Breast cancer, early stage

Chair(s) S. Delaloge (Villejuif, France) C. Palmieri (Liverpool, United Kingdom)

Session Poster Discussion session

Type

Details  ESMO 2014, 27.09.2014, 12:45 - 13:45, Pamplona

258PD - Investigating the clinical relevance of genomic characteristics in luminal A and B breast cancer (BC)

V. Kotoula (Athens, Greece) F. Zagouri (Athens, Greece) E. Timotheadou (Athens, Greece)
Z. Alexopoulou (Athens, Greece) R. Wirtz (Cologne, Germany) A. Lyberopoulou (Athens, Greece)
S. Lakis (Athens, Greece) H. Gogas (Athens, Greece) E. Charalambous (Athens, Greece)
G. Pentheroudakis (Athens, Greece) D. Pectasides (Athens, Greece) A. Koutras (Athens, Greece)
P. Papakostas (Athens, Greece) C. Christodoulou (Athens, Greece) P. Kosmidis (Athens, Greece)
K. Kalogeras (Athens, Greece) G. Fountzilas (Athens, Greece)

Aim
To address the major challenge of understanding the clinical relevance of the increasingly available large amount of tumour genomic data in BC.

Methods
Histologically reviewed, paraffin tumour DNA samples (N = 1092) from patients who had received anthracycline-based adjuvant chemotherapy in the frame of two randomized trials by HeCOG (HE10/00, pre-trastuzumab; HE10/05, post-trastuzumab era), were investigated with targeted massively parallel sequencing (Ion Torrent systems) for variants in 58 genes implicated in BC. Upon multiple stringent quality filters, pathogenic mutations (mut) and allelic imbalance (AI) were evaluable in 844 cases (77.3%). IHC4 was used for BC subtyping.

Results
Mut were observed in 499 and AI in 497 tumors (59%), reaching up to 55 and 20 affected genes in single tumours, respectively. Mut and AI often coexisted (p < 0.0001), while AI was positively related to nodal status (p = 0.0241). Mut were more frequent in TP53 (25%, excluding non-pathogenic p.P72R), PIK3CA (24.6%), GATA3 (8.8%), CDH1 (6.3%), MLL3 (5.5%), ARID1B (5.1%), TBX3 (5.1%) and PTEN (4.7%), while AI in EGFR (51.2%), TERT (41.4%), TP53 (40.8%), CASP8 (33.5), PARP2 (32.5%), GATA3 (28.9%), and BRCA1 (22.2%). TP53mut were more frequent in triple-negative and HER2-enriched BC (45% each), while PIK3CAmut (32%) in luminal A tumours (p < 0.0001). In luminal HER2-negative tumours, TP53mut were significantly associated with shorter disease-free survival (DFS) (log-rank, p = 0.0032), aggravating the prognosis of patients with any nodal status (p < 0.0001), irrespective of Ki67 status that was used for distinguishing between luminal A and B subtypes. In these luminal HER2-negative tumours, AI in less than 6 genes in the presence of PIK3CAmut conferred the longest, while AI in more than 6 genes in the absence of PIK3CAmut the shortest DFS (p = 0.0156); this AI/PIK3CAmut combination was associated with worse prognosis in patients with 0-3 positive nodes, which fared similarly to those with higher nodal involvement (p < 0.0001).
Conclusions
Combined assessment of AI and mutation status may provide useful prognostic information in patients with luminal A and B tumours treated with adjuvant anthracycline-based chemotherapy.

Disclosure
R. Wirtz: Dr R.W. has pending patent applications; G. Fountzilas: On behalf of the Hellenic Foundation for Cancer Research, Prof. G.F. has pending patent applications. All other authors have declared no conflicts of interest.

259PD - The 12-gene DCIS score assay and quantitative ER, PR, and HER2 across histologic subtypes: Experience in the first 2 years

A. Sing (Redwood City, United States of America) V. Tan (Redwood City, United States of America) H. Bailey (Redwood City, United States of America) J. Anderson (Redwood City, United States of America) M. Rothney (Redwood City, United States of America) F. Baehner (Redwood City, United States of America)

Aim
The 12-gene DCIS Score has been validated to predict 10yr risk of local recurrence (DCIS or invasive) (Solin et al, JNCI, 2013). Here we report the Clinical Laboratory experience in the first 2 yrs of assay availability for the score results, quantitative gene expression and results of the assay across histologic subtypes.

Methods
3045 patient (pt) samples from 12/11 to 1/14 were processed for DCIS score. The DCIS score is based on the validated algorithm using 7 of 16 cancer-related genes from the 21-gene assay. Low, intermediate, and high risk groups are defined as scores of <39, 39-54, and ≥55, respectively. Descriptive statistics for the score and single gene values for ER, PR, and HER2 were used. Positive cutoffs: ≥6.5 for ER; ≥5.5 for PR, and for HER2, ≥11.5 is positive, equivocal is 10.7 to 11.4, < 10.7 is negative.

Results
Of 3045 samples, 2264 (74%) were excisions and 781 (26%) were cores; median age was 60y (21-94). The mean DCIS Score was 29 (0-97) with a mean score result of 29 for excisions and 29 for cores. 2064 (68%) were low, 495 (16%) were intermediate, and 486 (16%) were high. Mean ER, PR, and HER2 levels were 9.6, 7.5, and 9.9, respectively, and similar between excisions and cores. A range of DCIS Score results were observed for each histologic subtype with the highest mean values observed in samples with >50% comedo necrosis (mean = 47) and solid (mean = 34) subtypes, although none of the scores were in the high risk category.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Distribution (%)</th>
<th>Mean DCIS Score (range)</th>
<th>Mean ER</th>
<th>Mean PR</th>
<th>Mean HER2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cribriform</td>
<td>1202 (39)</td>
<td>22 (0-90)</td>
<td>9.9</td>
<td>7.8</td>
<td>9.7</td>
</tr>
<tr>
<td>Solid</td>
<td>1053 (35)</td>
<td>34 (0-96)</td>
<td>9.4</td>
<td>7.2</td>
<td>9.9</td>
</tr>
<tr>
<td>DCIS with ≥50% comedo necrosis</td>
<td>345 (11)</td>
<td>47 (0-97)</td>
<td>8.4</td>
<td>6.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Papillary</td>
<td>281 (9)</td>
<td>17 (0-90)</td>
<td>10.9</td>
<td>8.6</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Micropapillary  146 (5)  26 (0-88)  9.4  7.3  10.0
Apocrine  11 (0.4)  26 (4-53)  7.6  6.0  9.7

Conclusions
In the first 2 yrs, there were > 3000 samples submitted for the 12-gene DCIS score assay. The proportion of score results that were low, intermediate and high was similar to the validation study. The mean DCIS score result between core bx and excision was also similar supporting assay use on cores. The overall experience shows that the score results reflect underlying biology differently than histology and are informative for guiding treatment decisions.

Disclosure
All authors have declared: Genomic Health, Inc. - employee and stock ownership

260PD - Chemosensitivity predicted by MammaPrint and BluePrint in the prospective Neo-adjuvant Breast Registry Symphony Trial (NBRST)

F. De Snoo (Amsterdam, Netherlands) P. Whitworth (Nashville, United States of America)
L. Stork-Sloots (Amsterdam, Netherlands) P. Beitsch (Dallas, United States of America)

Aim
The aim of the NBRST study is to compare a multi-gene classifier to conventional IHC/FISH subtyping to predict chemosensitivity as defined by pathological complete response (pCR), or endocrine sensitivity as defined by partial response (PR).

Methods
The study includes women with histologically proven breast cancer, who will receive neo-adjuvant chemotherapy (NCT) or neo-adjuvant endocrine therapy (NET). BluePrint in combination with MammaPrint classifies patients into four molecular subgroups: Luminal A, Luminal B, HER2 and Basal.

Results
426 patients had definitive surgery. 37/211 (18%) IHC/FISH HR + /HER2- patients were re-classified by BluePrint as Basal (35) or HER2 (2). 53/123 (43%) IHC/FISH HER2+ patients were re-classified as Luminal (36) or Basal (17). 4/92 (4%) IHC/FISH triple negative (TN) patients were re-classified as Luminal (2) or HER2 (2). NCT pCR rates were 2% in Luminal A and 7% Luminal B patients versus 10% pCR in IHC/FISH HR + /HER2- patients. The NCT pCR rate was 53% in BluePrint HER2 patients. This is significantly superior (p = 0.047) to the pCR rate in IHC/FISH HER2+ patients (38%). The pCR rate of 36/75 IHC/FISH HER2+ /HR+ patients re-classified as BPLuminal is 3%. NCT pCR for BluePrint Basal patients was 49/140 (35%), comparable to the 34/92 pCR rate (37%) in IHC/FISH TN patients.

Conclusions
BluePrint/MammaPrint molecular subtyping reclassifies 22% (94/426) of tumors, reassigning more responsive patients to the HER2 and Basal categories while reassigning less responsive patients to the Luminal category. These findings suggest that compared with IHC/FISH, BluePrint/MammaPrint more accurately identifies patients likely to respond (or not respond) to neo-adjuvant chemotherapy.

Disclosure
F. De Snoo: Employee of Agendia; L. Stork-Sloots: Employee of Agendia. All other authors have declared no conflicts of interest.

261PD - The effect of physician’s characteristics on adjuvant chemotherapy (CT) decisions for early stage HR +, HER2- breast cancer (BC) patients (pts)

M. De Laurentiis (Naples, Italy) M. Aapro (Genolier, Switzerland) C. Markopoulos (Athens, Greece)
T. Mamounas (Orlando, United States of America) R. Rouzier (Paris-Saint-Cloud, France)
C. Thomsson (Halle (Saale), Germany) J. Bargallo Rocha (Mexico City, Mexico)
D. Rea (Birmingham, United Kingdom) P. Neven (Leuven, Belgium) B. Linderholm (Gothenburg, Sweden)
V. Smit (Leiden, Netherlands) L. Landherr (Budapest, Hungary) A. Petrovsky (Moscow, Russian Federation)
C. Svedman (Stockholm, Sweden) M. Martin Jimenez (Madrid, Spain)

Aim
For early stage HR +, HER2- BC pts with intermediate risk by clinical/pathologic criteria, treatment decisions should be based on sensitivity to endocrine therapy, risk of recurrence, and predicted benefit from CT. The ESMO guidelines highlight that multigene assays (MGA) may be used in these cases (Ann Oncol. 2013;suppl6:vi7-23). The MAGIC survey evaluated criteria considered for CT decisions and simulated CT recommendations for pts with different characteristics. We present CT recommendations for intermediate-risk BC pts based on characteristics of respondents.

Methods
The online survey was completed by physicians working in multidisciplinary BC teams, having ≥5 year experience. A conjoint analysis was used to model CT recommendations for simulated pts.

Results
Overall recommendations (n = 911, 52 countries) showed that BC pt profiles associated with a request for more information tended to have an intermediate/high age (>50 yr), intermediate/small tumor size, grade 1/2, low ER/intermediate Ki67 expression, and node-negative status. The table summarizes CT recommendations for 4 selected intermediate-risk BC pts. On average, CT was recommended for the 4 pt profiles by 29%, 42%, 31%, and 44% of responders. CT recommendation varied greatly among different countries for each pt profile. Physicians who always use international guidelines tended to prescribe CT more often, while those who use MGA, as expected, recommended CT less frequently for each pt profile. More-experienced physicians (ie, those who prescribe CT personally or who treat >200 pts/year) showed a slight trend to fewer CT recommendations.

Conclusions
There is high variation in CT recommendations for intermediate-risk BC pts, primarily according to country of residence. There is a need for more broadly available tools, such as MGA, to help make more-informed treatment decisions in this pt population.

<table>
<thead>
<tr>
<th>Selected MAGIC survey respondent</th>
<th>Patient profile 1</th>
<th>Patient profile 2</th>
<th>Patient profile 3</th>
<th>Patient profile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(age 35–50, tumor size 1–2 cm)</td>
<td>(age 35–50, tumor size 1–2 cm)</td>
<td>(age 51–70, tumor size 2.1–3 cm)</td>
<td>(age 51–70, tumor size 2.1–3 cm)</td>
<td></td>
</tr>
<tr>
<td>Groups recommending CT for selected patient profiles</td>
<td>Tumor grade 2, high ER, high PR, 14%–20% Ki67, node negative</td>
<td>Tumor grade 2, high ER, low PR, 14%–20% Ki67, node negative</td>
<td>Tumor grade 2, high ER, high PR, 14%–20% Ki67, node negative</td>
<td>Tumor grade 2, high ER, low PR, 14%–20% Ki67, node negative</td>
</tr>
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<td>-----------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>All physicians (excluding pathologists, n = 877)</td>
<td>29%</td>
<td>42%</td>
<td>31%</td>
<td>44%</td>
</tr>
<tr>
<td>All physicians – range between countries with &gt;30 respondents</td>
<td>15%–41%</td>
<td>33%–50%</td>
<td>14%–48%</td>
<td>28%–56%</td>
</tr>
<tr>
<td>Physicians personally prescribing CT (n = 610)/not prescribing CT (n = 267)</td>
<td>27%/31%</td>
<td>42%/44%</td>
<td>30%/34%</td>
<td>43%/46%</td>
</tr>
<tr>
<td>Physicians treating 1–50 pts per year (n = 310)/ &gt; 200 pts per year (n = 86)</td>
<td>32%/26%</td>
<td>45%/38%</td>
<td>36%/26%</td>
<td>49%/38%</td>
</tr>
<tr>
<td>Physicians always (n = 31%)/often (n = 482)/using international guidelines</td>
<td>45%/39%</td>
<td>34%/27%</td>
<td>47%/40%</td>
<td></td>
</tr>
<tr>
<td>Physicians using (n = 487)/not using (n = 390) MGA</td>
<td>26%/31%</td>
<td>39%/46%</td>
<td>29%/34%</td>
<td>41%/48%</td>
</tr>
<tr>
<td>Medical oncologist (n = 485)/surgeons or gynecologists (n = 324)/radiation oncologists (n = 38)</td>
<td>27%/30%/32%</td>
<td>42%/42%/46%</td>
<td>30%/32%/33%</td>
<td>45%/44%/46%</td>
</tr>
<tr>
<td>Physicians working in an academic hospital (n = 540)/community-based or private hospital (n = 240)/office-based or private practice (n = 77)</td>
<td>29%/27%/34%</td>
<td>42%/43%/45%</td>
<td>31%/31%/36%</td>
<td>43%/47%/47%</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; PR, progesterone receptor

Disclosure
M. De Laurentiis: Advisory board: Genomic Health; M. Aapro: Advisory board: Genomic Health Corporate-sponsored research: Genomic Health; C. Markopoulos: Other
substantive relationships: Genomic Health – Speaker's Honoraria; T. Mamounas: Advisory board: Genomic Health Inc. Other substantive relationships: Speaker's Bureau: Genomic Health Inc.; R. Rouzier: Advisory board: consultant for Genomic Health; C. Thomssen: Advisory board: Genomic Health Other substantive relationships: Speaker for Genomic Health; D. Rea: Advisory board: Genomic Health; B. Linderholm: Board of directors: Steering Committee for the BIG/EORTC/NABCG Male breast cancer project; V. Smit: Advisory board: Genomic Health Inc.; C. Svedman: Other substantive relationships: I am an employee of Genomic Health working in the medical department. All other authors have declared no conflicts of interest.

Invited discussant abstracts 258PD, 259PD, 260PD and 261PD

S. Delaloge (Villejuif CEDEX, France)

Questions to Discussant

262PD - Docetaxel + trastuzumab +/- non-pegylated liposomal doxorubicin +/- bevacizumab in the neoadjuvant treatment of early, HER2-positive breast cancer: First results of ABCSG-32

G. Steger (Vienna, Austria) R. Greil (Salzburg, Austria) M. Hubalek (Innsbruck, Austria)
M. Fridrik (Linz, Austria) C. Singer (Vienna, Austria) R. Bartsch (Vienna, Austria) M. Balic (Graz, Austria)
P. Dubsky (Vienna, Austria) D. Egle (Innsbruck, Austria) S. Gampenrieder (Salzburg, Austria)
G. Pfeiler (Vienna, Austria) D. Mayr (Linz, Austria) T. Czech (Innsbruck, Austria)
G. Rinnerthaler (Salzburg, Austria) A. Petzer (Linz, Austria) P. Sevelda (Vienna, Austria)
A. Lang (Feldkirch, Austria) M. Rudas (Vienna, Austria) S. Frantal (Vienna, Austria)
M. Gnant (Vienna, Austria)

Aim

ABCSG-32 was designed to evaluate the cardiac toxicity of bevacizumab (B) and non-pegylated liposomal doxorubicin (N) when added to docetaxel + trastuzumab (DH) in the neoadjuvant treatment of early, HER2-positive breast cancer (BC) within a randomized phase II trial. Secondary aims were to evaluate the non-cardiac safety and the efficacy of the 4 drug combinations as measured by the rates of pathological complete responses (pCR).

Methods

100 patients (pts) with biopsy-proven, invasive, early, HER2-pos breast cancer were stratified according to major risk factors including estrogen-receptor-status, histology, grading, and center and were randomized to receive 6 cycles (q 21 days) of either D100 mg/m² + H8/6 mg/kg (DH, n = 25), DH + B15 mg/kg (DHB, n = 25), D75H + N 50 mg/m² (DHN, n = 26), or D75HN + B 15 mg/m² (DHNB, n = 24). All pts received pegfilgrastim 6 mg sc on day 2. Left ventricular (LV) ejection fraction (EF) was measured at baseline, before each treatment cycle, and before surgery. A cardiac toxicity event (CTE) was defined as the occurrence of either symptomatic LV dysfunction NYHA II-IV, or an asymptomatic drop of EF (adEF) of >15% from baseline, or an adEF <50%, or
the appearance of significant arrhythmias requiring treatment. The trial was designed to detect a difference in the incidence of CTE of 8% in the control group (DH) vs. 44% in each of the experimental groups (power: 80%, two-sided alpha: 0.05).

Results

Cardiac toxicity was low with a CTE in only 3 pts (DH: 0, DHB: 1, DHN: 1, DHNB: 1). Non-cardiac toxicity/patient as evaluated by the incidence of serious adverse events (SAE, n = 50) and significant safety events (SSE, n = 114) was acceptable (SAE: DH: 8, DHB: 12, DHN: 14, DHNB: 16; SSE: DH: 23, DHB: 31, DHN: 29, DHNB: 31). No differences in the incidence of non-serious AE and no new safety signals for B and N were detected. In 8 pts the treatment was terminated early (DH: 0, DHB: 3, DHN: 2, DHNB: 3). The overall rate of pCR was 52% (DH: 36%, DHB: 50%, DHN: 63%, DHNB: 62%).

Conclusions

Our data show that neoadjuvant DH, DHB, DHN, and DHNB can be safely administered to pts with HER2-positive early BC. Cardiac toxicity is low when 6 cycles are given and non-cardiac toxicity is acceptable but higher during the 3/4-drug combinations leading to the early termination of treatment in some patients. All regimens tested are highly effective with pCR-rates >60% after DHN and DHNB.

Disclosure

G.G. Steger: Research grants, travel grants, advisory boards, and honoraria from Hoffmann La Roche, Roche Austria, Cephalon, TEVA/Ratiopharm, and Amgen; R. Greil: Research Support and advisory boards from Roche, Amgen, Ratiopharm/Teva, Cephalon; M. Hubalek, M.A. Fridrik, C. Singer, M. Balic, P. Dubsky, D. Mayr, P. Sevelda, A. Lang and S. Frantal: Research grants from Roche Austria, Cephalon, TEVA/Ratiopharm, Amgen; R. Bartsch: Research grants, lecture honoraria, travel support from Roche Austria, lecture honoraria Teva/Ratiopharm; D. Egle: Travel grants and honoraria from Roche Austria and TEVA/Ratiopharm; S.P. Gampenrieder: Research Support and travel Support from Roche and Amgen; G. Pfeiler: Honoraria and travel grants from Novartis, Amgen, Roche Austria; T. Czech: Travel Support from Roche Austria; G. Rinnerthaler: Research Support and travel Support from Roche and Amgen; A.L. Petzer: Research grants from Roche Austria, Cephalon, TEVA/Ratiopharm, Amgen, advisory boards and honoraria from Roche Austria, M. Gnant: Research and travel grants, advisory boards and honoraria from Roche Austria, Cephalon, TEVA/Ratiopharm, Amgen. All other authors have declared no conflicts of interest.

263PD - Time to initiation of adjuvant chemotherapy in patients with rapidly proliferating early breast cancer

A. Farolfi (Meldola, Italy) E. Scarpi (Meldola, Italy) A. Schirone (Meldola, Italy) S. Bravaccini (Meldola, Italy) R. Maltoni (Meldola, Italy) L. Ciecconetto (Meldola, Italy) S. Sarti (Meldola, Italy) P. Serra (Meldola, Italy) D. Amadori (Meldola, Italy) A. Rocca (Meldola, Italy)

Aim

The optimal time from surgery to commencing chemotherapy in early breast cancer (EBC) remains unclear. We assessed the influence of time to initiation of adjuvant chemotherapy (TTC) on the outcome of EBC patients enrolled onto a phase III clinical
Methods
The relationship between TTC, calculated as the time (in weeks) from definitive surgery to initiation of adjuvant chemotherapy, and disease-free (DFS) or overall survival (OS) was assessed in 1066 EBC patients with rapidly proliferating tumors (thymidine labeling index > 3% or G3 or Ki67 > 20%), randomized to receive adjuvant chemotherapy with or without anthracyclines (epirubicin → CMF vs CMF → epirubicin vs CMF). DFS, OS and their 95% confidence intervals (95% CI) were calculated by the Kaplan-Meier method. Multivariate Cox analysis was performed in relation to nodal involvement, estrogen receptor and HER2 status, Ki67 value, type of adjuvant chemotherapy, menopausal status and tumor size.

Results
Information on TTC was available for 713 women. At a median follow-up of 105 months (range 2-188), a prolonged TTC resulted in a significant increase of 16% in the risk of relapse (95% CI 1.03–1.30, p = 0.016) in a multivariable Cox regression model (Table 1). The impact on OS was not significant. Using a backward elimination procedure, TTC, tumor size and nodal involvement remained significantly associated with DFS (Hazard ratio [HR] = 1.15, 95% CI 1.02-1.29, p = 0.018; HR = 1.44, 95% CI 1.08-1.92, p = 0.012; HR = 1.44, 95% CI 1.08-1.92, p = 0.012, respectively). Again, nodal involvement and Ki67 were associated with OS (HR = 1.66, 95% CI 1.11-2.49, p = 0.014; HR = 1.63, 95% CI 1.03-2.59, p = 0.039, respectively).

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th></th>
<th>OS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>TTC</td>
<td>1.16 (1.03–1.30)</td>
<td>0.016</td>
<td>1.14 (0.97–1.35)</td>
<td>0.121</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.97–1.02)</td>
<td>0.829</td>
<td>0.99 (0.96–1.03)</td>
<td>0.615</td>
</tr>
<tr>
<td>ER Positive</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>ER Negative</td>
<td>1.20 (0.89–1.61)</td>
<td>0.242</td>
<td>1.20 (0.78–1.84)</td>
<td>0.397</td>
</tr>
<tr>
<td>HER2 Positive</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HER2 Negative</td>
<td>0.99 (0.73–1.33)</td>
<td>0.929</td>
<td>0.92 (0.60–1.42)</td>
<td>0.713</td>
</tr>
<tr>
<td>Lymph node status Negative</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Lymph node status Positive</td>
<td>1.53 (1.14–2.04)</td>
<td>0.004</td>
<td>1.71 (1.13–2.59)</td>
<td>0.011</td>
</tr>
<tr>
<td>Menopausal status Premenopausal</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Menopausal status Postmenopausal</td>
<td>1.32 (0.85–2.04)</td>
<td>0.219</td>
<td>1.56 (0.82–2.97)</td>
<td>0.177</td>
</tr>
<tr>
<td>Tumor size</td>
<td>&lt;2cm 1.00</td>
<td></td>
<td>≥2 cm 1.41 (1.05–1.88)</td>
<td>0.020</td>
</tr>
</tbody>
</table>
### Conclusions

Our results suggest that patients with rapidly proliferating EBC should be treated as soon as possible once their recovery from surgery is complete.

### Disclosure

All authors have declared no conflicts of interest.

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**264PD - GAIN2: Adjuvant phase III trial comparing an intensified dose-dense adjuvant therapy with EnPC compared with a dose-dense, dose-adapted therapy with dtEC dtDocetaxel in patients with primary breast cancer and a high risk of recurrence**

S. Noeding (Hannover, Germany) H. Forstbauer (Rheinsieg, Germany)
G. Wachsmann (Böblingen, Germany) A. Ober (Limburg, Germany) A. Schneeweiss (Heidelberg, Germany)
B. Christensen (Neuruppin, Germany) E. Von Abel (Schwäbisch-Gmünd, Germany)
E. Grischke (Tübingen, Germany) H. Höffkes (Fulda, Germany) P. Klare (Berlin, Germany)
Y. Ko (Bonn, Germany) S. Schmatloch (Kassel, Germany) N. Burchardi (Neu-Isenburg, Germany)
S. Loibl (Neu-Isenburg, Germany) G. Von Minckwitz (Neu-Isenburg, Germany) V. Möbus (Frankfurt, Germany)

**Aim**

Combined chemotherapy requires compromises in terms of dosage and treatment interval due to toxicities. The sequential administration of monotherapies allows high doses of single substances and dose-dense intervals. So far, such regimens have proved to be very effective in early breast cancer with high risk of recurrence. Nab-paclitaxel (nP) leads to a more favorable toxicity profile and greater efficacy compared with solvent-based taxanes.

**Methods**

The GAIN2 study compares toxicity and efficacy of a pre-defined dose-dense high-dose regimen (EnPC) with a dose-dense regimen, where single doses are adjusted depending on individual haematological and non-haematological toxicities (dtEC-dtD). Primary endpoint is the invasive disease-free survival in patients with primary node-positive or high-risk node-negative breast cancer.

Two safety interim analyses after 200 and 900 patients who have completed chemotherapy are planned. The results of the first safety analysis will be presented. In addition to the standard analyses for haematological and non-haematological toxicities, any affections of the cranial nerves as well as the rate of macular degeneration and anaphylactic reactions are of special interest.

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Ki67 ≤20%</th>
<th>Ki67 &gt;20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E»CMF</td>
<td>0.72 (0.49–1.04)</td>
<td>0.079 0.69 (0.41–1.16)</td>
</tr>
<tr>
<td>CMF»E</td>
<td>0.79 (0.55–1.14)</td>
<td>0.202 0.75 (0.45–1.25)</td>
</tr>
<tr>
<td>CMF</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
In terms of hematological adverse events, the rate of febrile neutropenia grade 3-4 (14% vs. 5%) and thrombocytopenia grade 3-4 (14% vs. 5%) was significantly increased in the EnPC arm. As for the non-haematological side effects, there were significantly more patients developing anorexia (grade 1-4) in the EnPC arm. There were no differences between the treatment arms for the toxicities of special interest. In the EnPC arm, 28% required dose-reductions due to hematological toxicities compared with only 11% in the dtEC dtD arm (p = 0.002). The dose could be escalated to the maximum in half of the patients receiving dtEC dtD. In 7% of women a reduction was required in the 4th cycle of docetaxel.

Conclusions
Due to similar toxicity profiles, the study will be continued without changes.

Disclosure
A. Schneeweiss: Honoraria, Research Funding and Advisory Role: Celgene and Roche; G. von Minckwitz: Honoraria and Research Funding: Amgen, Celgene and Roche; V. Möbus: Honoraria and Research Funding: Amgen, GSK, Sanofi-Aventis, Pfizer, Roche. All other authors have declared no conflicts of interest.

265PD - Ten-year safety and efficacy analyses of the BIG 02-98 phase III trial with an exploratory analysis on the role of Ki67 in predicting benefit of adjuvant docetaxel in ER positive patients

Aim
The BIG 2-98 is a randomized phase III trial that tested the effect of adding docetaxel with anthracycline-based adjuvant chemotherapy (CT) in women with node-positive breast cancer (BC). here we present the 10 year safety and efficacy analyses and report an exploratory analysis of the predictive value of Ki67 for docetaxel efficacy.

Methods
In total, 2,887 patients with node positive BC were randomly assigned to one of four treatments: (I) sequential control: doxorubicin (A, 75 mg/m2) × 4 → CMF; (II) concurrent control: AC × 4 → CMF; (III) A × 3 → docetaxel (T, 100 mg/m2) × 3 → CMF and (IV) : AT (50/75 mg/m2) × 4 → CMF. The primary objective was to evaluate the efficacy of docetaxel regardless of the schedule on disease free survival (DFS). Secondary objectives were toxicity, DFS between sequential arms and concurrent arms, and overall survival (OS). Ki67 expression was centrally evaluated by immunohistochemistry. Tumours with Ki67 ≥14% were considered to have a high proliferation index.

Results
After a median follow-up 10.1 years (max 12.9 years) and 1,072 DFS events, docetaxel treatment did not improve DFS or OS compared to control arms (DFS: HR = 0.91, 95%
CI = 0.81-1.04; P = 0.16; OS: HR = 0.88, 95% CI = 0.76-1.03; P = 0.11). Similar results were obtained in secondary comparisons where sequential docetaxel was compared with sequential control (DFS: HR = 0.86, 95% CI = 0.72-1.03, P = 0.1; OS: HR = 0.85, 95% CI = 0.68-1.06; P = 0.15) or with concurrent doxorubicin–docetaxel (DFS: HR = 0.88, 95% CI = 0.7-1.01; P = 0.09; OS: HR = 0.84, 95% CI = 0.7-1.01; P = 0.06). Worsening or development of treatment-related neurotoxicity following completion of adjuvant chemotherapy occurred in 1.6% and 1% of patients in the docetaxel and non-docetaxel-based regimens, respectively. Out of 1,492 patients with ER positive BC, central Ki67 evaluation was performed in 1,198 (80.2%), of whom 892 (74.4%) had Ki67 ≥ 14%. In a multivariate model, there was a trend for improved DFS and OS in patients with high Ki67 and treated with docetaxel (HR = 0.79, 95% CI = 0.63-1.01; P = 0.05 and HR = 0.76, 95% CI = 0.57-1.01; P = 0.06 respectively).

Conclusions
At a median follow-up of 10 years, the DFS benefit previously demonstrated with docetaxel is no longer present in node-positive BC patients. However, an exploratory analysis suggested a benefit of docetaxel in patients with highly proliferative ER-positive BC.

Disclosure
P. Francis: Travel support from Sanofi; J.P. Crown: Received research funding and speaking honoraria from Sanofi Aventis; M. Piccart: Board member: PharmaMar Consultant (honoraria): Amgen, Astellas, AstraZeneca, Bayer, Eli Lilly, Invivis, MSD, Novartis, Pfizer, Roche-Genentech, sanofi Aventis, Symphogen, Synthon, Verastem Research grants to my Institute: most companies. All other authors have declared no conflicts of interest.

Invited discussant abstracts 262PD, 263PD, 264PD and 265PD
C. Palmieri (London, United Kingdom)

Questions to Discussant