Hormonal Therapy in Breast Cancer

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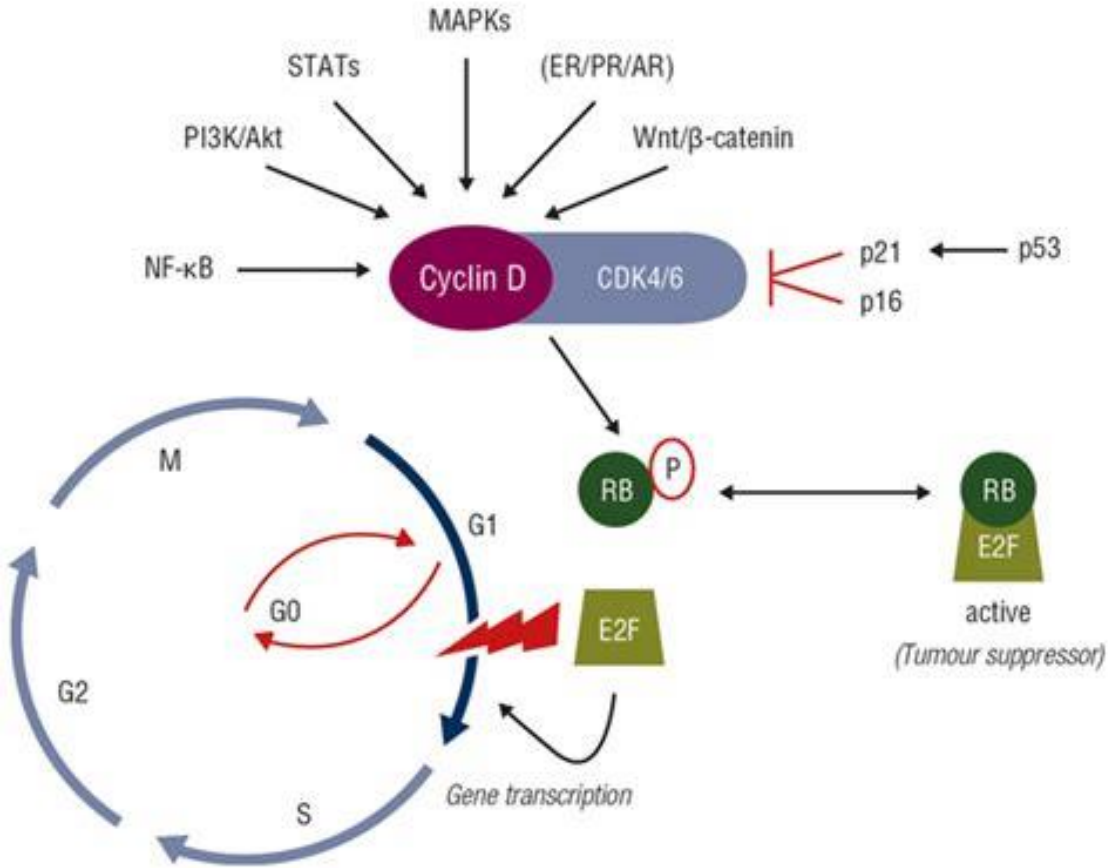
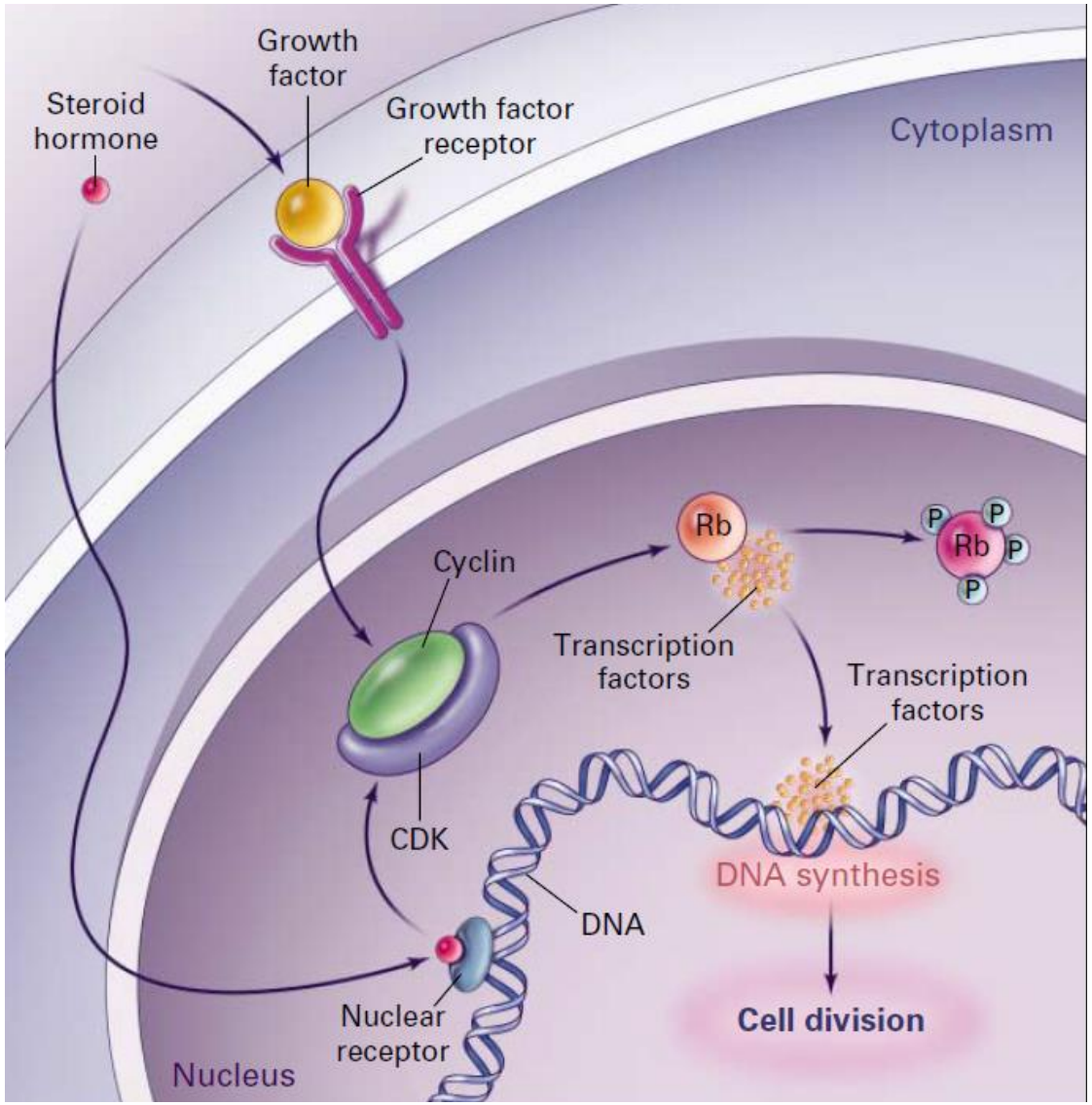
Outline

- Introduction
- Metastatic
- Adjuvant
  - RxPONDER
  - MINDACT (updates)
  - monarchE
  - PENELOPE-B
  - Ultralow risk

Metastatic ER+ Breast Cancer





N Engl J Med, Vol. 347, No. 20 November 14, 2002

CYCLIN E AND SURVIVAL IN PATIENTS WITH BREAST CANCER

KHANDAN KEYOMARSI, PH.D., SUSAN L. TUCKER, PH.D., THOMAS A. BUCHHOLZ, M.D., MATTHEW CALLISTER, M.D., YE DING, PH.D., GABRIEL N. HORTOBAGYI, M.D., ISABELLE BEDROSIAN, M.D., CHRISTOPHER KNICKERBOCKER, M.S., WENDY TOYOFUKU, B.S., MICHAEL LOWE, B.S., THADDEUS W. HERLICZEK, M.D., AND SARAH S. BACUS, PH.D.

N Engl J Med, Vol. 347, No. 20 · November 14, 2002 ·

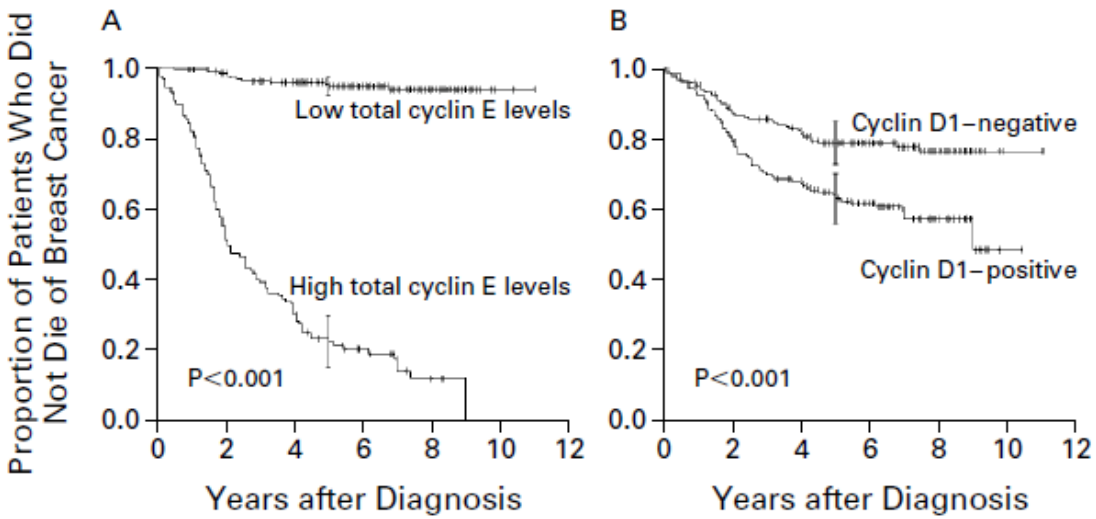


TABLE 2. INDEPENDENT FACTORS PREDICTIVE OF DEATH FROM BREAST CANCER AND DEATH FROM ANY CAUSE.*

FACTOR	DEATH FROM BREAST CANCER		DEATH FROM ANY CAUSE	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
High level of low-molecular-weight cyclin E	2.1 (1.1–4.0)	0.02	2.2 (1.2–4.2)	0.01
High total cyclin E level	13.3 (5.8–30.2)	<0.001	4.3 (2.2–8.4)	<0.001
Positive nodes	1.8 (1.2–2.8)	0.007	1.5 (1.1–2.2)	0.02
Stage IIIB–IV disease	1.7 (1.1–2.5)	0.01	1.7 (1.2–2.5)	0.004
Negative estrogen-receptor status	1.8 (1.3–2.7)	0.001	1.6 (1.1–2.2)	0.006

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens
First-Line Therapy
- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective estrogen receptors modulator (tamoxifen or toremifene)
- Steroidal aromatase inactivator (exemestane)

Preferred Regimens
Second- and Subsequent-Line Therapy
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[c]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f]
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Selective ER down-regulator (fulvestrant)
- Selective estrogen receptors modulator (tamoxifen or toremifene)

Useful in Certain Circumstances[d]
- Megestrol acetate
- Estradiol
- Abemaciclib[c,e]

HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[a] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).
[b] A single study (S0226) in patients with HR-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression and overall survival. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.
[c] If there is disease progression while on a CDK4/6 inhibitor, there are limited data to support the use of another CKD4/6 inhibitor. If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PIK3CA-containing regimen. If there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
[d] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).
[e] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.
[f] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal aromatase inhibitor).
[g] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[h] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.
[i] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab + pertuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Summary of CDK 4/6 Inhibitor Trials – NOT FOR CROSS-TRIAL COMPARISON

Study	N	ORR, %*	CBR, %	mPFS, mo (95% CI)	mPFS (HR)	P-value
First-Line Metastatic Breast Cancer						
PALOMA-1 Letrozole Letrozole + palbociclib	 81 84	 33 (39) 43 (56)	 58 81	 10.2 (5.7-12.6) 20.2 (13.8-27.5)	0.488 (0.319-0.748)	.0004
PALOMA-2 Letrozole + placebo Letrozole + palbociclib	 222 444	 35 (44) 42 (55)	 71 84	 14.5 (12.9-17.1) 24.8 (22.1-NR)	0.58 (0.46-0.72)	<.0001
MONALEESA-2 Letrozole + placebo Letrozole + ribociclib	 334 334	 28 (37) 41 (53)	 72 80	 14.7 (13.0-16.5) NR (19.3-NR)	0.556 (0.429-0.720)	<.0001
MONALEESA-7 (Pre-menopausal) Letrozole + goserelin + placebo Letrozole + goserelin + ribociclib	 337 335	 30 (36) 41 (51)	 67 80	 13.0 (11.0-16.4) 23.8 (19.2-NR)	0.553 (0.441-0.694)	<.0001
MONARCH 3 Letrozole + placebo Letrozole + abemaciclib	 165 328	 35 (44) 48 (59)	 69 79	 14.7 NR	0.543 (0.409-0.723)	<.0001
Second-Line Metastatic Breast Cancer						
BOLERO-2 Exemestane + placebo Exemestane + everolimus	 239 485	 9.4 0.4	 26.4† 51.3	 2.8 6.9	0.43 (0.35-0.54)	<.001
PALOMA-3 Fulvestrant + palbociclib Fulvestrant + placebo	 347 174	 10.4 6.3	 34.0 19.0	 9.2 (7.5-NR) 3.8 (3.5-5.5)	0.422 (0.318-0.560)	<.0001
MONARCH 2 Fulvestrant + abemaciclib Fulvestrant + placebo	 446 223	 35 (48) 16 (21)	 73 52	 16.4 9.3	0.553 (0.45-0.68)	<.0001
MONALEESA-3 **(1st/2nd Line)** Fulvestrant + ribociclib Fulvestrant + placebo	 484 242	 32.4 (40.9) 21.5 (28.7)	 69.4 59.7	 20.5 (18.5-23.5) 12.8 (10.9-16.3)	0.593 (0.480-0.732)	<.0001
Refractory Metastatic Breast Cancer						
MONARCH 1 (Phase II) Abemaciclib	132	(20)	42	6.0	N/A	N/A

Adjuvant therapy for ER+ breast cancer

Introduction

- Hormone receptor positive (HR+)/human epidermal growth factor receptor-2 negative (Her2-) tumors represent approximately 70% of all early breast cancers in the United States.
- Recent attempts have been made to better classify this heterogeneous group of cancers by genomic testing in order to personalize neo(adjuvant) treatments.
- Goal: de-escalation of therapy for lower-risk tumors and escalation for higher-risk tumors.

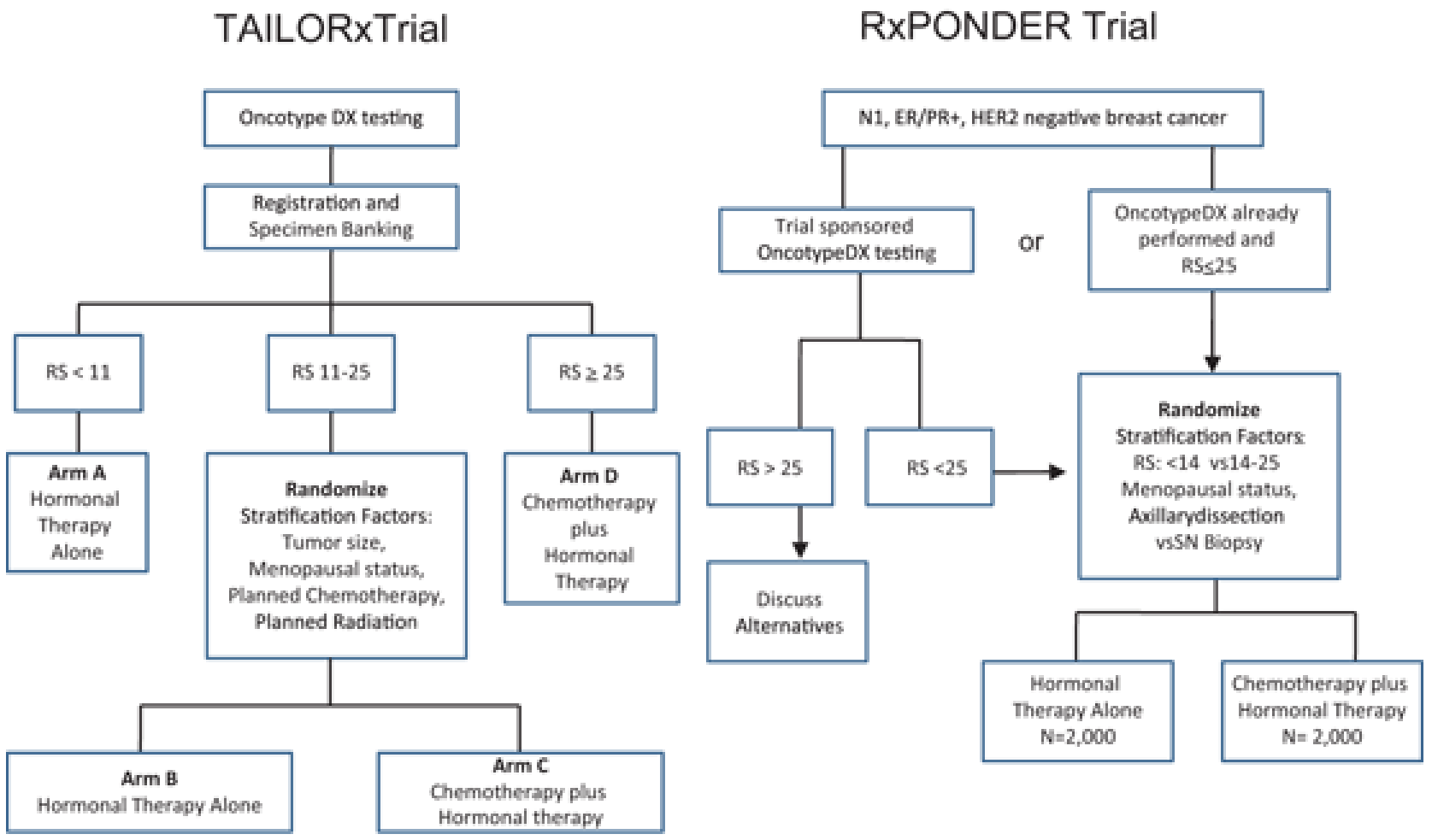
1. Anderson WF. Breast Cancer Res Treat. 2002 Nov;76(1):27-36.

RxPONDER: Background

- TAILORx: phase III randomized trial assessed safety of omitting chemotherapy in N0 pts with intermediate-risk recurrence score (RS, 11-25) by Oncotype Dx [1].
- HR+/Her2- cases only.
- Subjects randomized to either chemotherapy (CT) followed by endocrine therapy (ET) or ET alone.
- Findings: For women >50 years of age- no IDFS benefit of CT in intermediate risk RS population; for women ≤50, modest CT benefit noted for 16-25.

1. Sparano JA, et al. N Engl J Med 2018; 379:111-121.

Schema


TAILORxTrial
Oncotype DX testing
Registration and Specimen Banking
RS < 11
RS 11-25
RS ≥ 25
Arm A Hormonal Therapy Alone
Randomize Stratification Factors: Tumor size, Menopausal status, Planned Chemotherapy, Planned Radiation
Arm D Chemotherapy plus Hormonal Therapy
Arm B Hormonal Therapy Alone
Arm C Chemotherapy plus Hormonal therapy
RxPONDER Trial
N1, ER/PR+, HER2 negative breast cancer
Trial sponsored OncotypeDX testing
or
OncotypeDX already performed and RS≤25
RS > 25
RS <25
Discuss Alternatives
Randomize Stratification Factors: RS: <14 vs14-25 Menopausal status, Axillarydissection vsSN Biopsy
Hormonal Therapy Alone N=2,000
Chemotherapy plus Hormonal Therapy N= 2,000

RxPONDER

- Phase III randomized trial including 5015 subjects with HR+/Her2- breast cancer with 1-3+ LN's and RS 0-25 [1].
- ET+/- chemo.

Primary Objective

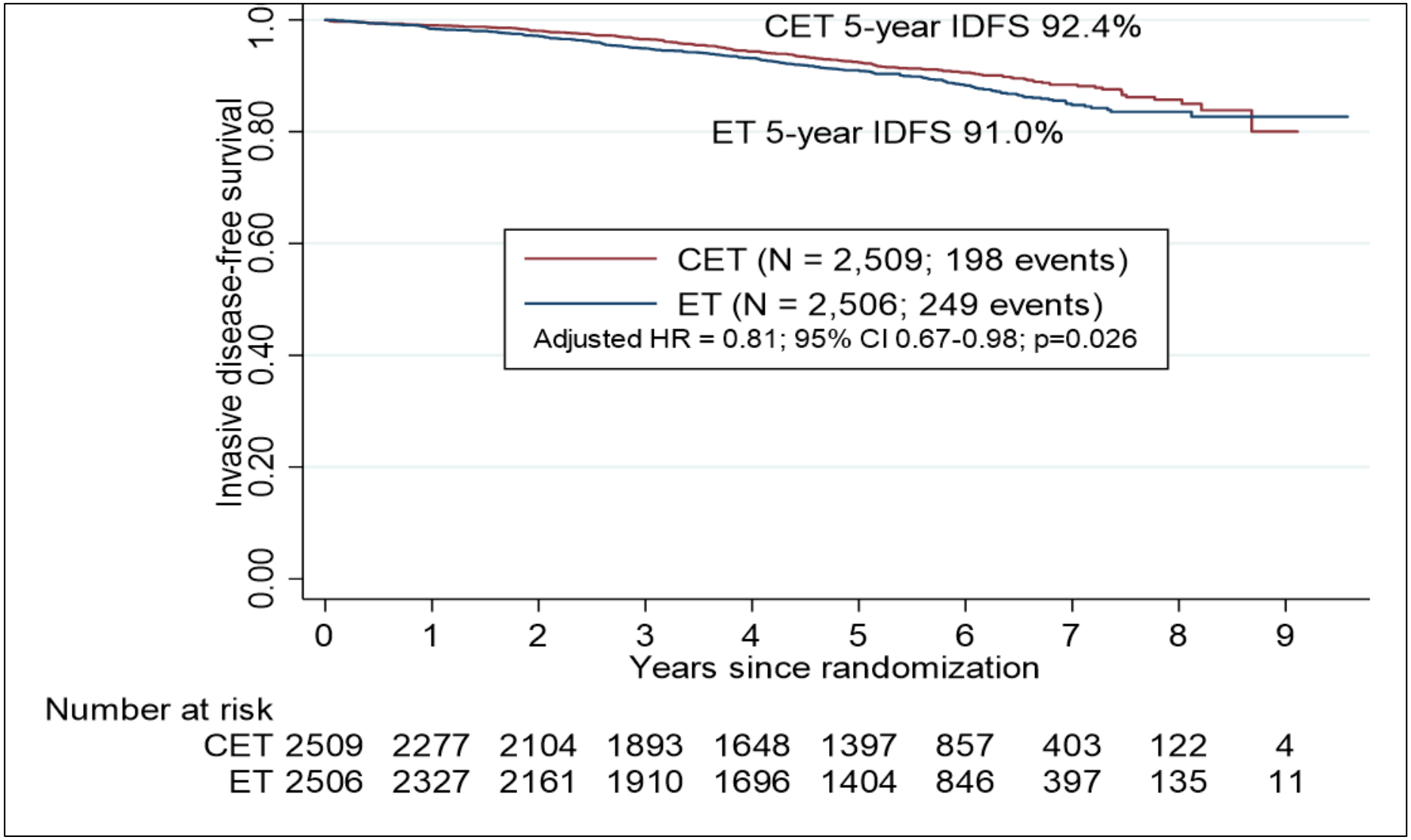
To assess the effect of chemotherapy on invasive disease-free survival (IDFS) in pts with 1-3 LN+ breast cancer and a RS < 25 and assess whether the effect depends on the RS.

Primary Hypothesis

Chemotherapy benefit will increase as the RS increases from 0 to 25 in an Intent-to-Treat (ITT) analysis.

1. Kalinsky K, et al. GS3-00. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). Oral Presentation at: The San Antonio Breast Cancer Symposium; December 10, 2020.

RxPONDER: IDFS by treatment arm (ITT population)



RxPONDER (cont.)

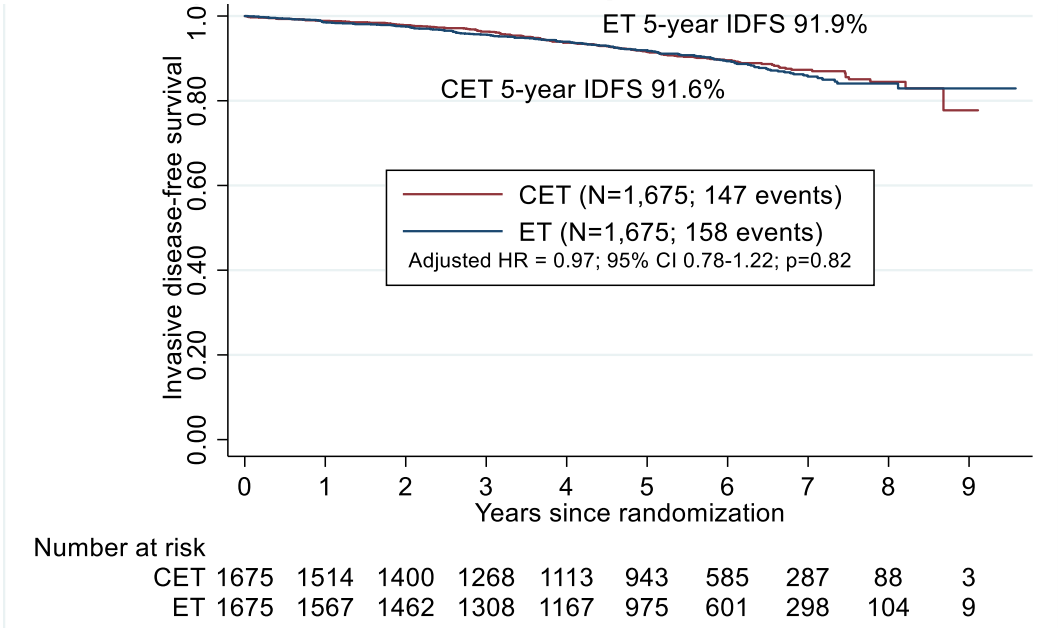
- Upon pre-specified analysis, CT benefit was noted dependent on menopausal status.

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.53	<0.001	0.37 – 0.76
RS (per unit change)	1.06	<0.001	1.04 – 1.08
Menopausal status	0.79	0.08	0.60-1.03
Chemo x Menopause Interaction	1.79	0.008	1.17-2.74

RxPONDER (cont.)

IDFS Stratified by Menopausal Status

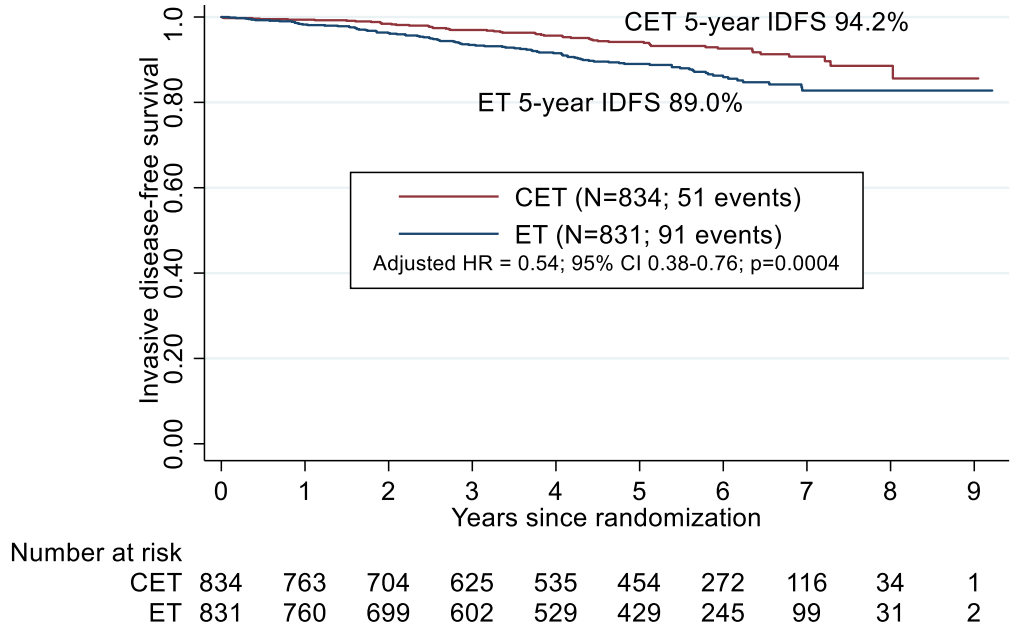
- Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

- 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%)

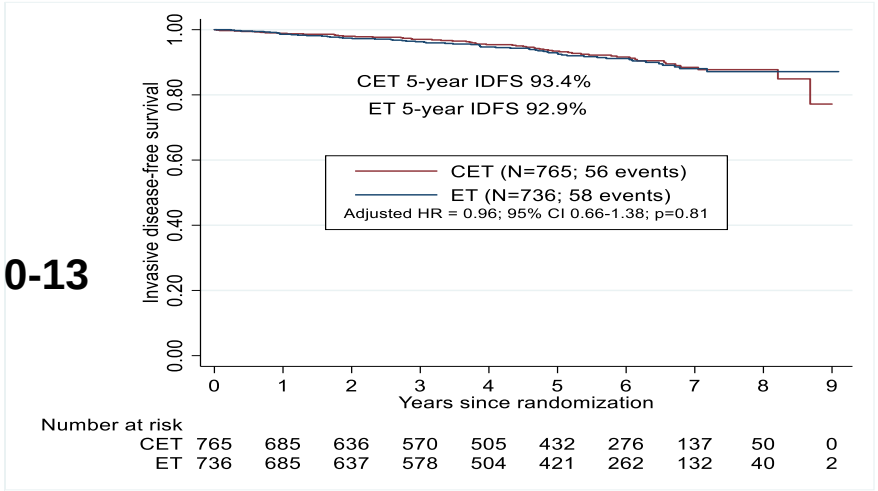
Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

RxPONDER (cont.)

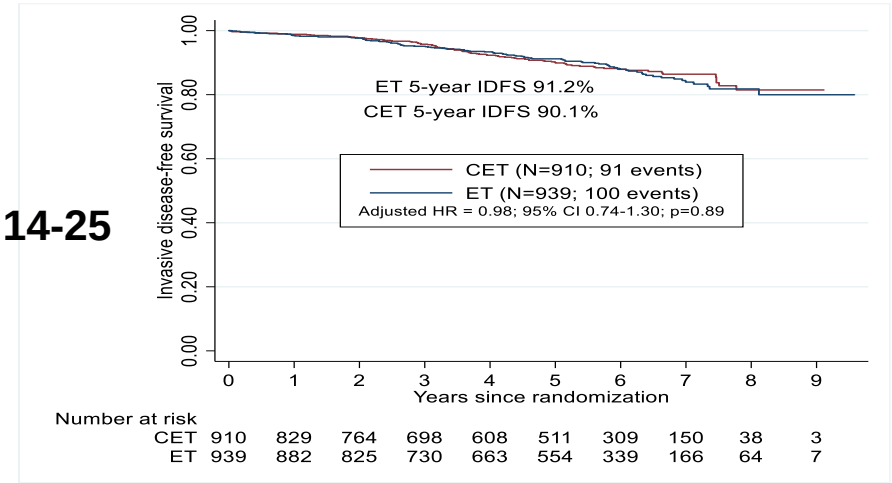
IDFS Stratified by Recurrence Score and Menopausal Status

- Postmenopausal

RS 0-13

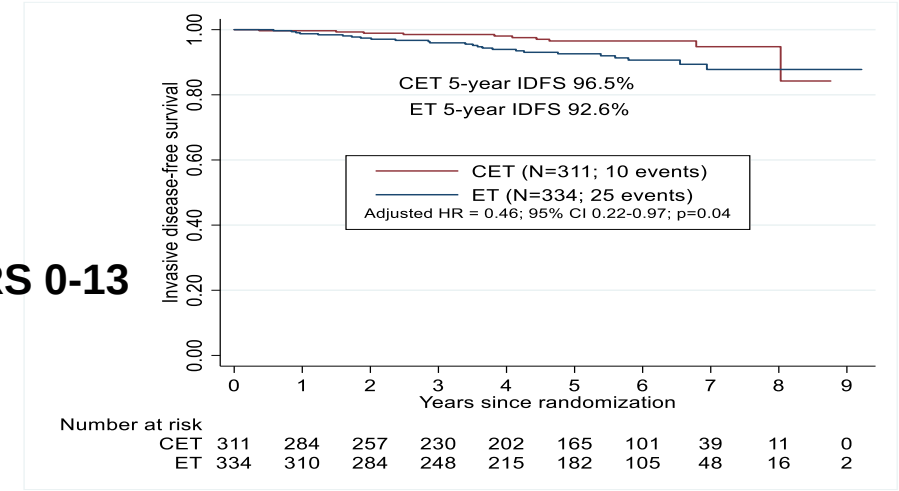


RS 14-25

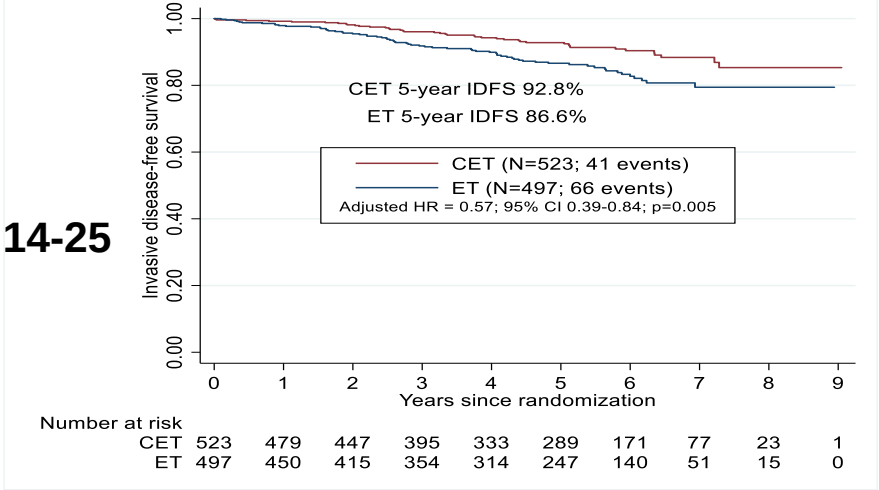


- Premenopausal

RS 0-13



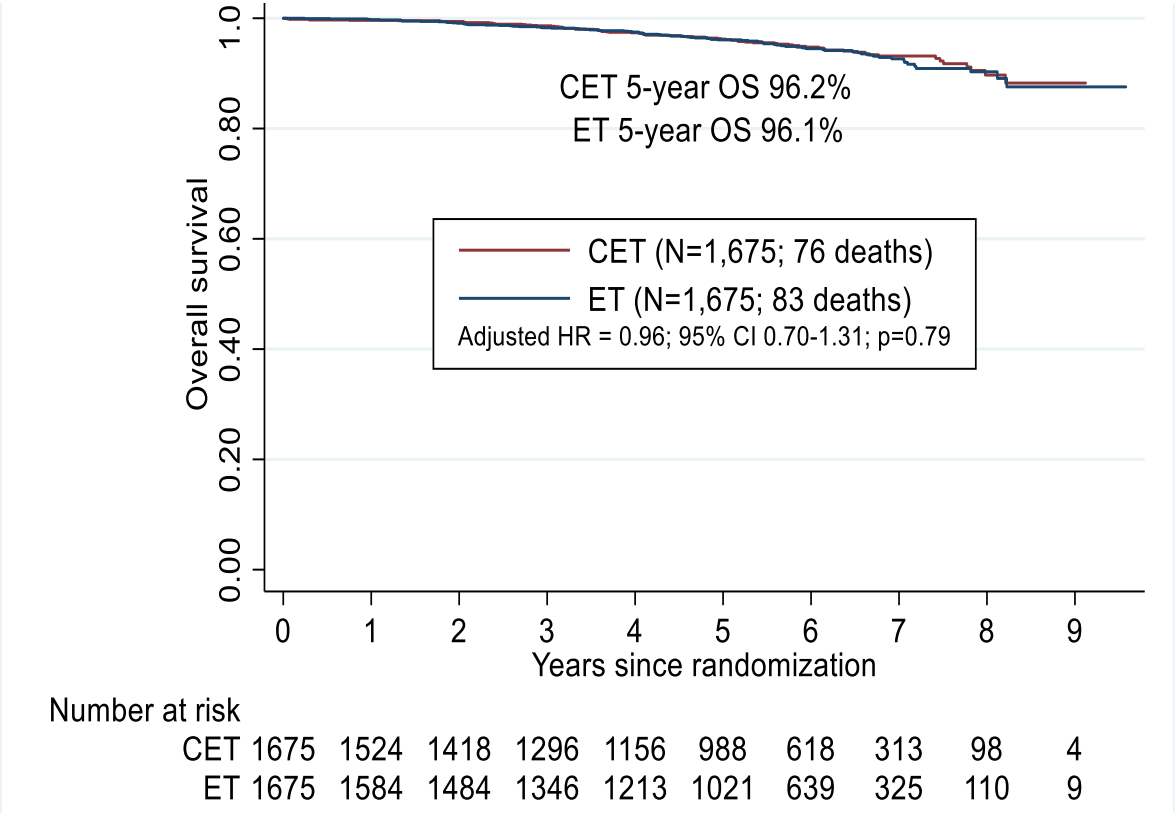
RS 14-25



RxPONDER (cont.)

Overall Survival by Menopausal Status

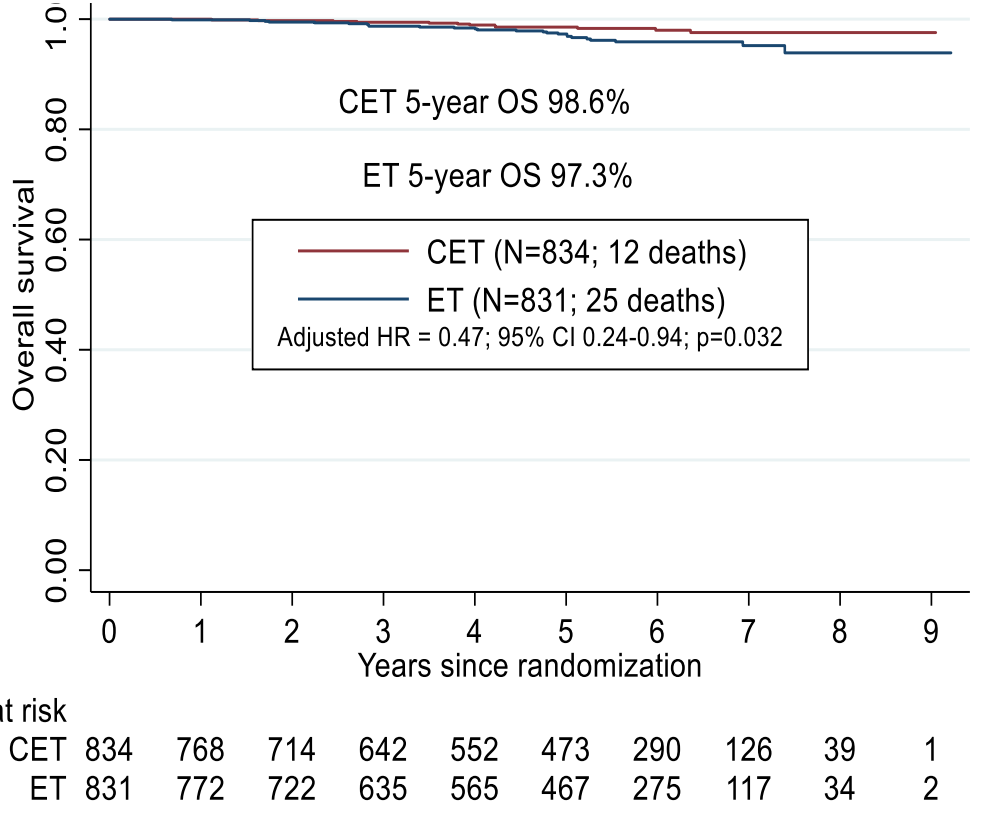
Postmenopausal



Number at risk

CET	1675	1524	1418	1296	1156	988	618	313	98	4
ET	1675	1584	1484	1346	1213	1021	639	325	110	9

Premenopausal



Number at risk

CET	834	768	714	642	552	473	290	126	39	1
ET	831	772	722	635	565	467	275	117	34	2

Goserelin Versus Cyclophosphamide, Methotrexate, and Fluorouracil as Adjuvant Therapy in Premenopausal Patients With Node-Positive Breast Cancer: The Zoladex Early Breast Cancer Research Association Study

By W. Jonat, M. Kaufmann, W. Sauerbrei, R. Blamey, J. Cuzick, M. Namer, I. Fogelman, J.C. de Haes, A. de Matteis, A. Stewart, W. Eiermann, I. Szakolczai, M. Palmer, M. Schumacher, M. Geberth, and B. Lisboa

Purpose: **Current adjuvant therapies have improved survival for premenopausal patients with breast cancer but may have short-term toxic effects and long-term effects associated with premature menopause.**

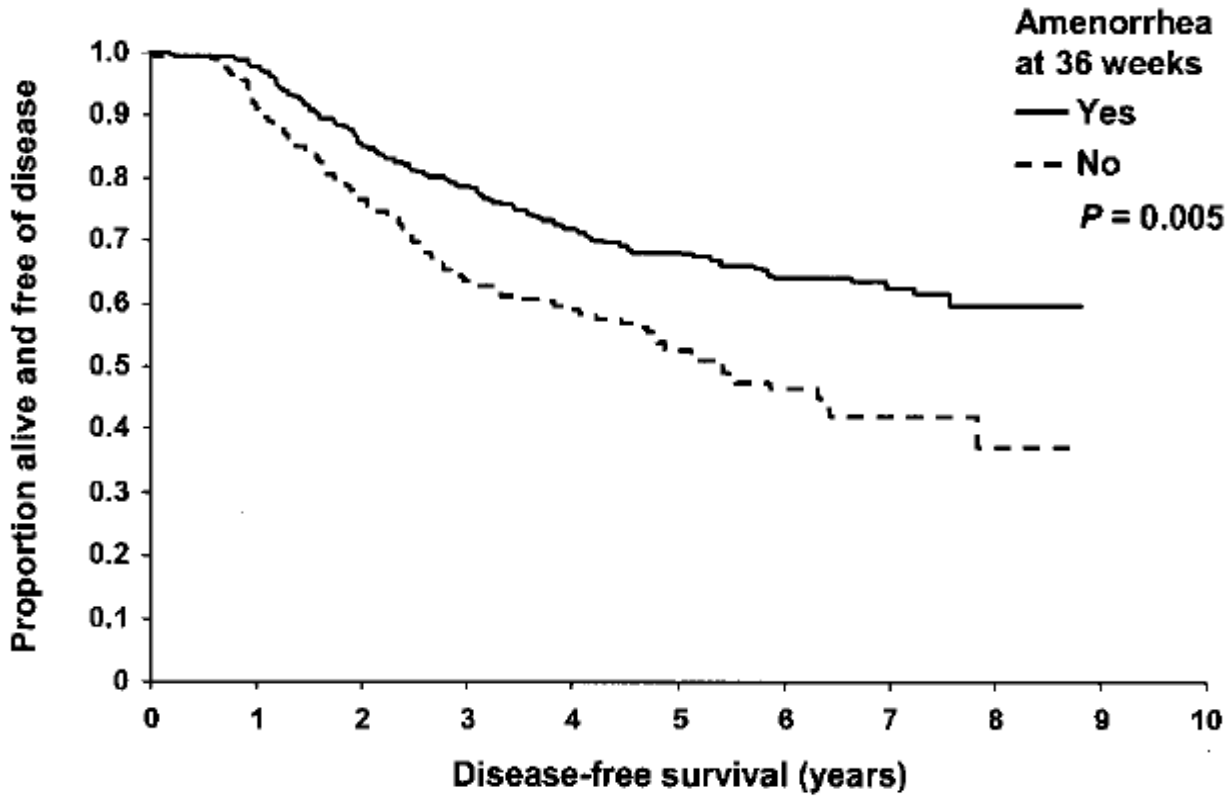
Patients and Methods: **The Zoladex Early Breast Cancer Research Association study assessed the efficacy and tolerability of goserelin (3.6 mg every 28 days for 2 years; n = 817) versus cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy (six 28-day cycles; n = 823) for adjuvant treatment in premenopausal patients with node-positive breast cancer.**

Results: **Analysis was performed when 684 events had been achieved, and the median follow-up was 6 years. A significant interaction between treatment and estrogen receptor (ER) status was found (*P* = .0016). In ER-positive patients (approximately 74%), goserelin was equivalent to CMF for disease-free survival (DFS) (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.84 to 1.20). In ER-negative patients, goserelin was inferior to CMF for DFS (HR, 1.76; 95% CI, 1.27 to 2.44). Amenorrhea occurred in more than 95% of goserelin patients by 6 months versus 58.6% of CMF patients. Menses returned in most goserelin patients after therapy stopped, whereas amenorrhea was generally permanent in CMF patients (22.6% *v* 76.9% amenorrheic at 3 years). Chemotherapy-related side effects such as nausea/vomiting, alopecia, and infection were higher with CMF than with goserelin during CMF treatment. Side effects related to estrogen suppression were initially higher with goserelin, but when goserelin treatment stopped, reduced to a level below that observed in the CMF group.**

Conclusion: **Goserelin offers an effective, well-tolerated alternative to CMF in premenopausal patients with ER-positive and node-positive early breast cancer.**

J Clin Oncol 20:4628-4635.

DFS in CMF-treated patients according to menstrual status at 36 weeks.



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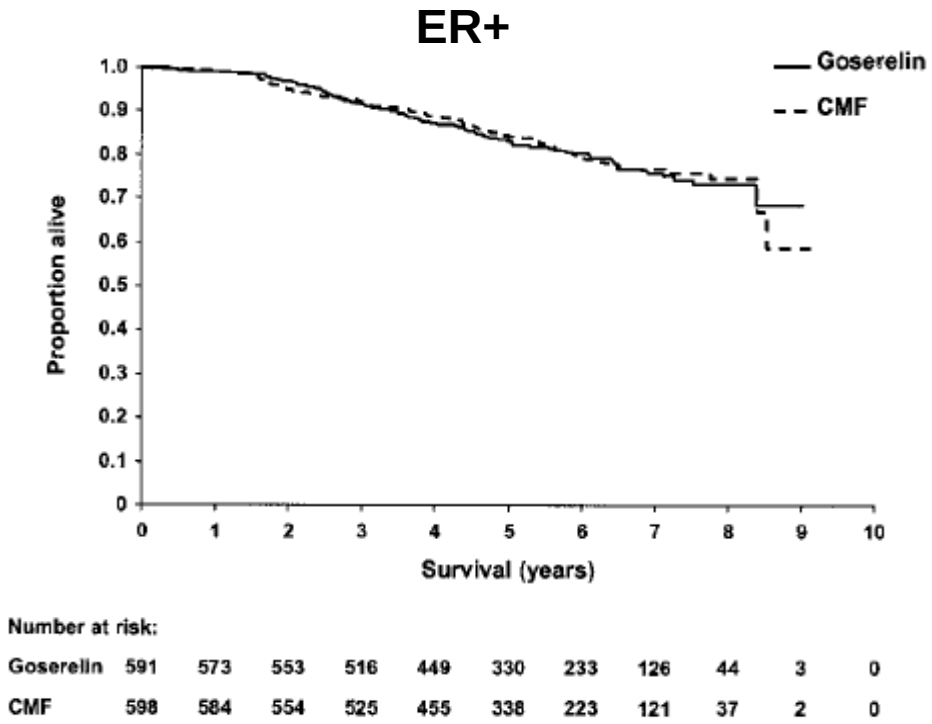
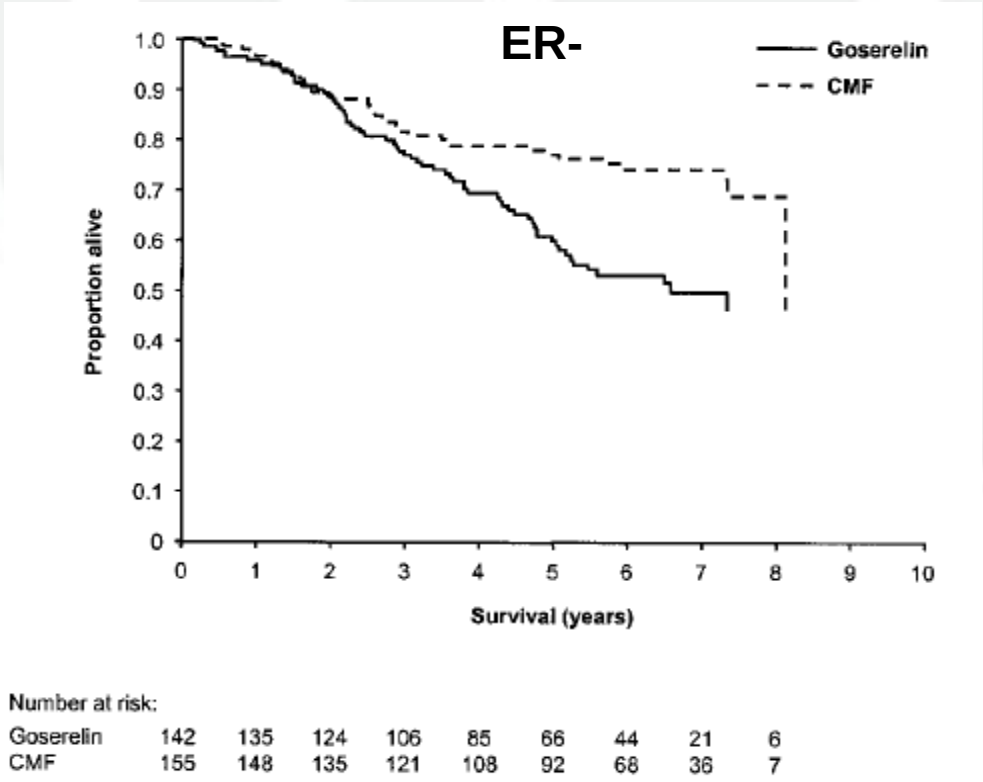
Jonat, W. et al. J Clin Oncol 20:4628-4635

OS by ER status in Zoladex trial





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Jonat, W. et al. J Clin Oncol 20:4628-4635

RxPONDER: Conclusions

- For RS 0-25, postmenopausal patients derive NO BENEFIT from the addition of CT to ET.
- For RS 0-25, premenopausal patients appear to derive some IDFS benefit (~5%) and OS (~1.3%) from the addition of CT to ET.
- It is unknown whether the benefits are due to premature ovarian failure (but likely given Zebra trial results).

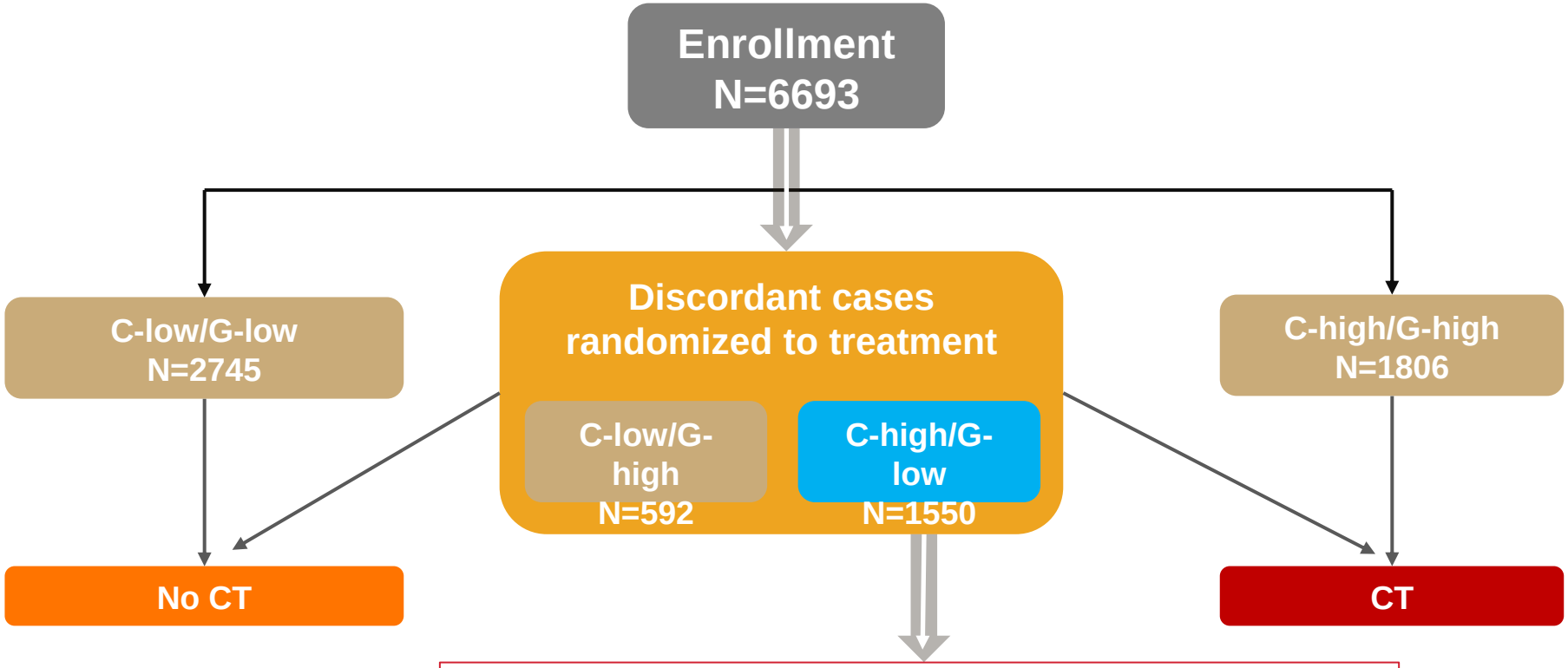
MINDACT

- MINDACT: phase III randomized de-escalation trial utilizing the 70-gene Mammaprint assay.
  - Hypothesis: clinical high/genomically low-risk tumors do not benefit from receipt of chemotherapy [1].
- 6,693 subjects with HR+/Her2- breast cancer were enrolled (up to 3 +LN's), and "clinical risk" and "genomic risk" were determined.
- C-low/G-low: ET only; C-high/G-high: CT followed by ET.
- C-high/G-low or C-low/G-high were randomized to receive CT + ET versus ET alone.

1. Cardoso F, et al. N Engl J Med 2016; 375:717-729.

MINDACT Study Design

The purpose of MINDACT is de-escalation, to identify **clinically high risk patients who DO NOT benefit from chemotherapy**



70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age

Martine Piccart, Laura J van 't Veer*, Coralie Poncet*, Josephine M N Lopes Cardozo, Suzette Delaloge, Jean-Yves Pierga, Peter Vuylsteke, Etienne Brain, Suzan Vrijaldenhoven, Peter A Neijenhuis, Sylvian Causeret, Tineke J Smilde, Giuseppe Viale, Annuska M Glas, Mauro Delorenzi, Christos Sotiriou, Isabel T Rubio, Sherko Kümmel, Gabriele Zoppoli, Alastair M Thompson, Erika Matos, Khalil Zaman, Florentine Hilbers, Debora Fumagalli, Peter Ravdin, Susan Knox, Konstantinos Tryfonidis, Aleksandra Peric, Bart Meulemans, Jan Bogaerts, Fatima Cardoso†, Emiel J T Rutgers†*

Lancet Oncol 2021; 22: 476–88

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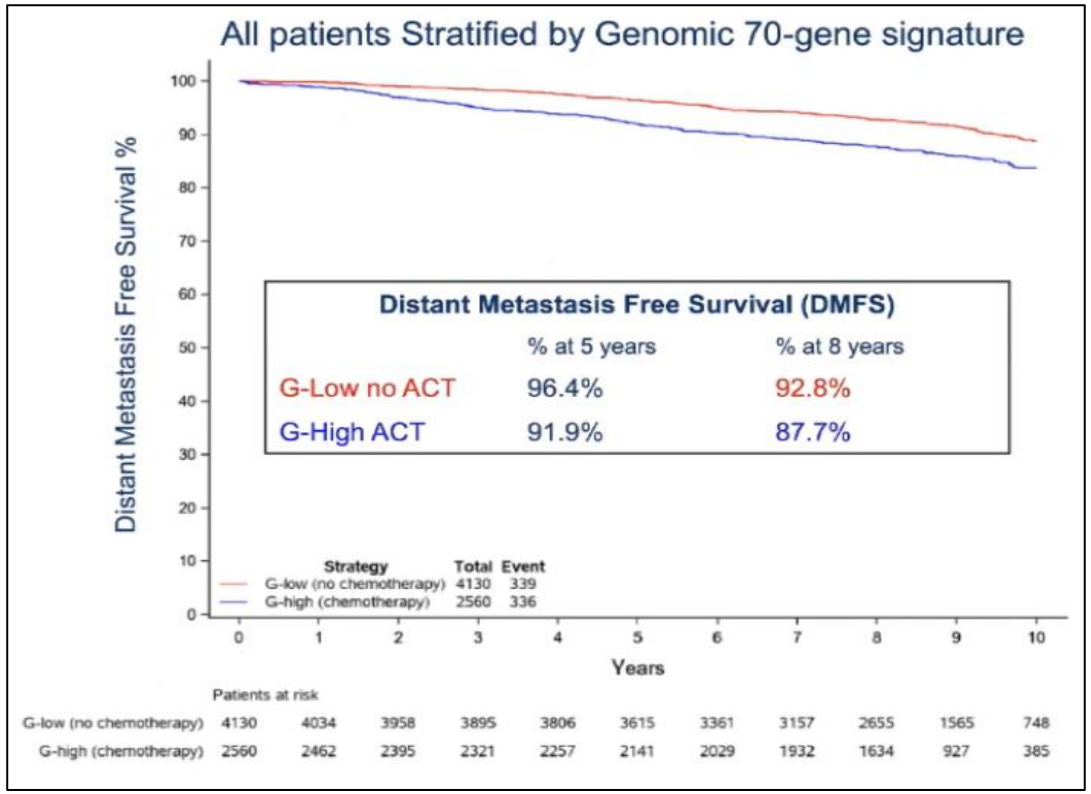
Summary

Background The MINDACT trial showed excellent 5-year distant metastasis-free survival of 94·7% (95% CI 92·5–96·2) in patients with breast cancer of high clinical and low genomic risk who did not receive chemotherapy. We present long-term follow-up results together with an exploratory analysis by age.

MINDACT: updated results

- median follow-up of 8.7 years
- 6,693 patients

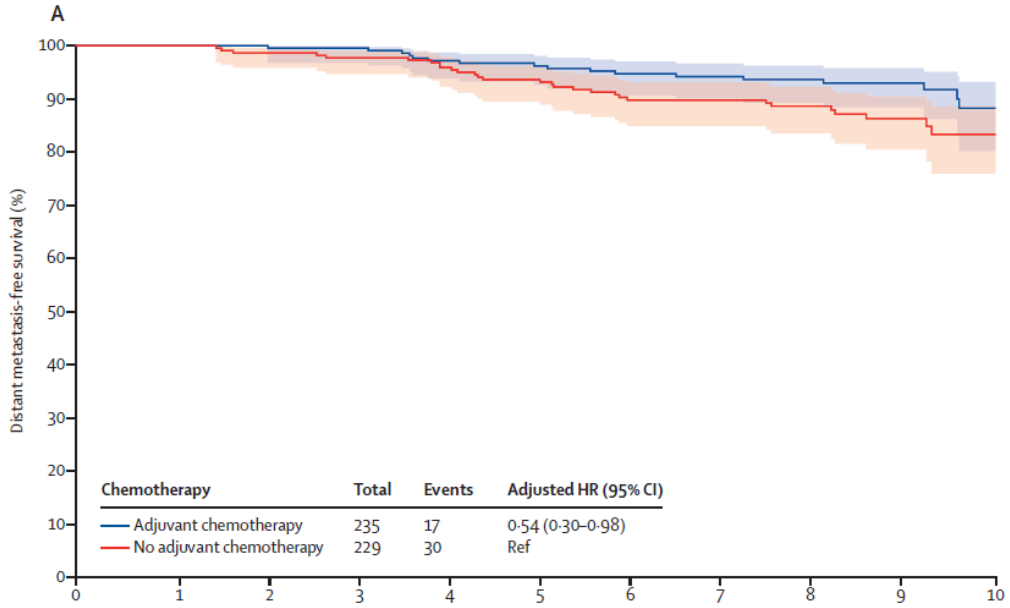


	Adjuvant chemotherapy*		No adjuvant chemotherapy*		Absolute difference, percentage points (SE; 95% CI) at 8 years	Hazard ratio (95% CI)†
	Events/patients	Survival estimate at 8 years, % (95% CI)	Events/patients	Survival estimate at 8 years, % (95% CI)		
High clinical risk and low genomic risk						
Distant metastasis-free survival	60/749	92·0% (89·6 to 93·8)	90/748	89·4% (86·8 to 91·5)	2·6 (1·6; −0·5 to 5·7)	0·66 (0·48 to 0·92)
Distant metastasis-free interval	50/749	93·1% (90·9 to 94·8)	75/748	90·7% (88·2 to 92·7)	2·4 (1·5; −0·5 to 5·4)	0·66 (0·46 to 0·95)
Disease-free survival	110/749	86·4% (83·5 to 88·8)	138/748	82·9% (79·8 to 85·6)	3·5 (2·0; −0·4 to 7·4)	0·79 (0·62 to 1·02)
Overall survival	37/749	95·7% (93·9 to 97·0)	53/748	94·3% (92·2 to 95·8)	1·4 (1·2; −0·9 to 3·8)	0·69 (0·45 to 1·05)

Piccard, M. et al. Lancet Oncol 2021; 22: 476–88

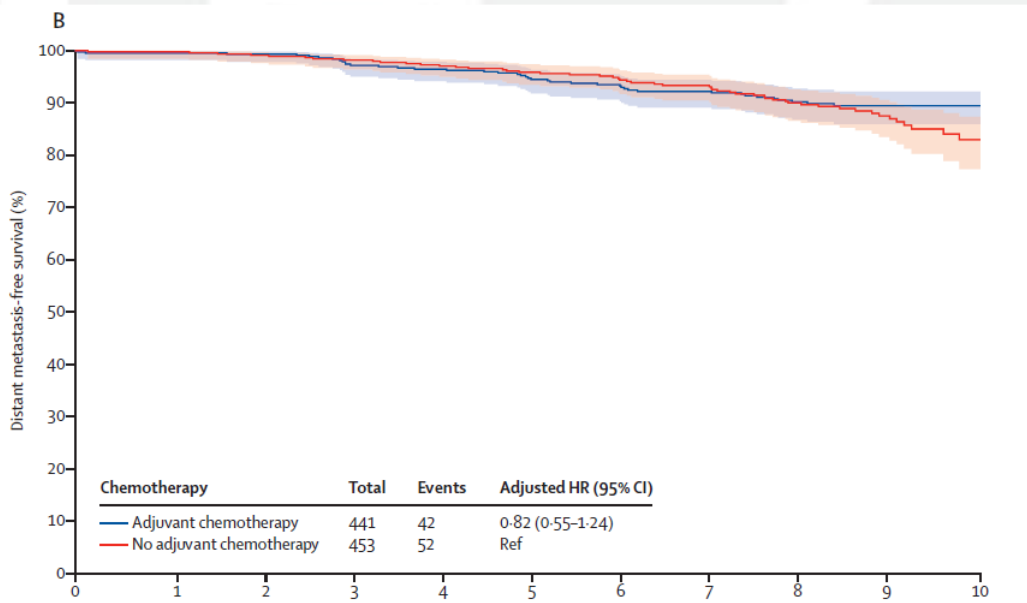
MINDACT: DMFS according to randomized treatment strategy in clinical high, genomic low-risk, HR+ HER2-negative subgroup, by age

Age ≤50



Number at risk (number censored)											
Adjuvant chemotherapy	235 (0)	226 (9)	221 (14)	215 (19)	205 (24)	194 (33)	187 (37)	174 (49)	148 (74)	88 (133)	36 (182)
No adjuvant chemotherapy	229 (0)	225 (4)	219 (7)	215 (9)	211 (9)	201 (14)	181 (26)	173 (34)	132 (73)	72 (130)	28 (172)

Age >50



Number at risk (number censored)											
Adjuvant chemotherapy	441 (0)	424 (15)	417 (21)	407 (23)	398 (28)	386 (34)	363 (51)	344 (65)	286 (116)	149 (251)	64 (336)
No adjuvant chemotherapy	453 (0)	443 (9)	434 (15)	430 (15)	420 (21)	399 (36)	376 (55)	353 (72)	283 (130)	162 (244)	68 (333)

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MINDACT - Conclusions:

- Both C-low and G-low tumors appears to have an overall excellent prognosis, especially C-low/G-low (DMFS 94.7% with ET alone).
- Stratification of C-low tumors into G-high versus G-low indicates a 3.6% decrease of DMFS for those of high-genomic risk.
- Among C-low/G-high subjects randomized to CT or not, ~1.5% DMFS benefit seen (underpowered).

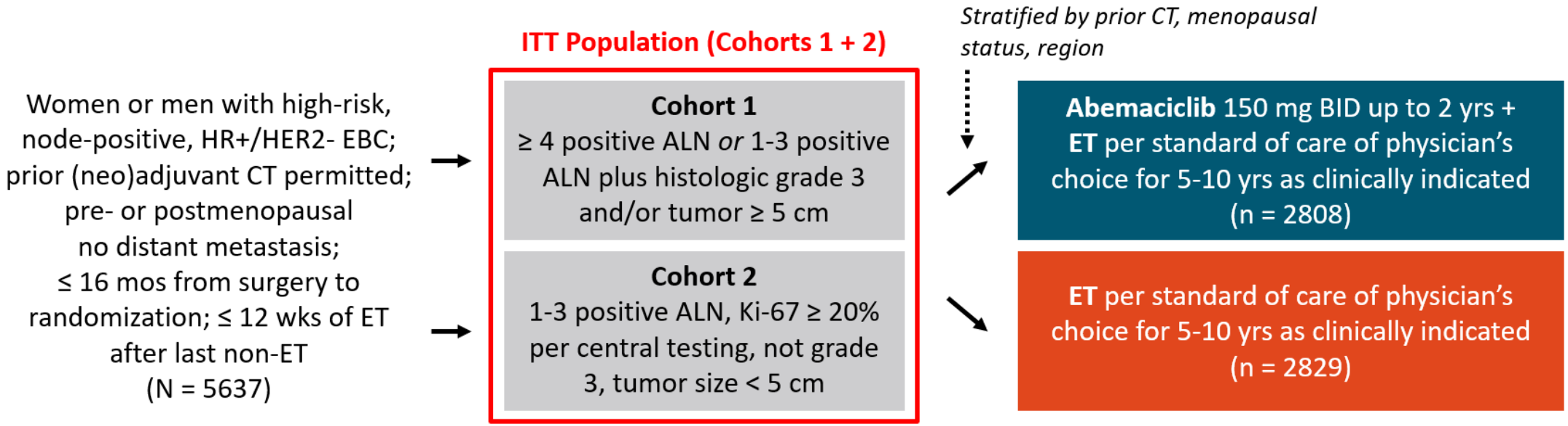
monarchE

- Use of cyclin-dependent kinases 4/6 inhibitors (CDK4/6i) has greatly improved clinical outcomes in advanced/metastatic HR+/Her2- BC.
- Results of CDK4/6i as adjuvant therapy have been mixed [1].
- monarchE was a phase III, randomized, trial assessing the potential effect of abemaciclib in the adjuvant setting.
- Abemaciclib is currently approved in combination with ET in the advanced/metastatic setting [2-3].

1. *Mayer EL, et al. Lancet Oncol. 2021 Feb;22(2):212-222.*
2. *Sledge GW, et al. J Clin Oncol. 2017 Sep 1;35(25):2875-2884.*
3. *Goetz MP, et al. J Clin Oncol. 2017 Nov 10;35(32):3638-3646.*

monarchE

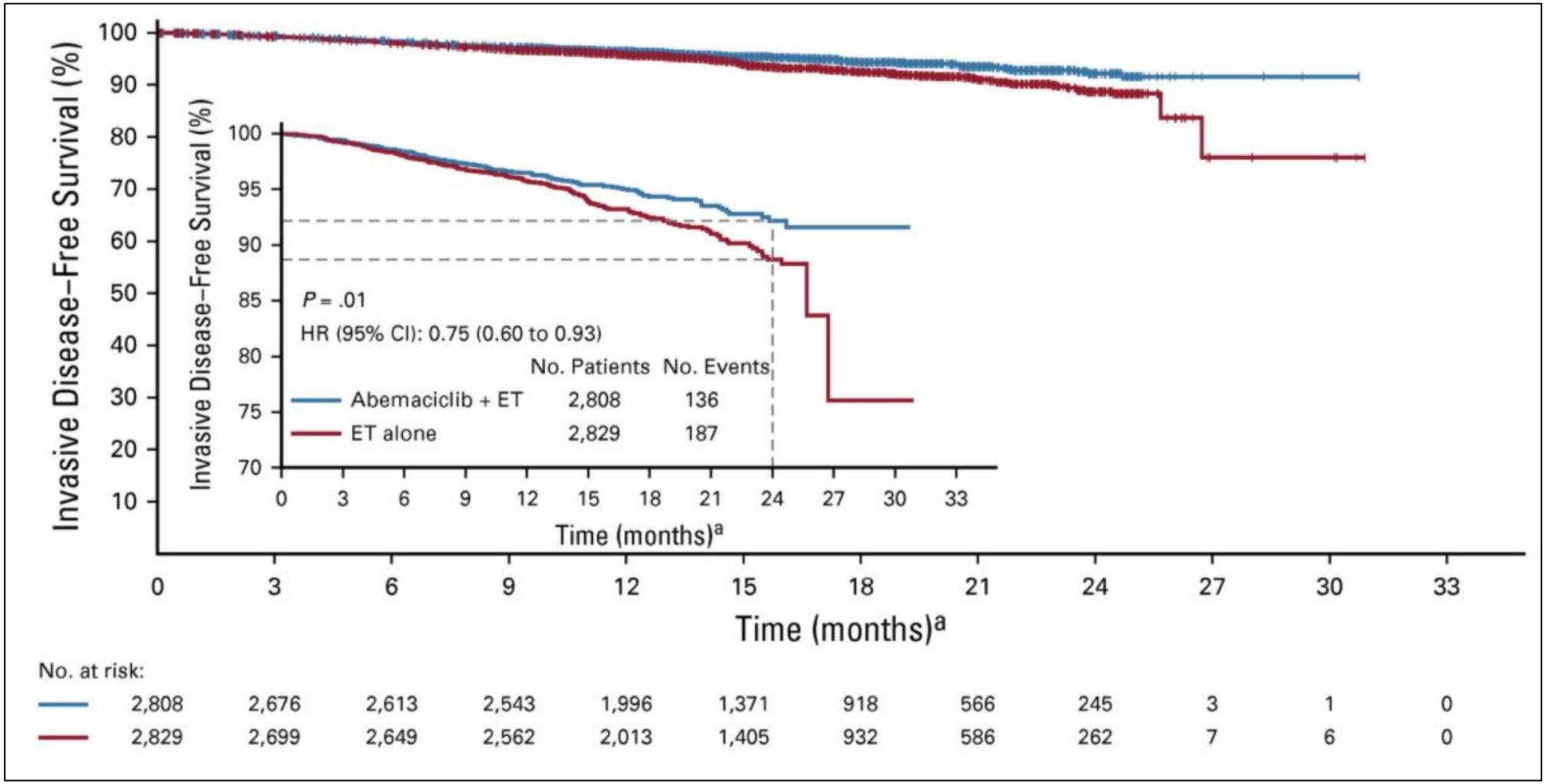
- International, randomized, open-label phase III trial



- Primary endpoint: iDFS
  - Planned for after ~ 390 iDFS events (~ 85% power, assumed iDFS HR 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

monarchE results

- The primary endpoint was IDFS.
- 2-year IDFS: **92.2%** versus **88.7%**.
- Majority of IDFS events were distant recurrence.



monarchE Conclusions

- This trial met its primary endpoint of IDFS improvement (absolute improvement of 3.5% at 2-years; 25% reduction of IDFS risk over ET).
- Grade ≥ 3 toxicities greater in abemaciclib arm (45.9% versus 12.9%).
- Higher treatment discontinuation for abemaciclib (16.6% versus 0.8%).
- Benefits not seen w/ adjuvant palbociclib (PALLAS, PENELOPE-B).
- Awaiting FDA review and determination.

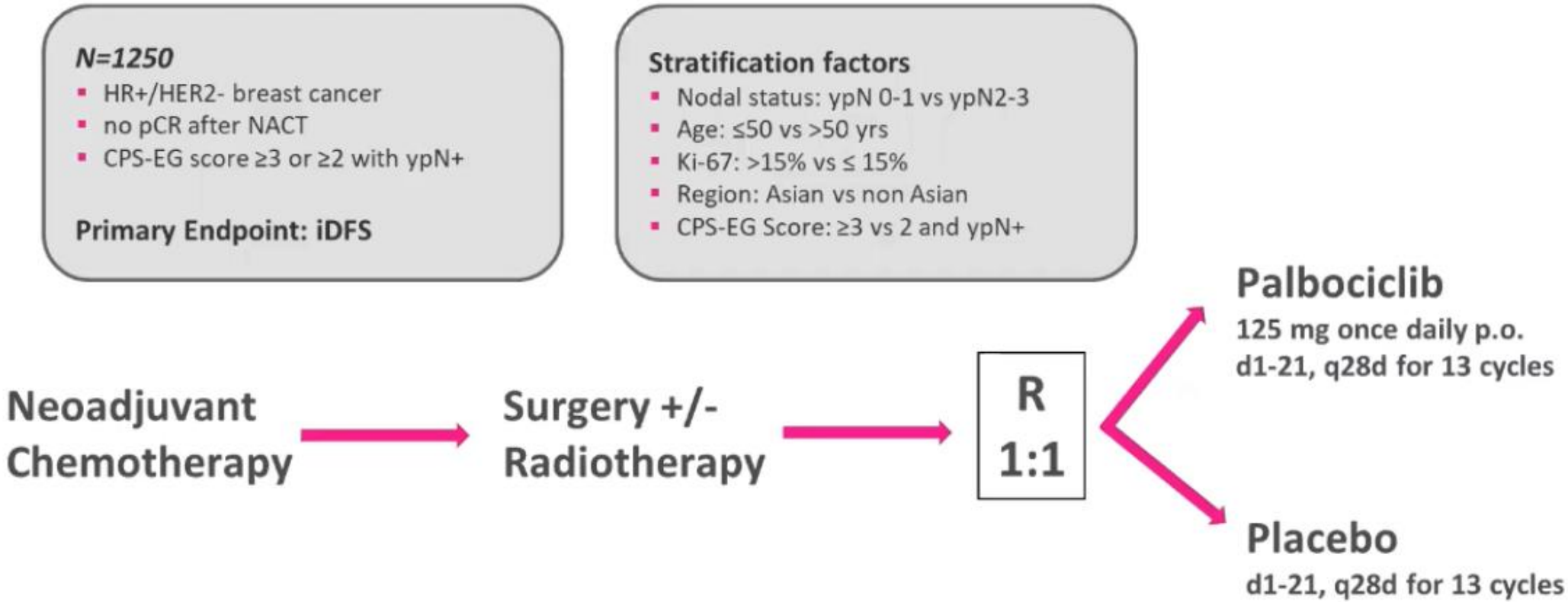

Seidman Cancer Center

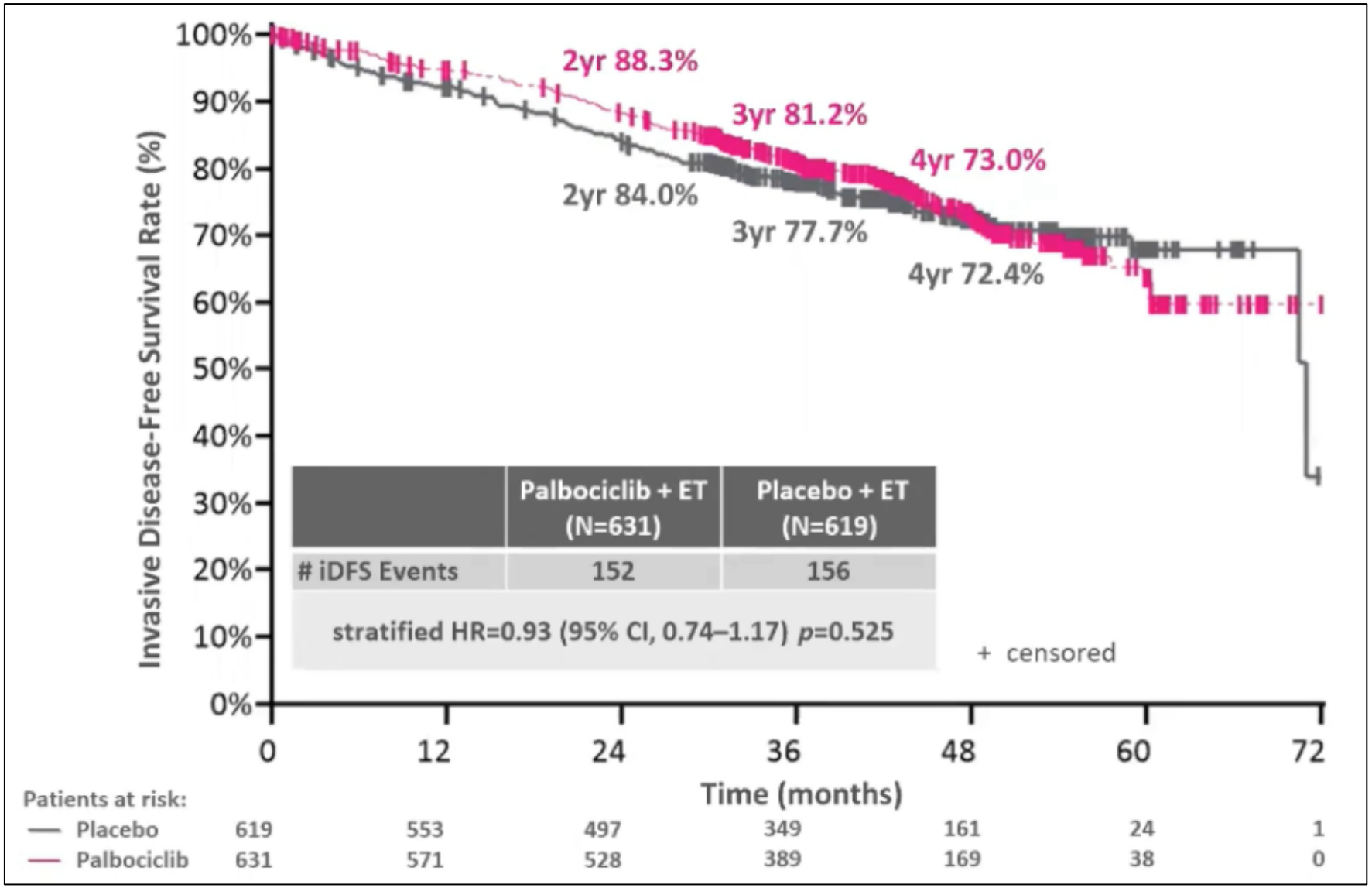
PENELOPE-B

- This double blind, placebo-controlled phase III trial was designed to assess the potential benefit of adjuvant palbociclib for subjects with residual disease after NACT [1].
- Patients who do not achieve a pathologic complete response from NACT are at higher risk of disease relapse [2].
- Eligible subjects had confirmed residual disease in either the breast or lymph nodes at the time of surgery.
- NACT ≥ 16 weeks (including 6 weeks of taxanes).

1. Loibl S, et al. GS1-02. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancer and with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B. Oral Presentation at: The San Antonio Breast Cancer Symposium; December 9, 2020.
2. Yee D, et al. JAMA Oncol. 2020 Sep 1;6(9):1355-1362.

PENELOPE-B (cont.)




Invasive Disease-Free Survival Rate (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2yr 88.3%
3yr 81.2%
4yr 73.0%
2yr 84.0%
3yr 77.7%
4yr 72.4%
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
+ censored
0
12
24
36
48
60
72
Time (months)
Patients at risk:
Placebo 619 553 497 349 161 24 1
Palbociclib 631 571 528 389 169 38 0

Patient Status	Palbociclib N (%)	Placebo N (%)	Overall N (%)
Number of patients screened			1708
Number of patients randomized	631	619	1250
Number of patients started treatment	628	616	1244
Completed at least 7 cycles of treatment	559 (88.6)	559 (90.3)	1118 (89.4)
Completed all 13 cycles regularly	508 (80.5)	523 (84.5)	1031 (82.5)
Discontinued endocrine therapy prematurely	28 (4.4)	36 (5.8)	64 (5.1)
Discontinued study treatment	123 (19.5)	96 (15.5)	219 (17.5)
- Disease recurrence	25 (4.0)	40 (6.5)	65 (5.2)
- Second primary (non-breast)	2 (0.3)	3 (0.5)	5 (0.4)
- Death	2 (0.3)	1 (0.2)	3 (0.2)
- Adverse event	33 (5.2)	5 (0.8)	38 (3.0)
- Patient´s wish	56 (8.9)	41 (6.6)	97 (7.8)
- Investigator´s decision	5 (0.8)	6 (1.0)	11 (0.9)

PENELOPE-B (cont.)

- On subgroup analysis, no group could be identified that benefitted from the addition of palbociclib (including age, type of ET administered, ki67, etc.).
- Distant recurrences accounted for ~75% of IDFS events.
- No OS benefit seen.
- ~20% of subjects discontinued palbociclib.

CONCLUSION:

- These data do not support the use of adjuvant palbociclib (no IDFS or OS noted).

Molecular signature for indolent ER+ disease:
Ultralow risk

University Hospitals
Cleveland | Ohio

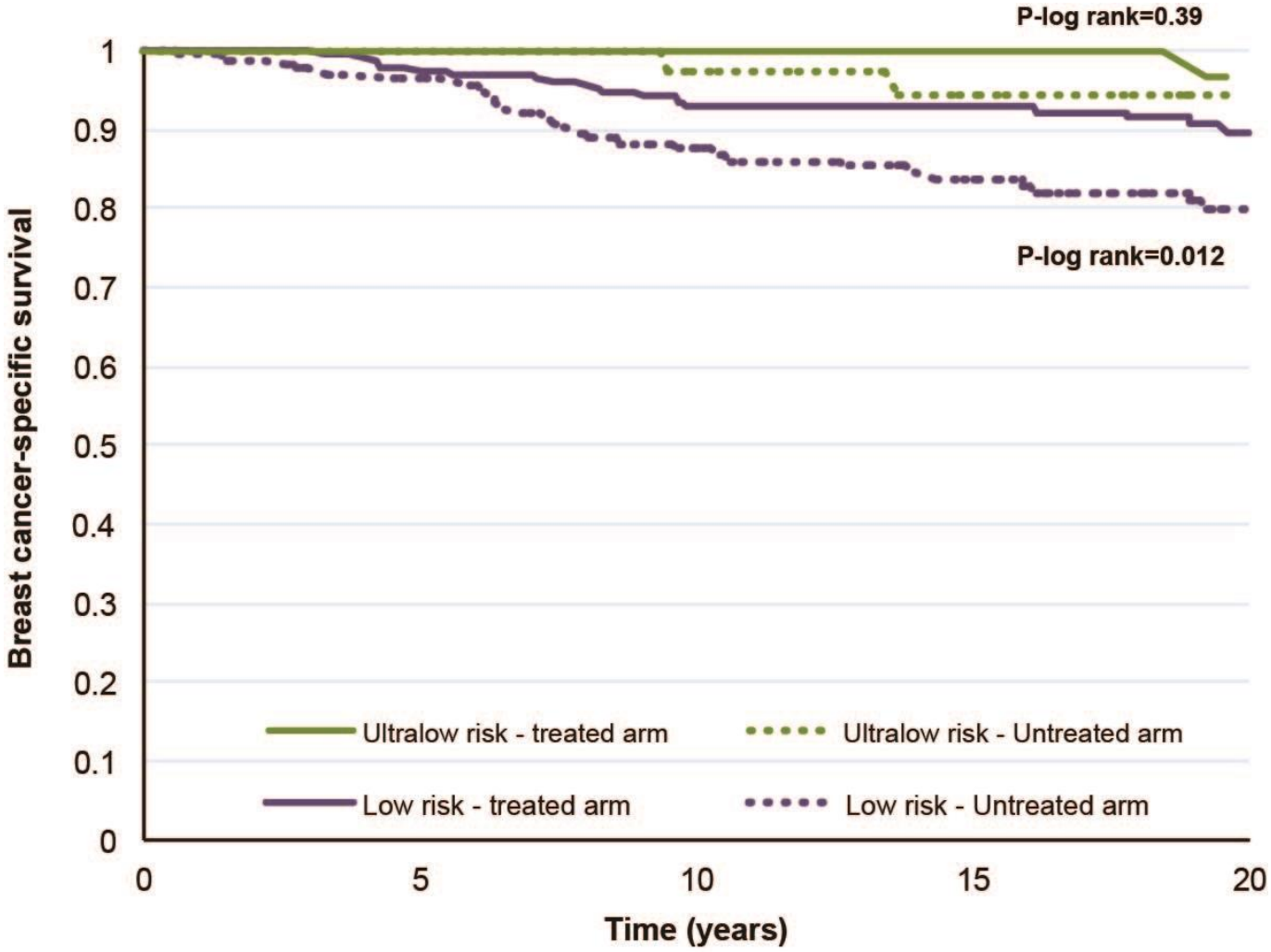
Research

JAMA Oncology | Original Investigation

Use of Molecular Tools to Identify Patients With Indolent Breast Cancers With Ultralow Risk Over 2 Decades

Laura J. Esserman, MD, MBA; Christina Yau, PhD; Carlie K. Thompson, MD; Laura J. van 't Veer, PhD; Alexander D. Borowsky, MD; Katherine A. Hoadley, PhD; Nicholas P. Tobin, PhD; Bo Nordenskjöld, MD, PhD; Tommy Fornander, MD, PhD; Olle Stål, PhD; Christopher C. Benz, MD; Linda S. Lindström, PhD

- **MammaPrint Low Risk Index >0.00 to +1.00 = No chemo benefit**
- **<u>Ultra Low Risk</u> Index = >0.355 to +1.00**
- **Stockholm Tamoxifen Study**: 652 post-menopausal women, T up to 3 cm, LN-
  - 339 randomized to: **No Endocrine therapy**
  - 313 randomized to: **Tamoxifen for 2 years**
  - **Ultra Low Risk** cohort (~19%)



Low Risk (not UltraLow)

- **ET: 90% BCSS @ 20 years**
- **No ET: 78% BCSS @ 20 years**

Ultra Low Risk

- **ET: 97% BCSS @ 20 years**
- **No ET: 94% BCSS @ 20 years**
- **Not the same as RS 0-10, those patients received 5 years of ET**

Esserman. et al. JAMA Oncology, 2016, June.

Conclusions: Adjuvant Therapy for ER+ breast cancer

- Genomically low-risk tumors favorable prognosis despite clinical risk.
  - Clinical utility of indolent ultralow signature should be explored
- Adjuvant CDK4/6i is not SOC
  - may be some benefit to abemaciclib in high-risk patients. No benefit for adjuvant palbociclib has been found at this time.