CONCERT NETWORK 2022
How to set up Cellular Therapies at your institution

RUEMU E. BIRHIRAY, MD

CEO, INDY HEMATOLOGY EDUCATION, INC.,

PARTNER, HEMATOLOGY ONCOLOGY OF INDIANA, AMERICAN ONCOLOGY NETWORK, PA, INDIANAPOLIS, IN

CLINICAL PROFESSOR OF MEDICINE,

MARIAN UNIVERSITY COLLEGE OF MEDICINE, INDIANAPOLIS, IN

CONCERT NETWORK
Community ONcology CEllulaR Therapy Network

HEMATOLOGY ONCOLOGY of INDIANA
A DIVISION OF AMERICAN ONCOLOGY PARTNERS, P.A.

MARIAN UNIVERSITY Indianapolis
College of Osteopathic Medicine

IHE

Community Oncology Cellular Therapy Network: CONCERT NETWORK

SUPPORTERS

Diamond Level

Silver Level

Bronze Level

CONFLICTS OF INTEREST

Speakers Bureau
Consultant,
Advisory Board

- JANSSEN BIOTECH, INC.
- AMGEN INC.
- PUMA BIOTECHNOLOGY, INC.
- LILLY USA, LLC
- NOVARTIS PHARMACEUTICALS CORPORATION
- INCYTE CORPORATION
- PHARMACYCLICS LLC, AN ABBVIE COMPANY
- SANOFF/GENZYME CORPORATION
- DOVA PHARMACEUTICALS
- TESARO, INC
- EXELIXIS INC.
- PFIZER INC.
- E.R. SQUIBB & SONS, L.L.C.
- ABBVIE, INC.
- ASTRAZENECA PHARMACEUTICALS LP
- BAYER HEALTHCARE PHARMACEUTICALS INC.
- ARRAY BIOPHARMA INC.
- GENENTECH USA, INC.
- JANSSEN SCIENTIFIC AFFAIRS, LLC
- MERCK SHARP & DOHM
- TAKEDA
- DIIACHI SANCHO
- MORPHOSYS
- REGENERON
- KITE
- IPSEN
- STEMLINE

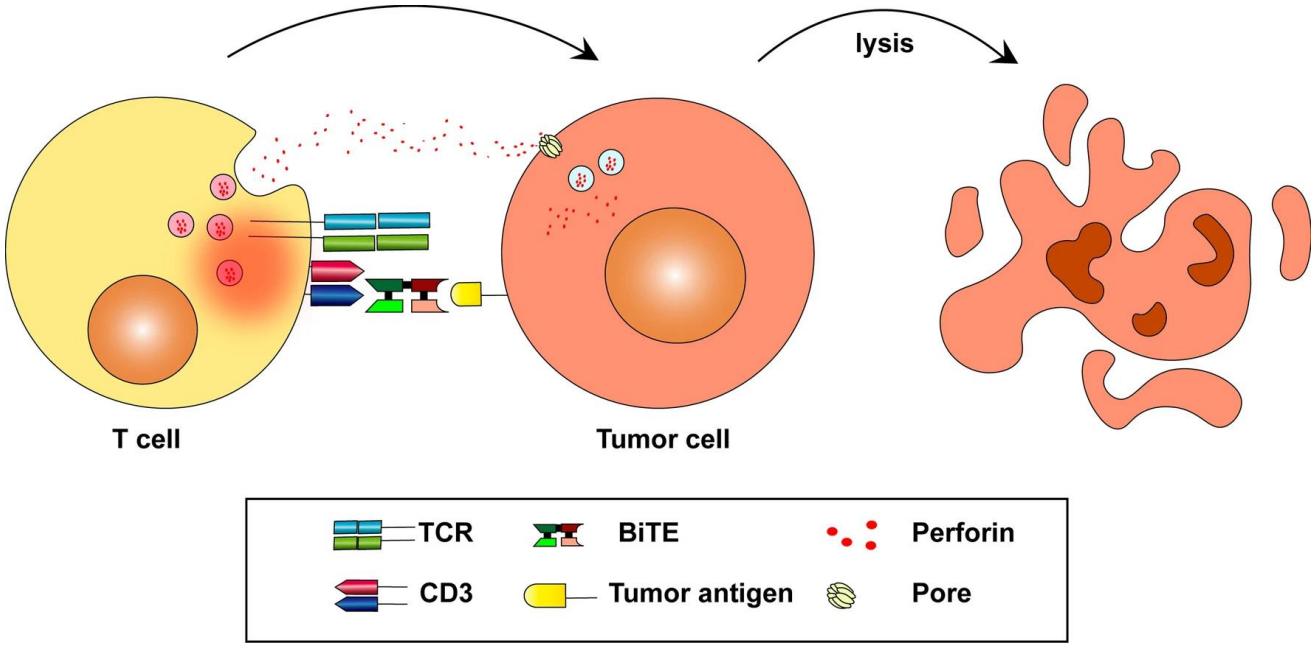
CONCERT NETWORK
Community ONcology CEllulaR Therapy Network

BiSpecific Antibodies in Hematologic Malignancies

NEW DRUGS IN LATE-STAGE DEVELOPMENT OR FDA APPROVED

- Bispecific Antibodies: T-Cell Engagers in Lymphoma
- Glofitamab
- Mosunetuzumab (FDA Approved for Follicular Lymphoma)
- Odronextamab
- Epcoritamab
- Bispecific Antibodies: T-Cell Engagers in Myeloma
- Teclisimab (FDA Approved for Multiple Myeloma)
- Talquetamab
- Elranatamab
- Cevostamab
- Bispecific Antibodies: T-Cell Engagers in Leukemia
- Blinatumomab (FDA Approved for Acute Lymphoblastic Leukemia)

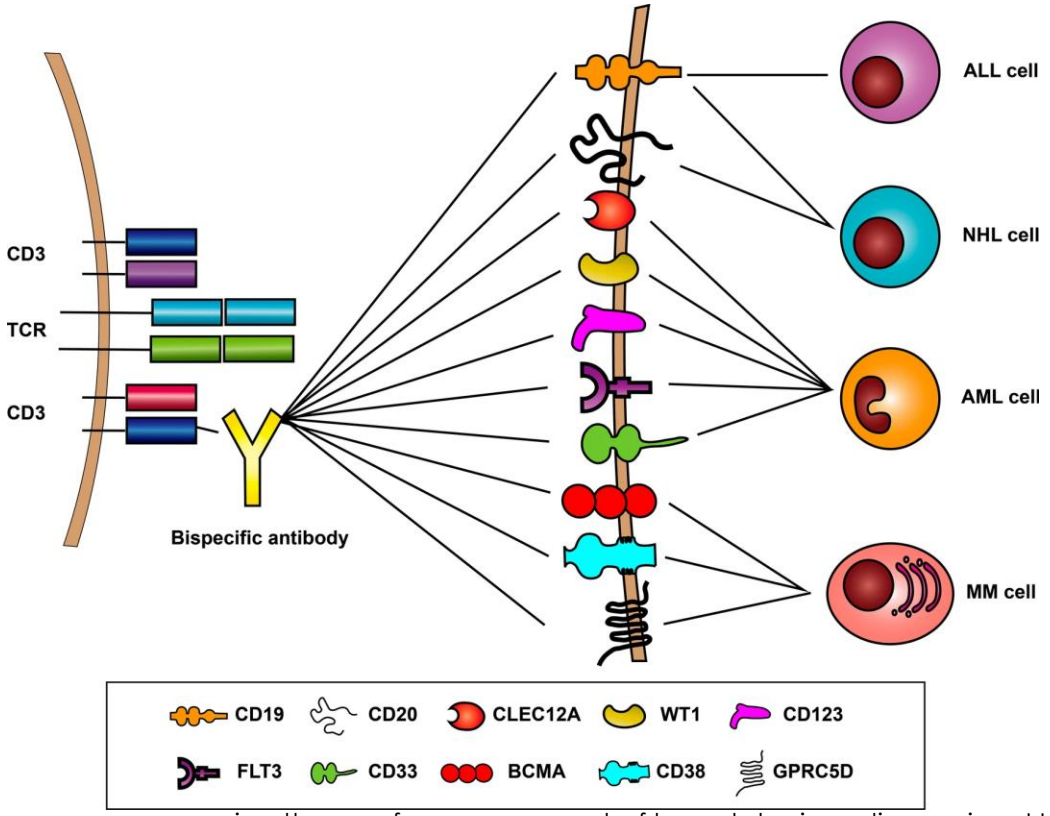
Mechanisms of tumor cell lysis mediated by Bispecific Antibodies



Tian, Z., Liu, M., Zhang, Y. et al. J Hematol Oncol 14, 75 (2021

Bispecific Antibodies in Hematologic Malignancies

Targets of bispecific B cell-recruiting antibodies



Tian, Z., Liu, M., Zhang, Y. et al. Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. J Hematol Oncol 14, 75 (2021

What is CONCERT?
CONCERT NETWORK (Community ONcology CEllulaR Therapy Network)

NETWORK of community providers for establishing the infrastructure for cellular therapies defined as Bi-specific antibodies, CAR-T therapies and other immunotherapies directed towards T-cells or malignant cells.	AIMS AND OBJECTIVES	PRIMARY	Create an organizational structure and infrastructure.	Create standard operating procedures for proving cellular therapy in the community.
Create treatment protocols for the administration of cellular therapies and immunotherapies.	Create treatment protocols for managing adverse reactions associated with cellular therapies.	Provide advice to manufacturers on cellular therapies.	Provide up to date education on the indications, adverse reactions, safety, and management of patients requiring cellular therapies.	Provide a forumfor exchanging ideas amongst providers, payers and manufacturers on the use of cellular therapies.
Advocacy for cellular therapies particularly for patients treated in the community.	Understand and provide the tools to promote diversity and equity in the delivery of cellular therapies in community oncology.	SECONDARY	Understand the financial challenges for the provision of cellular therapies in community oncology.	Establish the infrastructure for promoting research studies across the NETWORK.
	Create a structure for sharing data and collecting data including for but not limited to publications.	Membership	Providers: Community Oncologists, Pharmacists and Advance Providers, administrators, payers and manufacturers' representatives.	

How to set up your cellular therapy/bispecific therapy program 101; "Just do it"

"Nothing to fear but fear itself" (Franklin Delano Roosevelt/FDR, 32nd POTUS)

Set up a check list:

- ✓ Create an organizational structure and infrastructure.
- ✓ Create standard operating procedures and treatment protocols.
- ✓ Hospitalization procedure for adverse reactions and notification of management teams; Emergency department, critical care, infectious diseases, hospitalist teams, nursing, pharmacy, neurology etc.
- ✓ Procedures and Management of AE's: CRS and grading of CRS, ICANS and grading of ICANS: Steroids, tocilizumab, vasopressors
- ✓ Drug availability for management of AE's; including but not limited to tocilizumab, steroids, and antibiotics.
- ✓ Setting up local management teams for AE management: Emergency department, critical care, infectious diseases, hospitalist teams, nursing, pharmacy, neurology etc.
- ✓ Infectious disease prophylaxis and management of immune deficiencies: antibiotics, antivirals, antifungals, immunoglobulin, and COVID-19 antibody prophylaxis.
- ✓ Training of clinic, hospital nursing staff and physicians: hematologists/oncologists/pharmacists/ED, ID, Critical care, Neurology consultants.

ASCO GUIDELINE FOR THE MANAGEMENT OF IMMUNE RELATED TOXICITIES AFTER CAR-T THERAPY

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

Bianca D. Santomasso, MD, PhD[1]; Loretta J. Nastoupil, MD[2]; Sherry Adkins, RN, MS[2]; Christina Lacchetti, MHSc[3]; Bryan J. Schneider, MD[4]; Milan Anadkat, MD[5]; Michael B. Atkins, MD[6]; Kelly J. Brassil, PhD, RN[2]; Jeffrey M. Caterino, MD, MPH[7]; Ian Chau, MD[8]; Marianne J. Davies, DNP[9]; Marc S. Ernstoff, MD[10]; Leslie Fecher, MD[4]; Pauline Funchain, MD[11]; Ishmael Jaiyesimi, DO, MS[12]; Jennifer S. Mammen, MD, PhD[13]; Jarushka Naidoo, MD[14]; Aung Naing, MD[2]; Tanyanika Phillips, MD[15]; Laura D. Porter, MD[16]; Cristina A. Reichner, MD[17]; Carole Seigel, MBA[18]; Jung-Min Song, MSN, RN, CNS[11]; Alexander Spira, MD, PhD[19]; Maria Suarez-Almazor, MD[2]; Umang Swami, MD[20]; John A. Thompson, MD[21]; Praveen Vikas, MD[22]; Yinghong Wang, MD[2]; Jeffrey S. Weber, MD, PhD[23]; Kathryn Bollin, MD[24]; and Monalisa Ghosh, MD[25]

Santomasso BD et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol. 2021 Dec 10;39(35):3978-3992. Epub 2021 Nov 1. Erratum in: J Clin Oncol. 2022 Mar 10;40(8):919. PMID: 34724386.

CONCERT NETWORK
Community ONcology CEllulaR Therapy Network

Management of Immune-Related Adverse Events in Patients with T-cell Directed Therapy

- T-Cell related therapies results in treatment–related toxicities, including cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome,, (ICANS), B-cell aplasia, cytopenias, and infections.

- Management of short-term toxicities:
- Supportive and pharmacologic interventions for those without adequate response.
- Management of patients with prolonged or severe cytokine release syndrome: includes treatment with tocilizumab with or without a corticosteroid.
- Patients with moderate to severe immune effector cell–associated neurotoxicity syndrome (ICANS) should be managed with corticosteroids and supportive care.

Management of Immune-Related Adverse Events in Patients Treated With Chimeric T-Cell Directed Therapy

- **CRS** is defined by CTCAE as a *"disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines".*
- CRS is caused by the release of cytokines from bystander immune and nonimmune cells.
- Variable onset and dependent on the therapy and patient population, with peaks at 2-7 days after infusion and delays of up to 3 weeks.
- Presenting symptoms may include fever, tachycardia, hypoxia, nausea, headache, rash, shortness of breath, mild or serious hypotension requiring vasopressors, respiratory failure, coagulopathy, and/or multiorgan system failure.

Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

WORK-UP FOR TOXICITES

ASCO 2021 GUIDELINES: WORK UP FOR MANAGEMENT OF IMMUNE EFFECTOR THERAPY

Workup or evaluation and supportive care recommendations (all grades):

- CBC, CMP, magnesium, phosphorus, CRP, LDH, uric acid, fibrinogen, PT/PTT, and ferritin
- Assess for infection with blood and urine cultures, and a chest radiograph if fever is present
- If patient is neutropenic, follow institutional neutropenic fever guidelines
- Patients who experience grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function.
- Perform cardiac monitoring in patients who experience at least G2 CRS, clinically significant arrhythmia, and additionally as clinically indicated
- Consider screening for CMV and EBV
- Consider chest or abdominal CT imaging, brain MRI, and/or lumbar puncture.

ASTCT Consensus Grading for Cytokine Release Syndrome

The definition of CRS used to develop the ASTCT consensus criteria is "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."

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 cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

MANAGEMENT OF CRS

Grading (on the basis of ASTCT consensus grading)[10]	Management
G1: Fever[a]: temperature ≥ 38°C not attributable to any other cause Hypotension: none Hypoxia: none	Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms May consider empiric broad-spectrum antibiotics if neutropenic. May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended In patients with persistent (> 3 days) or refractory fever, consider managing as per G2
G2: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: not requiring vasopressors *And/or* Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at ≤ 6 L/min) or blowby	Continue supportive care as per G1 and include IV fluid bolus and/or supplemental oxygen as needed Administer tocilizumab[42-44] 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total In patients with hypotension that persists after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to two doses and then reassess Manage per G3 if no improvement within 24 hours of starting tocilizumab

MANAGEMENT OF CRS

G3: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: requiring a vasopressor with or without vasopressin *And/or* Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Continue supportive care as per G2 and include vasopressors as needed Admit patient to ICU If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring Tocilizumab as per G2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve If refractory, manage as per G4
G4: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: requiring multiple vasopressors (excluding vasopressin) *And/or* Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Continue supportive care as per G3 plus mechanical ventilation as needed Administer tocilizumab as per G2 if maximum is not reached within 24-hour period Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to G1 If not improving, consider methylprednisolone 1,000 mg IV 2 times a day or alternate therapy[b]

MANAGEMENT OF ICANS

Workup or evaluation and supportive care recommendations (all grades):

- Routine neurologic evaluation including the ICE score for cognitive assessment and assessment of motor weakness conducted at least two times a day
- Continually reassess for improvement or deterioration and escalate or de-escalate treatment and monitoring accordingly
- Serial monitoring of laboratory tests including CRP, ferritin, CBC, CMP, fibrinogen, and PT/PTT
- Consider seizure prophylaxis for CAR T-cell products known to be associated with ICANS or in patients at higher risk of seizure, such as those with seizure history, CNS disease, concerning EEG findings, or neoplastic brain lesions[4,49,50]
- Initiate neurology consultation in patients with signs of neurotoxicity
- Aspiration precautions and elevated head of bed
- Neuroimaging of the brain (MRI with and without contrast or CT if MRI is not available or feasible) for ≥ G2 neurotoxicity. For persistent grade ≥ 3 neurotoxicity, consider repeat neuroimaging (MRI or CT) every 2-3 days
- Lumbar puncture for ≥ G3 neurotoxicity and may consider for G2
- EEG evaluation for unexplained altered mental status to assess seizure activity or for ≥ G2 neurotoxicity
- Monitor and correct severe hyponatremia

MANAGEMENT OF ICANS:
Immune Effector Cell Encephalopathy (ICE) Score

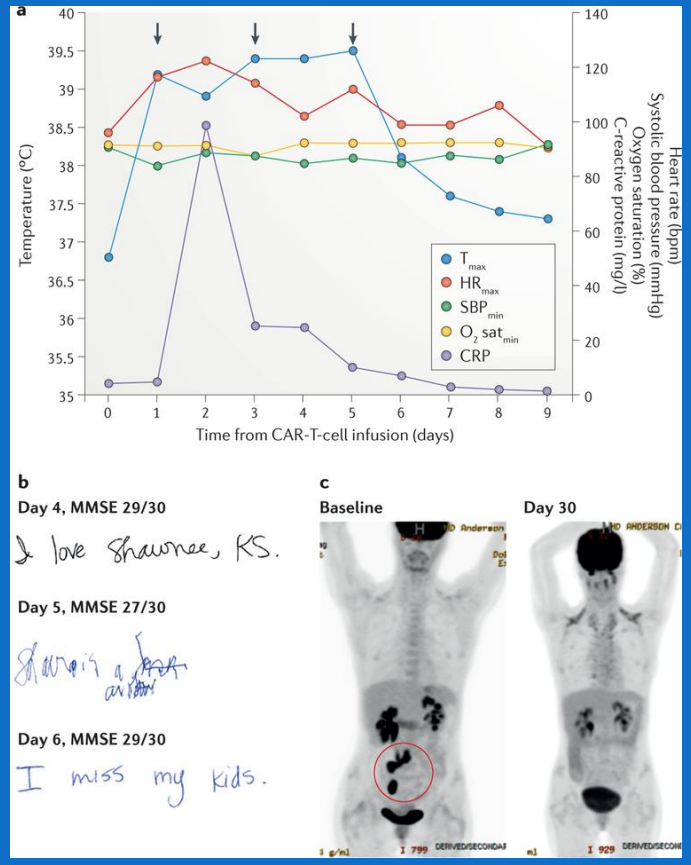
From: Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune Effector Cell Encephalopathy (ICE) Score
• *Orientation:* Orientation to year, month, city, hospital: 4 points
• *Naming:* Ability to name 3 objects (e.g., point to clock, pen, button): 3 points
• *Following commands:* Ability to follow simple commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue"): 1 point
• *Writing:* Ability to write a standard sentence (e.g., "our national bird is the bald eagle"): 1 point
• *Attention:* Ability to count backwards from 100 by 10: 1 point

Rees JH. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) 2022 Feb 7. In: Kröger N, Gribben J, Chabannon C, et al., editors. The EBMT/EHA CAR-T Cell Handbook [Internet]. Cham (CH): Springer; 2022. Table 27.1, [Immune Effector Cell Encephalopathy (ICE) Score]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK584157/table/ch27.Tab1/ doi: 10.1007/978-3-030-94353-0_27

MANAGEMENT OF ICANS:

Key clinical assessments for a representative patient with cytokine-release syndrome and chimeric antigen receptor (CAR)-T-cell-related encephalopathy syndrome after anti-CD19 CAR-T-cell therapy for refractory diffuse large-B-cell lymphoma



Neelapu SS et al. . Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.

MANAGEMENT OF ICANS

Grading (on the basis of ASTCT consensus grading)[10,a]	Management
G1: ICE score[b]: 7-9 with no depressed level of consciousness	No concurrent CRS Offer supportive care with IV hydration and aspiration precautions With concurrent CRS Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of three doses in a 24-hour period; maximum total of four doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose
G2: ICE score[b]: 3-6 *And/or* Mild somnolence awaking to voice	No concurrent CRS Offer supportive care as per G1 For high-risk products or patients, consider dexamethasone 10 mg IV × two doses (or equivalent) and reassess. Repeat every 6-12 hours if no improvement.[c] Rapidly taper steroids as clinically appropriate once symptoms improve to G1[d] With concurrent CRS Consider ICU transfer if ICANS associated with ≥ G2 CRS Administer tocilizumab as per G1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate[d]
G3: ICE score[b]: 0-2 *And/or* Depressed level of consciousness awakening only to tactile stimulus *And/or* Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention *And/or* Focal or local edema on neuroimaging	All G3 patients: Transfer patient to ICU No concurrent CRS Administer dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). With concurrent CRS Administer tocilizumab as per grade 1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate[d]
G4: ICE score[b]: 0 (patient is unarousable and unable to perform ICE) *And/or* Stupor or coma *And/or* Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between *And/or* Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad	All G4 patients: Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection No concurrent CRS Administer high-dose methylprednisolone IV 1,000 mg one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy[e] Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate[d] Status epilepticus to be treated as per institutional guidelines With concurrent CRS Administer tocilizumab as per grade 1 in addition to methylprednisolone 1,000 mg IV one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone IV two to three times a day or alternate therapy[e] Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate[d]

MANAGEMENT OF ICANS

Grading (on the basis of ASTCT consensus grading)[10,a]	Management
G1: ICE score[b]: 7-9 with no depressed level of consciousness	No concurrent CRS Offer supportive care with IV hydration and aspiration precautions With concurrent CRS Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of three doses in a 24-hour period; maximum total of four doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose
G2: ICE score[b]: 3-6 *And/or* Mild somnolence awaking to voice	No concurrent CRS Offer supportive care as per G1 For high-risk products or patients, consider dexamethasone 10 mg IV × two doses (or equivalent) and reassess. Repeat every 6-12 hours if no improvement.[c] Rapidly taper steroids as clinically appropriate once symptoms improve to G1[d] With concurrent CRS Consider ICU transfer if ICANS associated with ≥ G2 CRS Administer tocilizumab as per G1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate[d]

MANAGEMENT OF ICANS

G3: ICE score[b]: 0-2 *And/or* Depressed level of consciousness awakening only to tactile stimulus *And/or* Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention *And/or* Focal or local edema on neuroimaging	All G3 patients: Transfer patient to ICU No concurrent CRS Administer dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). With concurrent CRS Administer tocilizumab as per grade 1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate[d]
G4: ICE score[b]: 0 (patient is unarousable and unable to perform ICE) *And/or* Stupor or coma *And/or* Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between *And/or* Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad	All G4 patients: Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection No concurrent CRS Administer high-dose methylprednisolone IV 1,000 mg one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy[e] Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate[d] Status epilepticus to be treated as per institutional guidelines With concurrent CRS Administer tocilizumab as per grade 1 in addition to methylprednisolone 1,000 mg IV one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone IV two to three times a day or alternate therapy[e] Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate[d]

MANAGEMENT OF HLH

Workup or evaluation[55]: CBC with differential and coagulation studies (PT, aPTT, fibrinogen, and D-dimer) Liver function tests (ALT, AST, GGT, total bilirubin, albumin, and lactate dehydrogenase) Serum triglycerides (fasting) and serum ferritin Soluble IL-2 receptor alpha (sCD25 or sIL-2R) and/or CXCL9 The following testing should be performed in all patients, on the basis of the signs and symptoms of specific organ involvement and/or the degree of suspicion for the presence of HLH[55]: Cultures of blood, bone marrow, urine, and CSF, and viral titers and quantitative PCR testing for EBV, CMV, adenovirus, and other suspected viruses. Follow levels of any identified virus during treatment with the appropriate antiviral therapy Bone marrow aspirate and biopsy Electrocardiograph, chest radiography, and echocardiogram Lumbar puncture with CSF analysis Brain MRI scan, with and without contrast. Imaging of the CNS may show parameningeal infiltrations, subdural effusions, necrosis, and other abnormalities

Grading	Management[14,56,57]
All grades	Offer supportive care Use corticosteroids if the patient is deteriorating or unstable Although data are insufficient to recommend a transfusion threshold, replacement of fibrinogen should be considered in patients with a fibrinogen level below 150 mg/dL Manage G ≥ 3 organ toxicity with IL-6 antagonist plus corticosteroids If insufficient response after 48 hours, consider adding anakinra[11,58,59] Etoposide could be considered in severe, refractory cases, although there is a lack of data in this setting and concern for effect on lymphocytes.[16,60] Intrathecal cytarabine, with or without hydrocortisone, may also be considered for patients with HLH-associated neurotoxicity

MANAGEMENT OF CYTOPENIAS

Workup or evaluation:
CBC with differential, peripheral blood smear, reticulocyte count. If abnormalities are detected and further investigation is necessary for a diagnosis, proceed with bone marrow evaluation

Grading	Management
G1: anemia: LLN—10.0 g/dL; neutropenia: > 1,500 per mm^3; thrombocytopenia: > 75,000 per mm^3	Offer supportive care
G2: anemia: < 10.0-8.0 g/dL; neutropenia: > 1,000 per mm^3; thrombocytopenia: > 50,000 per mm^3	Offer supportive care and/or consider corticosteroids If improved to ≤ G1, taper steroids over 4-6 weeks
G3: anemia: < 8.0/dL; neutropenia: > 500 per mm^3; thrombocytopenia: > 25,000 per mm^3 G4: anemia: life-threatening; neutropenia: < 500 per mm^3; thrombocytopenia: < 25,000 per mm^3	Critical care support Use high-dose methylprednisolone Consider growth factor support for neutrophil recovery, per institutional guidelines

MANAGEMENT OF B-CELL APLASIA

Workup or evaluation: Full blood count	
Grading	**Management**[7,49,61,62]
All grades	Recommend influenza and COVID vaccination for patients and family members Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until the CD4 cell count is > 200 cells/μL Antifungal agents should be considered for high-risk patients including any patient receiving corticosteroids for management of CRS or ICANS
G1: asymptomatic, no intervention needed	Offer supportive care
G2: symptomatic (ie, recurrent infections), nonurgent intervention indicated	Consider treatment with IVIG replacement therapy at IgG levels < 400
G3: urgent intervention indicated G4: life-threatening	Consider treatment with IVIG replacement therapy at IgG levels < 400

MANAGEMENT OF DIC

Workup or evaluation: Full blood count to assess platelet number, fibrinogen, PT, PTT, and d-dimer. A test scoring system developed by the ISTH may be used to help determine if DIC is present.[63] The higher the score, the more likely it is that DIC is present	
Grading	**Management**
G1: —	Offer supportive care
G2: laboratory findings with no bleeding	Use IL-6 antagonist with or without corticosteroids If improved to ≤ G1, taper steroids over 4-6 weeks
G3: laboratory findings with bleeding G4: life-threatening; urgent intervention indicated	Critical care support Use IL-6 antagonist and methylprednisolone IV 1,000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days Consider replacement of fibrinogen in patients with a fibrinogen level below 150 mg/dL

MANAGEMENT OF INFECTIONS

Workup or evaluation: History and physical examination Full blood count Bacterial cultures and evaluation for other infection (fungal and viral)	
Grading	**Management**[7,49,61,62]
All grades	Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until the CD4 cell count is > 200 cells/μL Antifungal agents should be considered for high-risk patients G-CSF should be considered in patients after CRS with > 7 days of neutropenia
G1: mild infection only	Offer supportive care Empiric antimicrobials (antibiotics such as levofloxacin or ciprofloxacin, antifungals such as fluconazole or antivirals such as valacyclovir or acyclovir) should be considered upon onset of fever
G2: mild infection; oral intervention indicated (eg, antibiotic, antifungal, or antiviral)	Start course of oral antimicrobials
G3: severe infection; IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Start IV antimicrobials
G4: life-threatening consequences; urgent intervention indicated	Critical care support

Teclistamab in Relapsed or Refractory Multiple Myeloma

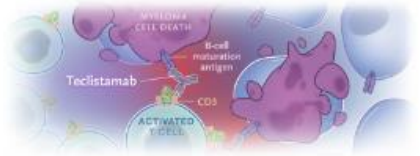
RESEARCH SUMMARY

Teclistamab in Relapsed or Refractory Multiple Myeloma

Moreau P et al. DOI: 10.1056/NEJMoa2203478

CLINICAL PROBLEM

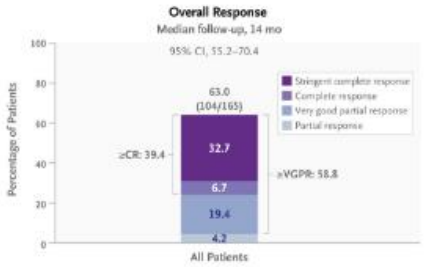
Effective therapies are lacking for relapsed or refractory multiple myeloma after standard treatment with immunomodulatory agents, proteasome inhibitors, and anti-CD38 antibodies. Teclistamab — a bispecific antibody that targets both CD3 expressed on the surface of T cells and B-cell maturation antigen expressed on myeloma cells — showed promising efficacy in a phase 1 dose-defining portion of the study.



CLINICAL TRIAL

Design: A phase 1–2, multinational study assessed the efficacy and safety of teclistamab in patients with relapsed or refractory multiple myeloma after at least three lines of therapy, including triple-class exposure to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

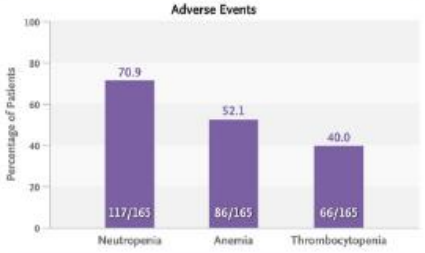
Intervention: 165 adult patients received once-weekly subcutaneous injections of teclistamab at a dose of 1.5 mg per kilogram of body weight after receiving step-up doses of 0.06 mg and 0.3 mg per kilogram. The primary end point was overall response, which was defined as partial response or better according to International Myeloma Working Group criteria.



RESULTS

Efficacy: During a median follow-up period of 14 months, responses occurred in nearly two thirds of the patients, and complete responses in more than one third, despite extensive previous treatment. Responses were durable and deepened over time.

Safety: Adverse events occurred in all the patients, most of whom had a grade 3 or 4 event. Cytokine release syndrome (mostly low-grade), neutropenia, anemia, and thrombocytopenia were the most common adverse events, and infections were frequent. More than half the patients skipped a dose because of adverse events.



LIMITATION

- Comparison of teclistamab against other available therapies for relapsed or refractory multiple myeloma is limited to cross-trial comparisons.

CONCLUSIONS

In patients with triple-class–exposed relapsed or refractory multiple myeloma, once-weekly subcutaneous teclistamab induced a high rate of lasting response.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

TECVAYLI can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions *[see Adverse Reactions (6.1)]*.

In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days.

Table 2. Adverse Events in 165 Patients (Safety Population).*

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)