Recent advances in hormone therapy

Suzette DELALOGE
Gustave Roussy, Villejuif, France
## Conflicts of interest

<table>
<thead>
<tr>
<th></th>
<th>Consulting / expert</th>
<th>Conferences / formations</th>
<th>Research grants /clinical trials</th>
<th>Stock options</th>
<th>Patent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abott</td>
<td></td>
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<tr>
<td>Amgen</td>
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<td>Astra Zeneca</td>
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<td>Eisei</td>
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<tr>
<td>Genomic Health</td>
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<td>GSK</td>
<td>x</td>
<td></td>
<td>x</td>
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<tr>
<td>Iris/Servier</td>
<td></td>
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<tr>
<td>Novartis</td>
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<td>x</td>
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<tr>
<td>Pfizer</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Puma</td>
<td>x</td>
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<td>Roche</td>
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<tr>
<td>Sanofi</td>
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</tr>
</tbody>
</table>
Outline

• Prevention
• Adjuvant setting
• Advanced disease
Outline

- Prevention
- Adjuvant setting
- Advanced disease
## SERMs for BC prevention: TAM

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Pop Description</th>
<th>FUs</th>
<th>Nb K Placebo</th>
<th>Nb K Tam</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher NSABPP1 JNCI 2005</td>
<td>13388</td>
<td>Gail ≥ 1.66% at 5 yrs</td>
<td>7</td>
<td>347</td>
<td>205</td>
<td>0.57</td>
</tr>
<tr>
<td>Veronesi Italy JNCI 2007</td>
<td>5408</td>
<td>Hysterectomy</td>
<td>11</td>
<td>74</td>
<td>62</td>
<td>0.84 NS</td>
</tr>
<tr>
<td>Powles Marsden JNCI 2007</td>
<td>2471</td>
<td>Familial risk</td>
<td>13</td>
<td>104 (inf)</td>
<td>82 (inf)</td>
<td>0.78 NS</td>
</tr>
<tr>
<td>Cuzick IBIS1 JNCI 2007</td>
<td>7145</td>
<td>High risk</td>
<td>8</td>
<td>195</td>
<td>142</td>
<td>0.73</td>
</tr>
</tbody>
</table>
SERMs for BC prevention: meta-analysis 2013

Figure 1: Cumulative incidence for all breast cancer (including ductal carcinoma in situ) and all ER-positive invasive cancers in years 0–10 according to treatment allocation. SERM = selective oestrogen receptor modulator. ER = oestrogen receptor.

42 women treated to avoid 1 BC
SERMs for BC prevention: meta-analysis 2013
### Table 3: Major non-breast cancer events in the prevention trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Endometrial cancer</th>
<th>All other cancer</th>
<th>Any death</th>
<th>Breast cancer death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsden</td>
<td>12 vs 5</td>
<td>55 vs 60</td>
<td>54 vs 54</td>
<td>12 vs 9</td>
</tr>
<tr>
<td>IBIS-I</td>
<td>19 vs 11</td>
<td>110 vs 113</td>
<td>65 vs 55</td>
<td>10 vs 12</td>
</tr>
<tr>
<td>NSABP-P-1</td>
<td>36 vs 15</td>
<td>101 vs 103</td>
<td>59 vs 71</td>
<td>4 vs 6</td>
</tr>
<tr>
<td>Italian</td>
<td>--</td>
<td>106 vs 91</td>
<td>36 vs 38</td>
<td>2 vs 2</td>
</tr>
<tr>
<td>MORE/CORE</td>
<td>6 vs 8</td>
<td>112 vs 132</td>
<td>81 vs 84</td>
<td>--</td>
</tr>
<tr>
<td>RUTH</td>
<td>21 vs 17</td>
<td>204 vs 203</td>
<td>548 vs 585</td>
<td>2 vs 0</td>
</tr>
<tr>
<td>STARs</td>
<td>37 vs 65</td>
<td>354 vs 323</td>
<td>202 vs 236</td>
<td>4 vs 11</td>
</tr>
<tr>
<td>PEARL (0.5 mg vs 0.25 mg vs placebo)</td>
<td>2 vs 2 vs 3</td>
<td>25 vs 20 vs 22</td>
<td>92 vs 73 vs 65</td>
<td>--</td>
</tr>
<tr>
<td>GENERATIONS</td>
<td>9 vs 4</td>
<td>74 vs 75</td>
<td>103 vs 98</td>
<td>--</td>
</tr>
<tr>
<td>All events</td>
<td>105 vs 63</td>
<td>787 vs 799</td>
<td>1038 vs 1050</td>
<td>30 vs 29</td>
</tr>
<tr>
<td>HR or OR (95% CI)</td>
<td><strong>HR 1.56 (1.13-2.14)</strong></td>
<td>HR 0.98 (0.89-1.08)</td>
<td>HR 0.98 (0.90-1.06)</td>
<td><strong>HR 1.03 (0.55-1.92)</strong></td>
</tr>
</tbody>
</table>

Data are number of patients for selective estrogen receptor modulator versus vs placebo, unless otherwise in pulmonary embolism, retinal thrombosis; excluding superficial thrombosis. Including myocardial infarction.
### SERMs for BC prevention: meta-analysis 2013

<table>
<thead>
<tr>
<th>Venous thrombotic events†</th>
<th>Cardiovascular events‡</th>
<th>All fractures</th>
<th>Non-vertebral fractures</th>
<th>Vertebral fractures</th>
<th>Cataracts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 vs 43</td>
<td>40 vs 38</td>
<td>229 vs 252</td>
<td>221 vs 244</td>
<td>8 vs 8</td>
<td>76 vs 70</td>
</tr>
<tr>
<td>55 vs 29</td>
<td>90 vs 82</td>
<td>502 vs 539</td>
<td>480 vs 509</td>
<td>22 vs 30</td>
<td>578 vs 513</td>
</tr>
<tr>
<td>11 vs 10</td>
<td>14 vs 10</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>47 vs 25</td>
<td>82 vs 78</td>
<td>353 vs 450</td>
<td>214 vs 225</td>
<td>139 vs 225</td>
<td>275 vs 280</td>
</tr>
<tr>
<td>106 vs 73</td>
<td>487 vs 481</td>
<td>529 vs 591</td>
<td>470 vs 499</td>
<td>59 vs 92</td>
<td>570 vs 561</td>
</tr>
<tr>
<td>154 vs 202</td>
<td>233 vs 220</td>
<td>1272 vs 1364</td>
<td>1195 vs 1299</td>
<td>65 vs 77</td>
<td>603 vs 739</td>
</tr>
<tr>
<td>48 vs 37</td>
<td>47 vs 54</td>
<td>359 vs 422</td>
<td>203 vs 233</td>
<td>156 vs 189</td>
<td>320 vs 317</td>
</tr>
<tr>
<td>48 vs 18</td>
<td>47 vs 76</td>
<td>359 vs 508</td>
<td>203 vs 246</td>
<td>156 vs 262</td>
<td>320 vs 330</td>
</tr>
<tr>
<td>43 vs 17</td>
<td>71 vs 64</td>
<td>426 vs 508</td>
<td>316 vs 327</td>
<td>110 vs 181</td>
<td>382 vs 400</td>
</tr>
<tr>
<td>375 vs 215</td>
<td>831 vs 829</td>
<td>2198 vs 2848</td>
<td>1904 vs 2050</td>
<td>494 vs 798</td>
<td>2201 vs 2154</td>
</tr>
<tr>
<td>OR 1·73</td>
<td>OR 0·99</td>
<td>OR 0·85</td>
<td>OR 0·93</td>
<td>OR 0·66</td>
<td>OR 1·01</td>
</tr>
<tr>
<td>(1·47–2·05)</td>
<td>(0·91–1·09)</td>
<td>(0·80–0·89)</td>
<td>(0·87–0·99)</td>
<td>(0·59–0·73)</td>
<td>(0·95–1·06)</td>
</tr>
</tbody>
</table>

*Hazard ratio. OR = odds ratio. †Excluding endometrial cancer. ‡Including deep vein thrombosis, cerebrovascular accident, and transient ischaemic accident. §STAR data not included for overall effect.
AI for prevention: exemestane

FU 35 months

Hazard ratio, 0.35 (95% CI, 0.18–0.70)
P=0.002 by stratified log-rank test

Annual Incidence (95% CI)
Placebo
0.55% (0.36–0.73)
Exemestane
0.19% (0.08–0.30)

32 cases - 65%
11 cases

Goss et al NEJM 2011
AI for prevention: anastrozole

Breast cancer incidence

- All breast cancer: HR=0.47 (0.32-0.68), P<0.0001
- ER+-invasive: HR=0.42 (0.25-0.71), P=0.001

Cumulative incidence (%) vs. Follow-up time (years)

Number at risk
- Placebo: 1944, 1927, 1645, 1445, 1241, 975, 706, 506
- Anastrozole: 1920, 1909, 1654, 1463, 1264, 978, 720, 516

- 53% decrease in breast cancer incidence with anastrozole.
AI for prevention: anastrozole

Subgroup analysis

- All
- DCIS
- All invasive*
- Invasive ER+
- Invasive ER-

Hazard ratio

- 40 vs 85
  - HR = 0.47 (0.32-0.68)
- 6 vs 20
  - HR = 0.30 (0.12-0.74)
- 32 vs 64
  - HR = 0.50 (0.32-0.76)
- 20 vs 47
  - HR = 0.42 (0.25-0.71)
- 11 vs 14
  - HR = 0.78 (0.35-1.72)

Missing: invasive status (N=3), ER-status (N=4)

Cuzick et al SABCS Dec 2013
AI for prevention: anastrozole

Compliance

HR = 0.84 (0.75-0.95), P = 0.005

Cuzick et al SABCS Dec 2013
## AI for prevention: anastrozole

### Fractures/Musculoskeletal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anastrozole vs Placebo (Patients (%))</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td>164 (8.5%) vs 149 (7.7%)</td>
<td>1.11 (0.90-1.38)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1226 (63.9%) vs 1124 (57.8%)</td>
<td>1.10 (1.05-1.16)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>972 vs 894</td>
<td>1.10 (1.03-1.18)</td>
</tr>
</tbody>
</table>

### Joint stiffness

- **Mild**: Anastrozole 143 vs Placebo 96, RR 1.51 (1.17-1.94)
- **Moderate**: Anastrozole 67 vs Placebo 43, RR 1.58 (1.08-2.30)

### Arthralgia

- Mild: Anastrozole 20% vs Placebo 20%
- Moderate: Anastrozole 22% vs Placebo 19%
- Severe: Anastrozole 8% vs Placebo 6%
AI for prevention: anastrozole

### Vasomotor/Gynaecological

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole vs Placebo (Patients (%))</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasomotor</strong></td>
<td>1090 (56.8%) vs 961 (49.4%)</td>
<td>1.15 (1.08-1.22)</td>
</tr>
<tr>
<td><strong>Gynaecological</strong></td>
<td>460 (23.9%) vs 423 (21.8%)</td>
<td>1.10 (0.98-1.24)</td>
</tr>
<tr>
<td><strong>Vaginal dryness</strong></td>
<td>357 vs 304</td>
<td>1.19 (1.03-1.37)</td>
</tr>
</tbody>
</table>
International recommendations

Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline

Kala Visvanathan, Patricia Hurley, Elissa Bantug, Powel Brown, Nananda F. Col, Jack Cuzick, Nancy E. Davidson, Andrea DeCensi, Carol Fabian, Leslie Ford, Judy Garber, Maria Katapodi, Barnett Kramer, Monica Morrow, Barbara Parker, Carolyn Runowicz, Victor G. Vogel III, James L. Wade, and Scott M. Lippman

**Key Recommendations**

- Tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal or postmenopausal women age ≥ 35 years at increased risk of breast cancer or with lobular carcinoma in situ (LCIS). Tamoxifen is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack; during prolonged immobilization; or in women who are pregnant, may become pregnant, or are nursing mothers. Tamoxifen is not recommended in combination with hormone therapy.

-Raloxifene (60 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 years at increased risk of breast cancer or with LCIS. It should not be used for breast cancer risk reduction in premenopausal women. Raloxifene is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.

- Exemestane (25 mg per day orally for 5 years) should be discussed as an alternative to tamoxifen or raloxifene to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 years at increased risk of breast cancer or with LCIS or atypical hyperplasia. Exemestane should not be used for breast cancer risk reduction in premenopausal women.
Outline

• Prevention
• Adjuvant setting
• Advanced disease
Current questions – adjuvant HT

• Treatment duration?
• How to anticipate resistance?
• Can we decrease treatments? Not for now…
HR+: long term risk of relapse is a major issue

Recurrences

Annual risk of relapse appears stable after 5 years (1-2% per year)

Dowsett meta analysis
AI jan 2010, J Clin Oncol

ATAC 2008, The Lancet
Can we predict for late relapse?

Breast cancer Index: early relapse (TransATAC)

Groi et al, Lancet Oncol Sept 2013
Can we predict for late relapse?

Breast cancer Index: late relapse (TransATAC)
Benefits of prolonged HT?

Meta-analysis recurrences

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

* Early Breast Cancer Trials’ Collaborative Group (EBCCTG)*

Lancet 2005; 365: 1687–1717

<table>
<thead>
<tr>
<th>Recurrence/woman-years</th>
<th>Events/woman-years</th>
<th>Longer:events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
<td><em>Allocated longer</em></td>
<td><em>Allocated shorter</em></td>
<td>Logrank 0-E</td>
</tr>
<tr>
<td>(a) Node-negative ($\chi^2_1=6.1; p=0.05$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4 vs 1–2 years</td>
<td>41/1456</td>
<td>57/1663</td>
<td>-3.5</td>
</tr>
<tr>
<td>≈5 vs 1–2 years</td>
<td>639/20640</td>
<td>737/19951</td>
<td>1.96</td>
</tr>
<tr>
<td>≈10 vs ≈5 years</td>
<td>141/6645</td>
<td>127/6777</td>
<td>9.8</td>
</tr>
<tr>
<td>(b) Node-positive or node-unknown ($\chi^2_2=2.8; p&gt;0.1; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4 vs 1–2 years</td>
<td>473/5603</td>
<td>506/5548</td>
<td>-18.9</td>
</tr>
<tr>
<td>≈5 vs 1–2 years</td>
<td>1424/25137</td>
<td>1675/24228</td>
<td>-141.4</td>
</tr>
<tr>
<td>≈10 vs ≈5 years</td>
<td>142/3394</td>
<td>177/3159</td>
<td>-20.5</td>
</tr>
<tr>
<td>(a + b) All women ($\chi^2_2=2.3; p&gt;0.1; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4 vs 1–2 years</td>
<td>514/7059</td>
<td>563/7211</td>
<td>-22.4</td>
</tr>
<tr>
<td>≈5 vs 1–2 years</td>
<td>2063/45777</td>
<td>2412/44179</td>
<td>-201.0</td>
</tr>
<tr>
<td>≈10 vs ≈5 years</td>
<td>283/10039</td>
<td>304/9936</td>
<td>-10.7</td>
</tr>
<tr>
<td><strong>Total (a + b)</strong></td>
<td>2866/62875</td>
<td>3279/61326</td>
<td>-234.1</td>
</tr>
</tbody>
</table>

Heterogeneity between proportional effects in (a) and in (b): $\chi^2_1=1.0; 2p>0.1; NS$
Benefits of prolonged HT?

Meta-analysis

Mortality

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Lancet 2005; 365: 1687–1717
Treatment duration: recent data

Atlas trial
1995-2005

Open design
TAM 10 yrs vs 5 yrs (rando at 5 yrs)
Treatment duration: recent data

Atlas Relapse Breast cancer mortality

Davies et al Lancet 2012
Treatment duration: recent data

Atlas

- RR pulm embolism 1.87
- RR Endometrial cancer 3.1
- Overmortality endometrial cancer 0.2%
At-TOM: same design

Relapses

580 versus 672 relapses

RR = 0.85

IC₉₅ : 0.76-0.95 p = 0.003

2p = 0.003

Gray et al ASCO 2013
Treatment duration: recent data

At-TOM

BC deaths

404 versus 452 events

RR = 0.88

p = 0.05

Gray et al ASCO 2013
## Treatment duration: recent data

**At-TOM**

<table>
<thead>
<tr>
<th></th>
<th>10 years n (%)</th>
<th>5 years n (%)</th>
<th>RR (IC&lt;sub&gt;95&lt;/sub&gt;)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>102 (2,9)</td>
<td>45 (1,3)</td>
<td>2,20 (1,31-2,84)</td>
<td>&lt; 0,0001</td>
</tr>
<tr>
<td><strong>Death from endometrial cancer</strong></td>
<td>37 (1,1)</td>
<td>20 (0,6)</td>
<td>1,83 (1,09-3,09)</td>
<td>0,02</td>
</tr>
</tbody>
</table>

*Gray et al ASCO 2013*
Treatment duration: no definitive proof of concept + a risk-benefit balance...

**Benefits**
- Overall survival
- Local relapse free survival
- Metastatic free survival
- Prevention of new breast cancer

**Risks**
- Climateric symptoms
- Ovarian cysts
- Arthralgia
- Weight gain
- Cognitive and emotional symptoms
- Pregnancy precluded
- Dyslipidemia
- Asthenia
- TED
- Osteoporosis
- Alopecia

**HT duration**

**Treatment duration:**
No definitive proof of concept + a risk-benefit balance...
Treatment duration: no definitive proof of concept + a risk-benefit balance...

Benefits
- Overall survival
- Local relapse free survival
- Metastatic free survival
- Prevention of new breast cancer

Risks
- Climateric symptoms
- TED
- Ovarian cysts
- Arthralgia
- osteoporosis
- asthenia
- Weight gain
- Cognitive and emotional symptoms
- Pregnancy precluded
- Dyslipidemia
- Alopecia

Treatment duration: no definitive proof of concept + a risk-benefit balance...

Overall survival
Local relapse free survival
Metastatic free survival
Prevention of new breast cancer
Climateric symptoms
TED
Ovarian cysts
Arthralgia
osteoporosis
asthenia
Weight gain
Cognitive and emotional symptoms
Pregnancy precluded
Dyslipidemia
Alopecia
Outline

• Prevention
• Adjuvant setting
• Advanced disease
Challenge towards 2020

• Individually identify and prevent/treat hormone resistance
Current targeted developments towards hormone resistance reversion/prevention

Voies mTOR/AKT
- mTOR C1C2
- PI3K
- PI3Kα
- PI3Kβ
- AKT

Voies IGF
- IGF1R
- IGF1
- Insulin R

Voies MET
- Met

Prolactin R

CDK4/6

FGFR
- FGFR1
- FGFs

HDAC

src

Her3

Aurora kinase

Androgen R

γsecretase

PR

Frizzled R

bcatenin

Smoothened R

Zarvadas et al Nature Treat Rev 2013
Initial proof of concept: mTOR inhibitor can reverse HT resistance (everolimus: Affinitor®)
Anti CDK4/6: ex palbociclib randomised phase II

Finn et al SABCS 2012
Thanks a lot