

Restricted Axillary Staging in Clinically and Sonographically Node-Negative Early Invasive Breast Cancer (c/iT1–2) in the Context of Breast Conserving Therapy: First Results Following Commencement of the Intergroup-Sentinel-Mamma (INSEMA) Trial

Eingeschränktes Axilla-Staging bei klinisch und sonografisch nodal-negativen Patientinnen mit frühem invasiven Mammakarzinom (c/iT1–2) im Rahmen der brusterhaltenden Therapie: erste Erkenntnisse nach Start der Intergroup-Sentinel-Mamma-(INSEMA-)Studie

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ABSTRACT

Axillary lymph node status remains an important prognostic factor in early breast cancer. It is regarded as an indicator for (neo)adjuvant systemic treatment and postoperative radiotherapy of the regional lymphatics. Commenced in September 2015, the INSEMA trial is investigating whether operative determination of nodal status as part of breast conserving therapy (BCT) for early stage breast cancer (c/iT1–2 c/iN0) can be avoided without reducing oncological safety. After inclu-

sion of 1001 patients there was general acceptance of the complex study design by patients and study doctors so that recruitment for the first randomisation (axillary sentinel lymph node biopsy [SLNB]: yes or no) achieved predicted case numbers. The second randomisation however (SLNB alone versus complete axillary dissection when one or two macrometastases are present at SLNB) recruited fewer cases than expected for the following three reasons: a) the 13% rate of one or two macrometastases after SLNB in the INSEMA trial collective was lower than expected; b) around 20% of patients refused the second randomisation; c) there was delayed inclusion of the Austrian study centres, which only recruited for the second randomisation. Lack of knowledge of nodal status when SLNB is avoided represents a new challenge for the postoperative tumour board. In particular decisions on chemotherapy for luminal-like tumours and irradiation of the lymphatics (excluding axilla) must be guided by tumour biological parameters. The INSEMA trial does not provide answers to some important questions, e.g. it remains unclear whether patients without SLNB can be offered partial breast irradiation alone in low-risk situations and whether SLNB can also be avoided in patients with stage T1–2 tumours who have a mastectomy indication.

ZUSAMMENFASSUNG

Der axilläre Nodalstatus wird beim frühen Mammakarzinom immer noch als wichtiger Prognosefaktor und Indikator für eine (neo-)adjuvante System- und postoperative Strahlentherapie der Lymphabflusswege (LAW) gesehen. Die im September 2015 gestartete INSEMA-Studie untersucht, ob beim frühen Mammakarzinom (c/iT1–2 c/iN0) auf die operative Bestimmung des Nodalstatus im Rahmen der brusterhaltenden Therapie (BET) verzichtet werden kann, ohne dass die onkologische Sicherheit beeinträchtigt wird. Nach Einschluss von 1001 Patientinnen war die Akzeptanz des komplexen Studiendesigns bei Patientinnen und Prüfärzten gegeben, sodass die Rekrutierung für die erste Randomisierung (axilläre Sentinel-Lymphknoten-Biopsie [SLNB]: ja oder nein) im Rahmen der Fallzahlprognose liegt. Die 2. Randomisierung (SLNB allein versus Komplettierung der Axilladisektion bei 1 oder 2 Makrometastasen in der SLNB) rekrutiert dagegen aus 3 Gründen weniger als erwartet: a) Der Nachweis von 1 bis 2 Makrometastasen nach der SLNB im INSEMA-Kollektiv ist mit 13% geringer als erwartet; b) etwa 20% der Patientinnen lehnten die 2. Randomisierung ab; c) der Einstieg der österreichischen Prüfzentren, die ausschließlich für die 2. Randomisierung rekrutieren, erfolgt zeitlich verzögert. Die Unkenntnis des Nodalstatus bei Verzicht auf die SLNB bringt eine neue Herausforderung für die postoperative Tumorkonferenz. Insbesondere

die Indikation zur Chemotherapie bei Luminal-like-Tumoren und zur Bestrahlung der LAW (ohne Axilla) muss nun an den tumorbiologischen Parametern ausgerichtet werden. Einige wichtige Fragen können durch die INSEMA-Studie nicht beantwortet werden. Unklar bleibt

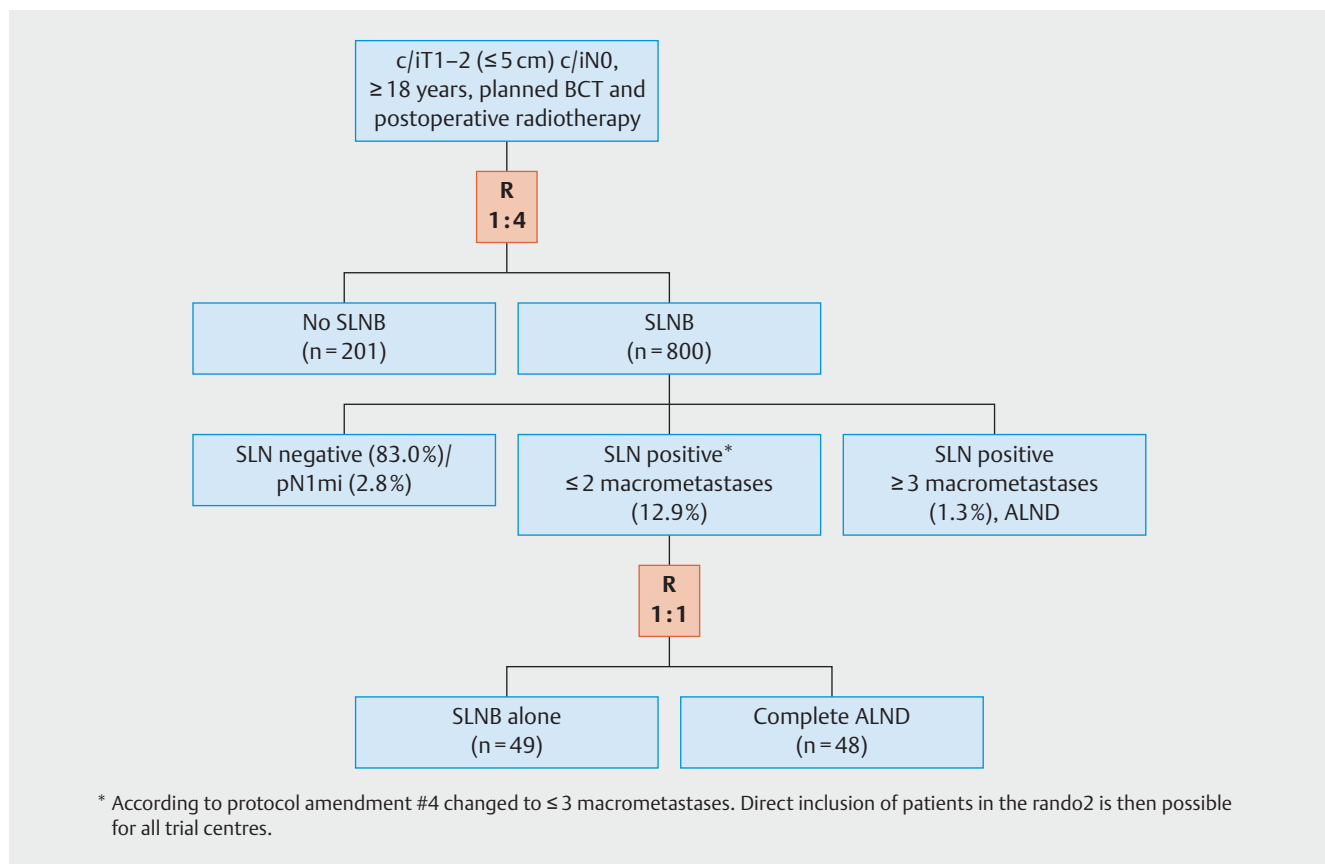
beispielsweise, ob Patientinnen ohne SLNB eine alleinige Teilbrustbestrahlung in Low-Risk-Situationen angeboten werden kann bzw. ob auch bei Patientinnen mit einer Mastektomieindikation auf die SLNB im Stadium T1–2 verzichtet werden kann.

Introduction

The Intergroup-Sentinel-Mamma (INSEMA) trial (NCT02466737, GBG75, ABCSG43) is a prospective, randomised trial comparing sentinel lymph node biopsy (SLNB) versus no axillary surgery in patients with early invasive breast carcinoma (clinically/radiologically ≤ 5 cm; c/iT1–2 c/iN0) who are having breast conserving therapy (BCT) including postoperative whole breast irradiation (► Fig. 1). In a second phase, analogous to the ACOSOG Z0011 trial [1], patients with sentinel lymph node positivity are randomised to either no further surgery or complete axillary lymph node dissection (ALND). The INSEMA trial is sponsored by the University Medicine Rostock; it is financed by the Deutsche Krebshilfe GmbH (German Cancer Aid Ltd); data management is performed by the German Breast Group (GBG) (Neu-Isenburg, Germany). Over 130 German trial centres recruit for both analyses; the “first patient in” was on 17.09.2015 in Rostock. On 09.03.2016 the first patient

was recruited in Austria at the Salzburg centre. The remaining Austrian Breast & Colorectal Cancer Study Group (ABCSG) centres will only recruit for the second randomisation.

The rationale of the study is based on the available data at the time of protocolling (2011–2014) [2, 3]. This sees the removal of the axillary sentinel lymph node (SLN) in a critical light – at least in the context of BCT when lymph nodes are normal on palpation and ultrasound. Complete ALND appears to be of no benefit even to patients with one to two positive SLNs whereas avoidance of SLNB could reduce costs (marking, operative capacity, pathology), reduce axilla-related morbidity (e.g. lymphoedema) and improve quality of life [4]. Review of the Rostock Cancer Registry from 2014 and 2015 found that for the Rostock University Women’s Hospital 53.1% of newly diagnosed breast cancer patients fulfilled INSEMA inclusion criteria. Thus results of the INSEMA trial could potentially influence the operative management of every second breast cancer patient.



► Fig. 1 Flow chart of the INSEMA trial showing the distribution after recruitment of 1001 patients.

► **Table 1** Selected patient characteristics of the first 1 001 INSEMA patients.

Parameter	Category	SLNB (n = 800)	No SLNB (n = 201)	Total (n = 1 001)	p-value
Age (years)	mean	61.1	60.0	60.9	0.236
	median	61.0	60.0	61.0	
	min-max	36–87	36–89	36–89	
BMI (kg/m ²)	mean	27.0	27.2	27.1	0.707
	median	25.8	25.9	25.8	
HR status	ER/PgR negative	23 (2.9%)	8 (4.0%)	31 (3.1%)	0.493
	ER and/or PgR positive	774 (97.1%)	193 (96.0%)	967 (96.9%)	
HER2 status	negative	728 (92.0%)	178 (89.4%)	906 (91.5%)	0.255
	positive	63 (8.0%)	21 (10.6%)	84 (8.5%)	
Grading	G1	269 (33.6%)	65 (32.3%)	334 (33.4%)	0.942
	G2	488 (61.0%)	125 (62.2%)	613 (61.2%)	
	G3	43 (5.4%)	11 (5.5%)	54 (5.4%)	
Histological subtype	invasive ductal	586 (73.5%)	152 (75.6%)	738 (73.9%)	0.774
	invasive lobular	89 (11.2%)	24 (11.9%)	113 (11.3%)	
	mixed or other	122 (15.3%)	25 (12.5%)	147 (14.7%)	
Ki-67	≤ 20%	648 (84.3%)	160 (82.9%)	808 (84.0%)	0.661
	> 20%	121 (15.7%)	33 (17.1%)	154 (16.0%)	

BMI = body mass index; HR = hormone receptor; ER = estrogen receptor; PgR = progesterone receptor

Materials and Methods

Essential inclusion criteria for the INSEMA trial (recent changes according to protocol amendment #4 from 15.09.2016 in bold type):

- Histologically confirmed unilateral invasive breast carcinoma (punch biopsy, Mammotome biopsy or **open biopsy** possible)
- **Age ≥ 18 years**
- Tumour size clinically and radiologically ≤ 5 cm (iT1/iT2) independent of hormone receptor and HER2 status
- Clinically and sonographically tumour-free axillary lymph nodes before biopsy (c/iN0); if cN0/iN+ negative core biopsy or fine needle aspiration of suspicious lymph node required
- No suspicion of distant metastases
- Planned BCT with postoperative whole-breast irradiation and adequate systemic therapy

Essential exclusion criteria for the INSEMA trial:

- History of carcinoma in the previous 5 years
- Invasive breast cancer treated with neoadjuvant therapy
- c/iT3-T4 tumours
- Planned mastectomy
- Planned exclusive intraoperative partial breast irradiation (e.g. INTRABEAM) or exclusive postoperative partial breast irradiation (e.g. multi-catheter technique); both methods allowed as boost
- Pregnancy and breastfeeding
- Male breast cancer

Study aims

Statistical analysis in the INSEMA trial is based on non-inferiority so that per protocol analysis is mainly performed. The primary outcome for both study questions is invasive disease-free survival. Secondary outcomes are overall survival, local and axillary recurrence rates and determination of actual applied radiotherapy dose at each axillary level. In addition, analyses of quality of life and translational research in the form of a biobanking program are integrated.

Approximately 6000 patients will be recruited in 130 trial centres in Germany and one in Austria for both INSEMA trial analyses. A further 10 ABCSG centres will contribute 800 cases exclusively for the second randomisation. The 1000th study patient was recruited on 22.06.2016, the INSEMA trial thus linking up with the SOUND study (Sentinel Node versus Observation After Axillary UltraSound, NCT02167490) [4], which has been running since 2012. In the SOUND study 1560 patients with breast tumours up to 2 cm in size (T1 stage) and BCT are to be randomised 1:1 to axillary SLNB versus no axillary surgery. In contrast to the INSEMA trial the primary outcome measure is distant disease-free survival.

Results

A first analysis of patient characteristics (n = 1001) is summarised in ► **Table 1**. The median age of the study population as a whole was 61 years, though there were somewhat more premenopausal women recruited to the non-SLNB group (< 50 years: 17.4 vs. 10.8% in the SLNB group). Statistical analysis of the age distribution showed no significant difference between the groups (p = 0.051).

► **Table 2** Prospective randomised trials with avoidance of axillary lymphadenectomy in patients with early stage breast cancer vs. complete axillary dissection/axillary radiotherapy.

Author/Study	Patients	n	Follow-up	Axillary recurrence	Disease-free survival	Overall survival
Fisher et al. [50] (2002) NSABP B-04	All ages, cN0, MRM vs. ME alone vs. ME plus radiation, no systemic therapy	1 079	25 y	18.6% in ME-only arm	19 vs. 19 vs. 13%; p = 0.65	25 vs. 26 vs. 19%; p = 0.68
Veronesi et al. [51] (2005) [#]	> 45 y, tumour < 1.2 cm, cN0	435	63 mo.	0.5 vs. 1.5%	97 vs. 95%; p = 0.19	99 vs. 97%; p = 0.23
Rudensam et al. [52] (2006) IBCSG 10-93	> 60 y, pT1-2*, cN0	473	6.6 y	0.9 vs. 2.5%; n. s.	67 vs. 66%; p = 0.69	75 vs. 73%; p = 0.77
Martelli et al. [53] (2014)	≥ 65 y, pT1 cN0, tamoxifen	238	15 y	0 vs. 6%	DDFS p = 0.95	p = 0.64
Agresti et al. [54] (2014) INT09/98	30–65 J., cT1cN0, tamoxifen ± chemotherapy	565	10 y	0 vs. 9%	92.4 vs. 91.3%; p = 0.9	93.3 vs. 91.5%; p = 0.78

[#] Veronesi et al. randomised patients without axillary surgery to no further treatment vs. axillary radiation.

* 42% of patients with tumours > 2 cm

y = years, mo. = months, ME = mastectomy, MRM = modified radical mastectomy, DDFS = distant disease-free survival

After analysis of preoperative imaging 889 cases (88.9%) were assigned to stage cT1 (≤ 2 cm) and 111 cases (11.1%) to stage cT2 (> 2 cm). The vast majority of the 1001 breast carcinomas were hormone receptor positive (96.9%). Only 8.5% of all tumours were HER2 positive and only 5.4% of all cases were G3 on tumour grading. These figures support the assumption that in Germany triple negative and HER2 positive tumours are currently more likely to be treated during neoadjuvant therapy.

In the SLNB arm (n = 755 after exclusion of drop-outs) the detection rate for the sentinel lymph node was 99.5%. Pathology analysis of 751 SLNBs performed showed the following distribution of nodal status: 83.0% pN0 (n = 623); 2.8% micrometastasis (pN1mi; n = 21); 12.9% with 1–2 macrometastases (n = 97); and 1.3% ≥ 3 macrometastases (n = 10). Thus the case rate of 85.8% without demonstrable axillary lymph node macrometastasis was significantly above the 70% predicted at protocolling. This can be credited to the thorough preoperative workup at the trial centres (e.g. ultrasound ± axillary core biopsy) during INSEMA recruitment. On the other hand many breast centres (internationally too) currently achieve pN0 rates of around 80% for SLNB through increased screening.

Discussion

Avoidance of SLNB and oncological safety

The oncological safety of avoiding SLNB is often questioned during informed consent to INSEMA trial participation. The request for maximal oncological safety from patients and relatives must be weighed up against the desire for adequate cosmesis in the axilla and the avoidance of operative morbidity. Studies from the pre-SLNB era compared ALND to no axillary surgery for clinically tumour-negative axillary lymph nodes. Case numbers were often low, however with adequate long-term follow-up these studies showed that although the rate of axillary recurrence is slightly in-

creased, this does not affect disease-free survival or overall survival (► **Table 2**).

When discussing oncological safety it must be mentioned that the randomised trials that lead to the acceptance of SLNB in routine clinical practice had false negative rates of 5–8%, which however did not influence disease-free or overall survival [5, 6].

In the IBCSG 23-01 trial 931 patients with SLN micrometastases were randomised to either no further axillary surgery or complete axillary dissection [7]. After adequate systemic therapy, radiotherapy and a median follow-up of 5 years the locoregional recurrence rate (0.9% in both arms), disease-free survival (87.8 vs. 84.4%) and overall survival (98.0 vs. 97.6%) were not significantly different. Since publication of these data complete axillary dissection has generally been avoided – even outside of clinical trials – when SLNB shows pN1mi (St. Gallen 2013 consensus recommendation) [8].

Oncological safety with avoidance of complete axillary dissection despite SLNB tumour cell positivity

The ACOSOG Z0011 trial provides data on this subject that were first presented at the ASCO 2010 and brought up to date after extended follow-up at the ASCO 2016. In the Z0011 trial almost 900 patients with BCT and SLN micro- and macrometastases were randomised to either no further axillary surgery or complete ALND. Here too, after a median follow-up of 9.25 years, there were no significant differences in recurrence rates locally (5.6% in the ALND arm vs. 3.8% in the “SLNB only” arm; p = 0.13) or in the axilla (0.5% in the ALND arm vs. 1.5% in the “SLNB only” arm), nor in locoregional recurrence-free survival (p = 0.36) [9]. It is noteworthy that 4 of the total 5 axillary lymph node recurrences in the “SLNB only” arm (1.5%) occurred within the first five years. Indeed, 3.6% of cases in the “SLNB only” arm were found to have more than two macrometastases at definitive histology.

The previously mentioned limitations of the Z0011 trial (e.g. 37.5% only SLN axillary micrometastasis, numerous violations of protocol during postoperative radiotherapy) lead to the com-

mencement of further validation trials. Almost all subsequent protocols focus on patients with SLN axillary macrometastasis. Interestingly, some study groups extend the inclusion criteria beyond those of the classical Z0011 design: Inclusion of mastectomy patients (POSNOG [10], SENOMAC [11], Dutch BOOG 2013-07 [12], SINODAR ONE [13]); inclusion of patients with SLNB before neoadjuvant systemic treatment, T3 tumours and male patients (SENOMAC [11]); inclusion of patients with more than two macrometastases at SLNB (Dutch BOOG 2013-07, French SERC/IPC 2012-001).

The need for a second INSEMA randomisation

As a result of the ACOSOG Z0011 trial avoidance of ALND is regarded by many as standard. Thus in the USA 54% of patients with one or two involved SLNs already no longer undergo complete lymphadenectomy [14]. The Oncology Working Group – Breast (AGO-Mamma) has given this approach (avoidance of complete ALND with one or two involved SLNs and breast conserving operation) a +/- recommendation, thus not yet declaring it standard [15]. The second INSEMA randomisation therefore deals with a still unresolved issue. In order to increase the power of validation studies investigators from the SENOMAC and INSEMA trials will aim for pooled analysis of BCT cases.

The following changes to recruitment for the second study question of the INSEMA trial are contained in the current protocol amendment #4:

1. Inclusion of patients with **one to three** macrometastases following SNLB;
2. German trial centres may recruit directly for the second randomisation.

In contrast to the ACOSOG Z0011 – where 37.5% of patients “only” had axillary micrometastasis – the INSEMA trial will only include patients with macrometastasis, meaning that the axillary tumour load between the two study collectives will differ significantly [16]. It is also expected that postoperative radiotherapy in the two studies will not be identical. In the Z0011 approx. 50% of patients received a so-called high tangent with significant dose to the axilla levels I and II; in addition 18.9% of cases had received radiation to the regional lymph drainage areas, which was not consistent with protocol. On the other hand 11% of patients did not receive postoperative whole-breast irradiation [17]. In the INSEMA protocol ascertainment of the actually administered radiotherapy dose for each axilla level was made a secondary study outcome. Also, a central review of the first three radiation treatment plans in each case was integrated. Up until the end of August 2016 144 radiotherapy protocols from 58 centres have been reviewed and are already complete for 24 centres.

Significance of transcapsular spread in involved lymph nodes

The prognostic significance of lymph node capsule infiltration and capsule rupture with extranodal tumour spread is controversial. For instance capsule infiltration/rupture was classified as pN1biii in the 5th edition of the American Joint Committee on Cancer (AJCC)’s “Cancer Staging Manual”, but in the currently valid 6th edition is not specifically listed [18, 19]. In the ACOSOG Z0011 tri-

al only “matted nodes” or evidence of macroscopic extranodal tumour (“gross extranodal disease”) at the time of SNLB were exclusion criteria.

In a current meta-analysis of 5 analysable studies including a total 624 patients (163 with, 461 without transcapsular spread) with a median follow-up of 58 months, patients with transcapsular spread had a significantly increased recurrence rate (RR = 2.07, 95% CI: 1.38–3.10, $p < 0.0001$) and mortality (RR = 2.51; 95% CI: 1.66–3.79, $p < 0.0001$) [20]. Other studies have shown, however, that extracapsular tumour spread ≤ 2 mm, and thus also capsule infiltration alone, did not significantly worsen prognosis [21–24]. Capsule rupture itself has shown significant correlation with further involved axillary lymph nodes and other unfavourable tumour parameters. In a study that took the ACOSOG Z0011 criteria into account (pT1–2, cN0, ≤ 2 positive SLNs) only 1109 cases from a study population of 11 730 were found to have one to two positive SLNs on H&E staining. Of these, 30% ($n = 331$) had capsule rupture (≤ 2 mm: $n = 180$; > 2 mm: $n = 151$) [22]. Local operative treatment i.e. complete axillary dissection does not appear to be necessary for transcapsular spread in the current era of modern multimodality treatment. In a study at the Memorial Sloan-Kettering Cancer Center in New York only 45 of 111 patients with capsule rupture underwent axillary dissection. After a median follow-up of 21 months there was not a single case of local recurrence among the 66 patients without complete axillary dissection [25]. There is currently no standard pathological definition of capsule rupture. Neoplastic emboli, nests of free tumour cells or marginal sinus metastases should not be documented as relevant transcapsular spread [20]. The pathological diagnosis “sentinel macrometastasis with transcapsular spread” does not preclude inclusion in the INSEMA randomisation 2, therefore there is no need for the INSEMA protocol to define these parameters. Other studies (e.g. AMAROS, SENOMAC) also recruit (or have recruited) cases with lymph node metastases and transcapsular spread.

Deciding on irradiation of the regional lymphatics depending on nodal status

Three prospective randomised trials (MA.20, EORTC, French-trial) [26–28] and one cohort study (DBCG-IMN) [29] have dealt with the effects of irradiating the regional lymphatics (parasternal \pm supraclavicular) in patients with node-positive or node-negative high-risk tumours or tumours with medial location. All three randomised trials found no significant advantage for overall survival (primary study outcome) after a follow-up period of 10 years. A meta-analysis of these three trials did however show a significant effect (HR 0.90; 95% CI: 0.82–0.99) [30]. The Danish cohort study DBCG-IMN achieved its primary study outcome (significant difference in overall survival after 8.9 years: 75.9% with and 72.2% without parasternal irradiation; $p = 0.005$). This positive effect was however only demonstrated when ≥ 4 lymph nodes were involved. These data are confirmed by a Swedish cohort study in which irradiation of the regional lymphatics in patients with 1–3 involved lymph nodes was not associated with a survival advantage, only well-known side effects [31]. The AGO treatment guidelines give a single “plus” recommendation (= of limited use, may be used) to irradiation of regional lymphatics in the presence of 1–3 involved axillary lymph nodes only when further risk factors

► **Table 3** Axillary recurrence rates in studies comparing whole breast vs. partial breast irradiation alone in the context of breast conserving treatment.

Study	Number of cases (n)	Proportion of pN+	Follow-up	Regional lymph node recurrence (n)		p-value
				WBI	PBI	
Dodwell [55] (2005)	174	41% (PBI-arm)	8 years	4	10	0.05
Rodriguez [56] (2013)	102	0%	5 years	0	0	n. s.
ELIOT [35] (2013)	1 305	26%	5.8 years	2	9	0.03
TARGIT-A [36] (2014)	3 451	16%	5 years	6	8	0.609
GEC-ESTRO [37] (2016)	1 184	1% pN1mi	5 years	1	3	0.39

WBI = whole breast irradiation, PBI = partial breast irradiation

are present (medial/central tumour localisation, G2–3, ER/PgR negative, premenopause) [15].

It must however be critically noted that in all the studies on regional lymphatic irradiation mentioned above, tumour biology in terms of intrinsic subtypes was not adequately taken into consideration, and systemic treatments did not match current standards (e.g. no anti-HER2) [32]. In addition, these study populations are not comparable with the INSEMA collective since they have a significantly higher proportion of node-positive cases (MA.20 trial: 90% pN+, DBCG-IMN: 100% pN+). The current INSEMA protocol (amendment #4) has adopted irradiation of the regional lymphatics as clearly indicated when 4 or more lymph nodes are involved (\geq stage pN2a).

Rate of axillary recurrence in studies using partial breast irradiation alone

It is currently assumed that in the context of BCT axillary recurrence is minimised by postoperative whole breast irradiation, even in patients with negative SLNB [33]. In practice there is significant incidental irradiation of the ipsilateral axilla, at least at level I, even when so-called “standard tangents” are used [34]. This is considered an important contributor to the results of the Z0011 trial. Modern radiotherapy techniques (e.g. RapidArc technology) may soon enable reduction of this “collateral” irradiation of the ipsilateral axilla.

With this in mind the interpretation of published studies with partial breast irradiation alone becomes more interesting. In this context, dependent on tumour localisation, the ipsilateral axilla levels may receive no or only very little irradiation. ► **Table 3** summarises an analysis of 5 studies on this theme. Among these only the ELIOT study showed a significantly increased regional lymph node recurrence rate [35]. In contrast no significant difference was found between the different treatment arms in the TARGIT-A and GEC-ESTRO trials [36, 37]. One explanation for this is certainly the significantly higher proportion of node-positive cases in the ELIOT. Nevertheless the axillary recurrence rate of 1.4% in the ELIOT study, with intraoperative partial breast irradiation, is still very low. A meta-analysis of three studies, taking 5–8 years of follow-up into account, found no significant increase in axillary recurrence rate following partial breast irradiation alone [38].

Thus there is no clear evidence that minimising postoperative radiotherapy of the remaining breast in a low-risk SLNB collective

increases the axillary recurrence rate. It is still unclear whether the concept of avoiding SLNB can also be applied to patients receiving partial breast irradiation alone. Currently partial breast irradiation alone is not a treatment option for INSEMA trial participants. The results of SOUND and INSEMA will thus not be applicable to this patient group. This interesting and relevant question lends itself to an INSEMA follow-on project.

Deciding on systemic treatment and radiotherapy without knowledge of nodal status

With subtyping of breast carcinoma according to hormone receptor (HR) status, HER2 status, tumour grade and Ki-67 systemic treatment is planned according to the intrinsic tumour subtypes rather than nodal status [39]. Chemotherapy \pm anti-HER2 therapy is always indicated for triple-negative and HER2 positive tumours (stage pT1b and above). There is consensus in all guidelines and treatment recommendations that chemotherapy is not automatically indicated for luminal-like tumours with axillary lymph node involvement [15, 40–45]. In particular luminal-A subtype tumours with \leq 3 involved lymph nodes can be sufficiently treated with endocrine therapy alone [46]. Analysis of the ABCSG-8 study (HR positive cases, endocrine therapy alone) using the PAM50 test to classify tumours according to intrinsic subtypes showed clear differences within the node-positive subgroup (n = 431) dependent on luminal status. The 10-year survival rate without distant metastases was 90.6% for node-positive luminal-A patients and 71.0% for node-positive luminal-B tumours [47]. Chemotherapy is indicated for the luminal-like subtype when 4 or more lymph nodes are involved (► **Table 4**).

Information on the number of involved lymph nodes is naturally missing for cases in the non-SLNB arm of the INSEMA trial. Following the AMAROS data analysis it was expected for INSEMA that approx. 3% of all luminal-like tumours in a SLNB collective could potentially have more than three lymph nodes involved [48]. In the INSEMA control arm with SLNB after recruitment of the first 1001 patients only 11 of 771 cases (1.4%) were found to have three or more involved lymph nodes. Of these 11 patients 8 had three, and 1 had 4, 5 and 6 involved nodes respectively so that the proportion of patients with the relevant pN2a tumour stage was only 0.375%. Thus guideline conform systemic treatment is

► **Table 4** Indications for adjuvant postoperative chemotherapy dependent on tumour biology according to the current St. Gallen consensus recommendations [46].

MaCa-subtype	Indications for postoperative chemotherapy	Comments
Luminal-like	<ul style="list-style-type: none"> ▪ grading G3 ▪ low-level ER/PgR expression ▪ high Ki-67 ▪ extensive lymphovascular invasion ▪ HER2 positivity (triple-positive) <p>Not applicable to INSEMA patients in the non-SLNB arm: ≥ 4 positive axillary lymph nodes* [46]</p>	* ... Expected rate of pN+ with ≥ 4 positive lymph nodes 3.7% of the whole non-SLNB population (after AMAROS data [57]). The proportion of luminal-like cases in INSEMA with pN+ (≥ 4 LKs) will constitute 3% of the non-SLNB population at most.
HER2 positive	Chemotherapy in combination with anti-HER2 treatment from stage pT1b independent of nodal status	No anti-HER2 treatment at stage pT1a
TNBC (triple-neg.)	Chemotherapy regardless of nodal status	

theoretically possible in 99% of INSEMA patients without SLNB on the basis of tumour biological parameters alone.

The discussion surrounding indications for irradiation of the regional lymphatics (excluding the axilla) dependent on nodal status/number of involved nodes (see above) is similarly controversial. Most guidelines and treatment recommendations regard more than three positive axillary lymph nodes as the only definite indication [49]. This however only applies to a few individual cases within the INSEMA cohort. The current version of the INSEMA protocol (amendment #4) has taken this treatment recommendation into account following the full text publication of the MA.20 and EORTC data.

Take Home Message

As anticipated there have been no unexpected results from the INSEMA trial after recruitment of the first 1001 patients. Acceptance of study participation is high among both patients and doctors. Fortunately economic aspects such as DRG downgrading (from DRG J07B to J25Z) through SLNB avoidance have not played an ostensible role for participating study centres. In the longer term however further negotiations with financing institutions/medical insurance companies will be required in order to unlink

the DRG from the SLNB procedure (as is already the case e.g. in Austria). The proportion of patients with pN0/pN1mi-status in the control arm where SLNB was performed is very high (83% pN0, 3% pN1mi). A degree of selection bias at the trial centres before recruitment is probably contributory, high-risk cases being more likely to receive neoadjuvant therapy. The field of neoadjuvant therapy also has approaches that attempt to reduce the radicality of axillary surgery, especially after publication of the SENTINA and ACOSOG Z1071 data. Postoperative treatment decisions with respect to adjuvant systemic and radiotherapy can be made in accordance with guidelines without knowledge of nodal status in almost all cases, based solely on available tumour parameters. Future studies should investigate the avoidance of axillary SLNB in patients with a mastectomy indication and in those with partial breast irradiation alone after breast conserving surgery.

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We thank the patients and trial centres for their participation in the INSEMA trial, see ► **Table 5** for the top 10 recruiting trial centres. The INSEMA trial is financially supported by the Deutsche Krebshilfe gGmbH (Bonn, Projekt 110580). Mrs S. Klöcking enabled access to data from the Rostock clinical cancer registry.

► **Table 5** Top 10 INSEMA trial recruiting centres (at 30.06.2016; n = 1 000 for Rando1).

Trial centre	Location	Patients (rando1)	Patients (rando2)
University Women's Hospital at Klinikum Südstadt	Rostock	73	8
University Hospital	Ulm	37	3
Ev. Waldkrankenhaus Spandau	Berlin	33	2
University Hospital	Heidelberg	30	2
Klinikum Hanau GmbH	Hanau	30	2
Breast Centre/Practice Network	Troisdorf	30	3
Niels-Stensen-Kliniken, Franziskus-Hospital Harderberg	Georgsmarienhütte	29	4
HELIOS Klinikum	Schwerin	29	2
Klinikum Worms gGmbH	Worms	25	1
Klinikum Esslingen	Esslingen a. N.	25	2

Conflict of Interest

None.

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