Endocrine Therapy for Early Stage Breast Cancer:
Who needs more?

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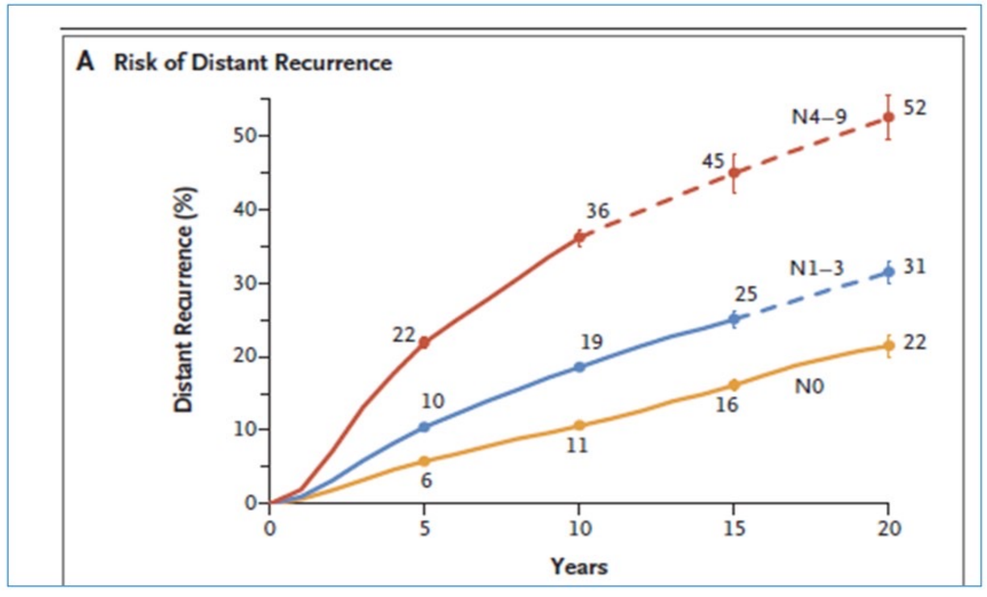
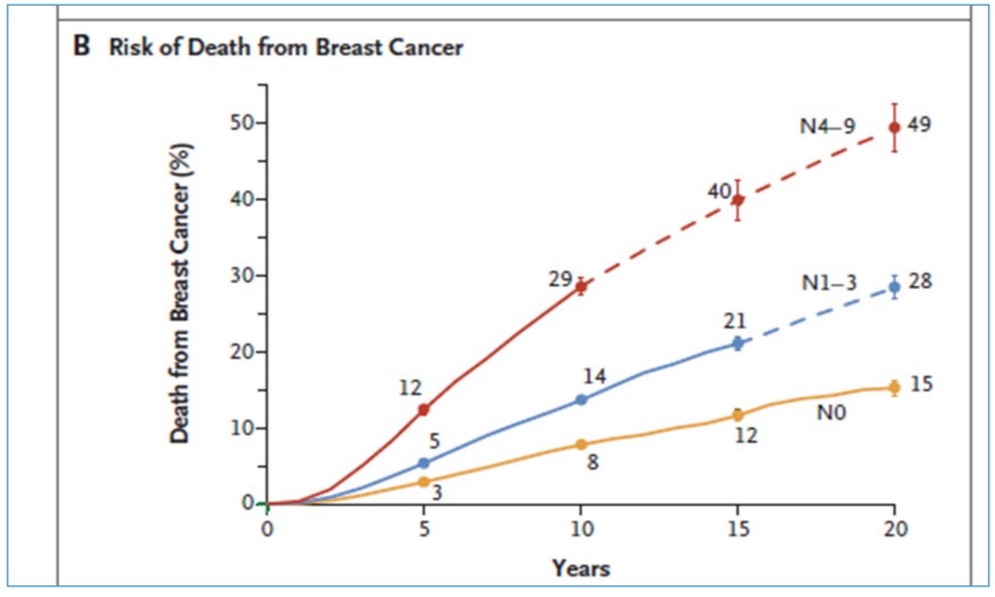
2023

Long-term recurrence risk after 5 years of ET

Meta-analysis of 88 trials: 62 923 women with HR+ EBC and disease-free after 5y ET

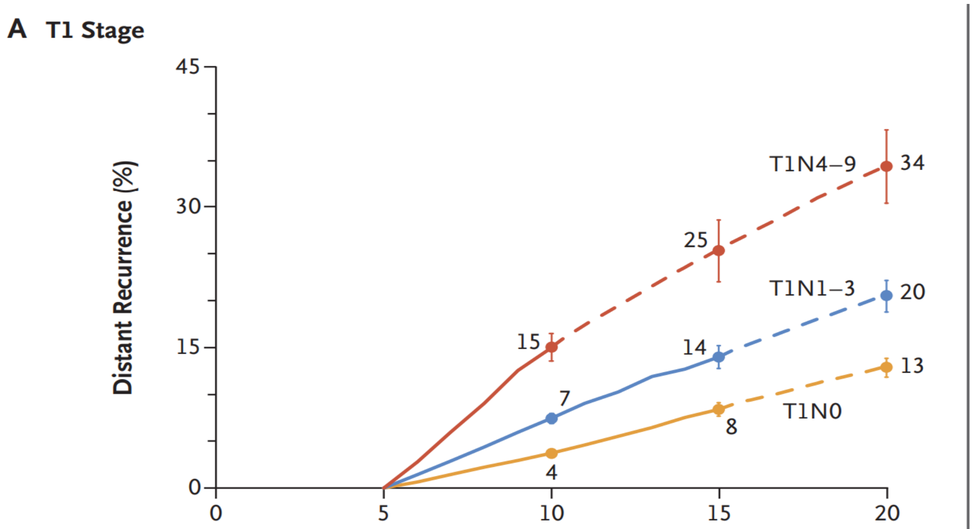




- DR increases steadily throughout 20year period
- >50% of recurrences occur after the first 5 years of treatment with ET

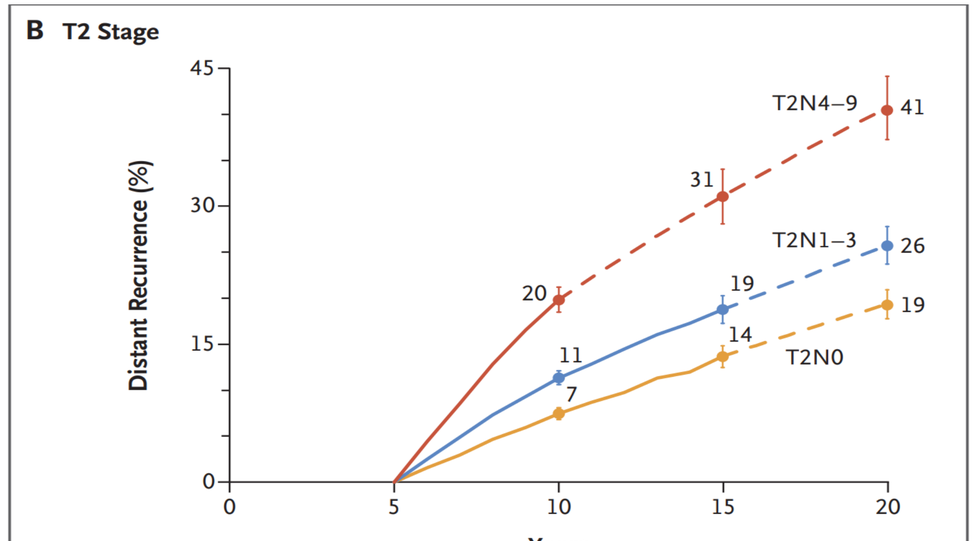
N Engl J Med 2017;377:1836-46

Long-term recurrence risk after 5 years of ET



No. at Risk				
T1N4–9	3,832	1193	214	32
T1N1–3	14,342	5138	817	154
T1N0	19,402	8020	2345	440

No. of Events — annual rate (%)			
T1N4–9	391 (3.2)	68 (2.6)	11 (2.2)
T1N1–3	734 (1.5)	162 (1.5)	35 (1.7)
T1N0	509 (0.8)	218 (1.0)	58 (1.0)



No. at Risk				
T2N4–9	4,952	1517	285	51
T2N1–3	10,950	3551	614	114
T2N0	9,445	3901	1129	218

No. of Events — annual rate (%)			
T2N4–9	688 (4.5)	106 (3.3)	12 (1.7)
T2N1–3	842 (2.4)	134 (1.8)	28 (1.9)
T2N0	512 (1.6)	152 (1.4)	37 (1.3)

- Tumor diameter and Nodal Status were strong determinants of recurrence
- Ki67 and Tumor garde were predictors of recurrence during the first 5 years

N Engl J Med 2017;377:1836-46

TAM-TAM or TAM-AI

Type of treatment and duration	Trial	Population	Follow-up (mos)	iDFS [95%CI]	OS [95%CI]	Subgroup analysis
1 2 3 4 5 6 7 8 9 10						
TAM 5 y	**ATTOM**[1]	6953 pre-post-menopausal Stage I-III*	108	≥10-year RR 0.75 [0.66-0.86]	≥10-year RR 0.86 [0.75-0.97]	***Similar proportional risk reduction across subgroups***
TAM 5 y → TAM 5 y	**ATLAS**[2]	6846 pre-post-menopausal Stage I-III	≈120	≥10-year RR 0·75 [0·62–0·90] **Absolute reduction 3.7%**	BCSS 0·71 [0·58–0·88] **Absolute reduction 2.8%**	
TAM 5 y	**MA-17**[3]	5187 postmenopausal Stage I-III	80	0.58 [0.45 to 0.76] **Absolute reduction 4.6%**	0.82 [0.57 to 1.19] **No difference**	***OS improvement in patients:*** • ***N+ BC*** • ***>5y tamoxifen***
TAM 5 y → AI 5 y						

Benefit of extending ET with improvement in OS and IDFS across all ages (pre/postmenopausal)

1. ATTOM Journal of Clinical Oncology 2013 31:18_suppl, 5-5; 2. ATLAS Lancet 2013; 381: 805–16; 3. MA17 Breast Cancer Res Treat (2007) 105:45–53

TAM-TAM or TAM-AI

Table 2
Outcomes for patients treated in MA.17 trial and ATLAS trial (statistically significant results are printed **bold**).

End point	MA.17 [18,20,30,31]		ATLAS [17]	
	DFS HR	OS HR	DFS HR	OS HR
ITT analysis				
Follow-up 5–9 years	**0.58** (7.5 yrs)	0.76 (7.5yrs)	0.90	0.97
Follow-up ≥10 years	**0.68**	0.98	**0.75**	**0.71**
Follow-up ≥10 years (IPCW)	**0.52**[a]	**0.61**	NA	NA
Analysis by Nodal Status				
Negative	**0.45**	1.52	0.85	NA
Positive	**0.61**	**0.61**	**0.83**	
Previous duration of TAM				
<5 year	**0.58**	1.19	0.90	NA
≥5 years	**0.59**	**0.56**	**0.82**	
Analysis by menopausal status at breast cancer diagnosis				
Premenopausal	**0.25**	0.36	0.81	NA
Postmenopausal	**0.69**	0.85	**0.85**	

ITT: intention to treat; IPCW: inverse probability of censoring weighted; HR: hazard ratio (statistically significant results are printed bold); NA: not available.

[a] Analysis by IPCW, adjusting for treatment crossover.

- Benefit of extended therapy with Tam was noted after 9y of therapy vs impact of AI years5-9
- Pre-menopausal patients gain higher benefit when switch to AI
- Node positive had higher benefit

The Breast 22 (2013) S171eS175

TAM/AI - AI

Type of treatment and duration	Trial	Population	Follow-up (mos)	iDFS [95%CI]	OS [95%CI]	Subgroup analysis
1 2 3 4 5 6 7 8 9 10						
AI / TAM → AI / TAM → AI 5 y	**NSABP B-42**[1]	3923 postmenopausal Stage I-IIIA	120	0.84 [0.74-0.96] 16% RR **Absolute reduction 3.8%** (Contralateral BC: 1.5% absolute reduction)	0.97 [0.82-1.16] **No differnce**	**Homogenous DFS benefit across all subgroups**
AI 5 y → AI 5 y / AI 5 y	**MA-17R**[2] 20% AI alone	1918 postmenopausal Stage I-III	75.6	0.66 [0.48-0.91] 34%RR **Absolute reduction 4%** (Contralateral BC:1.8% absolute reduction)	0.97 [0.73-1.28] **No difference**	

Longer breast cancer free interval (time to recurrence or contralateral breast cancer) independent of nodal status, prior exposure to chemotherapy and duration of prior therapy with Tamoxifen

1. NSABP B42 Lancet Oncol 20:88-99, 2019; 2. MA 17R N Engl J Med 2016; 375:209-219

Optimal duration of AI

Type of treatment and duration	Trial	Population	Follow-up (mos)	iDFS [95%CI]	OS [95%CI]	Subgroup analysis
1 2 3 4 5 6 7 8 9 10						
AI / TAM → AI 2-2.5y	**IDEAL**[1]	1824 Postmenopausal Stage I-III	79.2	0.92 [0.74-1.16] **No difference** Contralateral BC 0.39 [0.19-0.81]	1.04 [0.78-1.38] **No difference**	**No prespecified subgroup benefited from 10y**
AI / TAM → AI 5 y	**ABCSG 16**[2]	3484 Postmenopausal Stage I-III	118.0	0.99 [0.85-1.15]§ **No difference**	1.02 [0.83-1.25]§ **No difference**	
TAM 2.5 y → AI 2.5 y	**DATA**[3]	1860 Postmenopausal Stage I-III	120	0·79 [0·62–1·02]* **No difference** Contralateral BC 0.50 [0.23-1.07]	0.91 [0.65-1.29]* **No difference**	**Absolute Benefit in DFS seen in high risk population (N+, T>2)**
TAM 2.5 y → AI 5 y	**GIM-4**[4]	2056 Postmenopausal Stage I-III	140.4	0·78 [0·65–0·93] **Absolute reduction:5%**	0.77 [0.60-0.98] **Absolute reduction: 4%**	

Optimal duration of Extended ET with AI in postmenopausal women is on average 3y

1. IDEAL J Natl Cancer Inst. 2018 Jan 1;110(1).; 2. ABCSG 16/SALSA N Engl J Med 2021; 385:395-405; 3. DATA Lancet Oncol. 2017 Nov;18(11):e642;; 4. GIM 4 Journal of Clinical Oncology 2019 37:15_suppl, 504-504

How to approach Extended ET

<table>
<tr><td rowspan="2">TAM 5 Y</td><td>any N
• Premenopausal patients who have become postmenopausal after TAM 5y</td><td>AIs 5 Y</td></tr>
<tr><td>any N
• Patients who remained premenopausal after TAM 5y
• Postmenopausal patients who do not tolerate AIs</td><td>TAM 5 Y</td></tr>
<tr><td colspan="2">TAM 2-3 Y → AIs 2-3 Y</td><td rowspan="2">N0-N1
• Postmenopausal patients
• Premenopausal patients who have become postmenopausal after TAM</td><td>AIs 2-3 Y</td></tr>
<tr><td colspan="2">AI 5 Y</td><td>N2-N3
• Postmenopausal patients
• Premenopausal patients who have become postmenopausal after TAM</td><td>AIs 5 Y</td></tr>
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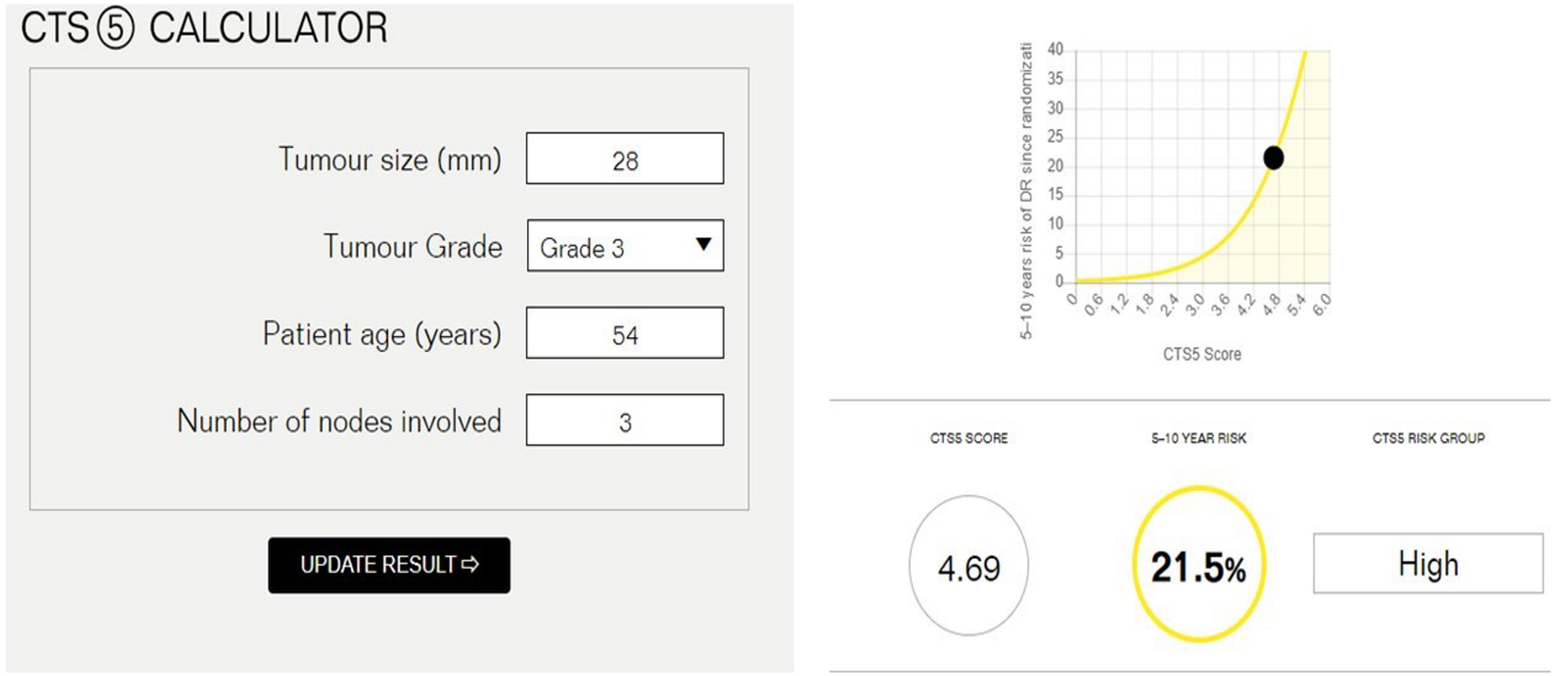
Predictive vs Prognostic Tools

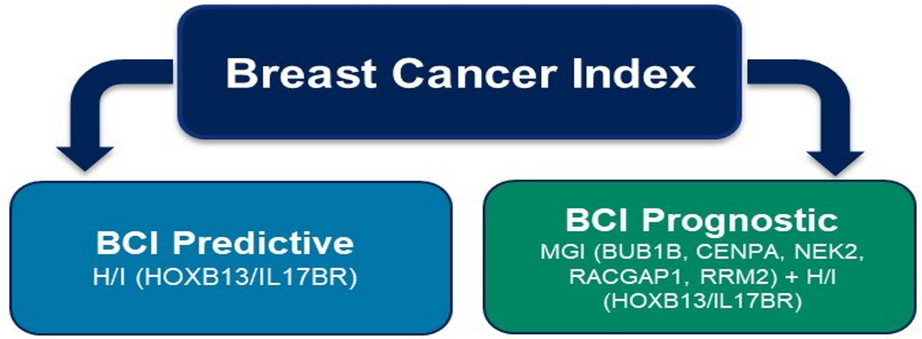
Can we optimize the selection of patients that will benefit from ET with prognostic or predictive Tools?



- The clinical Treatment Score post 5 years (CTS5) is an algorithm incorporating four clinicopathologic variables (nodes, age, tumor size and grade) which has been shown to be prognostic for late DR
- Initial validation using the combined patient cohorts of the ATAC and BIG-1-98 trial
- Validation of CTS5 in patient of the TEAM and the IDEAL trial.-
    - -Overestimates the risk of later DR in High Risk patients
    - -Did not predict the benefit of Extended ET

Dowsett M, *J Clin Oncol.* 2018;36(19):1941–1948; Noordhoek, I J Clin Oncol. 2020;38(28),3273-3281

- The Breast Cancer Index (BCI) is a gene expression-based signature comprising two functional biomarker panels, the Molecular Grade index (MGI) and the two-gene ratio, *HOXB13/IL17BR* (H/I)[4-7]:
  - **Predictive**: H/I ratio, has been shown to predict endocrine response across several different treatment scenarios
  - **Prognostic**: Integration of MGI and H/I quantifies both the risk of late (5–10 years) and overall (0–10 years) distant recurrence



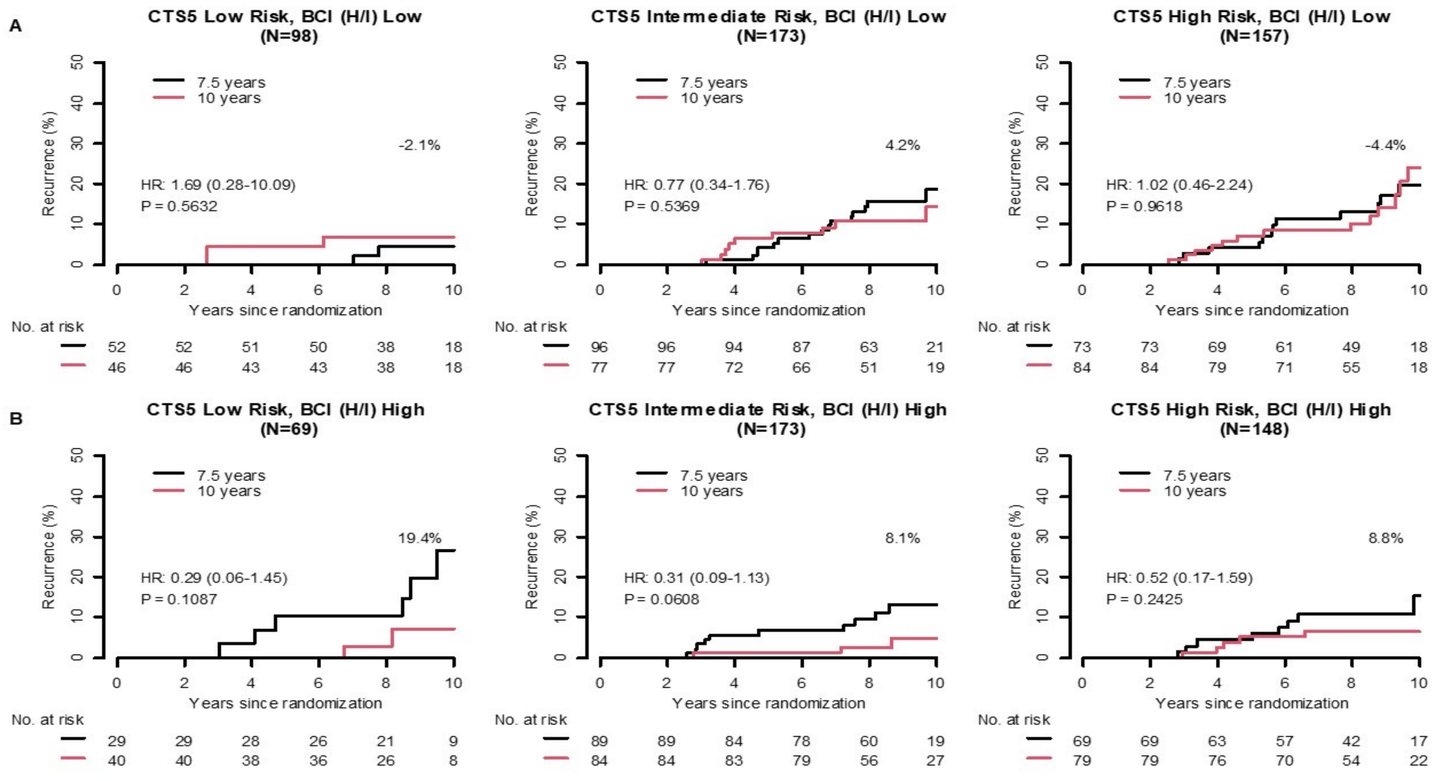
STUDY	N	BCI (H/I) AND OUTCOME
MA-17	249 Postmenopausal or premenopausal who became postmenopausal	High H/I ratio benefit from letrozole (DR OR = 0.33; 95% CI, 0.15 to 0.73; p=0.006); **abs risk reduction 16.5%**
Trans-aTTom	583 Postmenopausal and premenopausal	High H/I ratio benefit from tamoxifen (RFI HR = 0.35; 95%CI, 0.15-0.86; p=0.02 **abs risk reduction 10.2%**
IDEAL	908 73% N+	High H/I ratio benefit from letrozole (RFI HR 0.42; 95% CI 0.21-0.84; p = 0.011) **abs risk reduction 10.8%**
NSABP-B42	2179 40% N+	High H/I ratio benefit from letrozole (DR HR 0.29; 95% CI 0.12-0.69; p = 0.003) **abs risk reduction 3.8%**

Barlett JMS, Ann Oncol. 2019;30:1776-83; Mamounas EP, J Clin Oncol. 2021; 39(15-suppl):501; BCI Clin Cancer Res (2021) 27 (1): 311–319

Predictive performance of breast cancer index (BCI) and clinical treatment score post-5 years (CTS5) in the IDEAL study

Results

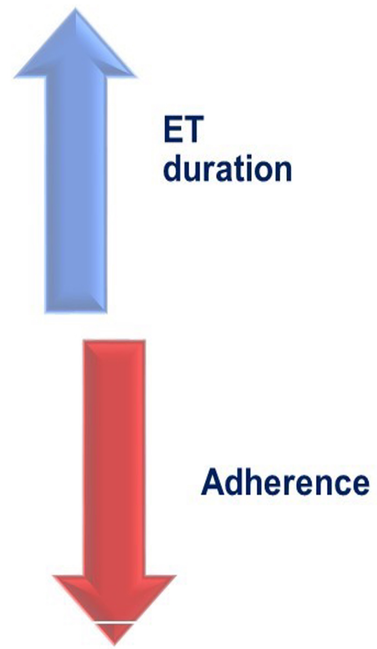
- When re-stratifying CTS5 risk categories by BCI (H/I) or vice versa, only BCI (H/I)-High patients showed consistent absolute benefit regardless of CTS5 risk category (B).
- Conversely, CTS5-High patients did not show any benefit in the BCI (H/I)-Low group (A).



ASCO 2022 (28-04-2022) https://meetings.asco.org/abstracts-presentations/211140

Longer duration implies a higher risk of non-adherence

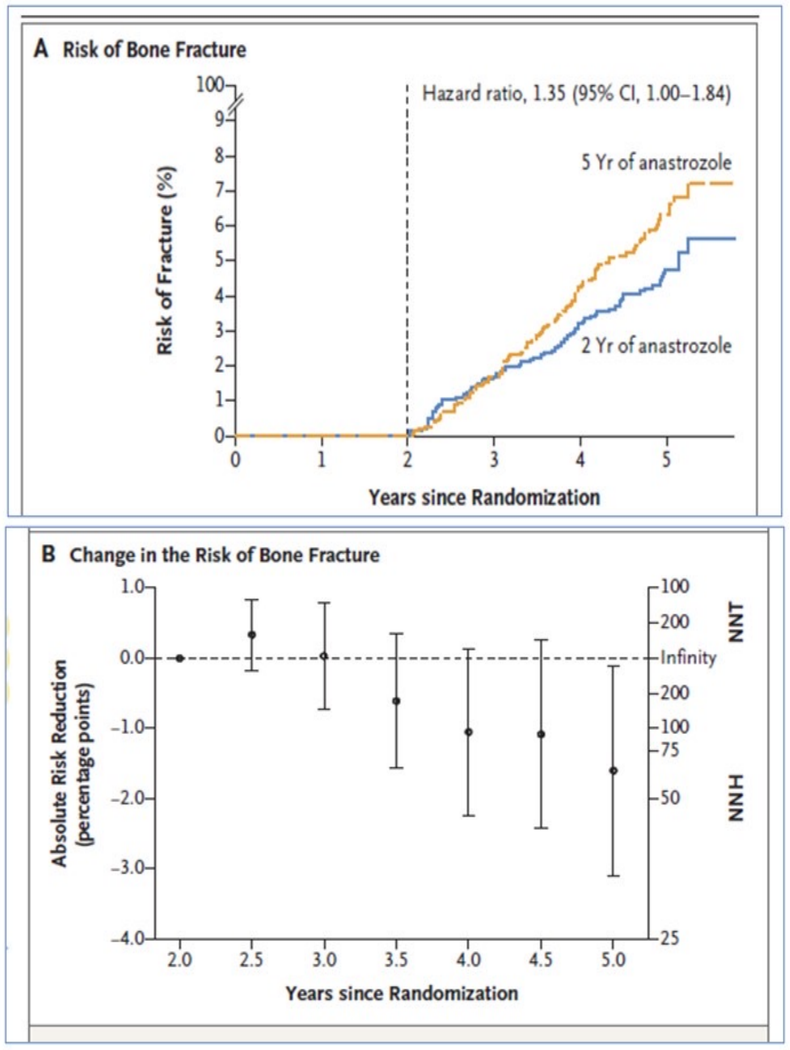
Total ET duration	Trial	Adjuvant ET prior to randomization	Treatment	Adherence
10 years vs 5	ATLAS	5 years of TAM	5 years of TAM vs observation	≈80%
	MA-17	5 years of TAM	5 years of LET vs placebo	≈80%
	NSAPB B-42	5 years of ET (AI or TAM + AI)	5 years of LET vs placebo	62%
	MA-17R	4.5- 6 years of AI and prior TAM any duration	5 years of LET vs placebo	62%
7-8 years vs 5	DATA	2-3 years of TAM	6 vs 3 years of ANA	67% vs 78%
	GIM-4	2-3 years of TAM	5 vs 2-3 years of LET	63% vs 80%
10 years vs 7.5	IDEAL	5 years of any ET	5 vs 2.5 years of LET	60% vs 78%
	ABCSG 16	4-6 years of ET (AI, TAM or TAM + AI)	5 vs 2 years of anastrazole	67% vs 80%



- ***Higher rate of discontinuation with longer treatment duration***
- ***Treatment-related AEs were the main reason for treatment discontinuation***
- ***Adherence can be overestimated***
  - ***based on patients self-reports***
  - ***selection of patients that were adherent over the first 5 y***

Cumulative risk of some toxicities increases with longer treatment

BONE FRACTURES



Gnant et al, N Engl J Med 2021; Del Mastro et al, ESMO 2021

Bone fractures risk increased overtime

NNH decreased overtime

OTHER BONE-RELATED SYMPTOMS

	Control arm 2-3-year letrozole (n=983)		Extended arm 5-year letrozole (n=977)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Arthralgia	263 (27%)	22 (2%)	311 (32%)	29 (3%)
Myalgia	65 (7%)	7 (1%)	95 (10%)	9 (1%)
Hot flashes	119 (12%)		127 (13%)	
Alopecia	31 (3%)		35 (4%)	
Osteoporosis	47 (5%)		81 (8%)	
Hypertension	7 (1%)		19 (2%)	
Bone fractures[a]	5 (<1%)		9 (1%)	
Hypercholesterolemia[b]	32 (3%)		22 (2%)	
Cardiovascular event[c]	1 (<1%)		6 (1%)	

Higher risk of arthralgia, myalgia and osteoporosis with longer ET

NNH= number needed to harm

MonarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial

Women or men with high-risk, node-positive, HR+/HER2- EBC; prior (neo)adjuvant CT permitted; pre- or postmenopausal; no distant metastasis; ≤16 mo from surgery to randomization; ≤12 wk of ET after last non-ET (N = 5637)

ITT Population (Cohorts 1 + 2)

Cohort 1
≥4 positive ALN *or* 1-3 positive ALN plus histologic grade 3 and/or tumor ≥5 cm

Cohort 2
1-3 positive ALN, Ki-67 ≥20% per central testing, not grade 3, tumor size <5 cm

Stratified by prior CT, menopausal status, region

Abemaciclib 150 mg BID up to 2 yr + **ET** per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2808)

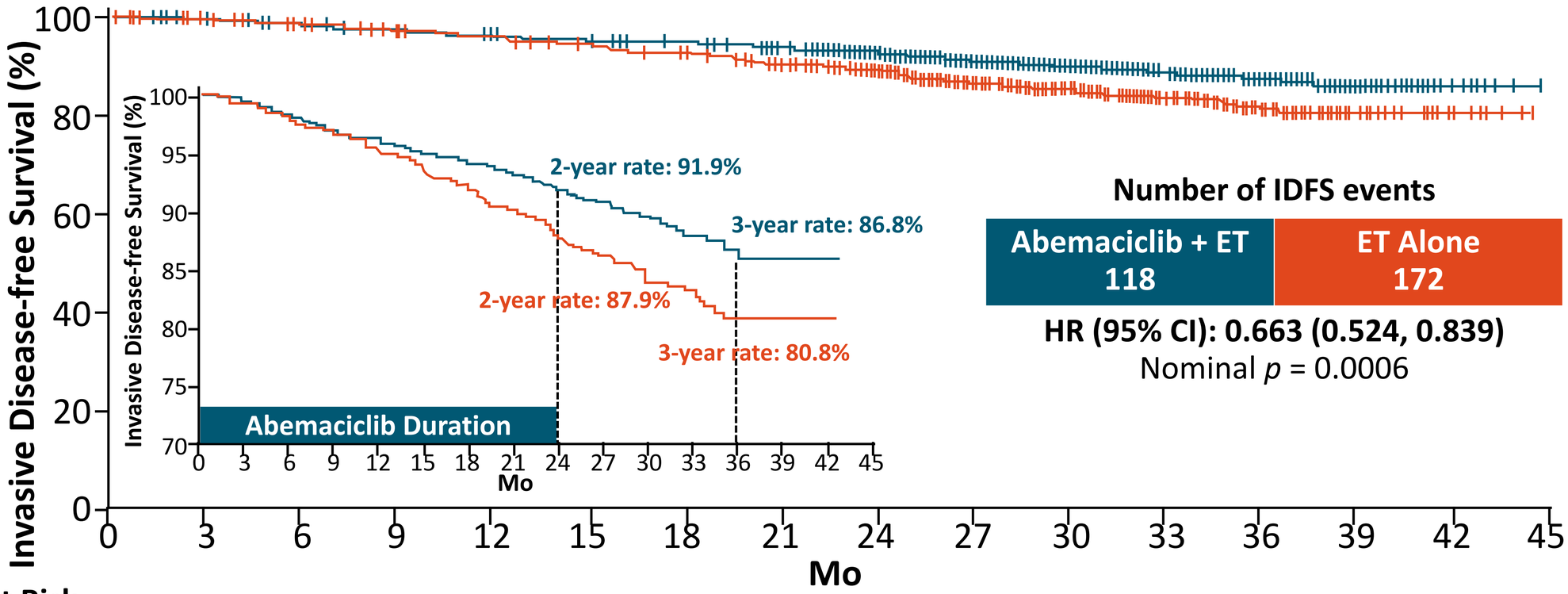
ET per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2829)

- Primary endpoint: iDFS
  - Planned for after ~390 iDFS events (~85% power, assumed iDFS hazard ratio of 0.73, cumulative 2-sided $\alpha = 0.05$)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki-67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. SABCS 2020. Abstr GS1-01.

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

- 44.3% of all randomized patients had tumors with high Ki-67 index



No. at Risk																
Abemaciclib+ET	1262	1221	1189	1167	1155	1139	1123	1094	870	546	377	203	109	25	2	0
ET alone	1236	1197	1177	1158	1142	1114	1096	1041	827	520	367	198	107	25	3	0

- 33.7% reduction in risk of iDFS event
- Absolute difference in iDFS at 3 years: 6.0%

O'Shaughnessy. ESMO 2021. Abstract VP8-2021. Harbeck. Ann Oncol. 2021;32:1571.

Subgroup analysis of patients with no prior chemotherapy in EMERALD: A phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC)

Kaklamani V,[1] Bardia A,[2] Aftimos P,[3] Cortes J,[4] Lu J,[5] Neven P,[6] Streich G,[7] Montero AJ,[8] Forget F,[9] Mouret-Reynier MA,[10] Sohn JH,[11] Taylor D,[12] Harnden KK,[13] Khong H,[14] Kocsis J,[15] Dalenc F,[16] Dillon P,[17] Tonini G,[18] Grzegorzewski KJ,[19] Bidard FC[20]

[1]University of Texas Health Sciences Center, Houston, TX; [2]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [3]Institut Jules Bordet – Université Libre de Bruxelles, Brussels, Belgium; [4]International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain; [5]University Of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [6]Universitaire Ziekenhuizen (UZ) – Leuven Cancer Institute, Leuven, Belgium; [7]Centro Médico Austral, Buenos Aires, Argentina; [8]University Hospitals Seidman Cancer Center – Case Western Reserve University, Cleveland, OH, USA; [9]Centre Hospitalier de l'Ardenne – Site de Libramont, Libramont-Chevigny, Belgium; [10]Centre Jean Perrin, Clermont-Ferrand, France; [11]Yonsei Cancer Center, Yonsei University Health System – Medical Oncology, Seoul, Republic of Korea; [12]Université catholique de Louvain, CHU UCL Namur – Site Sainte-Elisabeth, Namur, Belgium; [13]Inova Schar Cancer Institute, Fairfax, Virginia; [14]Moffit Cancer Center & Research Institute, Tampa, FL, USA; [15]Bács-Kiskun Megyei Kórház, Kecskemét, Hungary; [16]Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; [17]University of Virginia Cancer Center, Charlottesville, VA, USA; [18]Menarini Group, Florence, Italy; [19]Stemline Therapeutics/Menarini Group, New York, NY, USA; [20]Institut Curie, Paris and Saint Cloud, France

Presented at ASCO® 2022
Abstract: 1100

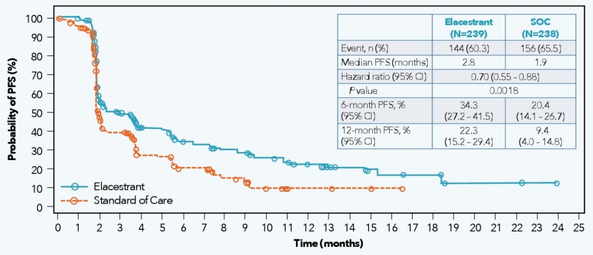
Poster Selected for the 2022 GRASP Advocate Choice Award

EMERALD

BACKGROUND

- Endocrine therapy, with aromatase inhibitor (AI) or fulvestrant, plus cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is the recommended first-line treatment of estrogen receptor-positive (ER+)/HER2- mBC.[1-3]
- Subsequent disease progression is associated with endocrine resistance, including the development of *ESR1* mutations (*mESR1*).[4]
- Treatment guidelines recommend use of sequential endocrine therapy before chemotherapy, in the absence of visceral crisis or until all endocrine therapy (ET) options have been exhausted.[1-3,5]
- Standard single-agent endocrine therapy (eg, fulvestrant) in patients who have received prior CDK4/6i or mTOR inhibitor is associated with poor median progression-free survival (~2 months),[6-9] highlighting a major unmet need for patients with ER+/HER2- mBC.
- Elacestrant (RAD1901) is an oral SERD that blocks ER and inhibits estradiol-dependent gene transcription induction and cell proliferation in ER+ BC cell lines with higher efficacy than fulvestrant.[10]
- In a phase 3 study of elacestrant in postmenopausal women with ER+/HER2- mBC (EMERALD), elacestrant significantly reduced the risk of disease progression or death by 30% in all patients and by 45% in patients with *ESR1* mutation (Figure 1a & b).[11]
- In this analysis, we compared PFS between elacestrant and SOC in patients without prior chemotherapy in the metastatic setting.

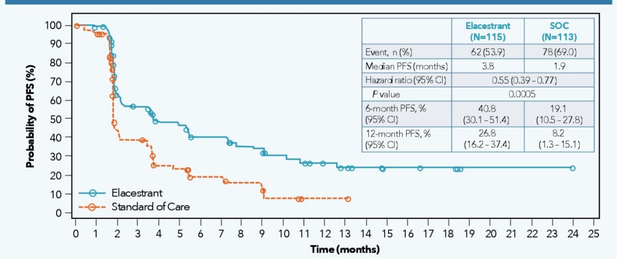
Figure 1a: PFS in all patients (ITT) (N=477)



	Elacestrant (N=239)	SOC (N=238)
Event, n (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.8	1.9
Hazard ratio (95% CI)	0.70 (0.55 – 0.88)	
P value	0.0018	
6-month PFS, % (95% CI)	34.3 (27.2 – 41.5)	20.4 (14.1 – 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 – 29.4)	9.4 (4.0 – 14.8)

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

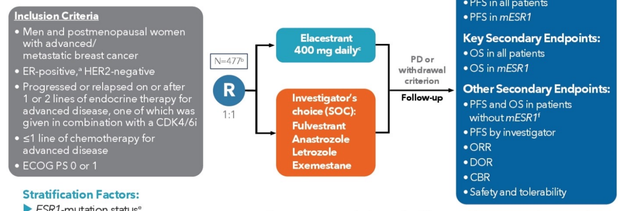
Figure 1b: PFS in all patients with detectable m*ESR1* (N=228)



	Elacestrant (N=115)	SOC (N=113)
Event, n (%)	62 (53.9)	75 (69.0)
Median PFS (months)	3.8	1.9
Hazard ratio (95% CI)	0.55 (0.39 – 0.77)	
P value	0.0005	
6-month PFS, % (95% CI)	40.8 (30.1 – 51.4)	19.1 (10.5 – 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 – 37.4)	8.2 (1.3 – 15.1)

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

EMERALD STUDY DESIGN[12]



SOC guidance recommended use of a different ET than previously received (ie, fulvestrant recommended for patients who had not previously received fulvestrant, and selection of AI was based on prior AI therapy)

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry (local laboratory). [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 cell-free circulating DNA analysis using the Guardant360® CDx (Guardant Health, Redwood City, CA). [f]Restaging CT scans every 8 weeks.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; *mESR1*, *ESR1*-mutant breast cancer population; PFS, progression-free survival; R, randomized; SOC, standard of care.

RESULTS

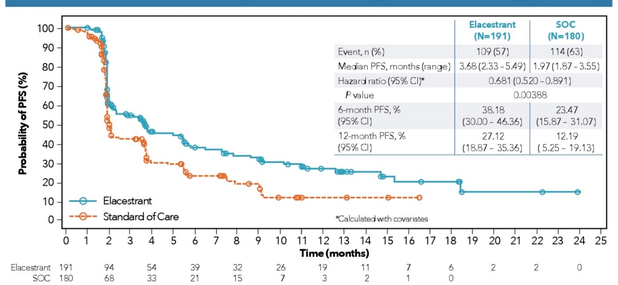
Baseline demographic and disease characteristics

Among the 477 patients enrolled in the trial, 77.8% (n=371) had not received prior chemo for mBC

Parameter	Elacestrant All (N=191)	Elacestrant *mESR1* (N=89)	SOC All (N=180)	SOC *mESR1* (N=81)
Median age, years (range)	64 (28-89)	64 (28-89)	64 (35-83)	63 (35-83)
Gender, n %				
Female	185 (96.9)	89 (100)	180 (100)	81 (100)
Male	6 (3.1)	0	0	0
ECOG PS, n (%)				
0	111 (58.1)	48 (53.9)	100 (55.6)	44 (54.3)
1	80 (41.9)	41 (46.1)	180 (44.4)	37 (45.7)
Visceral metastasis*, n (%)	127 (66.5)	62 (69.7)	125 (69.4)	61 (75.3)
Bone-only disease, n (%)	32 (16.8)	10 (11.2)	25 (13.9)	10 (12.3)
Prior adjuvant therapy, n (%)	129 (67.5)	50 (56.2)	114 (63.3)	51 (63.0)
Prior CDK4/6 inhibitor, n (%)	191 (100)	89 (100)	180 (100)	81 (100)
Number of prior lines of endocrine therapy,** n (%)				
1	103 (53.9)	56 (62.9)	115 (63.9)	56 (69.1)
2	88 (46.1)	33 (37.1)	65 (36.1)	25 (30.9)
Number of prior lines of chemotherapy,** n (%)				
0	191 (100)	89 (100)	180 (100)	81 (100)

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

PFS: elacestrant vs SOC in all patients without prior chemotherapy (N=371)

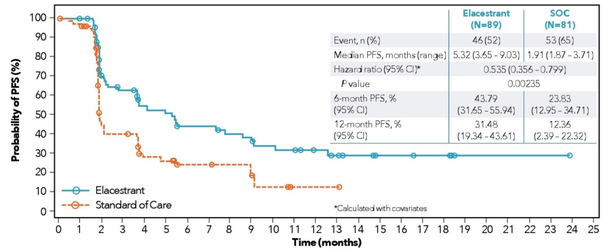


	Elacestrant (N=191)	SOC (N=180)
Event, n (%)	109 (57)	114 (63)
Median PFS, months (range)	3.68 (2.33 – 5.49)	1.97 (1.87 – 3.55)
Hazard ratio (95% CI)*	0.681 (0.520 – 0.891)	
P value	0.00388	
6-month PFS, % (95% CI)	38.18 (30.00 – 46.36)	23.47 (15.87 – 31.07)
12-month PFS, % (95% CI)	27.12 (18.87 – 35.36)	12.19 (5.25 – 19.13)

Elacestrant	191	94	54	39	32	26	19	11	7	6	2	2	0											
SOC	180	68	33	21	15	7	3	2	1	0														

Among patients with ER+/HER2– mBC without prior chemotherapy, elacestrant significantly prolonged PFS compared to SOC

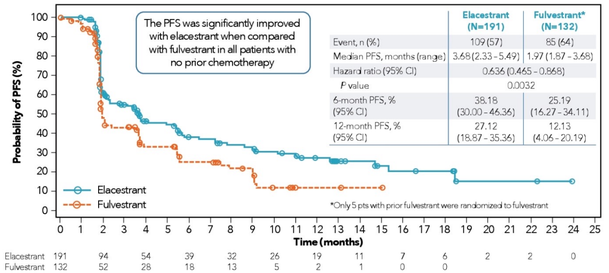
PFS: elacestrant vs SOC in patients with *mESR1* without prior chemotherapy (N=170)



	Elacestrant (N=89)	SOC (N=81)
Event, n (%)	46 (52)	53 (65)
Median PFS, months (range)	5.32 (3.65 – 9.03)	1.91 (1.87 – 3.71)
Hazard ratio (95% CI)*	0.535 (0.356 – 0.799)	
P value	0.00235	
6-month PFS, % (95% CI)	43.79 (31.65 – 55.94)	23.83 (12.95 – 34.71)
12-month PFS, % (95% CI)	31.48 (19.34 – 43.61)	12.36 (2.39 – 22.32)

Elacestrant	89	48	31	24	20	15	11	7	5	4	1	1	0											
SOC	81	29	15	10	9	4	1	0																

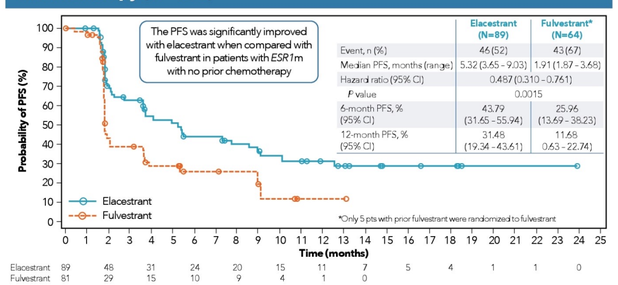
PFS: elacestrant vs fulvestrant in all patients without prior chemotherapy (N=323)



	Elacestrant (N=191)	Fulvestrant* (N=132)
Event, n (%)	109 (57)	85 (64)
Median PFS, months (range)	3.68 (2.33 – 5.49)	1.97 (1.87 – 3.68)
Hazard ratio (95% CI)	0.636 (0.465 – 0.868)	
P value	0.0032	
6-month PFS, % (95% CI)	38.18 (30.00 – 46.36)	25.19 (16.27 – 34.11)
12-month PFS, % (95% CI)	27.12 (18.87 – 35.36)	12.13 (4.06 – 20.19)

Elacestrant	191	94	54	39	32	26	19	11	7	6	2	2	0											
Fulvestrant	132	52	26	18	13	5	2	1	0	0														

PFS: elacestrant vs fulvestrant in patients with *mESR1* without prior chemotherapy (N=153)



	Elacestrant (N=89)	Fulvestrant* (N=64)
Event, n (%)	46 (52)	43 (67)
Median PFS, months (range)	5.32 (3.65 – 9.03)	1.91 (1.87 – 3.68)
Hazard ratio (95% CI)	0.487 (0.310 – 0.761)	
P value	0.0015	
6-month PFS, % (95% CI)	43.79 (31.65 – 55.94)	25.96 (13.69 – 38.23)
12-month PFS, % (95% CI)	31.48 (19.34 – 43.61)	11.68 (0.63 – 22.74)

Elacestrant	89	48	31	24	20	15	11	7	5	4	1	1	0											
Fulvestrant	81	29	15	10	9	4	1	0																

Treatment-emergent adverse events (≥10% in either arm)

	Elacestrant N=189, n (%)		SOC Total N=175, n (%)		SOC Fulvestrant N=129, n (%)		SOC Aromatase inhibitor N=46, n (%)	
Preferred term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	64 (33.9%)	2 (1.1)	34 (19.4%)	–	21 (16.3%)	–	13 (28.3%)	–
Fatigue	36 (19.0%)	–	28 (16%)	–	21 (16.3%)	–	7 (15.2%)	–
Vomiting	33 (17.5%)	1 (0.5)	12 (6.9%)	–	9 (7.0%)	–	3 (6.5%)	–
Arthralgia	28 (14.8%)	–	30 (17.1%)	–	23 (17.8%)	–	7 (15.2%)	–
Decreased appetite	25 (13.2%)	1 (0.5)	13 (7.4%)	–	9 (7.0%)	–	4 (8.7%)	–
Back pain	25 (13.2%)	1 (0.5)	14 (8.0%)	–	10 (7.8%)	–	4 (8.7%)	–
Diarrhea	24 (12.7%)	–	19 (10.9%)	–	13 (10.1%)	–	6 (13.0%)	–
Headache	24 (12.7%)	1 (0.5)	21 (12%)	–	15 (11.6%)	–	6 (13.0%)	–
Hot flush	24 (12.7%)	–	15 (8.6%)	–	11 (8.5%)	–	4 (8.7%)	–
AST increased	23 (12.2%)	–	21 (12%)	–	16 (12.4%)	–	5 (10.9%)	–
Constipation	22 (11.6%)	–	11 (6.3%)	–	7 (5.4%)	–	4 (8.7%)	–
Dyspepsia	19 (10.1%)	–	5 (2.9%)	–	4 (3.1%)	–	1 (2.2%)	–

- Key treatment-related adverse events (AEs) in the no prior chemotherapy elacestrant group were nausea (25.9%), fatigue (12.7%), and hot flush (11.1%). There were no treatment-related deaths in either group.

CONCLUSIONS

- Among patients with ER+/HER2– mBC without prior chemotherapy, elacestrant significantly prolonged PFS compared to SOC endocrine therapy and showed favorable outcomes in this subgroup.
  - 31% reduction in the risk of progression or death with elacestrant vs SOC in all patients (HR=0.681 [95% CI: 0.520 – 0.891]; P=0.00388) and prolonged median PFS (3.68 vs 1.97 months).
  - 46% reduction in the risk of progression or death with elacestrant vs SOC in patients with *mESR1* (HR=0.535 [95% CI: 0.356 – 0.799]; P=0.00235) and prolonged median PFS (5.32 vs 1.91 months).
- In exploratory subgroup analyses, elacestrant significantly reduced the risk of progression or death and prolonged median PFS vs fulvestrant in all patients (HR=0.636 [95% CI: 0.465-0.868]; mPFS 3.68 vs 1.97 months), and in patients with *mESR1* (HR=0.487 (95% CI: 0.310-0.761; mPFS 5.32 vs 1.91 months).
- Elacestrant had a manageable safety profile consistent with other endocrine therapies.
- Final overall survival analysis of elacestrant vs SOC endocrine therapy expected late 2022/early 2023.
- Further elacestrant combinations in earlier lines and with other targeted therapies, including CDK4/6 and mTOR inhibitors, are ongoing/planned for patients with ER+/HER2- breast cancer.

REFERENCES:
1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated December 20, 2021. Accessed March 24, 2022; **2.** Gennari A, et al. *Ann Oncol*. 2021;32:1475-1495; **3.** Burstein HJ, et al. *J Clin Oncol*. 2021;39:3959-3977; **4.** Jeselsohn R, et al. *Clin Cancer Res*. 2014;20:1757-1767; **5.** Moy B, et al. *J Clin Oncol*. 2021;39:3938-3958; **6.** Linderman GJ, et al. *J Clin Oncol*. 2021;39 (suppl 15): abstr 1004; **7.** Turner NC, et al. *Lancet Oncol*. 2020;21:1296-1308; **8.** Di Leo A, et al. *Lancet Oncol*. 2018;19:87-100; **9.** André F, et al. *N Engl J Med*. 2019;380:2019-1929-1940; **10.** Bihani T, et al. *Clin Cancer Res*. 2017;23:4793-4804; **11.** Bidard FC, et al. *J Clin Oncol*. 2022: In press.

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Take Home Message

- Extended ET should be offered for patients with higher risk of recurrence
  - 7-8y of adjuvant ET for patients at intermediate risk of recurrence
  - 10y of adjuvant ET should be consider on patients that meet High Risk Criteria
- BCI is a predictive and prognostic tool that may guide decisions on Extended ET
- Treatment duration should be informed by patient comorbidities and QOL