Current and Future Management of ER-Positive mBC After Disease Progression on CDK4/6 Inhibition

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Disclosure

No relevant conflicts of interest to disclose.
Case Presentation: Dr Sparano

43 year old female stage IV breast cancer with liver and bone mets in July 2017, ER/PR+, HER2-, relapsed on adjuvant OFS + AI.

• Progressive disease on fulvestrant/ribociclib, capecitabine, carboplatin/gemcitabine, fulvestrant/alisertib (Aurora kinase inhibitor) on clinical trial.

• Previously found to have PIK3CA E545K mutation with allele frequency 1.6% in May 2017, same mutation in tumor from liver biopsy and MSS, intermediate TMB (10 mutations/MB) in October 2017.
Patient receives radiation therapy followed by oophorectomy and letrozole. Near the completion of the 5-year course of letrozole and at the age of 46 (2017), the patient developed abdominal pain and imaging demonstrated multiple hypodense liver lesions. A bone scan, in addition to the liver lesions, revealed an area of uptake in the right ilium as well as the left femoral head.

A biopsy of liver lesion revealed moderately differentiated adenocarcinoma, estrogen receptor-positive, PR-negative, HER2- negative.

After 2 years, she exhibited progression in the liver. A liver biopsy was negative for a PIK3CA mutation.
Mechanisms of Resistance to CDK4/6 Inhibitors

Pandey K, et al.
Int J Cancer 2019;145:1179
BOLERO-2. Cumulative risks for grade ≥ 2 adverse events

Stomatitis

Hyperglycemia / diabetes

Pneumonitis

Fatigue
Frequency of PIK3CA mutations in ER+, HER2- breast cancers

Hortobagyi, JCO, 2016
Men or postmenopausal women with HR+, HER2− ABC
- Recurrence/progression on/after prior AI
- Identified PIK3CA status (in archival or fresh tumor tissuea)
- Measurable disease or ≥ 1 predominantly lytic bone lesion
- ECOG performance status ≤ 1 (N = 572)

1:1, stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

PIK3CA-mutant cohort (n = 341)
- ALP 300 mg PO QD + FUL 500 mg IMb n = 169
- PBO + FUL 500 mg IMb n = 172

PIK3CA-non-mutant cohort (n = 231)
- ALP 300 mg PO QD + FUL 500 mg IMb n = 115
- PBO + FUL 500 mg IMb n = 116

Primary endpoint
- PFS in PIK3CA-mutant cohort (locally assessed)

Secondary endpoints include
- OS (PIK3CA-mutant cohort)
- PFS (PIK3CA-non-mutant cohort)
- PFS (PIK3CA mutation in ctDNA)
- PFS (PIK3CA-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

The primary endpoint included all randomized patients in the PIK3CA-mutant cohort; PFS was analyzed in the PIK3CA-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2−, human epidermal growth factor receptor 2-negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

a More than 90% of patients had mutational status identified from archival tissue.
b Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

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SOLAR-1: Progression-Free Survival Outcomes

Cohort with PIK3CA-Mutated Cancer

Cohort without PIK3CA-Mutated Cancer

No. at Risk
Alpelisib + fulvestrant 169 145 123 97 85 75 62 50 39 30 17 14 3 1 1 0
Placebo + fulvestrant 172 120 89 80 67 58 48 37 29 20 14 9 3 2 0 0

No. at Risk
Alpelisib + fulvestrant 116 110 86 76 48 48 31 29 14 12 7 5 3 0
Placebo + fulvestrant 116 110 79 72 43 42 31 30 20 20 8 5 3 0
Alpelisib: Toxicity Management

Protocol Guidance for Treatment of Hyperglycemia in SOLAR-1

Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.  

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Alpelisib–Fulvestrant Group (N = 284)</th>
<th>Placebo–Fulvestrant Group (N = 287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>282 (99.3)</td>
<td>183 (64.4)</td>
</tr>
<tr>
<td>Hyperglycemia†</td>
<td>151 (63.7)</td>
<td>91 (32.7)</td>
</tr>
<tr>
<td>Diarrhea‡</td>
<td>164 (57.1)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>Nausea‡</td>
<td>127 (44.7)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>101 (35.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Rash‡</td>
<td>101 (35.6)</td>
<td>28 (9.9)</td>
</tr>
<tr>
<td>Vomiting‡</td>
<td>77 (27.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>76 (26.8)</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>70 (24.6)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69 (24.3)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>58 (20.4)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>56 (19.7)</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>52 (18.3)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>51 (18.0)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>50 (17.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Dysgeusa</td>
<td>47 (16.5)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>32 (11.3)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

SOLAR-1: PFS by Prior CDK4/6 Inhibitor Treatment in the PIK3CA-mutant Cohort

With prior CDK4/6 inhibitor therapy

- ALP + FUL (n = 9)
- PBO + FUL (n = 11)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>ALP + FUL</th>
<th>PBO + FUL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>5.5</td>
<td>1.8</td>
</tr>
<tr>
<td>HR, (95% CI)</td>
<td>0.48 (0.17-1.36)</td>
<td>0.67 (0.51-0.87)</td>
</tr>
</tbody>
</table>

Without prior CDK4/6 inhibitor therapy

- ALP + FUL (n = 160)
- PBO + FUL (n = 161)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>ALP + FUL</th>
<th>PBO + FUL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>11.0</td>
<td>6.8</td>
</tr>
<tr>
<td>HR, (95% CI)</td>
<td>0.67 (0.51-0.87)</td>
<td>0.67 (0.51-0.87)</td>
</tr>
</tbody>
</table>

- Previous treatment with any CDK4/6 inhibitor was a stratification factor, but the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Treatment benefit with alpelisib was observed regardless of prior use with a CDK4/6 inhibitor

Juric D et al. San Antonio Breast Cancer Symposium 2018;Abstract GS3-08.
Turner NC, et al.
Lancet 2017;389:2403

Tyrosine kinase

PTEN

PI3K

AKT1

PIP2

PIP3

LKB1

AMPK

TSC2

TSC1

TORC1

mTOR

S6K1

4EBP1

eIF4E

Alpelisib

Capivasertib, ipatasertib, etc

everolimus
AKT Inhibition:
FAKTION: Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant in ER+ MBC

Phase 1b
3+3 design N=9 participants - Capivasertib Starting dose with fulvestrant 500mg: 400mg bd 4 days on / 3 days off
No DLT but 2 withdrawals in 9 participants - Dose not increased to the established single agent dose 480mg bd 4/7

Eligibility
- Post-menopausal women
- ER+/HER2- Metastatic or unresectable LABC
- Prior AI therapy for MBC/LABC with PD or relapse on adjuvant AI
- Maximum 1 line chemotherapy for MBC
- Maximum 3 lines ET for MBC
- Measurable or non-measurable disease
- Controlled type II diabetes allowed

Primary endpoint:
PFS in overall population

Secondary endpoints:
Safety and toxicity
Objective Response rates, CBR and OS: in overall population and pathway activated
Effects of Capivasertib on the PK of fulvestrant

Fulvestrant 500mg q4weeks + loading dose
Placebo bd 4 days on/3 off from C1D15 N=69

Fulvestrant 500mg q4weeks + loading dose
Capivasertib bd 4 days on/3 off from C1D15 N=71

N = 140
FAKTION: PFS ITT and by PI3K/AKT/mTOR pathway activation status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Events</th>
<th>Median (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>2-sided p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant + Placebo</td>
<td>63</td>
<td>4.8 months (3.1 to 7.7)</td>
<td>0.58 (0.39 to 0.84)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fulvestrant + Capivasertib</td>
<td>49</td>
<td>10.3 months (5.0 to 13.2)</td>
<td>2-sided p=0.004</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant + Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulvestrant + Capivasertib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio 0.58 (0.39 to 0.84) 2-sided p=0.004

Jones et al, ASCO 2019
Venetoclax plus tamoxifen in ER+, Bcl-2+ advanced breast cancer

Select adverse events with venetoclax plus tamoxifen in ER+, Bcl-2+ advanced breast cancer

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>&lt;800 mg</th>
<th>800 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=9</td>
<td>n=24</td>
<td>n=33</td>
</tr>
<tr>
<td>Decreased white cell count</td>
<td>8 (89)</td>
<td>21 (88)</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9 (100)</td>
<td>20 (83)</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (56)</td>
<td>19 (79)</td>
<td>24 (73)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (67)</td>
<td>16 (67)</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (56)</td>
<td>8 (33)</td>
<td>13 (39)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (44)</td>
<td>7 (29)</td>
<td>11 (33)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (33)</td>
<td>8 (33)</td>
<td>11 (33)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (22)</td>
<td>7 (29)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Infection (any)</td>
<td>0 (0)</td>
<td>9 (38)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (33)</td>
<td>5 (21)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0 (0)</td>
<td>4 (17)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0)</td>
<td>4 (17)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (33)</td>
<td>3 (13)</td>
<td>4 (12)</td>
</tr>
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</table>
A Phase II Study Comparing The Efficacy Of Venetoclax + Fulvestrant Versus Fulvestrant In Women With Estrogen Receptor-Positive, HER2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy

Eligibility

- ER+
- Not received more than two lines of therapy
- ECOG PS 0-1

Primary endpoint: Complete Response (CR), Partial Response (PR) or Stable Disease (SD).
Secondary endpoints: Progression Free Survival (PFS)