52-06
Survival advantage of anastrozol compared to tamoxifen for lobular breast cancer in the ABCSG-8 study

Dr. Knauer: Nothing to disclose.
Dr. Gruber: Nothing to disclose.
Dr. Dietze: Nothing to disclose.
Dr. Greil: Nothing to disclose.
Dr. Stöger: Nothing to disclose.
Dr. Rudas: Nothing to disclose.
Dr. Baro-Horvath: Nothing to disclose.
Dr. Mlineritsch: Nothing to disclose.
Dr. Kwasny: Nothing to disclose.
Dr. Singer: Nothing to disclose.
Dr. Dubsky: Nothing to disclose.
Dr. Jakesz: Nothing to disclose.

Dr. Fitzal: Nothing to disclose.
Dr. Steger: Nothing to disclose.
Dr. Bartsch: Nothing to disclose.
Dr. Fesl: Nothing to disclose.
Dr. Gnant: Nothing to disclose.
Survival Advantage of Anastrozole Compared to Tamoxifen for Lobular Breast Cancer in the ABCSG 8 Study

Michael Knauer

Background

- Aromatase inhibitors (AI) improve outcomes for postmenopausal breast cancer patients compared to tamoxifen monotherapy

- 2014 patient-level meta-analysis
  - 11,798 patients in randomized trials of 5 years tamoxifen (TAM) vs. a sequence of TAM → AI
  - On AVERAGE postmenopausal breast cancer:
    - Significant reduction in recurrence: RR 0.84 (0.73-0.97)
    - Significantly fewer deaths: RR 0.84 (0.73-0.97)

1: Forbes JF et al., J Clin Oncol 2014 (suppl; abstr 529)
Letrozole and Lobular Cancer: BIG 1-98

- Phase III 4-arm randomized study
- Substantial cross-over: 40%
- 8 years median follow-up1
- Patients: 3788 IDC vs. 502 ILC2

Pathologic surrogates of intrinsic subtypes:
- ER+ and/or PgR+ and Her2-neg.
- Cut-off: Ki-67 14%


BIG 1-98: Disease-free survival

- IDC: no advantage for letrozole containing arms regarding DFS and OS
- ILC: only Letrozole 5y vs. Tamoxifen 5y significant: DFS HR 0.49 (0.30-0.82), OS HR 0.39 (0.20-0.76)
- Interaction p-value n.s. for treatment by histology
- Trend towards higher efficacy of letrozole both for Luminal A and Luminal B breast cancer as assessed by clinical subtyping

Metzger-Filho O et al., J Clin Oncol 2013 (suppl abstr 529)

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ABCsG 8

Relevant inclusion criteria:
- Postmenopausal patients with endocrine-responsive cancer
- Grade 1/2
- No adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>3714</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at surgery</td>
<td>64</td>
</tr>
<tr>
<td>T1</td>
<td>75%</td>
</tr>
<tr>
<td>N0</td>
<td>75%</td>
</tr>
<tr>
<td>Breast conserving surgery</td>
<td>82%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>70%</td>
</tr>
</tbody>
</table>

- Low to intermediate risk population
Distant disease-free survival (DDFS): HR 0.78 (0.60-0.996), p=0.046

Dubaey P et al., J Clin Oncol 2012

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Luminal A vs. B

Grant M et al., Ann Oncol 2014

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Study Aims

- Little known about molecular alterations and their significance in lobular cancer
- Tamoxifen induces gene expression as partial agonist in lobular cancer xenograft models, resulting in de novo tamoxifen resistance\(^1\)
- Gene expression profiling can better identify subgroups predictive for benefit from aromatase inhibitors than pathologic surrogates

1. Sikora MJ et al., Cancer Res 2014

Study Population and Methods

- Informed re-consent obtained from ABCSG 8 patients alive\(^1\)
- Available tumor tissue collected
- Median follow-up: 11 years

- Multigene-assay PAM50 (Prosigna\textsuperscript{TM}) to identify intrinsic subtypes\(^2\)
- PAM50 test performed on FFPE sections using Nanostring nCounter device\(^3\)
- Intrinsic subtypes may be used for adjuvant treatment recommendations since St. Gallen 2011\(^4\)


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Statistical Analysis

Endpoints
  • Disease-free survival (DFS)
  • Overall survival (OS)

Analyses
  • Kaplan-Meier survival plots
  • Cox proportional hazards regression models including
    • treatment as time-dependent covariate to account for
treatment changes in this “switch-trial”
    • interaction between treatment and histology

Study Flowchart

3714 enrolled in ABCSG 8

2285 estimation of available
tissue specimen

142 failed PAM50 analysis
  44 failed QC
  25 insufficient cancer
  in specimen
  73 insufficient RNA

579 refused to sign or
could not be contacted
  5 no data available
  16 no tissue available

1478 evaluable tissue
specimen

123 other types of
histology

270 invasive lobular

1085 invasive ductal

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Luminal B Subtype

Summary

- Among all patients with lobular cancer, anastrozole was associated with a significant reduction in OS events compared to tamoxifen.

- However, anastrozole efficacy was strongly depending on histology and intrinsic subtype of breast cancer.
  - In Luminal A cancer, anastrozole was associated with a significant reduction in DFS and OS events only in DUCTAL cancers.
  - In Luminal B cancer, anastrozole was associated with a significant reduction in DFS and OS events only in LOBULAR cancers.
Limitations

- Retrospective and unplanned subgroup analysis of a phase III trial
- E-cadherin was rarely used in most ABCSG centers (1996 – 2004) – diagnosis was based on morphology only

Discussion

- ILC and IDC are different on a genetic level and can be identified by a 75-gene profile\(^1\)
- In ILC, different genes like IGF1 and PIK3CD are overexpressed compared to IDC\(^1\)
- Identification of 915 genes uniquely regulated by estradiol in ILC cell lines\(^2\)
- Differences in gene expression between ILC and IDC are maintained during letrozole therapy\(^3\)

- Meta-analyses provide evidence for a small benefit for the average patient
- Evaluation of biology-based subgroups is necessary

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Conclusions

- Based on these ABCSG-8 results, we confirm the findings on lobular breast cancer from BIG 1-98:
  - in both phase III trials, the benefit of the aromatase inhibitor in reducing DFS and OS events was different between lobular and ductal cancer
  - when IHC-based subtyping was used, similar trends for Luminal A and B cancer were observed in BIG 1-98
- In our analysis, PAM50-based intrinsic subtyping shows distinct effects with significant interaction between treatment and histology
  - in Luminal A: benefit of anastrozole was only significant in ductal cancer
  - in Luminal B: benefit of anastrozole was confined to lobular cancer

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Conclusions

- PAM50 was predictive for benefit of anastrozole over tamoxifen in Luminal A and B breast cancer in combination with classic histopathology
- PAM50 may be useful to refine adjuvant endocrine treatment decisions

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Acknowledgments

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ABCSG trial office team

St. Gallen Breast Center Team