

con il Patrocinio di



Designated Centers
of Integrated
Oncology and
Palliative Care

7^a edizione

Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2017?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:

Stefania Gori

Giovanni L. Pappagallo

PROGRAMMA

Ospedaleto di Pescantina (VR) 31 Marzo / 1 Aprile 2017
Villa Quaranta Park Hotel

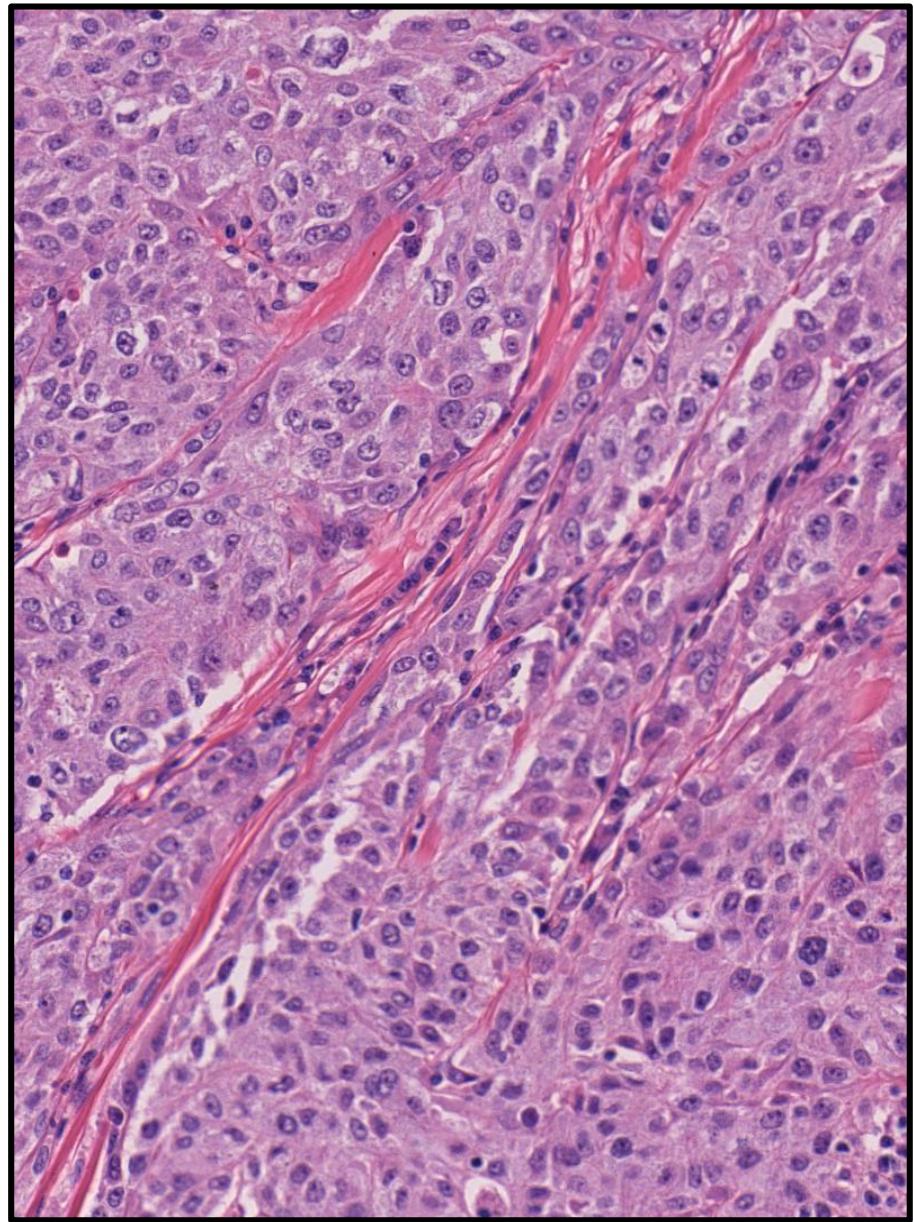
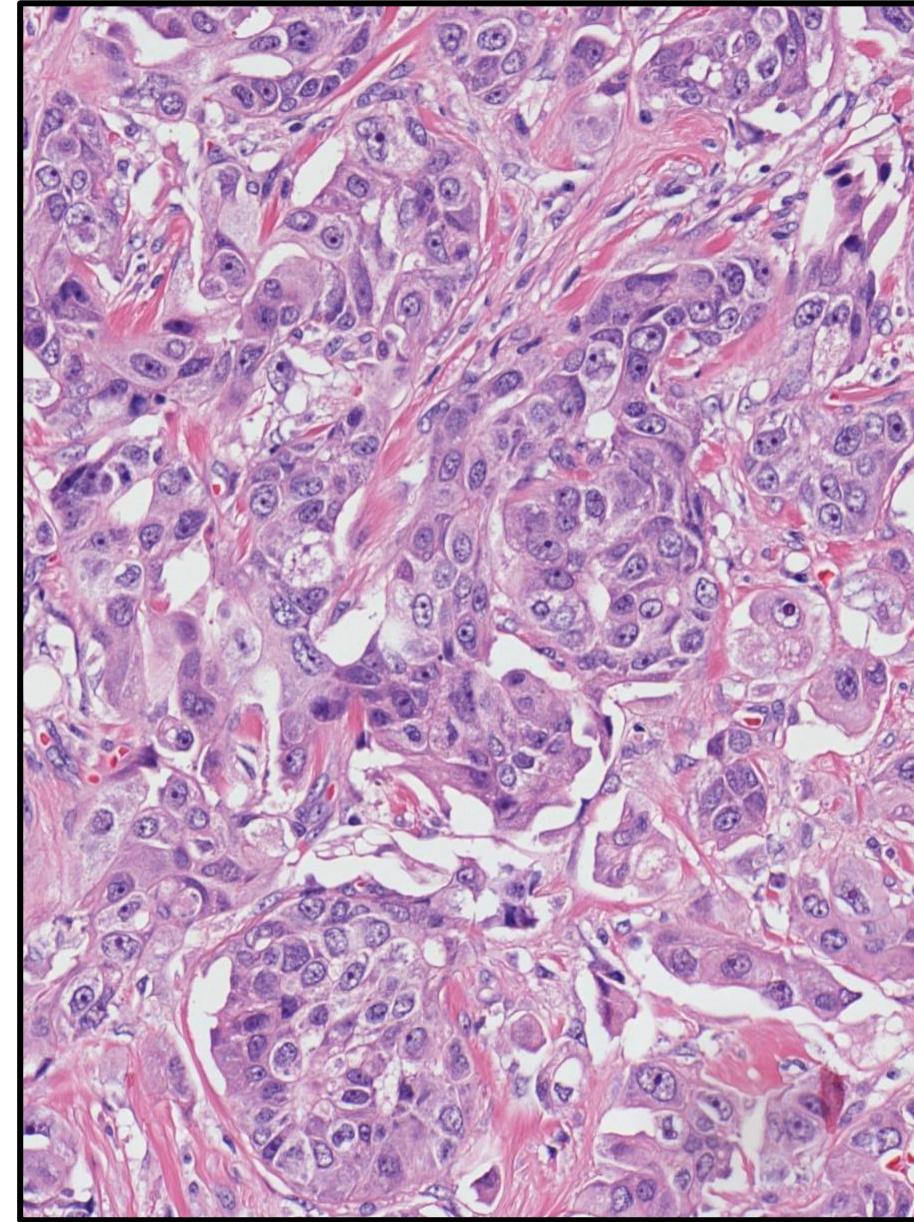
LE NUOVE COLLABORAZIONI....

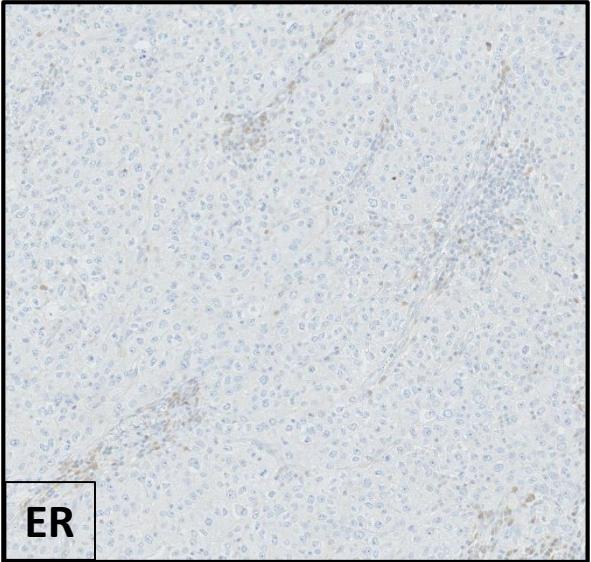
...con l'anatomo-patologo: la valutazione di PDL-1
e TILs nei tumori mammari TN

Bogina Giuseppe

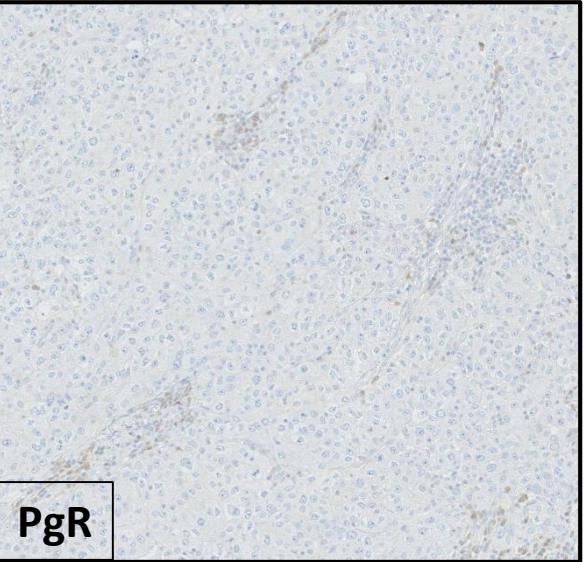
Ospedale Sacro Cuore Negar

giuseppe.bogina@sacrocuore.it

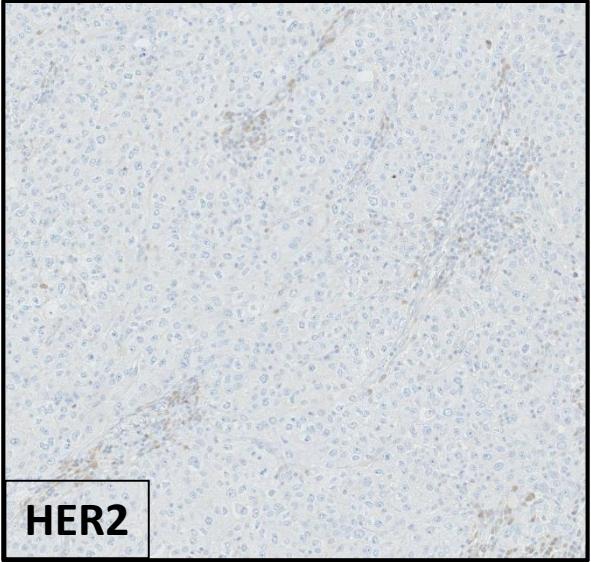
A**B**

A**B**

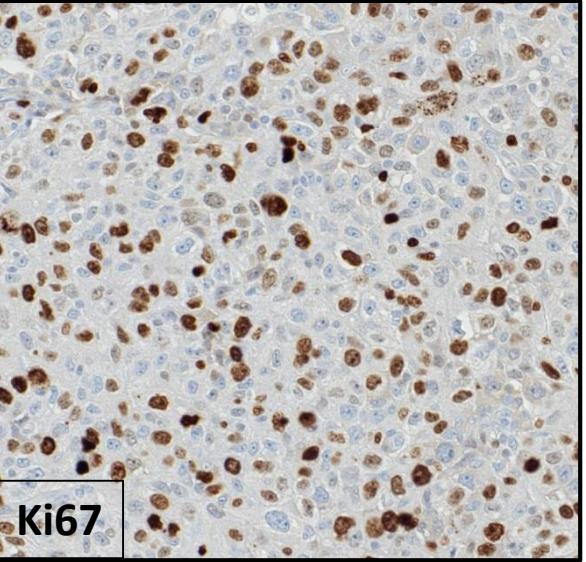
ER



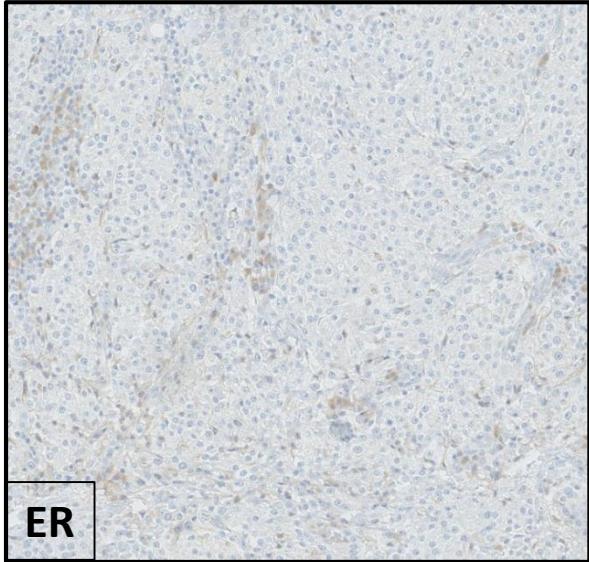
PgR



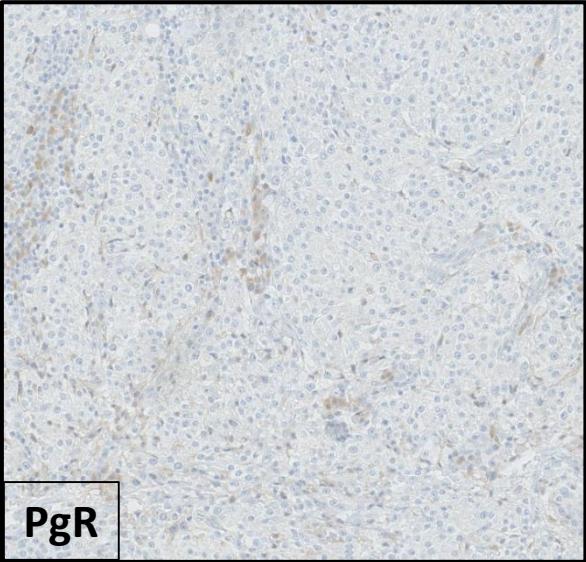
HER2



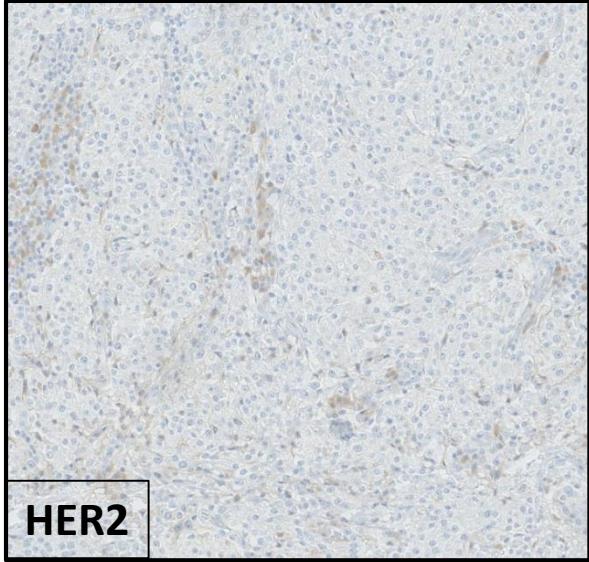
Ki67



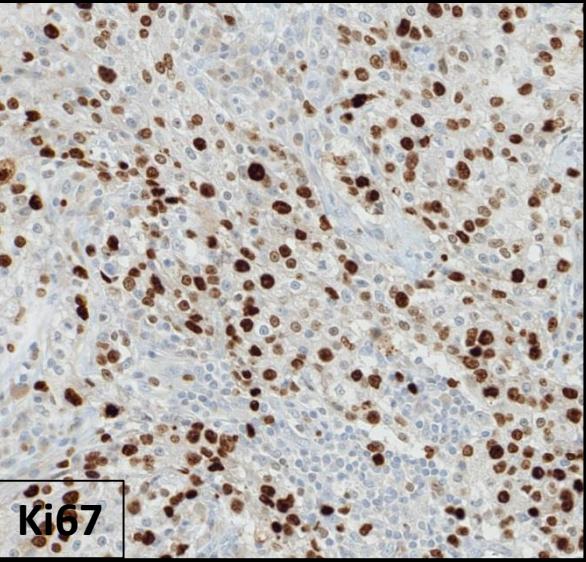
ER



PgR



HER2



Ki67

A

Età 46

Diagnosi:

Carcinoma duttale infiltrante della mammella

Diametro massimo della componente infiltrante: mm 18

Grado di differenziazione : G3

Invasioni vascolari: non evidenti

Linfonodo sentinella: esente da metastasi

Caratterizzazione Immunofenotipica:

ER: negativi

PgR: negativi

HER-2: negativo (score 0)

Ki 67: 30%

B

Età 48

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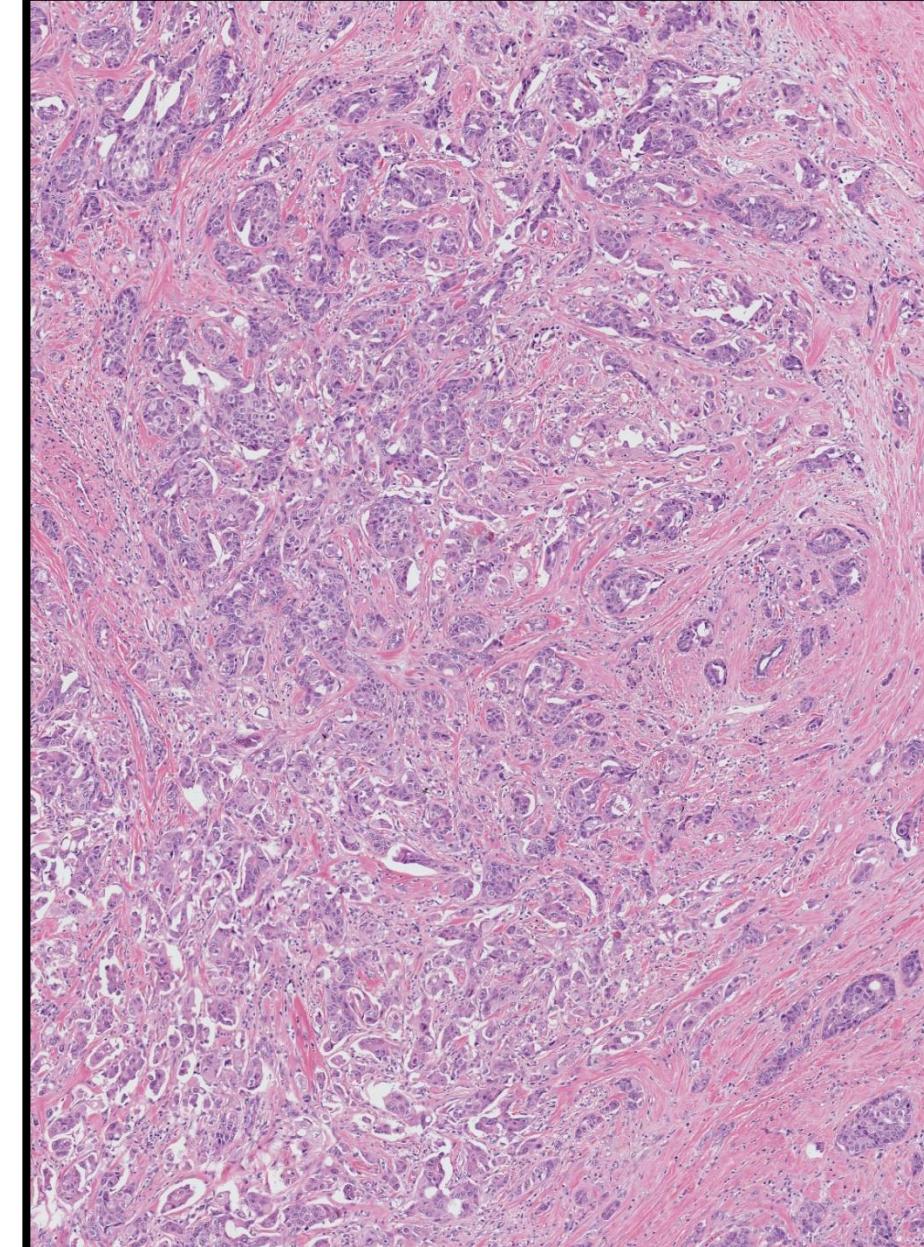
HER-2: negativo (score 0)

Ki 67: 35%

A

B



A**B**

INFLAMED CANCER



"Doc" Sistrunk, 1891-1966

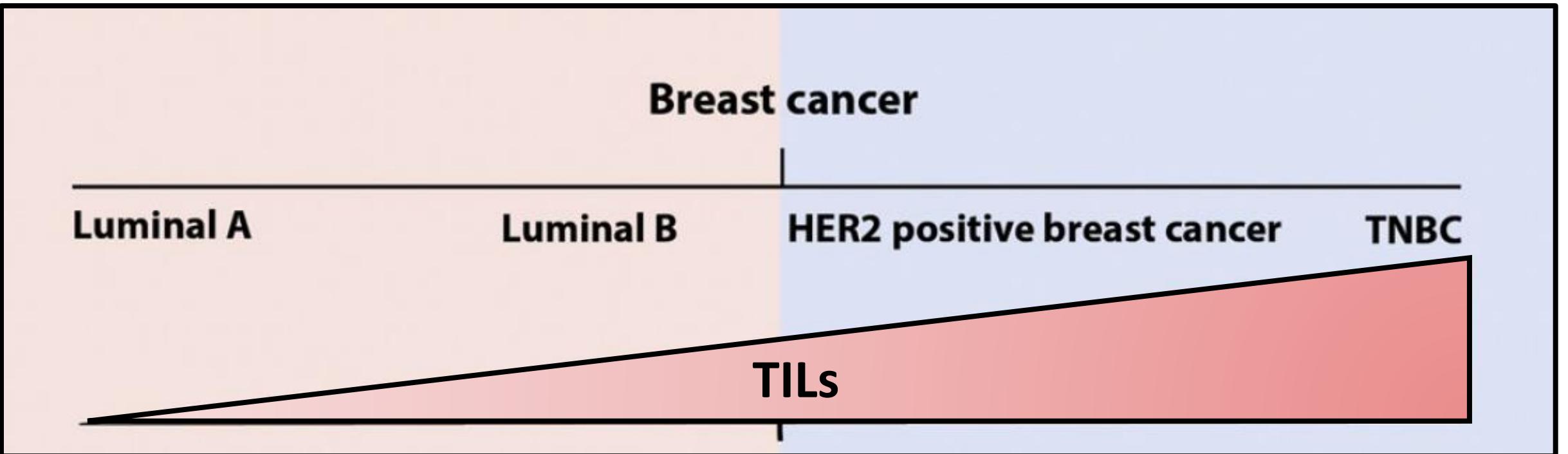
Ann. Surg. 1922

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

BY WALTER E.ISTRUNK, M.D.
OF THE SECTION ON SURGERY
AND

WILLIAM C. MACCARTY, M.D.
OF THE SECTION ON SURGICAL PATHOLOGY, OF THE MAYO CLINIC,
ROCHESTER, MINN.

9. The average length of postoperative life of patients with local lymphocytic infiltration alone was 28 per cent. greater than the average length of postoperative life of the ninety-one patients.



TILs in TNBC

- High TILs in 10-50%
- Fattore prognostico positivo: 15% riduzione rischio di recidiva ogni incremento del 10% di TILs
- Fattore predittivo positivo: Terapia Adiuvante
Terapia Neoadiuvante

TILs

The evaluation of TILs in breast cancer: recommendations by an International TILs Working Group 2014

Full sections preferred over biopsies

Stromal TILs reported as %

No formal TILs threshold can be recommended

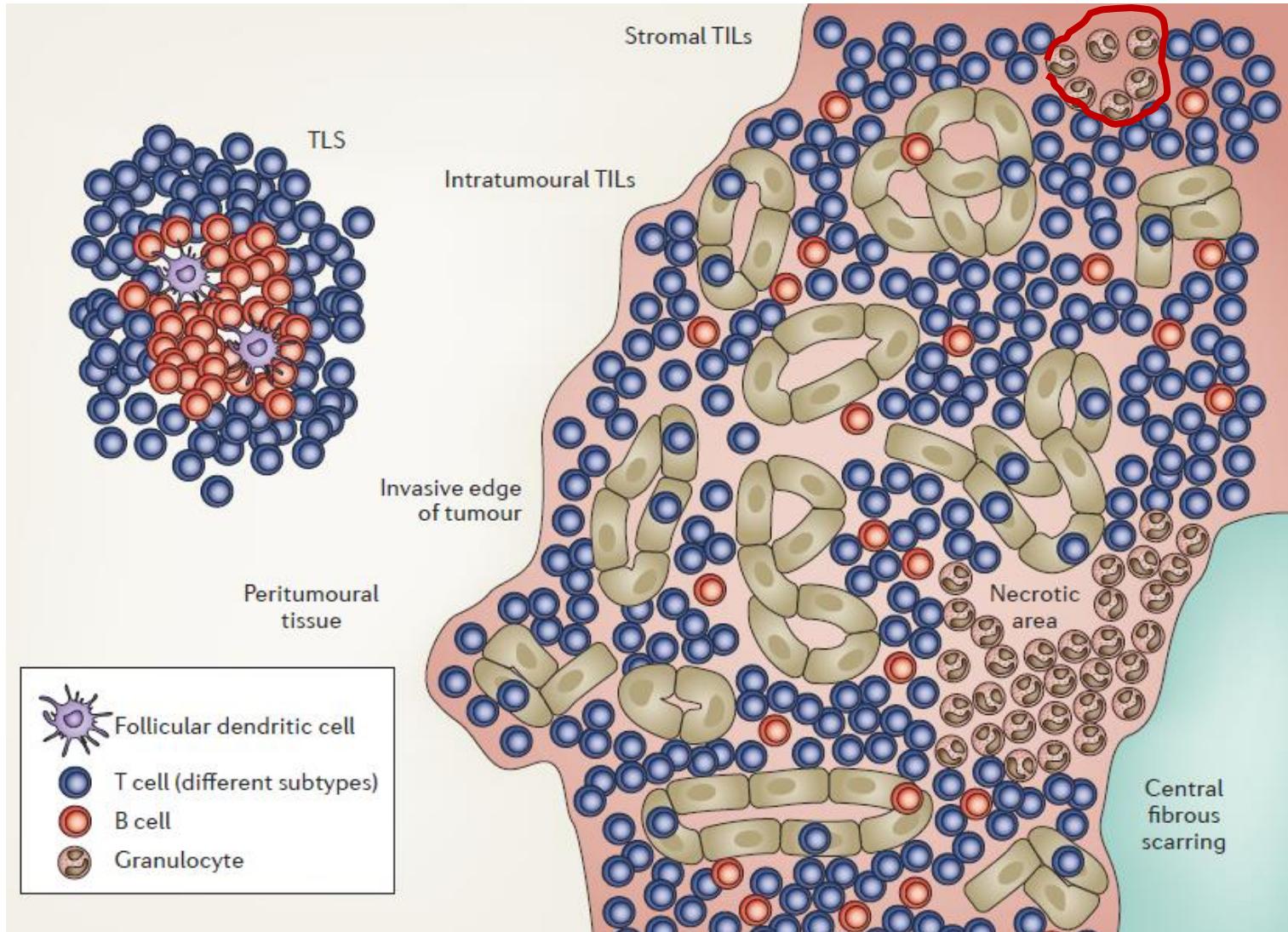
Within the borders of invasive component

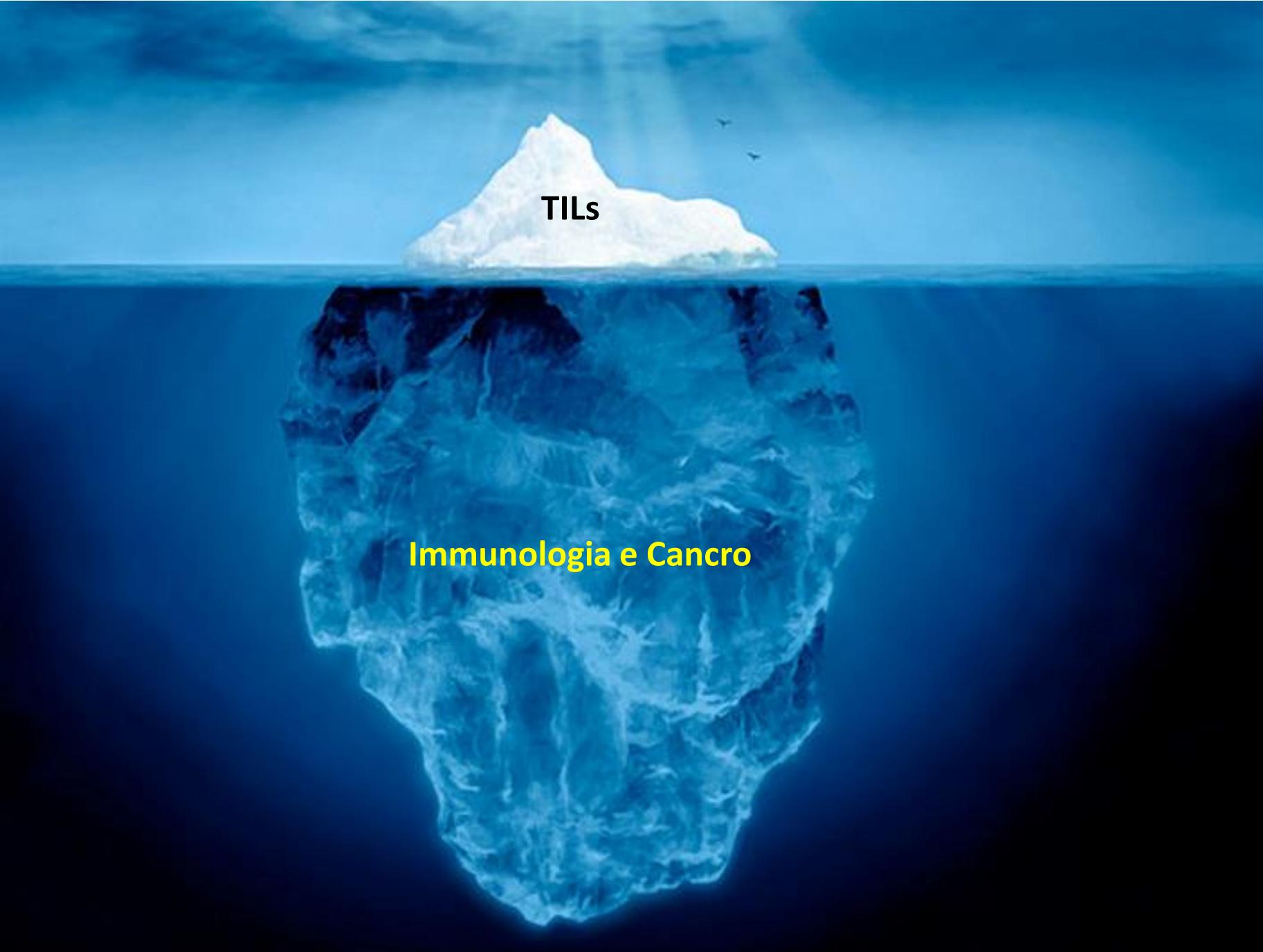
A full assessment of overall TILs

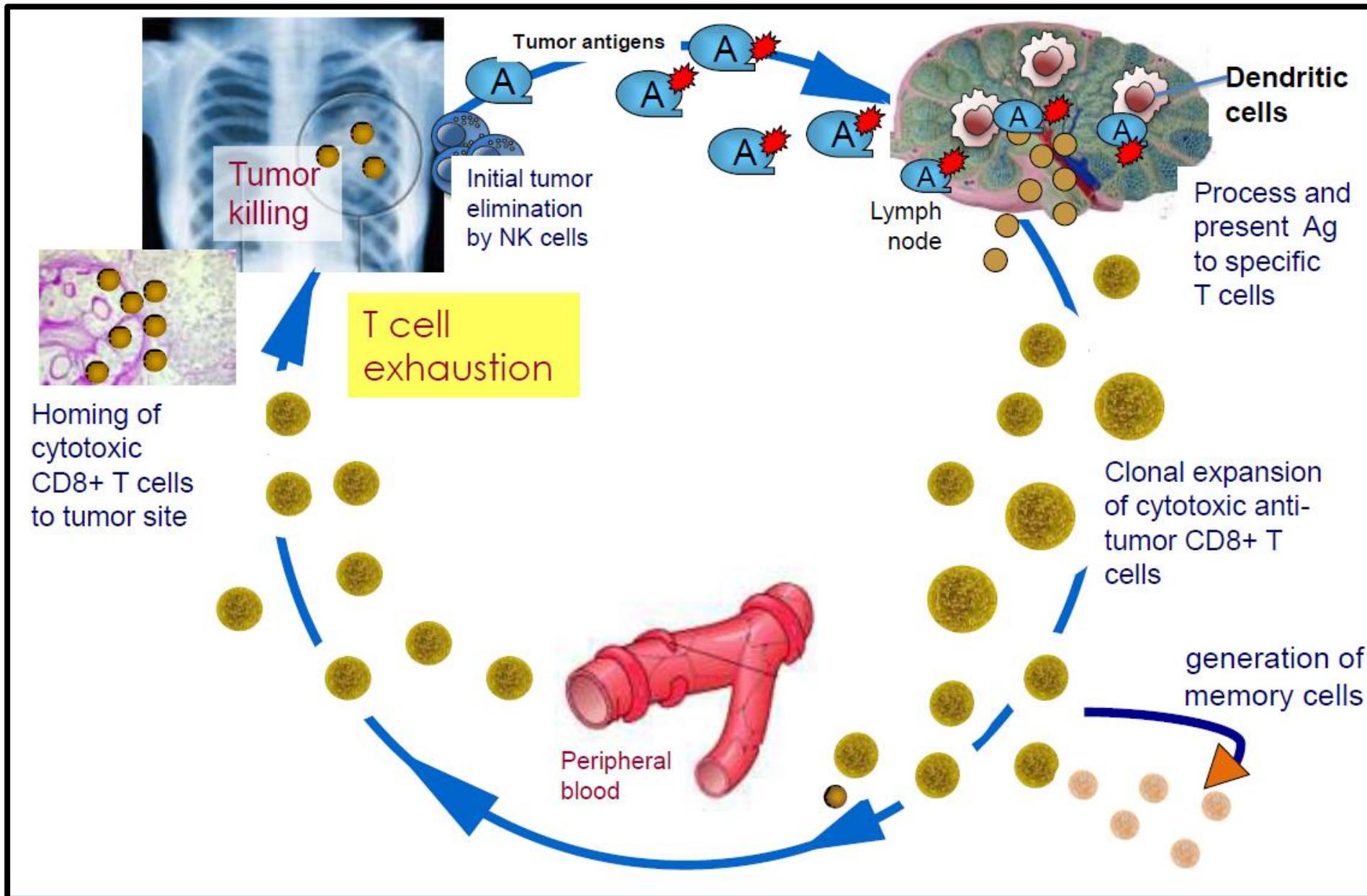
Do not focus on hotspots

Mononuclear cells should be

Polymorphonuclear leukocytes are excluded









ELIMINAZIONE DEL TUMORE

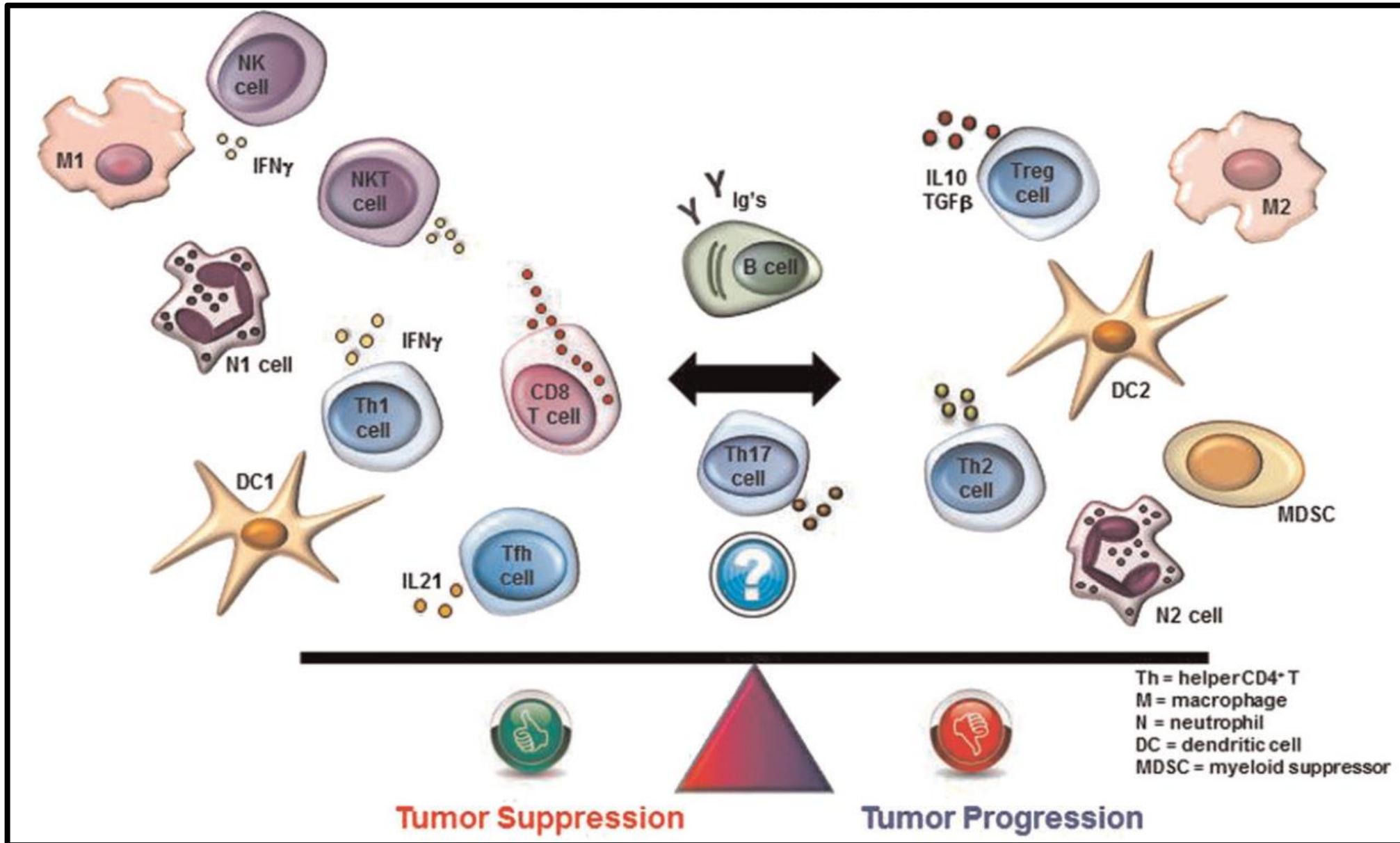
RISPOSTA IMMUNITARIA ECESSIVA



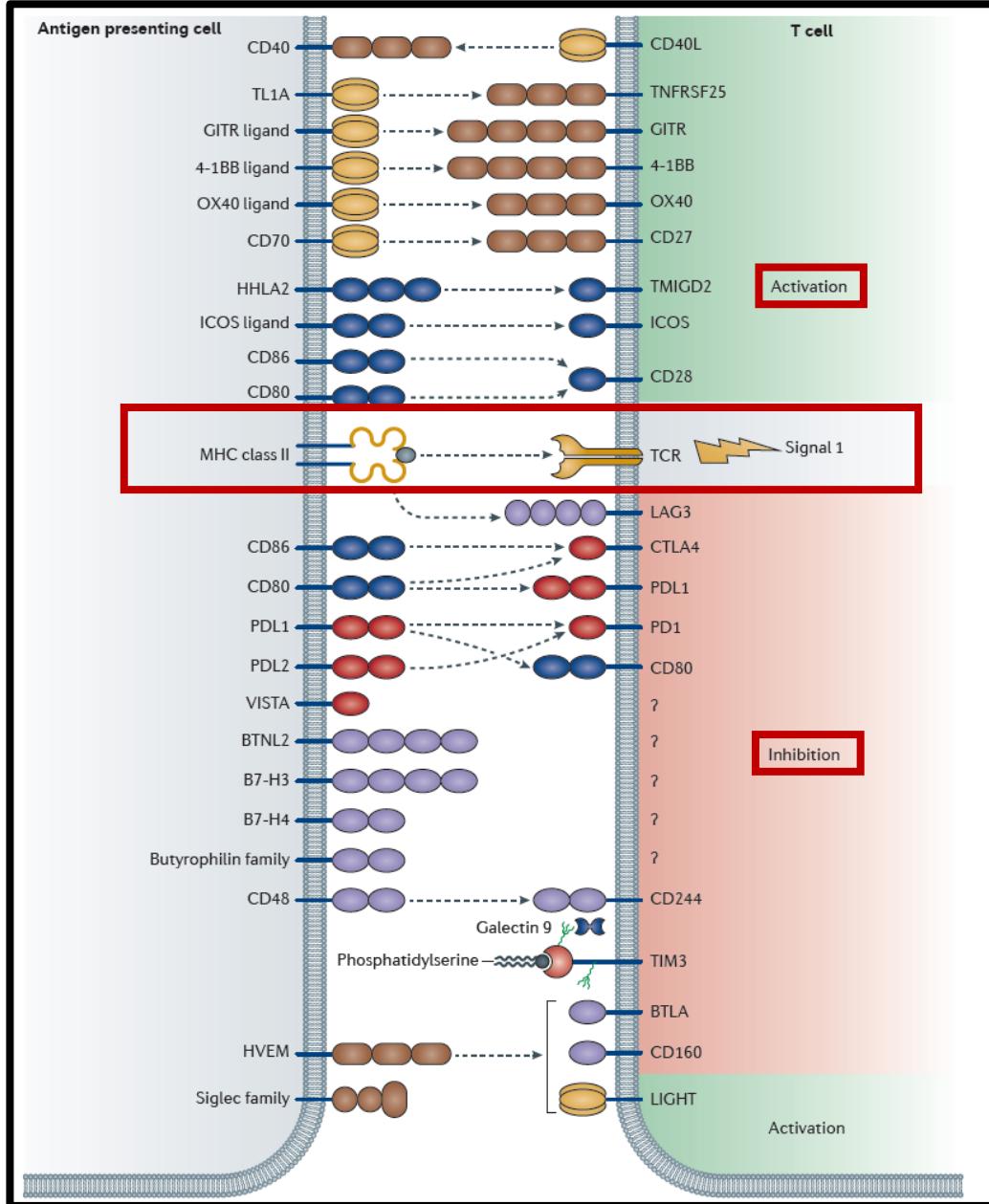
CELLULE IMMUNITARIE

CITOCHINE

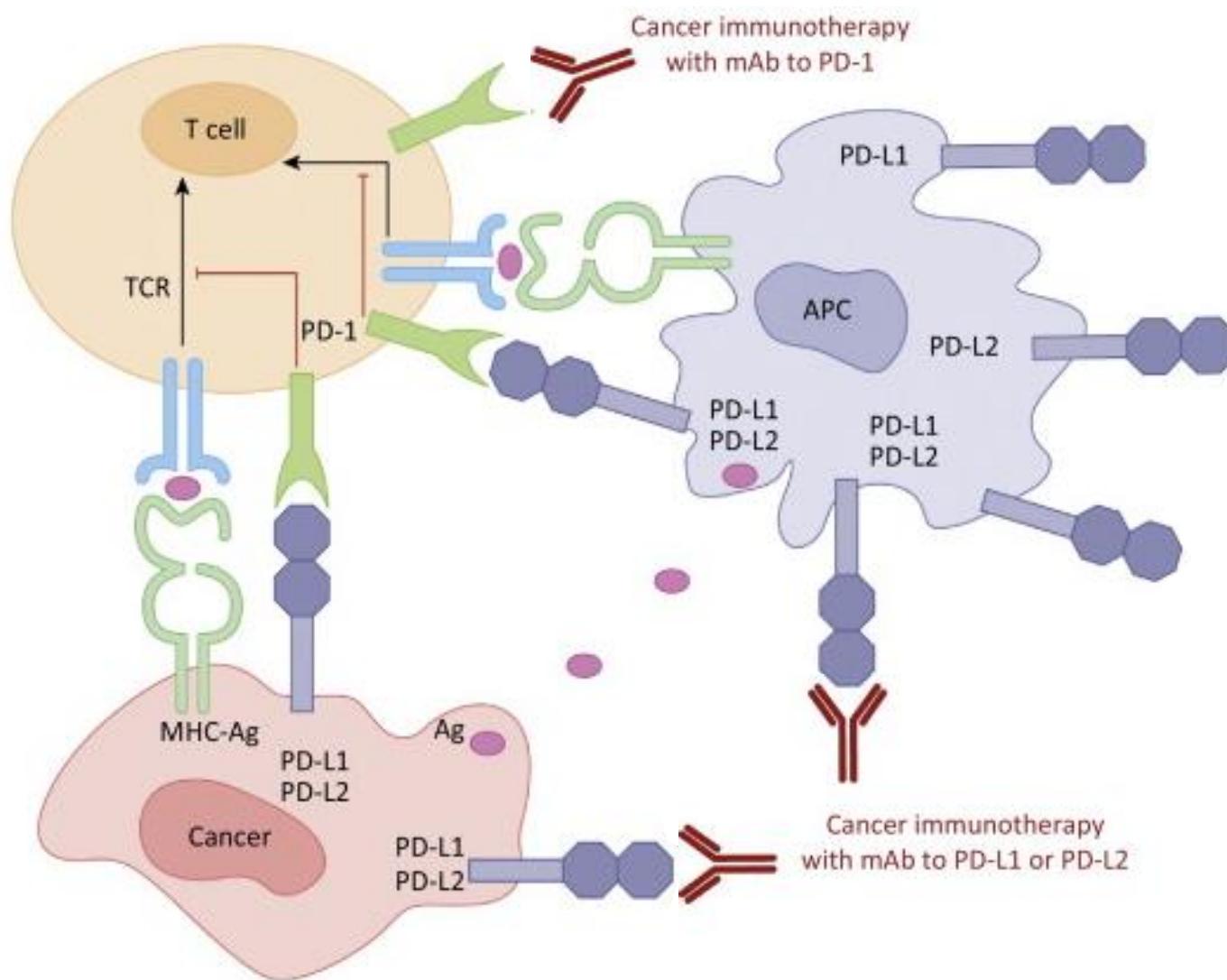
CECKPOINT IMMUNITARIO



CHECKPOINT IMMUNITARIO

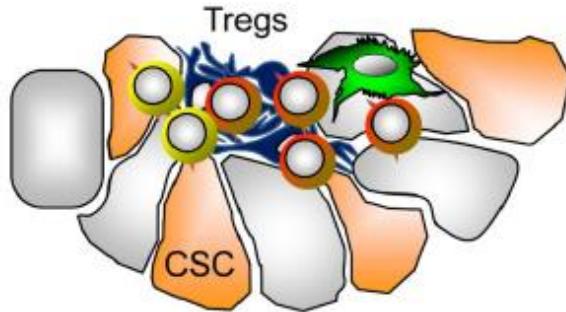


CHECKPOINT IMMUNITARIO



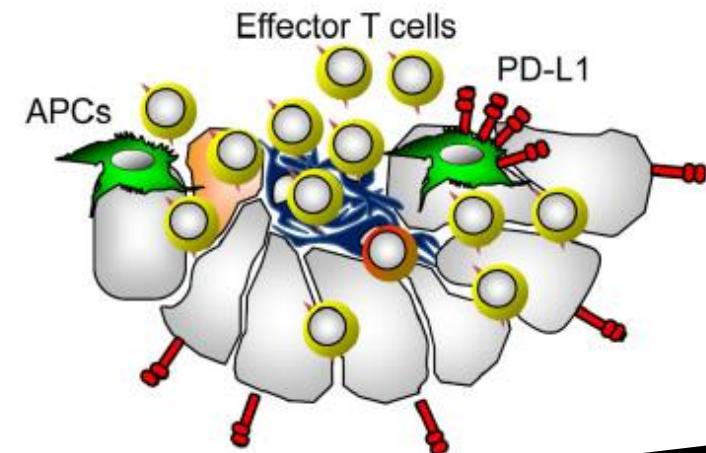
No or limited response to treatment

“non-inflamed cancer”



Active response to treatment

“inflamed cancer”

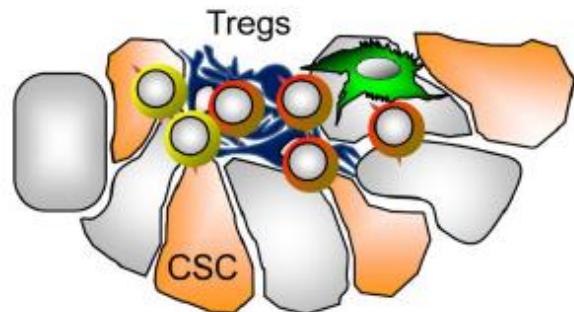


TIL
PD1-PDL1

- “Carico Mutazionale”
- Neoantigeni

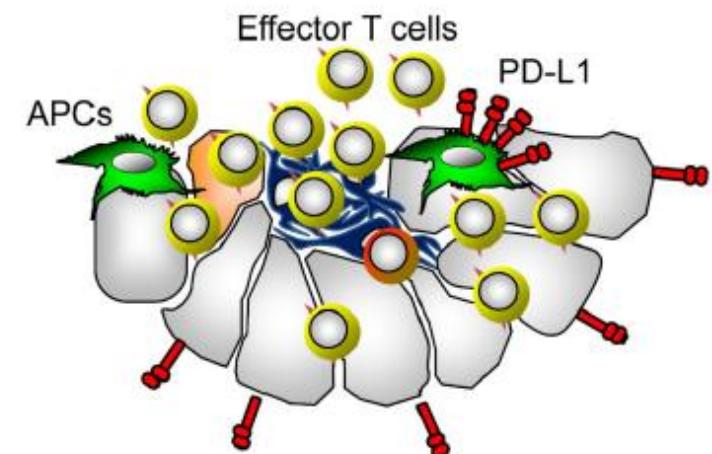
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CARCINOMI PANCREAS

CARCINOMI PROSTATA

CARCINOMI MAMMELLA

MELANOMI

NSCLC

CARCINOMI VESCICA

CARCINOMA RENE

Breast cancer

Luminal A

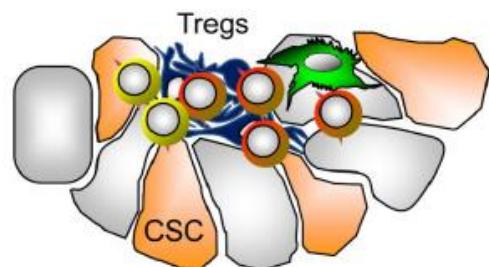
Luminal B

HER2 positive breast cancer

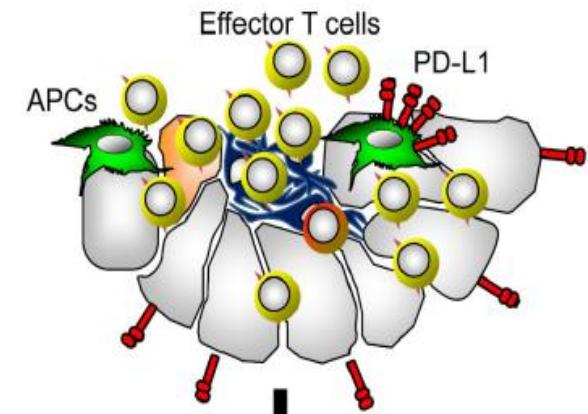
TNBC

PD1-PDL1

No or limited response to treatment
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Active response to treatment
“inflamed cancer”



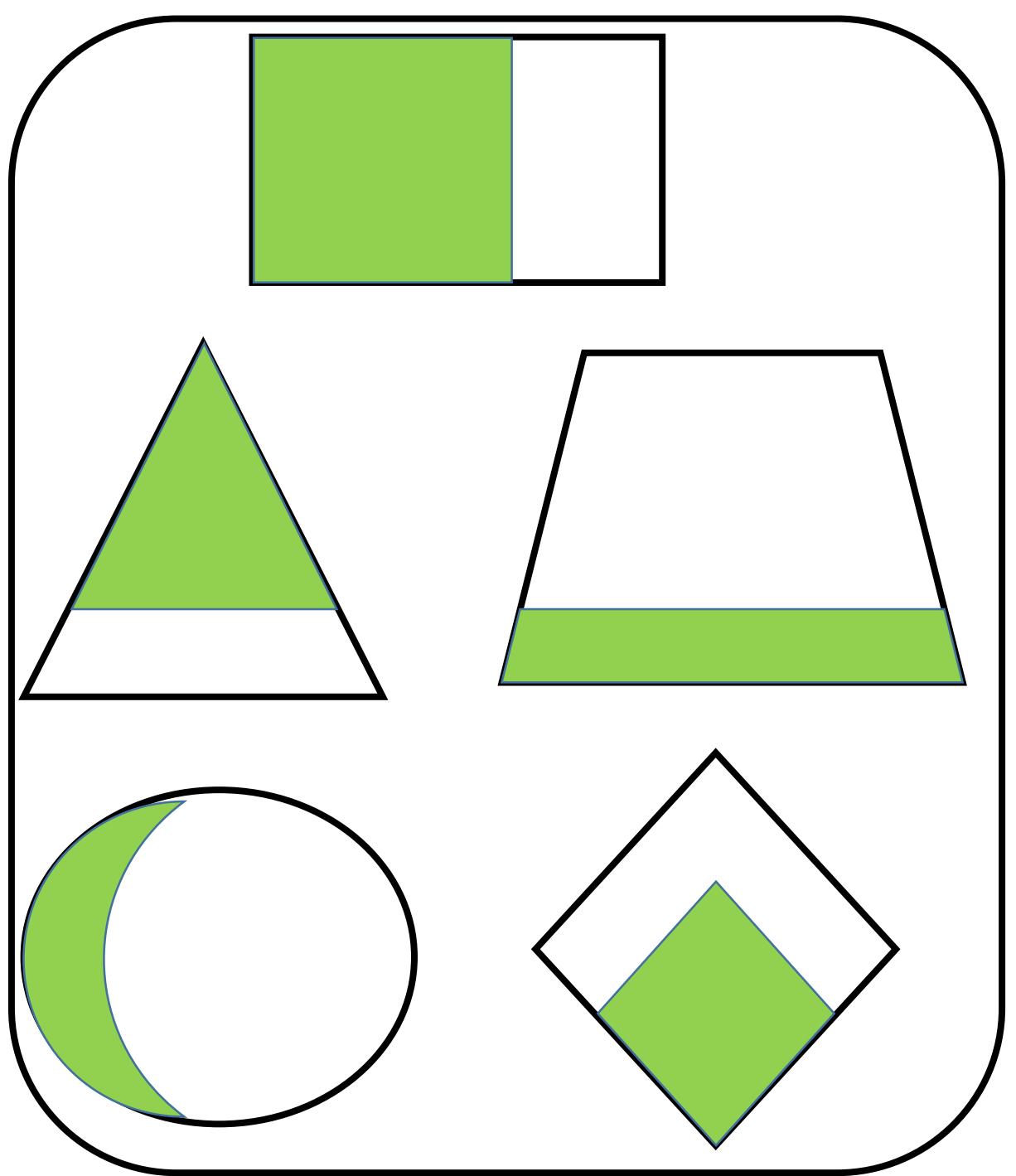
Disease setting	Phase	Clinical trial reference number	Breast cancer	Immunotherapies (alone or in combination)
<i>Trials including only patients with TNBC</i>				
Metastatic	I/II	NCT02513472	TNBC	Pembrolizumab*/eribulin mesylate
	II	NCT02499367	TNBC	Nivolumab*/ doxorubicin (low dose) or cyclophosphamide metronomic or radiation therapy or cisplatin
		NCT02447003	TNBC	Pembrolizumab
	III	NCT02555657	TNBC	Pembrolizumab
		NCT02425891	TNBC	Atezolizumab*/nab-paclitaxel
Adjuvant	II	NCT02539017	TNBC	Vaccine (DC-CIK)/EC followed by docetaxel
Neoadjuvant	I/II	NCT02489448	TNBC	Durvalumab*/nab-paclitaxel followed by ddAC
	II	NCT02530489	TNBC	Atezolizumab/nab-paclitaxel
	III	NCT02620280	TNBC (LABC only)	Atezolizumab/nab-paclitaxel/ carboplatin

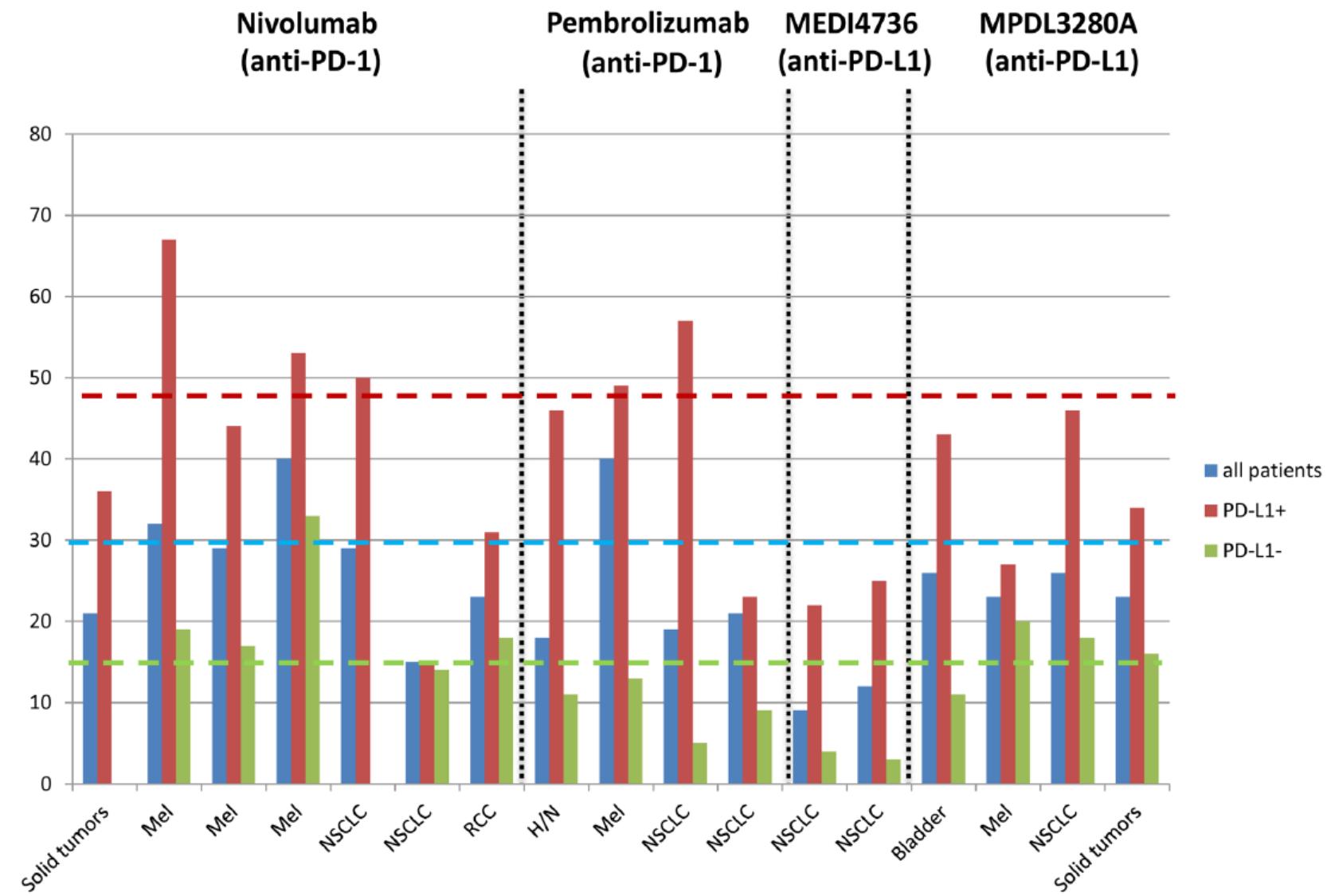
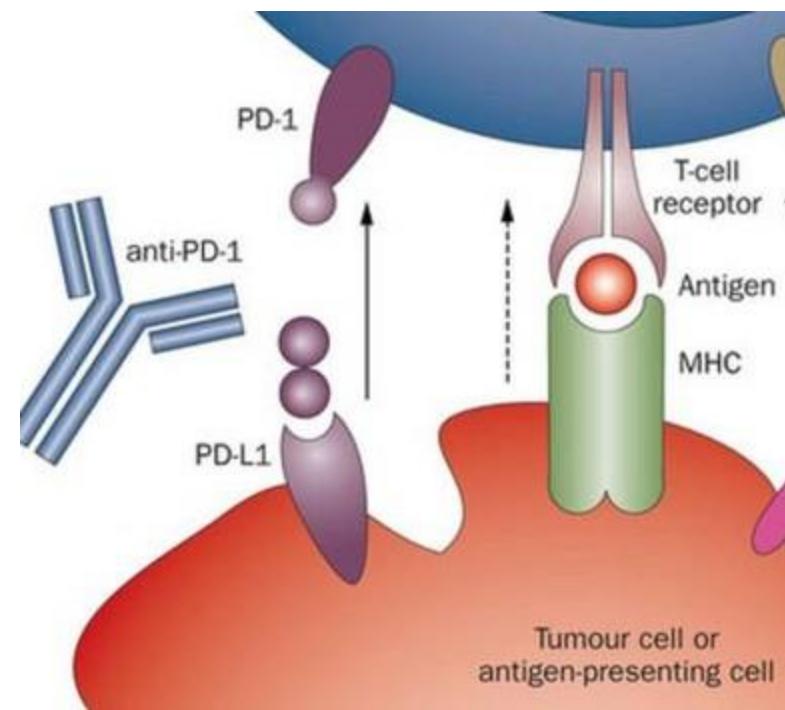
Pembrolizumab: ORR: 18,5% (32 TNBC)

(Nanda R et al. San Antonio Breast cancer 2014)

Atezolizumab: ORR: 19% (21 TNBC)

(Emens L. et al. San Antonio Breast cancer 2014)





Programmed Death Ligand-1 Immunohistochemistry

Friend or Foe?

Keith M. Kerr, BSc, MB, ChB, FRCPath, FRCPE; Fred R. Hirsch, MD, PhD

Preanalitiche

-Fissazione: tipo di fissativo, tempo di fissazione..

-Processazione

Analitiche

-Validazione e standardizzazione procedure

-Competenza staff tecnico

-Anticorpo: **Clone**, concentrazione, tempo e temperatura di incubazione

-Tipo di smascheramento antigenico

-Uso di campioni di controllo

Postanalitiche

-Criteri di interpretazione: eterogeneità, intensità, soglia di positività

-Competenza del patologo

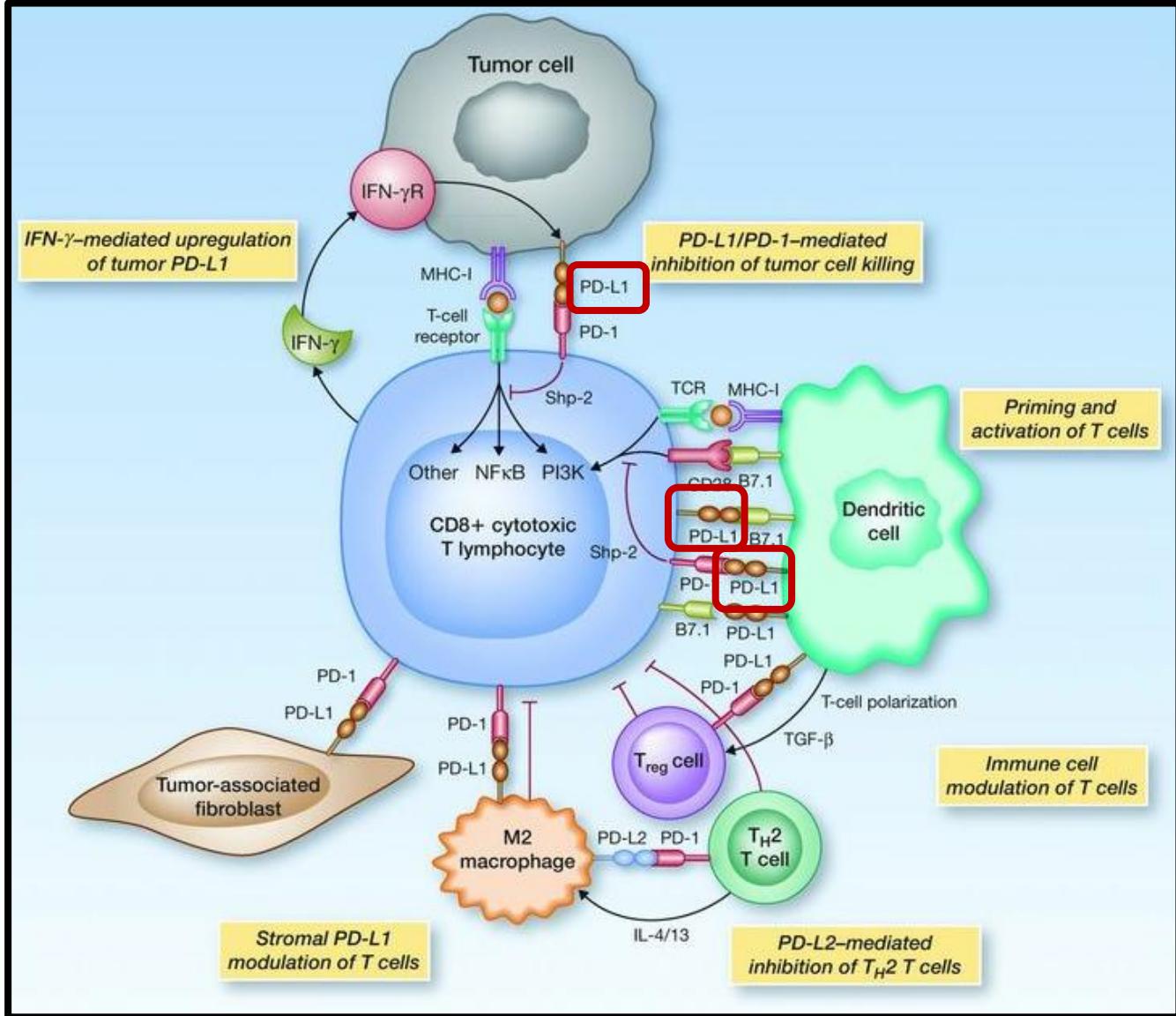
-Refertazione

-Controlli di qualità

CLONE	FARMACO	%
Dako 28-8	Nivolumab	++
Dako 22-C3	Pembrolizumab	++
Ventana SP142	Atezolizumab	+
Ventana SP263	Durvalumab	+++

- Intratumorale
- Primitivo vs Metastasi

- 1%
- 5%
- 10%
- 50%





	Tutti i pazienti	Risposta Obiettiva
Anti-PDL1 Tumour		
+	56%	39%
-	44%	6%
Anti-PDL1 IC		
+	56%	35%
-	44%	11%
Anti-PD1 TIL		
+	43%	44%
-	57%	14%

Patient diagnosis (*n* = 41)

Melanoma	16
NSCLC ^a	12
Kidney cancer	6
Colorectal cancer	5
CRPC	2



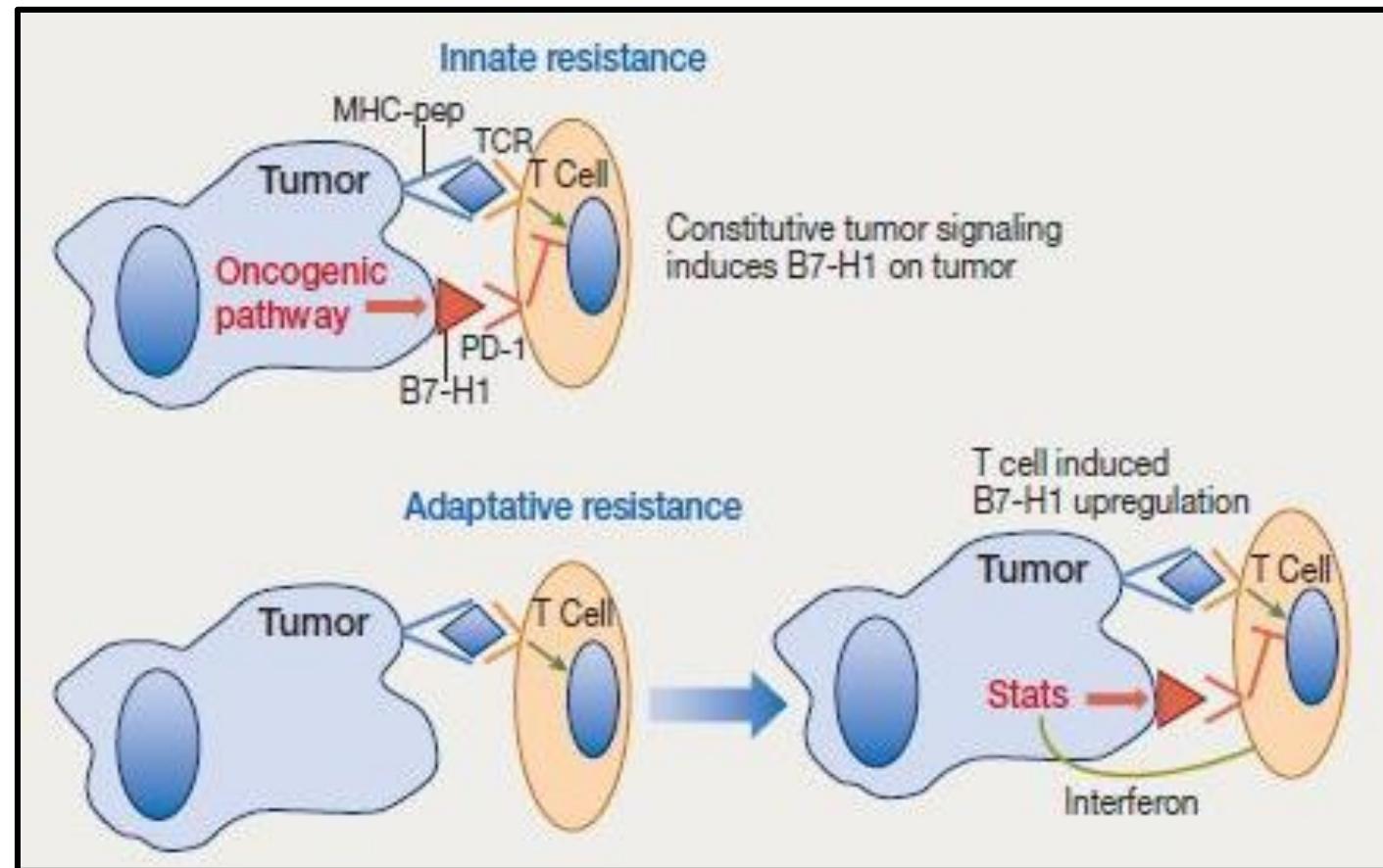
PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

Indication	<i>n</i>	Percentage of PD-L1 positive (IC)	Percentage of PD-L1 positive (TC)
NSCLC	184	26	24
RCC	88	25	10
Melanoma	58	36	5
HNSCC	101	28	19
Gastric cancer	141	18	5
CRC	77	35	1
Pancreatic cancer	83	12	4

“The association of response to MPDL3280A treatment and tumour-infiltrating immune cell PD-L1 expression reached statistical significance, while the association with tumour cell PD-L1 expression did not.”

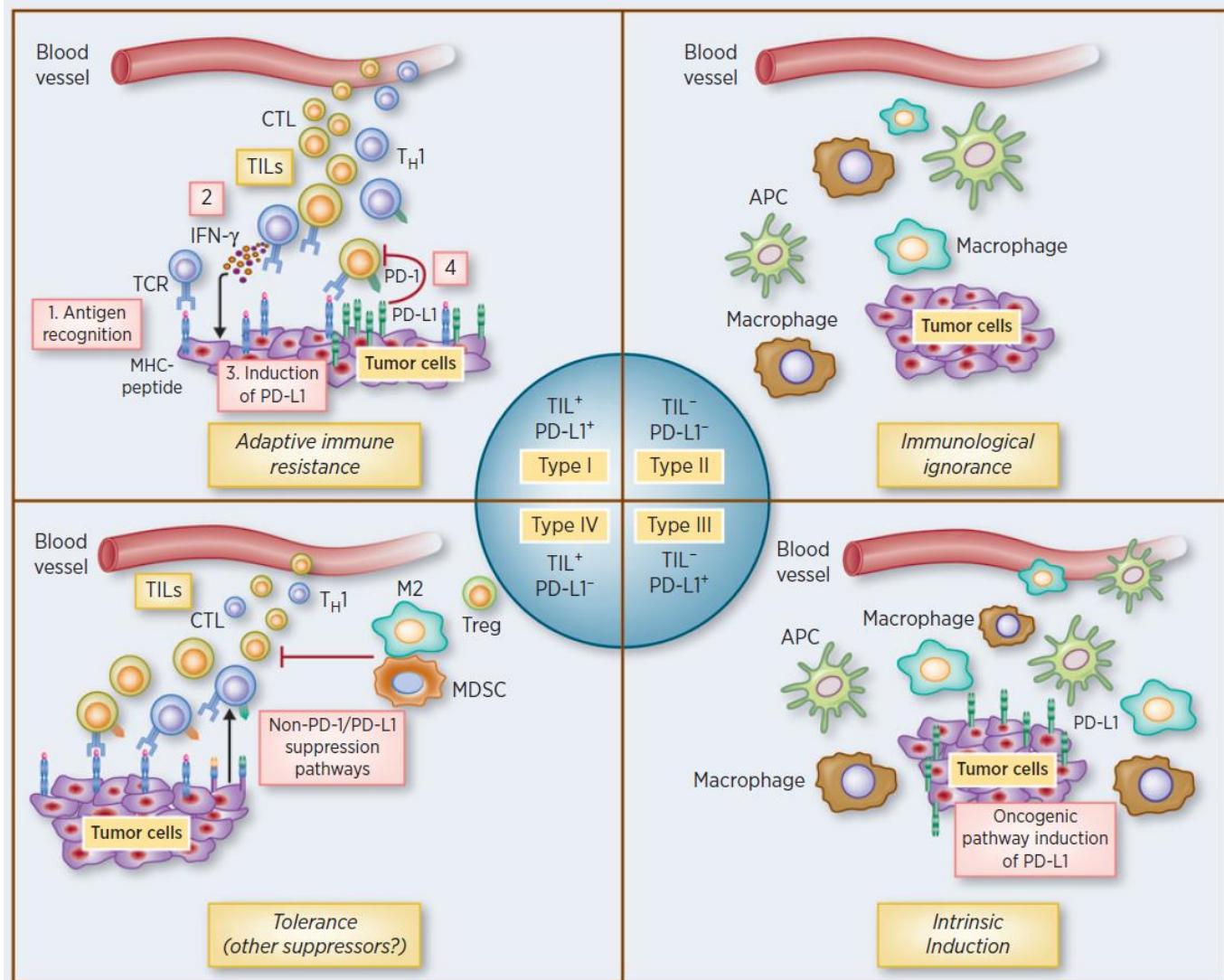
IPERESPRESSIONE PD-L1

- Amplificazione gene 9p24.1
- Mutazione PTEN (Glioblastomi)
- Iperespressione ALK (Linfomi, NSCLC)
- Mutazione KRAS (NSCLC)



T-cell exhaustion
Anti-PD1/PDL1

Other suppressive cells
Other checkpoint target

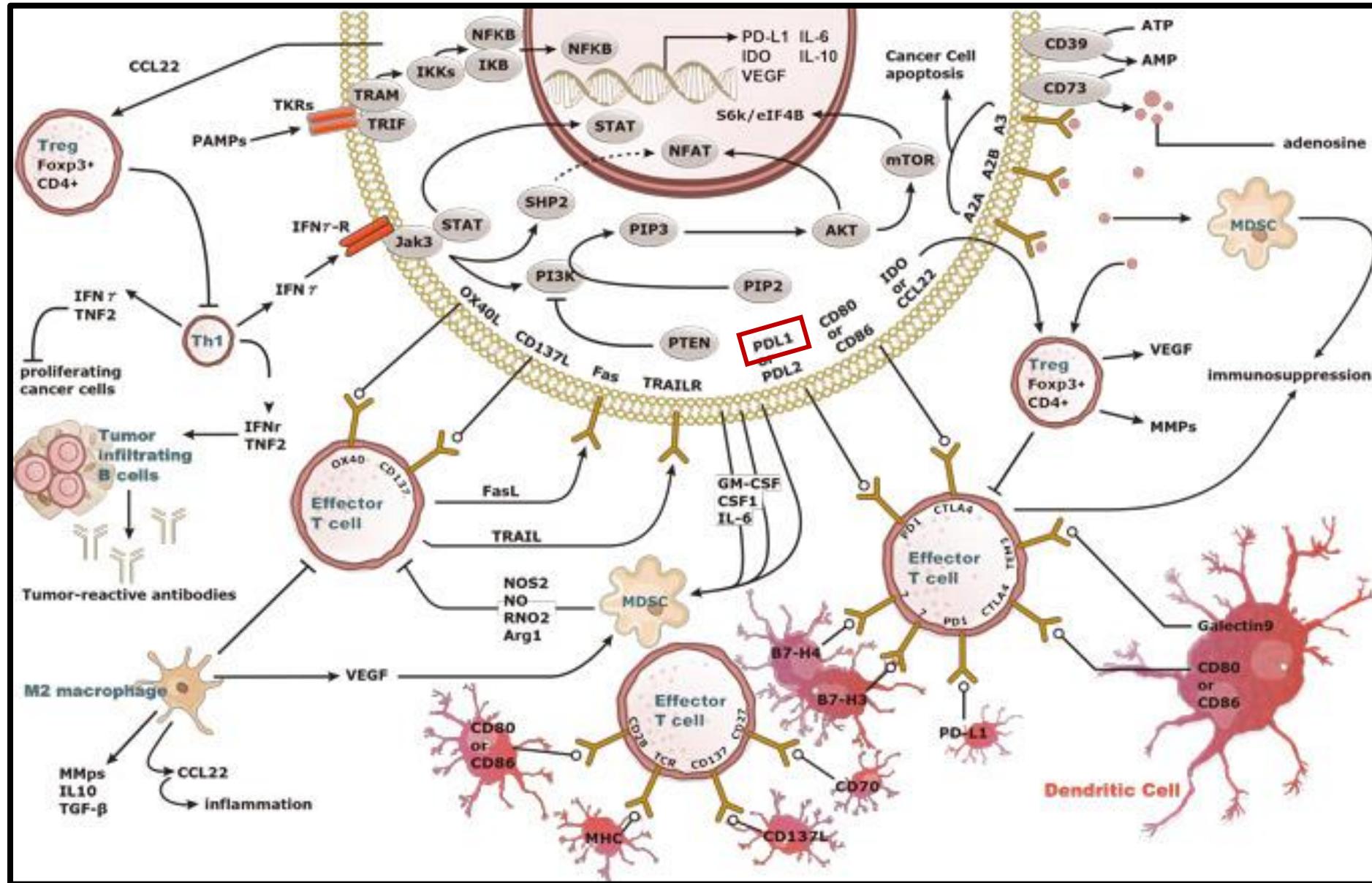


Inadequate antigen presentation
Anti-PD1/PDL1 + Anti-CTLA4....
Induction type 1 IFN response

PDL1 constitutive expression
Anti-PD1/PDL1 + Anti-CTLA4....
Induction type 1 IFN response

PD-1/PD-L1, Only a Piece of the Puzzle

Ross A. Miller, MD; Tara N. Miller, MD; Philip T. Cagle, MD



A

Diagnosi:

Carcinoma duttale infiltrante della mammella

Diametro massimo della componente infiltrante: mm 18

Grado di differenziazione : G3

Invasioni vascolari: non evidenti

TILs: < 1%

Linfonodo sentinella: esente da metastasi

Caratterizzazione Immunofenotipica:

ER: negativi

PgR: negativi

HER-2: negativo (score 0)

Ki 67: 30%

B

Diagnosi:

Carcinoma duttale infiltrante della mammella

Diametro massimo della componente infiltrante: mm 16

Grado di differenziazione : G3

Invasioni vascolari: non evidenti

TILs: 70%, con follicoli linfoidi

Linfonodo sentinella: esente da metastasi

Caratterizzazione Immunofenotipica:

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HER-2: negativo (score 0)

Ki 67: 35%

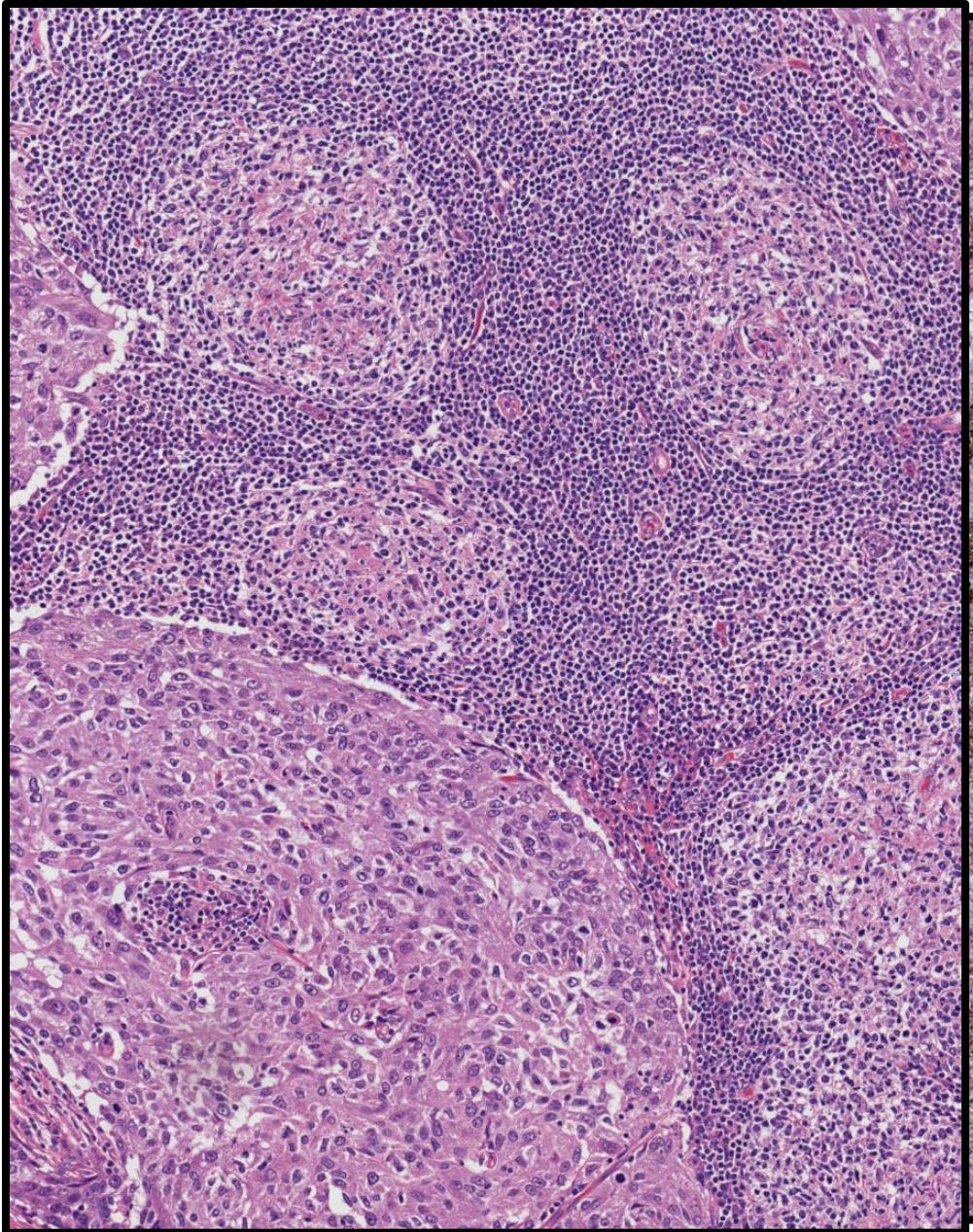
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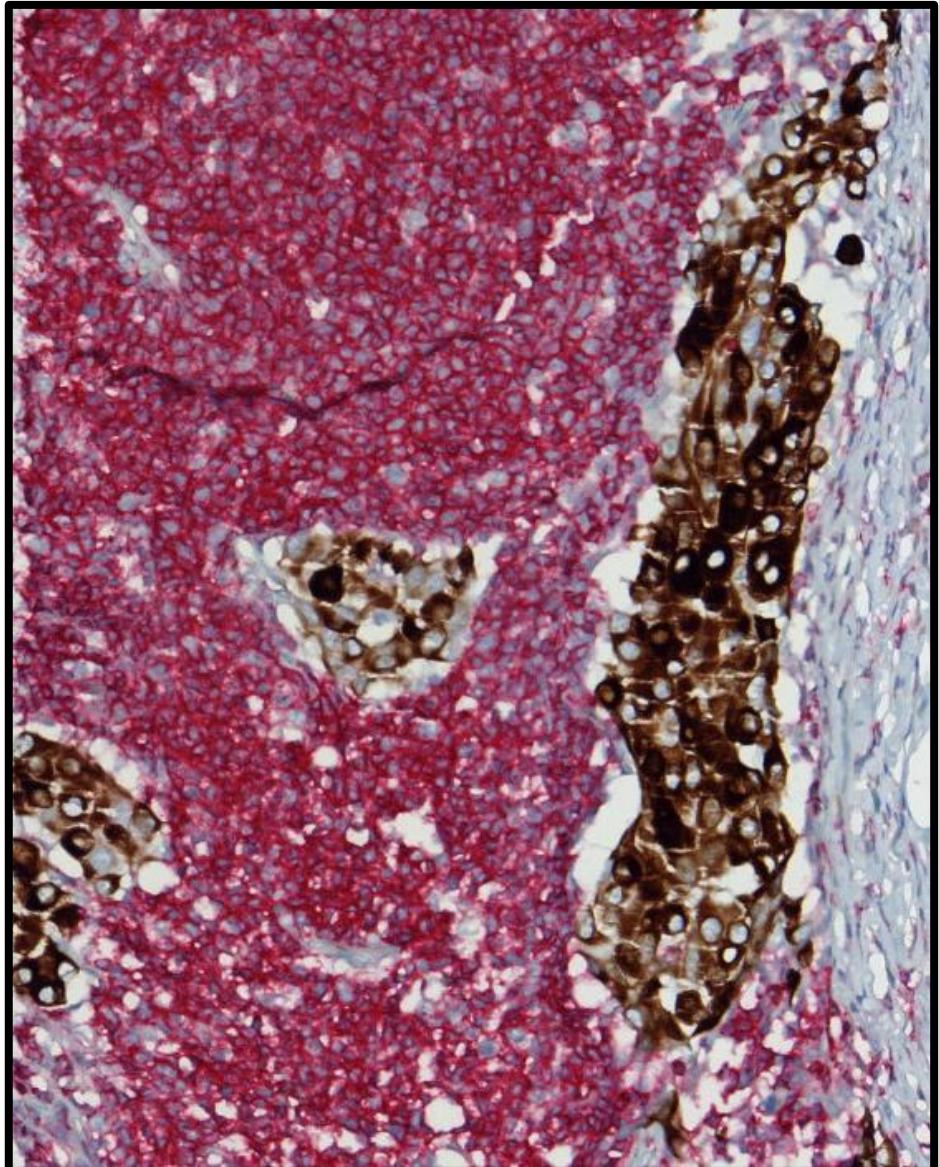


Grazie per l'attenzione

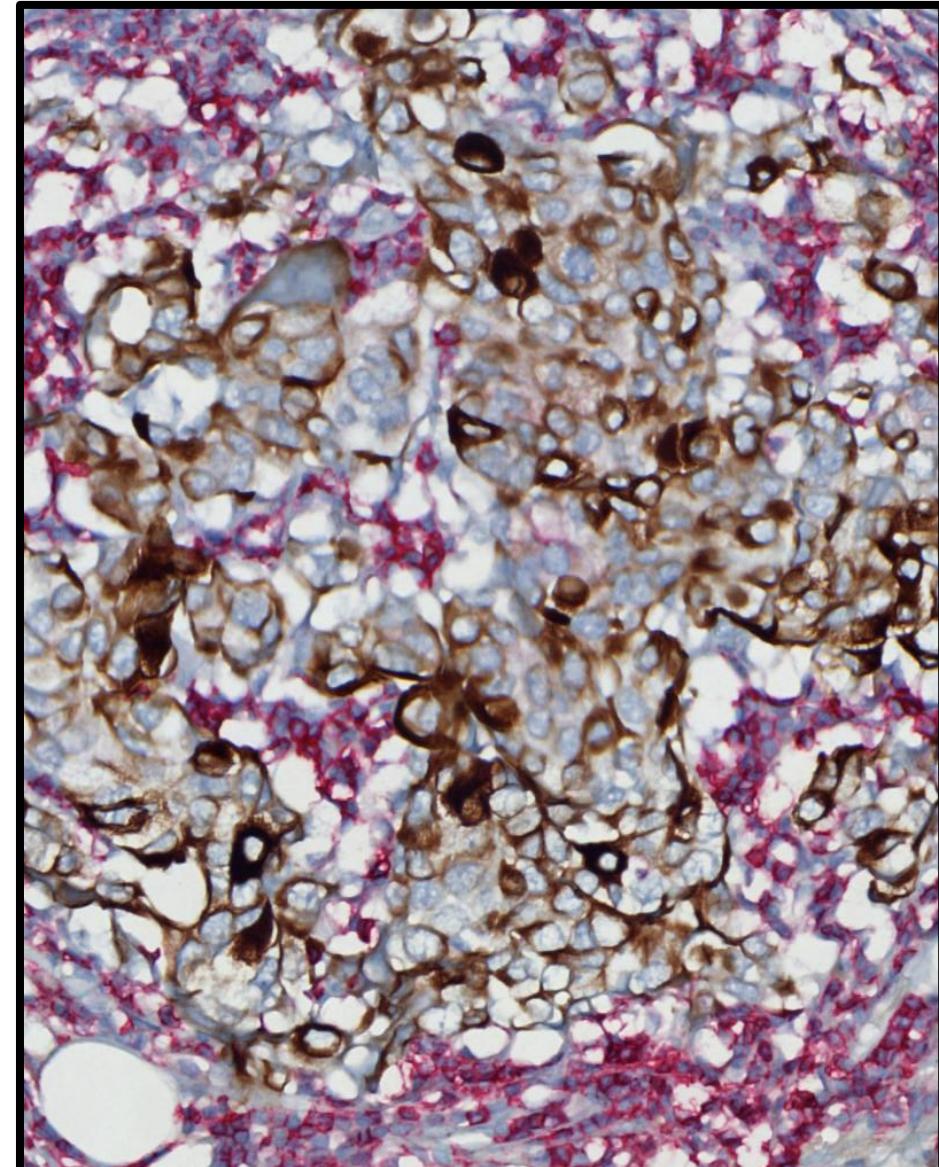
INFLAMED CANCER



INFLAMED CANCER

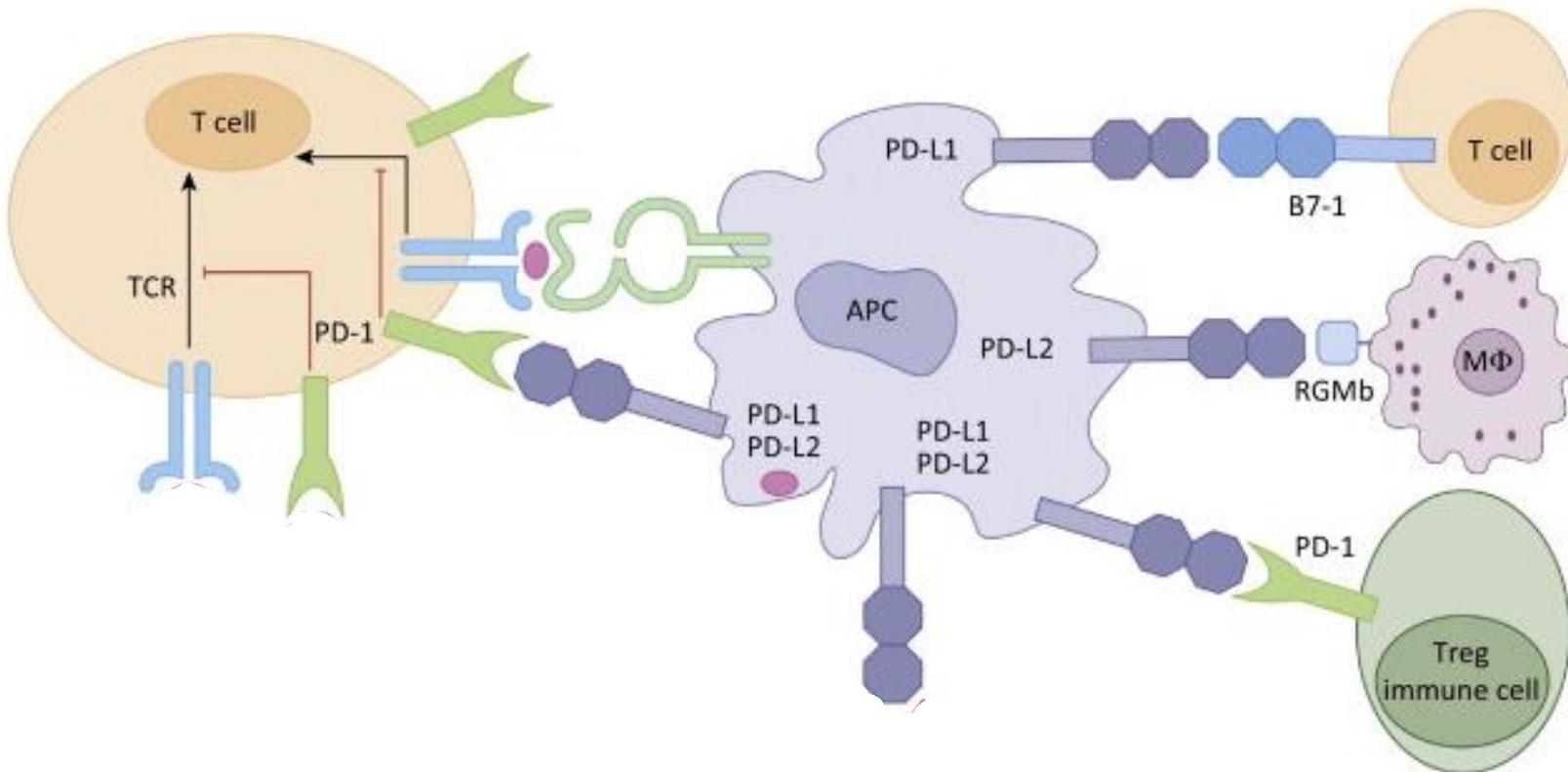


STROMAL TILs

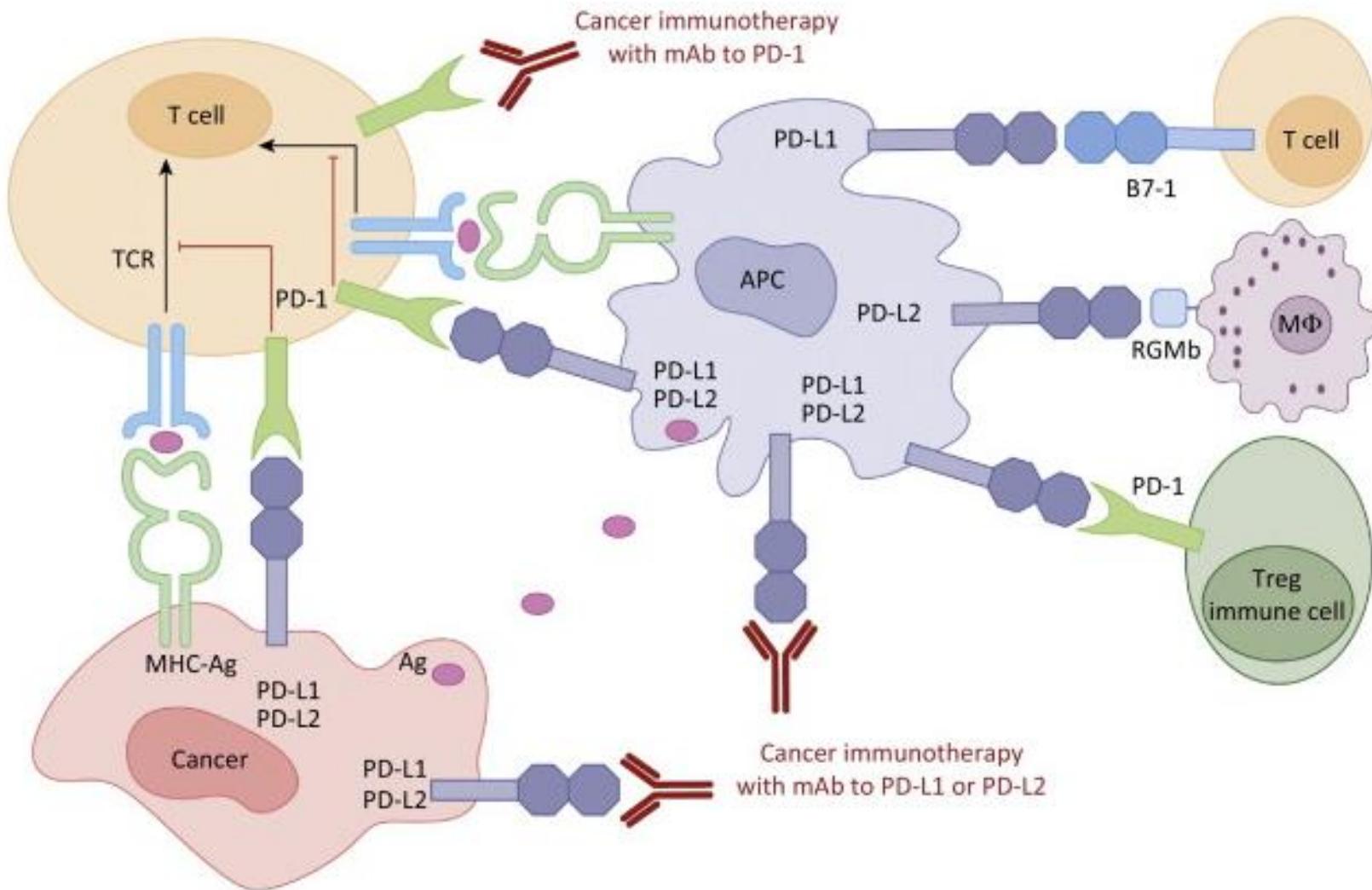


INTRATUMORAL TILs

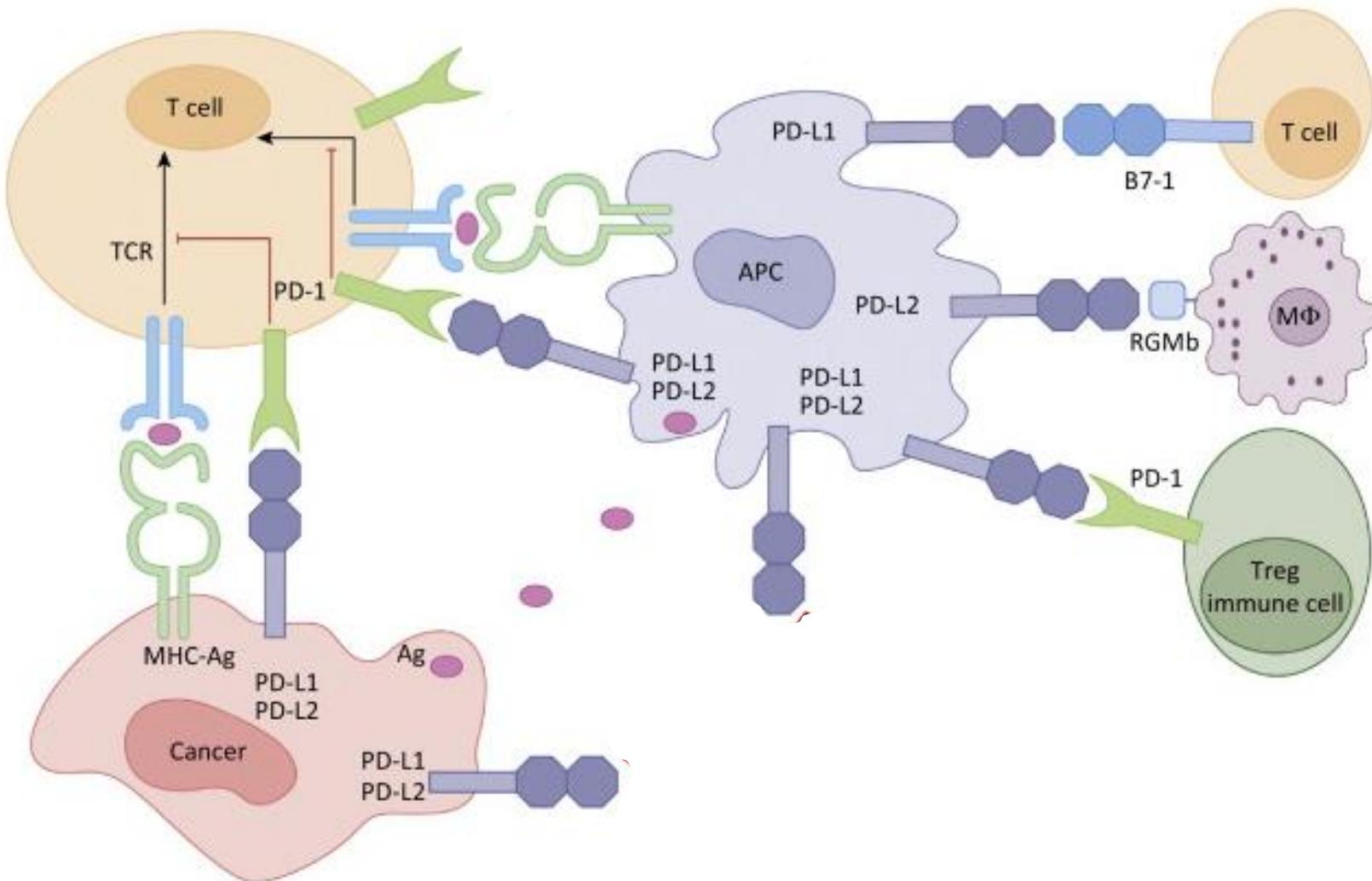
CECKPOINT IMMUNITARIO



CECKPOINT IMMUNITARIO



CHECKPOINT IMMUNITARIO



PITFALLS TEST ICH ANTI-PDL1

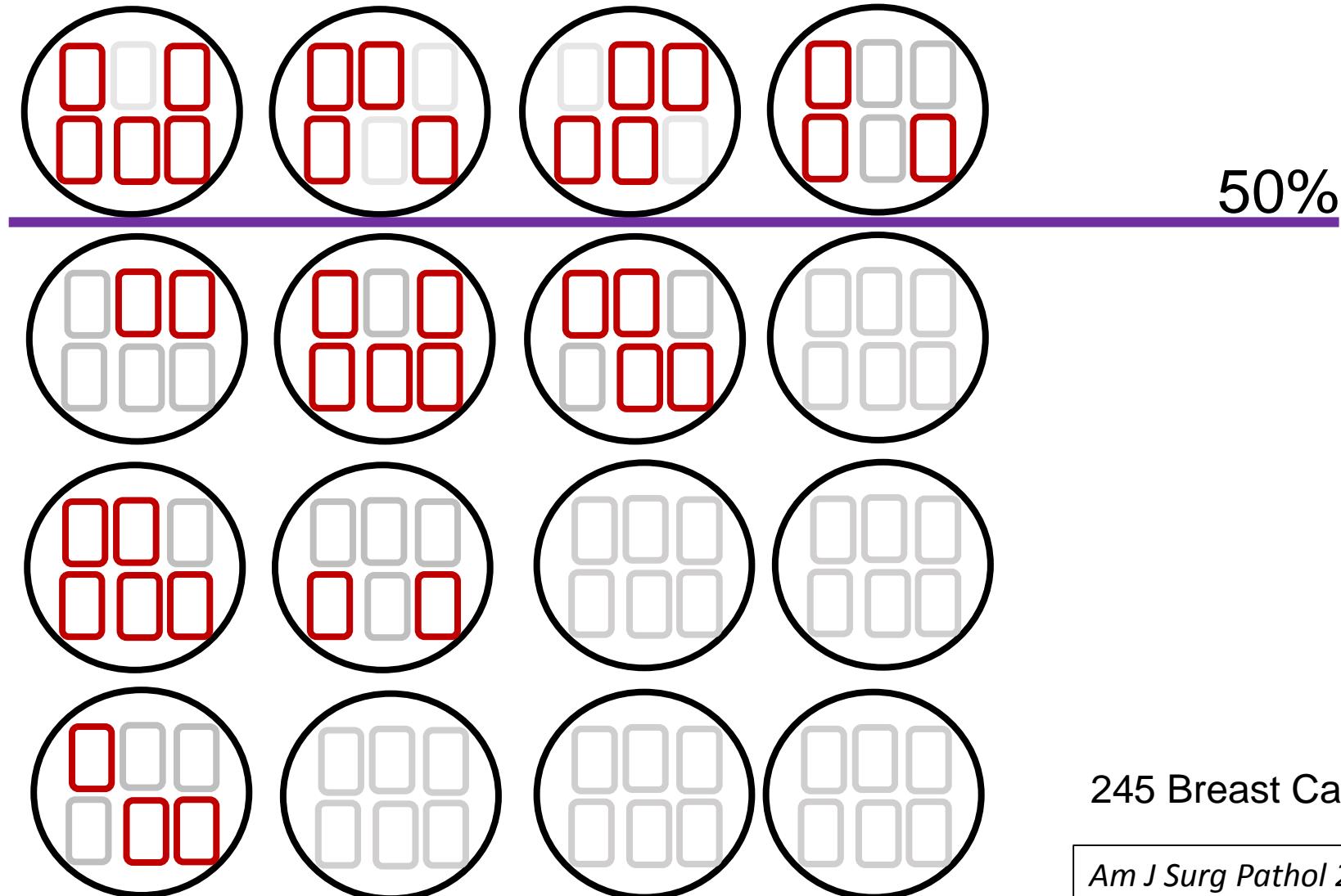
➤ Cloni anticorpali

CLONE	FARMACO	INTENSITA'	PERCENTUALE
Dako 28-8	Nivolumab	++	++
Dako 22-C3	Pembrolizumab	++	++
Ventana SP142	Atezolizumab	+++	+
Ventana SP263	Durvalumab	+++	+++

«...although two assays seemed comparable in intensity and proportions of stained tumor cells (28-8, 22C3), two assays appeared to be more intense (SP142, SP263) and to stain lower proportions (SP142) or higher proportions of carcinoma cells (SP263)»

PITFALLS TEST ICH ANTI-PDL1

- Eterogeneità intratumorale



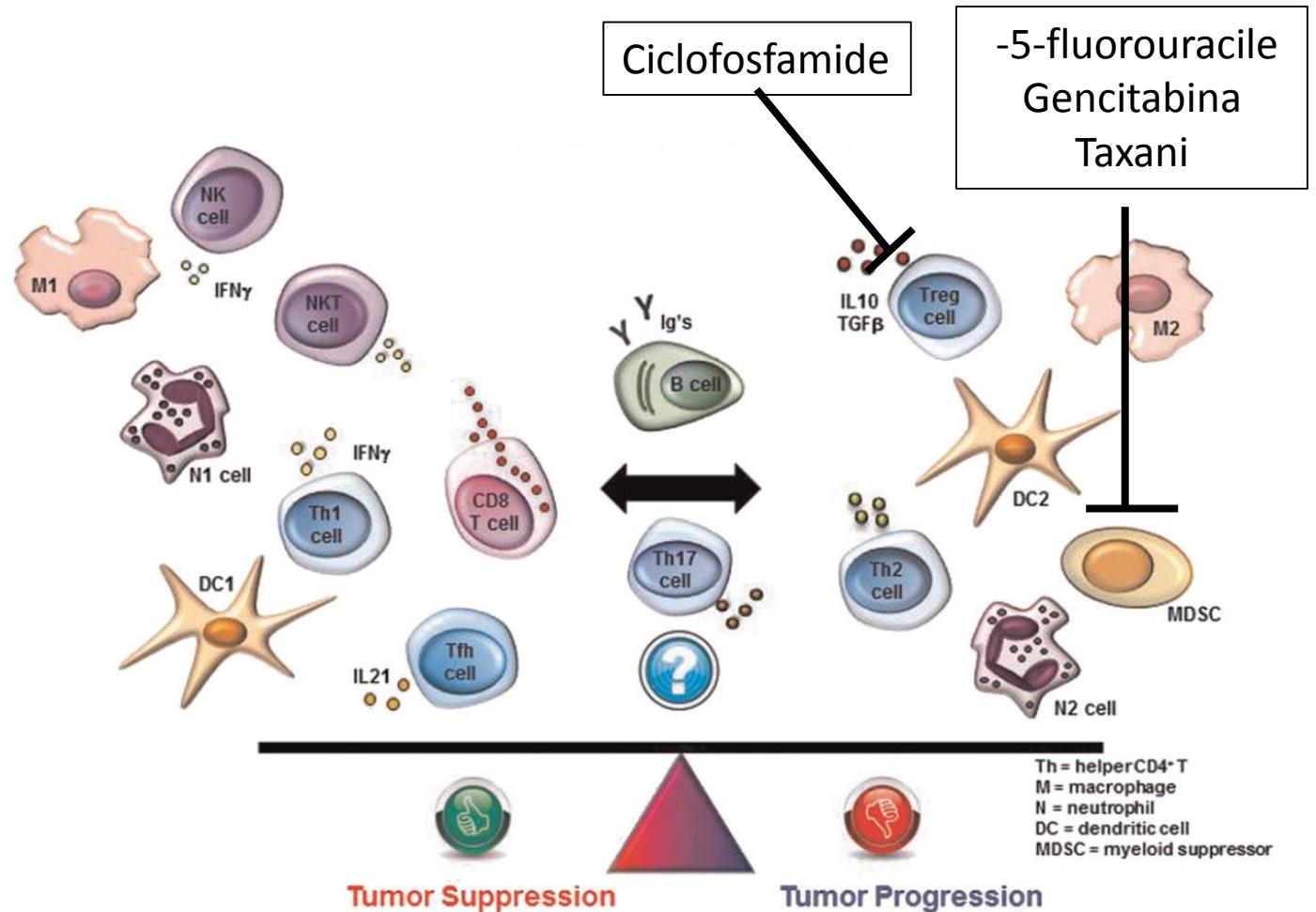
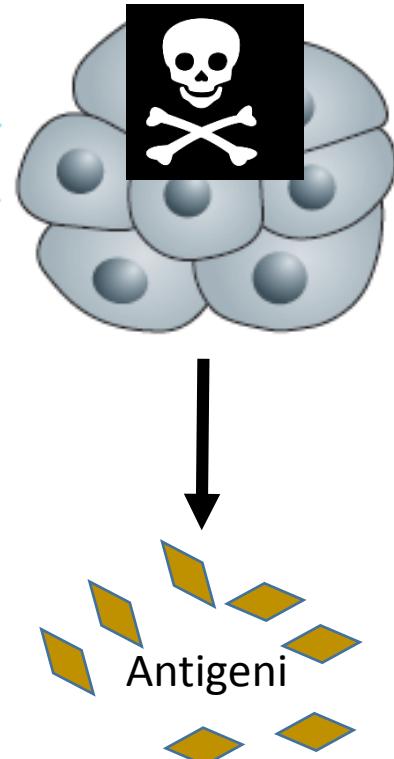
PITFALLS TEST ICH ANTI-PDL1

➤ Eterogeneità Primitivo VS Recidiva VS Metastasi

PDL1	Melanoma Primitivo	Recidiva Locale	Metastasi a Distanza
22%	-	-	-
50%	+	-	-
	+	-	+
	+	-	-
	-	+	+
	-	-	+
	-	+	+
28%	+	+	+

PITFALLS TEST ICH ANTI-PDL1

➤ Eterogeneità temporale secondaria a terapie



PITFALLS TEST ICH ANTI-PDL1

➤ Cloni anticorpali

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PITFALLS TEST ICH

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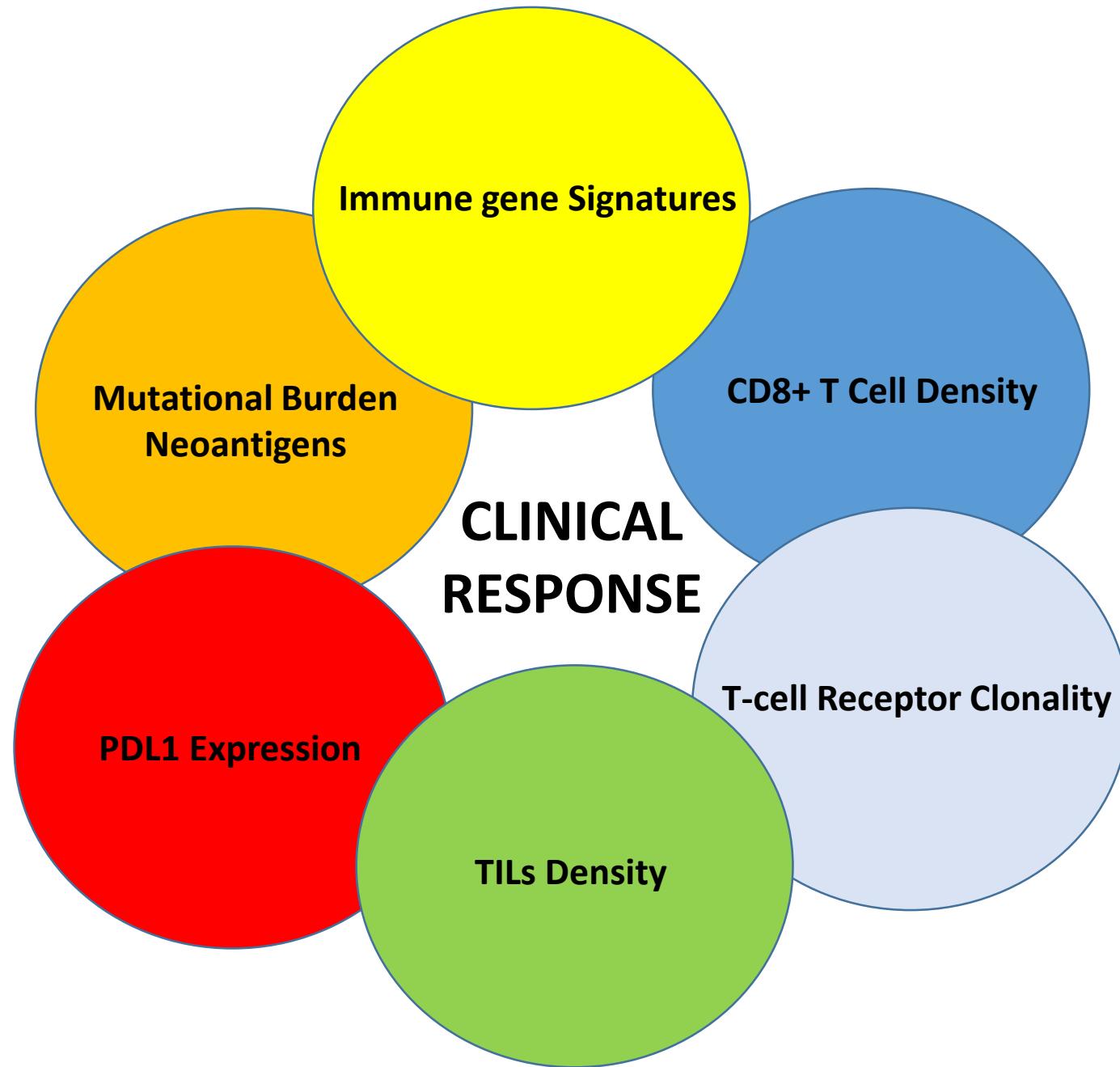
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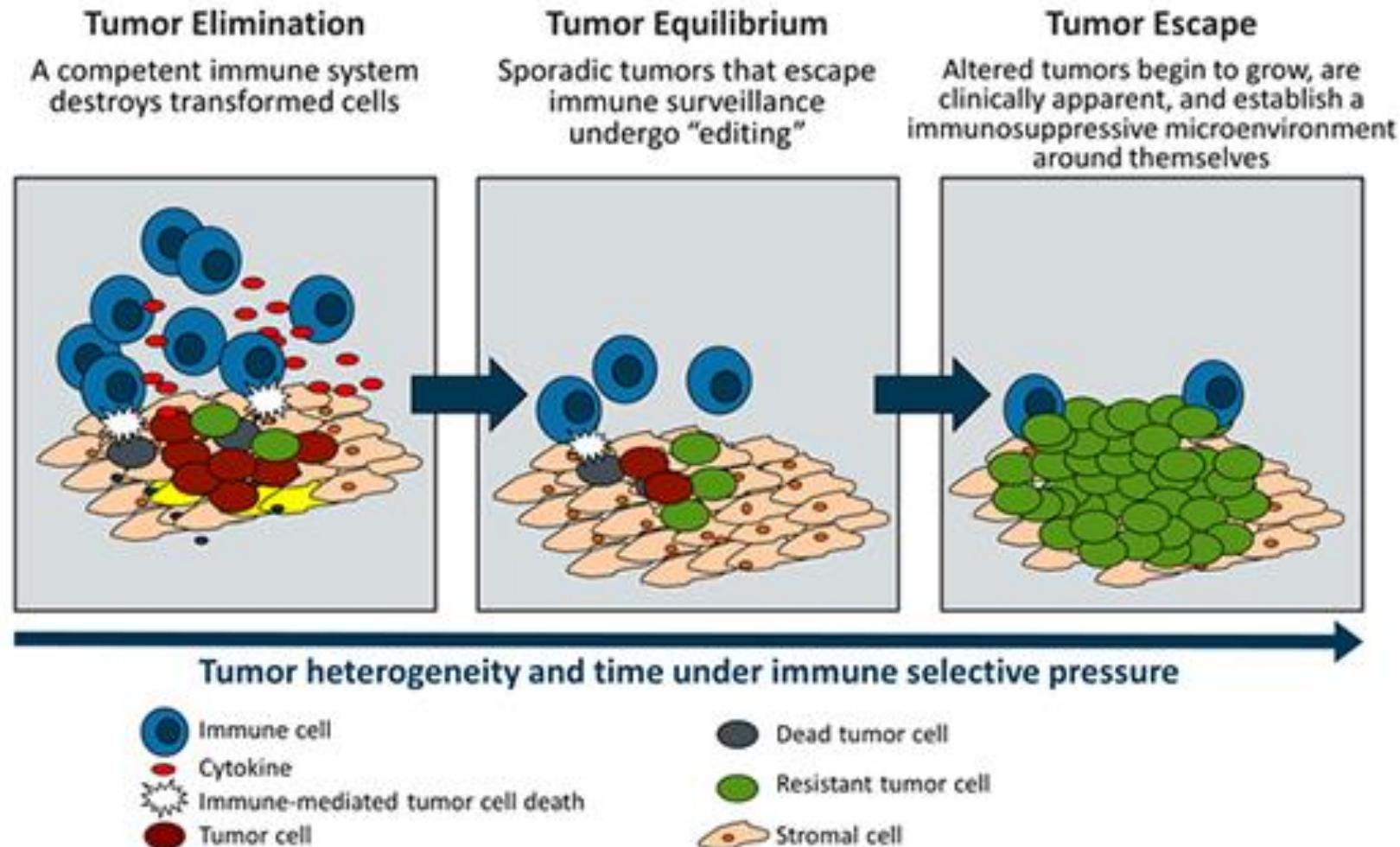
IMMUNOLOGIA E CANCRO



1950 Burnet and Thomas: Immunosorveglianza

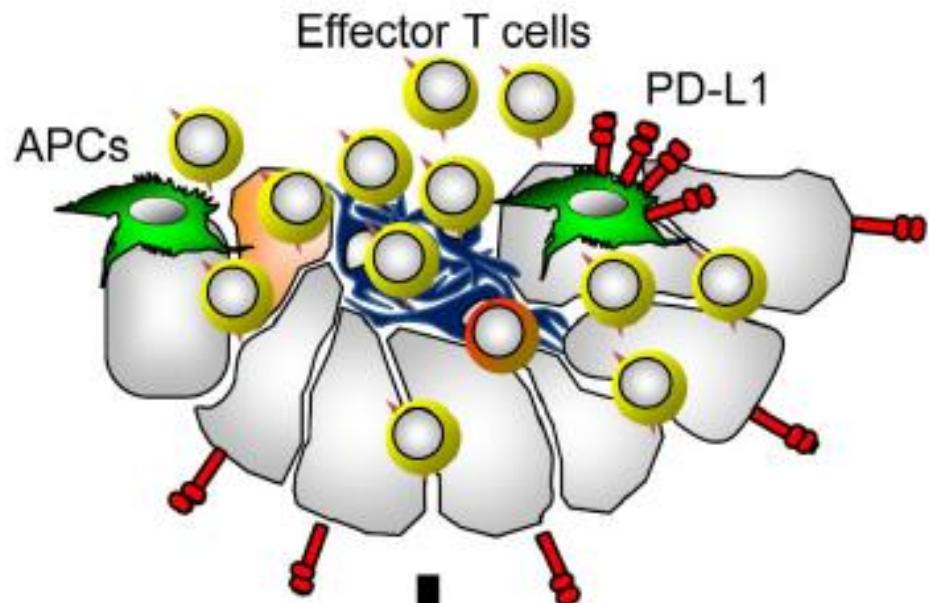
2002 Paul Schreiber: Cancer Immunoediting

IMMUNOEDITING



A

“inflamed cancer”



B

“non-inflamed cancer”

