Gemeinschaftsklinikum Mittelrhein
Kemperhof

San Antonio 2017
Frühes Mammakarzinom
Neo- / Adjuvant - Operativ

A. Franzen

Themenübersicht

Gemeinschaftsklinikum Mittelrhein

- Dosisdichte / - intensivierte Chemotherapie sinnvoll ?
- Wie lange Bisphosphonate geben in der Adjuvanz ?
- Was ist der sichere Resektionsrand ?
- Ist die Vermeidung der Axilladissektion sicher ?
- Ovarielle Suppression zur Ovarprotektion während Chemotherapie ?
- Ovarielle Suppression plus Tam / AI besser als Tam / AI alleine für das onkologische Outcome?
- Trastuzumab auch bei HER2 + / ++ wirksam ?

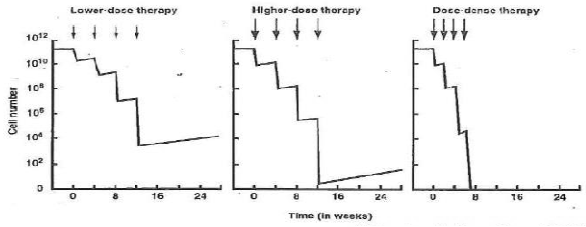
GS1-01:
Gray et al., Oxford, UK
Early **B**reast **C**ancer **T**rialists´ **C**ollaborative **G**roup

Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality:
an EBCTCG meta-analysis of 21,000 women in 16 randomised trials.

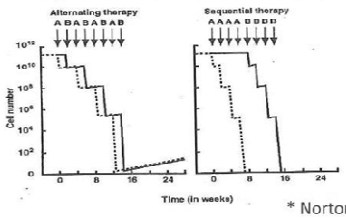
Hintergrund:

- - Anthrazyklin- und taxanbasierte Chemotherapie führt zu einer relativen Verbesserung um 1/3 im Vergleich zu alten Chemotherapien (z.B. CMF)
- - Dosisintensität könnte zu einer weiteren Verbesserung der Effektivität führen
  → Höhere Dosis
  → Kürzere Intervalle
  → Sequentielle vs. Simultane Gabe

Models of tumour cytoreduction and regrowth following conventional, dose-escalated and dose-dense chemotherapy*



Models of tumour cytoreduction and regrowth following alternating and sequential dose-dense chemotherapy*



Broken lines indicate cells sensitive to treatment A; solid lines cells sensitive to treatment B

* Norton L. Sem Oncol 1997

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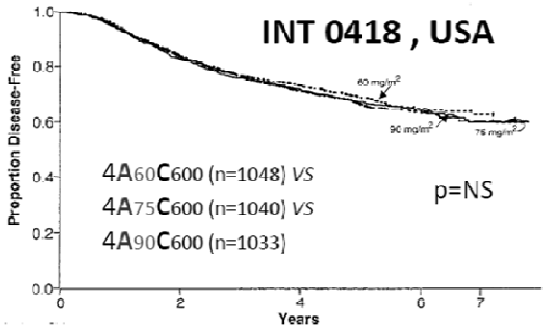
Anthracyclines : no apparent benefit from escalation beyond standard dose



Henderson IC, et al. *J Clin Oncol* 2003; 21:976-983

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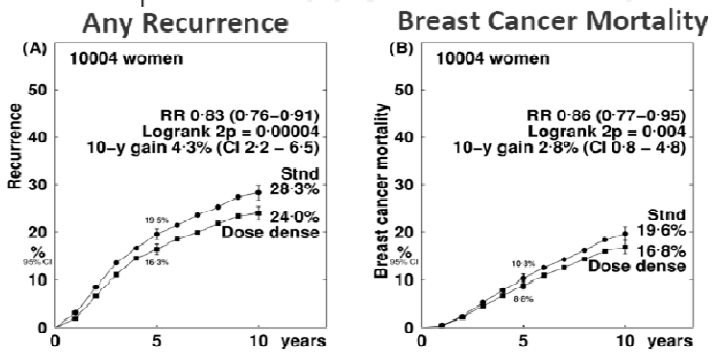
2-weekly (dose dense) *vs* the same chemotherapy given 3-weekly



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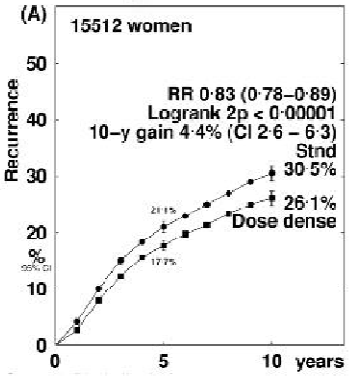
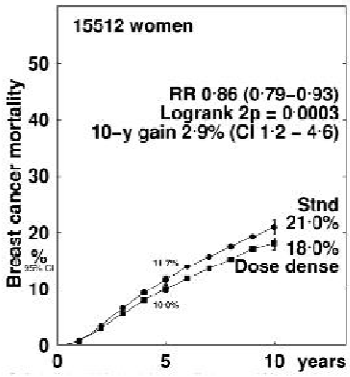
2-weekly vs 3-weekly chemotherapy: all trials

(including the 5 trials where chemotherapy differed between arms)

Any Recurrence



Breast Cancer Mortality



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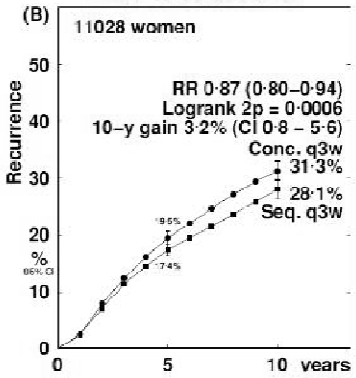
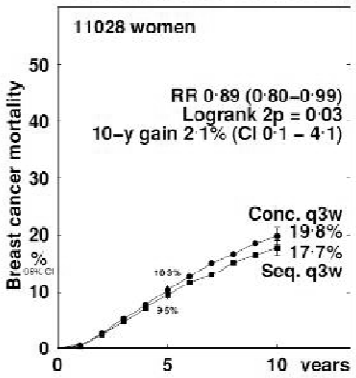
Sequential (3-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence



Breast Cancer Mortality



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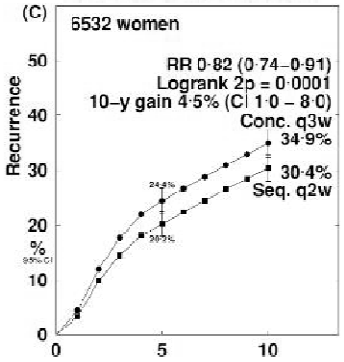
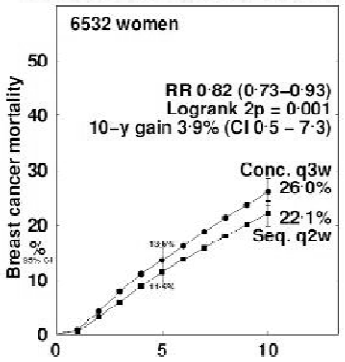
Sequential (2-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence



Breast Cancer Mortality



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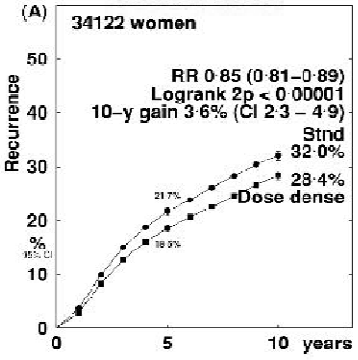
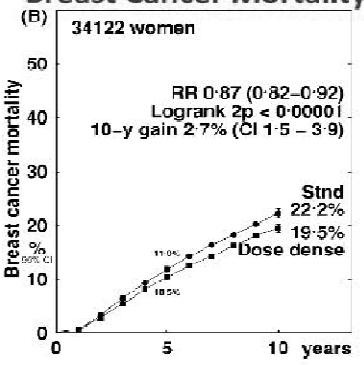
Pooled analysis of all 25 dose-dense and sequential trials

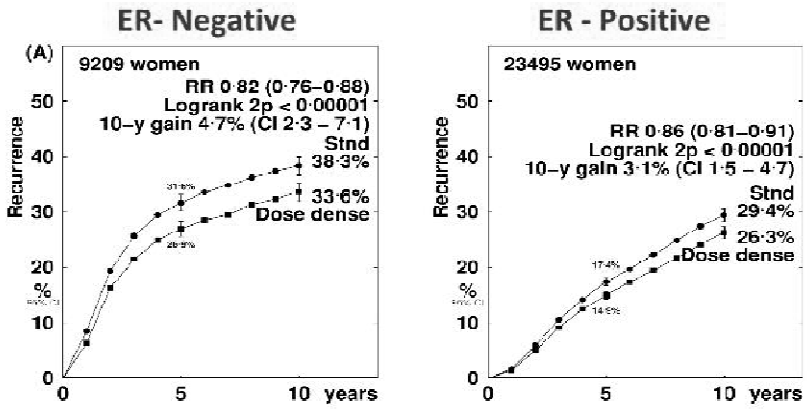
Recurrence



Breast Cancer Mortality



Pooled Analysis: recurrence by ER status



Fazit:

- Dosiseskalation scheint zu keinem Überlebensvorteil zu führen
- Kürzere Therapieintervalle u. sequentielle Therapie : ca. 15 % Verbesserung des rezidivfreien Überlebens
- Effekte weitgehend unabhängig von Tumorbiologie
- Keine höhere therapieassozierte Mortalität durch Dosisintensivierung
- Praxisrelevanz : Hoch

GS1-06

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AGO-B BREAST STUDY GROUP

San Antonio Breast Cancer Symposium, December 5-9, 2017

SUCCESS

Extended adjuvant bisphosphonate treatment over five years in early breast cancer does not improve disease-free and overall survival compared to two years of treatment: Phase III data from the SUCCESS A study

Wolfgang Janni, Thomas WP Friedl, Tanja Fehm, Volkmar Mueller, Werner Lichtenegger, Jens Blohmer, Ralf Lorenz, Helmut Forstbauer, Emanuel Bauer, Visnja Fink, Inga Bekes, Jens Huober, Julia Jückstock, Andreas Schneeweiss, Hans Tesch, Sven Mahner, Sara Y Brucker, Georg Heinrich, Lothar Häberle, Peter A. Fasching, Matthias W Beckmann, Robert Coleman, Brigitte Rack

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Hintergrund Bisphosphonate:

- verhindern Knochenverlust und Skelettkomplikationen
- Adjuvante Therapie führt zu längerer brustkrebspezifischer Überlebenszeit und reduzierter Rezidivrate bei postmenopausalen Pat.
- Therapiedauer unklar

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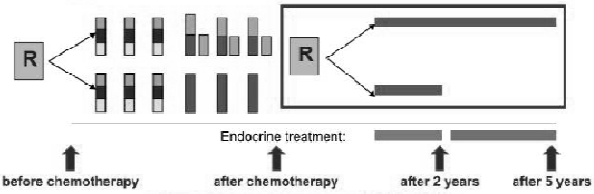
San Antonio Breast Cancer Symposium, December 5-9, 2017

SUCCESS

SUCCESS A – study design

(open-label, multicenter, 2x2 factorial design, randomized controlled Phase III study)



5- FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m² q3w

Docetaxel 100 mg/m² q3w

Docetaxel 75 mg/m², Gemcitabine 1.000 mg/m² d1,8 q3w

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)

Blood sampling for CTC assessment

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

Second randomization:
5 years vs. 2 years of zoledronate
(4 mg i.v. every 3 months for 2 years, followed by 4 mg i.v. every 6 months for 3 years vs. 4 mg i.v. every 3 months for 2 years)

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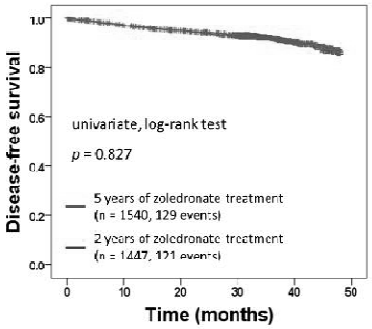
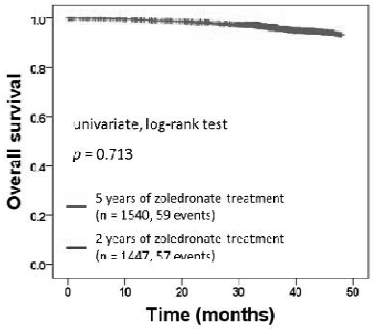
Adapted disease-free survival (DFS) and overall survival (OS) by zoledronate treatment arm





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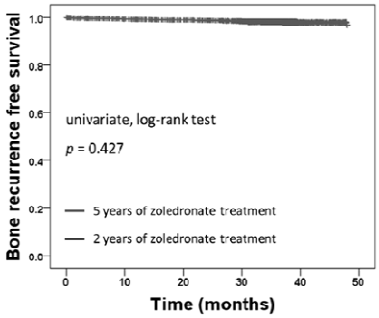
Bone recurrences by zoledronate treatment arm
(as of 2 years after the start of zoledronate treatment)

Bone recurrences as first distant recurrence*

- 5 years of zoledronate: 25 events
- 2 years of zoledronate: 28 events



* with or without concurrent other recurrence

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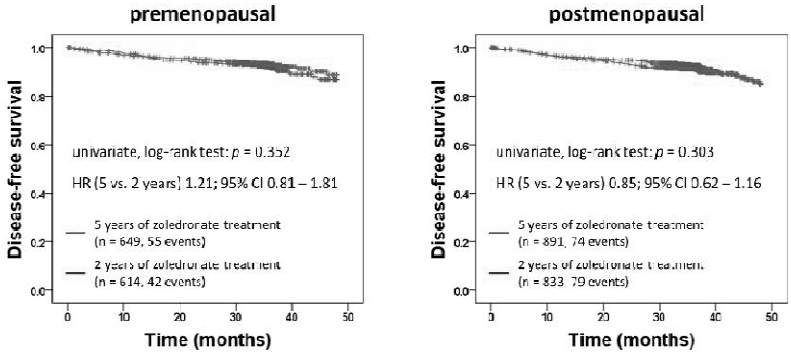
Subgroups – adapted DFS by menopausal status



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Adverse events by zoledronate treatment arm (as of 2 years after the start of zoledronate treatment)

Patient cohort	Number of adverse events observed (% of patients affected)	
	all grades	grade 3/4
Total	2845 (37.0%)	257 (6.4%)
5 years of zoledronate	1954 (46.2%)	159 (7.6%)
2 years of zoledronate	891 (27.2%)	98 (5.1%)
	p<0.001	P=0.006

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Häufigste Komplikationen : 5 vs 2 Jahre:

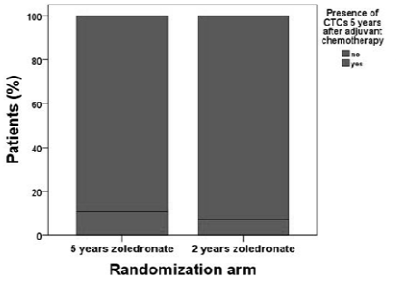
Knochenschmerzen (~ 8 vs 4 %), Arthralgien (~ 5 vs 3 %), Fatigue, Anämie

Kiefer-Osteonekrose: 11 vs 5 Fälle absolut

Zirkulierende Tumorzellen: CTC

San Antonio Breast Cancer Symposium, December 5-9, 2017

Presence of CTCs after 5 years



Presence of CTCs five years after adjuvant chemotherapy assessed in 714 patients

- 5 years of zoledronate (n = 410) 43 (10.5%) CTC positive
- 2 years of zoledronate (n = 304) 22 (7.2%) CTC positive

Chi-square test, $p = 0.135$

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Hintergrund CTC:

- Progn. Relevanz im adjuvanten und met. Setting etabliert
- Rolle der Bisphosphonate für Elimination von CTC´s vermutet

Fazit:

- Kein Unterschied in DFS / OS zwischen 2 (8 Gaben) oder 5 Jahre Therapie nach adj. Chemotherapie
- Unabhängig vom Menopausenstatus und anderen klinischen / tumorbiologischen Faktoren (multivariat)
- 5 Jahre Therapie führt zu mehr Toxizität
- Kein Unterschied in Prävalenz bei CTC´s nach 5 Jahren

- Adjuvant 6 – 8 Gaben Zoledronat (innerhalb 2 – 3 Jahren) sollte weiterhin postmenopausalen Patientinnen angeboten werden

- Ggf. längere Gaben bei Indikation : Osteopenie / Osteoporose

- Praxisrelevanz: Hoch

GS5-01

Appropriate margins for breast-conserving surgery in patients with early stage breast cancer: A meta-analysis

Frank Vicini, Vivek Verma, Harlan Sayles, Abram Recht, Chirag Shah

University of Nebraska Medical Center, Dept. Biostatistics
Cleveland Clinic Taussig Cancer Institute
Beth Israel Deaconess Medical Center, Harvard Medical School,
UCLA Medical School, Radiation Oncology

Hintergrund:

Viele Leitlinien empfehlen „No ink on tumor“ : AGO, SSO-ASTRO u.a.

Hier präsentiert :

- Kritische Diskussion des minimalen tumorfreien Randes nach BET
- Erweiterte Metaanalyse mit anderen Kriterien

Methods

- Systematic literature review (1995-2016)
- Inclusion criteria:
  - Minimum follow-up: 50 months
  - Explicit pathologic definition of margin status
  - Local recurrence reported in relation to margin status
- 38 studies with 55,302 patients identified, including 31 of the 33 studies from the previous meta-analysis (>***20,000 additional patients***)
  - 1 updated study
  - 1 follow-up <50 months (elimin
- Median follow up 7.2 years

Methods

- Margin definitions similar to previous analysis
- "Positive" = invasive cancer or DCIS at the surgical margin
- "Negative" = no tumor within specified distance from margin
- "Close" = no tumor on ink but there was tumor less than specified distance from the margin
- Series of models developed based on cut-point desired

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Methods

- 3 Models in Present Analysis:
  - Model 1: similar to previous analysis (Model 1) of negative vs. close/positive
  - Model 2: performed to assess impact of margin width range rather than a set margin width
    - 0-2 mm, 2-5 mm, >5 mm
    - Not included in previous analysis
  - Model 3: similar to previous meta-analysis (Model 2) of negative, close, positive margins

(entspr. New Yorker Gruppe, „No ink on tumor“)

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Crude Local Recurrence- Model 1

Negative vs close/positive

Margin (mm) and status	Number of studies providing data	Total number of observations	Total number of LR	LR %
≤0	28	3416	352	10.3
>0	38	46178	1758	3.8
≤1	29	3988	405	10.2
>1	27	33565	1161	3.5
≤2	32	5978	519	8.7
>2	23	31757	1053	3.3
≤5	38	9781	659	6.7
>5	8	19059	604	3.2

Benefit to wider margins observed with greatest difference (benefit) seen at 1 mm (6.7%), but similar rates of recurrence with all negative margin definitions (3.2-3.8%)

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Results- Model 1

Odds ratios for local recurrence for negative vs. close/positive margins

- >0 mm: 0.46 (0.40-0.53, p<0.001)
- >1 mm: 0.43 (0.36-0.51, p<0.001)
- >2 mm: 0.49 (0.42-0.55 p<0.001)
- >5 mm: 0.53 (0.43-0.66, p<0.001)

- Best odds ratio for 1 mm margin, as compared to close/positive margin
- Similar results to previous meta-analysis
- Odds ratios are very similar: unable to say what's the optimal margin

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Results –Model 2

- Looking at range of margins, a wider margin further reduced local recurrence and was validated on MVA
- Margin range (negative/close) vs. Positive Margin
  - >0-2 mm: 7.2%, OR: 0.56 (0.49-0.63, p<0.001)
  - 2-5 mm: 3.6%, OR: 0.44 (0.35-0.56, p<0.001)
  - >5 mm: 3.2%, OR: 0.32 (0.26-0.41, p<0.001)
- Multivariate Analysis: margin width only significant variable (larger margin, lower recurrence)

Results- Model 3

When modeling as negative, close, or positive margins, reduced rates seen with negative margins with lowest rates seen at 2 and 5 mm

MVA confirmed margin status and width as factors associated with local recurrence. Last two bullet points below are the difference from previous work

- Negative/Close/Positive Margins
  - 1 mm: 8.0%/13.0%/14.0%
  - 2 mm: 3.6%/5.5%/9.5%
  - 5 mm: 2.9%/4.1%/12.8%
- Odds Ratio for Local Recurrence by Margin Status
  - Close vs. Negative: 1.58 (1.32-1.89)
  - Positive vs. Negative: 2.49 (2.10—2.96)
  - **2 mm vs. 1 mm: 0.50 (0.42-0.59)**
  - **5 mm vs. 1 mm: 0.40 (0.33-0.48)**

Fazit

- Tumorfreie Resektionsränder (1 mm oder mehr) gehen ggf. doch mit niedrigerem Lokalrezidivrisiko einher
- Ältere Studien inkludiert – unterschiedliche Methoden
- Vorsichtige Interpretation von den Autoren angeregt
- Es bleibt unklar, ob eine Nachresektion einen Benefit für die Patientin generiert
- Kontroverse Methodendiskussion bzgl Überlegenheit für eine Metaanalyse (Statistiker)
- Praxisrelevanz : Abwarten

GS5-01

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2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

Axillary dissection vs. no axillary dissection in patients with cT1-T2 N0 breast cancer and micrometastases only in the sentinel node: ten-year results of the IBCSG 23-01 trial

Viviana Galimberti, MD
for the
International Breast Cancer Study Group

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Hintergrund

- Für Pat. mit pos. SNB: Axilladissektion war der Standard
- 5 Jahres-Daten IBCSG-23 und 10 Jahres-Daten Z0011 zeigen: kein Benefit zugunsten Axilladiss. bei moderatem Befall bzgl. DFS
- Ergebnisse nach 9,8 Jahren werden präsentiert

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Study Design

- Eligible consenting patients – who could be scheduled for mastectomy or conservative surgery – were registered before surgery
- If tumor/nodal eligibility criteria met, randomized:-
  - Prior to amendment (June 2006): Tumor size ≤ 3 cm; unicentric; one micrometastatic (≤2 mm) sentinel node; no extracapsular extension or macrometastatic involvement
  - After amendment: Tumor size ≤ 5 cm; uni or multicentric; one or more micrometastatic (≤2 mm) sentinel nodes

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Local Treatment

Treatment	AD (n=464)	No AD (n=467)	Total (n=931)
Type of breast surgery			
Conservative	420 (91%)	425 (91%)	845 (91%)
Mastectomy	44 (9%)	42 (9%)	86 (9%)
Radiotherapy (BCS)			
No	10/420 (2%)	12/425 (3%)	22 (3%)
Yes	410/420 (98%)	413/425 (97%)	823 (97%)
Radiotherapy in mastectomy			
No	42/44 (95%)	39/42 (93%)	81 (94%)
Yes	2/44 (5%)	3/42 (7%)	5 (6%)

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Disease-Free Survival Events and Deaths

	AD (n=464)		No AD (n=467)	
Total DFS events	**117**	**25.2%**	**101**	**21.6%**
Breast cancer events	**75**	**16.2%**	**74**	**15.8%**
Local	13	2.8%	14	3.0%
Regional	3	0.6%	9	1.9%
Ipsilateral axillary events	**2**	**0.4%**	**8**	**1.7%**
Distant	47	10.1%	41	8.8%
Contralateral breast	12	2.6%	10	2.1%
Non-breast cancer events	**42**	**9.1%**	**27**	**5.8%**
Second (non-breast) primary	23	5.0%	17	3.6%
Death without prior cancer event	2	0.4%	6	1.3%
Death with unknown cancer status	17	3.7%	4	0.9%
Deaths	**58**	**12.5%**	**45**	**9.6%**

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Disease-Free Survival Events According to Type of Surgery

	Mastectomy (n=86)		Breast conservation (n=845)	
Total DFS events	**23 (26.7%)**		**195 (23.1%)**	
Breast cancer events	**17 (19.8%)**		**132 (15.6%)**	
Ipsilateral axillary events	2		8	
	AD 1 (1.2%)	**No AD 1 (1.2%)**	**AD 1 (0.1%)**	**No AD 7* (0.8%)**
Non-breast cancer events	**6 (7.0%)**		**63 (7.5%)**	
Deaths	**14 (16.3%)**		**89 (10.5%)**	

*Five received intraoperative radiotherapy

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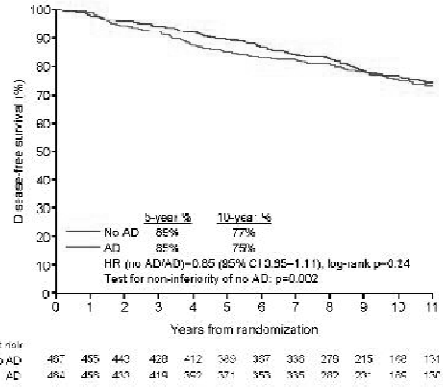
Disease-Free Survival



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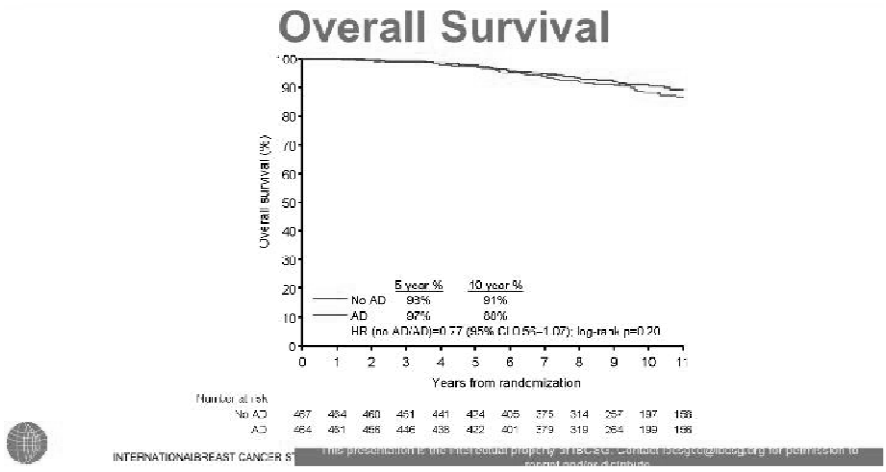
Gemeinschaftsklinikum Mittelrhein

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017



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Fazit:

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- Bestätigung früherer Ergebnisse , (insbes. Z0011)
- Kein Benefit für Axilladissektion bei axillären LK - Mikrometastasen
- Niedrige axill. Rezidivrate
- Auch für Mastectomie Pat. akzeptabel

- Keine Indikation für axilläre LNE bei Mikrometastasen im Sentinel

- Praxisrelevanz: Hoch (Routine bestätigt)

GS4-01

Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium, December 5-9, 2017

Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients

Matteo Lambertini[1], Halle C.F. Moore[2], Robert C.F. Leonard[3], Sibylle Loibl[4], Pamela Munster[5], Marco Bruzzone[6], Luca Boni[7], Joseph M. Unger[8], Richard A. Anderson[9], Keyur Mehta[4], Susan Minton[10], Francesca Poggio[6], Kathy S. Albain[11], Douglas J.A. Adamson[12], Bernd Gerber[13], Amy Cripps[14], Gianfilippo Bertelli[15], Sabine Seiler[4], Marcello Ceppi[6], Ann H. Partridge[16], and Lucia Del Mastro[6]

[1]Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium. [2]Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland, OH. [3]Imperial College, London, UK. [4]GBG - German Breast Group, Neu-Isenburg, Germany. [5]UCSF - University of California, San Francisco, CA. [6]Ospedale Policlinico San Martino-IST, Genova, Italy. [7]AOU Careggi and Istituto Toscano Tumori, Firenze, Italy. [8]SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA. [9]MRC Centre for Reprodcutive Health, University of Edinburgh, Edinburgh, UK. [10]Moffitt Cancer Center, Tampa, FL. [11]Loyola University Medical Center, Cardinal Bernardin Cancer Center, Maywood, IL. [12]Fayside Cancer Centre, Ninewells Hospital, Dundee, UK. [13]University Hospital Roatock, Rostock, Germany. [14]Nexgen Oncology, Dallas, TX. [15]Singleton Hospital, Swansea, UK. [16]Dana-Farber Cancer Institute, Boston, MA.

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Hintergrund:

- Fertilitätsprotektion hat hohe Priorität für junge Patientinnen
- Schwangerschaften nach Primärbehandlung führen zu keiner Prognoseverschlechterung
- Kryokonservierung am effektivsten, aber nicht effektiv bzgl. Ovarialinsuffizienz
- Heterogene Daten zum Ovarschutz mit GnRH

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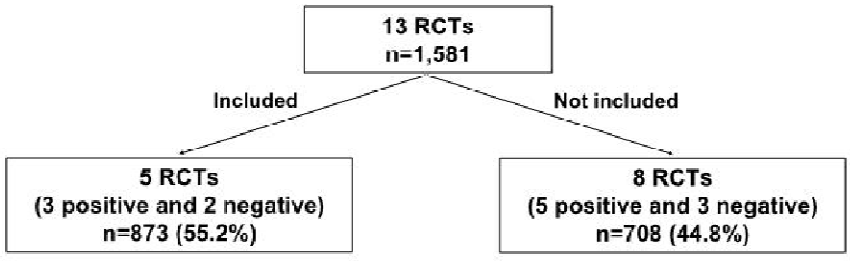
San Antonio Breast Cancer Symposium, December 5-9, 2017

Study Methods

- Systematic review and meta-analysis of individual patient data from RCTs that investigated the role of temporary ovarian suppression with GnRHa during chemotherapy for early breast cancer patients



PROSPERO registration number: CRD42014015638

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Study Characteristics

	PROMISE-GIM6[1,2]	POEMS/SWOG S0230[3]	Moffitt-led trial[4]	GBG-37 ZORO[5]	Anglo Celtic Group OPTION[6]
Definition of POI	No resumption of menstrual activity and postmenopausal levels of FSH and E2	Amenorrhea for the prior 6 months and postmenopausal levels of FSH	No maintenance of menses and no resumption of menses	No re-appearance of two consecutive menstrual periods within 21 to 35 days	Amenorrhea with elevated FSH
Timing of POI after chemotherapy	12 months	24 months	24 months	6 months	Between 12 and 24 months
Sample size	281	257	48	60	227
ER status for eligibility	ER positive and ER negative	ER negative only	ER positive and ER negative	ER negative only	ER positive and ER negative
Upper age limit for eligibility	≤ 45 years	≤ 49 years	≤ 44 years	≤ 45 years	None
Type of GnRHa	Triptorelin	Goserelin	Triptorelin	Goserelin	Goserelin

1. Del Mastro L et al. *JAMA* 2011;306:269-76. 2. Lambertini M et al. *JNMI* 2015;314:2632-40. 3. Moore HCF et al. *N Engl J Med* 2015;372:923-32. 4. Muncter P et al, *J Clin Oncol* 2012;30:633-38. 5. Gerber B et al, *J Clin Oncol* 2011;29:2334-41. 6. Leonard RCF et al, *Ann Oncol* 2017;28:1811-15.

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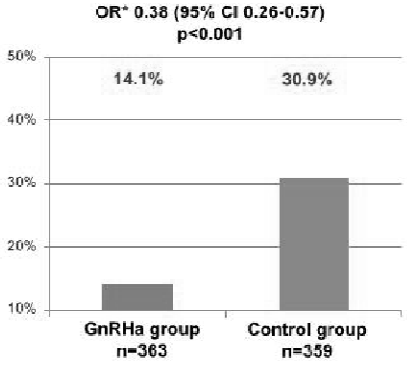
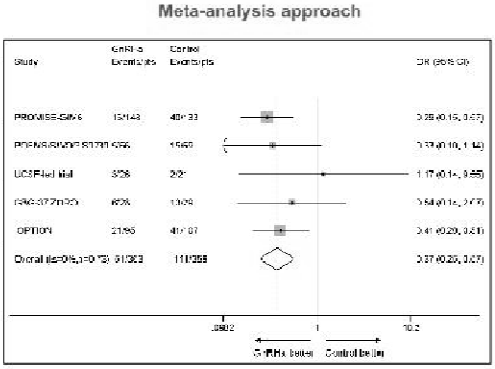
Premature-Ovarian Insufficiency Rate





*Odds ratio (OR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered

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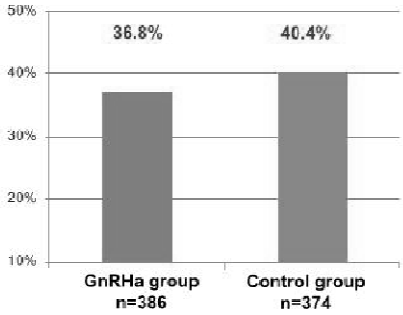
Amenorrhea Rates

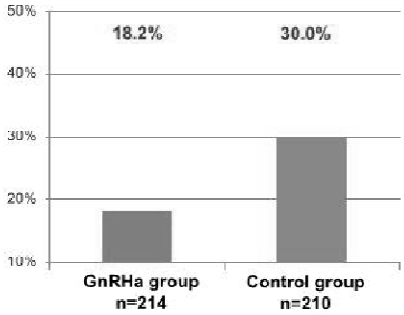
One-Year Amenorrhea

OR* 0.92 (95% CI 0.66-1.28); p=0.623



Two-Year Amenorrhea

OR* 0.51 (95% CI 0.31-0.85); p=0.009



*Odds ratio (OR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered

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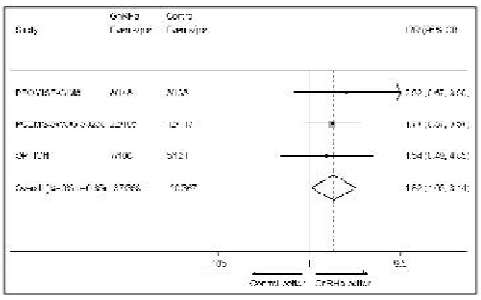
Post-Treatment Pregnancy Rate

GnRHa Group: 37/359 (10.3%)
vs.
Control Group: 20/367 (5.5%)

IRR* 1.83 (95% CI 1.06-3.15)
p=0.030

	GnRHa group (n = 37) No. (%)	Control group (n = 20) No. (%)
Age distribution, years		
≤ 40	37 (100)	20 (100)
≥ 41	0 (0.0)	0 (0.0)
Estrogen receptor status		
Positive	6 (15.2)	2 (10.0)
Negative	31 (83.8)	18 (90.0)

Meta-analysis approach



*Incidence rate ratio (IRR)

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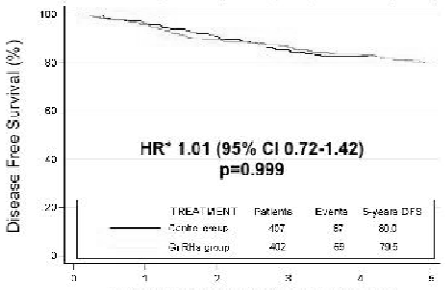
Disease-Free Survival

Median follow-up = 5.0 years (IQR, 3.0 - 6.3 years)



Number at risk

Control group	407	352	342	209	132	172
GnRHa group	402	353	323	255	240	174

*Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage

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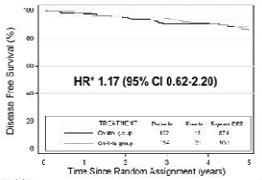
Disease-Free Survival

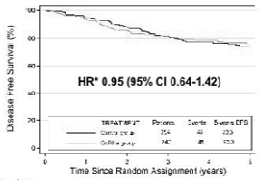
Estrogen receptor-positive disease



Number at risk

Control group	157	145	140	123	124	110
GnRHa group	156	151	144	107	125	132

Estrogen receptor-negative disease



Number at risk

Control group	250	206	202	135	109	62
GnRHa group	247	204	176	148	116	71

*Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage

$P_{interaction}$=0.857

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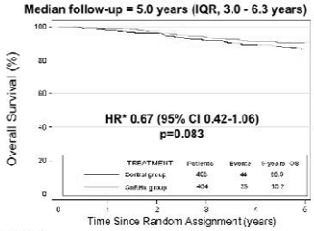
Overall Survival

Median follow-up = 5.0 years (IQR, 3.0 - 6.3 years)



Number at risk

Control group	405	362	342	201	264	166
GnRHa group	404	370	330	313	269	168

*Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage

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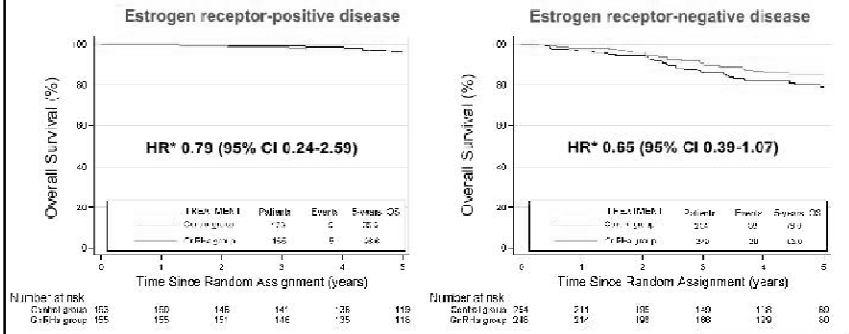
Overall Survival



*Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage

$p_{interaction}$=0.762

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Fazit:

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- Signifikant niedrigere Ovarialinsuffizienzrate nach Chemotherapie bei Einsatz von GnRH während der Chemotherapie
- Höhere Schwangerschaftsrate nach GnRH
- Überlebensdaten sind vergleichbar mit / ohne GnRH, unabhängig vom Rezeptorstatus
- Dran denken in der Beratung junger Frauen : Reproduktionsmedizin, Kryokonservierung, Fertiprotekt …
- Praxisrelevanz: Hoch - umsetzen

GS04-3

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2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

Randomized Comparison of Adjuvant Tamoxifen plus Ovarian Function Suppression vs Tamoxifen in Premenopausal Women with HR+ Early Breast Cancer: Update of the SOFT Trial

Gini Fleming, MD
on behalf of SOFT Investigators and
International Breast Cancer Study Group (IBCSG)

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Hintergrund:

- Vergleich der Arme der SOFT Studie mit einem Vergleichsarm ohne OFS. Follow UP- Daten nach 8 Jahren
- Erste Ergebnisse (5,6 Jahre) zeigten Vorteil (DFS) für T+OFS versus T v.a. bei prämenopausalen jungen Frauen nach Chemotherapie

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SOFT: Suppression of Ovarian Function Trial

Enrolled: Dec 2003-Jan 2011

Stratification
Receipt of (neo)adjuvant chemotherapy
-No chemo, enrolled within 12 weeks of surgery (47%)
-Prior chemo, premenopausal E2 level within 8 months (53%)

Nodal status
-Positive (34.5%)

OFS method intended
-Triptorelin (91%)

RAN DOM IZE

Median follow-up 8 years

- Tamoxifen x 5y (n=1018)
- **Tamoxifen+OFS x 5y (n=1015)**
- Exemestane+OFS x 5y (n=1014)

OFS=Ovarian Function Suppression

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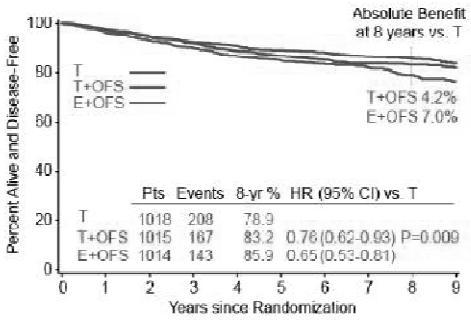
SOFT DFS

8 years median follow-up



T+OFS significantly improves DFS vs T-alone in the overall population

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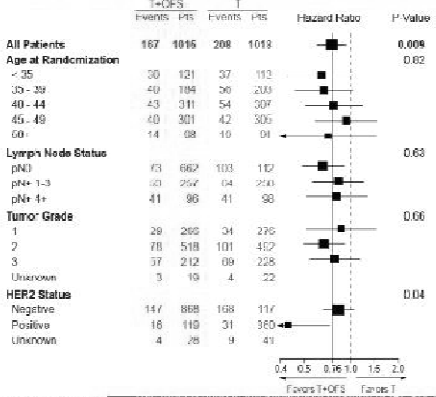
SOFT DFS: According to Subgroups



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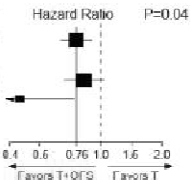
SOFT DFS: Effect of HER2 Status

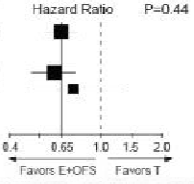
T + OFS vs T

	T+OFS Events	T+OFS Pts	T Events	T Pts
All Patients	167	1015	208	1018
HER2 Status				
Negative	147	868	168	860
Positive	16	118	31	117
Unknown	4	28	9	41



E + OFS vs T

	E+OFS Events	E+OFS Pts	T Events	T Pts
All Patients	143	1014	208	1018
HER2 Status				
Negative	105	858	168	860
Positive	31	130	31	117
Unknown	7	26	9	41



61% of HER2+ received trastuzumab

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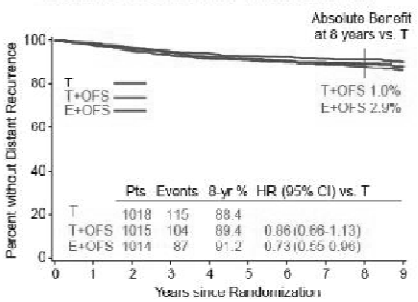
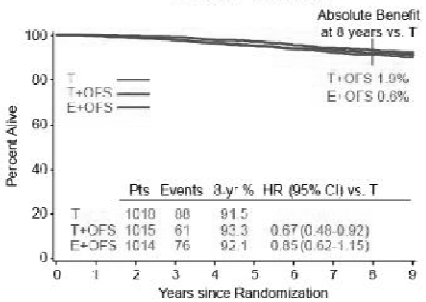
SOFT Secondary Endpoints

Distant Recurrence-Free Interval



	Pts	Events	8-yr %	HR (95% CI) vs. T
T	1018	115	88.4	
T+OFS	1015	104	89.4	0.86 (0.66-1.13)
E+OFS	1014	87	91.2	0.73 (0.55-0.96)

Overall Survival



	Pts	Events	8-yr %	HR (95% CI) vs. T
T	1018	88	91.5	
T+OFS	1015	61	93.3	0.67 (0.48-0.92)
E+OFS	1014	76	92.1	0.85 (0.62-1.15)

A small overall survival benefit is seen with T+OFS vs T, at 8 yrs median follow-up

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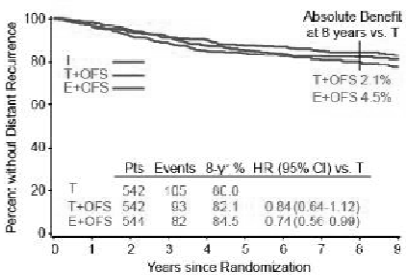
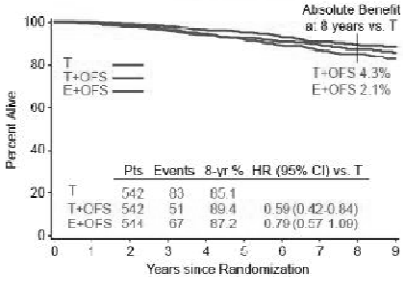
SOFT Secondary Endpoints: Prior Chemo

Distant Recurrence-Free Interval



Overall Survival



Prior Chemo cohort has small absolute OS improvements in OFS arms at 8 yrs

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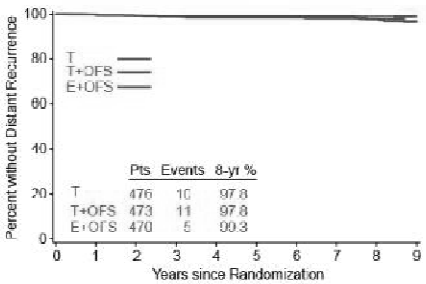
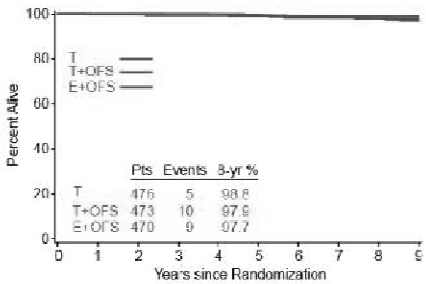
SOFT Secondary Endpoints: No Chemo

Distant Recurrence-Free Interval



Overall Survival



No Chemo cohort remains at low risk of distant recurrence with T alone;
12 of 24 deaths were in setting of no distant recurrence

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Therapie Adhärenz niedrig

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Protocol and Non-protocol Therapy

	T	T + OFS	E + OFS
Stopped assigned oral endocrine therapy early	22.5%	18.5%	27.8%
Stopped triptorelin early*		21.4%	19.6%
Received OFS (in first 5 yrs)	15.5%		
Used oral endocrine therapy at ≥6 yr**	24.7%	24.3%	12.6%

*and did not undergo oophorectomy or ovarian irradiation
**as adjuvant therapy; denominator is patients alive and in follow-up at 6 yrs

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Fazit:

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- Nach 9 Jahren erhöht sich der der Überlebensvorteil (DFS) für OFS (GnRH)
- Höchster Benefit für Frauen unter 35 Jahre (8,7 %)
- Kleiner OS Vorteil für Frauen nach Chemotherapie
- Frauen ohne Chemotherapie haben nach 8 Jahren Tamoxifen alleine ein niedriges Fernmetastasenrisiko

- Mit Frauen unter 35 Jahren , V.a nach Chemotherapie sollte die OFS (GnRH) Option angesprochen werden

- Praxisrelevanz: Hoch – umsetzen

GS4-02

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2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with HR+ Early Breast Cancer: Update Of The Combined TEXT and SOFT Trials

Prudence Francis
on behalf of Olivia Pagani, MD
TEXT and SOFT Investigators and
International Breast Cancer Study Group (IBCSG)

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Hintergrund:

- TEXT u. SOFT zeigten, daß E+OFS die Überlebenszeit (DFS) bei prämenopausalen HR+ Patientinnen verbessert im Vgl. zu T+OFS
- Mittlerweile Leitlinienoption: ASCO, NCCN, St. Gallen, AGO
- 9 Jahres Follow UP wird präsentiert

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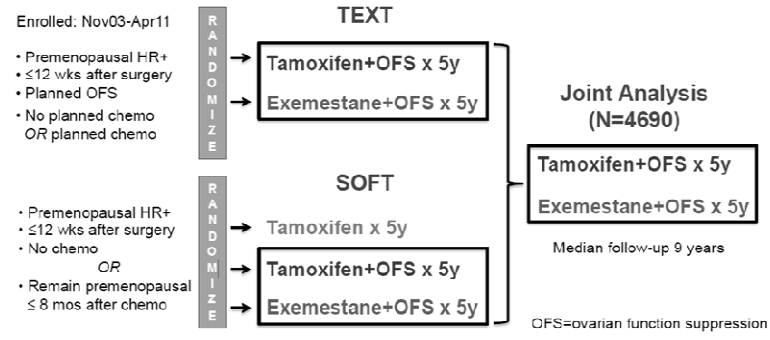
TEXT and SOFT Designs



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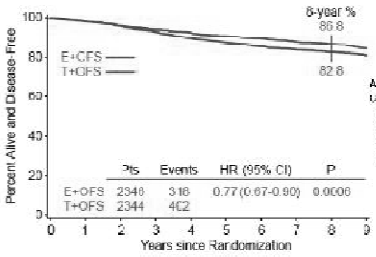
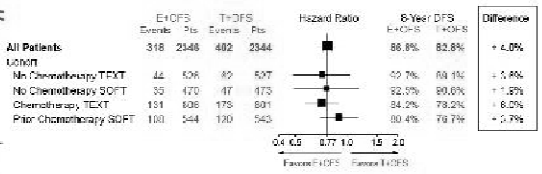
Sustained Improvement in DFS





4.0% absolute improvement in 8-yr DFS for E+OFS after 9 years median follow-up

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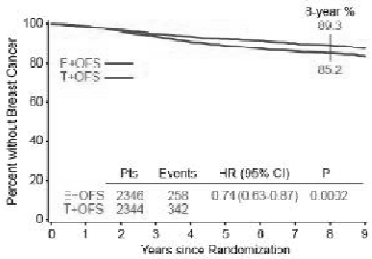
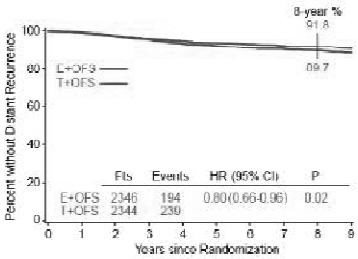
Significant Reductions in Recurrence

Breast Cancer-Free Interval



Distant Recurrence-Free Interval



4.1% absolute improvement in 8-yr freedom from breast cancer for E+OFS

2.1% absolute improvement in 8-yr freedom from distant recurrence for E+OFS

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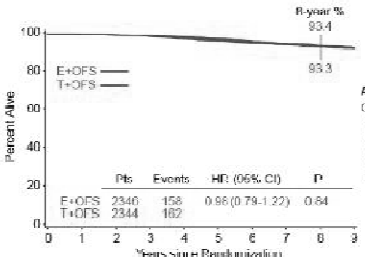
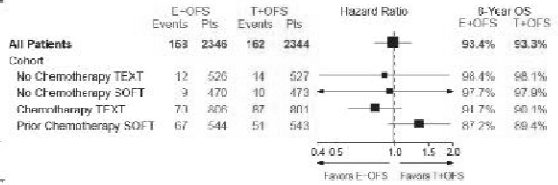
Overall Survival





E+OFS did not improve Overall Survival vs T+OFS, after 9 years median follow-up

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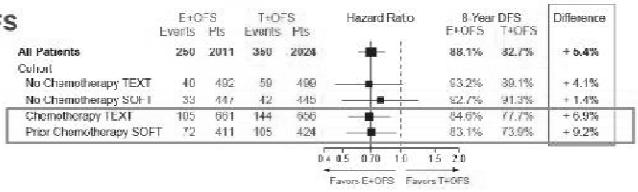
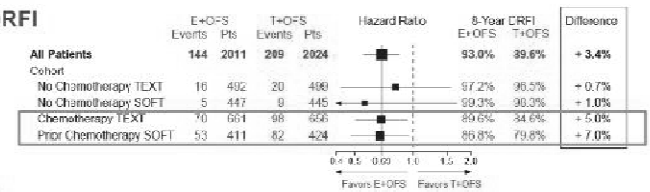
HER2-negative Patients (N=4035)

DFS



DRFI



- Consistent relative treatment effects in all cohorts
- Larger absolute benefits of E+OFS in chemo cohorts
- Overall Survival HR=0.86 (0.68-1.10)

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Treatment Effect by Age (HER2-neg)

DFS

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	Hazard Ratio	8 Year DFS E+OFS	8 Year DFS T+OFS	Difference
All Patients	250	2011	350	2024		88.1%	82.7%	**+ 5.4%**
Age at Randomization								
< 35	38	180	54	170		76.6%	68.7%	+ 8.2%
35 - 39	63	333	77	320		92.7%	76.6%	+ 7.1%
40 - 44	72	641	108	662		88.6%	83.8%	+ 4.8%
45 - 49	50	857	87	880		91.8%	87.4%	+ 4.3%
50+	19	200	26	177		92.6%	89.2%	+ 3.4%

0.4 0.5 0.70 1.0 1.5 2.0

Favors E+OFS Favors T+OFS

DRFI

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	Hazard Ratio	8 Year DRFI E+OFS	8 Year DRFI T-OFS	Difference
All Patients	144	2011	209	2024		93.0%	89.6%	**+ 3.4%**
Age at Randomization								
< 35	30	180	40	170		82.5%	74.9%	+ 7.6%
35 - 39	42	333	58	320		88.1%	82.5%	+ 5.6%
40 - 44	39	641	59	662		93.5%	90.7%	+ 2.8%
45 - 49	27	857	44	880		96.3%	93.7%	+ 2.6%
50+	6	200	8	177		97.9%	95.3%	+ 2.6%

0.4 0.5 0.69 1.0 1.5 2.0

Favors E+OFS Favors T+OFS

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2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

Selected Adverse Events (all patients)

	E + OFS (N=2317)	T + OFS (N=2326)
Endometrial cancer	**n=4**	**n=9**
Musculoskeletal symptoms (G3-4)	**11%**	**6%**
Osteoporosis (G2-4; T score< -2.5)	**15%**	**7%**
Fractures (G3-4)	**1.6%**	**1.0%**
Hot Flashes (G3)	10%	12%
Libido decrease (G2)	15%	12%
Vaginal dryness (G2)	27%	22%
Depression (G3-4)	4.1%	4.6%
Thrombosis/embolism (G2-4)	**1.2%**	**2.3%**

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2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

Adverse Events and Treatment Adherence

- Incidence of grade 3-4 targeted AEs was similar in the two groups (32% and 31%)
- Overall, 15% of patients stopped all protocol-assigned treatment early

More patients on E+OFS stopped assigned oral ET early

- 14% vs 6% by 1 year
- 25% vs 19% by 4 years

No difference in the rate of triptorelin cessation

- 18% vs 19% by 4 years

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Fazit:

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- Nach 9 Jahren weiterhin DFS Vorteil für E+OFS vs. T+OFS (4 % abs.)
- Kleiner Vorteil für fernmetastasenfreies Überleben (2 % abs.)
- Bei HER2-neg. Tumoren höherer Vorteil für E+OFS , unabhängig von Alter und Chemo. Höhere Effekte für Patientinnen , die Chemo erhielten bei Risikofaktoren
- Effekte waren altersunabhängig, absoluter Benefit höher bei jungen Frauen
- Kein OS Vorteil !

- Kernfrage: Abwägung von Benefit und Toxizität für die individuelle HR+ prämenopausale Patientin

- Praxisrelevanz : Hoch : Einzelfall - Beratung / Abwägung der individuellen Patientin / Risikosituation

GS1-02

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San Antonio Breast Cancer Symposium December 5-9, 2017

NSABP B-47 (NRG Oncology)
Phase III RCT Comparing Adjuvant Chemotherapy with AC→Weekly Paclitaxel or TC x 6 with or without Trastuzumab for 1 Year in High-risk, Invasive Breast Cancer Negative for HER2 by ISH and with IHC 1+ or 2+ (HER2-Low IBC)

Louis Fehrenbacher, Reena S. Cecchini, Charles E. Geyer, Jr., Priya Rastogi, Joseph P. Costantino, James N. Atkins, John Crown, Jonathan Polikoff, Jean -Francois Boileau, Louise Provencher, Christopher Stokoe, Timothy D. Moore, André Robidoux, Virginia Borges, Kathy S. Albain, Sandra M. Swain, Soonmyung Paik, Eleftherios P. Mamounas, Norman Wolmark

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Hintergrund aus Zulassungsstudien:

- Adj. Trastuzumab führt zu ca. 50% Verbesserung des rezidivfreien Überlebens
- Retrospektive Analyse NSABP B-31 und N9831 : Effekt auch bei Pat. mit IHC+ oder ICH++ sichtbar
- NSABP B-47 untersucht dieses Kollektiv

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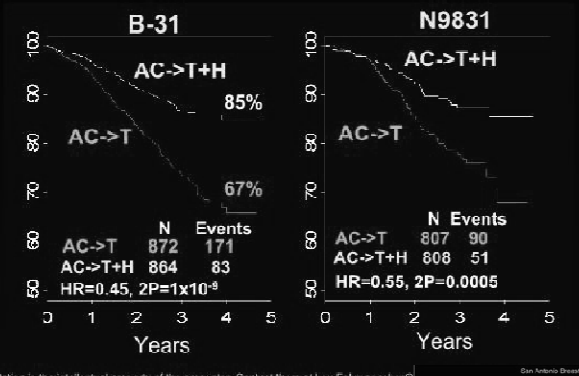
San Antonio Breast Cancer Symposium December 5-9, 2017

ASCO 2005: B-31/N9831 Disease-Free Survival



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San Antonio Breast Cancer Symposium, December 5-9, 2017

NSABP B-31 Study Details

- AC→Paclitaxel with or without trastuzumab
- HER2+ node-positive breast cancer
- Initial study entry criteria included
  - FISH+ ≥ 2.0 or IHC 3+
  - HER2 testing performed at local lab site
  - A tissue specimen sent to NSABP for later testing
- NSABP B-31: Central HER2 status performed as quality check after 529 patients enrolled

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B-47: Adjuvant Trastuzumab in HER2 Low Breast Cancer

STRATIFICATION

- HER2 IHC Score (1+, 2+)
- Number of Positive Nodes (0-3, 4-9, 10+)
- ER / PgR Status
- Intended ChemoRx regimen (AC→WP, TC)

RANDOMIZATION

GROUP 1	GROUP 2
ChemoRx*	ChemoRx* + Trastuzumab x 1year

Hormonal therapy and radiation as indicated. Chemotherapy by MD Choice:
*AC→WP: Doxorubicin 60mg/m2 and Cyclophosphamide 600mg/m2 q2 or 3 wks x 4 followed by qwk paclitaxel x 12
or TC: Docetaxel 75mg/m2 + Cyclophosphamide 600mg/m2 q3wk x 6

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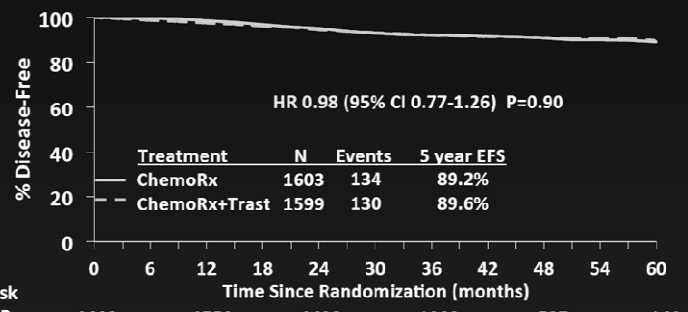
B-47: Invasive Disease-Free Survival



No. at Risk						
ChemoRx	1603	1558	1423	1003	595	140
ChemoRx+Trast	1599	1528	1403	1009	591	117

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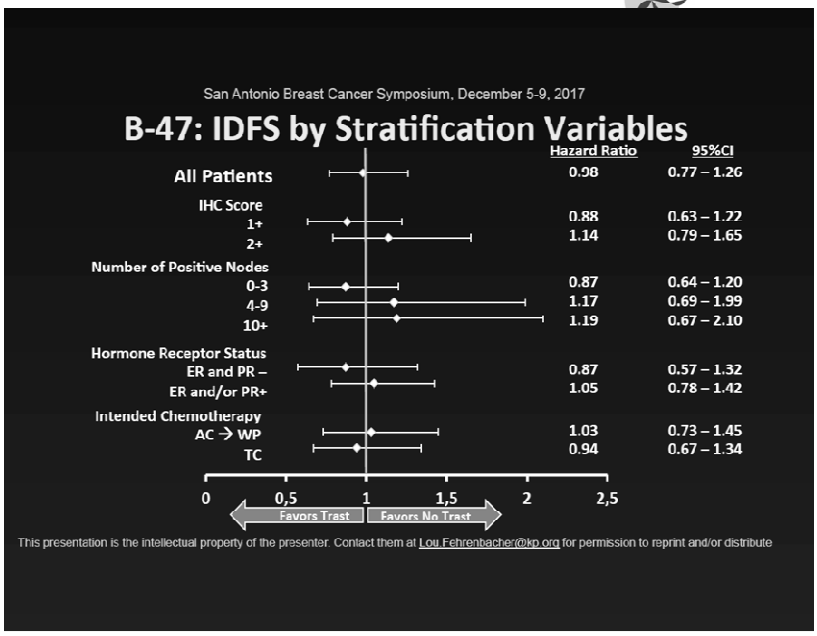

Fazit:

- Retrospektive Ergebnisse zugunsten eines Benefits von adjuvantem Trastuzumab mit niedrig HER2 exprimierenden Ma-Ca (ICH+ oder ICH++) konnten nicht bestätigt werden
- Standard bleibt HER-2 gerichtete Therapie bei ICH+++ oder ICH++ und FISH positiv
- Praxisrelevanz: Hoch , keine Änderung

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Zusammenfassung – Take Home

- **Dosisdichte, sequentielle Therapie macht Sinn (GS1-01, Gray et al, EBCTCG)**
- **2 (-3) Jahre Bisphosphonate adjuvant sind genug , Off Label ! (GS1-06, Janni et. al)**
- **Es bleibt (wahrscheinlich) bei „No ink on tumor“ für alle, Abweichung im Einzelfall möglich (GS5-01, Vicini et al)**
- **Es kann bei Verzicht auf Axilladissektion bleiben bei Mikromets und „Low Burden“, ggf auch nach Ablatio (GS5-01, Galimberti et al)**
- **Ovarschutz bei jungen Frauen nicht vergessen ! (GS4-01, Lambertini et al)**
- **Bedeutung der zusätzlichen ovariellen Suppression bei HR+ prämenopausalen Frau nimmt zu (GS4-02/03, Fleming/Francis, IBCSG)**
- **Trastuzumab nur bei HER2 +++ bleibt der Standard (GS1-02, Fehrenbacher et al)**

Danke für die Aufmerksamkeit

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