Innovations in Oncology Pharmacy

Jeanine F. Ewing PharmD, BCOP
Clinical Oncology Pharmacist
Florida Cancer Specialists & Research Institute

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Financial Disclosers

- No relevant financial disclosures

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Learning Objectives

- Review the mechanism of action for treatment options and targeted therapies available for a variety of cancers
- Recognize and treat specific oncology targeted-treatment related toxicities
- Discuss new regimens & mechanisms for therapies currently in development

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Pre-Assessment Question

- A companion diagnostic for a drug is used to

a) identify a specific gene mutation or biomarker that the drug targets
b) Induce genetic mutations that will make the drug more effective
c) Provide patient education on common adverse effects
d) All the above

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Pre-Assessment Question

- A companion diagnostic for a drug is used to

a) identify a specific gene mutation or biomarker that the drug targets
b) Induce genetic mutations that will make the drug more effective
c) Provide patient education on common adverse effects
d) All the above

- Several companion diagnostic tests exist for both hematologic and solid tumors to detect biomarkers for a specific patient to allow use of targeted therapy.
- Some examples include IDH1/2, KRAS, HER2, BRCA1/2, HRR genes, EGFR, BRAF, ALK, MSI-H, TMB, PD-L1, RET, ROS1, FOLR1, etc.

List of Cleared or Approved Companion Diagnostic Devices. FDA website. August 21, 2023.

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Precision Medicine

Targeted Oncology Treatment

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Agnostic Biomarkers

Target	Treatment	Trade Name	Route
BRAF V600E-positive	Dabrafenib + Trametinib	TAFINLAR + MEKINIST	PO
dMMR	Pembrolizumab Dostarlimab-gxly	KEYTRUDA JEMPERLI	IV IV
MSI-H or TMB-High	Pembrolizumab	KEYTRUDA	IV
NTRK gene fusion-positive	Larotrectinib Entrectinib	VITRAKVI ROZLYTREK	PO PO
RET fusion-positive	Selpercatinib	RETEVMO	PO

Clinical Trials Ongoing*		
ROS1	Taletrectinib	PO
KRAS G12C	Adagrasib Sotorasib	PO PO
HER2	Fam-trastuzumab deruxtecan	IV
ALK	Alectinib	PO
FGFRalt	Erdafitinib	PO

*List not all inclusive

Tatan, Y. et.al. Agnostic Approvals in Oncology. Pharmaceuticals: April 2023.
Rehali-Saab, T. et.al. Adagrasib in Advanced Solid Tumors Harboring a KRASG12C Mutation. JCO: April 2022
Paz, S. Tumor agnostic efficacy and safety of erdafitinib in patients with advanced solid tumors with FGFRalt. JCO: May 2021.

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Disease-Specific Biomarkers

Biomarker	Treatment	Indication	Branded Name
FOLR1	Mirvetuximab soravtansine-gynx	Ovarian	ELAHERE
ESR1	Elacestrant	Breast	ORSERDU
PIK3CA	Alpelisib	Breast	PIQRAY
MET	Capmatinib	NSCLC	TABRECTA
KRAS/NRAS WT	Cetuximab Panitumumab	CRC	ERBITUX VECTIBIX
Ki-67	Abemaciclib	Breast	VERZENIO
ALK	Alectinib* Crizotinib Ceritinib Lorlatinib Brigatinib	NSCLC	Alecensa Xalkori Zykadia Lorbrena Alunbrig

**List is not all inclusive - Several targeted therapies exist across multiple oncologic indications

List of Cleared or Approved Companion Diagnostic Devices. FDA website: August 21, 2023.

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Elacestrant

- FDA approval on January 27, 2023 for the treatment of postmenopausal ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer (mBC) with disease progression following at least 1 line of endocrine therapy.
- ESR1 mutation is an ACQUIRED mutation commonly seen in patients previously treated with an aromatase inhibitor.
- ESR1 is detectable in the blood and occurs in up to 40% of patients with mBC
- Elacestrant 345mg by mouth once daily with food until disease progression or unacceptable toxicity

FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. FDA website: January 27, 2023 .
Elacestrant (ORSERDU) [Prescribing Information]. New York, NY: Stemline Therapeutics, Inc: 2023.

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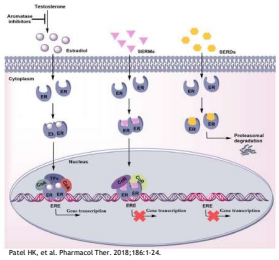
Elacestrant – Pharmacology



- Elacestrant binds to estrogen receptor-alpha
- Acts as a selective estrogen receptor degrader (SERD)
- Blocks transcriptional activity of the estrogen receptor and promotes degradation

Patel HK, et al. Pharmacol Ther. 2018;186:1-24.

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Elacestrant Safety

Lab Abnormality	All Grades	Grade 3-4
Cholesterol increased	30%	1%
Triglycerides increased	27%	2%
AST increased	29%	0%
ALT increased	17%	0%
SCr elevation	16%	0%
Anemia	26%	1%

Elacestrant (ORSERDU) [Prescribing Information]. New York, NY: Stemline Therapeutics, Inc; 2023.

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Antibody-Drug Conjugates

Targeted Therapy + Chemotherapy

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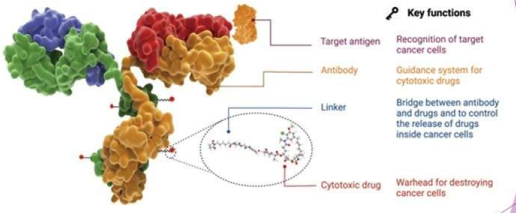
Antibody-Drug Conjugates (ADC)



Fu, Z. et.al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Nature: March 2022.

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FDA-Approved Treatments

ADC	Target	Payload	Indications	Branded Product
Gemtuzumab ozogamicin	CD33	Ozogamicin	AML	MYLOTARG®
Ado-trastuzumab emtansine	HER2	DM1	Breast	KADCYLA®
Trastuzumab deruxtecan	HER2	Camptothecin	Breast, Gastric, NSCLC	ENHERTU®
Sacituzumab govitecan	TROP-2	SN-38	Breast, Bladder	TRODELVY®
Mirvetuximab soravtansine	FOLR1	DM4	Ovarian	ELAHERE®
Loncastuximab tesirine-lpyl	CD19	SG3199	DLBCL	ZYNLONTA®
Enfortumab vedotin	Nectin-4	MMAE	Bladder	PADCEV®
Brentuximab vedotin	CD-30	MMAE	HL, ALCL, CTCL, PTCL	ADCETRIS®
Tisotumab vedotin-tftv	Tissue Factor	MMAE	Cervical	TIVDAK®
Polatuzumab vedotin-piiq	CD79b	MMAE	DLBCL	POLIVY®

NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; HL: Hodgkin's Lymphoma; ALCL: Anaplastic Large Cell Lymphoma; CTCL: Cutaneous T-Cell Lymphoma; PTCL: Peripheral T-Cell Lymphoma; DLBCL: Diffuse Large B-Cell Lymphoma

Khongorzul,P. et.al. Antibody-Drug Conjugates: A Comprehensive Review. Mol Cancer Res (Jan 2, 2020) 18(1):1-19

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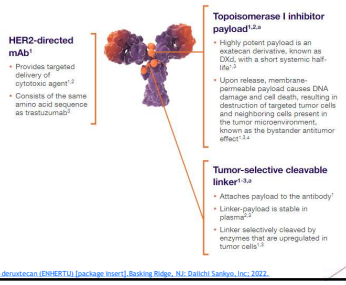
Fam-trastuzumab deruxtecan-nxki (ENHERTU®)



fam-trastuzumab deruxtecan (ENHERTU) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2022.

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Fam-trastuzumab deruxtecan-nxki (ENHERTU®)

- FDA-Approved Indications:
  - HER2+ metastatic Breast Cancer (mBC) 5.4mg/kg IV every 21 days
  - HER2-low metastatic Breast Cancer (mBC) 5.4mg/kg IV every 21 days
  - HER2-mutant metastatic Non-Small Cell Lung Cancer (mNSCLC) 5.4mg/kg IV every 21 days
  - HER+ advanced Gastric Cancer 6.4mg/kg IV every 21 days

fam-trastuzumab deruxtecan (ENHERTU) [package insert].Basking Ridge, NJ: Daiichi Sankyo, Inc; 2022.

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Fam-trastuzumab deruxtecan: DESTINY-PanTumor02

- Ongoing Phase II trial for Pan-Tumor efficacy
  - Locally advanced, unresectable, or metastatic previously treated HER-2 expressing solid tumors not eligible for curative therapy
  - Cervical, Endometrial, Ovarian, Biliary Tract (BTC), Bladder,, Pancreatic, & other rare cancers (head & neck, salivary gland cancer)

Efficacy	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other	All
n	40	40	40	41	25	41	40	267
ORR	50%	57.5%	45%	22%	4%	39%	30%	37.1%
CR	5%	17.5%	10%	2.4%	0%	2.4%	0%	5.6%
PR	45%	40%	35%	19.5%	4%	36.6%	30%	31.5%
SD	30%	32.5%	35%	61%	68%	43.9%	60%	46.1%
DoR (months)	9.8 (4.2-NE)	NR (9.9-NE)	11.3 (4.1-NE)	8.6 (2.1-NE)	NR	8.7 (4.3-11.8)	NR (4.1-NE)	11.8 (9.8-NE)

ORR: Overall Response Rate; CR: Complete Response; PR: Partial Response; SD: Stable Disease; DoR: Duration of Response; NR: Not Reached

AstraZeneca: Enhertu demonstrated clinical meaningful and durable responses across multiple HER2-expressing advanced solid tumors. June 5, 2023.

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Toxicities

Toxicity	All Grade*	Grade 3-4*
Nausea	76%	7%
Vomiting	44%	1.6%
Diarrhea	29%	1.2%
Anemia	66%	7-10%
Neutropenia	71%	16-51%
Febrile Neutropenia	---	1.1-4.8%
Renal Impairment	15%	1.1%
Hepatic Impairment	48%	3%
ILD/Pneumonitis	10-12%	1% (Fatal)
Left Ventricular Dysfunction	3.6-8%	0.4%

*Numbers are pooled from data across multiple clinical trials

- Early identification is key
- Counsel patients to report symptoms
- Monitor CBC w/diff, CMP, LVEF
- Monitor patients with moderate renal impairment more frequently
  - Higher incidence of ILD/pneumonitis reported
- Treatment includes dose interruptions, reductions, & pharmacologic intervention

fam-trastuzumab deruxtecan (ENHERTU) [package insert].Basking Ridge, NJ: Daiichi Sankyo, Inc; 2022.

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Immunotherapy Treatments

- Immune Checkpoint Inhibitors
- CAR T-cell Therapy
- Bispecific Therapy

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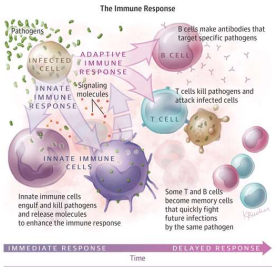
The Immune System



Thompson, Amy. The Immune System. JAMA. 2015;313(16):1686.

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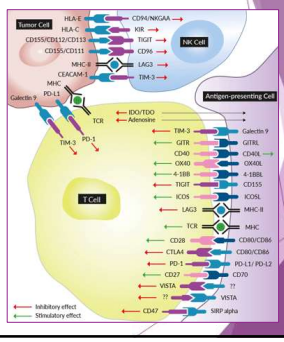
Cancer Cells

- Changes to DNA occur, allowing damaged cells to divide rapidly and uncontrollably
- Tumor cells can trigger angiogenesis
- The tumor cells deactivate T cells
- Tumor cells may travel, leading to metastasis via the bloodstream or lymph



Immune Checkpoints. InvivoGen

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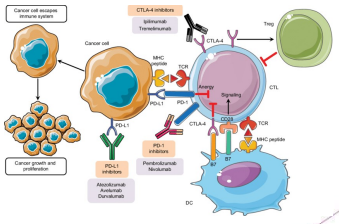
Immune Checkpoint Inhibitors - Pharmacology

- Block checkpoint proteins from binding with their partner proteins
- Prevents the "off" signal from being sent - allows T cell to kill cancer cells



Immune Checkpoint Inhibitors: National Cancer Institute, April 2022
Topalian, S. et.al. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nature: 16(275-287): 2016.

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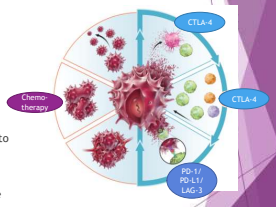
Synergistic Mechanism

- Combination immune checkpoint therapy delivers enhanced anti-tumor response over single agent
  - PD-1/PD-L1 Inhibition
    - Existing T-cells may discover the tumor
  - CTLA-4 Inhibition
    - Activate and proliferate cytotoxic T-cells
    - Suppresses Treg function
    - Some T-cells may become memory T-cells to allow for long-term immune response
  - LAG-3 Inhibition
    - Reduces inhibition of the immune response
- Combining immune checkpoint therapy with chemotherapy



www.opdivohcp.com - Bristol Myers Squibb: Princeton, NJ.

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FDA-Approved Immune Checkpoint Inhibitors

Target	Medication	Branded Product
CTLA-4	Ipilimumab	Yervoy®
CTLA-4	Tremelimumab-actl	Imjudo®
PD-1	Nivolumab	Opdivo®
PD-1	Pembrolizumab	Keytruda®
PD-1	Dostarlimab-gxly	Jemperli®
PD-1	Cemiplimab-rwlc	Libtayo®
PD-1	Retifanlimab-dlwr	Zynyz®
PD-L1	Atezolizumab	Tecentriq®
PD-L1	Avelumab	Bavencio®
PD-L1	Durvalumab	Imfinzi®
LAG-3	Relatlimab	Opdualag® (+ nivolumab)

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Immune Checkpoint Inhibitor-Related Toxicity

Common
- Rash
- Fatigue
- Endocrine adverse effects:
  - Hypothyroidism
  - Hyperthyroidism
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis

Rare, but serious
- Stevens-Johnson Syndrome (SJS) or Toxic epidermal necrolysis (TEN)
- Myocarditis
- Pancreatitis
- Hyperglycemia
- Vision Changes

National Comprehensive Cancer Network (2023). Management of Immunotherapy-Related Toxicities (version 2.2023). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf on August 28, 2023.

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IO Toxicity Treatment

- High dose steroids are mainstay of treatment (1-2 mg/kg/day)
- Prednisone is preferred oral steroid / Methylprednisolone is preferred IV
- Levothyroxine for hypothyroidism
- Infliximab or IVIG may be considered for some Grade 3-4 toxicities

National Comprehensive Cancer Network (2023). Management of Immunotherapy-Related Toxicities (version 2.2023). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf on August 28, 2023.

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Audience Response Question

- Which of the following are true regarding the use of dual immunotherapy?

a) Complimentary mechanism of actions to promote further T-cell proliferation
b) Increased anti-tumor effect over single agent use
c) A and B
d) None of the above

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Audience Response Question

- Which of the following are true regarding the use of dual immunotherapy?
  a) Complimentary mechanism of actions to promote further T-cell proliferation
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  c) A and B
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Audience Response Question

- Using dual immune checkpoint inhibitors or synergistic approaches of immune checkpoint inhibitors plus chemotherapy results in significantly higher toxicities without any additional clinical benefit?
  - True
  - False

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Audience Response Question

- Using dual immune checkpoint inhibitors or synergistic approaches of immune checkpoint inhibitors plus chemotherapy results in significantly higher toxicities without any additional clinical benefit?
  - True
  - False

- Combination immune checkpoint inhibitors may lead to higher IO toxicities with dual blockade, but data has showed improved outcomes with dual inhibition versus single agent.
- Combining immune checkpoint inhibitors with chemotherapy has similar toxicity profiles of each agent used in the regimen

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CAR T versus Bispecific Antibodies

Overview of Cellular Therapies

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Audience Response Question

- Chemotherapy that is given to a patient after confirming that CAR T-cells have been manufactured and received and prepares the patient's body to accept the CAR T-cells is known as:
  - A. Apheresis
  - B. Manufacturing
  - C. Bridging therapy
  - D. Lymphodepletion

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Audience Response Question

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Chimeric Antigen Receptor (CAR) T-Cell Therapy

Patient's own T-cells (a type of immune cell) are modified to express a chimeric antigen receptor (CAR)

↓

CAR is designed to **target specific antigens** against the patient's cancer cells

↓

CAR T-Cells are genetically engineered and replicated in a lab and **infused back** into the patient to attack cancer cells

Park JH, et al. Blood. 2016;127(26):3312-3320
Maude SL, et al. Blood. 2013 Jun 25; 125(26): 4017-4023

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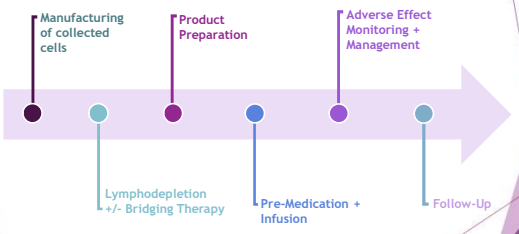
Patient's Road to CAR T



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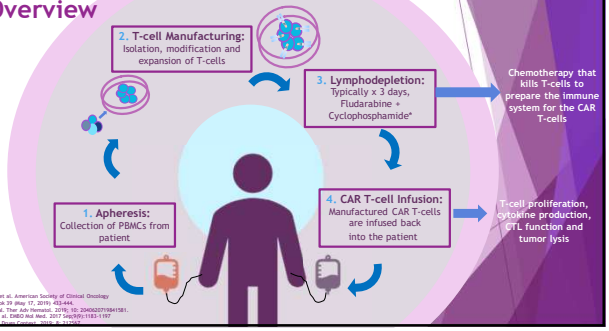
CAR T-Cell Therapy: An Overview



Santomasso B, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019): 433-444.
Chavez JC, et al. Ther Adv Hematol. 2019; 10: 2040620719841581.
Harrison J, et al. EMBO Mol Med. 2017 Sep;9(9):1183-1197.

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Identifying the Ideal Target: CD19 & BCMA

"Dream CAR" Target

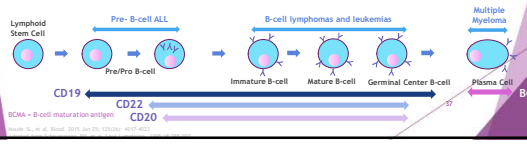
- Tumor specific
- Ubiquitously expressed on tumor cells
- Not expressed on normal cells

Next Best Thing: CD19 and BCMA CARs

- Expressed on a **single cell lineage**
- Dispensable and replaceable cell function

CD19 is a B-cell surface protein **expressed throughout B-cell development**

BCMA is a B-cell surface protein **expressed on plasma cells**



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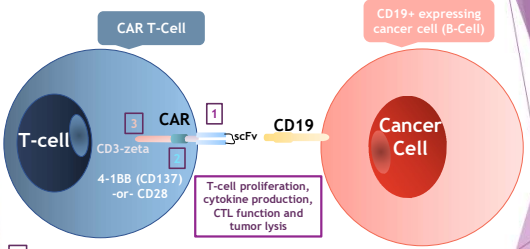
The Mechanics Behind the CAR

scFv = single-chain variable fragment
CTL = cytotoxic T lymphocyte



1 **Extracellular Antigen Recognition Domain:** recognizes CD19 antigen on B-cell

2 **Costimulatory Domain:** increases T-cell activation & enhances cytolytic function

3 **CD3-zeta intracellular signaling domain:** induces T-cell activation

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FDA Approved Indications

- Acute Lymphoblastic Leukemia (ALL)
- Large B-Cell Lymphoma (LBCL)
- Mantle Cell Lymphoma
- Follicular Lymphoma
- Multiple Myeloma

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CAR T-cell Adverse Reactions

- Risk of hypersensitivity reactions during infusion
  - Pre-medications should be administered 30-60 minutes prior to infusion
    - Acetaminophen and Diphenhydramine
    - **AVOID** prophylactic use of systemic steroids - may interfere with efficacy of therapy
  - Infusion rates are product and dose specific
- Cytokine Release Syndrome
  - Typical onset within the first 7 days
  - May occur up to 14 days when T-cells are expanding
  - High-risk patients: Bulky disease and comorbidities
- Neurotoxicity (ICANS)
  - Premedicate with levetiracetam 750mg PO BID Day -1 to 30

Lee DW, et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.
Santomasso B, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019) 433-444.

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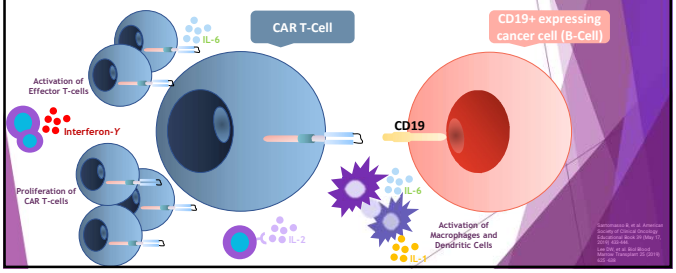
Cytokine Release Syndrome

- **Supraphysiologic response** following any **immune therapy** that results in the **activation** or **engagement** of **endogenous or infused T-cells** and/or other immune effector cells



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Multi-Organ Toxicity in CRS

Fever +/- nausea, fatigue, anorexia headache, myalgias, malaise

- **Respiratory:** Tachypnea, hypoxia, pulmonary edema
- **Hepatic:** Transaminitis, hyperbilirubinemia
- **Renal:** Acute kidney injury, azotemia
- **Cardiovascular:** Hypotension, tachycardia, arrhythmias
- **Dermatologic:** Rash
- **Gastrointestinal:** Diarrhea, nausea, vomiting
- **Hematologic:** Disseminated intravascular coagulation (DIC) - including elevated D-dimer, low fibrinogen, bleeding

Prevent life-threatening toxicities- DIC, acute respiratory failure, renal failure and liver failure

Lee DW, et al. Biol Blood Marrow Transplant. 25 (2019) 625 -638
Neelapu SS, et al. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.
Lee DW, et al. Blood. 2014 Jul 10; 124(2): 188-195

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Treatment of CRS

Supportive Care
- Antipyretics
- IV Fluids
- Vasopressors
- Oxygen Support
- Blood Products

Prevent End-Organ Damage

Empiric broad-spectrum antibiotic therapy should be initiated as appropriate given overlap of CRS and sepsis symptoms

Anti IL-6 Therapy
- Tocilizumab
- Siltuximab

Rapid Reversal of CRS Symptoms via prevention of JAK/STAT signaling

Corticosteroids
- Dexamethasone
- Methylprednisolone

Suppress inflammatory responses to prevent immune activation, including T-cell suppression

Lee DW, et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.

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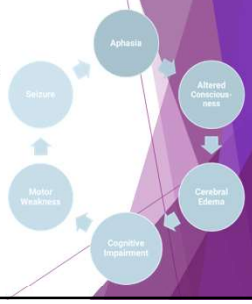
Neurotoxicity / ICANS (Immune Effector Cell Associated Neurologic Syndrome)

- **Second most common adverse effect** seen with CAR T-Cell Therapy
- "A disorder characterized by a pathologic process involving the central nervous system […] resulting in activation or engagement of endogenous or infused T cells and/or other immune effector cells"
  - Passive diffusion of cytokines into the brain
  - Trafficking of T-cells into the CNS
  - Disruption of blood brain barrier
- **Timing – Biphasic and Variable**
  - **Phase I – within 5 days:** Concurrently with CRS
  - **Phase II – beyond 5 days:** After CRS subsides
  - **Delayed – weeks after infusion:** Seizures, confusion



Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638
Neelapu SS, et al. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.

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Treatment of ICANS

Prophylactic levetiracetam 750 mg BID (day -1 to 30)

Self-Limiting
- Most cases of neurotoxicity resolve on its own within 3-4 weeks

Corticosteroids
- Dexamethasone
- Methylprednisolone

Treatment of Choice for Grade 2 or higher ICANS

Tocilizumab does not appear to benefit neurotoxicity but may be used in setting of concurrent CRS

Additional Considerations:
- **Avoid medications that cause CNS depression**
  - Lorazepam or haloperidol may be sued for agitation with careful monitoring
- **Minimize aspiration risk** (head of bed elevation, assess swallowing, NPO as appropriate)
- **Seizure prophylaxis and EEG monitoring**
- **MRI and LP**

Lee DW, et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.
Santomasso B, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019): 433-444.

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Additional Toxicities

- **Infections**
  - Acyclovir 800 mg BID x 1 year post-CAR T
  - Fluconazole 400 mg daily and ciprofloxacin 500 mg BID during neutropenia
  - PJP prophylaxis
- **Prolonged cytopenias**
  - Beyond 28-days in up to 1/3 of patients
- **Tumor lysis syndrome**
  - Allopurinol 300 mg daily starting the day prior to lymphodepletion therapy in high-risk patients

Lee DW, et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.
Santomasso B, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019) 433-444.

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CAR T-Cell Therapy REMS

- REMS program required for all products due to risk of serious adverse effects
  - Hospitals and their associated clinics must be enrolled in product-specific REMS program

Immediate access to tocilizumab
- Minimum of 2 doses per patient

Patient proximity to clinical site
- Example: within 2 hours for at least 4 weeks following treatment
- Products may have minimum daily/weekly monitoring requirements

Ensure those who prescribe, dispense, or administer CAR T-cell therapies are aware of how to identify and manage adverse effects

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Audience Response Question

- DL received her axicabtagene ciloleucel (Yescarta) infusion for her R/R DLBCL. On day +5 post-infusion, she begins to clinically deteriorate.
- It is determined that she has Grade 2 CRS based on hypotension requiring fluids and hypoxia requiring low-flow nasal cannula of 3L/hr.
- In addition to supportive care, what therapy should be initiated immediately in the setting of Grade 2 CRS?

A. Tocilizumab 8 mg/kg x 1 dose initially
B. Dexamethasone 5 mg IV q 6 hours
C. Tocilizumab 4 mg/kg Q 12 hours
D. No additional therapy is recommended at this time in addition to supportive care

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Pre-Assessment Question

- Which of the following is true of bispecific immune therapy?
  a) Collection of patients' immune cells for genetic engineering, then later reinfused into the patient
  b) Matched donor cells are infused into the patient
  c) Cytokine release syndrome must be vigilantly monitored
  d) All the above

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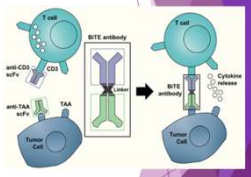
Bispecific Therapy

- Single monoclonal antibody with two immunoglobulin chains of differing specificity
- Brings two different antigens together to carry out its function
- Binds a T-cell and cancer cell, ultimately engaging T-cells to kill tumor cells
- Available as an off-the-shelf treatment option



Salvaris R, Ong J, Gregory GP. Bispecific Antibodies: A Review of Development, Clinical Efficacy and Toxicity in B-Cell Lymphomas. J Pers Med. 2021 Apr 29;11(5):335.

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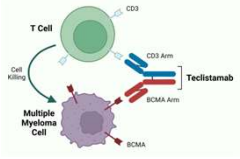
Teclistamab for Multiple Myeloma

- Teclistamab-cqyv is a bi-specific antibody that targets both CD3 expressed on the surface of T cells and BCMA expressed on the surface of myeloma cells, thus mediating T-cell activation and subsequent lysis of BCMA-expressing myeloma cells



- Teclistamab-cqyv has a similar function to BCMA-targeted CAR T-cell therapies for advanced multiple myeloma (ABECMA® and CARVYKTI™)

National Cancer Institute. "Teclistamab Shows Promise for People with Heavily Pretreated Multiple Myeloma." https://www.cancer.gov/news-events/cancer-currents-blog/2022/tecvayli-multiple-myeloma

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FDA Approved Therapies

Therapy	Indication	Target	Branded Name	Approval
Blinatumomab	B-cell ALL	CD19/CD3	BLINCYTO	2014
Amivantamab-vmjw	mNSCLC with EGFR exon 20 insertion mutation	EGFR/MET	RYBREVANT	2021
Tebentafusp-tebn	Uveal Melanoma	HLA/CD3	KIMMTRAK	2022
Teclistamab	R/R Multiple Myeloma	BCMA/CD3	TECVAYLI	2022
Mosunetuzumab-axgb	R/R Follicular Lymphoma	CD20/CD3	LUNSUMIO	2023
Epcoritamab-bysp	R/R DLBCL	CD20/CD3	EPKINLY	2023
Glofitamab-gxbm	R/R DLBCL or LBCL	CD20/CD3	COLUMVI	2023
Talquetamab-tgvs	R/R Multiple Myeloma	GPRC5D/CD3	TALVEY	2023
Elranatamab-bcmm	R/R Multiple Myeloma	BCMA/CD3	ELREXFIO	2023

Bispecific Antibodies: An Area of Research and Clinical Applications. FDA website: August 2, 2023.

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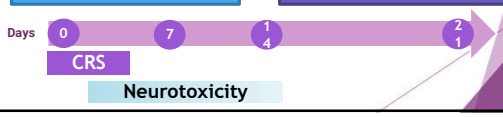
Bispecific Therapy Toxicities

ICANS = Immune effector cells associated neurologic syndrome

Cytokine Release Syndrome (CRS) | **Neurotoxicity (including ICANS)** | **"Other" Toxicities**

CRS
Median time to onset = 2 days
Median time to resolution = 2- 5 days

Neurotoxicity
Median time to onset = 4 - 14 days
Median time to resolution = 4 days



Adapted from Santomasso B, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019):433-444.

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Common Adverse Events Between CAR T-Cell Therapy & Bispecific Antibodies

Cytokine Release Syndrome (CRS)
Fever
Hypotension
Hypoxia
Tachycardia
Chills

Neurotoxicity (including ICANS)
Confusion
Delirium
Tremor
Agitation
Seizures

Cytopenias
Neutropenia
Anemia
Thrombocytopenia
Lymphopenia

Infections
Opportunistic infections
(e.g. herpes simplex, varicella zoster, PJP pneumonia)

Higher Rates and Severity of CRS and Neurotoxicity with CAR T-Cell Therapy
Most Common

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Adverse Event Management

Monitor & Administer Supportive Care as soon as possible (fluids, antipyretics, antimicrobial prophylaxis, etc.)

- Bispecific Therapy
  - Interrupt/hold therapy to manage
  - Administer steroids
  - Tocilizumab may be used
- CAR T-Cell Therapy
  - One-time infusion - cannot hold therapy
  - Reserve steroids for severe/refractory CRS
  - Administer tocilizumab

Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-3330.

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Audience Response Question

- Which one of the following bispecific antibody agents is indicated for relapsed/refractory multiple myeloma and administered subcutaneously?
  - A. Teclistamab
  - B. Blinatumomab
  - C. Mosunetuzumab
  - D. Glofitamab

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  - C. Mosunetuzumab
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Look into the Future: Cancer Vaccines

*NOT currently FDA approved

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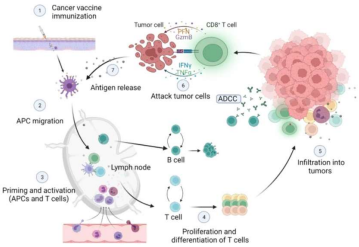
Cancer Vaccines



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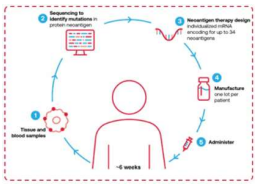
mRNA-4157 (V940) + Pembrolizumab

- Resected Stage IIIB, IIIC, IIID, or IV cutaneous melanoma
- mRNA-4157 is a personalized cancer vaccine
- The individualized neoantigen therapy is designed to target an individual patient's unique tumor mutations and encodes up to 34 neoantigens



Khattak, A. et.al. Abstract CT001: A personlized cancer vaccine, mRNA-4157, combined with pembrolizumab versus pembrolizumab in patients with resected high-risk melanoma. Cancer Res: April 2023.
Khattak, A. et.al. Distant metastatis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial. JCO 41(17): June 7, 2023.

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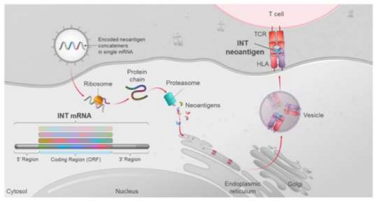
mRNA-4157 (V940) + Pembrolizumab

- These neoantigens then increase endogenous neoantigen T-cell responses & induce epitope spreading → drives antitumor responses and maintain memory with cytolytic properties, potentially producing long-term disease control



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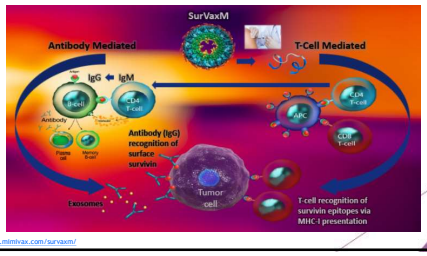
SurVaxM

- *Currently NOT FDA approved
- Clinical trials continuing in Glioblastoma, Multiple Myeloma, Neuroendocrine Tumors



https://www.mimivax.com/survaxm/

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SurVaxM in Malignant Glioma (GBM)

- Adults with newly diagnosed glioblastoma
- Resection/chemoradiation → 4 biweekly SUBQ doses of SurVaxM + sargramostim → adjuvant temozolomide once daily Day 1-5 q28days x6 cycles
- Continue SurVaxM maintenance dosage once every 12 weeks
- Phase IIa study results:
  - 63 patients evaluated
  - 60/63 (95.2%) remained progression free at 6 months
  - mPFS: 11.4 months
  - mOS: 25.9 months

Ahluwalia, M, et.al. Phase IIa Study of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma. March 01, 2023; JCO 41:7 (1453-1465).
https://www.mimivax.com/survaxm/

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Questions?

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