; no)
- Age (18-39; 40 and older)

NRG Chair: Eleftherios Mamounas, MD, MPH

Considerations for High-Risk HR+ Early Breast Cancer



Oncotype was 22
Neoadjuvant chemo with AC-T
Surgery with RD
OFS and AI for endocrine therapy
Other things to remember?



Bisphosphonates

CDK 4/6 inhibitors

PARP inhibition if +BRCA carrier

2023 ASCO® ANNUAL MEETING

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: primary results from the Phase III NATALEE trial

Dennis Slamon,[1] Daniil Stroyakovskiy,[2] Denise A. Yardley,[3] Chiun-Sheng Huang,[4] Peter A. Fasching,[5] John Crown,[6] Aditya Bardia,[7] Stephen Chia,[8] Seock-Ah Im,[9] Miguel Martin,[10] Sherene Loi,[11] Binghe Xu,[12] Sara Hurvitz,[13] Carlos Barrios,[14] Michael Untch,[15] Rebecca Moroose,[16] Frances Visco,[17] Rodrigo Fresco,[18] Tetiana Taran,[19] Gabriel N. Hortobagyi[20]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Moscow City Oncology Hospital No. 62 of Moscow Healthcare Department, Moscow Oblast, Russia; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; [4]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City, Taiwan; [5]University Hospital Erlangen Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [6]St. Vincent's University Hospital, Dublin, Ireland; [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [8]British Columbia Cancer Agency, Vancouver, BC, Canada; [9]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [11]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [12]Department of Medical Oncology Cancer Hospital, Chinese Academy of Medical Sciences (CAMS), and Peking Union Medical College (PUMC), Beijing, China; [13]University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; [14]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [15]Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [16]Orlando Health Cancer Institute, Orlando, FL; [17]National Breast Cancer Coalition, Washington DC; [18]TRIO - Translational Research in Oncology, Montevideo, Uruguay; [19]Novartis Pharma AG, Basel, Switzerland; [20]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

NATALEE study design[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

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Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

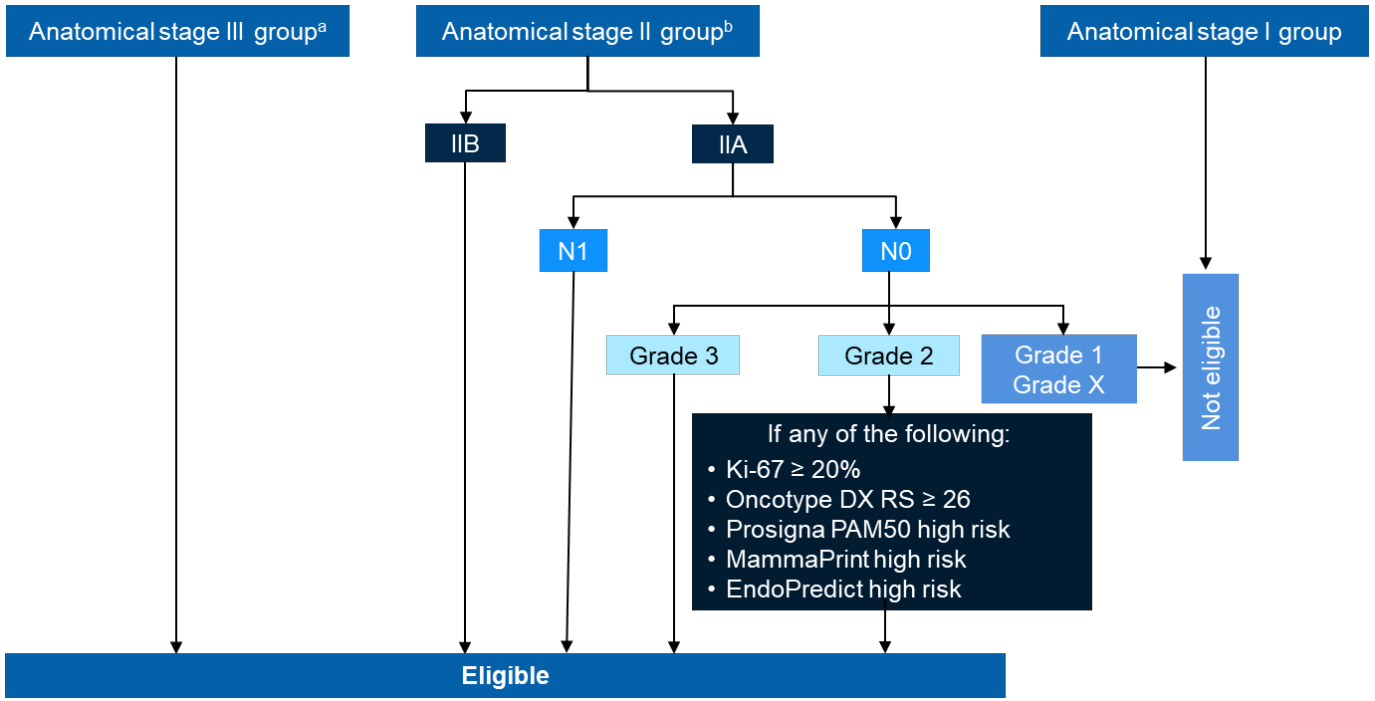
Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

NATALEE: eligible patients



AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk[c]
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement;; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or collarbone lymph nodes; RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm but less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing into the chest wall or skin, includes inflammatory breast cancer.

[a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3). [b] Capped at 40% (≈ 2000 patients). Simplified inclusion criteria are used in the illustration. [c] High risk as determined by Oncotype DX, Prosigna PAM50, MammaPrint, or EndoPredict EPclin Risk Score.

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(suppl 15) [abstract TPS597]. 3. Data on file. NATALEE CLEE011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020.

Baseline characteristics

Parameter	RIB + NSAI n = 2549	NSAI Alone n = 2552	All Patients N = 5101
Age, median (min-max), years	52 (24-90)	52 (24-89)	52 (24-90)
Menopausal status, n (%)			
Men[a] and premenopausal women	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomical stage,[b,c] n (%)			
Stage IIA	479 (19)	521 (20)	1000 (20)
Stage IIB	532 (21)	513 (20)	1045 (20)
Stage III	1528 (60)	1512 (59)	3040 (60)
Nodal status at diagnosis, n (%)			
NX	272 (11)	264 (10)	536 (11)
N0	694 (27)	737 (29)	1431 (28)
N1	1050 (41)	1049 (41)	2099 (41)
N2/N3	483 (19)	467 (18)	950 (19)
Prior ET, n (%)[d]			
Yes	1824 (72)	1801 (71)	3625 (71)
Prior (neo)adjuvant CT, n (%)			
Yes	2249 (88)	2245 (88)	4494 (88)
ECOG PS, n (%)			
0	2106 (83)	2132 (84)	4238 (83)
1	440 (17)	418 (16)	858 (17)

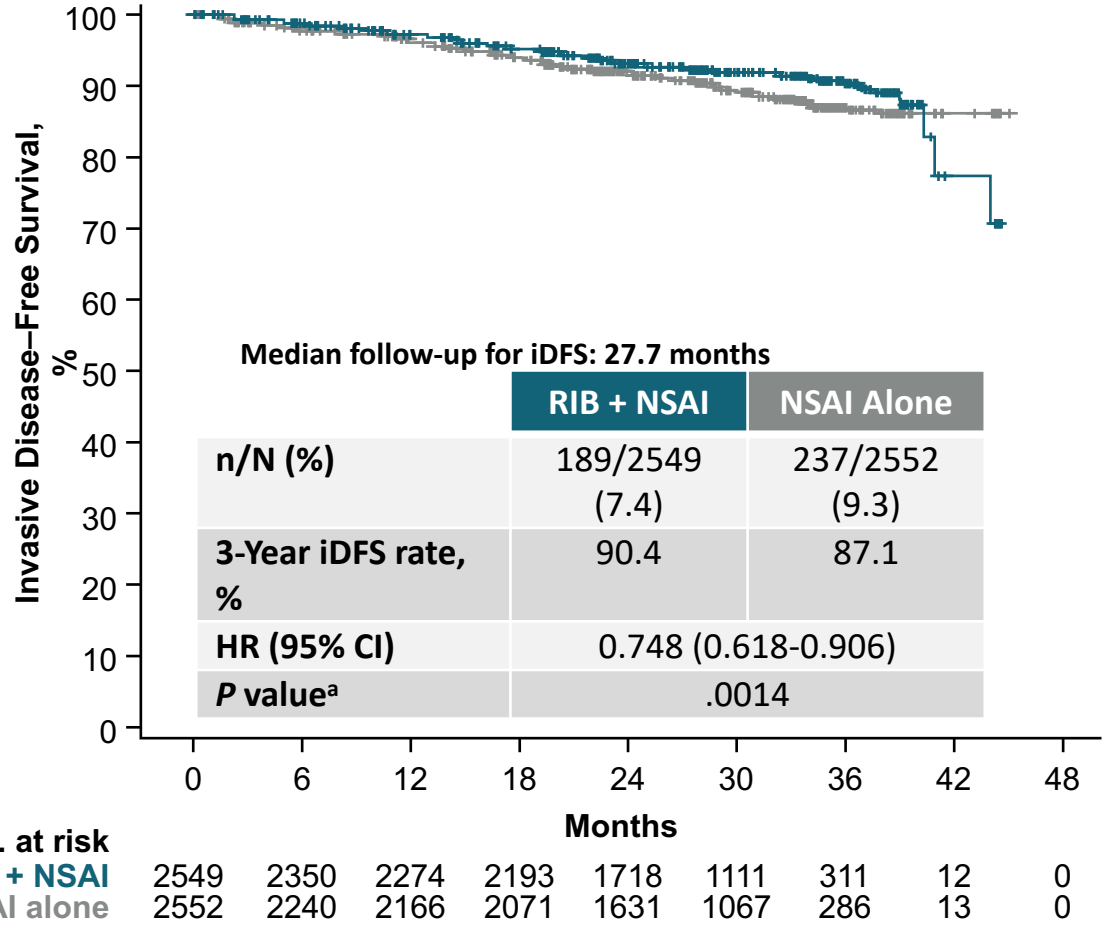
Patient disposition

Median follow-up of 34.0 months (minimum, 21 months)[a]

Parameter, n %	RIB + NSAI n = 2549	NSAI alone n = 2552
Patients treated	2526 (99)	2442 (96)
Patients with treatment ongoing[b]	1984 (78)	1826 (72)
Patients who discontinued NSAI	542 (21)	617 (24)
Primary reason for treatment discontinuation (NSAI)[c]		
Adverse Event	118 (5)	105 (4)
Patient/Physician decision	256 (10)	296 (12)
Disease relapse	142 (6)	186 (7)
Other[d]	13 (0.5)	15 (0.6)
Lost to follow-up	8 (0.3)	12 (0.5)
Death[e]	5 (0.2)	3 (0.1)
Patients who completed ribociclib treatment		
≥2 years (including ongoing)	1449 (57)	-
Completed 3 years RIB	515 (20)	-
Primary reason for early discontinuation of RIB[f]		-
Adverse Event	477 (19)	-

Slamon et.al. ASCO 2023

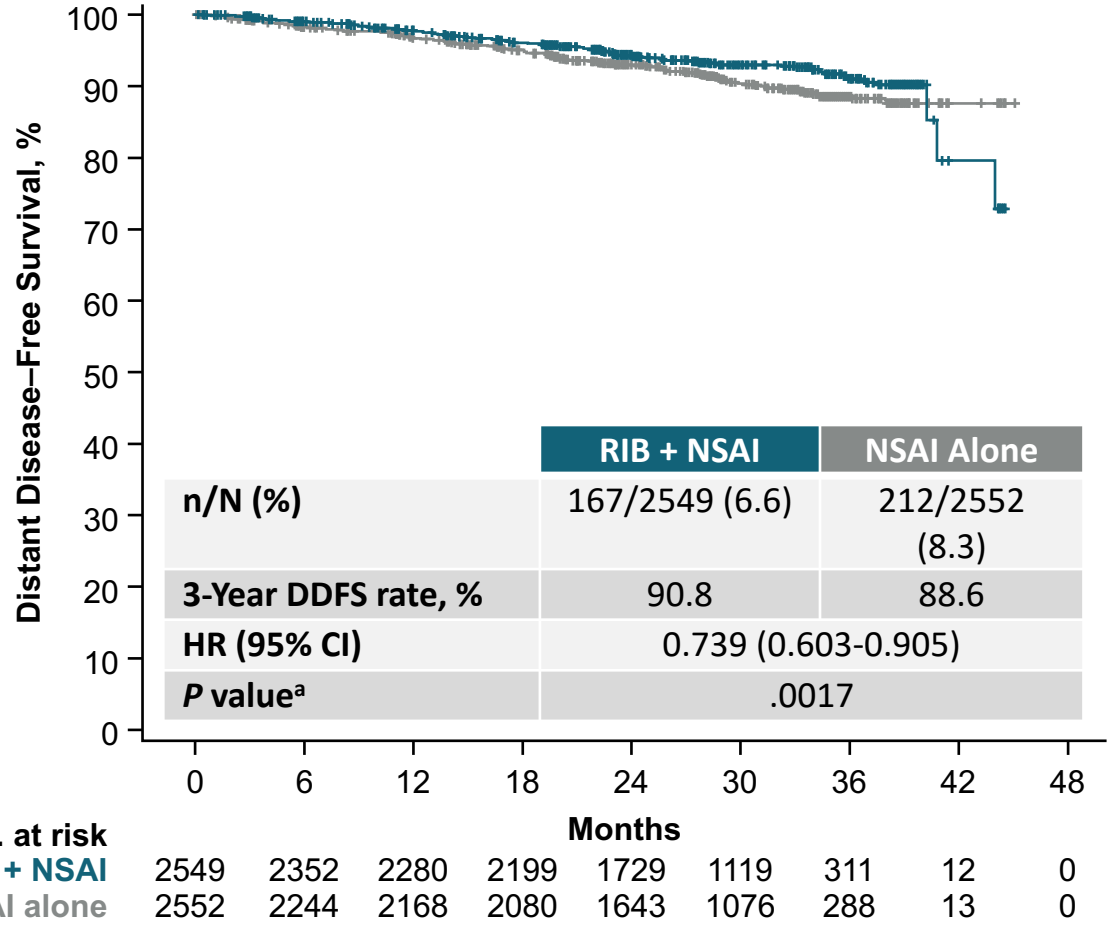
Ribociclib achieved significant iDFS benefit



Median follow-up for iDFS: 27.7 months

	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
***P* value[a]**	.0014	

No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0



	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
***P* value[a]**	.0017	

No. at risk									
RIB + NSAI	2549	2352	2280	2199	1729	1119	311	12	0
NSAI alone	2552	2244	2168	2080	1643	1076	288	13	0

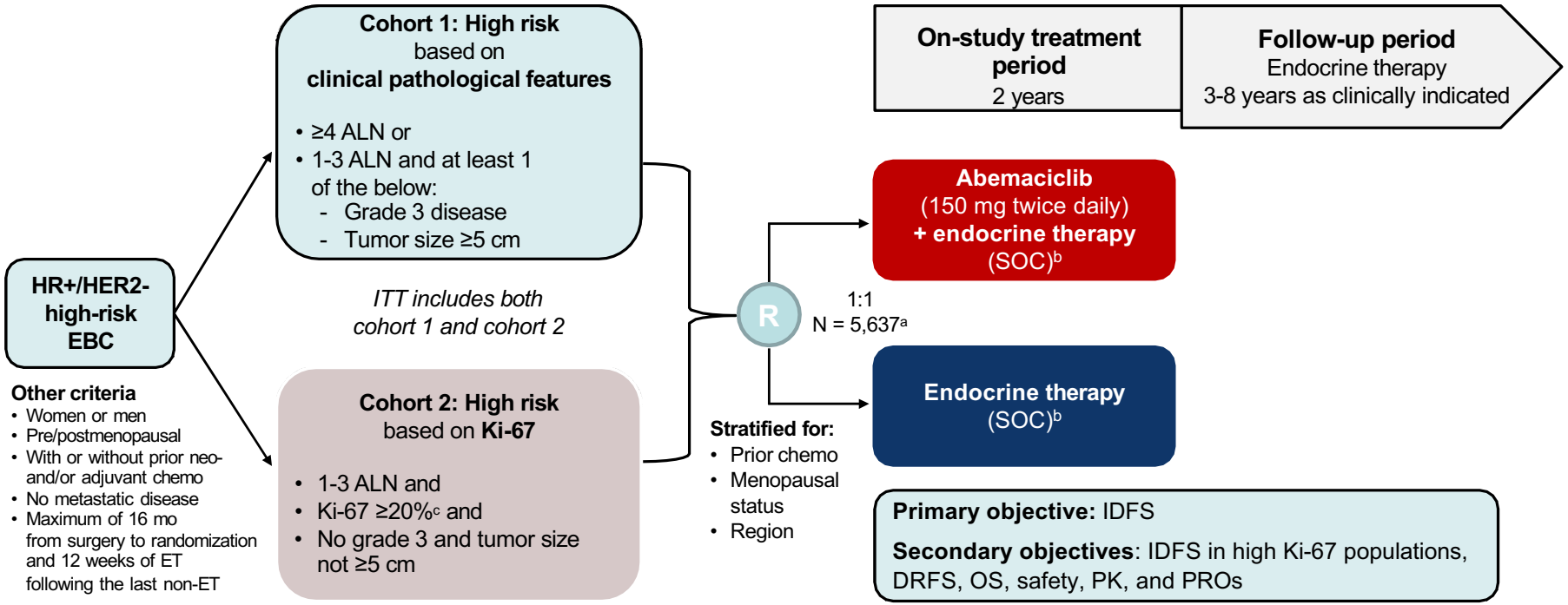
Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%

Ongoing patients will remain on treatment and follow-up will continue as prespecified

Absolute distant disease–free survival benefit with RIB + NSAI at 3 years was 2.2%

Slamon et.al. ASCO 2023

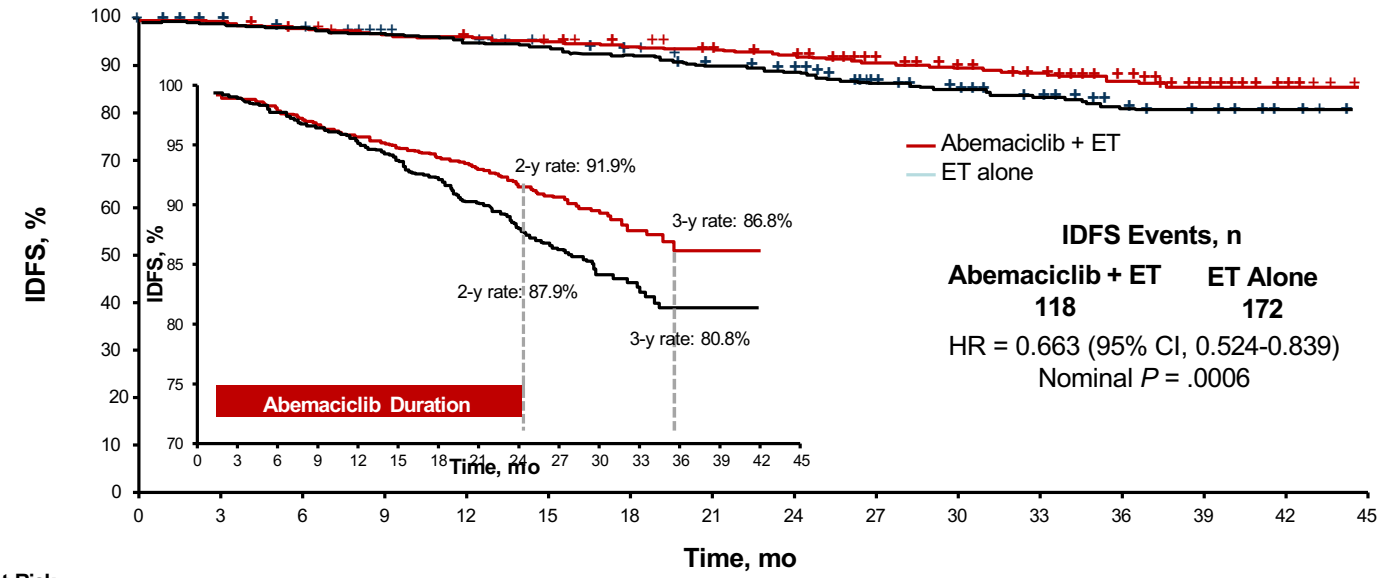
monarchE Study Design



[a] Recruitment from July 2017 to August 2019. [b] Endocrine therapy of physician's choice (eg, aromatase inhibitors, tamoxifen, LHRH agonist). [c] Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry.

O'Shaughnessy J et al. 2021 ESMO. Abstract VP8-2021; Harbeck N et al. *Ann Oncol.* 2021; 32(12):1571-1581.

monarchE: IDFS in ITT Ki-67 High (≥ 20%) Population



No. at Risk

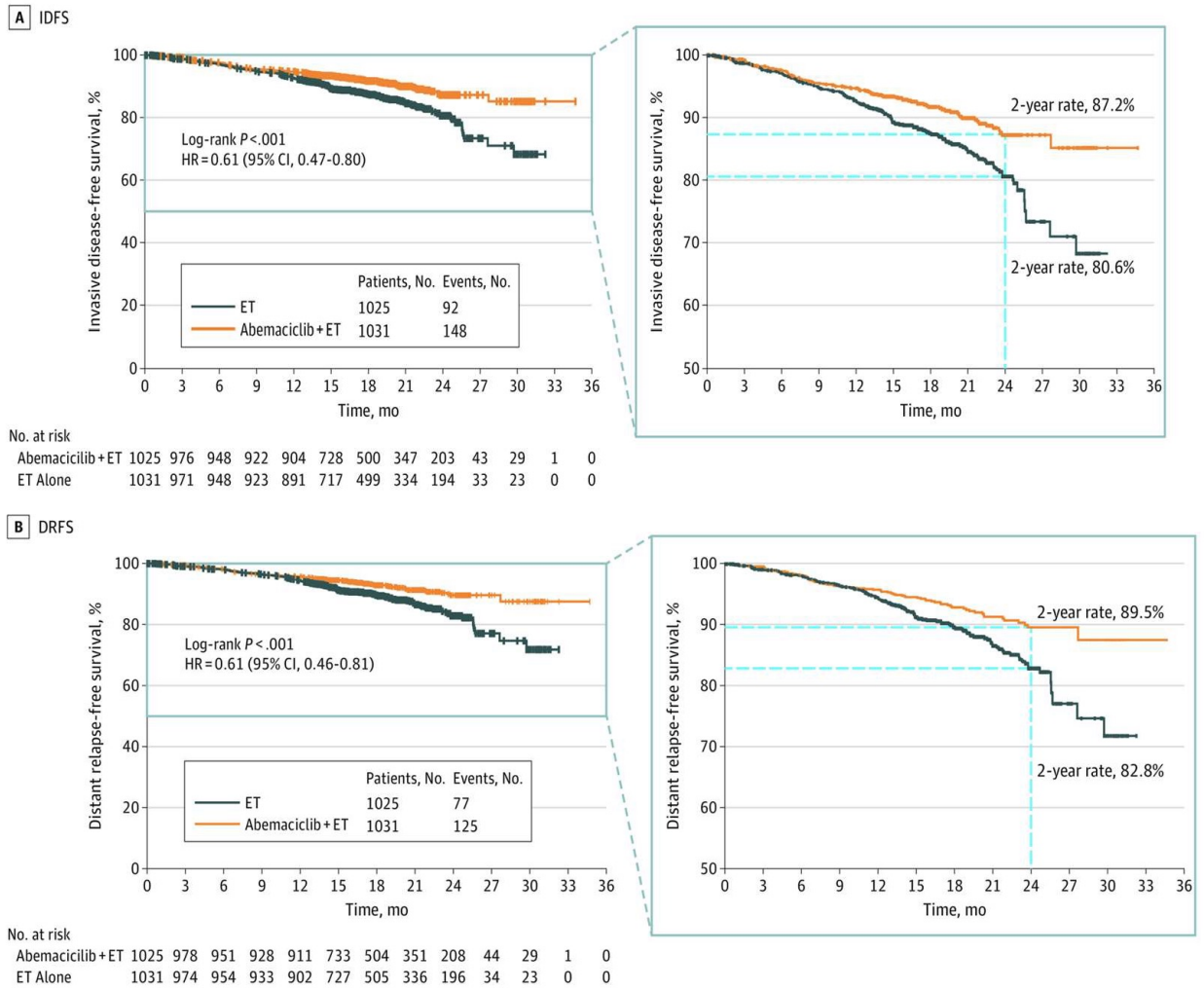
Abemaciclib + ET	1,262	1,221	1,189	1,167	1,155	1,139	1,123	1,094	870	546	377	203	109	25	2	0
ET alone	1,236	1,197	1,177	1,158	1,142	1,114	1,096	1,041	827	520	367	198	108	25	3	0

33.7% reduction in the risk of developing an IDFS event
The absolute difference in IDFS rates between arms was 6.0% at 3 years

O'Shaughnessy J et al. 2021 ESMO. Abstract VP8-2021; Harbeck N et al. *Ann Oncol.* 2021; 32(12):1571-1581.

monarchE

IDFS and DDFS following neoadjuvant chemotherapy



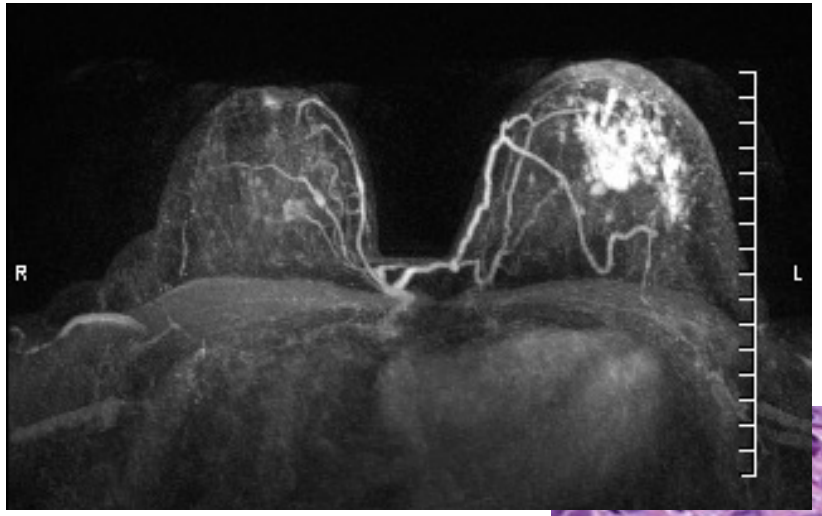
Martin M et al. JAMA Oncol. 2022 Jun 2:e221488.

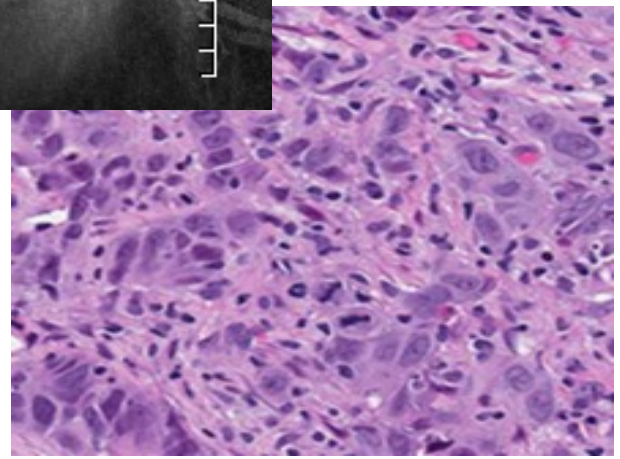
Friday afternoon in clinic….

38-year-old woman presents for consultation for her metastatic breast cancer

Breast Cancer History:

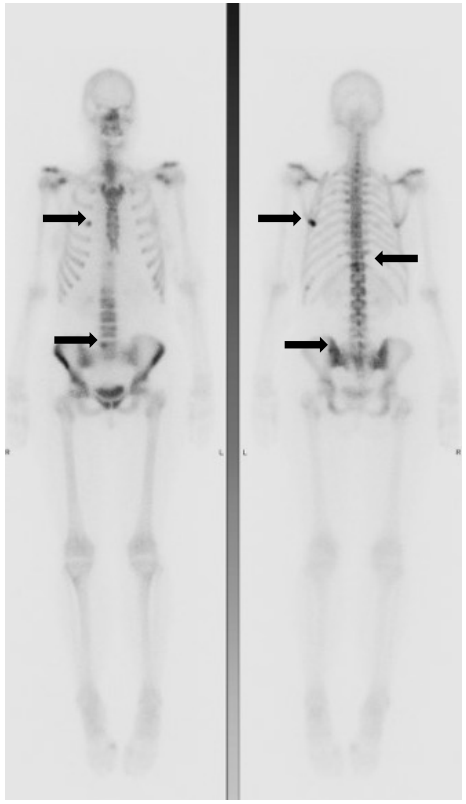
5 years ago, presented with L breast mass, BRCA2+
Stage III [T3N1M0]
Grade 2, Ki-67 19%
ER 60%, PR 40%, Her 2 IHC 0%
AC-T neoadjuvant chemo
Bilateral mastectomies with reconstruction
ypT1c,ypN1 (1 node) residual disease
PMCWXRT
Ovarian function suppression
tamoxifen x 3 years
tubal removal for BRCA risk reduction, still has ovaries
zolendronic acid q 6 months x 3 doses





Friday afternoon in clinic….

38-year-old woman presents for consultation for her metastatic breast cancer



She had noted a couple of weeks ago reporting vague back pain that did not go away with conservative measures after 6 weeks.

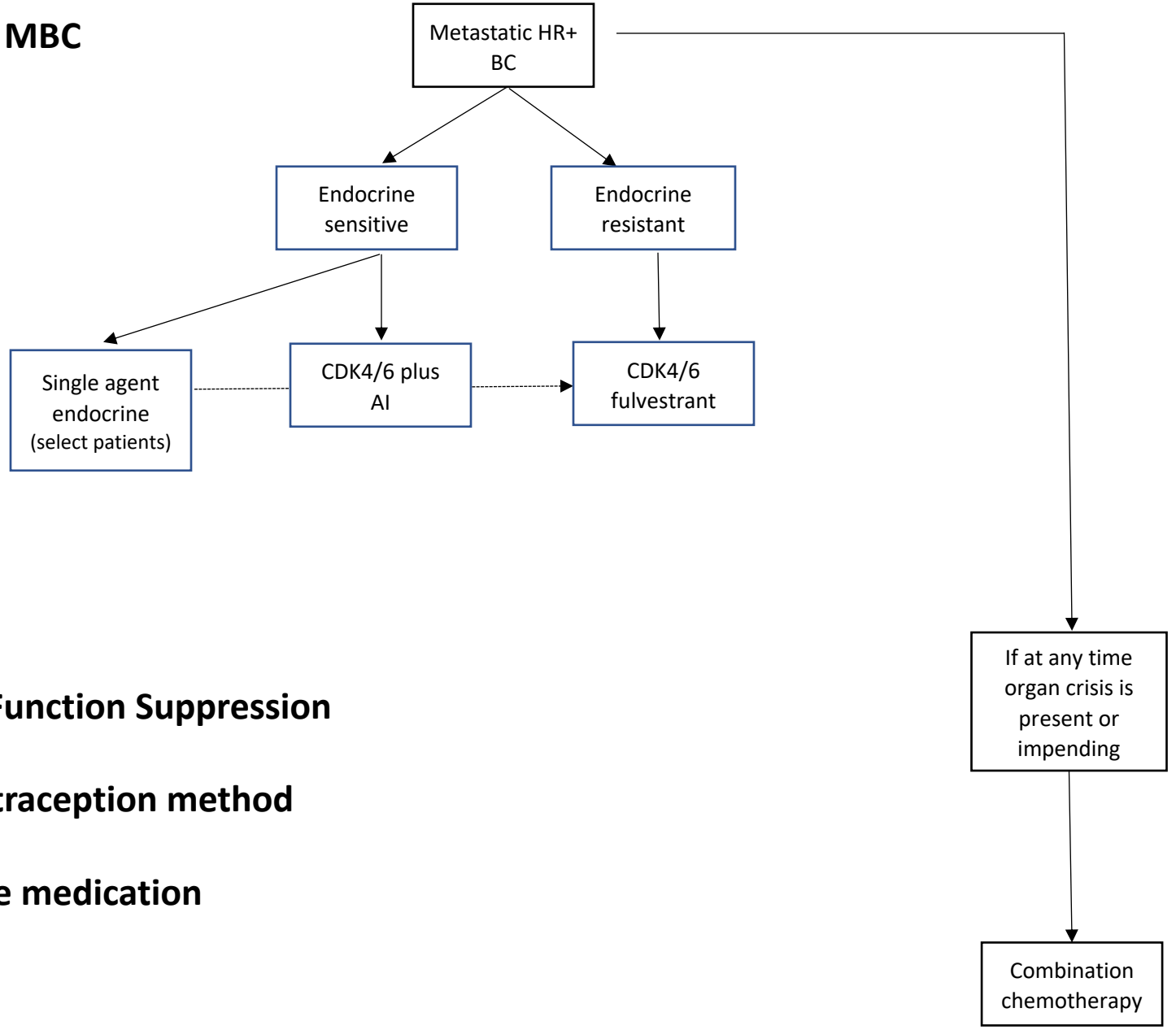
Labs were obtained and normal other than alk phos 1.5x ULN and CA27-29 of 65

Completion staging shows: bone only metastatic recurrence as seen by technetium-99m scintigraphic bone scan. CT CAP with single liver lesion.

Biopsy of liver lesion confirmed ER+ PR- Her2 0 by IHC and ESR1 WT, PIK3Ca mutated exon 9 by genomic analysis

What should her first line systemic therapy be?

Flow diagram for ER+/Her2- MBC treatment decisions



First line therapy

- **Re-initiate the Ovarian Function Suppression**
- **Check for adequate contraception method**
- **Re-start bone supportive medication**

Borges, JCO, Dec 2021

CDK 4/6 inhibitor	Study name	ET partner[1]	Menopausal Status[2]	Disease Status[3]	PFS[4] Exp v control (HR)	OS[5]
palbociclib	Paloma-1[34]	letrozole	Pre/post	AI sens	20.2 v 10.2 (0.48)	No
	Paloma-2[35]				27.6 v 14.5 (0.56)	NR
	Paloma-3[38]	fulvestrant		AI resis	9.5 v 4.6 (0.46)	NS
ribociclib	Monaleesa-2[41]	letrozole	Post	AI sens	25.3 v 16 (0.56)	yes
	Monaleesa-3[43]	fulvestrant		AI mixed	20.5 v 12.8 (0.59)	yes
	Monaleesa-7[44]	Tam/NSAI	Pre	AI sens	23.8 v 13.3 (0.55)	yes
abemaciclib	Monarch-1[49]	None (phase II)	Pre/post	AI resis	6.0 (single arm)	N/A
	Monarch-2[46]	fulvestrant		AI resis	16.4 v 9.3 (0.55)	yes
	Monarch-3[47]	NSAI		AI sens	28.1 v 14.7 (0.54)	NR

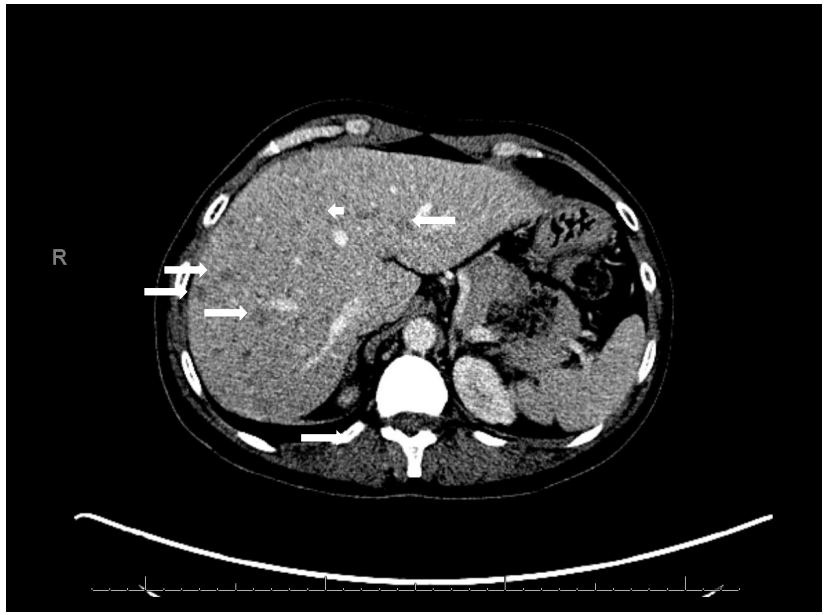
Borges, JCO, Dec 2021

A subsequent Friday afternoon in clinic….

38-year-old woman presents for follow up for her metastatic breast cancer

HPI:

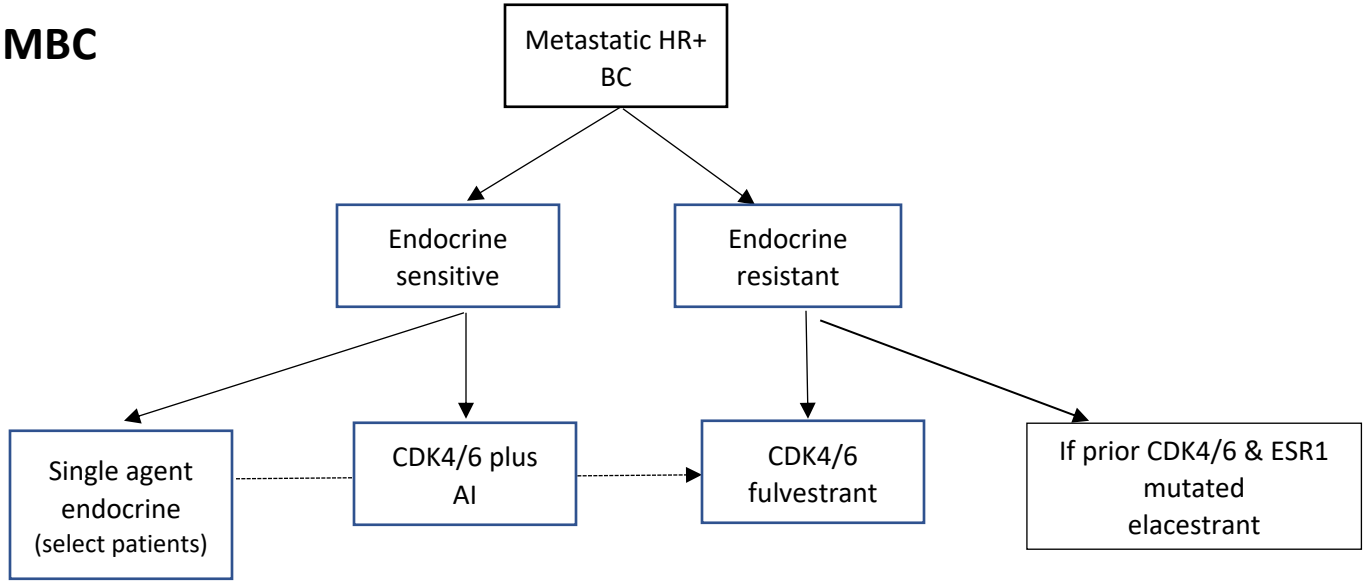
She's noted more fatigue
LFTs are newly elevated
CA27-29 has risen to 105
She completes staging scans prior to seeing you



Completion staging shows: bones look stable as seen by technetium-99m scintigraphic bone scan BUT disease progression with multiple new liver lesions as seen on contrast enhanced abdominal CT scan

What should her second line therapy be?

Flow diagram for ER+/Her2- MBC treatment decisions

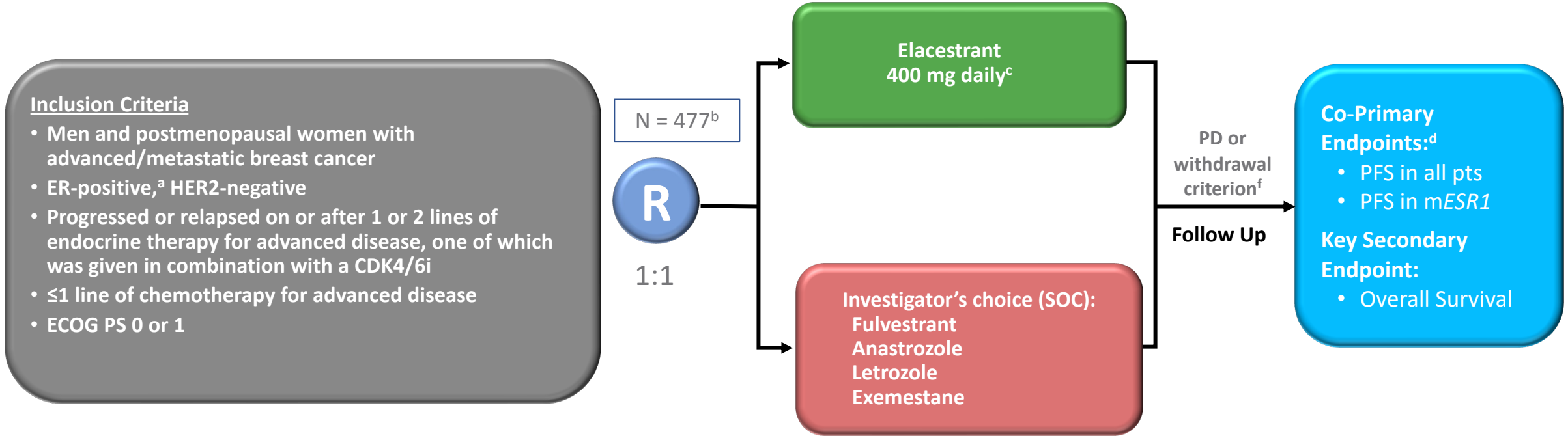


First line post CDK4/6 or second line therapy

For postmenopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

Borges, JCO, Dec 2021, modified

Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial



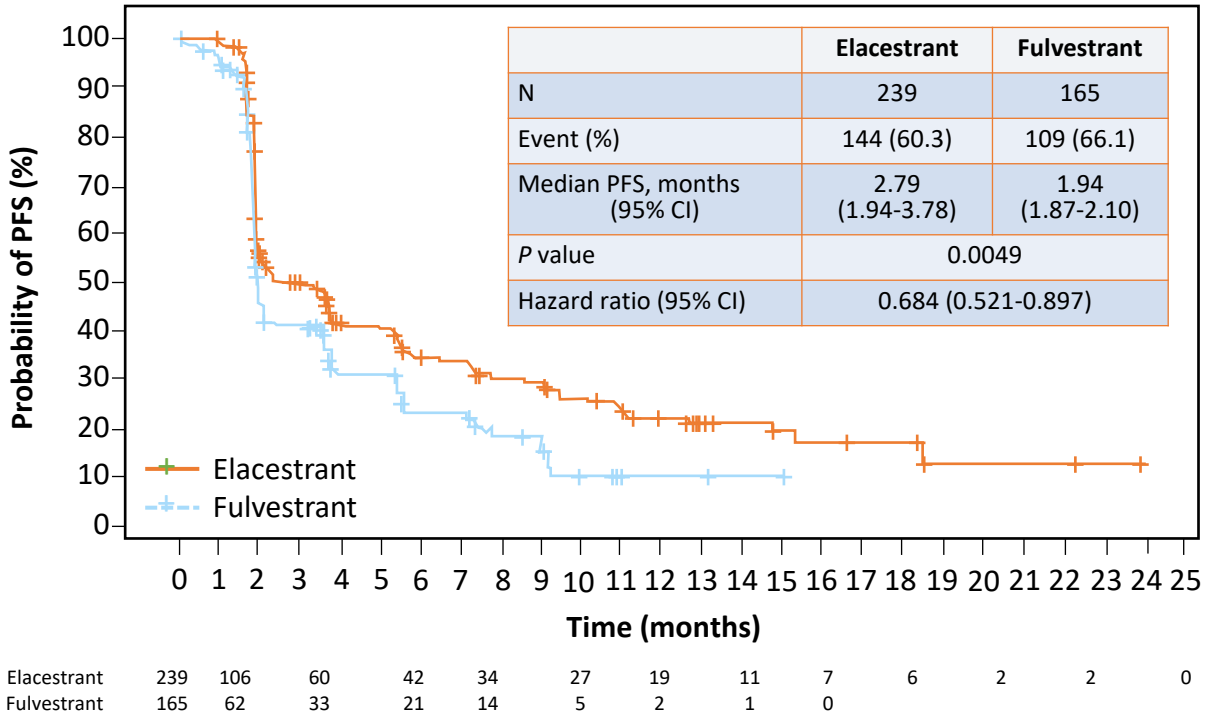
Stratification Factors:

- *ESR1*-mutation status[e]
- Prior treatment with fulvestrant
- Presence of visceral metastases

EMERALD

PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)

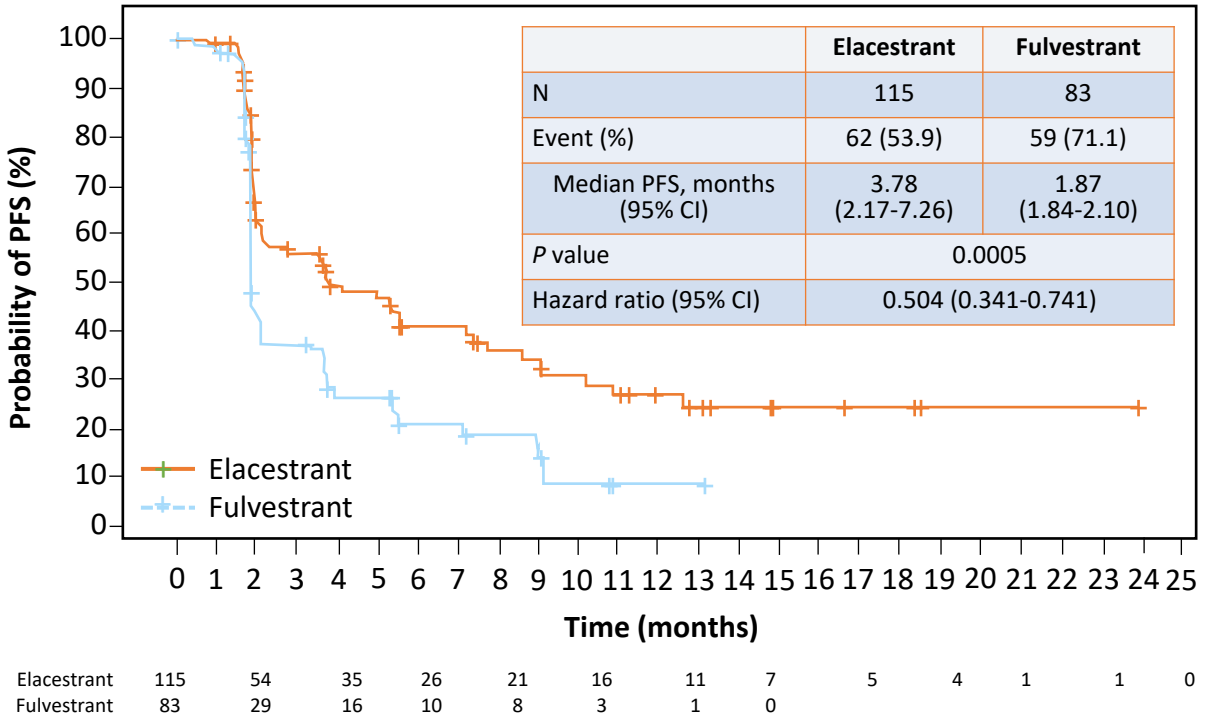
All Patients



	Elacestrant	Fulvestrant
N	239	165
Event (%)	144 (60.3)	109 (66.1)
Median PFS, months (95% CI)	2.79 (1.94-3.78)	1.94 (1.87-2.10)
P value	0.0049	
Hazard ratio (95% CI)	0.684 (0.521-0.897)	

Elacestrant	239	106	60	42	34	27	19	11	7	6	2	2		0
Fulvestrant	165	62	33	21	14	5	2	1	0					

Patients With Tumors Harboring *mESR1*



	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

Elacestrant	115	54	35	26	21	16	11	7		5	4	1	1	0
Fulvestrant	83	29	16	10	8	3	1	0						

Elacestrant demonstrated a significant improvement versus Fulvestrant as SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

Baseline Demographic and Disease Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*mESR1* (N=115)	All (N=238)	*mESR1* (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.5 (32-83)	63.0 (32-83)
Gender, n % Female Male	233 (97.5) 6 (2.5)	115 (100) 0	237 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.7) 102 (42.9) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	168 (70.6)	83 (73.5)
Bone-only disease, n (%)	38 (15.9)	14 (12.2)	29 (12.2)	14 (12.4)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	141 (59.2) 97 (40.8)	69 (61.1) 44 (38.9)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.6) 58 (24.4)	81 (71.7) 32 (28.3)

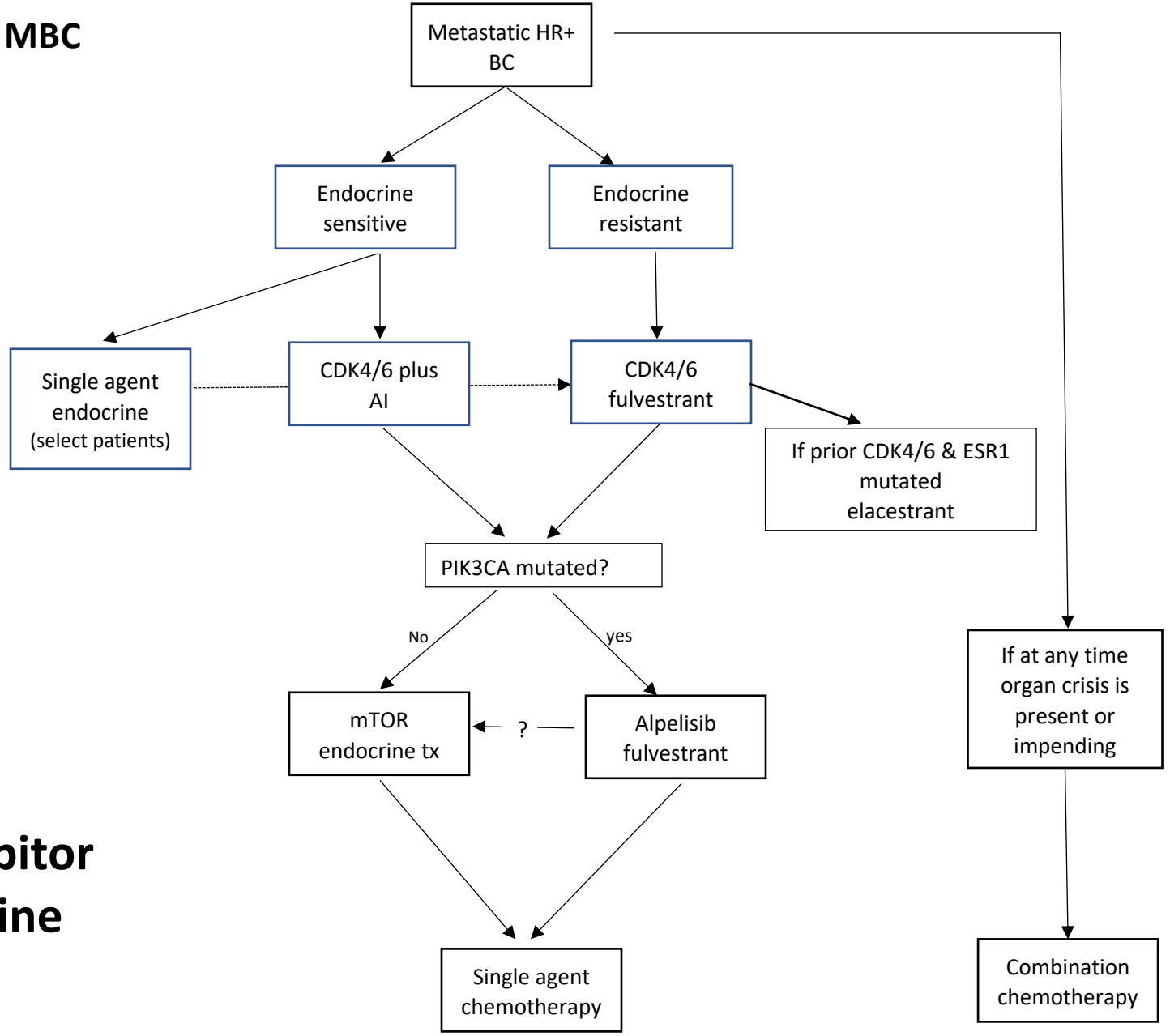
*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

EMERALD Study Conclusions

- Elacestrant is the first oral SERD that demonstrated a statistically significant and clinically meaningful improvement in PFS vs SOC endocrine therapy in a randomized global phase 3 study in men and postmenopausal women with ER+/HER2- mBC in the 2^{nd}/3^{rd}-line post-CDK4/6i setting:
  - 30% reduction in the risk of progression or death with elacestrant vs SOC in all patients (HR=0.697 [95% CI: 0.552 – 0.880]; *P*=0.0018)
  - 45% reduction in the risk of progression or death with elacestrant vs SOC in patients with *mESR1* (HR=0.546 [95% CI: 0.387 – 0.768]; *P*=0.0005)

- Elacestrant was well tolerated with a predictable and manageable safety profile consistent with other endocrine therapies.

Flow diagram for ER+/Her2- MBC treatment decisions



Second - line therapy

Also PARP inhibitor BRCA2 + germline mutation

Borges, JCO, Dec 2021, updated 2023

Second line pivotal trials

- SOLAR-1 – PFS 11 months v 5.7 months alpelisib + fulvestrant v. ful
  - AI resistant, 6% had had CDK4/6 inhibitor therapy
- OlympiAD – olaparib v SOC chemo: 100 ER+ - no PFS difference seen
- EMBRACA –talazoparib v SOC chemo -241 HR+ -improved PFS
  [HR 0.47] and prolonged QOL benefit , no OS difference

Moy, JCO Dec 2021

A few years later….

HR positive and Her 2 negative unresectable or stage IV (M1) disease

M1 in Visceral Crisis or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline BRCA 1/2	Systemic chemotherapy
	Germline BRCA 1/2	PARPi (olaparib, talazoparib)

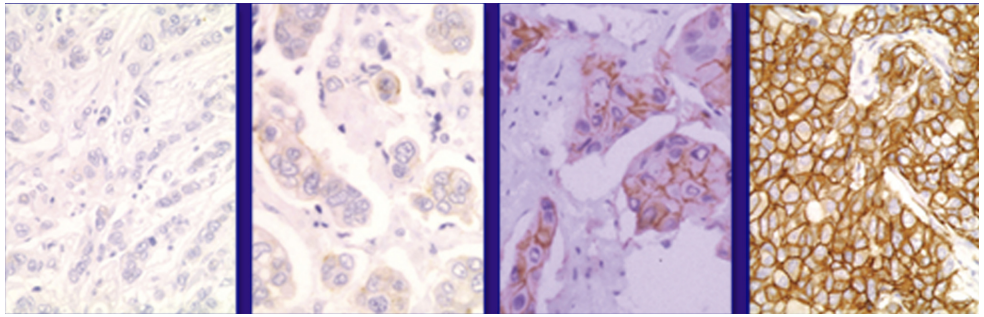
Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative[a,s,t,u]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**

• Anthracyclines
  ▸ Doxorubicin
  ▸ Liposomal doxorubicin
• Taxanes
  ▸ Paclitaxel
• Anti-metabolites
  ▸ Capecitabine
  ▸ Gemcitabine
• Microtubule inhibitors
  ▸ Vinorelbine
  ▸ Eribulin
	• Cyclophosphamide
	• Docetaxel
	• Albumin-bound paclitaxel
	• Epirubicin
	• Ixabepilone
		• AC (doxorubicin/cyclophosphamide)
		• EC (epirubicin/cyclophosphamide)
		• CMF (cyclophosphamide/ methotrexate/fluorouracil)
		• Docetaxel/capecitabine
		• GT (gemcitabine/paclitaxel)
		• Gemcitabine/carboplatin
		• Carboplatin + paclitaxel or albumin-bound paclitaxel

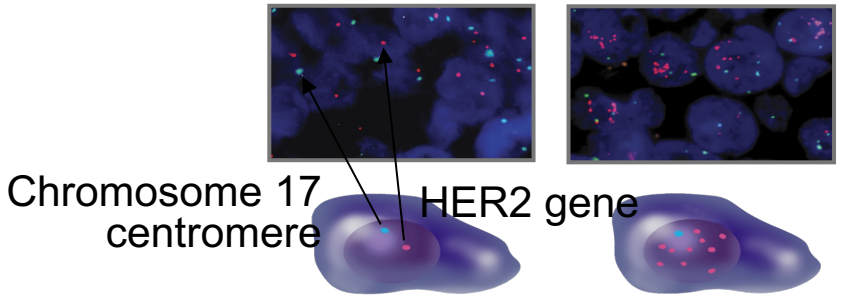
NCCN Breast Cancer Guidelines Version 4.2023 BINV-Q 1 of 14, accessed April 9 2023

HR positive and Her 2 negative unresectable or stage IV (M1) disease

M1 in Visceral Crisis or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline BRCA 1/2	Systemic chemotherapy
	Germline BRCA 1/2	PARPi (olaparib, talazoparib)
"Second Line"	Her 2 low	TDxD
	Not Her 2 low	Sacituzumab-govitecan



IHC 0 IHC I+ IHC 2+ IHC 3+



HER2-normal Ratio <2.0 **HER2-amplified Ratio ≥2.0**

NCCN Breast Cancer Guidelines Version 4.2023 BINV-Q 1 of 14, accessed April 9 2023

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

An open-label, multicenter study (NCT03734029)

Patients[a]

- HER2-low (IHC 1+ vs IHC 2+/ISH−) mBC
- 1-2 prior lines of chemo in met dx
- HR+ disease considered endocrine refractory

T-DXd
5.4 mg/kg Q3W
(n = 373)

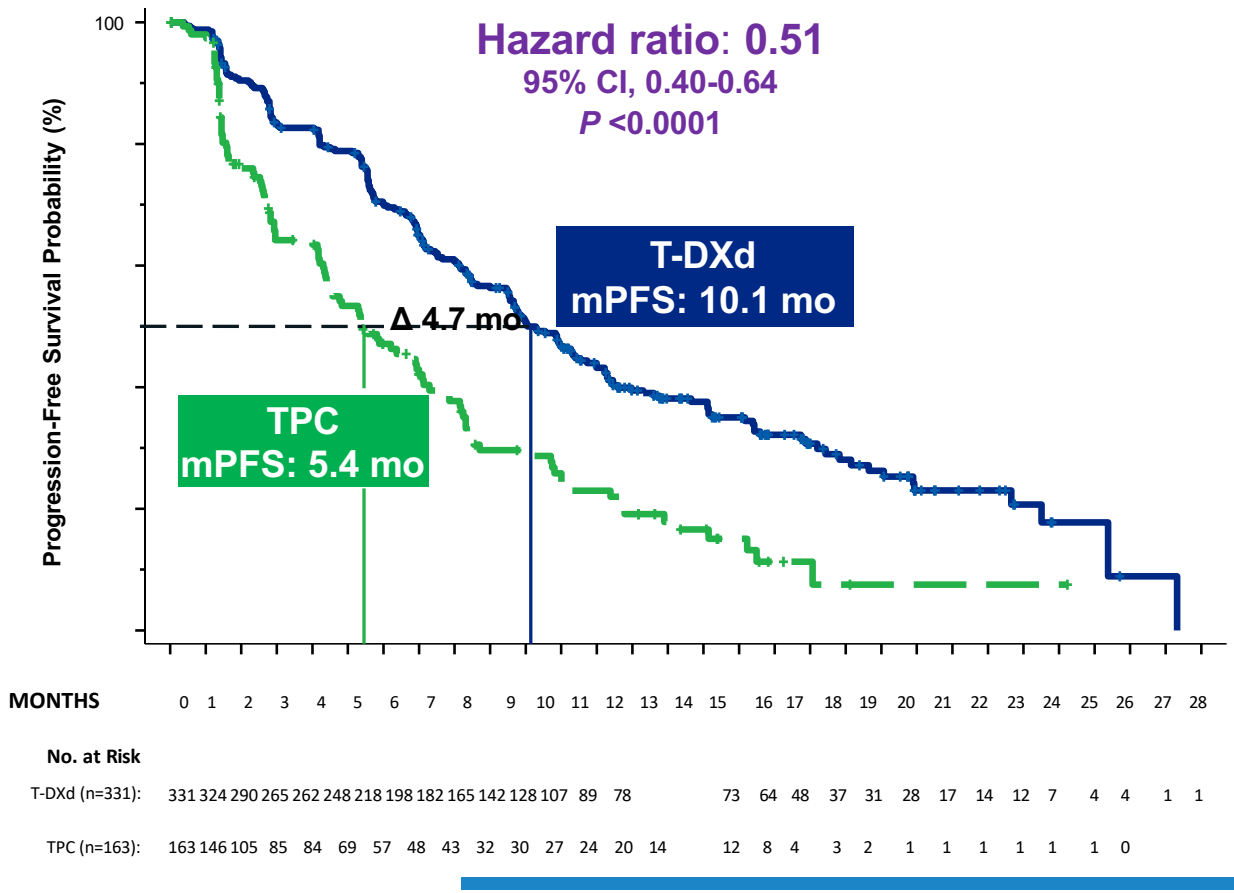
HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

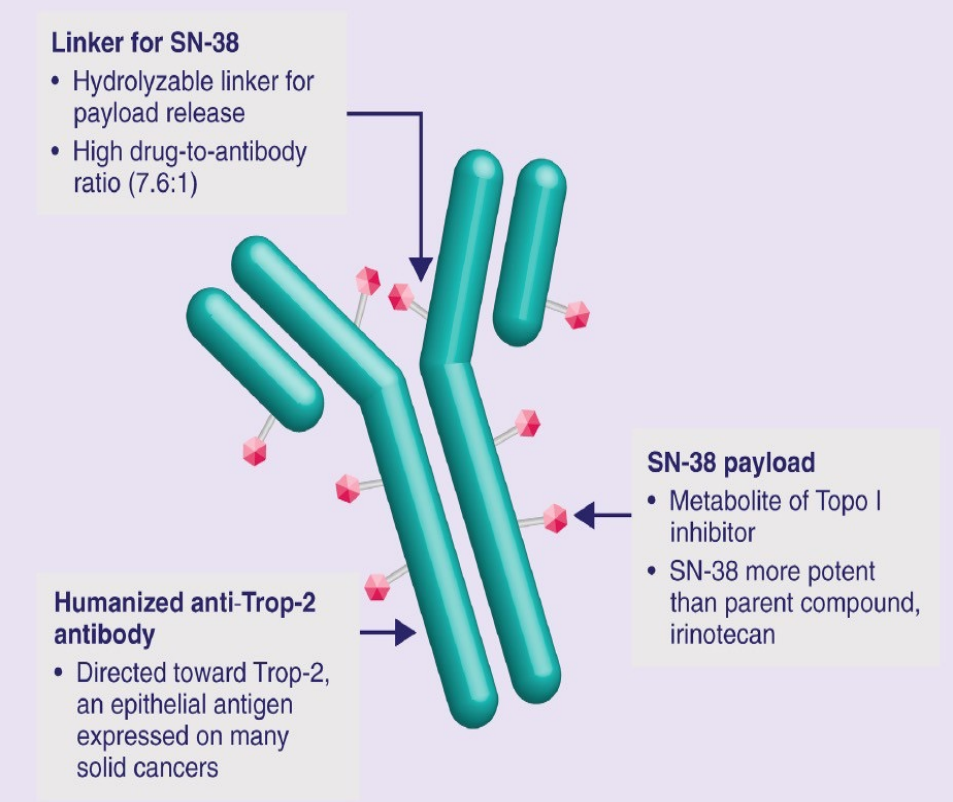
Stratification factors

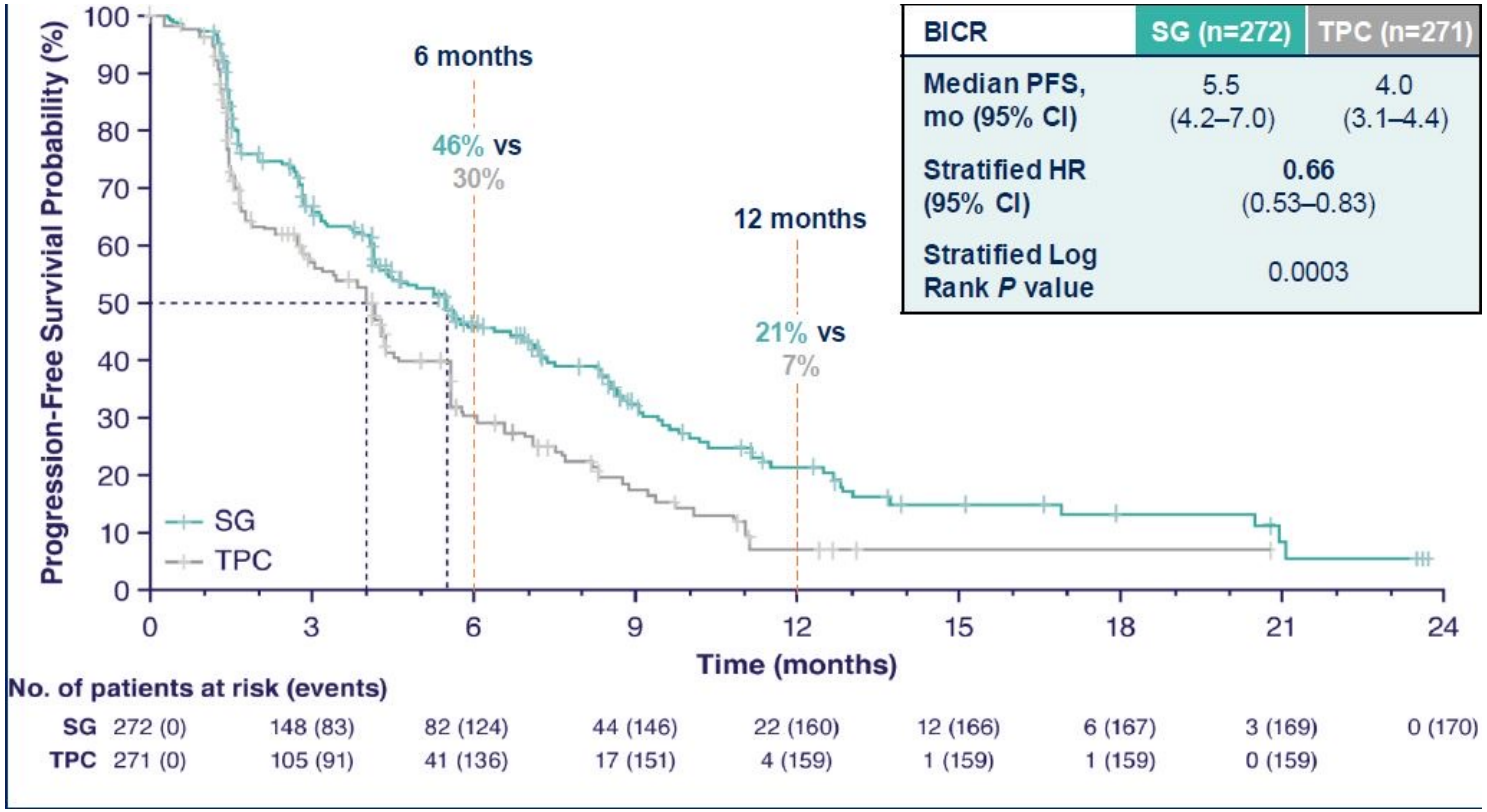
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR−

PFS Hormone receptor-positive



TROPiCS-02 phase 3 study of Sacituzumab-govitecan (SG) in patients (pts) with hormone receptor–positive/HER2-negative (HR+/HER2–) metastatic breast cancer (mBC)





BICR	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	0.66 (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	

Rugo HS et al. ASCO 2022.

ASCO 2023: Final overall survival (OS) analysis

OS SG versus TPC (median, 14.5 vs 11.2 mo; HR, 0.79 [95% CI, 0.65-0.95]; nominal *P*=0.01).

SG improved OS versus TPC in the HER2 IHC0 (median, 13.6 vs 10.8 mo; HR, 0.86 [95% CI, 0.63-1.13]) and HER2-low (median, 15.4 vs 11.5 mo, HR, 0.74 [95% CI, 0.57-0.97) groups.

ER+ Her2- Conclusions:

- Controversy remains over the true benefit of chemotherapy in premenopausal women with HR+/Her2- disease – watch for the OFSET trial!
- Importance of looking for the biomarkers = BRCA, ESR1, PIK3CA, Her 2 IHC results and status as low v true negative.
- Outstanding results with first line CDK4/6 inhibitor combinations in AI-sensitive disease
- Novel oral SERD elecestrant shows PFS advantage over fulvestrant or AI first line therapy.
- Ongoing trials will compare CDK4/6 options and other novel SERDS
- Second line or AI resistant disease therapy has options:
  - Fulvestrant plus CDK 4/6 inhibition if CDK4/6 naïve
  - Alpelisib if PIK3ca mutated
  - Talazaparib if BRCA+
  - Everolimus and exemestane

Thank you!

- ***Questions?***

- ***Virginia.borges@cuanschutz.edu***