Employing Immuno-Oncology Biomarkers to Guide Treatment Decision-Making

Managed Care and Specialty Pharmacists Perspectives

ASEMBIA CE Symposium

April 29, 2019

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by educational grants from Bristol-Myers Squibb and Merck & Co., LLC.

Accreditation

Postgraduate Healthcare Education, LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

UAN: 0430-0000-19-019-L01-P
Credits: 1.5 hour (0.15 CEU)
Type of Activity: Application

Faculty

Lisa Davis, PharmD, FCCP, BCPS, BCOP

Professor, Pharmacy Practice and Science
University of Arizona College of Pharmacy
Oncology Clinical Pharmacist
Banner University Medical Center
Tucson, AZ

Lisa Davis is a professor in the Department of Pharmacy Practice and Science at the University of Arizona College of Pharmacy. Her practice is with the Early Phase Clinical Trials Program at the University of Arizona Cancer Center, where she is also a member of the Cancer Prevention and Control Research Program.
Lisa received her Bachelor of Science degree in Pharmacy at the University of Arizona and her Doctor of Pharmacy from the University of Kentucky. Her research focuses on drug development, drug resistance, and the influence of genomics and other factors that contribute to variability in drug disposition and patient outcomes in oncology. Lisa is board certified in pharmacotherapy and oncology pharmacy.

Faculty

Matthew Farber, MA

Senior Director, Patient Care and Advocacy:
Oncology, Fertility, and Multiple Sclerosis
Walgreen Company

Matt Farber serves as Senior Director, Patient Care and Advocacy for Oncology, Fertility, and Multiple Sclerosis for Walgreens and is responsible for the development and implementation of Walgreens national oncology, fertility, and multiple sclerosis strategies. Matt also works with external partners such as the Leukemia and Lymphoma Society and the Oncology Nursing Society. Prior to joining Walgreens, Matt worked for almost 10 years with the Association of Community Cancer Centers. Matt earned a Bachelor of Arts degree in International Affairs and a Master's degree in Political Management, both from The George Washington University.

Learning Objectives

- **Describe** the potential biomarkers being examined to predict response to immunotherapy
- **Compare** the treatment options for biomarker-based immunotherapy management for formulary inclusion
- **Analyze** the costs and benefits of utilizing biomarkers in determining immunotherapy treatment
- **Describe** the data that should be considered when completing the formulary review process for biomarker and immunotherapy options

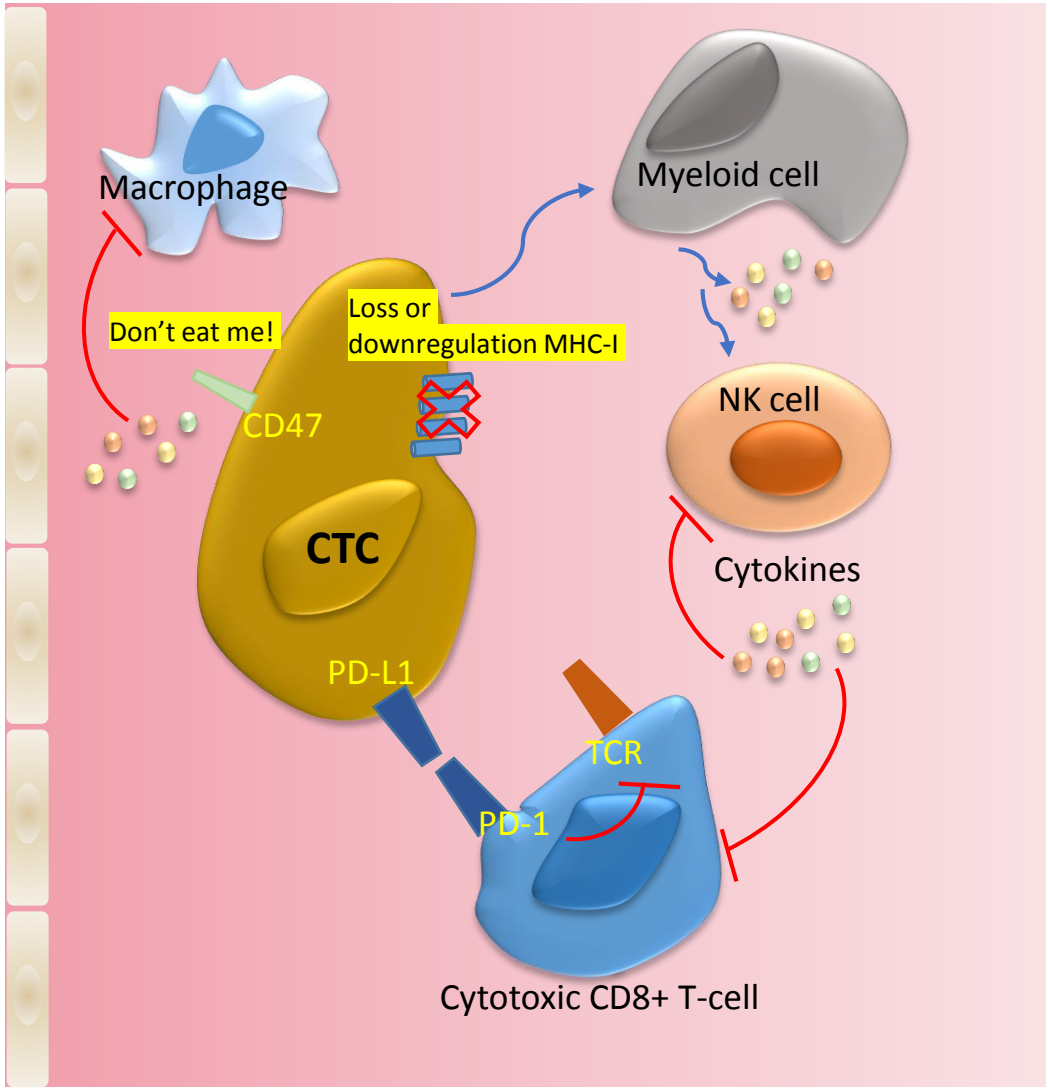
Malignant Cells Evoke an Immune Response

- The immune response is capable of destroying the tumor
- T-cells (especially CD8+) mediate the most critical part of controlling malignant cells
  - Activated by antigen presented by Class I MHC molecules
  - Although CD8+ cells are cytotoxic, continued stimulation by antigen renders exhaustion
  - Continued stimulation also induces expression of molecules similar to those expressed by CD4+, CD25+, and regulatory T-cells (Tregs)
    - Cytotoxic T-lymphocyte associated protein-4 (CTLA-4)
    - Programmed cell death protein 1 (PD-1)
    - Programmed death-ligand 1 (PD-L1)
    - T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT)
    - Lymphocyte activation gene-3 (LAG-3)
    - T-cell immunoglobulin and mucin domain-3 (TIM-3)
  - CD8+ effector T-cells bind to these respective ligands, thereby inhibiting the immune response or causing T-cell death

Singh P, et al. *Trans Med Comm.* 2019;4:2.

MHC, major histocompatibility complex.

Tumor Cells Escape Immune Surveillance



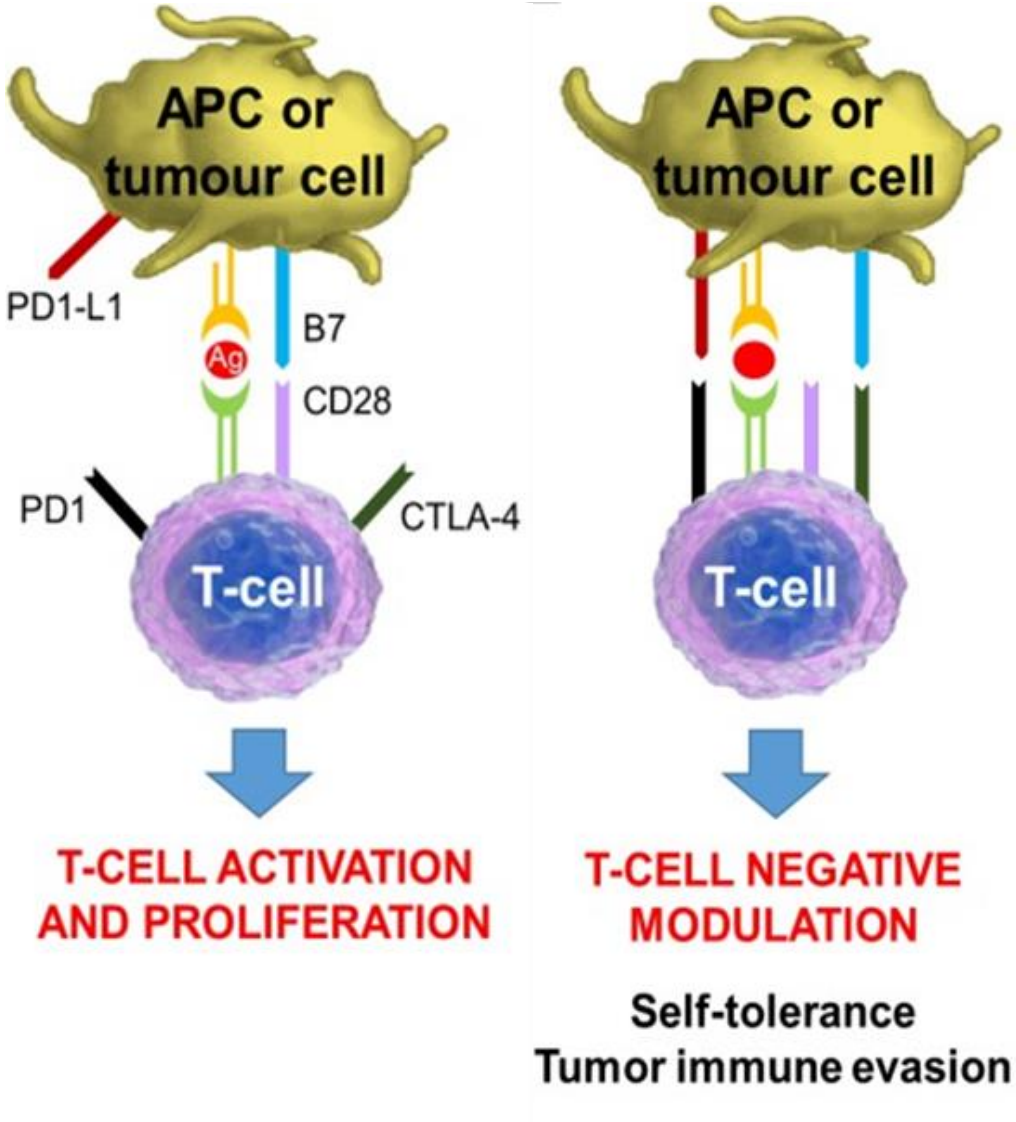
- Immunosuppressed primary tumor environment enables tumor cell to escape into peripheral blood
- Interactions between tumor and immune cells facilitate tumor cell evasion from MHC-I-mediated recognition by natural killer (NK) and tumor cells
- Anti- and pro-inflammatory cytokines
- Upregulated PD-L1
- Presentation of antiphagocytic CD47 receptor and altered expression of other proteins, ligands, and receptors

Mohme M, et al. *Nat Rev Clin Oncol*. 2017;14(3):155-67.

MHC-I, Major Histocompatibility Complex class I; CTC, circulating tumor cells; TCR, T-cell receptor.

Immune Checkpoints

- T-cells drive elimination of cancer cells
- Immune checkpoints minimize collateral tissue damage from uncontrolled immune activation
  - Cancer cells exploit this mechanism
- CTLA-4 induced upon initial response to antigen
- Activated T-cells upregulate PD-1 and inflammatory signals in tissue induce PD-L1 expression

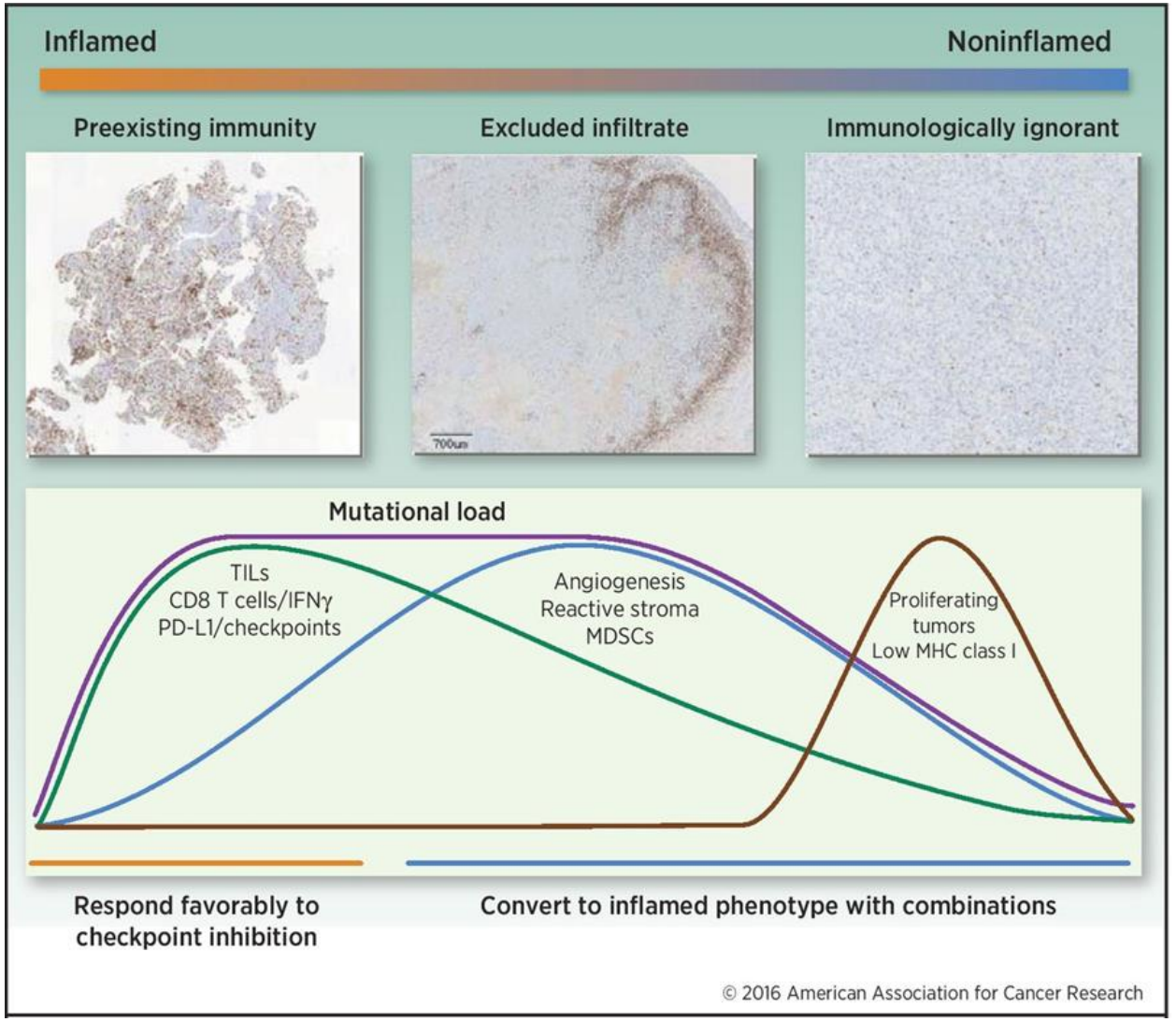


Prete A, Salvatori R. Hypophysitis. https://www.ncbi.nlm.nih.gov/books/NBK519842/.

APC, antigen-presenting cell.

Initial Inflamed Tumors Become Non-Inflamed

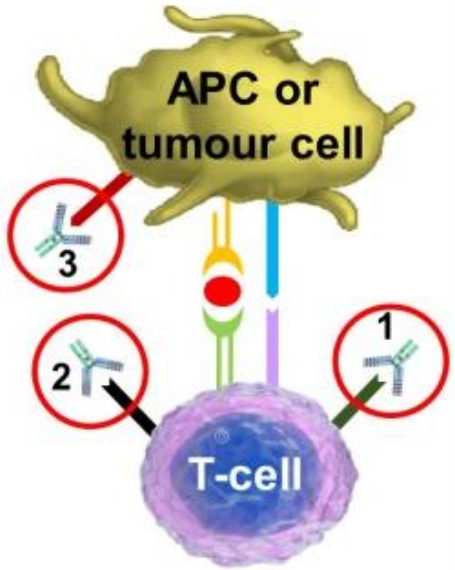
- Tumors with pre-existing immunity
  - Abundant TILs
  - Dense CD8+ T-cell infiltrate
  - Expression of checkpoint proteins
  - High mutational burden
- Despite high mutational burden, T-cell infiltration into tumors and activation become suppressed
- Non-inflamed tumors contain low infiltration of T-cells with highly proliferating tumor cells



Hegde PS, et al. *Clin Cancer Res*. 2016;22(8):1865-74.

TILs, tumor-infiltrating lymphocytes.

Immune Checkpoint Inhibitors



1: mAbs targeting CTLA-4
2: mAbs targeting PD1
3: mAbs targeting PD1-L1

Drug classification	Product
PD-1 inhibitors	Nivolumab (Opdivo) Pembrolizumab (Keytruda) Cemiplimab-rwlc (Libtayo)
PD-L1 inhibitors	Atezolizumab (Tecentriq) Avelumab (Bavencio) Durvalumab (Imfinzi)
CTLA-4 inhibitor	Ipilimumab (Yervoy)

Prete A, Salvatori R. Hypophysitis. https://www.ncbi.nlm.nih.gov/books/NBK519842/.

mAbs, monoclonal antibodies.

Tumor Mutations and Neoantigens

- Genetic alterations in tumor cells can give rise to neoantigens
  - Unique to the tumor and not present on normal cells
- A single DNA mutation can result in multiple neoantigens
  - Potentially recognizable by T-cells
- Tumors with a greater mutational load could possess more neoantigens and be more easily recognized by immune system
- High tumor mutation burden (TMB) correlates with an increased number of neoantigens and is associated with tumor infiltration of cytotoxic T-cells
- Tumors with DNA mismatch repair (MMR) deficiency (dMMR) and alterations in DNA repeat sequences (microsatellites) have high mutational loads and are genomically unstable

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

Biomarkers for Immunotherapy

- Tumor immunogenicity
  - TMB
  - dMMR
  - Microsatellite instability (MSI)
- Inflamed tumor microenvironment
  - PD-L1

Tumor Mutation Burden

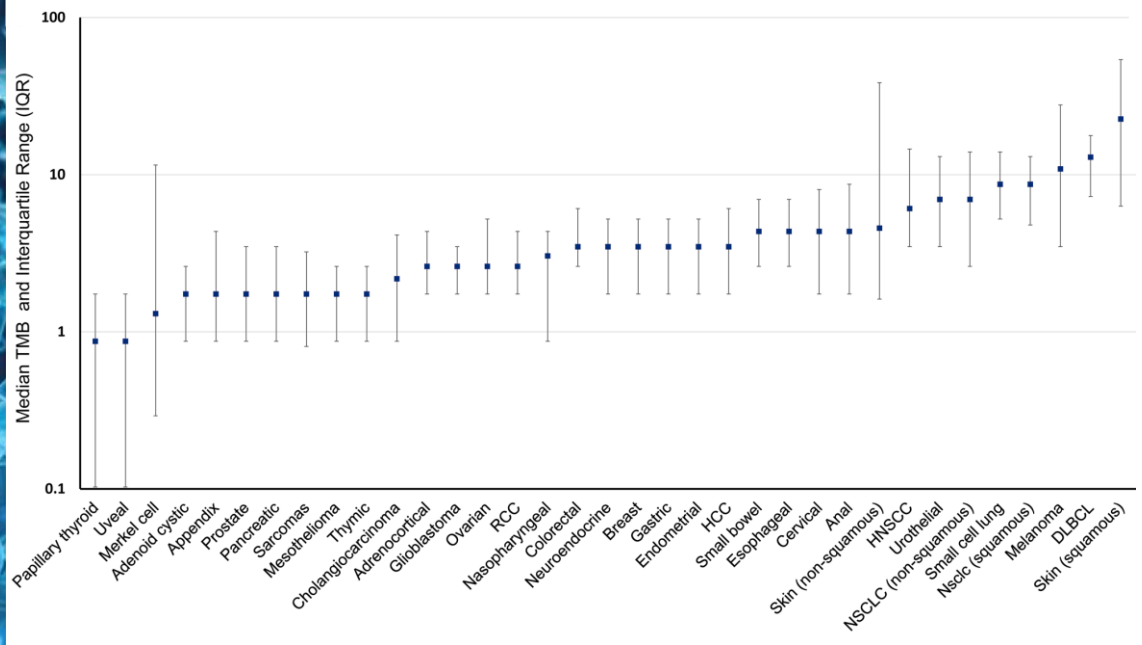
- Measured by DNA sequencing
  - Number of nonsynonymous mutations per megabase sequenced
- Cancers with the highest median mutation loads demonstrated response rates to anti-PD-1/PD-L1 therapies exceeding 15%
  - NSCLC, SCCHN, gastric, bladder, melanoma
  - Melanoma carries one of the highest mutational loads among cancers and has a response rate of 30%-40%
- Response rates among cancers with lower median mutational loads are generally low
  - Prostate, pancreas
- Hodgkin's lymphoma is highly sensitive to PD-1 blockade, yet carries virtually no mutation
- Significant overlap in mutation range between responders and non-responders

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

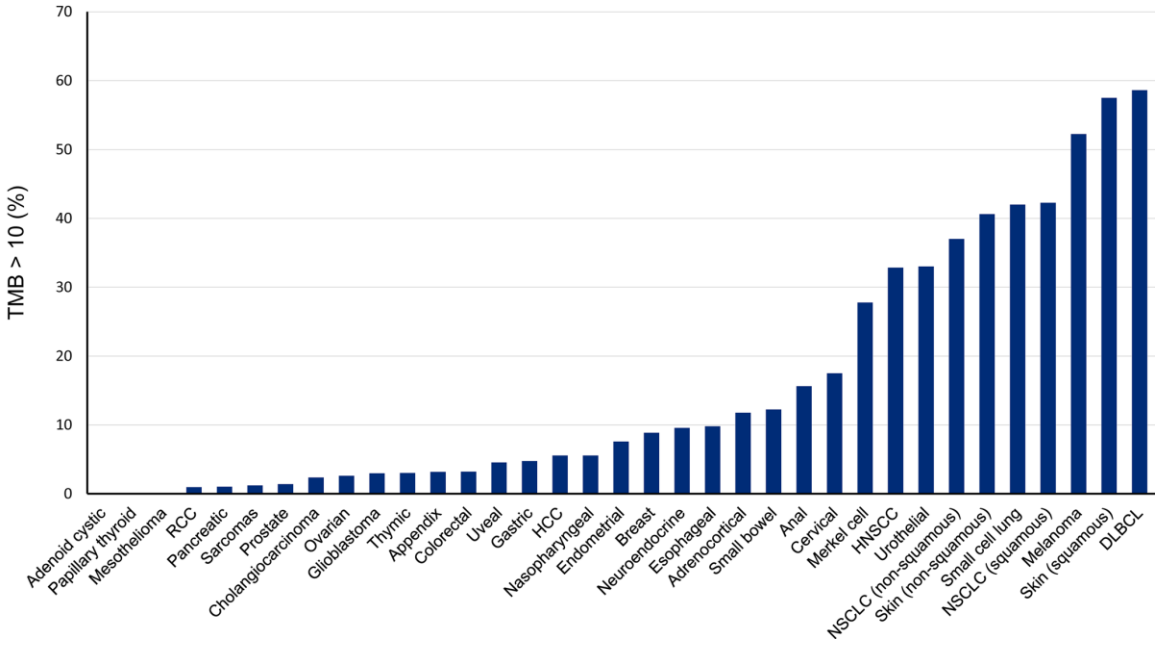
NSCLC, non-small cell lung cancer; SCCHN, squamous cell cancer of head and neck.

TMB Across Tumor Types

Median TMB and interquartile range

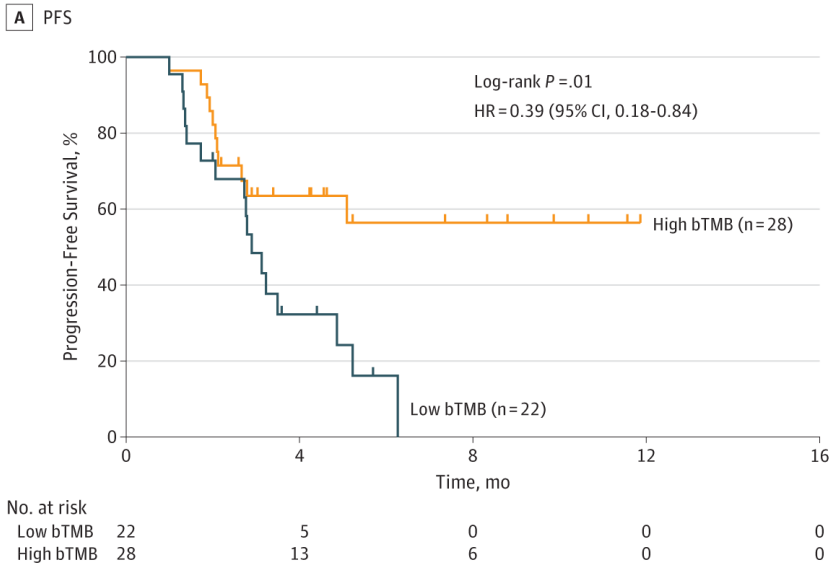


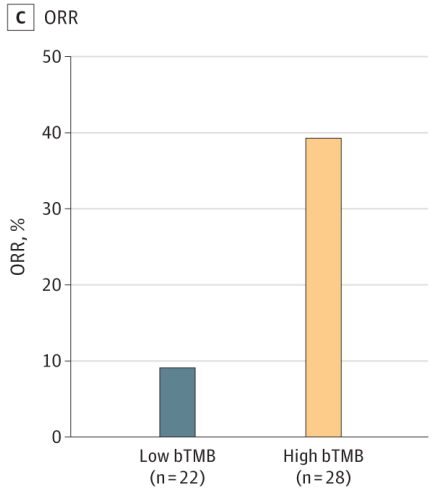
Percentage of tumor samples with TMB >10 Mb

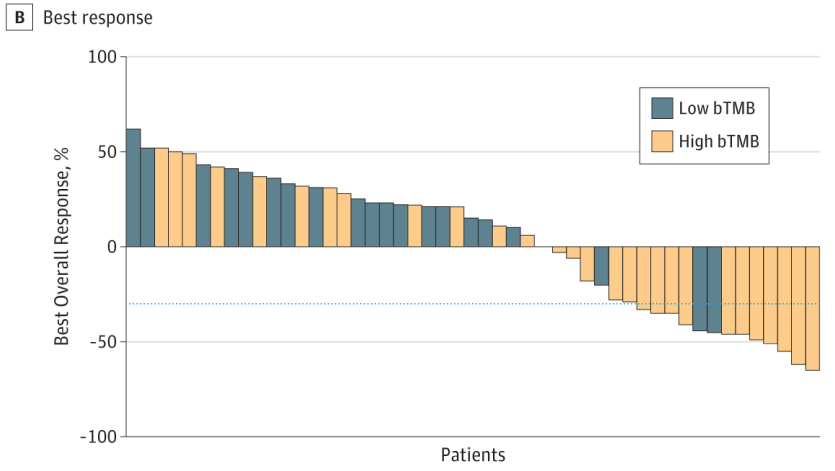


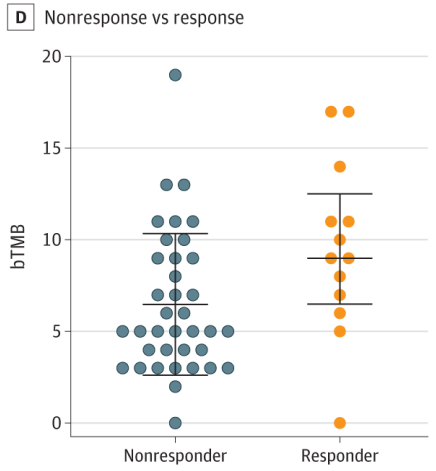
Yarchoan M, et al. *JCI Insight*. 2019;4(6). pii:126908.

TMB and Immunotherapy Response in NSCLC









A: Progression-free survival (PFS) by blood TMB status

B: Waterfall plot of observed best response from anti-PD-1 and anti-PD-L1 checkpoint inhibitors

C: Comparison of objective response rates (ORRs) between the high and low blood TMB groups (P = 0.02)

D: Comparison of blood TMB level between non-response and response groups (P =0 .02)

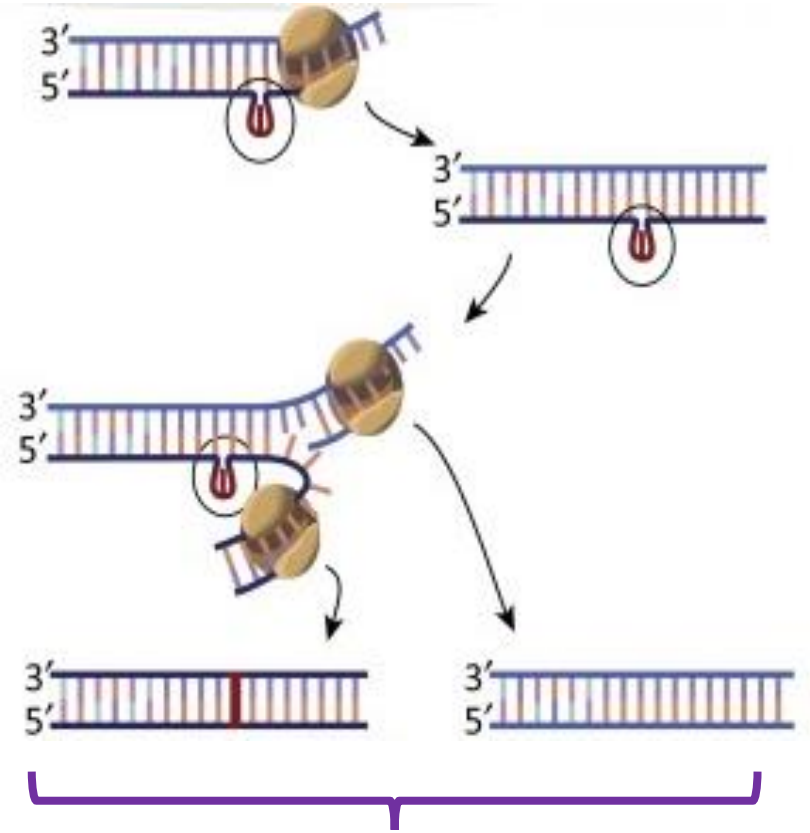
Wang Z, et al. *JAMA Oncol.* 2019. doi: 10.1001/jamaoncol.2018.7098.

dMMR Gene Deficiency

- Defect in 1 or more genes that encode a component of the DNA MMR complex
  - Detects and repairs DNA replication errors produced during the S phase
- Errors more likely in long, repetitive DNA sequences (microsatellites)
- dMMR can be inherited -
  - Familial cancer syndrome termed Lynch syndrome
- Genes deleted, mutated, or epigenetically silenced, predisposing patients to sporadic cancers such as gastric, prostate, duodenal, and endometrial, in addition to colorectal cancer (CRC)
- Determined through DNA sequencing to identify mutation in MMR gene or through absence of an MMR protein using immunohistochemistry (IHC)
- Approximately 4% of adult solid tumors are MMR deficient
  - Present in 15%-17% of CRCs overall, but lower rate (4%) in metastatic disease

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

dMMR Leads to MSI-H Tumors



Increased rate of tumor mutations

- Inactivation of DNA mismatch repair genes leads to absent or dysfunctional MMR protein → dMMR

  Unrepaired DNA replication errors accumulate, causing abnormal lengths of microsatellite repeats in DNA sequences across the genome → MSI

  MSI-high (MSI-H) tumors harbor mutations in at least 2 of 5 specific microsatellites tested

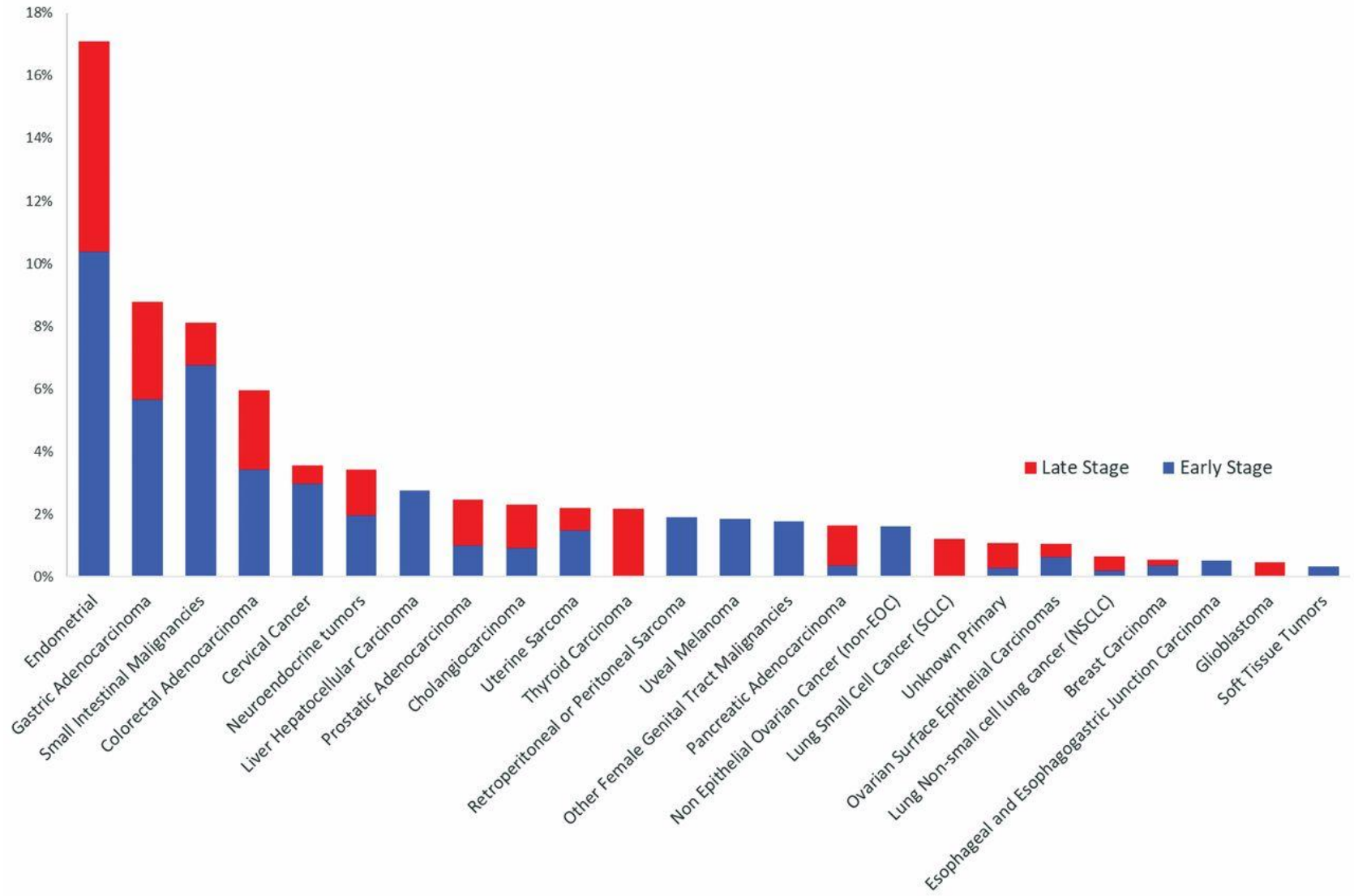
  dMMR tumors are hypermutated with accumulated nucleotide base mismatches, indels, and frameshift mutations that can generate immunogenic neoantigens
- Number of mutations in dMMR tumors are 10- to 100-fold higher than in other malignancies

Li SKH, Martin A. *Trends Mol Med*. 2016;22(4):274-89.

Determining MSI Status

- Polymerase chain reaction (PCR): amplifies selected microsatellites from healthy and tumor tissue DNA
  - An automated sequencer or gel electrophoresis is used to analyze fragment sizes
  - A panel of 5 microsatellites is used
    - If 2 or more of the 5 markers show instability (e.g., insertion/deletion mutations) in ≥30% of the repeats tested, the tumor is categorized as MSI-H
- IHC: identifies loss or absence of at least 1 of the MMR proteins (MLH1, MSH2, MSH6, and PMS2)
  - Proteins are expressed in normal tissue and show positive nuclear staining
- Next-generation sequencing (NGS): detects mutations in areas of selected microsatellites

DNA Mismatch Repair Deficiency Across 12,019 Solid Tumors



Le DT, et al. *Science.* 2017;357(6349):409-13.

dMMR/MSI as Agnostic Indication for Immunotherapy

- KEYNOTE-016: first prospective evaluation of dMMR/MSI-H as a predictive biomarker for PD-1 inhibition with pembrolizumab
  - 11 patients with dMMR CRC, 21 with proficient MMR (pMMR) CRC, and 9 with dMMR non-CRC
  - ORR 40% and 71% in dMMR CRC and dMMR non-CRC versus 0% in pMMR CRC
  - PFS (updated in 2017): 78%, 67%, and 11%
- FDA granted accelerated approval to pembrolizumab for adult and pediatric refractory dMMR/MSI-H tumors on the basis of data from 5 clinical trials of 149 patients
  - ORR was 36% in CRC and 46% in non-CRC patients
  - Among responders, 78% of responses were for 6+ months

Le DT, et al. *Science.* 2017;357(6349):409-13.;
Overman MJ, et al. *Lancet Oncol.* 2017;18(9):1182-91.;
Overman MJ, et al. *J Clin Oncol.* 2018;36(8):773-9.

FDA, United States Food & Drug Administration.

Pembrolizumab Activity Against Multiple MSI-H/dMMR Solid Tumors

	N	ORR		DOR range (months)
		n (%)	95% CI	
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

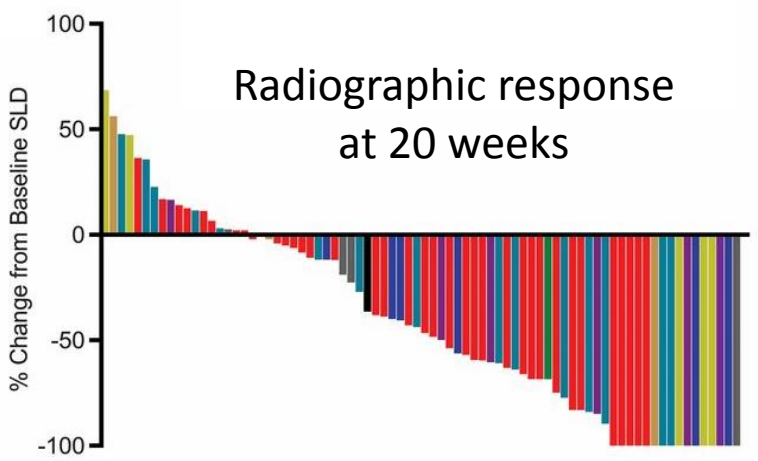
CR, complete response;
DOR, duration of response;
GE, gastroesophageal;
NE, not evaluable;
PD, progressive disease;
PR, partial response;
SD, stable disease.

ORR = 40%, CR = 7%

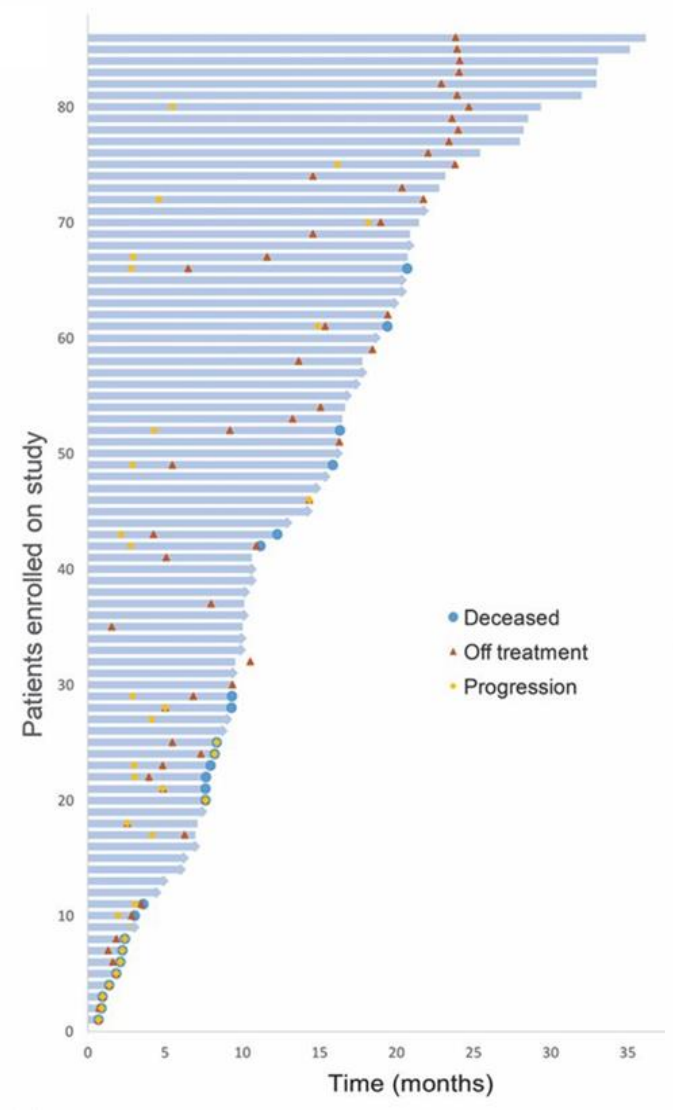
Summary from 5 trials – All patients had 1+ prior regimens

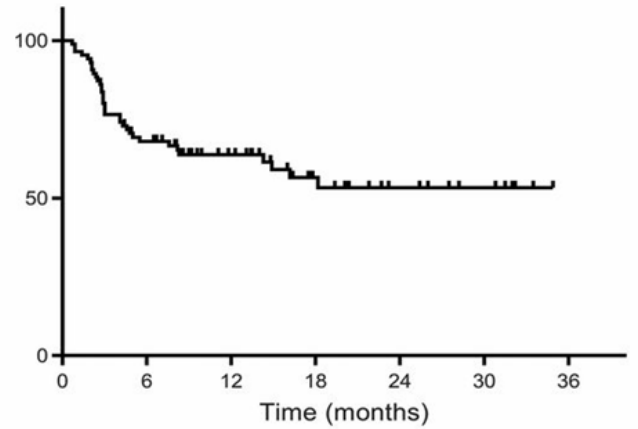
Pembrolizumab [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 2019.

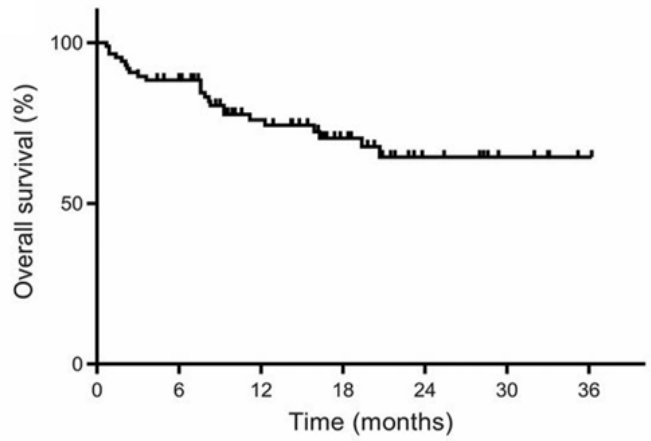
Pembrolizumab Activity in dMMR Tumors



- Phase 2 trial
- 86 patients, 12 tumor types
- At least 1 prior therapy with PD
- Evidence of dMMR by PCR or IHC
- Germline sequencing of *MSH2*, *MSH6*, *PMS2*, *MLH1* showed Lynch syndrome in 32 cases (48%)
- ORR 53%; CR 21%

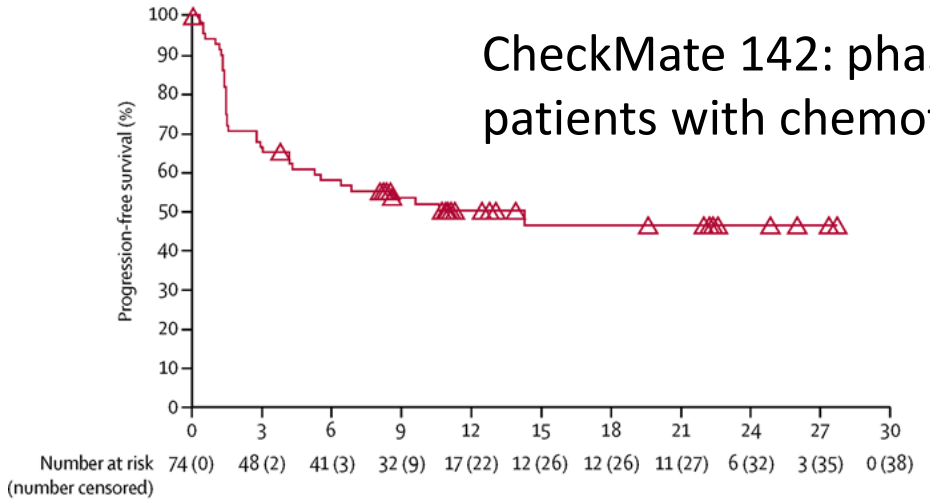


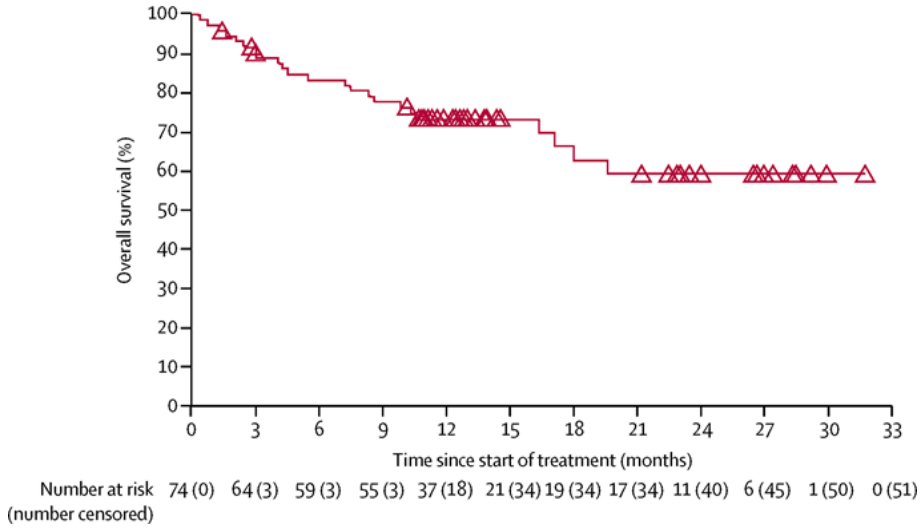




Le DT, et al. *Science.* 2017;357(6349):409-13.

Nivolumab in dMMR/MSI-H CRC





CheckMate 142: phase 2 trial of nivolumab or nivolumab plus ipilimumab in patients with chemotherapy-refractory dMMR/MSI-H CRC

- ORR 31% with monotherapy and sustained disease control (≥12 weeks) in 69% of patients
- PFS was 54% at 9 months and 50% at 12 months, with OS of 78% and 73% and 9 and 12 months, respectively
- At median follow-up of 21 months, ORR was 34% with 9% CR; median PFS was 6.6 months, but median OS not reached

Overman MJ, et al. *Lancet Oncol.* 2017;18(9):1182-91; Overman MJ, et al. 2018 Gastrointestinal Cancers Symposium; January 18-20, 2018; San Francisco, CA. Abstract 554

Programmed Death-Ligand 1

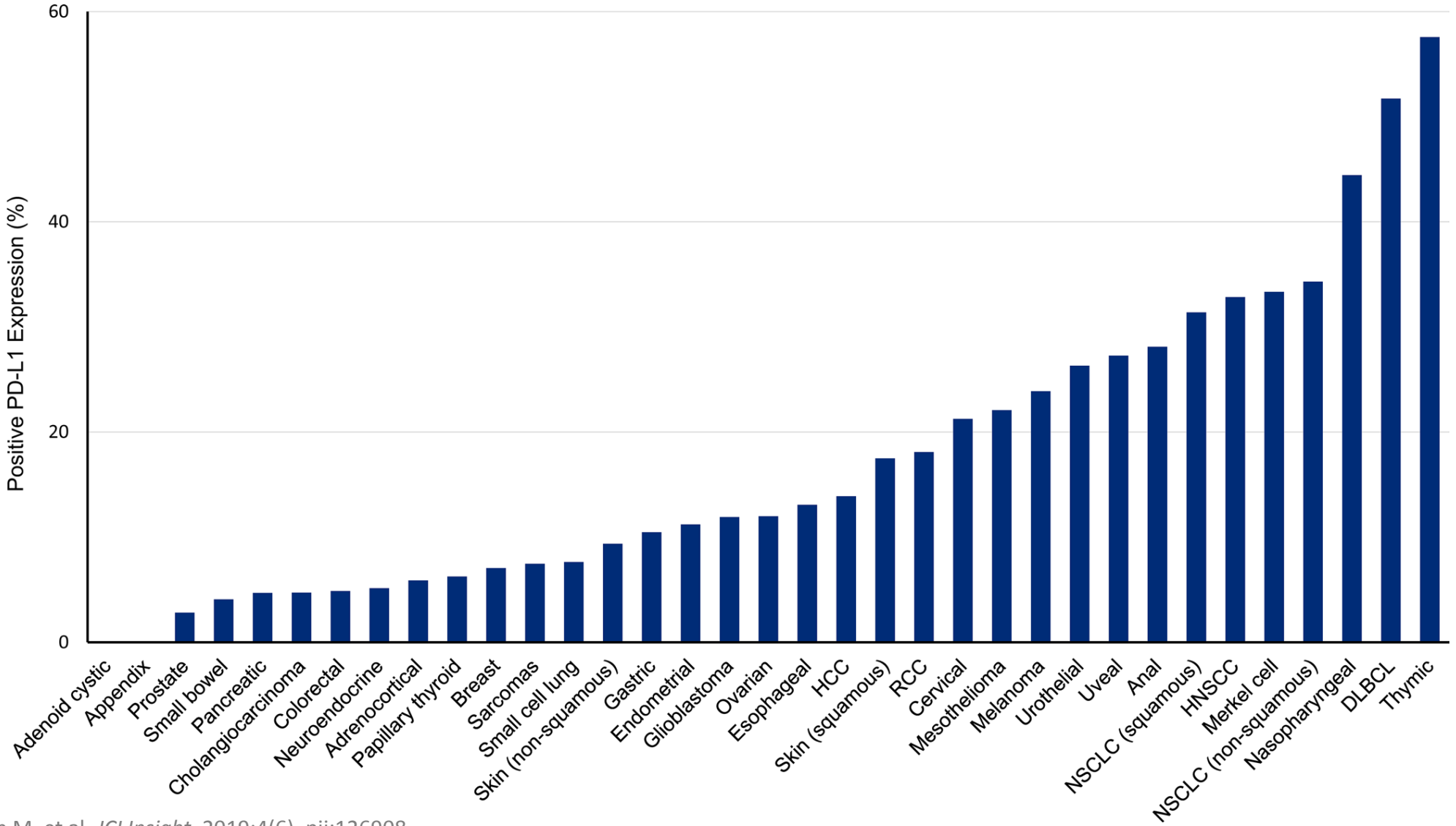
- Expressed on tumor cells and tumor-infiltrating immune cells
- Expression is temporally and spatially heterogeneous
  - Induced by proinflammatory cytokines and is, therefore, dynamic
  - In a study in renal cancer, PD-L1 expression was inconsistent in 20.8% of patients when sampled at 2 different sites
- Imperfect sensitivity and specificity
  - Not all patients with PD-L1-positive tumors respond to PD-1 inhibition
  - Patients with PD-L1-negative tumors consistently respond to PD-1 inhibition
- Tumor proportion score (TPS): proportion of viable tumor cells that show partial or complete membrane staining at any intensity
- Combined positive score (CPS): includes PD-L1 expression for tumor and immune cells

Patel SP, Kurzrock R. *Mol Cancer Ther.* 2015;14(4):847-56.; Zhang M, et al. *Front Med*. 2018;13(1):32-44.

Biomarkers for FDA-Approved Indications

Malignancy	Biomarker	Product
Cervical cancer	PD-L1 CPS ≥1	Pembrolizumab
CRC	MSI-H or dMMR tumors	Nivolumab Nivolumab + ipilimumab Pembrolizumab
Gastric cancer	PD-L1 CPS ≥1	Pembrolizumab
NSCLC	High PD-1 expression (TPS) ≥50% (first-line) PD-L1 expression (TPS) ≥1%	Pembrolizumab
Triple-negative breast cancer (TNBC)	PD-L1 expression ≥1%	Atezolizumab + paclitaxel protein-bound
Urothelial carcinoma	PD-L1 expression ≥5% PD-L1 CPS ≥10	Atezolizumab Pembrolizumab
MSI-H cancer	MSI-H or dMMR tumors	Pembrolizumab

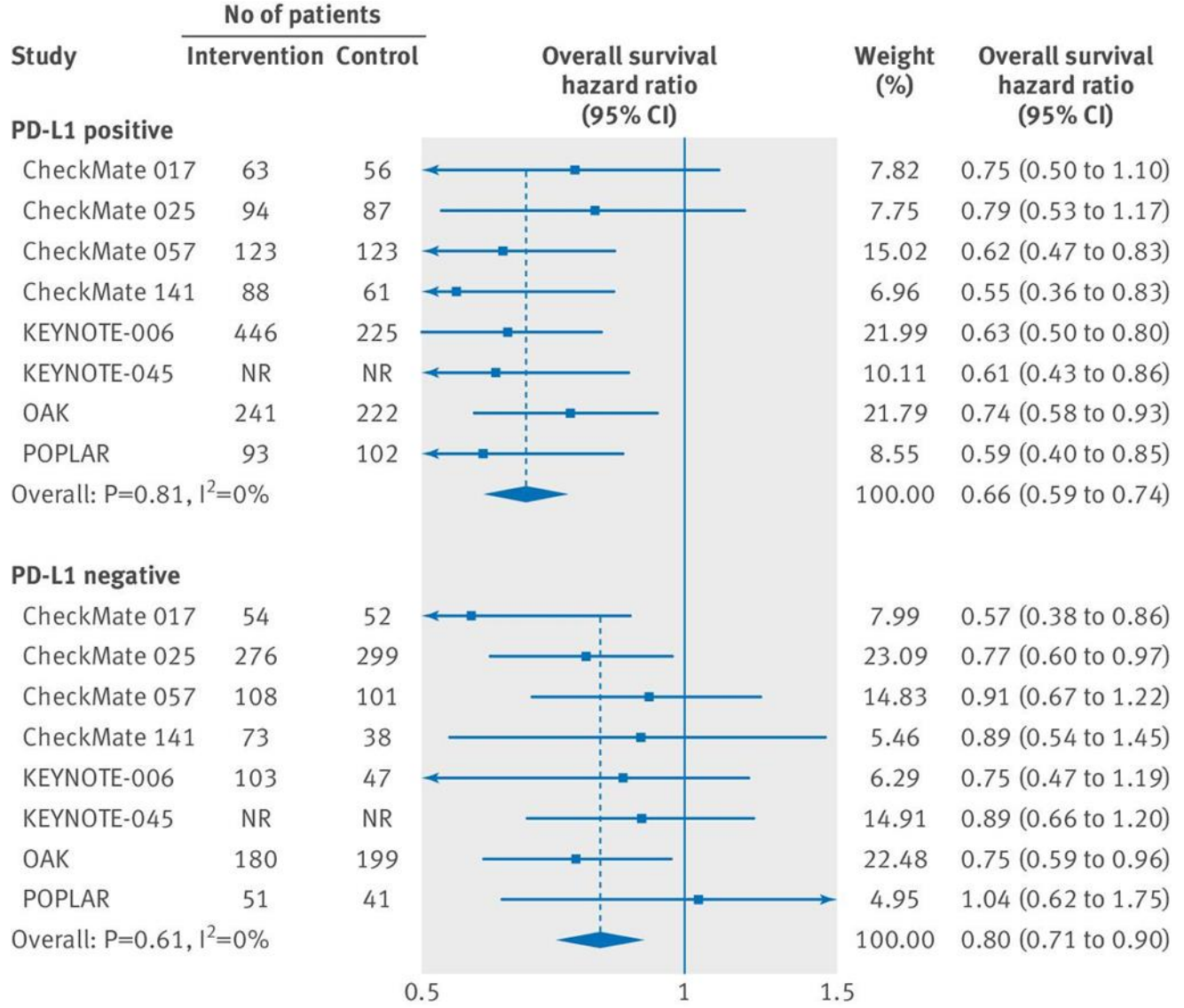
PD-L1 Expression Across Major Tumor Types



Yarchoan M, et al. *JCI Insight*. 2019;4(6). pii:126908.

PD-L1 Expression and Response to PD-1 Inhibition

- Analyzed in a meta-analysis including 4174 patients with advanced or metastatic cancer from 8 randomized controlled trials
- Compared to conventional therapies, PD-1 inhibition significantly prolonged OS in patients who were PD-L1 positive (HR 0.66, 0.59-0.74) and PD-L1 negative (HR 0.80, 0.71 to 0.90)
- Magnitude of benefit greater in patients with PD-L1-positive tumors



Shen X, Zhao B. *BMJ*. 2018;362:k3529

Which Test to Order?

- Pembrolizumab

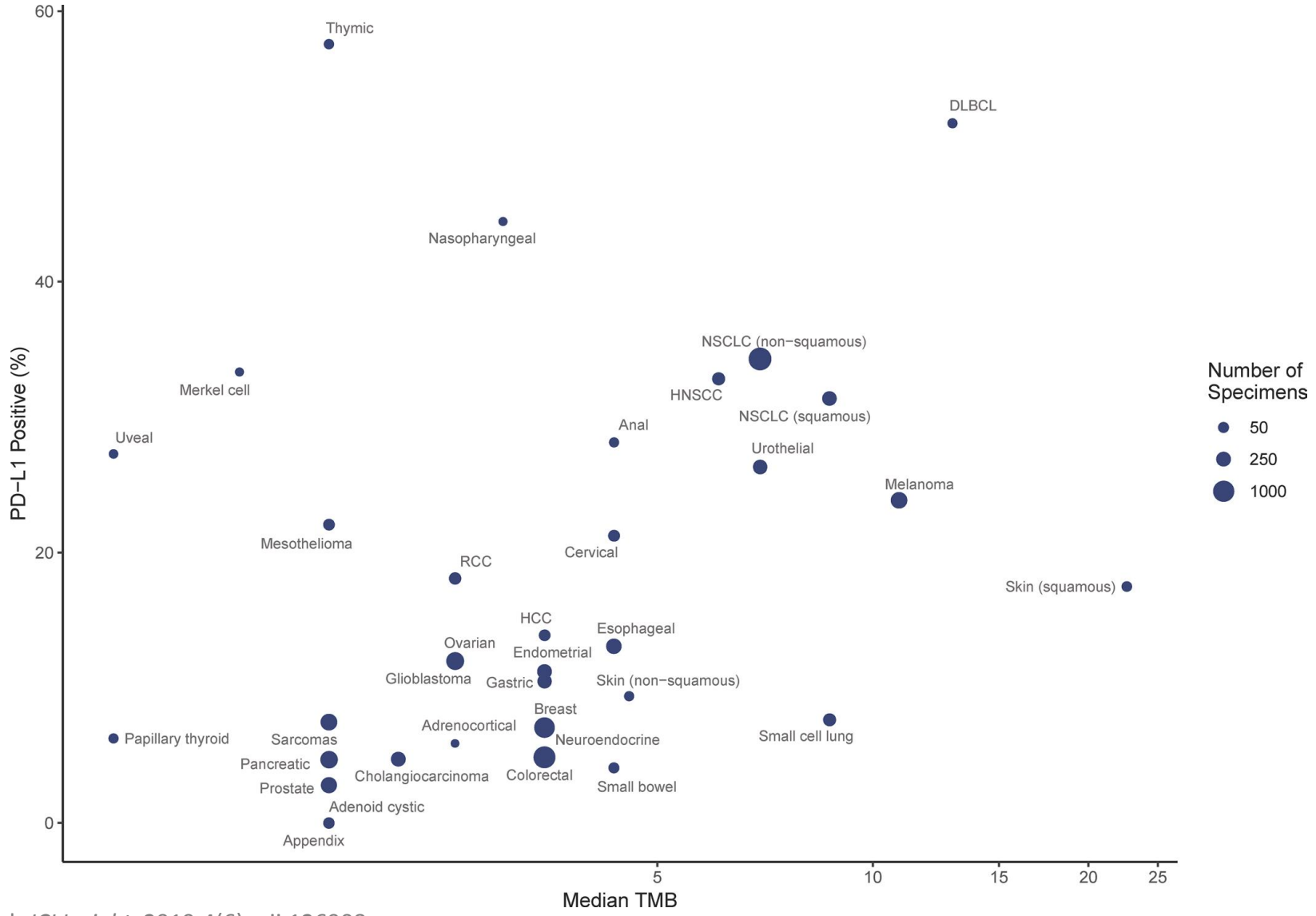
  Dako PD-L1 IHC 22C3 PharmDx Assay approved as a companion diagnostic to aid in identifying NSCLC patients for treatment with pembrolizumab as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.

- Nivolumab

  Dako PD-L1 IHC 28-8 PharmDx Assay in non-squamous NSLC may be associated with enhanced survival from nivolumab. Tumors considered as having PD-L1 expression had ≥ 1% of tumor cells expressing PD-L1.

http://www.fda.gov/CompanionDiagnostics

PD-L1 and TMB – Independent Biomarkers Across Tumor Types (N=9887)



Yarchoan M, et al. *JCI Insight*. 2019;4(6). pii:126908.

Could TMB Become Another Agnostic Indication for Immunotherapy?

- 240 patients with NSCLC treated with anti-PD-1/PD-L1 therapy were profiled using targeted NGS (MSK-IMPACT Assay) and evaluated for response
  - TMB and gene alterations were compared among patients who experienced a durable clinical benefit (PR/SD >6 months) and those with no durable benefit
  - TMB using targeted NGS strongly correlated to TMB as determined by whole exome sequencing was associated with durable clinical benefit, was independent of PD-L1 expression, and had similar predictive capacity
- In a separate study of 454 patients treated with atezolizumab, TMB was assessed using a 315-gene NGS panel
  - ORR, PFS, and OS were all improved significantly in patients classified as having a high TMB
- Prospective studies of TMB as a predictive biomarker for immunotherapy are underway

Rizvi H, et al. *J Clin Oncol*. 2018;36(7):633-41.; Steuer CE, Ramalingam SS. *J Clin Oncol*. 2018;36(7):631-2.

TMB May Not Correlate with Outcomes with Targeted Therapies

- The impact of TMB on response to targeted therapies is unknown
- 153 patients with *EGFR*-mutant lung cancer receiving treatment with 1st/2nd-generation EGFR tyrosine kinase inhibitors (TKIs) underwent pre- and post-treatment NGS sequencing (MSK-IMPACT assay)
  - TMB lower in *EGFR*-mutant disease than in wild-type
  - Time to treatment discontinuation shorter in patients with highest TMB
    - Median OS also shorter (21 vs. 37 and 41 months in high, intermediate, and low tertiles)
  - TMB increased in post-progression samples (with disease resistance)
  - In contrast to immunotherapy, TMB was negatively associated with clinical outcomes in patients with EGFR-mutant lung cancer receiving EGFR TKIs
- Majority of mutations are generated by tumor-specific mutations, not typically known oncogene mutations
  - Therefore, driver mutations may not be highly immunogenic
- TMB may be an indirect marker of different underlying biological mechanisms

Offin M, et al. *Clin Cancer Res*. 2019;25(3):1063-9.

EGFR, epidermal growth factor receptor.

Next-Generation Sequencing

- Targeted NGS for genomic tumor profiling is increasingly routine
- TMB
  - Cancer gene panel NGS sequencing less expensive than whole exome sequencing
  - Circulating tumor DNA in blood potential alternative to tissue
- MSI
  - Applicable among tumor types
  - Does not require normal tissue
- PD-L1 expression
  - Variability in IHC scoring methods has contributed to confounding results in interpreting PD-L1 expression values across tumor types and clinical trials
  - IHC assays use different antibody clones, staining platforms, and scoring systems
  - NGS to assess PD-L1 mRNA by RNA-seq correlates with IHC testing and has the advantage of being able to be standardized

Conroy JM, et al. *J Immunother Cancer*. 2019;7(1):18.; Vanderwalde A, et al. *Cancer Med*. 2018;7(3):746-56.

Case: Tumor Molecular Profile – Metastatic CRC

Biomarker	Method	Result
Lineage-relevant biomarkers		
MSI	FA	High
	NGS	High
Mismatch repair status*		Deficient
MLH1	IHC	Positive | 2+, 90%
MSH2	IHC	Negative | 0, 100%
MSH6	IHC	Negative | 0, 100%
PMS2	IHC	Positive | 1+, 90%
Total mutational load		High | 91 mutations/Mb
KRAS	NGS	Mutation not detected
NRAS	NGS	Mutation not detected
BRAF	NGS	Mutation not detected

Biomarker	Method	Result
Lineage-relevant biomarkers		
PIK3CA	NGS	Mutated, pathogenic
		Exon 21 | p.H1047R
ERBB2 (Her2/Neu)	NGS	Amplification not detected
PTEN	IHC	Positive | 1+, 90%
TS	IHC	Positive | 2+, 20%
TOPO1	IHC	Positive | 2+, 90%
ERCC1	IHC	Negative | 1+, 10%
Other notable biomarker results		
PD-1	IHC	Negative | 0/HPF
PD-L1	IHC	Negative | 0, 100%

FA, fragment analysis; HPF, high power fields.

Mismatch repair status is determined by the presence or absence of the repair proteins MLH1, MSH2, MSH6, and PMS2 by IHC.
If any of these IHC's is negative, mismatch repair status is considered deficient.

Biomarker Approach to First-Line NSCLC Treatment Decisions

- Tumor histology
- Molecular testing
- Smoking cessation
- Palliative care

→ Adenocarcinoma Large cell NSCLC

→ Squamous cell carcinoma

EGFR-sensitizing mutation positive	→ *EGFR* inhibitor
ALK positive	→ *ALK* inhibitor
ROS1 positive	→ Crizotinib or ceritinib
BRAF V600E positive	→ Dabrafenib + trametinib
NTRK positive	→ Larotrectinib
PD-L1 positive (≥50%), and *EGFR*, *ALK* negative or unknown	→ Pembrolizumab ± systemic therapy or Atezolizumab + systemic therapy
EGFR, *ALK*, *ROS1*, *BRAF* negative or unknown; PD-L1 <50% or unknown	→ Systemic therapy

Molecular testing for adenocarcinomas (consider for squamous cell carcinoma, especially in light/never smokers):
EGFR, ALK, ROS1, BRAF, Broad profiling, PD-L1

NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2019 — January 18, 2019.

Initial Treatment for Metastatic NSCLC Adenocarcinoma

Excellent performance status (PS 0-1)

- **Pembrolizumab**
- **Pembrolizumab/carboplatin/pemetrexed**
- **Pembrolizumab/cisplatin/pemetrexed**
- **Atezolizumab/carboplatin/paclitaxel/bevacizumab**

Contraindications to PD-1/PD-L1 inhibitor

Bevacizumab plus:

- **Carboplatin/paclitaxel**
- **Carboplatin/pemetrexed**
- **Cisplatin/pemetrexed**

- **Carboplatin plus:**
  nab-paclitaxel/docetaxel/etoposide/gemcitabine/paclitaxel/pemetrexed
- **Cisplatin plus:**
  docetaxel/etoposide/gemcitabine/paclitaxel/pemetrexed
- **Gemcitabine/docetaxel**
- **Gemcitabine/vinorelbine**

- **Not a candidate for or disease progression on EGFR/ALK/ROS1 inhibitor**
- **PD-L1 assay positive ≥50%**

NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2019 — January 18, 2019.

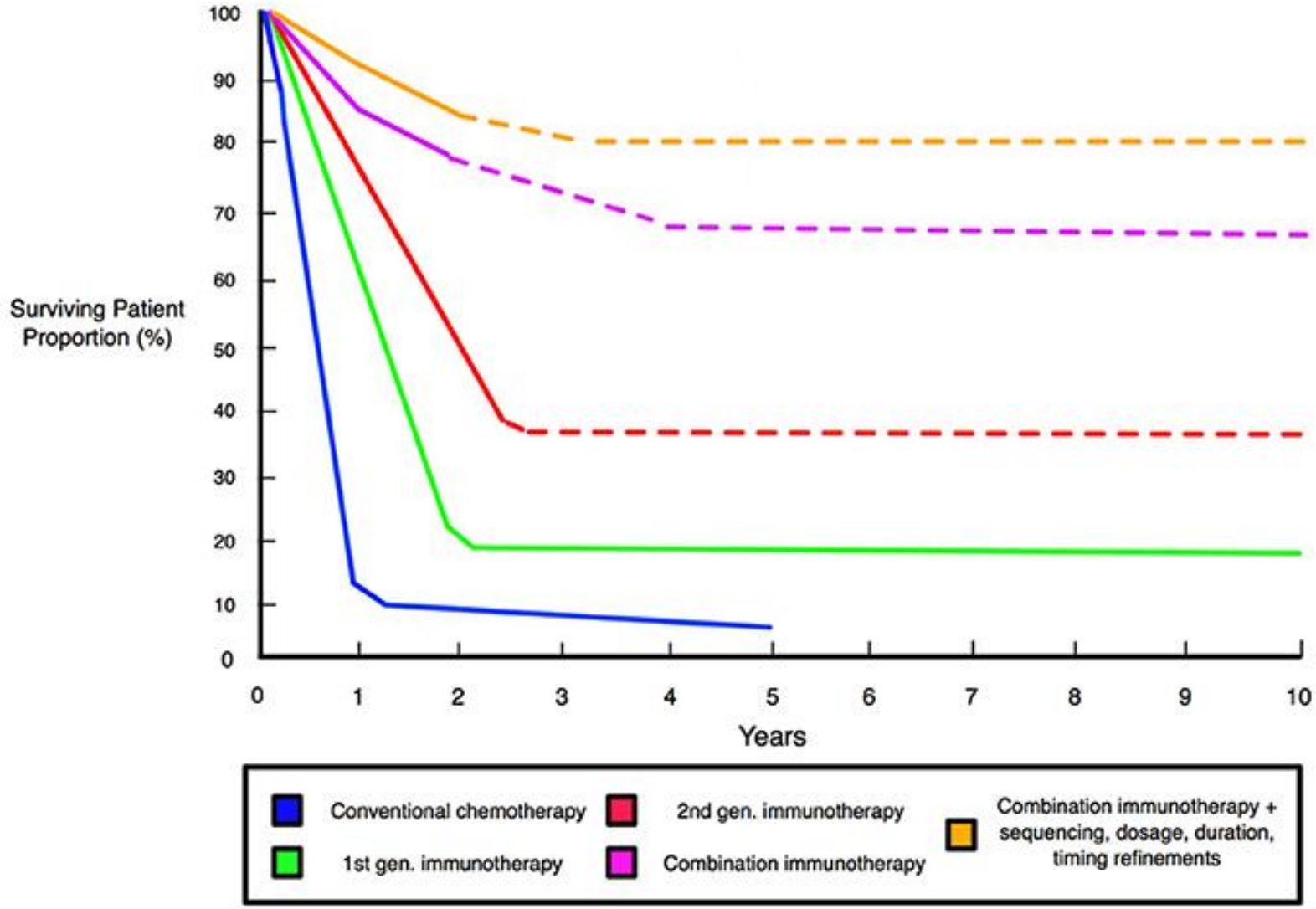
Immune Checkpoint Inhibitor Treatment Combinations

- Despite unprecedented durable responses achieved with immune checkpoint inhibition, incomplete efficacy and immune-related side effects remain challenges
- 2nd-generation immunotherapy targets under investigation
  - LAG-3, TIGIT, TIM-3, others
- Combination immunotherapy
  - Costimulatory mAbs plus checkpoint inhibitors
  - Cancer vaccines introducing tumor-specific antigens to prime T-cells
  - Small molecules (TKIs, inhibitors of VEGF, HDAC, and other cell pathways)
  - Cytokines (GM-CSF, interleukins, interferons)
  - Oncolytic viruses (kill cells and stimulate antitumor immune response)
  - Adoptive T-cell therapy (CAR-T cells)
  - Immune checkpoint inhibitors with radiotherapy or cytotoxic chemotherapy

Marshall HT, Djamgoz MBA. *Front Oncol*. 2018;8:315.

CAR, chimeric antigen receptor; GM-CSF, granulocyte-macrophage colony stimulating factor; HDAC, histone deacetylase; VEGF, vascular endothelial growth factor.

Improved Patient Survival With Immunotherapy



Marshall HT, Djamgoz MBA. *Front Oncol*. 2018;8:315.

Rationale for Combining Immunotherapy with Conventional Treatments

- Radiotherapy
  - Stimulates DNA-damage repair mechanisms, release of tumor antigens, and proinflammatory cytokines
  - Localized radiotherapy can produce significant immunostimulatory regression of distant sites of disease – “abscopal effect”
- Cytotoxic chemotherapy
  - Promotes anti-tumor immune response through stimulation of proinflammatory cytokines, reducing loss of cytotoxic T-cells, and producing immunomodulatory effects
  - “Low-dose” chemotherapy followed by immunotherapy may convert “cold” nonimmunogenic tumors into “hot” immunogenic tumors by priming T-cells
- Targeted therapies
  - Synergistic effects of inhibiting angiogenesis promotes T-cell infiltration
  - Decrease tumor cell proliferation by inhibiting signaling pathways
  - Epigenetic modulation and CDK4/6 inhibition promote tumor immunity

Marshall HT, Djamgoz MBA. *Front Oncol*. 2018;8:315.

Protein-Bound Paclitaxel Plus Atezolizumab for TNBC

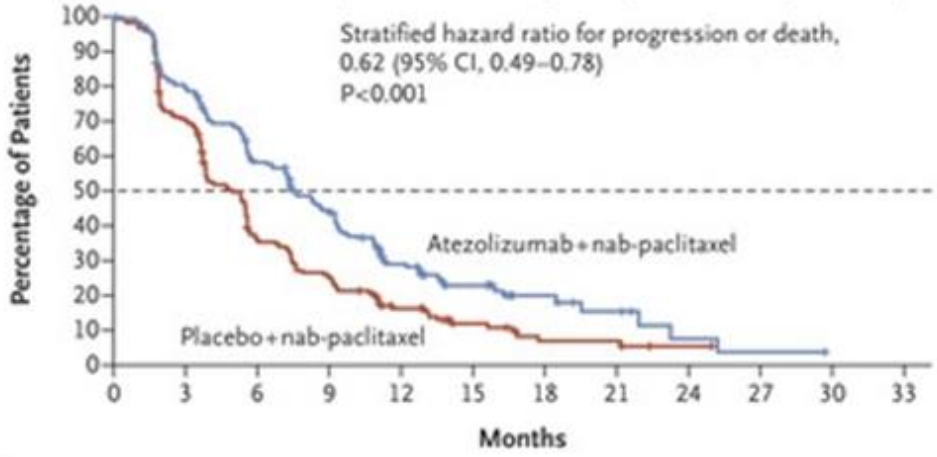
- Atezolizumab gained accelerated approval in combination with paclitaxel protein-bound for treatment of patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 staining of any intensity covering ≥1% of the tumor area), as determined by an FDA approved test
- Patients with no prior therapy randomized to atezolizumab plus nab-paclitaxel or nab-paclitaxel alone (N=451 each group)
- Stratification factors: presence of liver metastases, prior neoadjuvant or adjuvant taxane, PD-L1 expression on tumor-infiltrating immune cells as a percentage of tumor area (<1% vs. ≥2%)
- Primary endpoints: PFS and OS
- 185 and 184 patients with PD-L1 positive disease randomized to combination or single-agent nab-paclitaxel, respectively

Schmid P, et al; IMpassion130 Trial Investigators. *N Engl J Med*. 2018;379(22):2108-21.

Survival Outcomes – IMpassion130 Trial

PFS
PD-L1-positive subgroup

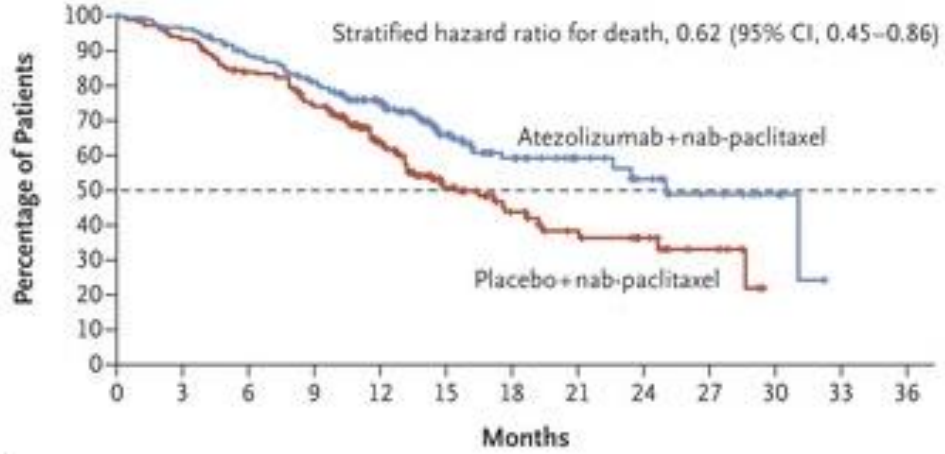
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab + Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo + Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

OS
PD-L1-positive subgroup

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab + Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo + Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

Schmid P, et al; IMpassion130 Trial Investigators. *N Engl J Med*. 2018;379(22):2108-21.

Managed Care and Specialty Pharmacy Considerations

- **Analyze** the costs and benefits of utilizing biomarkers in determining immunotherapy treatment
- **Describe** the data that should be considered when completing the formulary review process for biomarker and immunotherapy options

  - Treatment decisions based on mutation results
  - Costs associated with mutation tests and treatment
  - Prior authorization
  - Patient assistance
  - Formulary considerations

Evaluating the Cost of the Test

- Is it covered by insurance?
- Coverage depends on the type of test

Test itself

Other associated costs

- Is test offered at treatment site?
- What are the travel-related costs?

- Most IO treatments only covered for select patients
- Tests are only way to prove medical necessity

Ultimately necessary

What does the coverage landscape look like?

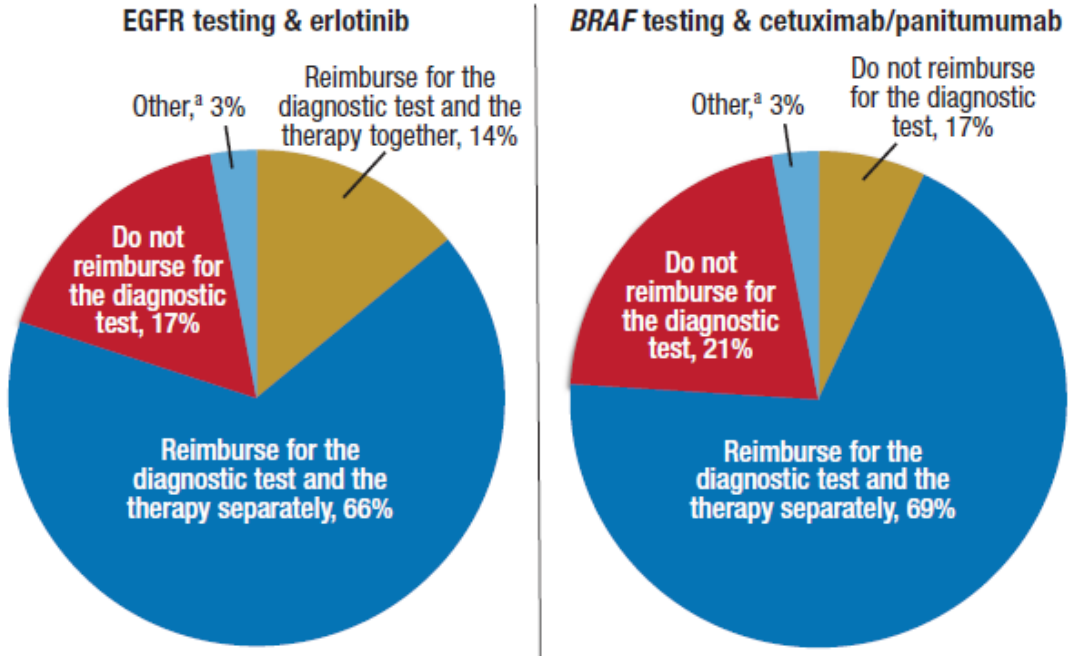
- Payers support biomarker testing in oncology
  - Usually means they will be paying for drugs a patient is likely to respond to rather than paying for treatment that may have little therapeutic effect
- 2011 survey of commercial and government managed care health plans
  - Reluctant to reimburse biomarker tests without evidence of clinical utility
    - May prove ineffective in improving patient outcomes, and, therefore, are financially wasteful
  - 62% of payers felt that, for oncology diagnostic tests to gain acceptance, they must be accompanied by a demonstration of cost-effectiveness

62%

Shelley S. *Pharmaceutical Commerce.* 2012;7:12.;
Trogan G. *American Health & Drug Benefits.* 2011;4(4).

Certain Tests Are Receiving Good Coverage

Figure 4 Majority of Plans Reimburse Diagnostic Testing Separately from Therapeutic

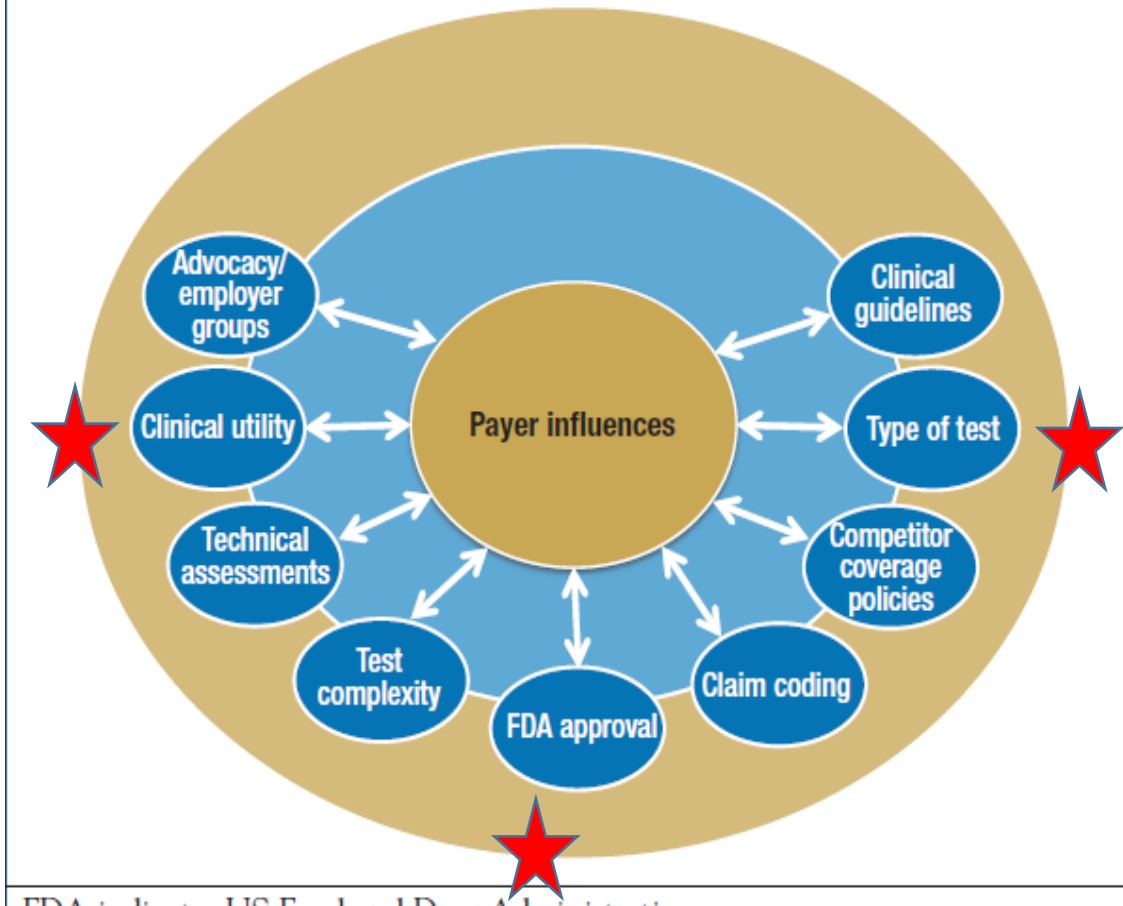


Q: How does your plan currently reimburse for *EGFR* mutation test for lung cancer patients who may be candidates for erlotinib (Tarceva) therapy?

Q: How does your plan reimburse for *BRAF* mutation analysis to predict nonresponse to cetuximab (Erbitux) and panitumumab (Vectibix) in the treatment of metastatic colorectal cancer and small bowel adenocarcinoma?

[a]Unsure.
Source: Reimbursement Intelligence. 2011.

Figure 1 Factors Impacting Payer Reimbursement of Oncologic Diagnostics



FDA indicates US Food and Drug Administration.
Source: Reimbursement Intelligence, 2011.

Cost of Testing

- Prior to 2018: CMS “14 Day Rule”
  - Did not allow reference and independent laboratories to bill Medicare directly for molecular pathology tests if they were ordered less than 14 days from an outpatient’s hospital discharge date
- The 2018 CMS Hospital Outpatient Prospective Payment System final rule created an exception to the “14 Day Rule”
  - Modified date-of-service (DOS) policy for hospital outpatients who undergo molecular biomarker tier 1 and tier 2 tests and advanced diagnostic laboratory tests.
    - Beginning January 1, 2018, the DOS must be the date the test was performed instead of the date the specimen was obtained, only if certain conditions are met:
      - Test is performed following a hospital outpatient’s discharge from the hospital outpatient department
      - Test was medically appropriate to have collected the sample from the hospital outpatient during the hospital outpatient encounter
      - Test was reasonable and medically necessary for the treatment of an illness

Centers for Medicare & Medicaid Services. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Lab-DOS-Policy.html.

Importance of Understanding Testing

- "A failure to properly understand molecular biomarkers has prevented their widespread adoption in treatment, comparative benefit analyses, and their integration into individualized patient outcome predictions for clinical decision-making."

Burke HB. *Biomark Cancer.* 2016;8:89-99.

Universe of Testing is Only Expanding

- NSCLC
  - Mutations in *ALK*, *EGFR*, *FGFR*, *HER2*, *KRAS*, *MET*, *RET*, and *ROS1* will inform targeted therapies
  - Expression of PD-1/PD-L1 will prompt the use of immunotherapy with immune checkpoint inhibitors
- Dr. Geoff Oxnard, a thoracic oncologist at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School:
  - PD-L1 does not stand on its own
  - "I use PD-L1 staining plus the clinical features, smoking history, the patient's genomic features, presence of a genotype like *EGFR* and/or *ALK*."

What tests should oncologists request first?

Which tests should be covered?

Where does the pharmacist fit in?

Oxnard GR. *Personalized Medicine in Oncology.* 2018. http://www.personalizedmedonc.com/article/precision-therapy-in-cancer/#impact.

Companion Diagnostic Status is Important

Michael Kolodziej, MD:

- "Current state of affairs in immunotherapy biomarkers is that pembrolizumab has a companion diagnostic and nivolumab has a complimentary test. And our current coverage policy does require at least an attestation that a companion has been done for prescribing pembrolizumab, and there is no such requirement for nivolumab."
- "I can assure you that there is no health plan in America that has the bench strength to go in there and analyze each of the individual assays, antibodies, performance characteristics. It doesn't work that way."

This is a major factor in determining formulary inclusion

Kolodziej M. *AJMC.com*. August 16, 2016. https://www.ajmc.com/insights/clinical-progress-and-coverage-policies-in-immuno-oncology/health-plan-coverage-of-diagnostic-tests-for-pd-l1-expression.

Examples of Certain Tests

- For pembrolizumab, the PD-L1 IHC 22C3 pharmDx Assay has status as a companion diagnostic
- For nivolumab and atezolizumab, the assays PD-L1 IHC 22C3 pharmDx and Ventana PD-L1 (SP142) have status as complementary diagnostics
  - There are no requirements for testing included in the labeling for these drugs
- Aetna considers the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) medically necessary for the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded urothelial carcinoma tissue to determine individuals who are more likely to respond to durvalumab therapy

Aetna.com. http://www.aetna.com/cpb/medical/data/700_799/0715.html. Accessed April 11, 2019.

Oncology + Pathology + …. Pharmacy?

- Geoff Oxnard, MD
  - "I generally tell my patients with lung cancer that we have 3 broad tools: we have oral targeted therapies, we have immunotherapies, and we have chemotherapies. Before I start treatment for you, I am going to determine whether I can find a targetable genotype such as *EGFR* or *ALK*. I am going to look to see if your cancer is sensitive or vulnerable to immunotherapy using a marker such as PD-L1. If I do not have compelling evidence that one of those is going to work, I am going to reach towards chemotherapy. At each decision point I say, 'I need these data quickly to make an informed decision.'"
- Lauren Ritterhouse, MD, PhD, a molecular pathologist and Co-Director of the Molecular Diagnostics and Clinical Genomics Laboratories, University of Chicago, IL
  - "As a pathologist, and particularly a molecular pathologist, running a molecular diagnostics laboratory, [I am] constantly thinking about new biomarkers that we need to incorporate into the laboratory, trying to be ahead of the curve. If there is a new biomarker that is released based on a clinical trial, the time for us to bring that new test in house, develop it, find validation samples, and actually launch it clinically is a much longer process than we, our oncologists, and the patients would like."

Oxnard GR. *Personalized Medicine in Oncology.* 2018. http://www.personalizedmedonc.com/article/precision-therapy-in-cancer/#impact.

Testing May Not Be One and Done

Dr. Oxnard: "We have some systems where we can acknowledge each time we ordered an NGS that it conforms to certain specifications. If it is an advanced lung cancer and they have not had an NGS in the past 6 months, we can facilitate the approval. The payers' idea is that you should not need this more than once for lung cancer. That is not a reality."

Cancer patients also present at different stages of their disease, their disease can progress, and the cancer can metastasize…

Oxnard GR. *Personalized Medicine in Oncology.* 2018. http://www.personalizedmedonc.com/article/precision-therapy-in-cancer/#impact.

Understanding the Prior Authorization Landscape

Physicians need to order tests in order for treatments to be approved

Many of these will run through hospital path labs

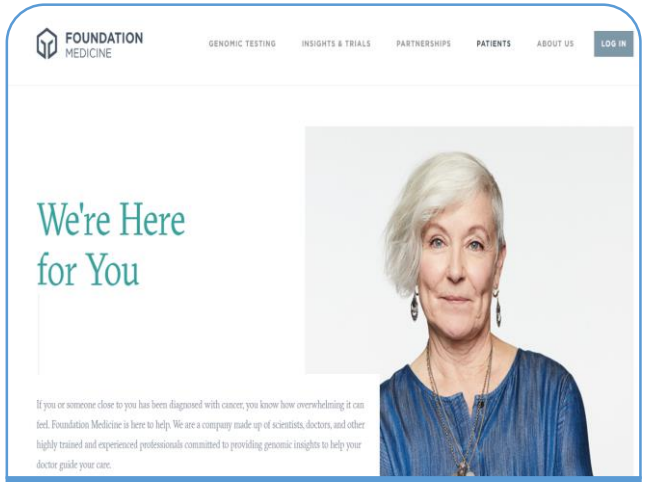
Pharmacies may see this fall to them as certain treatments are prescribed

Payers are still requiring documentation for approvals

Patient Assistance for Testing

- Test makers are offering financial assistance, as are traditional financial assistance organizations:

Patient Advocate Foundation (PAF)



Foundation Medicine

Myriad