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DECEMBER 9–12, 2025

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Insights of applied radiotherapy among patients undergoing breast-conserving surgery with or without axillary sentinel lymph node biopsy: secondary results from the INSEMA trial

Guido Hildebrandt[1], Angrit Stachs[2], Kristina Veselinovic[3], Thorsten Kühn[3,4], Jörg Heil[5,6], Silke Polata[7], Frederik Marmé[8], Dietmar Zierhut[9], David Krug[10], Beyhan Ataseven[11], Roland Reitsamer[12], Sylvia Ruth[13], Carsten Denkert[14], Julia Kaiser[15], Inga Bekes[3,16], Dirk-Michael Zahm[17], Marc Thill[18], Michael Golatta[5,6], Johannes Holtschmidt[19], Michael Knauer[20], Valentina Nekljudova[19], Sibylle Loibl[19,21], Bernd Gerber[2], Toralf Reimer[2]

on behalf of the INSEMA investigators

1 Department of Radiotherapy, University Medicine Rostock, Germany; 2 Department of Obstetrics and Gynecology, University of Rostock, Germany; 3 Department of Obstetrics and Gynecology, University Hospital Ulm, Germany; 4 The Filderhospital, Filderstadt-Bonlanden, Germany; 5 Breast Center of St. Elisabeth Hospital, Heidelberg, Germany; 6 Department of Gynecology and Obstetrics, University of Heidelberg, Germany; 7 Evangelical Forest Hospital Spandau, Germany; 8 Faculty of Medicine Mannheim, University Heidelberg, Department of Obstetrics and Gynecology Mannheim, Germany; 9 Department of Radiotherapy, Hanau City Hospital, Hanau, Germany; 10 Department of Radiotherapy and Radiation Oncology, University Hospital Hamburg-Eppendorf (UKE), Germany; 11 University of Bielefeld, Department of Obstetrics and Gynecology, Klinikum Lippe, Germany; 12 University Hospital Salzburg, Department of Senology, Salzburg, Austria; 13 Johanniter-Hospital Genthin-Stendal, Germany; 14 Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM)-University Hospital Marburg, Germany; 15 Department of Radiotherapy and Radio-Oncology, Paracelsus Medical University, University Hospital Salzburg, Landeskrankenhaus, Salzburg, Austria; 16 HOCH Health Ostschweiz, Kantonsspital St. Gallen, Universitäres Lehr- und Forschungsspital, Brustzentrum, St. Gallen, Switzerland; 17 SRH Wald-Klinikum Gera GmbH, Germany; 18 Department of Gynecology and Gynecological Oncology, Agaplesion Markus Hospital, Frankfurt am Main, Germany; 19 GBG c/o GBG Forschungs GmbH, Neu-Isenburg, Germany; 20 Tumor and Breast Center Eastern Switzerland, St. Gallen, Switzerland; 21 Goethe University, Frankfurt, Germany

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Disclosure Information

Guido Hildebrandt

I have the following relevant financial relationships to disclose:

Employee of:	Department of Radiotherapy and Radiation Oncology, University of Rostock, Germany
Consultant for:	Astra Zeneca, Boehringer, Elekta, Janssen-Cilag, MSD, Novocure
Speaker's Bureau for:	Amgen, Astra Zeneca, Boehringer, Merck, MSD, Roche
Grant/Research support from:	B. Braun Foundation; European Research Framework Programme; European Regional Development Fund; Federal Ministry of Research Technology and Space (BMFTR, former BMBF); German Academic Exchange Service (DAAD); German Cancer Aid (DKH); German Research Foundation (DFG)
Stockholder in:	none
Honoraria from:	Amgen, Astra Zeneca, Boehringer, Elekta, Janssen-Cilag, Merck, MSD, Novocure, Roche

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Background

- De-escalation of axillary surgery during breast-conserving surgery (BCS) must be considered alongside radiotherapy to interpret oncological outcomes accurately.
- Analyses from other de-escalation trials (ACOSOG Z0011, SENOMAC) revealed that a significant percentage of pts received regional nodal irradiation (RNI).
- Previously, we reported primary and secondary outcomes of the INSEMA trial:
  - omission of SLNB in cN0 patients with early breast cancer and scheduled for breast-conserving therapy is oncologically safe regarding 5-year invasive disease-free survival (iDFS)[1]
  - patient-reported outcomes (PROs) with Quality-of-Life data results showed that patients with no SLNB benefited regarding arm symptoms and functioning[2]
  - pre-planned central quality assurance review process for postoperative radiotherapy planning and axillary contouring (N=276)[3]
- **INSEMA documented dose distribution in ipsilateral axillary levels I-III and captured RNI. This analysis investigates how patients' parameters, surgical axillary extent, and radiation techniques affect ipsilateral axillary dose distribution.**

1 Reimer et al. SABCS 2024, NEJM 2025; 2 Reimer et al. EClinicalMedicine 2022; 3 Hildebrandt et al. Int J Radiat Oncol Biol Phys 2020

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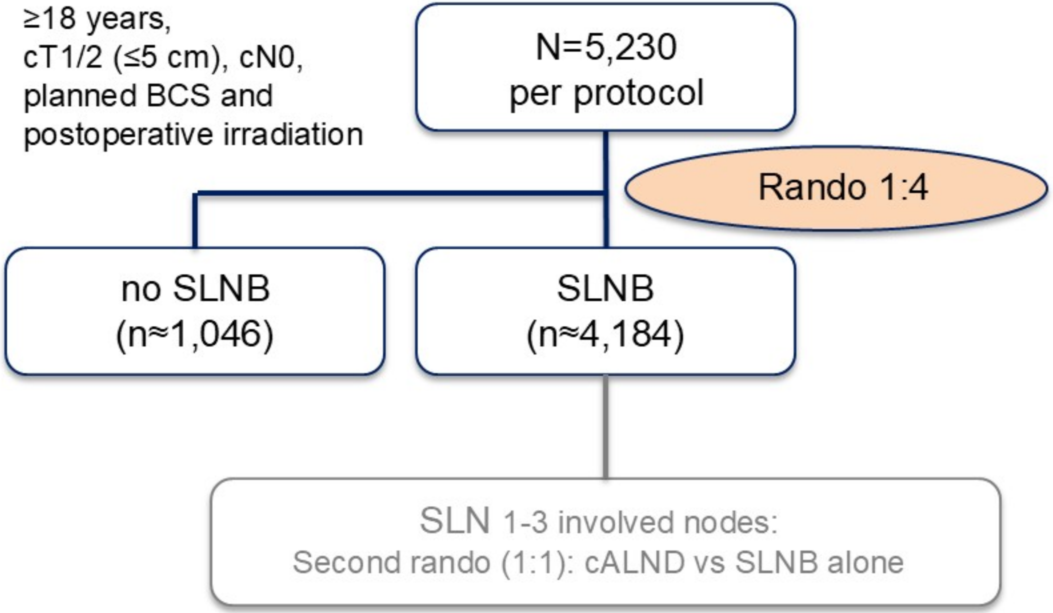
Study Design INSEMA Trial

≥18 years,
cT1/2 (≤5 cm), cN0,
planned BCS and
postoperative irradiation



Primary objective:

- To compare iDFS after BCS (non-inferiority question) between no axillary surgery and SLNB patients (first randomization)

Secondary objective:

- Determination of the actually applied radiotherapy doses at the respective axillary levels I-III (QA of RT)

- Recruitment in Germany and Austria (09/2015-04/2019), **n=108 RT facilities**

iDFS, invasive disease-free survival; BCS, breast-conserving surgery;
SLNB, sentinel lymph node biopsy; cALND, completion axillary lymph node dissection

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In 4 patients (both ITT and PP set) SLNB result is missing

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Methods

- The INSEMA protocol mandated whole-breast irradiation (WBI ± tumor bed boost)
- RNI was only permitted in patients with 4 or more involved lymph nodes (≥ pN2a; *after amend. #4 (Sep 2016)*)
- Contouring of the ipsilateral axilla (level I-III) followed the Radiation Therapy Oncology Group (RTOG) consensus definitions

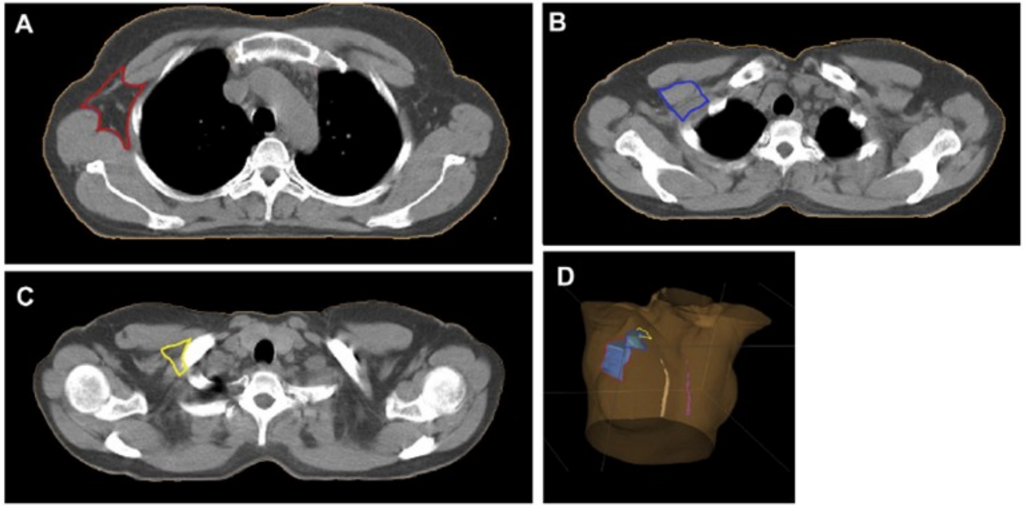

Fig. 2. Representative example of detailed radiation therapy planning record that was classified as receiving standard tangents with acceptable contouring of axillary levels I-III. A: contour level I (red); B: contour level II (blue); C: contour level III (yellow); D: contouring levels I-III (3D illustration).[1]

- Dose parameters are presented as relative doses (in % of the prescribed breast dose) to allow biological interpretation since absolute physical doses differ between conventionally and hypofractionated cases.

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1 Hildebrandt et al. Int J Radiat Oncol Biol Phys 2020

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Central RT-QA – contouring & planning

Axillary dose parameters in INSEMA patients treated with postop. WBI after BCS[1]

Parameter	SLNB (N = 184)	No SLNB (N = 45)
Axillary level I dose median (percentage of breast dose)		
Mean	72.8	68.6
SD	31.4	30.6
Median	85.9	82.7
Range	1.3-110.5	0.8-99.0
Q1-Q3	54.8-96.6	42.5-95.1
Missing		
Axillary level II dose median (percentage of breast dose)		
Mean	39.9	29.7
SD	38.2	30.8
Median	20.8	13.2
Range	0.4-114.5	0.4-95.8
Q1-Q3	4.5-85.1	4.9-50.0
Missing		
Axillary level III dose median (percentage of breast dose)		
Mean	16.4	12.0
SD	27.1	21.5
Median	3.8	4.0
Range	0.1-105.8	1.1-87.1
Q1-Q3	2.1-12.1	2.4-6.0
Missing		

1 Hildebrandt et al. Int J Radiat Oncol Biol Phys 2020

- analysis of first 3 RT-plans of all study centres (n=276)
  - contouring according to protocol 85 %
  - 3D-CRT 76 %
  - conv. fractionation 83.8 %
  - Boost 88.1 %
- Incidental RT-exposure axillary level I *(SLNB and no SLNB)*
  - ≥ 95% prescribed dose: 25 %
  - ≥ 85% prescribed dose: 50 %

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Statistical Methods

- The radiotherapy parameters were analyzed on the per-protocol (PP) set *(as it was the analysis set for the primary analysis for non-inferiority)* [1]

  and repeated on the ITT set (similar results, data not shown).

- Kaplan-Meier product-limit method was used to estimate 5-year iDFS rates (reported with the two-sided 95% CI).

- Categorical and binary parameters are reported in frequency tables where all percent values are valid percents (excluding missings); for continuous parameters, mean, StD, median, and IQR were reported.

- The Pearson χ2-test (for categorical parameters with more than two categories), Fisher's exact test (for binary parameters), and Mann-Whitney test (for continuous parameters) were used to compare radiotherapy parameters between treatment arms.

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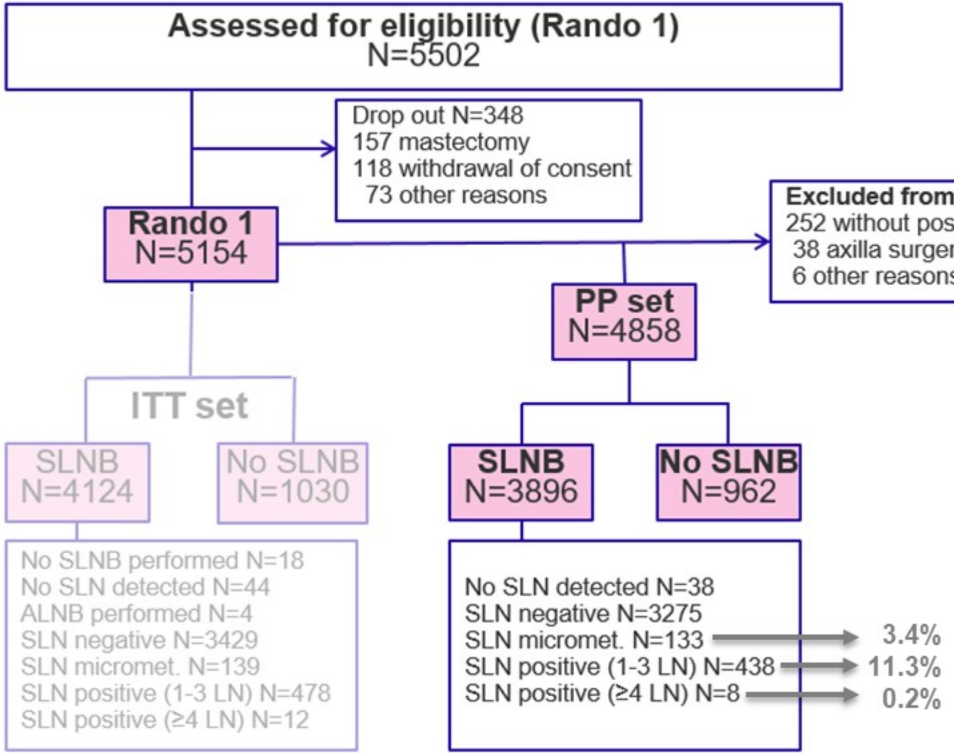
1 European Medicines Agency: ICH Topic E 9 statistical principles for clinical trials

Consort Flow Diagram



In 4 patients (both ITT and PP set) SLNB result is missing

Baseline Characteristics: Per-Protocol Set

10.8% were aged <50 years

Parameter	Category	No SLNB N=962 N (%)	SLNB N=3896 N (%)
Age	**median (IQR)**	**62 (53-68)**	**62 (53-68)**
	<65 years	**583 (60.6)**	**2387 (61.3)**
	≥65 years	**379 (39.4)**	**1509 (38.7)**
Preop. tumor size	**≤2 cm**	**871 (90.5)**	**3521 (90.4)**
	>2 cm	**91 (9.5)**	**375 (9.6)**
Grading	**G1**	**372 (38.7)**	**1463 (37.6)**
	G2	**552 (57.4)**	**2294 (58.8)**
	G3	**38 (3.9)**	**139 (3.6)**
Tumor type	NST	726 (75.5)	2828 (72.6)
	Invasive/mixed lobular carcinoma	125 (13.0)	491 (12.6)
	other	111 (11.5)	576 (14.8)
ER/PgR	both negative	15 (1.6)	58 (1.5)
	ER and/or PgR positive	946 (98.4)	3835 (98.5)
HER2 status	negative	914 (95.4)	3755 (96.7)
	positive	44 (4.6)	130 (3.3)

95.2% had HR+/HER2- subtype

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RT-parameters - 1st randomization: PP Set

- 3D-CRT 58 %
- IMRT 22 %
- conv. fract. 66 %
- hypofract. 34 %
- Boost 78 %

Parameter	Category	No SLNB N=962 N (%)	SLNB N=3896 N (%)	p-value
RT-technique	- 3D-CRT (tangential fields)	541 **(56.9)**	2247 **(58.4)**	0.788
	- IMRT / VMAT	215 **(22.6)**	836 **(21.7)**	
	- Simultaneous integrated boost	101 (10.6)	407 (10.6)	
	- Deep inspiration breathhold	18 (1.9)	84 (2.2)	
	- Other	76 (8.0)	273 (7.1)	
Fractionation	- conventional	644 **(68.1)**	2499 **(65.5)**	0.135
	- hypofractionation	302 (31.9)	1318 (34.5)	
Boost	- yes	739 **(77.1)**	3033 **(78.2)**	0.487
	- no	219 (22.9)	847 (21.8)	
Boost technique	- External beam (3D-CRT)	395 **(53.7)**	1638 **(54.6)**	0.976
	- External beam (IMRT/VMAT)	173 **(23.5)**	654 **(21.8)**	
	- External beam (Electrons)	7 (1.0)	28 (0.9)	
	- Intraoperative (Electrons)	36 (4.9)	147 (4.9)	
	- Intraoperative (Photons)	11 (1.5)	54 (1.8)	
	- Interstitial brachytherapy	9 (1.2)	42 (1.4)	
	- Other	104 (14.1)	435 (14.5)	

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WBI - 1st randomization: PP Set

- 3D-CRT 58 %
- IMRT 22 %
- SIB 11 %
- DIBH 2 %
- other 7 %

Parameter	Category	No SLNB N=962	SLNB N=3896	p-value
PTV1 (WBI) (ml)	- Mean	**1083**	**1109**	0.139
	- StD	698	664	
	- **Median**	**957**	**994**	
	- Q1, Q3	673, 1383	707, 1376	
Dose (median) (Gy)	- Mean	**47.8**	**47.8**	0.953
	- StD	5.5	5.4	
	- **Median**	**50.6**	**50.5**	
	- Q1, Q3	42.5, 51.3	42.3, 51.5	
Dose (average) (Gy)	- Mean	**47.9**	**47.8**	0.357
	- StD	5.8	5.6	
	- **Median**	**50.4**	**50.3**	
	- Q1, Q3	42.4, 51.4	42.0, 51.5	

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Boost - 1st randomization: PP Set

- Boost 78 %
  - external 77.6 %
  - intraop. 6.6 %
  - interstitial 1.4 %
  - other 14.4 %

Parameter	Category	No SLNB N=739	SLNB N=3033	p-value
PTV2 (Boost) (ml)	- Mean	**88**	**88**	0.412
	- StD	100	93	
	- **Median**	**65**	**65**	
	- Q1, Q3	36, 101	38, 105	
Dose (median) (Gy)	- Mean	**11.1**	**11.1**	0.504
	- StD	4.1	4.2	
	- **Median**	**10.1**	**10.1**	
	- Q1, Q3	9.5, 11.8	9.4, 11.9	
Dose (average) (Gy)	- Mean	**10.6**	**10.7**	0.947
	- StD	3.6	4.3	
	- **Median**	**10.0**	**10.0**	
	- Q1, Q3	9.0, 11.3	9.0, 11.4	

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Axillary level I - 1st randomization: PP Set

RNI

- **No SLNB**
  n=3 (0.6 %)
- **SLNB**
  n=85 (4.1 %)

SLNB-Arm

≥ 4 positive SLN
n=8 ***(0.2%)***

1-3 positive SLN
n=438 ***(11.3%)***

RNI documentation started delayed with amend. #4 (Mar 2017)

Parameter	Category	No SLNB N=962	SLNB N=3896	p-value
Axillary level I (volume) (ml)	- Mean	**70**	**70**	0.551
	- StD	66	67	
	- **Median**	**55**	**56**	
	- Q1, Q3	37, 84	38, 86	
Dose (median) *(as percentage of WBI dose)*	- Mean	**69.9**	**75.9**	**<.001**
	- StD	33.0	31.2	
	- **Median**	**86.3**	**91.3**	
	- Q1, Q3	47.6, 95.8	62.8, 97.0	
Dose (average) *(as percentage of WBI dose)*	- Mean	**66.0**	**70.4**	**<.001**
	- StD	27.3	27.4	
	- **Median**	**73.2**	**78.3**	
	- Q1, Q3	52.1, 87.0	58.1, 90.6	

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Axillary level II - 1st randomization: PP Set

RNI

- **No SLNB**
  n=3 (0.6 %)
- **SLNB**
  n=85 (4.1 %)

SLNB-Arm

≥ 4 positive SLN
*n=8 **(0.2%)***

1-3 positive SLN
*n=438 **(11.3%)***

RNI documentation started delayed with amend. #4 (Mar 2017)

Parameter	Category	No SLNB N=962	SLNB N=3896	p-value
Axillary level II (volume) (ml)	- Mean	**24**	**25**	0.375
	- StD	24	33	
	- **Median**	**18**	**19**	
	- Q1, Q3	12, 28	12, 29	
Dose (median) (as percentage of WBI dose)	- Mean	**37.7**	**44.3**	**<.001**
	- StD	35.1	37.3	
	- **Median**	**23.3**	**37.8**	
	- Q1, Q3	5.5, 71.4	6.7, 84.1	
Dose (average) (as percentage of WBI dose)	- Mean	**39.0**	**44.5**	**<.001**
	- StD	29.7	31.8	
	- **Median**	**34.9**	**42.1**	
	- Q1, Q3	9.7, 63.3	13.7, 71.6	

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Axillary level III - 1st randomization: PP Set

RNI

- **No SLNB n=3 (0.6 %)**
- **SLNB n=85 (4.1 %)**

SLNB-Arm

≥ 4 positive SLN** n=8 **(0.2%)

1-3 positive SLN** n=438 **(11.3%)

RNI documentation started delayed with amend. #4 (Mar 2017)

Parameter	Category	No SLNB N=962	SLNB N=3896	p-value
Axillary level III (volume) (ml)	- Mean	**18**	**18**	0.513
	- StD	30	30	
	- Median	**13**	**13**	
	- Q1, Q3	8, 19	8, 20	
Dose (median) (as pecentage of WBI dose)	- Mean	**15.1**	**20.1**	**0.002**
	- StD	24.7	30.5	
	- **Median**	**4.5**	**5.2**	
	- Q1, Q3	2.6, 11.6	2.8, 18.3	
Dose (average) (as percentage of WBI dose)	- Mean	**17.0**	**21.9**	**<.001**
	- StD	22.2	27.6	
	- **Median**	**6.4**	**8.3**	
	- Q1, Q3	3.0, 22.4	3.2, 30.9	

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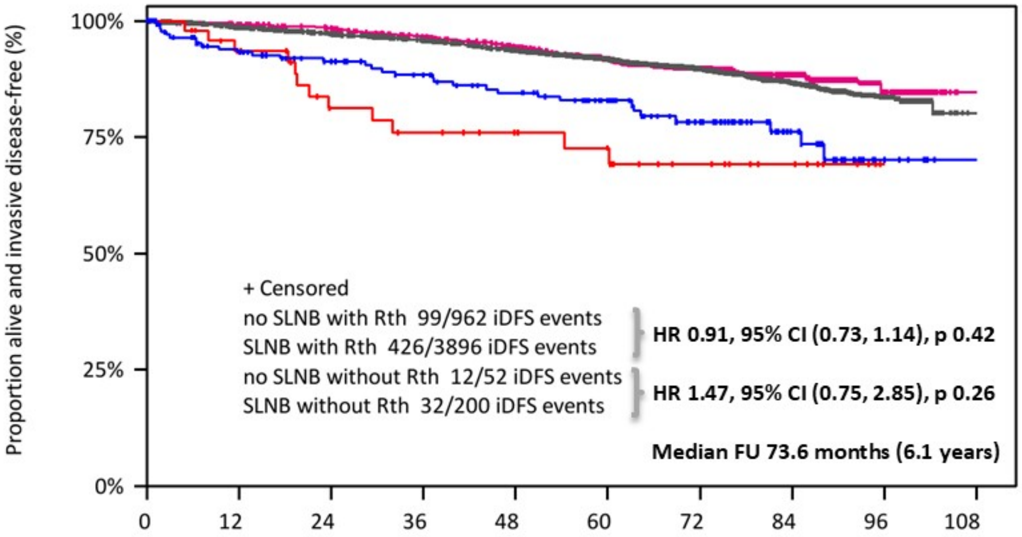
iDFS: per-protocol analysis: with RT (N=4858) / without RT (N=252)*



	0	12	24	36	48	60	72	84	96	108
no SLNB with Rth	962	942	918	877	832	743	477	272	82	0
SLNB with Rth	3896	3726	3582	3459	3286	2950	1842	1008	329	0
no SLNB without Rth	52	41	31	28	24	22	13	8	0	0
SLNB without Rth	200	146	132	120	108	91	59	30	7	0

iDFS, months

First iDFS event	with RT N=4858 N(%)	no RT* N=252 N(%)
Total	525 (10.8)	44 (17.5)
Invasive LRR	**72 (1.5)**	**13 (5.2)**
- Axillary	22 (0.5)	3 (1.2)
- ipsilateral breast	50 (1.0)	10 (4.0)
Invasive contralateral BC	35 (0.7)	2 (0.8)
Distant relapse	130 (2.7)	10 (4.0)
Secondary malignancy	182 (3.7)	4 (1.6)
Death	106 (2.2)	15 (6.0)

*(*post hoc analysis, only pts who would be included in PP set, if they had Rth)*

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Conclusion

- Approximately 50% of all INSEMA pts received a potentially therapeutic dose in axillary level I *(defined as median dose of ≥ 85% of the prescribed breast dose)*.
- A higher incidental axillary dose and an increased use of RNI were observed in the SLNB arm compared to no SLNB pts.
  - level I 91.3% vs. 86.3% ($p<0.001$)
  - level II 37.8% vs. 23.3% ($p<0.001$)
  - level III 5.2% vs. 4.5% ($p=0.002$)
- In the no SLNB arm, RNI was applied in <1% of patients.
  - RNI 4.0% vs. 0.6% ($p<0.001$)
- For pts without postoperative RT, the iDFS did not differ significantly between the arms
  - HR for no SLNB to SLNB = 1.47 [95% CI: 0.75-2.85]($p=0.26$)
- **Clinical implication: omission of SLNB during BCS does not need compensation by escalated axillary RT concepts (RT volume & RT dose).**

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Acknowledgement

- All patients and their families, all participating sites, and IDMC

Cooperating partners

Collaborating study groups:

AGO-B BREAST STUDY GROUP

NOGGO NORDOSTDEUTSCHE GESELLSCHAFT FÜR GYNÄKOLOGISCHE ONKOLOGIE

ABCSG AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

SUCCESS

WSG Westdeutsche Studiengruppe West German Study Group

Financial Support:

Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.

Supported by German Cancer Aid (Deutsche Krebshilfe, Bonn, Germany), Grant No. 110580 and Grant No. 70110580 to University Medicine Rostock.

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Members of the Subboard GBG and AGO-B

PM and Monitoring:
Teresa Jeri, Margit Simon, Udo Pfeil

Translational Research:
Bärbel Felder, Christiane Rothhaar, Stefanie Lettkemann

Data Management:
Britta Hormann, Keyur Mehta

Medical Team:
Natalie Donde, Nader Hirmas

Medical Writing:
Alena Leunov

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