The following section of the CARE™ Perspectives from ASCO 2019 report covers updates breast cancer with a focus on the GIM, MONALEESA-7, and Trans-aTTom Studies.

This section of the report was prepared by:
Dr. Stephen Chia (BC Cancer Agency) - Member of the CARE™ Oncology Faculty.

**ASCO Abstract 504. Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of Gruppo Italiano Mammella (GIM).**

Lucia Del Mastro et al.

**ABSTRACT SUMMARY**

**GIM4 Study Design**

<table>
<thead>
<tr>
<th>Postmenopausal at randomization</th>
<th>R</th>
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<tbody>
<tr>
<td>ER+ and/or PR+</td>
<td>3-2 yrs Letrozole (up to 5 yrs of ET)</td>
<td>Extended 5 yrs Letrozole (up to 7-8 yrs of ET)</td>
</tr>
<tr>
<td>T1-3; N0-N+</td>
<td>No sign of disease recurrence</td>
<td>Tam for 2-3 yrs</td>
</tr>
</tbody>
</table>

N=2056
Recruitment in 64 centres in Italy (GIM group), 2005-2010
Median follow-up: 10.4 years (IQR 8.8-11.4)

- **Primary Study Endpoints:**
  - Invasive Disease Free Survival (DFS)- local recurrence, distant metastases, contralateral or ipsilateral breast tumour, excluding ductal carcinoma in situ, second primary malignancy, death from any cause, and loss to follow-up or end of study
  - Intention- to-treat population: DFS was computed from date of randomization to the date of the event (or last follow-up) in the overall patient population
  - Landmark analysis: patients with a DFS event or lost to follow-up before treatment divergence (2 to 3.3 years after randomization, depending on the duration of pre-random HT) were excluded. DFS was computed from the time of treatment divergence to the date of the event

- **Secondary Study Endpoints:**
  - Overall survival
  - Adverse events

**Results:**

**Disease-Free Survival - ITT population. N=2056**

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tr>
<td>Control</td>
<td>1030</td>
<td>999</td>
<td>979</td>
<td>973</td>
<td>905</td>
<td>731</td>
<td>611</td>
<td>552</td>
<td>485</td>
<td>352</td>
<td>216</td>
<td>135</td>
<td>35</td>
<td>5</td>
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<tr>
<td>Extended</td>
<td>1026</td>
<td>990</td>
<td>963</td>
<td>979</td>
<td>814</td>
<td>759</td>
<td>636</td>
<td>512</td>
<td>397</td>
<td>254</td>
<td>120</td>
<td>38</td>
<td>3</td>
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</tr>
</tbody>
</table>

Median follow up: 10.4 years

- Extended adjuvant treatment with additional 5 years of letrozole is associated with a 19% reduction in iDFS events (HR 0.84; 0.69-1.03; p=0.09) was not statistically significant

**Disease-Free Survival - Landmark analysis. N=1891**

<table>
<thead>
<tr>
<th>Years</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>948</td>
<td>895</td>
<td>844</td>
<td>773</td>
<td>682</td>
<td>552</td>
<td>403</td>
<td>284</td>
<td>175</td>
<td>83</td>
</tr>
<tr>
<td>Extended</td>
<td>943</td>
<td>901</td>
<td>850</td>
<td>788</td>
<td>692</td>
<td>574</td>
<td>451</td>
<td>326</td>
<td>217</td>
<td>80</td>
</tr>
</tbody>
</table>

Time 0 is time when treatment diverged in the two arms (i.e. 2-3 yrs after randomization); *Adjusted HR 0.815, 95% CI 0.66-1.01*

- Landmark analysis which excluded patient before the randomized switch showed a non-statistical trend in favor of iDFS (HR 0.81; 0.35-1.00, p=0.051).
CARE™ FACULTY PERSPECTIVES:

- In the intent to treat population (ITT) – the study did not meet its primary endpoint of a 23% relative risk reduction in iDFS (estimated to be a 4% absolute increase in 8-year DFS).
- There is no difference in overall survival with 10.4 years of median follow-up.
- In all the randomized studies (except MA17R) extending the duration of an adjuvant AI beyond 5 years of adjuvant hormonal therapy (of which at least 2 years was with an AI) did not meet any of the study’s primary endpoints.
- Thus, it is very likely that the benefit of extending adjuvant AIs has a modest to minimal effect at best in a general population.
- We are awaiting genomic assay studies on material collected on these trials that can hopefully demonstrate predictive power for a greater differential benefit in a particular cohort – rather than relying on current prognostic factors (e.g. nodal burden).
ASCO LBA 1008. Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2- advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: Overall survival (OS) results.

Sara A. Hurvitz et al.

ABSTRACT SUMMARY

MONALEESA-7 Study Design
First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients

Stratification Factors
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

Results:
- Safety:
  - The median treatment duration was approximately 2 years in the ribociclib arm and approximately 1 year in the placebo arm
  - After 15 months of additional follow-up, the adverse event profile for the ribociclib arm remained consistent with the known safety profile
  - The rates of grade 3 or 4 adverse events of special interest in the ribociclib and placebo arms, respectively, were:
    - Neutropenia, 63.5% and 4.5%
    - Hepatobiliary toxicity, 11% and 6.8%
    - Prolonged QT interval, 1.8% and 1.2%
  - In patients who received a NSAI (n=495), RIB + ET demonstrated a consistent OS improvement vs PBO + ET (HR, 0.699 [95% CI, 0.535-0.948])

Overall Survival

Landmark Analysis
- 36 months: 71.9% vs 69.6%
- 42 months: 69.2% vs 67.4%

- 29% relative reduction in risk of death
- The P value of 0.00973 crossed the prespecified boundary to claim superior efficacy

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration. *Premenopausal status was defined as either patient had last menstrual period ≤ 12 months or if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range or in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or NH and plasma estradiol levels in normal postmenopausal range). Patients could not be 60 years of age. Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg, and ANA dose was 1 mg. GOS 3.6 mg was administered by subcutaneous injection.
The benefit of ribociclib extends beyond initial treatment based on time to subsequent chemotherapy and PFS 2: (time from randomization to progression on the next line of therapy or death)

**Time to First Subsequent Chemotherapy**

<table>
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<tr>
<th>Months</th>
<th>Ribociclib + ET</th>
<th>Placebo + ET</th>
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</thead>
<tbody>
<tr>
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<td>100</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
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</tbody>
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**Progression-Free Survival 2**

<table>
<thead>
<tr>
<th>Months</th>
<th>Ribociclib + ET</th>
<th>Placebo + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>10</td>
<td>0</td>
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</tbody>
</table>

**No. of Patients Still at Risk**

- Ribociclib: 335
- Placebo: 337

**Kaplan-Meier Estimate**

- 36 months: 67.29% vs. 53.8%
- 42 months: 65.8% vs. 49.0%

**Median time to CT, months**

- Not reached

**HR (95% CI)**

- 0.596 (0.459-0.774)

**CARE™ FACULTY PERSPECTIVES:**

- Over the past 2 decades very little impact has been made in improving overall survival (OS) in ER+/HER2- MBC.
- MONALEESA 7 is the first study to demonstrate an OS benefit in the full study population with a 1st line CDK 4/6 inhibitor and hormonal therapy.
- This study solidifies the recommendation for a CDK 4/6 inhibitor in the 1st line setting.
- Over time we hope this translates to a population based improvement in OS in ER+/HER2- MBC.
- The next important question is what is the next (2nd) line of targeted therapy in combination with hormonal therapy? PIK3CA inhibitor? AKT inhibitor? mTOR inhibitor?
- Genomic alterations (identified by NGS of ctDNA) can potentially identify mechanisms of resistance and possibly match to the next line of targeted therapy.
ASCO Abstract 505. Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence (DR) in patients with HR+ breast cancer treated in the adjuvant tamoxifen—To offer more? (aTTom) trial.

John Bartlett et al.

ABSTRACT SUMMARY

- This study examined the predictive performance of the BCI (H/I) in the EET setting in patients treated in the aTTom trial (a prospective phase III trial that randomized 6953 HR+ women to stop or continue tamoxifen for 5 more years after completing at least 4 years of prior TAM)

Trans-aTTom Study Design

- Planned ~2500 cases
- N0 and N+
- Confirmed HR+
- HER2- or HER2+
- BCI testing
  - Blinded to clinical outcome
- Centralized testing of HR status
  - Blinded to clinical outcome
  - ER, PR, HER2

Interim Analysis

- Planned analysis N' ~1200 HR+
- Prespecified p value stopping boundary: 0.0334

Final Analysis

- Planned analysis N' ~1800 HR+
- Final p value stopping boundary: 0.0336

- Primary and secondary endpoints were recurrence-free interval (RFI) and disease-free interval (DFI), respectively

- Results:

Benefit of Extended Tamoxifen is Dependent on the Classification of BCL (H/I)

All N+ Patients

<table>
<thead>
<tr>
<th>Years</th>
<th>Risk of Recurrence (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk</td>
</tr>
<tr>
<td>5-year</td>
<td>10-year</td>
</tr>
<tr>
<td>5</td>
<td>291</td>
</tr>
<tr>
<td>10</td>
<td>292</td>
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HR: 0.88 (0.65-1.18)  P = 0.398

BCI (H/I)-Low

<table>
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<tr>
<th>Years</th>
<th>Risk of Recurrence (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk</td>
</tr>
<tr>
<td>5-year</td>
<td>10-year</td>
</tr>
<tr>
<td>5</td>
<td>141</td>
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<tr>
<td>10</td>
<td>155</td>
</tr>
</tbody>
</table>

HR: 1.07 (0.69-1.65)  P = 0.768

BCI (H/I)-High

<table>
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<tr>
<th>Years</th>
<th>Risk of Recurrence (%)</th>
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<tbody>
<tr>
<td></td>
<td>No. at risk</td>
</tr>
<tr>
<td>5-year</td>
<td>10-year</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>10</td>
<td>137</td>
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</tbody>
</table>

HR: 0.35 (0.15-0.86)  P = 0.027
These data provide further validation and establish level 1B evidence for BCI as a predictive biomarker for preferential benefit from EET in HR+ breast cancer.

CARE™ FACULTY PERSPECTIVES:

- The BCI is an 11-gene expression molecular signature comprised of two functional panels:
  - Molecular Grade Index (MGI)- 5 genes measuring tumour proliferative status
  - HOXB13 and IL17BR (H/I)- 2 gene ratio measuring estrogen signalling
- The benefit of 10 years of tamoxifen over 5 years is of modest benefit in an overall population of ER+ patients.
- The BCI has predictive ability to identify a cohort (approximately 50% of node positive patients) that derives significantly greater benefit for 5 additional years of tamoxifen.
- Pending a cost effective analyses, the BCI may have clinical utility in the Canadian landscape for our pre-menopausal patients contemplating extended tamoxifen or for our post-menopausal patients whom an AI was intolerant/contra-indicated for extended tamoxifen.
- The BCI should not be used to decide extended adjuvant AI until larger validation studies in appropriate populations (e.g. NSABP B42) are performed.

### Summary of BCI (H/I) Predictive Biomarker of all trials

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Relative Risk Reduction</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment: Adjuvant TAM vs none</strong>&lt;br&gt;Stockholm (n=600)¹&lt;br&gt;H/I-High HR: 0.35 (0.19-0.65); p=0.0005&lt;br&gt;H/I-Low HR: 0.67 (0.36-1.24), p=0.204</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment: Extended AI vs Placebo</strong>&lt;br&gt;MA.17 (n=249)²&lt;br&gt;H/I-High OR: 0.35 (0.16-0.75); p=0.007&lt;br&gt;H/I-Low OR: 0.68 (0.31-1.52), p=0.35</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment: Extended TAM vs Stop</strong>&lt;br&gt;Trans-aTTom N+ (n=583)&lt;br&gt;H/I High HR: 0.35 (0.15-0.86); p=0.027&lt;br&gt;H/I-Low HR: 1.07 (0.69-1.65), p=0.768</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

ASCO 2019: Key Areas of Oncology Covered by the CARE™ Faculty
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The mission of the CARE™ Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

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