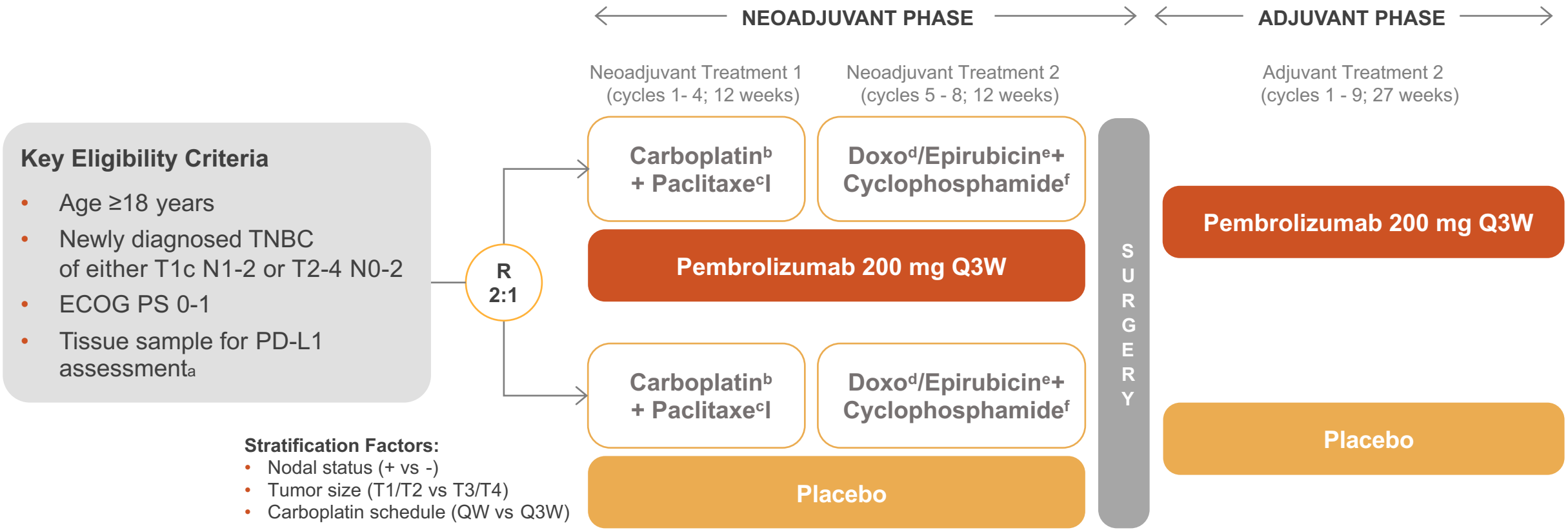
Breast Cancer ACADEMY

EARLY BREAST CANCER

KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC)

Peter Schmid, Javier Cortes, Rebecca Dent, Lajos Pusztai, Heather McArthur, Sherko Kümmel, Jonas Bergh, Carsten Denkert, Yeon Hee Park, Rina Hui, Nadia Harbeck, Masato Takahashi, Theodoros Foukakis, Peter A. Fasching, Fatima Cardoso, Liyi Jia, Vassiliki Karantza, Jing Zhao, Gursel Aktan, Joyce O'Shaughnessy

KEYNOTE-522 Study Design (NCT03036488)



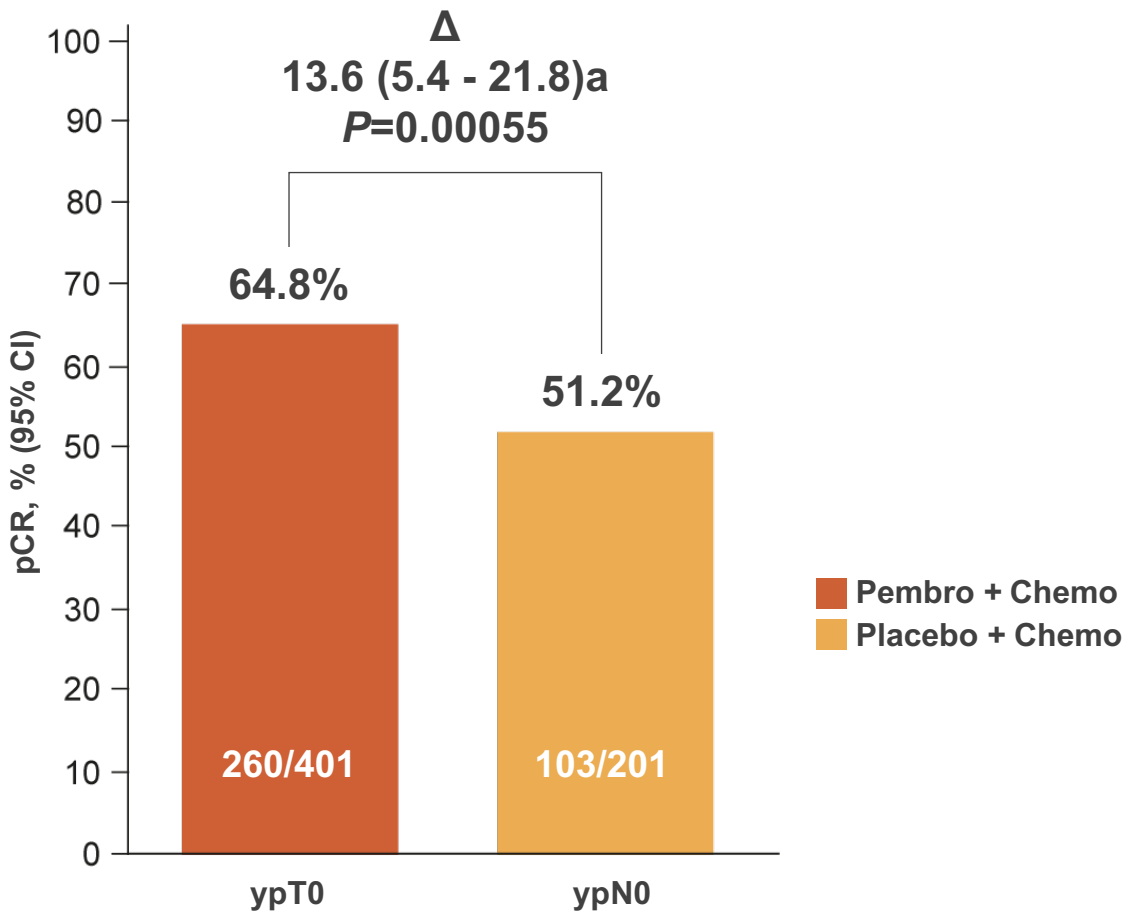
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m$_2$ QW. [d]Doxorubicin dose was 60 mg/m$_2$ Q3W. [e]Epirubicin dose was 90 mg/m$_2$ Q3W. [f]Cyclophosphamide dose was 600 mg/m$_2$ Q3W.

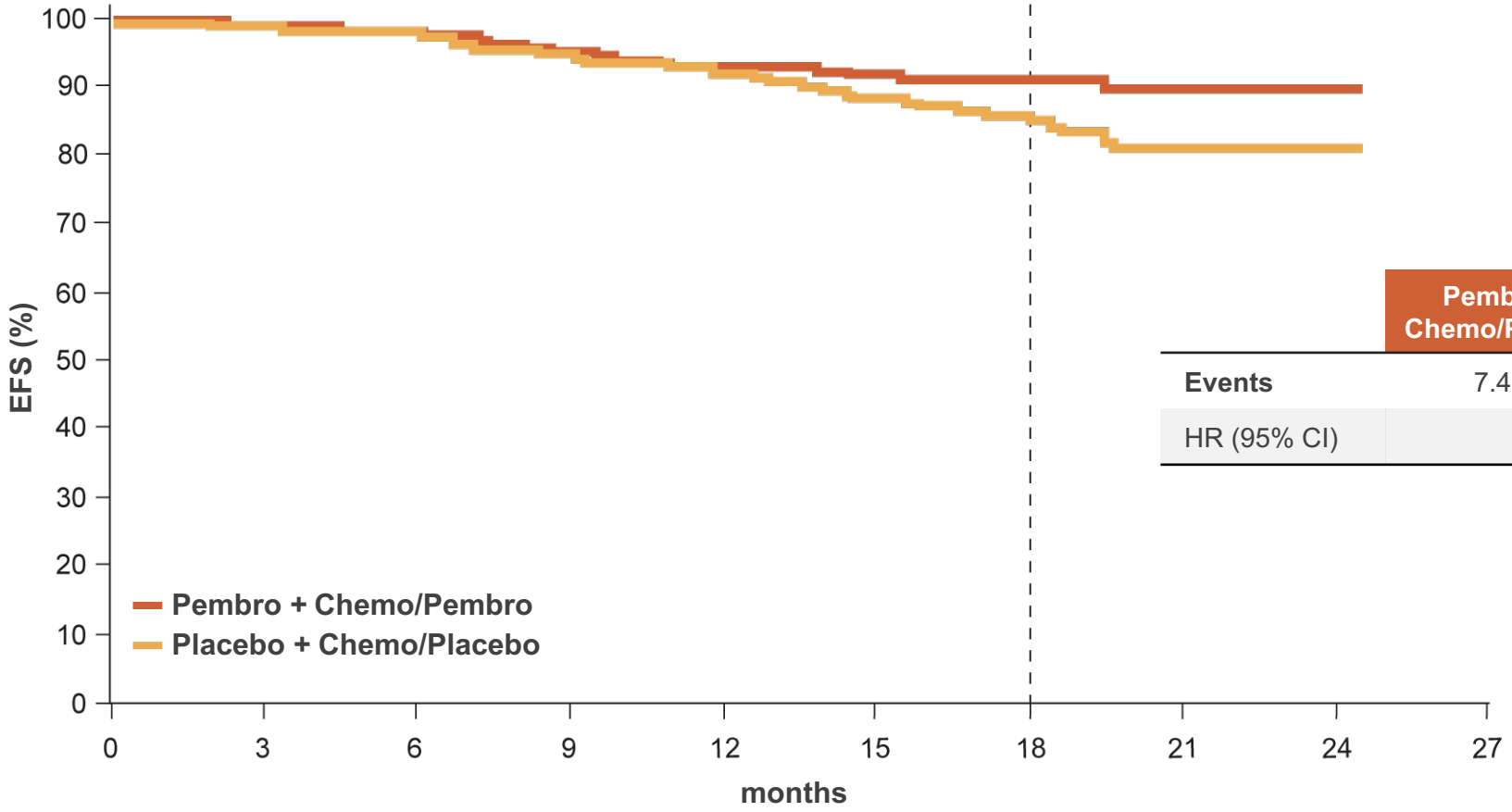
Pathological Complete Response at IA1

PRIMARY ENDPOINT



aEstimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. Data cutoff date: September 24, 2018.

Event-Free Survival at IA2



	Pembro + Chemo/Pembro	Placebo + Chemo/Placebo
Events	7.4%	11.8%
HR (95% CI)	**0.63[a] (0.43-0.93)**	

[a]Prespecified *P* value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS).
HR (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

Breast Cancer ACADEMY

Peripheral neuropathy, thrombocytopaenia, and central nervous system recurrence: an update of the phase III Katherine trial of post-neoadjuvant trastuzumab emtansine (T-DM1) or trastuzumab in patients with residual invasive HER2-positive breast cancer

Michael Untch, *Charles E. Geyer, Jr., Chiun-Sheng Huang, Sibylle Loibl, Norman Wolmark, Max S. Mano, Gunter von Minckwitz, Adam Brufsky, Xavier Pivot, Jonathan Polikoff, Andrea Fontana, Bella Kaufman, Juan Carlos Alcedo, Thomas Boulet, Haiying Liu, Chunyan Song, Eleftherios P. Mamounas*

Access slides at: https://bit.ly/2NGjKsV

Effect of baseline peripheral neuropathy on treatment-induced peripheral neuropathy

On-Study Peripheral Neuropathy[a] (safety population)	BL Neuropathy		No BL Neuropathy	
	T-DM1	H	T-DM1	H
All Grades, %	36.3	17.5	31.1	16.8
Grade 1	18.5	12.3	23.1	14.3
Grade 2	14.3	5.2	7.0	2.3
Grade 3	3.6	0.0	1.0	0.2
Grade 4	0.0	0.0	0.0	0.0
Median Duration, d	352	337	243	232
Resolution[b] Rate, %	66.0	63.6	81.2	82.5

[a]Incidence refers to peripheral neuropathy; duration and resolution applies to peripheral sensory neuropathy; [b]Reported by investigator as "resolved."

- BL neuropathy was well balanced between treatment arms: T-DM1 22.7%; H 21.4%
- Incidence of peripheral neuropathy was higher with T-DM1, regardless of BL neuropathy
- Resolution rate was similar in both arms, regardless of BL neuropathy
- Irrespective of study treatment, BL neuropathy was associated with:
  - Longer median peripheral neuropathy duration
  - Lower rates of peripheral neuropathy resolution

BL, baseline; d, days; H, trastuzumab.

Effect of prior Taxane type on incidence of peripheral neuropathy

On-Study Peripheral Neuropathy (safety population)	Docetaxel		Paclitaxel	
	T-DM1 (n=402)	H (n=411)	T-DM1 (n=351)	H (n=319)
All Grades, %	32.1	17.8	31.9	16.6
Grade 1	22.1	14.1	21.7	13.8
Grade 2	8.0	3.6	9.4	2.5
Grade 3	2.0	0.0	0.9	0.3
Grade 4	0.0	0.0	0.0	0.0

- The type of neoadjuvant taxane was similar between treatment arms:
  - Docetaxel: T-DM1 54%; H 57%
  - Paclitaxel: T-DM1 47%; H 44%
  - Nab-paclitaxel: T-DM1 0.8%; H 0%
- BL neuropathy incidence was the same between treatment arms in patients with prior docetaxel (T-DM1 23%; H 23%) but was numerically higher in the T-DM1 arm in those with prior paclitaxel (T-DM1 23%; H 18%)
- The incidence of peripheral neuropathy was similar within each treatment arm, irrespective of the type of neoadjuvant taxane received

BL, baseline; H, trastuzumab.

Effect of prior platinum therapy on T-DM1–associated thrombocytopaenia

Thrombocytopaenia (safety population)	Prior platinum		No prior platinum	
	T-DM1	H	T-DM1	H
All Grades, %	36.2	3.3	26.7	2.1
Grade 1	15.6	3.3	13.9	1.6
Grade 2	7.1	0.0	9.0	0.2
Grade 3	8.5	0.0	2.5	0.2
Grade 4	5.0	0.0	1.3	0.2
Median Duration of Grade 3–4, d	33	-	29	110[a]
Resolution Rate of Grade 3–4, %	95	-	96	100[a]

[a]Based on two events.

- Overall, 20% of patients received prior carboplatin or cisplatin (T-DM1 arm 19%, H arm 21%)
- Prior platinum was associated with a higher incidence of thrombocytopaenia in the T-DM1 arm
- The median duration and resolution rate of grade 3–4 thrombocytopaenia were similar irrespective of prior platinum therapy

D, days; H, trastuzumab.

CNS recurrence: background

Site of First Invasive Disease Event		
Event, n (%)	T-DM1 (n=743)	H (n=743)
Any Invasive-Disease Event	91 (12.2)	165 (22.2)
Category of Invasive Event		
Distant Recurrence	78 (10.5)	118 (15.9)
CNS	44 (5.9)	32 (4.3)
Non-CNS	34 (4.6)	86 (11.6)
Locoregional Recurrence	8 (1.1)	34 (4.6)
Contralateral Breast Cancer	3 (0.4)	10 (1.3)
Death without Previous Event	2 (0.3)	3 (0.4)

Patients with additional IDFS event(s) within 61 days of their first event were reported in the category according to the following hierarchy: (1) distant recurrence; (2) locoregional recurrence; (3) contralateral breast cancer; (4) death without prior event.

- In the primary KATHERINE results, there was a numerically higher rate of CNS recurrence as first site of recurrence in the T-DM1 arm1
- To better understand these data and the potential impact on overall survival, additional analyses were performed

1. von Minckwitz G, et al. N Engl J Med. 2019;380:617–28.

Higher CNS recurrence as first IDFS event is likely due to competing risk; T-DM1 was not associated with an increased overall risk of CNS recurrence

CNS Recurrence	T-DM1 (n=743)	H (n=743)
Patients with CNS Recurrence, n (%)	45 (6.1)	40 (5.4)
As First IDFS Event[a]	44 (5.9)	32 (4.3)
After First IDFS Event[b]	1 (0.1)	8 (1.1)
Patients with CNS as Only Event[c]	36 (4.8)	21 (2.8)
Median Time to CNS Recurrence, mo	17.5	11.9

Note: CNS recurrence within[a] or after[b] 61 days of first IDFS event, or any time[c].

- The numerically higher rate of CNS recurrence as a first IDFS event in the T-DM1 arm may be explained by competing risk,1,2 as seen in adjuvant trastuzumab trials3
  - Competing risk: The substantial reduction in the incidence of non-CNS recurrences as a first event observed with T-DM1 leads to an increased likelihood of a CNS recurrence as a first event and as the only recurrence
- This is supported by
  - Similar cumulative incidence of CNS recurrence in both arms
  - Longer time (Δ5.6 m) to CNS recurrence in the T-DM1 arm
  - Higher incidence of CNS recurrence as the only recurrence in the T-DM1 arm

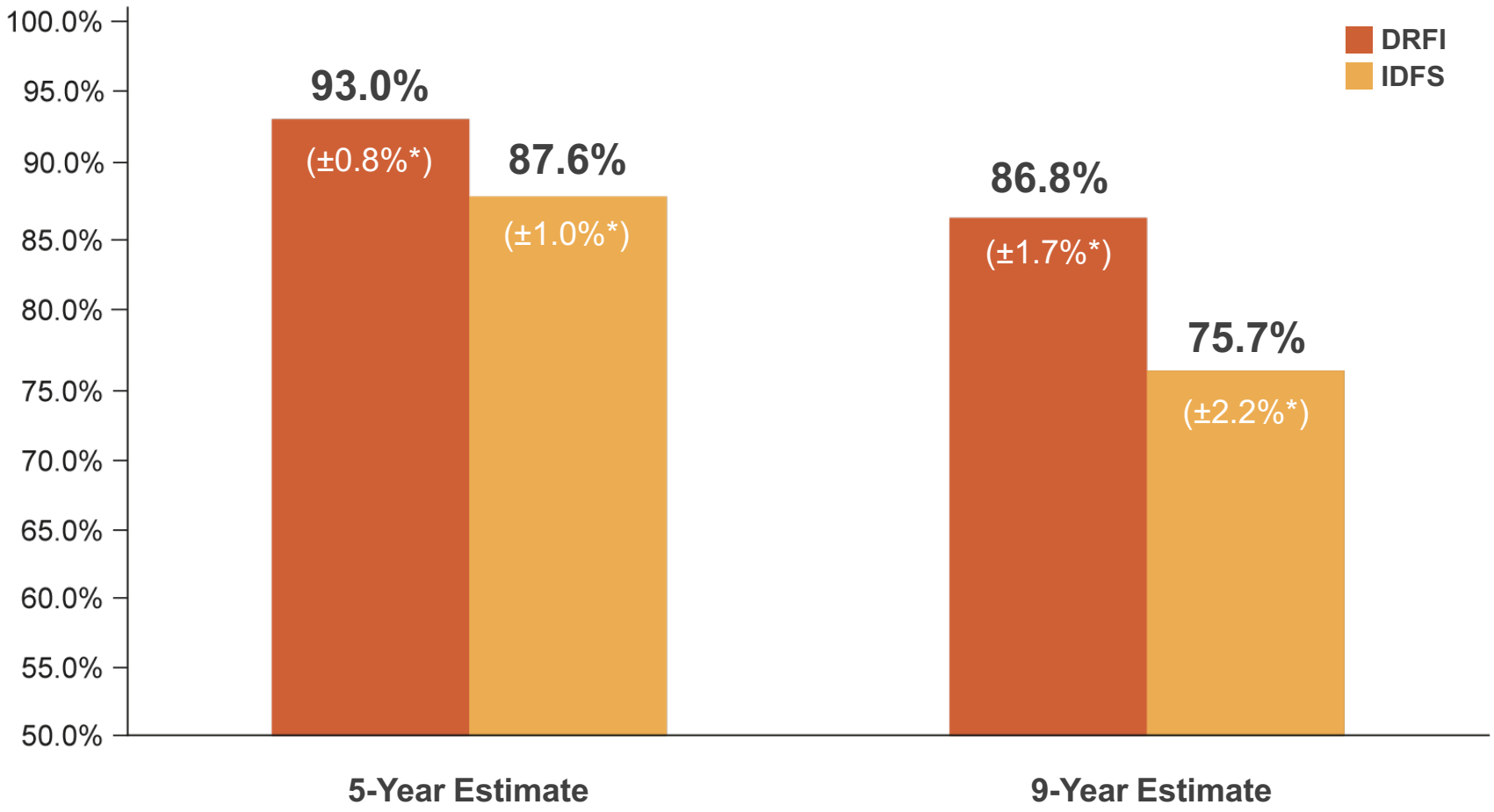
1. Wolkewitz M, et al. BMJ. 2014; 349:g5060; 2. Gooley TA, et al. Stat Med. 1999;18:695–706; 3. Pestalozzi BC, et al. Lancet Oncol. 2013;14:244–8.

Clinical Outcomes by Chemotherapy Regimen in Patients with RS 26-100 in TAILORx

Joseph A. Sparano, Robert J. Gray, Della F.Makower, Kathy S. Albain, Thomas J. Saphner, Lynne I. Wagner, Sunil Badve, Catalin Mihalcioiu, Christine Desbiens, Daniel F.Hayes, Elizabeth C. Dees, Charles E. Geyer Jr., John A. Olson, Jr., William C. Wood, Tracy G. Lively, Soonmyung Paik, Matthew J. Ellis, Jeffrey Abrams, George W.Sledge,Jr.

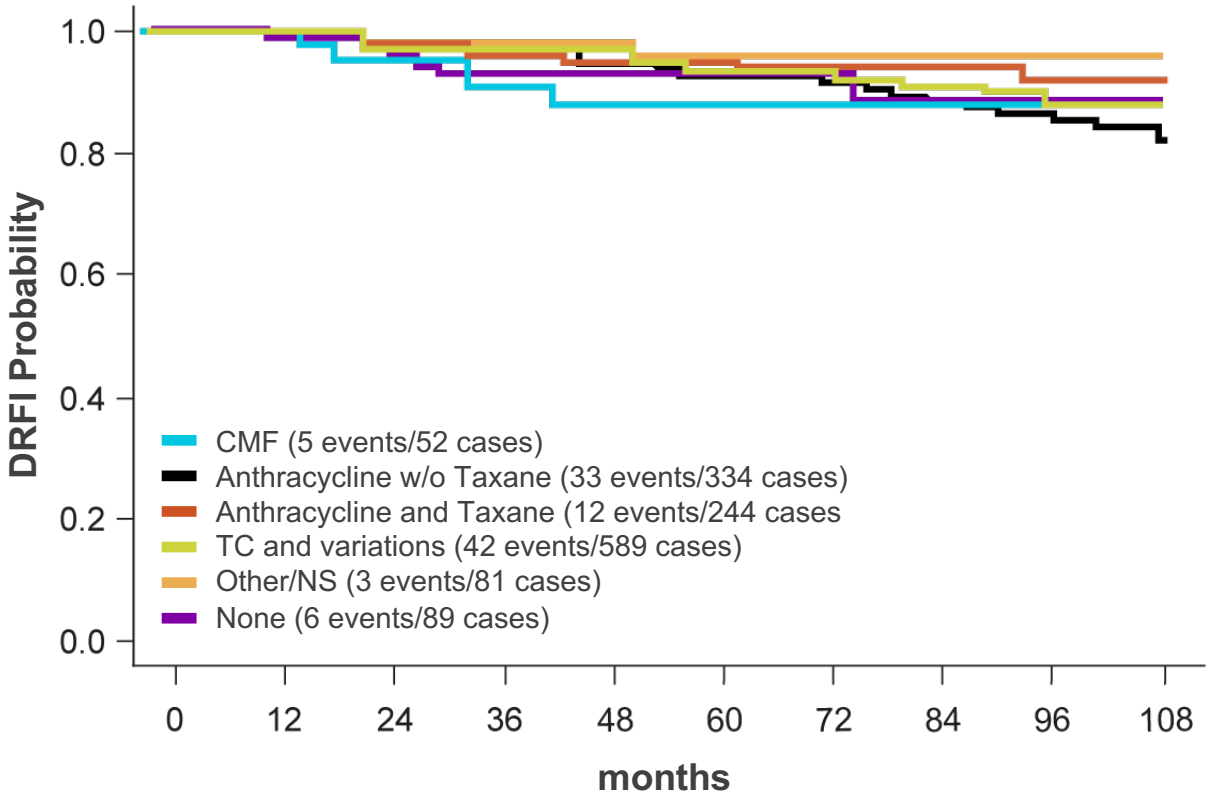
on behalf of the TAILORx Investigators

Results-Arm D: Kaplan Meier Estimates in Overall Population (n=1389)



* Standard error (SE)

Results - Arm D: KM Estimates of Distant Relapse-Free Interval (DRFI) by Chemotherapy Regimen



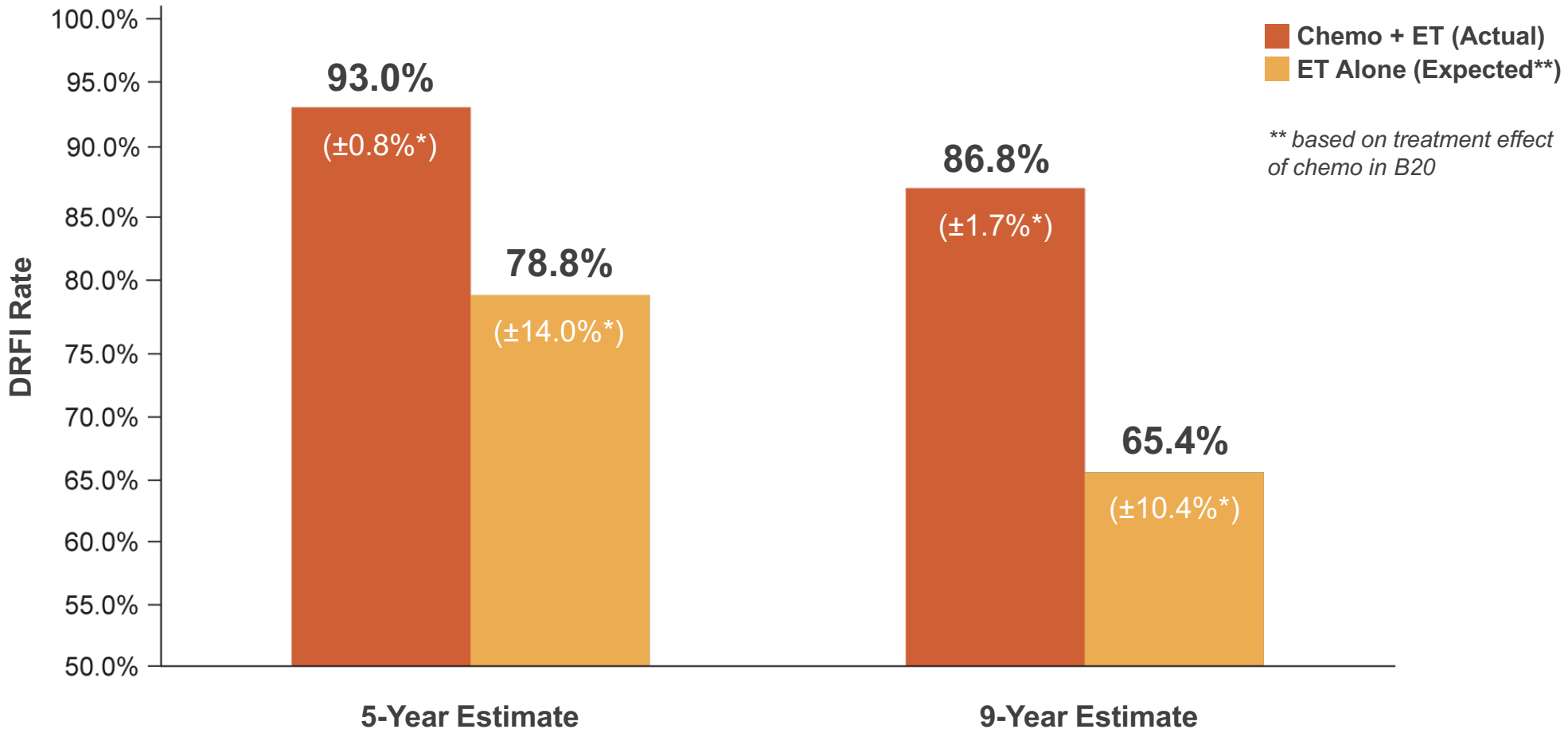
Regimen	5-Year Rate	SE*
TC	92.7%	+ 1.2%
A without T	92.3%	+ 1.6%
A and T	95.1%	+ 1.5%
CMF	88.5%	+ 4.8%
Other	95.5%	+ 2.5%

Cox model: any chemo regimen (N=1300) versus none (N=89)

- Adjustment for tumor size (>2 vs. <=2 cm), grade, RS, and age (>65 vs. 51-65 vs.<=50 years)
- Estimated hazard ratios 0.74 (95% CI 0.32,1.69) for administration of any chemotherapy vs. none

** Standard error (SE)*

Results - DRFI: Comparison of Actual Outcomes For Patients Treated with Chemotherapy plus Endocrine Therapy (N=1300) vs. Expected Outcomes with Endocrine Therapy Alone



* Standard error (SE)

Intrinsic prognostic value of tumor infiltrating lymphocytes (TILs) in early-stage triple negative breast cancer (TNBC) not treated with adjuvant chemotherapy

A POOLED ANALYSIS OF 4 INDIVIDUAL COHORTS

Ji Hyun Park, Sarah Flora Jonas, Guillaume Bataillon, Carmen Criscitiello, Roberto Salgado, Sherene Loi, Giuseppe Viale, Hee Jin Lee, Maria Vittoria Dieci, Sung-Bae Kim, Anne Vincent-Salomon, Giuseppe Curigliano, Fabrice Andre, Stefan Michiels.

This presentation is the intellectual property of the author/presenter. Contact irvineusa@hanmail.net for permission to reprint and/or distribute.

Description of 4 cohorts

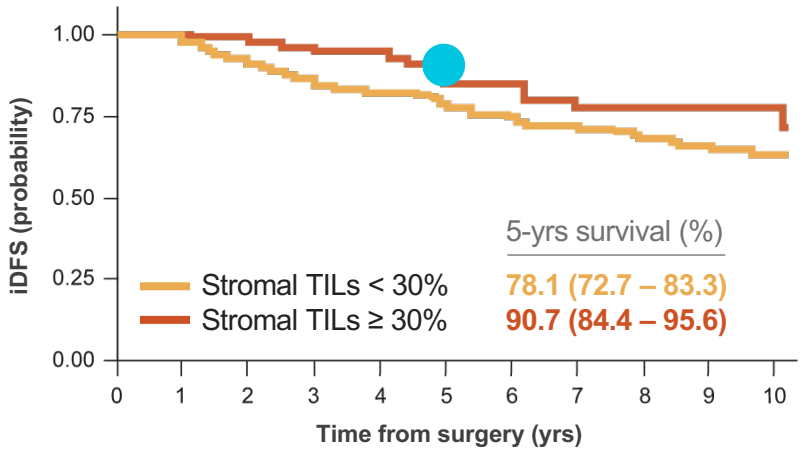
Data series	No. of pts	Definition of TNBC	Reference of original study	Inclusion period (date of surgery)
Instituto Europeo di Oncologia (IEO) Milan, Italy	**159**	***By local protocol of institute**** Using IHC for defining ER, PR negativity Using IHC and FISH for defining HER2 negativity	Retrospective single center	**1995-2015**
Institute Curie, Paris, France	**150**	***By local protocol of institute**** Using IHC for defining ER, PR negativity Using IHC and FISH for defining HER2 negativity	Retrospective single center	2005-2013
Gustave Roussy (GR) Villejuif, France	**95**	Using IHC ER and HER2 only on tissue array containing three spots from each primary tumor	PhIII RCT cohort*	1989-1995
Asan Medical Center Seoul, Korea	**72**	***By local protocol of institute*** Using IHC for defining ER, PR negativity Using IHC and FISH for defining HER2 negativity	Retrospective single center	1999-2012
Total	**476**			1989-2015

** Follows the guideline from American Society of Clinical Oncology/College of American Pathologists*

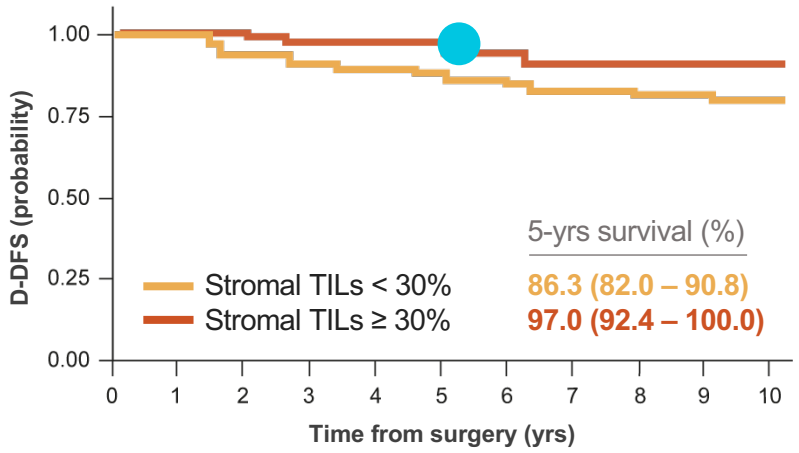
Dieci, Goubar et al, Ann Oncol. 2015

Further Excellent Outcomes In pStage I tumors

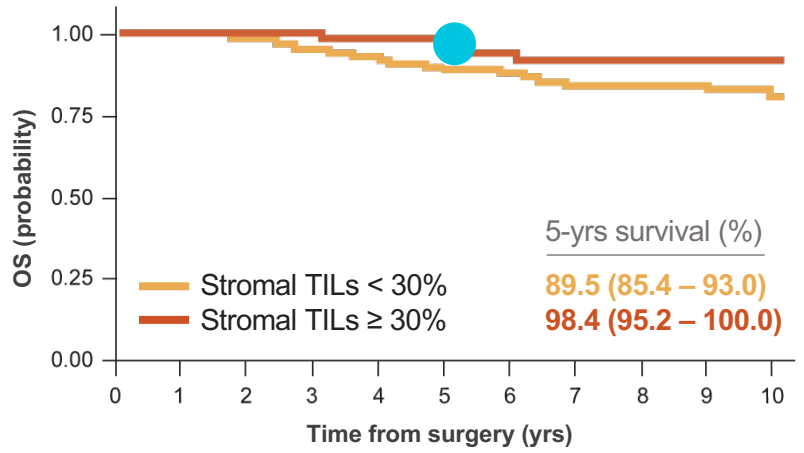
5Y iDFS: 91%	3Y: 93%
84-96	89-96

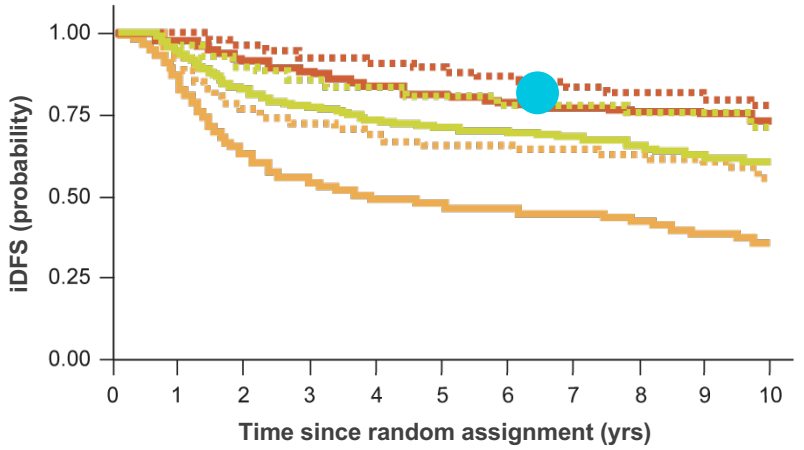


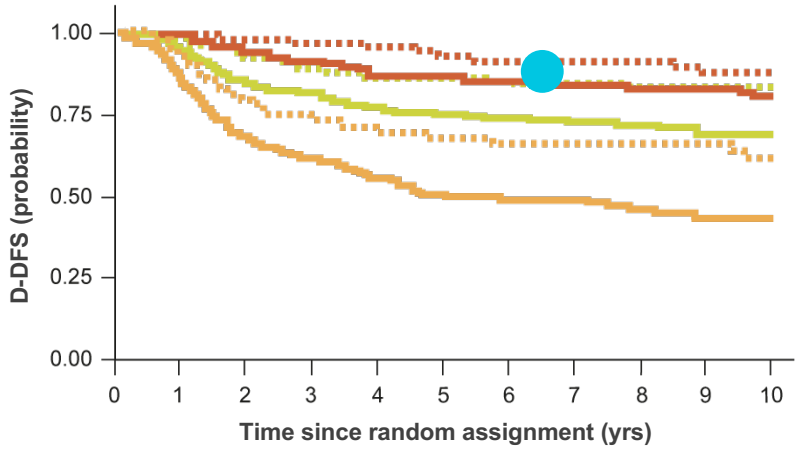
5Y D-DFS: 97%	3Y: 97%
95-100	95-99

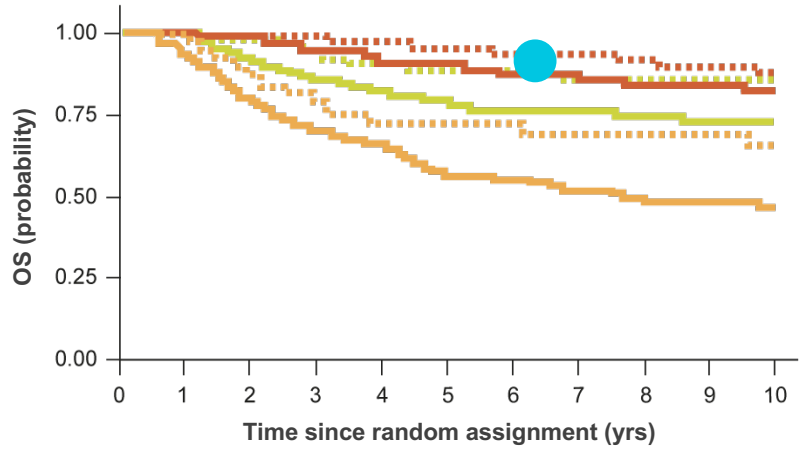


5Y OS: 98%	3Y: 99%
95-100	97-100









0 positive node and stromal TILs < 30%
0 positive node and stromal TILs ≥ 30%
1-3 positive nodes and stromal TILs < 30%
1-3 positive nodes and stromal TILs ≥ 30%
> 3 positive nodes and stromal TILs < 30%
> 3 positive nodes and stromal TILs ≥ 30%