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DECEMBER 10–13, 2024
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No axillary surgery versus axillary sentinel lymph node biopsy in patients with early invasive breast cancer and breast-conserving surgery: Final primary results of the Intergroup-Sentinel-Mamma (INSEMA) trial

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on behalf of the INSEMA investigators

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Disclosure Information

Toralf Reimer

I have the following relevant financial relationships to disclose:

Employee of: Department of Obstetrics and Gynecology, University of Rostock, Germany

Consultant for: Menarini, MSD, Myriad

Speaker's Bureau for: Astra Zeneca, Daiichi-Sankyo, MSD, Novartis, Pfizer, Roche

Grant/Research support from: German Cancer Aid, Else Kröner-Fresenius-Foundation, German Society of Senology

Stockholder in: none

Honoraria from: Pfizer

My additional financial relationship disclosures are: T. Reimer received funding for the INSEMA trial by two grants from the German Cancer Aid (Deutsche Krebshilfe).

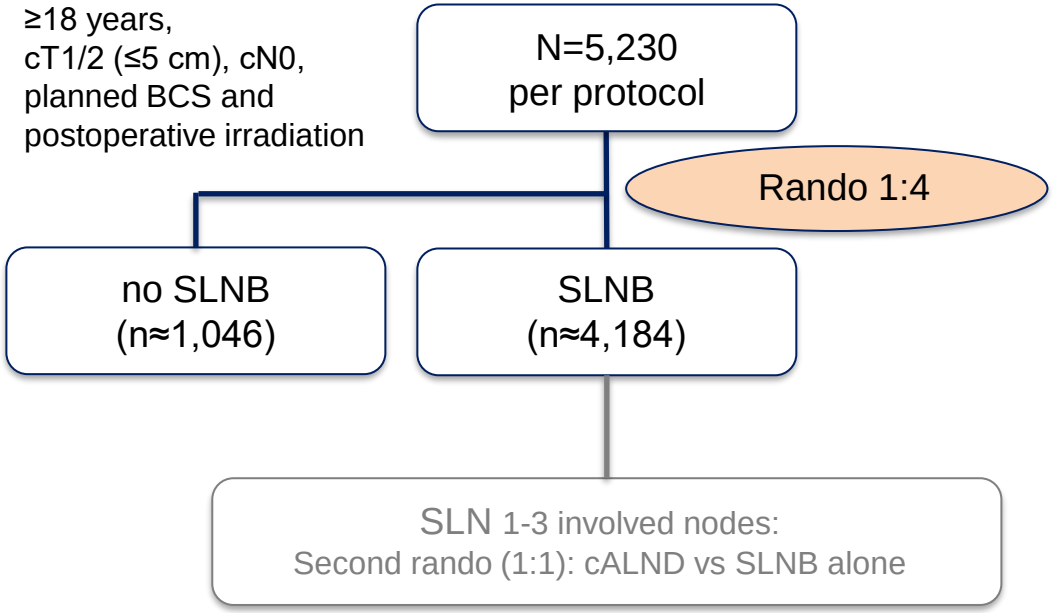
All payments to the University Medicine Rostock (UMR), Germany.

Background

- INSEMA is one of 4 ongoing de-escalation trials evaluating complete omission of axillary surgery in patients with breast-conserving surgery (BCS).
- Results of the SOUND[1] study showed that avoiding an axillary procedure in patients with small breast cancer up to 2 cm is not inferior to sentinel lymph node biopsy (SLNB).
- Previously, we reported secondary outcomes of the INSEMA trial:
  - pre-planned central quality assurance review process for postoperative radiotherapy planning and axillary contouring (N=276)[2]
  - patient-reported outcomes (PROs) with Quality-of-Life data results showed that patients with no SLNB benefitted regarding arm symptoms and functioning[3]
- **Goal of the INSEMA study is to demonstrate that complete omission of axillary surgery does not result in inferior invasive disease-free survival (iDFS) compared to the standard SLNB in early breast cancer with BCS.**

1 Gentilini et al. JAMA Oncol 2023
2 Hildebrandt et al. Int J Radiat Oncol Biol Phys 2020
3 Reimer et al. EClinicalMedicine 2022

Study Design INSEMA Trial



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

Primary objective:

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

Key secondary objective:

- To compare iDFS after BCS between SLNB alone and completion ALND patients (second randomization)

- Recruitment in Germany and Austria (2015-2019)

Methods

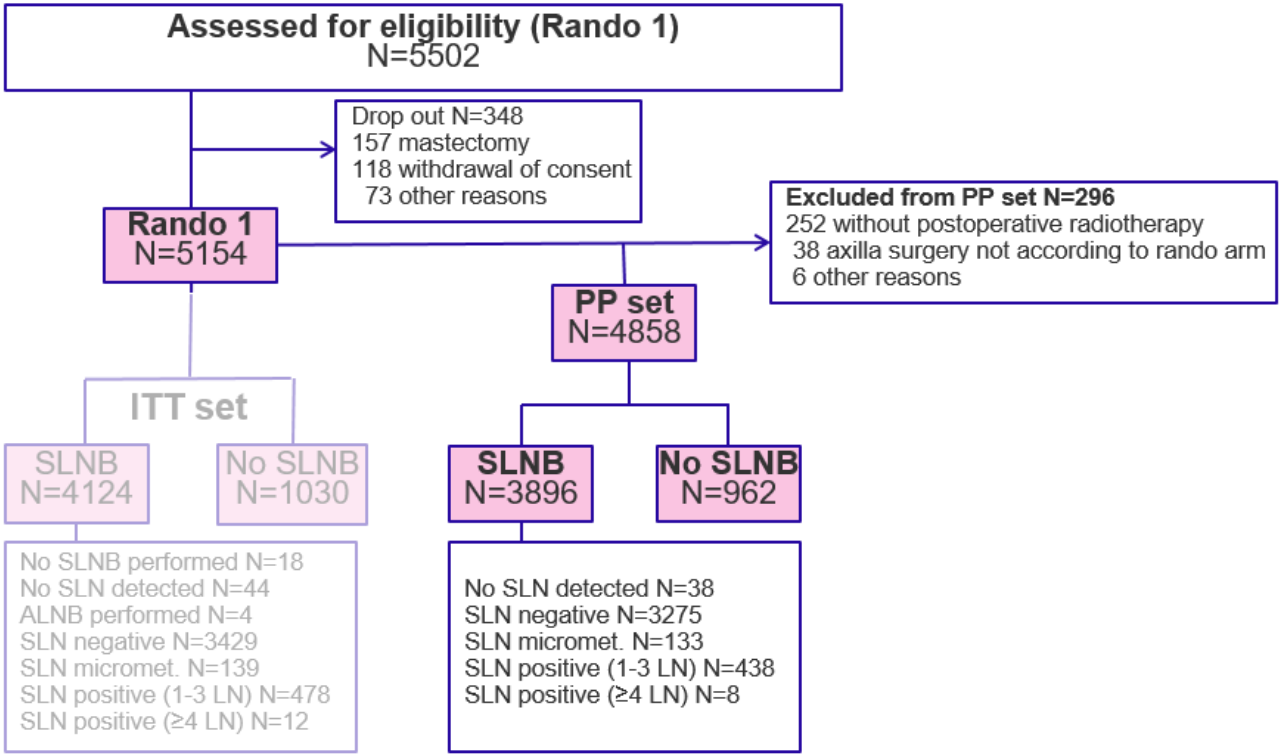
- The analysis of the primary end point was performed **on the per-protocol (PP) set** due to the non-inferiority study design[1].
- Kaplan-Meier product-limit method was used to estimate 5-year iDFS rates (reported with the two-sided 95% CI).
- **The non-inferiority was tested based on the CI of the hazard ratio (HR) from the Cox proportional hazard model to exclude the HR of 1.271 for the primary objective.**
  - **corresponding to the absolute decrease in 5-year iDFS rate from 88% (SLNB arm) to 85%.**
- A multivariate Cox proportional hazards model was used to adjust HRs for stratification factors:
  - age (<65y vs. ≥65y),
  - clinical tumor size (≤2 cm vs. >2 cm),
  - tumor grading (G1/2 vs. G3).
- Homogeneity of findings was explored in subgroups according to stratification factors and histological subtypes by univariate Cox regressions.

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

Sample Size Calculation

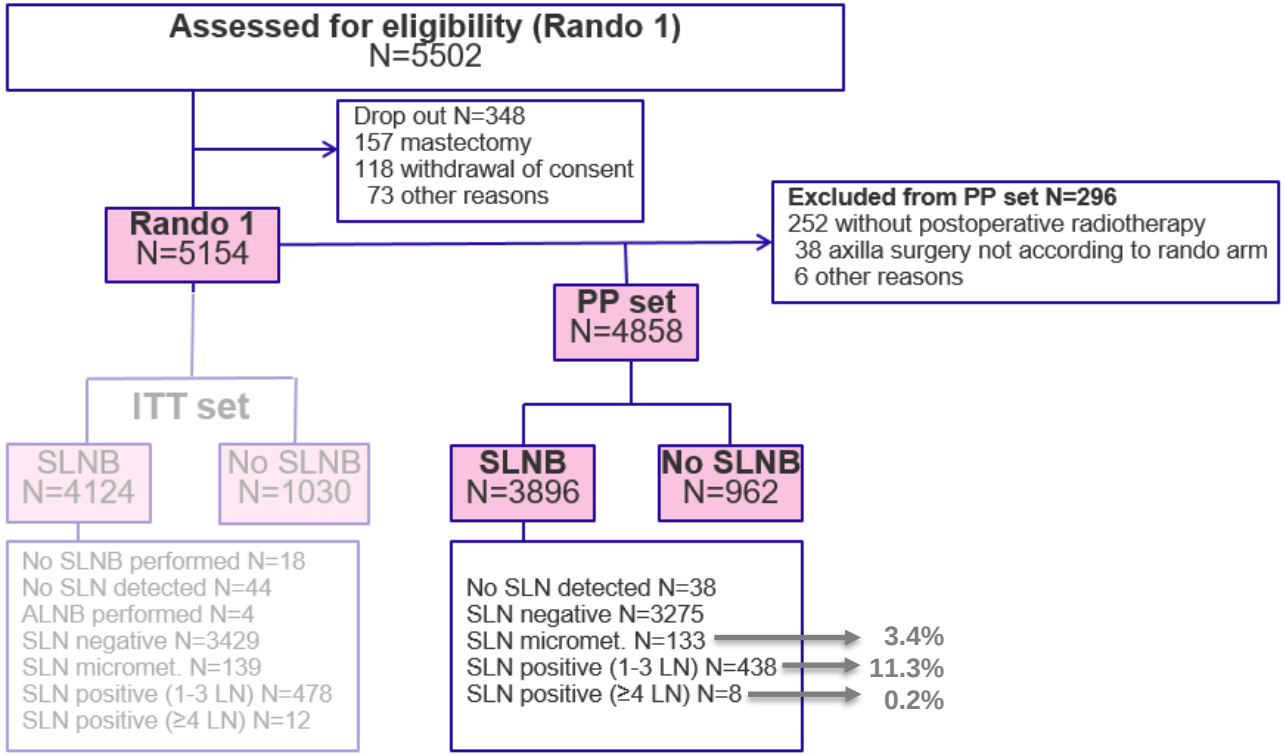
- Adjusting for 1:4 randomization, 851 events and 5,230 PP patients were needed in total for the first randomization (1,046 in no SLNB arm and 4,184 in SLNB arm).
- Assuming a 5% rate of patients who have to be excluded from the PP analysis, about 5,505 patients need to be randomized into the first part.
- The final efficacy analysis was planned event-driven when 851 events for the first randomization occurred in the PP set.
- A time-driven analysis was preplanned after a follow-up of 5.5 years of the last recruited patient, in case of lower event rates than expected.

Consort Flow Diagram



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

Consort Flow Diagram



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Baseline Characteristics: Per-Protocol Set

10.8% were aged <50 years

95.2% had HR+/HER2- subtype

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)

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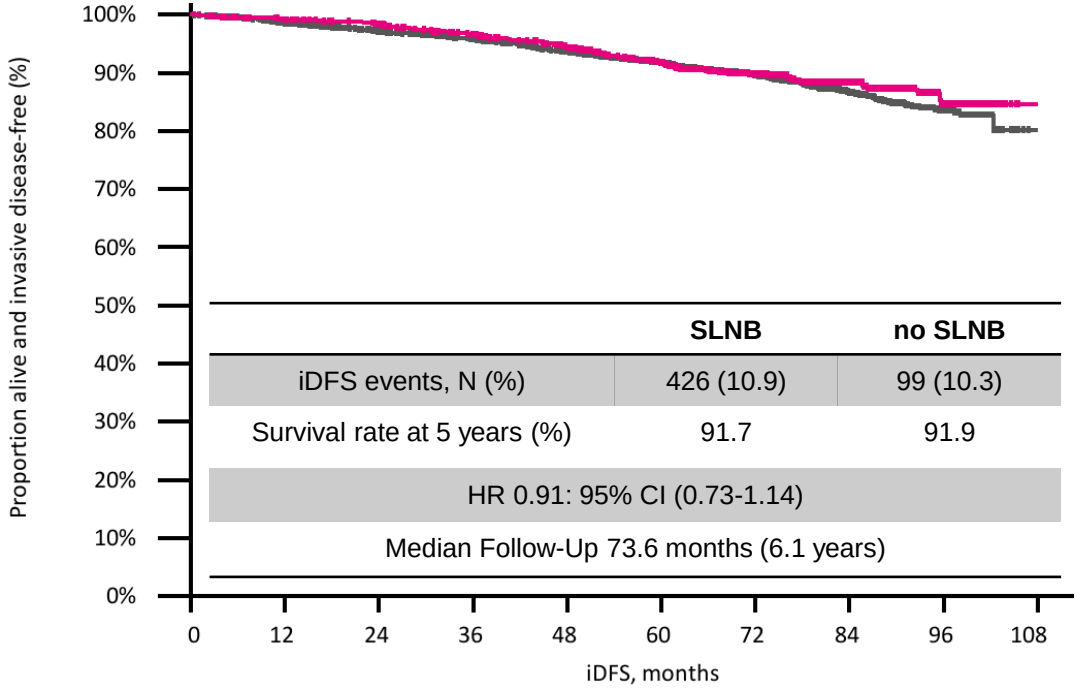
Primary Endpoint: Per-Protocol Analysis

Confidence interval for the HR lies entirely below the non-inferiority margin of 1.271

The primary endpoint in ITT set was also met

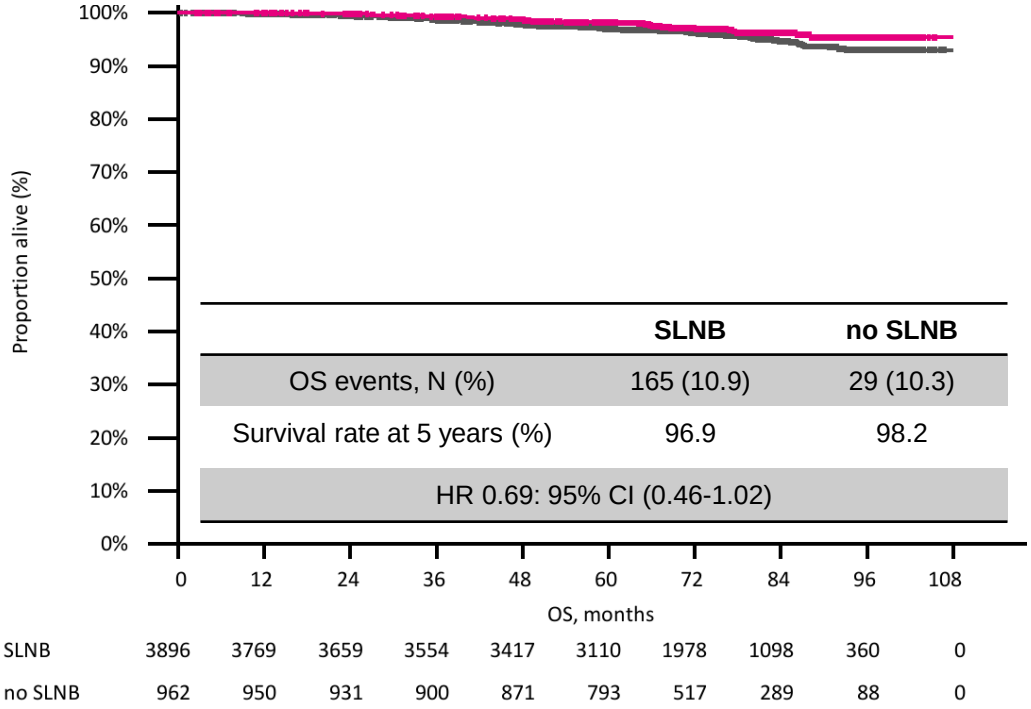


	SLNB	no SLNB
iDFS events, N (%)	426 (10.9)	99 (10.3)
Survival rate at 5 years (%)	91.7	91.9
HR 0.91: 95% CI (0.73-1.14)		
Median Follow-Up 73.6 months (6.1 years)		

Primary Endpoint Events (N=525)

Parameter	Category	no SLNB N=962	SLNB N=3896	Overall N=4858
First iDFS event	**Invasive locoregional recurrence**	**18 (1.9)**	**54 (1.4)**	**72 (1.5)**
	- Axillary recurrence	10 (1.0)	12 (0.3)	22 (0.5)
	- Invasive ipsilateral breast recurrence	8 (0.8)	42 (1.1)	50 (1.0)
	Invasive contralateral BC	10 (1.0)	25 (0.6)	35 (0.7)
	Distant relapse	26 (2.7)	104 (2.7)	130 (2.7)
	Secondary malignancy	32 (3.3)	150 (3.9)	182 (3.7)
	Death	13 (1.4)	93 (2.4)	106 (2.2)

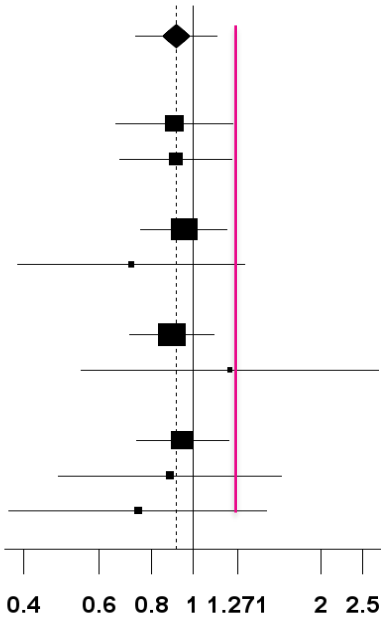
Overall Survival: Per-Protocol Analysis



	SLNB	no SLNB
OS events, N (%)	165 (10.9)	29 (10.3)
Survival rate at 5 years (%)	96.9	98.2
HR 0.69: 95% CI (0.46-1.02)		

Invasive Disease-Free Survival In Subgroups

Subgroup	N patients	Hazard Ratio (95% CI)	p-Value	Test for Interaction
Overall	4858	.913 (.734, 1.14)	0.417	
Age				0.954
under 65 years	2970	.903 (.658, 1.24)	0.527	
65 years or older	1888	.911 (.673, 1.23)	0.546	
Clinical tumor size				0.389
up to 2cm	4392	.951 (.752, 1.20)	0.674	
over 2cm	466	.715 (.387, 1.32)	0.285	
Tumor grading				0.446
G1/G2	4682	.891 (.710, 1.12)	0.320	
G3	176	1.22 (.545, 2.72)	0.631	
Histological tumor type				0.806
Invasive carcinoma NST	3554	.943 (.735, 1.21)	0.647	
Invasive or mixed lobular carcinoma	616	.882 (.483, 1.61)	0.683	
other	687	.741 (.368, 1.49)	0.400	



Conclusion

- The INSEMA trial enrolling 5,500 patients significantly demonstrated that omitting SLNB in cN0 patients with early breast cancer and scheduled for breast-conserving therapy, did not result in inferior outcome (HR 0.91 [95% CI: 0.73-1.14]; non-inferiority margin 1.271).
- Patients had very good overall survival with 96.9% and 98.2% at 5 years with vs without SLNB.
- This de-escalation concept is suitable for patients:
  - aged ≥50 years with
  - grading G1-G2 and
  - HR+/HER2- subtype and
  - a preoperative tumor size up to 2 cm

Acknowledgement

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

Cooperating partners

Collaborating study groups:

AGO-B BREAST STUDY GROUP

NOGGO

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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ORIGINAL ARTICLE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

T. Reimer, A. Stachs, K. Veselinovic, T. Kühn, J. Heil, S. Polata, F. Marmé, T. Müller, G. Hildebrandt, D. Krug, B. Ataseven, R. Reitsamer, S. Ruth, C. Denkert, I. Bekes, D.-M. Zahm, M. Thill, M. Golatta, J. Holtschmidt, M. Knauer, V. Nekljudova, S. Loibl, and B. Gerber