Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

PD-L1 Overview

Allen M. Gown, M.D.

Clinical Professor of Pathology

University of British Columbia,

Vancouver, BC

#LearnACI

Disclosures

- Speakers bureau, Agilent Technologies

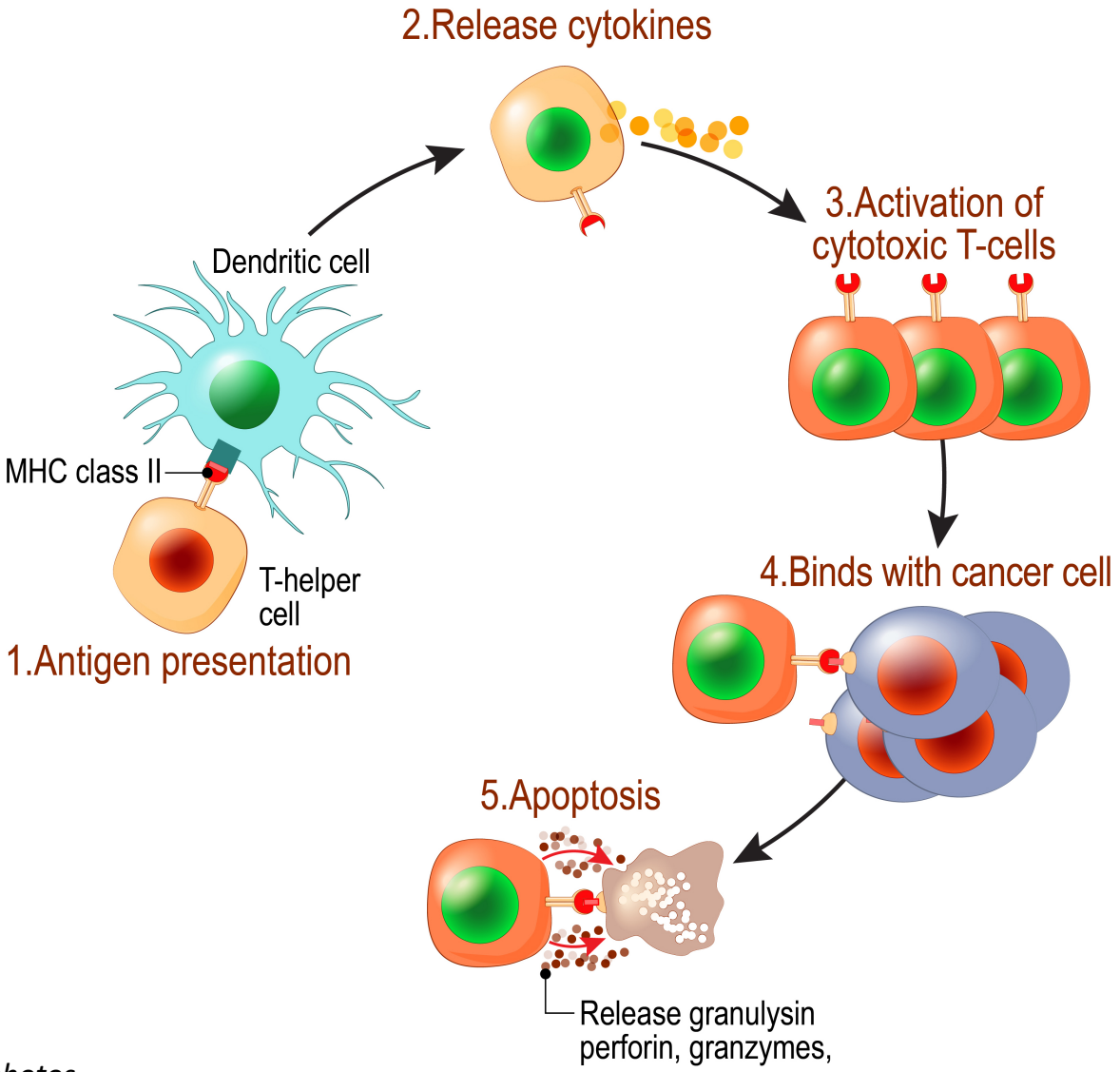
Questions: PD-L1

- What is PD-L1 and why test for its expression?
- How do we predict which patients will respond to PD-L1 therapy?
- How is PD-L1 expression assessed?
- Why can’t there be just one universal PD-L1 assay?
- What other than PD-L1 expression can predict response to PD-L1 therapy?

Questions: PD-L1

- **What is PD-L1 and why test for its expression?**
- How do we predict which patients will respond to PD-L1 therapy?
- How is PD-L1 expression assessed?
- Why can’t there be just one universal PD-L1 assay?
- What other than PD-L1 expression can predict response to PD-L1 therapy?

Cancer and cytotoxic T-cells

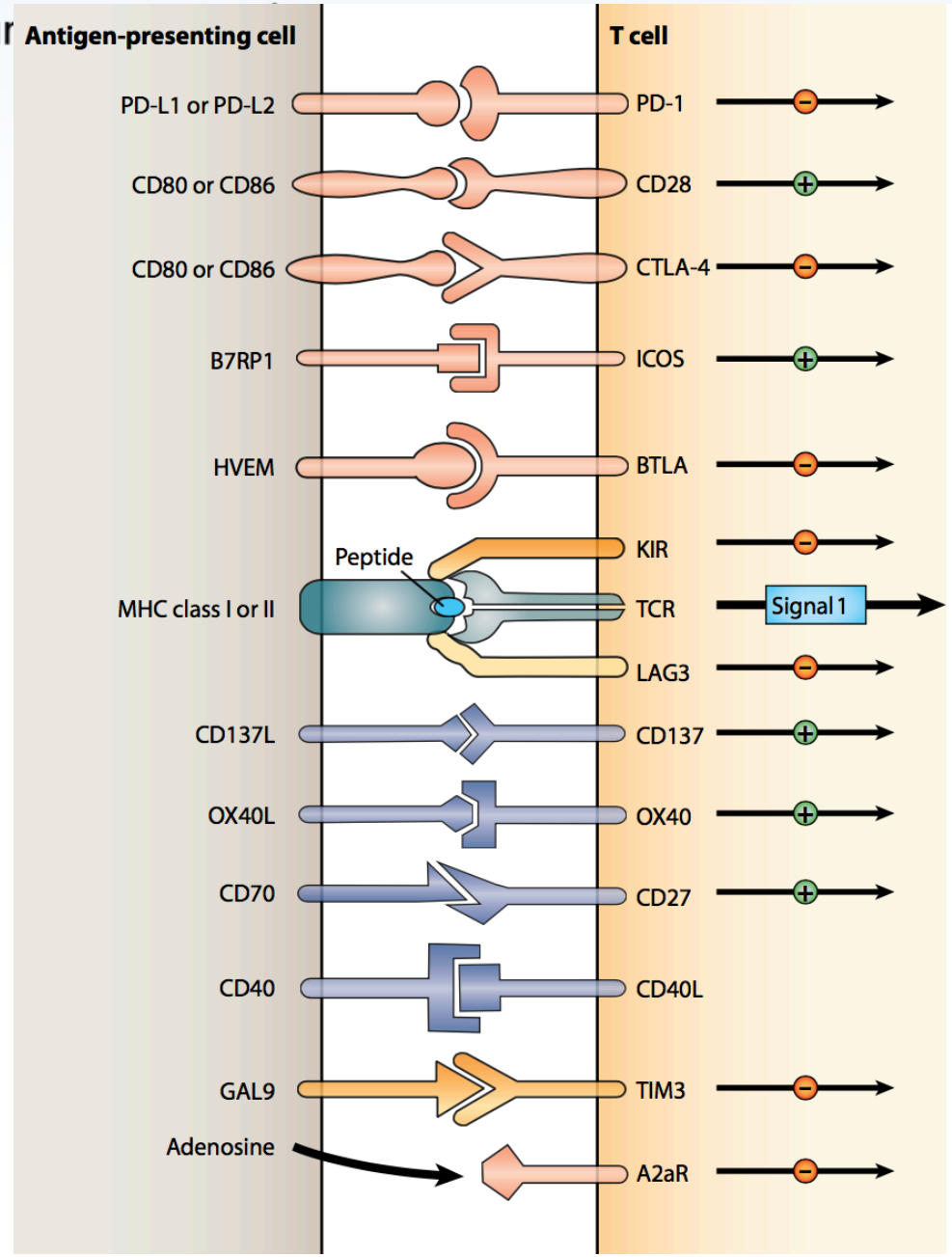


Function and Dysfunction of T Cells

- T cells play critical role in antiviral and anti tumor immune responses
- Appropriate activation of antigen-specific T cells leads to clonal expansion and acquisition of effector function
- Cytotoxic T lymphocytes (CTLs) enabled to lyse target cells

Function and Dysfunction of T Cells

- In some cases there is T cell dysfunction, where CTLs lose ability to proliferate in presence of antigen (“exhaustion”)
- There are various receptors that negatively regulate T cell function and promote exhaustion
- One of these is PD-1 (CD279)



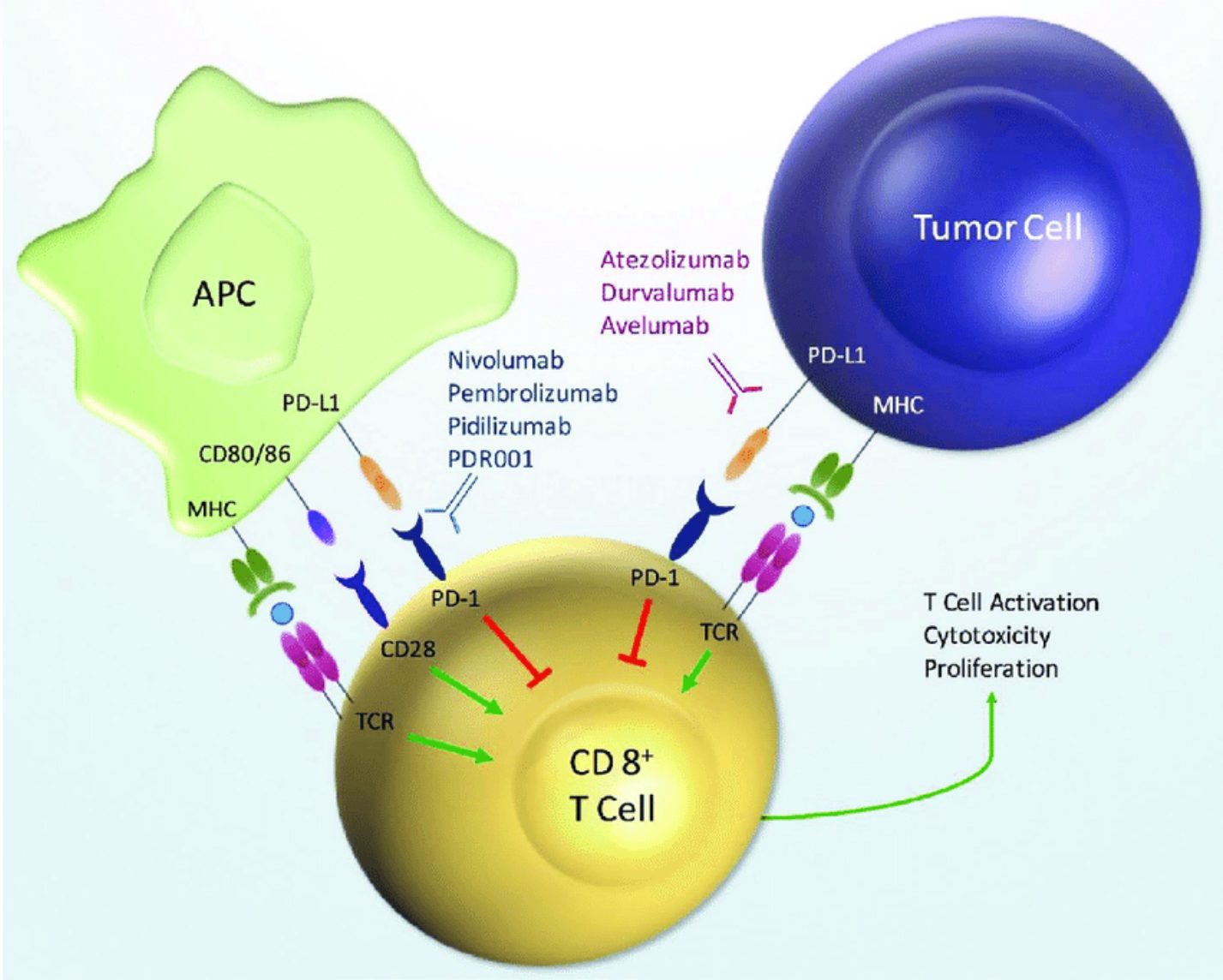
Multiple immune modulators (of which PD-1/PD-L1 is just one)

Nature Rev Immunol Jan 2015

PD-1

- Programmed Death 1 Receptor
- An “immune checkpoint” protein
- Expressed on activated T cells
- Engaged by ligands PD-L1 and PD-L2, expressed by infiltrating immune cells and, in some cases, by tumor cells

Immune Cell and Tumor Cell Interactions



#LearnACI

Maughan BL et al., Frontiers Oncol 7:56, 2017

The Potential

- The immune system has the capability of destroying host tumor cells
- Under certain conditions the host immune system can be hijacked by tumor cells through the PD-1/PD-L1 pathway and rendered ineffective
- Drugs targeting the PD-1/PD-L1 can remove this “brake” on the immune system and accelerate host killing of tumor cells

Questions: PD-L1

- What is PD-L1 and why test for its expression?
- **How do we predict which patients will respond to PD-L1 therapy?**
- How is PD-L1 expression assessed?
- Why can’t there be just one universal PD-L1 assay?
- What other than PD-L1 expression can predict response to PD-L1 therapy?

BIOMARKERS of RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

- PD-L1 expression on tumor cells
- PD-L1 expression on immune/inflammatory cells
- MMR deficiency in tumor cells
- Mutational burden of tumor

Tasuku Honjo, M.D., Ph.D.

2018 Nobel Prize Science and Medicine

with James Allison Ph.D.

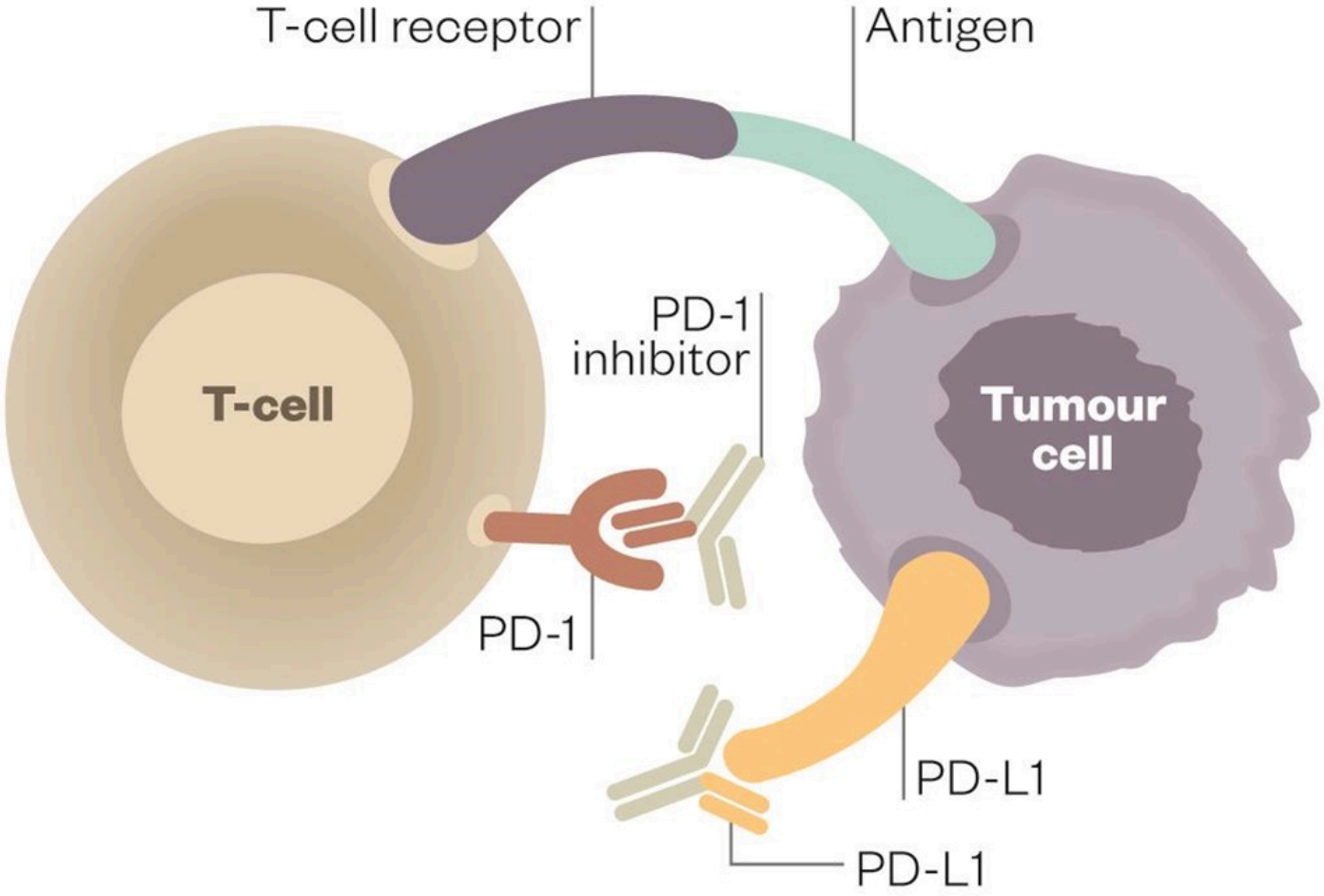
- Discovered PD-1 on T cells - 1992
- Blocked PD-1 and restored T-cell targeting of cancer cells

#LearnACI

The Logic

Identifying tumors with the target molecules (PD-L1) identifies patients who will be most likely to respond to PD-L1-targeted drugs

T cell Activation by PD1/PDL1 Blockade



#LearnACI

The Pharmaceutical Journal Vol 293, No 7837/8, 2014, DOI: 10.1211/PJ.2014.20067127

US FDA Approved Drugs Targeting PD-1 and PD-L1

Drug	Name	Target	First Approval
Pembrolizumab	Keytruda™	PD-1	2014
Nivolumab	Opdivo™	PD-1	2014
Atezolizumab	Tecentriq™	PD-L1	2016
Avelumab	Bavencio™	PD-L1	2017
Durvalumab	Imfinzi™	PD-L1	2017
Cemiplimab	Libtayo™	PD-1	2018
Dostarlimab	Jemperli™	PD-1	2021

#LearnACI

March 2022

Tumors with FDA approval: Pembrolizumab]

H&N Squamous (2nd line)	*No testing required*
H&N Squamous (1st line)	**22C3 IHC: ≥ 1% TPS**
Melanoma	*No testing required*
NSLC (2nd line therapy)	**22C3 IHC: ≥ 1% TPS**
NSLC (1st line therapy, stage III or metastatic)	**22C3 IHC: ≥ 1% TPS**
NSLC (combo with chemo in 1st line therapy)	*No testing required*
Urothelial CA	*No testing required*
Cervical CA (2nd line)	**22C3 IHC: ≥ 1% CPS**
Breast cancer, triple negative	**22C3 IHC: ≥ 10% CPS**
Esophageal squamous cell carcinoma	**22C3 IHC: ≥ 10% CPS**
Urothelial CA, not eligible platinum	*No testing required*
Hepatocellular carcinoma	*No testing required*
Renal cell carcinoma	*No testing required*
Merkel cell carcinoma	*No testing required*
Hodgkin's Lymphoma	*No testing required*
ALL TUMORS	**MMR IHC or MSI PCR**
ALL TUMORS	**TMB ≥ 10**

(Partial list)

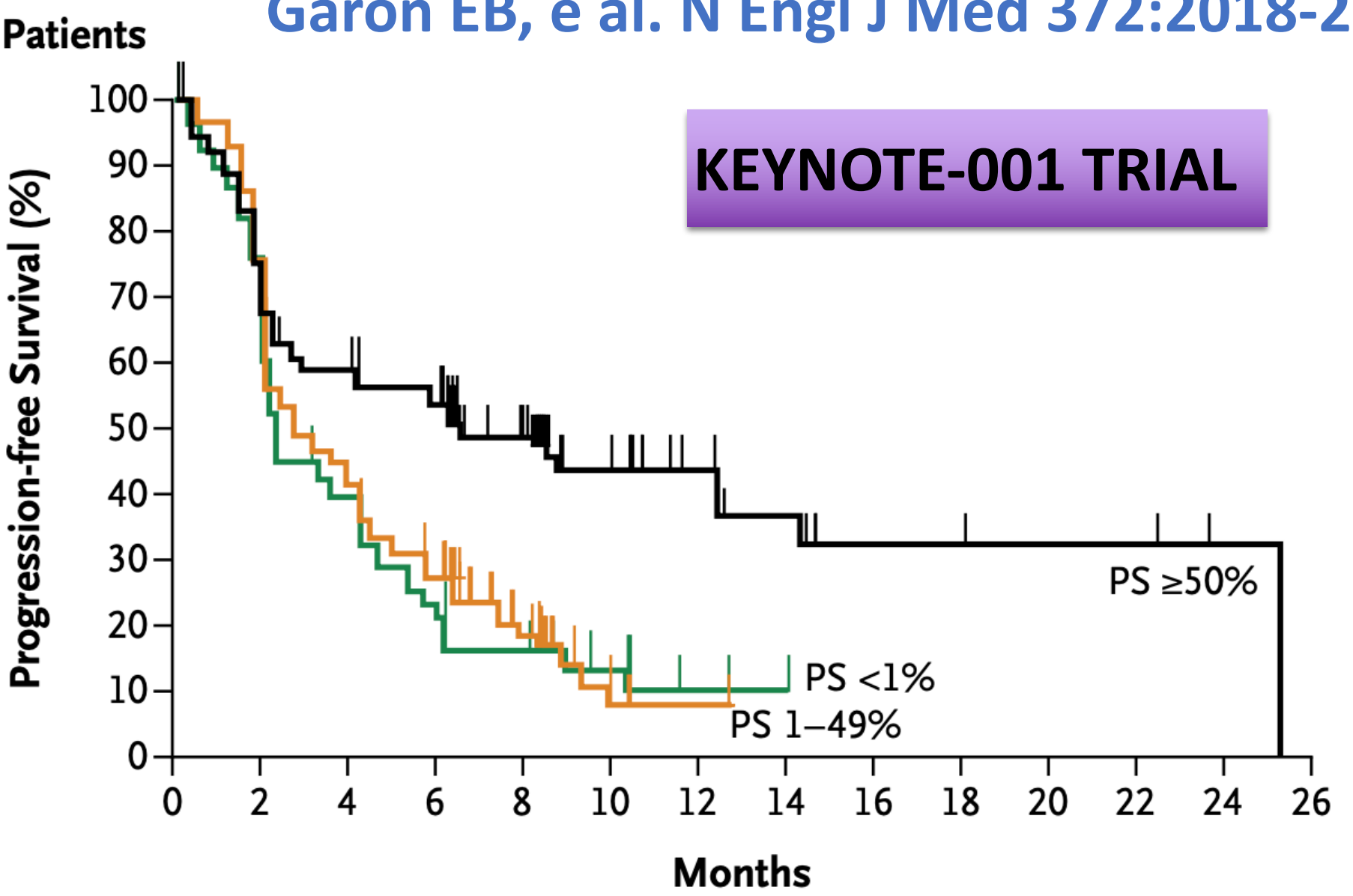
Tumors with FDA approval: Pembrolizumab]

Calendar Years 2021- 2022

Renal Cell Carcinoma - adjuvant	**Keynote 564**	**HR 0.68 DR or death**	*No testing required*
Cervical CA - +/- bevacizumab	**Keynote 826**	**HR 0.64 OS**	**22C3 IHC: ≥ 1% CPS**
Renal cell CA first line with lenvatinib	**Keynote 581**	**HR = 0.39 PFS**	*No testing required*
TNBC - neoadjuvant with chemotherapy and continued single agent	**Keynote 522**	**HR = 0.63 OS**	*No testing required*
Endometrial CA combo with levatinib (2nd line)	**Keynote 775**	**HR - 0.68 (OS)**	*No testing required*
Squamous cell CA, skin, mono therapy 2nd line	**Keynote 629**	**ORR 35-50%**	*No testing required*
~~**Gastroesophageal CA montherapy 3rd line**~~	~~**WITHDRAWN**~~	~~**WITHDRAWN**~~	~~**22C3 IHC: ≥ 1% CPS**~~
Gastroesophageal CA, first line combo with transtuzumab and chemotherapy	**Keynote 811**	**OS 75% (vs. 52% T + C)**	*HER2 testing*
Gastroesophageal CA, combo with platinum plus fluropyrimidine chemo	**Keynote 590**	**HR = 0.73 (OS)**	*No testing required*
~~**Small cell lug carcinoma**~~	~~**WITHDRAWN**~~	~~**WITHDRAWN**~~	~~*No testing required*~~

#LearnACI

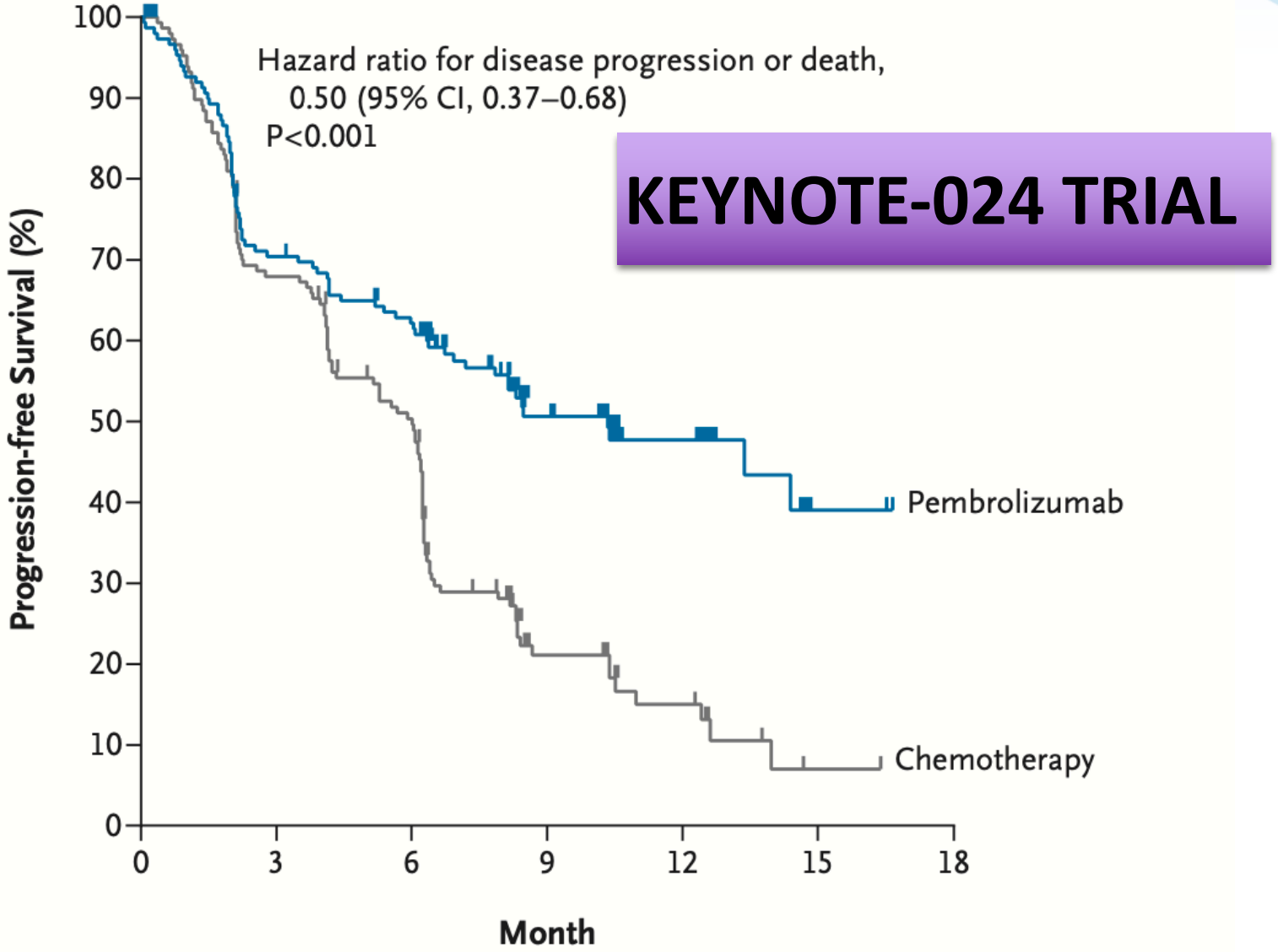
Garon EB, e al. N Engl J Med 372:2018-28, 2015



KEYNOTE-001 TRIAL

#Learn

Reck M, e al. N Engl J Med 375:1823-33, 2016



Reck M, e al. N Engl J Med 375:1823-33, 2016

- Pembrolizumab group showed higher response rate (44.8% v. 27.8%)
- Pembrolizumab group showed longer median progression free survival (10.3 months v 6.0 months)
- Hazard ratio for death at 6 months = 0.6
- **Pembrolizumab associated with significantly longer progression-free survival in patients with PD-L1 high expression**

Tumors with FDA approval: Nivolumab

Update: March 2022

H&N Squamous	*No testing required*
Hodgkin's Lymphoma	*No testing required*
NSLC (1st line therapy)**	**28-8 IHC: ≥ 1% TPS**
Renal cell CA,*****	*No testing required*
Urothelial CA	*No testing required*
Colorectal AdenoCA**	**dMMR or MSI-H**
Esophageal squamous cell CA	*No testing required*
Hepatocellular CA**	*No testing required*
Gastroesophageal CA	*No testing required*
Mesothelioma	*No testing required*
Gastroesophageal adenoCA	**28-8 IHC: ≥ 5 CPS**

In combination with other chemotherapy* or immunotherapy** or TKI***

Tumors with US FDA approval: Atezolizumab

Urothelial carcinoma	SP142 IHC ≥5% IC
NSCLC (1st line)	SP142 IHC ≥50% TC / ≥10% IC
NSCLC* (first line)	*No testing required*
Small cell lung CA*	*No testing required*
Hepatocellular CA* **	*No testing required*
Melanoma**	**BRAF V600 mutation**

Breast TNBC approval withdrawn 2021

In combination with other chemotherapy* or immunotherapy** or anti-VEGF***

Update: March 2022

Anti-PD-L1 Therapies

Monotherapy	**Melanoma** **Cutaneous squamous cell CA** **Head & Neck squamous cell CA** **NSCLC** **Cervical cancer** **Esophageal squamous cell CA** **TN Breast CA** **Renal cell CA** **All dMMR/MSI solid tumors** **All high TMB solid tumors** **Urothelial carcinoma** **Gastroesophageal adenocarcinoma** **Hepatocellular carcinoma**

Anti-PD-L1 Therapies

Combination with cytotoxic chemotherapy	NSCLC, Small Cell Lung CA, Head & Neck SCC, TN Breast CA, Gastroesophageal CA
Combination with VEGF inhibitors	Hepatocellular CA, Renal Cell CA, Endometrial CA
Combination with CTLA-4 inhibitors	Melanoma, MSI Colorectal CA, Renal cell CA, Hepatocellular CA, NSCLC, Pleural Mesothelioma
Combination with tyrosine kinase inhibitors	Renal cell CA
Combination with VEGF inhibitors and chemotherapy	NSCLC
Combination with BRAF and MEK inhibitors	Melanoma

Questions: PD-L1

- What is PD-L1 and why test for its expression?
- How do we predict which patients will respond to PD-L1 therapy?
- **How is PD-L1 expression assessed?**
- Why can’t there be just one universal PD-L1 assay?
- What other than PD-L1 expression can predict response to PD-L1 therapy?

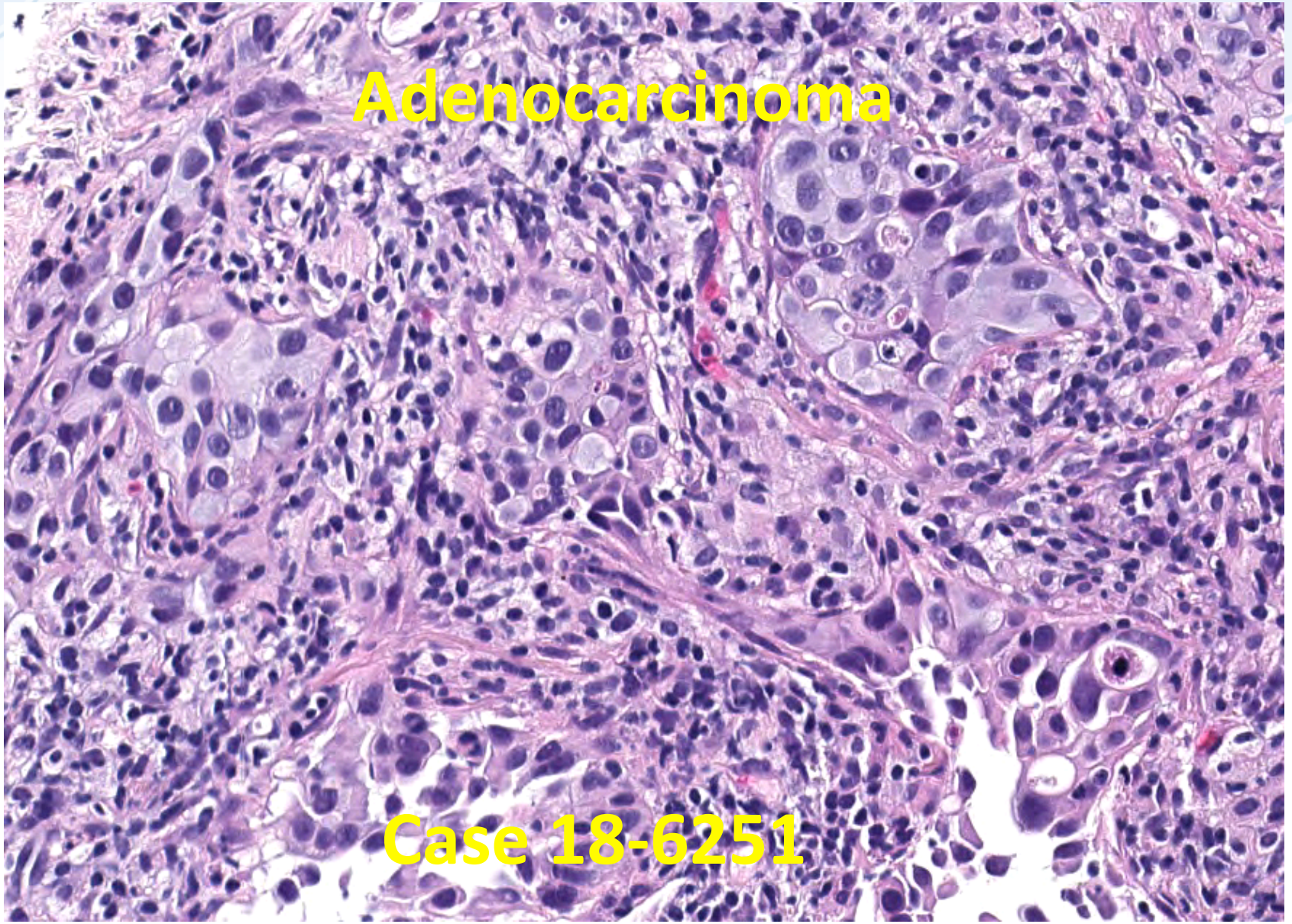
Source of Confusion

PD-L1 Testing Has Predictive Value but is **dependent** upon the **tumor type** and the **PD-L1 Test** employed

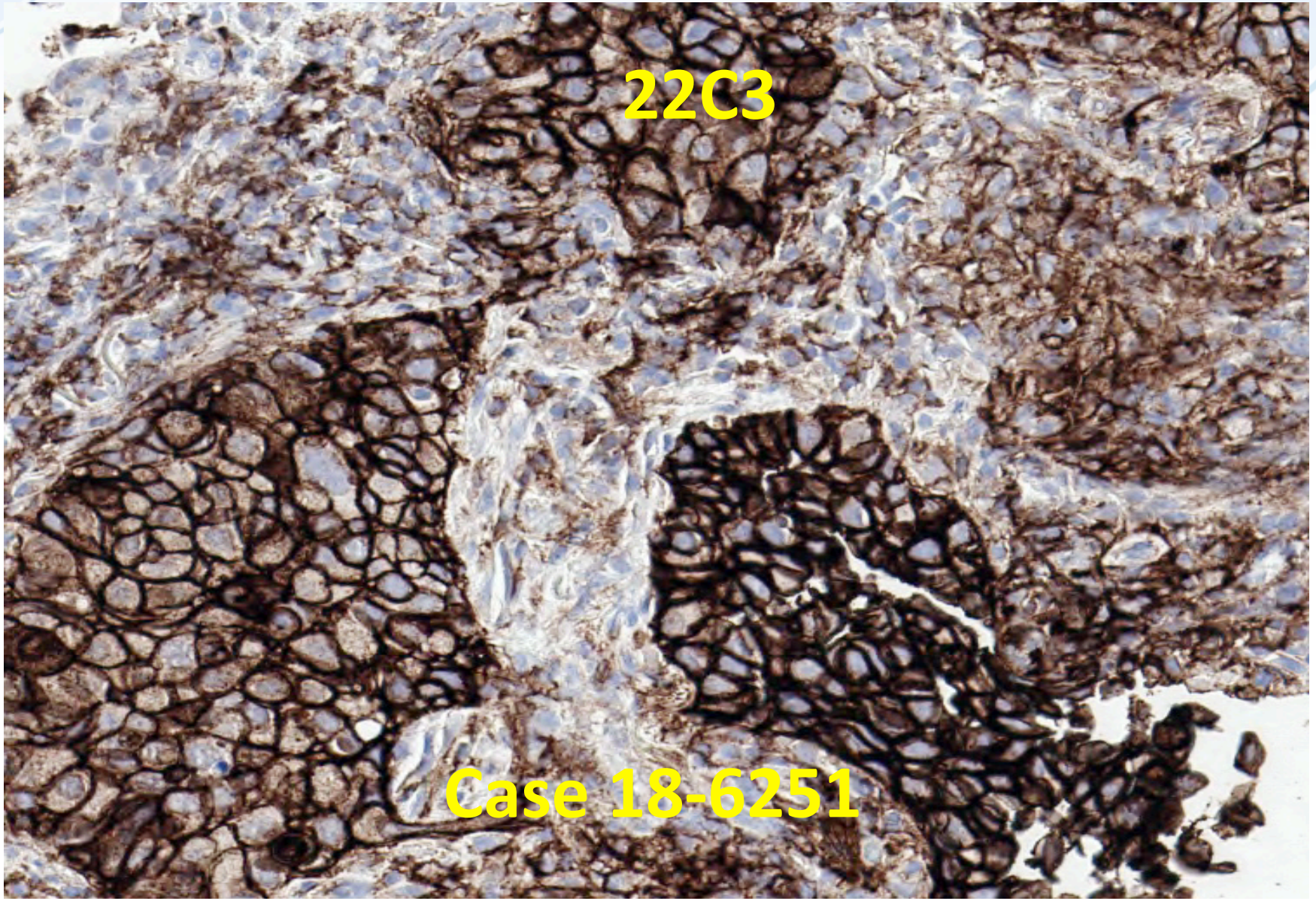
TPS(Tumor Proportion Score)

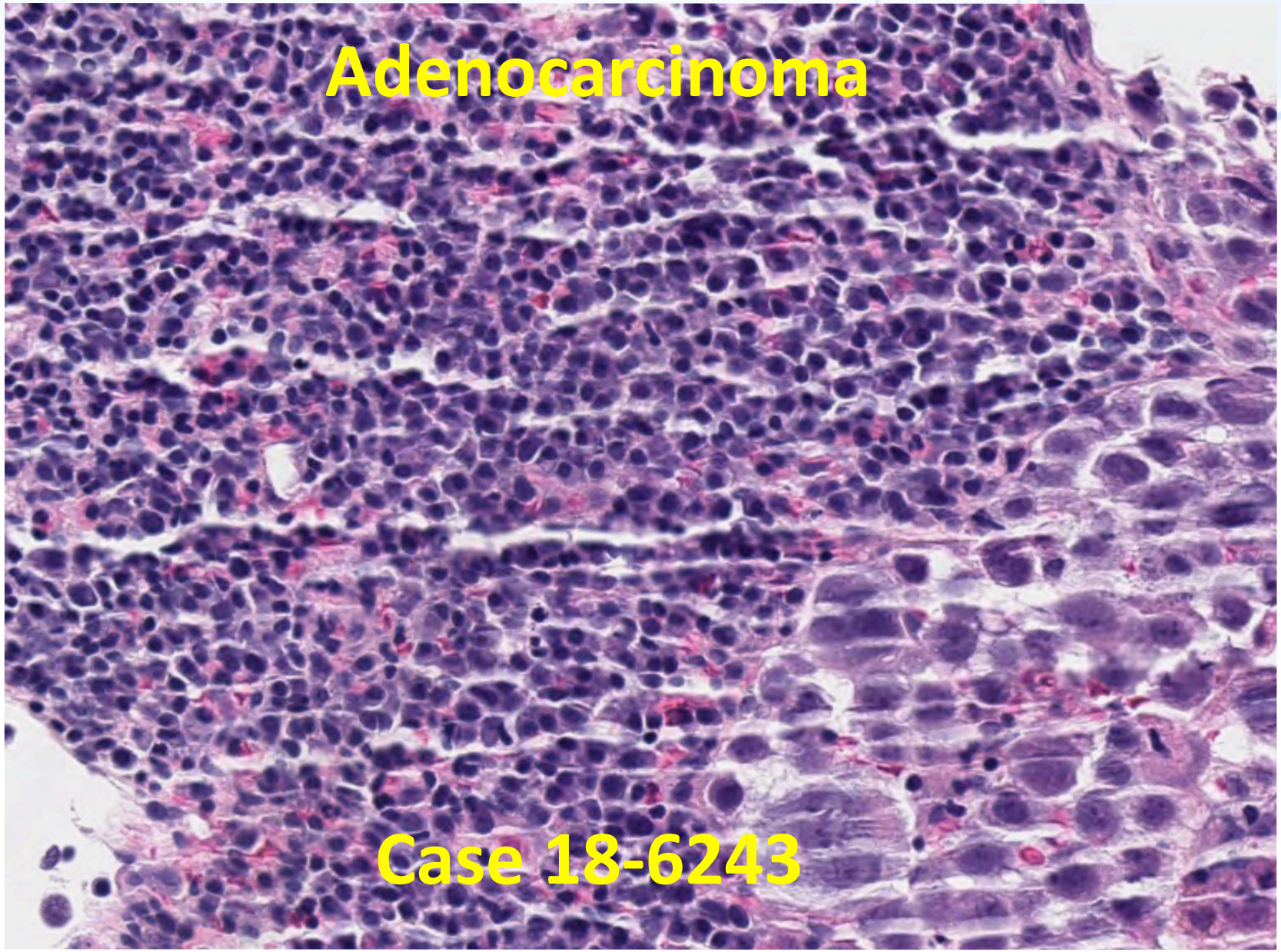
Determined by estimating the number of PD-L1-positive tumor cells divided by the total number of tumor cells

$$\frac{N_{\text{Positive Tumor}}}{N_{\text{Total tumor}}} \times 100$$

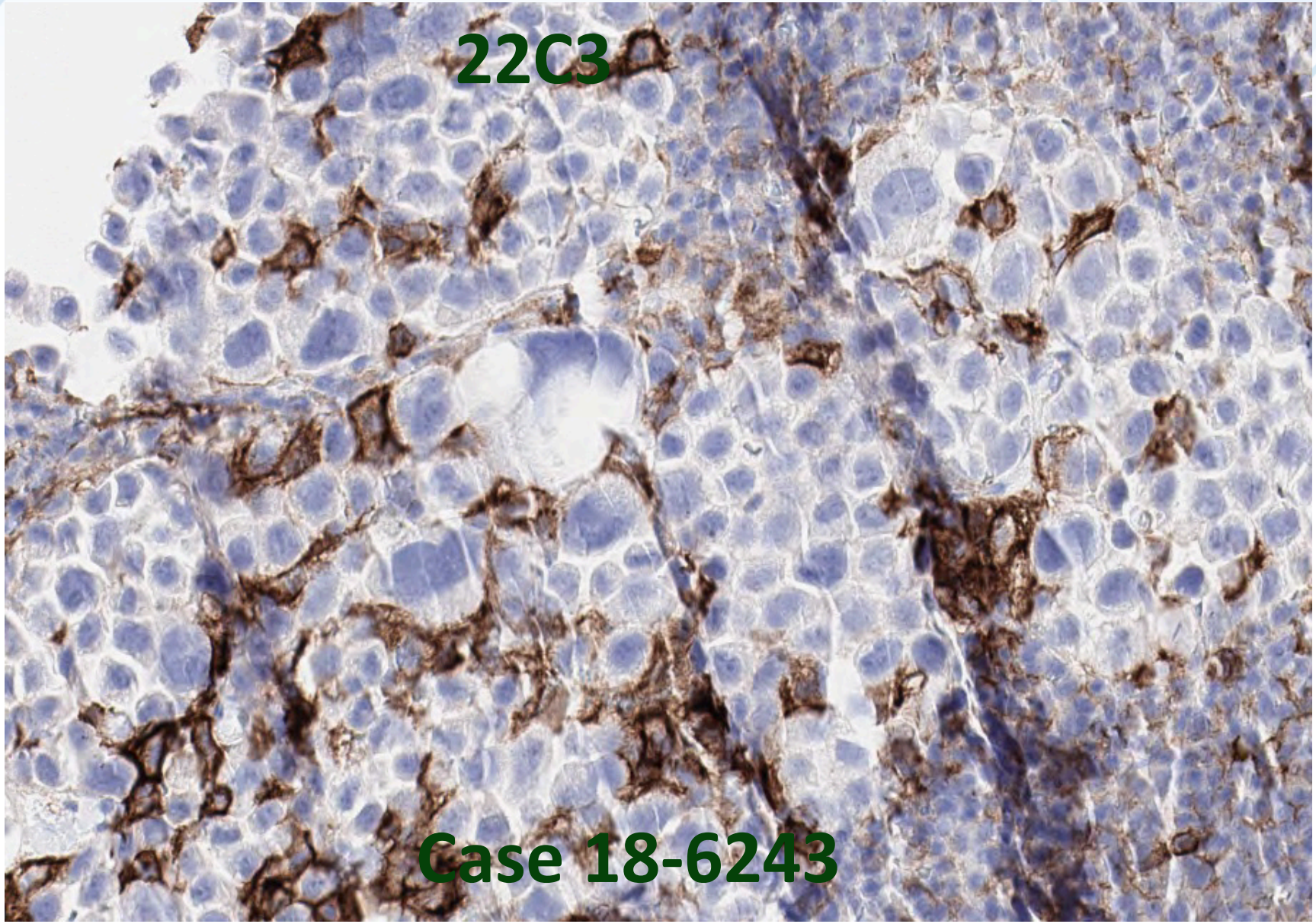


TPS = 100%





TPS <1%



CPS(Combined Proportion Score)

Determined by calculating the number of PD-L1-positive tumor cells PLUS immune cells divided by the total number of tumor cells

$$\frac{N_{\text{+ Tumor}} + N_{\text{+ Macrophages}} + N_{\text{+ Lymphocytes}}}{N_{\text{Total tumor}}} \times 100$$

(Max score = 100)

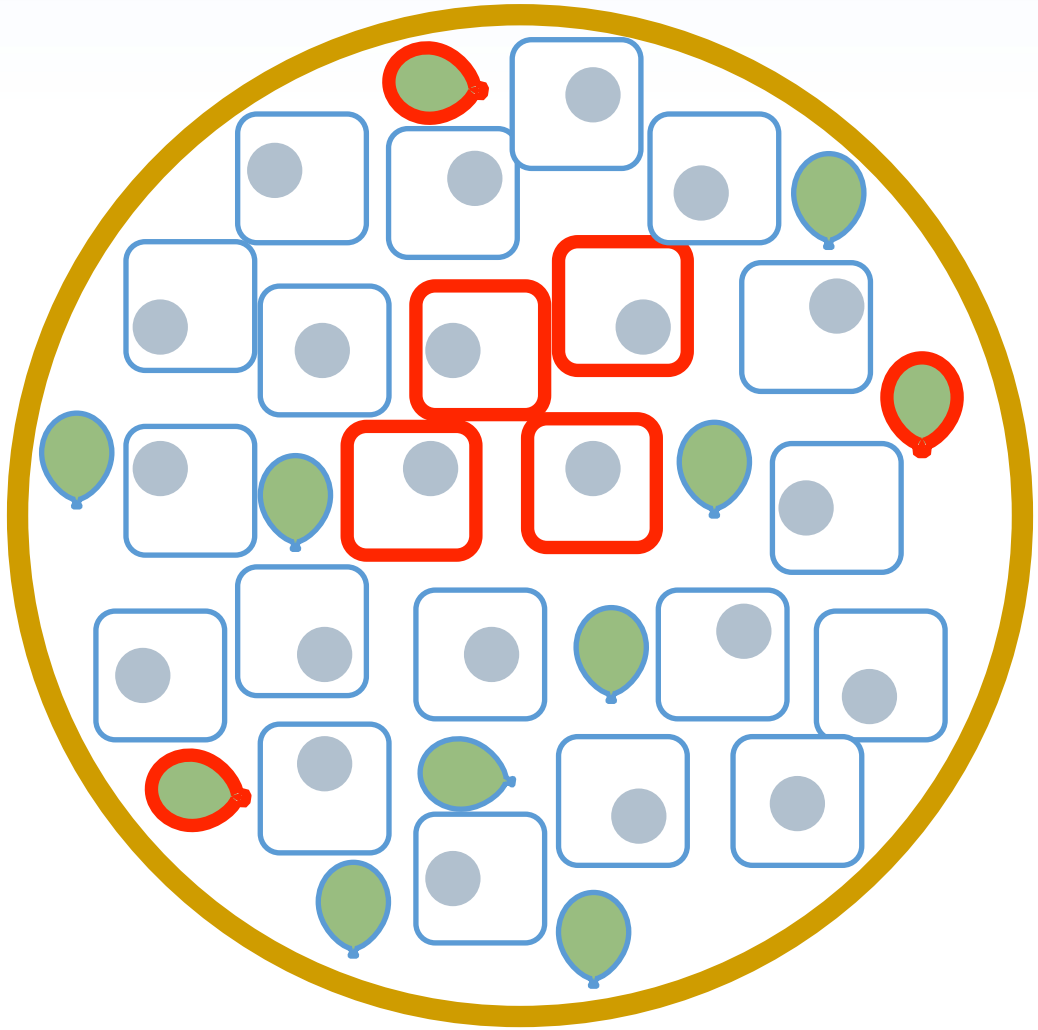
How To Perform CPS

Immune cell
PD-L1-negative

Tumor cell
PD-L1-negative

Immune cell
PD-L1 positive

Tumoor cell
PD-L1 positive



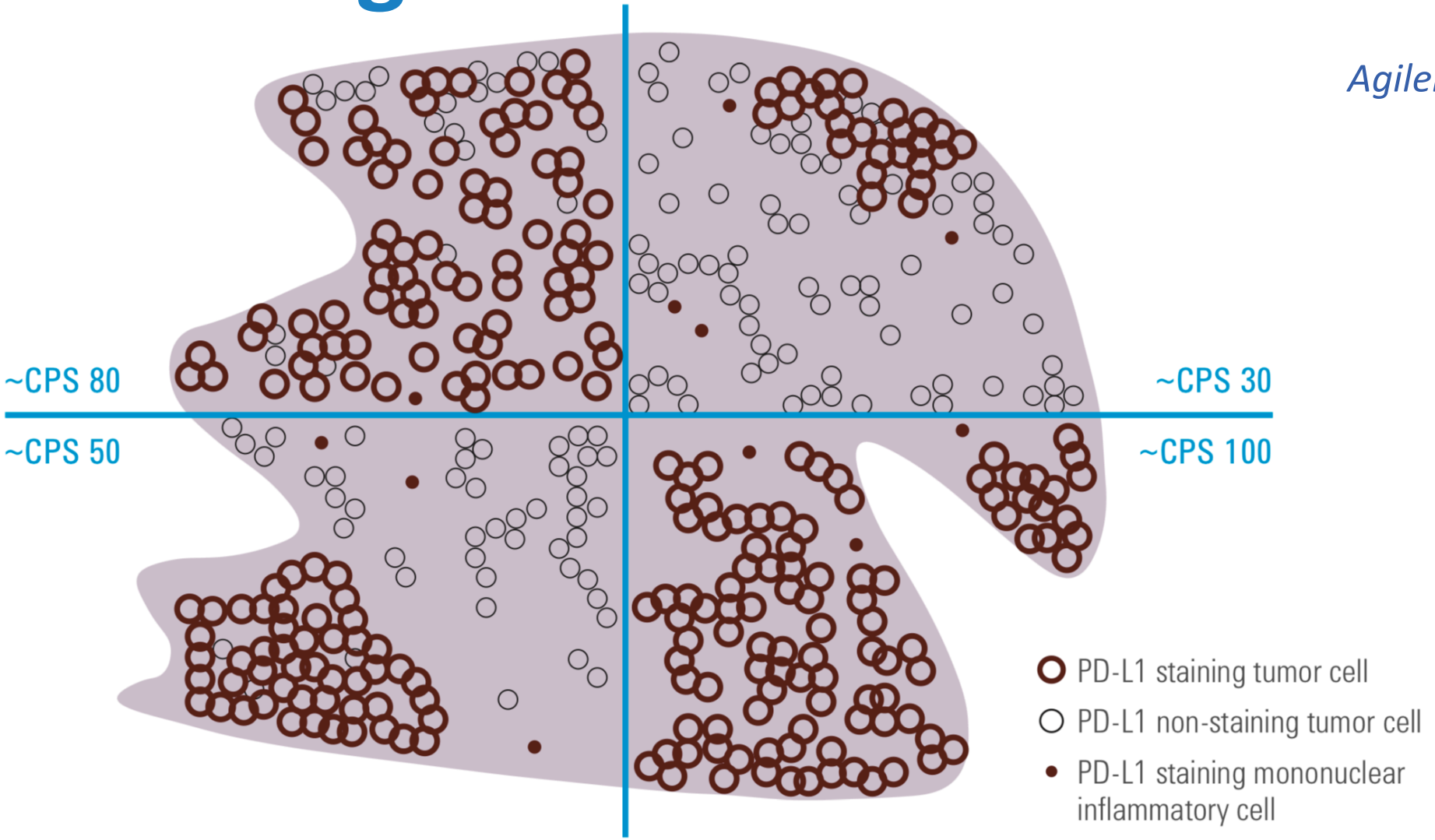
- Select 20x field
- Determine number of tumor cells
- Count PD-L1 positive cells (red)
- Repeat over 10 20x fields

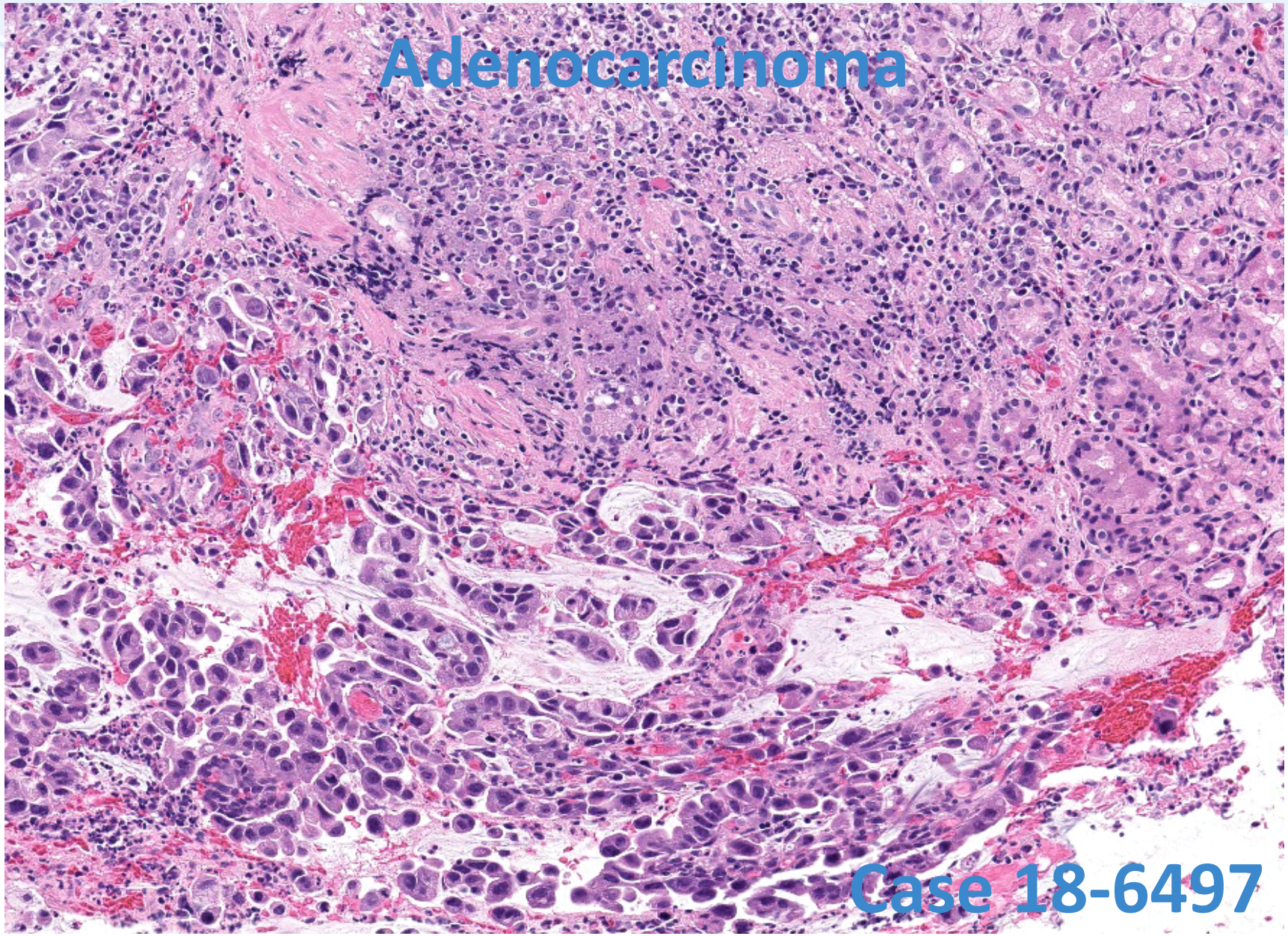
CPS = (4 + 3) /22 => 32

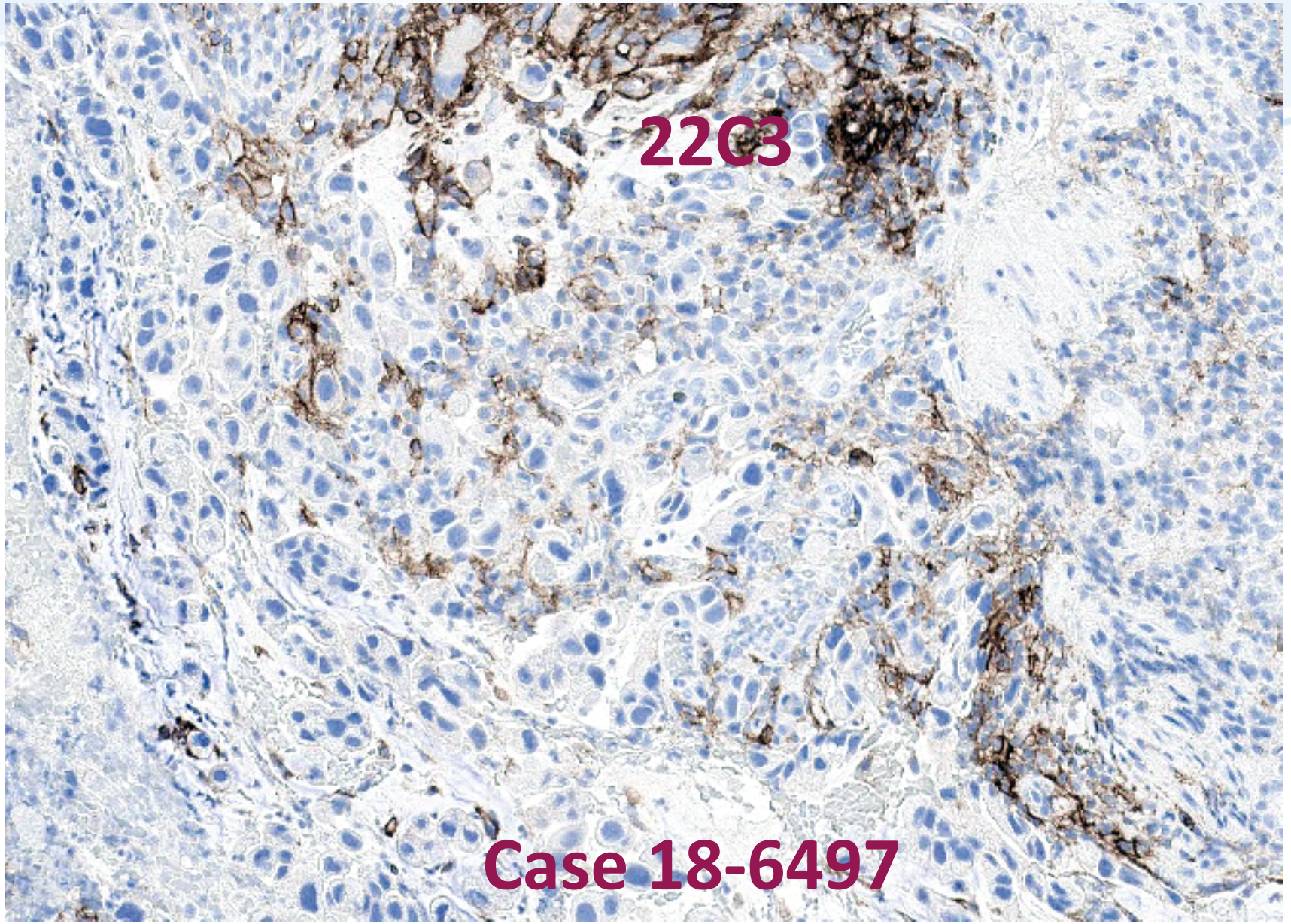
#LearnACI

Strategies for CPS Calculation

Agilent/Dako

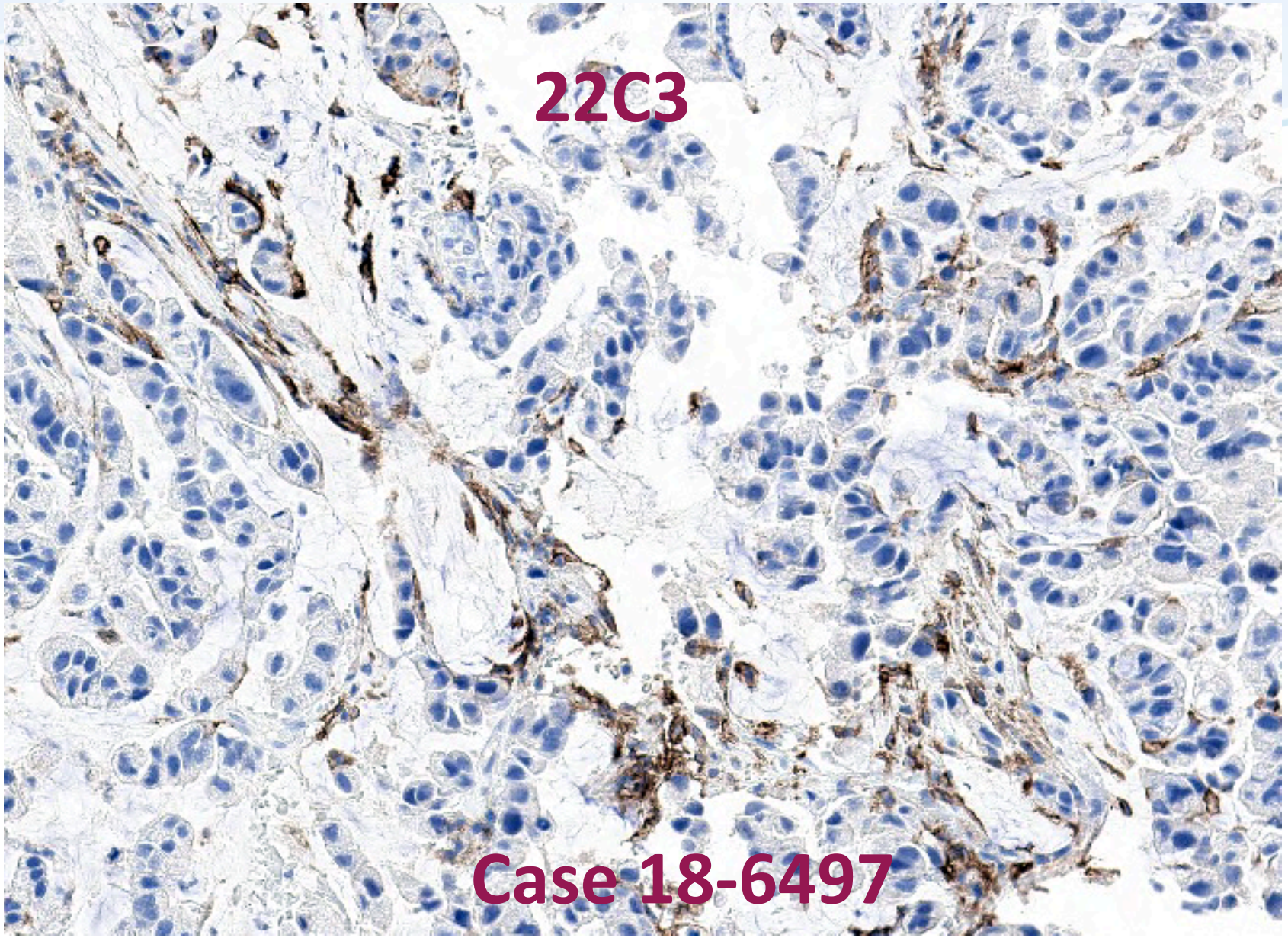






#LearnACI

CPS = 18



Yet Another Different Tumor and Immune Cell Scoring System

(e.g., SP142, companion diagnostic for atezolizumab in lung cancer)

- Tumor cells scored as percentage of viable tumor cells showing membranous signal of any intensity
- Immune cells scored as proportion of **tumor area*** occupied by PD-L1 staining immune cells of any intensity
- Cutoff ≥ 50% tumor cells OR IC covering ≥ 10% of tumor area

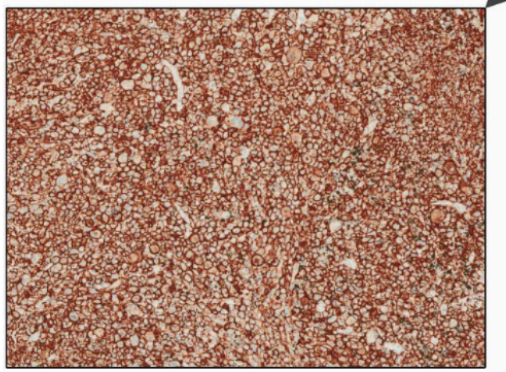
**area occupied by viable tumor cells, intra and peritumoral stroma*

Does the NSCLC tissue show PD-L1 expression in ≥ 50% of TC?

Yes

No

≥ 50% TC



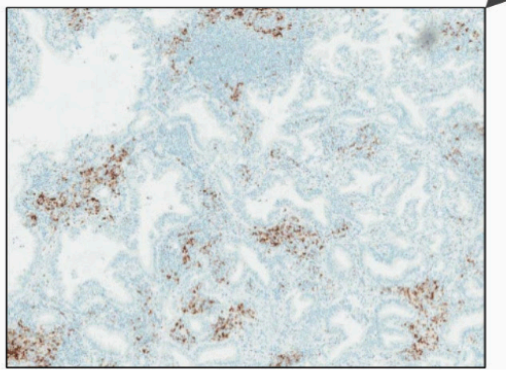
STEP 2

Does the NSCLC tissue show ≥ 10% of tumor area covered with PD-L1 Staining IC?

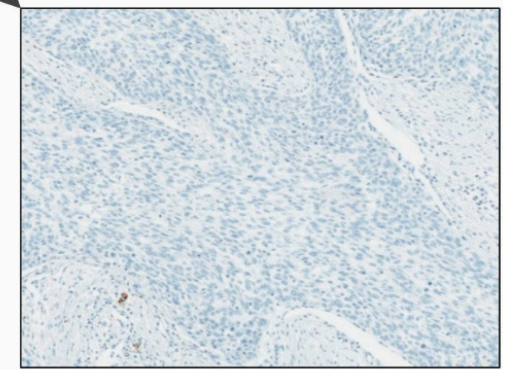
Yes

No

≥ 10% IC



< 50% TC and < 10% IC



#LearnACI

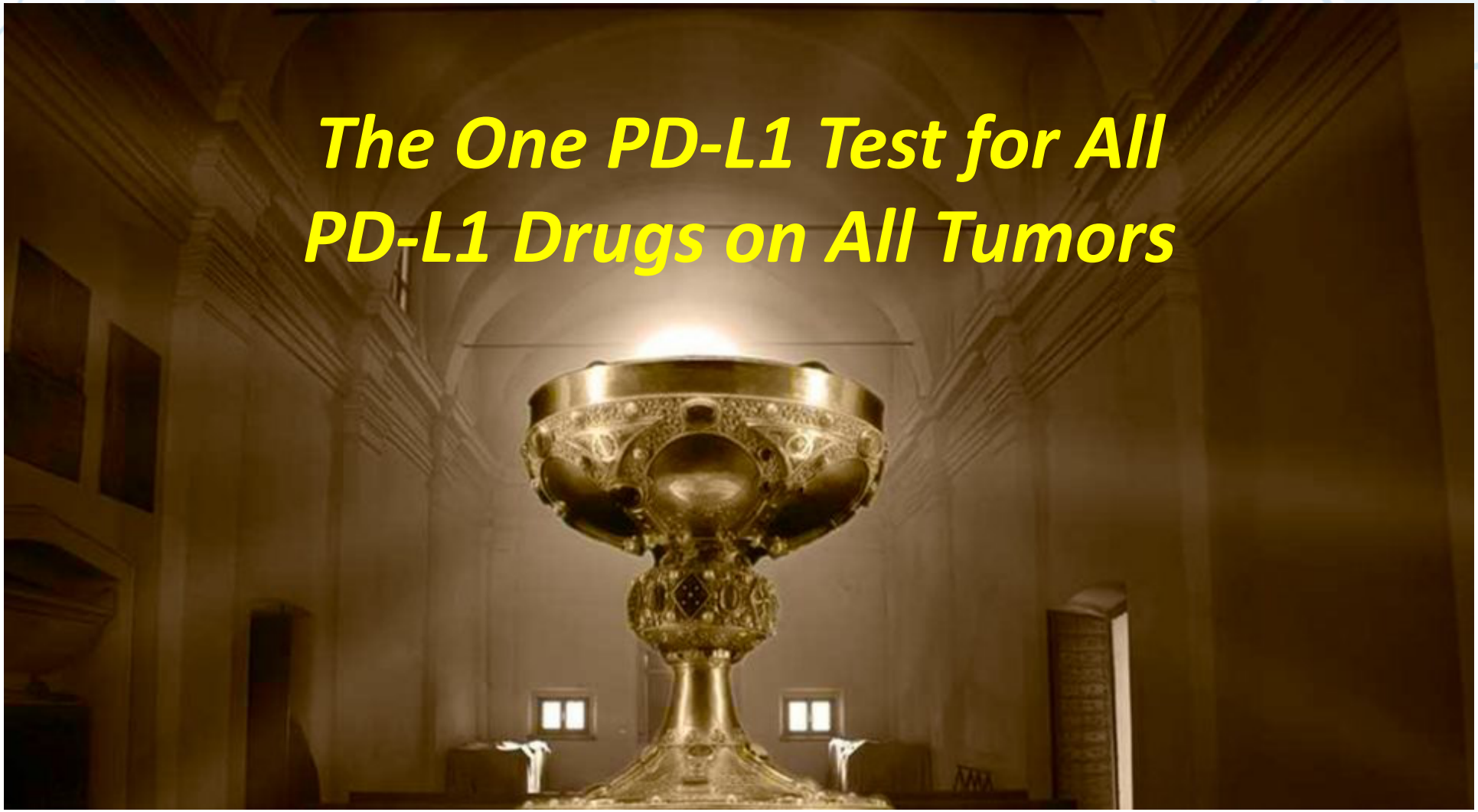
Comparison of PD-L1 Assays NSCLC

Drug	*Pembrolizumab*	*Nivolumab*	*Atezolizumab*	*Cemiplimab*
Target of Drug	PD-1	PD-1	PD-L1	PD-1
Anti-PDL1 antibody used in test	22C3	28-8	SP142	22C3
Type of diagnostic	Companion	Complementary	Complementary	Companion
Platform	Dako Link 48	Dako Link 48	Ventana	Dako Link 48
Scoring system cutoff NSCLC	≥1% TPS (1st line)	≥ 1% TPS (2nd line)	≥ 50% TC ≥ 10% IC	TPS ≥ 50%

Questions: PD-L1

- What is PD-L1 and why test for its expression?
- How do we predict which patients will respond to PD-L1 therapy?
- How is PD-L1 expression assessed?
- **Why can't there be just one universal PD-L1 assay?**
- What other than PD-L1 expression can predict response to PD-L1 therapy?

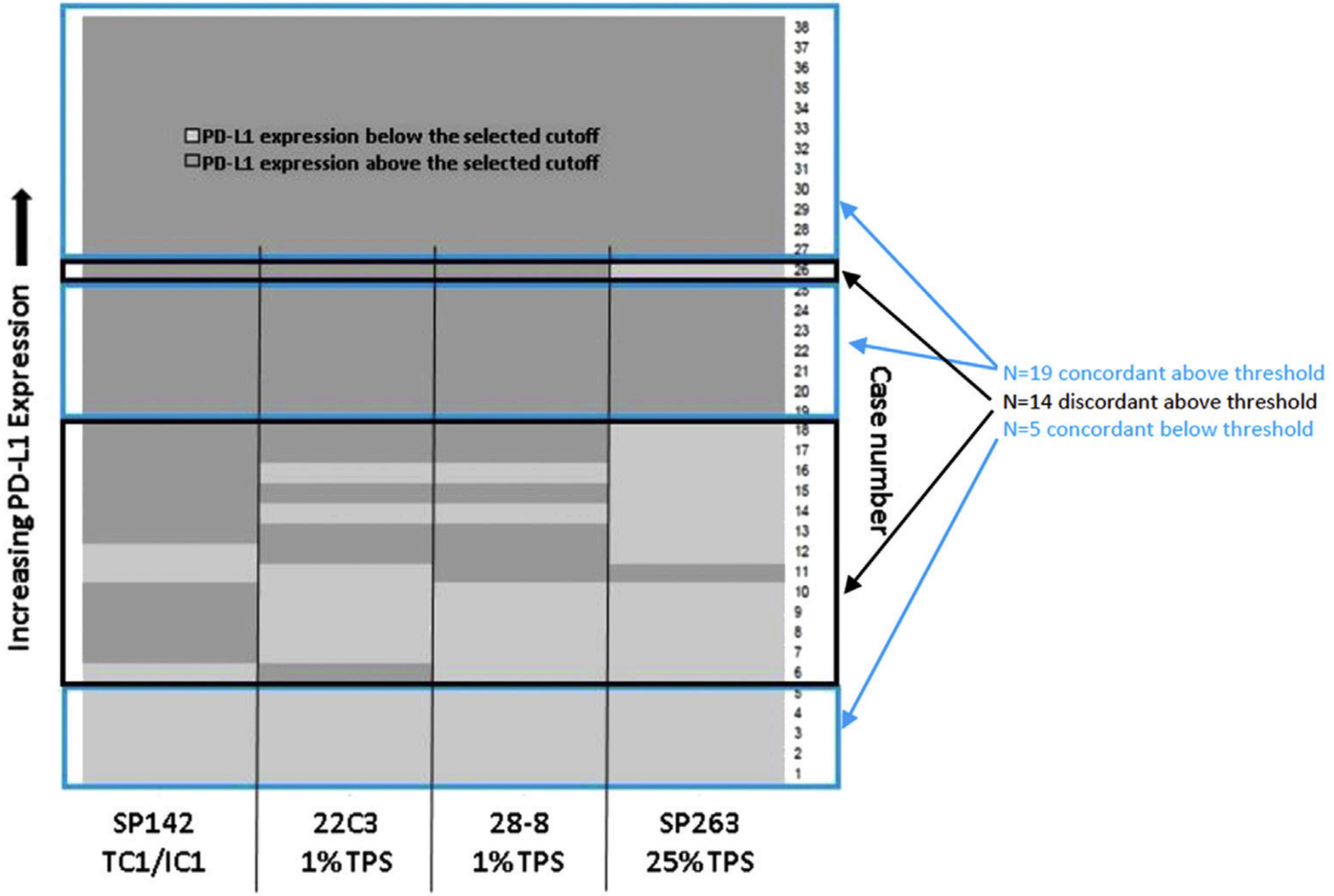
The Holy Grail



"Blueprint" PD-L1 IHC Assay Comparison Project

- Percent positive tumor cells comparable with 22C3, 28-8, and SP263
- SP142 positive on fewer cells
- Variability in immune cell signals greater
- For 14/38 cases (37%) different PD-L1 classification would be made depending upon which assay employed

Hirsch FR et al., J Thorac Oncol 12:208-222, 2017



Hirsch FR et al., J Thorac Oncol 12:208-222, 2017

Diagnostic Accuracy in Fit-for-Purpose PD-L1 Testing

Carol C. Cheung, MD, PhD, JD,† Hyun J. Lim, PhD,‡ John Garratt, RT(cyto),§ Jennifer Won, PhD,§ C. Blake Gilks, MD,§‖ and Emina E. Torlakovic, MD, PhD§¶*

- Analytical sensitivity and specificity no longer sufficient as measurements of quality in IHC biomarker testing such as PD-L1
- **Diagnostic accuracy, not concordance, is most critical**

App Immunohistochem Mol Morphol 27:251-7, 2019

Diagnostic Accuracy in Fit-for-Purpose PD-L1 Testing

Carol C. Cheung, MD, PhD, JD,† Hyun J. Lim, PhD,‡ John Garratt, RT(cyto),§ Jennifer Won, PhD,§ C. Blake Gilks, MD,§‖ and Emina E. Torlakovic, MD, PhD§¶*

App Immunohistochem Mol Morphol 27:251-7, 2019

- No direct links connecting analytical sensitivity and specificity with diagnostic sensitivity and specificity.
- Accuracy should be assessed by laboratory comparing their results with gold standard/reference laboratory
- **Each approved "drug-disease-diagnostic assay" combination is unique and the 3 components are typically linked together by clinically validated results (ie, response data from clinical trials).**

D D D

#LearnACI

Same Tumor, But Different Assays and Scoring Cutoffs for Different Drugs in Different Clinical Settings

Tumor	*Drug*	*Antibody*	*IHC scoring*	*Cutoff*
NSCLC	**Pembrolizumab**	**22C3**	**TPS**	**≥ 1%**
NSCLC	**Nivolumab***	**28-8**	**TPS**	**≥ 1%**
NSCLC first line metastatic	**Atezolizumab**	**SP142**	**Complicated**	**≥ 50% TC or IC ≥ 10% tumor area**
NSCLC adjuvant	**Atezolizumab**	**SP263**	**TPS**	**≥ 1%**
NSCLC	**Cemiplimab**	**22C3**	**TPS**	**≥ 50%**

*combo with ipilumumab

Same Drug, Same Assay, but Different Scoring Cutoffs for Different Tumors

Tumor	*Drug*	*Antibody*	*IHC scoring*	*Cutoff*
NSCLC	**Pembrolizumab**	**22C3**	**TPS**	**≥ 1%**
H&N SCCA	**Pembrolizumab**	**22C3**	**CPS**	**≥ 1%**
TNBC	**Pembrolizumab**	**22C3**	**CPS**	**≥ 10%**

*combo with ipilumumab

Questions: PD-L1

- What is PD-L1 and why test for its expression?
- How do we predict which patients will respond to PD-L1 therapy?
- How is PD-L1 expression assessed?
- Why can't there be just one universal PD-L1 assay?
- **What other than PD-L1 expression can predict response to PD-L1 therapy?**

"Pan Tumor" FDA Approvals Checkpoint Inhibitors

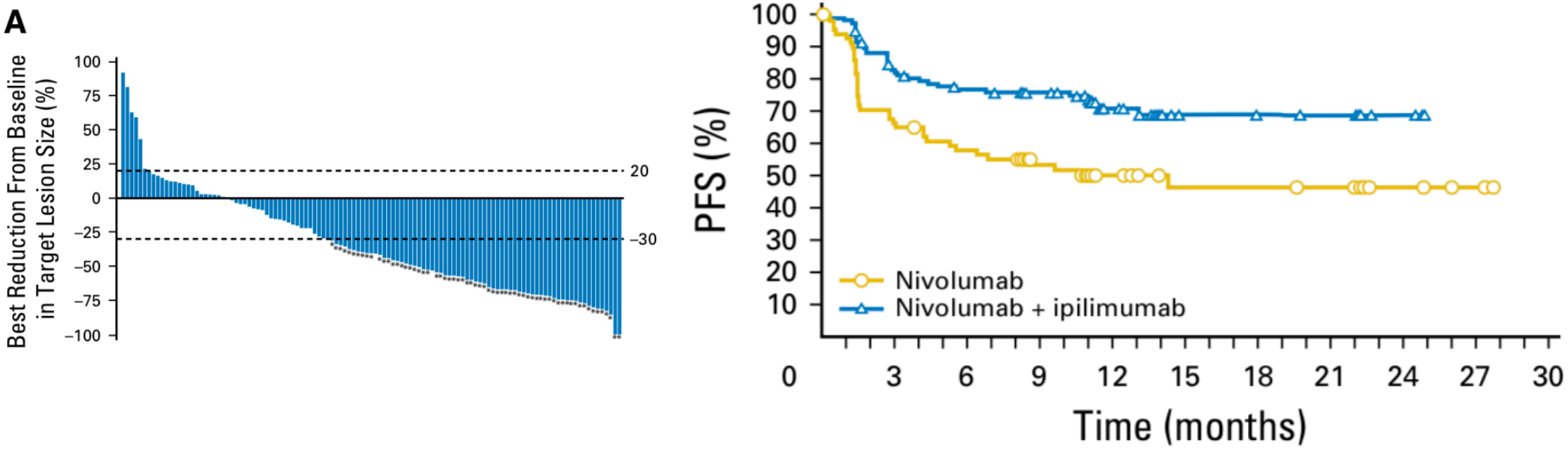
dMMR or MSI-H	Pembrolizumab*	2017
dMMR or MSI-H	Nivolumab**	2017
TMB	Pembrolizumab*	2020
dMMR	Dostarlimab*	2021

**2nd line unresectable or metastatic solid cancers*

***Progression following treatment with fluoropyrimidine, oxalplatin, irinotecan*

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

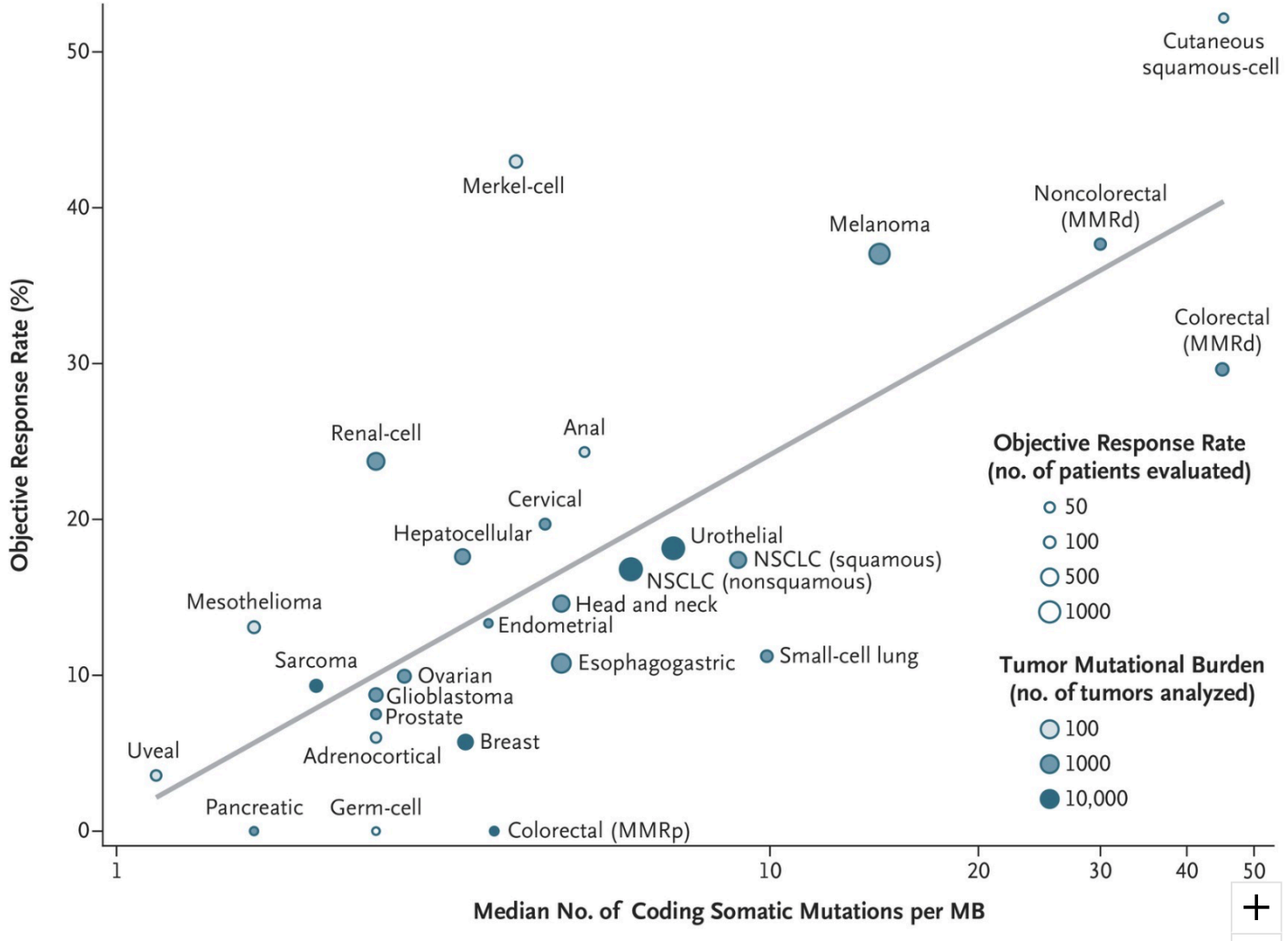
Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André



#LearnACI

J Clin Oncol 36:773-779, 2018

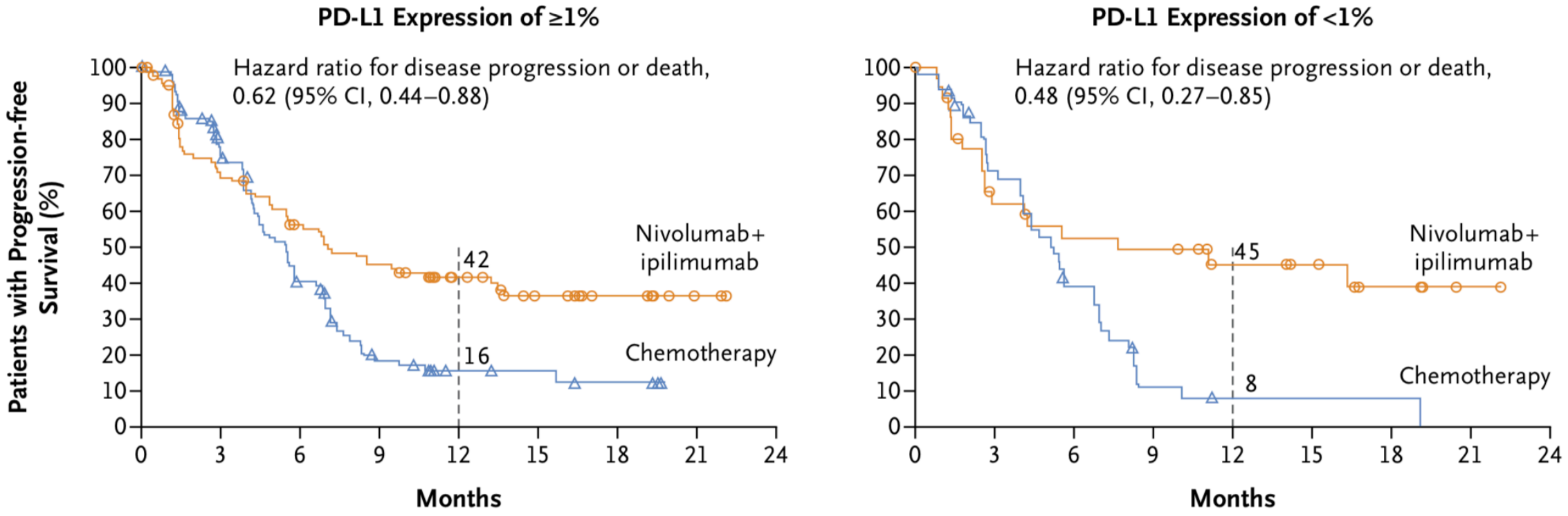
Tumor Mutational Burden and Response Rate to PD-1 Inhibition



Yarchoan L et al., NEJM 377:2500-1, 2017

#LearnACI

Effect of high TMB independent of PD-L1 Expression



Hellmann MD et al., NEJM 378:2093-2104, 2018

Summary

- Your pathologist will not appreciate an isolated request for “PD-L1 testing”
- What is the tumor? What drug is being contemplated? What is the clinical setting?