Ten-year results from NRG Oncology/NSABP B-42: A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant therapy with an aromatase inhibitor (AI)

EP Mennounos1, H Bandos1, BC Lembarky1, JH Jarmakani1, CE Geyer Jr.1, P Rashidi2, L Freiermuth1, BL Grundy1, SL Chin1, AM Buagn1, CM Watkins1, GS Scott3, SJ Blank1, TE Sandy1, RL Wade4, P McCarron5, S Poli6, SJ Swan7, DL Weickert2,8, R Wolters9

San Antonio Breast Cancer Symposium December 12, 2019

NSABP B-42: Background/Rational

- Extended adjuvant endocrine therapy after 5 years of TAM with either AI or TAM improves DFS in early-stage breast cancer
- Optimal duration of adjuvant AI therapy beyond 5 years continues to evolve
- NSABP B-42 aimed to determine whether 5 years of letrozole vs. placebo improves DFS in patients who have completed 5 years of hormonal therapy with either an AI or TAM → AI
NSABP B-42: Schema
- Postmenopausal pts with ER+ or PR+ breast cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free after 5 years of endocrine therapy
  - All x 5 years
  - TAM x 3 yrs & to Complete 5 years
- Stratification:
  - Pathological nodal status (Negative, Positive)
  - Prior adjuvant TAM (Yes, No)
  - Lowest BMD T score: spine, hip, femur (>2.0, 2-2.0 SD)

Endpoints
- Primary endpoint:
  - Disease-Free Survival (DFS):
    - Local, regional, distant recurrence, contralateral BC, 2nd non-breast primary cancer, and death from any cause as first events
- Secondary endpoints:
  - Overall Survival (OS)
  - Breast Cancer-Free Interval (BCFI):
    - Recurrence or contralateral BC as first event
    - Distant Recurrence (DR)
    - Osteoporotic Fractures (OF)
    - Arterial Thrombotic events (AT)

Cohort Characteristics
- From SEP 2006 to JAN 2010, 3966 pts were randomized
- No significant differences in the distribution of patient, tumor, and prior treatment characteristics between P and L:
  - 34% <60 years of age
  - 93% white; 4% black
  - 57% node-negative
  - 25% had lowest BMD score < -2.0
  - 39% received prior tamoxifen
  - 61% breast-conserving surgery
  - 78% HER2 negative (8% unknown)
Summary of Primary Results

- Presented at SABCS 2016 (published at Lancet Oncology 2019)
- The beneficial effect of extended L therapy on DFS did not reach statistical significance (HR=0.85, p=0.048)
  - To adjust for interim analyses, statistical significance level of 0.0418 was used
- No significant difference in Overall Survival with L vs. P
- Extended L provided:
  - 29% reduction in rate of BCFI events (HR=0.71, p=0.003)
  - 28% reduction in rate of DR events (HR=0.72, p=0.03)
- L did not significantly increase risk of osteoporotic fractures
- Risk of arterial thrombotic events was elevated for L after 2.5 years

Updated Results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Median follow-up, years</th>
<th>DFS</th>
<th>OS</th>
<th>BCFI</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-yr</td>
<td>6.9</td>
<td>631</td>
<td>310</td>
<td>306</td>
<td>175</td>
</tr>
<tr>
<td>10-yr</td>
<td>9.3</td>
<td>890</td>
<td>495</td>
<td>413</td>
<td>229</td>
</tr>
</tbody>
</table>

Disease-Free Survival
### DFS First Events by Treatment

<table>
<thead>
<tr>
<th>First Event</th>
<th>Placebo (n=1953)</th>
<th>Letrozole (n=1950)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>Distant Recurrence</td>
<td>111</td>
<td>5.7</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>43</td>
<td>2.2</td>
</tr>
<tr>
<td>Second Primary Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>230</td>
<td>11.8</td>
</tr>
<tr>
<td>Non-Breast</td>
<td>149</td>
<td>7.6</td>
</tr>
<tr>
<td>Death</td>
<td>95</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>Total First Event</strong></td>
<td>479</td>
<td>24.5</td>
</tr>
</tbody>
</table>

### Letrozole Effect on DFS in Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR 95% CI</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0.84 (0.74, 0.95)</td>
<td>0.3</td>
</tr>
<tr>
<td>Nodal Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.79 (0.65, 0.97)</td>
<td>0.3</td>
</tr>
<tr>
<td>Positive</td>
<td>0.79 (0.65, 0.97)</td>
<td>0.3</td>
</tr>
<tr>
<td>Prior TAM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.74 (0.60, 0.90)</td>
<td>0.19</td>
</tr>
<tr>
<td>Yes</td>
<td>0.74 (0.60, 0.90)</td>
<td>0.19</td>
</tr>
<tr>
<td>T-score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2.0</td>
<td>0.83 (0.69, 0.98)</td>
<td>0.81</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>0.83 (0.69, 0.98)</td>
<td>0.81</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>0.84 (0.65, 1.13)</td>
<td>0.8</td>
</tr>
<tr>
<td>≥ 60</td>
<td>0.84 (0.65, 1.13)</td>
<td>0.8</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>0.87 (0.72, 1.06)</td>
<td>0.55</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>0.79 (0.69, 0.89)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

### Overall Survival

<table>
<thead>
<tr>
<th>Event</th>
<th>HR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-yr</td>
<td>0.97 (0.63-1.49)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Note: Patients excluded: 4 (no follow-up), 2 not at risk for DFS.
NSABP B-42: Summary

- Ten-year results demonstrate a statistically significant improvement in DFS with extended L therapy:
  - 16% reduction in DFS event
  - 4% absolute improvement
- No significant difference in overall survival with L vs. P
- Extended L provided:
  - Statistically significant improvement in BCFI
  - 26% reduction in BCFI event; 3% absolute improvement with L
  - Statistically significant reduction in DR
  - 29% reduction in DR; 1.8% absolute improvement with L
- L did not significantly increase risk of osteoporotic fractures or arterial thrombotic events

NSABP B-42: Conclusion and Perspective

- Our findings continue to suggest that careful assessment of potential risks and benefits is necessary for selecting appropriate candidates for extended letrozole therapy in patients with early-stage BC, including:
  - Patient and tumor characteristics (age, nodal status)
  - Existing co-morbidities
  - Information on bone mineral density
  - Tolerance of the AI in the initial 5 years
- Genomic classifiers that predict risk of late recurrence and/or benefit from extended endocrine therapy may further assist with the decision to recommend extended aromatase inhibitor therapy

Improvements since 2000 in the outcome of ER+ disease after 5 years of adjuvant endocrine therapy:
Analyses of 86,000 women in 110 trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Adjuvant endocrine therapy (ET) in ER+ disease

- In women given 5 years adjuvant ET, appreciable risks continue during years 5-20, even for T1N0
- After 5 years of ET for N0 disease, the risks of distant recurrence during years 5-20 were reported to be T1N0: 13% & T2N0: 19%

Adjuvant endocrine therapy (ET) in ER+ disease

- In women given 5 years adjuvant ET, appreciable risks continue during years 5-20, even for T1N0 (NEJM 2017; 377: 1836)
- After 5 years of ET for N0 disease, the risks of distant recurrence during years 5-20 were reported to be T1N0: 13% & T2N0: 19%
- In disease diagnosed since 2000 and given 5 years adjuvant ET, it is not yet known how much lower the 10- & 20-year risks will be

Material and methods

- 86,000 women in 110 trials in EBCTCG database with T1/T2 ER+ disease who were scheduled to stop adjuvant ET at year 5
- Median age at diagnosis 55 (31% pre-menopausal)
- Analyze FIRST DISTANT recurrence (ignoring any other recurrences) by period of diagnosis: < 2000, 2000-4, ≥ 2005

Analyses: Kaplan-Meier risks (with 95% CIs) & Cox regressions (adjusted for TN & mm diameter) for BMI, T1 or T2 tumours (≤ 20 or 21-50 mm) with < 10 nodes and age < 60 at year 5 of ET
The original TN status was the main prognostic factor for distant recurrence after 5 years of adjuvant ET

Its proportional relevance was similarly strong for disease diagnosed in different periods (< 2000, 2000-4, ≥ 2005)

Treatment changed, < 2000 vs ≥ 2000, with wider use of chemotherapy, aromatase inhibitors and trastuzumab
(Chemo 43% vs 64%, AI 12% vs 98%, trastuzumab for HER2+ 0% vs 40%)

All analyses of RRs by period of diagnosis are fully adjusted for type of systemic therapy, TN status, mm diameter, grade & 5-year age group

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**ER+ N+ disease: Distant recurrence during years 5-9,* by period of diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>No. of women</th>
<th>No. of events</th>
<th>Fully adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2000</td>
<td>17,874</td>
<td>1,968</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>2000-04</td>
<td>18,446</td>
<td>1,048</td>
<td>0.75 (0.69-0.82)</td>
</tr>
<tr>
<td>≥ 2005</td>
<td>8,683</td>
<td>394</td>
<td>0.76 (0.67-0.85)</td>
</tr>
</tbody>
</table>

*Note: Women diagnosed since 2000 have limited follow-up beyond year 10

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**ER+ N0 disease: Distant recurrence during years 5-9,* by period of diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>No. of women</th>
<th>No. of events</th>
<th>Fully adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2000</td>
<td>19,924</td>
<td>898</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>2000-04</td>
<td>11,691</td>
<td>220</td>
<td>0.81 (0.69-0.96)</td>
</tr>
<tr>
<td>≥ 2005</td>
<td>9,648</td>
<td>131</td>
<td>Heterogeneity NS RR = 0.73 (0.63-0.85)</td>
</tr>
</tbody>
</table>

*Note: Women diagnosed since 2000 have limited follow-up beyond year 10

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20-year perspective on ER+ disease prognosis

- Better prognosis since 2000, even after allowing for tumour size, nodal status, use of chemotherapy or AI
- T1N0 with only 5 years of ET, by period of diagnosis: Diagnosed <2000: ~13% distant recurrence in years 5-20 Diagnosed ≥2000: ~10% distant recurrence in years 5-20

* 25% fewer distant recurrences ≥ 2000 vs < 2000 in years 5-9; so, maybe, about 25% fewer distant recurrences in years 10-20.

Possible reasons for the improvement

- Treatment: Real improvements (in surgery, radiotherapy, chemotherapy, endocrine therapy & HER2-directed therapy)
- Treatment guidelines: More patients get optimal therapies
- Stage migration: Apparent improvements in all TN categories
- Screening: Earlier detection, and lower-risk lesions

UK & US, 1980-2016: Breast cancer mortality at ages 30-69

LARGE effect on UK/US breast cancer mortality by combining several MODERATE effects
Further MODERATE effects are still being achieved
Long-term prognosis should be even better for disease diagnosed in the 2020s

Source: WHO mortality & US population estimates
Validation of the Clinical Treatment Score post 5 years (CTS5) in women with hormone receptor positive, HER2-negative, node-negative disease from the TAILORx study

Yvou Sardal, Michael Cragin, Jack Cuzick, Mitch Dowsett, Steven Shah, Dong Tang, Robert J. Gray, Joseph A. Sparano

Background

• Continued risk of late recurrence in ER-positive disease

• Extended endocrine therapy can reduce risk of recurrence

Identification of patients who are at high risk of late recurrence is crucial

Background

• Clinical Treatment Score (CTS5) developed to predict late distant recurrence

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Background

- Clinical Treatment Score (CT55) developed to predict late distant recurrence

  ATAC     △CT55
  BRCA1    △CT55
  BRCA2    △CT55
  Tumor size
  Tumor grade
  Hormone status

- CT55: node status, tumor size, tumor grade, and age

Objectives

Primary Objectives:

- To evaluate CT55 for prediction of late distant recurrence (DR) in TAILORx
- To evaluate cut-off points and risk stratification

Secondary Objectives:

- To evaluate CT55 separately
  - By patient age: <65 years versus >60 years
  - In the four study arms of TAILORx

Statistical analysis

- Women aged 18 to 75 with HR-positive, HER2-negative and node-negative breast cancer who were distant recurrence-free after 5 years
- Primary endpoint: Distant recurrence (DR) after 5 years
- Cox regression models used to determine prognostic value of CT55
  (Chemotherapy use as stratification factor. Hazard Ratio for a change in one SD)
- Pre-defined cut-off points for risk group stratification:
  - Low ≤ 5% DR risk in years 5-10
  - Intermediate 5-10% DR risk in years 5-10
  - High > 10% DR risk in years 5-10
Conclusions

- Low rates of late DR were observed in the TAILORx cohort
  - RR 0-25 (ET only): 3.1% (2.4-4.0)
  - RR 15-100 (ISET): 3.8% (2.9-4.8)

- CTSS highly prognostic for prediction of late DR
  - specifically for patients older than 50 years
  - much less prognostic in women aged ≤ 50 years

Conclusions

- Most prognostic value of CTSS in intermediate or high risk group by Oncotype Dx (11-100)
- CTSS not significantly prognostic in low risk women by Oncotype Dx (0-10)
- Short median follow-up time of 2.66 years post 5 years
  - Few late DR in all arms
- Further evaluation in premenopausal cohorts is needed before CTSS can be applied to younger patients

Should age be integrated together with clinical and genomic risk for adjuvant chemotherapy decision in early luminal breast cancer? MINDACT results compared to those of TAILORx

M. A. Piccart, C. Perren, C. Cardoso, I. van’t Veer, S. Delhaye, I. Perga, E. Wilke, S. Vrielinghoven, P. Nuyten, C. Alden, S. Bitter, on behalf of the MINDACT Investigators
MINDACT TRIAL DESIGN

MINDACT proves the clinical utility of MammaPrint

Efficacy Secondary Endpoint: CT vs no CT in discordant risk group c-High/g-Low in ITT analysis

No statistical difference at 5 years for CT vs no CT for c-High/g-Low patients (95.9 vs. 94.4%) (p=1.9, non-significant)

Among the c-high risk patients, the trial shows that 46% who are genomic low risk (MammaPrint) can safely forego chemotherapy.
TailorX is also a DE-ESCALATION STUDY

Primary endpoint:
RS 11-25: ET non-inferior to chemotherapy + ET

TAILORx Results AT MEDIAN FU OF 9 YEARS: Summary

- Primary conclusions
  - RS 11-25: ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  - RS 26-100: Distant recurrence rates: very low (2.3%) with ET alone at 9 years
  - RS 26-100: Significantly higher event rates, driven by more recurrences despite adjuvant chemotherapy

- Other observations
  - Age - RS - Chemo treatment interaction:
  - Hormone therapy benefit in women 70 or younger with a RS 10-25
  - Greatest impact on distant recurrence with RS 21-25

Results, Absolute Differences in Distant Recurrence Rates by Chemo Use in Women < 50 yrs & RS 10-25 Stratified by RS and Clinical Risk

UNPLANNED, UNDER-POWERED ANALYSES
GENERATED A LOT OF CONTROVERSY ("true" effect of CT vs OFS-effect of CT)
VERY CAREFUL INTERPRETATION NEEDED
LARGE STANDARD DEVIATIONS

Sporano et al. JCO 2019
Addition of S-1 to endocrine therapy in the post-operative adjuvant treatment of hormone receptor-positive and human epidermal growth factor receptor 2-negative primary breast cancer: A multicenter, open-label, phase 3 randomized trial (POTENT trial)


1. This unplanned and underpowered subgroup analysis of MINDACT was initiated following the observation inTAILORx of heterogeneous clinical outcomes according to age in women at "high clinical risk" using MINDACT’s definition.

2. Although cautious interpretation is needed (i.e. large confidence intervals), the present analysis suggests that in women younger than 50, in the cl/v group, taxotere alone might not be the optimal treatment, though the difference seen between CT and no-CT groups is small (3%).

3. It is possible that this age-dependent effect is due to chemotherapy-induced ovarian function suppression. Neither MINDACT nor TAILORx are able to answer this question.

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CONCLUSIONS

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Background

- Standard adjuvant chemotherapy for HR+/HER2- breast cancer patients contains anthracycline and/or taxane
- Dose escalation of these chemotherapeutic agents may not result in remarkable survival advantages
- Chemotherapy with oral FU is active for metastatic diseases
- Multiple adjuvant trials with oral FU have shown positive signals
- We hypothesized that adjuvant treatment with standard endocrine therapy and S-1 could improve survival outcomes compared with endocrine therapy alone

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**S-1 Administration**

- S-1 is a combination drug, based on a biochemical modification of fluorouracil containing tegafur, gimeracil, and oteracil in a molar ratio of 1:0.4:1
- S-1 will be orally administered twice daily for 14 consecutive days at a dose specified based on body surface area and creatinine clearance (Table), and subsequently off for 7 days.
- The q3 wks administration was repeated for 1 year

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**POTENT Trial Design**

- Standard Therapy: Neoadjuvant chemotherapy
  - Preoperative chemotherapy
  - Neoadjuvant chemotherapy
  - Neoadjuvant chemotherapy
- Radiation Therapy

**Randomization**

- Randomization: 1:1
- Treatment arm: Neoadjuvant Anthracycline + Taxane

**Primary endpoint**

- Tumor Downstaging

**Secondary endpoints**

- Clinical complete response
- Biopsy complete response
- Tumor downstaging
- Baseline tumor number
- Baseline tumor volume
- Baseline tumor size
- Baseline tumor grade
- Baseline tumor hormone receptor status
- Baseline tumor HER2 status
- Baseline tumor Ki-67 status
- Baseline tumor molecular characteristics

Patients were enrolled between February 2015 and February 2016.
Key Inclusion Criteria

- Age: 20y-75y
- PS: 0-2
- Stage I to Stage IIIA at first diagnosis and Stage IIIB with radical resection after preoperative systemic therapy (PST)
- Estrogen receptor (ER)-positive and HER2-negative
- The risk of recurrence: Intermediate or higher with or without PST
- Within one-year after surgery, and within 6-months after starting adjuvant endocrine therapy
- Sufficient organ function
- Written informed consent

Risk Assessment

Without PST

With preoperative chemotherapy

- History for PST
- Categorical

Non-OR

- Regressions of pathological response

With preoperative endocrine therapy

- Status after PST
- Categorical

Disease-free

- Regressions of pathological response

Baseline Demographic Characteristics (Full Analysis Set)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete Response (%)</th>
<th>PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median</td>
<td>62.0</td>
<td>59.5</td>
</tr>
<tr>
<td>BMI, median</td>
<td>25.5 (22.1-29.0)</td>
<td>25.5 (22.1-29.0)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>551 (82.2)</td>
<td>544 (80.1)</td>
</tr>
<tr>
<td>Histological grade</td>
<td>190 (30.8)</td>
<td>190 (30.8)</td>
</tr>
<tr>
<td>ER positive</td>
<td>595 (82.1)</td>
<td>563 (56.0)</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>296 (42.7)</td>
<td>296 (42.7)</td>
</tr>
<tr>
<td>N-stage status</td>
<td>377 (55.1)</td>
<td>345 (51.5)</td>
</tr>
<tr>
<td>MIBC status</td>
<td>612 (93.9)</td>
<td>612 (93.9)</td>
</tr>
<tr>
<td>Ki67 LI (%)</td>
<td>92.3 (32.8)</td>
<td>72.3 (32.8)</td>
</tr>
<tr>
<td>14 ≤ Ki67 LI (%)</td>
<td>366 (42.7)</td>
<td>378 (32.8)</td>
</tr>
<tr>
<td>15 × 14 ≤ Ki67 LI (%)</td>
<td>206 (32.9)</td>
<td>206 (32.9)</td>
</tr>
<tr>
<td>15 × 15 ≤ Ki67 LI (%)</td>
<td>120 (14.0)</td>
<td>120 (14.0)</td>
</tr>
<tr>
<td>PST, chemotherapy</td>
<td>297 (32.8)</td>
<td>297 (32.8)</td>
</tr>
<tr>
<td>Advanced Chemotherapy</td>
<td>958 (94.9)</td>
<td>958 (94.9)</td>
</tr>
<tr>
<td>Invasive Diameter</td>
<td>3.02 (2.20-4.92)</td>
<td>3.02 (2.20-4.92)</td>
</tr>
<tr>
<td>2.0 cm × 2.0 cm</td>
<td>293 (32.8)</td>
<td>293 (32.8)</td>
</tr>
<tr>
<td>2.0 cm × 3.0 cm</td>
<td>293 (32.8)</td>
<td>293 (32.8)</td>
</tr>
<tr>
<td>T3N0M0 stage</td>
<td>184 (19.2)</td>
<td>184 (19.2)</td>
</tr>
</tbody>
</table>

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Invasive Disease Free Survival

- Control Group
- Treatment Group
- Endocrine therapy
- Endocrine + S-1 therapy

5-year DFS estimate was 81.6% in the Endocrine therapy group and 86.9% in the Endocrine + S-1 therapy group.
The trial was terminated early because the primary endpoint was met at this interim analysis.

Safety

<table>
<thead>
<tr>
<th></th>
<th>Endocrine therapy</th>
<th>Endocrine + S-1 therapy</th>
<th>P-value (Fisher's exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All AEs</td>
<td>Grade ≥3</td>
<td>All AEs</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>117 (12.1)</td>
<td>1 (0.7)</td>
<td>401 (42.6)</td>
</tr>
<tr>
<td>Platelet</td>
<td>63 (6.5)</td>
<td>4 (0.4)</td>
<td>307 (32.2)</td>
</tr>
<tr>
<td>AST increased</td>
<td>197 (20.3)</td>
<td>10 (1.0)</td>
<td>409 (42.9)</td>
</tr>
<tr>
<td>Insulin</td>
<td>154 (15.9)</td>
<td>5 (0.5)</td>
<td>368 (38.6)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>16 (1.6)</td>
<td>0</td>
<td>376 (39.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (2.5)</td>
<td>0</td>
<td>358 (37.3)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>33 (3.4)</td>
<td>0</td>
<td>466 (48.3)</td>
</tr>
</tbody>
</table>

Conclusions

- The oral formulation S-1, one year adjuvant therapy combined with endocrine therapy, would be an important treatment option for ER+ and HER2- primary breast cancer patients having intermediate/high risk of recurrence.
- Overall, the safety profile of S-1 was manageable.
Thank You