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Conflicts of interest

Advisory role: Novartis, Pfizer, Eli Lilly, Daiichi Sankyo

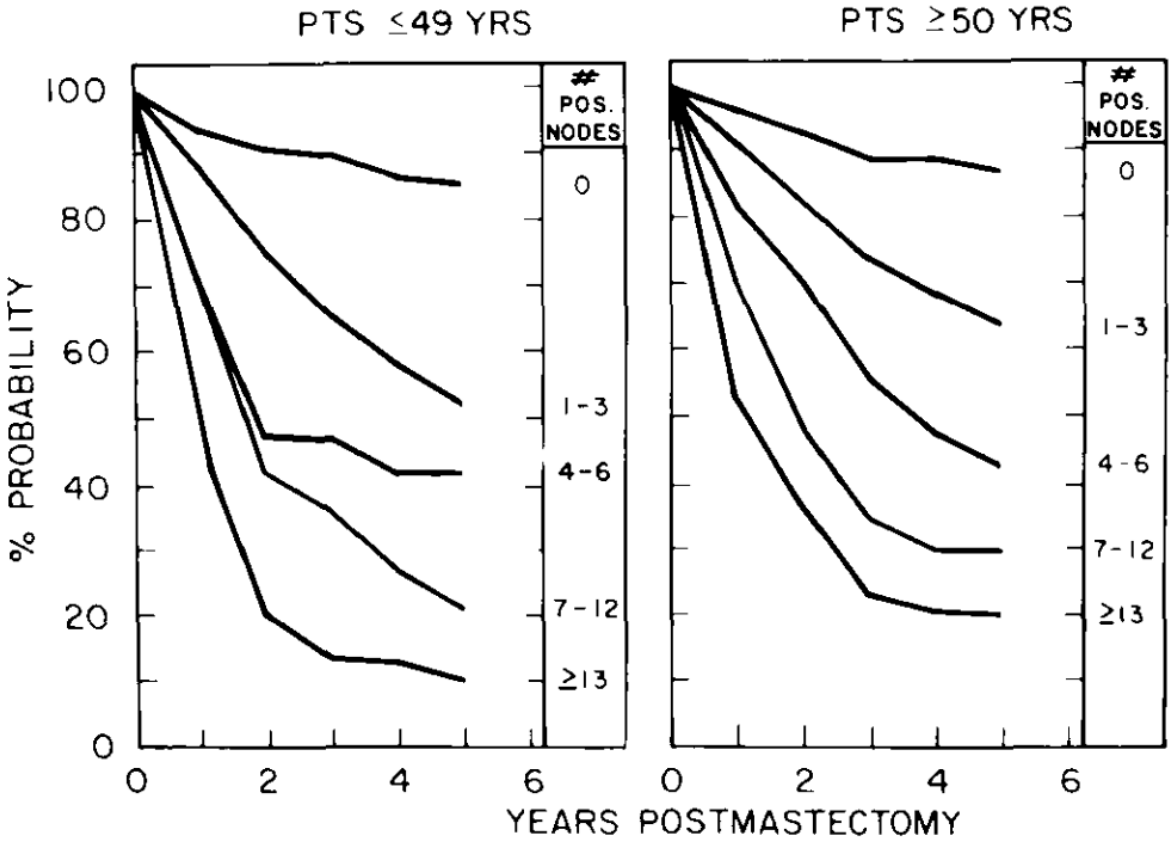
Honoraria as a speaker: Novartis, Pfizer, Istituto Gentili

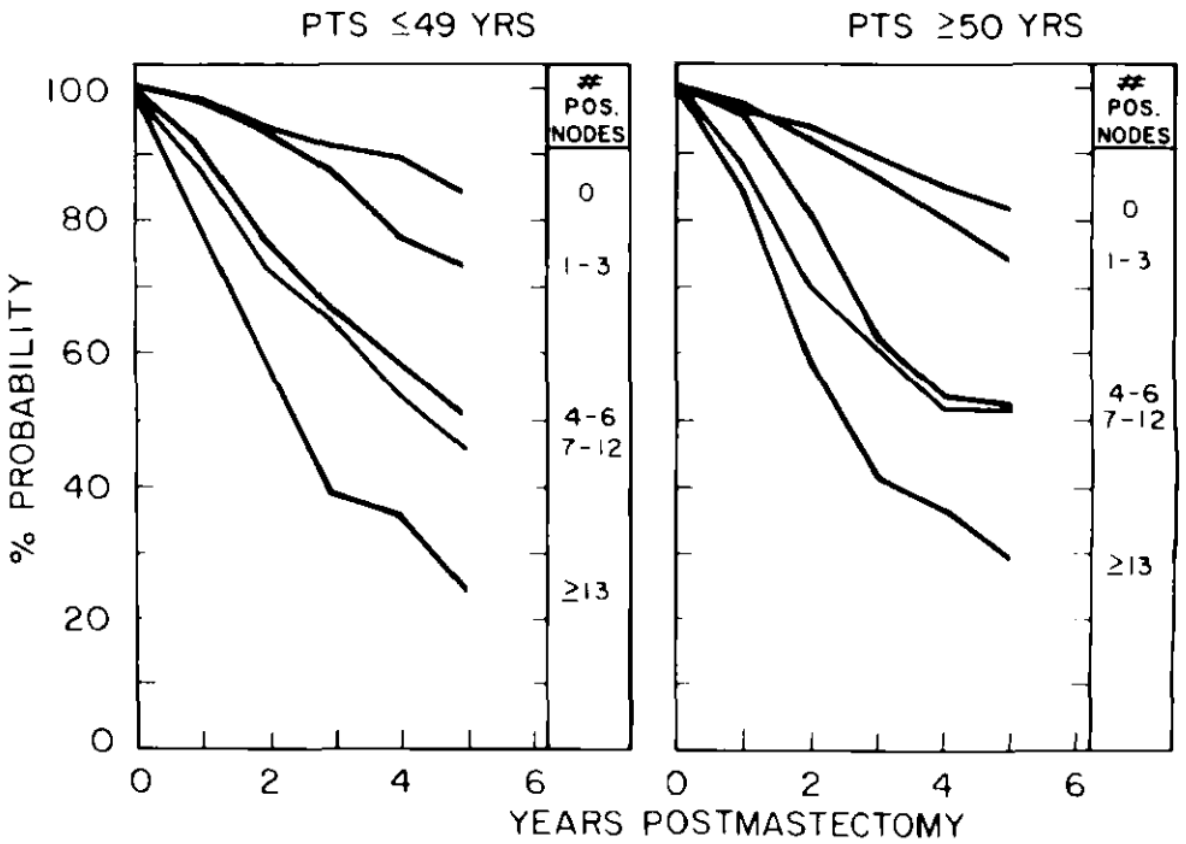
Research grants: Roche

When and how SNB vs. ALND could affect therapeutic decisions in patients with surgically resected, sentinel node(s)-positive breast cancer in 2023

From 2023 back to 1983

Lymph node involvement is the most impactful prognostic factor in surgically resected BC patients

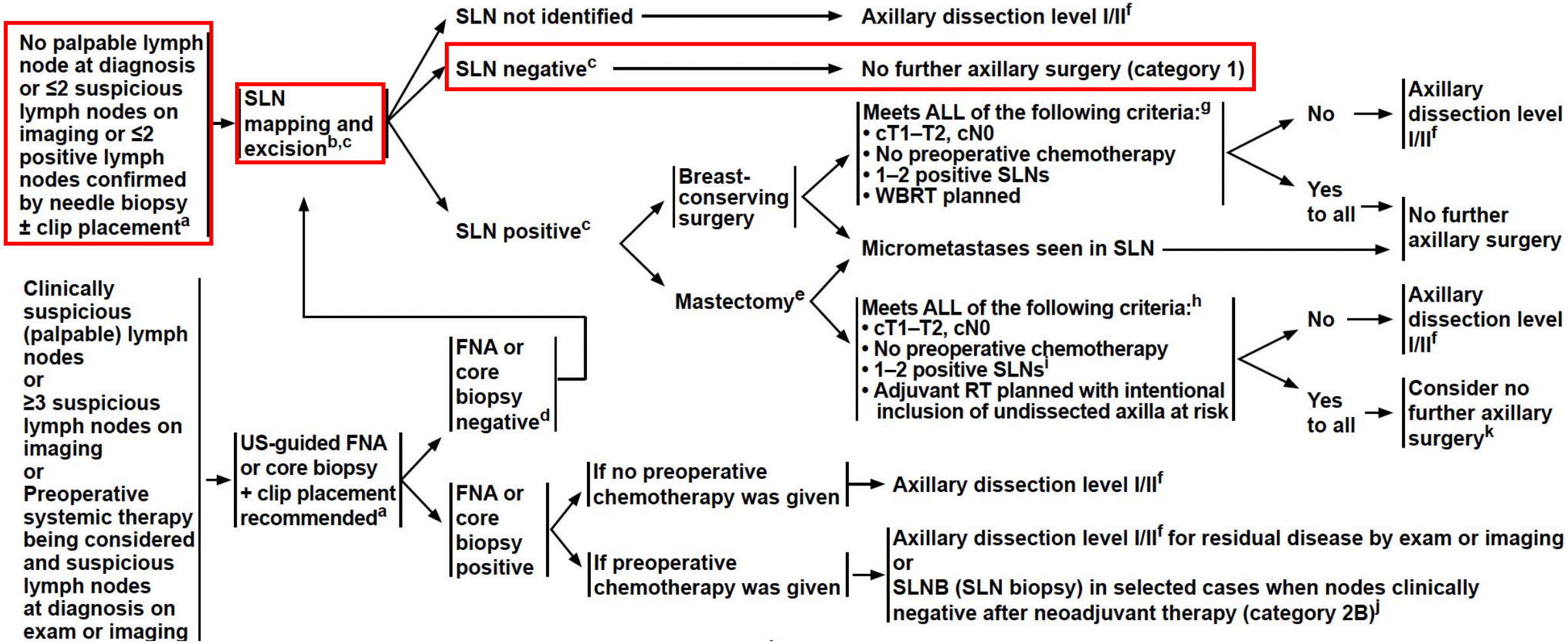




Fisher B et al. Cancer 1983

NCCN Guidelines Version 4.2023
Invasive Breast Cancer

CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



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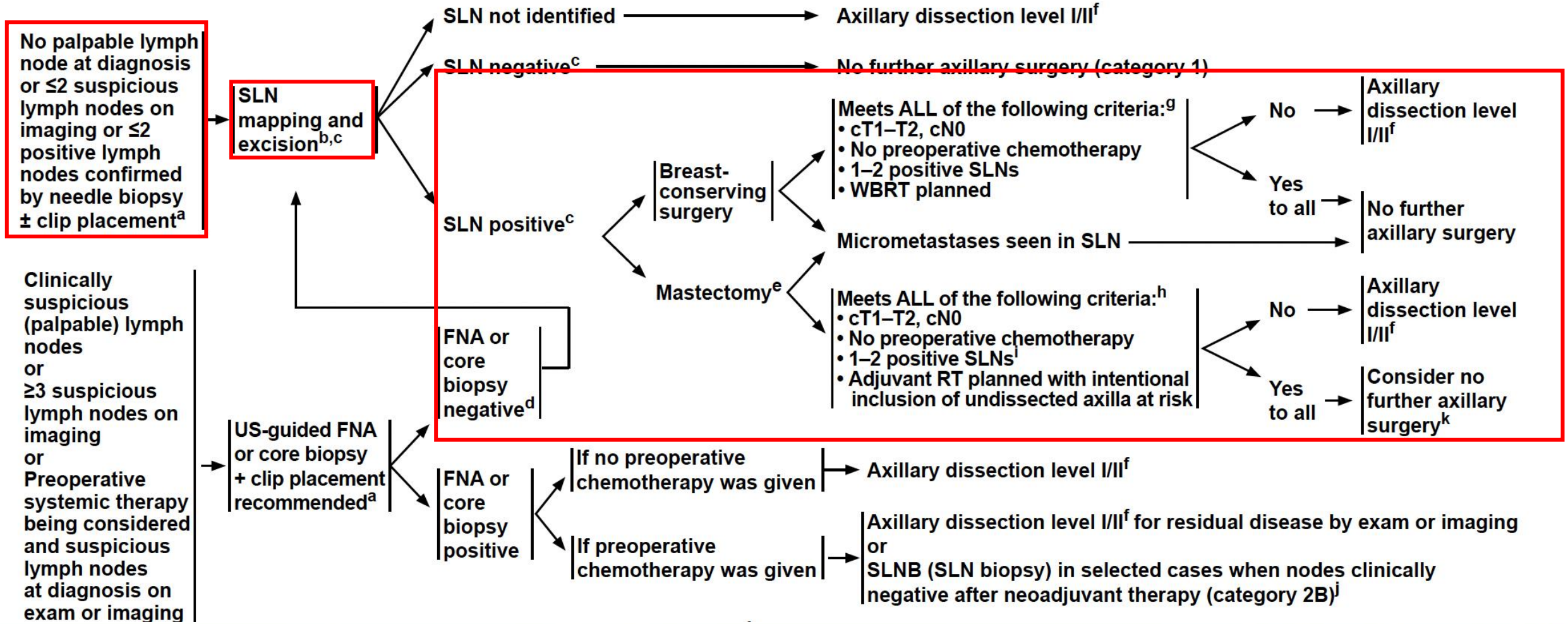


Recommendations:

- SLNB, rather than full nodal clearance, is the standard of care for axillary staging in early, clinically node-negative breast cancer [II, A].
- Further axillary surgery following positive SLNB is not required in case of low axillary disease burden (micrometastases or 1–2 SLNs containing metastases, treated with post-operative tangential breast RT) [II, A].
- Axillary radiation is a valid alternative in patients with positive SLNB, irrespective of the type of breast surgery [II, A].

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1194–1220, 2019
doi:10.1093/annonc/mdz173
Published online 4 June 2019

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6,7], I. T. Rubio[8], S. Zackrisson[9] & E. Senkus[10], on behalf of the ESMO Guidelines Committee*

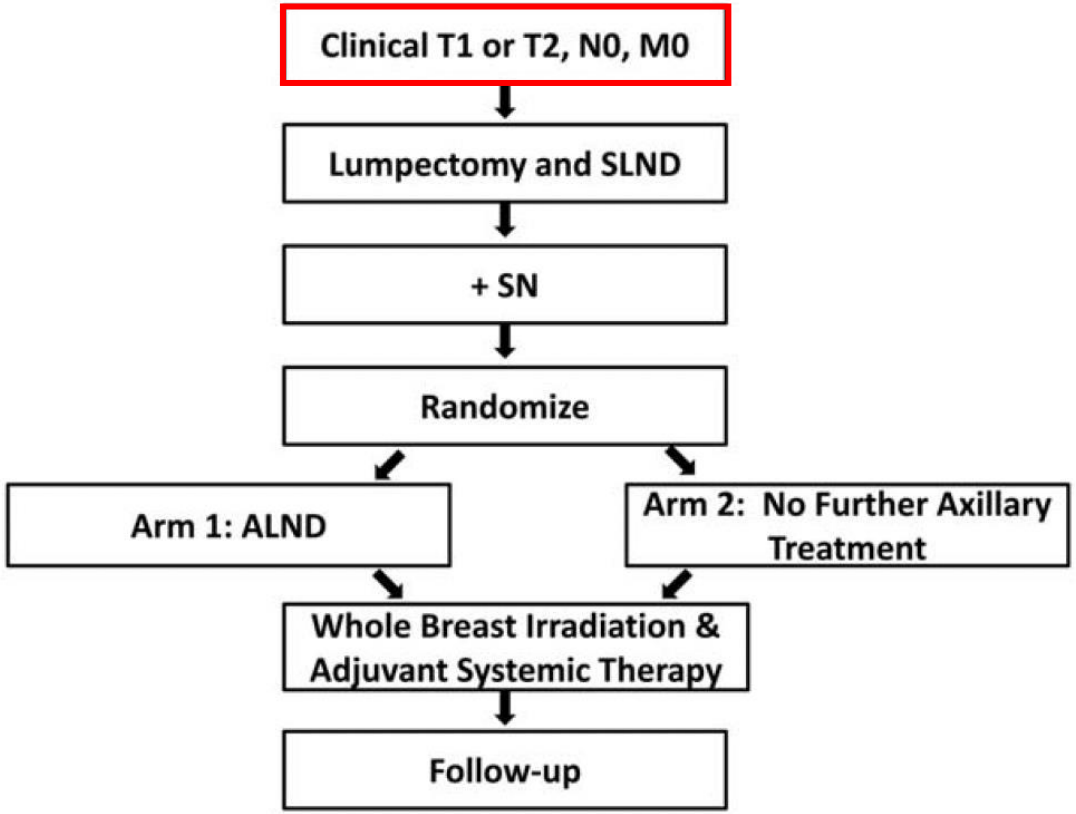
LOCAL-REGIONAL THERAPY

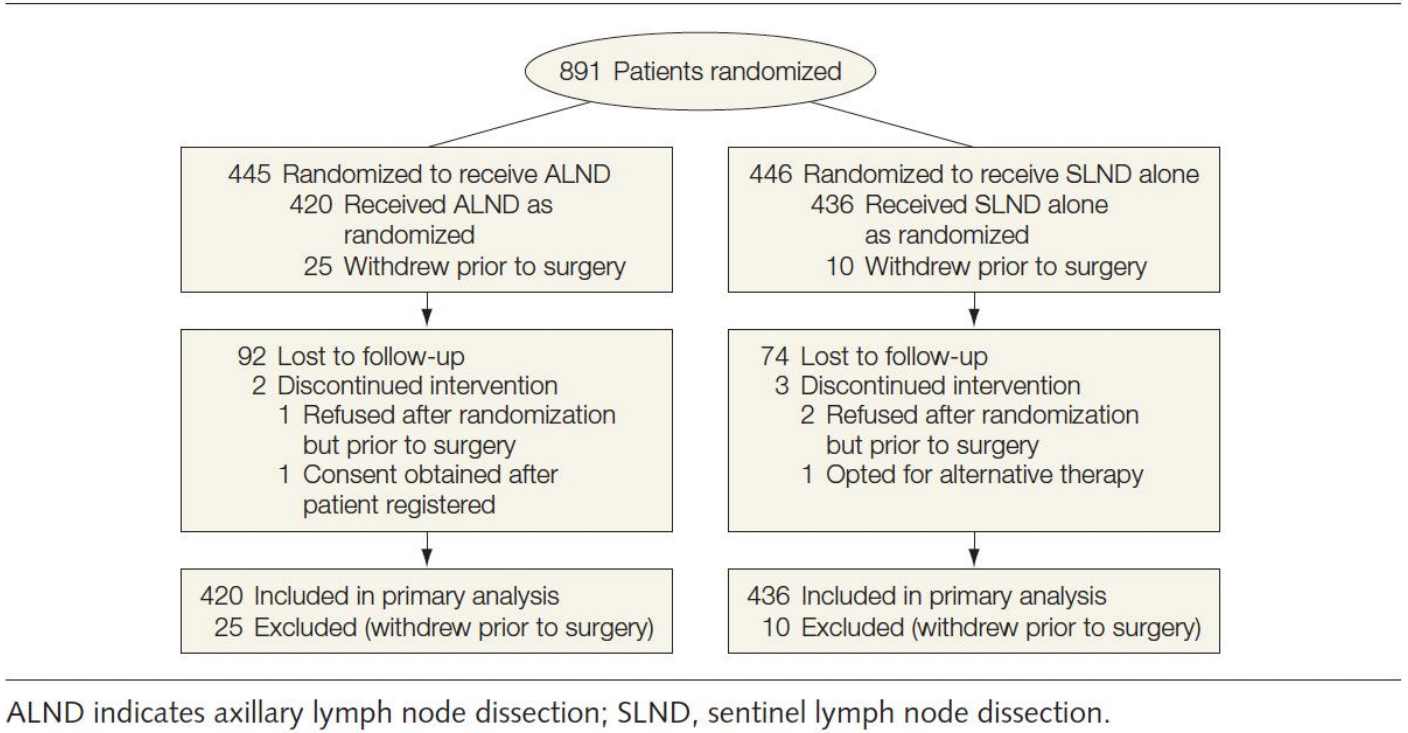
Historically, surgery was the initial treatment of women with newly diagnosed breast cancer. That remains true for most women diagnosed with early-stage tumors, where deciding between a mastectomy and breast-conserving surgery depends on the size of the tumor, the extent of radiological changes in the breast, the anticipated cosmetic outcomes and the patient's candidacy for radiation treatment and personal preferences. Surgical resection to remove known malignancy and achieve 'no ink on tumor' margins is the standard, regardless of tumor histology or grade, or the patient's age. At the time of breast surgery, women additionally undergo axillary surgery to stage the axillary lymph nodes. Sentinel node biopsy (SNB) is the standard approach in patients presenting with a clinically negative axilla, whether undergoing mastectomy or breast-conserving surgery. Patients with negative sentinel nodes require no further axillary surgery. Women with T1-T2, clinically node-negative cancers with positive sentinel nodes who meet the criteria of the ACOSOG Z0011 trial[16] (breast-conserving surgery, with one or two positive sentinel lymph nodes) or the EORTC 10981-22023 AMAROS trial[17] [breast-conserving surgery or mastectomy, with positive sentinel node(s)], with planned breast radiation after breast-conserving surgery or axillary radiation after mastectomy, do not need additional axillary surgery in most cases. A complete axillary dissection remains standard for women with more than two positive sentinel lymph nodes, when radiation therapy is to be omitted, or in the clinical situations when knowing the extent of axillary involvement would affect systemic or radiation recommendations.

Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021

H. J. Burstein[1*†], G. Curigliano[2*†], B. Thürlimann[3], W. P. Weber[4], P. Poortmans[5], M. M. Regan[1], H. J. Senn[6], E. P. Winer[1] & M. Gnant[7], Panelists of the St Gallen Consensus Conference[‡]

ALND vs. no further axillary treatment in patients with sentinel node-positive, surgically resected breast cancer: the ACOSOG Z0011 trial





ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Giuliano AE et al. JAMA 2011
Giuliano AE et al. Ann Surgery 2016

Study objectives

- **Primary objective:** to demonstrate that OS is not inferior with SLND vs. ALND in patients with surgically-resected, cT1-2cN0 BC patients

SLND alone is not associated with higher local recurrence rates despite a lower number of total and positive lymph nodes

	ALND (N = 420)	SLND Only (N = 436)	P
Total number of nodes removed			
Median	17	2	<0.001
IQR*	13–22	1–4	
Number of positive nodes			
Median	1	1	<0.001
IQR*	1–2	1–1	
Number of positive nodes, no. (%)			
1	199 (58.0)	295 (71.1)	<0.001
2	68 (19.8)	76 (18.3)	
≥3	72 (21.0)	15 (3.6)	
Size of SN Mets, no. (%)			
Micro	137 (37.5)	164 (44.8)	0.05
Macro	228 (62.5)	202 (55.2)	

*IQR is the interquartile range, which is the 25th percentile, 75th percentile.

SLND alone underestimates the number of positive lymph nodes!

Giuliano AE et al. Ann Surgery 2016

SLND alone is not associated with higher local recurrence rates despite a lower number of total and positive lymph nodes

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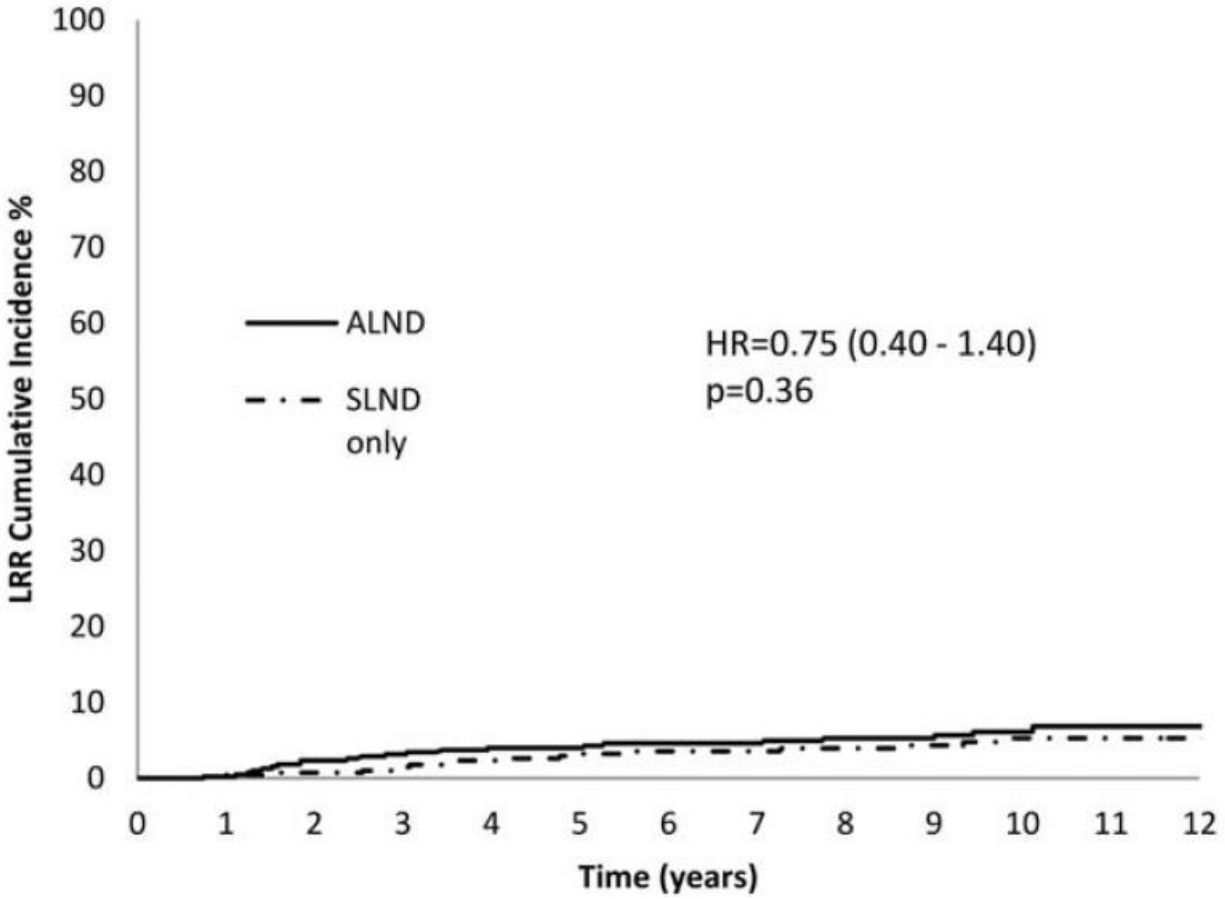
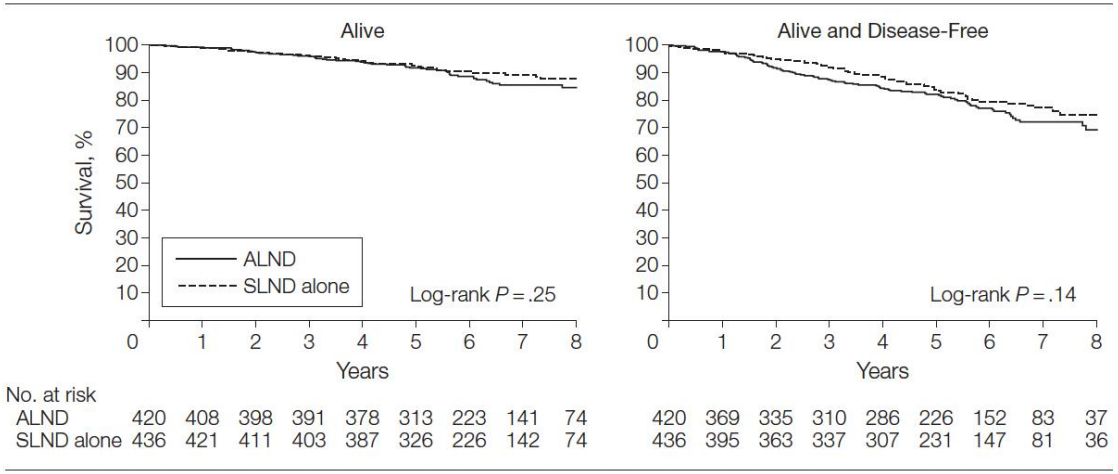


Giuliano AE et al. Ann Surgery 2016

SLND alone is associated with similar DFS and OS when compared to ALND



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

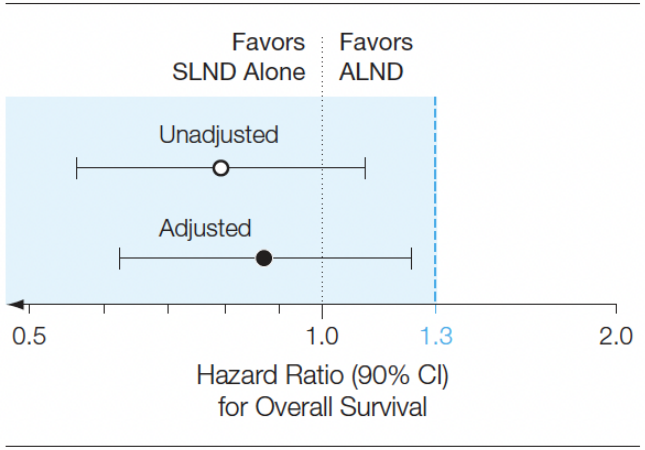


Table 2. Adjusted Hazard Ratios for Overall Survival Comparing SLND-Alone vs ALND Groups

Model Variables	No. Patients	No. Events	Adjusted HR (90% CI)	Noninferiority *P* Value
Treatment group (SLND alone vs ALND), age (≤50 vs >50 y), adjuvantly treated (yes vs no)	839	92	0.87 (0.62-1.23)	.03
Variables in row 1 + primary tumor size (per 1 cm, continuous)	818	92	0.89 (0.62-1.25)	.03
Variables in row 1 + estrogen receptor status (negative vs positive)	778	87	0.92 (0.64-1.30)	.05
Variables in row 1 + modified Bloom-Richardson score (1 vs 2 vs 3)	839	92	0.86 (0.61-1.21)	.02
Variables in row 1 + tumor type (ductal vs lobular vs other)	839	92	0.88 (0.63-1.25)	.03

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLND, sentinel lymph node dissection.

Table 3. Adjusted Hazard Ratios for Disease-Free Survival Comparing SLND-Alone vs ALND Groups

Model Variables	No. Patients	No. Events	Adjusted HR (95% CI)	*P* Value
Treatment group (SLND alone vs ALND), age (≤50 vs >50 y), adjuvantly treated (yes vs no)	839	127	0.88 (0.62-1.25)	.47
Variables in row 1 + primary tumor size (per 1 cm, continuous)	818	125	0.86 (0.60-1.22)	.40
Variables in row 1 + estrogen receptor status (negative vs positive)	778	117	0.84 (0.58-1.20)	.33
Variables in row 1 + modified Bloom-Richardson score (1 vs 2 vs 3)	839	127	0.87 (0.61-1.23)	.43
Variables in row 1 + tumor type (ductal vs lobular vs other)	839	127	0.89 (0.62-1.27)	.52

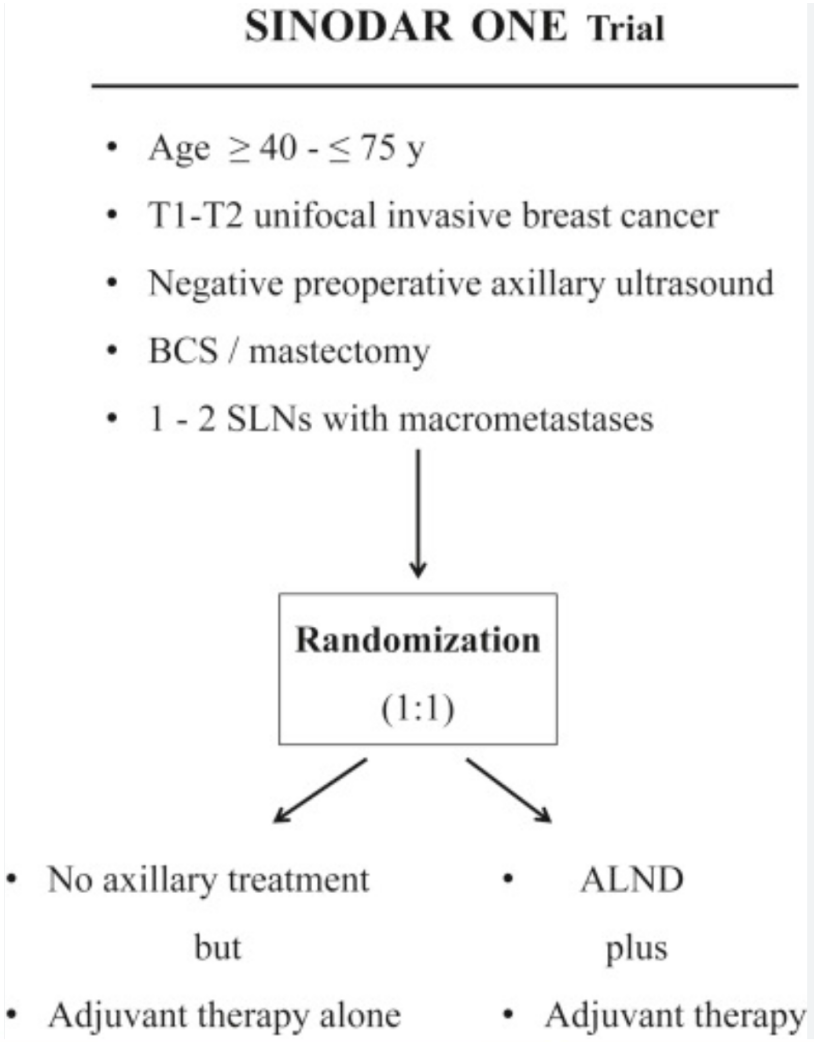
Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLND, sentinel lymph node dissection.

Giuliano AE et al. JAMA 2011

Limitations of the ACOSOG Z0011 trial

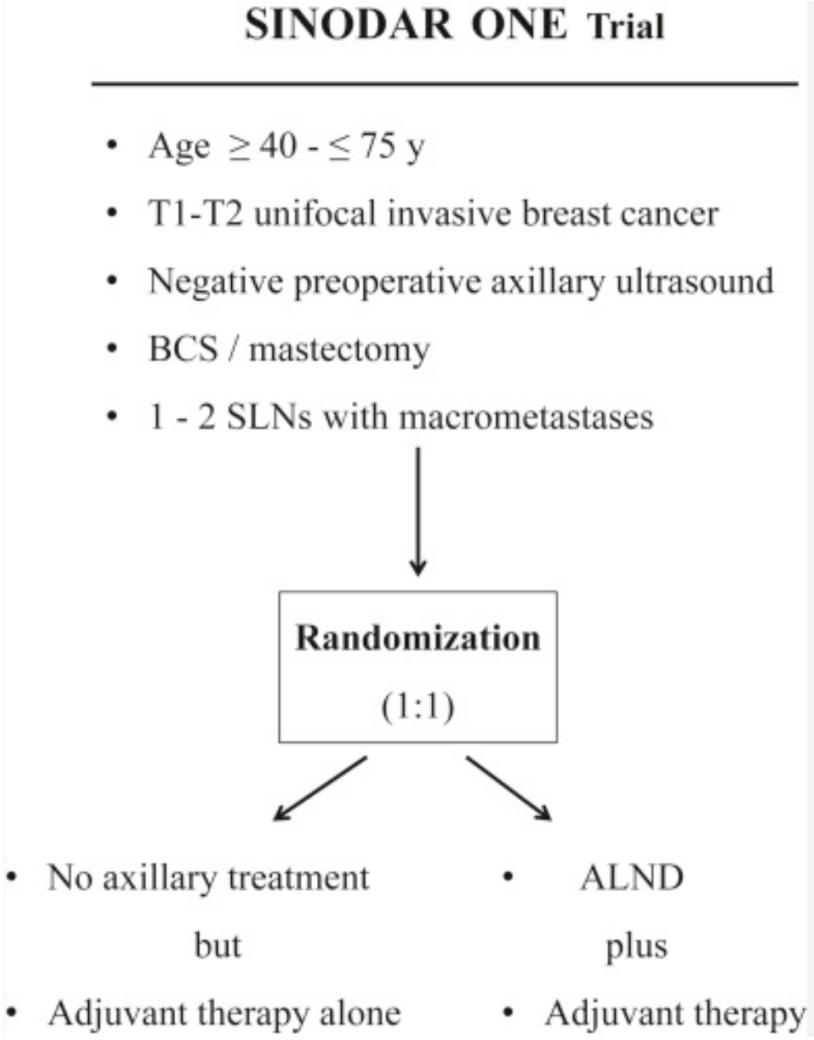
- Premature conclusion of patient enrollment
- ~ 50% of enrolled patients had micrometastases (rather than macrometastases) in SLN(s)
- ~ 20% of patients lost to follow-up
- Statistical issues (non-inferiority design with an expected HR for OS < 1.3)
- Slow accrual (~ 1.4 patients enrolled per site per year)

ALND vs. no further axillary treatment in patients with sentinel node-positive, surgically resected breast cancer: the SINODAR-ONE trial



Tinterri C et al. Ann Surg Oncol 2022

ALND vs. no further axillary treatment in patients with sentinel node-positive, surgically resected breast cancer: the SINODAR-ONE trial



Study objectives

- **Primary objective:** to demonstrate that no axillary treatment is not inferior to ALND in terms of overall survival (OS) in patients with cT1-2cN0 BC and 1-2 positive SLNs (with macrometastases)

- **Secondary endpoints:**

1. Relapse-free survival (RFS)

Tinterri C et al. Ann Surg Oncol 2022

ALND vs. no further axillary treatment in patients with sentinel node-positive, surgically resected breast cancer: the SINODAR-ONE trial

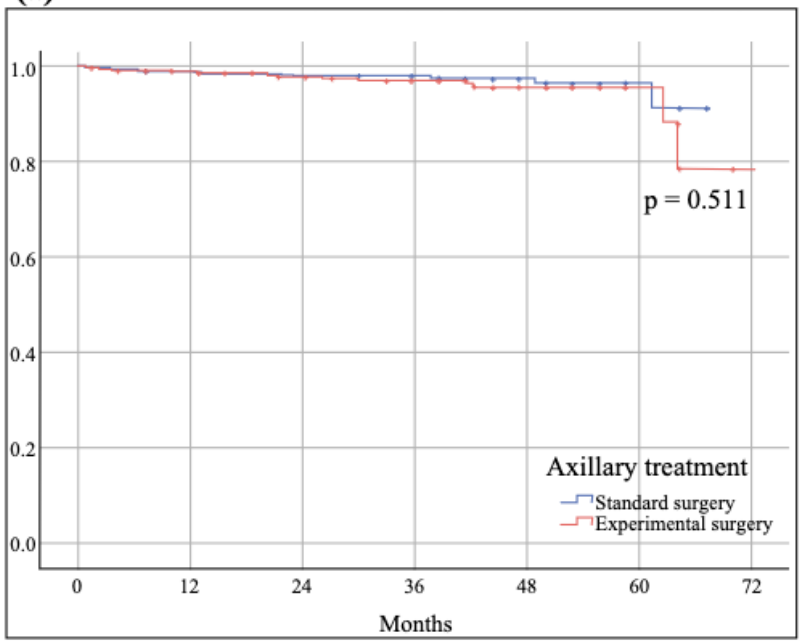
SINODAR ONE Trial

- Age ≥ 40 - ≤ 75 y
- T1-T2 unifocal invasive breast cancer
- Negative preoperative axillary ultrasound
- BCS / mastectomy
- 1 - 2 SLNs with macrometastases

Randomization
(1:1)

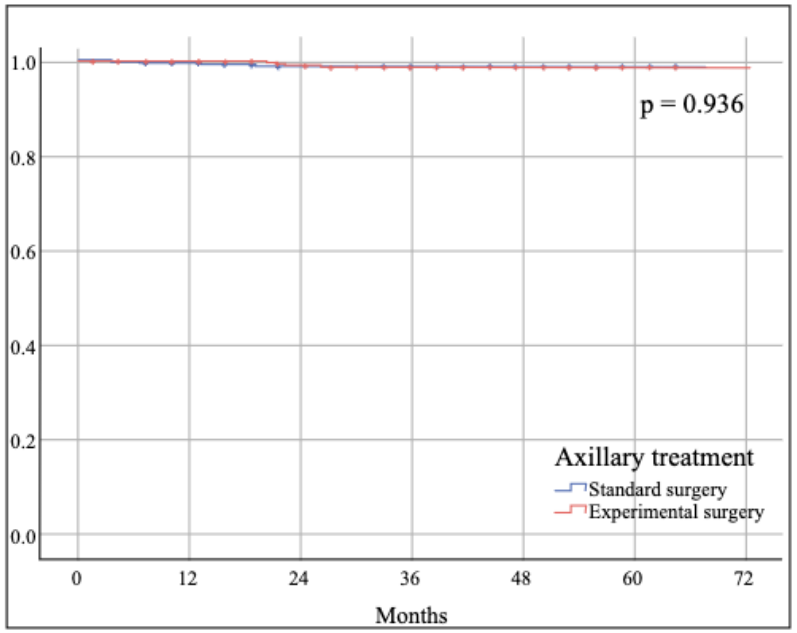
- No axillary treatment but Adjuvant therapy alone
- ALND plus Adjuvant therapy

Recurrence-free survival



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

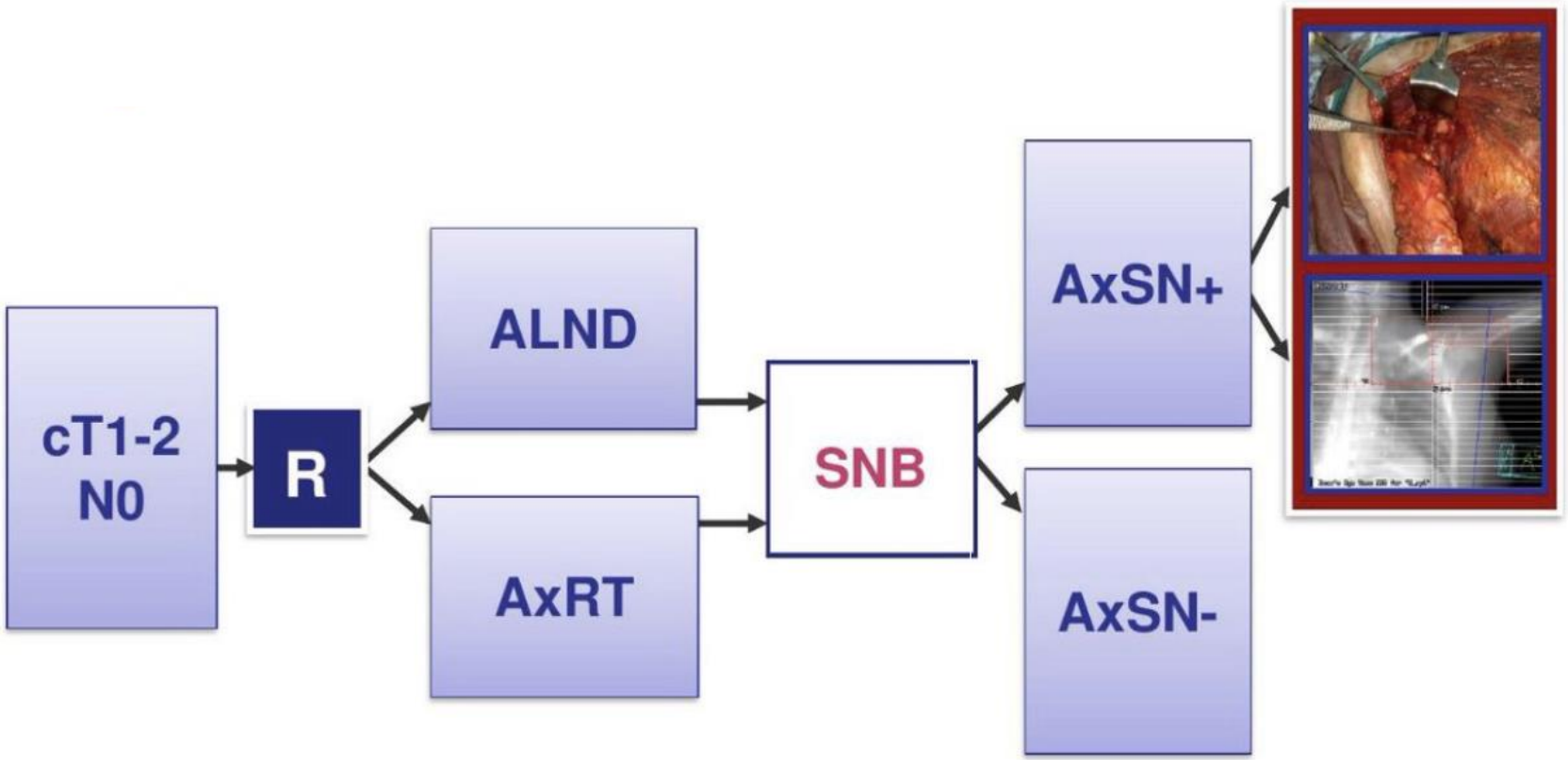
Overall survival



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

Tinterri C et al. Ann Surg Oncol 2022

ALND vs. axillary radiotherapy in SN-positive, surgically resected cT1-2N0 breast cancer patients: the AMAROS trial



Stratification: institution
Adjuvant systemic therapy by choice

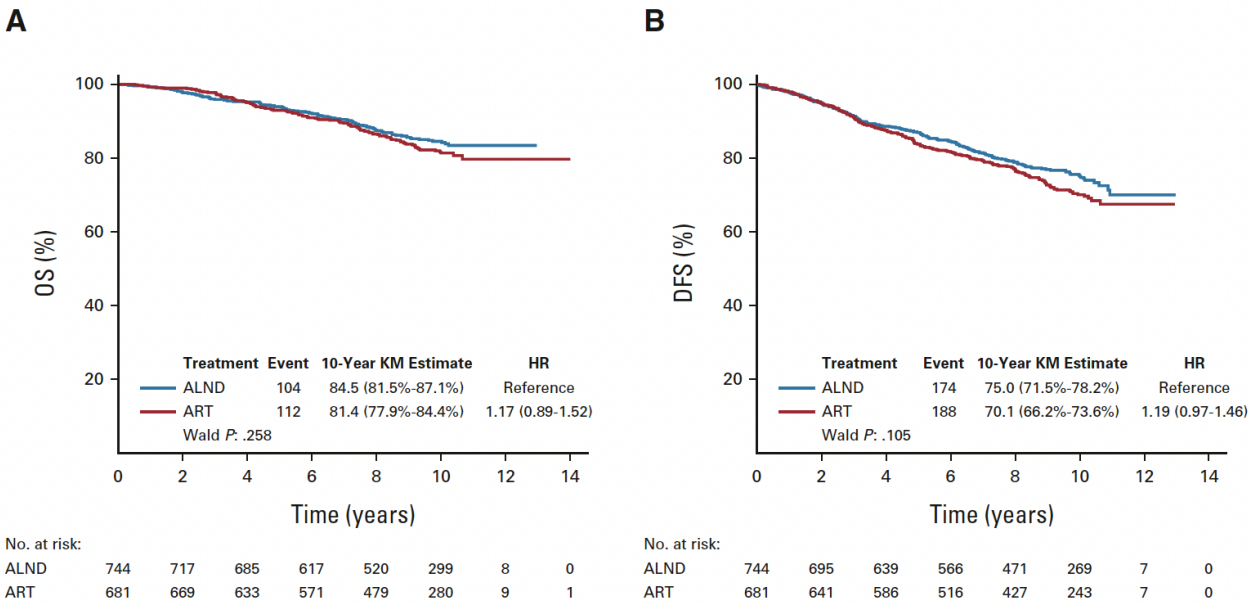
Study objectives

- **Primary objective:** to demonstrate that ART is not inferior to ALND in terms of 5-year axillary recurrence rate (ARR), as defined as tumor recurrence in ipsilateral axilla, infraclavicular fossa, or interpectoral area

- **Secondary endpoints:**

1. Axillary Recurrence-Free Survival (ARFS)
2. OS
3. DFS
4. Lymphedema
5. Shoulder mobility
6. QoL

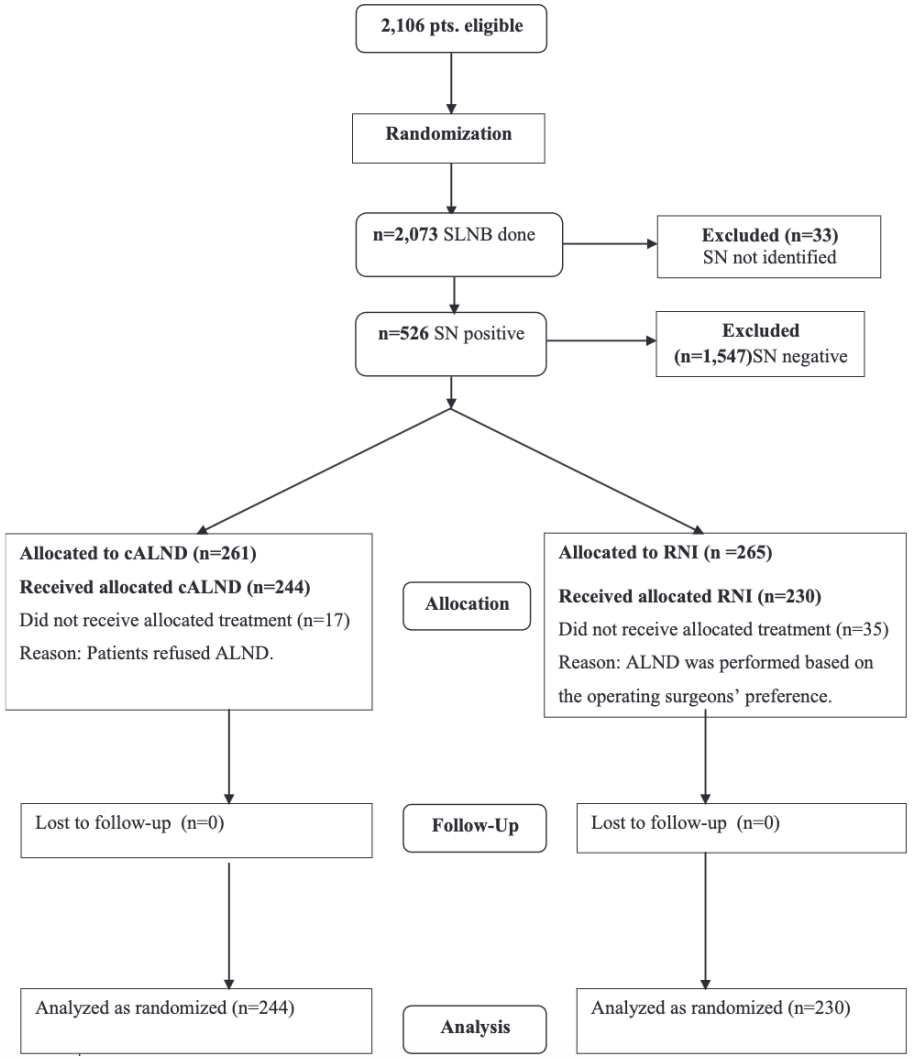
ALND and ART are associated with non statistically significantly different DFS and OS in patients with cT1-2cN0, SLN-positive BC, while the incidence of lymphedema is reduced with ART



	ALND	AxRT
SN characteristics		
SNs removed, No.		
Median (IQR)	2 (1-3)	2 (1-3)
1, No. (%)	332 (44.6)	293 (43.0)
2, No. (%)	201 (27.0)	217 (31.9)
3, No. (%)	127 (17.1)	105 (15.4)
≥ 4, No. (%)	84 (11.3)	66 (9.7)
Size of the largest SN metastasis, No. (%)		
Macrometastases	442 (59.4)	419 (61.5)
Micrometastases	215 (28.9)	195 (28.6)
Isolated tumor cells	87 (11.7)	67 (9.8)
Positive SNs, No. (%)		
1	581 (78.1)	512 (75.2)
2	127 (17.1)	134 (19.7)
3	29 (3.9)	27 (4.0)
≥ 4	7 (0.9)	8 (1.2)

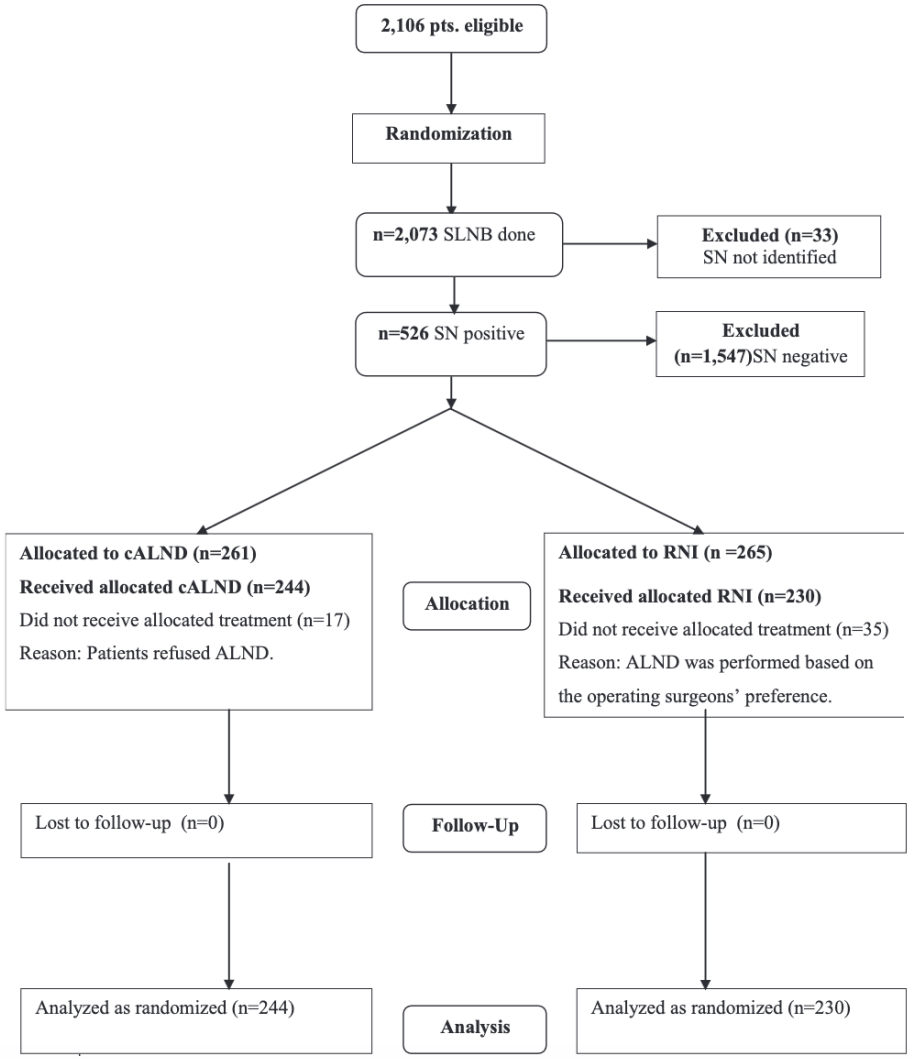
Bartels SAL et al. J Clin Oncol 2022

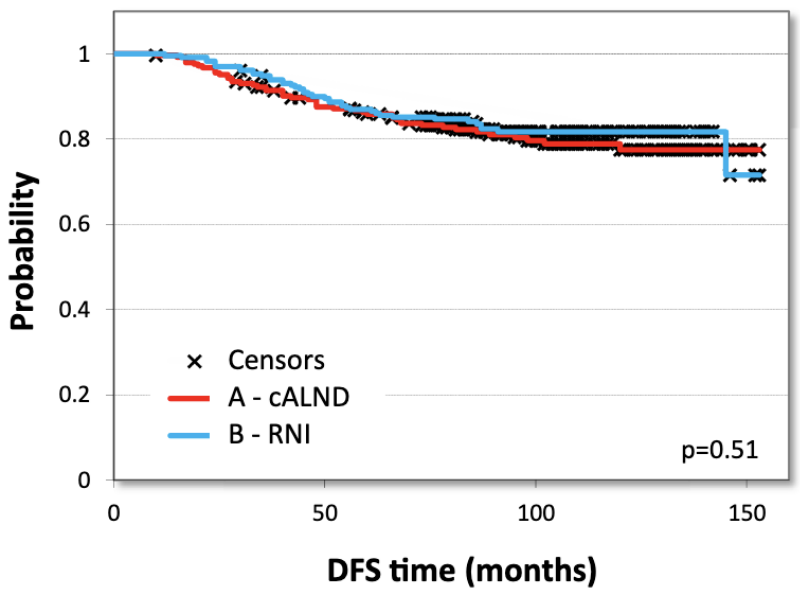
ALND vs. axillary radiotherapy in SN-positive, surgically resected cT1-2N0 breast cancer patients: the OTOASOR trial

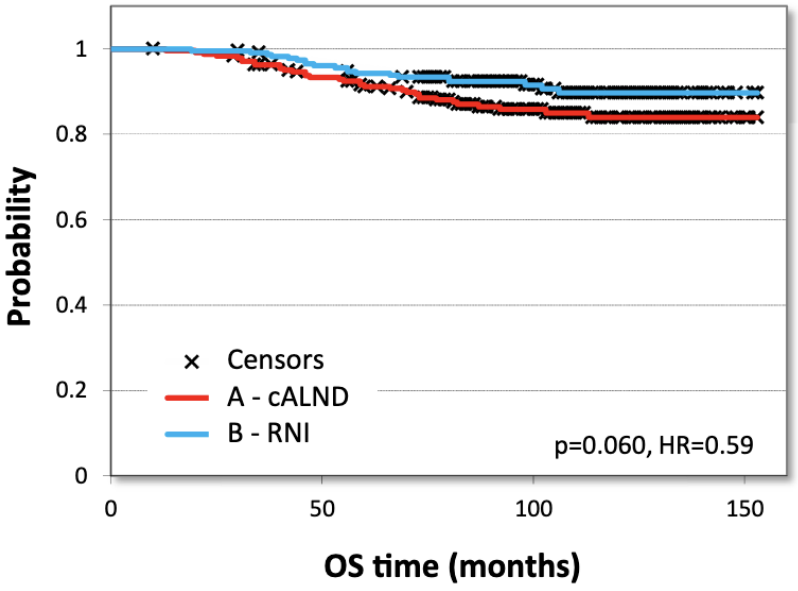


Sávolt À et al. Eur J Surg Oncol 2022

ALND vs. axillary radiotherapy in SN-positive, surgically resected cT1-2N0 breast cancer patients: the OTOASOR trial







Sávolt À et al. Eur J Surg Oncol 2022

Clinical trials comparing ALND with SLND in patients with cT1-2N0 BC patients undergoing upfront surgery

Study name	Enrollment initiation	Enrollment completion	N. pts
ACOSOG Z0011	May 1999	December 2004	891
SINODAR-ONE	April 2015	April 2020	889
AMAROS	February 2001	April 2010	1425
OTOASOR	August 2002	June 2009	474

What has changed after the initiation of these trials?

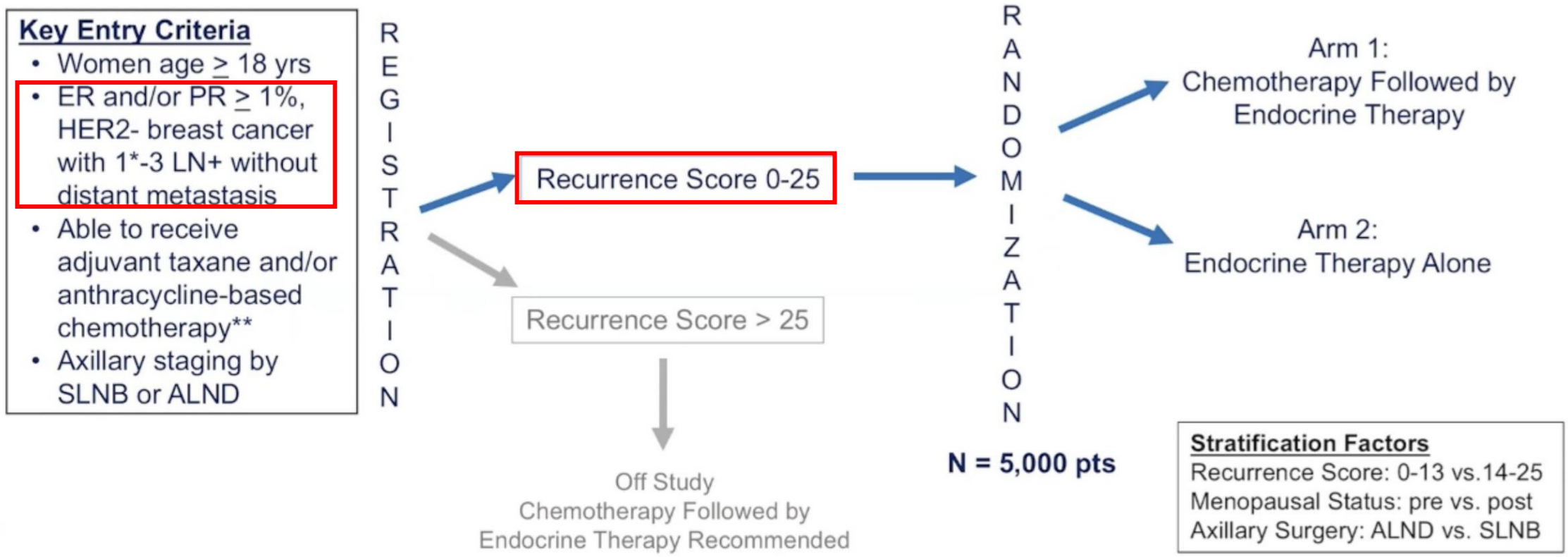
Now we have more aggressive and effective therapies for patients with high-risk disease, and less aggressive, but similarly effective treatments for patients with lower risk disease

However, the most important variable to define high-risk disease in the most recent clinical trials is the number of positive lymph nodes!

Recent clinical trials tailoring adjuvant treatment in surgically resected BC patients

Study name	Enrollment initiation	Enrollment completion	N. pts
RxPONDER	February 2011	September 2017	5018
MonarchE	July 2017	August 2019	5637
OlympiA	June 2014	May 2019	1836

RxPONDER trial



* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

Approximately two-thirds of enrolled patients underwent ALND

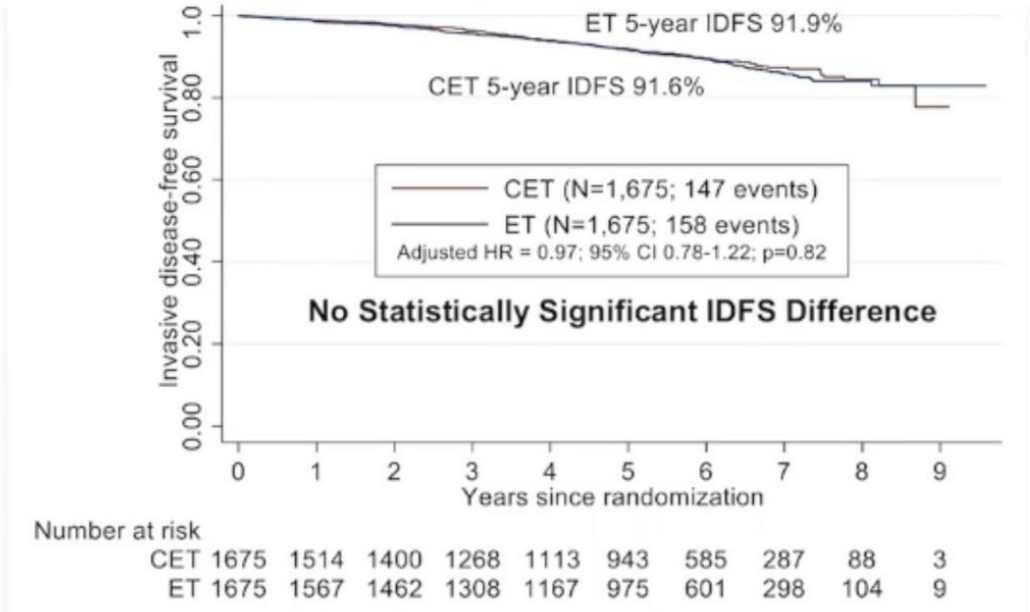
Table 1. Baseline Characteristics of the Participants.*

Characteristic	Endocrine-Only Group (N=2507)	Chemoendocrine Group (N=2511)	All Participants (N=5018)
Median age (range) — yr	57.2 (18.3–86.0)	57.9 (28.0–87.6)	57.5 (18.3–87.6)
Age category — no. (%)			
<40 yr	80 (3.2)	67 (2.7)	147 (2.9)
40–49 yr	547 (21.8)	530 (21.1)	1077 (21.5)
50–59 yr	838 (33.4)	837 (33.3)	1675 (33.4)
60–69 yr	761 (30.4)	777 (30.9)	1538 (30.6)
≥70 yr	281 (11.2)	300 (12.0)	581 (11.6)
Menopausal status — no. (%)			
Premenopausal	831 (33.1)	834 (33.2)	1665 (33.2)
Postmenopausal	1676 (66.9)	1677 (66.8)	3353 (66.8)
Recurrence score — no. (%)†			
0–13	1071 (42.7)	1076 (42.9)	2147 (42.8)
14–25	1436 (57.3)	1435 (57.1)	2871 (57.2)
Axillary surgery — no. (%)			
Axillary lymph-node dissection, with or without sentinel-node mapping	1571 (62.7)	1569 (62.5)	3140 (62.6)
Sentinel-node biopsy without axillary lymph-node dissection	936 (37.3)	942 (37.5)	1878 (37.4)
Positive nodes — no. (%)			
1 node	1647 (65.7)	1628 (64.8)	3275 (65.3)
2 nodes	623 (24.8)	643 (25.6)	1266 (25.2)
3 nodes	229 (9.1)	231 (9.2)	460 (9.2)
Not reported	8 (0.3)	9 (0.4)	17 (0.3)

Kalinsky K et al. N Engl J Med 2021

In pre-menopausal women adding chemotherapy to ET results in iDFS benefit in the RS 0-25 range, while chemotherapy does not provide benefit to post-menopausal women

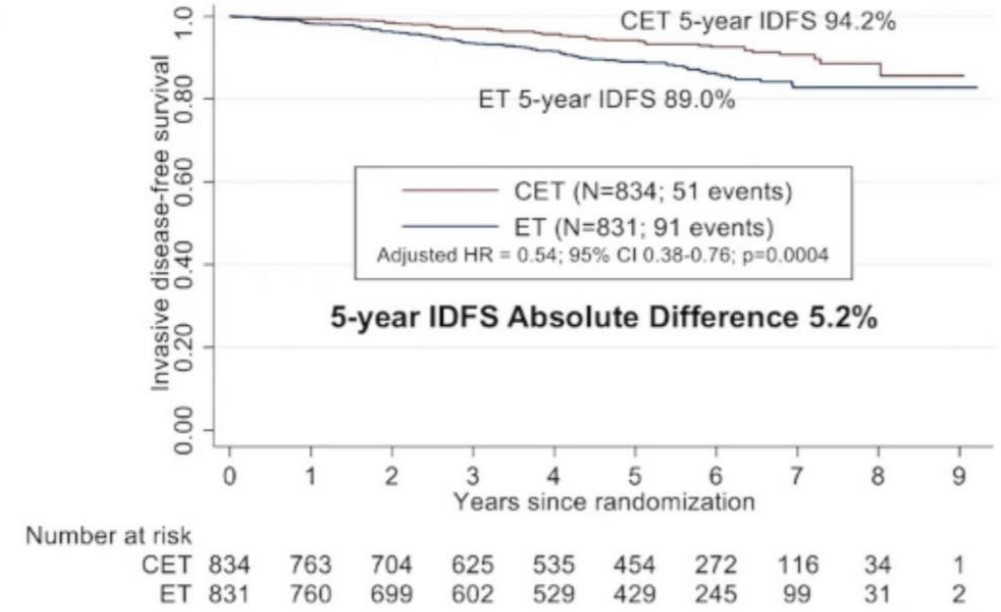
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

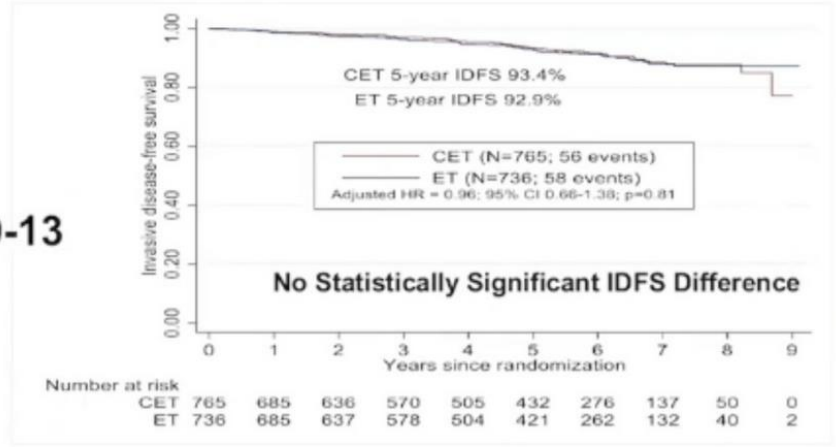
Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Kalinsky K et al. N Engl J Med 2021

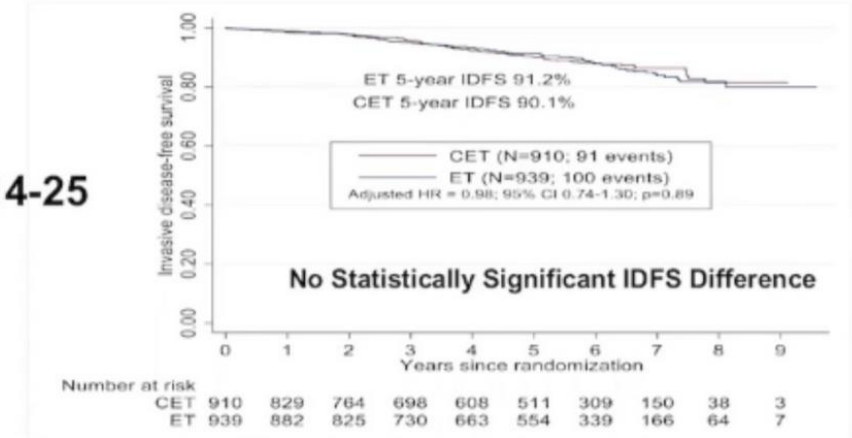
In pre-menopausal women adding chemotherapy to ET results in iDFS benefit regardless of RS (0-13 vs. 14-25), while chemotherapy does not improve clinical outcomes in post-menopausal women regardless of RS ranges

Postmenopausal

RS 0-13

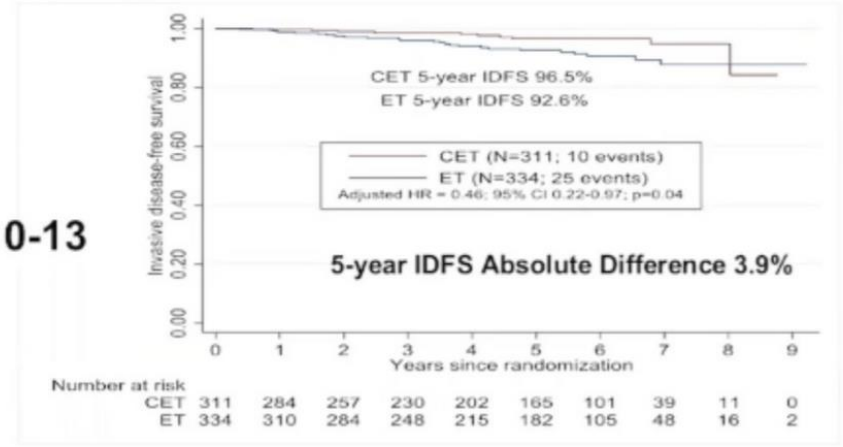


RS 14-25

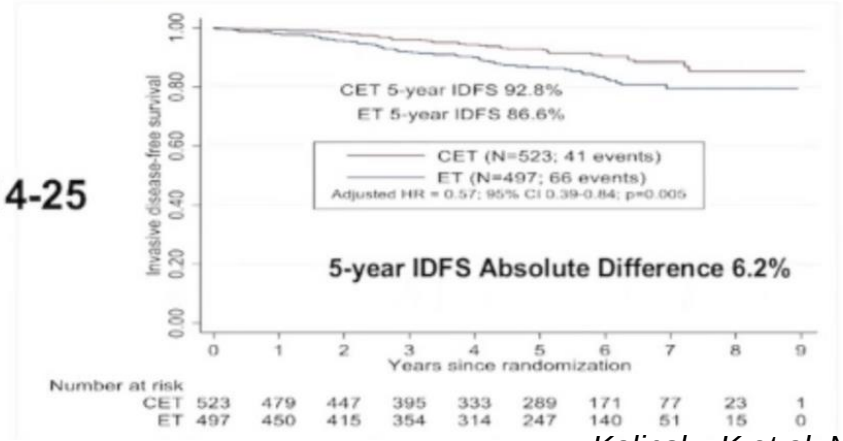


Premenopausal

RS 0-13



RS 14-25

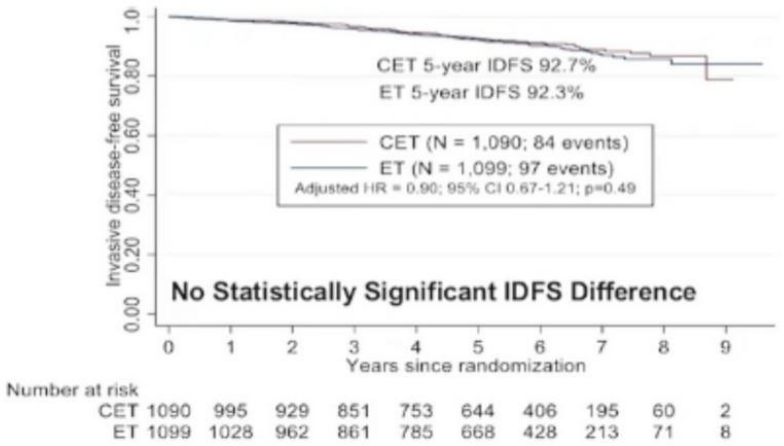


Kalinsky K et al. N Engl J Med 2021

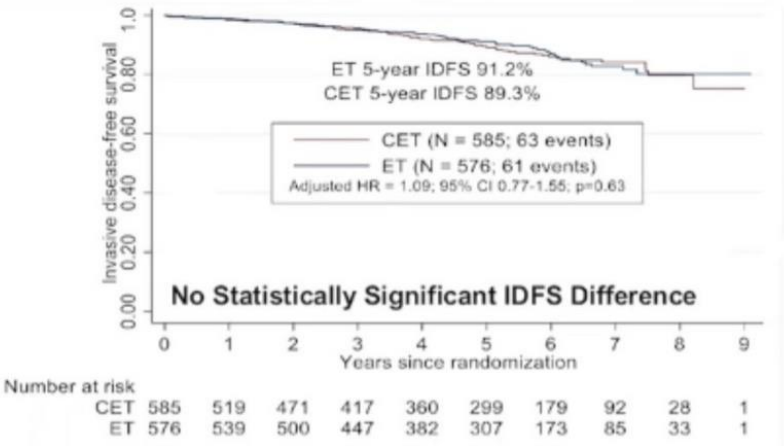
Premenopausal women benefit from adjuvant chemotherapy regardless of the number of involved lymph nodes, while post-menopausal women do not

Postmenopausal

1 Node

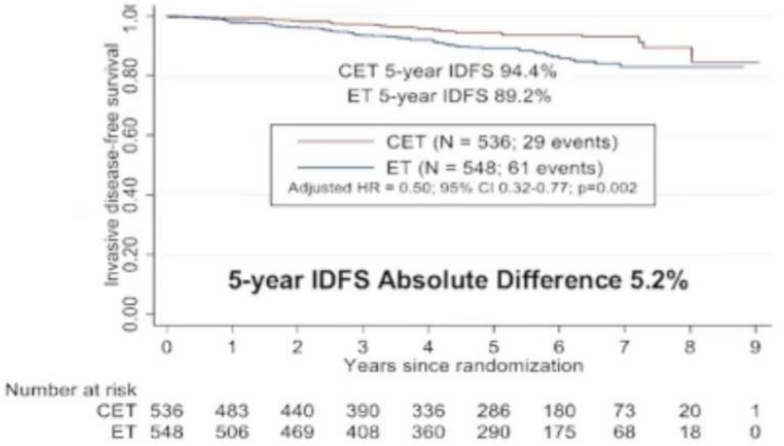


2-3 Nodes

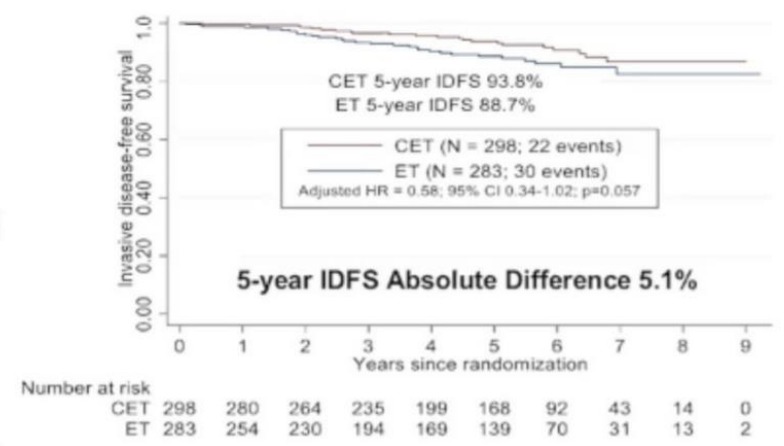


Premenopausal

1 Node



2-3 Nodes



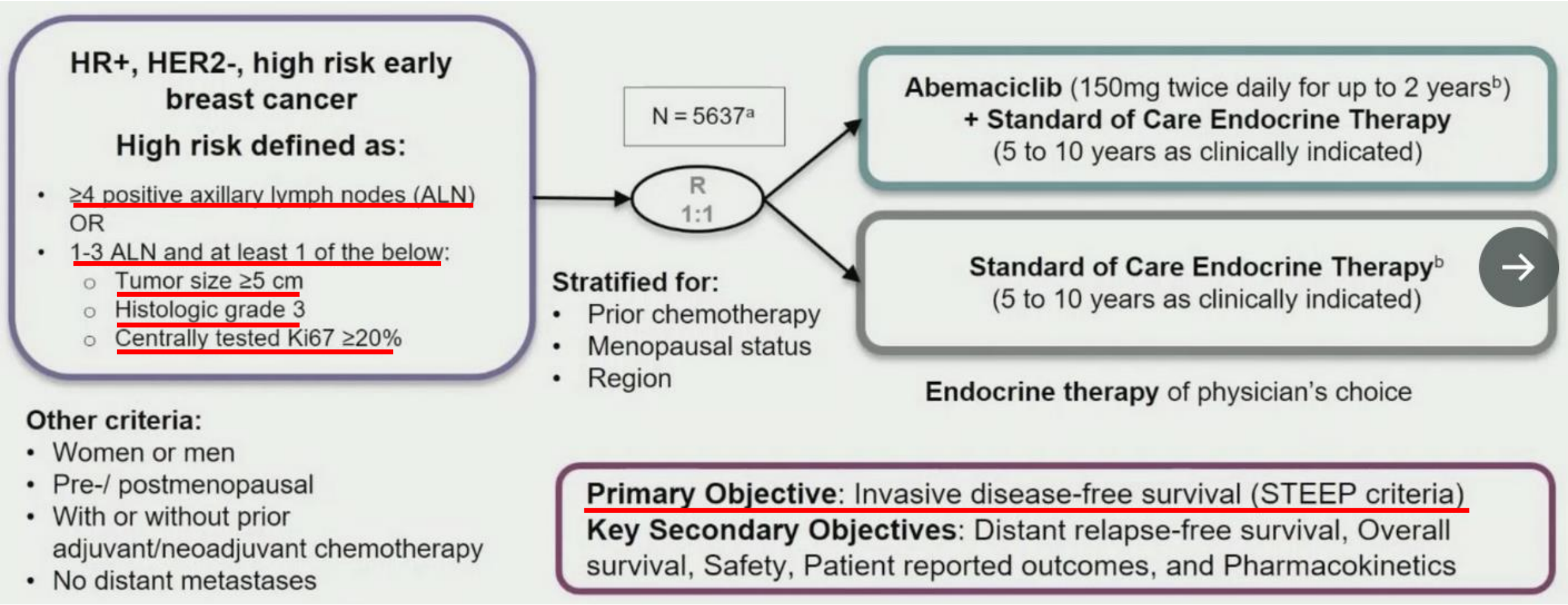
Kalinsky K et al. N Engl J Med 2021

Risks associated with SLNB vs. ALND

RxPONDER

- In post-menopausal women with HR+/HER2- BC, there is the risk of underestimating the number of positive lymph nodes in post-menopausal women (i.e., 1-3 rather than ≥ 4) or underestimating the RS (e.g., ≥ 26 vs. 0-25 in patients with 2-3 vs. 1 SLN+), thus avoiding the prescription of potentially useful chemotherapy
- In premenopausal women with at least one positive lymph node, adjuvant chemotherapy is prescribed regardless of the total number of positive lymph nodes. Therefore, performing SLNB rather than ALND does not affect therapeutic decisions in premenopausal women

MonarchE trial design

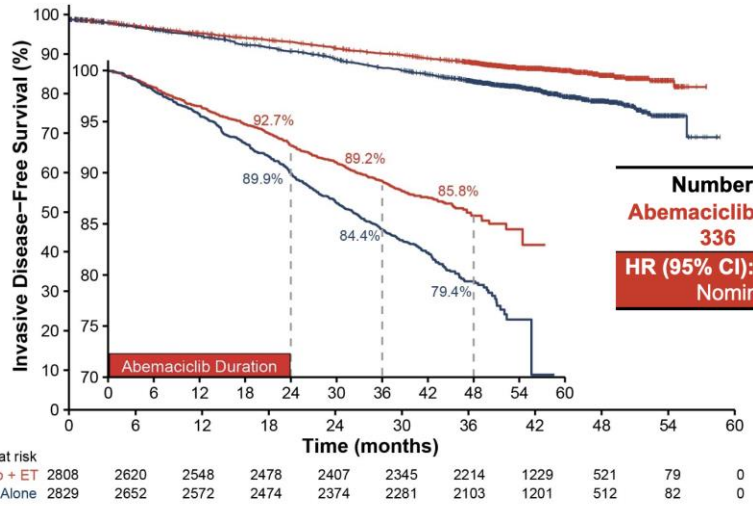


- **Patients may have up to 12 weeks of endocrine therapy following their last non-endocrine therapy (surgery, radiotherapy, or chemotherapy) prior to randomization**
- **Patients must be randomized within 16 months of definitive breast surgery for the current malignancy**

Adjuvant ET+abemaciclib improves iDFS when compared to ET

San Antonio Breast Cancer Symposium®, December 6-10, 2022

IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number at risk

Abemaciclib + ET	2808	2620	2548	2478	2407	2345	2214	1229	521	79	0
ET Alone	2829	2652	2572	2474	2374	2281	2103	1201	512	82	0

Number of IDFS events

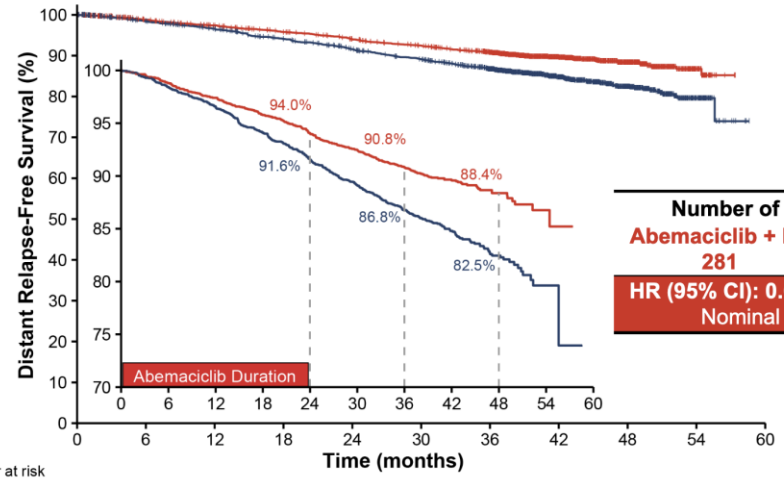
Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

San Antonio Breast Cancer Symposium®, December 6-10, 2022

DRFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number at risk

Abemaciclib + ET	2808	2629	2567	2500	2434	2374	2244	1251	535	81	0
ET Alone	2829	2659	2589	2499	2410	2327	2151	1231	526	85	0

Number of DRFS events

Abemaciclib + ET	ET Alone
281	421

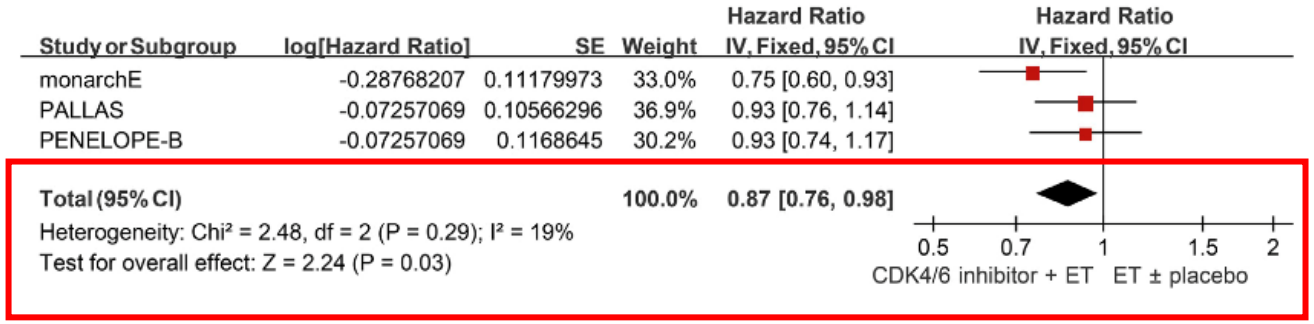
HR (95% CI): 0.659 (0.567, 0.767)
Nominal p < 0.0001

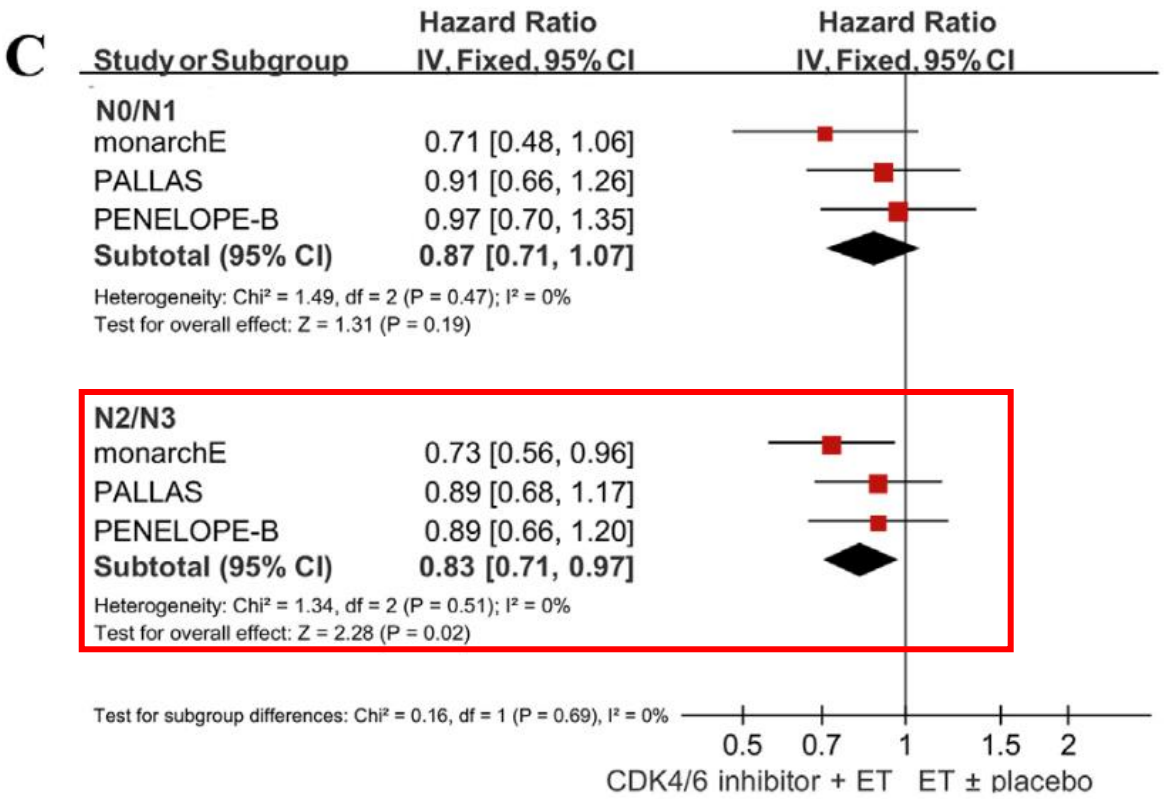
34.1% reduction in the risk of developing a DRFS event with an increase in absolute benefit in DRFS 4-year rates (5.9%), compared to 2-and 3-year rates (2.5% and 4.1%, respectively)

Johnston SRD et al. Lancet Oncol 2023

Adjuvant ET+CDK4/6i therapies especially benefit patients with N2/N3 disease

Trial	Design	Population characteristics	Regimen	Dose	ITT N	Median age, year	Median follow-up, mo	Primary endpoint	IDFS HR (95% CI) of overall patients
monarchE	Open label, randomized (1:1), phase III	HR + HER2-, pre- or post-menopausal, high risk[a], stage II or III, node positive, with or without NACT	Abemaciclib + ET vs ET alone	Abemaciclib 150 mg bid × 2 years; standard adjuvant ET[d]	5637 (2808/2829)	51; 51	15.5; 15.5	IDFS	0.75 (0.60–0.93)
PALLAS	Open label, randomized (1:1), phase III	HR + HER2-, pre- or post-menopausal, low risk or high risk[b], stage II or III, node positive or negative, with or without NACT	Palbociclib + ET vs ET alone	Palbociclib 125 mg once daily, d1-21 in a 28-day cycle × 2 years; standard adjuvant ET[d]	5760 (2883/2877)	52; 52	23.7; 23.7	IDFS	0.93 (0.76–1.15)
PENELOPE-B	Double blind, randomized (1:1), phase III	HR + HER2-, pre- or post-menopausal, high risk[c], early BC, node positive or negative, no pCR after NACT	Palbociclib + ET vs placebo + ET	Palbociclib 125 mg once daily, p.o., d1-21, q28d for 13 cycles; Placebo d1-21, q28d for 13 cycles; ET according to local standard	1250 (631/619)	49; 48	42.8; 42.8	IDFS	0.93 (0.74–1.17)

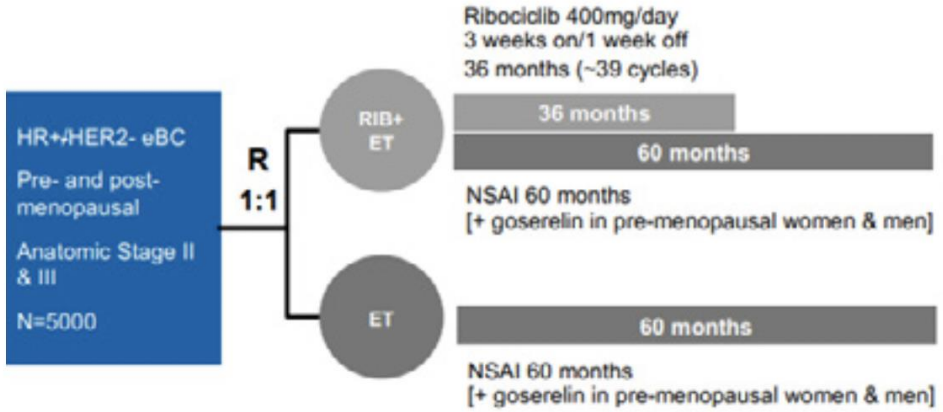




Aebi S et al. The Breast 2022

Ribociclib in addition to AI improves iDFS as compared to IAI alone in pazienti with surgically resected, stage II-III HR+/HER2- BC

NATALEE study design



- **Fully enrolled** as of April 2021
- **Primary analysis** planned at 500 iDFS events, expected in 2023
- Interim analyses at 70% and 85%

Novartis Kisqali® Phase III NATALEE trial meets primary endpoint at interim analysis demonstrating clinically meaningful benefit in broad population of patients with early breast cancer

Mar 27, 2023

Ad hoc announcement pursuant to Art. 53 LR

- *Kisqali plus endocrine therapy (ET) significantly reduced the risk of disease recurrence compared to standard ET alone in the adjuvant setting*[1]
- *NATALEE is the first and only positive Phase III study of a CDK4/6 inhibitor demonstrating consistent benefit in a broad population of patients with stage II and III HR+/HER2- early breast cancer (EBC) at risk of recurrence, including those with no nodal involvement*
- *Approximately 30-60% of people with HR+/HER2- stage II and III EBC treated with ET only remain at risk of breast cancer recurrence*[2]
- *NATALEE results will be presented at an upcoming medical meeting and submitted to regulatory authorities worldwide*

Basel, March 27, 2023 — Novartis today announced positive topline results from an interim analysis of NATALEE, a Phase III trial evaluating Kisqali® (ribociclib) plus endocrine therapy (ET) in a broad population of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC) at risk of recurrence[1]. The Independent Data Monitoring Committee recommended stopping the trial early as the primary endpoint of invasive disease-free survival (iDFS) has been met. Kisqali plus ET significantly reduced the risk of disease recurrence, compared to standard adjuvant ET alone, with consistent benefit in patients with stage II and stage III EBC regardless of nodal involvement[1].

NATALEE trial design

Key Inclusion Criteria

- Women/men with HR+/HER- EBC
- Stage III OR
  Stage II with N1 OR
  Stage II with T3 N0 OR
  Stage II with T2 N0 and
  G2-3 and/or Ki67≥20% and/or
  RS>25
- Completion of surgery, CT, RT

R
1:1

Ribociclib (400 mg) for up to 36m
+ **NSAI +/- LHRHa** (for up to 60m)

NSAI +/- LHRHa (for up to 60m)

Stratified for:
Menopausal status
Prior CT
Region

Risks associated with SLNB vs. ALND

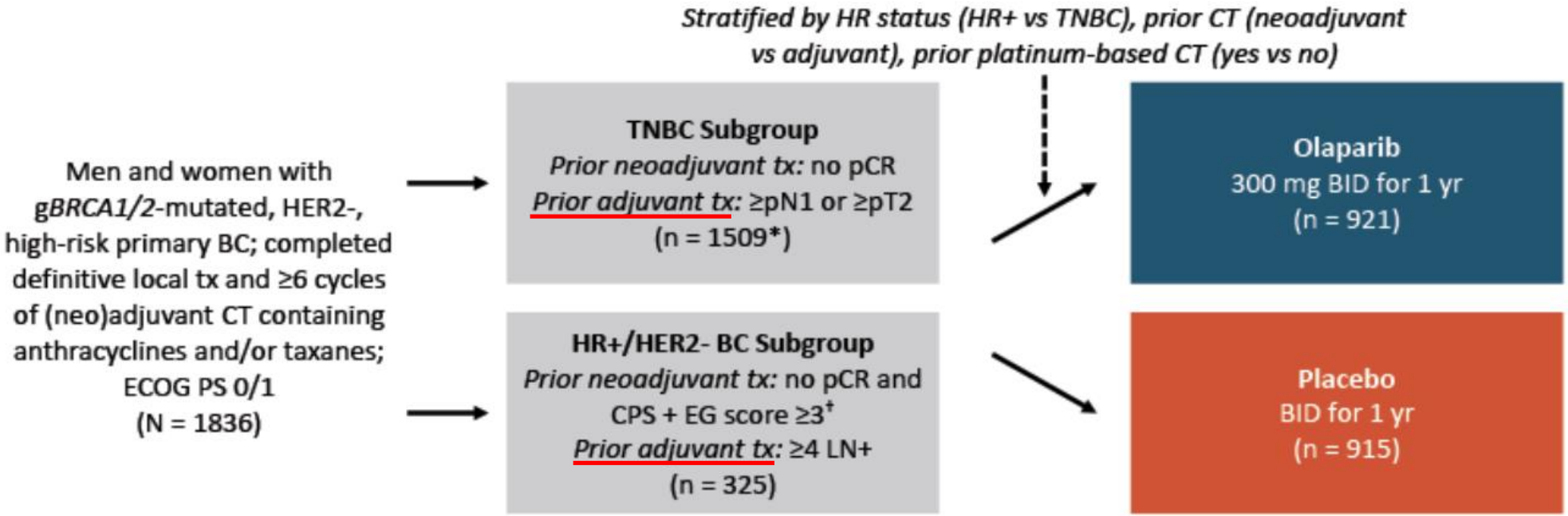
RxPONDER

- In post-menopausal women with HR+/HER2- BC, there is the risk of underestimating the number of positive lymph nodes in post-menopausal women (i.e., 1-3 rather than ≥ 4) or underestimating the RS (e.g., ≥ 26 vs. 0-25 in patients with 2-3 vs. 1 SLN+), thus avoiding the prescription of potentially useful chemotherapy In premenopausal women with at least one positive lymph node, adjuvant chemotherapy is prescribed regardless of the total number of positive lymph nodes. Therefore, performing SLNB rather than ALND does not affect therapeutic decisions in premenopausal women

MonarchE/NATALEE

- Underestimation of the number of positive lymph nodes (1-3 vs. ≥ 4), thus missing the opportunity to receive adjuvant abemaciclib if T < 5 cm, G1-2 AND Ki67 < 20% in both premenopausal and post-menopaudsal women
- If positive, results of the NATALEE trial in patients with stage II disease could minimize these risks

OlympiA trial: adjuvant olaparib improves iDFS, DDFS and OS in *gBRCA1/BRCA2* mutated patients with high-risk breast cancer



- **Primary endpoint:** iDFS
- **Secondary endpoints:** distant DFS, OS, safety

*Excluded n = 2 (both in olaparib arm) due to unconfirmed HER2- status.
†Staging system for BC-specific survival after neoadjuvant tx incorporating pretreatment clinical stage, ER status, nuclear grade, pathologic stage (range: 0-6).

- Prespecified interim analysis of ITT population triggered when 165 invasive disease or death events occurred in first 900 patients enrolled (mature cohort); type I error rate controlled with superiority boundaries per hierarchical multiple-testing procedure

Characteristics of patients enrolled in OlympiA

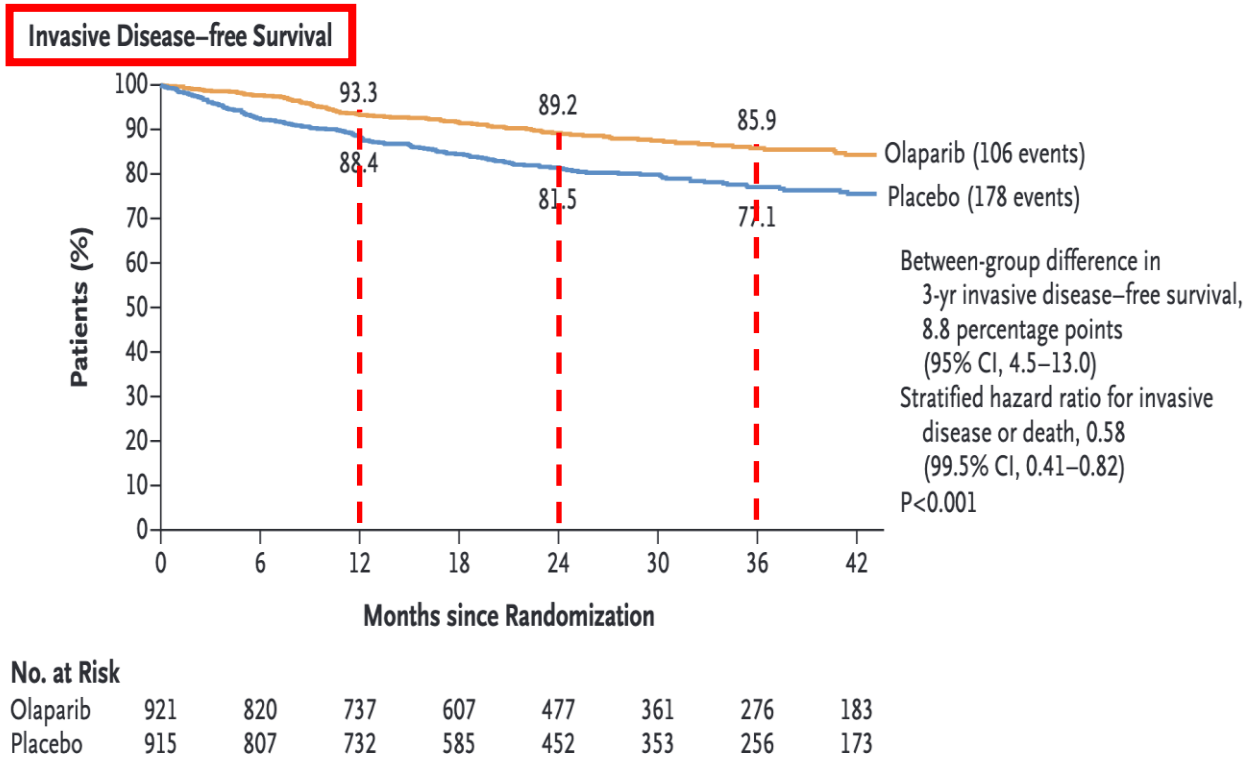
Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Olaparib (N=921)	Placebo (N=915)
Median age (interquartile range) — yr	42 (36–49)	43 (36–50)
Germline *BRCA* mutation — no. (%)†		
BRCA1	657 (71.3)	670 (73.2)
BRCA2	261 (28.3)	239 (26.1)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
Missing data	1 (0.1)	1 (0.1)
Previous adjuvant or neoadjuvant chemotherapy — no. (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Regimen with both anthracycline and taxane	871 (94.6)	849 (92.8)
Anthracycline regimen, without taxane	7 (0.8)	13 (1.4)
Taxane regimen, without anthracycline	43 (4.7)	52 (5.7)
Regimen not reported	0	1 (0.1)
<6 Cycles of neoadjuvant or adjuvant chemotherapy	7 (0.8)	15 (1.6)
Platinum-based neoadjuvant or adjuvant therapy		
No	674 (73.2)	676 (73.9)
Yes	247 (26.8)	239 (26.1)
Concurrent hormone therapy (hormone-receptor–positive patients only) — no./total no. (%)	146/168 (86.9)	142/157 (90.4)
Hormone-receptor status — no. (%)‡		
Hormone-receptor positive and HER2 negative§	168 (18.2)	157 (17.2)
Triple-negative breast cancer¶	751 (81.5)	758 (82.8)
Menopausal status (women only) — no./total no. (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Surgery for primary breast cancer — no. (%)		
Mastectomy	698 (75.8)	673 (73.6)
Conservative surgery only	223 (24.2)	240 (26.2)
Missing data	0	2 (0.2)

Tutt ANJ et al. N Engl J Med 2021

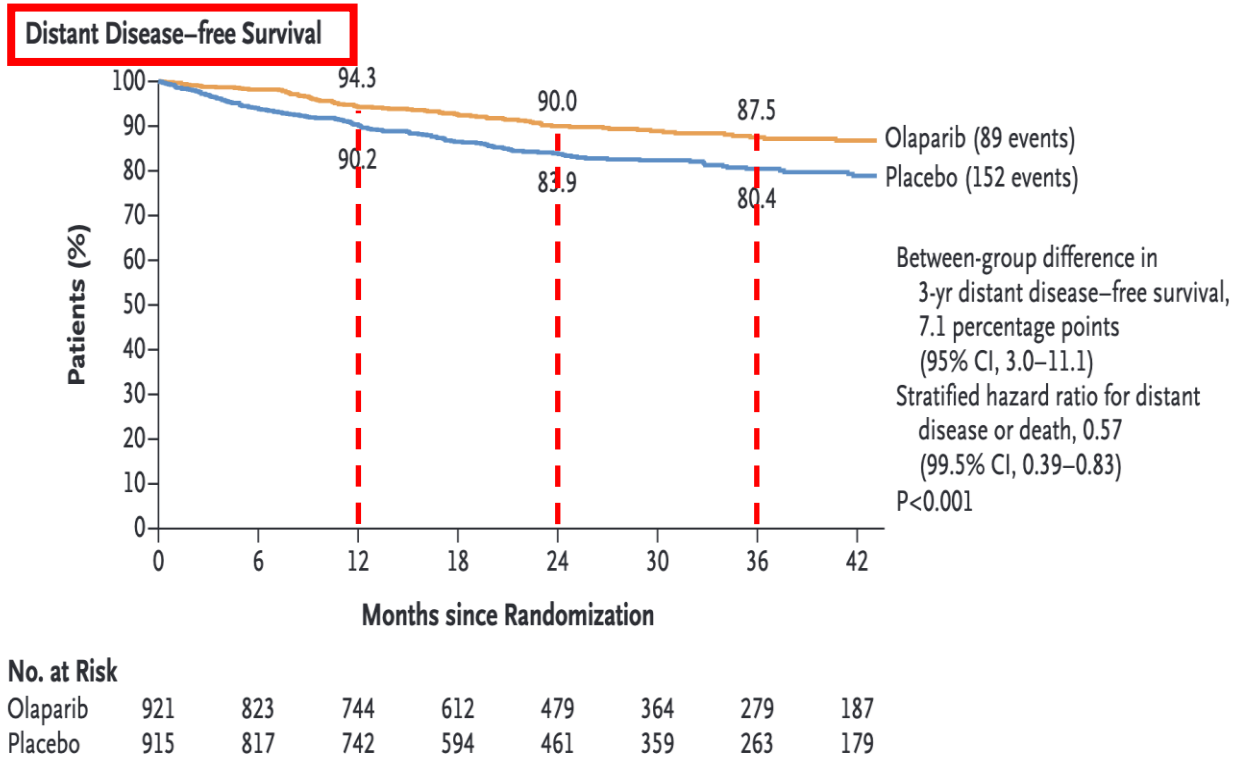
Tutt ANJ et al NEJM 2021

Adjuvant olaparib improves iDFS and DDFS in patients with surgically resected BC and who are carriers of pathogenic germline *BRCA1/BRCA2* mutations



No. at Risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173



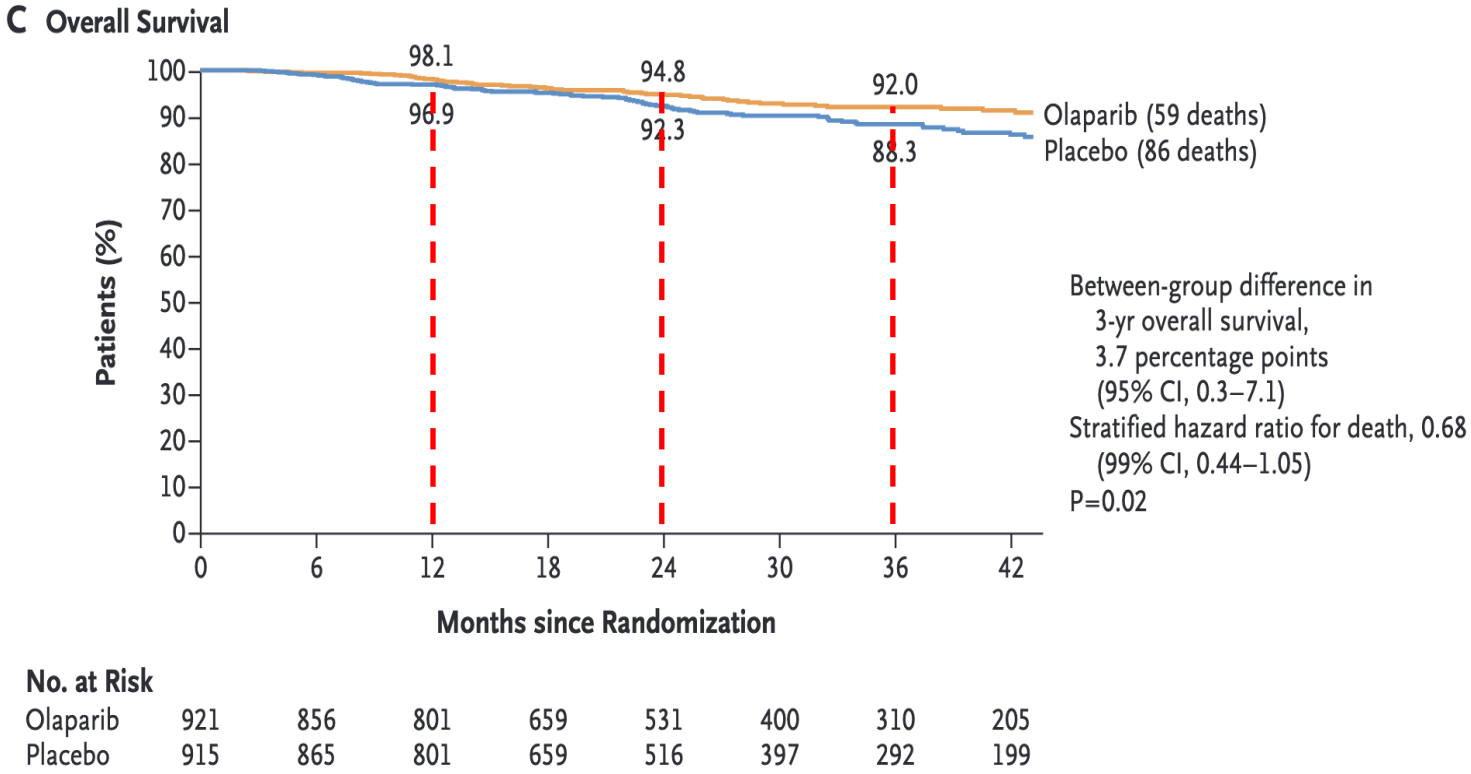
No. at Risk

Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

Tutt ANJ et al. N Engl J Med 2021

Tutt ANJ et al NEJM 2021

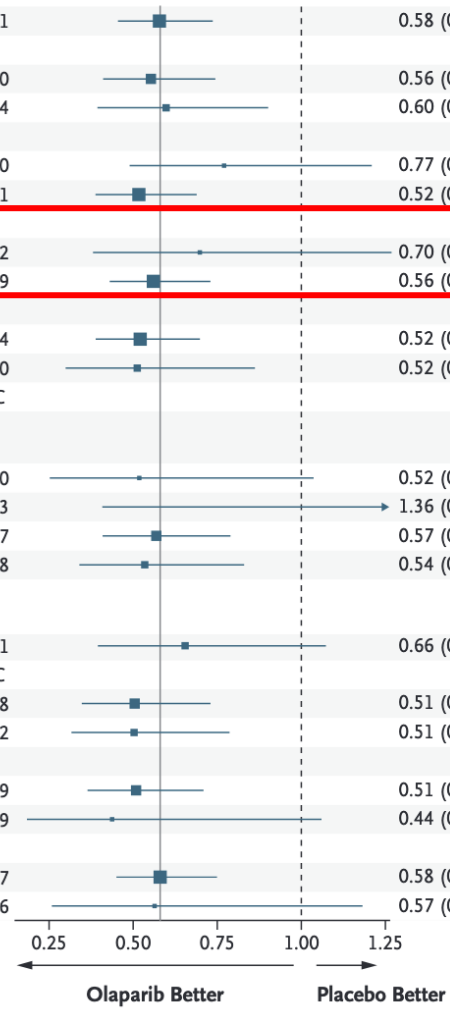
Adjuvant olaparib also improves OSin patients with surgically resected BC and who are carriers of pathogenic germline *BRCA1/BRCA2* mutations



Tutt ANJ et al. N Engl J Med 2021

Clinical benefit with olaparib is observed across subgroups

Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)



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Tutt ANJ et al NEJM 2021

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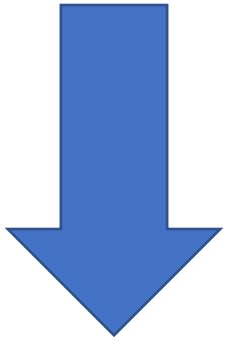
MonarchE/NATALEE

- Underestimation of the number of positive lymph nodes (1-3 vs. ≥ 4), thus missing the opportunity to receive adjuvant abemaciclib if T < 5 cm, G1-2 AND Ki67 < 20% in both premenopausal and post-menopaudsal women
- If positive, results of the NATALEE trial in patients with stage II disease could minimize these risks

OlympiA

- In patients with HR+/HER2- BC (and, in case, also with cT1a-cN0 TNBC not receiving neoadjuvant chemotherapy) and *gBRCA1/2* mutations, there is the risk of underestimating of the number of positive lymph nodes (1-3 vs. ≥ 4 in HR+/HER2- BC patients, or N+ vs. N- in TNBC patients), thus missing the opportunity to receive adjuvant Olaparib after adjuvant chemotherapy (→ Olaparib can be only prescribed after (neo)adjuvant chemotherapy in patients with high-risk BC). This is true for patients with both pre- and post-menopausal status



The worst scenario consists in the risk of missing the possibility to prescribe both adjuvant chemotherapy and adjuvant abemaciclib (and, potentially, also olaparib in *gBRCA1/2* mutated patients) in post-menopausal women with a RS of 0-25 and 1-3 positive lymmph nodes and the concomitancy of T < 5 cm, G1-2 and Ki67 < 20%.

How to minimize these risks in the clinical practice?

- In the most recent clinical trials patients were surgically approached according to the most recent guidelines (including SLND without ALND when appropriate). Actually, these trials showed positive results, thus demonstrating clinical advantage in the context of a conservative approach of the axilla, when appropriate

How to minimize these risks in the clinical practice?

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- Personalize surgical treatment of the axilla after post-surgery multidisciplinary discussion that takes into account the potential risks of axillary downstaging and, consequently, of missing the opportunity to prescribe abemaciclib, olaparib, or of administering chemotherapy, in individual patients

How to minimize these risks in the clinical practice?

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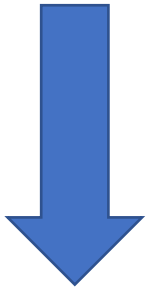
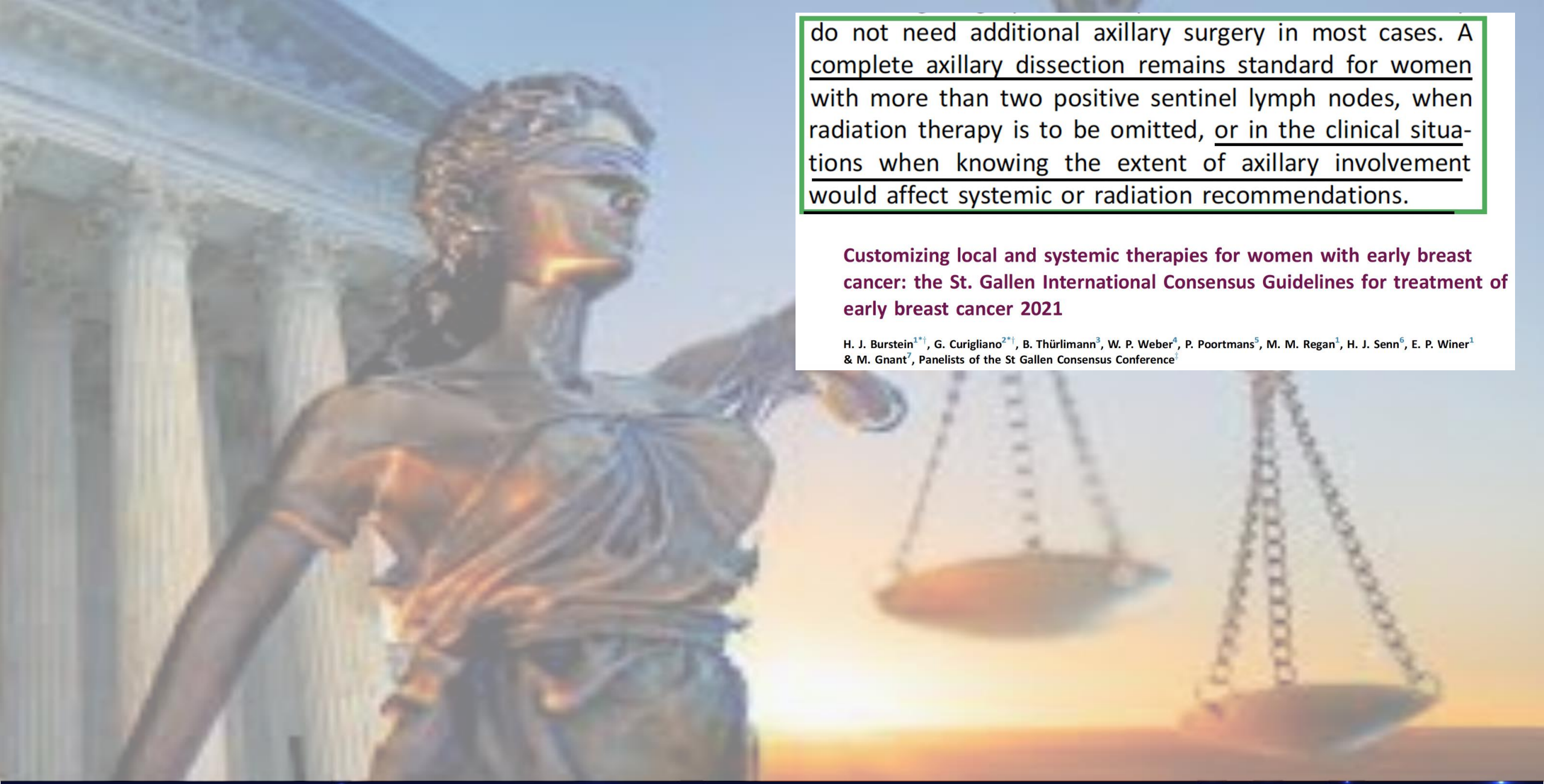
- Personalize surgical treatment of the axilla after post-surgery multidisciplinary discussion that takes into account the potential risks of axillary downstaging and, consequently, of missing the opportunity to prescribe abemaciclib, olaparib, or of administering chemotherapy, in individual patients

If there is the risk of missing an important therapeutic opportunities (e.g., adjuvant chemotherapy and/or abemaciclib, and/or olaparib in patients with *BRCA1/2* mutations)…



Discuss about the possibility to expand surgery in the axilla (ALND after SNB) to obtain a more precise staging and to undertake more appropriate therapeutic decisions



do not need additional axillary surgery in most cases. A complete axillary dissection remains standard for women with more than two positive sentinel lymph nodes, when radiation therapy is to be omitted, or in the clinical situations when knowing the extent of axillary involvement would affect systemic or radiation recommendations.

Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021

H. J. Burstein[1*†], G. Curigliano[2*†], B. Thürlimann[3], W. P. Weber[4], P. Poortmans[5], M. M. Regan[1], H. J. Senn[6], E. P. Winer[1] & M. Gnant[7], Panelists of the St Gallen Consensus Conference[‡]

Conclusions

- Recent therapeutic progress in patients with high-risk disease (abemaciclib, olaparib), or for treatment tailoring (e.g., adjuvant ChT vs. no ChT) in patients with surgically-resected, node positive BC have re-opened the debate about SLNB vs. ALND in patients with cT1-2 cN0 BC and 1-2 positive lymph nodes

- Despite the fact that several details regarding axillary surgery in patients enrolled in MonarchE, OLYMPIA and Rxponder, these studies were conducted in an era in which recent guidelines for the surgical treatment of the axilla had already been implemented in several centers. Therefore, excellent results from these trials are reassuring, and they suggest that the riskl of axillary downstaging and inappropriate therapeutic decisions is overall low

- However, discussing individual therapeutic decisions (also about SLND vs. ALND) in the context of multidisciplinary teams may lead to treatment personalization also regarding surgery of the axilla, thus increasing he chances to achieve an ccurate staging for the most appropriate therapeutic decision

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L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

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2023 ROMA
THE HIVE HOTEL
Via Torino, 6

Thank you for your attention!

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