

Immunotherapy 101

Paul Armistead MD, PhD

Associate Professor of Medicine
Division of Hematology / Oncology

University of North Carolina

Why This Topic?



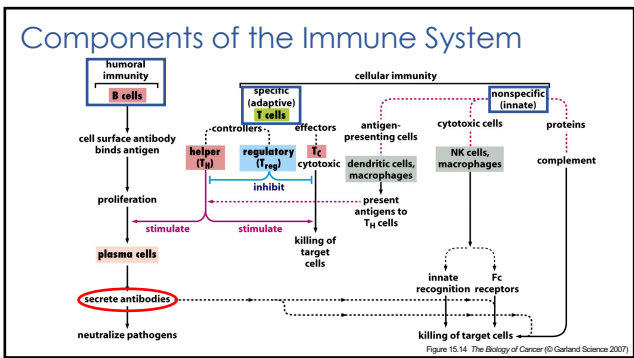
Objectives

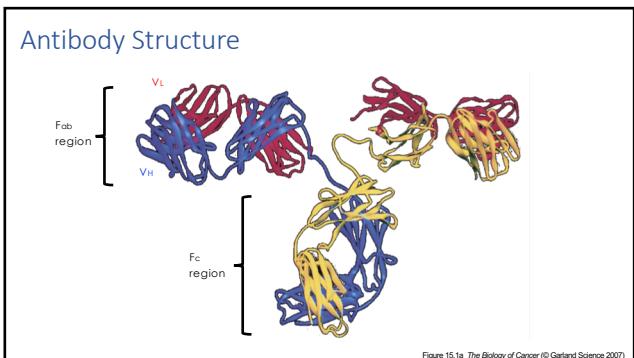
1. Organize the human immune system into its various components and understand how they work together to generate a coordinated immune response.
2. Explain the various mechanisms by which cancer can evade immune surveillance.
3. Explain the different types of active and passive immunotherapies that are clinically used and their relative strengths and weaknesses.

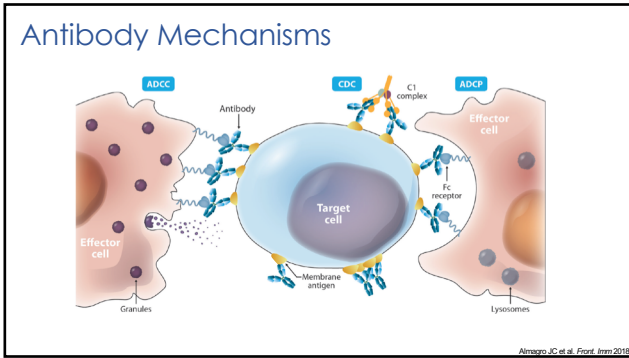
The Immune System Controls Cancer

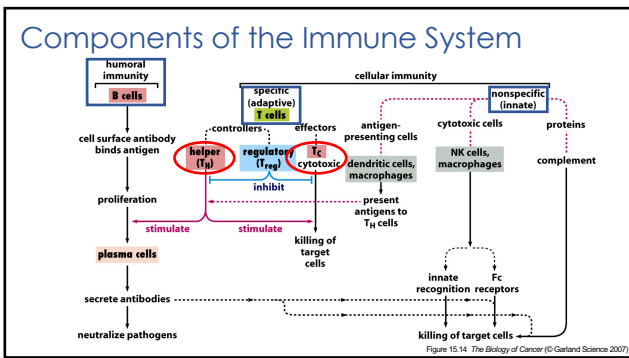
Site of cancer	No. of cases observed	No. of cases expected ^a	Ratio observed/expected
Non-melanoma skin	127	5.1	24.7
Thyroid, other endocrine	30	2.1	14.3
Mouth, tongue, lip	22	1.6	13.8
Cervix, vulva, vagina	39	3.6	10.8
Non-Hodgkin's lymphoma	25	2.4	10.3
Kidney, ureter	32	3.5	9.1
Bladder	26	4.7	5.5
Colorectal	38	10.5	3.6
Lung	30	12.5	2.4
Brain	10	4.1	2.4
Prostate	11	5.2	2.1
Melanoma	7	4.1	1.7
Breast	15	13.6	1.1

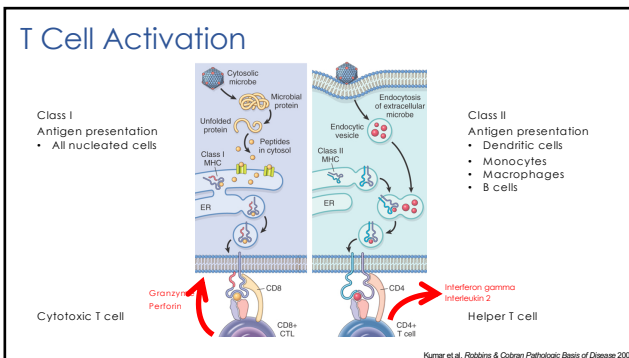
Table 15.1 The Biology of Cancer (© Garland Science 2007)

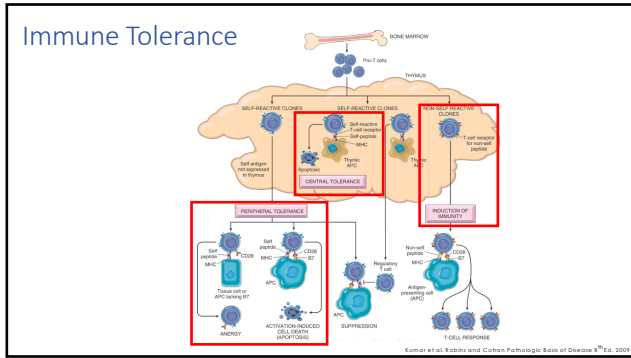










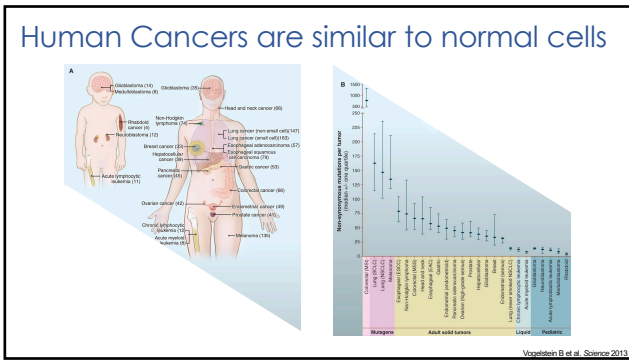


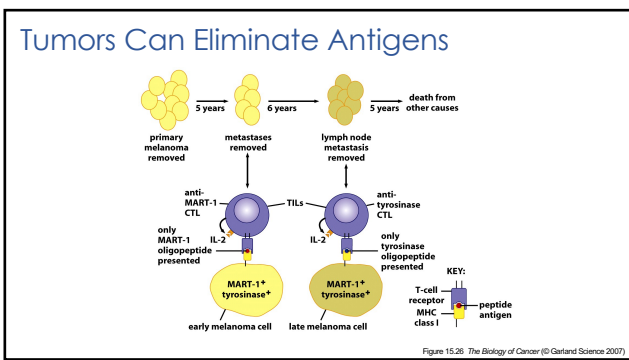
Organization of the Immune System

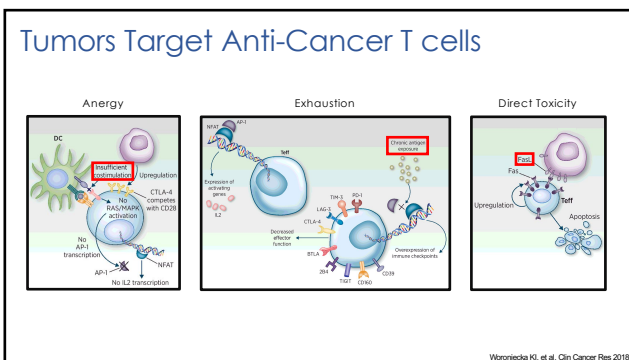
- Innate immune system responds non-specifically to foreign pathogens.
 - No immunologic memory
- Adaptive immune system responds to pathogens by enhancing recognition and developing memory
 - B cells differentiated to produce antibodies
 - CD8+ (cytotoxic) T cells directly kill cells presenting target antigens
 - CD4+ (helper) T cells produce cytokines to enhance immune responses
- Immune tolerance prevents pathologic immune responses (i.e. autoimmunity)

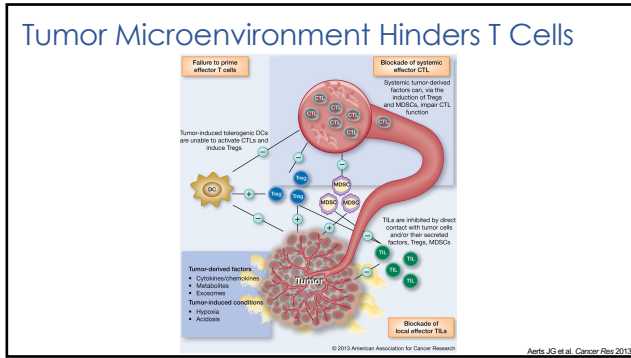
Immune Targeting of Cancer

- Infectious diseases are far more lethal to human beings than cancer
- The immune system is extremely well tuned to recognize and attack "non-self" infectious agents
 - Develop inflammation towards chemicals produced by bacteria and viruses
 - Develop both humoral and cellular adaptive immune responses against "non-self" proteins
- Cancer is significantly more "self" than "non-self", which makes immune targeting difficult.









- ### Tumor Immune Evasion
- Cancer cells are genetically very similar to normal cells
 - There are very few "good" immune targets in cancer
 - Cancer cells actively target immune cells
 - Induce T cell anergy and T cell exhaustion
 - Induce T cell death (activation induced cell death, Fas/FasL)
 - The tumor microenvironment impedes immune cell function
 - Hypoxia and impaired blood flow
 - Tumor recruits immunosuppressive immune cells
 - Non-cancer cells secrete immunosuppressive cytokines

Types of Immunotherapeutics

- Passive immunotherapy: the administration of an immunotherapy agent to a patient to target a disease.
- Active immunotherapy: the administration of an agent intended to enhance a patient's immune response to a disease.

Passive Immunotherapeutics	Active Immunotherapeutics
Anti-tumor antibodies	Cancer epitope vaccine
Allogeneic stem cell transplant	Dendritic cell vaccine
Tumor infiltrating lymphocytes	Anti-CTLA4 antibodies
CAR-modified lymphocytes	Anti-PD1/PD-L1 antibodies
	Cytokines

Types of Immunotherapeutics

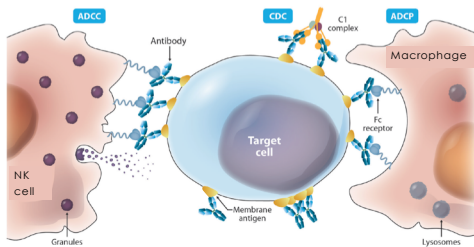
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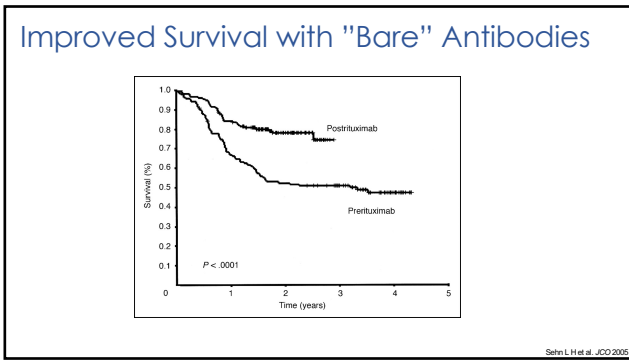
Targeting Cancer Surface Proteins

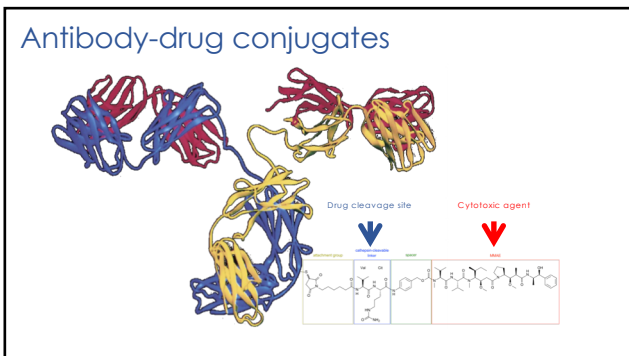
- Many tumors overexpress proteins on their plasma membranes
- Overexpressed proteins are NOT cancer-specific, but targeting them on tumors has improved clinical outcomes in many diseases.
 - Always a concern for targeting normal tissues.
- The best developed immunotherapeutics directed against overexpressed cell surface proteins are antibodies.

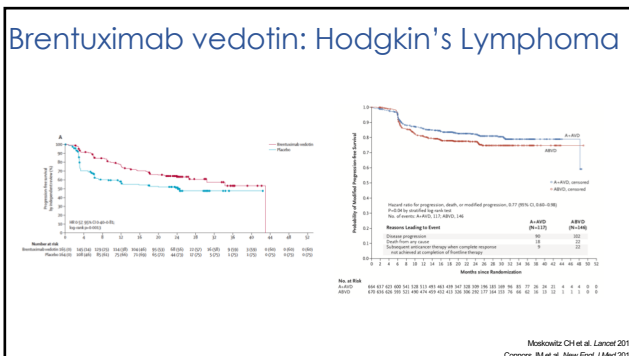
Antibody Mechanisms

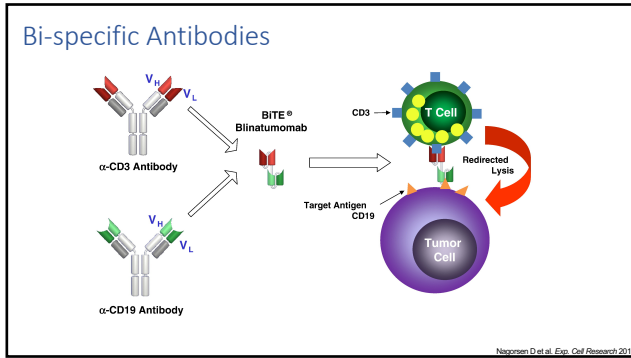


Almago JC et al. Front Immunol 2018









Blinatumomab

Response Category	Blinatumomab Group (N=271)		Chemotherapy Group (N=134)		Treatment Difference (95% CI)	P Value†
	no.	% (95% CI)	no.	% (95% CI)		
Complete remission with full hematologic recovery	91	33.6 (28.0-39.5)	21	15.7 (10.0-23.0)	17.9 (9.6-26.2)	<0.001
Complete remission with full, partial, or incomplete hematologic recovery	119	43.9 (37.9-50.0)	33	24.6 (17.6-32.8)	19.3 (9.9-28.7)	<0.001
Complete remission with partial hematologic recovery	24	8.9 (5.8-12.9)	6	4.5 (1.7-9.5)		
Complete remission with incomplete hematologic recovery	4	1.5 (0.4-3.7)	6	4.5 (1.7-9.5)		

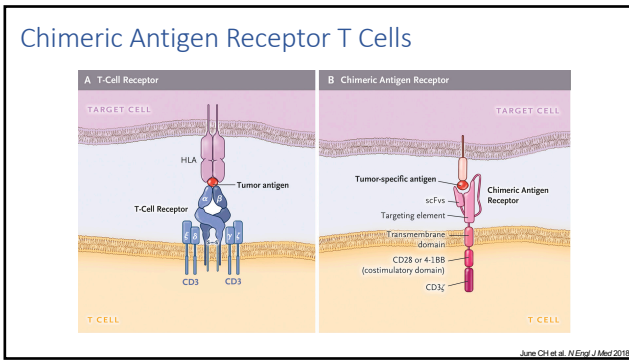
Median Overall Survival (mo)
 Blinatumomab: 7.7 (95% CI, 5.6-9.6)
 Chemotherapy: 4.0 (95% CI, 2.9-5.3)
 Hazard ratio, 0.71 (95% CI, 0.55-0.93)

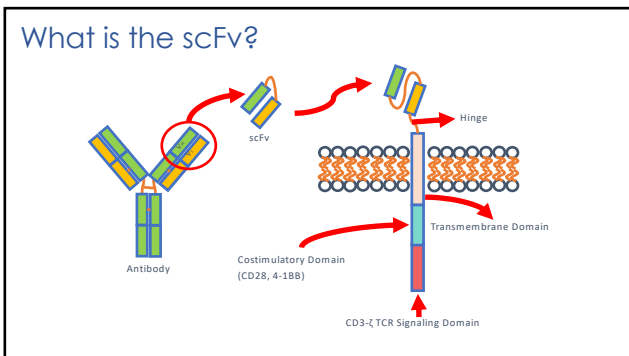
No. at Risk

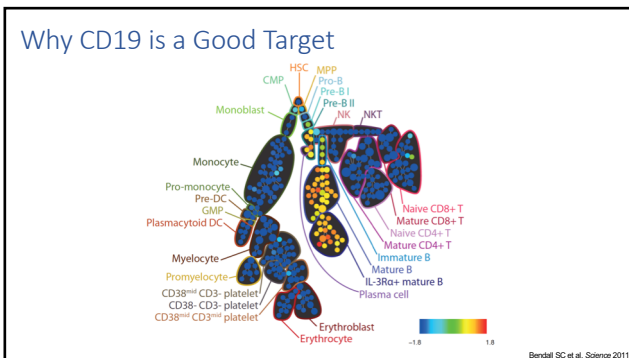
	0	1	2	3	4	5	6	7	8	9	10
Blinatumomab	271	176	124	79	45	27	9	4	0		
Chemotherapy	134	71	41	27	17	7	4	1	0		

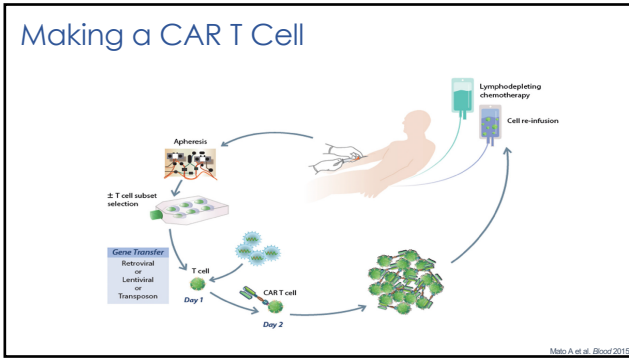
Kantarjian H et al. New England J Medicine 2017

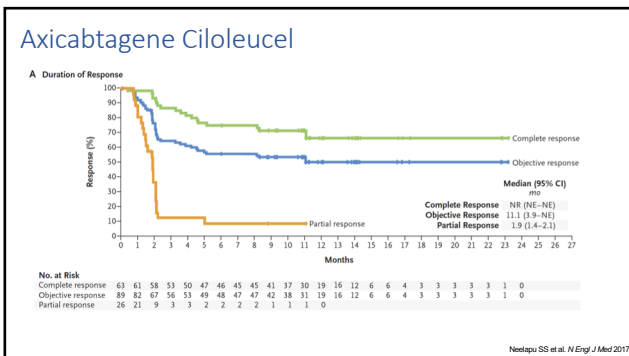
- ### Antibodies - Summary
- Antibodies target cell surface proteins
 - The targets are not cancer-specific
 - Antibody based therapies have improved clinical outcomes in many different cancer types
 - Antibody-drug conjugates kill cells by delivering cytotoxic agents at high concentrations to cells that overexpress the surface protein
 - Bi-specific antibodies couple T cells to cells that express the target surface protein, which enables T cell mediated cytotoxicity

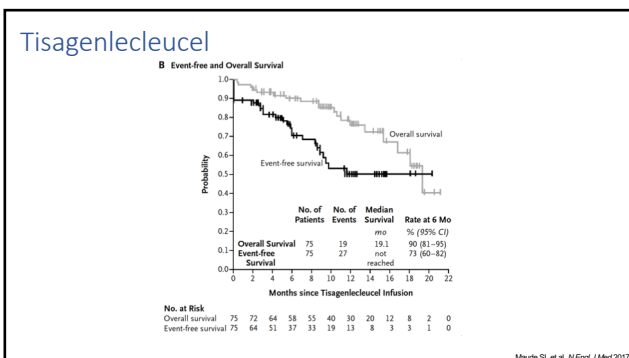












Success in Targeting CD19+ Cancers

	Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
Indications	Adults - R/R large cell lymphomas (DLBCL, transformed FL, etc) Age \leq 25 - ALL	R/R large cell lymphomas (DLBCL, transformed FL, etc)
Costimulatory domain	4-1BB	CD28
Dose	Lymphoma - 0.6-6 x 10 ⁶ cells/kg ALL - < 50kg 0.2-5 x 10 ⁶ cells/kg - >50kg 0.1-2.5 x 10 ⁶ cells/kg	2 x 10 ⁶ - 2 x 10 ⁸ cells/kg
ORR	Lymphoma - 50%	72%
CR	Lymphoma - 32% ALL - 83%	51%
DOR	Lymphoma - not reached ALL - not reached	9.2 months
DOR if CR	Lymphoma - not reached	Not reached

Toxicity from CAR T Cells (CRS)

Category	Sign/symptom	Grade 1	Grade 2	Grade 3	Grade 4
Vital Sign	Temp >38°	Yes	Any	Any	Any
	SBP <90	No	Fluid responsive or low-dose pressor	High-dose or multiple pressors	Life-threatening
	O ₂ Requirement for sat >90%	No	FiO ₂ <40%	FiO ₂ >40%	Ventilator support
Organ toxicity		Grade 1	Grade 2	Grade 3 or Grade 4 transaminitis	Grade 4 (except transaminitis)

- Develops 4-7 days after infusion
- 75-90% (15-50% grade 3+)
- Depends on product and disease

Lee DW et al. Blood 2014

Management of CRS

CRS grade	Sign/symptom	Management
Grade 1	Fever or organ toxicity	<ul style="list-style-type: none"> • Acetaminophen and hydrocortisone (if needed) for the treatment of fever • Oxygen can be used as an oral treatment option for fever. If oral corticosteroid • Consider oral low-dose (10-20 mg) prednisone, and if not tolerated, consider intravenous (IV) hydrocortisone • Monitor for signs of infection and sepsis if immunosuppressed • Consider tocilizumab 8mg/kg IV or subcutaneous 11 mg/kg IV for persistent feating >3 days and refractory fever
Grade 2	Hypotension	<ul style="list-style-type: none"> • IV fluid bolus (200-500 mL) of 0.9% saline • Consider tocilizumab 8mg/kg IV or subcutaneous 11 mg/kg IV for persistent feating >3 days and refractory fever • Consider IV bolus of 100 mg of methylprednisolone • If hypotension persists after two fluid boluses and anti-T-6 therapy start suppression, consider transfer to intensive care unit (ICU) for close monitoring and other advanced therapies as necessary • In patients at high risk for T-hyperimmune reaction after 1-2 doses of anti-CD-19 therapy, discontinuation can be considered (Borchmann et al)
	Hypoxia	<ul style="list-style-type: none"> • Supplemental oxygen • If FiO₂ < 0.40, consider corticosteroids and supportive care, as recommended for the management of hypotension
	Organ toxicity	<ul style="list-style-type: none"> • Supplemental oxygen • If FiO₂ < 0.40, consider corticosteroids and supportive care, as recommended for the management of hypotension
Grade 3	Hypotension	<ul style="list-style-type: none"> • IV fluid bolus as much as recommended for the treatment of grade 2 CRS • If FiO₂ < 0.40, consider corticosteroids and supportive care, as recommended for grade 2 CRS • Consider tocilizumab 8mg/kg IV or subcutaneous 11 mg/kg IV • Consider IV bolus of 100 mg of methylprednisolone, and perform hemodynamic monitoring as in the management of grade 2 CRS • Manage fever and constitutional symptoms as indicated for grade 1 CRS • Supplemental oxygen including high-flow nasal cannula and/or non-invasive positive pressure ventilation • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above • Supplemental management of organ toxicity as per standard guidelines • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above
	Hypoxia	<ul style="list-style-type: none"> • Supplemental oxygen including high-flow nasal cannula and/or non-invasive positive pressure ventilation • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above
	Organ toxicity	<ul style="list-style-type: none"> • Supplemental management of organ toxicity as per standard guidelines • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above
Grade 4	Hypotension	<ul style="list-style-type: none"> • IV fluid bolus with 6-8 therapy pressors, and hemodynamic monitoring as defined for the management of grade 3 CRS • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above
	Hypoxia	<ul style="list-style-type: none"> • Supplemental oxygen • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above
	Organ toxicity	<ul style="list-style-type: none"> • Supplemental management of organ toxicity as per standard guidelines • If FiO₂ < 0.40, consider corticosteroids and supportive care, as described above

- Antipyretics
- Sepsis management
 - Antibiotics
 - Fluids
- Anti-IL6
- Vasopressors
- Steroids

Neelapu SS et al. Nature Rev Clin Onc 2018

Toxicity from CAR T Cells (CRES)

Sign/Symptom	Grade 1	Grade 2	Grade 3	Grade 4
CARTOX-10 Score	Mild (7-9)	Moderate (3-6)	Severe (0-2)	Critical/obtunded
Raised ICP	-----	-----	Stage 1-2 papilledema <20 mmHg opening pressure	Stage 3-4 papilledema >20 mmHg opening pressure or cerebral edema
Seizure/motor weakness	-----	-----	Partial or non-convulsive Responds to BZD	Generalized seizures New motor weakness Status epilepticus

CARTOX-10 Scoring (1 point for each):

- Orientation to year, month, city, hospital, and president (5 points)
- Name three objects (e.g. point to pen, button, phone – 3 points)
- Write out a standard sentence (1 point)
- Count backward from 100 by tens (1 point)
- Can occur during CRS (roughly day 5) or after CRS (roughly day 7 – 14)

Neelapu SS et al. Nature Rev Clin Onc 2018

Management of CRES

Neurologic Event (Grading Assessment CTCAE 4.03)	Concurrent CRS	No Concurrent CRS
Grade 2 Examples include: Somnolence-moderate, limiting instrumental ADLs Confusion-moderate disorientation Encephalopathy-mild to moderate ADLs Dysphasia-moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab per the table on the other side for management of Grade 2 CRS If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenous every 6 hours if not already taking other corticosteroids Consider dexamethasone per oral the event is Grade 1 or less, then taper over 3 days Consider nonsteroidal antiinflammatory medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenous every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsteroidal antiinflammatory medicines (eg, levetiracetam) for seizure prophylaxis
Grade 3 Examples include: Somnolence-obtunded or stupor Confusion-severe disorientation Encephalopathy-mild to severe ADLs Dysphasia-severe impairing or expression Parosmia, impairing ability to eat, taste, or communicate intelligibly	Administer tocilizumab per the table on the other side for management of Grade 2 CRS In addition, administer dexamethasone 10 mg intravenous with the first dose of tocilizumab and repeat every 6 hours. Continue, or less, then taper over 3 days Reassess neurologic event if the event is Grade 3 or less, then taper over 3 days Consider nonsteroidal antiinflammatory medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenous every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsteroidal antiinflammatory medicines (eg, levetiracetam) for seizure prophylaxis
Grade 4 Life-threatening consequences Significant respiratory acidosis Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on the other side for management of Grade 2 CRS After start of tocilizumab, administer methylprednisolone 1000 mg intravenous per the oral the dose of tocilizumab and continue methylprednisolone 1000 mg intravenous per the oral the dose if improves, then manage as above Consider nonsteroidal antiinflammatory medicines (eg, levetiracetam) for seizure prophylaxis	Administer methylprednisolone 1000 mg intravenous per the oral the dose for 3 days, if improves, then manage as above Consider nonsteroidal antiinflammatory medicines (eg, levetiracetam) for seizure prophylaxis

www.yescartcells.com

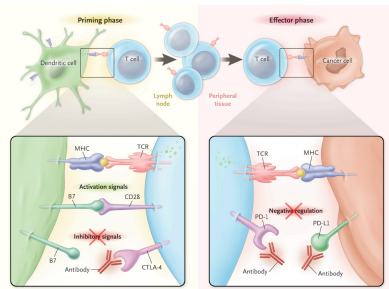
Toxicity Comparisons

	Tisagenlecleucel (Kymriah)	Axicicablagene ciloleucel (Yescarta)
Hospital certification	Yes	Yes
REMS requirement	Yes	Yes
Incidence of CRS	74-79% - 23-49% Grade 3+	94% - 13% Grade 3+
Median CRS onset	3 days	2 days
Median CRS duration	8 days	7 days
Incidence of CRES	58-72% - 18-21% Grade 3+	87% - 31% Grade 3+
Median CRES onset	6 days	4 days
Median CRES duration	6-14 days	17 days

CAR T Cell Summary

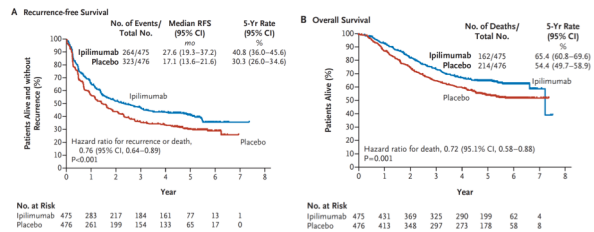
- Can provide long-term complete responses to patients with aggressive hematologic malignancies
 - Long-term disease control with persistent CAR T cells
- Very few good targets:
 - Highly expressed in cancer cells
 - Unnecessary for "normal" human physiology
- Personalized therapy that is very expensive
- Significant toxicity

Immune Checkpoint Blockade

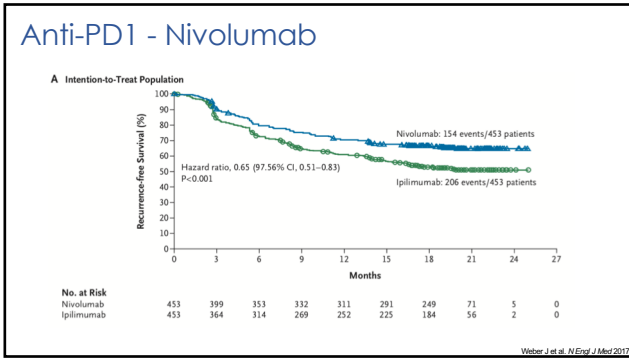


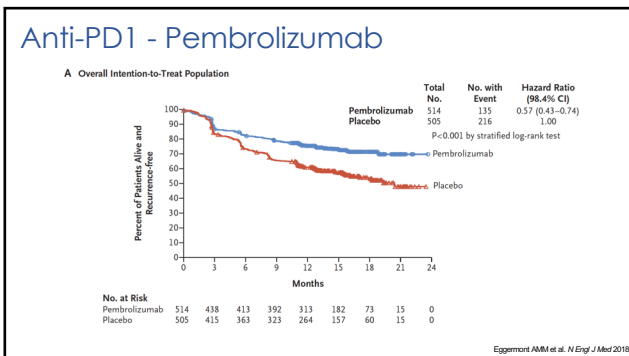
Ribas A. *N Engl J Med* 2012

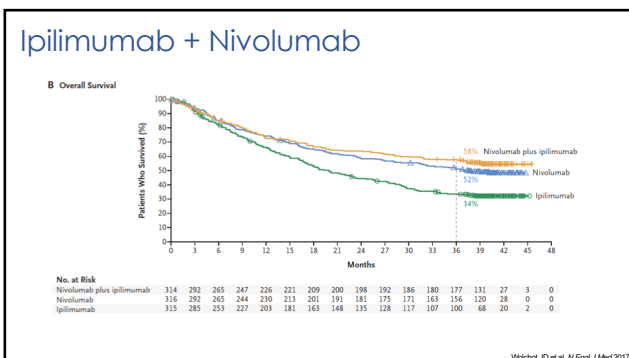
Anti-CTLA4 - Ipilimumab

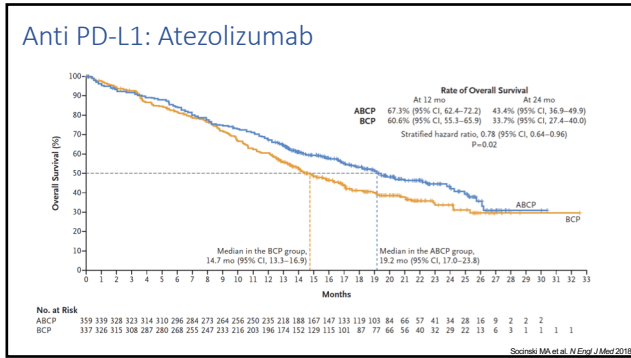


Eggermont AMM et al. *N Engl J Med* 2016









Anti-PD1 and Anti-CTLA-4 Toxicity

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event	418 (92.5)	313 (69.2)	446 (98.5)	333 (73.5)
Treatment-related adverse event	385 (85.2)	45 (10.0)	434 (95.8)	208 (45.9)
Fatigue	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
Diarrhea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Pruritus	140 (31.2)	0	123 (27.1)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	119 (26.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Headache	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	11 (2.4)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	44 (9.7)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	46 (10.1)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	40 (8.8)	19 (4.2)
Mucocutaneous rash	24 (5.3)	0	30 (6.6)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pneumonia	7 (1.5)	0	34 (7.5)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	11 (2.4)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

Source: Weber J et al. *N Engl J Med* 2017

What are Checkpoint Inhibitors Doing?

- **Neoantigens** are derived from mutated proteins that are specific to cancer
 - Single nucleotide variants
 - Gene fusions
 - Splice variants
- No central tolerance
 - Neoantigen specific T cells are present in patients
- Checkpoint inhibitors activate neoantigen specific T cells
