Bispecifics in Community Oncology

Cornerstone National Conference

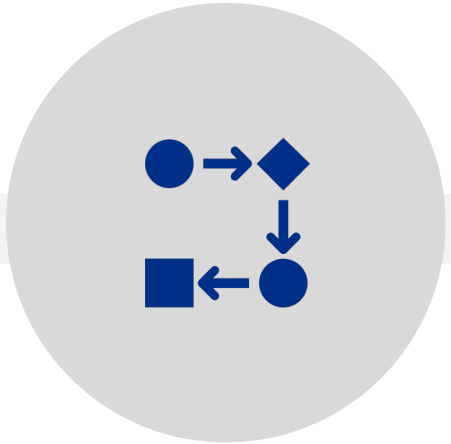
Las Vegas, NV

April 13, 2024

Why are we doing this?

BISPECIFICS REPRESENT A NEW MILESTONE IN THE TREATMENT OF PATIENTS

BUT INTEGRATION INTO COMMUNITY ONCOLOGY PRESENTS CHALLENGES



ALIGNING ON ACTIONABLE STEPS TO MAKE THIS A VIABLE OPTION LEADS TO VALUE FOR PRACTICES

AND ULTIMATELY IMPROVES TREATMENT AND MANAGEMENT OF PATIENTS FOR BETTER PATIENT OUTCOMES

Network identified this as a need....let's dig in!

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Non-sponsored discussion among our Network Members

Bispecifics in Community Oncology

Cornerstone Spring Summit

Las Vegas, NV
April 13, 2024

Pankit Vachhani, MD
Associate Professor of Medicine
University of Alabama at Birmingham

Amitkumar Mehta, MD
Director of Lymphoma Program
University of Alabama at Birmingham

Stephan Rosenfeld, MD
Highlands Oncology Group

Shruti Singh, MD
Northwest Cancer Centers

Ed Licitra, MD, PhD
Astera Cancer Care

Panel Discussion on Bispecifics

In Community Oncology, what are the top challenges?

1. ***Complexity and novelty***
2. ***Limited clinical experience***
3. *Treatment-related toxicities*
4. *Transition from in-patient to out-patient setting*

What are ways to best integrate bispecifics into community practice?

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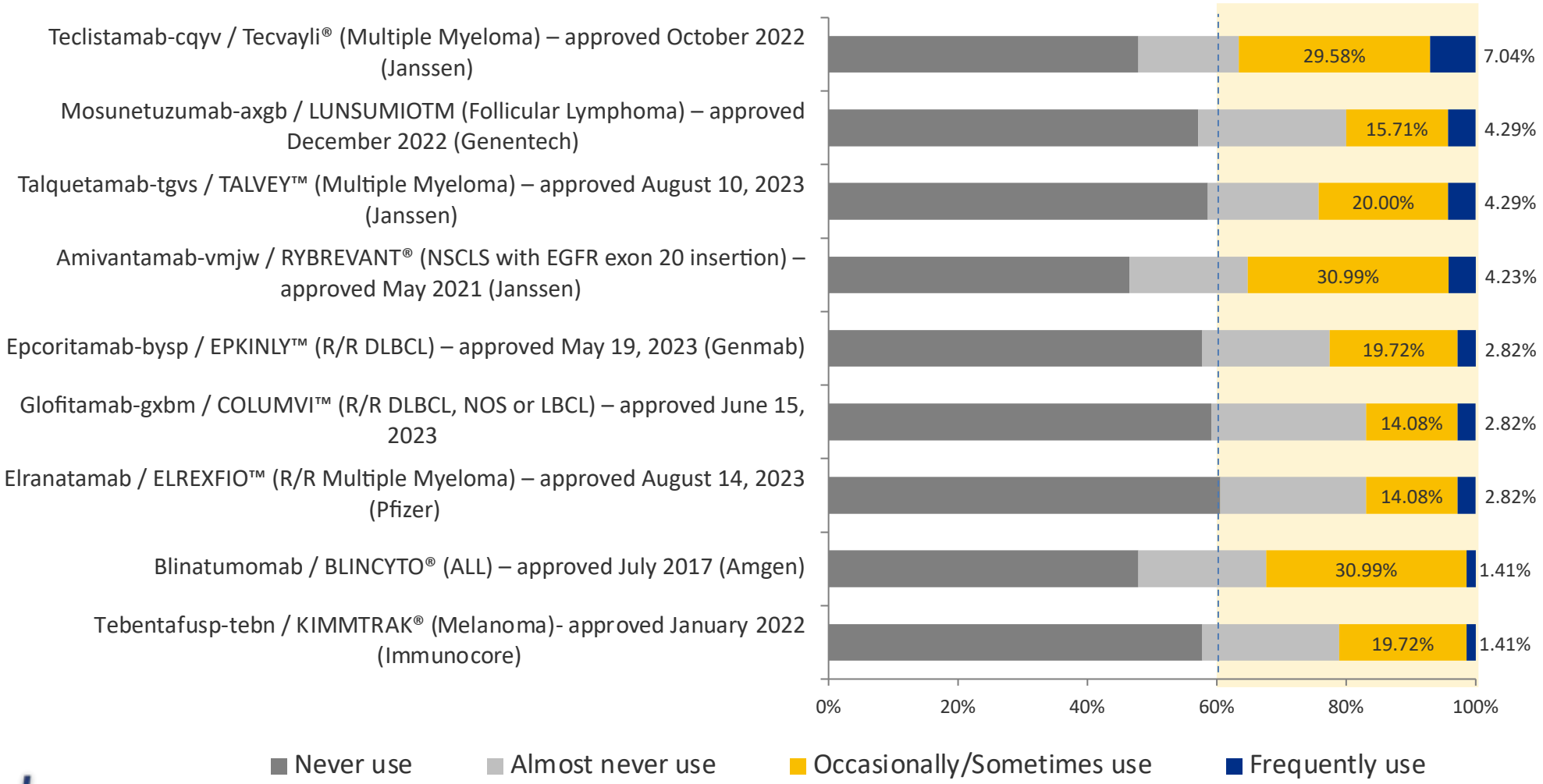
February 2024 Survey

Please indicate your utilization of the following FDA approved bispecific antibodies to date:



Answered: 71

Bispecific (BsAbs) Antibodies and CAR T-Cell Therapy

Efficacy and safety

- **CAR T**: long-term survival data and duration of therapy
- **Bispecifics**: lower toxicity

Accessibility

- **CAR T**: administered at a specialized center
- **Bispecifics**: off the shelf availability and easier access

Cost

- **CAR T**: higher upfront cost
- **Bispecifics**: overall, comparable in cost

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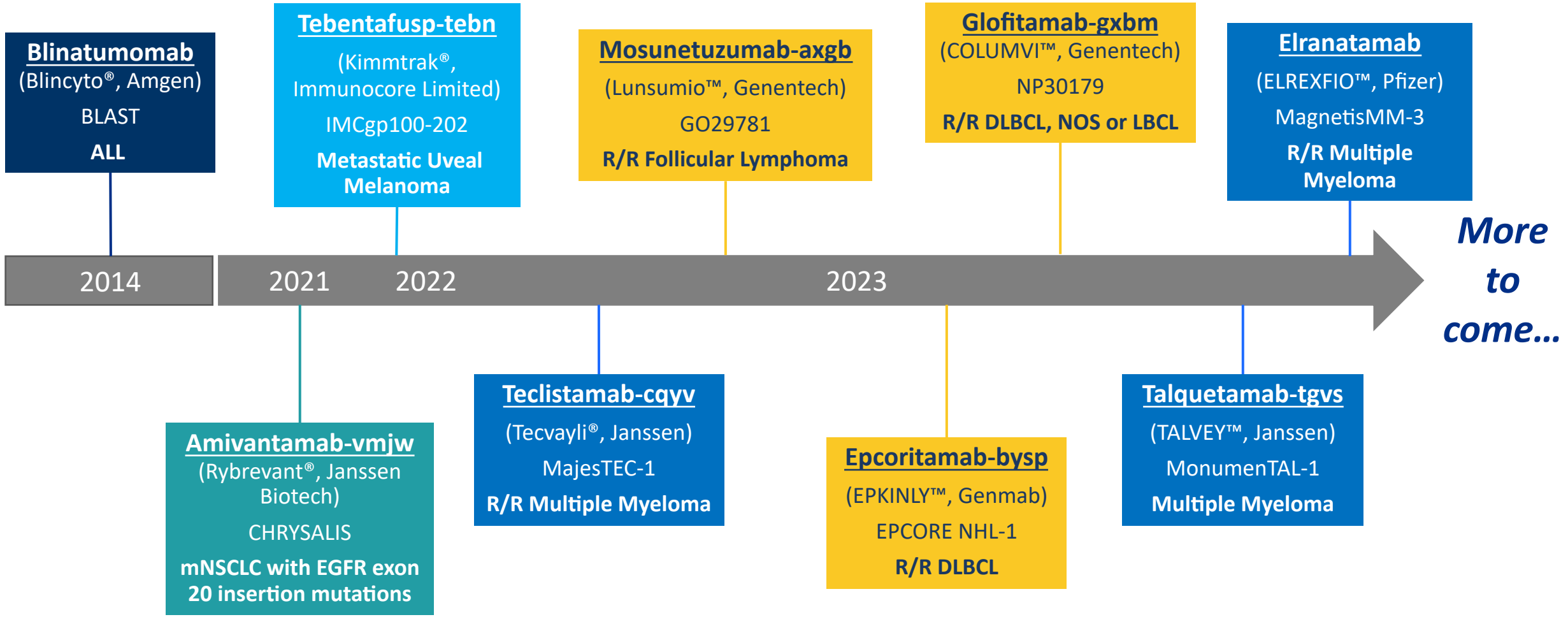
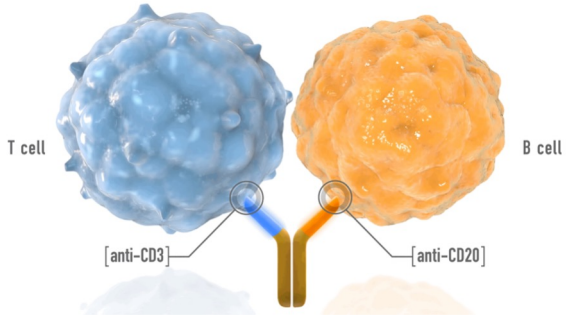
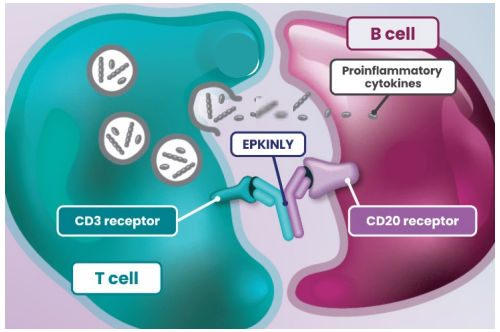
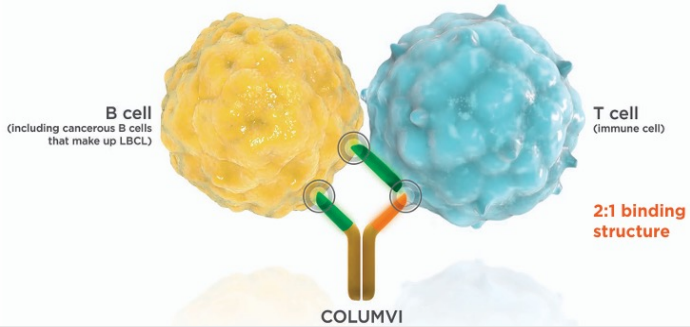
Bispecifics: Developmental Timeline in Oncology



Bispecifics in Lymphoma

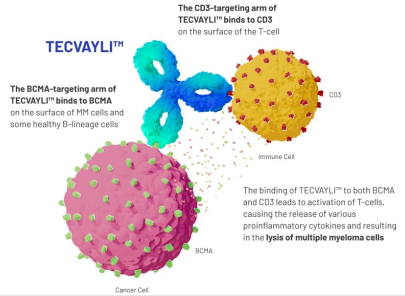
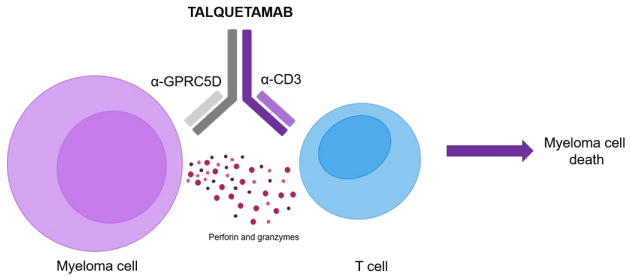
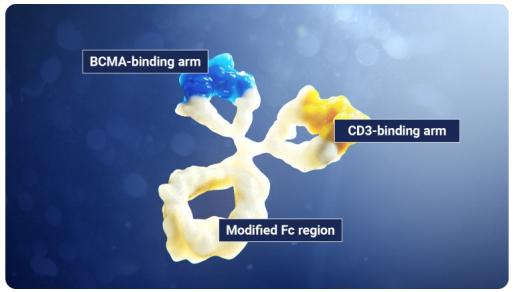
Drug	LUNSUMIO™ (mosunetuzumab-axgb)	EPKINLY™ (epcoritamab-bysp)	COLUMVI™ (glofitamab-gxbm)
FDA approval	LUNSUMIO is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with **relapsed or refractory follicular lymphoma** after two or more lines of systemic therapy.	EPKINLY is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with **relapsed or refractory diffuse large B-cell lymphoma (DLBCL)**, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy	COLUMVI is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with **relapsed or refractory diffuse large B-cell lymphoma**, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.
Structure			
Route of administration	IV	SC	IV
Dosing Schedule	Cycle 1: Day 1 – 1 mg Cycle 1: Day 8 – 2 mg Cycle 1: Day 15 – 60 mg 21-Day Treatment Cycles Administer over a minimum of 4 hours. Cycle 2: Day 1 – 60 mg Cycle 3+: Day 1 – 30 mg Administer over 2 hours if infusions from Cycle 1 were well-tolerated.	Cycle 1: Day 1 – 0.16 mg Cycle 1: Day 8 – 0.8 mg Cycle 1: Day 15 – 48 mg Cycle 1: Day 22 – 48 mg Cycles 2 & 3: Day 1,8,15, 22 – 48 mg Cycles 4 – 9: Day 1 & 15 – 48 mg Cycle 10+: Day 1 – 48 mg 28-Day Treatment Cycles	Cycle 1: Day 1 - Pretreat with a single 1,000 mg dose of obinutuzumab IV Cycle 1: Day 8 – 2.5 mg Cycle 1: Day 15 – 10 mg Cycle 2 -12: Day 1 – 30 mg 21-Day Treatment Cycles

LUNSUMIO™ (mosunetuzumab-axgb) for third-line or later follicular lymphoma | HCP (lunsumio-hcp.com)

EPKINLY™ for 3L+ Large B-cell Lymphoma - Official HCP Site (epkinlyhcp.com)

COLUMVI™ (glofitamab-gxbm) for third-line or later DLBCL | HCP (columvi-hcp.com)

Bispecifics in Myeloma

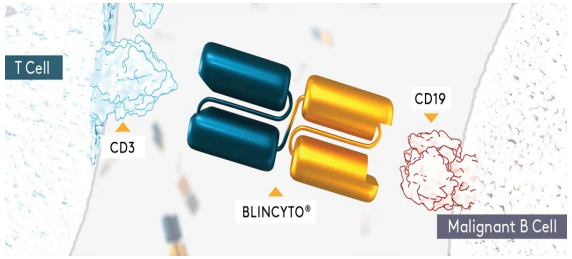
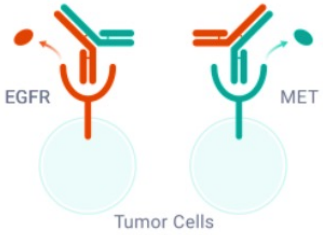
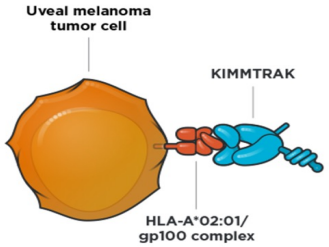
Drug	TECVAYLI® (teclistamab-cqyv)	TALVEY™ (talquetamab-tgvs)	ELREXFIO™ (elranatamab)
FDA approval	TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with **relapsed or refractory multiple myeloma** who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.	TALVEY is a bispecific GPRC5D-directed CD3 T-cell engager indicated for the treatment of adult patients **with relapsed or refractory multiple myeloma** who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.	ELREXFIO is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with **relapsed or refractory multiple myeloma** who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Structure			
Route of administration	SC	SC	SC
Dosing Schedule	Day 1 – 0.06 mg/kg Day 4 – 0.3 mg/kg Day 7 – 1.5 mg/kg Step up dosing schedule	Day 1 – 0.01 mg/kg Day 4 – 0.06 mg/kg Day 7 – 0.4 mg/kg Step up dosing schedule	Day 1 – 12 mg Day 4 – 32 mg Day 8 – 76 mg Step up dosing schedule
	One week after first treatment dose and weekly thereafter: 1.5 mg/kg once weekly	One week after first treatment dose and weekly thereafter: 0.4 mg/kg once weekly	One week after first treatment dose and weekly thereafter through week 24: 76 mg
	The dosing frequency may be decreased to 1.5 mg/kg every two weeks with CR or better for at least 6 months		Week 25 and every 2 weeks thereafter: responders only: 76 mg

[Official HCP Website | TECVAYLI™ (teclistamab-cqyv) HCP (tecvaylihcp.com)]

[Official HCP Website | TALVEY® (talquetamab-tgvs) HCP (talveyhcp.com)]

[ELREXFIO (pfizerpro.com)]

Bispecifics in Leukemia, NSCLC, and Uveal Melanoma

Drug	Blincyto® (Blinatumomab)	Rybrevant® (amivantamab-vmjw)	Kimmtrak® (tebentafusp-tebn)
FDA approval	BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adult and pediatric patients with: CD19-positive B-cell precursor **acute lymphoblastic leukemia (ALL)** in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% and **relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL)**	RYBREVANT is a bispecific EGF receptor-directed and MET receptor-directed antibody indicated: • <u>in combination with carboplatin and pemetrexed</u> for the first-line treatment of adult patients with **locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations**, as detected by an FDA-approved test or • as a **<u>single agent</u>** for the treatment of adult patients with **locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations**, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.	KIMMTRAK is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with **unresectable or metastatic uveal melanoma**
Structure			
Route of administration	IV	IV	IV
Dosing Schedule	**<u>Induction</u>** Cycle 1: Days 1 – 28 28 mcg/day if >45 kg Cycle 1: Days 1 – 28 15 mcg/day if <45 kg Days 29 – 42: 14-day treatment free interval **<u>Consolidation</u>** Cycles 2-4: Day 1 – 28 28 mcg/day if >45 kg Cycle 1: Days 1 – 28 15 mcg/day if <45 kg Days 29 – 42: 14-day treatment free interval	**<u>As a single agent</u>** If < 80 kg: 1050 mg Weeks 1-5 Week 7 onwards If ≥ 80 kg: 1400 mg Weeks 1-5 Week 7 onwards **<u>In combination with carboplatin and pemetrexed</u>** If < 80 kg Weeks 1 -4: 1400 mg Week 7 onwards: 1750 mg If ≥ 80 kg Weeks 1 – 4: 1750 mg Week 7 onwards: 2100 mg	Day 1: 20 mcg Day 8: 30 mcg Day 15: 68 mcg Once every week thereafter: 68 mcg

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[CD19-Positive B-Cell Precursor ALL Therapy | BLINCYTO® (blinatumomab) (blincytohcp.com)]

[RYBREVANT® (amivantamab-vmjw) HCP (rybrevanthcp.com)]

[KIMMTRAK HCP - Dosing, Admin, & Patient Support Information]

Panel Discussion on Bispecifics

In Community Oncology, what are the top challenges?

1. *Complexity and novelty*
2. *Limited clinical experience*
3. ***Treatment-related toxicities***
4. *Transition from in-patient to out-patient setting*

What are ways to best integrate bispecifics into community practice?

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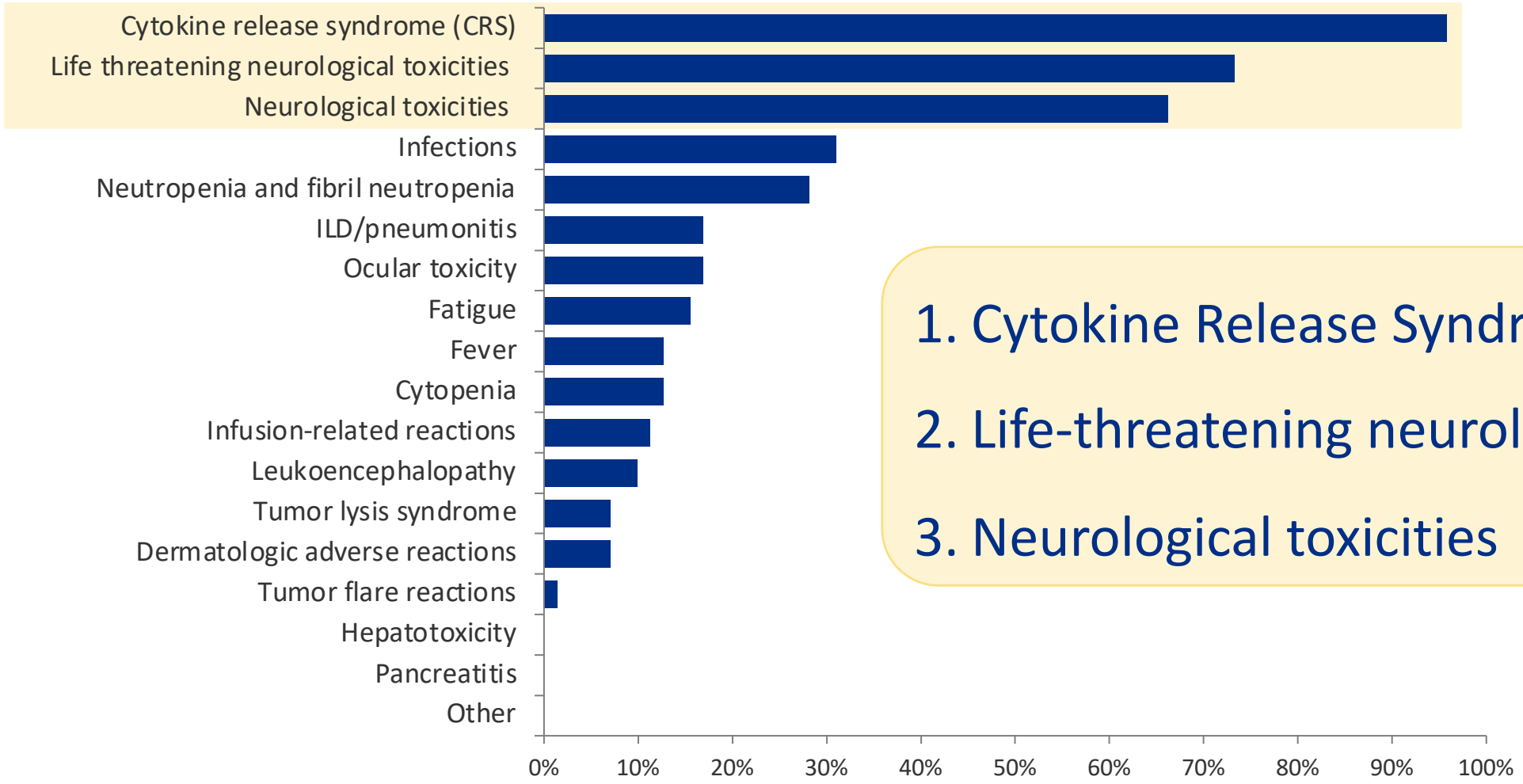
February 2024 Survey

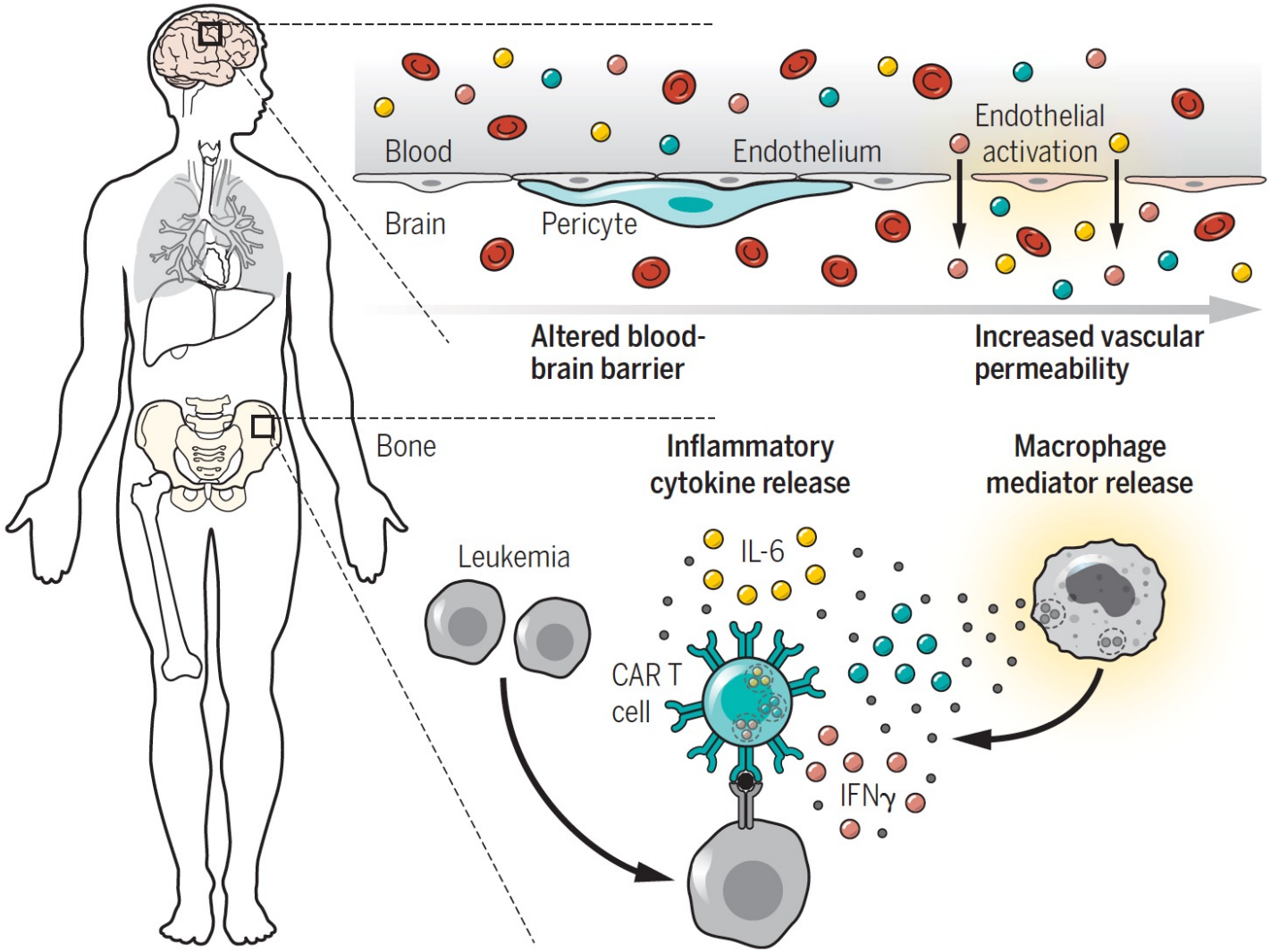
What are the greatest safety concerns when considering bispecific antibodies?



1. Cytokine Release Syndrome (CRS)
2. Life-threatening neurological toxicities
3. Neurological toxicities

Answered: 71

Treatment associated cytokine release syndrome and neurotoxicity



Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

June et al., Science. 2018 Mar 23;359(6382):1361-1365.

Grading Schemes of CRS:

CTCAE
Lee criteria
Penn criteria
MSKCC criteria
CARTOX criteria

Difficult to compare CRS across studies

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 4.03 [11]	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate)	Life-threatening consequences; pressor or ventilatory support indicated
CTCAE version 5.0 [13]	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention needed
Lee criteria [14]	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to i.v. fluids or low dose of one vasopressor OR • Grade 2 organ toxicity*	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity* or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity* (excluding transaminitis)
Penn criteria [17]	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for i.v. therapies (not including fluid resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
MSKCC criteria [16]	Mild symptoms requiring observation or supportive care only (eg, antipyretics, antiemetics, pain medication)	Hypotension requiring any vasopressors <24 h Hypoxia or dyspnea requiring supplemental oxygen <40%	Hypotension requiring any vasopressors ≥24 h Hypoxia or dyspnea requiring supplemental oxygen ≥40%	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation
CARTOX criteria [12]	Temperature ≥38°C Grade 1 organ toxicity†	Hypotension responds to i.v. fluids or low-dose vasopressor Hypoxia requiring FiO_2 <40% Grade 2 organ toxicity†	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥40% Grade 3 organ toxicity† or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity† except grade 4 transaminitis

Reviewed by D.W.Lee et al./BiolBloodMarrowTransplant25(2019)625 638

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Grading of CRS: CTCAE

Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.

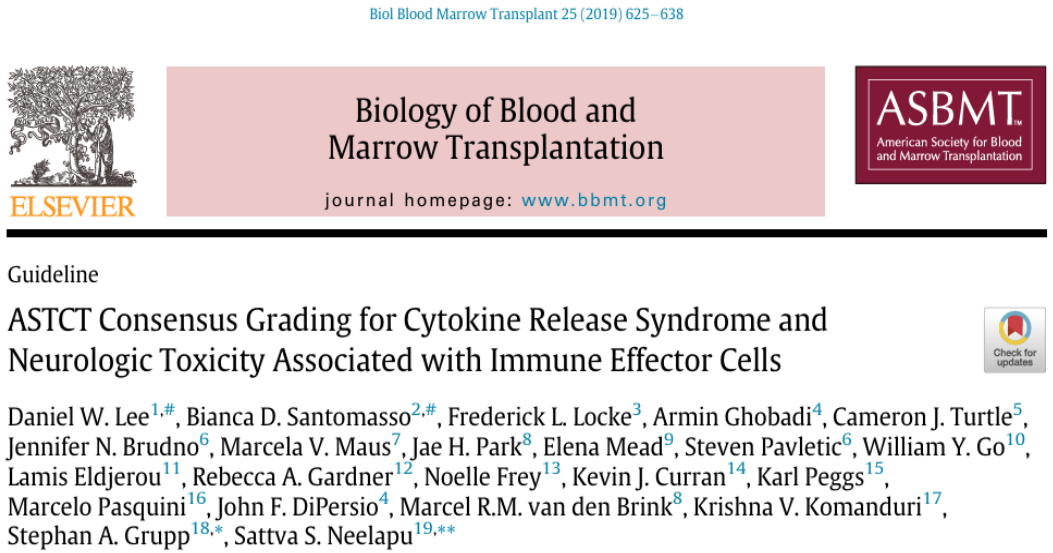
Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache

CTCAE Term	Grade 1	Grade2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death

Common Terminology Criteria for Adverse Events (CTCAE)
Version 5.0 Published: November 27, 2017

"In an effort to harmonize the definitions and grading systems for CRS and neurotoxicity, experts from all aspects of the field met on June 20 and 21, 2018, at a meeting supported by the American Society for Transplantation and Cellular Therapy (ASTCT; formerly American Society for Blood and Marrow Transplantation, ASBMT) in Arlington, VA".

ASTCT Consensus Grading for CRS



Biol Blood Marrow Transplant 25 (2019) 625–638

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Definition of CRS

- *"a 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. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."*

D.W.Lee et al./BiolBloodMarrowTransplant 25 (2019): 625-638

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
			With	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or	
Hypoxia	None	Requiring low-flow nasal cannulaz or blow-by	Requiring high-flow nasal can nulaz, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Premedication reduces CRS rates

Steroids

Tocilizumab

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

D.W.Lee et al./BiolBloodMarrowTransplant 25 (2019): 625-638

Incidence of CRS with teclistamab in MajecTEC-1 over time by grade

EXAMPLE:

Overall incidence of CRS with teclistamab in MajesTEC-1

- CRS occurred in 72.1% of patients (N=119/165) with the majority being:
  - **Grade 1 (50.3%)**
  - Grade 2 (21.2%)

- Most CRS occurred after:
  - Step-up dose 1 – 43.6%
  - Step-up dose 2 – 35.2%
  - Cycle 1 Day 1 - 24.2%
  - Cycle 1 Day 8 – 4.8%
  - Cycle 1 Day 15 – 2.4%
  - Cycle 2+ - 3.6%

- Only 1 percent of patients experienced CRS in subsequent cycles

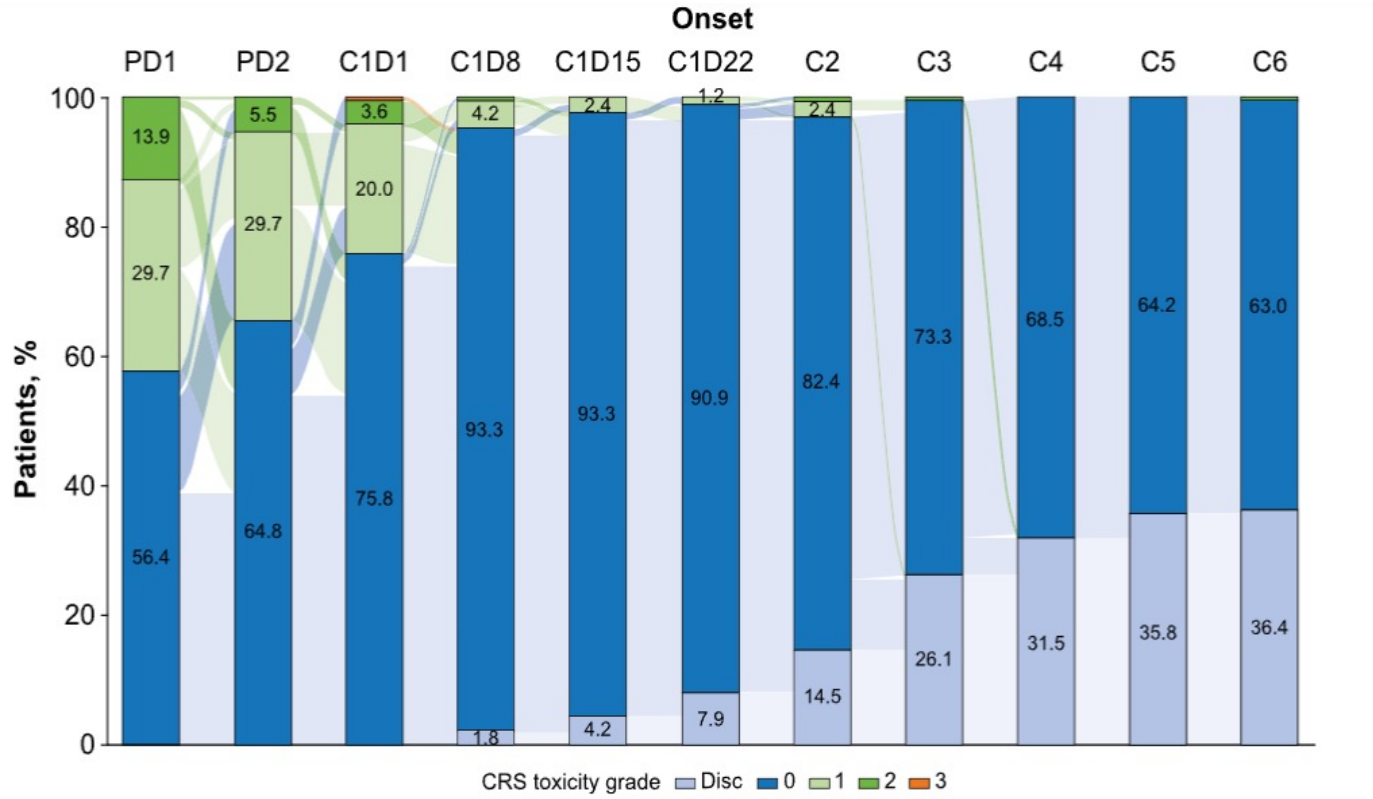


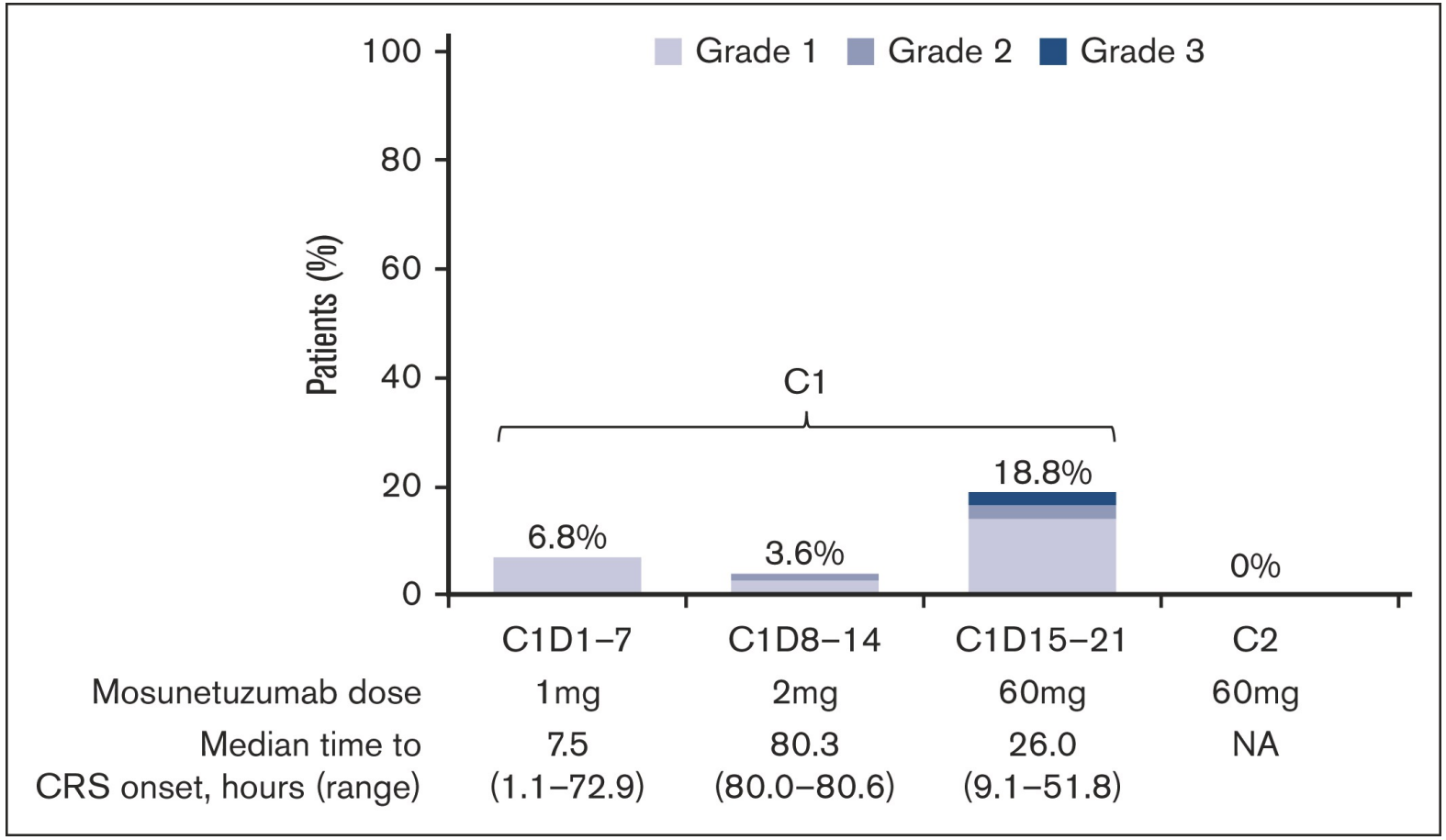
FIGURE 1 Incidence of CRS with teclistamab in MajesTEC-1 over time by grade. CRS was graded according to American Society for Transplantation and Cellular Therapy criteria.[6] If a patient had more than one event at a time point, the maximum grade is used. Repeat step-up before C1 is not displayed. One patient had a grade 1 CRS event after a repeat step-up dose before C1. No patients discontinued the study due to a CRS event. C indicates cycle; CRS, cytokine release syndrome; D, day; Disc, discontinued; PD, priming (step-up) dose.

Cancer. 2023;129:2035–2046.

Patients (%) with CRS events by cycle and grade

EXAMPLE:

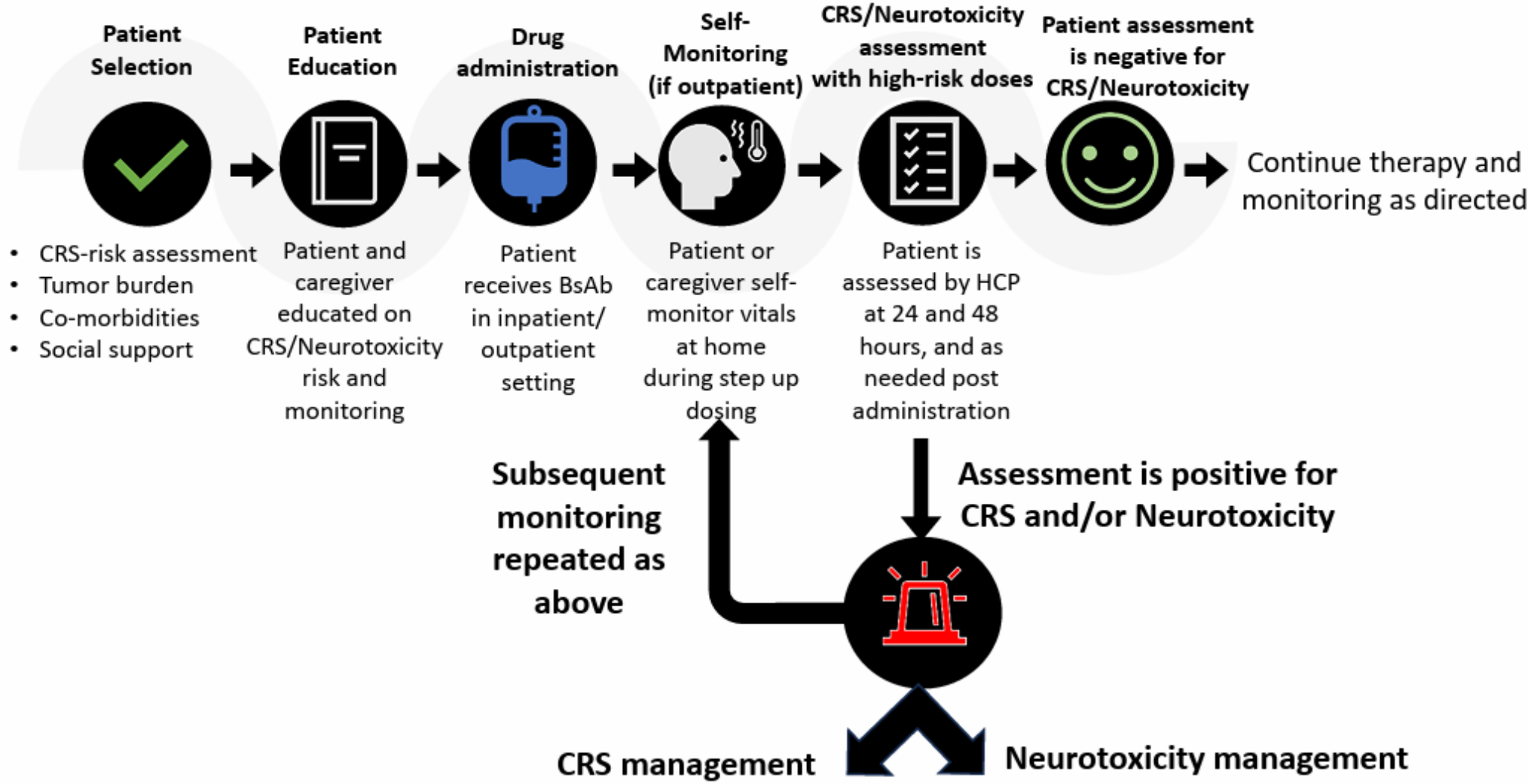
Mosunetuzumab monotherapy is active and tolerable in patients with relapsed/refractory diffuse large B-cell lymphoma



C, cycle; D, day; NA, not available.

Blood Adv (2023) 7 (17): 4926–4935

Bispecific Antibody (BsAb) Management in B-Cell Lymphomas



Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy
Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

Proposed management of CRS in patients with Bispecific antibody

Definition: CRS is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction

Symptoms: Fever (required) with possible hypoxia, hypotension, tachypnea, nausea, headache, fatigue, myalgias or malaise

Work up and evaluation:

- Pertinent history and physical exam including vital sign evaluation and evaluation of respiratory symptoms.
- Review medications including BsAb received, last dose of anti-pyretic therapy, steroids, or anti-cytokine administration.
- Assess for concurrent symptoms of neurotoxicity.
- Assess for alternate diagnosis including infection (including neutropenic fever), venous thromboembolism, respiratory infection (including COVID-19, influenza), volume overload or dehydration, exacerbation of underlying cardio-pulmonary condition. Treat as appropriate.
- For duration of symptoms over 1 week, consider excluding HLH/MAS[12]

Monitoring: Consider monitoring patient for 1-2 hours post infusion if outpatient administration of BsAb on day of step-up dosing

Next dose: Follow prescribing label

Grade and definition	Management
Grade 1: Fever[#] ≥100.4 F +/- constitutional symptoms requiring symptomatic treatment, no hypotension or hypoxia	Home: - A/P 650-1000 mg PO, can repeat if recurrent fever ≥ 6-8h later if clinically stable - Recommend aggressive oral hydration - Continue to check temperature every 1-2 hours and other vitals if able. Patients should recontact the clinic urgently or present to ED if BP goes less than < 10 mm Hg below baseline AND < 90 mm Hg systolic, new orthostatic symptoms, weakness, confusion, dizziness, or new hypoxia (<90%). Home versus outpatient/ED evaluation: - If refractory or recurrent fever (< 6-8h) consider dexamethasone 10 mg once. Home management may be appropriate if vital signs remain stable and no other concerning symptoms. Otherwise, patients should be evaluated in a healthcare facility. - Consider earlier administration of steroids and immediate in-person evaluation for patients with multiple disease risk factors or comorbidities (See text). - Consider daily dexamethasone with persistent symptoms.

Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy
Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

Proposed management of CRS in patients with Bispecific antibody

	Additional management: - Consider anti-cytokine therapy (e.g., tocilizumab) in cases of protracted fever (e.g. >48 hours despite corticosteroids). - Early tocilizumab after trial of dexamethasone should be considered in patients with multiple medical risk factors (e.g. comorbidities).
Grade 2: Fever ≥100.4 F with either hypotension not requiring pressors and/or hypoxia managed with low flow nasal canula or blow-by.	- All patients should be urgently evaluated in-person. Recommend inpatient management for most cases of Grade 2 CRS unless qualified outpatient day hospital/infusion center and no hypoxia. - If after hours without access to appropriate outpatient treatment area or if clinical scenario dictates, recommend ED evaluation. - A/P 650-1000 mg as need, up to 3-4 times daily. - Dexamethasone 10 mg every 12 hours. - Administer intravenous fluids/supplemental oxygen as appropriate. - Administer tocilizumab* if symptoms persist despite IV fluids and dexamethasone (approximately 4-6 hours after dosing) or if clinically unstable. Consider alternative agent (e.g. anakinra or siltuximab) if persistent symptoms despite maximal dosing
Grade 3: Fever ≥100.4 F with either hypotension (BP less than 90/60 or < 10 mmHg below not responsive to fluids and/or hypoxia requiring high-flow nasal canula, face mask or venturi mask	- Emergent inpatient admission (floor or ICU) for hemodynamic monitoring, IV fluids, oxygen therapy and vasopressors. - A/P 1000 mg IV as needed up to 3-4 times daily when safe. - Dexamethasone (e.g. 10 mg IV Q 6 hours), until resolution to grade ≤ 1, followed by dexamethasone taper. - Evaluate for sepsis and consider empiric antibiotics. - Administer tocilizumab* and consider alternative agent (e.g. anakinra or siltuximab) if persistent grade 3 CRS despite maximal dosing. - If refractory hypotension/hypoxia admit to ICU.
Grade 4: Fever ≥100.4 F with any of the following: Life threatening consequences, urgent intervention required; requiring multiple pressors and/or positive pressure respiratory support or mechanical intubation.	- Inpatient admission to ICU for hemodynamic monitoring, IV fluids, oxygen therapy and vasopressors. - A/P 1000 mg IV as needed up to 3-4 times daily when safe. - Dexamethasone (e.g. 20 mg IV Q 6 hours), until resolution to grade ≤ 1, followed by dexamethasone taper. - Administer tocilizumab and if repeated doses of tocilizumab have been utilized, consider alternative agent (e.g. anakinra or siltuximab) if persistent grade 4 CRS despite maximal dosing of first agent.

Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy
Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

NCCN Guidelines: Management of Immunotherapy-Related Toxicities
Version 1.2024 — December 7, 2023

The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities includes a section on CRS for patients treated with CAR T-cell therapy but does not include a section on CRS for patients treated with bispecific antibodies

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Management of CAR T-Cell-Related Toxicities

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CYTOKINE RELEASE SYNDROME (CRS)[g,h]

- Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression. Empiric treatment for infection is warranted in the patient with neutropenia. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.[i]
- Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension or hypoxia.

CRS Grade	Anti-IL-6 Therapy	Steroids[o,p,q]	Additional Supportive Care
Grade 1 Fever (≥38°C)	For prolonged CRS (>3 days)[l] in patients or those with significant symptoms, comorbidities, and/or are >65 years, consider 1 dose of IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg)[m,f,n]	For idecabtagene and lisocabtagene, consider IV dexamethasone 10 mg every 24 hours for early-onset CRS (<72 hours after infusion)[r]	• Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic[v] • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[j] requiring low-flow nasal cannula[k] or blow-by	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose).[n,o] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total[f]	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Consider IV dexamethasone 10 mg every 12–24 hours depending on product[a,r,s]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, ECG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours after starting anti–IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[k] face mask, nonrebreather mask, or Venturi mask	Anti-IL-6 therapy as per Grade 2[o] if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6–12 hours depending on the product.[a,r] If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/ or hypoxia requiring positive pressure (eg, continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, mechanical ventilation)	Anti-IL-6 therapy as per Grade 2[o] if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6 hours.[r] If refractory, consider 3 doses of IV methylprednisolone 1–2 g/day depending on the product.[a] If refractory, consider dosing every 12 hours.[t] Other lines of therapy may be considered[u]	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Footnotes on CART-5A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Discussion

Key points for CRS

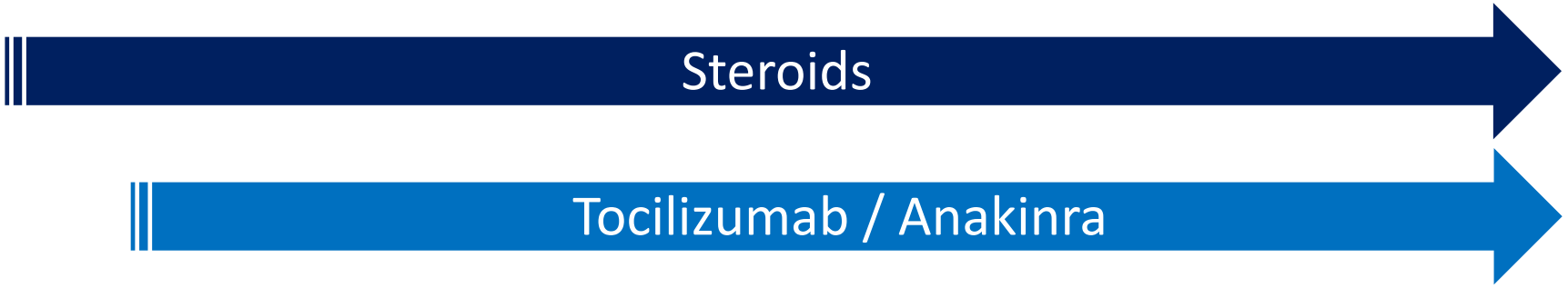
BsAbs have a relatively short half-life (compared to CAR T-cell therapy) and need to be administered repeatedly, therefore CRS symptoms tend to resolve relatively quickly by interrupting therapy and providing supportive care

- *Educate staff and develop toxicity management protocols*
- *Ensure tocilizumab is available*
- *Ensure emergency department staff and hospitalists are aware that an on-call physician is available to help manage any patient who may present with CRS*
- *Remind patients and their caregivers about signs and symptoms of CRS*

ASTCT ICANS Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or gen eralized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerbrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event



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Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy
Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

ICANS: Definition and ICE Scoring points

Definition: Neurological AE after BsAb therapy most frequently consist of headache and dizziness. Occasionally ICANS-like symptoms occur. These may or may not accompany CRS.

Symptoms: Delirium, dysgraphia, tremor, lethargy, difficulty concentrating, agitation, confusion, expressive aphasia, apraxia, depressed level of consciousness, encephalopathy, seizures

Recommendations: Patients and caregivers need to be educated on symptoms and that patients cannot operate drive or operate heavy machinery if symptomatic

Work up and evaluation:

- Pertinent history and PE
- Review medications including last dose of anti-pyretic therapy, steroids, or anti-cytokine therapy.
- Perform ICE score on all patients with neurologic symptoms.
- Assess for alternate cause of symptoms. Consider performing CT head, EEG, MRI, or LP as appropriate.
- Assess for concurrent symptoms of CRS (fever, hypoxia, hypotension). Treatment of CRS can occur concurrently if appropriate.
- If any concern for neurological AEs exists patient should be evaluated in outpatient center or ED. If any worsening symptoms (e.g. somnolence, worsening confusion, weakness, etc.), patients should be promptly referred to the ED.

ICE scoring system	
Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backwards from 100 by 10	1 point

Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

Proposed Management of ICANS

Grade	Management
Grade 1: ICE 7-9 or depressed level of consciousness but awakens spontaneously.	- Pending clinical scenario and social situation, can consider observation or close monitoring in outpatient setting. Can consider dexamethasone 10 mg x 1.
Grade 2: ICE 3-6 or depressed level of consciousness but awakens to voice.	- Admit patient to hospital for monitoring. - Dexamethasone 10mg IV Q 12 hours, followed by taper once grade 1 or better.
Grade 3: ICE 0 to 2 or depressed level of consciousness but awakens to tactile stimulus or any clinical seizure that resolves rapidly or focal/local edema on neuroimaging.	- Monitor in ICU setting. - Neurology consult. - Dexamethasone 10 mg IV Q 6 hours, followed by taper once grade 1or better. - Use antiepileptics for seizure management as needed. - Consider adding anakinra 100 mg every 12 hours if symptoms persist beyond 24 hours, continue until resolution.
Grade 4: ICE is 0 or patient is unarousable or requires vigorous or repetitive tactile stimuli or life-threatening prolonged seizure (greater than 5 minutes) or repetitive seizures without return to baseline or deep focal motor weakness or diffuse cerebral edema on neuroimaging.	- Monitor in ICU setting. - Neurology consult. - Dexamethasone 10 mg IV Q 6 hours, followed by taper once grade 1or better. - Use antiepileptics for seizure management as needed. - Consider adding anakinra 100 mg every 12 hours if symptoms persist beyond 24 hours, continue until resolution.

Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities includes a section on neurotoxicity for patients treated with CAR T-cell therapy but does not include a section on neurotoxicity for patients treated with bispecific antibodies

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Management of CAR T-Cell-Related Toxicities

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CAR T-CELL–RELATED NEUROTOXICITY GRADING

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool[h]

- **Orientation: orientation to year, month, city, hospital: 4 points**
- **Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points**
- **Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point**
- **Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point**
- **Attention: ability to count backwards from 100 by 10: 1 point**

ICE Scoring

- **7-9, grade 1**
- **3-6, grade 2**
- **0-2, grade 3**
- **0 due to patient unarousable and unable to perform ICE assessment, grade 4**

ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults[h]

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

Neurotoxicity Domain[w]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[x]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[y]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[z]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

[h] With permission from Elsevier: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-638. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

[w] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[x] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[y] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[z] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment (CART-7)

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Discussion

Key points for ICANS

ICANS can manifest with a range of effects, from mild symptoms like headaches to more severe conditions such as confusion, unconsciousness, and seizures

- *Early intervention is critical to be able to give the next dose*
- *Collaboration of neurologist and neuroradiologist is important*
- *Increase the dose (dexamethasone, anakinra) if not responding*
- *Avoid concurrent medications that might cause cognitive changes*

Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event.

- The purpose of the **TECVAYLI and TALVEY REMS** is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), by:
  - Ensuring prescribers are aware of the importance of monitoring for the signs and symptoms of CRS and neurologic toxicity, including ICANS, in patients exposed to TECVAYLI or TALVEY

- The goal of the **ELREXFIO REMS** is to mitigate the risks of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by ensuring prescribers are aware of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to ELREXFIO.

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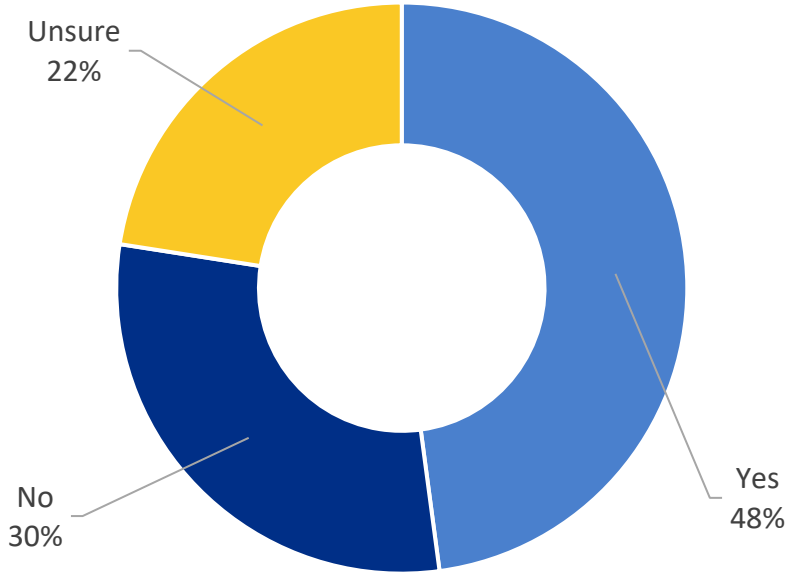
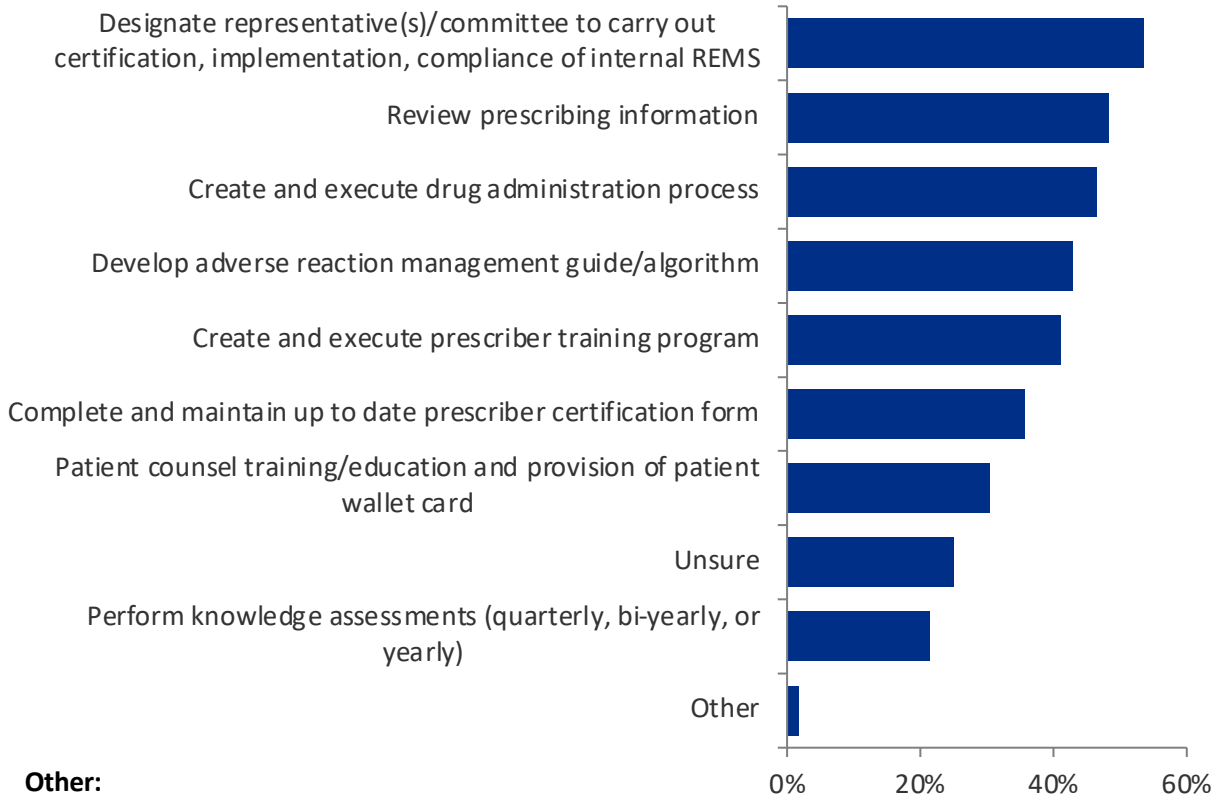
February 2024 Survey

Have you or your practice initiated a Risk Evaluation and Mitigations Strategy (REMS) program into your practice for the management of patients receiving any other bispecific antibodies without an FDA required REMS?



Answered: 71

Please indicate the steps involved in your REMS program (check all that apply)

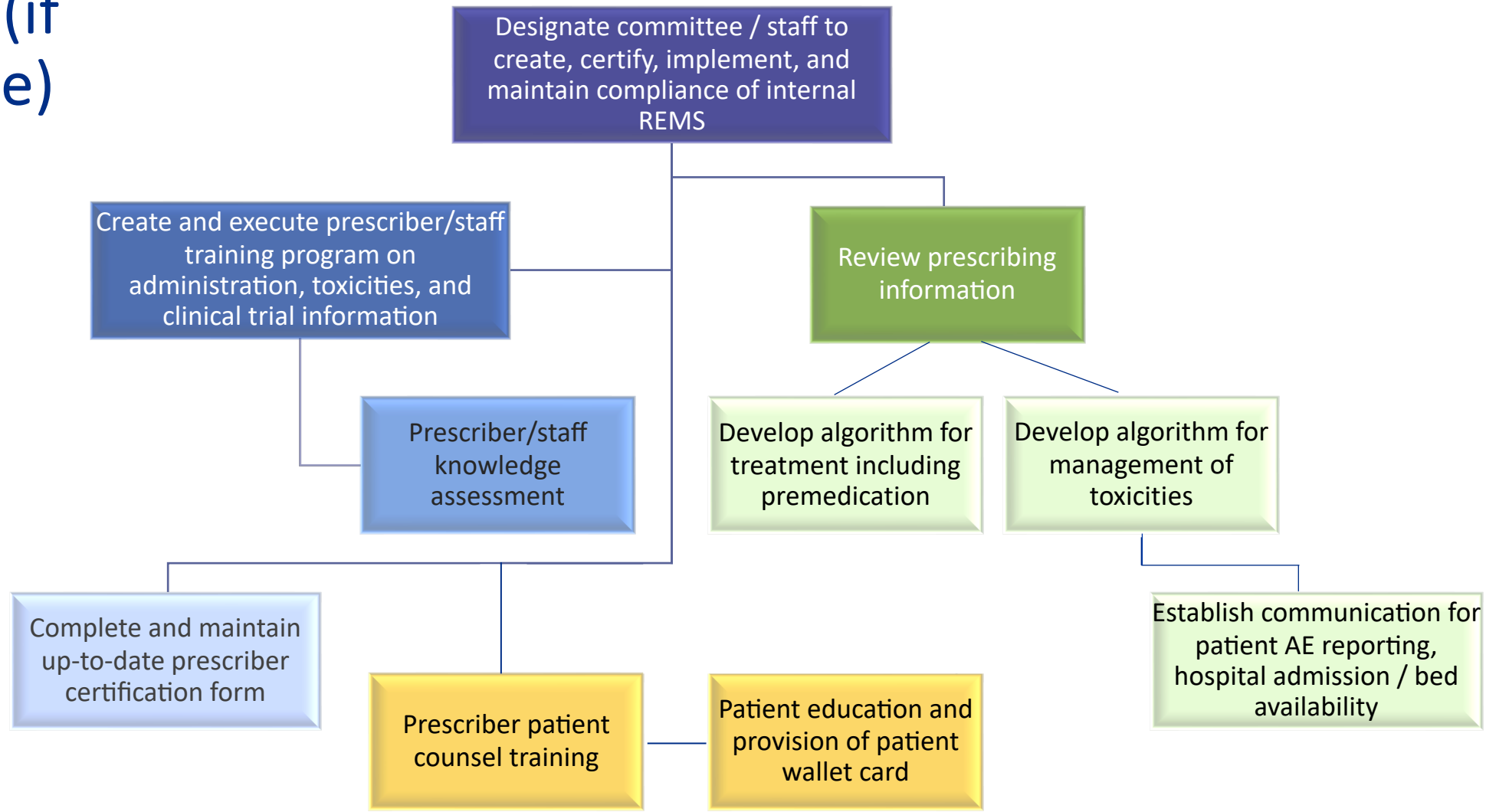


Other:

- *NA*

Answered: 34

Review the FDA required REMS program (if applicable)



Discussion

Key points for REMS

REMS programs focus on preventing, monitoring, and/or managing a specific serious risk(s) associated with certain drugs by informing, educating, and/or reinforcing actions to reduce the frequency and/or severity of a particular adverse event(s)

- *Unique adverse events*
- *Educate staff: prescriber, pharmacist, nurse*
- *Educate patients: inform, educate, and reinforce*
- *Close monitoring during critical phases*
- *Review and revise - Elements to Assure Safe Use (ETASU) for medication safety*

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Panel Discussion on Bispecifics

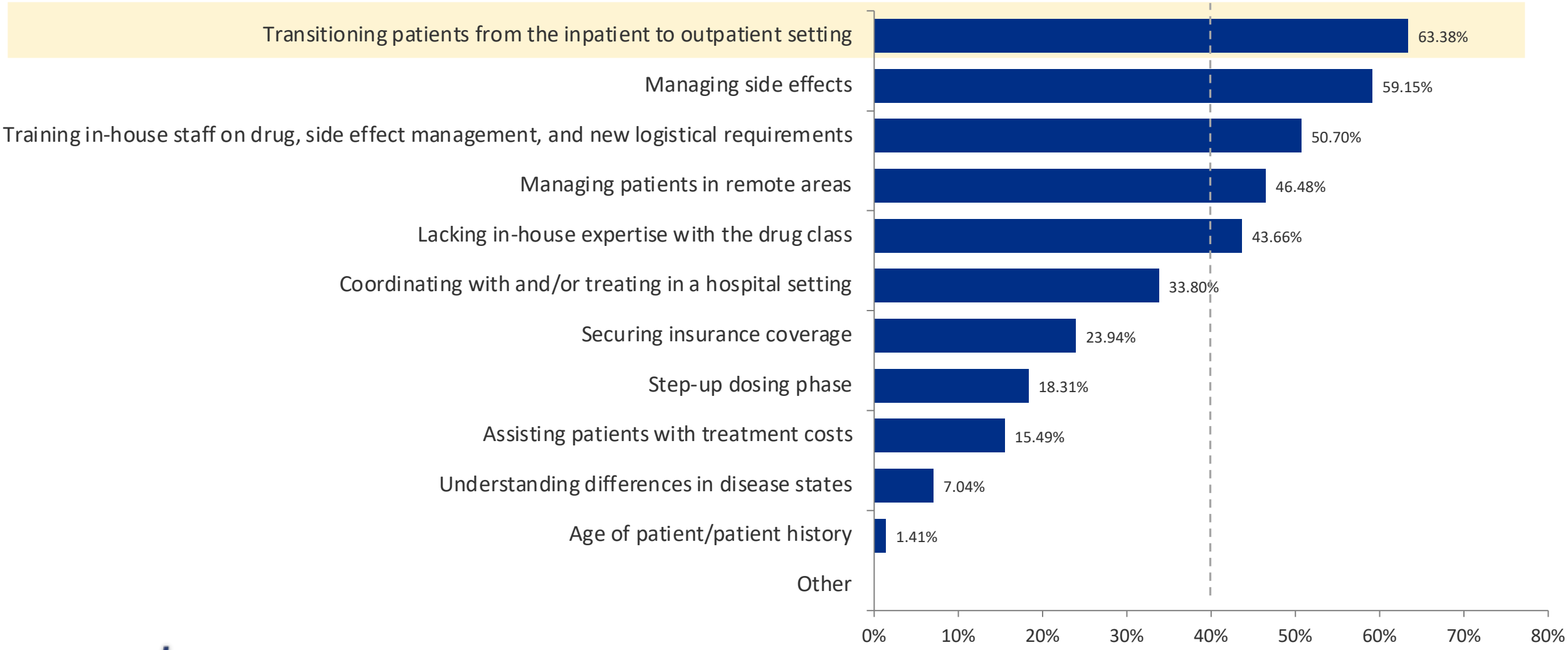
In Community Oncology, what are the top challenges?

1. *Complexity and novelty*
2. *Limited clinical experience*
3. *Treatment-related toxicities*
4. ***Transition from in-patient to out-patient setting***

What are ways to best integrate bispecifics into community practice?

February 2024 Survey

In your opinion, what are the biggest barriers to using bispecific antibodies?



Answered: 71

Transition from in-patient to out-patient setting

Importance of timely consultation and communication around patient urgency when transferring between community and hospital setting

- Establish strong relationships between clinicians working at academic and community cancer programs
  - Build on existing referral pathways
  - Ensure staff are familiar with referral process
- Utilize online resources to help prepare/educate patients
  - Provide patient information sheet
- Use telehealth to provide follow-up care and monitor for symptoms
- Use knowledgeable navigators (provide training) to coordinate logistics between community and academic medical centers

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Logistics and Financial challenges

Geographic and financial barriers can be challenging for more rural patients:

Long travel distances and limited resources to cover transportation, housing, and other expenses

Patients

- Potential hospital stays during step-up dosing
- Patient insurance can dictate treatment choice
- Assisting with treatment-related costs
- Medication assistance programs

Payers

- Open communication to understand urgency of approval
- Prior treatment history and rationale for bispecific
- Up-to-date on clinical data, guidelines, FDA approvals to support approval

Provider (Practice vs Hospital)

- Who is going to assume the cost?

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Checklist Prior to Starting Bispecifics

Patient Education & Caregiver: a must!

Wellness Tools: Basic Thermometer, BP instrument and Pulse Oximeter

Clear guidance: a flowchart with vitals log

Prescription: Dexamethasone (and acetaminophen and diphenhydramine)

Prophylaxis: Bactrim and Acyclovir

Assess comorbidities: DM and Echo (hint: Dex and IVF)

Key to Success

1. Start Slow (few select patients)
2. Select stable, low bulk, fit patients with good support
3. Start one patient at a time
4. Educate
   Educate
   Educate!
5. Plan for after hours
6. Make sure Tocilizumab is available!
   (Hint: Pharmacy)