Metastatic Breast Cancer: where are we and where are we going?

Dr. Stefania Redana
Clinical Research Fellow
The Royal Marsden Hospital
Thursday 5th November 2015
Outline

• Overview on Breast Cancer Statistics in the UK
• Standard of care and new treatments
  – Hormone receptor positive disease
  – HER2+ disease
  – Triple negative disease
• New drugs toxicities
Breast cancer Incidence over time

Breast Cancer (C50): 1975-2011
European Age-Standardised Incidence Rates per 100,000 Population, Females, Great Britain

www.cancerresearchuk.org
Last assessed October 2015
Breast cancer Incidence by stage

Breast (C50): 2013
Proportion of Cancers Diagnosed at Each Stage, All Ages, England

Percentage of Cases (%) vs. Stage at Diagnosis

www.cancerresearchuk.org
Last assessed October 2015
1 – 5 and 10 y Breast cancer Survival over time

www.cancerresearchuk.org
Last assessed October 2015
HR + disease

- Aromatase inhibitors and tamoxifen remain mainstays
- Fulvestrant – an estrogen receptor down-regulator:
  - CONFIRM
  - FIRST
- Overcoming endocrine resistance:
  - BOLERO 2
  - PALOMA 1 and 3
# Aromatase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>ANASTROZOLE $^{1,2}$ (n=1021)</th>
<th>LETROZOLE $^3$ (n=916)</th>
<th>EXEMESTANE$^4$ (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>7.0</td>
<td>6.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>8.5</td>
<td>9.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Median TTP (months)</td>
<td>40.1</td>
<td>30</td>
<td>43.3</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>39.2</td>
<td>34</td>
<td>37.2</td>
</tr>
</tbody>
</table>

Estrogen receptor down-regulator: Fulvestrant

- Fulvestrant non inferior to Tamoxifen as 1st line treatment for ER+ MBC\textsuperscript{1}
- Fulvestrant non inferior to Anastrozole as 2nd line treatment for ER+ MBC\textsuperscript{2}
- Fulvestrant and Exemestane are equally active in ER+ MBC recurring or progressing on NSAIs\textsuperscript{3,4}

Fulvestrant: CONFIRM trial

Phase III, double blind placebo controlled trial of two different doses of fulvestrant in postmenopausal women with advanced or MBC progressing on previous endocrine therapy

**Progression Free Survival**

Median PFS 6.5 vs 5.5 months for fulvestrant 500 mg vs 250 mg

Di Leo et al. JCO 2010

**Overall Survival**

Median OS 26.4 vs 22.3 months for fulvestrant 500 mg vs 250 mg

Di Leo et al. JNCI 2014
Fulvestrant vs AI: FIRST trial

Phase II, open label, randomized trial comparing fulvestrant and anastrozole as first line therapy for ER+ postmenopausal advanced or MBC

**Time to Progression**

![Graph showing Time to Progression](image1)

- Median TTP 23.4 vs 13.1 months for fulvestrant vs anastrozole

**Overall Survival**

![Graph showing Overall Survival](image2)

- Median OS 54.1 vs 48.4 months for fulvestrant vs anastrozole


Ellis et al. JCO 2015 (e-published)
Overcoming endocrine resistance

- **Primary or de novo** resistance: no initial benefit has been seen with endocrine therapy (50% ER+ve BC)

- **Secondary or acquired** resistance: resistance develops over time following an initial response to endocrine therapy.
  - Almost all patients with advanced disease will develop *acquired* resistance to endocrine therapies

- The mechanisms of *de novo* and *acquired* resistance are likely similar but are not completely understood

- Research focuses on understanding the molecular pathways allowing ER+ cancer cells to escape from endocrine therapy
Crosstalk between ER and mTOR Signalling

• mTORC1 activates ER in a ligand-independent fashion

• Hyperactivation of the PI3K/mTOR pathway is observed in endocrine resistant breast cancer cells

• mTOR is a rational target to enhance the efficacy of hormonal therapy

Yamnik, RL. J Biol Chem 2009; 284(10):6361-636
Miller, TW. J Clin Invest 2010; 120(7):2406-2413
BOLERO-2
Exemestane + Everolimus PFS

HR = 0.36, 95% CI (0.27, 0.47)
Logrank P Value: <0.0001

EVE + EXE: 10.6 Months
PBO + EXE: 4.1 Months

No. of Patients Still at Risk:

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (E/N=114/485)</th>
<th>Placebo + Exemestane (E/N=104/239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>485</td>
<td>239</td>
</tr>
<tr>
<td>6</td>
<td>385</td>
<td>168</td>
</tr>
<tr>
<td>12</td>
<td>281</td>
<td>94</td>
</tr>
<tr>
<td>18</td>
<td>201</td>
<td>55</td>
</tr>
<tr>
<td>24</td>
<td>132</td>
<td>33</td>
</tr>
<tr>
<td>30</td>
<td>102</td>
<td>20</td>
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<tr>
<td>36</td>
<td>67</td>
<td>11</td>
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<tr>
<td>42</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>48</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>54</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>60</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>66</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>72</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>78</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
BOLERO-2
Exemestane + Everolimus OS

mOS 31.0 vs 26.6 months for EVE + EXE vs PBO + EXE, respectively.

Piccard et al. Ann Oncol 2014
Palbociclib Mechanism of Action
Selective CDK4/6 inhibition

- Cyclin D1 is a direct transcriptional target of ER; inhibition of cyclin D1 inhibits oestrogen-induced S-phase entry
- PAL acts synergistically with tamoxifen in ER+ breast cancer cell lines

PAL arrests the cell cycle at G1 by selective inhibition of CDK4/6

Cyclin D is a target of palbociclib. Cyclin D1 is a direct transcriptional target of ER; inhibition of cyclin D1 inhibits oestrogen-induced S-phase entry. PAL acts synergistically with tamoxifen in ER+ breast cancer cell lines.
PALOMA-1

- Randomized phase II open label trial
- 165 Postmenopausal ER+ HER2- MBC patients
- No previous treatment for metastatic disease
- Cohort 1: ER+ HER2- MBC
- Cohort 2: p16 loss or cyclin D1 amplification
- Primary end point: investigator assessed PFS

Median PFS in both cohorts

- mPFS 10.2 months vs 20.2 months for LET and LET + PALBO, respectively
- Cohort 1: mPFS 5.7 vs 26.1 months for LET and LET + PALBO, respectively

Finn et al. Lancet Oncol 2015
PALOMA-3

- Phase III, randomized, double blind, placebo controlled trial
- Randomization 2:1
- Pre- or post-menopausal ER+ MBC relapsed on previous endocrine therapy
- Primary end point: PFS

Turner et al. NEJM 2015
HER2+ disease

- Aggressive behavior
- Poor prognosis
- Trastuzumab has changed the natural history of HER2+ MBC since 1998
- Can HER2+ MBC be cured?
- Overcome trastuzumab resistance
Trastuzumab for MBC

The New England Journal of Medicine

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANNY FUCHS, M.D., VIRGINIA PATON, PH.D., ALEX BALDACCI, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIRICH, M.D., JANET WALTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY HORTON, M.D.*

A

B

C

TTP 7.4 vs 4.6 months for chemotherapy and herceptin vs chemotherapy alone

TTP 6.9 vs 3.0 months for paclitaxel and herceptin vs paclitaxel alone
Trastuzumab for MBC

Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group

Michel Marty, Francesco Cognetti, Dominique Maraninchi, Ray Snyder, Louis Mauriac, Michèle Toubiana-Hulin, Stephen Chen, David Grimes, Antonio Antón, Ana Lluch, John Kennedy, Kenneth O’Byrne, PierFranco Comte, Michael Green, Carol Ward, Karen Mayne, and Jean-Marc Extea

Table 2. Summary of Efficacy Between the Two Treatment Arms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab + Docetaxel (n = 92)</th>
<th>Docetaxel Alone (n = 94)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>61</td>
<td>34</td>
<td>.0002</td>
</tr>
<tr>
<td>CR, %</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PR, %</td>
<td>54</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>SD, %</td>
<td>27</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>DR, median, months</td>
<td>11.7</td>
<td>5.7</td>
<td>.009</td>
</tr>
<tr>
<td>TTP, median, months</td>
<td>11.7</td>
<td>6.1</td>
<td>.0001</td>
</tr>
<tr>
<td>OS, median, months*</td>
<td>31.2</td>
<td>22.7</td>
<td>.0325</td>
</tr>
</tbody>
</table>

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; DR, duration of response; TTP, time to progression; OS, overall survival.

*Kaplan-Meier estimate.

Fig 2. Comparison of estimated overall survival between trastuzumab plus docetaxel and docetaxel-alone arms (Kaplan-Meier plots).
Long term survival in HER2+ MBC

- 15-20% HER2+ MBC patients achieve CR when treated with trastuzumab-based therapy$^{1-4}$
- Long term remission is possible$^4$
- Biomarkers to predict long term benefit from anti HER2 single agent therapy are under evaluation$^5$

The RMH experience

- Retrospective analysis of 251 consecutive HER2+ MBC patients who received 1\textsuperscript{st} line trastuzumab-based therapy between 2001 and 2010
- Primary end point: PFS
- Secondary end points: OS, ORR, cardiac toxicity, trastuzumab duration
- Median age at diagnosis of MBC 52y (range 26-91)
- 52% ER+
- 20% de novo stage IV disease
- 58% received prior adjuvant chemotherapy, 42% prior endocrine therapy and 4% had adjuvant herceptin
- Median DFI 2.96y (range 0.21-17.25)
- 53% had liver disease, 4% bone only and 9% CNS metastasis

Yeo et al, The Breast 2015
The RMH experience

Median PFS 12 months (95% CI 10.3-14.6)  
1y PFS 48%  
2y PFS 27%  
5y PFS 12%  

Median OS 2.6 years (95% CI 2.2-3.3)  
5y OS 29%

Yeo et al, The Breast 2015
Pertuzumab

- Monoclonal antibody blocking the dimerization of HER2 and HER3
- Pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action
- Pertuzumab and trastuzumab given together provide a more comprehensive blockade of HER2 signaling and result in greater antitumor activity than either agent alone in HER2+ tumor models\(^1,2\)


Metzger-Filho et al. Clin Cancer Res 2013
Phase III, randomized, double blind, placebo controlled trial
808 HER2+ MBC
First line treatment for recurrent or de novo stage IV HER2+ breast cancer
Docetaxel + trastuzumab + pertuzumab/placebo
Primary end point: PFS
Secondary end point: OS

Progression free survival
Median Follow-up 50 months
Pertuzumab arm: 18.7 months
Placebo arm: 12.4 months

Overall Survival
Median Follow-up 50 months
Pertuzumab arm: 56.5 months
Placebo arm: 40.8 months

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

Swain et al. NEJM 2015
PERTUZUMAB Side effects

**Table 3. Adverse Events in the Safety Population.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo plus Trastuzumab plus Docetaxel (N = 397)</th>
<th>Pertuzumab plus Trastuzumab plus Docetaxel (N = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td>number (percent)</td>
</tr>
<tr>
<td>Most common events, all grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>184 (46.3)</td>
<td>272 (66.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>240 (60.5)</td>
<td>248 (60.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>197 (49.6)</td>
<td>215 (52.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>165 (41.6)</td>
<td>172 (42.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>146 (36.8)</td>
<td>153 (37.6)</td>
</tr>
<tr>
<td>Rash</td>
<td>96 (24.2)</td>
<td>137 (33.7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>105 (26.4)</td>
<td>119 (29.2)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>79 (19.9)</td>
<td>113 (27.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>120 (30.2)</td>
<td>156 (38.0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>119 (30.0)</td>
<td>94 (23.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>99 (24.9)</td>
<td>61 (15.0)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>30 (7.6)</td>
<td>56 (13.8)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>17 (4.3)</td>
<td>43 (10.6)</td>
</tr>
<tr>
<td>Grade 3 or higher events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>182 (45.8)</td>
<td>199 (48.9)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>30 (7.6)</td>
<td>56 (13.8)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>58 (14.6)</td>
<td>50 (12.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (5.0)</td>
<td>32 (7.9)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>7 (1.8)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (3.5)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (1.5)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (3.3)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>9 (2.3)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>11 (2.8)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (2.0)</td>
<td>4 (1.0)</td>
</tr>
</tbody>
</table>

Baselga et al. NEJM 2012
T-DM1

• Antibody–drug conjugate incorporating the HER2–targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1
• the antibody and the cytotoxic agent are conjugated by means of a stable linker
• T-DM1 allows intracellular drug delivery specifically to HER2-overexpressing cells
• Phase 2 studies have shown the clinical activity of T-DM1 in patients with HER2+ advanced breast cancer

Barok et al. 2014
EMILIA

- Phase III, open label, randomized trial
- Metastatic or locally advanced HER2+ patients previously treated with trastuzumab and a taxane
- 991 pts (495 received T-DM1 and 496 received capecitabine lapatinib)
- Primary end points: PFS, OS and safety

Verma et al. NEJM 2012
EMILIA - OS

Verma et al. NEJM 2012
T-DM1 side effects

Table 3. Adverse Events in the Safety Population.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lapatinib plus Capecitabine (N = 488)</th>
<th>T-DM1 (N = 490)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events of Any Grade</td>
<td>Events of Grade 3 or Above</td>
</tr>
<tr>
<td>Any event</td>
<td>477 (97.7)</td>
<td>278 (57.0)</td>
</tr>
<tr>
<td>Specific events†</td>
<td></td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>389 (79.7)</td>
<td>101 (20.7)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysesthesia</td>
<td>283 (58.0)</td>
<td>80 (16.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>143 (29.3)</td>
<td>22 (4.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42 (8.6)</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>42 (8.6)</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>136 (27.9)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>218 (44.7)</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>93 (19.1)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>39 (8.0)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>43 (8.8)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>46 (9.4)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (2.5)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
Triple-Negative Breast Cancer (TNBC)

- ER negative, PgR negative, HER2 negative
- 10% - 17% of all breast carcinomas
- Significantly more aggressive than other molecular subtype tumours
  - Most frequently high grade (3) IDCs of no special type

- Peak risk of recurrence at 1-3yrs
  - Distant recurrence rarely preceded by local recurrence
  - Sites of relapse differ from luminal (CNS 46%)

- Increased mortality rate first 5yrs

Metastatic TNBC Outcomes

• Median OS: 13.3 months
• Median duration of first-line CT: 3 months
• Median duration of second-line CT: 9 weeks
  • 78% of patients received second-line CT
• Median duration of third-line CT: 4 weeks
  • 49% of patients received third-line therapy

TNBC – treatment options

- **Anthracyclines**: higher rates pCR in TNBC
- **Taxanes**: Review of TNBC subgroups in the CALGB 9344 study in node positive patients where they compared the addition of paclitaxel to different anthracycline doses - ER negative patients derived the greatest benefit in both DFS and OS
- **pCR to NACT** is higher in the TNBC patients but the DFS and OS are still lower than non-TNBC patients
- **BRCAness**
  - Platinum salts
  - PARP-inhibitors
- **Immunotherapy**
TNBC - Immunotherapy

**Pembrolizumab (MK-3475), Anti-PD-1 Antibody, Humanized IgG4, High-Affinity**

- High affinity for the PD-1 receptor (KD ≈ 29 pM)
- Dual ligand blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- PK supports dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Demonstrated clinical activity in multiple tumor types
- Approved in US for treatment of unresectable or metastatic melanoma progressing following ipilimumab and BRAF inhibitor

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KEYNOTE-012: Triple-Negative Breast Cancer Cohort

- Recurrent or metastatic ER⁻/PR⁻/HER2⁻ breast cancer
- ECOG PS 0-1
- PD-L1+ tumor
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

**Pembro**
10 mg/kg IV Q2W

- Complete Response
  - Discontinuation Permitted
- Partial Response or Stable Disease
  - Treat for 24 months or until progression or intolerable toxicity
- Confirmed Progressive Disease
  - Discontinue

- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

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**Notes:**

- PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.

- If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

Nanda SABCS 2014
Treatment-Related Adverse Events With Incidence ≥5%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade 3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>6 (18.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (18.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (15.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (15.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.3%)</td>
<td>1 (3.1%)</td>
</tr>
</tbody>
</table>

- Adverse events of a potentially immune-mediated nature, regardless of attribution, included pruritus (n = 3; all grade 1-2), hepatitis (n = 1; grade 3), and hypothyroidism (n = 1; grade 2)
- Grade 3 treatment-related AEs were anemia, headache, aseptic meningitis, and pyrexia (n = 1 each)
- Grade 4 treatment-related AE was decreased blood fibrinogen (n = 1)
* One AE attributed to treatment that resulted in death was disseminated intravascular coagulation (DIC)
  - This was the only treatment-related AE that led to discontinuation
**Best Overall Response**  
(RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Patients Evaluable for Response n = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response rate</strong></td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>No assessment</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>

- Previous therapy among the 5 patients with CR or PR
  - Capecitabine: 5 (100.0%)
  - Taxane: 5 (100.0%)
  - Anthracycline: 4 (80.0%)
  - Platinum: 3 (60.0%)
  - Eribulin: 1 (20.0%)
Change From Baseline Over Time and Time To and Duration of Response

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response: not reached (range, 15 to 40+ weeks)
- Median PFS: 1.9 months (95% CI, 1.7-5.4)
- PFS rate at 6 months: 23.3%
Toxicity of new drugs

- Cardiovascular:
  - *Cardiac failure*
  - *Hypertension*
  - *Thrombo-embolic events*
- Respiratory:
  - *Pneumonitis*
- Mucocutaneous:
  - *Stomatitis*
  - *Rashes*
- Metabolic
  - *Hyperglycaemia*
- Haematological
  - *Bone marrow suppression*
Toxicity of new drugs

- Cardiovascular:
  - Cardiac failure
  - Hypertension
  - Thrombo-embolic events

- Respiratory:
  - Pneumonitis

- Mucocutaneous:
  - Stomatitis
  - Rashes

- Metabolic
  - Hyperglycaemia

- Haematological
  - Bone marrow suppression
Respiratory

• Non-infectious pneumonitis and everolimus

• BOLERO-2 trial (exemestane/everolimus, n=482):
  • Any grade: 12%
  • Grade 3: 3%

Royal Marsden audit (exemestane/everolimus, n=71):
  • Any grade: 36%
  • Grade 1: 13 (18%)
  • Grade 2: 11 (15%)
  • Grade 3: 1 (1%)
  • Grade 4: 1 (1%)

Cumulative risk estimates for initial onset of grade ≥2 pneumonitis

# Non-infectious pneumonitis: management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Treatment and management</th>
<th>Everolimus dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic; radiographic findings only</td>
<td>Initiate appropriate monitoring</td>
<td>No change</td>
</tr>
</tbody>
</table>
| 2     | Symptomatic, not interfering with ADL | • CT scan with lung windows.  
• Oxygen saturations.  
• Consider pulmonary function tests: spirometry/DLCO. | 1<sup>st</sup> occurrence: interrupt dose until recovery to grade<1, re-start at reduced dose (ie 5mg/day).  
2<sup>nd</sup> occurrence: discontinue or further dose reduction. Steroids if cough troublesome. |
| 3     | Symptomatic, interfering with ADL, O2 required | • Consider infectious aetiology.  
• Consider bronchoscopy. | 1<sup>st</sup> occurrence: interrupt dose until recovery to grade<1, re-start at reduced dose (ie 5mg/day).  
2<sup>nd</sup> occurrence: discontinue or further dose reduction. Steroids if infectious aetiology ruled out. |
| 4     | Life-threatening, ventilator support indicated | | Discontinue treatment |
Muco-cutaneous: stomatitis

BOLERO-2 trial (exemestane/everolimus, n=482):
Any grade: 56%. Grade 3: 8%.
RMH audit (exemstane/everolimus, n=71).
Any grade: 71%. Grade 3: 14%.

De Oliveira MA et al. Oral Oncol 2011
Cumulative risk estimates for initial onset of grade ≥2 stomatitis

Stomatitis: patient education

- Inform patients of the possibility of developing mouth ulcers and oral mucositis
- Educate on good oral hygiene and diet and prompt reporting of symptoms\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Good oral hygiene</th>
<th>Dietary modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rinse mouth with baking soda (or equivalent product) regularly</td>
<td>• Warn to avoid foods and beverages that are spicy, acidic, salty, or very hot or cold</td>
</tr>
<tr>
<td>• Brush and floss after each meal</td>
<td>• Avoid hard, crunchy or crusty food that can damage oral mucosa</td>
</tr>
<tr>
<td>• Use mild toothpaste (e.g. children’s) and soft-bristled toothbrush</td>
<td>• Eat small meals frequently rather than large meals less often</td>
</tr>
<tr>
<td>• Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives</td>
<td><strong>Prompt reporting</strong></td>
</tr>
<tr>
<td>• Encourage regular dental examinations</td>
<td>• Educate patient on likely signs and symptoms</td>
</tr>
<tr>
<td></td>
<td>• Contact caregiver at first sign of mouth discomfort</td>
</tr>
<tr>
<td></td>
<td>• Lesions interfering with eating and drinking</td>
</tr>
</tbody>
</table>

Stomatitis – incidence comparing Treatment with Symptoms vs Prevention from Outset

<table>
<thead>
<tr>
<th></th>
<th>Treat only when get symptoms (n=38)</th>
<th>Prevention* from start cycle 1 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>81% (n=31)</td>
<td>51% (n=17)</td>
</tr>
<tr>
<td>Grades 1-2</td>
<td>63% (n=24)</td>
<td>36% (n=12)</td>
</tr>
<tr>
<td>Grades 3-4</td>
<td>18% (n=7)</td>
<td>15% (n=5)</td>
</tr>
</tbody>
</table>

- Prevention Regimen:
  Sucralfate suspension – 1gm in 5mls rinse around mouth & swallow qds
  Raspberry Mucilage + 300mg dispersible aspirin – rinse as mouthwash qds
  Oral Gelclair for symptomatic mouth ulcers

Thanapoulou et al, EBCC 2014
## Stomatitis: Management

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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal (normal diet)</td>
<td>Non-alcoholic mouthwash or 0.9% salt water.</td>
<td>No change</td>
</tr>
</tbody>
</table>
| 2     | Symptomatic, but able to eat and swallow modified diet | - Topical analgesic mouth treatments.  
- Topical corticosteroids.  
- Antiviral therapy if herpetic infection confirmed.  
- Antifungal therapy (topical preferred) may be administered on a case-by-case basis.  
- Avoid agents containing hydrogen peroxide, iodine and thyme derivatives. | 1<sup>st</sup> occurrence: maintain dose if tolerable.  
If intolerable hold dose until recovery to grade<1, then re-start at same/reduced dose (ie 5mg/day).  
2<sup>nd</sup> occurrence: discontinue or further dose reduction. |
| 3     | Symptomatic, unable to eat and swallow modified diet |                                                                                           | 1<sup>st</sup> occurrence: interrupt dose until recovery to grade<1, re-start at reduced dose (ie 5mg/day).  
2<sup>nd</sup> occurrence: discontinue or further dose reduction. |
| 4     | Symptoms associated with life-threatening consequences. |                                                                                           | Discontinue treatment                                                                       |
Mucocutaneous: skin rashes

- **Pertuzumab:**
  - Acneiform: 25% G1/2 and 1% G3
    

- **Everolimus:**
  - Acneiform: 39% all grades (BOLERO-2)

- **PI3 kinase inhibitors:**
  - Erythematous, non-blistering, maculopapular.
Rash associated with everolimus

- In BOLERO 2 study: any grade: 36%, grade 3: 1%
- RMH audit: any grade: 43% and grade 3: 5%
- Widespread erythema and blistering of the skin on trunk, upper and lower limbs, hands and feet
- Lesions recover slowly (skin remains dry and flaky, with sub-cuteaneous oedema)
Papulopustular/acneiform rash: management

• Topical:
  – Steroids: eg: Alclometasone 0.05% cream, Fluocinonide 0.05% cream. Low dose face, medium strength body
  – Antibiotics: clindamycin gel (1%), erythromycin.

• Systemic:
  – Antibiotics: doxycycline 100mg bd, Minocycline 100mg bd.
  – Isotretinoin 20-30mg/day.

Burtness B, JNCCN 2009: 7(Suppl 1):5-21
Lacouture ME, Supp Care Cancer 2011;1079-1095
Skin rash: patient education

- Inform patients of the risk of skin rash and educate on prompt reporting of symptoms

**Lifestyle modifications**

- Wear loose non-irritating clothing
- When bathing use a mild soap without perfumes
- When washing and drying the skin gently pat the area instead of rubbing with the towel or washcloth
- Use sunscreen or protective clothing when out in the sun, even on cloudy days
- Avoid tanning booths
- Avoid cosmetics containing retinoids

**Prompt reporting**

- Be aware of likely signs and symptoms
- Contact caregiver at first sign of skin rash
Metabolic

• Hyperglycaemia and hyperlipidaemia:
  • mTOR inhibitors and PI3Kinase inhibitors
  • Induction of insulin resistance and dysregulation of insulin action

  Busaidy et al, JCO 2012:2919-2928.

• BOLERO-2: hyperglycaemia 13% (all grades), grade 3 (4%).
  Predominantly in patients with abnormal fasting glucose levels pre-treatment.
Cumulative risk estimates for initial onset of grade $\geq 2$ hyperglycemia/new-onset diabetes mellitus

Haematological

- **Trastuzumab-Emtansine:**
  - Thrombocytopenia: any grade: 28% and G3/4 13%.
  

- **PD 0332991/Palbociclib:**
  - Neutropenia grade 3: 48%, grade 4: 6%.

  Finn R et al. Lancet Oncol 2015
Take home message

• Thanks to multidisciplinary management and new treatments MBC patients can live long (12-15% alive 10 years post diagnosis of MBC)
• ER+ MBC
  – Fulvestrant is an additional treatment option with minor side effects
  – Major improvements in PFS with mTOR and CDK 4/6 inhibitors
• HER2+ disease
  – Combination of trastuzumab and pertuzumab is the new well established 1st line standard of care
  – T-DM1 superseded Capecitabine and lapatinib for treating HER2+ MBC progressing or recurring on trastuzumab based therapy
• TNBC
  – Role for immunotherapy
• Toxicities
  – As patients live longer and new treatments become available in the management of MBC, physicians have to face new toxicities
  – Multidisciplinary management and early intervention are key points not only for treating cancer but also for managing side effects