Phase III trial of standard adjuvant endocrine therapy +/- chemotherapy in patients with 1-3 positive nodes, Hormone Receptor-positive and HER2-negative: SWOG S1007

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National Cancer Institute-Designated Comprehensive Cancer Center

Disclosures

Spouse, Stock: Grail, Array BioPharma and Pfizer (Prior Employee)

Advisory/Consulting: Eli-Lilly, Pfizer, Novartis, Eisai, AstraZeneca, Immunomedics, Merck, Seattle Genetics, and Cyclocel

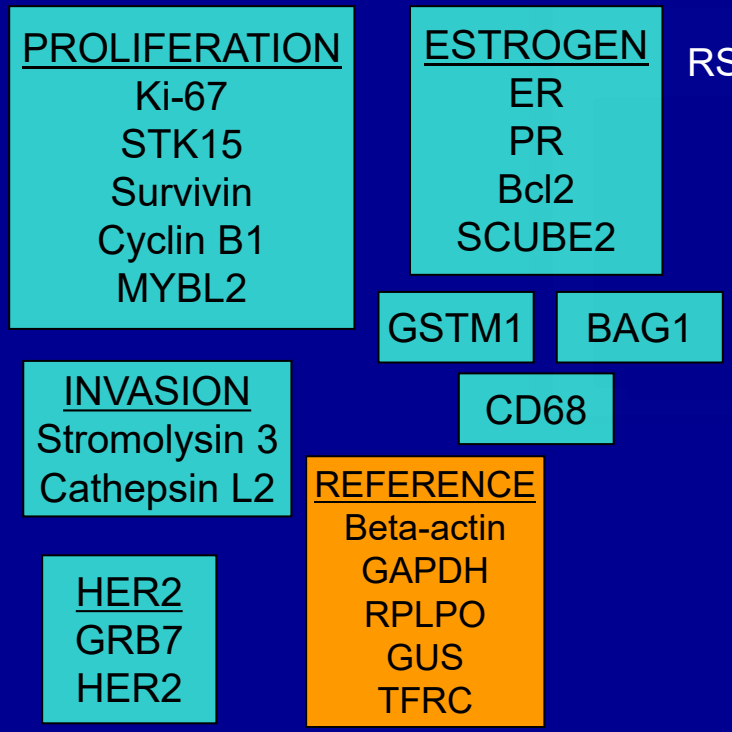
Breast Cancer Steering Committee Strategic Priorities

- **Decreasing toxicity/treatment/costs associated with therapy with negligible clinically meaningful benefits**
  - TAILORx: HR+/node negative
  - RxPONDER: HR+/node positive

- **Understanding biology and translating biology into diagnostic and therapeutic strategies**
  - NCTN Late Recurrence Project

Which patients with HR+/HER2- Breast Cancer Benefit from Adjuvant Chemotherapy?

21 Gene Recurrence Score (RS) Assay (HR+/HER2- only)

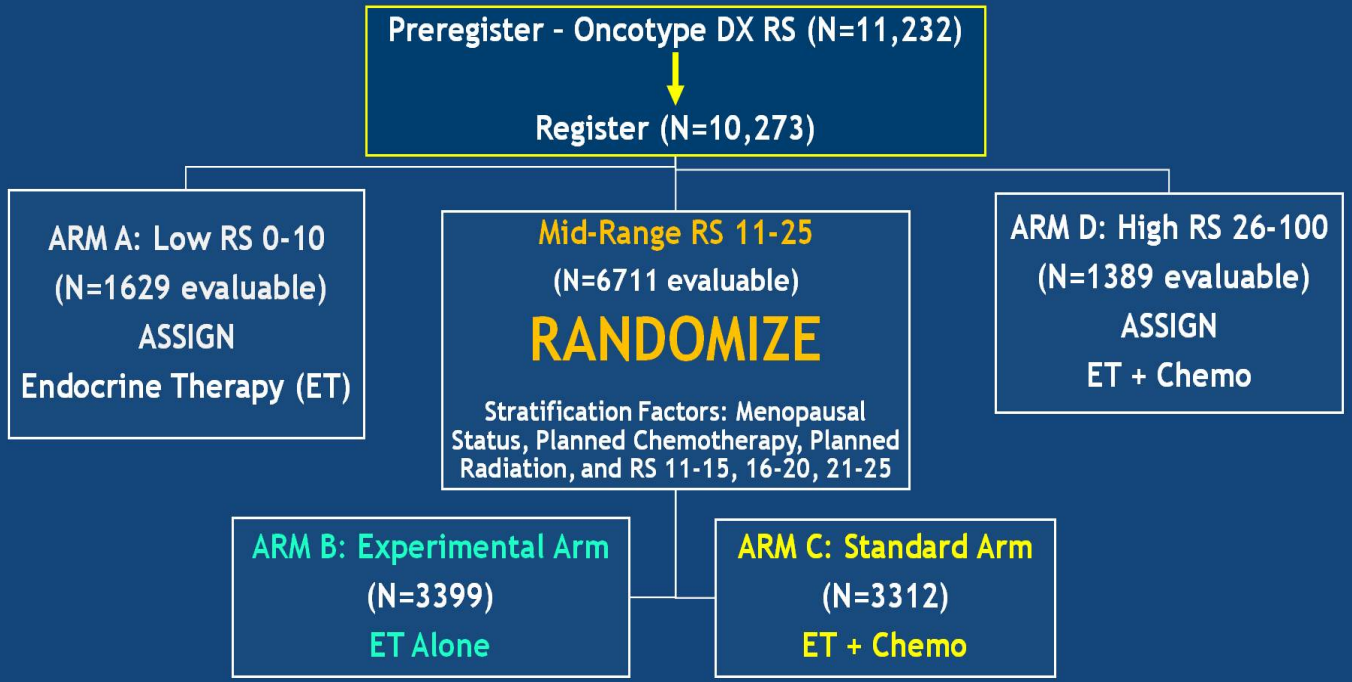


RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

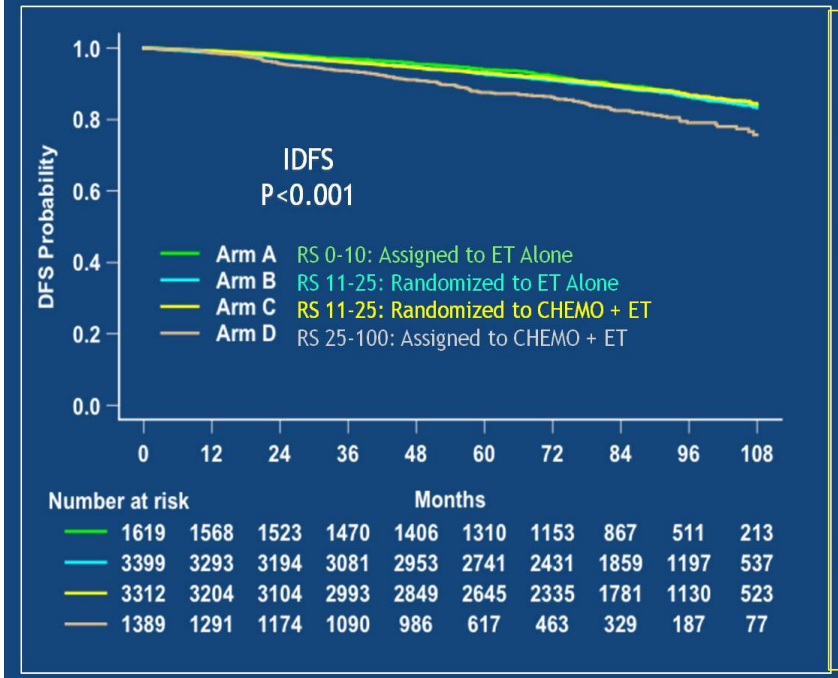
Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010



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



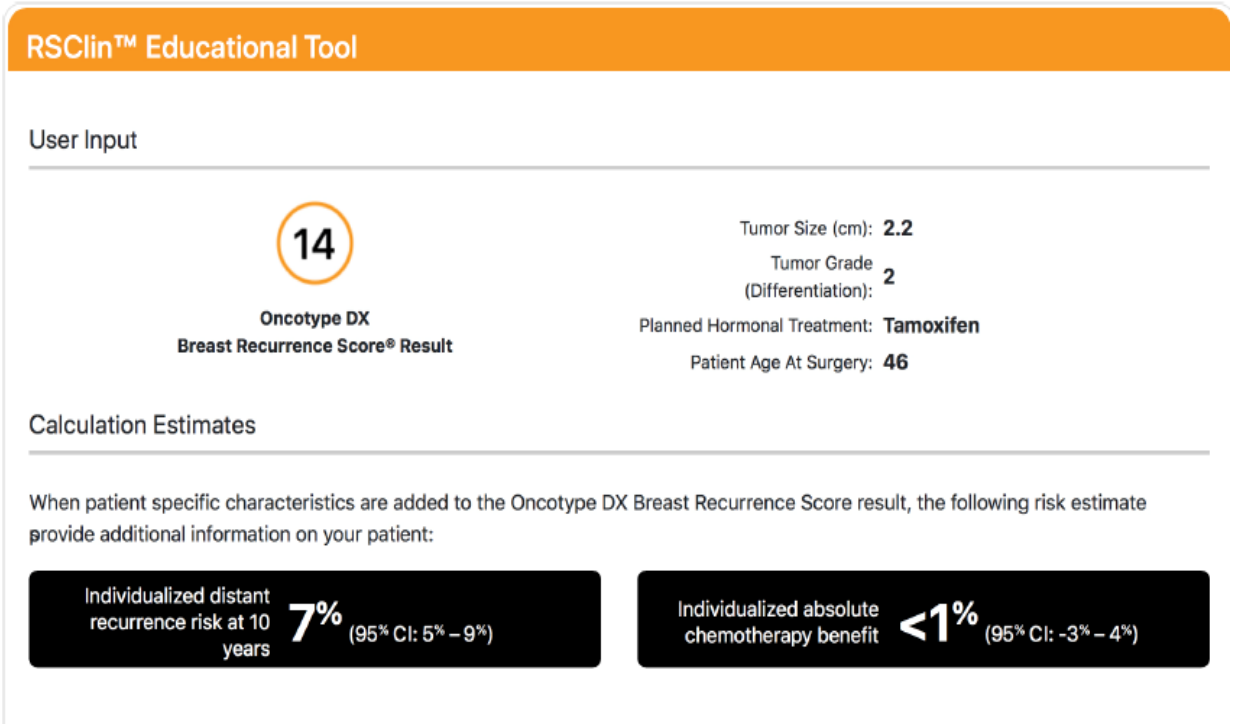
9-Year Event Rates

- **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

TAILORx Results – ITT Population: Potential Chemotherapy Benefit in Women ≤ 50 Years (N=2216) in RS 11-25 Arms

- **RS 16-25 - some chemo benefit**
  - RS 16-20: 9% fewer IDFS events, including 2% fewer distant recurrences
  - RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences
- **RS 0-15 - good prognosis with endocrine therapy**
  - 3% distant recurrence with ET alone
  - no evidence for chemo benefit in RS 11-15

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



- **What about the role of genomic assays for determination of risk and chemotherapy benefit in patients with HR+/HER2- and lymph node + 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

Statistical Analysis Plan

- **Primary Objective**
  - Determine 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

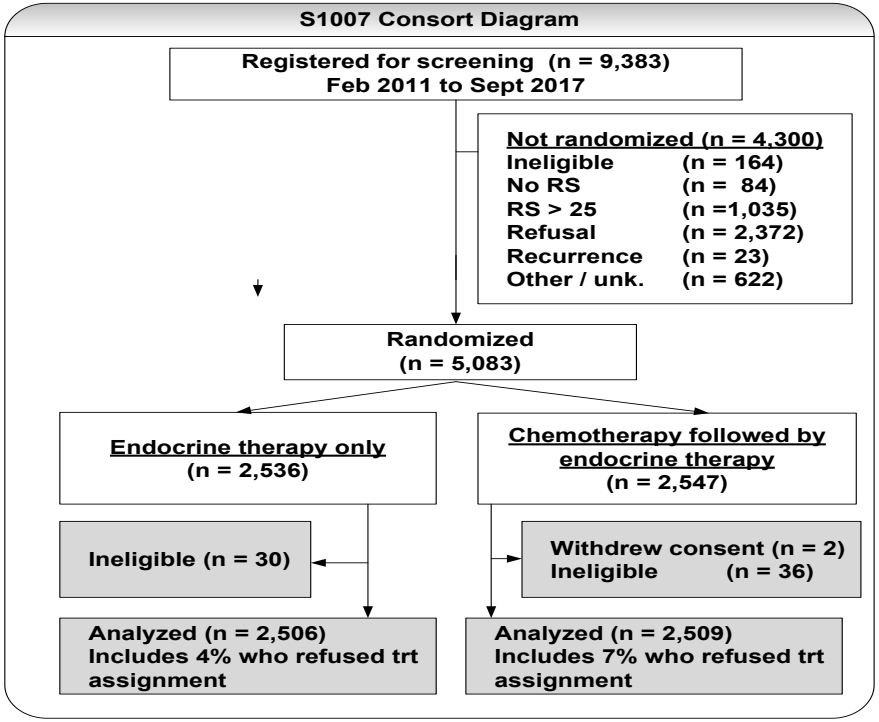
Hudis et al, JCO 2007

Statistical Analysis Plan

- **Pre-Specified Interim Analysis for IDFS**
  - Sept 2020: Third analysis at 410 events (49% of expected 832 events)
  - Nov 2, 2020: Decision made by independent DSMC and NCI to report data

- **Secondary Endpoints**
  - Overall survival
  - Distant DFS and local disease-free interval
  - Toxicity
  - Patient-reported quality of life outcomes

RxPONDER Results: Accrual and ITT population



- ✓ 50% randomized to chemotherapy received TC (4 or 6 cycles)
- ✓ Ovarian function suppression use in premenopausal pts (6-month post randomization data)
  - 16% in the ET arm and 3% in Chemotherapy + ET arm
- ✓ 2 treatment-related deaths in ET arm (stroke) and 3 in chemotherapy + ET arm (sepsis, typhlitis, and liver necrosis)

ET = Endocrine Therapy

Pre-specified Analysis by Menopausal Status

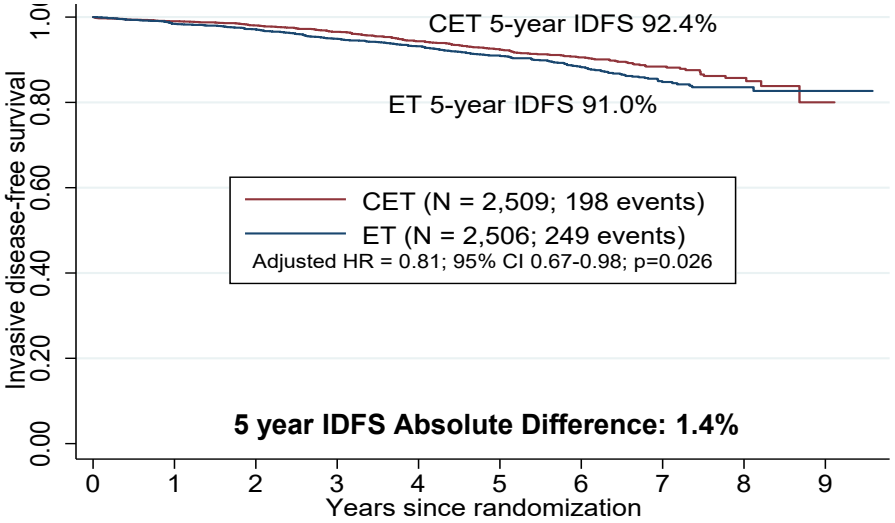
Chemotherapy benefit for IDFS is different depending on menopausal status

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

Baseline Characteristics by Treatment Arm

Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Race			
White	64.9%	66.4%	65.7%
Black	4.8%	5.1%	5.0%
Asian	6.8%	6.1%	6.5%
Other/Unknown	23.5%	22.3%	22.9%
Hispanic			
Yes	13.0%	11.9%	12.4%
No	67.6%	68.9%	68.3%
Unknown	19.4%	19.3%	19.3%
Menopausal status			
Premenopausal	33.2%	33.2%	33.2%
Postmenopausal	66.8%	66.8%	66.8%
Recurrence Score			
RS 0-13	42.7%	42.9%	42.8%
RS 14-25	57.3%	57.1%	57.2%
Nodal Dissection			
Full ALND	62.7%	62.5%	62.6%
Sentinel nodes only	37.4%	37.5%	37.4%
Positive Nodes			
1 node	65.9%	65.0%	65.5%
2 nodes	24.9%	25.7%	25.3%
3 nodes	9.2%	9.2%	9.2%
Grade			
Low	24.6%	24.7%	24.7%
Intermediate	64.1%	66.1%	65.1%
High	11.3%	9.2%	10.3%
Tumor size			
T1	58.5%	57.7%	58.1%
T2/T3	41.5%	42.3%	41.9%

IDFS in Overall Population by Treatment Arm



Number at risk

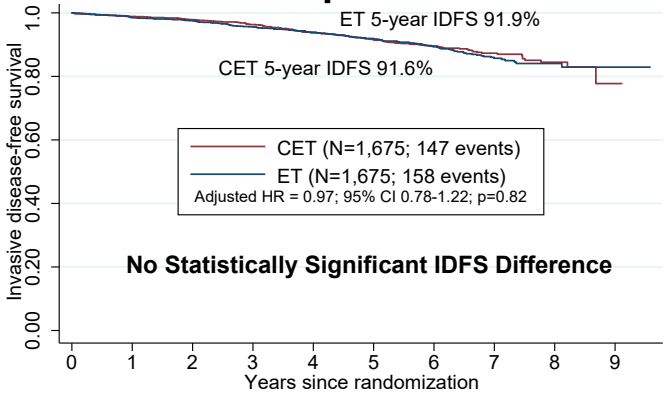
CET	2509	2277	2104	1893	1648	1397	857	403	122	4
ET	2506	2327	2161	1910	1696	1404	846	397	135	11

CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

IDFS Stratified by Menopausal Status

Postmenopausal



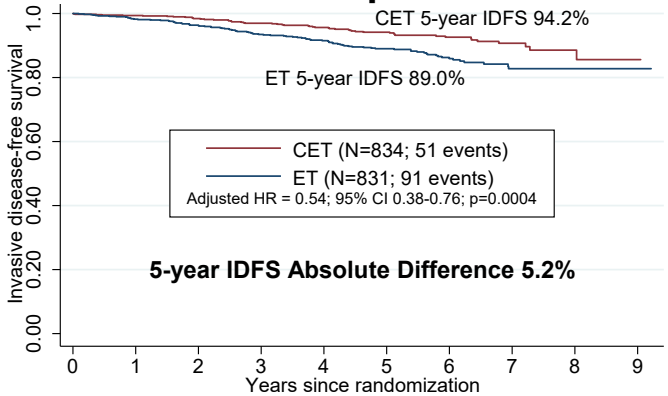
Number at risk

CET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

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 Recurrene as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



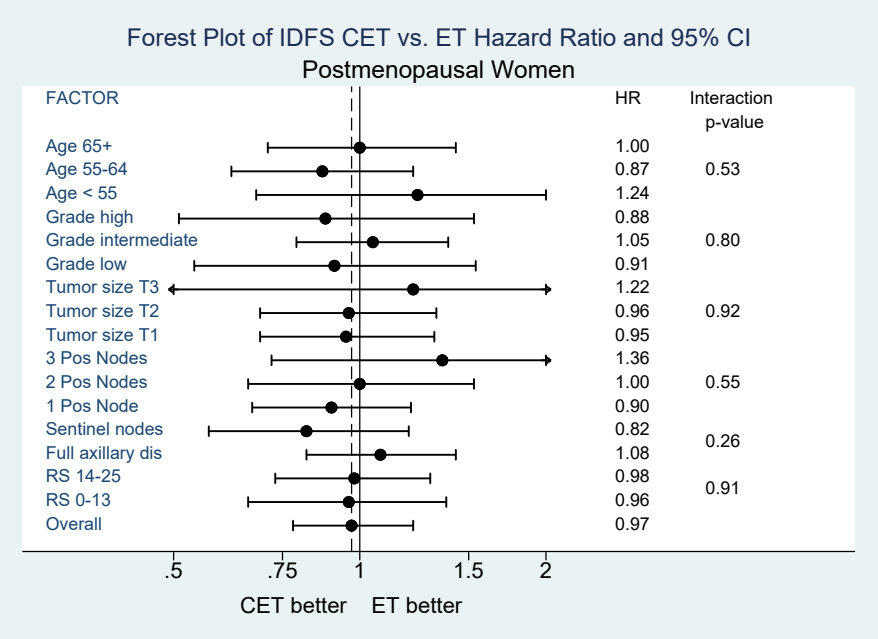
Number at risk

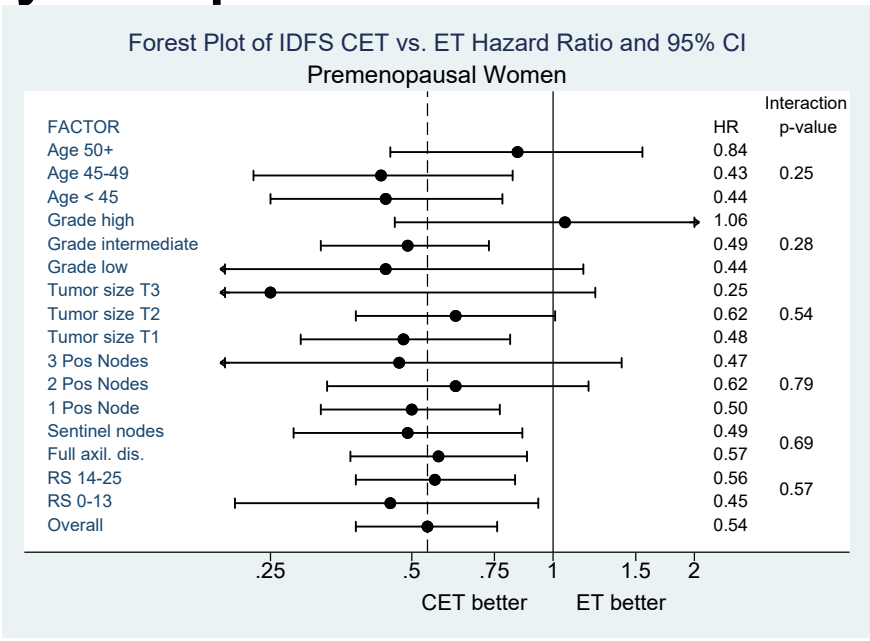
CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

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

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

Forest Plots of IDFS by Menopausal Status

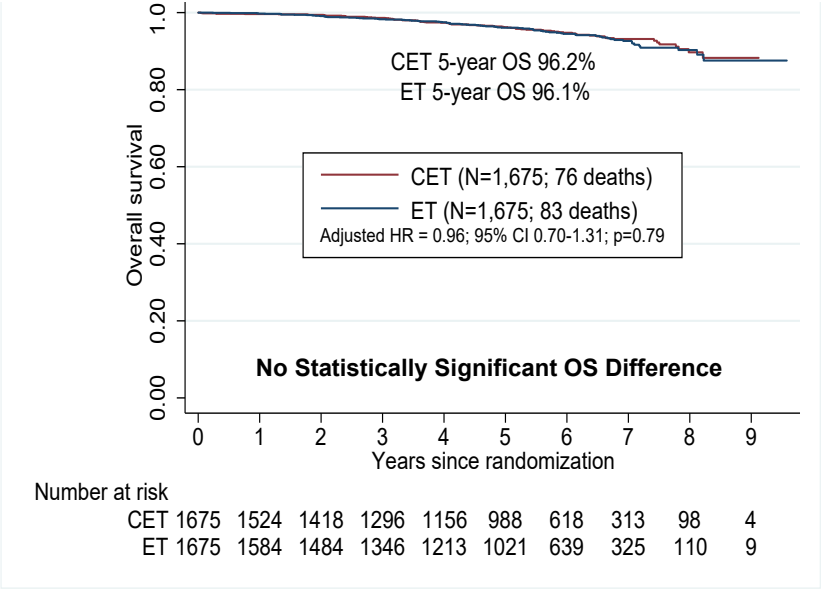




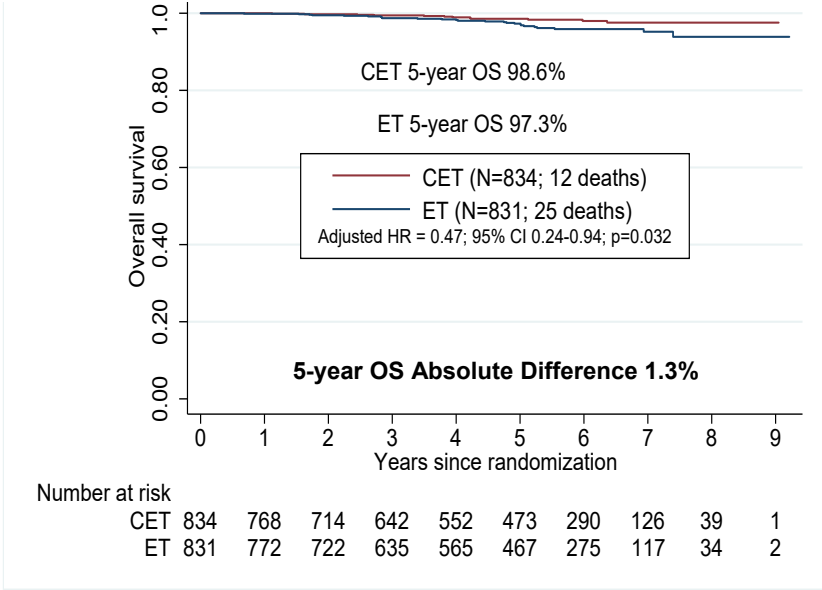
Landmarked Exploratory Analysis for IDFS in Premenopausal Women on Endocrine Therapy arm:
Ovarian Function Suppression (n=126) vs. no Ovarian Function Suppression (n=647) at 6 months: HR 0.73 (95% CI: 0.39-1.37), p=0.33

Overall Survival by Menopausal Status

Postmenopausal



Premenopausal



RxPONDER Conclusions

- ✓ **Postmenopausal women with 1-3 positive nodes and RS 0-25 can likely safely forego adjuvant chemotherapy without compromising IDFS**
  - ✓ **This will save tens of thousands of women the time, expense, and potentially harmful side effects that can be associated with chemotherapy infusions**
- ✓ **Premenopausal women with positive nodes and RS 0-25 likely benefit significantly from chemotherapy**

Limitations

- ✓ Still awaiting ~ 50% of the population to experience events
  - ✓ Unclear whether subgroup data will change with mature data?
- ✓ Is chemotherapy benefit in premenopausal women exclusively due to amenorrhea?
- ✓ Minority of patients underwent ovarian function suppression at 6 months
- ✓ 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

TransATAC:
Not All Genomic Assay are the Same!

Table 3. Univariate HRs and C Indexes for All Prognostic Signatures According to Nodal Status During Years 5 to 10

Gene Signature	Patient Group			
	Node-Negative Disease (n = 535)		Node-Positive Disease (n = 154)	
	HR (95% CI)[a]	C Index (95% CI)	HR (95% CI)[a]	C Index (95% CI)
CTS	1.95 (1.43-2.65)	0.721 (0.654-0.788)	1.61 (1.05-2.47)	0.644 (0.534-0.753)
IHC4	1.59 (1.16-2.16)	0.660 (0.576-0.745)	1.20 (0.79-1.81)	0.579 (0.460-0.697)
RS	1.46 (1.09-1.96)	0.585 (0.467-0.702)	1.24 (0.81-1.90)	0.555 (0.418-0.693)
BCI	2.30 (1.61-3.30)	0.749 (0.668-0.830)	1.60 (1.04-2.47)	0.633 (0.514-0.751)
ROR	2.77 (1.93-3.96)	0.789 (0.724-0.854)	1.65 (1.08-2.51)	0.643 (0.528-0.758)
EPclin	2.19 (1.62-2.97)	0.768 (0.701-0.835)	1.87 (1.27-2.76)	0.697 (0.594-0.799)

Sestak et al. JAMA Oncology 2018

Future Directions in HR+ Breast Cancer

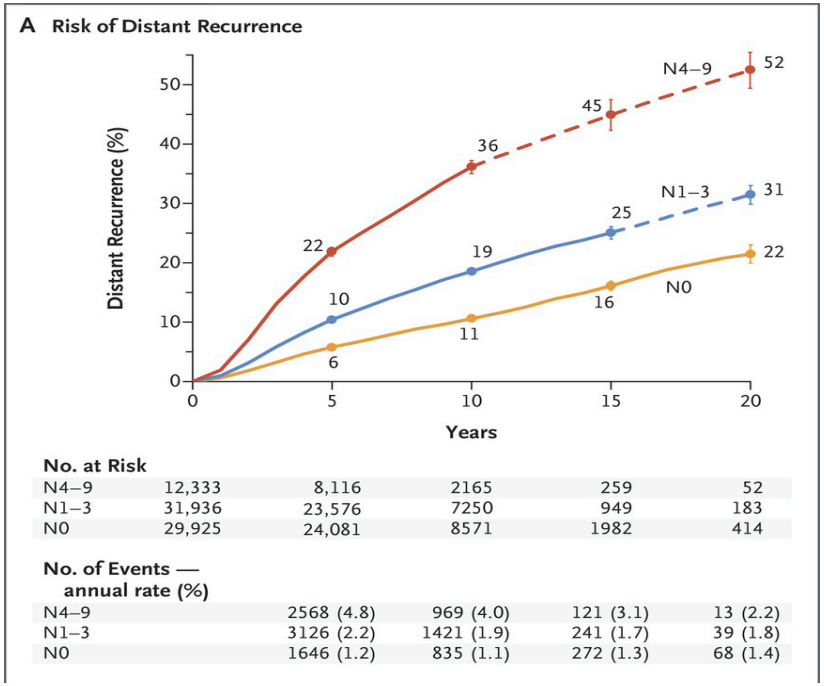
Is benefit of chemotherapy seen in TailoRx and RxPonder in premenopausal patients due to chemotherapy effect or ovarian suppression?

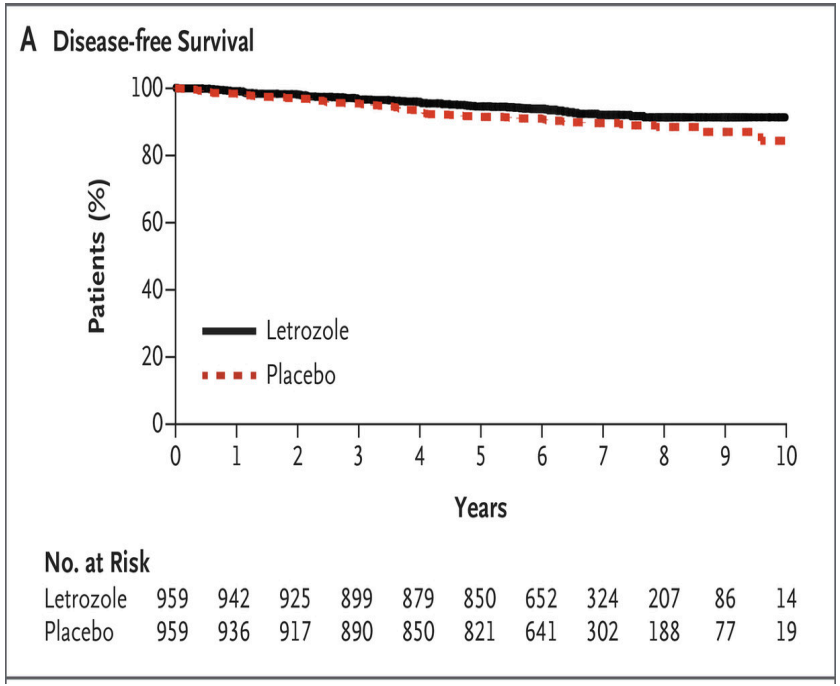
- Breast International Group (BIG)/NCTN collaboration: yearly scientific meetings and multiple collaborative efforts
  - Male Breast Cancer International Trial (NCT01101425): >1800 patients enrolled
  - POSITIVE study of endocrine therapy interruption for pregnancy (NCT02308085): 518 patients enrolled

Is there an additional opportunity to intervene in high-risk patients to prevent LATE recurrence of HR+ breast cancer?

Cardoso, Annals of Oncology, Ann Oncol. 2018 Feb 1;29(2):405-417

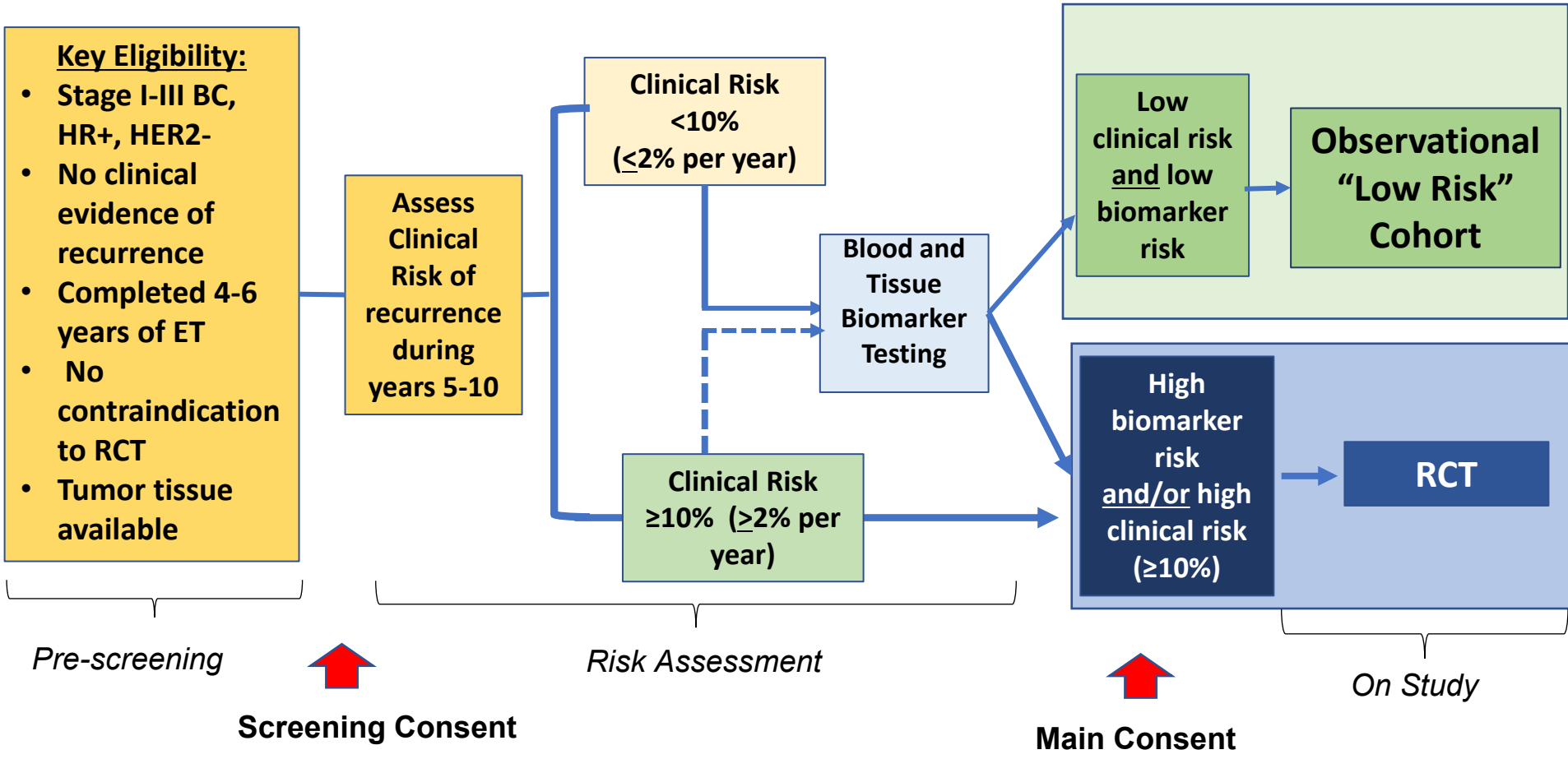
Future Direction: Late Recurrence Remains a Significant Issue in ER+/HER2- Breast Cancer





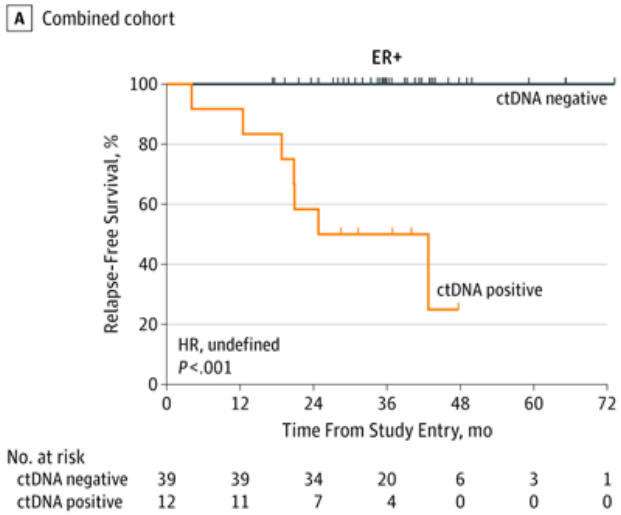
Pan H et al. N Engl J Med 2017;377:1836-1846, Goss PE et al. N Engl J Med 2016;375:209-219

Future NCTN Late Recurrence Trial: Phase III Schema



Why We are Not Ready for Phase III Trials

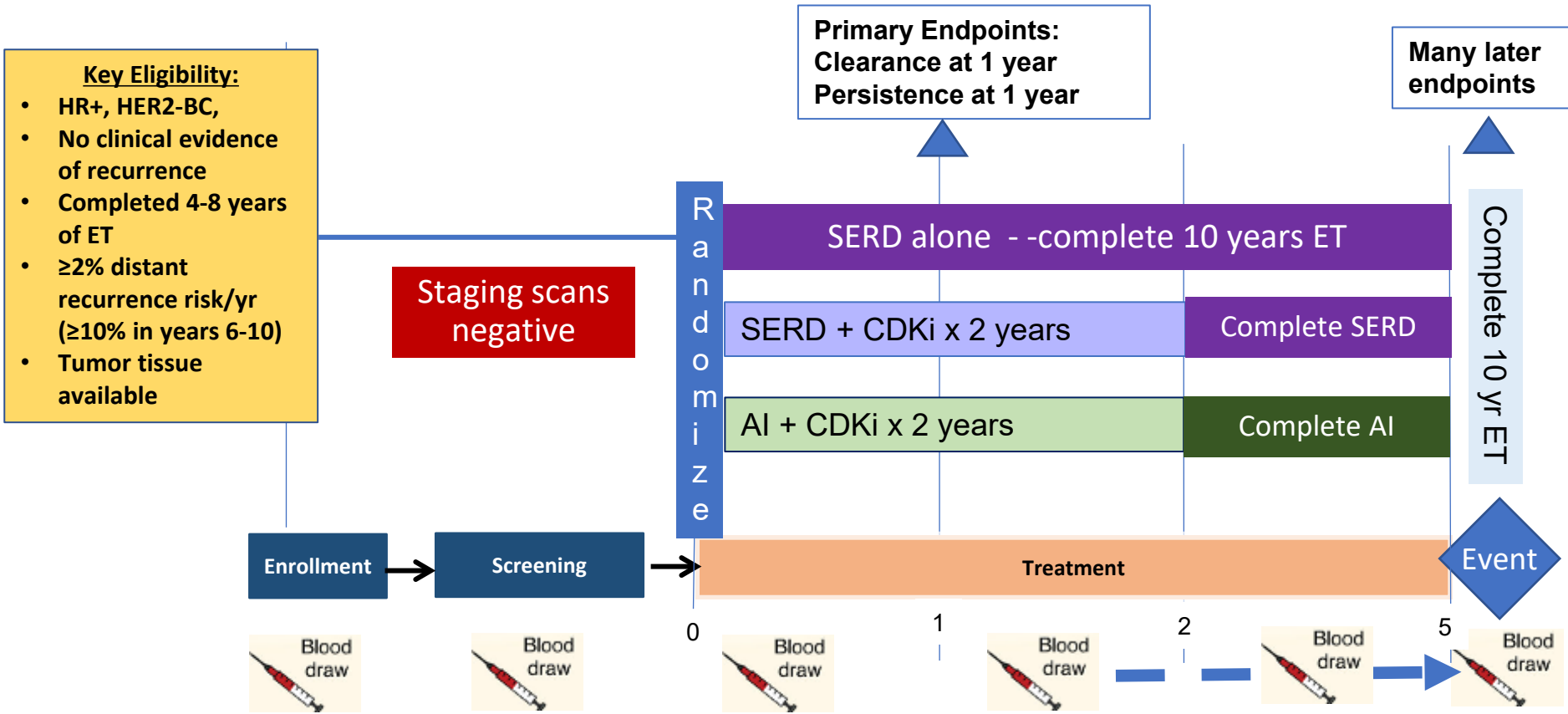
- **Role of blood-based marker detection in early-stage BC, such as ctDNA and CTCs**
  - Still in clinical validity phase
  - Differences in pre-analytic and analytic considerations
    - CTCs require real-time assessment
    - ctDNA platforms may require baseline tumor tissue
      - Bespoke vs. agnostic
    - Limited cross-platform analyses
    - Assays can vary in terms of sensitivity and detection
- **Best therapeutic intervention**
  - Oral SERDs – early in development
  - CDK4/6 inhibitors – effective in metastatic disease but conflicting data in adjuvant setting



Median lead time 10.7 months from ctDNA detection to clinical relapse

Garcia-Murillas I, et al. JAMA Oncol. 2019

Late Recurrence Phase 2 Trial Schema: Treatment Phase



- **Blood collection:** Biomarker assays are batched; patients are not informed of results
- **Timepoints:** 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, 60 months after enrollment. Anticipate two 10 mL tubes per blood-based assay

Conclusion

- **Significant Progress in Chemotherapy De-Escalation with TailorX and RxPONDER**
- **Premenopausal Patients: Identify De-escalation Strategies to Prevent Recurrence**
- **Late Recurrence: Assessing predictors and potential interventions remains critical**