NUOVE PROSPETTIVE EBC

Laura Pizzuti

Oncologia Medica 2

OECI COMPREHENSIVE Cancer Centre

IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA

ISG ISTITUTO DERMATOLOGICO SAN GALLICANO

ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

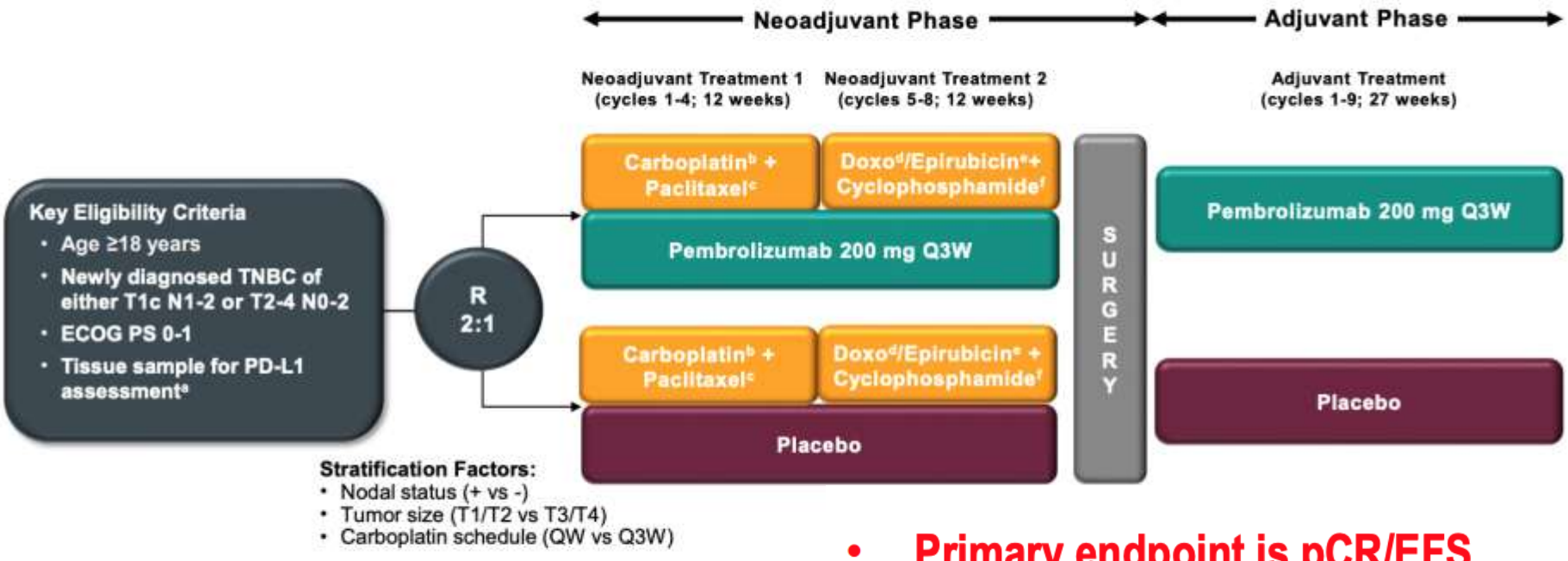
DISCLOSURES

- Travel grants: Eisai, Roche, Pfizer, Novartis
- Speaker fees: Roche, Pfizer, Novartis, Gentili

MY OUTLINE

- Adding IO to NACT in TNBC
  - Keynote-522
- Prognostic/predictive biomarkers
  - TILs in untreated EBC
  - Predictive and prognostic value of B-cell signatures and BCR
  - TailorX High Risk Arm
- Post-NACT
  - PNP with post-neoadj T-DM1 treatment

KEYNOTE-522 Study Design (NCT03036488)



- **Primary endpoint is pCR/EFS**

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.

Baseline Characteristics, ITT Population

Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Placebo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1–positive[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

- Largely PD-L1 pos
- CPS ≥1

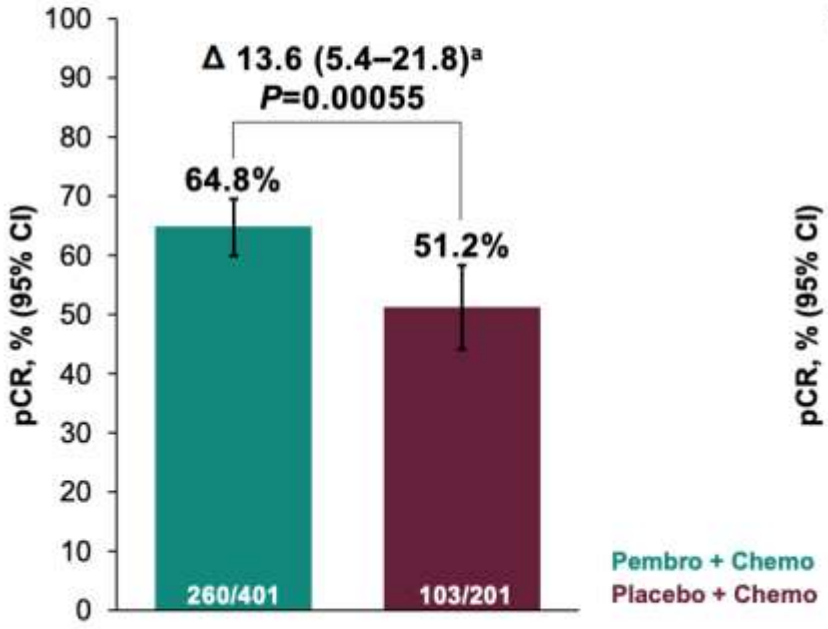
50% node neg
Stage 1B
T4
bilat

BARCELONA 2019 ESMO congress

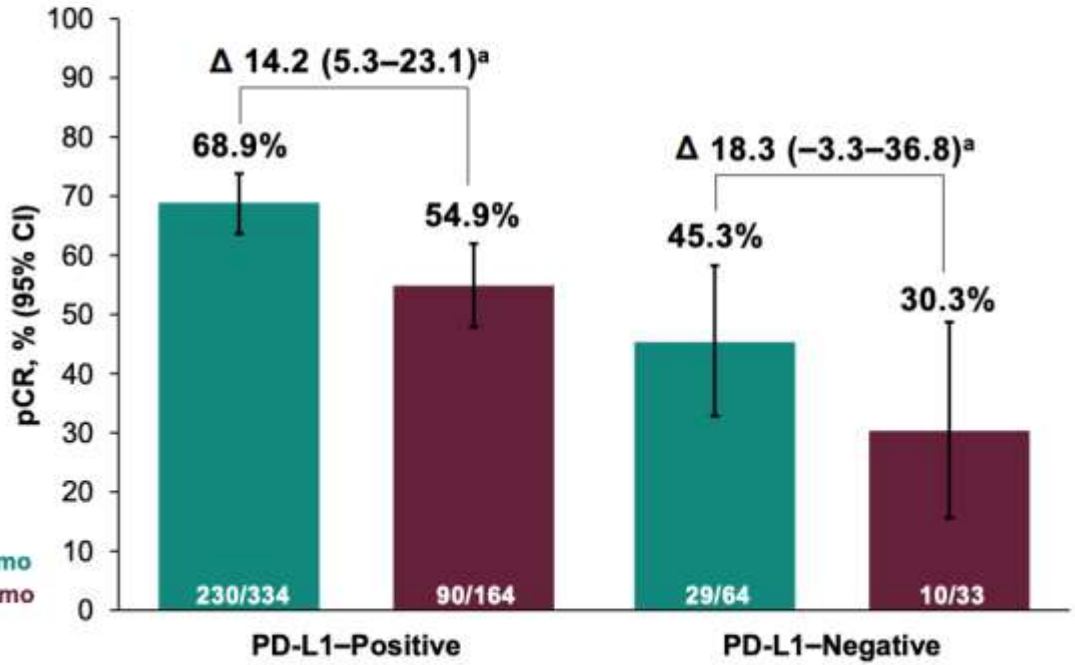
[a]The PD-L1 combined positive score was defined as number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by total number of tumor cells × 100. PD-L1 positivity was defined as CPS ≥1. Data cutoff date: April 24, 2019.

Pathological Complete Response at IA1

Primary Endpoint: ypT0/Tis ypN0

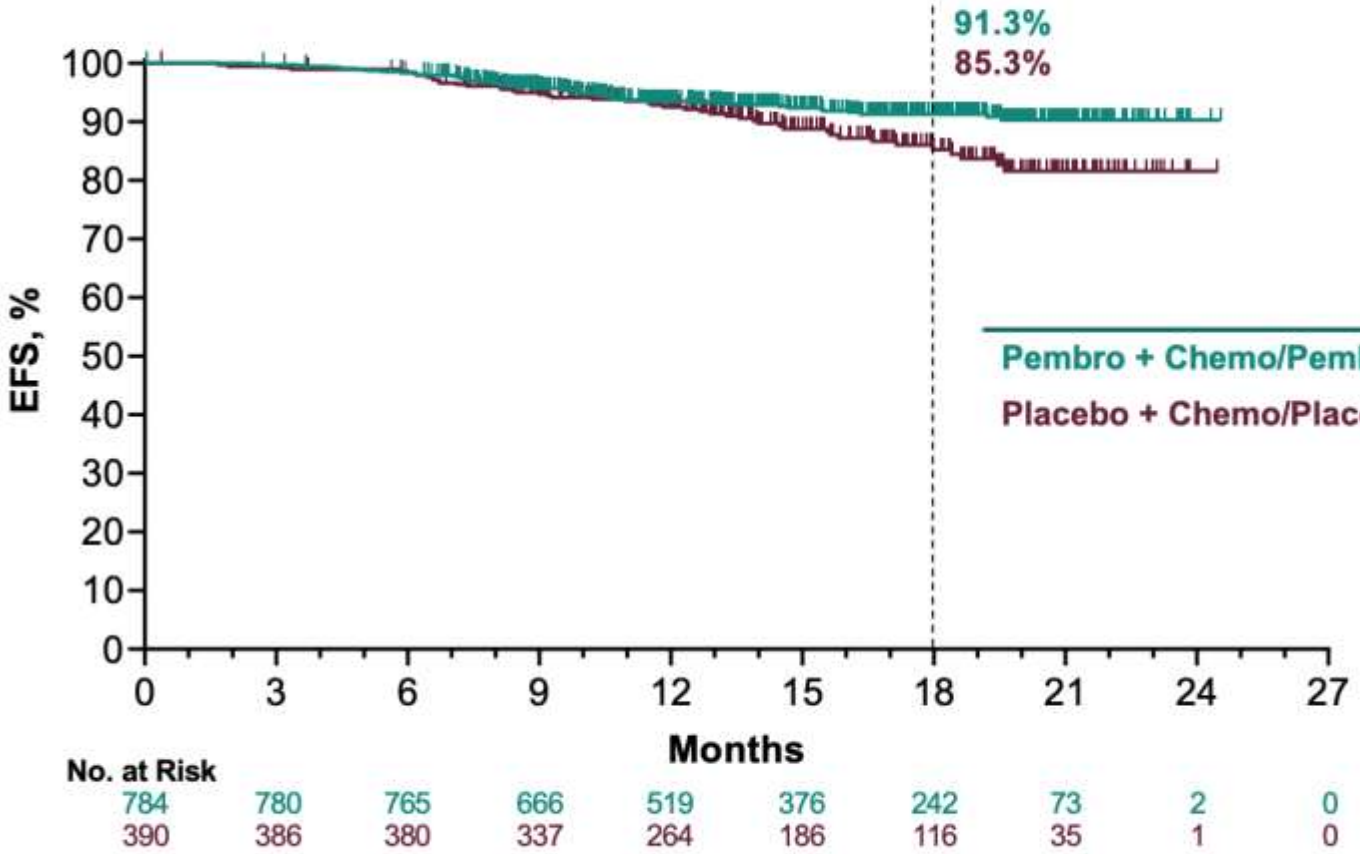


By PD-L1 Status[b]: ypT0/Tis ypN0



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

Event-Free Survival at IA2



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

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

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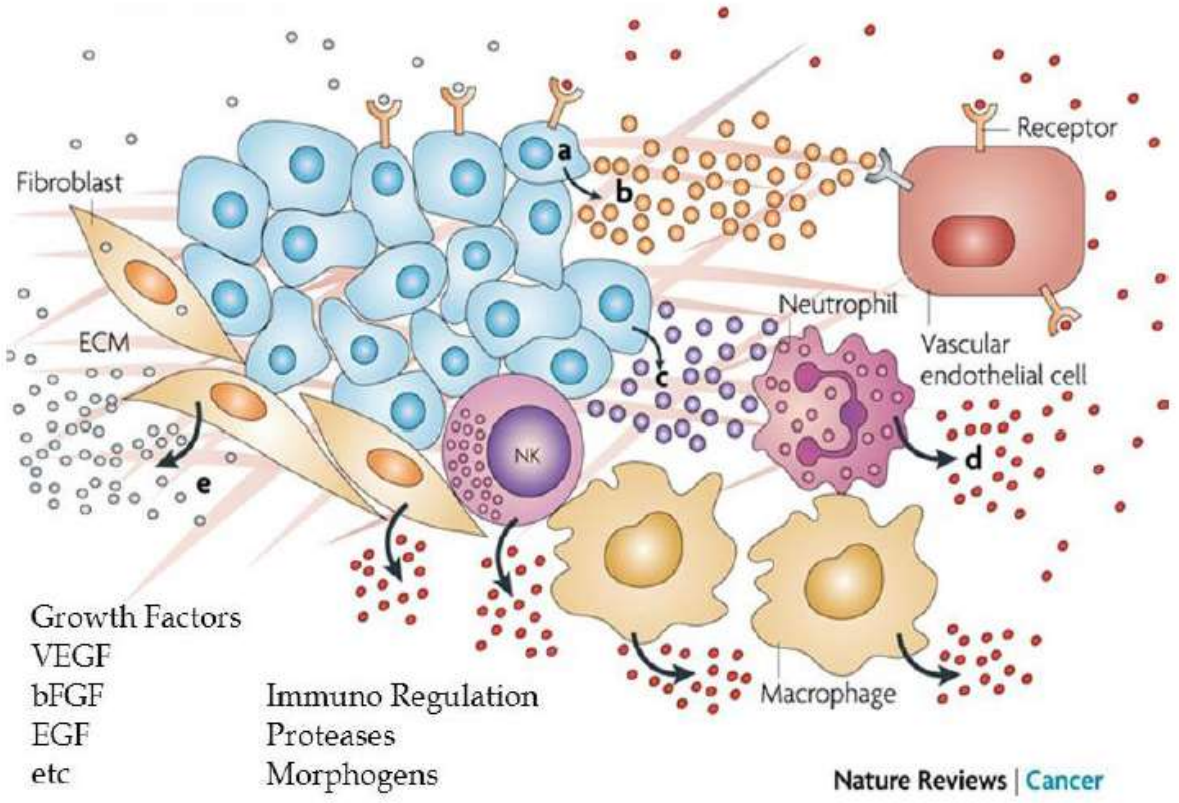
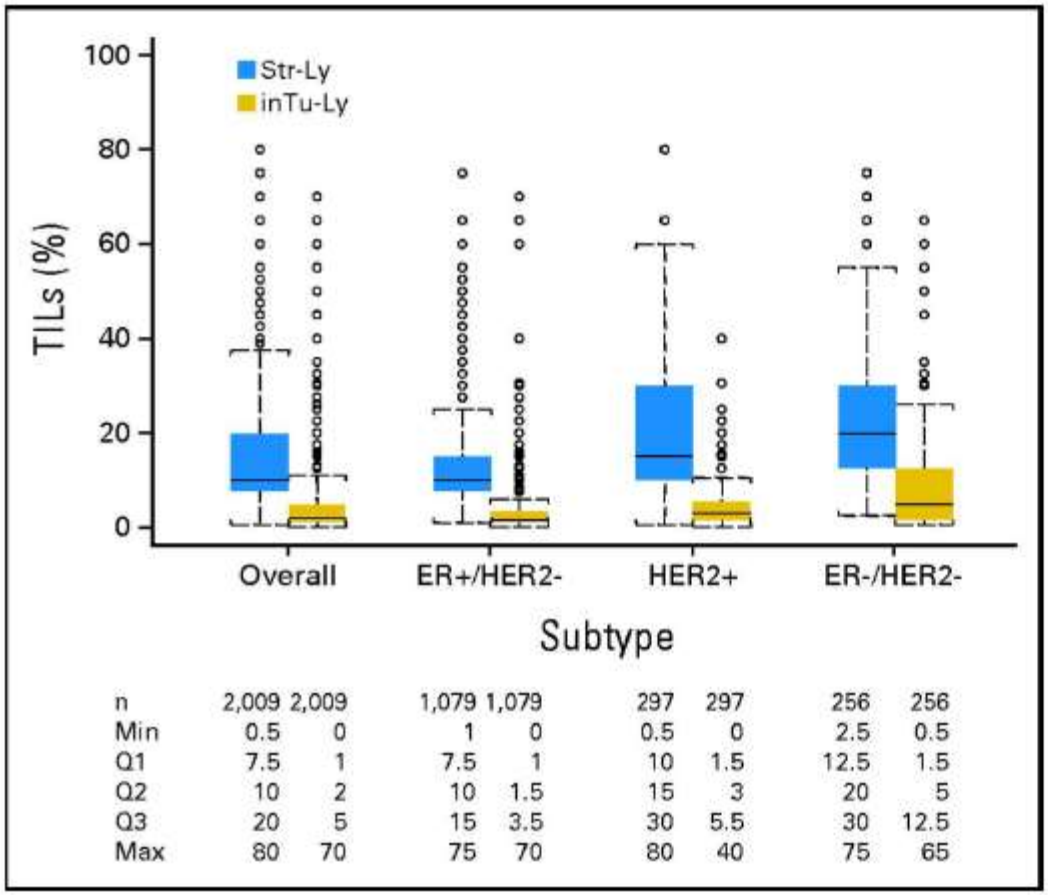
Immune tumor microenvironment in early breast cancer

What do we know?



Higher immune infiltrate in TNBC and HER2+ BC

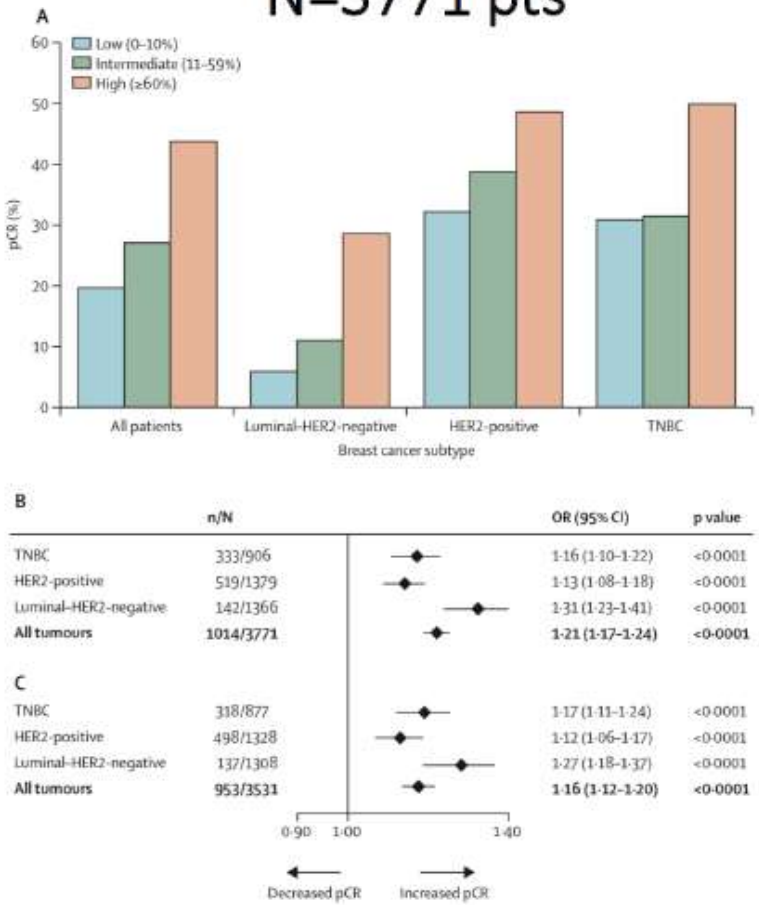


n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

Loi S et al., J Clin Oncol 2013

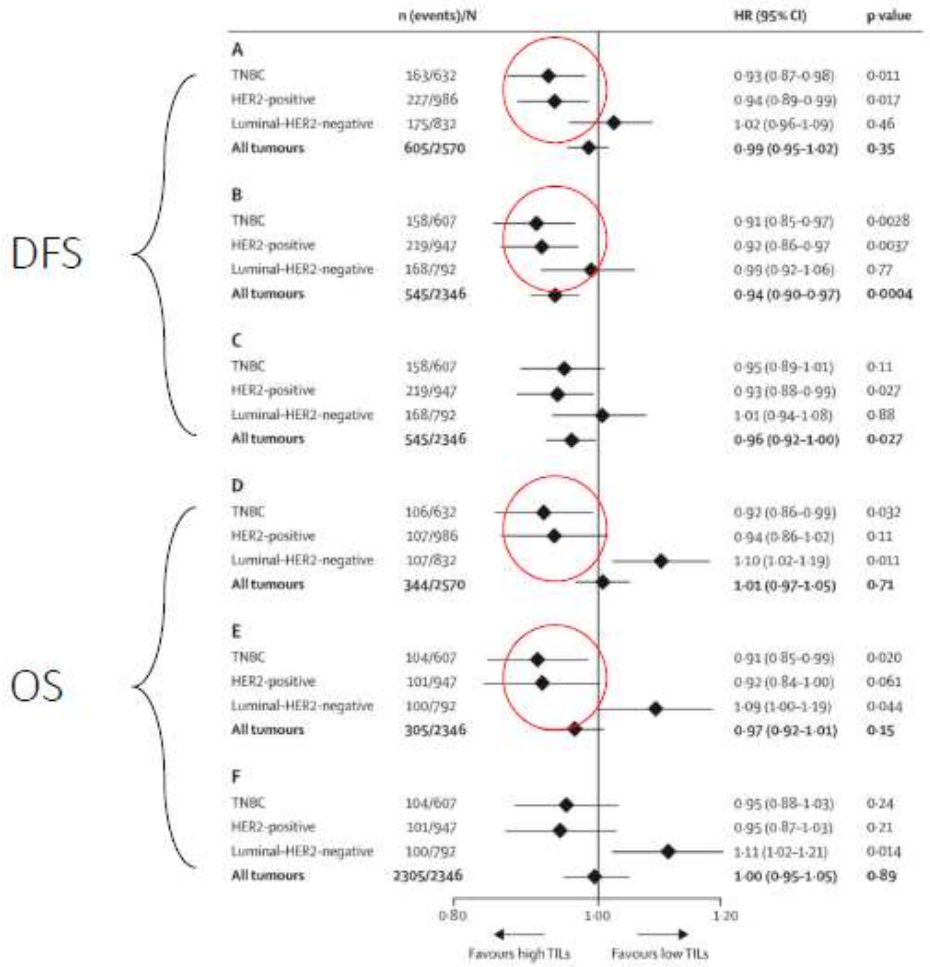
High TIL levels predict response to neoadjuvant treatment

N=3771 pts



Denkert C et al., Lancet Oncol 2018

TILs are *prognostic* in early stage TNBC and HER2+ BC (treated pts)



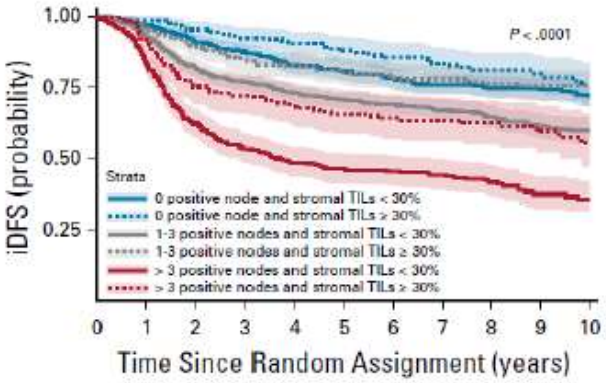
Denkert C et al., Lancet Oncol 2018

High TILs are associated with **excellent prognosis** in TNBC treated with adjuvant chemotherapy (anthracycline +/- taxane)

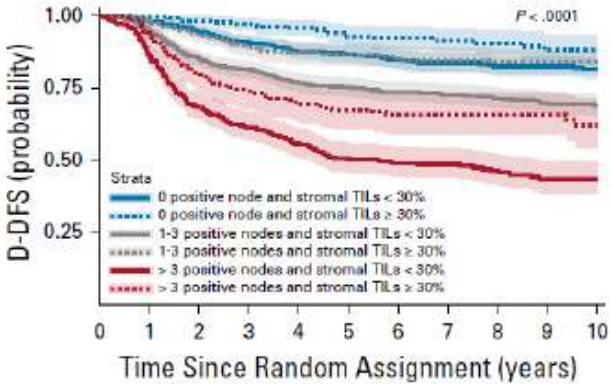
N=2148

In patients with *node-negative disease*: **TILs ≥ 30%** vs < 30%:

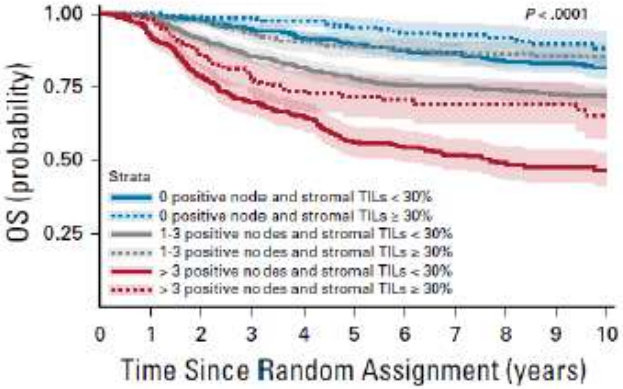
5y-iDFS: **88%** vs 81%



5y-D-DFS: **93%** vs 87%



5y-OS: **95%** vs 90%



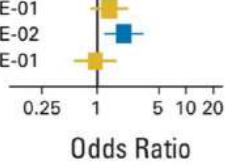
Loi S et al, J Clin Oncol 2019

High expression levels of immune signatures (T-cell) predict response to neoadjuvant chemotherapy (anthracycline +/- taxane)

TNBC

B

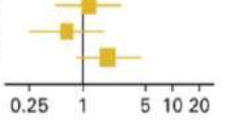
	OR	95% CI	P	FDR
GGI	1.88	1.16 to 3.09	1.2E-02	2.8E-02
Gene70	2.37	1.42 to 4.04	1.2E-03	8.3E-03
CIN70	1.81	1.15 to 2.87	1.1E-02	2.8E-02
Stroma1	0.71	0.45 to 1.11	1.3E-01	2.5E-01
Stroma2	0.72	0.46 to 1.1	1.3E-01	2.5E-01
Immune1	2.02	1.35 to 3.06	7.8E-04	8.3E-03
Immune2	1.71	1.15 to 2.54	7.7E-03	2.6E-02
RAS	0.76	0.51 to 1.09	1.6E-01	2.8E-01
MAPK	0.91	0.57 to 1.44	6.8E-01	8.3E-01
PTEN	2.05	1.33 to 3.21	1.5E-03	8.3E-03
AKTmTOR	1.06	0.72 to 1.58	7.7E-01	8.3E-01
PIK3CA	1.08	0.65 to 1.79	7.8E-01	8.3E-01
IGF1	0.90	0.57 to 1.43	6.6E-01	8.3E-01
SRC	0.87	0.57 to 1.33	5.2E-01	7.4E-01
MYC	1.29	0.88 to 1.9	1.9E-01	3.0E-01
E2F3	1.76	1.18 to 2.63	5.7E-03	2.4E-02
BetaCatenin	0.96	0.62 to 1.48	8.5E-01	8.5E-01



HER2+

C

	OR	95% CI	P	FDR
GGI	1.08	0.48 to 2.45	8.5E-01	8.5E-01
Gene70	1.37	0.55 to 3.45	5.0E-01	7.1E-01
CIN70	1.11	0.49 to 2.51	8.1E-01	8.5E-01
Stroma1	0.54	0.27 to 1.06	8.1E-02	3.4E-01
Stroma2	0.56	0.27 to 1.13	1.1E-01	3.4E-01
Immune1	4.94	2.19 to 12.41	2.9E-04	4.9E-03
Immune2	3.67	1.72 to 8.45	1.3E-03	1.1E-02
RAS	0.89	0.38 to 2.05	7.9E-01	8.5E-01
MAPK	1.37	0.68 to 2.82	3.7E-01	6.0E-01
PTEN	1.28	0.56 to 2.92	5.5E-01	7.2E-01
AKTmTOR	0.66	0.32 to 1.34	2.6E-01	5.4E-01
PIK3CA	1.51	0.71 to 3.32	2.9E-01	5.4E-01
IGF1	1.46	0.73 to 2.97	2.9E-01	5.4E-01
SRC	1.70	0.91 to 3.26	1.0E-01	3.4E-01
MYC	1.14	0.56 to 2.26	7.2E-01	8.5E-01
E2F3	0.71	0.32 to 1.54	3.9E-01	6.0E-01
BetaCatenin	1.71	0.88 to 3.42	1.2E-01	3.4E-01

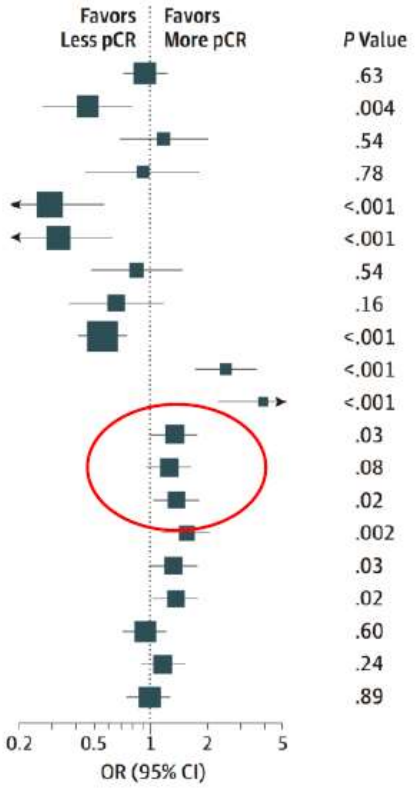


Ignatiadis M et al. J Clin Oncol, 2012

High expression levels of immune signatures (T-cell) predict response to neoadjuvant anti-HER2 therapy (NeoALTTO study)

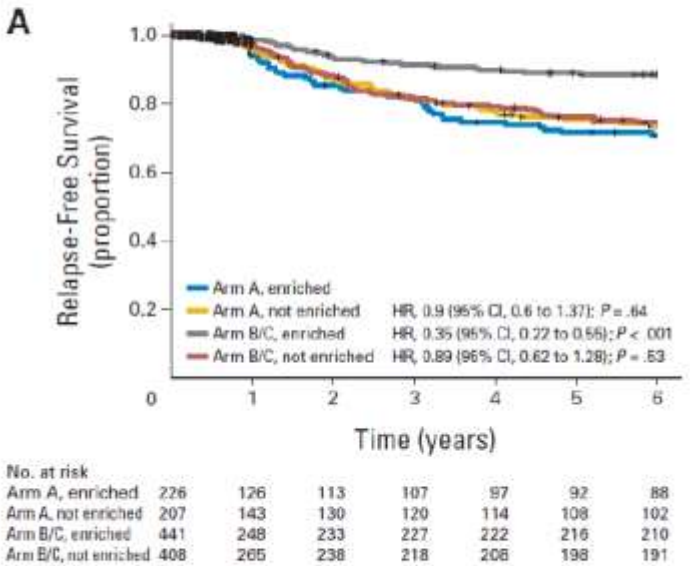
A Univariate model

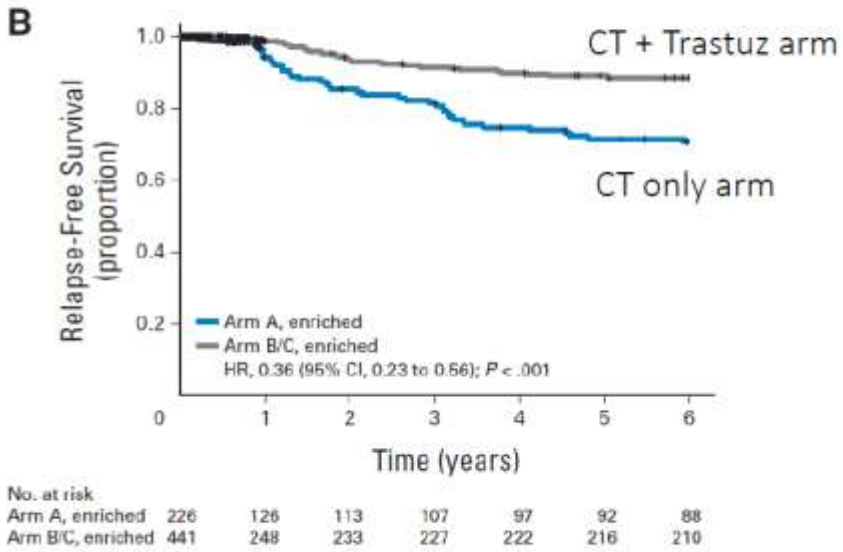
Parameter	OR (95% CI)	FDR
Age (continuous)	0.94 (0.72-1.2)	0.42
Estrogen receptor positive (yes vs no)	0.46 (0.27-0.78)	0.0065
Tumor size (≥T3 vs T2)	1.2 (0.70-2.0)	0.41
Lapatinib vs trastuzumab	0.91 (0.45-1.8)	0.49
Lapatinib vs combination	0.29 (0.15-0.55)	3.3×10^{-4}
Trastuzumab vs combination	0.32 (0.17-0.62)	0.0012
Grade (1-2 vs 3)	0.84 (0.49-1.5)	0.41
Nodal status (N0 vs N1-N3)	0.66 (0.37-1.2)	0.14
ESR1	0.56 (0.42-0.74)	1.2×10^{-4}
ERBB2/HER2	2.5 (1.7-3.6)	1.2×10^{-7}
HER2 enriched (PAM50)	4.0 (2.3-6.9)	1.8×10^{-6}
Immune1	1.3 (1.0-1.7)	0.034
Immune2	1.3 (0.97-1.6)	0.084
Immune3	1.4 (1.1-1.8)	0.024
Genomic Grade Index	1.6 (1.2-2.1)	0.0032
Aurka	1.3 (1.0-1.7)	0.036
AKT/mTOR	1.4 (1.0-1.8)	0.032
Stroma1	0.93 (0.72-1.2)	0.42
Stroma2	1.2 (0.90-1.5)	0.21
AR	0.98 (0.76-1.3)	0.53



Fumagalli D et al. JAMA Oncol 2016

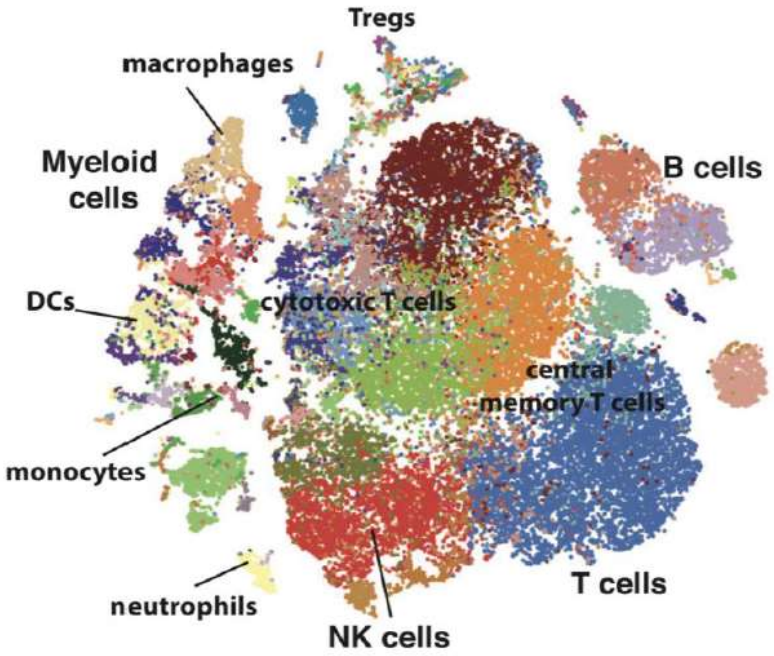
14-gene immune signature: EBC patients with immune gene enrichment had significant benefit from the addition of adjuvant *Trastuzumab* (N9831 trial)





Perez E et al., J Clin Oncol 2015

Single-cell map of diverse immune phenotypes in the breast tumor microenvironment



Can we use our knowledge of the immune tumor microenvironment to ***(de)-escalate*** *the treatment* of early breast cancer?

Do we have reliable ***biomarkers*** to do this?

Azizi E et al., Cell 2018

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*

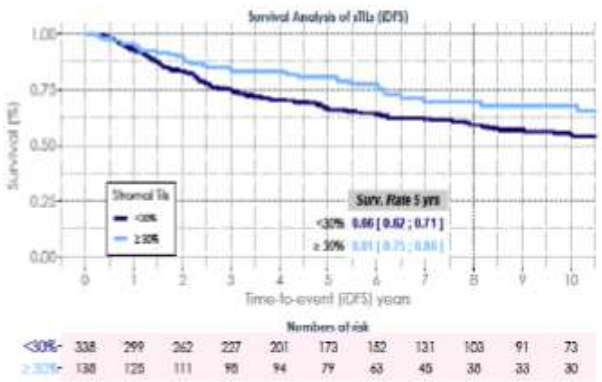
Ji Hyun Park, Sarah Flora Jonas, Guillaume Bataillon, Carmen Criscitiello, Roberto Salgado, Sherene Loi, Giuseppe Viale, Hee Jin Lee, Maria Vittoria Dieci, Sung-Bae Kim, Giuseppe Curigliano, Anne Vincent-Salomon, Fabrice Andre, Stefan Michiels.

What about the prognostic value of TILs in ***untreated*** TNBC?

TNBC patient series (N=518) ***not treated*** with chemotherapy → sTILs cut-off: ≥30% vs <30%:

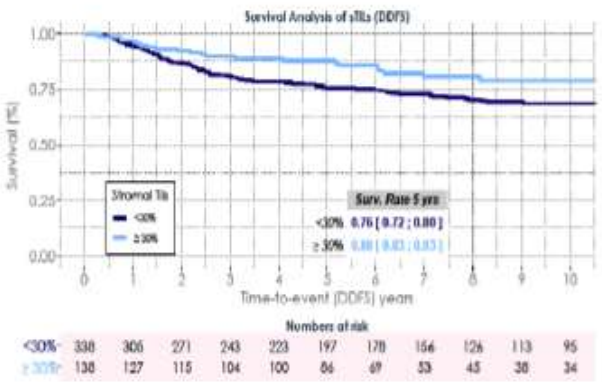
5y-iDFS: **88%** vs 81%

5y-iDFS: **81%** vs 66%



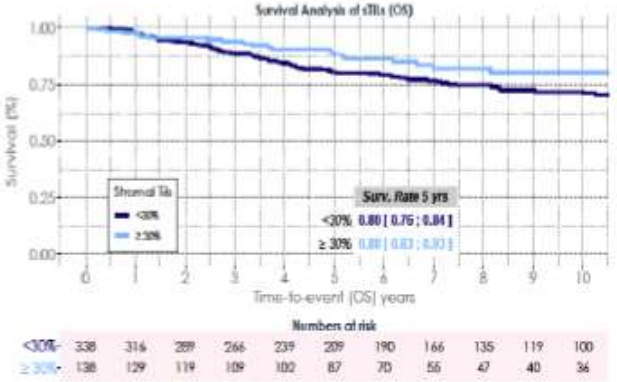
5y-D-DFS: **93%** vs 87%

5y-D-DFS: **88%** vs 76%



5y-OS: **95%** vs 90%

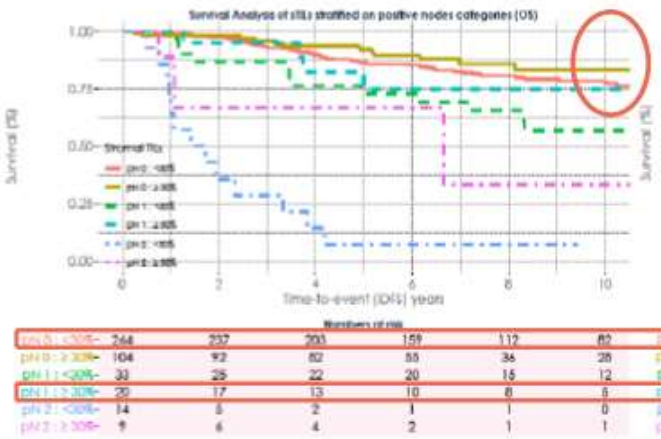
5y-OS: **88%** vs 80%



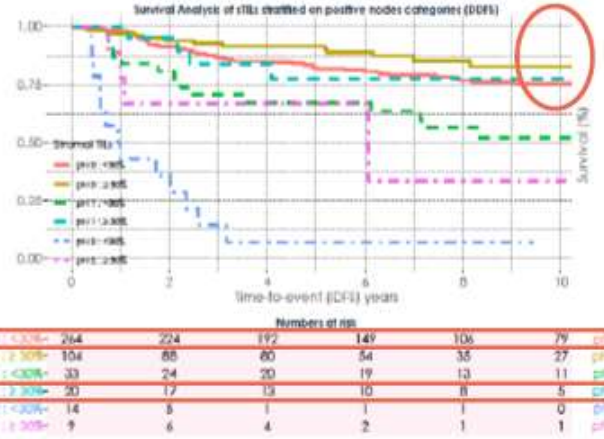
Worse prognosis as compared to the pooled analysis of treated TNBC N0 patients (in grey) – as expected

Independently Significant Beyond Nodal Status

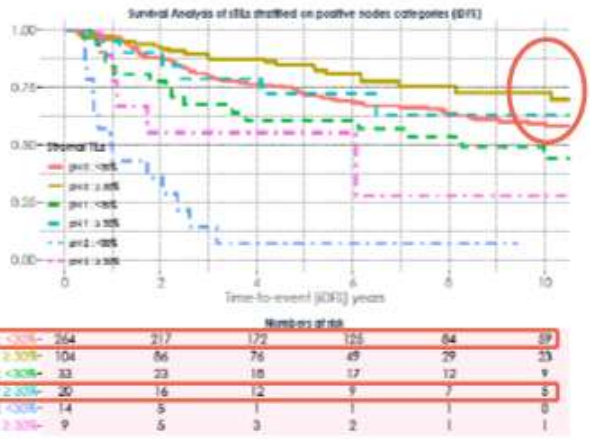
iDFS



D-DFS

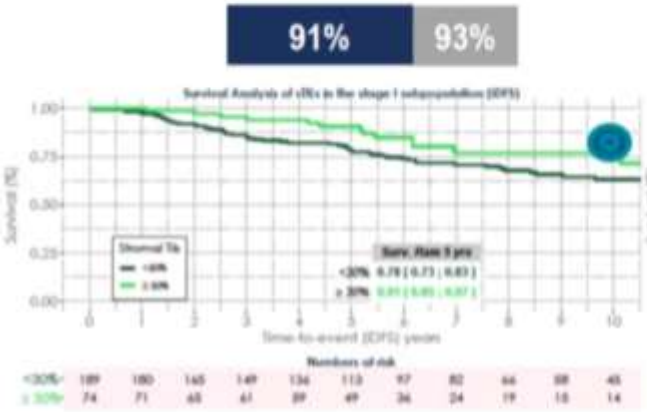


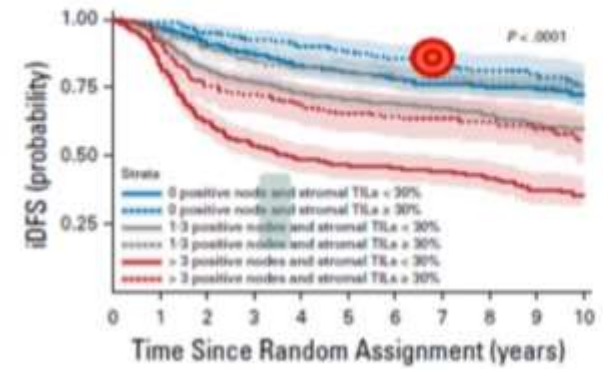
OS

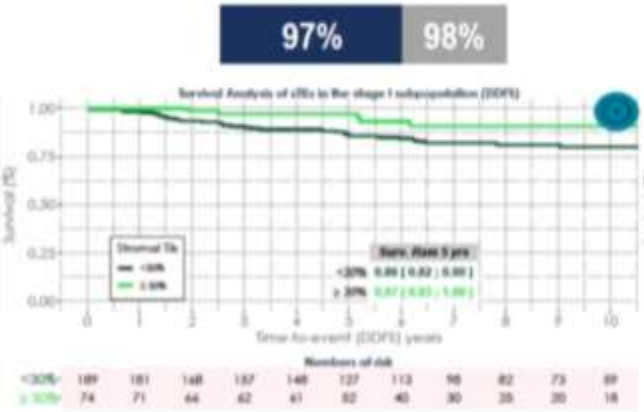


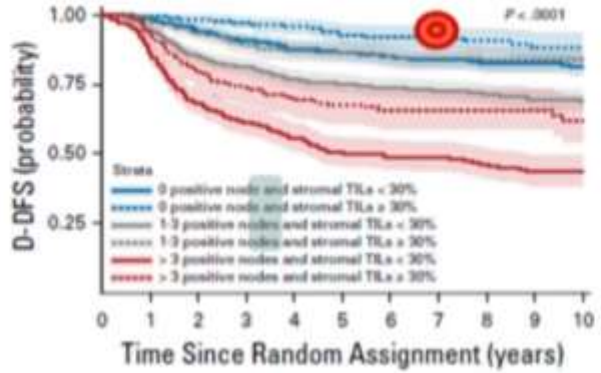
Similar survival outcomes of pN0<30% and pN1≥30%

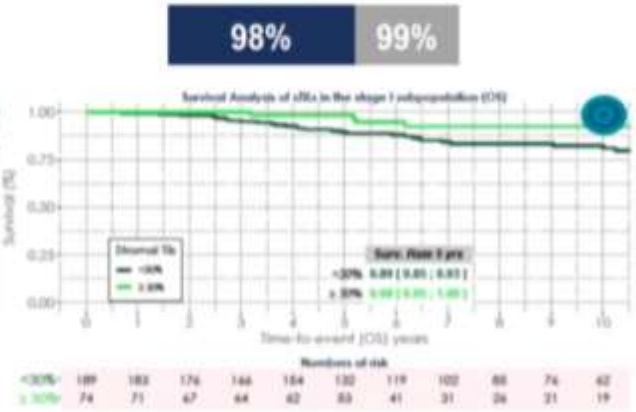
Further Excellent Outcomes In pStage I tumors,

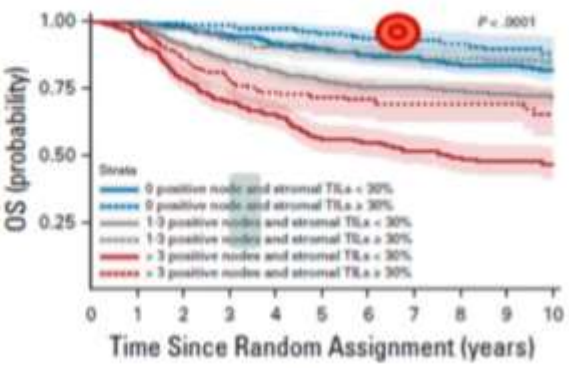












So, we can possibly omit adjuvant chemo in this group?

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  - PNP with post-neoadj T-DM1 treatment

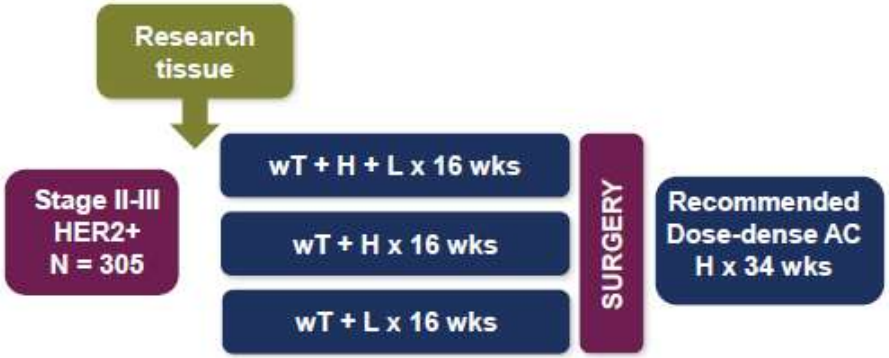
Predictive and prognostic value of B-cell gene-expression signatures and B-cell receptor (BCR) repertoire in HER2+ breast cancer: a correlative analysis of the CALGB 40601 clinical trial (Alliance).

Aranzazu Fernandez-Martinez, Maki Tanioka, Cheng Fan, Joel S. Parker, Katherine A. Hoadley, Ian Krop, Ann Partridge, Lisa Carey, and Charles Perou.

Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill

esmo.org

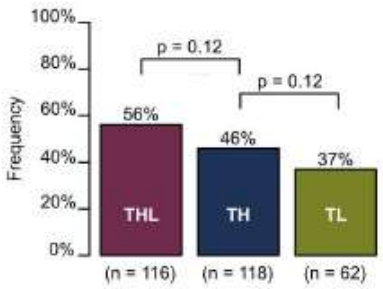
CALGB 40601: a phase III neoadjuvant study investigating the benefit of weekly paclitaxel and trastuzumab with or without lapatinib for HER2+ BC



*wT = weekly paclitaxel, H = trastuzumab, L = lapatinib

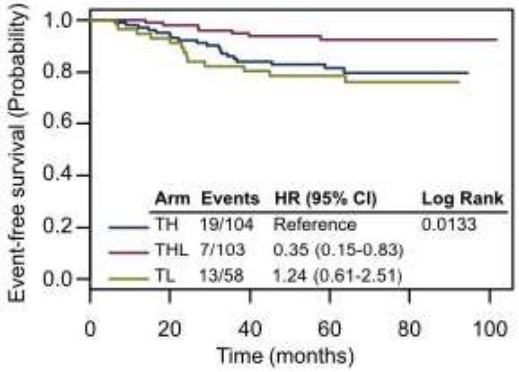
Primary endpoint: pCR breast
Secondary endpoint:
Clinical: EFS, OS
Correlative

pCR rate by treatment arm



Carey et al. JCO, 2015
PMID: 26527775

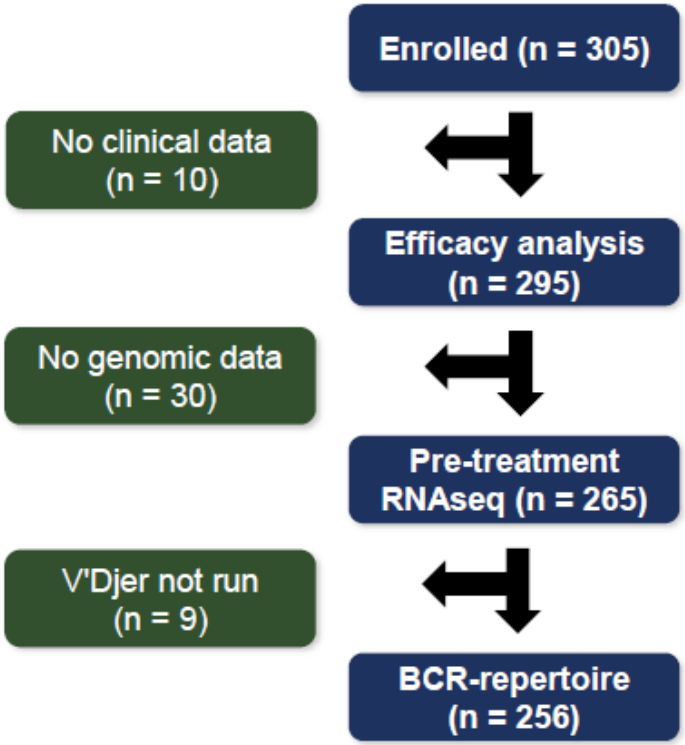
EFS at 5 years by treatment arm



Krop et al. SABCS, 2017

Goal: evaluate the prognostic and predictive value of B-cell gene-expression signatures and BCR diversity metrics in HER2+ BC

RNAseq subpopulation and Genomic biomarkers



Clinicopathologic factors
(HR, Stage, Treatment, pCR)

Single Genes by RNAseq
(ERBB2 and ESR1)

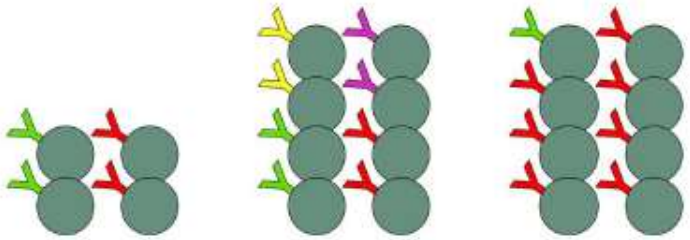
601 Gene-expression signatures
(immune signatures included)

10 Subtype-related signatures (PAM50)
(correlation to PAM50 centroids, ROR, proliferation)

BCR repertoire analysis (V'Djer)
(total counts, isotype, diversity metrics)

BCR repertoire diversity metrics

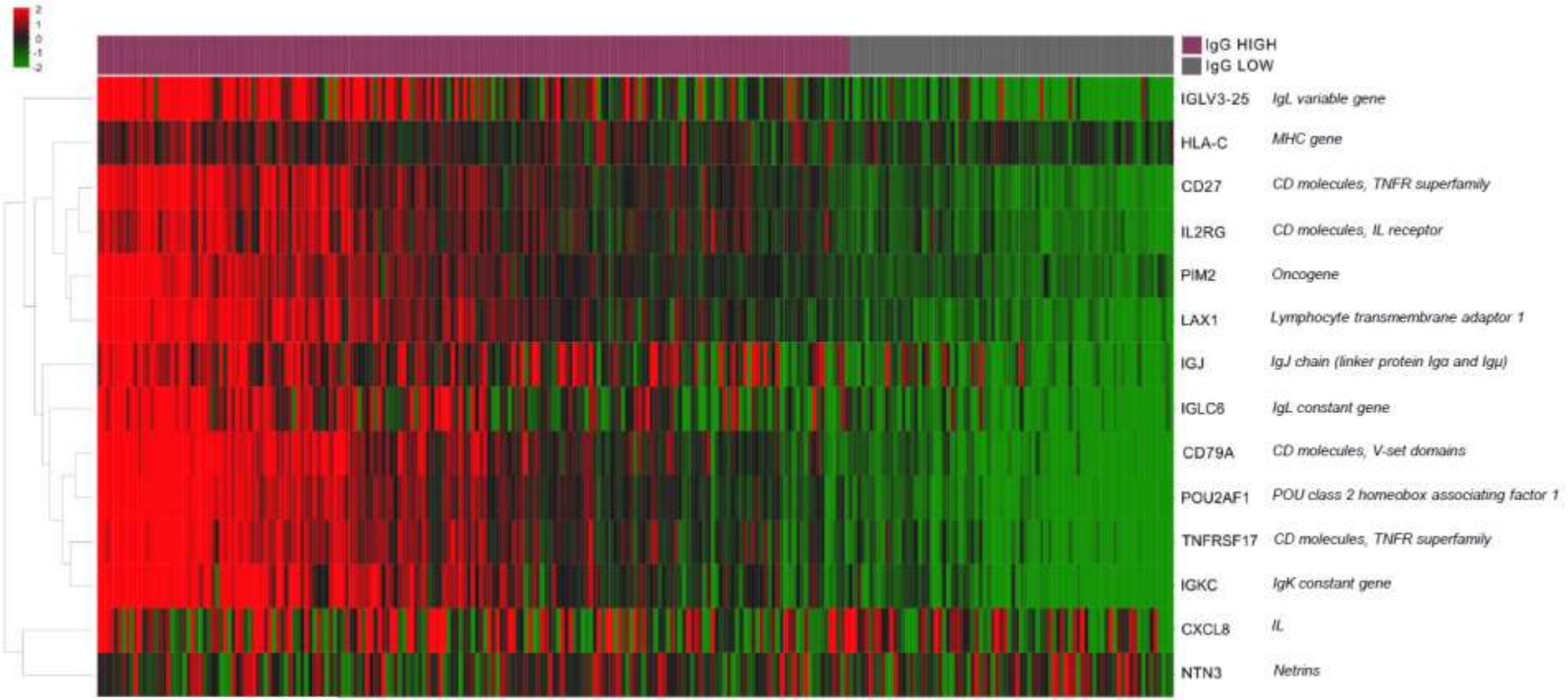
- **Total counts**: sum of the expression of all BCR reads normalized by total RNA-seq read counts
- **Richness:** number of different clones represented in the sample
- **Shannon entropy**: diversity metric that provides information about the species richness, taking also into account the relative abundance of the different clones.
- **Species evenness**: Shannon entropy normalized by species richness:
  - Clones with similar abundance = high evenness
  - Small number of clones expressed at higher levels than other clones = low evenness.



Diversity metric	Tumor 1	Tumor 2	Tumor 3
Total counts	4	8	8
Richness	2	4	2
Shannon entropy	0.69	1.38	0.38
Evenness	1	1	0.54

Selitsky et al. Genom Med, 2019

IgG signature distribution in CALGB 40601



Fan C, et al. BMC Med Genomics. 2011 PMID: 21214954

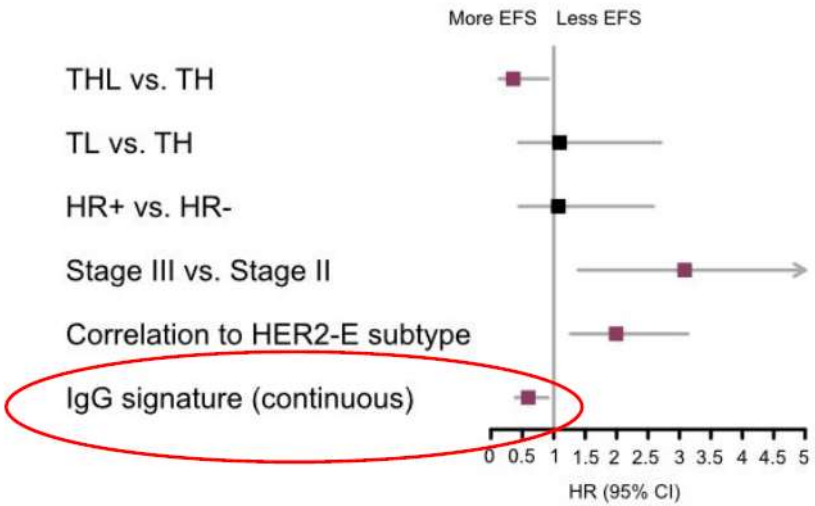
IgG signature was independently associated with *pCR*

	Univariable Model			Multivariable					
				Model One*			Model Two†		
Variable	OR	95% CI	*P*	OR	95% CI	*P*‡	OR	95% CI	*P*‡
Gene expression signature									
p53 mutation	2.40	1.69 to 3.50	< .001	2.06	1.17 to 3.70	.0119	2.33	1.18 to 4.71	.014
IgG	1.65	1.30 to 2.12	< .001	1.54	1.16 to 2.05	.0024	1.43	1.08 to 1.92	.0112
HER2 amplicon	1.54	1.23 to 1.93	< .001	1.35	1.04 to 1.77	.0252		NS	
HER2-E correlation	1.98	1.50 to 2.68	< .001		NS			NS	
ER signaling	0.47	0.33 to 0.66	< .001		NS			NS	
B cell	1.49	1.18 to 1.90	< .001		NS			NS	
PI3K signaling	1.72	1.25 to 2.41	< .001		NS			NS	
T cell	1.39	1.09 to 1.79	.0073		NS			NS	
HER1	1.50	1.10 to 2.07	.0103		NS			NS	
CD8	1.37	1.07 to 1.76	.0115		NS			NS	
Proliferation	1.43	1.07 to 1.93	.0153		NS			NS	
Immune cell	1.34	1.05 to 1.70	.0161		NS			NS	

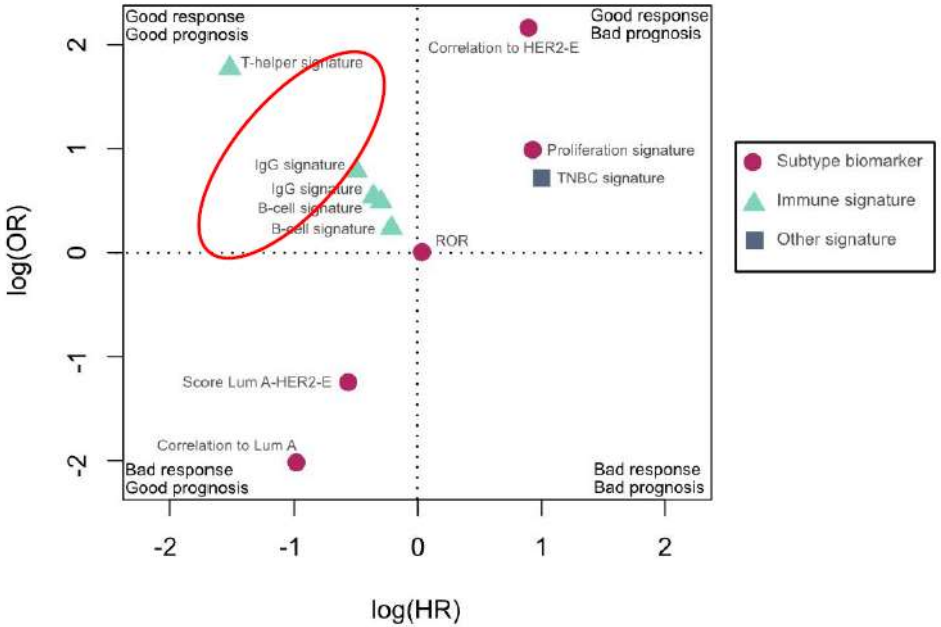
Carey LA et al., J Clin Oncol 2016

5 immune-related genomic biomarkers were *predictive* of higher pCR and better EFS (N=256 pts)

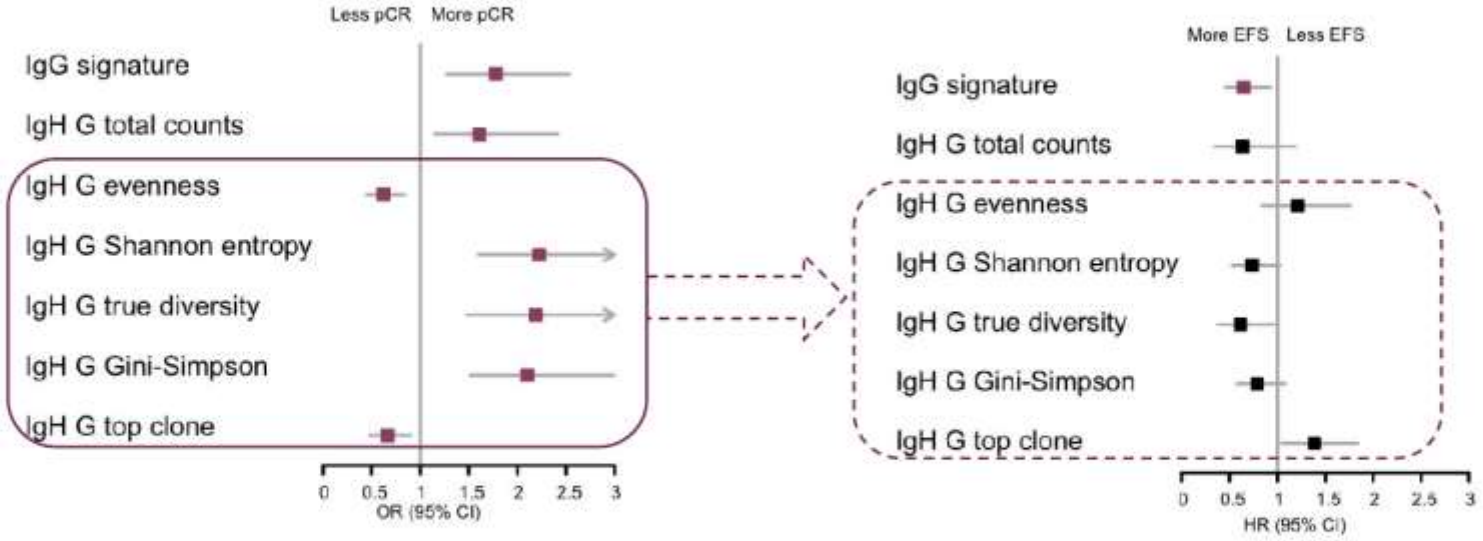
Patients with residual disease



>600 gene signatures



IgG signature and IgH G *diversity metrics*



↑ IgH G total counts → ↑ pCR

More "diverse" & *unevenly* distributed IgG → ↑ pCR

MY OUTLINE

- Adding IO to NACT in TNBC
  - Keynote-522
- Prognostic/predictive biomarkers
  - TILs in untreated EBC
  - Predictive and prognostic value of B-cell signatures and BCR
  - TailorX High Risk Arm
- Post-NACT
  - PNP with post-neoadj T-DM1 treatment

Trial Assigning IndividuaLized Options for TReatment (TAILORx):

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

Canadian Cancer Trials Group

ECOG-ACRIN cancer research group

Reshaping the future of patient care

SWOG CANCER RESEARCH NETWORK

Alliance for Clinical Trials in Oncology

Federally Funded Research

NATIONAL CANCER INSTITUTE

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Advancing Research. Improving Lives.

TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)

↓

Register (N=10,273)

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

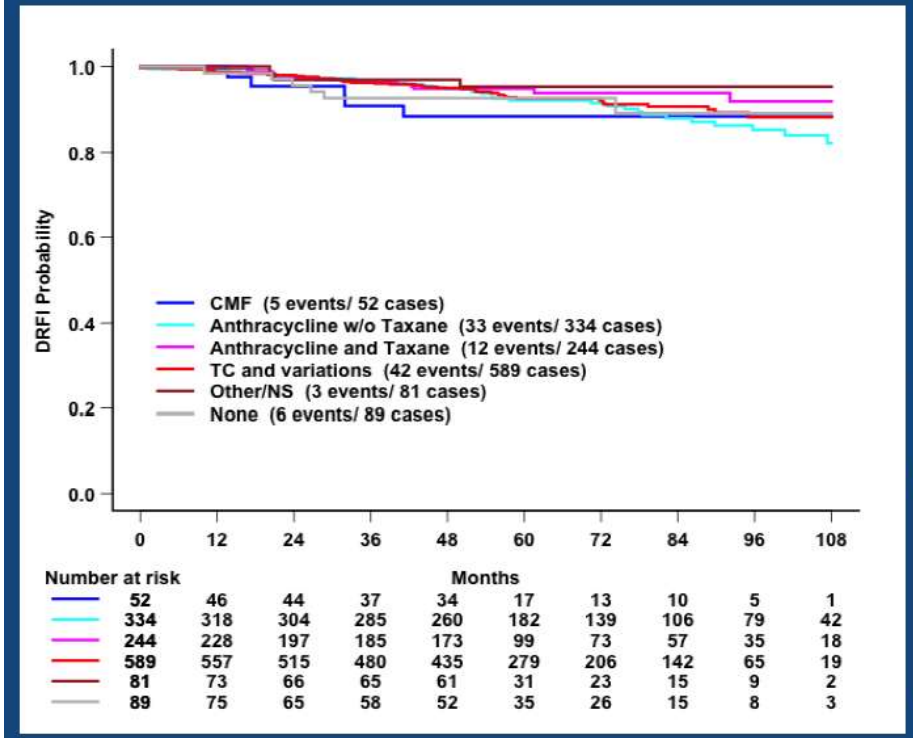
Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

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



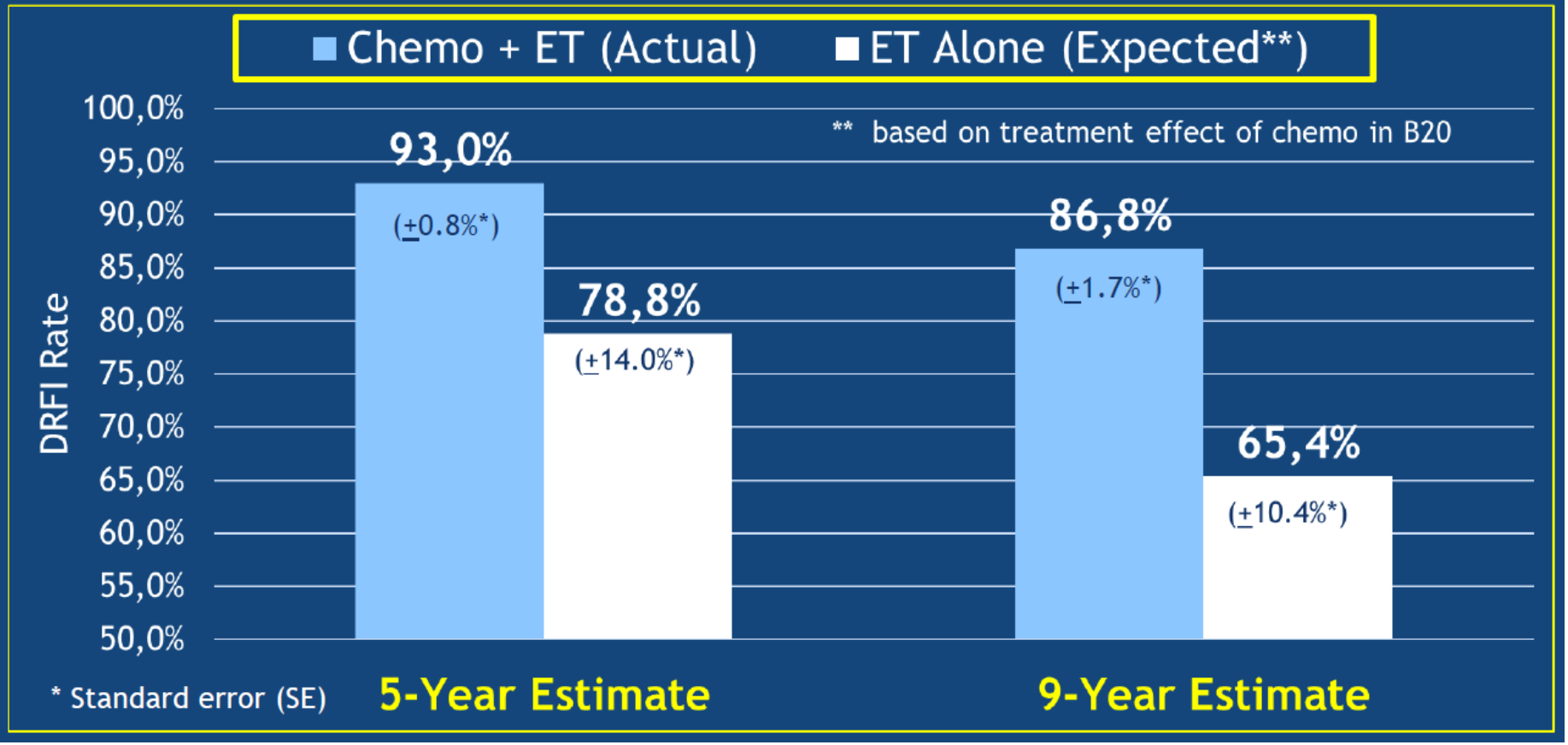
Regimen	5-Year Rate	SE*
TC	92.7%	± 1.2%
A without T	92.3%	± 1.6%
A and T	95.1%	± 1.5%
CMF	88.5%	± 4.8%
Other	95.5%	± 2.5%

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 with Chemotherapy plus Endocrine Therapy vs. Expected Outcomes with Endocrine Therapy Alone



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BARCELONA 2019 ESMO congress

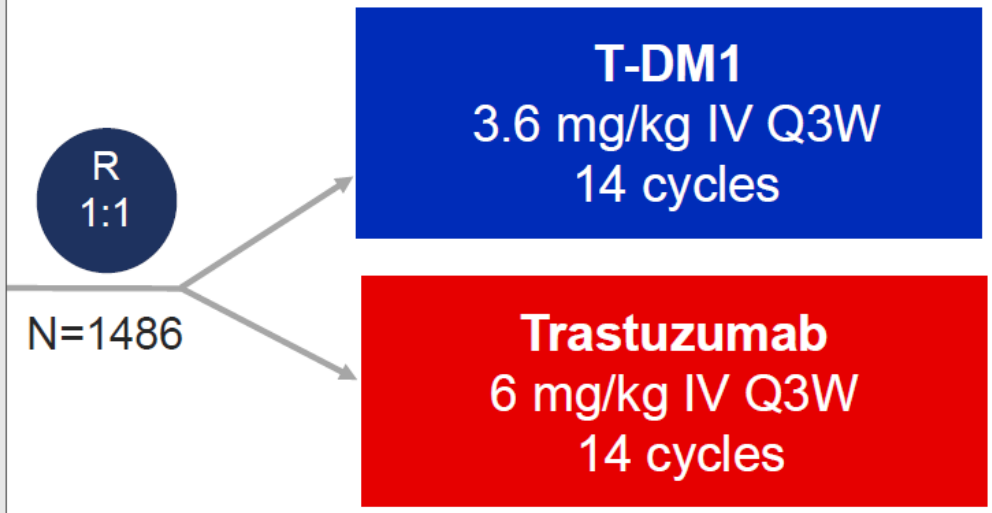
PERIPHERAL NEUROPATHY, THROMBOCYTOPAENIA, AND CENTRAL NERVOUS SYSTEM RECURRENCE: AN UPDATE OF THE PHASE III KATHERINE TRIAL OF POST-NEOADJUVANT TRASTUZUMAB EMTANSINE (T-DM1) OR TRASTUZUMAB IN PATIENTS WITH RESIDUAL INVASIVE HER2-POSITIVE BREAST CANCER

Michael Untch[1], Charles E. Geyer, Jr.[2], Chiun-Sheng Huang[3], Sibylle Loibl[4], Norman Wolmark[5], Max S. Mano[6], Gunter von Minckwitz[7], Adam Brufsky[8], Xavier Pivot[9], Jonathan Polikoff[10], Andrea Fontana[11], Bella Kaufman[12], Juan Carlos Alcedo[13], Thomas Boulet[14], Haiying Liu[15], Chunyan Song[15], Eleftherios P. Mamounas[16]

[1]AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany; [2]NSABP Foundation and Virginia Commonwealth University Massey Cancer Center, Richmond, VA, USA; [3]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [4]GBG, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany; [5]NSABP Foundation and The University of Pittsburgh, Pittsburgh, PA, USA; [6]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [7]GBG, Neu-Isenburg, Germany; [8]UPMC, Pittsburgh, PA, USA; [9]Centre Paul Strauss, l'Institut Régional du Cancer, Strasbourg, France; [10]Southern California Kaiser Permanente Medical Group, San Diego, CA, USA; [11]Azienda Ospedaliero Universitaria Pisana, Ospedale Santa Chiara, Pisa, Italy; [12]Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [13]Centro Hemato Oncologico, Panama City, Panama; [14]F. Hoffmann-La Roche, Basel, Switzerland; [15]Genentech, Inc., South San Francisco, CA, USA; [16]NSABP Foundation and Orlando Health University of Florida Health Cancer Center, Orlando, FL, USA

KATHERINE STUDY DESIGN

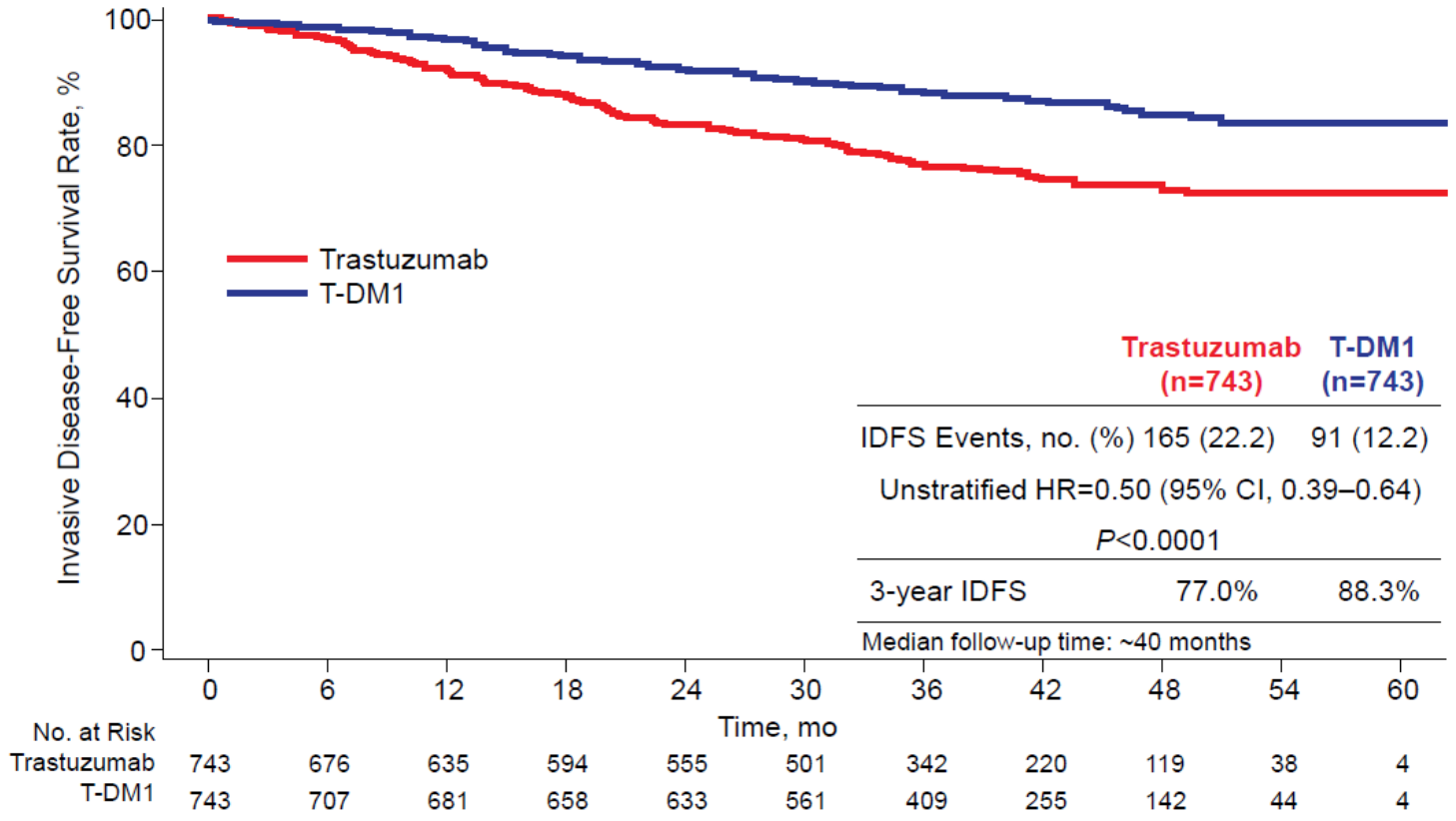
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive BC
- Neoadjuvant therapy
  - ≥6 cycles of chemotherapy
  - ≥9 weeks of taxane and trastuzumab
- Residual invasive tumour in breast or axillary nodes
- Randomization within 12 weeks of surgery
- Patients with grade 1 peripheral neuropathy were eligible



Radiation and endocrine therapy per protocol and local guidelines

Stratification factors: Clinical presentation (inoperable vs operable); hormone receptor status (ER+ or PR+ vs ER− and PR− or unknown); preoperative therapy (trastuzumab vs trastuzumab plus other HER2-targeted therapy); pathological nodal status after neoadjuvant therapy (+ vs − or not done)

PRIMARY ENDPOINT: INVASIVE DISEASE-FREE SURVIVAL



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

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

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

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

Summary

Adding IO to NACT in TNBC		
Keynote-522 (Schmid et al.)	Clear clinical relevance Promising but very early EFS	Do all early stage TNBC need AC-TC-pembro? Role of assay, role of chemotherapy, pCR rates in higher CPS scores?
Prognostic/predictive biomarkers		
TILs in untreated EBC (Park et al.)	Clear prognostic relevance (potential chemo-sparing tool)	For a limited number of pts
Predictive and prognostic value of B-cell signatures and BCR (Fernandez-Martinez et al.)	Further evidence for B-cells and BCR on prognosis and treatment of breast cancer	The other TILs? Treatment studied is not standard
TailorX High Risk Arm (Sparano et al.)	Outcome in pts with chemo better than expecte with ET. Results support chemo benefit in high risk pts	Not too much new
Post-NACT		
PNP with post-neoadj T-DM1 treatment (Untch et al.)	Incidence of peripheral neuropaty was higher with T-DM1, regardless of BL neuropathy. Platinum pre-treatment did, but type of taxane did not influence PNP	Of minor relevance, considering the survival benefit

laura.pizzuti@ifo.gov.it