



SAN ANTONIO  
BREAST CANCER  
SYMPOSIUM®

Henry B. Gonzalez Convention Center,  
San Antonio, Texas, USA

2017 DEC. 5-9

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INTERNATIONAL BREAST CANCER STUDY GROUP

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# Randomized Comparison of Adjuvant Tamoxifen plus Ovarian Function Suppression vs Tamoxifen in Premenopausal Women with HR+ Early Breast Cancer: Update of the SOFT Trial

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**on behalf of SOFT Investigators and  
International Breast Cancer Study Group (IBCSG)**



# SOFT: Suppression of Ovarian Function Trial

Enrolled: Dec 2003-Jan 2011

Stratification

**Receipt of (neo)adjuvant chemotherapy**

- No chemo, enrolled within 12 weeks of surgery (47%)
- Prior chemo, premenopausal E2 level within 8 months (53%)

**Nodal status**

- Positive (34.5%)

**OFS method intended**

- Triptorelin (91%)

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Tamoxifen x 5y (n=1018)

**Tamoxifen+OFS x 5y (n=1015)**

**Exemestane+OFS x 5y (n=1014)**

Median follow-up 8 years

OFS=Ovarian Function Suppression



# Patient Characteristics

|              | No Chemotherapy<br>N=1419 | Prior Chemotherapy<br>N=1628 | All<br>N=3047 |
|--------------|---------------------------|------------------------------|---------------|
| Age (median) | 46 yr                     | 40 yr                        | 43 yr         |
| <35 years    | <b>1.5%</b>               | <b>20.2%</b>                 | 11.5%         |
| Nodal status |                           |                              |               |
| positive     | <b>8.8%</b>               | <b>56.9%</b>                 | 34.5%         |
| negative     | 91.2%                     | 43.1%                        | 65.5%         |
| Grade        |                           |                              |               |
| 1            | 39.7%                     | 13.8%                        | 25.9%         |
| 2            | 52.8%                     | 49.5%                        | 51.0%         |
| 3            | <b>6.5%</b>               | <b>33.7%</b>                 | 21.0%         |
| HER2+        | <b>3.7%</b>               | <b>19.2%</b>                 | 12.0%         |



# Endpoints

## Primary:

- **Disease-free survival (DFS)**
  - Invasive recurrence (local, regional, distant)
  - Invasive contralateral breast cancer
  - Second (non-breast) invasive malignancy
  - Death without prior cancer event

## Secondary:

- **Breast cancer-free interval (BCFI)**
  - Invasive recurrence or contralateral breast cancer
- **Distant recurrence-free interval (DRFI)**
  - Distant recurrence
- **Overall survival (OS)**
  - Death from any cause



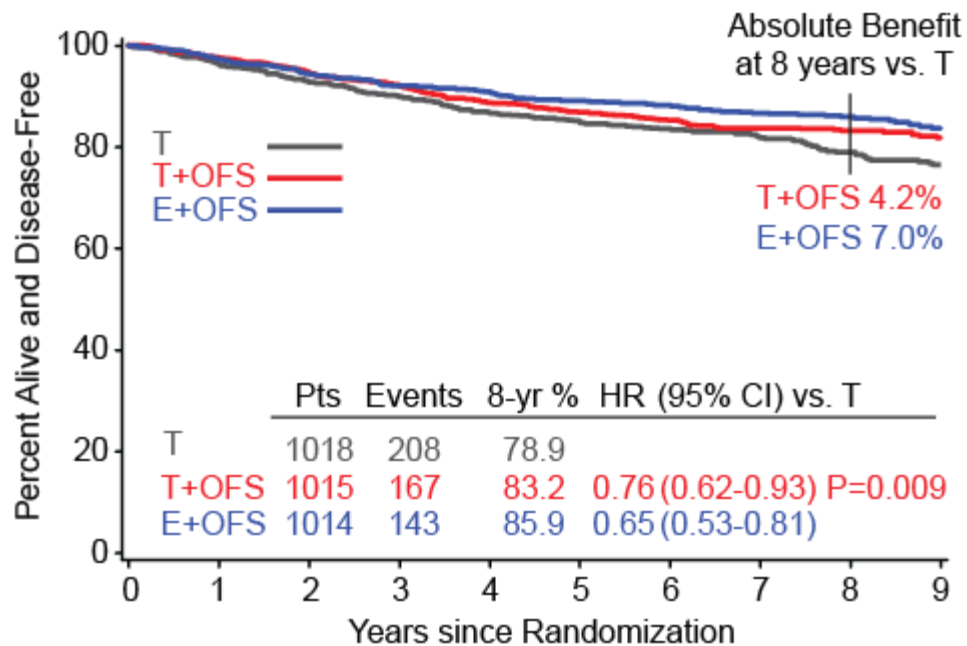
# SOFT Primary Results

- After 5.6 years median follow-up, the primary results of SOFT found adding OFS to T did not provide a significant benefit in the overall study population of premenopausal women with HR+ BC (*NEJM 2015*)
- For those women at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of OFS improved disease outcomes
- Follow-up was immature for overall survival
- We report a planned update after 8 years median follow-up



# SOFT DFS

## 8 years median follow-up



**T+OFS significantly improves DFS vs T-alone in the overall population**



# SOFT DFS

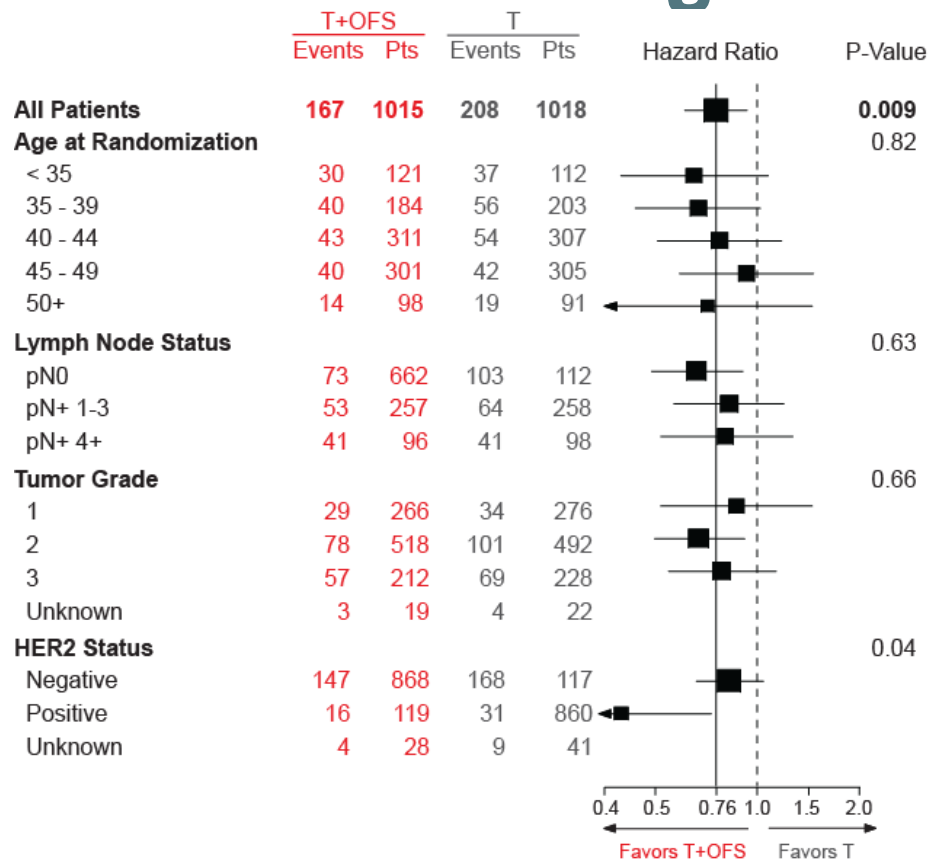
## 8 years median follow-up

|                   | 8-yr DFS<br>T | 8-yr DFS<br>T + OFS | HR: T + OFS<br>vs T | 8-yr DFS<br>E + OFS | HR: E + OFS<br>vs T |
|-------------------|---------------|---------------------|---------------------|---------------------|---------------------|
| All               | <b>78.9%</b>  | <b>83.2%</b>        | 0.76 (0.62-0.93)    | <b>85.9%</b>        | 0.65 (0.53-0.81)    |
| No chemo          | <b>87.4%</b>  | <b>90.6%</b>        | 0.76 (0.52-1.12)    | <b>92.5%</b>        | 0.58 (0.38-0.88)    |
| Prior chemo       | <b>71.4%</b>  | <b>76.7%</b>        | 0.76 (0.60-0.97)    | <b>80.4%</b>        | 0.68 (0.53-0.88)    |
| <35 years (n=350) | <b>64.3%</b>  | <b>73.0%</b>        | 0.66 (0.41-1.07)    | <b>77.4%</b>        | 0.52 (0.31-0.87)    |





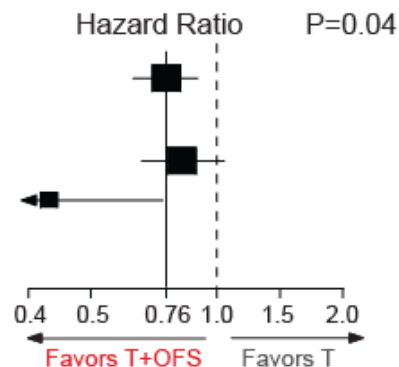
# SOFT DFS: According to Subgroups



# SOFT DFS: Effect of HER2 Status

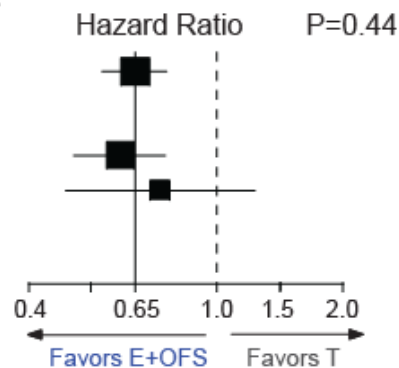
## T + OFS vs T

|                     | T+OFS  |      | T      |      |
|---------------------|--------|------|--------|------|
|                     | Events | Pts  | Events | Pts  |
| <b>All Patients</b> | 167    | 1015 | 208    | 1018 |
| <b>HER2 Status</b>  |        |      |        |      |
| Negative            | 147    | 868  | 168    | 860  |
| Positive            | 16     | 119  | 31     | 117  |
| Unknown             | 4      | 28   | 9      | 41   |



## E + OFS vs T

|                     | E+OFS  |      | T      |      |
|---------------------|--------|------|--------|------|
|                     | Events | Pts  | Events | Pts  |
| <b>All Patients</b> | 143    | 1014 | 208    | 1018 |
| <b>HER2 Status</b>  |        |      |        |      |
| Negative            | 105    | 858  | 168    | 860  |
| Positive            | 31     | 130  | 31     | 117  |
| Unknown             | 7      | 26   | 9      | 41   |

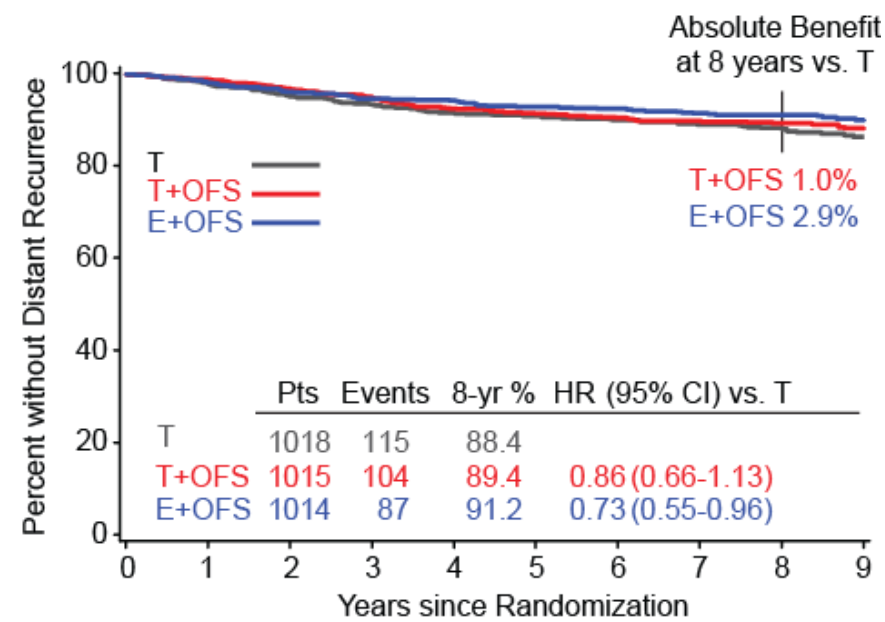


61% of HER2+ received trastuzumab

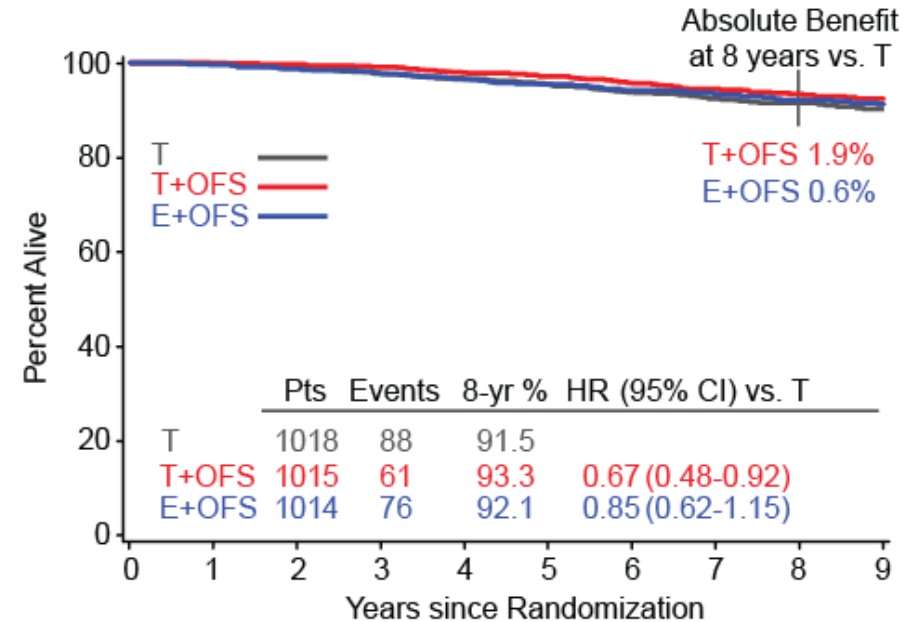


# SOFT Secondary Endpoints

## Distant Recurrence-Free Interval



## Overall Survival

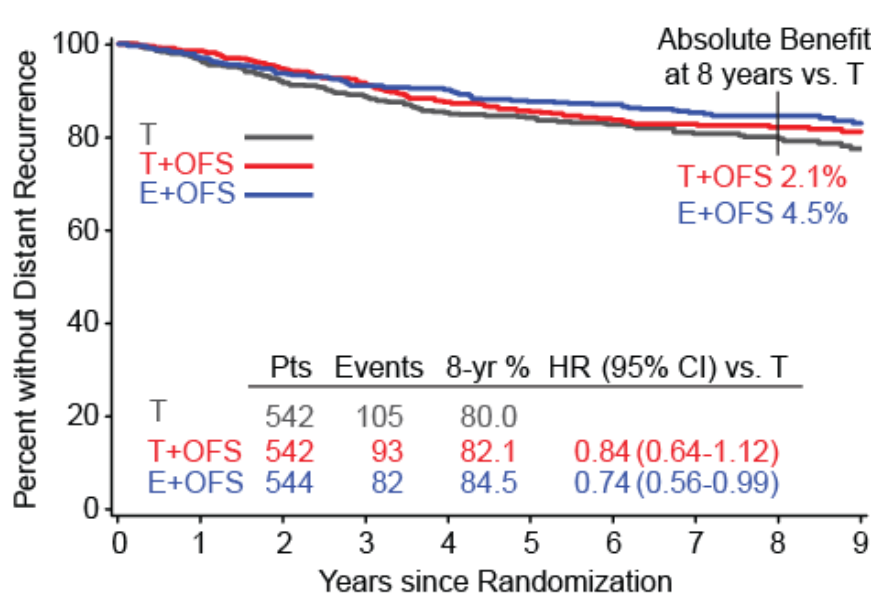


**A small overall survival benefit is seen with T+OFS vs T, at 8 yrs median follow-up**

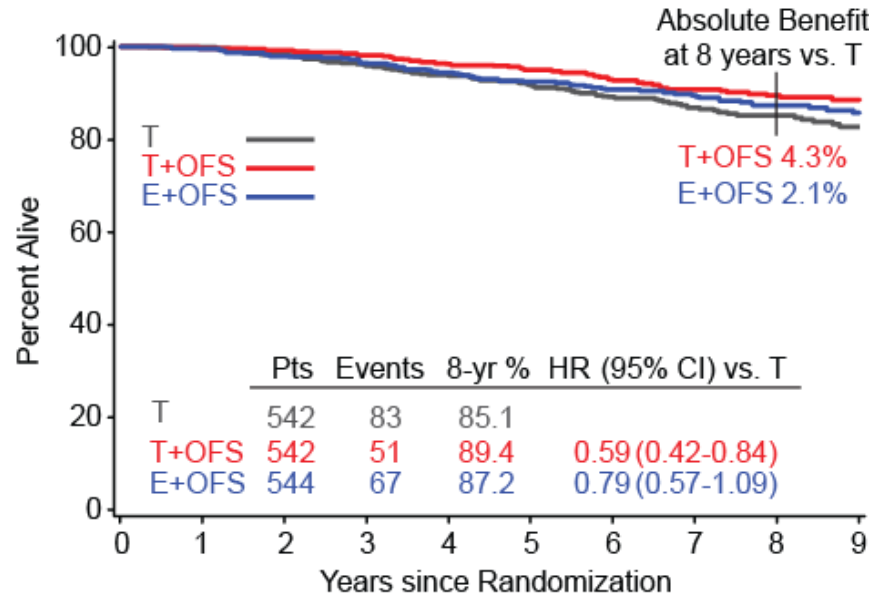


# SOFT Secondary Endpoints: Prior Chemo

## Distant Recurrence-Free Interval



## Overall Survival

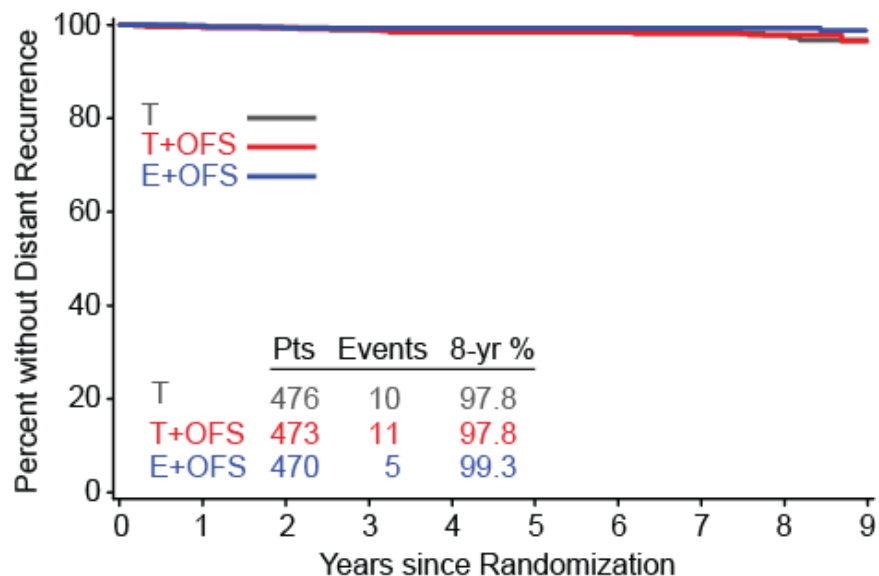


**Prior Chemo cohort has small absolute OS improvements in OFS arms at 8 yrs**

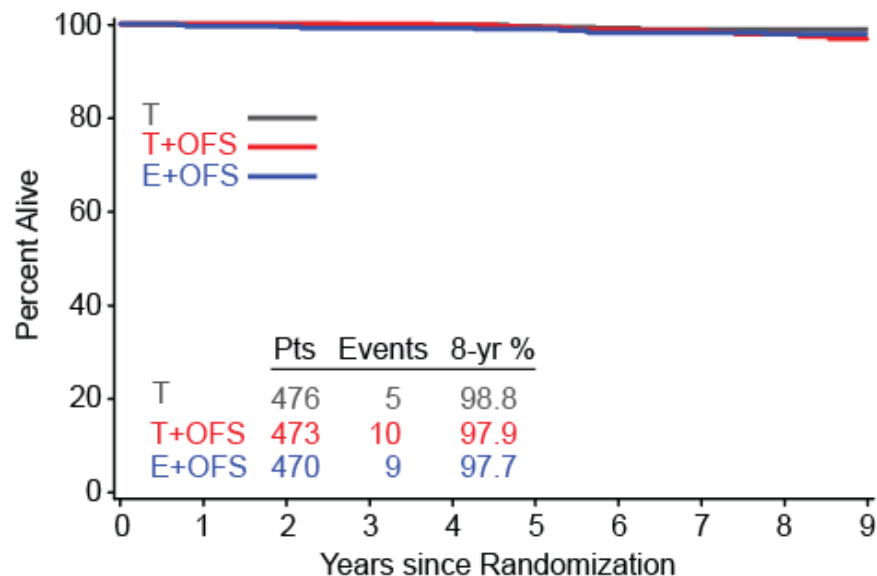


# SOFT Secondary Endpoints: No Chemo

Distant Recurrence-Free Interval



Overall Survival



**No Chemo cohort remains at low risk of distant recurrence with T alone;  
12 of 24 deaths were in setting of no distant recurrence**



# Protocol and Non-protocol Therapy

|   | T     | T + OFS | E + OFS |
|---|-------|---------|---------|
| Stopped assigned oral endocrine therapy early | 22.5% | 18.5%   | 27.8%   |
| Stopped triptorelin early*                    |       | 21.4%   | 19.6%   |
| Received OFS (in first 5 yrs)                 | 15.5% |         |         |
| Used oral endocrine therapy at $\geq 6$ yr**  | 24.7% | 24.3%   | 12.6%   |

\*and did not undergo oophorectomy or ovarian irradiation

\*\*as adjuvant therapy; denominator is patients alive and in follow-up at 6 yrs



# Selected Adverse Events

|                                   | T<br>(N=1005) | T + OFS<br>(N=1006) | E + OFS<br>(N=1000) |
|-----------------------------------|---------------|---------------------|---------------------|
| Endometrial cancer (n)            | <b>N=7</b>    | <b>N=4</b>          | N=3                 |
| Thrombosis/embolism (G2-4)        | <b>2.2%</b>   | <b>2.2%</b>         | 0.9%                |
| Hot flashes (G3)                  | 7.8%          | <b>13.2%</b>        | <b>10.7%</b>        |
| Libido decrease (G2)              | 11.5%         | <b>15.9%</b>        | <b>17.5%</b>        |
| Musculoskeletal symptoms (G3-4)   | 6.7%          | 5.9%                | <b>12.0%</b>        |
| Osteoporosis (G2-4; T score<-2.5) | 3.9%          | 6.1%                | <b>11.9%</b>        |
| Depression (G3-4)                 | 4.1%          | 4.5%                | 3.9%                |



# Conclusions

- Addition of OFS to tamoxifen significantly improves DFS at 8 yrs median follow-up
  - HR=0.66 (8.7% absolute benefit) in DFS for women under age 35
  - DFS outcomes further improved by use of exemestane plus OFS
- Small OS benefit is seen at 8 yrs
  - Evident in women with prior chemotherapy
  - Consistent with time course of events in ER+ disease
- Population not receiving chemotherapy has a low risk of distant metastases at 8 yrs with tamoxifen alone
- Follow-up continues

