Optimization of Hormone Treatment: New Alternative Sequences

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Improving Response to Hormone Therapy: Unmet Medical Need

- ER$^+$/HER2$^-$ disease (luminal A and luminal B subtypes) is the most common subtype of breast cancer
- Continuous risk of recurrence over time
  - EBCTCG evaluated 46,000 women enrolled in 91 trials with 5 years of endocrine therapy
  - From year 5 to year 20 substantial risk of distant recurrence
  - Results: risk of distant recurrence year 5-20
    - Distant recurrence risk from 14 – 47% depending on stage, tumor grade and Ki67
- Ongoing challenge in metastatic disease to maintain disease control while maintaining or improving QOL

Pan et al, ASCO 2016
**Actionable** Mechanisms of Endocrine Resistance

- **Upregulation of alternative signal transduction pathways**
  - Antagonizing the PIK3/AKT/mTOR pathway
  - Blocking cyclin dependent kinases
  - (Blocking growth factor receptors)

- **Loss of receptors**
  - ERα ‘loss’
    - Mechanisms of reduced expression
    - HDAC inhibitors to increase sensitivity to hormone therapy

- **Acquired resistance**
  - ESR1 mutations
PI3K/AKT/mTOR: The Most Altered Pathway in Breast Cancer

Alterations in up to ~48% of ER+ BC

- mTORC1 activates ER in a ligand-independent fashion.
- Estradiol suppresses apoptosis induced by PI3K/mTOR blockade.
- Hyperactivation of the PI3K/mTOR pathway promotes escape from hormone dependence.
  - Associated with lower ER and activity.
BOLERO-2: Improved PFS with mTOR Inhibition

**Local Assessment**

HR = 0.45 (95% CI, 0.38-0.54)
Log-rank \( P < 0.0001 \)

Kaplan-Meier medians
- EVE+EXE: 7.8 mo
- PBO+EXE: 3.2 mo

**Central Assessment**

HR = 0.38 (95% CI, 0.31-0.48)
Log-rank \( P < 0.0001 \)

Kaplan-Meier medians
- EVE+EXE: 11.0 mo
- PBO+EXE: 4.1 mo

**Similar Results**

- In combination with tamoxifen (Bachelot et al, JCO 2012)
- In combination with fulvestrant (PrECOG 0102, Kornblum et al, SABCS 2016)

CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.
Yardley et al, Adv Ther 2013; Baselga et al, NEJM 2012
PrECOG 0102: Fulvestrant plus Everolimus
Prolongs PFS Compared to Fulvestrant

- Fulvestrant/everolimus (45 events/66 pts), Median PFS **10.4 mos**
- Fulvestrant/placebo (56 events/65 pts), Median PFS **5.1 mos**
- Hazard Ratio 0.60, 95% CI 0.40 - 0.92
- Stratified Log rank p = 0.02

Kornblum et al, SABCS 2016
BOLERO-2: Rapid Onset of Grade ≥ 2 Stomatitis

The incidence of grade ≥2 stomatitis by 8 weeks for SWISH was 2.4% (n = 2, 95% CI 0.29-8.24, P < 0.001) compared with 33% over the total study duration, and 27.4% by 8 weeks in BOLERO-2 (primary endpoint).

*Stomatitis assessed in SWISH in the full analysis set (N = 86) using CTCAE v4.0 + NDS and/or VAS score. BOLERO-2 stomatitis grading based on CTCAE v3.0.

Rugo et al, Lancet Oncology 2017
Benefit from Everolimus Regardless of Mutation Status

- 209/485 (43%) on the everolimus arm and 93/239 (39%) on placebo
- No difference in PFS in the NGS subgroup
- Most frequently altered genes were:
  - PIK3CA (47.6%), CCND1 (31.3%), TP53 (23.3%), and FGFR1 (18.1%)
- Greater benefit from everolimus in those with a lower chromosomal instability score
  - Lower CIN: larger PFS benefit (effect seen only in the everolimus arm)
  - CIN score <75th% had a 5.5 month gain in PFS (8.4 v 2.9 mos)
  - CIN > 75% had a median PFS gain of 1.5 mo. months in (5.6 v 4.1 mos)

Two ongoing adjuvant trials

Hortobagyi et al, J Clin Oncol 2016
PI3K / TORC / AKT Inhibitors in Clinical Development 2017

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

BELLE-3

Baselga J et al, SABCS 2015 Oral Abstract S6-01

Alpelisib
Taselisib
Buparlisib
Pictilisib
Gedatolisib

FERGI


Vistusertib
AZD5363

PI3K / TORC / AKT Inhibitors in Clinical Development 2017

RTKs
PI3K
RAPTOR
p85
p110
RAS

PTEN
PIP3

TORC2
AKT
PDK1
LKB1

TORC1
S6K
4EBP1
eIF4E F-G

S6

Probability of Progression-Free Survival, %

Time (months)

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

0 20 40 60 80 100
BELLE-2: Fulvestrant +/- Buparlisib based on ctDNA PI3K status

- PFS in entire population: **1.9 month benefit**
- PFS in PI3K activated: No different (4 vs 6.8 mo)
- Evaluation of PIK3CA mutation in ctDNA: 587 pts analyzed (51%), 34% with PIK3CA mutations
- **Toxicity significant**
  - 6.8% grade 4 ALT, 3% grade 4 AST (grade 3/4 >20%)
  - Grade 3/4 hyperglycemia (15.4%), rash (8%), depression/anxiety (10%)
- Future development of pan PI3K inhibitors not feasible but biomarker data intriguing
Belle 3 (after mTOR): PFS by \(PIK3CA\) Status

**Primary tumor tissue (PCR)** N=321

- \(PIK3CA\) mutant: 34%

**ctDNA samples at study entry (BEAMing)** N=348

- \(PIK3CA\) mutant: 39%

DiLeo et al, SABCS 2016

**Median PFS, months (95% CI)**

- **Tissue (mutant)**
  - Buparlisib + Fulvestrant: 4.7 (2.9–6.7)
  - Placebo + Fulvestrant: 1.4 (1.4–2.2)
  - HR (95% CI): 0.39 (0.23–0.65); \(p<0.001\)

- **Tissue (WT)**
  - Buparlisib + Fulvestrant: 2.8 (2.0–3.7)
  - Placebo + Fulvestrant: 2.7 (1.4–2.9)
  - HR (95% CI): 0.83 (0.60–1.14); \(p=0.117\)

- **ctDNA (mutant)**
  - Buparlisib + Fulvestrant: 4.2 (2.8–6.7)
  - Placebo + Fulvestrant: 1.6 (1.4–2.8)
  - HR (95% CI): 0.46 (0.29–0.73); \(p<0.001\)

- **ctDNA (WT)**
  - Buparlisib + Fulvestrant: 3.9 (2.8–4.3)
  - Placebo + Fulvestrant: 2.7 (1.5–3.6)
  - HR (95% CI): 0.73 (0.53–1.00); \(p=0.026\)

PCR, polymerase chain reaction; WT, wild-type. \(p\)-values are one-sided.
Next Steps: PI3K Inhibition Enhances ER Activity

- Toxicity from pan-PI3K inhibitors have limited efficacy and development
- SERDS enhance anti-tumor activity of PI3Ki
- Significant clinical activity/modest toxicity with alpha-specific inhibitors
- Phase III trials ongoing with fulvestrant
  - Sandpiper (taselisib)
  - Solar 1 (alpelisib)
- Biomarker analysis critical

Bosch et al, Science Translational Medicine 2015
Cyclin Dependent Kinases 4/6 in Breast Cancer

- Resistance to endocrine therapy presents a major clinical challenge
- The growth of HR+ BC is dependent on Cyclin D1
  - Direct transcriptional target of ER
- Cyclin D1 activates CDK 4/6
  - Results in G1–S phase transition and cell cycle entry
- Cell line models of endocrine resistance are dependent on cyclin D1 and CDK4/6

Figure adapted from Asghar U, et al. Nat Rev Drug Discov. 2015;14:130–146.
Sensitivity to CDK4/6 inhibition: Luminal and HER2+ Breast Cancer

EMT, epithelial mesenchymal transition

## CDK 4/6 Inhibitors in Clinical Development

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Pharmaceutical company</th>
<th>Status</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib (Ibrance)</td>
<td>Pfizer</td>
<td>FDA approved. 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; line therapy for ER+, HER2- metastatic breast cancer. Phase III adjuvant trial enrolling.</td>
<td>2015</td>
</tr>
<tr>
<td>Ribociclib (Kisqali)</td>
<td>Novartis</td>
<td>FDA approved. 1&lt;sup&gt;st&lt;/sup&gt; line therapy for ER+, HER2- metastatic breast cancer. Additional phase III trials pending.</td>
<td>2017</td>
</tr>
<tr>
<td>Abemaciclib (LY2853219)</td>
<td>Lilly</td>
<td>FDA breakthrough designation. Single agent activity, 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; line phase III data reported in press release. Additional phase III trials pending.</td>
<td>(2017)</td>
</tr>
</tbody>
</table>
### PALOMA 1: PFS AND OS (ITT)

#### Progression Free Survival (PFS)

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>41 (49)</td>
<td>59 (73)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.7, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.488 (0.319, 0.748)</td>
<td>0.511 (0.325, 0.776)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

#### Overall Survival (OS)

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>30 (36)</td>
<td>31 (38)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>37.5 (28.4, NR)</td>
<td>33.3 (26.4, NR)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.813 (0.492, 1.345)</td>
<td>0.871 (0.465, 1.658)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.2105</td>
<td>0.2105</td>
</tr>
</tbody>
</table>

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Finn et al, Lancet Oncol 2015
There was no clear association between the frequency of grade 3–4 neutropenia and all grade infections.

First line AI sensitive: Primary Endpoint PFS

**PALOMA2 (2:1)**

- Number of patients at risk:
  - PCB + LET: 22
  - PAL + LET: 44

- Number of Events:
  - PAL + LET: 194 (44)
  - PCB + LET: 137 (62)

- Progression-Free Survival, %
  - Median (95% CI):
    - PCB + LET: 24.8 (22.1 - NR)
    - PAL + LET: 14.5 (12.9 - 17.1)

- HR (95% CI): 0.58 (0.46 - 0.72), P < 0.000001

**MONALEESA2 (1:1)**

- Number of patients at risk:
  - PCB + LET: 222
  - PAL + LET: 444

- Number of Events:
  - PCB + LET: 69 (32)
  - PAL + LET: 98 (36)

- Progression-Free Survival, %
  - Median (95% CI):
    - PCB + LET: 14.5 (12.9 - 17.1)
    - PAL + LET: 24.8 (22.1 - NR)

- HR (95% CI): 0.592 (0.412 - 0.852; p=0.002)

3/17: Updated PFS 16 vs 25.3 mo.

Finn *et al* NEJM 2016

Hortobagyi *et al* NEJM 2016

Overall survival not yet reached in either trial

MONALEESA reported early based on independent review: hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)
PFS Subgroups

PALOMA-2

MONALEESA-2

Finn et al, NEJM 2016; Hortobagyi et al, NEJM 2016
CDK 4/6 Inhibitors: Toxicity of Palbociclib and Ribociclib is Similar

**PALOMA-2**

**MONALEESA-2**

Finn et al, NEJM 2016; Hortobagyi et al, NEJM 2016
Toxicity Differences: QTc Interval

- Palboclib: no apparent impact, avoid strong CYP3A inhibitors (Ruiz et al, SABCS 2016)

- Ribociclib: prolongs QT interval in dose dependent manner
  - In the first 4 weeks of treatment in MONALEESA-2:
    - One pt with >500 msec increase in QTcF, 9 pts >60 msec increase in QTcF; all reversible with dose interruption
    - 9 pts had syncope (2.7%) on ribociclib vs 3 pts (0.9%) on placebo
    - One pt receiving ribociclib had sudden death (0.3%) with grade 3 hypokalemia and grade 2 QT prolongation
  - Recommended monitoring:
    - ECG before treatment, start only if QTcF < 450 msec, repeat at d14 and start of cycle 2, monitor electrolytes, replace as needed
    - Avoid ribociclib in pts at risk for QTc prolongation, and concomitant CYP3A inhibitors
Paloma 2 Biomarker Analysis for PFS: no Difference Among Biologic Subsets

Qualitative Analysis

<table>
<thead>
<tr>
<th>n</th>
<th>HR (95% CI)</th>
<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>
<td>All patients</td>
<td>666</td>
</tr>
<tr>
<td>ER+</td>
<td>504</td>
<td>0.57 (0.44–0.74)</td>
<td>ER &gt;25th to &lt;75th</td>
<td>142</td>
</tr>
<tr>
<td>ER−</td>
<td>62</td>
<td>0.41 (0.22–0.75)</td>
<td>≥75th</td>
<td>142</td>
</tr>
<tr>
<td>Rb+</td>
<td>512</td>
<td>0.53 (0.42–0.68)</td>
<td>Rb ≤25th</td>
<td>154</td>
</tr>
<tr>
<td>Rb−</td>
<td>51</td>
<td>0.68 (0.31–1.48)</td>
<td>&gt;25th to &lt;75th</td>
<td>249</td>
</tr>
<tr>
<td>Cyclin D1+</td>
<td>549</td>
<td>0.56 (0.44–0.71)</td>
<td>≥75th</td>
<td>160</td>
</tr>
<tr>
<td>Cyclin D1−</td>
<td>15</td>
<td>1.0 (0.29–3.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p16+</td>
<td>466</td>
<td>0.52 (0.40–0.67)</td>
<td>Cyclin D1 ≤25th</td>
<td>141</td>
</tr>
<tr>
<td>p16−</td>
<td>84</td>
<td>0.73 (0.39–1.36)</td>
<td>&gt;25th to &lt;75th</td>
<td>247</td>
</tr>
<tr>
<td>Ki-67 ≤20%</td>
<td>318</td>
<td>0.53 (0.38–0.74)</td>
<td>≥75th</td>
<td>176</td>
</tr>
<tr>
<td>Ki-67 &gt;20%</td>
<td>235</td>
<td>0.57 (0.41–0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p16 status</td>
<td>140</td>
<td>0.74 (0.46–1.20)</td>
<td>≥75th</td>
<td>152</td>
</tr>
</tbody>
</table>

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

Finn et al, ESMO 2016
FALCON Trial in Patients with Endocrine Naïve Advanced Breast Cancer: PFS based on Presence of Visceral Disease

- NO hormone therapy in any setting, prior chemotherapy allowed
- Forest plot for subset analysis:
  - No difference among predefined subsets EXCEPT visceral disease
    - HR 0.992 (visceral disease) vs 0.592 (non-visceral disease)
  - No difference in OS to date

Ellis et al, ESMO 2016; Robertson et al, Lancet 2016
# Recent Phase III First-Line Studies in HR+ MBC

<table>
<thead>
<tr>
<th>Study design</th>
<th>Paloma-2</th>
<th>Monaleesa-2</th>
<th>Falcon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Letrozole/Pla vs Letrozole/Palbociclib</td>
<td>Letrozole/Pla vs Letrozole/Ribociclib</td>
<td>Anastrozole/Pla vs Fulvestrant/Pla</td>
</tr>
<tr>
<td>No. of pts</td>
<td>666 No progression on AIs</td>
<td>668 No progression on AIs</td>
<td>462 No prior hormone therapy</td>
</tr>
<tr>
<td>PFS</td>
<td>14.5 vs 24.8 mo HR 0.58 (0.46-0.72) p&lt;0.000001</td>
<td>14.7 vs NR mo HR 0.556 (0.43-0.72) p=0.00000329</td>
<td>13.8 vs 22.3 mo in n= 218 (47%) without visceral disease</td>
</tr>
<tr>
<td>All oral</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Subset difference</td>
<td>No</td>
<td>No</td>
<td>13.8 v 22.3 mo in n= 218 (47%) without visceral disease</td>
</tr>
</tbody>
</table>

4.24.17 Lilly Press-release: A pre-planned interim analysis for Monarch 3 met its primary endpoint demonstrating a significant PFS advantage with abemaciclib/AI vs placebo/AI; ORR was also increased (n=493).
PALOMA-3: Study Design

Phase III, double-blind study involving 144 centers in 17 countries (NCT01942135)

- HR+, HER2– MBC
- Pre/perimenopausal\(^a,b\) or postmenopausal\(^b\)
- Progressed on prior endocrine therapy:
  - on or within 12 months of completion of adjuvant treatment
  - on or within 1 month after treatment for MBC
- ≤1 prior chemotherapy regimen for advanced cancer

2:1 Randomization

N=521\(^c\)

Stratification:
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs. postmenopausal

Palbociclib
(125 mg QD; 3 weeks on/1 week off)
+ fulvestrant\(^d\)
(500 mg IM Q4W)

Placebo
(3 weeks on/1 week off)
+ fulvestrant\(^d\)
(500 mg IM Q4W)

\(^a\)All received goserelin; \(^b\)Must have progressed on adjuvant tamoxifen or other prior endocrine therapy (pre-/perimenopausal) or AI therapy (postmenopausal);
\(^c\)Patients randomised; \(^d\)Administered d1 and 15 of Cycle 1, then q 28 d

Data cutoff March 16 2015 used for final analysis; median follow-up 8.9 months

PALOMA-3: Addition of Palbociclib to Fulvestrant in Endocrine Pre-treated

No difference in PFS based on neutropenia (≥Gr 3 vs not)

**Updated PFS at SABCS 2016:**
11.2 vs 4.6mo

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos (95% Cl)</th>
<th>HR (95% CI); P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAL+FUL</td>
<td>9.2 (7.5–NE)</td>
<td>0.422 (0.318–0.560)</td>
</tr>
<tr>
<td>PCB+FUL</td>
<td>3.8 (3.5–5.5)</td>
<td>P&lt;0.0000001</td>
</tr>
</tbody>
</table>

Similar toxicity to first-line studies

Effective across all subsets

Turner *et al*. NEJM 2015 and SABCS 2016
Verma *et al*, The Oncologistst 2016
## PALOMA-3: Interim Analysis of PFS by Patient Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>HR and 95% CI</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized patients (ITT)</td>
<td>521 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>392 (75.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>129 (24.8)</td>
<td></td>
<td>0.480</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>385 (73.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>105 (20.2)</td>
<td></td>
<td>0.412</td>
</tr>
<tr>
<td>Black and other</td>
<td>29 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Menopausal status at study entry</strong></td>
<td></td>
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<tr>
<td>Pre/peri</td>
<td>108 (20.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>413 (79.3)</td>
<td></td>
<td>0.940</td>
</tr>
<tr>
<td><strong>Site of metastatic disease</strong></td>
<td></td>
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</tr>
<tr>
<td>Visceral</td>
<td>311 (59.7)</td>
<td></td>
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</tr>
<tr>
<td>Non-visceral</td>
<td>210 (40.3)</td>
<td></td>
<td>0.624</td>
</tr>
<tr>
<td><strong>Sensitivity to prior hormonal therapy</strong></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>410 (78.7)</td>
<td></td>
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<tr>
<td>No</td>
<td>111 (21.3)</td>
<td></td>
<td>0.302</td>
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<tr>
<td><strong>Receptor status</strong></td>
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<tr>
<td>ER+ / PR+</td>
<td>349 (67.0)</td>
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<tr>
<td>ER+/PR−</td>
<td>139 (26.7)</td>
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<td>0.883</td>
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<tr>
<td><strong>Disease-free interval</strong></td>
<td></td>
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<tr>
<td>≤24 months</td>
<td>65 (1.5)</td>
<td></td>
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<tr>
<td>&gt;24 months</td>
<td>281 (53.9)</td>
<td></td>
<td>0.149</td>
</tr>
<tr>
<td><strong>Prior chemotherapy</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(Neo)adjuvant only</td>
<td>219 (42.0)</td>
<td></td>
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</tr>
<tr>
<td>Metastatic (neo)adjuvant</td>
<td>170 (32.6)</td>
<td></td>
<td>0.427</td>
</tr>
<tr>
<td>No prior chemotherapy</td>
<td>132 (25.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior lines of therapy in advanced setting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>129 (24.8)</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>202 (38.8)</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>133 (25.5)</td>
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<tr>
<td>≥3</td>
<td>57 (10.9)</td>
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</tr>
</tbody>
</table>

$^a$Race was unspecified in 2 patients (1 in each group)

Data cutoff December 5 2014 used for interim analysis; median follow-up 5.6 months

Data cutoff March 16 2015 used for final analysis; median follow-up 8.9 months

HR, hazard ratio; PR, progesterone receptor


Turner NC, et al. ASCO 2015 (Abstract LBA502)
Acquired Resistance to AIs: *ESR1* Mutations in Paloma-3

- *ESR1* mutations strongly associated with acquired resistance to prior AIs
  - Prior response then progression rather than de novo resistance
- Mutations detected in 27%
- Fulvestrant/palbociclib superior to fulvestrant regardless of *ESR1* or PIK3CA mutation status

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*Turner et al, Lancet 2016; Cristofanilli, Lancet Oncol 2016*
Response to Treatment
Post Progression in Paloma 3

- The most common sites of PD were liver (72/75%) and bone (28/33%) in Palbo/Pla
- Data suggests that the treatment effect of palbociclib may be retained through the next line of Rx postPD
  - Progression after palbo has no apparent effect on the therapeutic benefit derived from subsequent treatments

Turner et al. SABCS 2016
## Comparison of Trials in Patients with Progression on Prior NSAI

<table>
<thead>
<tr>
<th>Study design</th>
<th>PALOMA 3</th>
<th>BOLERO 2</th>
<th>PreCOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant/pla vs fulvestrant/palbociclib</td>
<td></td>
<td>Exemestane/pla vs exemestane/EVE</td>
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</tr>
<tr>
<td>Patient #</td>
<td>521</td>
<td>724</td>
<td>131</td>
</tr>
<tr>
<td>PFS (mo) p value (HR)</td>
<td>4.6 vs 11.2 (updated) p&lt;.0001, (HR 0.5)</td>
<td>3.2 vs 7.8 (inv) 4.1 vs 11 (central) p&lt;.0001 (HR .38)</td>
<td>5.1 vs 10.4 p=.02 (HR .6)</td>
</tr>
</tbody>
</table>

Monarch 2 (similar design to Paloma 3 in 669 patients:
- Press release 3.20.17: ‘The addition of abemaciclib to fulvestrant resulted in a statistically significant improvement in PFS, when compared to the control arm of placebo plus fulvestrant. Detailed efficacy and safety results will be presented at an upcoming medical meeting.'
Specific Subgroup Analyses

• Palbociclib (pooled analysis of Paloma 1, 2 and 3)
  – Improved PFS across age groups
    • Myelosuppression more common in >75 yrs
    • No increase in grade ≥3 or febrile neutropenia
  – Long-term safety (527 palbociclib vs 345 placebo)
    • Median duration of Rx from 330 to 421 days (up to 1615 days)
    • No evidence of specific cumulative or delayed toxicity from prolonged treatment

• Ribociclib (Monaleesa-2)
  – De Novo metastatic disease (n=227)
    • 12 month PFS 81.6% with ribo vs 65.7% with placebo

Rugo et al, Dieras et al, O’Shaughnessy et al, SABCS 2016
Abemaciclib

- Potent inhibitor of CDK4 > CDK6 (14x)
- Phase I: ORR 31% in HR+ MBC (Patnaik et al, Cancer Discov 2016)
- Monarch 1: Phase II single agent trial in pretreated patients with HR+ MBC (1-2 prior chemo regimens)
  - N=132; 200 mg BID
  - 90% with visceral metastases; 51% with ≥ 3 sites
- Efficacy
  - **Confirmed ORR: 19.7% (all PR); CBR: 42.4%**
  - Median PFS 6 months (95% CI 4.2, 7.5)
  - Median time to response: 3.7 mo.
  - Median OS: 22.3 months (17, 7, NR)
- Toxicity
  - Grade 3 diarrhea: 19.7%; grade 2: 28.8%

Dickler et al, ASCO 2016; Rugo et al, AACR 2017
Abemaciclib (2)

- NeoMonarch
  - Neoadjuvant biomarker trial
    - 223 pts
    - Anastrozole, abemaciclib + anastrozole, or abemaciclib alone
  - Ki67 at 2 wks and 16 wks
  - ORR 55% (imaging); pCR in 3/95
  - Appears to induce an immune infiltrate
- Unique features of abemaciclib
  - Greater CDK4 inhibition
  - Continuous dosing
  - Diarrhea as primary toxicity
  - Single agent efficacy
  - Crosses the blood brain barrier

Hurvitz et al, SABCS 2016; Sahebjam et al, ASCO 2016
Tumor Differentiation & Immune Infiltrates Over Time

- Similar cell cycle suppression seen in smaller neoadjuvant trial with palbociclib (n=43) and a window of opportunity trial with ribociclib (n=14)
- Ma et al: Addition of palbociclib to AI converts most non-responders to CCCS

Ongoing/Planned Neoadjuvant Studies

- **PREDIX LumB** (NCT02603679) Neoadjuvant response-guided treatment of luminal A/B LN+ tumors (Karolinska, goal N=200)
  - Paclitaxel 12 weeks → palbo/endocrine 12 weeks or reverse order

- **PREDIX LumA** (NCT02592083) Slowly proliferating (Ki67<20%) HR+ (>50%) tumors (Karolinska, goal N=200)
  - Endocrine tx x 4 weeks: if Ki67 decreases then randomize to AI vs AI/palbo x 12 wks; If no Ki67 decrease, receive 12 weeks AI/palbo

- **PALLE** (NCT02296801) (NSABP/Royal Marsden/ICR-UK, goal N=306)
  - Letrozole (L) vs. L→L+P vs. P→L+P vs L+P x 14 weeks

- **FELINE** (NCT02712723) Letrozole plus ribociclib (continuous or 3 wk on/1 week off) or placebo (University of Kansas, goal N=120)
  - 24 wks therapy, endpoint: proportion of patients with pre-operative Endocrine Prognostic Index (PEPI) score of 0 at surgery
Overcoming Resistance to CDKi

• Combinations with PI3K inhibitors and endocrine therapy
  – Reduces cycle D1, blocks adaptation
  – Could prevent resistance to CDK 4/6i, but could not resensitize acquired resistance

• Clinical application: ongoing trials
  – Ribociclib/everolimus/exemestane (Triniti trial)
  – Ribociclib/alpelisib/letrozole
  – Gedatolisib/palbociclib/fulvestrant or letrozole

Herrera-Abreu et al, Cancer Res 2016
More data to come for CDK4/6 inhibitors in HR+/HER2- BC

**Palbociclib**
- PALOMA trials further analysis
  - NCT00721409
  - NCT01740427
  - NCT01942135
- PEARL
  - NCT02028507
  - Exemestane/palbo vs cape
- PALLAS
  - NCT02513394
  - Early BC
  - Two years of palboc vs none
- PENEOLE-B
  - NCT01864746
  - Post-Neoadjuvant
  - One year of palbo vs placebo

**Ribociclib**
- MONALEESA-2 further analysis
  - NCT01958021
- MONALEESA-7
  - NCT02278120
- MONALEESA-3
  - NCT02422615
- 2 adjuvant trials planned to open in 2017

**Abemaciclib**
- MONARCH-2
  - NCT02107703
- MONARCH-3
  - NCT02246621
- Brain Metastases in HR+ Disease
- Adjuvant trial planned

**HER2 positive disease**: T-DM1 plus palbociclib, abemaciclib + trastuzumab, palbociclib after THP in HR+, neoadjuvant pilot studies
More Targets!

Histone Deacetylase (HDAC) Inhibitors

- HDAC may silence ER post-translation
  - Inhibition of HDAC could restore sensitivity to hormone therapy

- Phase II ENCORE trial demonstrated 2 month difference in PFS but 9 month difference in OS with exemestane plus entinostat versus exemestane alone.

- E2112: ongoing 600 patient phase III trial with same design in BOLERO 2 population
Optimal Sequencing of Endocrine Therapy in ER+ MBC

1st line approach

A. Conventional endocrine mono-therapy
   - AI alone: 8–14 months

B. Optimally selected endocrine mono-therapy
   - Fulvestrant 500: 22 months
   - (ie. endo Rx naïve, non-visceral mets, biomarker)

C. Combination Endocrine Strategy
   - AI + CDK4/6 i: 24 months

2nd line approach

- AI/fulvestrant + everolimus: 7.8-11 months
- Fulvestrant + CDK4/6i: 11.2 months
- AI alone: 8–14 months
- AI + everolimus: 7–9 months?
- Fulvestrant 500: 5-6.5 months? PI3K inhibitors?
- AI + everolimus: 7–11 months?

Impact on Overall Survival: an elusive endpoint

Delay Start of Chemotherapy

2nd line post Fulvestrant: responsive to 2nd line combinations?

2nd Line post CDK 4/6 inhibitors: still endocrine responsive and to what therapy?

Cumulative Median Progression-Free Survival (PFS) in months

Adapted from Johnston, SABCS 2016
Summary and Next Steps

• Tremendous progress in new potential agents to improve response to hormone therapy
  – Two approved CDK 4/6 inhibitors with efficacy results for all three.
  – Most promising new agents: CDK 4/6 inhibitors, PI3K inhibitors, HDAC inhibitors, immune checkpoint blockade?
  – Trials in early stage disease underway
  – Desperate need for biomarkers to identify the patients and tumors most likely to benefit, and those who will do well with hormone therapy alone

**These studies represent a new paradigm in the treatment of metastatic ER+ breast cancer**

Rugo, Burstein et al ASCO Guidelines, JCO 2016
Thank you!