News in adjuvant therapy of HR+ disease

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Tamoxifen alone for 5 years is indicated for low risk patients.

Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively post-menopausal. Tamoxifen for 10 years should be considered in high-risk patients, if tolerated.

The addition of a GnRH agonist to tamoxifen is indicated in patients at higher risk who remain premenopausal after chemotherapy. AIs alone are contra-indicated in pre-menopausal women.

The combination of an aromatase inhibitor and a GnRH agonist (or ovarian ablation) should be considered in high risk patients if tolerated.
SOFT and TEXT Designs

Enrolled: Nov03 - Apr11

- Premenopausal HR+
- Planned OFS
- No planned chemo (40%) OR planned chemo (60%)
- ≤12 wks after surgery

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**TEXT (n=2672)**

- Randomize
- Median follow-up 9 years

→ Tamoxifen+OFS x 5y
→ Exemestane+OFS x 5y

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**SOFT (n=3066)**

- Randomize
- Median follow-up 8 years

→ Tamoxifen x 5y
→ Tamoxifen+OFS x 5y
→ Exemestane+OFS x 5y

OFS=ovarian function suppression
T+OFS significantly improves DFS vs T-alone in the overall population

P Francis, O Pagani, G. Fleming, M Regan, NEJM 2018;379(2):122
SOFT Secondary Endpoints

Distant Recurrence-Free Interval

Absolute Benefit at 8 years vs. T

- T+OFS 1.0%
- E+OFS 2.9%

Overall Survival

Absolute Benefit at 8 years vs. T

- T+OFS 1.9%
- E+OFS 0.6%

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

P Francis, O Pagani, G. FlemIng, M Regan, NEJM 2018;379(2):122
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

P Francis, O Pagani, G. FlemIng, M Regan, NEJM 2018;379(2):122
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

P Francis, O Pagani, G. FlemIng, M Regan, NEJM 2018;379(2):122
Sustained 4% improvement in 8-yr DFS

P Francis, O Pagani, G. Fleming, M Regan, NEJM 2018;379(2):122
Breast Cancer-Free Interval

- 8-year %: 89.3
- 8-year %: 85.2

Distant Recurrence-Free Interval

- 8-year %: 91.8
- 8-year %: 89.7

4.1% absolute improvement

2.1% absolute improvement

P Francis, O Pagani, G. Fleming, M Regan, NEJM 2018;379(2):122
HER2-negative Patients (N=4035)

### DFS

<table>
<thead>
<tr>
<th>Cohort</th>
<th>E+OFS</th>
<th>T+OFS</th>
<th>Hazard Ratio</th>
<th>8-Year DFS</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Chemotherapy TEXT</td>
<td>40</td>
<td>59</td>
<td>0.932</td>
<td>89.1%</td>
<td>+4.1%</td>
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<tr>
<td>No Chemotherapy SOFT</td>
<td>33</td>
<td>42</td>
<td>0.927</td>
<td>91.3%</td>
<td>+1.4%</td>
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<tr>
<td>Chemotherapy TEXT</td>
<td>105</td>
<td>144</td>
<td>0.846</td>
<td>77.7%</td>
<td>+6.9%</td>
</tr>
<tr>
<td>Prior Chemotherapy SOFT</td>
<td>72</td>
<td>105</td>
<td>0.831</td>
<td>73.9%</td>
<td>+9.2%</td>
</tr>
</tbody>
</table>

### DRFI

<table>
<thead>
<tr>
<th>Cohort</th>
<th>E+OFS</th>
<th>T+OFS</th>
<th>Hazard Ratio</th>
<th>8-Year DRFI</th>
<th>Difference</th>
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<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Chemotherapy TEXT</td>
<td>16</td>
<td>20</td>
<td>0.972</td>
<td>96.5%</td>
<td>+0.7%</td>
</tr>
<tr>
<td>No Chemotherapy SOFT</td>
<td>5</td>
<td>9</td>
<td>0.993</td>
<td>98.3%</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Chemotherapy TEXT</td>
<td>70</td>
<td>98</td>
<td>0.896</td>
<td>84.6%</td>
<td>+5.0%</td>
</tr>
<tr>
<td>Prior Chemotherapy SOFT</td>
<td>53</td>
<td>82</td>
<td>0.868</td>
<td>79.8%</td>
<td>+7.0%</td>
</tr>
</tbody>
</table>

- Consistent relative treatment effects in all cohorts
- Larger absolute benefits of E+OFS in chemo cohorts
- Overall Survival HR=0.86 (0.68-1.10)

P Francis, O Pagani, G. Fleming, M Regan, NEJM 2018;379(2):122
STEPP of 8-yr Freedom from Distant Recurrence according to Composite Risk

- \( \geq 40 \) yrs
- N0
- T\( \leq 2 \) cm
- ER \( \geq 50\% \)
- PgR \( \geq 50\% \)
- Grade 1
- Ki-67 \( < 14\% \)

<table>
<thead>
<tr>
<th>Median Composite Risk in HR+/HER2- Subpopulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemestane+OFS</td>
</tr>
<tr>
<td>99.3% E+OFS</td>
</tr>
<tr>
<td>98.3% T+OFS</td>
</tr>
<tr>
<td>98.0% T</td>
</tr>
<tr>
<td>1.3% avg. improvement E+OFS vs T</td>
</tr>
<tr>
<td>&lt;1% avg. improvement T+OFS vs T</td>
</tr>
</tbody>
</table>

Regan M, Pagani O, Francis P, ASCO 2018
STEPP of 8-yr Freedom from Distant Recurrence according to Composite Risk

\[ \begin{align*}
\geq 40 \text{ yrs} & \quad N^+ 1-3 \quad ER \geq 50\% \quad \text{Grade 2 or 3} \\
T \leq 2 \text{ cm} & \quad PgR \geq 50\% \quad Ki-67 \geq 20\%
\end{align*} \]

86.2% E+OFS
80.3% T+OFS
81.0% T
5.2% improvement E+OFS vs T

\[ \begin{align*}
<40 \text{ yrs} & \quad N^+ 1-3 \quad ER \geq 50\% \quad \text{Grade 2 or 3} \\
T > 2 \text{ cm} & \quad PgR < 50\% \quad Ki-67 \geq 20\%
\end{align*} \]

E+OFS vs T, max 10% for higher composite risks

Regan M, Pagani O, Francis P, ASCO 2018
Very young women
385 HER2- pts < 35
93% received CT
Timing of OFS

Regan MM, Pagani O, Ann Oncol. 2017;28(9):2225
Role of adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy: the ASTRRA study

Woo Chul Noh, Jong Won Lee, Seok Jin Nam, Seho Park, Seock-Ah Im, Eun Sook Lee, Yong Sik Jung, Jung Han Yoon, Sung Soo Kang, Soo-Jung Lee, Kyong Hwa Park, Joon Jeong, Se-Heon Cho, Sung Yong Kim, Hee-Jung Kim, Hyun-Ah Kim, Chanheun Park, Se-Hwan Han, Wonshik Han, Min Hee Hur

1483 Patients
Disease free survival (Primary Endpoint)

- Definition
  - Local/ regional recurrence
  - Distant recurrence
  - Contralateral breast cancer
  - Secondary malignancy
  - Death, any reason

3.6% ABSOLUTE BENEFIT
Overall Survival (Secondary Endpoint)

1.6% ABSOLUTE BENEFIT
Conclusions

• Recent results of SOFT/TEXT after 8-9 years of median follow-up confirm efficacy of escalating ET in women at intermediate/high risk of relapse

• The degree of benefit in different clinical scenarios can be estimated

• Treatment burden needs to be part of the risk/benefit decision making

• In the era of combined ET the additional benefit of adjuvant chemotherapy in patients at intermediate risk of relapse still needs to be elucidated
Grazie per l’attenzione