The role of tumor infiltrating lymphocytes in immunotherapy

Federico Rojo

Lymphocytic infiltration in breast cancer increases postoperative life

LIFE EXPECTANCY FOLLOWING RADICAL AMPUTATION FOR CARCINOMA OF THE BREAST: A CLINICAL AND PATHOLOGIC STUDY OF 218 CASES*

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The study of these cases was undertaken for the purpose of determining, as nearly as possible, the life expectancy of patients on whom primary radical amputations of the breast have been performed for carcinoma. The factors which seem important in determining the expectancy of life were carefully studied from a clinical and a pathologic standpoint in a series of 218 patients with carcinoma of the breast operated on in the Mayo Clinic. The conclusions reached from the clinical findings and the findings at operation are discussed first, the microscopic picture of the tumors removed and the bearing which these different pictures seem to have on the prognosis are next considered.

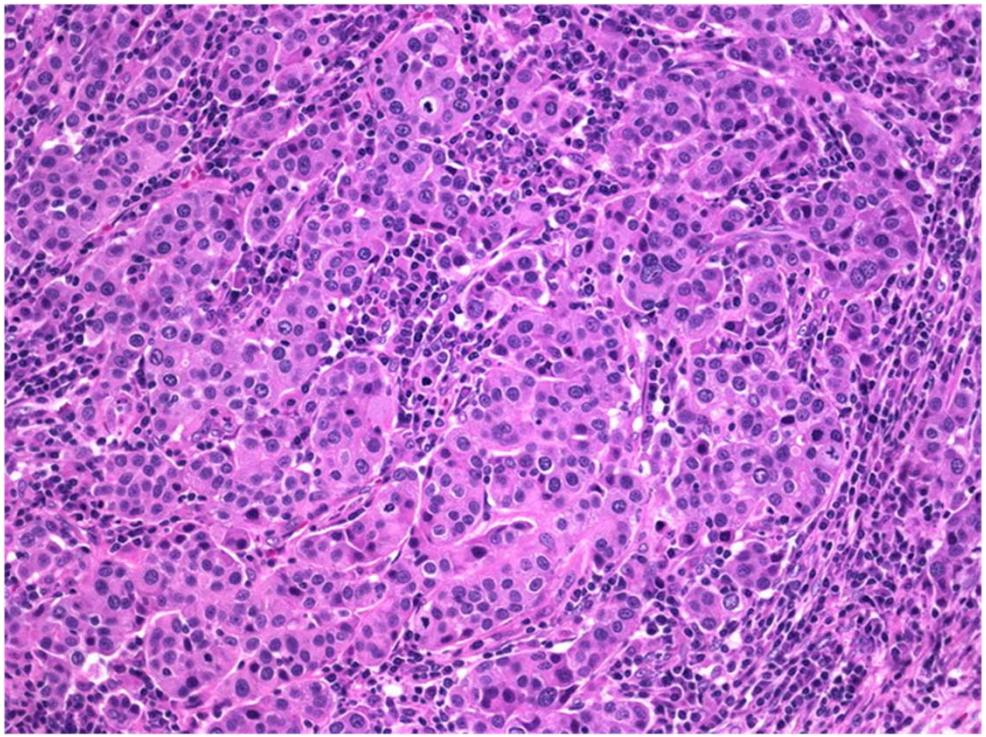
It is impossible to foretell the duration of life of all patients with carcinoma of the breast, because the degree of malignancy varies widely, and persons react differently to the disease. For instance, certain types of carcinoma of the breast cause death within a few months after they are recognized, and other types metastasize slowly and do not prove fatal for many years; the latter, however, are rare and constitute only a small percentage of carcinomas of the breast. In the majority of these it is possible to make a fairly accurate prognosis with regard to the duration of life following operation.

It was gratifying to find, from our statistics, that the results obtained from early operations for carcinoma of the breast are probably better than those obtained in operating for any other type of malignant growths, with the exception of basal-cell epitheliomas and epitheliomas of the lip. Patients who apply for treatment may be classed in three groups:

Group 1.—Patients with inoperable growths; growths firmly fixed to the chest-wall; extensive ulcerating growths with metastatic skin nodules; fixed masses in the axilla; extensive involvement of the axillary and supraclavicular glands, or internal metastasis. Operation is of no avail and is probably harmful.

Group 2.—Patients who have removable growths, but in whom, because of the extent of the growth, or the glandular involvement, a cure cannot be expected by operation. Operation is often performed from an humanitarian

* Presented before the Southern Surgical Association, December, 1920.



11. The average length of postoperative life of the patients with lymphocytic infiltration, hyalinization, and fibrosis was 37.8 per cent. greater than the average length of postoperative life of the ninety-one patients as a group.

12. The average length of postoperative life of patients without lymphocytic infiltration, hyalinization, and fibrosis was 42 per cent. less than the average length of postoperative life of patients with lymphocytic infiltration, hyalinization, and fibrosis.

Lymphocytic-predominant phenotype is in 20-28% of breast cancers and correlates with outcome

Eur J Cancer. 1992;28A(4-5):859-64.

Lymphocyte infiltrates as a prognostic variable in female breast cancer.

Aaltomaa S[1], Lipponen P, Eskelinen M, Kosma VM, Marin S, Alhava E, Syrjänen K.

Abstract

The predictive value of lymphocyte infiltrates (LI) was studied in 489 patients with breast cancer followed-up for over 10 years. LI were positively correlated to axillary lymph-node status, tumour diameter and histological and morphometric variables (P less than 0.001). In a multivariate analysis LI were independently related to axillary lymph-node status. LI predicted recurrence-free survival (RFS) in rapidly proliferating tumours (P = 0.0269). LI predicted RFS (P = 0.08) and breast cancer related survival (BS) (P = 0.0164) in rapidly proliferating, axillary lymph-node negative tumours. In a multivariate analysis LI independently predicted BS (P = 0.08) in rapidly proliferating tumours. LI independently predicted BS in rapidly (P = 0.025) and slowly (P = 0.09) proliferating, axillary lymph-node negative tumours. If the tumours were not categorised according to proliferation rate, LI and outcome were not significantly related. The results clearly confirm the presence of efficient immunological antitumour defence mechanisms in human breast cancer. Consequently tumour-host interactions are subject to further studies particularly in axillary lymph-node negative breast cancer.

PMID: 1524909 [PubMed - indexed for MEDLINE]

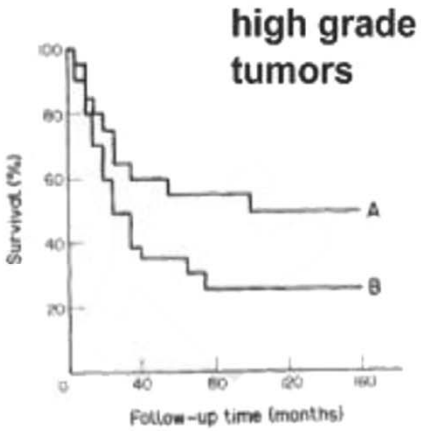


Fig. 2. The RFS of patients with *M/V* index > 15/mm² categorised according to LI ($\chi^2 = 4.9$; $P = 0.0269$). Curve A: moderate or dense LI, $n = 27$; Curve B: weak or absent LI, $n = 192$.

Outline

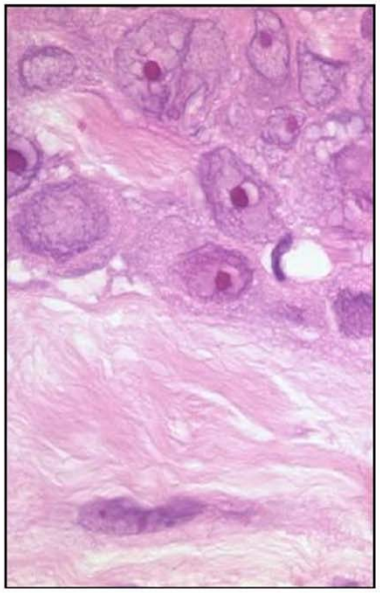
1. Clinical importance of TILs in cancer

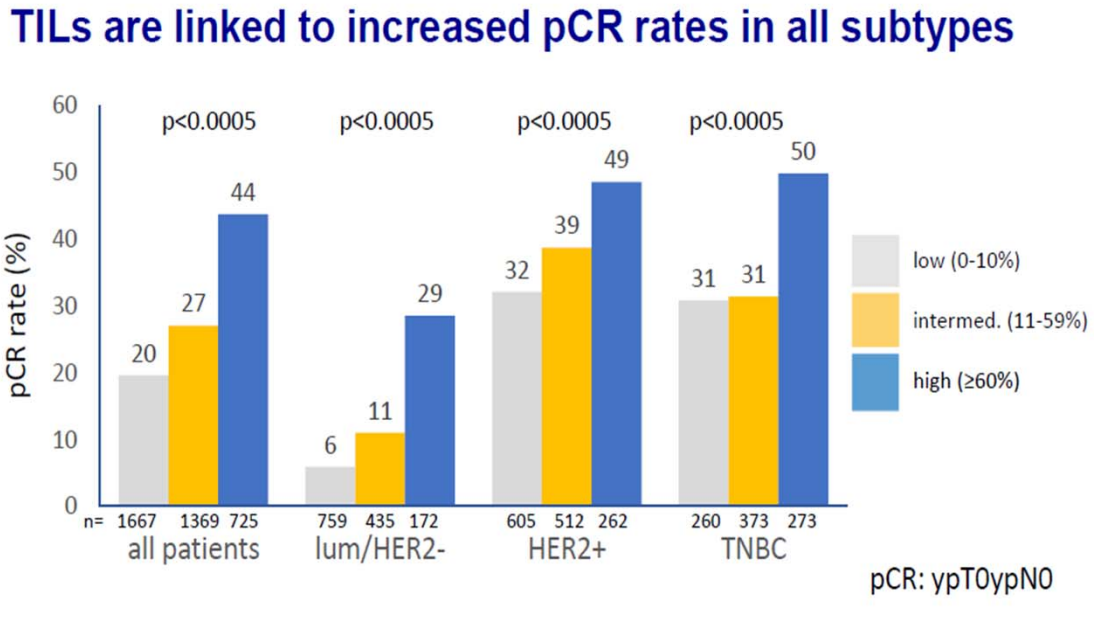
2. Immune-inflammed cancer phenotype and benefit to immunotherapy

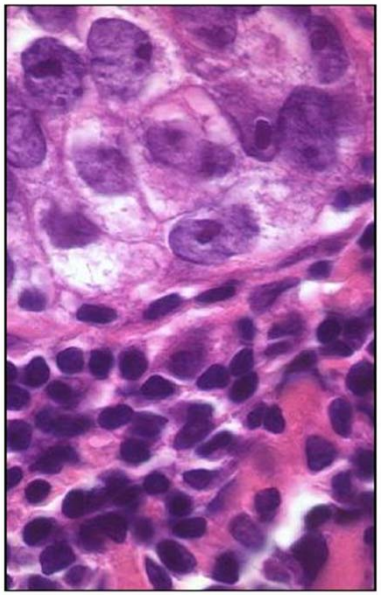
3. Assesing TILs in practice: recommendations and reproducibility

TILs as predictive and prognostic biomarker in breast cancer

Metaanalysis of 3,771 patients from 6 neoadjuvant trials





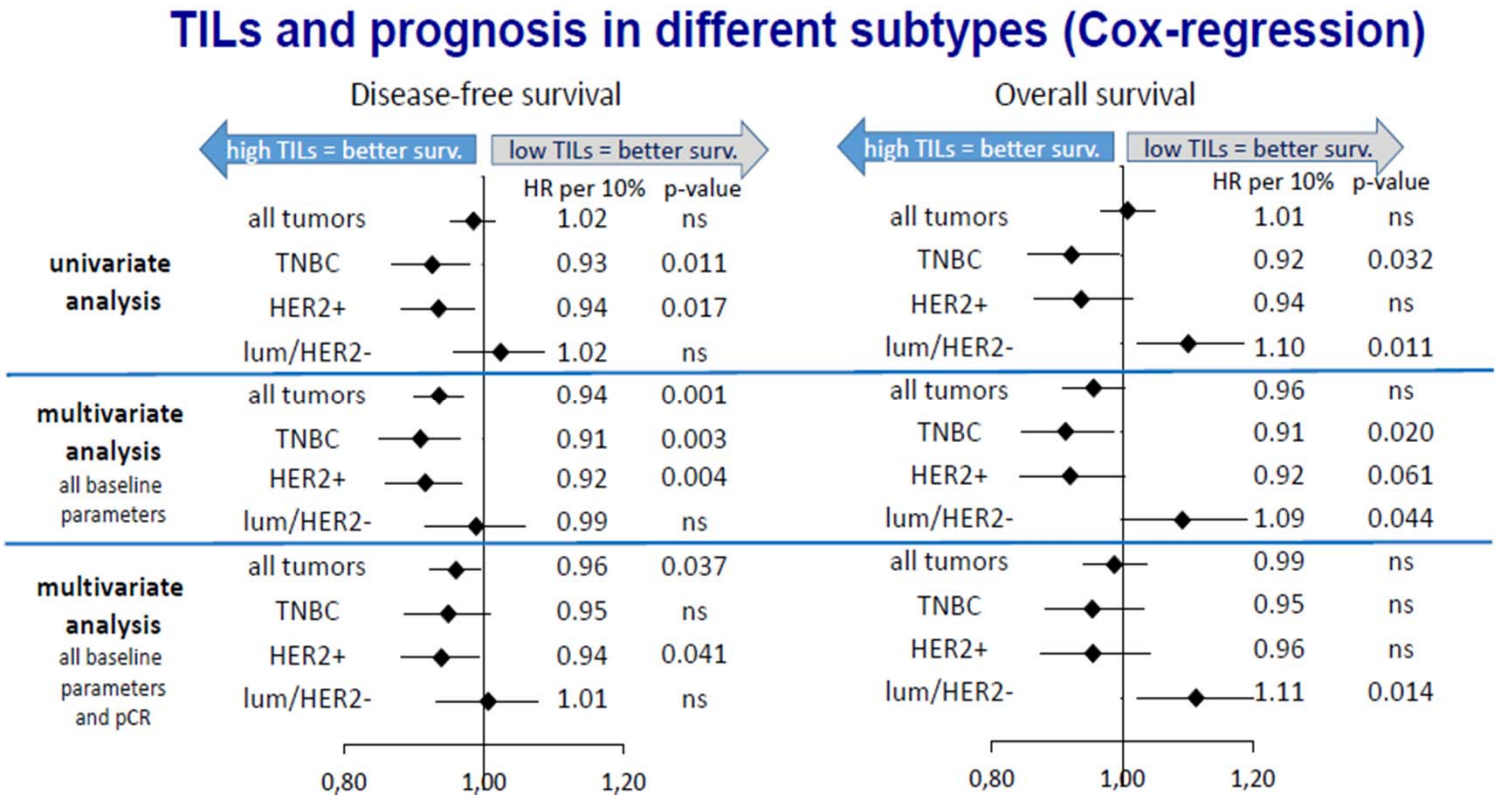


Lymphocyte predominant breast cancer (LPBC)

Denkert, C et al. SABCS 2016

TILs as predictive and prognostic biomarker in breast cancer

Metaanalysis of 3,771 patients from 6 neoadjuvant trials



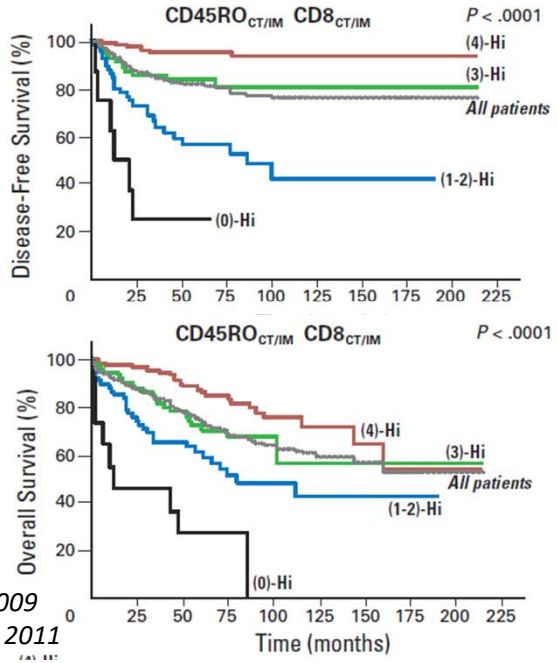
Denkert, C et al. SABCS 2016

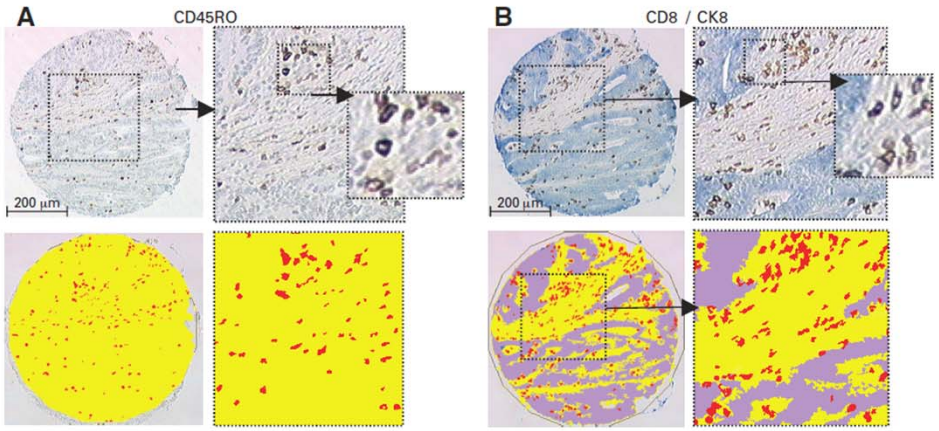
Association of immunoscore with prognosis in colorectal cancer

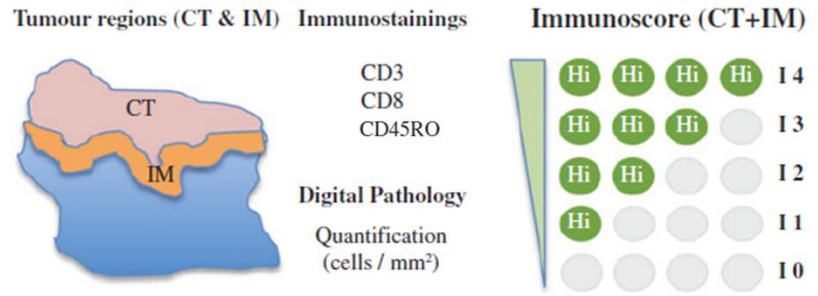
Article in Science · October 2006

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[1*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]





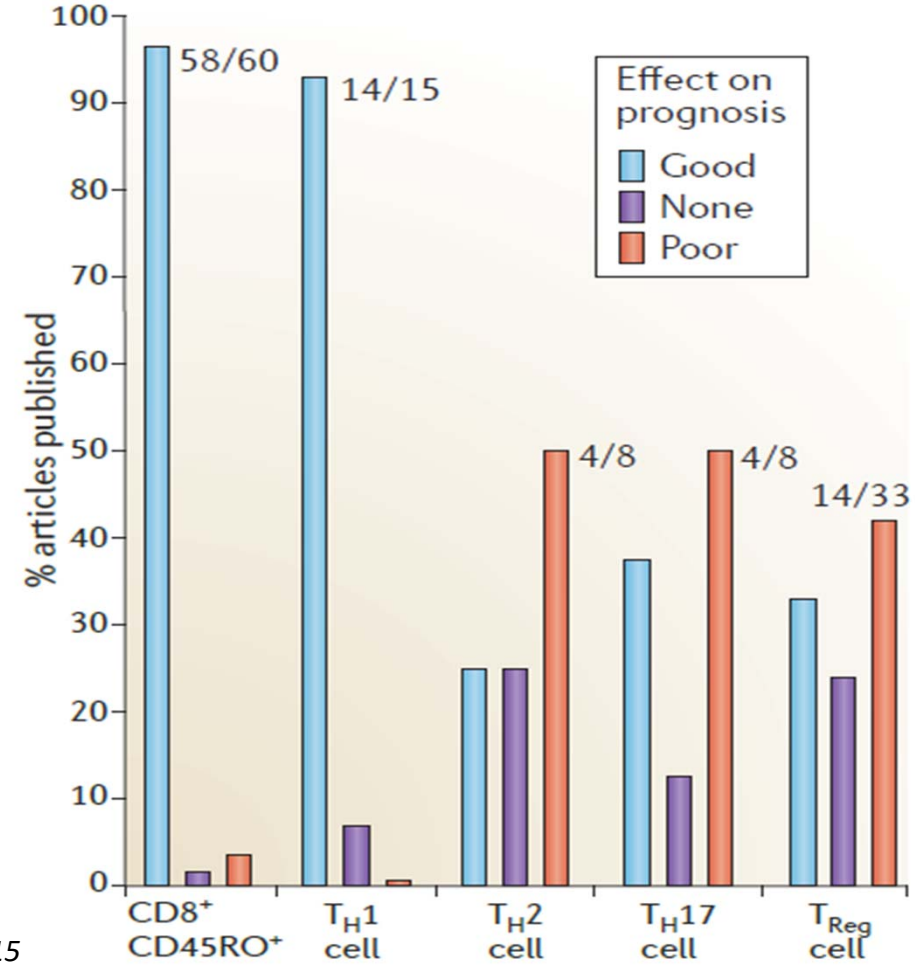


Type	CD3, CD8, CD45RO	Immunoscore
Density	Cells/mm^2	
Location	Centre, Margin	

Pages, F et al. NEJM 2005
Pages, F et al. J Clin Oncol 2009
Mlecnik, B et al. J Clin Oncol 2011

Association of immunoscore with prognosis in various types of cancer

124 studies



Fridman, WH et al. Nat Rev Oncol 2015

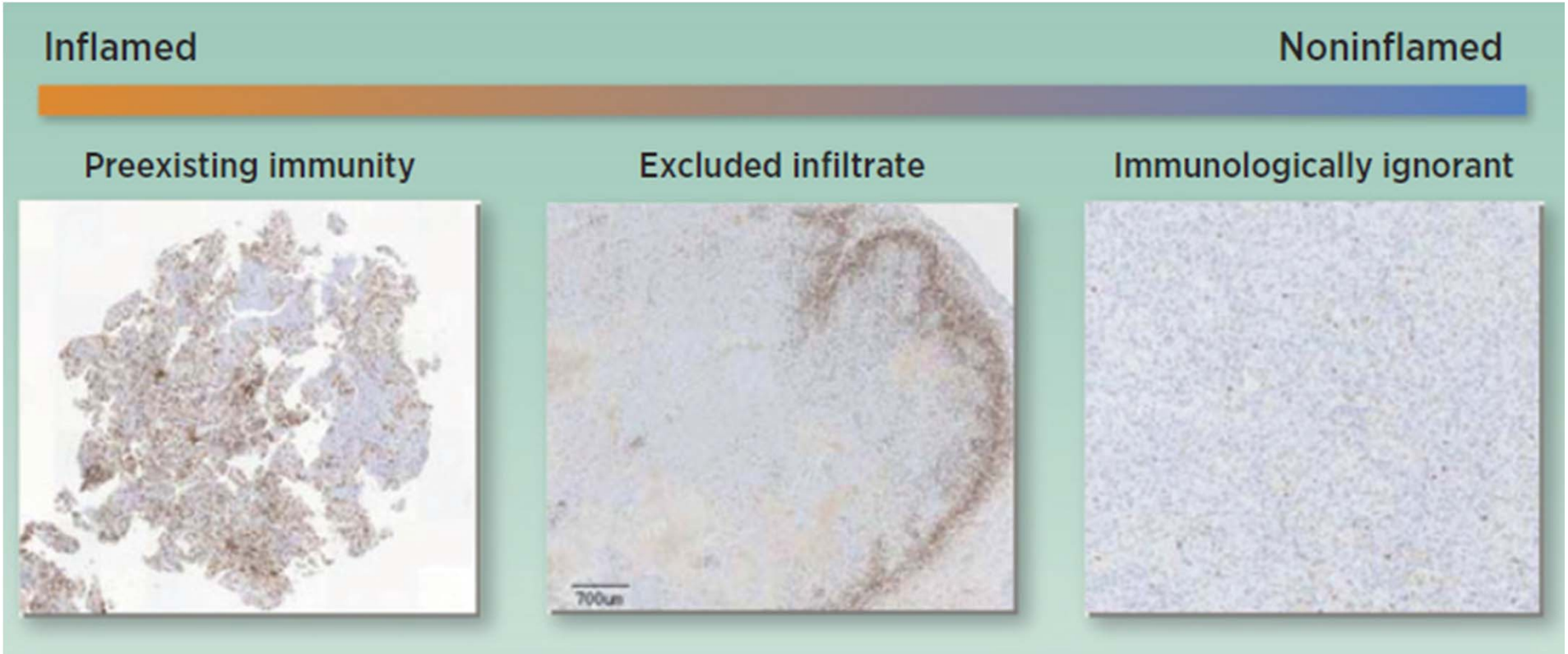
Outline

1. Clinical importance of TILs in cancer

2. Immune-inflammed cancer phenotype and benefit to immunotherapy

3. Assesing TILs in practice: recommendations and reproducibility

Tumor immunity continuum



Hedge, PS et al. Clin Cancer Res 2015

Tumor immunity continuum: 1. Immune-desert phenotype

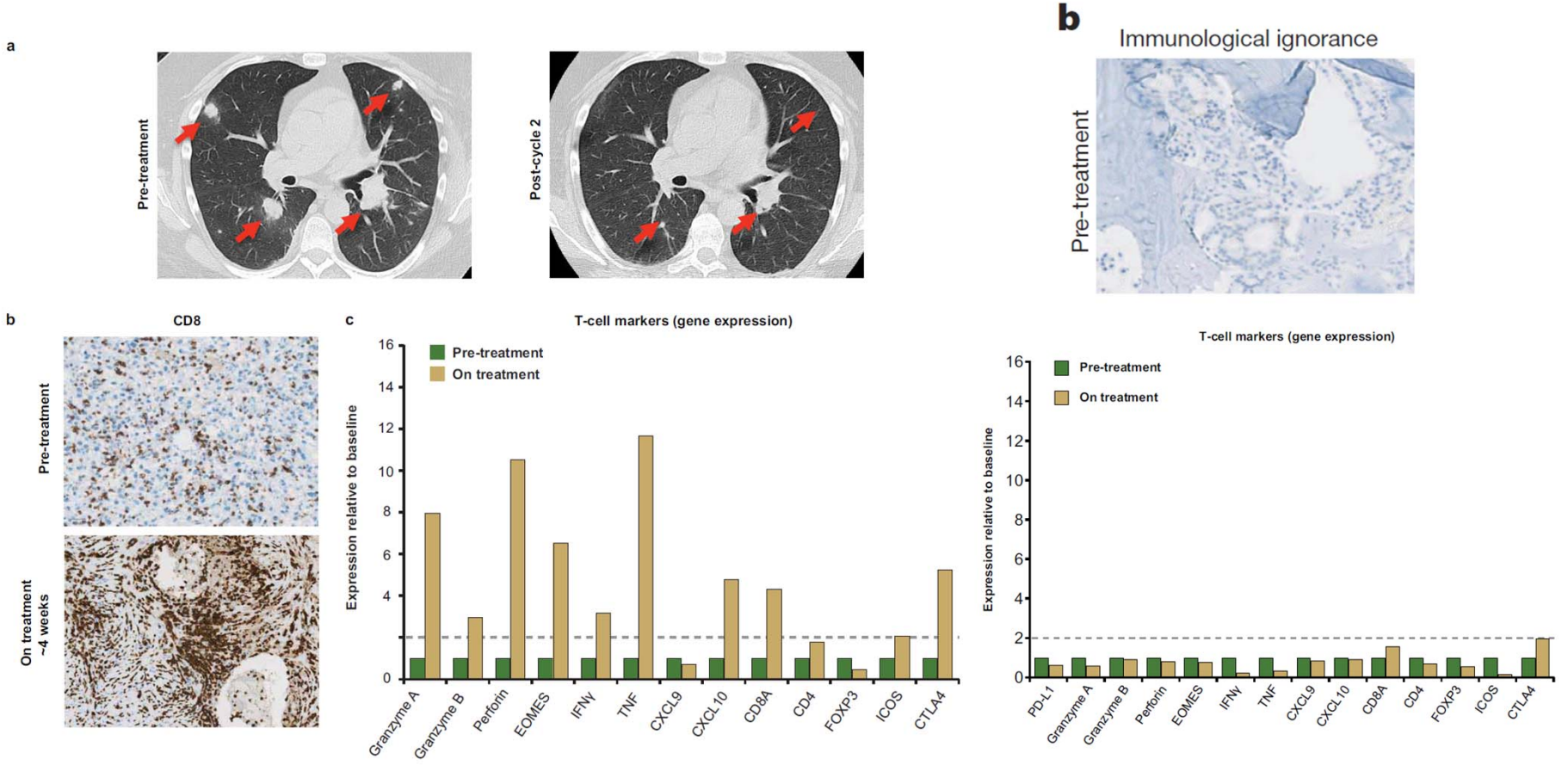
✓Paucity of T cells in the stroma of the tumor. Although myeloid cells may be present, the general feature of this profile is the presence of a non-inflamed tumour microenvironment with few or no CD8-carrying T cells

✓Rarely respond to anti-PD-L1/PD-1 therapy

✓This phenotype probably reflects the absence of pre-existing antitumour immunity, which suggests that the generation of tumour-specific T cells is the rate-limiting step

1. Immune-desert phenotype

Atezolizumab activity is associated with presence of TILs in stroma



Herbst, RS et al. Nature 2014

Tumor immunity continuum: 2. Immune-excluded phenotype

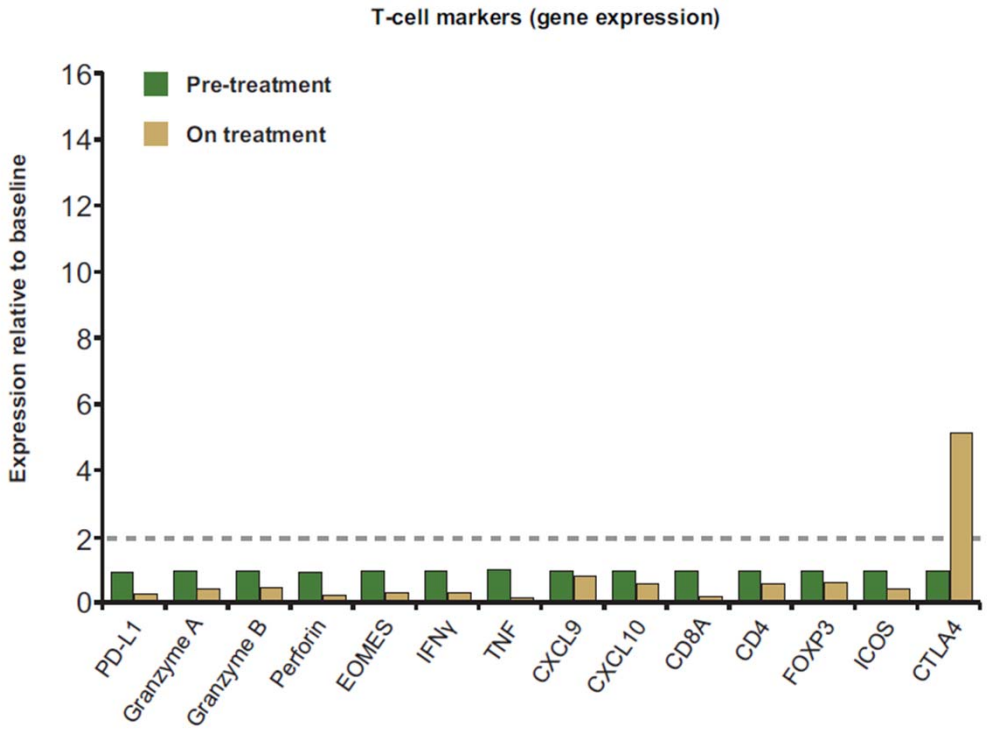
✓Abundant immune cells in the stroma that surrounds nests of tumor and not penetrate the parenchyma

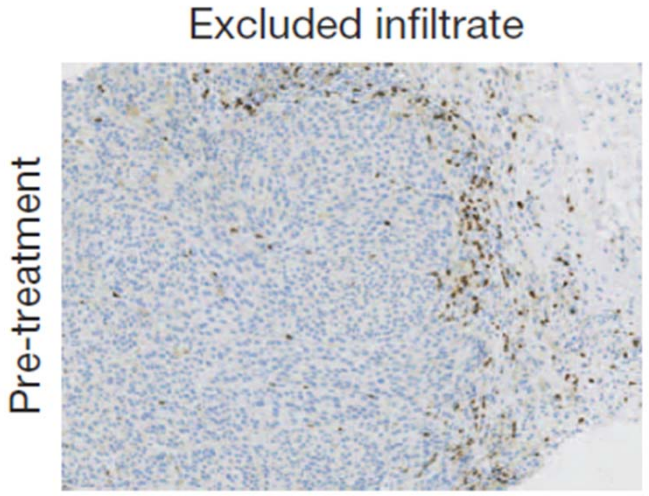
✓After treatment with anti-PD-L1/PD-1 agents, stroma-associated T cells can show evidence of activation and proliferation but not infiltration, and clinical responses are uncommon

✓These features suggest that a pre-existing antitumor response might have been present but was rendered ineffective by a block in tumor penetration through the stroma or by the retention of immune cells in the stroma

2. Immune-excluded phenotype

Atezolizumab activity is associated with presence of TILs in stroma





Herbst, RS et al. Nature 2014

Tumor immunity continuum: 3. Immune-inflamed phenotype

✓Presence of both CD4- and CD8 cells, often accompanied by myeloid and monocytic cells, which are positioned in proximity to the tumor cells

✓Inflamed tumors exhibit staining for PD-L1 on infiltrating immune cells and, in some cases, tumor cells

✓Many proinflammatory and effector cytokines can be detected

✓This profile suggests the presence of a pre-existing antitumour immune response that was arrested probably by immunosuppression

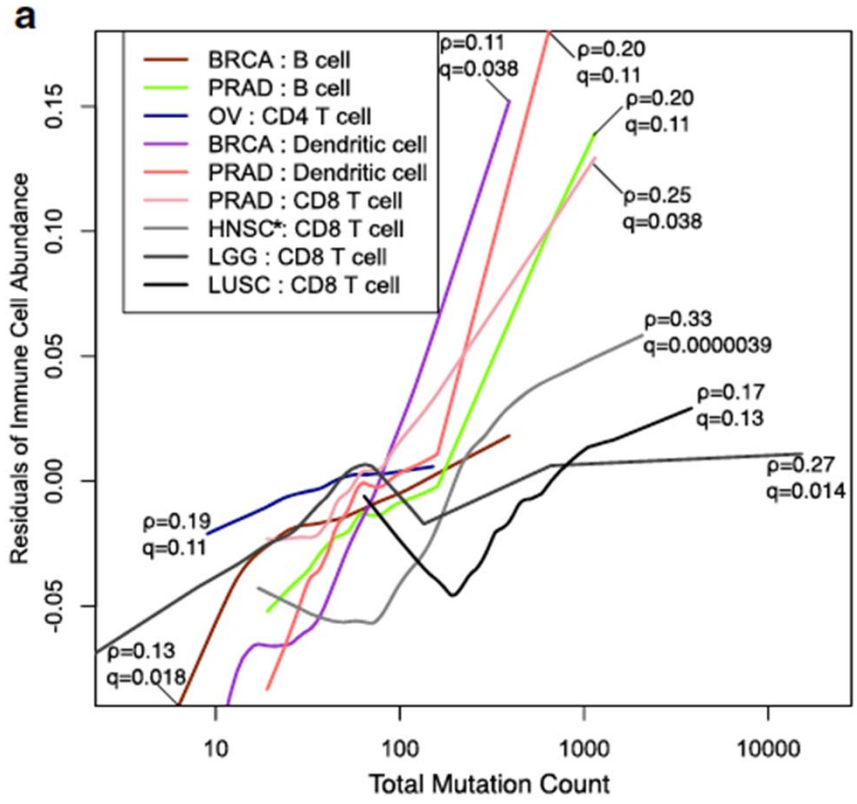
✓Clinical responses to anti-PD-L1/PD-1 therapy occur most often in patients with inflamed tumors

✓However, a response is not assured in these individuals, which indicates that immune-cell infiltration is necessary but insufficient for inducing a response.

Chen, DS and Mellman, I. Nature 2017

3. Immune-inflamed phenotype

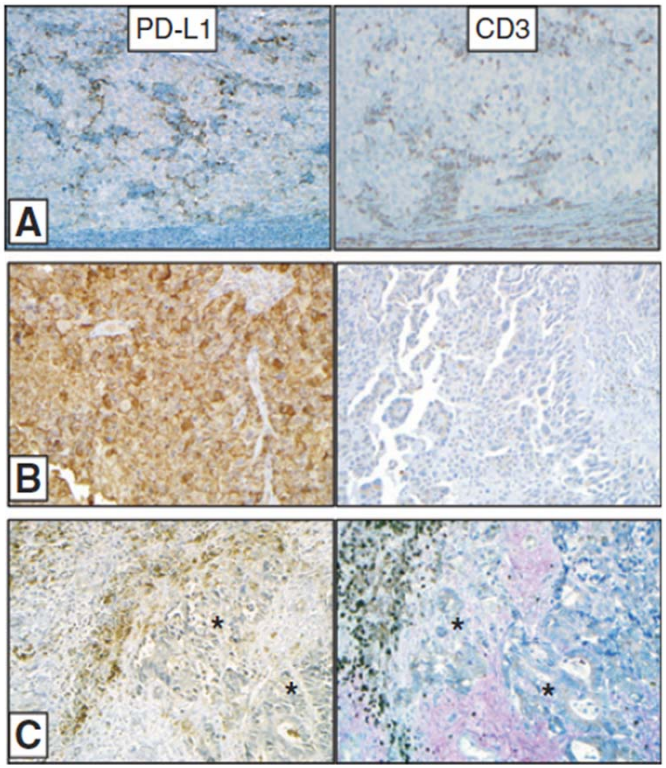
Association between mutational burden and immune cells in tumor stroma



Li, B et al. Genom Biol 2016

3. Immune-inflamed phenotype

TILs are associated with PD-L1 expression in melanoma, NSCLC and RCC



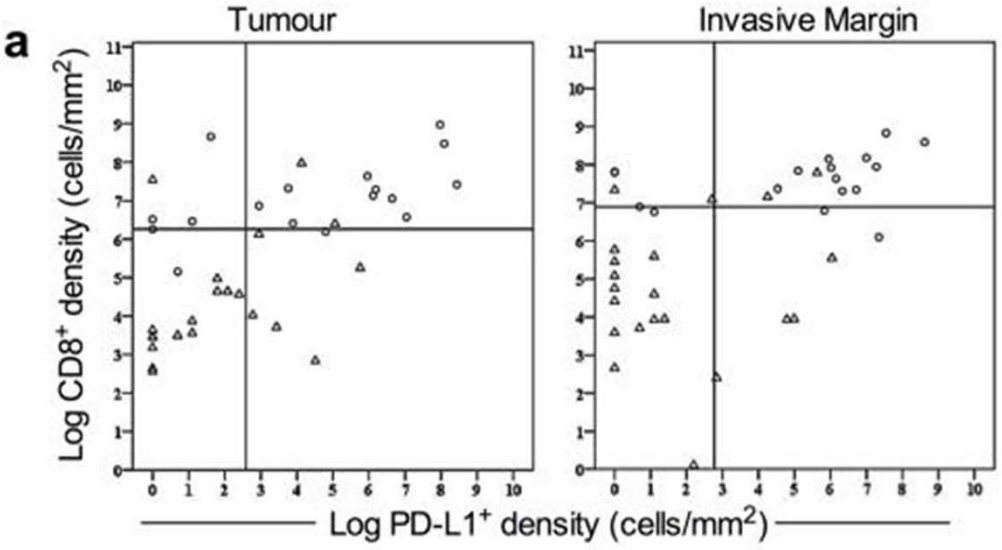
Parameter (number of specimens examined)	Specimens *n* (%)	Tumor cells PD-L1(–) *n* (%)	Tumor cells PD-L1(+)[b] *n* (%)	Tumor cells *P* value[c]	Infiltrating immune cells PD-L1(–) *n* (%)	Infiltrating immune cells PD-L1(+)[b] *n* (%)	Infiltrating immune cells *P* value[c]
Tumor type ($n = 68$)							
Melanoma	30 (44)	14 (47)	16 (53)	0.005	15 (50)	15 (50)	0.007
NSCLC	17 (25)	8 (47)	9 (53)		8 (47)	9 (53)	
Kidney cancer	9 (13)	1 (11)	8 (89)		0 (0)	9 (100)	
Colorectal cancer	8 (12)	7 (87)	1 (13)		4 (50)	4 (50)	
CRPC	4 (6)	4 (100)	0 (0)		4 (100)	0 (0)	
Tumor site ($n = 68$)							
Lymph node	17 (25)	11 (65)	6 (35)	0.219	10 (59)	7 (41)	0.339
Lung	15 (22)	5 (33)	10 (67)		5 (33)	10 (67)	
Other	36 (53)	18 (50)	18 (50)		16 (44)	20 (56)	
Primary vs. metastatic tumor ($n = 68$)							
Primary	29 (43)	17 (59)	12 (41)	0.327	15 (52)	14 (48)	0.463
Metastasis	39 (57)	17 (44)	22 (56)		16 (41)	23 (59)	
Immune infiltrate score[d] ($n = 68$)							
0	14 (21)	13 (93)	1 (7)	0.001	N/A	N/A	0.69
1	35 (51)	16 (46)	19 (54)		12 (34)	23 (66)	
2	16 (24)	5 (31)	11 (69)		5 (31)	11 (69)	
3	3 (4)	0 (0)	3 (100)		0 (0)	3 (100)	
Proportion of TILs expressing PD-1[e] ($n = 63$)							
0	38 (60)	25 (66)	13 (34)	0.001	22 (58)	16 (42)	0.005
1	13 (21)	5 (38)	8 (62)		4 (31)	9 (69)	
2	12 (19)	1 (8)	11 (92)		1 (8)	11 (92)	
3	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
CD4:CD8 ratio ($n = 50$)							
CD4 $\geq$ CD8	22 (44)	9 (41)	13 (59)	0.565	7 (32)	15 (68)	1.000
CD4 < CD8	28 (56)	9 (32)	19 (68)		10 (36)	18 (64)	
$CD20^+$ B cells ($n = 51$)							
Absent	34 (67)	23 (68)	11 (32)	0.006	21 (62)	13 (38)	0.017
Present[f]	17 (33)	4 (24)	13 (76)		4 (24)	13 (76)	
Lymphoid aggregates ($n = 68$)							
Absent	58 (85)	32 (55)	26 (45)	0.083	30 (52)	28 (48)	0.017
Present	10 (15)	2 (20)	8 (80)		1 (10)	9 (90)	
Necrosis ($n = 68$)							
Absent	50 (74)	27 (54)	23 (46)	0.41	25 (50)	25 (50)	0.276
Present	18 (26)	7 (39)	11 (61)		6 (33)	12 (67)	
Small sample ($n = 68$)							
No	44 (65)	19 (43)	25 (57)	0.204	17 (39)	27 (61)	0.135
Yes	24 (35)	15 (62)	9 (38)		14 (58)	10 (42)	

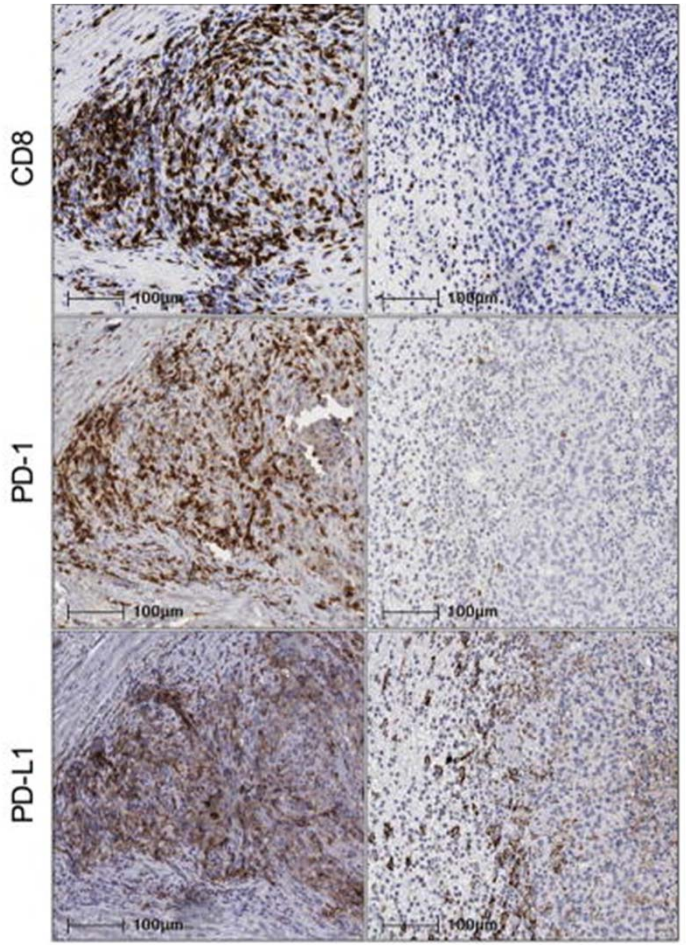
Taube, JM et al. Clin Cancer Res 2014

3. Immune-inflamed phenotype

CD8+ TILs are associated with PD-L1 expression in advanced melanoma

Relationship between CD8 and PD-L1 expression in advanced melanoma





Tumeh, PC et al Nature 2015

3. Immune-inflamed phenotype

Mismatch-repair deficiency and PD-1 blockade benefit in CRC and others

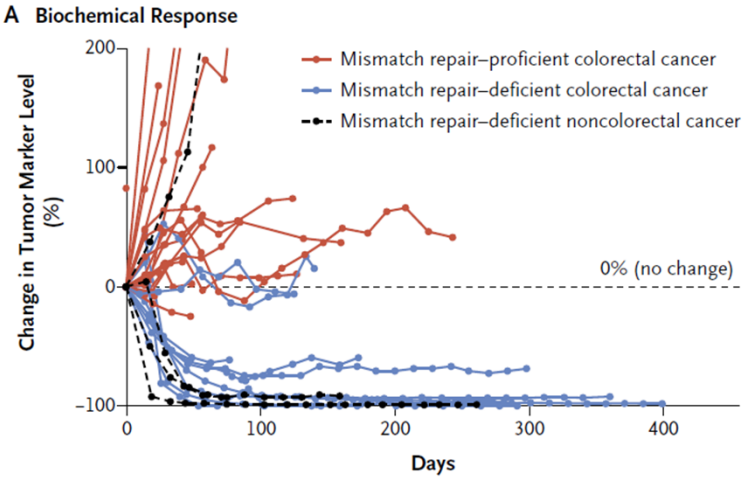
N ENGL J MED 372;26 NEJM.ORG JUNE 25, 2015

The NEW ENGLAND JOURNAL of MEDICINE

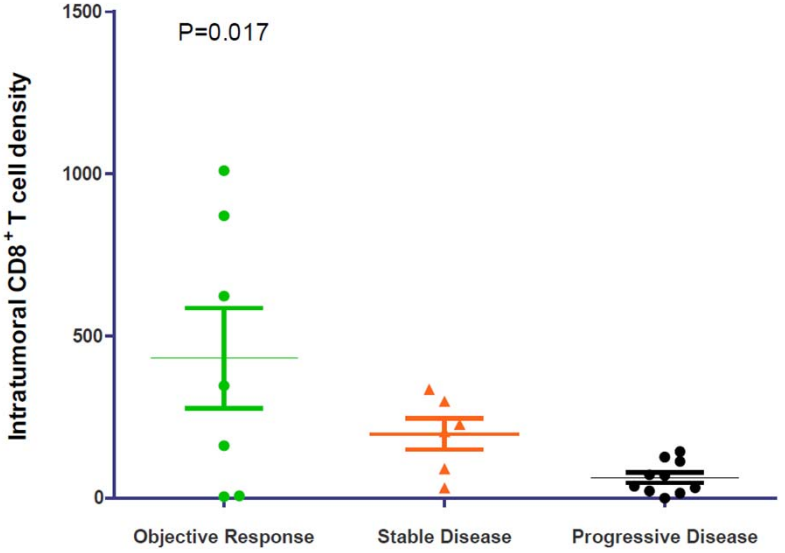
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.



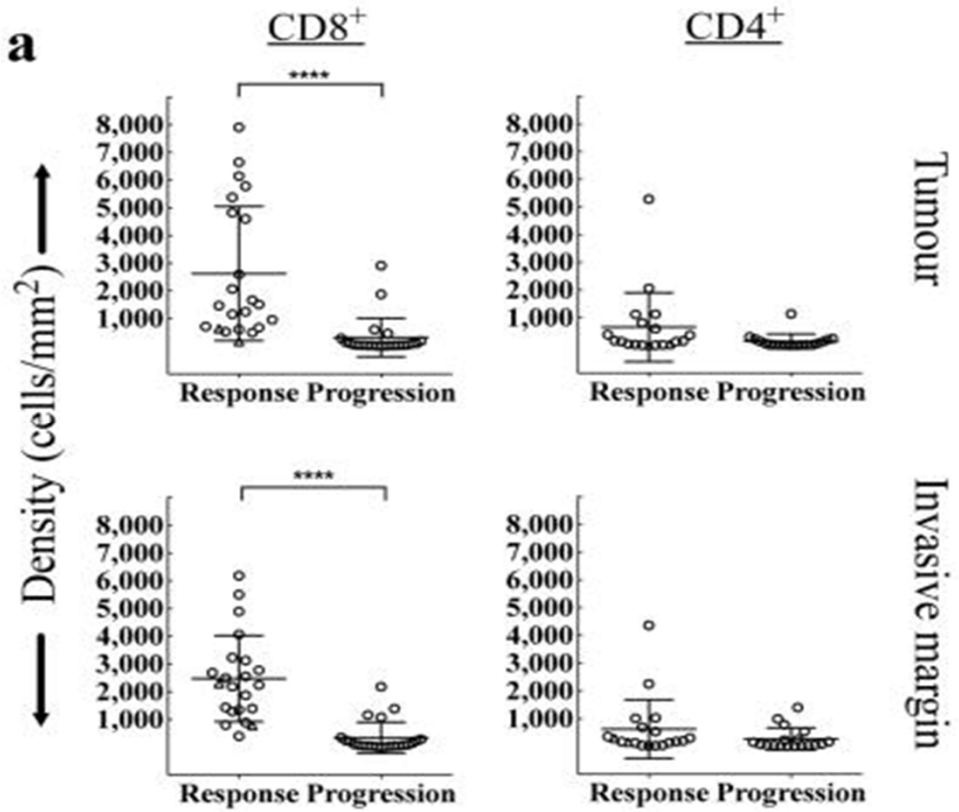
KEYNOTE016: pembrolizumab and MSI colorectal and non-colorectal tumors



3. Immune-inflamed phenotype

CD8+ TILs are associated with benefit to pembrolizumab in advanced melanoma

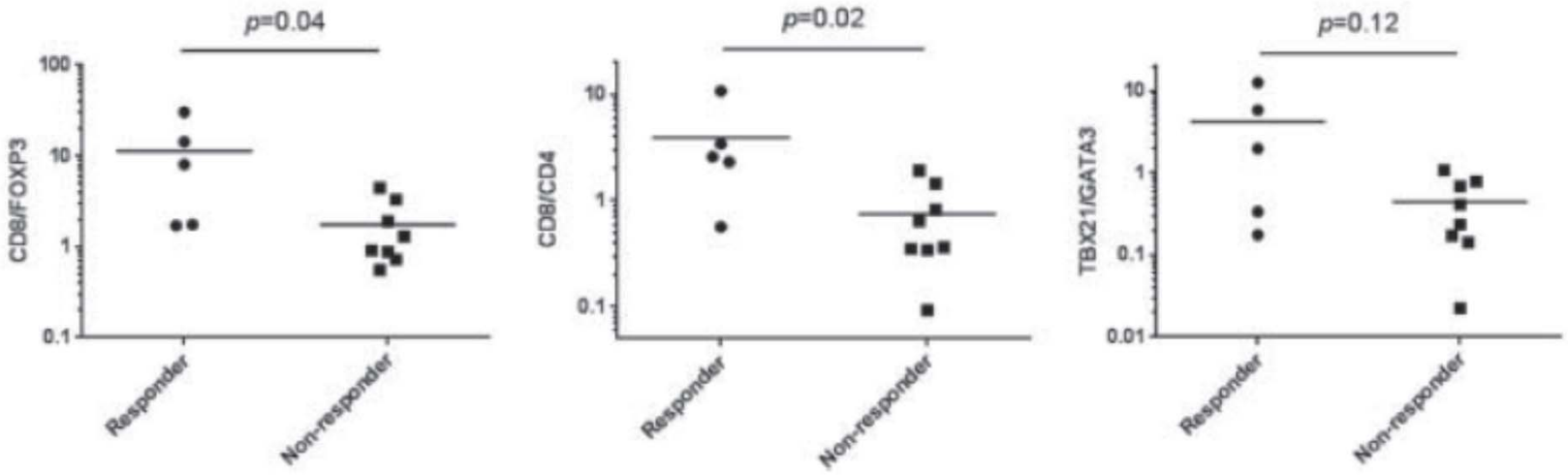
Pembrolizumab benefit in advanced melanoma and TILs



Tumeh, PC et al. Nature 2015

3. Immune-inflamed phenotype

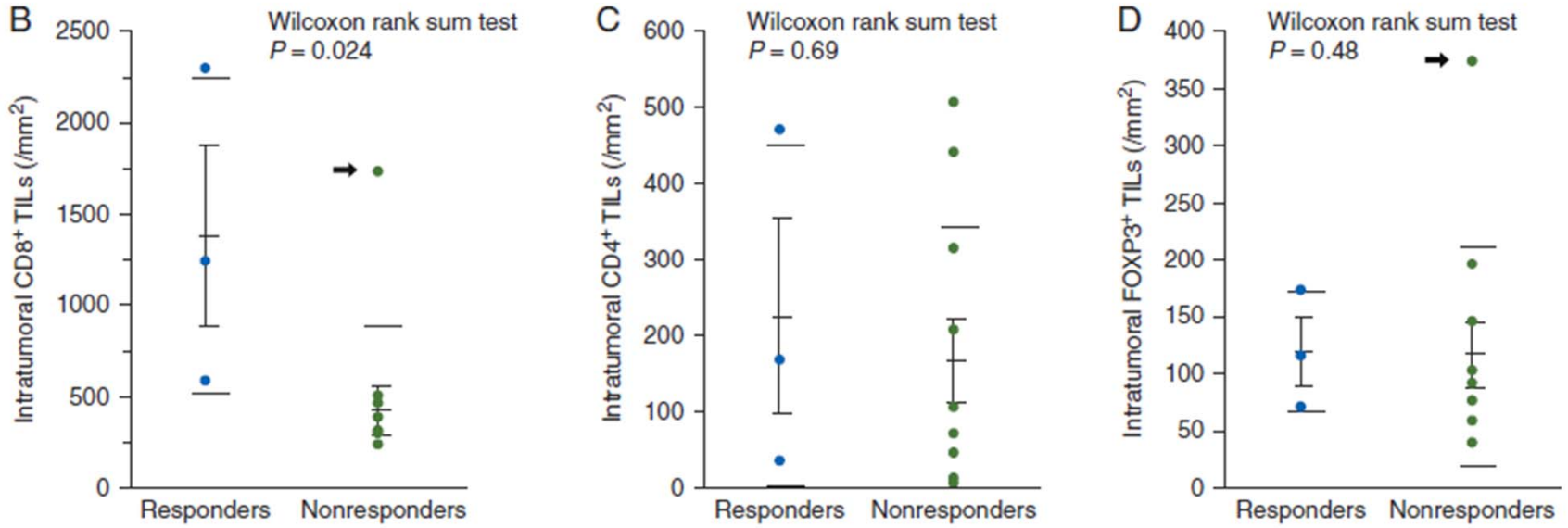
Immune repertoire predicts nivolumab response in melanoma



Inoue, H et al. Oncoinmunology 2016

3. Immune-inflamed phenotype

Nivolumab efficacy in T790 EGFR mutated NSCLC is associated with presence of CD8+ TILs



Haratani, K et al. Ann Oncol 2017

3. Immune-inflamed phenotype

TILs predict benefit to nivolumab in advanced NSCLC

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

112P - Pathological evaluation of tumor infiltrating lymphocytes and the benefit of nivolumab in advanced non-small cell lung cancer (NSCLC).

I. Gataa[1], L. Mezquita[1], E. Auclin[1], S. Le Moulec[2], P. Alemany[3], M. Kossai[3], J. Massé[4], C. Caramella[5], J. Remon Masip[1], J. Lahmar[1], R. Ferrara[1], A. Gazzah[1], J. Soria[6], D. Planchard[1], B. Besse[1], J. Adam[3]

» Background

Assessment of tumor infiltrating lymphocytes (TIL) by pathologists using Hematoxylin-Eosin (H&E), has been described as a prognostic factor in resected NSCLC. We aimed to correlate TIL to the benefit from nivolumab in patients (pts) with treated advanced NSCLC.

» Methods

Patients with advanced NSCLC treated with nivolumab, with biopsy available for evaluation, were included between November 2012 and February 2017 in two cancer centers. Patients characteristics and outcome were collected. The percentage of tumor infiltrating lymphocytes in the stroma was evaluated using H&E staining from archival pretreatment tumor tissue samples. Primary endpoint was to correlate TIL density with progression free survival (PFS).

» Results

Out of ninety-eight patients included. 60 (61%) pts were male, with median age of 61 years and 85 (89%) were smokers. Sixty three (73%) pts were PS 0-1. Sixty tumors (61%) were adenocarcinoma, 29 (30%) squamous and 9 (10%) other histologies. Among 83 tumors with known molecular profile, 22 (27%) were KRAS mutated 7 (8%) EGFR mutated, 1(1%) ALK positive. The median treatment line was 3 (2-4). The median follow up was 8 months (m)(95%CI[6-19]). The median PFS was 2 m (95%CI[1-5]). The ORR was for 16%. The median TIL density was 5% (2-15). TIL density ≥5% correlated with PFS in univariate and multivariate analysis (HR: 0.48 [0.28-0.82] p = 0.007 and HR:0.31 [0.14-0.68] p = 0.004 respectively). TIL density ≥5% was also associated with better ORR (OR = 3.5, 95%CI [1.06-11.7], p = 0.04).

» Conclusions

Pathological assessment of TIL allows an easy evaluation of immune infiltration in NSCLC and independently correlates PFS in NSCLC pts treated with nivolumab. Results from validation cohorts and combination with other morphological and immunohistochemical parameters will be reported.

3. Immune-inflamed phenotype

TILs predict response to pembrolizimab in mTNBC

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

BREAST CANCER, METASTATIC

LBA13 **Relationship between tumor infiltrating lymphocyte (TIL) levels and response to pembrolizumab (pembro) in metastatic triple-negative breast cancer (mTNBC): Results from KEYNOTE-086**

S. Loi[1], S. Adams[2], P. Schmid[3], J. Cortés[4], D.W. Cescon[5], E.P. Winer[6], D.L. Toppmeyer[7], H.S. Rugo[8], M. De Laurentiis[9], R. Nanda[10], H. Iwata[11], A. Awada[12], A. Tan[13], A. Wang[14], G. Aktan[15], V. Karantza[15], R. Salgado[16]

Background: TILs have been observed in TNBC and are thought to represent pre-existing antitumor immunity. Thus, TILs could be a biomarker for response to immune checkpoint blockade. We assessed if TIL levels were associated with response to pembro monotherapy in the phase 2 KEYNOTE-086 study of previously treated mTNBC of any PD-L1 expression (cohort A) or previously untreated, PD-L1–positive mTNBC (cohort B) (NCT02447003).

Methods: Stromal TILs were quantified by a single pathologist blinded to clinical data using a published method of light microscopy of H&E-stained slides obtained from tumor biopsies. PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx. Response was assessed every 9 wk for 12 mo, then every 12 wk (RECIST v1.1, central review). Relationships between transformed TIL levels and ORR and DCR (CR + PR + SD $\geq$ 24 wk) were assessed using logistic regression adjusted for cohort (A vs B) and biopsy site (lymph node vs non-lymph node). All P values are 1 sided.

Results: 193 of the first 222 patients (pts) enrolled had evaluable tumor samples: 147 from cohort A, 46 from cohort B; 146 samples were newly collected (mostly from metastatic sites), 47 were archival (mostly from primary breast tumors). Median [IQR] TIL level was higher in cohort B vs A (17.5% [6.2-57.5%] vs 5% [1-10%], Wilcoxon rank sum $P < .001$), and in archival vs newly collected samples (10% [5-40%] vs 5% [1.2-15%], $P < .001$), and lymph node vs non-lymph node samples (10% [5-50%] vs 5% [2-15%], $P = .01$). ORR in pts with TIL level $\geq$ vs $<$ median was 6% vs 2% in cohort A and 39% vs 9% in cohort B. Median (IQR) TIL level in responders vs nonresponders was 10% (7.5-25%) vs 5% (1-10%) in cohort A and 50% (5-70%) vs 15% (5-37.5%) in cohort B. In the combined cohorts, higher TIL levels were associated with significantly improved ORR (odds ratio 1.26, 95% CI 1.03- 1.55, $P = .01$) and DCR (odds ratio 1.22, 95% CI 1.02-1.46, $P = .01$). Area under the ROC curve was 0.75 for ORR and 0.69 for DCR. PD-L1 expression significantly correlated with TIL levels ($\rho = 0.4962$, $P < .001$).

Conclusions: TIL levels can identify pts with mTNBC with a greater chance of achieving response to pembro monotherapy, particularly in the first-line setting.

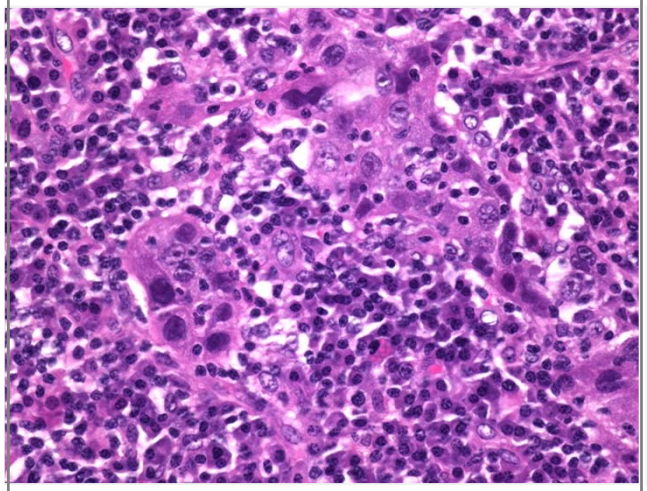
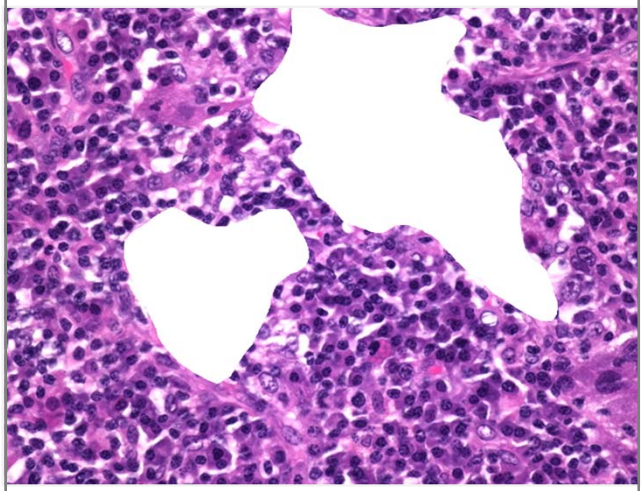
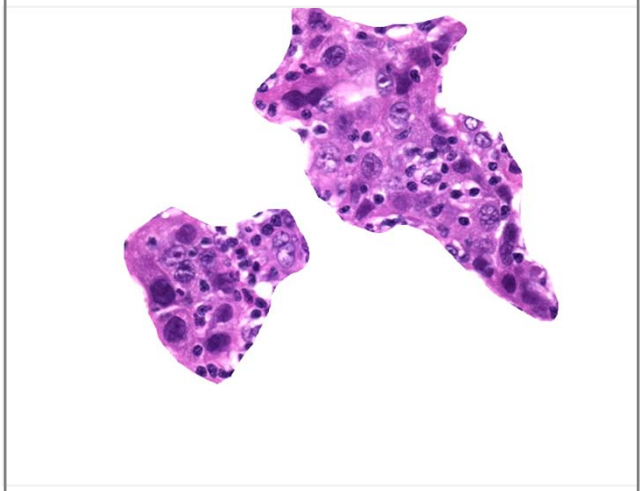
Outline

1. Clinical importance of TILs in cancer

2. Immune-inflammed cancer phenotype and benefit to immunotherapy

3. Assesing TILs in practice: recommendations and reproducibility

Standardized methodology for pathological TILs evaluation in cancer

Lymphocyte-predominant cancer (LPC)	Stromal TILs	Intratumoral TILs
		
Definitions vary across studies with stromal TILs of 50–60% used as a threshold. LPC can be used for predefined subgroup analyses in tumors with a particularly high immune infiltrate. However, TILs are a continuous parameter and the threshold is arbitrary.	Stromal TILs have been shown to be predictive for increased response to neoadjuvant chemotherapy as well as improved outcome after adjuvant chemotherapy. This parameter is the best one for characterization of TILs.	Several studies have shown that intratumoral TILs are more difficult to evaluate and do not provide additional predictive/ prognostic information compared to stromal TILs.

REVIEW ARTICLE

Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method From the International Immunooncology Biomarkers Working Group: Part 1: Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma In Situ, Metastatic Tumor Deposits and Areas for Further Research

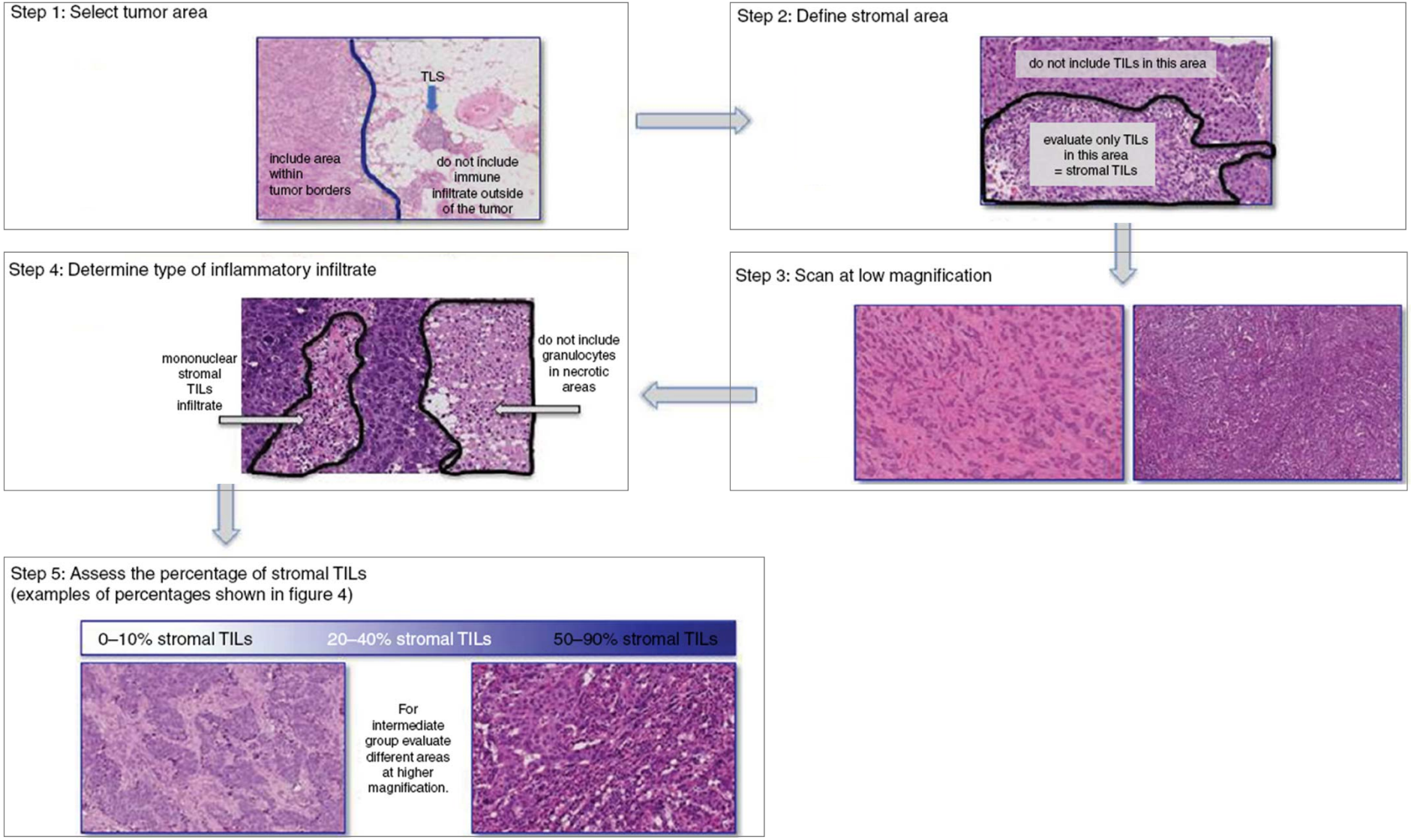
REVIEW ARTICLE

Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non–Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors

*S Hendry, R Salgado, T Gevaert, PA Russell, T John, B Thapa, M Christie, K van de Vijver, MV Estrada, PI Gonzalez-Ericsson, M Sanders, B Solomon, C Solinas, G Van den Eynden, Y Allory, M Preusser, J Hainfellner, G Pruneri, A Vingiani, S Demaria, F Symmans, P Nuciforo, L Comerma, EA Thompson, S Lakhani, SR Kim, S Schnitt, C Colpaert, C Sotiriou, SJ Scherer, M Ignatiadis, S Badve, RH Pierce, G Viale, N Sirtaine, F Penault-Llorca, T Sugie, S Fineberg, S Paik, A Srinivasan, A Richardson, Y Wang, E Chmielik, J Brock, DB Johnson, J Balko, S Wienert, V Bossuyt, S Michiels, N Ternes, N Burchardi, SJ Luen, P Savas, F Klauschen, PH Watson, B Nelson, C Criscitiello, S O'Toole, D Larsimont, R de Wind, G Curigliano, F Andre, M Lacroix-Triki, M van de Vijver, **F Rojo**, G Floris, S Bedri, J Sparano, D Rimm, T Nielsen, Z Kos, S Hewitt, B Singh, G Farshid, S Loibl, K Allison, N Tung, S Adams, K Willard-Gallo, H Horlings, L Gandhi, A Moreira, F Hirsch, M Dieci, M Urbanowicz, I Brcic, K Korski, F Gaire, H Koeppen, A Lo, J Giltnane, M Rebelatto, K Steele, J Zha, K Emancipator, J Juco, C Denkert, J Reis-Filho, S Loi and S Fox*

Standardized methodology for pathological TILs evaluation

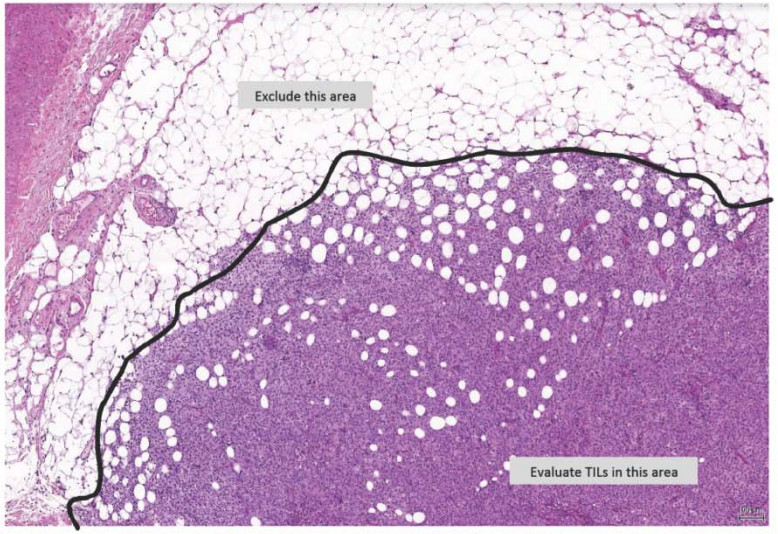
Recommendations for assessing tumor-infiltrating lymphocytes (TILs) in breast cancer

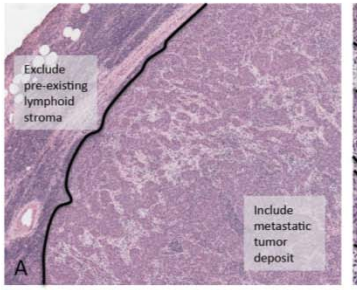


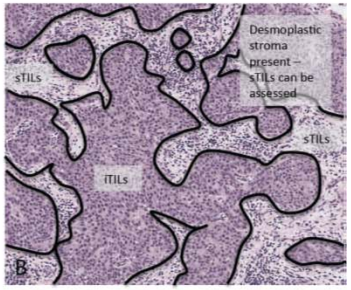
Standardized methodology for pathological TILs evaluation

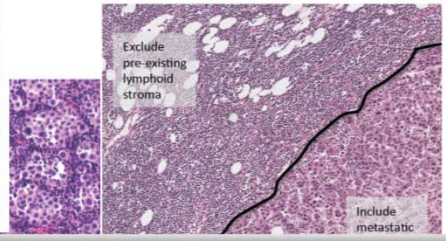
Recommendations for assessing TILs in melanoma, NSCLC, glioma, GU, endometrial, ovarian, GI and HN tumors

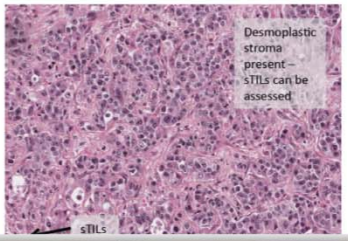
TILs within the border of the invasive tumor are evaluated.
The TILS along the invasive edge are included in the evaluation.
Immune infiltrates outside of the tumor borders are not included.

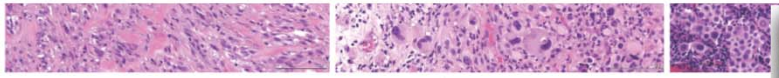








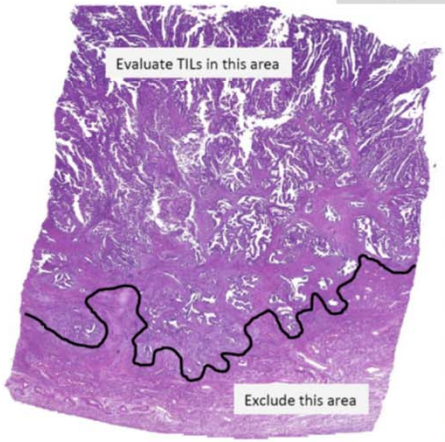


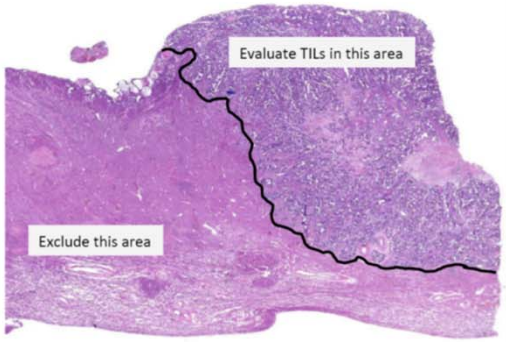


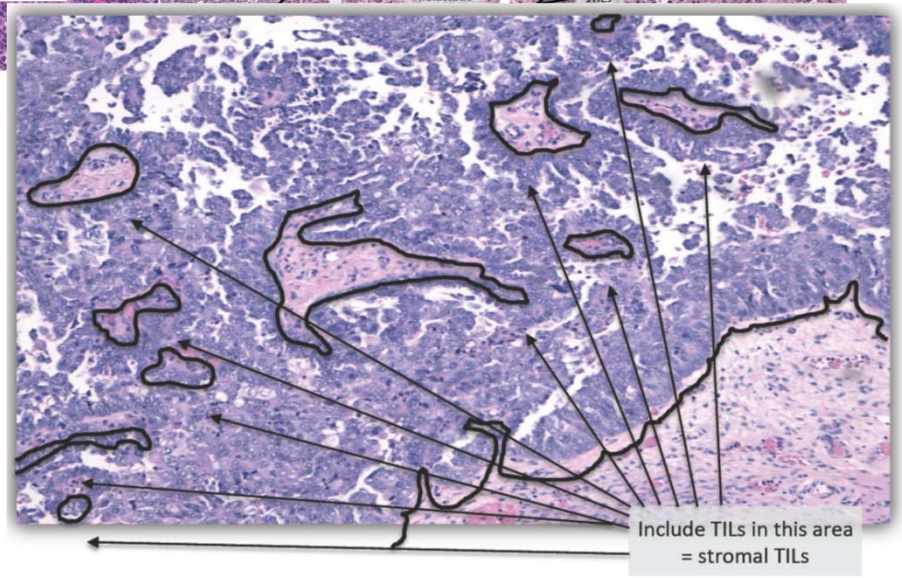
Mild TILs (5%)

Moderate TILs (30%)

Evaluate TILs within the borders of the tumor, both in the central tumor and at the invasive margin.





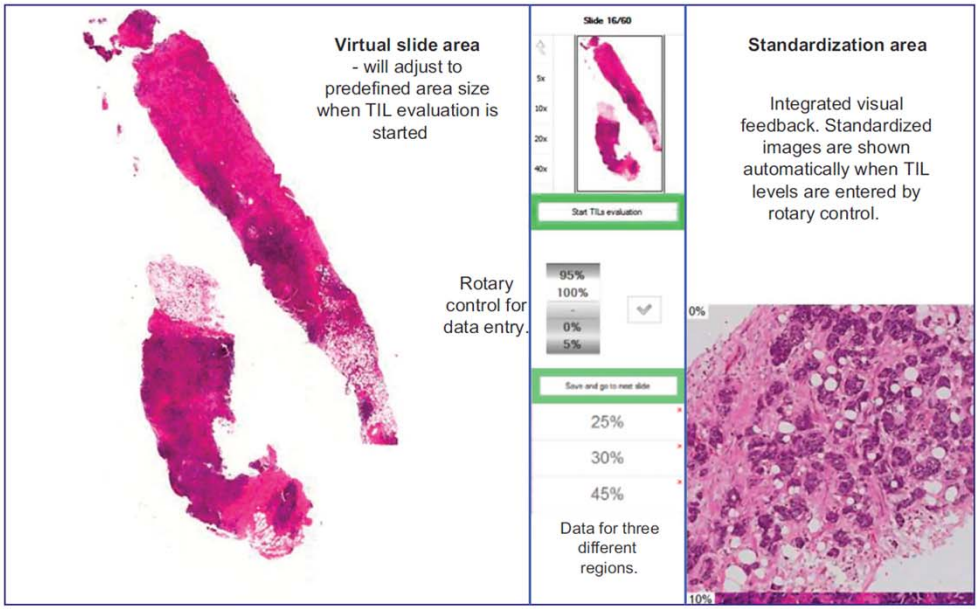


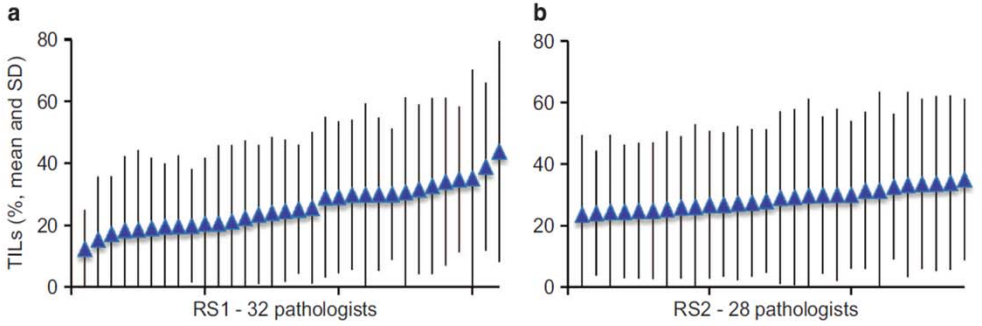
Standardized methodology for pathological TILs evaluation

Ring studies for standardized evaluation of TILs in breast cancer

Table 1 Comparison of ring study 1 and 2 for primary and secondary endpoints

	Ring study 1	*Ring study 2*
ICC	0.7 (0.62–0.78)	0.89 (0.85–0.92)
Fleiss' kappa		
TILs >60 *vs* ≥60%	0.45	0.63
TILs >50 *vs* ≥50%	0.51	0.72
TILs 0–20% *vs* 21–49% *vs* ≥50%	0.46	0.65
Concordance rates[a]		
TILs >60 *vs* ≥60%	0.88 (±0.05)	0.92 (±0.03)
TILs >50 *vs* ≥50%	0.89 (±0.05)	0.93 (±0.04)
TILs 0–20% *vs* 21–49% *vs* ≥50%	0.78 (±0.07)	0.85 (±0.07)





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