2025 Breast Cancer Congress
with Updates from the 2024 SABCS

Updates to Radiation Therapy for Invasive Breast Cancer with SABCS Updates

Meena S. Moran, MD

Yale Cancer Center/Smilow Cancer Hospital

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal

Sequencing of a radiation boost in the breast conservation setting

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
  - 3-D CT-based treatment planning should routinely be utilized to delineate target volumes & organs at risk, and assess dose distribution across the entire treatment volume.
  - Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons ± electrons.
  - Treatment planning should be optimized to maximally improve homogeneity across the target volume while minimizing dose to organs at risk.
  - Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
  - At a minimum, weekly imaging to verify treatment setup should be utilized. More frequent imaging may be needed for selected cases with inconsistent reproducibility. Image-guided radiation therapy (IGRT) may be utilized with deep inspiration breath-hold (DIBH) technique to reduce normal tissue exposure of the heart, lung or liver.
  - Dose-volume histograms (DVHs) should be used to evaluate, dose and constraints to normal tissues (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated.

Whole Breast Radiation

- Target definition is the breast tissue at risk.
- RT dosing:
  - The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
  - A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.
  - Ultra-hypofractionated WBRT of 28.5 Gy in 5 (once a week) fractions may be considered for selected pts over 50 years following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.[a,b]
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
  - 3-D CT-based treatment planning should routinely be utilized to delineate target volumes & organs at risk, and assess dose distribution across the entire treatment volume.

- Whole breast should receive modHF dose of 40-42.5 Gy/15-16 Fx; in selected cases CF may be considered
- A boost to the tumor bed is recommended in pts at higher risk of recurrence. Typical boost doses are 10-16 Gy/4-8 fx

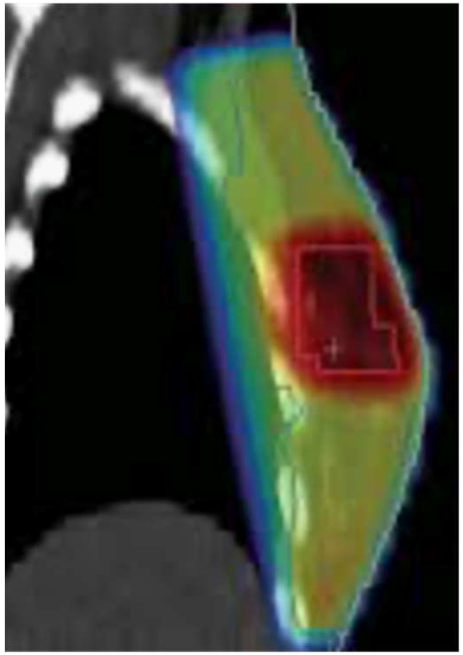
Whole Breast Radiation

- Target definition is the breast tissue at risk.
- RT dosing:
  - The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
  - A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.
  - Ultra-hypofractionated WBRT of 28.5 Gy in 5 (once a week) fractions may be considered for selected pts over 50 years following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.[a,b]
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer.

Radiation Boost in Breast Cancer

- RT boost: additional dose of radiation targeting the tumor bed following whole breast radiation therapy (RT)
- The use of a RT boost further ↓ risk of LR by ~ 4% @ 20-yrs (absolute benefit)
- Magnitude of benefit greatest in younger women
- Significantly diminishes LR across all subgroups of pts



Bartelink H, et al. NEJM 2001; Bartelink H, et al. Lancet Oncology 2015

How a Boost is Sequenced with Whole Breast RT: Sequential Boost vs. Simultaneous

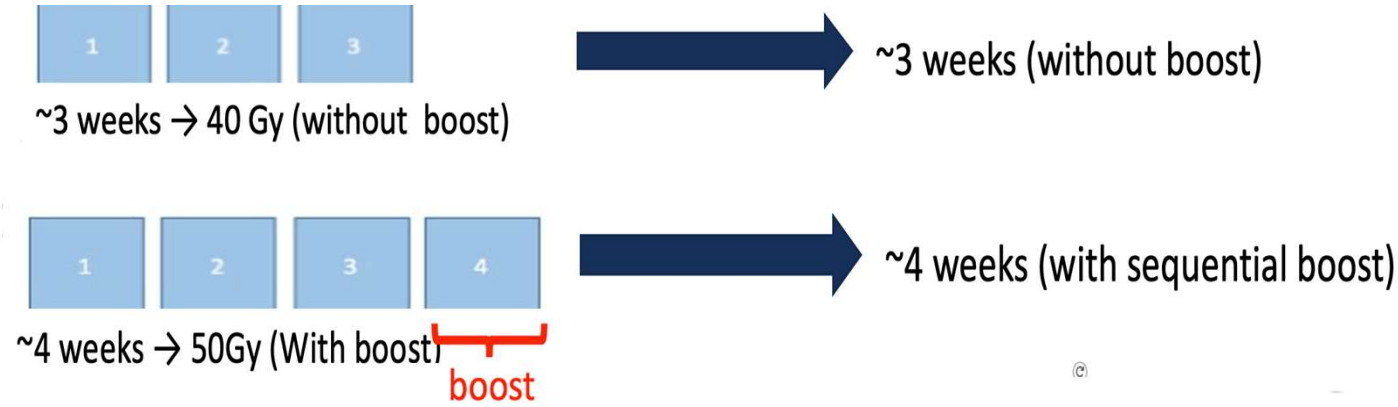
Moderately Hypofractionated WBRT: 3 weeks to whole breast

~3 weeks → 40 Gy (without boost)

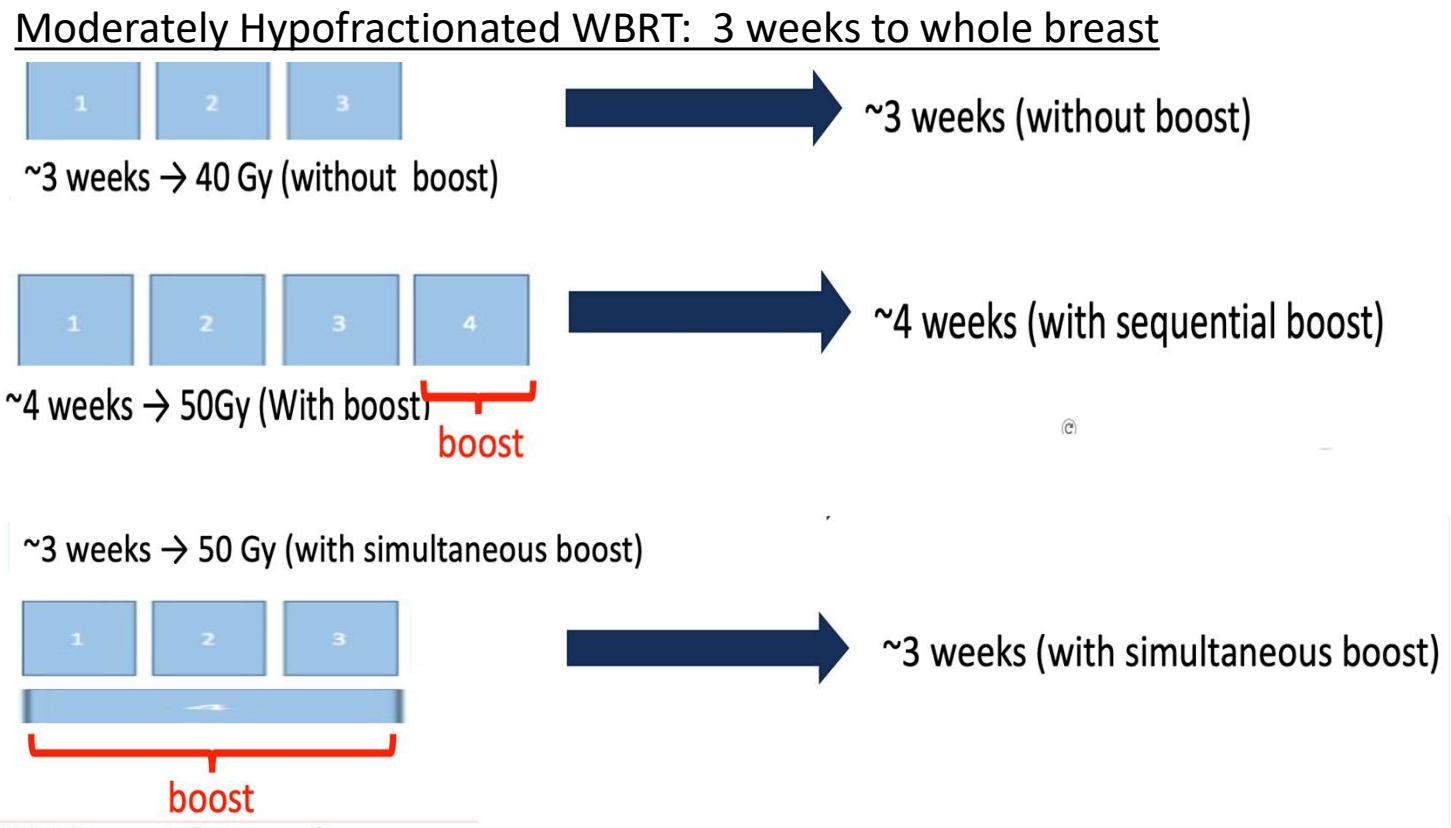
~3 weeks (without boost)

How a Boost is Sequenced with Whole Breast RT: Sequential Boost vs. Simultaneous

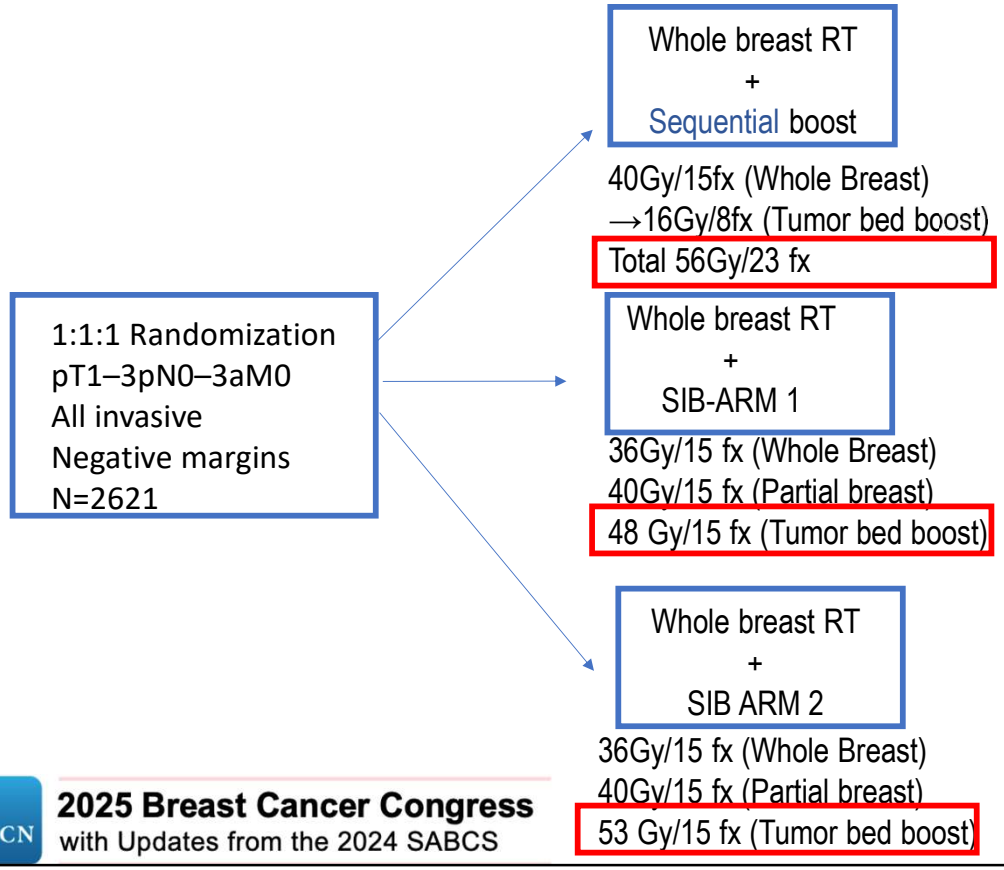
Moderately Hypofractionated WBRT: 3 weeks to whole breast



How a Boost is Sequenced with Whole Breast RT: Sequential Boost vs. Simultaneous



IMPORT HIGH Trial: PIII Trial Sequential vs. Simultaneous Boost (SIB)



Cole CE, et al. Lancet 2023

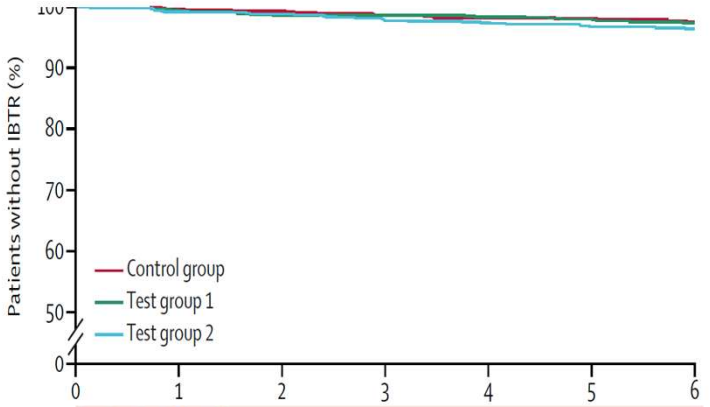
IMPORT HIGH Trial: PIII Trial Sequential vs. Simultaneous Boost (SIB)

1:1:1 Randomization
pT1–3pN0–3aM0
All invasive
Negative margins
N=2621

Whole breast RT + Sequential boost
40Gy/15fx (Whole Breast)
→16Gy/8fx (Tumor bed boost)
Total 56Gy/23 fx

Whole breast RT + SIB-ARM 1
36Gy/15 fx (Whole Breast)
40Gy/15 fx (Partial breast)
48 Gy/15 fx (Tumor bed boost)

Whole breast RT + SIB ARM 2
36Gy/15 fx (Whole Breast)
40Gy/15 fx (Partial breast)
53 Gy/15 fx (Tumor bed boost)



Local-regional relapse¶				
Control group	32/871 (3·7%)	3·0% (2·0 to 4·4)	1 (ref)	..
Test group 1	32/874 (3·7%)	3·1% (2·1 to 4·5)	0·99 (0·60 to 1·61), p=0·96	-0·04% (-1·2 to 1·8)
Test group 2	48/872 (5·5%)	4·7% (3·4 to 6·3)	1·50 (0·96 to 2·35), p=0·072	1·5% (-0·1 to 3·9)

Cole CE, et al. Lancet 2023

IMPORT HIGH Trial: PIII Trial Sequential vs. SIB

QOL/Adverse Events:

Test Group 1 (48Gy) non-inferior
Test Group 2 (56Gy) worse for*:

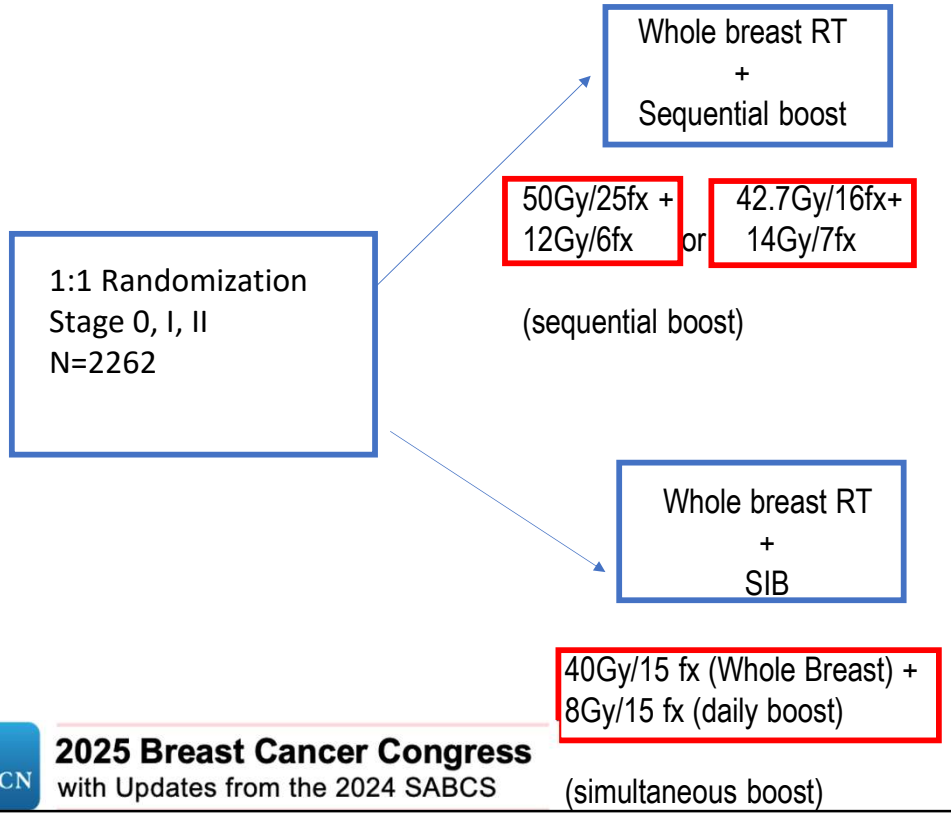
- Overall adverse events
- Induration
- Tenderness on palpation
- Discomfort
- Distortion

*Relative to control and/or Group 1

		By 5 years	Test groups *vs* control‡§	Test group 2 *vs* 1¶‖
Any adverse event in the breast**				
Control group	283/817 (34·6%)	33·1% (29·8–36·7)	1 (ref)	..
Test group 1	271/836 (32·4%)	29·9% (26·8–33·3)	0·90 (0·76–1·06), p=0·21	1 (ref)
Test group 2	302/834 (36·2%)	34·5% (31·2–38·0)	1·06 (0·90–1·24), p=0·50	1·18 (1·00–1·39), p=0·026
Breast distortion				
Control group	126/814 (15·5%)	13·8% (11·5–16·6)	1 (ref)	..
Test group 1	108/834 (12·9%)	12·2% (10·1–14·8)	0·82 (0·63–1·06), p=0·13	1 (ref)
Test group 2	140/833 (16·8%)	15·7% (13·3–18·5)	1·11 (0·87–1·41), p=0·39	1·36 (1·05–1·74), p=0·0085
Breast shrinkage				
Control group	145/813 (17·8%)	15·7% (13·2–18·6)	1 (ref)	..
Test group 1	143/834 (17·1%)	15·2% (12·8–18·0)	0·93 (0·74–1·17), p=0·56	1 (ref)
Test group 2	142/832 (17·1%)	15·7% (13·3–18·6)	0·95 (0·76–1·20), p=0·70	1·02 (0·81–1·29), p=0·42
Breast induration (index quadrant)				
Control group	143/814 (17·6%)	16·6% (14·1–19·5)	1 (ref)	..
Test group 1	134/834 (16·1%)	14·3% (12·0–16·9)	0·90 (0·71–1·14), p=0·40	1 (ref)
Test group 2	183/832 (22·0%)	20·0% (17·3–23·0)	1·31 (1·05–1·63), p=0·015	1·45 (1·16–1·81), p=0·0005
Telangiectasia				
Control group	17/815 (2·1%)	1·9% (1·1–3·2)	1 (ref)	..
Test group 1	14/835 (1·7%)	1·0% (0·5–2·0)	0·80 (0·40–1·63), p=0·56	1 (ref)
Test group 2	14/834 (1·7%)	1·6% (0·9–2·9)	0·82 (0·41–1·67), p=0·56	1·02 (0·49–2·14), p=0·48
Breast oedema				
Control group	70/814 (8·6%)	8·6% (6·8–10·8)	1 (ref)	..
Test group 1	44/836 (5·3%)	5·2% (3·9–7·0)	0·59 (0·41–0·87), p=0·0062	1 (ref)
Test group 2	54/834 (6·5%)	5·7% (4·3–7·6)	0·74 (0·52–1·05), p=0·091	1·24 (0·83–1·85), p=0·14
Breast tenderness on palpation				
Control group	112/804 (13·9%)	13·6% (11·3–16·3)	1 (ref)	..
Test group 1	111/821 (13·5%)	11·9% (9·8–14·5)	0·96 (0·73–1·24), p=0·74	1 (ref)
Test group 2	142/813 (17·5%)	15·0% (12·6–17·8)	1·26 (0·98–1·62), p=0·066	1·32 (1·03–1·69), p=0·014
Breast discomfort				
Control group	112/796 (14·1%)	13·6% (11·3–16·3)	1 (ref)	..
Test group 1	114/811 (14·1%)	13·1% (10·9–15·8)	0·98 (0·76–1·28), p=0·91	1 (ref)
Test group 2	153/804 (19·0%)	17·0% (14·5–19·9)	1·39 (1·09–1·77), p=0·0081	1·41 (1·10–1·79), p=0·0025

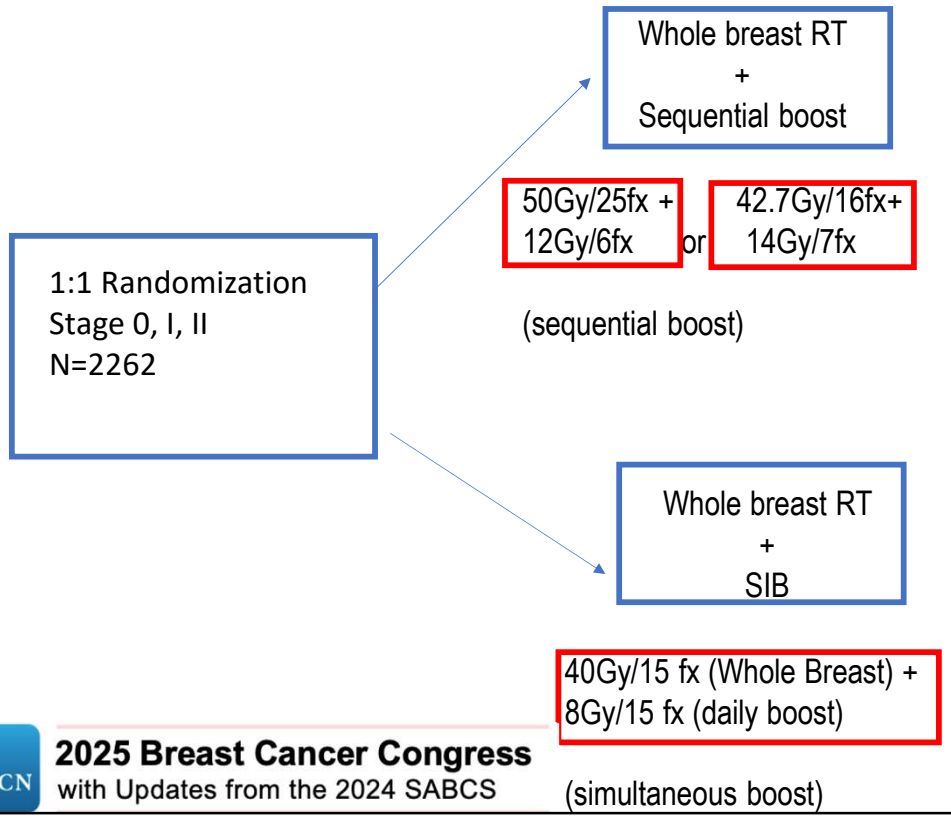
Cole CE, et al. Lancet 2023

NRG-RTOG 1005
Sequential vs. Simultaneous Boost (SIB)



Vincini F et al. Abstract ASTRO 2023 114:S1

NRG-RTOG 1005
Sequential vs. Simultaneous Boost (SIB)



Results:

- Median follow-up: 7.3 years
- IBTR $_{total}$ = 56
- 7-yr IBTR 2.2% (CB) vs. 2.6% (SIB)
- 3DCRT 81% vs 19% IMRT

- No differences in AEs noted between arms (p=0.79)
- No difference in physician-reported 3-yr good/excellent cosmesis by arm: 86% vs 84% (p=0.61)

Vincini F et al. Abstract ASTRO 2023 114:S1

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
  - 3-D CT-based treatment planning should routinely be utilized to delineate target volumes & organs at risk, and assess dose distribution across the entire treatment volume.
  - Radiation is generally delivered with single or mixed energy photons ± electrons.
  - Treatment planning should be optimized to maximally improve homogeneity across the target volume while minimizing dose to organs at risk.
  - Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
  - At a minimum, weekly imaging to verify treatment setup should be utilized. More frequent imaging may be needed for selected cases with inconsistent reproducibility. Image-guided radiation therapy (IGRT) may be utilized with deep inspiration breath-hold (DIBH) technique to reduce normal tissue exposure of the heart, lung or liver.
  - Dose-volume histograms (DVHs) should be used to evaluate dose, normal tissue constraints (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated. See BINV-I 2 of 3.
- In the setting of oligometastatic breast cancer, the currently available data do not support ablative metastasis-directed RT (ie, SBRT) for extending overall survival OS or PFS. In some cases, SBRT may be preferred over palliative radiotherapy to provide more durable local control and pain relief.

Whole Breast RT

- Target definition is the breast tissue at risk.
- RT dosing:
  - The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
  - A boost to the tumor bed is recommended in patients at higher risk for recurrence. The boost can be given sequentially after whole breast RT or as a simultaneous integrated boost. Typical boost doses when given sequentially are 10–16 Gy in 4–8 fractions. When given concurrently, the whole breast should receive 40 Gy in 15 fractions and the lumpectomy site should receive 48 Gy in 15 fractions.[a,b] Ultra-hypofractionated whole breast RT of 26 Gy in 5 (once a week) fractions may be considered for selected patients over 50 years following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.[c,d]
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.

[a] Vicini FA, Winter K, Freedman GM, et al. NRG RTOG 1005: A phase III trial of hypo fractionated whole breast irradiation with concurrent boost vs. conventional whole breast irradiation plus sequential boost following lumpectomy for high risk early-stage breast cancer. Int J Radiation Oncol 2022;114;S1.
[b] Coles CE, Haviland JS, Kirby AM, et al. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. Lancet 2023;401:2124-2137.
[c] Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. (Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks [FAST-Forward]: 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.)
[d] Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020;38:3261-3272.

Note: All recommendations are category 2A unless otherwise indicated.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

A boost can be delivered after whole breast RT or as a simultaneous integrated boost. Typical doses when given sequentially are 10-16 Gy in 4-8 fx. When given concurrently, the whole breast should receive 40 Gy in 15 fx and the lumpectomy site should receive 48 Gy in 15 fractions.

Whole Breast RT

- Target definition is the breast tissue at risk.
- RT dosing:
  - The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions
  - A boost to the tumor bed is recommended in patients at higher risk for recurrence. The boost can be given sequentially after whole breast RT or as a simultaneous integrated boost. Typical boost doses when given sequentially are 10–16 Gy in 4–8 fractions. When given concurrently, the whole breast should receive 40 Gy in 15 fractions and the lumpectomy site should receive 48 Gy in 15 fractions.[a,b]
    Ultra-hypofractionated whole breast RT of 26 Gy in 5 (once a week) fractions may be considered for selected patients over 50 years following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.[c,d]
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.

[a] Vicini FA, Winter K, Freedman GM, et al. NRG RTOG 1005: A phase III trial of hypo fractionated whole breast irradiation with concurrent boost vs. conventional whole breast irradiation plus sequential boost following lumpectomy for high risk early-stage breast cancer. Int J Radiation Oncol 2022;114;S1.
[b] Coles CE, Haviland JS, Kirby AM, et al. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. Lancet 2023;401:2124-2137.
[c] Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. (Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks [FAST-Forward]: 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.)
[d] Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020;38:3261-3272.

Note: All recommendations are category 2A unless otherwise indicated.

The use of moderately hypofractionated RT in the post-mastectomy setting

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Post-mastectomy Radiation (including breast reconstruction)

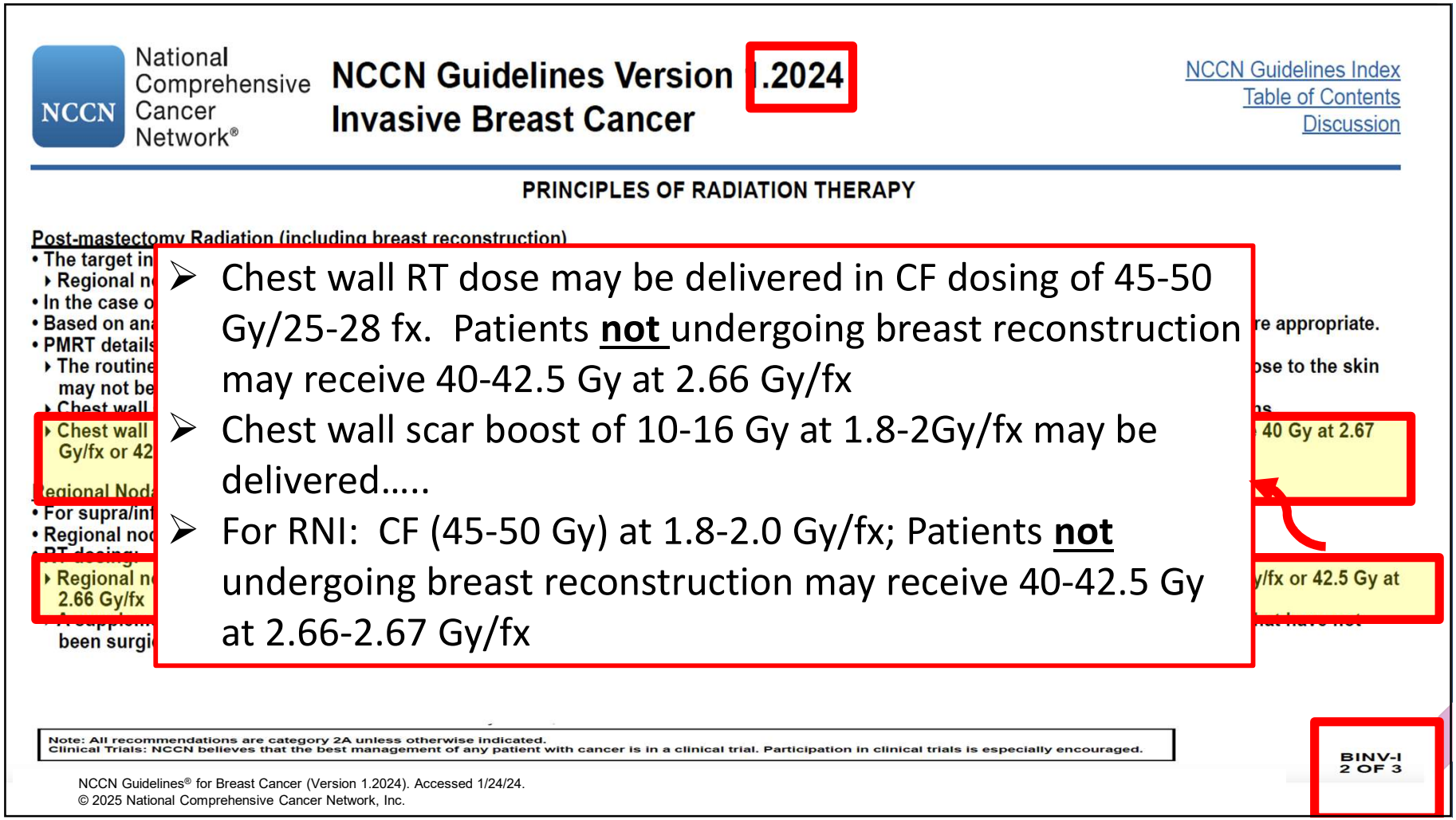
- The target includes the ipsilateral chest wall and the entire mastectomy scar ± drain sites.
  - Regional nodal RT is typically delivered with the chest wall. See below.
- In the case of cT3N0, high-risk features for considering PMRT include, but are not limited to, young age and/or LVI.
- Based on anatomic considerations and presence of reconstruction, various 3-D-, IMRT, or VMAT techniques using photons and/or electrons are appropriate.
- PMRT details and dosing:
  - The routine use of bolus is not recommended. Bolus should be considered in the use of IBC or clinical-pathologic situations where the dose to the skin may not be adequate.
  - Chest wall scar boost of 10-16 Gy/fx at 1.8 to 2.0 Gy/fx total 5-8 fractions may be delivered with or without bolus using electrons or photons
  - Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx in 25-28 fractions. Patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx

Regional Nodal Radiation

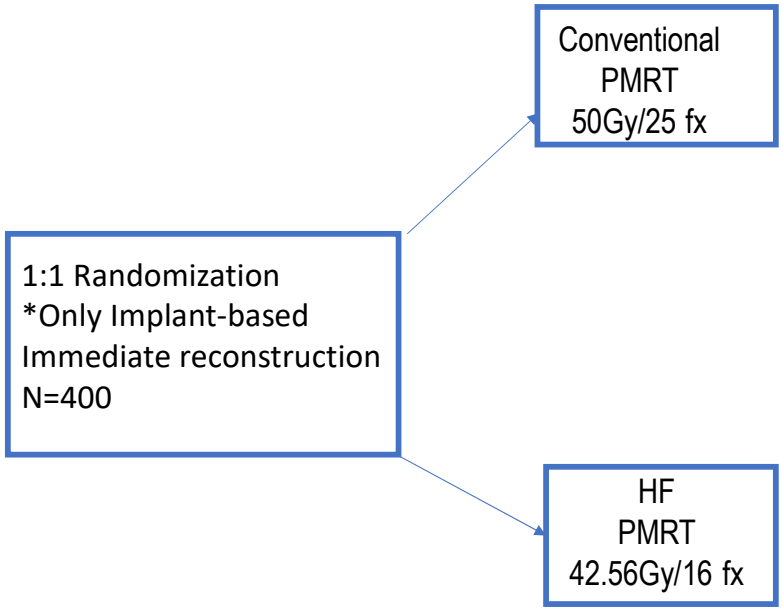
- For supra/infra-clavicular and axillary nodes, prescription depth varies based on the patient anatomy.
- Regional nodes should be contoured when considering regional nodal RT. Refer to breast atlases for contouring guidelines.[c,d]
- RT dosing:
  - Regional node dose is 45–50.4 Gy at 1.8–2 Gy/fx; patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx
  - A supplemental boost of RT can be delivered to grossly involved or enlarged lymph nodes (ie, internal mammary, supra/infra-clavicular) that have not been surgically removed.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines® for Breast Cancer (Version 1.2024). Accessed 1/24/24.



FABREC TRIAL: Hypofractionated vs. Conventionally Fractionated RT after Implant-based Reconstruction



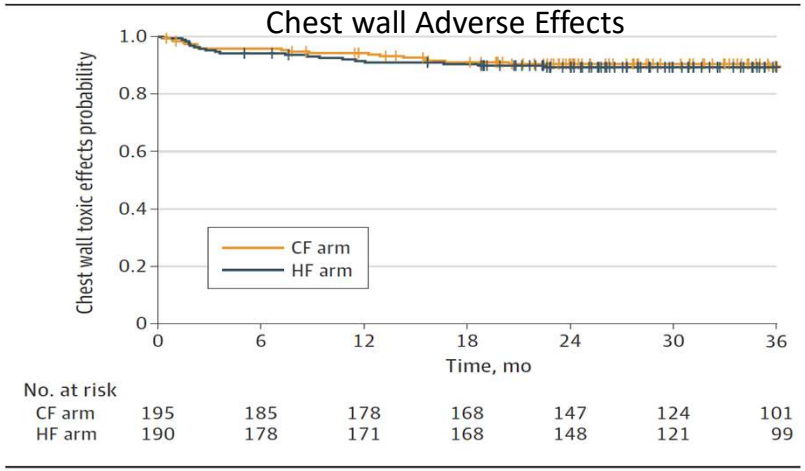
Wong JS et al. JAMA Oncology 2024

FABREC TRIAL: Hypofractionated vs. Conventionally Fractionated RT after Implant-based Reconstruction

1:1 Randomization
*Only Implant-based
Immediate reconstruction
N=400

Conventional
PMRT
50Gy/25 fx

HF
PMRT
42.56Gy/16 fx

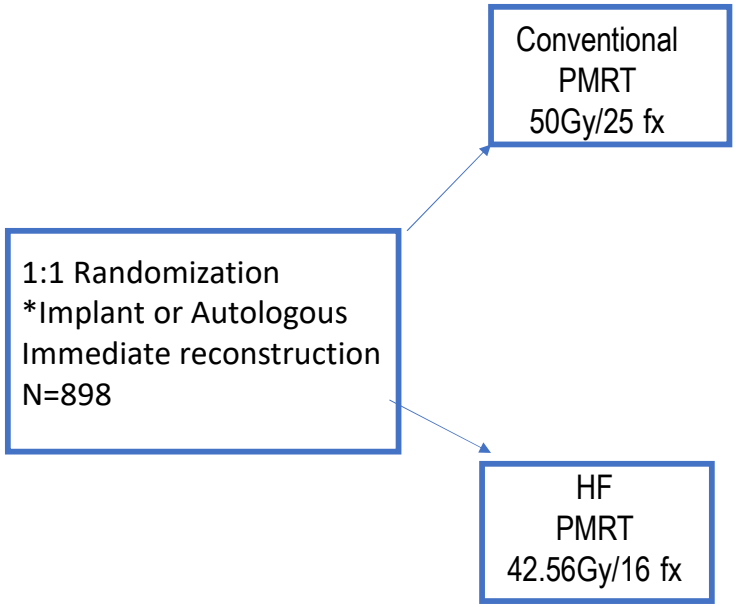


CF indicates conventionally fractionated; HF, hypofractionated.

No difference in toxicity or physical well being between CF & HF PMRT at 36 months

Wong JS et al. JAMA Oncology 2024

RT CHARM : Alliance A221505

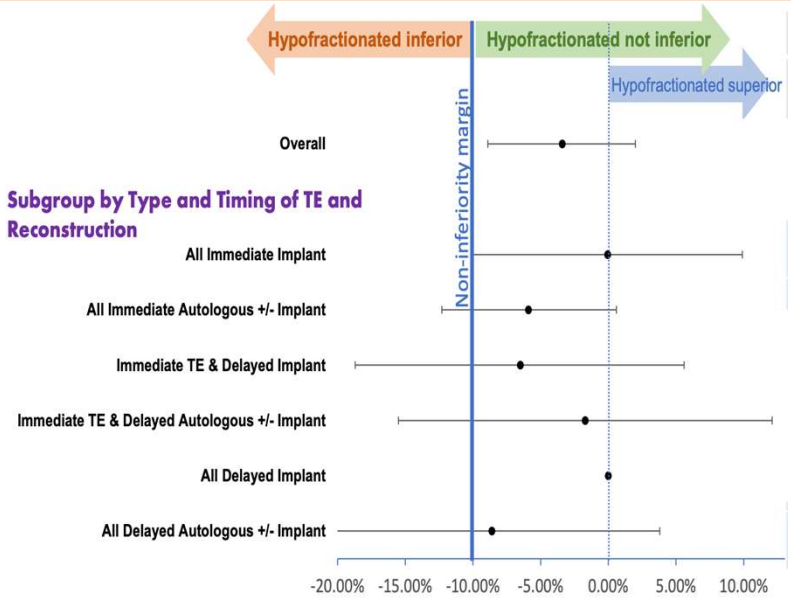


Poppe M ASTRO 2024

RT CHARM : Alliance A221505

1:1 Randomization
*Implant or Autologous
Immediate reconstruction
N=898

- Conventional PMRT 50Gy/25 fx
- HF PMRT 42.56Gy/16 fx



LR @ 3 yrs: 7 CF vs. 9 HF, p=NS

HF PMRT is non-inferior to CF PMRT for reconstruction complications, toxicity & local control.

Poppe M ASTRO 2024

National Comprehensive Cancer Network®

NCCN Guidelines Version .2025
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

PMRT (including breast reconstruction)

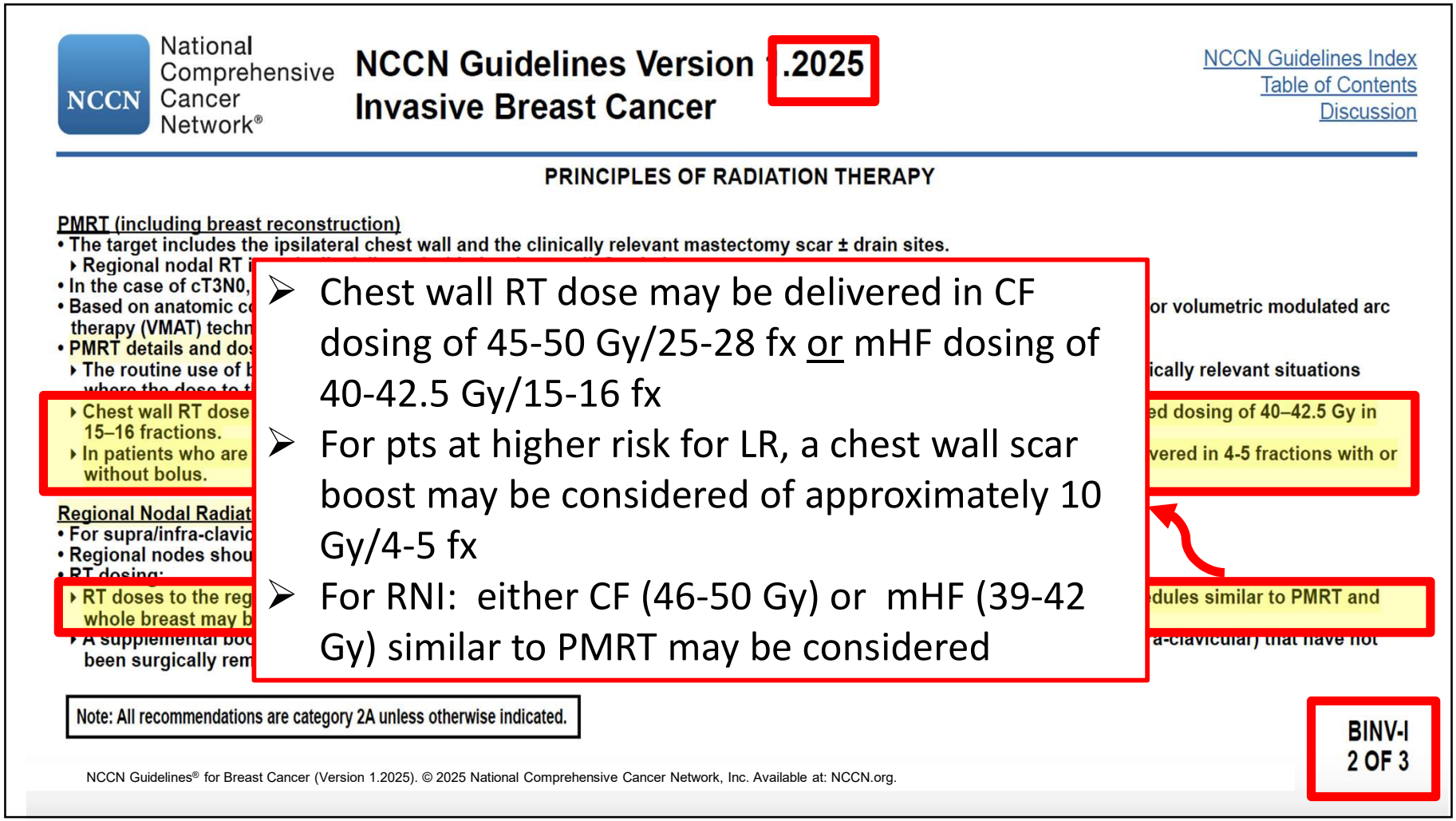
- The target includes the ipsilateral chest wall and the clinically relevant mastectomy scar ± drain sites.
  - Regional nodal RT is typically delivered with the chest wall. See below.
- In the case of cT3N0, high-risk features for considering PMRT include, but are not limited to, young age and/or LVI.
- Based on anatomic considerations and presence of reconstruction, various 3-D-, intensity modulated radiation therapy [IMRT], or volumetric modulated arc therapy (VMAT) techniques using photons and/or electrons are appropriate.
- PMRT details and dosing:
  - The routine use of bolus is not recommended. Bolus should be used for inflammatory breast cancer and considered in clinically relevant situations where the dose to the skin may not be adequate.
  - Chest wall RT dose may be delivered in conventional dosing of 45–50.4 Gy in 25–28 fractions or moderately hypofractionated dosing of 40–42.5 Gy in 15–16 fractions.
  - In patients who are at high risk for local recurrence, a chest wall scar boost may be considered of approximately 10 Gy delivered in 4-5 fractions with or without bolus.

Regional Nodal Radiation

- For supra/infra-clavicular and axillary nodes, prescription depth varies based on the patient anatomy.
- Regional nodes should be contoured when when RNI is indicated. Refer to breast atlases for contouring guidelines.[e,f]
- RT dosing:
  - RT doses to the regional nodes of 46–50 Gy (conventional fractionation) or 39–42 Gy (moderately fractionated) dosing schedules similar to PMRT and whole breast may be considered.
  - A supplemental boost of RT can be delivered to grossly involved or enlarged lymph nodes (ie, internal mammary, supra/infra-clavicular) that have not been surgically removed.

Note: All recommendations are category 2A unless otherwise indicated.

BINV-I
2 OF 3



ACCELERATED PARTIAL BREAST IRRADIATION

PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)

- **APBI/PBI offers comparable local control to WBRT in selected patients with low-risk early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined.**
  - **Patients are encouraged to participate in clinical trials.**
  - **The NCCN Panel recommends APBI/PBI for any patient with *BRCA* 1/2 mutations meeting the criteria outlined in the 2016 ASTRO consensus statement for guidance on APBI/PBI use.**

According to the 2016 ASTRO criteria, patients aged ≥50 years are "suitable" for APBI/PBI if they have:

- ◊ **Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, and ER-positive tumors or**
- ◊ **Low/intermediate nuclear grade, screening-detected DCIS measuring size ≤2.5 cm with negative margin widths of ≥3 mm.**

- **RT dosing:**

Regimen	Method	Reference
30 Gy/5 fractions QOD (preferred)	External beam RT (EBRT)[e]	Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 2015;51:451-463. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020;38:4175-4183.
40 Gy/15 fractions	EBRT	Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048-1060.
34 Gy/10 fractions BID	Balloon/ Interstitial	Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394:2155-2164.
38.5 Gy/10 fractions BID	EBRT	Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019;394:2165-2172.

[e] The protocol mandated IMRT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines® for Breast Cancer (Version 1.2024). Accessed 1/24/24.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)

- **APBI/PBI offers comparable local control to WBRT in selected patients with low-risk early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined.**
  - **Patients are encouraged to participate in clinical trials.**
  - **The NCCN Panel recommends APBI/PBI for any patient with *BRCA* 1/2 mutations meeting the criteria outlined in the 2016 ASTRO**

According to the 2016 ASTRO criteria, patients aged ≥50 years are "suitable" for APBI/PBI if they have:
- **◊ Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, and ER-positive tumors**
- **or**
- **◊ Low/intermedia… …ns of ≥3 mm.**

- **RT dosing:**

Regimen		
30 Gy/5 fractions QD (preferred)		…ty-modulated radiotherapy …ontrolled trial. Eur J Cancer
40 Gy/15 fractions		…d with whole-breast …PBI-IMRT-Florence Trial. J …vation surgery for patients …randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048-1060.
34 Gy/10 fractions BID	Balloon/ Interstitial	Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394:2155-2164.
38.5 Gy/10 fractions BID	EBRT	Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019;394:2165-2172.

- According to 2016 ASTRO APBI criteria, pts >50 yrs are "suitable" for APBI if they have….
- Table:
  -Included 38.5 Gy/10 fx BID EBRT APBI

[e] The protocol mandated IMRT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines® for Breast Cancer (Version 1.2024). Accessed 1/24/24.

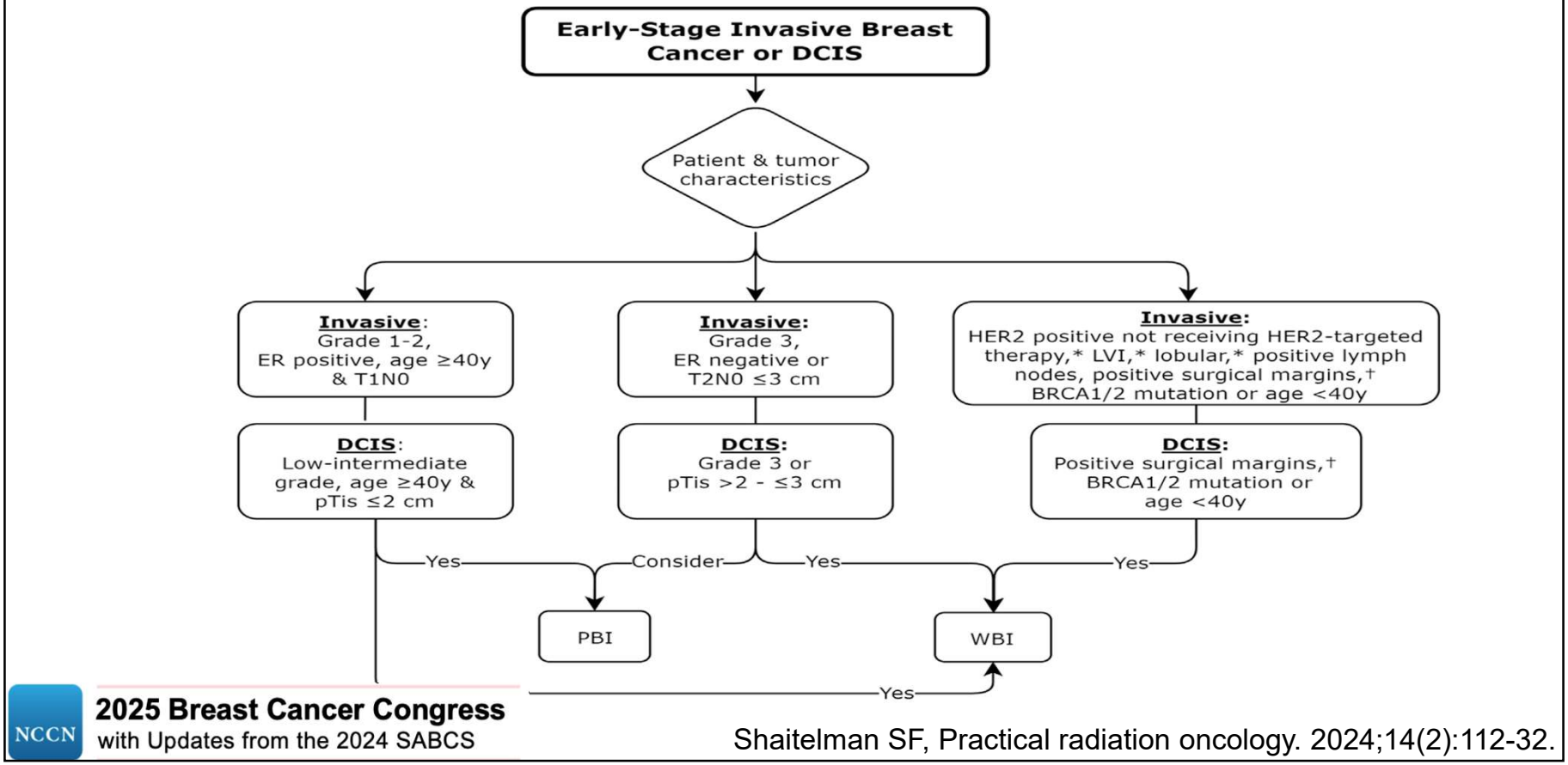
ASTRO APBI Practice Guideline 2023 vs. 2016

Factor	2016 Guideline	2023 Guideline
Age	≥50 years	≥40
Tumor Size	≤2 cm	≤3cm (*nuanced)
Margins	≥2mm	No-ink on tumor
DCIS	Screen detected ≤2.5cm GI or GII Margins ≥3mm	Screen detected ≤3cm (*nuanced) GIII (*nuanced)

Contra-indications 2023:

1. +LVSI
2. Invasive Lobular
3. + Surgical margins
5. Involved LNs
6. BRCA mutations
7. HER2+ if no HER2-targeted therapy

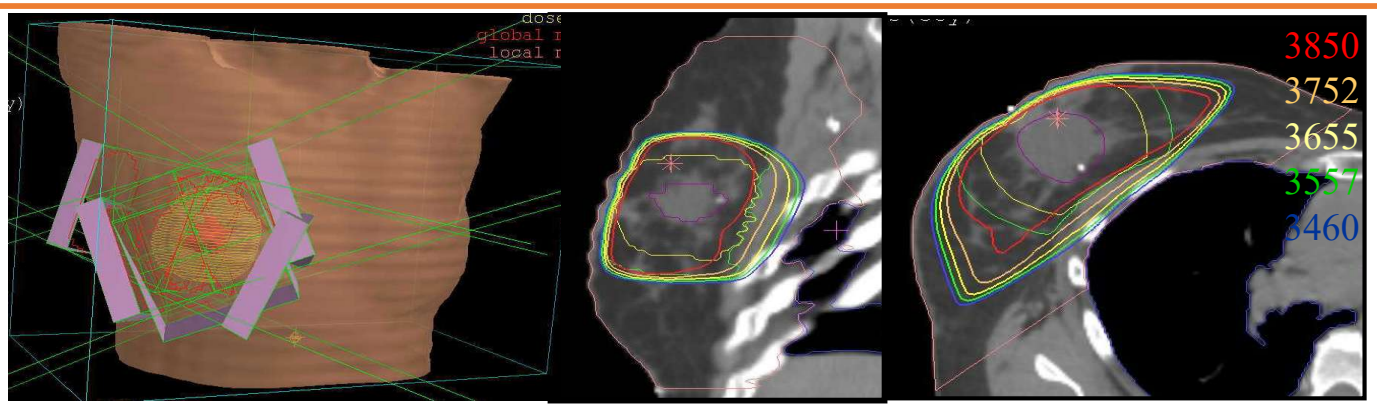
ASTRO APBI Practice Guideline 2023



NCCN **2025 Breast Cancer Congress** with Updates from the 2024 SABCS

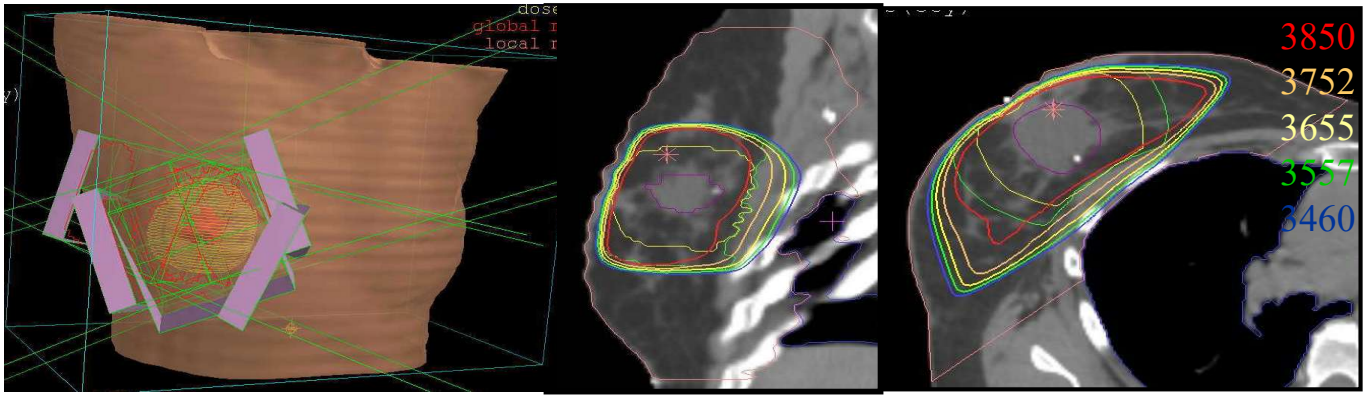
Shaitelman SF, Practical radiation oncology. 2024;14(2):112-32.

APBI: External Beam-Based



PIII Trials:	Dose :	Technique
▪ IMPORT low ▪ Danish PBI	2.67 Gy qd x 15 fx Total: 40.05 Gy qd (WBRT fx w/ PBI volume)	3D

APBI: External Beam-Based



PIII Trials:	Dose :	Technique
▪ IMPORT low ▪ Danish PBI	2.67 Gy qd x 15 fx Total: 40.05 Gy qd (WBRT fx w/ PBI volume)	3D
▪ Florence ▪ Milan	6 Gy qod x 5 fx Total: 30 Gy	IMRT VMAT

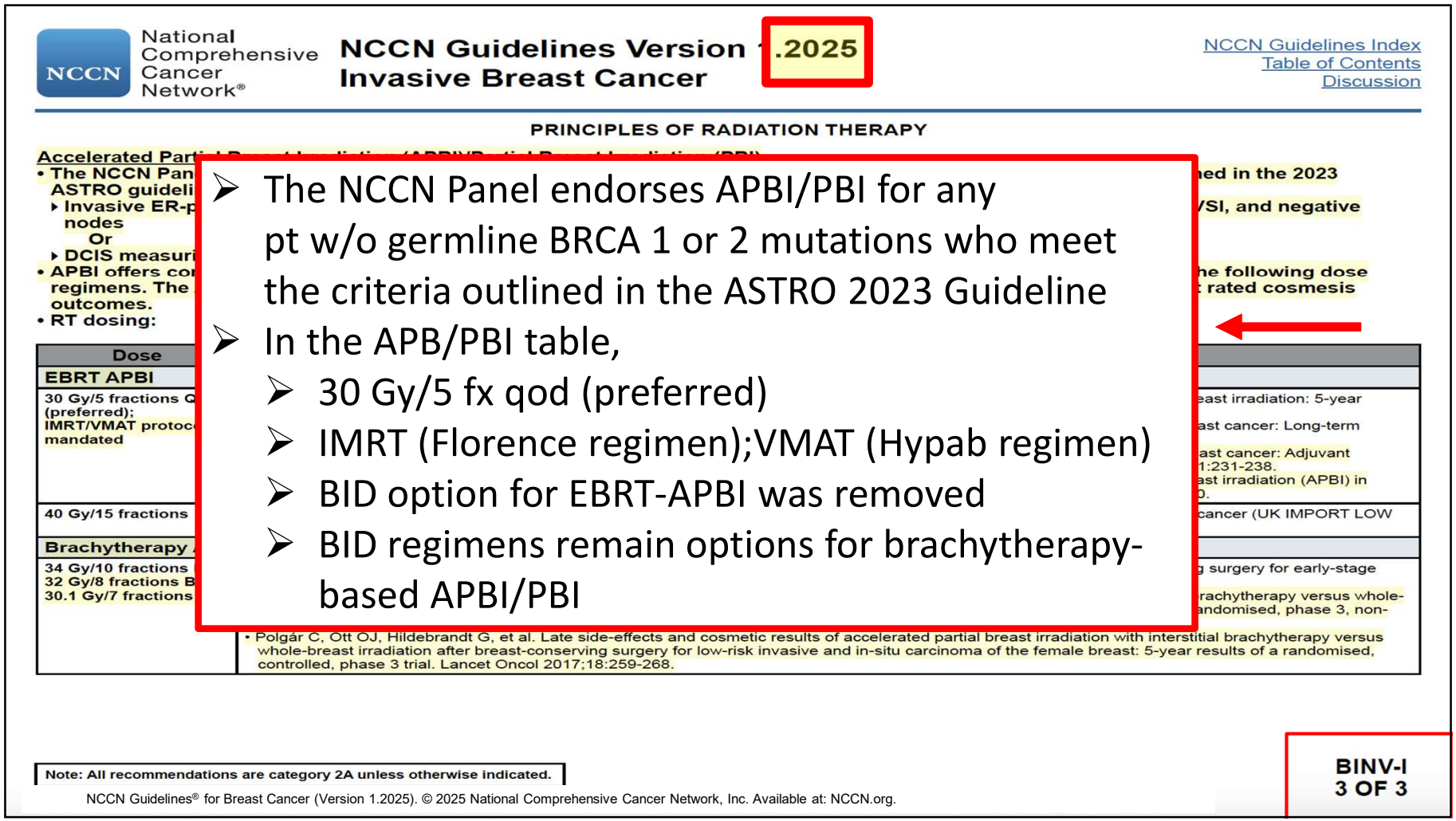
PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)

- **The NCCN Panel endorses APBI/PBI for any patient without germline *BRCA* 1/2 mutations who meets the criteria outlined in the 2023 ASTRO guidelines. Patients aged ≥40 years are recommended "suitable" for APBI/PBI if they have:**
  - **Invasive ER-positive ductal carcinoma measuring ≤2 cm (pT1 disease), grade 1–2, with negative margin widths, no LVSI, and negative nodes**
    Or
  - **DCIS measuring size ≤2 cm with low-intermediate grade with negative margins**
- **APBI offers comparable local control and comparable or improved cosmesis to whole breast RT when delivered with the following dose regimens. The APBI regimens have not been compared directly but 30 Gy/5 fractions is preferred based on the highest rated cosmesis outcomes.**
- **RT dosing:**

Dose	Regimen
EBRT APBI	
30 Gy/5 fractions QOD (preferred); IMRT/VMAT protocol mandated	• Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 2015;51:451-463. • Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020;38:4175-4183. • Franceschini D, Loi M, Chiola I, et al. Preliminary results of a randomized study on postmenopausal women with early stage breast cancer: Adjuvant hypofractionated whole breast irradiation versus accelerated partial breast irradiation (HYPAB Trial). Clin Breast Cancer 2021;21:231-238. • Lo Faro L, Fogliata A, Franceschini D, et al. Adjuvant hypofractionated whole breast irradiation (WBI) vs. accelerated partial breast irradiation (APBI) in postmenopausal women with early stage breast cancer: 5 years update of the HYPAB trial. Clin Breast Cancer 2024;24:253-260.
40 Gy/15 fractions	• Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048-1060.
Brachytherapy APBI (including balloon/interstitial)	
34 Gy/10 fractions BID; 32 Gy/8 fractions BID; 30.1 Gy/7 fractions BID	• Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394:2155-2164. • Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 2016;387:229-238. • Polgár C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. Lancet Oncol 2017;18:259-268.

Note: All recommendations are category 2A unless otherwise indicated.

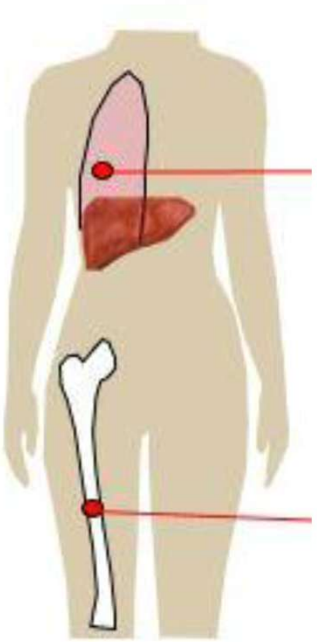


Should Stereotactic Body Radiation Therapy (SBRT) be used in the Setting of Oligometastatic Breast Cancer?

'Oligometastatic Breast Cancer' (oligoBC))

Oligometastatic Disease

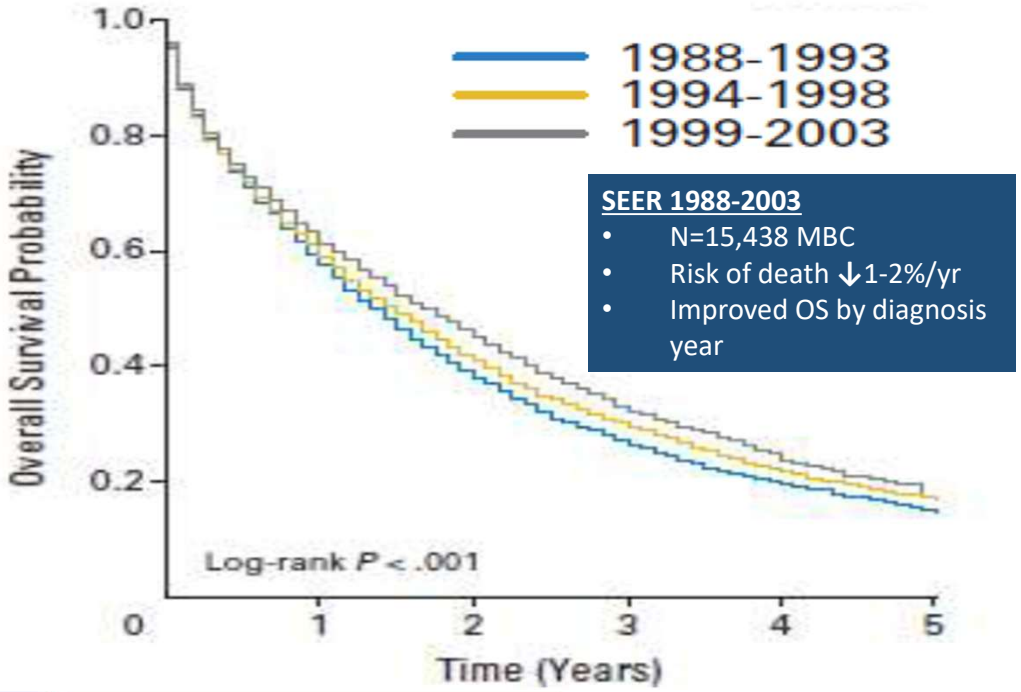
- Distant disease in a limited number of regions
- Varying definitions, can be up to ≤3 sites or ≤5 sites



- There are a few instances where long-term DFS occurs in MBC
- Suggests the possibility of cure
- Treatment of low-volume oligoMBC can produce long-term survivors

Freedman et al. Int J Radiat Onc Bio Phy 2022
Sledge G, J Oncol Practice, 2016

Trends in Improvements in OS for MBC

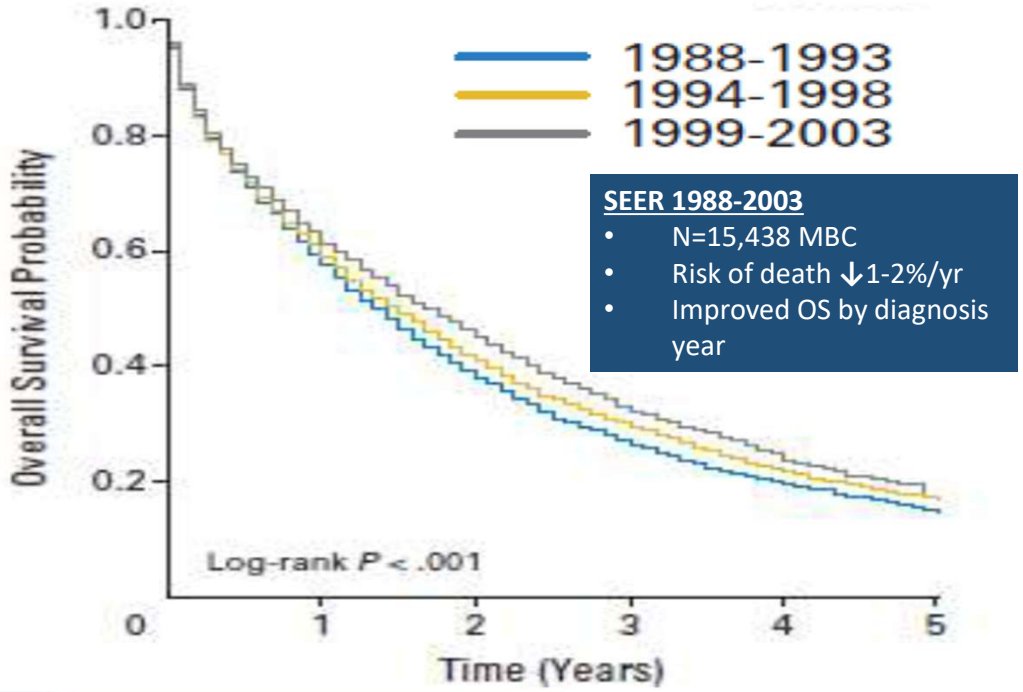


SEER 1988-2003

- N=15,438 MBC
- Risk of death ↓1-2%/yr
- Improved OS by diagnosis year

Dawood et al, JCO 26:2008

Trends in Improvements in OS for MBC



SEER 1988-2003

- N=15,438 MBC
- Risk of death ↓1-2%/yr
- Improved OS by diagnosis year

Dawood et al, JCO 26:2008

Improved PFS/OS MBC Attributed To:

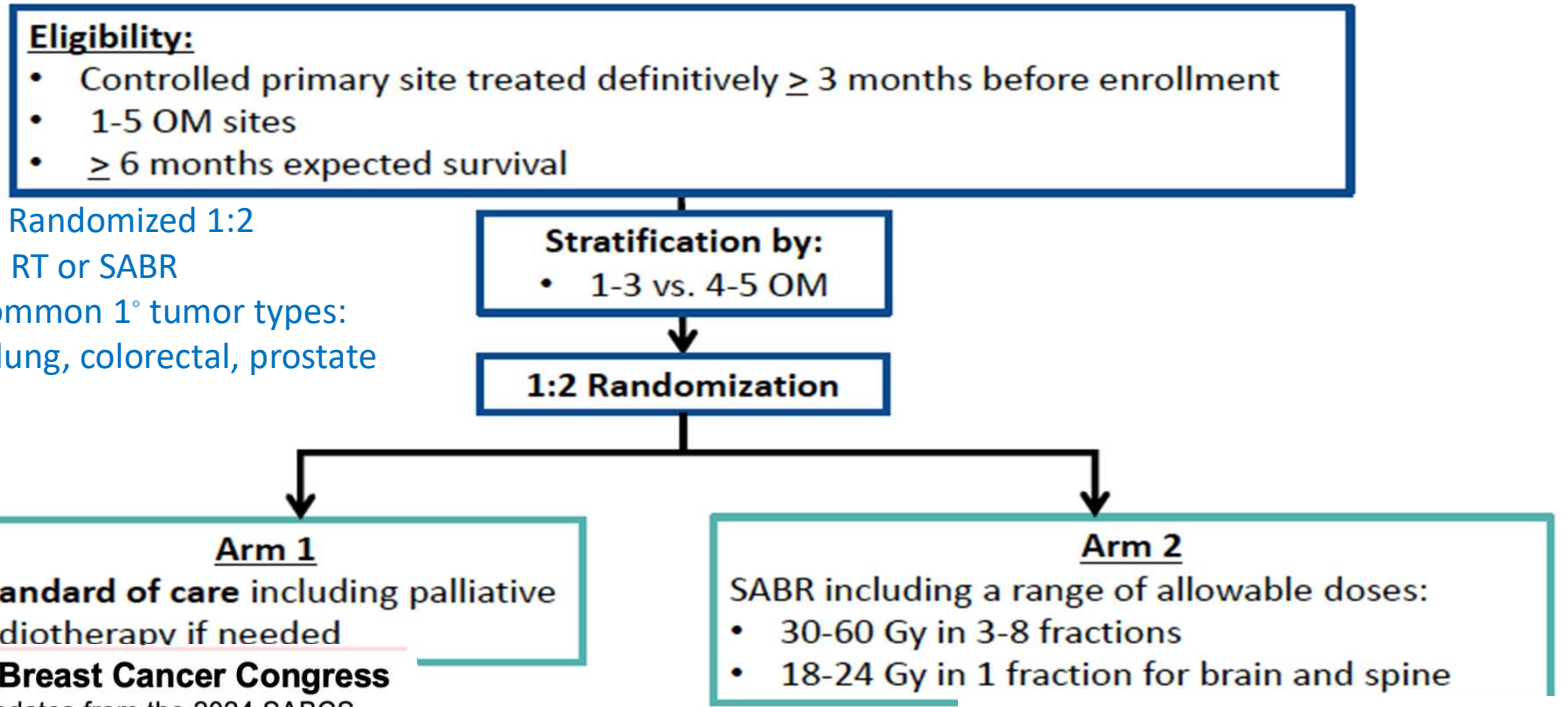
-Contemporary systemic therapies for the various BC subtypes

Subtype	Agent	
HER2 +	Monoclonal Antibody:	Pertuzumab
	Antibody-drug conjugate:	TDM1
	Tyrosine kinase inhibitor:	Neratinib, Tucatinib
HR+, HER2 -	CK 4/6 inhibitors:	Abemaciclib, Palbociclib, Ribociclib
	MTOR inhibitor:	Everolimus
	PI3K inhibitor:	Alpelisib
	SERD:	Elacestrant (RAD 1901)
TN	PDL1 inhibitors:	Atezolizumab
	Trop-2 antibody-drug conjugates:	Sacituzumab govitecan
BRCA1/2	PARP inhibitors:	Olaparib, talazoparib

-Improved diagnostics allow for earlier detection of low volume disease

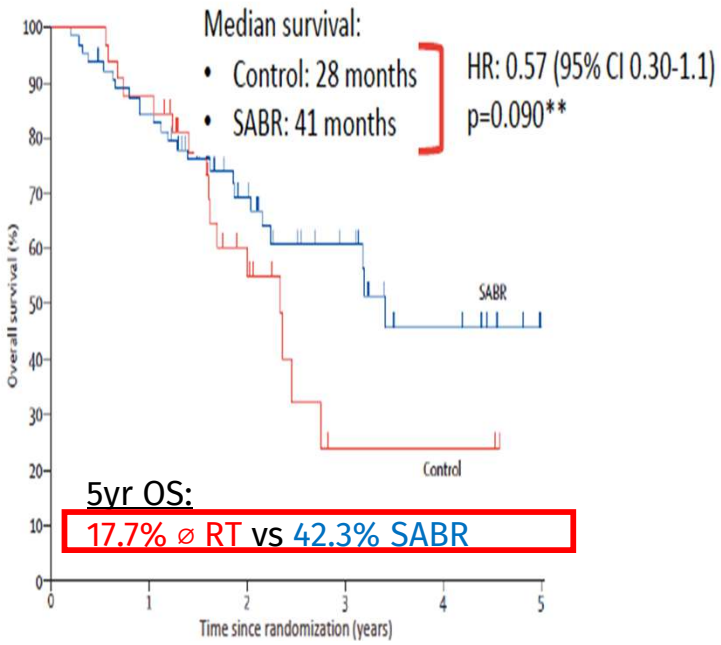
Available Data: COMET Trial
Stereotactic ABlative Radiotherapy (SABR) vs. Standard of Care (SoC) for 1-5 OM

- Phase II Randomized 1:2
- SOC/No RT or SABR
- Most common 1° tumor types: breast, lung, colorectal, prostate



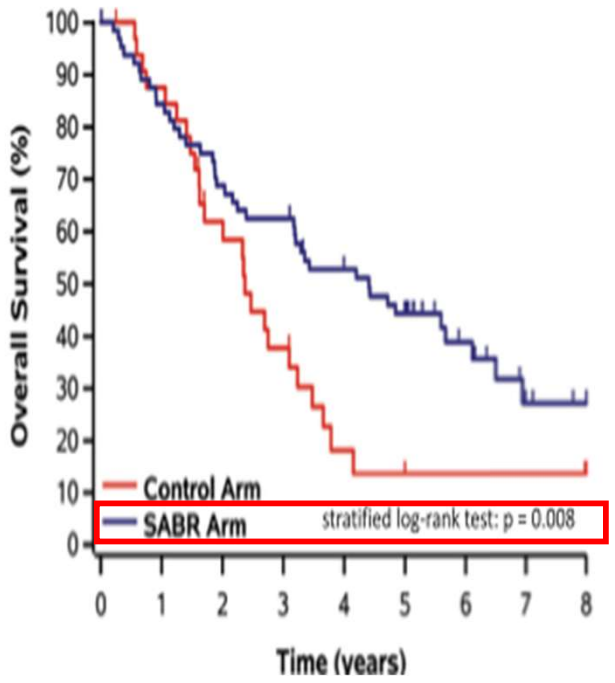
Palma, et. al., Lancet 2019

COMET: OS Outcomes



5yr OS:
17.7% ⌀ RT vs 42.3% SABR

Palma, et. al., Lancet 2019



Harrow S, et al. Int J Radiat Oncol Biol Phys 2022

SABR-COMET

Phase II Randomized Trial of Oligometastatic Cancers

	Control (n=33)	SABR group (n=66)
Female	14 (42%)	26 (39%)
Breast	5 (15%)	13 (20%)
Time from dx to trial		
	2.3 years	2.4 years
# Mets		
1	12 (36%)	30 (46%)
2	13 (40%)	19 (29%)
Location of metastases		
Lung	34/64 (53%)	55/127 (43%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)

Lung/bone most common

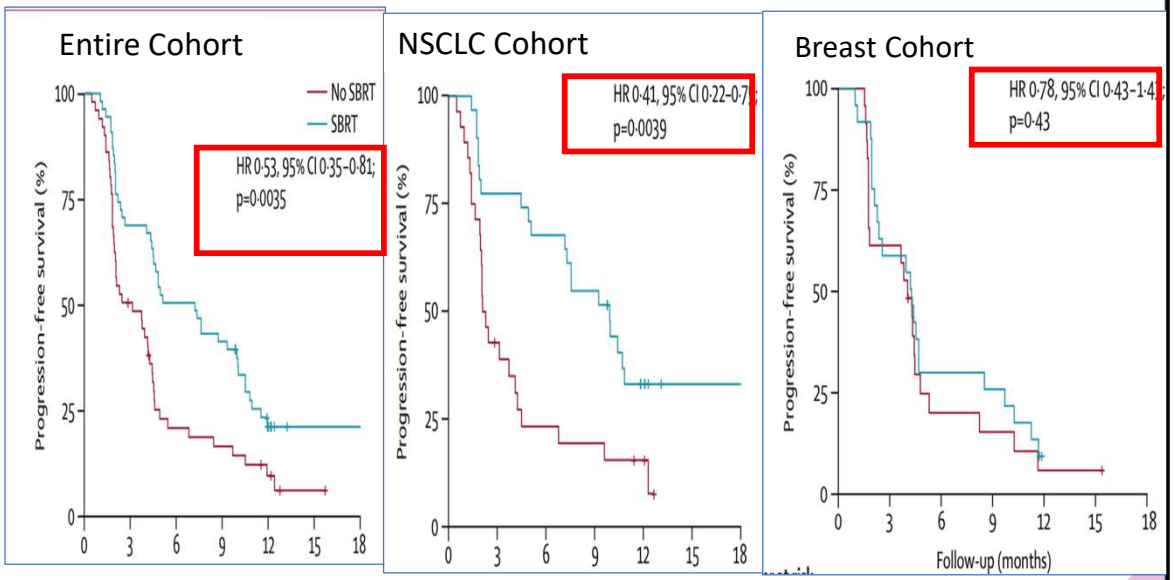
Palma, et al Lancet 2019

CURB Trial-SBRT for Lung or Breast with Oligo-progressive Disease

- Open-label, randomised, controlled,phase II study
- Only oligoprogressive breast or lung (NSCLC)
- ≤5 lesions
- Standard systemic tx +/- SBRT
- Primary endpoint:
  - PFS @ 12 months

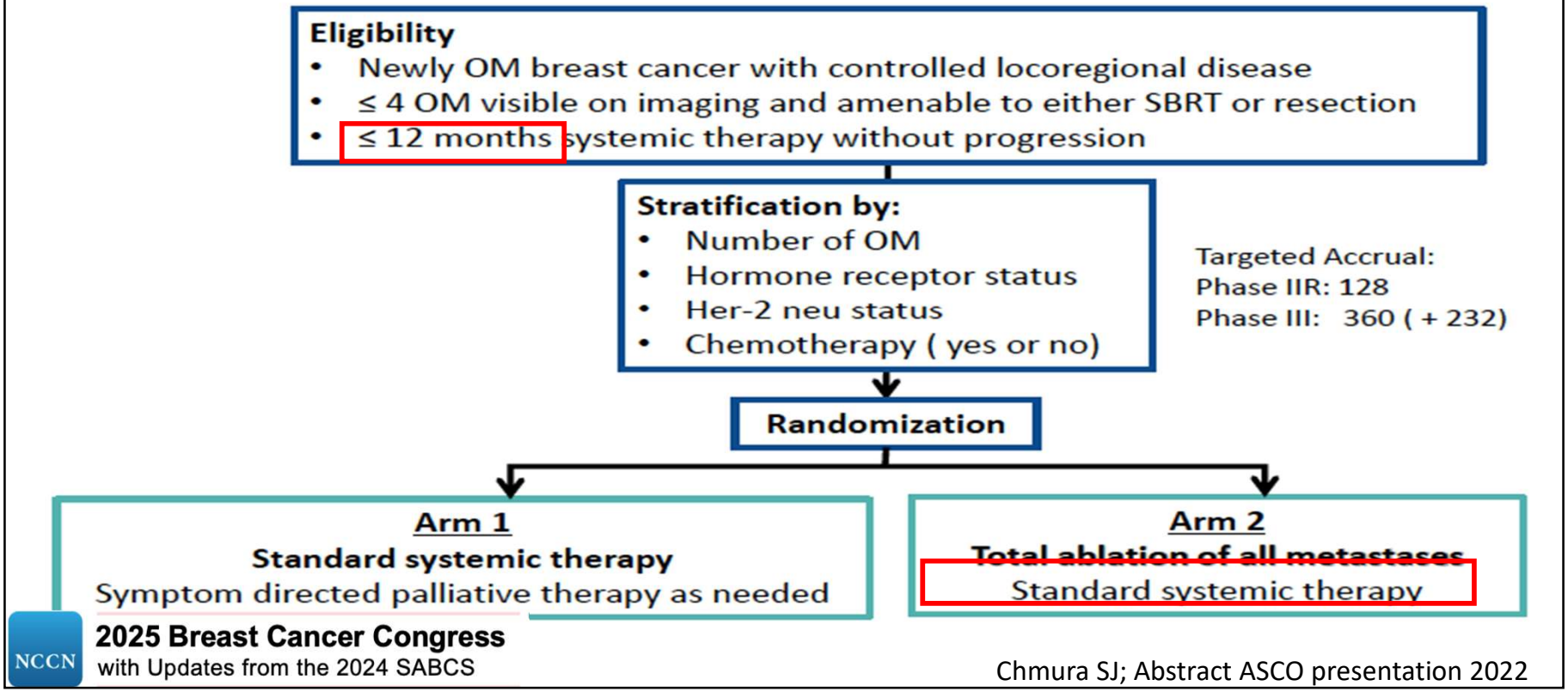
N=106

Breast cancer		Non-small-cell lung cancer	
SOC (n=23)	SBRT (n=24)	SOC (n=28)	SBRT (n=31)



Tsai CJ, et al, Lancet 2024

NRG-BR002 New Oligo MBC
PIIR/IIIR trial: Standard of Care vs. SBRT/SABR



NCCN **2025 Breast Cancer Congress**
with Updates from the 2024 SABCS

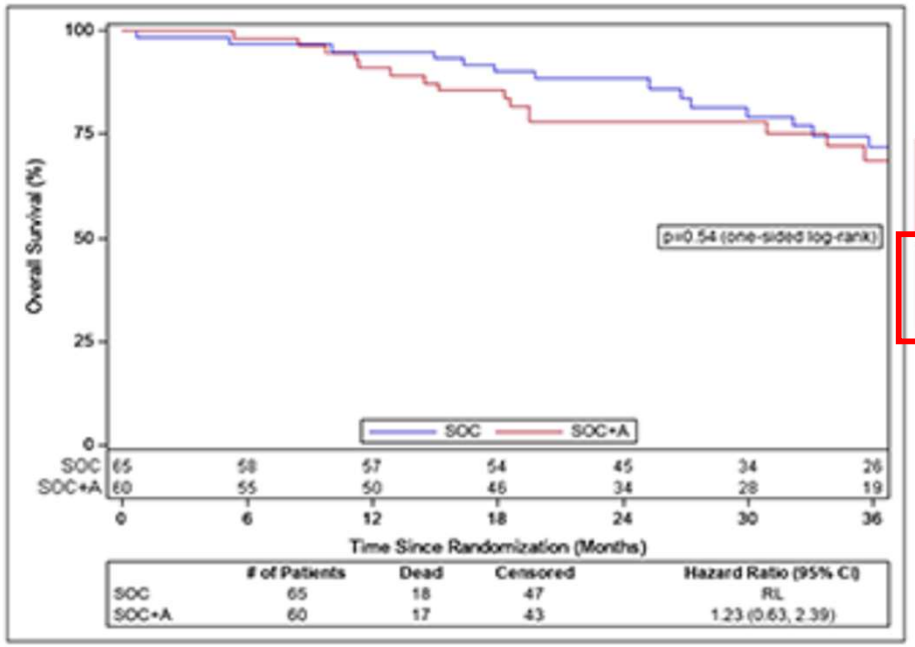
Chmura SJ; Abstract ASCO presentation 2022

NRG-BR002 Newly Diagnosed OligoBC
PII: Standard of care vs. SABR

Patient Characteristics	n	%
Number of Metastatic Sites:		
1	67	62%
>1	42	39%
Receptor/HER2 Status		
ER+ and/or PR+ / HER2-	84	77%
ER- and PgR- / HER2-	11	10%
HER2+	14	12%
Chemotherapy—Yes	48	44%
Hormonal Therapy—Yes	67	62%

Chmura SJ; Abstract ASCO presentation 2022

NRG-BR002 PII: Standard of care vs. SABR Overall Survival @35 months



	SOC (65 pts)	SOC+A (60 pts)
36-month estimate (95% CI)	71.8% (58.9%, 84.7%)	68.9% (55.1%, 82.6%)

HR [SOC+A/SOC] (95% CI): 1.23 (0.63, 2.39)

NCCN **2025 Breast Cancer Congress**
with Updates from the 2024 SABCS

Chmura SJ; Abstract ASCO presentation 2022

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 1.2024

2025 Breast Cancer Congress
with Updates from the 2024 SABCS

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 1.2024

Insufficient data:

-No recommendations for using localized therapy (SABR or Surgery) in the oligometastatic BC setting

2025 Breast Cancer Congress
with Updates from the 2024 SABCS

RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE

WORKUP[a]

- History and physical exam
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Imaging for systemic staging:
  - Chest diagnostic CT ± contrast
  - Abdomen ± pelvis diagnostic CT with contrast or MRI with contrast
  - Brain MRI with contrast if suspicious CNS symptoms[fff]
  - Spine MRI with contrast if back pain or symptoms of cord compression
  - Bone scan or sodium fluoride PET/CT (category 2B)
  - Useful in certain circumstances:
    - ◇ FDG-PET/CT (consider FES-PET/CT for ER-positive disease and lobular histology)
  - X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Biomarker testing:
  - Biopsy of at least first recurrence of disease (consider re-biopsy if progression)
  - Evaluation of ER/PR and HER2 status[d,ggg,hhh]
  - Comprehensive germline and somatic profiling to identify candidates for targeted therapies,[iii] see BINV-Q 6
- Genetic counseling if patient is at risk[e] for hereditary breast cancer
- Assess for distress[g]

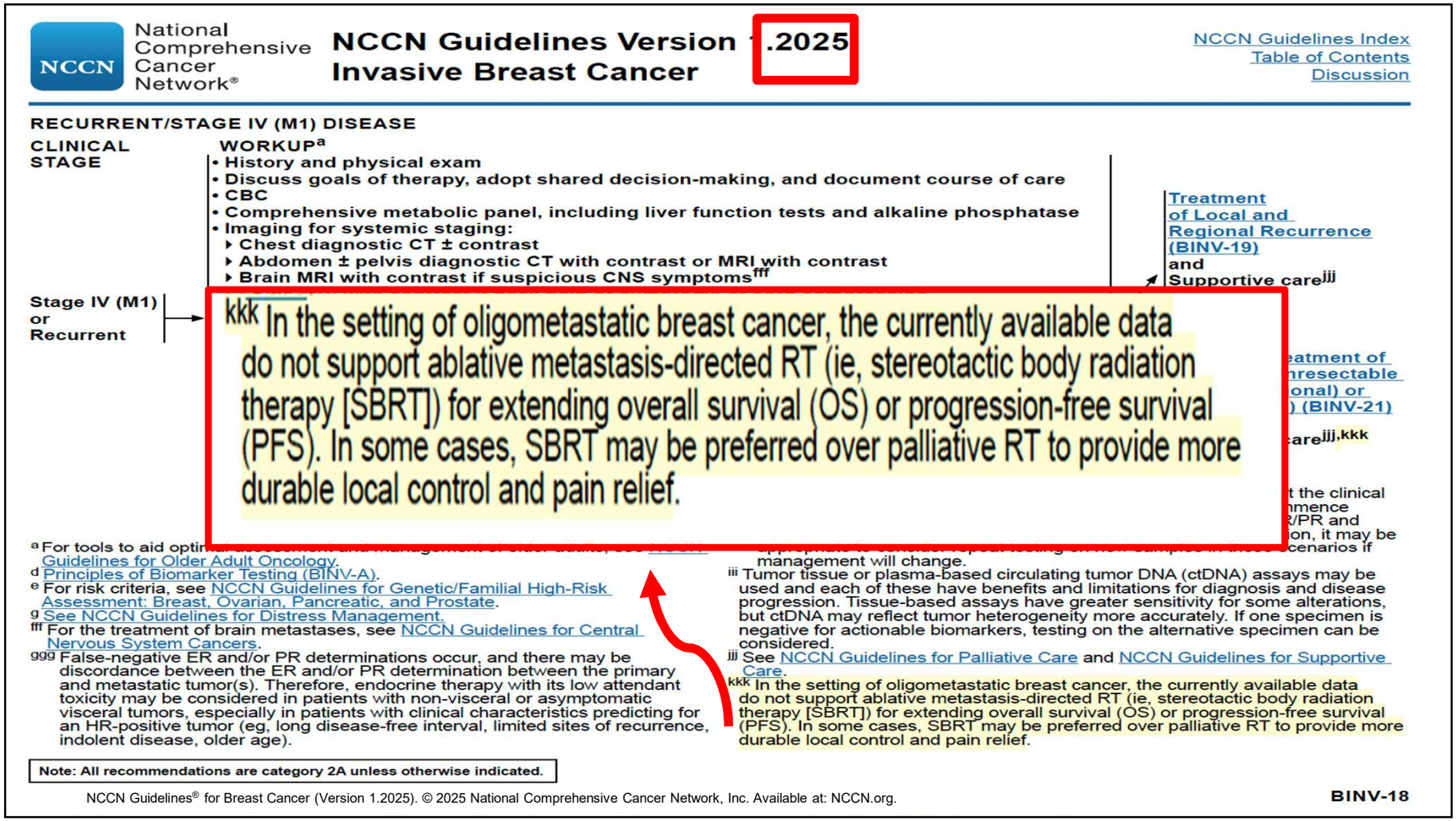
Stage IV (M1) or Recurrent →

→ Treatment of Local and Regional Recurrence (BINV-19) and Supportive care[jjj]

→ Systemic Treatment of Recurrent Unresectable (local or regional) or Stage IV (M1) (BINV-21) and Supportive care[jjj,kkk]

[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] Principles of Biomarker Testing (BINV-A).
[e] For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[g] See NCCN Guidelines for Distress Management.
[fff] For the treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[ggg] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for an HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[hhh] In clinical situations where a biopsy cannot safely be obtained but the clinical evidence is strongly supportive of recurrence, treatment may commence based on the ER/PR/HER2 status of the primary tumor. Since ER/PR and HER2 status can change with treatment and metastatic progression, it may be appropriate to consider repeat testing on new samples in these scenarios if management will change.
[iii] Tumor tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used and each of these have benefits and limitations for diagnosis and disease progression. Tissue-based assays have greater sensitivity for some alterations, but ctDNA may reflect tumor heterogeneity more accurately. If one specimen is negative for actionable biomarkers, testing on the alternative specimen can be considered.
[jjj] See NCCN Guidelines for Palliative Care and NCCN Guidelines for Supportive Care.
[kkk] In the setting of oligometastatic breast cancer, the currently available data do not support ablative metastasis-directed RT (ie, stereotactic body radiation therapy [SBRT]) for extending overall survival (OS) or progression-free survival (PFS). In some cases, SBRT may be preferred over palliative RT to provide more durable local control and pain relief.

Note: All recommendations are category 2A unless otherwise indicated.



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE

WORKUP[a]

- History and physical exam
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Imaging for systemic staging:
  - Chest diagnostic CT ± contrast
  - Abdomen ± pelvis diagnostic CT with contrast or MRI with contrast
  - Brain MRI with contrast if suspicious CNS symptoms[fff]

Stage IV (M1) or Recurrent →

Treatment of Local and Regional Recurrence (BINV-19)
and
Supportive care[jjj]

[kkk] In the setting of oligometastatic breast cancer, the currently available data do not support ablative metastasis-directed RT (ie, stereotactic body radiation therapy [SBRT]) for extending overall survival (OS) or progression-free survival (PFS). In some cases, SBRT may be preferred over palliative RT to provide more durable local control and pain relief.

[a] For tools to aid optim… Guidelines for Older Adult Oncology.
[d] Principles of Biomarker Testing (BINV-A).
[e] For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[g] See NCCN Guidelines for Distress Management.
[fff] For the treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[ggg] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for an HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

management will change.
[iii] Tumor tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used and each of these have benefits and limitations for diagnosis and disease progression. Tissue-based assays have greater sensitivity for some alterations, but ctDNA may reflect tumor heterogeneity more accurately. If one specimen is negative for actionable biomarkers, testing on the alternative specimen can be considered.
[jjj] See NCCN Guidelines for Palliative Care and NCCN Guidelines for Supportive Care.
[kkk] In the setting of oligometastatic breast cancer, the currently available data do not support ablative metastasis-directed RT (ie, stereotactic body radiation therapy [SBRT]) for extending overall survival (OS) or progression-free survival (PFS). In some cases, SBRT may be preferred over palliative RT to provide more durable local control and pain relief.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
  - 3-D CT-based treatment planning should routinely be utilized to delineate target volumes & organs at risk, and assess dose distribution across the entire treatment volume.
  - Radiation is generally delivered with single or mixed energy photons ± electrons.
  - Treatment planning should be optimized to maximally improve homogeneity across the target volume while minimizing dose to organs at risk.
  - Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
  - At a minimum, weekly imaging to verify treatment setup should be utilized. More frequent imaging may be needed for selected cases with inconsistent reproducibility. Image-guided radiation therapy (IGRT) may be utilized with deep inspiration breath-hold (DIBH) technique to reduce normal tissue exposure of the heart, lung or liver.
  - Dose-volume histograms (DVHs) should be used to evaluate dose, normal tissue constraints (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated. See BINV-12 OF 3.
- In the setting of oligometastatic breast cancer, the currently available data do not support ablative metastasis-directed RT (ie, SBRT) for extending overall survival OS or PFS. In some cases, SBRT may be preferred over palliative radiotherapy to provide more durable local control and pain relief.

[c] Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. (Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks [FAST-Forward]: 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.)

[d] Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020;38:3261-3272.

Note: All recommendations are category 2A unless otherwise indicated.

SABC 2024 Abstract 1:

De-escalation of LR treatment in older women with small, ER+ tumors treated with BCS followed by ET or RT

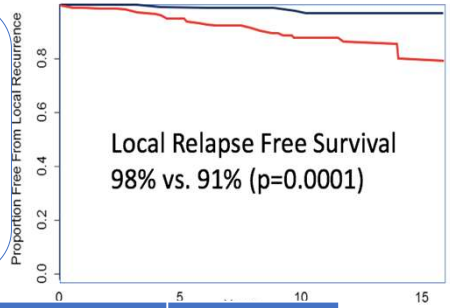
Background:

Eligible patients:

- Tamoxifen
- Tamoxifen + WBRT

CALGB 9343:

Eligibility:
≥70 yrs;
≤2cm, cN0, ER+
Surgical eval of axilla not necessary

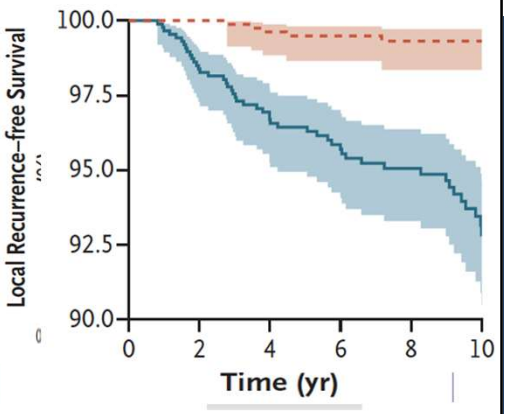


10 yr Outcomes	No RT	RT
Local Relapse	9%	2%
Axillary Rec	1%	0%
Distant Mets	5%	5%
10 yr BCSS	98%	97%

Hughes et. al. JCO 2013

PRIME II TRIAL:

Eligibility:
>65 yrs; <3cm, pN0, ER+*Axilla surgically assessed



Pt Characteristics:
Median age: 70 yrs
Tumors <2 cm: 90%
Grade I or II: 90%

10 yr Outcomes	No RT	RT
Local Relapse	9.5%	0.9%

Kunkler et. al. Feb 2023 NEJM

- The goal of CALGB 9343/PRIME II: identify a cohort of elderly, low-risk pts in whom RT could be safely omitted
- RT was considered toxic & burdensome
  - Traditional breast RT courses: 5-7 weeks
  - Caused significant acute/long term side effects
- Contemporary RT delivery to the breast has significantly evolved
  - More precise delivery; routine sparing of heart, lung, skin; using 3D-delivery
  - Shorter, accelerated treatments (3-4 weeks vs. 5 fractions in most patients)
- Resulted in the perception that breast RT is better tolerated & less burdensome
- Can these older, low risk-patients do an abbreviated course of RT instead of 5 years of ET?
- Many issues with compliance/adherence/side effects associated with ET
- No prospective data comparing single modality RT versus ET
- No quality-of-life measures for RT versus ET

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
DECEMBER 10–13, 2024
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Exclusive endocrine therapy or radiation therapy in women aged 70+ years with luminal-like early breast cancer (EUROPA): preplanned interim analysis of a randomized phase 3 trial

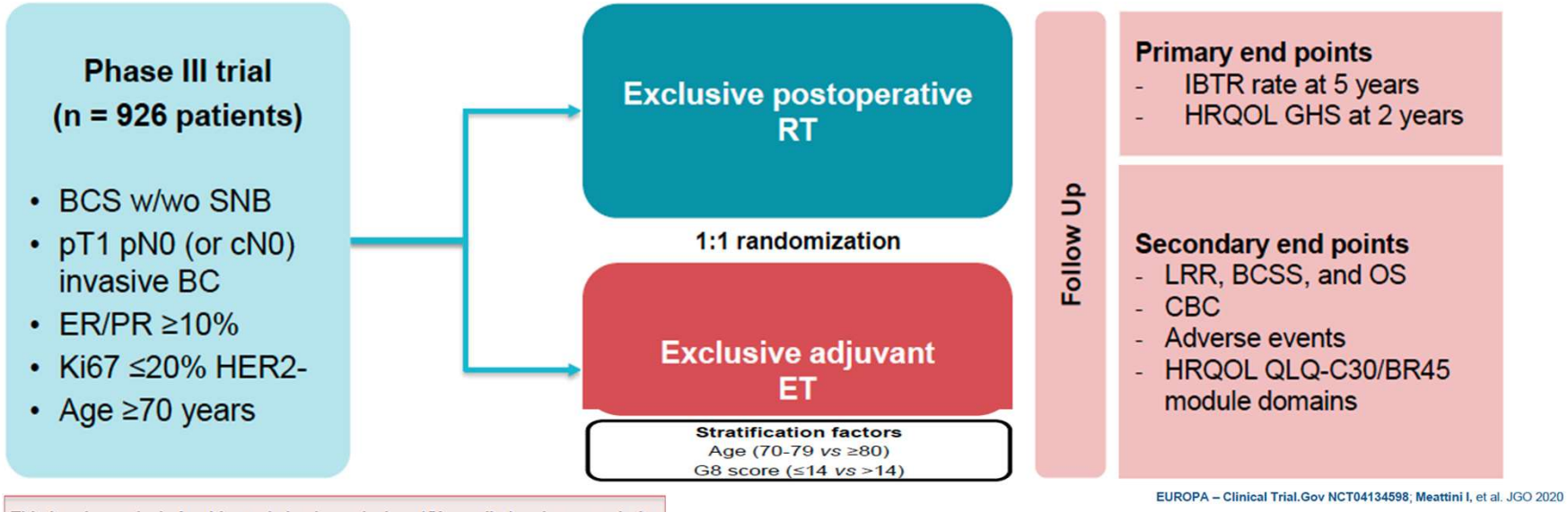
Icro Meattini, MD

University of Florence, Florence, Italy

Icro Meattini, Maria Carmen De Santis, Luca Visani, Marta Scorsetti, Alessandra Fozza, Bruno Meduri, Fiorenza De Rose, Elisabetta Bonzano, Agnese Prisco, Valeria Masiello, Eliana La Rocca, Ruggero Spoto, Carlotta Becherini, Gladys Blandino, Luca Moscetti, Riccardo Ray Colciago, Francesca Martella, Lorenzo Vinante, Sara Ramella, Marco Gatti, Sara Pedretti, Patrizia Vici, Nadia G. Di Muzio, Alice Pastorino, Maria Cristina Leonardi, Ivica Ratosa, Jure Verbancic, Riccardo A. Audisio, Etienne Brain, Saverio Caini, Marije Hamaker, Orit Kaidar-Person, Matteo Lambertini, Livia Marrazzo, Calogero Saieva, Tanja Spanic, Vratislav Strnad, Sally Wheelwright, Philip M. P. Poortmans, Lorenzo Livi, on behalf of the EUROPA trial Investigators

Europa
fro
UNIVERSITÀ DEGLI STUDI FIRENZE

Interim Analysis: EUROPA Trial



EUROPA – Clinical Trial.Gov NCT04134598; Meattini I, et al. JGO 2020

This interim analysis for this study is planned when 152 enrolled patients reach the 2-year GHS HRQOL follow up control

Stopping rules

>2% IBTR rate per year

>7% Distant Metastases rate at any time

- Preplanned analysis
- Primary Endpoint: HR-QOL- RT vs. ET
- Co-primary endpoint: RT IBTR had to be non-inferior to ET at years

UNIVERSITÀ DEGLI STUDI FIRENZE

Interim Analysis: EUROPA Trial

Patient Characteristics:

	RT (N = 104)	ET (N = 103)
Total number of patients in the ITT population considered in this analysis	104 (100.0%)	103 (100.0%)
Total number of patients in the SAF population considered in this analysis	97 (93.3%)	89 (86.4%)
Treatment assigned		
Exclusive Endocrine Therapy (ET)	0 (0.0%)	103 (100.0%)
Exclusive RT – Partial Breast Irradiation	88 (84.6%)	0 (0.0%)
Exclusive RT – Whole breast irradiation	16 (15.4%)	0 (0.0%)
Age class		
70-79 years	77 (74.0%)	74 (71.8%)
80+ years	27 (26.0%)	29 (28.2%)
G8 score class		
≤14	42 (40.4%)	41 (39.8%)
>14	62 (59.6%)	62 (60.2%)

Interim Analysis: EUROPA Trial

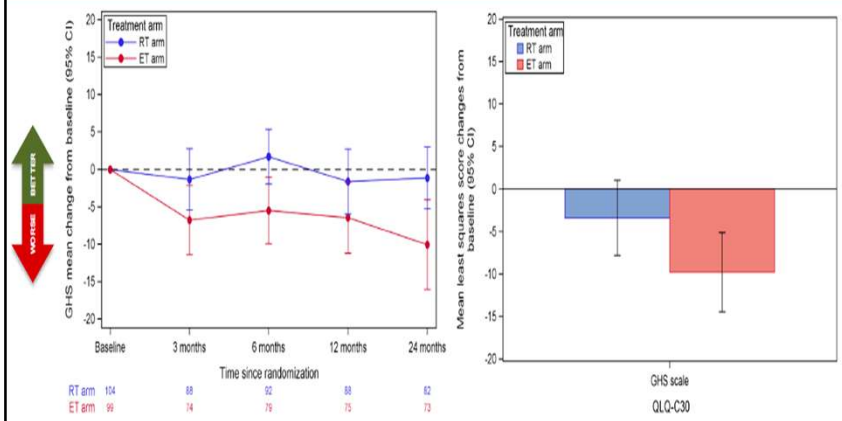
Patient Characteristics:

	RT (N = 104)	ET (N = 103)
Age (years)		
Mean (SD)	76.4 (4.57)	76.1 (4.90)
Median	75.0	74.0
Laterality, n (%)		
Left	65 (62.5%)	54 (52.4%)
Right	39 (37.5%)	49 (47.6%)
pT stage, n (%)		
pT1a	8 (7.7%)	8 (7.7%)
pT1b	54 (51.9%)	50 (48.5%)
pT1c	42 (40.4%)	45 (43.7%)
N status, n (%)		
pN0	95 (91.4%)	95 (92.2%)
pNx	9 (8.7%)	8 (7.8%)
Grading, n (%)		
G1	37 (35.6%)	35 (34.0%)
G2	67 (64.4%)	68 (66.0%)

	RT (N = 104)	ET (N = 103)
Surgical Margins, n (%)		
≥2 mm	97 (94.2%)	79 (79.0%)
no ink to <2 mm	6 (5.8%)	21 (21.0%)
ER categories		
≤50%	0 (0.0%)	0 (0.0%)
>50%	104 (100.0%)	103 (100.0%)
PR categories		
≤50%	23 (22.1%)	26 (25.2%)
>50%	81 (77.9%)	77 (74.8%)
Ki67 categories		
≤13.25%	68 (65.4%)	70 (68.0%)
>13.25%	36 (34.6%)	33 (32.0%)
HER2 negative		
Score 0	47 (45.2%)	60 (58.3%)
Score 1+	46 (44.2%)	31 (30.1%)
Score 2+, not amplified	11 (10.6%)	12 (11.7%)

EORTC QLQ-C30 Score

Overall Quality of Life Questionnaire, 30-item core module

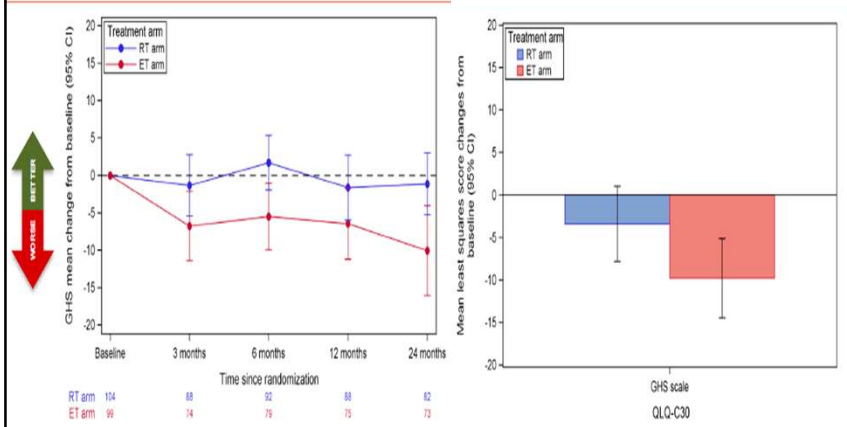


		Actual value			Change from baseline	
Group	Visit	n	Mean	SD	Mean	SD
RT arm	Baseline	104	71.9	19.1		
	24 months	82	70.7	20.4	-1.1	18.8
ET arm	Baseline	99	75.5	19.3		
	24 months	74	67.2	23.2	-10.0	25.8

- Across the entire C30 scale, the deviation from baseline is significantly less for RT than ET

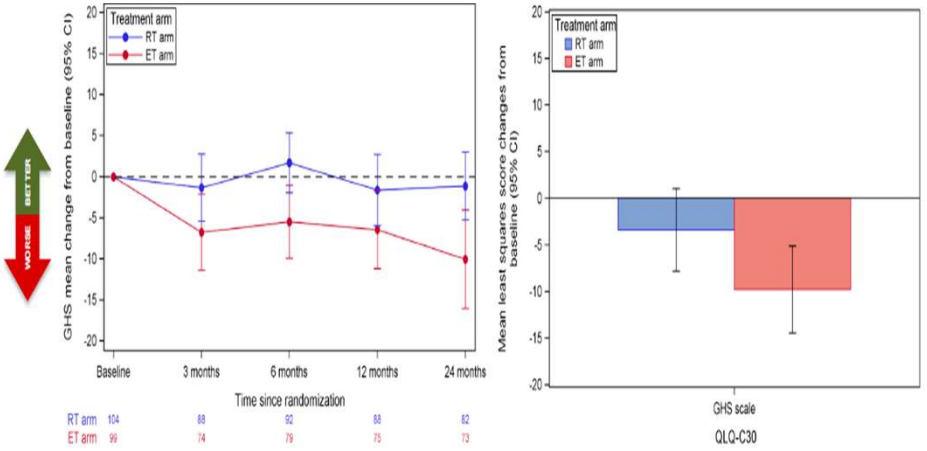
EORTC QLQ-C30 Score

Overall Quality of Life Questionnaire, 30-item core module



Group	Visit	n	Actual value Mean	SD	Change from baseline Mean	SD
RT arm	Baseline	104	71.9	19.1		
	24 months	82	70.7	20.4	-1.1	18.8
ET arm	Baseline	99	75.5	19.3		
	24 months	74	67.2	23.2	-10.0	25.8

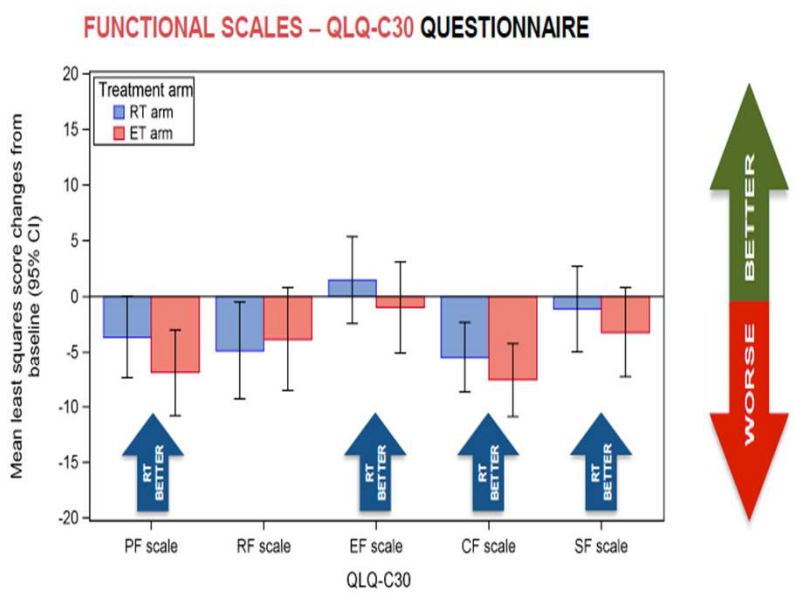
- Across the entire C30 scale, the deviation from baseline is significantly less for RT than ET

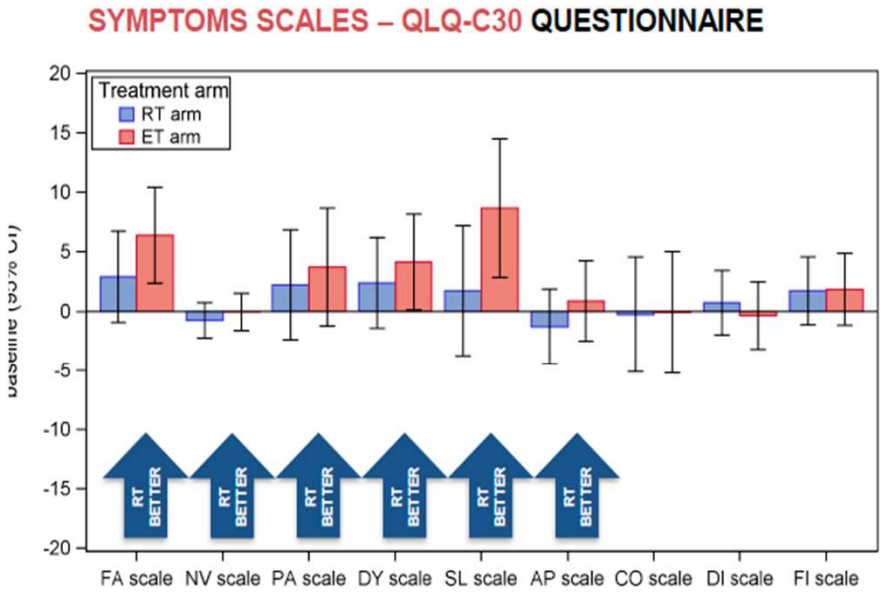


			Value	p-value
Age/G8 adjusted means	RT arm	24 months	-3.40	0.13
Age/G8 adjusted means	ET arm	24 months	-9.79	<0.0001
Mean differences	RT vs ET	24 months	6.39	0.045

These differences in RT vs. ET remained significant after adjusting for age and G8 score

EUROPA Trial: QLQ-C30 Functional & Symptoms Scales



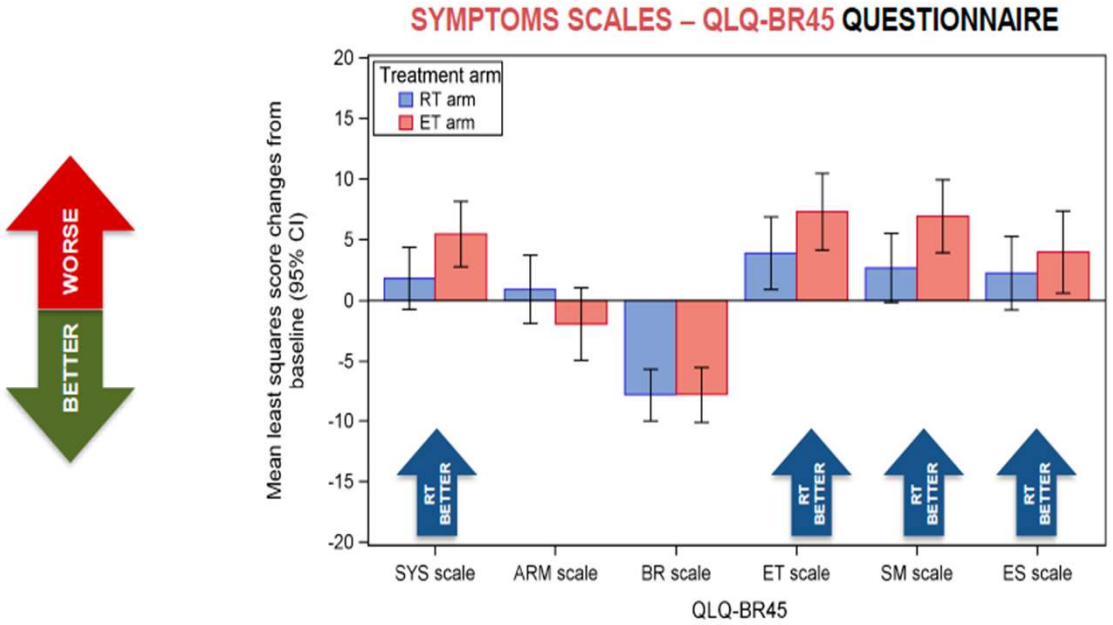


Functioning: Physical, role, emotional, cognitive, social

Symptoms Scale : Fatigue, nausea/vomiting, pain, dyspnea, appetite, constipation, diarrhea, financial difficulties

RT arm did better than ET arm across many of the functioning & symptoms scales, suggesting better tolerability for RT than ET

QLQ-B45 Symptoms Scales



ET did significantly worse for systemic therapy-related, skin-related and endocrine/sexual symptoms scales than RT

(p=0.038)

SYS=systemic therapy side effects; ARM=arm symptoms; BR=breast symptoms; ET=endocrine therapy symptoms; SM=skin mucosis symptoms; ES=endocrine sexual symptom

EUROPA Trial: 24 Month Outcomes

Patient Outcomes:

Clinical event, n (%)	RT (n = 104)	ET (n = 103)
IBTR	0 (0)	0 (0)
LRR	0 (0)	0 (0)
CBC	2 (1.9)	1 (1)
Distant Metastases	0 (0.0)	0 (0)
Death	4 (3.8)	2 (1.9)
Breast cancer-related death	0 (0)	0 (0)

EUROPA Trial: 24 Month Outcomes

Patient Outcomes:

Clinical event, n (%)	RT (n = 104)	ET (n = 103)
IBTR	0 (0)	0 (0)
LRR	0 (0)	0 (0)
CBC	2 (1.9)	1 (1)
Distant Metastases	0 (0.0)	0 (0)
Death	4 (3.8)	2 (1.9)
Breast cancer-related death	0 (0)	0 (0)

Overall Tx-related Adverse Effects:
RT(67%) vs. ET (85%) (Mostly GI-II)
Serious/fatal events: RT (2%) vs. ET (3%)
***neither arm had a disproportionately high-risk of serious complications

	RT (n = 97)			ET (n = 89)		
Adverse event, n (%)	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Arthralgia (Joint pain)	28 (28.9)	0	0	62 (69.7)	5 (5.6)	1 (1.1)
Fatigue	32 (33)	0	0	40 (44.9)	2 (2.2)	0
Breast pain	37 (38.1)	0	0	8 (9)	0	0
Hot flashes	10 (10.3)	0	0	29 (32.6)	2 (2.2)	0
Myalgia (Muscle pain)	13 (13.4)	0	0	28 (31.5)	2 (2.2)	0
Bone pain	23 (23.7)	0	0	25 (28.1)	2 (2.2)	0
Alopecia (Hair loss)	7 (7.2)	0	0	23 (25.8)	0	0
Depression	15 (15.5)	1 (1)	0	21 (23.6)	1 (1.1)	0
Insomnia	15 (15.5)	0	0	21 (23.6)	0	0
Osteoporosis	3 (3.1)	0	0	20 (22.5)	0	0
Hypercholesterolemia	0	0	0	17 (19.1)	0	0
Vaginal dryness	7 (7.2)	0	0	17 (19.1)	0	0
Irritability	15 (15.5)	0	0	12 (13.5)	1 (1.1)	0
Arthritis	15 (15.5)	0	0	14 (15.7)	0	0
Constipation	14 (14.4)	1 (1)	0	12 (13.5)	1 (1.1)	0
Dermatitis	14 (14.4)	0	0	9 (10.1)	0	0
Weight gain	12 (12.4)	0	0	12 (13.5)	0	0
Headache	9 (9.3)	0	0	10 (11.2)	0	0
Hypertension	9 (9.3)	0	0	9 (10.1)	0	0

EUROPA Trial: 24 Month Outcomes

Patient Outcomes:

Clinical event, n (%)	RT (n = 104)	ET (n = 103)
IBTR	0 (0)	0 (0)
LRR	0 (0)	0 (0)
CBC	2 (1.9)	1 (1)
Distant Metastases	0 (0.0)	0 (0)
Death	4 (3.8)	2 (1.9)
Breast cancer-related death	0 (0)	0 (0)

Overall Tx-related Adverse Effects:
RT(67%) vs. ET (85%) (Mostly GI-II)
Serious/fatal events: RT (2%) vs. ET (3%)
***neither arm had a disproportionately high-risk of serious complications

22.5% ET switch

12.4% ET discontinuation

	RT (n = 97)			ET (n = 89)		
Adverse event, n (%)	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Arthralgia (Joint pain)	28 (28.9)	0	0	62 (69.7)	5 (5.6)	1 (1.1)
Fatigue	32 (33)	0	0	40 (44.9)	2 (2.2)	0
Breast pain	37 (38.1)	0	0	8 (9)	0	0
Hot flashes	10 (10.3)	0	0	29 (32.6)	2 (2.2)	0
Myalgia (Muscle pain)	13 (13.4)	0	0	28 (31.5)	2 (2.2)	0
Bone pain	23 (23.7)	0	0	25 (28.1)	2 (2.2)	0
Alopecia (Hair loss)	7 (7.2)	0	0	23 (25.8)	0	0
Depression	15 (15.5)	1 (1)	0	21 (23.6)	1 (1.1)	0
Insomnia	15 (15.5)	0	0	21 (23.6)	0	0
Osteoporosis	3 (3.1)	0	0	20 (22.5)	0	0
Hypercholesterolemia	0	0	0	17 (19.1)	0	0
Vaginal dryness	7 (7.2)	0	0	17 (19.1)	0	0
Irritability	15 (15.5)	0	0	12 (13.5)	1 (1.1)	0
Arthritis	15 (15.5)	0	0	14 (15.7)	0	0
Constipation	14 (14.4)	1 (1)	0	12 (13.5)	1 (1.1)	0
Dermatitis	14 (14.4)	0	0	9 (10.1)	0	0
Weight gain	12 (12.4)	0	0	12 (13.5)	0	0
Headache	9 (9.3)	0	0	10 (11.2)	0	0
Hypertension	9 (9.3)	0	0	9 (10.1)	0	0

EUROPA Trial: Conclusions

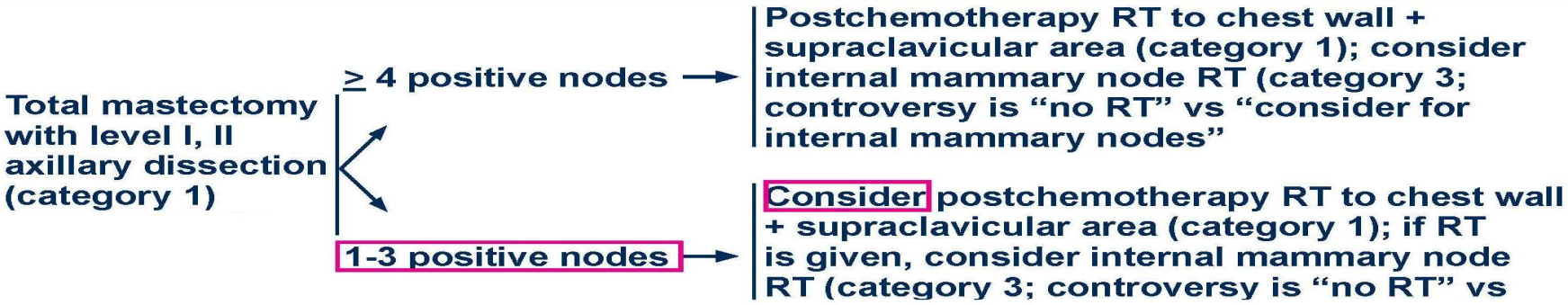
- This trial suggests that for pts ≥70 that may be eligible for RT-omission, RT-alone may offer better QOL than ET-alone at 2 yr f/u
- Overall lower incidence of adverse events for RT than ET
- Excellent outcomes with either RT or ET:
  - No IBTR in either arm
  - No BC-specific mortality in either arm
- Suggests that ET or RT alone may be reasonable options for patients who meet CALGB 9343 criteria
- Will be interesting to see ongoing compliance for ET and longer f/u in patients who discontinued

SABC 2024 Abstract 2:

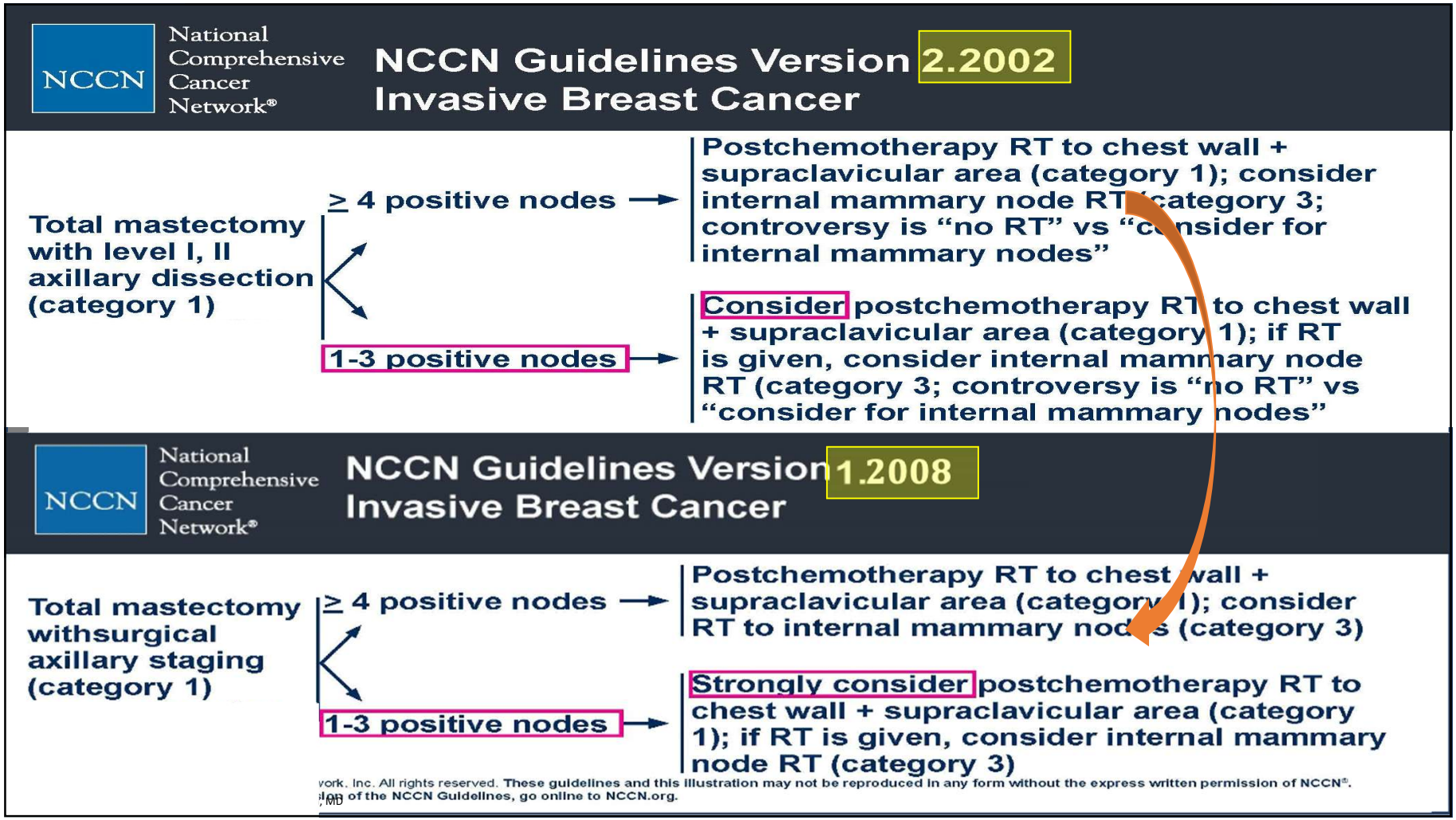
Is PMRT needed for all node+ patients after mastectomy?

National Comprehensive Cancer Network®

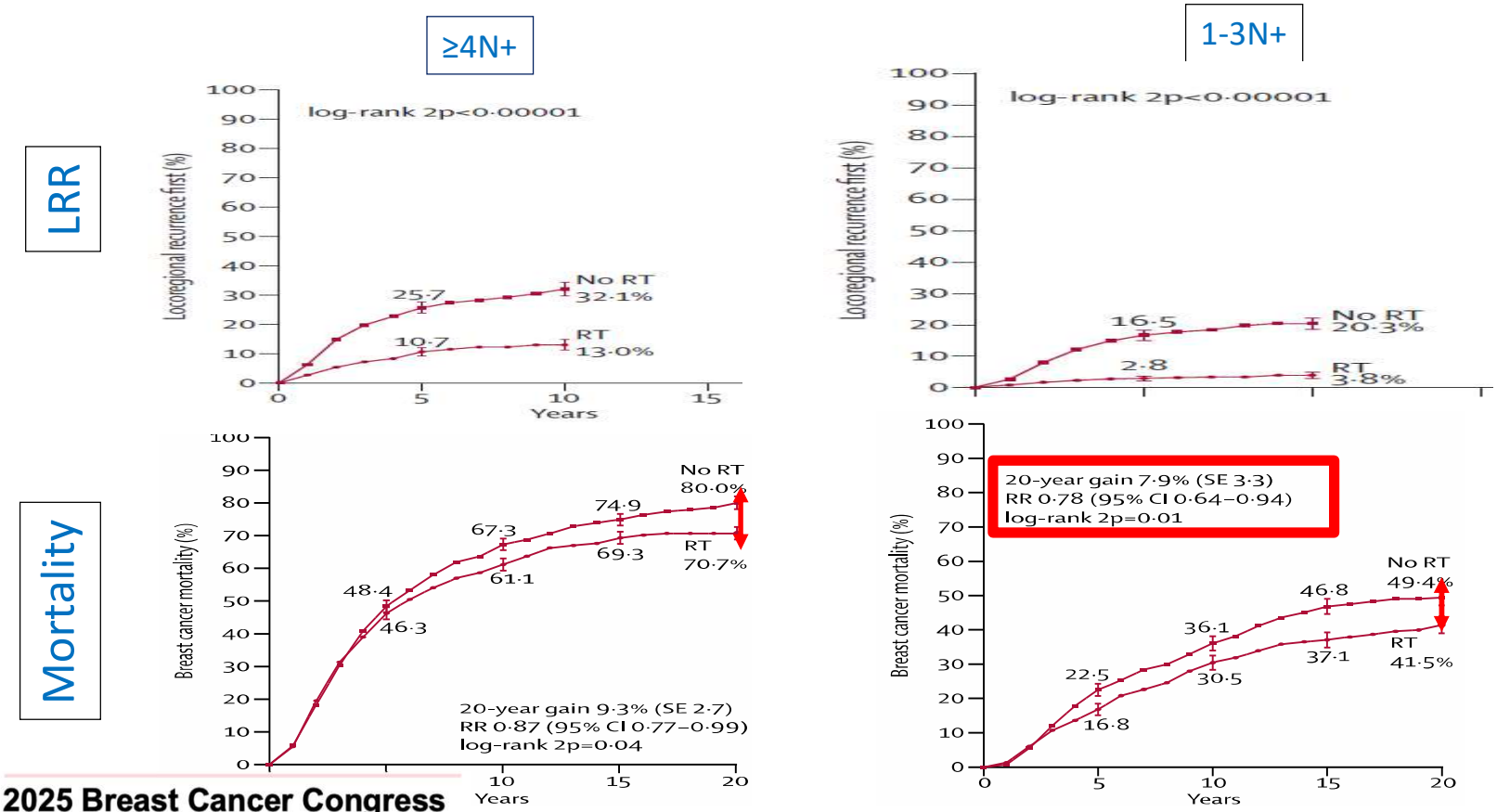
NCCN Guidelines Version 2.2002
Invasive Breast Cancer



, MD



Background:2014 Oxford Meta-Analysis of PMRT Trials



NCCN **2025 Breast Cancer Congress**
with Updates from the 2024 SABCS

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), The Lancet 2014

Background: Additional PMRT Guidelines

ESMO Breast Guideline:

Senkus E et al. Ann Oncol 2015

- PMRT always recommended for high-risk pts: +resection margins, 4+ nodes [I,A], and T3/T4 N0[II, B],
- "We should now also consider routine use of PMRT for patients with 1-3+ nodes" [I,A]

St Gallen Consensus:

Coates AS et al; Ann Oncol 2015
Curigliano G,. Ann Oncol. 2017

- PMRT is standard for 1-3 +nodes with adverse pathology

ASCO 2016 PMRT Update:

Recht A, et al 2016, JCO

- Unanimously agreed available evidence for T1/T2, N1-3+, PMRT demonstrates:
  - ↓ LRR, ↓ any recurrence, ↓ BR-ca sp mortality
  - Clinical judgement needed in lower-risk pts, where risks may outweigh benefits

Background: Why Continued Controversy?

- Criticisms of PMRT Trials:
  - LRR in those trials w/o PMRT much higher than current practice
  - Less effective systemic therapies utilization
    - No taxanes
    - No dose-dense scheduling
    - No targeted agents (HER-2, etc.)
    - Less ET options, widespread utilization, no extension beyond 5 yrs

    ↓LRR
  - Criticisms regarding axillary management
- With contemporary systemic agents, is PMRT needed all patients?

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio Mays Cancer Center

AACR American Association for Cancer Research

DECEMBER 10–13, 2024

HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC randomized trial on behalf of the SUPREMO trial investigators

Ian Kunkler, FRCR
Institute of Genetics and Cancer
University of Edinburgh

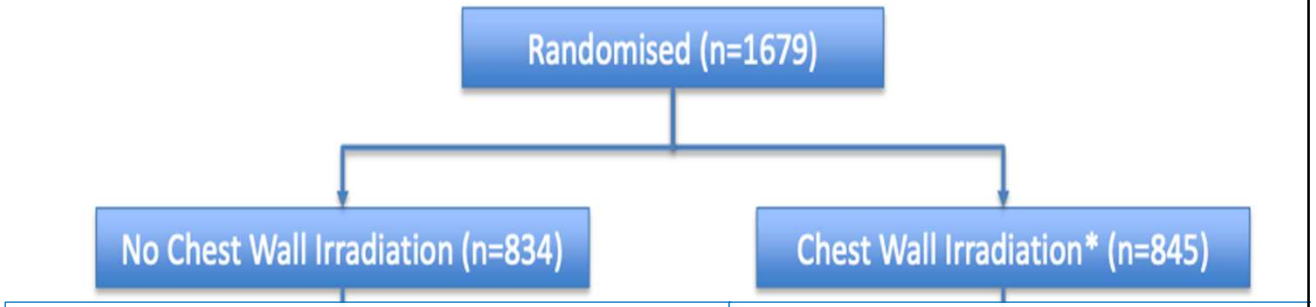
MRC Medical Research Council

SUPREMO: Study Design

N=1650
2006-2013

Eligibility criteria:

- T1/T2, pN1 (1-3 +)
- T3N0
- T2N0 if GIII or LVSI
- Mast + Ax surgery
- ALND if pN+
- Removal of >8 nodes if node +
- No comprehensive RT to Axilla permitted



1600 patients (800 per arm) for 80% power to detect a statistically significant difference at the 5% level if the true rates of survival at 10 years are 56% and 63% allowing for attrition.
(ie 7% difference)

Primary: overall survival at 10 yea

Secondary:

- Local and regional recurrence
- Disease free and metastasis free survival
- Cause of death
- Acute and late morbidity
- Quality of life
- Cost effectiveness

RESULTS: Basic Characteristics

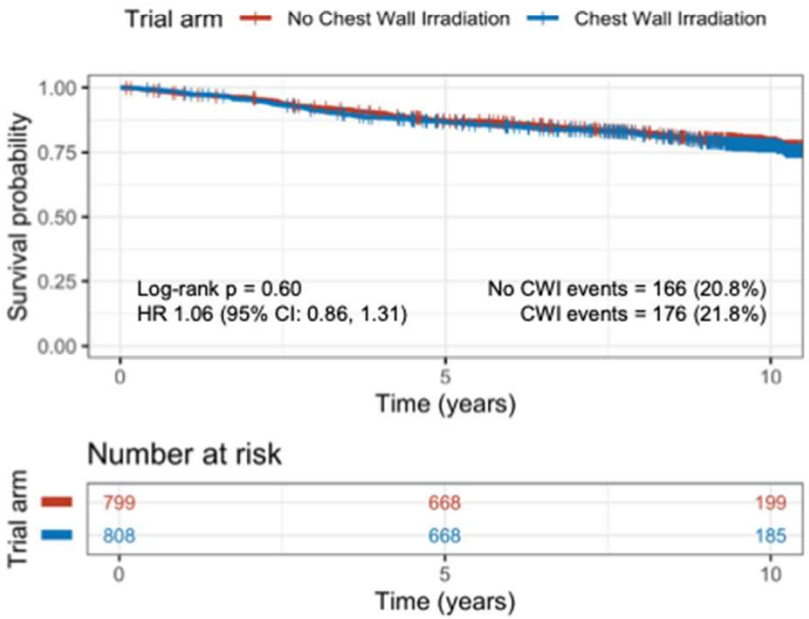
Characteristic	No Chest Wall Irradiation (N=799)	Chest Wall Irradiation (N=808)	Overall (N=1607)
Age (Median (Q1, Q3), years)	55 (48, 64)	54 (47, 64)	55 (47, 64)
Age range (years)			
<45 years	121 (15.1%)	130 (16.1%)	251 (15.6%)
45-54 years	267 (33.4%)	285 (35.3%)	552 (34.3%)
55-69 years	309 (38.7%)	283 (35.0%)	592 (36.8%)
70+ years	102 (12.8%)	110 (13.6%)	212 (13.2%)
Histological grade			
1	42 (5.3%)	58 (7.2%)	100 (6.2%)
2	329 (41.2%)	324 (40.2%)	653 (40.7%)
3	420 (52.6%)	414 (51.4%)	834 (52.0%)
Missing	8 (0.8%)	12 (1.2%)	20 (1.1%)
Number of nodes involved			
0	211 (26.4%)	191 (23.7%)	402 (25.1%)
1	312 (39.1%)	330 (41.0%)	642 (40.0%)
2	171 (21.4%)	195 (24.2%)	366 (22.8%)
3	104 (13.0%)	89 (11.1%)	193 (12.0%)
Missing	1 (0.1%)	3 (0.4%)	4 (0.2%)
Tumor size			
<21mm	239 (29.9%)	253 (31.4%)	492 (30.6%)
21-50mm	556 (69.7%)	548 (68.1%)	1104 (68.7%)
>50mm	3 (0.4%)	4 (0.5%)	7 (0.4%)
Missing	1 (0.1%)	3 (0.4%)	4 (0.2%)

Characteristic	No Chest Wall Irradiation (N=799)	Chest Wall Irradiation (N=808)	Overall (N=1607)
TN stage			
T1N1	226 (28.3%)	246 (30.4%)	472 (29.4%)
T2N0	205 (25.7%)	183 (22.6%)	388 (24.1%)
T2N1	361 (45.2%)	368 (45.5%)	729 (45.4%)
T3N0	3 (0.4%)	4 (0.5%)	7 (0.4%)
Missing	4 (0.5%)	7 (0.9%)	11 (0.7%)
HER-2 positive?			
Yes	158 (19.8%)	173 (21.4%)	331 (20.6%)
No	556 (69.6%)	554 (68.6%)	1110 (69.1%)
Missing	85 (10.6%)	81 (10.0%)	166 (10.3%)
Triple negative?			
Yes	83 (10.4%)	90 (11.1%)	173 (10.8%)
No	682 (85.4%)	692 (85.6%)	1374 (85.5%)
Missing	34 (4.2%)	26 (3.3%)	60 (3.7%)
Lymphatic/ vascular invasion?			
Yes	302 (37.8%)	316 (39.1%)	618 (38.5%)
No	477 (59.7%)	470 (58.2%)	947 (58.9%)
Missing	20 (2.5%)	22 (2.7%)	42 (2.6%)
Axillary surgery			
Sentinel node biopsy only	118 (14.8%)	115 (14.2%)	233 (14.5%)
Clearance only	349 (43.7%)	393 (48.6%)	742 (46.2%)
Sentinel or Sample + Clearance	245 (30.7%)	239 (29.6%)	484 (30.1%)
Sample only	40 (5.0%)	31 (3.8%)	71 (4.4%)
Missing	47 (5.9%)	30 (3.7%)	77 (4.8%)

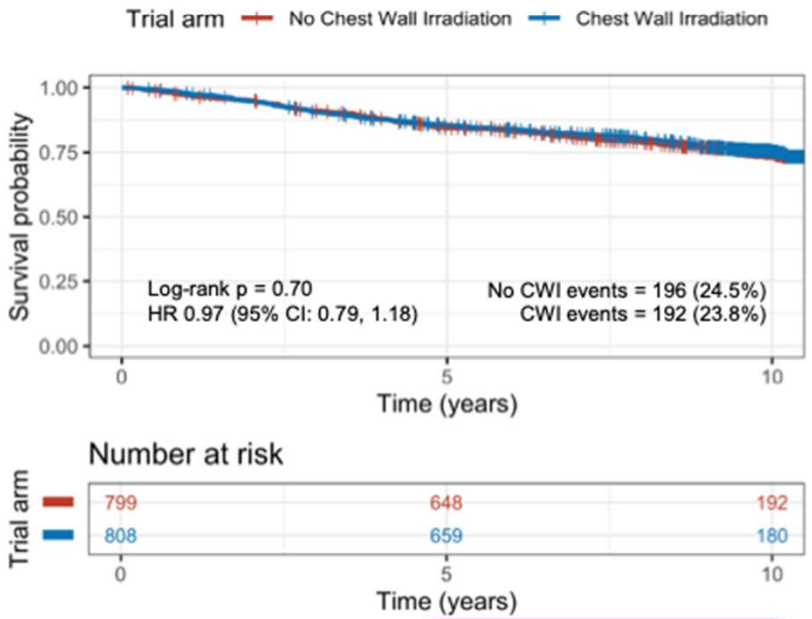
SUPREMO: Metastasis-free & Disease-free Survival

SAN ANTONIO BREAST CANCER SYMPOSIUM®
December 10-13, 2024

Kaplan-Meier Curves for ITT Population: Metastasis-free Survival by Randomized Treatment



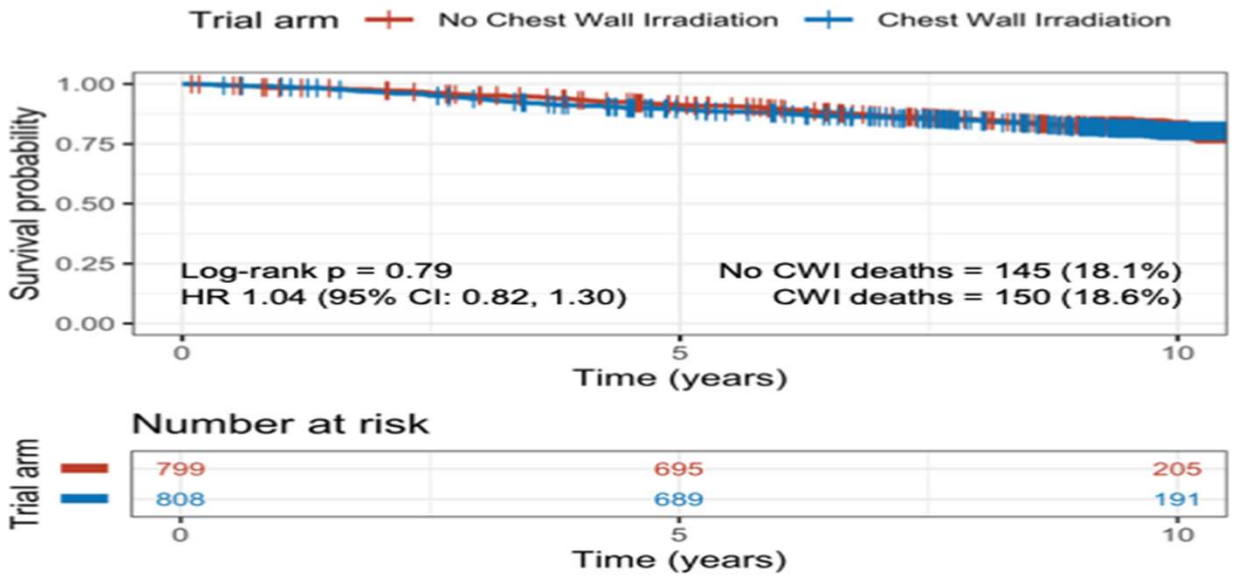
Kaplan-Meier Curves for ITT Population: Disease-free Survival by Randomized Treatment



MRC Medical Research Council

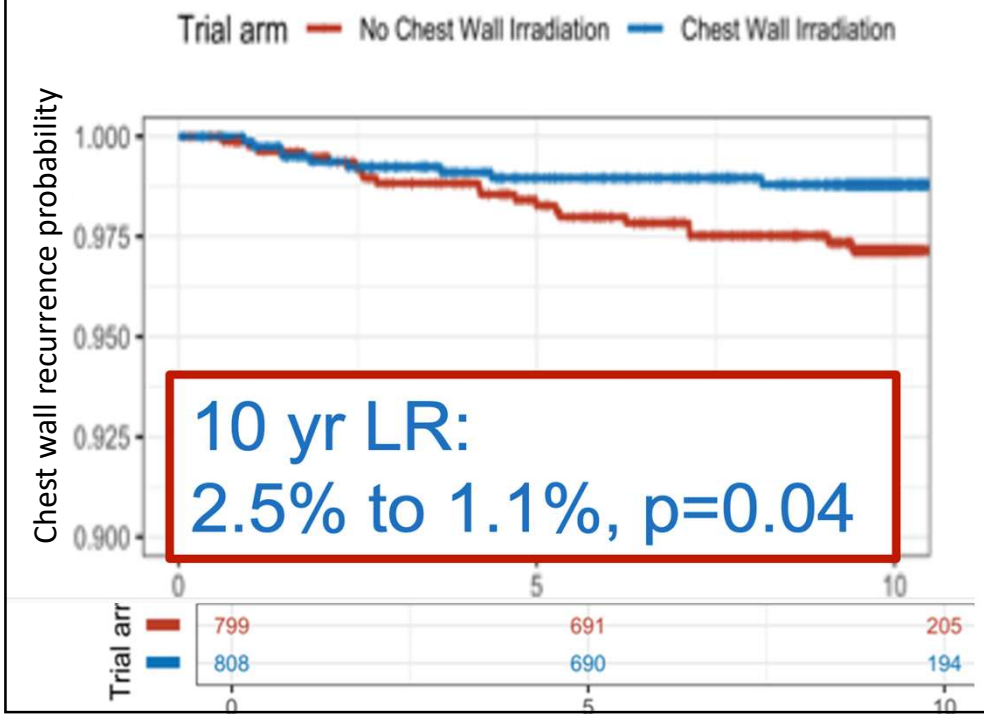
SUPREMO: Overall Survival

Kaplan-Meier Curves for ITT Population: Overall Survival by Randomized Treatment

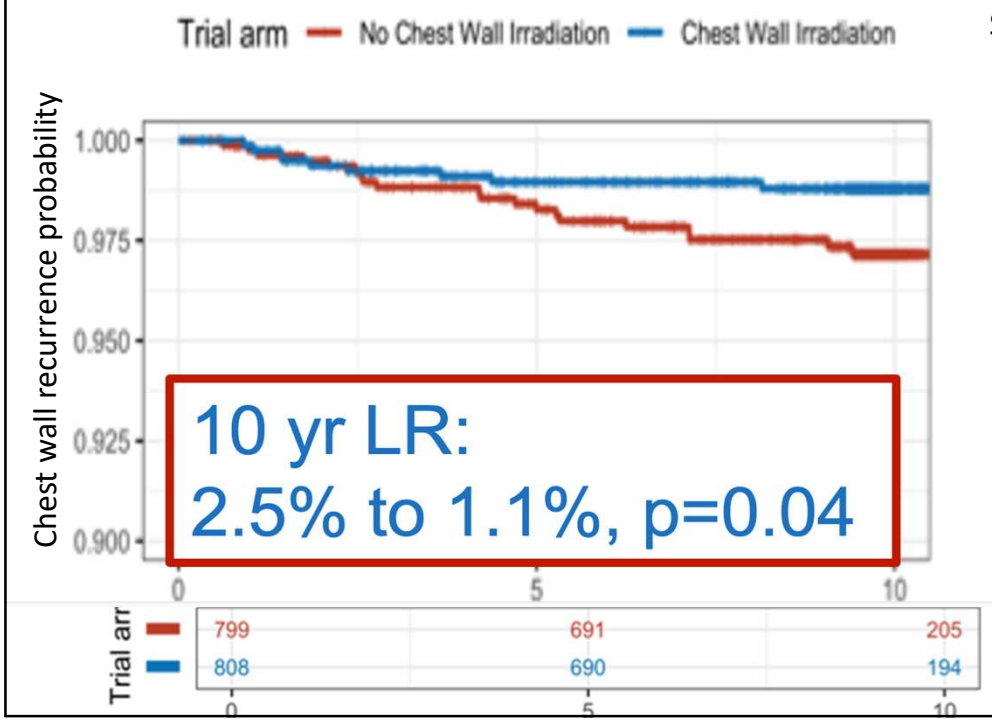


No significant differences in OS by nodal status (pN0 vs. pN+)

SUPREMO: Chest Wall Recurrences 10 yrs



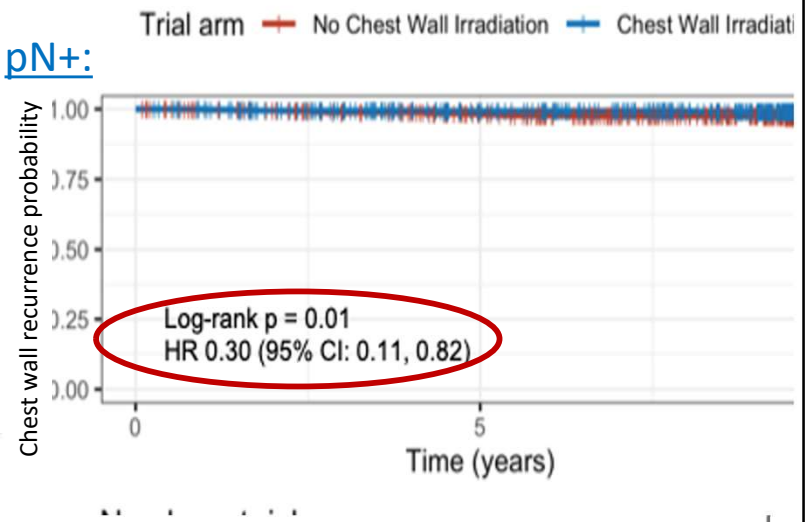
SUPREMO: Chest Wall Recurrences 10 yrs



Subset analysis by nodal involvement (pN0 vs. pN1)

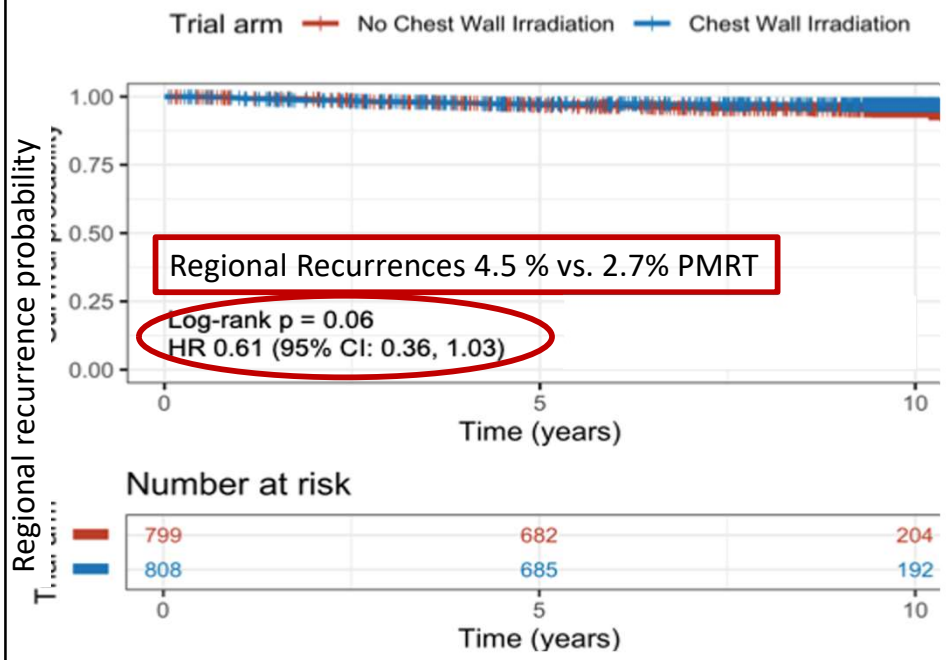
pN0: Log-rank p = 0.90
HR 1.13 (95% CI: 0.28, 4.54)

pN+:



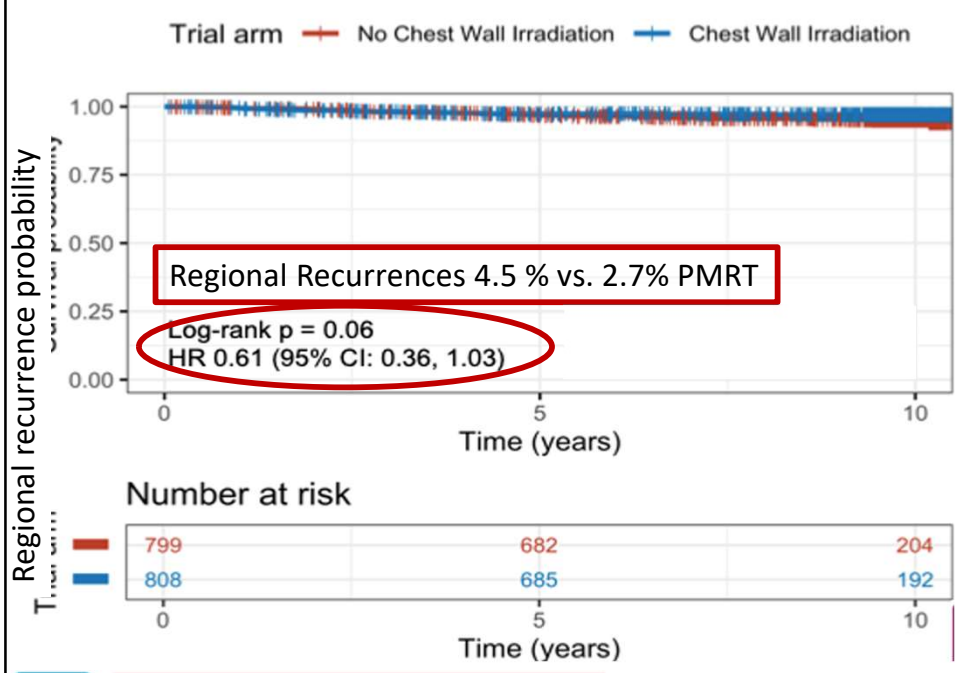
SUPREMO: Regional Recurrences 10 yrs

Kaplan-Meier Curves: Regional Recurrences by ITT



SUPREMO: Regional Recurrences 10 yrs

Kaplan-Meier Curves: Regional Recurrences by ITT

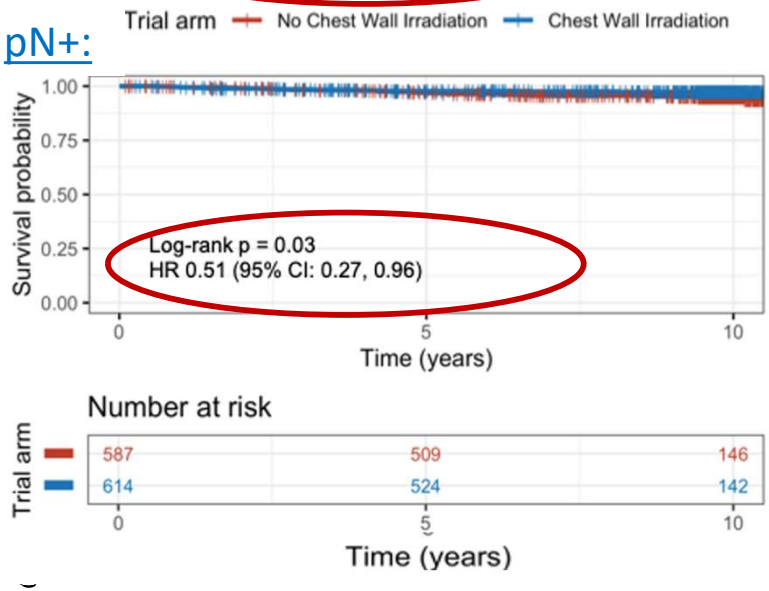


Subset analysis by nodal involvement (pN0 vs. pN1)

pN0:

Log-rank p = 1.0
HR 1.00 (95% CI: 0.36, 2.77)

pN+:



NCCN **2025 Breast Cancer Congress**
with Updates from the 2024 SABCS

Take Home Points: SUPREMO Abstract

- Important trial suggesting PMRT may not be required for high-risk N0 patients & **all** 1-3+ nodes pts when using contemporary systemic tx
- Identification criteria for selecting omission of PMRT needs further refining (awaiting trial publication)

Take Home Points: SUPREMO Abstract

- Important trial suggesting PMRT may not be required for high-risk N0 patients & **all** 1-3+ nodes pts when using contemporary systemic tx
- Identification criteria for selecting omission of PMRT needs further refining (awaiting trial publication)
- Current practices of LR 'de-escalation' strategies have ↓ Ax surgery
  - pN(1 or 2 + nodes) by SLNB are having omission of ALND
  - Axillary RT replacing the more morbid axillary surgery
  - pN+ pts on SUPREMO had ALND (no RT-axilla permitted)

Take Home Points: SUPREMO Abstract

- Important trial suggesting PMRT may not be required for high-risk N0 patients & **all** 1-3+ nodes pts when using contemporary systemic tx
- Identification criteria for selecting omission of PMRT needs further refining (awaiting trial publication)
- Current practices of LR 'de-escalation' strategies have ↓ Ax surgery
  - pN(1 or 2 + nodes) by SLNB are having omission of ALND
  - Axillary RT replacing the more morbid axillary surgery
  - pN+ pts on SUPREMO had ALND (no RT-axilla permitted)
- Likely will require a more nuanced approach taking into consideration multiple factors (to identify possible long-term benefit in certain subsets)

Take Home Points: SUPREMO Abstract

- Important trial suggesting PMRT may not be required for high-risk N0 patients & **all** 1-3+ nodes pts when using contemporary systemic tx
- Identification criteria for selecting omission of PMRT needs further refining (awaiting trial publication)
- Current practices of LR 'de-escalation' strategies have ↓ Ax surgery
  - pN(1 or 2 + nodes) by SLNB are having omission of ALND
  - Axillary RT replacing the more morbid axillary surgery
  - pN+ pts on SUPREMO had ALND (no RT-axilla permitted)
- Likely will require a more nuanced approach taking into consideration multiple factors (to identify possible long-term benefit in certain subsets)
  - Absolute number of +nodes
    - (1 vs. 2 vs. 3 instead of 1-3)
  - Patient age
  - Expected longevity / co-morbidities
  - Functional status
  - Other clinical/ pathologic/ biologic factors

Take Home Points: SUPREMO Abstract

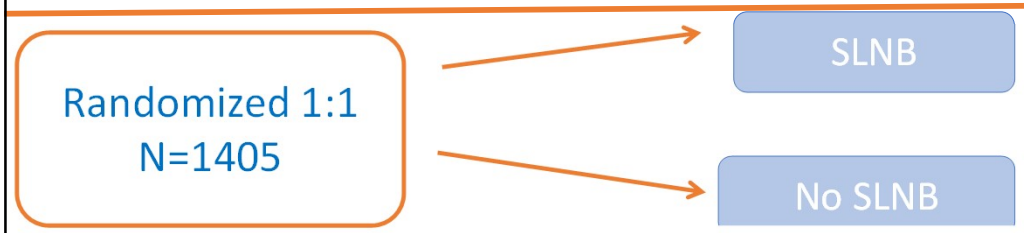
- Important trial suggesting PMRT may not be required for high-risk N0 patients & **all** 1-3+ nodes pts when using contemporary systemic tx
- Identification criteria for selecting omission of PMRT needs further refining (awaiting trial publication)
- Current practices of LR 'de-escalation' strategies have ↓ Ax surgery
  - pN(1 or 2 + nodes) by SLNB are having omission of ALND
  - Axillary RT replacing the more morbid axillary surgery
  - pN+ pts on SUPREMO had ALND (no RT-axilla permitted)
- Likely will require a more nuanced approach taking into consideration multiple factors (to identify possible long-term benefit in certain subsets)
- Additional ongoing trials may also shed some light on this 'intermediate-risk' population
  - South Korean PORT N-1 (NCT 05440149) N1 patients → PMRT vs. ⌀ PMRT
  - Canadian TAILOR RT (NCT 03488693) incorporates T1/T2/N1, Oncotype RS <25 →PMRT vs. ⌀ PMRT

- Absolute number of +nodes
  - (1 vs. 2 vs. 3 instead of 1-3)
- Patient age
- Expected longevity / co-morbidities
- Functional status
- Other clinical/ pathologic/ biologic factors

SABC 2024 Abstract 3:

Axillary Surgery De-escalation: Do all patients need SNLB?

SOUND Trial: SLNB or Ultrasound of Axilla



Eligibility:
T≤5cm
cN0
Negative ax US
Age ≥18
Intending adj RT

1° Endpoint:
Distant DFS

ni OD, et al JAMA Onc 2023

SOUND Trial: SLNB or Ultrasound of Axilla

Randomized 1:1
N=1405

SLNB

No SLNB

Eligibility:
T≤5cm
cN0
Negative ax US
Age ≥18
Intending adj RT
1° Endpoint:
Distant DFS

Characteristics:

- All arms well balanced
- Adjuvant RT (>98%)
- 6% <40 y.o.; <20% pre-meno
- Median Tumor size=1.1cm
- 88% ER(+) Her2(-)
  ~5% TNBC
- <20% GIII
- >90% got endocrine tx
- Chemo: 20% SLNB vs 17.5% ØSLNB

Characteristic	Patients, No. (%) SLNB (n = 708)	No axillary surgery (n = 697)
Age at surgery, y		
<40	10 (1.4)	10 (1.4)
40-49	114 (16.1)	128 (18.4)
50-64	324 (45.8)	298 (42.8)
≥65	260 (36.7)	261 (37.4)
Median (IQR)	60 (52-68)	60 (51-68)
pT1mic or pT1a	71 (10.0)	61 (8.8)
pT1b	251 (35.5)	240 (34.4)
pT1c	355 (50.1)	361 (51.8)
pT2	31 (4.4)	35 (5.0)
Median (IQR), cm	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Grade[b]		
1	194 (27.7)	204 (29.9)
2	377 (53.8)	356 (52.2)
3	130 (18.5)	122 (17.9)

Gentilini OD, et al JAMA Onc 2023

SOUND trial (JAMA Oncol 2023)

Results: Median f/u: 5.7 yrs

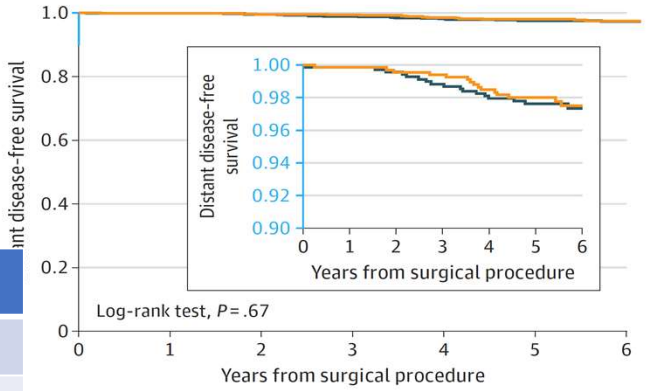
- 13.7% pN+ on SLNB arm

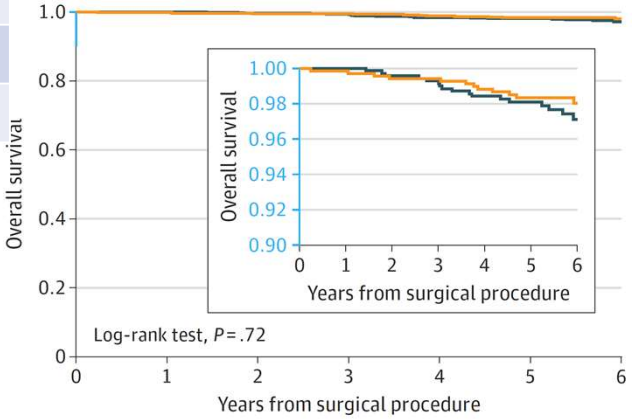
No differences:

- Local relapse
- Axillary relapse
- Distant disease
- DFS
- BCSS
- OS

6 yr Outcomes	SLNB	⌀SLNB
Local Relapse	1%	<1%
Axillary Rec	0.4%	0.7%
Distant Mets	1.8%	2%
BCSS	100%	100%

- For post-menopausal, ER+, T1 breast cancers, a pre-op axUS can safely replace SLNB for those not needing pathologic information for tx decisions





Gentilini OD, et al JAMA Onc 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE[a]: BREAST-CONSERVING SURGERY (BCS) + WHOLE BREAST RT

SURGERY: BCS[i,j] ± surgical axillary staging (category 1)[k,l,m] ± oncoplastic reconstruction[n]

ADJUVANT SYSTEMIC THERAPY: See BINV-4 to determine whether adjuvant systemic therapy is indicated. RT is typically given after systemic therapy. See BINV-I for sequencing of systemic therapy and RT.

NODAL STATUS / RT:

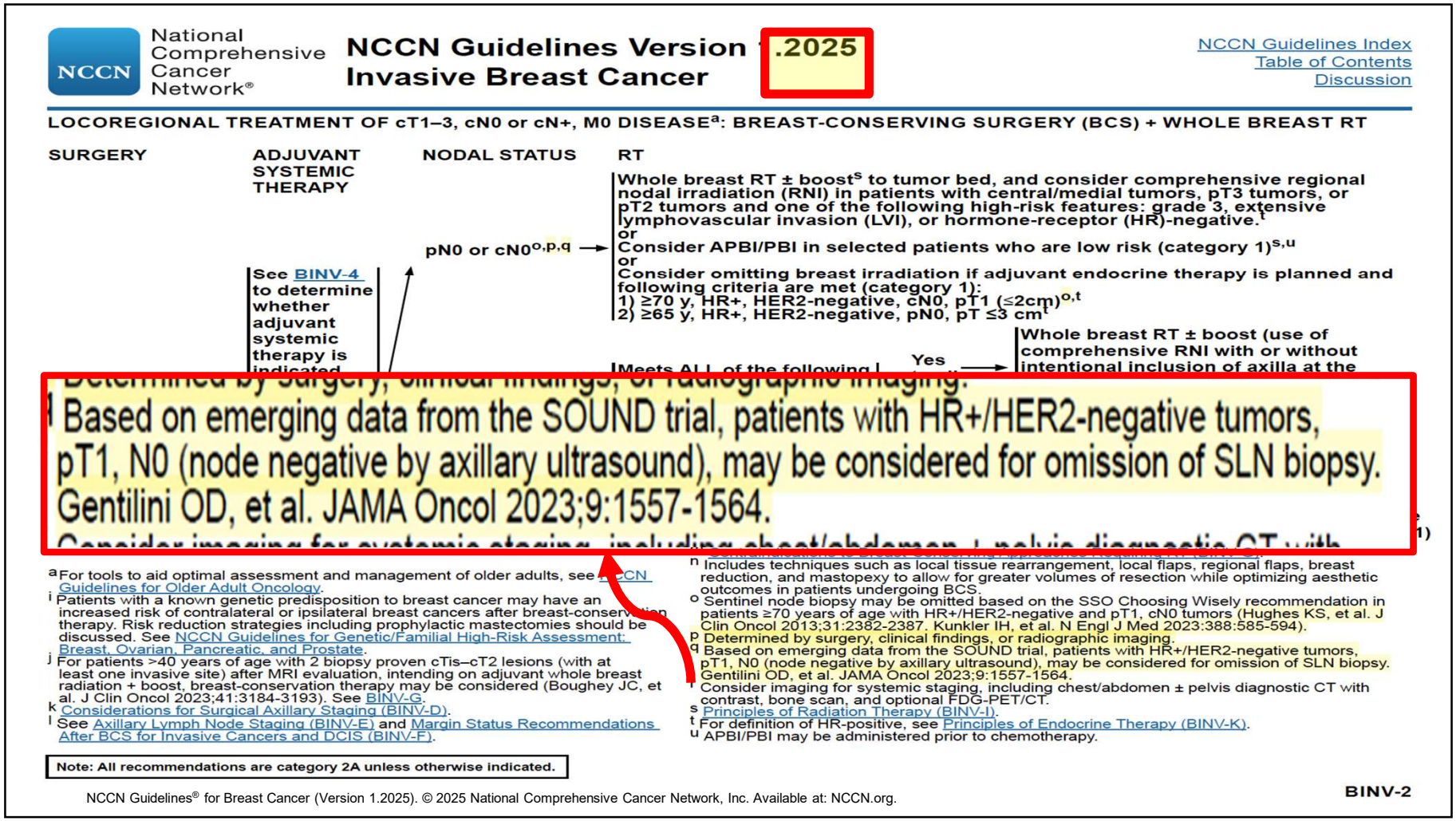
- **pN0 or cN0[o,p,q]** → Whole breast RT ± boost[s] to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors and one of the following high-risk features: grade 3, extensive lymphovascular invasion (LVI), or hormone-receptor (HR)-negative.[t]
  or
  Consider APBI/PBI in selected patients who are low risk (category 1)[s,u]
  or
  Consider omitting breast irradiation if adjuvant endocrine therapy is planned and following criteria are met (category 1):
  1) ≥70 y, HR+, HER2-negative, cN0, pT1 (≤2cm)[o,t]
  2) ≥65 y, HR+, HER2-negative, pN0, pT ≤3 cm[t]
- **pN1a (1–3 positive axillary nodes)** → Meets ALL of the following criteria:
  - cT1–T3, cN0
  - No preoperative chemotherapy
  - 1–2 positive sentinel lymph nodes (SLNs)
  - Whole breast RT planned

  Yes to all → Whole breast RT ± boost (use of comprehensive RNI with or without intentional inclusion of axilla at the discretion of the radiation oncologist) (category 1)

  No → Whole breast RT with inclusion of any portion of the undissected axilla at risk ± boost[s] to tumor bed (category 1). Strongly consider comprehensive RNI.
- **pN2–3[r] (≥4 positive axillary nodes)** → Whole breast RT ± boost[s] to tumor bed (category 1) + comprehensive RNI, including any portion of the undissected axilla at risk (category 1)

[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[i] Patients with a known genetic predisposition to breast cancer may have an increased risk of contralateral or ipsilateral breast cancers after breast-conservation therapy. Risk reduction strategies including prophylactic mastectomies should be discussed. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[j] For patients >40 years of age with 2 biopsy proven cTis–cT2 lesions (with at least one invasive site) after MRI evaluation, intending on adjuvant whole breast radiation + boost, breast-conservation therapy may be considered (Boughey JC, et al. J Clin Oncol 2023;41:3184-3193). See BINV-G.
[k] Considerations for Surgical Axillary Staging (BINV-D).
[l] See Axillary Lymph Node Staging (BINV-E) and Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).
[m] Contraindications to Breast-Conserving Approaches Requiring RT (BINV-G).
[n] Includes techniques such as local tissue rearrangement, local flaps, regional flaps, breast reduction, and mastopexy to allow for greater volumes of resection while optimizing aesthetic outcomes in patients undergoing BCS.
[o] Sentinel node biopsy may be omitted based on the SSO Choosing Wisely recommendation in patients ≥70 years of age with HR+/HER2-negative and pT1, cN0 tumors (Hughes KS, et al. J Clin Oncol 2013;31:2382-2387. Kunkler IH, et al. N Engl J Med 2023:388:585-594).
[p] Determined by surgery, clinical findings, or radiographic imaging.
[q] Based on emerging data from the SOUND trial, patients with HR+/HER2-negative tumors, pT1, N0 (node negative by axillary ultrasound), may be considered for omission of SLN biopsy. Gentilini OD, et al. JAMA Oncol 2023;9:1557-1564.
[r] Consider imaging for systemic staging, including chest/abdomen ± pelvis diagnostic CT with contrast, bone scan, and optional FDG-PET/CT.
[s] Principles of Radiation Therapy (BINV-I).
[t] For definition of HR-positive, see Principles of Endocrine Therapy (BINV-K).
[u] APBI/PBI may be administered prior to chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE[a]: BREAST-CONSERVING SURGERY (BCS) + WHOLE BREAST RT

SURGERY

ADJUVANT SYSTEMIC THERAPY

See BINV-4 to determine whether adjuvant systemic therapy is indicated

NODAL STATUS

pN0 or cN0[o,p,q] →

RT

Whole breast RT ± boost[s] to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors and one of the following high-risk features: grade 3, extensive lymphovascular invasion (LVI), or hormone-receptor (HR)-negative.[t]
or
Consider APBI/PBI in selected patients who are low risk (category 1)[s,u]
or
Consider omitting breast irradiation if adjuvant endocrine therapy is planned and following criteria are met (category 1):
1) ≥70 y, HR+, HER2-negative, cN0, pT1 (≤2cm)[o,t]
2) ≥65 y, HR+, HER2-negative, pN0, pT ≤3 cm[t]

Meets ALL of the following [illegible] → Yes →

Whole breast RT ± boost (use of comprehensive RNI with or without intentional inclusion of axilla at the

Determined by surgery, clinical findings, or radiographic imaging.

Based on emerging data from the SOUND trial, patients with HR+/HER2-negative tumors, pT1, N0 (node negative by axillary ultrasound), may be considered for omission of SLN biopsy. Gentilini OD, et al. JAMA Oncol 2023;9:1557-1564.

Consider imaging for systemic staging, including chest/abdomen ± pelvis diagnostic CT with

[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[i] Patients with a known genetic predisposition to breast cancer may have an increased risk of contralateral or ipsilateral breast cancers after breast-conservation therapy. Risk reduction strategies including prophylactic mastectomies should be discussed. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[j] For patients >40 years of age with 2 biopsy proven cTis–cT2 lesions (with at least one invasive site) after MRI evaluation, intending on adjuvant whole breast radiation + boost, breast-conservation therapy may be considered (Boughey JC, et al. J Clin Oncol 2023;41:3184-3193). See BINV-G.
[k] Considerations for Surgical Axillary Staging (BINV-D).
[l] See Axillary Lymph Node Staging (BINV-E) and Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).
[n] Includes techniques such as local tissue rearrangement, local flaps, regional flaps, breast reduction, and mastopexy to allow for greater volumes of resection while optimizing aesthetic outcomes in patients undergoing BCS.
[o] Sentinel node biopsy may be omitted based on the SSO Choosing Wisely recommendation in patients ≥70 years of age with HR+/HER2-negative and pT1, cN0 tumors (Hughes KS, et al. J Clin Oncol 2013;31:2382-2387. Kunkler IH, et al. N Engl J Med 2023:388:585-594).
[p] Determined by surgery, clinical findings, or radiographic imaging.
[q] Based on emerging data from the SOUND trial, patients with HR+/HER2-negative tumors, pT1, N0 (node negative by axillary ultrasound), may be considered for omission of SLN biopsy. Gentilini OD, et al. JAMA Oncol 2023;9:1557-1564.
[r] Consider imaging for systemic staging, including chest/abdomen ± pelvis diagnostic CT with contrast, bone scan, and optional FDG-PET/CT.
[s] Principles of Radiation Therapy (BINV-I).
[t] For definition of HR-positive, see Principles of Endocrine Therapy (BINV-K).
[u] APBI/PBI may be administered prior to chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.

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

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

on behalf of the INSEMA investigators

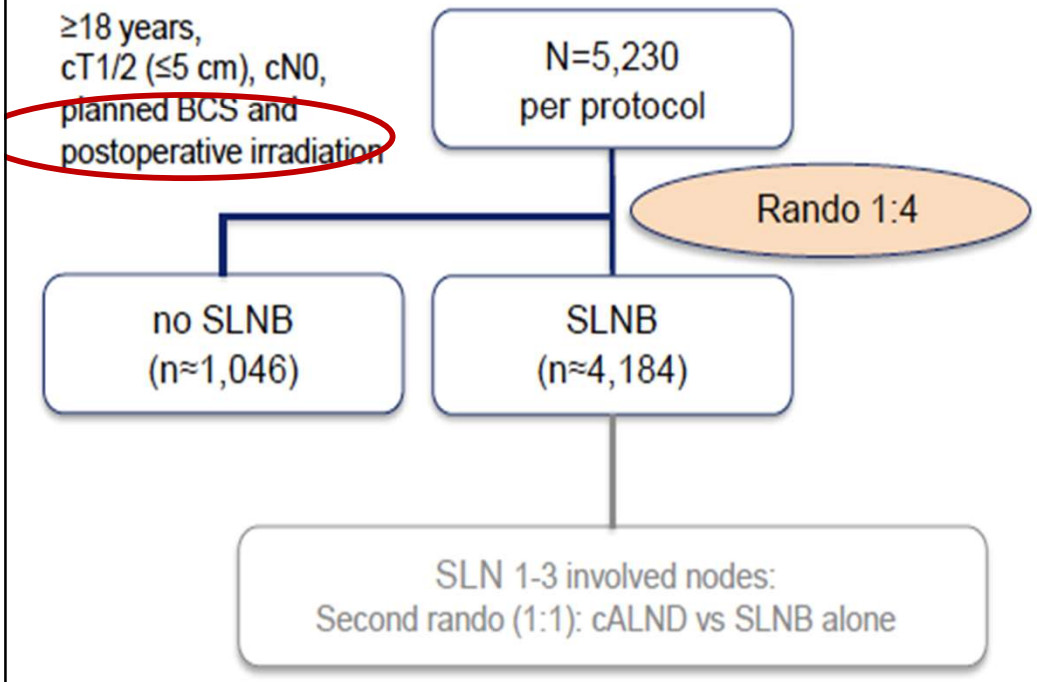
1 Department of Obstetrics and Gynecology, University of Rostock, Germany; 2 Department of Obstetrics and Gynecology, University Hospital Ulm, Germany; 3 The Filderhospital, Filderstadt-Bonlanden, Germany; 4 Breast Center of St. Elisabeth Hospital, Heidelberg, Germany; 5 Department of Gynecology and Obstetrics, University of Heidelberg, Germany; 6 Evang. Waldkrankenhaus Spandau, Germany; 7 Faculty of Medicine Mannheim, University Heidelberg, Department of Obstetrics and Gynecology Mannheim, Germany; 8 Department of Obstetrics and Gynecology, Hanau City Hospital GmbH, Hanau, Germany; 9 Department of Radiotherapy, University Medicine Rostock, Germany; 10 Department of Radiotherapy and Radiation Oncology, University Hospital Hamburg-Eppendorf (UKE), Germany; 11 KEM, Evangelical Clinics Essen Centre, Essen, 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), Marburg, Germany; 15 Breast Center St. Gallen, Kantonsspital St. Gallen, Switzerland; 16 SRH Wald-Klinikum Gera GmbH, Germany; 17 Agaplesion Markus Hospital, Frankfurt am Main, Germany; 18 German Breast Group, Neu-Isenburg, Germany; 19 Tumor and Breast Center Eastern Switzerland, St. Gallen, Switzerland; 20 Austrian Breast and Colorectal Cancer Study Group (ABCSG), Vienna, Austria.

Universität Rostock Traditio et Innovatio

Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.

GBG GERMAN BREAST GROUP

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)

INSEMA: Radiation Protocol Details

- All patients underwent BCS with the intention to treat with adjuvant RT
- Adjuvant RT had to be whole breast RT
- No APBI allowed
- Whole breast technique: 3D-conformal or IMRT
- The axilla was not specifically targeted
- The use of 'high-tangents' or regional nodal RT not permitted
- A boost was generally recommended (but at MD discretion if very low risk)
- Quality control: First 3 cases from each center were centrally reviewed
- Dosimetric data collected as part of medical record (not reported)

Reimer T, et al. New England Journal Med 2024

San Antonio Breast Cancer Symposium®, December 10-13, 2024

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)

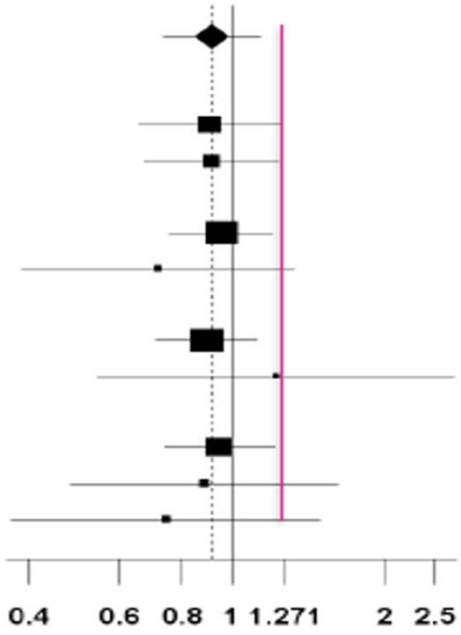
Primary Endpoint Events (N=525)

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)

San Antonio Breast Cancer Symposium®, December 10-13, 2024

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	

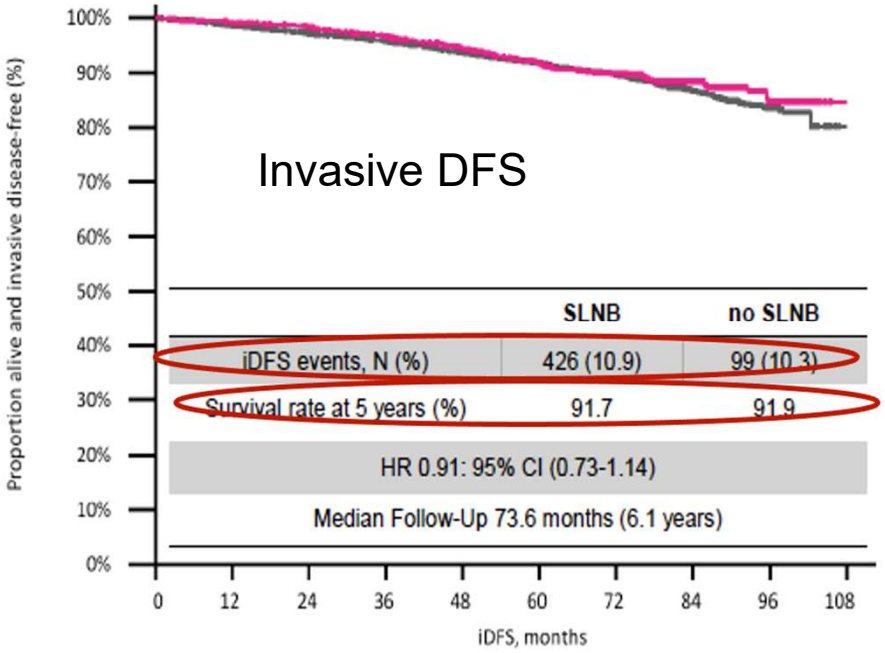


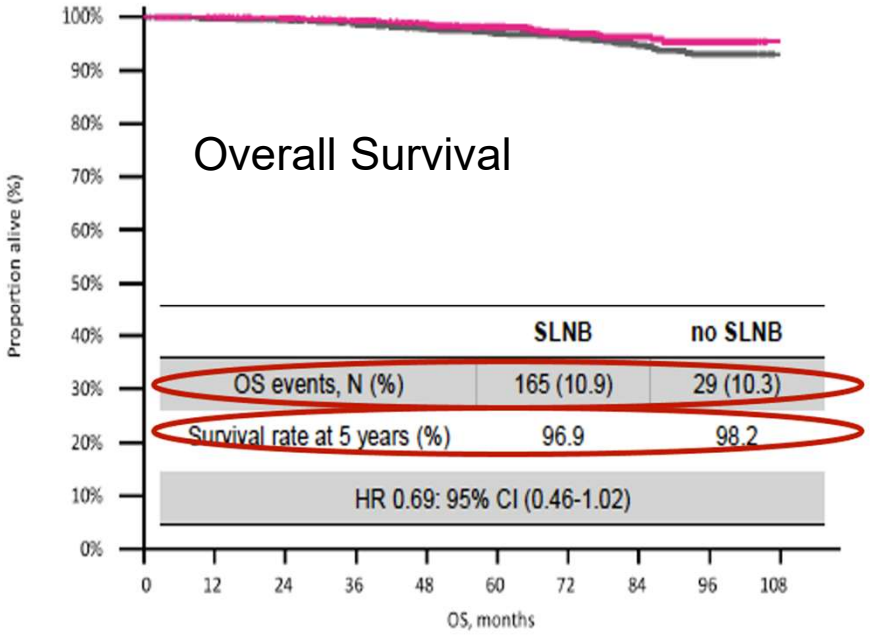
Universität Rostock Traditio et Innovatio

GBG GERMAN BREAST GROUP

iDFS and OS Outcomes Median 6.1 yrs

Median F/u: 6.1 years
Invasive DFS and OS were both non-inferior





NCCN **2025 Breast Cancer Congress**
with Updates from the 2024 SABCS

Reimer T, et al. New England Journal Med 2024

INSEMA: Patient-reported Outcomes

- PROs were measured primarily using the EORTC QLQ-C30 & QLQ-BR23 questionnaires for all pts on the INSEMA trial
- Data collected at baseline assessment (pre-surgery) then 6, 12, and 18 mo postoperatively
- Results: No differences in general health status (GHS/QoL) scores @ 18 months
- Specific arm symptoms worse after SLNB vs. no SLNB
- Breast symptoms significantly worse in both cohort after surgery, but a gradual recovery was observed in the no-SLNB group between 12 to 18 months & SLNB group did not show same level of recovery
- The mean pain scores in the arm/shoulder higher in the SLNB group
  - Most pronounced difference @ 1 mo. (mean scores of 23.6 SLNB vs. 12.6 no-SLNB).
- Persistent differences were observed for arm swelling and impaired mobility at all time points for SLNB vs. no-SLNB

Reimer T, et al. eClinicalMedicine. 2023

INSEMA: Take Home Points

- Significantly larger cohort with similar pt characteristics to SOUND:
  - Age >50
  - Tumors <2cm
  - GI or GII
  - Clinically N0 and by ax US
  - HR+
- Supports omission of SLNB in this cohort
- Suggests excellent outcomes, though whole breast RT is delivered
- These trials will have additional implications for radiation oncology:
  - How does this affect who is eligible for omission of RT?
  - Overlapping eligibility for omission of RT vs. omission of SLNB
  - RT fields to deliver (i.e. intentional coverage of axilla)
  - Analysis of what was actually treated relative to protocol requirements
- Will likely further refine LR treatment considerations for this cohort

National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

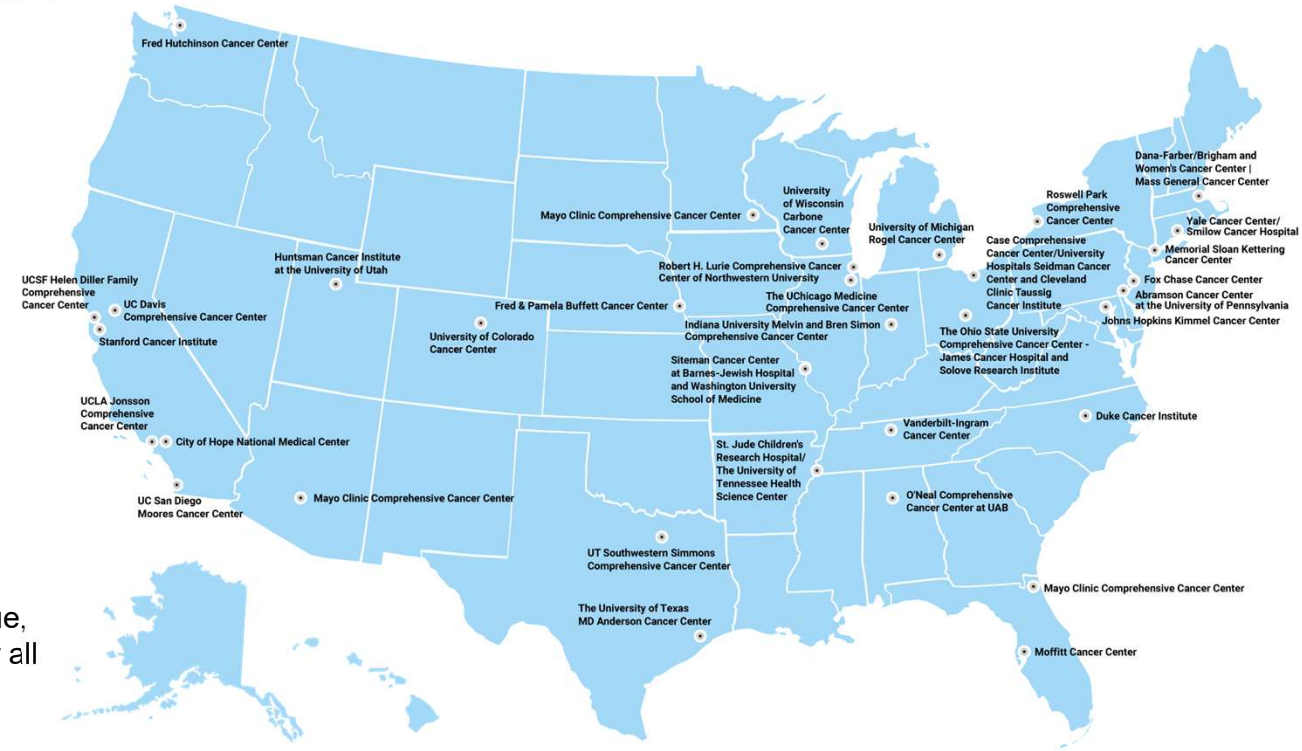
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

Our Vision

Access to high-quality, high-value, patient-centered cancer care for all people globally



NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal