DEAR COLLEAGUES

It is my pleasure to present this IBCSG slide set which has been designed to highlight and summarise key findings in breast cancer from the major congresses in 2017. This slide set specifically focuses on the ESMO 2017 Congress and is available in English, French, Italian, German, Spanish and Japanese. The area of clinical research in oncology is a challenging and ever changing environment. Within this environment, we all value access to scientific data and research that helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. I hope you find this review of the latest developments in breast cancer is of benefit to you in your practice. If you would like to share your thoughts with us we would welcome your comments. Please send any correspondence to ibcsgcc@ibcsg.org.

Finally, we are also very grateful to Lilly Oncology for their financial, administrative and logistical support in the realisation of this activity.

Yours sincerely,

Rolf Stahel
President, IBCSG Foundation Council
Contents

• Early stage breast cancer
• Advanced/metastatic breast cancer
  – First line
  – Later lines
Early stage breast cancer
LBA9: Letrozole and palbociclib versus 3rd generation chemotherapy as neoadjuvant treatment of luminal breast cancer. Results of the UNICANCER-NeoPAL study – Cottu P et al

Study objective

- To evaluate letrozole + palbociclib as neoadjuvant treatment in luminal breast cancer

Key patient inclusion criteria

- Newly diagnosed stage II–III BC in postmenopausal women
- Biopsy ER+, HER2–
- Nodal status available
- ER Allred ≥4
- Not candidate for breast conservation (n=184)

Primary endpoint

- Ability to provide RCB 0–1 at surgery, with a null hypothesis of RCB 0–1 observed in at least 20% of the cases (p0 – 0.20)

* Surgery was performed 24 h after the last palbociclib dose

Secondary endpoints

- Efficacy, safety, biomarkers

### Key results

<table>
<thead>
<tr>
<th></th>
<th>Letrozole + palbociclib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95%CI</td>
</tr>
<tr>
<td><strong>Interim analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local RCB 0–1</td>
<td>1 (3.3)</td>
<td>0, 9.8</td>
</tr>
<tr>
<td><strong>Local RCB class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–I</td>
<td>4 (7.7)</td>
<td>0.4, 14.9</td>
</tr>
<tr>
<td>II–III</td>
<td>48 (92.3)</td>
<td></td>
</tr>
</tbody>
</table>

### Safety

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Letrozole + palbociclib (n=53)</th>
<th>Chemotherapy (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 neutropenia</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Grade 4 neutropenia</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>SAEs</td>
<td>2*</td>
<td>17†</td>
</tr>
<tr>
<td>Dose reduction/temporary interruption</td>
<td>10</td>
<td>16 (docetaxel)</td>
</tr>
<tr>
<td>Premature treatment termination</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

*Endometrial carcinoma; neutropenia; †neutropenia events/sigmoid abscess/occlusive syndrome/pyelonephritis/diarrhoea

Key results (cont.)

- Final RCB 0 (pCR) and RCB III rates were similar between treatment arms
  - RCB class 0: 2/52 (3.8%) in letrozole + palbociclib vs. 3/51 (5.9%) in the chemotherapy arm
  - RCB class III: 21/52 (40.4%) in letrozole + palbociclib vs. 24/51 (47.1%) in the chemotherapy arm
- Sharp decreases in Ki67 were observed in both arms (–0.95 for letrozole + palbociclib and –0.86 for chemotherapy)

Conclusions

- This pilot, non-comparative randomized study failed to meet its primary endpoint; patients with high-risk luminal breast cancers demonstrated low pCR rates in both arms
- A similar clinical efficacy was observed in patients who received palbociclib + letrozole and those who received neoadjuvant chemotherapy
- A shared endpoint between chemotherapy and non-chemotherapy in the neoadjuvant setting needs to be defined
- Further studies are required to validate CDKi use as a replacement strategy in these patients

LBA10_PR: Primary results of LORELEI: a phase II randomized, double-blind study of neoadjuvant letrozole (LET) plus taselisib versus LET plus placebo (PLA) in postmenopausal patients (pts) with ER+/HER2-negative early breast cancer (EBC) – Saura C et al

**Study objective**
- To assess neoadjuvant letrozole + taselisib vs. letrozole + placebo in postmenopausal women with ER+/HER2– early breast cancer

**Key patient inclusion criteria**
- Untreated postmenopausal women
- Stage I–III operable BC
- ER+/HER2–
- ≥2 cm tumours by MRI (n=334)

**CO-PRIMARY ENDPOINTS**
- ORR by centrally assessed breast MRI; pCR rate in breast and axilla

**SECONDARY ENDPOINTS**
- ORR and pCR in PIK3CA-mutant patients, Ki67 levels, PEPI score, safety, PRO

LBA10_PR: Primary results of LORELEI: a phase II randomized, double-blind study of neoadjuvant letrozole (LET) plus taselisib versus LET plus placebo (PLA) in postmenopausal patients (pts) with ER+/HER2-negative early breast cancer (EBC) – Saura C et al

Key results

All randomized patients

Odds ratio 1.55
(95%CI 1.00, 2.38; p=0.049)

ORR

Patients with PIK3CA-mutant tumours

Odds ratio 2.03
(95%CI 1.06, 3.88; p=0.033)

pCR

Patients with PIK3CA-mutant tumours

Odds ratio NE
(95%CI NE; p=0.480)

Key results (cont.)

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Letrozole + tasselisib (n=167)</th>
<th>Letrozole + placebo (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE (any grade)</td>
<td>152 (91.0)</td>
<td>139 (83.2)</td>
</tr>
<tr>
<td>≥1 grade 3–4 AE</td>
<td>43 (25.7)</td>
<td>13 (7.8)</td>
</tr>
</tbody>
</table>

Conclusions

- The primary endpoint, ORR by centrally assessed breast MRI in all enrolled patients and patients with PIK3CA mutations, was met
- A significant increase in ORR was demonstrated with treatment with a PI3K selective inhibitor plus ET in ER+/HER2– patients with early BC
  - A more pronounced effect was observed in the PIK3CA-mutation population
- pCR rate was low, but this may be typical of only 4 months of endocrine-based therapy in these patients
- The safety and toxicity profile was satisfactory and manageable
- Further research into the anti-tumour responses observed with this combination is required, which would be facilitated by ongoing comprehensive biomarker analyses

LBA11: Prognostic impact of Recurrence Score (RS), grade/Ki67 central pathological review and anthracycline (A)-free vs. A-containing chemotherapy (CT) on distant and locoregional disease-free survival (DDFS/LRFS) in high clinical risk HER2- early breast cancer (EBC): WSG PlanB trial results – Gluz O et al

**Study objective**

- To compare anthracycline-free vs. anthracycline-containing chemotherapy in high-risk HER2– early BC

**Key patient inclusion criteria**

- pN+ or high risk pN0
- Age ≤75 years
- M0

**Endpoints**

- DDFS, LRFS, DFS

**Key patient inclusion criteria**

- HR–
- HR+ and 0–3 LN and RS>11 or ≥4 LN

**Docetaxel 75 mg/m² + cyclophosphamide 600 mg/m²**

- 6 cycles (n=1222)

**Epirubicin 90 mg/ m² + cyclophosphamide 600 mg/m²**

- (4 cycles) followed by docetaxel 100 mg/m² (4 cycles) (n=1227)

**Endocrine therapy (according to national guidelines)**

- (n=348)

**Key results**

- Patients with RS 0–11 treated by endocrine therapy had 5-year DDFS of 97.8% (pN0: 98%; pN1: 97%)
- In patients with RS 12–25 5-year DDFS was 96.9% and 89.7% in RS >25
- RS was the strongest independent predictor for DDFS in multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coding</th>
<th>Multivariable HR</th>
<th>95%-LCL</th>
<th>95%-UCL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence score</td>
<td>Fractionally ranked (75th to 25th percentile)</td>
<td>2.99</td>
<td>1.75</td>
<td>5.11</td>
<td>0.000</td>
</tr>
<tr>
<td>Nodal status</td>
<td>pN1−3 vs. pN0</td>
<td>2.15</td>
<td>1.26</td>
<td>3.66</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>pN2−3 vs. pN0−1</td>
<td>2.19</td>
<td>1.18</td>
<td>4.06</td>
<td>0.013</td>
</tr>
<tr>
<td>Local grade</td>
<td>Grade 3 vs. grade 1/2</td>
<td>2.50</td>
<td>1.53</td>
<td>4.11</td>
<td>0.000</td>
</tr>
<tr>
<td>Tumour size</td>
<td>T2−4 vs. T1</td>
<td>1.79</td>
<td>1.09</td>
<td>2.94</td>
<td>0.022</td>
</tr>
</tbody>
</table>

- RS was also prognostic for 5-year LRFS (99% in the RS 0–11 and 11–25 groups vs. 98% in the RS >25 group)

**Conclusions**

- Anthracycline-containing chemotherapy had no differential impact on DDFS in this population
- RS, local grade, nodal status and tumour size were independent factors for DDFS

148O: Phase III evaluating the addition of fulvestrant (F) to anastrozole (A) as adjuvant therapy in postmenopausal women with hormone receptor positive HER2 negative (HR+/HER2-) early breast cancer (EBC): Results from the GEICAM/2006-10 study – Ruíz-Borrego M et al

**Study objective**
- To assess anastrozole + fulvestrant compared with anastrozole alone to determine whether complete oestrogen blockade can prevent resistance to aromatase inhibitors in the adjuvant setting

**Key patient inclusion criteria**
- Postmenopausal women
- Stage I, II, IIIA and IIIC invasive BC
- HR+/HER2–
- Received prior surgery ± neo/adjuvant chemotherapy
- WHO PS ≤2

(n=872*)

**Stratification**
- (Neo) adjuvant chemotherapy (yes vs. no)
- Number of positive lymph nodes (0 vs. 1–3 vs. ≥4)
- HR status (both positive vs. one positive)
- Site

**PRIMARY ENDPOINT**
- DFS

**SECONDARY ENDPOINTS**
- Breast cancer-specific survival, time to recurrence, OS, safety

*Study stopped at 872 patients in 2010, after negative results in the FACT trial; †500 mg on Day 0, 250 mg on Day 14 and 28, 250 mg every 28 days for 3 years

148O: Phase III evaluating the addition of fulvestrant (F) to anastrozole (A) as adjuvant therapy in postmenopausal women with hormone receptor positive HER2 negative (HR+/HER2-) early breast cancer (EBC): Results from the GEICAM/2006-10 study – Ruíz-Borrego M et al

Key results

Median follow-up: 6.41 years

<table>
<thead>
<tr>
<th>Events</th>
<th>Anastrozole</th>
<th>Anastrozole + fulvestrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 0.839 (95% CI 0.576, 1.220)</td>
<td>62</td>
<td>49</td>
</tr>
</tbody>
</table>

Disease-free survival probability, %

Log-rank p-value = 0.3569

No. at risk

Anastrozole: 434 425 410 390 372 361 279 99
Anastrozole + fulvestrant: 417 404 376 363 352 338 277 93

Key results (cont.)

- After a median follow-up of 6.41 years:
  - OS was 95.34% in the anastrozole group and 94.81% in the anastrozole + fulvestrant group
  - BC-specific survival was 92.39% in the anastrozole group and 93.17% in the anastrozole + fulvestrant group

Conclusions

- Among patients with early BC, the addition of fulvestrant 250 mg to anastrozole was not associated with a significant increase in DFS
  - It should be noted that recruitment to the study was halted at 872 patients, which was far less than the original target of 2852 patients. Therefore, the sample size may have been insufficient to detect a true difference and underpowered to test the hypothesis of improved outcome when combining anastrozole with fulvestrant
Study objective

- To evaluate the efficacy of neratinib at a 5-year follow-up of the international, multicentre, randomized, double-blind, placebo-controlled phase 3 ExteNET trial

Key patient inclusion criteria

- Early stage HER2+ BC
- IHC3+ or ISH amplified
- Prior adjuvant trastuzumab + chemotherapy
- Lymph node ±, or residual invasive disease after neoadjuvant therapy (n=2840)

Stratification

- Nodal status
- HR status
- Concurrent vs. sequential trastuzumab

5-year follow-up (exploratory) (neratinib, n=1028; placebo, n=1089)

Primary endpoint

- Invasive DFS at 2 years

Secondary endpoints

- DFS-ductal carcinoma in situ (DCIS), time to distant recurrence, DDFS, CNS recurrences, OS, safety

†Patients who consented to re-collection of data; non-consenting patients were censored at their last physical examination

149O: Neratinib after trastuzumab (T)-based adjuvant therapy in early-stage HER2+ breast cancer (BC): 5-year analysis of the phase III ExteNET trial – Martin Jimenez M et al

Key results

**Invasive DFS events by site**

<table>
<thead>
<tr>
<th>Event site</th>
<th>Neratinib (n=1420)</th>
<th>Placebo (n=1420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any invasive DFS event, n (%)</td>
<td>116 (8.2)</td>
<td>163 (11.5)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>91 (6.4)</td>
<td>111 (7.8)</td>
</tr>
<tr>
<td>Local/regional invasive recurrence</td>
<td>12 (0.8)</td>
<td>35 (2.5)</td>
</tr>
<tr>
<td>Invasive ipsilateral breast cancer recurrence</td>
<td>5 (0.4)</td>
<td>7 (0.5)</td>
</tr>
<tr>
<td>Invasive contralateral breast cancer</td>
<td>4 (0.3)</td>
<td>11 (0.8)</td>
</tr>
<tr>
<td>Death without prior recurrence</td>
<td>4 (0.3)</td>
<td>5 (0.4)</td>
</tr>
</tbody>
</table>

**5-year analysis by endpoint**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Estimated event-free rate,* %</th>
<th>Hazard ratio† (95%CI)</th>
<th>p-value‡ (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive DFS</td>
<td>Neratinib (n=1420) 90.2</td>
<td>Placebo (n=1420) 87.7</td>
<td>0.73 (0.57, 0.92)</td>
</tr>
<tr>
<td>DFS with DCIS</td>
<td>89.7</td>
<td>86.8</td>
<td>0.71 (0.56, 0.89)</td>
</tr>
<tr>
<td>DDFS</td>
<td>91.6</td>
<td>89.9</td>
<td>0.78 (0.60, 1.01)</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>91.8</td>
<td>90.3</td>
<td>0.79 (0.60, 1.03)</td>
</tr>
<tr>
<td>CNS recurrences*</td>
<td>1.30</td>
<td>1.82</td>
<td>–</td>
</tr>
</tbody>
</table>

*Event-free rates for all endpoints, except CNS recurrences which is reported as cumulative incidence
†Stratified by randomization factors
‡Gray’s method

Conclusions

- Extended adjuvant neratinib was associated with sustained benefit
  - Five-year results show a 2.5% absolute benefit in the ITT population and a 4.4% absolute benefit in HR+ patients
- Compared with placebo, there was no evidence of long-term toxicity with neratinib
  - No increased symptomatic cardiac toxicity or secondary primary malignancies
  - There were no late-term consequences from neratinib-associated diarrhoea
- The data for OS are expected in 2019
Study objective

- To assess the clinical utility of the 70-gene signature (MammaPrint) in patients with subcentimetric node-negative tumours

Methods

- Patients from the MINDACT study who had node-negative tumours and data on tumour size were divided into two groups
  - T1ab = tumour size ≤1 cm (main analysis population; n=826)
  - T1c-T2-T3 = tumour size >1 cm (control cohort; n=4461)
  - Clinical risk was assessed by a modified version of Adjuvant! Online and classified as low (cL) or high (cH)
  - Genomic risk was assessed with MammaPrint and classified as low (gL) or high (gH)

- Endpoints included
  - Distant metastasis-free survival (distant relapses, deaths)
  - DFS (distant relapses, deaths, local/regional relapse, ipsilateral/contralateral breast cancer or DCIS, secondary cancers)
  - OS (all-cause)
150O_PR: Not all small node negative (pT1abN0) breast cancers are similar: Outcome results from an EORTC 10041/BIG 3-04 (MINDACT) trial substudy – Tryfonidis K et al

Key results

<table>
<thead>
<tr>
<th>cL/gL vs. cL/gH risk in &lt;1 cm tumours at 5 years</th>
<th>Outcome results for discordant patients at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1ab N0</td>
<td>T1ab N0</td>
</tr>
<tr>
<td>cL/gL (n=624) vs. cL/gH (n=196)</td>
<td>CT (n=91) vs. No CT (n=98)</td>
</tr>
<tr>
<td>DMFS</td>
<td>CT (n=189) vs. No CT (n=187)</td>
</tr>
<tr>
<td>Events</td>
<td>Events</td>
</tr>
<tr>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>99.0 (96.6, 99.0)</td>
<td>97.3 (89.4, 99.3)</td>
</tr>
<tr>
<td>97.3 (89.4, 99.3)</td>
<td>13</td>
</tr>
<tr>
<td>94.5 (89.5, 97.1)</td>
<td>91.4 (82.6, 95.9)</td>
</tr>
<tr>
<td>94.3 (89.7, 96.9)</td>
<td>8</td>
</tr>
<tr>
<td>92.3 (83.5, 96.5)</td>
<td>13</td>
</tr>
<tr>
<td>89.6 (82.6, 92.6)</td>
<td>90.4 (84.5, 94.1)</td>
</tr>
<tr>
<td>92.3 (83.5, 96.5)</td>
<td>17</td>
</tr>
<tr>
<td>89.6 (82.6, 92.6)</td>
<td>18</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>95.8 (89.1, 98.4)</td>
<td>9</td>
</tr>
<tr>
<td>96.1 (92.1, 98.1)</td>
<td>5</td>
</tr>
<tr>
<td>98.6 (97.3, 99.3)</td>
<td>98.2 (94.4, 99.4)</td>
</tr>
<tr>
<td>97.2 (93.3, 98.8)</td>
<td>5</td>
</tr>
<tr>
<td>97.2 (93.3, 98.8)</td>
<td>5</td>
</tr>
<tr>
<td>98.6 (97.3, 99.3)</td>
<td>98.2 (94.4, 99.4)</td>
</tr>
<tr>
<td>97.2 (93.3, 98.8)</td>
<td>98.2 (94.4, 99.4)</td>
</tr>
</tbody>
</table>

- There was a trend to an effect with chemotherapy among cL/gH HR+ tumours for DMFS and DFS, but the analysis is underpowered

Conclusions

- Among patients with T1ab node-negative breast cancer:
  - Most were HR+ of luminal A or B subtypes
  - Clinical risk was low
  - Genomic risk was high (present in 24% of tumours)
- Consistent with the MINDACT study, patients with cL/gL had good outcomes regardless of tumour size
  - For T1ab tumours, DMFS and DFS outcomes were better for low genomic risk tumours
- The administration of adjuvant chemotherapy was associated with DMFS and DFS benefit among patients with cL/gH T1ab node-negative tumours and patients with cL/gH HR+ tumours
- Tumour biology is an important consideration in the decision-making process for patients with T1ab/node-negative cancer
Study objective

- To evaluate the impact of trastuzumab and/or lapatinib on the risk of developing TRA and its effect on prognosis in premenopausal patients with HER2+ early BC

Key patient inclusion criteria

- HER2+ early BC
- Premenopausal (n=2862 in this analysis)

ENDPOINTS

- DFS, OS

TRA, treatment-related amenorrhea

**Key results**

- A significant interaction between TRA and hormone receptor status was observed for both DFS and OS ($p_{interaction}$ of 0.009 and 0.002, respectively)

![DFS in HR+ patients](chart1.png)

**DFS in HR+ patients**

- HR 0.64 (95%CI 0.52, 0.79)

![OS in HR+ patients](chart2.png)

**OS in HR+ patients**

- HR 0.53 (95%CI 0.38, 0.74)

**Conclusions**

- No correlation was found between the type of anti-HER2 treatment and TRA rate
- TRA was associated with significant survival benefits (PFS and OS) in patients with HR+/HER2+ early BC

159PD: Neoadjuvant therapy with trastuzumab emtansine and pertuzumab in patients with HER2-positive primary breast cancer (A randomized, phase 2 study; JBCRG-20) – Masuda N et al

Study objective
- To assess the efficacy and safety of trastuzumab emtansine (T-DM1), pertuzumab and tailored response guided therapy in patients with HER2+ primary BC

Key patient inclusion criteria
- HER2+ primary BC
- cT1c–T3, cN0–N1, M0, tumour ≤7 cm (n=206)

PRIMARY ENDPOINT
- pCR rate

SECONDARY ENDPOINTS
- Safety, ORR, breast conservation rate

Note: Based on data from abstract only

*Responders assigned to 4 cycles T-DM1 + pertuzumab were assigned to 2 more cycles (C1); non-responders assigned to 4 cycles FEC (C2)
159PD: Neoadjuvant therapy with trastuzumab emtansine and pertuzumab in patients with HER2-positive primary breast cancer (A randomized, phase 2 study; JBCRG-20) – Masuda N et al

Key results

<table>
<thead>
<tr>
<th>Variable, % (n/N)</th>
<th>Group A (n=51)</th>
<th>Group B (n=52)</th>
<th>Group C1 (n=80)</th>
<th>Group C2 (n=21)</th>
<th>Group C (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate</td>
<td>56.9 (29/51)</td>
<td>71.2 (37/52)</td>
<td>62.5 (50/80)</td>
<td>38.1 (8/21)</td>
<td>57.4 (58/101)</td>
</tr>
<tr>
<td>pCR rate, ER–</td>
<td>76.2 (16/21)</td>
<td>73.9 (17/23)</td>
<td>72.2 (26/36)</td>
<td>33.3 (2/6)</td>
<td>66.7 (28/42)</td>
</tr>
<tr>
<td>pCR rate, ER+</td>
<td>43.3 (13/30)</td>
<td>69.0 (20/29)</td>
<td>54.5 (24/44)</td>
<td>40.0 (6/15)</td>
<td>50.8 (30/59)</td>
</tr>
<tr>
<td>ORR</td>
<td>96.1 (49/51)</td>
<td>86.5 (45/52)</td>
<td>88.8 (71/80)</td>
<td>85.7 (18/21)</td>
<td>88.1 (89/101)</td>
</tr>
<tr>
<td>cCR</td>
<td>47.1 (24/51)</td>
<td>51.9 (27/52)</td>
<td>38.8 (31/80)</td>
<td>38.1 (8/21)</td>
<td>38.6 (39/101)</td>
</tr>
<tr>
<td>Breast conservation rate</td>
<td>52.0 (26/50)</td>
<td>51.9 (27/52)</td>
<td>54.4 (43/79)</td>
<td>38.1 (8/21)</td>
<td>51.0 (51/100)</td>
</tr>
<tr>
<td>Breast conservation rate from planned mastectomy</td>
<td>34.4 (11/32)</td>
<td>38.7 (12/31)</td>
<td>36.7 (18/49)</td>
<td>14.3 (2/14)</td>
<td>31.7 (20/63)</td>
</tr>
</tbody>
</table>

Dose was administered every 3 weeks as adjuvant therapy; ER (+) patients received concurrent endocrine therapy during T-DM1 treatment

Key results (cont.)

- No treatment discontinuation due to AEs was recorded
- Similar drug-related SAEs were observed among all the groups
- There was less drug-related alopecia in group C1 (5.0%) compared with A, B or C2 (81–94%), and less febrile neutropenia in C1 (0%) compared with A, B or C2 (15–33%)

Conclusions

- T-DM1 + pertuzumab in combination with standard TCHP regimen could be more efficacious than TCHP alone and particularly in the ER+ subgroup
- Tailored T-DM1 + pertuzumab may have less toxicity than TCHP with similar efficacy
Study objective

- To evaluate the impact on long-term survival of carboplatin added to neoadjuvant therapy in patients with triple-negative BC and HER2+ early BC

Key patient inclusion criteria

- cT_{2-4} \textit{or}  
- cT_{1c} in N+ triple-negative BC \textit{or}  
- HER2+ (n=595)

Stratification

- Subtype (HER+ vs. triple-negative)

Primary endpoint

- pCR

Secondary endpoints

- DFS, distant DFS (DDFS), OS

**Key results**

- Patients with triple-negative BC randomized to concurrent carboplatin had a better DFS, there was no difference in those with HER2+ BC

![DFS in triple-negative BC patients](image1.png)

Log-rank p=0.0224
+carboplatin vs. –carboplatin HR 0.56
(95%CI 0.34, 0.93)
p=0.0244

![DFS in HER2+ patients](image2.png)

Log-rank p=0.2933
+carboplatin vs. –carboplatin HR 1.34
(95%CI 0.77, 2.34)
p=0.2951

**Conclusion**

- Carboplatin added to anthracycline/taxane-based neoadjuvant chemotherapy improved disease-free survival in patients with triple-negative BC

**Study objective**

- To develop a molecular test that can predict tumour-infiltrating lymphocytes after neoadjuvant chemotherapy and to determine its prognostic value for survival in patients with triple-negative BC

**Key patient inclusion criteria**

- Triple-negative BC treated with neoadjuvant chemotherapy (n=185)

**Training**

- Training sample set to generate a genomic predictor and to assess prognostic value (n=99)

**Independent validation**

- Patients with triple-negative BC (n=185)

**PRIMARY ENDPOINT**

- Association of four-gene signature* with distant relapse-free survival

*HLF, CXCL13, SULT1E1 and GBP1

Key results

- Using regression modelling (LASSO technique), four genes were identified that predicted the extent of lymphocytic infiltration after neoadjuvant chemotherapy:
  - HLF, CXCL13, SULT1E1 and GBP1
- Multivariate Cox analysis performed on the training set revealed that a one-unit increase in the signature value was associated with distant relapse-free survival (HR 0.28; 95%CI 0.13, 0.63; p=0.002)
- In the validation dataset (clinical data of tumour biopsies prior to pre-neoadjuvant chemotherapy), the four-gene signature was significantly associated with distant relapse-free survival in:
  - The entire set (HR 0.29; 95%CI 0.13, 0.67; p=0.004)
  - The subset of patients with residual disease (HR 0.17; 95%CI 0.06, 0.43; p<0.001)
Conclusions

• A four-gene signature was developed that successfully predicted outcomes in patients with triple-negative BC at diagnosis
  – This signature is based on samples taken prior to neoadjuvant chemotherapy and predicts the extent of tumour-infiltrating lymphocytes after neoadjuvant chemotherapy
• These results are promising and the four-gene signature could represent a valuable method by which patients can be identified – at diagnosis – whether they are likely to experience a poor treatment outcome with standard drugs/those who may benefit most from new investigational treatments
Advanced/metastatic breast cancer
Advanced/metastatic breast cancer
Study objective

- To assess the efficacy and safety of abemaciclib as initial therapy in patients with HR+/HER2– advanced BC

Key patient inclusion criteria

- HR+, HER2– advanced BC
- Postmenopausal
- Metastatic or locally recurrent disease with no prior systemic therapy
- If neoadjuvant or adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS ≤1 (n=493)

Stratification

- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

Abemaciclib 150 mg bid (continuous schedule) + anastrozole 1 mg or letrozole 2.5 mg/day (n=328)

Placebo bid (continuous schedule) + anastrozole 1 mg or letrozole 2.5 mg/day (n=165)

Primary endpoint

- PFS (investigator assessed)

Secondary endpoints

- OS, response rates, safety

a Per physician’s choice: 79.1% received letrozole, 19.9% received anastrozole

Key results

<table>
<thead>
<tr>
<th>Response</th>
<th>Abemaciclib + NSAI</th>
<th>Placebo + NSAI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n</td>
<td>328</td>
<td>165</td>
<td>0.002</td>
</tr>
<tr>
<td>ORR, % (95%CI)</td>
<td>48.2 (42.8, 53.6)</td>
<td>34.5 (27.3, 41.8)</td>
<td></td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>5 (1.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit rate, % (95%CI)</td>
<td>78.0 (73.6, 82.5)</td>
<td>71.5 (64.6, 78.4)</td>
<td>0.101</td>
</tr>
<tr>
<td>Patients with measurable disease at BL, n</td>
<td>267</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>ORR, % (95%CI)</td>
<td>59.2 (53.3, 65.1)</td>
<td>43.8 (35.3, 52.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>5 (1.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit rate, % (95%CI)</td>
<td>79.4 (74.5, 84.3)</td>
<td>69.2 (61.3, 77.2)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Conclusions

- PFS and ORR significantly improved following initial treatment with abemaciclib + NSAI in HER2-advanced BC in postmenopausal patients
- Abemaciclib was efficacious across subgroups based on hazard ratios (risk reduction)
- The addition of abemaciclib had a beneficial effect in patients with indicators of poor prognosis. Single-agent endocrine therapy may be a more preferable alternative in patients with long treatment-free interval or bone-only disease
- Abemaciclib dosed on a continuous schedule had a satisfactory safety profile in this patient population
  - Any grade venous thromboembolic events occurred in 4.9% of patients in the abemaciclib arm and 0.6% of patients in the placebo arm
  - Grade 3 and 4 neutropenia was observed in 21.1% of patients, which was not associated with neutropenic fever
  - Grade 3 diarrhoea was observed in 9.5% and generally occurred early. This was managed with antidiarrheal medication and dose adjustment

Advanced/metastatic breast cancer

Later lines
LBA13: Relationship between tumor infiltrating lymphocyte (TIL) levels and response to pembrolizumab (pembro) in metastatic triple-negative breast cancer (mTNBC): Results from KEYNOTE-086 – Loi S et al

Study objective
• To assess the stromal tumour-infiltrating lymphocyte (sTIL) levels in previously treated and untreated mTNBC patient samples as a biomarker of response to PD-1 inhibitors

Key patient inclusion criteria

All patients:
• Centrally confirmed triple-negative BC
• ECOG PS 0–1, LDH <2.5 x ULN
• Tumour biopsy sample
• No radiographic evidence of CNS metastases

Cohort A:
• ≥1 prior systemic treatment for metastatic triple-negative BC with documented PD
• PD-L1 positive or negative

Cohort B:
• No prior systemic treatment for metastatic triple-negative BC
• PD-L1 positive
(n=254)

Pembrolizumab 200 mg q3w
(Cohort A, n=170)
(Cohort B, n=84)

For 2 years until PD/withdrawal/toxicity

PRIMARY ENDPOINTS
• ORR and safety

SECONDARY ENDPOINTS
• DoR, DCR, PFS, OS

LBA13: Relationship between tumor infiltrating lymphocyte (TIL) levels and response to pembrolizumab (pembro) in metastatic triple-negative breast cancer (mTNBC): Results from KEYNOTE-086 – Loi S et al

Key results

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTIL levels by tumour response (ORR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sTIL levels</td>
<td>Responder (n=7)</td>
<td>Non-responder (n=140)</td>
<td>Responder (n=11)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.062</td>
<td>0.009</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CPS, combined positive score

Key results (cont.)

Univariate and multivariate analysis of ORR: combined cohort

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95%CI)</td>
<td>p-value</td>
<td>Odds ratio (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>sTIL level (continuous)</td>
<td>1.029 (1.012, 1.046)</td>
<td>&lt;0.001</td>
<td>1.022 (1.002, 1.041)</td>
<td>0.014</td>
</tr>
<tr>
<td>Cohort (B vs. A)</td>
<td>6.075 (2.358, 16.465)</td>
<td>&lt;0.001</td>
<td>4.191 (1.407, 13.005)</td>
<td>0.005</td>
</tr>
<tr>
<td>LDH concentration (continuous)</td>
<td>0.683 (0.477, 0.896)</td>
<td>0.009</td>
<td>0.688 (0.468, 0.924)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Conclusions

- sTIL levels significantly varied by cohort, time and site of biopsy, and showed a significant positive correlation with PD-L1 expression
- sTIL levels may act as a surrogate of pre-existing anti-tumour immunity and assist in the identification of patients with metastatic triple-negative BC who have a higher chance of responding to pembrolizumab monotherapy
  - sTIL levels, LDH, and cohort were independent predictors of response to pembrolizumab monotherapy

237O: A phase II trial of pan-HER inhibitor poziotinib, in patients with HER2-positive metastatic breast cancer who have received at least two prior HER2-directed regimens: The results of NOV120101-203 trial – Park YH et al

Study objective
• To evaluate the efficacy and safety of poziotinib (an oral pan-HER kinase inhibitor) monotherapy in patients with HER2+ metastatic BC who have progressed after prior HER2-directed therapies

Key patient inclusion criteria
• HER2+ metastatic breast cancer (relapsed or initially stage IV)
• Progressed after ≥2 prior HER2-directed therapies
• ECOG PS 0–2 (n=106)

Poziotinib 12 mg/day* (14-days on/7-days off)

PD/toxicity

Primary endpoint
• PFS

Secondary endpoints
• ORR, OS and safety

*Dose escalation up to 16 mg was allowed at appropriate time point and dose reduction to 8–10 mg were performed according to toxicities

237O: A phase II trial of pan-HER inhibitor poziotinib, in patients with HER2-positive metastatic breast cancer who have received at least two prior HER2-directed regimens: The results of NOV120101-203 trial – Park YH et al

Key results

- At time of data cut-off (median follow-up of 12.2 months), median OS had not been reached; the one-year OS rate was 63%

<table>
<thead>
<tr>
<th>Overall response, n (%)</th>
<th>ORR</th>
<th>ORR (confirmed)</th>
<th>DCR</th>
<th>DCR (confirmed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26 (27.4)</td>
<td>20 (21.1)</td>
<td>71 (74.7)</td>
<td>71 (74.7)</td>
</tr>
</tbody>
</table>

Data cut-off date: 23 February 2017

Median PFS 4.04 months (95%CI 2.96, 4.40)
Key results (cont.)

<table>
<thead>
<tr>
<th>Patients with any SAE, n (%)</th>
<th>Safety (n=106)</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>2 (1.9)</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (0.9)</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (0.9)</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Catheter site pain</td>
<td>1 (0.9)</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1 (0.9)</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>1 (0.9)</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (0.9)</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Fracture</td>
<td>1 (0.9)</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Flank pain</td>
<td>1 (0.9)</td>
<td>Grade 3</td>
</tr>
</tbody>
</table>

Conclusions

- Among heavily-treated patients with HER2+ metastatic breast cancer, poziotinib showed meaningful clinical activity
- Diarrhoea (14.2%), stomatitis (12.3%), rash (3.8%) and dermatitis acneiform (3.8%) were the most common treatment-related AEs (grade ≥3)
- In order to further the understanding of the role of poziotinib in HER2-positive metastatic breast cancer, a biomarker study is being analysed from pre- and on-treatment biopsies

LBA14: Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple negative breast cancer: TONIC-trial – Kok M et al

**Study objective**

- To assess if short-term induction with radiation or chemotherapy modulates the anticancer immune response

**Key patient inclusion criteria**

- Metastatic triple-negative BC
- ≤3 lines of chemotherapy for metastatic disease
- LDH <2x ULN
- Accessible lesion for biopsy
- WHO PS 0–1
- No history of leptomeningeal disease, no symptomatic CNS disease
(n=50)*

**Radiation 3x8 Gy**

**Doxorubicin 15 mg x2**

**Cyclophosphamide 50 mg/day**

**Cisplatin 40 mg/m² x2**

**Biopsy and nivolumab 3 mg/kg q2w until PD**

**No treatment**

**ENDPOINTS**

- PFS (RECIST, iRECIST), ORR, clinical benefit, safety, OS, translational endpoints

**Minimum sample of 10 allows early discontinuation if in cohort ≤30% of the patients respond**

LBA14: Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple negative breast cancer: TONIC-trial – Kok M et al

Key results

<table>
<thead>
<tr>
<th></th>
<th>Total (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best ORR (CR + PR) iRECIST, %</td>
<td>24</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + SD)</td>
<td>26</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
</tr>
<tr>
<td>SD ≥24 weeks</td>
<td>2</td>
</tr>
<tr>
<td>ORR RECIST v1.1, %</td>
<td>22</td>
</tr>
<tr>
<td>Median PFS, months (95%CI)</td>
<td>3.4 (2.5, 3.7)</td>
</tr>
<tr>
<td>Median time to response, months (range)</td>
<td>2.1 (0.5–3.5)</td>
</tr>
<tr>
<td>Median DoR, months (95%CI)</td>
<td>9 (5.5, NA)</td>
</tr>
</tbody>
</table>

Safety

<table>
<thead>
<tr>
<th>Treatment-related AEs</th>
<th>Any grade, n (%)</th>
<th>Grade 3, n</th>
<th>Grade 4, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>During nivolumab (n=53)</td>
<td>43 (81)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Nivolumab after RT (n=11)</td>
<td>9 (82)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nivolumab after docetaxel (n=11)</td>
<td>8 (73)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nivolumab after cyclophosphamide (n=10)</td>
<td>9 (90)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nivolumab after cisplatin (n=10)</td>
<td>9 (90)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nivolumab only (n=11)</td>
<td>8 (73)</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Grade 4 AEs (n=3) were asymptomatic increases in amylase/lipase/yGT. Grade 5 AE (n=1) was death NOS

Key results (cont.)

• 1-year OS in patients with CR/PR was 83% compared with 13% in those with PD

Conclusions

• This is the first study that investigated immune induction using radiotherapy or chemotherapy
• In metastatic triple-negative BC, nivolumab after a short immune induction is feasible, with promising response rates
• Further studies are required to evaluate the priming effect of radiotherapy and chemotherapy on the tumour microenvironment
Study objective

- To evaluate niraparib + pembrolizumab combination treatment in patients with advanced or metastatic triple-negative BC or recurrent ovarian cancer.

Key patient inclusion criteria

- Advanced or metastatic triple-negative BC
- ≤4 lines prior cytotoxic therapy
- [Or epithelial ovarian, fallopian tube, or primary peritoneal cancer with platinum-resistant disease]

Dose level 1: Niraparib 200 mg + pembrolizumab 200 mg

Dose level 2: Niraparib 300 mg + pembrolizumab 200 mg

Endpoint assessment

**PRIMARY ENDPOINTS**

- ORR (RECIST)

**SECONDARY ENDPOINTS**

- Safety and tolerability

Key patient inclusion criteria

- Advanced or metastatic triple-negative BC
- ≤2 lines prior cytotoxic therapy*
- [Or high-grade serous or endometroid ovarian, fallopian tube, or primary peritoneal cancer with platinum-resistant disease]

RP2D: Niraparib 200 mg (escalation to niraparib 300 mg after two cycles allowed) + pembrolizumab 200 mg

Endpoint assessment

**PRIMARY ENDPOINT**

- ORR (RECIST)

**SECONDARY ENDPOINT**

- Safety and tolerability

*Adjuvant and/or neoadjuvant therapies are not counted in the number of lines of therapy.

1143PD: Dose-finding combination study of niraparib and pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC) or recurrent platinum-resistant epithelial ovarian cancer (OC) (TOPACIO/Keynote-162) – Konstantinopoulos P et al

Key results

• In phase 1, the recommended dose for niraparib was determined to be 200 mg/day
• As of August 2017, 47 patients with triple-negative BC have been enrolled in phase 2

Conclusions

• In combination with pembrolizumab 200 mg IV, the recommended oral phase 2 dose of niraparib was established as 200 mg/day, increasing to 300 mg after cycle 2 in patients with no haematological toxicities
• Preliminary activity data are encouraging with no new safety signals