PI3K/AKT/mTOR Inhibitors in Breast Cancer

Dr Yoon-Sim YAP
Division of Medical Oncology,
National Cancer Centre Singapore
Global Breast Cancer Conference 2015
Outline

• Overview of PI3K/Akt/mTOR Pathway

• Rationale and Preclinical Data

• Clinical Trials and Predictive Biomarkers
  – Hormone receptor +, HER2 –
  – HER2 +
  – Triple Negative

• Toxicities

• Overcoming Resistance; Novel Combinations
PI3K/AKT/mTOR Pathway

Rodon et al, Nature Reviews Clin Onc 2013
In ER+ breast cancer

Activating mutations in the catalytic domain of PI3K (PIK3CA) have been identified in 30-40% of ER+ breast cancers

15-35% of breast cancer demonstrate reduced expression of PTEN, which has been associated with poor response to tamoxifen

Other factors (loss of LKB1) can activate mTOR independent of the upstream growth factor / PI3K / Akt axis

Akt and mTOR (via S6K) can phosphorylate ER independent of E2 ligand

Johnston, ASCO 2013
Role of PI3K/AKT/mTOR pathway in Endocrine Resistance

- Long term estrogen deprivation (LTED) & acquired endocrine resistance:
  - Studies have demonstrated persistence of an active ER pathway ¹
  - LTED can ↑ ERα levels & ↑ activation of the PI3K/mTOR pathway ²
  - Hyper-activation of the PI3K/mTOR pathway is a key mediator ³


Role of PI3k/AKT/mTOR in HER2+ Breast Cancer

~30% of HER2+ breast cancers have PI3K mutations

mTOR inhibition blocks downstream tumorigenic effects of aberrantly activated PI3K/AKT/mTOR pathway
Synergy of Rapamycin with Trastuzumab to induce complete tumour regression

Miller et al, CCR 2009
PI3K Inhibitor GDC-0941: Efficacy in Treating Trastuzumab-Resistant and Trastuzumab-Sensitive Tumors In Vivo

Junttila et al, Cancer 2009
Integrated analysis of the PI3K pathway (TCGA, Nature 2012) shows overexpression of pAkt, pS6, p4EBP1 on RPPA, and correlation with INPP4B and PTEN loss in basal-like subtypes. PI3K pathway protein and mRNA signatures were enriched in basal subtypes.
Rapamycin synergizes cisplatin sensitivity in triple negative breast cancer cells

A

![Graph showing the synergistic effect of Rapamycin (Rapa) and Cisplatin (Cis) on apoptosis in MDA-MB-231, MDA-MB-468, and T47D cells.](image)

B

![Western blot images showing protein levels of p73, mTOR, pS6K, and S6K in untreated, Cis, Rapa, and Cis + Rapa conditions.](image)

Wong, BCRT 2011
Clinical Trials

Oncology for All

Queenie?
You're next!

Finally!

I thought it was my turn!

Axman

Sit. Stay.
Clinical Trials

• Focus on Randomised Studies

• mTOR Inhibitors
  – Hormone receptor + (HORIZON, BOLERO-2, TAMRAD)
  – HER2 + (BOLERO-3, BOLERO-1)
  – Triple Negative

• PI3K Inhibitors

• AKT Inhibitors
Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy (HORIZON)

**A**
- Progression-Free Survival (probability)
- Stratified log-rank test: $P = .25$
- HR, 0.90; 95% CI, 0.76 to 1.07
- LET + TEMSR
- LET + placebo

**B**
- Overall Survival (probability)
- Stratified log-rank test: $P = .50$
- HR, 0.90; 95% CI, 0.66 to 1.23
- LET + TEMSR
- LET + placebo

Why?
- Drug factor?
- Dosing?
- Setting?
- Patient Selection?

Wolff et al, JCO 2012
BOLERO-2 (Ph III): Everolimus in advanced BC

N = 724
• Postmenopausal HR+ HER2-
• Unresectable locally advanced or metastatic BC
• Recurrence or progression after letrozole or anastrozole

Endpoints

- **Primary**: PFS (local and central assessment)
- **Secondary**: OS, ORR, QOL, safety, bone markers, PK

Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases
BOLERO-2: PFS Results

A Local Assessment

Hazard ratio, 0.43 (95% CI, 0.35–0.54) P<0.001 by log-rank test

Everolimus plus exemestane (median PFS, 6.9 mo)

Placebo plus exemestane (median PFS, 2.8 mo)

B Central Assessment

Hazard ratio, 0.36 (95% CI, 0.27–0.47) P<0.001 by log-rank test

Everolimus plus exemestane (median PFS, 10.6 mo)

Placebo plus exemestane (median PFS, 4.1 mo)

No. at Risk

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No. at Risk

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Baselga et al, NEJM 2011
BOLERO-2: Overall Survival Results

Why?
Not statistically powered to detect 4-6mth OS benefit?
Higher rate of discontinuation of EVE due to AE: 29% vs 5%
Imbalance in poststudy salvage chemo use?
Paradoxical activation of AKT via negative feedback loop?
Need predictive biomarkers?

HR = 0.89 (95% CI = 0.73–1.10)
Log-rank $P = 0.1426$

Piccart et al, Ann Onc 2014
Impact on Treatment by Genetic Status
The Most Frequently Altered Single Genes and Pathways

Positive treatment effect in favor of everolimus across the various genetic marker subgroups

Pathway composition

- **PI3K**: PIK3CA, PTEN, AKT (PIK3CA Alt: 47.6%, total alteration: 55.5%)
- **Cell Cycle**: CCND1, CDK4, CDK6, CDKN2A, CDKN2B, (CCND1 Alt: 31.3%, total alteration: 35.7%)
- **p53**: TP53, MDM2, MDM4 (TP53 Alt: 23.3%, total alteration: 36.1%)
- **FGFR1/2**: FGFR1, FGFR2 (FGFR1 Alt: 18.1%, total alteration: 21.1%)
Patients With No or Single Genetic Alteration in PIK3CA/PTEN/CCND1 or FGFR1/2 Derive Greater PFS Benefit With EVE (BOLERO-2)

<table>
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<tr>
<th>Subgroup</th>
<th>N</th>
<th>Events (%)</th>
<th>Median PFS (d)</th>
<th>HR* (95%CI)</th>
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<td>EVE: WT</td>
<td>43</td>
<td>19 (44%)</td>
<td>356</td>
<td>0.24 (0.11 - 0.54)</td>
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<td>PBO: WT</td>
<td>18</td>
<td>14 (78%)</td>
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<td>EVE: Single</td>
<td>76</td>
<td>48 (63%)</td>
<td>214</td>
<td>0.26 (0.16 - 0.43)</td>
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<tr>
<td>PBO: Single</td>
<td>35</td>
<td>31 (89%)</td>
<td>77</td>
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<tr>
<td>EVE: multiple</td>
<td>38</td>
<td>27 (71%)</td>
<td>138</td>
<td>0.78 (0.39 - 1.54)</td>
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<tr>
<td>PBO: multiple</td>
<td>17</td>
<td>14 (82%)</td>
<td>128</td>
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</table>

*HR adjusted with imbalanced covariates

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<th>Subgroup</th>
<th>Definition</th>
<th>Size, %</th>
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<tr>
<td>WT</td>
<td>No alteration in PIK3CA AND PTEN AND FGFR1/2 AND CCND1</td>
<td>Minimal</td>
</tr>
<tr>
<td>Single</td>
<td>Single alteration only in PIK3CA OR PTEN OR FGFR1/2 OR CCND1</td>
<td>Minimal</td>
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<tr>
<td>Multiple</td>
<td>Two or more alterations in PIK3CA OR PTEN OR FGFR1/2 OR CCND1 genes</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EVE, everolimus; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; WT, wild type.

Hortobagyi et al, ASCO 2013
TAMRAD: Phase II in patients with metastatic breast cancer and prior exposure to AI

**Metastatic Breast Cancer (N = 111)**
- Hormone resistant
- Postmenopausal
- HR+, HER2–
- Previous AI therapy
- Previous adjuvant TAM or chemotherapy allowed

**TAM (20 mg/d)**
- (n = 57)

**TAM (20 mg/d) + EVE (10 mg/d)**
- (n = 54)

- **Stratification: Primary or secondary hormone resistance:**
  - **Primary:**
    Relapsing during or within 6 months of stopping adjuvant AI treatment or progressing within 6 months of starting AI treatment in the metastatic setting
  - **Secondary:**
    Relapsing 6 months after stopping adjuvant AIs or responding for 6 months to AIs in the metastatic setting

Bachelot et al, JCO 2012
TAMRAD: Time to Progression as a function of Intrinsic Hormone Resistance

- **Primary resistance**
  - TAM: 3.8 months
  - TAM + RAD: 5.4 months
  - HR = 0.70 (0.40-1.21)
  - $p = \text{NS (exploratory analysis)}$

- **Secondary resistance**
  - TAM: 5.5 months
  - TAM + RAD: 14.8 months
  - HR = 0.46 (0.26-0.83)
  - $p = 0.0087$ (exploratory analysis)

Candidate Markers for Everolimus Efficacy

Canonical pathway
- PI3K: mutation & IHC (Millipore)
- PTEN: IHC (Cell signaling)
- pAkt: IHC (Ser 473, Epitomics)
- KRAS: mutation

Downstream effectors
- pS6K: IHC (Ser 65, Cell signaling)
- 4EBP1 / p4EBP1: IHC (Ser 235/236, Cell signaling)

Metabolic Pathway
- LKB1: IHC (Abcam)

HIGH = mTOR ON
LOW = mTOR ON

IHC= immunohistochemistry.

Arnedos M, et al. ASCO 2013 Abstract # 510
Treatment Effect (TTP) as a Function of PI3K, LKB1 & p4EBP-1 Expression

HER2+ Breast Cancer
BOLERO-3: Study Design

Phase 3 Study
N = 569
- Locally advanced or metastatic HER2+ breast cancer
- Prior taxane required

Treatment Groups
- Everolimus (5 mg PO daily) + Vinorelbine (25 mg/m² weekly) + Trastuzumab (2 mg/kg weekly†) (n = 284)
- Placebo (PO daily) + Vinorelbine (25 mg/m² weekly) + Trastuzumab (2 mg/kg weekly†) (n = 285)

Follow-up/Survival

Key Endpoints:
- Primary: PFS
- Secondary: OS, ORR, time to deterioration of ECOG PS, safety, DoR, CBR, and QoL

Therapy until PD or intolerable toxicity
- Stratification by prior lapatinib use (yes/no)

*Resistance to prior trastuzumab required
†Following a 4-mg/kg loading dose on day 1, cycle 1 (1 cycle = every 21 days).

Presented by: Ruth M. O’Regan, ASCO 2013
BOLERO-3: PFS Results

Andre et al, Lancet Oncology 2014
### BOLERO-3: Forest plot of PFS

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>p value*†</th>
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<td>All</td>
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<td>0.78 (0.65-0.95)</td>
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<td>Age</td>
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<td>&lt;65 years</td>
<td>472</td>
<td>0.77 (0.62-0.95)</td>
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<tr>
<td>≥65 years</td>
<td>97</td>
<td>0.93 (0.56-1.57)</td>
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<td>Region</td>
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<td>Europe</td>
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<td>0.72 (0.53-0.99)</td>
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<td>North America</td>
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<td>0.86 (0.55-1.32)</td>
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<td>Asia</td>
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<td>36</td>
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<td>Other</td>
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<td>Previous lapatinib†</td>
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<tr>
<td>Yes</td>
<td>161</td>
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<tr>
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<td>408</td>
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<td>Previous adjuvant or neoadjuvant trastuzumab</td>
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<td>No</td>
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<td>1 or 2</td>
<td>186</td>
<td>0.75 (0.53-1.05)</td>
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<tr>
<td>ER+/PR+</td>
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<td>Visceral involvement</td>
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<td>130</td>
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This forest plot shows the hazard ratios (HR) and 95% confidence intervals (CI) for progression-free survival (PFS) across various subgroups. The p values indicate statistical significance of the differences between everolimus and placebo treatments.
PFS according to pS6, PTEN, and PIK3CA status in patients with assessable biomarker data (BOLERO-3)

<table>
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<tr>
<th>Biomarker assessable</th>
<th>n</th>
<th>PFS events</th>
<th>Median PFS (95% CI)</th>
<th>HR (95% CI)</th>
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<td><strong>Everolimus</strong></td>
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<td>0.88 (0.67–1.17)</td>
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Andre et al, Lancet Oncology 2014
BOLERO-1/TRIO 019

N = 719

- Locally advanced or metastatic HER2+ breast cancer
- No prior therapy for advanced or metastatic disease (except endocrine therapy)
- Prior (neo)adjuvant TRAS and/or chemotherapy allowed
- Measurable disease or presence of bone lesions (lytic or mixed)

Randomized 2:1

Everolimus (10 mg PO daily) + Paclitaxel + Trastuzumab

Placebo + Paclitaxel + Trastuzumab

Therapy until disease progression or intolerable toxicity

Endpoints

- Primary: PFS (investigator-assessed)
  - Overall population and HR-
  - subpopulation
- Secondary:
  - OS, ORR, CBR, Time to response, Safety, Duration of response

Notes:
1. Discontinued > 12 mo before randomization;
2. Paclitaxel: 80 mg/m² weekly;
3. Trastuzumab: 4 mg/kg loading dose on day 1 at cycle 1 followed by 2 mg/kg weekly doses
4. Patients could discontinue any study treatment due to AEs; other study treatments continued until disease progression or intolerable toxicity

Hurvitz et al, SABCS 2014
BOLERO-1/TRIO 019: PFS Full Population (Investigator-assessment)

Hurvitz et al, SABCS 2014
BOLERO-1/TRIO 019: PFS HR- Subpopulation (Investigator-assessment)

Hurvitz et al, SABCS 2014
**BOLERO-1/TRIO 019: Treatment exposure**

Safety profile was consistent with results previously reported: stomatitis, diarrhea, neutropaenia, anaemia etc. Higher rate of AE-related on-treatment deaths with everolimus (3.6% vs 0%); mainly related to respiratory problems/pneumonitis. Proactive monitoring and early management of AEs is critical.

Hurvitz et al, SABCS 2014

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<th>Therapy</th>
<th>Full Population</th>
<th>HR – subpopulation</th>
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<td>EVE + TRAS + PAC (N = 472)</td>
<td>PBO + TRAS + PAC (N = 238)</td>
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<tr>
<td>Relative dose intensity (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of exposure (median, weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>31</td>
<td>32</td>
</tr>
</tbody>
</table>
Open-label randomized clinical trial of neoadjuvant chemotherapy with paclitaxel followed by FEC versus the combination of paclitaxel and everolimus followed by FEC in triple negative breast cancer

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients per treatment arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T-FEC</td>
<td>TR-FEC</td>
</tr>
<tr>
<td>(n = 27)</td>
<td></td>
<td>(n = 23)</td>
</tr>
<tr>
<td>No. %</td>
<td></td>
<td>No. %</td>
</tr>
<tr>
<td>Response (12 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Response (24 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pathologic complete response</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

Gonzalez-Angulo et al, Ann Onc 2014
Neoadjuvant chemotherapy with paclitaxel + everolimus for breast cancers not responding to EC ± bevacizumab (Geparquinto)

pCR(ypT0 ypN0): Primary end-point

pCR: 5.6%

Huober et al, EJC 2013
How about targeting upstream?

- PI3K Inhibitors
- AKT Inhibitors
  (mainly Phase 1-2; no results from randomised trials currently)
FERGI Study Design – Part I

- ER+, HER2-, postmenopausal women with advanced or MBC
- Prior aromatase inhibitor in adjuvant (PD<6mo) or metastatic setting
- ECOG PS 0, 1
- No diabetic patients
- 0-1 chemotherapy or ≤2 prior endocrine therapies

Fulvestrant 500mg\(^1\) + pictilisib (GDC-0941) 340 mg QD

Treat to PD\(^2\)

Fulvestrant 500 mg\(^1\) + placebo QD

Treat to PD\(^2\)

Cross Over

pictilisib + fulvestrant

N = 168

Stratification factors

<table>
<thead>
<tr>
<th>Stratification factors</th>
<th>1° objective</th>
<th>2° objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA-MT and PTEN loss(^3)</td>
<td>PFS in the ITT</td>
<td>Objective response rate</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>PFS in PIK3CA-MT pts</td>
<td>Duration of objective response</td>
</tr>
<tr>
<td>1° vs. 2° resistance(^4)</td>
<td>Safety</td>
<td>PK</td>
</tr>
</tbody>
</table>

1 Administered on D1 of each 28 day cycle and C1D15; 2 Tumor assessments performed every 8 weeks; 3 Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 were detected by RT-PCR; 4 Disease relapse during or within 6 months of completing AI treatment in the adjuvant setting, or disease progression within 6 months of starting AI treatment in the metastatic setting. 5 Data presented is with an additional year of follow up per-protocol primary analysis

- Median duration of follow up 17.5 months

Courtesy of Dr. Ian Krop, SABCS 2014
Progression-Free Survival in the ITT Population

Number at Risk:
- Placebo+FLV: 79
- Pictilisib+FLV: 89

Number at Risk:
- Placebo+FLV: 79
- Pictilisib+FLV: 89

- Placebo+FLV: 54, 35, 27, 22, 21, 15, 8, 5, 4, 2, 1, 0
- Pictilisib+FLV: 63, 45, 37, 30, 26, 25, 18, 9, 8, 3, 2, 2

- Placebo+FLV Median Time (mo): 5.1
- Pictilisib+FLV Median Time (mo): 6.6
- Placebo+FLV Number of events (n): 61
- Pictilisib+FLV Number of events (n): 59
- Placebo+FLV Hazard Ratio: 0.738
- Pictilisib+FLV Hazard Ratio: (0.515, 1.057)
- Placebo+FLV Log-rank p-value: 0.0959

Courtesy of Dr. Ian Krop, SABCS 2014
Progression-Free Survival based on Tumor PIK3CA Mutation Status

- PIK3CA mutation status does not predict benefit of the addition of pictilisib to fulvestrant

Courtesy of Dr. Ian Krop, SABCS 2014
Progression-Free Survival in Patients with ER and PR Positive Disease Based on Tumor PIK3CA Mutation Status

PR+ and PIK3CA mutation

PR+ and PIK3CA “Wild-Type”

Courtesy of Dr. Ian Krop, SABCS 2014
### AEs Related to Any Study Drug

**Pictilisib (n=89)** | **Placebo (n=79)**
--- | ---
### Adverse Event | All Grades (%) | Grade ≥3 (%) | All Grades (%) | Grade ≥3 (%)
Diarrhea | 56 (63%) | 5 (7%) | 7 (9%) | -
Nausea | 43 (48%) | 3 (3.4%) | 15 (19%) | -
Rash | 38 (43%) | 15 (17%) | 5 (6%) | -
Dysgeusia | 31 (35%) | - | - | -
Fatigue | 24 (27%) | 5 (6%) | 16 (20%) | -
Vomiting | 18 (20%) | 3 (3%) | 3 (4%) | -
Decreased appetite | 17 (19%) | 1 (1%) | 5 (6%) | -
Hyperglycemia | 15 (17%) | 4 (5%) | 4 (5%) | -
Stomatitis | 14 (16%) | 2 (2%) | 2 (2%) | -
Hot flush | 10 (11%) | - | 10 (13%) | -
AST increased | 10 (11%) | 3 (3%) | 7 (8%) | 2 (3%)
Dyspepsia | 8 (9%) | - | 2 (3%) | -
Mucosal inflammation | 9 (10%) | - | 2 (3%) | -
Pneumonitis | 7 (8%) | 1 (1%) | 1 (1%) | -
Colitis | 4 (5%) | 3 (3%) | - | -

1. Adverse events independent of attribution; based on CTCAE v.3
2. Adverse events >10% except pneumonitis and colitis
3. Includes all rash, generalized, maculo-papular, pruritic, erythematous and papular rash

- There were 28 (31%) SAEs in treatment arm vs 16 (20%) in placebo arm
- Safety is consistent with our single agent phase I experience
- No drug-drug interaction between pictilisib and fulvestrant
- There were no treatment related deaths reported

Courtesy of Dr. Ian Krop, SABCS 2014
## Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Pictilisib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (ITT)</td>
<td>89</td>
<td>79</td>
</tr>
<tr>
<td>Treated (Safety evaluable)</td>
<td>89</td>
<td>79</td>
</tr>
<tr>
<td>Discontinued pictilisib/placebo(^1)</td>
<td>80 (90%)</td>
<td>69 (87%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>50 (56%)</td>
<td>57 (72%)</td>
</tr>
<tr>
<td>Non-PD</td>
<td>30 (34%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>16 (18%)</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>Protocol-violation</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Withdrawal by subject</td>
<td>5 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Physician Decision</td>
<td>8 (9%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued fulvestrant for non-PD(^1)</td>
<td>18 (20%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Dose reduction for an AE(^2)</td>
<td>21 (24%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

\(^1\)From treatment discontinuation eCRFs
\(^2\)From AE eCRFs

- High rate of discontinuation of pictilisib for non-PD events, most occurred in the early cycles

Courtesy of Dr. Ian Krop, SABCS 2014
PI3K Inhibitors in breast cancer

• PI3K mutation status not predictive of benefit?
  – Archived tissues? Not reflective of latest PI3K mutation status?
  – Other biomarkers?
    • PTEN, LKB1, pS6 etc?
  – Circulating markers?; tumour heterogeneity and evolution

• Toxicity Issues
• Some similarities with mTOR inhibitors

• Are all PI3K inhibitors the same?
Phase I-III trials in Breast Cancer and/or Solid Tumours

Growth factors

Receptor Tyrosine Kinase

PI3K/mTOR
BEZ235 PF-05212384
BGT226 PF-04691502
GDC-0980 GSK2126458
XL765 GSK1059615
LY3023414 DS7423
VS5584 SF1126

mTORC1 mTORC1 and 2
Everolimus AZD2014
Sirolimus AZD8055
Temsirolimus MLN0128
Ridaforolimus OSI-027

PI3K

AKT

mTOR

S6K

Pan PI3K
BKM120
GDC0941
BAY1082439
BAY80-6946
ZSTK474
PX-866
XL147
CH5132799
WX-037
CUDC-907

Isoform-selective(α/β)
BYL719(α)
GDC0032(α)
MLN1117 (α)
SAR260301(β)
AZD8186(β)
GSK2636771(β)

AKT1/2/3
MK2206
GDC0068
GSK2141795
AZD5363

Perifosine
BAY1125976
ARQ 092

AKT/p70S6 kinase
LY2780301

Not all PI3K/AKT/mTOR Inhibitors are the same!

https://www.clinicaltrials.gov/
Are all PI3K/AKT/mTOR Inhibitors the same?

• Different targets, different selectivity for various isoforms

• Different pharmacology

• Optimal dosing schedule?

• Any differences in toxicity profile?
BELLE-2 Study

Phase III study of buparlisib + fulvestrant in HR+/HER2– breast cancer

Postmenopausal patients with HR+/HER2– locally advanced or metastatic breast cancer refractory to AIs (N=1060)

Endpoints

Primary end point
• Progression-free survival†

Key secondary end point
• Overall survival‡

Other Secondary endpoints
• Progression-free survival§
• Overall survival§
• Objective response rate‡,§
• Clinical benefit rate‡,§
• Time to ECOG PS deterioration‡,§
• Safety
• Pharmacokinetic profile
• Quality of life

Molecular screening
Determination of PI3K pathway activation status*

Run-in treatment phase: fulvestrant (Days 1–14)

Randomization (1:1)
Stratification based on PI3K pathway activation status* and presence/absence of visceral disease

Buparlisib + fulvestrant†
Placebo + fulvestrant†
Toxicities

Toxicity profile may vary with different agents.

- Metabolic: hyperglycaemia, hyperlipidaemia
- Dermatological: rash, photosensitivity
- Gastrointestinal: mucositis, nausea/vomiting, diarrhoea, transaminitis
- Respiratory: pneumonitis
- Haematological: cytopaenias, immunosuppression, infections
- Constitutional: fatigue, anorexia

Possible drug interactions.

Optimal management of adverse effects is crucial for safety and compliance.
Overcoming Resistance

Potential Combinations

- PI3K/AKT/mTOR Inhibitor and Endocrine therapy
- PI3K/AKT/mTOR Inhibitor and anti-HER2 therapy +/- endocrine therapy?
- PI3K/AKT/mTOR Inhibitor and Chemotherapy
- PI3K inhibitor and mTOR Inhibitor
- PI3K/AKT Inhibitor and MEK Inhibitor
- PI3K Inhibitor and PARP Inhibitor
- PI3K Inhibitor and CDK Inhibitor
- PI3K Inhibitor and immunotherapy?
- Etc
Conclusions

• PI3K/AKT/mTOR Inhibitors have activity in breast cancer; clinical efficacy data is mainly in the setting of hormone receptor+, HER2- subtype for now. In HER2+ disease, benefit is seen mainly in ER- subset (BOLERO-1 and 3).

• Several other clinical trials in progress.

• Biomarkers predictive of benefit are currently unclear.

• Combination therapy with other agents may be more efficacious, though clinical data is awaited.

• Toxicity can be an issue; need to monitor and manage appropriately.
Thank you for your attention!