# Seamless Navigation of Bispecific Therapies: Optimizing Management and Outpatient Access With a Focus on Coordination

ZAHRA MAHMOUDJAFARI,[1] PharmD, MBA, BCOP, FHOPA, AMIR ALI,[2] PharmD, BCOP, JAMES DAVIS,[3] PharmD, BCOP, TYLER SANDAHL,[4] PharmD, BCOP, VICTORIA NACHAR,[5] PharmD, BCOP, and ROBERT MANCINI,[6] PharmD, BCOP, FHOPA

From [1]The University of Kansas Health System – Westwood Campus, Division of Hematologic Malignancies & Cellular Therapeutics, Westwood, Kansas; [2]University of Southern California – Pharmacy, Los Angeles, California; [3]Medical University of South Carolina – Pharmacy, Charleston, South Carolina; [4]Mayo Clinic Rochester – Pharmacy, Rochester, Minnesota; [5]University of Michigan Medical Center – Pharmacy, Ann Arbor, Michigan; [6]St Luke's Health System – Pharmacy, Boise, Idaho

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Correspondence to: Zahra Mahmoudjafari, PharmD, MBA, BCOP, FHOPA, 2330 Shawnee Mission Parkway, Westwood, KS 66205

E-mail: zmahmoudjafari@kumc.edu

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**Abstract**

Bispecific antibodies (BsAbs) have emerged as crucial therapeutic agents for patients with relapsed/refractory diffuse large B-cell lymphoma, multiple myeloma, and most recently, lung cancer. These therapies have demonstrated remarkable efficacy in clinical trials; however, multidisciplinary collaboration is essential to ensure optimal patient outcomes amid the operational complexities associated with BsAb therapy. As BsAbs are being prepared for broader adoption, clinicians and treatment centers must navigate operational challenges, including financial considerations, patient selection, caregiver involvement, and transitions of care. Centers must also be knowledgeable to manage toxicities such as cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome. We therefore convened a panel of academic and community practice pharmacists with experience using BsAbs in clinical trial and standard-of-care settings to provide comprehensive recommendations with a focus on successful onboarding and operationalization of BsAb therapies.

Bispecific antibodies (BsAbs) have emerged as important treatment options for patients with hematologic and oncologic malignancies (Budde et al., 2022; Chari et al., 2022; Dickinson et al., 2022; Kantarjian et al., 2017; Lesokhin et al., 2023; Moreau et al., 2022; Thieblemont et al., 2023; Ahn et al., 2023). The approval of blinatumomab (Blincyto), the first commercially available BsAb, challenged multidisciplinary teams due to its complex continuous infusion strategy. More recently, approvals

of immunoglobulin G (IgG)-like BsAbs with longer half-lives have gained momentum due to more practical and less frequent administrations (van de Donk & Zweegman, 2023). The recent bispecific constructs in hematologic malignancies are designed to bind CD3 on T cells and tumor-specific antigens on malignant cells, thereby activating T cells and causing degranulation and tumor cell death (Davis et al., 2022; Granger et al., 2023; van de Donk & Zweegman, 2023). Two BsAbs are currently approved in oncology. Tebentafusp (Kimmtrak)is a gp100 peptide-HLA-directed CD3 bispecific indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (Nathan et al., 2021). Tarlatamab (Imdelltra) is approved for the treatment of adult patients with relapsed/refractory extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. Specifically, tarlatamab is a bispecific T-cell engager that binds to DLL3 expressed on the surface of tumor cells and CD3 proteins (Ahn et al., 2023). As a drug class, one particular challenge for the multidisciplinary care team is the requirement to establish practice guidelines for the management of unique toxicities such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS; Oranges et al., 2020; Szoch et al., 2018). To mitigate toxicities, manufacturer labeling often recommends inpatient observation during or following each step-up dose. Some of the products also require enrollment into Risk Evaluation and Mitigation Strategy (REMS) programs. Due to less severe CRS and ICANS with BsAbs when compared with chimeric antigen receptor (CAR) T-cell therapy, many institutions have explored outpatient initiation to minimize healthcare resources.

As BsAbs become poised to expand into broader patient populations, it is imperative for clinicians to understand how to operationalize and onboard these products. Here, we sought to develop consensus recommendations for operationalizing and managing BsAb therapy.

## METHODS

The authors are active members of the multidisciplinary care team, and each are tasked with ensuring new therapies are onboarded within their respective organizations. The authors are responsible for understanding key facets, including clinical, safety, and financial considerations. In the writing of this manuscript, each author was assigned to work on a section specific to their area of expertise that was then reviewed and discussed by the panel to finalize the consensus. Nonbinding feedback was also solicited from key representatives from Genmab A/S, Genentech, Inc., and Janssen Biotech, Inc., the pharmaceutical companies who sponsored relevant BsAbs clinical trials for additional input on key challenges observed with a focus on operations. Authors conversed once via email correspondence with representatives from each company to obtain feedback. The companies did not provide any funding or other forms of support for these recommendations and were not provided opportunities for iterative comments.

## APPROVAL WORKFLOWS AND PHARMACY AND THERAPEUTICS COMMITTEES

Institutional approval workflows and decisions by pharmacy and therapeutics committees (P&T) play a crucial role in the effective integration of BsAbs. Given the complexity of BsAbs, approval workflows should adhere to institutional standards (DePadova et al., 2016). To reduce delays, institutions may adopt a non-formulary approval process as a temporary measure, which gives access to new treatments while awaiting a formal review. This necessitates the development of strong protective measures to mitigate safety risks. One of the most common sources of safety events is manually created treatment plans. This can lead to numerous risks, including the possibility of dosage, administration, and/or billing errors. The non-formulary request process should enable a pre-formulary order set to reduce these risks. A multidisciplinary team should review the BsAb order set request in the same way that they would any P&T-approved drug. This multidisciplinary team should include the treating hematologist or oncologist, a clinical pharmacist, advanced practice providers, the department chair, and any other individuals critical to approval and operationalizing these therapies (e.g., chair of P&T or drug use department). This approach uses a structured framework that adheres

to institutional standards and best practices while also making the transition to full approval easier.

A thorough P&T review should encompass an evaluation of efficacy, safety, and financial considerations, coupled with a detailed examination of practical aspects related to therapy implementation, including site of care and any other formulary restrictions. The P&T committee's responsibilities extend beyond formulary approval, encompassing a comprehensive review. The scope of this review includes ensuring adherence to treatment location requirements, methods for facilitating insurance approval, maintaining adequate drug stock, and addressing potential demands on inpatient bed utilization. Ultimately, the P&T committee plays a pivotal role in guaranteeing the presence of all necessary variables essential for the safe and effective implementation of BsAbs. Continuous vigilance is imperative, and the P&T committee — or an equivalent institutional body—should establish a method for the ongoing review of processes, guidelines, and procedures associated with BsAbs. This ensures that updates are promptly incorporated when necessary. This vigilant oversight contributes to the sustained safety and efficacy of BsAb implementation.

Standardization of management protocols and staff training is essential (Crist et al., 2020). This may involve presentations or learning modules for health-care providers involved in BsAb administration and fostering a robust knowledge base and skill set to promptly recognize and respond to adverse events. Institutionally approved BsAb toxicity grading and management protocols should also be built into BsAb order sets, either electronically or on paper, to aid in staff comfortability and facilitate urgent management that eliminates the risk of error.

## LEVERAGING THE ELECTRONIC HEALTH RECORD

The electronic health record (EHR) is integral to advancing patient-centered cancer care and promoting consistent practices while reducing errors (Balogh et al., 2011). Standardized EHR treatment plans for BsAbs offer a checklist of essential components, mitigate errors during step-up dosing, and allow for incorporation of medications crucial for acute complications. Decision support features ensure adherence to practice guidelines, providing autofill options with dropdown menus to minimize omission and transcription errors. Treatment plans for BsAbs within the EHR should include definitions and grading of CRS and neurotoxicity per guideline criteria, along with explicit guidance or links to institutional toxicity management protocols for emergent situations. Clear instructions on hold parameters, rescue medications, and distinctions between supportive medications administered promptly by infusion staff vs. those requiring provider instructions are crucial components. Configuration of the EHR to alert clinicians about REMS requirements enhances medication safety. Furthermore, the EHR can be instrumental in ensuring non-oncology providers are informed about patients receiving BsAb therapies, encouraging timely referrals to consult services or the treating oncologist in cases of urgent care or emergency department visits. The comprehensive use of the EHR optimizes the efficiency, safety, and consistency of BsAb treatment plans across the continuum of care.

## RISK EVALUATION AND MITIGATION STRATEGY

Notably, all currently approved BsAbs in multiple myeloma (MM) have a REMS program, while BsAbs in other indications do not. Prospective treatment centers must carefully analyze the REMS requirements specific to any therapy of interest, ensuring the establishment of proper education and staffing infrastructure before initiating treatment. A standardized REMS training toolkit coupled with documentation guidelines presents a proactive approach to mitigate medication safety risks, offering valuable materials for incorporation into training. While MM BsAb REMS mandate the use of a manufacturer-supplied patient wallet card before therapy initiation, institutions may consider supplying a general BsAb patient wallet card or medication bracelet for all BsAb recipients as a best practice (Pemmaraju et al., 2021). Of note, none of the REMS programs require hospitalization for the monitoring of CRS and neurotoxicity; however, several recommend hospitalization or observation for close monitoring. Designating an authorized representative within each institution to oversee REMS requirements and preparation

for manufacturer audits is essential, with providers ensuring REMS education and certification. While REMS certification facilitates safeguards and access to certain BsAbs, additional considerations, including financial, are needed prior to initiating any BsAb therapy.

## FINANCIAL CONSIDERATIONS

Understanding the financial implications of BsAb therapies is a crucial component of operationalizing these new treatment modalities. Reimbursement can vary based on the patient's primary insurance. Each manufacturer provides robust resources to support centers, including access and reimbursement guides and coding and billing guides, which can either be found directly on the manufacturer website or through the center's industry representatives. Correct coding is paramount to ensure the reimbursement of claims. Code sets can vary between inpatient hospital, outpatient hospital, and physicians' offices. The most essential codes are International Statistical Classification of Diseases and Related Health Problems (ICD-10), National Drug Code (NDC), Current Procedural Terminology (CPT) codes, revenue codes, place of service (POS) codes, and Healthcare Common Procedure Coding System (HCPCS) J codes and modifiers.

Healthcare Common Procedure Coding System codes for new drugs are not assigned initially upon drug approval; rather, they are updated quarterly by Centers for Medicare & Medicaid Services (CMS). As most products do not automatically have a J code assignment, most centers can utilize J3999. Once assigned, the appropriate J code should be updated in the center's records for adequate reimbursement (Table 1; CMS, 2024a).

### Inpatient

Manufacturer recommendations may include an acute care admission for 24 to 48 hours after step-up doses as outlined in the product labeling. Centers are challenged with operationalizing this recommendation as some products may require up to 12 days of admission if done exactly per the package insert (Janssen Oncology, 2023, 2024). Many practices have chosen to decrease this admission length by adjusting the dosing frequency (Graf et al., 2024). Medications administered in the inpatient setting are bundled into the overall reimbursement for inpatient services and are either negotiated between health-care facilities and commercial payers or using the Inpatient Prospective Payment System (IPPS) for Medicare. Medications provided during an inpatient stay are included in the diagnosis-related group (DRG) payment, and the correct DRG code should be used for reimbursement. The DRG payment is a predetermined amount based on the patient's diagnosis, severity of illness, and other factors. Reimbursement is based on the average costs for each DRG in the previous 2 years. Centers can use the CMS Web Pricer to estimate reimbursement and compare it to payments (CMS, n.d.-a). Another important consideration is the Medicare Two-Midnight rule during step-up dosing (CMS, 2015) The new technology add-on payment (NTAP) program provides an additional payment to recognize the cost of new medical services and technologies under the hospital IPPS and is intended as bridge payments for the 2 to 3 years it takes for a DRG to recalibrate (CMS, 2024b). Centers should be aware of products on the NTAP list (as it is updated annually) and ensure appropriate communication with the revenue cycle team to establish a pathway to ensure maximized reimbursement.

### Outpatient

Alternatively, outpatient reimbursement often involves separate billing and reimbursement processes for medications and health-care services. In the outpatient setting, medication reimbursement may be subject to different payment models, including fee-for-service, capitation, or bundled payments, depending on the health-care provider's practice and payer contracts. Medicare Part B covers certain outpatient medications administered by health-care providers, such as injectable drugs and vaccines, which are reimbursed based on the average sales price (ASP) plus a percentage markup using the Outpatient Prospective Payment System (OPPS). Centers who take care of a disproportionate number of uninsured patients may be eligible for 340B pricing. While Medicare is a national system, it relies on Medicare Administrative Contractors (MAC) divided into 12 geographical regions (CMS, n.d.-b) The MAC receives bills from hospitals and

**Table 1. Bispecific J Code Designation**

| HCPCS code | Medication | HCPCS code dosage |
|---|---|---|
| J9321 | INJ, epcoritamab-bysp | 0.16 mg |
| J9286 | INJ, glofitamab-gxbm | 2.5 mg |
| J9350 | INJ, mosunetuzumab-axgb | 1 mg |
| J9380 | INJ, teclistamab-cqyv | 0.5 mg |
| J1323 | INJ, elranatamab-bcmm | 1 mg |
| J3055 | INJ, talquetamab | 0.25 mg |

*Note.* HCPCS = Healthcare Common Procedure Coding System; INJ = injection.

outpatient clinics and submits them to CMS for payment. It is essential for centers to have processes in place to check updates from MAC and CMS as updates occur on a quarterly basis.

For patients, BsAb therapy may represent a cost-prohibitive therapeutic option with copayments and deductibles. Outpatient medication reimbursement may involve copayments, coinsurance, deductibles, and coverage restrictions depending on the patient's insurance plan and formulary, which may present a barrier to access. Consideration should also be given to the caregiver and their potential expenses and loss of income. There continues to be a lack of transparency in what these out-of-pocket costs can be.

Health-care settings should consider their precertification practices and ensure that outpatient authorization has been obtained prior to therapy initiation. One additional consideration is ensuring the precertification of tocilizumab (Actemra) at the same time as obtaining outpatient authorization by incorporating tocilizumab as an as needed or prn order in the treatment plan to minimize denied claims and ensure appropriate reimbursement.

Understanding the nuances of inpatient and outpatient medication reimbursement is crucial for health-care providers and patients to navigate the complexities of health-care financing and ensure access to essential medications.

## PATIENT SELECTION: INPATIENT VS. OUTPATIENT

Most institutions initiate BsAb step-up doses in an inpatient setting; however, with the appropriate infrastructure, select patients may be eligible to receive outpatient step-up doses based on specific patient and product characteristics.

Patients with high disease burden as indicated by circulating disease or high-risk biology may be at increased risk of severe CRS (Crombie et al., 2024). Elevation of baseline inflammatory markers such as lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP), as well as thrombocytopenia, have been previously associated with severe CRS with CAR T-cell therapy and should be considered when selecting patients for outpatient initiation (Crombie et al., 2024; Greenbaum et al., 2021; Tedesco & Mohan, 2021). Age above 70 years, frailty, and comorbidities have also been associated with severe CRS and neurotoxicity (Davis et al., 2024; Dima et al., 2023, 2024). For these reasons, the panel recommends patients with high disease burden, elevated inflammatory markers, those above 70 years old with comorbidities, those with active infections, and those with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 be excluded from consideration for outpatient initiation. Patients requiring granulocyte colony-stimulating factor (G-CSF) prior to step-up initiation should also be carefully considered due to the potential for exacerbation of CRS with concurrent use of G-CSF (Raje et al., 2023).

Because outpatient initiation requires travel to and from an infusion center, candidates should have a reliable vehicle, caregiver or driver, and have a history of compliance. Patients should also remain within 1 to 2 hours of a facility with access to intensive care unit (ICU)-level care and readily available tocilizumab (Crombie et al., 2024).

## CAREGIVER REQUIREMENTS

With rapid advances in cancer care, reliance on complex care given by family members continues to grow (Yáñez et al., 2019). There are little to no

standards for home-based care of BsAbs, especially as it relates to caregiver standards. However, the American Society of Clinical Oncology (ASCO) published a core set of monitoring guidelines, and it has been evaluated in the setting of hematopoietic stem cell transplant (HSCT) and CAR T-cell based therapies (Sean et al., 2018; Spanjaart et al., 2023). Two important components include screening caregivers as "fit for duty" and support to ensure caregiver well-being. Some standards describe key attributes of an effective caregiver as someone who has appropriate coping skills, problem-solving skills, and prioritization of issues, as well their own self-care (Jim et al., 2014; Metoyer, 2013). Jim and colleagues (2014) found that caregivers reported the need for more information and support for their role as caregivers.

Unlike with CAR T-cell therapy or transplant, the length of time needed for direct caregiving tends to be much shorter with BsAbs, depending on the product, but caregiver preparedness is still essential (Winterling et al., 2022). Therefore, these factors should be included in what is required to determine an adequate caregiver who can provide in-home care for patients for at least 48 hours after each step-up dose and first treatment dose, as well as subsequent doses based on the patient's initial course.

Providers should develop patient education that assists patients and caregivers with understanding the signs and symptoms of key toxicities, when and to whom to report toxicities, how to utilize monitoring devices, REMS requirements, and other techniques for assessing toxicity (e.g., immune effector cell–associated encephalopathy [ICE] score). Education should be completed by trained health-care providers and both the patient and caregivers should be present. To supplement this, providers should create patient education materials or use existing technology to allow for recording of said monitoring, such as booklets, wallet cards, or electronic tablets. An outline of caregiver requirements can be found in Table 2.

## OUTPATIENT MANAGEMENT

With appropriate patient selection, step-up dosing can be done safely in the outpatient setting when adequate monitoring capabilities and protocols for rapid escalation of care are in place (Bansal et al., 2023; Varshavsky-Yanovsky et al., 2023). There are several major resources to consider when determining if outpatient administration of the step-up dosing is possible for a health-care site, including monitoring capabilities, education for patients and clinical staff, drug preparation and administration, and plans for escalation of care in the event of toxicity. The identification and education of key stakeholders is essential to creating an outpatient practice for BsAbs.

### Monitoring

Vital signs should be monitored routinely during step-up dosing. Patients may have or should be provided with monitoring tools such as pulse oximeters, thermometers, and automatic blood pressure monitors. Patients should be given instructions on how to monitor and what to do in the event of abnormal vital signs in the presence or absence of symptoms. A designated contact line should be in place for answering patient questions and triaging patient alerts.

Patients should be assessed regularly for signs of CRS and neurotoxicity, including daily check-ins with clinical staff during higher-risk periods of treatment initiation. Patient check-ins can be both in-person or virtual; however, the panel recommends in-person physical assessments with a provider or nurse prior to each dose in the step-up schedule.

Regular lab monitoring during step-up and treatment dosing is necessary to monitor for any adverse effects of the drugs. There will be variability between different bispecific antibodies, institutional practices, and patient-specific needs. Consider monitoring complete blood count (CBC), comprehensive metabolic panel (CMP), CRP, and ferritin during treatment initiation prior to each step-up dose and at additional time points as clinically indicated.

### Drug Preparation and Administration

The site of care for step-up dosing and treatment dosing will dictate which pharmacy is involved in drug preparation. The use of free drug programs may dictate the site of care for certain products as well. Establishing workflows for patient evaluation prior to subsequent doses, order release and verification, premedication, drug preparation, drug

**Table 2. Operational Considerations for Implementing Bispecific Antibodies in Practice**

*Key Stakeholders*

- Physicians
- Advanced practice providers
- Pharmacists
- Nursing
- Social work
- Critical care staff
- Emergency department staff
- Administrators

*Written Guideline Requirements*

- Criteria for use and treatment setting (inpatient vs. outpatient)
- Designation of a specific unit for administration if applicable
- Detailed management protocols for CRS and neurotoxicity
- Infection prophylaxis standards
- In-home patient monitoring recommendations
- Institutional monitoring standards including who will monitor, how and when
- Procedures for patients to report adverse effects
- Workflows for toxicity management and care escalation

*Patient Selection of Treatment Location*

*Patient and Caregiver Requirements for Outpatient Administration*

Education
- Attend all consenting and education visits with the patient
- Demonstrate ability to recognize signs/symptoms of toxicity
- Understand when and who to call for signs and symptoms of toxicity

Direct Care
- Able to provide direct, in-home care for at least 48 hours
- Ability to provide transportation to any health-care visits for at least 72 hours[a]

Monitoring
- Ability to assist patient in utilizing monitoring equipment (blood pressure monitors, thermometers, pulse oximeters and any associated monitoring technology)
  - » Vitals should be taken every 4 hours while at home[a,b]
- Ability to administer a neurologic assessment (e.g., ICE score assessment)
  - » Completed at least twice daily (if not completed by health-care provider)[a,b]
- Ability to record and report all at-home monitoring and bring all data to each provider visit

*Considerations for Transitions Between Treatment Centers*

Insurance Authorization
- Obtain authorization for both centers to provide therapy prior to initiation.
  - » This may require additional documentation upfront
- Ensure financial assistance obtained will apply to either treatment center[c]
  - » Some assistance programs may be treatment site specific

Medication Access and Education
- Verify both centers have the ability to order and administer drug[c]
- Provide education on staff ordering, dispensing, and administering drug[c]

Handoff and Documentation
- Exact dates and doses of therapy, including when next dose is due after transition
- If there was toxicity, including grade, duration, and treatment, if applicable
- Recommended follow-up and management of subsequent toxicities
- Which center to call if there are concerns or symptoms at home
- Where to go in case of urgent or emergent needs

REMS
- If REMS programs exist, verify both centers appropriately enrolled prior to initiation of therapy[c]

*Note.* CRS = cytokine release syndrome; ICE = immune effector cell-associated encephalopathy; REMS = Risk Evaluation and Mitigation Strategy.
[a]Applies to the time period after each step-up dose and first treatment dose. May include subsequent doses depending on medication and patient's treatment course.
[b]Or more if patient experiencing any new symptoms. Assessments should be provided during normal waking hours.
[c]This is the responsibility of each center; however, drug manufacturers can assist in these areas.

delivery, and drug administration must be well coordinated to avoid significant delays in care to improve patient experience and reduce resource utilization. Monitoring periods post injection should be determined based on the median onset of CRS and ICANS for each product, with a minimum monitoring period of 30 minutes following initial administrations to assess for hypersensitivity reactions or early onset toxicities.

## TRANSITIONS BETWEEN CENTERS

Reported barriers to using BsAbs include transitions between treatment centers, managing patients who live far from treatment centers, insurance and financial issues, managing adverse events, and the lack of experience with a particular therapy (Atembina et al., 2021). In the operationalization of BsAbs, one of the biggest issues seen is transitions of care between centers. Due to the differences and complexities of the various BsAbs, many centers struggle with the ability to initiate these therapies. As a result, smaller or community cancer centers may refer to larger treatment centers or those with inpatient services for the initiation of therapy; however, this creates its own issue.

Pharmacists play an important role in transitions of care in patients with cancer. While most data evaluate this in the context of transition from inpatient to outpatient settings, they can fill the same role in transitions between centers (Shank et al., 2017). The most common scenario is when a patient is referred from one center to do step-up at another center, then transition back for continued dosing. While each bispecific has different step-up dosing schedules, it is recommended that one treatment center manage the patient through all step-up doses and their first treatment doses. If a patient can complete initiation without any CRS or neurotoxicity, they are likely safe to return to their referring treatment center for their second treatment dose. If a patient has CRS or neurotoxicity with this schedule, it is recommended that those patients be able to tolerate one full dose therapy at the step-up treatment center, without acute toxicity, before transitioning back to their referring treatment center for subsequent doses. To provide consistent timelines, some centers may adopt a plan where the first month of treatment (which can include step-up dosing and 1 to 3 treatment doses) be conducted at the initiating center before transition back to the referral center. Beyond this, all other considerations for ensuring a smooth transition between centers can be found in Table 2.

## TOXICITY MANAGEMENT

Bispecific antibodies demonstrate significant clinical efficacy, yet their use can be accompanied by toxicities such as CRS and ICANS, and may also include infections, cytopenias, tumor flare, and other side effects that may limit their adoption in patient care (Falchi et al., 2023). Effective mitigation and management of toxicities necessitates proactive measures well in advance of BsAb therapy initiation. Institutional readiness for the early identification and intervention of certain side effects (e.g., CRS/ICANS, infections) is imperative before commencing BsAb treatment.

### Management of CRS and ICANS

Cytokine release syndrome is a rapid and potentially severe systemic inflammatory response marked by fever, hypotension, hypoxia, and/or possible multiple organ dysfunction (Lee et al., 2019). Such systemic reactions may be associated with increased levels of pre-inflammatory cytokines (i.e., IL-6, IL-10, TNF-α) and activation of immune effector cells (IECs; Wang & Han, 2018). The timing, duration, and frequency of CRS episodes are influenced by the specific disease subtype, administration route, and the BsAb agent used. According to clinical trial and real-world data, most CRS events are classified as grade 1 or 2. Nonetheless, more severe presentations of CRS (≥ grade 3) have been infrequently observed (Budde et al., 2022; Chari et al., 2022; Dickinson et al., 2022; Dombret et al., 2019; Lesokhin et al., 2023; Moreau et al., 2022; Thieblemont et al., 2023).

Neurological toxicities including ICANS were also observed in clinical trials involving BsAbs. While the exact pathophysiological mechanisms remain unknown, it is hypothesized that systemic inflammatory responses and elevated cytokine levels contribute to the activation of endothelial cells and subsequent disruption of the blood-brain barrier, which may precipitate an inflammatory cascade within the central nervous system (Gust

et al., 2017). Immune effector cell–associated neurotoxicity syndrome commonly presents after the occurrence of CRS (may overlap with CRS); however, the presence of CRS is not a prerequisite for the development of ICANS, and both syndromes may manifest independently (Karschnia et al., 2023). Symptoms associated with potential neurologic toxicities have been frequently observed (up to 65% for any grade), yet the prevalence of severe neurotoxicity or ICANS of any severity remains low, under 7% and 9%, respectively (Budde et al., 2022; Chari et al., 2022; Dickinson et al., 2022; Dombret et al., 2019; Lesokhin et al., 2023; Moreau et al., 2022; Thieblemont et al., 2023).

The optimal pre-treatment evaluation for CRS and ICANS mandates a thorough and ongoing assessment strategy. Essential to this strategy is the attainment of CBC with differential, CMP, and LDH levels. Additionally, baseline cytokine profiles, CRP, ferritin levels, and coagulation parameters, including fibrinogen and D-dimer, may be ascertained. Such access is crucial for the continuous monitoring and assessment of a patient's reaction and tolerance to therapy, ensuring timely and informed clinical decisions. While data supporting the role of prophylactic tocilizumab exist, the panel does not support routine prophylactic use due to low rates of high-grade CRS (Scott et al., 2023).

While individual BsAb therapies come with their distinct management guides for CRS and ICANS, there is potential for a uniform approach to treatment across different products. Typically, CRS is characterized initially by fever ≥ 38°C, which may be accompanied by hypotension and/or hypoxia, with severity dictating the clinical response. Table 3 provides a consensus approach for CRS management based on the available literature; institutional protocols may vary (Lee et al., 2019). Cytokine release syndrome is typically low grade and managed with steroids; however, tocilizumab should be considered for symptoms that are ≥ grade 2 or refractory to steroids. If CRS is being managed in the outpatient setting, hospitalization should also be considered for those with ≥ grade 2 CRS or those not responding to initial management.

Immune effector cell–associated neurotoxicity syndrome is meticulously assessed using the ICE score, which evaluates mental status, seizures, motor weakness, and any imaging abnormalities. For mild ICANS, the approach prioritizes supportive care and diligent monitoring, including daily electroencephalogram until resolution and neuroimaging studies such as CT head and MRI of the brain. Should the condition intensify or fail to improve, an elevation in care to an ICU is indicated. Table 4 outlines the clinical grading and management of ICANS, including but not limited to supportive care and steroids (Lee et al., 2019).

### Management of Infection, Neutropenia, and Hypogammaglobulinemia

Bispecific antibody therapies bring forth a heightened risk of infectious complications corroborated by clinical trial observations, with upper respiratory tract infection as the most common. Infection prophylaxis and management are multifaceted, incorporating patient-specific factors (i.e., age, performance status, comorbidities) and disease severity (i.e., tumor burden, refractory status). The history of prior treatments, especially steroid use, previous infection profiles, and the anticipated length of BsAb treatment also critically inform risk stratification and mitigation strategies (Table 5; Raje et al., 2023).

Rare infections have been reported in this patient population and require attention in specific situations (Budde et al., 2022; Chari et al., 2022; Dickinson et al., 2022; Dombret et al., 2019; Lesokhin et al., 2023; Moreau et al., 2022; Thieblemont et al., 2023). For cytomegalovirus (CMV), routine prophylaxis is not recommended, but preemptive monitoring with polymerase chain reaction (PCR) is advised for CMV IgG seropositive patients, especially after the use of steroids. For human herpesvirus 6 (HHV-6), weekly monitoring by PCR is suggested in patients with prolonged neutropenia, after steroid use for CRS/ICANS (≥ 3 days), and/or developing hemophagocytic lymphohistiocytosis (HLH). In cases of suspected progressive multifocal leukoencephalopathy (PML), immunosuppressed patients with neurological events should undergo appropriate diagnostic evaluations.

Other concerns such as hypogammaglobulinemia, lymphopenia, and neutropenia should also be considered. For grade 3 or 4 neutropenia, growth factors may be used, except when CRS risk

**Table 3. Cytokine Release Syndrome Management by Grade**

| ASTCT CRS Consensus Grading | | Management |
|---|---|---|
| **Grade** | **CRS Parameter** | |
| 1 | Temperature ≥ 38°C[a]<br>*and*<br>No hypotension or hypoxia | • CBC w/differential, CMP, PT/INR, aPTT, fibrinogen, D-dimer, ferritin, CRP (baseline and trend)<br>• Sepsis workup: CXR, cultures, antibiotics<br>• Antipyretics and IV fluid hydration<br>• Consider pulse dexamethasone<br>• Consider issuing prescriptions for dexamethasone (i.e., as a single dose of 10–20 mg) to allow home administration upon the patients' (and their caregivers') competence in regular vital sign monitoring |
| 2 | Temperature ≥ 38°C<br>*with*<br>Hypotension not requiring vasopressors<br>*and/or*[b]<br>Hypoxia requiring low-flow nasal canular or blow-by | • Continue prior supportive care and monitoring in grade 1<br>• Administer supplemental oxygen as needed<br>• Consider dexamethasone (10 mg po or IV q12h) and/or tocilizumab (8 mg/kg IV; max 800 mg/dose; may repeat in 8 hr and ≤ 2 doses in 24 hr)<br>• Consider dexamethasone dose increase (10–20 mg po or IV q6–12h) if no improvement within 24 hr<br>• If no improvement with dexamethasone dose increase within 24 hr, subsequent dexamethasone dose increase or high-dose methylprednisolone may be considered<br>• For patients experiencing grade ≥ 2 CRS, hospitalization is recommended for institutions that do not have procedures for outpatient management. |
| 3 | Temperature ≥ 38°C<br>*with*<br>Hypotension requiring a vasopressor w/w/o vasopressin<br>*and/or*[b]<br>Hypoxia requiring low-flow nasal canular[c] or blow-by | • Continue prior supportive care and monitoring in grade 2<br>• Vasopressor support<br>• Dexamethasone[d] (10 mg IV q6h) or high-dose methylprednisolone (1,000–2,000 mg IV × 3 days, then taper every 3 days)<br>• Tocilizumab, if not tried yet<br>• If refractory to steroids and tocilizumab, may consider similar alternative agents used in CAR T-cell toxicities such as anakinra, siltuximab |
| 4 | Temperature ≥ 38°C<br>*with*<br>Hypotension requiring multiple vasopressors (excluding vasopressin)<br>*and/or*<br>Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) | • Continue prior supportive care and monitoring in grade 3<br>• Mechanical ventilation or CRRT may be indicated<br>• Dexamethasone[d] (20 mg IV q6h) or high-dose methylprednisolone (1,000–2,000 mg IV × 3 days, then taper every 3 days)<br>• Tocilizumab, if not tried yet<br>• If refractory to steroids and tocilizumab, may consider similar alternative agents used in CAR T-cell toxicities such as anakinra, siltuximab |

*Note.* CBC = complete blood count; CMP = comprehensive metabolic panel; PT/INR = prothrombin time/international normalized ratio; aPTT = activated partial thromboplastin time; CRP = C-reactive protein; CXR = chest X-ray; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure; CRRT = continuous renal replacement therapy. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading. If refractory or clinically unstable despite current management, manage per next grade recommendations. May consider similar alternative agents used in CAR T-cell toxicities such as anakinra, siltuximab. Information from Lee et al. (2019).

[a]Fever is defined as temperature 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c]Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

[d]Specifically for blinatumomab: Per prescribing information, dexamethasone 5 mg/m$^2$ (≤ 8 mg) po/IV q8h × 3 days. Hold infusion during grade 3–4 CRS/ICANS.

**Table 4. Neurotoxicity/ICANS Management by Grade**

| ASTCT ICANS Consensus Grading | | Management |
|---|---|---|
| **Grade** | **Neurotoxicity Domain** | |
| 1 | ICE[a] score 7–9<br>*and*<br>Awakens spontaneously<br>*and*<br>No seizure, motor findings[b], or elevated ICP/cerebral edema | • CBC w/differential, CMP, PT/INR, aPTT, fibrinogen, D-dimer, ferritin, CRP (baseline and trend)<br>• Aspiration precautions and IV hydration<br>• EEG (daily until symptom resolution)<br>• CT head or MRI brain<br>• Consider dexamethasone 10 mg po/IV qd<br>• Consider seizure prophylaxis with levetiracetam or benzodiazepines |
| 2 | ICE[a] score 3–6<br>*and*<br>Depressed level of consciousness[b]: Awakens to voice<br>*and*<br>No seizure, motor findings[c], or elevated ICP/cerebral edema | • Continue prior supportive care and monitoring in grade 1<br>• Consider lumbar puncture (cell count, culture, protein, glucose, cytology, etc.)<br>• Increase dexamethasone dose (10–20 mg IV q6h) if previously administered per grade 1<br>• High-dose methylprednisolone (1,000–2,000 mg IV qd × 3 days, then taper every 3 days) if no improvement with dexamethasone |
| 3 | ICE[a] score 0–2<br>*and*<br>Depressed level of consciousness[b]: Awakens only to tactile stimulus<br>*and*<br>Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention; focal/local edema on neuroimaging[c]<br>*and*<br>No motor findings[d] | • Continue prior supportive care and monitoring in grade 2<br>• Consider seizure prophylaxis/treatment with levetiracetam or benzodiazepines<br>• Dexamethasone (10–20 mg IV q6h)<br>• High-dose methylprednisolone (1,000–2,000 mg IV qd × 3 days, then taper every 3 days) if no improvement with dexamethasone<br>• Consider IT chemotherapy (cytarabine 50 mg, methotrexate 12 mg, hydrocortisone 50 mg) for steroid-refractory ICANS<br>• If refractory to steroids and tocilizumab, may consider similar alternative agents used in CAR T-cell toxicities such as anakinra, siltuximab |
| 4 | ICE[a] score 0 (patient is unarousable and unable to perform ICE). Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad | • Continue prior supportive care and monitoring in grade 3<br>• Consider seizure prophylaxis/treatment with levetiracetam or benzodiazepines<br>• Lower ICP/cerebral edema with hyperosmolar therapy and hyperventilation<br>• Imaging of spine for focal motor weakness<br>• Dexamethasone (20 mg IV q6h × 3 days, then taper) or methylprednisolone (1,000–2,000 mg IV qd × 3 days, then taper)<br>• If no improvement within 48 hr, consider IT chemotherapy (cytarabine 50 mg, methotrexate 12 mg, hydrocortisone 50 mg) or may consider similar alternative agents used in CAR T-cell toxicities such as anakinra, siltuximab |

*Note.* CBC = complete blood count; CMP = comprehensive metabolic panel; PT/INR = prothrombin time/international normalized ratio; aPTT = activated partial thromboplastin time; CRP = C-reactive protein; EEG = electroencephalogram; ICP = intracranial pressure. 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.

[a]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.

[b]Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

[c]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.

[d]Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

**Table 5. Infection Concerns and Recommendations for Antimicrobial Prophylaxis**

| Concern | Recommendation | Initiation | Discontinuation |
|---|---|---|---|
| Bacterial | • Levofloxacin[a] 500 mg po daily<br>• Ciprofloxacin[a] 500 mg po twice daily<br>• Cefpodoxime[a,b] 200 mg po twice daily<br>• Cefdinir[a,b] 300 mg po twice daily | Start when ANC ≤ 0.5 K/μL or ANC < 1.0 K/μL is expected to last ≥ 7 days | Continue until ANC > 0.5 K/μL for 3 consecutive days without growth factor support |
| HSV/VZV | • Acyclovir[a] 400-800 mg po twice daily<br>• Valacyclovir[a] 500 mg po twice daily | Start with treatment | Continue for at least 18 months after treatment; consider extension based on clinical judgment |
| Fungal | Note: A patient would either meet criteria for low-risk or high-risk fungal prophylaxis, but NOT BOTH (see footnotes[c] for high-risk criteria) | | |
| | Low risk<br>• Patients at low risk for invasive mold infections should receive prophylaxis with the following agents targeting *Candida*<br>• Preferred<br>» Fluconazole[a,d] 200-400 mg po/IV daily<br>• Alternatives<br>» Consider when patient unable to tolerate fluconazole due to liver dysfunction, QTc prolongations, and/or DDIs<br>» Micafungin 50 mg IV once daily | Start when ANC < 0.5 K/μL | Continue until ANC > 0.5 K/μL for 3 consecutive days without growth factor support |
| | High risk<br>• Patients at high risk for invasive mold infections should receive prophylaxis with the following agents, targeting both *Candida* and *Aspergillus*<br>• Isavuconazole 372 mg IV/po every 8 hours × 6 doses, then 372 mg IV/po once daily<br>• Posaconazole delayed release tablet or IV: 300 mg twice daily × 2 doses, then 300 mg once daily<br>• Posaconazole IR suspension: 200 mg 4 times daily or 400 mg twice daily | Start when ANC < 0.5 K/μL and when high-risk criteria[c] are met | Continue as clinically indicated (DO NOT stop prophylaxis if ANC < 1 K/μL) |

*Note.* ANC = absolute neutrophil count; HSV = herpes simplex virus; VZV = varicella zoster virus; DDI = drug-drug interaction; QTc = corrected QT interval; G6PD = glucose-6-phosphate dehydrogenase; PJP = *Pneumocystis jirovecii* pneumonia; TMP-SMZ = trimethoprim-sulfamethoxazole; HBV = hepatitis B virus; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; PCR = polymerase chain reaction; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; HLH = hemophagocytic lymphohistiocytosis.

[a]Renal dose adjustment needed.

[b]Pseudomonas not covered.

[c]High risk: Patients with leukemia, recent allogenic stem cell transplant, prior history of *Aspergillus* infection, neutropenia lasting ≥ 14 days, grade 3 or 4 CRS/ICANS and receiving ≥ 3 days of corticosteroids, recipients of > 1 dose of tocilizumab, use of second line agents such as anakinra or siltuximab for management of CRS and ICANS, or those who develop HLH. If corticosteroids are given, continue posaconazole for at least 1 month after completion of corticosteroids. In the event posaconazole, voriconazole, isavuconazole, or an echinocandin are contraindicated or pose affordability/access issues, then use fluconazole for prophylaxis and consider aspergillus antigen testing at least once a week during corticosteroids and for at least a month after completion of corticosteroids.

[d]Pentamidine may cause pancreatitis. Some institutions recommended pentamidine inhaled/IV within one week (before or after) infusion during count recovery.

[e]TMP-SMZ also has activity against toxoplasma and nocardia.

[f]Atovaquone also has activity against toxoplasma, but is inferior to TMP-SMZ.

[g]Dapsone can cause hemolytic anemia in patients with G6PD deficiency. Use caution if the patient has a sulfa allergy.

**Table 5. Infection Concerns and Recommendations for Antimicrobial Prophylaxis (cont.)**

| Concern | Recommendation | Initiation | Discontinuation |
|---|---|---|---|
| PJP | • Preferred<br>» TMP-SMZ[e] 1 double-strength tablet po every Monday, Wednesday, Friday or 1 single-strength tablet po daily<br>• Alternatives<br>» Atovaquone[f] 1,500 mg po daily with a fatty meal<br>» Dapsone[g] 100 mg po daily or 50 mg po every 12 hours (send G6PD test before initiation; avoid if G6PD deficient)<br>» Pentamidine[d] 300 mg inhaled every 28 days (albuterol nebulizer premedication recommended) or 4 mg/kg (max 300 mg) IV every 21 days | Start with treatment | Continue while on treatment or until CD4 count > 200 cells/µL (whichever is longer) |
| HBV | • Entecavir[a] 0.5 mg po daily<br>• TAF 25 mg po daily<br>• TDF[a] 300 mg po daily | Start when HBsAg-pos or HBsAg-neg and HBcAb-pos (2 weeks before treatment) | Continue for 6–12 months after treatment; monitor HBV DNA PCR once a month while on prophylaxis and for a year after stopping |

*Note.* ANC = absolute neutrophil count; HSV = herpes simplex virus; VZV = varicella zoster virus; DDI = drug-drug interaction; QTc = corrected QT interval; G6PD = glucose-6-phosphate dehydrogenase; PJP = *Pneumocystis jirovecii* pneumonia; TMP-SMZ = trimethoprim-sulfamethoxazole; HBV = hepatitis B virus; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; PCR = polymerase chain reaction; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; HLH = hemophagocytic lymphohistiocytosis.
[a]Renal dose adjustment needed.
[b]Pseudomonas not covered.
[c]High risk: Patients with leukemia, recent allogenic stem cell transplant, prior history of *Aspergillus* infection, neutropenia lasting ≥ 14 days, grade 3 or 4 CRS/ICANS and receiving ≥ 3 days of corticosteroids, recipients of > 1 dose of tocilizumab, use of second line agents such as anakinra or siltuximab for management of CRS and ICANS, or those who develop HLH. If corticosteroids are given, continue posaconazole for at least 1 month after completion of corticosteroids. In the event posaconazole, voriconazole, isavuconazole, or an echinocandin are contraindicated or pose affordability/access issues, then use fluconazole for prophylaxis and consider aspergillus antigen testing at least once a week during corticosteroids and for at least a month after completion of corticosteroids.
[d]Pentamidine may cause pancreatitis. Some institutions recommended pentamidine inhaled/IV within one week (before or after) infusion during count recovery.
[e]TMP-SMZ also has activity against toxoplasma and nocardia.
[f]Atovaquone also has activity against toxoplasma, but is inferior to TMP-SMZ.
[g]Dapsone can cause hemolytic anemia in patients with G6PD deficiency. Use caution if the patient has a sulfa allergy.

is heightened. Hypogammaglobulinemia is managed with intravenous immunoglobulin (IVIg) replacement, beginning at the second cycle of BsAb treatment and continuing until IgG levels stabilize above 400 mg/dL, with monthly monitoring, particularly if the patient develops recurrent infections (Mohan et al., 2023).

### Management of Other Serious Toxicities

Talquetamab (Talvey), the first-in-class CD3 × GPRC5D BsAb, is noted for its unique toxicity profile due to antigen expression on both plasma cells and epithelial cells (in keratinized tissues of the skin and tongue; Janssen Oncology, 2023). The pivotal MonumenTAL-1 trial reported that 80% of patients experienced oral toxicities, with 2.1% encountering grade 3 events. Common adverse effects included dysgeusia, dry mouth, dysphagia, and weight loss. Skin reactions, including rash, maculopapular rash, and erythema, occurred in 62% of individuals, with 0.3% facing severe manifestations (Chari et al., 2022). While these toxicities typically did not necessitate dosage adjustments, they necessitated management strategies to ensure the continuation of therapy (Rodriguez-Otero et al., 2024). Health-care providers are advised to prioritize nutritional support and dental health and educate patients on

recognizing symptoms of these toxicities to ensure early intervention. Management of skin reactions with emollients and steroids has proven effective in preliminary trials (Chari et al., 2022; Mailankody et al., 2022). Crucially, any decisions regarding the continuation or cessation of treatment should involve patients in a shared decision-making process, particularly when considering the severity of adverse effects and quality of life (Atembina et al., 2021; Shank et al., 2017).

## CONCLUSION

Bispecific antibodies represent a significant advancement in the care of patients with hematologic malignancies; however, the rollout and onboarding of BsAbs represent a unique challenge to institutions looking to utilize these therapies, and consideration should be given to operationalization, finances, patient selection, caregiver requirements, transitions of care, and toxicity management. Centers must work in a multidisciplinary fashion to ensure optimal patient outcomes with many of the operational hurdles these therapies present. ●

### Disclosure

Dr. Mahmoudjafari has served on advisory boards for Pfizer, Genentech, Sanofi, Janssen, BMS, and Jazz. Dr. Ali has received a consulting fee or honorarium from Takeda and served on a speakers bureau for Johnson & Johnson. Dr. Davis has served as a consultant and on a speakers bureau for Janssen Biotech. Dr. Sandahl has served on advisory boards for Janssen, Pfizer Inc, and BioLineRx and developed an educational presentation for Johnson & Johnson. Dr. Nachar has served on an advisory board for Genmab. Dr. Mancini has served as a consultant for GSK and on speakers bureaus for Genmab, AbbVie, and Johnson & Johnson.

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