Master Lecture Series: ER+/Her2- breast cancer

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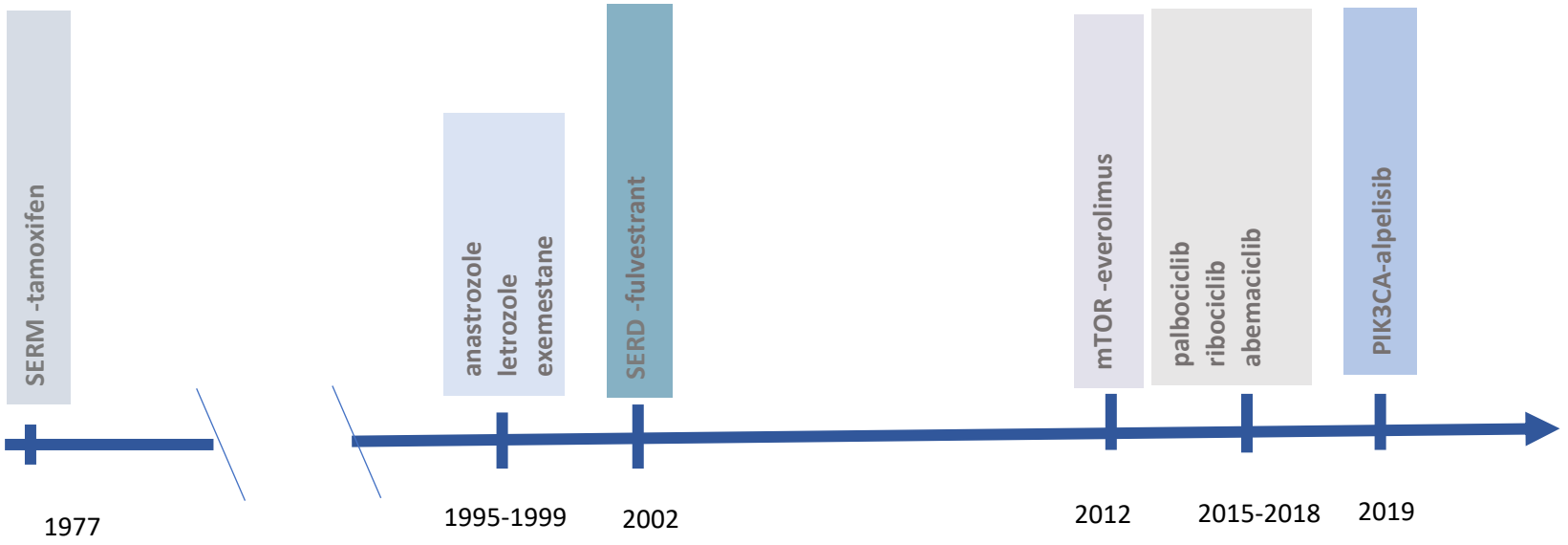
Objectives

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

Timeline of initial novel drug approvals for HR+ HER 2- metastatic breast cancer



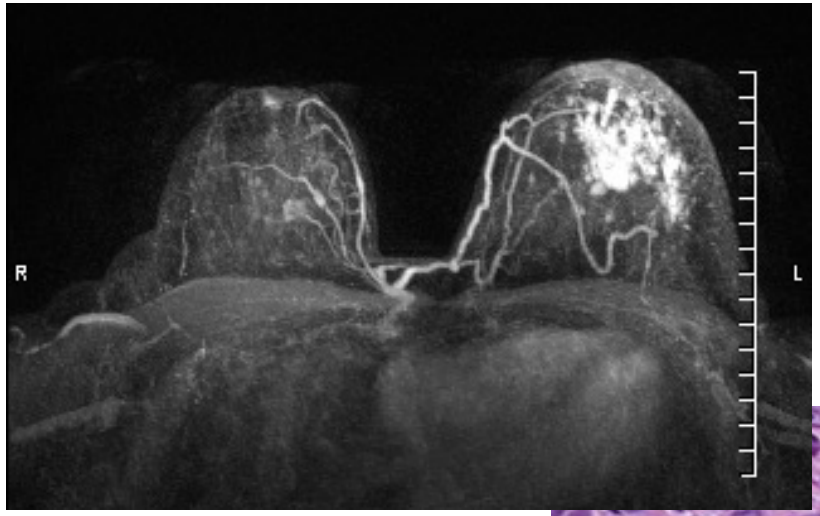
Borges, JCO, Dec 2021

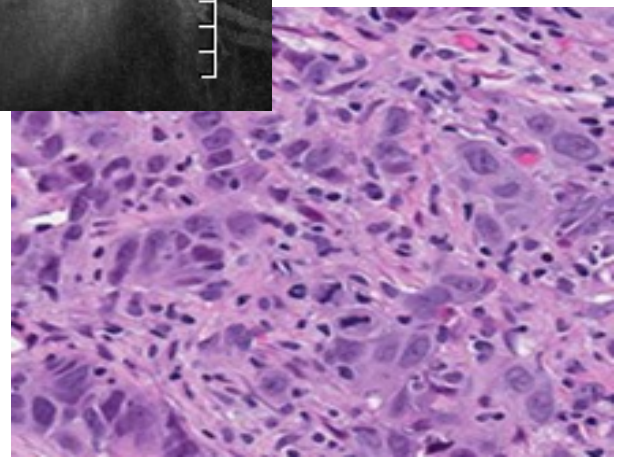
Friday afternoon in clinic….

35-year-old woman presents for consultation for her metastatic 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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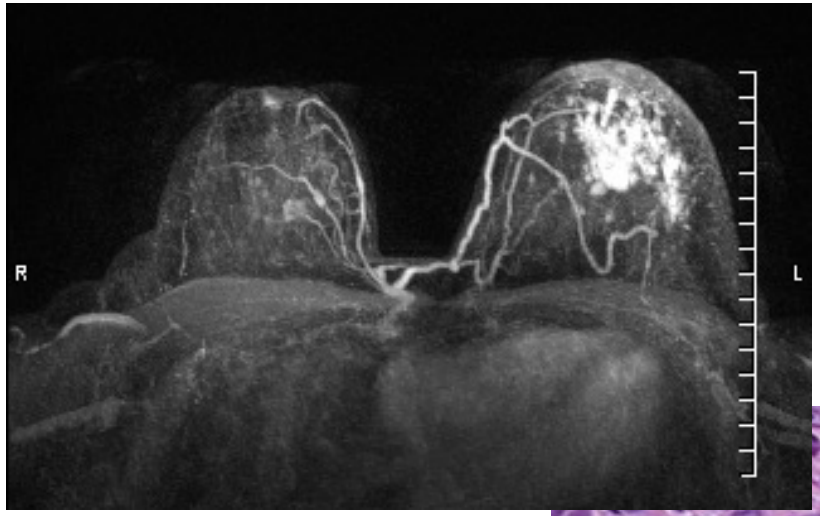
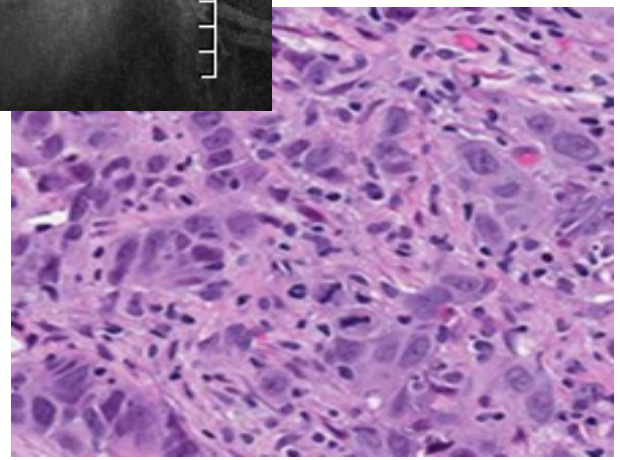




Surgery first?
Oncotype?
Neoadjuvant or adjuvant chemo?
Other things to remember?

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

First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy +/- chemotherapy in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007

Kevin Kalinsky, William E Barlow, Funda Meric-Bernstam, Julie R Gralow, 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, Miguel Gil Gil, Claudia Arce-Salinas, Etienne Brain, In Hae Park, Jean-Yves Pierga, Ana Lluch, Manuel Ramos Vazquez, Manuel Ruiz Borrego, Kyung Hae Jung, Jean-Marc Ferrero, Anne Schott, Steve Shak, Priyanka Sharma, Danika L Lew, Jieling Miao, Debu Tripathy, Gabriel N Hortobagyi, Lajos Pusztai

RxPONDER Schema

Key Entry Criteria

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

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

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

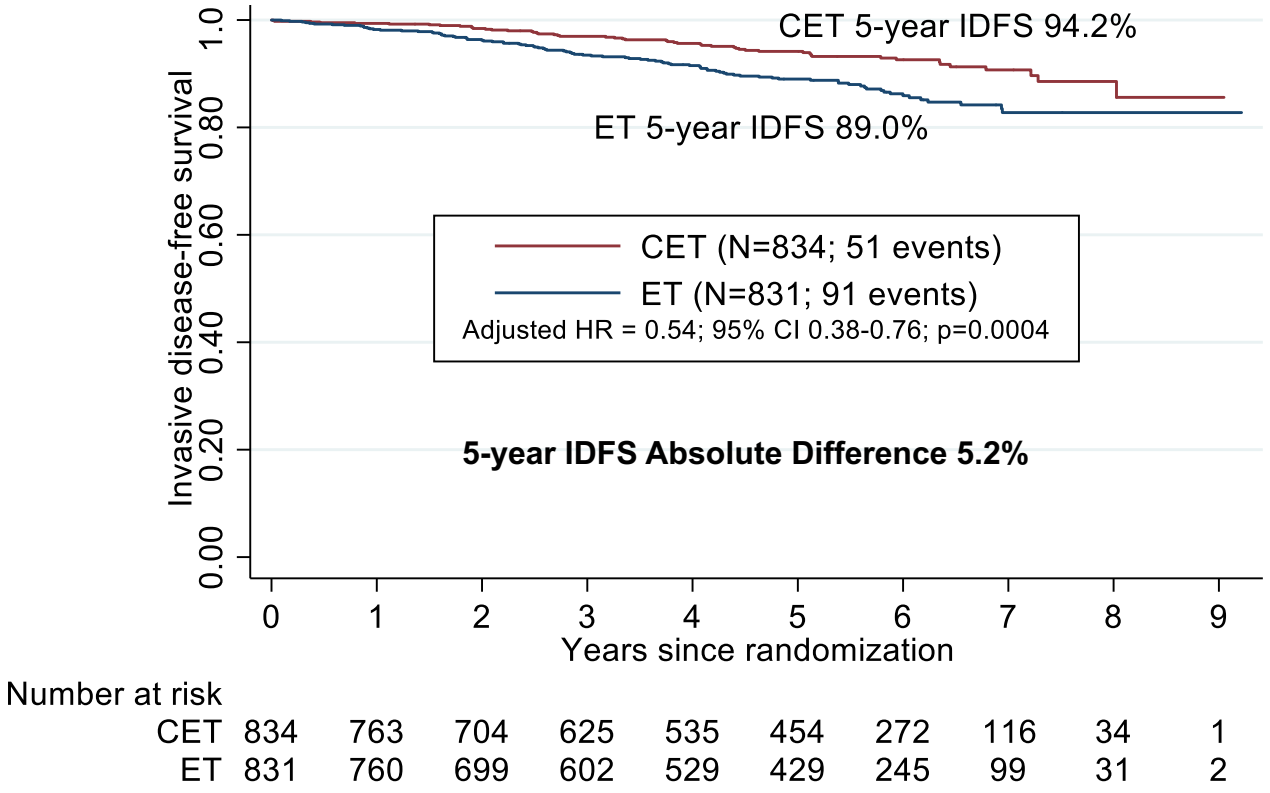
* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

Baseline Characteristics by Menopausal Status

Baseline variable	Postmenopausal (n=3,350)	Premenopausal (n=1,665)	Overall (n=5,015)
Age group			
< 40 years	0.2%	8.5% [141]	2.9%
40-49 years	1.9%	60.8%	21.5%
50-59 years	34.9%	30.5%	33.4%
60-69 years	45.7%	0.2%	30.6%
70+ years	17.3%	0%	11.6%
Recurrence Score			
RS 0-13	44.8%	38.7%	42.8%
RS 14-25	55.2%	61.3%	57.2%
Nodal Dissection			
Full ALND	60.7%	66.4%	62.6%
Sentinel nodes only	39.3%	33.6%	37.4%
Positive Nodes			
1 node	65.6%	65.3%	65.5%
2 nodes	25.1%	25.7%	25.3%
3 nodes	9.3%	9.0%	9.2%
Grade			
Low	26.0%	22.0%	24.7%
Intermediate	63.5%	68.3%	65.1%
High	10.6%	9.7%	10.3%
Tumor size			
T1	59.1%	56.2%	58.1%
T2/T3	41.9%	43.9%	41.9%

IDFS premenopausal women

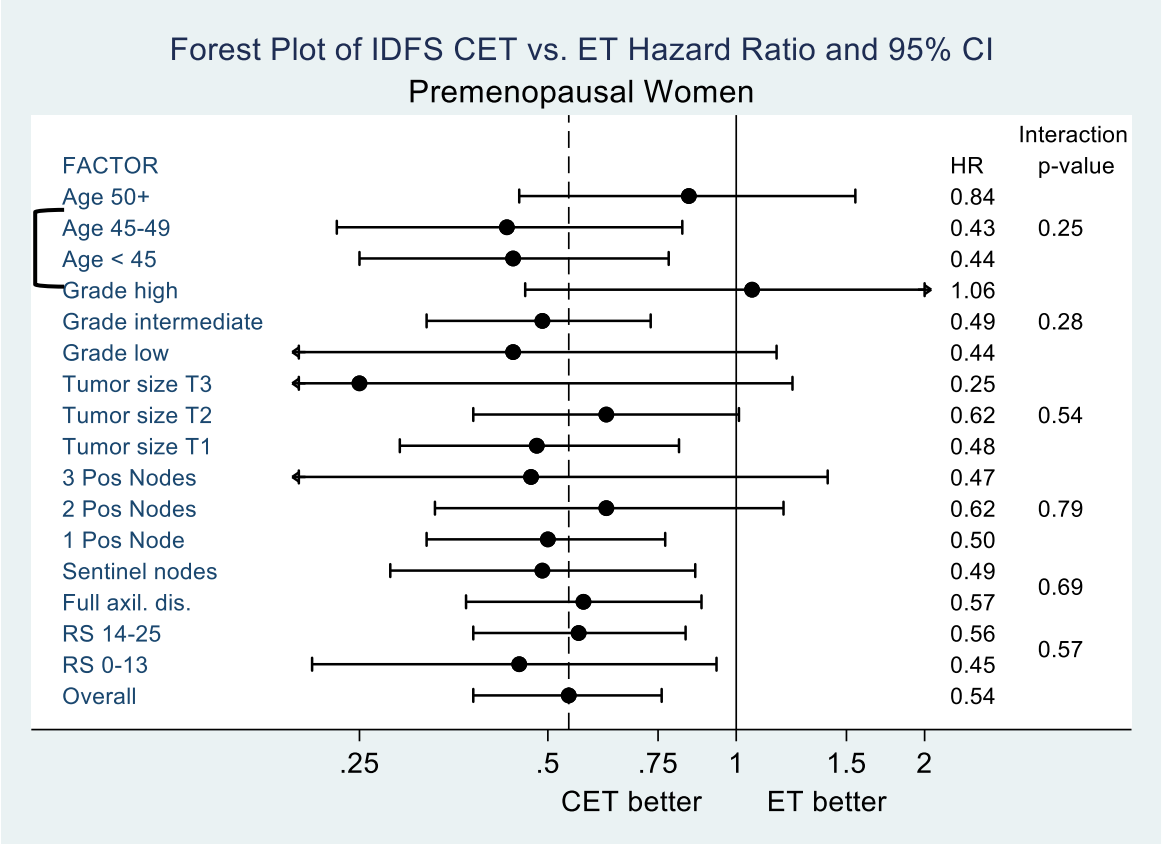
Premenopausal



IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Forest Plots of IDFS Premenopausal Women

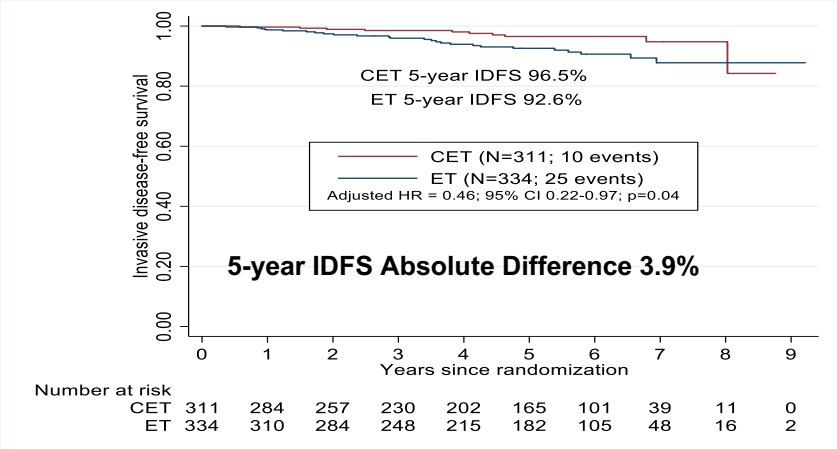


Landmarked Exploratory Analysis for IDFS in Premenopausal Women on Endocrine Therapy arm:
Ovarian Function Suppression (n=126) vs. no Ovarian Function Suppression (n=647) at 6 months: HR 0.73 (95% CI: 0.39-1.37), p=0.33

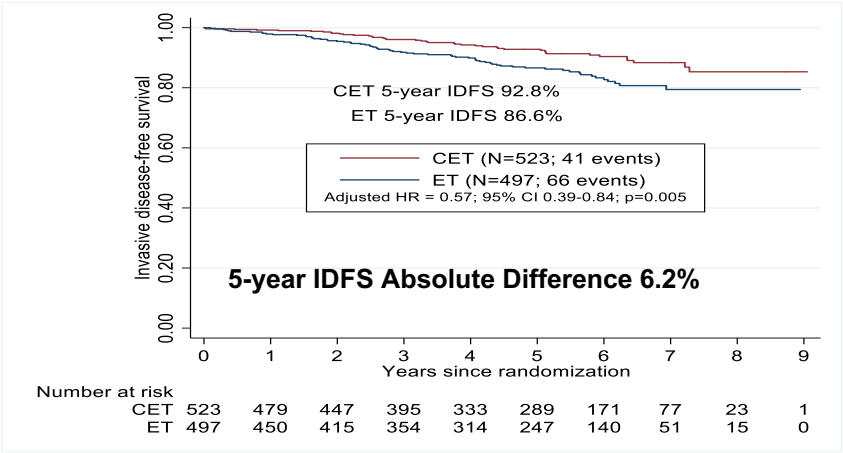
IDFS Stratified by Recurrence Score Premenopausal Status

Premenopausal

RS 0-13



RS 14-25



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

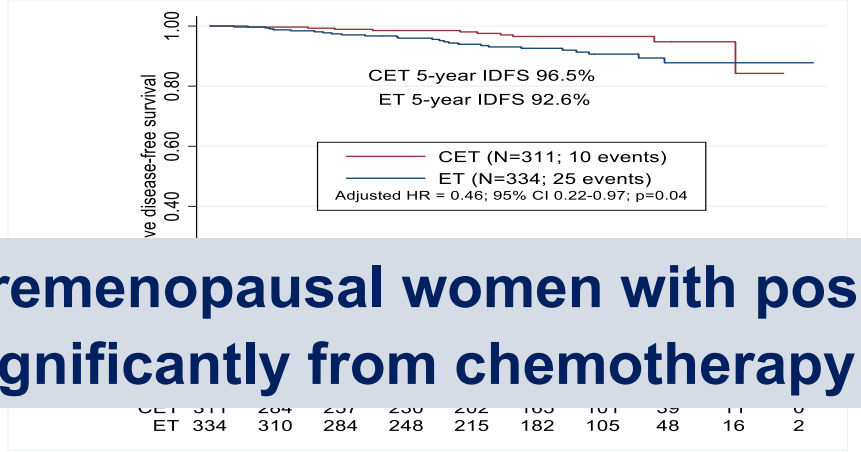
53% decrease in deaths, leading to a 5-year OS absolute improvement of 1.3%

1 node v 2-3 nodes – equal benefit at ~5% benefit

IDFS Stratified by Recurrence Score Premenopausal Status

Premenopausal

RS 0-13



Premenopausal women with RS 0-25 had benefit from the addition of chemotherapy to endocrine therapy

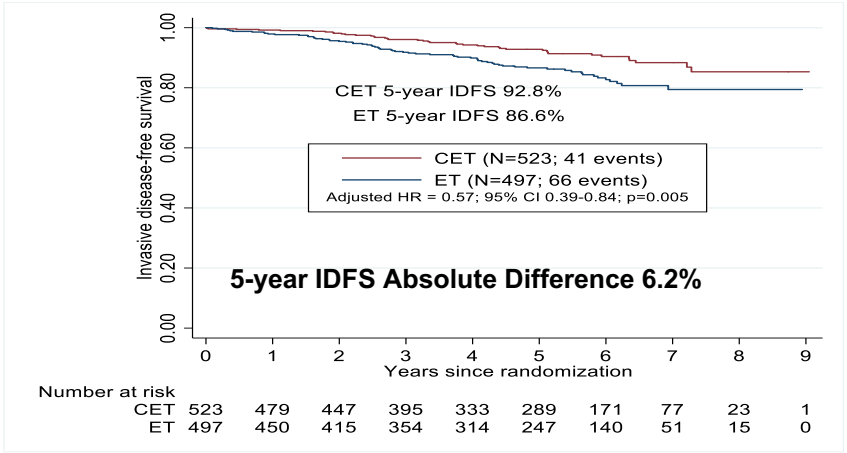
46% decrease in IDFS events; benefit was

✓ **Premenopausal women with positive nodes and RS 0-25 likely benefit significantly from chemotherapy**

absolute improvement of 1.3%

1 node v 2-3 nodes – equal benefit at ~5% benefit

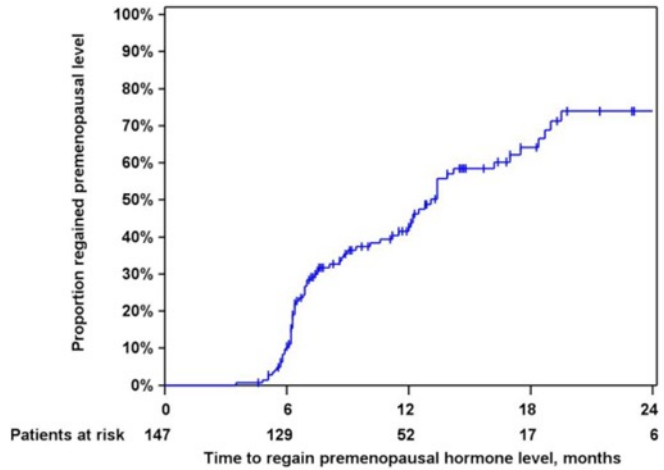
RS 14-25



- What factors are worth considering?
  - What's the biology? Who's the patient?
  - What is the expected benefit of the chemotherapy?
  - What does optimized hormonal therapy look like?

Original Research

Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials



Supplementary Figure 2. Time to regain of premenopausal hormone levels (actual time)

Furlanetto et al, EJC 2021

- **Patients under age 45**
- **85% experienced CIA at EOT**
- **Of those, 89% regained pre-menopausal hormone levels**
  - **6 Months: 33%**
  - **12 Months: 58%**
  - **18 Months: 83%**
  - **24 Months: 89%**

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**

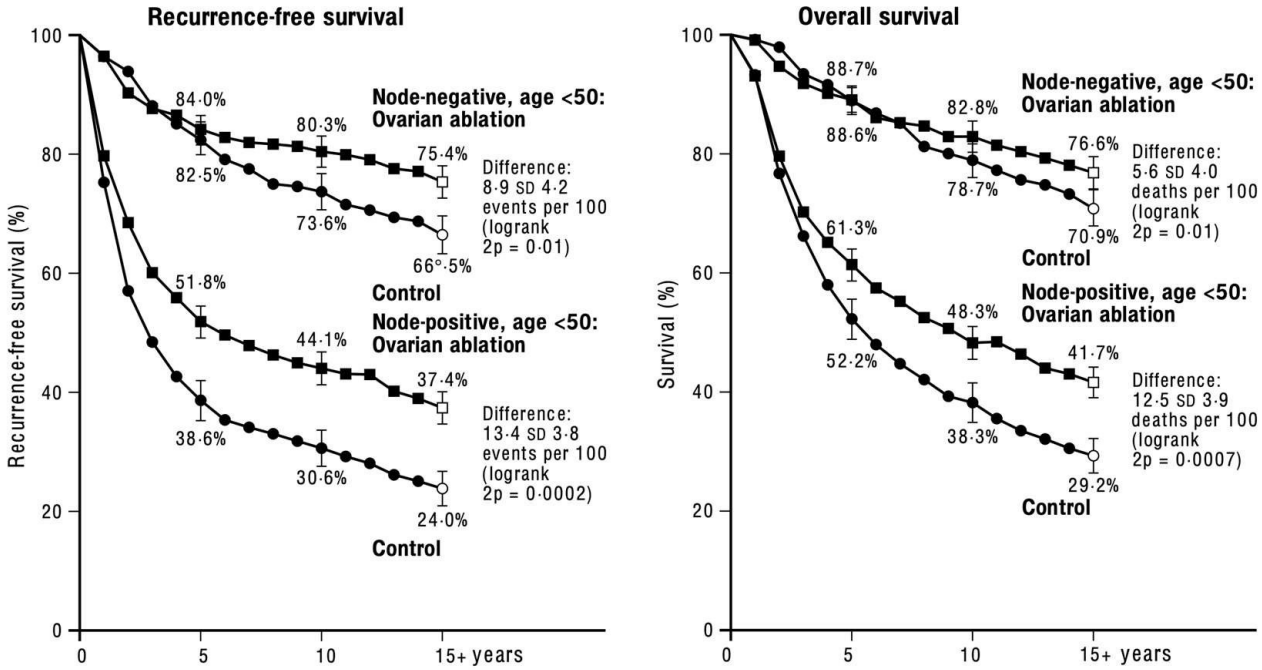
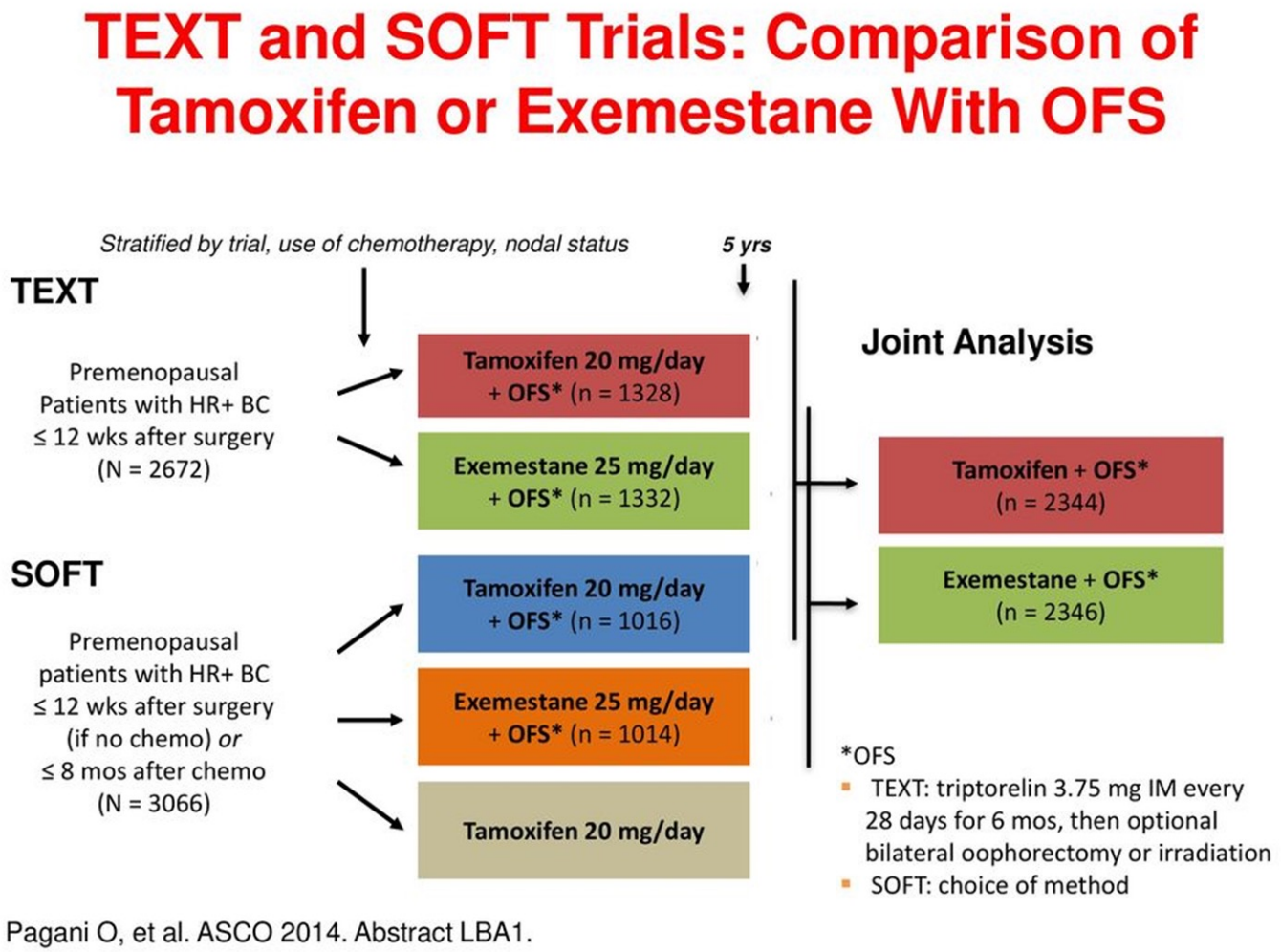


Figure 3: **Absolute effects of ovarian ablation in absence of routine chemotherapy in all trials combined among women aged under 50 at entry**

EBCTCG, Lancet 1996

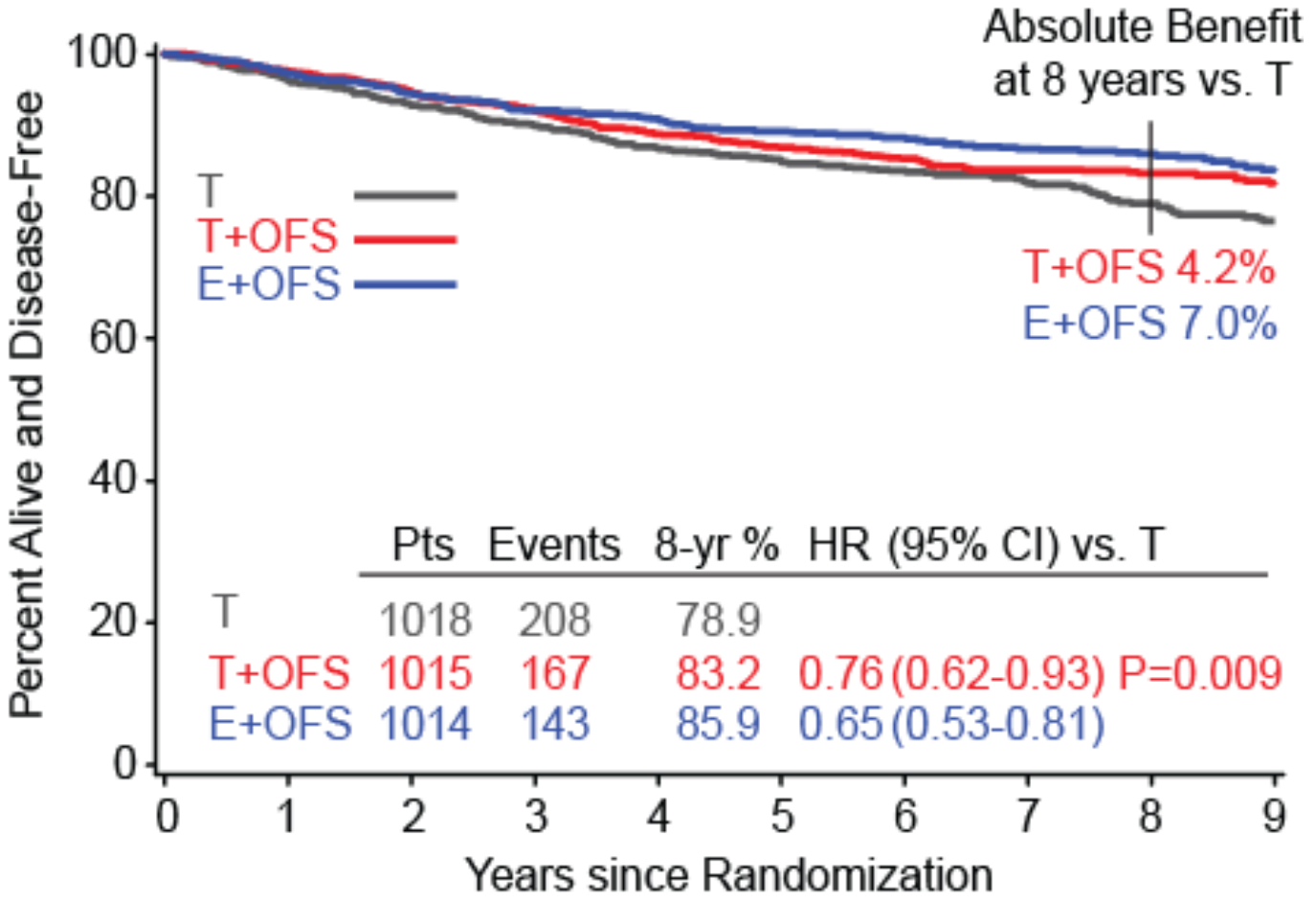
Optimized antiendocrine therapy

- 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.

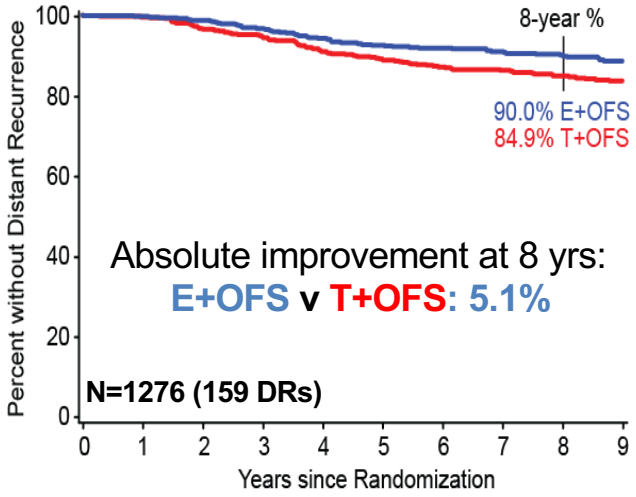
SOFT 8-Year Update: T+OFS Significantly Improves DFS vs. T-Alone; Exemestane Adds More Benefit



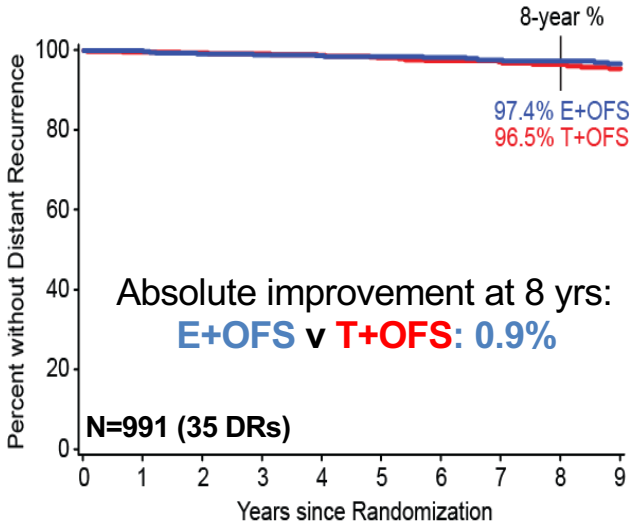
Distant Recurrence-free Interval by Cohort (HR+/HER2-)

TEXT

CHEMO



NO CHEMO



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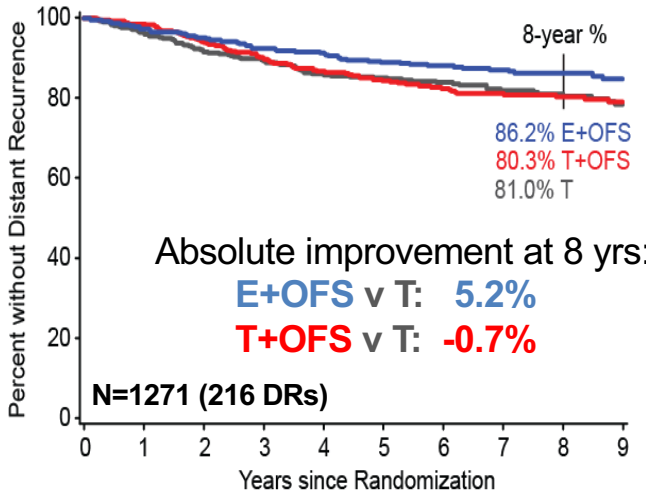
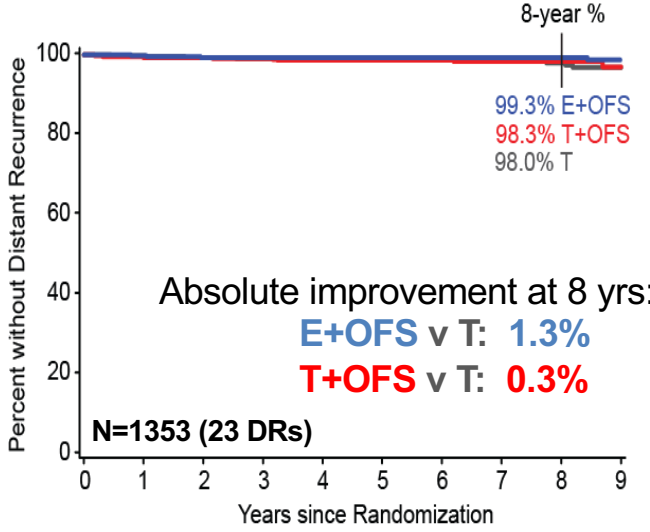
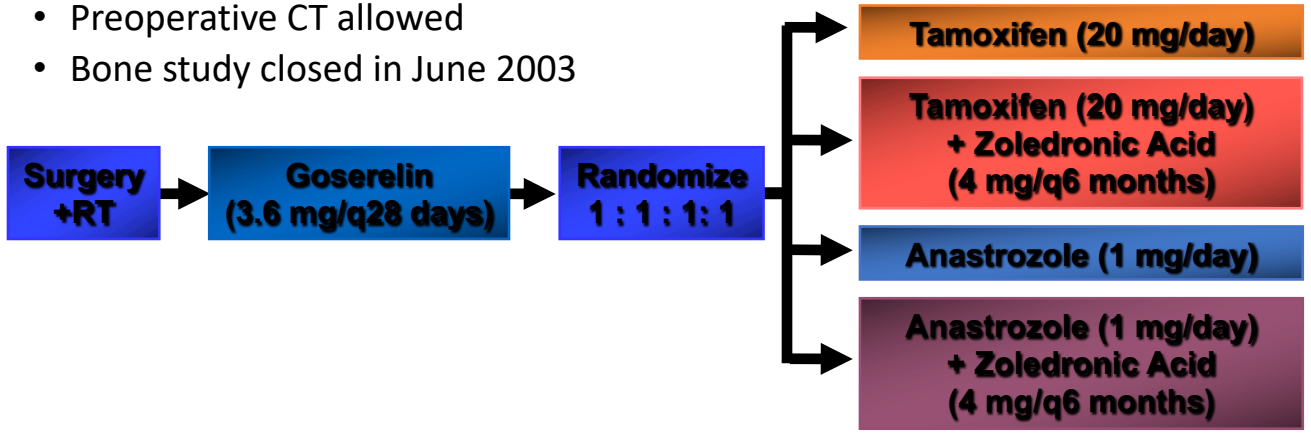




ABCSG 12 Trial:

- Accrual 1999-2006
- 1800 premenopausal patients
- Stage I and II, <10 positive nodes, ER+ and/or PgR+
- Treatment duration: 3 years
- Preoperative CT allowed
- Bone study closed in June 2003



ABCSG 12 = Austrian Breast and Colorectal Cancer Study Group 12;
BMD = bone mineral density; CT = chemotherapy; ER+ = estrogen receptor-positive;
PgR+ = progesterone receptor-positive; RT = radiation therapy.

Reproduced with permission from Gnant M et al. Presented at: 27th Annual San Antonio Breast Cancer Symposium; December 8-11, 2004; San Antonio, Tex.

Friday afternoon in clinic….

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

Breast Cancer History:

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Grade 2, Ki-67 22%
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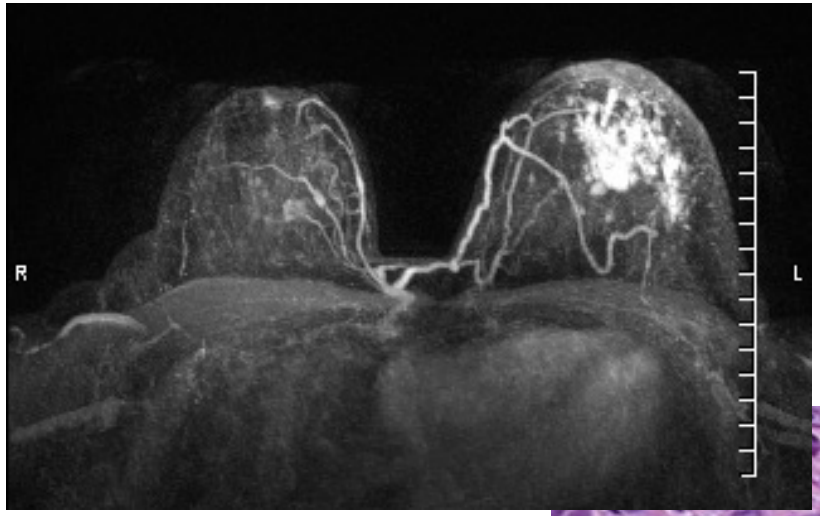
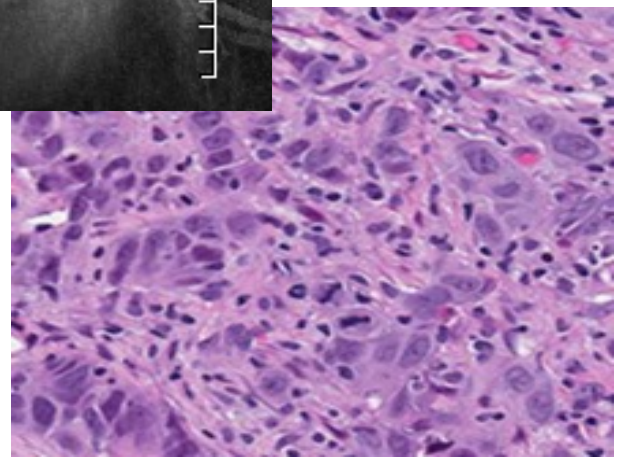




Oncotype was 22
Neoadjuvant chemo with AC-T
Other things to remember?

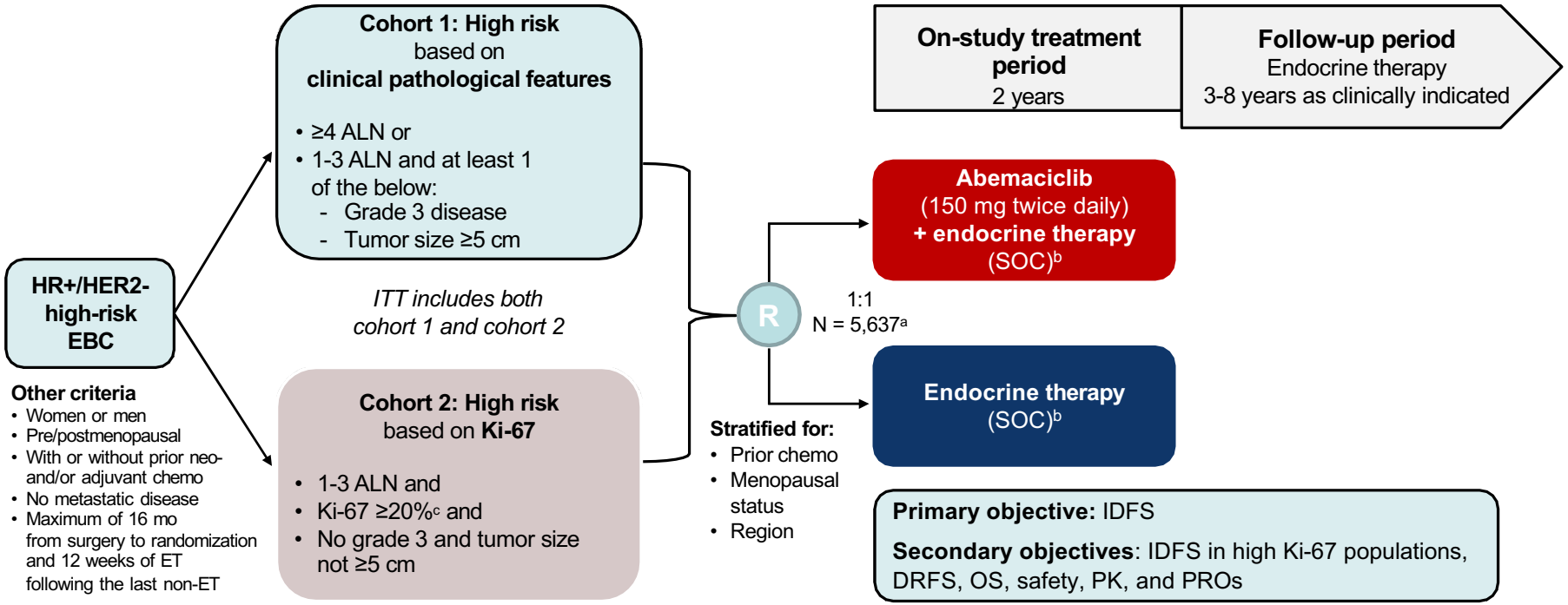
Fertility Issues

- 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 [awaiting the POSITIVE trial data at SABCS 2022]*
- Right now, is a REALLY BAD TIME for pregnancy, so fertility must be controlled in a definitive manner.

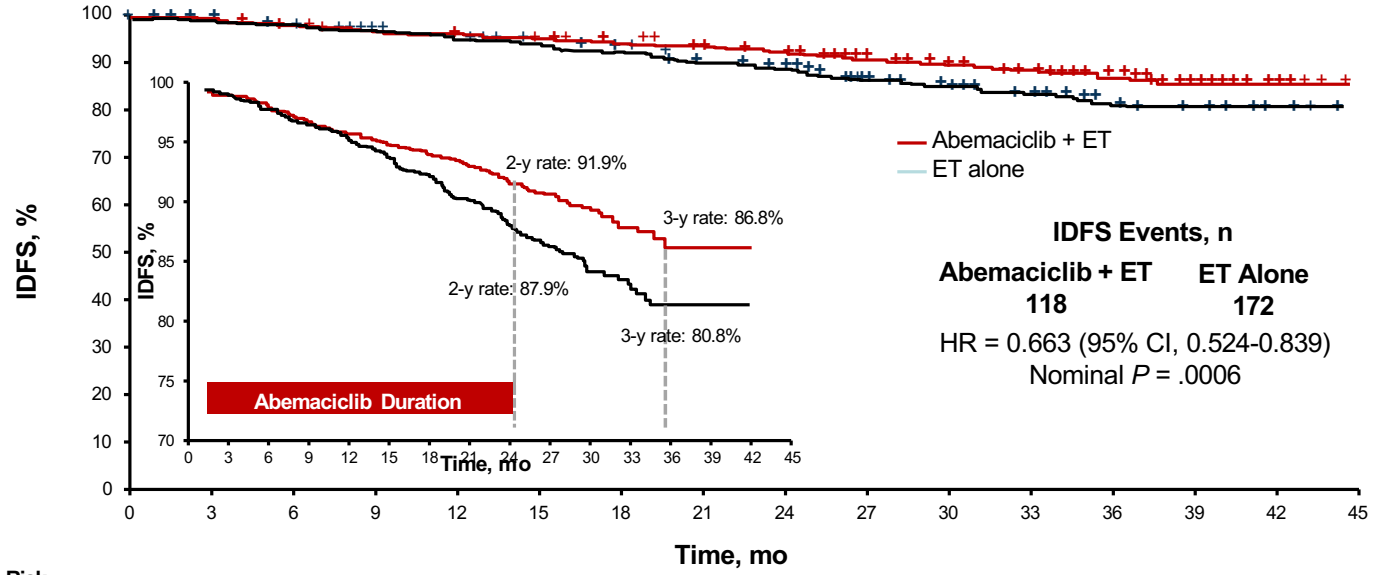
monarchE Study Design



[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

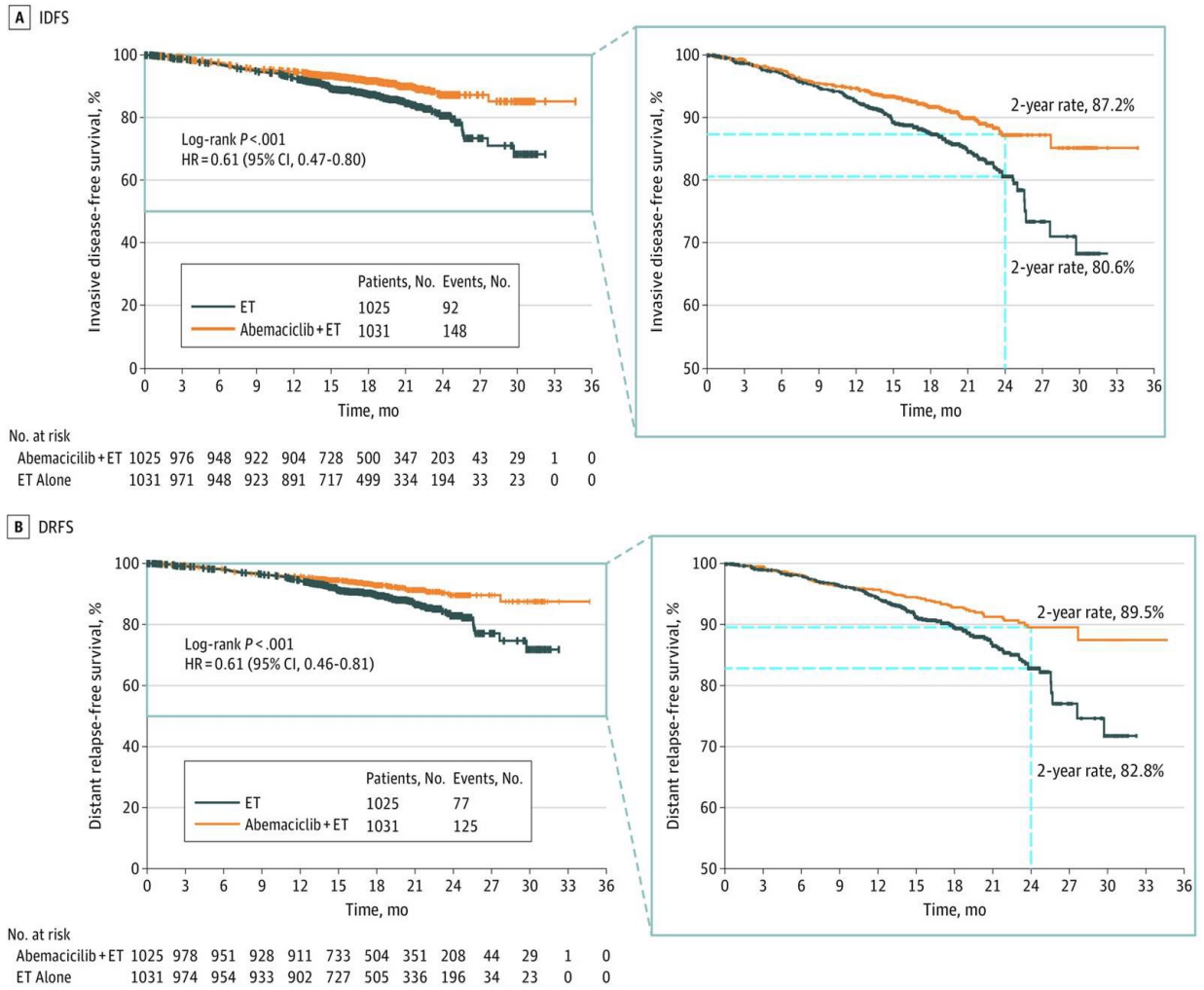
Abemaciclib + ET	1,262	1,221	1,189	1,167	1,155	1,139	1,123	1,094	870	546	377	203	109	25	2	0
ET alone	1,236	1,197	1,177	1,158	1,142	1,114	1,096	1,041	827	520	367	198	108	25	3	0

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

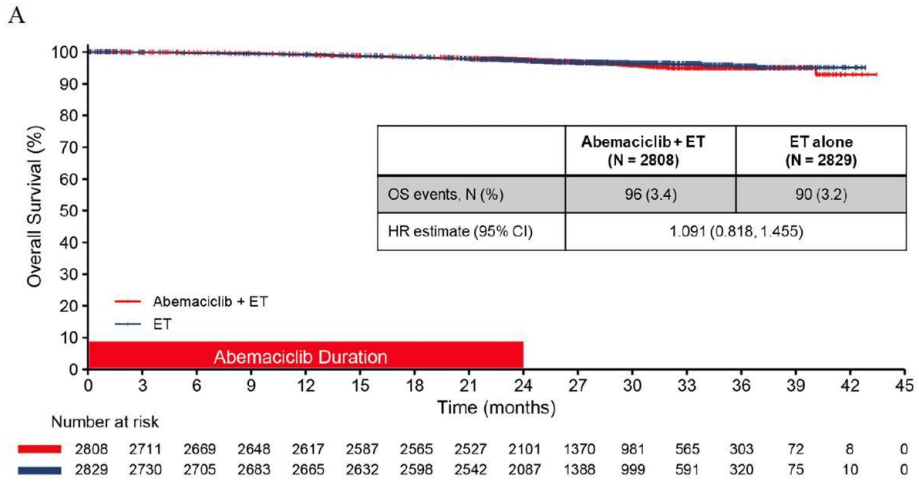
IDFS and DDFS following neoadjuvant chemotherapy



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

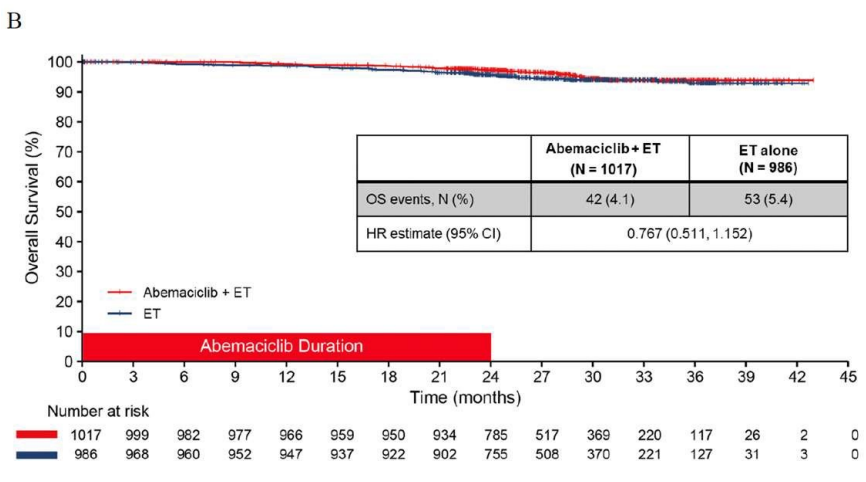
Preliminary OS Results

ITT Population



	Abemaciclib + ET (N = 2808)	ET alone (N = 2829)
OS events, N (%)	96 (3.4)	90 (3.2)
HR estimate (95% CI)	1.091 (0.818, 1.455)	

Ki-67 High Population



	Abemaciclib + ET (N = 1017)	ET alone (N = 986)
OS events, N (%)	42 (4.1)	53 (5.4)
HR estimate (95% CI)	0.767 (0.511, 1.152)	

Comparable number of deaths in both study arms (3.4% vs 3.2%)

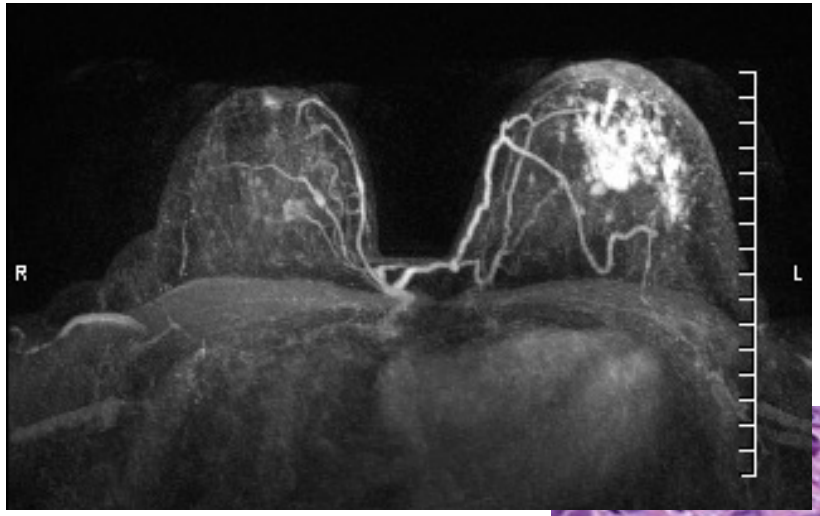
Harbeck N et al. *Ann Oncol.* 2021;32(12):1571-1581.

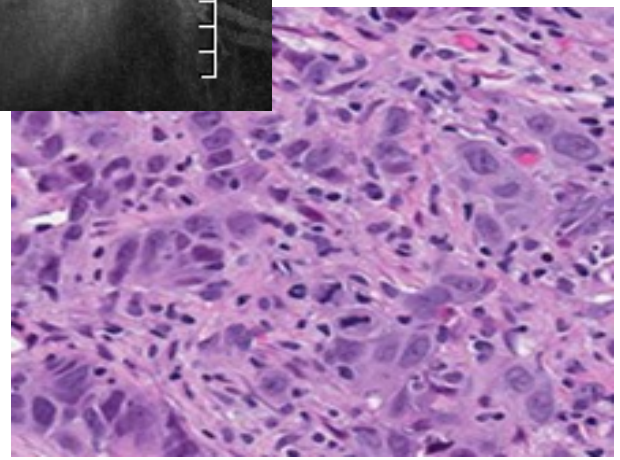
Friday afternoon in clinic….

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

<u>Breast Cancer History:</u>

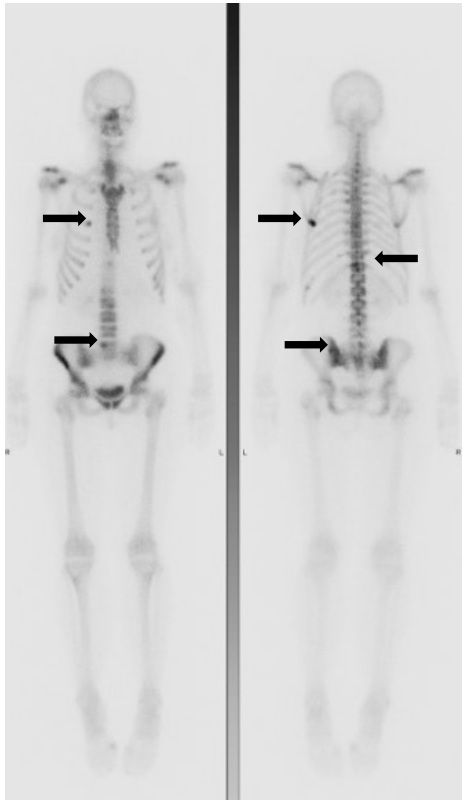
5 years ago, presented with L breast mass, BRCA2+
Stage III [T3N1M0]
Grade 2, Ki-67 19%
ER 60%, PR 40%, Her 2 IHC 0%
AC-T neoadjuvant chemo
Bilateral mastectomies with reconstruction
ypT1c,ypN1 (1 node) residual disease
PMCWXRT
Ovarian function suppression -> BSO
tamoxifen x 3 years
zolendronic acid 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.

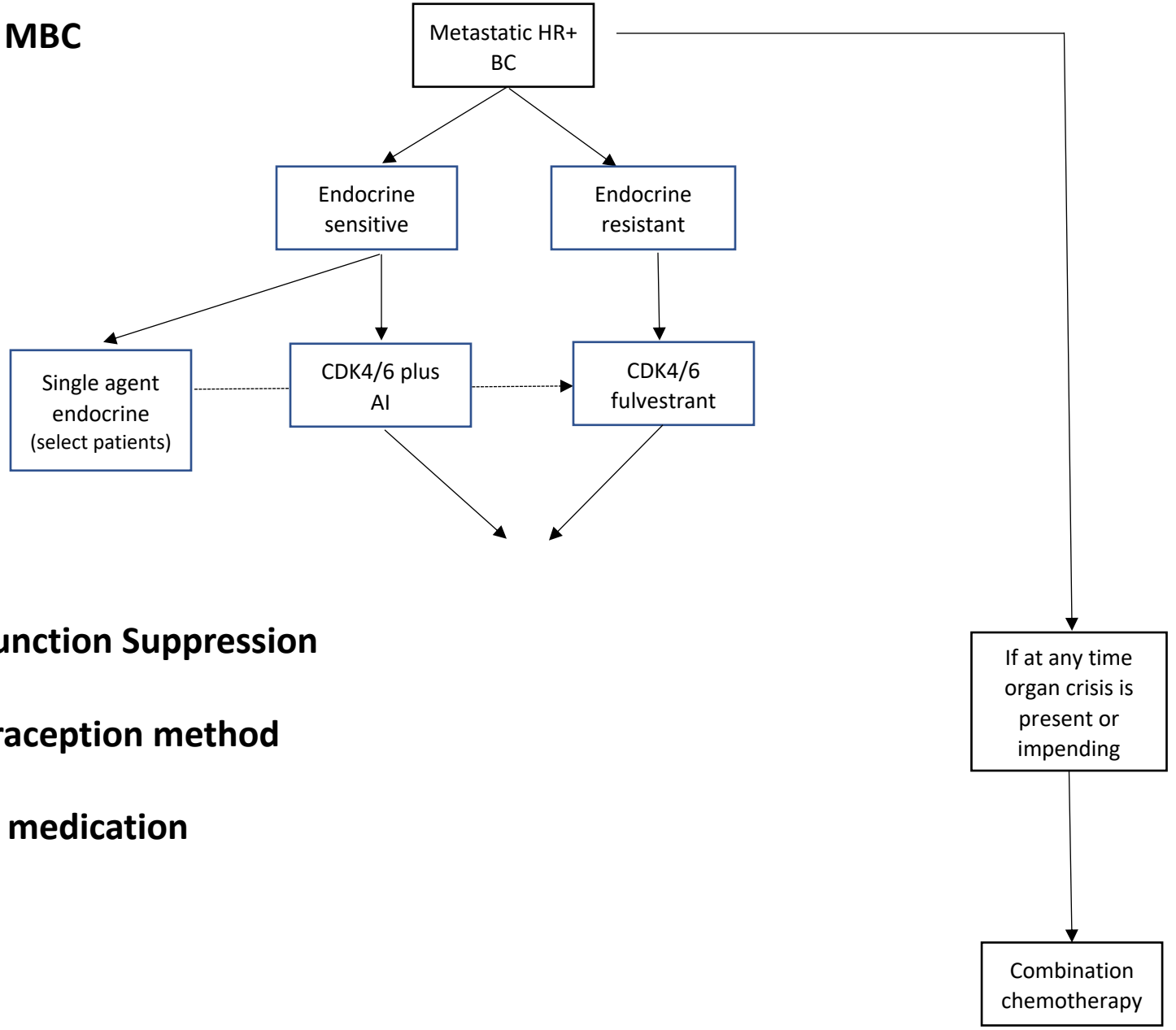
Labs were obtained and normal other than alk phos 1.5x ULN and CA27-29 of 65

Completion staging shows: bone only metastatic recurrence as seen by technetium-99m scintigraphic bone scan. CT CAP no other disease

Biopsy confirmed ER+ PR- Her2 0 by IHC and PIK3Ca mutated exon 9

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

New Phase III HARMONIA Trial Will Compare Palbociclib to Ribociclib for HR-Positive, HER2-Negative Advanced Breast Cancer

Press Release – September 19, 2021

"HARMONIA, an international, randomized, Phase III, multicenter, open-label study of ribociclib versus palbociclib, both in combination with endocrine therapy, in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer with a HER2-enriched (HER2E) intrinsic subtype [has been announced]. HARMONIA is the first prospective Phase III trial to enroll patients selected by RNA-based molecular subtyping of their tumors and the first to directly compare two CDK4/6 inhibitors in patients with HR+/HER2- advanced breast cancer.

The primary endpoint of HARMONIA is progression free survival, and the study will evaluate if ribociblib positively alters tumor biology, enabling a better response to endocrine therapy compared to palbociclib.

HARMONIA enrollment is expected to begin in Q1 2022. Patients with the basal-like subtype may also enroll. This exploratory cohort of patients will be treated with a chemotherapy-based regimen as these tumors behave more like triple-negative breast cancer."

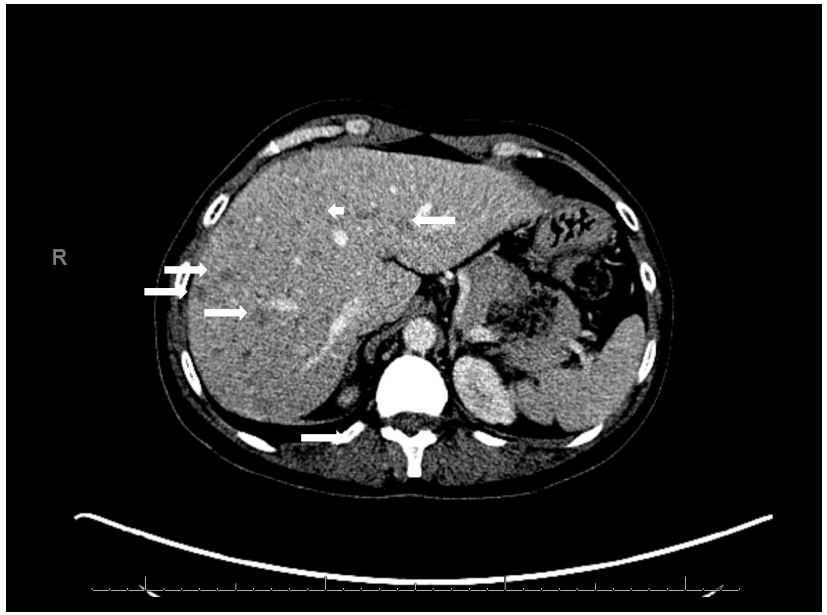
https://www.novartis.com/news/media-releases/novartis-announces-collaboration-harmonia-phase-iii-head-head-trial-evaluating-kisqali-vs-ibrance-patients-hrher2-advanced-breast-cancer

A subsequent Friday afternoon in clinic….

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

HPI:

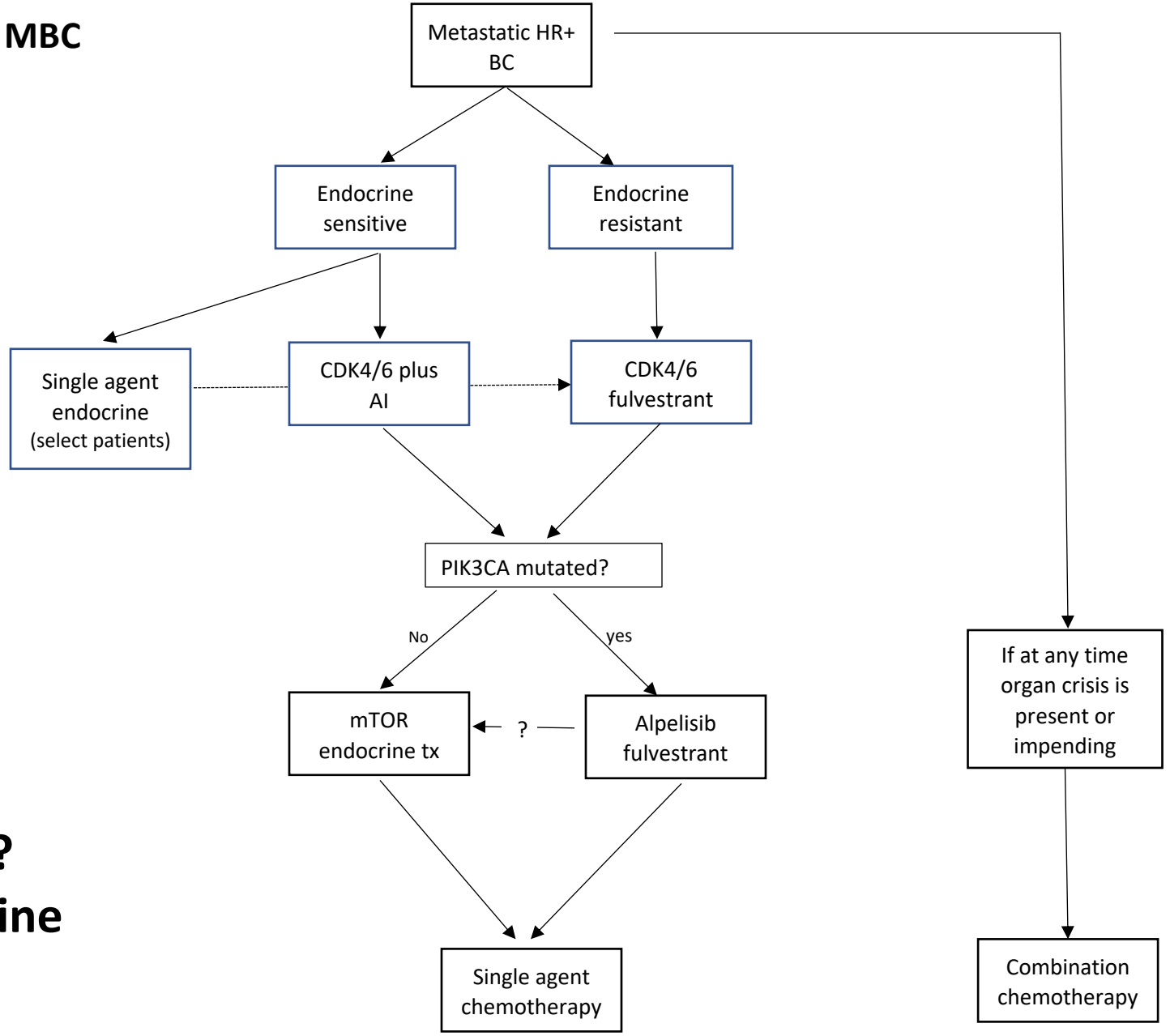
She's noted more fatigue
LFTs are newly elevated
CA27-29 has risen to 105
She completes staging scans prior to seeing you



Completion staging shows: bones look stable as seen by technetium-99m scintigraphic bone scan BUT disease progression with 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



Second line therapy

PARP inhibitor?
BRCA2 + germline mutation

Borges, JCO, Dec 2021

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

Lancet Oncol 2021;22:489-98.

Alpelisib plus fulvestrant in *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study

Hope S Rugo, Florence Lerebours, Eva Ciruelos, Pamela Drullinsky, Manuel Ruiz-Borrego, Patrick Neven, Yeon Hee Park, Aleix Prat, Thomas Bachelot, Dejan Juric, Nicholas Turner, Nickolas Sophos, Juan Pablo Zarate, Christina Arce, Yu-Ming Shen, Stuart Turner, Hemanth Kanakamedala, Wei-Chun Hsu, Stephen Chia

BYLieve: A Phase II, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) for patients with PIK3CA-mutated HR-positive, HER2-negative advanced breast cancer (ABC)

Men or pre/postmenopausal[a] women with HR+, HER2– ABC with a PIK3CA mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N = 112)[b] (Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N = 112) (Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N = 112) (Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Treatment crossover between cohorts is not permitted

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort

Secondary endpoints include (assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

[a]Men in the letrozole cohort and premenopausal women also received goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression. [b]Enrollment in each cohort continued until at least 112 patients with a centrally confirmed PIK3CA mutation was reached.
[c] IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter. [d]Oral QD.

Cohort A: Rugo HS et al. *Lancet Oncol* 2021.

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v1.1) or ≥
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At median follow up of 11.7 months 61/121 patients were alive and without progression at 6 months or more of therapy

without PD
each cohort

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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

Bardia A,[1] Neven P,[2] Streich G,[3] Montero AJ,[4] Forget F,[5] Mouret-Reynier MA,[6] Sohn JH,[7] Vuylsteke P,[8] Harnden KK,[9] Khong H,[10] Kocsis J,[11] Dalenc F,[12] Kaklamani V,[13] Dillon P,[14] Babu S,[15] Waters S,[16] Deleu I,[17] Garcia-Saenz J,[18] Bria E,[19] Cazzaniga M,[20] Lu J,[21] Aftimos P,[22] Cortes J,[23] Liu S,[24] Laurent D,[25] Conlan MG,[26] Bidard FC[27]

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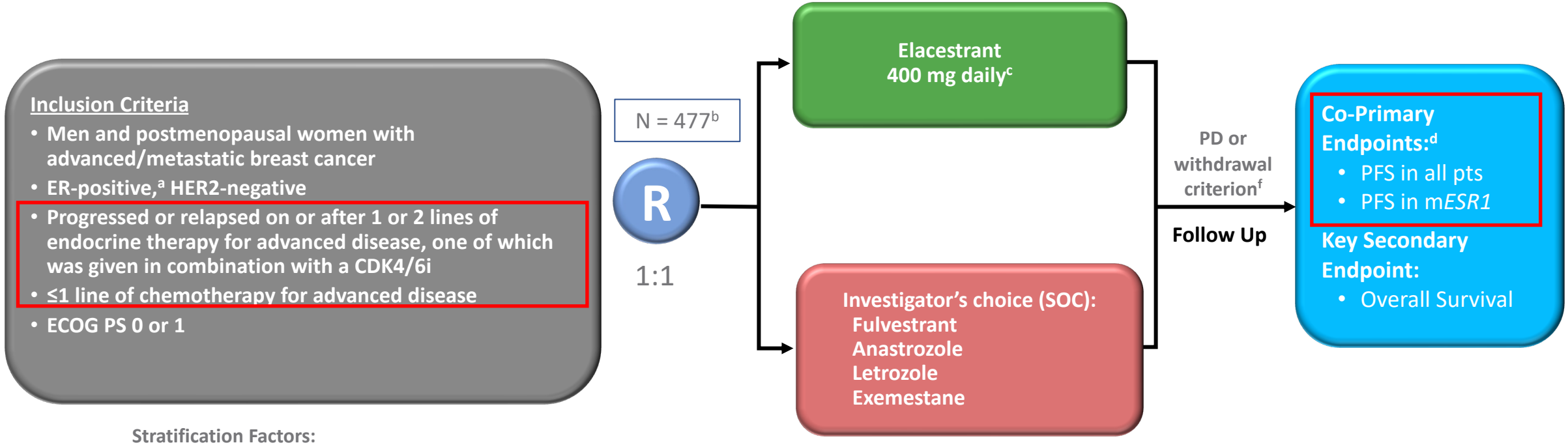
EMERALD Phase 3 Study Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded Independent Central Review. [e]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant health, Redwood City, CA). [f]Restaging CT scans every 8 weeks.

CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

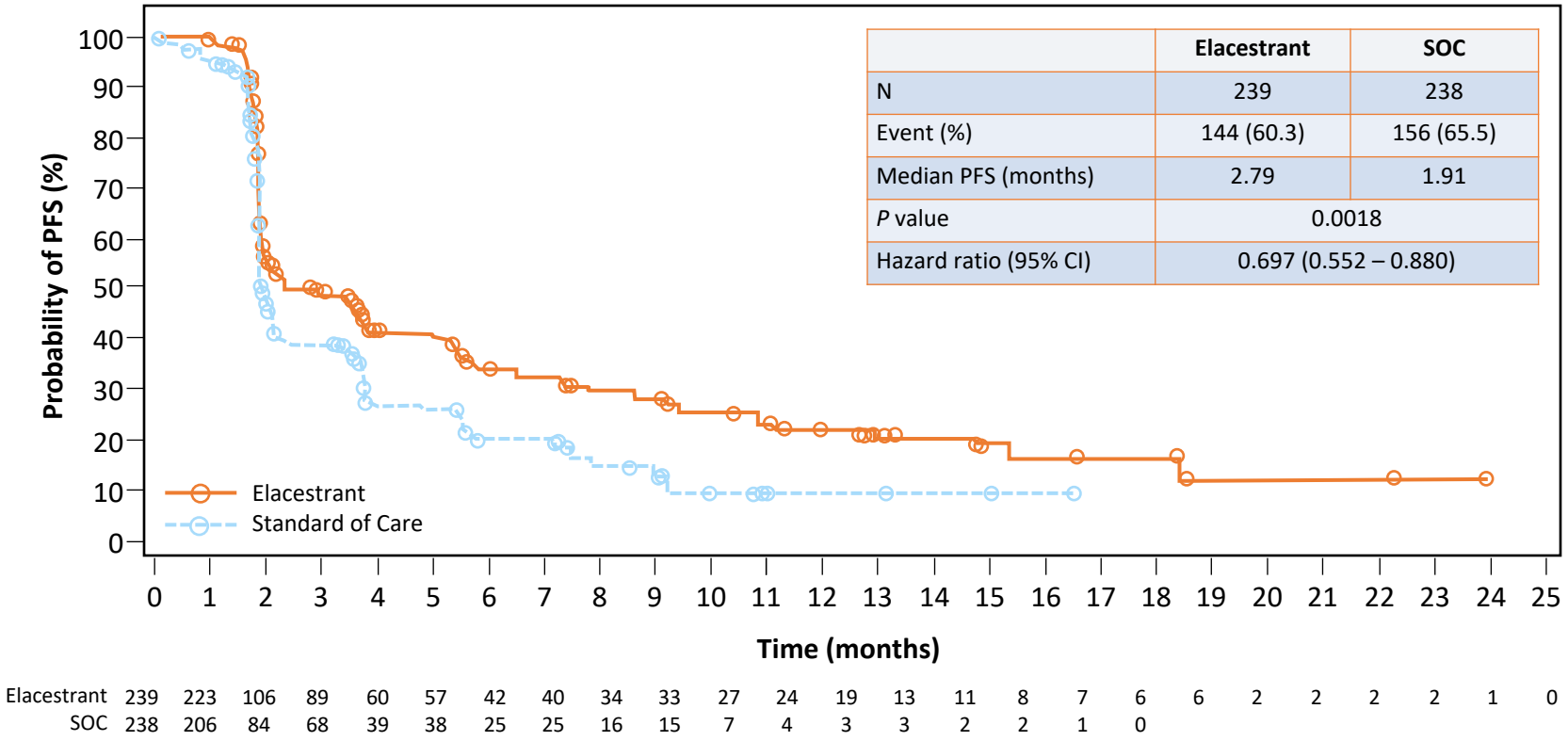
Baseline Demographic and Disease Characteristics

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

Primary Endpoint: PFS by IRC

All Patients (ITT)



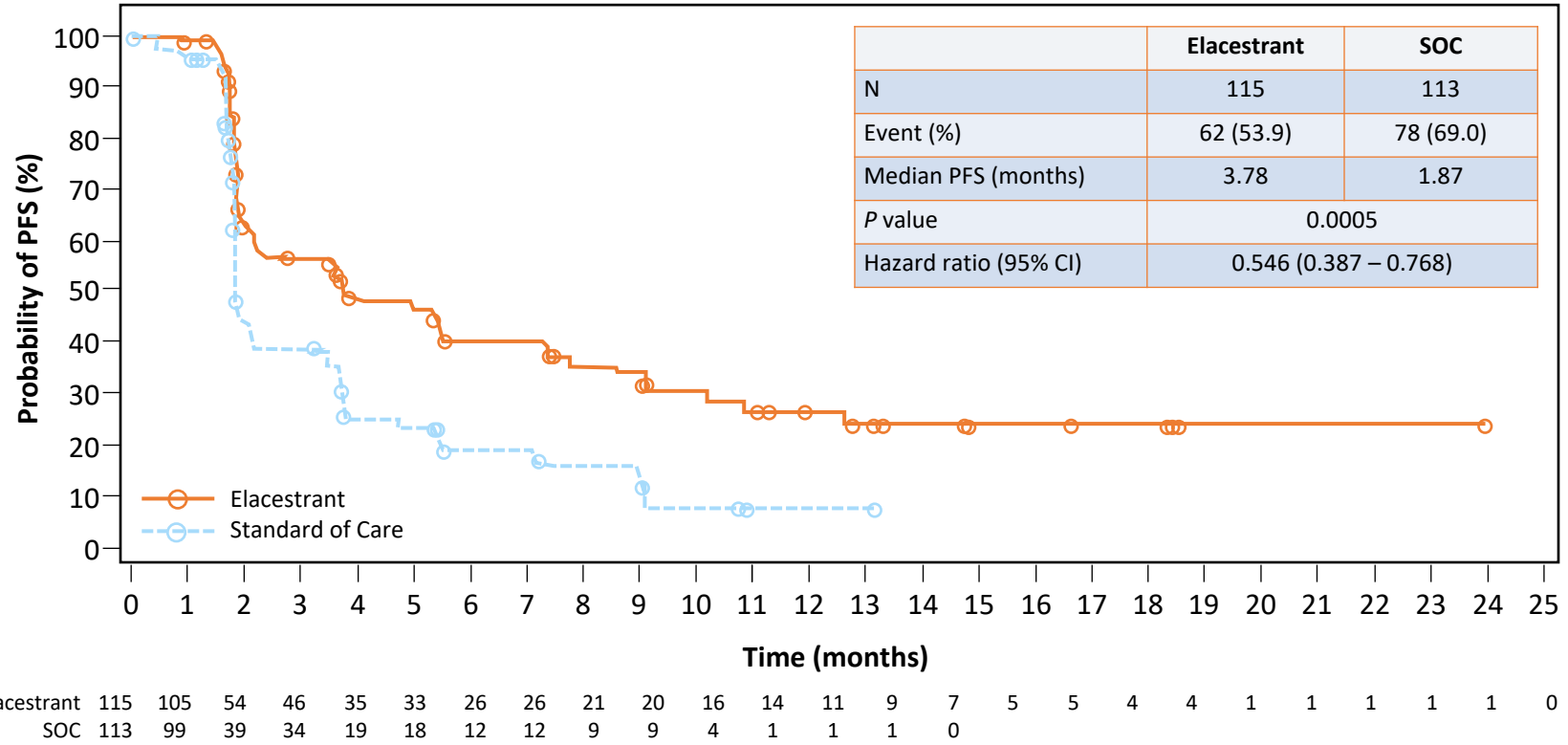
	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- mBC

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

Primary Endpoint: PFS by IRC

Patients With Tumors Harboring *mESR1*



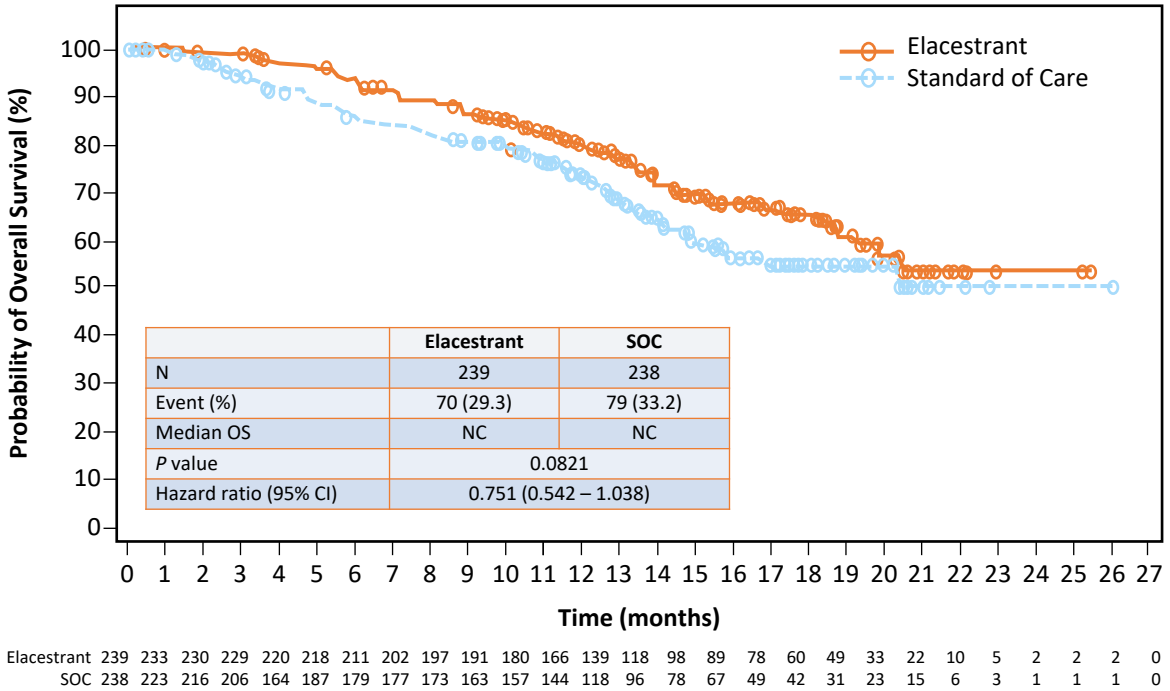
	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *mESR1*

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

Overall Survival (Interim Analysis)

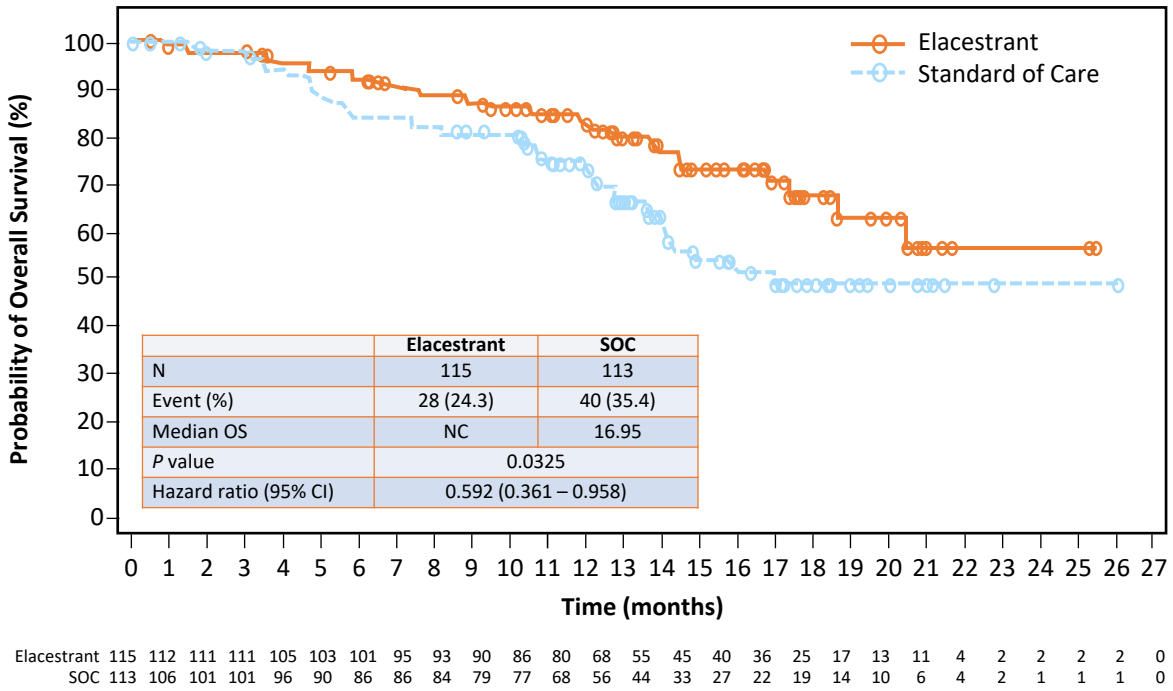
All Patients



	Elacestrant	SOC
N	239	238
Event (%)	70 (29.3)	79 (33.2)
Median OS	NC	NC
P value	0.0821	
Hazard ratio (95% CI)	0.751 (0.542 – 1.038)	

Elacestrant	239	233	230	229	220	218	211	202	197	191	180	166	139	118	98	89	78	60	49	33	22	10	5	2	2	2	0
SOC	238	223	216	206	164	187	179	177	173	163	157	144	118	96	78	67	49	42	31	23	15	6	3	1	1	1	0

Patients with *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	28 (24.3)	40 (35.4)
Median OS	NC	16.95
P value	0.0325	
Hazard ratio (95% CI)	0.592 (0.361 – 0.958)	

Elacestrant	115	112	111	111	105	103	101	95	93	90	86	80	68	55	45	40	36	25	17	13	11	4	2	2	2	2	0
SOC	113	106	101	101	96	90	86	86	84	79	77	68	56	44	33	27	22	19	14	10	6	4	2	1	1	1	0

- While no statistically significant differences were noted at the α=0.0001 level in OS, an evident trend favoring elacestrant over SOC was noted in both groups. Final analysis with mature data is expected to take place in late 2022/early 2023.

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 2nd/3rd-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.

Select Ongoing Phase II/III Trials of Oral SERDs in Development for ER-Positive, HER2-Negative Advanced Breast Cancer

Drug	Trial name (phase)	Treatment arms	Setting	Estimated study completion date
Amcenestrant (SAR439859)	AMEERA-3 (Phase II)	• Amcenestrant • Endocrine monotherapy	Prior hormonal tx	July 2025
Amcenestrant (SAR439859)	AMEERA-5 (Phase III)	• Amcenestrant + Palbociclib • Letrozole + Palbociclib	Untreated ABC	May 2027
Camizestrant (AZD9833)	SERENA-4 (Phase III)	• Camizestrant + Palbociclib • Anastrozole + Palbociclib	Untreated ABC	February 2029
Giredestrant (GDC-9545)	acelERA (Phase II)	• Giredestrant • Endocrine monotherapy	Prior systemic and/or targeted tx	January 2024
Giredestrant (GDC-9545)	persevERA (Phase III)	• Giredestrant + Palbociclib • Letrozole + Palbociclib	Untreated ABC	March 2027

SERD: Selective ER degrader

www.clinicaltrials.gov. Accessed August 2021

ER+ Her2- Conclusions:

- Controversy remains over the true benefit of chemotherapy in premenopausal women with HR+/Her2- disease – watch for the OFSET trial!
- 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?***
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