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## Background

- Previous studies (NSABP B-04 / IBCSG 10-93) showed high rates of locoregional control achieved with multimodality therapy, even without axillary lymph node dissection (ALND).<sup>1,2</sup>
- Despite increasing evidence disfavoring ALND, it remains part of guidelines for breast cancer (BC) treatment.
- Current approaches should include improved imaging, pathological evaluation, planning of surgical and radiation therapy, and more effective systemic treatment, emphasizing the need for ongoing re-evaluation of “standard” local therapy.
- **INSEMA (NCT02466737) aims to show that early-stage BC patients with reduced extent of axillary surgery do not have inferior prognosis regarding invasive disease-free survival (IDFS) outcome.**

## Materials and Methods

### Study design:

Patients with planned breast-conserving surgery (BCS) will be randomized in 1:4 ratio to no axillary surgery or sentinel lymph node biopsy (SLNB). Patients with SLNB and pN+(sn) status will then be randomized to SLNB alone or completion ALND (Figure 1).

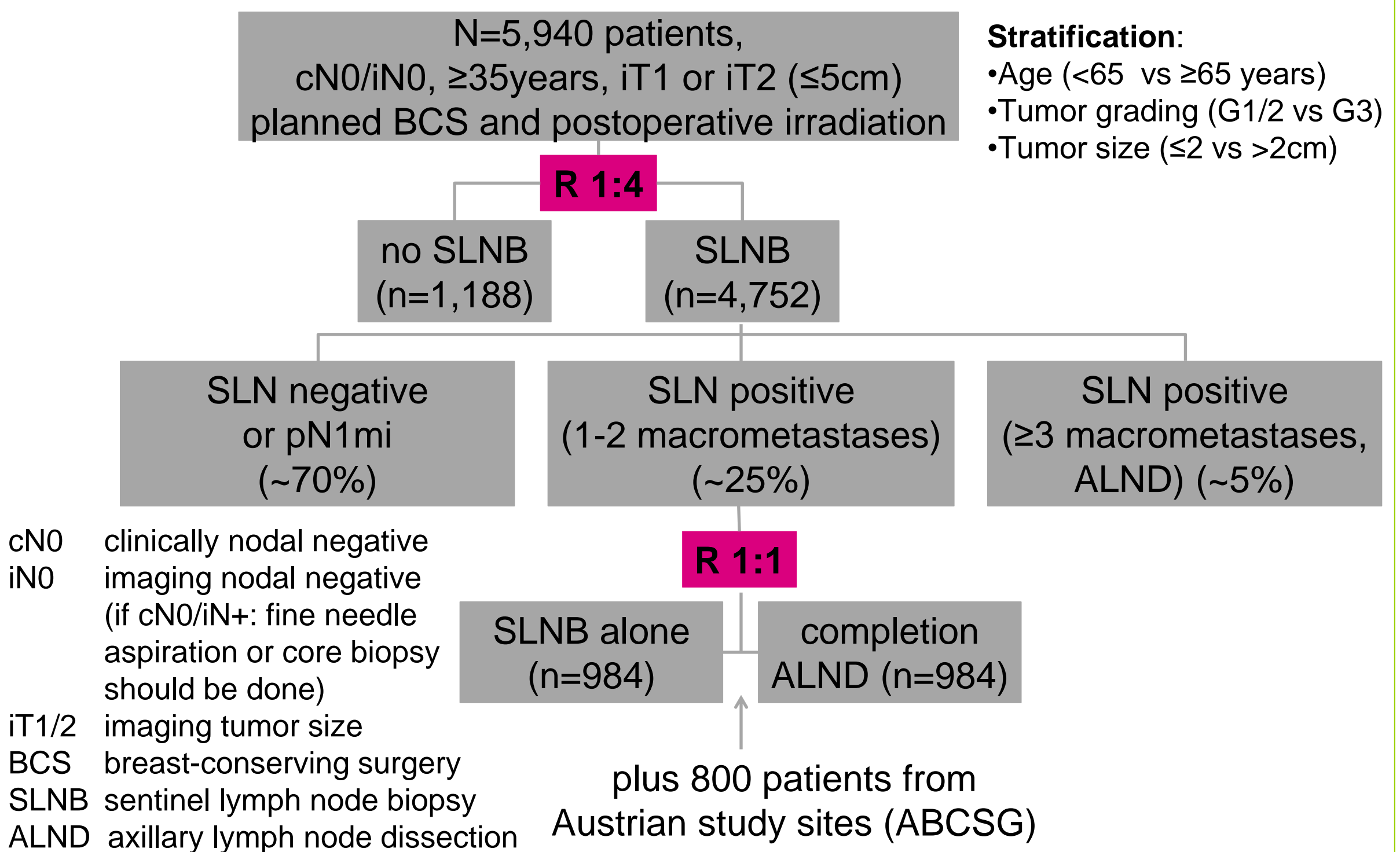
### Statistical considerations:

- 1<sup>st</sup> randomization: 5-year IDFS is considered to be 88%. Clinical non-inferiority is defined as a 5-year IDFS of ≥85% and hazard ratio <1.271 of the non-SLNB compared with SLNB group. Adjusting for 1:4 randomization, 936 events and 5,940 per-protocol patients are needed. Assuming a 5% exclusion rate from per-protocol analysis, 6,250 patients need to be randomized.
- 2<sup>nd</sup> randomization: 5-year IDFS is considered to be 81%. Clinical non-inferiority is defined as a 5-year IDFS of ≥76.5% and hazard ratio <1.271 of the SLNB alone compared with the completion ALND group. Assuming a 5% exclusion rate, 2,070 patients need to be randomized.

### Main inclusion criteria:

- Histologically confirmed (core biopsy) unilateral primary invasive BC.
- Age at diagnosis ≥35 years.
- Preoperative imaging techniques with estimated tumor size of ≤5 cm (iT1/iT2 irrespective of hormone sensitivity or HER2 status).
- Clinically and sonographically tumor-free axilla prior to core biopsy (cN0/iN0).
- In cases with cN0 and iN1, a negative core biopsy or fine needle aspiration biopsy of the sonographically suspected lymph node is required before randomization
- No clinical evidence for distant metastasis (M0).
- Planned BCS (R0 resection) with postoperative external whole-breast irradiation (conventional or hypofractionation).

Figure 1: INSEMA study design



## Objectives

### Primary objective is to compare IDFS after BCS (non-inferiority question)

- no axillary surgery vs SLNB patients (1<sup>st</sup> randomization),
- pN+(sn) with SLNB alone vs pN+(sn) with completion ALND (2<sup>nd</sup> randomization).

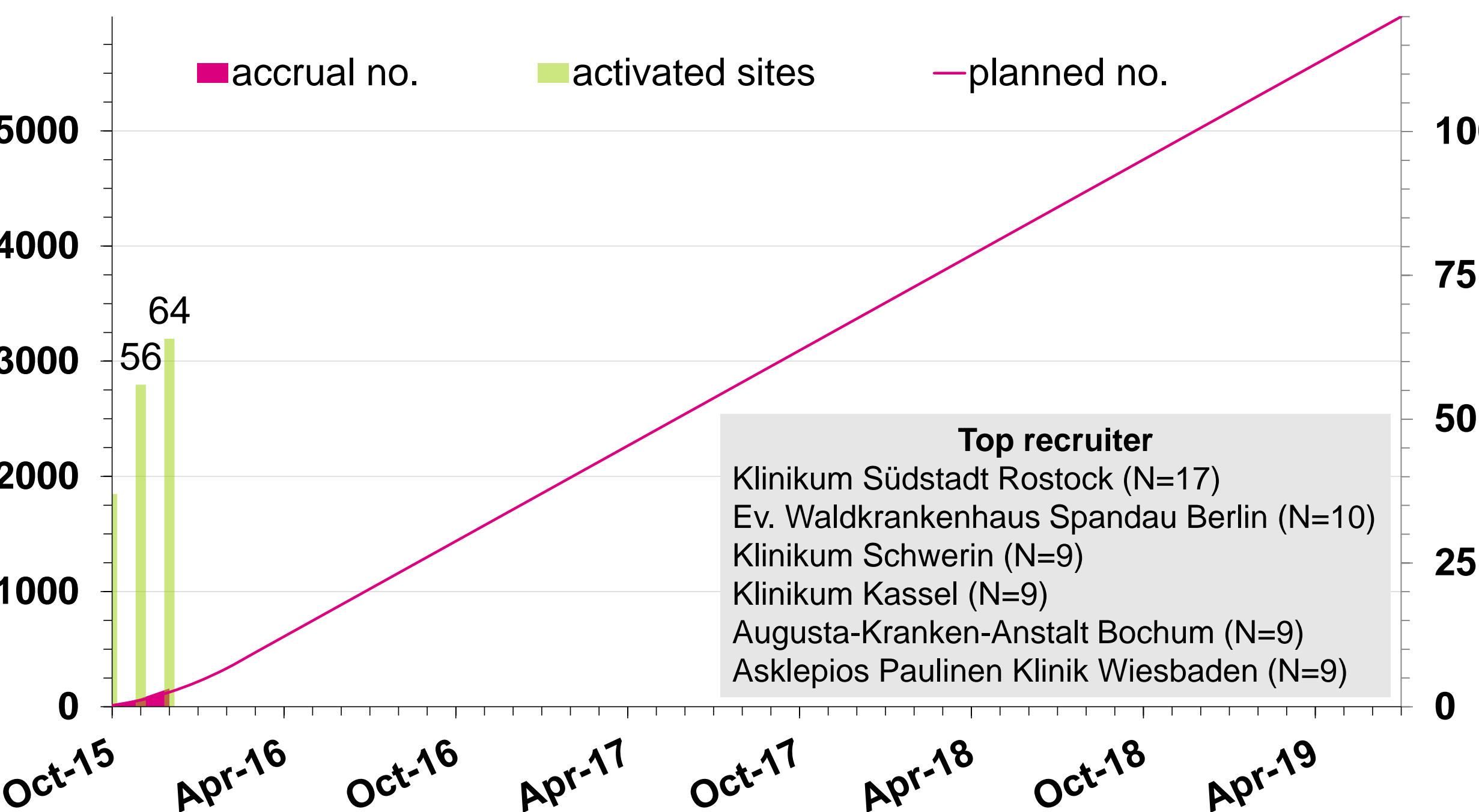
### Secondary objectives are to compare

- IDFS after BCS (no axillary surgery vs pN0(sn) patients, no axillary surgery vs pN+(sn) with SLNB alone, no axillary surgery vs pN+(sn) with completion ALND).
- overall survival between arms.
- locoregional DFS (no tumor in ipsilateral breast or supraclavicular, subclavicular, internal mammary or axillary nodes) between arms in both randomizations
- ipsilateral axillary recurrence rate.
- distant disease-free survival (DDFS)
- safety and quality of life between arms.
- IDFS in stratified subgroups and according to study site
- registration of delivered dose distribution in ipsilateral axilla levels I-III during postoperative whole-breast irradiation.

## Results

Recruitment started in September 2015 and is planned for 48 months at 130 German and 15 Austrian sites. So far, 159 patients have been recruited by 40 centres (Figure 2). After a 5 year follow-up, final analysis is planned for 2024.

Figure 2: INSEMA recruitment as of 30<sup>th</sup> November 2015



## Conclusions

**INSEMA investigates if less axillary surgery is better by means of achieving the same oncological outcomes with less surgical intervention, which will result in fewer surgical complications. INSEMA should be discussed in context with other ongoing trials like SOUND (SLNB vs no SLNB in T1-tumors and BCS) or SENOMAC and POSNOC (SLNB alone vs ALND in 1-2 SLN-macrometastases).**

## References

1. Fisher B et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002; 347:567-75.
2. Rudenstam CM et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 2006; 24:337-44.