



Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: 10-year results of the EORTC AMAROS trial

By the EORTC Breast Cancer Group and
Radiation Oncology Group
In collaboration with the Dutch BOOG Group
and ALMANAC Trialists' Group

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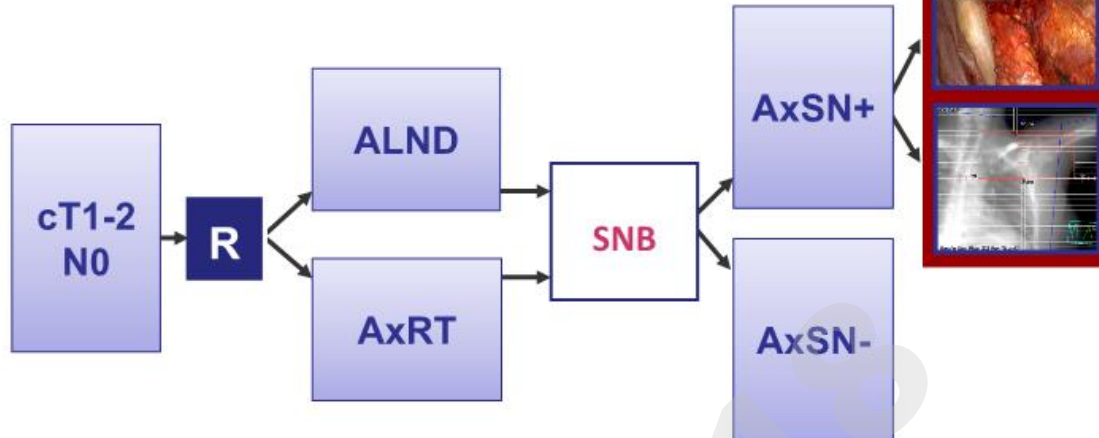
Clinical trial information: [NCT00014612](https://www.clinicaltrials.gov/ct2/show/study/NCT00014612)

@EORTC



No disclosures

Trial design



Stratification: institution
 Adjuvant systemic therapy by choice

Eligibility Criteria

Inclusion

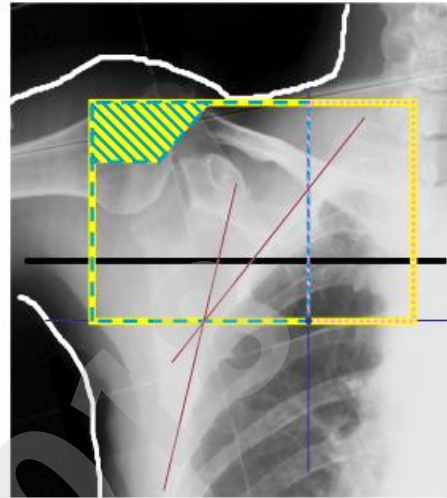
- Invasive breast cancer 0.5-5 cm
- Clinically N0
- BCT or mastectomy
- Any age
- Informed consent

Exclusion

- Multicentric disease
- Neoadjuvant systemic treatment
- Previous axillary treatment
- Prior malignancy

AxRT

- **Timing:**
Start < 12 weeks after SNB
- **Extent:**
level I + II + III + medial SC
- **Dose & schedule:**
25 x 2 Gy or equivalent
- **Quality control:**
dummy run



Hurkmans et al, Radiother Oncol 2003

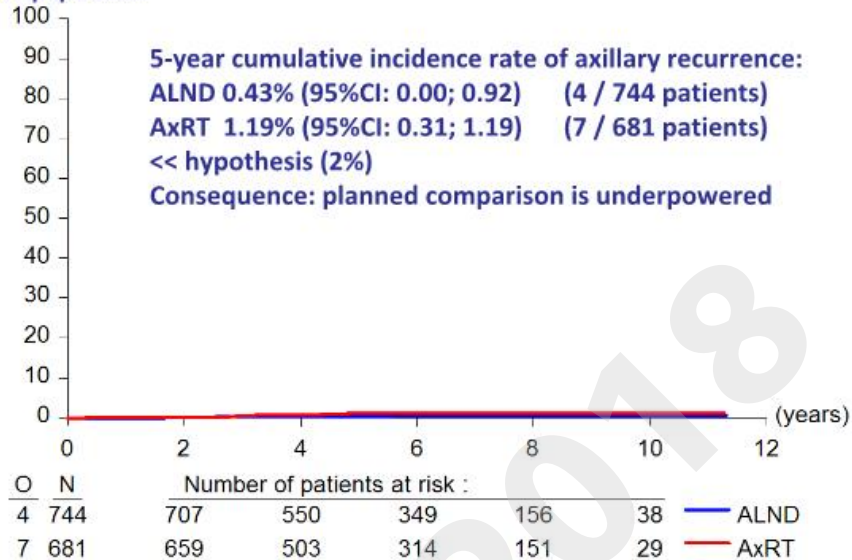
ALND

- **Timing:**
< 12 weeks after SNB
- **Extent:**
Level I + II mandatory
Level III optional
- **Additional AxRT:**
≥ 4 positive nodes

Axillary recurrence rate- Primary analysis

Primary analysis - median follow-up: 6.1 years (on 31 Oct 2012)

AxSN+ ITT population



Cumulative incidence analysis considers death as a competing risk
 Donker M, Van Tienhoven G, E Straver M, et al. Lancet Oncol 2014; 15 (12):1303-1310

Current analysis

- **Long-term follow-up analysis**
- **Patient population: AxSN+ patients**
- **Median follow-up: 10 years in both arms**
Clinical cut off date: 15 February 2018
- **Efficacy outcomes reported up to 10 years**
→ITT analysis given PP and ITT analysis gave the same results in the primary analysis
- **Arm morbidity, QoL: update of 5-years analysis**

Baseline clinical

	ALND (744 pts)	AxRT (681 pts)
Median age (Q1-Q3)	56 (48 - 64)	55 (48 - 63)
Menopausal stage		
pre-menopausal	38.1 %	42.5 %
post-menopausal	57.7 %	54.5 %
Median tumor size (Q1-Q3)	17 mm (13 - 22)	18 mm (13 - 23)
Grade		
1	24.1 %	22.6 %
2	47.8 %	45.7 %
3	25.8 %	29.4 %
Pre-operative ultrasound axilla	59.2 %	61.5 %

Donker M, Van Tienhoven G, E Straver M, et al. Lancet Oncol 2014; 15 (12):1303-1310

Baseline treatment

	ALND (744 pts)	AxRT (681 pts)
Breast surgery		
BCS	81.9 %	81.8 %
Mastectomy	17.1 %	17.8 %
Systemic treatment		
chemotherapy	60.9 %	61.3 %
hormonal therapy	78.6 %	77.1 %
immunotherapy	6.0 %	6.4 %
no systemic treatment	9.0 %	9.4 %
RT breast/chest wall	84.9 %	87.8 %

Donker M, Van Tienhoven G, E Straver M, et al. Lancet Oncol 2014; 15 (12):1303-1310

SN results

	ALND (744 pts)	AxRT (681 pts)
Median number of SN removed (Q1-Q3)	2 (1-3)	2 (1-3)
Size of metastases in SN		
macrometastases	59.4 %	61.5 %
micrometastases	28.9 %	28.6 %
ITC	11.7 %	9.8 %

Straver et al, Ann Surg Oncol 2010

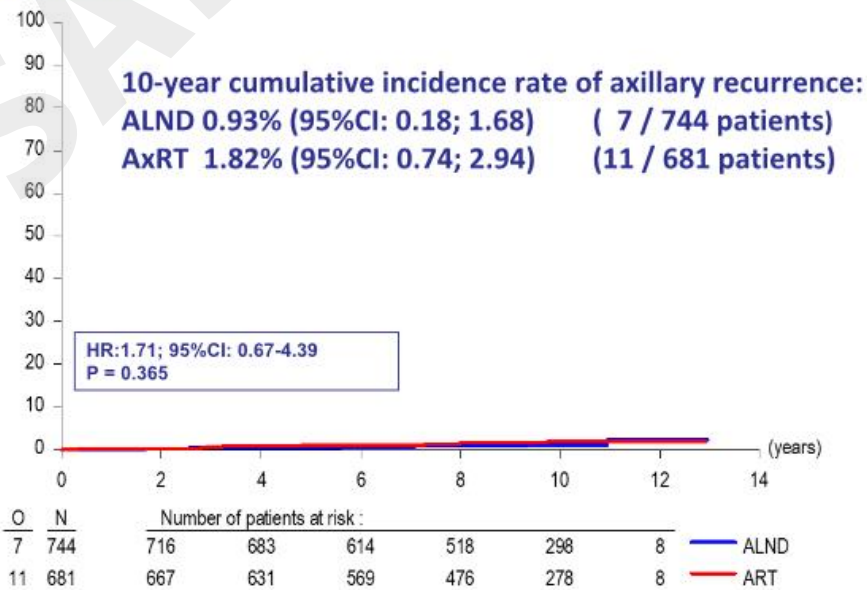
ALND results

	ALND (744 pts)
Median number of all nodes removed (Q1-Q3)	15 (12-20)
Number of additional positive nodes (besides SN)	
0	67.1 %
1-3	25.0 %
≥ 4	7.8 %

10 yrs results

Axillary recurrence rate

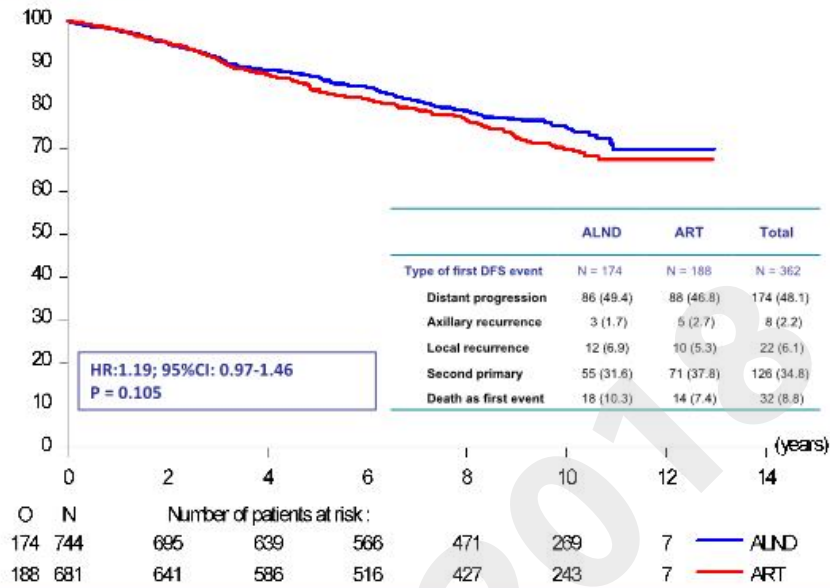
AxSN+ ITT population



Cumulative incidence analysis considers death as a competing risks. HR and Wald p-value based on Fine & Gray model

Disease-free survival

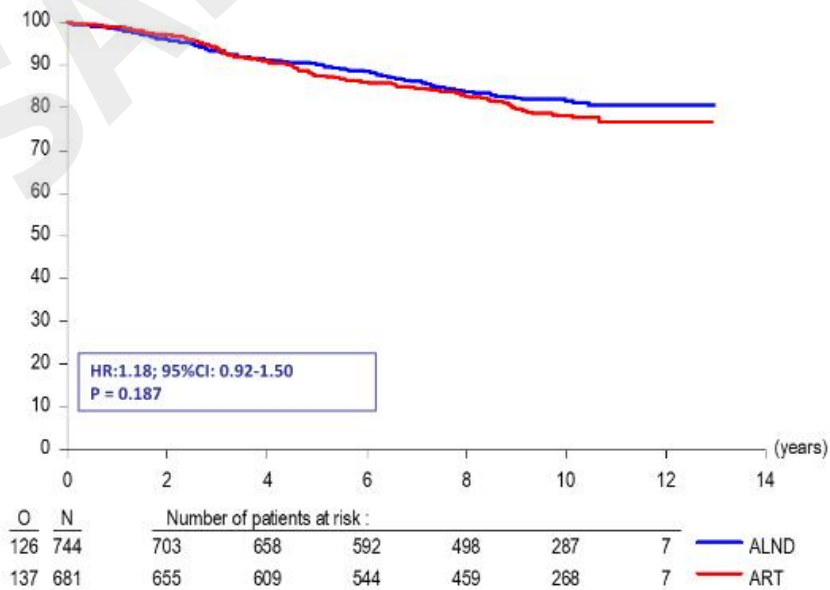
AxSN+ ITT population



Events : local recurrence (incl. ipsilateral DCIS), axillary recurrence, distant metastasis, second primary (including contralateral DCIS), death. If multiple events occurred within a 1-month time window, the following prioritization was applied: distant progression, axillary recurrence, local recurrence, second primary, death. HR and Wald p-value based on Cox proportional hazard model

Distant metastasis free survival

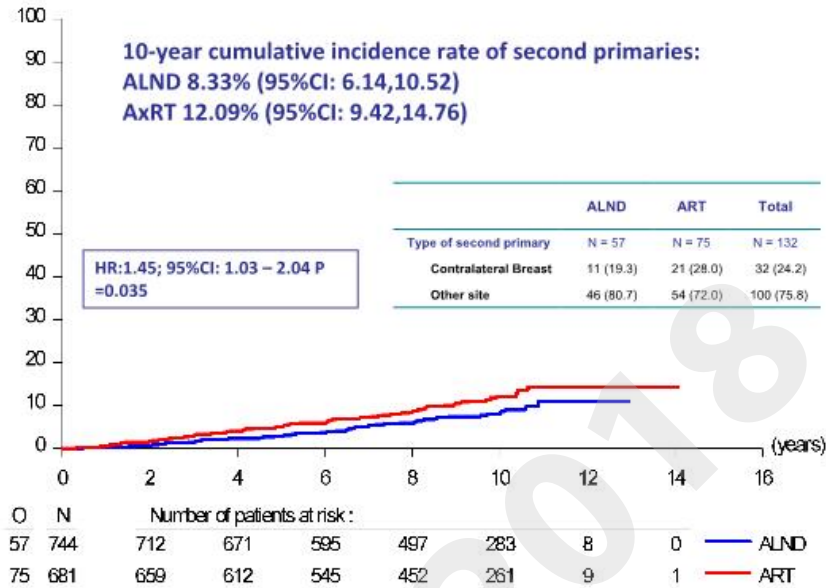
AxSN+ ITT population



Events : distant metastasis, death. HR and Wald p-value based on Cox proportional hazard model

Second primaries

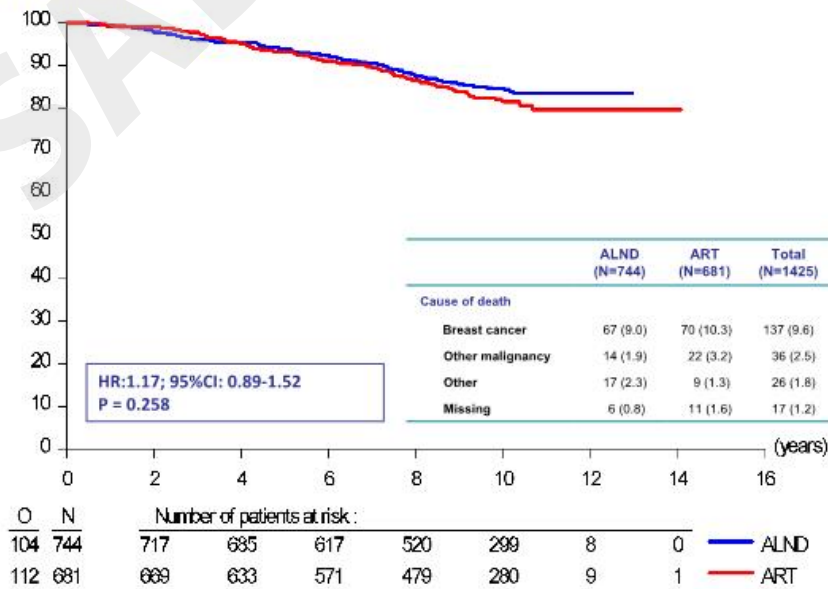
AxSN+ ITT population



Events for this endpoint: second primary (incl. contralateral DCIS). Cumulative incidence analysis considers death as a competing risks. HR and Wald p-value based on Fine & Gray model

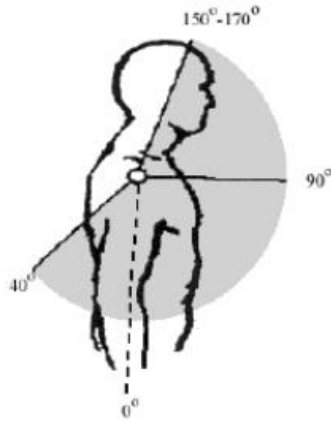
Overall survival

AxSN+ ITT population



HR and Wald p-value based on Cox proportional hazard model

Results side effects



50-70% form compliance at all time points

Form compliance

	% Valid forms received			
	1 year	2 years	3 years	5 years
Lymphedema	65.4	-	62.3	67.4
Shoulder function	59.7	-	57.1	62.5
Quality of Life	64.9	49.9	62.7	65.7

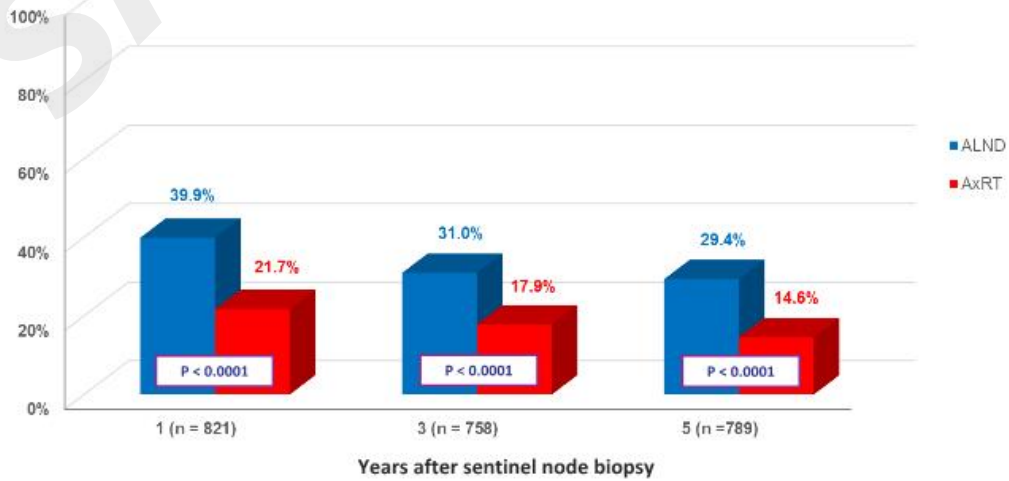
Lymphedema of the arm

Measured: 1, 3 and 5 years after treatment

Items:

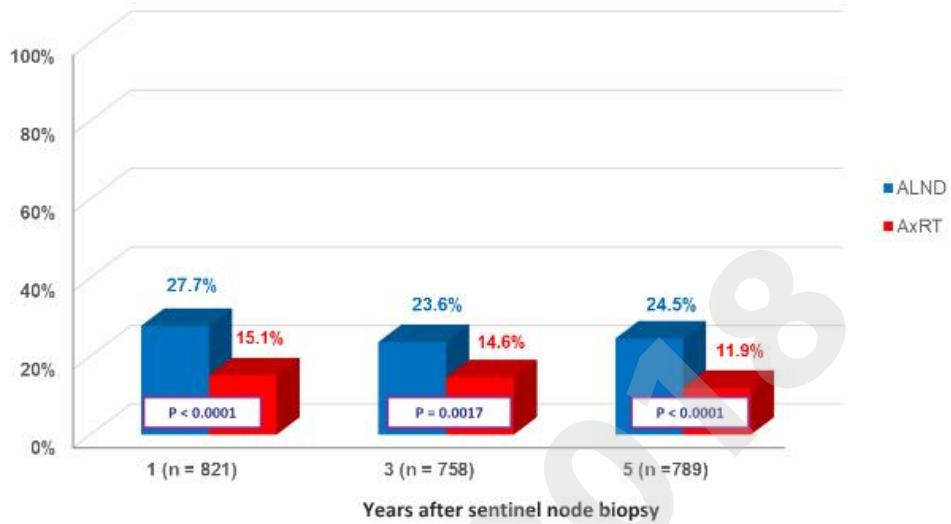
1. Clinical observation
2. Measurement

Lymphedema: clinical observation and/or treatment



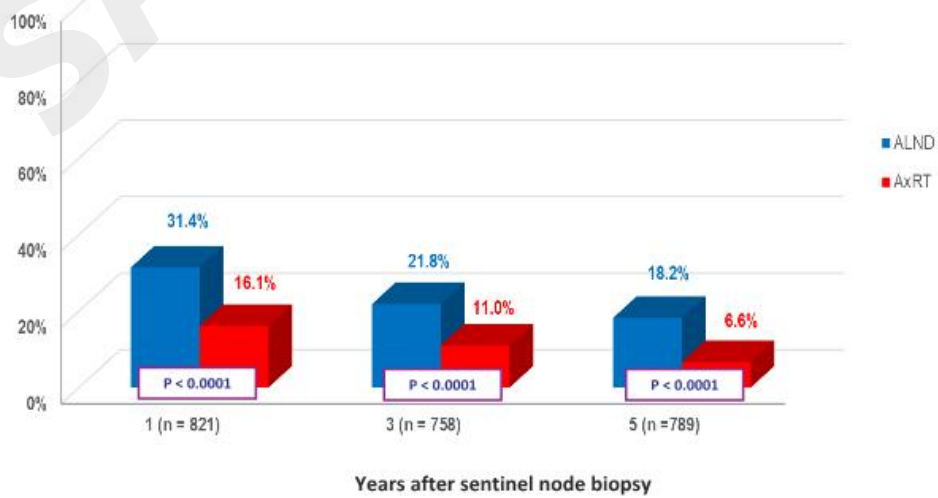
P-value from exact Fisher's test

Lymphedema: clinical observation



P-value from exact Fisher's test

Lymphedema: treatment



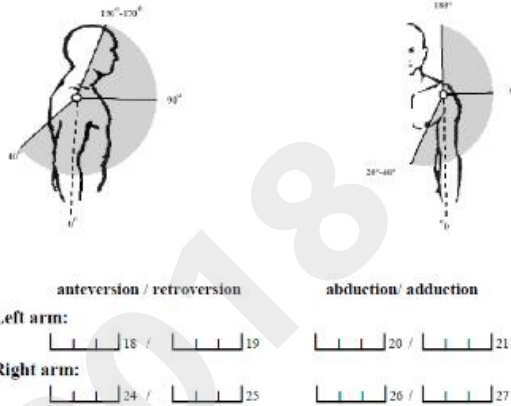
P-value from exact Fisher's test

Shoulder function

Measured: 1, 3 and 5 years after treatment

Items:

1. Ante/retroversion
2. Ab/adduction



Shoulder function

Results:

No significant differences in all 4 excursions

Trend towards impaired movement after AxRT in first year only

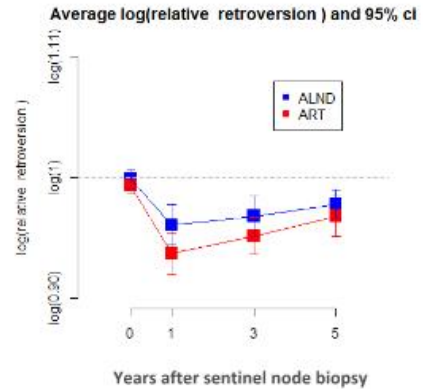
Relative movement:

$$\frac{\text{Excursion treated arm}}{\text{Excursion untreated arm}}$$

Composite endpoint combining the 4 movements

Multivariate ANOVA

- At 1 year: p = 0.28
- At 5 year: p = 0.44





Conclusion

- Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients after 10 years, and no differences in DFS and OS
- Diagnosis of axillary lymph node recurrence after 5 yrs is a very rare event
- Significantly less lymphedema after AxRT after 5 years



Conclusion

AxRT can be considered standard treatment for patients with Amaros eligibility criteria



Discussion

Please listen to Dr Wendy Woodward

(still: what to do with Z011 criteria, and after mastectomy)

Subgroup analysis is not meaningful, due to the extreme low numbers of events



Acknowledgement

We are very grateful to all the patients who participated in this trial



Acknowledgement

Research fellows: Mila Donker, Marieke Straver, Philip Meijnen

Principal investigators: Cornelis van de Velde, Robert Mansel,
Geertjan van Tienhoven

EORTC headquarters: Coralie Poncet, Corneel Coens, Catherine
Hermans, Saskia Litière, Bart Meulemans, Nicolas Sauv 

EORTC Breast Cancer Group
EORTC Radiation Oncology Group
Dutch BOOG Group
ALMANAC Trialists' Group

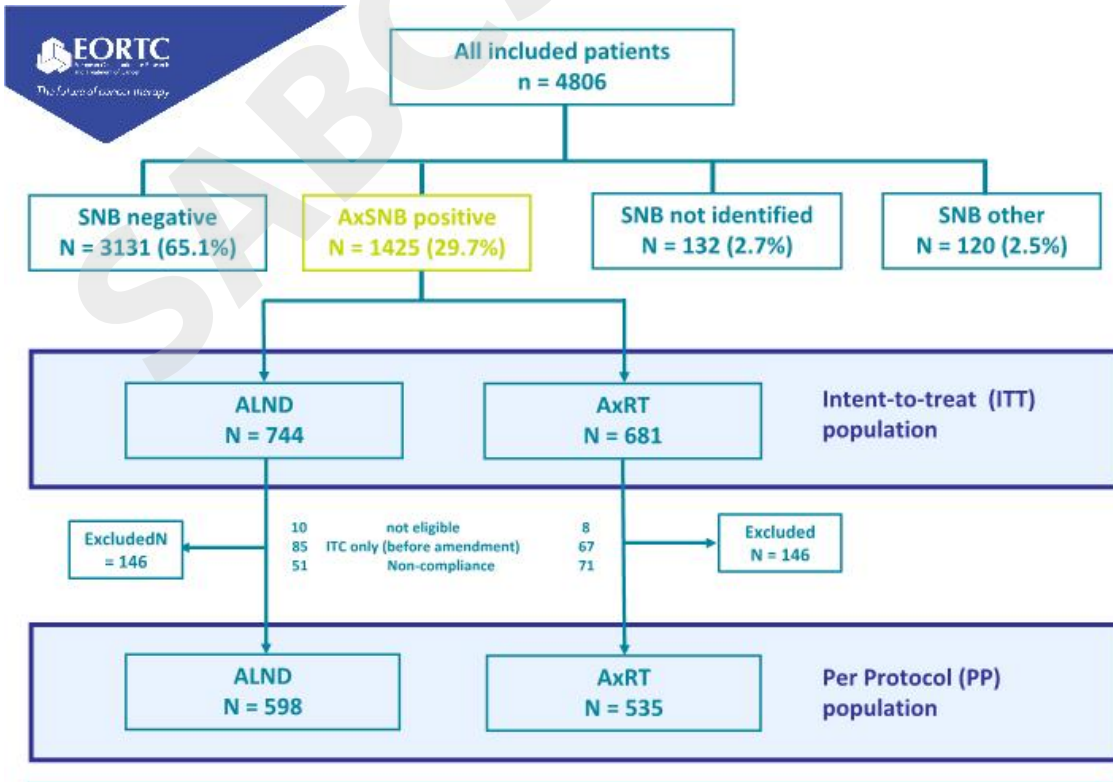


Participating institutes

Arnhem, ZH Rijnstate, the Netherlands
Hardewijk, St Jansdal ZH, the Netherlands
Amsterdam, NKI-AVL, the Netherlands
Firenze, Univ Hosp Careggi, Italy
Drachten, ZH Nij Smellinghe, the Netherlands
Utrecht, Diakonessenhuis, the Netherlands
Leiden, LUMC, the Netherlands
Amsterdam, AMC, the Netherlands
Den Haag, MCH Westeinde, the Netherlands
Ljubljana, Univ Hosp, Slovenia
Lille, Centre Oscar Lambret, France
Geneva, Hosp Cantonal, Swiss
Nijmegen, UMC St Radboud, the Netherlands
Grenoble, CHUG Grenoble, France
Gdansk, Medical Univ, Poland
Roermond, Laurentius ZH, the Netherlands

Den Haag, Bronovo ZH, the Netherlands
Groningen, UMCG, the Netherlands
Hardenberg, R pcke-Zweers ZH, the Netherlands
Den Haag, Haga ZH, the Netherlands
Cardiff, Univ Hosp Wales, United Kingdom
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Eindhoven, Catharina ZH, the Netherlands
Amstelveen, Amstelland ZH, the Netherlands
Delft, R de Graaf GH, the Netherlands
Haarlem, Kennemer GH, the Netherlands
Istanbul, Marmara Univ Hosp, Turkey
Haifa, Rambam Med Center, Israel
Paris, Inst Curie, France

Thank you!



Treatment compliance

	ALND (744 pts)	AxRT (681 pts)
Randomized treatment	631 (84.8 %)	590 (86.6 %)
Both treatments	41 (5.5 %)	1 (0.1 %)
Cross-over	46 (6.2 %)	68 (10.0 %)
No axillary treatment	24 (3.2 %)	22 (3.2 %)

Donker M, Van Tienhoven G, E Straver M, et al. Lancet Oncol 2014; 15 (12):1303-1310

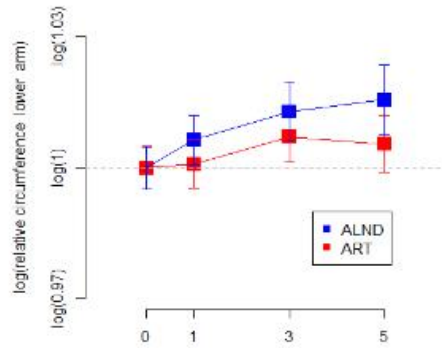
SNB

- **Conduct:**
 - Use of radiocolloid mandatory
- **Definition of “positive axillary SN” (AxSN+):**
 - At least 1 positive sentinel node in axilla
 - Positive: Macrometastases/micrometastases/ITC*
- **Quality control:**
 - Learning phase with ≥ 30 SNB required

* ITC only excluded from AxSN+ group since April 2008

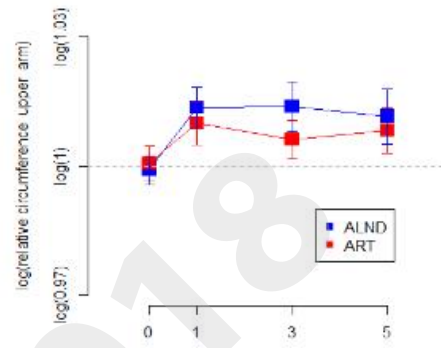
Lymphedema: arm circumference

Lower arm



Years after sentinel node biopsy

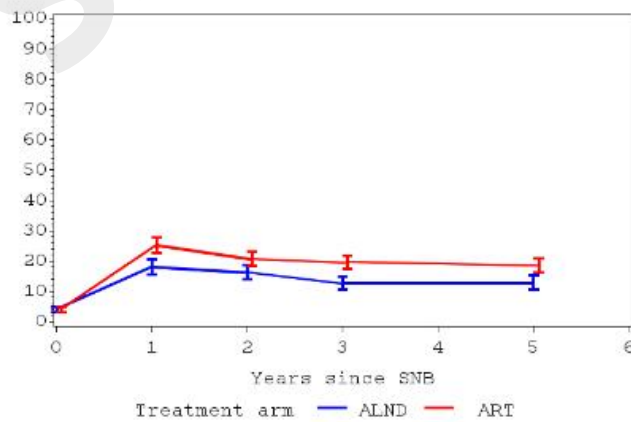
Upper arm



Years after sentinel node biopsy

Quality of Life

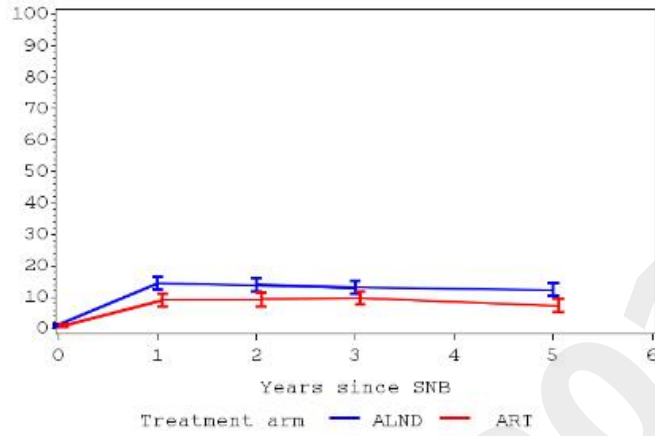
Trend towards more difficulties to move the arm after ART



*Question 19 from the BR23 module, item of the 'Arm symptom' scale.

Quality of Life

Trend towards more swelling after ALND



*Question 18 from the BR23 module, item of the 'Arm symptom' scale.

SABCS 2018