S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

Evento Formativo Residenziale

FORMAZIONE MULTIDISCIPLINARE e AGGIORNAMENTO PERMANENTE PER LE UNITA'
DIAGNOSTICO-TERAPEUTICHE DI SENOLOGIA
Settembre 2019

"Tumor-infiltrating lymphocytes (TILs)" aggiornamenti da ST Gallen

Francesca Pietribiasi

Anatomia Patologica

Moncalieri

TILs

- Definizione
- Composizione
- Valutazione (%)
- Significato clinico

TILs

- Definizione
- Composizione
- Valutazione (%)
- Significato clinico

TILs

- Cellule immunitarie mononucleate infiltranti il tessuto tumorale
- Tumori solidi (mammella, colon, polmone, melanomi)
- Linfociti T CD8+, CD4+, linfociti B, rare NK, rari macrofagi
- In vitro attività citolitica e secretiva (citochine)

Table 2 | **Tumour-infiltrating lymphocyte subpopulations and molecular markers**

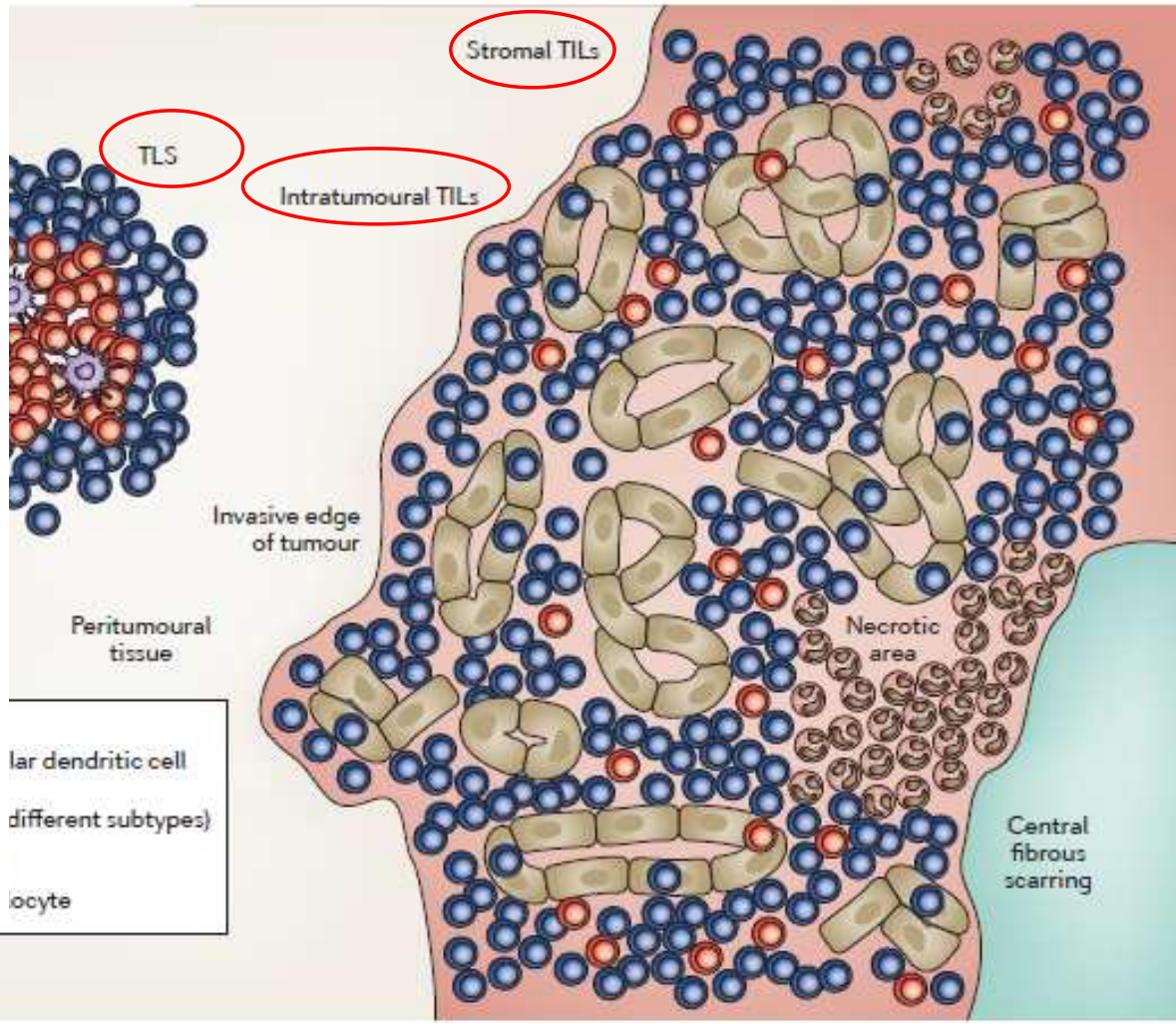
Cell	Markers	Subtypes	Normal function	Checkpoint markers	Known/suspected function in tumour microenvironment	Proportion of TILs
Cytotoxic T cells	CD3, CD8	NA	Cytolysis of virally infected cells	PD-1, PD-L1, CTLA-4, TIM3, OX40	Cytolysis of tumour cells	~20%
Helper T cells	CD3, CD4	T_H1	Response to intracellular pathogens	OX40	Support $CD8^+$ T cells by secreting IFNγ	~40%
		T_H2	Response to parasites	NA	Associated with ineffective antitumour immunity	
		T_H17	Response to fungi and extracellular bacteria	NA	Antitumour and protumour effects	
		T_{FH}	B-cell help	NA	Role in tertiary lymphoid structures	
		T_{REG}	Self-tolerance	CTLA-4	Tolerance of tumour antigens	
B cells	CD19, CD20	NA	Antibody production	NA	Antitumour antibodies Possible direct cytotoxic action	<20%
Macrophages	CD14, CD11b, HLA-DR	M1	Inflammation and response to intracellular pathogens	IDO	Secretion of antitumour cytokines	<5%
		M2	Wound response, angiogenesis	NA	Immunosuppressive cytokines, angiogenesis	
NK cells	CD16, CD56, NKG2D	NA	Innate immunity	IDO	Killing of tumour cells	<5%
Dendritic cells	CD135, Flt3, CD117, CD26, CD103	NA	Antigen presentation Co-stimulation	IDO	Cross presentation of tumour peptide antigens	1%

Clinical relevance of host immunity in breast cancer: from TILs to the clinic

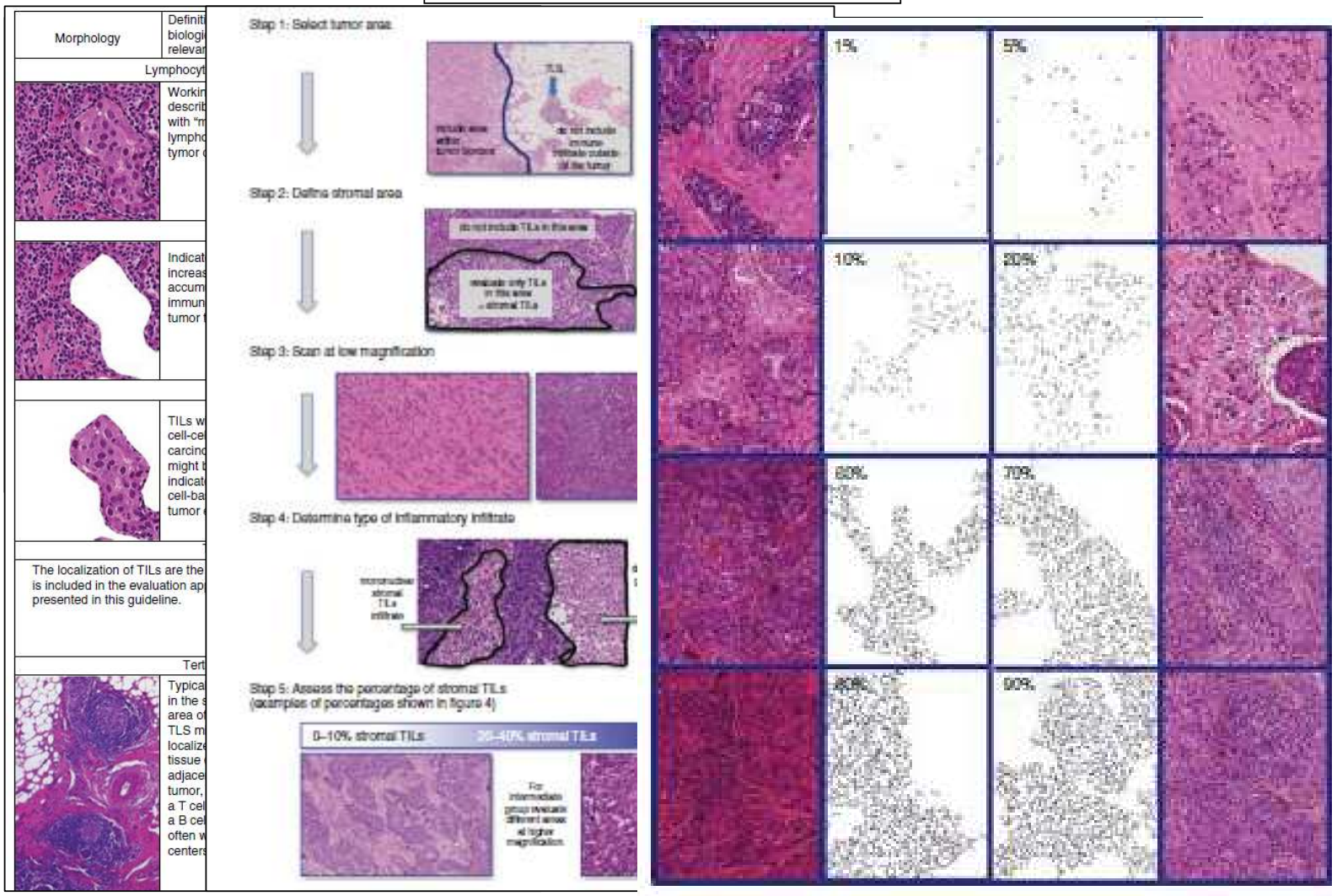
NATURE REVIEWS | CLINICAL ONCOLOGY
VOLUME 13 | APRIL 2016 | 233

Table 1 | Standardized evaluation of TILs as a biomarker in H&E sections[22]

Parameter	Recommendation
Selection of tumour area	Evaluate only immune cells within the tumour margin, do not include immune infiltrate around DCIS or normal tissue next to the tumour
	Do not focus on the invasive edge, but include invasive edge in overall assessment
	Do not focus on hot spots, but provide overall assessment of TILs
	Do not include necrosis or large fibrous areas in the tumour centre
Type of immune cell	Evaluate all mononuclear lymphocytes and plasma cells
	Do not include granulocytes in necrotic areas
Localization of immune cells	Stromal TILs: in the fibrotic tissue between tumour cell nests
	Intratumoural TILs: directly infiltrating the tumour cell nest, direct contact to tumour cells
	Stromal and intratumoural TILs should be evaluated separately and reported semi-quantitatively as a percentage of the total area occupied by the infiltrate
	Example images for standardized reporting of percent stromal infiltration have been published[22]; software-based systems are in preparation
Analysis of immune biomarkers	Stromal TILs: it is currently recommended that this is used as the primary end point as a continuous variable
	Intratumoural TILs: can be reported as a secondary end point



VALUTAZIONE DEI TILS



Analytical validation of TILs in cancer

2010

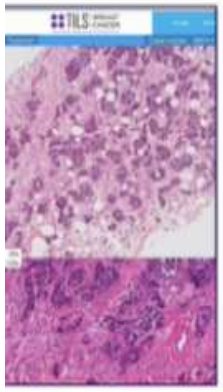
- 2010 Geparduo trial; GeparTrio trial: Standardize definition of sTILs and iTILs
  (Denkert et al, JCO, 2010)
- 2013 International TIL working group
- 2014 International TIL guidelines breast cancer
  (Salgado et al. Ann Oncol. 2015)
- 2016 Ring trials;
  (Denkert et al. Mod. Pathol., 2016)
- 2017 TILs in other types of tumors
  (Hendry et al. (100 coauthors),
  Adv. in Anat. Pathol.2017)
- 2017 International web site

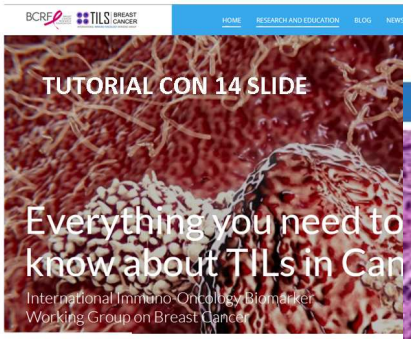
www.TILsinbreastcancer.org

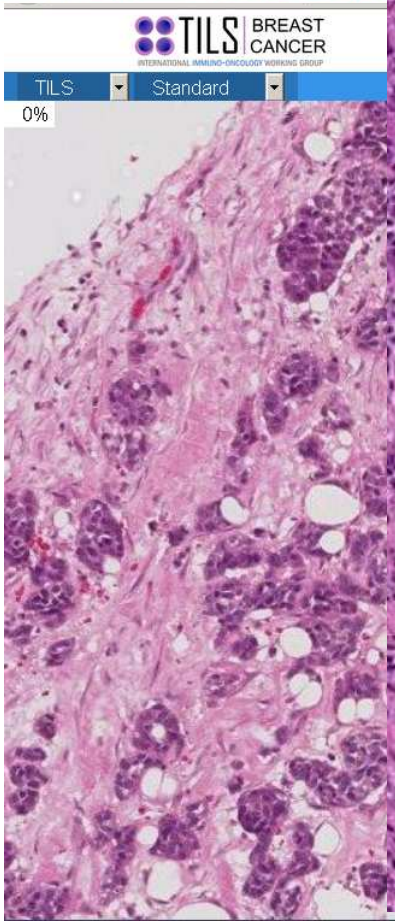
2019

- standardized method since 2010
- TIL working group:
  - strong international consensus
- Ring trials:
  - high consensus rates for a continuous biomarker (ICC>0.7)
  - similar to final phase of Ki67 ring trials
  - higher than consensus rates for PD-L1 (ICC<0.7)
- Web site:
  - continuous training
  - ring trials

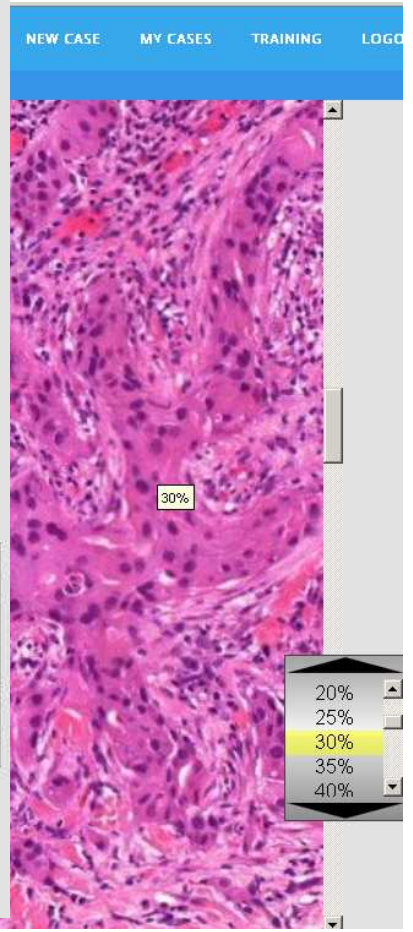
All TIL evaluations since 2010 use the identical method




TUTORIAL CON 14 SLIDE
Everything you need to
know about TILs in Can
International Immuno-Oncology Biomarker
Working Group on Breast Cancer


TILS BREAST CANCER
INTERNATIONAL IMMUNO-ONCOLOGY WORKING GROUP
TILS
Standard
0%


TILS BREAST CANCER
INTERNATIONAL IMMUNO-ONCOLOGY WORKING GROUP
HOME
PROFILE
NEW CASE
MY CASES
TRAINING
LOGOU
TILS
Standard
80%
75%
80%
85%
90%


NEW CASE
MY CASES
TRAINING
LOGO
30%
20%
25%
30%
35%
40%

ALMA MATER STUDIORUM - UNIVERSITA' DI BOLOGNA
Dipartimento di Scienze Biomediche e Neuromotorie

Controllo di qualità in patologia mammaria

RER – GIPaM

Venerdì 13 settembre 2019

Aula Magna, Padiglione Tinozzi, Ospedale Bellaria, Bologna

TILs 0-10 11-59 60-100

TIL (3 categorie, 40 valutatori		15 valutatori
Percent Agreement	0.7579	0.7114

TILs

- Definizione
- Composizione
- Valutazione (%)
- **Significato clinico:**

Biomarcatore prognostico

Biomarcatore predittivo

Biomarcatore di malattia residua

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:
	RCT	FEC Trastuzumab		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
SEARCH, BCCA, NBCS, NEAT[19]	Pr O R		IHC for CD8 in tumour (iCD8)			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.

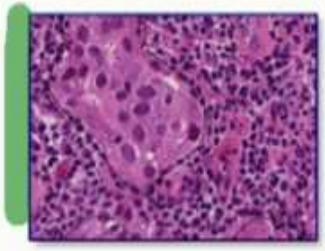
In HER 2 and TN breast cancer each 10% increase in TILs is associated with 15-20% decrease in risk of relapse and death

Lymphocyte-predominant breast cancer (> 50-60%) have significant higher pathologic complete response rates than breast tumors with fewer TILs (40% vs 5%)

Table 4 | Neoadjuvant trials that have assessed TILs

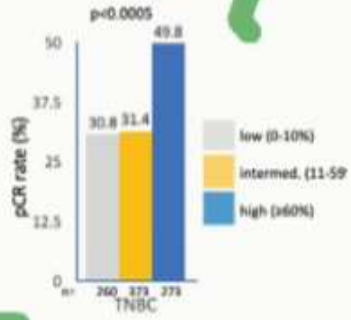
Trial and treatments	Subtype	n	TILs assessment	Outcome	Multivariate analysis
GeparDuo[24] Doxorubicin Docetaxel Cyclophosphamide	All	218	sTILs and iTILs on H&E	>60% sTILs: pCR 41.7% <60% sTILS: pCR 9.3%	OR 1.38 of pCR per 10% iTILs (95% CI 1.08–1.78, P = 0.012)
GeparTrio[24] Capecitabine	All	840	sTILs and iTILs	>60% sTILs: pCR 40% TILs: pCR 13.9%	OR 1.21 of pCR per 10% iTILs (95% CI 1.08–1.35, P = 0.001)
GeparQuattro[48] 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)
Everolimus					
GeparSixto[34] 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[58] Trastuzumab Paclitaxel FEC	HER2+	105	sTILs and iTILs on H&E	>60% sTILs: pCR 59% <60% sTILs: pCR 27% (P < 0.015)	Not reported

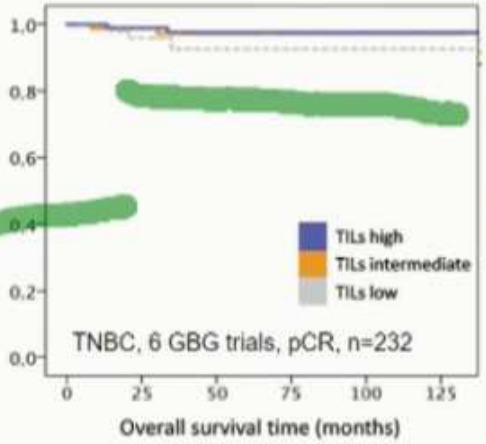
Early TNBC – neoadjuvant therapy as a main approach



Immune markers:
Predictive for
Increased pCR rate

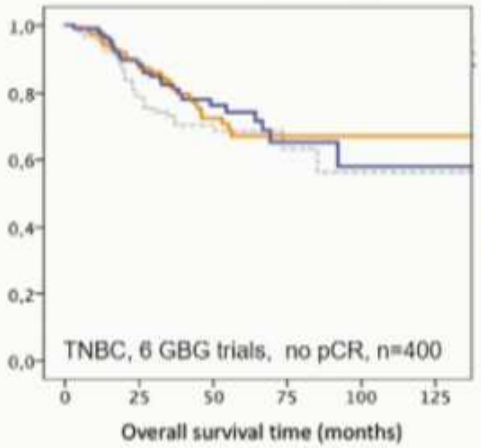
pCR





TNBC with pCR:
excellent
prognosis

no pCR



TNBC no pCR:
poor
prognosis

Denkert et al. Lancet Oncol 2018

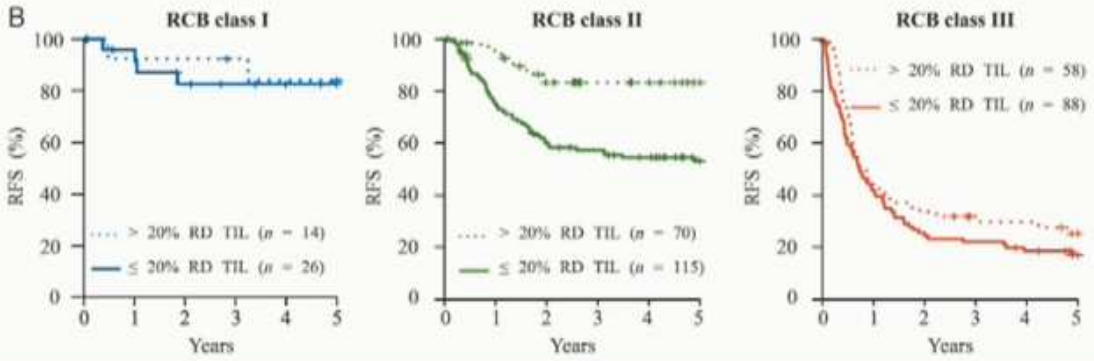
Philipps Universität Marburg

GBG

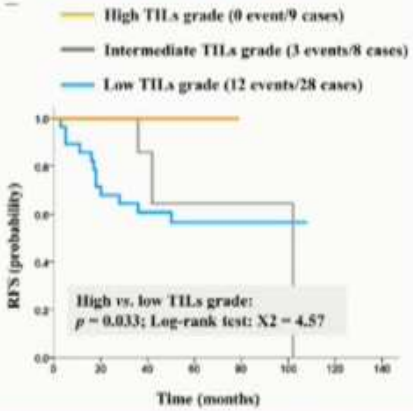
sTILs in Residual Disease

- sTILs in residual disease after neoadjuvant systemic therapy for TNBC or HER2+ disease may add prognostic information to pCR/RCB

TNBC (n=375)



HER2+ (n=45)



Luen et al., Ann Oncol 2018

Kurozumi et al, Sci Rep 2019

Presented by Meredith Regan, St. Gallen 2019

- TILs are a strong prognostic marker in TNBC and HER2+ BC
- TILs can be used for clinical decisions regarding neoadjuvant therapy and for assessment of prognosis.
- TILs can be measured on standard H&E slides – no additional costs.
- They are affordable in all clinical centers.
- Strong analytical validation data – continuous ring trials on website.
- TILs will be included in the new WHO classification of breast cancer

- TILs are a new standard parameter in early breast cancer:
  - Tumor type
  - Grade
  - Ki67
  - TILs

Pathology: TNBC only

50.

TILs should routinely be characterized and reported according to consensus criteria:

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Estimating the Benefits of Therapy for Early Stage Breast Cancer The St Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer 2019

Harold J Burstein, Giuseppe Curigliano, Sibylle Loibl, Peter Dubsky, Michael Gnant, Philip Poortmans, Marco Colleoni, Carsten Denkert, Martine Piccart-Gebhart, Meredith Regan ... Show more

Author Notes

Annals of Oncology, mdz235, https://doi-org.bibliopass.unito.it/10.1093/annonc/mdz235

Published: 02 August 2019

In addition to these familiar biomarkers, the Panel recommended that tumor infiltrating lymphocytes (TILs) be routinely characterized in triple negative breast cancer (TNBC) because of their prognostic value. However, data are inadequate to recommend TILs as a test to guide neo/adjuvant treatment choices in TNBC, as treatments are largely governed by anatomic stage. Tumor PD-L1 or immune-cell PD-1 expression are

TILs

- Definizione
- Composizione
- Valutazione (%)
- Significato clinico:

Biomarcatore prognostico

Biomarcatore predittivo

Biomarcatore di malattia residua

Implicazioni terapeutiche?

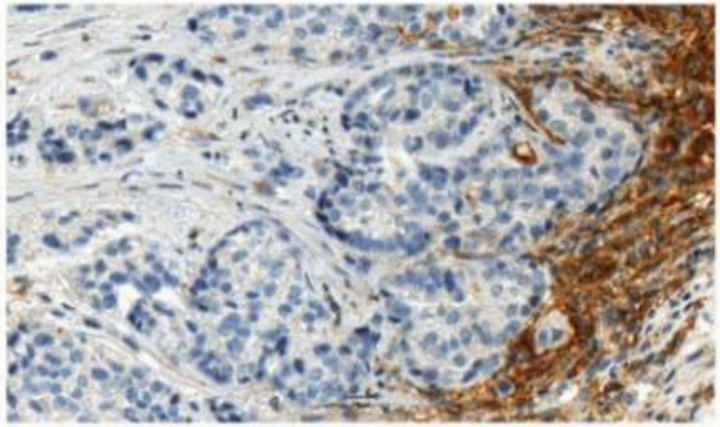
Clinical Review & Education

JAMA Oncology | Review

JAMA Oncol. 2019;5(8):1205-1214.

Current Landscape of Immunotherapy in Breast Cancer
A Review

Sylvia Adams, MD, MS; Margaret E. Gatti-Mays, MD, MPH; Kevin Kalinsky, MD, MS; Larissa A. Korde, MD, MPH; Elad Sharon, MD, MPH; Laleh Amiri-Kordestani, MD; Harry Bear, MD, PhD; Heather L. McArthur, MD, MPH; Elizabeth Frank, MA; Jane Perlmutter, PhD, MBA; David B. Page, MD; Benjamin Vincent, MD; Jennifer F. Hayes, PhD; James L. Gulley, MD; Jennifer K. Litton, MD; Gabriel N. Hortobagyi, MD; Stephen Chia, MD; Ian Krop, MD, PhD; Julia White, MD; Joseph Sparano, MD; Mary L. Disis, MD, MS; Elizabeth A. Mittendorf, MD, PhD



PD-1 molecola espressa su T CD8-CD4,B e NK;
l' interazione con i due ligandi PD-L1 e PD-L2 inibisce la produzione di citochine, la proliferazione e la formazione di granuli citotossici

Challenge for the next years : PD-L1 immunohistochemistry – new biomarker in TNBC

- PD-L1 is a new biomarker for metastatic TNBC in 2019
  - currently only for atezolizumab, other trials ongoing
- pathologists know PD-L1 from other tumor types (extensive existing training material, currently adapted to TNBC)
- clinicians with a focus on breast cancer will need some basic information to understand the pathology reports
- Typical questions:
  - Which antibody to use?
  - **Which scoring system?**
  - Which cell type?
    - (tumor cell, immune cell (Which type of immune cell?)
  - Which cutpoint? – depends on clinical setting

Pathology: TNBC only

52.

Tumour PDL1 expression should routinely be reported:

Pathology: TNBC only

53.

Immune cell PDL1 expression should routinely be reported:

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Author Notes

Annals of Oncology, mdz235, https://doi-org.bibliopass.unito.it/10.1093/annonc/mdz235

Published: 02 August 2019

Tumor PD-L1 or immune-cell PD-1 expression are recognized as markers that may predict benefit from immunotherapy treatment in advanced breast cancer. However, the Panel recommended against routine PD-L1 tumor or PD-1 immune cell testing in early stage TNBC, as current treatment algorithms are not based on such testing.

Per concludere

- TILs fattore prognostico-predittivo
- Valutazione su core-biopsy (TN e HER2 pos)
- Valutazione su sezione pezzo oper (TN e HER2 pos)
- Valutazione su residuo post-neoad (TN e HER2 pos)
- E&E
- Indicazioni del WG

Prox appuntamenti per patologi:

- 22 novembre 2019-controllo di qualità marcatori prognostico-predittivi:

concordanza valutazione TILs

-5 Maggio 2020 GIPaM a Bologna