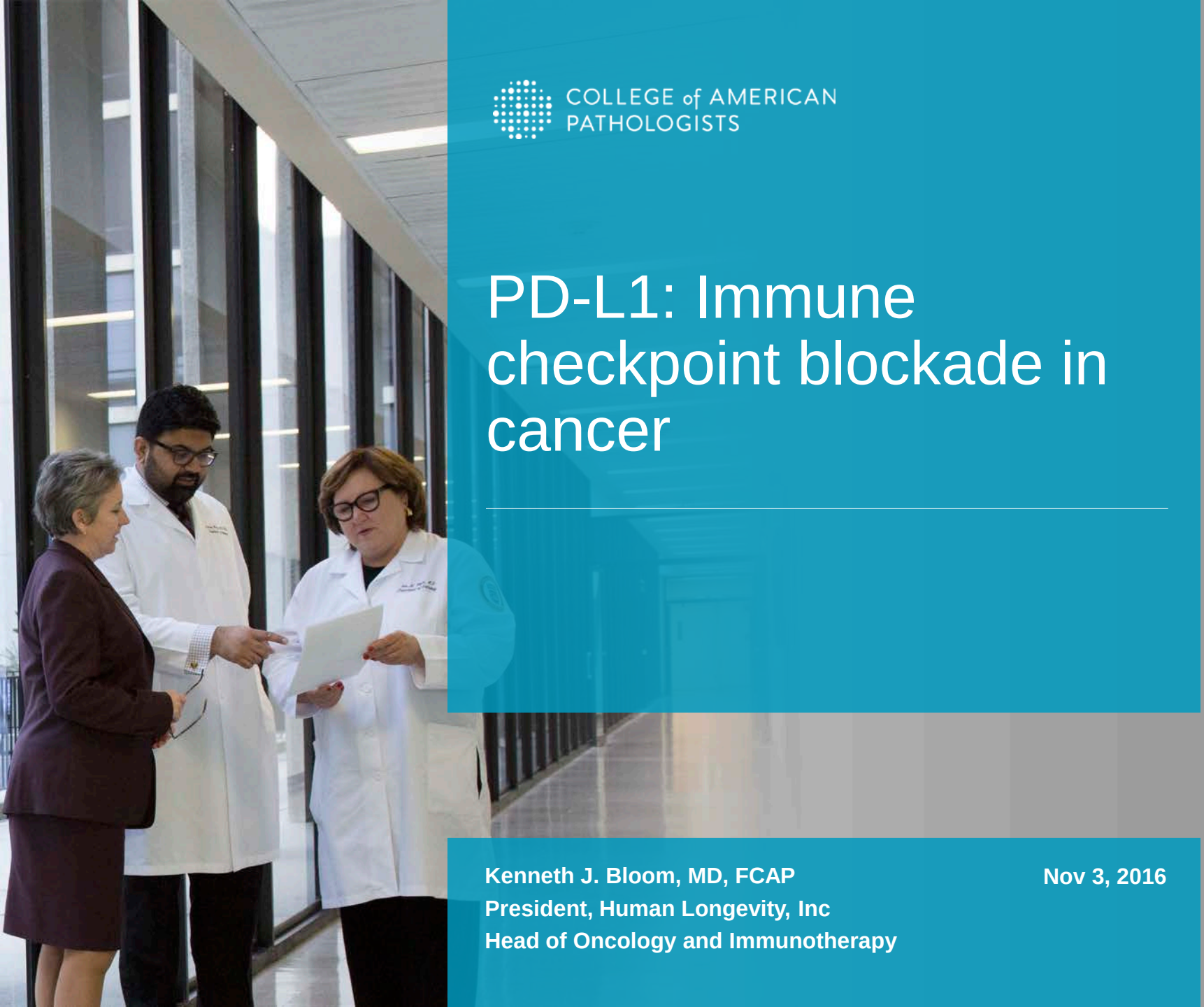

COLLEGE of AMERICAN PATHOLOGISTS

PD-L1: Immune checkpoint blockade in cancer

Kenneth J. Bloom, MD, FCAP
President, Human Longevity, Inc
Head of Oncology and Immunotherapy

Nov 3, 2016

Webinar Host

- **This series is sponsored by the Personalized Healthcare (PHC) Committee**
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Kenneth J. Bloom, MD, FCAP

- **President and Head of oncology and immunotheraphy at Human Longevity, Inc**
- **Has published over 50 peer-reviewed articles, more than 100 abstracts, and several book chapters**

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Disclosures

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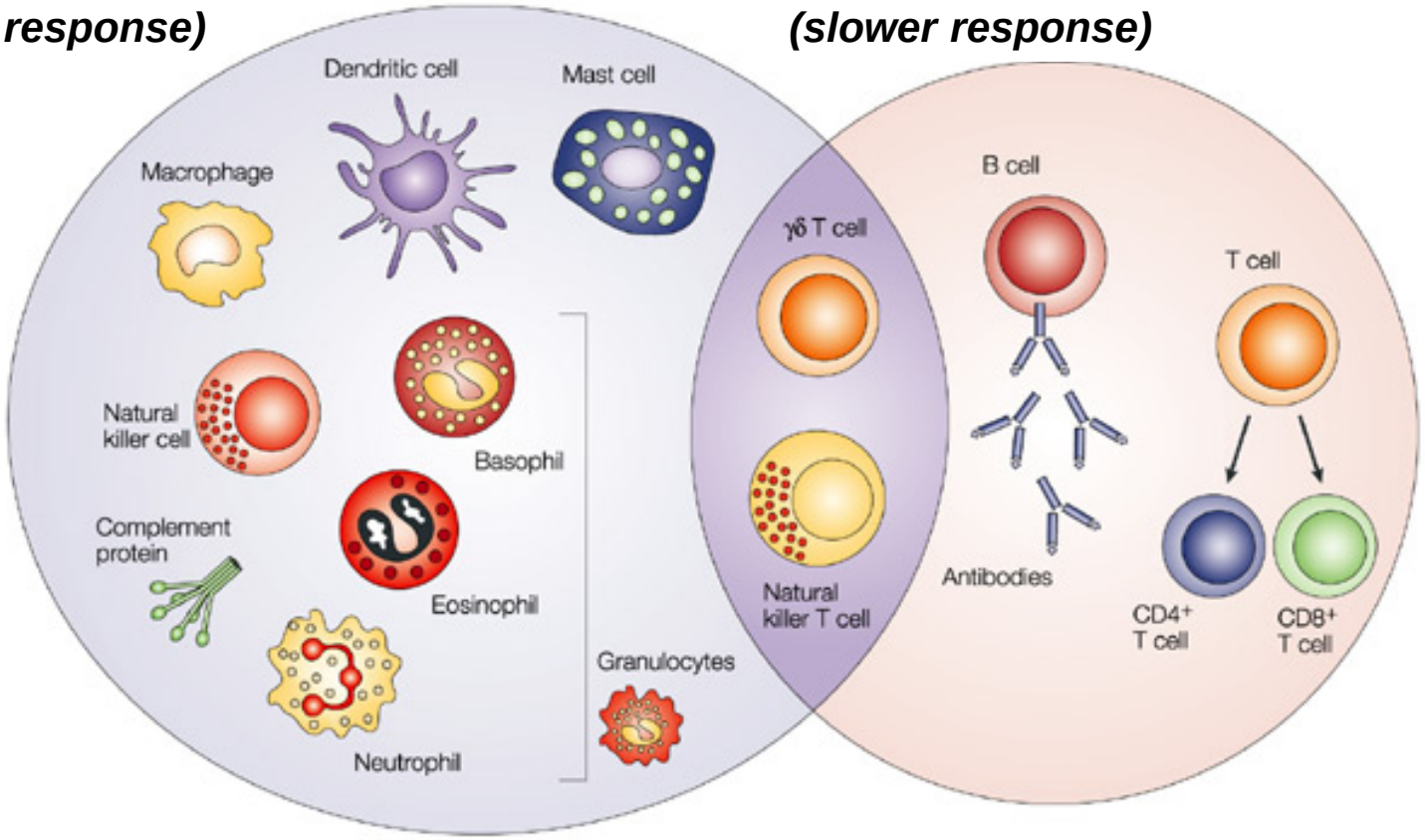
Your Immune System has two main ways to respond to foreign invaders:

Innate versus adaptive

Innate Immunity
(rapid response)

Adaptive Immunity
(slower response)

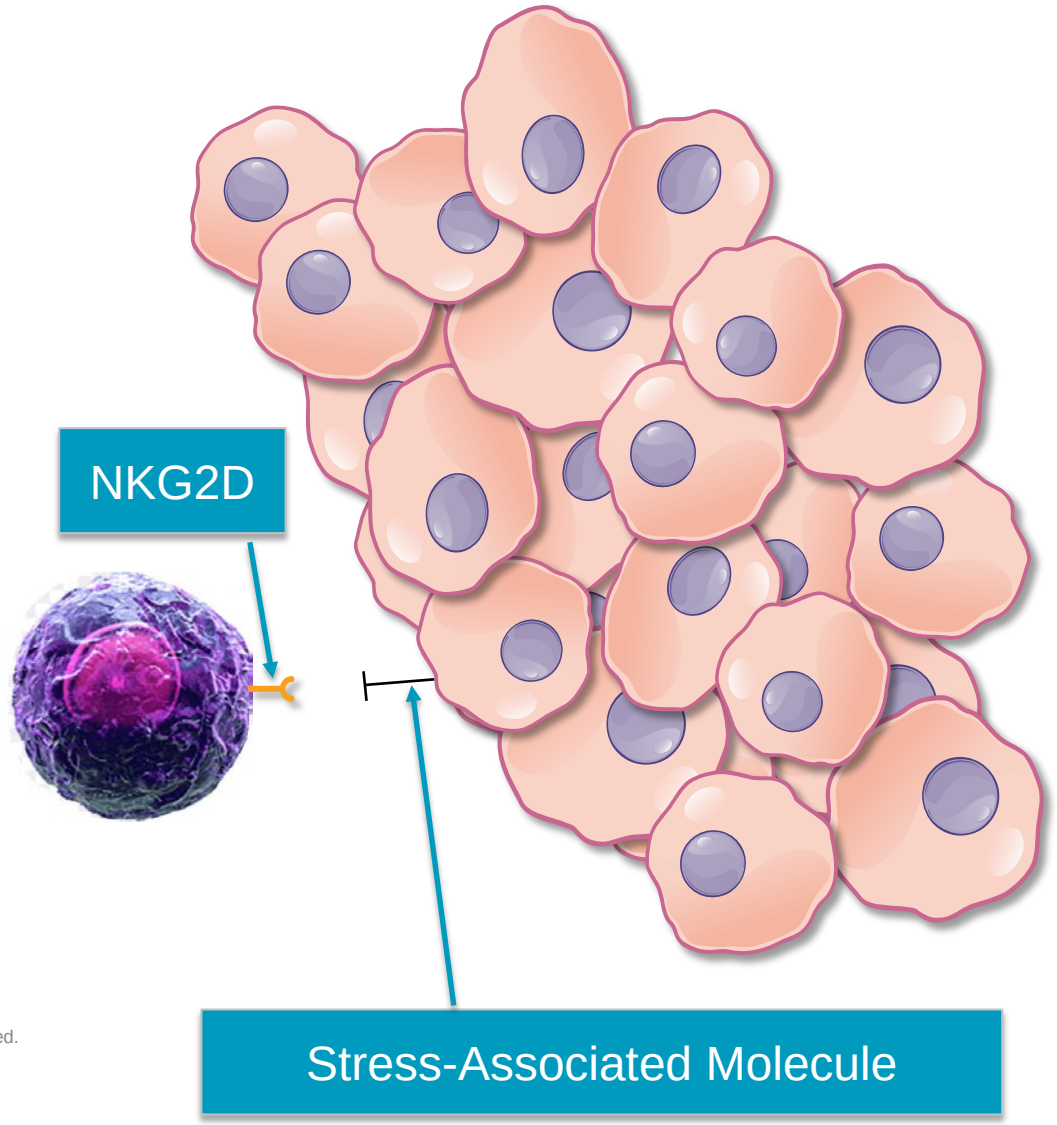


Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004;4(1):11-22.

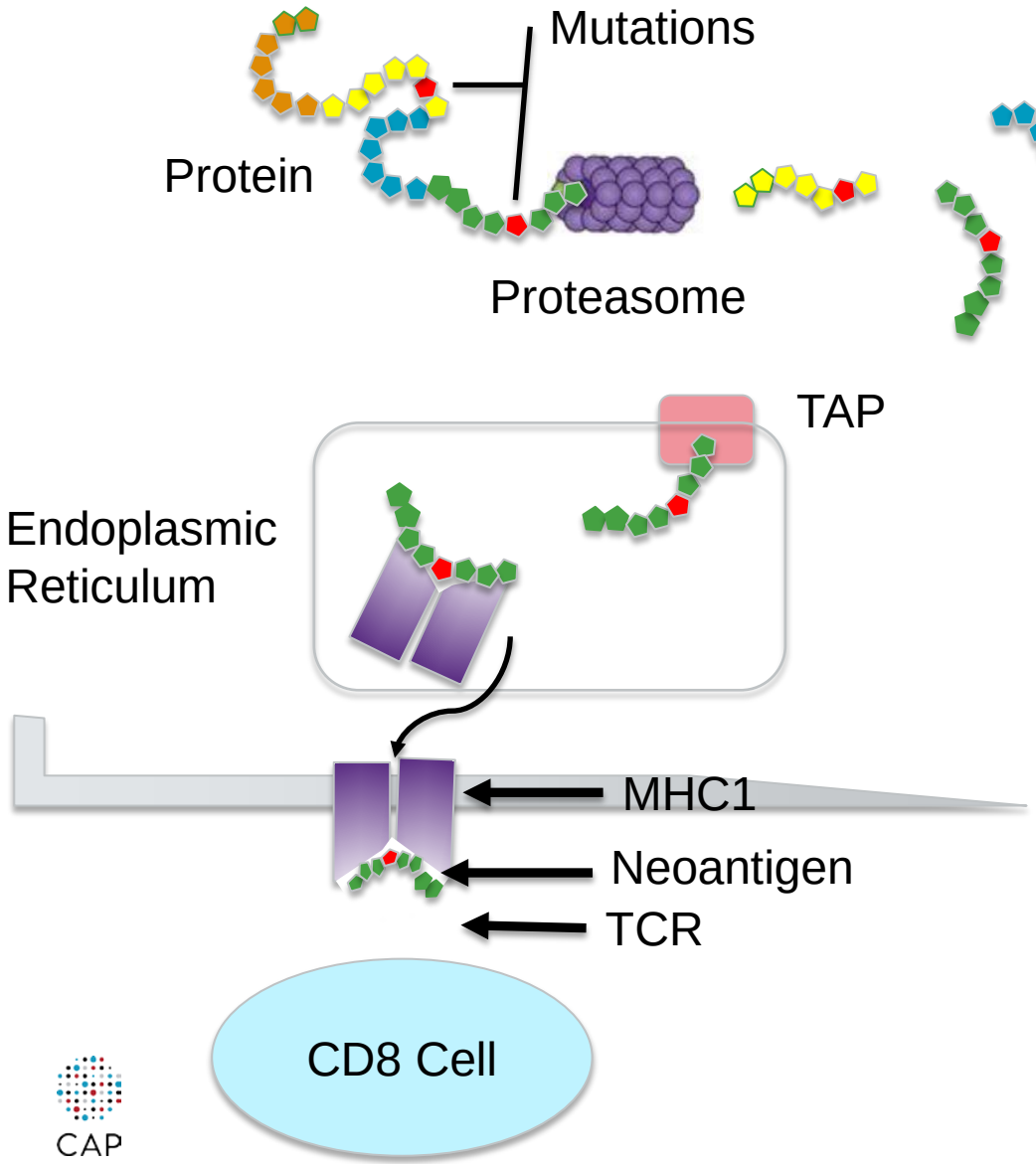
Nature Reviews | Cancer

The Cells of Our Immune System Are Constantly Monitoring Our Tissues

Natural Killer cells or NK cells sense stress associated molecules on the surface of cancerous and damaged cells



Tumor Mutations Create Neoantigen T-Cell Targets



- **The proteasome degrades intracellular proteins into short peptides that will be transported to the ER via TAP transport. Most peptides won't bind to MHC class 1 molecules but if a peptide binds with high affinity, the stable complex will be transported to the membrane surface.**

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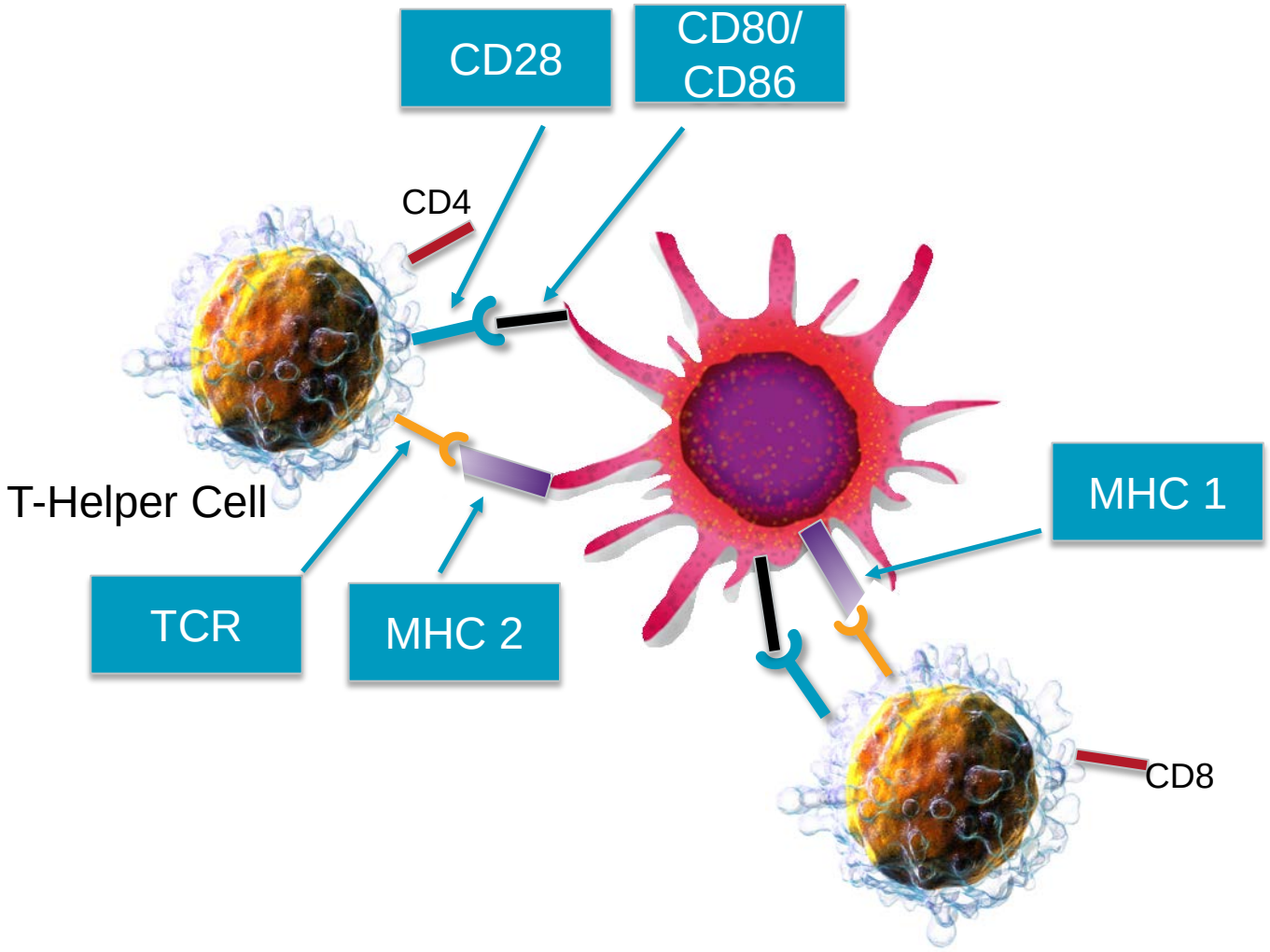
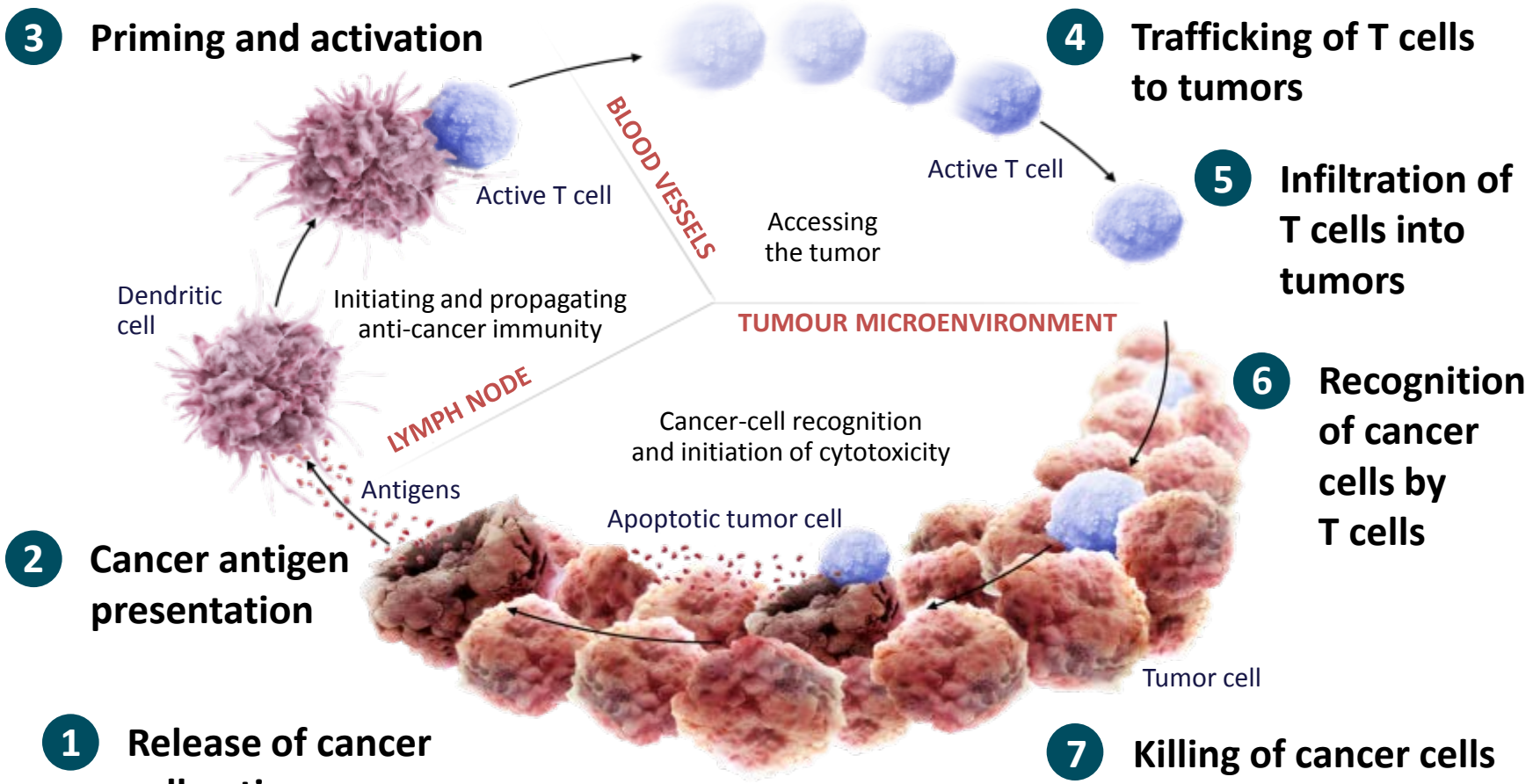
Dendritic Cells Activate Cytotoxic T-Cells

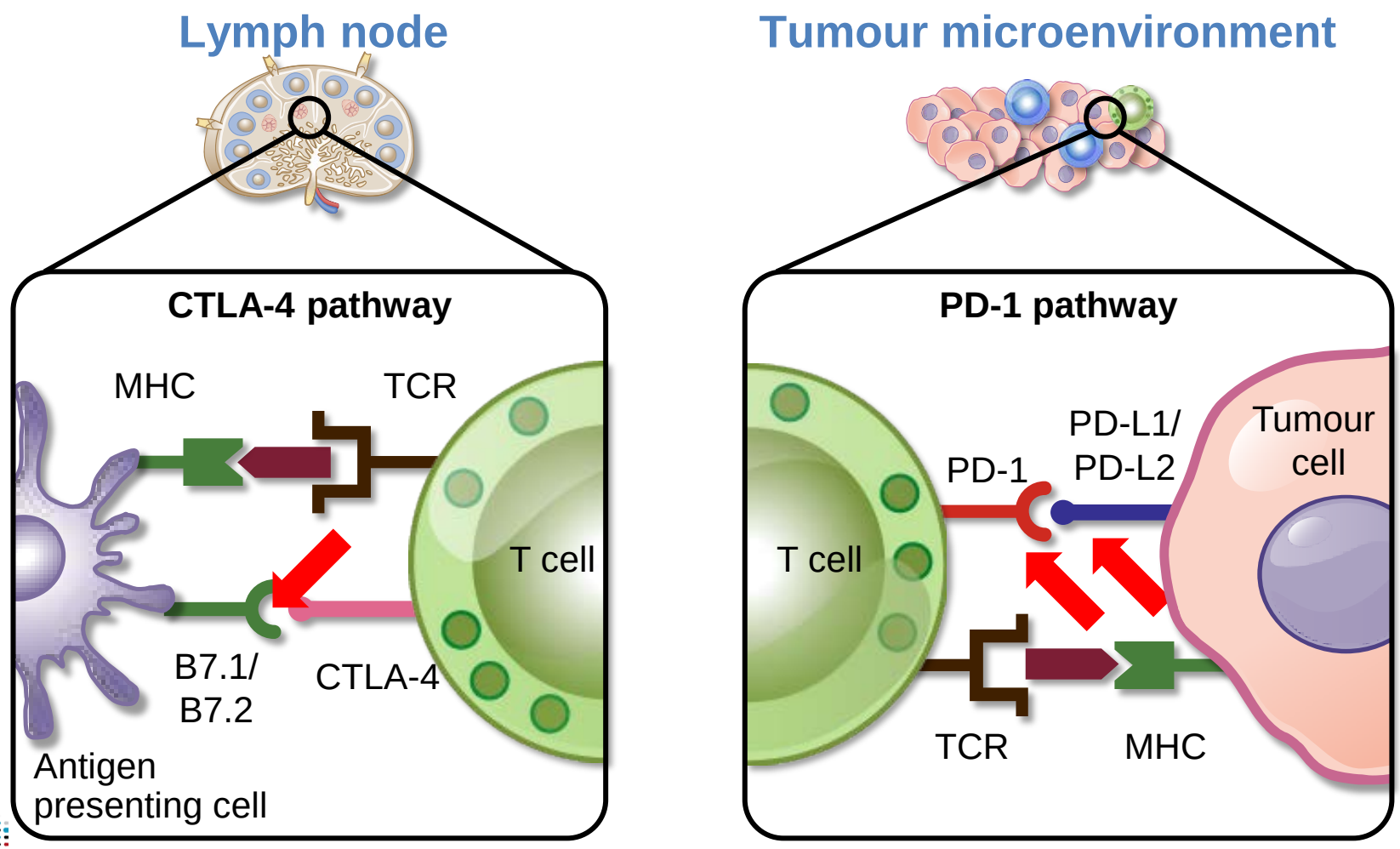


The Cancer-immunity Cycle



CAP Modified from Chen and Mellman. Immunity 2013

From theory to practice

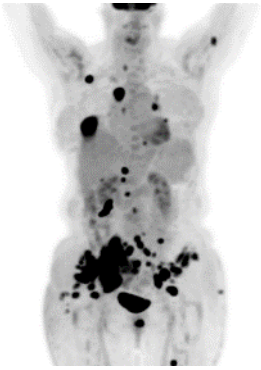


Pardoll. Nat Rev Cancer 2012

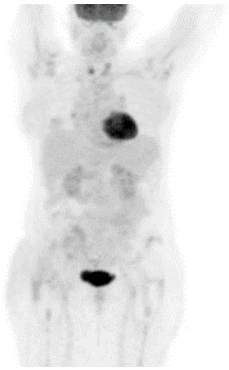
Immunotherapies targeting PD-L1 and PD-1 are having a dramatic impact in the clinic

Patient with NSCLC treated with atezolizumab (FIR study)[1]

Baseline

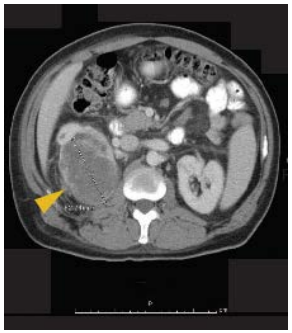


Post C2 (Week 6)

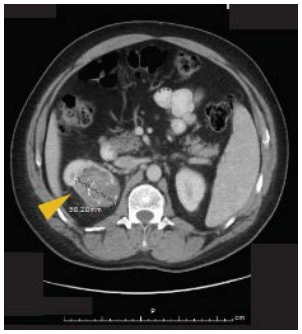


Patient with RCC treated with nivolumab (NCT00730639)[2]

Baseline

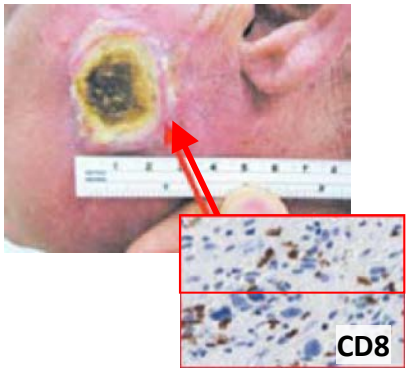


23 months

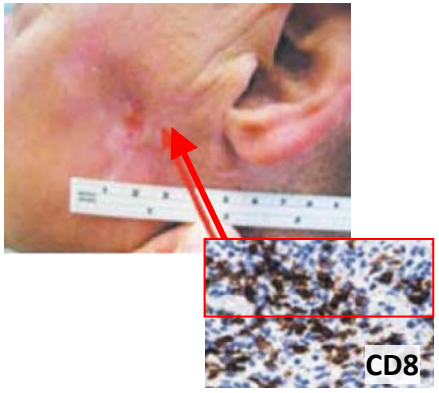


Patient with melanoma treated with pembrolizumab (KEYNOTE-001)[3]

Baseline



Day 90

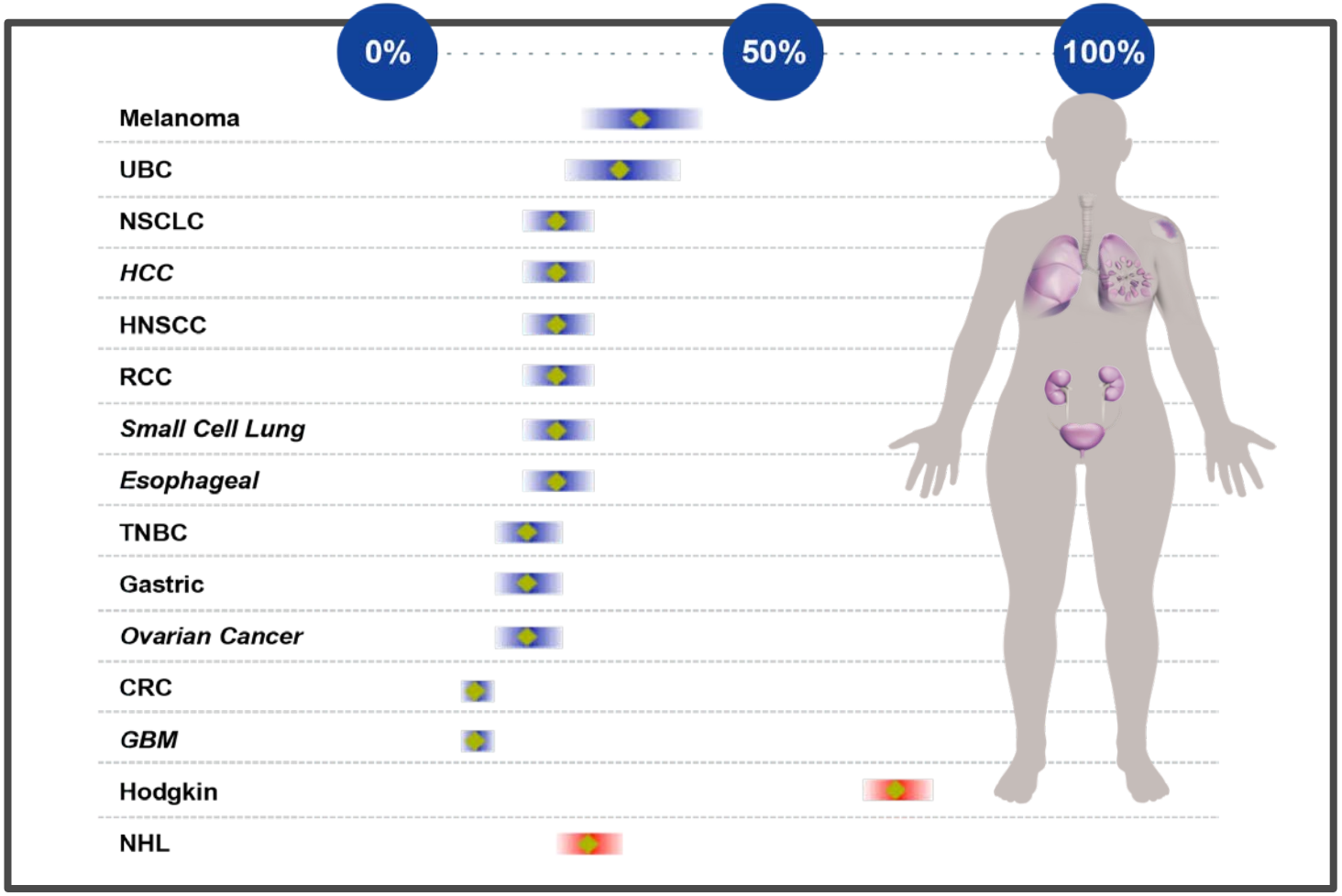


1. Chaft et al. WCLC 2015; 2. McDermott et al. J Clin Oncol 2015; 3. Hamid et al. N Engl J Med 2013

Key Differences Between Targeted Therapy and Immunotherapy

Targeted Therapy	Immunotherapy
Tends to be organ specific	Pan tumor potential
Patients negative for biomarker get no benefit	Patients negative for biomarker still get benefit
Benefits seen early	Benefit not always seen early
Duration of benefit limited	Extended duration of benefit
Impact on survival limited	Impact on overall survival
Biomarker in tumor cells	Tumor cells + TME

Broad pan-tumor potential with anti-PDL1/PD1 inhibitors: approximate ORR in all-comers with monotherapy



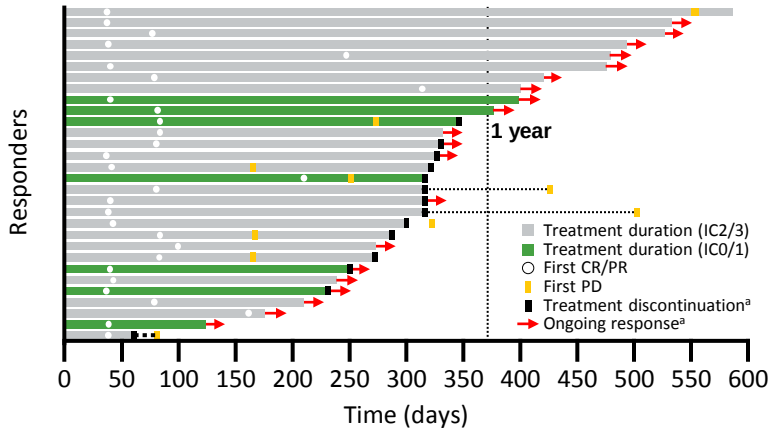
Modified from Chen. BioScience Forum 2015

Durable responses for PD-L1/PD-1 inhibitors

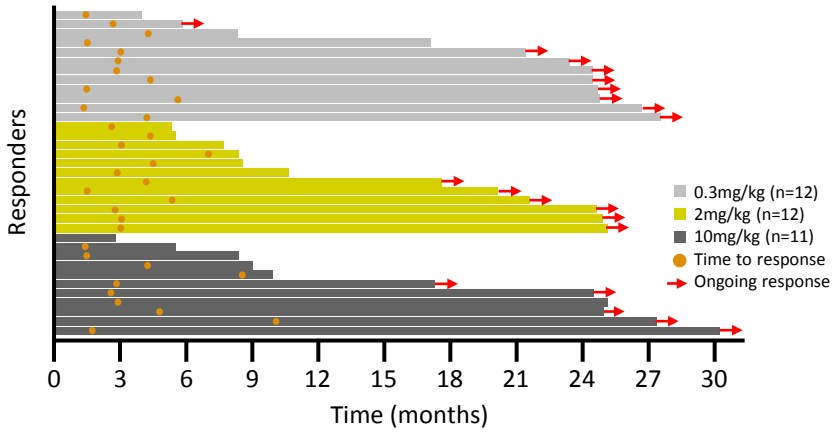
Durable responses have been seen across a range of tumour types

Atezolizumab in UBC[1]

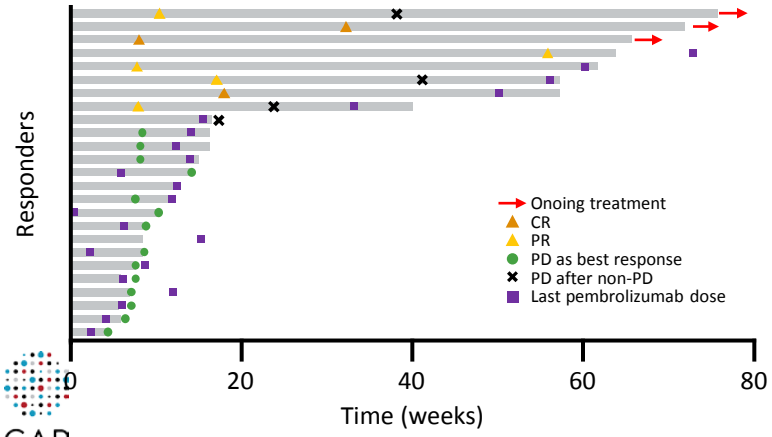
Patients with UBC and CR or PR as best response



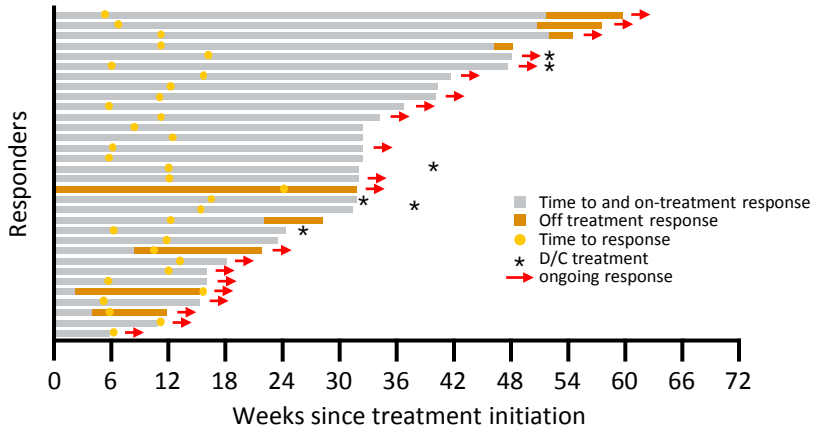
Nivolumab in RCC[3]



Pembrolizumab in UBC[2]



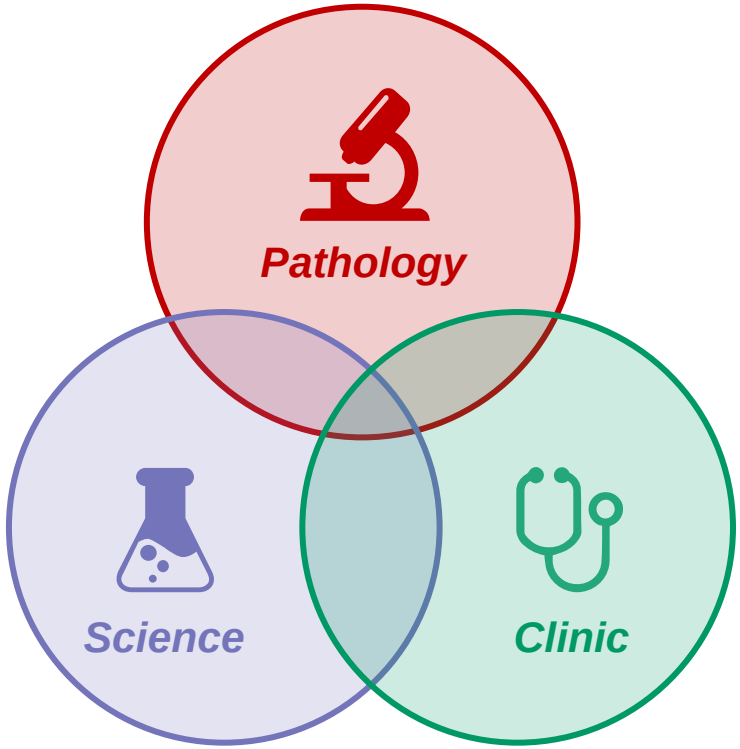
Durvalumab in NSCLC[4]



1. Petrylak et al. ASCO 2015; 2. Plimack et al. ASCO 2015; 3. Motzer et al. ASCO 2014; 4. Spigel et al. ASCO 2015

How can we realise the promise of cancer immunotherapy?

More comprehensive analysis of tumor and tumor microenvironment



Better understand the underlying immune response to tumor cells

Personalize cancer immunotherapy to improve patient outcomes

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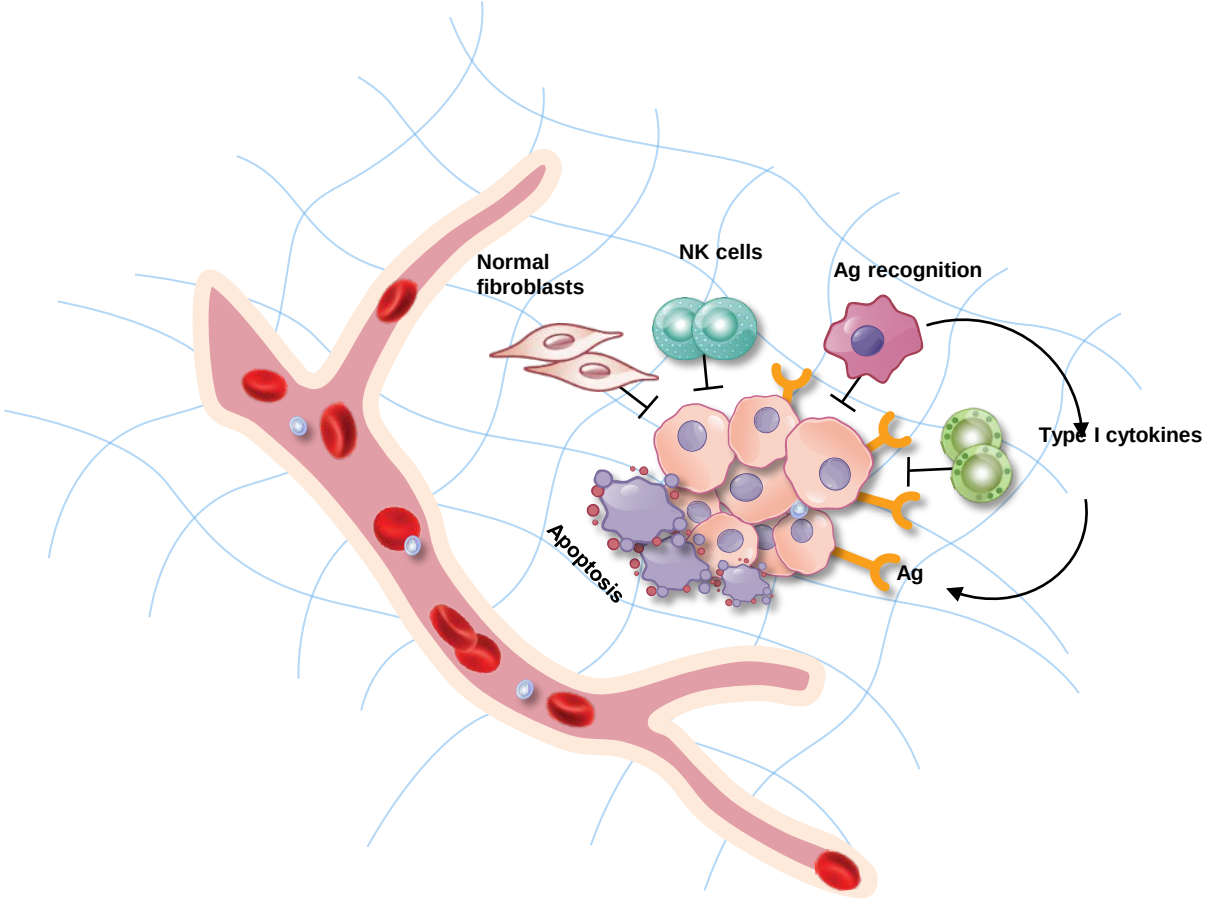
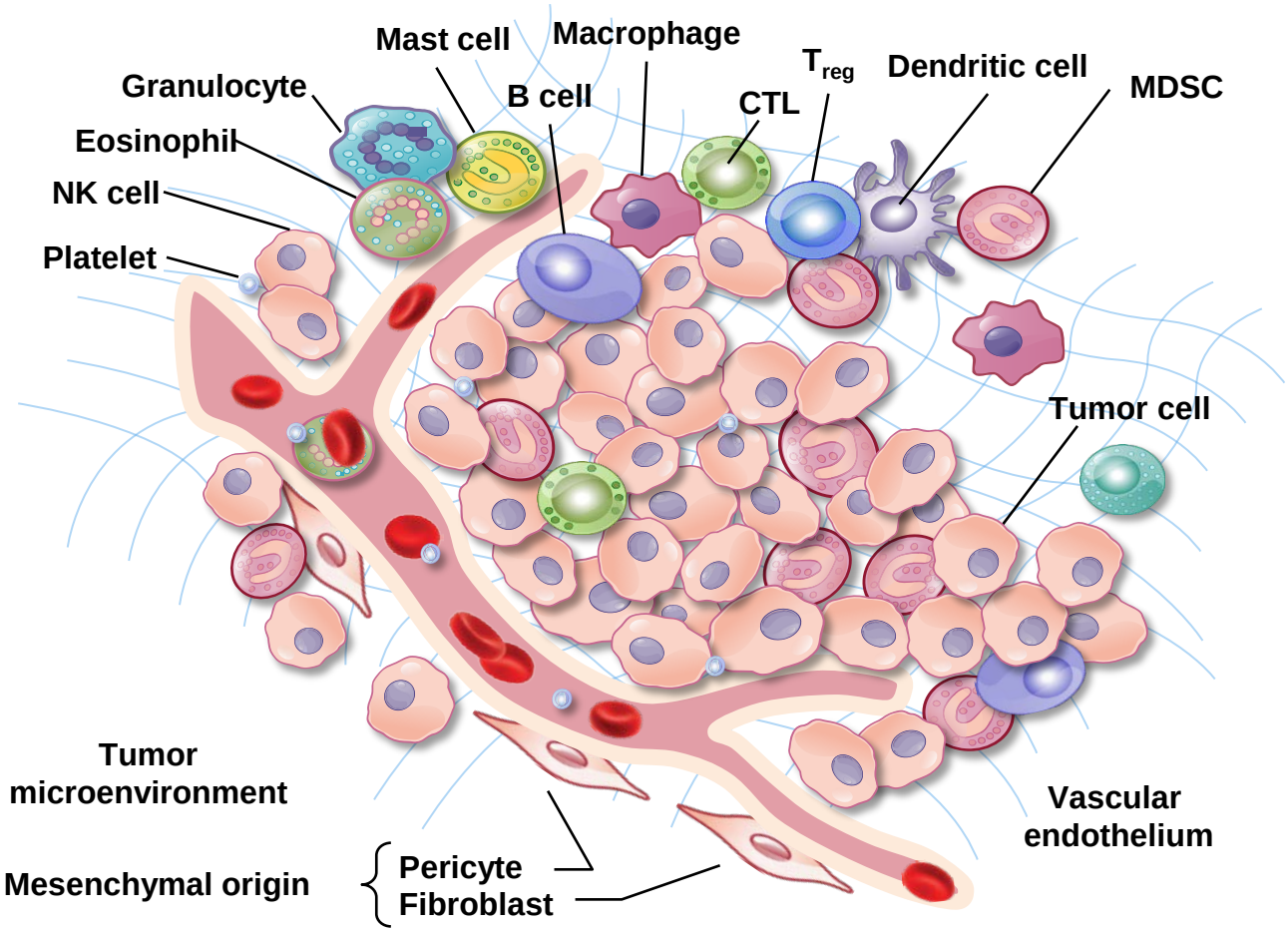
The Tumor Microenvironment (TME) Shapes Tumor Evolution

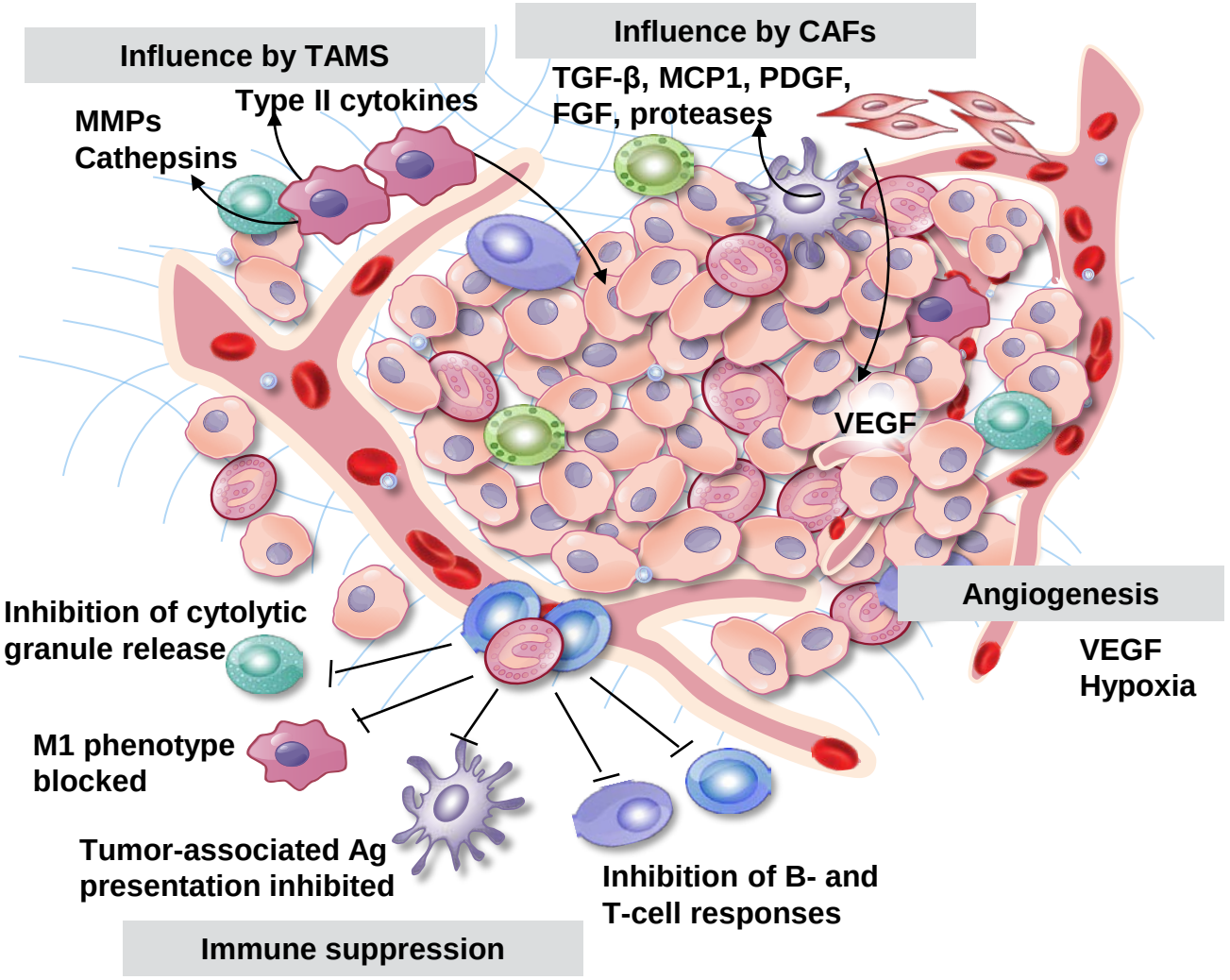


- **The immune system naturally identifies and eliminates cancerous cells**

The TME Aids T-Cell Tolerance Contributing to Uncontrolled Tumor Growth



Tumors Exploit Different Pathways to Evade the Immune System



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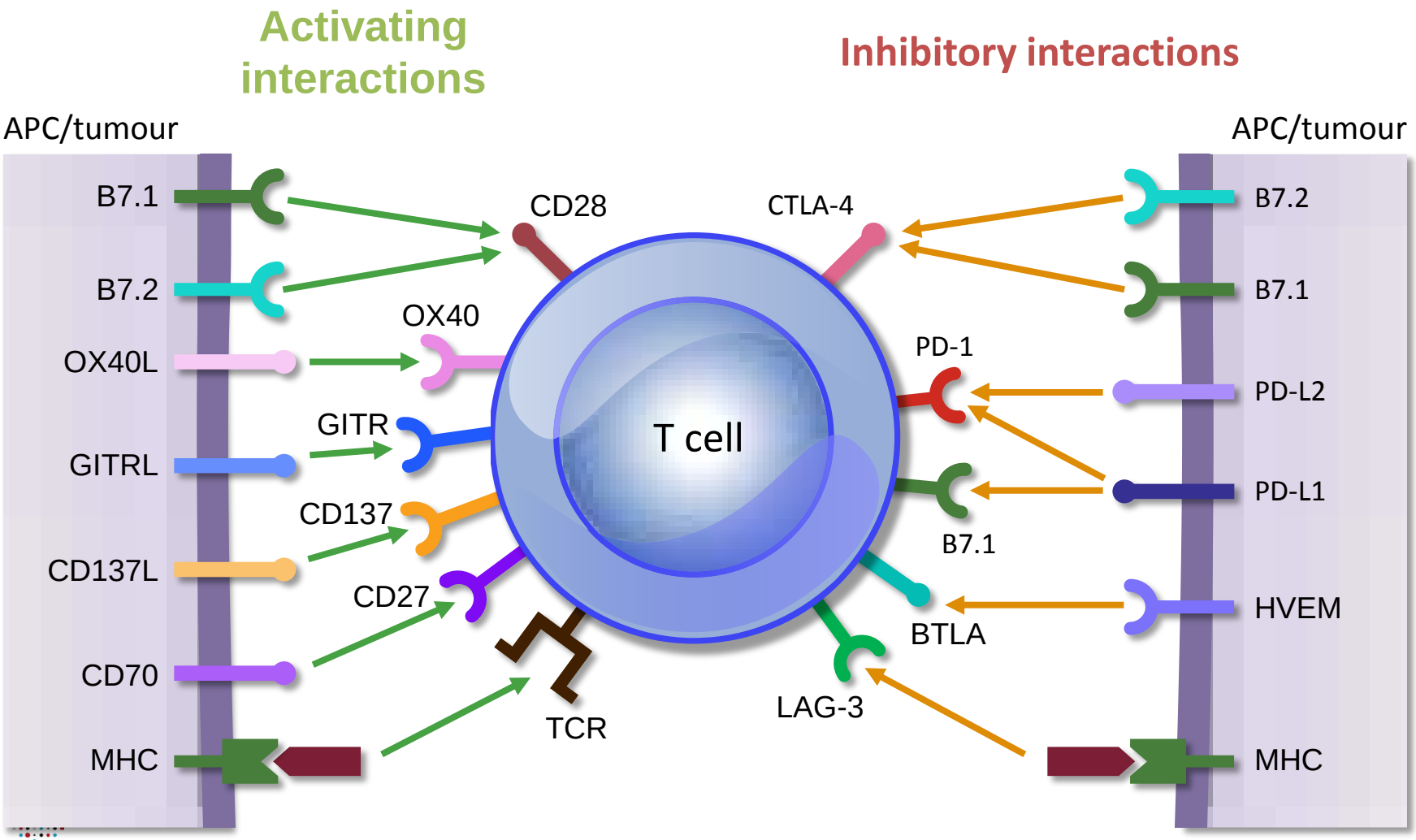
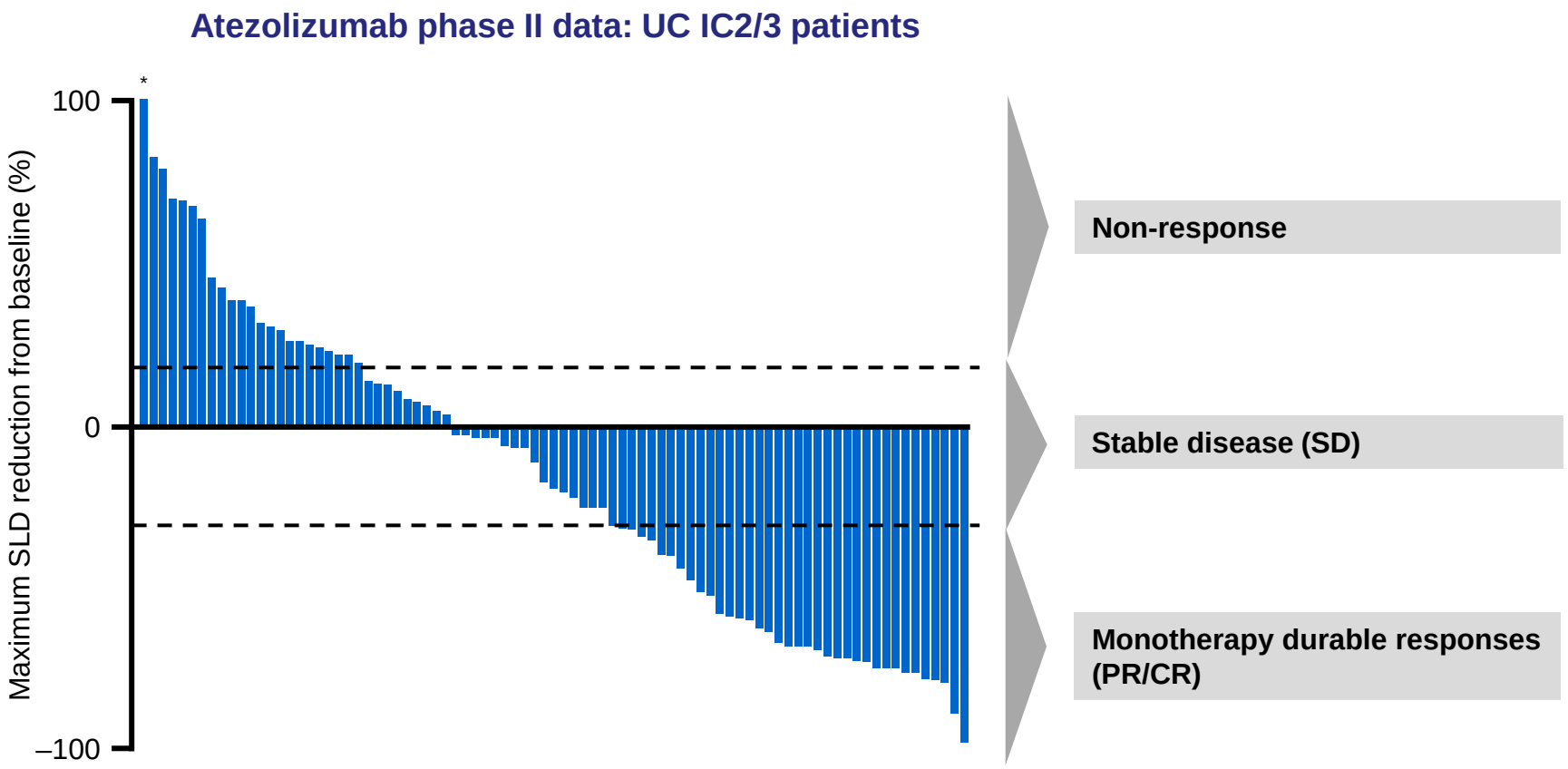
Checkpoint pathways



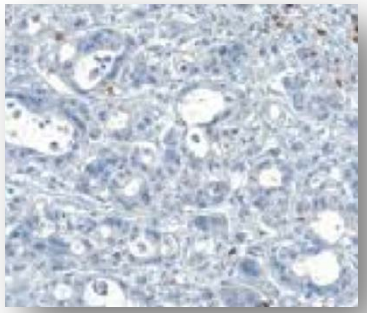
Pardoll. Nat Rev Cancer 2012

Why do some patients not respond?

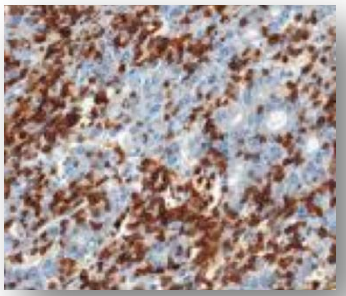


SLD, sum of longest diameters. * >100% increase.
Per RECIST v1.1 (independent review). Data cutoff September 14, 2015. Patients without post-baseline tumor assessments included those who discontinued before the first tumour assessment and are not plotted. Several patients with CR had <100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1. Rosenberg et al. Lancet 2016

Pathology assessment for anti-PDL1/PD1 therapy



Is the tumor inflamed?



NO

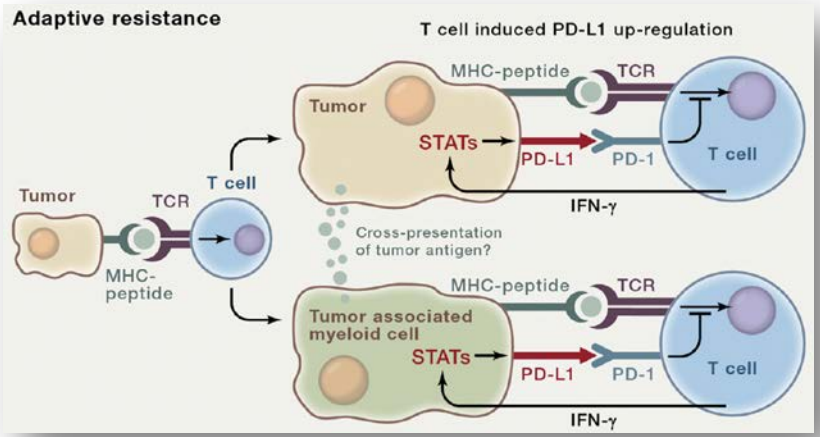
YES

No recognizable antigen

- Immune compromised
- Lack of presentation
- Lack of priming
- Trafficking of CD8 cells
- Infiltration of T cells
- Other TME issues

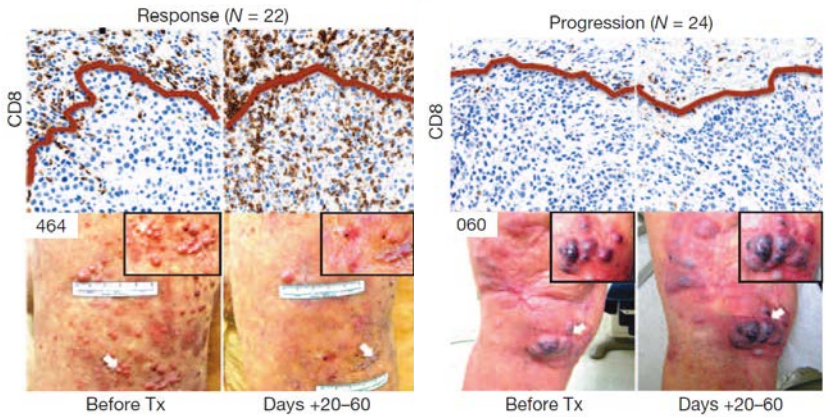
Is there evidence of an adaptive immune response?

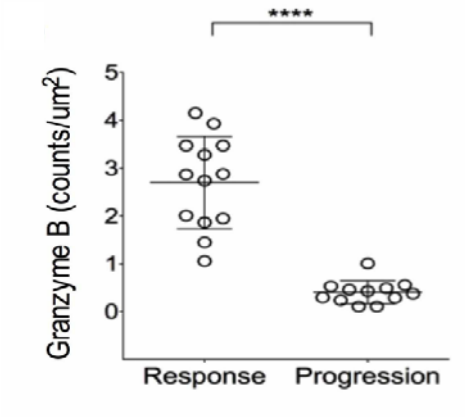
?PD-L1 expression

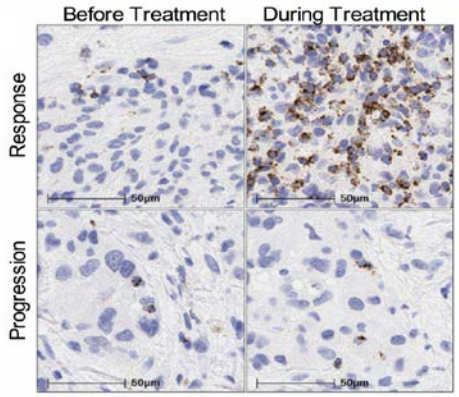


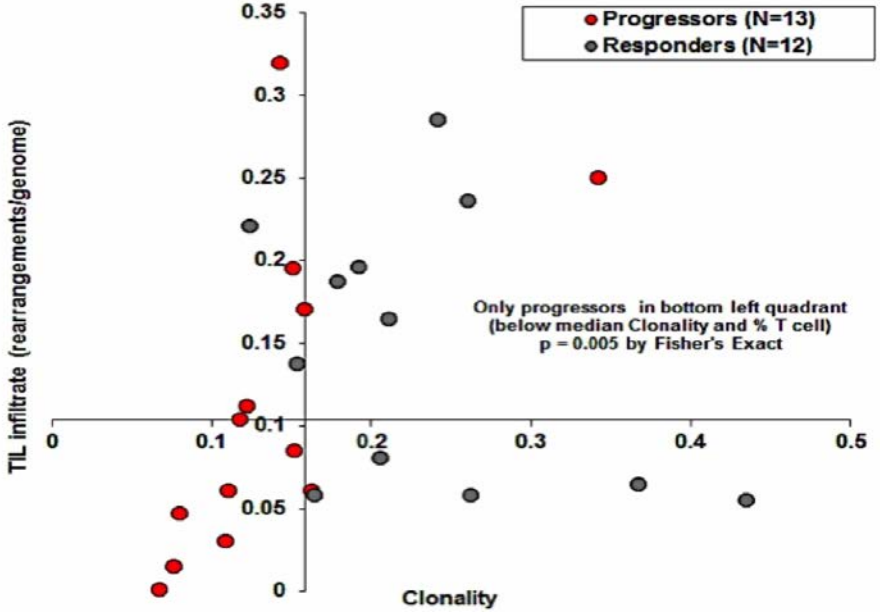
Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer. 2016;16(5):275-87.

TILs and TIL clonality as a predictor of response in melanoma patients receiving PD-1 therapy





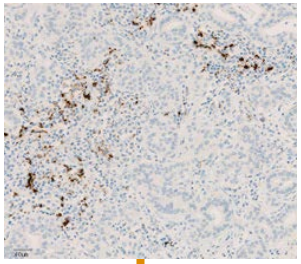




Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-71.

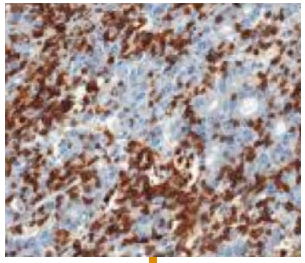
Inflamed versus non-inflamed tumors

Inflamed



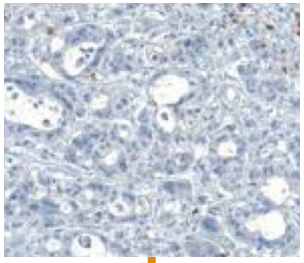
Respond poorly to checkpoint inhibition

Inflamed



Respond favourably to checkpoint inhibition

Non-inflamed



Least likely to respond to checkpoint inhibition

How can we further enhance T cell function?

How can we convert these tumours to become inflamed?

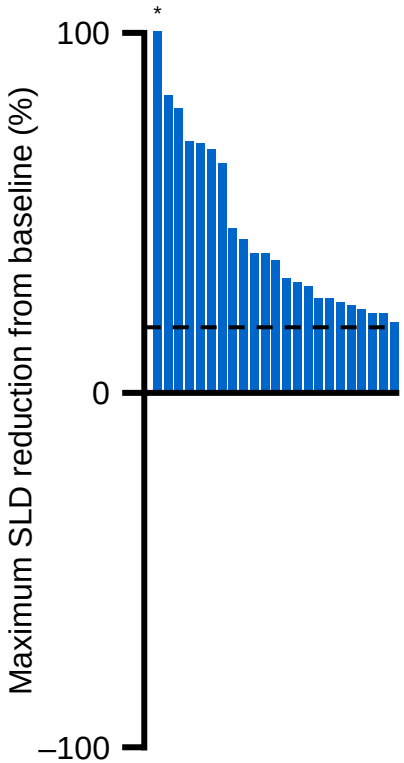
CAP

Schmid et al. ECC 2015; Herbst et al. Nature 2014

Tumeh et al. Nature 2014; Ji et al. Cancer Immunol Immunother 2012

Why do some patients not respond?

Atezolizumab phase II data: UC IC2/3 patients



Non-response

Tumour infiltrating lymphocytes?

PD-L1 expression?

Mutational load?

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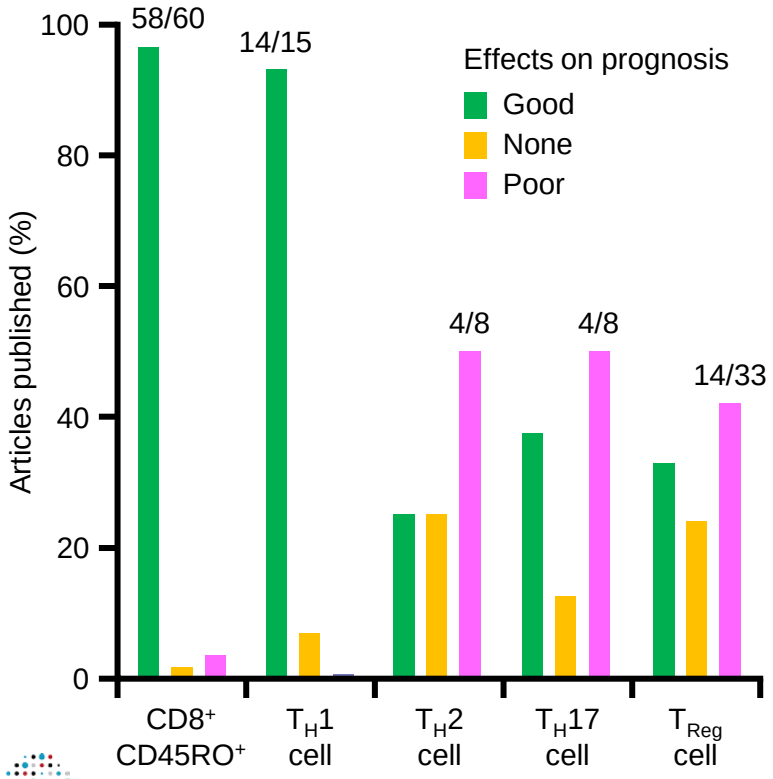
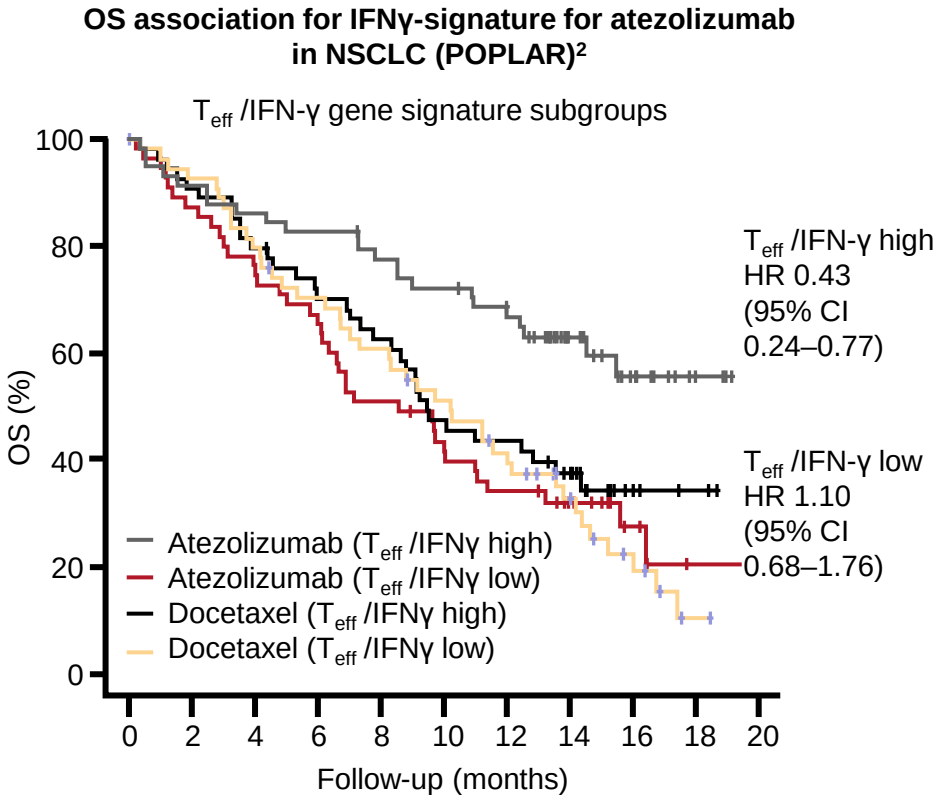
Presence of tumor infiltrating lymphocytes influences outcome

The association of immune cell infiltrates with prognosis in cancer[1]



Patients with a pre-existing immune response derive the most benefit from checkpoint inhibitors[2]



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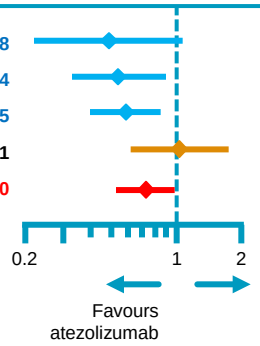
T_{eff}/IFN-γ: CD8A, GZMA, GZMB, CXCL9, EOMES, IFNg, CXCL10, T-bet

1. Fridman et al. Nat Rev Cancer 2012; 2. Fehrenbacher et al. Lancet 2016

Higher levels of PD-L1 expression associated with improved OS

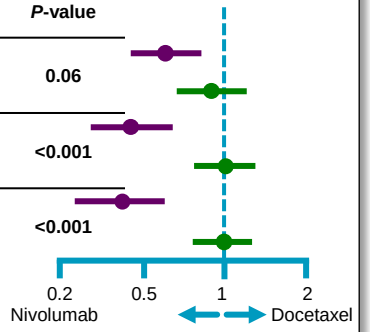
OS in POPLAR (2L+ NSCLC; atezolizumab)[1]

	n (%)	HR*	95% CI	p value
TC3 or IC3	47 (16%)	0.49	0.22–1.07	0.068
TC2/3 or IC2/3	105 (37%)	0.54	0.33–0.89	0.014
TC1/2/3 or IC1/2/3	195 (68%)	0.59	0.40–0.85	0.005
TC0 and IC0	92 (32%)	1.04	0.62–1.75	0.871
Intention to treat	287	0.73	0.53–0.99	0.040



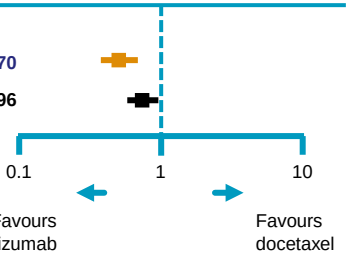
OS in CheckMate 057 (2L Non-Squamous NSCLC; nivolumab)[3]

PD-L1 expression level	Nivolumab n	Docetaxel N	Unstratified HR (95% CI)	Interaction *P*-value
≥1%	123	123	0.59 (0.43–0.82)	0.06
<1%	108	101	0.90 (0.66–1.24)	
≥5%	95	86	0.43 (0.30–0.63)	<0.001
<5%	136	138	1.01 (0.77–1.34)	
≥10%	86	79	0.40 (0.26–0.59)	<0.001
<10%	45	145	1.00 (0.76–1.31)	



OS in KEYNOTE-010 (2L+ NSCLC; pembrolizumab)[2]

	Events/patients (n)	HR	95% CI
≥50%	204/442	0.53	0.40–0.70
1–49%	317/591	0.76	0.60–0.96



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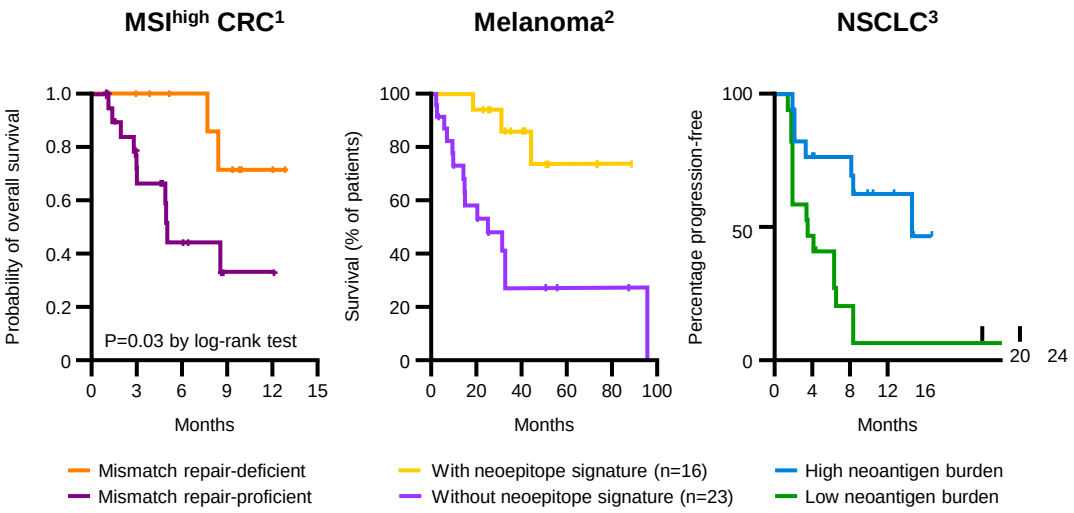
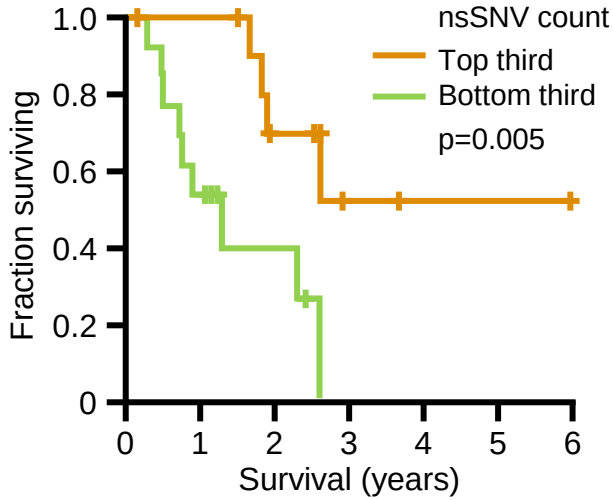
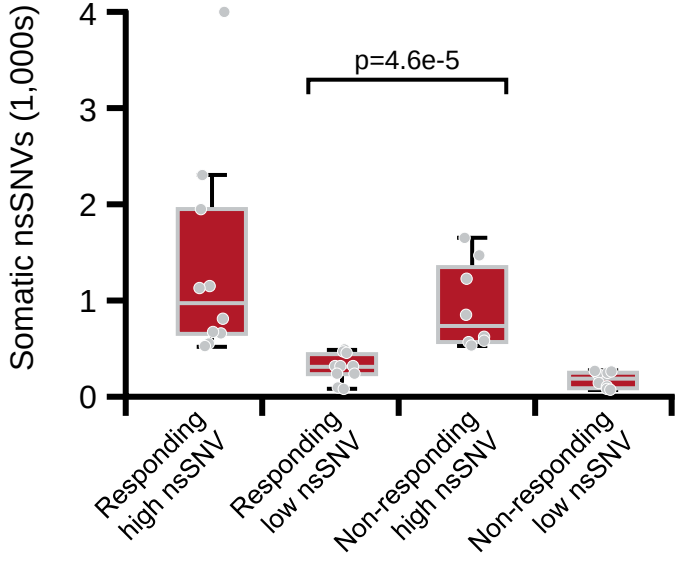
1. Fahrenbacher et al. Lancet 2016; 2. Herbst et al. Lancet 2015
3. Borghaei et al. N Engl J Med 2015 (suppl)

Mutational load may influence outcomes

For a given tumor type, mutations/neo-antigens correlate with clinical benefits



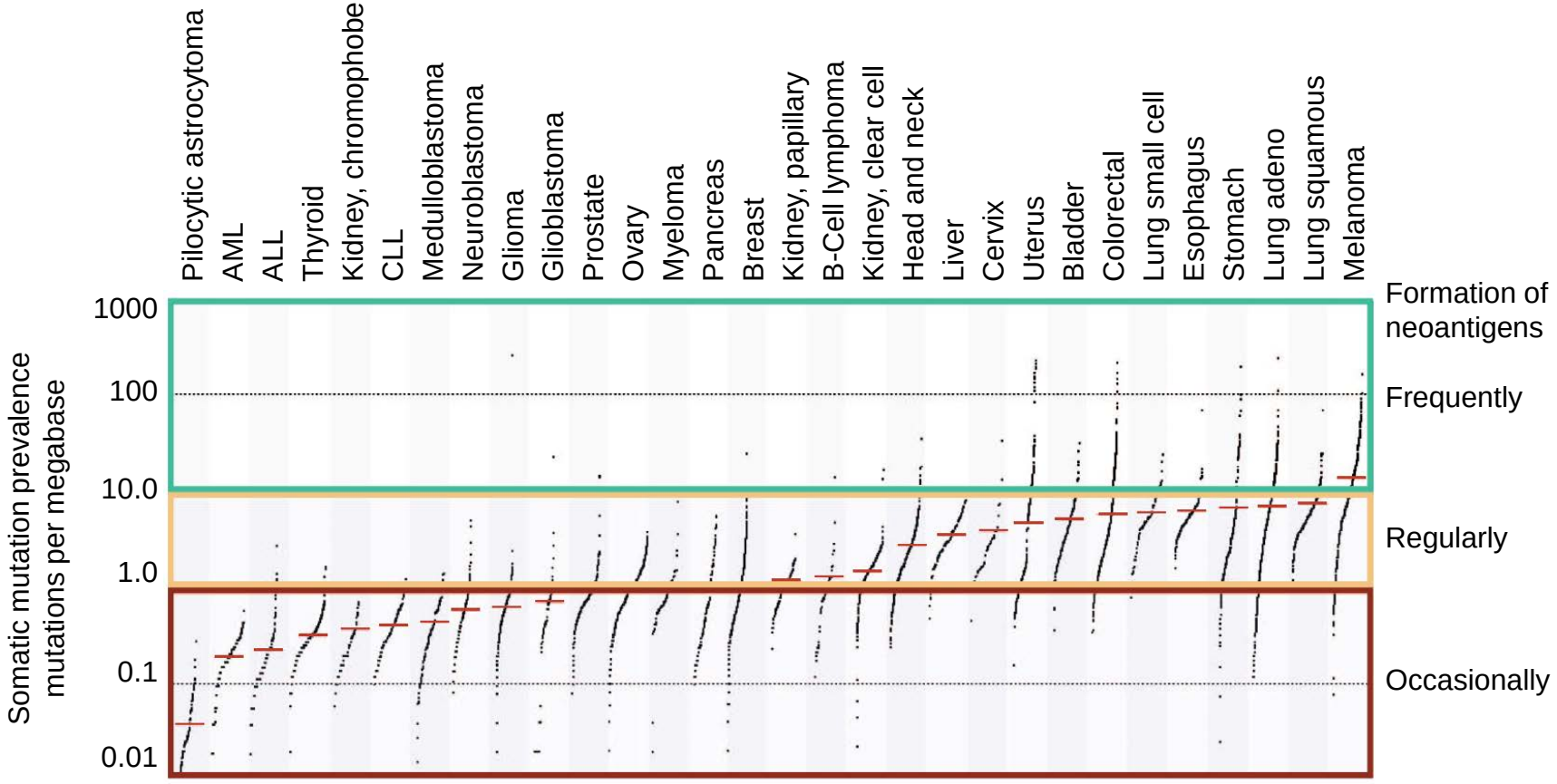




*p=0.017

1. Le et al. N Engl J Med 2015; 2. Snyder et al. N Engl J Med 2014;
3. Rizvi et al. Science 2015; 4. Madore et al. Clin Cancer Res 2016; 5 Hugo et al. Cell 2016

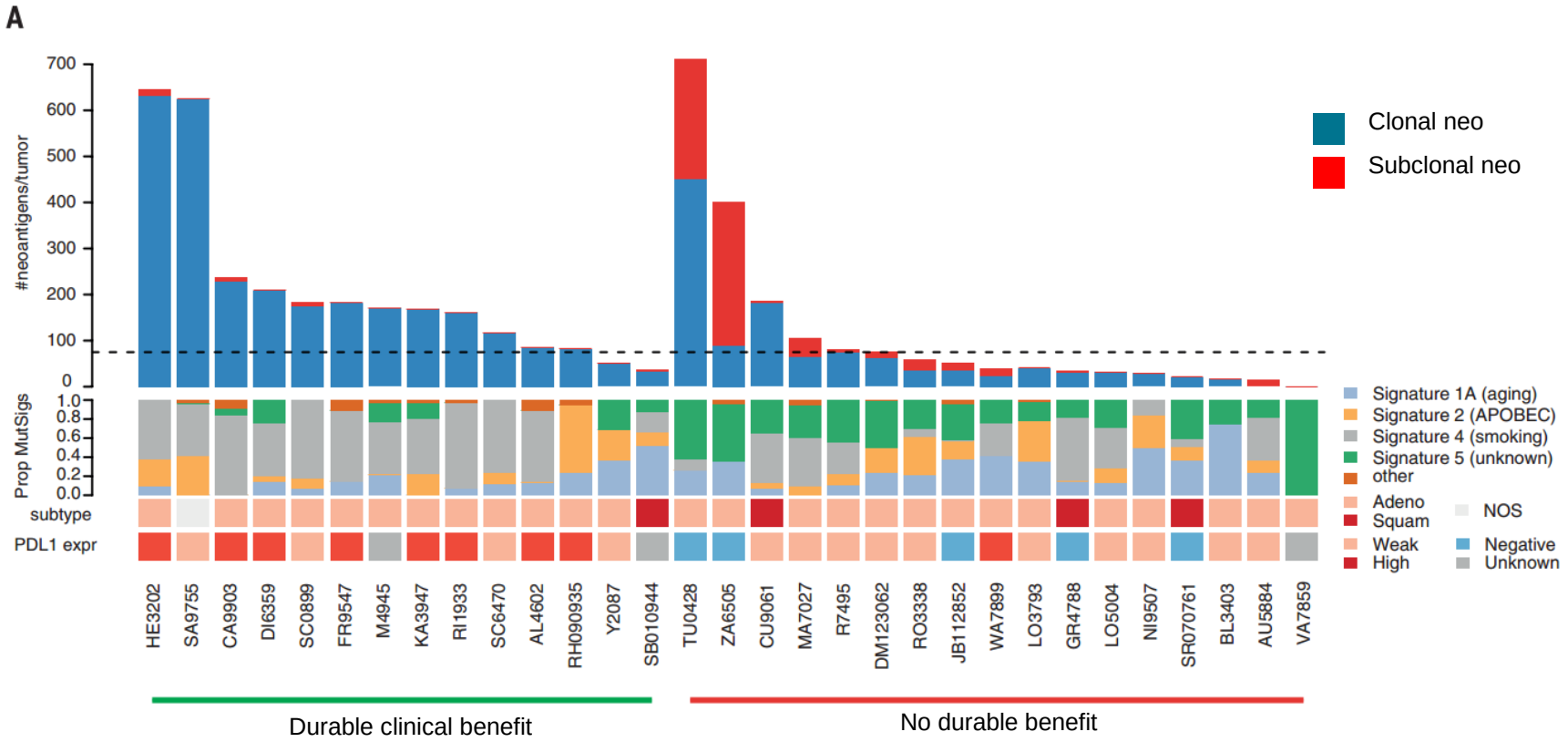
Likelihood of neoantigen expression by human cancer



CAP

Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69-74.

Clonal neoantigens show responsiveness to immunotherapy in NSCLC[1]



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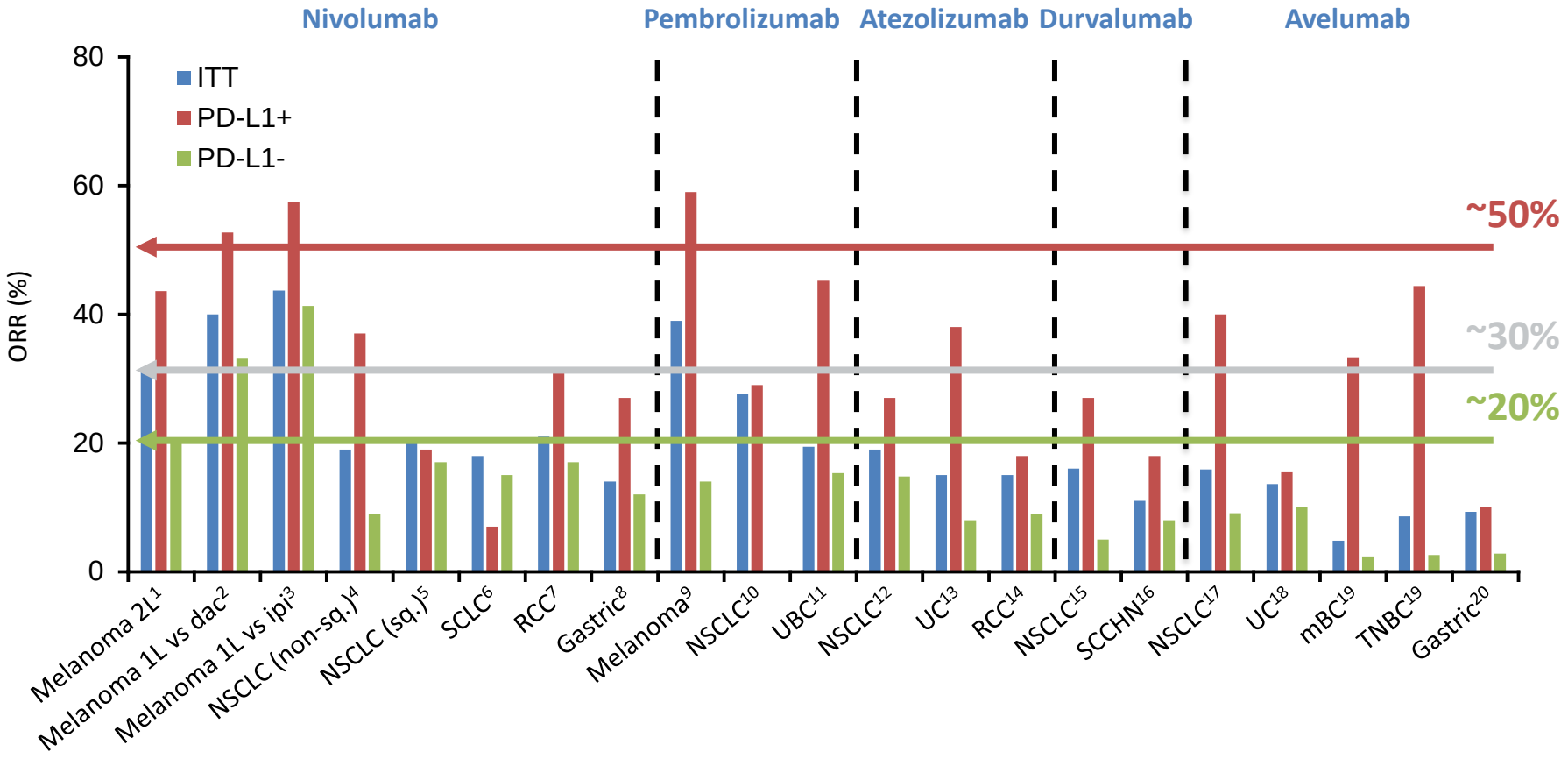
1. McGranahan et al. Science 2016; 2. Rizvi et al. Science 2015

PD-L1 is not good enough



Non-sq.=non-squamous; sq.=squamous

1. Weber et al. Lancet 2015; 2. Robert et al. Lancet 2015; 3. Larkin et al. N Engl J Med 2015; 4. Borghaei et al. N Engl J Med 2015
5. Brahmer et al. N Engl J Med 2015; 6. Antonia et al. ASCO 2015; 7. Motzer et al. J Clin Oncol 2015; 8. Le et al. ASCO GI 2016
9. Kefford et al. ASCO 2014; 10. Garon et al. N Engl J Med 2015; 11. Plimack et al. ASCO 2015; 12. Vansteenkiste et al. ECC 2015
13. Rosenberg et al. Lancet 2016; 14. McDermott et al. J Clin Oncol 2015; 15. Rizvi et al. ASCO 2015; 16. Segal et al. ASCO 2015
17. Gulley et al. ASCO 2015; 18. Apolo et al. ASCO GU 2016; 19. Dirix et al. SABCS 2015; 20. Chung et al. ASCO GI 2016

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What are the limitations of PD-L1 as a biomarker?

Agent	Atezolizumab[1,2] (Genentech/Roche)	Nivolumab[3,4] (BMS)	Pembrolizumab[5,6] (Merck)	Durvalumab[7] (AZ/MedImmune)
Therapeutic Target	PD-L1	PD-1	PD-1	PD-L1
PD-L1 IHC Assay	Ventana SP142	Dako 28-8	Dako 22C3	Ventana SP263
Class III IVD in the market	No (RUO available)	Yes	Yes	No (Class I available)
Cell types scored	NSCLC – TC/IC UBC – IC	NSCLC - TC	NSCLC – TC UBC – TC/IC	NSCLC - TC
Cut-off definitions (NSCLC)	TC or IC≥1% TC or IC≥5% TC≥50% or IC≥10%	TC≥1% TC≥5% TC≥10%	TC=1%-49% TC≥50%	TC≥25%
Cut-off definitions (UBC)	IC≥10%; IC≥5%; IC≥1%	NA	≥1% TC or any stromal staining	NA

1. Fehrenbacher, et al. Lancet 2016; 2. Rosenberg, et al. Lancet 2016; 3. Borghaei, et al. N Engl J Med 2015 4. Brahmer, et al. N Engl J Med 2015; 5. Herbst, et al. N Engl J Med 2015; 6. Plimack, et al. ASCO 2015; 7. Rebelatto, et al. ASCO 2015

PD-L1 confusion

Different drugs

Different assays

- **Clones**
- **Staining protocols**
- **Platforms and scoring methods**
- **Clinical decision points**
- **Tumor indications**
- **The use of tumor cells or TILs or both**

Different tissues

- **Different cut-offs in the same tissue for first- and second-line indications**

PD-L1 biomarker is dynamic and heterogeneous both spatially and temporally

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Differences in Scoring IHC assays

Dako 28-8/Ventana SP263

Staining pattern	Result
<1% of the viable tumor cells exhibit complete circumferential or partial linear plasma membrane staining at any intensity	PD-L1 expression <1%
>1% of the viable tumor cells exhibit complete circumferential or partial linear plasma membrane staining at any intensity	PD-L1 expression ≥1%
>5% of the viable tumor cells exhibit complete circumferential or partial linear plasma membrane staining at any intensity	PD-L1 expression ≥5%
>10% of the viable tumor cells exhibit complete circumferential or partial linear plasma membrane staining at any intensity	PD-L1 expression ≥10%

Dako 22C3

Staining pattern	Result
Partial or complete membrane staining (≥1+) in <1% of viable tumor cells	No PD-L1 expression
Partial or complete membrane staining (≥1+) in 1-49% of viable tumor cells	Low PD-L1 expression
Partial or complete membrane staining (≥1+) in ≥50% of viable tumor cells	High PD-L1 expression

Ventana SP142

Staining pattern	Result
IC ≥10%	IC3
IC ≥5% and <10%	IC2
IC ≥1% and <5%	IC1

Staining pattern	Result
TC ≥50%	TC3
TC ≥5% and <50%	TC2
IC ≥1% and <5%	TC1

IC = Immune cells TC = Tumor cells

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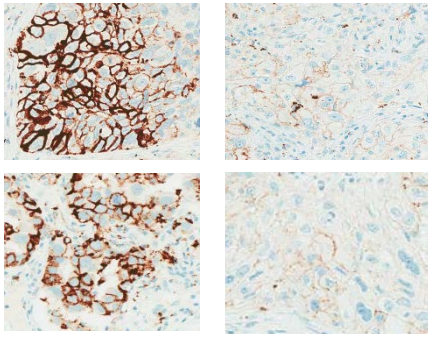
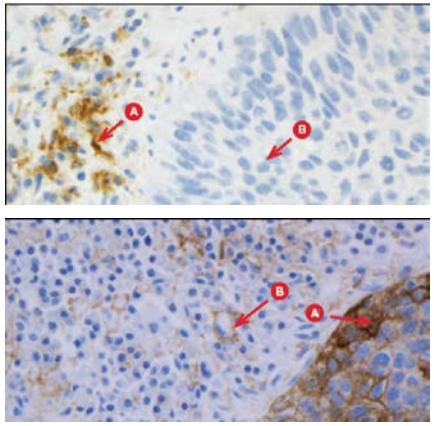
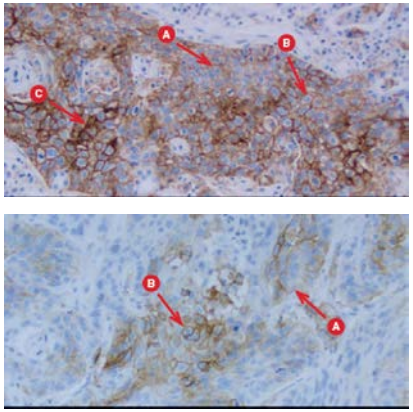
Appropriate Training is Essential for Proper Interpretation

- **Staining patterns can be difficult to interpret**
- **Must distinguish tumor cells from tumor associated immune cells**
- **Some assays score only tumor cells while other assays score tumor cells + immune cells**
- **Weak staining can be difficult to interpret**







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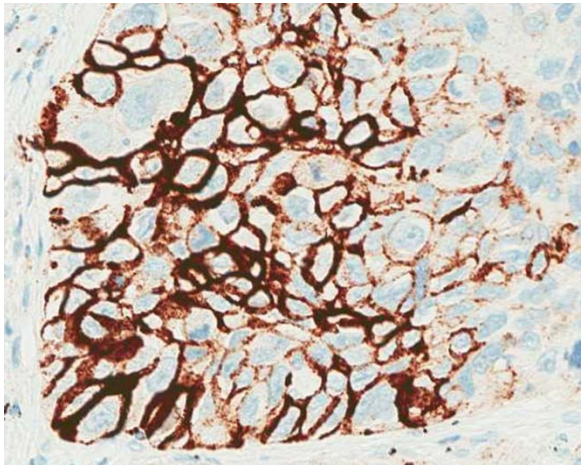
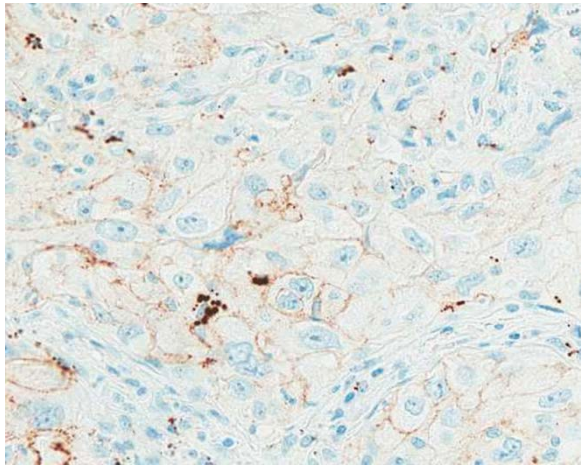
Staining Patterns Can be Difficult to Interpret

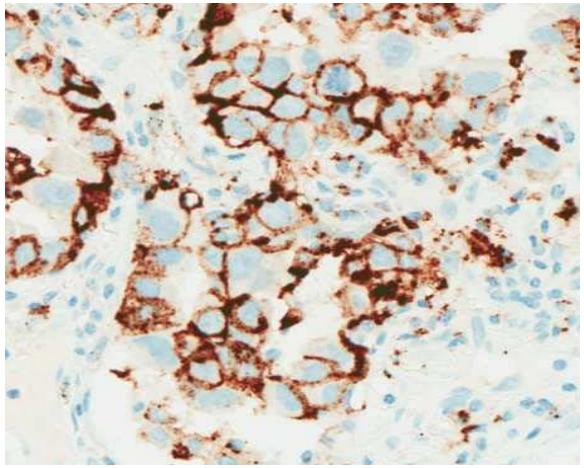
Moderate to strong circumferential



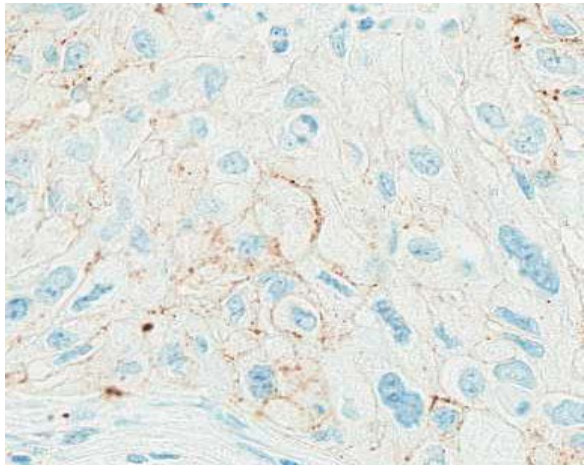
Weak circumferential



Basolateral



Granular membrane



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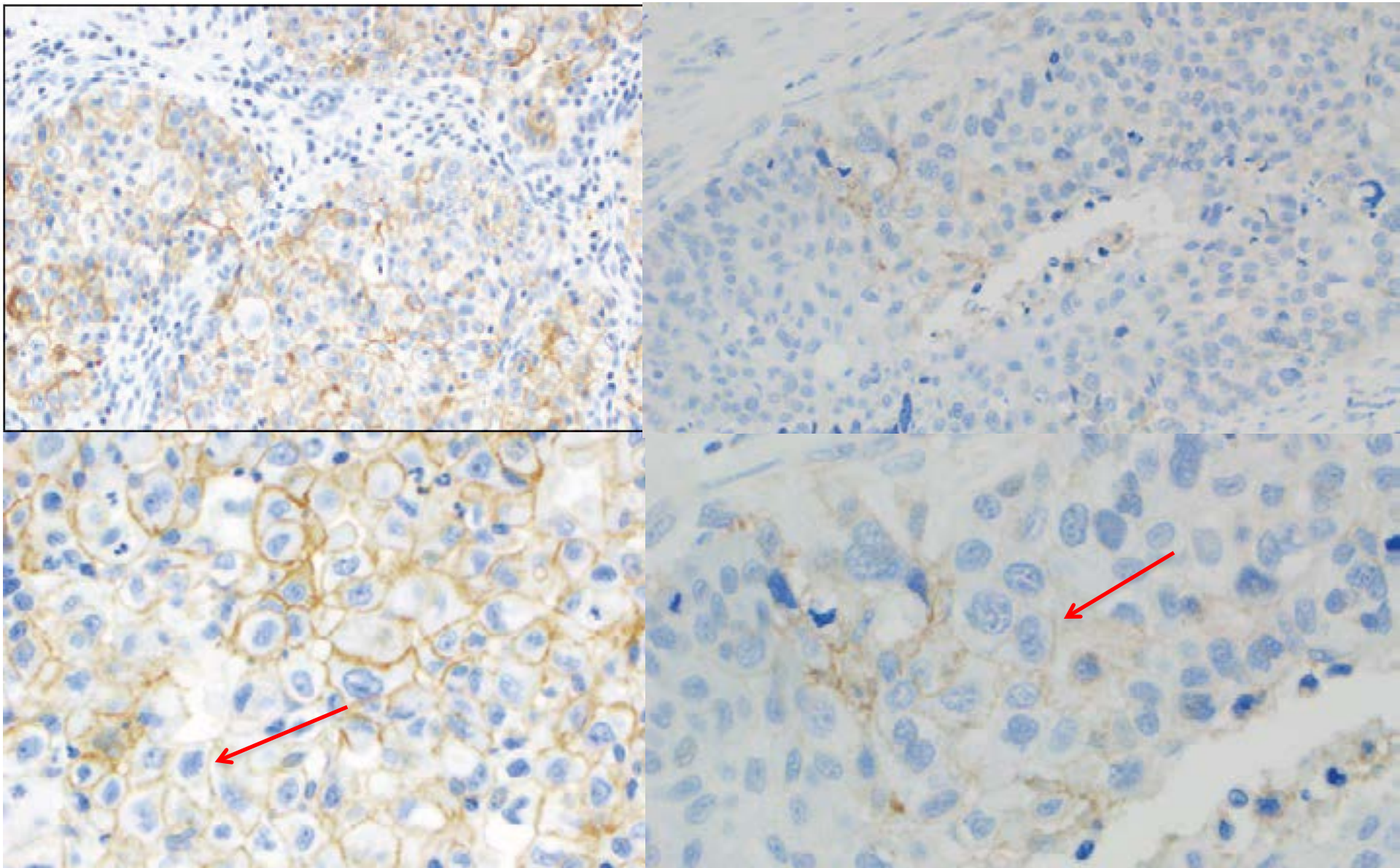
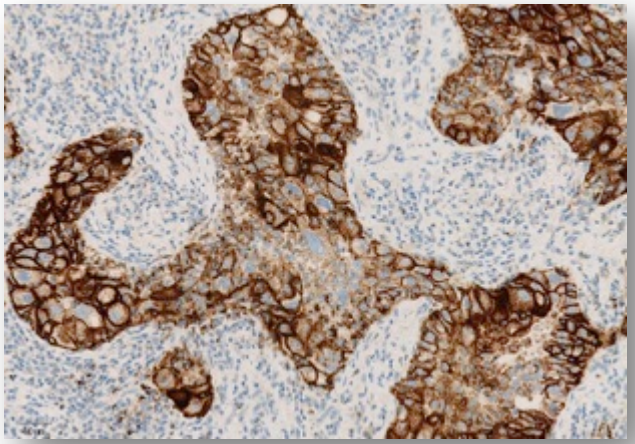
Examples of weak expression

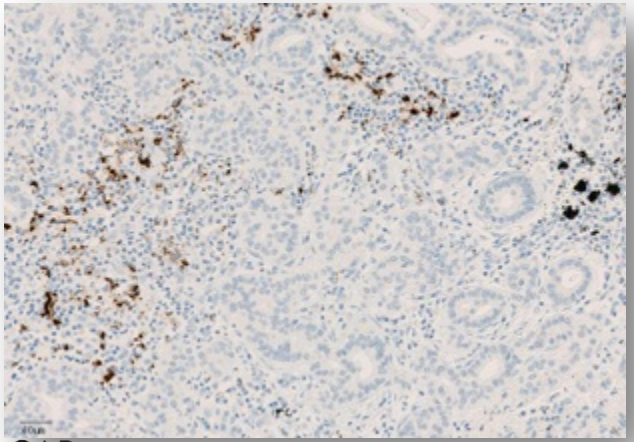


PD-L1 staining can be observed in tumor cells, immune cells or both

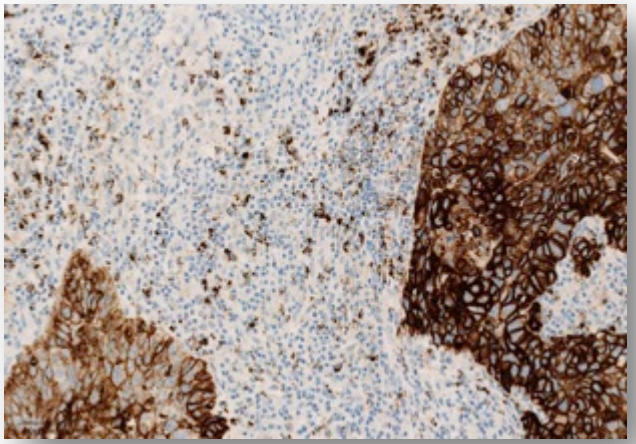
Tumor cells (TCs)



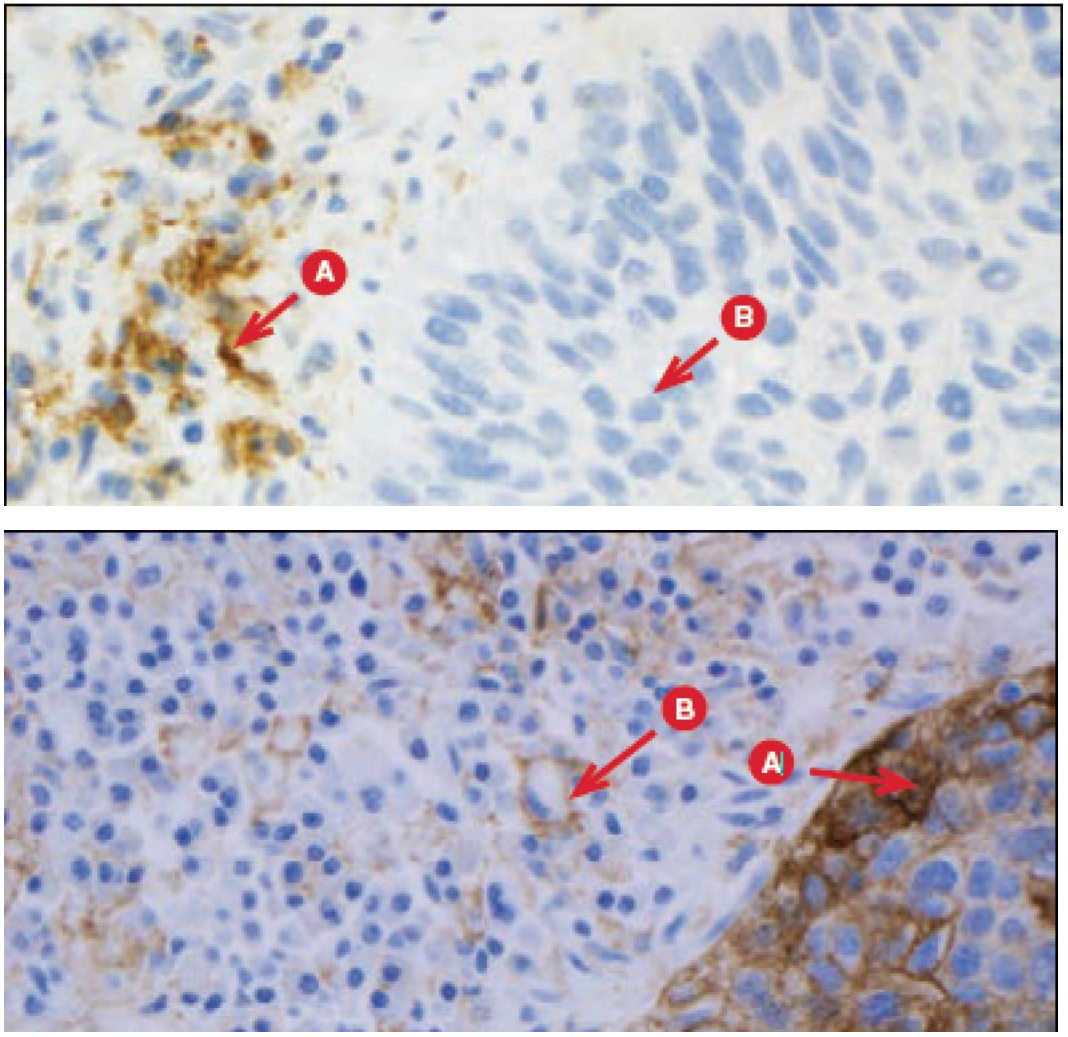
Immune cells (ICs)



Tumor and immune cells (TCs and ICs)



Distinguishing tumor associated immune cells



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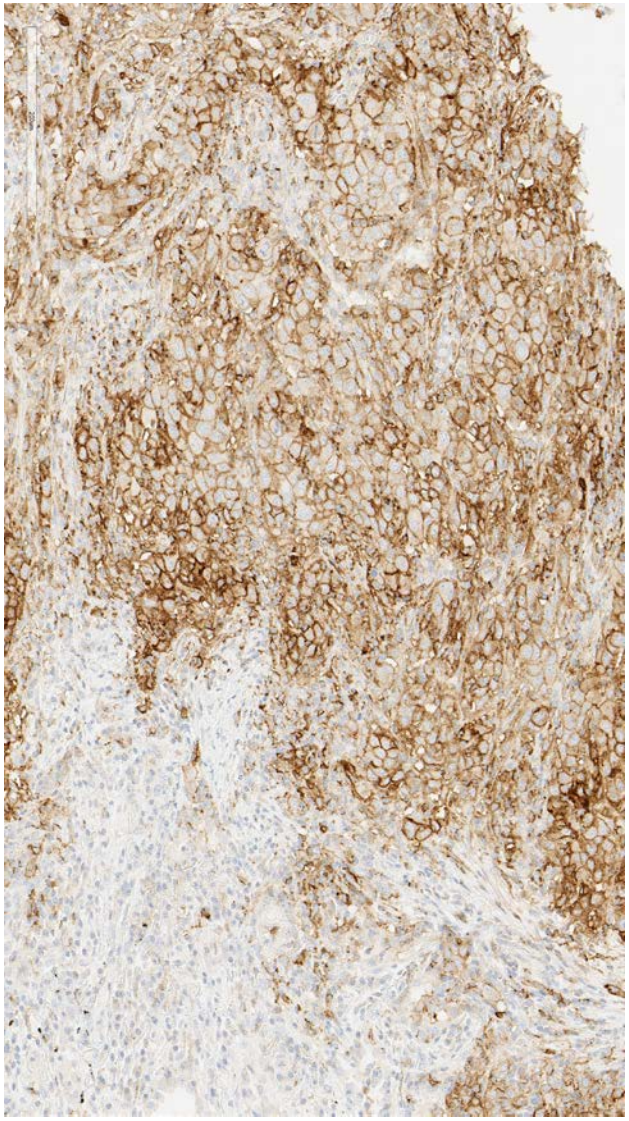
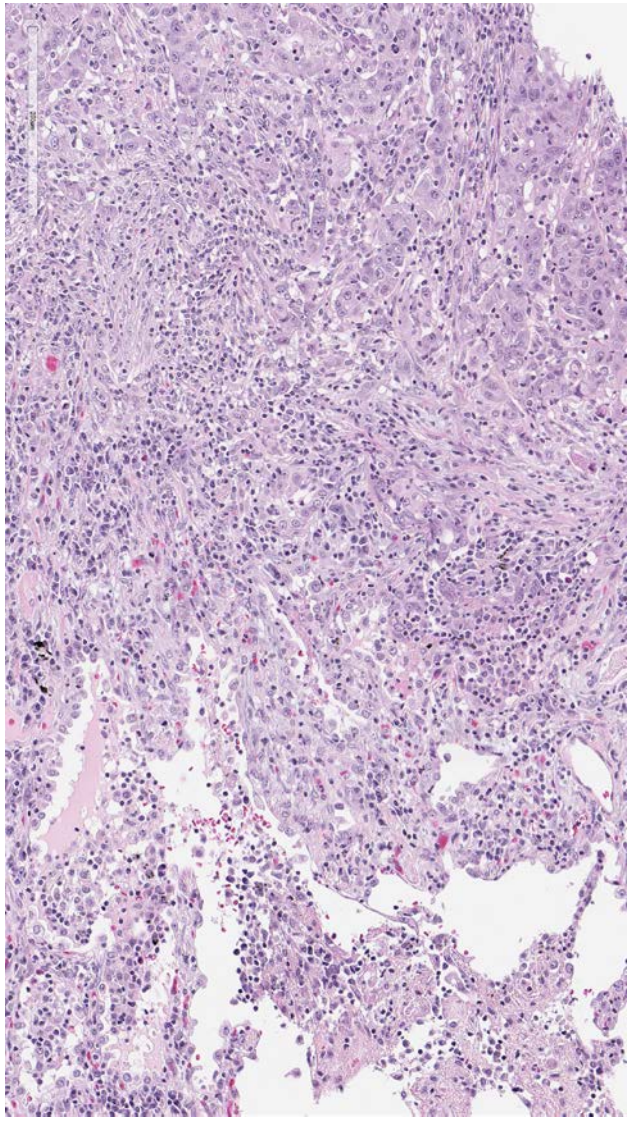
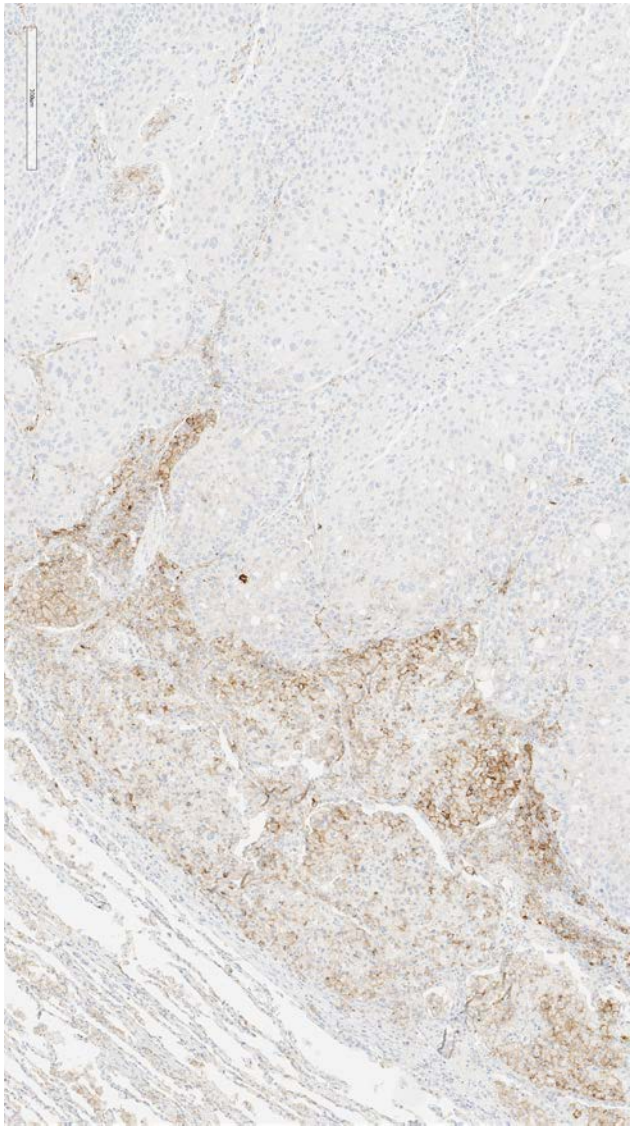
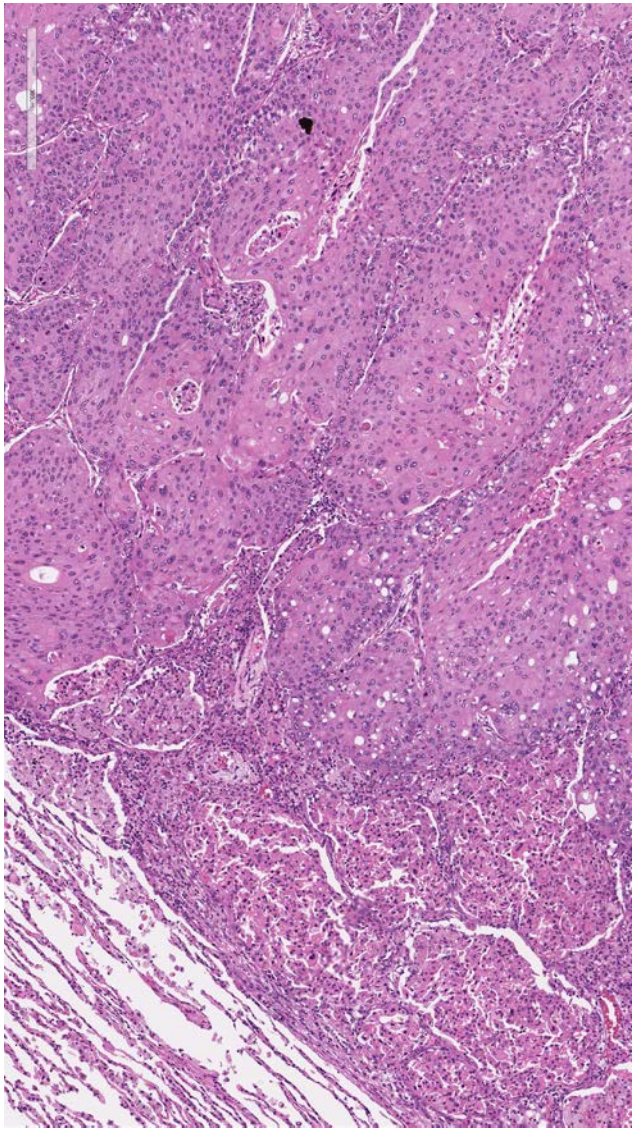
PD-L1 Positive Lung Cancer



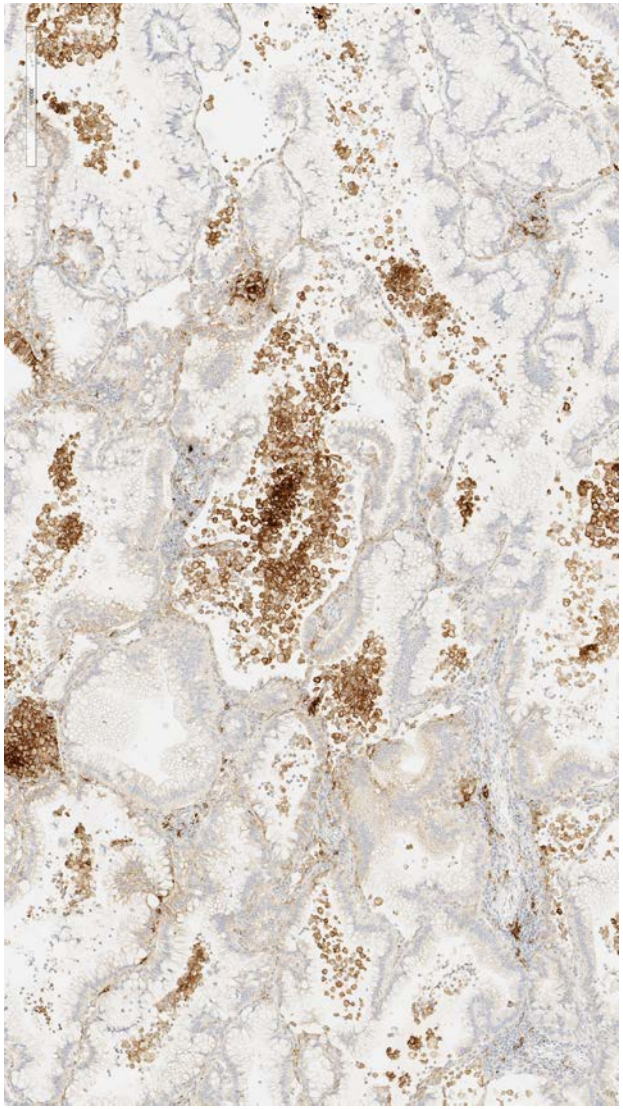


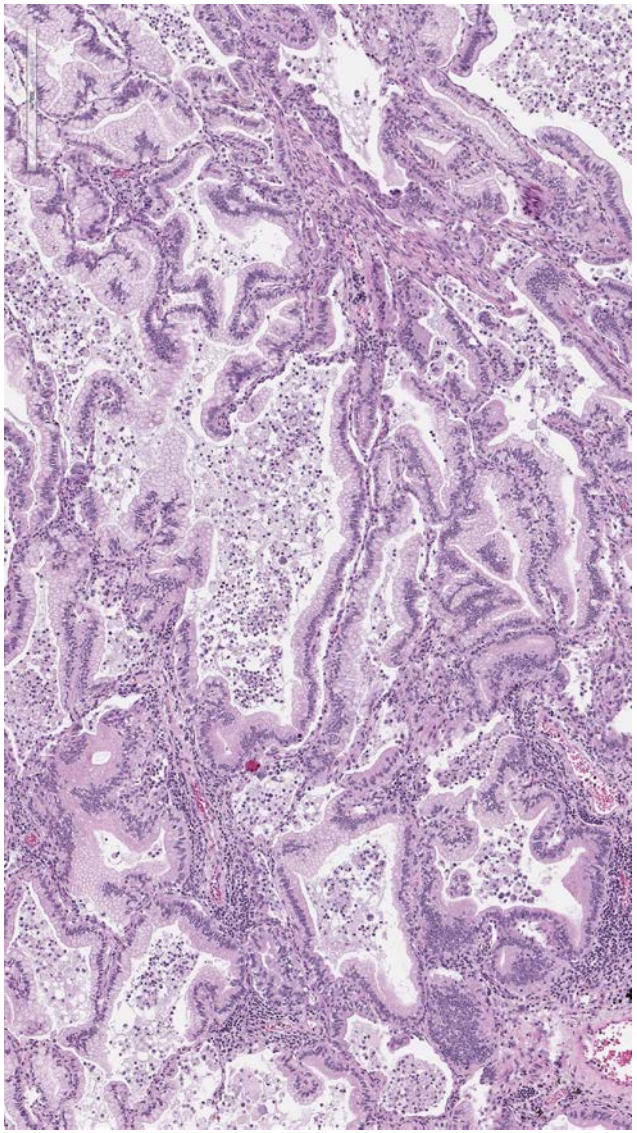
PD-L1 Negative Lung Cancer





PD-L1 Negative Lung Cancer

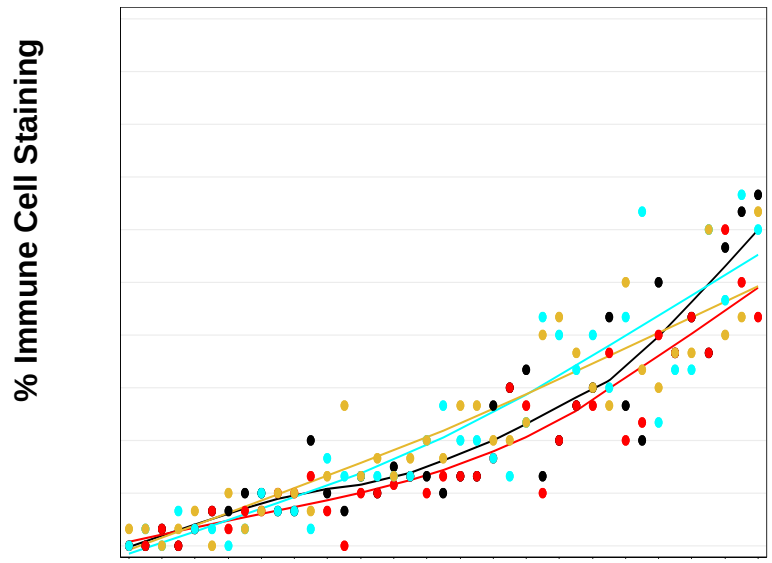




IC Scoring Unique for SP142 and New for Pathologists

Underscores need for pathologist training

Blueprint study
Immune Cell Scoring



German Harmonization Study
Immune Cell Scoring

"Scoring of the tumor-associated immune cells yielded low concordance levels.

Given that the SP142 assay has been used reproducibly in published clinical trials, we assume that specific instructions and training may raise concordance of immune cell scoring."

CAP Hirsch F. Presented at AACR New Orleans 2016

Scheel AH, Dietel M, Heukamp LC, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. Mod Pathol. 2016;29(10):1165-72.

Structured Pathologist Training Produces Excellent Results

Pathologist Training Proficiency Test Scores

Results from 129 pathologists

Indication	Proficiency Test Score
UC	97.0%
NSCLC	95.0%

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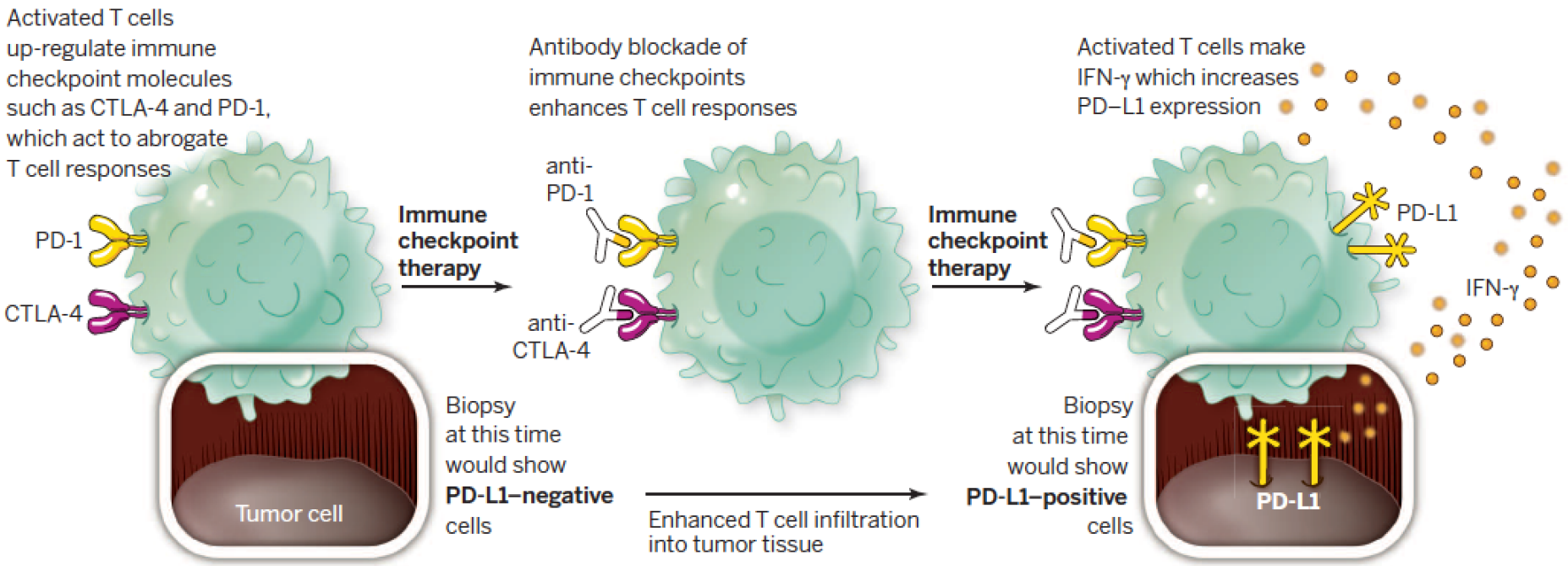
PD-L1 expression can be temporal and heterogeneous



Tumor cell initially PD-L1 Negative

Tumor cell expressed PD-L1 after T-cell activation

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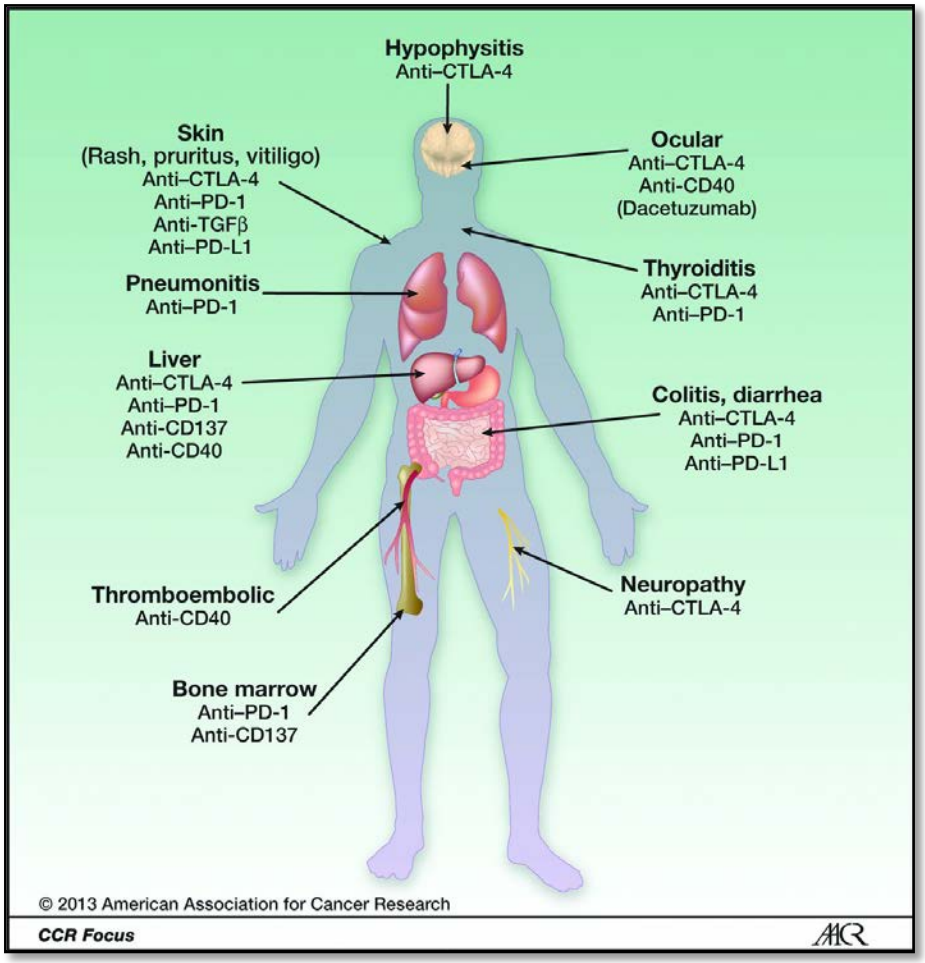
Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61.

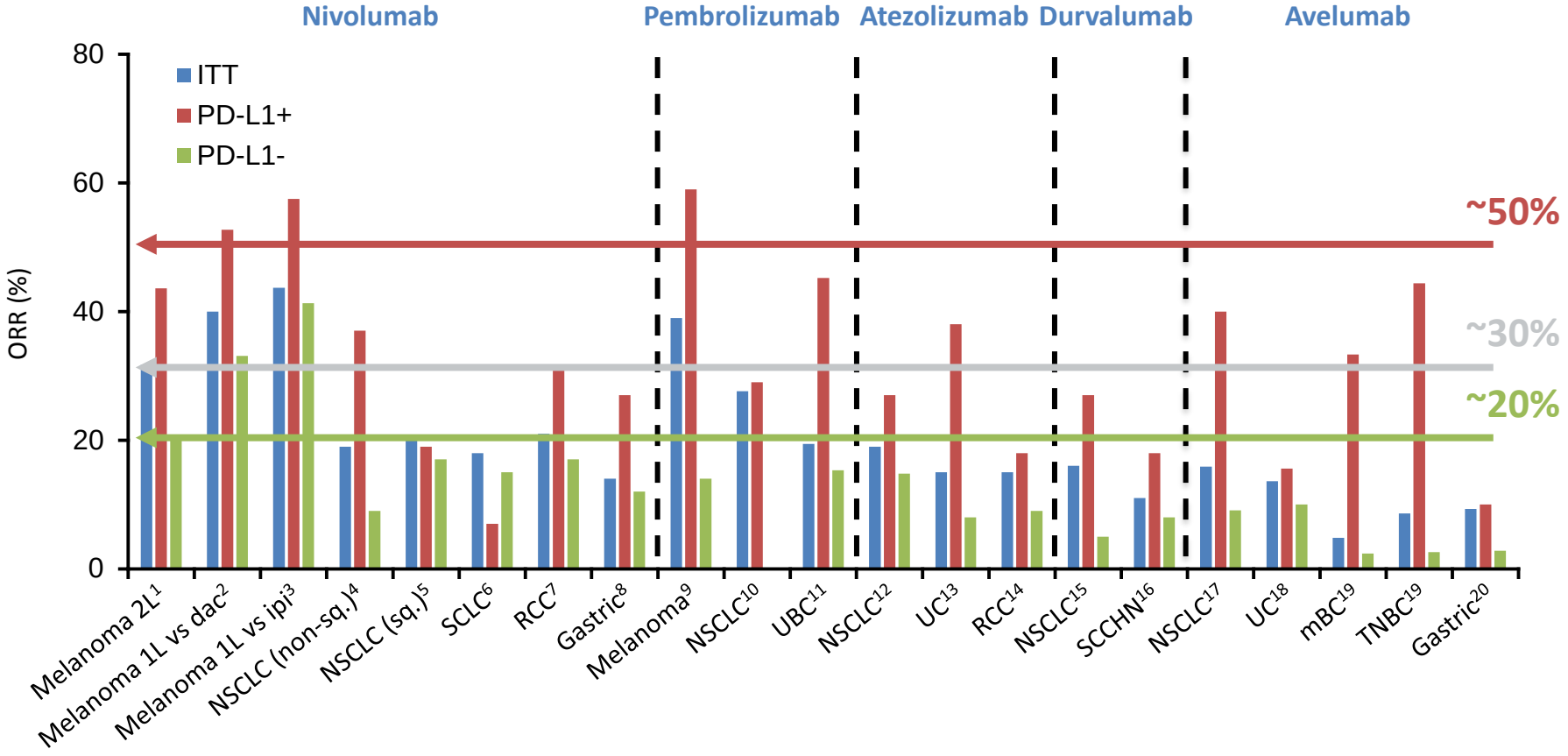
Side effects of cancer immunotherapy may impact prognosis



In general, the side effect profile of PD-L1 therapy is favorable compared to chemotherapy

Melero I, Grimaldi AM, Perez-gracia JL, Ascierto PA. Clinical development of immunostimulatory monoclonal antibodies and opportunities for combination. Clin Cancer Res. 2013;19(5):997-1008.

The ORR for 2nd line PD-L1 negative patients is similar to chemotherapy



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1. Weber et al. Lancet 2015; 2. Robert et al. Lancet 2015; 3. Larkin et al. N Engl J Med 2015; 4. Borghaei et al. N Engl J Med 2015
5. Brahmer et al. N Engl J Med 2015; 6. Antonia et al. ASCO 2015; 7. Motzer et al. J Clin Oncol 2015; 8. Le et al. ASCO GI 2016
9. Kefford et al. ASCO 2014; 10. Garon et al. N Engl J Med 2015; 11. Plimack et al. ASCO 2015; 12. Vansteenkiste et al. ECC 2015
13. Rosenberg et al. Lancet 2016; 14. McDermott et al. J Clin Oncol 2015; 15. Rizvi et al. ASCO 2015; 16. Segal et al. ASCO 2015
17. Gulley et al. ASCO 2015; 18. Apolo et al. ASCO GU 2016; 19. Dirix et al. SABCS 2015; 20. Chung et al. ASCO GI 2016

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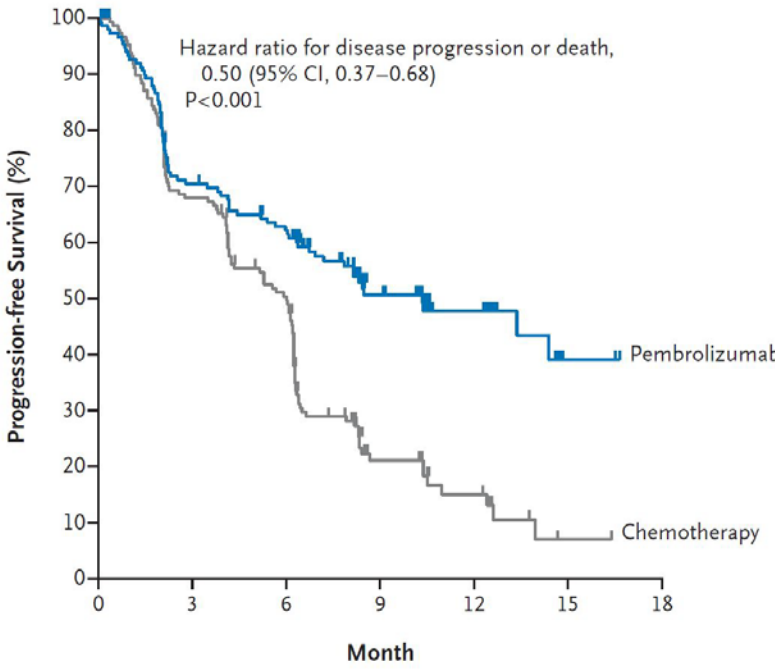
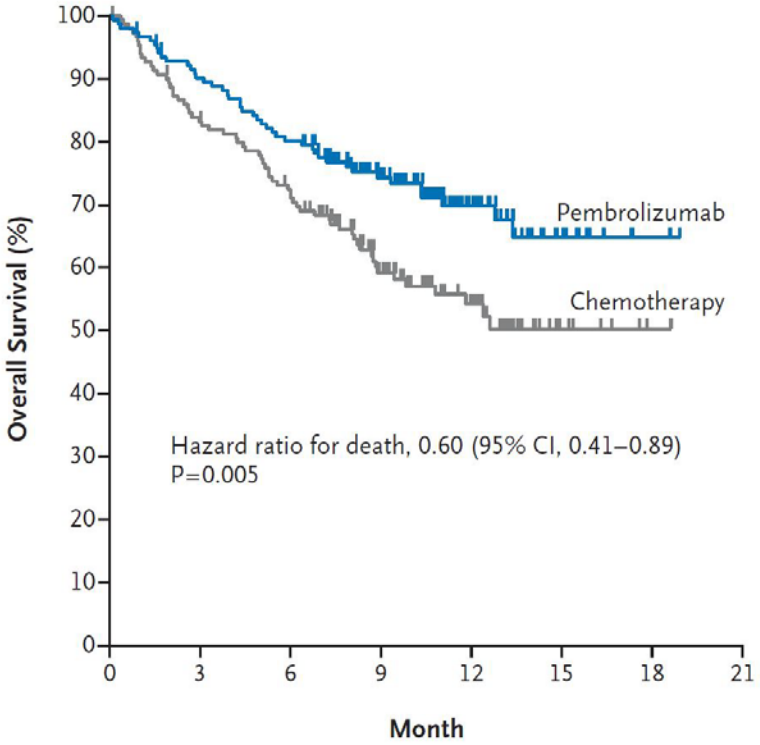
Pembrolizumab in Front-line NSCLC

PD-L1 expression in >50% of tumor cells



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0



No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators.. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8.

DOI: 10.1056/NEJMoa1606774

Not Much Progress with Traditional Chemotherapy: 1975–2011

	Response Rate	1-Year Survival	2-Year Survival
No Chemotherapy	0%	10%	0%
Single Agent	15%	20%	10%
2 Agents	25%	35%	20%
3 Agents	35%	35%	20%
2 Agents + Bevacizumab	35%	50%	22%

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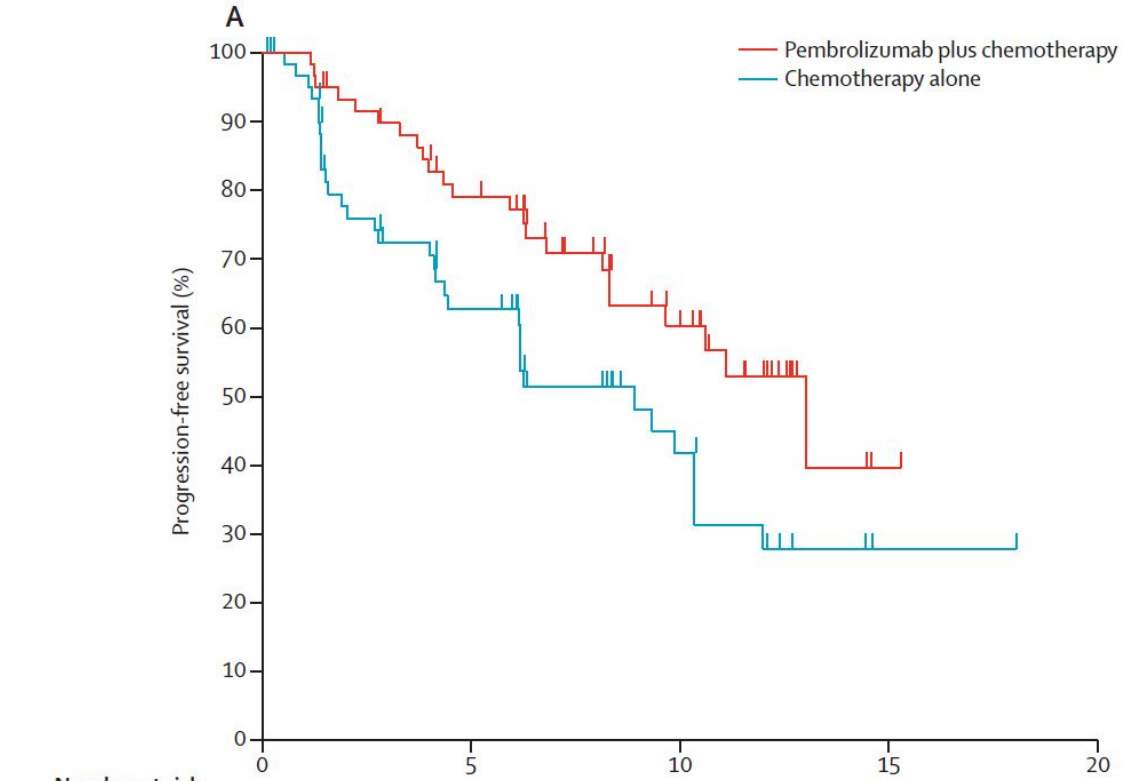
Current regimens:
Squamous: Gemcitabine with cisplatin/carboplatin; paclitaxel with carboplatin
Adenocarcinoma: Pemetrexed with cisplatin/carboplatin

Addition of Pembrolizumab to Carboplatin and Pemetrexed Improves Efficacy in NSCLC



Number at risk (number censored)					
Pembrolizumab plus chemotherapy	60 (0)	43 (5)	20 (20)	1 (36)	0 (37)
Chemotherapy	63 (0)	32 (10)	13 (21)	1 (29)	0 (30)

Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016; S1470-2045(16)30498-3

http://dx.doi.org/10.1016/S1470-2045(16)30498-3

The Opportunity for Pathologists:

How do we use our understanding of the tumor microenvironment to choose the right therapy?

We need to better understand immune response and tumor biology

We need to understand causes of failure and convert them to clinical benefit

We need to personalize cancer immunotherapy treatment

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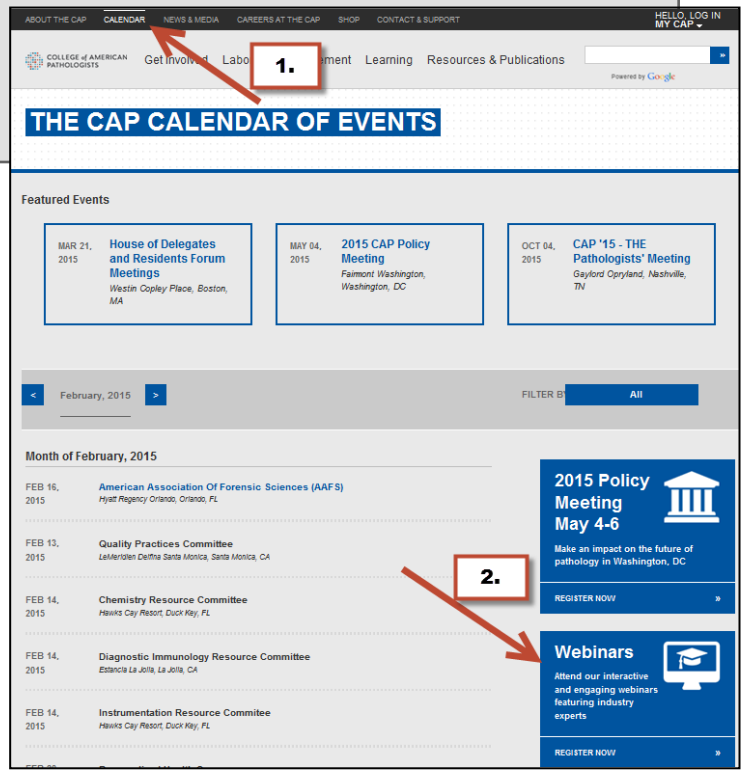
Save the Date for Upcoming Complimentary CAP PHC Webinars

DATE	TOPIC	SPEAKER
Dec 14, 2016 11 AM CT	Preanalytics and Biospecimen Quality Imperative	Carolyn Compton, MD, PhD, FCAP

Register for upcoming webinars:
www.CAP.org > Calendar > Webinars



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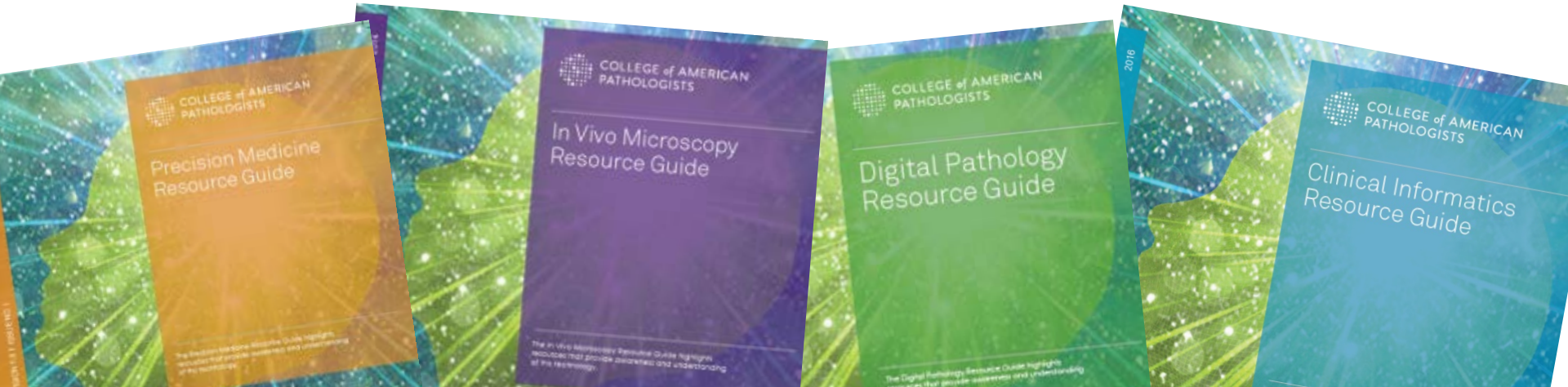
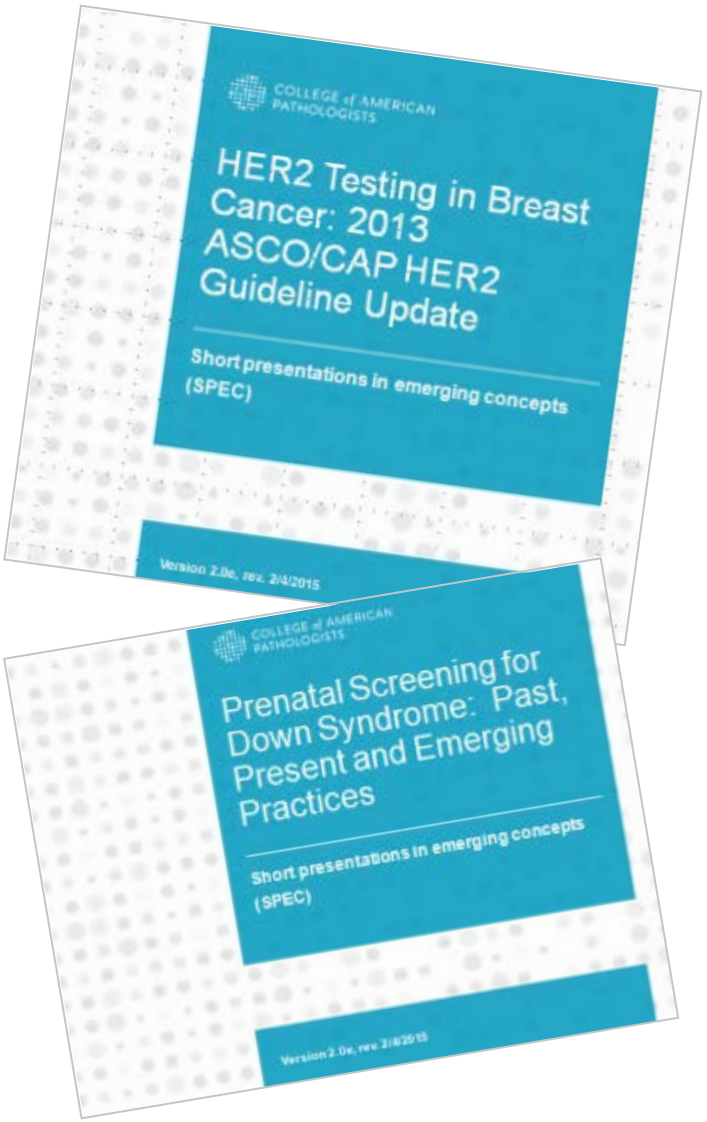
CAP's Pathology Resource Guide: Precision Medicine

- **The CAP has created the Pathology Resource Guides to assist pathologists in understanding key emerging technologies.**
  - **Printed guides are now available for members ($39) and non-members ($69)**
  - **The digital copy of the Resource Guides are a complimentary member benefit**
  - **Access them www.cap.org > Resources and Publications**



Short Presentations on Emerging Concepts (SPECS)

- **Pathology SPECs are:**
  - **short PowerPoints, created for pathologists**
  - **Focused on diseases where molecular tests play a key role in patient management**
- **New topics are Renal Tumors, cell free DNA (cfDNA), and PD-L1 as well as other emerging topics**
- **Access them www.cap.org > Resources and Publications**



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New Survey for 2017
Cancer Biomarker and Companion Diagnostic Testing

- **PD-L1 Immunohistochemistry (PDL1)**
  - **Program includes one 10-core tissue microarray slide**
  - **One shipment per year**
  - **Program ships November 13, 2017**

New

PDL1 PDL1		
Procedure	**Program Code**	**Challenges/Shipment**
	PDL1	
PDL1	▮	10

Order by December 1, 2016 to ensure material availability

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See, Test & Treat® brings cancer screenings to women in need!

- See, Test & Treat is a CAP Foundation-funded program that brings free, same-day cervical and breast cancer screening, diagnoses and follow-up care to women in medically underserved communities across the U.S.

- CAP member pathologists' partner with gynecologists, radiologists and other medical professionals to lead See, Test & Treat programs in hospitals, clinics and other facilities

- Women learn the importance of preventive care through annual exams, a Pap test, Mammogram and a healthy lifestyle

See, Test & Treat Needs Your Financial Support

Visit foundation.cap.org and click on DONATE!

THANK YOU!

- Thank you for attending our webinar, **“PD-L1: Immune Checkpoint Blockade in Cancer” by Kenneth J. Bloom, MD, FCAP.**

- For comments about this webinar or suggestions for upcoming webinars, please contact phcwebinars@cap.org.

- **NOTE:** There is no CME/CE credit available for today’s free webinar. The PDF of the presentation will be sent out in a week.

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