Endocrine Therapy in the Neoadjuvant & Adjuvant Setting

ER+ HER-2 normal Node Negative and Node Positive Breast Cancer

Vicente Valero, M.D., F.A.C.P.
Professor of Medicine and Deputy Chairman
Department of Breast Medical Oncology
U. T. MD Anderson Cancer Center
Houston, Texas

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Conflict of Interest

- Novartis: Consulting/Honorarium
- Roche/Genetech: Consulting/Honorarium
- Exact Science: Honorarium
- Biotheranostics: Consulting/Honorarium

Outline

- Overview in hormonal therapy in EBC
- Overview of genomic signatures
- Overview in adjuvant CDK trials.
- SABC 2021 abstracts
- Conclusions

HR+ Early Breast Cancer (EBC) 2022

- Breast cancer is one of the most common cancer with approximately 1,500,000 cases and 500,000 deaths each year worldwide. More than 200, 000 women are diagnosed with invasive breast cancer in USA every year.

- Greater than 70% of these patients will have ER/PR+, and HER2- breast cancer.

- Standard treatment is multidisciplinary including systemic therapy

- There is a constant risk of late relapse according to clinical and pathological characteristics.

- Adjuvant endocrine therapy (ET) is standard for ER/PR+, and HER2- EBC
  - Decreases risk of recurrence and death
  - Tamoxifen and aromatase inhibitors are the standard agents uses worldwide in early ER+EBC
  - Chemotherapy potentially add clinical benefit in certain subgroups of patients
  - **Genomic signatures are now part of standard of care to determine the need for adjuvant or neoadjuvant chemotherapy and extended hormonal therapy**
  - **CDK inhibitor and PARP inhibitor adjuvant therapy are now indicated in node positive ER+ EBC and high risk BRCA+ ER EBC, respectively**

Adjuvant Hormonal Therapy Premenopausal Early Breast Cancer 2022

- Low risk: Tamoxifen 5 years
- High risk: Ovarian ablation or suppression plus aromatase inhibitor x 5 years
- High risk: If poor tolerance to aromatase inhibitor, tamoxifen x 10 years
- Extended endocrine therapy is potential option according to residual risk of relapse.
- Be aware of recovery of chemotherapy-induced ovarian function failure

Adjuvant Hormonal Therapy Premenopausal Early Breast Cancer 2022

- Is tamoxifen for 5 years an acceptable option?
- Is extended endocrine therapy an option for premenopausal women with breast cancer?
- Is chemotherapy plus hormonal therapy an option for all premenopausal ER EBC?
- Are genomic signature (s) are indicated in premenopausal ER+ EBC?

Adjuvant Hormonal Therapy Postmenopausal Early Breast Cancer 2021

- Low risk, an aromatase inhibitor x 5 years
- Low risk, an aromatase inhibitor/tamoxifen x 2-3 years follow by tamoxifen/aromatase inhibitor 2-3 years
- If poor tolerance to aromatase inhibitor, tamoxifen x 5 (low risk) to 10 years (high risk)
- High risk, an aromatase Inhibitors x 10 years

Adjuvant Hormonal Therapy Postmenopausal Early Breast Cancer 2022

- Is extended endocrine therapy an option for all or selected patients postmenopausal women with breast cancer?

- Is chemotherapy plus hormonal therapy an option for for a subgroup of patients with postmenopausal ER EBC?

- Are genomic signature (s) are indicated in all postmenopausal ER+ EBC?

TEXT and SOFT Designs

TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)

Enrolled: Nov'03-Apr'11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (N=1053)
  OR planned chemo (N=1607)

RANDOMIZE

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Median follow-up 13 years

SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (N=1419)

OR

- Remain premenopausal ≤8 mos after chemo (N=1628)

RANDOMIZE

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Median follow-up 12 years

OFS=ovarian function suppression, by GnRH analogue triptorelin or oophorectomy

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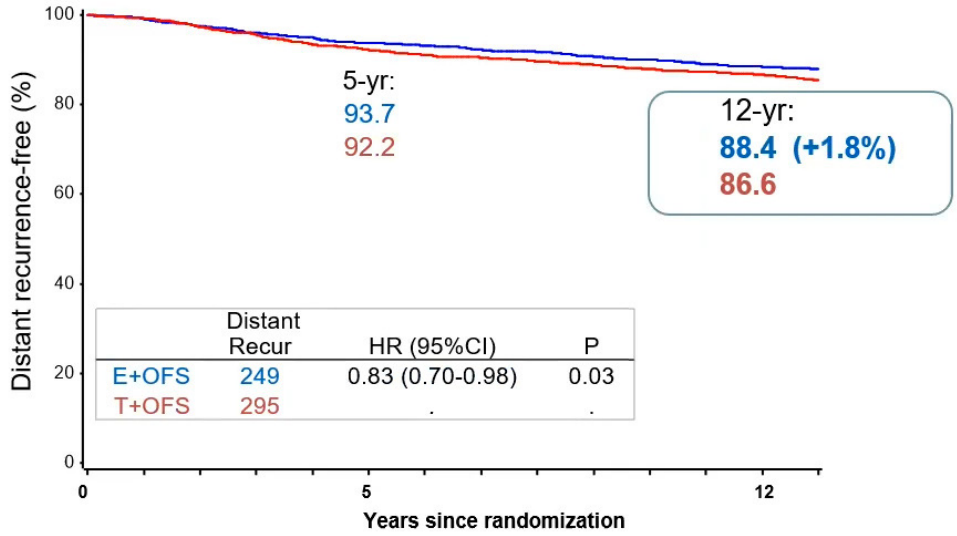
AI Question: SOFT+TEXT Overall Populations

42% LN+; 13 years median follow-up

Distant Recurrence-free Interval



	Distant Recur	HR (95%CI)	P
E+OFS	249	0.83 (0.70-0.98)	0.03
T+OFS	295	.	.

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

Overall Survival

	Death	HR (95%CI)	P
E+OFS	228	0.93 (0.78-1.11)	0.43
T+OFS	245	.	.

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

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

pyfu=person-years follow-up

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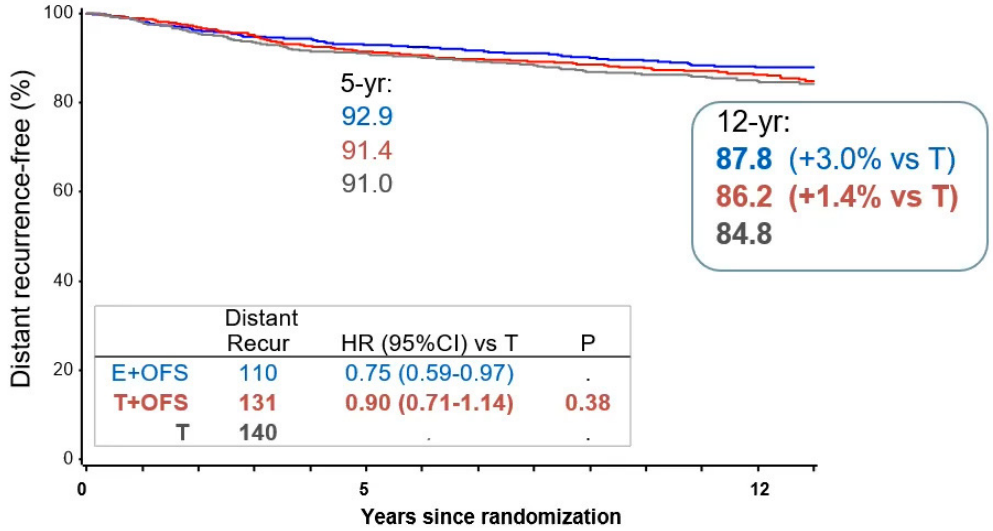
OFS Question: SOFT Overall Population

35% LN+; 12 years median follow-up

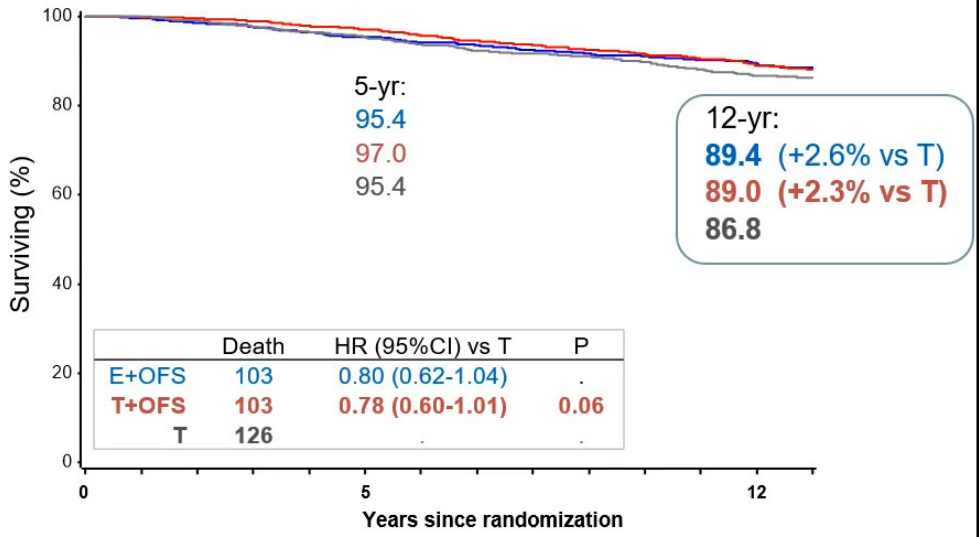
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI) vs T	P
E+OFS	110	0.75 (0.59-0.97)	.
T+OFS	131	0.90 (0.71-1.14)	0.38
T	140	.	.

	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	68	0.76 (0.55-1.04)	42	0.74 (0.50-1.12)
T+OFS:	83	0.93 (0.69-1.25)	48	0.85 (0.58-1.26)
T:	87	.	53	.
At risk:	**3047** pts	13787 pyfu	2521 pts	16343 pyfu

Overall Survival



	Death	HR (95%CI) vs T	P
E+OFS	103	0.80 (0.62-1.04)	.
T+OFS	103	0.78 (0.60-1.01)	0.06
T	126	.	.

	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	45	1.00 (0.66-1.51)	58	0.70 (0.50-0.98)
T+OFS:	29	0.63 (0.40-1.01)	74	0.86 (0.63-1.18)
T:	45	.	81	.
At risk:	**3047** pts	14524 pyfu	2745 pts	18383 pyfu

T+OFS vs T: absolute reductions in distant recurrence and death 1.4% and 2.3% at 12 years

E+OFS vs T: absolute reductions in distant recurrence and death 3.0% and 2.6% at 12 years

pyfu=person-years follow-up

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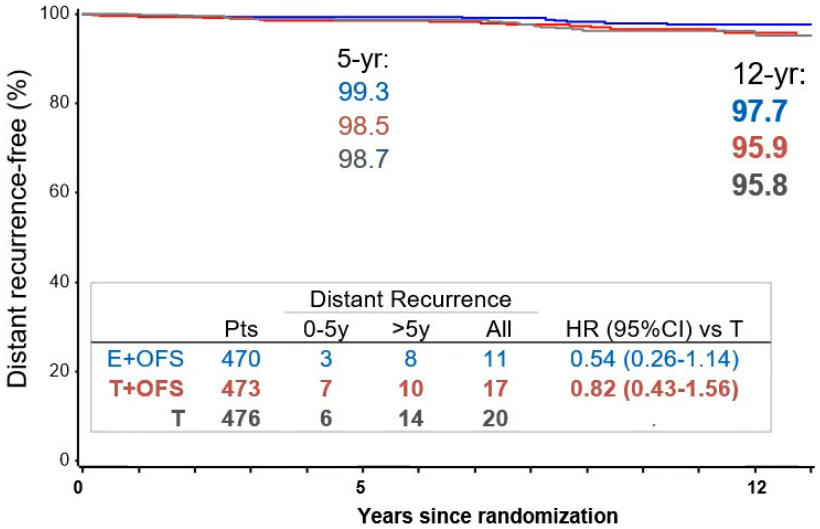
SOFT No Chemotherapy Cohort

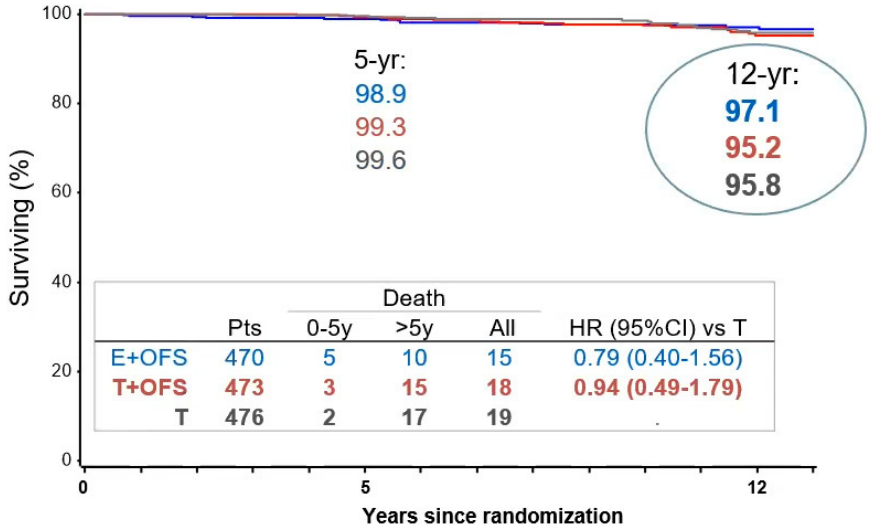
9% LN+; 12 years median follow-up

Distant Recurrence-free Interval



	Distant Recurrence				
	Pts	0-5y	>5y	All	HR (95%CI) vs T
E+OFS	470	3	8	11	0.54 (0.26-1.14)
T+OFS	473	7	10	17	0.82 (0.43-1.56)
T	476	6	14	20	.

Overall Survival



	Death				
	Pts	0-5y	>5y	All	HR (95%CI) vs T
E+OFS	470	5	10	15	0.79 (0.40-1.56)
T+OFS	473	3	15	18	0.94 (0.49-1.79)
T	476	2	17	19	.

Numbers of deaths, relative to a BC event or 2nd (non-breast) cancer

SOFT	All Deaths	After BC Event	2nd Cancer	No Cancer	Unkn. Cancer
E+OFS	15	7	4	2	2
T+OFS	18	10	4	1	3
T	19	12	2	4	1

Unkn (unknown)=death with no information about breast or 2nd (non-breast) cancer events

>95% of women surviving at 12 years
56% deaths after a BC event

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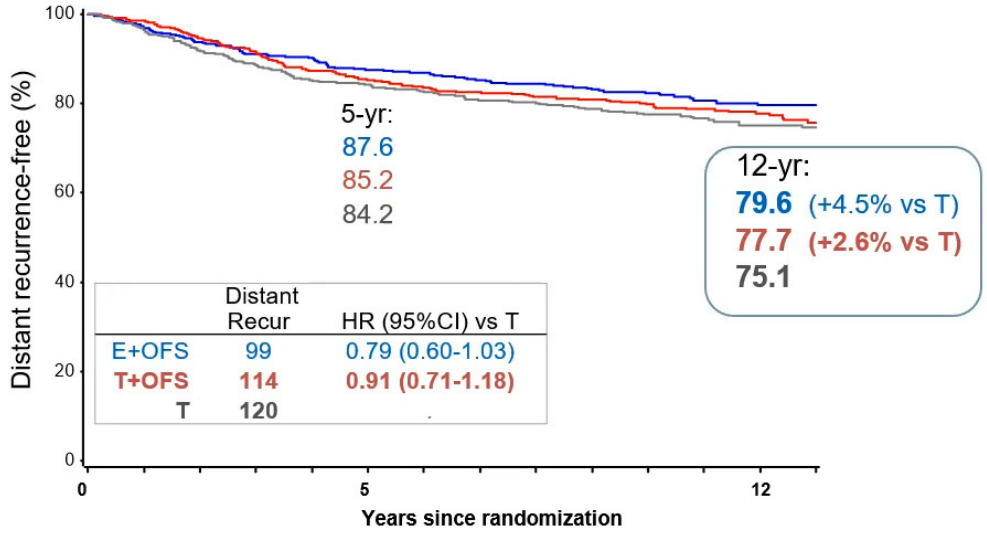
SOFT Prior Chemotherapy Cohort

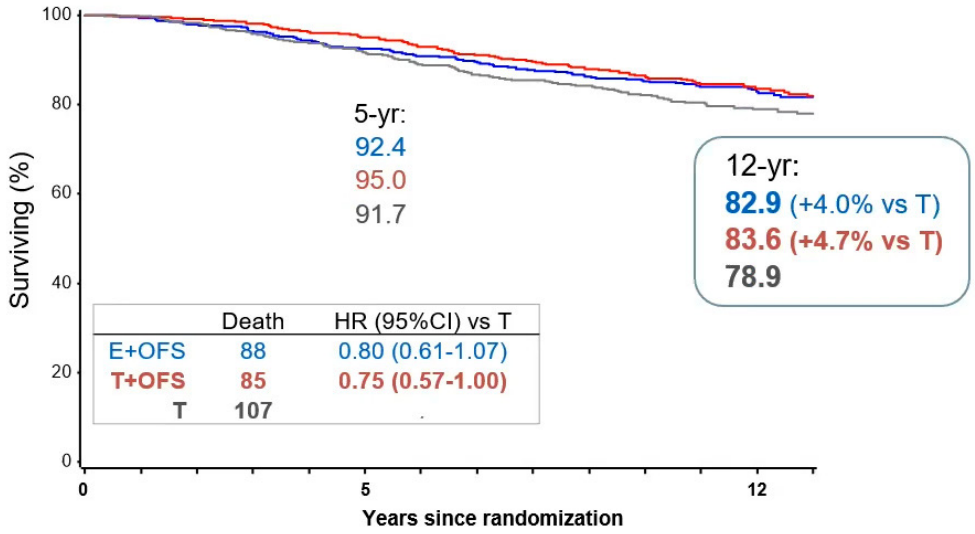
57% LN+; 12 years median follow-up

Distant Recurrence-free Interval



	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	65	0.77 (0.56-1.07)	34	0.81 (0.51-1.29)
T+OFS:	76	0.91 (0.67-1.24)	38	0.92 (0.59-1.44)
T:	81	.	39	.
At risk:	1628 pts	7131 pyfu	1257 pts	8005 pyfu

Overall Survival



	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	40	0.93 (0.61-1.43)	48	0.72 (0.50-1.05)
T+OFS:	26	0.60 (0.37-0.97)	59	0.86 (0.60-1.22)
T:	43	.	64	.
At risk:	1628 pts	7681 pyfu	1427 pts	9295 pyfu

T+OFS vs T: absolute reduction in distant recurrence, 2.6% at 12 years
reduction in death persists, absolute reduction 4.7% at 12 years

E+OFS vs T: reductions of 4.5% and 4.0%, at 12 years

pyfu=person-years follow-up

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SOFT and TEXT after 12 & 13 years Median Follow-up

- Distant recurrences and deaths from BC continue to occur among this premenopausal HR+ population
  - Follow-up continues for a further 5 years
- Meaningful relative reductions in distant recurrence and death persist for use of OFS (with either oral ET) vs tamoxifen alone, requires appropriate selection of patients to receive OFS
  - Absolute reductions at 12 years more clinically substantial (~10%) for those at higher clinical risk
  - With low clinical risk, >95% were surviving at 12 years with all 3 treatments (and no chemotherapy)
- Reduction in distant recurrence with E+OFS vs T+OFS is consistent with postmenopausal women, of substantial magnitude for those at higher risk
  - Emergent later survival improvement with E+OFS, 3.3% at 12 years for those with HER2-negative BC who had received chemotherapy

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Late Distant Relapse after 5 year of HT by size and node status

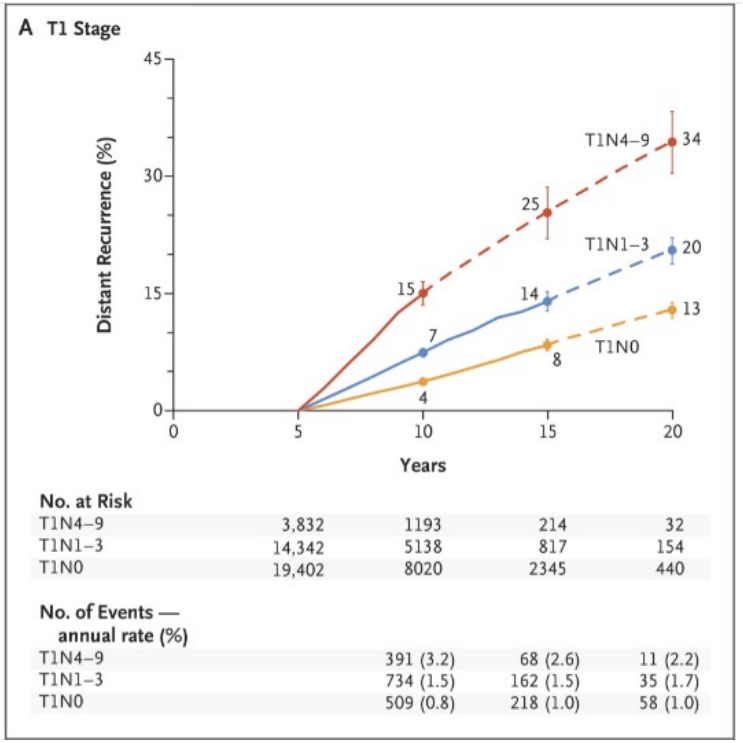


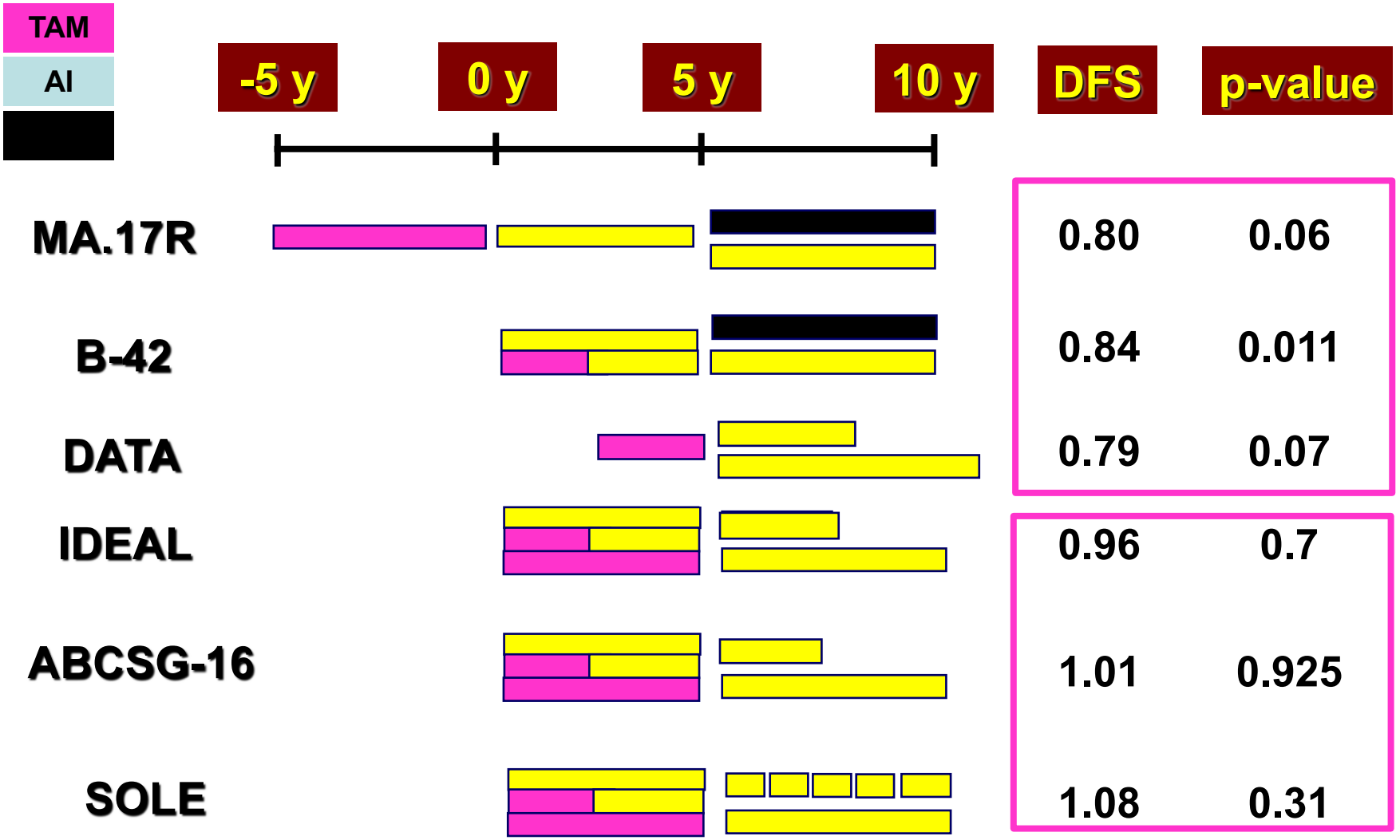
Table 1. Association of Tumor Size and Nodal Status and Grade with the Risk of Distant Recurrence in Years 5 to <10 and in Years 10 to 20.*

Variable	Women Who Were Event-free at 5 Yr		Annual Rate of Distant Recurrence		Cumulative Risk from 5 Yr to 20 Yr
	Total	Chemotherapy Scheduled	5 to <10 Yr	10 to 20 Yr	
	no.	*no. (%)*	*percent*		*percent*
Nodal involvement					
N0	28,847	9,136 (32)	1.0	1.1	15
N1–3	25,292	17,280 (68)	1.9	1.7	23
N4–9	8,784	6,664 (76)	3.9	2.8	38
Tumor diameter in N0 only					
T1a or T1b: ≤1.0 cm	5,527	910 (16)	0.5	0.8	10
T1c: 1.1–2.0 cm	13,875	4,034 (29)	0.8	1.1	14
T2: 2.1–3.0 cm	6,700	2,859 (43)	1.5	1.4	19
T2: 3.1–5.0 cm	2,745	1,333 (49)	1.7	1.4	20
Tumor grade in T1N0 only					
Low	3,524	401 (11)	0.4	0.8	10
Moderate	7,363	1,861 (25)	0.7	1.0	13
High	3,054	1,414 (46)	0.9	1.5	17

* Data are for 62,923 women with T1 or T2 estrogen-receptor–positive disease with 0 to 9 positive nodes who were scheduled to receive 5 years of adjuvant endocrine therapy and were disease-free at year 5. Most of the women entered the study at the time of diagnosis, but some entered later, having already received 2 to 5 years of endocrine therapy, and were randomly assigned to stop therapy at 5 years. P<0.001 for all subgroup comparisons.

Pan H, et al. *N Engl J Med*. 2017;377:1836-1846.

Summary of Extended Aromatase Inhibitors Trials



Mamounas E 2022

ASCO SPECIAL ARTICLE

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Check for updates

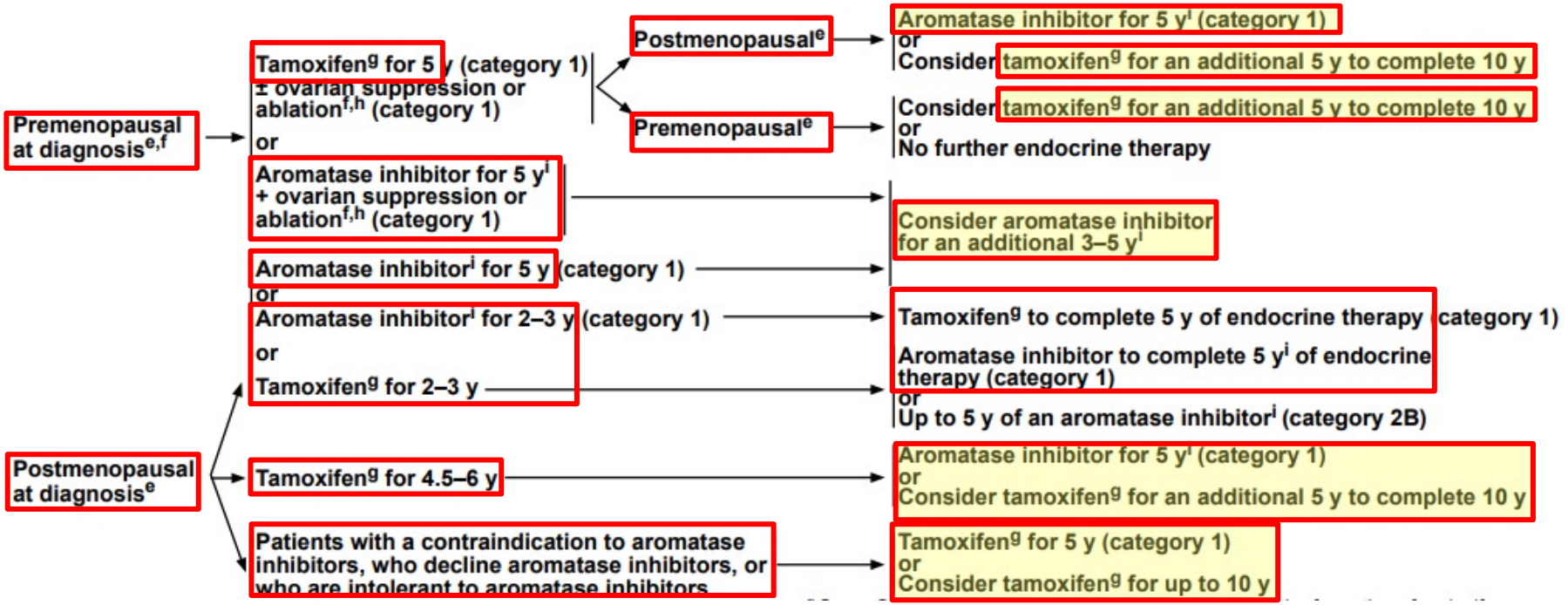
Harold J. Burstein, MD, PhD[1]; Christina Lacchetti, MHSc[2]; Holly Anderson, RN[3]; Thomas A. Buchholz, MD[4]; Nancy E. Davidson, MD[5]; Karen A. Gelmon, MD[6]; ...

- *Recommendation:* Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.
- *Recommendation:* Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

- *Qualifying Statement*. To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.

J Clin Oncol. 2019;37:423-438.

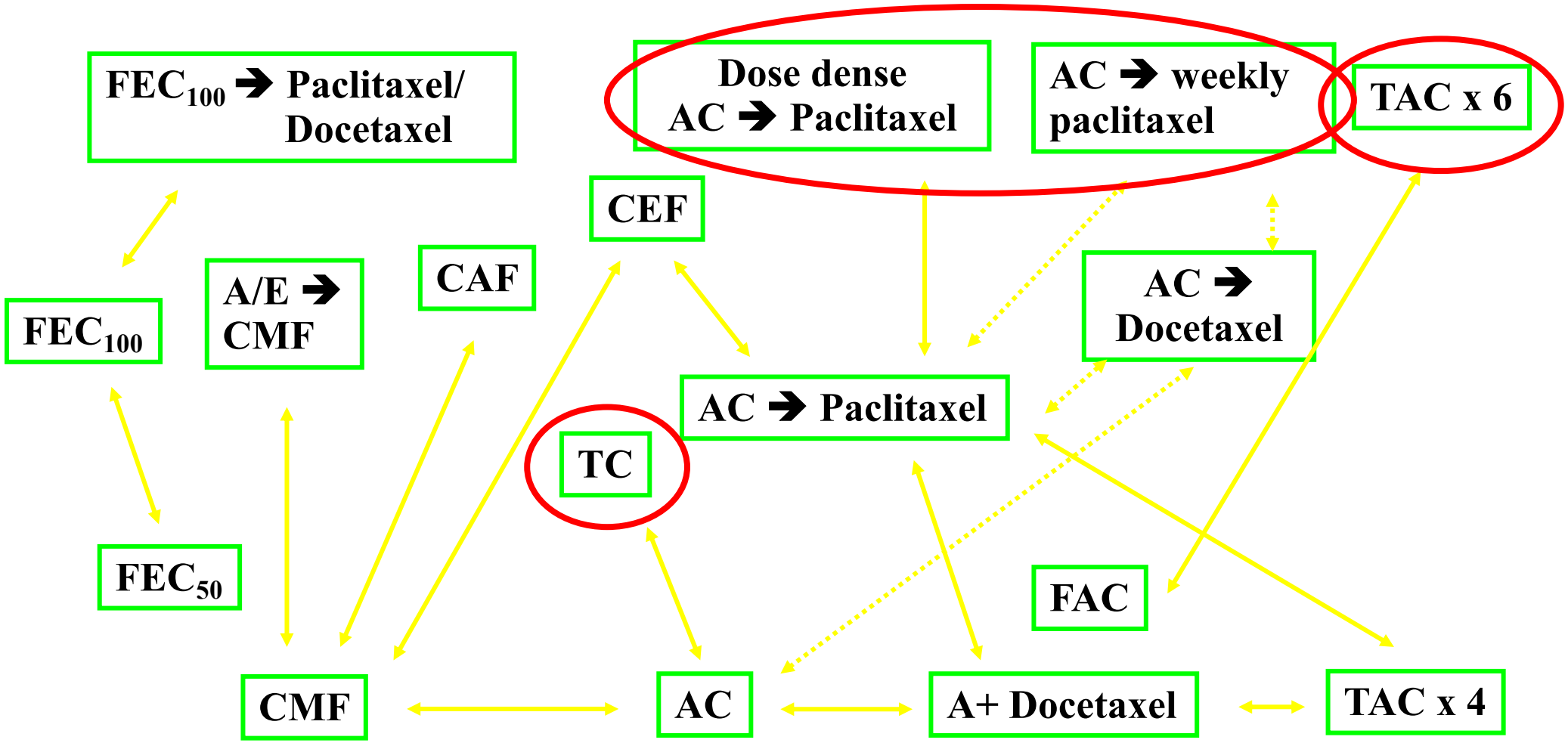
NCCN Guidelines Version 2.2022



Adjuvant Chemotherapy Therapy

HR+ Early Breast Cancer

Adjuvant Chemotherapy Options 2022



Arrows indicated direct comparisons from randomized trials
Benefits not drawn to scale

Outstanding Questions in Node Negative and Node Positive (micro, 1-3+) HER-2- ER+ Breast Cancer

- To identify patients a low risk at baseline
- To select patients for adjuvant hormonal therapy alone
- To select patients for adjuvant chemotherapy and hormonal therapy
- To identify patients at high residual risk after 5 years of adjuvant hormonal therapy
- To select patients for extended hormonal therapy

NCCN® Clinical Practice Guidelines in Oncology

Gene Expression Assays for Consideration of Adjuvant Systemic Therapy[a,b]

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene (21-genomic signature) (for pN0)	Yes	Yes	Preferred	1
21-gene (21-genomic signature) for pN1 (1-3 positive nodes)[c]	Yes	Yes	Postmenopausal: Preferred Premenopausal: Other	1 2A
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A

a. Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (21-genomic signature) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
b. See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
c. In the overall study population of the RxPONDER trial, 10.3% had high grade disease and 9.2% had 3 involved nodes.

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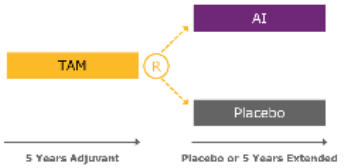
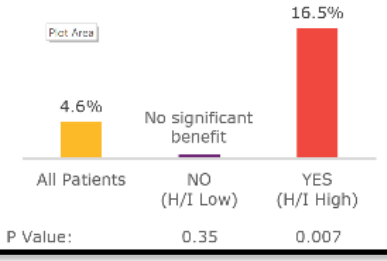
BCI (H/I) is Predictive for Extended Endocrine Therapy Benefit

BCI MA.17 (n=249)[1]

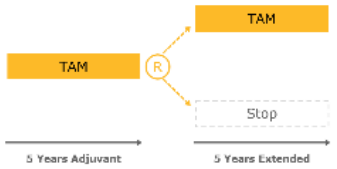


Recurrence Free Survival (RFS) Benefit

Cohort = 41% N0 / 59% LN+



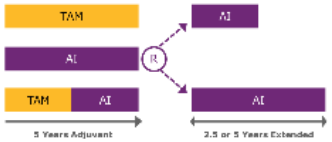
Trans-aTTom (n=583)[2]



Recurrence Free Interval (RFI) Benefit

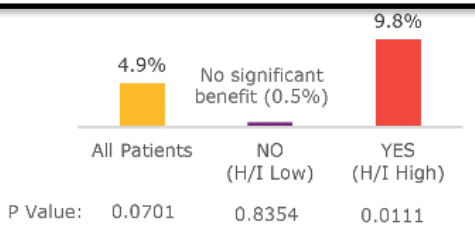
Cohort = 100% LN+

BCI IDEAL (n=908)[3]

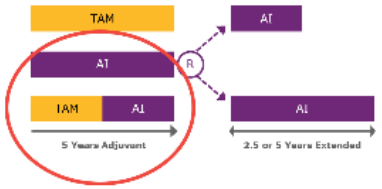


Recurrence Free Interval (RFI) Benefit

Cohort = 27% N0 / 73% LN+

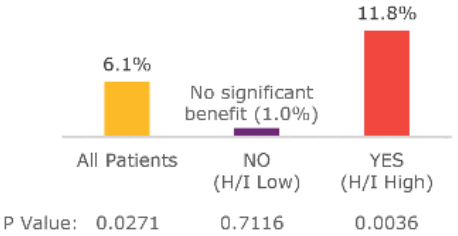


Adjuvant AI Subset (n=794)[3]



Recurrence Free Interval (RFI) Benefit

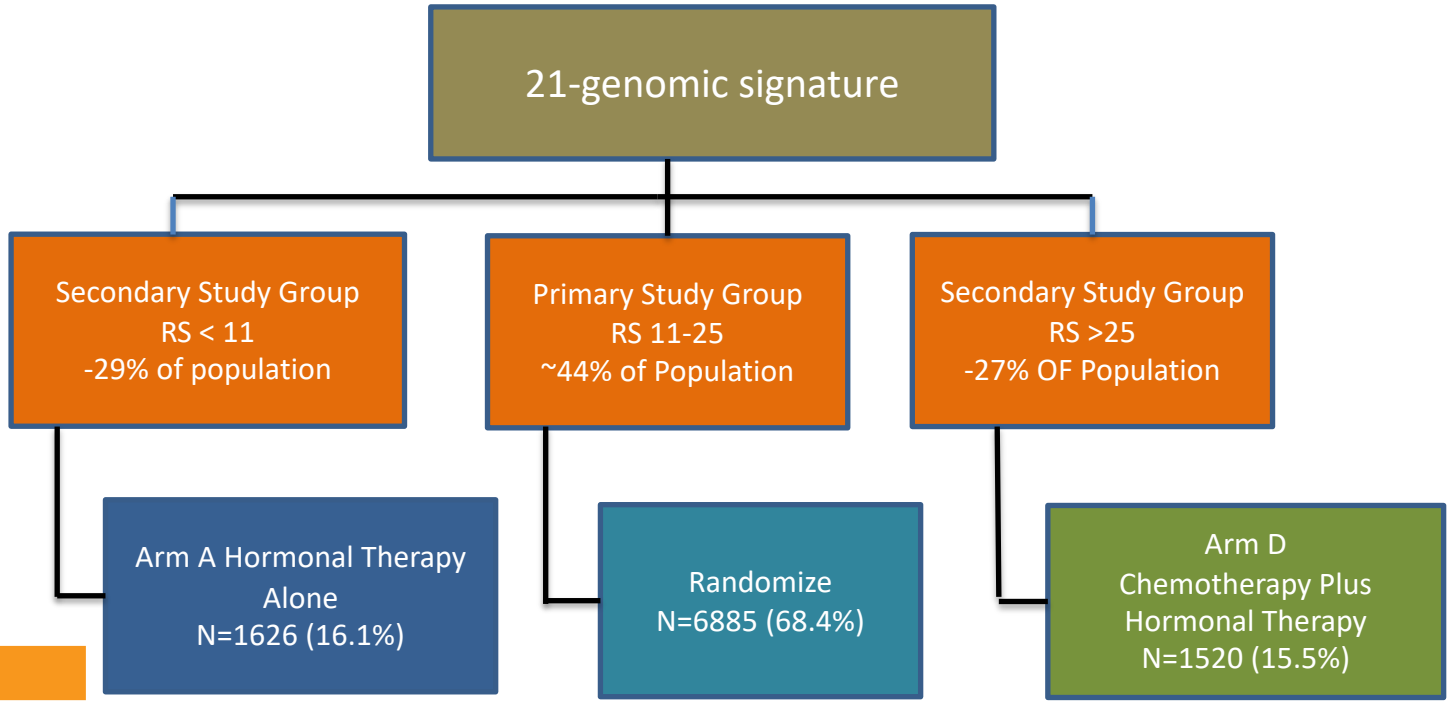
Cohort = 27% N0 / 73% LN+



1 Sgroi DC, et al. *J Natl Cancer Inst*. 2013;105:1036-1042. 2. Bartlett JMS, et al. *Ann Oncol*. 2019;30:1776-1783. 3. Noordhoek I, et al. *Clin Cancer Res*. 2021;27:311–319.

TAILORx: A Clinical Trial Assigning Individualized Options for Treatment (Rx)

Eligible 10,253 pts prospectively enrolled (2006-2010)

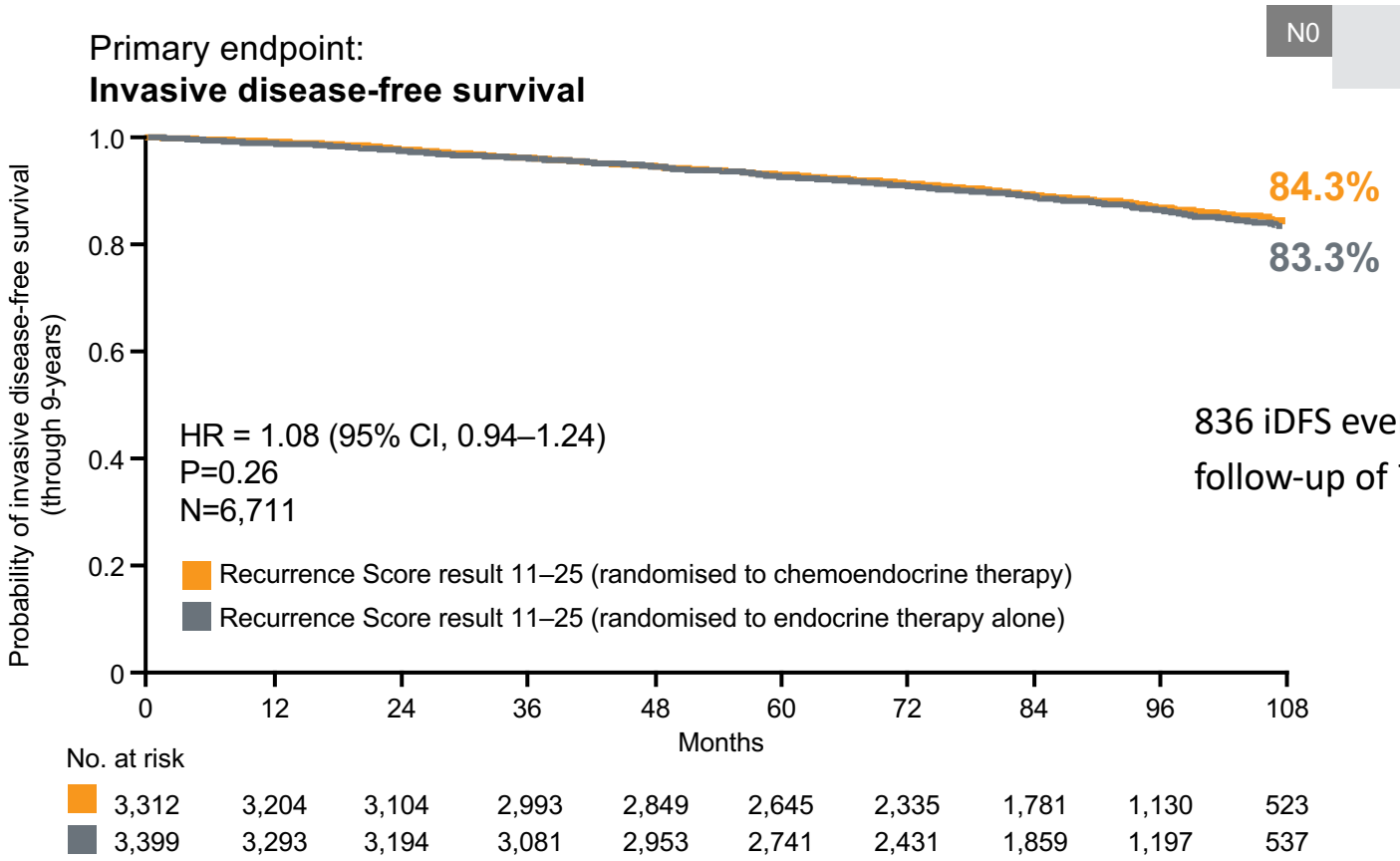


RS: Recurrence Score result

Sparano et al. *N Engl J Med*. 2015 and 2018.

TAILORx primary endpoint: endocrine therapy alone is non-inferior to chemoendocrine therapy in patients with Recurrence Score® results 11–25

N0 | TAILORx (Level 1A evidence)



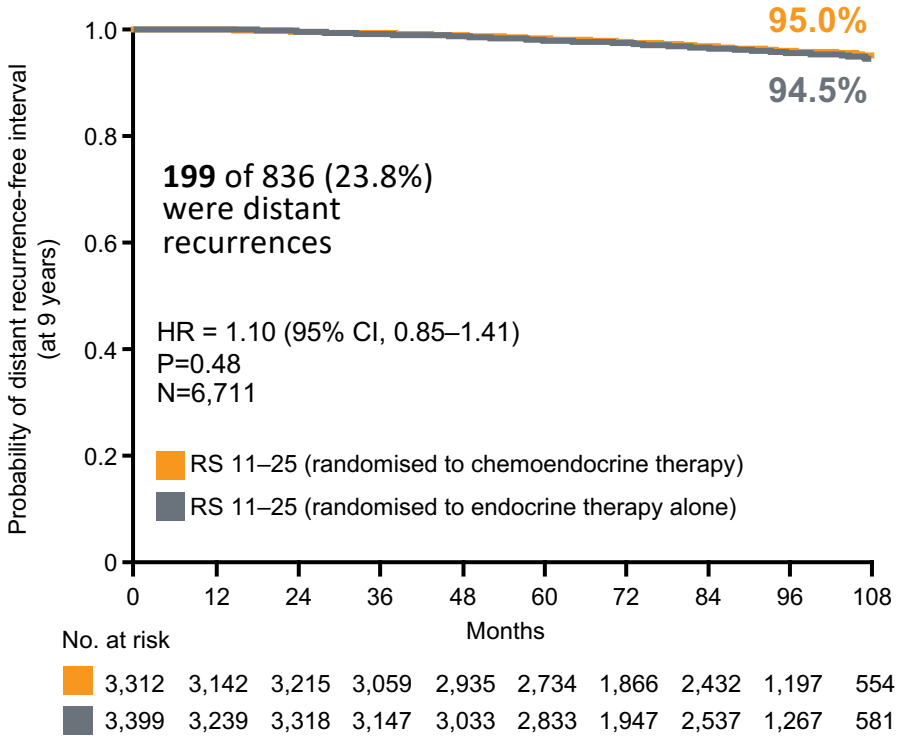
Sparano et al. *N Engl J Med.* 2018.

HR = hazard ratio; CI = confidence interval

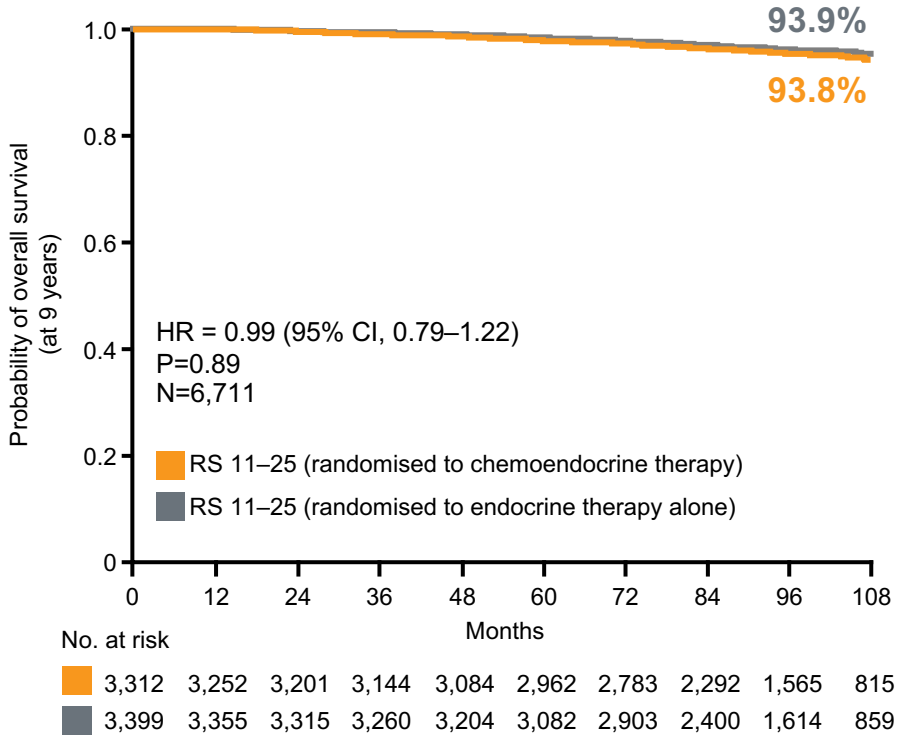
TAILORx secondary endpoints: endocrine therapy alone is non-inferior to chemoendocrine therapy for patients with Recurrence Score® results 11–25

N0 | TAILORx (Level 1A evidence)

Secondary endpoint:
Distant recurrence-free interval



Secondary endpoint:
Overall survival



Sparano et al. *N Engl J Med.* 2018.

HR = hazard ratio; CI = confidence interval; RS = Recurrence Score result

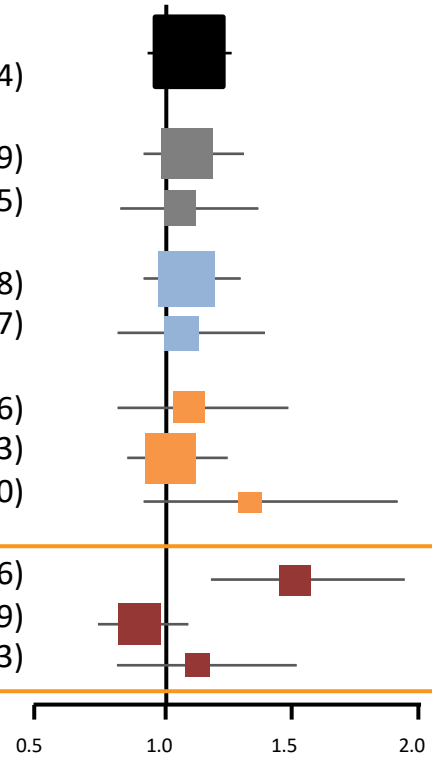
Classical clinical parameters do not predict chemotherapy benefit while younger patients (age ≤50) may derive some benefit from chemotherapy

TAILORx Exploratory analyses

N0 TAILORx exploratory

DFS hazard ratio
ET vs CT-ET therapy

Group	n	ratio	95% CI
Patients RS 11-25	6711	1.08	(0.94, 1.24)
Clinical risk low	4799	1.08	(0.91, 1.29)
Clinical risk high	1697	1.05	(0.82, 1.35)
Tumour size ≤ 2cm	5122	1.08	(0.92, 1.28)
Tumour size > 2cm	1587	1.06	(0.82, 1.37)
Grade low	1893	1.09	(0.82, 1.46)
Grade intermed.	3721	1.02	(0.85, 1.23)
Grade high	884	1.32	(0.92, 1.90)
Age ≤ 50	2216	1.51	(1.17, 1.96)
Age 51-65	3545	0.89	(0.73, 1.09)
Age >65	950	1.12	(0.81, 1.53)



No statistically significant chemotherapy treatment interactions were found in any of these subgroups

Younger patients (age ≤50) may derive some benefit from chemotherapy in the RS 11-25

*Low clinical risk defined by low grade and tumour size ≤3cm, intermediate grade and tumour size ≤2cm, and high grade and tumour size ≤1cm; high clinical risk defined as all other cases with known values for grade and tumour size

Sparano et al. *N Engl J Med* 2018, Supplement

Clinical Impact in 2022

- **TAILORx study met primary objective and represent an step toward to precision medicine**
- **Chemotherapy did not add to HT in ER+, HER-2 normal, node negative breast cancer RS 11-25. Therefore, it reduce of overtreatment in woman with low risk ER+ node negative EBC**

- In an exploratory analysis, there was interaction between age and chemotherapy benefit. There is a potential role of chemotherapy in women <50 and RS 16-25 (iDFS 6%) HR 1.36 especially those with RS 21-25. The impact of CT is potentially related to CT induced ovarian suppression/ablation

- RS 0-10 group treated with HT alone continues to show low risk for distant metastasis
- The high risk RS (>25) shows residual high risk for relapse despite of CT and HT.
- Clinical risk is associated with prognosis. However, it does not predict chemotherapy benefit.

The Role of the 21-genomic signature Breast Cancer Assay in the Neoadjuvant Setting

The 21-genomic signature Assay Neoadjuvant Studies

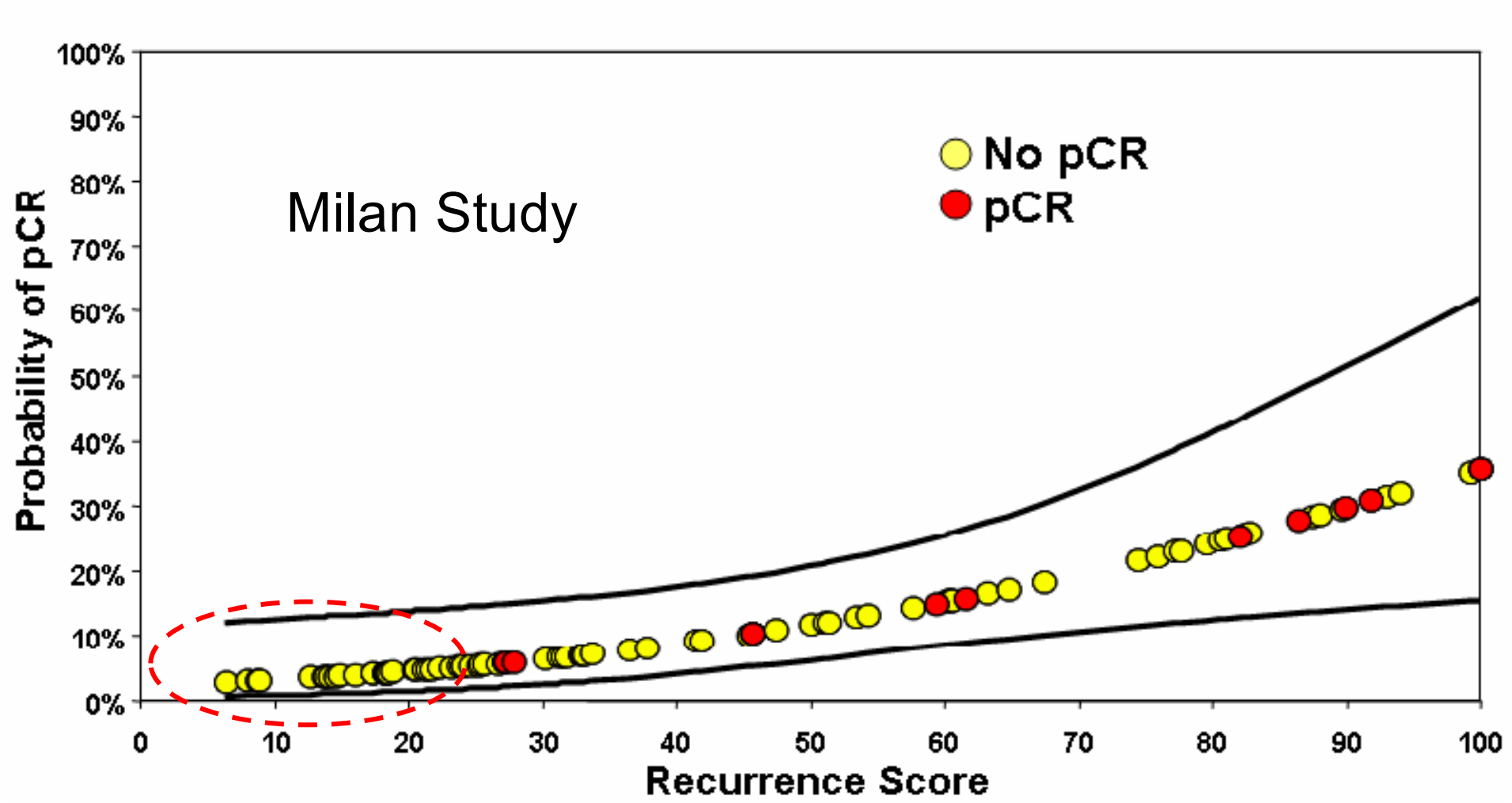
Study	N	Neoadjuvant Chemotherapy
Gianni et al[1]	89	Doxorubicin/Paclitaxel x 3 cycles then weekly paclitaxel x 12
Chang et al[2]	72	Docetaxel x 4 cycles
Yardley et al[3]	108	Ixabepalone/Cyclophosphamide x 6 cycles

Study	N	Neoadjuvant Endocrine Therapy
Akashi-Tanaka et al[4]	87	Anastrozole or Tamoxifen x 4 months
Masuda et al[5]	64	Exemestane 16 weeks → 8 weeks more if no progression at 16 weeks

Study	N	Neoadjuvant Chemotherapy or Endocrine Therapy
Zelnak et al[6]	46	Recurrence Score® result ≤ 10 → Exemestane Recurrence Score result 11-24 → Exemestane OR Docetaxel Cyclophosphamide x 6 cycles Recurrence Score result ≥ 25 → Docetaxel Cyclophosphamide x 6 cycles

1. Gianni et al. J Clin Oncol. 2005.
2. Chang et al. Breast Cancer Res Treat. 2008.
3. Yardley et al. SABCS 2011. Abstract P5-13-09.
4. Akashi-Tanaka et al. Breast. 2009.
5. Masuda et al. ASCO 2011. Abstract 558.
6. Zelnak et al. ASCO 2013. Abstract 562.

Patients with a Low Recurrence Score Result Are Less Likely to Respond to Neoadjuvant Anthracyline-Taxane Treatment



N=89

P=0.005

Gianni et al. J Clin Oncol. 2005.

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

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

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

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

On Behalf of the RxPonder Investigators

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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

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

ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

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Statistical Analysis Plan

- **Primary Outcome**
  - IDFS: Updated analysis with 553 events and a median follow-up 6.1 years in ITT population
    - Prior analysis: median follow-up 5.3 years (481 IDFS events)[2]

Outcome[3]	Local-Regional Invasive Recurrence	Second Invasive Primary (Breast or Not)	Distant Recurrence	Death from Non-Breast Cancer or Unknown Cause	Death from Breast Cancer
Invasive Disease-Free Survival	**X**	**X**	**X**	**X**	**X**
Distant Relapse-Free Survival			**X**	**X**	**X**
Distant Recurrence-Free Interval			**X**		**X**

[1]Kalinsky et al, San Antonio Breast Cancer Symposium 2020; [2] Kalinsky et al, New England Journal of Medicine: December 1, 2021; [3]Tolaney et al, Journal of Clinical Oncology 2021

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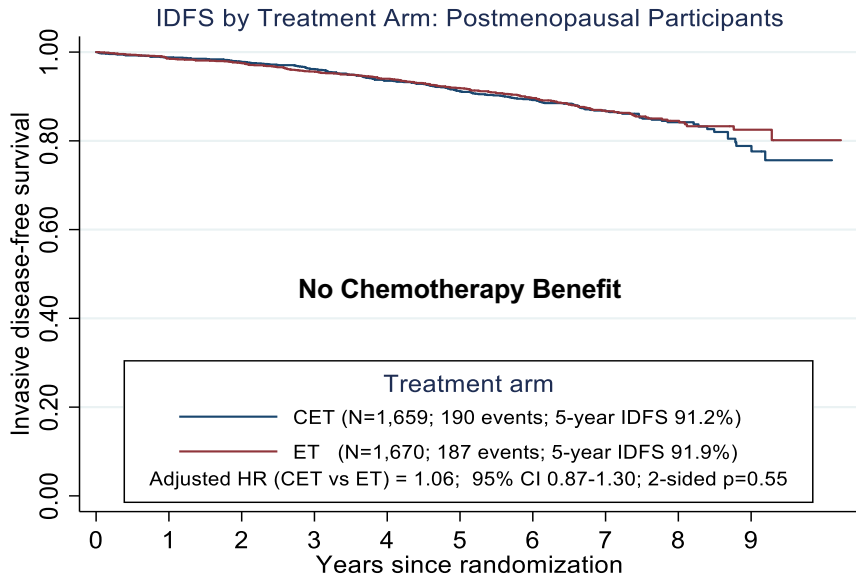
Updated Analysis: Postmenopausal Women Have No Chemotherapy Benefit

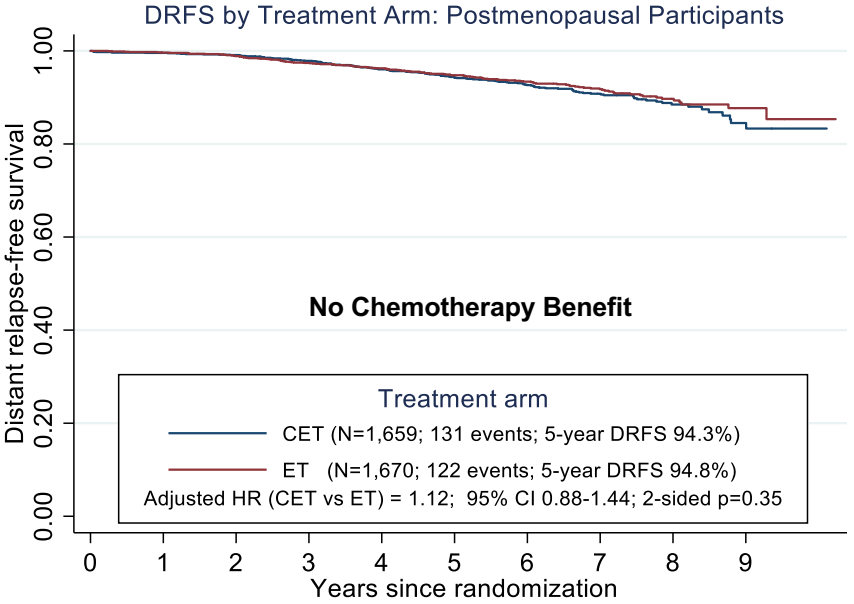
Invasive Disease-Free Survival



Number at risk

CET	1659	1557	1498	1427	1258	1118	848	540	243	64
ET	1670	1599	1550	1465	1314	1164	879	547	247	67

Distant Relapse-Free Survival



Number at risk

CET	1659	1567	1514	1448	1291	1152	884	571	261	71
ET	1670	1614	1569	1491	1345	1201	916	582	264	71

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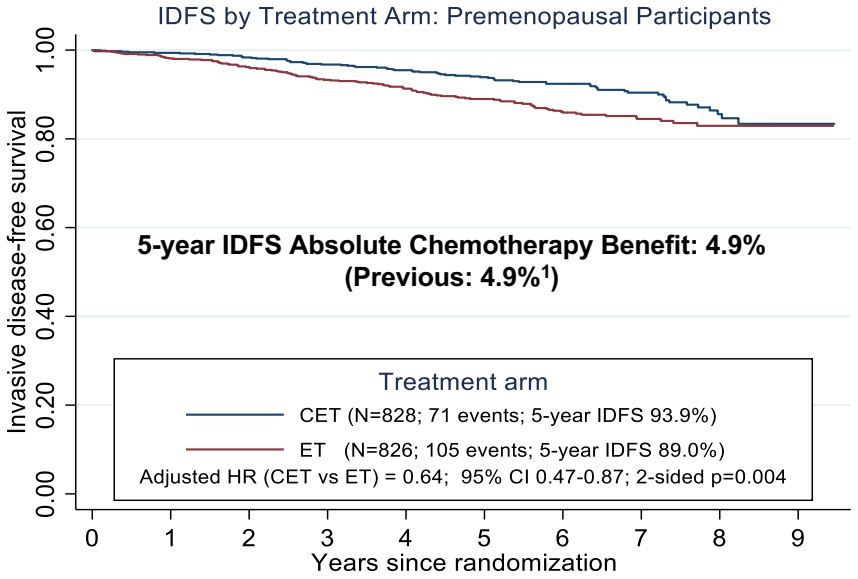
Updated Analysis: Premenopausal Women Have Chemotherapy Benefit

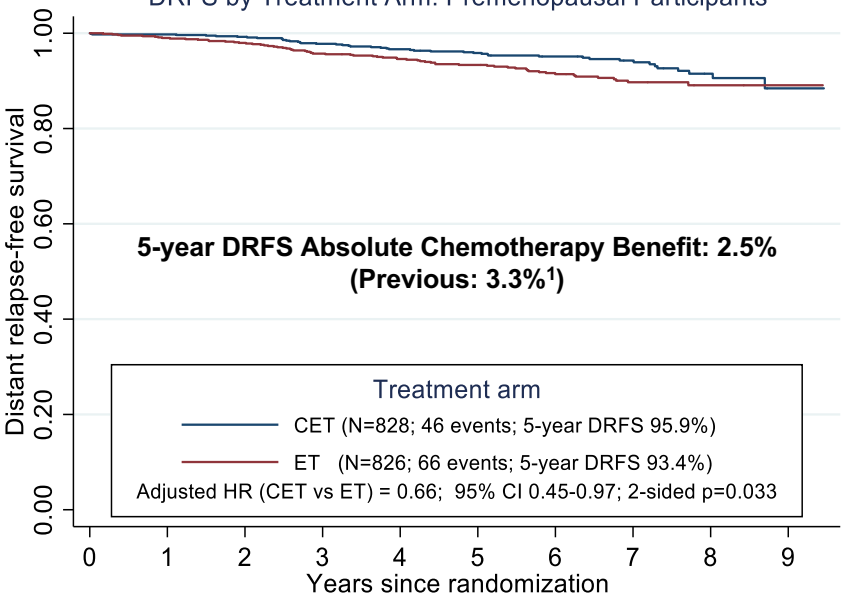
Invasive Disease-Free Survival



Number at risk

CET	828	783	754	706	632	561	408	252	99	21
ET	826	774	737	694	610	533	398	236	86	27

Distant Relapse-Free Survival



Number at risk

CET	828	786	761	714	641	575	421	266	106	22
ET	826	780	751	712	631	555	420	247	93	28

[1] Kalinsky et al, New England Journal of Medicine: December 1, 2021

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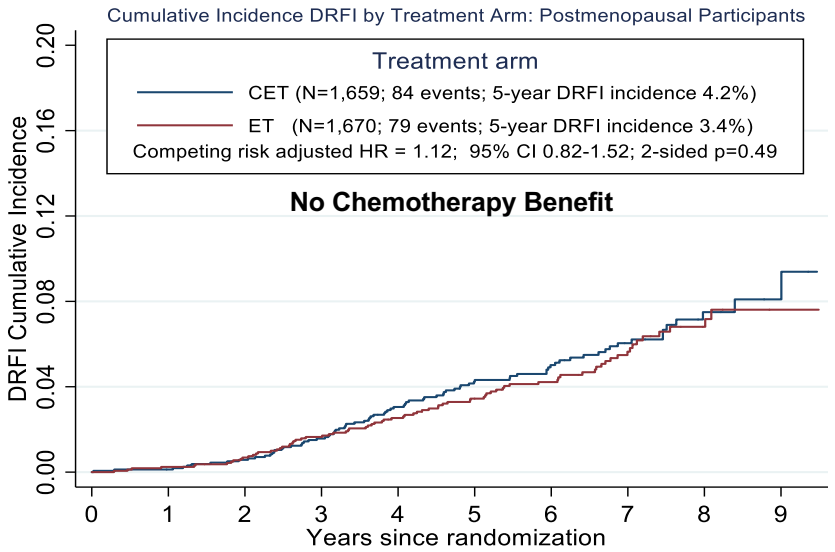
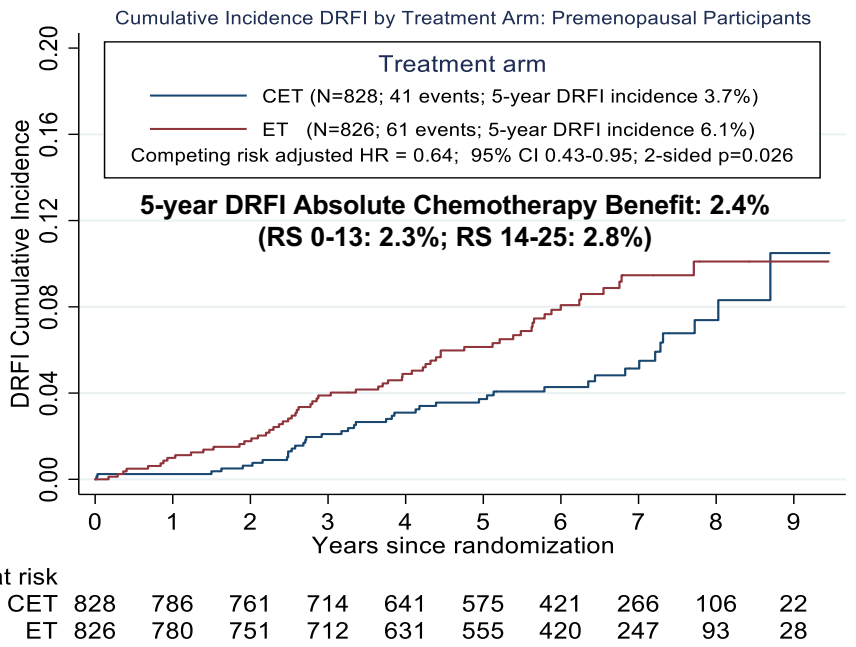
New Analysis: DRFI Stratified by Menopausal Status

Postmenopausal



Premenopausal



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

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

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Post Hoc Analyses in Premenopausal Women

- IDFS between treatment arms in pts with pN1mi
    - In 2014, protocol amended to exclude enrollment if pN1mi
- Two-year landmarked IDFS analysis between ovarian function suppression or not in the ET arm
- Two-year landmarked IDFS analysis between pts with regular menstrual periods or not in both treatment arms

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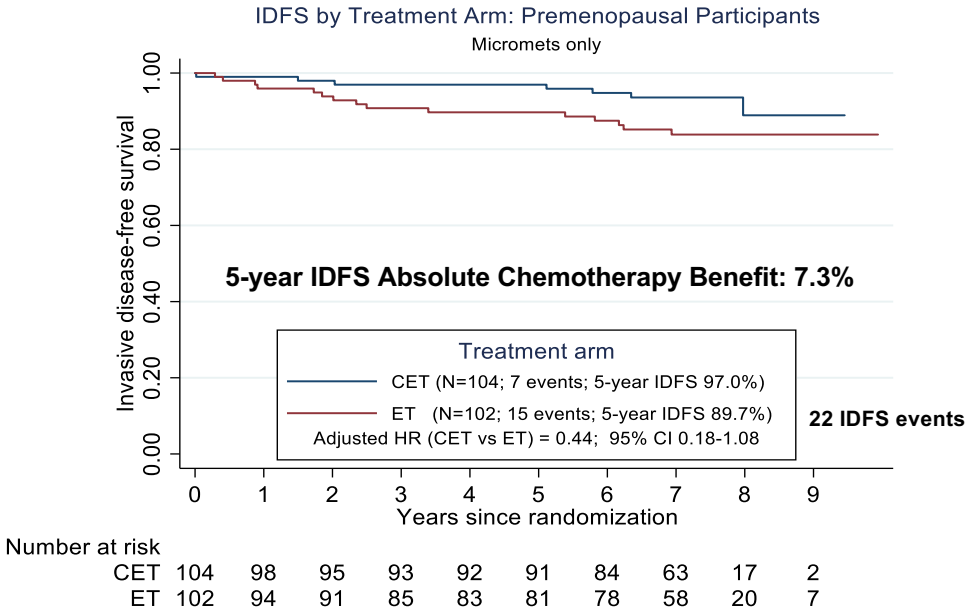
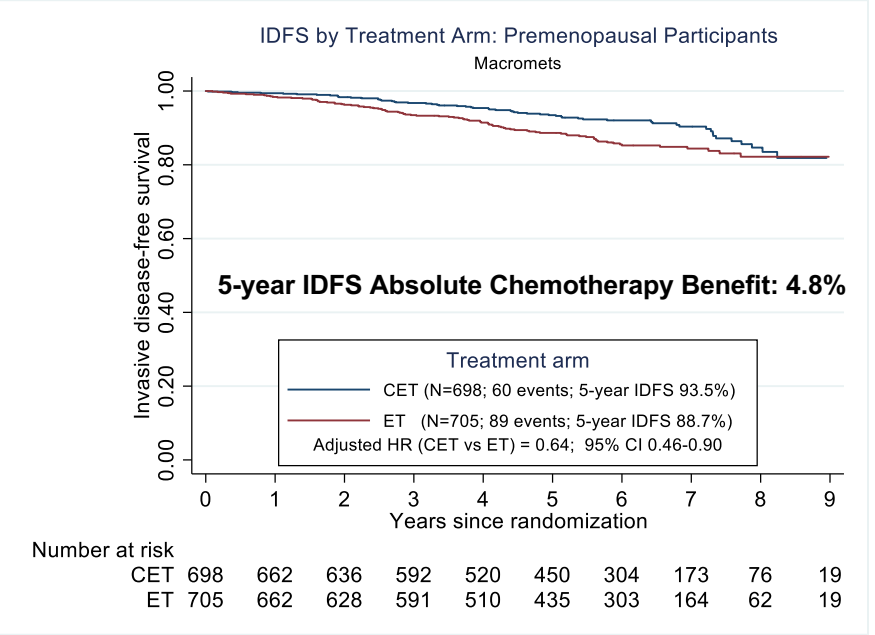
Premenopausal Women with p1Nmi and pN1 Benefit from Chemotherapy

pN1mi (N=206)



pN1 (N=1403)



Prior to the amendment, 206/738 (27.9%) eligible premenopausal pts had micrometastases only and 45 pts (6%) unknown

Cox regression test for interaction of chemotherapy with micrometastases p= 0.40

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RxPONDER Conclusions

- In updated analysis, we report with longer follow-up that postmenopausal women with RS 0-25 continue to not benefit from adjuvant chemotherapy

- Premenopausal women with RS 0-25 benefit from the addition of chemotherapy to endocrine therapy, with a 44-46% decrease in IDFS, DRFS, DRFI events

- Exploratory analyses in premenopausal women (small subgroups)
  - pN1mi benefit from chemotherapy; though, limited number of events
  - 58.9% in ET arm (including majority of those with OFS) and 80.8% in CET arm stopped having regular menstrual periods in first 24 months and had a numerically improved IDFS, regardless of treatment arm

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RxPONDER Conclusions

- RxPONDER not powered for subgroups differences, and data interpretation in premenopausal pts can be challenging, given that confounding factors can change over time
- It remains unclear if OFS can replace chemotherapy in premenopausal women with HR+/HER2-, node-positive breast cancer
- A future randomized trial should be considered to address this important clinical question

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Limitations

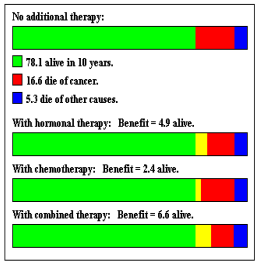
- ✓ Still awaiting ~ 1/3d of the population to experience events
- ✓ Is chemotherapy benefit in premenopausal women exclusively due to amenorrhea?
- ✓ Minority of patients underwent ovarian function suppression
- ✓ Did not capture rate of pathologically or clinically node + breast cancer prior to surgery
- ✓ Generalizability
  - ✓ Only 9.2% of patients had 3 LN+
  - ✓ 5.0% had T3 tumors
  - ✓ 5.0% Black

Kalinsky K, et al. *N Engl J Med.* 2021;385:2336-47.

Clinical Impact in 20212

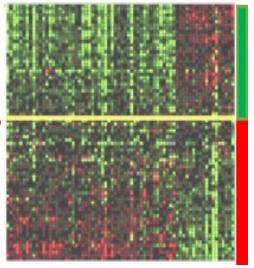
- The biology of ER+, HER-2 negative low burden node positive breast cancer is similar to node negative breast cancer. However, the risk of distant relapse is higher.
- The results of genomic signatures from several non-randomized and randomized studies in node positive ER+ EBC showed findings consistent with the results in node negative ER+EBC studies
- RxPonder showed that patients with ER+, HER-2- with 1-3+ LN and recurrence score 0-25 that received hormonal or hormonal therapy and chemotherapy have an excellent 5-year iDFS, 91% and 92.4%, respectively.
- RxPonder showed that patients with ER+, HER-2- with 1-3+ LN and recurrence score 0-25 that chemotherapy did not clinically add additional benefit to hormonal therapy
- RxPonder showed that patients with post-menopausal ER+, HER-2- with 1-3+ LN and recurrence score 0-25 that chemotherapy did not add additional benefit to hormonal therapy
- RxPonder showed that patients with pre-menopausal ER+, HER-2- with 1-3+ LN and recurrence score 0-25 that chemotherapy did add a moderate additional benefit (5-year iDFS 5%) to hormonal therapy regardless of RS or nodal burden

MINDACT TRIAL DESIGN



Registration & Screening
Surgery

6693 patients | 112 hospitals, 9 countries



Clinical-Pathological (C) risk (Adjuvant! Online)

Genomic (G) risk (70-gene signature)

C-low/G-low

Discordant cases
C-low/G-high or C-high/G-low

C-high/G-high

C-Low per modified Adjuvant! Online: 10-year BCS without AT of >88% for ER+ and >92% for ER-

MINDACT population:
HR+/HER2- 81%
HER2+ 9.5%
TNBC 9.6%
Enrollment 2007-2011

1st randomization to treatment
use Clinical vs. Genomic risk

No Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

Chemotherapy

HR +

Endocrine therapy

HR +

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

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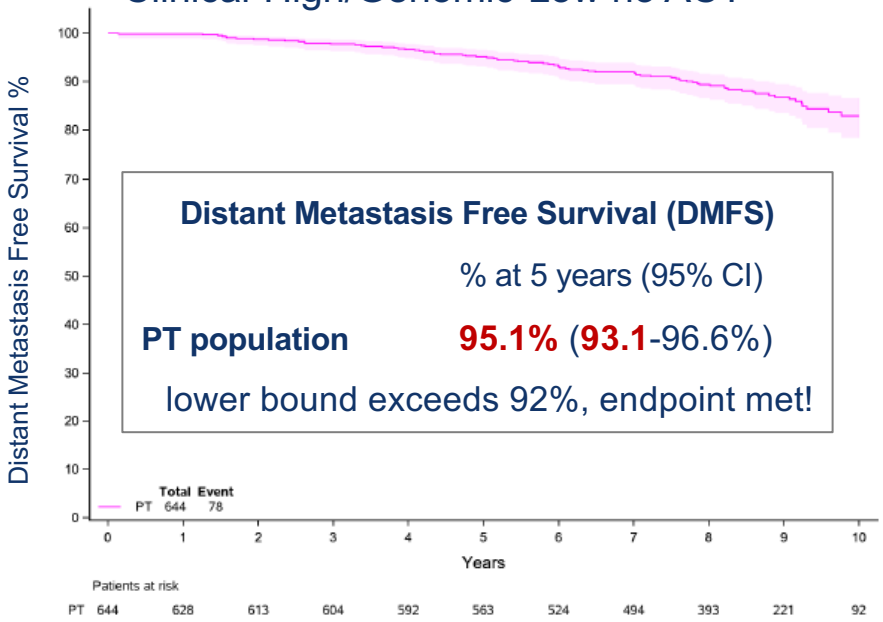
SAN ANTONIO BREAST CANCER SYMPOSIUM®
December 8-11, 2020

MINDACT UPDATED ANALYSIS RESULTS

PRIMARY ENDPOINT

Clinical-High/Genomic-Low no ACT



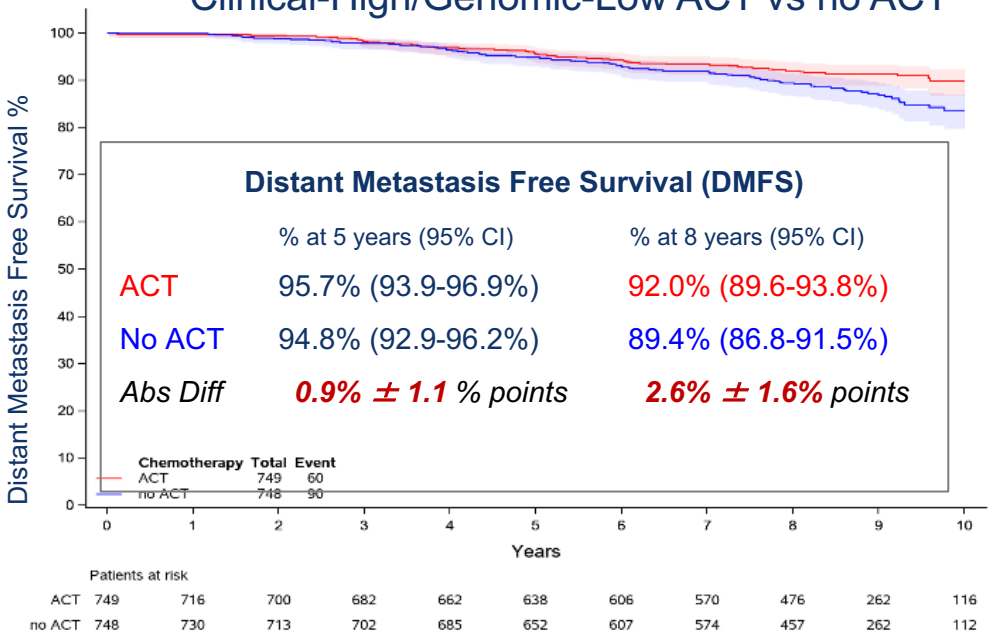
Distant Metastasis Free Survival (DMFS)

	% at 5 years (95% CI)
PT population	**95.1%** (**93.1**-96.6%)

lower bound exceeds 92%, endpoint met!

SECONDARY ENDPOINT

Clinical-High/Genomic-Low ACT vs no ACT



Distant Metastasis Free Survival (DMFS)

	% at 5 years (95% CI)	% at 8 years (95% CI)
ACT	95.7% (93.9-96.9%)	92.0% (89.6-93.8%)
No ACT	94.8% (92.9-96.2%)	89.4% (86.8-91.5%)
Abs Diff	***0.9% ± 1.1** % points*	***2.6% ± 1.6%** points*

Type of first event (n = 150)

- distant recurrences: 74.7%
- death of any cause: 25.3%

F. Cardoso, ASCO 2020; Piccart M, et al. Lancet Oncol 2021;22:476-488.

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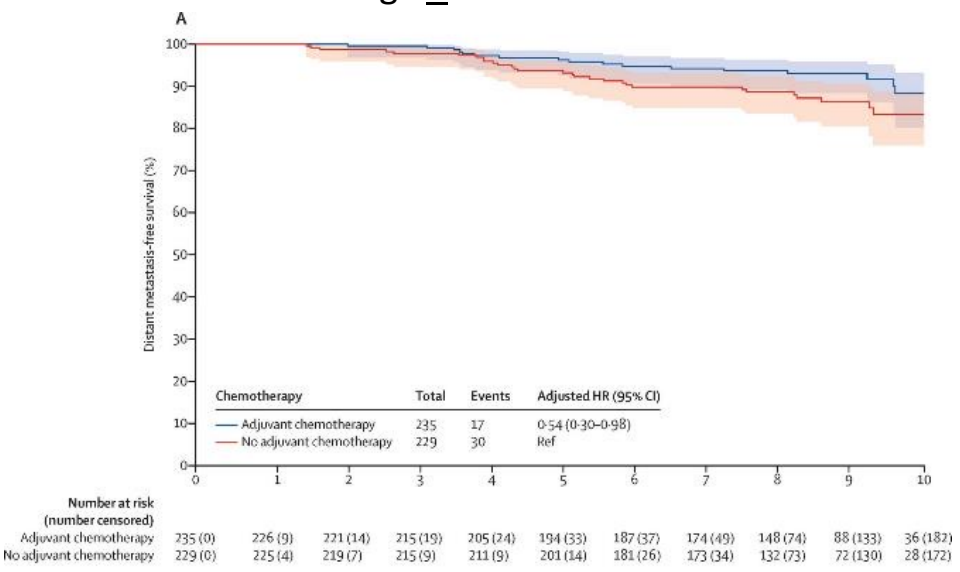
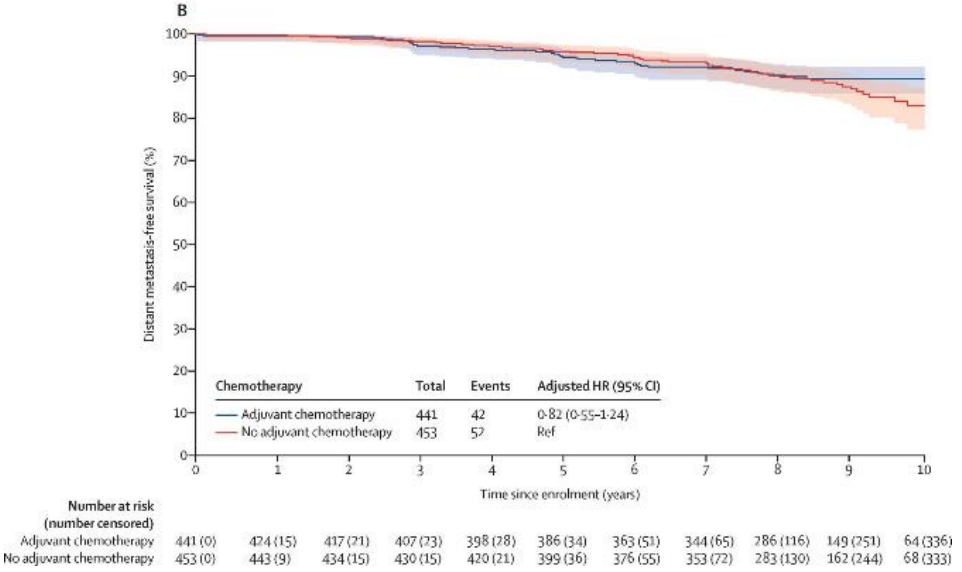
EORTC The future of cancer therapy
BIG Breast International Group
TRANSBIG

MINDACT: DMFS in ER+ HER2- with high clinical but low genomic risk

Age ≤ 50



Age > 50



Piccart M, et al. *Lancet Oncol.* 2021;22:476-488.

Targeted Therapy in ER+ Early Breast Cancer

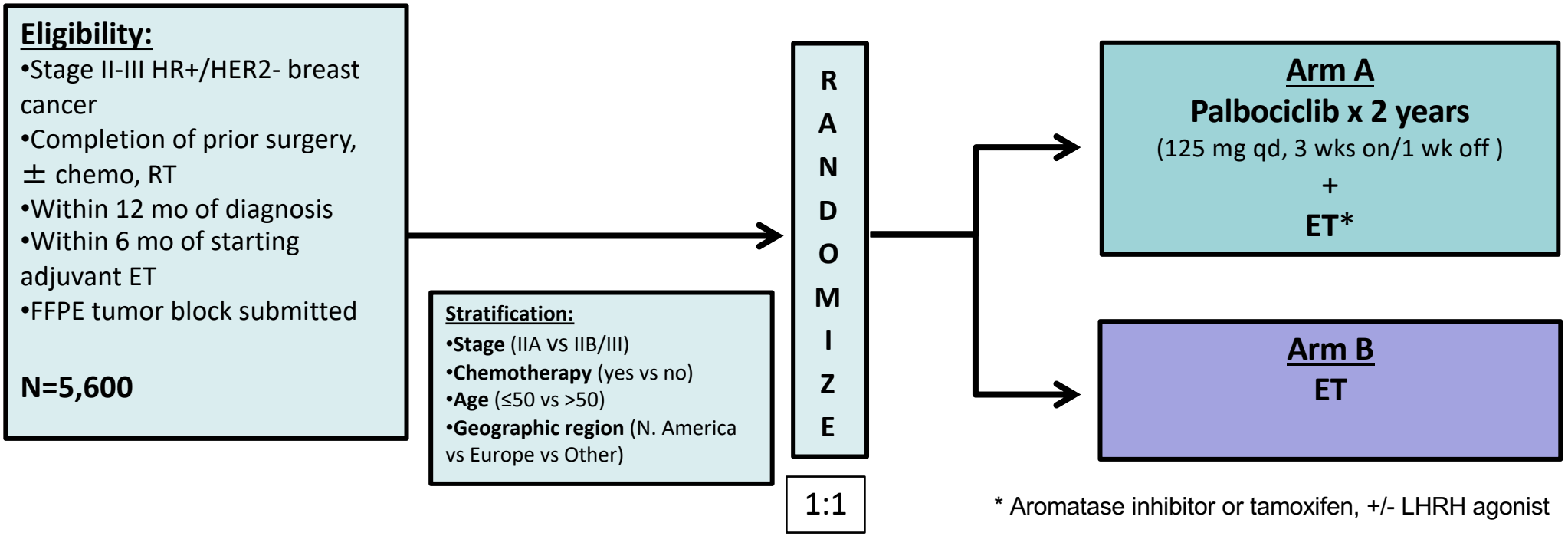
Cell Cycle Control in Breast Cancer and CDK Inhibition

Randomized Phase III Clinical Trials Evaluating CDK 4/6 Inhibitors in Early-Stage ER-Positive/HER2-Negative Breast Cancer

Trial name and identifier	Estimated enrollment	Study treatment	Study population	Primary endpoint
PALLAS NCT02513394	5600	Standard adjuvant endocrine therapy (at least 5 years) ± 125 mg **palbociclib** (2 years)	Stage II (stage IIA limited to max. 1000 patients) or stage III Can enroll after 6 months of adjuvant endocrine therapy	Invasive disease-free survival (iDFS)
PENELOPE-B NCT01864746	1250	Standard adjuvant endocrine therapy ± **palbociclib** in a 28-day cycle for 13 cycles	Patients with residual disease and high risk of relapse (based on CPS-EG score) after neoadjuvant CT of at least 16 weeks	Invasive disease-free survival (iDFS
NataLEE NCT03701334	4000	Standard adjuvant endocrine therapy (at least 5 years) ± 400 mg **ribociclib** (3 years)	Stage II/III breast cancer Can enroll after 6 months of adjuvant endocrine therapy	Invasive disease-free survival (iDFS
monarchE NCT03155997	4580	Standard adjuvant endocrine therapy ± **abemaciclib** (2 years)	High-risk node-positive, breast cancer (⩾4 lymph nodes, tumor >5 cm, grade 3 or central Ki67 ⩾20%) Can enroll after 12 weeks of adjuvant endocrine therapy	Invasive disease-free survival (iDFS

Completed (neo)adjuvant chemotherapy and radiation as per institutional guidelines and surgery with clear margins

PALLAS: Phase III Open-Label Study of Palbociclib and Adjuvant Endocrine Therapy

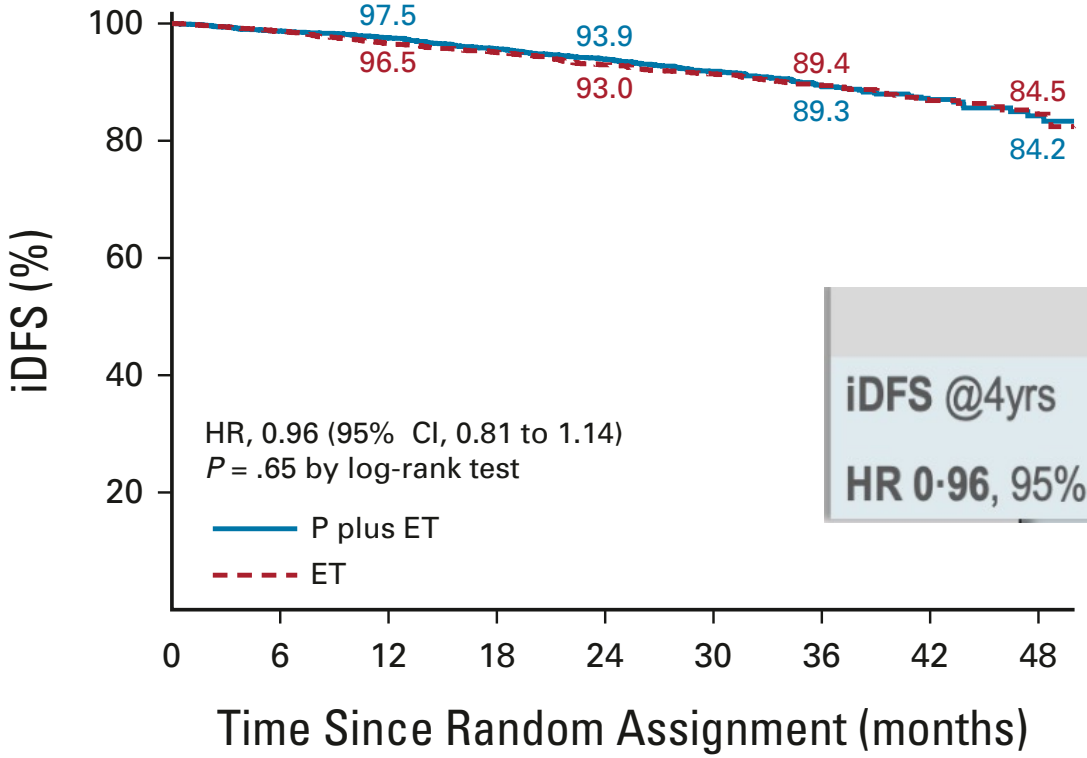


Primary Endpoint: invasive Disease-Free Survival (iDFS)

ET, endocrine therapy

Mayer EL, et al. *Lancet Oncol*. 2021;22:212-222.

PALLAS Primary Endpoint: iDFS



	Palbociclib + ET	ET alone
iDFS @4yrs	84.2%	84.5%

HR 0·96, 95% CI 0·81-1·14; log-rank p = 0·65

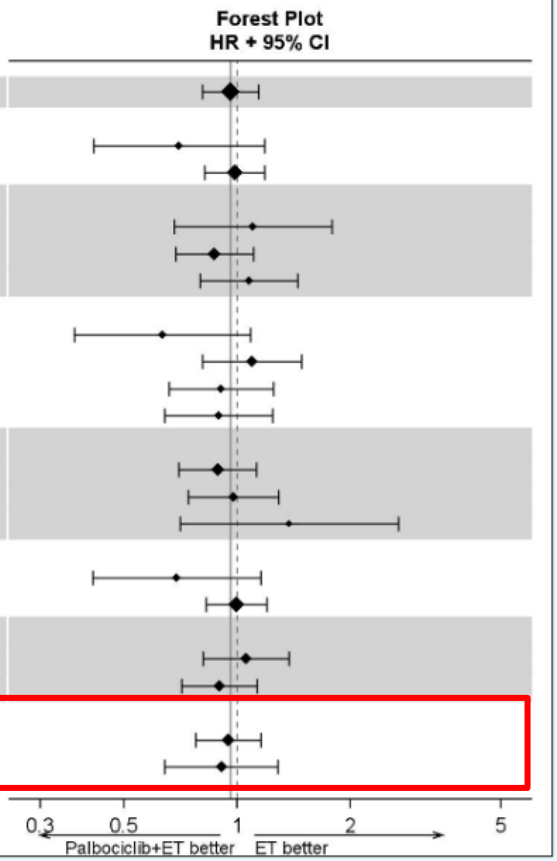
No. at risk:

P + ET	2,884	2,686	2,593	2,494	2,098	1,542	939	382	107
ET	2,877	2,651	2,560	2,481	2,102	1,548	960	393	113

Gnant M, et al. SABCS 2021. Abstract GS1-07.
Gnant M, et al. *J Clin Oncol*. 2022;40:282-293.

PALLAS: iDFS in Subgroups

Subgroup	Palbociclib+ET Events / N	ET Events / N	HR (95% CI)
All patients	253 / 2884	263 / 2877	0.96 (0.81 - 1.14)
Anatomic Staging			
I/IIA	23 / 513	36 / 519	0.70 (0.41 - 1.18)
IIB/III	230 / 2370	227 / 2358	0.98 (0.82 - 1.18)
T-Stage			
T0/T1/Tis/TX	36 / 558	31 / 501	1.10 (0.68 - 1.78)
T2	127 / 1603	149 / 1636	0.87 (0.69 - 1.10)
T3/T4	90 / 722	83 / 740	1.07 (0.80 - 1.45)
N-Stage			
N0	21 / 365	36 / 385	0.63 (0.37 - 1.08)
N1	86 / 1431	80 / 1411	1.09 (0.81 - 1.48)
N2	73 / 700	78 / 709	0.91 (0.66 - 1.25)
N3	73 / 386	69 / 372	0.89 (0.64 - 1.24)
Grading			
G1/G2	129 / 1926	150 / 1971	0.89 (0.70 - 1.12)
G3	105 / 836	97 / 769	0.98 (0.74 - 1.29)
GX	19 / 122	16 / 137	1.37 (0.71 - 2.67)
Neo/adjuvant Chemotherapy			
No	24 / 499	37 / 507	0.69 (0.41 - 1.15)
Yes	229 / 2384	226 / 2370	0.99 (0.83 - 1.20)
Age group			
<=50	116 / 1310	109 / 1304	1.05 (0.81 - 1.37)
>50	137 / 1573	154 / 1573	0.90 (0.71 - 1.13)
Clinical Risk			
high risk	194 / 1711	193 / 1673	0.95 (0.77 - 1.15)
low risk	59 / 1171	70 / 1204	0.91 (0.64 - 1.28)



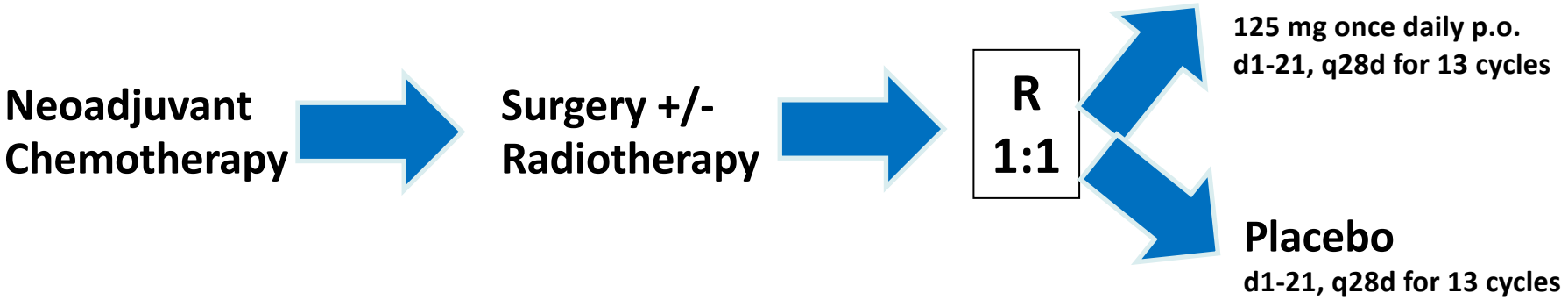
Gnant M, et al. SABCS 2021. Abstract GS1-07.
Gnant M, et al. *J Clin Oncol*. 2022;40:282-293.

PENELOPE-B: Study Design

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

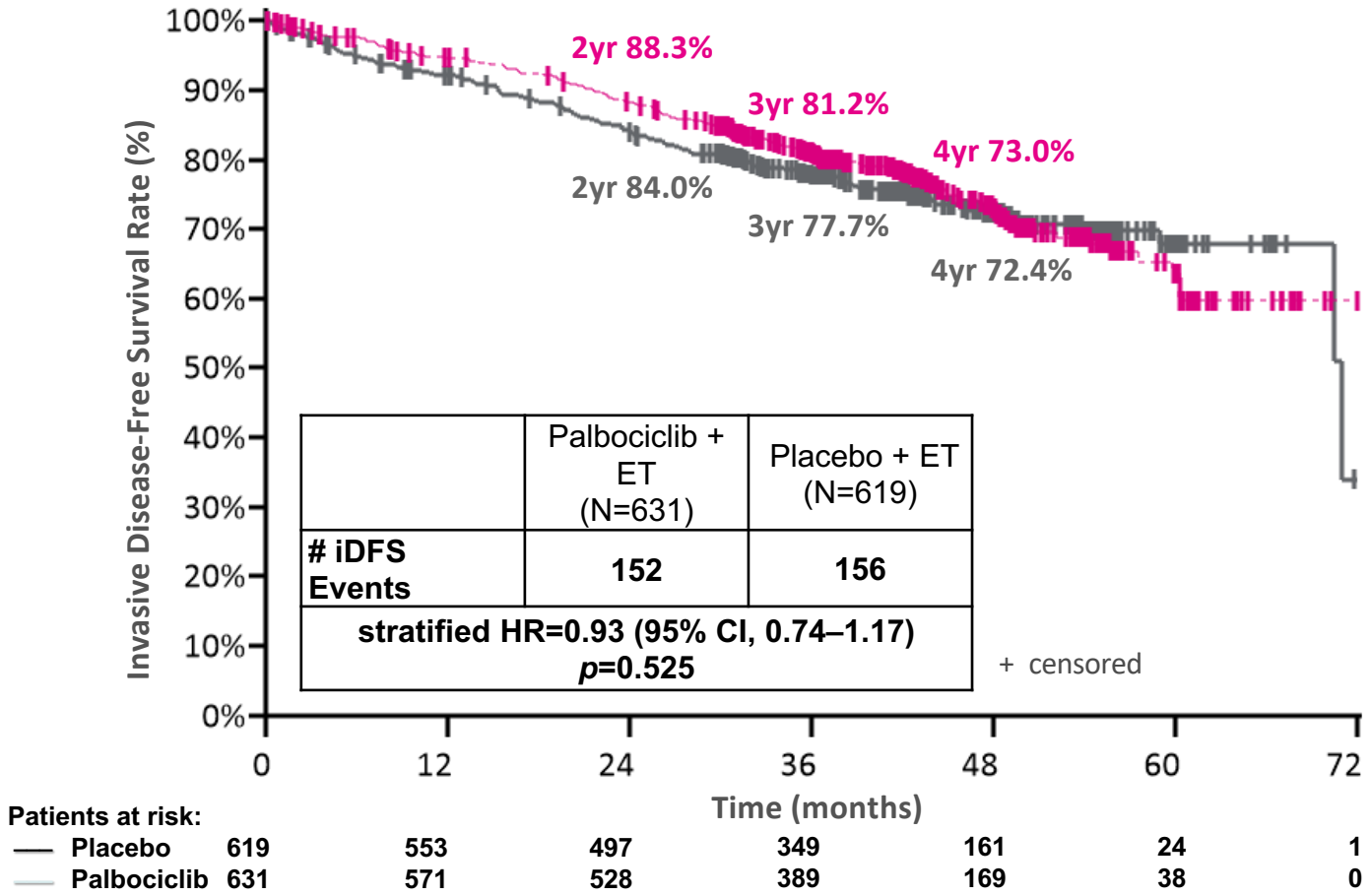


All patients will receive concomitantly ET according to local standards

Penelope-B: ClinicalTrials.gov NCT01864746

Loibl S, et al. *J Clin Oncol*. 2021;39:1518-1530.

PENELOPE-B: IDFS



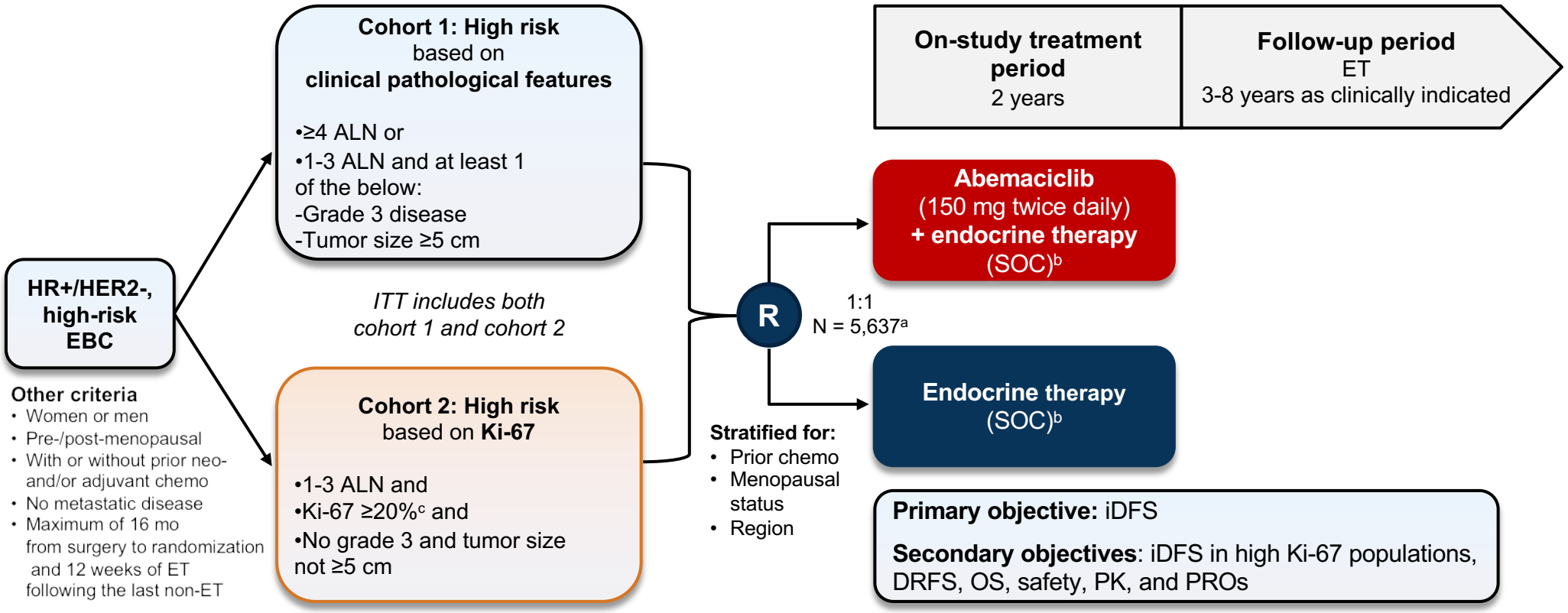
	Palbociclib + ET (N=631)	Placebo + ET (N=619)
# iDFS Events	152	156
stratified HR=0.93 (95% CI, 0.74–1.17) *p*=0.525		

Median Follow-Up 42.8 Months

* Weighted log-rank test based on the CHW method, taking into account the adaptive sample size re-estimation and group-sequential nature of the design

Loibl S, et al. *J Clin Oncol*. 2021;39:1518-1530.

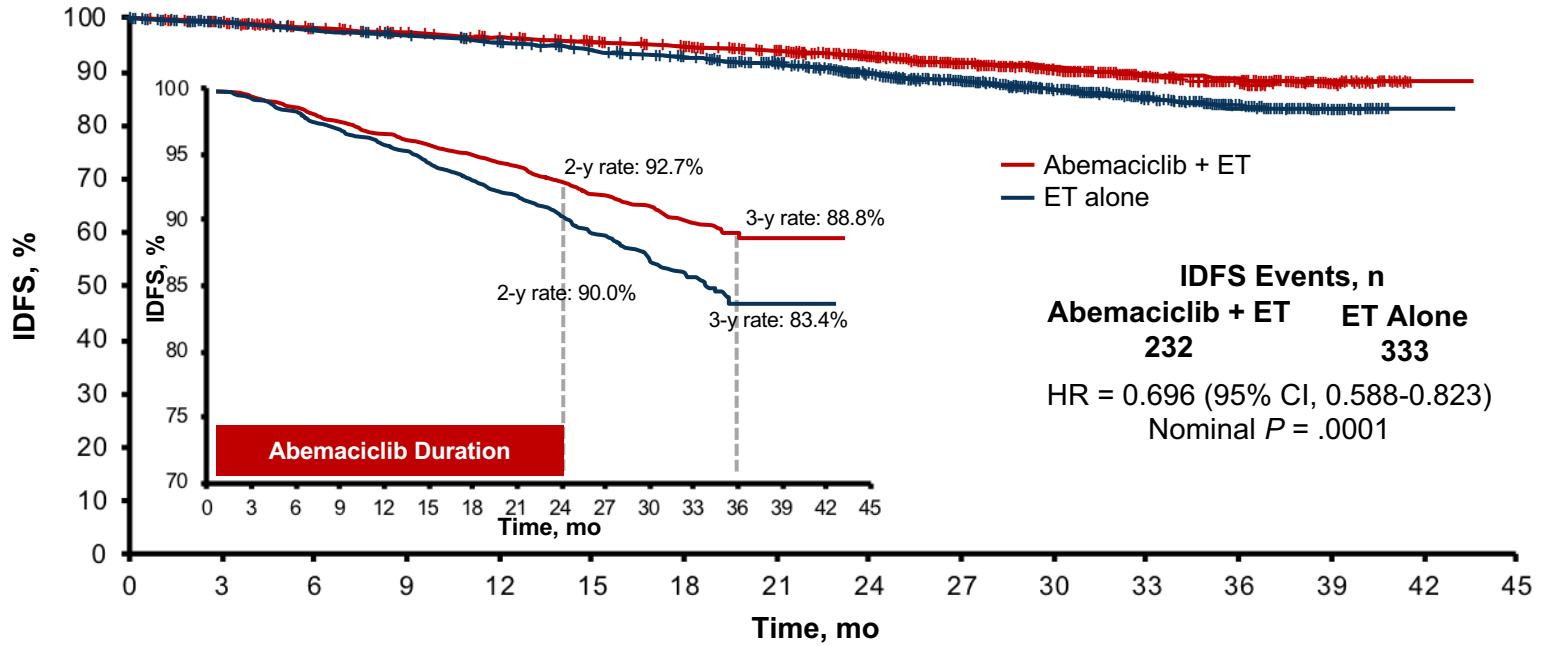
monarchE Study Design



[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 et al. ESMO 2021. Abstract VP8-2021. Harbeck N et al. *Ann Oncol*. Ann Oncol. 2021;32:1571-1581.

monarchE: iDFS Benefit Maintained With Additional Follow-Up in ITT Population



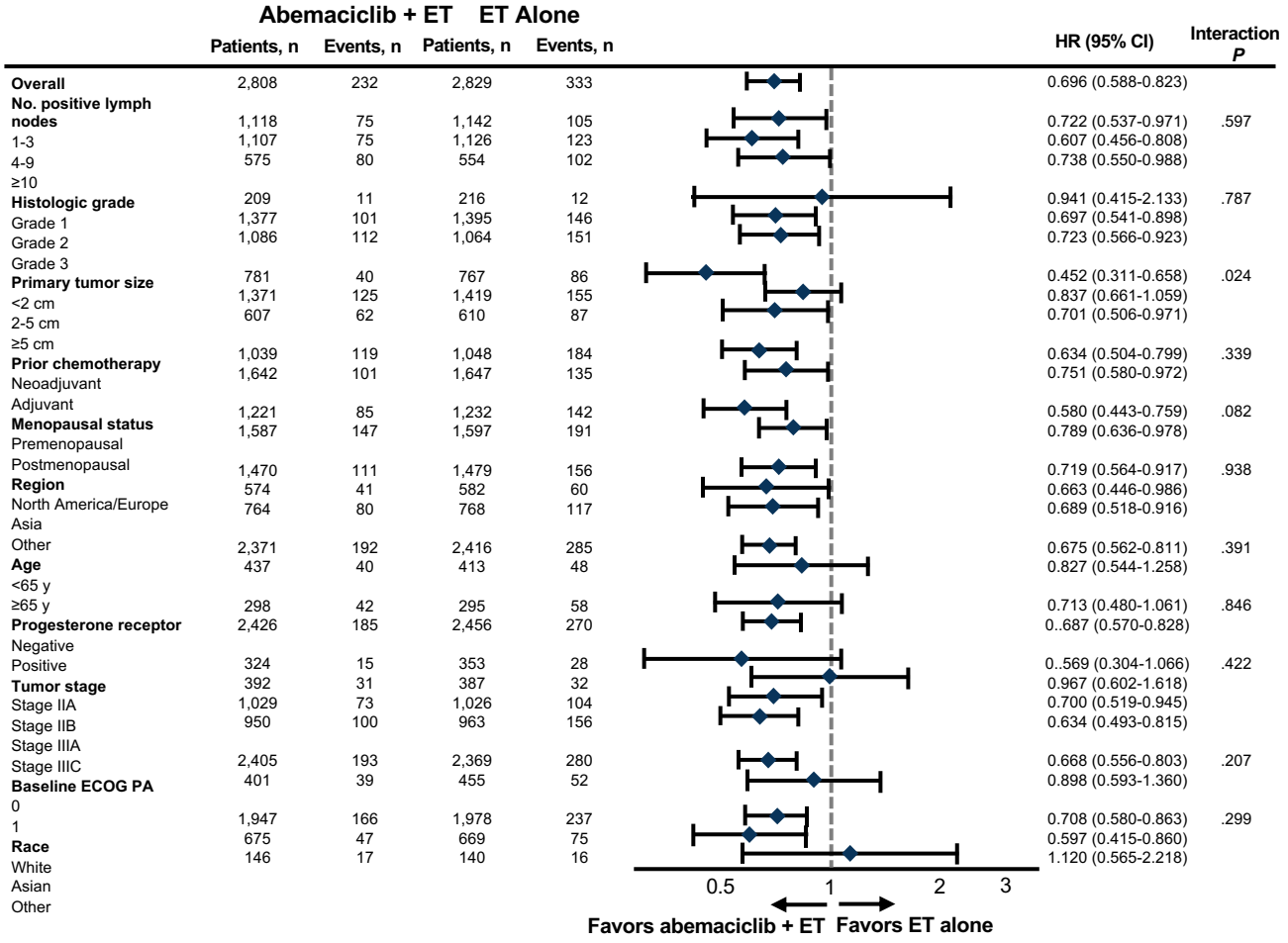
No. at Risk

Abemaciclib + ET	2,808	2,680	2,621	2,579	2,547	2,508	2,47	2,430	1,970	1,287	919	522	275	67	8	0
ET alone	2,829	2,700	2,652	2,608	2,572	2,513	2,472	2,400	1,930	1,261	906	528	281	64	10	0

30.4% reduction in the risk of developing an iDFS event
The absolute difference in iDFS rates between arms was 5.4% at 3 years

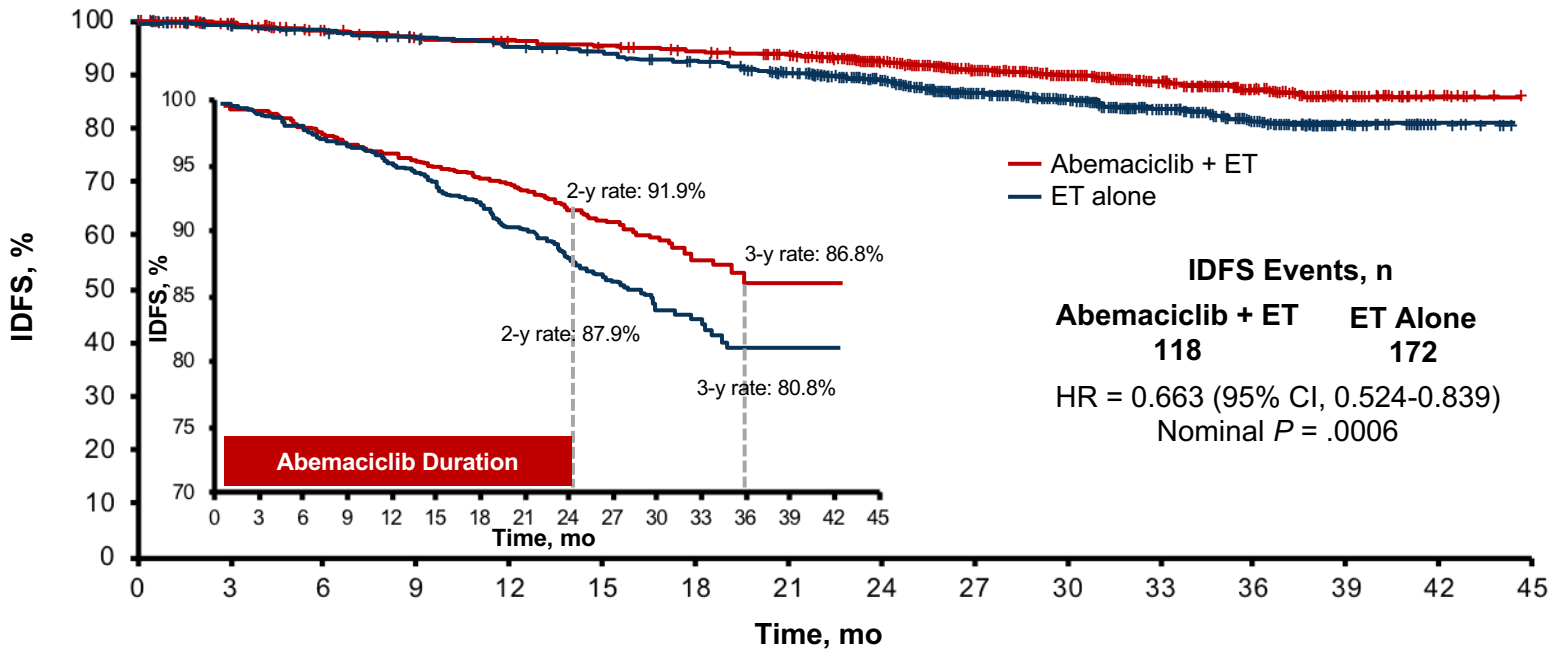
O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. Harbeck N et al. *Ann Oncol*. 2021;32:1571-1581.

monarchE: Consistent iDFS Treatment Benefit Observed in Prespecified Subgroups[1,2]



1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. 2. Harbeck N et al. *Ann Oncol*. 2021;32:1571-1581..

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 et al. ESMO 2021. Abstract VP8-2021. Harbeck N et al. *Ann Oncol.* 2021;32:1571-1581.

ASCO Recommendation Update on Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for EBC

- Based on secondary predefined analysis conducted by FDA, 2 years of abema (150 mg BID) + ET may be offered to patients with HR+, HER2-, N+, EBC with a high risk of recurrence and a Ki-67 score of ≥ 20% as determined by an FDA-approved test

- The Panel also recommends, based on analyses reported by Harbeck et al, that abema for 2 + ET for ≥ 5 years may be offered to the broader ITT of patients with resected, HR+, HER2-, N+, EBC at high risk of recurrence, defined as having ≥ 4 positive ALNs, or as having 1-3 positive ALNs and ≥ 1 of the following features: histologic grade 3 disease, tumor size ≥ 5 cm, or Ki-67 index ≥ 20%

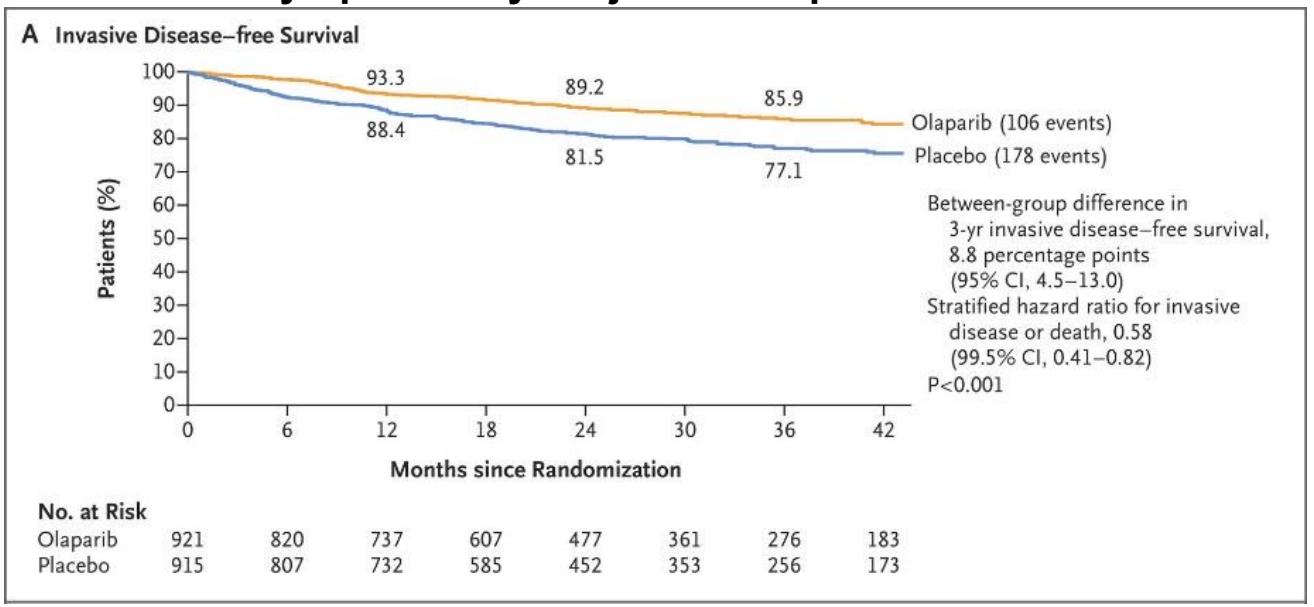
Qualifying Statements:

- Although exploratory analyses suggested similar HRs in favor of abema regardless of Ki-67 status, there were relatively few Ki-67 low tumors in monarchE
- When discussing treatment options with patients, the potential benefits (improved iDFS) should be weighed against the potential harms (treatment toxicity, financial cost)

Denduluri N, et al. *J Clin Oncol*. 2021;39:685-693.

What about patients with g*BRCA*m?

OlympiA Study: Adjuvant Olaparib vs Placebo



- **42% reduction risk of iDFS events**
- **~18% HR+, but benefit consistent with overall population**

Tutt ANJ, et al. *N Engl J Med*. 2021;384:2394-2405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