Managing ICANS

General Principles

- Consider neurologic consult for grade ≥1 ICANS
- Assess for concurrent symptoms of CRS (can treat concurrently with ICANS)
- Levetiracetam 500 mg PO/IV twice daily for seizure prophylaxis for grade ≥2 (consider earlier for grade 1)
- Assess for alternative causes of symptoms – consider CT head, MRI, EEG, or LP, as appropriate
- For recurrent grade 3, grade ≥3 seizure, or any grade 4 ICANS, discontinue agent permanently

Does not include blinatumomab

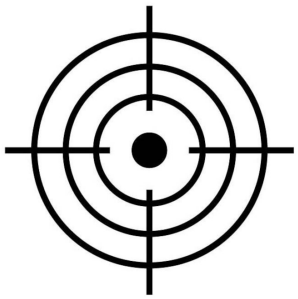
ICANS	Pharmacologic
Grade 1	• Observation can generally be considered • Consider dexamethasone 10 mg (PO/IV) once, especially if patient at high risk for complications or high tumor burden; may schedule daily for persistent symptoms
Grade 2	Dexamethasone 10 mg PO/IV every 8 to 12 hours • May consider increasing dexamethasone dose to 20 mg if no improvement
Grade 3	Dexamethasone 10 to 20 mg IV every 6 hours • May consider increasing dexamethasone dose to 20 mg if no improvement (could consider high-dose methylprednisolone 500-1000 mg every 24 hours, or divided doses)
Grade	Dexamethasone 20 mg IV every 6 hours (could consider increasing to methylprednisolone 1000 mg IV every 24 hours)

Tocilizumab does NOT cross the blood brain barrier (so should not be used for ICANS)

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

For tarlatamab & tebentafusp: May consider lower dexamethasone doses within the range provided; for grade 2, recommend one-time dexamethasone dose for initial management

19



On Target, OFF TUMOR

Uveal melanoma (HLA-A*02:01-positive; Example: Tebentafusp)

- **Target = GP100** - expressed weakly by melanocytes
- **Toxicity:** Rash

Small cell lung cancer (Example: Tarlatamab)

- **Target = DLL3** - expressed intracellularly
- **Toxicity:** ?

Lymphoma (Example: Glofitamab)

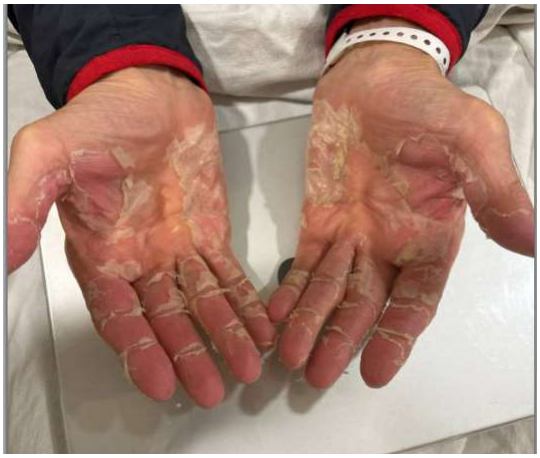
- **Target = CD20**- expressed on B-cells
- **Toxicity:** Hypogammaglobulinemia

20

GPRC5D Expression in Keratinized Tissue

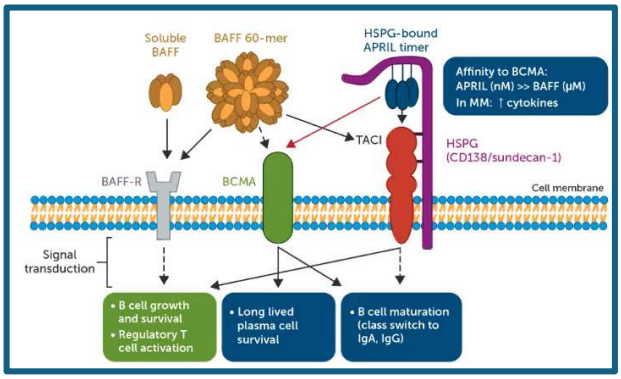
GPRC5D protein is expressed on CD138+ multiple myeloma cells
- However, it is also normally expressed in hair follicles and keratinized tissue (e.g., hair, skin, tongue, nails)

On-target, OFF TUMOR inhibitory effects of GPRC5D therapy, including talquetamab:
- Skin: palmar-plantar erythrodysesthesia (hand foot syndrome), skin discoloration, desquamation, fissure, rash
- Nails: hypertrophy, nail changes
- Oral toxicity/weight loss: Dysgeusia, dry mouth, dysphagia, stomatitis (80%)



GPRC5D = G protein-coupled receptor class C group 5 member D

21



Target = Toxicity

B-Cell Maturation Antigen (BCMA)

Examples: Elranatamab and teclistamab

Since BCMA found on plasma cells, expect decreased production of antibodies, or immunoglobulins

Toxicity: Hypogammaglobulinemia (75%)

- Infections: >80% (grade 3/4: >40-50%)
  - *Viral:* Hepatitis B Virus, Hepatitis C Virus (HCV), Cytomegalovirus (CMV), COVID-19, Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Respiratory Syncytial Virus (RSV)
  - *Bacterial:* Gram+/Gram-
  - Fungal infections

22

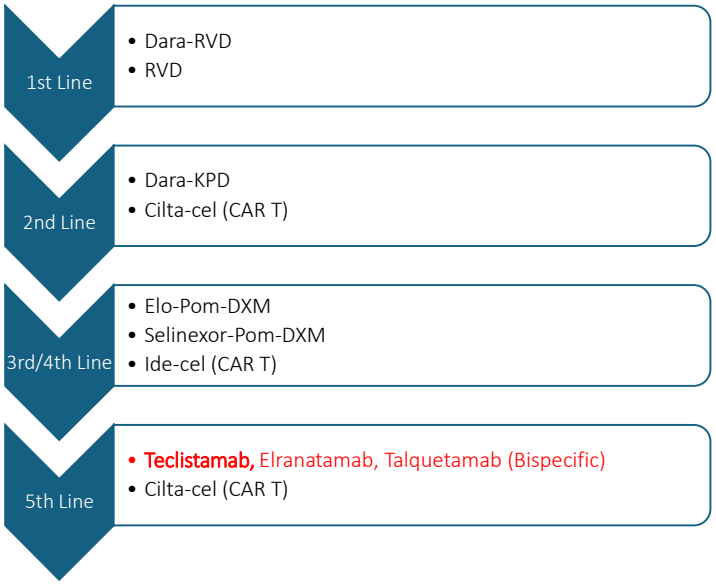
Blinatumomab in B-ALL

- Blinatumomab (CD19 BITE) should be used in most patients with B-ALL
- May be used in….
  - Frontline B-ALL in combination with reduced intensity chemotherapy and antibody therapy (Inotuzumab, rituximab) in older, frailer patients
  - Minimal residual disease (MRD) positivity (often as bridge to consolidation with alloBMT)
  - Relapsed/Refractory disease
  - MRD negative patients as consolidation to prevent relapse, in combination with standard chemoimmunotherapy
- Short duration hospital stay recommended for C1 and 2 (3-9 days)
- Lots of coordination needed with home infusion due to continuous pump administration

23

Myeloma Treatment

Bispecifics
Target=BCMA, GPRC5D



Abbreviations: CAR T=chimeric antigen receptor CAR T-cell therapy; Cilta-cel=Ciltacabtagene autoleucel; Ide-cel=Idecabtagene vicleucel

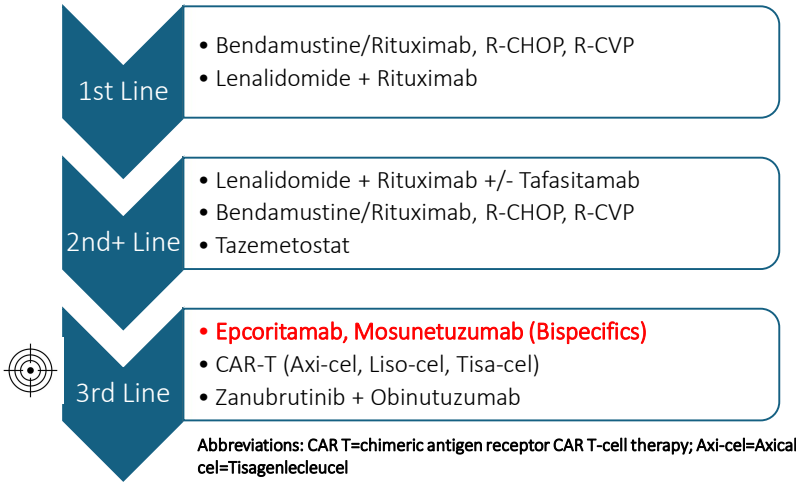
24

Bispecifics in Multiple Myeloma

- Very promising single agent activity with durable remissions in multiply R/R patients
- Hospitalization/observation for approximately 1 week while stepping up doses
- Multiple Bispecific targets in R/R MM space (BCMA, GPRC5D)
  - Current FDA approval in 5th line setting, triple class refractory
- CRS is common but rarely high grade. ICANS is uncommon (<10%) and rarely high grade.
- Caution using BCMA targeted Bispecifics in potential CAR-T candidates (antigen loss)
  - CAR T now approved as second line and is prioritized earlier in treatment

25

Follicular Lymphoma Treatment



Bispecifics
Target=CD20

Abbreviations: CAR T=chimeric antigen receptor CAR T-cell therapy; Axi-cel=Axicabtagene ciloleucel; Liso-cel=Lisocabtagene maraleucel; Tisa-cel=Tisagenlecleucel

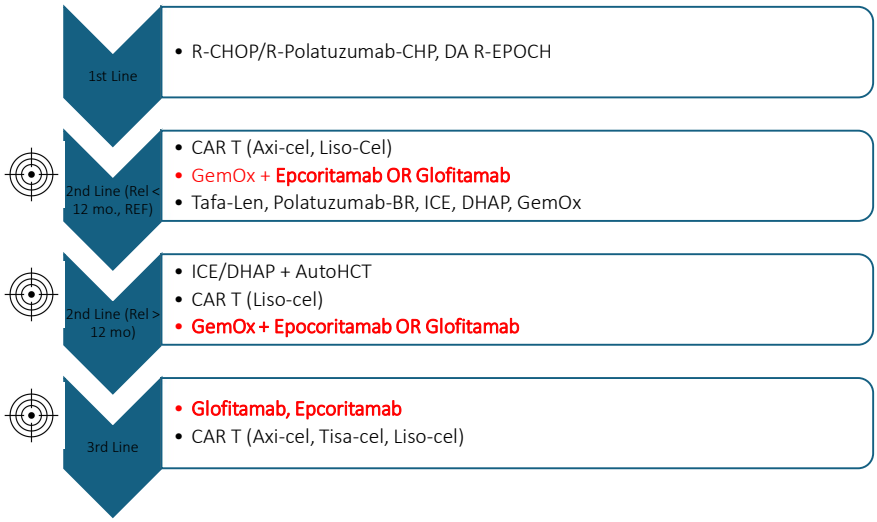
26

Bispecifics in FL

- FL bispecifics appear to have similar ORR and CR rates (~80% and 60%) in R/R setting, with durable remission
- Epcoritamab given until progression, whereas Mosunetuzumab given as fixed duration therapy 8-17 cycles
  - Potential for re-treatment with Mosunetuzumab upon progression
- CRS is common but almost all low-grade. Neurotox is uncommon.
- Hospitalization not required for Mosunetuzumab or Epcoritamab for FL
- Mosunetuzumab vs. CAR T – more neurotox with CAR-T. Overall similar response rates and durable remissions.

27

Diffuse Large B-cell Lymphoma Treatment



28

Bispecifics in DLBCL

- Glofitamab and Epcoritamab both received accelerated FDA approval in R/R DLBCL. Response rates ~50-60% with CR rates ~40%. Responses can be durable
- Epcoritamab given until disease progression; Glofitamab given as fixed duration for 12 cycles
- 24-hour hospitalization is recommended for 1st dose of glofitamab (day 8) and 1st full dose of epcoritamab (day 15)
- Bispecifics can be combined safely with chemotherapy (Gem-Ox) in salvage setting as second line, although data for CAR T in refractory or REL < 12 mo is strongest and thus preferred

29

Tarlatamab for Small Cell Lung Cancer

- Bispecific targeting DLL3 (~85% of SCLC overexpress DLL3)
- FDA accelerated approval for 2nd line in extensive stage SCLC (2024)
- Phase II DELPHI 301 study established 10 mg as maximally effective dose, given every 2 weeks
- IV infusion given over 1 hour
- Per NCCN, one of preferred treatments for chemo-free interval (CTFI) ≤6 months
  - Consider rechallenging with platinum-based doublet if CTFI >3-6 months

PJ2

Tarlatamab Dosing[2]

Dosing and Schedule

Tarlatamab:

- Step-Up: 1 mg C1D1, 10 mg C1D8, 10 mg C1D15
- Maintenance: 10 mg on day 1 & 15 of C2+
- Premeds: 1L NS over 4-5 hours after all doses in C1, DXM 8 mg IV prior to C1D1 and D8

Recommended Post Infusion Monitoring

- Administer 1st 2 step-up doses in AHCI outpatient infusion center and then admit to bedded outpatient status for 24 hours
- If well tolerated, further monitoring in outpatient setting
- C1D15 & C2: observe for 6-8 hr
- C3 & 4: observe for 3-4 hr
- C5 onwards: observe for at least 2 hr post infusion
- Recommend that patient remain within 1 hr of a healthcare facility

Tarlatamab tip sheet.pdf

30

Slide 30

PJ1 Our tip sheet says the following: Administer the first 2 step-up doses in AHCI Infusion, then admit to inpatient oncology unit under Bedded Outpatient status* for cytokine release syndrome (CRS) and neurotoxicity/ICANS monitoring. • C1D1 and C1D8: 22-24 hour observation from the start of the infusion • The manufacturer recommends a 22-24 hour observation period when resuming therapy after experiencing CRS or ICANS ≥ grade 2 Administer subsequent doses and monitor in an AHCI infusion center: • Cycle 1, day 15 and cycle 2: 6-8 hour post infusion observation • Cycles 3-4: 3-4 hour post infusion observation • Cycles 5+: 2 hour post infusion observation .

Dexamethasone 8 mg IV prior to C1D1 and C1D8 doses • 1 liter of NaCl 0.9% over 4-5 hours after all doses in cycle 1
Preedit, Justine, 2025-02-17T20:21:32.787

PJ2 It doesn't look like NCCN prefers tarlatamab over topotecan, lurbinectedin, or irinotecan - also can consider rechallenge of platinum doublet for CTFI 3-6 months
Preedit, Justine, 2025-02-17T20:23:02.808

FDA-Approved Agents for Relapsed ES-SCLC

Study	N	ORR, %	mDoR, Mo	mPFS, Mo	mOS, Mo	6-Mo Survival, %	IC Activity Reported
Topotecan[1]	101	21.7	7.6	2.8	5.4	-	Y
Lurbinectedin[2,3]	105[2]	35.2[2]	5.3[2,3]	3.5[2]	9.3[2]	67.1[2]	N
Tarlatamab (10 mg)[4,5]	100[5]	40[5]	9.7[5]	4.3[5]	15.2[5]	73.4[5]	Y (10/16)[6]

1. Ardizzoni. JCO. 1997;15:2090. 2. Trigo. Lancet Oncol. 2020;21:645. 3. Peters. Lung Cancer. 2024;188:107448. 4. Ahn. NEJM. 2023;389:2063. 5. Sand. WCLC 2024. Abstr OA10.03. 6. Dowlati. JCO.

31