Immunotherapy and predictive biomarkers

Vasiliki Siozopoulou
Pathologist
Antwerp University Hospital
CORE – University of Antwerp

Immunecheckpoint Inhibitory (ICI) therapy

Agilent Dako

Tumor cells use PD-L1 to inactivate T cells & stop the attack on the tumor.

Tumor cells down regulate the immune response & continues to grow, unchecked.

Immunotherapy blocks PD-1 on the T cell, the tumor cell cannot use PD-L1 to inactivate the T cell.

Immunotherapy enables T cells to stay active and attack the tumor.

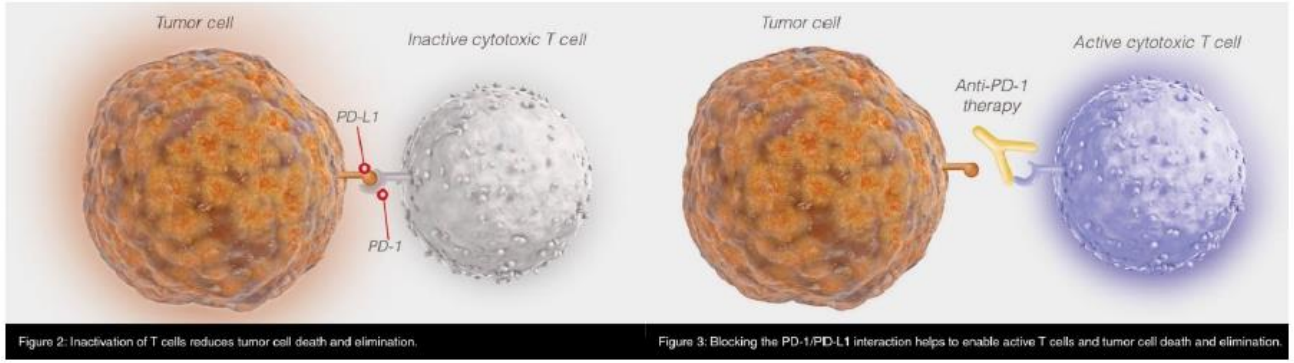


Figure 2: Inactivation of T cells reduces tumor cell death and elimination.

Figure 3: Blocking the PD-1/PD-L1 interaction helps to enable active T cells and tumor cell death and elimination.

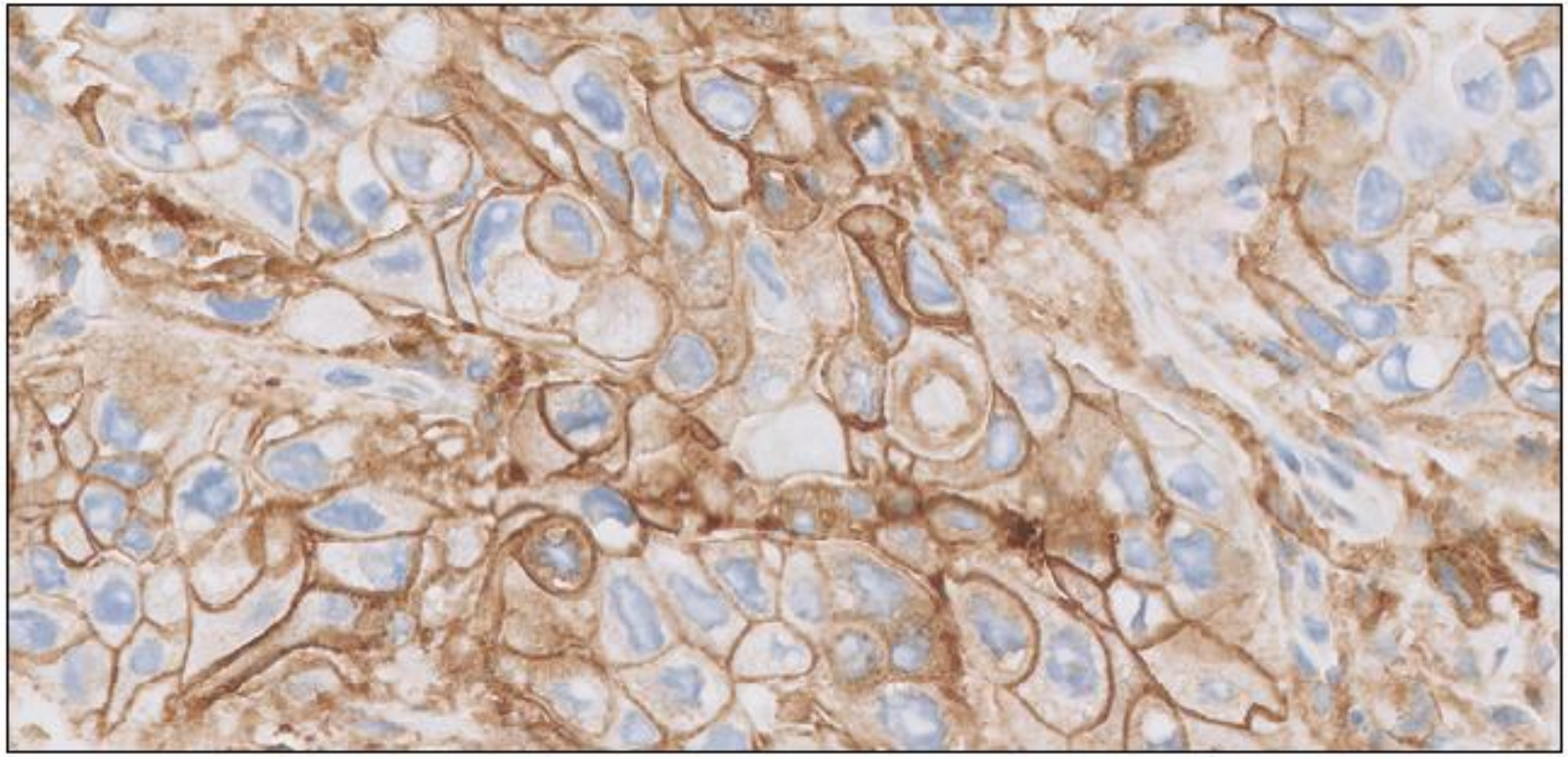
PD-1 programmed death protein-1, PD-L1 programmed death protein ligand-1

Reference: SK00621-5 PD-L1 IHC 22C3 pharmDx Interpretation manual

UZA

ICI therapy

Tumor cells exhibiting convincing partial and/or complete linear membrane staining are considered PD-L1 staining cells. Linear membrane staining can be present at any intensity and must be convincing at no higher than 20× magnification.



ICI therapy

Disadvantages of PD-L1 as a single-analyte biomarker

- Heterogeneity
  - Poor negative predictive value

- Relationship of PD-L1 to prognosis is controversial
  - Differs between tumor types

ICI therapy

Table 1. Anti-PD-1/PD-L1 immunotherapies, indications and diagnostic assay requirement

Cancer type	Drug(s)	Drug target(s)	Indications in US			Indications in EU	
Melanoma	Pembrolizumab	PD-1	Unresectable or metastatic			Unresectable or metastatic	
	Nivolumab	PD-1					
	Nivolumab + ipilimumab	PD-1, CTLA-4				Unresectable or metastatic with low tumour PD-1 expression	
Non-small-cell lung cancer	Nivolumab	PD-1	Metastatic disease with progression on/after platinum-based chemotherapy or after FDA-approved treatment if EGFR+ or ALK+			Locally advanced or metastatic disease after prior chemotherapy in adults	
	Atezolizumab	PD-L1				If progression after chemotherapy or after targeted treatment if EGFR+ or ALK+	
	Pembrolizumab	PD-1	1st line with pemetrexed & carboplatin	1st line monotherapy if EGFR−/ALK−	2nd line monotherapy if progression on/after platinum-based chemotherapy or after FDA-approved treatment if EGFR+ or ALK+	1st line monotherapy if EGFR−/ALK−	If progression on/after platinum-based chemotherapy or after targeted treatment if EGFR+ or ALK+
Renal cell carcinoma	Nivolumab	PD-1	Advanced disease after prior anti-angiogenic therapy			Advanced disease after prior therapy	
Classical Hodgkin lymphoma	Nivolumab	PD-1	Relapsed or progressed disease after auto-HSCT and BV, or 3 or more lines of therapy including auto-HSCT			Relapsed or refractory disease after auto-HSCT and treatment with BV	
	Pembrolizumab	PD-1	With refractory disease or who have relapsed after 3 or more prior lines of therapy			Relapsed or refractory disease after auto-HSCT and BV, or are transplant-ineligible and have failed BV	
Bladder cancer	Atezolizumab	PD-L1	Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy			Locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-based chemotherapy or considered cisplatin ineligible	
	Nivolumab	PD-1				Locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-based chemotherapy	
	Durvalumab	PD-L1				NO	
	Avelumab	PD-L1				NO	
	Pembrolizumab	PD-1	Locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy or who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy			Locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy or who have disease progression during or following platinum-based chemotherapy	
Head and neck cancer	Pembrolizumab	PD-1	Recurrent or metastatic squamous cell carcinoma with disease progression on or after platinum-based therapy			NO	
	Nivolumab	PD-1				Squamous cell cancer progression on or after platinum-based therapy	
Merkel cell carcinoma	Avelumab	PD-L1	Metastatic disease			Metastatic disease	
Gastric cancer	Pembrolizumab	PD-1	Recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy			NO	
Liver cancer	Nivolumab	PD-1	Hepatocellular carcinoma previously treated with sorafenib			NO	
MSI-H or dMMR-deficient solid tumours	Pembrolizumab	PD-1	Unresectable or metastatic solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan			NO	
MSI-H or dMMR-deficient colorectal tumours	Nivolumab	PD-1	Metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan			NO	

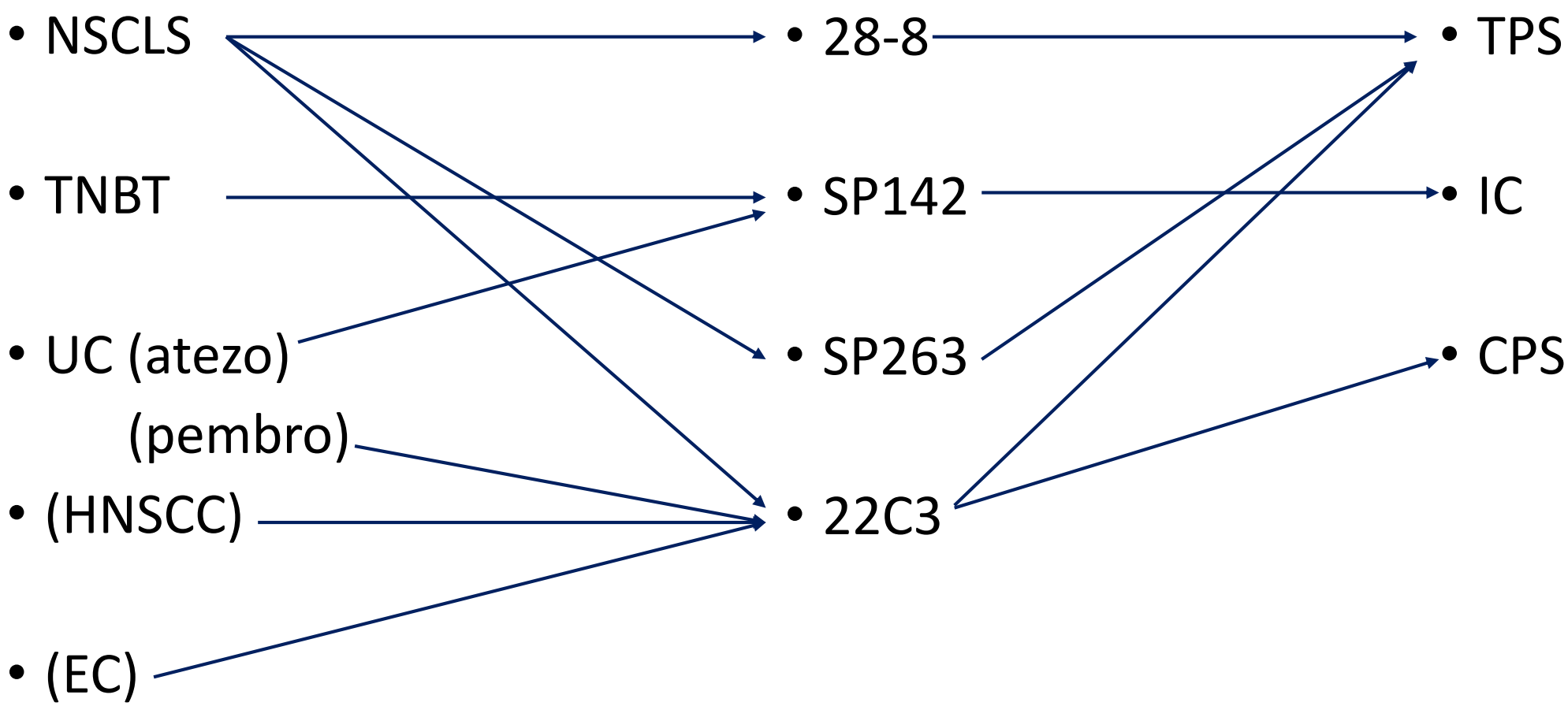
PD-L1 in Cancer: ESMO Biomarker Factsheet

Important information for the pathologist

Indication and potential immunotherapeutic drug? →

- Different clone (28-8, SP142, 22C3, SP263…)
- Different scoring systems

ICI therapy


• NSCLS
• TNBT
• UC (atezo)
(pembro)
• (HNSCC)
• (EC)
• 28-8
• SP142
• SP263
• 22C3
• TPS
• IC
• CPS

Scoring systems

TPS: Tumor Proportion Score (%)

IC: Tumor-infiltrating immune cell score (%)

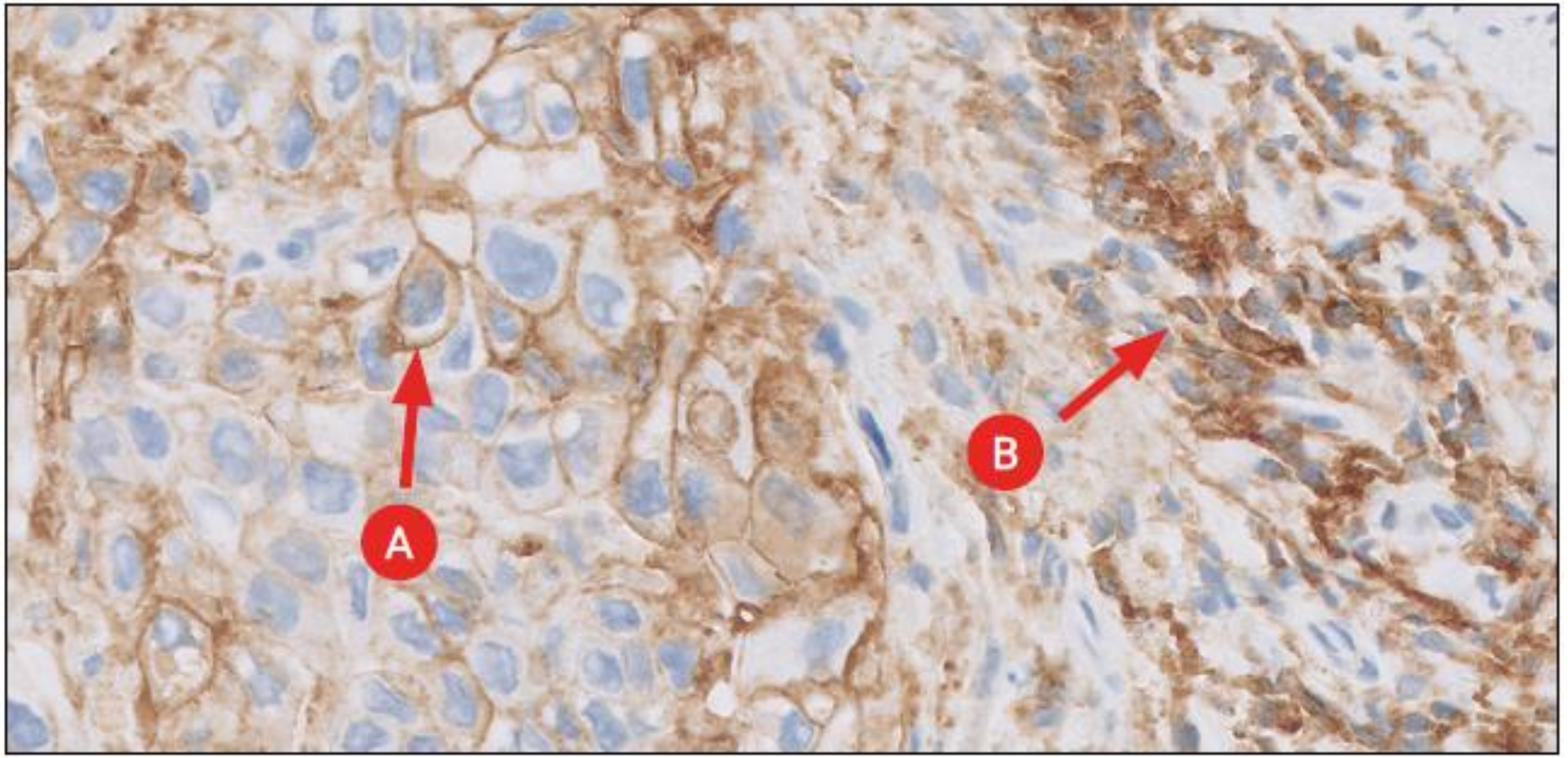
CPS: Combined Positive Score (not a %)

ICI therapy

$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

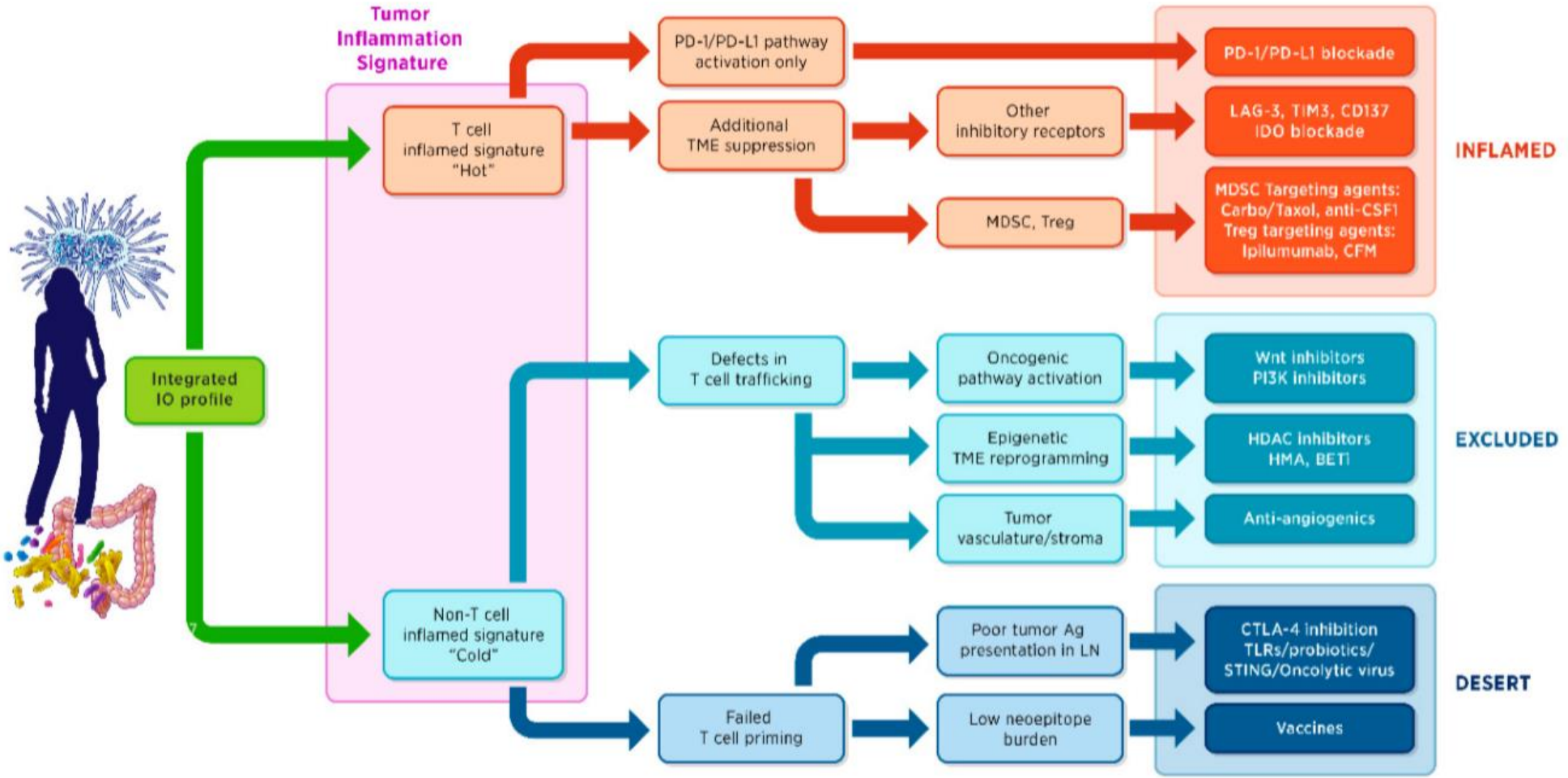
Indication	UC	HNSCC	Esophageal ca
Cutoff(s)	$< 10\ and\ \geq 10$	$< 1, \geq 1\ and\ \geq 20$	$< 10\ and\ \geq 10$
Scoring of tumor cells	Invasive carcinoma and high grade dysplasia / carcinoma in situ	Only invasive carcinoma cells	Invasive carcinoma including intramucosal adenocarcinoma
Scoring of immune cells	Tumor associated lymphocytes, histiocytes, macrophages		
	Ecxlude BCG granulom.	Include giant cells	Include giant cells
Scoring of other cell types	Excluded from scoring		
Reported score	CPS 0-100		
Staining sample			

The tumor micro-environment (TME)



A: tumor cells
B: immune celles

The tumor micro-environment

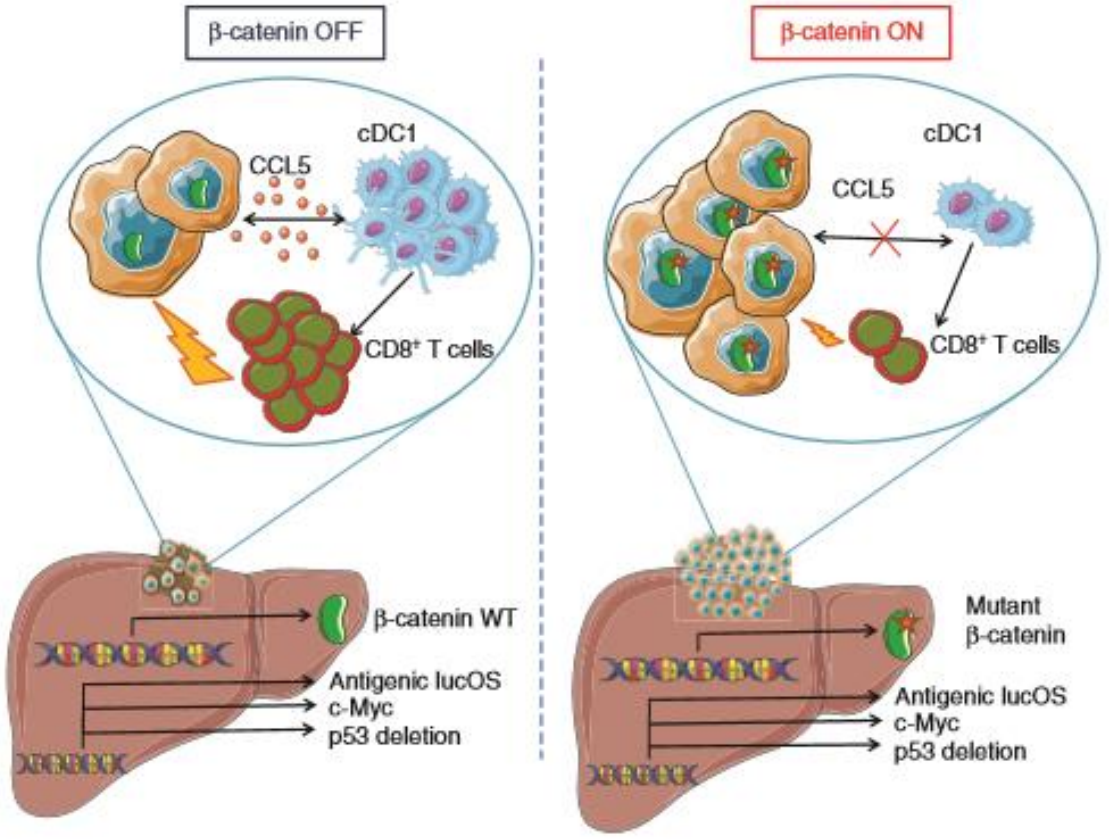


Biomedicines **2018**, *6*, 14

The tumor micro-environment – β-catenine

β – catenine pathway gives rise to a T cells exclusion phenotype

VIEWS



CANCER DISCOVERY AUGUST 2019

The tumor micro-environment – β-catenine

- Patients with activation of β-catenine are very unlikely to benefit from ICI therapy
- Potential negative predictor
- Biomarker candidate

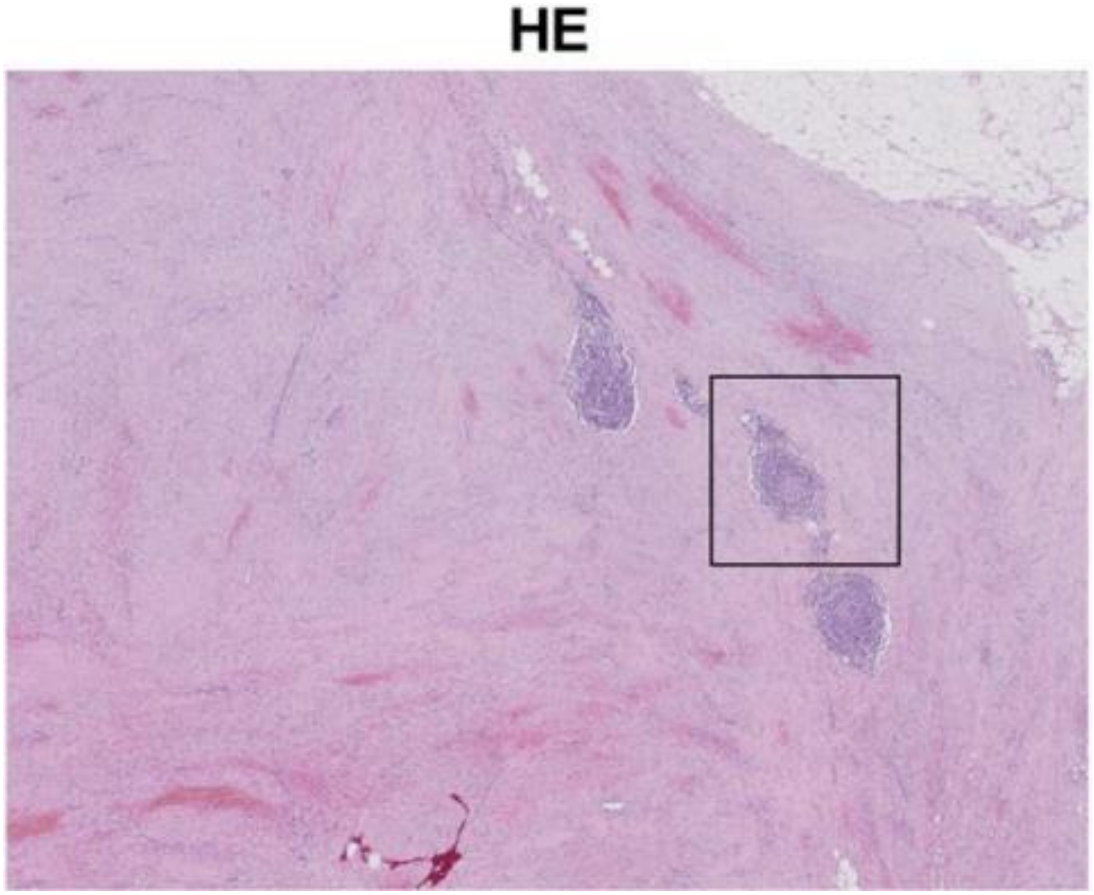
The tumor micro-environment – β-catenine

Cancer Immunology, Immunotherapy
October 2019, Volume 68, Issue 10, pp 1573–1583 | Cite as

Desmoid tumors display a strong immune infiltration at the tumor margins and no PD-L1-driven immune suppression

Authors | Authors and affiliations

Vasiliki Siozopoulou, Elly Marcq, Julie Jacobs, Karen Zwaenepoel, Christophe Hermans, Jantine Brauns, Siegrid Pauwels, Clément Huysentruyt, Martin Lammens, Johan Somville, Evelien Smits, Patrick Pauwels



DT:

- Mesenchymal neoplasms
- β-catenine mutation

The tumor micro-environment

Published in final edited form as:
Cancer Discov. 2015 August ; 5(8): 860–877. doi:10.1158/2159-8290.CD-14-1236.

Co-occurring genomic alterations define major subsets of *KRAS* - mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities

Ferdinandos Skoulidis[1], **Lauren A. Byers**[1], **Lixia Diao**[2], **Vassiliki A. Papadimitrakopoulou**[1], **Pan Tong**[2], **Julie Izzo**[3], **Carmen Behrens**[1], **Humam Kadara**[3], **Edwin R. Parra**[3], **Jaime Rodriguez Canales**[3], **Jianjun Zhang**[4], **Uma Giri**[1], **Jayanthi Gudikote**[1], **Maria A. Cortez**[5], **Chao Yang**[1], **You Hong Fan**[1], **Michael Peyton**[11], **Luc Girard**[11], **Kevin R. Coombes**[13], **Carlo Toniatti**[10], **Timothy P. Heffernan**[10], **Murim Choi**[14], **Garrett M. Frampton**[12], **Vincent Miller**[12], **John N. Weinstein**[2], **Roy S. Herbst**[15], **Kwok-Kin Wong**[16], **Jianhua Zhang**[10], **Padmanee Sharma**[8], **Gordon B. Mills**[7], **Waun K. Hong**[9], **John D. Minna**[11], **James P. Allison**[6], **Andrew Futreal**[4], **Jing Wang**[2], **Ignacio I. Wistuba**[3], and **John V. Heymach**[1]

Published in final edited form as:
Cancer Discov. 2016 February ; 6(2): 202–216. doi:10.1158/2159-8290.CD-15-0283.

Loss of PTEN promotes resistance to T cell-mediated immunotherapy

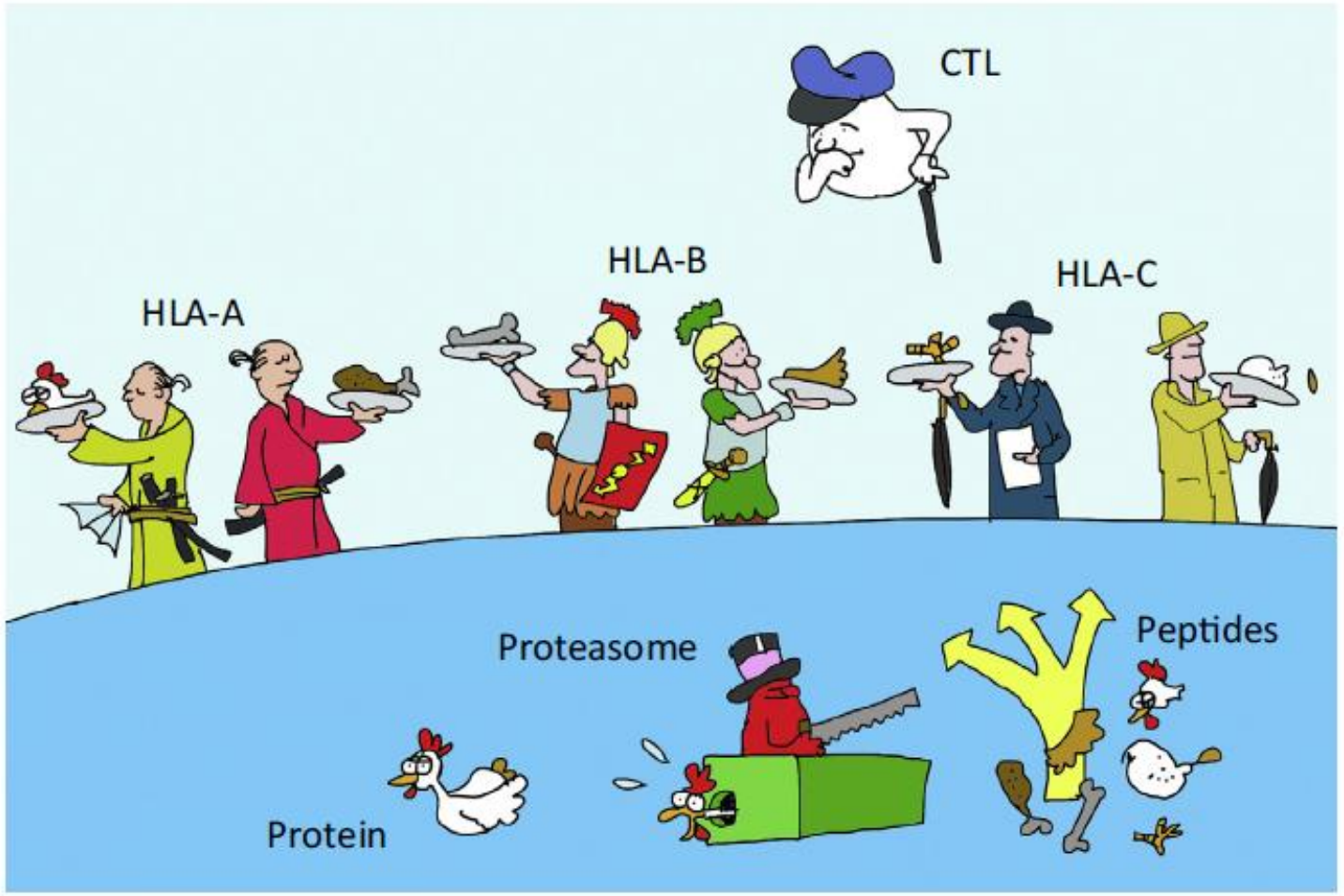
Weiyi Peng[1], **Jie Qing Chen**[1], **Chengwen Liu**[1], **Shruti Malu**[1], **Caitlin Creasy**[1], **Michael T Tetzlaff**[2,3], **Chunyu Xu**[1], **Jodi A McKenzie**[1], **Chunlei Zhang**[1], **Xiaoxuan Liang**[1], **Leila J Williams**[1], **Wanleng Deng**[1], **Guo Chen**[1], **Rina Mbofung**[1], **Alexander J Lazar**[2], **Carlos A Torres-Cabala**[2], **Zachary A Cooper**[4,5], **Pei-Ling Chen**[2], **Trang N Tieu**[6], **Stefani Spranger**[7], **Xiaoxing Yu**[1], **Chantale Bernatchez**[1], **Marie-Andree Forget**[1], **Cara Haymaker**[1], **Rodabe Amaria**[1], **Jennifer L McQuade**[8], **Isabella C Glitza**[1], **Tina Cascone**[8], **Haiyan S Li**[9], **Lawrence N Kwong**[5], **Timothy P Heffernan**[6], **Jianhua Hu**[10], **Roland L Bassett Jr.**[10], **Marcus W Bosenberg**[11], **Scott E Woodman**[1], **Willem W Overwijk**[1], **Gregory Lizée**[1], **Jason Roszik**[1,5], **Thomas F Gajewski**[7], **Jennifer A Wargo**[4,5], **Jeffrey E Gershenwald**[4], **Laszlo Radvanyi**[1,‡], **Michael A Davies**[1,*], and **Patrick Hwu**[1,*]

The tumor micro-environment

Characterization of the tumor micro-environment:

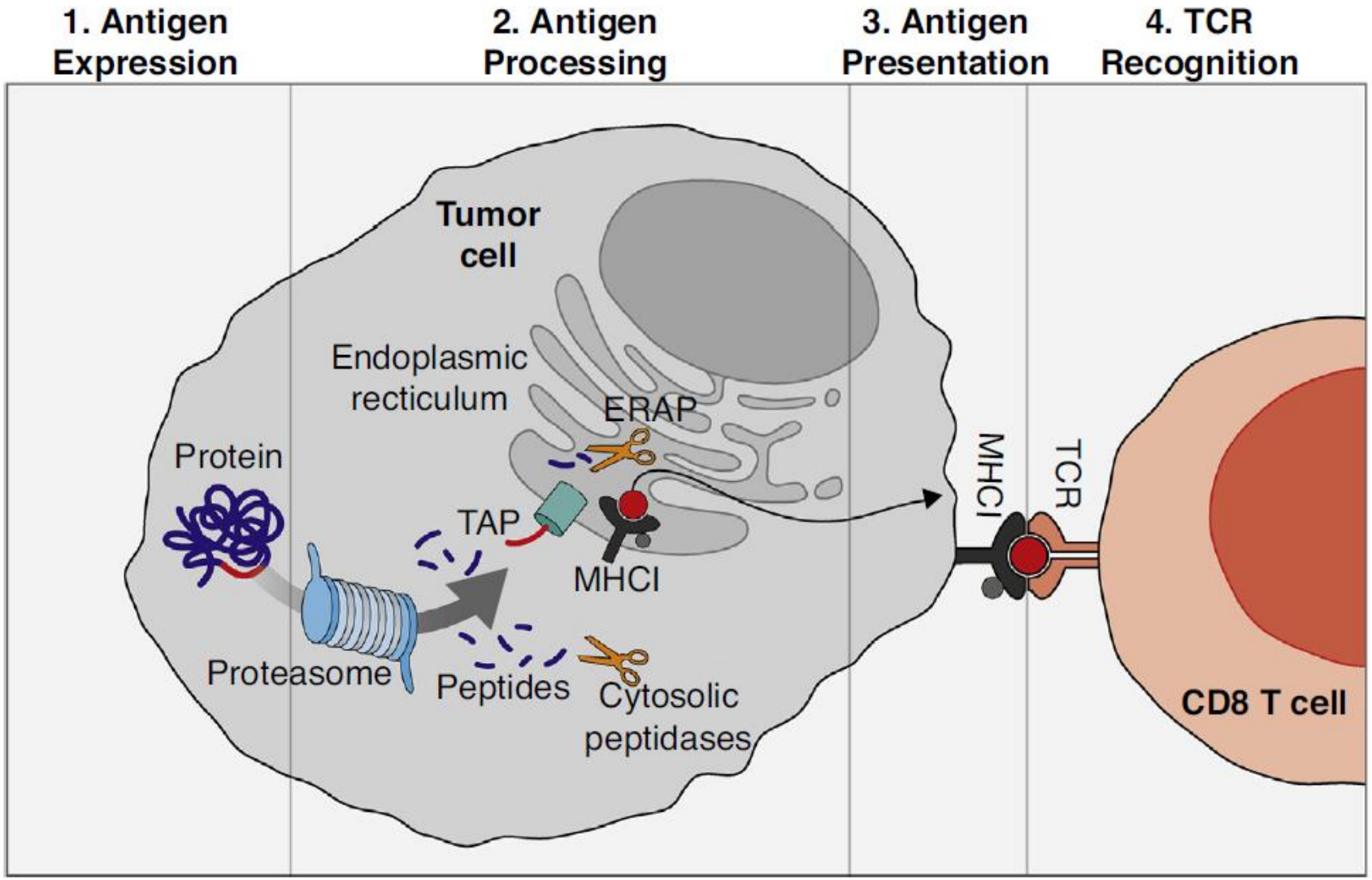
- CD3/CD8/CD45Ro
- Exhausted phenotype?
- Regulatory cells?

Antigen presentation



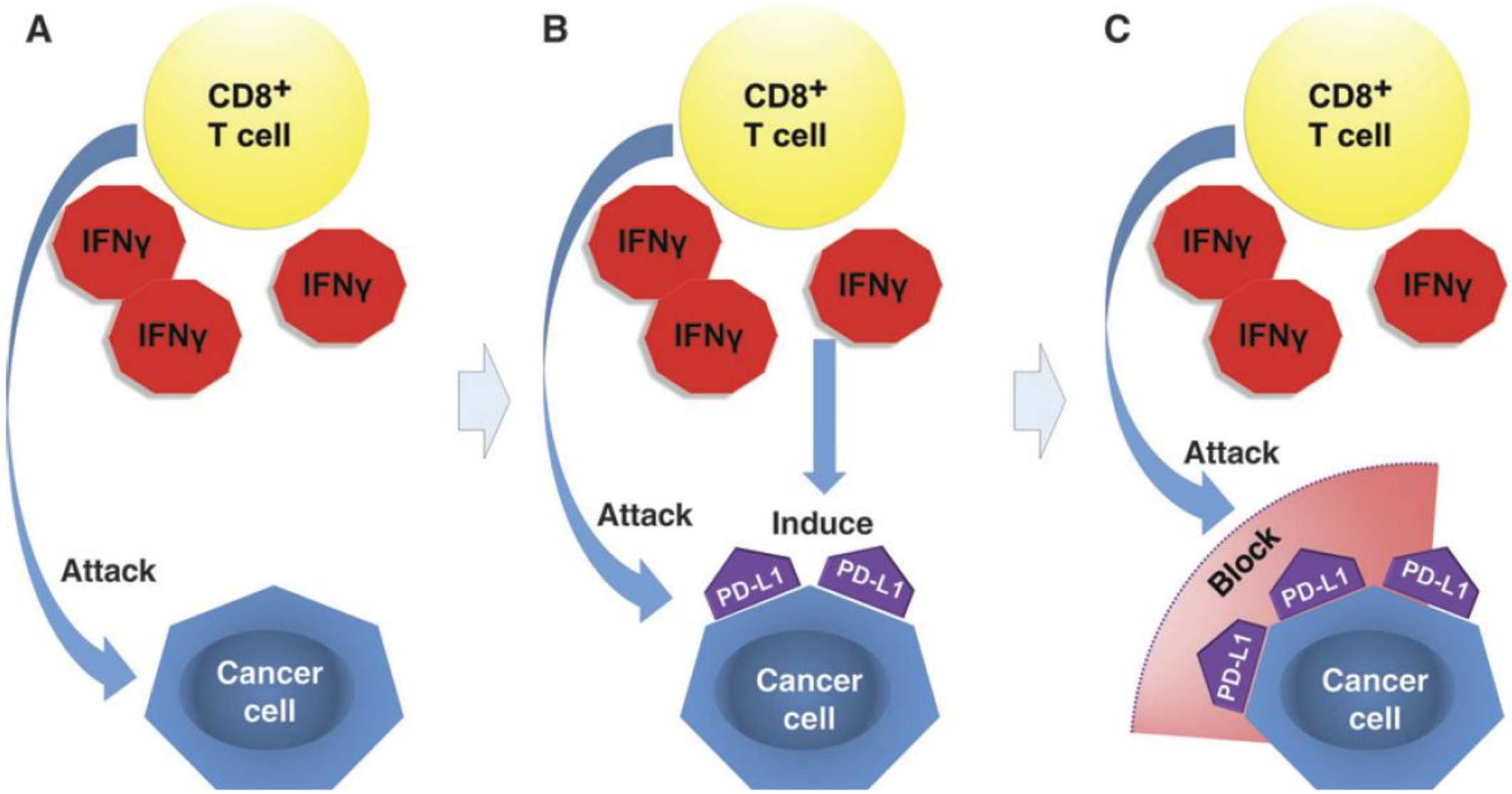
Trends in Immunology

Antigen presentation



Current Opinion in Immunology

The role of INFγ



Clin Cancer Res; 22(10) May 15, 2016

The role of INFγ

Possible Mechanism Underlying the Controversial Effects of IFNγ in Tumor Immunity

- INFγ insensitivity / deletion signature (mutations of deletions of genes involved in the INF signaling pathway and antigen presentation)
- MHC downregulation and loss of immunogenicity

- Induction of IDO → Tregs
- Expression of PD-L1

Tumor Mutational Burden (TMB) and the role of Microsatellite Instability (MSI)

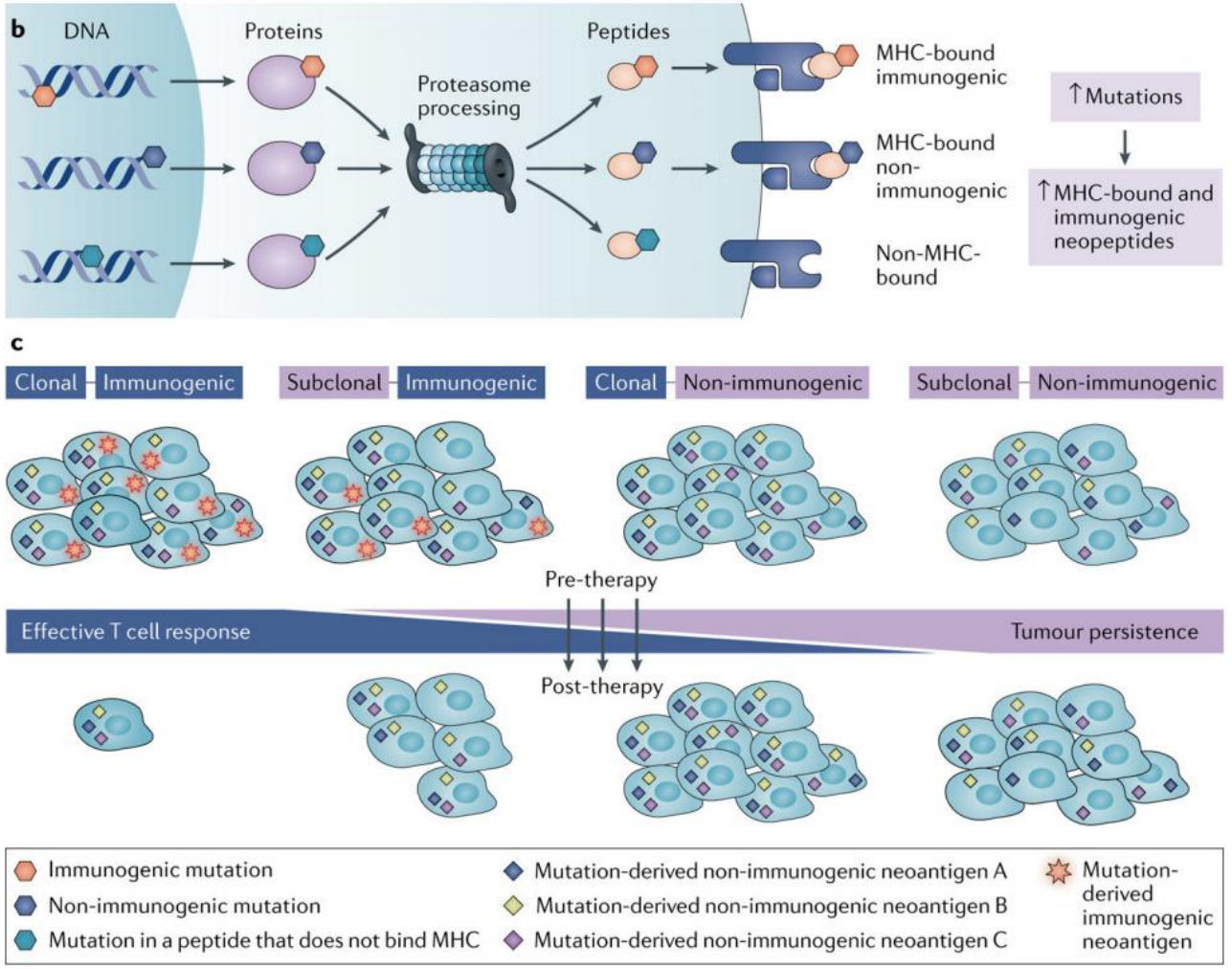
Tumor Mutational Burden (TMB) or Tumor Mutation Load (TML)

TMB or TML: total number of somatic/acquired mutations per coding area of a tumor genome (Mut/Mb)

The number of mutations can vary across different tumor types.

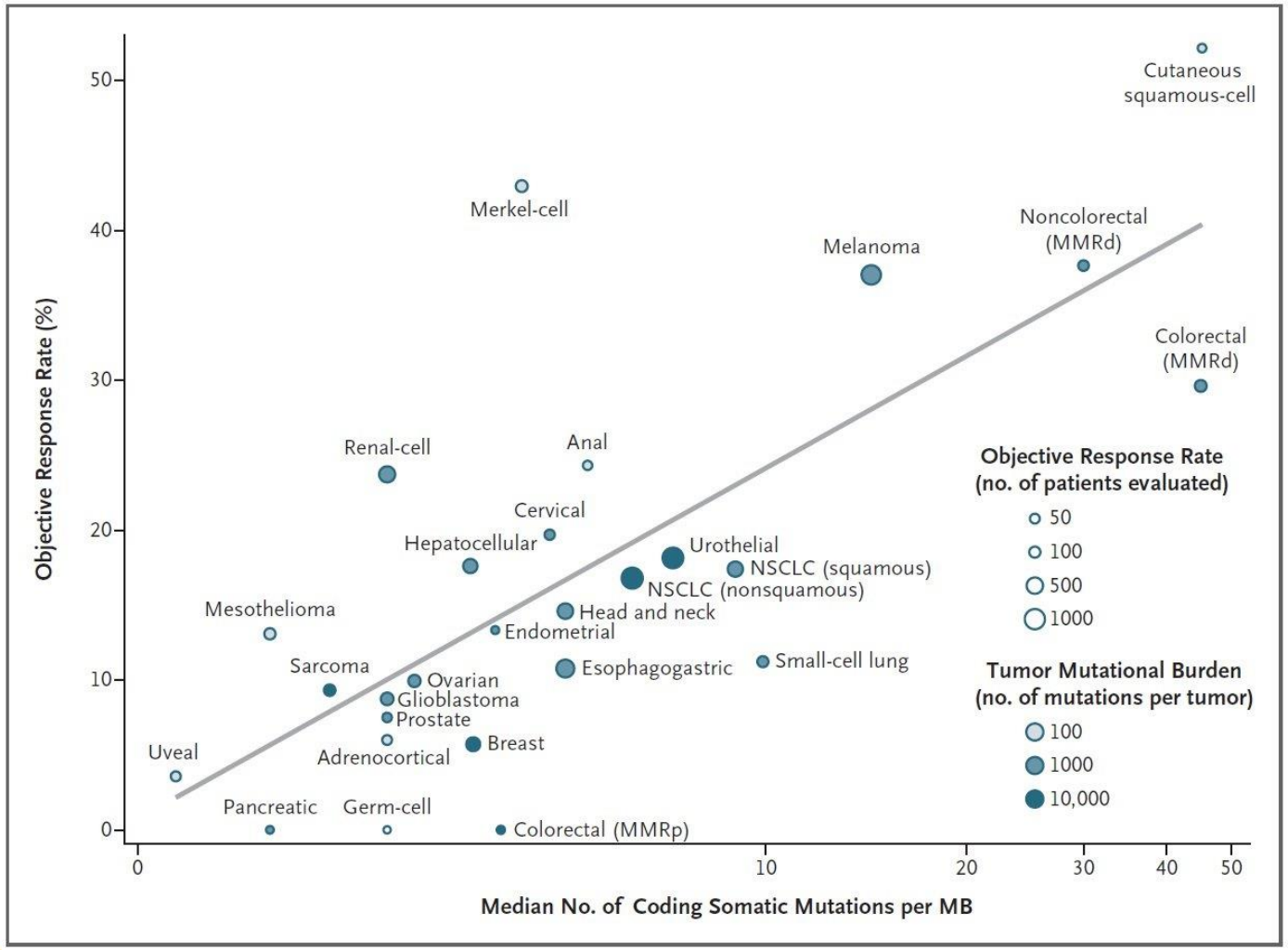
True neoantigen burden: the number of mutations actually targeted by T cells

Tumor Mutational Burden (TMB)



Nat Rev Cancer. 2019 March ; 19(3): 133–150

Tumor Mutational Burden (TMB)



Lowest mutational load

- Low grade tumors
- Pediatric malignancies (sarcomas)

Highly mutated

- Environmental DNA damage

Microsatellite Instability

Cancer Medicine

Open Access

ORIGINAL RESEARCH

Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients

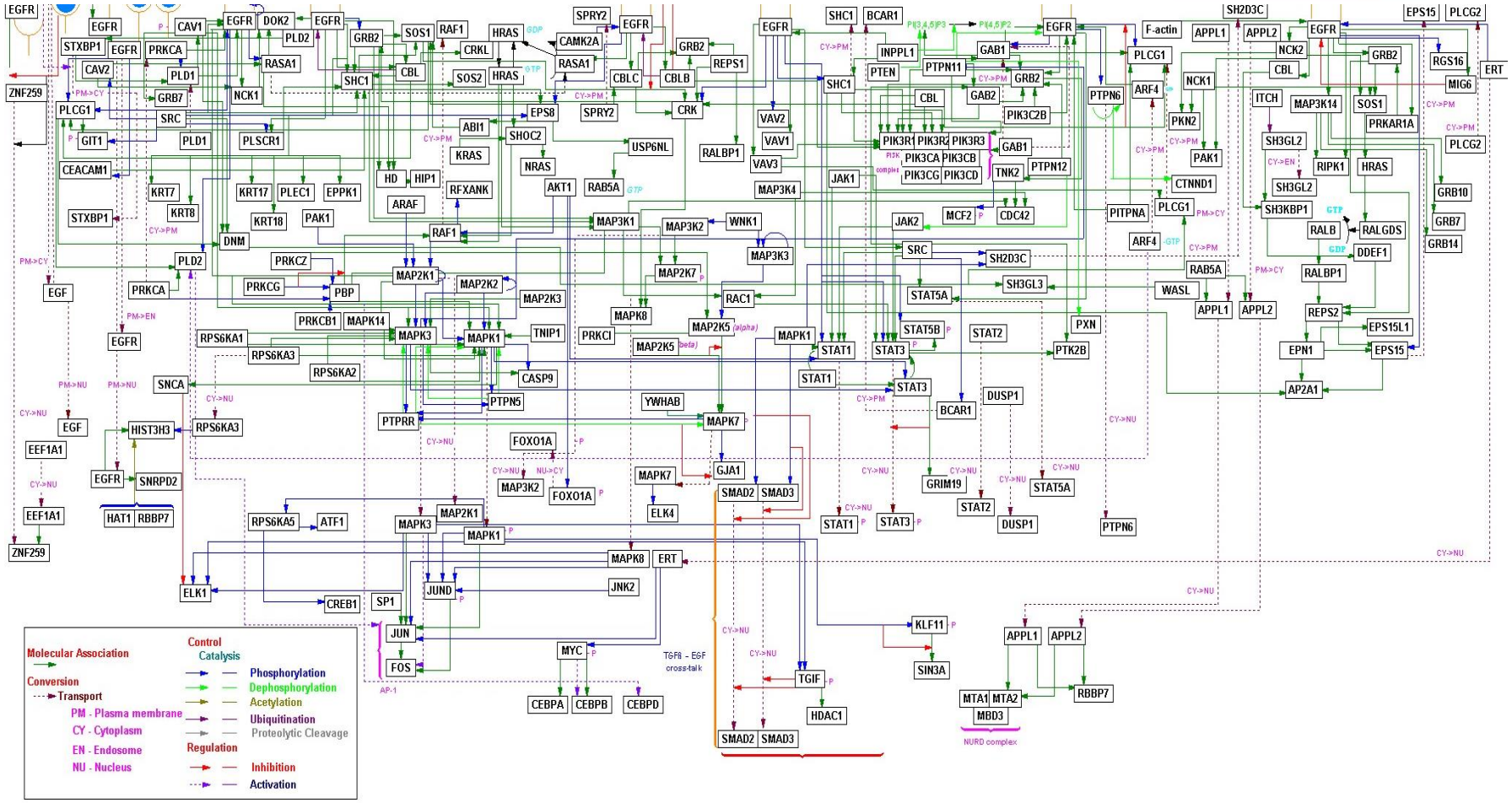
Ari Vanderwalde[1], David Spetzler[2], Nianqing Xiao[2], Zoran Gatalica[2] & John Marshall[2,3]

[1]The University of Tennessee Health Science Center and West Cancer Center, Memphis, Tennessee
[2]Caris Life Sciences, Phoenix, Arizona
[3]Lombardi Cancer Center, Georgetown University Hospital, Washington, District of Columbia

Microsatellite Instability

- MSI-positive tumor are specific type of high TMB tumor
- Generate numerous neopetpides → hypermutated phenotype
- MSI is highly sensitive to ICI therapy regardless of the tissue of origin

The Role of EGFR, non-immunogenic PD-L1 expression



- EGFR activation mutations can lead to overexpression of PD-L1 without neoantigen recognition

Conclusions

- PDL1 IHC more or less retains its position as a predictive marker
- MSI: very interesting
- TMB: ?
- TME/TILs: interesting but not yet in practice
- Specific mutations as predictive biomarkers (β-catenine, EGFR, KRAS/STK11, PTEN…)
- Multicomponent predictive biomarker?