La selezione del paziente CAR-T e l'importanza della rete.

B Bruno

CD19 and BCMA Targeted CAR Therapies Approved in the United States

Disease	CAR T therapy Approved	Date of Approval	Target	Costimulatory Domain	Pivotal Trial
Large B cell Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)** **Lisocabtagene maraleucel (Liso-cel)**	Oct 2017 May 2018 Feb 2021	CD19 CD19 CD19	CD28-CD3zeta 41BB-CD3zeta 41BB-CD3zeta	ZUMA-1[1,2] JULIET[3] TRANSCEND[4]
Mantle Cell Lymphoma	**Brexucabtagene autoleucel (Brexu-cel)**	July 2020	CD19	CD28-CD3zeta	ZUMA-2[5]
Follicular Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)**	Mar 2021 May 2022	CD19 CD19	CD28-CD3zeta 41BB-CD3zeta	ZUMA-5[6] ELARA[11]
Multiple Myeloma	**Idecabtagene vicleucel (Ide-cel)** **Ciltacabtagene autoleucel (Cilta-cel)**	Mar 2021 Feb 2022	BCMA BCMA	41BB-CD3zeta 41BB-CD3zeta	KarMMa[7] CARTITUDE-1[10]
Pediatric ALL	**Tisagenlecleucel (Tisa-cel)**	Aug 2017	CD19	41BB-CD3zeta	ELIANA[8]
Adult ALL	**Brexucabtagene autoleucel (Brexu-cel)**	Oct 2021	CD19	CD28-CD3zeta	ZUMA-3[9]

[1] Neelapu et al. NEJM 2017 [2]Locke et al. Lancet Oncol 2019 [3] Schuster et al. NEJM 2019 [4] Abramson et al. Lancet 2020 [5] Wang et al. NEJM 2020
[6] Jacobson et al. ASH 2020 [7] Munshi et al NEJM 2021 [8] Maude et al NEJM 2018
[9] Shah et al Lancet 2021 [10] Berdeja et al Lancet 2021 [11] Fowler et al Nat Med 2022

EMA Approvals

Disease	CAR T therapy Approved	Date of Approval	Target	Co-Stimulatory Domain	Pivotal Trial
Large B cell Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)**	Aug 2018 Aug 2018	CD19 CD19	CD28-CD3zeta 41BB-CD3zeta	ZUMA-1[1,2] JULIET[3]
Pediatric ALL	**Tisagenlecleucel (Tisa-cel)**	Aug 2018	CD19	41BB-CD3zeta	ELIANA[5]
Follicular Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)**	Jun 2022 May 2022	CD19 CD19	CD28-CD3zeta 41BB-CD3zeta	ZUMA-5[4] ELARA[6]

[1] Neelapu et al. NEJM 2017 [2]Locke et al. Lancet Oncol 2019 [3] Schuster et al. NEJM 2019 [4] Jacobson et al. ASH 2020 [5] Maude et al NEJM 2018 [6] Fowler et al Nat Med 2022

Patient Assessment for CAR T Therapy: Factors Considered in Initial Studies

- Each institution can develop their own specific guidelines based on experience within framework of FDA label

Factors to consider when selecting patients for CAR T therapy:

1. Age
2. Organ function
3. ECOG PS
4. Underlying neurological disorders, including seizures
5. Active infections
6. CNS disease
7. Concomitant medications/comorbidities, prior allo-HSCT

CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status.

Practice Changes Based on Post-Marketing Data

Post-marketing data has shown a shift toward a more inclusive approach in the following areas:

1. Biologic age/frailty/ECOG PS rather than chronologic age
2. More latitude in organ function, especially in GFR
3. Patients with aggressive disease requiring bridging therapy are now considered eligible
4. Patients with active CNS disease have been treated in case reports
5. Prior and currently controlled hepatitis and HIV are no longer absolute contraindications
6. Patients post-allogeneic stem cell transplant, without active GvHD, have been treated with CARs
7. Availability of previously collected autologous cells should be explored for pts with poor marrow function

CAR, chimeric antigen receptor; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; GvHD, graft versus host disease; HIV, human immunodeficiency virus.

Efficacy in real-world studies (22000)

	LBCL	ALL	MM
ORR	55%-82%	NA	32%-83%
CR	32%-64%	86% (95% CI 80.6-89.7)	34%-35%
12-month PFS	32%-45%	NA	NA
12-month OS	54%-64%	NA	56%

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

They surveyed 1 CAR-T expert (director of MM and/or CAR-T program) each from 20 centers (selected for adequate geographic representation of the highest-volume MM CAR-T therapy centers across the US

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

The first section assessed current use and prioritization of ethical principles for slot allocation, and the second section addressed organization and the process of patient selection.

The median year of the earliest CAR-T infusion (SOC/trial) was 2017 (range, 2010 to 2019).

In 2021, 13/17 centers treated more than 50 patients with MM (SOC/trial) (All centers reported no major decrease in CAR-T practice volume in the previous year despite the COVID-19 pandemic)

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

A median of **1 ide-cel slot was allocated per month** per center,

and 15 centers were allocated 2 slots per month (range, 0 to 4/month/center).

However, the median number of patients per center on the waitlist since ide-cel approval was 20 per month (range, 5 to 100).

patients remained on the waitlist for a median of 6 months prior to leukapheresis (range, 2 to 8).

results reported across 14 centers showed that **approximately 25% of patients received a leukapheresis slot for commercial CAR-T therapy, 25% enrolled on another non-CAR-T clinical trial, 25% enrolled on a CAR-T clinical trials, and approximately 25% died or enrolled in hospice**

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

Criterium	Numbers of Centers
availability of alternative therapy options	14
patients more likely to successfully undergo leukapheresis	13
receive CAR-T therapy after leukaphe-resis	13
time spent on the waitlist among their prioritization criteria	12
high disease burden	11

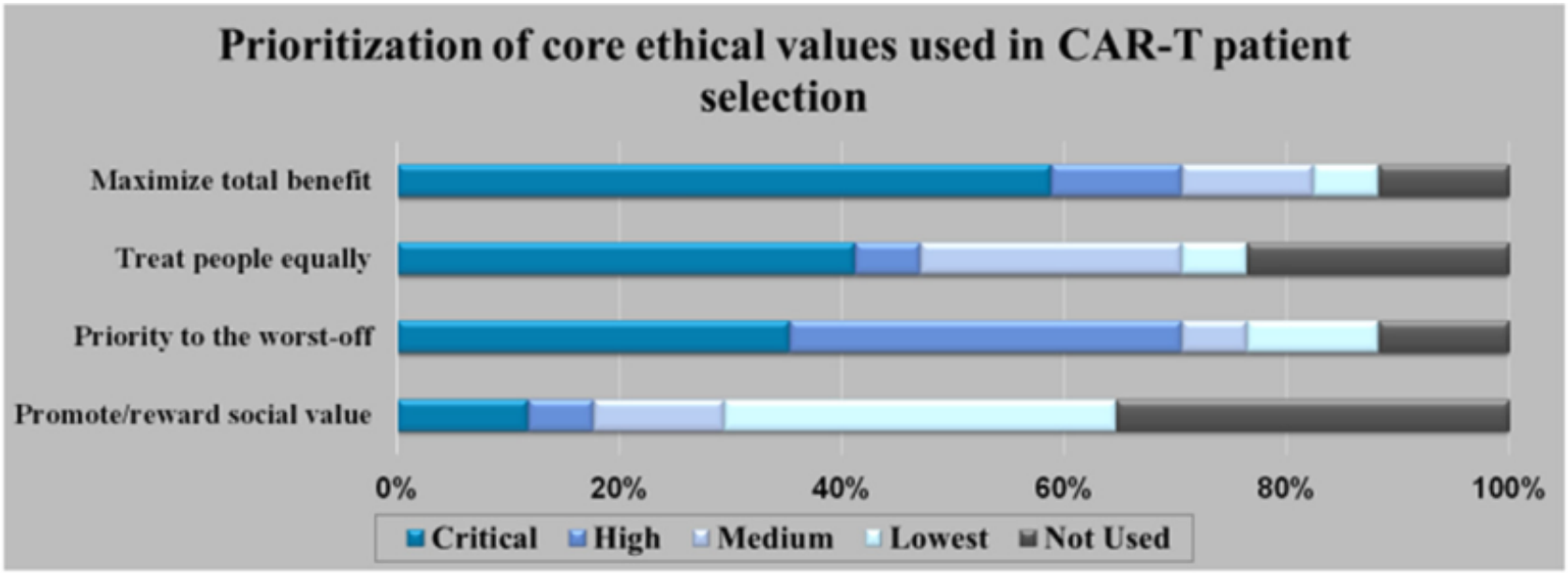
Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

Criterion	Numbers of Centers
more likely to achieve clinical response	5
higher HCT-CI	5
social value (young patient with family)	3
using a lottery system	1
selecting 1 patient per CAR-T clinician on a rotating basis	1

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience



The simple ethical principles of CAR-T slot allocation that embody the core values. The bar graph shows prioritization of the core ethical values used in patient selection for CAR-T therapy from highest to lowest as a percentage of total survey respondents.

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

Core Ethical Value	Numbers of Centers
Maximizing the total benefit	10
treating people equally	7
giving priority to the worst off	6
promoting social value	2

Kourelis et al. / TCT 00 (2023) 1-4, in press

Principles for allocation of scarce medical interventions

	Principles included	Advantages	Objections
UNOS points systems for organ allocation in the USA	First-come, first-served; sickest-first; prognosis	Can combine all possible principles; flexible	Includes least justifiable principles: first-come, first-served and sickest-first; low priority given to prognosis; vulnerable to bias and manipulation, such as being listed on multiple transplantation lists and misrepresentation of health status; allows multiple organ transplants, thus saving fewer lives
QALY allocation	Prognosis; excludes save the most lives	Maximises future benefits; considers quality of life; used in many existing, quantitatively sophisticated frameworks	Outcome measure disadvantages disabled people; incorrect conception of equality by focusing on equality of QALYs rather than equality of persons; does not incorporate many relevant principles
DALY allocation	Prognosis; instrumental value; excludes save the most lives	Maximises future benefits; includes instrumental value, saving people whose productivity is key to a flourishing society	Outcome measure disadvantages disabled people; age considered as modifying value of individual life-years, rather than from standpoint of distributive justice; definition of instrumental value is too focused on economic worth, and could justify bias towards heads of household and other "traditional" social positions; does not incorporate many relevant principles
Complete lives system	Youngest-first; prognosis; save the most lives; lottery; instrumental value, but only in public health emergency	Matches intuition that death of adolescents is worse than that of infants or elderly; everyone has an interest in living through all life stages; incorporates the largest number of relevant principles; resistant to corruption	Reduced chances for persons who have lived many years; life-years are not a relevant health care outcome; unable to deal with international differences in life expectancy; need lexical priority rather than balancing; complete lives system is not appropriate for general distribution of health care resources

UNOS=United Network for Organ Sharing. QALY=quality-adjusted life-years. DALY=disability-adjusted life-years.

Table 2: **Four multiprinciple systems**

Persad G. Lancet Vol. 373 Dec 2013

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

cilta-cel was approved shortly after completion of the initial survey

in October 2022 centers were asked how many slots per month they had received for cilta-cel and how patients were selected for ciltacel over ide-cel.

(15/17 responded) The median number of **monthly cilta-cel slots was 2 (range, 1 to 4).**

All centers identified physician and patient preference as the most common factor influencing the decision to prescribe one product over the other.

Five centers reported that longer manufacturing times for cilta-cel also influenced their decision regarding which product to prescribe according to the clinical scenario, but no center reported the use of formal criteria for patient allocation to each product.

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

"*This makes it even harder when I have patients dying off our list that we couldn't get this therapy to in time.*"

"*Some patients are delaying or refusing other treatment options including good clinical trials because of the focus on wanting CAR-T therapy and concern that they may become ineligible for future CAR-T treatment.*"

"*Commercial CAR-T has become the last resort.*"

"*.. .very difficult to justify who gets the 'golden ticket' and who does not This is affecting our mental health for the those of us taking care of these patients.*"

Kourelis et al. / TCT 00 (2023) 1-4, in press

EBMT

www.nature.com/bmt

CORRESPONDENCE

Check for updates

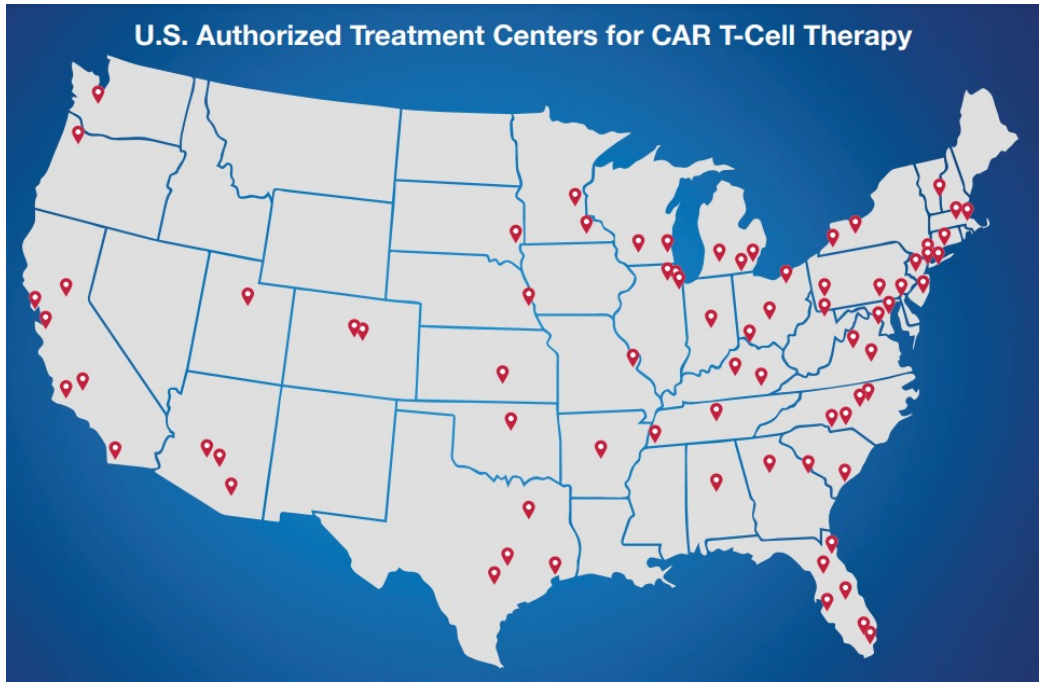
Clinical outcome of patients with relapsed refractory multiple myeloma listed for BCMA directed commercial CAR-T therapy

Al Hadidi S. et al. / Bone Marrow Transplant. 2022


DEMAND
SUPPLY


DEMAND
SUPPLY

Locations of CAR T Centers



Alabama
- UAB Medicine

Arizona
- Banner Gateway Medical Center BMDACC SCTCT program
- Banner University Medical Center/HCTT Program
- Honor Health Cancer Transplant Institute
- Mayo Clinic Arizona

Arkansas
- University of Arkansas for Medical Sciences

California
- Cedars-Sinai
- City of Hope
- Stanford Health Care
- UC Davis Health
- UC San Diego Health
- UCLA Health
- UCSF Helen Diller Family Comprehensive Cancer Center
- USC Norris Comprehensive Cancer Center

Colorado
- Colorado Blood Cancer Institute in partnership with Sarah Cannon Cancer Institute at Presbyterian/St. Luke's Medical Center
- UC Health University of Colorado Cancer Center

Connecticut
- Smilow Cancer Hospital/Yale Cancer Center

Delaware
- ChristianaCare Helen F. Graham Cancer Center and Research Institute

Florida
- AdventHealth Cancer Institute
- Mayo Clinic Florida
- Memorial Hospital West
- Moffitt Cancer Center
- Sylvester Comprehensive Cancer Center
- UF Health

Georgia
- Augusta University Health
- Northside Hospital Cancer Institute
- Winship Cancer Institute of Emory University

Illinois
- Advocate Health Care
- Cancer Treatment Centers of America® Chicago
- Loyola Medicine
- Northwestern Medicine Robert H. Lurie Comprehensive Cancer Center of Northwestern University
- Rush University System for Health
- UI Health
- University of Chicago Medicine

Indiana
- Franciscan Health Cancer Center - Indiana Bone & Marrow Transplant Program
- Indiana University Health

Iowa
- University of Iowa Health Care

Kansas
- Ascension Via Christi
- The University of Kansas Cancer Center

Kentucky
- Norton Cancer Institute
- University of Kentucky Markey Cancer Center

Maryland
- The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital
- University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center

Massachusetts
- Beth Israel Deaconess Medical Center
- Dana-Farber/Brigham and Women's Cancer Center
- Massachusetts General Hospital Cancer Center
- UMass Memorial Medical Center

Michigan
- Barbara Ann Karmanos Cancer Institute
- Henry Ford Cancer Institute
- Spectrum Health
- University of Michigan Comprehensive Cancer Center

Minnesota
- Mayo Clinic
- M Health/University of Minnesota

Missouri
- Siteman Cancer Center
- SSM Health Saint Louis University Hospital

Nebraska
- Nebraska Medicine

New Hampshire
- Dartmouth Hitchcock Medical Center

New Jersey
- Hackensack University Medical Center - John Theurer Cancer Center
- Rutgers Cancer Institute of New Jersey/ Robert Wood Johnson University Hospital

New York
- Memorial Sloan Kettering Cancer Center
- Montefiore Medical Center
- NewYork-Presbyterian/Columbia University Medical Center
- NewYork-Presbyterian/Weill Cornell Medical Center
- North Shore University Hospital
- Perlmutter Cancer Center
- Roswell Park Comprehensive Cancer Center
- The Tisch Cancer Institute at Mount Sinai
- UR Medicine Wilmot Cancer Institute
- Westchester Medical Center

North Carolina
- Atrium Health Wake Forest Baptist
- Duke Cancer Institute
- Levine Cancer Institute
- Novant Health Presbyterian Medical Center
- UNC Cancer Care

Ohio
- Cleveland Clinic Cancer Center
- The Jewish Hospital Blood Cancer Center
- The Ohio State University Comprehensive Cancer Center
- UC Health University of Cincinnati Medical Center
- University Hospitals of Cleveland

Oklahoma
- OU Medicine

Oregon
- Oregon Health and Science University Hospital

Pennsylvania
- Allegheny Health Network Cancer Institute
- Fox Chase - Temple University Hospital Bone Marrow Transplant Program
- Penn Medicine Abramson Cancer Center
- Penn State Cancer Institute
- Sidney Kimmel Cancer Center - Jefferson Health
- UPMC Hillman Cancer Center

South Carolina
- MUSC Health

South Dakota
- Avera Mckennan Transplant Institute

Tennessee
- Baptist Memorial Hospital
- Center for Blood Cancer at Tri-Star Centennial Hospital
- Methodist Healthcare
- Tennessee Valley Healthcare System Veteran Affairs
- Vanderbilt University Medical Center

Texas
- Baylor University Medical Center/Texas Oncology - Baylor Charles A. Sammons Cancer Center
- Houston Methodist
- Medical City
- St. David's Healthcare
- The University of Texas MD Anderson Cancer Center
- Texas Transplant Institute, Methodist Hospital
- UT Southwestern Simmons Comprehensive Cancer Center

Utah
- Huntsman Cancer Institute at the University of Utah
- Intermountain LDS Hospital

Virginia
- University of Virginia
- VCU Massey Cancer Center

Washington
- Seattle Cancer Care Alliance
- Swedish Health Services

Washington, DC
- MedStar Georgetown University Hospital

West Virginia
- WVU Medicine Cancer Institute

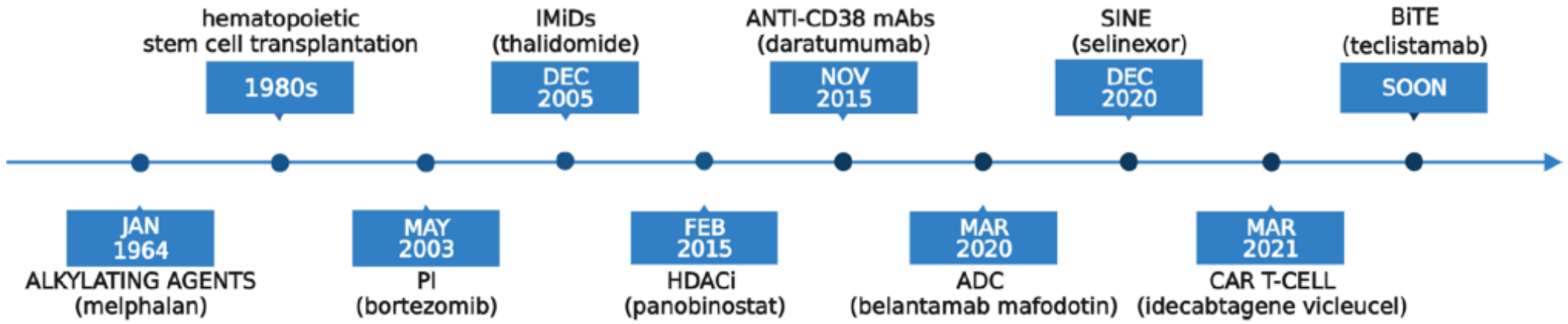
Wisconsin
- Advocate Aurora
- Froedtert & The Medical College of Wisconsin Cancer Network
- University of Wisconsin Hospital and Clinics - Carbone Cancer Center

Ideas for Optimized Program Growth

1. Create commercial and research workflows to enhance capacity for CAR T support
    a. Leverage existing resources and communication pathways
        - Balance other institutional programs (for example, BMT or disease-specific practices)
        - Shared personnel resources may include clinicians
        - Physical plant resources may include apheresis center, cell processing lab, infusion beds
2. Recognize when new cell therapies and indications require new stakeholder engagement (for example, solid tumor oncologists and surgeons)
3. Develop and advance a coherent clinical and research portfolio to optimize patient enrollment and focus on clinical strengths
4. Allow for collaborative projects between sponsors and institutional researchers

BMT, bone marrow transplantation.

Patient selection for CAR T or BiTE therapy in multiple myeloma: Which treatment for each patient?



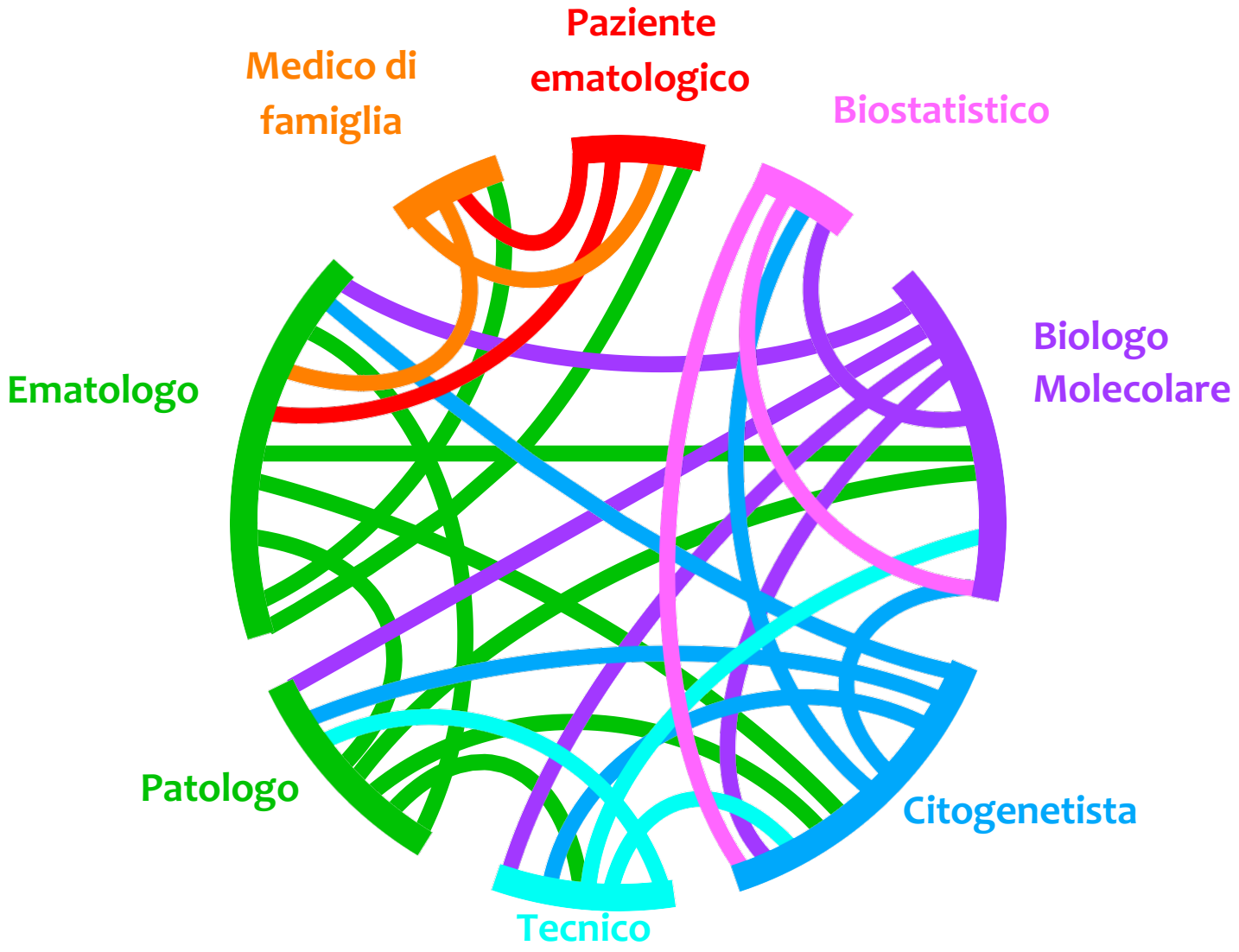
Kegyes D, et al. J Hematol Oncol. 2022

Patient selection for CAR T or BiTE therapy in multiple myeloma: Which treatment for each patient?

	Car	BiTE
Advantages	Strong and rapid anti-tumor effects	Off-the-shelf available
	Efficient in different subgroups	Good anti-tumor control
	Autologous or allogeneic products	Dosing can be stopped in case of adverse effects
Disadvantages	Delay in production	Continuous treatment
	Side effects	Costs + +
	costs + + +	

Kegyes D, et al. J Hematol Oncol. 2022

Interazioni tra diverse professionalità



Progettualità della Rete

- **Attivazione commissioni e gruppi multidisciplinari**

- **Razionalizzazione delle risorse**

- **Raccolta di informazioni epidemiologiche e flussi**

Conclusions

Network !!

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Laboratory Staff
Transplant Unit
Nurses
Data Managing Staff
Statisticians

European Myeloma Network (EMN)
Prof. Mario Boccadoro

Thank you for your attention!!

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