KENYA SOCIETY OF HAEMATOLOGY AND ONCOLOGY
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Speaker Presentation

Title: ..............................................................

Author(s): ..........................................................
Updates in The management of Hormone positive Advanced Breast cancer in Postmenopausal Women

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Objectives…

• Burden of HP MBC in PMP the disease
• Options of Current Management
• Challenges with Treatment
• Summary of recommendations
• Announcements
Breast cancer… and Metastasis

- Breast cancer is the most common cancer in women worldwide, with nearly 2088,849 new cases diagnosed in 2018.
- “De Novo” Metastatic: Approximately 6-10% of new breast cancer cases are initially Stage IV or metastatic.
- 20-30% of all existing breast cancer cases are overall metastatic and 75% of them are Hormone positive.

\[\begin{align*}
\text{Incidence per 100,000} \\
\text{Age (years)}
\end{align*}\]

WHO cancer statistics.
Metastatic HP Breast Cancer

• A vast Majority of Metastatic breast Cancer is in Post menopausal Women are hormone positive

• A biopsy of a metastatic lesion should be performed, if accessible, to confirm diagnosis – its important!
Treatment Selection in Her 2 Neu Negative MBC – Post Menopausal

- Prior treatment History
- Interval from last treatment
- Burden of disease
- Situation – of crisis – or not
- Patient Preference
- Cost and Affordability } RCS
- Availability } RCS
- Physician Comfort level } RCS
Choices Of treatment

Traditional Style
- Hormonal therapy
- Chemotherapy
- Supportive

Current Standards
- Hormone therapies +
- CDK 4/6 Inhibitors
- PI3 K Inhibitors
- mToR inhibitors
- Immunotherapies ?
Endocrine Therapy

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance, or there is disease needing a fast response.
Metastatic breast cancer – SABCS 2014

Visceral metastases from hormone receptor positive BC as sensitive to endocrine therapy as non visceral metastasis

Robertson JFR et al. SABCS 2014 – P1-13-02
Initial Treatment of HR-Positive Advanced Breast Cancer in PMP

- AIs are the current standard of care for initial treatment of postmenopausal women with HR-positive advanced breast cancer
- AIs have demonstrated improved efficacy compared with tamoxifen
  - TTP, anastrozole vs tamoxifen: 10.7 vs 6.4 mos
  - TTP, letrozole vs tamoxifen: 9.4 vs 6.0 mos
  - PFS, exemestane vs tamoxifen: 9.9 vs 5.8 mos
  - Fulvestrant has demonstrated improved efficacy compared with anastrozole
  - TTP, fulvestrant vs anastrozole: 23.4 vs 13.1 mos
  - Fulvestrant has demonstrated similar efficacy compared with tamoxifen[^9]
  - Combination fulvestrant and anastrozole was not more efficacious than anastrozole alone[^10]

Main challenges in the treatment of hormone receptor positive breast cancer

Non-response and side effects

- Substantial Number of patients with ER+ breast cancer do not respond to the initial endocrine therapy
- The majority of patients who responded initially to an endocrine therapy develop resistance
- Patients may develop side effects / intolerance to medical therapies (Chemo- and endocrine therapy)

Development of resistance

- Often caused by activation of an alternative signaling pathway

Hormonal Therapy for Advanced Breast Cancer: Milestones

1896
Oophorectomy and response to advanced disease (George Beatson)

1951
Estrogen drives breast cancer

1977
Immunohistochemistry developed for ER and PR analysis

1990's
Estrogen receptor (ER) identified Tamoxifen approved

1999
First selective aromatase inhibitor (AI) approved for ABC

2002
ER downregulator approved AI approved as adjuvant therapy

2010
mTOR inhibitor + AI approved

2012
Anti-HER2 + AI approved for ER/HER2+ ABC

2015
CDK 4/6 Inhibitor + AI approved

AR, androgen receptor; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3-kinase; RB, retinoblastoma protein; TSC2, tuberous sclerosis complex 2 (tuberin).

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### Table 1. Randomized phase II/III clinical trials of CDK4/6 inhibitors as first-line treatment of advanced ER-positive breast cancer.

<table>
<thead>
<tr>
<th></th>
<th>PALOMA-1</th>
<th>PALOMA-2</th>
<th>MONALEESA-2</th>
<th>MONARCH-3</th>
<th>MONALEESA-7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Phase II open-label</td>
<td>Phase III placebo control</td>
<td>Phase III placebo control</td>
<td>Phase III placebo control</td>
<td>Phase III placebo control in pre-/perimenopausal women</td>
</tr>
<tr>
<td><strong>Treatment arms</strong></td>
<td>Letrozole ± palbociclib</td>
<td>Letrozole ± palbociclib</td>
<td>Letrozole ± ribociclib</td>
<td>NSAI ± abemaciclib</td>
<td>Tamoxifen/NSAI ± goserelin ± ribociclib</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>165</td>
<td>666</td>
<td>668</td>
<td>493</td>
<td>672</td>
</tr>
<tr>
<td><strong>Median PFS (months)</strong></td>
<td>20.2 versus 10.2</td>
<td>24.8 versus 14.5</td>
<td>25.3 versus 16</td>
<td>NR versus 14.7</td>
<td>23.8 versus 13</td>
</tr>
<tr>
<td><strong>HR, 95% CI</strong></td>
<td>0.49 [0.32-0.75]</td>
<td>0.58 [0.46-0.72]</td>
<td>0.56 [0.43-0.72]</td>
<td>0.54 [0.41-0.72]</td>
<td>0.55 [0.44-0.69]</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>55 versus 39</td>
<td>55 versus 44</td>
<td>53 versus 37</td>
<td>59 versus 44</td>
<td>51 versus 36%</td>
</tr>
<tr>
<td><strong>CBR (ITT), %</strong></td>
<td>81 versus 58</td>
<td>85 versus 70</td>
<td>80 versus 73</td>
<td>78 versus 71.5</td>
<td></td>
</tr>
</tbody>
</table>

* In patients with measurable disease at baseline.

CBR, clinical benefit rate; NR, not reached; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; PFS, progression-free survival.
PALOMA-2: Study Design (1008)¹

- Postmenopausal
- ER+, HER2− advanced breast cancer
- No prior treatment for advanced disease
- AI-resistant patients excluded

N=666¹

RANDOMIZATION

2:1

Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)

Placebo (3/1 schedule) + letrozole (2.5 mg QD)

Primary endpoint
Investigator-assessed PFS

Secondary endpoints
Response, OS, safety, biomarkers, patient-reported outcomes

Stratification factors
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic; ≤12 mo, >12 mo)
- Prior (neo)adjuvant hormonal therapy (yes, no)

- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided α=0.025
  Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos
- Blinded independent central review of efficacy endpoints performed as supportive analysis

¹Actual: AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

Presented By Richard Finn at 2016 ASCO Annual Meeting
PFS: Blinded Independent Central Review
Confirmed PFS Advantage Seen Using Investigator Assessment

Number of Events, n (%)

- PAL+LET (N=444): 152 (34)
- PCB+LET (N=222): 96 (43)

Median (95% CI) PFS

- PAL+LET: 30.5 (27.4–NR)
- PCB+LET: 19.3 (16.4–30.6)

HR (95% CI); 1-sided P value

- PAL+LET: 0.65 (0.51–0.84); P=0.0005

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>PAL+LET</th>
<th>PCB+LET</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 months</td>
<td>444</td>
<td>222</td>
</tr>
<tr>
<td>1-2 months</td>
<td>384</td>
<td>167</td>
</tr>
<tr>
<td>2-3 months</td>
<td>344</td>
<td>144</td>
</tr>
<tr>
<td>3-4 months</td>
<td>319</td>
<td>131</td>
</tr>
<tr>
<td>4-5 months</td>
<td>281</td>
<td>111</td>
</tr>
<tr>
<td>5-6 months</td>
<td>252</td>
<td>94</td>
</tr>
<tr>
<td>6-7 months</td>
<td>228</td>
<td>76</td>
</tr>
<tr>
<td>7-8 months</td>
<td>149</td>
<td>49</td>
</tr>
<tr>
<td>8-9 months</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>9-10 months</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>10-11 months</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>11-12 months</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Presented By Richard Finn at 2016 ASCO Annual Meeting
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer


Abstract

Probability of Progression-free Survival

Hazard ratio, 0.56 (95% CI, 0.43–0.72) 

P=3.29x10^-6 for superiority

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib</td>
<td>334</td>
<td>294</td>
<td>277</td>
<td>257</td>
<td>240</td>
<td>226</td>
<td>164</td>
<td>119</td>
<td>68</td>
<td>20</td>
</tr>
<tr>
<td>Placebo</td>
<td>334</td>
<td>279</td>
<td>264</td>
<td>237</td>
<td>217</td>
<td>192</td>
<td>143</td>
<td>88</td>
<td>44</td>
<td>23</td>
</tr>
</tbody>
</table>

Ribociclib group

Placebo group
Table 2. Major clinical trials of CDK4/6 inhibitors in patients with advanced ER-positive breast cancer who had previously progressed on endocrine therapy.

<table>
<thead>
<tr>
<th></th>
<th>PALOMA-3</th>
<th>MONARCH-2</th>
<th>MONALEESA-3*</th>
<th>MONARCH-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Phase III placebo control, second line</td>
<td>Phase III placebo control, second line</td>
<td>Phase III placebo control, second line</td>
<td>Phase II</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>Fulvestrant ± palbociclib</td>
<td>Fulvestrant ± abemaciclib</td>
<td>Fulvestrant ± ribociclib</td>
<td>Abemaciclib monotherapy</td>
</tr>
<tr>
<td>Patients, n</td>
<td>521</td>
<td>669</td>
<td>725</td>
<td>132</td>
</tr>
<tr>
<td>Patient population</td>
<td>≤1 prior CT for MBC; any line of previous ET in MBC</td>
<td>Previous CT for MBC not permitted; one line of previous ET in MBC</td>
<td>Progression on or after prior endocrine therapy; 1–2 lines prior CT for MBC</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>9.5 versus 4.6</td>
<td>16.4 versus 9.3</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.46 [0.36–0.59]</td>
<td>0.55 [0.45–0.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (measurable disease), %</td>
<td>25 versus 11</td>
<td>48 versus 21</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>CBR (ITT), %</td>
<td>67 versus 40</td>
<td>72 versus 56</td>
<td>42.4</td>
<td></td>
</tr>
</tbody>
</table>

* Not yet reported.

CBR, clinical benefit rate; CT, chemotherapy; ET, endocrine therapy; MBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival.
Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer

A. Overall Survival

- Placebo+fulvestrant
- Palbociclib+fulvestrant

Stratified hazard ratio for death, 0.81 (95% CI, 0.64–1.03)
P=0.09

Unstratified hazard ratio for death, 0.79 (95% CI, 0.63–1.00)
P=0.05

No. at Risk
- Palbociclib+fulvestrant: 347 321 286 247 209 165 148 126 17 —
- Placebo+fulvestrant: 174 155 135 115 86 68 57 43 7 —

B. Subgroup Analyses

Median Overall Survival (95% CI)
- Palbociclib+fulvestrant: 34.9 (28.8–40.0)
- Placebo+fulvestrant: 28.0 (23.6–34.6)

PALOMA 3
<table>
<thead>
<tr>
<th>Trial name/ ClinicalTrial.gov identifier</th>
<th>Estimated enrollment</th>
<th>Study treatment</th>
<th>Study population</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALLAS NCT02513394</td>
<td>4600</td>
<td>Standard adjuvant ET (at least 5 years) ± palbociclib (2 years)</td>
<td>Stage II (stage IIA limited to max. 1000 patients) or stage III patients</td>
<td>iDFS</td>
</tr>
<tr>
<td>PENEOLOPE-B NCT01864746</td>
<td>1250</td>
<td>Standard adjuvant ET ± palbociclib in a 28-day cycle for 13 cycles</td>
<td>Patients with residual disease and high risk of relapse (based on CPS-EG score) after neoadjuvant CT of at least 16 weeks</td>
<td>iDFS</td>
</tr>
<tr>
<td>EarLEE-1 NCT03078751</td>
<td>2000</td>
<td>Standard adjuvant ET (at least 5 years) ± ribociclib (2 years)</td>
<td>High-risk breast cancer (= stage III breast cancer [AJCC 8th edition] treated with adjuvant CT; OR residual disease (=1 positive nodes (&gt;2 mm) and residual tumor &gt;10 mm in breast) after neoadjuvant CT.</td>
<td>iDFS</td>
</tr>
<tr>
<td>monarchE NCT03155997</td>
<td>3580</td>
<td>Standard adjuvant ET ± abemaciclib</td>
<td>High-risk node-positive, breast cancer (=4 lymph nodes, tumor &gt;5 cm, grade 3 or central Ki67 ≥20%)</td>
<td>iDFS</td>
</tr>
</tbody>
</table>

*Already completed.
CPS-EG, clinical-pathologic stage – estrogen/grade; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease-free survival.
mTOR

Protein Synthesis

- Cyclin D1
- HIF-1α
- Glut 1
- LAT 1
- Glycolytic enzymes
- p21
- Survivin
- Other?

M

G1

G2

S

- VEGF
- PDGF
- bFGF
- Ang-1

Nutrient availability
Metabolism

DNA Repair
Apoptosis
Autophagy

Cell Growth & Proliferation
Angiogenesis
Bioenergetics
Survival
BOLERO-2: Exemestane ± Everolimus in Nonsteroidal AI–Refractory ABC

Postmenopausal women with HR-positive, HER2-negative advanced breast cancer refractory to letrozole or anastrozole (N = 724)

- Refractory to therapy:
  - Recurrence during or within 12 mos of end of adjuvant treatment
  - Progression during or within 1 mo after end of treatment for advanced disease

Everolimus 10 mg/day + Exemestane 25 mg/day (n = 485)

Placebo + Exemestane 25 mg/day (n = 239)

- Stratification:
  - Sensitivity to previous hormonal therapy
  - Presence of visceral disease
- No crossover allowed
- Primary endpoint: PFS
  - Secondary endpoints: OS, ORR, CBR, safety, QoL, bone markers

BOLERO-2: Central Review PFS at 18-Mo

HR = 0.38 (95% CI: 0.31-0.48)
Log-rank P value: < .0001
Kaplan-Meier medians
EVE 10 mg + EXE: 11.0 months
PBO + EXE: 4.1 months
A study of alpelisib and fulvestrant for breast cancer that has come back or continued to grow despite hormone therapy (SOLAR-1)

Everyone taking part is put into 1 of 2 groups at random

Fulvestrant and alpelisib

Fulvestrant and a dummy drug

In patients with PIK3CA mutated HR+/HER2-advanced breast cancer, BYL719 plus fulvestrant demonstrated a median progression-free survival (PFS) of 11 months (95% CI: 7.5-14.5 months) compared to 5.7 months (95% CI: 3.7-7.4 months) for fulvestrant alone.
Non Cytotoxic Pathways – Available in Breast Cancer Patients

- CDK 4/6 Inhibitors (..Ciclibs) PALOMA, MONALEESA, MONARCH
- PI3 K Pathway Inhibitors (Eg. Alpesalib, Talesilib) SOLAR1, SANDPIPER Trial
- mToR pathways (Evrolimus) BOLERO
- Immunotherapy (Permbro/Atezolizumab) KEYNOTE-028 / Impassion
- HDAC inhibitors (Chidamide - HDAC inhibitors are a type of epigenetic therapy, meaning they can switch genes on or off without changing the underlying DNA sequence. HDAC inhibitors have previously been shown to reverse resistance to hormone therapy)
Conclusion

• Majority of MBC in PMP women are hormone positive
• Endocrine therapy should be the standard of care for them, with aromatase inhibitors being the preferred first-line treatment option
• Combination of targeted agent for previously AI naïve women with Newer agents like CDK inhibitors improves Survival and is now Standard of care
• Combination with an mTOR inhibitor (evrolimus) with Examestine for those who have progressed on a previous AI improves Survival
• Understanding on potential side effects and their treatment is improving and emerging.
• Oncologists Should prepare themselves for overwhelming new knowledge on molecular Pathways
Thank you...