



Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1–2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial

Corrado Tinterri, MD^{1,2}, Damiano Gentile, MD¹, Wolfgang Gatzemeier, MD¹, Andrea Sagona, MD¹, Erika Barbieri, MD¹, Alberto Testori, MD¹, Valentina Errico, MD¹, Alberto Bottini, MD¹, Emilia Marrazzo, MD³, Carla Dani, MD⁴, Beatrice Dozin, MD⁴, Luca Boni, MD⁴, Paolo Bruzzi, MD, MPH, PhD⁴, Bethania Fernandes, MD⁵, Davide Franceschini, MD⁶, Ruggero Spoto, MD⁶, Rosalba Torrisi, MD⁷, Marta Scorsetti, MD, PhD^{2,6}, Armando Santoro, MD^{2,7}, Giuseppe Canavese, MD¹
the SINODAR-ONE Collaborative Group

¹Breast Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; ²Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; ³Breast Unit, Ospedale Maggiore di Lodi, Lodi, Italy; ⁴Department of Epidemiology, Biostatistics and Clinical Trials, IRCCS S. Martino, IST, Genoa, Italy; ⁵Department of Pathology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; ⁶Radiotherapy and Radiosurgery Department, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; ⁷Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; ⁸UOSVD Chirurgia Senologica – Breast Unit ASL BA P.O. San Paolo, Bari, Italy; ⁹IRCCS – Azienda Ospedaliero Universitaria di Bologna – Policlinico di Sant’Orsola, Bologna, Italy; ¹⁰U.O. Chirurgia Senologica Dipartimento Chirurgie Specialistiche, USL di Bologna, Bologna, Italy; ¹¹Oncologia e Senologia, Azienda di Rilievo Nazionale Alta Specializzazione ARNAS, Cagliari, Italy; ¹²Unità semplice di Chirurgia Senologica, Ospedale Ramazzini di Carpi, AUSL Modena, Modena, Italy; ¹³Humanitas Istituto Clinico Catanese, Misterbianco, CT, Italy; ¹⁴U.O.C. di Chirurgia Generale a indirizzo Senologico – EUSOMA Breast Centre ASL 2 Abruzzo, Abruzzo, Italy; ¹⁵U.O. Chirurgia Senologica, Ospedale Degli Infermi, Faenza, Italy; ¹⁶Chirurgia Senologica Ospedale di Forlì – Ravenna, Azienda USL della Romagna, Emilia-Romagna, Italy; ¹⁷UO Clinica di Chirurgia Policlinico San Martino – IRCCS, Genoa, Italy; ¹⁸SSD Breast Unit ASST Lecco, Lecco, Italy; ¹⁹Chirurgia Oncologica Senologica, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy; ²⁰Breast Unit – Surgery – San Gerardo Hospital, Monza, Italy; ²¹UOC Chirurgia Senologica IRCCS Sacro Cuore Don Calabria, Presidio Ospedaliero Accreditato, Regione Veneto, Italy; ²²Breast Surgery, Istituto Oncologico Veneto, Padua, Italy; ²³Breast Surgery Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; ²⁴Oncology Department AUSL Romagna, Ravenna Hospital, Ravenna, Italy; ²⁵Breast Surgery Unit, Azienda USL – IRCCS di Reggio Emilia, Emilia-Romagna, Italy; ²⁶UOC Senologia, Azienda Ospedaliero San Giovanni-Addolorata, Rome, Italy; ²⁷Chirurgia Senologica, Dipartimento Scienze Chirurgiche, IRCCS ‘Casa Sollievo della Sofferenza’ Opera di San Pio da Pietralcina, San Giovanni Rotondo, FG, Italy; ²⁸Breast Unit, Civic Hospital of Sanremo, ASL 1 Imperiese, Sanremo, Italy; ²⁹SCDU Gin e Ost, Ospedale Mauriziano Umberto primo, Torin, Italy; ³⁰S.S.D. Breast Unit, Centro Ricerche in Senologia, Università degli Studi dell’Insubria, ASST SetteLaghi, Varese, Italy; ³¹UOC Chirurgia Senologica – Breast Unit, AOUI Verona, Verona, Italy; ³²Breast Unit, Ospedale Montecchio Maggiore, Vicenza, Italy

ABSTRACT

Background. The SINODAR-ONE trial is a prospective noninferiority multicenter randomized study aimed at assessing the role of axillary lymph node dissection (ALND) in patients undergoing either breast-conserving surgery or mastectomy for T1–2 breast cancer (BC) and presenting one or two macrometastatic sentinel lymph

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First Received: 10 December 2021

Accepted: 20 April 2022

D. Gentile, MD
e-mail: damiano.gentile@humanitas.it

Published online: 12 May 2022

nodes (SLNs). The endpoints were to evaluate whether SLN biopsy (SLNB) only was associated with worsening of the prognosis compared with ALND in terms of overall survival (OS) and relapse.

Methods. Patients were randomly assigned (1:1 ratio) to either removal of ≥ 10 axillary level I/II non-SLNs followed by adjuvant therapy (standard arm) or no further axillary treatment (experimental arm).

Results. The trial started in April 2015 and ceased in April 2020, involving 889 patients. Median follow-up was 34.0 months. There were eight deaths (ALND, 4; SNLB only, 4), with 5-year cumulative mortality of 5.8% and 2.1% in the standard and experimental arm, respectively ($p = 0.984$). There were 26 recurrences (ALND 11; SNLB only, 15), with 5-year cumulative incidence of recurrence of 6.9% and 3.3% in the standard and experimental arm, respectively ($p = 0.444$). Only one axillary lymph node recurrence was observed in each arm. The 5-year OS rates were 98.9% and 98.8%, in the ALND and SNLB-only arm, respectively ($p = 0.936$).

Conclusions. The 3-year survival and relapse rates of T1–2 BC patients with one or two macrometastatic SLNs treated with SLNB only, and adjuvant therapy, were not inferior to those of patients treated with ALND. These results do not support the use of routine ALND.

Axillary lymph node dissection (ALND) has always been part of breast cancer (BC) treatment. However, during the past 25 years, the surgical management of the axilla has shifted towards a more conservative approach.^{1–4} It is certainly true that ALND is an effective procedure for accurate axillary staging, but it is also associated with a significant risk of complications such as pain, lymphedema, numbness, and restricted shoulder movement.^{3,5} The minimally invasive and less morbid procedure of sentinel lymph node biopsy (SLNB) has replaced ALND in clinically node-negative BC axillary staging.^{6,7} Until now, ALND has remained the standard surgical technique when the sentinel lymph node (SLN) is macrometastatic. However, complete axillary dissection may now be considered overtreatment for early-stage BC, and this recommendation starts to be challenged based on the following considerations: diagnosis tends to be earlier by screening mammography, so patients present with smaller tumors and lower axillary burden;⁸ less than half of patients with SLN metastasis present additional metastases in other lymph nodes;^{9–11} the majority of SLN-positive patients not undergoing ALND will receive chemotherapy and/or endocrine treatment maintaining low locoregional failure rate.^{12,13} Over the last decade, the American College of Surgeons Oncology Group Z0011 randomized clinical trial has questioned the therapeutic benefit of ALND in patients

with metastatic SLN,¹⁴ setting the ground for the introduction of axillary dissection omission in the surgical management of node-positive patients. Patients undergoing breast-conserving surgery (BCS) and whole-breast radiotherapy with one or two metastatic SLNs were randomized to ALND or no further axillary treatment. The trial concluded that axillary dissection did not provide outcome advantages, and no significant difference between ALND and no ALND groups was reported with respect to axillary recurrence, recurrence-free survival (RFS), and overall survival (OS) at 9.3 years.¹⁵ However, these results are controversial due to various study limitations: the trial was underpowered because of premature enrollment conclusion, too many patients were lost to follow-up, and about half of the patients presented micrometastases. These limitations make it difficult to generalize the findings of the trial and imply the need for stronger evidence to support the recommendation of ALND omission in SLN-positive BC patients. Based on these considerations, the Breast Unit of Humanitas Research Hospital (Milan, Italy) promoted the Italian SINODAR-ONE multicenter randomized clinical trial.

METHODS

Study Design and Endpoints

The SINODAR-ONE trial is a prospective noninferiority multicenter randomized study aimed at assessing the therapeutic role of ALND in patients undergoing either BCS or mastectomy for T1–2 BC presenting one or two macrometastatic SLNs. The study design and endpoints have been described previously.¹⁶ Briefly, patients fulfilling all eligibility criteria (Table 1) after SLNB were randomly assigned (1:1 ratio) to either removal of ≥ 10 axillary level I/II nonsentinel nodes followed by adjuvant therapy (standard arm) or no further surgical intervention on the axilla but only adjuvant therapy (experimental arm). The search of the SNL entailed radioguided surgery after periareolar injection of a radioactive compound (technetium-labeled albumin) and subsequent detection with lymphoscintigraphy. The histopathological examination could be performed both using the standard method (hematoxylin/eosin + immunohistochemistry) and the one-step nucleic acid amplification (OSNA) technique. In addition to the radiotracer, vital dye could also be used. The primary endpoint was to evaluate whether SLNB only (experimental treatment) was associated with clinically relevant worsening of the prognosis compared with complete axillary dissection (standard treatment) in terms of OS. The secondary endpoint was to evaluate whether there was increased regional (lymph node recurrence) or distant

TABLE 1 Enrollment criteria*Eligibility*Age ≥ 40 and ≤ 75 years

Invasive BC (cytology/core biopsy assessment)

Unilateral lesion

Tumor size ≤ 5 cm (cT1–2) (ultrasound/mammography assessment)

Clinically negative axillary nodes (N0) (ultrasound assessment)

No more than two SLNs proven metastatic (histological assessment)

Involved SLNs with macrometastasis (≥ 2 mm)

No distant metastasis (M0)

No neoadjuvant therapy

No previous invasive BC

Signed and dated written informed consent

Exclusion

Ongoing pregnancy or breast-feeding

Inflammatory BC

In situ BC

Synchronous contralateral BC

Comorbidity possibly preventing adjuvant therapy

Disease, comorbidity, or psychological conditions preventing compliance to regular follow-up

Previous neoplasm within the 3 years preceding randomization (with the exception of in situ carcinoma of the cervix, basalioma, and spinocellular carcinoma of the skin)

BC breast cancer, *SLN* sentinel lymph node

recurrence in terms of RFS in patients with macrometastatic SLN who did not undergo ALND. After completing surgery, the patients received further treatment according to biological and pathological tumor characteristics. Each patient was evaluated by a multidisciplinary tumor board composed of breast surgeons, oncologists, radiotherapists, radiologists, plastic surgeons, and pathologists. The completion of the course of treatment could entail chemotherapy, endocrine therapy, and/or human epidermal growth factor receptor 2 (HER2)-targeted treatment as appropriate. Patients receiving BCS also underwent whole-breast irradiation. Follow-up was planned according to these modalities: clinical breast examination every 6 months for the first 5 years, then yearly; mammography and breast ultrasound every year; ultrasound of the axilla every year in patients in whom ALND was not performed. The present study complied with the guidelines for human studies. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Institutional Review Board of all centers approved this trial. All patients provided written informed consent for treatment and clinical data acquisition.

Randomization and Data Collection

Randomization could be performed after either intra-operative or definitive histopathological SNL examination, allowing each center to freely manage SLNB modality. The randomization was performed via a dedicated website. The trial investigators inserted into the mentioned site all the necessary data to verify the eligibility of the patients. The system, once eligibility was verified, allocated the patients to the treatment (standard versus experimental) randomly, stratifying them by center and using the Moses–Oakford algorithm described by Meinert CL.¹⁷ The randomization system, in addition to assigning the treatment, also assigned to each randomized patient a specific number, identifying them for the entire duration of the trial. Information about patients enrolled in the trial was entered through the same dedicated website on electronic Case Report Forms (e-CRF), and the data were stored in a database managed by the Clinical Trials Centre of the IRCCS Ospedale Policlinico San Martino (Genova, Italy).

Statistical Analysis

The primary endpoint was OS, defined as time from date of randomization until date of last contact or death from any cause. The secondary endpoint was RFS defined as

regional disease-free survival (recurrence in the ipsilateral axillary lymph nodes) or distant metastases-free survival. Enrollment of 2000 patients with a minimum follow-up period of 5 years was initially planned.¹⁶ The alternative hypothesis was that patients with T1–2 BC presenting one or two macrometastatic SLNs treated with SLNB only did not present superior mortality and relapse rates compared with patients treated with ALND. The analysis was programmed after the observation of 535 events, to provide a power of 80% to reject the null hypothesis that omission of ALND was associated with an increase of 24% in the 5-year mortality rate. Trial enrollment closed early because of poor accrual rates and fewer than anticipated events. The protocol specified that patients were to be followed up for a minimum of 5 years; and the analysis of OS and RFS after the completion of patients' enrollment was not prespecified. However, in this study, as in all noninferiority studies, futility analyses are of particular importance for the safety of the patients assigned to the experimental arm, since if the intermediate results should clearly suggest superiority of the standard arm, it would be unethical to continue randomizing further patients. Therefore, futility analyses for OS and RFS were performed on an annual basis, and the results were evaluated by a Data Monitoring Committee (DMC) outside the trial. Overall survival and RFS of the two arms of treatment were compared using the Kaplan–Meier product limit estimator and the log-rank test. Statistical analyses were performed on both the intention-to-treat (ITT) and the per-protocol (PP) populations. In the ITT analysis, all patients were included and considered in the treatment arm allocated at randomization, ignoring noncompliance, withdrawal of consent, missing data, and errors of randomization. However, the presence of major protocol deviations (including incorrect treatment allocation, failure to meet the inclusion criteria, or noncompliance), in noninferiority studies, may bias ITT analysis against the null hypothesis (inferiority of the experimental arm). Therefore, PP analysis was carried out, including only patients who completed the study without major protocol deviations and who received the allocated intervention.¹⁸ Five-year cumulative incidence of mortality and recurrence, and 95% confidence intervals of incidence rate per 100 patients were calculated. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with IBM SPSS 25.0 software.

RESULTS

Patient Characteristics

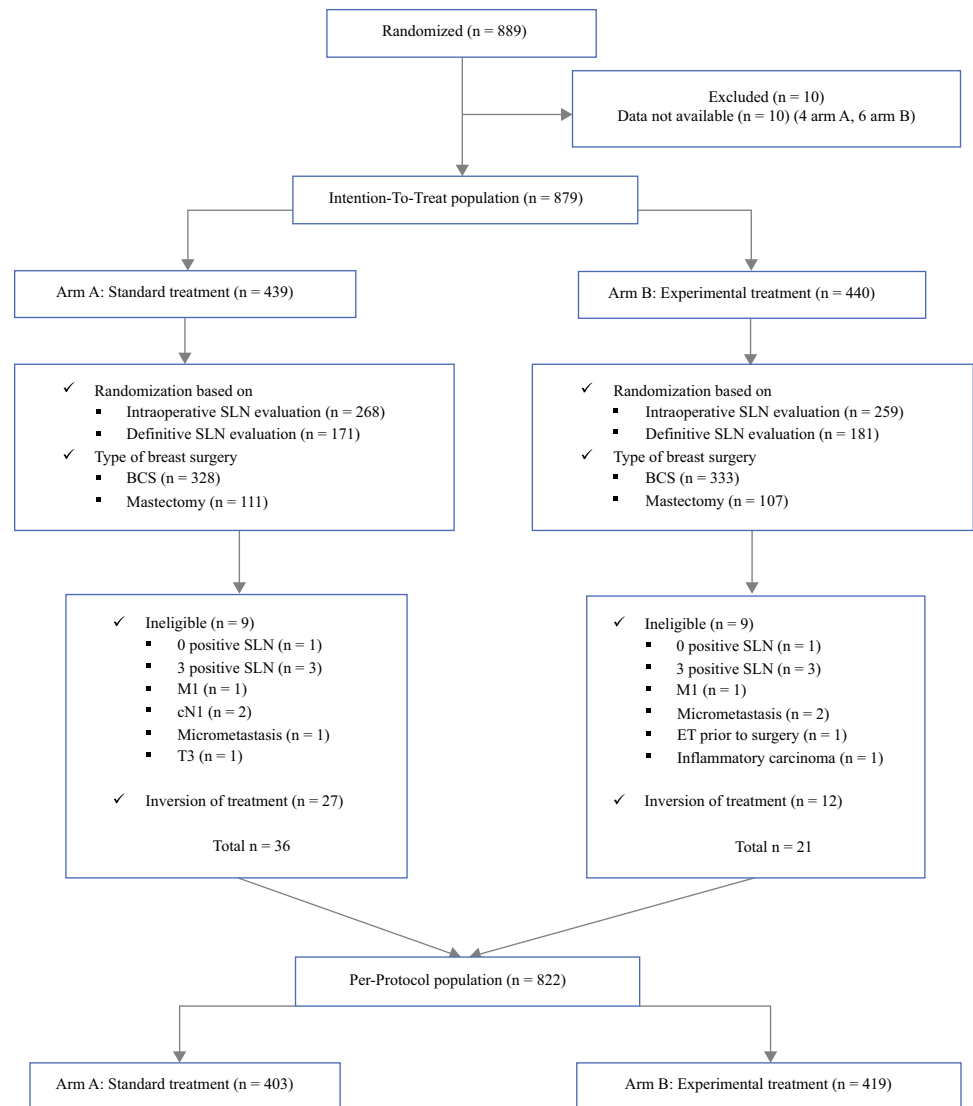
The SINODAR-ONE trial started in April 2015, and enrollment ceased in April 2020, involving 889 patients

from 52 different Italian centers. No data were available for ten patients. The ITT population was composed of 879 patients, who were randomly assigned to the ALND group ($n = 439$ patients) or the SNLB-only group ($n = 440$ patients) (Fig. 1). Overall, the majority of patients ($n = 527$) were randomized based on intraoperative evaluation of SNL. Because this was a noninferiority trial, a more conservative analysis was performed on the PP population ($n = 822$ patients) after exclusion of an additional 57 patients, for either ineligibility or inversion of treatment (Fig. 1). No qualitative differences were observed between ITT and PP population analyses, so only IIT results are reported. Clinical and histopathological characteristics at baseline were well balanced between the two groups (Table 2).

Treatment Results

Overall, the majority of the enrolled patients (75.2%) underwent BCS: 328 of 439 patients (74.7%) in the standard treatment arm, and 333 of 440 patients (75.7%) in the experimental treatment arm. Two hundred eighteen patients (24.8%) underwent mastectomy. Breast surgical data are summarized in Table 2. Sentinel lymph node status at randomization was comparable between the two different groups of treatment, with a median number of two SLNs removed and a median number of one positive SLN in both arms. Definitive histopathological evaluation identified micrometastases only in the SLNs of 2 of 439 patients (0.5%) in the ALND group compared with 3 of 440 patients (0.7%) in the SLNB-only group. The median number of non-SLNs identified at definitive histopathological evaluation was 16 (interquartile range [IQR] 12–21) in the ALND group. Overall, 193 of 439 patients (44.0%) in the standard treatment arm had additional macrometastases in the removed axillary lymph nodes. However, the median number of positive non SLNs was 0 (IQR 0–1) in the ALND group. Lymph nodes data are detailed in Table 3. No difference in adjuvant therapy was observed between the standard and experimental treatment arm, in both the BCS and mastectomy group. Overall, the majority of the enrolled patients (71.0%) underwent adjuvant whole-breast radiotherapy (WBR) following BCS; moreover, 429 of 624 patients (68.8%) who underwent WBR also had an additional tumor bed radiotherapy boost after BCS. In the mastectomy group, 38 patients (17.4%) underwent adjuvant radiotherapy. Modality and type of administered adjuvant chemotherapy were similar between the two different groups of treatment. Overall, postoperative chemotherapy was delivered to 428 patients in total (48.7%): 232 of 439 patients (52.9%) in the standard treatment arm, and 196 of 440 (44.6%) in the experimental treatment arm. In the mastectomy group, 116 patients

FIG. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram reporting the phases of randomization and selection of a population of 889 breast cancer patients presenting one or two metastatic sentinel lymph nodes and undergoing two different types of axillary surgical treatment (either standard axillary dissection or experimental sentinel lymph node biopsy only). *SLN* sentinel lymph node, *BCS* breast-conserving surgery, *ET* endocrine therapy



(53.2%) underwent postoperative chemotherapy. Anthracycline and taxane-based combination regimens were the most common type of administered adjuvant chemotherapy (49.1%), in both the BCS and mastectomy group. Adjuvant endocrine therapy was administered to the majority of the enrolled patients (90.2%), and the most common type of administered endocrine treatment was aromatase inhibitor (60.8%). In the mastectomy group, only 22 patients (10.1%) were not treated with adjuvant endocrine therapy. Adjuvant HER2-targeted immunotherapy was administered to 82 patients (9.3%).

Outcomes

Overall, median follow-up was 34.0 months (IQR 20.5–46.5 months). In the ITT population, there were eight deaths (ALND, 4; SNLB only, 4), with 5-year cumulative mortality of 5.8% and 2.1% in the standard and

experimental treatment arm, respectively ($p = 0.984$). Overall, there were 26 recurrences (ALND 11; SNLB only, 15), with 5-year cumulative incidence of recurrence of 6.9% and 3.3% in the standard and experimental treatment arm, respectively ($p = 0.444$) (Table 4). Only one axillary lymph node recurrence was observed in each group of treatment. Three ipsilateral BC recurrences were observed in the experimental treatment arm. Additionally, seven and eight patients presented distant metastases in the ALND and SNLB-only group, respectively. Analysis in the PP population yielded similar oncological results (Table 4). The use of SNLB only, compared with ALND, did not appear to result in statistically inferior survival, in both the ITT and PP population (Figs. 2, 3, 4). In the ITT population, the 5-year OS rates were 98.9% and 98.8% in the ALND and SNLB-only arm of treatment, respectively ($p = 0.936$). In the PP population, the 5-year OS rates were 99.2% and 98.7%, in the ALND and SNLB-only arm of

TABLE 2 Clinical, surgical, and histopathological data by treatment arm (ITT population)

	Standard treatment (no. 439), no. (%)	Experimental treatment (no. 440), no. (%)	All (no. 879), no. (%)
Clinical characteristics			
Age (years) [mean (SD)]	56.1 (9.3)	56.2 (9.6)	56.2 (9.4)
Menopausal status			
Premenopausal	164 (37.4)	156 (35.5)	320 (36.4)
Perimenopausal	16 (3.6)	20 (4.5)	36 (4.1)
Postmenopausal	259 (59.0)	264 (60.0)	523 (59.5)
Race/ethnicity data			
Caucasian white	439 (100)	440 (100)	879 (100)
Breast surgery			
BCS	328 (74.7)	333 (75.7)	661 (75.2)
Mastectomy	107 (24.4)	93 (21.1)	200 (22.8)
BCS mastectomy	4 (0.9)	14 (3.2)	18 (2.0)
Histopathological characteristics			
Type of tumor			
Unifocal	337 (76.8)	344 (78.2)	681 (77.5)
Multifocal	72 (16.4)	73 (16.6)	145 (16.5)
Multicentric	29 (6.6)	23 (5.2)	52 (5.9)
Missing value	1 (0.2)	0 (0)	1 (0.1)
Tumor size (mm) [mean (SD)]	19.6 (9.8)	18.0 (8.6)	18.8 (9.2)
Histotype			
Invasive ductal carcinoma NST	339 (77.3)	350 (79.5)	689 (78.4)
Invasive lobular carcinoma	69 (15.7)	61 (13.9)	130 (14.8)
Tubular carcinoma	1 (0.2)	1 (0.2)	2 (0.2)
Cribiform carcinoma	0 (0)	4 (0.9)	4 (0.5)
Mucinous carcinoma	3 (0.7)	3 (0.7)	6 (0.7)
Apocrine carcinoma	1 (0.2)	1 (0.2)	2 (0.2)
Invasive papillary carcinoma	6 (1.4)	7 (1.6)	13 (1.5)
Mixed ductal–lobular carcinoma	15 (3.4)	9 (2.1)	24 (2.7)
Other	4 (0.9)	4 (0.9)	8 (0.9)
Missing value	1 (0.2)	0 (0)	1 (0.1)
Grading			
G1	43 (9.8)	49 (11.1)	92 (10.5)
G2	290 (66.1)	279 (63.4)	569 (64.7)
G3	104 (23.7)	105 (23.9)	209 (23.8)
GX	1 (0.2)	7 (1.6)	8 (0.9)
Missing value	1 (0.2)	0 (0)	1 (0.1)
Resection margins			
Uninvolved	420 (95.7)	413 (93.9)	833 (94.8)
Involved	18 (4.1)	27 (6.1)	
Missing value	1 (0.2)	0 (0)	1 (0.1)
Lymphatic invasion			
No	281 (64.0)	306 (69.5)	587 (66.8)
Yes	157 (35.8)	134 (30.5)	291 (33.1)
Missing value	1 (0.2)	0 (0)	1 (0.1)
Vascular invasion			
No	252 (57.4)	276 (62.7)	528 (60.1)
Yes	186 (42.4)	164 (37.3)	350 (39.8)
Missing value	1 (0.2)	0 (0)	1 (0.1)

Table 2 (continued)

	Standard treatment (no. 439), no. (%)	Experimental treatment (no. 440), no. (%)	All (no. 879), no. (%)
Skin involvement			
No	411 (93.6)	407 (92.5)	818 (93.1)
Yes	27 (6.2)	33 (7.5)	60 (6.8)
Missing value	1 (0.2)	0 (0)	1 (0.1)
Intraductal component			
≤ 25%	356 (81.1)	346 (78.6)	702 (79.9)
> 25%	82 (18.7)	94 (21.4)	176 (20.0)
Missing value	1 (0.2)	0 (0)	1 (0.1)
Hormone receptors status			
ER- PGR-	20 (4.6)	23 (5.2)	43 (4.9)
ER+ PGR-	26 (5.9)	17 (3.9)	43 (4.9)
ER- PGR+	0 (0)	2 (0.5)	2 (0.2)
ER+ PGR+	391 (89.0)	395 (89.7)	786 (89.4)
Missing value	2 (0.5)	3 (0.7)	5 (0.6)
Ki67 (%)			
0–13%	146 (33.3)	164 (37.3)	310 (35.3)
> 14%	291 (66.3)	276 (62.7)	567 (64.5)
Missing value	2 (0.4)	0 (0)	2 (0.2)
HER2 status			
Negative	373 (84.9)	380 (86.4)	753 (85.7)
Positive	50 (11.4)	47 (10.7)	97 (11.0)
Not evaluable	9 (2.1)	5 (1.1)	14 (1.6)
Missing value	7 (1.6)	8 (1.8)	15 (1.7)
Molecular subtype			
Luminal A like	133 (30.3)	154 (35.0)	287 (32.7)
Luminal B like	228 (51.9)	211 (47.9)	439 (49.9)
HER2+	50 (11.4)	47 (10.7)	97 (11.0)
Triple negative	11 (2.5)	15 (3.4)	26 (3.0)
Missing value	17 (3.9)	13 (3.0)	30 (3.4)

SD standard deviation, *BCS* breast-conserving surgery, *NST* no special type, *ER* estrogen receptor, *PGR* progesterone receptor, *HER2* HER2 evaluated either on immunohistochemistry or on in situ hybridization, according to the ASCO CAP guidelines

treatment, respectively ($p = 0.753$). Similarly, RFS did not differ significantly between the two different groups of axillary treatment, in both the ITT and PP population (Figs. 2, 3, 4). In the ITT population, the 5-year RFS rates were 96.3% and 95.6%, in the ALND and SNLB-only arm of treatment, respectively ($p = 0.511$). In the PP population, the 5-year RFS rates were 96.4% and 95.6%, in the ALND and SNLB-only arm of treatment, respectively ($p = 0.491$).

DISCUSSION

The SINODAR-ONE randomized clinical trial demonstrated that patients with T1–2 BC presenting one or two macrometastatic SLNs treated with SLNB only did not

present inferior OS and RFS outcomes compared with patients treated with ALND. Axillary dissection is an invasive procedure that is associated with substantial morbidity, seriously affecting the quality of life of BC patients even in the long term. In the SINODAR-ONE randomized trial, only one axillary lymph node recurrence was observed in each group of treatment at median follow-up of almost 3 years, with nearly identical recurrence-free and overall survival rates between the standard and experimental treatment group. Usually, axillary lymph node recurrence is an early event. In the National Surgical Adjuvant Breast and Bowel Project B-04 clinical trial, Fisher et al. reported that the median time from mastectomy to identification of axillary recurrence was 14.8

TABLE 3 Lymph nodes characteristics by treatment arm (ITT population)

	Standard treatment (no. 439), no. (%)	Experimental treatment (no. 440), no. (%)	All (no. 879), no. (%)
<i>SLN status at randomization</i>			
Number of SLNs [median (IQR)]	2 (1–3)	2 (1–3)	2 (1–3)
Number of positive SLNs [median (IQR)]	1 (1–1)	1 (1–1)	1 (1–1)
<i>SLN status at pathological evaluation</i>			
No metastases	2 (0.5)	1 (0.1)	3 (0.3)
Micrometastases only	2 (0.5)	3 (0.7)	5 (0.6)
Macrometastases only	403 (91.8)	402 (91.4)	805 (91.6)
Micro- and macrometastases	31 (7.1)	34 (7.8)	65 (7.4)
Missing value	1 (0.1)	0 (0)	1 (0.1)
<i>Non-SLNs status at pathological evaluation</i>			
Number of evaluated non-SLNs [median (IQR)]	16 (12–21)	–	16 (12–21)
Number of positive non-SLNs [median (IQR)]	0 (0–1)	–	0 (0–1)
Number of patients with one positive non-SLN	97 (22.1)	–	97 (11.0)
Number of patients with two positive non-SLNs	39 (8.9)	–	39 (4.4)
Number of patients with three positive non-SLNs	14 (3.2)	–	14 (1.6)
Number of patients with more than 3 positive non-SLNs	43 (9.8)	–	43 (4.9)

SLN sentinel lymph node, IQR interquartile range

months (range 3.0–134.5 months).¹⁹ Greco et al. evaluated the impact of T1–2 BC surgery without ALND on axillary and distant relapses on 401 patients, reporting a lower than expected relapse rate with median time to axillary node recurrence of 30.6 months.²⁰ Hwang et al. evaluated the role of ALND omission in 196 BC patients with positive SLNs, reporting no axillary recurrence at median follow-up of 29.5 months, and a median time to distant metastases of 32 months.¹² Sekine et al. analyzed the results of ALND omission in 49 BC patients with one or two positive SLNs, reporting a median time to axillary lymph node recurrence of 23 months (range 8–92 months).²¹ The low rates of regional recurrence in the SINODAR-ONE trial combined with the results of previous reports suggest that relapse and survival differences between the standard and experimental group of treatment are unlikely to emerge with longer follow-up.

The long-term results of the Z0011 clinical trial provided additional evidence and demonstrated that complete axillary dissection is not necessary for prolonged locoregional control and survival for patients with T1–2 BC and one or two positive SNLs undergoing BCS and adjuvant systemic therapy, avoiding ALND-related morbidity without decreasing disease control.¹⁵ Even though the Z0011 clinical trial was affected by important study limitation and its first results generated widespread controversy,^{22–24} the trial represented a practice-changing study, especially in North America. Since 2011, in the

USA, the Memorial Sloan Kettering Cancer Center and the MD Anderson Cancer Center approved the omission of complete axillary dissection in patients with the same characteristics as in the Z0011 clinical trial.^{25,26} Tsao et al. reported that, after the update of practice guidelines to address the issue of complete axillary dissection following positive SLNB in a 12-hospital network, ALND rates decreased significantly over time, from 82% pre-Z0011 to 58% post-Z0011, and 39% after the approval of the final version of the guidelines.²⁷ Using the National Cancer Data Base, Yao et al. examined the results of 74,309 lumpectomy patients who fulfilled the Z0011 clinical trial criteria, reporting that the use of SLNB only increased substantially from 2009 to 2011.²⁸ However, in 2018, Morrow et al. published a survey showing that 49% of breast surgeons would still definitively or probably recommend ALND for one SLN macrometastasis and 62.6% would definitively or probably recommend ALND for two SLNs with macrometastasis, in the USA.²⁹

The publication of the first results of the Z0011 study coincided with the start of numerous European clinical trials^{30–32} which tried to resolve the issues of the previous one. However, in Europe, practice guidelines seem to be heterogeneous across countries.³³ In 2016, Gondos et al. published a study including patients from institute-specific cancer registries from numerous European countries (Norway, Denmark, the Netherlands, Sweden, Italy, Belgium, and Germany), showing that, for pT1 tumors, there is

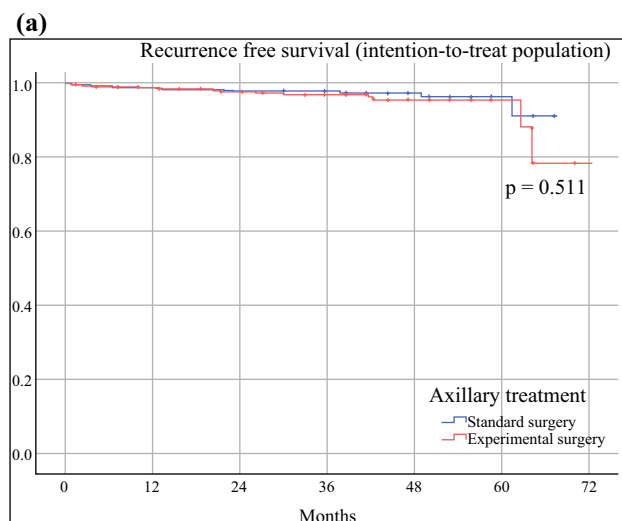
TABLE 4 Comparison of event rates by treatment arm (standard versus experimental)

Outcome	Standard treatment (ITT) (N = 439)	Experimental treatment (ITT) (N = 440)	p-Value
<i>Mortality</i>			
No. of events	4	4	
5-Year cumulative incidence (%)	5.8	2.1	
Incidence rate per 100 py	0.3	0.3	
95% CI	0.1–0.8	0.1–0.8	
Rate ratio	1	0.99	0.984
95% CI	Ref	0.23–4.17	
<i>Incidence of relapses</i>			
No. of events	11	15	
Ipsilateral breast	0	3	
Contralateral breast	3	3	
Regional lymph node	1	1	
Distant metastasis	7	8	
5-Year cumulative incidence (%)	6.9	3.3	
Incidence rate per 100 py	0.9	1.2	
95% CI	0.5–1.6	0.7–2.1	
Rate ratio	1	1.35	0.444
95% CI	Ref	0.62–3.02	
Outcome	Standard treatment (PP) (N = 403)	Experimental treatment (PP) (N = 419)	p-Value
<i>Mortality</i>			
No. of events	3	4	
5-Year cumulative incidence (%)	5.8	2.1	
Incidence rate per 100 py	0.3	0.3	
95% CI	0.1–0.8	0.1–0.9	
Rate ratio	1	1.29	0.734
95% CI	Ref	0.29–6.57	
<i>Incidence of relapses</i>			
No. of events	10	14	
Ipsilateral breast	0	3	
Contralateral breast	2	3	
Regional lymph node	1	0	
Distant metastasis	7	8	
5-year cumulative incidence (%)	6.9	3.3	
Incidence rate per 100 py	0.9	1.2	
95% CI	0.4–1.6	0.7–2.0	
Rate ratio	1	1.36	0.451
95% CI	Ref	0.61–3.16	

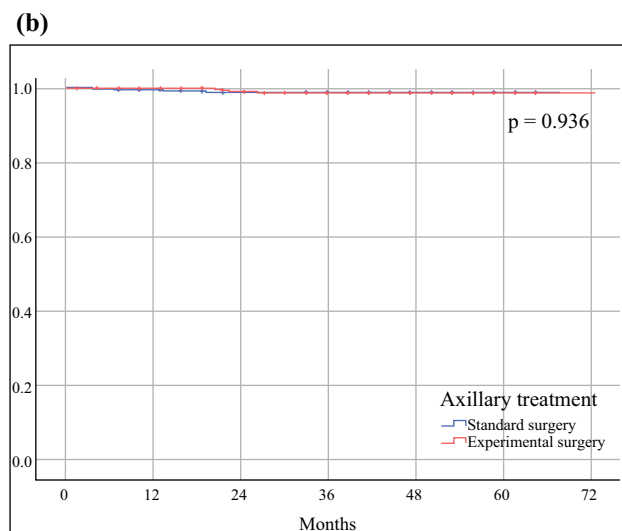
ITT intention-to-treat population, PP per-protocol population, CI confidence interval, py person-years

heterogeneous use of complete axillary dissection ranging from 12 to 47%.³⁴ The SINODAR-ONE randomized trial can be placed among the previously cited European studies, corroborating the oncological outcomes of BC patients with the same characteristics as in the Z0011 study and partially overcoming its limitations. Indeed, 301 of 731

patients (41.2%) and 5 of 879 patients (0.6%) presented micrometastases in the SLNs, in the Z0011 and in the SINODAR-ONE trial, respectively. Additionally, the role of axillary nodal irradiation in the Z0011 trial is controversial. In fact, 19% of patients received prohibited third-field irradiation, while in the SINODAR-ONE study,



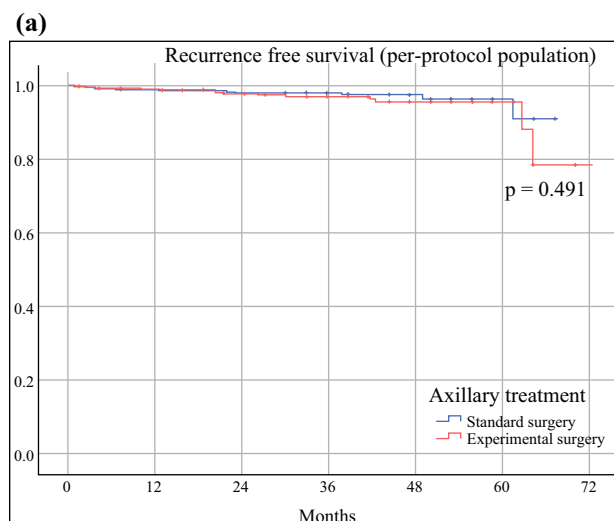
Patients at risk	0	1 year	2 years	3 years	4 years	5 years
Standard surgery	439	374	286	189	105	26
Experimental surgery	440	400	300	194	98	26



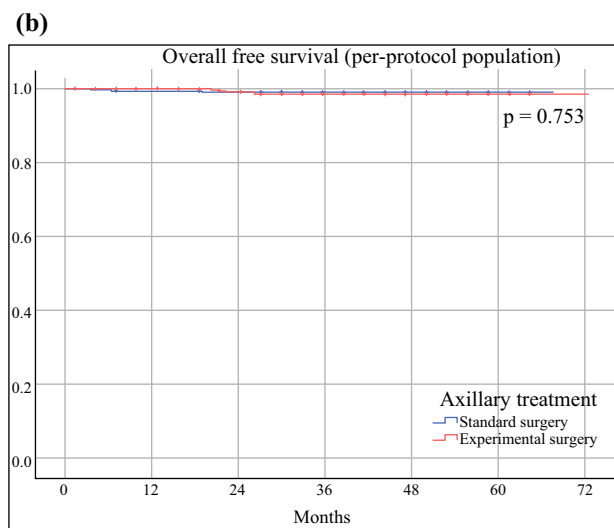
Patients at risk	0	1 year	2 years	3 years	4 years	5 years
Standard surgery	439	376	289	191	107	26
Experimental surgery	440	405	303	198	101	27

FIG. 2 Recurrence-free (a) and overall survival (b) of the ITT population of randomized breast cancer patients presenting one or two metastatic sentinel lymph nodes according to different axillary surgical treatments (either standard axillary dissection or experimental sentinel lymph node biopsy only). Figure created with IBM SPSS 25.0 software

patients were treated only with whole breast \pm boost radiotherapy and no nodal irradiation. Finally, in the Z0011 trial, BC patients who were candidates for mastectomy were not eligible; on the other hand, in the SINODAR-ONE study, T1–2 BC patients undergoing BCS or mastectomy were enrolled and their oncological outcome analyzed.



Patients at risk	0	1 year	2 years	3 years	4 years	5 years
Standard surgery	403	352	270	175	98	25
Experimental surgery	419	378	281	186	95	26



Patients at risk	0	1 year	2 years	3 years	4 years	5 years
Standard surgery	403	354	273	177	100	25
Experimental surgery	419	382	283	189	97	27

FIG. 3 Recurrence-free (a) and overall survival (b) of the PP population of randomized breast cancer patients presenting one or two metastatic sentinel lymph nodes according to different axillary surgical treatments (either standard axillary dissection or experimental sentinel lymph node biopsy only). Figure created with IBM SPSS 25.0 software

It remains necessary to underline that this clinical trial has some major limitations. Firstly, similarly to the Z0011 study, due to low accrual rates and fewer than anticipated events, the SINODAR-ONE trial did not reach the pre-specified sample size of 2000 participants or 535 events. Moreover, the SINODAR-ONE trial presents a relatively short follow-up; therefore, our present results need to be

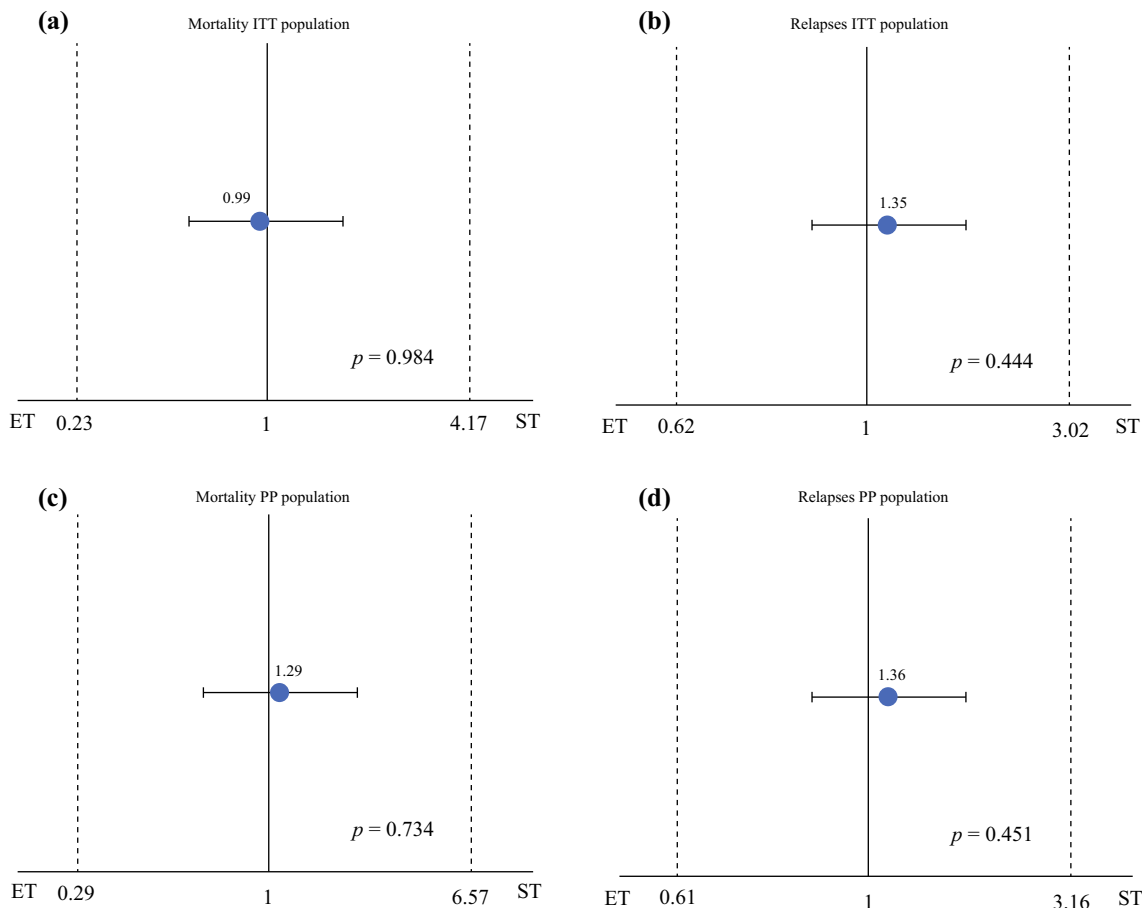


FIG. 4 Testing noninferiority between treatment arms (standard versus experimental), showing noninferiority outcomes in terms of mortality and relapses rates of the experimental treatment (sentinel lymph node biopsy only) compared with the standard treatment

(axillary dissection) in both the ITT (a, b) and PP population (c, d). *ITT* intention-to-treat, *PP* per-protocol, *ET* experimental treatment, *ST* standard treatment

confirmed by a longer observation period. In addition, only 218 of 879 patients (24.8%) underwent mastectomy, so generalization of the long-term oncological results of the SINODAR-ONE trial, even to this category of T1–2 BC patients, remains questionable.

CONCLUSIONS

The 3-year survival, regional, and distant relapse rates of patients with T1–2 BC and one or two macrometastatic SLNs treated with BCS, SLNB only, and adjuvant therapy were not inferior to those of patients treated with ALND. These results do not support the use of routine ALND in this category of patients. Further prospective trials are needed to extend the recommendation of ALND omission even to T1–2 BC patients undergoing mastectomy.

ACKNOWLEDGMENT We thank Mrs Elena Biscolotti for clinical data acquisition and collection.

The SINODAR-ONE Collaborative Group: Olindo Custodero, MD⁸, Vito Leopoldo Troilo, MD⁸, Mario Taffurelli, MD⁹, Maria Cristina Cucchi, MD¹⁰, Valentina Galluzzo, MD¹⁰, Carlo Cabula, MD¹¹, Roberta Cabula, MD¹¹, Maria Grazia Lazzaretti, MD¹², Francesco Caruso, MD, PhD¹³, Gaetano Castiglione, MD¹³, Simona Grossi, MD¹⁴, Maria Saveria Tavoletta, MD¹⁴, Camilla Rossi, MD¹⁵, Annalisa Curcio, MD, PhD¹⁶, Daniele Friedman, MD¹⁷, Piero Fregatti, MD, PhD¹⁷, Carla Magni, MD¹⁸, Giovanni Tazzioli, MD¹⁹, Simona Papi, MD¹⁹, Riccardo Giovanazzi, MD²⁰, Camelia Chifu, MD²⁰, Rossella Bettini, MD²¹, Modestino Pezzella, MD²¹, Silvia Michieletto, MD²², Tania Saibene, MD²², Manuela Roncella, MD²³, Matteo Ghilli, MD²³, Andrea Sibilio, MD²⁴, Anna Cariello, MD²⁴, Saverio Coiro, MD²⁵, Giuseppe Falco, MD²⁵, Emanuele Zarba Meli, MD²⁶, Lucio Fortunato, MD²⁶, Luigi Ciuffreda, MD²⁷, Roberto Murgo, MD, PhD²⁷, Claudio Battaglia, MD²⁸, Luca Rubino, MD²⁸, Nicoletta Biglia, MD, PhD²⁹, Valentina Bounous, MD, PhD²⁹, Francesca Angela Rovera, MD³⁰, Corrado Chiappa, MD³⁰, Giovanni Pollini, MD³¹, Sara Mirandola, MD³¹, Graziano Meneghini, MD³², Francesco Di Bartolo, MD³²

⁸UOSVD Chirurgia Senologica – Breast Unit ASL BA P.O. San Paolo, Bari, Italy; ⁹IRCCS – Azienda Ospedaliero Universitaria di Bologna – Policlinico di Sant’Orsola, Bologna, Italy; ¹⁰U.O. Chirurgia Senologica Dipartimento Chirurgie Specialistiche USL di Bologna, Italy; ¹¹Oncologia e Senologia Azienda di Rilievo Nazionale Alta Specializzazione ARNAS – Cagliari, Italy; ¹²Unità semplice

di Chirurgia Senologica, Ospedale Ramazzini di Carpi, AUSL Modena, Italy; ¹³Humanitas Istituto Clinico Catanese – Contrada Cubba SP 54 n. 11, 95045, Misterbianco (CT), Italy; ¹⁴U.O.C. di Chirurgia Generale a indirizzo Senologico – EUSOMA Breast Centre ASL 2 Abruzzo, Italy; ¹⁵U.O. Chirurgia Senologica, Ospedale degli Infermi, Viale Stradone 9, Faenza, Italy; ¹⁶Chirurgia Senologica Ospedale di Forlì – Ravenna, Azienda USL della Romagna, Italy; ¹⁷UO Clinica di Chirurgia Policlinico San Martino – IRCCS, Genova, Italy; ¹⁸SSD Breast Unit ASST Lecco, Italy; ¹⁹Chirurgia Oncologica Senologica, Azienda Ospedaliera-Universitaria di Modena, Italy; ²⁰Breast Unit – Surgery – San Gerardo Hospital, Monza, Italy; ²¹UOC Chirurgia Senologica IRCCS Sacro Cuore Don Calabria, Presidio Ospedaliero Accreditato – Regione Veneto, Italy; ²²Breast Surgery, Istituto Oncologico Veneto, Padova, Italy; ²³Breast Surgery Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; ²⁴Oncology Department AUSL Romagna, Ravenna Hospital, Ravenna, Italy; ²⁵Breast Surgery Unit, Azienda USL – IRCCS di Reggio Emilia, Italy; ²⁶UOC Senologia, Azienda ospedaliera San Giovanni-Addolorata, Rome, Italy; ²⁷Chirurgia Senologica, Dipartimento Scienze Chirurgiche, IRCCS ‘Casa Sollievo della Sofferenza’ Opera di San Pio da Pietralcina, 71013, San Giovanni Rotondo (FG), Italy; ²⁸Breast Unit, Civic Hospital of Sanremo, ASL 1 Imperiese, Sanremo, Italy; ²⁹SCDU Gin e Ost, Ospedale Mauriziano Umberto primo, Torino, Italy; ³⁰Centro Ricerche in Senologia, Università degli Studi dell’Insubria, S.S.D. Breast Unit, ASST SetteLaghi, Varese, Italy; ³¹UOC Chirurgia Senologica – Breast Unit, AOUI Verona, Italy; ³²Breast Unit, Ospedale Montecchio Maggiore, Vicenza, Italy

AUTHOR CONTRIBUTIONS CT, DG, and GC had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the analyses. Concept and design: CT, DG, WG, AS, EB, AT, VE, AB, EM, BF, DF, RS, RT, MS, AS, GC, and the SINODAR-ONE Collaborative Group. Acquisition, analysis, and interpretation of data: CT, DG, WG, AS, EB, AT, VE, AB, EM, CD, BD, LB, PB, GC, and the SINODAR-ONE Collaborative Group. Statistical analyses: DG, CD, BD, LB, PB. Drafting of the manuscript: DG, PB, CT, GC. Critical revision of the manuscript for important intellectual content: All authors and the SINODAR-ONE Collaborative Group. Supervision: CT, GC. Final approval of the version to be published: All authors and the SINODAR-ONE Collaborative Group.

FUNDING The clinical trial was supported by Fondazione Humanitas per la Ricerca – Rozzano (MI). No other disclosures or conflicts of interest are declared.

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