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Special thanks to Des Hanna, PharmD, BCPS for custom chemo man

# Disclosure

The presenters have no conflicts of interest to disclose

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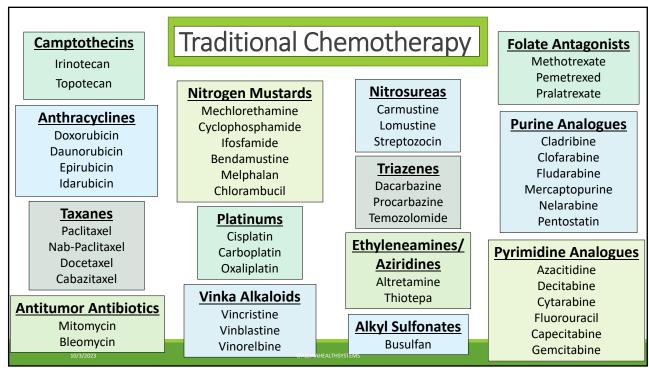
# Objectives

- Learn common toxicities for traditional chemotherapy and targeted therapy
- Describe how to monitor patients for treatment-related toxicities
- Identify techniques used to prevent and mitigate common toxicities

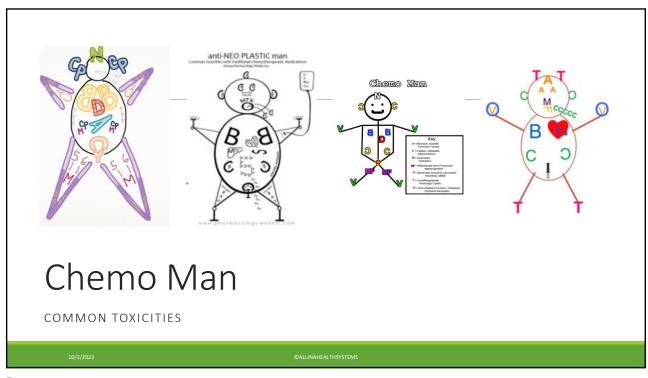
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# Traditional Chemotherapy Toxicity

- Severity varies greatly from person to person
  - Schedule and dose
  - Patient factors (eg, organ function, treatment history)
  - Disease
  - Concomitant medications
- Chemotherapy regimens usually combine drugs with different toxicity profiles
- Normal cells most likely to be damaged by chemo:
  - Blood-forming cells in the bone marrow
  - Hair follicles
  - Cells in the mouth, digestive tract, and reproductive system

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Chemotherapy Side Effects | American Cancer Society

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### **Camptothecins**

Irinotecan Topotecan

# Camptothecins

Mechanism of Action: Inhibit topoisomerase I, stabilizing the cleavable complex, causing single strand DNA breaks

#### Irinotecan

- Commonly used for colorectal cancer (FOLFIRI)
- Early and late diarrhea
  - Early stage (within 24 hours)
  - Late stage (~3-10 days after chemo)
- Treat with atropine 0.25-1 mg subQ/IV
- Treat with loperamide 4 mg at onset of diarrhea then 2 mg every 2 hours as need (or 4 mg every 4 hours overnight) until cessation of diarrhea for 12 hours. Limit to 48 hours of treatment.

Monitor and replace electrolytes!!!

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# Anthracyclines

Anthracyclines
Doxorubicin

Daunorubicin
Epirubicin
Idarubicin

*Mechanism of action:* Inhibit topoisomerase II, preventing re-ligation of DNA and strand breaks. Form oxygen free radicals that add to cytotoxicity and toxicity.

### Doxorubicin and daunorubicin

- Red-orange urine
- Mucositis
- Diarrhea
- · Potent vesicants
  - Dexrazoxane for antidote
  - Administer ice to areas of extravasation









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# Anthracyclines

### Cardiotoxicity

- Cause: Myocardial cell injury
- Risk greatly increases after ~450 mg/m2 of doxorubicin
  - Dexrazoxane inhibits cardiotoxic effects
  - Avoid combination with other cardiotoxic agents (eg, trastuzumab)
- If not diagnosed early, can lead to symptomatic heart failure
  - Prophylaxis and treatment with ACE inhibitors (eg, lisinopril) and beta blockers (eg, metoprolol)
  - Monitoring: Baseline ejection fraction (EF) required then repeat monitoring periodically

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# Microtubule Destabilizing Agents

### **Taxanes**

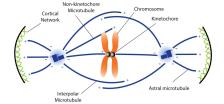
*Mechanism of action:* Stimulate microtubule formation

### Vinca Alkaloids

*Mechanism of action:* Inhibit microtubule formation

### **Taxanes**

Paclitaxel Nab-Paclitaxel Docetaxel Cabazitaxel



Vinka Alkaloids

Vincristine Vinblastine Vinorelbine

End result = Suppression of microtubule and mitotic spindle activity inhibits mitosis

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## **Taxanes**

### Paclitaxel and docetaxel

Alopecia

- Complete hair loss
- Cold caps

Hypersensitivity reactions

- Paclitaxel
  - Cremophor
  - Pre-med with dexamethasone, diphenhydramine, famotidine
- Docetaxel
  - Tween80
  - Pre-med with dexamethasone for 3 consecutive days, starting one day prior to docetaxel

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# Taxanes

- Chemotherapy-induced peripheral neuropathy (CIPN)
  - Numbness, tingling, and/or pain in fingers & toes
  - Risk increases with cumulative dose and certain preexisting medical conditions
    - Encourage patient reporting
  - Management: Delay dose, dose reduce, or switch agents; consider duloxetine
- Taxane-associated pain syndrome (TAPS)
  - Myalgia or arthralgia symptoms within 24-48 hours of taxane administration that may last up to 7 days
  - Management: Gabapentin, duloxetine, ibuprofen, corticosteroids

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# Vinca Alkaloids

### Vincristine

- Potent vesicant
  - Hyaluronidase for antidote increases distribution and absorption of locally injected extravasated substances
  - Use warm compress for extravasation
- Fatal if given intrathecally should be prepared in an IV bag (not syringe)
- Vincristine-induced neuropathy
  - Sensory: Numbness, tingling
  - Motor weakness: Altered gait, impaired balance
  - Autonomic: Constipation

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### **Folate Antagonists** Methotrexate Pemetrexed **Antimetabolites** Pralatrexate Mechanism of action: Damage cell DNA by either competing for enzyme **Purine Analogues** binding sites or inserting directly into DNA or RNA strands Cladribine Clofarabine Fludarabine Mercaptopurine Nelarabine Pentostatin **Pyrimidine Analogues** Azacitidine Decitabine Cytarabine Fluorouracil Capecitabine Gemcitabine

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# Folate Antagonists



### **Folate Antagonists** Methotrexate

Pemetrexed Pralatrexate

- Mucositis
  - Pemetrexed
    - Folic acid and Vitamin B-12 supplements can reduce incidence of myelosuppression and mucositis
      - Start 1 week prior to treatment, take throughout therapy, and continue until 21 days after the last dose
  - Methotrexate
    - Do not supplement with folic acid
- Rash
  - Pemetrexed pre-med with dexamethasone starting day prior to

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# Folate Antagonists



### High-dose Methotrexate (>500-1000 mg/m<sup>2</sup>)

- Leucovorin rescue
  - Allows DNA synthesis to begin again, preventing toxicity (eg, myelosuppression, mucositis, and hepatotoxicity)
  - Start leucovorin 24 to 36 hours after start of methotrexate
- Alkalinization of urine & continuous hydration
  - Keep urine pH ≥7
    - Methotrexate is 6-10 times more soluble in alkaline urine prevents crystallization in renal tubule
    - Frequent urine pH checks
  - Avoid excess use of diuretics

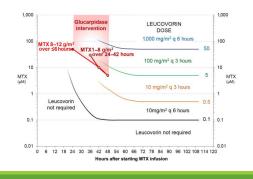
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# Folate Antagonists

### High-dose Methotrexate (>500-1000 mg/m2)

- Avoid drug interactions
- Methotrexate levels
  - Drawn at various intervals, beginning 24 hours after methotrexate infusion **BEGINS**
  - Use methotrexate levels to ensure patient receiving adequate dose of leucovorin
  - Glucarpidase antidote used to convert methotrexate into non-toxic metabolites
    - Administered when methotrexate levels and renal function elevated
    - · Medical emergency!

| Example Agents                                      |
|---|
| Aspirin, salicylates, ibuprofen, ketorolac          |
| Penicillins, probenecid, ciprofloxacin, doxycycline |
| Sulfonamides, tetracyclines                         |
| Aminoglycosides, amphotericin                       |
| Omeprazole, pantoprazole                            |
| Phenytoin, carbamazepine                            |
| Folic acid, ascorbic acid, MVI                      |
|   |



Pyrimidine Analogues
Azacitidine
Decitabine

Cytarabine Fluorouracil Capecitabine

Gemcitabine

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# Pyrimidine Analogues

### Fluorouracil (5FU)

- Administration
  - Infusion
  - Bolus leucovorin helps to improve 5FU efficacy
- Toxicity
  - Hand-foot syndrome
  - Diarrhea
  - Neutropenia & thrombocytopenia: 5FU bolus
  - Mucositis oral cryotherapy (30 mins) during 5FU bolus

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# Pyrimidine Analogues

### Cytarabine (AraC)

- High-dose cytarabine (>1000 mg/m²) can diffuse into tears and cross the blood-brain-barrier
  - Requires steroid eye drops to prevent chemical conjunctivitis
    - Prednisolone: 2 drops in each eye every 6 hours starting prior to start of highdose cytarabine → Continue for 48-72 hours after cytarabine complete
  - Frequent neuro checks during therapy
  - Neurotoxicity can manifest acute cerebellar toxicity, personality changes, or may be severe (eg, seizure/coma)

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# **Alkylating Agents**

Mechanism of action: Form highly reactive carbonium ion intermediates that bind to nucleophilic sites on DNA

 Cell kill results from DNA strand breaks, DNA mispairing, and inhibition of DNA replication & transcription

#### Common class toxicities

- Myelosuppression
- Mucositis
- Nausea & vomiting
- Alopecia
- Secondary leukemias

### **Nitrogen Mustards**

Mechlorethamine Cyclophosphamide Ifosfamide Bendamustine Melphalan Chlorambucil

### **Platinums**

Cisplatin
Carboplatin
Oxaliplatin

#### **Nitrosureas**

Carmustine Lomustine Streptozocin

#### **Triazenes**

Dacarbazine Procarbazine Temozolomide

## Ethyleneamines/

<u>Aziridines</u>

Altretamine Thiotepa

Alkyl Sulfonates

Busulfan

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# Nitrogen Mustards

### Ifosfamide and cyclophosphamide

- Hemorrhagic cystitis
  - Caused by acrolein byproduct
  - Mesna binds to an inactivates acrolein byproduct
    - Must be given with ifosfamide
    - Recommended for cyclophosphamide doses >1000 mg/m2

### **Nitrogen Mustards**

Mechlorethamine Cyclophosphamide Ifosfamide Bendamustine Melphalan Chlorambucil

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# **Platinums**

### <u>Platinums</u>

Cisplatin Carboplatin Oxaliplatin

- Cisplatin
  - Nephrotoxicity
  - Ototoxicity
  - Electrolyte wasting
  - Nausea & vomiting acute and delayed
- Carboplatin
  - Increased risk of hypersensitivity reactions after ~6-8 doses
  - Calvert formula accounts for renal function and ability to clear carboplatin
    - Dose = AUC x (CrCL + 25)
- Oxaliplatin
  - · Neuropathy symptoms exaggerated by cold

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## **Platinums**

### Chemotherapy-induced nausea & vomiting

- Definitions
  - Acute (0-24 hours after chemo)
  - Delayed (>24 hours after chemo)
  - Anticipatory (conditioned response from previous chemo treatment)
- Risk factors
  - Female gender
  - Younger age
  - · History of motion or morning sickness

- Anti-emetic Prophylaxis
- Examples: Fosaprepitant, dexamethasone, palonsetron, olanzapine
- May require multiple agents for adequate anti-nausea control (especially if highly emetogenic chemotherapy



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# **Antitumor Antibiotics**

### **Antitumor Antibiotics**

Mitomycin Bleomycin

*Mechanism of action:* Cytotoxic effects result from the generation of activate oxygen radicals, leading to single- and double-strand DNA breaks

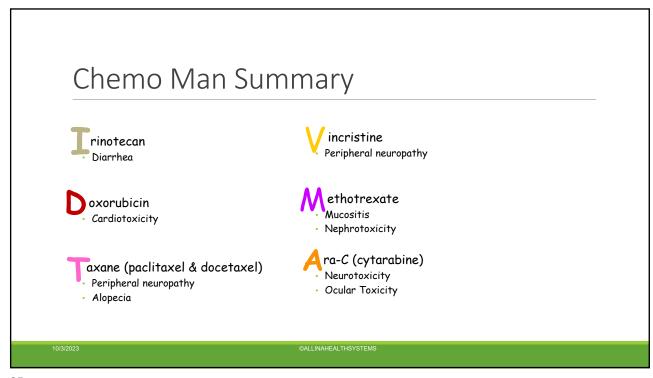
- Bleomycin
  - Pulmonary toxicity
    - Manifests as interstitial pneumonitis or pulmonary fibrosis
    - Risk increases when cumulative dose >400 units
    - Monitor
      - PFTs
      - Baseline DLCO & vital capacity
      - Chest x-ray

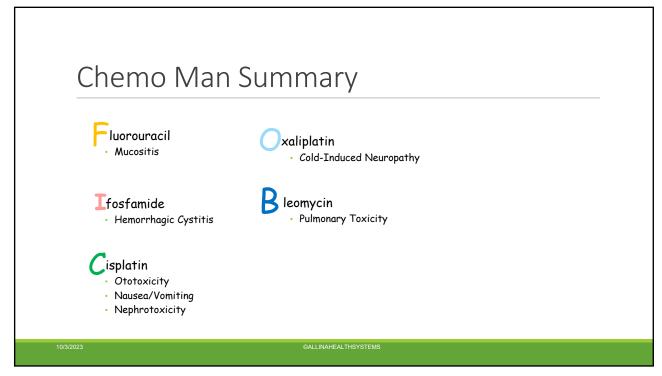


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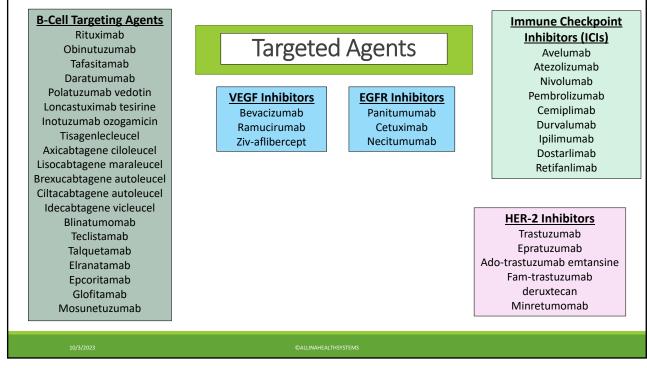




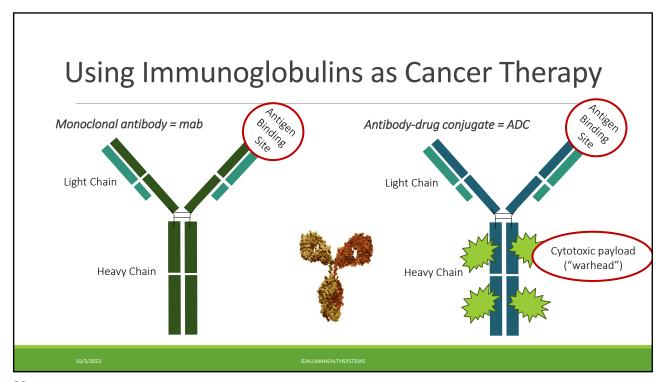
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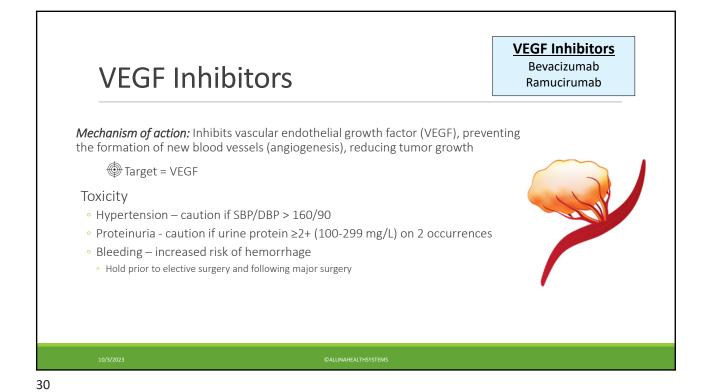
#### **Targeted Agents Chimeric Antigen** Receptor (CAR) T-cell Tisagenlecleucel Axicabtagene ciloleucel Lisocabtagene maraleucel Monoclonal Pembrolizumab **Antibody Drug Conjugates** Brexucabtagene autoleucel Cemiplimab (ADCs) **Antibodies** Ciltacabtagene autoleucel Gemtuzumab ozogamicin Durvalumab Rituximab Idecabtagene vicleucel Brentuximab vedotin **Ipilimumab** Obinutuzumab Polatuzumab vedotin Nivolumab Daratumumab **Bispecific Antibodies** Loncastuximab tesirine Isatuximab Inotuzumab ozogamicin (BsAbs) Ofatumumab Moxetumomab pasudotox Blinatumomab Alemtuzumab Enfortumab vedotin Teclistamab Trastuzumab Sacituzumab govitecan Talquetamab Ado-trastuzumab emtansine Elranatamab Bevacizumab Fam-trastuzumab deruxtecan **Epcoritamab** Ramucirumab Tisotumab vedotin Glofitamab Ibritumomab Mirvetuximab soravtansine Mosunetuzumab Naxitamab **Emcizumab** Avelumab **Amivantamab** Atezolizumab **Tebentafusp** Nivolumab

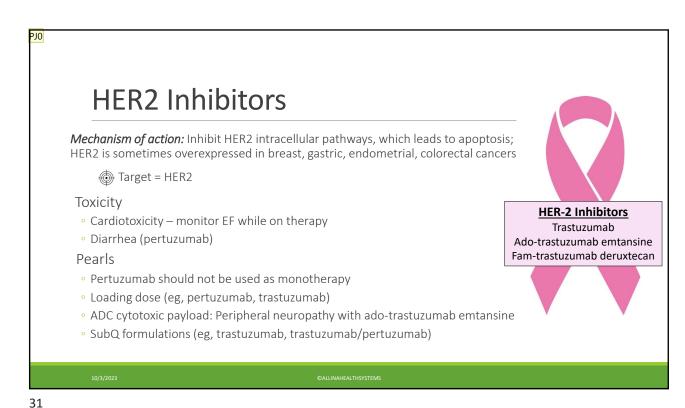
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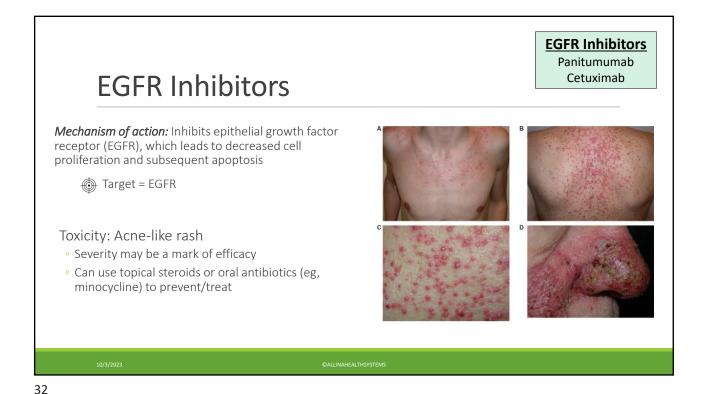


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### **PJO** Picture???? HER-2 receptor?

Preedit, Justine, 2023-09-25T02:11:04.188

# **Checkpoint Inhibitors**







Healthy

Cancer

Immune system

IMFINZI

*Mechanism of action:* Inhibit checkpoint proteins from binding with their partner proteins, preventing the "off" signal from being sent, allowing T-cells to kill cancer cells

Targets = PD-1, PD-L1, CTLA4

# Immune Checkpoint Inhibitors (ICIs)

Nivolumab (PD-1) Pembrolizumab (PD-1) Durvalumab (PD-L1) Ipilimumab (CTLA4)

### Immune System Evasion



**Recognition & Destruction** 



Immune Checkpoint Inhibitors - NCI (cancer.gov)

Immunotherapy for BTC, uHCC, NSCLC & ES-SCLC – IMFINZI® (durvalumab)

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# **Checkpoint Inhibitors**

LEGS

Treat a variety of cancer types

 Breast, bladder, cervical, endometrial, colon/stomach/rectal, liver, head and neck, renal cell, melanoma, Hodgkin lymphoma

Toxicity: Immune-related adverse effects (irAE)

- · Liver: hepatotoxicity; Endocrine: hypothyroidism, GI: diarrhea/colitis, Skin: maculopapular rash/pruritis
- Other: pneumonitis, headache, acute kidney injury, myocarditis
- Grade irAEs using CTCAE (Common Terminology Criteria for Adverse Events)

#### Pearls

- $\circ$  Should be used cautiously in patients with immune-mediated disease (eg, rheumatoid arthritis, multiple sclerosis)
- Risk vs benefit in patients taking concomitant steroids (prednisone equivalent >10 mg)
- Ipilimumab should not be used as monotherapy

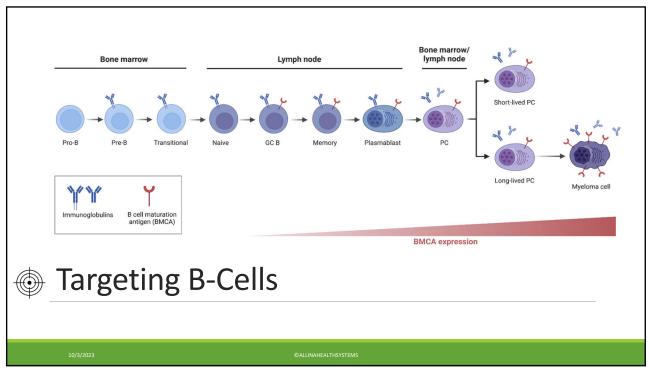
Immune Checkpoint
Inhibitors (ICIs)

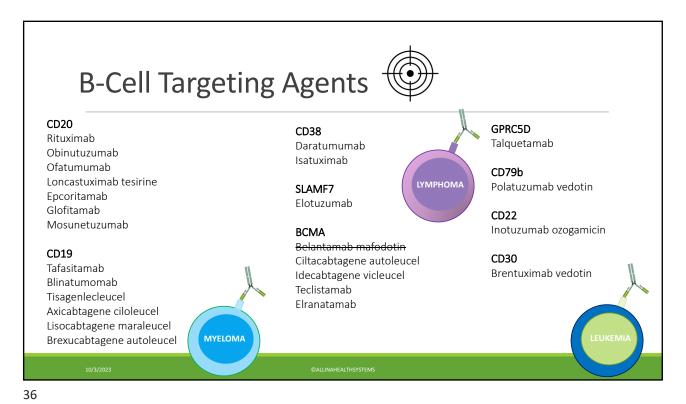
Nivolumab (PD-1) Pembrolizumab (PD-1) Durvalumab (PD-L1) Ipilimumab (CTLA4)

Immune Checkpoint Inhibitors - NCI (cancer.gov)

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# **B-Cell Targeting Agents**

**Mechanism of action:** Bind to target antigen expressed on B-cells, activating complement-dependent B-cell cytotoxicity and antibody-dependent cellular cytotoxicity

### Toxicity

- ADC cytotoxic payload: Peripheral neuropathy with polatuzumab vedotin, veno-occlusive disease (VOD) with inotuzumab ozogamicin
- Infusion-related or hypersensitivity reactions (eg, rituximab, <del>daratumumab IV</del>)
- Increased risk of infections
  - · Pancytopenia
  - · Reactivation of Hepatitis B
  - Decreased response to vaccines

CAR T Cells to Treat Cancer - NOLLINAHEALT

#### Pearl:

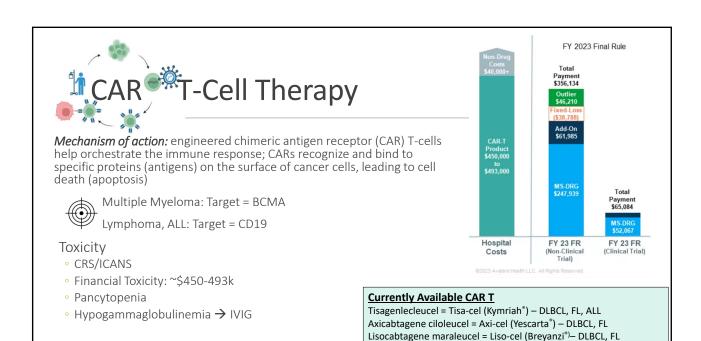
· SubQ formulation available: rituximab, daratumumab

### **Monoclonal antibodies**

#### & ADCs

Rituximab
Obinutuzumab
Tafasitamab
Daratumumab
Polatuzumab vedotin
Loncastuximab tesirine
Inotuzumab ozogamicin

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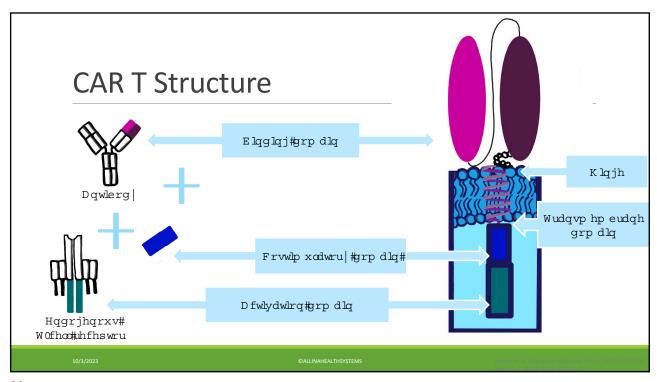


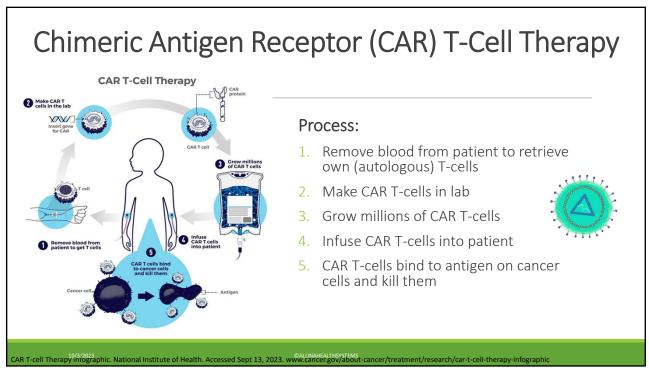
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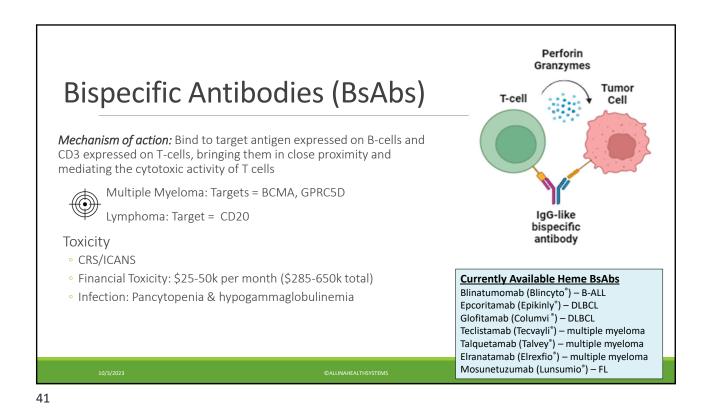
Brexucabtagene autoleucel = Brexu-cel (Tecartus®) – MCL, ALL Ciltacabtagene autoleucel = Cilta-cel (Carvykti®) – multiple myeloma

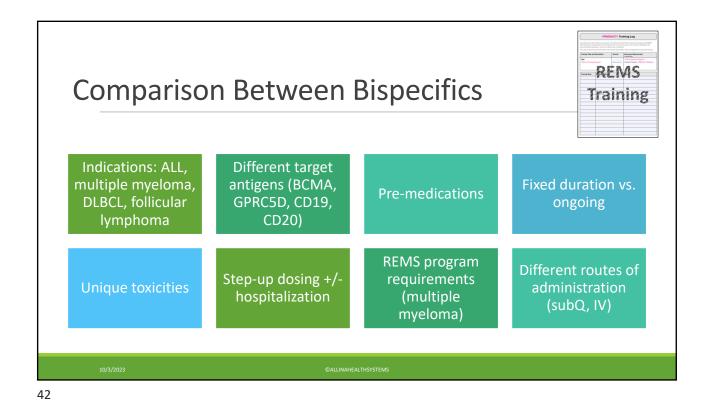
!decabtagene vicleucel = Ide-cel (Abecma®) – multiple myeloma

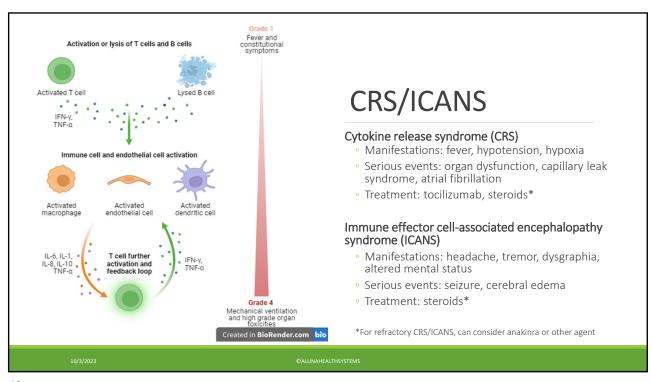


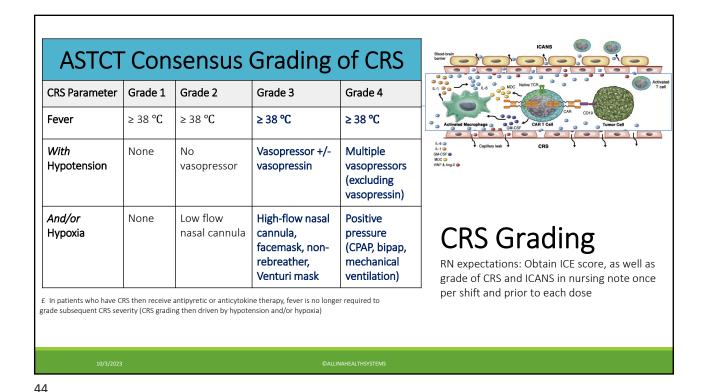


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# Managing CRS for Bispecifics

### **General Principles**

- Administer aggressive supportive care
- Wait until CRS resolves prior to administering next bispecific dose
- · Consider treating as next higher grade:
  - If clinical status worsens or does not improve within 24 hours
- If patient frail or elderly
- Monitor cardiac, renal, and hepatic function closely
- Avoid growth factors during CRS risk
- For recurrent grade 3 or any grade 4 CRS, discontinue agent permanently

|  | CRS       | Pharmacologic  | Supportive  |  |
|--|-----------|--|---|--|
|  | Grade 1   | Consider dexamethasone 10 mg (PO/IV)   | <ul> <li>Treat fever and<br/>neutropenia if<br/>present, monitor</li> </ul>                   |  |
|  | Grade 2-3 | Dexamethasone 10-20 mg PO/IV every 6 hours • If no improvement in 4 hours, consider tocilizumab 8 mg/kg (max 800 mg) | fluid balance, and administer antipyretics & analgesics as needed  IV fluids, vasopressors, & |  |
|  | Grade 4   | Methylprednisolone 1000 mg IV daily  | oxygen as needed  |  |

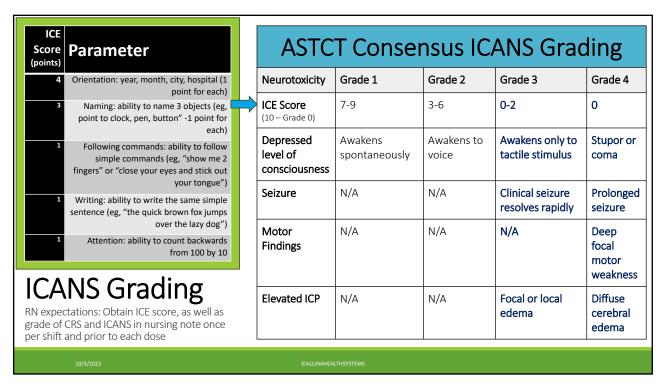
Consider anakinra for refractory ICANS - if used, add levofloxacin and anti-mold coverage due to increased risk of infections

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Does not include blinatumomab

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# Managing ICANS for Bispecifics

### General Principles

- Administer aggressive supportive care
- Wait until ICANS resolves prior to administering next bispecific dose
- · Low threshold to initiate levetiracetam
- · Consider treating as next higher grade:
  - If clinical status worsens or does not improve within 24 hours
  - If patient frail or elderly
- Consider neurologic consult for grade ≥3 ICANS
- For recurrent grade 3, grade ≥3 seizure, or any grade 4 ICANS, discontinue agent permanently

|   | CRS       | Pharmacologic   | Supportive  |
|---|-----------|---|---|
| 5 | Grade 1   | <ul> <li>Consider dexamethasone 10 mg (PO/IV)</li> <li>Consider levetiracetam 500 mg (PO/IV) for seizure prophylaxis</li> </ul> | Treat fever and<br>neutropenia if<br>present, monitor<br>fluid balance, and<br>administer<br>antipyretics & |
|   | Grade 2-3 | Dexamethasone 10-20 mg<br>PO/IV every 6 hours   | <ul><li>analgesics as needed</li><li>IV fluids,</li></ul>   |
| ' | Grade 4   | Methylprednisolone 1000 mg IV daily   | vasopressors, & oxygen as needed  |

Consider anakinra for refractory ICANS - if used, add levofloxacin and anti-mold coverage due to increased risk of infections

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Does not include blinatumomab

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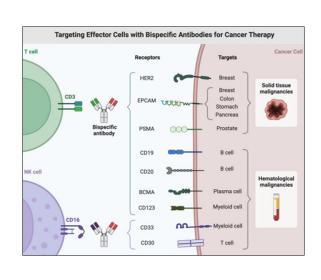
# Managing CRS/ICANS for Blinatumomab

- Grade 1: Continue blinatumomab and administer supportive care
- Grade 2: Pause blinatumomab immediately and administer supportive care
- Grade 3-4: Pause blinatumomab immediately and administer supportive care
  - Dexamethasone 8 mg IV/PO every 8 hours for up to 3 days (tapered quickly)
  - Consider tocilizumab 8 mg/kg (max 800 mg) for severe or life-threatening CRS
    - Do NOT use tocilizumab for isolated ICANS (does not cross blood brain barrier)
- Grade 4 or >1 seizure: Discontinue blinatumomab permanently

If blinatumomab infusion paused for ≥4 hours, dexamethasone must be redosed prior to restarting infusion. Provider decision to restart blinatumomab based on patient clinical status.

\*Of note, the PI gives different guidance for when to pause blinatumomab infusion
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When are thousing to pause the infusion at grade 2 (with the hones that spaller provider assessment of CRS/ICANS will lead to prevention of worse complications

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## **Future Directions**

- Use various constructs & target antigens in multiple cancers
- Tarlatamab lung cancer bispecific in clinical trials; target = DLL-3
- Move bispecifics from inpatient to outpatient infusion clinic
  - Minimize financial toxicity (AllinaForward)
  - Increase revenue
- Learn how to sequence these agents & manage toxicity

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# Summary of Targeted Agents

- Most agents have the potential to cause an infusion-related or hypersensitivity reaction
- Target antigen determines toxicity
- · Bispecifics. . .they're coming
  - Several bispecifics have come out in the last year there are similarities and differences amongst all the products
  - All have risk for cytokine release syndrome (CRS) and neurotoxicity (ICANS), so be aware of how to recognize & manage toxicity (KNOW YOUR RESOURCES)

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# FUN Bispecific • Oncology Nursing Society Resources

- ONS Nursing Society Meeting: Sarah Hayes, PharmD, BCOP & Justine Preedit, PharmD, BCOP presenting at the October 10th for the Oncology Nursing Society Meeting (Boludo – Downtown
- Podcast Episode 275: Bispecific Monoclonal Antibodies in Hematologic and Solid Tumors
- Podcast Episode 176: Oncologic Emergencies 101: Cytokine Release Syndrome

### Research to Practice Podcast

Disease experts, including RN/APPs, discuss their experience with administering chemoimmunotherapy in large academic medical centers & how community hospitals can use lessons learned to successfully administer these complex agents to patients

#### WolverHeme Podcast

- Two malignant heme pharmacists drink and nerd out about data
- Podcast Episode 12: Tinder for T cells Bispecifics in DLBCL

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