Cancer Immunotherapy: Primer on Biomarkers and Mechanisms of Action

Peter P. Lee, MD
Billy and Audrey Wilder Professor and Chair
Dept. of Immuno-Oncology
City of Hope Cancer Center

I have no declarations.

Definition of Cancer Immunotherapy

- Treatments that harness patients' immune system for cancer therapy
- Monoclonal antibodies
  - Target cancer cells
  - Modulate immune function: Immune Checkpoint Blockade (ICB)
- Cytokines
- Cancer vaccines (+/- dendritic cells)
- Adoptive cellular therapy (+/- engineered receptors: TCR or chimeric antigen receptor, CAR)

Approved Immunotherapies for Solid Tumors

2010: Sipuleucel-T (dendritic cell vaccine) for prostate cancer

2011: Ipilimumab (anti-CTLA4 Ab) for advanced melanoma

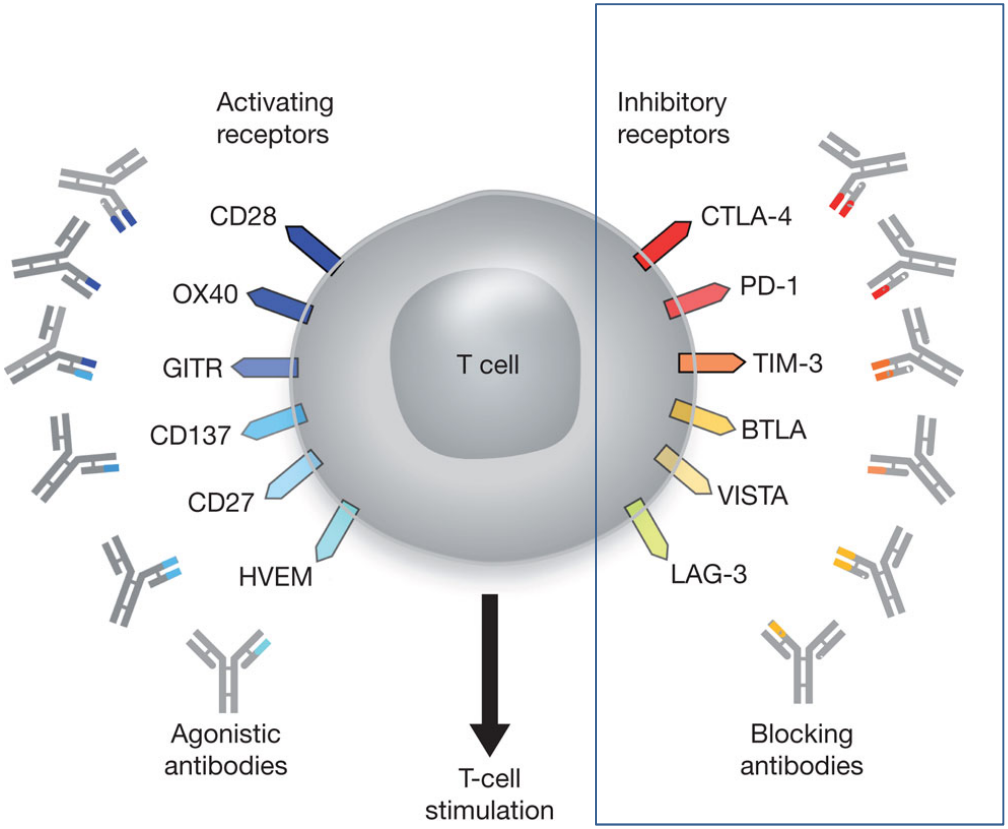
2014: Pembrolizumab and Nivolumab (anti-PD1 Ab) for advanced melanoma

2015: Nivolumab for lung cancer and kidney cancer; Nivo/Ipi combination for melanoma; T-VEC (oncolytic virus) for melanoma

2016 on: multiple other cancer types; MSI tumors

These treatments still only work for subsets of patients and some cancer types – need for biomarkers

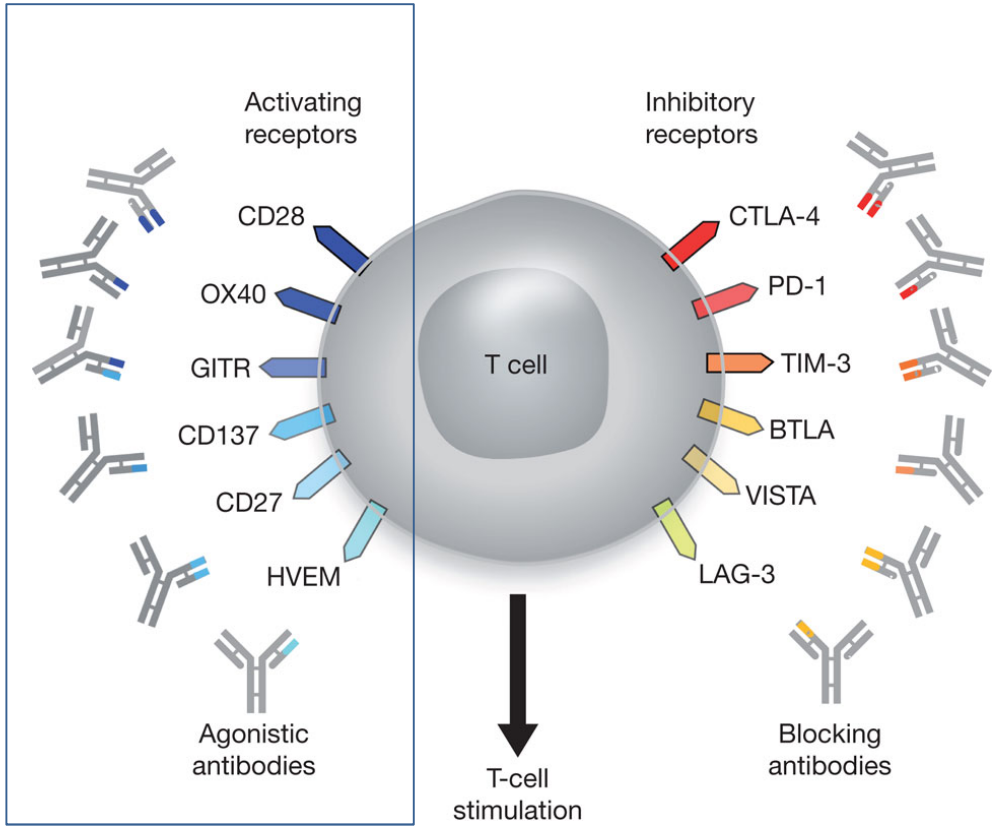
Inhibitory Immune Checkpoints



I Mellman *et al. Nature* **480**, 480-489 (2011) doi:10.1038/nature10673

nature

Activating Immune Checkpoints



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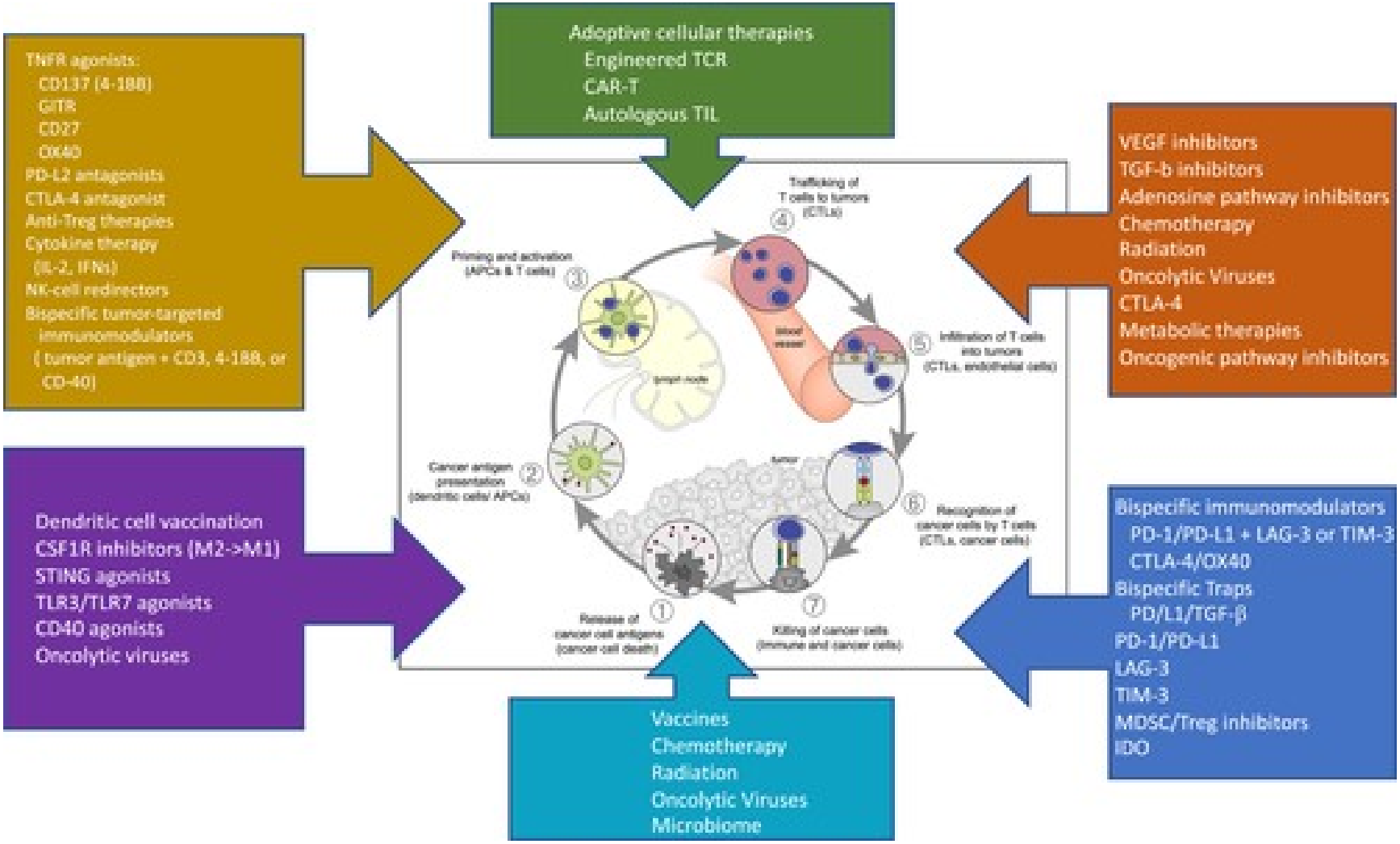

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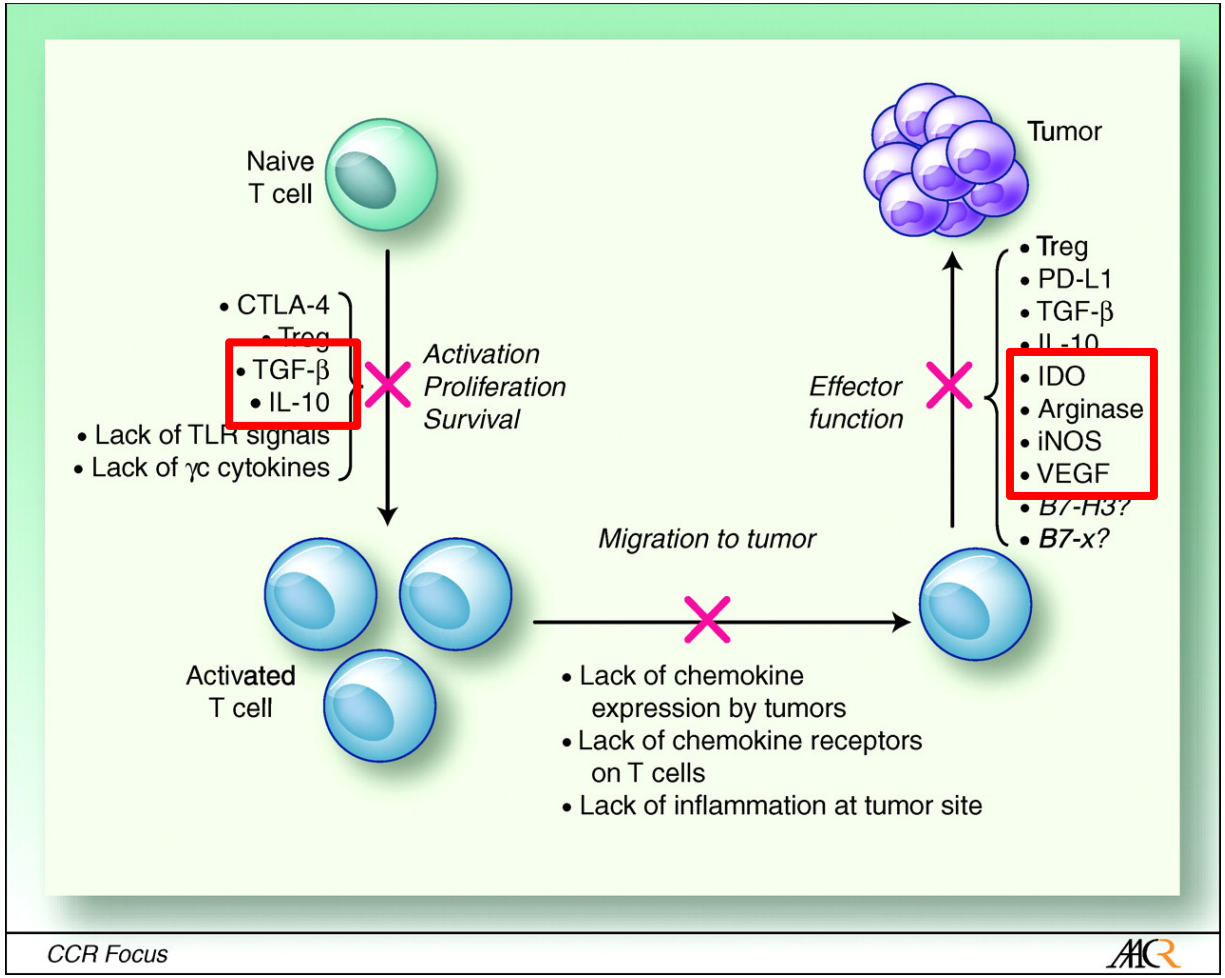
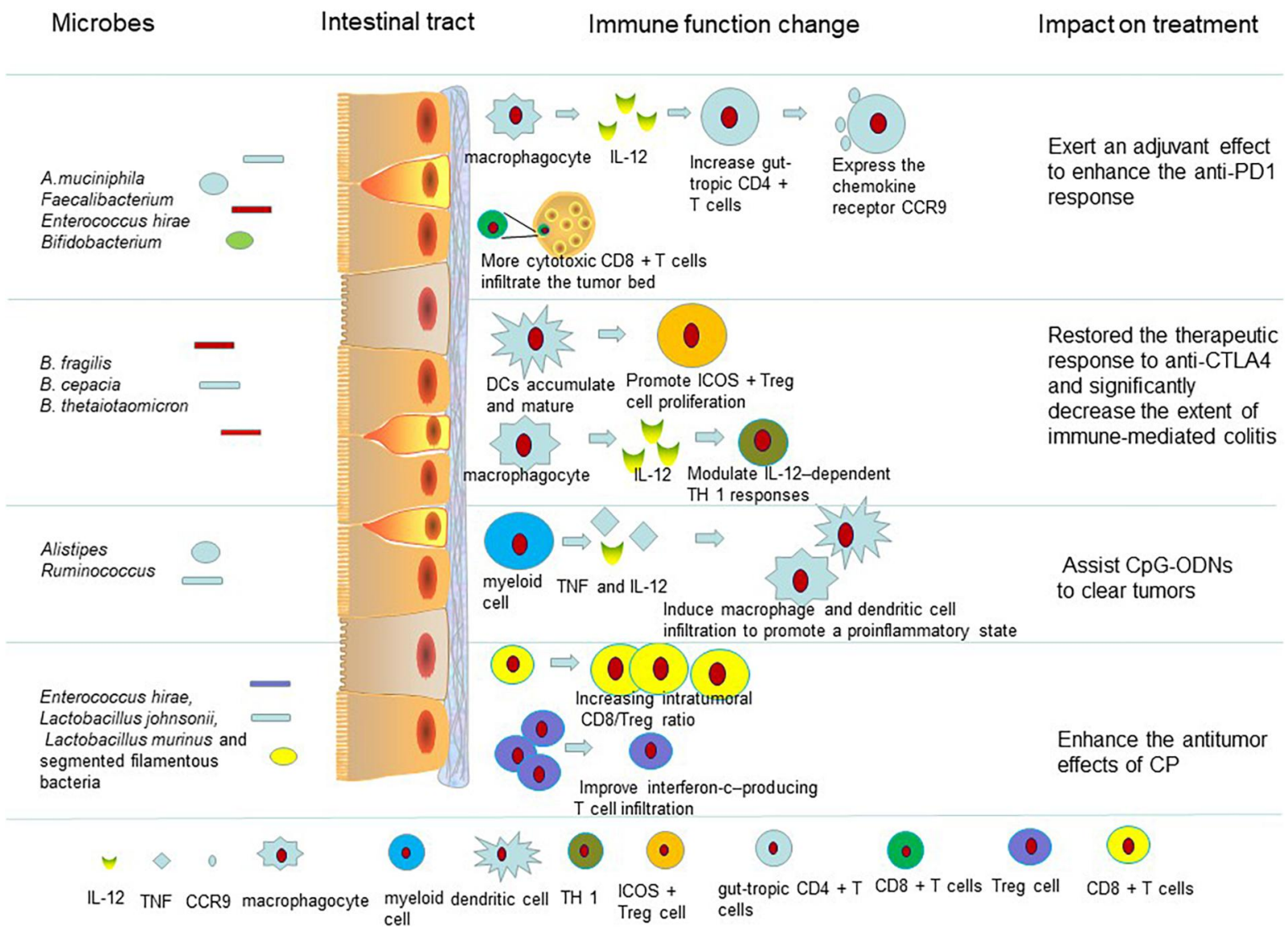
Barriers to effective anti-tumor T cell immunity



Lizée G et al. *Clin Cancer Res* 2007;13:5250-5255

GI Microbiome



Biomarkers: Tissue

Table. Comparison of Pooled Diagnostic Sensitivity and Specificity and Predictive Values for Responders vs Nonresponders After Anti–PD-1/PD-L1 Therapy Between Different Assay Modalities[a]

Modality	Pooled Sensitivity	Pooled Specificity	Pooled PPVs	Pooled NPVs
PD-L1 IHC (n = 24)	0.50 (0.48-0.53)	0.63 (0.62-0.65)	0.34 (0.32-0.36)	0.78 (0.76-0.79)
TMB (n = 10)	0.57 (0.51-0.62)	0.70 (0.66-0.73)	0.42 (0.38-0.47)	0.80 (0.77-0.83)
GEP (n = 9)	0.71 (0.67-0.75)	0.51 (0.48-0.54)	0.42 (0.39-0.46)	0.77 (0.74-0.81)
mIHC/IF (n = 7)	0.60 (0.53-0.66)	0.78 (0.73-0.82)	0.63 (0.56-0.70)	0.75 (0.70-0.80)
Multimodality (n = 6)	0.58 (0.50-0.65)	0.79 (0.75-0.82)	0.41 (0.33-0.48)	0.88 (0.85-0.91)

Abbreviations: GEP, gene expression profiling; mIHC/IF, multiplex immunohistochemistry/immunofluorescence; PD-L1 IHC, programmed cell death ligand 1 immunohistochemistry; TMB, tumor mutational burden.

[a] All data are reported as a proportion (95% CI). Nonoverlapping 95% CIs suggest statistical significance.

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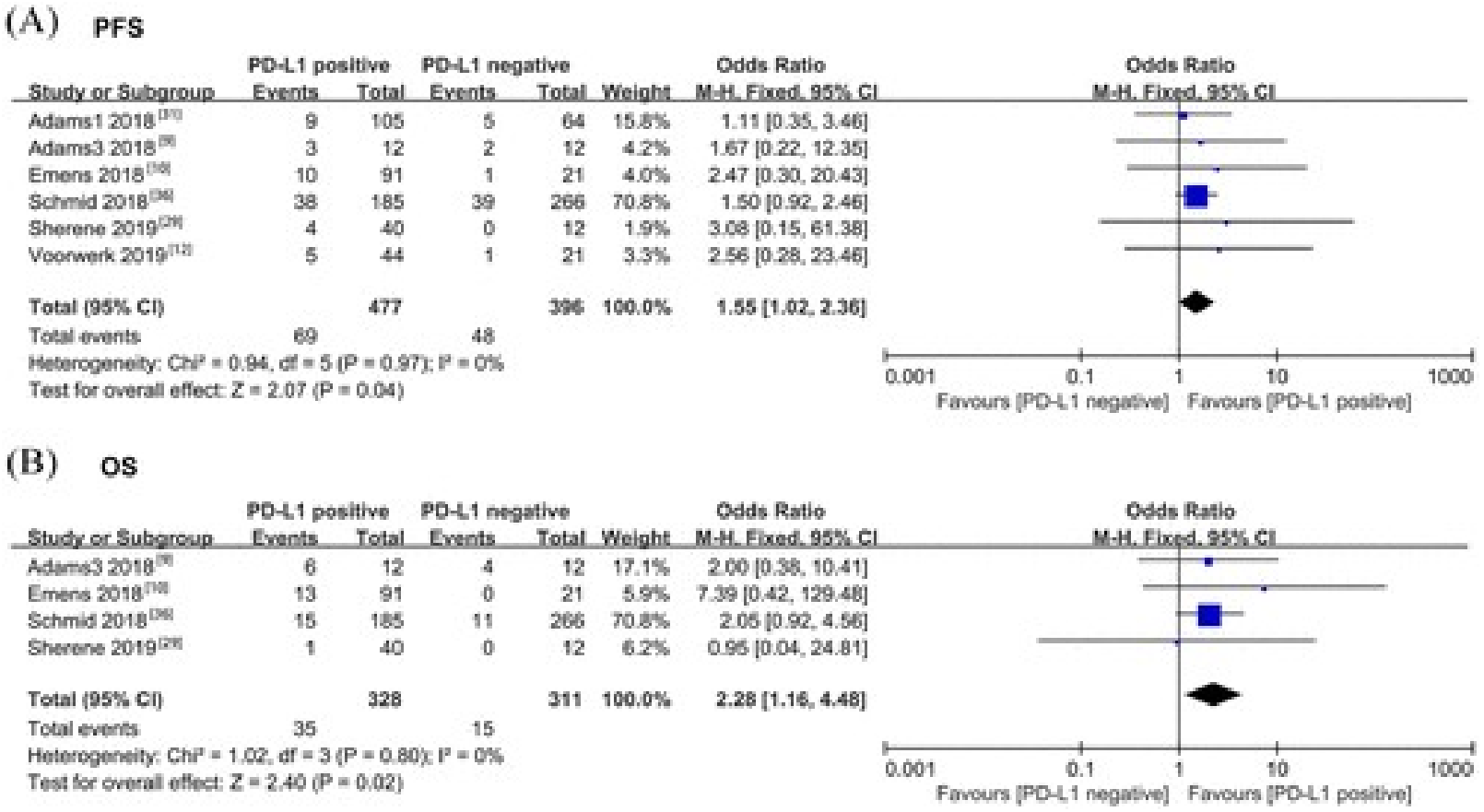
From: **Comparison of Biomarker Modalities for Predicting Response to PD-1/PD-L1 Checkpoint Blockade: A Systematic Review and Meta-analysis**

JAMA Oncol. Published online July 18, 2019. doi:10.1001/jamaoncol.2019.1549

Tumor PD-L1 is a borderline predictor



Zou et al. 2020

PD-L1 expressed on cancer cells or immune cells?

Blood Biomarkers

- Immune cell subsets: PD1+ CD8 T cells, Tregs
- Serum cytokines: IL-6
- Immune cells signaling responses
- T cell receptor (TCR) clonality
- Peripheral blood shed PD-L1
- Cell-free (cf)DNA

Multi-parameter blood biomarkers

Biomarker	Cancer type	No. of patients	Main results	Reference
(%Ki-67^{+} cells/PD-1^{+}CD8^{+} T cells 3-wk post-treatment)/baseline tumor burden (Ki67/TB)	Melanoma	Discovery cohort: 23	Higher Ki67/TB significantly associated with superior ORR (p=0.03) and PFS (p=0.004).	Huang et al. (34)
		Validation cohort: 18	Higher Ki67/TB associated with superior ORR (p=0.14) and PFS (p=0.06).	
(%Ki-67^{+} cells/PD-1^{+}CD8^{+} T cells 1-wk post-treatment)/(%Ki-67^{+} cells/PD-1^{+}CD8^{+} T cells at baseline) (Ki-67$_{D7/D0}$)	TET	Discovery cohort: 31	Higher Ki-67$_{D7/D0}$ significantly associated with durable clinical benefit (PR, or SD for 6 months or longer; p<0.001) and PFS (p=0.027)	Kim et al. (32)
	NSCLC	Discovery cohort: 33	Higher Ki-67$_{D7/D0}$ significantly associated with durable clinical benefit (PR, or SD for 6 months or longer; p<0.01), PFS (p=0.004), and OS (p=0.001)	
		Validation cohort: 46	Higher Ki-67$_{D7/D0}$ significantly associated with durable clinical benefit (PR, or SD for 6 months or longer; p<0.01), PFS (p=0.002), and OS (p=0.037)	
%FoxP3^{-}PD-1^{hi}CD4^{+} T cells/CD4^{+} T cells (4PD1^{hi}) 3-wk post-treatment Fold change of 4PD1^{hi}	Melanoma	52	Higher frequency of 4PD1^{hi} 3-wks post treatment (p=0.0005) and fold change of 4PD1^{hi} (p=0.046) associated with poorer OS.	Zappasodi et al. (36)
TCR diversity of PD-1^{+}CD8^{+} T cells at baseline and post-treatment	NSCLC	Discovery cohort: 25 Validation cohort: 15	Higher baseline diversity in PD-1^{+}CD8^{+} T cells (p=0.021) and increased clonality after treatment (p=0.002) associated with superior PFS.	Han et al. (39)
%CD27^{-}CD28^{-} cells/CD4^{+} T cells at baseline	NSCLC	51	Higher frequency of CD27^{-}CD28^{-}CD4^{+} T cells associated superior PFS (p=0.001).	Zuazo et al. (42)
Ratio of the frequency of Treg cells and PMN-MDSCs at baseline	NSCLC	Discovery cohort: 34	Higher ratio of the frequency of Treg cells and PMN-MDSCs associated with superior PFS (p=0.0079).	Kim et al. (44)
		Validation cohort: 29	Higher ratio of the frequency of Treg cells and PMN-MDSCs associated with superior PFS (p=0.0017).	
%Effector/memory (CCR7^{-}CD45RA^{-}) cells/CD8^{+} T cells at baseline	NSCLC	263 (flow cytometry analysis in 144)	Lower frequency of effector/memory CD8^{+} T cells with development of hyperprogressive disease (p<0.001) and poor PFS (p<0.001) and OS (p<0.001).	Kim et al. (53)
%TIGIT^{+} cells/PD-1^{+}CD8^{+} T cells at baseline			Higher frequency of TIGIT^{+} cells among PD-1^{+}CD8^{+} T cells in peripheral blood at baseline significantly associated with development of hyperprogressive disease (p<0.001) and poor PFS (p<0.001) and OS (p=0.01).	

NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TET, thymic epithelial tumor; CCR7, C-C chemokine receptor type 7.

Kim et al. 2020

Biomarkers for irAEs

Biomarker	Cancer type	# pts	Main results	Reference
Fold change of effector Treg cells 1-wk post- Th17 to Th1 ratio at baseline %Ki-67^{+}/PD-1^{+}CD8^{+} T cells 1-wk post-treatment %TNF-α^{+}/CD4^{+} or CD8^{+} T cells 1-wk post-treatment	TET NSCLC	31 60	Patients with irAEs can be distinguished into 4 distinct subtypes according to the T-cell parameters and each T-cell parameter predicts the corresponding subtype of irAEs	Kim et al. (63)
Memory cytotoxic (CD45RO^{+}GzmB^{+}Ki-67^{+}) CD4^{+} T cells	Melanoma	3	Activated memory CD4^{+} T cells were highly enriched in inflammed, affected region of cases with	Johnson et al. (68)
Early B cell changes (decline in B cells, increase in CD21^{lo} B cells)	Melanoma	23	Decline in B cells but an increase in CD21^{lo} B cells more prominent in patients with severe irAEs that received combined anti-PD-1 and anti-CTLA-4	Das et al. (72)
Cytokine expression-based score	Melanoma	98	Eleven cytokines were integrated into a single score (CYTOX) and it significantly predicted development of severe irAEs in patients treated with combined anti-PD-	Lim et al. (77)
		49	CYTOX score significantly predicted development of	
Auto-Abs (rheumatoid factor, antinuclear Ab, antithyroglobulin, and antithyroid peroxidase)	NSCLC	137	Preexisting rheumatoid factor or auto-Abs significantly correlates with development of any grade irAEs	Toi et al. (75)
Anti-thyroid Abs (anti-microsomal and anti-thyroglobulin)	NSCLC	51	Presence of anti-thyroid Abs either at baseline or during anti-PD-1 treatment was significantly associated	Osorio et al. (76)

NSCLC, non-small-cell lung cancer; TET, thymic epithelial tumor.

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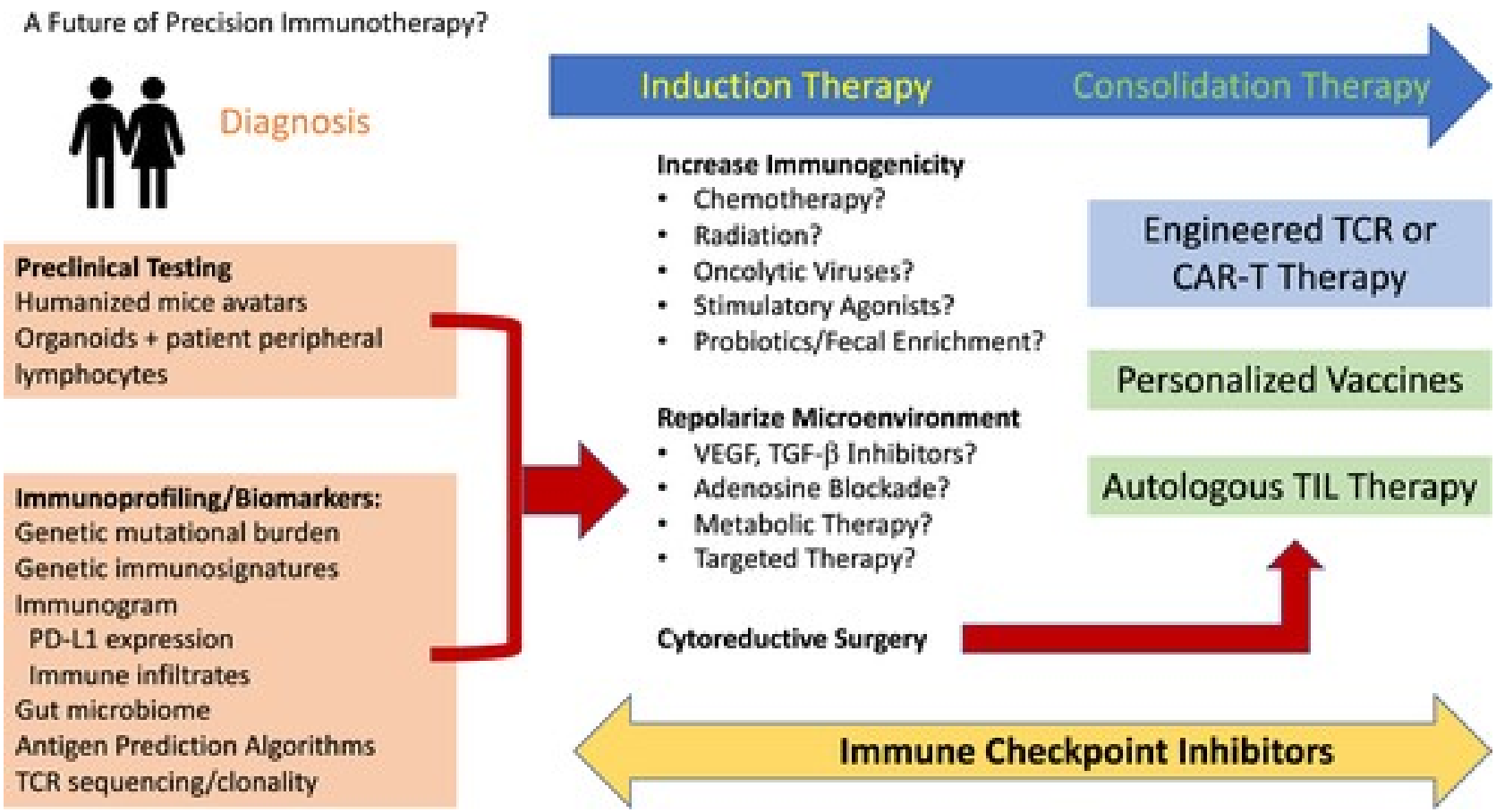
Precision Immunotherapy



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Summary and Future Directions

Integrative algorithms:

Response	Resistance	Future Directions
High tumor mutational burden	Lack of T cell infiltration	Refining PD-L1 antibody precision
Checkpoint protein expression (PD-L1)	High quantities of T-regs, TAMs, MDSCs	Biomarkers for CTLA-4 response
High quantities of infiltrating CD8+ T cells	Expression of alternative checkpoint proteins	Neoantigen signatures superior to TMB in some tumors
Low circulating neutrophil:lymphocyte ratio	High stromal burden (cancer-associated fibroblasts)	Implementing new technologies to assess immune microenvironment
Higher diversity of gut microbiomes	High suppressive cytokines (VEGF, cofactors, IL-6, TGF-β)	Statistical models to incorporate multiple biomarkers
High expression of immune-related genes (Tumor Inflammation immunosignature)	Genetic mutations (JAK 1/2, PTEN loss, β-catenin/Wnt signaling)	

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