MAYO CLINIC

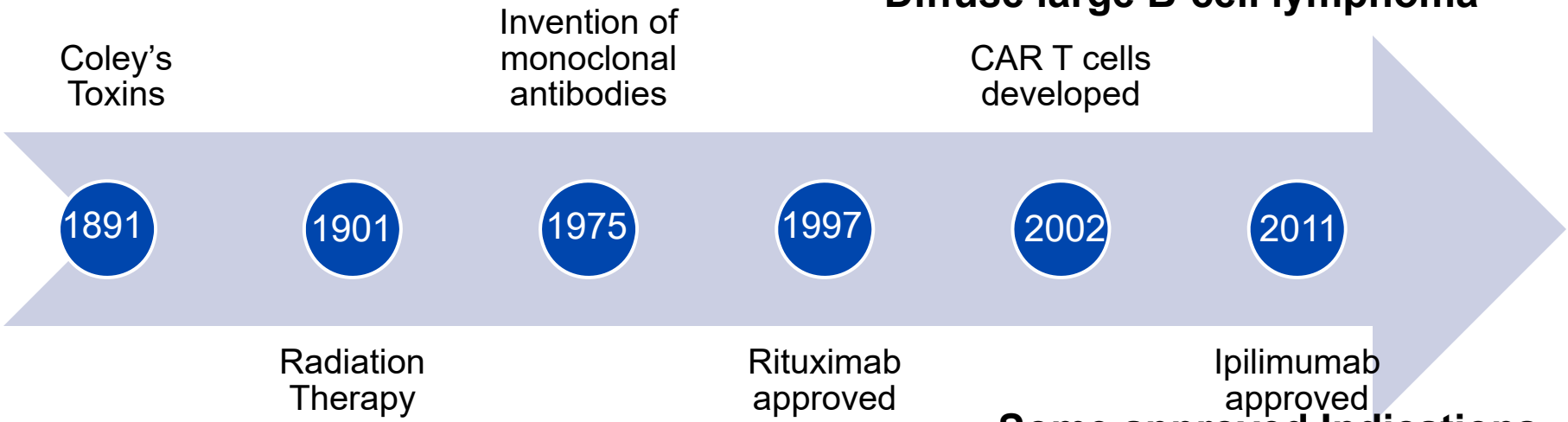
Let's Get Ready to CAR-T: Management of Immunotherapy Toxicities

Victoria Milano, PharmD

Learning Objectives

- Describe the mechanism of immune checkpoint inhibitor and CAR T-cell therapy toxicities
- Review the most common types of toxicities and risk factors associated with immunotherapy treatment
- Discuss literature and guideline recommendations for the management of immunotherapy toxicities

Timeline



Approved Indications

- **Primary mediastinal large B-cell lymphoma**
- **Acute lymphoblastic leukemia**
- **Diffuse large B-cell lymphoma**

Some approved Indications

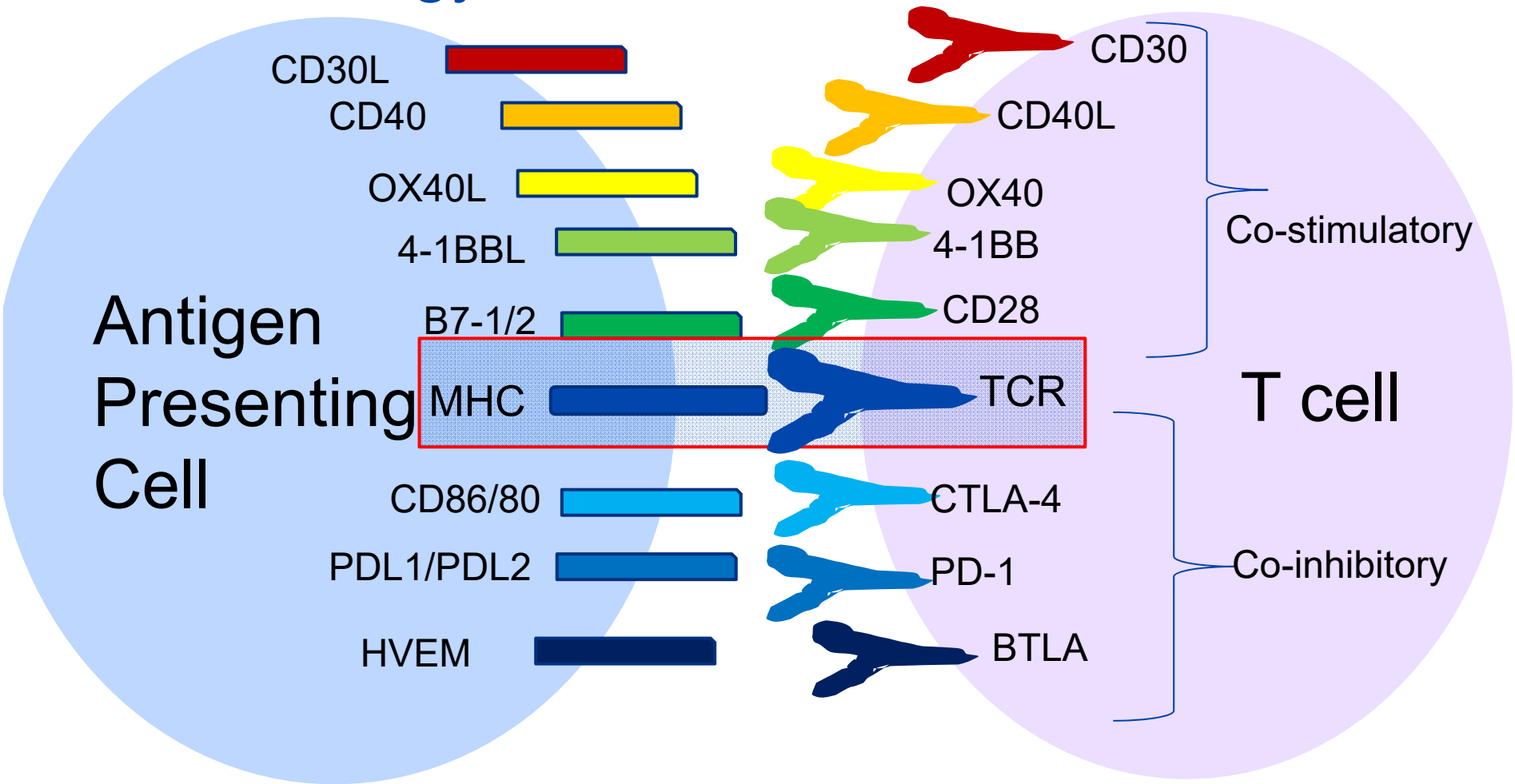
- **Malignant melanoma**
- **Head and neck cancer**
- **Hepatocellular carcinoma**
- **Renal cell carcinoma**
- **Cervical cancer**
- **Non-small cell lung cancer**
- **Hodgkin's lymphoma**

Marshall HT, et al. Front Oncol 2018; 8:315

What is Immunotherapy?

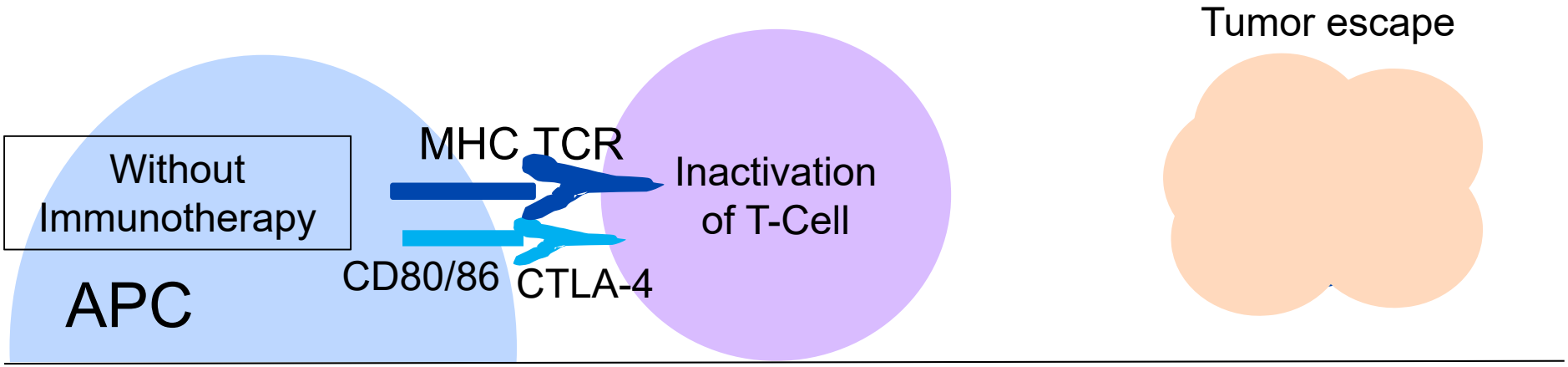
- Uses an individual's immune system to fight cancer
  - Monoclonal antibodies
  - Cancer vaccines
  - Immune checkpoint inhibitors
  - T-cell transfer therapy

Immunology



Marshall HT, et al. Front Oncol 2018; 8:315

CTLA-4 Inhibitors Mechanism of Action

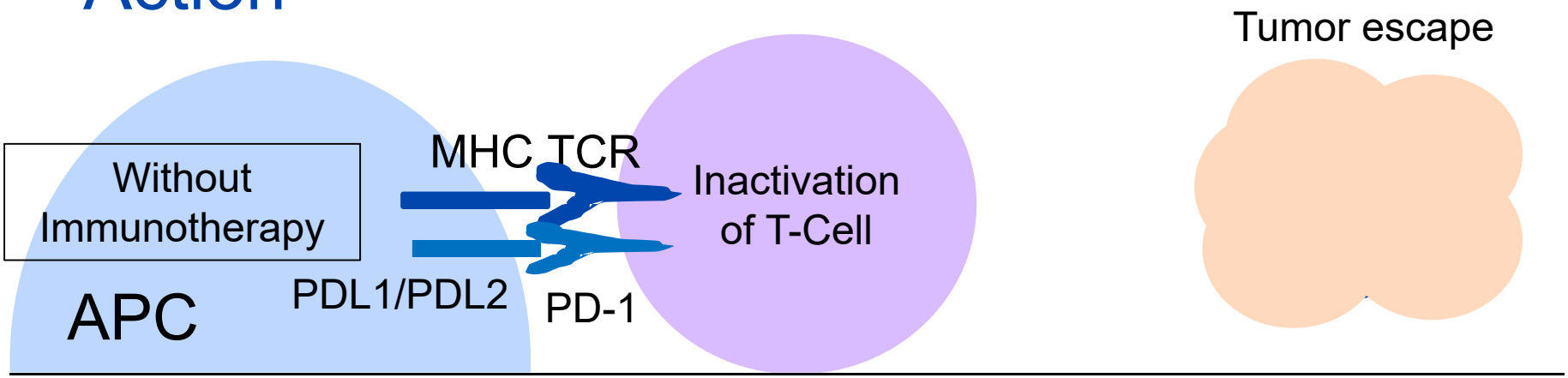


- Ipilimumab

Marshall HT, et al. Front Oncol 2018; 8:315

APC=antigen presenting cell

PD-1 and PD-L1 Inhibitors Mechanism of Action



<u>PD-1 inhibitors</u>

- Nivolumab
- Pembrolizumab
- Cemiplimab

<u>PD-L1 Inhibitors</u>

- Atezolizumab
- Avelumab
- Durvalumab

Marshall HT, et al. Front Oncol 2018; 8:315

APC=antigen presenting cell

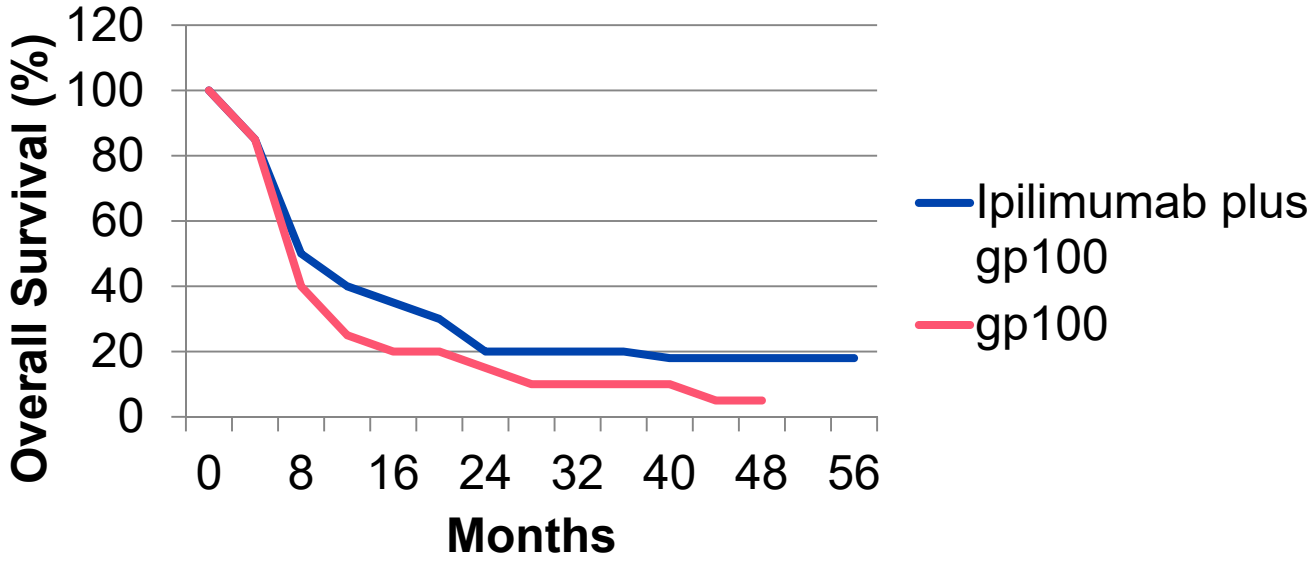
Ipilimumab Efficacy Trial

Population

- Unresectable stage III or IV melanoma

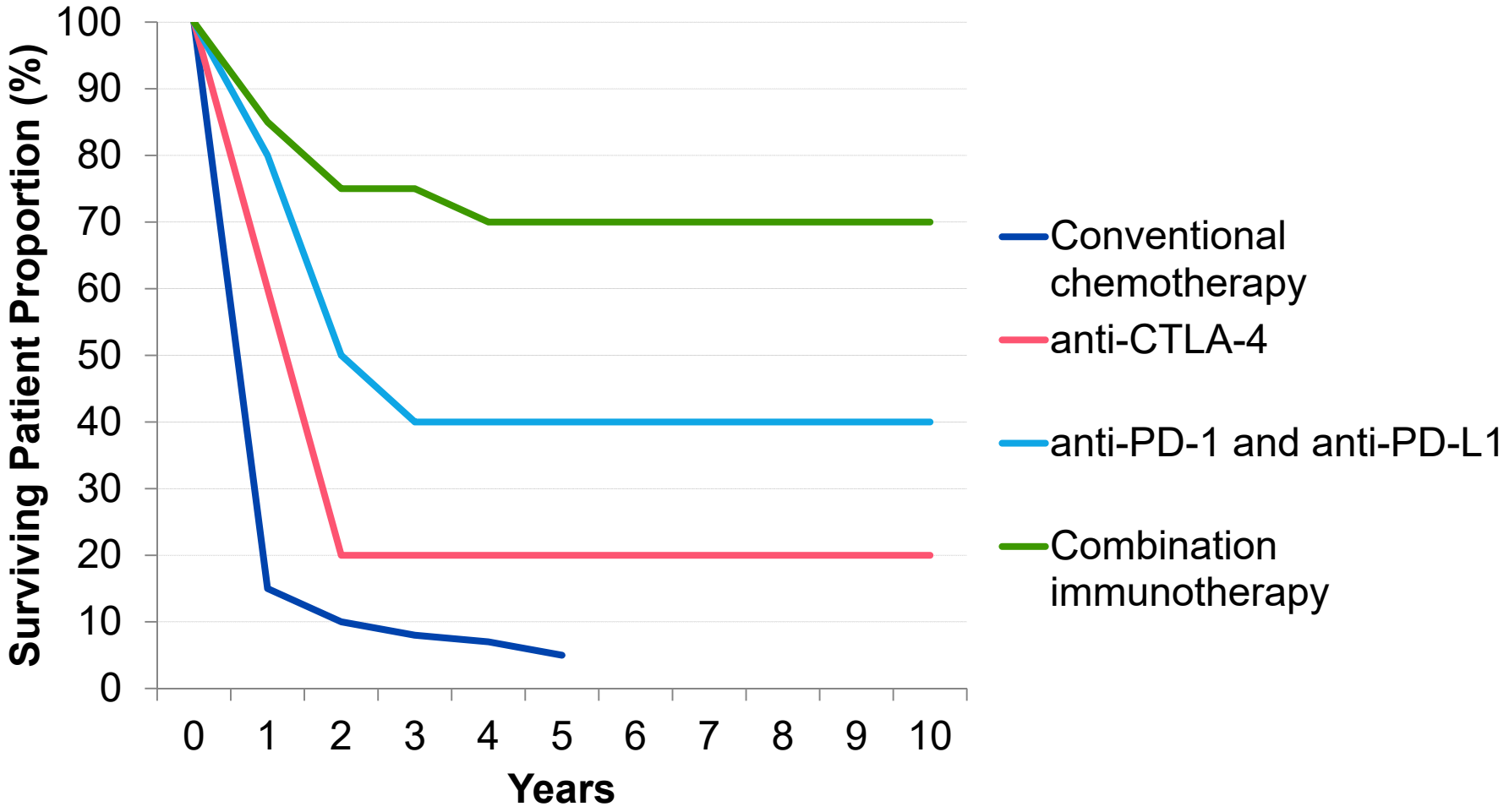
Intervention

- Ipilimumab plus gp100
- gp100 alone



Hodi FS, et al. NEJM 2010; 363:711-723

Survival Rates



MAYO CLINIC

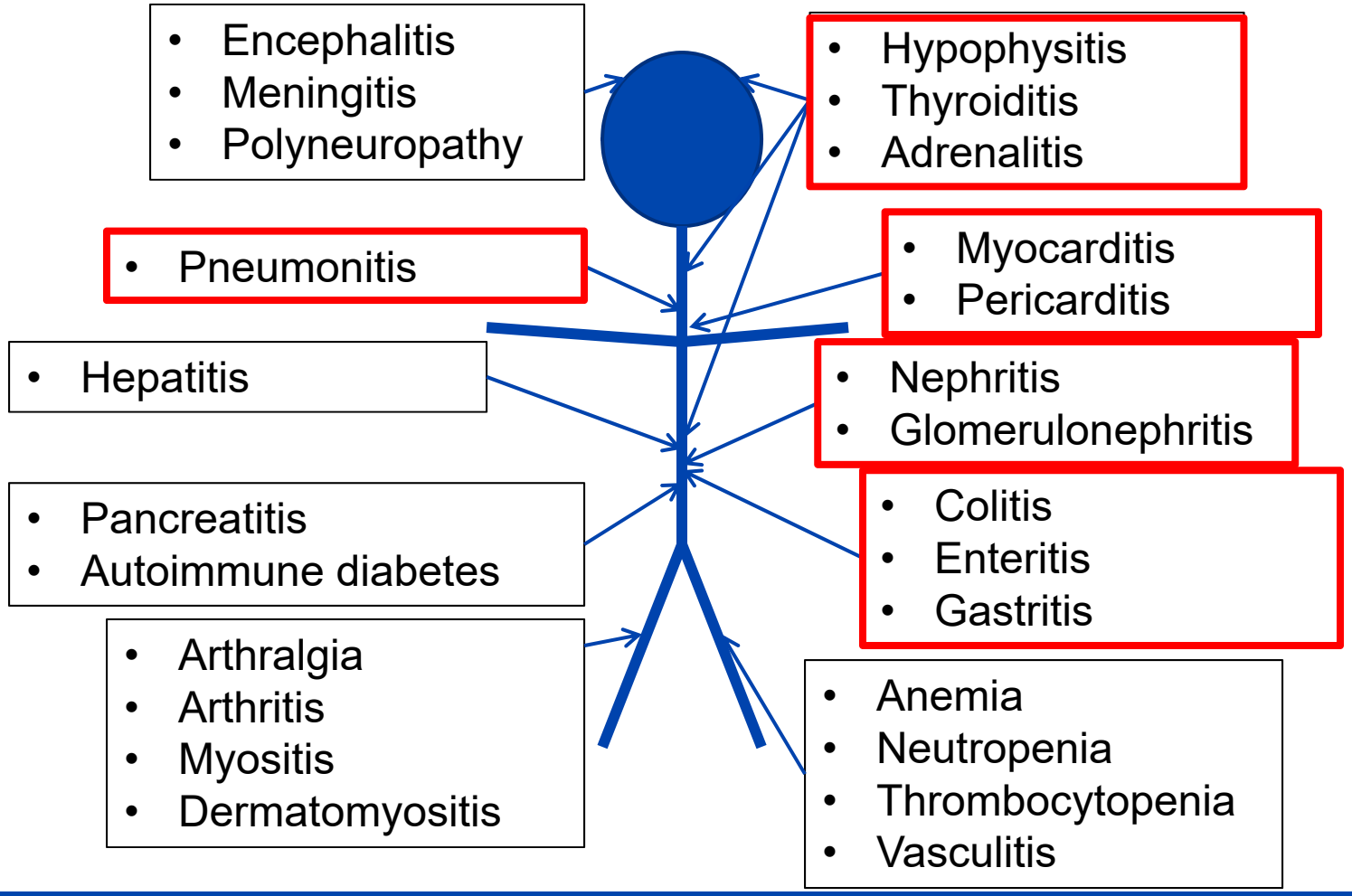
Marshall HT, et al. Front Oncol 2018; 8:315

Immunotherapy Toxicities

Class of agent	Examples of drugs	Type of toxicity	Mechanism of toxicity
Immune checkpoint blockade	Anti-CTLA-4, anti-PD-1, anti-PD-L1	Immune related adverse events	Auto-immune like
CAR-T cells	Tisagenlecleucel, axicabtagene ciloleucel	Cytokine release syndromes (CRS), neurologic	Cytokines (IL-6 and interferon-gamma), T-cell migration to the CNS

Michot JM, et al. Eur J Cancer 2016; 54:139-48
Lee DW, et al. Blood 2014; 124: 188-95

Types of Toxicities



Martins F, et al. Clinical Oncology 2019; 16: 563-580

Immune Checkpoint Inhibitor Adverse Event Management

- Grade 1: symptomatic treatment
- Grade 2: suspend immunotherapy and start oral corticosteroids
- Grade 3-4: IV corticosteroids, consult specialist in organ affected, alternative immunosuppressive therapy if corticosteroids not sufficient
- Exceptions: treat endocrinopathies with replacement therapy

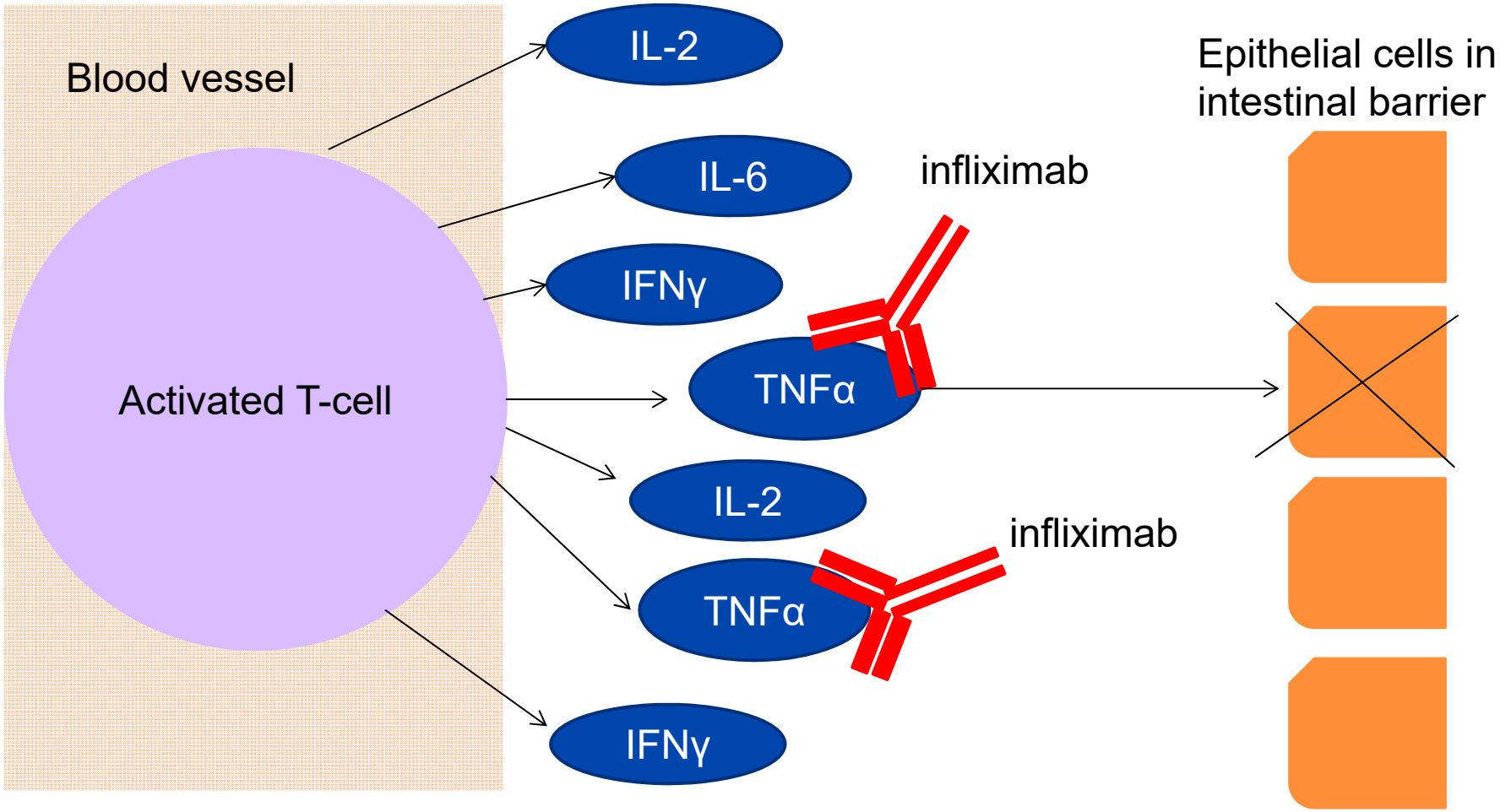
Brahmer J, et al. J Clin Oncology 2018; 36: 1714-1768

Gastrointestinal

- **Clinical marker:** increase in stool frequency
- **Onset time:** 5-10 weeks after initiation
- **Most likely agents:** anti-CTLA-4, combination
- **Treatment:**
  - Prednisone or methylprednisolone 1-2 mg/kg/day
  - Infliximab 5-10 mg/kg if symptoms persist
  - Vedolizumab may be considered

Haanen J, et al. Annals of Oncology 2017; 28:i119-i142

Infliximab Mechanism of Action

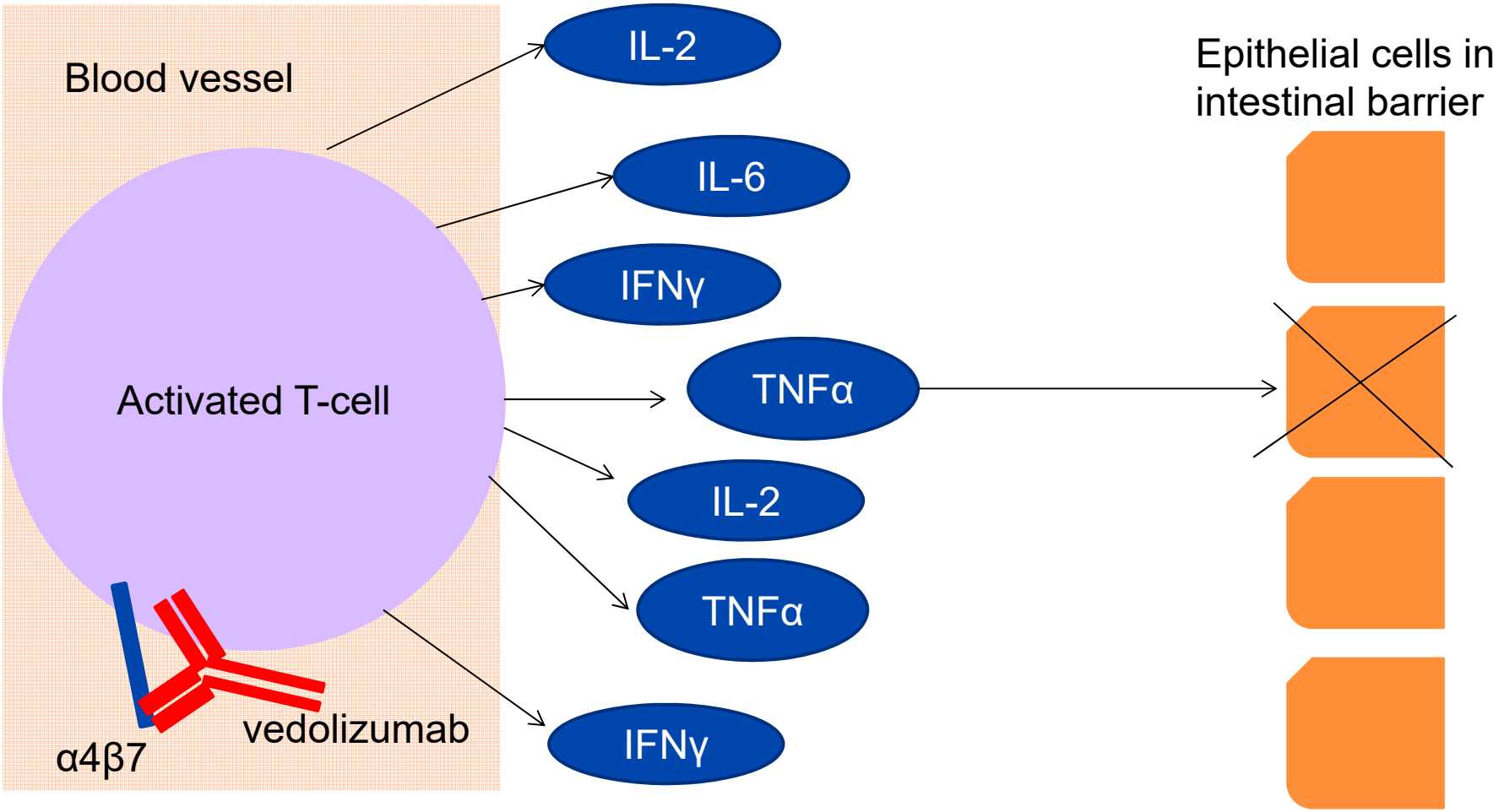


Infliximab Case Series

Population	• Five patients with steroid dependent or partially-refractory enterocolitis
Intervention	• Infliximab 5 mg/kg every 2 weeks for 1-2 doses
Outcome	• Resolution of symptoms within 2-3 days in all patients

Johnston RL, et al. Dig Dis Sci 2009; 54: 2538-2540

Vedolizumab Mechanism of Action



Vedolizumab Case Series

Population

- Seven patients with ipilimumab or nivolumab induced enterocolitis
- Steroid-dependent and/or partially refractory

Intervention

- Vedolizumab infusion 300 mg at 0, 2 and 6 weeks

Outcome

- 6/7 patients achieved steroid-free enterocolitis remission at a median of 56 days

MAYO CLINIC

Bergqvist V, et al. Cancer Immunol Immunother 2017; 66:581-592

Pulmonary

- **Clinical marker:** increase in oxygen requirements and radiographic evidence
- **Onset time:** median ~3 months (2-24 months)
- **Most likely agents:** PD-1, combination therapy
- **Treatment:**
  - Methylprednisolone 1-2 mg/kg/day
  - Infliximab 5 mg/kg
  - Mycophenolate mofetil IV 1 g BID
  - IVIG for 5 days
  - Cyclophosphamide

Brahmer J, et al. J Clin Oncology 2018; 36: 1714-1768

Renal

- **Clinical marker:** laboratory markers (creatinine)
- **Onset time:** ~90d after initiation (21-245 days)
- **Most likely agents:** combination
- **Treatment:**
  - Prednisone 0.5-2 mg/kg/day
  - Mycophenolate

Brahmer J, et al. J Clin Oncology 2018; 36: 1714-1768

Endocrine

- **Clinical marker:** signs/symptoms, laboratory markers (TSH, free T4, ACTH, ketosis in urine)
- **Onset time:** 4-12 weeks
- **Most likely agents:** ipilimumab (hypophysitis), anti-PD1/PDL1 (diabetes, thyroiditis)
- **Treatment:**
  - Hormone replacement
  - Steroids if life-threatening, critical illness

Brahmer J, et al. J Clin Oncology 2018; 36: 1714-1768

Cardiovascular

- **Clinical marker:** cardiac biomarkers, ECG, echocardiogram
- **Onset time:** 10 weeks (2-32 weeks)
- **Most likely agents:** all agents
- **Treatment:**
  - Hold ICPi and permanently discontinue after grade 1
  - Methylprednisolone 1-2 mg/kg/day up to 1 g
  - +/- mycophenolate, infliximab, IVIG

Mahmood S, et al. J Am Coll Cardiol 2018; 71: 1755-64
Brahmer J, et al. J Clin Oncology 2018; 36: 1714-1768

ICPi = immune checkpoint inhibitor

Higher dose steroids

Population

- 35 patients from an 8-center institutional registry (November 2013-July 2017) with ICPi-associated myocarditis
- 46% (16/35) developed MACE

	No MACE (n=19)	MACE (N=16)	P Value
Initial steroid dose, mg	160 (0-1,000)	72.5 (0-1,000)	0.055
Initial steroid dose/body weight (mg/kg)	2.06 (0-20.20)	0.84 (0-14.0)	0.041
Time from admission to steroid administration, h	18.3 ± 12.8	27.2 ± 17.5	0.12

Mahmood S, et al. J Am Coll Cardiol 2018; 71: 1755-64

ICPi = immune checkpoint inhibitor
MACE=major adverse cardiac event

Poll-Everywhere Question

- Which of the following immune-related adverse events should NOT be treated with steroids?
  - Adrenal insufficiency
  - Pneumonitis
  - Hyperthyroidism
  - Myocarditis

Summary

- Prednisone or methylprednisolone 1 to 2 mg/kg/day
- Rule-out underlying infection
- Should be given prophylaxis
- Taper progressively over a period of at least 1 month

Prophylaxis

PCP prophylaxis and consider prophylactic fluconazole for anyone on long-term immunosuppressive drugs

Aspergillus fumigatus pneumonia

Brahmer J, et al. J Clin Oncology 2018; 36: 1714-1768
Chrisann K, et al. Journal for ImmunoTherapy of Cancer 2014; 2:19
Haanen J, et al. Ann Oncol 2017; 28: iv119-iv142

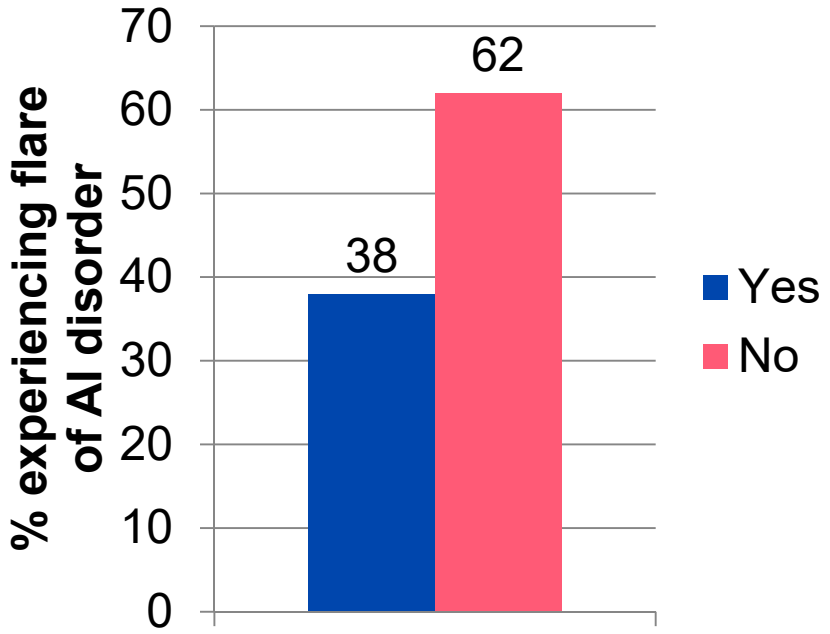
Risk Factors for Checkpoint Inhibitor Toxicities

- Baseline autoimmune diseases

Autoimmune Disorders

Patient population	52 patients w/ advanced melanoma and preexisting autoimmune disorders
Intervention	Anti-PD-1 antibodies
Outcome	Flare of autoimmune disorder

Baseline characteristics	
Activity of AI disorder at PD1 start	
Not clinically active	37 (71%)
Clinically active	15 (29%)
Treatment of AI disorder at PD1 start	
No immunosuppression	32 (62%)
Corticosteroids	9 (17%)
Steroid-sparing agent	5 (10%)
Steroids and SSAs	5 (10%)



Menzies AM, et al. Annals of Oncology 2017; 28: 368-376

AI=autoimmune
SSA=steroid sparing agent

Risk Factors for Checkpoint Inhibitor Toxicities

- Baseline autoimmune diseases
- Chronic organ dysfunction
  - Renal failure/dialysis
  - Respiratory failure
  - Heart failure
- Chronic viral infection
  - HIV
  - Viral hepatitis
- Organ transplant

Does treatment with immune-modulating agents affect efficacy of ICPi?

Retrospective analysis of 576 patients with advanced melanoma
Received at least one dose of nivolumab

N=114

Received systemic immune-modulating agents

N=462

Did not receive systemic immune-modulating agents

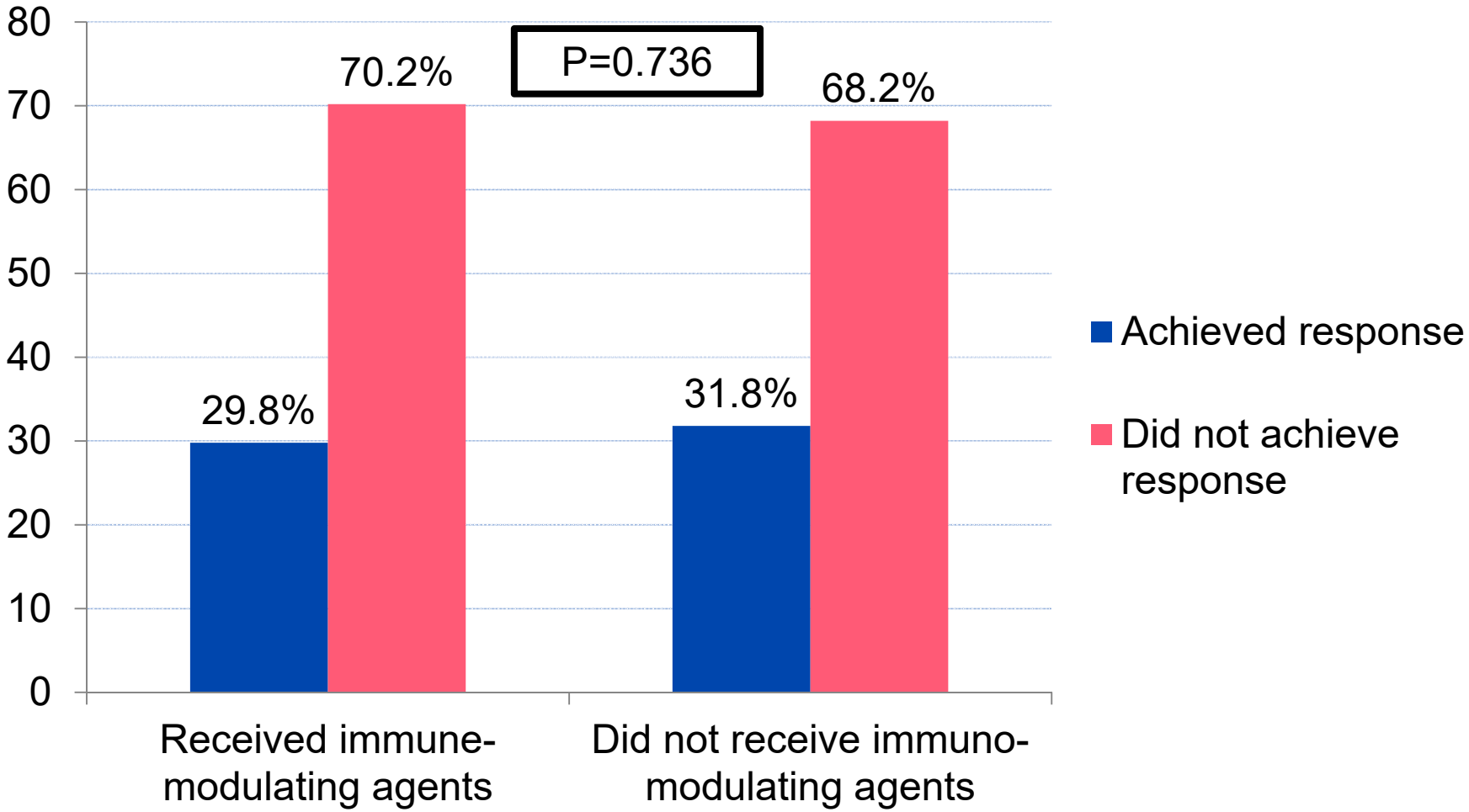
Outcome: impact of systemic immune-modulating agents on tumor response rate

MAYO CLINIC

Weber J, et al. J Clin Oncology 2017; 35: 785-791

ICPi = immune checkpoint inhibitor

Immune-modulating agents affect on tumor response rate



Weber J, et al. J Clin Oncology 2017; 35: 785-791

Does treatment with systemic corticosteroids affect survival?

Retrospective analysis of 298 patients with melanoma
Received at least one dose of ipilimumab

N=103

Received systemic corticosteroids for an irAE

N=195

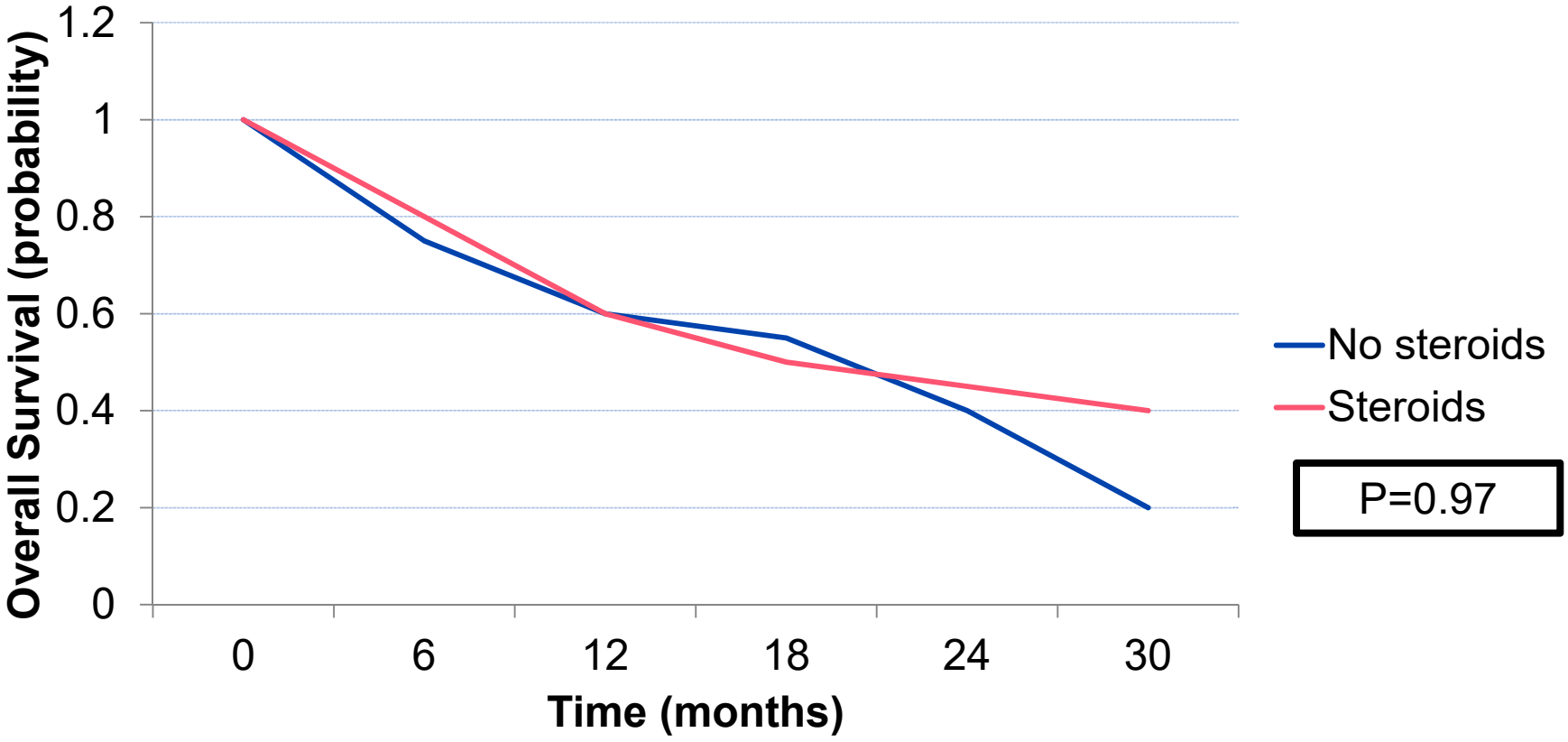
Did not receive systemic corticosteroids

Outcome: impact of systemic immunosuppression on overall survival

Horvat T, et al. J Clin Oncology 2015; 33: 3193-3198

ICPi = immune checkpoint inhibitor
irAE=immune related adverse event

Immunosuppression affect on overall survival



Horvat T, et al. J Clin Oncology 2015; 33: 3193-3198

Resuming ICPi

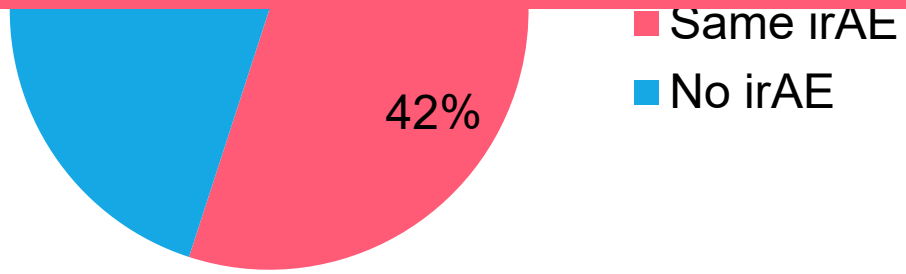
Patients

- Cohort study of 93 patients with ICPi irAE

Inte

O

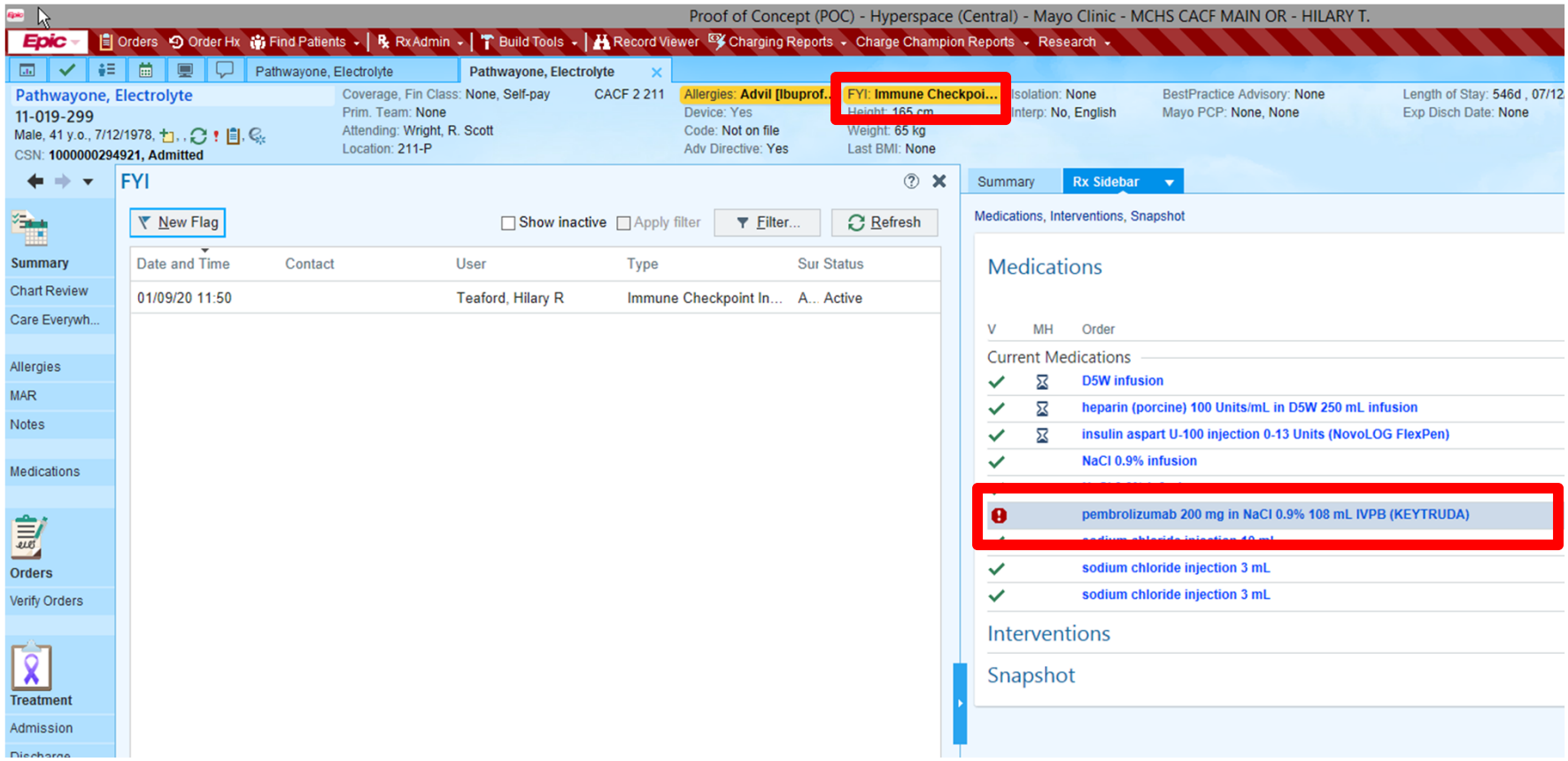
- **Consider rechallenging when symptoms/labs improve to grade 1 or less**
- **Grade 4: consider permanent discontinuation**



Simonaggio A, et al. JAMA Oncology 2019; 5: 1310-1317

ICPi = immune checkpoint inhibitor
irAE = immune related adverse event

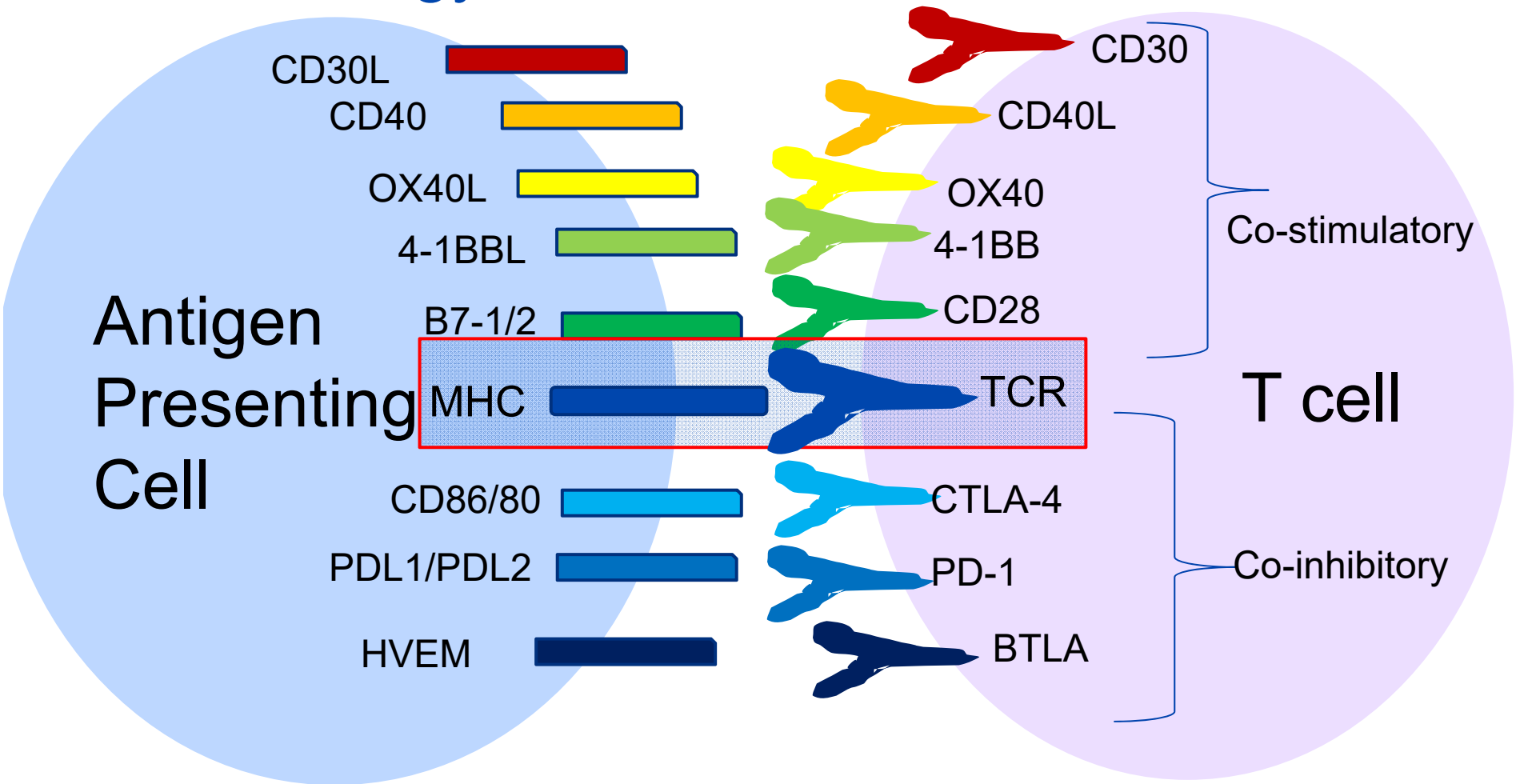
Immune Checkpoint Inhibitor Warning in Epic



Poll Everywhere Question

- Which of the following is a risk factor for checkpoint inhibitor toxicity?
  - Baseline autoimmune disease
  - Acute organ failure
  - Increased age
  - Poor performance status

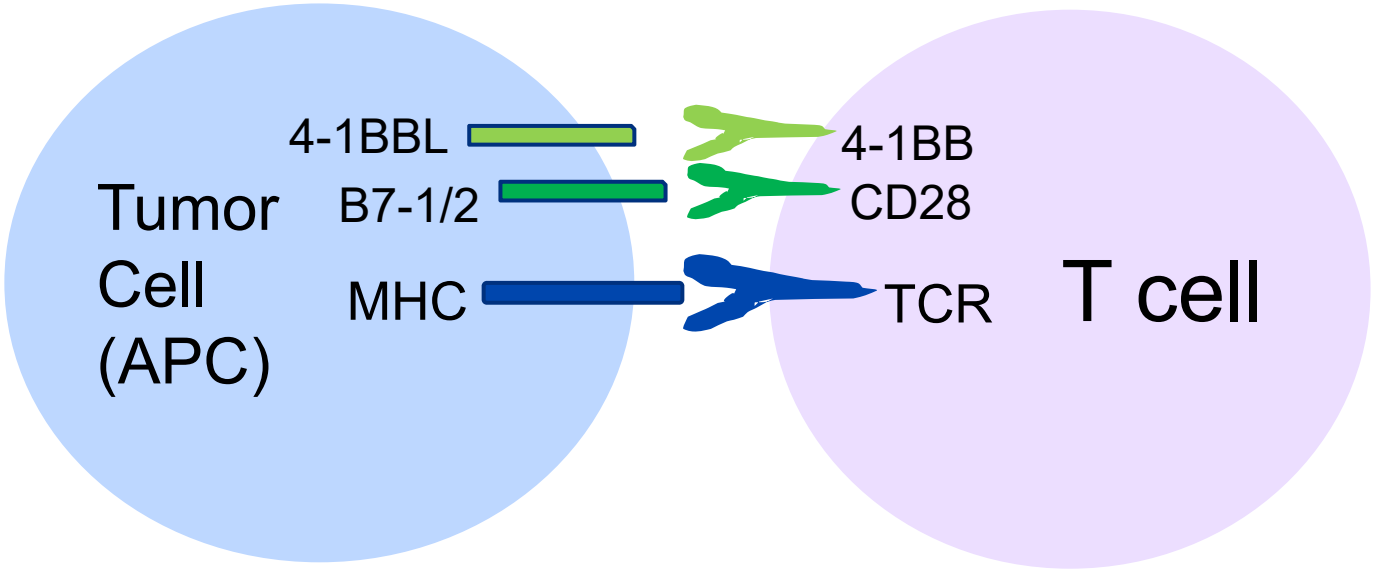
Immunology



Marshall HT, et al. Front Oncol 2018; 8:315

CAR T-cell Therapy

Remove T cells from patient's blood → Genetically alter cells in a lab to contain certain proteins → Inject cells back into the patient after preconditioning with chemotherapy → Modified proteins help immune cells find and kill cancer cells



Neelapu S, et al. NEJM 2017; 377:2531-2544
Maude S, et al. NEJM 2018; 378:439-448

APC=antigen presenting cell

CAR T-cell Toxicities

- Cytokine release syndrome
- Neurotoxicity

Cytokine Release Syndrome Pathophysiology

- Activation and expansion of the CAR T-cells and lysis of normal and tumor cells
- Release of several cytokines
  - Interferon-gamma
  - Tumor-necrosis factor alpha
- Triggers the activation of monocytes and macrophages with enhanced tumoricidal capacity
- Activated macrophages secrete high levels of pro-inflammatory cytokines (IL-6, IL-1, IL-10) and inducible nitric oxide synthase (iNOS)

Neelapu S, et al. NEJM 2017; 377:2531-2544
Maude S, et al. NEJM 2018; 378:439-448
Yanez L, et al. HemaSphere 2019; 3:1-9

Cytokine Release Syndrome

- **Incidence:** 57-93%
- **Timing:** ~2-3 days (1-12d) up to 3 weeks
- **Risk factors**
  - Higher burden malignancy
  - Higher CAR T-cell doses
- **Signs/symptoms**
  - Prodromal: Flu-like syndrome with fever, fatigue, headache, arthralgia, myalgia, and malaise
  - Pyrexia, GI symptoms, hemodynamic instability, organ dysfunction

Neelapu S, et al. NEJM 2017; 377:2531-2544
Maude S, et al. NEJM 2018; 378:439-448
Yanez L, et al. HemaSphere 2019; 3:1-9

American Society for Transplantation and Cellular Therapy (ASTCT) Consensus for Diagnosis of Cytokine Release Syndrome

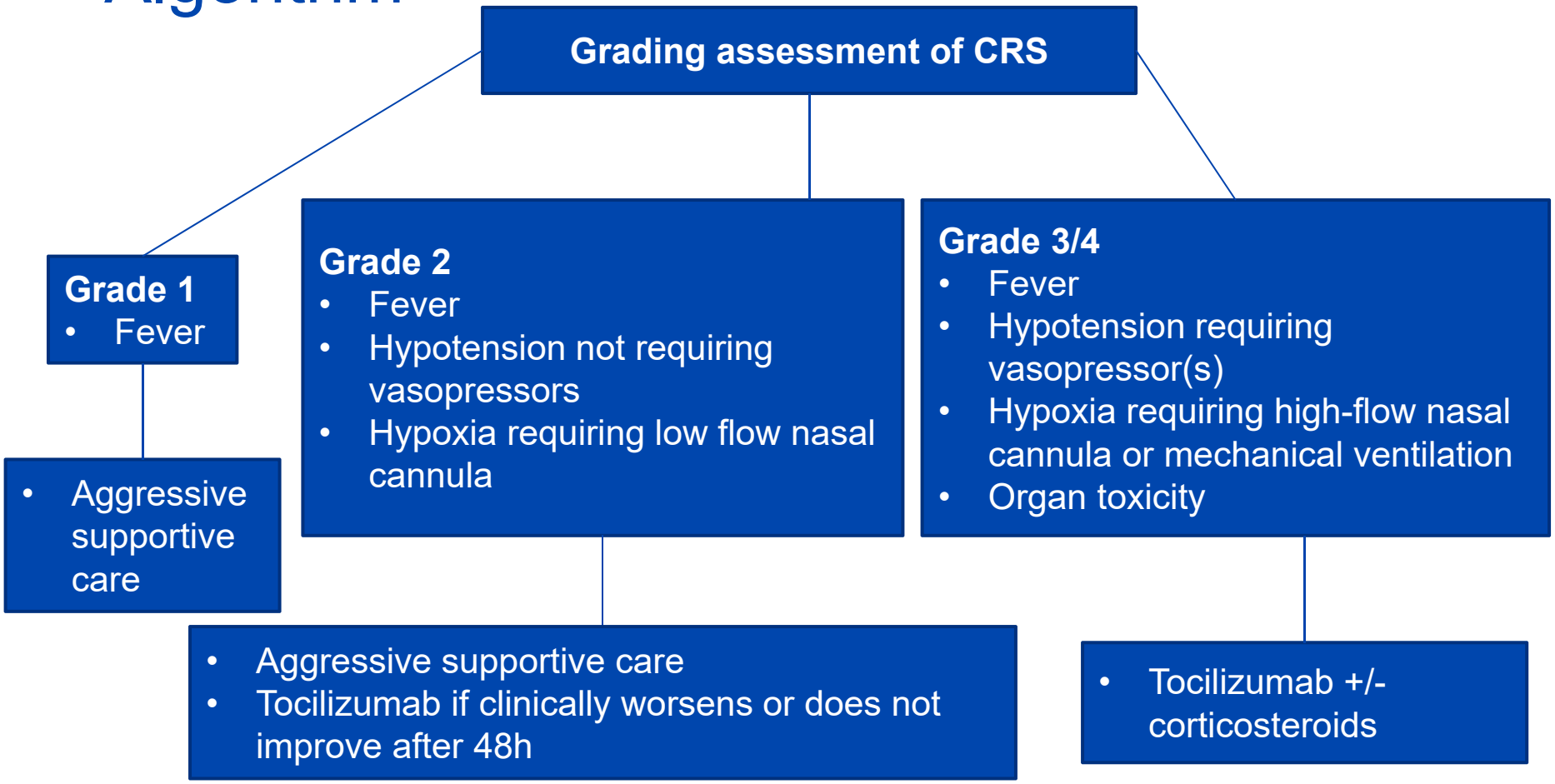
- Grade 1: fever ≥ 38°C
- Grade 2: hypotension not requiring vasopressor and/or hypoxia requiring ≤6 L/min O2
- Grade 3: hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring >6 L/min O2 (nasal cannula, facemask, or nonrebreather mask)
- Grade 4: hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Lee DW, et al. BBMT 2019; 25: 625-638

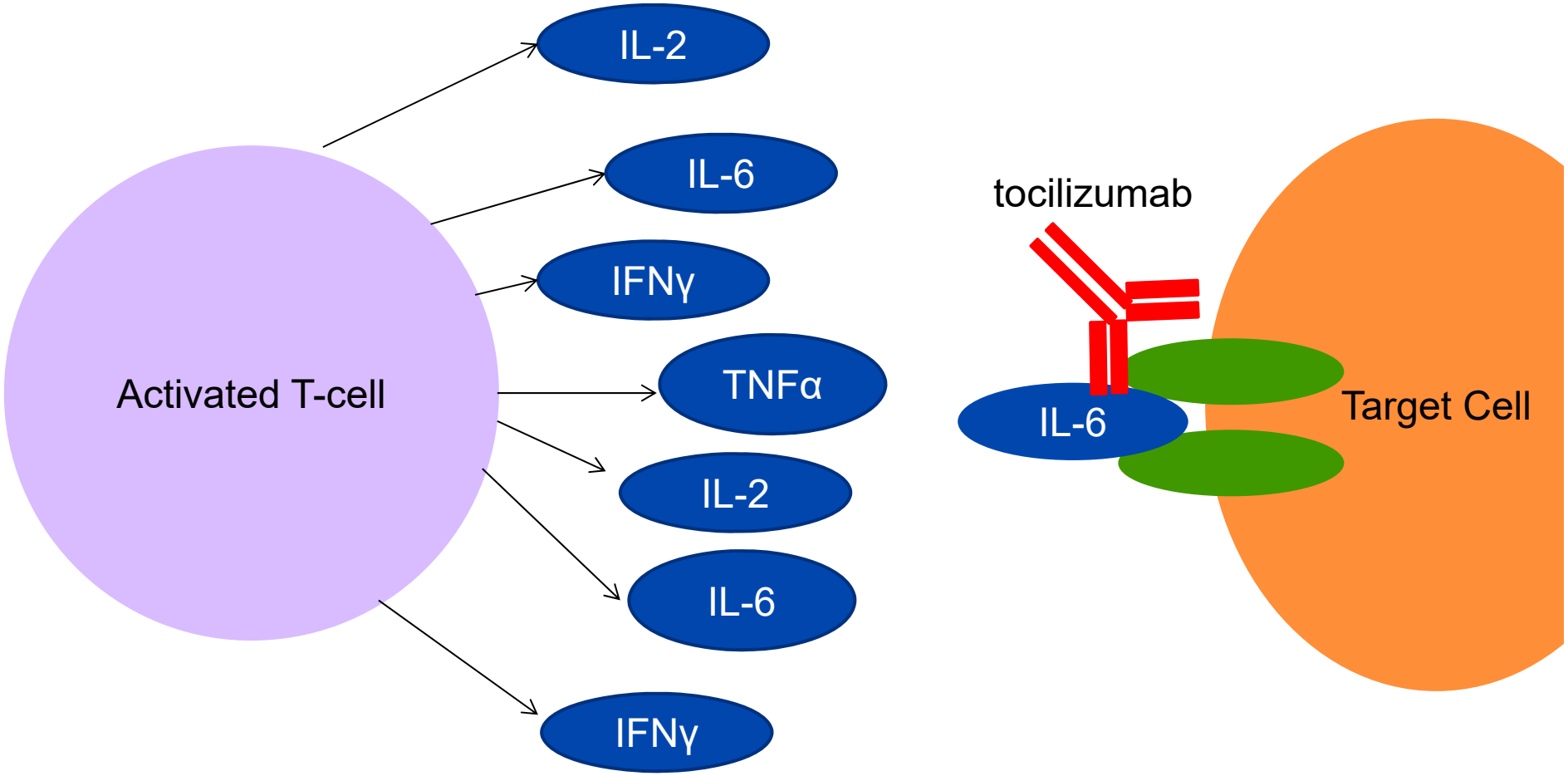
Current Management

- Standard supportive therapies
  - Consider antibiotics
- Tocilizumab
  - 8 mg/kg IV every 8 h up to 3 doses
- Corticosteroids
  - Dexamethasone 10 mg PO/IV
  - Methylprednisolone 1 gram IV daily

Algorithm



Tocilizumab Mechanism of Action



Le R, et al. The Oncologist 2018; 23:943-947

Tocilizumab

Retrospective analysis of pooled data from prospective clinical trials of CAR T-cell therapies
Patients with severe CRS
IV tocilizumab 8 mg/kg (12 mg/kg if <30 kg)
Nine studies total

N=45

Tisagenlecleucel (Kymriah™)

N=15

Axicabtagene ciloleucel (Yescarta®)

Primary outcome = characterize resolution of CRS

Le R, et al. The Oncologist 2018; 23:943-947

CRS = cytokine release syndrome

Baseline Characteristics

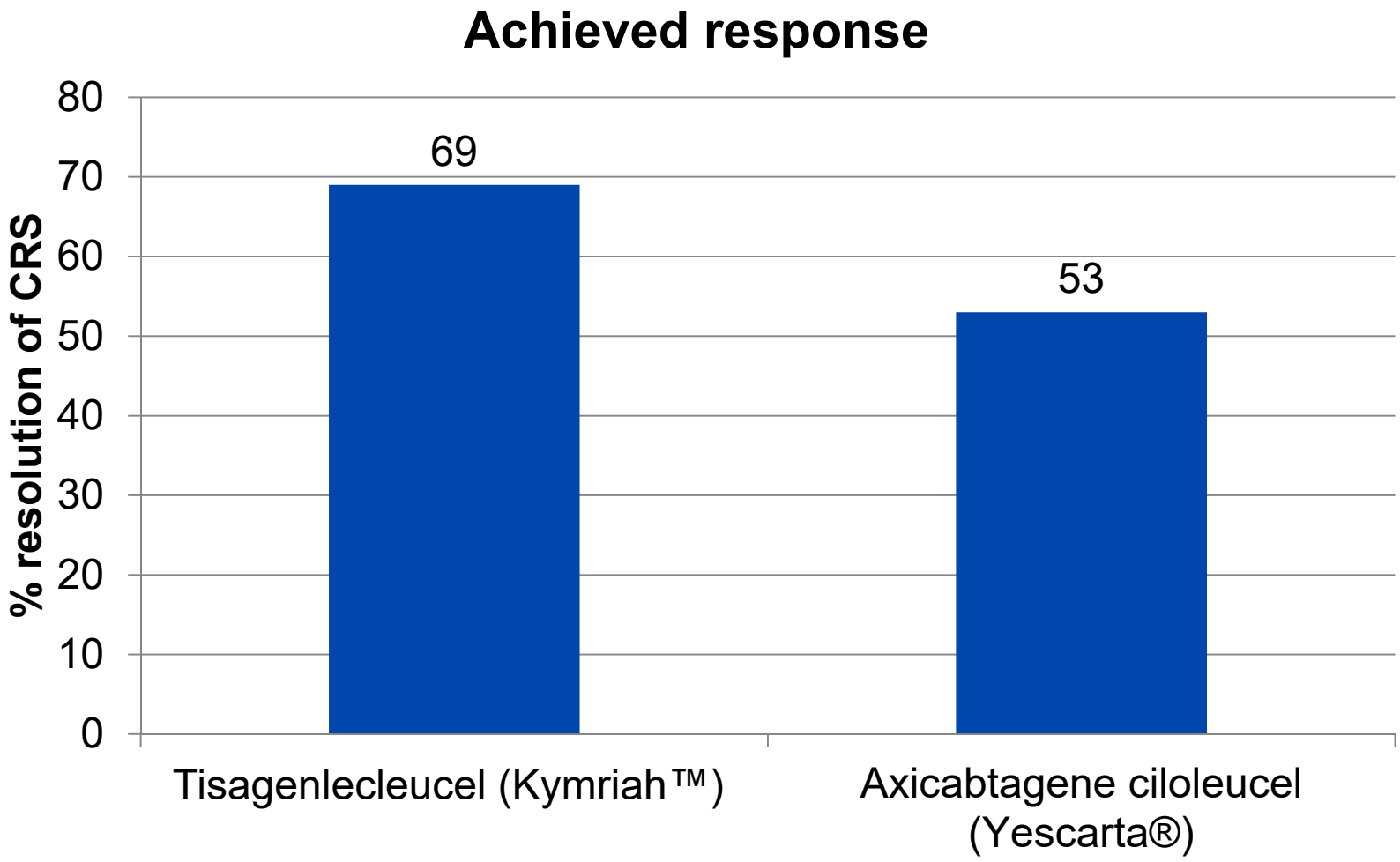
	Tisagenlecleucel (Kymriah™) (n=45)	Axicabtagene ciloleucel (Yescarta®) (n=15)
Underlying malignancy		
ALL	45 (100%)	2 (13.3%)
DLBCL	0	12 (80.0%)
PMBCL	0	1 (6.7%)
Baseline CRS grade		
Grade 3	10 (22.2%)	15 (93.3%)
Grade 4	35 (77.8%)	1 (6.7%)
CRS duration prior to tocilizumab		
0-4 days	23 (51.1%)	12 (80.0%)
>4 days	22 (48.9%)	3 (20.0%)
Number of tocilizumab doses daily		
Single daily dose	43 (95.6%)	10 (66.7%)
Multiple doses per day	2 (4.4%)	5 (33.3%)

MAYO CLINIC

Le R, et al. The Oncologist 2018; 23:943-947

ALL = acute lymphoblastic leukemia
DLBCL = diffuse large B cell lymphoma
PMBCL = primary mediastinal B cell lymphoma

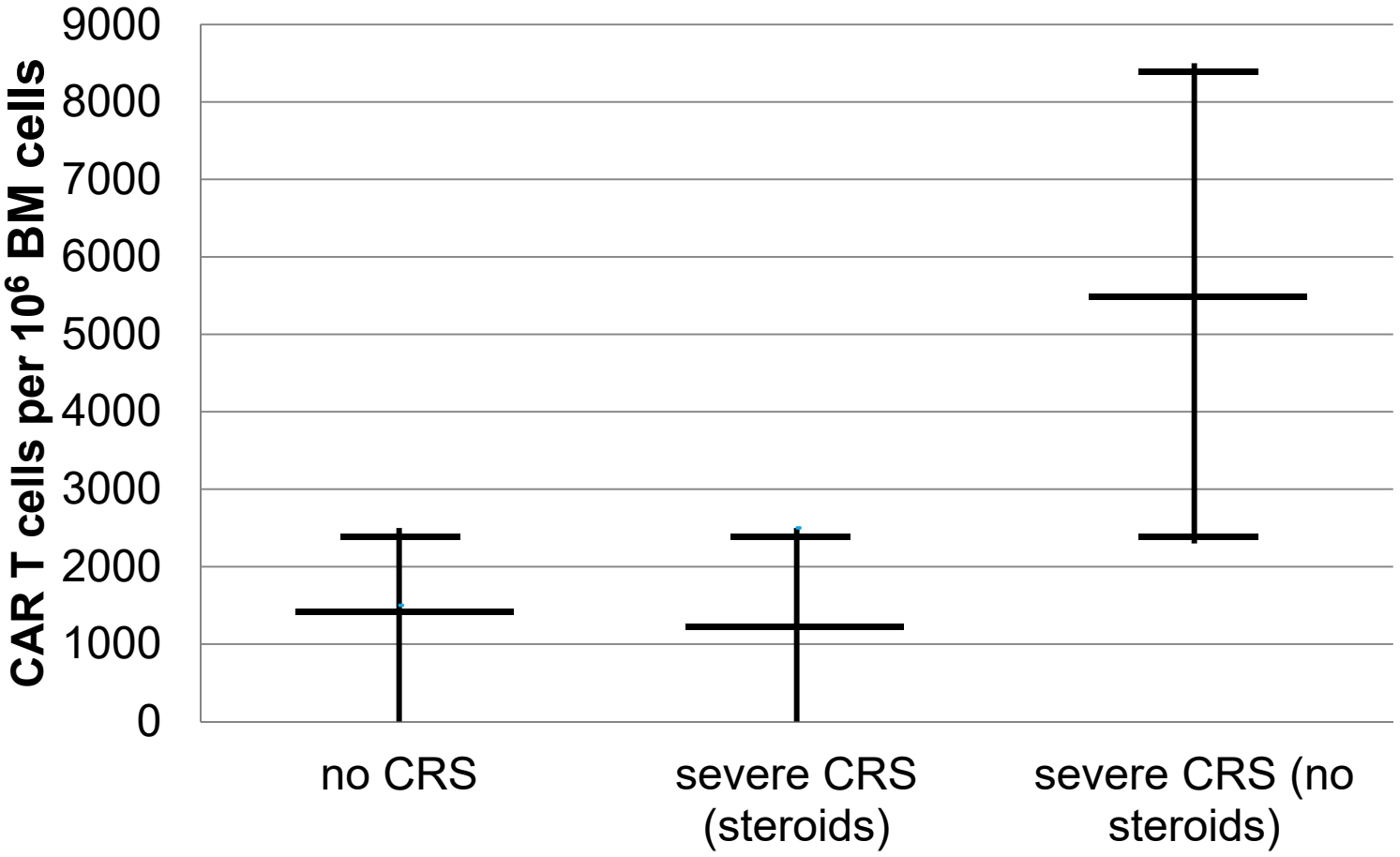
Resolution of CRS by Day 14



Le R, et al. The Oncologist 2018; 23:943-947

CRS = cytokine release syndrome

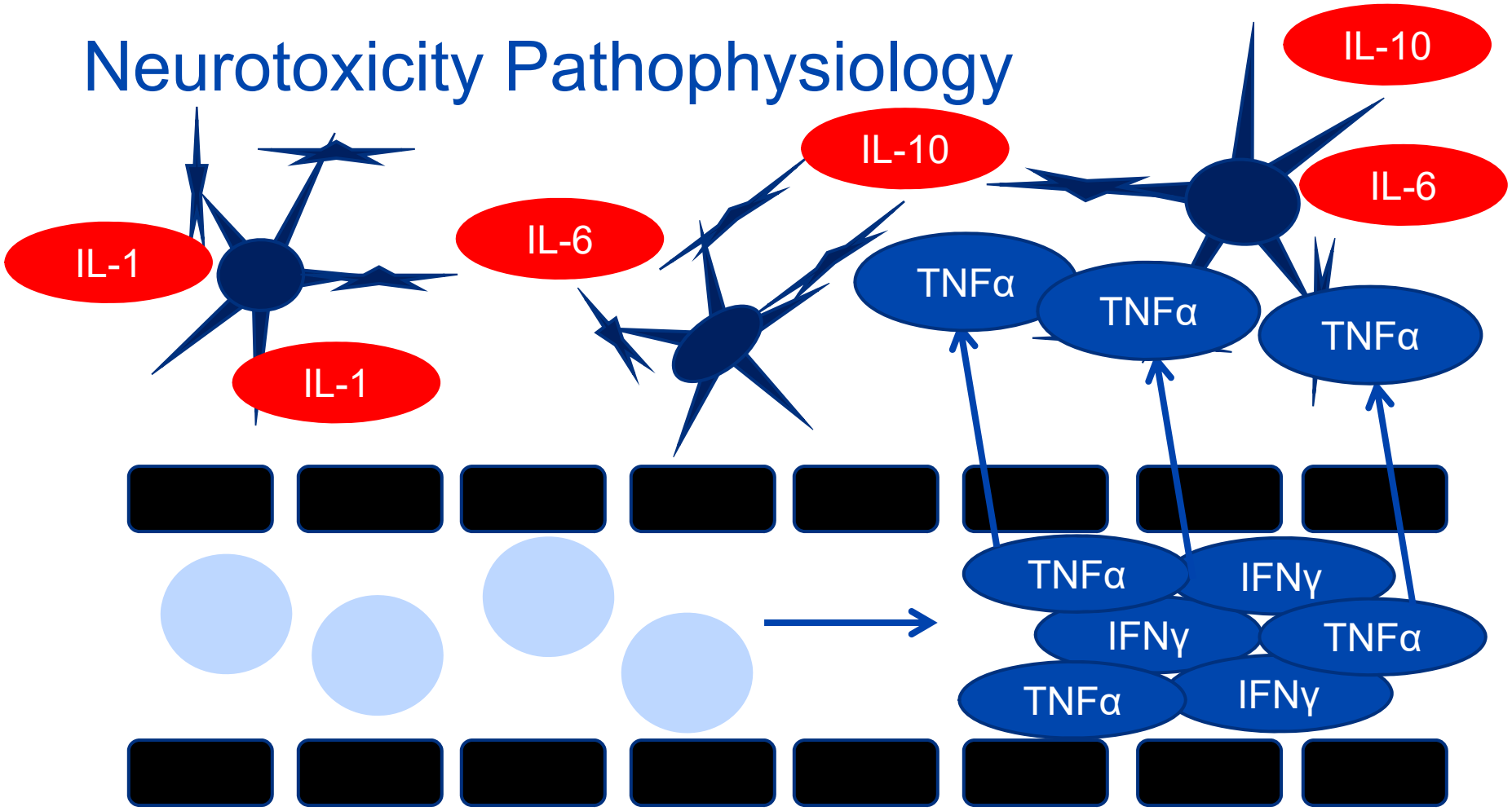
Does treatment with immunosuppression affect efficacy of CAR T-cell therapy?



Davila M, et al. Sci Transl Med 2014; 6: 1-23

CRS = cytokine release syndrome

Neurotoxicity Pathophysiology



Yanez L, et al. HemaSphere 2019; 3:1-9

Neurotoxicity

- **Incidence:** 0-87%
- **Median time of onset:** 4-6 days
- Often occurs concurrently with CRS
- **Signs/symptoms**
  - Headache, pain, memory loss, dizziness, alterations in mental status, movement disorders, impaired speech, seizures

Neelapu S, et al. NEJM 2017; 377:2531-2544
Maude S, et al. NEJM 2018; 378:439-448
Yanez L, et al. HemaSphere 2019; 3:1-9

CRS = cytokine release syndrome

Diagnosis

Task		Maximum Points (total=10)
Orientation	Name year, month, city, hospital	4
Naming	Point to 3 objects and ask the subject to name them	3
Following commands	Example, show me 2 fingers; OR close your eyes; OR stick out your tongue	1
Writing	Ask the subject to write a complete sentence. Examine the writing for legibility. Example: “it is warm today”	1
Attention	Count backwards from 100 to 10s	1

Neurotoxicity Management

- Corticosteroids
  - Dexamethasone 10 mg IV every 6 h until grade 1, then taper rapidly over 3 days
- Tocilizumab
  - Not helpful and may make it worse
  - Does not cross the blood brain barrier

CAR-T Best Practice Advisory in Epic

Poll-Everywhere Question

- 55-year-old patient presenting with neurotoxicity after receiving CAR-T cell infusion 5 days prior. What should be started first?
  - Tocilizumab
  - Dexamethasone
  - Hydrocortisone
  - Infliximab

Summary

- Immune related adverse events are common from checkpoint inhibitors
  - Treat with prednisone or methylprednisolone 1-2 mg/kg for more severe adverse events with slow taper to prevent recurrence
- Cytokine release syndrome and neurotoxicity are adverse events from CAR T-cell therapy
  - Treat severe cytokine release syndrome with tocilizumab +/- corticosteroids
  - Treat severe neurotoxicity with corticosteroids

