Operable HR+/HER2- Breast Cancer: When to Do Less and When To Do More

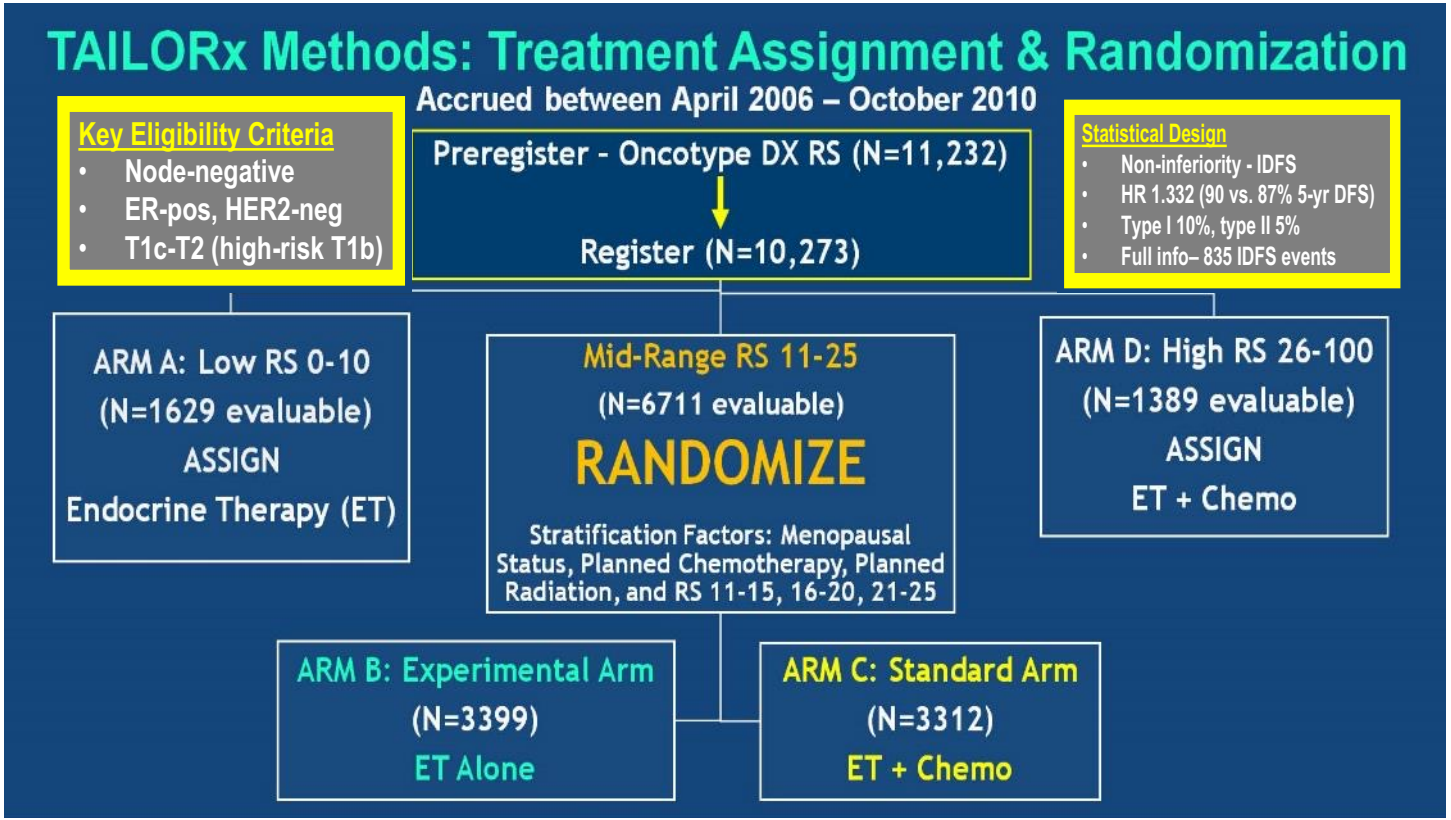
Kevin Kalinsky, MD, MS
Director, Glenn Family Breast Center
Director, Breast Medical Oncology
Louisa and Rand Glenn Family Chair in Breast Cancer Research

Disclosures

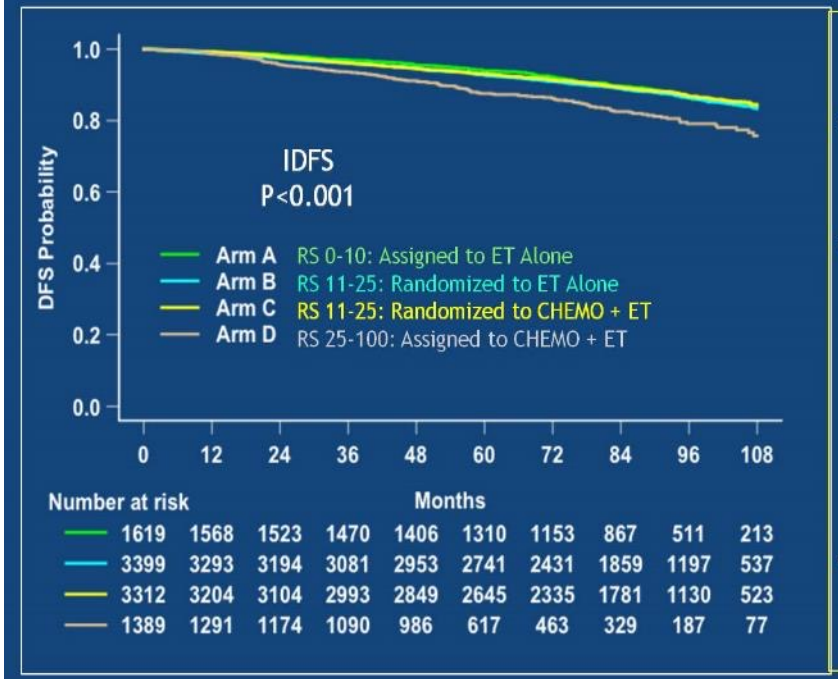
- Spouse, Stock: Grail, Array BioPharma and Pfizer (Prior Employee)
- Advisory/Consulting: Eli-Lilly, Pfizer, Novartis, Eisai, AstraZeneca, Daiichi Sankyo, Puma, 4D Pharma, Oncosec, Immunomedics, Merck, Seattle Genetics, and Cyclocel

Critical Issues in Biomarker Development

- Analytic validity
  - Assay reliability/reproducibility
- Clinical validity
  - Association with clinical outcome
- Clinical utility
  - Treatment change?
  - Do patients benefit from change?


TAILORx Methods: Treatment Assignment & Randomization
Accrued between April 2006 – October 2010
Key Eligibility Criteria
• Node-negative
• ER-pos, HER2-neg
• T1c-T2 (high-risk T1b)
Preregister - Oncotype DX RS (N=11,232)
Register (N=10,273)
Statistical Design
• Non-inferiority - IDFS
• HR 1.332 (90 vs. 87% 5-yr DFS)
• Type I 10%, type II 5%
• Full info– 835 IDFS events
ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)
Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25
ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo
ARM B: Experimental Arm
(N=3399)
ET Alone
ARM C: Standard Arm
(N=3312)
ET + Chemo

TAILORx Results - ITT Population: All Arms (A,B,C & D)



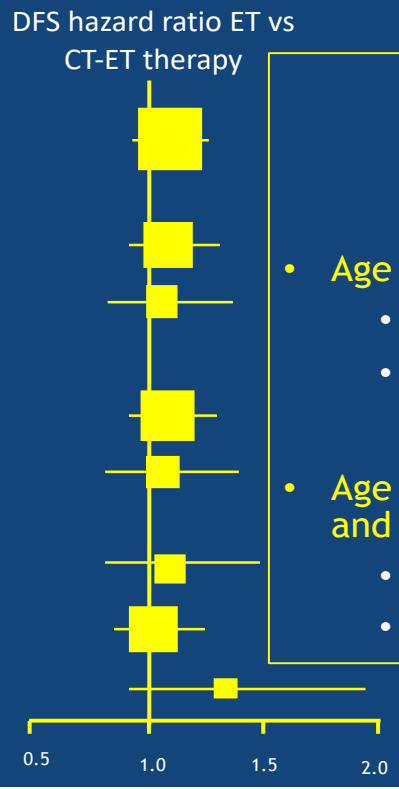
9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone
- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)
- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET

Sparano et al. *N Engl J Med* 2018;379:111-121.

TAILORx Subgroup Analyses:
Clinicopathologic parameters do not predict chemotherapy benefit

Group	n	ratio	95% CI
Overall	n=6711	1.08	(0.94, 1.24)
Clinical risk low	n=4799	1.08	(0.91, 1.29)
Clinical risk high	n=1697	1.05	(0.82, 1.35)
Tumor size ≤ 2cm	n=5122	1.08	(0.92, 1.28)
Tumor size > 2cm	n=1587	1.06	(0.82, 1.37)
Grade low	n=1893	1.09	(0.82, 1.46)
Grade intermed	n=3721	1.02	(0.85, 1.23)
Grade high	n=884	1.32	(0.92, 1.90)



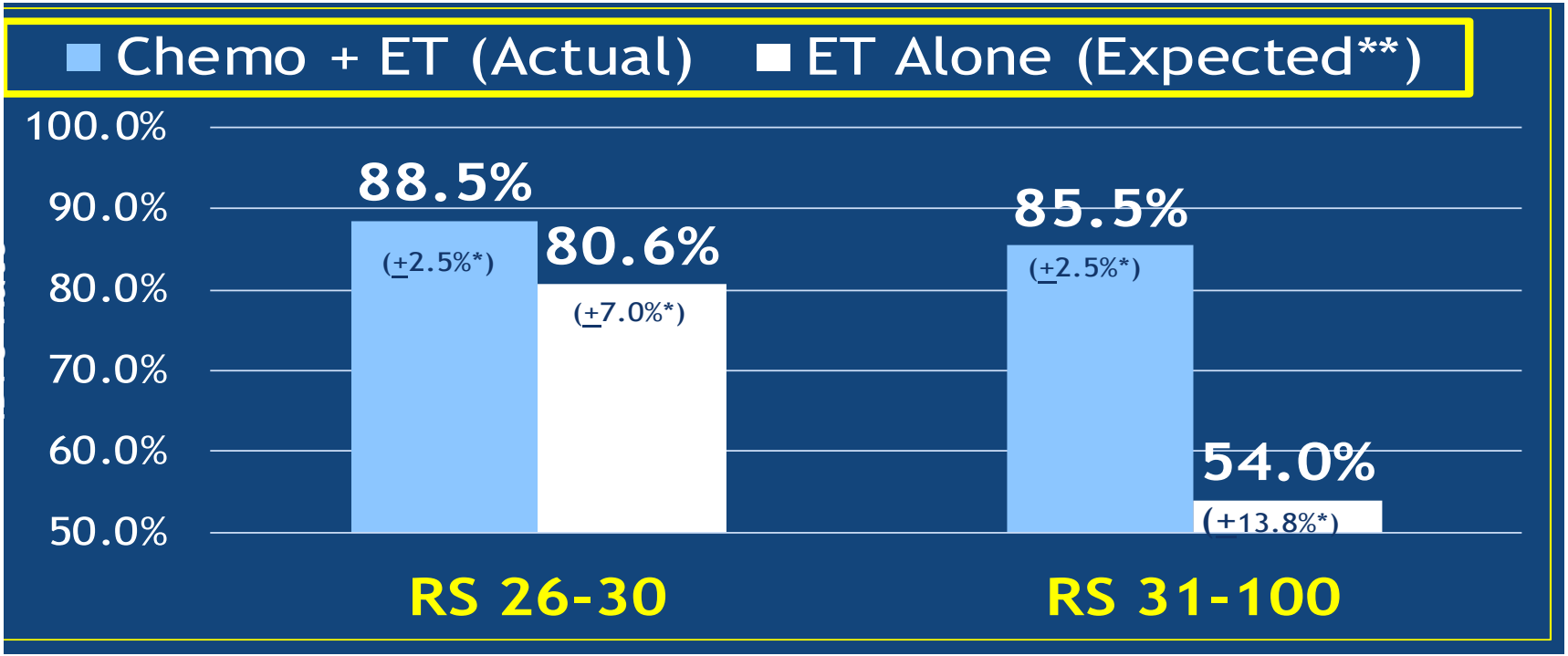
Statistically significant

chemo treatment interactions

- Age (≤ 50, 51-65, > 65) and chemo benefit
  - IDFS (p=0.003)
  - RFI (p=0.02)
- Age (or menopause), RS (11-15, 16-20, 21-25), and chemo benefit
  - IDFS - Age-RS (p=0.004)
  - IDFS - Menopause-RS (p=0.02)

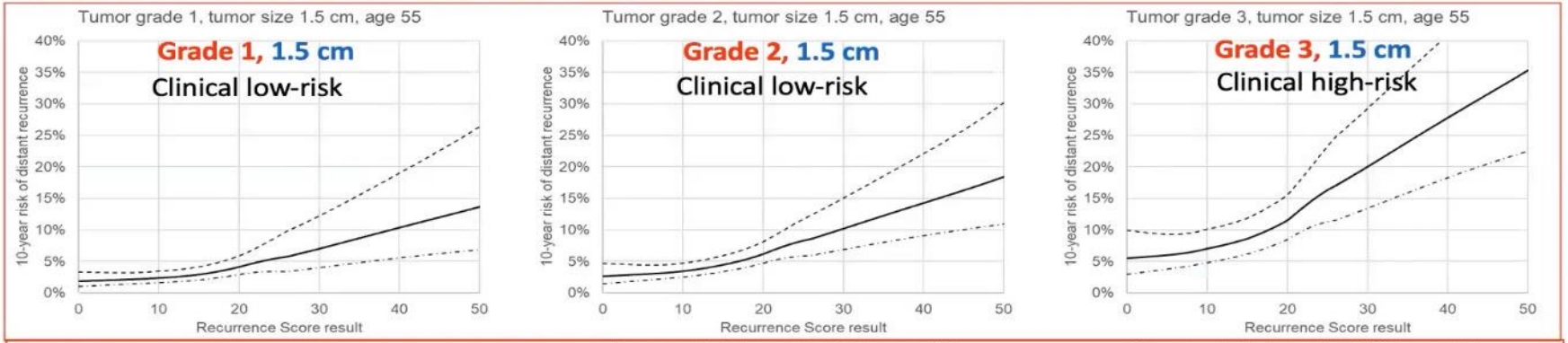
Sparano et al. *N Engl J Med* 2018;379:111-121

Results Arm D: Rate of Freedom From Recurrence



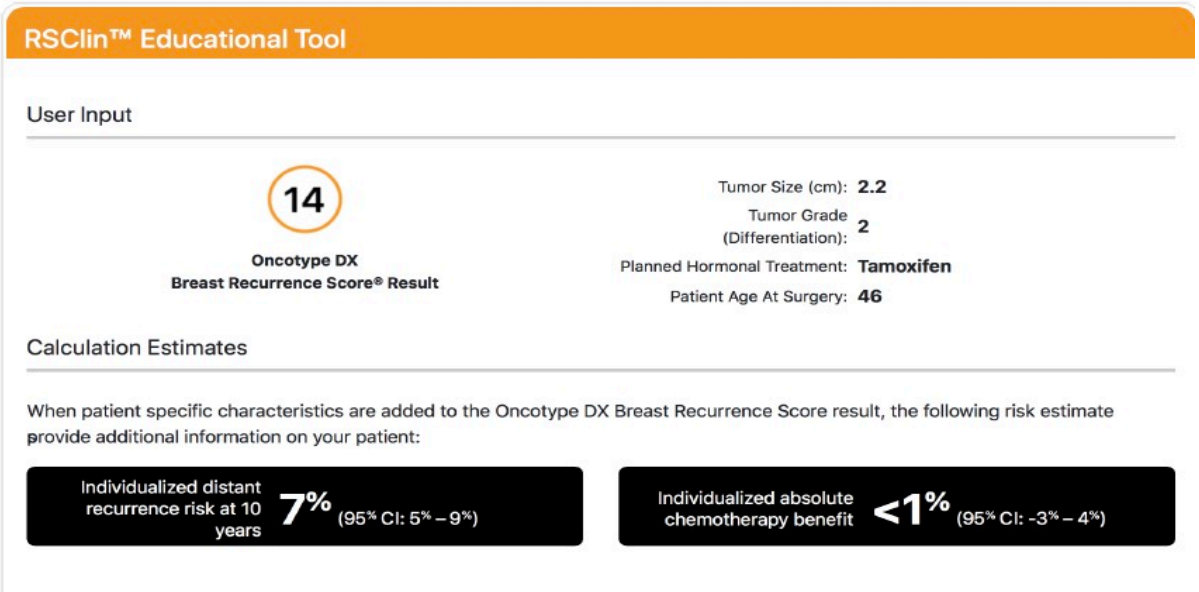
Sparano et al. *JAMA Oncol*. 2020;6; 367-374.

Results – prognosis: RSClin™ 10-year distant recurrence risk estimates (95% CI)
Impact of tumor grade and size – 55 year old



Sparano JA, et al. *J Clin Oncol*. 2021;39:557-564.

RSClin: Tool Available for patients with HR+/HER2-, LN- Breast Cancer



- ✓ **Important Considerations:**
  - ✓ **Only applies to node-negative disease**
  - ✓ **Subgroups limited, such as very young women 4.6% in TAILORx**
  - ✓ **No validation set for prediction in patients with node-negative breast cancer**

RxPONDER Schema

Key Entry Criteria

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

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

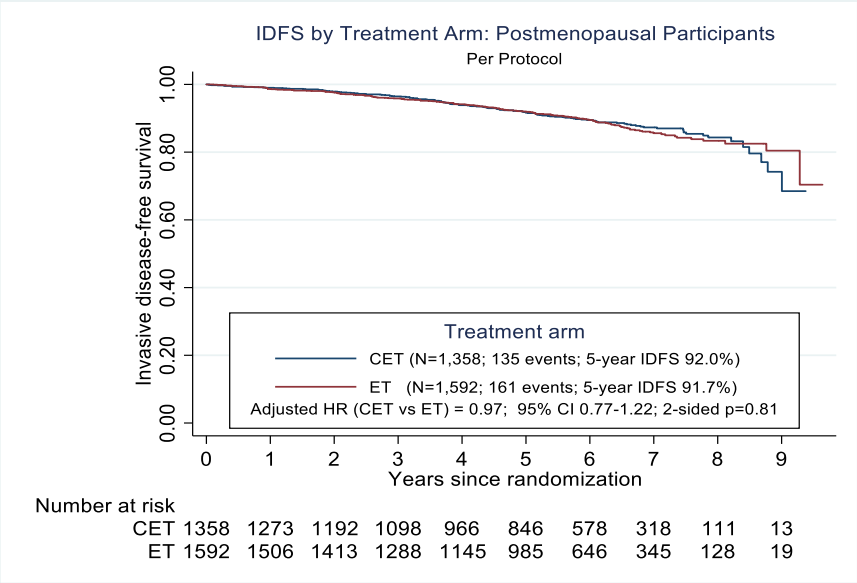
Arm 1:
Chemotherapy Followed by Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

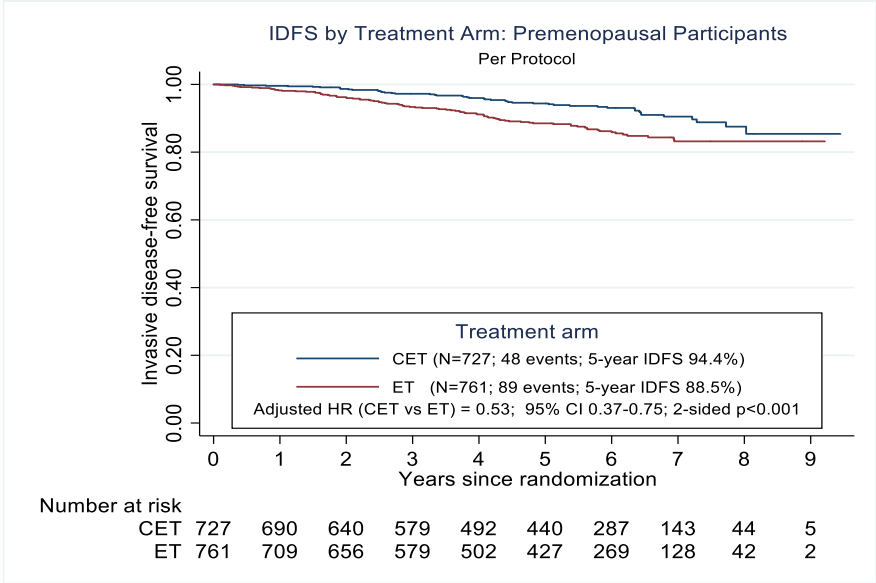
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

IDFS Stratified by Menopausal Status

Postmenopausal

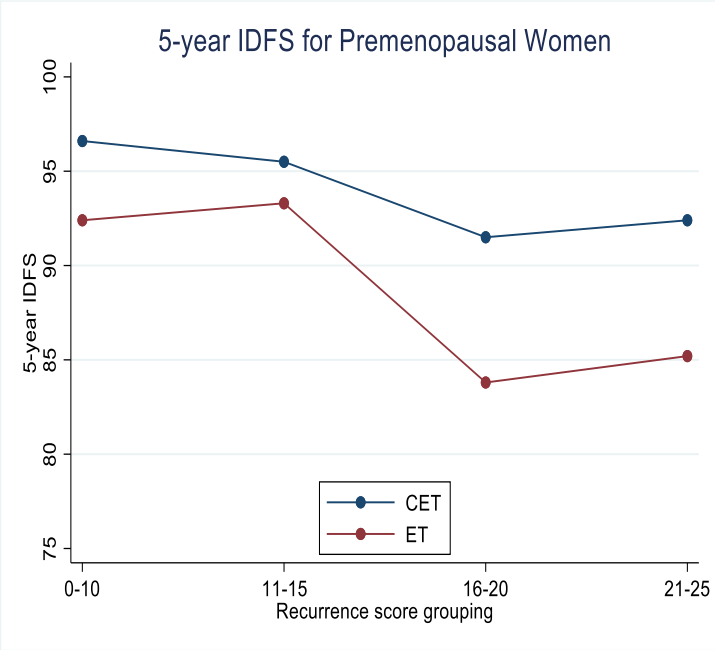


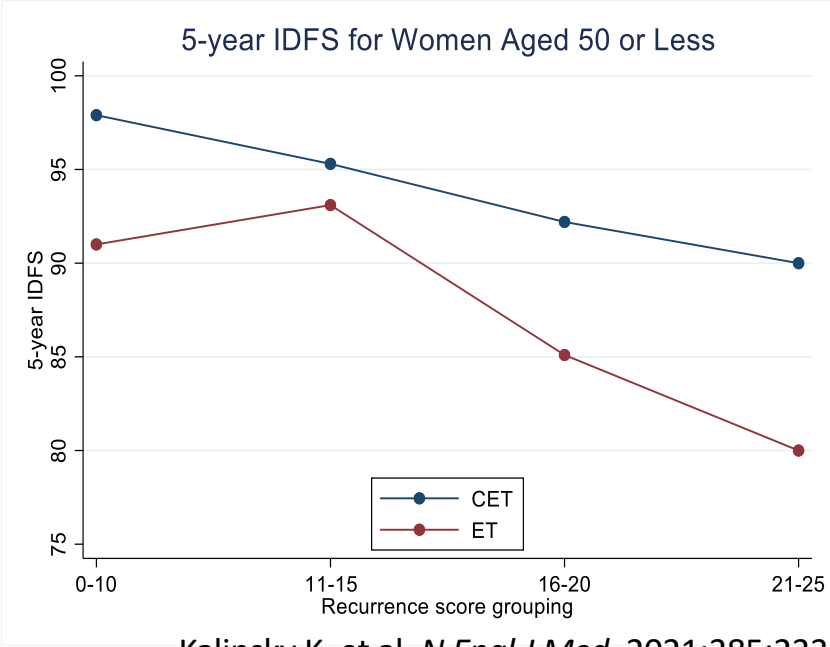
Premenopausal



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

5-year IDFS: CET vs. ET

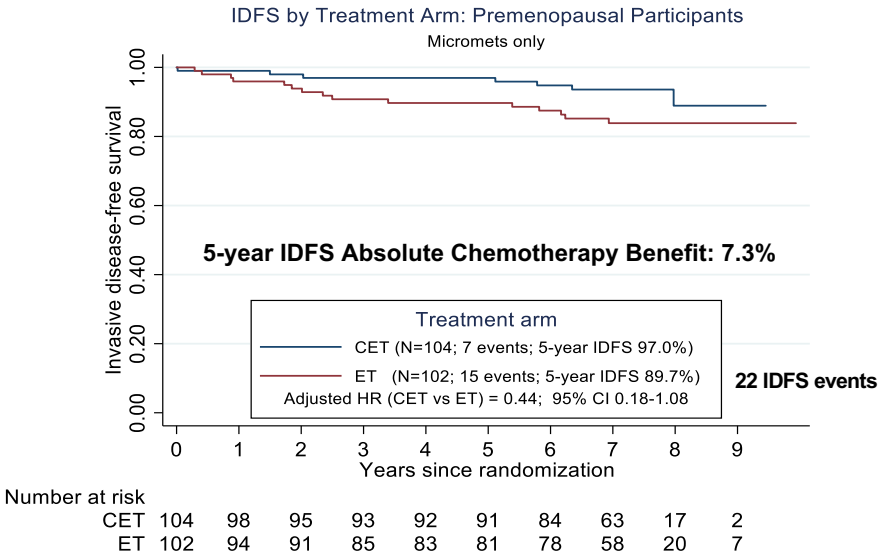




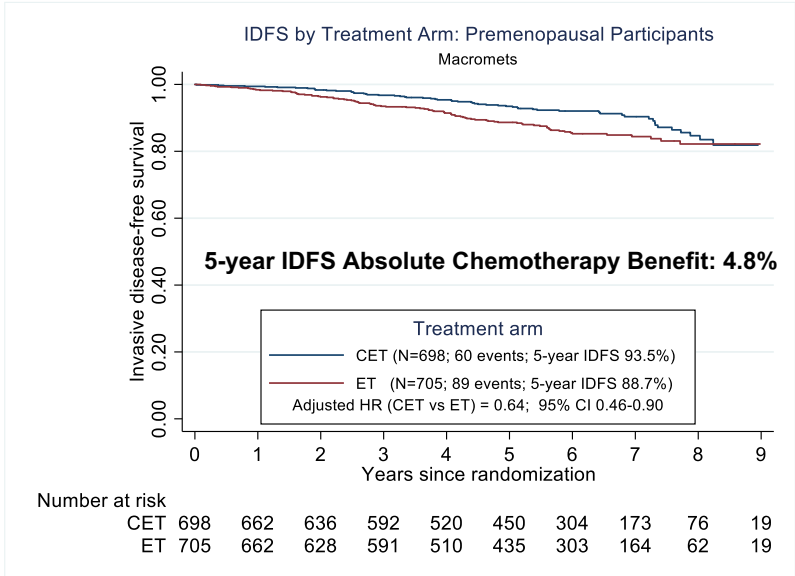
Kalinsky K, et al. *N Engl J Med.* 2021;385:2336-47.

Premenopausal Women with p1Nmi and pN1 Benefit from Chemotherapy

pN1mi (N=206)



pN1 (N=1403)



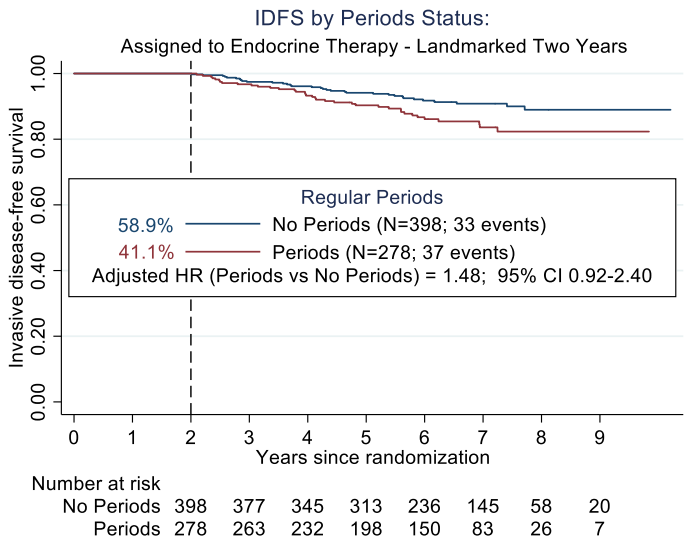
Prior to the amendment, 206/738 (27.9%) eligible premenopausal pts had micrometastases only and 45 pts (6%) unknown

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

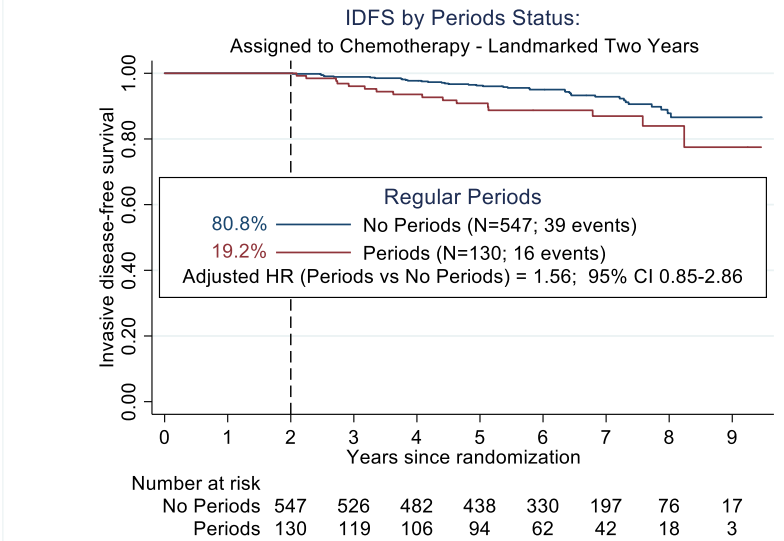
Kalinsky K, et al. *N Engl J Med.* 2021;385:2336-47.

Landmarked Two-Year IDFS by Regular Periods or Not in Premenopausal Pts in Both Tx Arms

Endocrine Tx Alone (n=676)



Chemo then Endocrine Tx (N=677)



Numerically improved IDFS in premenopausal pts no longer having regular menstrual periods in first 24 months in both tx arms**

*Adjusted for Age, RS

**No regular menstrual periods = At least two 6-month time intervals in first 24 months

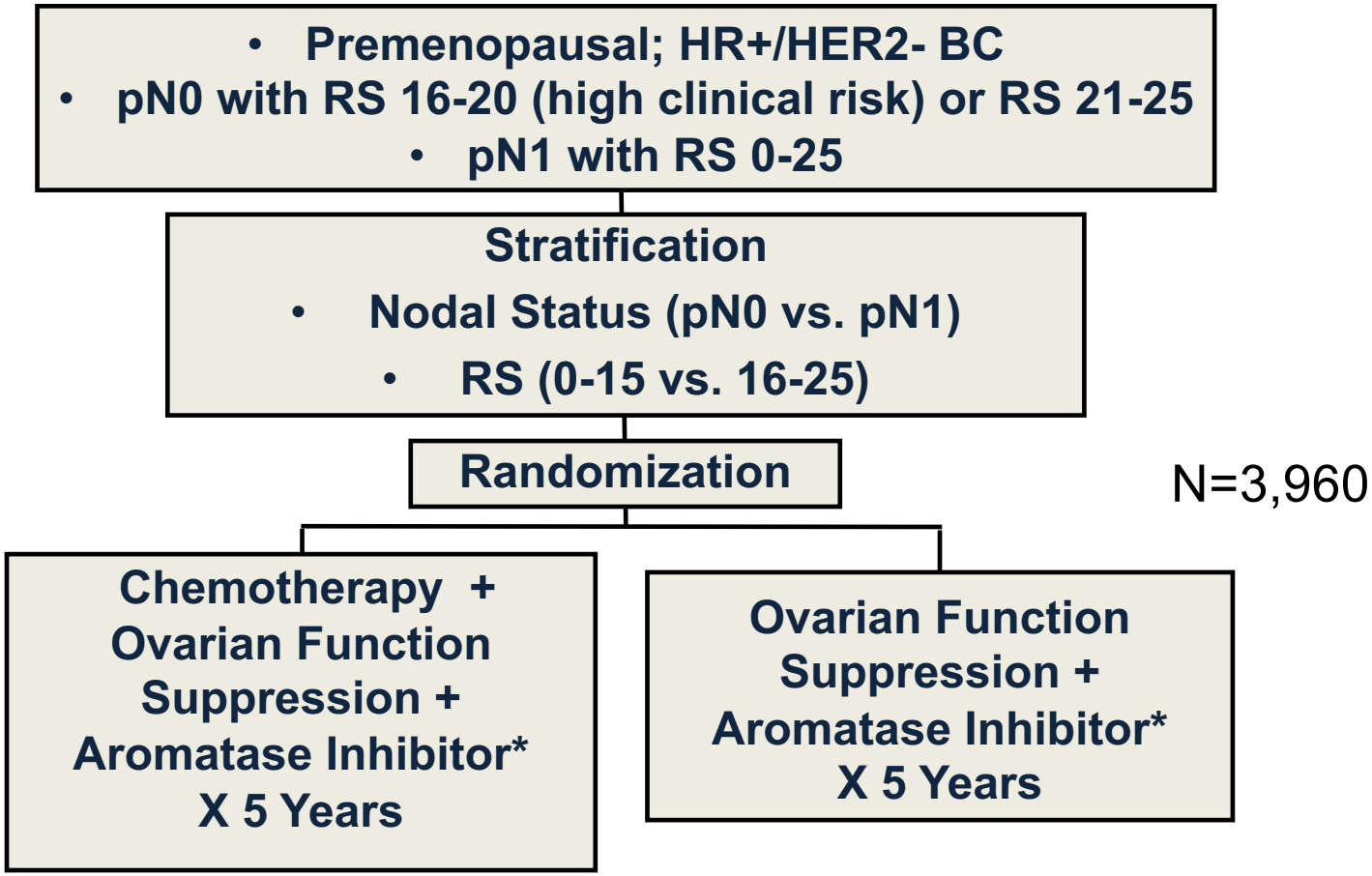
Kalinsky K, et al. *N Engl J Med.* 2021;385:2336-47.

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+
  - ✓ 5.8% had T3 tumors
  - ✓ 5.0% Black

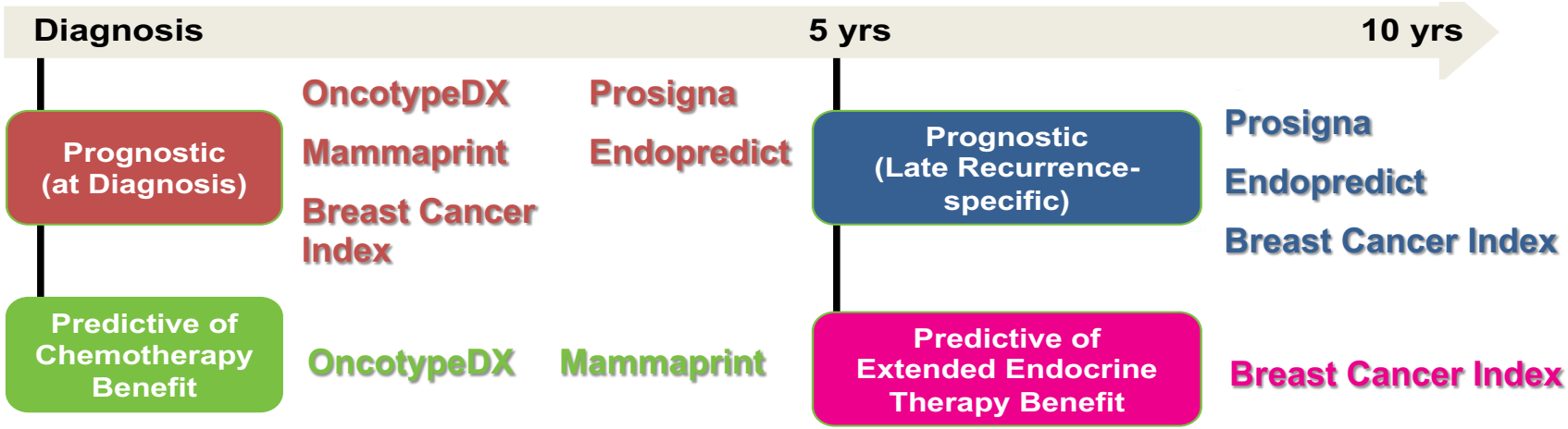
Kalinsky K, et al. *N Engl J Med.* 2021;385:2336-47.

BR009: Schema



N=3,960

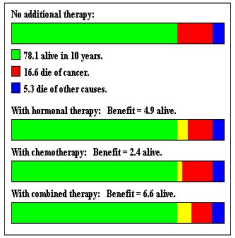
Use of Genomic Assays Across the Continuum of Early-Stage ER+ Breast Cancer



	Oncotype DX® (Genomic Health)	MammaPrint® (Agendia)	Prosigna™ (Nanostring)	Breast Cancer Index℠ (Biotheranostics)	Endopredict (Myriad)
Number of Genes	21	70	50	11	12
Platform	RT-PCR	Microarray	NanoString nCounter	RT-PCR	RT-PCR

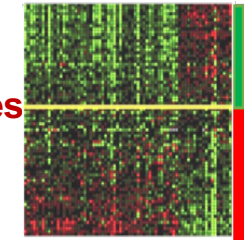
MINDACT TRIAL DESIGN

December 8-11, 2020



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-

1st randomization to treatment
use Clinical vs. Genomic risk

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

No Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

Chemotherapy

HR +

Endocrine therapy

HR +

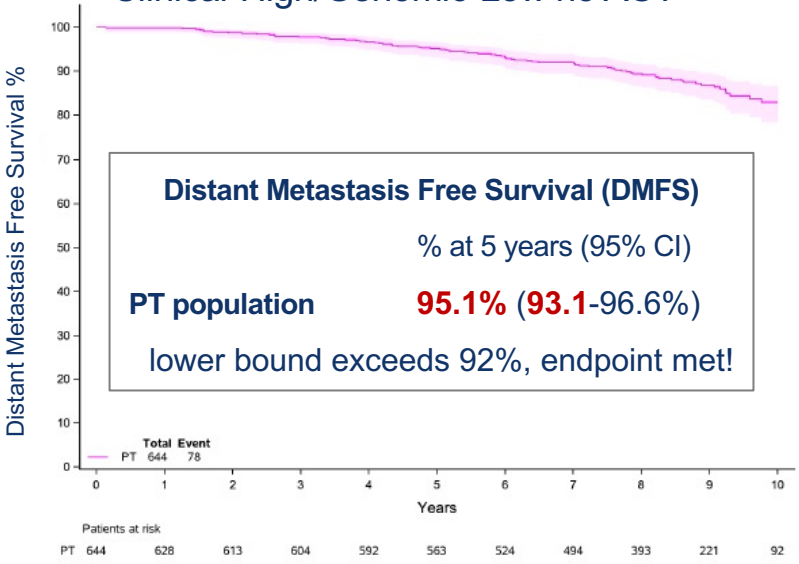
3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

MINDACT UPDATED ANALYSIS RESULTS

December 8-11, 2020

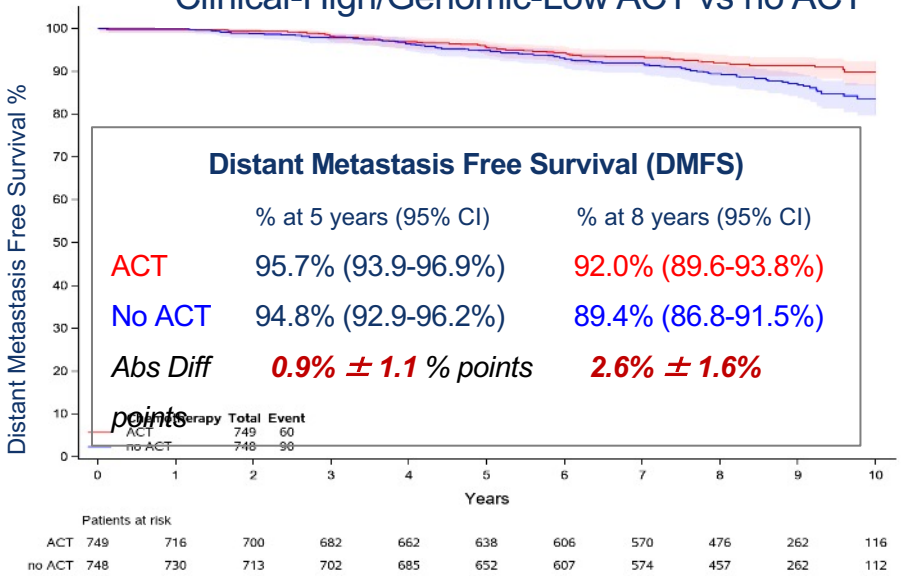
PRIMARY ENDPOINT

Clinical-High/Genomic-Low no ACT



SECONDARY ENDPOINT

Clinical-High/Genomic-Low ACT vs no ACT



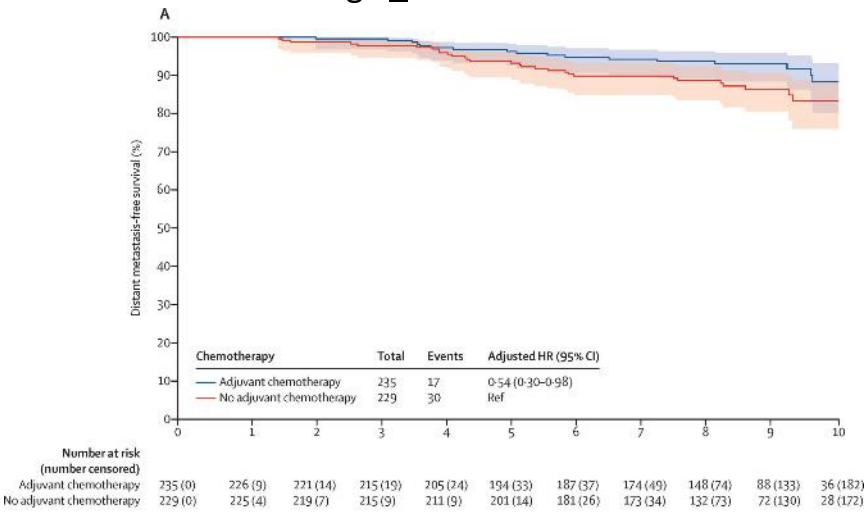
Type of first event (n = 150)

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

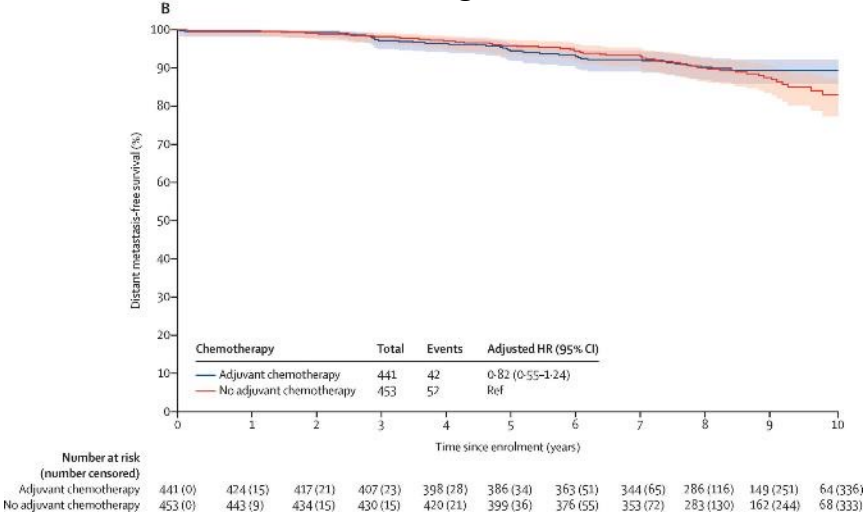
F. Cardoso, ASCO 2020; Piccart M, et al. Lancet Oncol 2021;22:476-488.

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.

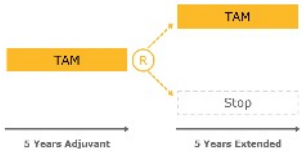
BCI (H/I) is Predictive for Extended Endocrine Therapy Benefit

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

Recurrence Free Survival (RFS) Benefit

Cohort = 41% N0 / 59% LN+

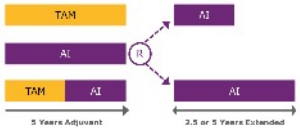
Trans-aTTom (n=583)[2]



Recurrence Free Interval (RFI) Benefit

Cohort = 100% LN+

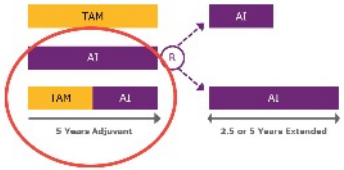
BCI IDEAL (n=908)[3]



Recurrence Free Interval (RFI) Benefit

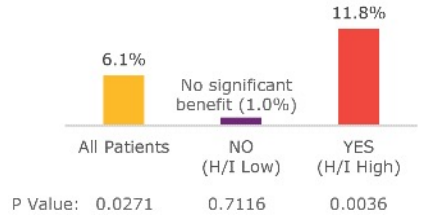
Cohort = 27% N0 / 73% LN+

Adjuvant AI Subset (n=794)[3]



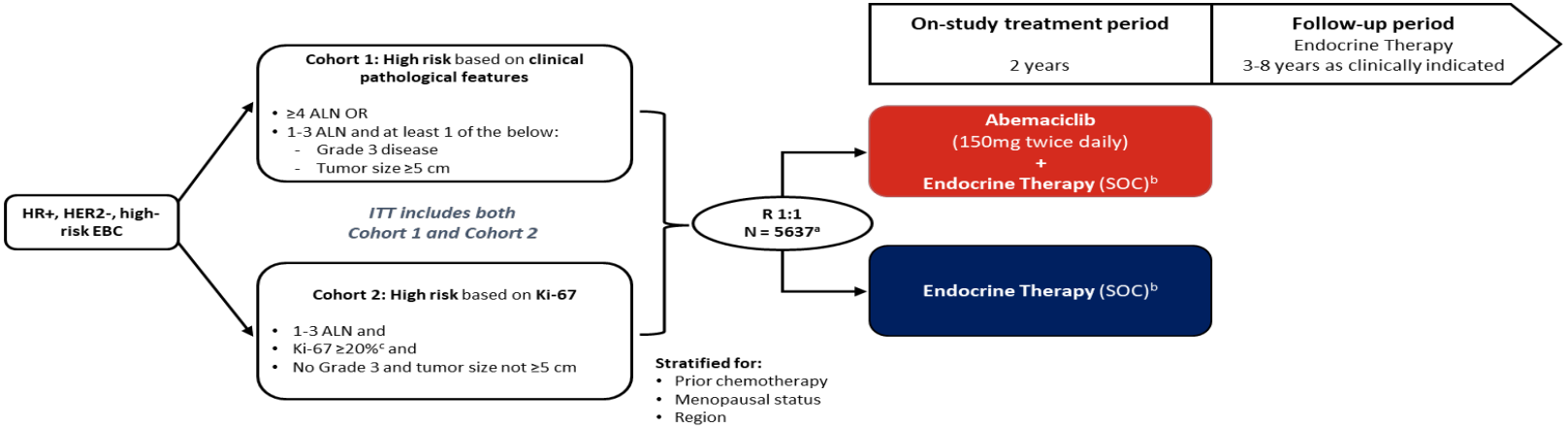
Recurrence Free Interval (RFI) Benefit

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.

monarchE Study Design (NCT03155997)



Primary Objective: **Invasive Disease-Free Survival (IDFS) in ITT Population**

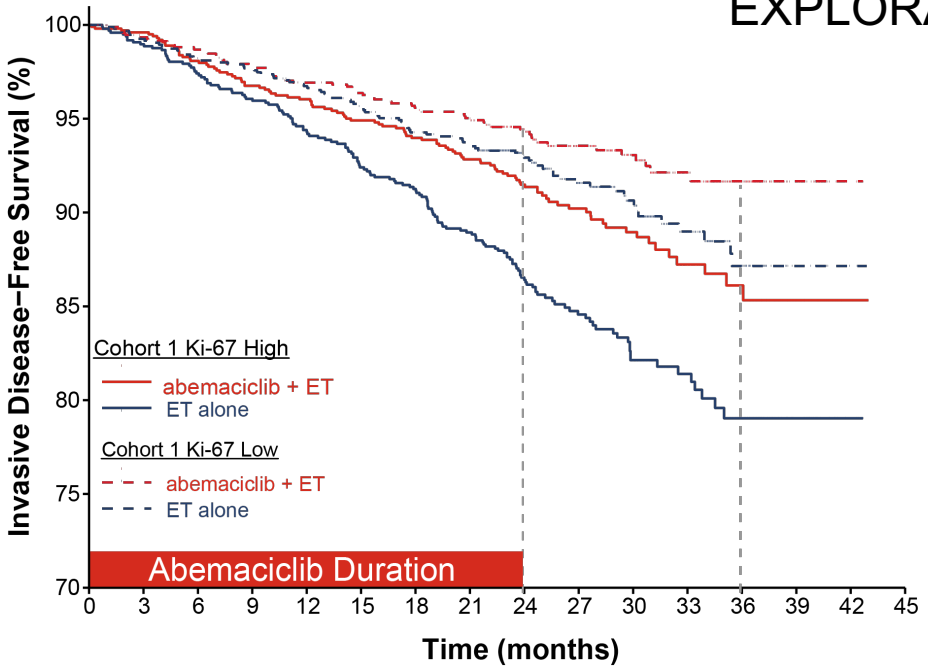
Secondary Objectives: IDFS in high Ki-67 populations, Distant Relapse-Free Survival (DRFS), OS, Safety, PK, Patient Reported Outcomes (PRO)

Other criteria:

- Women or men
- Pre-/ postmenopausal
- With/without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 mo from surgery to randomization and 12 weeks of ET following the last non-ET

Harbeck N, et al. *Ann Oncol*. 2021;S0923-7534(21)04494-X.
Johnston SRD, et al. *J Clin Oncol*. 2020;38(34):3987-3998.

MONARCHE: KI-67 AS A PROGNOSTIC MARKER IN COHORT 1—EXPLORATORY



	Abema + ET	ET alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

Ki-67 is prognostic

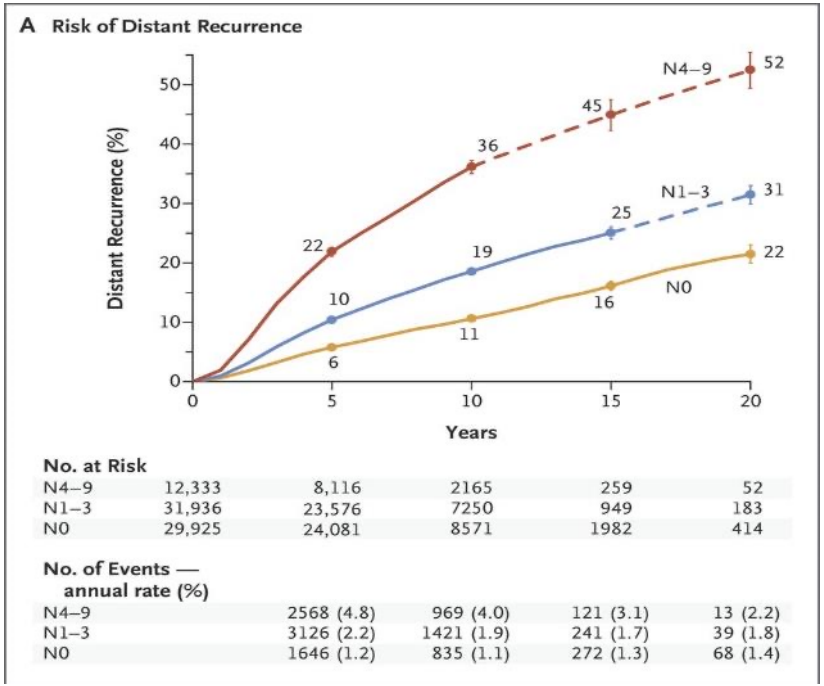
Ki-67 is not predictive of abemaciclib benefit

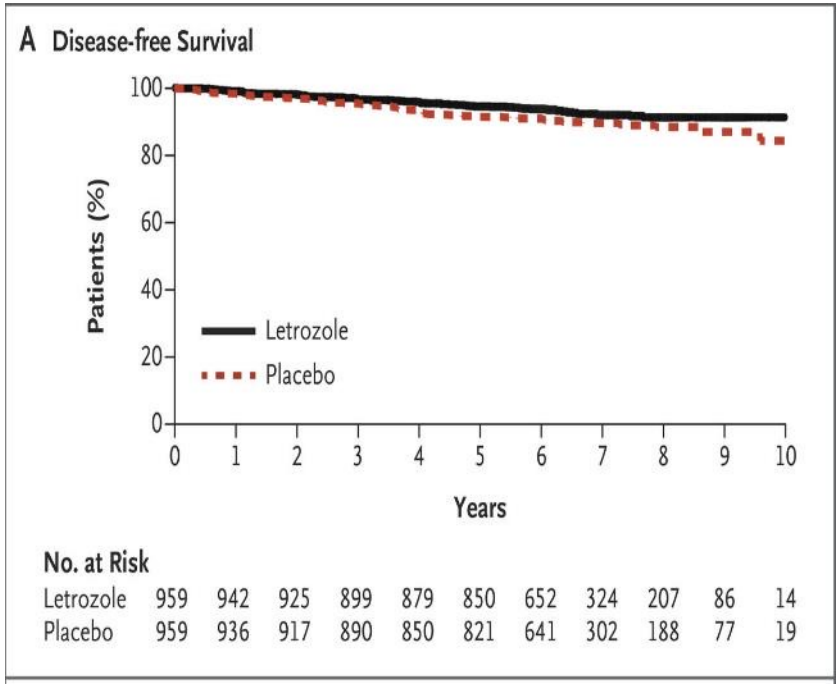
As expected, high Ki-67 index was prognostic of worse outcome.
However, abemaciclib benefit was consistent regardless of Ki-67 index.

27 months median follow-up.
DRFS, distant relapse-free survival.

Harbeck N, et al. Ann Oncol. 2021;S0923-7534(21)04494-X.O'Shaughnessy J, et al. ESMO 2021. Abstract VP8-2021.

Glimpse to the Future: Late Recurrence Remains a Significant Issue in ER+/HER2- Breast Cancer

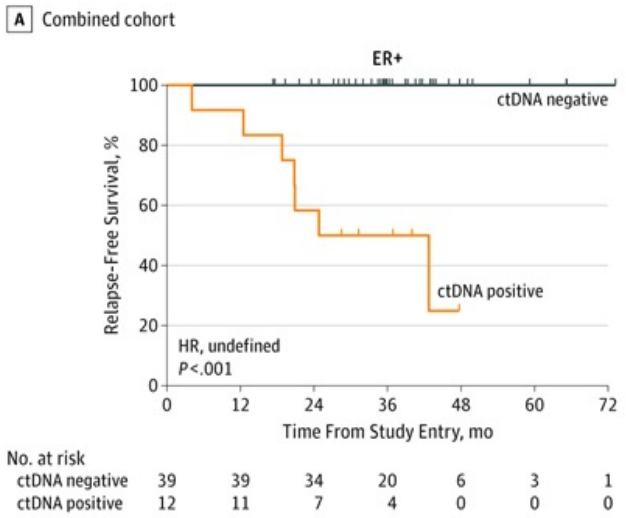




Pan H et al. *N Engl J Med*. 2017;377:1836-1846, Goss PE et al. *N Engl J Med*. 2016;375:209-219.

Glimpse to the Future:
The role of circulating biomarkers in HR+/HER2- BC

- **Blood-based marker detection in early-stage BC, such as ctDNA and CTCs**
  - Still in clinical validity phase
  - Differences in pre-analytic and analytic
  - considerations
    - CTCs require real-time assessment
    - ctDNA platforms may require baseline tumor tissue
      - Bespoke vs. agnostic
    - Limited cross-platform analyses
    - Assays can vary in terms of sensitivity and detection



Median lead time 10.7 months from ctDNA detection to clinical relapse

Garcia-Murillas I, et al. *JAMA Oncol*. 2019;5:1473-1478.

Conclusion

- **Significant progress in chemotherapy de-escalation with TAILORx, RxPONDER, and MINDACT**
- **Premenopausal Patients: Identify de-escalation strategies to prevent recurrence**
- **Abemaciclib is approved in pts with high-risk, early-stage breast cancer**
- **Late Recurrence: Assessing predictors and potential interventions remains critical**

Question

65 year yo female with a 2.1 cm ER 95%, PR 60%, HER2 negative breast cancer – 2/5 LN. Oncotype 18. What systemic therapy would you discuss?

A. AC/T followed by AI
B. TC followed by AI
C. AI