Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)

Gunter von Minckwitz, Sibylle Loibl, Andreas Schneeweiss, Christophe Salat, Eric Hahnen, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens Uwe Blohmer, Hans Tesch, Fariba Khandan, Peter Fasching, Christian Jackisch, Rita Schmutzler, Valentina Nekljudova, Michael Untch

for the

GBG/AGO-B study groups
Subtype Specific Targeted Therapy

N=595 centrally confirmed TNBC or HER2-positive breast cancer

PM

PMCb

Subtype Specific Targeted Therapy

Non-pegylated liposomal doxorubicin 20 mg/m² q1w

Carboplatin AUC 1.5* q1w

Lapatinib 750 mg/d 18 wks

*reduced from AUC 2 at amendment 1 after enrolment of 330 patients

Primary Endpoint: pCR

ypT0 ypN0

P=0.107

( Level for significance α = 0.2 )

PM
N=293

PMCb
N=295

von Minckwitz et al. Lancet Oncology 2014
Effect of Carboplatin in Patients with TNBC

3 yr DFS 85.8%
3 yr DFS 76.1%

San Antonio Breast Cancer Symposium – December 8-12, 2015

pCR Rates by gBRCA Status and Carboplatin Treatment in Patients with TNBC

ypT0 ypN0

OR 2.09 (1.24-3.53)  P=0.005
OR 1.60 (0.52-4.93)  P=0.413

33.1%  50.8%  50.0%  61.5%
Mean 41.9%  Mean 55.7%  Δ 17.7%  Δ 11.5%

von Minckwitz G et al., ASCO 2014, updated data; E. Hahnen in prep.
Conclusion

- Carboplatin induces a significantly (HR=0.56, p=0.035) improved disease-free survival in patients with TNBC but not in patients with HER2-positive disease (HR 1.33, p=0.372) (Interaction Test p=0.046).
- Survival effect of carboplatin was correctly predicted by its effect on pCR, supporting surrogacy of pCR in case of large pCR differences (like NOAH trial).
- Addition of carboplatin appeared more relevant (pCR and DFS) for patients with wt gBRCA. We hypothesize that the DNA damaging effect of non-pegylated doxorubicin is already sufficient in highly DNA instable mutant gBRCA tumors, so that no additional effect of carboplatin can be demonstrated in this subgroup. The potential impact of bevacizumab in GeparQuinto will be elucidated by P. Fasching on Friday at 10.45 am.
- Prognostic information of pCR was confirmed also in patients with mt gBRCA.
- Overall, survival analysis of the GeparSixto study support the use of carboplatin as part of neoadjuvant treatments in patients with TNBC.

Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance)

William M Sikov, Donald A Berry, Charles M Perou, Baljit Singh, Constance T Cirrincione, Sara M Tolaney, George Somlo, Elisa R Port, Rubina Qamar, Keren Sturtz, Eleftherios Mamounas, Mehra Golshan, Jennifer R Bellon, Deborah Collyar, Olwen M Hahn, Lisa A Carey, Clifford A Hudis, Eric P Winer for the CALGB/Alliance
CALGB 40603: Schema – Randomized Phase II

Arm

A

Paclitaxel 80 mg/m² wkly x 12  
Surgery
XRT*

B

Paclitaxel 80 mg/m² wkly x 12  
Bevacizumab 10 mg/kg q2wks x 9

C

Paclitaxel 80 mg/m² wkly x 12  
Carboplatin AUC 6 q3wks x 4

D

Paclitaxel 80 mg/m² wkly x 12  
Carboplatin AUC 6 q3wks x 4  
Bevacizumab 10 mg/kg q2wks x 9

*MD discretion

2 X 2 Randomization

Research biopsies-frozen and fixed

CALGB 40603 – OS by pCR Breast/Axilla

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CALGB 40603 – EFS for carboplatin vs. not

**CALGB 40603 – EFS for bevacizumab vs. not**

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CALGB/Alliance 40603: Conclusions

- Achievement of a pCR with weekly paclitaxel followed by ddAC +/- carboplatin and/or bevacizumab is associated with significant improvements in EFS and OS
  - Substantial reductions are seen in both LRR and DR
  - Inferior outcomes are seen in clinical stage III disease with failure to achieve a pCR and in clinically node-positive patients with persistently positive axillary LNs after NACT
- Results are consistent with the FDA-requested meta-analysis
- EFS and OS Hazard Ratios were lower for pCR Breast/Axilla than for pCR Breast, but the addition of RCB I patients did not diminish the prognostic significance of achieving pCR Breast/Axilla

CALGB/Alliance 40603: Conclusions

- Our study was underpowered to determine whether the increases in the pCR rates seen with the addition of carboplatin and bevacizumab improve EFS or OS

- Previous studies (BEATRICE, E5103, GeparQuinto, NSABP B-40) have failed to demonstrate improvements in long-term outcomes (EFS, RFS or OS) in stage I-III TNBC with the addition of bevacizumab to a control (neo)adjuvant chemotherapy regimen
CALGB/Alliance 40603: Conclusions

• Results from other completed (GeparSixto) and ongoing (BrighTNess, NRG-003) studies in the neoadjuvant and adjuvant settings should help to clarify whether the addition of carboplatin benefits patients with early stage TNBC

• Despite the significantly higher pCR rates seen in CALGB 40603, neither carboplatin nor bevacizumab have been shown to improve RFS or OS when administered as part of neoadjuvant therapy in stage II-III TNBC

Comparison of 12 weeks neoadjuvant Nab-Paclitaxel combined with Carboplatinum vs. Gemcitabine in triple-negative breast cancer: WSG-ADAPT TN randomized phase II trial


West German Study Group, Moenchengladbach; Bethesda Hospital, Moenchengladbach; University Hospital Schleswig-Holstein, Campus Lübeck; Institut of Pathology, MHH, Hanover; University Hospital Tübingen; Oncological practice Troisdorf; Clinics Rotkreuz, Munich; Clinics Hettewald, Cologne; MarienHospital Witten, Gynecological Practice, Hildenham, University Hospital, Essen; St. Elisabeth Clinics, Cologne, University Hospital Charite, Berlin, Diakonie Clinics, Hamburg, Clinics Essen-Mitte, Hospital Mutterhaus, Trier; Evangelical Waldkrankenhaus, Berlin, St. Antonius Hospital, Eschweiler, Institute of Pathology, Vierns Ludwig Maximilian University Clinics Munich
Adjuvant Dynamic marker-Adjusted Personalized Therapy trial (ADAPT)

umbrella trial, n ~ 5,000

Prognosis
HR+
HER2+
TN
Subtype-specific therapy
3 weeks

Efficacy
Low risk + good response:
endocrine therapy (ET)
EFS

HR+
HER2+
TN

Risk assessment
Avoiding over- and undertreatment
Early-response markers / pCR surrogates
Novel drugs

Efficacy
High risk + poor response:
Chemotherapy → ET

Pertuzumab, T-DM1:
efficacy w/o chemotherapy
pCR

Added efficacy of platinum;
nab-paclitaxel; PARPi

Recurrence Score
Proliferation
additional biomarkers
RS
Proliferation Biomarkers

WG AM06 Principal Investigators: Nadia Harbeck (LKP), Munich; Ulrike Nitz, Mönchengladbach, Germany.

ADAPT HR-/HER2-:
Trial Design

Standard chemotherapy (4xEC) recommended after surgery / 12-week biopsy (in case of clinical non-pCR)

Endpoint
pCR vs. pCR

Surgery or biopsy*

1 2 3 4 5 6 7 8 9 10 11 12

EOT

pCR vs. pCR

nab-Paclitaxel
125 mg/m²
Carboplatin
AUC2

Gemcitabine
1000 mg/m²

Proliferation
3 weeks therapy

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### ADAPT HR-/HER2-

#### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nab-Pac/Gem</th>
<th>Nab-Pac/Carbo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>182</td>
<td>154</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>50 (26-75)</td>
<td>52 (29-76)</td>
</tr>
<tr>
<td><strong>cT</strong></td>
<td>68 (37.4%)</td>
<td>57 (37%)</td>
</tr>
<tr>
<td>≥2</td>
<td>114 (62.6%)</td>
<td>97 (62.9%)</td>
</tr>
<tr>
<td><strong>cN</strong></td>
<td>135 (74.2%)</td>
<td>113 (73.4%)</td>
</tr>
<tr>
<td>≥1</td>
<td>47 (25.8%)</td>
<td>41 (26.6%)</td>
</tr>
<tr>
<td><strong>Ki-67</strong></td>
<td>median</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Central grade 3</strong></td>
<td>172 (94.5%)</td>
<td>140 (90.9%)</td>
</tr>
</tbody>
</table>

### ADAPT HR-/HER2-

#### Pathological complete response

![Graph showing PCR rate comparison between A and B treatments](image)

- **A (nab-Pac+Gem):** 28.7%
- **B (nab-Pac+Carbo):** 45.9%
- **PCR rate:** 67/146

*p<0.001*
ADAPT HR-/HER2-:
Conclusions

• Nab-Pac/Carbo is associated with less toxicity and significant superiority to Nab-Pac/Gem in terms of pCR
• Early morphological changes seem to be predictive for pCR, irrespective of treatment arm
• No predictive factors for carboplatin efficacy have been identified so far; further correlative analyses (e.g. subtypes, family history, BRCA1-ness etc.) are ongoing
• Validation of these results in larger studies seems warranted

BRCA mutations, therapy
response and prognosis in the neoadjuvant GeparQuinto Study.


for the
GBG/AGO-B study groups
HER2-negative part

if NC: went to non-responder part

- EC
- Doc
- Surgery (d28-d35 after last Bev infusion)

E: Epirubicin 90 mg/m²
C: Cyclophosphamide 600 mg/m²
Bev: Bevacizumab 15 mg/kg

(all 3 week cycles)

Surgery

Core biopsy

Sonography

ECBev

DocBev

Bevacizumab – N=202 (42.9%)
Bevacizumab + N=187 (39.7%)

BRCA1/2 Mutations and distribution over treatment arms

471 patients, TNBC with BRCA1/2 successful genotyping

- BRCA1/2 wildtype N=389 (82.6%)
- BRCA1/2 mutation N=82 (17.4%)
  - 69 BRCA1, 13 BRCA2

Bevacizumab – N=47 (10.0%)
Bevacizumab + N=35 (7.4%)
Results: BRCA1/2 mutations and pCR in all analyzed TNBC

- Results seem to be consistently similar for BRCA1 and BRCA2 mutation carriers, when analyzed separately, however very small sample sizes

![Graph showing pCR rates for BRCA1/2 mutations](image)

- pCR (ypT0 ypN0) rate (%)
  - BRCA1/2 Mutations: 30.8% vs. 50.0%
  - p-value = 0.001

- pCR (ypT0/is ypN0) rate (%)
  - BRCA1/2 Mutations: 36.0% vs. 53.7%
  - p-value = 0.004

Results exploratory analysis pCR according to randomization arms

- p (interaction) = 0.1912
Conclusion

- Patients with *BRCA1* or *BRCA2* mutations have significantly higher pCR rates after a neoadjuvant chemotherapy.

- The effect seems to be stronger in patients treated with bevacizumab.

- *BRCA1/2* mutations had a marginal effect on prognosis.

- The effect of pCR on prognosis was smaller in patients with a *BRCA1/2* mutation, than in patients with wildtype genotype, but test for interaction was not significant.

- Taken the results from GeparSixto into consideration (von Minckwitz et al., Presentation S3-04), effects of *BRCA1/2* mutation status on pCR and prognosis might be highly dependent on given therapies.

Persistence of circulating tumor cells in high risk early breast cancer patients during follow-up care suggests poor prognosis:
Results from the adjuvant SUCCESS A trial

Wolfgang Janni, Brigitte Rack, Peter A Fasching, Lothar Haeberle, Thomas WP Friedl, Hans Tesch, Ralf Lorenz, Julia Neugebauer, Julian Koch, Bernadette Jaeger, Tanja Fehm, Volkmar Mueller, Andreas Schneeweiss, Werner Lichtenegger, Matthias W Beckmann, Christoph Scholz, Klaus Pantel, Elisabeth Trapp
SUCCESS A – study design

First randomization:
3 cycles FEC100 followed by 3 cycles docetaxel vs. 3 cycles FEC100 followed by 3 cycles docetaxel plus gemcitabine

Second randomization:
2 years vs. 5 years of zoledronate

Blood sampling for CTC assessment

- Before chemotherapy
- After chemotherapy
- After 2 years
- After 5 years

Endocrine treatment:
- Tamoxifen 20 mg qid p.o. x 2a (plus Goserelin 3.6 mg depot x 2a in premenopausal pts)
- Anastrozole 1 mg qid p.o. x 3a in postmenopausal pts (Tam in premenopausal pts)

Patient characteristics

- 3754 patients with high-risk early breast cancer (defined as pN1-3, or pT2-4, or G3, or hormone receptor negative, or age ≤ 35) randomized for SUCCESS A
- Data from 1087 patients with CTC determination both before and two years after chemotherapy available for analysis
- No significant differences with regard to patient and tumor characteristics between the 1087 patients included and the remaining 2667 patients (all p > 0.05)
FT2 von mir hinzugefügt...
Friedl Thomas, 12/1/2015
Results I: Prevalence of CTCs after two years

198 (18.2%) of the 1087 patients with at least one CTC in the blood two years after adjuvant chemotherapy (median 1 CTC, range 1 – 99 CTCs)

Results IV: Prognostic value of CTCs assessed two years after adjuvant chemotherapy
Results V: Subgroups – CTC status before and two years after adjuvant chemotherapy

Summary

- 198 (18.2%) of 1087 patients with at least one CTC in the blood two years after adjuvant chemotherapy
- Presence of CTCs two years after adjuvant chemotherapy is a significant independent prognostic factor for poor OS and DFS
- Patients with CTCs both before and two years after adjuvant chemotherapy had worst survival outcome
- The prognostic value of the presence of CTCs two years after chemotherapy was not evident for patients with HER2-positive tumors (but no significant interaction between presence of CTCs two years after adjuvant chemotherapy and biological subtype)
VM14    Da die Beschriftung eher an die Kurven, ist so nicht schnell genug zu erfassen denke ich
Volkmar Müller, 11/30/2015

FT4    sehe ich problematisch - ich wüsste nicht, wie man die Beschriftungen zu den Kurven platziert ohne dass es sehr unübersichtlich wird...
Friedl Thomas, 12/1/2015
A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04)

Capecitabine for RESidual cancer as Adjuvant Therapy

San Antonio Breast Cancer Symposium, December 8-12, 2015

Lee S-J¹, Toi M², Lee E-S³, Ohtani S⁴, Im Y-H⁵, Im S-A⁶, Park B-W⁷, Kim S-B⁸, Yanagita Y⁹, Takao S¹⁰, Ohno S¹¹, Aogi K¹², Iwata H¹³, Kim A¹⁴, Sasano H¹⁵, Yokota J¹⁶, Ohashi Y¹⁷ and Masuda N¹⁸

¹Yeungnam University Hospital; ²Kyoto University Hospital; ³National Cancer Center; ⁴Hirosima City Hospital; ⁵Samsung Medical Center; ⁶Seoul National University Hospital; ⁷Severance Hospital, Yonsei University College of Medicine; ⁸Asan Medical Center; ⁹Gunma Prefectural Cancer Center; ¹⁰Hyogo Cancer Center; ¹¹National Kyusyu Cancer Center; ¹²NHO Shikoku Cancer Center; ¹³Aichi Cancer Center; ¹⁴Korea University Guro Hospital; ¹⁵Tottori University; ¹⁶Kyoto Prefectural University of Medicine; ¹⁷Chuo University and ¹⁸NHO Osaka National Hospital

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CREATE-X: Trial Design

HER2-

NAC  Surgery

Pathology
Non-pCR or node +

Control: Standard therapy

Standard therapy + Capecitabine

R

(n=900)

Stratification factors:
ER, Age, NAC, ypN, SFU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment
Capecitabine Therapy

Capecitabine (X): 2,500 mg/m²/day, po, day 1-14
Repeat every 3 weeks for 8 cycles

According to the safety interim analysis of the first 50 pts treated with 6 cycles of X, the IDMC recommended extending X to 8 cycles.

Compliance of capecitabine

<table>
<thead>
<tr>
<th></th>
<th>Total (N=439)</th>
<th>Cases planned for 6 cycles (N=159)</th>
<th>Cases planned for 8 cycles (N=280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion</td>
<td></td>
<td>92 (58.0)</td>
<td>106 (37.9)</td>
</tr>
<tr>
<td>Reduction</td>
<td></td>
<td>38 (23.9)</td>
<td>104 (37.1)</td>
</tr>
<tr>
<td>Discontinued</td>
<td></td>
<td>29 (18.2)</td>
<td>70 (25.0)</td>
</tr>
<tr>
<td>RDI* (%) Mean (SD)</td>
<td></td>
<td>87.9 (21.6)</td>
<td>79.1 (29.0)</td>
</tr>
</tbody>
</table>

* RDI: Relative dose intensity
Safety

<table>
<thead>
<tr>
<th>≥G3 (N, %)</th>
<th>Capecitabine arm (N=440)</th>
<th>Control arm (N=445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia *</td>
<td>29 (6.6)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Diarrhea *</td>
<td>13 (3.0)</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>

- significantly higher in the capecitabine arm (Neutropenia: p<0.001, Diarrhea: p=0.004)
- All grade incidence is significantly higher in the capecitabine arm as below,
  - Leucopenia, Neutropenia, Anemia, Thrombocytopenia
  - Elevated AST/ALT, Total bilirubin
  - Appetite loss, Diarrhea, Stomatitis and Fatigue

Ohtani S, et al. SABCS2013MP3-12-03

Overall Survival

- 5yr OS
  - 94.0% Capecitabine
  - 89.2% Control
  - 83.9% Control

HR (95%CI) 0.60 (0.40-0.92)

One-sided p<0.01
Conclusions

- After standard neoadjuvant chemotherapy containing A and/or T, postoperative adjuvant use of capecitabine improved DFS significantly in HER2-negative primary breast cancer patients with pathologically proven residual invasive disease.
- OS was significantly improved by capecitabine adjuvant therapy for non-pCR or node-positive patients after NAC.
- The balance of benefit and toxicity would favor the use of capecitabine in the post-NAC situation, but prediction for the therapeutic benefit needs to be investigated further.
- The cost-effectiveness analysis will be carried out.
Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase Ib JAVELIN Solid Tumor trial

Luc Y. Dirix1, Istvan Takacs2, Petros Nikolinakos3, Guy Jerusalem4, Hendrik-Tobias Arkenau5, Erika P. Hamilton6, Anja von Heydebreck7, Hans-Jürgen Grote7, Kevin Chin8, Marc E. Lippman9

1Sint Augustinus-University of Antwerp, Antwerp, Belgium; 2Semmelweis University, Budapest, Hungary; 3University Cancer & Blood Center, LLC, Athens, Georgia, United States; 4CHU Sart Tilman Liège and Liège University, Liège, Belgium; 5Sarah Cannon Research Institute, London, United Kingdom; 6Sarah Cannon Research Institute, Nashville, Tennessee, United States; 7Merck KGaA, Darmstadt, Germany; 8EMD Serono, Bilance, Massachusetts, United States; 9University of Miami Miller School of Medicine, Miami, Florida, United States


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Avelumab* (MSB0010718C)


* Avelumab is the proposed international nonproprietary name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C).

• Fully human anti-PD-L1 IgG1 antibody
• Binds PD-L1
  – Inhibits PD-1/PD-L1 interactions
  – Leaves PD-1/PD-L2 pathway intact
• Half-life ≈4-5 days; >95% TO over whole 2-week dosing period at 10 mg/kg dose
• ADCC may contribute to activity, as shown in preclinical models
• Doses up to 20 mg/kg Q2W safely administered
• Antitumor activity in patients with lung, gastric, ovarian, bladder, and other malignancies, all unselected for PD-L1 expression

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Phase Ib cohort expansion

- Standard 3 + 3 dose escalation
- Phase Ib dose: 10 mg/kg Q2W

MBC, Small cell lung cancer; MBC, NSCLC 1L, CRPC; NSCLC, NSCLC 1L; NSCLC, NSCLC 2L; CRC, CRC; ACC, ACC; CRC, CRC; CRC, CRC; CRPC, CRPC; MBC, MBC; MBC, MBC; Ovarian, Ovarian; ACC, ACC; ACC, ACC; Mesothelioma, Mesothelioma; Other, Other; Mesothelioma, Mesothelioma; Urothelial, Urothelial; Urothelial, Urothelial; RCC, RCC; RCC, RCC; RCC, RCC; Gastric/GEJ 3L, Gastric/GEJ 3L; Gastric/GEJ 3L, Gastric/GEJ 3L; Ovarian, Ovarian; platinum-refract, platinum-refract; Urothelial post-platinum, Urothelial post-platinum; SCCHN post-platinum, SCCHN post-platinum.

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Demographics and disease characteristics of patients with TNBC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>52.5 (31.0-80.0)</td>
</tr>
<tr>
<td>Gender, n (%) Female</td>
<td>58 (100.0)</td>
</tr>
<tr>
<td>ECOG PS, n (%) 0</td>
<td>33 (56.9)</td>
</tr>
<tr>
<td>1</td>
<td>25 (43.1)</td>
</tr>
<tr>
<td>Subsite of tumor, n (%) Ductal</td>
<td>36 (62.1)</td>
</tr>
<tr>
<td>Lobular</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma, NOS</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>Other*</td>
<td>16 (27.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td># of prior regimens for LA/M disease, excluding (neo-)adjuvant, n [%]† ≥3</td>
<td>13 (22.4)</td>
</tr>
<tr>
<td>2</td>
<td>16 (27.6)</td>
</tr>
<tr>
<td>≤1</td>
<td>29 (50.0)</td>
</tr>
<tr>
<td>Median time since diagnosis of metastatic disease, months (range)†</td>
<td>13.2 (0.7, 176.8)</td>
</tr>
</tbody>
</table>

* Other denotes patients who were uncoded (11) or other histology (5).† Regimen for LA/M disease may have included hormonal therapy, either alone or in combination with chemotherapy.‡ Data cut-off date: February 27, 2015.

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Potentially immune-related, treatment-related toxicity

<table>
<thead>
<tr>
<th>Patients with any event</th>
<th>Treatment-related, potentially immune-related TEAEs, n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>17 (10.1)</td>
</tr>
<tr>
<td>Autoimmune hepatitis*</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>

* Autoimmune hepatitis temporarily resolved with medical treatment, but led to discontinuation in 2 patients; the third patient who experienced autoimmune hepatitis died of acute liver failure in a setting of progressive liver failure.

Antitumor activity of avelumab in patients with MBC

<table>
<thead>
<tr>
<th>Best overall response*</th>
<th>Overall population (n=168)</th>
<th>Patients with TNBC (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>7 (4.2)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>SD†, n (%)</td>
<td>39 (23.2)</td>
<td>13 (22.4)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>106 (63.1)</td>
<td>38 (65.5)</td>
</tr>
<tr>
<td>Non-evaluable‡, n (%)</td>
<td>15 (8.9)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>4.8 (2.1, 9.2)</td>
<td>8.6 (2.9, 19.0)</td>
</tr>
<tr>
<td>DCR§, %</td>
<td>28.0</td>
<td>31.0</td>
</tr>
</tbody>
</table>

* Unconfirmed best overall response according to RECIST 1.1
† Stable disease at the first post-baseline tumor assessment after 6 weeks was required to qualify for a BOR of SD
‡ Non-evaluable includes ‘missing’ and ‘not assessable’
§ DCR is defined as responses + SD

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• Median duration of F/U: 10.0 months (range, 6.0-15.2 months)
• Median time to response: 11.4 weeks (range, 5.7-17.7 weeks)
• Median DoR: 28.7 weeks (95% CI: 6.1, ne)
• Responses observed in patients with different molecular subtypes
• Response ongoing in 5/8 patients at time of analysis

Tumor shrinkage by ≥30% was observed in 16 patients (9.5%) in overall MBC population, including 2 patients with PD by RECIST who had PRs by modified irRC

17.2% (10/58) of TNBC patients had tumor shrinkage of ≥30%

* Number of patients with baseline tumor assessment and ≥1 post-baseline assessment.
Percent change from baseline in TNBC population (n=46*)

![Graph showing percent change from baseline in TNBC population.]

* Number of patients with baseline tumor assessments and ≥1 post-baseline assessment.

ORR according to molecular subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n/N1 (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>5/58 (8.6)</td>
<td>2.9, 19.0</td>
</tr>
<tr>
<td>HER2-/ER+ or PR+</td>
<td>2/72 (2.8)</td>
<td>0.3, 9.7</td>
</tr>
<tr>
<td>HER2+</td>
<td>1/26 (3.8)</td>
<td>0.1, 19.6</td>
</tr>
</tbody>
</table>

* N1 = total number of patients in subgroup.

- Five of 8 responders had TNBC (62.5%)
- Responses also achieved by patients in other subtypes
# PD-L1 expression status according to molecular subtype

<table>
<thead>
<tr>
<th>PD-L1 expression (total evaluable=136)*</th>
<th>Molecular subtype (evaluable, n)</th>
<th>PD-L1+, n/N1† (%)</th>
<th>PD-L1–, n/N1 † (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1% tumor cells cut-off</td>
<td>TNBC (48)</td>
<td>33/48 (68.8)</td>
<td>15/48 (31.2)</td>
</tr>
<tr>
<td></td>
<td>HER2-/+ or PR+ (56)</td>
<td>31/56 (55.4)</td>
<td>25/56 (44.6)</td>
</tr>
<tr>
<td></td>
<td>HER2+ (21)</td>
<td>15/21 (71.4)</td>
<td>6/21 (28.6)</td>
</tr>
<tr>
<td>≥5% tumor cells cut-off</td>
<td>TNBC (48)</td>
<td>13/48 (27.1)</td>
<td>35/48 (72.9)</td>
</tr>
<tr>
<td></td>
<td>HER2-/+ or PR+ (56)</td>
<td>4/56 (7.1)</td>
<td>52/56 (92.9)</td>
</tr>
<tr>
<td></td>
<td>HER2+ (21)</td>
<td>5/21 (23.8)</td>
<td>16/21 (76.2)</td>
</tr>
<tr>
<td>≥25% tumor cells cut-off</td>
<td>TNBC (48)</td>
<td>2/48 (4.2)</td>
<td>46/48 (95.8)</td>
</tr>
<tr>
<td></td>
<td>HER2-/+ or PR+ (56)</td>
<td>1/56 (1.8)</td>
<td>55/56 (98.2)</td>
</tr>
<tr>
<td></td>
<td>HER2+ (21)</td>
<td>0/21 (0.0)</td>
<td>21/21 (100.0)</td>
</tr>
<tr>
<td>≥10% immune cell “hotspots” cut-off</td>
<td>TNBC (48)</td>
<td>9/48 (18.8)</td>
<td>39/48 (81.2)</td>
</tr>
<tr>
<td></td>
<td>HER2-/+ or PR+ (56)</td>
<td>2/56 (3.6)</td>
<td>54/56 (96.4)</td>
</tr>
</tbody>
</table>

* N1=Total number of patients in subgroup

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# ORR according to PD-L1 expression level in patients evaluable for PD-L1 expression

<table>
<thead>
<tr>
<th>PD-L1 expression (total evaluable=136)*</th>
<th>PD-L1+, n/N1† (%)</th>
<th>PD-L1–, n/N1 † (%)</th>
<th>p-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1% tumor cells cut-off</td>
<td>3/85 (3.5)</td>
<td>4/51 (7.8)</td>
<td>0.425</td>
</tr>
<tr>
<td>≥5% tumor cells cut-off</td>
<td>1/23 (4.3)</td>
<td>6/113 (5.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>≥25% tumor cells cut-off</td>
<td>0/3 (0)</td>
<td>7/133 (5.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>≥10% immune cell “hotspots” cut-off</td>
<td>4/12 (33.3)</td>
<td>3/124 (2.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* PD-L1 expression data is unknown for the patient who achieved a CR; non-evaluable specimens included those that were missing, of poor quality or quantity (insufficient tissue on slide or insufficient tumor sample) or otherwise not available to provide results; all biopsy or surgical samples were required to be collected within 90 days of the administration of avelumab.  
‡ Fisher’s exact test  
† N1=number of patients with evaluable PD-L1 expression

- PD-L1 expression by immune cells within the tumor (“hotspots”) was associated with response to avelumab
ORR according to PD-L1 expression level in TNBC patients evaluable for PD-L1 expression

<table>
<thead>
<tr>
<th>PD-L1 expression (total evaluable=48)</th>
<th>PD-L1+, n/N1* (%)</th>
<th>PD-L1–, n/N1* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1% cut-off</td>
<td>2/33 (6.1)</td>
<td>3/15 (20.0)</td>
</tr>
<tr>
<td>≥5% cut-off</td>
<td>1/13 (7.7)</td>
<td>4/35 (11.4)</td>
</tr>
<tr>
<td>≥25% cut-off</td>
<td>0/2 (0)</td>
<td>5/46 (10.9)</td>
</tr>
<tr>
<td>≥10% immune cell &quot;hotspots&quot; cut-off</td>
<td>4/9 (44.4)</td>
<td>1/39 (2.6)</td>
</tr>
</tbody>
</table>

* N1=number of patients with evaluable PD-L1 expression

- Among patients with TNBC, PD-L1 expression by immune cells within the tumor was associated with response to avelumab
- Among 5 TNBC responders, 4 (80%) had PD-L1+ immune cells

Conclusions

- Avelumab has an acceptable safety profile in patients with MBC
- Despite low ORR in overall unselected MBC cohort, signs of greater clinical activity in specific subsets of patients
  - Among 58 patients with TNBC, 5 (8.6%) had responses to avelumab
  - Patients expressing PD-L1 in immune cells showed higher response rate compared with PD-L1– immune cells (33.3% [4/12] vs 2.4% [3/124])
  - In patients with TNBC, PD-L1 expression by immune cells was associated with clinical response to avelumab (44.4% [4/9] vs 2.6% [1/39])
- Further analysis of PD-L1 expression and clinical activity of avelumab in MBC is ongoing
Thank you!