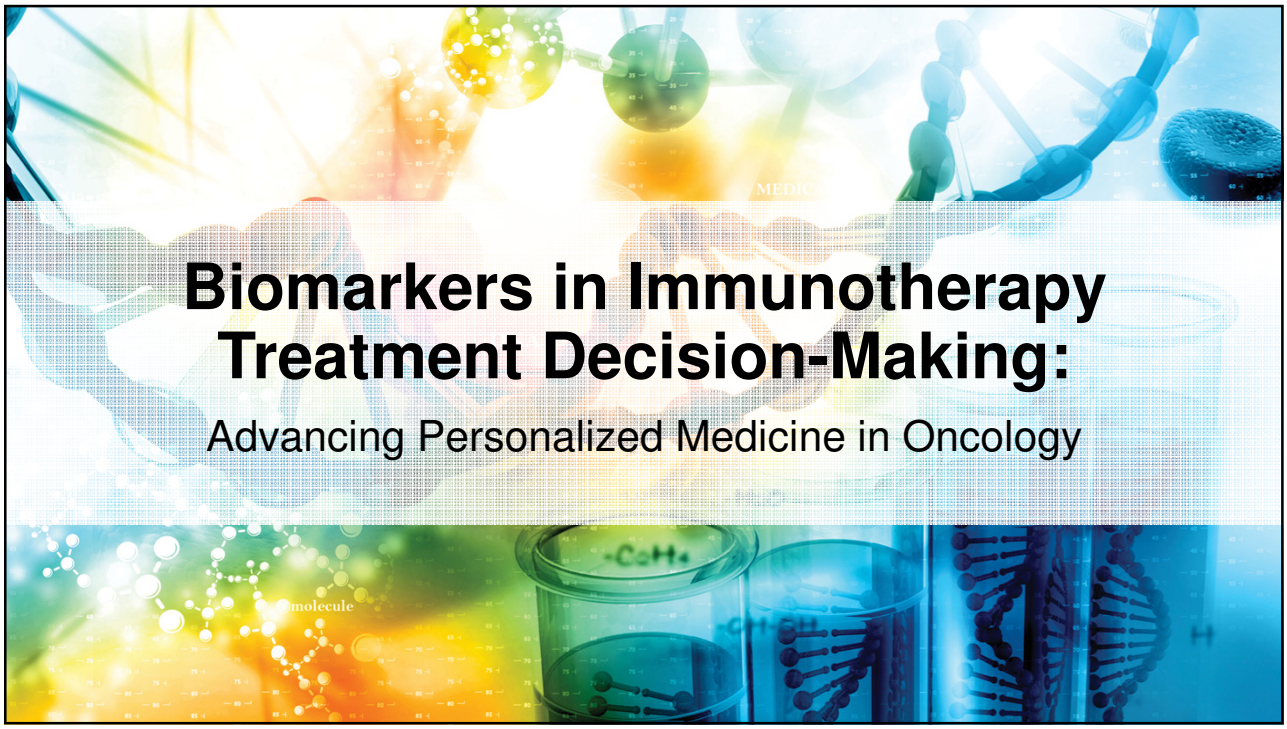
Biomarkers in Immunotherapy Treatment Decision-Making:

Advancing Personalized Medicine in Oncology



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Faculty

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Associate Professor
Surgical Oncology and Genomic Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Dr. Wargo is Associate Professor of Surgical Oncology and Genomic Medicine at The University of Texas MD Anderson Cancer Center in Houston. She received her MD from the Medical College of Pennsylvania and her MMSc from Harvard University. She completed a clinical fellowship in surgical oncology at the National Cancer Institute and is certified by the American Board of Surgery. Dr. Wargo is the recipient of numerous awards, including the Rising STARS and Regents Health Scholars Award, the Stand Up 2 Cancer/AACR Innovative Research Award, and the Society for Melanoma Research Outstanding Investigators Award, among others. She is recognized internationally as a leader in cancer research and is leading innovative efforts globally.

Faculty

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Clinical Pharmacy Specialist
Department of Pharmacy
Thoracic/Head and Neck Medical Oncology
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Dr. Wong is a clinical pharmacy specialist at the University of Texas MD Anderson Cancer Center. She collaborates with a multidisciplinary team specializing in thoracic and head and neck cancers. She received both her Bachelor of Science and Doctor of Pharmacy degrees from the University of Florida. She completed a pharmacy practice residency at Mount Sinai St. Luke's in New York City and a PGY-2 hematology/oncology pharmacy residency at Smilow Cancer Hospital at Yale New Haven. Her interests includes leadership and mentorship to students and residents.

Disclosures

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Dr. Wong has no relevant affiliations or financial relationships with a commercial interest to disclose.

The clinical reviewer, Lisa Holle, PharmD, BCOP, has no actual or potential conflict of interest in relation to this program.

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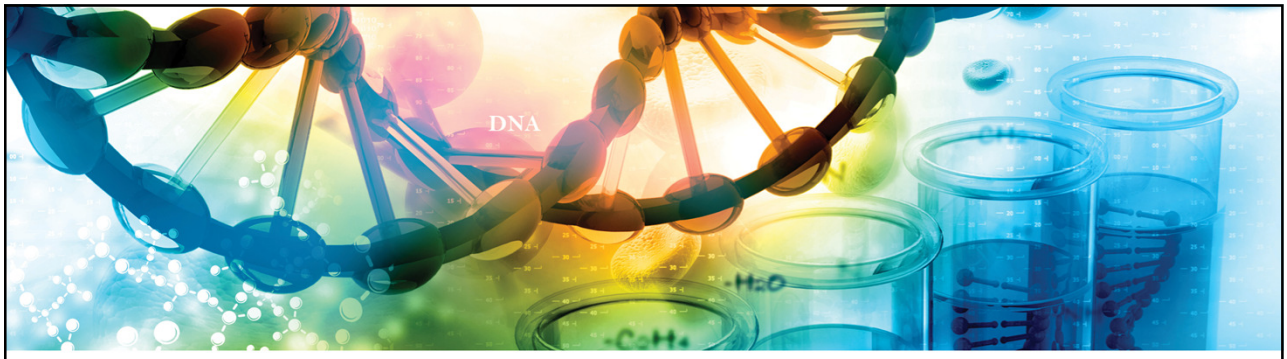
UAN: 0430-0000-18-048-L01-P
Credits: 1.0 hour (0.10 CEU)
Type of Activity: Application

Learning Objectives

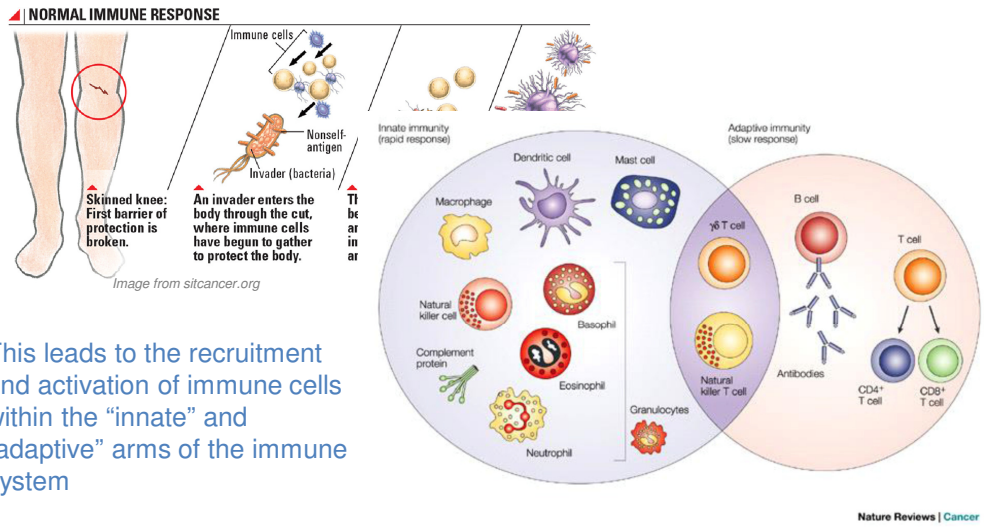
- **Describe** the potential biomarkers being examined to predict response to immunotherapy, specifically immune checkpoint inhibitors (ICIs)
- **Assess** the variety of biomarker assessments available to determine biomarker status in patients
- **Discuss** strategies for the potential selection of ICIs with consideration of biomarkers in specific patient situations



Overview of Immuno-oncology and Known and Novel Biomarkers of Response

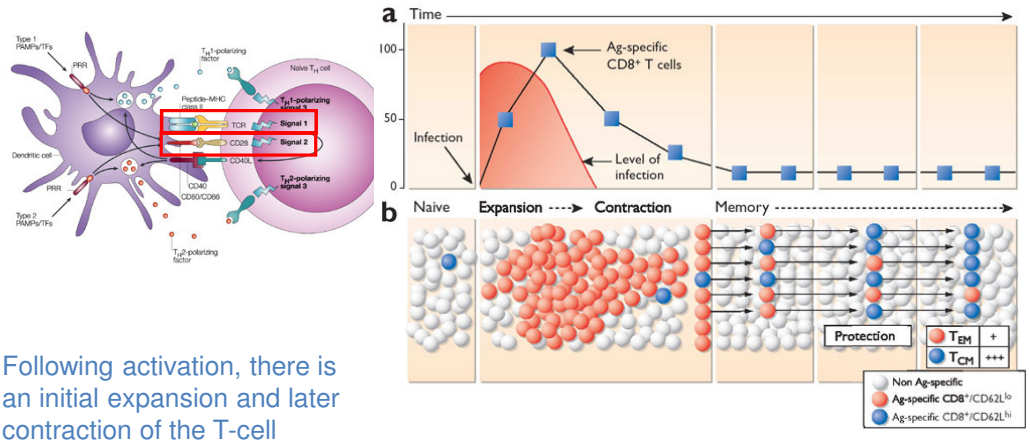
Jennifer A. Wargo, MD, MMSc

Immune Response Involves Innate and Adaptive Immunity



This leads to the recruitment and activation of immune cells within the "innate" and "adaptive" arms of the immune system

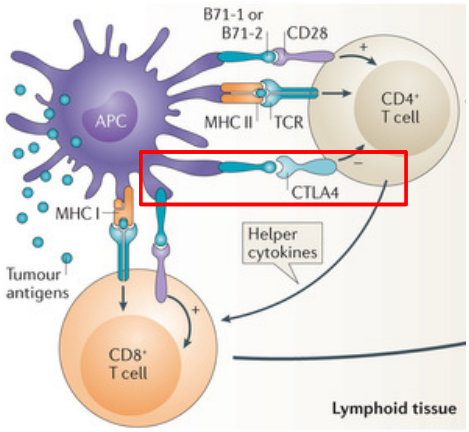
T-cell Activation Requires 2 Signals: TCR and Co-stimulation



Following activation, there is an initial expansion and later contraction of the T-cell repertoire (with formation of "immunologic memory")

TCR, T-cell receptor.

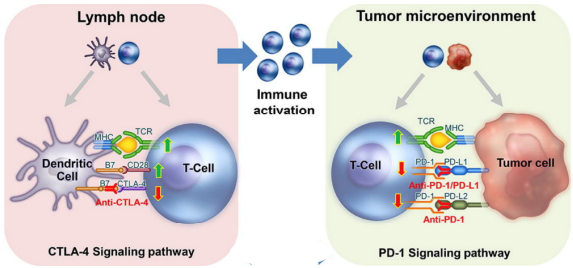
Downregulation of Response Involves Checkpoint Molecules



Nature Reviews | Cancer

The ligands for these inhibitory molecules are often expressed in cancer

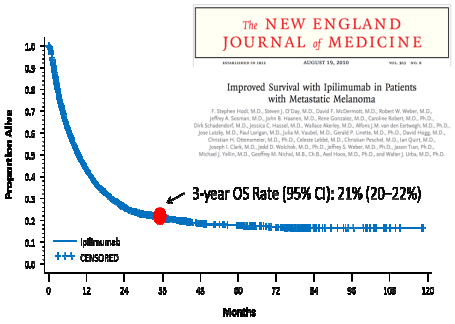
Targeting These Checkpoints is Effective for Treating Cancer

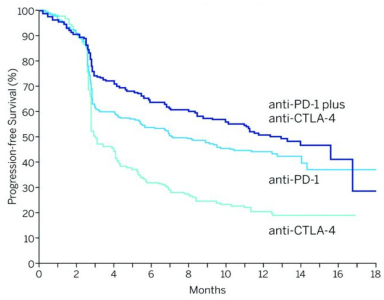


Co-targeting of CTLA-4 and PD-1 is associated with higher response rates but also with higher toxicity

CTLA-4, cytotoxic T-lymphocyte-associated protein 4;
PD-1, programmed cell death protein 1.

Checkpoint Inhibitors Were First Approved in 2011 (aCTLA-4)

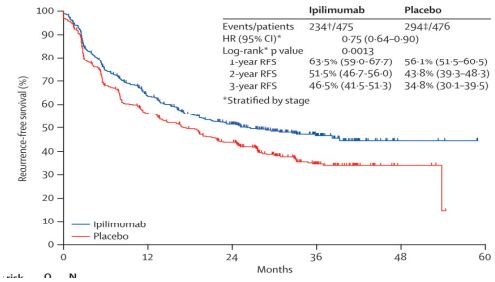




Larkin NEJM 2015

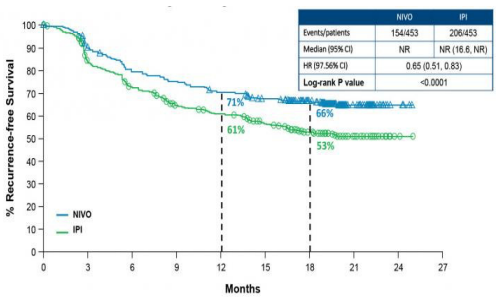
Now, checkpoint blockade targeting several different inhibitory molecules (CTLA-4 +/- PD-1) is being used successfully across cancer types

Checkpoint Inhibitors are Being Used as Adjuvant Therapy



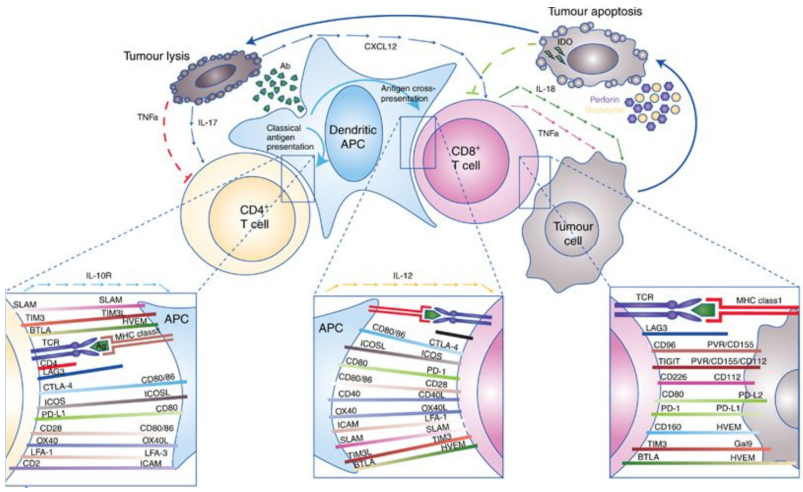
	Ipilimumab	Placebo
Events/patients	234/1/475	294/1/476
HR (95% CI)*	0·75 (0·64–0·90)	
Log-rank* p value	0·0013	
1-year RFS	63·5% (59·0–67·7)	56·1% (51·5–60·5)
2-year RFS	51·5% (46·7–56·0)	43·8% (39·3–48·3)
3-year RFS	46·5% (41·5–51·3)	34·8% (30·1–39·5)

*Stratified by stage



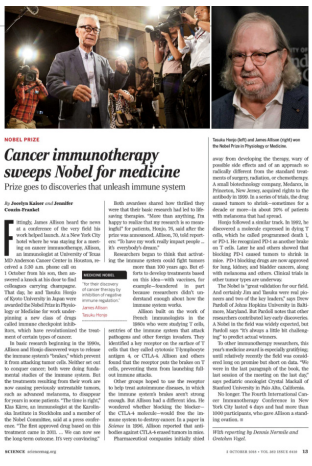
	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank P value	<0.0001	

More Immuno-modulatory Molecules Are Now Being Targeted



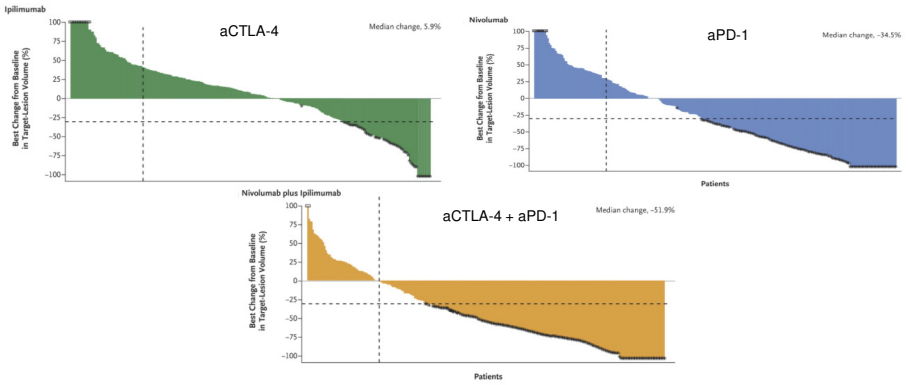
Cogdill AP, et al. *Br J Cancer.* 2017;117(1):1-7.

Cancer Immunotherapy Was Named a Breakthrough in 2013



The Nobel Prize for Medicine & Physiology was awarded to Jim Allison & Tasuku Honjo in 2018

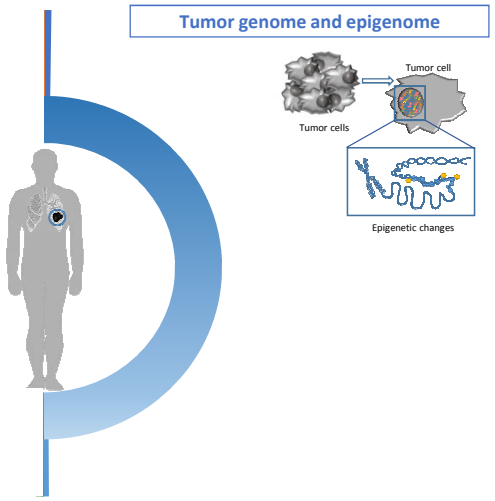
However, Responses Are Heterogeneous and May Not Be Durable



There is a critical need to better understand who will benefit from therapy, as well as proper timing, sequence, and combination of different therapeutic agents

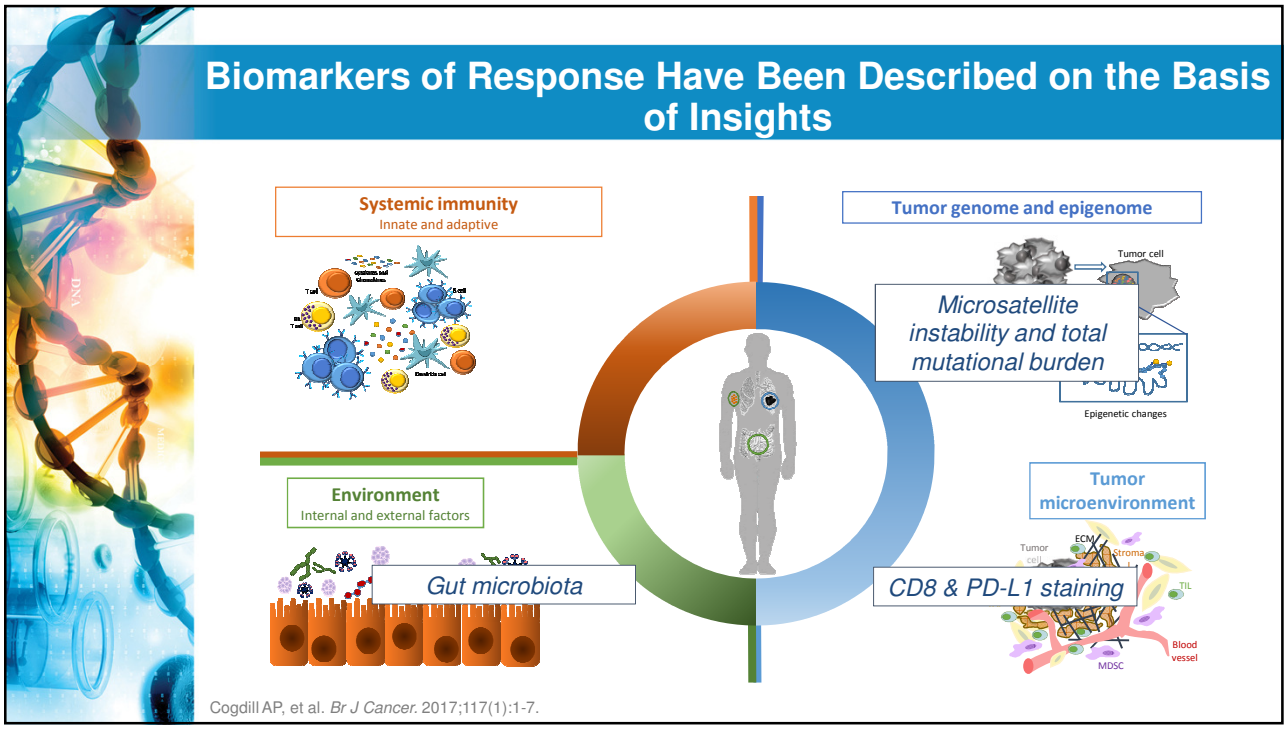
Larkin J, et al. *New Engl J Med.* 2015;373(1):23-34.; Menzies AM, et al. *Cancer.* 2015;121(21):3826-35.

Responses Are Dependent on Factors That Shape Tumor Growth & Immunity

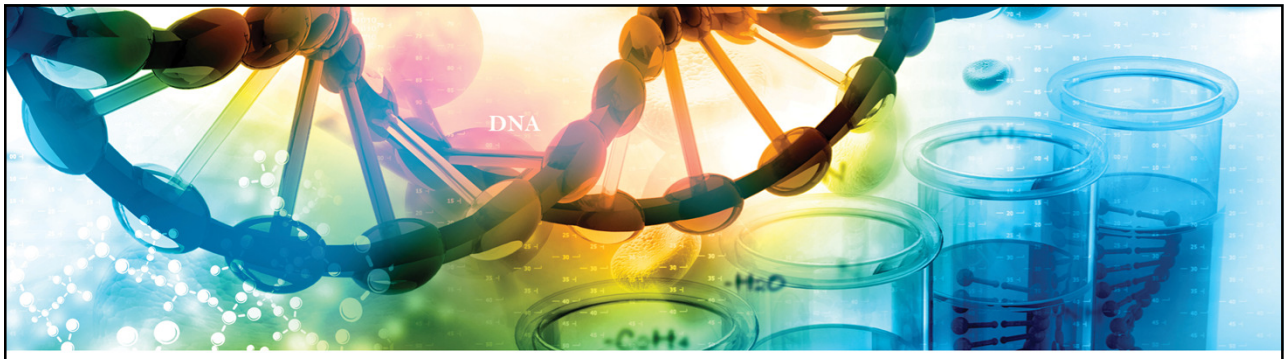


Cogdill AP, et al. *Br J Cancer.* 2017;117(1):1-7.

Biomarkers of Response Have Been Described on the Basis of Insights

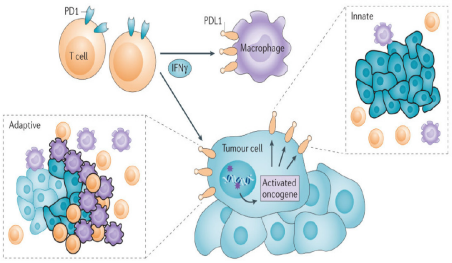


Cogdill AP, et al. *Br J Cancer.* 2017;117(1):1-7.



Known Biomarkers of Checkpoint Blockade Response

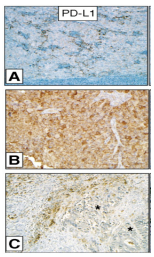
Programmed Death Ligand 1 (PD-L1) Expression



PD-L1 is one of the ligands for PD-1 and can be expressed by tumor cells (with mutations such as PI3K in Hodgkin lymphoma) and may also be induced (with secretion of pro-inflammatory cytokines)

Topalian SL, et al. *Nat Rev Cancer.* 2016;16(5):275-87.

Baseline PD-L1 staining



PD-L1 tumors have been shown to be more likely to respond to checkpoint blockade (and this is an approved biomarker for some indications)

Taube JM, et al. *Clin Cancer Res.* 2014;20(19):5064-74.

However, complexities exist:

- Many antibodies and cut-offs are used
- PD-L1 is not a perfectly predictive biomarker

Table 2 Dichotomous Scoring Used Across Antibodies for PD-L1 IHC Tests in Lung Cancer

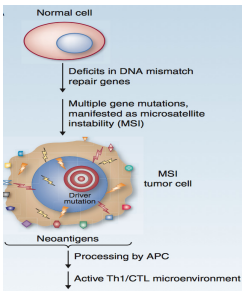
Antibody (developer) [drug against which the study validated the test]	Cutoff/Threshold
22C3 (Dako) [pembrolizumab]	1% (used in training group): 1 study [4][a] 50% (determined as optimal cutoff): 1 study [4][a]
28-8 (Dako) [nivolumab]	1%: 3 studies [7, 10, 12][a] 5%: 2 studies [10, 11][a] 10%: 1 study [10][a] 50%: 1 study [11][a]
SP263 (Roche) [durvalumab]	25%: 3 studies [7, 14, 28][a,b]
SP142 (Roche) [atezolizumab]	1%: 2 studies [19, 20][a] 5%: 2 studies [19, 20][a,c] 50%: 1 study [20][a]
E1L3N (Cell Signaling Technology; reagent provider) [not applicable]	1%: 2 studies [20, 21][a] 5%: 4 studies [11, 20, 21, 23][a,c] 50%: 3 studies [11, 20, 21][a]

[a]Tested in tumor cells. [b] Tested in tumor-infiltrating immune cells. [c] Tested in tumor stroma

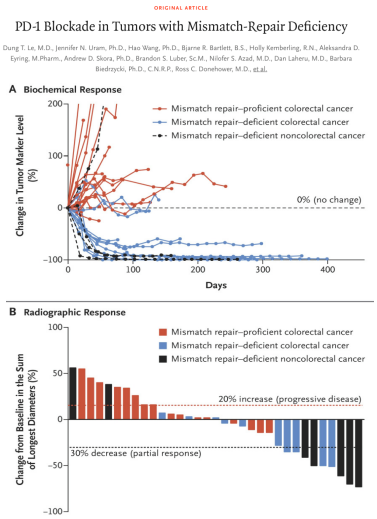
Udall M, et al. *Diagn Pathol.* 2018;13(1):12.

Microsatellite Instability (MSI)

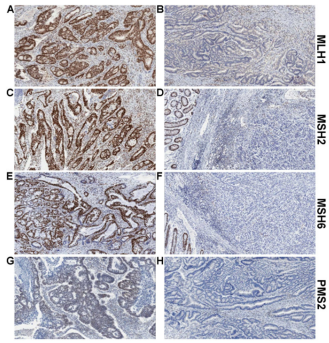
- Tumors with defects in mismatch repair (MMR) genes (detected by measurement of MSI) are unable to correct errors due to replication
- These tumors have ~100x the mutational burden of MMR-competent tumors



Xiao Y, Freeman GJ. *Cancer Discov.* 2015;5(1):16-8.



Le DT, et al. *New Engl J Med.* 2015;372(26):2509-20.

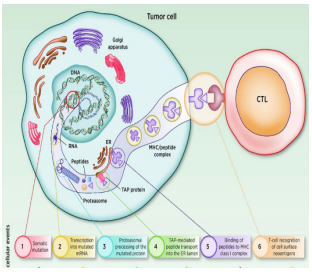


https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm.;

http://www.pathologyoutlines.com.

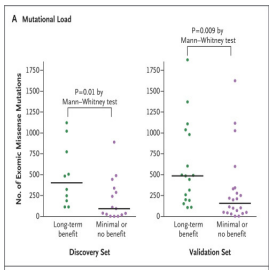
Tumor Mutational Burden (TMB)

Mutations in tumors may add to their oncogenic potential, but they may also make tumors more "visible" to the immune system through the expression of neoantigens



Chabanon RM, et al. *Clin Cancer Res.* 2016;22(17):4309-21.

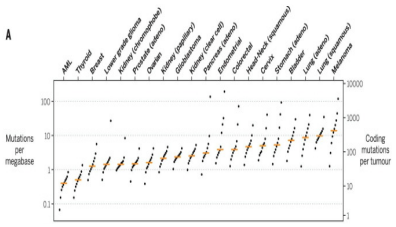
Mutational burden



Patients with a higher mutational burden tend to have a higher likelihood of long-term clinical benefit

Snyder A, et al. *N Engl J Med.* 2014;371(23):2189-99.

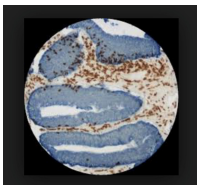
However, tumors have varying degrees of mutational burden, and there is not a perfectly linear relationship between mutational burden and response to therapy



Martincorena I, Campbell PJ. *Science.* 2015;349(6255):1483-9.

CD8+ T-cell Infiltrate

Because of their central role in anti-tumor immunity, CD8+ T-cells have served as biomarkers for overall prognosis in cancer

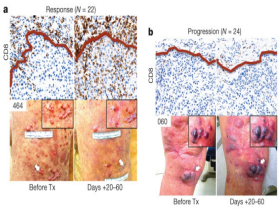


Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon, Anne Costes, Fatima Sanchez-Cabo, Amos Kirilovsky, Bernhard Mlecnik, Christine Lagorce-Pagès, Marie Tosolini, Matthieu Camus, Anne Berger, Philippe Wind, Franck Zinzindohoué, Patrick Bruneval, Paul-Henri Cugnenc, Zlatko Trajanoski, Wolf-Herman Fridman, Franck Pagès

Galon J, et al. *Science.* 2006;313(5795):1960-4.

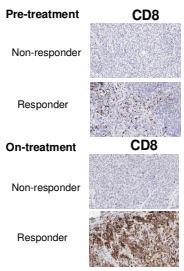
Baseline CD8+ T-cell density/distribution



The density and distribution of CD8+ T-cells at baseline can help predict response (in baseline tumor biopsies)

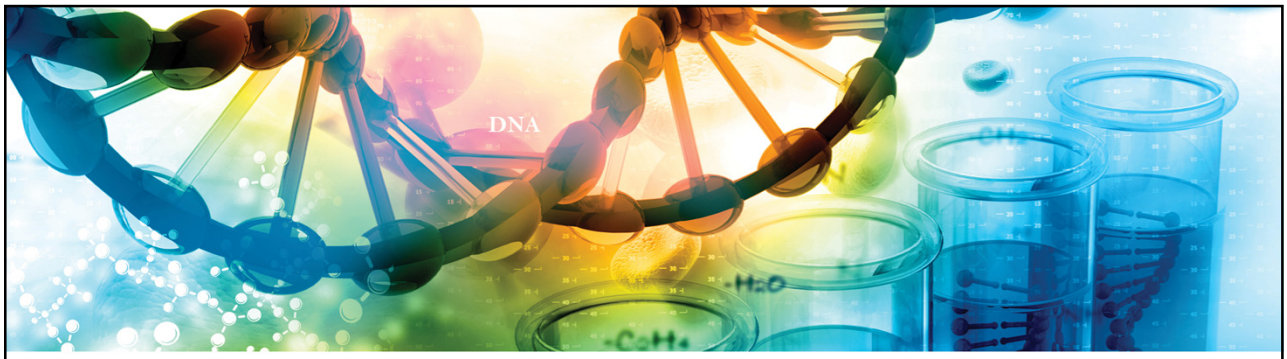
Tumeh PC, et al. *Nature.* 2014;515(7528);568-71.

Measurement of CD8+ T-cell infiltrates in early on-treatment biopsies was predictive of response to anti-PD-1



Chen PL, et al. *Cancer Discov.* 2016;6(8):827-37.

CD8+ T-cell count is not currently an approved biomarker and is not used as an indication for therapy (though studies are underway exploring its use)



Novel Biomarkers of Checkpoint Blockade Response

Environmental Factors (e.g., Microbiome) May Also Influence Responses

Cogdill AP, et al. *Br J Cancer.* 2017;117(1):1-7.

The Human Microbiome

100 trillion microbes

3% of human body mass

1-10X microbes: human cells

10-100X microbial: human genes

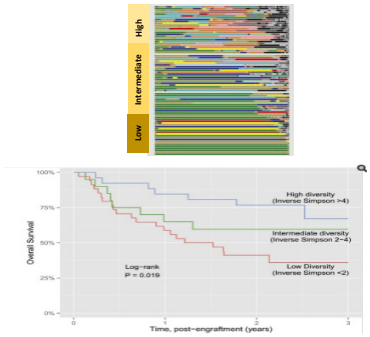
Largest number of microbes in GI tract

Slide credit: Ami Bhatt and Robert Jenq

GI, gastrointestinal.

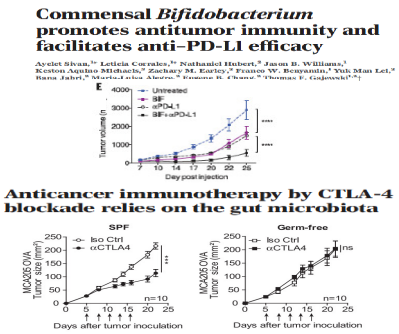
Gut Microbiome May Influence Response to Transplant & Immunotherapy

Diversity of the gut microbiome is associated with differential outcomes in the setting of stem cell transplant in patients with AML



Taur Y, et al. *Blood*. 2014;124(17):1174-82.

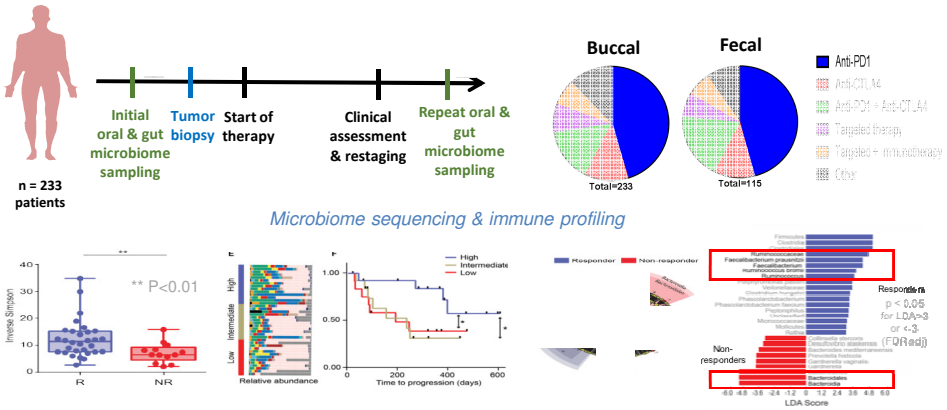
Composition of the gut microbiome is associated with differential responses to checkpoint blockade in murine models



Sivan A, et al. *Science*. 2015;350(6264):1084-9.; Vetizou M, et al. *Science*. 2015;350(6264):1079-84.

AML, acute myeloid leukemia.

Oral and Gut Microbiome Samples From Melanoma Patients



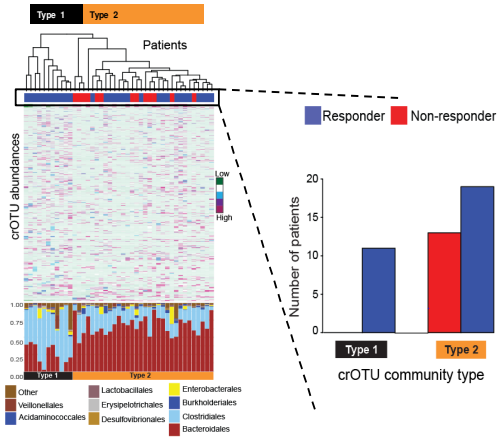
Responders to anti-PD-1 had a higher diversity of gut bacteria associated with prolonged PFS (along with additional compositional differences)

Deepak Gopalakrishnan, PhD

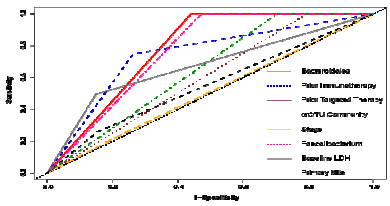
Gopalakrishnan V, et al. *Science*. 2018;359(6371):97-103.

PFS, progression-free survival.

Gut Microbiome "Signature" Is Associated with Response

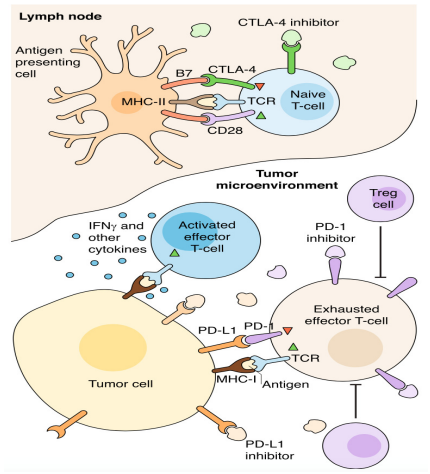


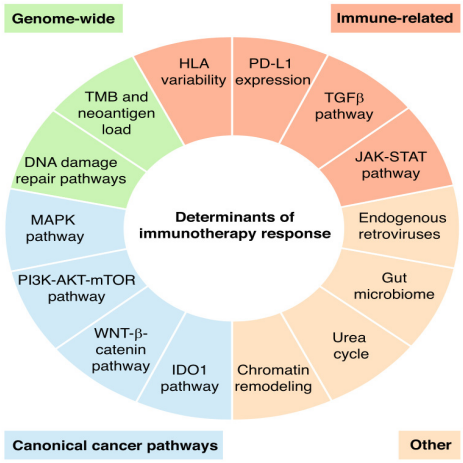
Gut microbiome could be used as a biomarker of response to immune checkpoint blockade: patients with a "type I" signature are more likely to respond



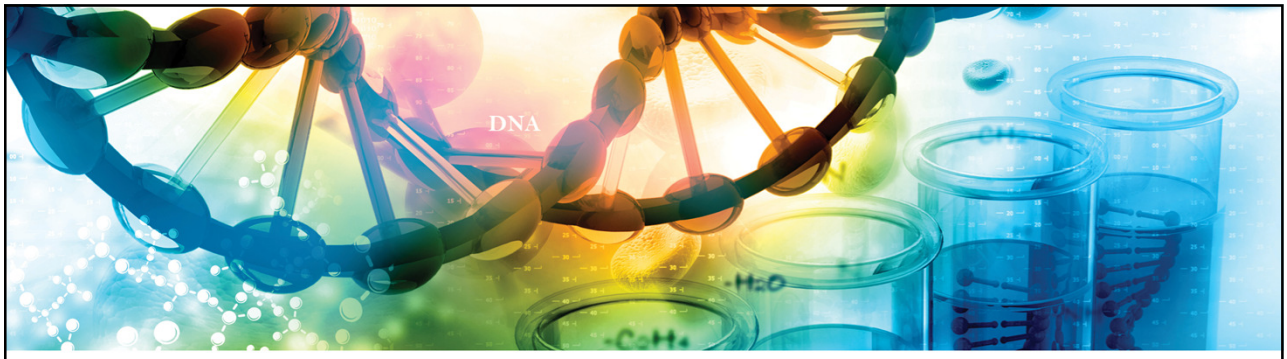
Gopalakrishnan V, et al. *Science*. 2018;359(6371):97-103.

Integrated Biomarker Approach Will Yield the Best Results





*For further reading, an excellent review was recently published in Genome Medicine (*Conway JR, et al. *2018*;10(1):93.*)*



Therapeutic Approaches Based on Biomarkers in Immune Checkpoint Inhibition

Milena G. Wong, PharmD, BCOP

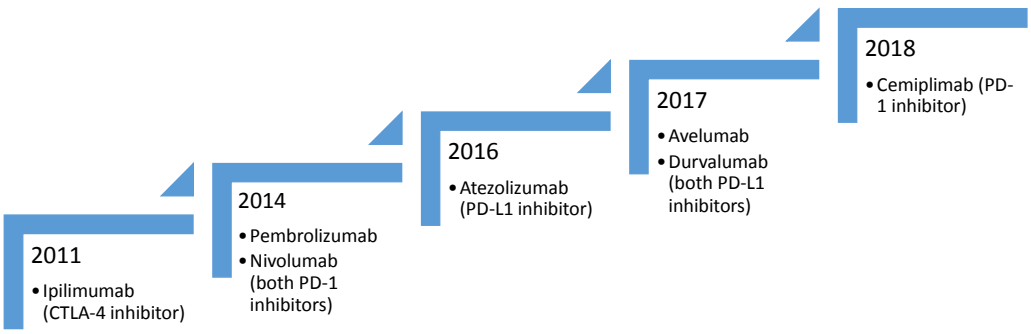
Oncology Biomarkers

In vitro diagnostic devices help determine biomarker status

- Companion diagnostics: required information for safe and effective use of a corresponding therapeutic product
- Complementary diagnostics: not required for drug use, but can improve disease management, diagnosis, risk stratification, or drug monitoring

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US). Understanding Prognostic versus Predictive Biomarkers. https://www.ncbi.nlm.nih.gov/books/NBK402284/. Published December 22, 2016. Accessed December 5, 2018.; U.S. Food & Drug Administration. In vitro diagnostics. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm. Updated December 6, 2018. Accessed December 12, 2018.

Initial FDA Approval of ICIs



Bavencio (avelumab) [prescribing information]. Rockland, MA: EMD Serono Inc; 2018.; Imfinzi (durvalumab) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.; Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018.; Libtayo (cemiplimab-rwlc) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2018.; Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2018.; Tecentriq (atezolizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; 2018.; Yervoy (ipilimumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2018.

Pharmacist's Role

- Indications that require companion diagnostic or genomic testing for ICIs
- Appropriate companion diagnostic or genomic testing
- Practical considerations among tests
  - Sample requirement
  - Turnaround time
  - Cost
- Practical considerations among treatments
  - Convenience
  - Cost

Genomic Tests/Companion Diagnostics for ICIs

Biomarker	Diagnostic name	Analysis method	ICIs	Indication
PD-L1 expression	PD-L1 IHC 22C3 pharmDx	IHC	Pembrolizumab 200 mg IV Q3W	Metastatic NSCLC 1st line single agent with **TPS≥50%;** 2nd line single agent with **TPS≥1%** Locally advanced/metastatic urothelial carcinoma 1st line not eligible for cisplatin with **CPS≥10** Recurrent locally advanced/metastatic GEJ adenocarcinoma Progression after ≥2 lines of therapy, including fluoropyrimidine + platinum-containing, and, if appropriate, HER2/neu-targeted therapy with **CPS≥1** Recurrent/metastatic cervical cancer 2nd line after chemotherapy with **CPS≥1**
	PD-L1 (SP142)	IHC	Atezolizumab 1200 mg IV Q3W	Locally advanced/metastatic urothelial carcinoma 1st line not eligible for cisplatin with **IC≥1**

CPS, combined positive score; GEJ, gastric or gastroesophageal junction; IC, tumor-infiltrating immune cells; IHC, immunochemistry; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PD-L1, programmed death ligand 5; Q3W, every 3 weeks; TPS, tumor proportion score.

Center for Devices and Radiological Health. List Of Cleared or Approved Companion Diagnostic Devices (in Vitro and Imaging Tools). https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm Updated December 6, 2018. Accessed December 6, 2018.; Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018.; Tecentriq (atezolizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; 2018.; U.S. Food & Drug Administration. Premarket Approval (PMA) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160002s006. Updated December 10, 2018. Accessed December 16, 2018.

Genomic Tests/Companion Diagnostics for ICIs

Biomarker	Diagnostic name	Analysis method	ICIs	Indication
MSI-H dMMR	MMR MSI FoundationOne®CDx Caris Molecular Intelligence®	IHC PCR NGS	Pembrolizumab Adults 200 mg IV Q3W Pediatrics 2 mg/kg IV (cap 200 mg) Q3W	Adult and pediatric patients with • Solid tumors Progression after prior treatments and no satisfactory alternative options • CRC Progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
			Nivolumab ± ipilimumab	Adults and pediatric (12 years or older) patients with CRC Progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV Q3W x 4 doses, then nivolumab 240 mg IV Q2W. If single-agent nivolumab: 240 mg IV Q2W
TMB*	FoundationOne CDx	NGS	Nivolumab ± ipilimumab #	Metastatic NSCLC 1st line with high TMB (**TMB≥10** mutations per megabase)

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy; #, not yet approved by FDA.

CRC, colorectal cancer; dMMR, mismatch repair deficient; MSI microsatellite instability MSI-H, microsatellite instability-high; NGS, next-generation sequencing; PCR, polymerase chain reaction; Q2W, every 2 weeks.

Caris Life Sciences. Microsatellite Instability (MSI). https://www.carislifesciences.com/microsatellite-instability-msi. Accessed December 10, 2018.; Foundation Medicine. FoundationOne CDx™ technical information. https://assets.ctfassets.net/vhribv12lmne/6Rt6csmCPuaguuqmgi2iY8/e3a9b0456ed71a55d2e4480374695d95/FoundationOne_CDx.pdf. Accessed December 6, 2018.; Gibson J, et al. *Clin Gastroenterol Hepatol.* 2014;12(2):171-6.; Hellmann MD, et al. *N Engl J Med.* 2018;378(22):2093-104.; Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018.; Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2018.; Tecentriq (atezolizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; 2018.; Yervoy (ipilimumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2018.

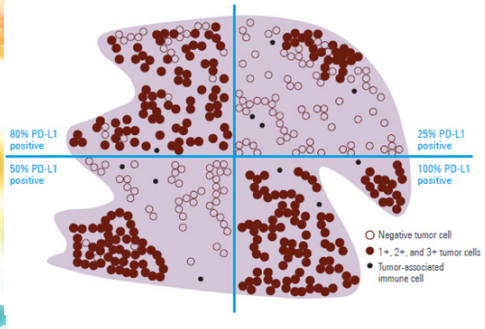
PD-L1 Expression – Efficacy Data

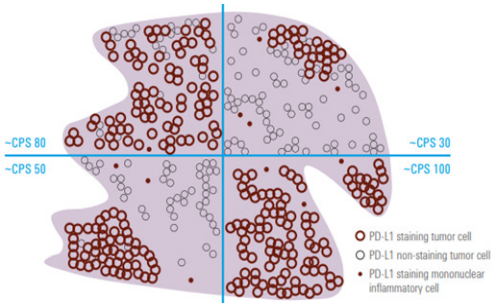
Pembrolizumab indication	Cut-off	Efficacy data			
NSCLC 1st line single agent KN-024	TPS≥50%	Improvement in mPFS 10.3 vs. 6.0 months chemotherapy (HR 0.50 [95% CI: 0.37, 0.68]; p<0.001) Improvement in OS (HR 0.60 [95% CI: 0.41, 0.89]; p<0.005)			
NSCLC 2nd line single agent KN-010	TPS≥1%	Improvement in mOS 2mg/kg arm: 10. 4 months (HR 0.71 [95% CI: 0.58, 0.88]; p<0.001) 10 mg/kg arm: 12.7 months (HR 0.61 [95% CI: 0.49, 0.75]; p<0.001) Docetaxel: 8.5 months			
GEJ adenocarcinoma 3rd line KN-059	CPS≥1	CPS≥1 n=75 CPS<1 n=58	ORR (95% CI) 22.7% (13.8, 33.8) ORR (95% CI) 8.6% (2.9, 19.0)	mDOR (range) 8.1 (1.6+, 17.3) months mDOR (range) 6.9 (4.4+, 7.0+) months	
Cervical carcinoma 2nd line KN-158	CPS≥1	ORR 16% (95% CI: 8.8, 25.9) CR 2.6%; mDOR NR (range 4.1, 18.6+ months); 91% had a response ≥6 months; No response with CPS<1			
Urothelial 1st line ineligible for cisplatin KN-052	CPS≥10	ORR (95% CI)	All subjects (n=370) 29% (24, 34)	PD-L1 CPS<10 (n=260) 21% (16,26)	PD-L1 CPS≥10 (n=110) 47% (38,57)
Atezolizumab indication	**Cut-off**	**Efficacy data**			
Urothelial carcinoma 1st line ineligible for cisplatin IMVigor210	IC≥5	ORR (95% CI)	All subjects (n=119) 23.5% (16.2, 32.2)	PD-L1 IC<5 (n=87) 21.8% (13.7, 32)	PD-L1 IC≥5 (n=32) 28.1% (13.8, 46.8)

CI, confidence interval; HR, hazard ratio; KN, KEYNOTE; mDOR, median duration of response; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; ORR, objective response rate; OS, overall survival.

KN-024: Reck M, et al. *New Engl J Med.* 2016;375(19):1823-33.; Reck M, et al. *J Thorac Oncol.* 2018;13(4):S112-3.; KN-010: Herbst RS, et al. *Lancet.* 2016;387(10027):1540-50.; KN-059: Fuchs CS, et al. JAMA Oncol. 2018;4(5):e180013.; KN-158: Chung HC, et al. *J Clin Oncol.* 2018;36(15_suppl):5522-52.; KN-052: Balar AV, et al. *Lancet Oncol.* 2017;18(11):1483-92.; IMVigor210: Rosenberg JE, et al. *Lancet.* 2016;387(10031):1909-20.

PD-L1 IHC 22C3 Pembrolizumab: Tumor Proportion Score and Combined Positive Score



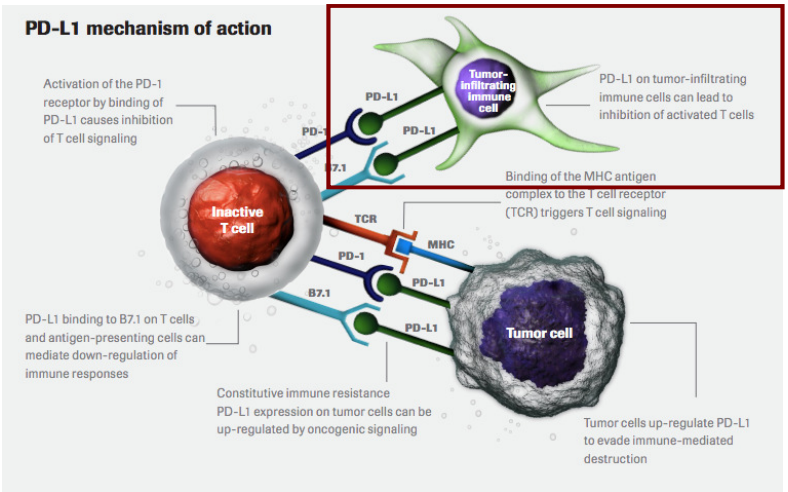


TPS = # of PD-L1 positive tumor cells x 100
total number of tumor cells

CPS = # of PD-L1 positive cells (tumor cells, lymphocytes, macrophages) x 100
total number of tumor cells

Agilent Technologies, Inc. PD-L1 IHC 22C3 pharmDx is FDA-approved for in vitro diagnostic use. https://www.agilent.com/cs/library/usermanuals/public/29158_pd-l1-ihc-22C3-pharmdx-nsclc-interpretation-manual.pdf. Accessed November 2, 2018.; Agilent Technologies, Inc. https://www.agilent.com/cs/library/usermanuals/public/29219_pd-l1-ihc-22C3-pharmdx-gastric-interpretation-manual_us.pdf. Accessed November 2, 2018.

PD-L1 (SP142) Atezolizumab: IC Tumor-Infiltrating Immune Cells



VENTANA PD-L1 (SP142) Assay. http://reagent-catalog.roche.com/documents/PD-L1_SP142-UC-Brochure.pdf. Accessed December 8, 2018.

MSI-H Cancer

MSI or MMR testing

- IHC to test MMR or PCR to test MSI
- May use NGS in patients with metastatic disease who require genotyping of RAS and BRAF
- Recommended in all patients with personal history of CRC or rectal cancer
- Should be performed for all patients with metastatic disease
- The presence of BRAF V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome
- Stage II MSI-H patients may have good prognosis and do not benefit from fluorouracil-based adjuvant therapy

National Comprehensive Cancer Network. Colon Cancer (Version 4.2018). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Updated October 19, 2018. Accessed December 8, 2018.; Sargent DJ, et al. *J Clin Oncol.* 2010; 28(2):3219-26.

MSI-H Cancer

Pembrolizumab

- Adult and pediatric patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- Adult and pediatric patients with CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

Study	Population	# patients (total 149)
KN-016	CRC and other tumors	28 CRC 30 non-CRC
KN-164	CRC	61
KN-012	PD-L1-positive gastric, bladder, or triple-negative breast cancer	6
KN-028	PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5
KN-158	MSI-H/dMMR non-CRC	19

Keytruda [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018.

MSI-H Cancer

Pembrolizumab

Tumor	N	ORR
CRC	90	36%
Non- CRC	59	46%
Endometrial	14	36%
Biliary	11	27%
Gastric/GEJ	9	56%
Pancreatic	6	83%
Small intestinal	8	38%
Breast	2	PR, PR
Prostate	2	PR, SD
Esophageal, retroperitoneal	1 each	PR
SCLC	1	CR

Endpoint	n=149
ORR (95% CI)	39.6% (31.7, 49.9)
mDOR – months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

CR, complete response; PR, partial response; SD, stable disease; NR, not reached.

Keytruda [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018.; U.S. Food & Drug Administration. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560040.htm. Updated May 30, 2017. Accessed November 25, 2018.

MSI-H Cancer

Nivolumab

- Used as a single agent or in combination with ipilimumab
- Adult and pediatric (≥12 years old) patients with CRC that has progressed with a fluoropyrimidine, oxaliplatin, and irinotecan

CheckMate-142

Patients with prior treatment*	Nivolumab (n=53)	Nivolumab + ipilimumab (n=82)
ORR (95% CI)	28% (17,42)	46% (35,58)
≥6 months response duration	67%	89%
≥12 months response duration	40%	21%

*Fluoropyrimidine, oxaliplatin, and irinotecan

Tumor PD-L1 expression	ORR	Disease control ≥12 weeks
≥1% (n=26)	54%	77%
<1% (n=65)	52%	78%
Unknown (n=28)	61%	86%

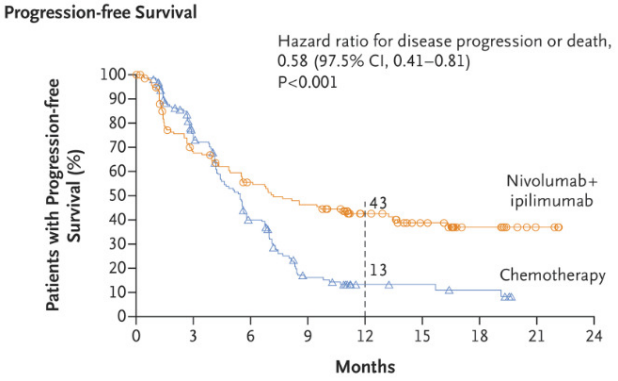
Responses were observed irrespective of tumor PD-L1 expression

Opdivo [prescribing information]. Bristol-Myers Squibb. Princeton, NJ; 2018.; Overman MJ, et al. *J Clin Oncol.* 2018;36(8):773-9.; Overman MJ, et al. *Lancet Oncol.* 2017;18(9):1182-91.

TMB – Emerging Biomarker

- No consensus on how to measure TMB
- FDA treatment not yet approved
- NCCN guidelines: nivolumab ± ipilimumab for high TMB (category 2A)
- CheckMate 227: multipart phase 3 trial in untreated metastatic NSCLC

Nivolumab + ipilimumab with high TMB (≥10 mutations per megabase)

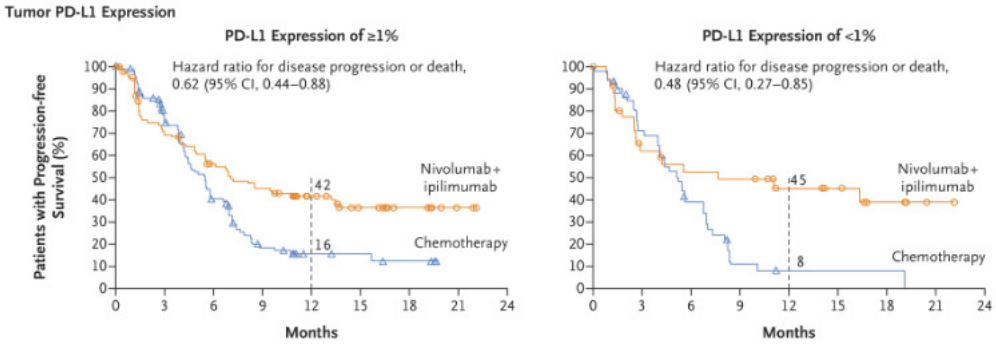


Hellmann MD, et al. *N Engl J Med.* 2018;378(22):2093-104.; National Comprehensive Cancer Network. NSCLC (Version 2.2019). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Published November 21, 2018. Accessed December 8, 2018.

TMB – Emerging Biomarker

Nivolumab + ipilimumab for TMB+

CheckMate 227: longer PFS, irrespective of PD-L1 expression level



Hellmann MD, et al. *N Engl J Med.* 2018;378(22):2093-104.

FDA Indications NOT Requiring Companion Tests

Treatment	Indication
Atezolizumab 1200 mg IV Q3W	Metastatic NSCLC • 1st line in combination with bevacizumab, paclitaxel, and carboplatin (without EGFR or ALK genomic tumor aberrations) • Progression during or after platinum-containing chemotherapy Locally advanced/metastatic urothelial carcinoma • 1st line for those not eligible for any platinum-containing (cisplatin/carboplatin) chemotherapy regardless of PD-L1 status • Progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy with platinum-containing chemotherapy
Avelumab 800 mg IV Q2W	Metastatic Merkel cell carcinoma Adults and pediatric patients (12 years and older) Urothelial carcinoma Progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy with platinum-containing chemotherapy
Cemiplimab 350 mg IV Q3W	Metastatic/locally advanced cutaneous SCC Not candidate for curative surgery or curative radiation
Durvalumab 10 mg/kg IV Q2W	Locally advanced/metastatic urothelial carcinoma Progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy with platinum-containing chemotherapy Unresectable stage III NSCLC Disease has not progressed after concurrent platinum-based chemotherapy and radiation therapy

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; SCC, squamous cell carcinoma.

Bavencio (avelumab) [prescribing information]. Rockland, MA: EMD Serono Inc; 2018.; Imfinzi (durvalumab) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.; Libtayo (cemiplimab-rwlc) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2018.; Tecentriq (atezolizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; 2018.

FDA Indications NOT Requiring Companion Tests

Treatment	Indication
Ipilimumab	Unresectable or metastatic melanoma 3 mg/kg IV Q3W x 4 doses Adjuvant cutaneous melanoma Undergone complete resection: 10 mg/kg IV Q3W x 4 doses, followed by 10 mg/kg Q12W up to 3 years
Nivolumab + ipilimumab	Untreated advanced RCC patients with intermediate or poor risk Unresectable or metastatic melanoma Nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg Q3W x 4 doses, then nivolumab 240 Q2W mg or 480 mg Q4W
Nivolumab 240 mg IV Q2W or 480 mg IV Q4W	Unresectable/metastatic melanoma BRAF V600 (WT or positive) As single agent Adjuvant melanoma Lymph node involvement or metastatic disease who have undergone complete resection up to 1 year Metastatic NSCLC Progression during or after platinum-based chemotherapy Metastatic SCLC Progression during or after platinum-based chemotherapy; only dose 240 mg IV Q2W Advanced RCC Received prior antiangiogenic therapy cHL Relapsed/progressed after HSCT and brentuximab vedotin or ≥3 lines of systemic therapy including autologous HSCT Recurrent/metastatic HNSCC Progression during or after platinum-based chemotherapy Locally advanced/metastatic urothelial carcinoma Progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy with platinum-containing chemotherapy HCC Previously treated with sorafenib

cHL, classical Hodgkin lymphoma; HNSCC, head and neck squamous cell carcinoma; HCC, hepatocellular carcinoma; HSCT, autologous hematopoietic stem cell transplantation; Q4W, every 4 weeks; RCC, renal cell carcinoma; SCLC, small cell lung cancer; WT, wild type.

Yervoy (ipilimumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2018.
Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2018.

FDA Indications NOT Requiring Companion Tests

Treatment	Indication
Pembrolizumab Adults: 200 mg IV Q3W [§]Pediatrics: 2 mg/kg (up to 200 mg) IV Q3W	Unresectable/metastatic melanoma Metastatic NSCLC • Nonsquamous: 1st line when combined with pemetrexed + platinum therapy (if no EGFR or ALK genomic aberrations) • Squamous: 1st line when combined with carboplatin +paclitaxel/nab-paclitaxel Recurrent/metastatic HNSCC Progression during or after platinum-based chemotherapy cHL[§] Refractory or who have relapsed after ≥3 lines of therapy PMBCL[§] Have relapsed after ≥2 prior lines of therapy; not recommended for those who require urgent cytoreductive therapy Urothelial carcinoma • 1st line not eligible for any platinum-containing (cisplatin/carboplatin) chemotherapy regardless of PD-L1 status • Progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy with platinum-containing chemotherapy HCC Previously treated with sorafenib

[§]Pediatric population

PMBCL, primary mediastinal large B-cell lymphoma.

Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018.

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Proteomic and Genomic Analysis Methods

Technology	IHC (protein)	PCR (DNA)	NGS (DNA)
Description	Detects antigens through specific antibodies in biological tissues	Detects mutations within short regions of DNA	Simultaneously detects genetic alterations across large regions of DNA
Biomarkers	dMMR	MSI	MSI-H
	PD-L1 expression (TPS, CPS, IC)		TMB
Sample requirements	FFPE block; 1 for each test required plus 3-4 additional unstained slides, positively charged (+) slides	FFPE specimens	FFPE samples, including core-needle biopsy specimens, fine-needle aspirates, and effusion cytologies
Turnaround time	1-2 days	5-14 days	10-14 days (depends on regional coverage, may take longer)
Estimated cost	$150 - $300	$1000 - $2000	$6000 - $8000

FFPE, formalin-fixed paraffin embedded.

Caris Life Sciences. CMI overview. https://www.carislifesciences.com/cmi-overview/. Accessed December 10, 2018.; Foundation Medicine. FoundationOne CDx™ technical information. https://assets.ctfassets.net/vhribv12lmne/6Rt6csmCPuaguuqmgi2iY8/e3a9b0456ed71a55d2e44803746 95d95/FoundationOne_CDx.pdf. Accessed December 10, 2018.; Foundation Medicine. FoundationOne CDx™ home page. https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx. Accessed December 10, 2018.; Frampton GM, et al. *Nat Biotechnol.* 2013;31(11):1023-31.; Gibson J, et al. *Clin Gastroenterol Hepatol.* 2014;12(2):171-6.; Ma W, et al. *J Hematol Onc.* 2016;9(1):47.; PhenoPath Laboratories. 3.1 General specimen requirements. http://phenopath.com/uploads/pdf/specimen-requirements.pdf. Accessed December 10, 2018.; Ramos-Vara JA, Miller MA. *Vet Pathol.* 2014;51(1):42-87.; Zeron-Medina J, et al. *Semin Onc.* 2015;42(6):775-87.

Pharmacist's Role

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- Appropriate companion diagnostic or genomic testing
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- Practical considerations among treatments
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Considerations Among Treatments

Treatment	IV duration (hours)	Estimated cost per dose AWP	Estimated cost for 3 months (12 weeks)
Nivolumab 480 mg Q4W	0.5	$15,103	$45,309
Infusion every 3 weeks			
Atezolizumab 1200 mg	1 → 0.5	$10,657	$42,628
Cemiplimab 350 mg	0.5	$10,920	$43,680
Pembrolizumab 200 mg	0.5	$11,327	$45,308
Nivolumab 240 mg + ipilimumab 80 mg*	1-2	$7,552 + $13,774 = $21,360	$85,440
Infusion every 2 weeks			
Avelumab 800 mg	1	$7,438	$44,628
Durvalumab 800 mg‡	1	$6,730	$40,380
Nivolumab 240 mg	0.5	$7,552	$45,312

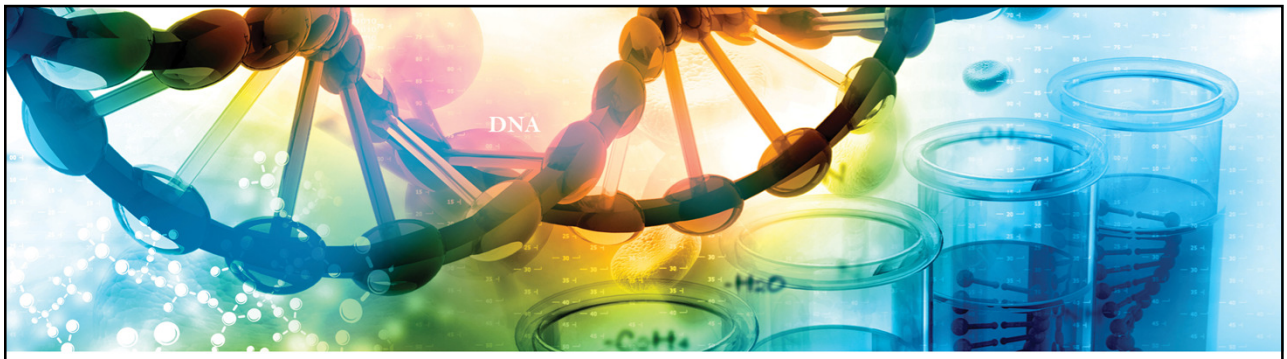
*Nivolumab 3 mg/kg + ipilimumab 1 mg/kg using 80 kg weight
‡Durvalumab 10 mg/kg using 80 kg weight

AWP, average wholesale price.

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed December 10, 2018.

Summary

- Biomarkers of checkpoint blockade are being developed, and several have already been approved
- Complexities exist with the use of biomarkers and better biomarkers are needed
- Pharmacists can help optimize ICI treatments by considering the appropriate indication, testing requirements, and cost of treatments



Question & Answer

How to Claim Credit

- **DO NOT CLOSE YOUR BROWSER**
  - You will be redirected to the post-test and evaluation
    - https://www.powerpak.com/course/preamble/117489
- Also, in about 45 minutes, you will receive an e-mail with a link to the post-test and evaluation
- You must complete the post-test and evaluation in order to earn credit
- Your credit will automatically be uploaded to CPE Monitor

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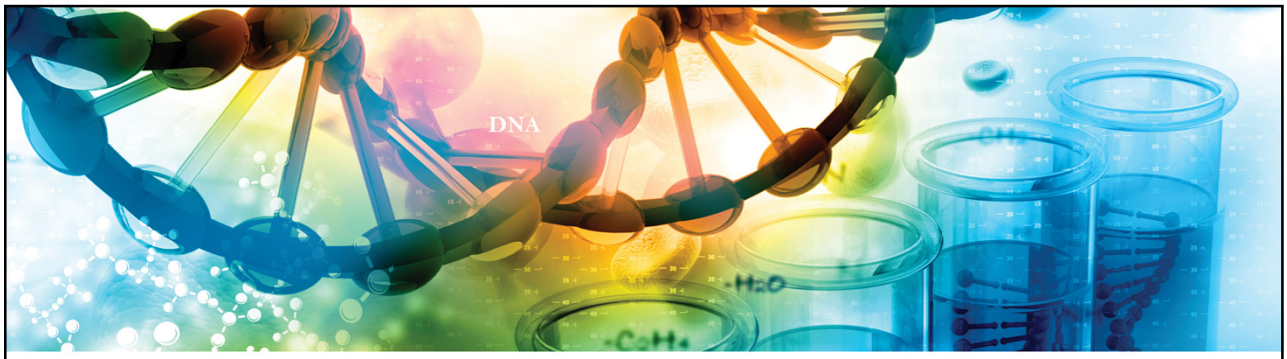

Thank you!