Metastatic Disease – Treatment and Palliative Care

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Metastatic Disease
Treatment and Palliative Care

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1 out of 8 to 10 women will have BC during their lifespan
About 1/3 EBC will relapse
MBC at diagnosis: 10-15% developed to 50-60% developing countries

There will be an estimated 626,679 deaths worldwide in 2018 and an estimated 805,116 by 2030, representing a 43% increase in absolute number of deaths from BC

In Europe:
1 diagnosis every 2.5 minutes
1 death every 6.5 minutes
More than half a million deaths worldwide every year
**HOW MANY MBC PATIENTS EXIST?**

*GLOBOCAN 2018 data*

If 1 third would be MBC: about 2.2 million MBC patients

BUT it is just a very rough estimation

Phased implementation TARGET: prioritise management of metastatic patients as we can not ignore them and only concentrate on curative cases

MAIN FINDINGS

- By January 2017: 154,292 women living with MBC in the US.
- 3 out of 4: relapsed BC (initially diagnosed with early BC and who later progressed); 1 out of 4 de novo MBC.
- Survival for de novo MBC increased over the years, especially in younger women. (Estimate: two-fold increase in 5-year survival (from 18% to 36%) for de novo MBC, at age 15–49, between 1992–1994 and 2005–2012)

MAIN PROBLEMS

- Estimates, not the real numbers.
- US situation very different from many other parts of the world.

The number of women living with MBC increased 4% from 1990 to 2000, 17% from 2000 to 2010, and is projected to increase by 31% from 2010 to 2020.
OVERALL SURVIVAL AND SEQUENTIAL TREATMENT OF PATIENTS WITH MBC

- 134 sites, 298 oncologists, all over Germany
- > 3,700 pts/1409 MBC pts
- (goal: 4,500 BC pts/2250 MBC pts by end 2015)

- Luminal is the most frequent subtype in MBC as well.
- If a drug/class of drugs improves OS, it will change substantially the median OS of MBC

Phased implementation TARGET: ensure proper diagnosis and treatment for luminal cancers

Oral Presentation, ABC 2
Marschner, N, et al, TMK Registry Group
GOALS OF THE TREATMENT IN MBC

- Balancing treatment efficacy and toxicity is the main objective
- Goals of treatment:
  - Improve survival *(very few agents achieve it!)*
  - Delay disease progression
  - Prolong duration of response
  - Palliate symptoms
  - Improve or maintain quality of life
  - Transform into a chronic disease

- Phased implementation TARGET: ensure palliation and pain control, focus on QOL
Resource-stratified guidelines: BHGI Incremental allocation & implementation

- **Basic level**: Core resources or fundamental services necessary for any breast health care system to function.
- **Limited level**: Second-tier resources or services that produce major improvements in outcome such as survival.
- **Enhanced level**: Third-tier resources or services that are optional but important, because they increase the number and quality of therapeutic options and patient choice.
- **Maximal level**: Highest-level resources or services used in some high resource countries with lower priority on the basis of extreme cost.


Eniu A et al, *Cancer* 113 (8 suppl), 2008
What has changed in 10 years?

...addition of CDK4/6 inhibitors
What has changed in 10 years?

...palliative & supportive care more structured
What has changed in 10 years?
…addition of new anti-HER2 therapies

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What has changed in 10 years?  
...new preference, new anti-HER2 therapies
CLEOPATRA: First-line Trastuzumab + Pertuzumab vs. Trastuzumab (mFU 50 mos)

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab + trastuzumab+docetaxel</th>
<th>Placebo + trastuzumab+docetaxel</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR(^1)</td>
<td>80.2%</td>
<td>69.3%</td>
<td>0.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PFS(^2)</td>
<td>18.7 months</td>
<td>12.4 months</td>
<td>0.66</td>
<td>0.0001</td>
</tr>
<tr>
<td>OS(^2)</td>
<td>56.5 months</td>
<td>40.8 months</td>
<td>0.66</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Most common adverse events ≥Grade 3 in the pertuzumab+trastuzumab+docetaxel group:
Neutropenia (48.9%), febrile neutropenia (13.8%), leukopenia (12.3%), and diarrhea (7.9%)
Long term cardiac safety maintained

First-line Metastatic ER+/HER2- Breast Cancer
PALOMA-2, MONALEESA 2, and MONARCH 3

**MCBS SCORE = 3**

**Primary endpoint: PFS (investigator-assessed)**

**ORR: 32.4**

**ORR: 59.2%**
Second line: Fulvestrant vs CDK4/6 inh + Fulvestrant

Primary Endpoint: PFS (ITT Population)

MONARCH 1: Response Summary

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Confirmed Objective Response Rate (ORR = CR + PR)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Stable Disease ≥ 6 months</th>
<th>Clinical Benefit Rate (CBR = CR + PR + SD ≥ 6 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abemaciclib 200 mg (N = 122)</td>
<td>13.3%</td>
<td>3.3%</td>
<td>19.3%</td>
<td>42.4%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Veliparib 150 mg (N = 122)</td>
<td>13.3%</td>
<td>7.4%</td>
<td>19.3%</td>
<td>42.4%</td>
<td>22.7%</td>
</tr>
</tbody>
</table>

Assessments based on independent review were comparable.

MCBS SCORE = 4

MONALEESA 3- second line

Second line + early relapsers

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Is Getting CDKi 1st Line Important?

**PALOMA-2 Progression-free survival**
- Ribociclib + letrozole (mPFS 27.6 mo)
- Placebo + letrozole (mPFS 14.5 mo)

**PALOMA-3 Progression-free survival**
- Ribociclib + fulvestrant (mPFS 11.2 mo)
- Placebo + fulvestrant (mPFS 4.6 mo)

*Δ 6.5 months - seems clinically significant*

CDKi 2nd line PFS: 25.7 months

**MONALEESA-2 Progression-free survival**
- Ribociclib + letrozole (n=334) Median PFS 16.8 months (95% CI: 12.7-20.6)
- Placebo + letrozole (n=334) Median PFS 9.1 months

*Δ 3.8 months*

Ribociclib 1st line: PFS 34.4 months

Ribociclib 2nd line PFS 30.6 months
Several essential, old and inexpensive drugs (tamoxifen, doxorubicin, cisplatin, 5-FU, bleomycin...) are in shortage

Not always an issue of resources!

Phased implementation TARGET: prioritise access to essential medicines

Metastatic breast cancer
(formulary inclusion and cost to patients): Anti-Her2 therapy

- Phased implementation TARGET: next step is to prioritise access to “valuable” new agents
- No “new miraculous” medicine can correct for bad management or unavailability of essential interventions

Palliation: availability of opioids

Many governments are failing patients with cancer in the delivery of adequate pain relief!

The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial. (LoE/GoR: Expert opinion/A) (100%)  

All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy to understand information about their disease and its management. Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, (LoE/GoR: 1/A) (97%)  

From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care. The approach must be personalized to meet the needs of the individual patient. (LoE: Expert opinion/A) (100%)
The medical community is aware of the problems raised by the cost of ABC treatment. Balanced decisions should be made in all instances; patients’ well being, length of life and preferences should always guide decisions. 
(LoE/GoR: Expert opinion/A) (100%)

PI TARGET: resource-appropriate, value-based decisions

We strongly recommend the use of objective scales, such as the ESMO Magnitude of Clinical Benefit Scale or the ASCO Value Framework, to evaluate the real magnitude of benefit provided by a new treatment and help prioritize funding, particularly in countries with limited resources. 
(LoE/GoR: Expert opinion/A) (88%)

PI TARGET: value frameworks

The ABC community strongly supports the use of biosimilars both for treatment of breast cancer (i.e. trastuzumab) and for supportive care (i.e. growth factors). To be used, the biosimilar must be approved after passing the stringent development and validation processes required by EMA or FDA or other similarly strict authority. 
(LoE/GoR: I/A) (90%)

PI TARGET: biosimilars
Minimal staging workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone. (LoE/GoR: II/A) (67%)

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. (LoE/GoR: I/A) (93%)

Many trials in ER+ ABC have not included pre-menopausal women. Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies. (LoE/GoR: Expert Opinion/A) (95%)

- **PI TARGET:** scale-up resource-appropriate radiology/lab availability (LABC vs M1?)
- **PI TARGET:** scale-up availability endocrine treatments
- **PI TARGET:** focus on endocrine treatment for PREMENOPAUSAL
Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.
(LoE/GoR: I/A) (100%)  

**Early** introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.
(LoE/GoR: I/A) (100%)  

Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief.
(LoE/GoR: I/A) (100%)  

- PI TARGET: ensure palliation and pain control, access to morphine, focus on QOL  

Alternative therapies (i.e. therapies used instead of scientifically based medicines) are not recommended in any phase or stage of cancer treatment.
(LoE/GoR: NA/E)  

- PI TARGET: educate on lack of efficacy of alternative treat.
Implementation does not equal copying

- Many patients are treated as we speak with very limited resources
- In the process of PI (A-->B) situation analysis is key (=A)
- Stakeholders involvement
- Setting the goals (=B)
- Numerous target/goals for phased implementation
- Lots of work to do in the afternoon panel!