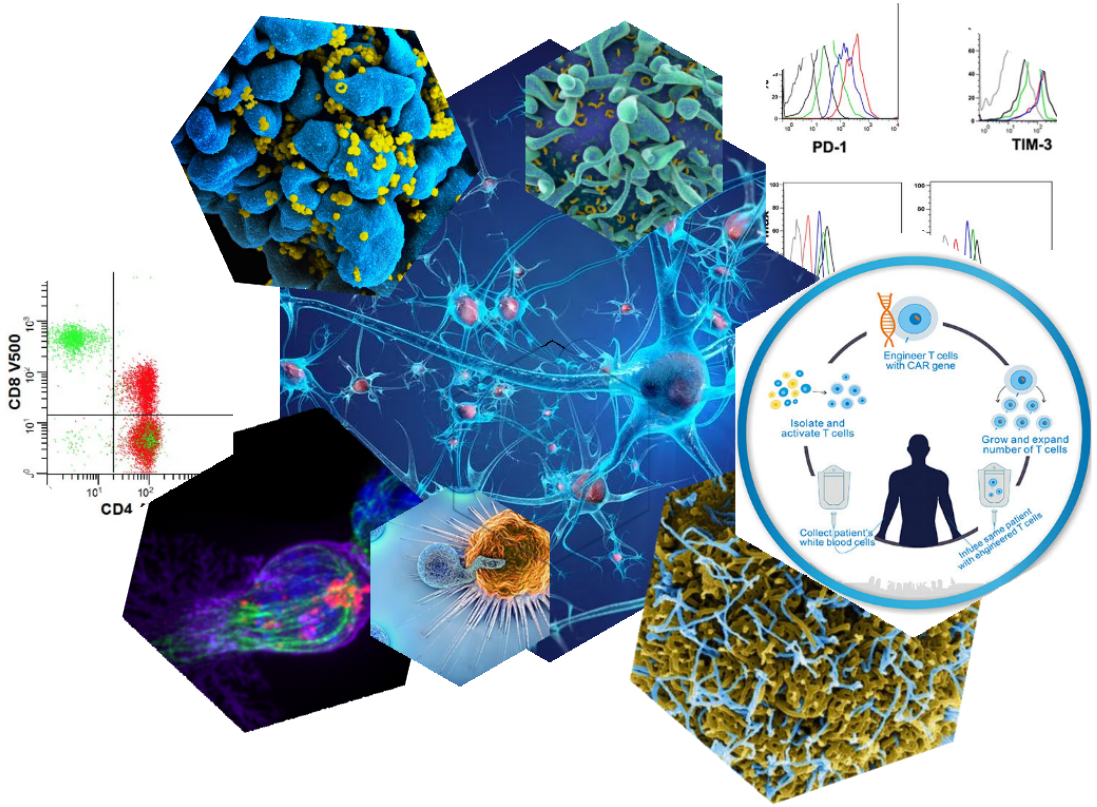
Massachusetts General Hospital



FOX CHASE CANCER CENTER
TEMPLE HEALTH

Immune Checkpoint Inhibitor–Based Therapy as a Backbone in Cancer Treatment

Krista Rubin, MS, RN, FNP-BC, and Anthony Olszanski, MD

2019 JADPRO Live
THE ANNUAL APSHO MEETING

Financial Disclosure

- Ms. Rubin has acted as a consultant for Merck.
- Dr. Olszanski has received research support and acted as a consultant for Alkermes, Array, Merck, Merck-EMD Serono, Novartis and Pfizer.

Learning Objective

1. Evaluate emerging data for ICI-based combinations that are being explored in late-stage clinical trials

Agenda

Immunotherapy Landscape	Terminology & Concepts	Aspects of Care	Success Examples	New Investigations
• Indications • FDA approvals	• Immunotherapy 101 • Scientific MOA	• Microbiome • HCP communications • Survivorship	• Lung • Hodgkin • Melanoma	• TIGIT • ICOS • TLR-9

Audience Question

There are _____ immune checkpoint regimens currently FDA approved in the United States.

A. Three
B. Seven
C. Eight
D. I have no idea what a checkpoint inhibitor is.
E. Zero. None are approved in the United States.

Audience Question

A positive PLD-L1 expression status must be confirmed prior to a patient starting treatment with an anti-PD-1.

A. True
B. False

Audience Question

Proton pump inhibitors (e.g. omeprazole, pantoprazole) are an absolute contraindication for patient undergoing immune checkpoint inhibitor therapy.

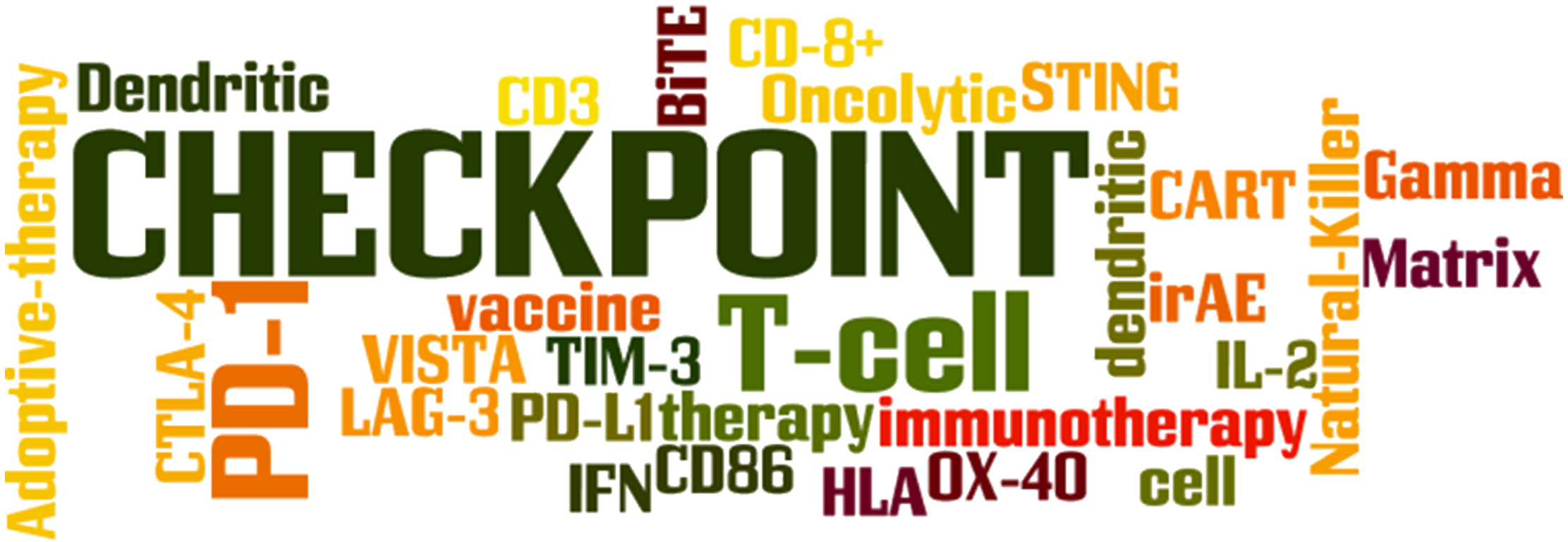
A. True
B. False

Audience Question

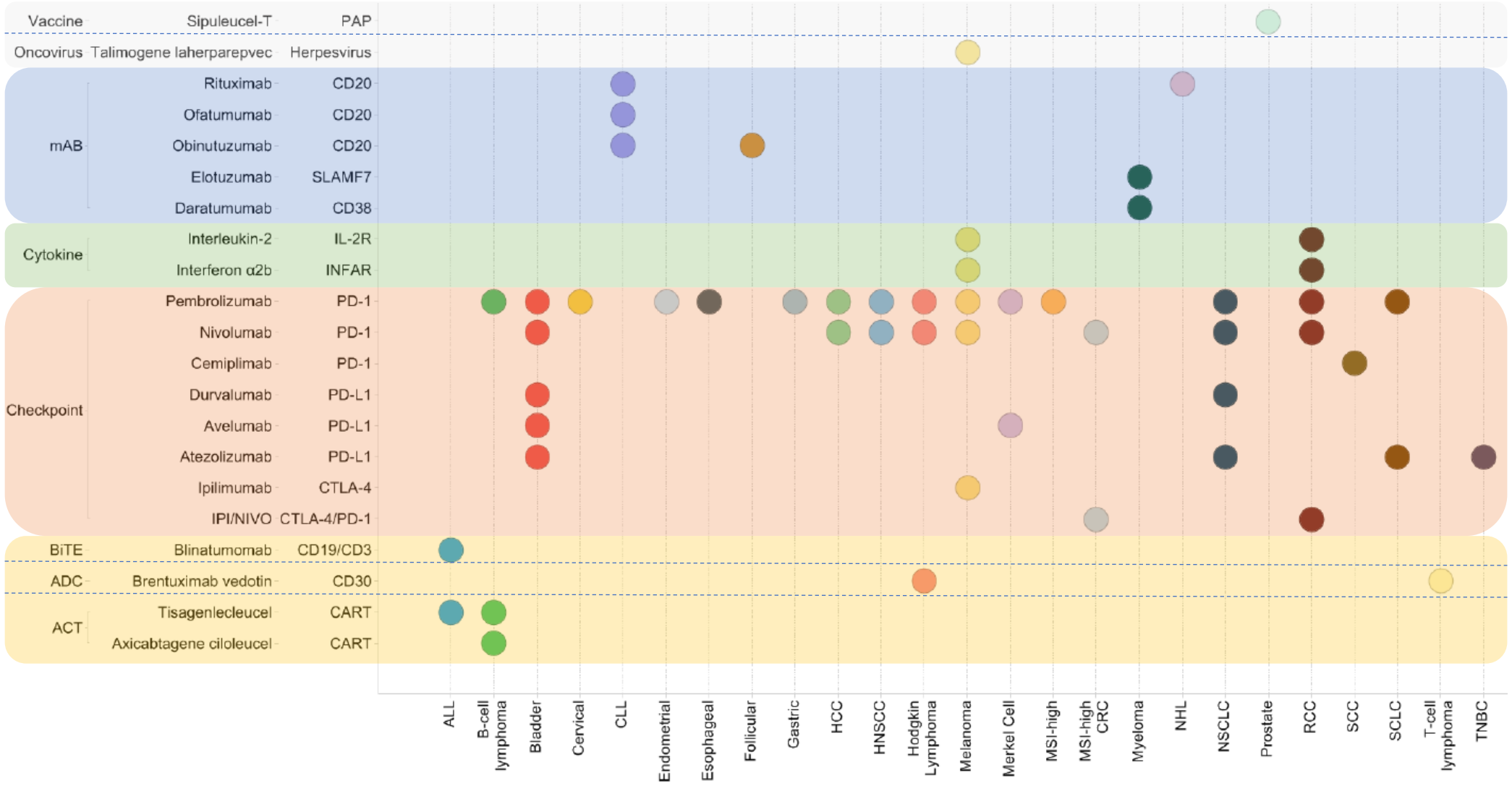
All of the following are examples of investigational agents EXCEPT:

A. LAG-3
B. VISTA
C. WIGIT
D. 4-1BB
E. OX40

A Changing Landscape



Current Approvals (circa Fall 2019)*



*Not all-inclusive

mAB: monoclonal antibody
BiTE: Bi-specific T-cell engager
ADC: Antibody-drug conjugate
ACT: Adoptive cellular therapy

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Basic Concepts of Immunotherapy

A new reality

The Language of Lymphocytes

CD8+: Cytotoxic T-lymphocytes

- Direct cytotoxicity

CD4+: Helper cells

- Indirect cytotoxicity

Treg: Regulatory cells

- Establish tolerance
- Supressive function

NK: Natural killer cell

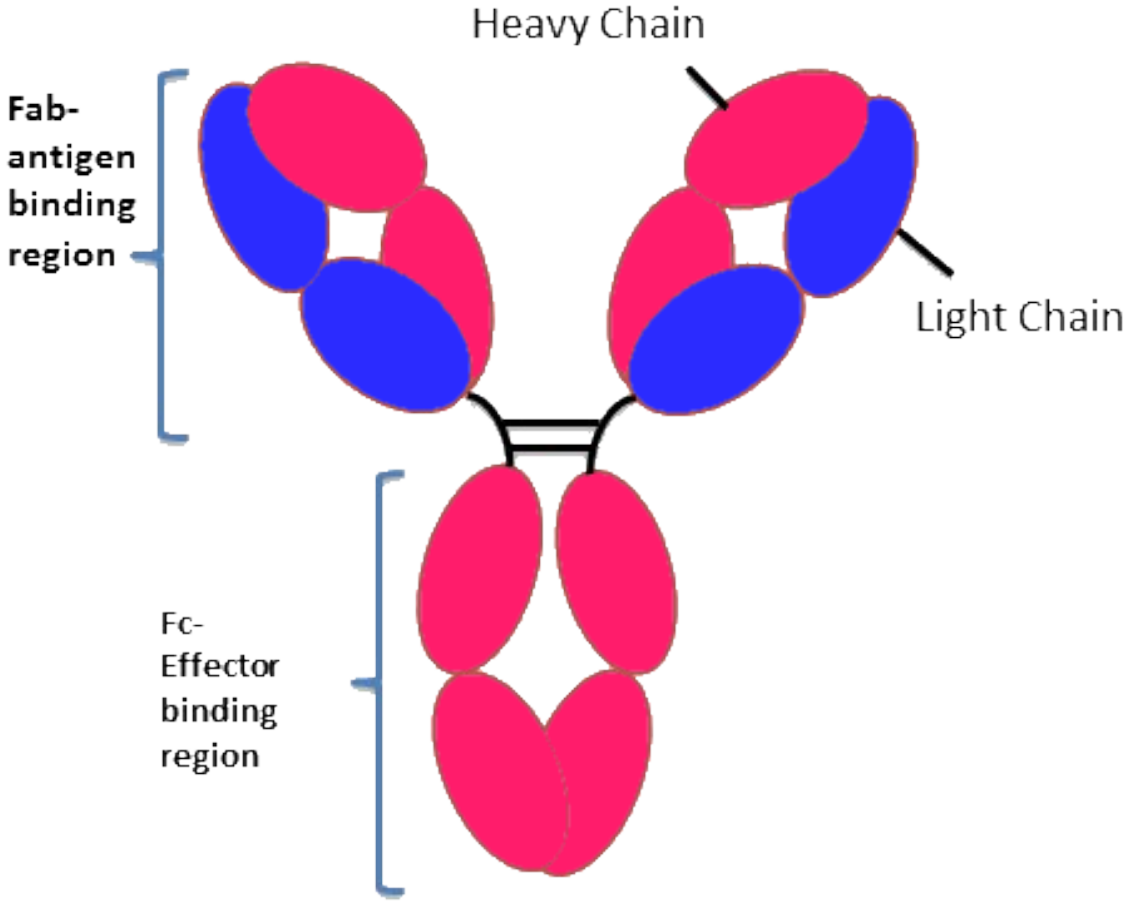
- 1st line defense: acts autonomously
- Lack CD8 and MHC-1

DC: Dendritic cell

- Antigen presenting (APC)

Monoclonal Antibodies

- Similar to endogenous
  - i.e., B-lymphocyte antibodies
- Very specific
- Potential infusion reaction
- Long half-life (typically)
- Large molecules
- Few drug-drug interactions
- No metabolized/excreted
- Receptor-mediated clearance

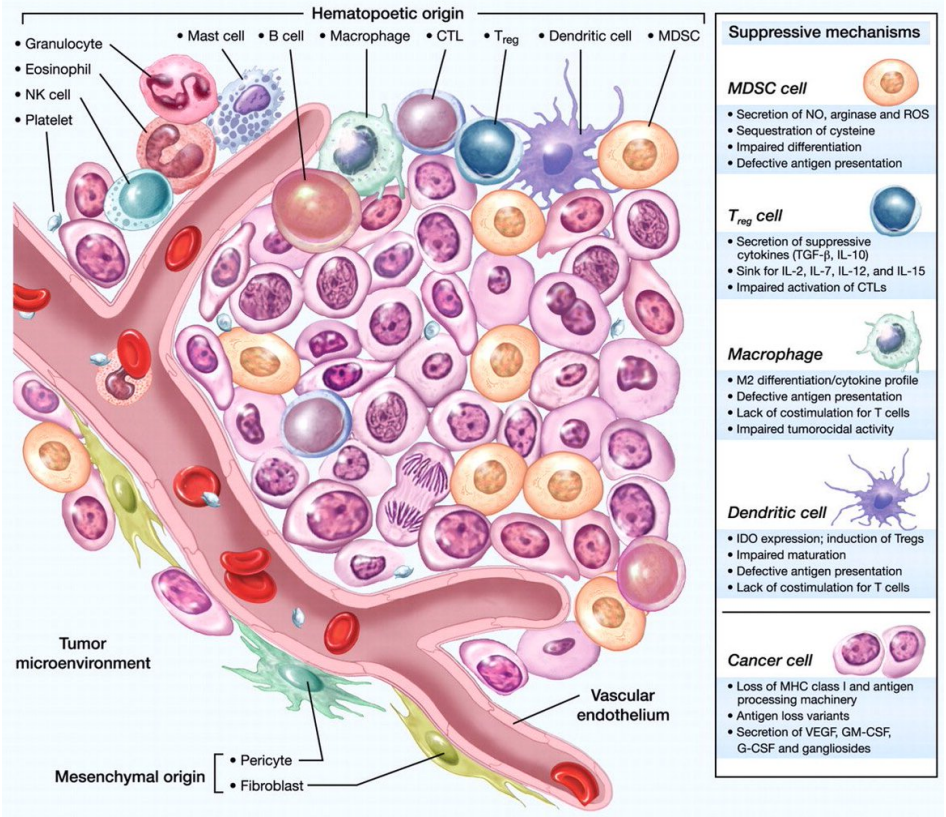


Tumor-Infiltrating Lymphocytes

Process

- Remove tumor
- Isolate T-cells
- Select responsive T-cell
- Stimulate T-cells *ex vivo*
- Expand *ex vivo*
- Reinfuse activated T-cells
- Augment with IL-2

Physiology



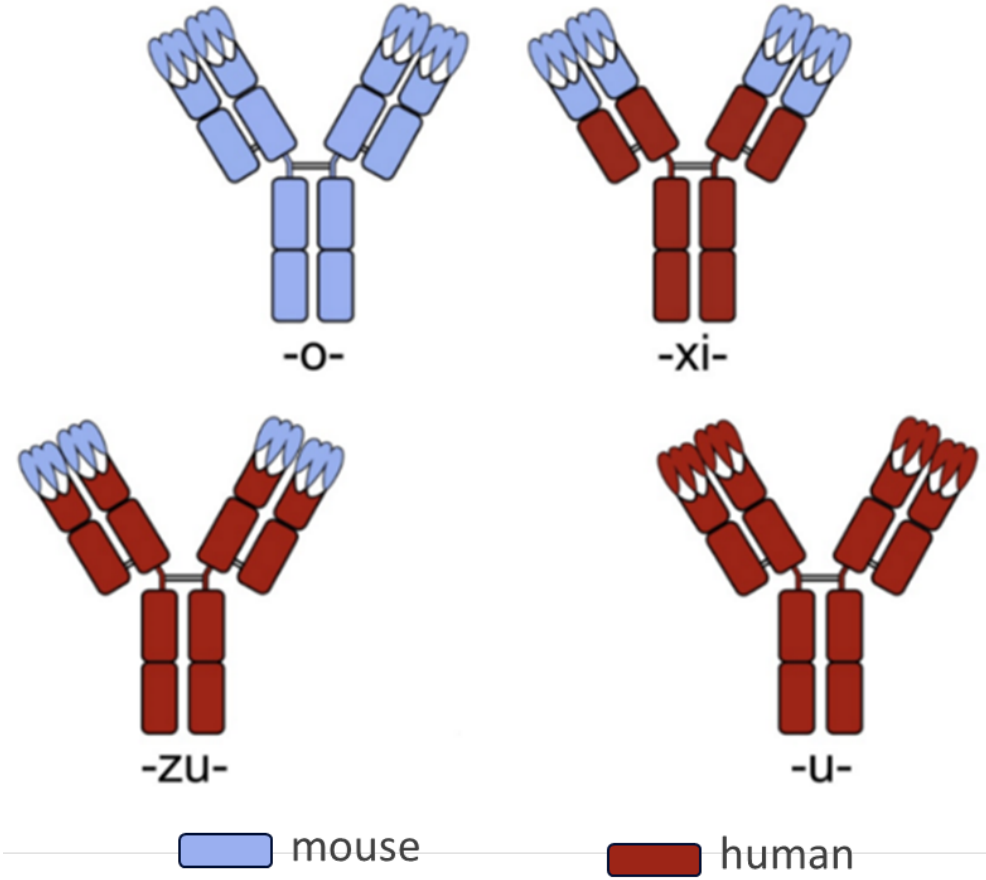
Kerkar SP, Restifo NP. *Cancer Res*. 2012;72:3125-30

Chimeric Antibodies

- Chimera
  - Greek mythical creature
  - Lion/goat/serpent
- Chimeric antibody
  - Composed of more than one species
  - Most typical mouse-human
- Less antigenicity
- Retained CDC and ADCC
  - Complement-dependent cytotoxicity
  - Antibody-dependent cellular cytotoxicity

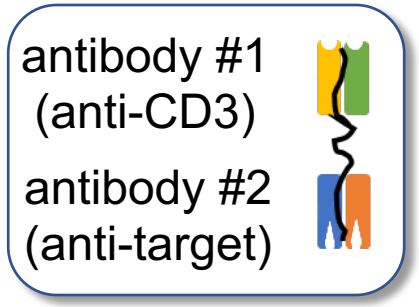
Antibody Nomenclature

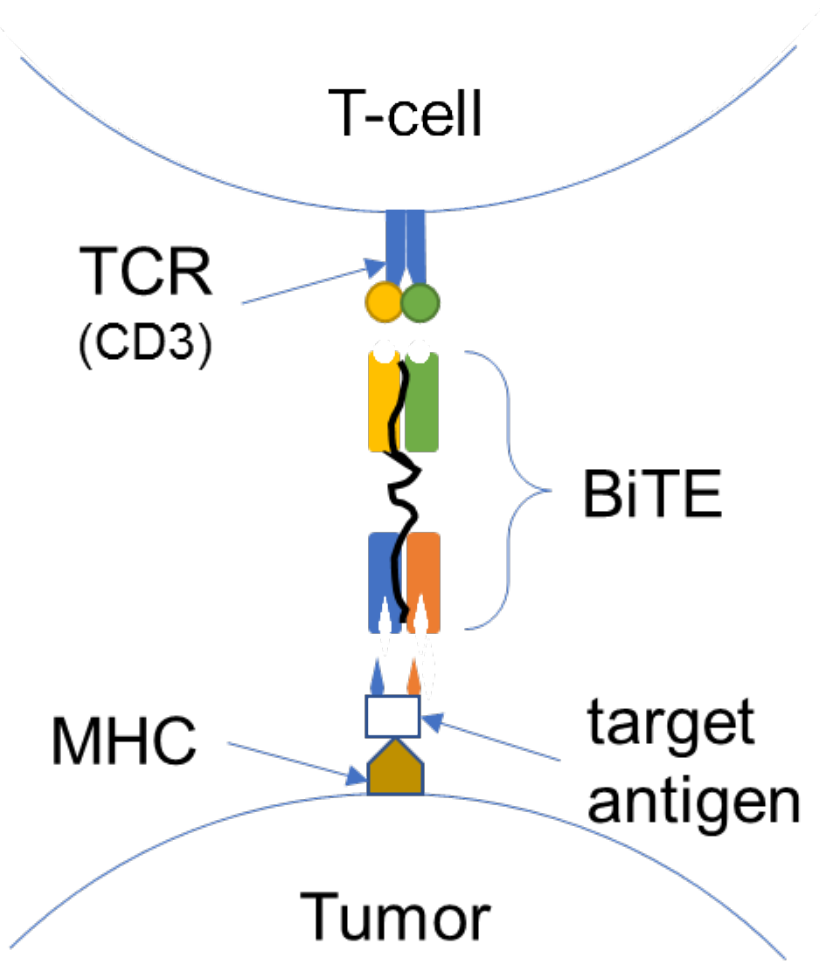
- Pembroli**zu***mab*
  - li(m) = immune system
  - zu = humanized
  - mab = monoclonal antibody
- Cetu**xi***mab*
  - tu(m) = tumor
  - xi = chimeric
- Panitum**u***mab*
  - tu(m) = tumor
  - u = human



Bi-specific T-cell Engager (BiTE)

- Antibody with dual specificity
- Usually two variable regions
  - Joined by linker
- Specific to T-cells
  - CD3
- Specific to target
  - e.g., CD19
- Blinatumomab
  - Acute lymphoblastic leukemia

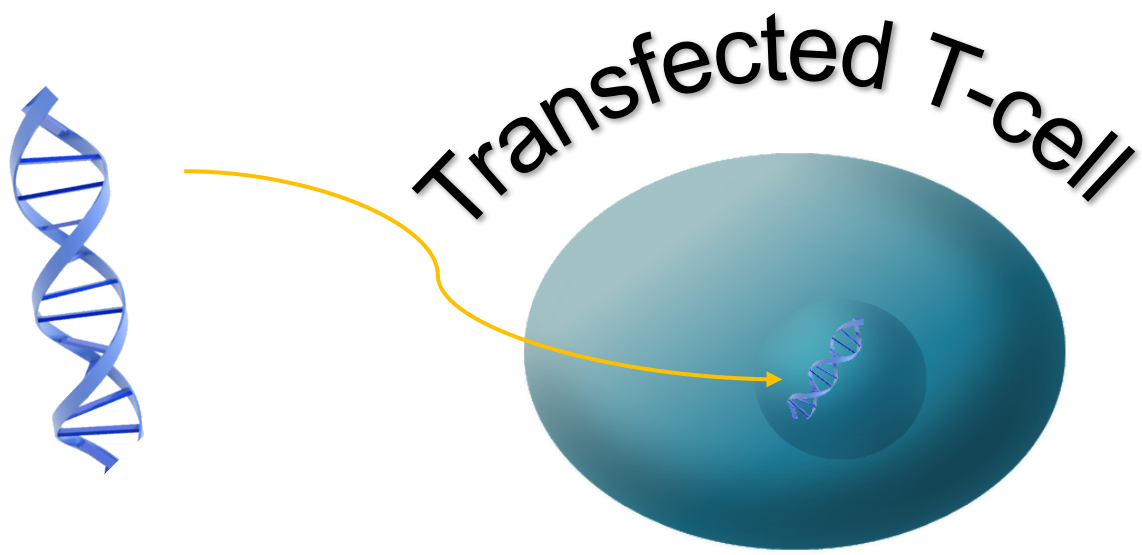




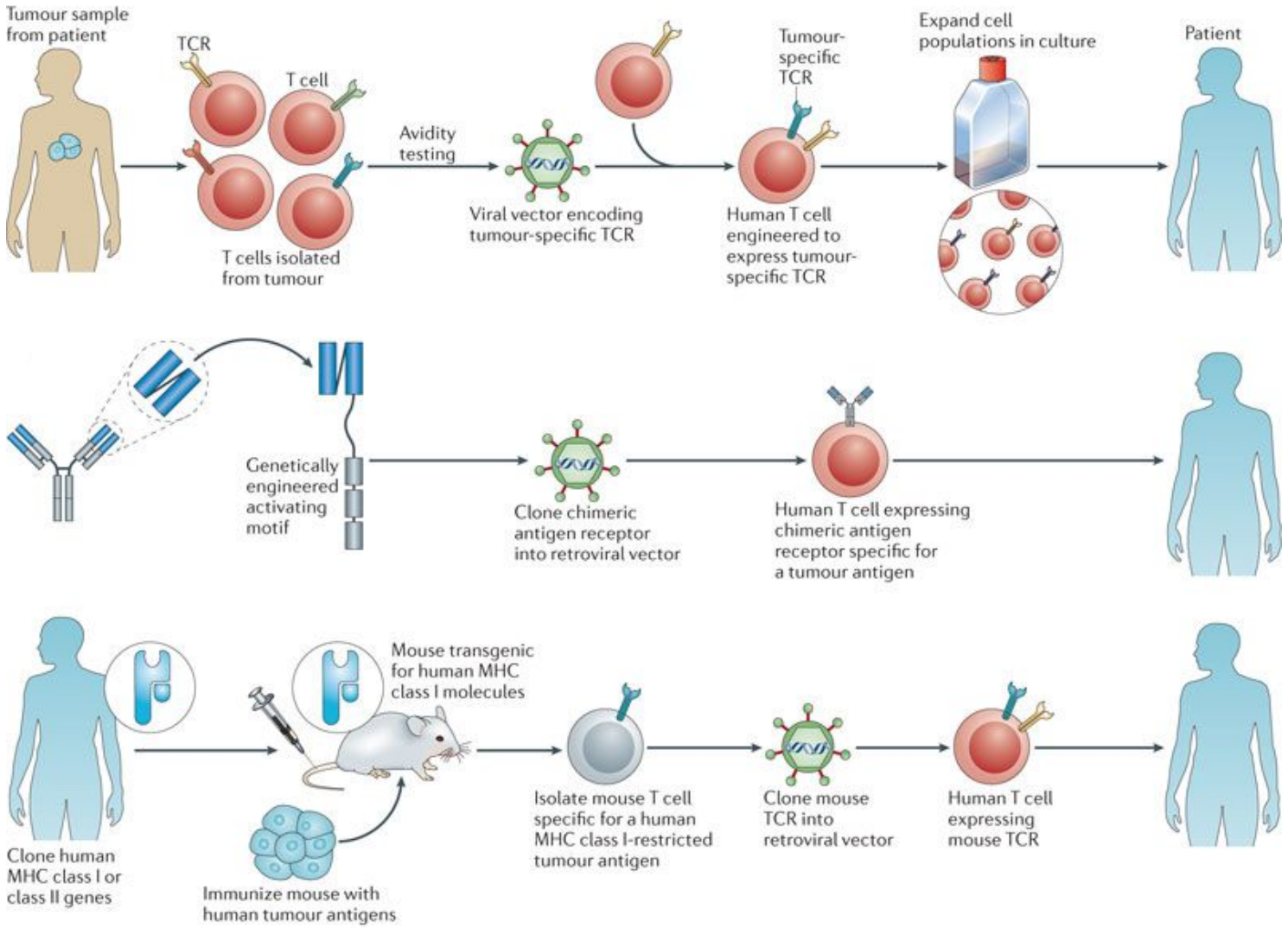
Chimeric Antigen Receptor T-cell Therapy

Procedure

- Leukapheresis
- Isolate T-cells
- Transfect T-cell with a new TCR gene
- Select augmented T-cells
- Re-infuse



Adoptive T-Cell Therapy



Evolution of CAR-T

1st generation

One signaling domain

2nd generation

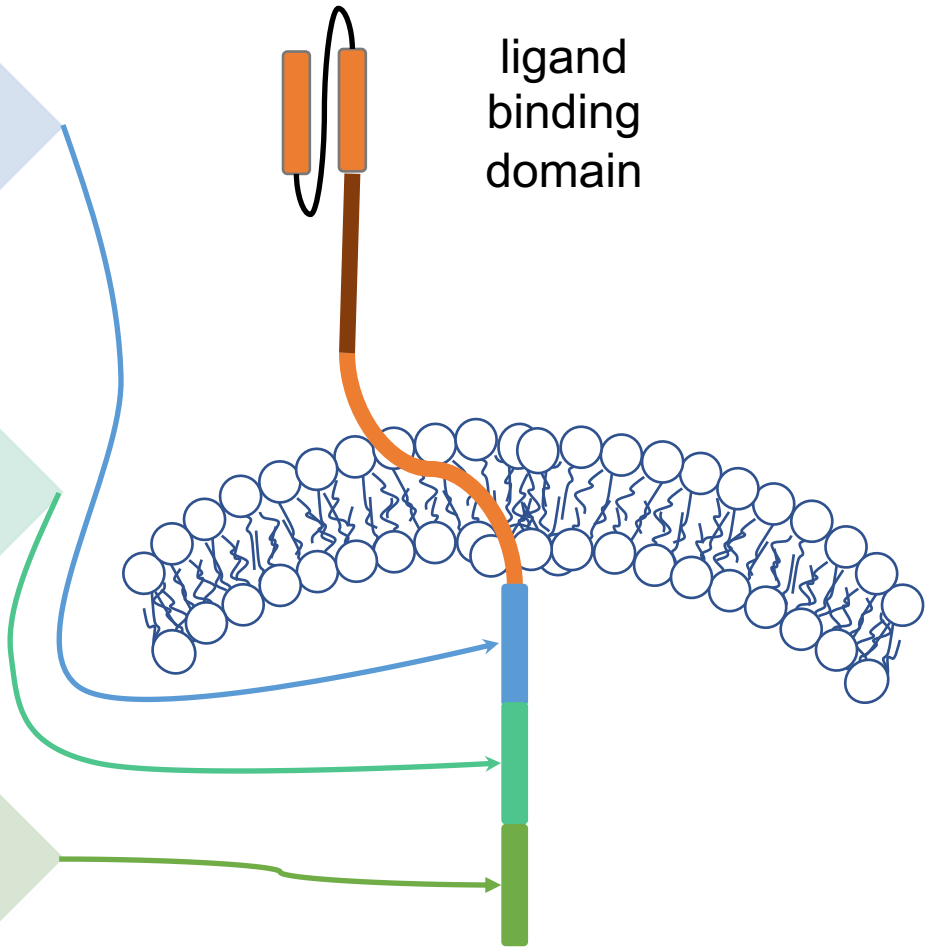
Two signaling domains

- CD28 co-stimulatory
- 41BB co-stimulatory

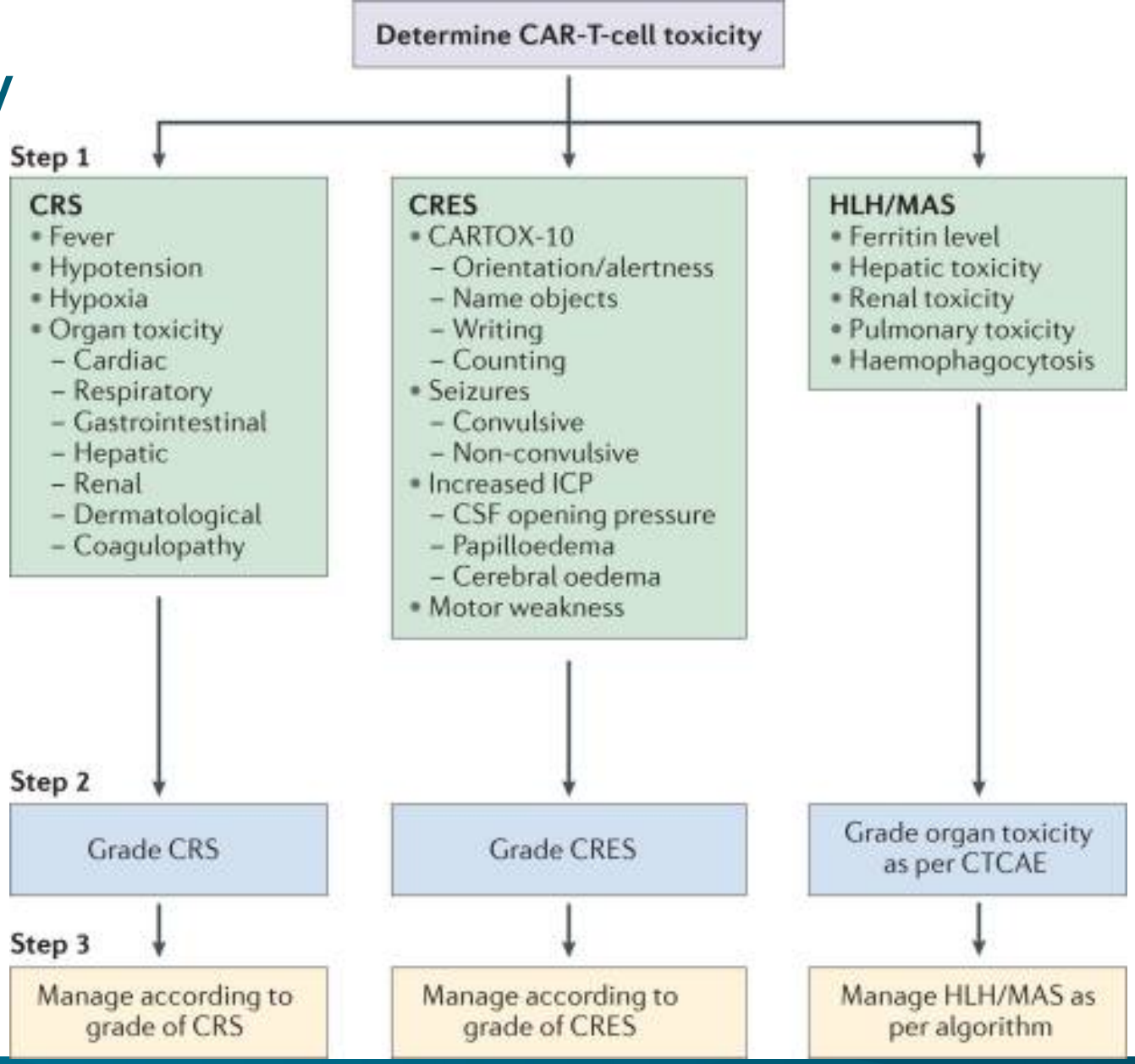
3rd generation

3-4 signaling domains

(OX40; ICOS; etc)



CAR-T Toxicity



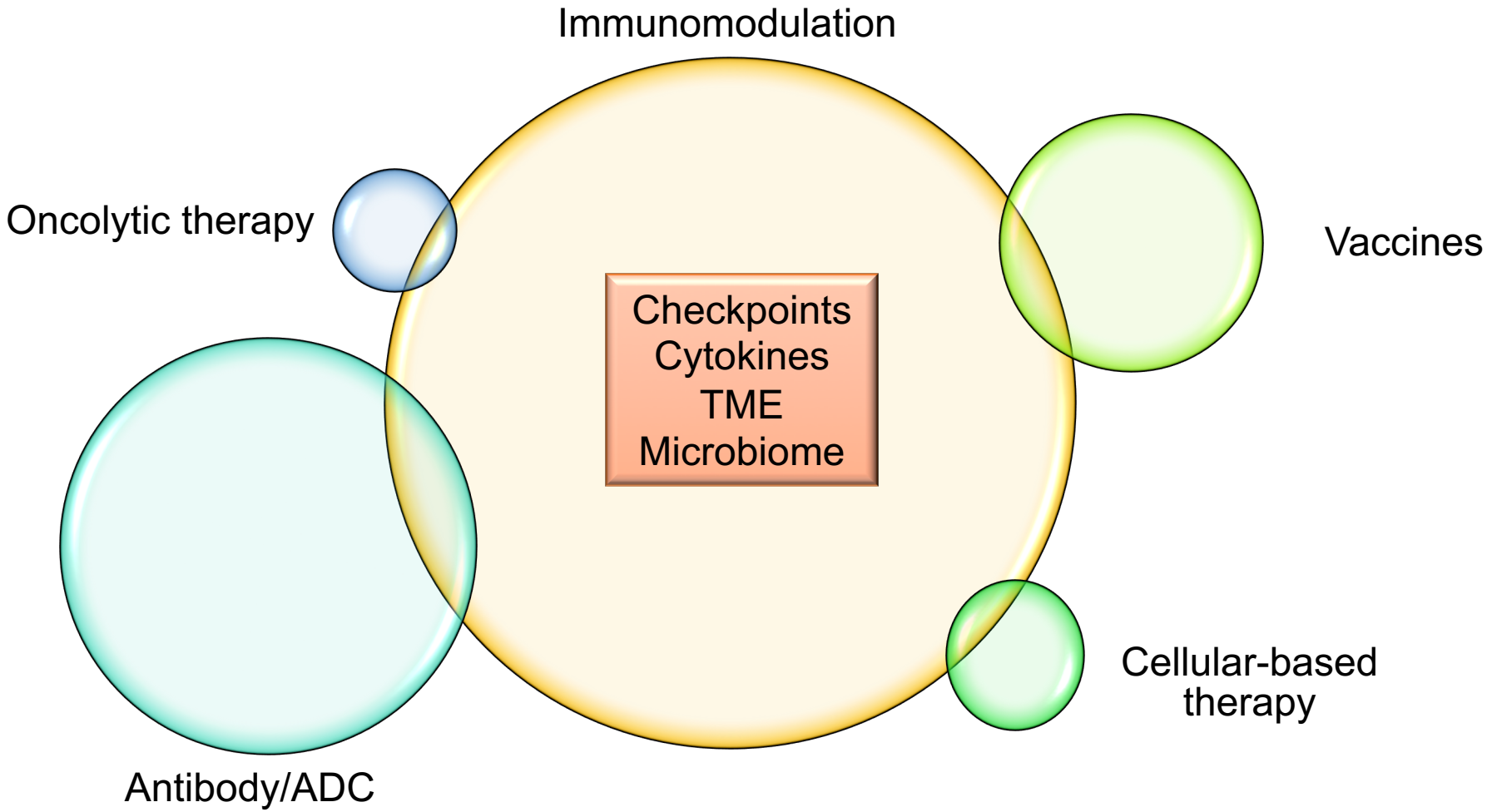
CRS = cytokine release syndrome;
CRES = CAR-T related encephalopathy syndrome
HLH/MAS = hemophagocytic lymphohistiocytosis/ macrophage-activation syndrome.

Neelaup SS, et al. *Nat Rev Clin Oncol* 2018;15:47-62

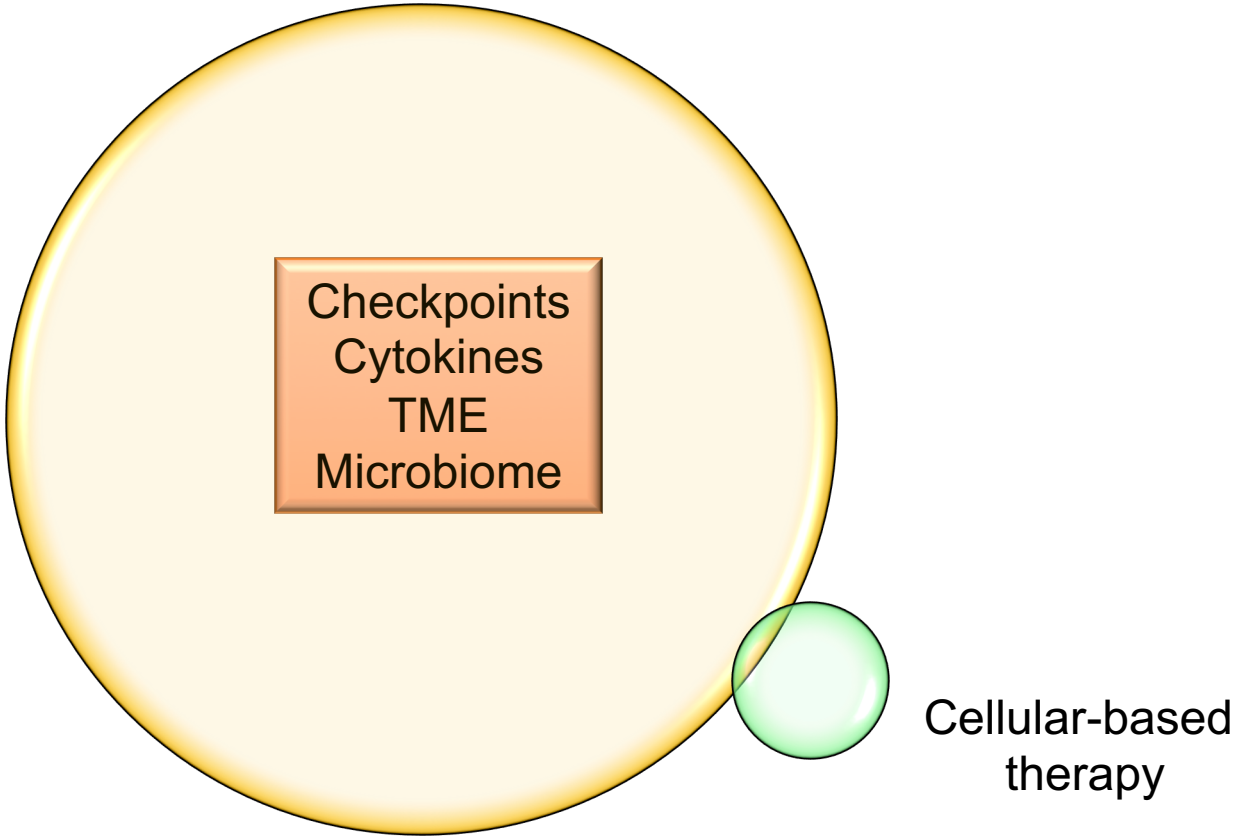
Immunotherapy 2019

Where we are today

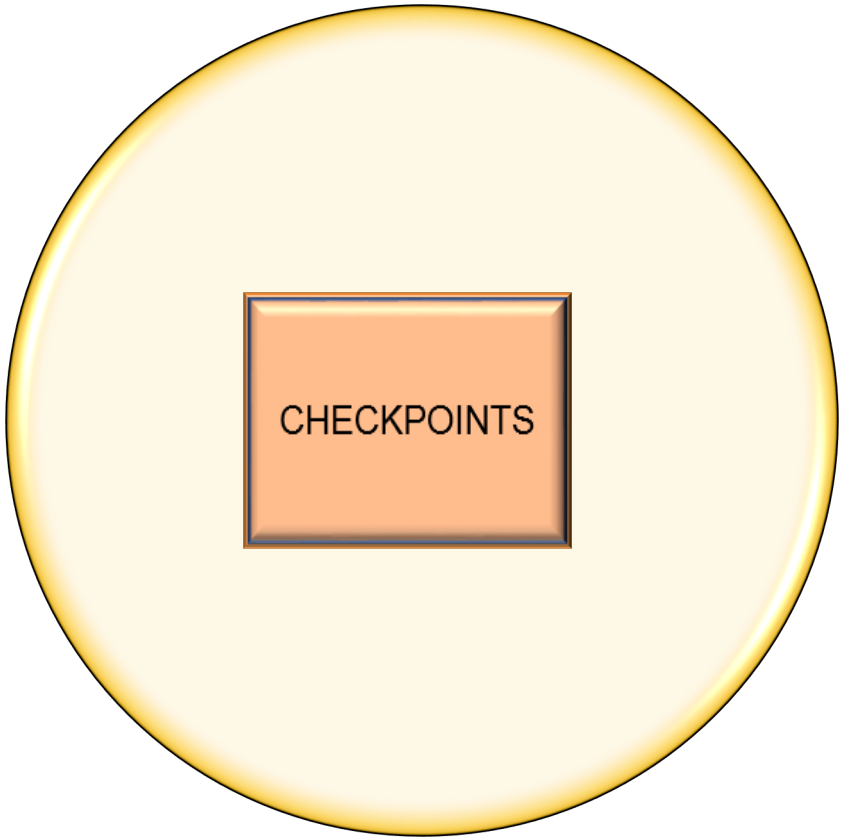
Immunotherapy, circa 2019



Immunotherapy, circa 2019



Immunotherapy, circa 2019



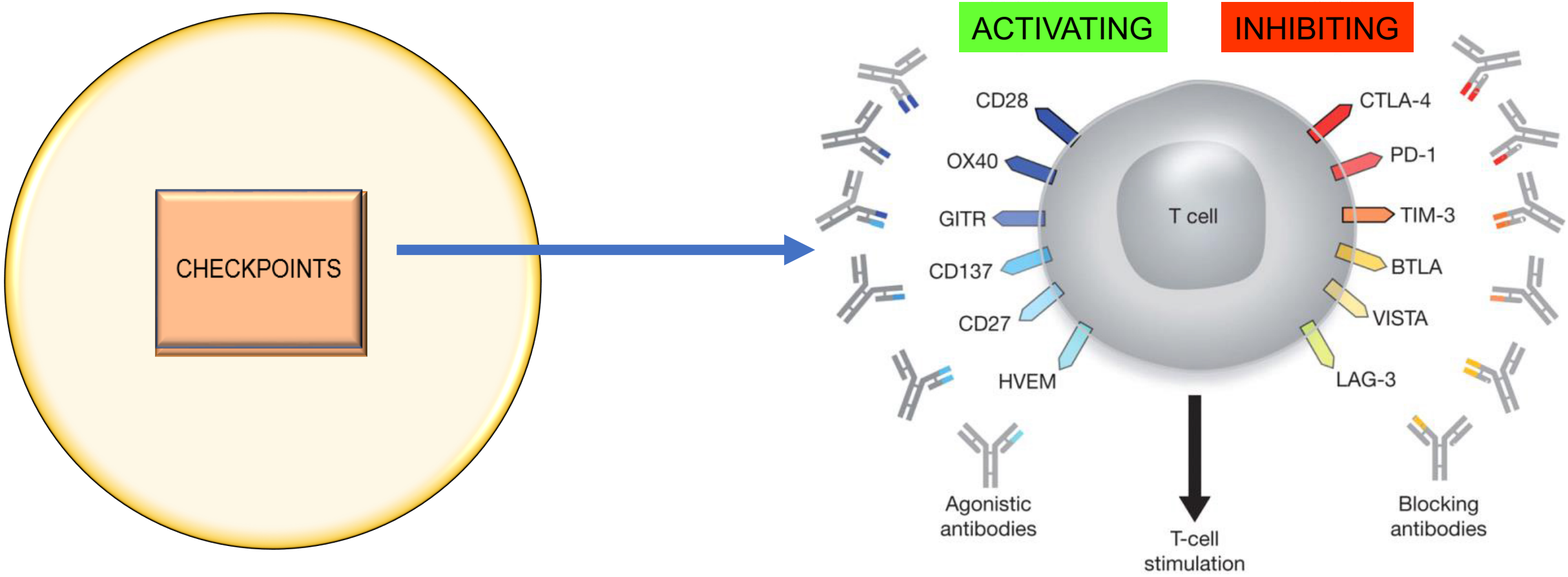
FDA Approved*
Immune Checkpoint Inhibitors (ICIs)

Anti-CTLA-4	Anti-PD-1	Anti-PD-L1
Ipilimumab	Pembrolizumab	Atezolizumab
	Nivolumab	Avelumab
	Cemiplimab	Durvalumab

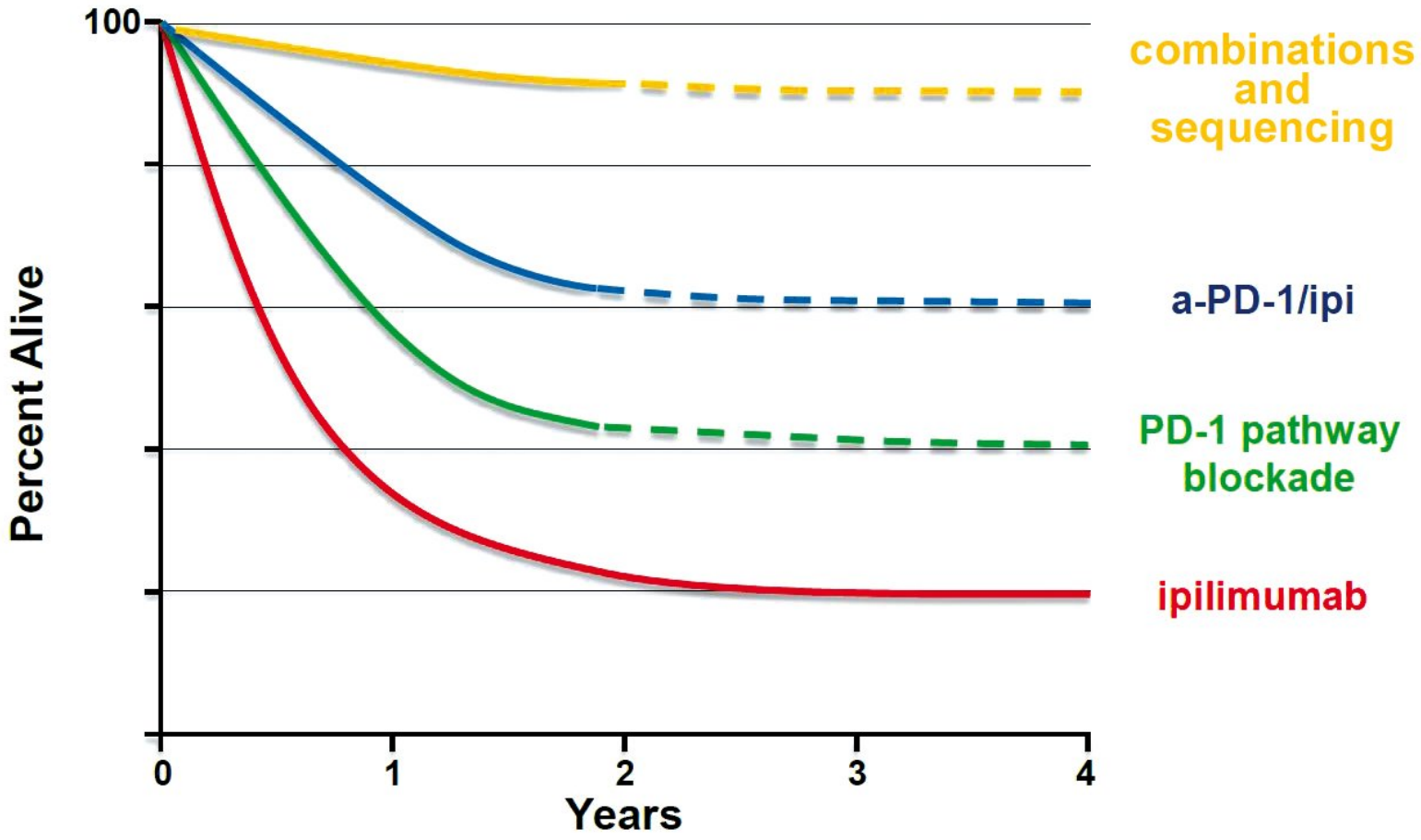
Combination: ipilimumab + nivolumab

*As of 8/2019

Immunotherapy, circa 20??



Duration of Effect

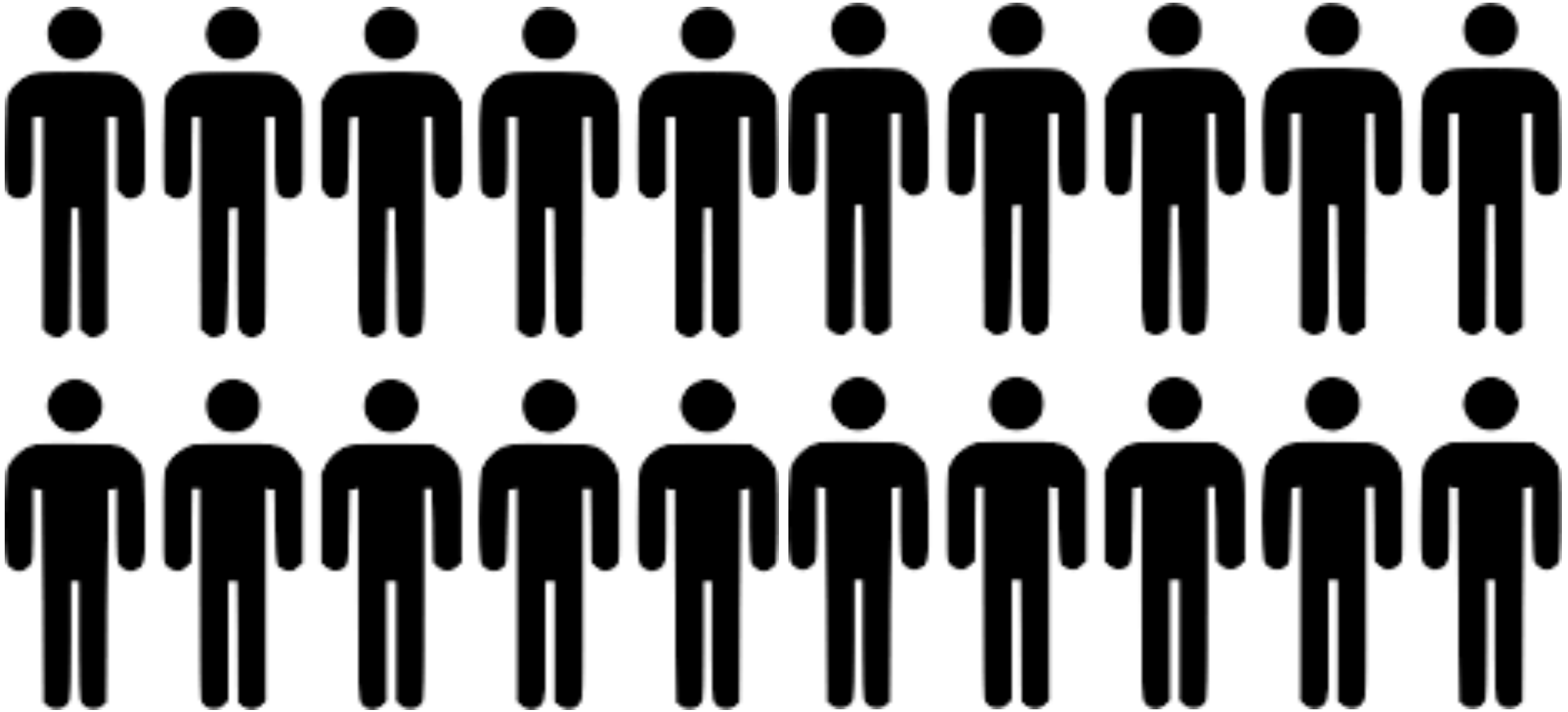


A model illustrating the potential impact of single agent & combination cancer immunotherapies on survival

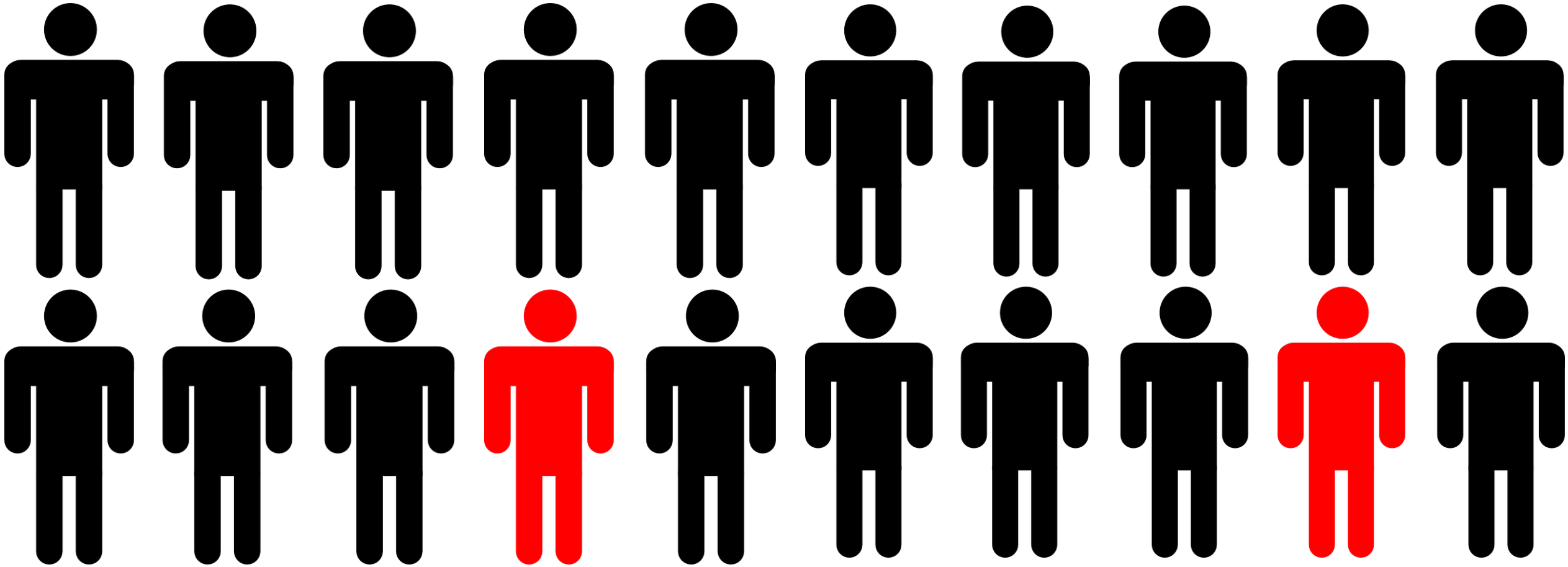
Emens LA, et al., *Eur J Cancer*. 2017;81:116e129

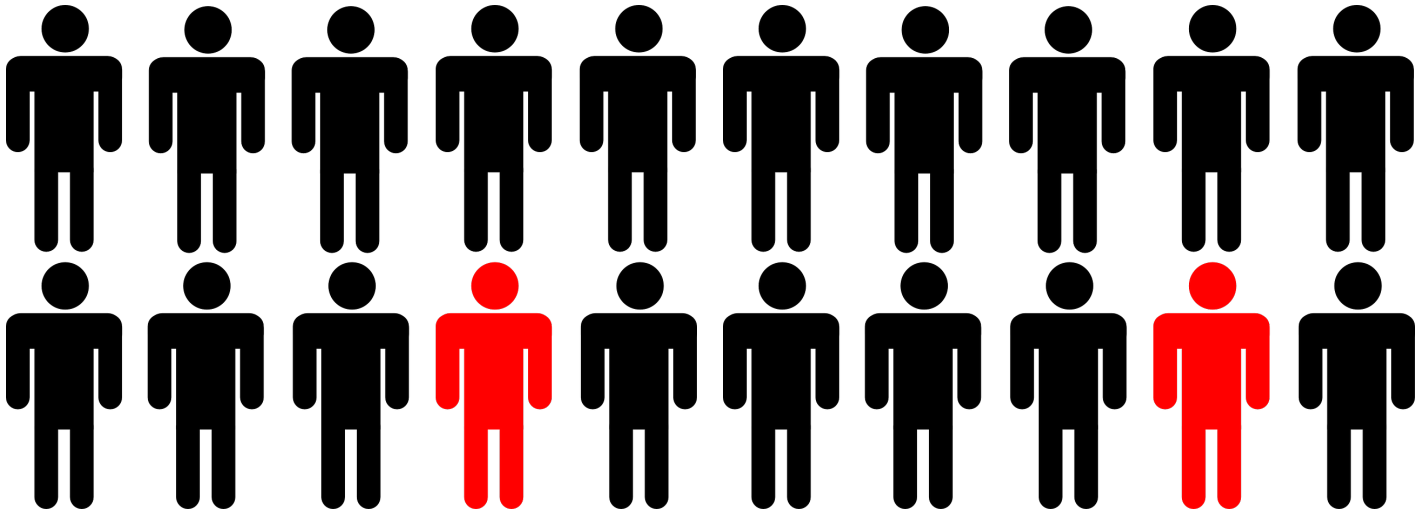
Important Care Aspects

Microbiome, Communication, Survivorship

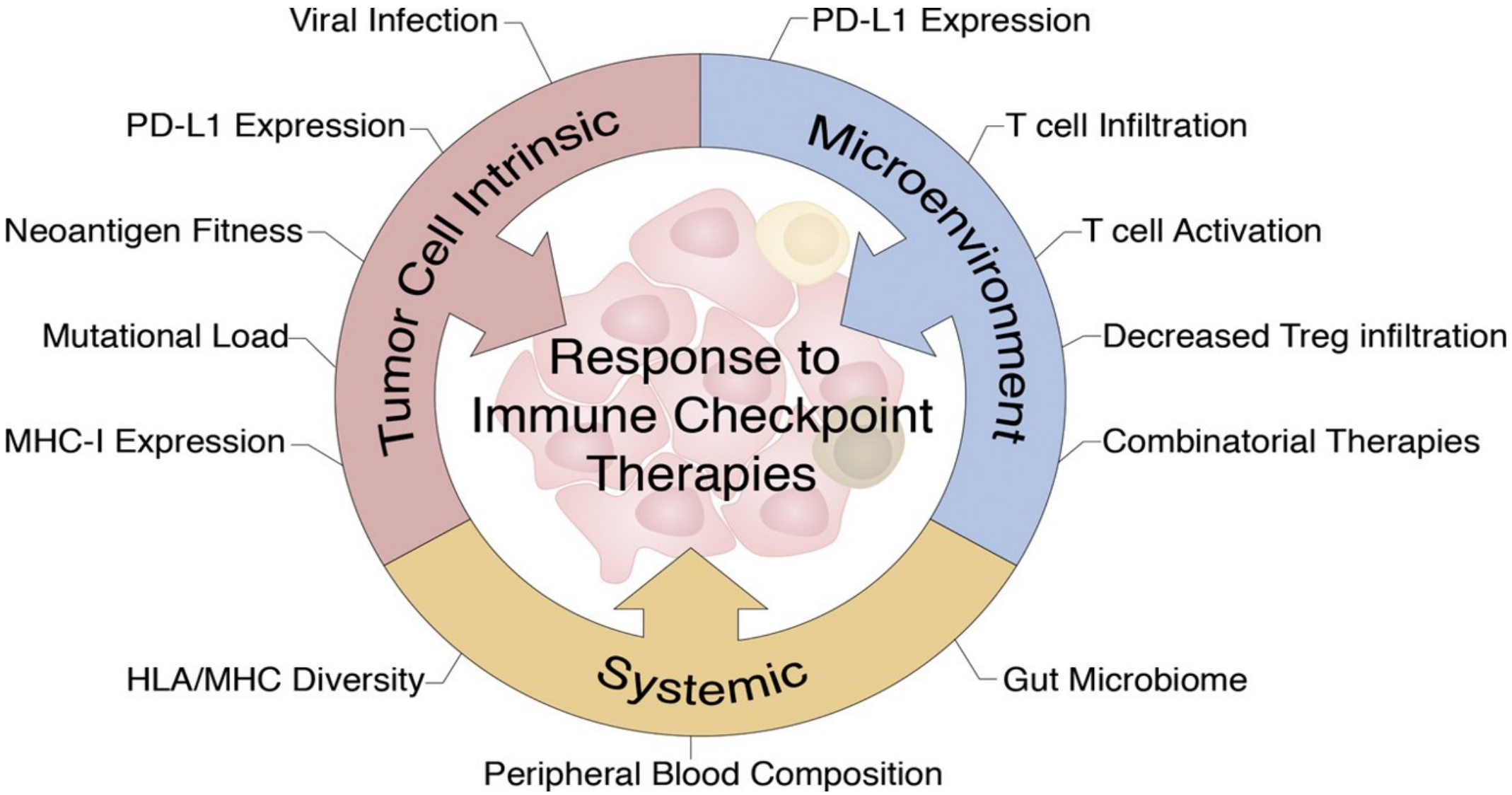


Selecting the “Right Patients”





How do we improve responses?


Viral Infection
PD-L1 Expression
PD-L1 Expression
T cell Infiltration
Neoantigen Fitness
T cell Activation
Mutational Load
Decreased Treg infiltration
MHC-I Expression
Combinatorial Therapies
HLA/MHC Diversity
Gut Microbiome
Peripheral Blood Composition
Tumor Cell Intrinsic
Microenvironment
Systemic
Response to Immune Checkpoint Therapies

Examples

- CD8+ T-cell infiltrate in tumors
- Tumor mutational burden (TMB)
- PD-L1 expression
- Gut microbiome

PD-L1 Expression

- PD-L1 expression has been associated with likelihood of response to ICI therapy
- Has both positive and negative prediction values
- Is not straightforward:
  - A proportion of patients PD-L1 negative tumors can derive benefit from treatment
  - Assays vary

Microbiome

DEVELOPMENTAL THERAPEUTICS—IMMUNOTHERAPY

Association of the diversity and composition of the gut microbiome with responses and survival (PFS) in metastatic melanoma (MM) patients (pts) on anti-PD-1 th

Jenn
Alex

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

November

DOI: 10.112

The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy

Vancheswaran
Alexandre Reub

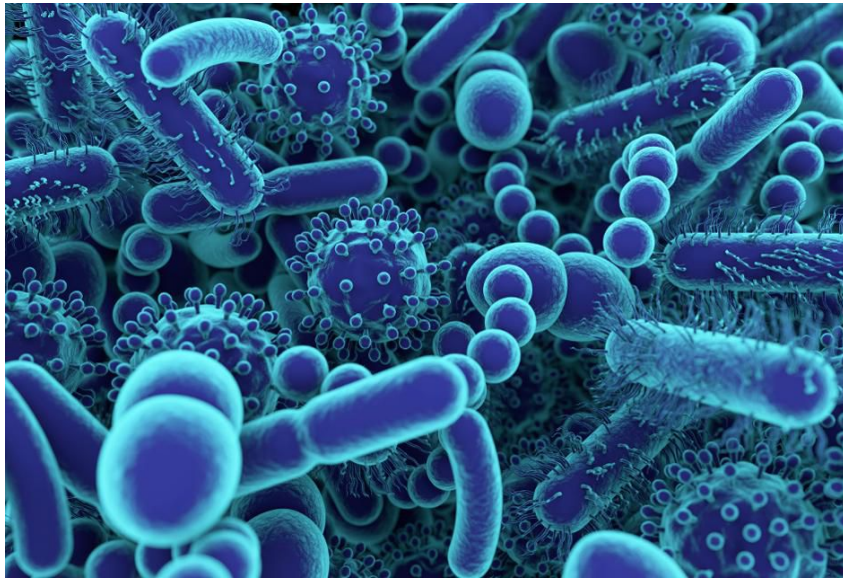
Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non–s

L Derosa, M D Hellmann,
N Long, A J Plodkowski, K
G Zalcman, L Albiges, B Es

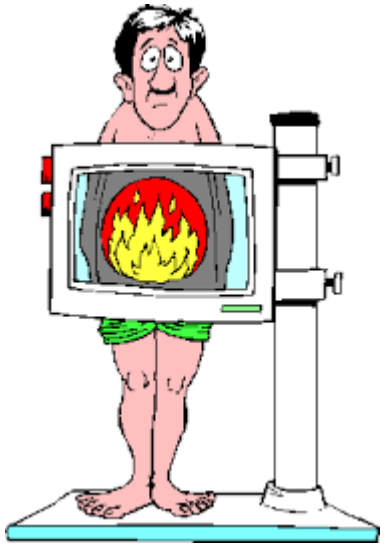
Modulating the microbiome to improve therapeutic response in cancer

Jennifer L McQuade MD, Carrie R Daniel PhD, Beth A Helmink MD and Jennifer A Wargo

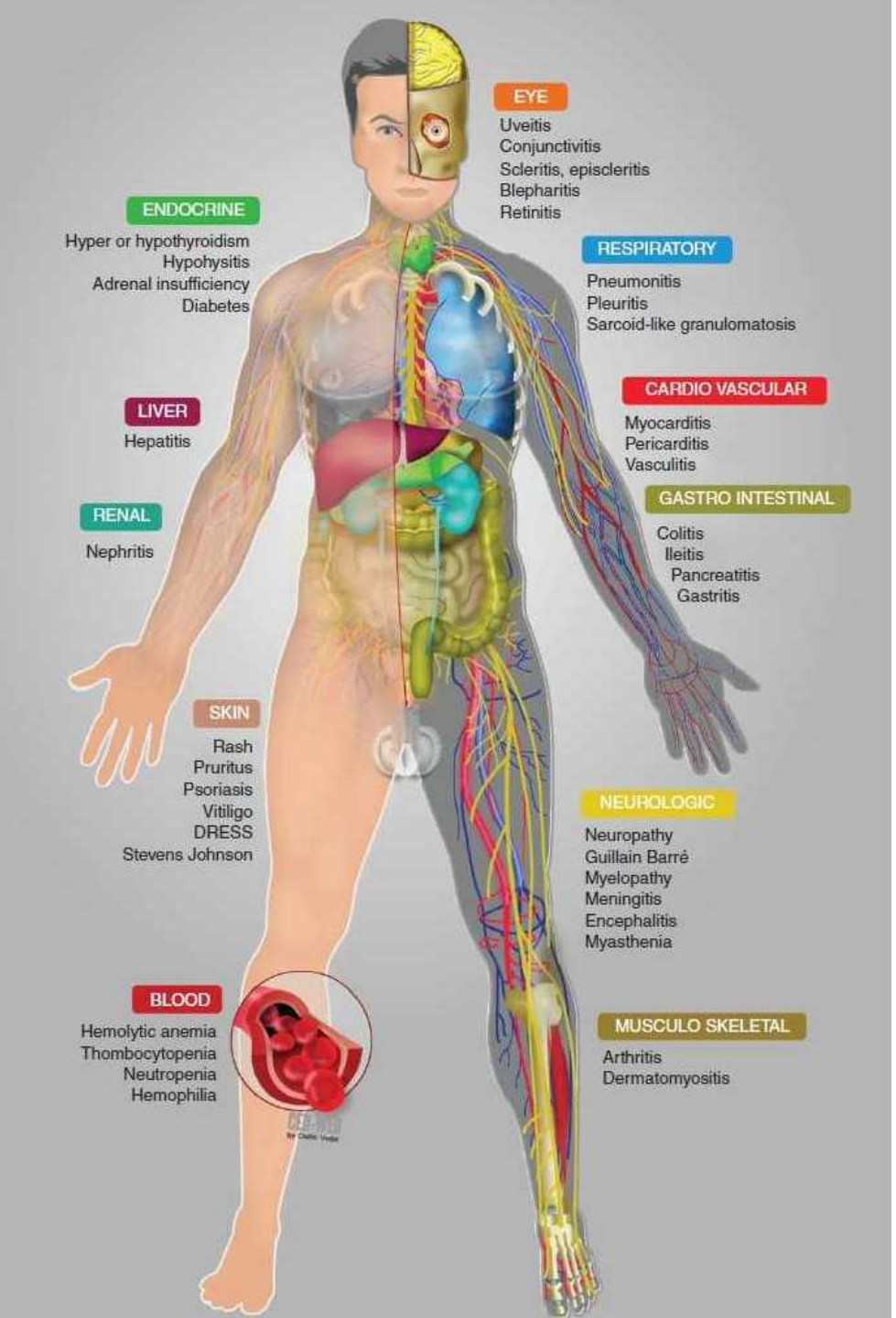
Lancet Oncology, The, 2019-02-01, Volume 20, Issue 2, Pages e77-e91. Copyright © 2019 Elsevier Ltd



Proton Pump Inhibitors



Effects of change on the microbiome



Influence of Biomarkers

- Toxicity
- Duration of treatment
- Likelihood of response

Toxicity

Monotherapy

Table 2. Incidence of treatment-related AEs of interest in major trials of nivolumab monotherapy in melanoma, lung cancer, and renal cell carcinoma

	Patients reporting event, %											
	Melanoma[a]				Lung[a]						RCC[b]	
	CheckMate 037		CheckMate 066		CheckMate 017		CheckMate 057		CheckMate 153[b]		CA209-010	
Event	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Pruritus	16.0	0	17.0	0.5	2	0	8	0	NR		9	2
Rash	9.3	0.4	15.0	0.5	4	0	9	<1	1.9	0	7	0
Diarrhea	11.2	0.4	16.0	1.0	8	0	8	1	6.5	0.3	11	0
Colitis	1.1	0.7	1.0	0.5	1	1	NR		NR		NR	
Elevated ALT	2.6	0.7	1.5	1.0	2	0	3	0	NR		4	2
Elevated AST	4.1	0.4	1.0	0.5	2	0	3	<1	NR		7	2
Hypothyroidism	5.6	0	4.4	0	4	0	7	0	3.8	0.1	7	2
Hypophysitis	NR		0.5	0.5	NR		NR		NR		NR	
Pneumonitis	1.9	0	1.5	0	5	1	3	1	0.8	0.3	4	0

Patients were treated with NIVO 3 mg/kg in the melanoma and lung cancer studies. Patients received NIVO 0.3, 2, or 10 mg/kg in the RCC study CA209-010; only data from the NIVO 2 mg/kg group are reported.
[a]AEs of potential immunological etiology.
[b]Based on patients with an Eastern Cooperative Oncology Group performance status of 0 or 1.
Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIVO, nivolumab; NR, not reported; RCC, renal cell carcinoma.

Combination

Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors

	Patients reporting event, %							
	NIVO[a,b]		NIVO + IPI[a,c]		IPI[a,d]		Pembro[e,f]	
AE	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3-5
Pruritus	18.8	0	33.2	1.9	35.4	0.3	14.1	0
Rash	25.9	0.6	40.3	4.8	32.8	1.9	13.4	0
Diarrhea	19.2	2.2	44.1	9.3	33.1	6.1	14.4	1.1
Colitis	1.3	0.6	11.8	7.7	11.6	8.7	2.9	1.8
Elevated ALT	3.8	1.3	17.6	8.3	3.9	1.6	1.4	0.4
Elevated AST	3.8	1.0	15.3	6.1	3.5	0.6	2.2	0.4
Hypothyroidism	8.6	0	15.0	0.3	4.2	0	7.6	0
Hypophysitis	0	0	0.3	0	0	0	0.4	0.4
Pneumonitis	1.3	0.3	6.4	1.0	1.6	0.3	1.8[g]	0.4[g]

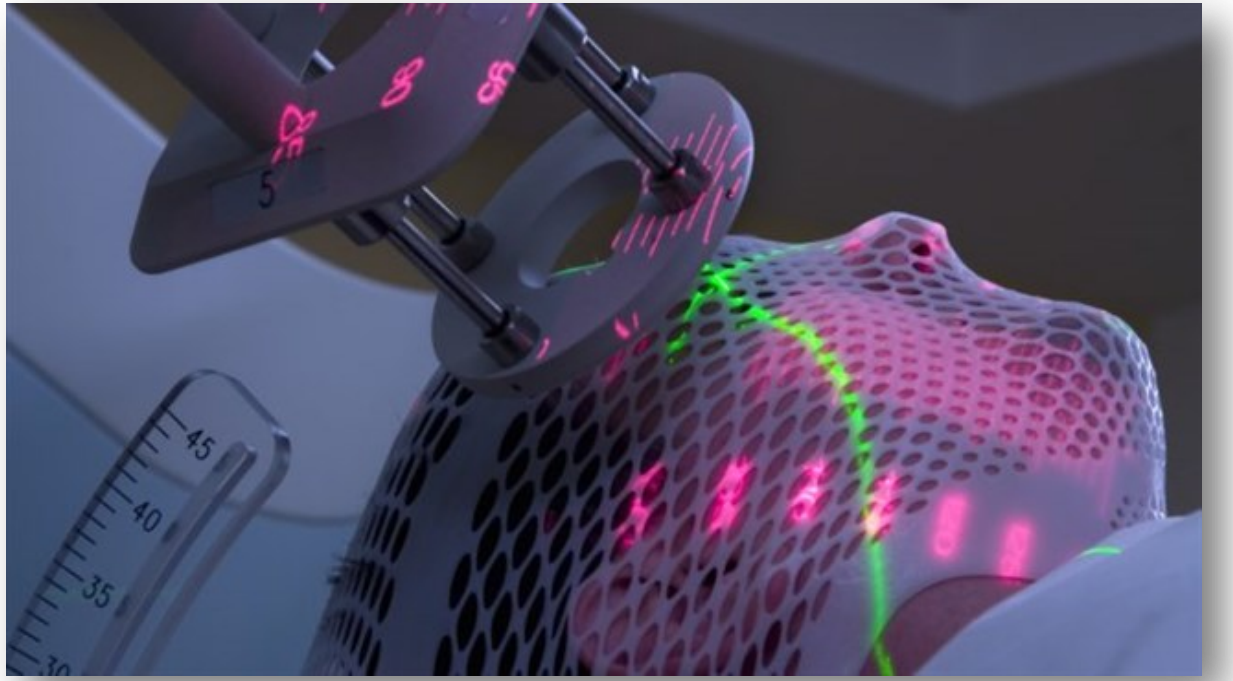
[a]Based on data from the phase 3 study CheckMate 067 [6]. Incidence of hypophysitis and pneumonitis is based on unpublished data from CheckMate 067.
[b]One treatment-related death (neutropenia) was reported.
[c]No treatment-related deaths were reported.
[d]One treatment-related death (cardiac arrest) was reported.
[e]Based on data from the phase 3 study KEYNOTE-006 every 3 week dosing group [4].
[f]No treatment-related deaths were reported.
[g]AE of special interest, regardless of attribution of study drug.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab; Pembro, pembrolizumab.

Weber, et al. *The Oncologist.* 2016;21:1230-40.

Enhancing Treatment Effects

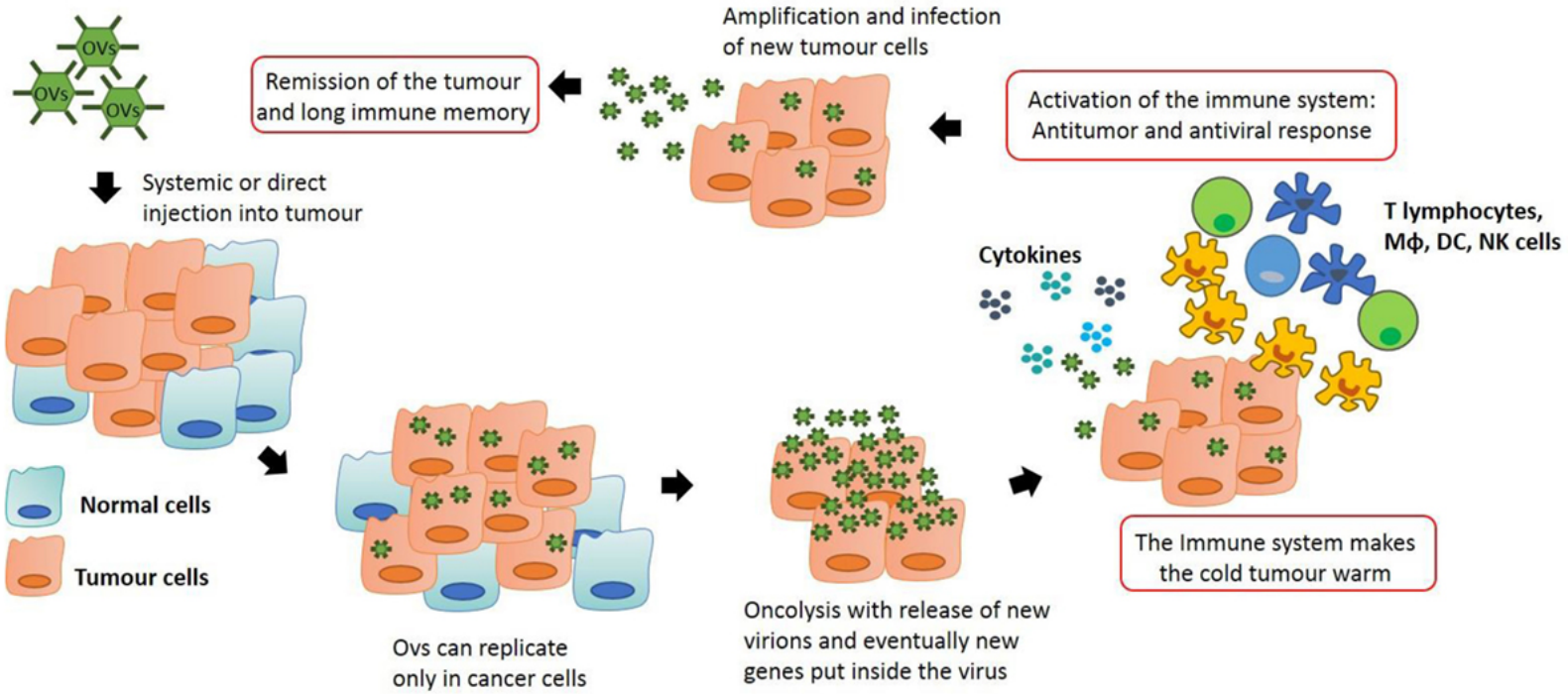
Combining modalities

- XRT (abscopal effect)
  - Radiotherapy exerts direct cytotoxic effects on tumor cells
    → **LOCAL EFFECT**
  - **But also reprograms the tumor microenvironment to exert a potent antitumor immune response and enhances antitumor immunity**
    → **DISTANT EFFECT**



Weichselbaum RR, et al. *Nat Rev Clin Oncol*. 2017;14:365-79

Oncolytic Viruses



Change the local tumor microenvironment

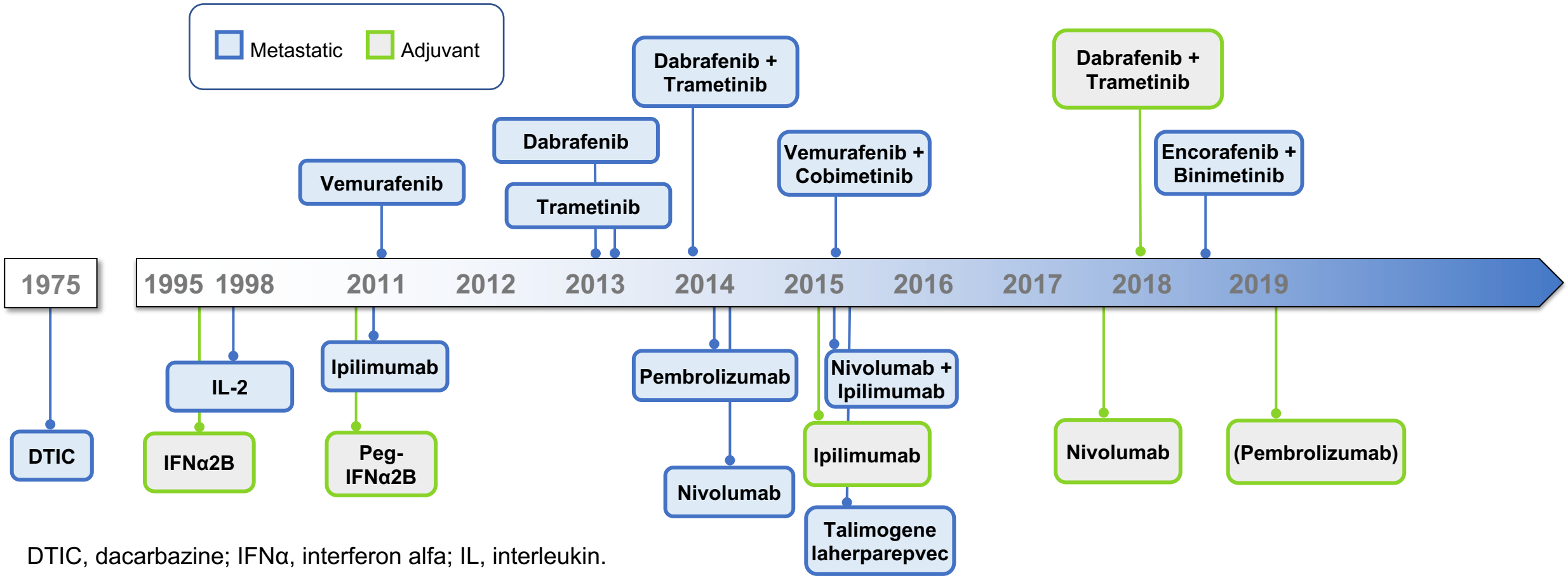
- Make an immunologically "cold" tumor (lacking T cells) into a "hot" inflamed tumor
- May sensitize tumors to immunoRx

Marelli G, et al. *Front Immunol*. 2018;9:866; Kaufman HL, et al. *J Clin Oncol*. 2015;1;33(25):2780-8.

Defining Success

Where are we now?

Melanoma Landscape (circa 2019)

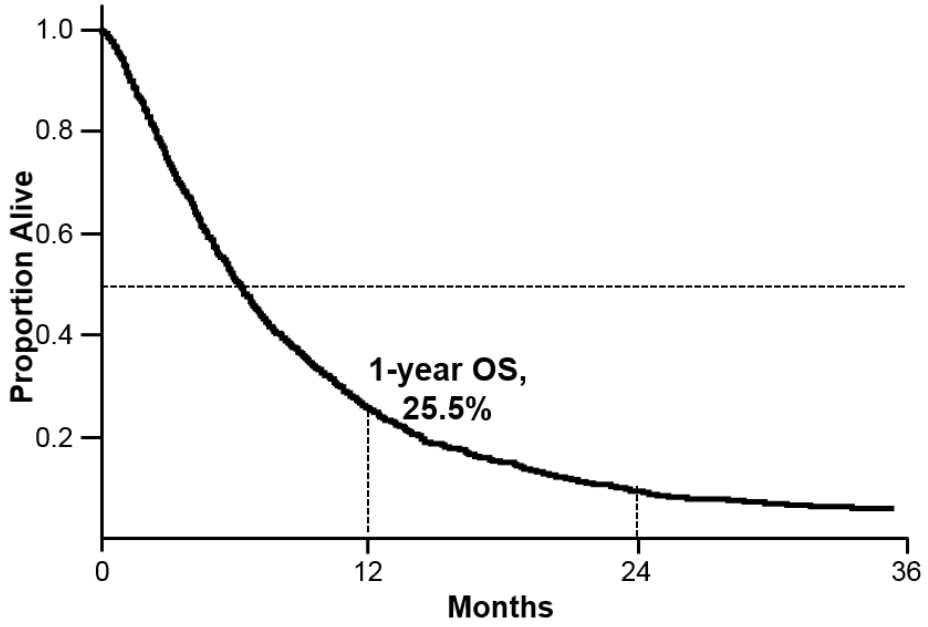


DTIC, dacarbazine; IFNα, interferon alfa; IL, interleukin.

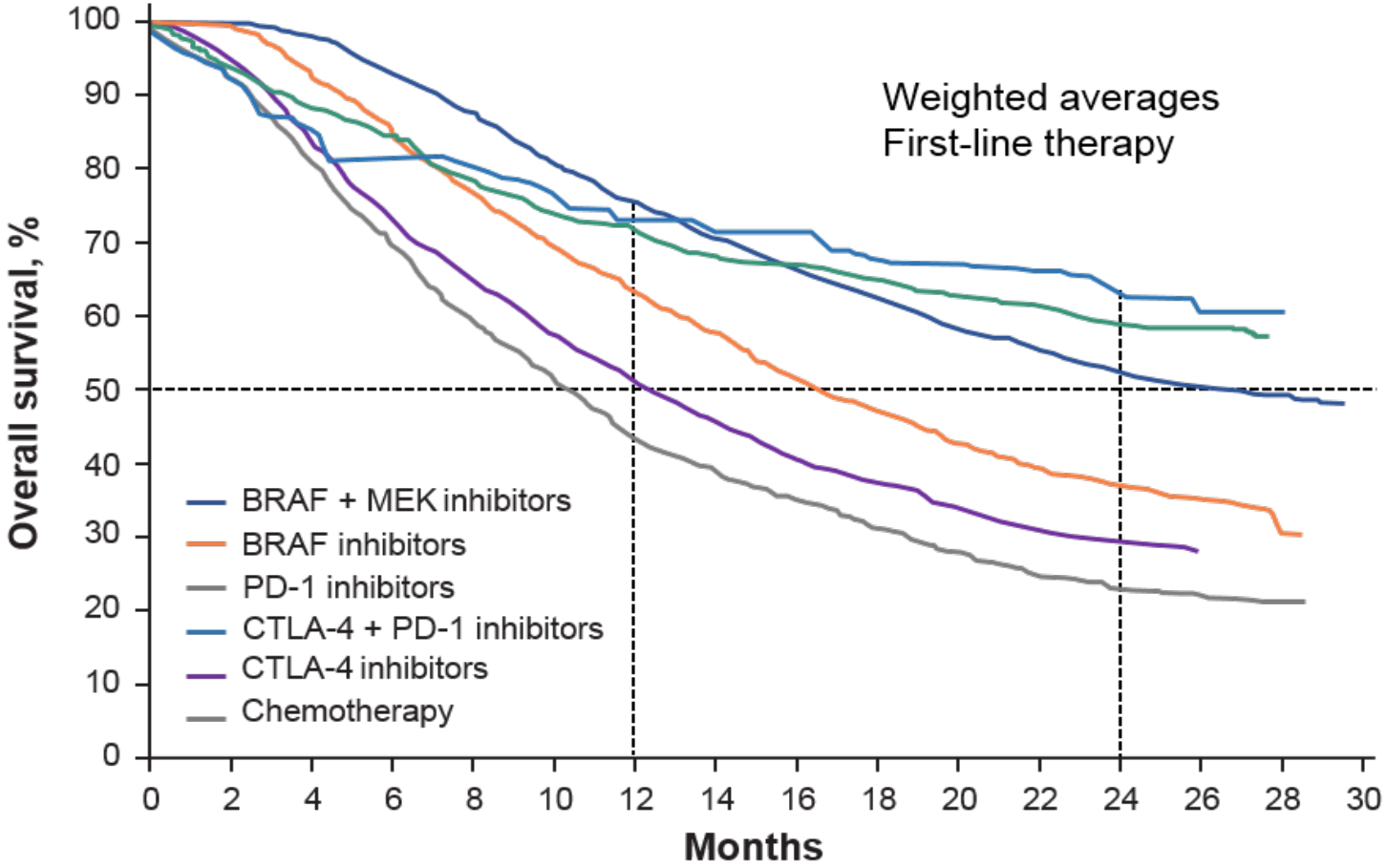
Approved in the United States.

Impact of Current Therapies

Historical OS



Current OS With Available Therapies



Korn EL, et al. *J Clin Oncol*. 2008;26(4):527-534; Ugurel S, et al. *Eur J Cancer*. 2017;83:247-257

The Problem With Miracle Cancer Cures

By Robert M. Wachter

Dr. Wachter is a hospitalist, a physician who cares for patients in hospitals and studies how to make hospitals safer and more efficient.

April 19, 2018

"A recent analysis estimated that about 15% of patients with advanced cancer might benefit from immunotherapy, and it's all but impossible to determine which patients will be the lucky ones."

"Sadly, for some patients, a cure will prove elusive. As we continue to chase progress in cancer, let's be sure that we don't rob dying patients of a smaller, more subtle miracle: a death with dignity and grace, relatively free from pain and discomfort."

Strategies for Success

Direct patient care

- Education/counseling
- Partnering with patients and caregivers
- Setting expectations
- Early ID of barriers to care

Indirect patient care

- Ensuring/establishing multidisciplinary directed
- Toxicity directed algorithms
- End-of-life or survivorship care
- Peer/coworker education

communication

Communication

Meeting the Challenge of Immune-Related Adverse Events With Optimized Telephone Triage and Dedicated Oncology Acute Care

Brianna Hoffner, MSN, ANP-BC, AOCNP®, and Krista M. Rubin, MS, FNP-BC

New Investigations

Co-inhibitory

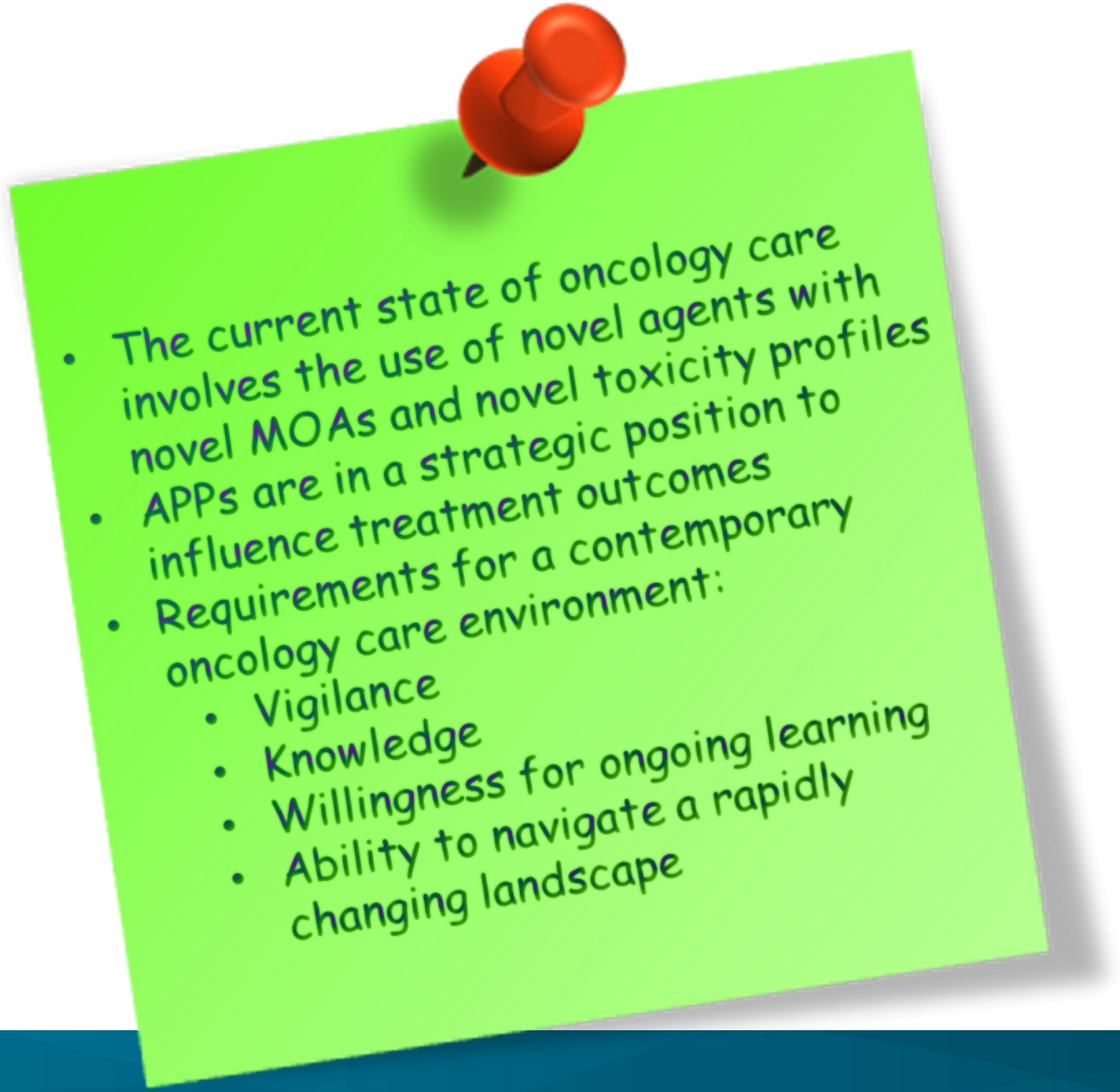
- TIGIT (T-cell immunoglobulin and ITIM domain)
- TIM-3 (T-cell immunoglobulin and mucin domain 3)
- TLR-9 (Toll-like receptor 9)
- LAG-3 (Lymphocyte activation gene-3)
- VISTA (V-domain Ig suppressor of T-cell activation)

Co-stimulatory

- OX40
- CD40
- 4-1BB

} Molecules in the tumor necrosis factor (TNF) receptor superfamily

- GITR (glucocorticoid-induced TNF receptor)


The current state of oncology care involves the use of novel agents with novel MOAs and novel toxicity profiles
APPs are in a strategic position to influence treatment outcomes
Requirements for a contemporary oncology care environment:
Vigilance
Knowledge
Willingness for ongoing learning
Ability to navigate a rapidly changing landscape

More Questions?

Come see us at Booth **#829** (next to the APSHO Booth)
in the Exhibit Hall from **2:50 to 3:50 pm** today

SMARTIE

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019