

**POST ASCO 2010
GYNÄKOLOGISCHE ONKOLOGIE**

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Oral Abstract Session 07.06.2010



ASCO
Abstract
LBA505

NSABP PROTOCOL B-32

**A Randomized, Phase III Clinical Trial to
Compare Sentinel Node Resection to Axillary
Dissection in Clinically Node-Negative
Breast Cancer Patients**

Definitive Analysis of the Primary Outcomes

DN Krag, SJ Anderson, TB Julian, A Brown, SP
Harlow, JP Costantino, T Ashikaga, D Weaver, EP
Mamounas, N Wolmark

NSABP Protocol B-32

B-32 OS

Overall Survival for Sentinel Node Negative Patients



* 300 deaths triggered the definitive analysis

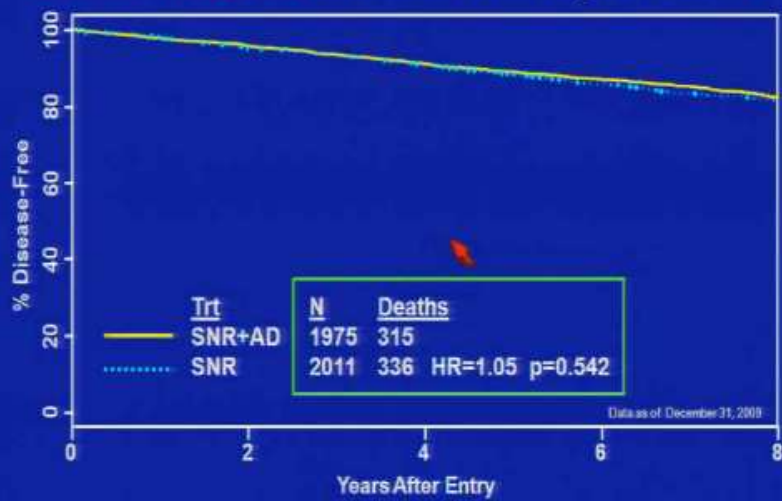
* 309 reported as of 12/31/2009

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NSABP Protocol B-32

B-32 DFS

Disease-Free Survival for Sentinel Node Negative Patients



3

Local and Regional Recurrences as First Events

	Group 1	Group 2
Local	54 (2.7%)	49 (2.4%)
Axillary	2 (0.1%)	8 (0.3%)
Extra-axillary	5 (0.25%)	6 (0.3%)

Zusammenfassung

- Kein signifikanter Unterschied bzgl. OS, DFS oder Lokalrezidive
- Senkung der Morbidität (Ödem, Armbewegungsstörung, etc)

FAZIT:

Bei klinisch unauffälligen LK und histologisch negativem Sentinel ist die alleinige SLNE indiziert, sicher und effektiv

ACOSOG Z0011: A Randomized Trial of Axillary Node Dissection in Women with Clinical T1-2 N0 M0 Breast Cancer who have a Positive Sentinel Node

Giuliano AE, McCall L, Beitsch PD, Whitworth PW,
Blumencranz PW, Leitch AM, Saha S, Hunt K,
Morrow M, Ballman KV



I

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SLNE=AD bei positivem Sentinel?

H

ACOSOG Z0011

*A randomized trial of axillary node
dissection in women with clinical
T1-2 N0 M0 breast cancer who have a
positive SN*

165 Investigators / 177 Institutions

50 investigators with 5 or more patients

Target accrual 1900 patients (non-inferiority)

Closed early



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Ergebnisse I



Locoregional Recurrences

Recurrence	ALND (420 pts)	SLND (436 pts)
Local (Breast)	15 (3.6%)	8 (1.8%)
Regional (Axilla, Supraclavicular)	2 (0.5%)	4 (0.9%)
Total Locoregional	17 (4.1%)	12 (2.8%)

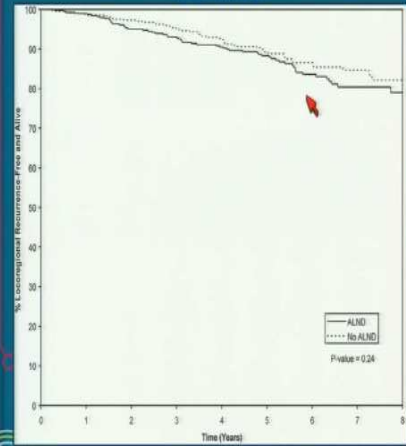
$P = 0.11$

Median follow-up = 6.3 years

Regional recurrence seen in only 0.7% of the entire population



Locoregional Recurrence-Free Survival

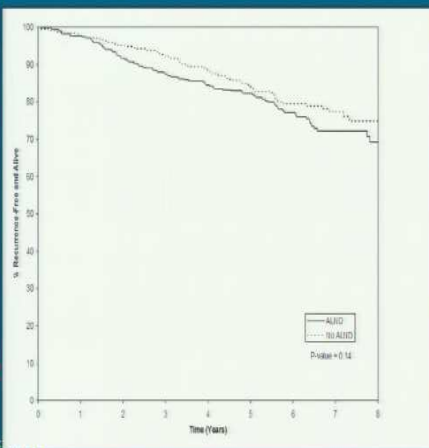


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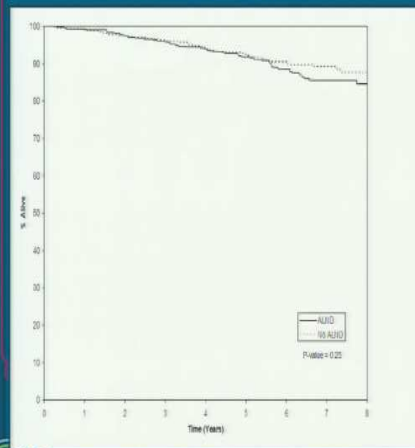
Ergebnisse II



Disease-Free Survival



Overall Survival



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Adjuvant Systemic Therapy

	ALND	SLND
Chemotherapy	57.9%	58.0%
Hormonal therapy	46.4%	46.6%
Either/Both	96.0%	97.0%

P = N.S.

Zusammenfassung



Summary

Locoregional Recurrence-Free Survival

- Locoregional recurrence in only 2.8% of SLND and 4.1% of ALND patients.
- Only age (≤ 50) and higher Bloom-Richardson score were associated with locoregional recurrence by multivariable analysis.
- Neither number of positive SN, size of SN metastasis, nor number of lymph nodes removed was associated with locoregional recurrence.

Summary

Disease-Free and Overall Survival

- No significant difference in DFS between patients treated with SLND (83.9%) or ALND (82.2%)
- No significant difference in OS between patients treated with SLND (92.5%) or ALND (91.8%)
- Only older age, ER-, and lack of adjuvant systemic therapy - not operation - were associated with worse OS by multivariable analysis.

Fazit



Conclusion
 In this prospective randomized study SLND alone provided excellent locoregional control and survival comparable to completion ALND.

This study does not support the routine use of ALND in early nodal metastatic breast cancer. The role of this operation should be reconsidered.



SENTinel node biopsy before or after NeoAdjuvant systemic treatment - The German SENTINA Trial -

T. Kuehn (1), I. Bauerfeind (2), T. Fehm (3), B. Fleige (4), G. Helms (3), A. Lebeau (5), C. Liedtke (6), M. Mai (1), G. v. Minckwitz (7), A. Staebler (3), M. Untch (4)

(1) Klinikum Esslingen, (2) Klinikum Landshut, (3) Uniklinikum Tübingen, (4) Helios Klinikum Berlin-Buch, (5) Uniklinikum Hamburg-Eppendorf, (6) Uniklinikum Münster, (7) German Breast Group (GBG), Frankfurt-Henrburg, GERMANY

<h3>1 BACKGROUND</h3> <p>For patients with breast cancer undergoing primary systemic treatment (PST) the optimal timing of sentinel node biopsy (SLNB) is unclear. While adequate axillary staging prior to PST could allow for a priori tailoring of systemic treatment, SLNB after PST could spare those patients from complete axillary lymph node dissection (ALND), who are free of metastases in the axilla or convert from a positive (Npos) to a histologically negative (Nneg) axillary status following PST. For these patients, however, the reliability of SLNB to predict the axillary status remains yet to be prospectively confirmed.</p>	<h3>5 STUDY DESIGN</h3>	<h3>7 SUBSTUDY "TRANSSENTINA"</h3> <p>The substudy "TransSentina" allows for: a) the validation of known prediction models in the setting of sentinel lymph node assessment (Van Zee et al., Ann Surg Oncol. 2003; Coutant et al., J Clin Oncol. 2009) b) the development of novel prediction models that may be employed in the setting of SLNB among patients undergoing PST. The following prediction models may be analyzed:</p> <p>Prediction model I (Arm A + B) Pre-PST: clinically node negative Post-PST: positive/negative SLN → to predict positive lymph node status in clinically node negative patients</p> <p>Prediction model II (Arm C) Pre-PST: positive sentinel lymph node Post-PST: negative additional nodes → to predict which patients will not need additional ALND despite positive SLN (modification of MSKCC „Additional Nodal Metastasis Nomogram“)</p> <p>Prediction model III (Arm C) Pre-PST: clinically node positive Post-PST: clinically node negative → to predict which patients will experience conversion of their lymph node status through PST</p> <p>Prediction model IV (Arm B) Pre-PST: positive sentinel lymph node Post-PST: negative lymph node → to predict which patients will experience conversion of their lymph node status through PST</p>	<h3>9 CONCLUSION</h3> <p>To our knowledge the SENTINA trial is the first prospective multicenter study to evaluate the role of SLNB in the neoadjuvant setting. The SENTINA protocol will allow for a direct comparison of the feasibility and reproducibility of a standardized SLNB-procedure before and after PST. The study will provide reliable data on the predictive value of SLNB before and after PST in patients converting from a clinically positive to a negative axillary status and offer insights into the biology of axillary response to PST. The SENTINA subprograms provide the unique opportunity to develop and validate breast cancer nomograms and molecular markers in the assessment of lymph node status in patients undergoing PST.</p>
<h3>2 MATERIAL AND METHOD</h3> <p>The German SENTINA protocol, which was initially designed as a substudy of the German Geparquinto neoadjuvant trial of the AGO and the German Breast Group (GBG), is a 4-arm prospective multicenter cohort study designed to examine the role of SLNB in patients undergoing PST.</p>	<h3>6 RECRUITMENT</h3> <p>To date, 66 German centers participate in the SENTINA study</p>	<h3>8 SUBSTUDY "LYMPH NODE ASSESSMENT"</h3> <p>The Substudy "lymph" node assessment" will be conducted to compare a new molecular method for the rapid detection of cytokeratin 19 mRNA (One-step nucleic acid amplification, OSNA) with intraoperative frozen section and definite H/E staining before and after primary systemic treatment. (Tamaki et al., Clin Cancer Res. 2009)</p>	<h3>10 PARTICIPATING CENTERS</h3> <p>APK Wiesbaden, Frauenklinik Bad Cannstatt (Stuttgart), BZC Linz, Bad Mergentheim, Frauenklinik Bad Reichenhald, Helios Klinikum Berlin Buch, Frauenklinik Berlin Köpenick, Frauenklinik Berlin St. Gertrauden, Frauenklinik Bochum, Frauenklinik Deggendorf, Diakonia Karlsruhe, Luitpoldkrankenhaus Düsseldorf, Frauenklinik Frankfurt Höchst, Frauenklinik Marneburg, Frauenklinik Pforz, Frauenklinik Georgsmarienhütte, GYN Ansbach, UFK Halle (Saale), Helios Kliniken Schwelm, Harvensteinklinik Hannover, Frauenklinik Mainz, St. Franziskus Münster, Johanna-Eleonore KKH Neuss, Johanner Frauenklinik Sersitz, Frauenklinik Cuxhaven, Frauenklinik Gilsberg, Frauenklinik Limburg, Frauenklinik Offsbach, Frauenklinik Rottweil, Klinikum Bremen, Klinikum Chemnitz, Klinikum Esslingen, Klinikum Frankfurt (Oder), Klinikum Kassel, Klinikum Landshut, Klinikum Ravensburg, Klinikum Ravensburg, Klinikum Traunstein, Klinikum Villingen, Klinikum Weisenthal, Krankenhaus Wangen, Krankenhaus Ludwigsfelde, Klinikum Eisenberg, Marienhilf Magdeburg, Med. Hochschule Hannover, Robert Busch KKH Stuttgart, St. Barbara Klinik Hamm, St. Vincenzus Klinik Karlsruhe, UFK Halle, UFK Hamburg, UFK Rostock, UFK Tübingen, UFK-Grosshadern-München, UFK Magdeburg, UFK Koi, UFK-Centrum-Lipnik-UFK-Münster-UFK-Limburg</p> <h3>10 STUDY SPONSORS</h3> <p>AGO-b, Deutsche Gesellschaft für Senologie (German Society of Senology) Brustkrebs Deutschland e.V., German Breast Group GmbH, Novartis Pharma</p>

CALGB 9343

Comparison of Lumpectomy Plus Tamoxifen With and Without Irradiation in Women 70 or Older with Clinical Stage I, ER+ Breast Carcinoma

Kevin S. Hughes, Lauren A. Schnaper, Constance Cirincione, Donald Berry, Beryl McCormick, Hyman B. Muss, Clifford Hudis, Eric Winer, Barbara L. Smith

Cancer and Leukemia Group B
Radiation Therapy Oncology Group
Eastern Cooperative Oncology Group

ASCO Annual Meeting



ELIGIBILITY

Age \geq 70
Clinically Node Negative
Lumpectomy, Negative Margin
Tumor size \leq 2 cm
ER Positive or Indeterminate

R
A
N
D
O
M
I
Z
E

Radiation
Tamoxifen

Tamoxifen

CALGB 9343

ASCO Annual Meeting



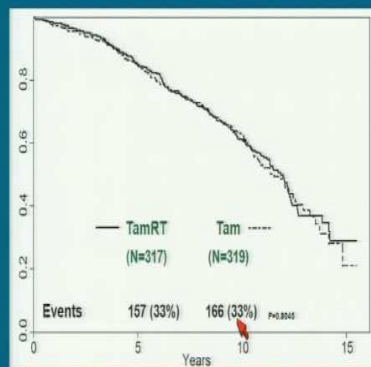
Patient characteristics

	RT+Tam	Tam
Total treated	317	319
Age >75	176 (56%)	172 (54%)
ER Positive	308 (97%)	310 (97%)
Size ≤ 2cm	295 (93%)	296 (93%)
No Ax dissection	200 (63%)	203 (64%)

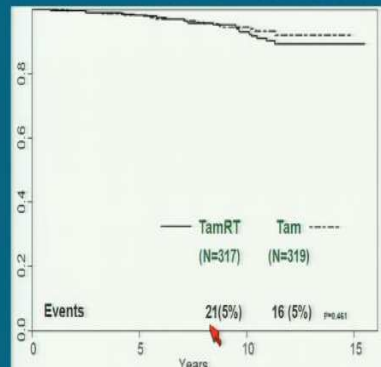
Ergebnisse II

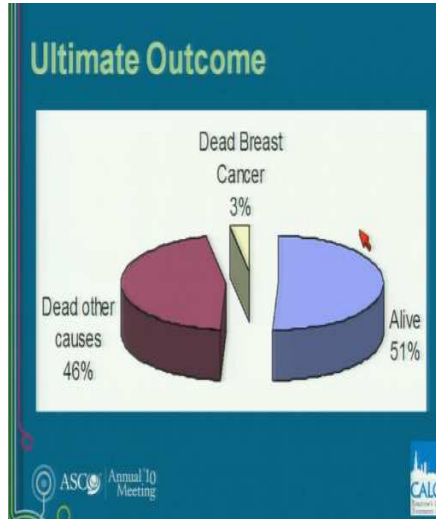
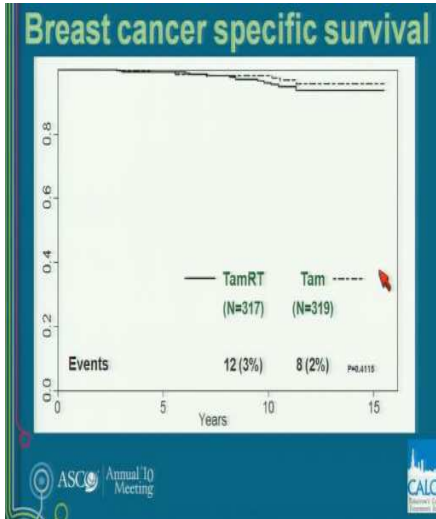


Overall Survival



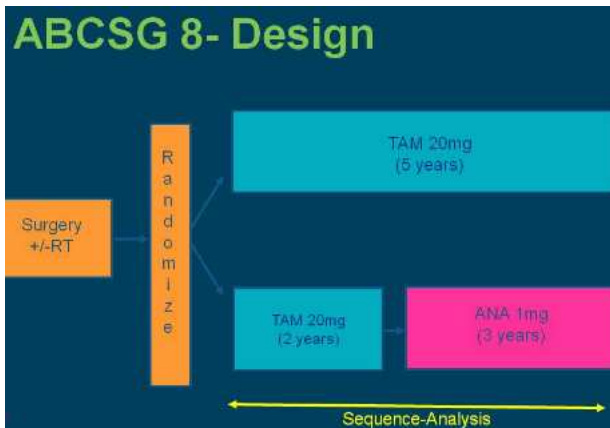
Free from distant metastasis





Dubsky Abs. # 534 1/3

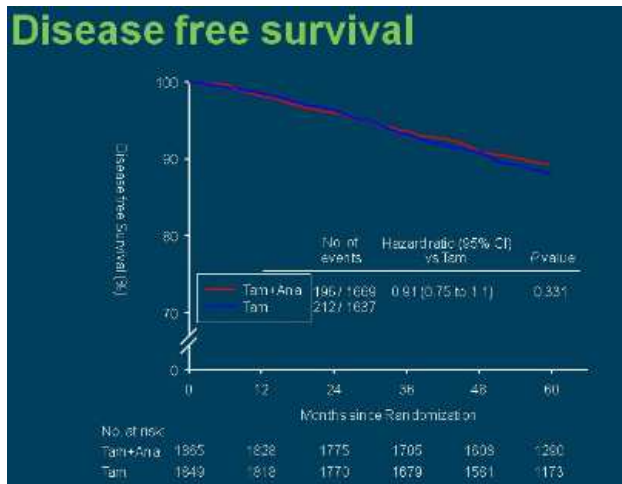
Two years of tamoxifen followed by 3 years of anastrozole versus 5 years of tamoxifen alone in postmenopausal women with hormone-responsive early breast cancer: Efficacy results from 3,714 patients from the Austrian Breast and Colorectal Cancer Study Group



ABCSG-8 trial in PMW with ER+ and/or PgR+, prospective Ph III trial
 After surgery, pts were randomized to
 5 yrs of TAM vs. TAM (2yrs)-> ANA (3yrs)

Dubsky Abs. # 534 2/3

Two years of tamoxifen followed by 3 years of anastrozole versus 5 years of tamoxifen alone in postmenopausal women with hormone-responsive early breast cancer: Efficacy results from 3,714 patients from the Austrian Breast and Colorectal Cancer Study Group

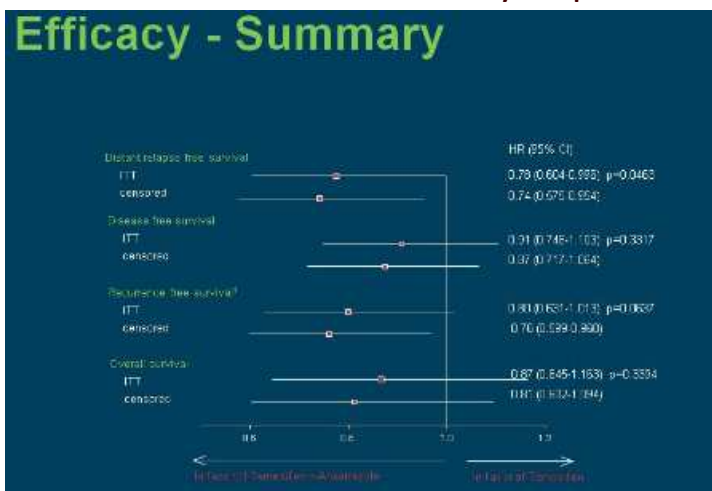


Median f/up: 76.7 mo (ITT)
75% N0
75% T1

DFS (ITT analysis):
196 vs. 212 events
HR of 0.91 (p = 0.331)

Dubsky Abs. # 534 3/3

Two years of tamoxifen followed by 3 years of anastrozole versus 5 years of tamoxifen alone in postmenopausal women with hormone-responsive early breast cancer: Efficacy results from 3,714 patients from the Austrian Breast and Colorectal Cancer Study Group



Tamoxifen / Aromatase Inhibitoren (AI)

© AGO e.V.,

 in der DGGG e.V.,

 sowie

 in der DKG e.V.

Guidelines Breast

 Version 2010.1.0.D

Further Information

References

FORSCHEN

 LEHREN

 HEILEN

Oxford / AGO
LoE / GR

- > **AI für 5 Jahre**
1a A +
- > **Sequentielle Therapie für 5 Jahre**
++
 - > **Tam gefolgt von AI**
1a A
 - > **AI* gefolgt von Tam**
1b C

 Präferenz bei N+
- > **Tamoxifen 20 mg/d für 5 Jahre**
1a A +

*derzeit Daten nur für Letrozol verfügbar

ABCSG 12: Impact of BMI



Results

Events

	Normal weight		Overweight	
	TAM	ANA	TAM	ANA
All events	56 (10.3%)	51 (8.9%)	30 (10.2%)	42 (15.0%)
Recurrence				
Locoregional	16 (2.9%)	13 (2.3%)	6 (2.0%)	9 (3.2%)
Distant	26 (4.8%)	29 (5.1%)	15 (5.1%)	25 (9.0%)
Others	14 (2.6%)	9 (1.5%)	9 (3.1%)	8 (2.8%)
Death				
All	16 (3.0%)	20 (3.5%)	8 (2.7%)	22 (7.9%)
Without previous recurrence	0	0	1	1

Diskussion: ABCSG 12 - Impact of BMI



- ungeplante retrospektive Analyse
- Imbalance bezüglich des Alters (übergewichtige ANA-Pat. häufiger <40J.)
- sehr kleine Anzahl von Todesfällen in einigen Subgruppen (8 im Arm der übergewichtigen Tam-Pat.)
- BMI-assoziiertes Effekt sehr viel geringer ausgeprägt für DFS als für OS
 - Frage: Hat der BMI in unabhängiger Weise zur Mortalität beigetragen? (nur 2 Todesfälle waren nicht-Mamma-Ca-assoziiert)



Trotzdem ist die biologische Plausibilität stark !

*Pfeiler G et al., ASCO 2010, #512
Discussion: Goodwin P, ASCO 2010*

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ABCSG 12: Impact of Zoledronat

ABCSG-12 Update 2010 vs. 2008



	2010	2008	Difference
• Median Follup-Up (months)	62	47.8	+28%
• Number of Events	186	137	+34%
– Recurrences			
• Locoregional	45	30	+50%
• Controlateral	14	16	-13%*
• Distant	100	70	+43%
– Bone	53	40	+33%
– Deaths	73	42	+72%

* several cases were corrected in quality control checks

ABCSG-12 ASCO 2010

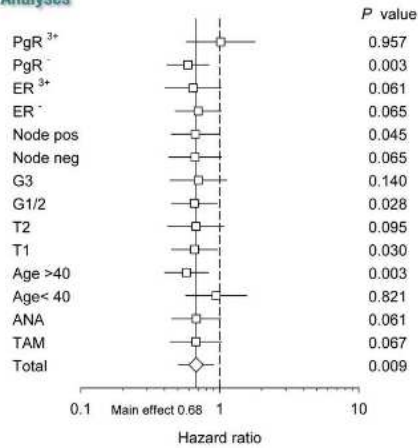
M. Grant

25
Grant et al., ASCO 2010, #533

ABCSG 12: Impact of Zoledronat

Subgroup Analyses of DFS ZOL-Treatment

Retrospective Analyses



ABCSG-12 ASCO 2010

M. Gnant 12

26
Gnant et al., ASCO 2010, #533

Ellis LBA # 513 2/2

ACOSOG Z1031: A randomized neoadjuvant phase II screening study comparing exemestane, letrozole, and anastrozole in postmenopausal women with clinical stage II/III estrogen receptor-positive breast cancer.

Results:

Clinical Response (WHO Criteria)	Treatment Arm		
	EXE (n=124)	LET (n=127)	ANA (n=123)
Complete Response	25 (20.2%)	26 (20.5%)	20 (16.3%)
Partial Response	50 (40.3%)	66 (52.0%)	64 (52.0%)
No Change	26 (21.0%)	18 (14.2%)	16 (13.0%)
Progression	8 (6.5%)	6 (4.7%)	9 (7.3%)
Unable to evaluate	15 (12.1%)	11 (8.7%)	14 (11.4%)
ITT Clinical response rate (95% CI)	60.5% (51.3-69.1%)	72.4% (63.8-80.0%)	68.3% (59.3-76.4%)
Per Protocol Clinical Response rate (95% CI)	69% (59.2-77.3%)	79.3% (70.8-86.3%)	77% (71.1-87.2%)

BCS rates:

marginal for BCS group: 78% (163/207)

mastectomy only (MO): 42% (77/163)

inoperable group (IO): 75% (3/4)

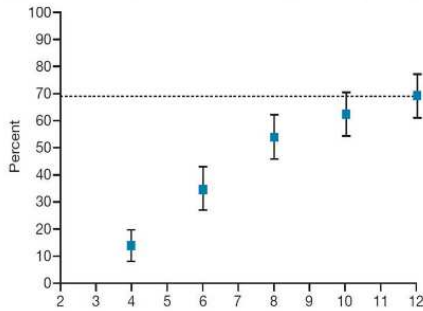
➔ neoadjuvant AI therapy allows for high response and breast conservation rates and low rates of disease progression

Carpenter Abs. # 670: 3/3

A multicenter study to determine the optimum duration of neoadjuvant letrozole on tumor regression to permit breast-conserving surgery

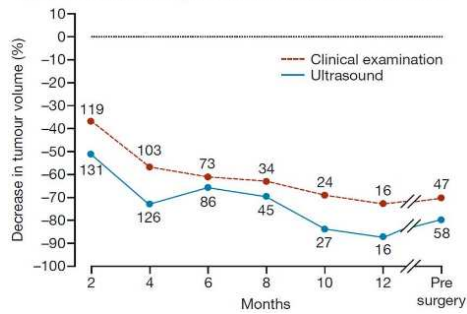
Results (cont'd)

Figure 2. Percentage of Patients Ready for BCS (95% CI)



Results (cont'd)

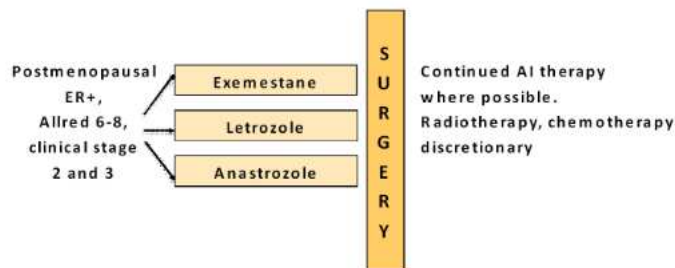
Figure 3. Median Changes in Tumour Volume from Baseline



Ellis LBA # 513 1/2

ACOSOG Z1031: A randomized neoadjuvant phase II screening study comparing exemestane, letrozole, and anastrozole in postmenopausal women with clinical stage II/III estrogen receptor-positive breast cancer.

ACOSOG Z1031 COHORT A



Z1031 was designed as a preliminary study to a comparison of endocrine therapy with chemotherapy

- 16 weeks neoadjuvant either EXE, LET or ANA377 postmenopausal women enrolled, median tumor size was 4.0 cm (range: 2-13 cm).
- **Primary Endpoint:** "best" 16-week clinical response rate (cRR) (based on caliper measurements)
- **Secondary Endpoint:** extent of surgery, radiologic and pathologic response rates.

Impact of treatment characteristics on response of different breast cancer subtypes: pooled multi-layer analysis of the German neo-adjuvant chemotherapy trials

Gunter von Minckwitz, Michael Untch, Eveline Nüesch, Manfred Kaufmann, Sherko Kümmel, Peter Fasching, Wolfgang Eiermann, Jens Blohmer, Sibylle Loibl, Peter Jüni
for the

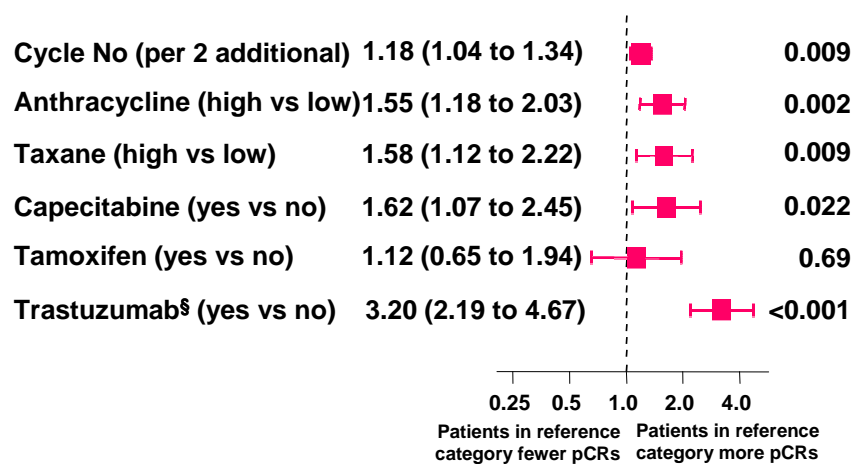
AGO



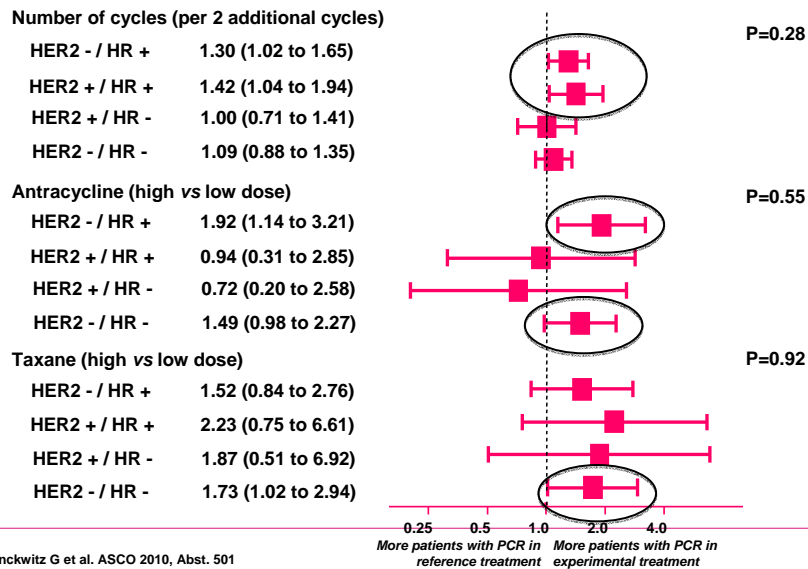
and



Association of pCR with treatment characteristics*

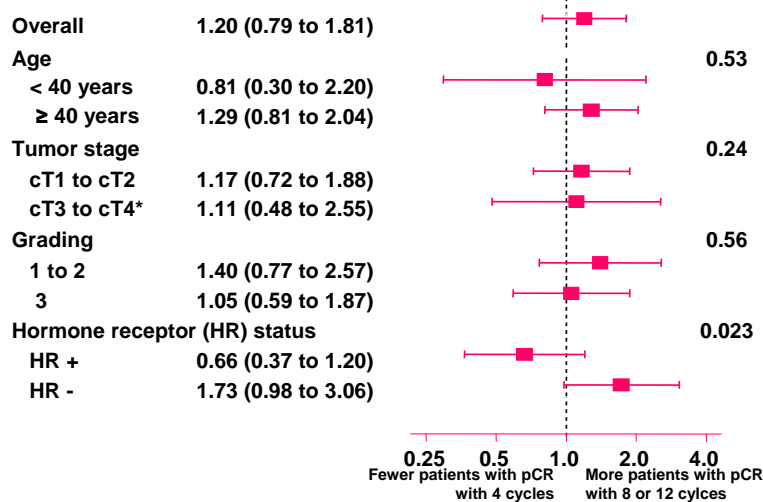


Association of pCR with treatment characteristics stratified by HR & HER2 status*



von Minckwitz G et al. ASCO 2010, Abstr. 501

Association of pCR with tumor characteristics in patients with HER2-positive tumors treated with 4 – 12 cycles trastuzumab



von Minckwitz G et al. ASCO 2010, Abstr. 501

*Analysis not adjusted for tamoxifen because of collinearity problems

Conclusions

Dosing characteristics appear important for the successful treatment of breast cancer:

- In general, longer treatment, higher cumulative anthracycline / taxane doses, and use of capecitabine provide higher pCR rates
- Tumors with assumed partial resistance (e.g. HR-positive tumors) require more cycles of adequately dosed chemotherapy
- Highly sensitive tumors may be sufficiently treated with less aggressive treatment
 - HER2-positive cancers: low cumulative dose of anthracyclines & few trastuzumab cycles
 - HR-negative cancers: short duration of chemotherapy

Results should be taken into account for new trial concepts and current treatment planning

von Minckwitz G et al. ASCO 2010, Abst. 501

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