SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®

DECEMBER 5-9, 2023 | @SABCSSanAntonio

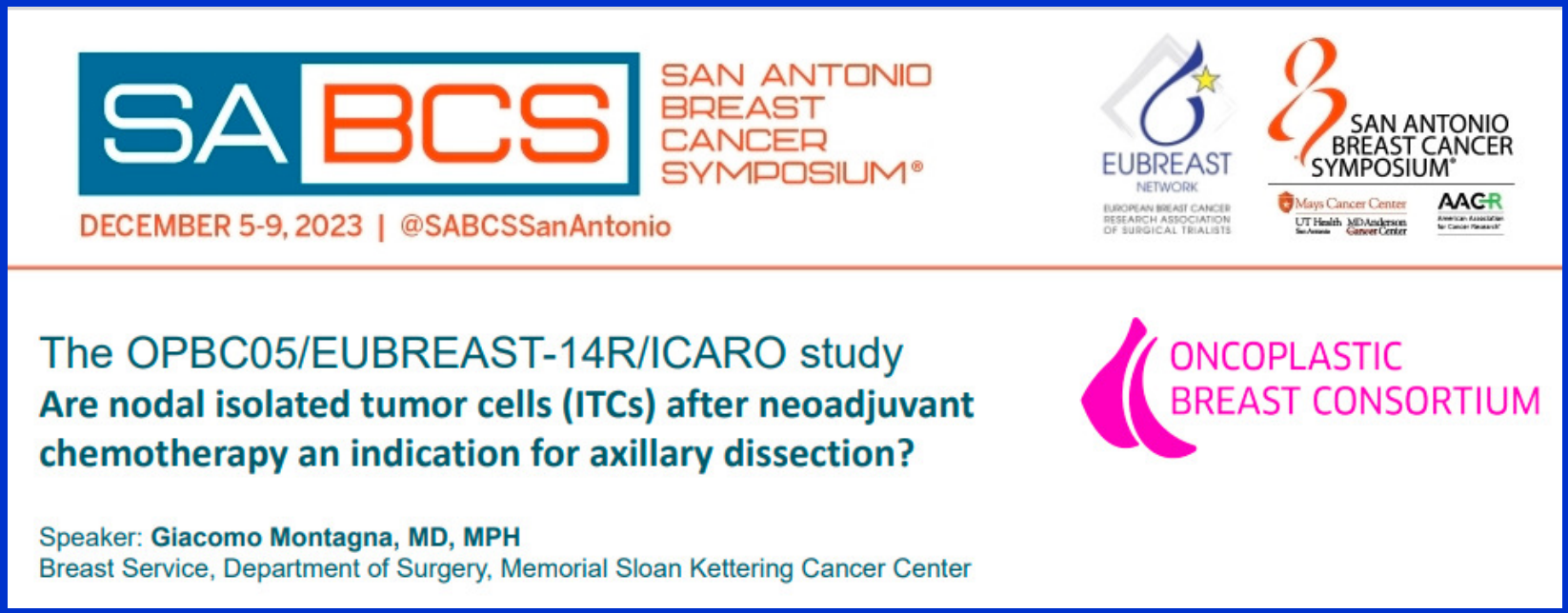
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center

AACR American Association for Cancer Research

Jan Dünnebacke
Marienhof

Isolierte Tumorzellen im Lymphknoten nach NCT



Positiver Sentinel nach NAC

Background: Nodal Burden in Patients with Residual Nodal Disease After NAC

- Patients with a positive sentinel lymph node (SLN) after neoadjuvant chemotherapy (NAC) have a high residual nodal burden, and axillary lymph node dissection (ALND) is currently considered standard of care

	ACOSOG Z1071	SN FNAC	MSKCC
Micromets	164/273 **(60.1%)**	3/8 **(37%)**	34/61 **(56%)**
Macromets		28/44 **(64%)**	75/121 **(62%)**

Zeichnen

Residual Isolated Tumor Cells

- Residual isolated tumor cells (ITCs) are found in ~1.5% of patients undergoing neoadjuvant chemotherapy
- Data on the likelihood of finding additional positive lymph nodes in patients with residual ITCs are scarce, and the benefit of ALND is unclear

	ACOSOG Z1071	SN FNAC	MSKCC	OVERALL
ITCs	4/11	4/7	1/6	**9/24 (37.5%)**

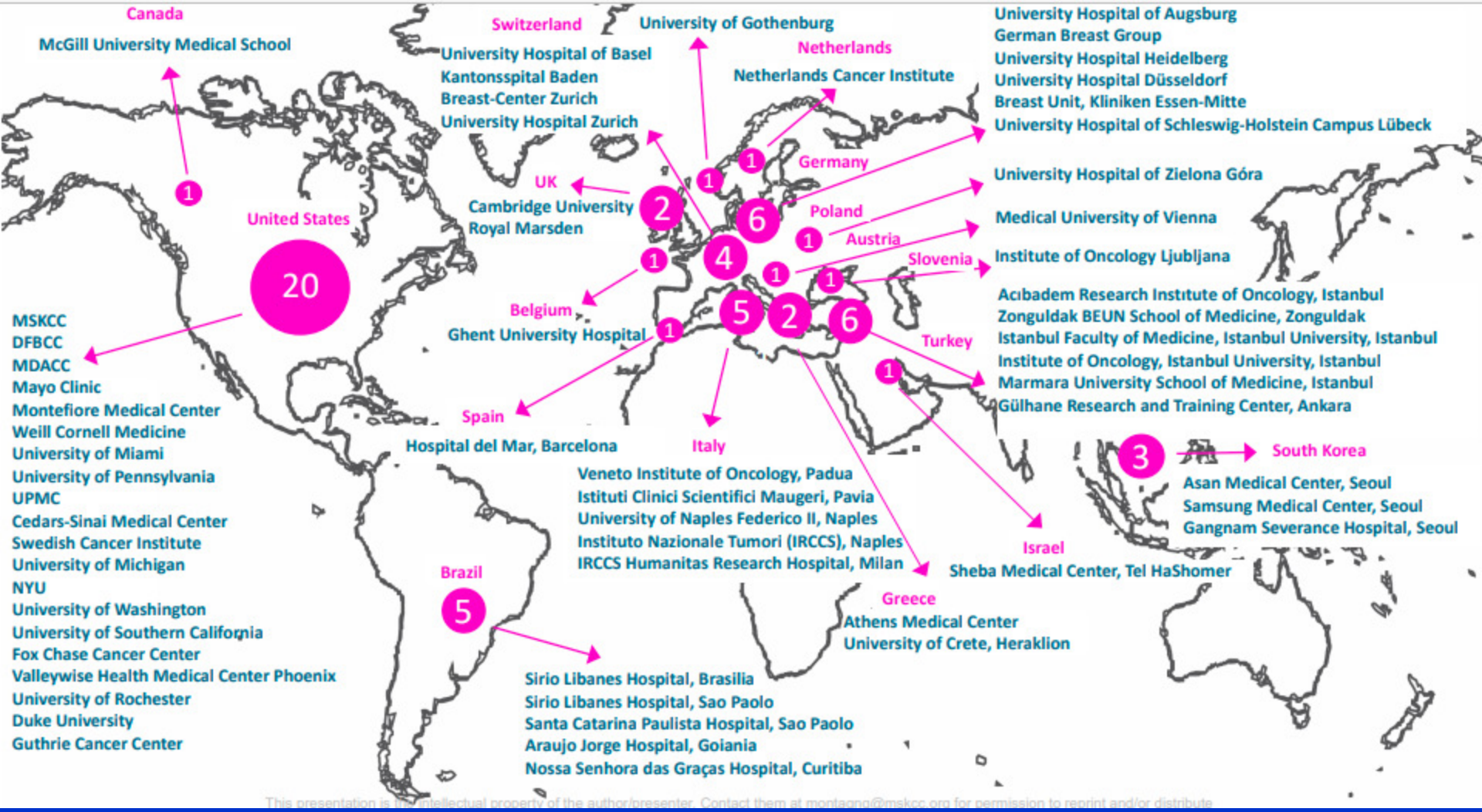
- As a consequence, surgical management of the axilla in these patients is not standardized

Wong SM et al. ASO 2019
Burstein HJ et al. Ann Onc 2021

Weitere pos LK, Rezidive, outcome…?

Aims

- To determine how often additional positive LNs are found in patients with residual ITCs
- To evaluate rates of axillary and any invasive recurrence
- To compare outcomes in patients treated with and without ALND



Study Population

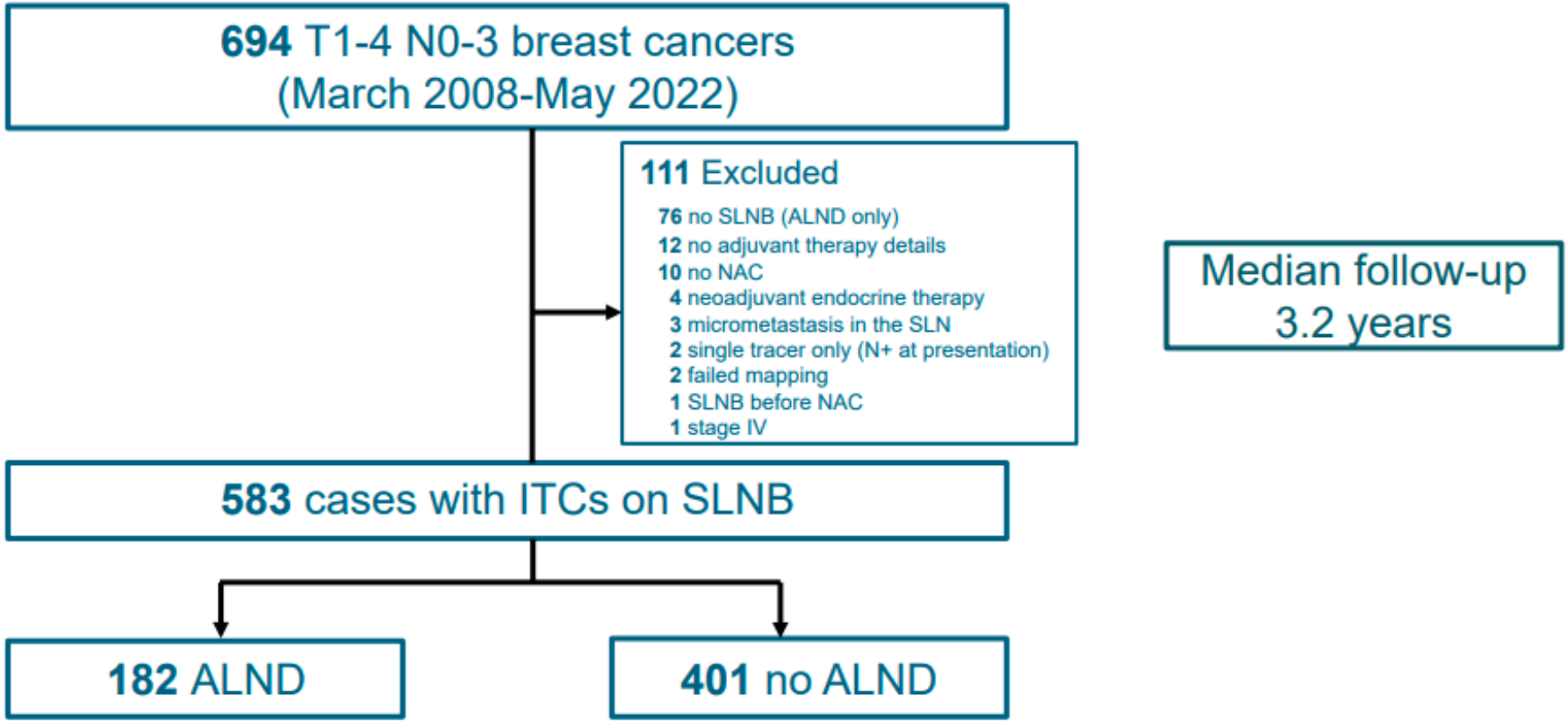
Inclusion criteria

- T1-4 N0-3 BC patients
- Surgery after NAC with detection of ITCs [ypN0(i+)] at frozen section or final pathology
- SLNB performed with dual-tracer mapping *or* TAD *or* MARI for N+ and with single tracer for N0
- Detection of ITCs by H&E or IHC

Exclusion criteria

- No SLNB/TAD
- Inflammatory breast cancer
- Stage IV
- NET
- Detection by OSNA (quantitative measurement of target mRNA) due to lack of standardized cut-off

Flow Diagram



Clinical Characteristics

	Overall n = 583	No ALND n = 401	ALND n = 182	p value
Age, years (IQR)	48 (41, 57)	48 (40, 57)	49 (43, 58)	0.11
Race/Ethnicity				0.5
Asian	11%	10%	13%	
Black	5%	6%	3%	
Hispanic	5%	6%	4%	
White	77%	76%	77%	
Other/unknown	2%	3%	2%	
Clinical T stage				0.15
1	16%	17%	15%	
2	57%	55%	62%	
3	23%	25%	19%	
4	3%	3%	4%	
X	0.2%	0%	0.5%	
Clinical N stage				**<0.001**
0	26%	30%	16%	
1	64%	63%	67%	
2	8%	5%	13%	
3	2%	2%	4%	

Axillary Staging Characteristics

	Overall n = 583	No ALND n = 401	ALND n = 182	p value
Staging technique (cN+ only)	**n = 433**			
SLNB with dual tracer mapping	58%	52%	69%	**< 0.001**
TAD	34%	37%	28%	
MARI	8%	11%	3%	
Entire cohort (cN0 and cN+)				
# of SLNs removed (mean, min, max)	3.3 (0, 16)	3.5 (1, 16)	2.8 (0, 10)	**< 0.001**
# of SLNs with ITCs (mean, min, max)	1.2 (0, 6)	1.2 (0, 6)	1.2 (0, 6)	0.6
ITCs detected on frozen section				**< 0.001**
Yes	25%	8%	62%	
Not performed/unknown	20	11	9	
Total # of LNs removed (mean, min, max)	7 (1,37)	4 (1, 16)	15 (4, 37)	**< 0.001**

Treatment Characteristics

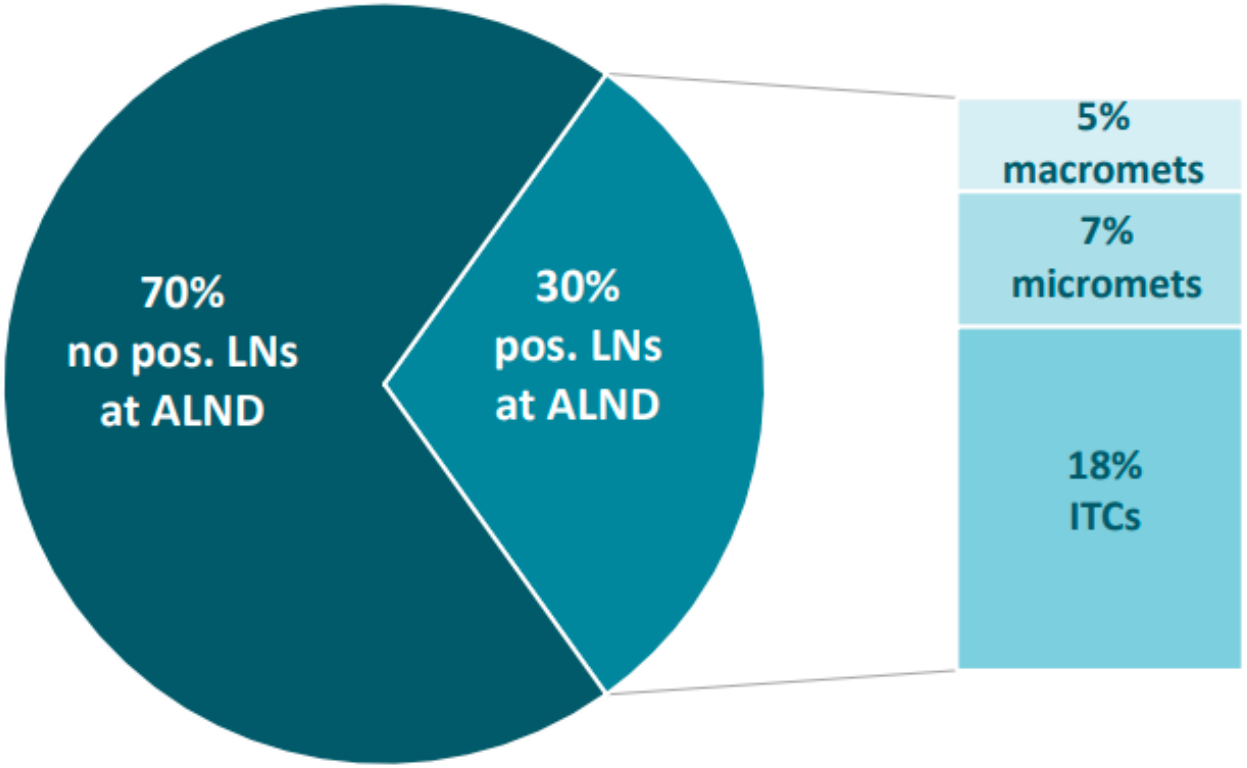
	Overall n = 583	No ALND n = 401	ALND n = 182	p value
NAC regimen				
HER2-	**n = 362**			0.8
AC-T	79%	78%	81%	
AC-T + Carbo	6.6%	6.0%	8.1%	
AC-T + Carbo with pembrolizumab	2.8%	2.8%	2.7%	
Anthracycline-free regimen	2.8%	3.2%	1.8%	
Other	8.6%	9.6%	6.3%	
HER2+	**n = 221**			0.068
AC-TH	22%	20%	27%	
AC-THP	29%	29%	31%	
TC-H	1.8%	1.3%	2.8%	
TC-HP	30%	36%	18%	
Other	16.5%	13.7%	18%	

Radiatio

Treatment Characteristics

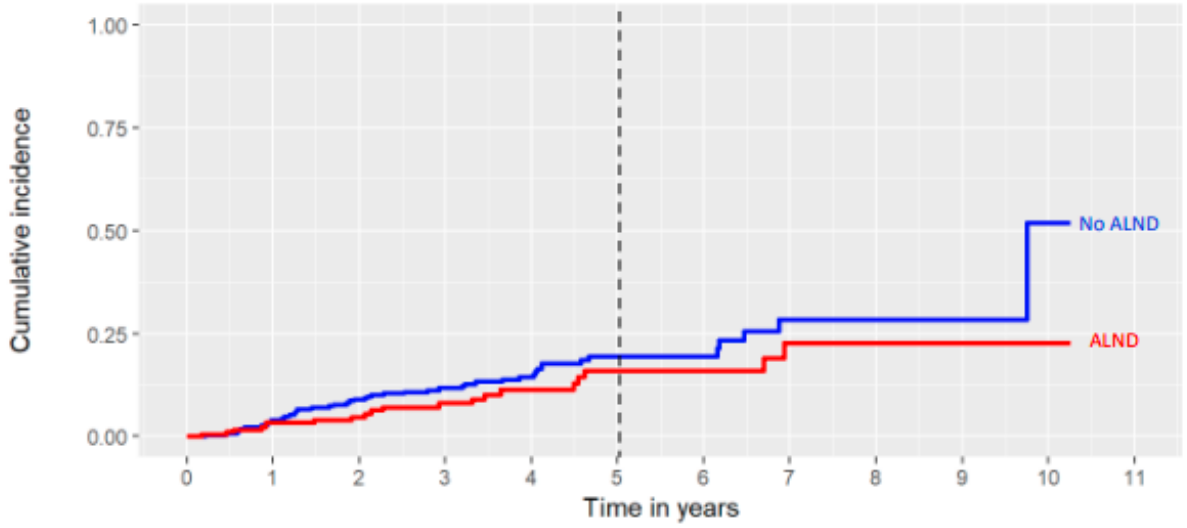
	Overall n = 583	No ALND n = 401	ALND n = 182	p value
Type of breast surgery				0.13
Breast conservation	46%	48%	41%	
Mastectomy	54%	52%	59%	
Radiation therapy (RT)				
Breast (n = 267)	98%	97%	100%	0.3
Chest wall (n = 316)	82%	78%	89%	**0.024**
Nodal RT				**0.038**
Yes	77%	75%	82%	

Additional Positive Lymph Nodes in the ALND Group (n=182)



Any Invasive Recurrence (No ALND vs ALND)

5-year rate of any invasive recurrence no ALND vs ALND
19% vs 16%, p = 0.13



Number at risk

Strata												
No ALND	401	349	266	185	129	71	43	20	9	5	2	2
ALND	182	165	127	95	68	50	37	19	13	10	5	3

Outcome nicht abhängig von ALND

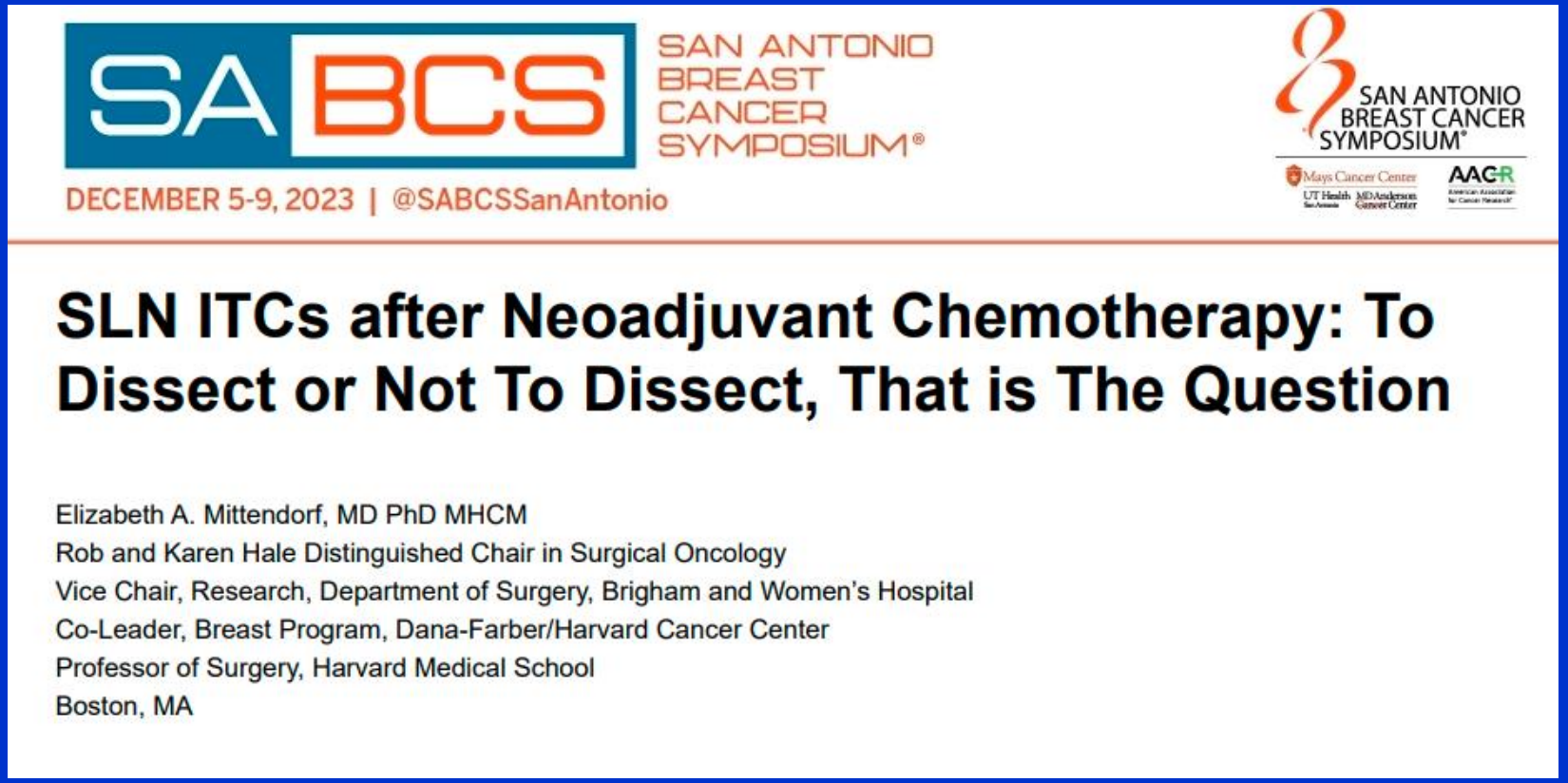
Conclusions

- The likelihood of finding additional positive lymph nodes in patients with residual ITCs is lower than in patients with residual micro- and macrometastases
  - macrometastases were found at ALND in 5% of cases
  - no impact of nodal status at presentation
- Detection of ITCs on frozen section was strongly associated with ALND
- Rates of axillary and invasive recurrence did not statistically differ based on the use of ALND

Conclusions

- These results do not support routine ALND in patients with residual ITCs after NAC
- Randomized trials (NASBP-B51) will provide further insight to whether nodal RT is needed in this setting

Diskussion…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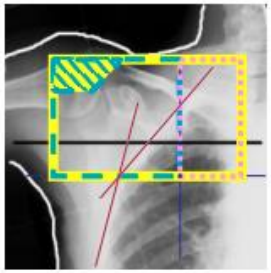
AACR
SLN ITCs after Neoadjuvant Chemotherapy: To Dissect or Not To Dissect, That is The Question
Elizabeth A. Mittendorf, MD PhD MHCM
Rob and Karen Hale Distinguished Chair in Surgical Oncology
Vice Chair, Research, Department of Surgery, Brigham and Women's Hospital
Co-Leader, Breast Program, Dana-Farber/Harvard Cancer Center
Professor of Surgery, Harvard Medical School
Boston, MA

Evolution of Axillary Surgery

1960-1980s	1990s	2000s	2010s
ALND	SLNB for cN0	SLNB ± RT for pN+	SLNB for cN1 after NAC



Adapted from T King, MD and M Morrow, MD

Keine Axilla-Dissektion bei ITC

Conclusions

- Rad Onc
  - Interpretation of the data pending results of NSABP-B51
- Pathology
  - Routine use of IHC not required
- Surgery
  - Routine ALND not indicated
- Multidisciplinary care is critical for treating breast cancer patients

DCIS

(PS01-10) Surgical margins in breast conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and clinical outcomes: significant associations with increased recurrence and overall survival.

DCIS

(PS01-10) Surgical margins in breast conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and clinical outcomes: significant associations with increased recurrence and overall survival.

Conclusion:

Patients with DCIS with histological margins of < 2mm, adjusted for other clinical factors, have significantly worse TTR and OS rates compared to margins ≥2mm; the increased annual event rate is consistent out to 15 years.

More than 1 BCS is also associated with an increased risk of recurrence.

These findings are important for the treatment of patients with DCIS.

(PS01-10) Surgical margins in breast conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and clinical outcomes: significant associations with increased recurrence and overall survival.

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DCIS >2mm

BRCA 1….Mastektomie bds?

Surgical Treatment of Women with Breast Cancer and a *BRCA1* Pathogenic Variant: An International Analysis of the Impact of Bilateral Mastectomy on Survival

Kelly A. Metcalfe, RN, PhD, FAAN, FCAHS, FCAN
Senior Scientist, Women's College Research Institute, Toronto, ON
Professor, Bloomberg Faculty of Nursing, University of Toronto, Toronto, ON

UNIVERSITY OF TORONTO

WCHRI
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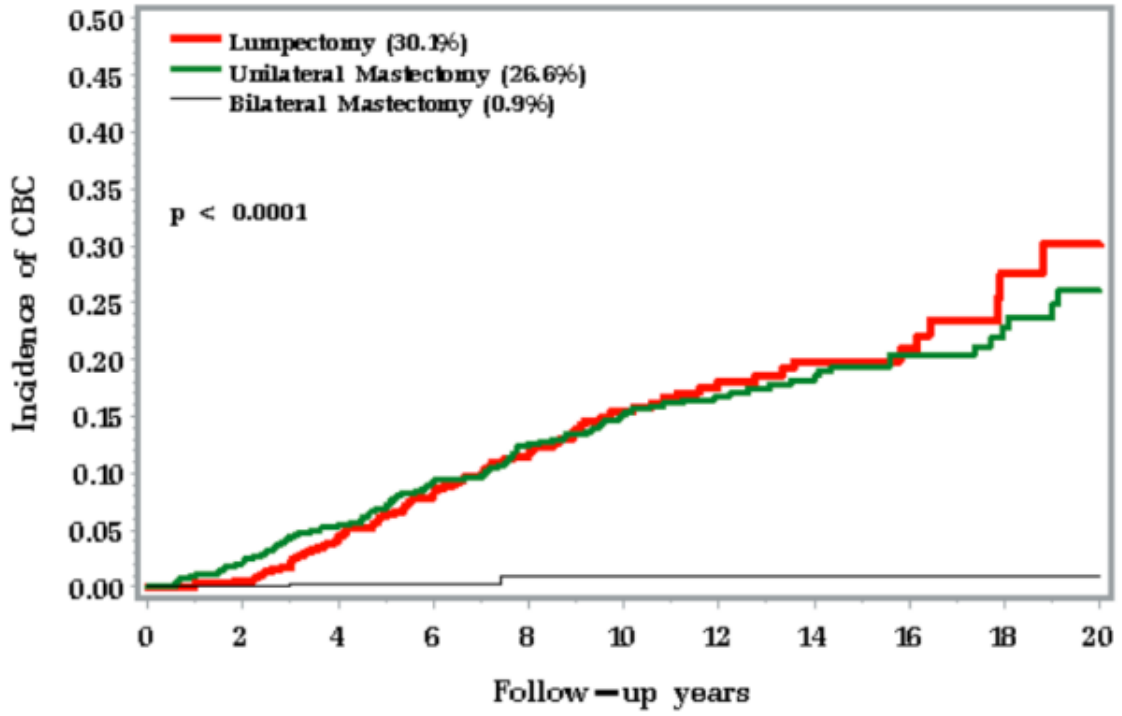
Health care for women | REVOLUTIONIZED

Study Cohort

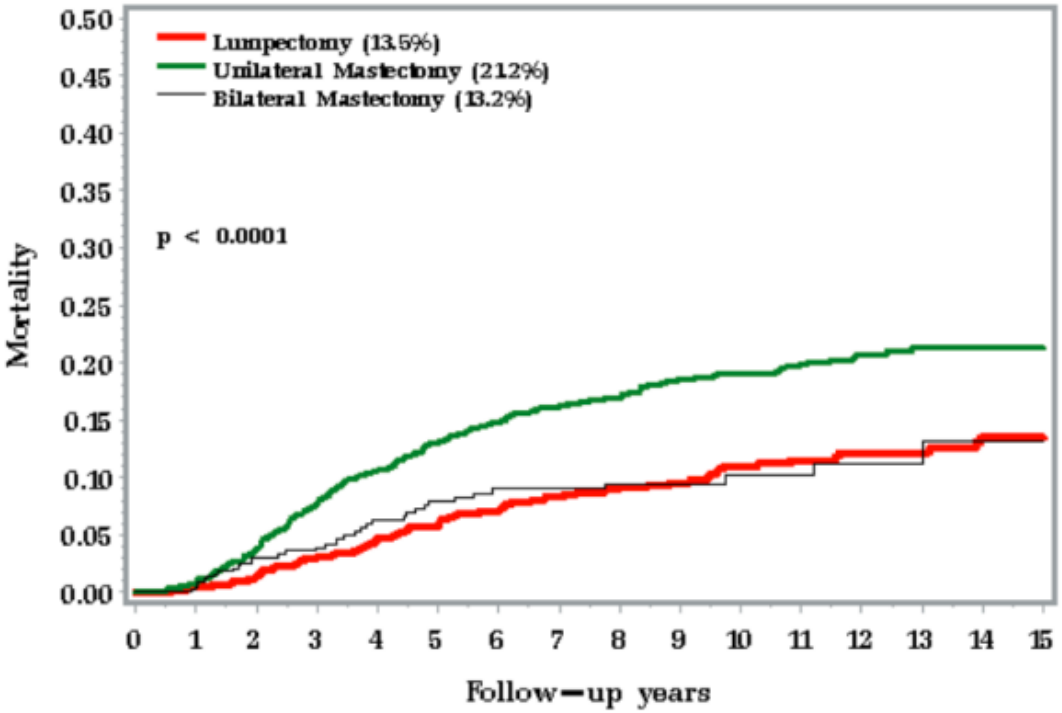
- 2482 eligible participants
- 26 centers
- 11 countries

Variable	Mean (range) / frequency (%)
Date of diagnosis	2011.1(1995-2021)
Follow up (years)	8.9 (0.0-26.0)
Age at Diagnosis (years)	
Mean	43.1 (18-70)
<=40	1049 (42.3)
40-50	833(33.6)
50+	600(24.2)
Surgery	
BCT	852 (34.3)
Mastectomy	1141 (46.0)
Bilateral Mastectomy	489(19.7)

Contralateral Breast Cancer by Surgery



Breast Cancer Mortality by Surgery



Results: Clinical Characteristics

Variable	BCT N=852	Unilateral mastectomy N=1141	Bilateral Mastectomy N=489	P-value
Size (cm)	2.1 (0-20)	3.0 (0-40)	2.2 (0-27)	<0.0001
<=2	506 (59.4)	451 (39.5)	263 (53.8)	
2-5	277 (32.5)	508 (44.5)	188 (38.4)	<0.0001
5+	24 (2.8)	101 (8.9)	21 (4.3)	
Nodes				
Neg	647 (78.1)	683 (62.4)	354 (75.6)	
Pos	182 (21.9)	412 (37.6)	114 (24.4)	0.03
Grade				
I	20 (2.5)	22 (2.2)	23 (2.6)	
II	173 (22.1)	243 (24.1)	75 (16.1)	0.05
III	591 (75.4)	744 (73.7)	380 (81.4)	
ER				
Neg	614 (72.2)	826 (73.4)	360 (74.2)	
Pos	233 (27.4)	300 (26.6)	124 (25.6)	0.52

Breast Cancer Mortality

- 285 (11.5%) died of breast cancer

Variable	BCT N=852	Unilateral mastectomy N=1141	Bilateral Mastectomy N=489	P-value
Died of BC				
No	667 (78.3)	968 (84.8)	453 (92.6)	
Yes	76 (6.9)	173 (15.2)	36 (7.4)	<0.0001

Conclusions

- Women with *BRCA1* PV and bilateral mastectomy
  - Significantly less likely to develop contralateral breast cancer ($p<0.0001$)
- Women with *BRCA1* PV and contralateral breast cancer
  - Twice as likely to die of breast cancer (HR 2.22, $p<0.0001$)
- Bilateral mastectomy not significantly associated with reduction in mortality compared to BCT (HR 0.83, $p=0.52$)

Strahlentherapie

Strahlentherapie

- …nach neoadjuvanter Chemotherapie

cN+, nach NACT ypn0

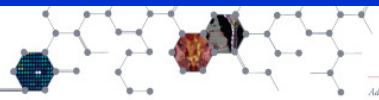
Loco-regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

ypN0, Radiatio LAW…?

Background/Rationale

- For patients who undergo upfront surgery, the benefit of adjuvant regional nodal irradiation including the chest wall after mastectomy (CWI+RNI) or when added to whole breast irradiation after lumpectomy (WBI+RNI) is well established in patients with pathologically positive axillary lymph nodes.[1]
- Patients who present with axillary node involvement, receive neoadjuvant chemotherapy (NAC), and are found to be pathologically node-negative at surgery (ypN0), have lower loco-regional recurrence rates compared to those who remain pathologically node-positive (ypN+).[2]
- In this phase III, randomized trial we evaluated whether CWI+RNI after mastectomy or WBI+RNI after lumpectomy significantly improves invasive breast cancer recurrence-free interval in clinically node (+) patients who are found to be ypN0 after NAC.

Study Schema



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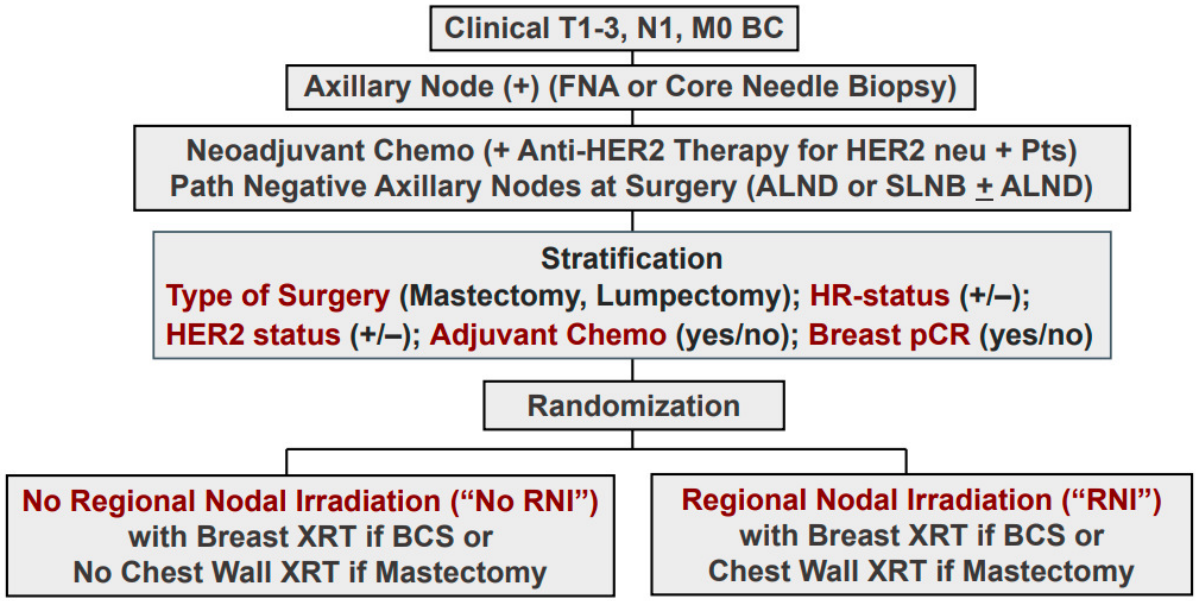


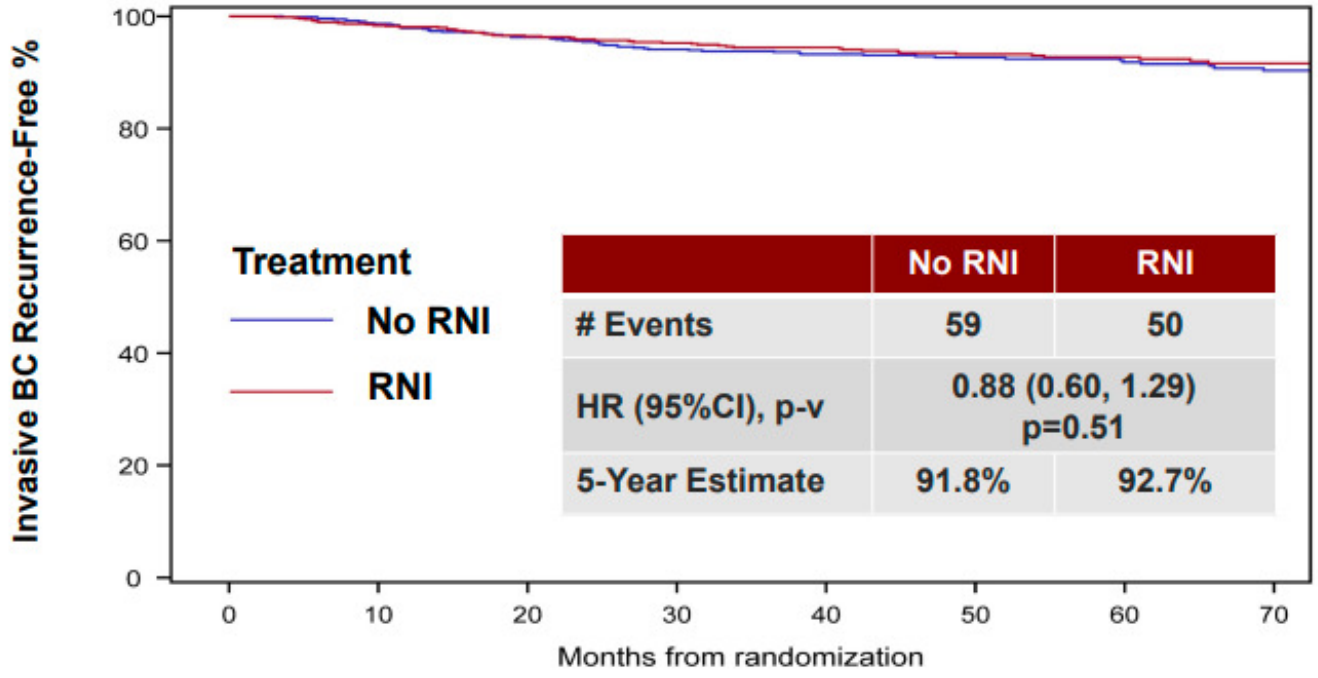
FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation

Baseline Characteristics (2)

Characteristic		No RNI (%) n=821	RNI (%) n=820
Tumor Subtype	Triple-negative ER+ and/or PR+/HER2- ER- and PR-/HER2+ ER+ and/or PR+/HER2+	21 22 25 31	23 20 24 33
Breast Surgery	Lumpectomy Mastectomy	58 42	58 42
Axillary Surgery	SLNB ALND (+/-SLNB)	55 45	56 44
pCR in Breast	No Yes	22 78	21 79
Adjuvant Chemotherapy	No Yes	100 <1	99 1

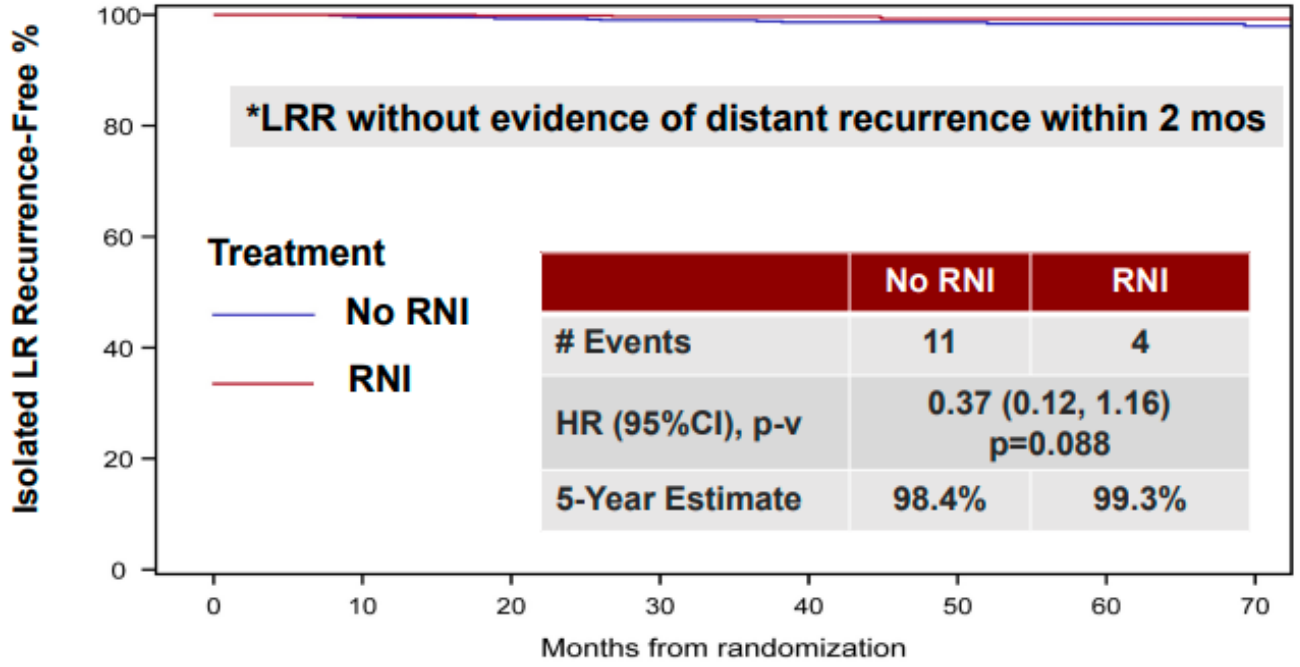
Primary Endpoint

Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

Isolated Loco-Regional Recurrence-free Interval (ILRRFI)*

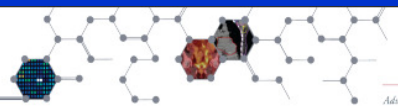


	No RNI	RNI
# Events	11	4
HR (95%CI), p-v	0.37 (0.12, 1.16) p=0.088	
5-Year Estimate	98.4%	99.3%

cN+, nach NACT ypn0

Radiatio der LAW?

Conclusions



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- In patients who present with biopsy-proven axillary node involvement (cN+) and convert their axillary nodes to ypN0 after NAC, CWI+RNI after mastectomy, or WBI+RNI after lumpectomy, did not improve the 5-year IBCRFI, LRRFI, DRFI, DFS, or OS
- These findings suggest that downstaging involved axillary nodes with neoadjuvant chemotherapy can optimize adjuvant radiotherapy use without adversely affecting oncologic outcomes
- Follow-up of patients for long-term outcomes continues

Strahlentherapie

Strahlentherapie

- …oder einfach mal nicht?

IDEA

I ndividuell D ecision E ndocrine A lone

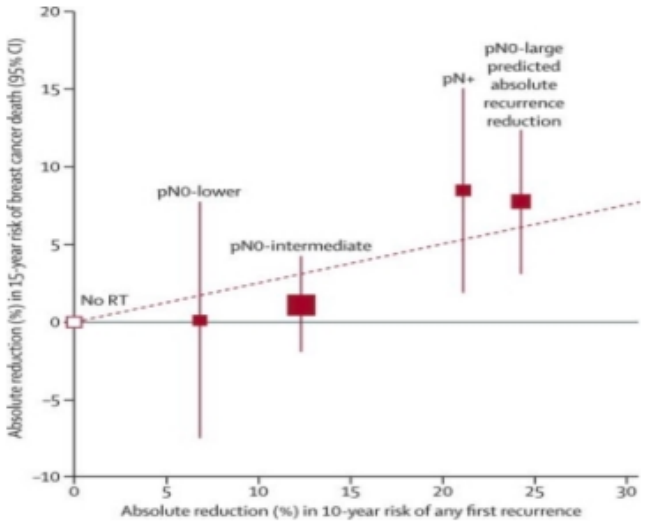
Five-year outcomes of the IDEA trial of endocrine therapy without radiotherapy after breast-conserving surgery for postmenopausal patients aged 50-69 with genomically-selected favorable Stage I breast cancer

Speaker: Reshma Jagsi, MD, DPhil
Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA

Lokale Kontrolle, Survival…

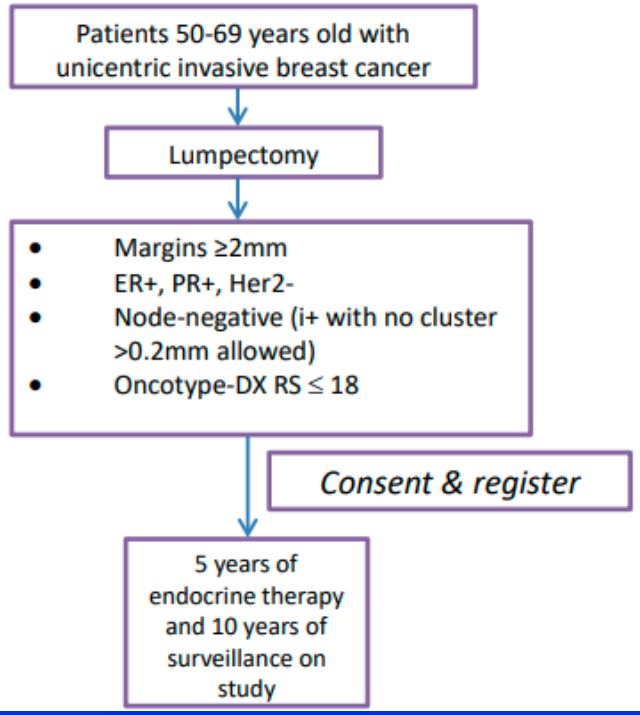
Background

- Multiple randomized trials have demonstrated that RT after breast conserving surgery (BCS) substantially improves the local control of invasive breast cancer
  - EBCTCG meta-analysis suggests modest survival benefit
- Not all subgroups attain the same absolute benefit from RT, and survival benefit appears restricted to those with a larger absolute reduction in recurrence risk from RT
  - Motivates further research



Strenge Kriterien…

IDEA: Individualized Decisions for Endocrine therapy Alone



- Prospective multicenter cohort trial, first to use genomic assay and consider younger post-menopausal patients (NCT02400190)
- 200 patients enrolled over 3.3 years (June 2015-October 2018) at 13 collaborating sites:
  - University of Michigan, MSKCC, Hopkins, Harvard (MGH/BIDMC), Penn, Stanford, Yale, Loyola, MCW, ECU, UTSW, CINJ/Rutgers, Northwell
- Primary analysis to be conducted 5 years after last patient enrolled completed surgery

Patient Characteristics

- Mean age 62 years
- Mean tumor size 10 mm
- Mean 21-gene RS = 11
- MRI obtained in 33%

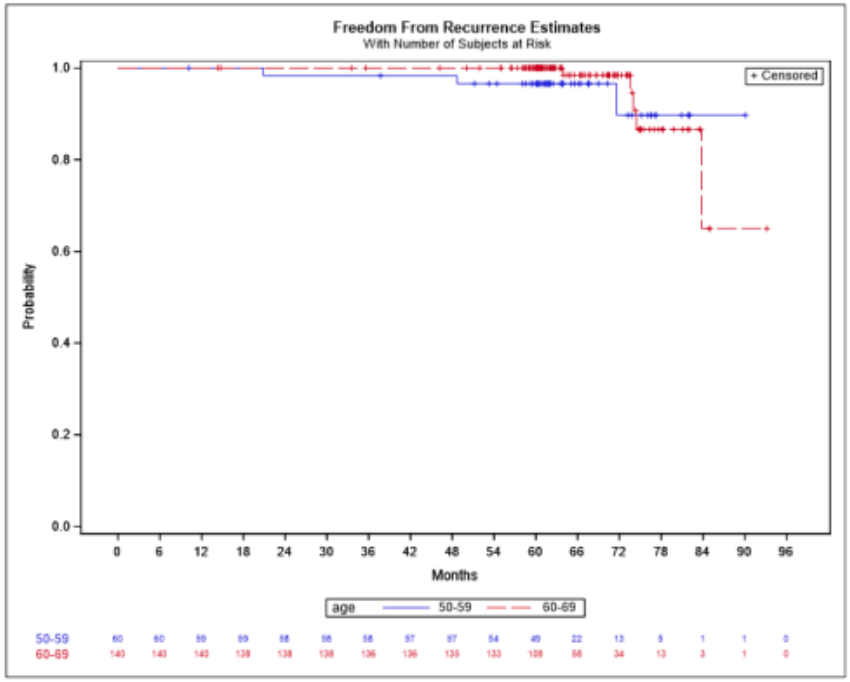
Estrogen receptor+	100%
Progesterone receptor+	100%
Her2 negative	100%
pN0	100%
Histology	
Ductal	85%
Lobular	10%
Mixed	2%
Grade 1	42.5%
Grade 2	54.5%
Grade 3	3%
No LVI	85.5%

Results

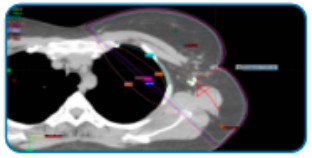
- Median f/u 5.2 years
- Among the 186 patients with clinical follow-up of at least 56 months
  - overall and breast cancer-specific survival rates at 5 years were both 100%
  - 5-year freedom from any recurrence was 99% (95% CI, 96%-100%)

Results

- Crude rates of IBE for the entire follow-up period
  - 3.3% (2/60) for patients aged 50-69
  - 3.6% (5/140) for patients aged 60-69
- Crude rates of overall recurrence
  - 5.0% (3/60) for patients aged 50-59
  - 3.6% (5/140) for patients aged 60-69



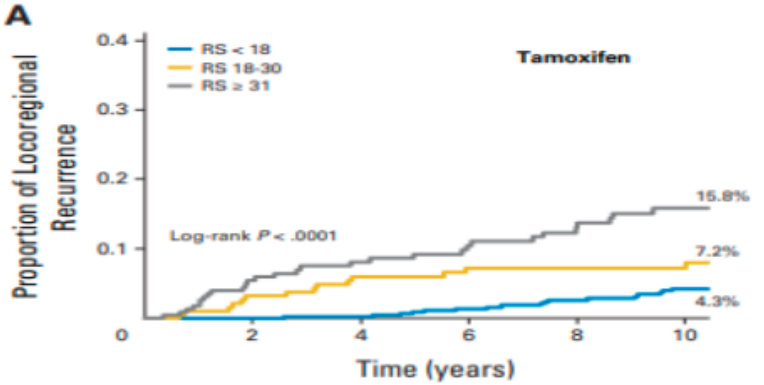
Should Tumor Biology Be Incorporated Into Decisions for RT After Lumpectomy?



Systemic therapy recommendations altered by tumor biology

Radiotherapy standardly recommended after lumpectomy in women age < 70 years, irrespective of tumor subtype

LRR is associated with RS and Age



	HR	95% CI	P
Age (≥ 50y vs < 50y)	0.4	0.25-0.65	0.0002
RS	2.16	1.26-3.68	.005

IDEA vs LUMINA: How Should We Select Patients for Omission of RT?

	IDEA n = 200	LUMINA n = 500
Age	62 (mean)	67 (median)
Tumor size	1 cm (mean)	1 cm (median)
Histology	12% lobular or mixed	Lobular or mixed excluded
Grade	3% grade 3	Grade 3 excluded
LVI	14.5%	LVI excluded
EIC	allowed	EIC excluded
Margins	2 mm	1 mm
Low-risk assay	RS ≤18	Ki-67 ≤ 13.25%
ET adherence	85%	83%

Jagsi R, SABCS 2023; Whelan T, NEJM 2023

IDEA vs LUMINA: How Should We Select Patients for Omission of RT?

	IDEA n = 200	LUMINA n = 500
Age	62 (mean)	67 (median)
Tumor size	1 cm (mean)	1 cm (median)
Histology	12% lobular or mixed	Lobular or mixed excluded
Grade	3% grade 3	Grade 3 excluded
5-year LR	**1%**	**2.3%**
Low-risk assay	RS ≤18	Ki-67 ≤ 13.25%
ET adherence	85%	83%

RS low, gute Biologie…

Conclusions

- IDEA shows a very low 5-year risk of recurrence using a genomic assay in combination with classic clinical and biologic features for treatment selection, including postmenopausal patients younger than age 60
- Long-term follow-up of this trial and others will help determine whether the option of avoiding initial radiotherapy can be offered to a broader group of women than current guidelines recommend
- Such efforts strive to empower patients with choices and return to them a sense of agency that can be deeply meaningful in the context of a recent cancer diagnosis

Exakte Kriterien, hohe Compliance

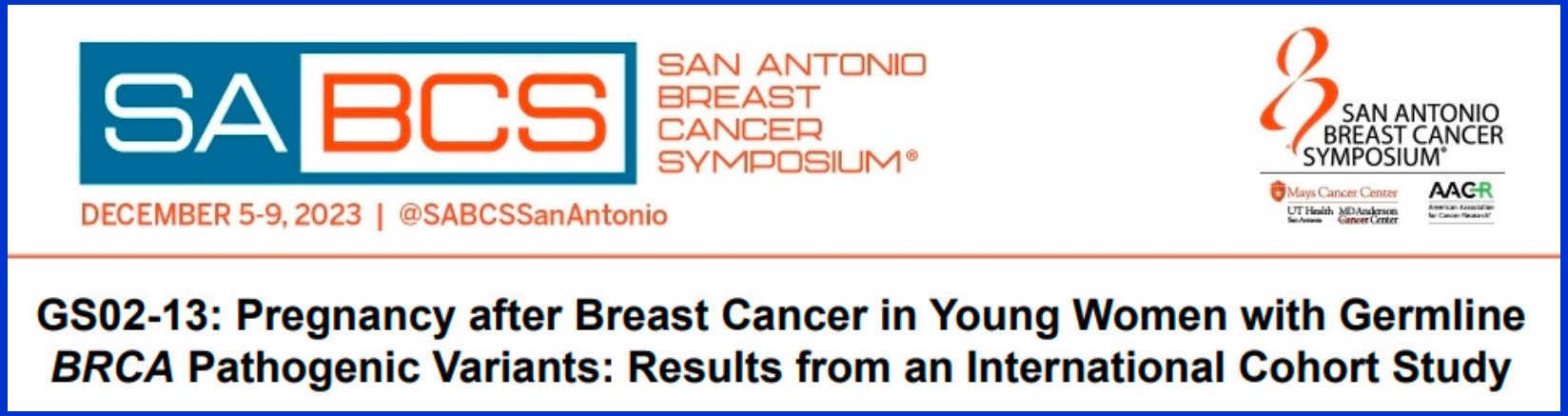
Cautionary Notes

- Absent other evidence, the findings should not be generalized to patients who have less extensive surgery than the pathologic nodal evaluation and margin requirements of the study, and caution is necessary if compliance with endocrine therapy is not expected, given that compliance was high in this sample of women who enrolled on trial
- Must recognize that advances in RT have substantially reduced toxicity and short-term burden of treatment since this trial was initiated, with implications for the risk-benefit ratio of receiving RT, particularly among women with long life expectancies
  - The patients eligible for IDEA are now also candidates for emerging regimens treating the whole breast or partial breast in 5 fractions or less
  - Regardless, some women will wish to avoid the burden and potential toxicity of radiotherapy altogether

Schwangerschaft…

Young pregnant BRCA carriers

retrospective Studie



Background

- A substantial proportion of young women with newly diagnosed breast cancer are interested in future fertility[1]
- More than 12% of young women with breast cancer carry a germline pathogenic variant in the *BRCA1* or *BRCA2* genes[2]
- Additional challenges should be considered in the reproductive counseling of *BRCA* carriers:
  - The psychological fear of transmitting the pathogenic variant to their offspring[3]
  - The possible negative impact of deficient BRCA function on ovarian reserve and fertility potential[4]
  - The indication to undergo risk-reducing bilateral salpingo-oophorectomy at a young age[5]
- While several studies have demonstrated the safety of conceiving following breast cancer diagnosis and treatment, the evidence in *BRCA* carriers is very limited[6]

Background

- We previously reported preliminary results from a study including 1252 *BRCA* carriers from 30 centers showing no apparent negative consequences in maternal prognosis or fetal outcomes in patients with a pregnancy after breast cancer[1]
- Main limitations of this study included:[1]
  - The relatively limited number of patients with a pregnancy after breast cancer (n=195)
  - The smaller number than expected of patients with no pregnancy (n=1057)
  - The few subgroup analyses performed (only based on specific *BRCA* gene and hormone receptor status)
- Concerns remain regarding feasibility and safety of pregnancy in this population[2,3]
- To provide more solid evidence in the field, additional centers and patients have been included in this larger international study, which also includes the 1252 *BRCA* carriers in the first report[1]

Study Design and Participants

- International, multicenter, hospital-based, retrospective cohort study

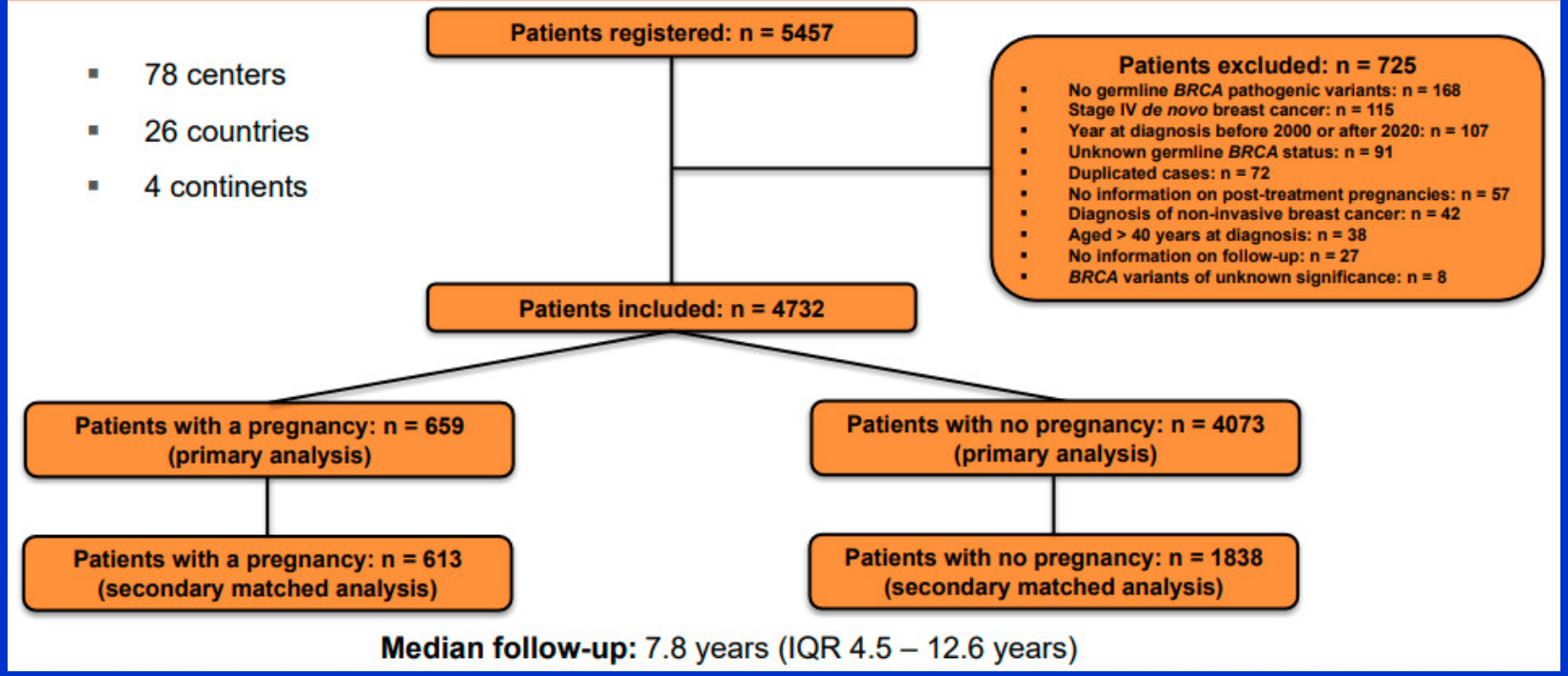
Key inclusion criteria

- Stage I - III invasive breast cancer
- Diagnosis between January 2000 and December 2020
- Age ≤ 40 years at diagnosis
- Known germline likely pathogenic or pathogenic variants in *BRCA1* and/or *BRCA2* genes

Key exclusion criteria

- Stage IV *de novo* breast cancer
- Lack of data on follow-up or post-treatment pregnancies
- History of ovarian cancer or other malignancies without prior breast cancer
- *BRCA* VUS or *BRCA* healthy carriers

Participant Flow



Median follow-up: 7.8 years (IQR 4.5 – 12.6 years)

Participant and Treatment Characteristics

Key participant characteristics at breast cancer diagnosis

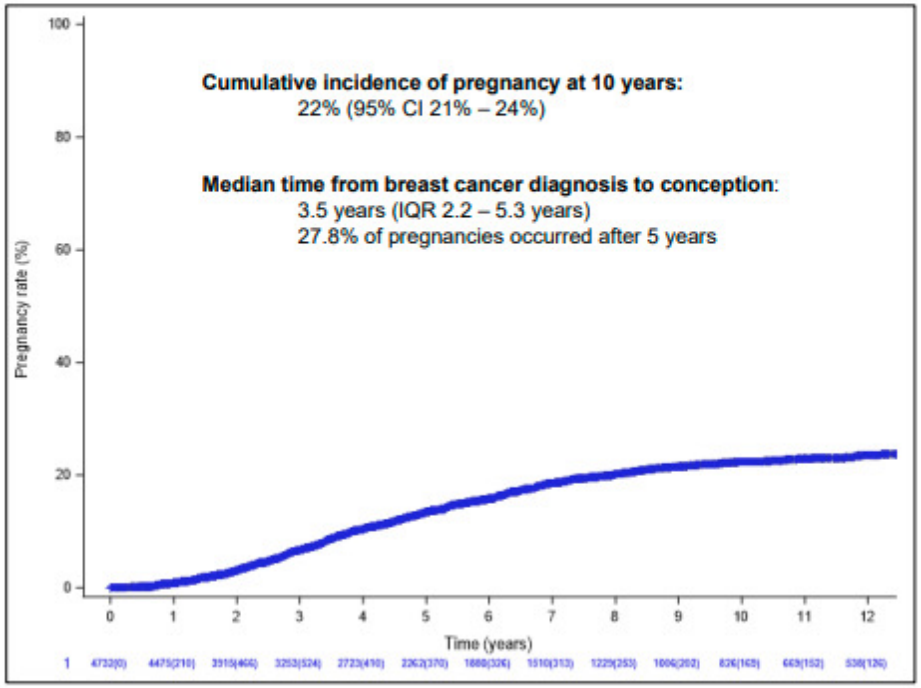
	Patients with a pregnancy n = 659, N (%)	Patients with no pregnancy n = 4073, N (%)
Region:		
Southern Europe	303 (46.0)	1777 (43.6)
Asia	130 (19.7)	650 (16.0)
Northern Europe	110 (16.7)	599 (14.7)
North America	59 (9.0)	460 (11.3)
Eastern Europe	22 (3.3)	282 (6.9)
Australia/Oceania	26 (3.9)	167 (4.1)
Latin/South America	9 (1.4)	138 (3.4)
Year at diagnosis:		
2000 – 2004	106 (16.1)	498 (12.2)
2005 – 2008	141 (21.4)	647 (15.9)
2009 – 2012	170 (25.8)	835 (20.5)
2013 – 2016	159 (24.1)	999 (24.5)
2017 – 2020	83 (12.6)	1094 (26.9)
Age at diagnosis, median (IQR) years	30 (28 – 33)	35 (32 – 38)
Specific *BRCA* gene		
BRCA1	483 (73.3)	2550 (62.6)
BRCA2	170 (25.8)	1493 (36.7)
BRCA1 and *BRCA2*	3 (0.5)	23 (0.6)
BRCA, unknown if 1 or 2	3 (0.5)	7 (0.2)
Tumor size:		
T1 (≤ 2 cm)	282 (44.8)	1529 (39.5)
T2 (>2 – ≤ 5 cm)	270 (42.9)	1780 (46.0)
T3 (> 5 cm) - T4	77 (12.2)	562 (14.5)
Unknown	30	202
Nodal status:		
N0	399 (62.5)	2035 (52.1)
N1	180 (28.2)	1376 (35.2)
N2 – N3	59 (9.3)	497 (12.7)
Unknown	21	165
Hormone receptor status:		
ER and/or PR positive	216 (33.3)	1910 (47.7)
ER and PR negative	432 (66.7)	2097 (52.3)
Unknown	11	66
HER2 status:		
HER2 negative	589 (94.2)	3562 (92.2)
HER2 positive	36 (5.8)	303 (7.8)
Unknown	34	208

Treatment patterns

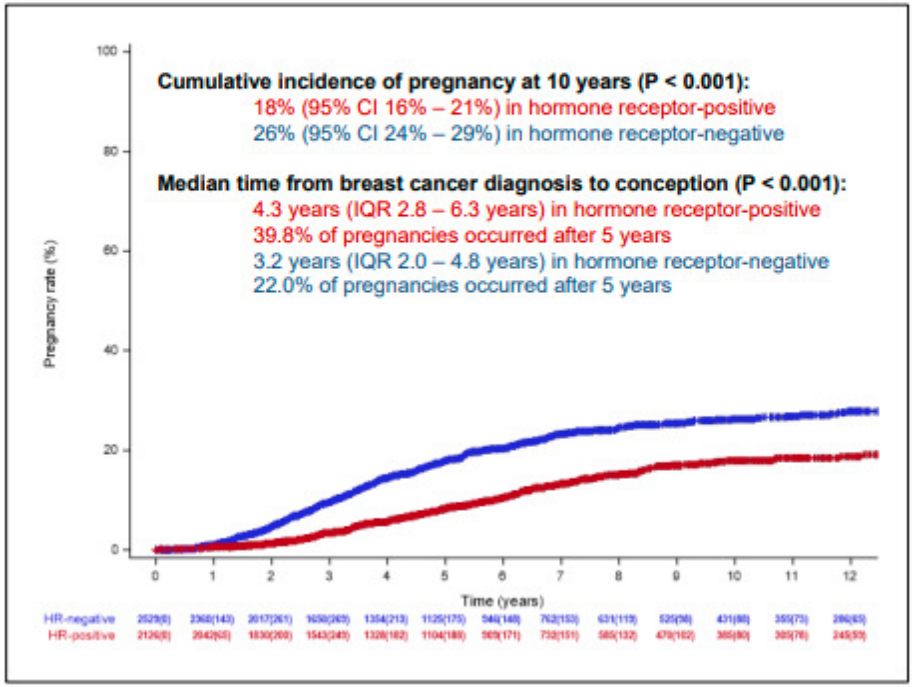
	Patients with a pregnancy n = 659, N (%)	Patients with no pregnancy n = 4073, N (%)
Breast surgery:		
None	2 (0.3)	13 (0.3)
Breast-conserving surgery	315 (48.8)	1511 (37.9)
Mastectomy	329 (50.9)	2465 (61.8)
Unknown	13	84
Received chemotherapy:		
No	47 (7.1)	334 (8.2)
Yes	611 (92.7)	3780 (91.0)
Unknown	1	31
Type of chemotherapy:		
Anthracycline- and taxane-based	414 (69.2)	2637 (73.8)
Anthracycline-based	143 (23.9)	655 (18.3)
Taxane-based	19 (3.2)	169 (4.7)
Other	22 (3.7)	110 (3.1)
Unknown	13	137
Received endocrine therapy:		
No	18 (8.3)	93 (4.9)
Yes	197 (91.6)	1790 (93.7)
Unknown	1	27
Type of endocrine therapy:		
Tamoxifen alone	64 (32.7)	638 (36.0)
Tamoxifen + LHRHa	81 (41.3)	469 (26.5)
LHRHa alone	7 (3.6)	36 (2.0)
AI ± LHRHa	21 (10.7)	334 (18.8)
Tamoxifen and AI (± LHRHa)	19 (9.7)	274 (15.5)
Other	4 (2.0)	22 (1.2)
Unknown	1	17
Duration of endocrine therapy, median (IQR) months	48 (24 – 60)	60 (28 – 60)
Unknown	40	467
Risk-reducing salpingo-oophorectomy:		
No	379 (57.6)	1844 (46.0)
Yes	279 (42.4)	2164 (54.0)
Unknown	1	65

Study Results – Cumulative Incidence of Pregnancy

Overall cohort



According to hormone receptor status



Study Results – Reproductive Outcomes

	Patients with a pregnancy n = 659, N (%)
Age at pregnancy, median (IQR) years	34.7 (31.8-37.3)
Type of conception	
Spontaneous pregnancy	461 (79.2)
Use of assisted reproductive technology	121 (20.8)
Unknown	77
Pregnancy outcome	
Delivered a child	517 (79.7)
Ongoing pregnancy	24 (3.7)
Miscarriage	63 (9.7)
Induced abortion	45 (6.9)
Unknown	10
Number of live births at the first pregnancy after breast cancer	
1	463 (89.6)
2	54 (10.4)
Timing of delivery	
At term (≥ 37 weeks)	406 (91.0)
Preterm (< 37 weeks)	40 (9.0)
Unknown	71
Pregnancy complications	
None	365 (86.3)
Pregnancy complications	27 (6.4)
Delivery complications	22 (5.2)
Congenital abnormalities	4 (0.9)
Fetal complications	3 (0.6)
Other complications	2 (0.5)
Unknown	94
Breastfeeding	
No	270 (67.0)
Yes	133 (33.0)
Unknown	114
Duration of breastfeeding, median (IQR), months	5 (2 – 6)
Unknown duration of breastfeeding	50

Study Results – Secondary Survival Outcomes

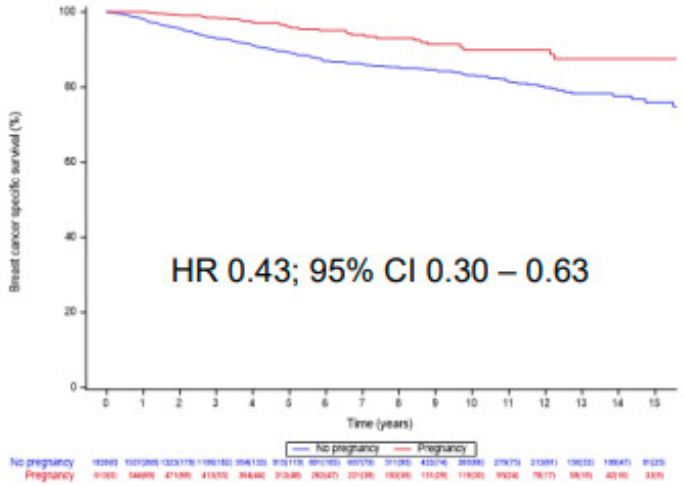
Breast cancer-specific survival

Extended Cox model:

Unadjusted HR 0.53; 95% CI 0.37 – 0.74

Adjusted HR* 0.60; 95% CI 0.40 – 0.88

Secondary matched analysis:



*Adjusted for: region, age, nodal status, hormone receptor status and type of breast surgery

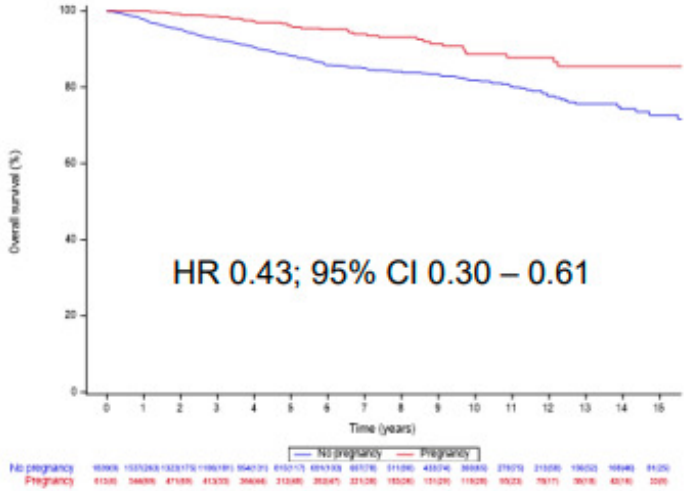
Overall survival

Extended Cox model:

Unadjusted HR 0.52; 95% CI 0.38 – 0.72

Adjusted HR* 0.58; 95% CI 0.40 – 0.85

Secondary matched analysis:



Study Results – Disease-free Survival

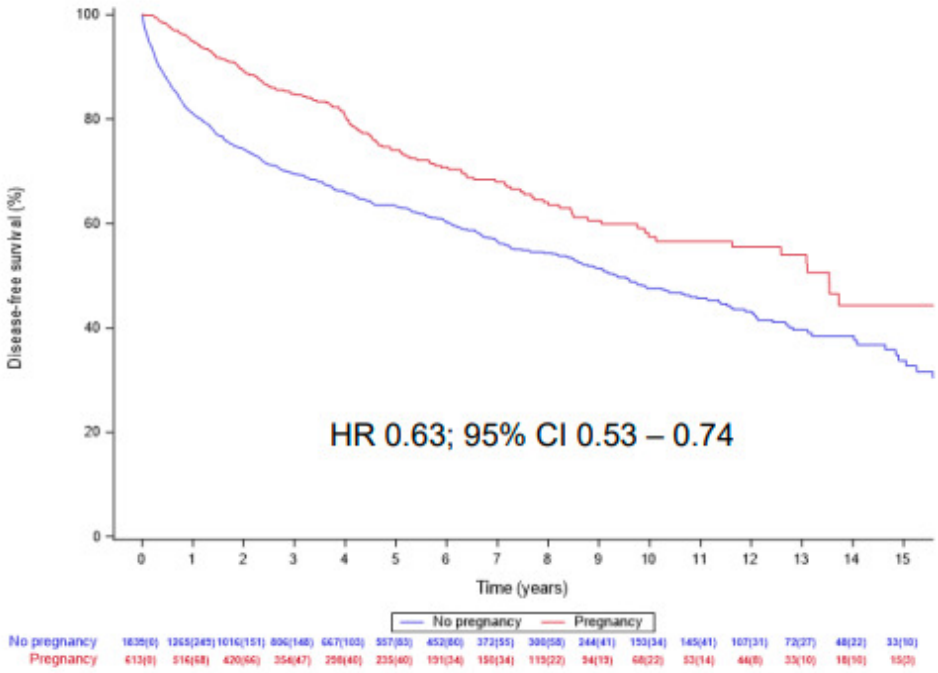
Primary analysis – Extended Cox model with occurrence of pregnancy as a time-varying covariate

Unadjusted HR 0.97; 95% CI 0.82 – 1.15
Adjusted HR* 0.99; 95% CI 0.81 – 1.20

Subgroup analyses	Multivariate HR* (95% CI)	P value for interaction
Specific *BRCA* gene		
BRCA1	0.80 (0.63 – 1.01)	0.007
BRCA2	1.55 (1.12 – 2.16)	
BRCA1 and *BRCA2*	4.49 (0.28 – 72.17)	
BRCA, unknown if 1 or 2	Not evaluable	
Hormone receptor status:		
ER and/or PR positive	1.30 (0.95 – 1.76)	0.009
ER and PR negative	0.76 (0.60 – 0.95)	
Unknown	0.28 (0.04 – 2.21)	
HER2 status:		
HER2 negative	0.61 (0.22 – 1.71)	0.08
HER2 positive	1.07 (0.87 – 1.31)	
Unknown	0.42 (0.17 – 1.02)	
Received chemotherapy:		
No	0.77 (0.39 – 1.52)	0.47
Yes	1.00 (0.82 – 1.23)	
Unknown	0.77 (0.39 – 1.52)	
Received endocrine therapy:		
No	0.85 (0.67 – 1.08)	0.01
Yes	1.55 (1.08 – 2.21)	
Unknown	0.13 (0.01 – 2.95)	

*Adjusted for: region, age, nodal status, hormone receptor status and type of breast surgery

Secondary matched analysis



Keine nennenswerten Unterschiede oder Risiken bei BRCA - Trägern

Conclusions

- This global study including 4732 young *BRCA* carriers from 78 centers worldwide provides reassuring evidence for the oncofertility counseling of young *BRCA* carriers interested in conceiving following diagnosis and treatment for breast cancer
- More than one out of five (22%) young *BRCA* carriers became pregnant within 10 years after a breast cancer diagnosis
- The rate of pregnancy, fetal and obstetric complications was low and in line with the expectations in a population of women with similar age and no history of breast cancer
- No detrimental prognostic effect of pregnancy after breast cancer was observed, particularly in *BRCA1* carriers
- **Conceiving after proper treatment and follow-up for breast cancer should not be contraindicated in young *BRCA* carriers**

POSITIVE

Fertility preservation and assisted reproductive technologies in breast cancer patients interrupting adjuvant endocrine therapy to attempt pregnancy

Results from the POSITIVE Trial
(IBCSG 48-14 / BIG 8-13 / Alliance A221405)

Hatem A. Azim Jr, MD, PhD
School of Medicine, Monterrey Institute of Technology, MX

On behalf of the POSITIVE Consortium

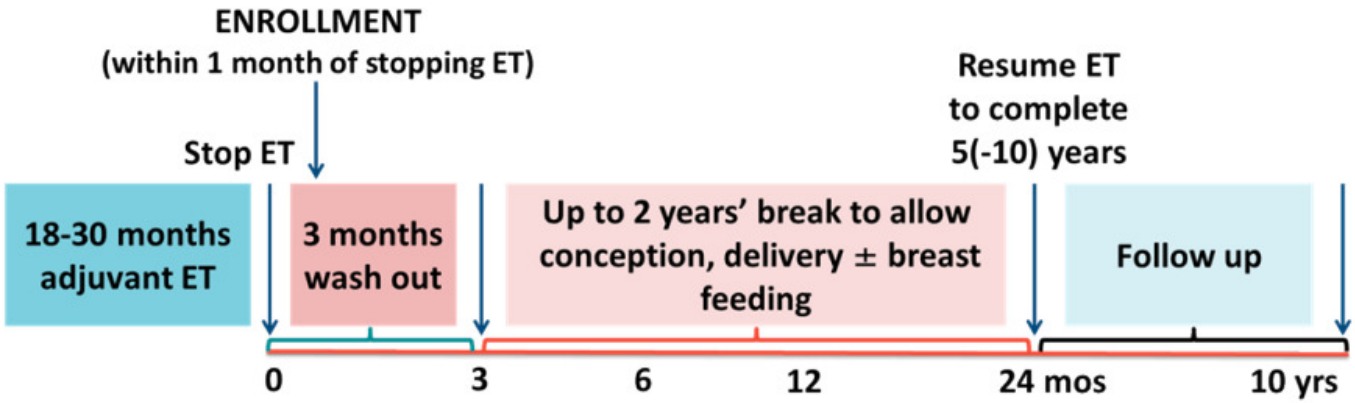
Background

IBCSG

- Pregnancy after breast cancer (BC) does not worsen disease outcomes, regardless of hormone receptor (HR) status [1, 2]
- The 1ry results of the POSITIVE trial showed that temporary interruption of endocrine therapy (ET) to attempt pregnancy does not impact disease outcomes, at a median follow-up (FU) of 41 months [3]
- Adjuvant therapy often affects measures of ovarian function including menses, and may compromise chances of future fertility [4]
- Uncertainty exists regarding the efficacy and safety of ovarian stimulation for fertility preservation and use of assisted reproductive technologies (ART) in women with early HR+ BC desiring future pregnancy

POSITIVE trial design

- Prospective, international, multicenter, investigator-initiated, single-arm trial



Key eligibility criteria

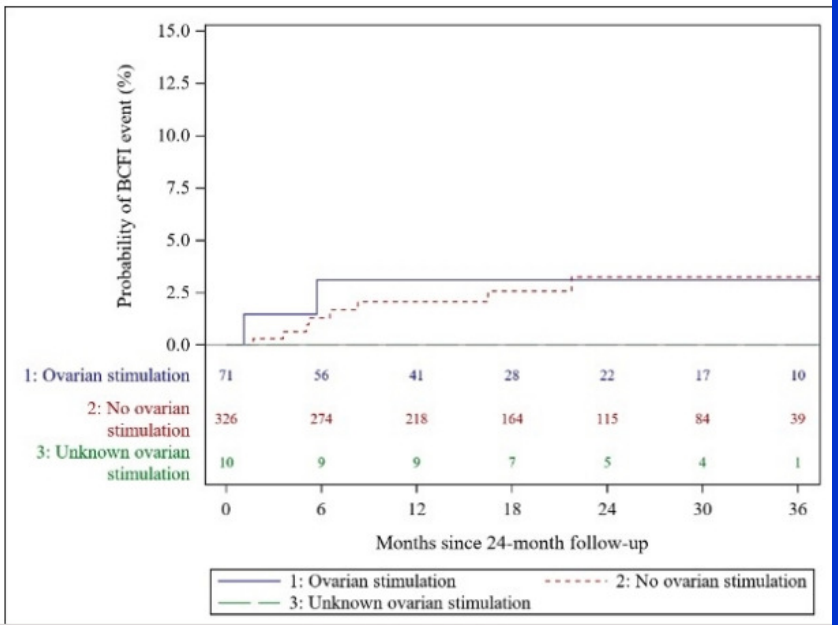
- Premenopausal women stage I-III HR+ BC
- Wishing to become pregnant
- Age ≤42 years at study entry
- At least 18 months and no more than 30 months of prior adjuvant ET for
- No clinical evidence of recurrence

Ovarian stimulation & breast cancer outcome

IBCSG

2) As part of ART - after enrollment

- **397 patients alive and BC free at 24-months (landmark analysis)**
  - 2 BC events amongst 71 patients in the ovarian stimulation group
  - 8 BC events amongst 326 patients in the non-ovarian stimulation group



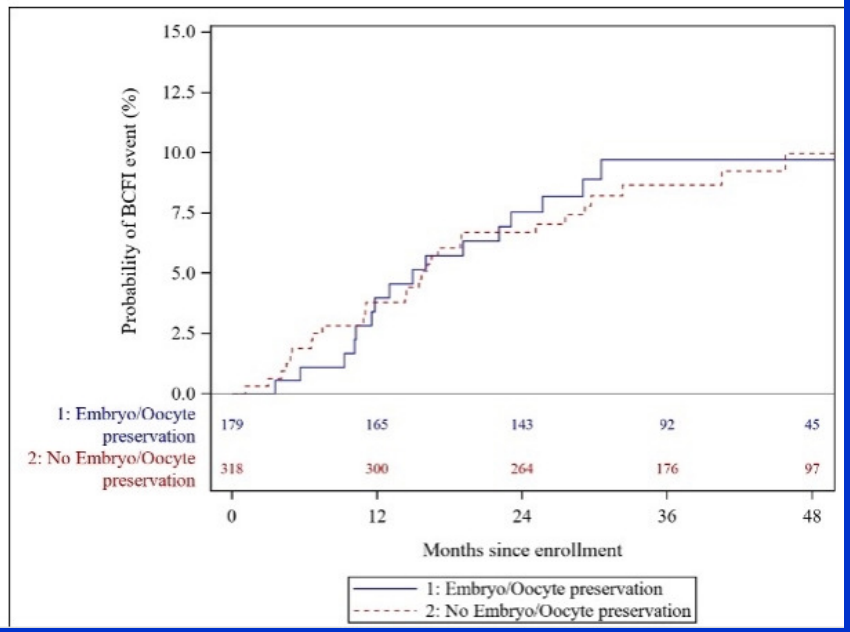
Ovarian stimulation & breast cancer outcome

IBCSG

1) As part of embryo/oocyte cryopreservation - after BC diagnosis

At 3-years, BCFI-events cumulative incidence

- **9.7%** (95% CI: 6.0% to 15.4%) for the 179 patients who underwent ovarian stimulation
- **8.7%** (95% CI: 6.0% to 12.5%) for the 318 patients who did not



Trial procedures

IBCSG

- At enrollment, all patients were asked to complete a menstrual diary for 2 years
- Information on use of fertility preservation at diagnosis, prior to enrollment was collected:
  - Ovarian stimulation for oocyte/embryo cryopreservation
  - GnRHa use during chemotherapy
  - Ovarian tissue cryopreservation
- Use of any ART modality on study was allowed (per physician/patient discretion) including:
  - Transfer of cryopreserved embryo
  - Ovarian stimulation for IVF
  - Intrauterine insemination
  - Clomiphene use

Multivariate logistic regression model	OR (95% CI)
35-39 vs <35	0.50 (0.29 - 0.86)
40-42 vs <35	0.16 (0.08 - 0.29)
Ovarian stimulation for IVF after enrollment vs No ART	0.85 (0.48 - 1.50)
Cryopreserved embryo transfer * vs No ART	2.41 (1.17 - 4.95)
Other ART vs No ART	1.80 (0.92 - 3.57)
Chemotherapy + GnRHa vs Chemotherapy no GnRHa	1.41 (0.70 - 2.82)
None vs Chemotherapy without GnRHa	1.10 (0.70 - 1.75)

* 82% of patients reported at least 1 pregnancy

POSITIVE

Conclusions

IBCSG

- This is the **largest prospective study** to investigate fertility preservation and ART in patients with early HR+ BC who desired pregnancy
- More than **90% of women presenting with amenorrhea resumed menses**, mostly during the first 6 months
- **Young age was the main factor associated with shorter time to pregnancy**; whereas type of ET was not
- **Embryo/oocyte cryopreservation at BC diagnosis followed by embryo transfer** after ET interruption **had higher pregnancy rates but was not associated with worse prognosis**
- **No increase in breast cancer events** was observed in patients undergoing **IVF on study** albeit few events. **Longer follow-up is needed**

POSITIVE

Prospektive Studie

Kryokonservierung…

Keine Zunahme der Rezidive

Conclusions

IBCSG

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now take home

Take home…

- Vorteile durch neoadjuvante Chemotherapie
- Zurückhaltendere Operation
- Zurückhaltendere Radiatio
- Gute Entwicklung der Daten bei Schwangerschaften


Danke

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Thank you


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