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

First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy +/- chemotherapy in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007

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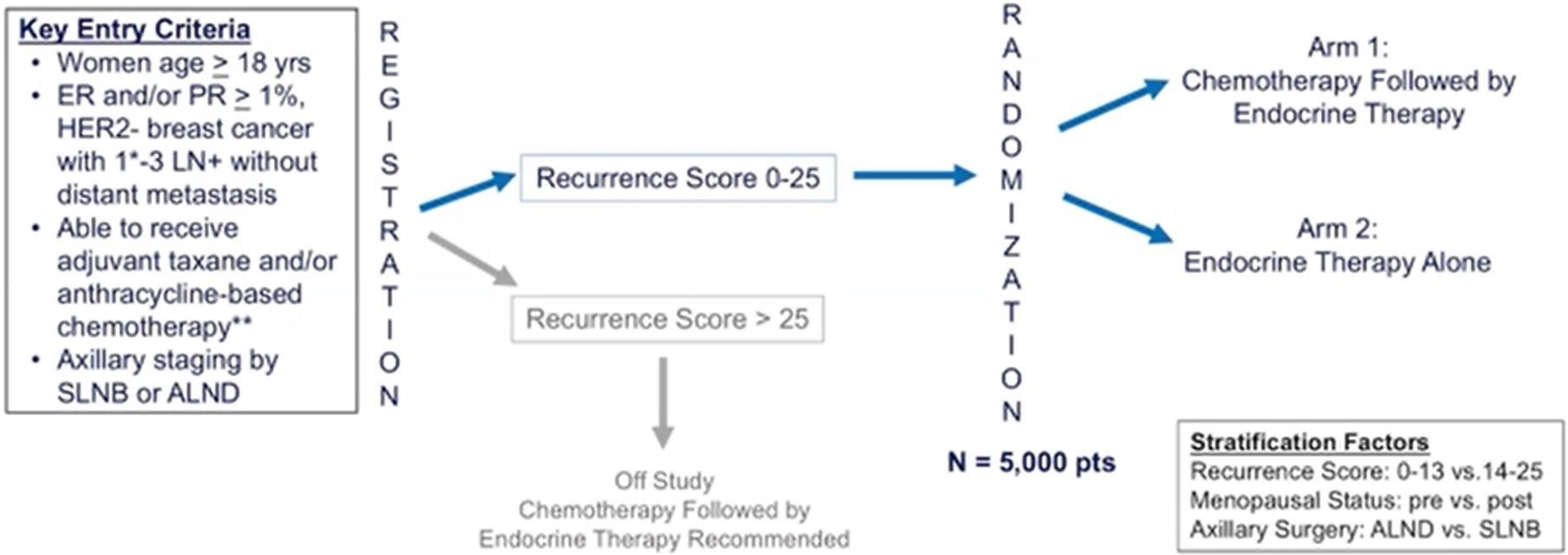
RxPONDER Background

- Clinical utility of the 21-gene Oncotype DX Recurrence Score (RS) to identify pts with HR+, HER2-, lymph node negative (LN-) breast cancer who can safely forego chemotherapy is established
- In LN- breast cancer, exploratory analysis from the TAILORx trial
    - Age $\leq$ 50: RS 16-25 may derive chemotherapy benefit
    - Age > 50: RS $\leq$ 25 have no chemotherapy benefit
- It has been unclear whether the TAILORx results can be extrapolated to LN+ breast cancer
- Retrospective analysis of SWOG S8814 suggested a predictive role of the RS for chemotherapy benefit in postmenopausal pts with LN+ breast cancer

Pan et al, NEJM 2017; Sparano et al, NEJM 2018; Sparano al, NEJM 2019, Albain et al, Lancet Oncology 2016

RxPONDER Schema



* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

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

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 $\leq$ 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

- **Primary Analysis for Prediction**
  - Test for **interaction** of chemotherapy and continuous RS for IDFS in a Cox regression model
    - If significant
      - Conclude that RS has a predictive effect on the relative benefit of chemotherapy within RS 0-25
    - If not significant
      - In patients with RS 0-25, determine whether RS and chemotherapy are independently prognostic for IDFS, adjusting for menopausal status

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    - If significant
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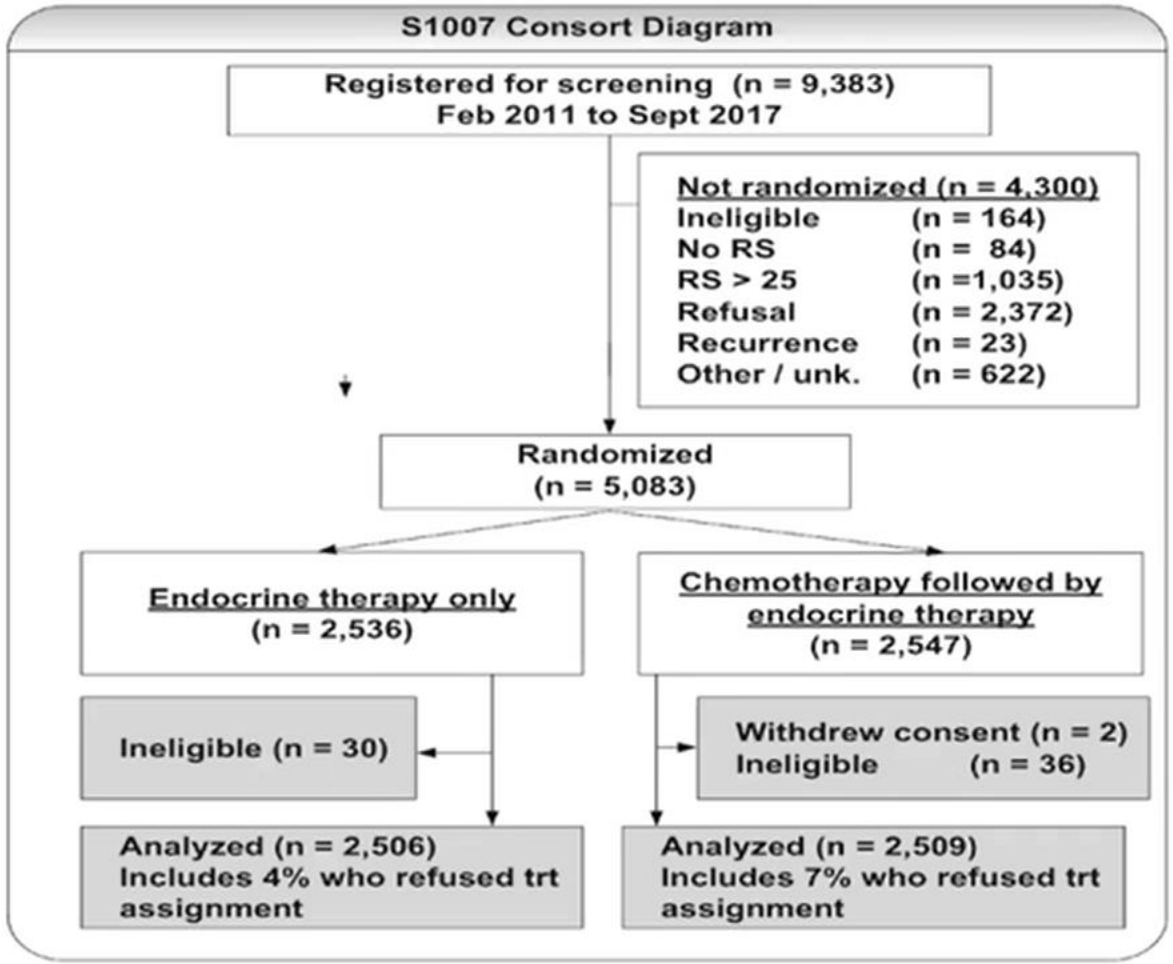
    - If not significant
      - In patients with RS 0-25, determine whether RS and chemotherapy are independently prognostic for IDFS, adjusting for menopausal status
  - 86.3% power to detect a predictive effect with a 5-year overall IDFS rate of 92.4%
  - Pre-specified test for the interaction of chemotherapy and each stratification factor

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

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%

Baseline Characteristics by Menopausal Status

Baseline variable	Postmenopausal (n=3,350)	Premenopausal (n=1,665)	Overall (n=5,015)
Age group			
< 40 years	0.2%	8.5%	2.9%
40-49 years	1.9%	60.8%	21.5%
50-59 years	34.9%	30.5%	33.4%
60-69 years	45.7%	0.2%	30.6%
70+ years	17.3%	0%	11.6%
Recurrence Score			
RS 0-13	44.8%	38.7%	42.8%
RS 14-25	55.2%	61.3%	57.2%
Nodal Dissection			
Full ALND	60.7%	66.4%	62.6%
Sentinel nodes only	39.3%	33.6%	37.4%
Positive Nodes			
1 node	65.6%	65.3%	65.5%
2 nodes	25.1%	25.7%	25.3%
3 nodes	9.3%	9.0%	9.2%
Grade			
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Intermediate	63.5%	68.3%	65.1%
High	10.6%	9.7%	10.3%
Tumor size			
T1	59.1%	56.2%	58.1%
T2/T3	41.9%	43.9%	41.9%

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Primary Analysis with Interaction Term

Amongst pts with RS 0-25, RS does not predict the relative benefit of chemotherapy for IDFS

Relative benefit of chemotherapy is not smaller with a lower RS and not greater with a higher RS

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.56	0.07	0.30 – 1.05
RS (per unit change)	1.05	<0.001	1.02 – 1.07
Menopausal status	1.00	0.97	0.82-1.24
Chemo x RS Interaction	1.02	0.30	0.98-1.06

Since the interaction of chemotherapy and RS was not significant, the next step in the primary analytic plan was to drop this interaction term and assess the prognostic significance of these variables

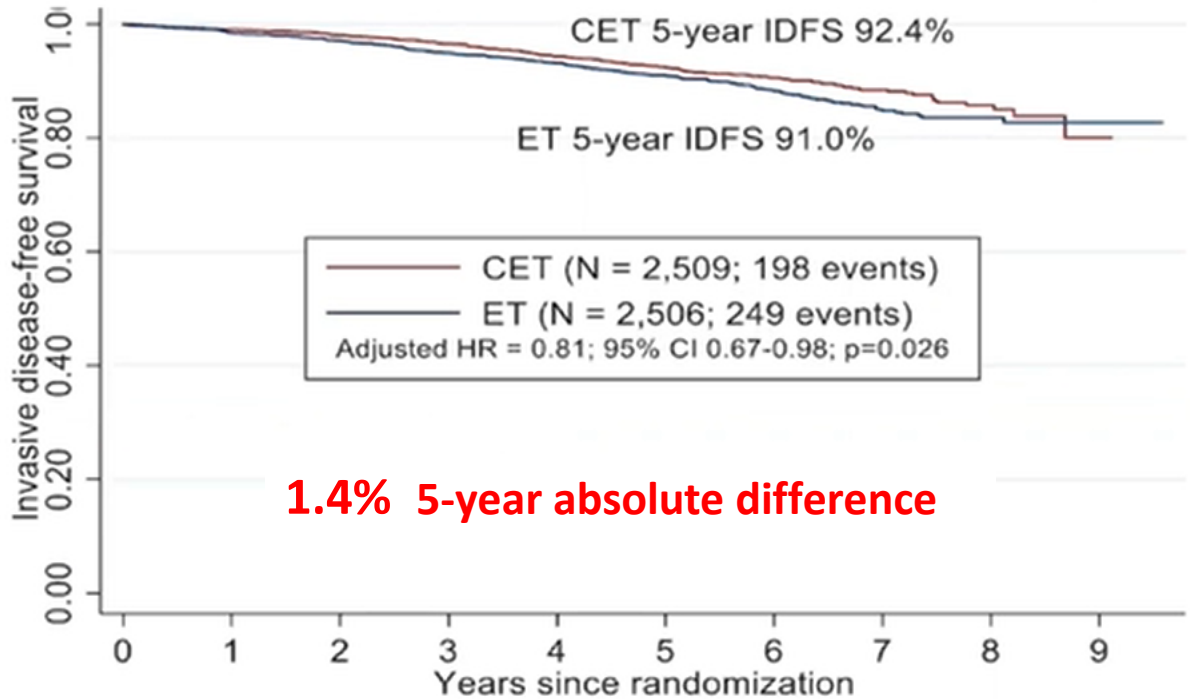
Primary Analysis without Interaction Term:

Chemotherapy use and RS are independently prognostic for IDFS

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.81	0.026	0.67 – 0.96
RS (per unit change)	1.06	<0.001	1.04 – 1.07
Menopausal status	1.03	0.77	0.82-1.26

Pts who received chemotherapy less likely to have an IDFS event

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

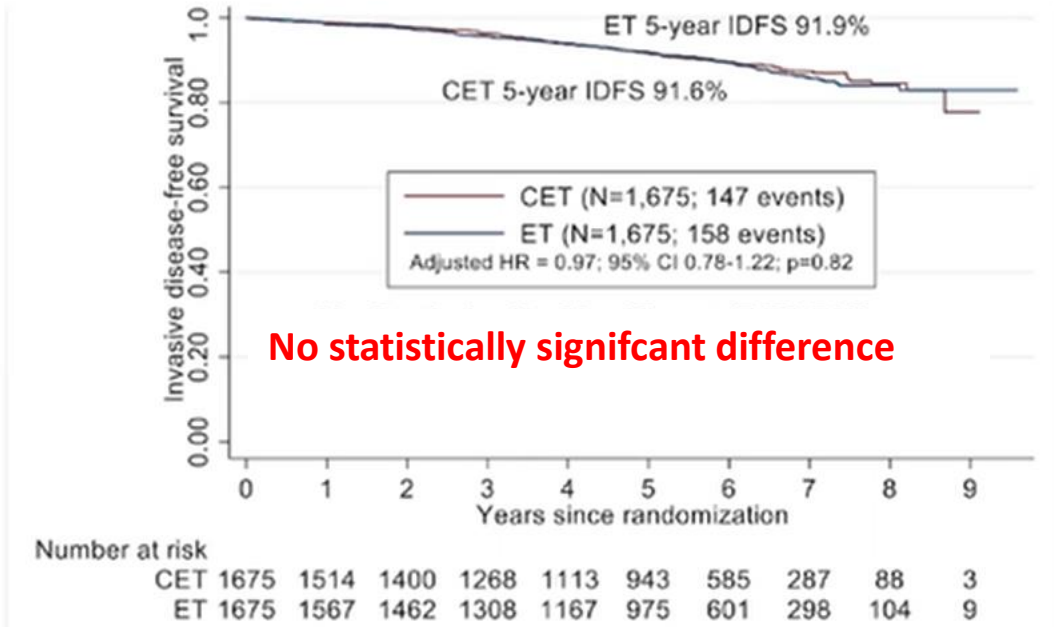
Pre-specified Analysis by Menopausal Status

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

IDFS Stratified by Menopausal Status

Postmenopausal

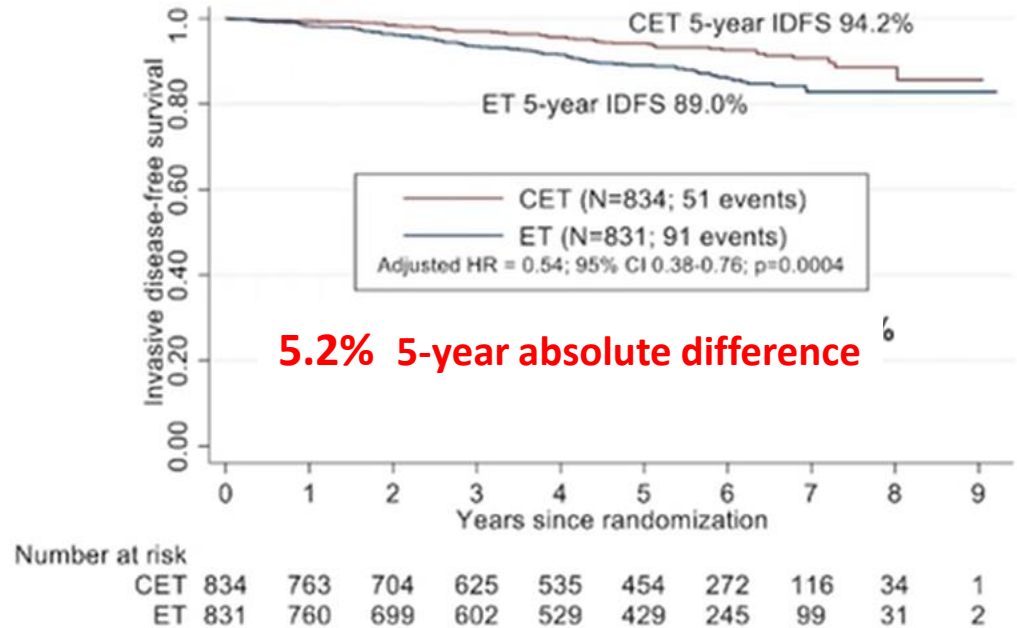


No statistically signifcant difference

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

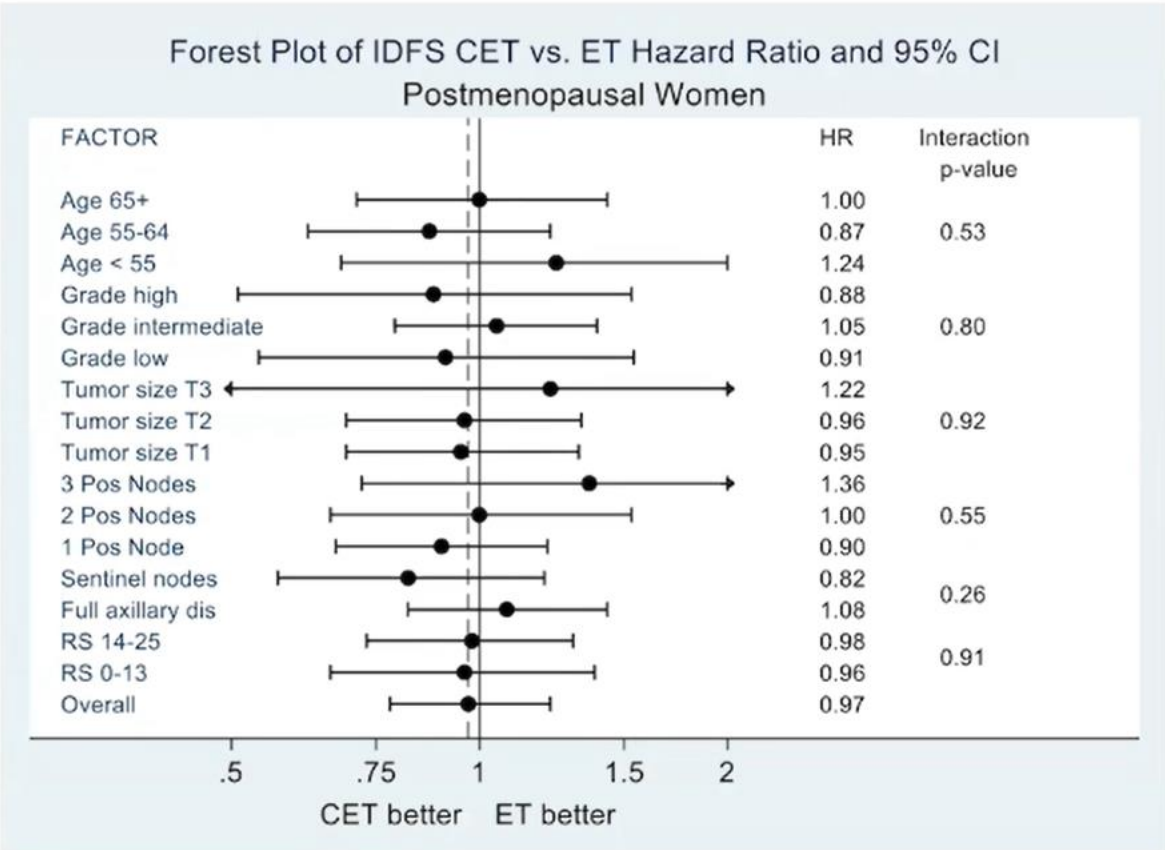


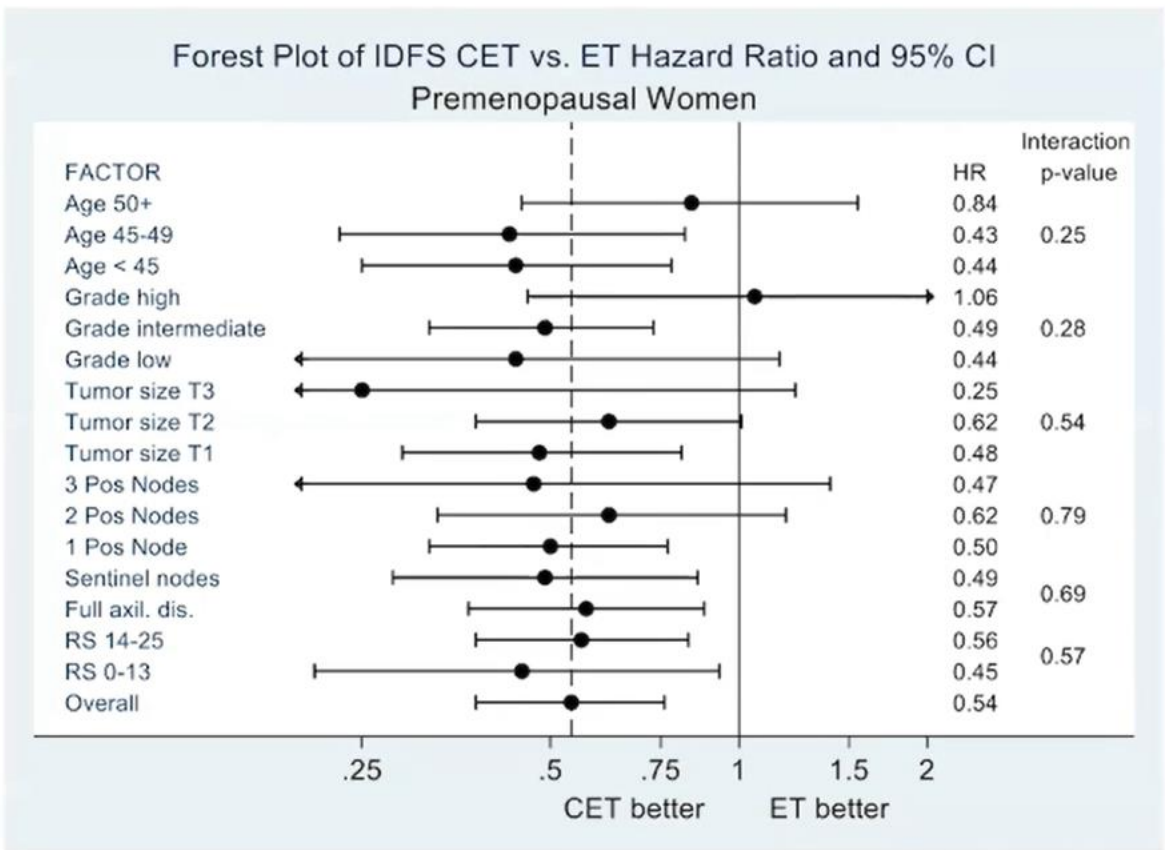
5.2% 5-year absolute difference

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



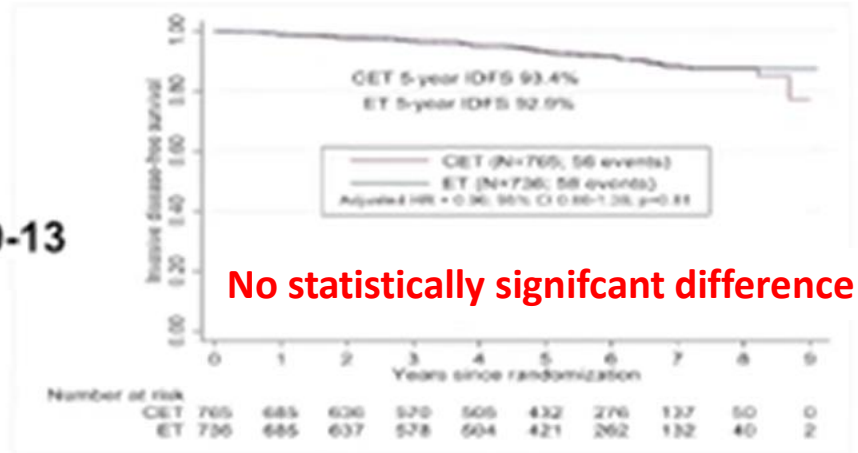


Landmarked Exploratory Analysis for IDFS in Premenopausal Women on Endocrine Therapy arm:
Ovarian Function Suppression (n=126) vs. no Ovarian Function Suppression (n=647) at 6 months: HR 0.73 (95% CI: 0.39-1.37), p=0.33

IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

RS 0-13



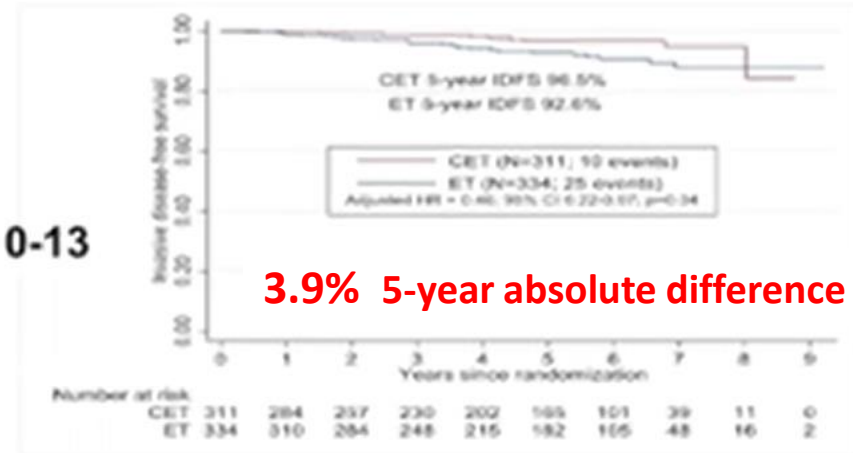
No statistically signifcant difference

RS 14-25

No statistically signifcant difference

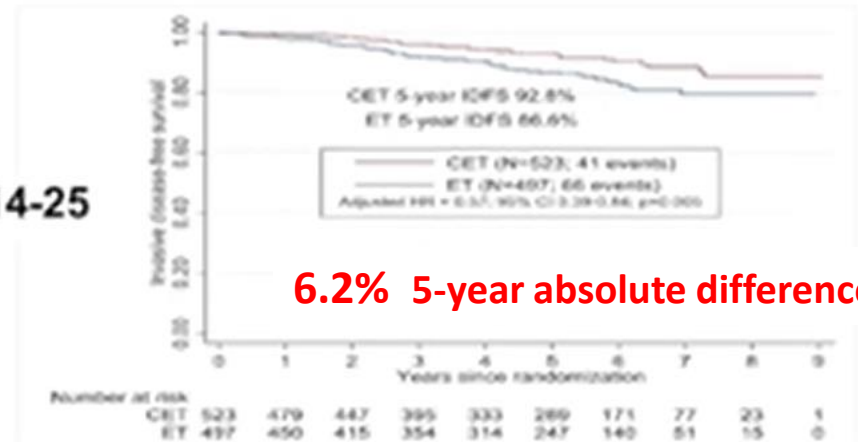
Premenopausal

RS 0-13



3.9% 5-year absolute difference

RS 14-25

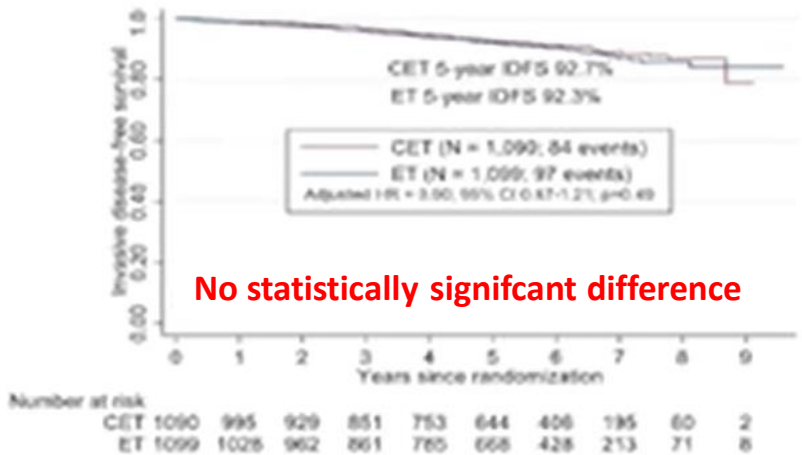


6.2% 5-year absolute difference

IDFS Stratified by Number of Nodes and Menopausal Status

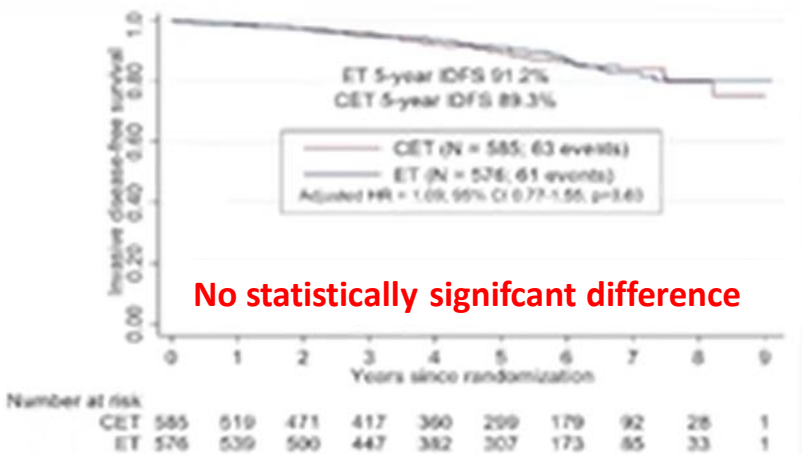
Postmenopausal

1 Node



No statistically signifcant difference

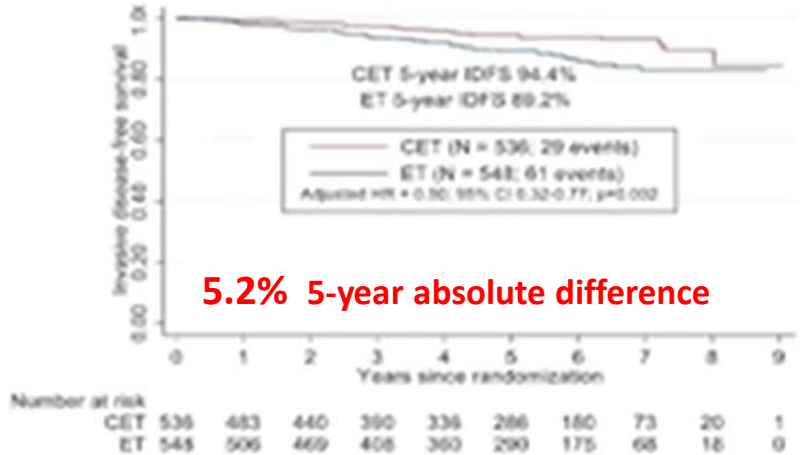
2-3 Nodes



No statistically signifcant difference

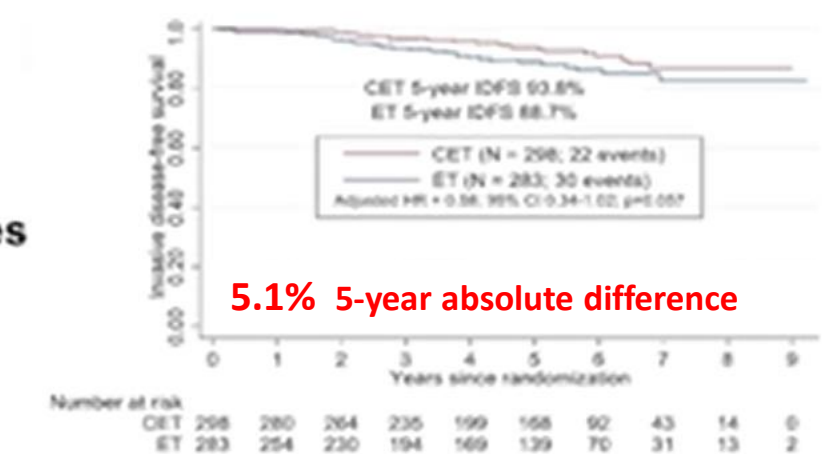
Premenopausal

1 Node



5.2% 5-year absolute difference

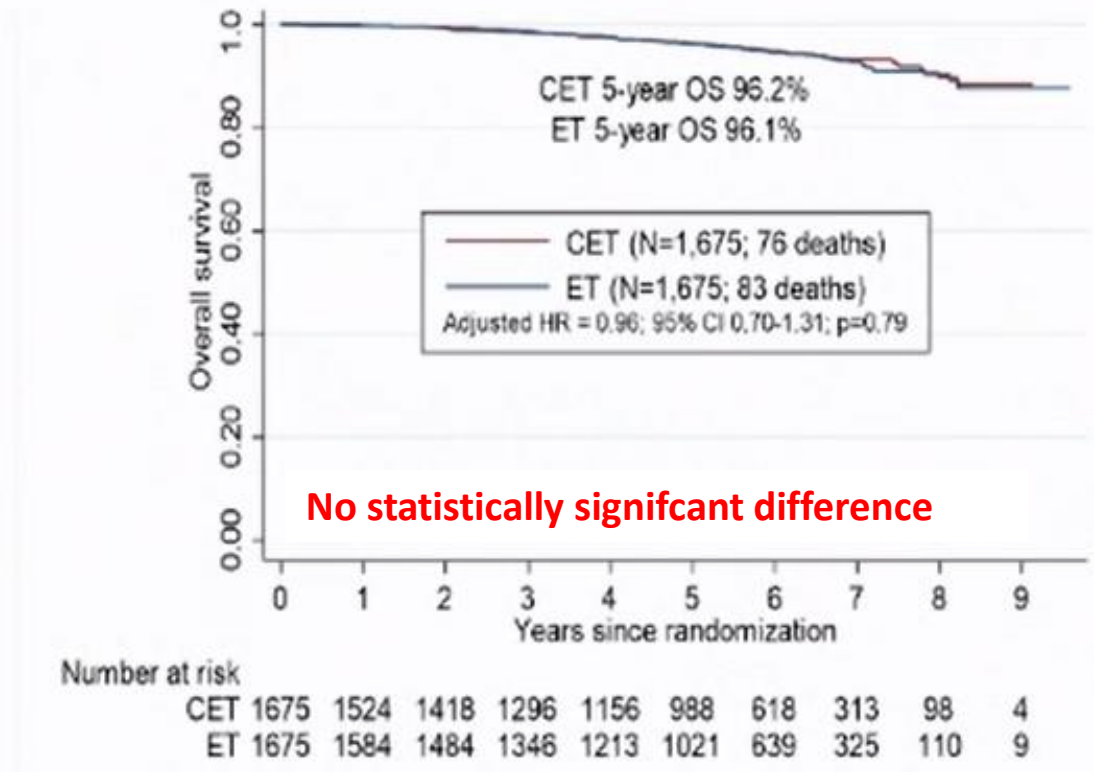
2-3 Nodes



5.1% 5-year absolute difference

Overall Survival by Menopausal Status

Postmenopausal



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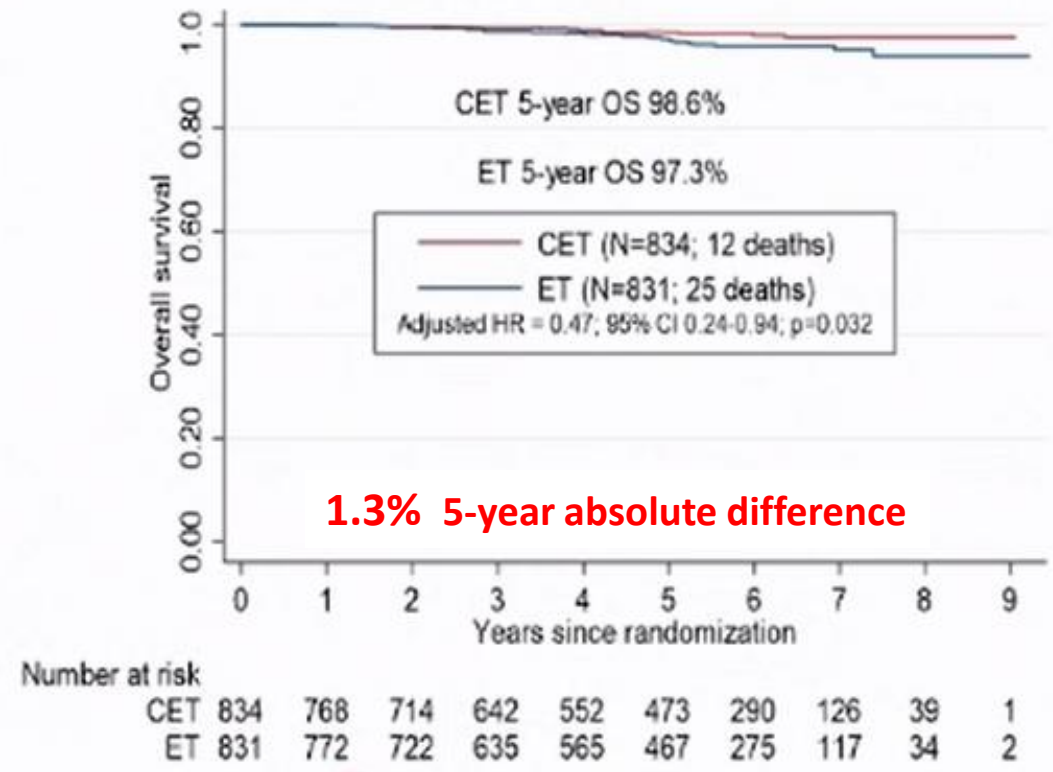

1.3% 5-year absolute difference

RxPONDER Conclusions

- At this interim analysis with 54% of anticipated IDFS events in the overall population, the 21-gene RS 0-25 was prognostic but did not show a treatment interaction with chemotherapy
  - Relative benefit of chemotherapy was similar across RS 0-25
- Postmenopausal women with RS 0-25 did not benefit from adjuvant chemotherapy in any subgroup
- Premenopausal women with RS 0-25 had benefit from the addition of chemotherapy to endocrine therapy
  - 46% decrease in IDFS events; benefit was observed across premenopausal subgroups
  - 53% decrease in deaths, leading to a 5-year OS absolute improvement of 1.3%
- Additional follow-up is ongoing, and future analyses will also include QOL and other outcomes

RxPONDER Conclusions

- ✓ Postmenopausal women with 1-3 positive nodes and RS 0-25 can likely safely forego adjuvant chemotherapy without compromising IDFS

- ✓ Premenopausal women with positive nodes and RS 0-25 likely benefit significantly from chemotherapy

Acknowledgements

- Patients and their support system
- National Cancer Institute
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  - Breast Cancer Research Foundation
  - Susan G. Komen for the Cure® Research Program
  - Unicancer Breast Group
- Exact Sciences
- Collaborating Groups: SWOG international sites in Mexico and Korea, ECOG-ACRIN, NRG, Alliance, NCIC-CTG, Unicancer Breast Group, GEICAM
- 632 Participating Sites - health care providers and research staff
- Ana M. Gonzalez-Angulo, MD; Dawn Hershman, MD, MS; Jo Anne Zujewski, MD; Larissa Korde, MD, MPH; Ginny Mason; Elda Railey