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Istituto Europeo di Oncologia

1st conquer breast

Corso avanzato per il management di pazienti con tumore mammario

16,17,18 Novembre 2017
Padova

IOV - ISTITUTO ONCOLOGICO VENETO
Via Gattamelata, 64

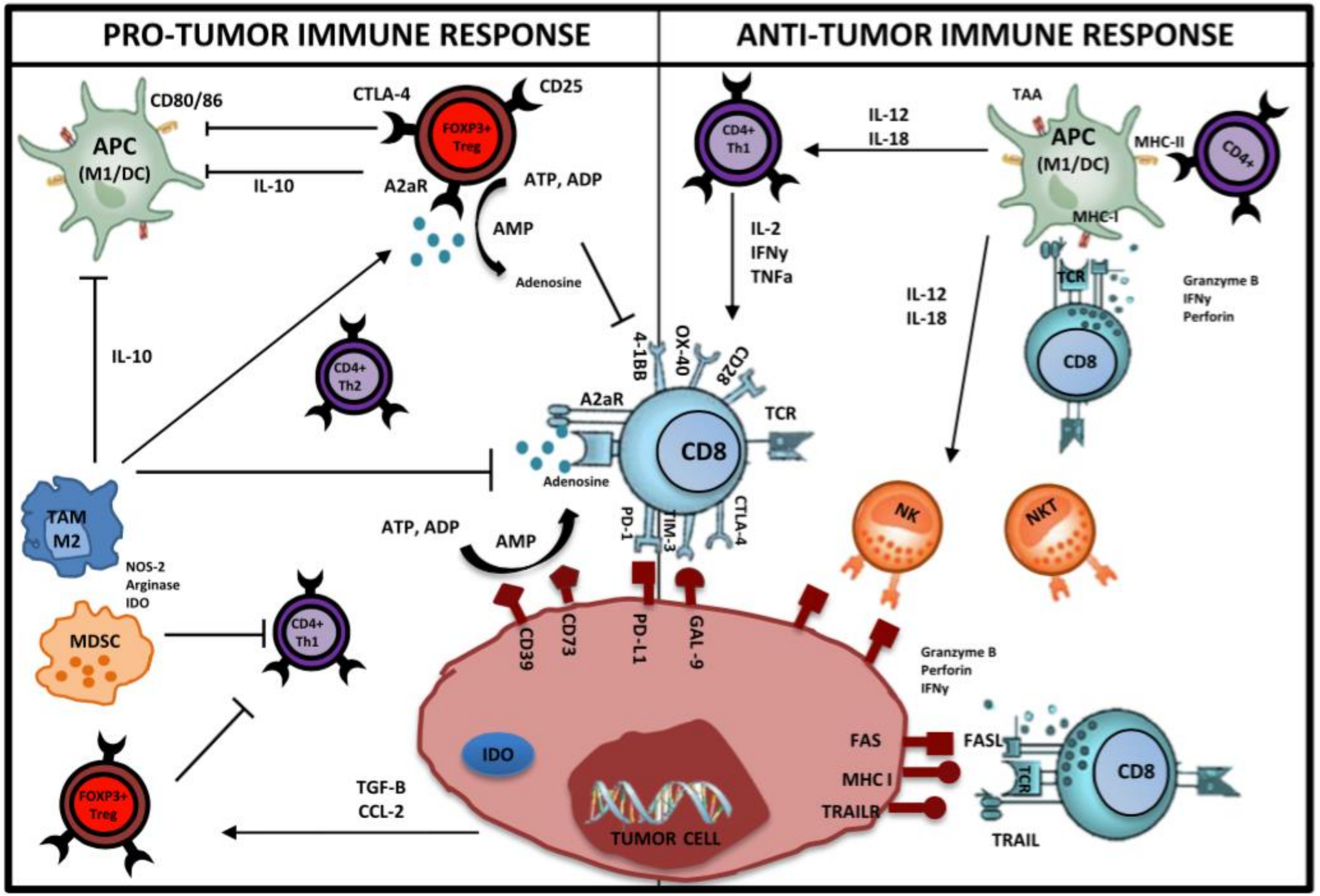
14,15,16 Settembre 2017
Milano

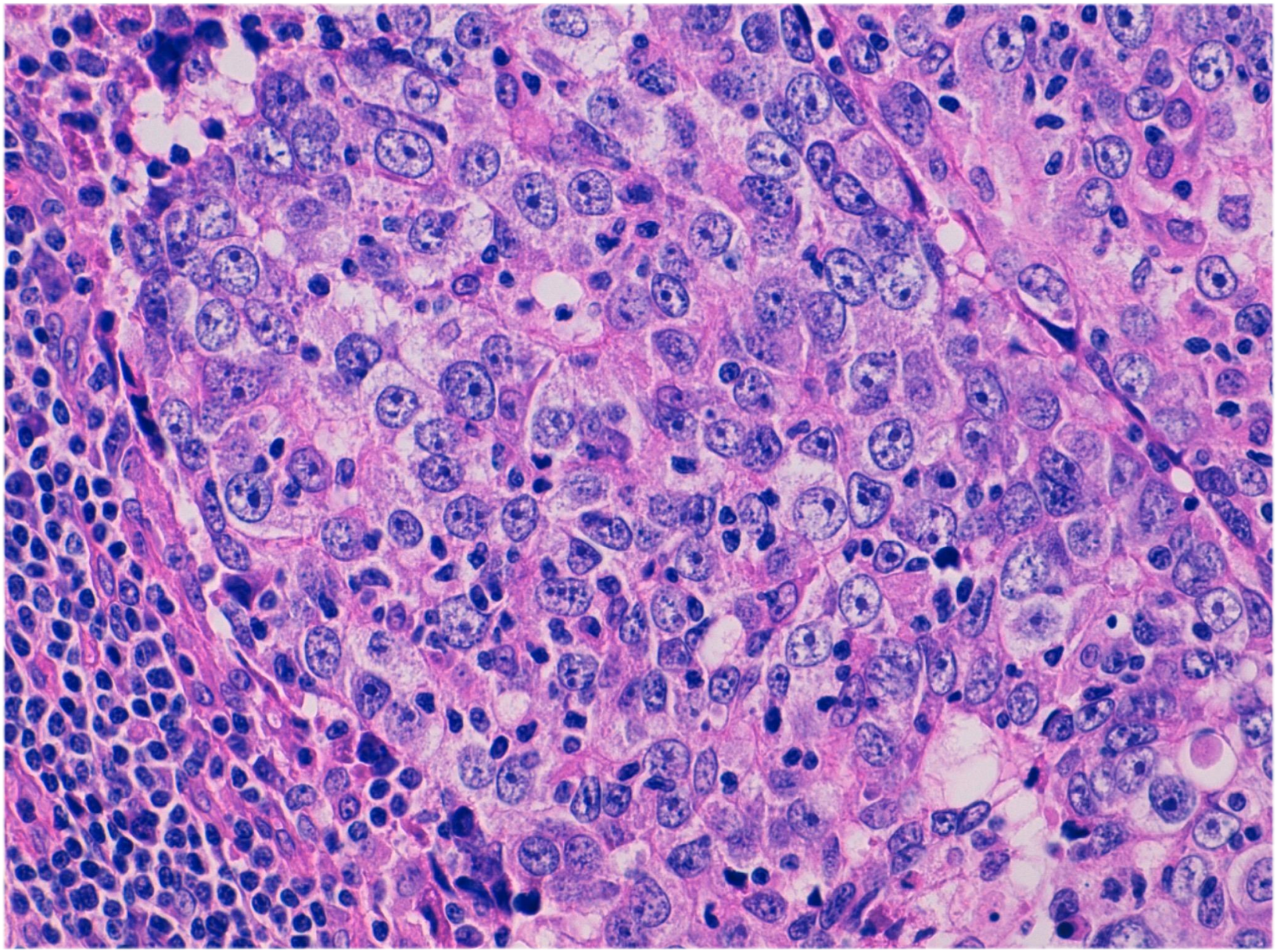
IEO - ISTITUTO EUROPEO DI ONCOLOGIA
Via Giuseppe Ripamonti, 435

Ruolo del sistema immune nel tumore mammario

Andrea Vingiani
Anatomia Patologica
IEO

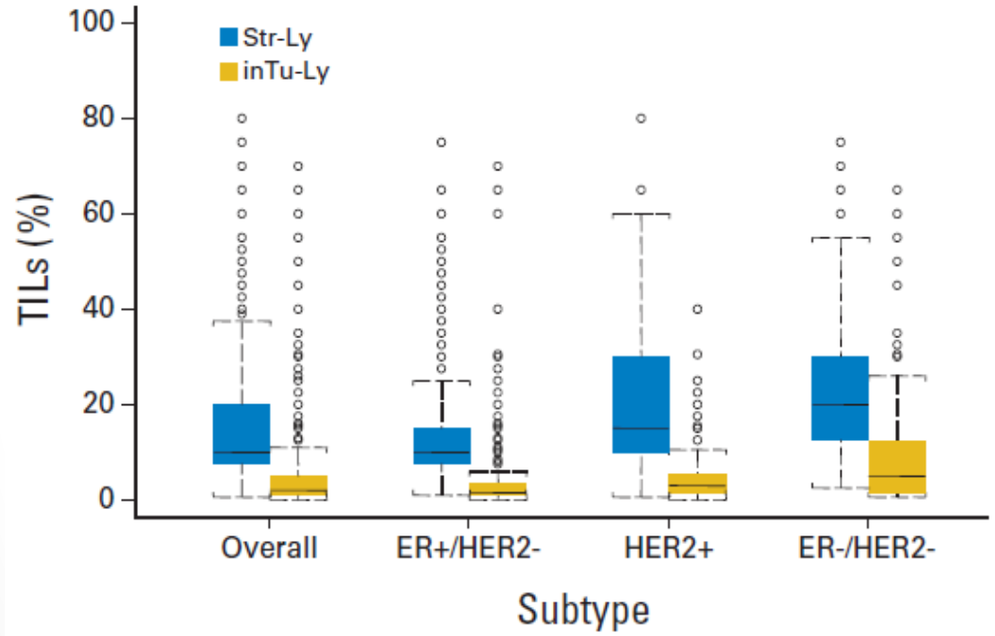
Cancer Immunoediting





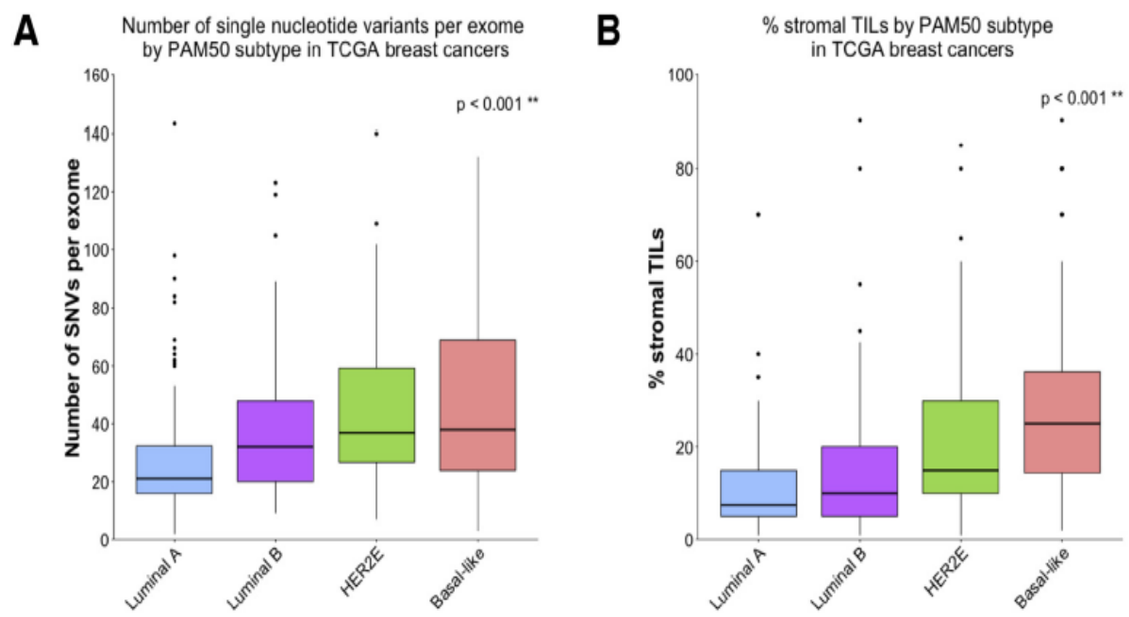
Prevalenza dei TILs nel carcinoma mammario

- Elevata incidenza di TILs in tumori con elevata proliferazione (Altomaa, Eur J Cancer,1992)
- Il carcinoma mammario triplo negativo ed HER2 positivo rappresentano i sottotipi più frequentemente associati ad infiltrato linfocitario



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, JCO, 2013



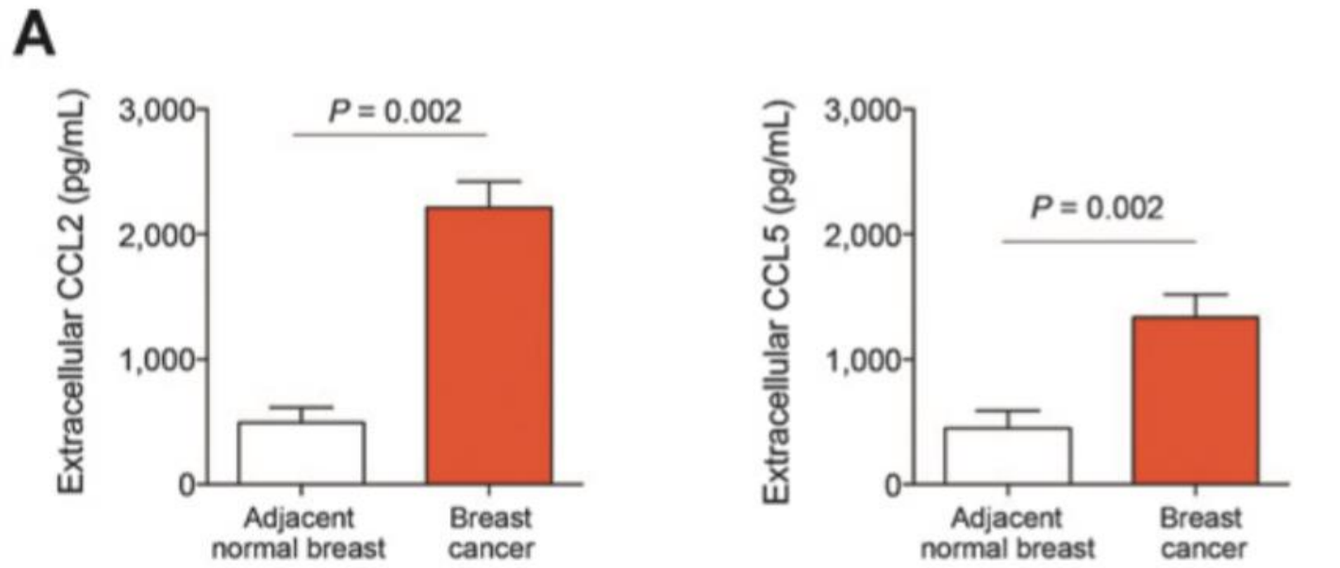
Luen, The Breast, 2016

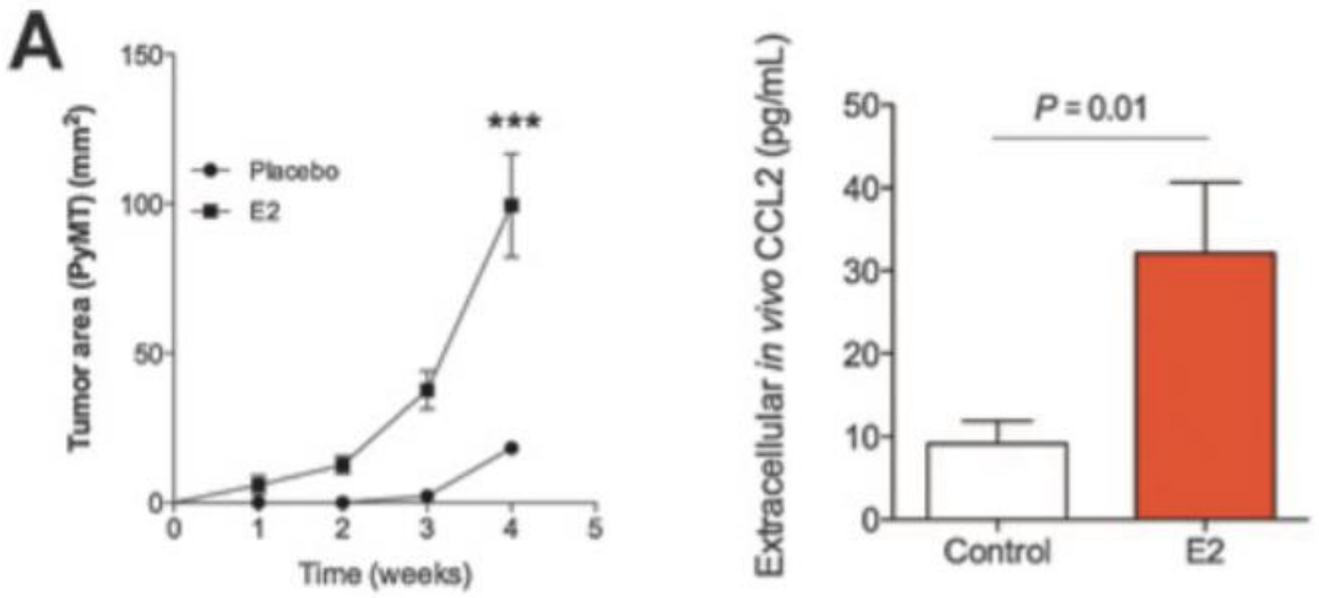
TILs nei sottotipi molecolari

Possibili spiegazioni della minore immunogenicità dei tumori luminali

- Tumori luminali albergano mediamente un numero inferiore di mutazioni rispetto ai HER2+ BC ed ai TNBC, e conseguentemente meno neoantigeni
- Velocità di crescita significativamente inferiore, con conseguente incremento della fase di immunoediting e selezione dei cloni "invisibili" al sistema immunitario
- Possibile attività immunosoppressiva esercitata dal pathway di ER

Estradiolo induce la produzione di chemochine che orientano la risposta macrofagica in senso M2





Svensson, Clin Cancer Res, 2015

Validità clinica: valore prognostico e predittivo in Trials adiuvanti

Table 3 | **Adjuvant trials in which TILs have been assessed**

Trial analysed	Trial type	Treatment	TILs assessment	Population	n	Recurrence end points
BIG 2-98 (REF. 18)	Adjuvant Prospective RCT	Doxorubicin Cyclophosphamide CMF Docetaxel	Stromal on H&E	ER+/HER2-	1,079	Not significant
				HER2+	297	Not significant
				TNBC	256	For each 10% increment of sTILs: DFS, HR = 0.84 (95% CI 0.74–0.98, *P* = 0.025)
FinHER[38]	Adjuvant Prospective RCT	Docetaxel Vinorelbine FEC Trastuzumab	Stromal on H&E	ER+/HER2-	591	Not significant
				HER2+	209	Not significant
				TNBC	134	For each 10% increment of sTILs: DDFS, HR = 0.79 (95% CI 0.64–0.98, *P* = 0.032)
E2197 and E1199 (REF. 39)	Adjuvant Prospective RCT	Doxorubicin Cyclophosphamide Docetaxel	Stromal on H&E	TNBC	481	For each 10% increment of sTILs: DFS, HR = 0.84 (95% CI 0.74–0.95, *P* = 0.005)
SEARCH, BCCA, NBCS, NEAT[19]	Prospective Observational RCT (NEAT)	Various, not standardised No trastuzumab	IHC for CD8 in stroma (sCD8) IHC for CD8 in tumour (iCD8)	ER+ (including HER2+)	8,775	Presence versus absence of iCD8: Breast cancer-specific survival, HR = 0.95 (95% CI 0.85–1.07, *P* = 0.43)
				ER-/HER2+ TNBC	3,591	Presence versus absence of sCD8: Breast cancer-specific survival, HR = 0.79 (95% CI 0.67–0.93, *P* = 0.004)
NeoALTTO[40]	Neoadjuvant Prospective RCT	Trastuzumab Lapatinib Paclitaxel FEC	Stromal on H&E	HER2+	387	3% decrease in rate of recurrence (event free survival) for every 1% increase in TILs *P* = 0.002

Trials overall include a total of 15,800 patients. BIG, Breast International Group; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; DDFS, distant disease-free survival; DFS, disease-free survival; ER, oestrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H&E, haematoxylin and eosin; HR, hazard ratio; IHC, immunohistochemistry; PR, progesterone receptor; RCT, randomized controlled trial; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte; TNBC, triple-negative breast cancer.

Savas, Nat Rev Clin Oncol, 2016

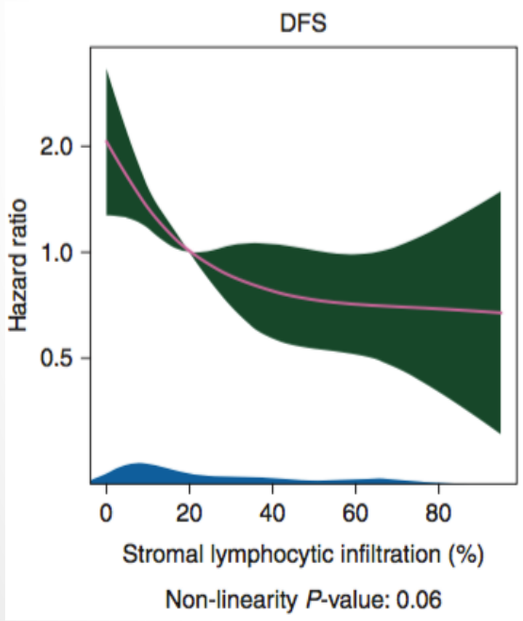
original articles

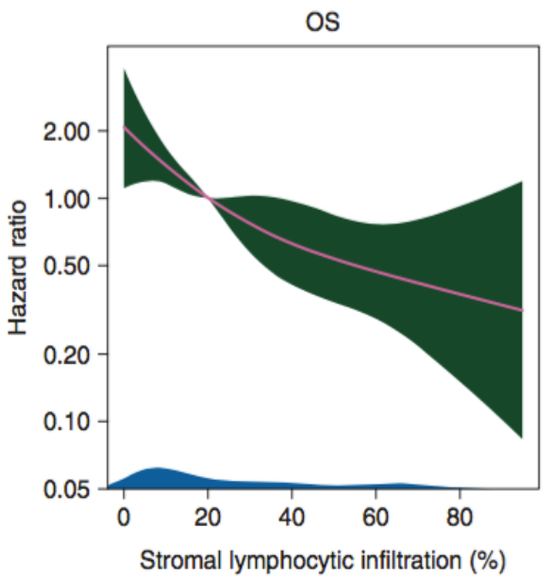
Annals of Oncology 27: 249–256, 2016
doi:10.1093/annonc/mdv571
Published online 23 November 2015

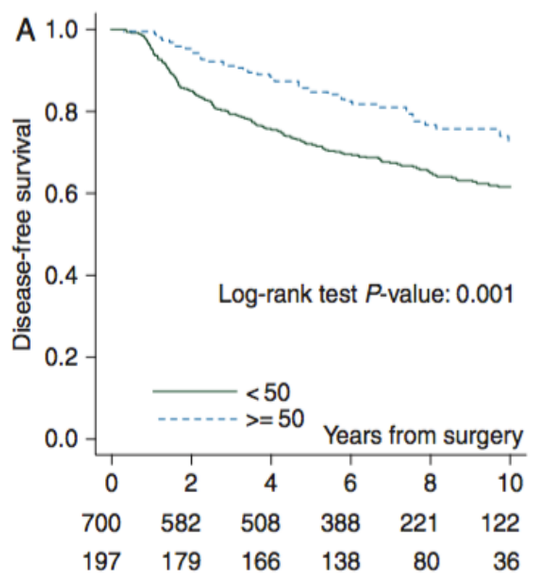
Clinical validity of tumor-infiltrating lymphocytes analysis in patients with triple-negative breast cancer

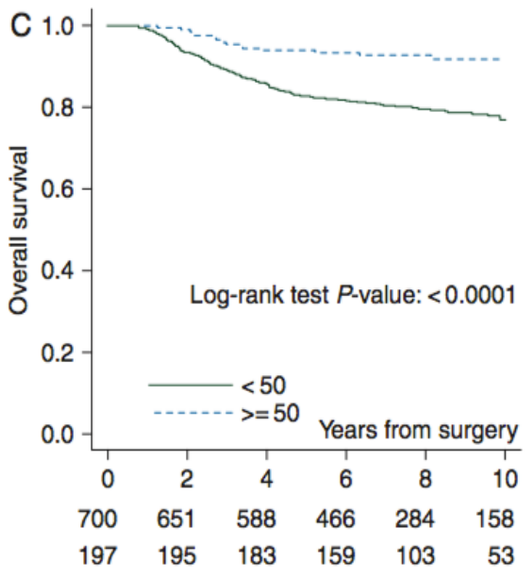
G. Pruneri[1,6,†*], A. Vingiani[2,6,†], V. Bagnardi[3,7], N. Rotmensz[3], A. De Rose[2], A. Palazzo[4], A. M. Colleoni[4], A. Goldhirsch[5,8] & G. Viale[2,6]

[1]Department of Pathology, Biobank for Translational Medicine Unit; Divisions of [2]Pathology; [3]Epidemiology and Biostatistics; [4]Medical Senology; [5]Program of Breast Health (Senology), European Institute of Oncology, Milan; [6]University of Milan, School of Medicine, Milan; [7]Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy; [8]International Breast Cancer Study Group, Bern, Switzerland

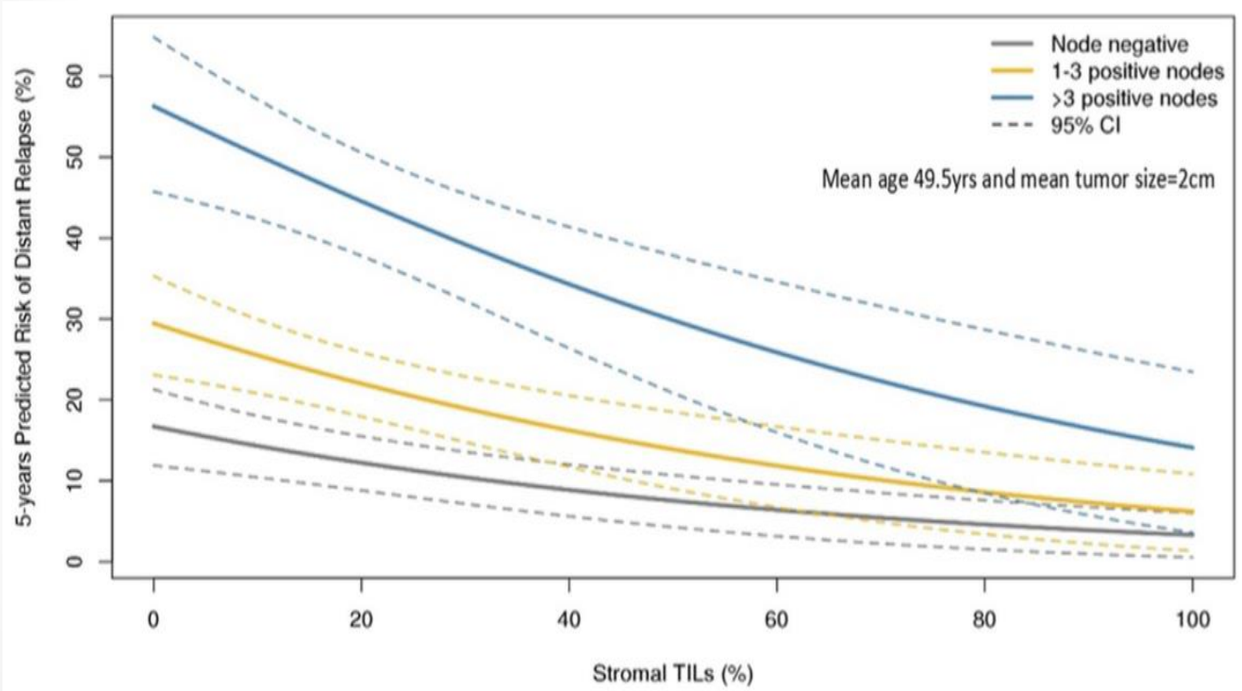


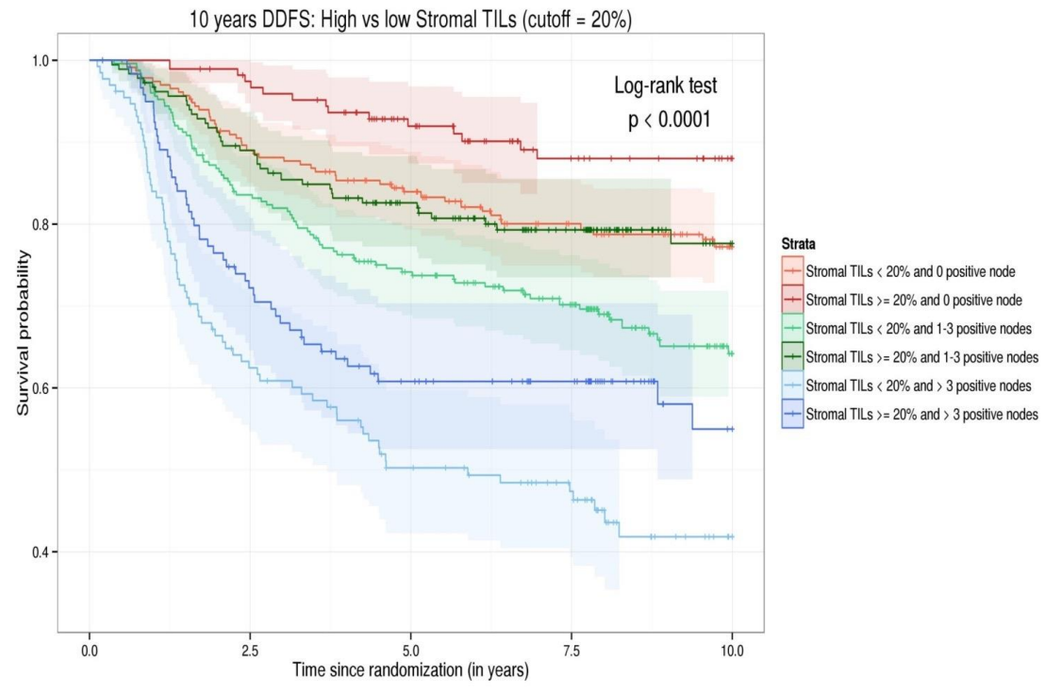






Model to predict risk of distant recurrence at 5 years (%) by tumor infiltrating lymphocytes (TILs) and nodal status in TNBC



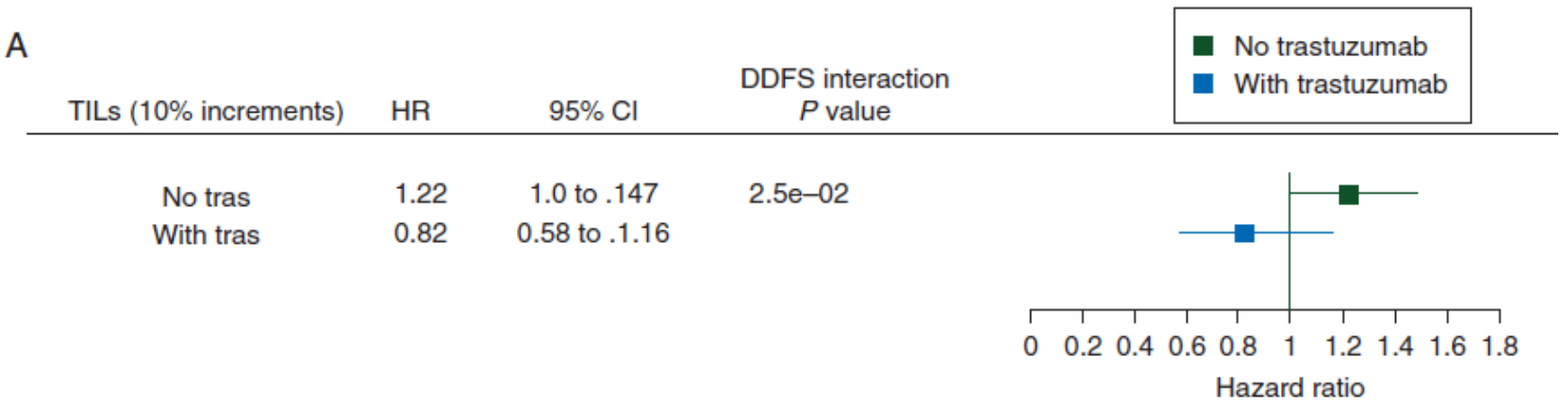


Loi, San Antonio BC Symposium, 2015

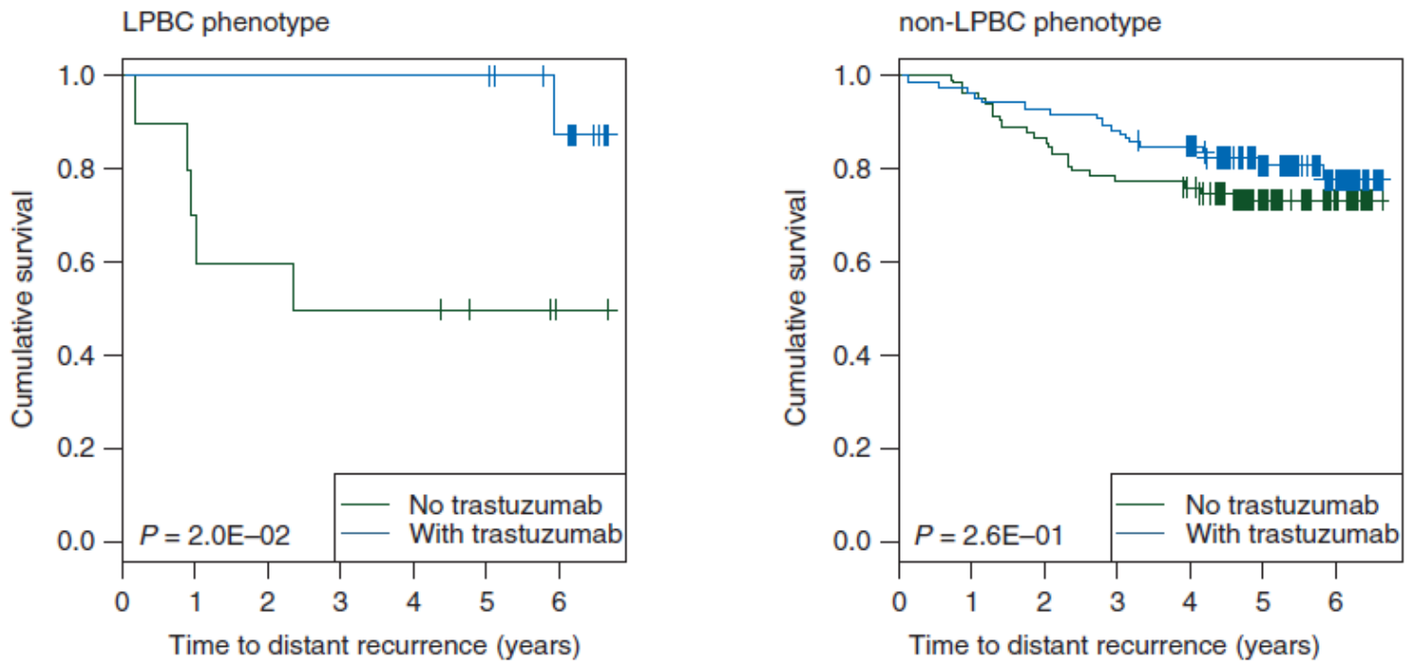
Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial

S. Loi[1,2*], S. Michiels[1,3], R. Salgado[4], N. Sirtaine[4], V. Jose[1], D. Fumagalli[1], P.-L. Kellokumpu-Lehtinen[5], P. Bono[6], V. Kataja[7], C. Desmedt[1], M. J. Piccart[8], S. Loibl[9], C. Denkert[10], M. J. Smyth[11], H. Joensuu[6] & C. Sotiriou[1]

A



B



Annals of Oncology

Annals of Oncology 25: 1544–1550, 2014
doi:10.1093/annonc/mdu112
Published online 7 March 2014

Validità clinica: TILs ed associazione alla risposta alla chemioterapia neoadiuvante

Table 4 | **Neoadjuvant trials that have assessed TILs**

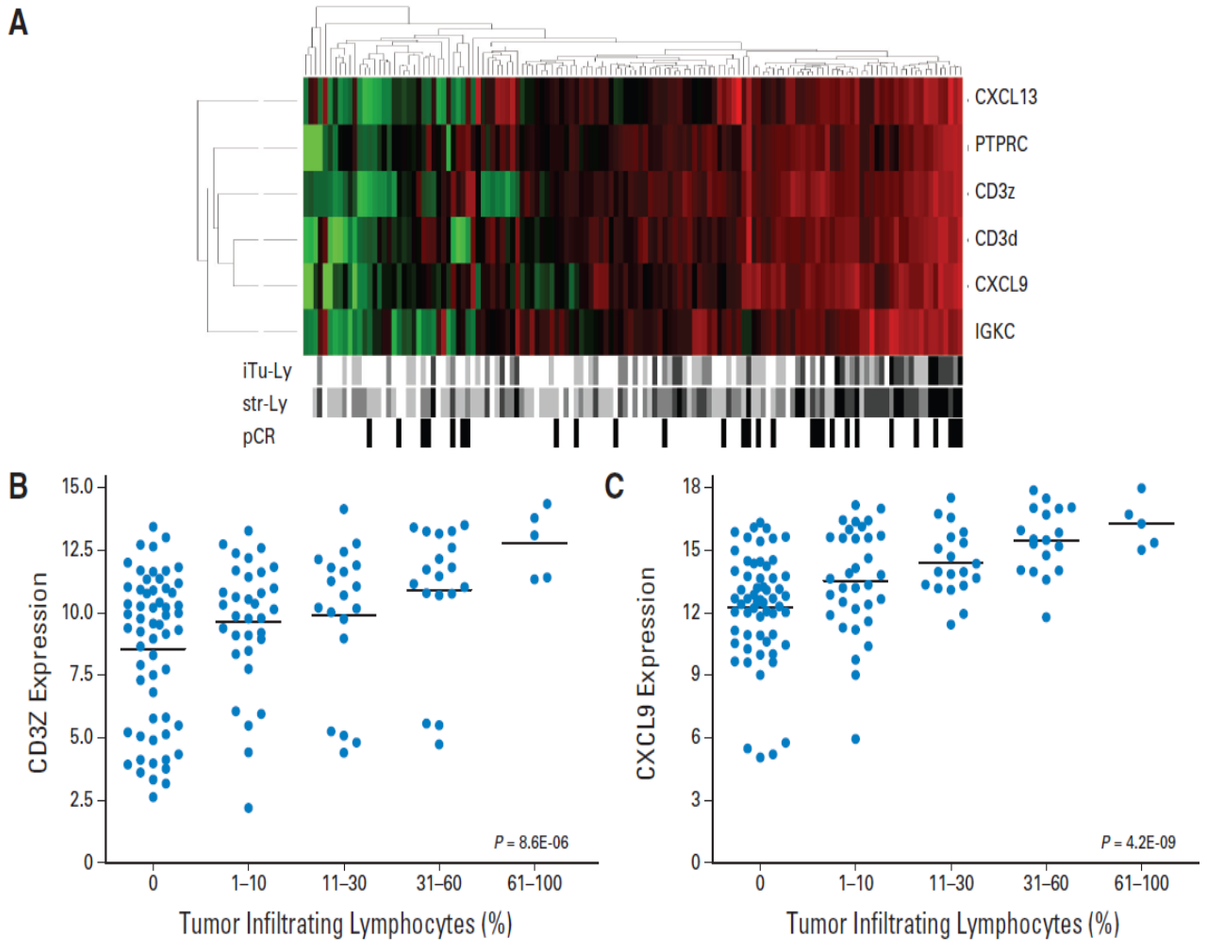
Trial and treatments	Subtype	*n*	TILs assessment	Outcome	Multivariate analysis
GeparDuo[24] Doxorubicin Docetaxel Cyclophosphamide	All	218	sTILs and iTILs on H&E	>60% sTILs: pCR 41.7% <60% sTILS: pCR 9.3%	OR 1.38 of pCR per 10% iTILs (95% CI 1.08–1.78, $P = 0.012$)
GeparTrio[24] Doxorubicin Docetaxel Cyclophosphamide Vinorelbine Capecitabine	All	840	sTILs and iTILs on H&E	>60% sTILs: pCR 40% <60% sTILs: pCR 13.9%	OR 1.21 of pCR per 10% iTILs (95% CI 1.08–1.35, $P = 0.001$)
GeparQuattro[46] Epirubicin Cyclophosphamide Docetaxel Capecitabine Trastuzumab	HER2$^+$	156	sTILs on H&E	>50% sTILs: pCR 47.4% <50% sTILs: pCR 31.7%	OR 1.16 of pCR per 10% sTILs (95% CI 1.01–1.32, $P = 0.038$)
GeparQuinto[43] Epirubicin Cyclophosphamide Taxane Everolimus	ER$^+$ and TNBC	313	sTILs and iTILs on H&E	>60% sTILs: pCR 36.6% <60% sTILs: pCR 14.3% ($P < 0.001$)	OR 1.2 of pCR per 10% sTILs (95% CI 1.0–1.3, $P = 0.01$)
GeparSixto[31] Paclitaxel Liposomal Doxorubicin Carboplatin Bevacizumab Trastuzumab	HER2$^+$ and TNBC	580	sTILs and iTILs on H&E	>60% sTILs: pCR 59.9% <60% sTILs: pCR 33.8% ($P < 0.001$) Significant test for interaction between increased TILs and response to carboplatin therapy	OR 1.2 of pCR per 10% sTILs (95% CI 1.11–1.29, $P < 0.001$) OR 2.66 of pCR for >60% versus <60% sTILs (95% CI 1.76–4.02, $P < 0.001$)
EORTC 10994 and BIG 00-01 (REF. 44) FEC Docetaxel	ER$^-$	111	gTILs	High gTILs: pCR 74.2% Low gTILs: pCR 31.3%	OR 6.42 of pCR for high versus low gTILs (95% CI 2.08–19.83, $P = 0.001$)
CHER-LOB[50] Trastuzumab Paclitaxel FEC	HER2$^+$	105	sTILs and iTILs on H&E	>60% sTILs: pCR 59% <60% sTILs: pCR 27% ($P < 0.015$)	Not reported

Trials overall include a total of 2,323 patients. ER, oestrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; gTIL, gene-expression surrogate TIL; H&E, haematoxylin and eosin; iTIL, intratumoural TIL; OR, odds ratio; pCR, pathological complete response; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte.

Savas, Nat Rev Clin Oncol, 2016

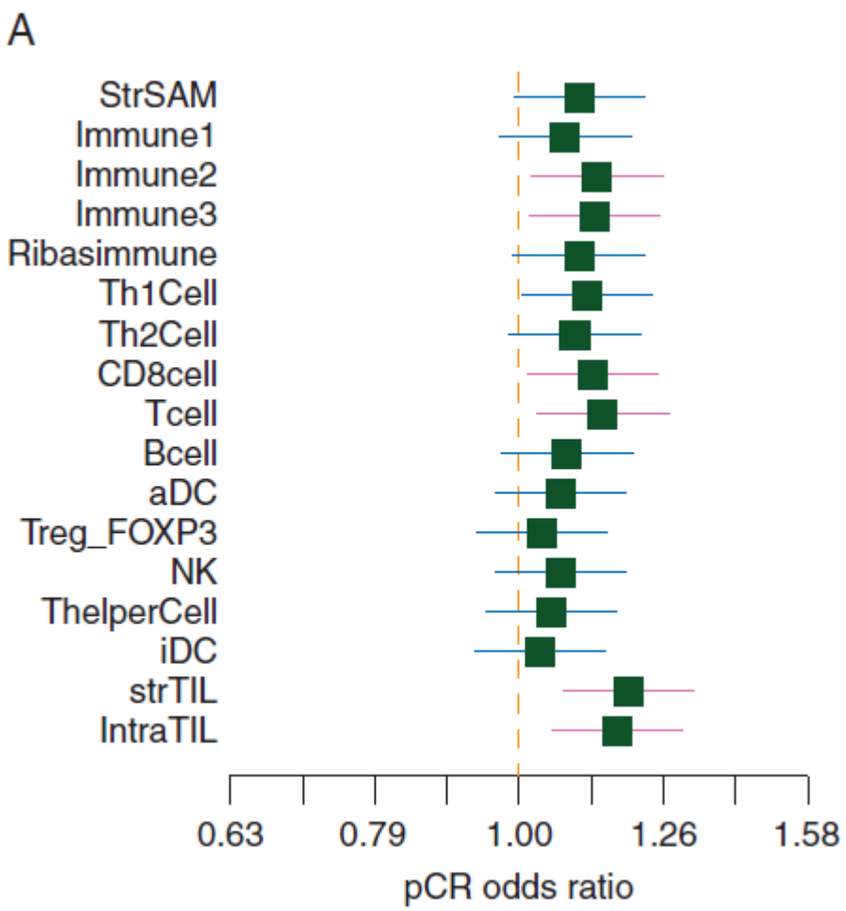
TILs, sottopopolazioni linfocitarie e gene signatures

- L'entità dell'infiltrato linfocitario tumorale correla con la presenza delle diverse sottopopolazioni linfocitarie e dati di espressione genica
- Ad oggi, non ci sono evidenze inequivoche dell'esistenza di sottopopolazioni linfocitarie o marcatori molecolari prognosticamente e predittivamente superiore ai TILs

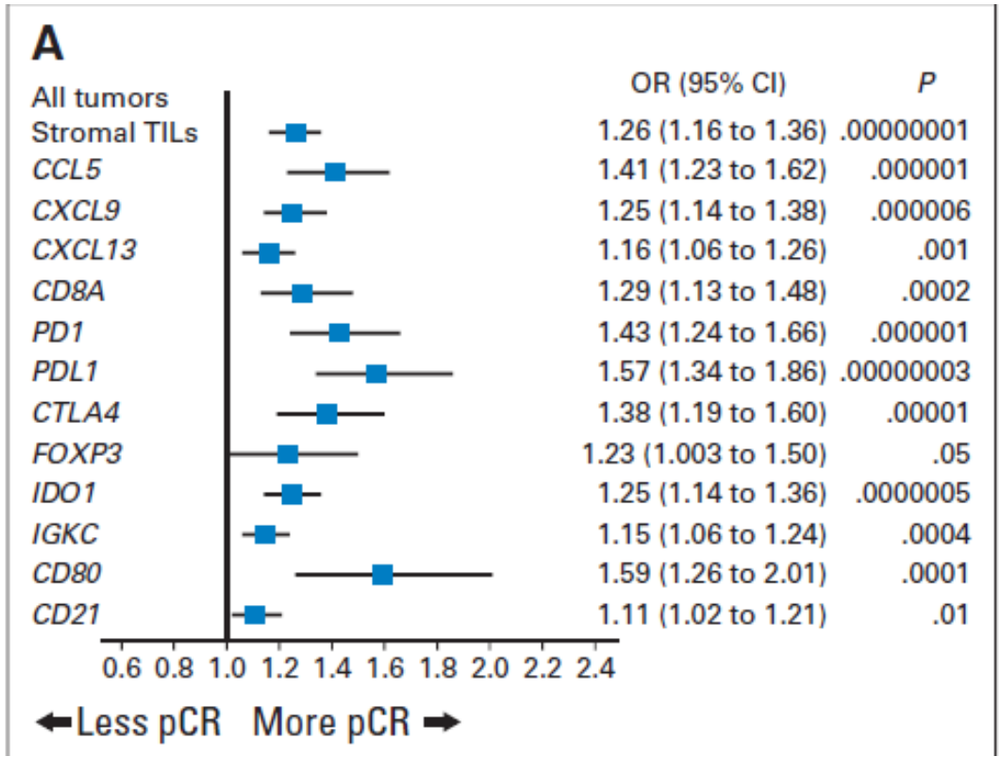


Denkert, JCO, 2010

TILs, sottopopolazioni linfocitarie e gene signatures

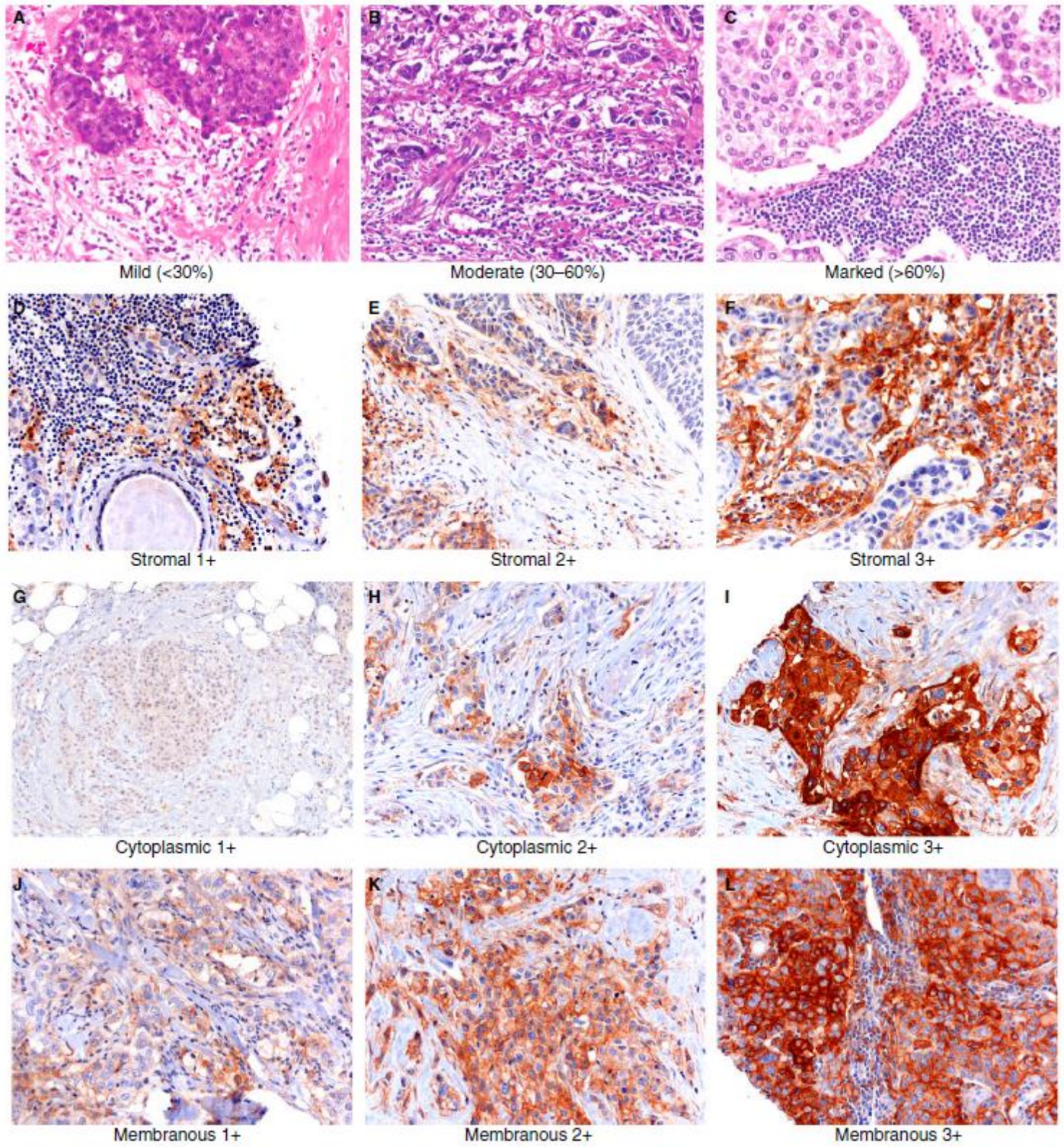


Dieci, Annals Oncol, 2016



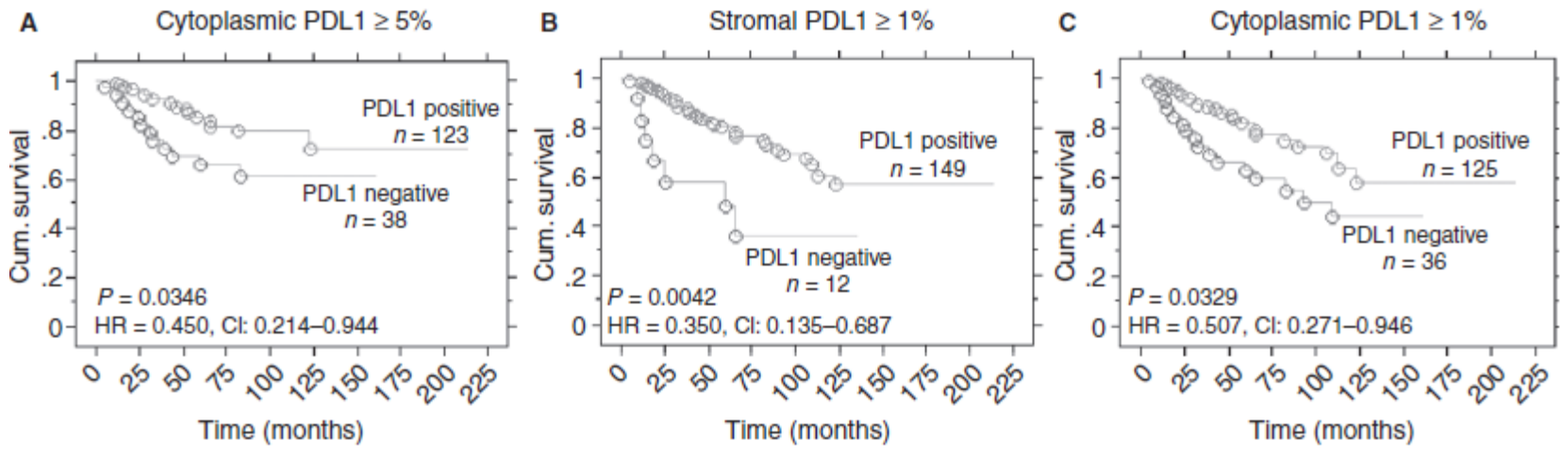
Denkert, JCO, 2016

PDL1 nel carcinoma mammario



Beckers, Histopathology, 2016

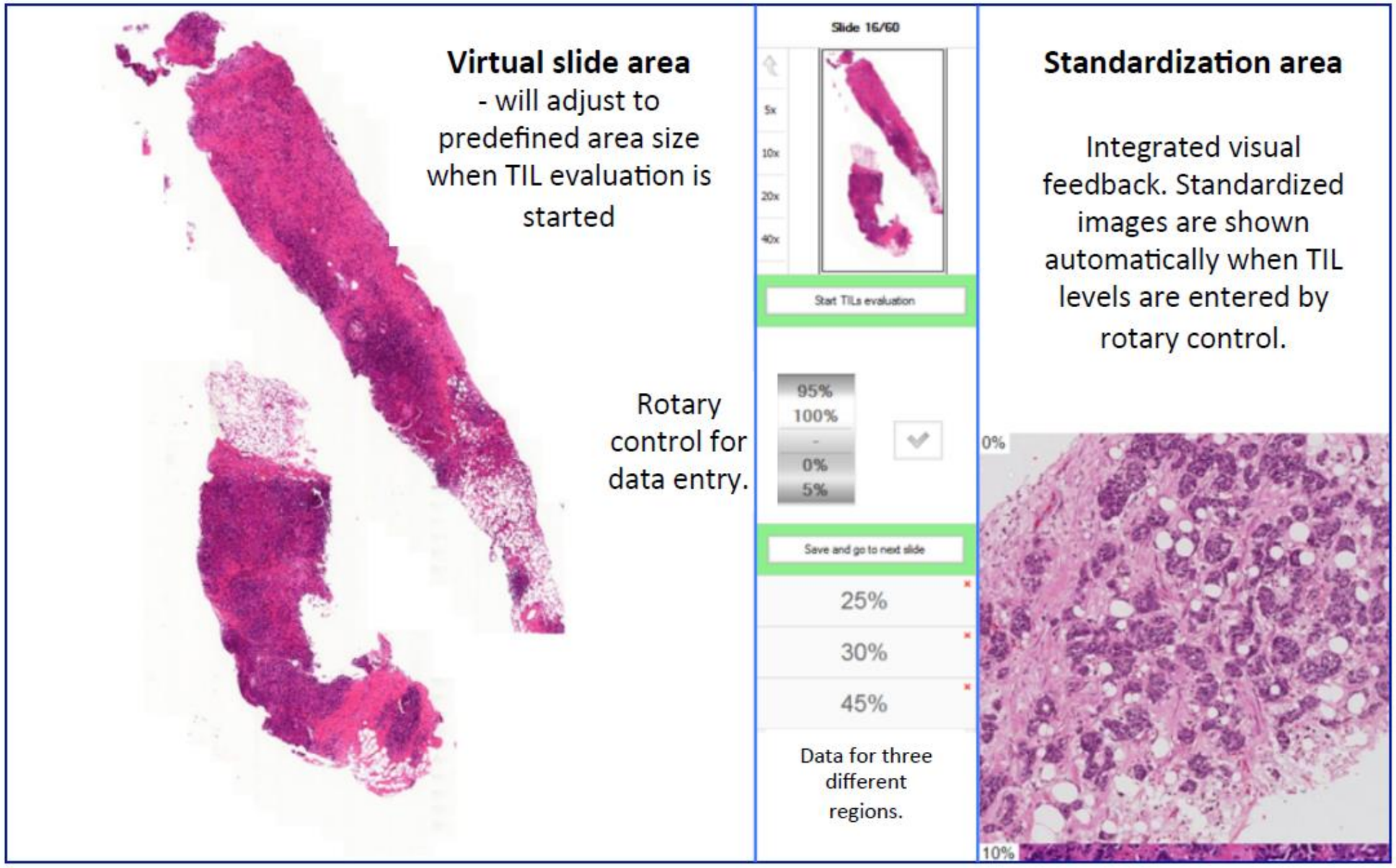
PDL1 expression	Membranous tumoral	Cytoplasmic tumoral	Stromal immune
Absent (0)	36%	22%	7%
Low (1 +)	41%	62%	50%
Intermediate (2 +)	14%	14%	40%
Strong (3 +)	9%	2%	3%
PDL1 expression ≥1%	64%	80%	93%
PDL1 expression ≥5%	60%	77%	93%



Variable	Hazard ratio (CI 95%)	*P*-value
Step 1 (clinicopathological features)		
Size >20 mm	1.364 (0.628–2.964)	0.1364
TIL score ≥2	0.484 (0.187–1.253)	0.1348
Stromal PDL1 expression ≥5%	0.492 (0.190–1.275)	0.1445
LVI	1.932 (0.949–3.935)	0.0694
Final step: resolved model		
LVI	2.236 (1.210–4.133)	0.01

Beckers, Histopathology, 2016

Validità analitica: TILs Working Group ring study



Annals of Oncology 26: 259–271, 2015
doi:10.1093/annonc/mdu450
Published online 11 September 2014

The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014

R. Salgado[1,2,†], C. Denkert[3,†], S. Demaria[4,†], N. Sirtaine[5], F. Klauschen[3], G. Pruneri[6], S. Wienert[3], G. Van den Eynden[7], F. L. Baehner[8,9], F. Penault-Llorca[10], E. A. Perez[11], E. A. Thompson[12], W. F. Symmans[13], A. L. Richardson[14,15], J. Brock[15,16], C. Criscitiello[17], H. Bailey[8], M. Ignatiadis[18], G. Floris[19], J. Sparano[20], Z. Kos[21], T. Nielsen[22], D. L. Rimm[23], K. H. Allison[24], J. S. Reis-Filho[25], S. Loibl[26], C. Sotiriou[18], G. Viale[27], S. Badve[28], S. Adams[4,†], K. Willard-Gallo[29,†] & S. Loi[30*,†]

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

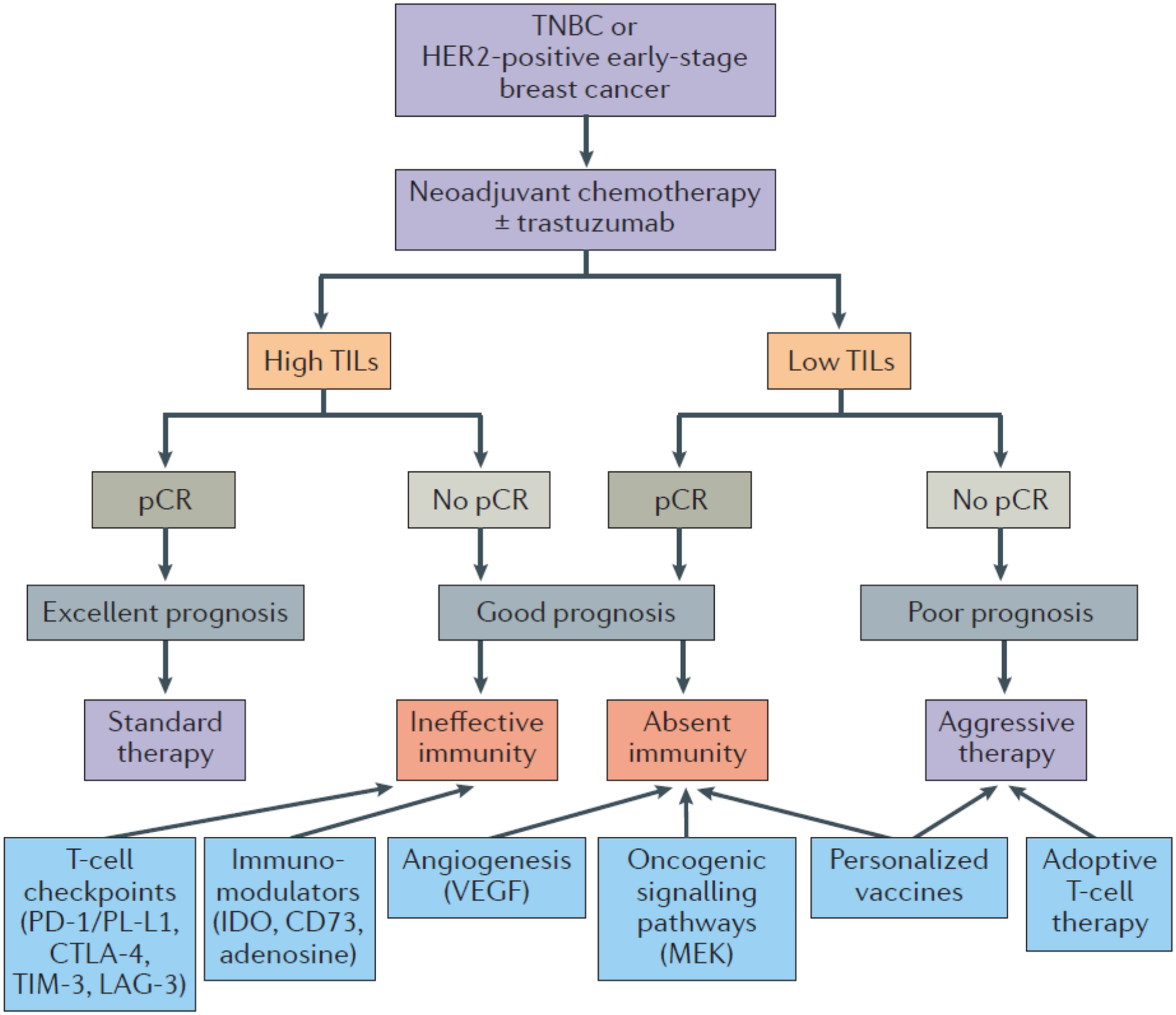
Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Cathy van Poznak, Robert C. Bast, and Daniel F. Hayes

- If a patient has ER/PgR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use TILs lymphocytes to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use TILs to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: strong.

TILs come biomarcatore: direzioni future

- Identificazione di sottopopolazioni di pazienti affette da tumori HER2+ e TNBC ad ottima prognosi
    - Treatment de-escalation
    - Design di nuovi trials clinici, sia nel setting adiuvante che neoadiuvante
- Possibile biomarker di risposta ai Checkpoint-inhibitors



Savas, Nat Rev Clin Oncol, 2016

TILs come biomarcatore: direzioni futureIdentificazione di sottopopolazioni di pazienti affette da tumori HER2+ e TNBC ad ottima prognosi

- Treatment de-escalation
- Design di nuovi trials clinici, sia nel setting adiuvante che neoadiuvante

- Possibile biomarker di risposta ai Checkpoint-inhibitors

Sommario dei trials clinici anti PD1/PDL1 nel BC metastatico

Trial	Phase	Study population	Participants	Study compound	PD-L1 antibody	PD-L1 status	ORR
JAVELIN[78]	Phase Ib	All subtypes	168	Avelumab	Unknown	Unselected	4.8%
KEYNOTE-012[79]	Phase I	TNBC	32	Pembrolizumab	Merck 22C3 antibody	PD-L1 $\geq$ 1% of tumour cells or any staining in the stroma	18.5%
NCT01375842[80]	Phase I	TNBC	21	Atezolizumab/ MPDL3280A	Ventana SP142 antibody	PD-L1 $\geq$ 5% of infiltrating immune cells[a]	19.0%
KEYNOTE-028[81]	Phase Ib	ER-positive/ HER2-negative	25	Pembrolizumab	Merck 22C3 antibody	PD-L1 $\geq$ 1% of tumour cells or any staining in the stroma	14.0%
NCT01633970[83]	Phase Ib	TNBC	32	Atezolizumab + nab-paclitaxel	Ventana SP142 antibody	Unselected	42.0%[b]

Grazie per l’attenzione

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