BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto study


for the GBG/AGO-B study groups
Introduction

- Germline BRCA1/2 mutation status might serve as both,
  - predictor for the responsiveness to certain therapies, and
  - as a prognostic marker.
- Germline BRCA1/2 mutations occur most frequently in triple negative breast cancer patients.
- We examined within the triple negative subgroup of the GeparQuinto prospective study
  - whether germline BRCA1/2 mutation status can predict response to therapy,
  - how pCR and germline BRCA1/2 mutation status influence the prognosis after surgery.

HER2-negative part of GeparQuinto

- Recruitment of n=1948 HER2 negative patients,
- N=678 having triple negative tumors.

- Epirubicin 90 mg/m²
- Doc:Docetaxel 100mg/m²
- C: Cyclophosphamide 600 mg/m²
- Bev: Bevacizumab 15 mg/kg
  (all 3 week cycles)
- * non responders continued with a prespecified non responder therapy
Slide 5 / 17

**pCR (ypT0/ypN0) in all HER2 negative patients and in the triple negative subgroup**

- **All HER2 negative patients**
  - EC → Doc: 14.9%
  - EC+BEV → Doc+BEV: 18.4%
  - P = 0.042
- **Only triple negative patients**
  - EC → Doc: 27.9%
  - EC+BEV → Doc+BEV: 39.3%
  - P = 0.003


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Slide 6 / 17

**DFS and OS in all HER2 negative patients according to randomization arm (±BEV)**

- **DFS**:
  - EC-T: 90% (Censored)
  - ECD-T: 80% (Censored)
  - Logrank p = 0.7837
  - EC-T: 155/565 events
  - ECB-TB: 202/565 events

- **OS**:
  - EC-T: 90% (Censored)
  - ECD-TB: 80% (Censored)
  - Logrank p = 0.8422
  - EC-T: 115/565 deaths
  - ECB-TB: 116/565 deaths

*von Minckwitz et al. Ann Oncol, 2014*
BRCA1/2 genotyping and treatment arms

N=678 TNBC Patients

N=471 patients, TNBC with BRCA1/2 successful genotyping*

BRCA1/2 wildtype*
N=389 (82.6%)

Bevacizumab — N=202

Bevacizumab + N=187

BRCA1/2 mutation*
N=82 (17.4%)
N=69 BRCA1, N=13 BRCA2

Bevacizumab — N=47

Bevacizumab + N=35

N=147 patients did not take part in scientific germline DNA genotyping, N=50 samples failed QC

*Genotyping by custom capture NGS

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Results are similar for BRCA1 and BRCA2 mutation carriers, when analyzed separately, however sample sizes for this analysis were very small.

BRCA1/2 mutation status and DFS

- BRCA1/2 Mutation Carriers
- BRCA1/2 Wildtype Patients

Survival Probability

HR = 0.640 (95% CI: 0.401 - 1.022)
p-value = 0.0815
exploratory subgroup analysis: pCR according to randomization arms

- Hypoxia has been described to cause DNA damage.
- Synthetic lethality is a described phenomenon in BRCA1/2 mutation carriers.
- Angiogenic factors such as VEGF, Ang-1 and Ang-2 are overexpressed in BRCA mutated tumors.

**Slide 13 / 17**

**pCR according to treatment and BRCA1/2 status**

- **Patients without BRCA1/2 mutation**
  - pCR (ypT0ypN0) rate (%)
  - BEV-MUT- N=202: 26.2%
  - BEV+MUT- N=187: 35.8%
  - BEV-MUT+: 35.8%
  - BEV+MUT+: 35.8%

- **Treatment with chemo only**
  - Treatment with chemo and BEV

**Slide 14 / 17**

**pCR according to treatment and BRCA1/2 status**

- **Patients with BRCA1/2 mutation**
  - p (interaction) = 0.1912
  - Patients without BRCA1/2 mutation
    - pCR (ypT0ypN0) rate (%)
    - BEV-MUT- N=202: 26.2%
    - BEV+MUT- N=187: 35.8%
    - BEV-MUT+: 38.3%
    - BEV+MUT+: 65.7%
  - **Treatment with chemo only**
  - Treatment with chemo and BEV
**Conclusion**

- BRCA1/2 mutation carriers had
  - a better prognosis (HR=0.64; p=0.06).
  - a significantly higher pCR rates after neoadjuvant chemotherapy ± bevacizumab.

- pCR rate was highest in BRCA1/2 mutation carriers treated with bevacizumab, but better outcome could not be demonstrated.

- The prognostic information of pCR with regards to prognosis appeared to be weaker in patients with a BRCA1/2 mutation compared to wildtype patients (test for interaction was not significant).
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Slides can be downloaded from [www.gbg.de](http://www.gbg.de).