Best of the Year 2015
Breast Cancer

Fabrice ANDRE
Gustave Roussy
Outline

- Fine tuning « old » therapies to improve outcome
  - Endocrine therapy
  - Chemotherapy

- New biomarkers for breast cancer stratification
  - TILs
  - ctDNA

- New Her2-3 inhibitors

- New targets in breast cancer
  - CDK4
  - PI3K
  - Mutational load
Fine-tuning endocrine therapy: LH-RH analogs combined with exemestane in pre-menopausal women

Pagani, NEJM, 2014
Fine-tuning chemotherapy: carboplatin in TNBC

Logrank $p=0.0325$

HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), $p=0.0350$

3 yrs DFS 85.8%

3 yrs DFS 76.1%

Von Minckwitz, SABCS, 2015
Fine-tuning chemotherapy: capecitabine in patients with high risk breast cancer
Take home message

• Fine-tuning « old » therapies could be a research strategy to improve outcome

• Need massive investment in academic research

• This academic research on drug repositioning and fine-tuning could decrease expenses on new drugs by improving outcome
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  – TILs
  – ctDNA

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  – PI3K
  – Mutational load
TILs to predict risk of distant recurrence in TNBC: A meta-analysis

Patients with TIL+ / N0 TNBC do not need any additional therapy than chemo

Loi S, SABCS, 2015
Patients with ctDNA during follow-up have a high risk of relapse

Take home message

- New biomarkers could help better defining which population should be the target of adjuvant trials & further approvals in early breast cancers:
  - TIL- TNBC
  - ctDNA+ ER+ BC

- First reports of prospective genomic trials (Sparano, NEJM, 2015)

- Investment on academic research could allow narrowing the labels of new drugs
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  – Prospective validation of gene signatures

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Pertuzumab improves dramatically OS in Her2-overexpressing mBC...

15 months absolute difference

Hazard ratio, 0.68 (95% CI, 0.56–0.84)
P<0.001

Swain, ESMO 2014, NEJM 2015
... but only modestly improves PFS

Need to substitute PFS by other surrogates of OS in drugs that activate immune system: Spider plots ? Tumor growth rate ? Lymphocytic infiltration at PD ? Etc...
Neratinib (TKI) after trastuzumab

First trial showing that a TKI targeting oncogenic event can improve outcome in the adjuvant setting

Two-sided P-value = 0.023
HR (95% CI) = 0.74 (0.56–0.96)

Chan, SABCS, 2015
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• New Her2-3 inhibitors

• New targets in breast cancer
  – CDK4
  – PI3K
  – AKT
  – Mutational load
## Randomized trials testing CDK4 inhibitors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>setting</th>
<th>Pre treatment</th>
<th>phase</th>
<th>n</th>
<th>Effect on primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole +/- paclitaxel (Finn, Lancet Oncol, 2015)</td>
<td>meta</td>
<td>Endocrine sensitive</td>
<td>Phase II randomized</td>
<td>165</td>
<td>PFS: 20 versus 10 months HR: 0.49 (0.32–0.75) P: 0.0004</td>
</tr>
<tr>
<td>Fulvestrant +/- palbociclib (Turner, NEJM, 2015)</td>
<td>meta</td>
<td>Resistant to AI</td>
<td>Registration trial</td>
<td>521</td>
<td>PFS: 9.2 versus 3.8 months PFS: HR: 0.42 (0.32–0.56) &lt;0.001</td>
</tr>
</tbody>
</table>

**Palbociclib prolongs PFS in two randomized trials**

**Results pending for abemaciclib and ribociclib**

**Adjuvant trials started**
Efficacy of non-selective PI3K inhibitors in overall trial population

- **Buparlisib + fulvestrant (n/N=349/576)**
- **Placebo + fulvestrant (n/N=435/571)**

### Full Population (N=1147)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>One-sided P value</th>
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</thead>
<tbody>
<tr>
<td>Buparlisib + Fulvestrant (n=576)</td>
<td>6.9 (6.8–7.8)</td>
<td>0.78 (0.67–0.89)</td>
<td>&lt;0.001</td>
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<tr>
<td>Placebo + Fulvestrant (n=571)</td>
<td>5.0 (4.0–5.2)</td>
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</table>

**Baselga, SABCS, 2015**
Efficacy of non-selective PI3K inhibitors in patients with PIK3CA mutation on ctDNA

<table>
<thead>
<tr>
<th>ctDNA PIK3CA Mutant n=200</th>
<th>Buparlisib + Fulvestrant n=87</th>
<th>Placebo + Fulvestrant n=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.0 (5.0–10.0)</td>
<td>3.2 (2.0–5.1)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.56 (0.39–0.80)</td>
<td>&lt;0.001</td>
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<tr>
<td>One-sided nominal P value</td>
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</table>

Baselga, SABCS, 2015
The best is still to come: Alpha-selective PI3K inh

Alpelisib + FUL

[Graph showing treatment effectiveness]

Taselisib + FUL

Juric, SABCS, 2015

Juric, SABCS, 2013

Promising antitumor activity in PIK3CA mutant, in combination with ET
Ongoing phase III registration trials (SOLAR1, SANDPIPER)
Efficacy of AZD5363 in patients with AKT1 mutations (breast cancer)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ongoing</th>
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<tr>
<td>14</td>
<td>2.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Tumor shrinkage but early relapse, need to combine with endocrine therapy

Hyman, AACR/NCI/EORTC, 2015
A subset of ER+/Her2- mBC (10%) present a high mutational load. This subset does not exist in eBC and is associated with very poor outcome.

Lefebvre, MAP conference, 2015
Conclusion

• Fine-tuning & repositioning old drugs could improve outcome in BC

• New biomarkers are being validated that would allow narrowing the population that would be eligible for adjuvant therapies & future approvals

• Pertuzumab is an illustration that PFS is not an appropriate surrogate for mAb

• Neratinib is an illustration that a TKI can improve outcome in the adjuvant setting

• New targets include: CDK4, PI3K, AKT1 and PD1