Best of SABCS 2018 - Onkologi

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Onkologiska Kliniken USÖ

Disposition

- Neoadjuvant behandling
- TDM1 vid residual tumor (KATHERINE)
- Adjuvant
- Strålbehandling (AMAROS; NSABP B-39; RAPID)
- Metastaserad sjukdom
- Immunterapi (IMpassion130)

SAN ANTONIO BREAST CANCER SYMPOSIUM

SABCS, December 4-8, 2018

Phase III Study of Trastuzumab Emtansine (T-DM1) vs Trastuzumab as Adjuvant Therapy in Patients with HER2-Positive Early Breast Cancer with Residual Invasive Disease after Neoadjuvant Chemotherapy and HER2-Targeted Therapy Including Trastuzumab: Primary Results from KATHERINE (NSABP B-50-I, GBG 77 and Roche BO27938)

Charles E. Geyer, Jr., Chiun-Sheng Huang, Max S. Mano, Sibylle Loibl, Eleftherios P. Mamounas, Michael Untch, Norman Wolmark, Priya Rastogi, Andreas Schneeweiss, Andrés Redondo, Hans H. Fischer, William Jacot, Alison K. Conlin, Claudia Arce-Salinas, Irene L. Wapnir, Christian Jackisch, Michael P. DiGiovanna, Peter A. Fasching, John P. Crown, Pia Wülfing, Zhimin Shao, Elena Rota Caremoli, Haiyan Wu, Lisa H. Lam, David Tesarowski, Melanie Smitt, Hannah Douthwaite, Stina M. Singel, and Gunter von Minckwitz, on behalf of the KATHERINE investigators

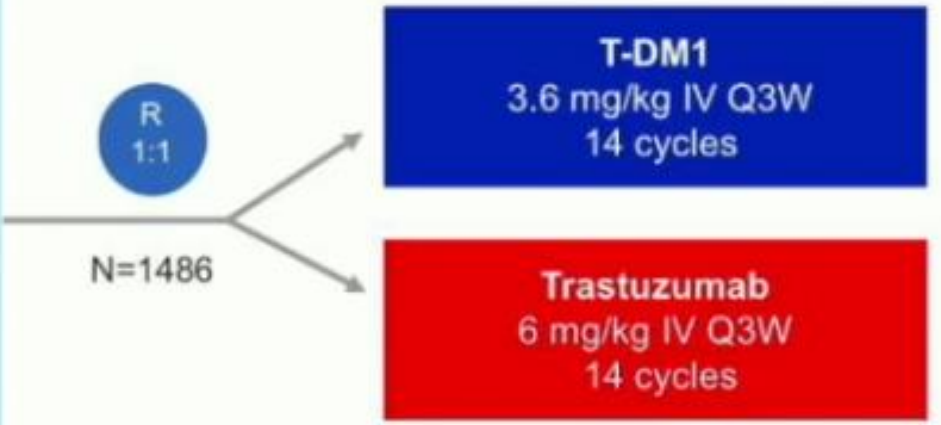
GBG GERMAN BREAST GROUP

NSABP Foundation, Inc.

Roche Genentech

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

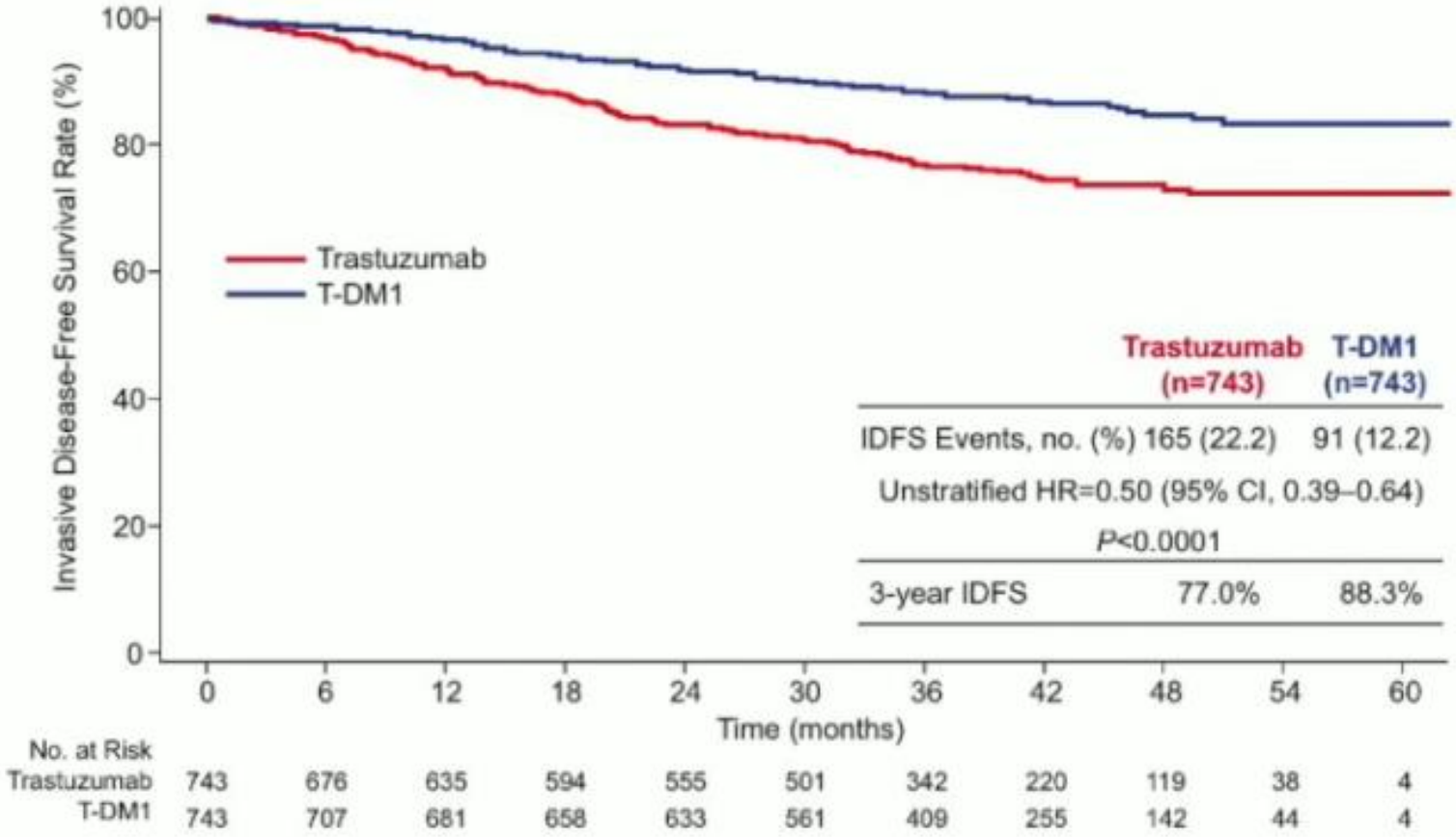
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Characteristics of ITT Population (2): Stratification Factors

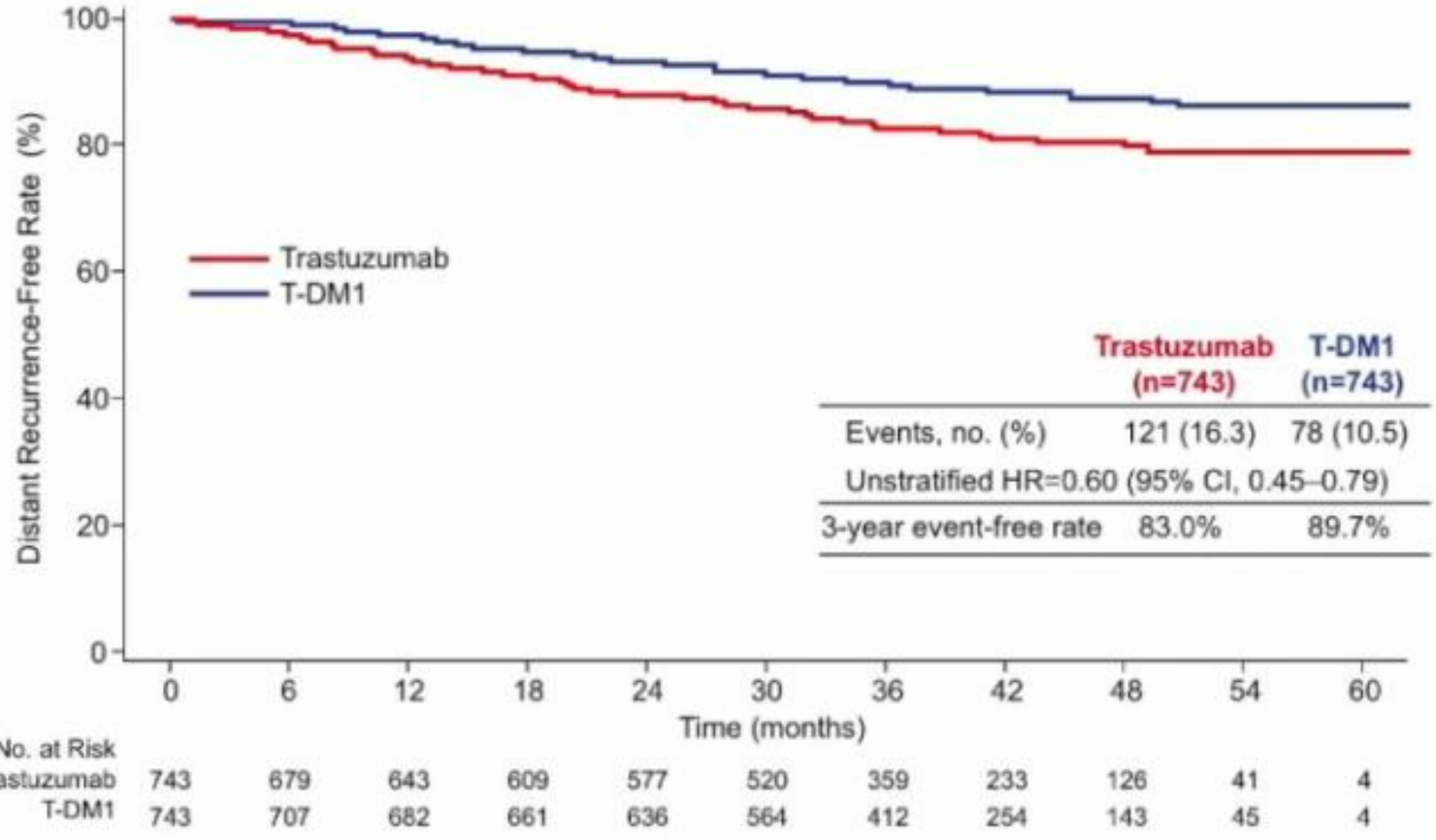
	Trastuzumab (n=743)	T-DM1 (n=743)
Clinical stage at presentation, n (%)		
Operable (stages cT1-3N0–1M0)	553 (74.4)	558 (75.1)
Inoperable (stage cT4NxM0 or cTxN2–3M0)	190 (25.6)	185 (24.9)
Hormone receptor status, n (%)		
ER and/or PgR positive	540 (72.7)	534 (71.9)
ER negative and PgR negative/unknown	203 (27.3)	209 (28.1)
Preoperative HER2-targeted therapy, n (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-targeted agent(s)^ - Trastuzumab plus pertuzumab*	147 (19.8) 139 (18.7)	143 (19.2) 133 (17.9)
Pathologic nodal status after preoperative therapy, n (%)		
Node positive	346 (46.6)	343 (46.2)
Node negative/not done	397 (53.4)	400 (53.8)

^Non-pertuzumab HER2-targeted agents included: neratinib, dacomitinib, afatinib, lapatinib.
*Not a stratification factor, included for informational purposes.

Invasive Disease-Free Survival

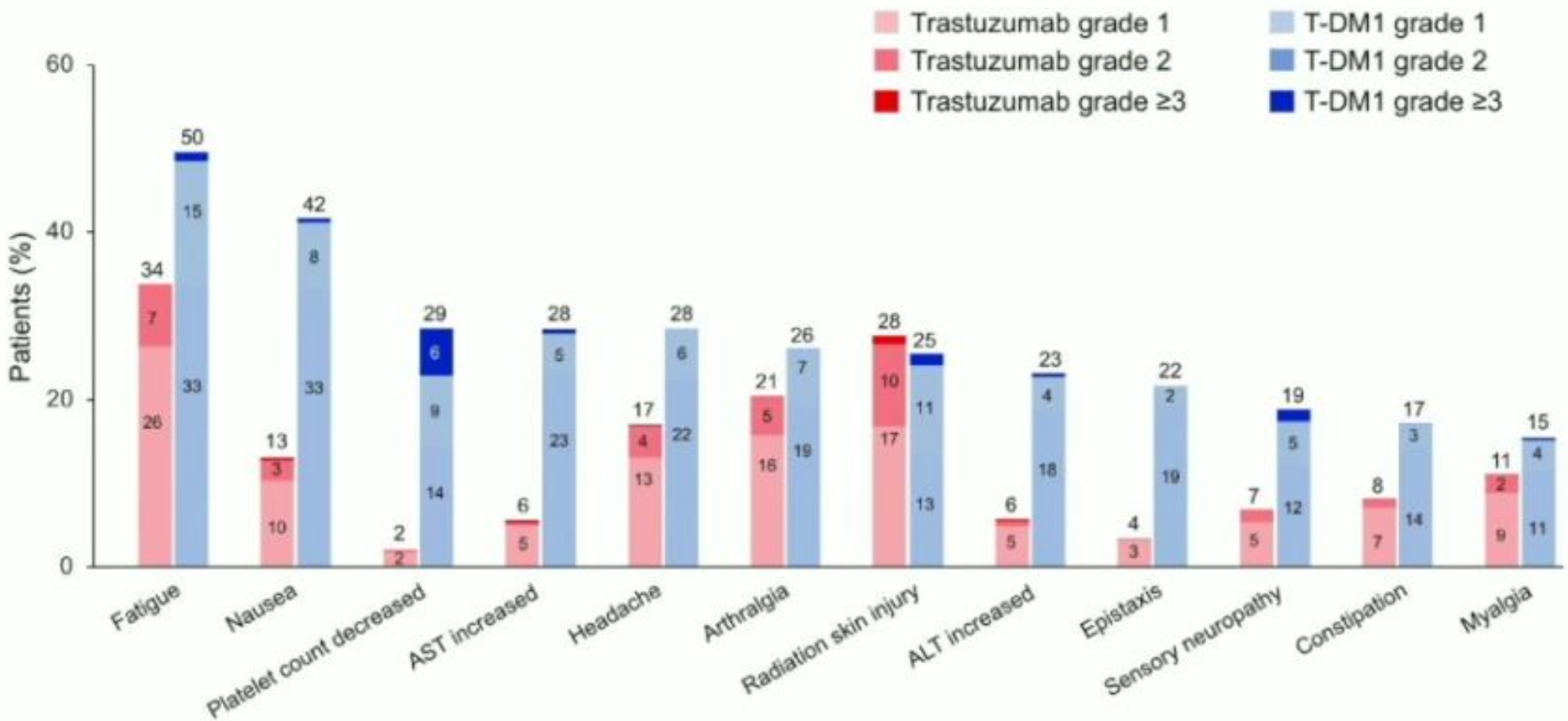


Distant Recurrence



	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	121 (16.3)	78 (10.5)
Unstratified HR=0.60 (95% CI, 0.45–0.79)		
3-year event-free rate	83.0%	89.7%

All Grade AEs ≥15% Incidence in Either Arm



KATHERINE Summary and Conclusions

- Adjuvant T-DM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab
  - Unstratified HR=0.50; 95% CI 0.39–0.64; *P*<0.0001
  - 3-year IDFS rate improved from 77.0% to 88.3% (difference=11.3%)
- Benefit of T-DM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy
- The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in AEs associated with T-DM1 compared to trastuzumab
- Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS
- The KATHERINE data will likely form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive EBC

Diskussion - implikationer

- Resultat är practice-changing:
- Stor riskminskning (50% lägre risk; absolut vinst på 11%)
- Bättre resultat än tillägg av pertuzumab som adjuvant (19-23% lägre risk; absolut vinst på 0,9-2,2%)
- Smart sätt att välja patienter som får nytta (ej one-size-fits-all approach)
- Frågor som behöver svaras:
- Överlevnadsvinst?
- Är vinsten samma om pertuzumab ges som neoadjuvant?

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

Emiel J Rutgers
The Netherlands Cancer Institute,
Amsterdam

Clinical trial information: NCT00014612

Eligibility Criteria

Inclusion

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

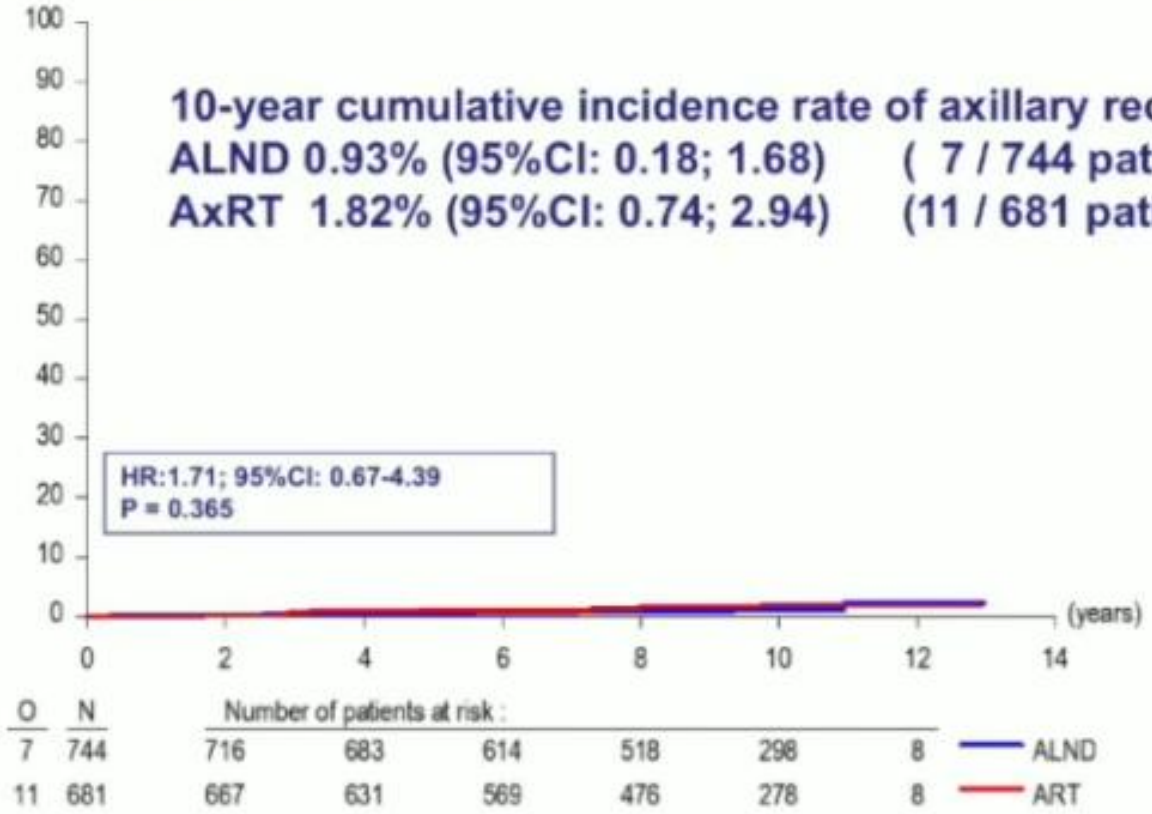
Exclusion

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

- RNI was given in patients with ≥ 4 LNs after ALND (about 10%)
- Radiotherapy to internal mammary chain in about 10 % in both arms
- About 60% of patients with macrometastasis in SNB

Axillary recurrence rate

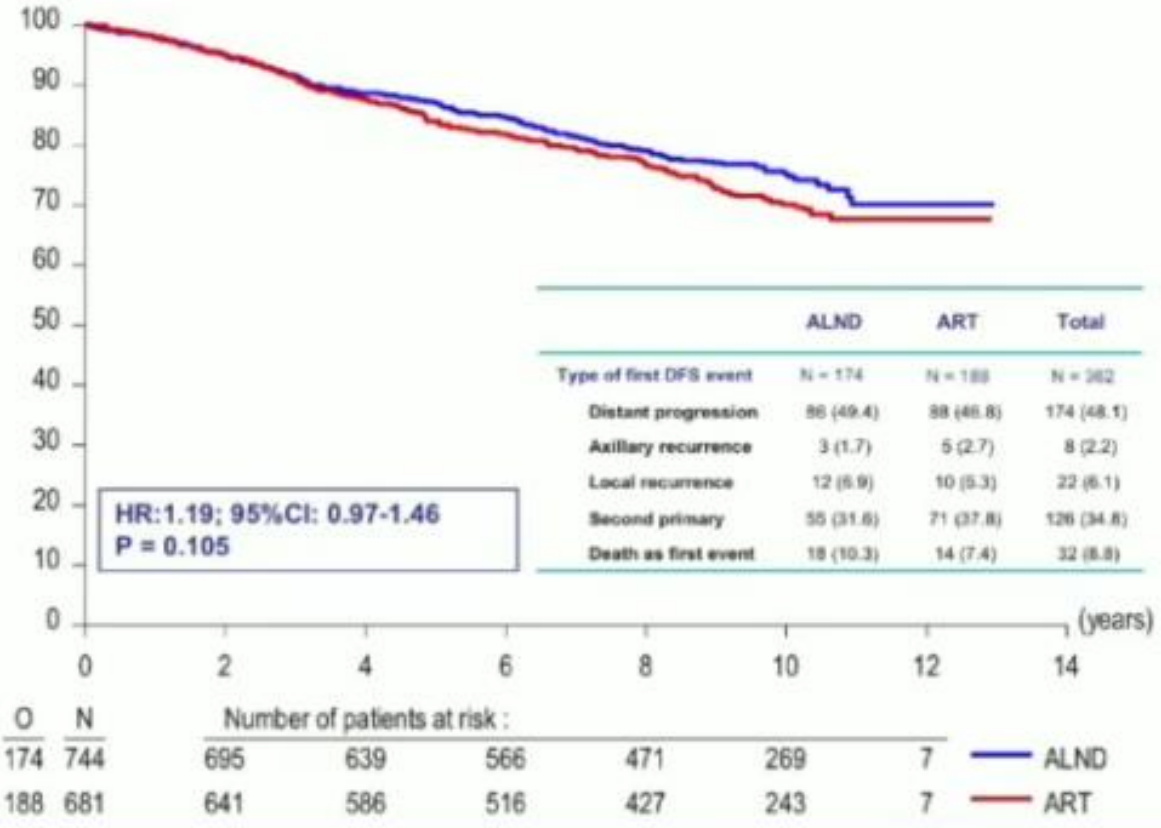
AxSN+ ITT population



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

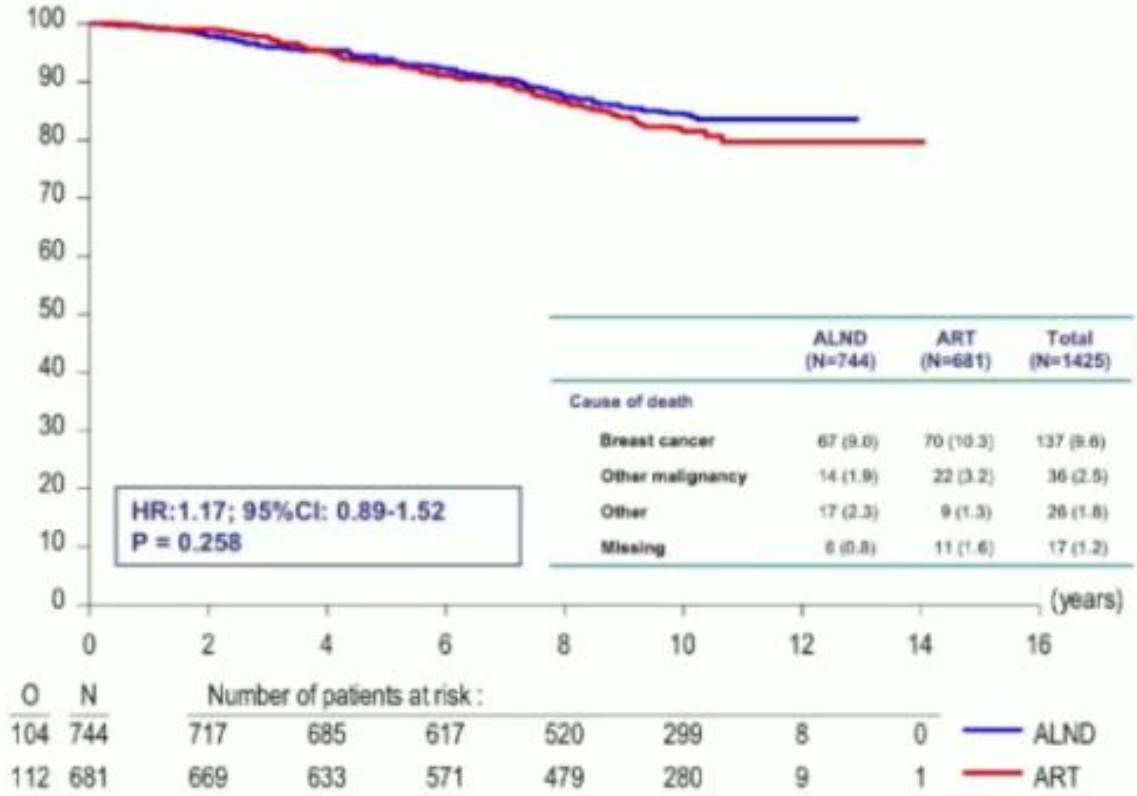


	ALND	ART	Total
Type of first DFS event	N = 174	N = 188	N = 362
Distant progression	86 (49.4)	88 (46.8)	174 (48.1)
Axillary recurrence	3 (1.7)	5 (2.7)	8 (2.2)
Local recurrence	12 (6.9)	10 (5.3)	22 (6.1)
Second primary	55 (31.6)	71 (37.8)	126 (34.8)
Death as first event	18 (10.3)	14 (7.4)	32 (8.8)

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

Overall survival

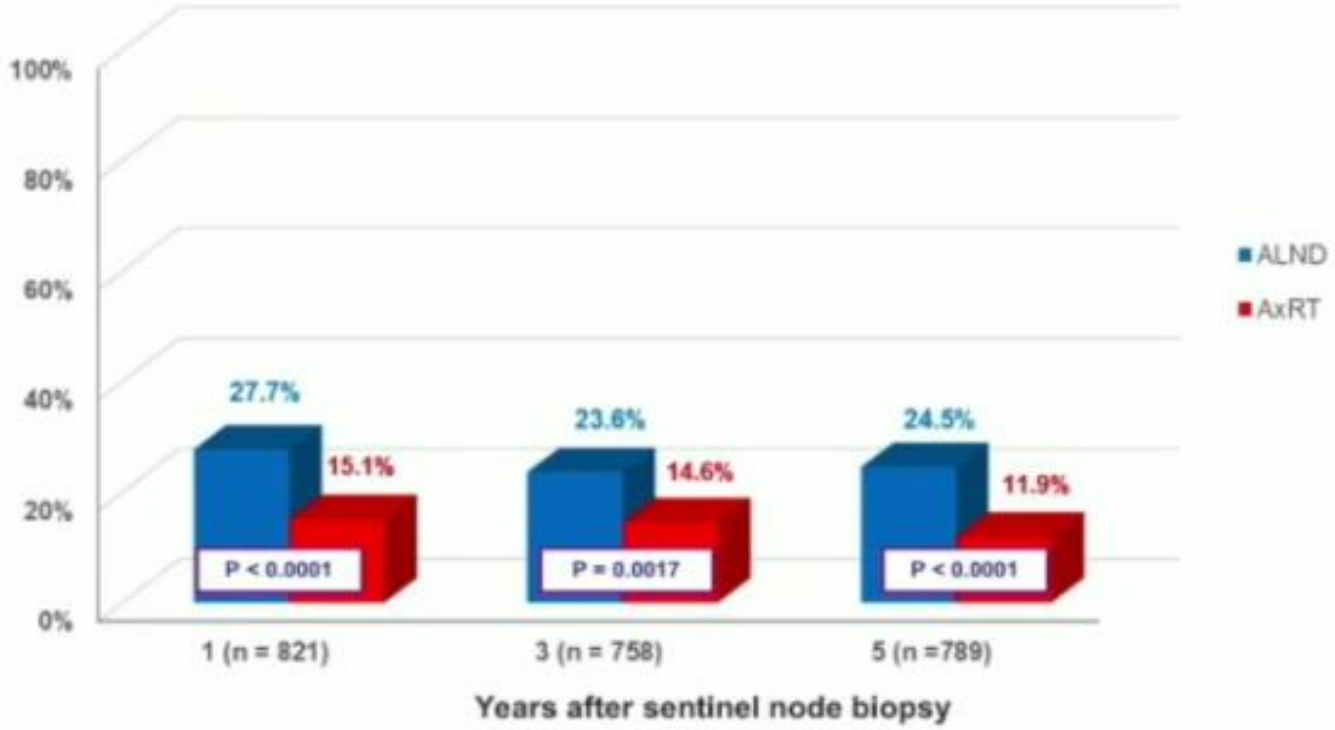
AxSN+ ITT population



	ALND (N=744)	ART (N=681)	Total (N=1425)
Cause of death			
Breast cancer	67 (9.0)	70 (10.3)	137 (9.6)
Other malignancy	14 (1.9)	22 (3.2)	36 (2.5)
Other	17 (2.3)	9 (1.3)	26 (1.8)
Missing	6 (0.8)	11 (1.6)	17 (1.2)

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

Lymphedema: clinical observation



P-value from exact Fisher's test

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

Diskussion - implikationer

- Axillutrymning = strålbehandling (inkl level I) för cT1-2N0 bröstcancer med positiv sentinel node men färre biverkningar
- Frågor som inte är besvarade (SENOMAC studie):

- cT3
- cN0 men cytologi-verifierad metastas
- Strålbehandling utan inklusion av level I

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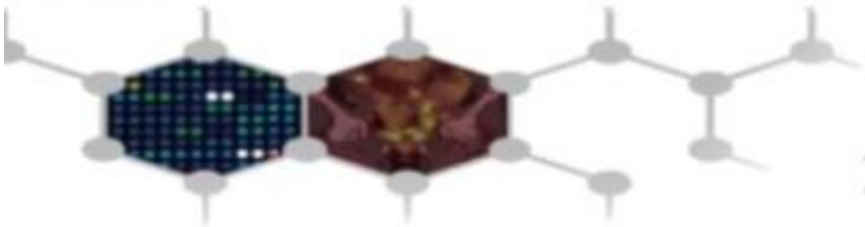
SABCS, December 4-8, 2018



NRG ONCOLOGY

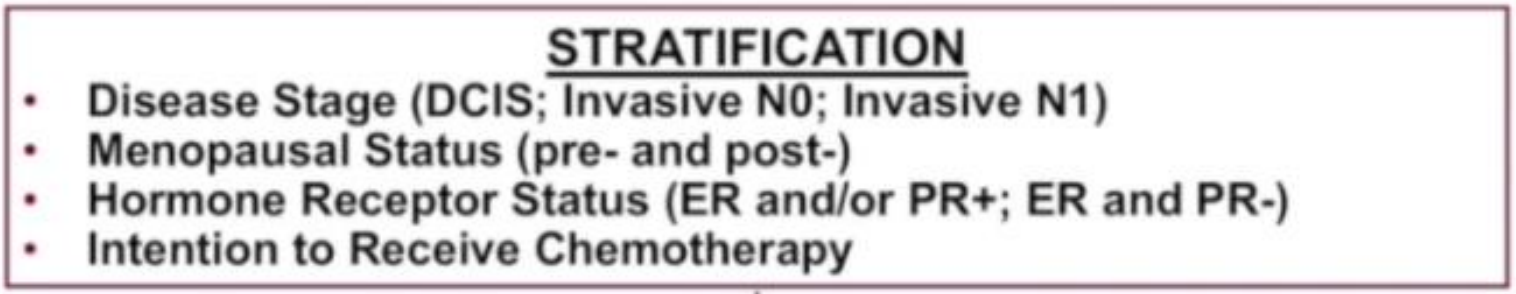
Advancing Research. Improving Lives.™

Primary results of NSABP B-39/ RTOG 0413 (NRG Oncology): A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) for women with stage 0, I, or II breast cancer

F Vicini (NSABP PI), R Cecchini, J White (RTOG PI), T Julian, D Arthur, R Rabinovitch, R Kuske, D Parda, P Ganz, M Scheier, K Winter, S Paik, H Kuerer, L Vallow, L Pierce, E Mamounas, J Costantino, H Bear, I Germain, G Gustafson, L Grossheim, L Petersen, R Hudes, W Curran, N Wolmark

San Antonio Breast Cancer Symposium Dec. 4-8, 2018

NSABP B-39/RTOG 0413 Schema



T size > 3 cm was excluded
Lobular histology was included

Whole Breast Irradiation after Adjuvant Chemotherapy

50 Gy (2.0 Gy/fraction) or
50.4 Gy (1.8 Gy/fraction) to whole breast,
followed by optional boost to ≥ 60 Gy

Partial Breast Irradiation prior to Adjuvant Chemotherapy

For a total of 10 treatments given on 5 days over 5 to 10 days:

34 Gy in 3.4 Gy fractions Interstitial Brachytherapy
or Mammosite Balloon Catheter
or 38.5 Gy in 3.85 Gy fractions
3D Conformal External Beam

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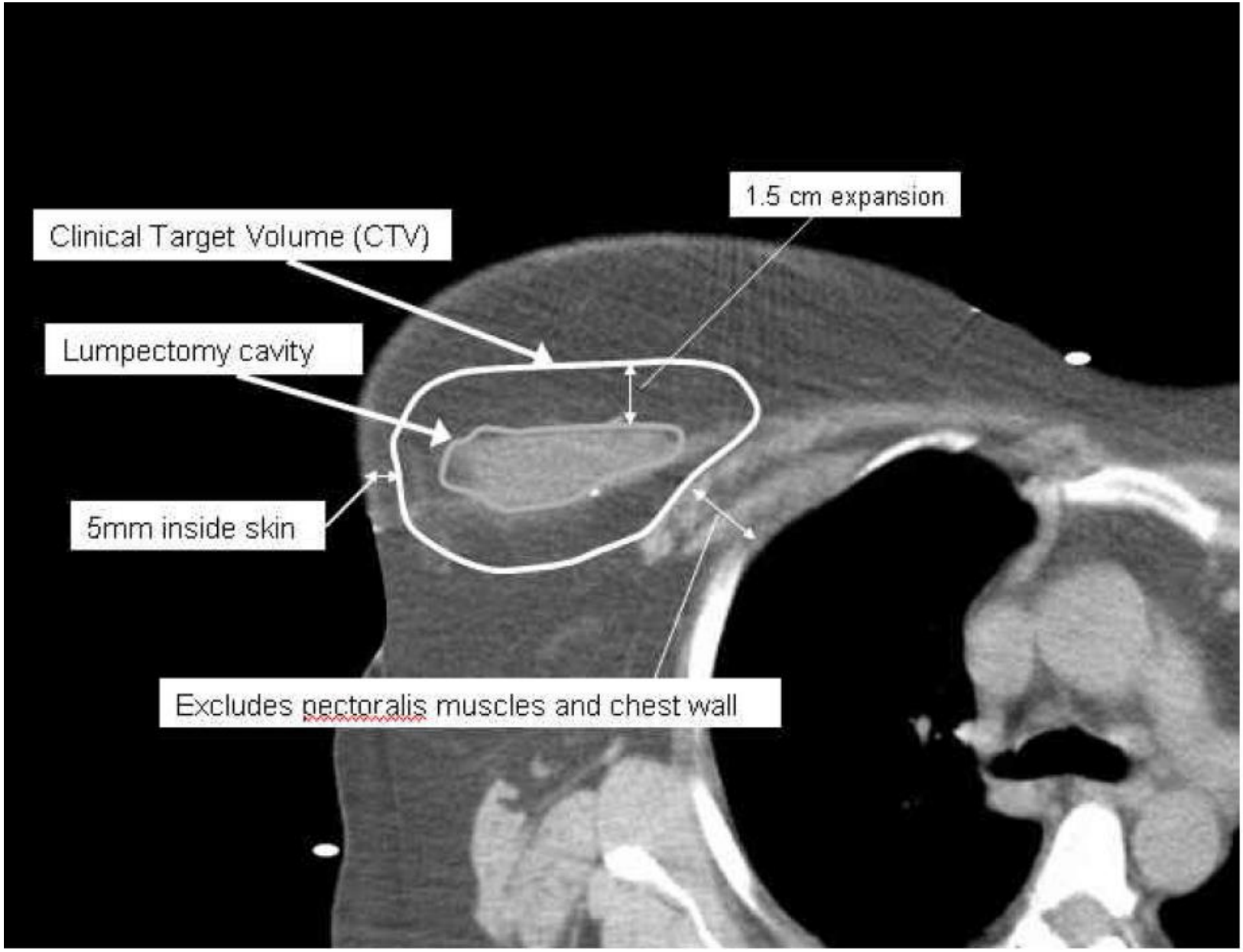
Clinical Target Volume (CTV)
1.5 cm expansion
Lumpectomy cavity
5mm inside skin
Excludes pectoralis muscles and chest wall

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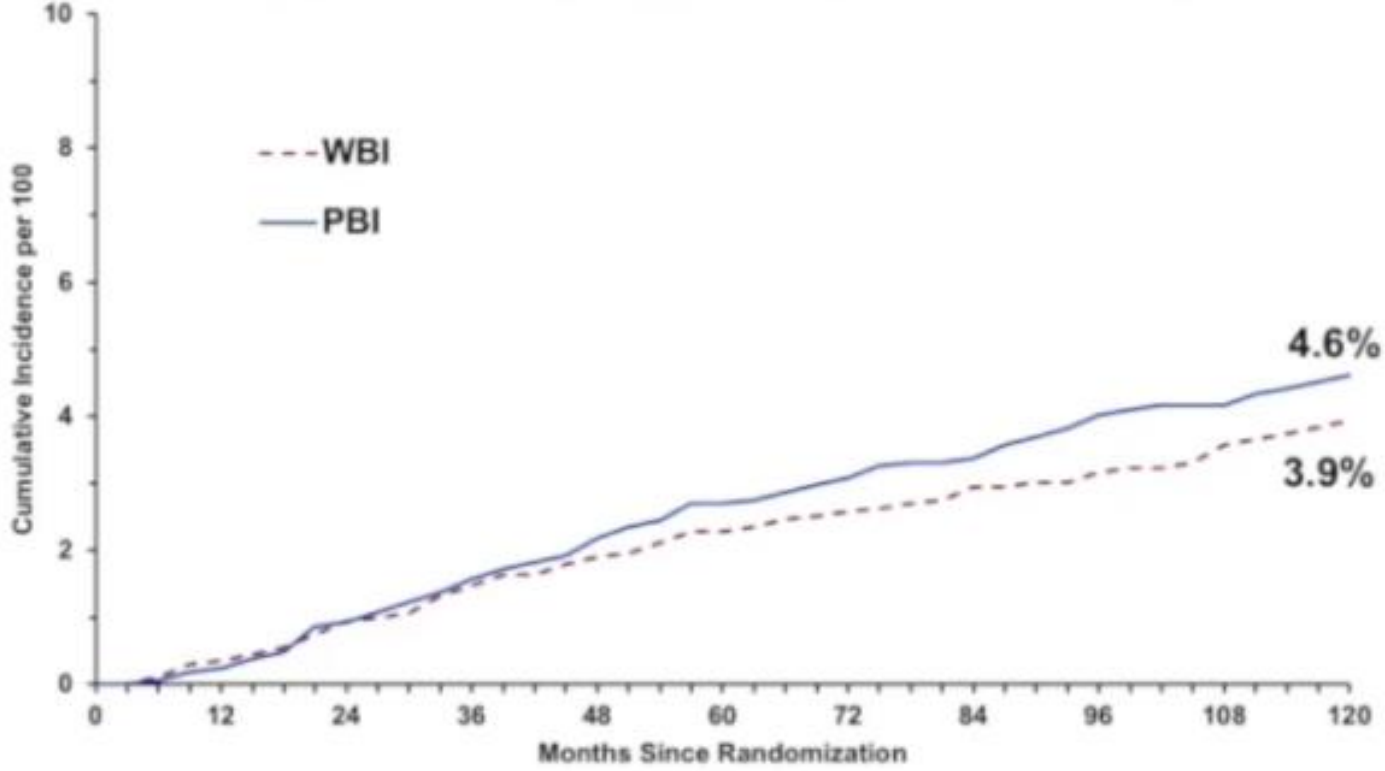
Cumulative Incidence of IBTR



No. at Risk						
WBI	2109	1920	1759	1557	1236	869
PBI	2107	1993	1834	1608	1269	876

Absolute difference in 10-yr rate of IBTR between PBI and WBI was *0.7%*

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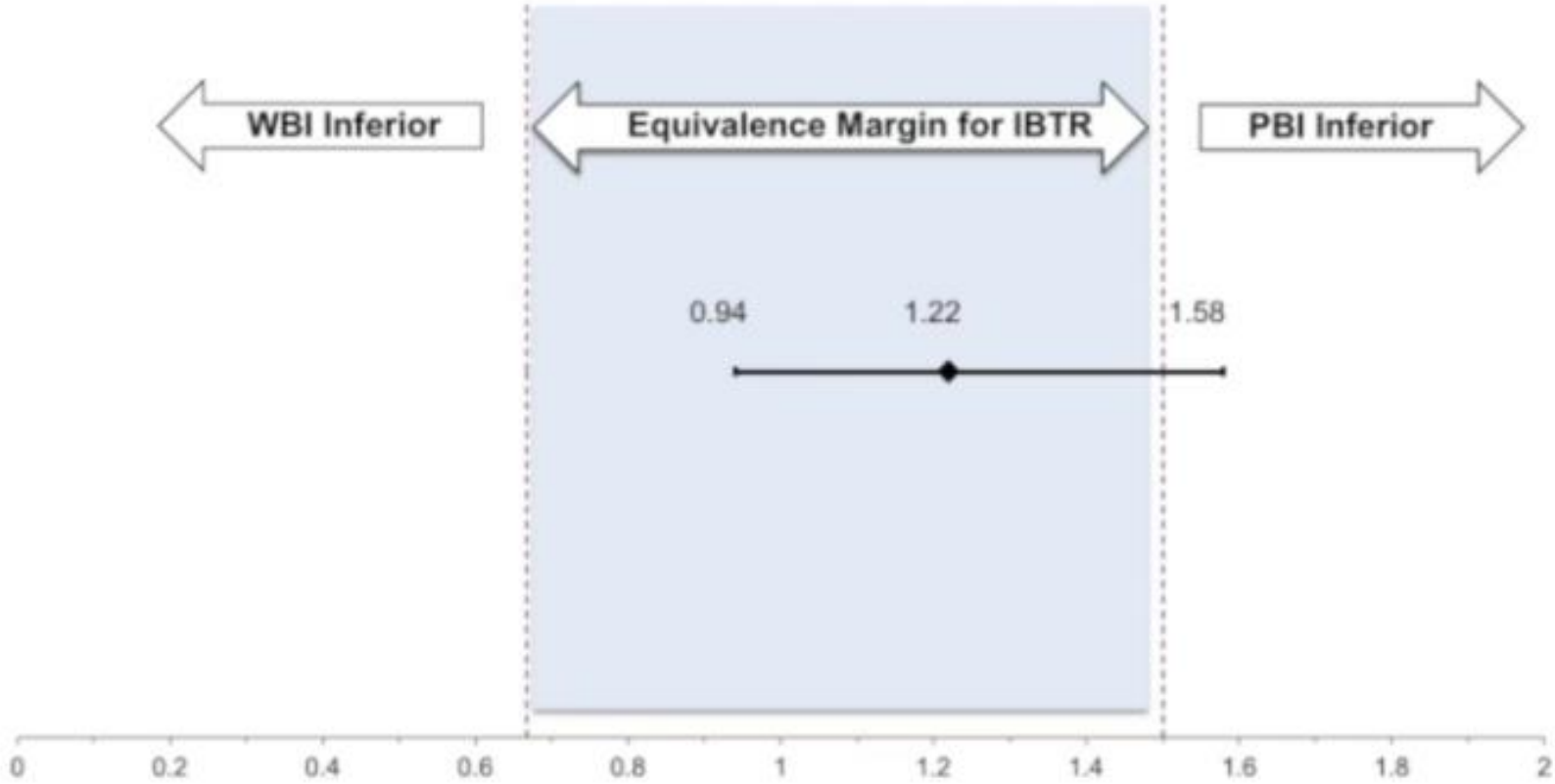
Ipsilateral Breast Tumor Recurrence (IBTR)



Hazard Ratio and 90%CI for IBTR

IBTR by PBI Method

Treatment Group	# of Pts	# of Events	Hazard Ratio (HR)	HR 95% Confidential Interval	10-yr Cum Incidence
WBI	2,011	67	REF		3.8%
PBI					
Multi-catheter brachytherapy	130	9	2.21	1.10 – 4.46	7.7%
Single-entry brachytherapy device	358	24	2.15	1.34 – 3.44	7.8%
3DCRT (external beam)	1,535	55	1.04	0.73 – 1.49	3.7%

This analysis used a per-protocol population, which excluded those who did not receive their randomly assigned treatment

Conclusions

- Intent-to-treat and as-treated analyses could not refute the hypothesis that PBI is inferior and cannot declare that WBI and PBI are equivalent in controlling local in-breast tumor recurrence. However, the absolute difference in the 10-yr cumulative incidence of IBTR was only 0.7%.
- Risk of an RFI event was statistically significantly higher for PBI *v* WBI, but again, the absolute difference in 10-yr RFI cumulative incidence was also small (1.6%)
- Breast cancer event rates at a median follow-up of 10.2 yrs in this population were overall low: IBTR rate: ~4.5%, DM rate: ~3%, and breast cancer death rate: ~2%

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RAPID

Randomized Trial of Accelerated Partial Breast Irradiation using 3-Dimensional Conformal Radiotherapy (3D-CRT)

T Whelan, J Julian, M Levine, T Berrang, DH Kim, CS Gu, I Germain, A Nichol, M Akra, S Lavertu, F Germain, A Fyles, T Trotter, F Perera, S Balkwill, S Chafe, T McGowan, T Muanza, W Beckham, B Chua, I Olivotto, for the RAPID Trial Investigators

Ontario Clinical Oncology Group

Patient Population

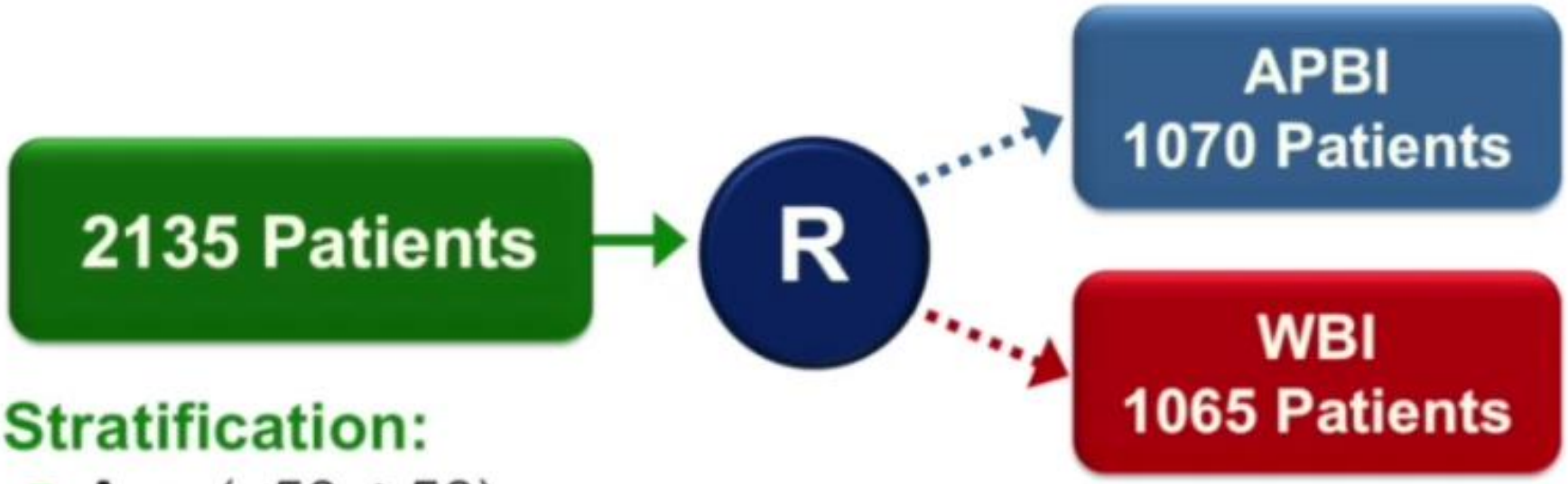
Inclusion Criteria:

- Invasive breast cancer or DCIS
- ≤ 3 cm in size
- Microscopically clear margins post-BCS
- Node negative

Exclusion Criteria:

- < 40 years of age
- Lobular histology only
- Multi-centric disease

Trial Design



Stratification:

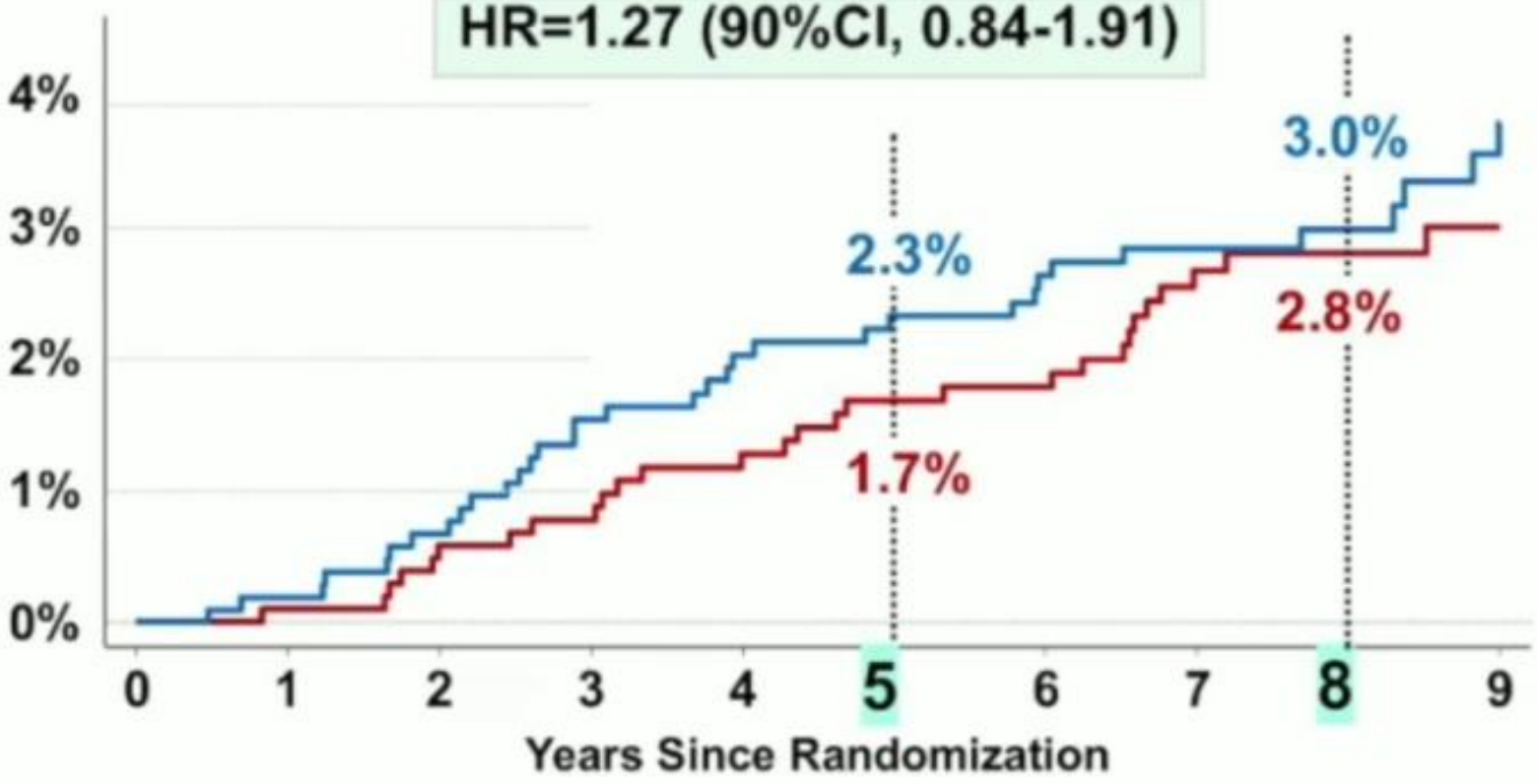
- **Age** (<50, ≥50)
- **Histology** (DCIS only, Invasive disease)
- **Tumor Size** (<1.5, ≥1.5 cm)
- **ER Status** (Pos, Neg)

APBI

- 3-5 non-coplanar fields using 3D-CRT or IMRT
- Treat surgical cavity + 1cm margin of surrounding breast tissue
- **Dose: 38.5 Gy/10 fractions given BID** (>6h between fractions)
- Dosimetric restrictions
- RTQA program

IBTR

APBI –	WBI –
37 events	28 events
HR=1.27 (90%CI, 0.84-1.91)	



RAPID studie – toxicitet och kosmetisk resultat

	WBRT	PBI	P-value
Akut toxicitet (grad 2)	44%	25%	< 0.001
Akut toxicitet (grad 3)	2%	2%	ns
Sen toxicitet (grad 2)	12%	28%	< 0.001
Sen toxicitet (grad 3)	1%	4%	ns
Dålig kosmetisk resultat (patient)	16%	32%	< 0.001
Dålig kosmetisk resultat (ssk)	18%	30%	< 0.001

Conclusions

- **APBI** non-inferior to **WBI** in preventing local recurrence
- IBTR rate very low; Absolute differences very small
- **APBI** associated with less acute toxicity but increased late toxicity and adverse cosmesis
- Unable to recommend the *twice-a-day* regimen
- *Once-a-day* treatment may not adversely affect cosmesis, and is being investigated

Diskussion - implikationer

- NSABP B-39: hypotesgenererande att 3D-CRT inte är sämre avs risk för recidiv än standard men brakyterapi kanske sämre
- RAPID: bekräftande att 3D-CRT inte är sämre avs recidivrisk men sämre avs toxicitet och kosmetiska resultat
- Partiell bröstbestrålning (3D-CRT) kan vara ett alternativ för selekterade patienter

Correa C, et al. Pract Radiat Oncol. 2017;7:73-79

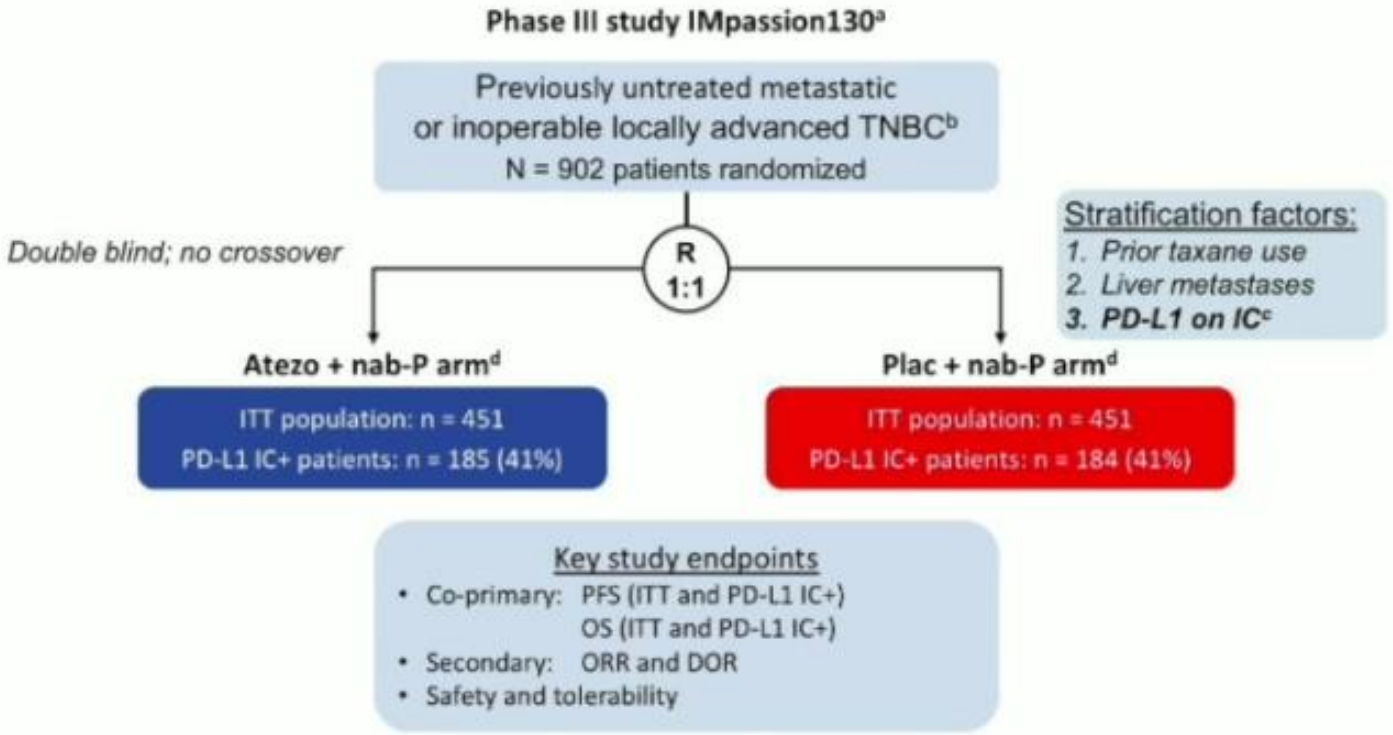
- Brakyterapi som metod att leverera partiell bröstbestrålning fortfarande experimentell

IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

Leisha A. Emens,[1] Sherene Loi,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Véronique Diéras,[5] Hiroji Iwata,[6] Carlos H. Barrios,[7] Marina Nechaeva,[8] Luciana Molinero,[9] Anh Nguyen Duc,[10] Roel Funke,[9] Stephen Y Chui,[9] Amreen Husain,[10] Eric P. Winer,[11] Sylvia Adams,[12] Peter Schmid[13]

[1]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital Heidelberg, Heidelberg, Germany; [5]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [6]Aichi Cancer Center Hospital, Aichi, Japan; [7]Department of Medicine, PUCRS School of Medicine, Porto Alegre, Brazil; [8]Arkhangelsk Regional Clinical Oncology Dispensary, Arkhangelsk, Russia; [9]Genentech, Inc., South San Francisco, CA; [10]F. Hoffmann-La Roche AG, Basel, Switzerland; [11]Dana-Farber Cancer Institute, Boston, MA; [12]New York University Langone Medical Center, New York, NY; [13]Barts Cancer Institute, Queen Mary University of London, London, UK

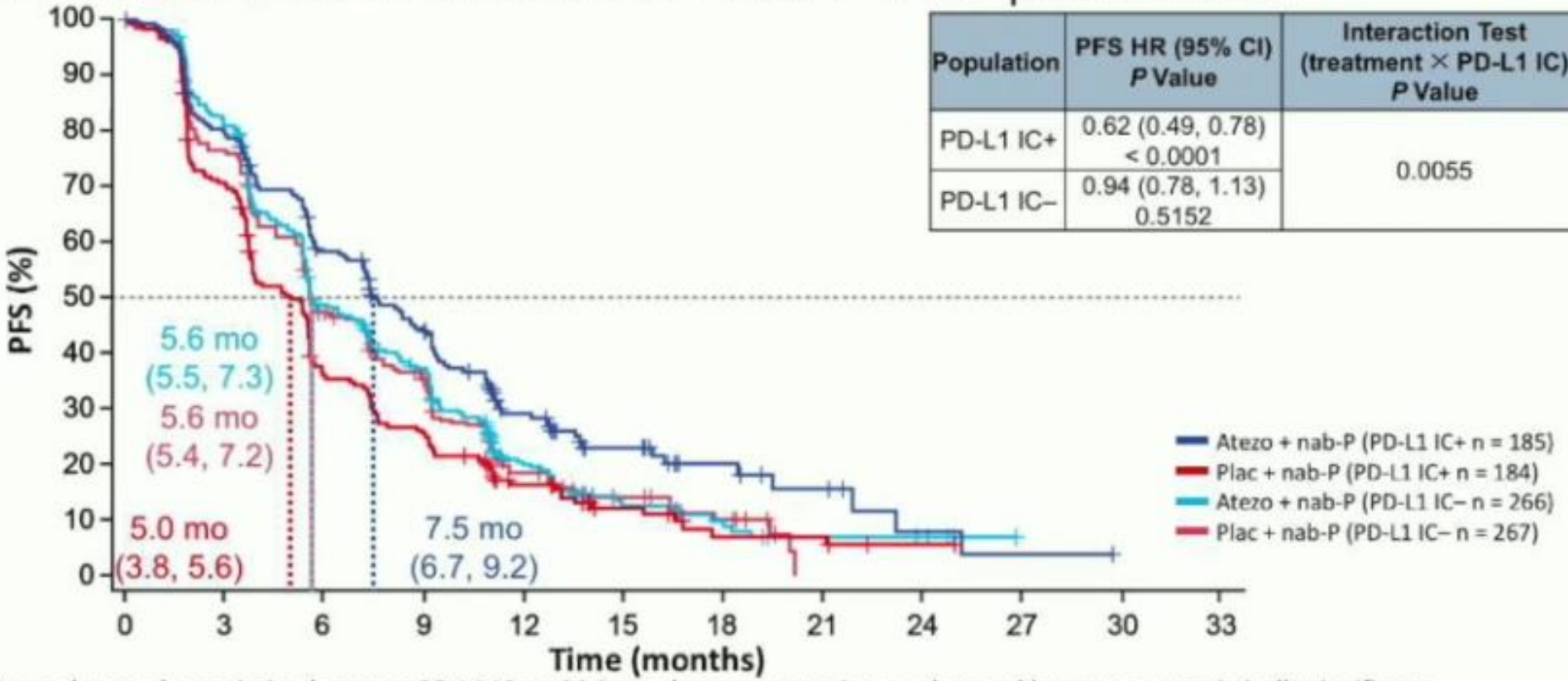
IMpassion130 study design: Prespecified analyses in the ITT and PD-L1 IC+ population



[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab or placebo 840 mg IV on days 1 and 15 + nab-paclitaxel 100 mg/m² IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD. 1. Schmid *N Engl J Med* 2018.

PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel

Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	



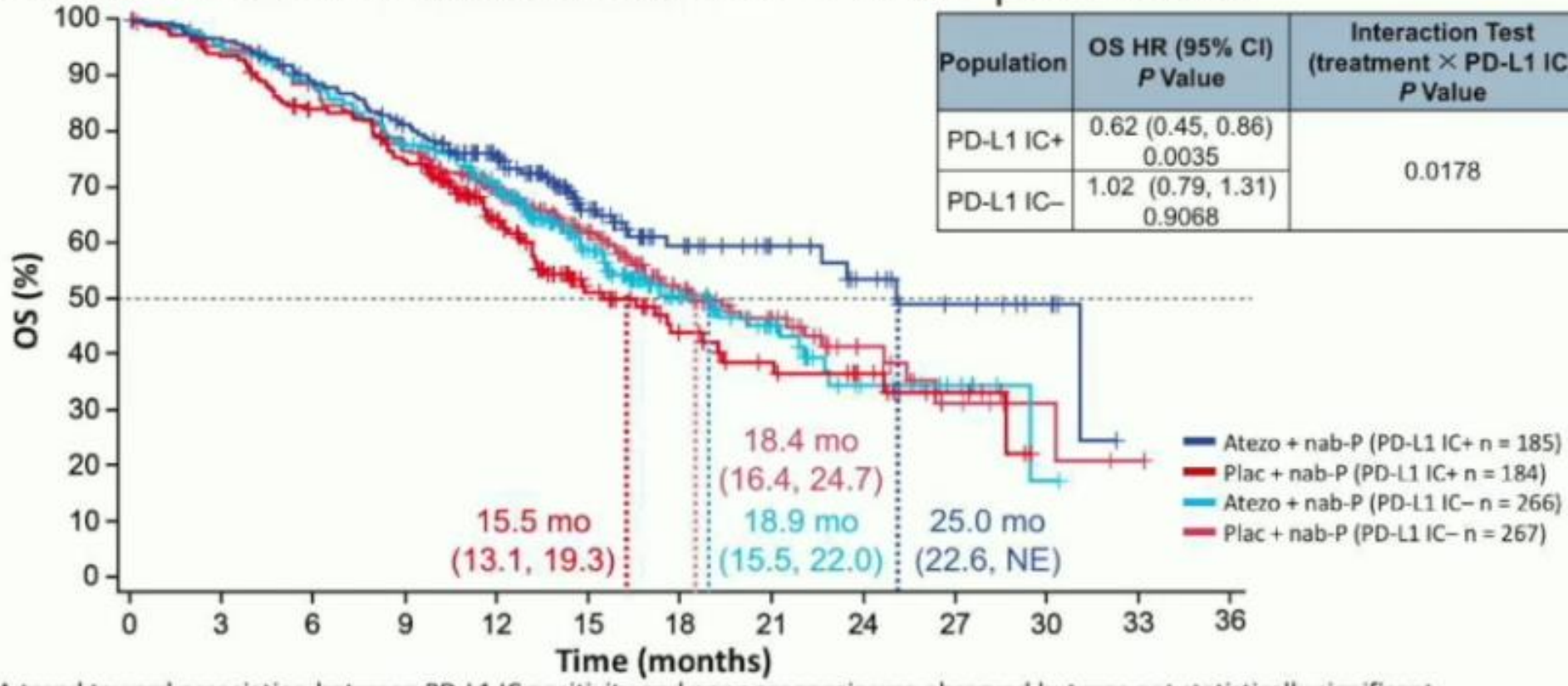
- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel

Population	OS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.45, 0.86) 0.0035	0.0178
PD-L1 IC–	1.02 (0.79, 1.31) 0.9068	



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Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

Conclusions

- In the Phase III IMpassion130 study, PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + *nab*-paclitaxel treatment for mTNBC
  - PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1% (by VENTANA SP142 IHC assay)
  - A treatment effect was not seen for adding atezolizumab to chemotherapy in the PD-L1–negative subgroup
- PD-L1 expression on TC did not provide additional information beyond PD-L1 IC status
  - Prevalence of tumor-cell PD-L1 expression was low, and the majority of these tumors were also PD-L1 IC+
- PD-L1 IC expression was the best predictor of clinical benefit as the patient subgroups with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T cells (CD8+) derived clinical benefit with atezolizumab + *nab*-paclitaxel if their tumors were also PD-L1 IC+
- PFS and OS results were consistent regardless of *BRCA1/2* mutation status
- Patients with newly diagnosed metastatic and unresectable locally advanced TNBC should be routinely tested for PD-L1 IC status to determine whether they might benefit from atezolizumab + *nab*-paclitaxel

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

Diskussion -implikationer

- Resultat är practice-changing: kombination av nab-paclitaxel + Atezolimumab förväntas bli godkänd
- Prediktiv biomarkör med PD-L1 expression på immunceller (≥ 1%)
- Behov för standardisering av PD-L1 analys
- Frågor som behöver besvaras

- Är kombinationen effektiv vid > 1:a linje?
- Är immunterapi effektiv i kombination med andra cytostatika (premedicinering med kortison)?

Sammanfattning

- TDM1 förväntas bli standard of care efter neoadjuvant behandling när pCR inte uppnås
- Strålbehandling (inkl level I) kan väljas i st för axillutrymning vid positiv sentinel node
- 3D-CRT för partiell bröstbestrålning kan vara ett alternativ för selekterade patienter men risk för sämre kosmetisk resultat och högre toxicitet
- PD-L1 expression på immunceller är prediktiv biomarkör för atezolimumab + nab-paklitaxel vid tippel negativ metastaserad bröstcancer