L’omissione della stadiazione ascellare nel carcinoma mammario ER-positivo:

implicazioni per le terapie adiuvanti

ore 11.20 Implicazioni per la terapia sistemica adiuvante
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Università degli Studi di Milano-Bicocca

Disclosure

Honoraria for Consultancy and Advisory Board from:

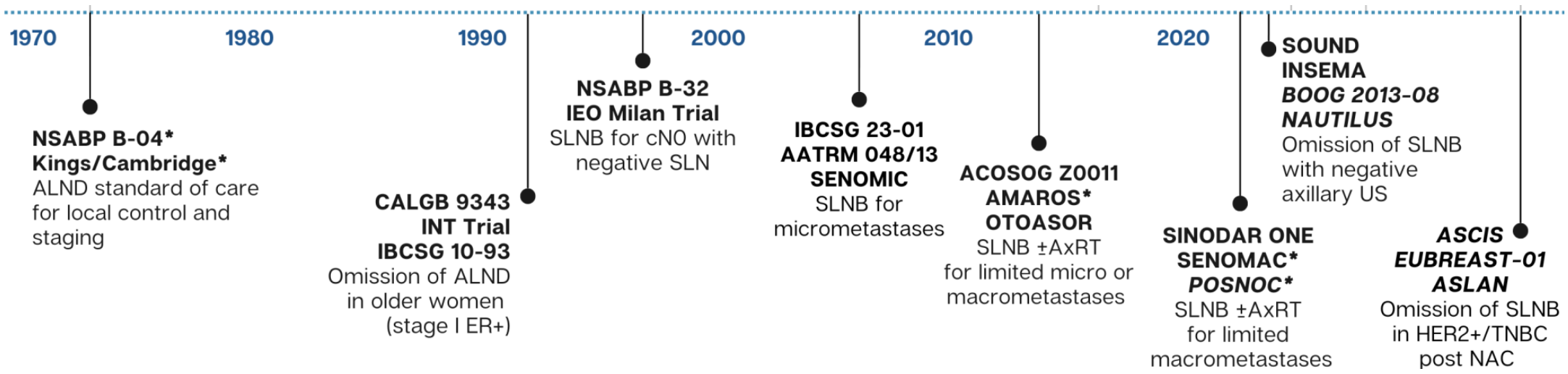
Roche, Novartis, Lilly, AstraZeneca, Pfizer, MSD, Daiichi Sankyo, Gilead, MenariniStemline, Merck, Exact Sciences.

Key Points

- ✓ No randomized trials have ever shown a disease-free survival or ovarall survival advantage b/w ALND vs. AxRT

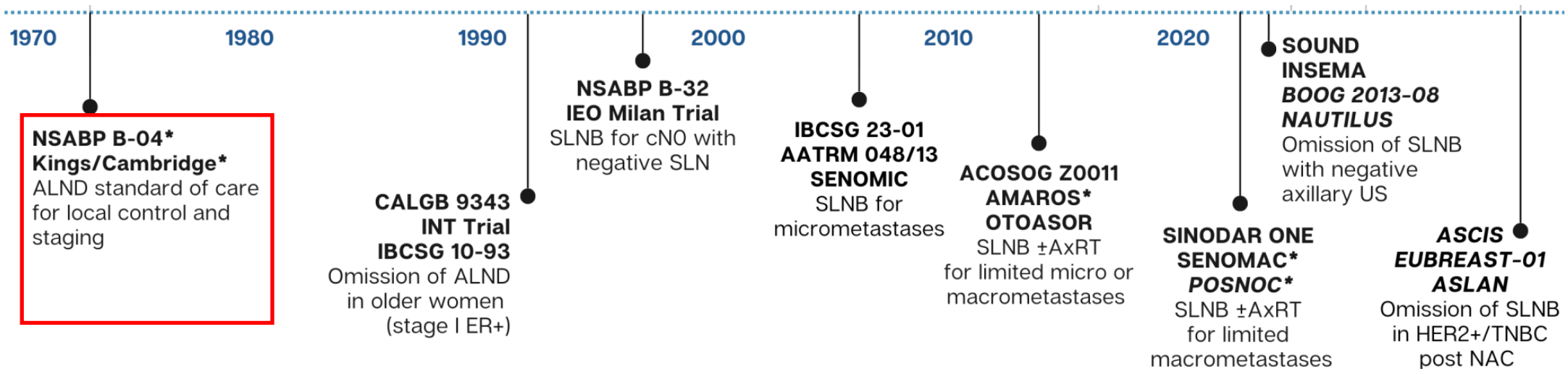
- ✓ Isolated axillary recurrences are a rare event

Axillary management cN0



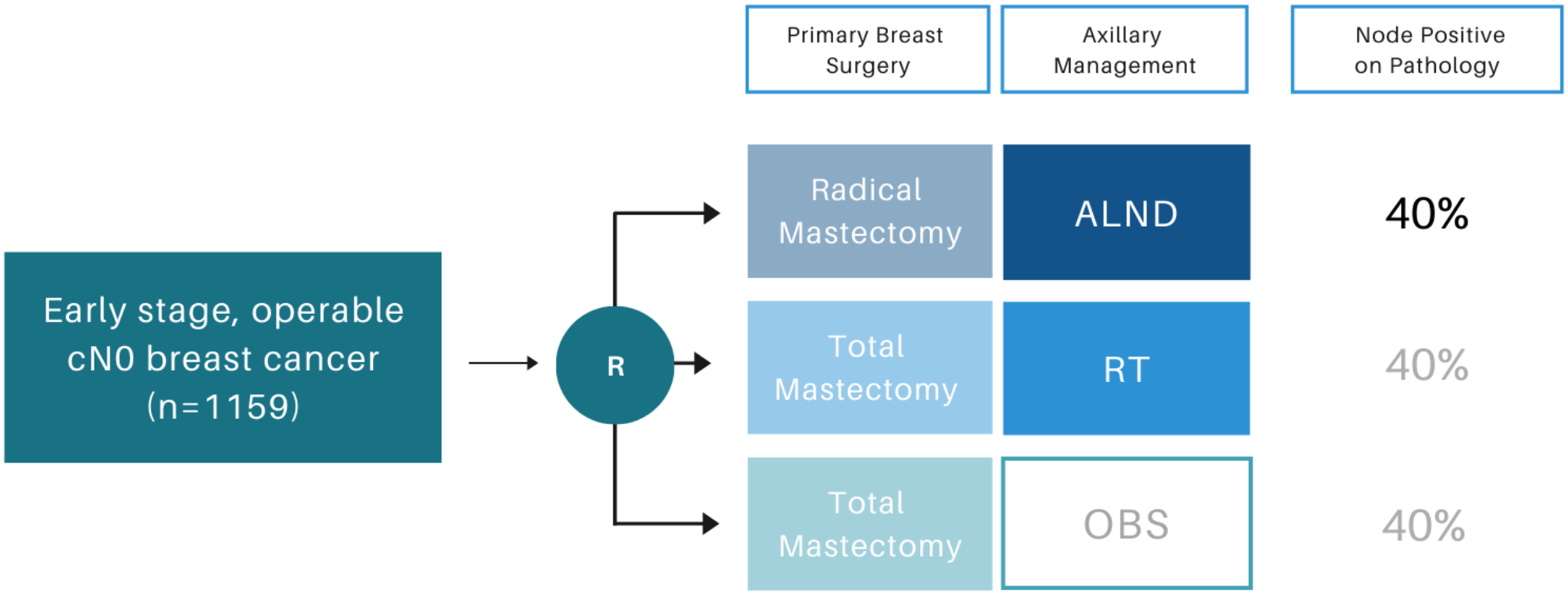
Adapted from T King; *Axillary RT used; *Italics indicate ongoing trials*

Axillary management cN0



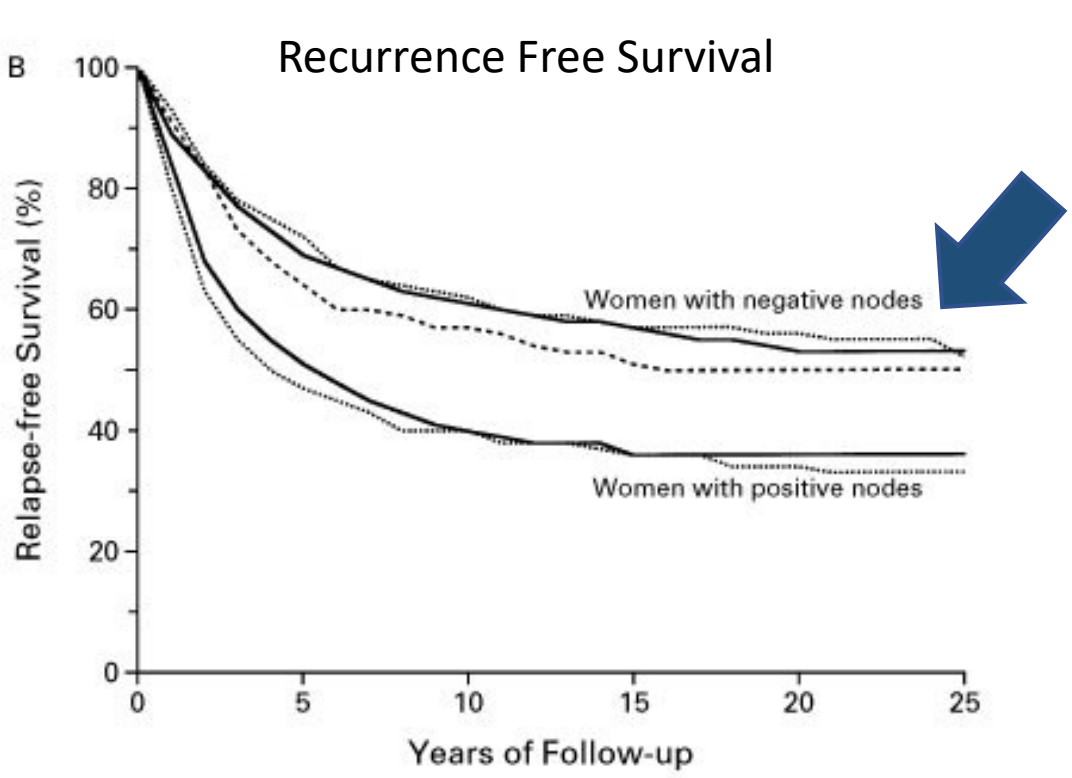
Adapted from T King; *Axillary RT used; *Italics indicate ongoing trials*

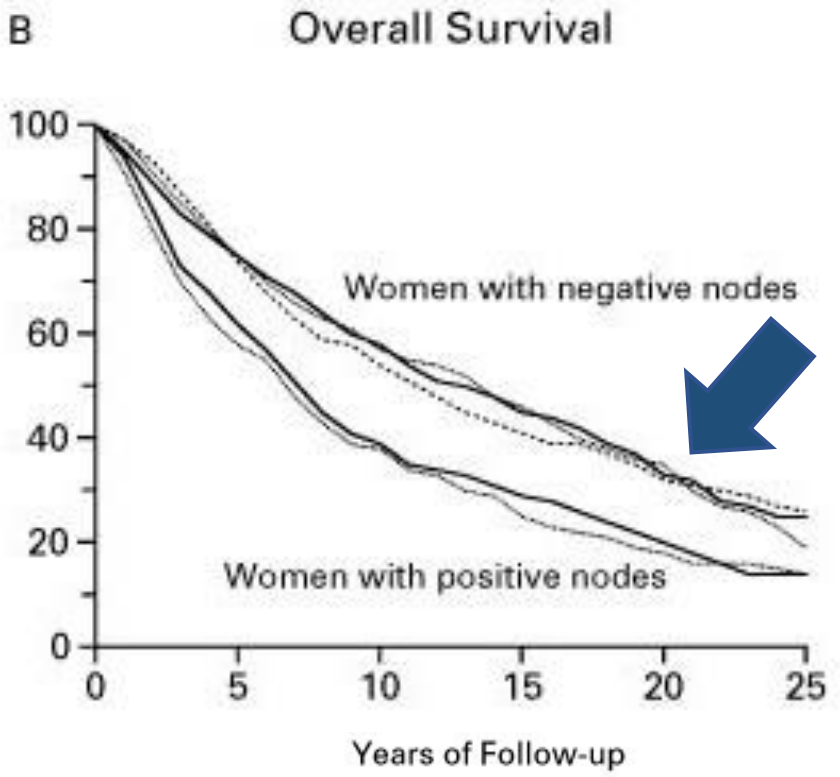
NSABP-B04 (cN0)



Fisher et al. NEJM 1985, NEJM 2002

NSABP-B04

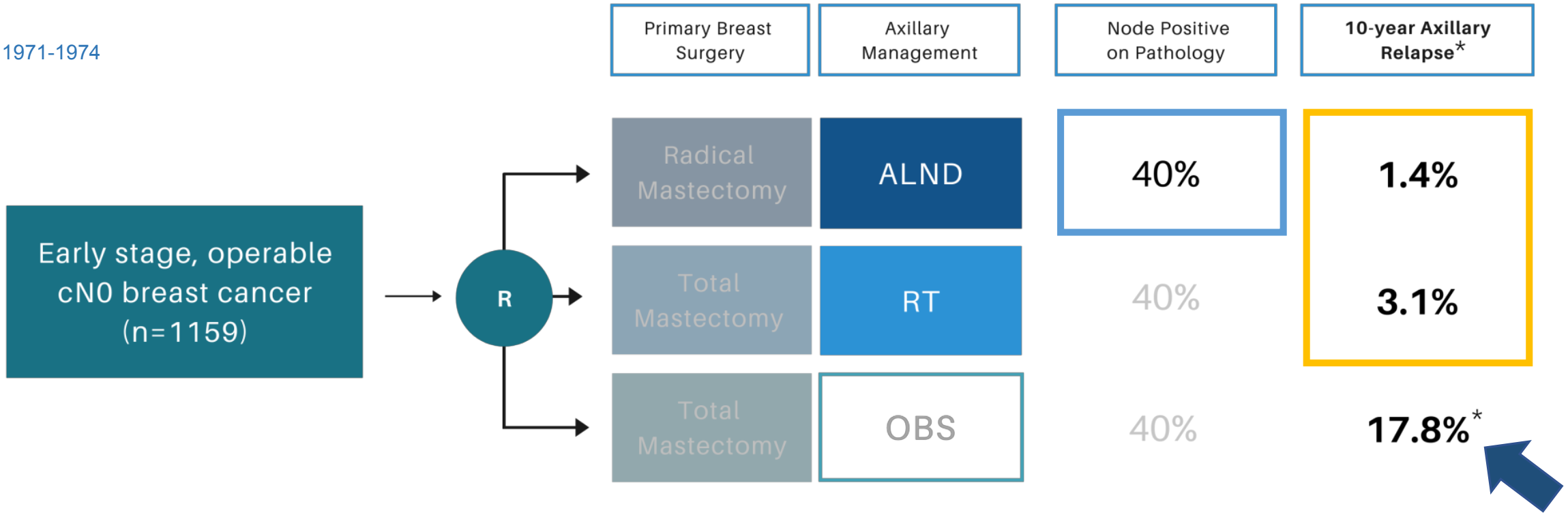




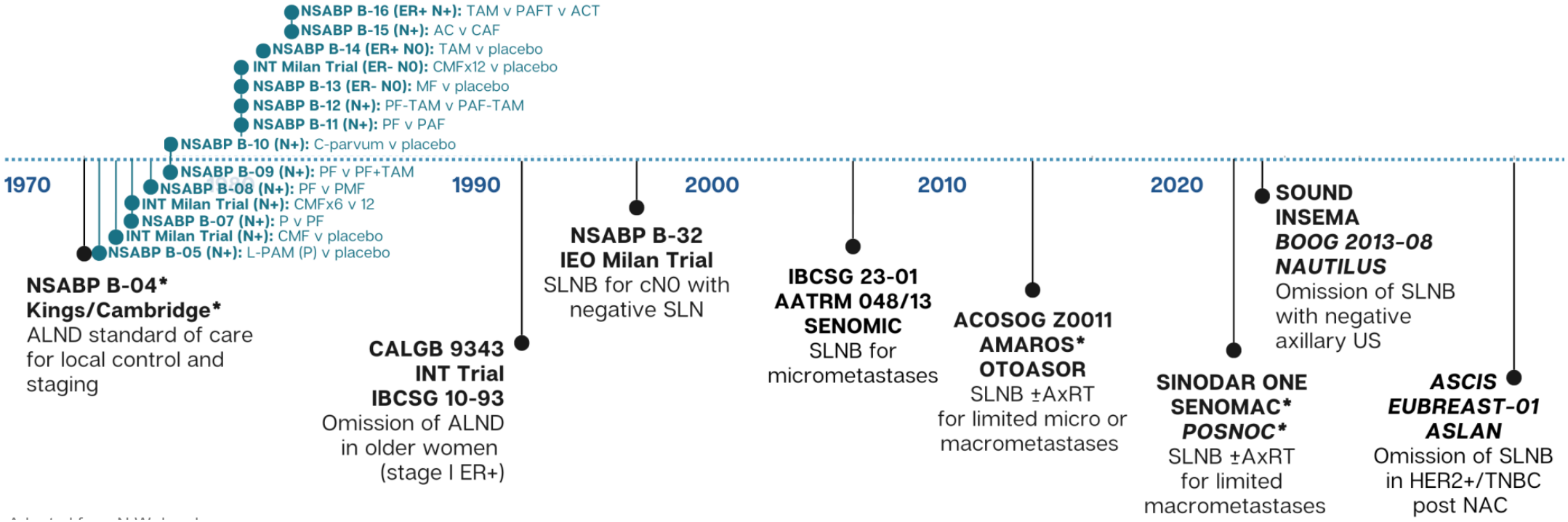
Axillary management (ALND vs. RT) did not alter survival

NSABP-B04

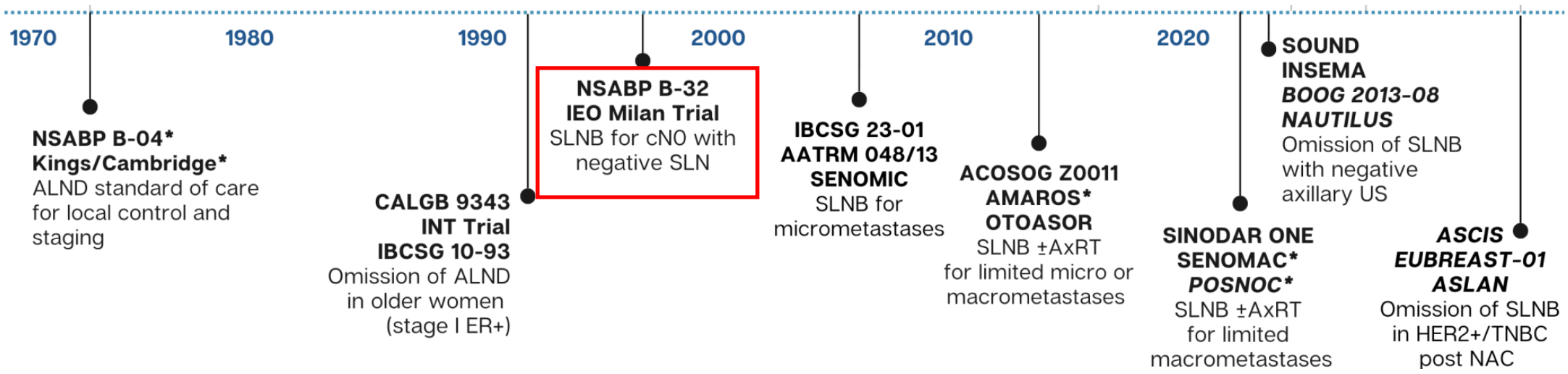
1971-1974



Adj CT trials required ALND for N staging



Axillary management cN0



Adapted from T King; *Axillary RT used; *Italics indicate ongoing trials*

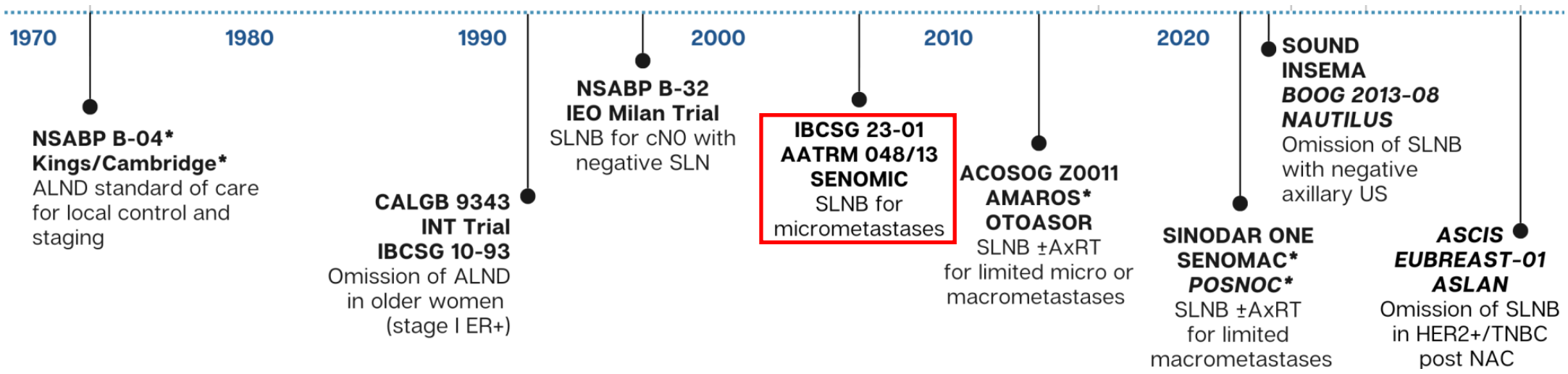
SNLB validation trials

	SIR	No. SLN Removed	FNR	% SLN+	Outcomes: ALND *v* SLNB in SLN- patients
Milan Trial (n=516) 1998-1999 <2 cm, Treated with BCS Neg SLN: ALND *v* SLNB alone	98.8%	Mean 1.7	8.8%	35.5%	Median FU: 3.8 years No difference in DFS, OS **Axillary recurrences:** 0 both arms
NSABP B-32 (n=5611) 1994-2004 Treated with BCS or mastectomy Neg SLN: ALND *v* SLNB alone	97.3%	Median 2 (IQR, 1-4)	9.8%	26%	No difference in 10-yr LRR, DFS, OS **Axillary recurrences:** <0.5% both arms

SLN+ (ALND arm): in 61.4% of cases, the SLN was the only one positive node identified

Veronesi et al, NEJM 2003;
Krag et al, Lancet Oncol 2007

Axillary management cN0



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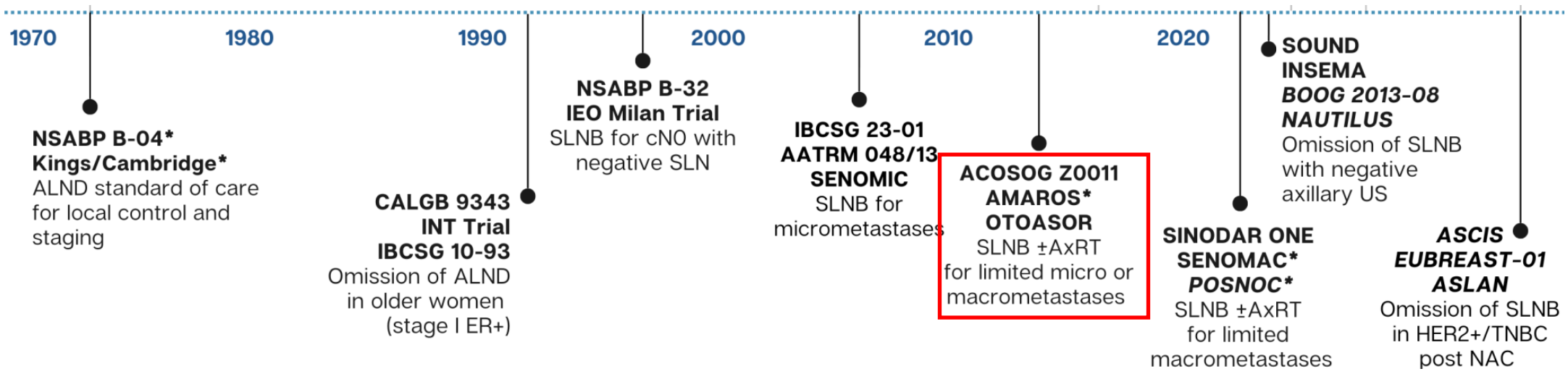

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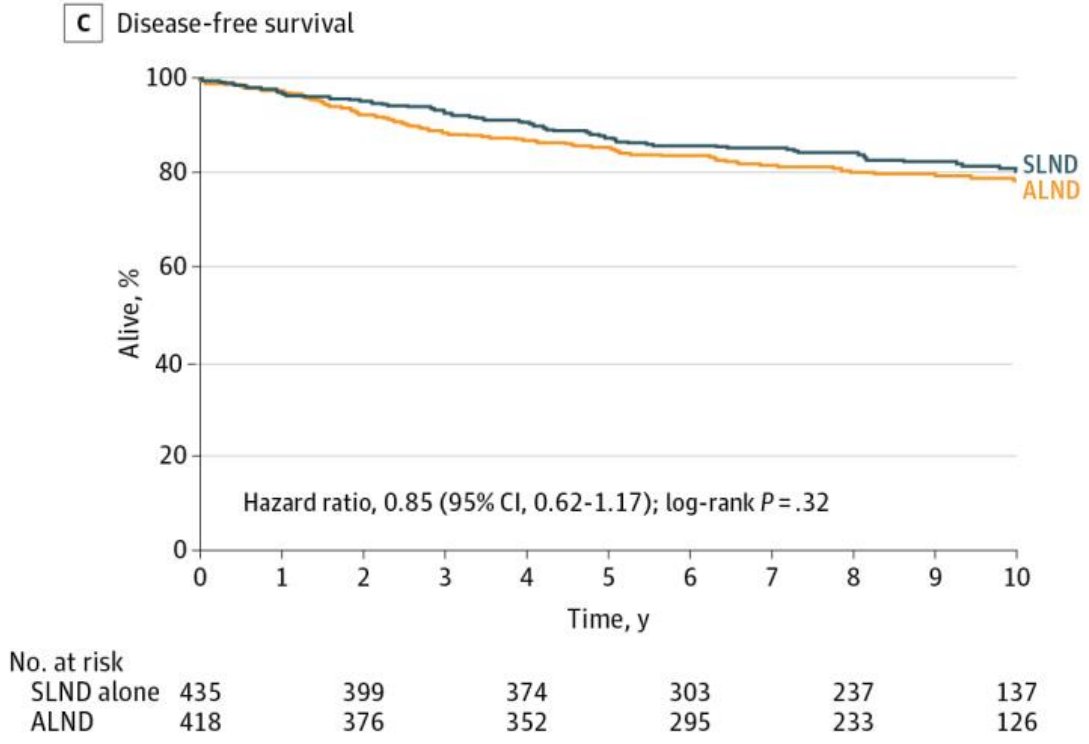
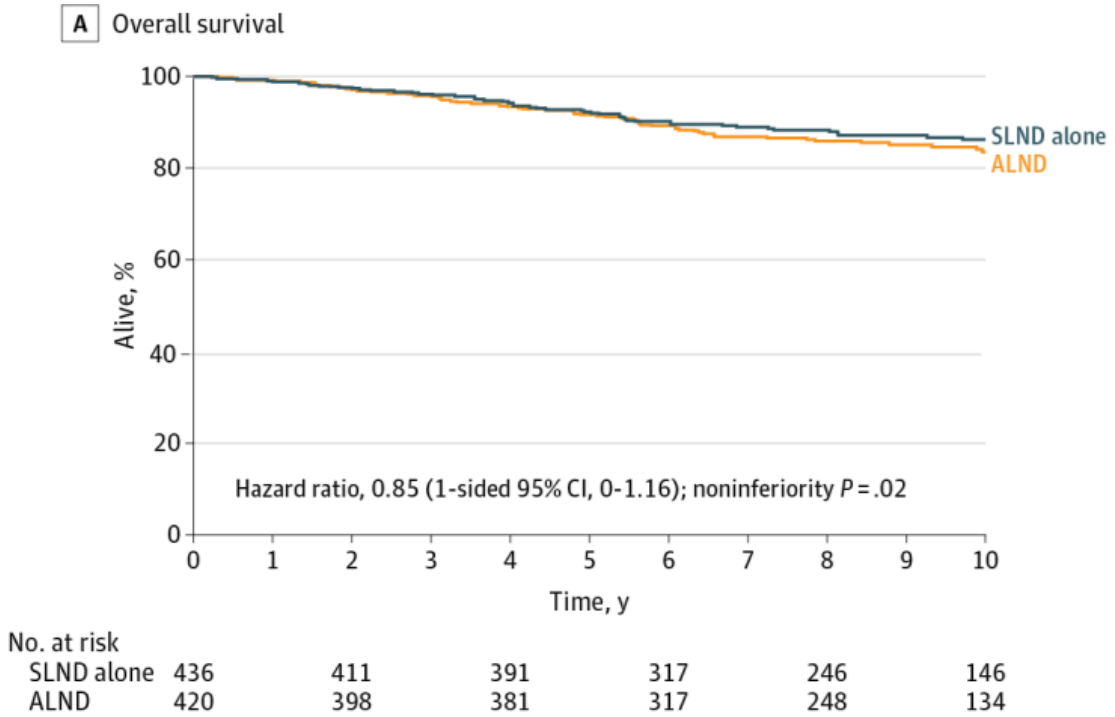
ACOSOG Z0011

1999-2004





10-yrs Axillary recurrence: 0.5 (ALND) vs 1.5% (SLNB alone)

Outcomes from cN0 SLN+ trials in upfront surgery

Micrometastatic SLN	Tumor Size	No. SLN+	BCS (%)	Axillary management	Positive non-SLN on cALND (%)	**Axillary recurrences (%)**	Median FU (years)
IBCSG 23-01 (n=931)	≤5 cm	≤2	91%	ALND *v* observation	13%	**<1.0% *v* 2.0%**	10
AATRM (n=233)	<3.5 cm	≥1	88%	ALND *v* observation	13%	**1.0% *v* 1.7%**	5.1
SENOMIC (n=566)	≤5 cm	≤3	62%	Observation	-	**0.9%**	3.2

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Micro- and Macrometastatic SLN							
Z0011 (n=856)	≤5 cm	≤2	100%	ALND *v* observation	27%	**0.5% *v* 1.5%**	10
AMAROS (n=1425)	≤5 cm	≤4[†]	83%	ALND *v* AxRT	33%	**0.9% *v* 1.8%**	10
OTOASOR (n=474)	≤3 cm	≤2	84%	ALND *v* AxRT	39%	**2.0% *v* 1.7%**	8

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Macrometastatic SLN							
SINODAR ONE (n=889)	≤5 cm	≤2	76%	ALND *v* observation	44%	**0.2% *v* 0.2%**	2.8
SENOMAC (n=2540)	≤10 cm	≤2	64%	ALND *v* AxRT*	35%	**<0.4% *v* <0.5%**	3.9

Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
- cNo mastectomy population with 1-2 SLN+
- Pts with 3 pts SLNs
- ALND to determine eligibility for adj systemic therapies

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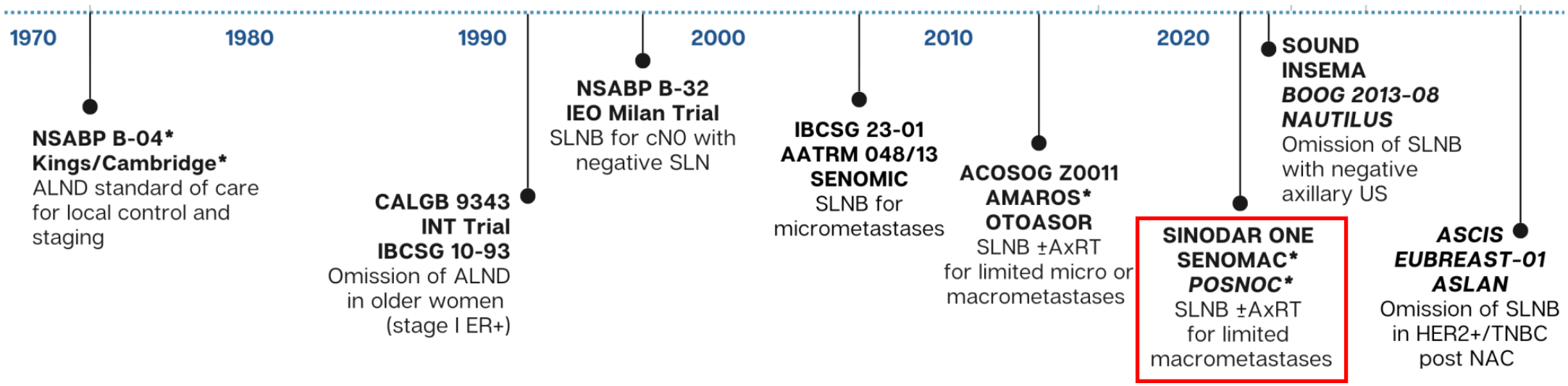
Axillary management cN0

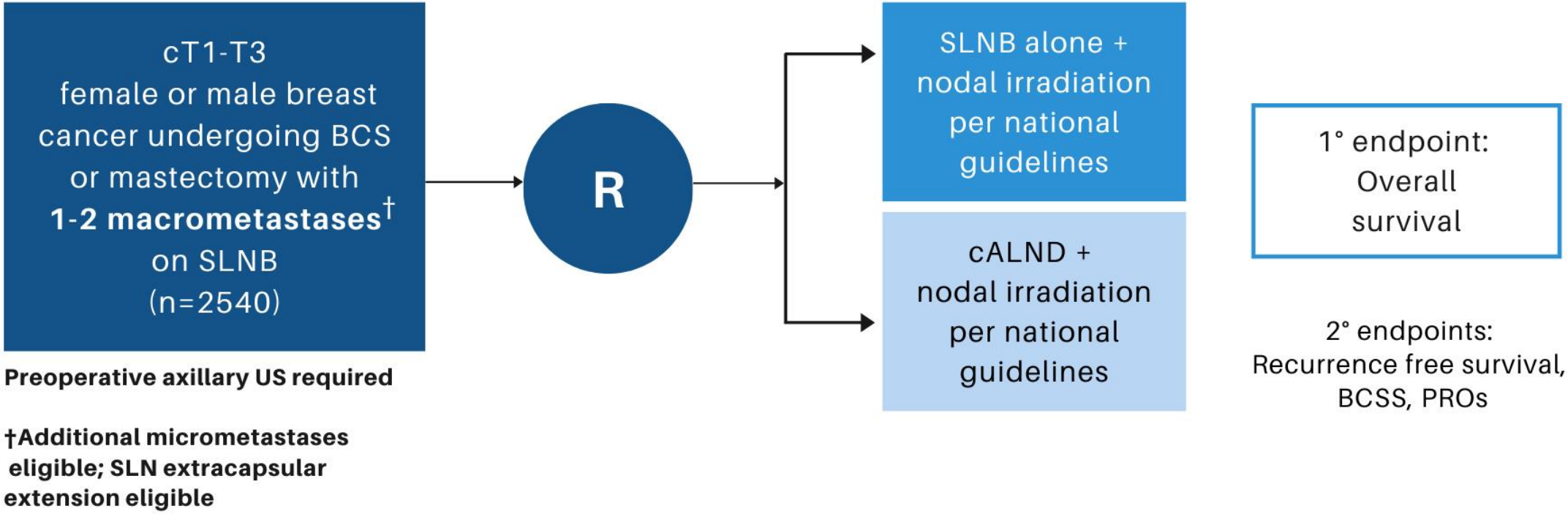


Adapted from T King; *Axillary RT used; *Italics indicate ongoing trials*

SENOMAC

2015-2021

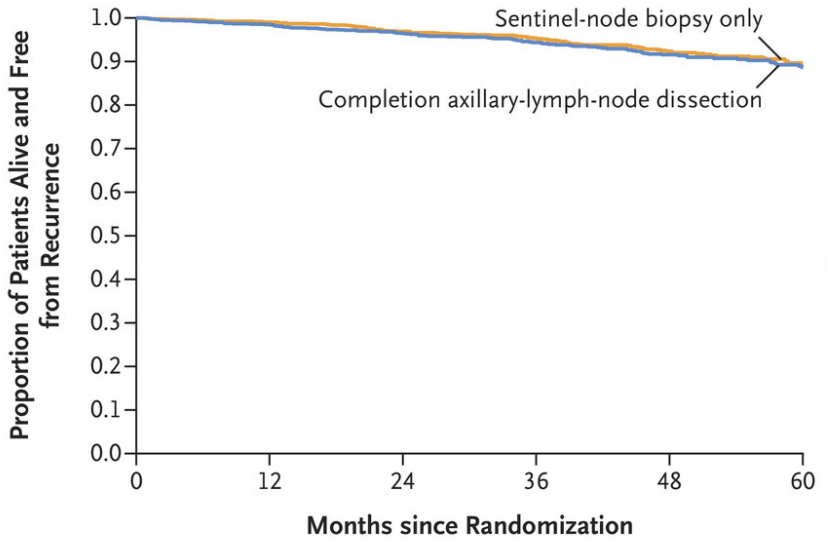
Cohort characteristics:
Median age: 61 years
94% T1-T2 tumors
87% HR+HER2-
89% received nodal RT



No difference in 5-yrs RFS: 89.7% SLNB vs. 88.7% cALND (HR=0.89 (CI 0.66-1.19)

SENOMAC: results (cT3)

2015-2021



No. at Risk

Sentinel-node biopsy only	1335	1276	1069	832	577	307
Dissection	1205	1159	1009	772	544	274

Tumor Size	SLNB only	cALND	HR for recurrence or death (95% CI)
T1 or T2 (n=2393)	84/1262	81/1131	0.94 (0.69-1.28)
T3 (n=147)	5/73	10/74	0.47 (0.16-1.39)
Extracapsular extension			
Yes (n=870)	34/461	31/409	0.94 (0.58-1.54)
No (n=1662)	55/871	60/791	0.86 (0.60-1.25)

SLNB better 1.0 cALND better

No difference in 5-yrs RFS: 89.7% SLNB vs. 88.7% cALND (HR=0.89 (CI 0.66-1.19)

Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
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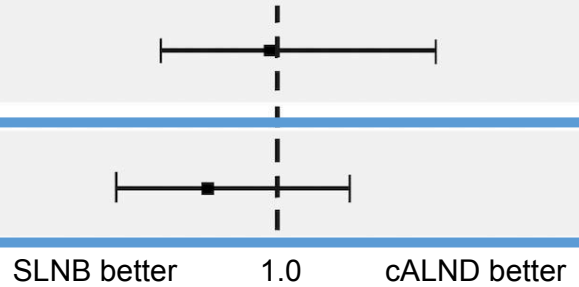
Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
- **cNo mastectomy population with 1-2 SLN+**
- Pts with 3 pts SLNs
- ALND to determine eligibility for adj systemic therapies

SENOMAC (mastectomy)

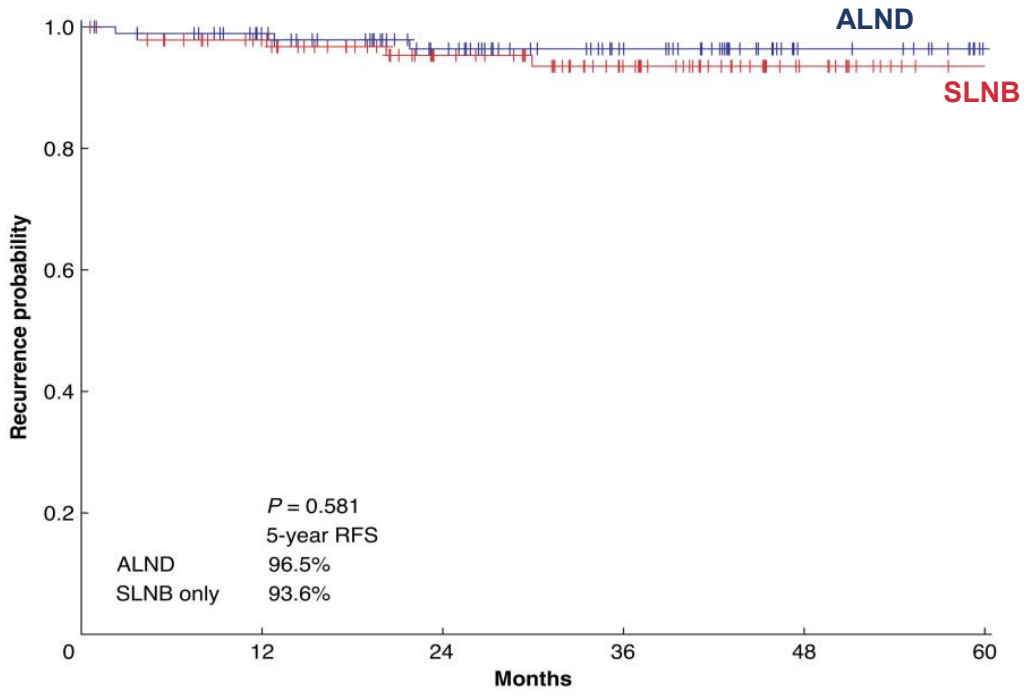
Breast Surgery	SLNB only	cALND	HR for recurrence or death (95% CI)
BCS (n=1620)	48/845	46/775	0.98 (0.65-1.47)
Mastectomy (n=920)	41/490	45/430	0.79 (0.52-1.21)



Mastectomy pts with 1-2 SLN+ (macromets)
Axillary RT recommended to provide effective local control

SINODAR-ONE (mastectomy)

Mastectomy cohort:
Median age: 53 years
45% T1-T2 tumors
84% HR+HER2-
17% received RT
(8% in the SLNB arm)



No. at risk						
ALND	100	86	65	43	20	9
SLNB only	100	87	58	39	17	4

No difference in 5-yrs RFS (mastectomy cohort): 93.6% SLNB vs. 96.5% cALND (p=0.58)

Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
- cNo mastectomy population with 1-2 SLN+
- Pts with 3 pts SLNs
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Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
- cNo mastectomy population with 1-2 SLN+
- **Pts with 3 pts SLNs**
- ALND to determine eligibility for adj systemic therapies

A rare subgroup that is managed w/o ALND

"For exactly three positive lymph nodes, there is not enough evidence to make a recommendation, and therefore, we recommend **proceeding with ALND and considering locoregional nodal irradiation**."

cN0 with 3-4 SLN+	% AxUS	% ≥3 SLN+	No. pts	Axillary management
AMAROS (n=1425)	**60%**	**4.9%**	71	ALND *v* AxRT
SENOMAC (n=2540)	**100%**	**2%**†	52	ALND *v* AxRT
INSEMA R2 (n=485)	**100%**	-		ALND *v* observation

†Up to 2 macrometastatic SLN with additional micrometastases in 1 or more SLN

Donker et al, Lancet 2015;
Bonafice et al, NEJM 2024;
Reimer et al, Lancet 2023

Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
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Evolving data, current controversies

- cT3N0 (& extracapsular extension with 1-2 SLN+)
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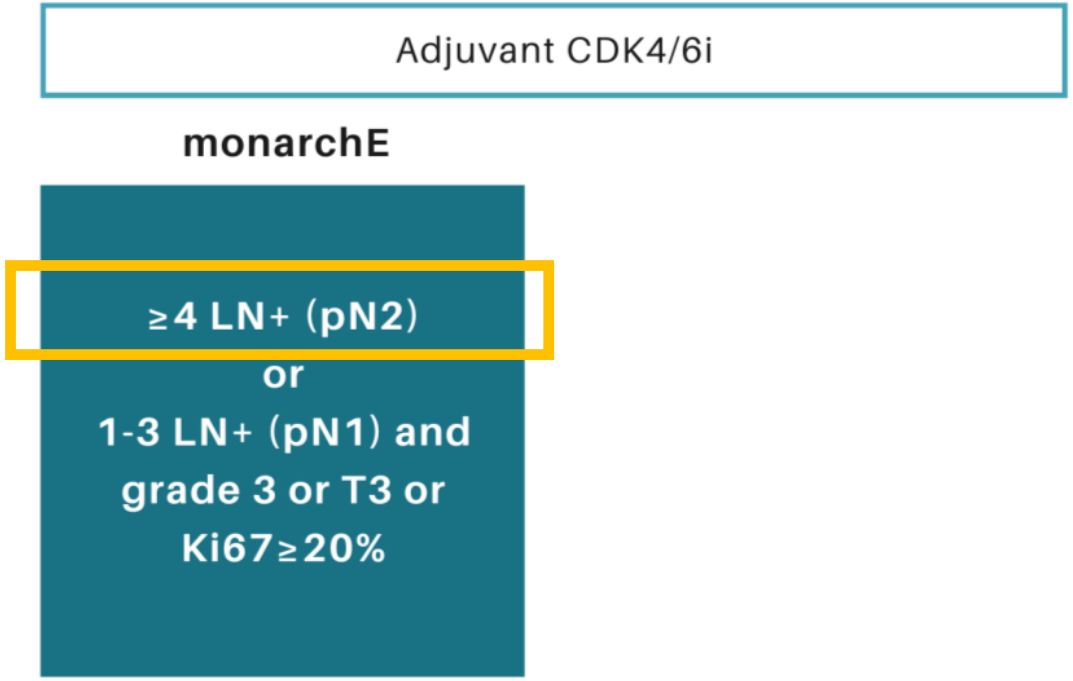
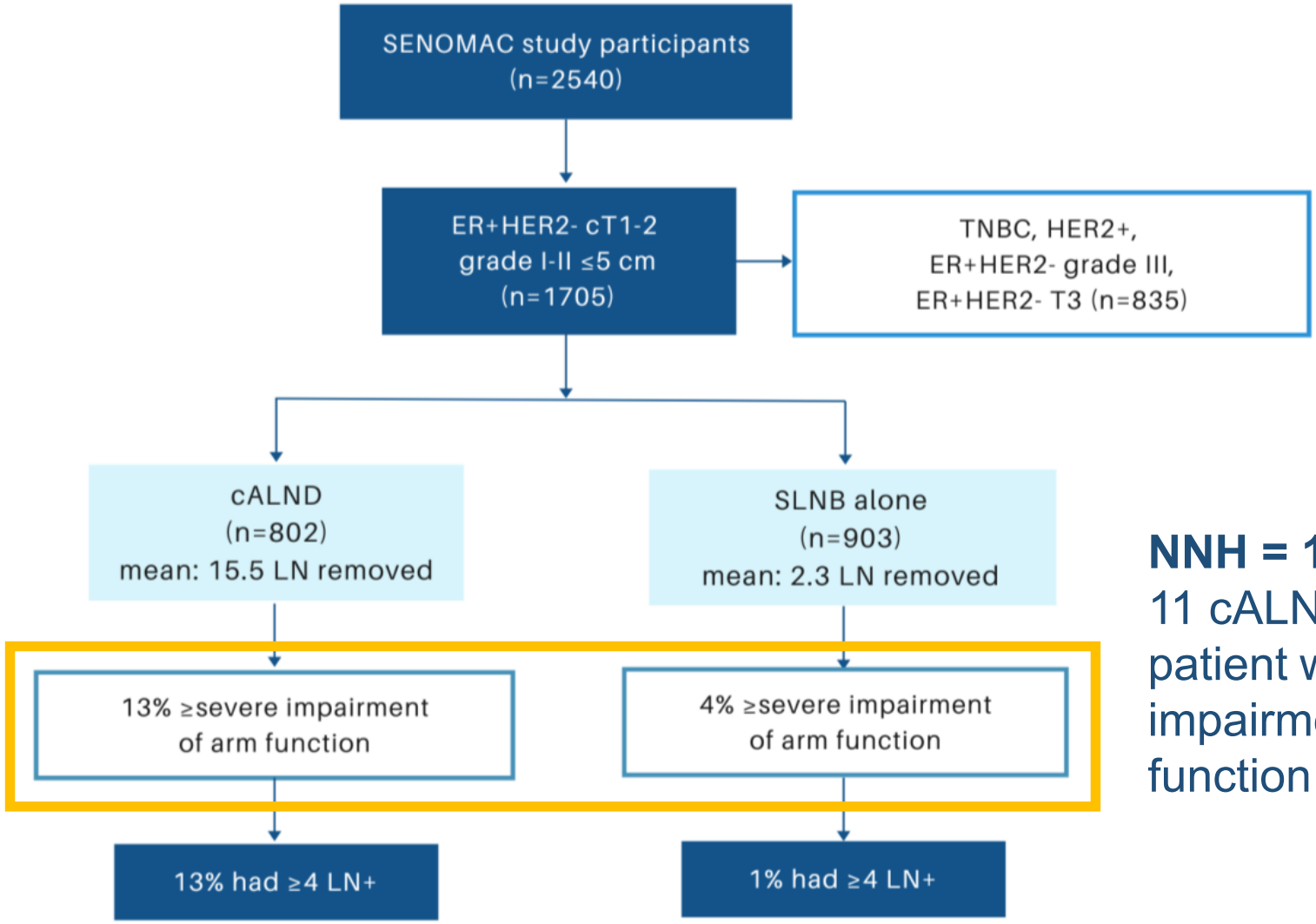
- **ALND to determine eligibility for adj systemic therapies**

Systemic adjuvant Tx according to N+



Tutt et al, NEJM 2021;
Johnston et al, JCO 2020;
Rastogi et al, JCO 2024

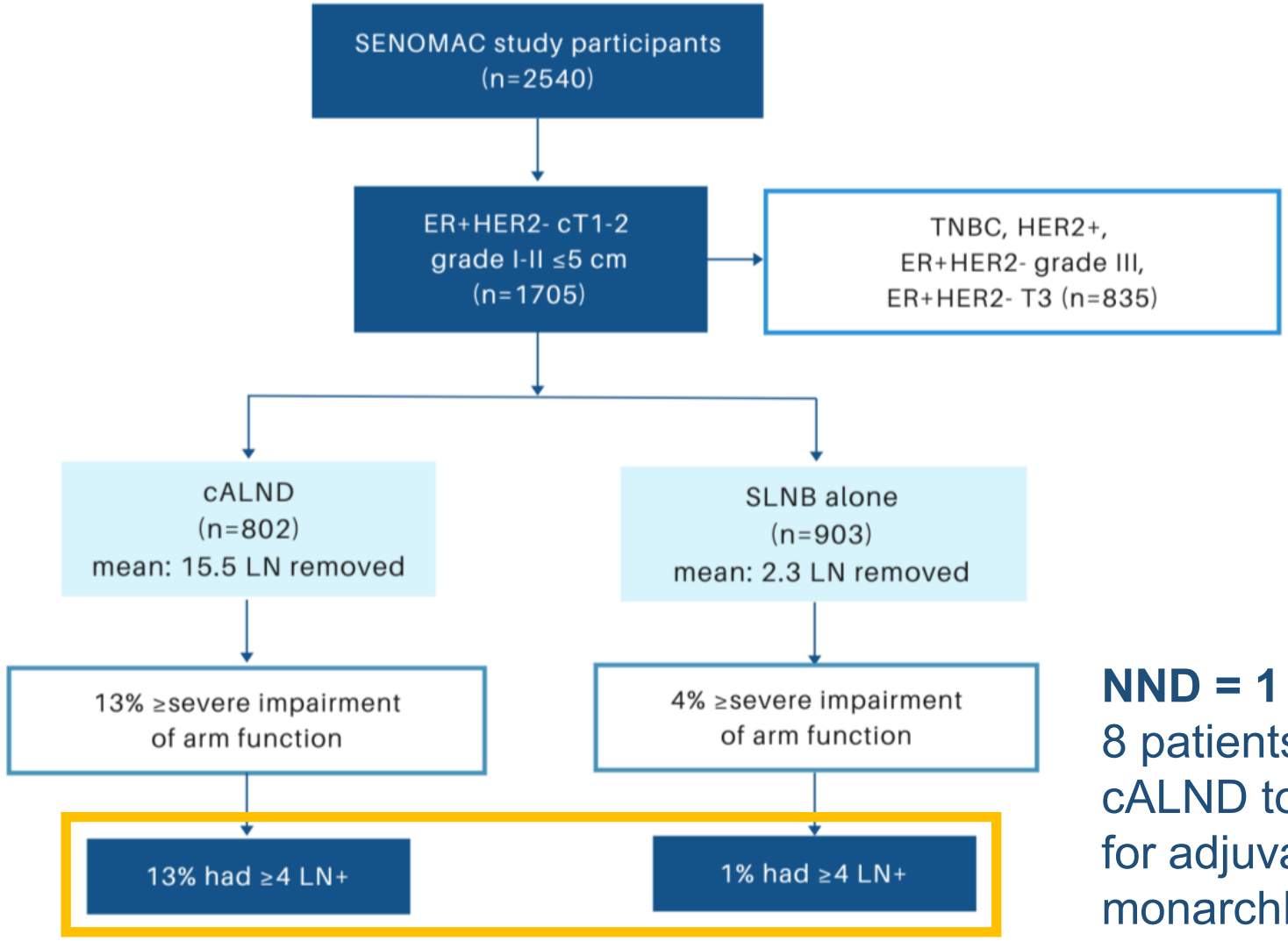
SENOMAC



NNH = 1 / 0.09 = 11

11 cALND results in one patient with ≥ severe impairment in physical arm function

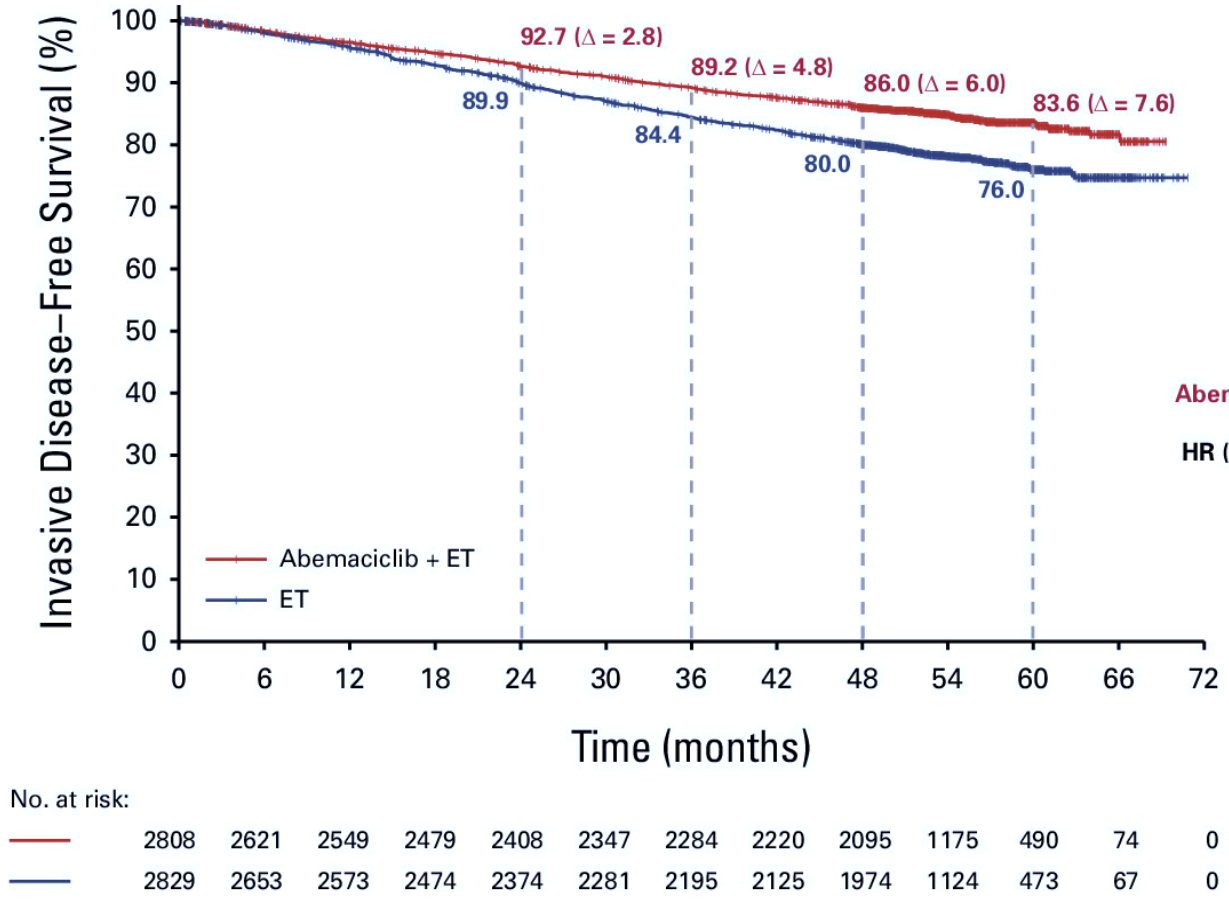
SENOMAC



NND = 1 / 0.12 = 8

8 patients needed to undergo cALND to identify 1 candidate for adjuvant abemaciclib per monarchE eligibility criteria

MonarchE



NNT = 1 / 0.076 = 13

13 patients need to be treated with two years of abemaciclib to avoid 1 IDFS event at 5-years

Abemaciclib + ET	ET alone
n = 407	n = 585

HR (95% CI): 0.680 (0.599,0.772)

Nominal *P* < .001

Clinical impact (HR+/HER2-)

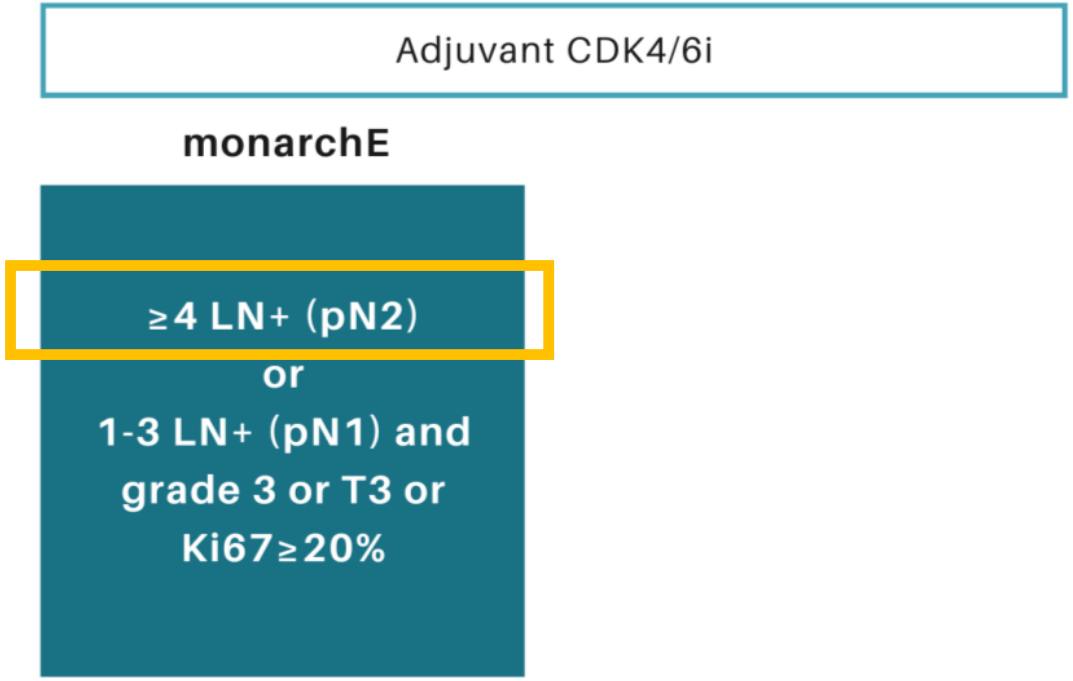
NND x NNT = 104 patients

would need to undergo cALND to avoid one invasive disease-free survival event at 5-years due to the use of abemaciclib;

NNH = 11 patients

needing to undergo cALND results to harm one patient with severe or very severe impairment in physical arm function

Systemic adjuvant Tx according to N+



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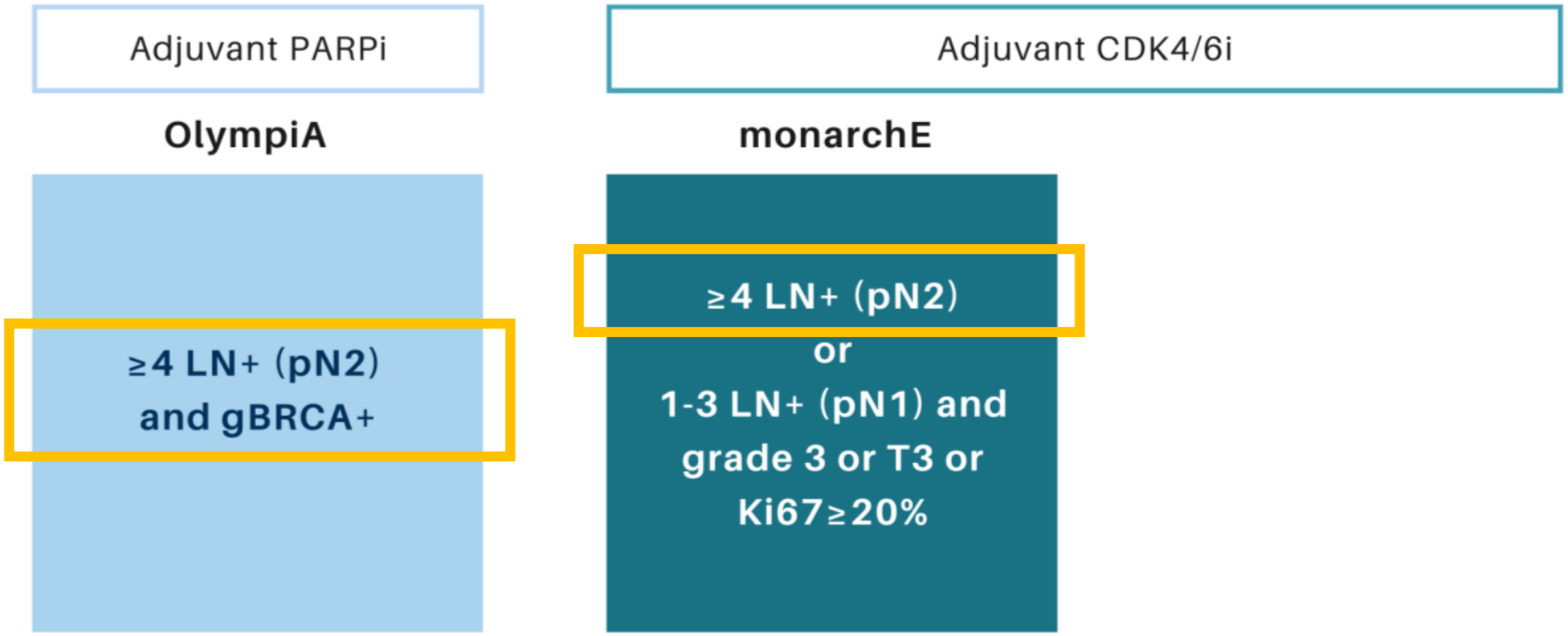

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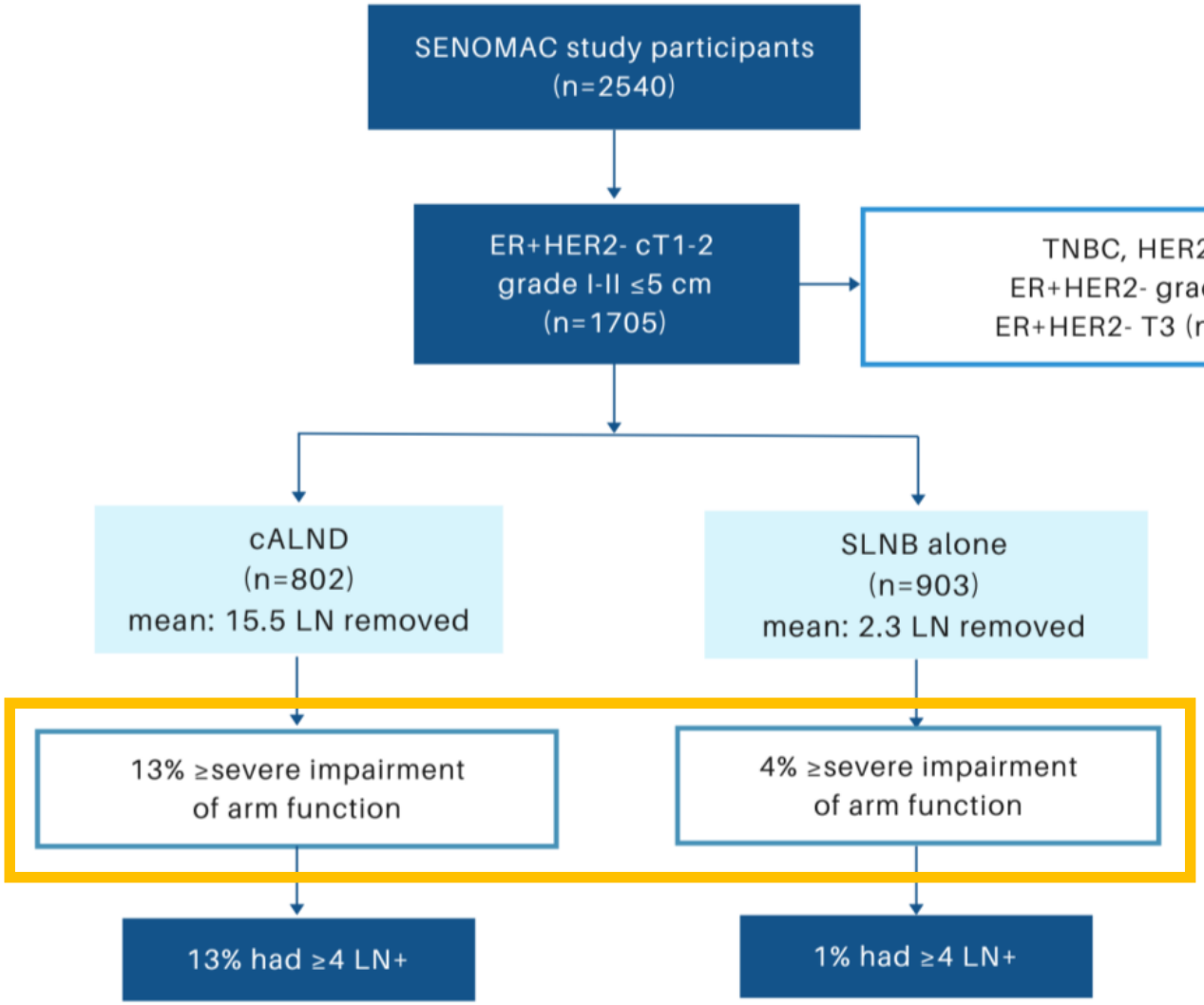
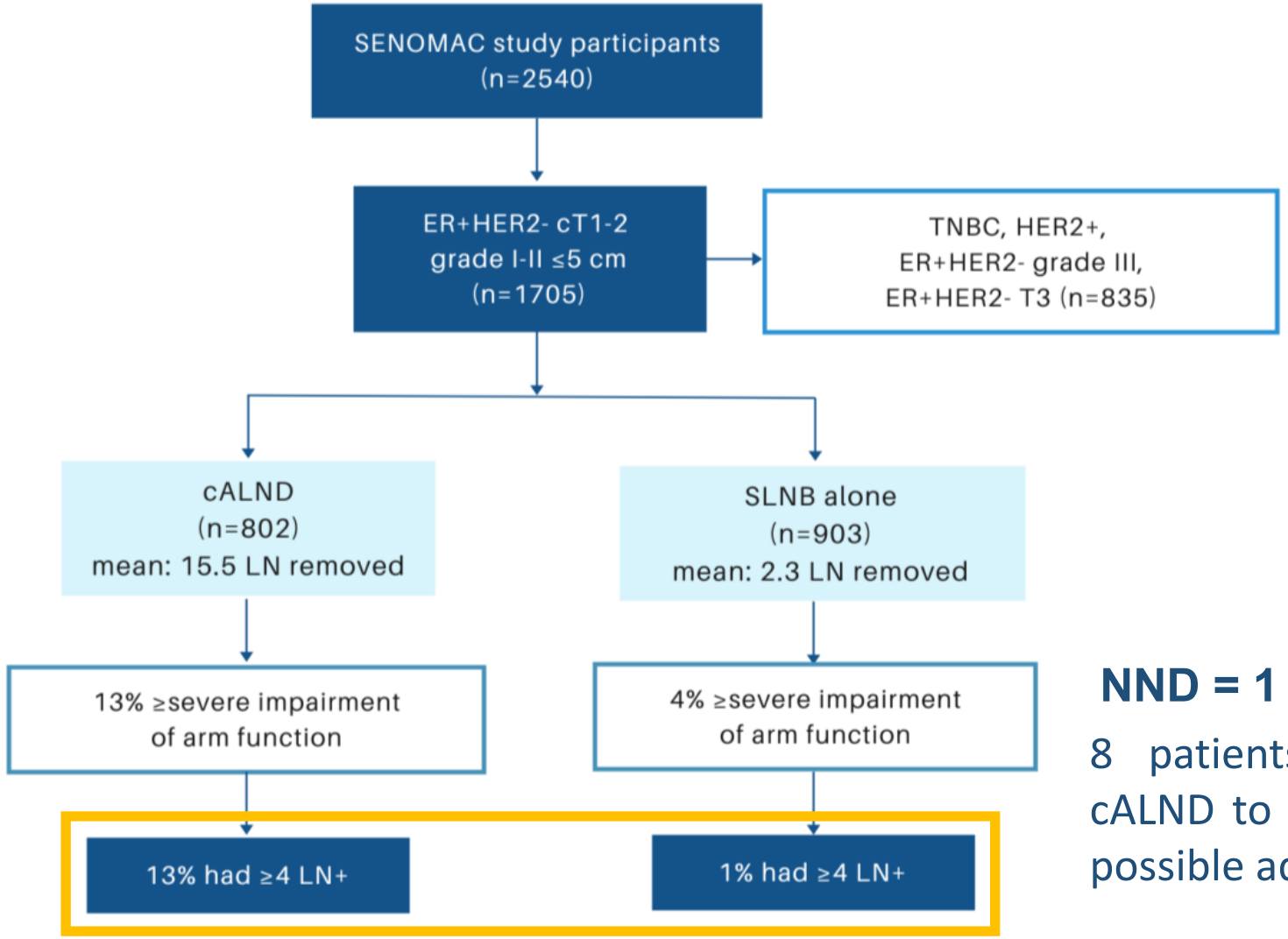
SENOMAC



NNH = 1 / 0.09 = 11

11 cALND results in one patient with ≥ severe impairment in physical arm function

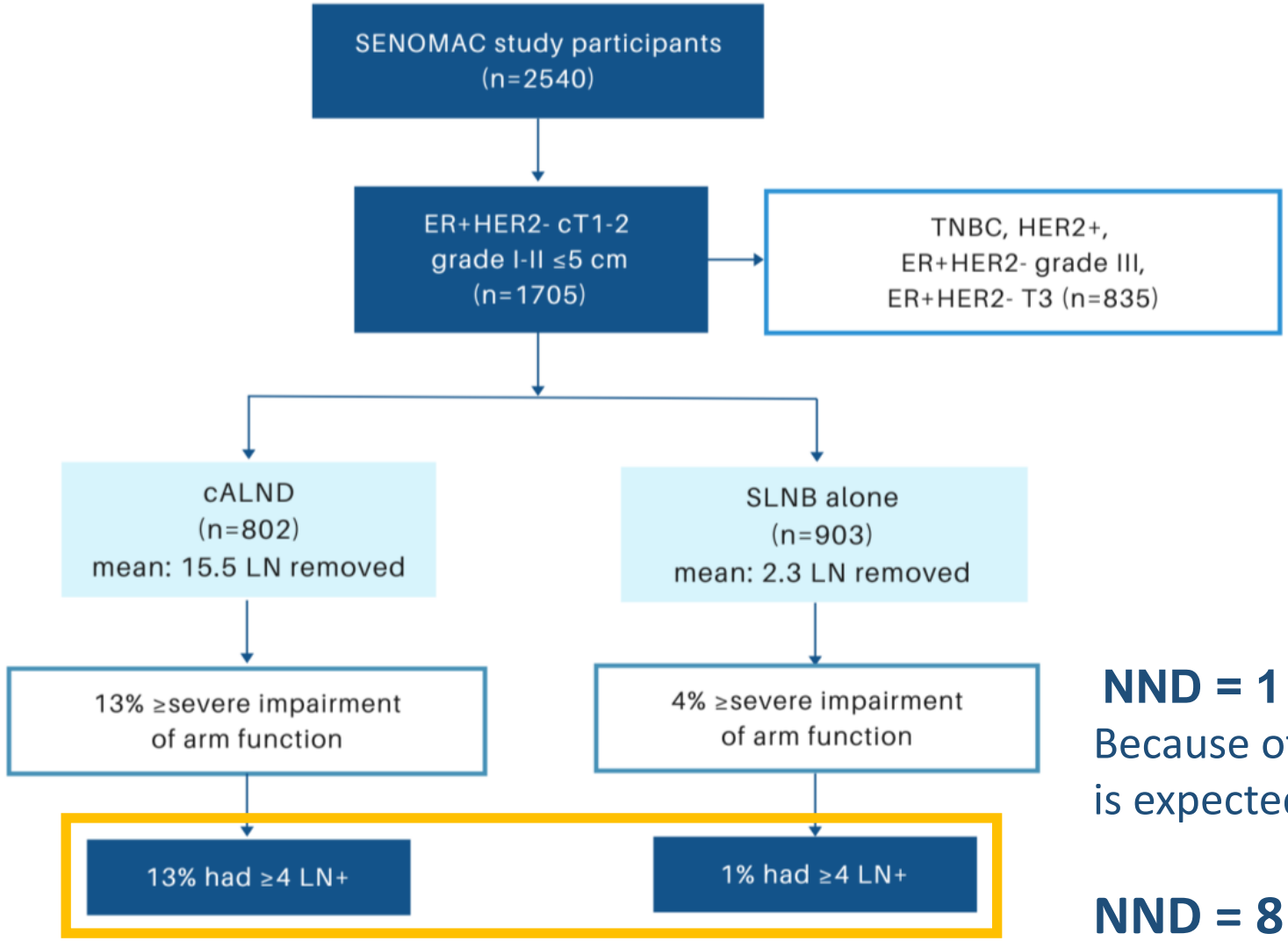
SENOMAC



NND = 1 / 0.12 = 8

8 patients needed to undergo cALND to identify 1 candidate for possible adj olaparib if gBRCAm

SENOMAC

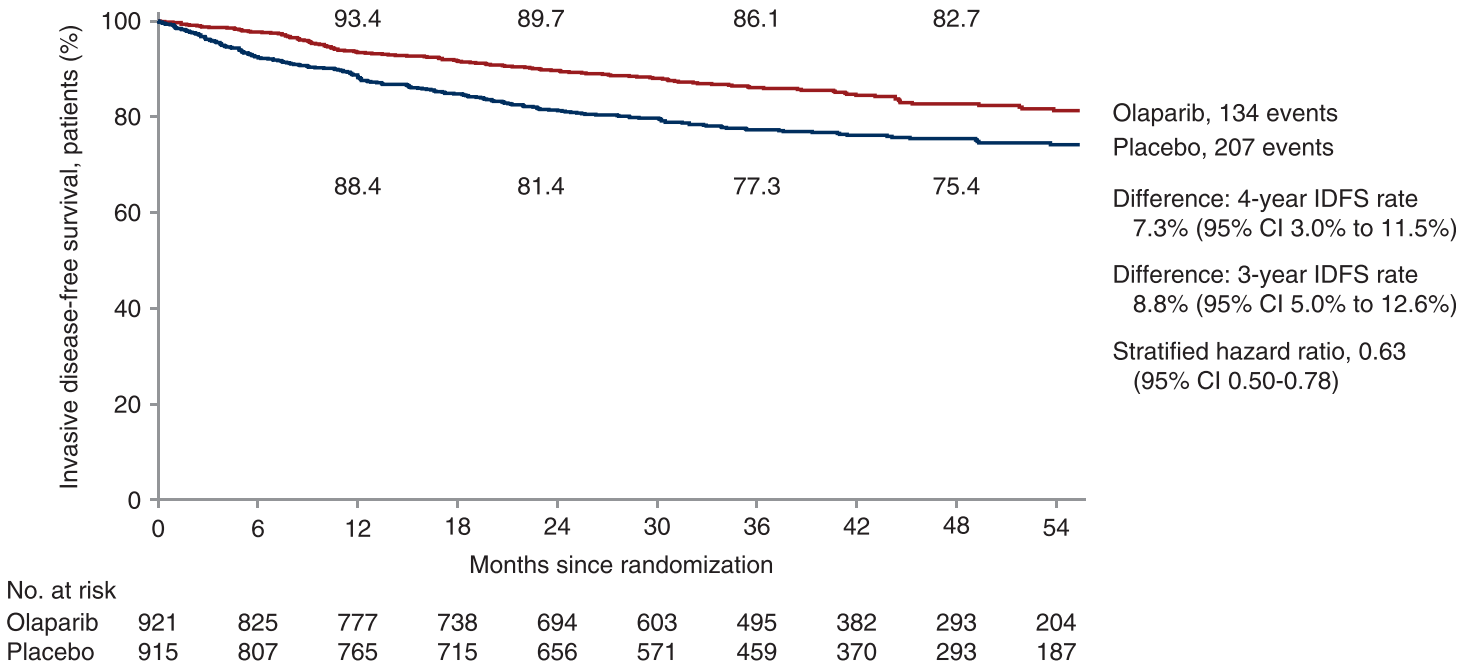


NND = 1 / 0.12 = 8

Because of gBRCAm prevalence is expected up to 5% in HR+ eBC

NND = 8 x 20 = 160

OlympiA results



Olaparib, 134 events
Placebo, 207 events

Difference: 4-year IDFS rate
7.3% (95% CI 3.0% to 11.5%)

Difference: 3-year IDFS rate
8.8% (95% CI 5.0% to 12.6%)

Stratified hazard ratio, 0.63
(95% CI 0.50-0.78)

NTT= 1 / 0.073 = 13

13 patients need to be treated with 1 y of olaparib to avoid 1 IDFS event at 5yrs

Clinical impact (gBRCAm)

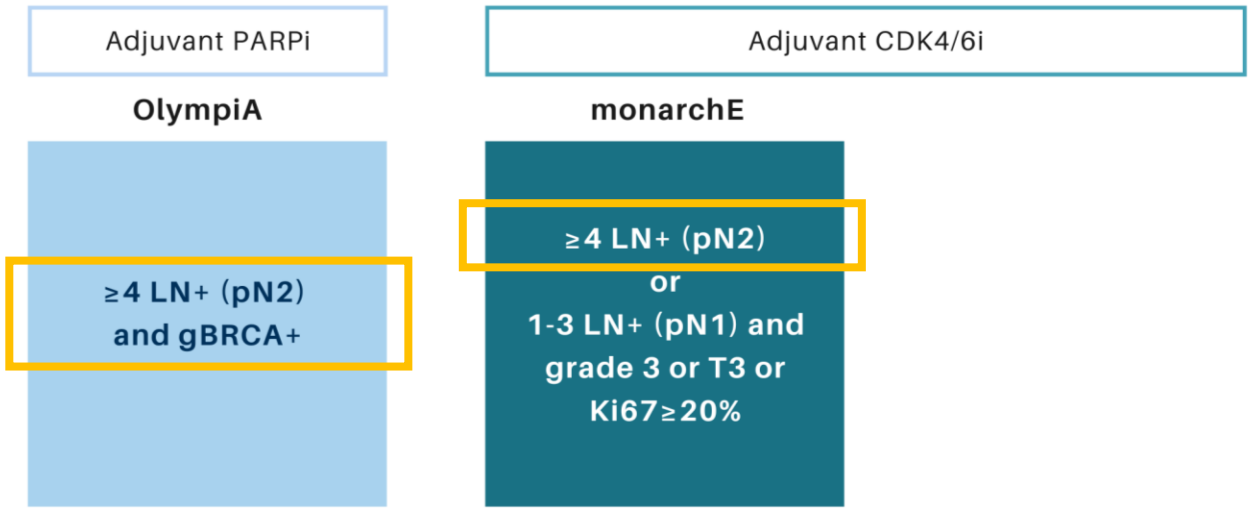
NND x NNT = 2080 patients

would need to undergo cALND to avoid one invasive disease-free survival event at 5-years due to the use of olaparib

NNH = 11 patients

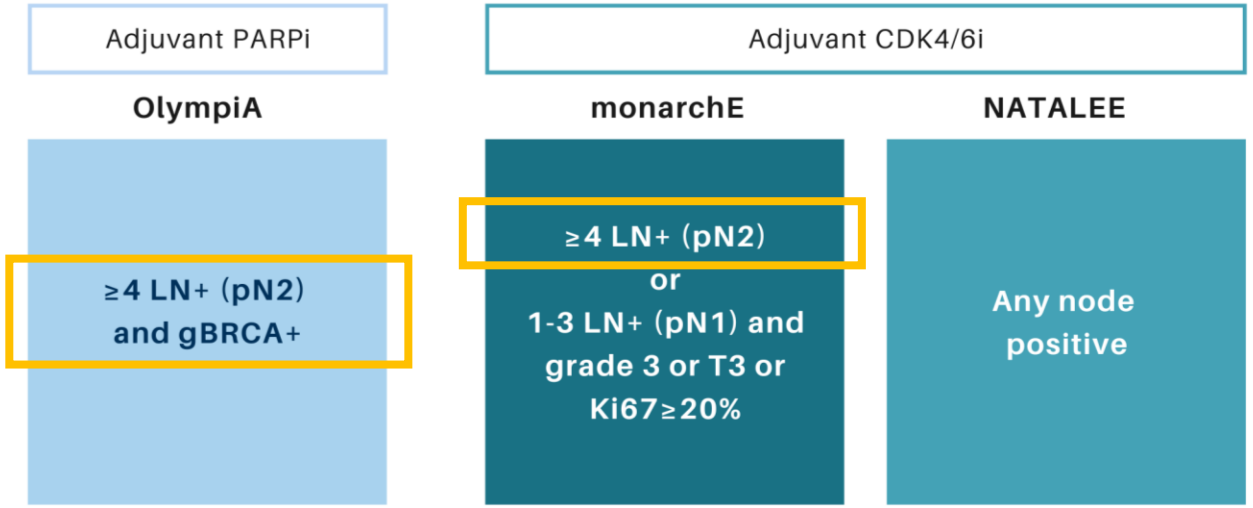
needing to undergo cALND results to harm one patient with severe or very severe impairment in physical arm function

Clinical impact (gBRCAm)



cALND is likely to do more harm than good.

Clinical impact (gBRCAm)

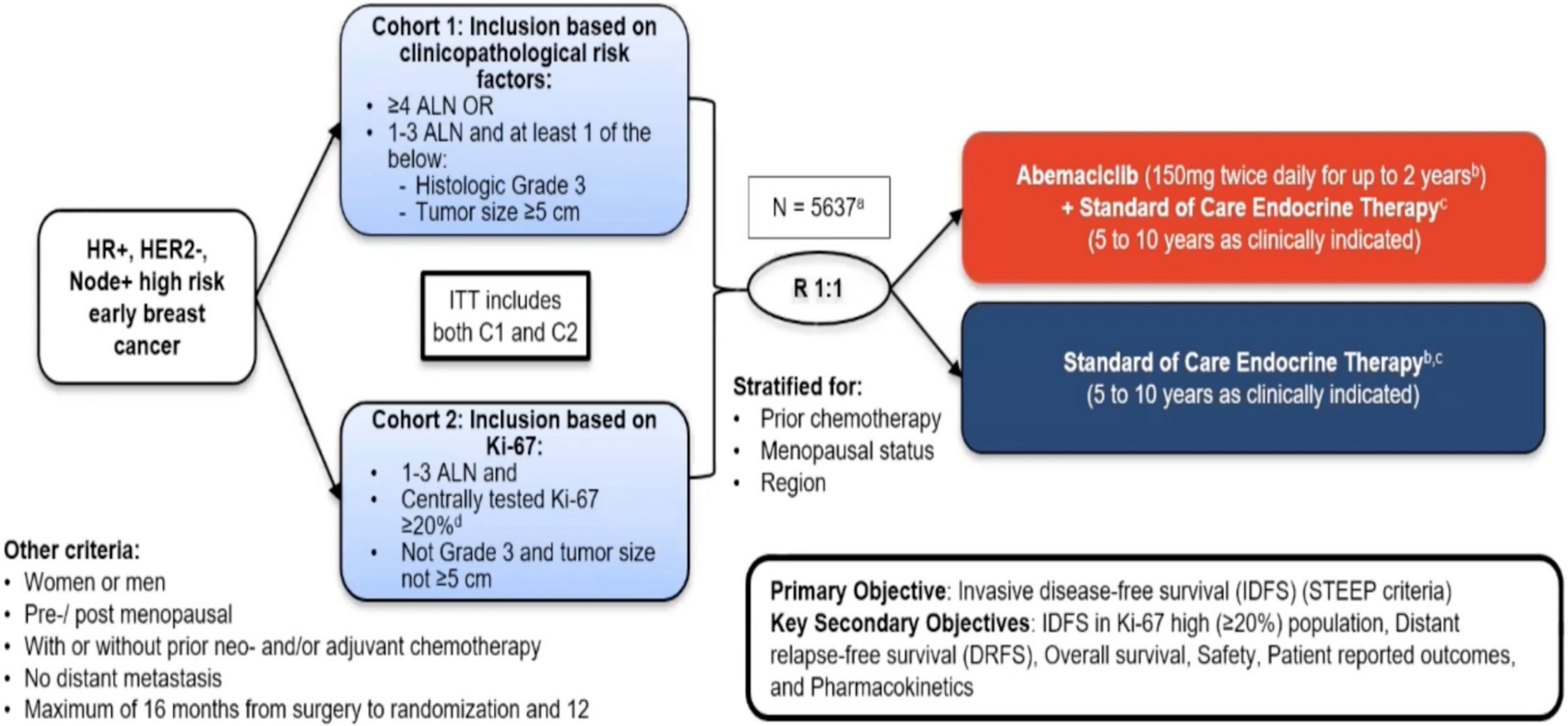


cALND is likely to do more harm than good.

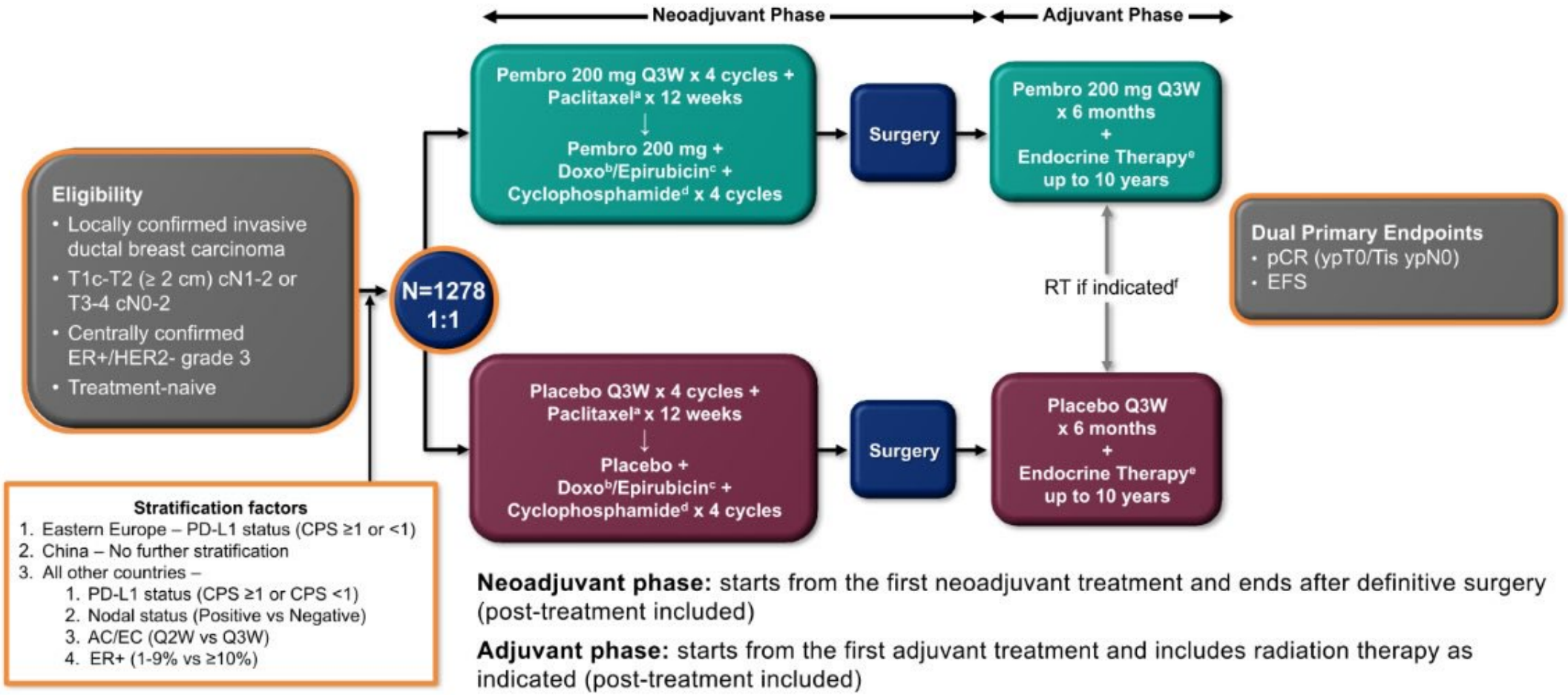
NATALEE did not require N>3 for treatment elegibility

Neoadjuvant Treatment

Abemaciclib postNAT (HR+/HER2-)



Pembrolizumab postNAT (HR+/HER2-)

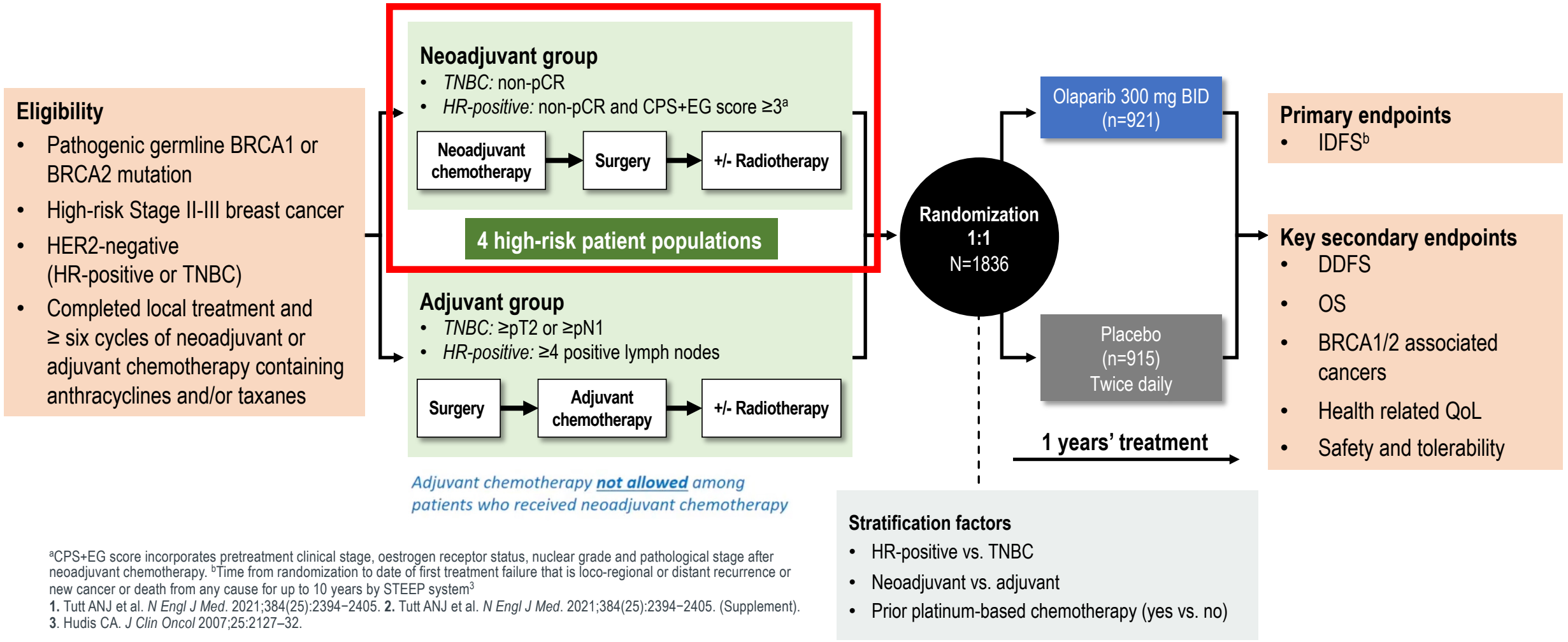


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

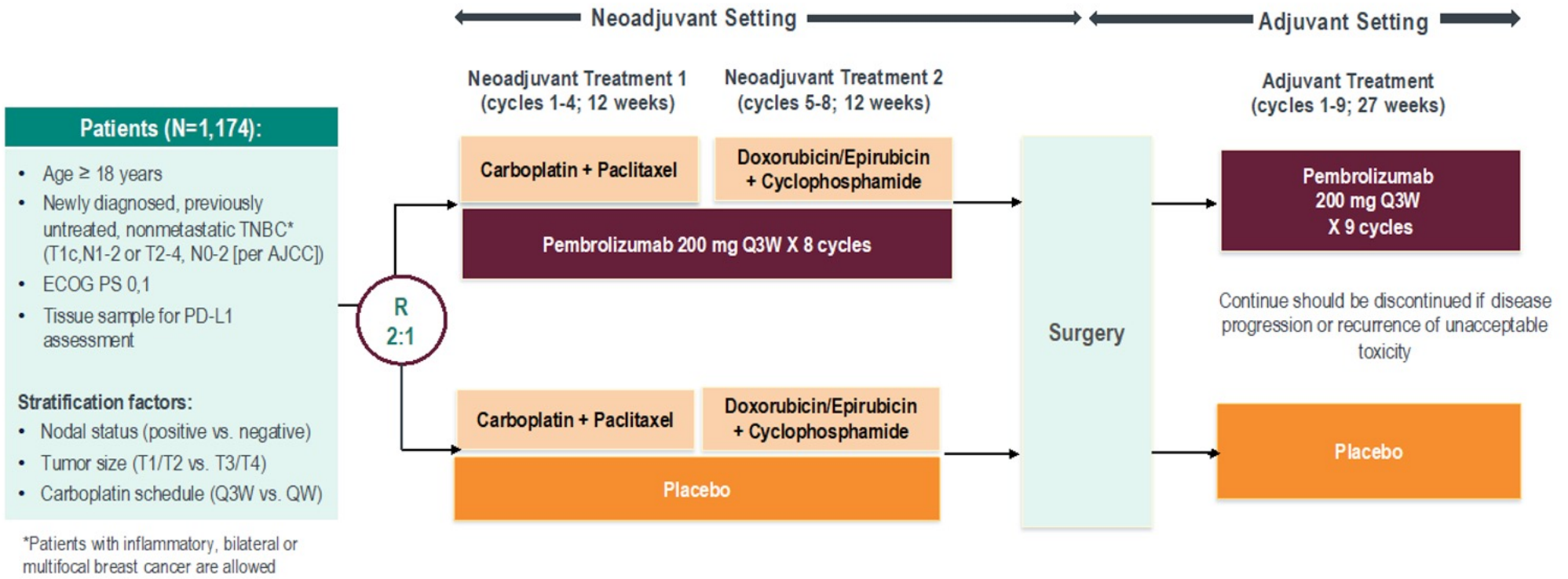
Olaparib postNAT (gBRCAm)



[a]CPS+EG score incorporates pretreatment clinical stage, oestrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy. [b]Time from randomization to date of first treatment failure that is loco-regional or distant recurrence or new cancer or death from any cause for up to 10 years by STEEP system[3]

1. Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405. **2.** Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405. (Supplement).
3. Hudis CA. *J Clin Oncol* 2007;25:2127–32.

Pembrolizumab postNAT (TN)



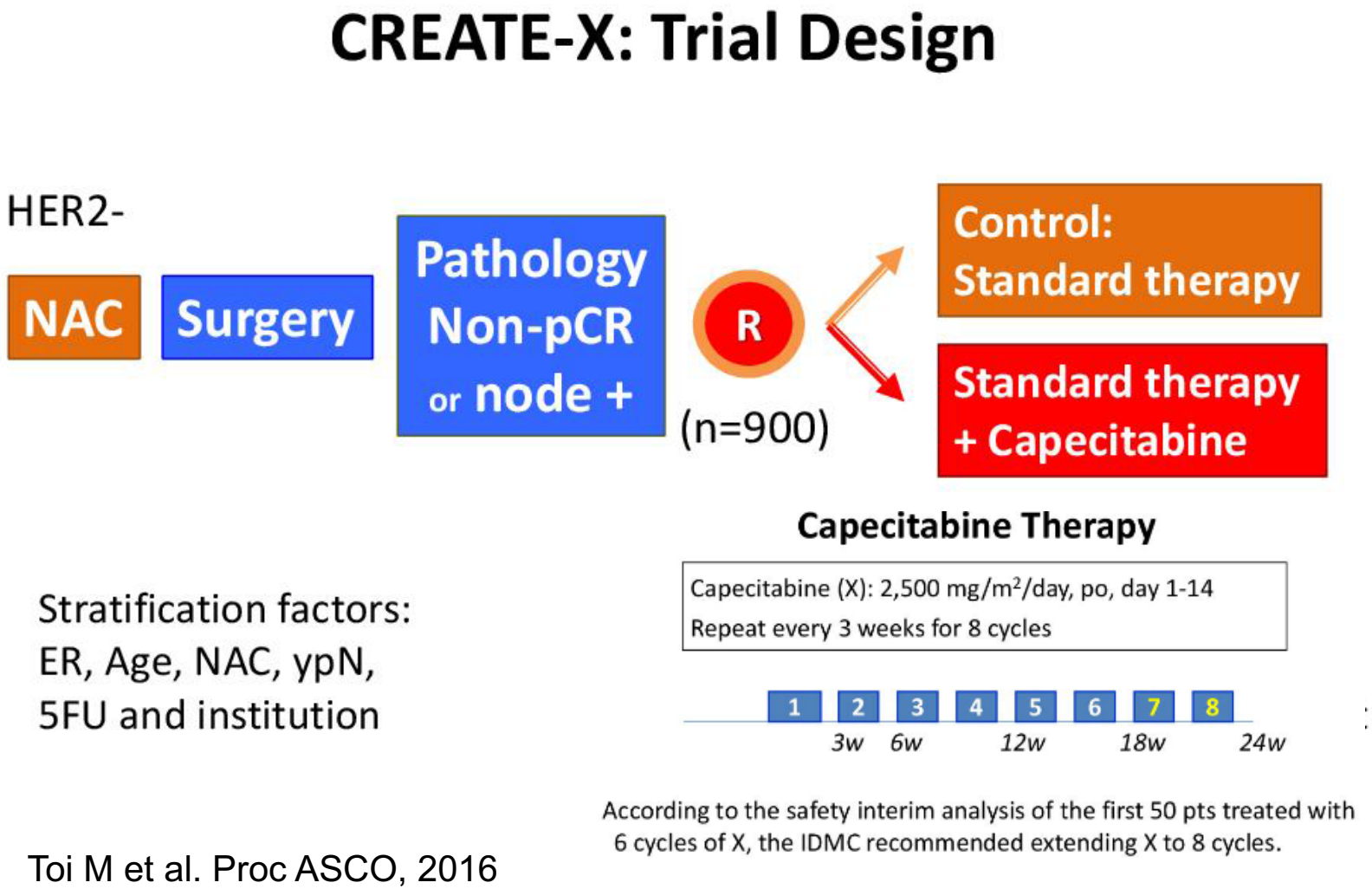
Primary Endpoints

- pCR (ypT0/Tis ypN0) assessed by local pathologist per AJCC criteria at time of definitive surgery
- EFS assessed by investigator

Secondary Endpoints

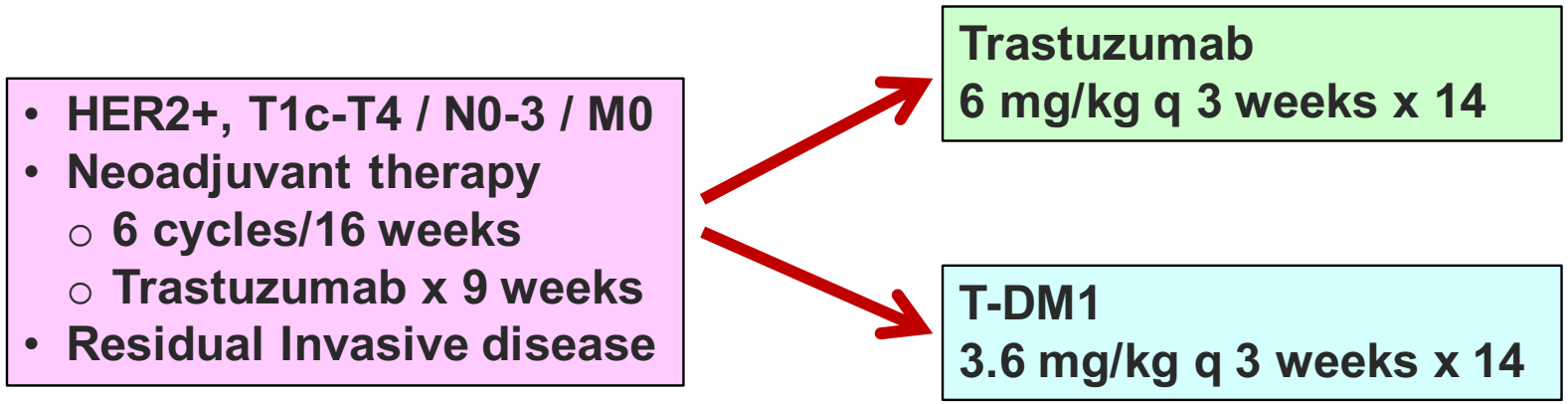
- pCR using alernative definitions (ypT0 ypN0 and ypT0/Tis)
- OS, Safety, PROs (EORTC-QLQ-C30, EORTC-QLQ-BR23, EQ-5D-5L)
- pCR (ypT0/Tis ypN0, ypT0 ypN0 and ypT0/Tis), EFS and OS in patients with PD-L1+ tumors (CPS ≥ 1%)

Capecitabine postNAT



Toi M et al. Proc ASCO, 2016

T-DM1 postNAT



N = 1484

Axillary management in cN1 / ypN0 pts

SLNB for biopsy-proven N+ who convert to cN0 after NAC is feasible and accurate –

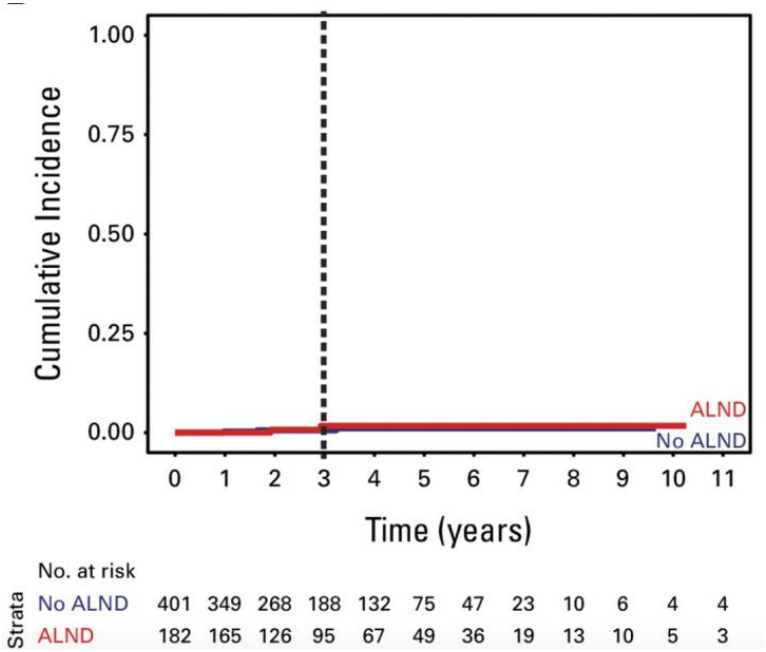
…but is it oncologically safe?

Omission of ALND in cN1 / ypN0

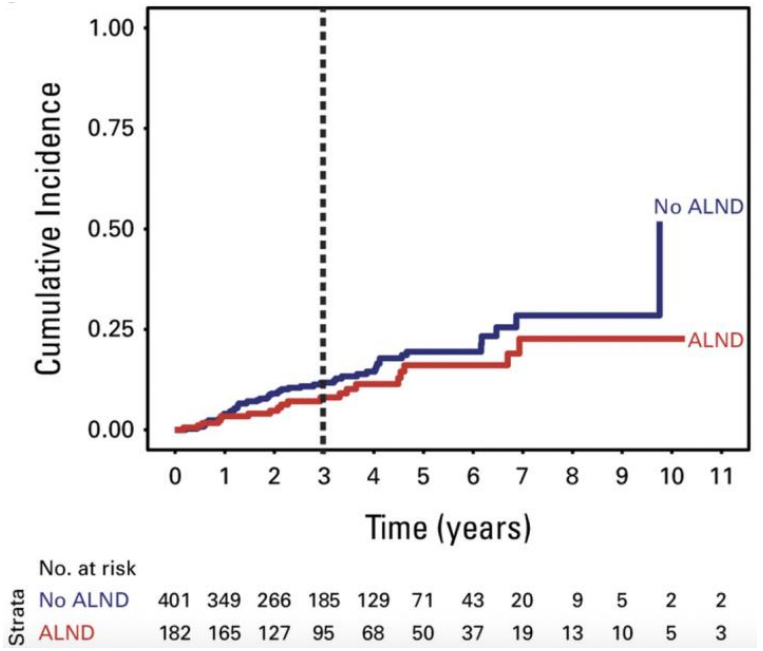
	Type of Surgery	No. ypN0 with SLN alone	% AxRT	Median FU (months)	Axillary Recurrence	Distant Recurrence
IEO Milan (n=147) 2000-2010	SLNB	70	35%	61	**0**	12.8% at 4 yrs
Mayo (n=315) 2009-2019	SLNB	159	78%	34	**0.6% at 3 yrs**	-
McGill (n=132) 2013-2018	SLNB	60	71%	36	**0**	13.7% at 5 yrs
MSKCC (n=555) 2014-2019	SLNB	234	78%	35	**0.4% at 3 yrs**	6.1% at 4 yrs
EUBREAST 06 (n=1144) 2014-2020	SLNB	666	78%	50	**0.8% at 3 yrs**	7.8% at 3 yrs
	TAD	478	85%	32	**0.5% at 3 yrs**	7.3% at 3 yrs
NEOSENTITURK (n=2358) 2018-2020	SLNB / TAD	1179	100%	28	**0.3% at 3 yrs**	-

Galimberti et al, EJSO 2016; Piltin et al, Ann Surg Onc 2020; Wong et al, Ann Surg Onc 2021; Barrio et al, JAMA Oncol 2021; Montagna et al, JAMA Oncol 2024; Cabioglu et al, SABCS 2022
Adapted from Mittendorf SABCS 2023

Residual ICT postNAC: ICARO study



No diff. in isolated axillary recurrences at 5 yrs
(ALND 1.7% *v* No ALND 1.1%; *P* = 0.7)



No diff. in any invasive recurrence at 5 yrs
(ALND 16% *v* No ALND 19%; *P* = 0.13)

Supports the safety of omitting ALND in initially cN1 patients with ypN0/i+ post NAC

Conclusion

- ✓ No randomized trials have ever shown a disease-free survival or ovarall survival advantage b/w ALND vs. AxRT
- ✓ Isolated axillary recurrences are a rare event
- ✓Limited clinical conditions support the need of ALND to support optimal systemic (neo)adjuvant decision making process