Immunotherapy in breast cancer

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Outline

- Rational for immune-based therapy in breast cancer
- Immunogenic chemotherapy
- Targeting immune checkpoints
- Predicting immune-response in breast cancer

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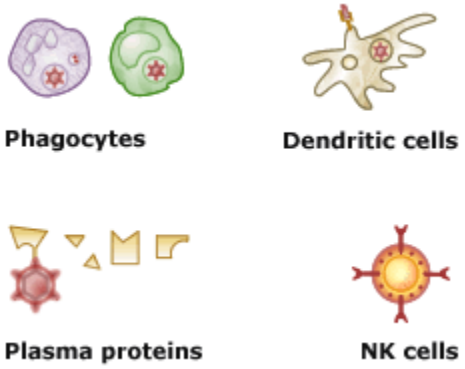
- ***Rational for immune-based therapy in breast cancer***
- Immunogenic chemotherapy
- Targeting immune checkpoints
- Predicting immune-response in breast cancer

Immune system

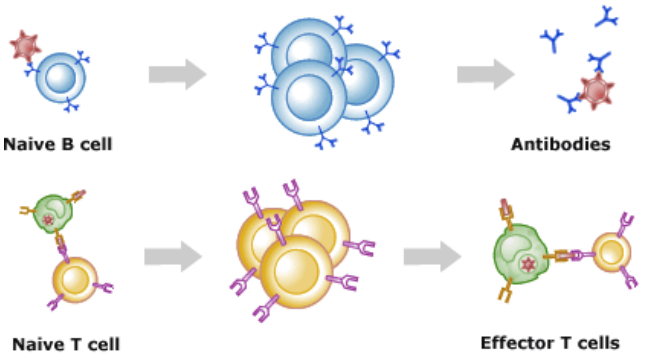
Innate immune system

Cells and mechanisms that defend the host from infection by other organisms in a non-Ag specific manner

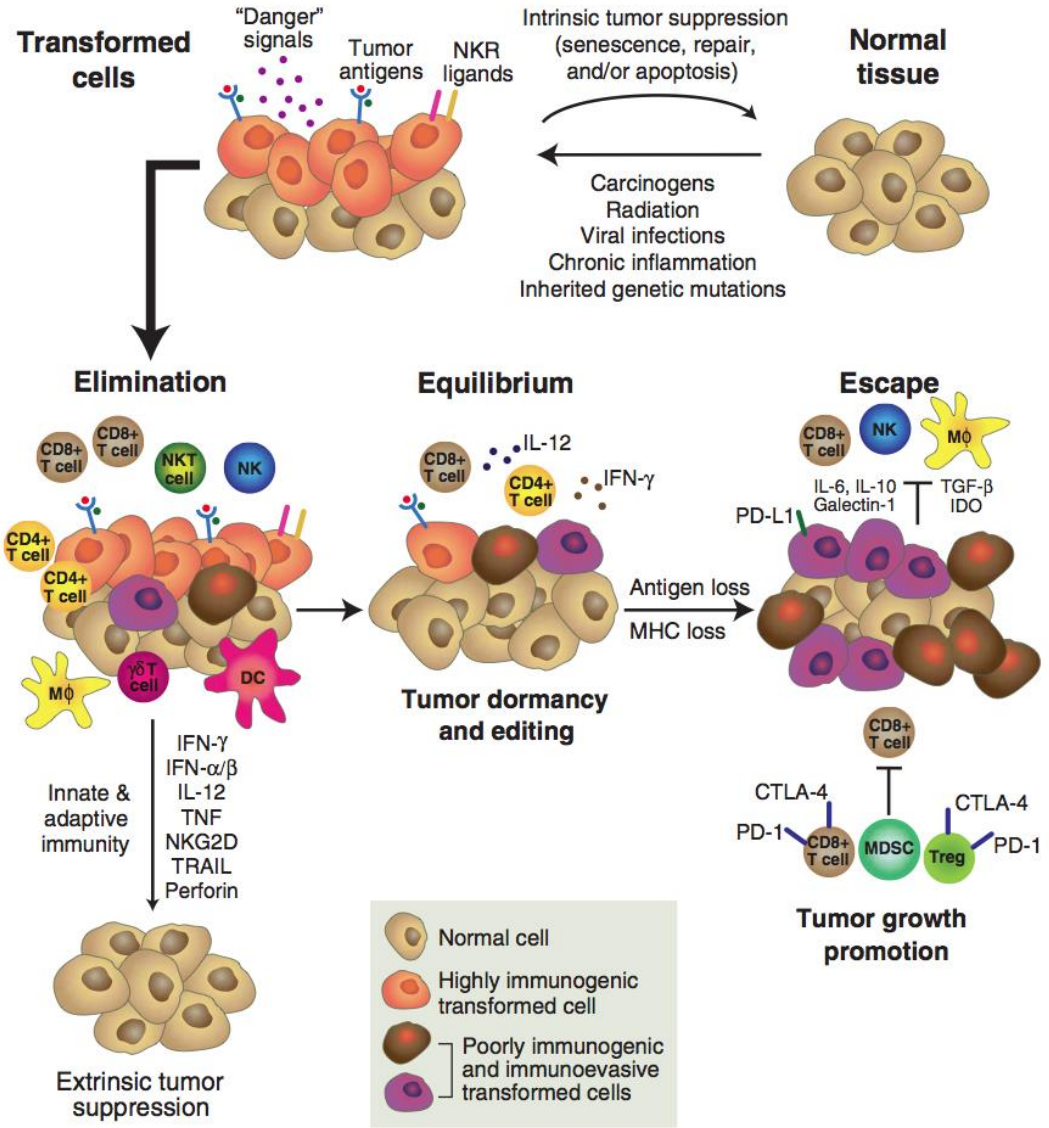


Adaptive immune system

Specialized immune cells that respond in an Ag specific manner to recognize and eliminate pathogens and aberrant cells



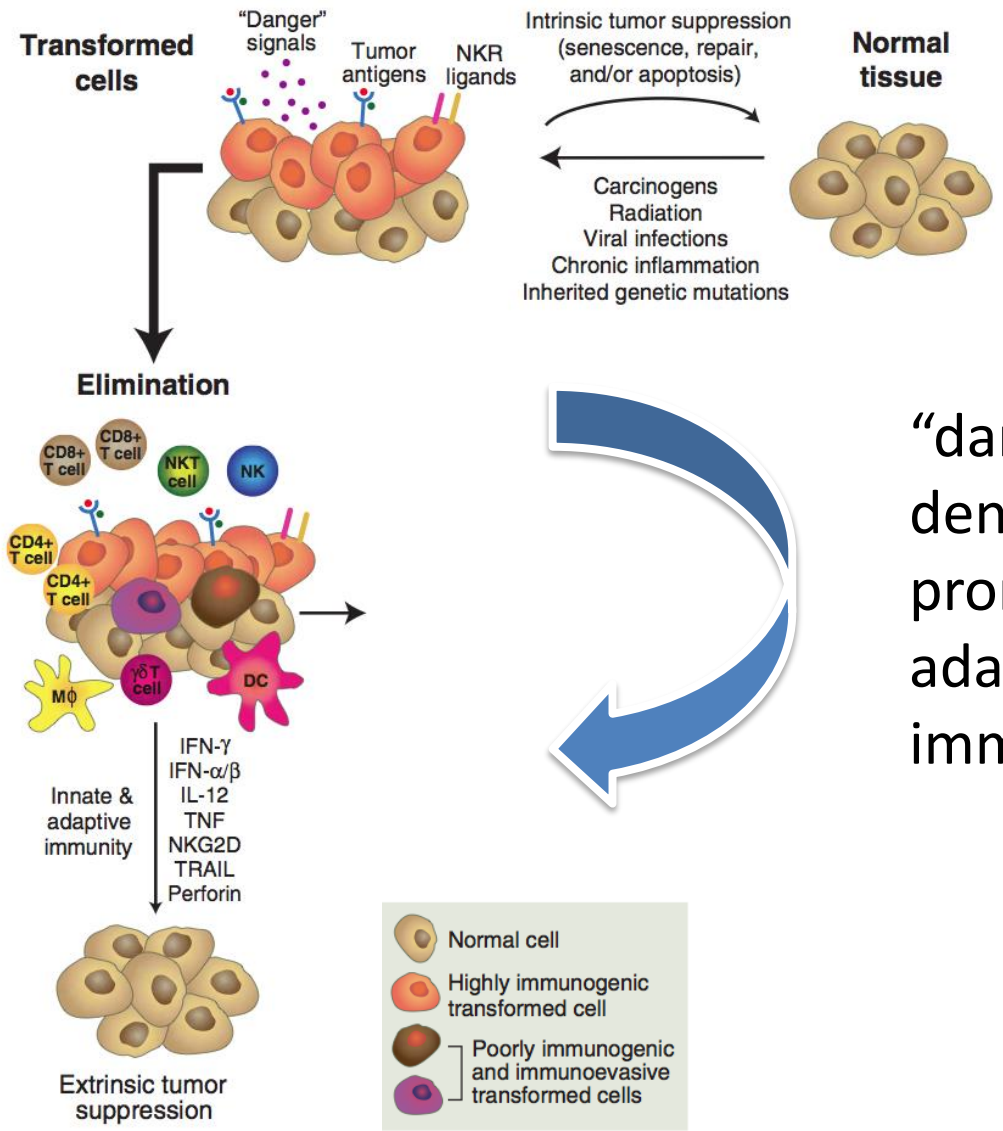
Cancer Immunoediting



The notion that the immune system not only protects the host against tumor formation but also **shapes tumor immunogenicity** is the basis of the cancer immunoediting hypothesis, which stresses the dual host-protective and tumor-promoting actions of immunity on developing tumors and proceeds sequentially through **three distinct phases** termed "elimination," "equilibrium," and "escape"

R Schreiber and al. Science, vol 331, 2011

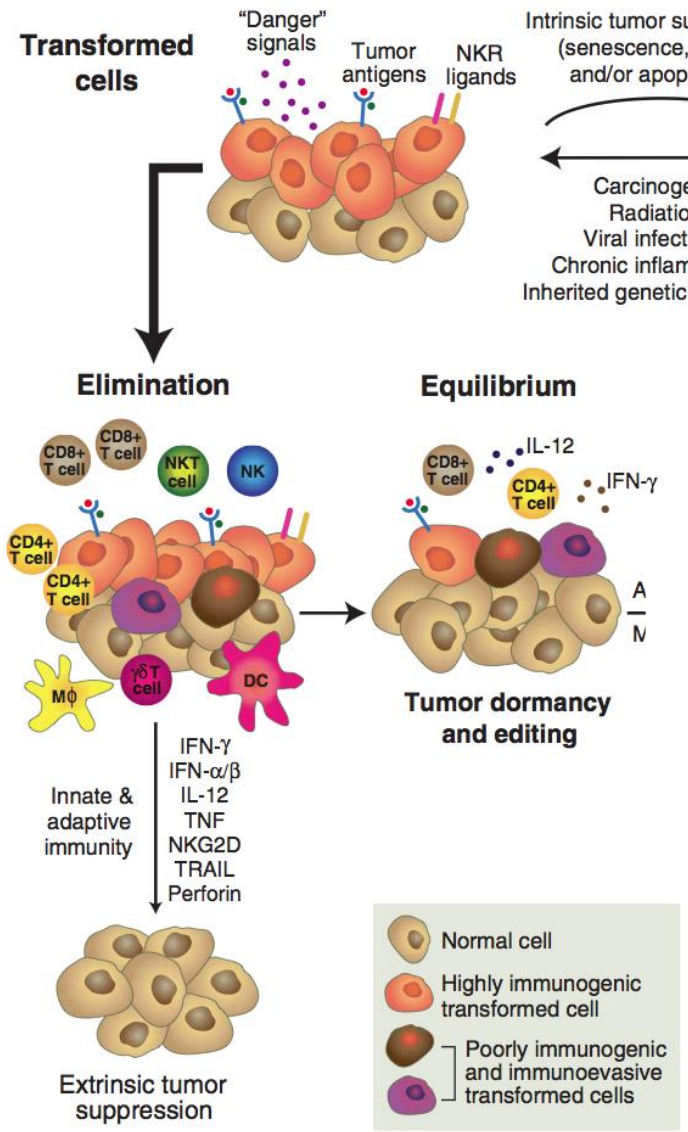
The “Elimination” Phase



“danger signals” activate dendritic cells and promote induction of adaptive anti-tumor immune response

R Schreiber and al. Science, vol 331, 2011

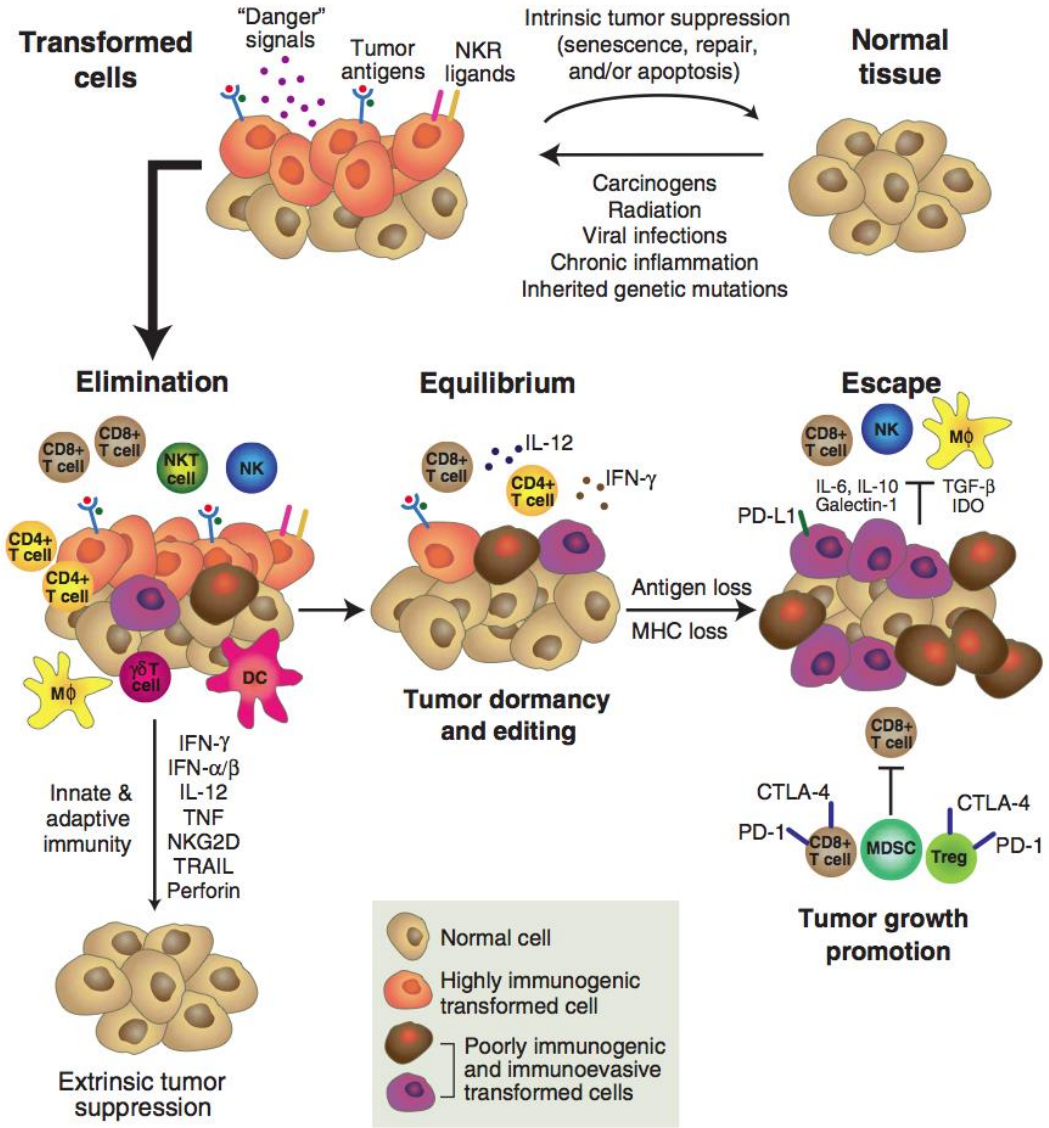
The “Equilibrium” Phase



the adaptive immune system maintains residual tumor cells in a functional state of dormancy, before eventually resuming growth as either recurrent primary tumors or distant metastases

R Schreiber and al. Science, vol 331, 2011

The “Escape” Phase



The escape phase can occur because:

1) **tumor cell population changes** in response to the immune system’s editing functions

2) **the host immune system changes** in response to increased cancer-induced immunosuppression or immune system deterioration.

R Schreiber and al. Science, vol 331, 2011

Evidence for Immunity in Cancer

- Spontaneous tumor regressions (melanoma and lymphoma)
- Higher incidence of tumors in immunosuppressed, immunodeficient (AIDS) patients
- Regression of metastases after removal of primary tumor (renal cell ca)
- Lymphocyte infiltration of tumors and associations with prognosis

Evidence for immunity in BC

Lymphocyte Infiltrates as a I
Female Breast

S. Aaltomaa, P. Lipponen, M. Eskelinen, V
and K. Syrjä

European Journal of Cancer 19

Prognostic and Predictive Value of Tumor-Infiltrating Lymphocytes in a Phase III Randomized Adjuvant Breast Cancer Trial in Node-Positive Breast Cancer Comparing the Addition of Docetaxel to Doxorubicin With Doxorubicin-Based Chemotherapy: BIG 02-98

Sherene Loi, Nicolas Sirtaine, Fanny Piette, Roberto Salgado, Giuseppe Viale, Françoise Van Eenoo, Ghizlane Rouas, Prudence Francis, John P.A. Crown, Erika Hitre, Evandro de Azambuja, Emmanuel Quinaux, Angelo Di Leo, Stefan Michiels, Martine J. Piccart, and Christos Sotiriou

R Research

Open Access

s a good
: cancer
Ian O Ellis‡

Biological Processes Associated with Breast Cancer Clinical Outcome Depend on the Molecular Subtypes

Christine Desmedt,[1] Benjamin Haibe-Kains,[1,2] Pratyaksha Wirapati,[3,4] Marc Buyse,[5] Denis Larsimont,[1] Gianluca Bontempi,[2] Mauro Delorenzi,[3,4] Martine Piccart,[1] and Christos Sotiriou[1]

Clinical Cancer Research 2008

Immunosuppressed patients with breast cancer have worse outcomes than their immunocompetent counterparts

Immune signatures and prognosis

Author Year	# of patients	Signatures	ER-	HER2+	ER+ Lum B	ER+ Lum A
Teschendorff et al. 2007	1056	7-gene immune module	+			
Alexe et al. 2007	286	651 lymphocyte-associated genes		+		
Schmidt et al. 2008	788	B-cell metagene	+	+	+	
Desmedt et al. 2008	1605	Stat1 metagene	+	+		
Rody et al. 2009	1781	lymphocyte-specific kinase (LCK)	+	+		
Bianchini et al. 2010	684	B-cell/plasma cell metagene	+	+	+	

Immune signatures and prediction

VOLUME 30 · NUMBER 16 · JUNE 1 2012

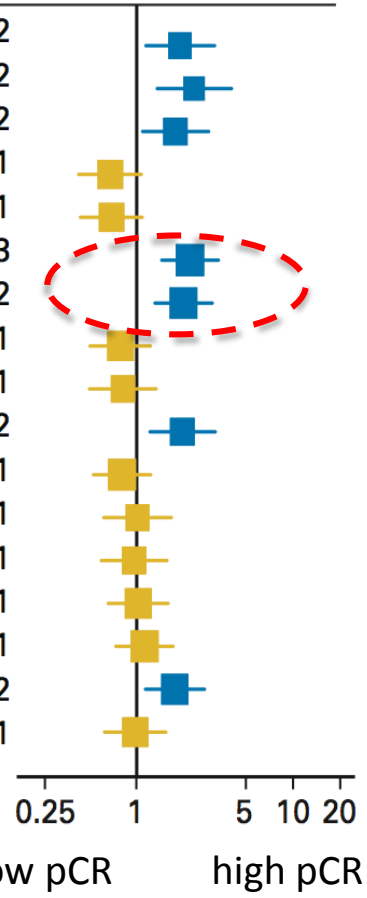
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Gene Modules and Response to Neoadjuvant Chemotherapy in Breast Cancer Subtypes: A Pooled Analysis

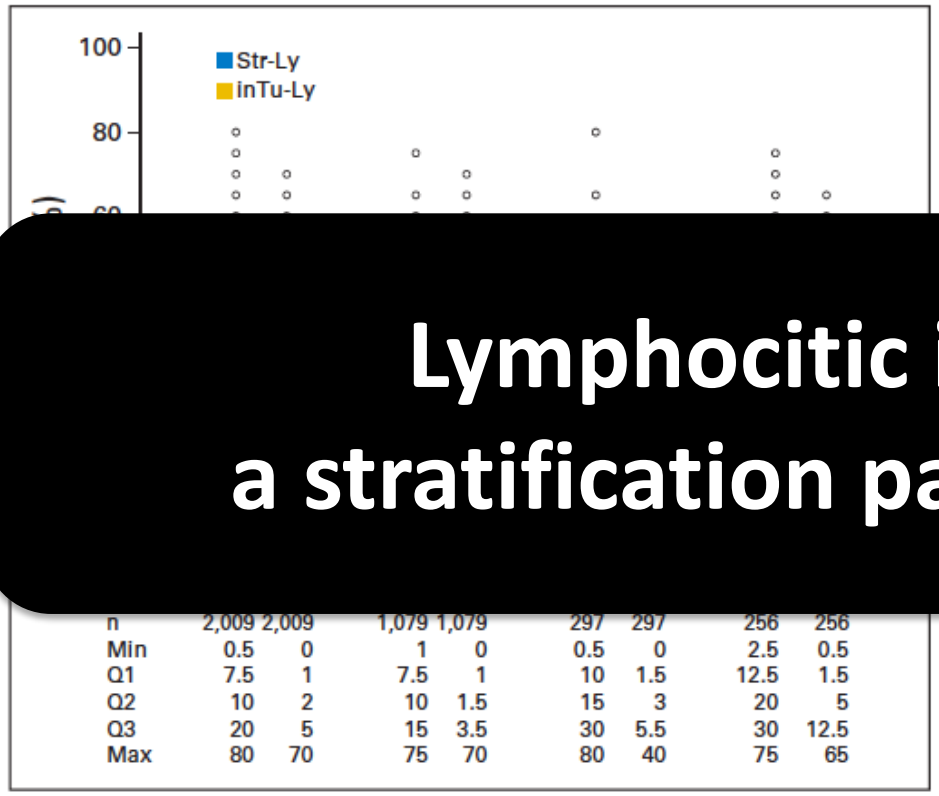
Michail Ignatiadis, Sandeep K. Singhal, Christine Desmedt, Benjamin Haibe-Kains, Carmen Criscitiello, Fabrice Andre, Sherene Loi, Martine Piccart, Stefan Michiels, and Christos Sotiriou

See accompanying editorial on page 1912

			95% CI	*P*	FDR
Proliferation	GGI	1.70	1.12 to 2.6	1.3E-02	3.7E-02
	Gene70	2.02	1.29 to 3.2	2.4E-03	1.3E-02
	CIN70	1.61	1.08 to 2.42	2.1E-02	5.1E-02
Stromal	Stroma1	0.73	0.49 to 1.06	1.0E-01	2.1E-01
	Stroma2	0.74	0.5 to 1.07	1.1E-01	2.1E-01
	Immune1	1.92	1.36 to 2.73	2.2E-04	3.7E-03
	Immune2	1.78	1.25 to 2.53	1.3E-03	1.1E-02
Pathways	RAS	0.82	0.57 to 1.18	3.0E-01	4.9E-01
	MAPK	0.85	0.56 to 1.27	4.2E-01	6.0E-01
	PTEN	1.75	1.18 to 2.62	5.8E-03	2.5E-02
	AKTmTOR	0.84	0.59 to 1.19	3.2E-01	4.9E-01
	PIK3CA	1.01	0.67 to 1.53	9.5E-01	9.5E-01
	IGF1	0.97	0.65 to 1.45	8.9E-01	9.5E-01
	SRC	1.02	0.71 to 1.47	9.1E-01	9.5E-01
	MYC	1.10	0.78 to 1.56	5.8E-01	7.6E-01
	E2F3	1.60	1.12 to 2.3	1.1E-02	3.7E-02
	BetaCatenin	0.98	0.68 to 1.43	9.4E-01	9.5E-01

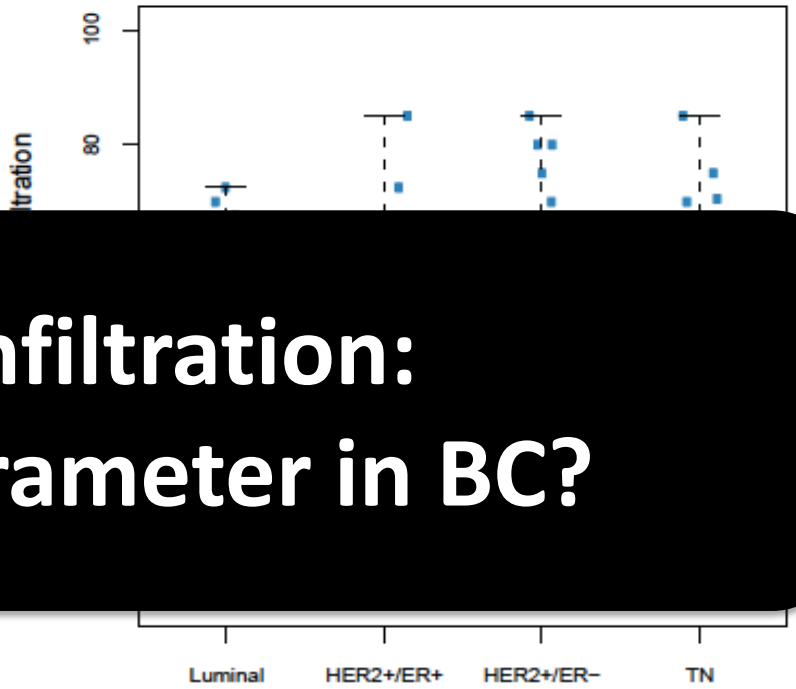


TILs in BC



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

Lymphocitic infiltration: a stratification parameter in BC?



n	591	103	106	134
Min	0.5	2.5	0	3
Q1	5	7.5	10	12.5
Q2	7.5	11	20	25
Q3	12.5	21.2	42.5	40
Max	72.5	85	85	85

Loi et al, JCO 2013; Ann Oncol 2014

TILs and pCR

VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

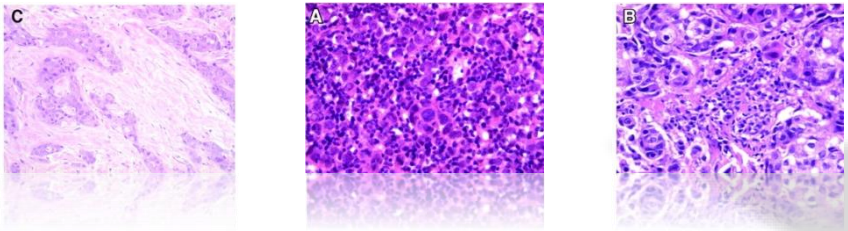
ORIGINAL REPORT

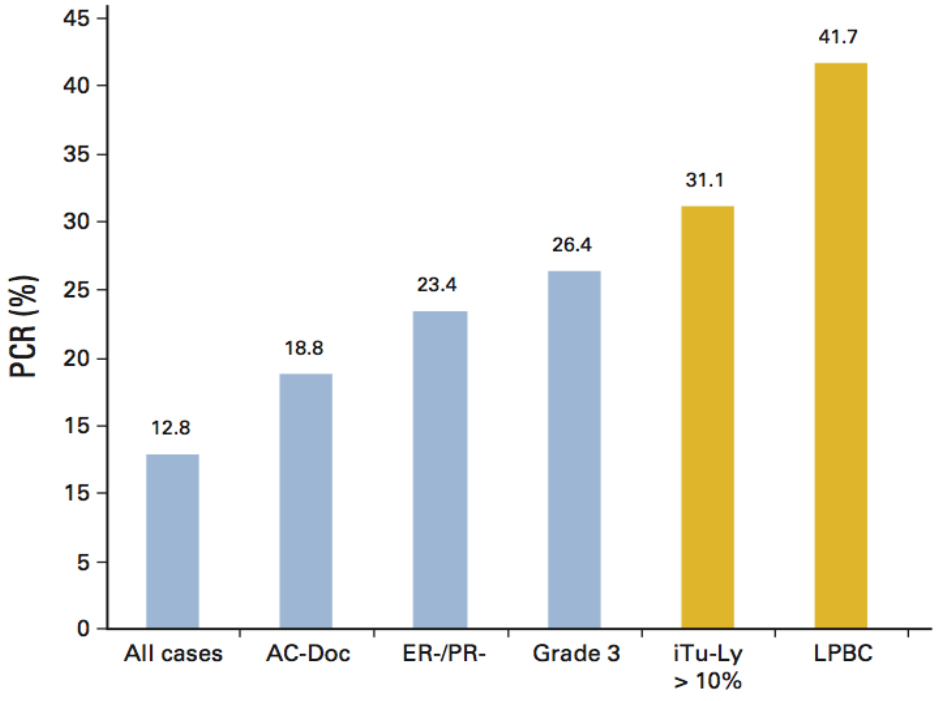
Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer

Carsten Denkert, Sibylle Loibl, Aurelia Noske, Marc Roller, Berit Maria Müller, Martina Komor, Jan Budczies, Silvia Darb-Esfahani, Ralf Kronenwett, Claus Hanusch, Christian von Törne, Wilko Weichert, Knut Engels, Christine Solbach, Iris Schrader, Manfred Dietel, and Gunter von Minckwitz

% of intratumoral / stromal lymphocytes

0 | 0-60 | > 60 - LPBC





Denkert C et al. JCO 2010

VOLUME 33 · NUMBER 9 · MARCH 20 2015

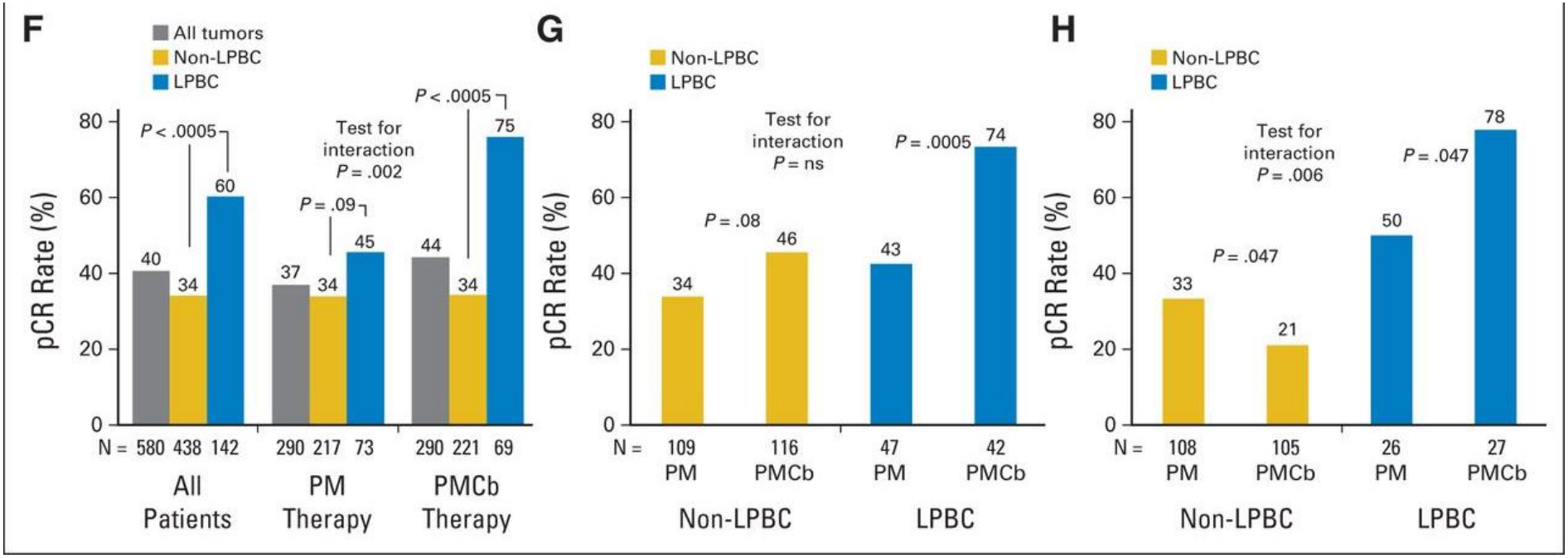
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2–Positive and Triple-Negative Primary Breast Cancers

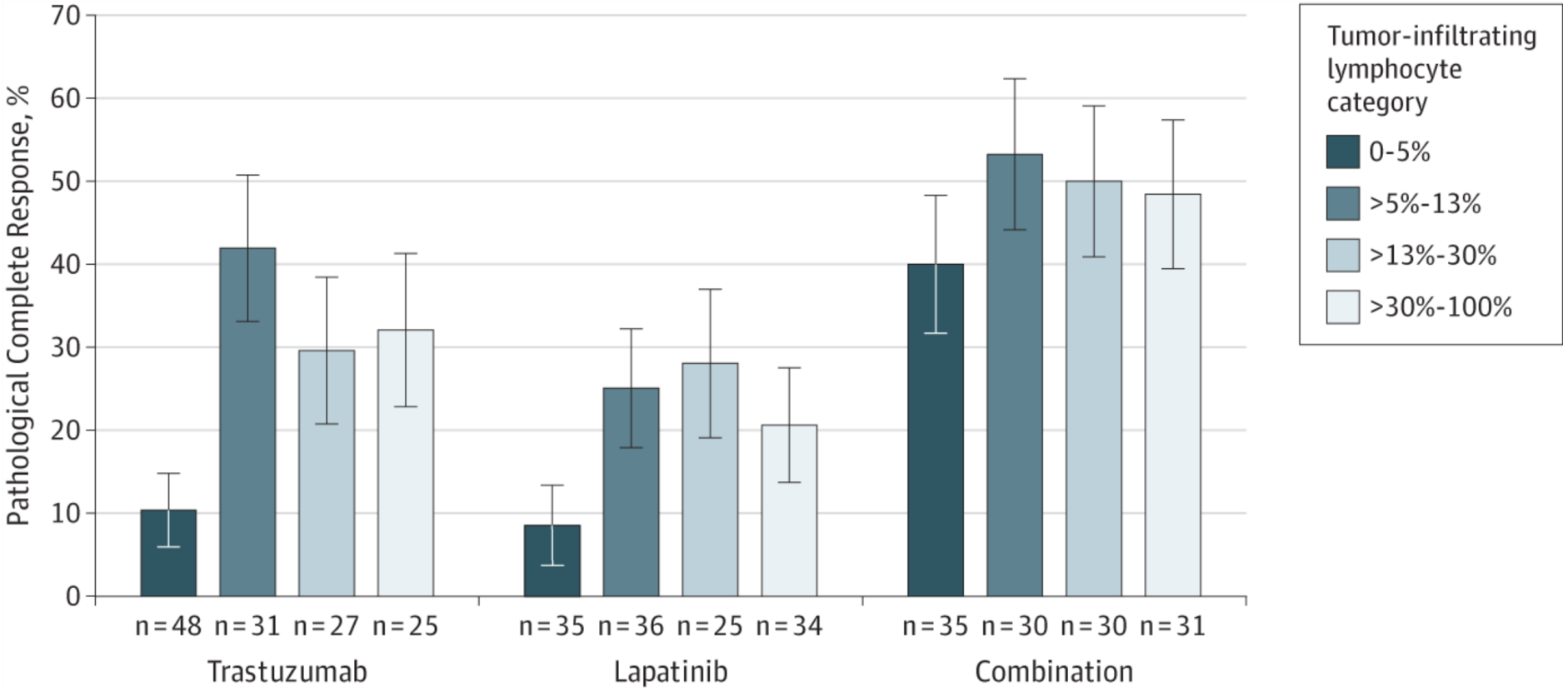
Carsten Denkert, Gunter von Minckwitz, Jan C. Brase, Bruno V. Sinn, Stephan Gade, Ralf Kronenwett, Berit M. Pfitzner, Christoph Salat, Sherene Loi, Wolfgang D. Schmitt, Christian Schem, Karin Fisch, Silvia Darb-Esfahani, Keyur Mehta, Christos Sotiriou, Stephan Wienert, Peter Klare, Fabrice André, Frederick Klauschen, Jens-Uwe Blohmer, Kristin Krappmann, Marcus Schmidt, Hans Tesch, Sherko Kümmel, Peter Sinn, Christian Jackisch, Manfred Dietel, Toralf Reimer, Michael Untch, and Sibylle Loibl

All tumors TNBC HER2+



Denkert C. et al. JCO 2015

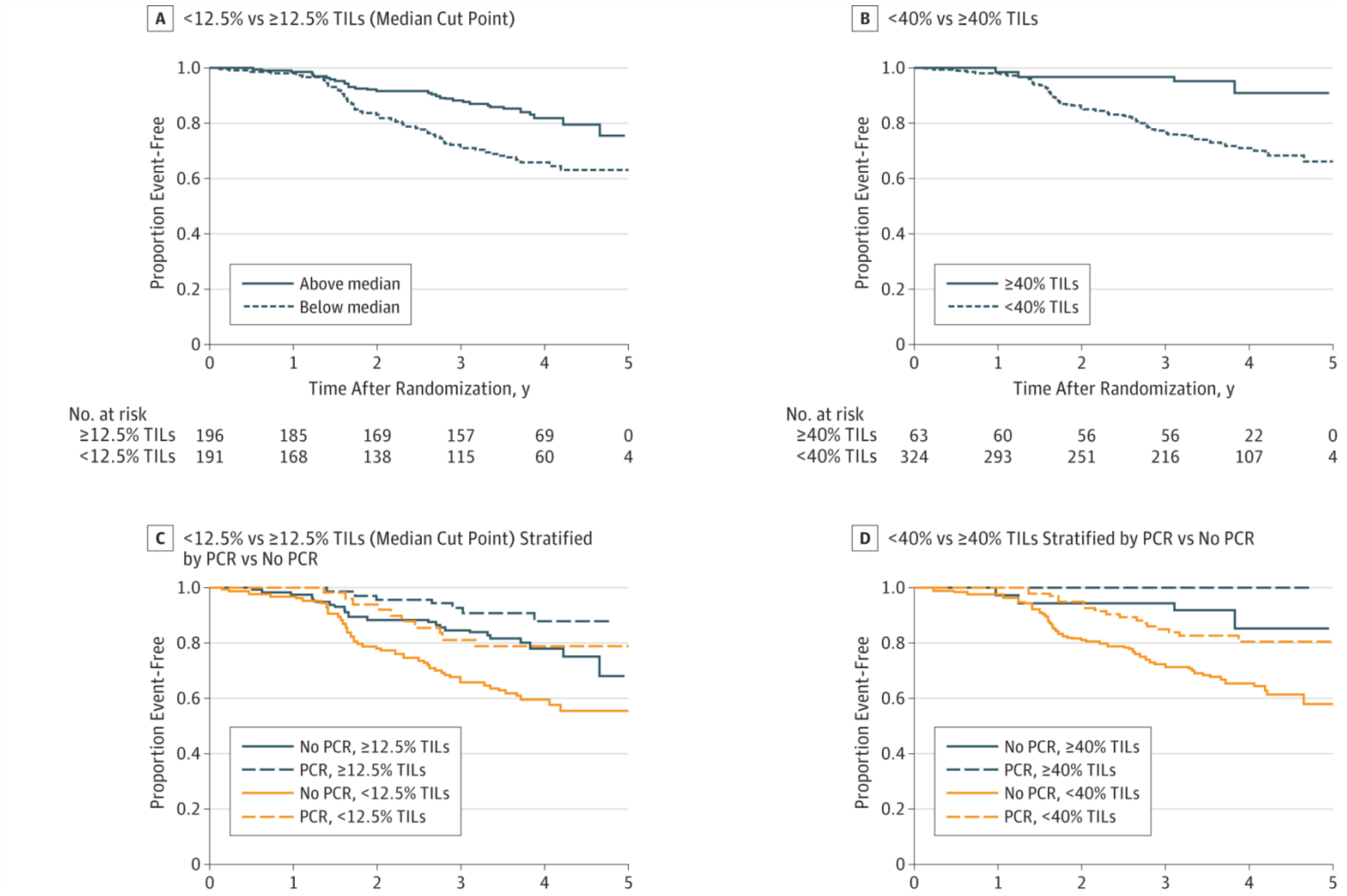
TILs and associations with pCR in HER2+ BC: a secondary analysis of the NeoALTTO trial



Salgado R. et al, JAMA Oncol. 2015

TILs and prognosis

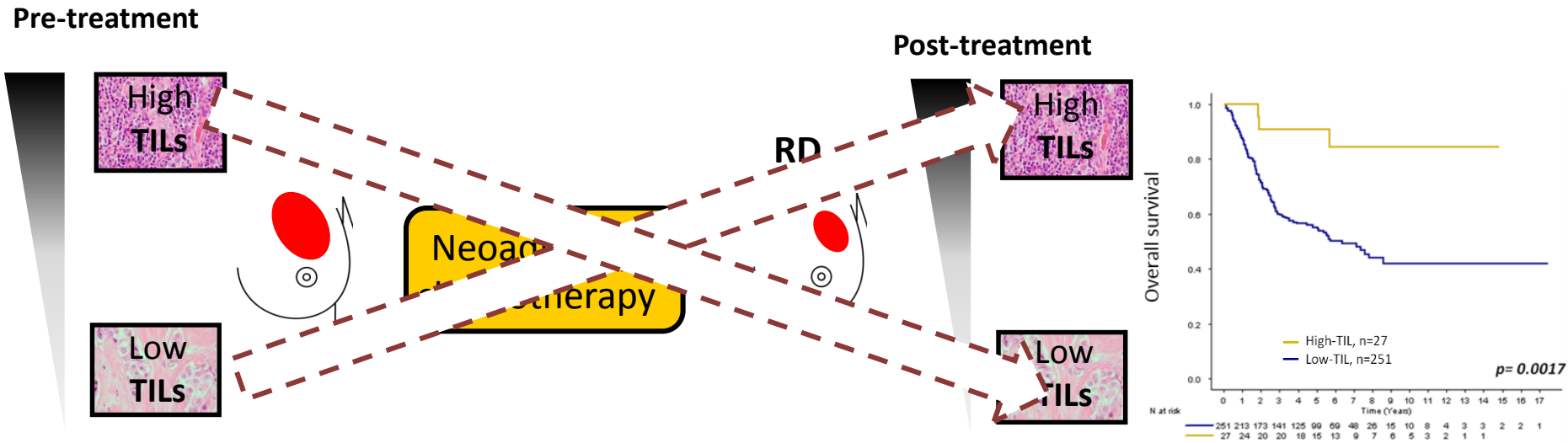
Higher levels of TILs result in better EFS, independently of pCR in the NeoALTTO trial



For every 1% increase in TILs, a 3% decrease in the rate of an event

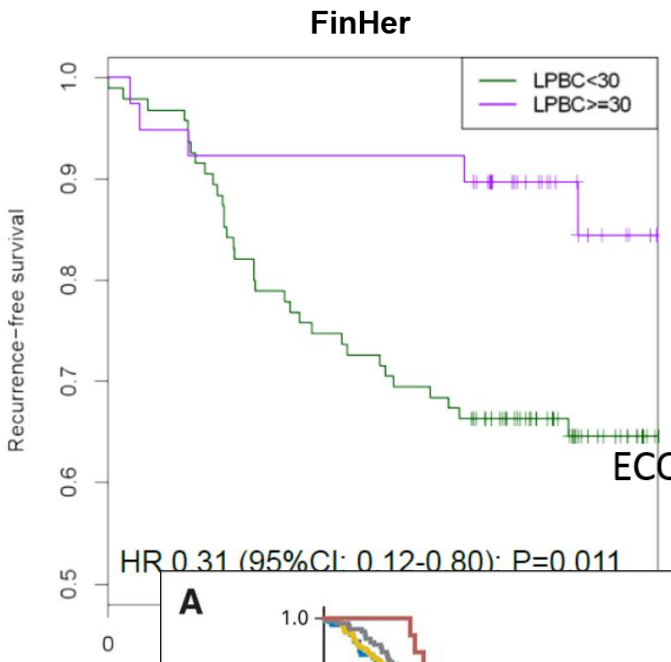
Salgado R. et al, JAMA Oncol. 2015

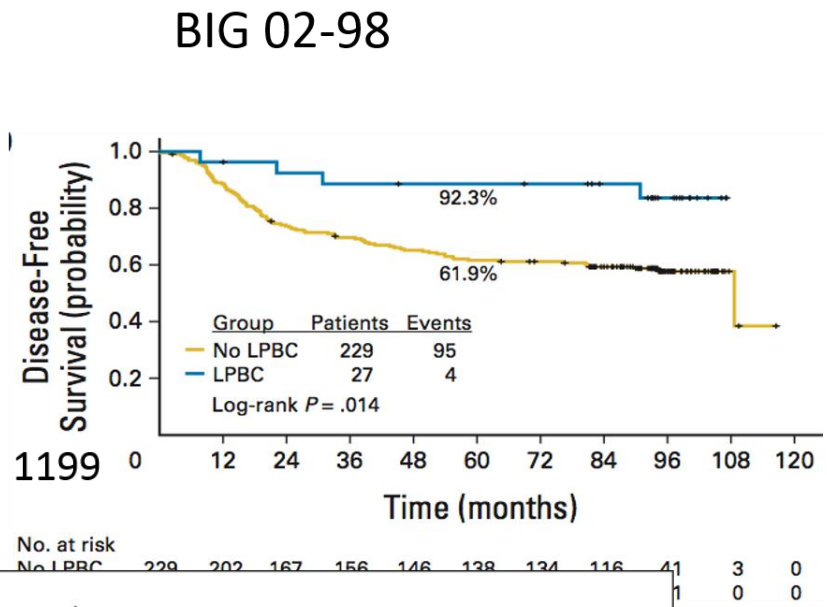
Prognostic value of TILs on residual disease after NACT for TNBC



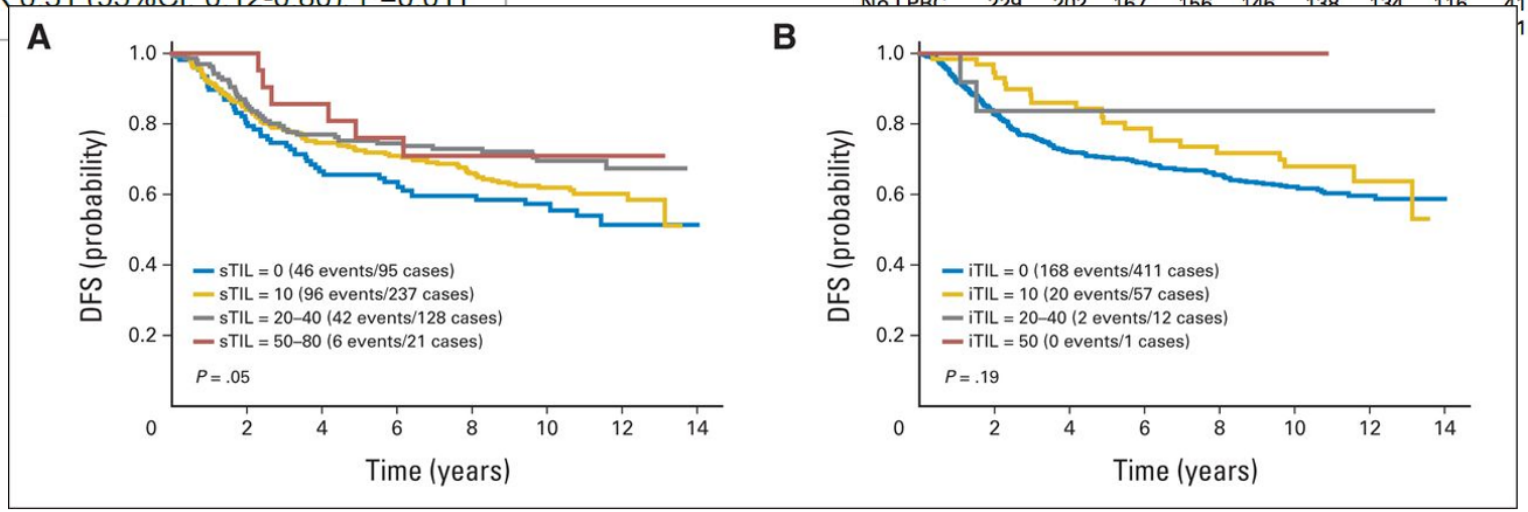
Dieci et al. Ann Oncol 2014

TILs can identify a subset of TNBC with good prognosis





ECOG 2197 and ECOG 1199



Adams S, JCO 2014

TILs and prediction

Predictive ability of TILs

Anthracyclines-only vs Anthracyclines+ taxanes

Table 2. Predictive Ability of TILs and Interaction *P* Tests Between Anthracycline-Only (A1 and A2) and Anthracycline-Taxane–Containing Arms (B and C)*

Variable	No. of Patients	DFS Interaction *P*	OS Interaction *P*
LPBC†			
Global population	2,009	.47	.94
ER positive/HER2 negative	1,078	.074	.042
HER2 positive	297	.025	.059
ER negative/HER2 negative	256	.73	.93
Intratumoral lymphocytic infiltration‡			
Global population	2,009	.28	.64
ER positive/HER2 negative	1,078	.54	.36
HER2 positive	297	.16	.32
ER negative/HER2 negative	256	.15	.40
Stromal lymphocytic infiltration‡			
Global population	2,009	.28	.37
ER positive/HER2 negative	1,078	.28	.14
HER2 positive	297	.042	.018
ER negative/HER2 negative	256	.17	.51

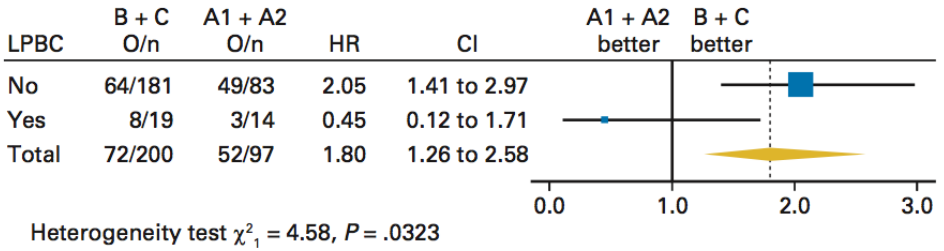
Abbreviations: DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LPBC, lymphocyte-predominant breast cancer; OS, overall survival; TIL, tumor-infiltrating lymphocyte.

*Treatment effect and interaction *P* tests between anthracycline-only (A1 and A2) and anthracycline-docetaxel–containing arms (B and C) and TIL variables in breast cancer overall and by subtype.

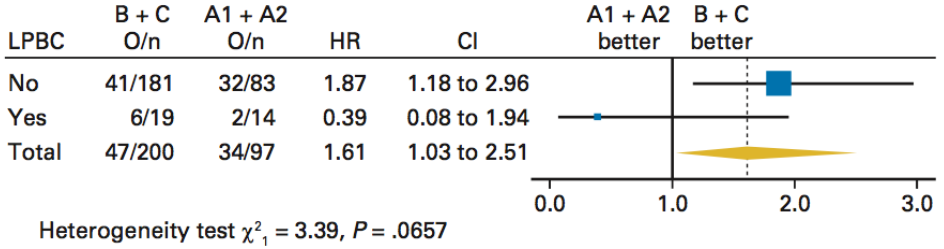
†Binary variable; < or ≥ 50% of either stromal or intratumoral lymphocytes.

‡Treated as a continuous variable for each 10% increment.

DFS



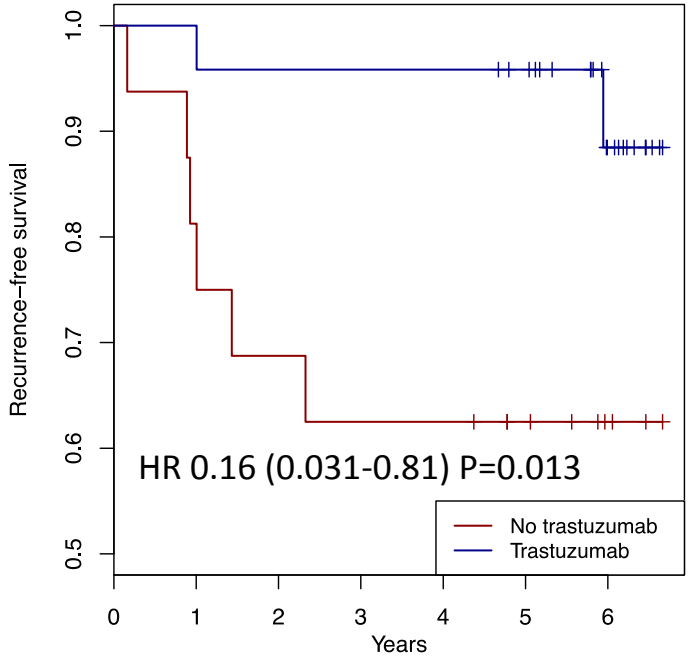
OS



Loi et al. J Clin Oncol, 2013

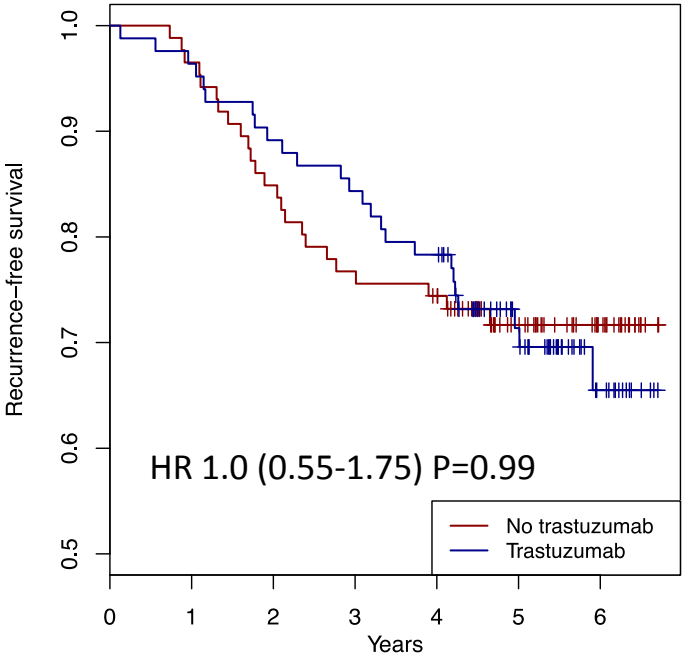
High levels of TIL associated with trastuzumab benefit in HER2+ disease

LPBC



No. At Risk							
No trastuzumab	16	14	12	11	11	8	4
Trastuzumab	24	24	24	24	24	22	11

Non-LPBC



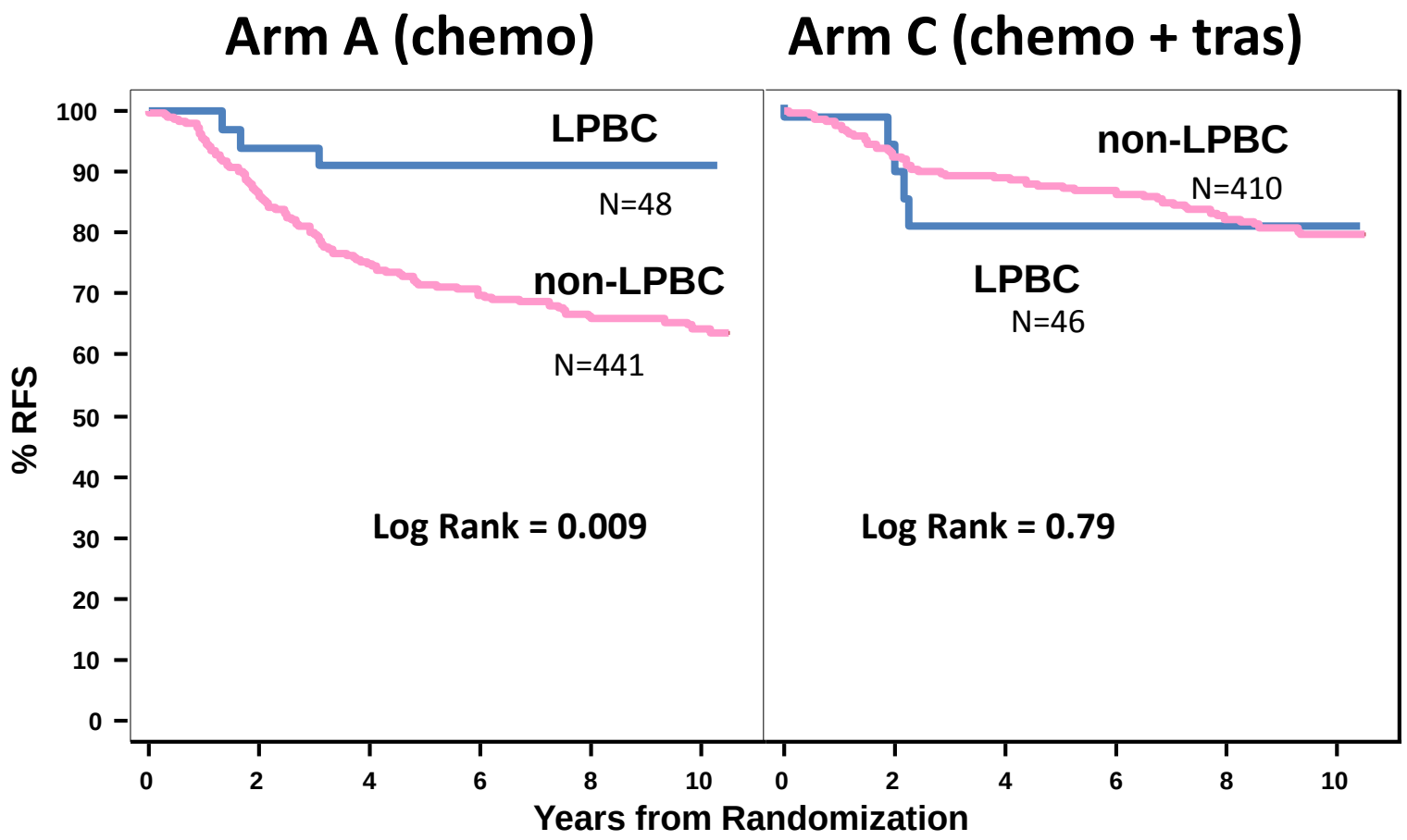
No. At Risk							
No trastuzumab	86	84	74	67	64	40	20
Trastuzumab	83	81	75	71	66	41	15

Significant interaction test p=0.02

For every 10% increase in TILs, there was increasing benefit to trastuzumab

Loi et al, Annals Oncol 2014

Str-TILs are associated with chemotherapy benefit but not associated with trastuzumab benefit



LPBC= lymphocyte predominant breast cancer

E. Perez et al, Abstract S1-06, SABCS 2014

KEYNOTE-086: Phase 2 Study of Pembrolizumab Monotherapy For mTNBC

Cohort A
- ≥1 prior systemic treatment for mTNBC with documented PD
- PD-L1 positive or negative

Cohort B
- No prior systemic treatment for mTNBC
- PD-L1 positive

All Patients
- Centrally confirmed TNBC[a]
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample
- No radiographic evidence of CNS metastases

Cohort A
N = 170

Cohort B
N = 84

Pembrolizumab 200 mg IV Q3W

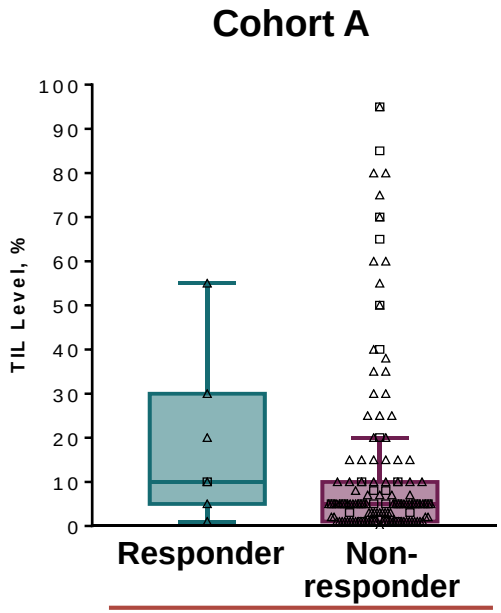
for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

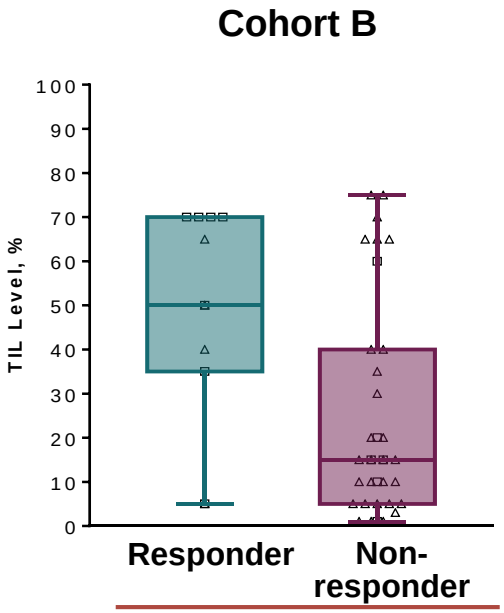
Protocol-specified follow-up

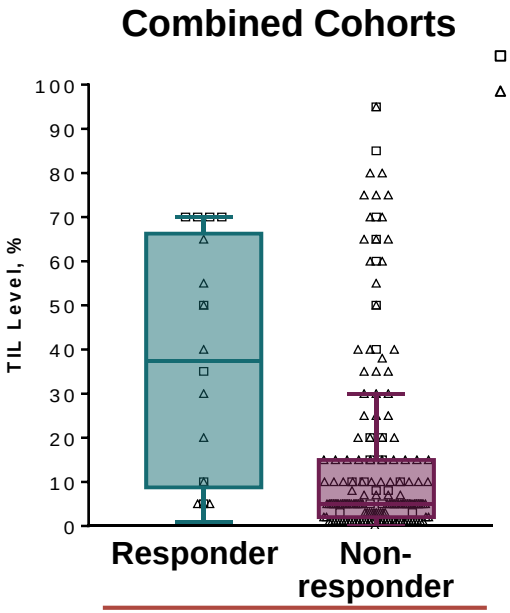
- Primary end points: ORR and safety
- Secondary end points: DOR, DCR,[b] PFS, OS

[a]<1% tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative.
[b]DCR = disease control rate = SD ≥24 wk + CR + PR.
ClinicalTrials.gov identifier NCT02447003.

sTIL Levels by Tumor Response







	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
n	7	140	11	35	18	175
Median (IQR)	10% (5-30)	5% (1-10)	50% (35-70)	15% (5-40)	37.5% (8.75-66.25)	5% (2-15)
***P*[a]**	0.062		0.009		<0.001	

sTIL were significantly associated with response to pembrolizumab monotherapy in mTNBC, particularly in the first-line setting

Summary

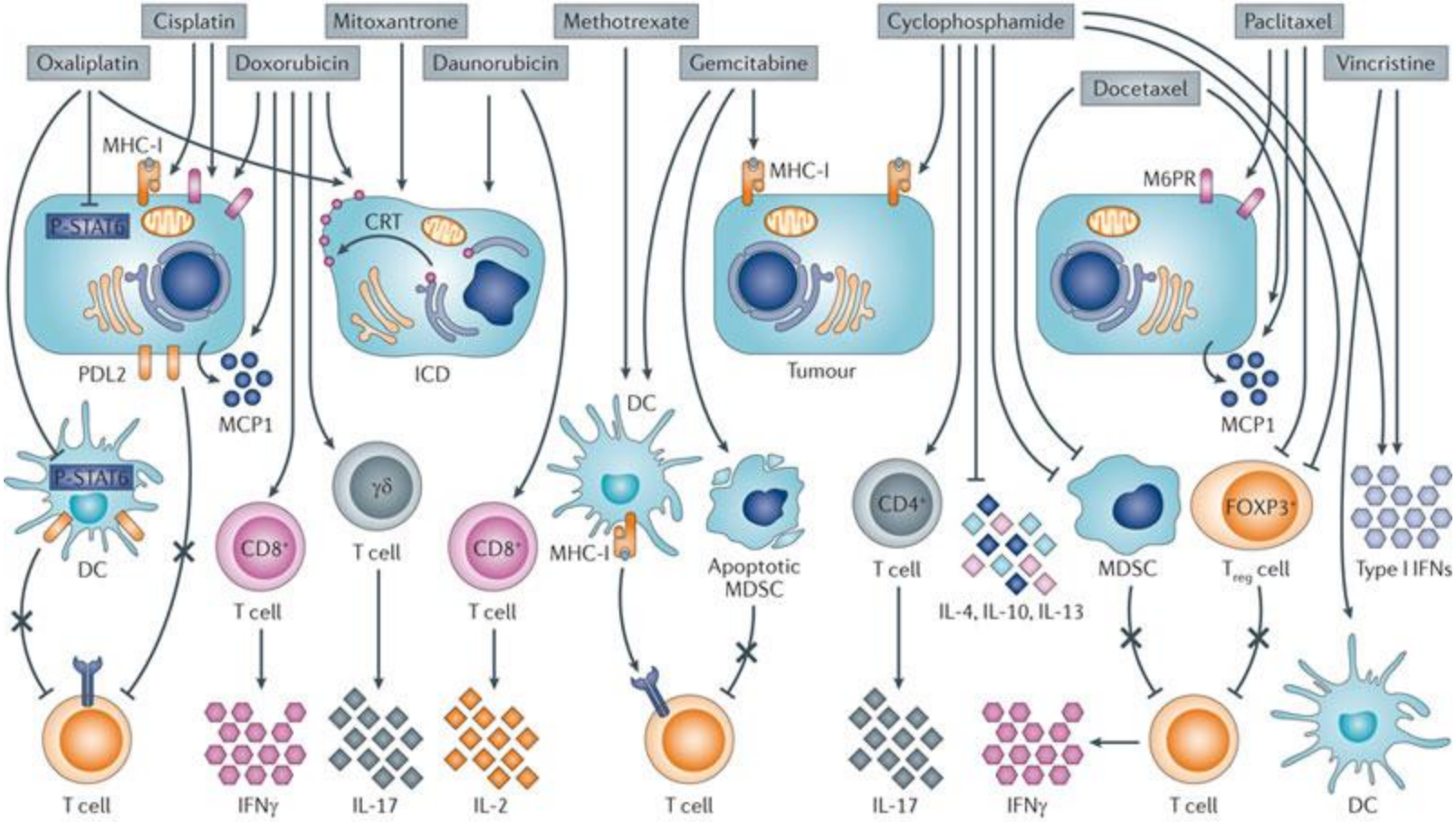
Positive immune signal (TILs/immune signatures) - which reflects the adaptive immune system - suggests:

- Better outcome (natural history)
- Benefit from chemotherapy
- Benefit from trastuzumab (further evaluation needed)
- Benefit from pembrolizumab

Outline

- Rational for immune-based therapy in breast cancer
- ***Immunogenic chemotherapy***
- Targeting immune checkpoints
- Predicting immune-response in breast cancer

Mechanisms of immune stimulation



Galluzzi L. et al, Nat Rev Drug Discov. 2012 Feb 3

Interplay between drugs and the immune system

Chemotherapy can modulate the anticancer immune response:

- Doxorubicin increases production of interferons, reduces MDSC-induced immune suppression[1,2]
- Cyclophosphamide (low dose) depletes Tregs in human breast tumors[3]
- Cisplatin stimulates class I HLA and vulnerability of tumor cells for T cell killing[4,5]

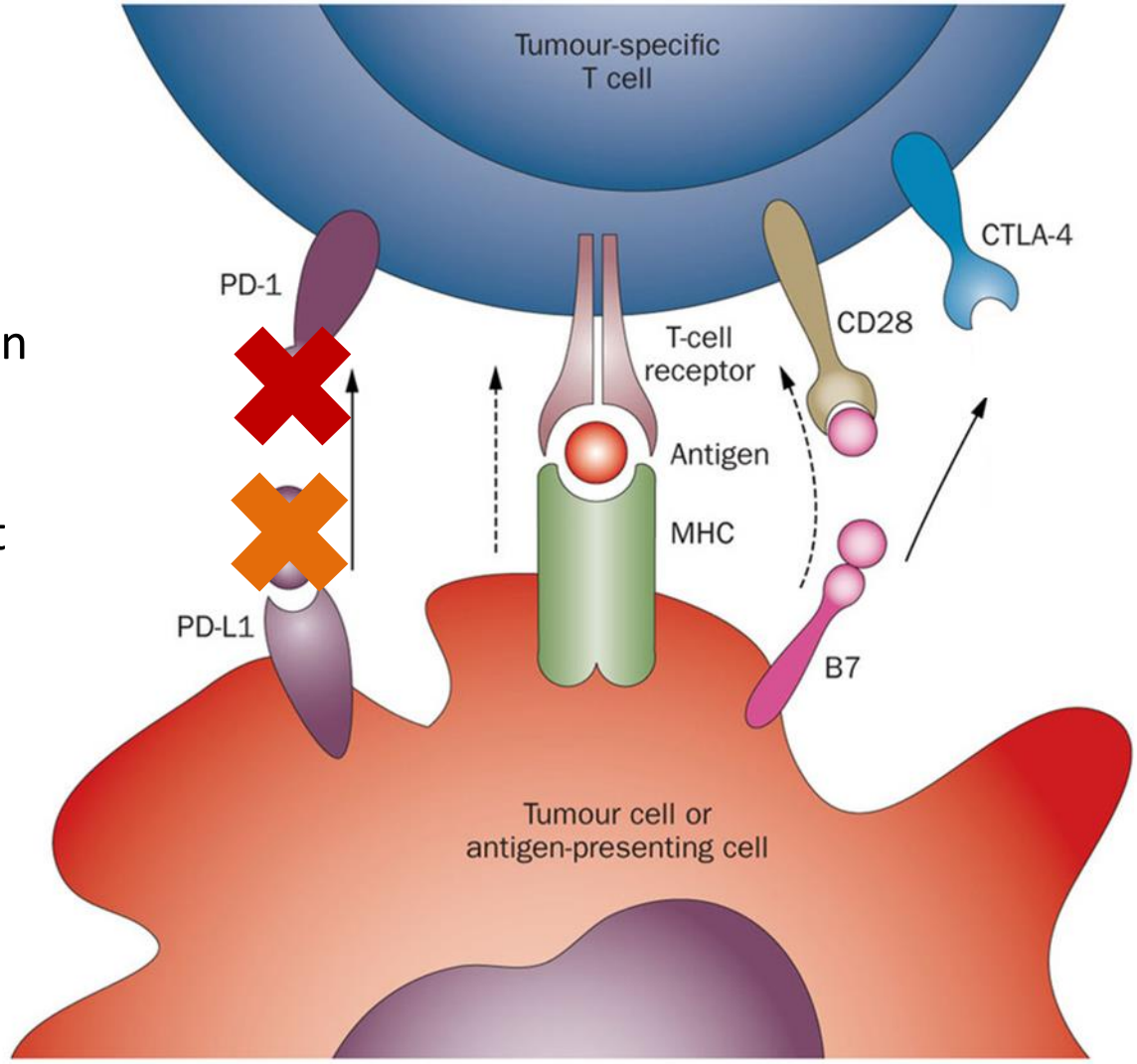
1.Sistigu et al. Nature Med 2014, 2.Alizadeh et al. Cancer Res 2014, 3.Ghiringhelli et al. CeII 2007,
4.Lesterhuis et al. JCI 2011, 5.Ramakrishnan et al. JCI 2010

Outline

- Rational for immune-based therapy in breast cancer
- Immunogenic chemotherapy
- ***Targeting immune checkpoints***
- Predicting immune-response in breast cancer

Anti-PD-1/PD-L1

Various ligand-receptor interactions between T cells and antigen presenting cells that regulate the T cell response to antigen



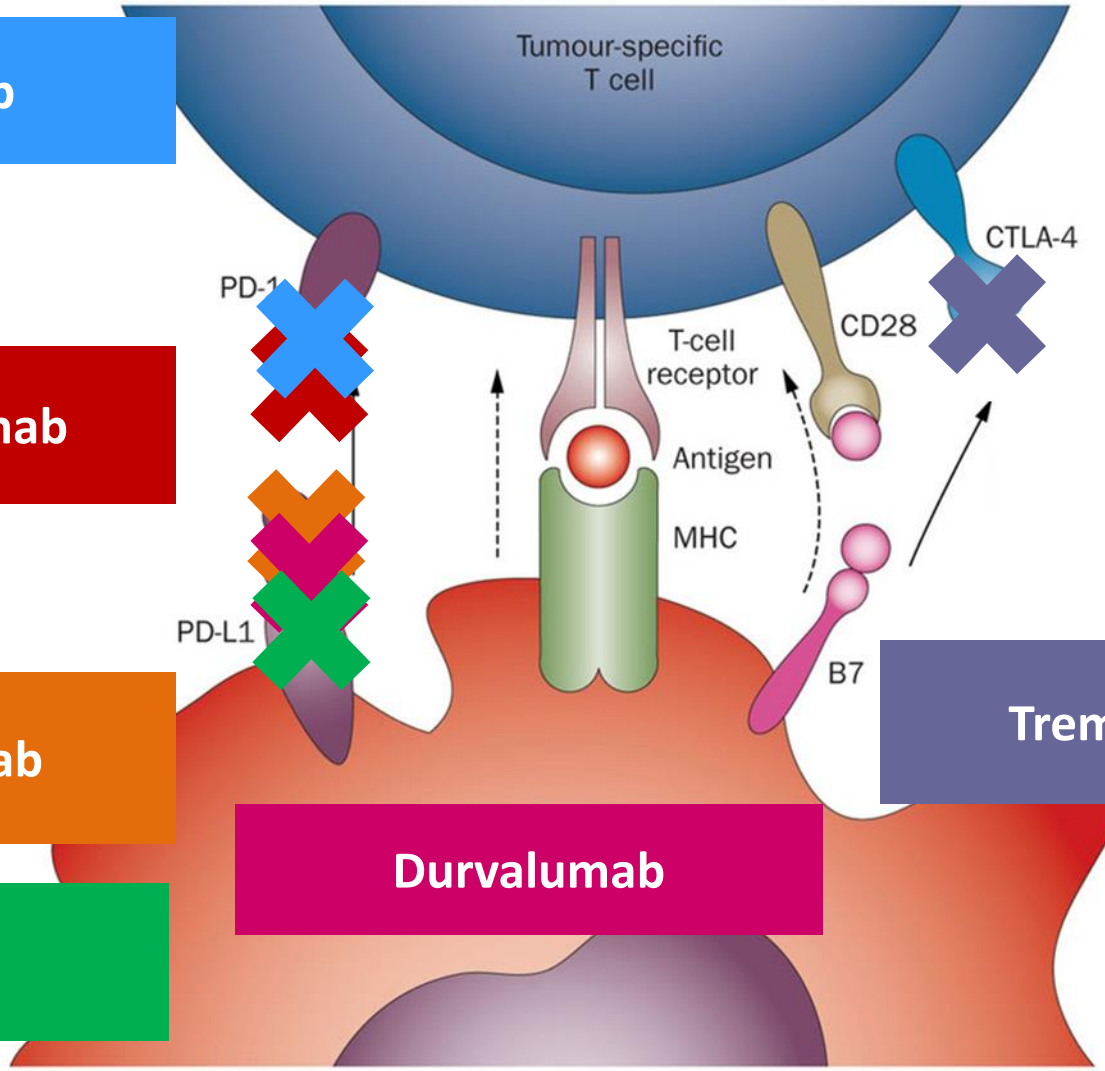
Immunotherapy in TNBC

Nivolumab

Pembrolizumab

Atezolizumab

Avelumab



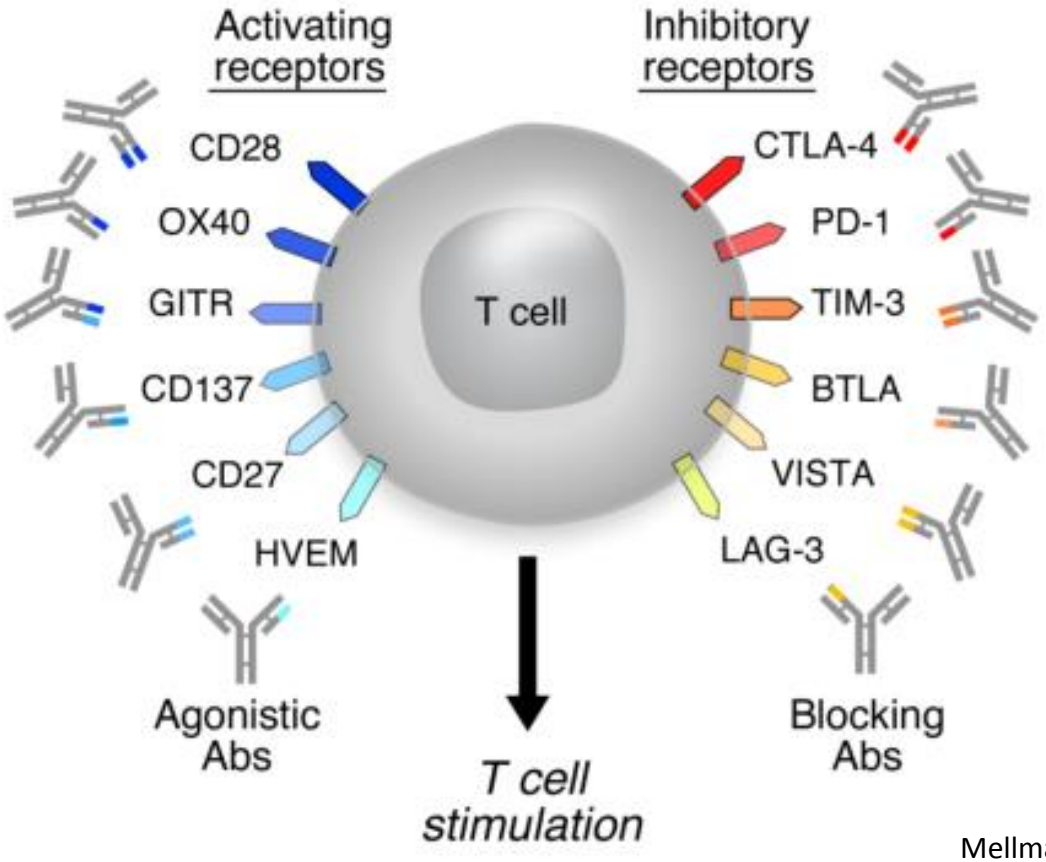
Tremelimumab

Durvalumab

T cell Targets for Antibody Therapy

Enhancing T cell stimulation to promote tumor destruction

- Agonistic antibodies vs activating receptors
- Blocking antibodies vs inhibitory receptor



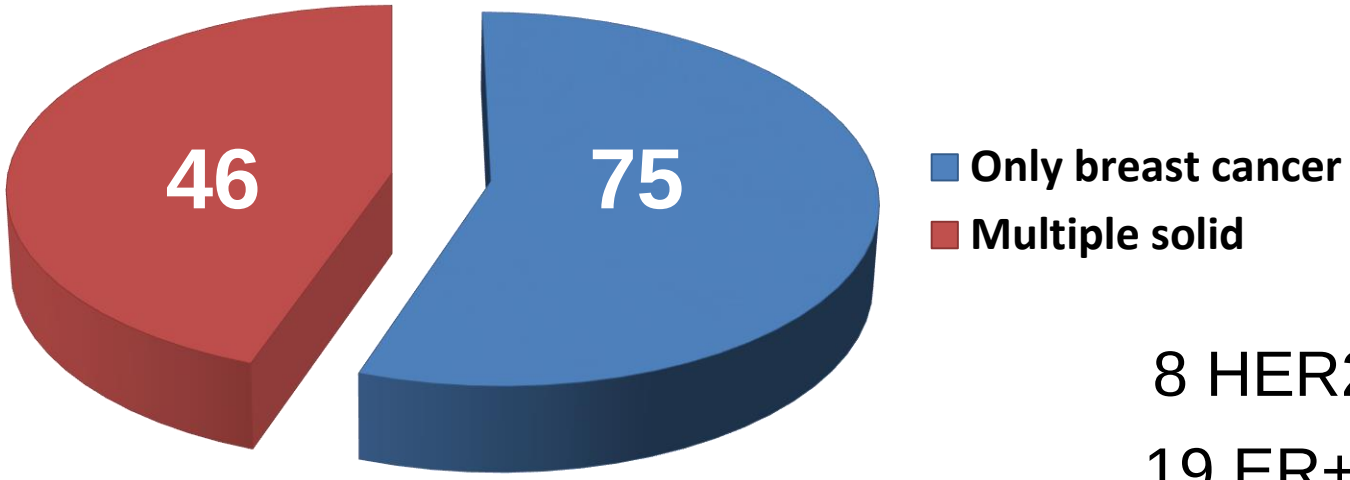
Mellman I, et al. *Nature* 2011

Immune checkpoint inhibitors monotherapy in mBC

Molecular subtype	Author	Drug	No. Pts	ORR	Selection	ORR			
						PDL1+§	PDL1-§	1L	2L+
TN	Nanda R	Pembrolizumab	27	18.5%	PDL1+				
	Adams S	Pembrolizumab	170	4.7%	All	4.8%	4.7%		4.7%
	Adams S	Pembrolizumab	52	23.1%	All			23.1%	
	Emens L	Atezolizumab	21	19.0%	PDL1+				
	Emens L	Atezolizumab	112	10.0%	All	13.0%	5.0%	26.0%	7.0%
	Dirix L	Avelumab	58	8.6%	All	44.0%	2.6%		
ER+/HER2-	Hugo R	Pembrolizumab	25	12.0%	PDL1+				
	Dirix L	Avelumab	72	2.8%	All				
HER2+	Dirix L	Avelumab	24	3.8%	All				

§ PDL1+ and PDL1- were defined differently in different studies

Trial ongoing with immunechekpoint inhibitors in breast cancer



8 HER2+ (only)

19 ER+ (included)

8 Phase III trials (TNBC)

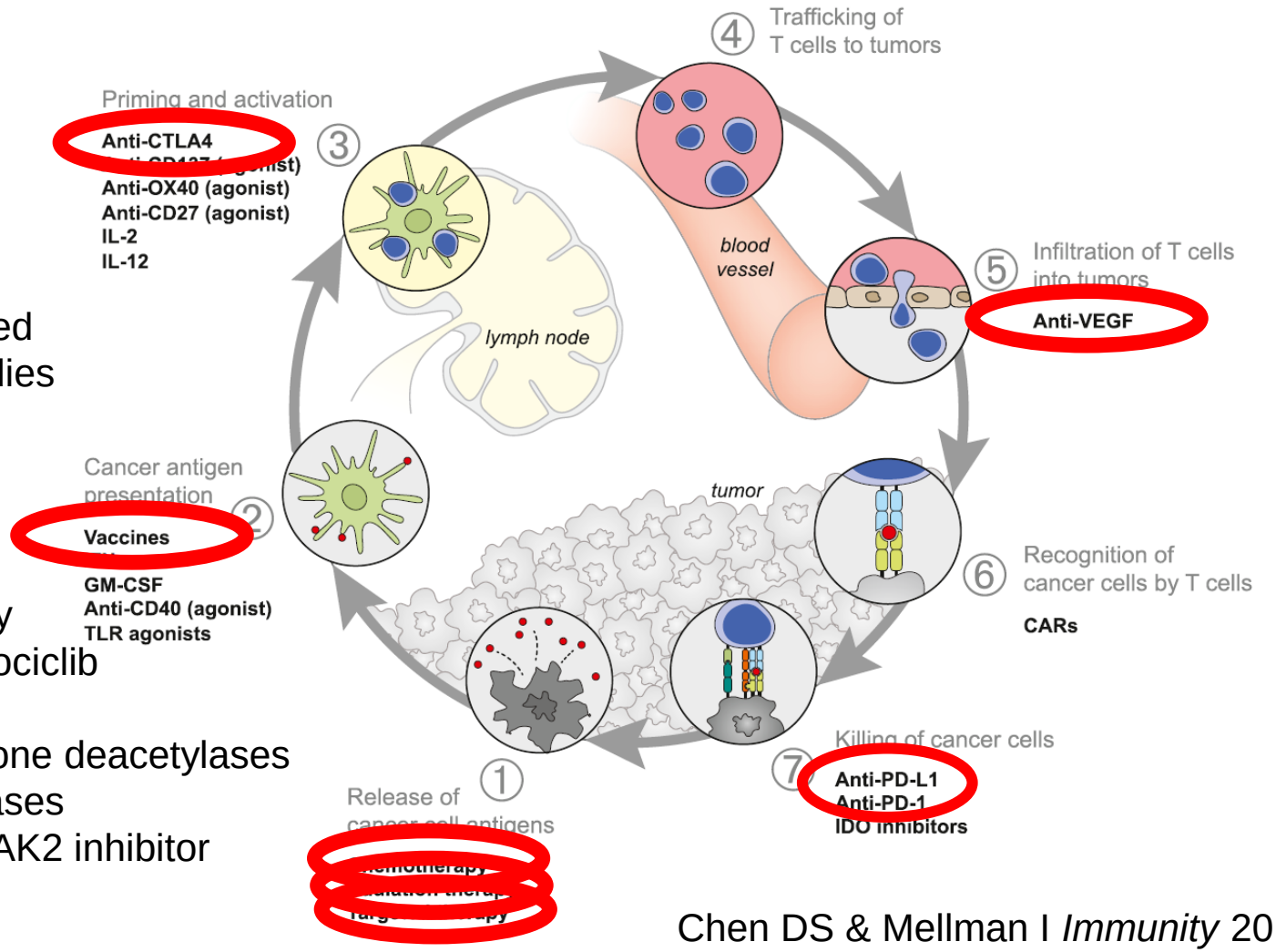
- 2 Neoadjuvant
- 2 Adjuvant
- 3 Metastatic (1st line)
- 1 Metastatic (2nd/3rd line)

ClinicalTrialsGov (updated 01-05-2017)

Trials ongoing with immunechekpoint inhibitors – Combination therapies

50 trials with
anti-PD1/PDL1
in combination

29 chemotherapies
4 radiotherapy
6 anti-HER2 targeted monoclonal antibodies
3 anti-CTLA4
2 vaccines
1 bevacizumab
1 anti-androgen
4 endocrine therapy
1 endocrine + palbociclib
1 abemaciclib
1 endocrine + hystone deacetylases
1 histone deacetylases
1 PARP inhibitor, JAK2 inhibitor
1 MEK inhibitor
2 cryoablation

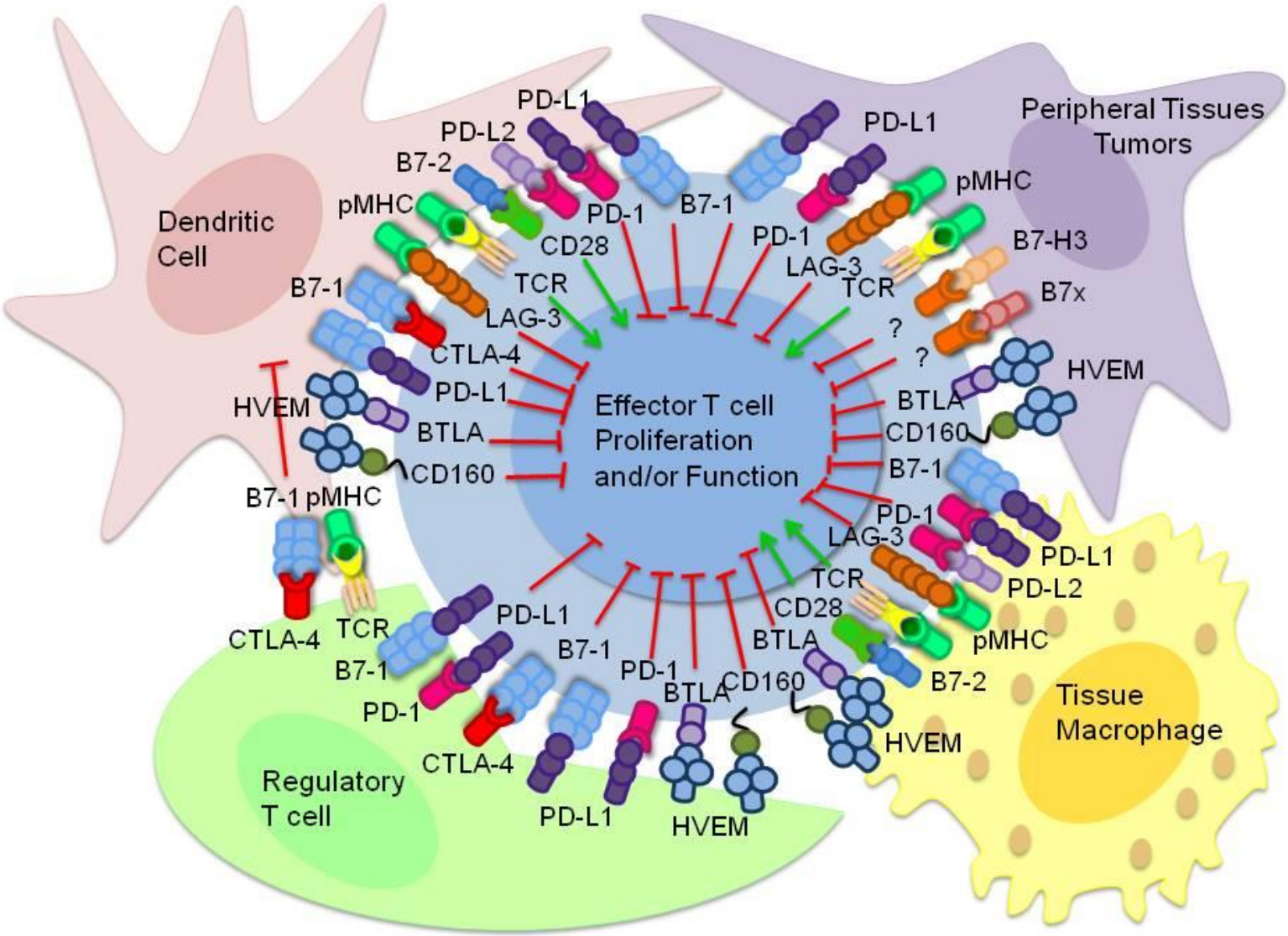


Chen DS & Mellman I *Immunity* 2013

Outline

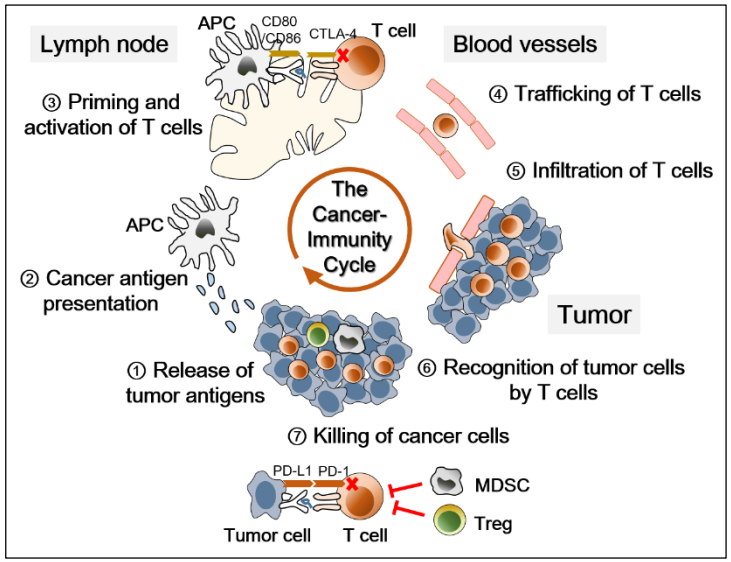
- Rational for immune-based therapy in breast cancer
- Immunogenic chemotherapy
- Targeting immune checkpoints
- ***Predicting immune-response in breast cancer***

Predicting immune-response in BC



Predicting immune-response in BC

- Anti-tumor immunity is dynamic and evolves over time
- Expression of a single biomarker is not adequate to select patients for treatment
- Comprehensive assessment of cancer-immunity is required for successful cancer immunotherapy



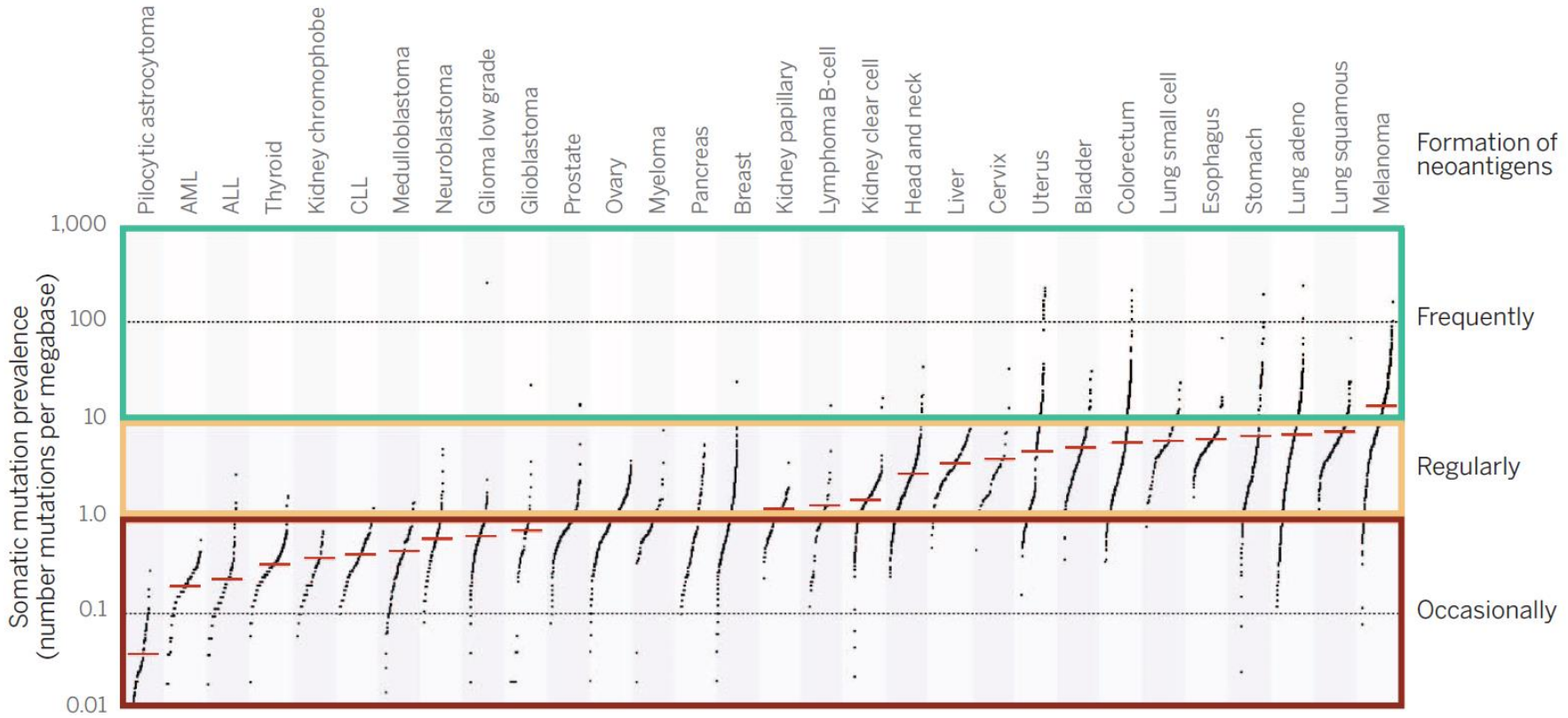
Adapted from Chen DS et al. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013

Predicting immune-response in BC

- The more “immunogenic” → higher likelihood to respond

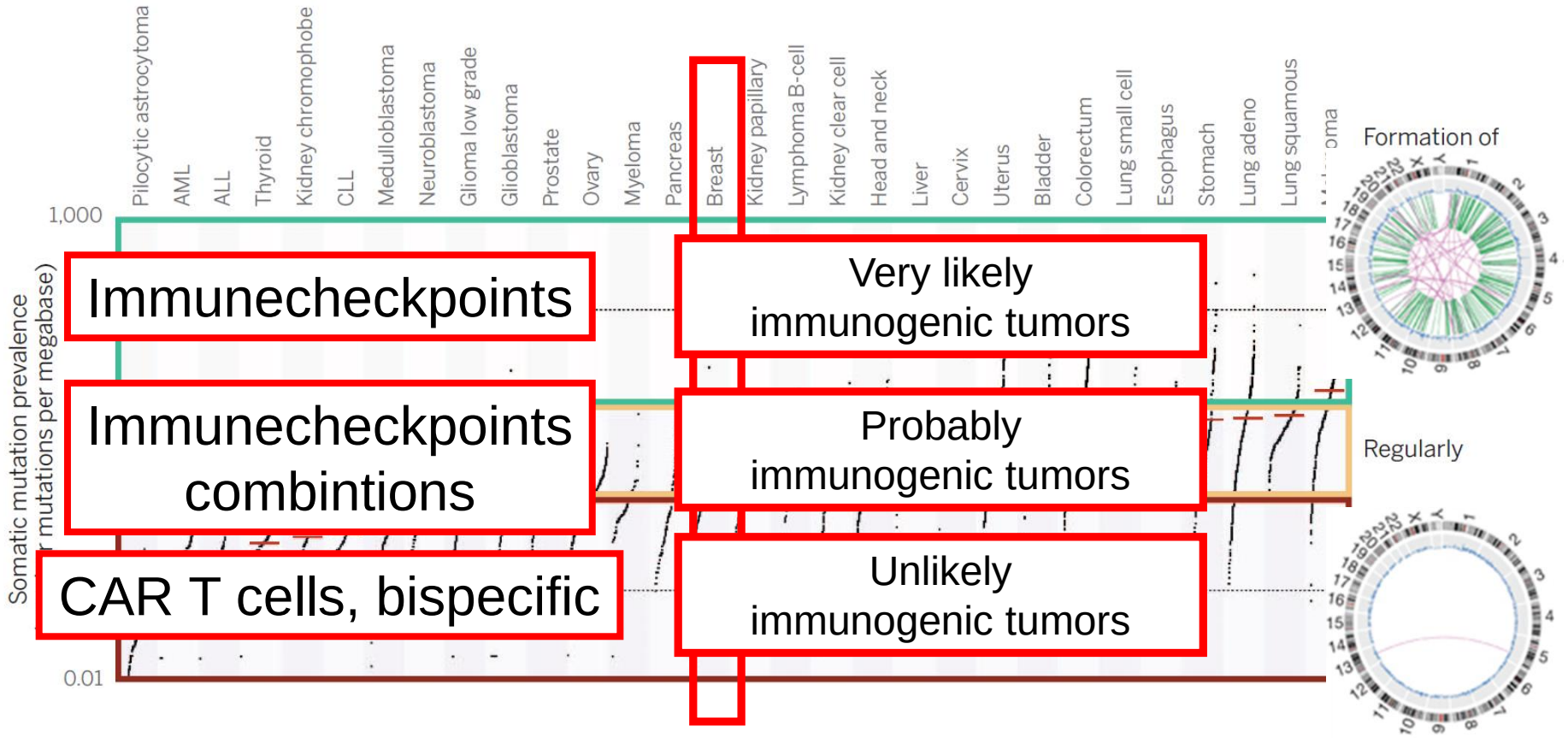
- How to define “immunogenic”?
  TILs, presence of MHC I and/or II, immune determinants (neo-antigens), PD1/PD-L1 expression?

Mutational burden as surrogate of "likelihood of non-self" (neoantigen generation)



Schumacher TN Science 2015

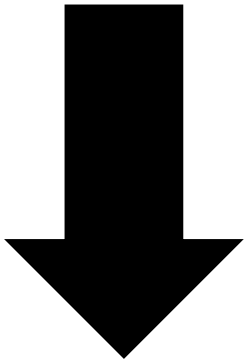
Mutational burden as surrogate of "likelihood of non-self" (neoantigen generation)



Schumacher TN Science 2015

Future directions

To predict at diagnosis which TNBCs will be infiltrated by TILs after chemo



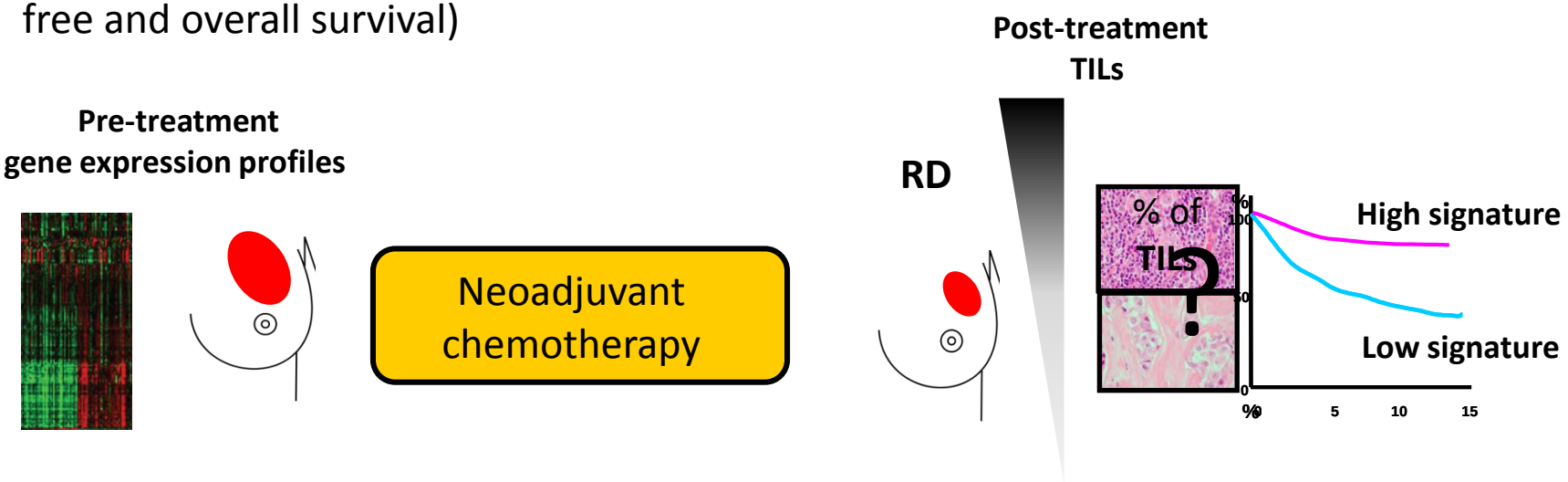
This will help identifying patients with poor outcome who require additional new drugs

Study Design

Step 1: Training

1.To generate – on pre-treatment biopsies - a genomic predictor for the extent of post-chemo TIL in TNBCs with residual disease

2.To assess the prognostic value of the genomic predictor (distant relapse-free and overall survival)

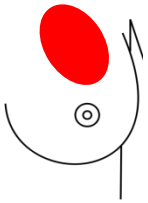


Study Design

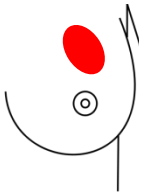
Step 2 : Validation

1. To assess - in an independent series of pre-NACT biopsies of TNBC - the prognostic value of the genomic predictor

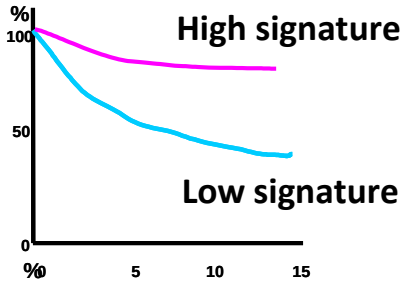
Gene expression signature predictive for post-treatment TILs



Neoadjuvant chemotherapy



?



A 4-gene signature to predict post-chemo TILs

We used a regression model with a penalized variable selection method (called LASSO) to identify on pre-treatment GEPs a parsimonious set of genes that predicts for post-treatment TILs, while controlling for important clinicopathological factors in the model.

PROBEID	Gene	Description	Coefficient
202269_x_at	GBP1	guanylate binding protein 1, interferon-inducible	0.288
204753_s_at	HLF	hepatic leukemia factor	-1.027
205242_at	CXCL13	chemokine (C-X-C motif) ligand 13	0.392
219934_s_at	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	-1.726

The four-gene signature is the linear combination of the gene expressions weighted by the regression coefficients; to facilitate the interpretation of the values of the four-gene signature thus obtained, the signature was scaled within the training set, so that the 2.5% and 97.5% quantiles equaled 0 and +1. A positive coefficient indicates that an increasing gene expression is associated with an increased quantity of TILs. A negative coefficient indicates that an increasing gene expression is associated with a decreased quantity of TILs.

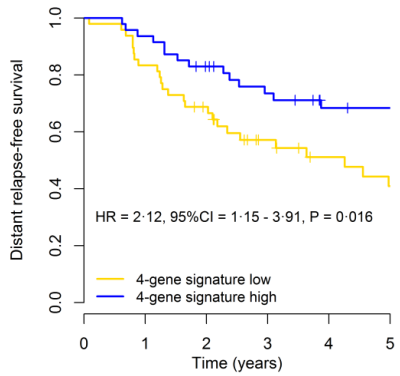
GBP1 and CXCL13 are two proteins involved in anti-tumor immune response

HLF could be involved in treatment induced immunogenic cell death

SULT1E1 when suppressed could create a more immunogenic microenvironment

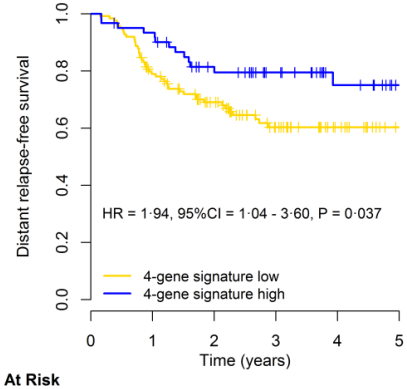
4-gene signature and outcome

training set - DRFS



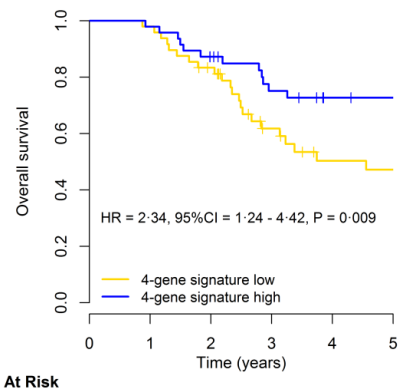
No. At Risk						
4-gene signature low	48	40	31	20	15	12
4-gene signature high	47	44	37	31	25	24

validation set - DRFS



No. At Risk						
4-gene signature low	124	94	67	39	22	7
4-gene signature high	61	56	42	31	17	9

training set - OS



No. At Risk						
4-gene signature low	48	47	38	23	16	15
4-gene signature high	47	46	38	31	26	25

The 4-gene signature could represent a new prognostic parameter that will allow identifying – at diagnosis - patients with poor outcome despite standard treatments who could benefit the most from new investigational drugs

Conclusions

- Some patients have an active immune response to their breast cancer which is suppressed
- Consistent retrospective analyses suggest that TIL could stratify some breast cancers in low versus high risk of relapse
- Immunotherapy can produce durable antitumor responses in some patients with breast cancer
- Seems that immune checkpoint inhibition may be an effective strategy for some breast cancers (clinical trials ongoing)

Open questions

- Predictive Biomarkers
  - Which tumors to treat?
  - Which patients to treat?
- Other combinations?
- Line of therapy?
- How to enhance tumor immunogenicity (TILs, Presence of MHC I and/or II, neo-antigens, PD1/PD-L1 expression)

It’s time to work together…

CD…What ???
T-cells…what???
TH1, TH2, What???

Medical oncologist

CD3, CD4, CD5, CD8, CD10,
CD19, CD20, CD25, CD40,
CD45, CD59, …

Immunologist