Breast Cancer Highlights from 2020 International Oncology Meeting

ENDOCRINE THERAPY ABSTRACTS

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July 16, 2020
Disclosure

- Advisory board for Biotheranostics

Note:
- Please note that some of the studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered to be preliminary until published in a peer-reviewed journal.
Endocrine Therapy Abstracts

▶ Adjuvant
  • MINDACT TRIAL UPDATE (#506)
  • BREAST CANCER INDEX IDEAL TRIAL (#512)

▶ Metastatic
  • BYLIEVE TRIAL (#1006)
Does the 70-gene signature help discern which ER+ breast cancers with high clinical risk are associated with good prognosis without chemotherapy?
MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients

EORTC-10041/BIG3-04 (EudraCT Number2005-002625-31)

MINDACT TRIAL DESIGN

Registration & Screening Surgery

N= 6693

Clinical-Pathological (C) risk (Adjuvant! Online)

Genomic (G) risk (70-gene signature)

C-low/G-low

No Chemotherapy

HR+

C-high/G-high

MINDACT population:
HR+/HER2-  81%
HER2+      9.5%
TNBC       9.6%

Chemotherapy

HR+
MINDACT is a **DE-ESCALATION STUDY**

- **Primary endpoint**
  Distant metastasis free survival (DMFS) at 5 years for C-High / G-Low without chemotherapy

- **Primary statistical test**
  Null hypothesis: 5-year DMFS rate C-High / G-Low no CT in Primary Test population = 92%
  Power: 80% when true 5-year DMFS rate = 95%
  Primary test 5-year DMFS rate significant if 2-sided 95% Confidence Interval exceeds 92%

*F. Cardoso, NEJM 2016*
SECONDARY ENDPOINT

**Efficacy**: CT vs no CT population of discordant risk groups (in ITT population)

- **C-Low / G-High risk at enrollment**
  - N=690
  - Randomized to CT: N=344
  - Randomized to no CT: N=346

- **C-High / G-Low risk at enrollment**
  - N=1497
  - Randomized to CT: N=749
  - Randomized to no CT: N=748

*Trial not powered for the comparisons of yes or no chemotherapy*

F. Cardoso, NEJM 2016
How high was CLINICAL HIGH risk population in MINDACT?

How MINDACT and TAILOR-X populations compare (for CT vs no CT question)

F. Cardoso, NEJM 2016

MINDACT population
Clinical High / MammaPrint Low

- N = 1551 (577 premenopausal)
- median age = 55 y
- T size > 2cm 58%
- Grade 3 28%

In HR+/HER2- C-high/G-low patients: 49% Node (1-3) positive and 27% grade 3

Tailor-X population
Recurrence score 11-25

- N = 6711 (2415 premenopausal)
- med. age = 55y
- T size > 2cm 24%
- Grade 3 14%

J. Sparano, NEJM 2018
UPDATED ANALYSIS AT 8.7 YEARS MEDIAN FOLLOW-UP

RESULTS
Update of PRIMARY ENDPOINT with more mature data at 5 years (>90% of pts with at least 5 years FU)

Clinical-High/Genomic-Low no chemotherapy

Null Hypothesis 5-year DMFS: set at 92% 

Lower bound of 95%CI exceeds 92%!

*Confirmation of primary results Supported by sensitivity analyses*
MINDACT proves the clinical utility of MammaPrint

Type of first event (n = 650)
- distant recurrences: 68.8%
- death of any cause: 31.2%
SECONDARY ENDPOINT
DMFS C-High/G-Low risk (ITT population) CT vs no CT

Absolute difference in DMFS between CT and no CT groups:
• at 5 years: $0.9 \pm 1.1$ % points
• at 8 years: $2.6 \pm 1.6$ % points

Type of first event (n = 150)
• distant recurrences: 74.7%
• death of any cause: 25.3%
Effect of chemotherapy by age in HR+/HER2- subgroup C-High/G-Low group
DMFS in C-High / G-Low risk patients with luminal cancers (HR+/HER2-) stratified by age
ITT population

Age >50 years

Distant Metastasis Free Survival (Distant Metastasis Free Survival %)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% at 5 years (95% CI)</th>
<th>% at 8 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>95.0 (92.4-96.7%)</td>
<td>90.2 (86.8-92.7%)</td>
</tr>
<tr>
<td>No ACT</td>
<td>95.8 (93.5-97.4%)</td>
<td>90.0 (86.6-92.6%)</td>
</tr>
<tr>
<td>Abs. diff</td>
<td>-0.9 ± 1.4</td>
<td>0.2 ± 2.1</td>
</tr>
</tbody>
</table>

NO difference

Presented By Fatima Cardoso at TBD
CONCLUSIONS

• At 8.7 years medium FU, the primary endpoint continues to be met in CT untreated C-High/G-Low risk women, confirming MINDACT as a positive de-escalation study
<table>
<thead>
<tr>
<th>Clinical Population</th>
<th>MINDACT TRIAL</th>
<th>TAILORx TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&gt;2cm</td>
<td>58%</td>
<td>24%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>LN+ (1-3)</td>
<td>48%</td>
<td>0%</td>
</tr>
</tbody>
</table>
70-gene signature is able to identify subsets of patients who have a low likelihood of distant recurrence despite high-risk clinical features.
- Must decide whether the 5-year DMFS endpoint is adequate for ER+ patients with high risk disease
- Study is not powered to predict a benefit from chemotherapy

Both MINDACT and TAILORx trials highlight that chemotherapy discussion will need to be modified by age
- Some of the postulated benefit of chemotherapy may be due to ovarian function suppression in women <50 years old, but this has not yet been proven

RxPonder trial results are still pending to evaluate the 21-gene RS in LN+ patients
Abstract 512:

Breast Cancer Index IDEAL TRIAL

In patients treated with an AI during the first 5 years of endocrine therapy, does BCI predict benefit of extending treatment with an AI for an additional 2.5 v. 5 years?
Persistent Long-Term Risk of Distant Recurrence

- Patients with early-stage (I/II), HR+ have good overall prognosis
  - >50% of recurrences occur after Year 5
  - Risk is persistent
  - Risk of late distant recurrence after 5 years of adjuvant endocrine therapy persists across all clinical stages

## Extension of Adjuvant Endocrine Therapy: 5 vs 10 Years

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of Therapy (y)</th>
<th>N</th>
<th>Median Follow-up (y)</th>
<th>Disease-free Survival¹</th>
<th>Absolute Benefit</th>
<th>Hazard Ratio or Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA.17</td>
<td>TAM x 5y → Placebo x 5y → Al x 5y</td>
<td>2587 / 2583</td>
<td>2.5</td>
<td>89.8% / 94.4%</td>
<td>4.6%</td>
<td>HR 0.58 (0.45-0.76) P&lt;0.001</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>TAM x 5y → Placebo x 5y → Al x 5y</td>
<td>779 / 783</td>
<td>2.5</td>
<td>89% / 91%</td>
<td>2%</td>
<td>RR: 0.68 P=0.07</td>
</tr>
<tr>
<td>ABCSG 6A</td>
<td>TAM x 5y → Placebo x 3y → Al x 3y</td>
<td>469 / 387</td>
<td>5.2</td>
<td>88.2% / 92.9%</td>
<td>4.7%</td>
<td>HR 0.62 (0.40-0.96) P=0.031</td>
</tr>
<tr>
<td>aTTom</td>
<td>TAM x 5y → No treatment → TAM x 5y</td>
<td>3485 / 3468</td>
<td>10</td>
<td>68% / 72%</td>
<td>4%</td>
<td>RR 0.85 (0.76-0.95) P=0.003</td>
</tr>
<tr>
<td>ATLAS</td>
<td>TAM x 5y → No treatment → TAM x 5y</td>
<td>3418 / 3428</td>
<td>7.6</td>
<td>74.9% / 78.6%</td>
<td>3.7%</td>
<td>RR 0.84 (0.76-0.94) P=0.002</td>
</tr>
<tr>
<td>MA.17R</td>
<td>TAM x 0-5y → Placebo → Al x 5y</td>
<td>959 / 959</td>
<td>6.3</td>
<td>91% / 95%</td>
<td>4%</td>
<td>HR 0.66 (0.48-0.91) P=0.01</td>
</tr>
<tr>
<td>NSABP B-42</td>
<td>Al x 5y → Placebo x 5y → Al x 5y</td>
<td>1983 / 1983</td>
<td>9.3</td>
<td>72.1% / 76.1%</td>
<td>4%</td>
<td>HR 0.84 (0.74-0.96) P=0.011</td>
</tr>
<tr>
<td>AERAS (N-SAS BC 05)*</td>
<td>Al x 5y → No treatment → Al x 5y</td>
<td>843 / 840</td>
<td>4.9</td>
<td>84.4% / 91.9%</td>
<td>7.5%</td>
<td>HR 0.548 P=0.0004</td>
</tr>
</tbody>
</table>

¹ Based on disease-free survival or cumulative risk of recurrence rates as reported in the primary publications (note that the definitions of disease-free were not identical across trials)
Sequencing of ET Agents and Nodal Status are Important

Greater benefit from extended AIs seen with more positive nodes in an unselected population
Breast Cancer Index (BCI) Clinical Assay Reports Results from Two Biomarkers

**BCI Prognostic**
Individualized Risk of Cumulative Overall (0-10 yr) and *Late* Recurrence (5-10 yrs)

- Algorithmic combination of proliferation-related gene signature (Molecular Grade Index, MGI) and an estrogen signaling pathway signature (HoxB13/IL17BR, a.k.a. H/I)

**BCI Predictive**
Individualized Prediction of Likelihood of Benefit from *Extended* Endocrine Therapy

- A separate algorithm based exclusively on H/I to provide a quantitative molecular assessment of estrogen signaling pathways

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**Breast Cancer Index**

![BCI Diagram](image_url)
BCI Predictive Assay Summary

• BCI (H/I) has demonstrated consistent predictive ability in patients with LN- and LN+ disease, treated with an initial 5 years of tamoxifen, followed by an additional 5 years tamoxifen (trans-aTTOM) or AI (MA-17)

• Previous BCI predictive data had not evaluated the benefit of EET with 5 years of AI after initial treatment with AI during the first 5 years

• The BCI IDEAL study sought to determine whether BCI (H/I) (High vs Low) is predictive of extended endocrine benefit in patients treated in the IDEAL trial

Investigation on the Duration of Extended Letrozole (IDEAL)

STUDY DESIGN

- Study explored whether a shorter extension of AI therapy is sufficient vs a full additional 5 years
- 88% of patients received either AI only (29%) or sequence of tamoxifen + AI (59%) in the first 5 years
- 73% of patients had LN+ disease
- HR 0.92 (0.74-1.16) for 5 vs 2.5 years
- Similar to studies such as ABCSG16, results suggested that shorter duration of AI therapy might be as effective as full 10 years

Bloq et al 2018 JNCI 110(1): djx134
Breast Cancer Index IDEAL Study

- The primary endpoint was recurrence-free interval (RFI)
  - Events during first 2.5 years not counted (both arms on therapy)
- Median follow-up was 9.3 years after randomization
- Overall cohort (n=908) represents ~50% of parent trial and included LN- and LN+ patients
- Secondary objective was to determine if BCI (H/I) is predictive of extended AI benefit in patients treated with AIs in the primary adjuvant setting (n=794; 29% AI only primary adjuvant, 59% sequence of TAM/AI primary adjuvant)

Benefit from an Additional 2.5y vs 5y of Extended Endocrine Therapy is Dependent on Classification by BCI (H/I): Overall Cohort

- Overall cohort included both N0 (27%) and N+ (73%) patients
- BCI (H/I) patients demonstrate a 58% relative risk reduction and a 9.8% absolute RFI benefit from an additional 2.5 years of endocrine therapy (full 10 years of therapy)

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 years</td>
<td>0.0</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>10 years</td>
<td>0.0</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Overall, Unselected**

- HR: 0.69 (0.47-1.03)  
P = 0.0701  
4.9%

**Overall, H/I-Low (N)**

- HR: 0.95 (0.58-1.56)  
P = 0.8354  
0.5%

**Overall, H/I-High (N)**

- HR: 0.42 (0.21-0.84)  
P = 0.0111  
9.8%

52.8% of patients = H/I Low  
47.2% of patients = H/I High
Benefit from an Additional 2.5y vs 5y of Extended Endocrine Therapy is Dependent on Classification by BCI (H/I): Any AI Cohort

- Any AI cohort = 5 y of adjuvant AI monotherapy (27% of patients) or 2-3 y tamoxifen followed by 2-3 yrs. of adjuvant AI (60% of patients)
- BCI (H/I) patients demonstrate a 66% relative risk reduction and an 11.8% absolute RFI benefit from an additional 2.5 years of AI therapy (full 10 years of therapy)

52.6% of patients = H/I Low
47.4% of patients = H/I High
Summary of BCI Clinical Evidence For Prediction of Endocrine Benefit

• BCI (H/I) has consistently and significantly predicted preferential benefit from endocrine therapy in HR+ early stage breast cancer across multiple studies

• BCI (H/I) patients have consistently demonstrated a ~58-66% relative risk reduction from additional endocrine therapy

• The current IDEAL study demonstrates that BCI predicts benefit of extended AI therapy in patients previously treated with primary adjuvant AI, which is relevant for the current standard of care for the majority of HR+ early stage breast cancer patients

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Relative Risk Reduction</th>
<th>Absolute Benefit (High H/I)†</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment: Adjuvant TAM vs none</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm (n=600)</td>
<td>H/I-High HR: 0.35 (0.19-0.65); p=0.0005 H/I-Low HR: 0.67 (0.36-1.24), p=0.204</td>
<td>17.5%</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Treatment: Extended AI vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA.17 (n=249)</td>
<td>H/I-High OR: 0.35 (0.16-0.75); p=0.007 H/I-Low OR: 0.68 (0.31-1.52), p=0.35</td>
<td>16.5%</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Treatment: Extended TAM vs Stop</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trans-aTTom N+ (n=583)</td>
<td>H/I-High HR: 0.35 (0.15-0.86); p=0.027 H/I-Low HR: 1.07 (0.69-1.65), p=0.768</td>
<td>10.2%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Treatment: 5y vs 2.5y Extended AI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDEAL (n=908)</td>
<td>H/I-High HR: 0.42 (0.21-0.84); p=0.0111 H/I-Low HR: 0.95 (0.58-1.56), p=0.835</td>
<td>9.8%</td>
<td>0.045</td>
</tr>
</tbody>
</table>

†Hazard Ratios were reported for all studies, except in MA.17 where odds ratios were reported due to nested case-controlled study

* Low H/I patients demonstrated no significant benefit across all study cohorts

4. Liefers et al J Clin Oncol 38: 2020 (suppl; abstr 512)
DISCUSSION

• BCI IDEAL STUDY
  – BCI predictive assay was able to predict the benefit of EET with AI for 10 years over 7.5 years in 47% of patients treated with AI during the first 5 years of treatment
  – However, IDEAL was not the best trial to determine whether a patient previously treated with 5 years of an AI would benefit from any additional AI. This is probably one of our most important clinical questions.
    • NSABP B42
    • AERAS
Breast Cancer Index Test Results

Extended Endocrine Benefit & Risk of Late Distant Recurrence

PREDICTIVE RESULT
Am I likely to benefit from extended endocrine therapy?
YES

PROGNOSTIC RESULT
What is my risk of late distant recurrence?
X.X%

Additional Comments
Equid exit, debrec llorep iripe sed magnar. Sapi laboris volupts temlorgae landthrone. Lorem esset sequetemere valore peram que nemo quam quidigit niquo valores cerease sincilmpor berum hit versi illaut premam earam exstrumiqui sunt ant unit dit perantes et lat. Set versi illaut premat.

Treating Provider
First Last, M.D.
Facility
Address
City, ST, Zip
Phone: XXX-XXX-XXXX
Fax: XXX-XXX-XXXX

Submitting Pathologist
First Last, M.D.
Facility
Address
City, ST, Zip
Phone: XXX-XXX-XXXX
Fax: XXX-XXX-XXXX
Abstract 1006:

BYLIEVE TRIAL

Is fulvestrant with alpelisib effective in patients with PIK3CA mutations previously treated with AI+CDK4/6 inhibition?
Alpelisib + Fulvestrant in Patients With PIK3CA-Mutated Hormone-Receptor Positive (HR+), Human Epidermal Growth Factor Receptor-2-Negative (HER2–) Advanced Breast Cancer (ABC) Previously Treated With Cyclin-Dependent Kinase 4/6 Inhibitor (CDKi) + Aromatase Inhibitor (AI): BYLieve Study Results

Hope S. Rugo,1 Florence Lerebours,2 Eva Ciruelos,3 Pamela Drullinsky,4 Manuel Ruiz-Borrego,5 Patrick Neven,6 Yeon Hee Park,7 Aleix Prat,8 Thomas Bachelot,9 Dejan Juric,10 Nicholas Turner,11 Nickolas Sophos,12 Juan Pablo Zarate,12 Christina Arce,12 Yu-Ming Shen,13 Stuart Turner,12 Hemanth Kanakamedala,14 Wei-Chun Hsu,14 Stephen Chia16

1University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 2Institut Curie, Saint-Cloud, France; 3University Hospital 12 de Octubre, Madrid, Spain; 4Memorial Sloan Kettering Cancer Center, New York, NY, USA; 5Hospital Virgen del Rocio de Sevilla, Seville, Spain; 6University Hospital Leuven Breast Centre, Leuven, Belgium; 7Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; 8University of Barcelona, Barcelona, Spain; 9Centre Léon Bérard, Lyon, France; 10Massachusetts General Hospital Cancer Center, Boston, MA, USA; 11The Royal Marsden Hospital, London, UK; 12Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 13Novartis Pharmaceuticals Corporation, Munich, Germany; 14Genesis Research, Hoboken, NJ, USA; 15British Columbia Cancer Agency, Vancouver, BC, Canada

Abstract 1006
PI3 Kinase Pathway
Original Article

Alpelisib for \textit{PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer}

Fabrice André, M.D., Eva Ciruelos, M.D., Gabor Rubovszky, M.D., Mario Campone, M.D., Sibylle Loibl, M.D., Hope S. Rugo, M.D., Hiroji Iwata, M.D., Pierfranco Conte, M.D., Ingrid A. Mayer, M.D., Bella Kaufman, M.D., Toshinari Yamashita, M.D., Yen-Shen Lu, M.D., Kenichi Inoue, M.D., Masato Takahashi, M.D., Zsuzsanna Pápai, M.D., Anne-Sophie Longin, M.Sc., David Mills, M.Sc., Celine Wilke, M.D., Samit Hirawat, M.D., Dejan Juric, M.D., for the SOLAR-1 Study Group
In patients with PIK3CA mutation, alpelisib combined with fulvestrant led to a median progression-free survival of 11 months, compared with 5.7 months with fulvestrant plus placebo.

Hyperglycemia, rash, and diarrhea were more common with alpelisib.
Subgroup Analysis of Progression-free Survival in the Cohort with PIK3CA-Mutated Cancer.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio for Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>341</td>
<td>0.65 (0.50-0.85)</td>
</tr>
<tr>
<td>Lung or liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>170</td>
<td>0.62 (0.44-0.89)</td>
</tr>
<tr>
<td>No</td>
<td>171</td>
<td>0.69 (0.47-1.01)</td>
</tr>
<tr>
<td>Bone-only disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77</td>
<td>0.62 (0.33-1.18)</td>
</tr>
<tr>
<td>No</td>
<td>94</td>
<td>0.67 (0.40-1.15)</td>
</tr>
<tr>
<td>Previous CDK4/6 inhibitor treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>0.48 (0.17-1.36)</td>
</tr>
<tr>
<td>No</td>
<td>321</td>
<td>0.67 (0.51-0.87)</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neadjuvant</td>
<td>46</td>
<td>0.37 (0.17-0.80)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>161</td>
<td>0.64 (0.42-0.95)</td>
</tr>
<tr>
<td>None</td>
<td>133</td>
<td>0.87 (0.58-1.32)</td>
</tr>
<tr>
<td>Endocrine status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary resistance</td>
<td>45</td>
<td>0.64 (0.33-1.32)</td>
</tr>
<tr>
<td>Secondary resistance</td>
<td>247</td>
<td>0.66 (0.40-0.99)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>39</td>
<td>0.87 (0.35-2.17)</td>
</tr>
<tr>
<td>Line of treatment in advanced disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>177</td>
<td>0.71 (0.49-1.03)</td>
</tr>
<tr>
<td>Second line</td>
<td>161</td>
<td>0.61 (0.42-0.89)</td>
</tr>
<tr>
<td>No. of metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>234</td>
<td>0.59 (0.43-0.83)</td>
</tr>
<tr>
<td>≥3</td>
<td>107</td>
<td>0.77 (0.50-1.20)</td>
</tr>
<tr>
<td>PIK3CA mutation subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E545X</td>
<td>60</td>
<td>0.60 (0.29-1.23)</td>
</tr>
<tr>
<td>E545X</td>
<td>105</td>
<td>0.61 (0.37-1.00)</td>
</tr>
<tr>
<td>H1047X</td>
<td>193</td>
<td>0.68 (0.48-0.95)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>173</td>
<td>0.56 (0.39-0.81)</td>
</tr>
<tr>
<td>North America</td>
<td>43</td>
<td>0.41 (0.19-0.91)</td>
</tr>
<tr>
<td>Asia</td>
<td>70</td>
<td>0.76 (0.42-1.37)</td>
</tr>
<tr>
<td>Latin America</td>
<td>31</td>
<td>1.43 (0.54-3.79)</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>0.93 (0.25-3.45)</td>
</tr>
</tbody>
</table>
BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

**Goal:** In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with PIK3CA-mutated HR+, HER2– ABC

**Patients who received CDKI + AI as immediate prior treatment (N=112)**

(Cohort A)

- Alpelisib 300 mg oral QD + fulvestrant 500 mg

**Primary endpoint**

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort

**Secondary endpoints include**

(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

**Men or pre-/postmenopausal women with HR+, HER2– ABC with a PIK3CA mutation**

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

*Treatment crossover between cohorts is not permitted*

**Presented By Hope Rugo at TBD**
Statistical Analyses

• For efficacy endpoints, the primary population for analysis included patients who received one dose of study treatment and had a centrally confirmed PIK3CA mutation

  – PIK3CA mutation status was determined in tumor tissue by PCR analysis designed to detect mutations in the C2, helical, and kinase domains of PIK3CA (exons 7, 9, and 20, respectively)

  – Primary endpoint: Proportion of patients alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1, calculated with 2-sided 95% CIs
    – Clinically meaningful treatment effect and the primary endpoint would be met if the lower bound of the 95% CI was >30%

  – ORR and CBR were summarized with descriptive statistics (N, %) along with 2-sided exact binomial 95% CIs

• The safety set included all patients who received at least one dose of study treatment

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*Disease progression refers to patients who progressed, died, or discontinued study by 6 months as failure.

CBR, clinical benefit rate; CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, PFS on next-line treatment; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria In Solid Tumors.

# Previous Treatments and Endocrine Status

<table>
<thead>
<tr>
<th>Characteristic, No. (%)</th>
<th>Prior CDKi + AI (Cohort A) (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Analysis Set</strong></td>
<td></td>
</tr>
<tr>
<td>Lines of prior medication therapy in the metastatic setting</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (11.8)</td>
</tr>
<tr>
<td>1</td>
<td>89 (70.1)</td>
</tr>
<tr>
<td>2</td>
<td>21 (16.5)</td>
</tr>
<tr>
<td>3</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Lines of prior ET in the metastatic setting</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (11.8)</td>
</tr>
<tr>
<td>1</td>
<td>98 (77.2)</td>
</tr>
<tr>
<td>2</td>
<td>14 (11.0)</td>
</tr>
<tr>
<td>Previous exposure to fulvestrant or chemotherapy as first-line treatment in the metastatic setting</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td><strong>Endocrine status at study entry</strong></td>
<td></td>
</tr>
<tr>
<td>Primary endocrine resistance</td>
<td>26 (20.5)</td>
</tr>
<tr>
<td>Secondary endocrine resistance</td>
<td>76 (59.8)</td>
</tr>
<tr>
<td>Endocrine sensitivity</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

15 patients received CDKi in the adjuvant setting.

**Primary endocrine resistance:** relapse < 24 mos on ET (adjuvant) or progression < 6 months on ET (metastatic).

**Secondary endocrine resistance:** relapse ≥ 24 mos on ET or relapse < 12 mos after end of ET (adjuvant), or progression ≥ 6 mos on ET (metastatic).

**Endocrine sensitivity:** relapse ≥ 12 mos after the end of ET (adjuvant) or progression occurring ≥ 12 mos after the end of ET (metastatic).

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AI: aromatase inhibitor; CDKi: cyclin-dependent kinase inhibitor; ET: endocrine therapy.*
Efficacy: Primary Endpoint and PFS Results

**Endpoint**

<table>
<thead>
<tr>
<th>Prior CDKi + Al (Cohort A) (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint:</strong> Patients who were alive without disease progression at 6 mo</td>
</tr>
<tr>
<td>50.4% (n=61; 95% CI, 41.2-59.6)</td>
</tr>
<tr>
<td><strong>Secondary endpoint:</strong> Median PFS</td>
</tr>
<tr>
<td>7.3 mo [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)</td>
</tr>
</tbody>
</table>

The primary endpoint for the prior CDKi + Al cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months.
Efficacy: Best Percent Change From Baseline in Tumor Size

BYLieve,
Prior CDK1 + Al (Cohort A)
Alpelisib + Fulvestrant

SOLAR-1
Alpelisib + Fulvestrant

 Decrease in best % change from baseline
BYLieve, Prior CDK1 + Al (Cohort A) (n=87)
70.1%
SOLAR-1 (n=116)
75.9%

Increase/zero change in best % change from baseline
BYLieve, Prior CDK1 + Al (Cohort A) (n=87)
26.4%
SOLAR-1 (n=116)
18.1%

SOLAR-1 data cutoff date: June 12, 2018; BYLieve data cutoff date: December 17, 2010.
*Best percentage change in sum of diameters per investigator assessment, for patients with measurable disease at baseline.
*Patients with missing best percentage change or those with best percentage change in target lesion but overall response of unknown are excluded.

Presented By Hope Rugo at TBD
### Safety of Alpelisib + Fulvestrant in the Prior CDKi + AI Cohort (Safety Set)

<table>
<thead>
<tr>
<th>CDKi + AI (Cohort A)</th>
<th>All Grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>126 (99.2)</td>
<td>85 (66.9)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>126 (99.2)</td>
<td>79 (62.2)</td>
</tr>
<tr>
<td>SAEs</td>
<td>33 (26.0)</td>
<td>31 (24.4)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>20 (15.7)</td>
<td>18 (14.2)</td>
</tr>
<tr>
<td>Fatal SAEs</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>26 (20.5)</td>
<td>15 (11.8)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>23 (18.1)</td>
<td>13 (10.2)</td>
</tr>
<tr>
<td>AEs leading to dose adjustment/interruption</td>
<td>82 (64.6)</td>
<td>68 (53.5)</td>
</tr>
</tbody>
</table>

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*Patients may have had more than one AE documented as leading to discontinuation.

*Adverse events leading to discontinuation included skin and subcutaneous tissue disorders (7), GI disorders (6), investigations (4), general disorders and administration site conditions (3), metabolism and nutrition disorders (2), infections and infestations (1), nervous system disorders (1), and respiratory, thoracic and mediastinal disorders (1).

AE, adverse event; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; GI, gastrointestinal; SAE, serious adverse event.
# AEs Leading to Discontinuation and Dose Intensity Compared With SOLAR-1

## BYLieve

<table>
<thead>
<tr>
<th>AEs leading to discontinuation (≥ 1.5%)</th>
<th>Prior CDKI + AI (Cohort A) Alpelisib + fulvestrant (N=127)</th>
<th>All grades, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>26 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Median relative dose intensity for alpelisib in BYLieve was 89.9%**

## SOLAR-1

<table>
<thead>
<tr>
<th>AEs leading to discontinuation (≥ 1.5%)</th>
<th>Alpelisib + fulvestrant (N=284)</th>
<th>All grades, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>71 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>18 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>9 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (1.8)</td>
<td></td>
</tr>
</tbody>
</table>

**Median relative dose intensity for alpelisib in SOLAR-1 was 83.7%**

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Weighted/Matched PFS Analyses: BYLieve and a Real-World Cohort of Patients

- PFS results from BYLieve were compared with real-world PFS of a similar group of patients (N=95) with HR+, HER2−, PIK3CA-mutated ABC in the US after CDKi-based therapy from the de-identified US Flatiron Health-Foundation Medicine (FMI) clinicogenomics database.

- Differences in prognostic factors for PFS between cohorts were mitigated by 3 different matching/weighting techniques that accounted for baseline covariates.

- Treatments in the real-world setting varied, with 33 unique treatment regimens reported:
  - The most common treatments regimens were:
    - Capecitabine monotherapy (n=14, 14.7%)
    - Fulvestrant monotherapy (n=14, 14.7%)
    - Fulvestrant + palbociclib (n=13, 13.7%)
    - Everolimus + exemestane (n=11, 11.6%)
    - Fulvestrant + letrozole + palbociclib (n=5, 5.3%)
### PFS Effect of Alpelisib Over Standard Treatments in Real-World Setting

<table>
<thead>
<tr>
<th>Analysis Method (In Patients With PIK3CA Mutation)</th>
<th>BYLieve Prior CDKi +AI (Cohort A)</th>
<th>Flatiron/FMI Standard Treatment</th>
<th>median-PFS (mo) (95% CI), n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted results</td>
<td>7.3</td>
<td></td>
<td>3.6 (3.1-6.1), n=95</td>
</tr>
<tr>
<td>Weighting by odds</td>
<td>7.3</td>
<td></td>
<td>3.7 (3.1-6.1), n=116</td>
</tr>
<tr>
<td>Propensity score matching</td>
<td>8.0</td>
<td></td>
<td>3.5 (3.0-5.4), n=76</td>
</tr>
<tr>
<td>Exact matching</td>
<td>6.5</td>
<td></td>
<td>3.4 (2.9-3.9), n=61</td>
</tr>
</tbody>
</table>

Matched analysis comparing BYLieve with RWE standard treatment in post-CDK4/6i setting further supports use of alpelisib + fulvestrant.

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*PFS comparison is based on PFS per RECIST v1.1 in BYLieve and real-world PFS in Flatiron/FMI.*
DISCUSSION

- BYLIEVE TRIAL
  - Is a single-arm study that attempts to evaluate whether patients with PIK3CA mutations previously treated with an AI and CDK 4/6 inhibitor would benefit from alpelisib with ET.
    - Primary endpoint of lower bound CI >30% met (41.2%), with median PFS of 7.3 months
    - Results appear comparable to SOLAR-1 at face value
    - Authors compare efficacy to “real world” cohorts using statistical models, suggesting that the combination may be better than standard of care
  - Underscores the importance of management of side effects such as rash, hyperglycemia, and diarrhea, to maintain dose intensity
    - Overall discontinuation for AEs in BYLieve was 20.5%, compared to 25% in SOLAR-1
    - Fewer discontinuations for hyperglycemia in BYLieve (1.6%) compared to 6.3% in SOLAR-1