Precision medicine in metastatic breast cancer: Strengths and pitfalls

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Application of genomics to personalize therapy in metastatic breast cancer

- Neoantigens and mutational load
- Expression of ligands of immune checkpoint proteins
- Identification of cancer cells resistant to CTLs (TAP1mut, absent MHC1)
- Characterization of the local immune system
- Analysis of polymorphisms related to immune defects (TLR4, P2RX7)

Outline

1. Genomic landscape of breast cancer
2. Molecular screening initiatives in breast cancer
   a. SOLTI’s AGATA
   b. AURORA
   c. VHIO experience
3. Targeting the genomic drivers of breast cancer:
   clinical experience
4. Challenges in precision medicine for MBC
1. GENOMIC LANDSCAPE OF BREAST CANCER
- Around **20 genomic segments** with potentially targetable alterations and that would warrant specific drug targeting

- Most of these segments occur in **<5% breast cancers**

- Molecular alterations may be clustered in **driver pathways**: PI3K/AKT/mTOR, FGFR, Rb1, DNA repair

- Unknown: influence of **clonality** (mutant allele fraction) in drug response
Landscape of molecular alterations in primary and metastatic ER+ BC

Landscape of molecular alterations in primary and metastatic ER+ BC

- Acquisition of genomic events and pathway alteration involved in treatment resistance (ESR1, TSC1...) and metastatic process

- Need for genomic characterization of the metastatic disease
  - Fresh biopsies
  - Liquid biopsies
2. MOLECULAR SCREENING INITIATIVES IN BREAST CANCER
Ongoing molecular screening programs worldwide

<table>
<thead>
<tr>
<th>Local efforts</th>
<th>Pilot studies</th>
<th>1st generation trials</th>
<th>Randomized trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No NGS</td>
<td>SAFIR02 breast</td>
</tr>
<tr>
<td>VHIO</td>
<td>preSAFIR</td>
<td>MOSCATO</td>
<td>SAFIR02 lung</td>
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<tr>
<td>MSKCC</td>
<td>AGATA</td>
<td>WINThER</td>
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<tr>
<td>MDACC</td>
<td>preAURORA</td>
<td>Profiler</td>
<td></td>
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<td></td>
<td></td>
<td>AURORA</td>
<td></td>
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<td></td>
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<td>SHIVA</td>
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<td></td>
<td>MOST</td>
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</table>

PILOT STUDY DESIGN

Max 21 calendar days

N=25.215 new cases of BC in Spain/year
N=6.075 deaths of BC in Spain/year
N=187.683 patients with BC in Spain
N=19.061 patients with MBC in Spain (10% of all BC patients)

260 patients in AGATA / 19.061 patients with mBC in Spain = 1.4%
THE NETWORK TODAY
OUR PROGRESS TO DATE

Consort Diagram

219 patients enrolled

Excluded (n=11)
- Not meeting inclusion criteria (n=7)
- No sample available (n=4)

208 patients with biopsy

Excluded – No more sample available (n=14)
- Low percentage of tumor cells (n=12)
- DNA quality test failed (n=2)

Ongoing (n=19)
- Not meeting quality criteria (n=8); pending confirmation sample availability
- Pending quality control (n=7)
- Pending sequencing (n=4)

175 patients with sequenced sample

11 Pending advisory board meeting

164 evaluated patients

RESULT:
- 47% patients with potential actionable mutations
Advanced breast cancer “Omics” research integration

- nCounter (Nanostring)
- MiSeq (Illumina)
- BEAMing (Sysmex)
- OncoPlexDx
SOLTI’s Biomarker Program Design

DNA: 61-gene panel
RNA: Expression of 120 genes (intrinsic subtype + immune + AR + Others)
Protein: Expression of 40 proteins → ONCOPLEXDX collaboration
Blood: discussing with various companies....
SOLTI’s Biomarker Program Design

- LABS
- SITES
- PATIENTS
- RESEARCHERS

Clinical trials
Off-label Drug Use
Clinical blood tissue
**Study Design**

**AURORA MS Platform:**
1300 newly diagnosed or 1st line MBC: Real time TGS on primary and metastatic lesions and blood RNA sequencing (done at a later stage) on both primary and metastatic lesions supported by a secure AURORA IT platform

Objective: To improve the understanding of metastatic breast cancer heterogeneity associated with disease progression (part I)

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Screening failure ~300
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**“Actionable” mutation(s) (n~300)**

Separate consent

Objective: To triage patients in new drugs trials in collaboration with Pharma Industry

**AURORA Q3 months clinical follow-up program**

- **R+**
- **P+**

**AURORA in depth characterization on primary and metastatic lesions and blood (whole exome sequencing combined with RNA sequencing data) of outliers patients**

*R = Exceptional Responders or *P = Rapid Progressors

Objective: To improve the understanding of the mechanisms of early resistance versus exquisite sensitivity (part II)

**“Non actionable” mutation(s) (n~700)**

Standard therapies

- Endocrine therapies
- Chemotherapies
- Chemotherapy + anti HER2 therapies
Pre-screening in Breast Cancer at VHIO

Oliveira M et al, SABCS 2015
## Clinical Trials Portfolio: targeted agents for MBC

<table>
<thead>
<tr>
<th>MBC Trial</th>
<th>N</th>
<th>Treatment</th>
<th>Subtype</th>
<th>Type of trial</th>
<th>Molecular inclusion criteria</th>
<th>Potential enrichment</th>
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</thead>
<tbody>
<tr>
<td><strong>CDK4/6 inhibitor</strong></td>
<td>3</td>
<td>Palbociclib</td>
<td>ER+</td>
<td>Combo with ET</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palbociclib</td>
<td>HER2+</td>
<td>Combo with Trast</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ribociclib</td>
<td>ER+</td>
<td>Combo with everolimus</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abemaciclib</td>
<td>ER+</td>
<td>Combo with ET</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>PI3K inhibitors</strong></td>
<td>6</td>
<td>Taselisib</td>
<td>ER+</td>
<td>Combo with ET</td>
<td>No</td>
<td>CDDN1 amplification, PI3KCAmut</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taselisib</td>
<td>ER+/TN</td>
<td>Combo with CT</td>
<td>PI3KCAmut</td>
<td>PI3KCAmut, PI3CA amplification (?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF384</td>
<td>PIK3CAmut</td>
<td>Basket trial</td>
<td>No</td>
<td>PTENnull, PIK3CBmut</td>
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<tr>
<td></td>
<td></td>
<td>AZD8186</td>
<td>TN</td>
<td>Combo with CT</td>
<td>No</td>
<td>PTENnull, PTEN del</td>
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<tr>
<td><strong>mTOR inh</strong></td>
<td>4</td>
<td>Everolimus</td>
<td>ER+</td>
<td>Combo with ET</td>
<td>No</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>AZD2014</td>
<td>ER+</td>
<td>Combo with ET</td>
<td>No</td>
<td>?</td>
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<tr>
<td></td>
<td></td>
<td>GDC-0068</td>
<td>TN</td>
<td>Combo with ET</td>
<td>No</td>
<td>PTEN null</td>
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<tr>
<td><strong>AKT inh</strong></td>
<td>3</td>
<td>AZD5363</td>
<td>ER+</td>
<td>Combo with CT</td>
<td>No</td>
<td>PTEN null, PTENmut, AKT mut</td>
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<tr>
<td></td>
<td></td>
<td>AZD5363</td>
<td>AKTmut</td>
<td>Single agent</td>
<td>PIK3CAmut</td>
<td>AKT1mut</td>
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<tr>
<td><strong>Demetilator</strong></td>
<td>1</td>
<td>Azacitidine</td>
<td>ER+</td>
<td>Combo with ET</td>
<td>No</td>
<td>?</td>
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<tr>
<td><strong>HER2 TKI</strong></td>
<td>1</td>
<td>Neratinib</td>
<td>HER2mut</td>
<td>Basket trial</td>
<td>ERBB2/ERBB3mut</td>
<td>EGFR1 amplification</td>
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<tr>
<td><strong>FGFR1 inh</strong></td>
<td>1</td>
<td>Lucitaniib</td>
<td>ER+</td>
<td>Single agent</td>
<td>No</td>
<td>FGFR1 ampl, FGFR2 ampl, 11q ampl</td>
</tr>
<tr>
<td><strong>ESR1 degraders</strong></td>
<td>1</td>
<td>GDC-0810</td>
<td>ER+</td>
<td>Single agent</td>
<td>No</td>
<td>ESR1mut, ESR1 amplifications, ESR1 fusions</td>
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<td><strong>Checkpoint inhibitors</strong></td>
<td>1</td>
<td>Pembrolizumab</td>
<td>TN</td>
<td>Single agent</td>
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<td>PD-1/PD-L1, immune signature</td>
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<tr>
<td></td>
<td></td>
<td>Atezolizumab</td>
<td>TN, BRCAmut</td>
<td>Single agent</td>
<td>PD-L1 high</td>
<td>PD-1/PD-L1, immune signature</td>
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<td></td>
<td>PDR001</td>
<td>TN</td>
<td>Single agent</td>
<td>No</td>
<td>PD-1/PD-L1, immune signature</td>
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<tr>
<td><strong>Notch inhibitor</strong></td>
<td>1</td>
<td>LY3039478</td>
<td>TN</td>
<td>Single agent</td>
<td>Notch alt</td>
<td>Notch ampl, Notch mut</td>
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</tbody>
</table>

*Internal Data*
3. TARGETING THE GENOMIC DRIVERS OF BREAST CANCER: CLINICAL EXPERIENCE
Proportion of alterations in primary breast tumors (METABRIC)
BELLE-2: Buparlisib plus Fulvestrant for MBC
Phase Ib Study of GDC-0032 in ER+ MBC

- Multiple **partial responses** observed in heavily pretreated HR+ breast cancer patients
- Anti-tumor activity observed in patients who had prior letrozole, fulvestrant or everolimus
- Increased anti-tumor activity observed in patients with **PIK3CA mutant** breast cancer

Juric D et al. SABCS 2013
Saura C et al. SABCS 2014
BYL719 (α-Specific Inhibitor) in Combination With Fulvestrant

N=84
Median number of lines for metastatic treatment: 5 (1-16)

PIK3CA mut patients (n=50)
ORR 24%
DCR 80%

PIK3CA WT patients (n=34)
ORR 0%
DCR 45%

Janku F et al. SABCS 2014
Patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer
Postmenopausal, recurrence or progression during or after an aromatase inhibitor therapy
Enrollment enriched for patients with PIK3CA mutant tumors via central testing
(N=600)

2:1 randomization

- Taselisib + Fulvestrant
- Placebo + Fulvestrant

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.

- Patients with PIK3CA-mutant tumors will be randomized separately from patients without PIK3CA-mutant tumors to receive taselisib plus fulvestrant or placebo plus fulvestrant.
- Randomization will be stratified by visceral disease, endocrine sensitivity, and geographical region.
SOLAR-1

Primary End Point:
Progression-free survival in patients with PIK3CA-mutant status

Key Secondary End Point:
Overall survival in patients with PIK3CA-mutant status

www.ClinicalTrials.gov: NCT02437318
PFS: Investigator-Assessed - (ITT Population)

PI3K inhibitors
CDK4/6 inhibitors
AKT inhibitors
HER2 inhibitors
ER degraders
FGFR inhibitors

Presented By Richard Finn at 2016 ASCO Annual Meeting
Subgroup Analysis of PFS by Biomarker

Qualitative Analysis

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
</tr>
<tr>
<td>ER+</td>
<td>504</td>
<td>0.57 (0.44–0.74)</td>
</tr>
<tr>
<td>ER−</td>
<td>62</td>
<td>0.41 (0.22–0.75)</td>
</tr>
<tr>
<td>Rb+</td>
<td>512</td>
<td>0.53 (0.42–0.68)</td>
</tr>
<tr>
<td>Rb−</td>
<td>51</td>
<td>0.68 (0.31–1.48)</td>
</tr>
<tr>
<td>Cyclin D1+</td>
<td>549</td>
<td>0.56 (0.44–0.71)</td>
</tr>
<tr>
<td>Cyclin D1−</td>
<td>15</td>
<td>1.00 (0.29–3.46)</td>
</tr>
<tr>
<td>p16+</td>
<td>466</td>
<td>0.52 (0.40–0.67)</td>
</tr>
<tr>
<td>p16−</td>
<td>84</td>
<td>0.73 (0.39–1.36)</td>
</tr>
<tr>
<td>Ki-67 ≤20%</td>
<td>318</td>
<td>0.53 (0.38–0.74)</td>
</tr>
<tr>
<td>Ki-67 &gt;20%</td>
<td>235</td>
<td>0.57 (0.41–0.79)</td>
</tr>
</tbody>
</table>

Quantitative Analysis

<table>
<thead>
<tr>
<th>Percentile</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
</tr>
</tbody>
</table>
| ER status \(\leq 25\%
\) | 142 | 0.50 (0.32–0.78) |
| \(>25\% \text{ to } <75\%
\) | 282 | 0.53 (0.37–0.74) |
| \(\geq 75\%
\) | 142 | 0.65 (0.41–1.05) |
| Rb status \(\leq 25\%
\) | 154 | 0.57 (0.36–0.88) |
| \(>25\% \text{ to } <75\%
\) | 249 | 0.46 (0.32–0.67) |
| \(\geq 75\%
\) | 160 | 0.63 (0.42–0.95) |
| Cyclin D1 status \(\leq 25\%
\) | 141 | 0.41 (0.26–0.65) |
| \(>25\% \text{ to } <75\%
\) | 247 | 0.69 (0.48–1.00) |
| \(\geq 75\%
\) | 176 | 0.52 (0.34–0.78) |
| p16 status \(\leq 25\%
\) | 140 | 0.74 (0.46–1.20) |
| \(>25\% \text{ to } <75\%
\) | 258 | 0.62 (0.44–0.89) |
| \(\geq 75\%
\) | 152 | 0.33 (0.21–0.52) |

HR=hazard ratio; LET=letrozole; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.
**MONALEEESA2**

- **PFS results by independent central review:** hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)

Let, letrozole; NR, not reached.

**Probability of Progression-free Survival (%)**

### PFS (Investigator Assessment)

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + Let (n=334)</th>
<th>Placebo + Let (n=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of events, n (%)</strong></td>
<td>93 (28)</td>
<td>150 (45)</td>
</tr>
<tr>
<td><strong>Median PFS, months (95% CI)</strong></td>
<td>NR (19.3–NR)</td>
<td>14.7 (13.0–16.5)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td>0.556 (0.429–0.720)</td>
<td>0.000000329</td>
</tr>
<tr>
<td><strong>One-sided p value</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### No. of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + Let</th>
<th>Placebo + Let</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time (months)</strong></td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>20</td>
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<tr>
<td></td>
<td>16</td>
<td>24</td>
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<tr>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td></td>
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</tbody>
</table>

- **PI3K inhibitors**
- **CDK4/6 inhibitors**
- **AKT inhibitors**
- **HER2 inhibitors**
- **ER degraders**
- **FGFR inhibitors**
AZD5363 for AKTmut cancer

Partial responses observed in ER+ breast, TNBC, cervix, endometrial, lung

Hyman D et al. AACR/EORTC 2015
Study D3610C0001 part E and F

- AZD5363 is a novel, potent, selective inhibitor of the kinase activity of AKT.
- Study D3610C0001 is an open-label, multicentre study to assess the safety, tolerability, and anti-tumour activity of AZD5363 in combination with fulvestrant in patients with ER+ve advanced or metastatic breast cancer (mBC) whose tumours harbour mutations in \textit{AKT1} (Part E) or \textit{PTEN} (Part F)
- Recommended dose; twice-daily 400mg dose of AZD5363 in a 4 days on and 3 days off regimen in combination with fulvestrant as background therapy (as per labelled dose).

<table>
<thead>
<tr>
<th>E reverse</th>
<th>\textit{AKT1} ER+ mBC: fulvestrant+AZD5363</th>
<th>n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>E delay</td>
<td>\textit{AKT1} ER+ mBC: fulvestrant+AZD5363</td>
<td>n=24</td>
</tr>
<tr>
<td>F reverse</td>
<td>\textit{PTEN} ER+ mBC: fulvestrant+AZD5363</td>
<td>n=24</td>
</tr>
<tr>
<td>F delay</td>
<td>\textit{PTEN} ER+ mBC: fulvestrant+AZD5363</td>
<td>n=24</td>
</tr>
</tbody>
</table>

- Part F recruitment requires sites to have local capability to characterise the molecular profile of tumour and/or blood samples using next generation sequencing methods.

www.clinicaltrials.gov NCT01226316
Paclitaxel + GDC-0068 / placebo in TNBC

**FAIRLANE**
Neoadjuvant

**LOTUS**
First line MBC

Pls: M Oliveira & S Isakoff
ClinicalTrials.gov identifier: NCT02162719 & NCT02301988
HER2 Mutations are Rare Events in Breast Cancer and Display Differential Sensitivity to anti-HER2 TKIs

Sequencing identified 27 HER2 mutations (25 cases) from ~ 1500 cases
Many are HER2 Negative (ie non-overexpressed or non-amplified) cases

HER2 mutant BC = 1.6% of 220,000 US cases/year = 4000 cases

Open-label, non-randomized, multicenter, multinational, multihistology phase 2 signal-seeking study of neratinib as monotherapy or in combination in patients with tumors harboring EGFR, ERBB2 or ERBB3 mutations (NCT 01953926)

Primary endpoint: Objective response rate at 8 weeks (ORR₈) (by RECIST v1.1 or modified PET response criteria)

Secondary endpoints: Objective response rate (ORR, confirmed); Clinical Benefit Rate (CBR); Progression Free Survival (PFS); Safety; Patient Reported Outcomes (PROs)

Exploratory endpoints: Central confirmation of ERBB2 somatic mutation; molecular profiling of tumor and plasma cell free DNA

Simon 2-stage design: If ≥1 response in first evaluable 7 patients expand cohort to Stage 2 (N=18); if ≥4 responses in Stage 2, then further expand cohort or consider breakout strategy

Inclusion criteria for breast cancer subset:
• Histologically confirmed breast cancer
• Evidence of tumor ERBB2 mutation (local)
• ECOG PS ≤2
• ≥1 measurable lesion (RECIST v1.1 or modified PET response criteria)

*Neratinib + fulvestrant or other hormone therapy in eligible patients with hormone receptor-positive breast cancer (protocol amendment 3)
Best change in tumor burden

*One patient had a response evaluation by both RECIST and PET response criteria and is therefore represented twice on this chart.*
Sample case

*ERBB2* mutant (L755_E757delinsS) ER+/ HER2– ductal breast carcinoma

Confirmed PR: 52% reduction by RECIST following neratinib monotherapy
ESR1 mutations in circulating plasma DNA are present in 37% of AI-resistant MBC patients

ESR1 mutations in:
- Luminal A vs Luminal B tumors
  41% vs 32%
- PIK3CA mutant vs WT tumors
  44% vs 30%

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Prognostic Effect of *ESR1* Mutation on OS

<table>
<thead>
<tr>
<th>Mutations</th>
<th>N</th>
<th>Events</th>
<th>Median OS (95%CI) (months)</th>
<th>HR (95%CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>385</td>
<td>217</td>
<td>32.1 (28.1-36.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT</td>
<td>156</td>
<td>112</td>
<td>20.7 (17.7 - 28.1)</td>
<td>1.40 (1.2 - 1.65)</td>
<td>0.000037</td>
</tr>
<tr>
<td>D538G</td>
<td>83</td>
<td>57</td>
<td>26.0 (19.2-32.4)</td>
<td>1.25 (1.02-1.54)</td>
<td>0.033</td>
</tr>
<tr>
<td>Y537S</td>
<td>42</td>
<td>30</td>
<td>20.0 (13.0-29.3)</td>
<td>2.31 (1.34-3.97)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Double MT</td>
<td>30</td>
<td>24</td>
<td>15.2 (10.9-27.4)</td>
<td>1.77 (1.31-2.39)</td>
<td>0.00018</td>
</tr>
</tbody>
</table>

- Both D538G and Y537S mutations were poor prognostic factors associated with shorter OS.
- In a multivariate analysis adjusting for sensitivity to prior hormonal therapy, visceral disease and ECOG status, the effect of ESR1 mutation (compared to wild-type) on OS remained significant.

*CI, confidence interval; HR, hazard ratio; MT, mutation; OS, overall survival; WT, wild-type. *All p-values were unadjusted for multiple testing.
GDC-0810 (Oral Selective ER Degrader) in ER+/HER2- MBC

- N=41
- 9 dose escalation cohorts
- Only 1 DLT (Grade 3 diarrhea) was observed in the 800 mg QD F cohort.
- Most common treatment-related AEs:
  - Diarrhea (63%)
  - Fatigue (46%)
  - Nausea (44%)
  - Flatulence (24%)
  - Anemia (22%)
  - Vomiting (22%).
- Most AEs were Grade 1 or 2
ER-degraders in clinical development

- **GDC-0810, GDC-0927 (Genentech)**
- **AZD9496 (Astra Zeneca)**
  - Phase I completed
- **LSZ102 (Novartis)**
  - LSZ102 Single Agent
  - LSZ102 + LEE011 or LSZ102 + BYL719
Radiological response in a heavily pre-treated MBC Patient with Lucitanib

Baseline
Sept. 20, 2011

C3D1
Nov. 18, 2011

- HR+/HER2-, $FGFR1$ ampl (ratio 2.21) and CGH
- Bone, lung and pleura metastases. 14 prior treatment lines, including 5 Phase 1 trials
- E-3810 at 20 mg/day

FINESSE: a Phase II Trial of Lucitanib in HR+/HER2- patients

Co-Lead PIs: Dr. Javier Cortés and Dr. Fabrice André

ClinicalTrials.gov identifier: NCT02202746
CHALLENGES IN PRECISION MEDICINE FOR MBC
Challenges in precision medicine for MBC

• Quest for **biomarkers** of response (and resistance)
Development of biomarkers for new drugs: the neoadjuvant model in breast cancer

N = 330 in 110 global sites

ER+/Her2-ve Stage I-III operable BC
Untreated Postmenopausal ≥ 2cm tumors

Stratification factors:
- Tumor size (T1-T2 vs. T3)
- Nodal status

Letrozole + GDC-0032
Letrozole + Placebo

Letrozole 2.5 mg QD + Taselisib 4 mg or placebo 5 days on/2 days off

16 weeks

ClinicalTrials.gov: NCT02273973
Pre-treatment cfDNA captured tumor heterogeneity

<table>
<thead>
<tr>
<th>Mutant Gene</th>
<th>Pre-treatment liver biopsy</th>
<th>Post progression liver biopsy</th>
<th>Pre-treatment cfDNA</th>
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POD scan on AZD5363 Monotherapy
F/U scan on Fulvestrant + AZD5363

ddPCR Results

RECIST progression of disease (POD):
Fulvestrant added to AZD5363

Molecular response

Change in MAF (%)

Days on study
Challenges in precision medicine for MBC

- Quest for **biomarkers** of response (and resistance)
- **Biomarker driven trials** using tissue and ctDNA
Primary tumor

Metastatic lesion

ctDNA

Biomarker-driven trial 1

Biomarker-driven trial 2

Biomarker-driven trial n
Challenges in precision medicine for MBC

- Quest for **biomarkers** of response (and resistance)
- **Biomarker driven trials** using tissue and ctDNA
- Integration of **immune and epigenetic modulation** in the precision medicine model
Challenges in precision medicine for MBC

- Quest for **biomarkers** of response (and resistance)
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- **Availability** of targeted therapy and **technical issues** of tissue testing
Challenges in precision medicine for MBC

- Quest for **biomarkers** of response (and resistance)
- **Biomarker driven trials** using tissue and ctDNA
- Integration of **immune and epigenetic modulation** in the precision medicine model
- **Availability** of targeted therapy and **technical issues** of tissue testing
- Validation of this approach in **prospective** clinical trials
Sponsor: UNICANCER
Partnership: ARC, AstraZeneca
Sample size: 210 patients randomized
Recruitment ongoing

Illustration of Personalized Medicine Trial: SAFIR02

NGS
Array CGH: 51 genomic alterations

mBC
Her2-negative

Geriatric alteration

Therapeutic phase

Targeted therapy according to genomic alteration (8 different therapies)

Standard of care

No alteration: follow-up

ctDNA NGS with multiple genes panel

MBC

Genomic alteration in ctDNA

No alteration: follow-up

Targeted therapy according to genomic alteration

Standard of care
Take home messages

• Molecular information improves precision in patients’ categorization and treatment

• Matching alteration to therapy is challenging: smarter molecular screening programs, addressing metastatic disease, availability of clinical trials

• Need for biomarkers!

• Prospective well designed clinical trials will define how to better select populations to maximize the benefit of new agents (probably large phase 3 trials not needed)
Thank you!

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