# International Myeloma Working Group Recommendations: Sequencing Immunotherapy in Multiple Myeloma

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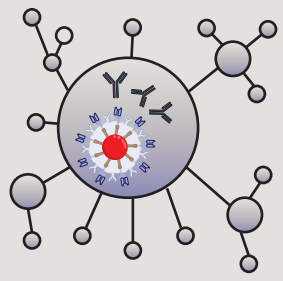


As T-cell redirecting therapy (TCRT) options (CAR T-cells and bispecific TCEs) expand and global access varies, new sequencing combinations will continue to emerge. Understanding how each TCRT influences tumor biology and the immune microenvironment is essential to guide optimal sequencing and anticipate effects on subsequent therapies.

To address this need, the IMWG Immunotherapy Committee convened a panel of 30 experts in March 2024 to review patient- and disease-related factors affecting efficacy and safety of immunotherapy, summarize existing information on sequencing therapy, and provide a series of 9 core recommendations.

## AUTHORS

**Luciano J. Costa**
*University of Alabama, AL, USA*

**Hira Mian**
*McMaster University, ON, CA*

**Susan Bal**
*University of Alabama, AL, USA*

**Maung M. Htut**
*City of Hope Cancer Center, CA, USA*

**Cesar Rodriguez**
*The Tisch Cancer Institute, Mount Sinai School of Medicine, NY, USA*

**Matthew J. Frigault**
*Massachusetts General Hospital Cancer Center and Harvard Medical School, MA, USA*

**Niels W.C.J. van de Donk**
*Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, NL*

**Benjamin Puliafito**
*Massachusetts General Hospital Cancer Center and Harvard Medical School, MA, USA*

**Rakesh Popat**
*NIHR UCLH Clinical Research Facility, University College London Hospitals NHS Foundation Trust, London, UK*

**P. Joy Ho**
*Royal Prince Alfred Hospital and University of Sydney, NSW, AU*

**Prashant Kapoor**
*Mayo Clinic, MN, USA*

**Fredrik Schjesvold**
*Oslo University Hospital, Oslo, NO*

**Hermann Einsele**
*University Hospital, Wurzburg, DE*

**Joseph Mikhael**
*City of Hope Cancer Center, AZ, USA; International Myeloma Foundation, CA, USA*

**S. Vincent Rajkumar**
*Mayo Clinic, MN, USA*

**Thomas G. Martin**
*UCSF Helen Diller Family Comprehensive Cancer Center, CA, USA*

**Rahul Banerjee**
*University of Washington, Fred Hutchinson Cancer Center, WA, USA*

**Katja Weisel**
*University Medical Center Hamburg-Eppendorf, Hamburg, DE*

**Benjamin A. Derman**
*University of Chicago Medical Center, IL, USA*

**Chandramouli Nagarian**
*Singapore General Hospital, SG*

**Joshua Richter**
*The Tisch Cancer Institute, Mount Sinai School of Medicine, NY, USA*

**Jing C. Ye**
*MD Anderson Cancer Center, University of Texas, TX, USA*

**Peter M. Voorhees**
*Levine Cancer Institute, Atrium Health Wake Forest Baptist, NC, USA*

**Nizar Bahlis**
*Arnie Charbonneau Cancer Research Institute, University of Calgary, AB, CA*

**Wee Joo Chng**
*National University Cancer Institute, National University Health System, and National University of Singapore, SG*

**Gurbakhash Kaur**
*Tisch Cancer Institute, Mount Sinai School of Medicine, NY, USA*

**Juan Du**
*Shanghai Changzheng Hospital, Navy Medical University, Shanghai, CN*

**Jesus Berdeja**
*Greco-Hainsworth Centers for Research, Tennessee Oncology, TN, USA*

**Adam D. Cohen**
*University of Pennsylvania, PA, USA*

**Yelak Biru**
*International Myeloma Foundation, CA, USA*

**Yi Lin**
*Mayo Clinic, MN, USA*

**Ajai Chari**
*UCSF Helen Diller Family Comprehensive Cancer Center, CA, USA*

## TREATMENT PHASES IN CAR T-CELL THERAPY

**APHERESIS** → **CAR T-CELL INFUSION**

### HOLDING THERAPY

- Definition - Before apheresis
- Goal - Control disease without jeopardizing feasibility of CAR T-cell therapy
- Not standardized
- Often used PIs, IMiDs, anti-CD38 mAbs, dexamethasone
- Avoid - Alkylators, bendamustine, polychemotherapy, TCEs

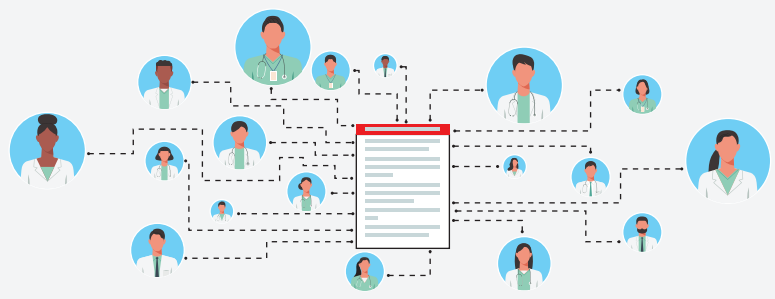
### BRIDGING THERAPY

- Definition - After apheresis, waiting for CAR T-cell therapy
- Goal - Avoid clinical deterioration, reduce disease burden
- Not standardized
- Often used - PIs, IMiDs, anti-CD38 mAbs, dexamethasone
- Acceptable - Alkylators, bendamustine, polychemotherapy, TCEs

### LYMPHODEPLETION CHEMOTHERAPY

- Standardized
- Timed with CAR T-cell infusion
- Goal - Induce extreme lymphopenia and corresponding cytokine milieu
- Fludarabine and cyclophosphamide
- Limited data for bendamustine
- Dose adjustment/drug choice influenced by renal function

## CONSENSUS RECOMMENDATIONS



**1** There are no concerns about proceeding with TCRT in patients receiving a PI, IMiD, (naked) monoclonal antibody, a corticosteroid or any combination of these classes as most recent line of therapy.

- When used as "holding therapy" before T-cell collection, the IMWG Immunotherapy Committee recommends a 2-week washout between last dose of conventional agent and apheresis of mononuclear cells for CAR T-cell manufacturing or before the first dose of TCE

**2** If feasible, avoid collection of mononuclear cells for CAR T-cell manufacturing in patients receive a TCE.

- If such sequence is the best option for the patient, aim for a minimum of 4-week washout between the last dose of the TCE and apheresis collection
- Alternatively, if possible, consider T-cell collection prior to TCE initiation

**3** Avoid high-dose alkylators and bendamustine in patients for whom next therapy is likely to be CAR T-cell and/or a TCE.

**4** Strongly consider bridging therapy after apheresis for CAR T-cell manufacturing in patients with high disease burden or at risk of developing morbidity from MM during the 4–6 weeks of manufacturing.

- The ideal bridging therapy will contain agent(s) without known resistance from the patient's myeloma, be short, with low risk of infection or prolonged cytopenias

**5** Assuming equal access, in patients who are reasonable candidates to both BCMA-targeted ADC and BCMA-targeted TCRT,the IMWG Immunotherapy Committee recommends pursuing TCRT first given its higher activity and lower efficacy of TCRT after prior BCMA-targeted ADC.

**6** Assuming equal access, in patients who are reasonable candidates to both BMCA CAR T-cell and TCE, the IMWG Immunotherapy Committee recommends pursuing CAR T-cell therapy.

- This recommendation considers more robust data supporting activity of TCEs upon progression after CAR T-cell therapy and also the extended treatment-free interval post-CAR-T that is typically associated with more salvage options at the time of progression

**7** For patients with rapidly progressing disease and unlikely to transit through apheresis and bridging without disease-related morbidity, proceed with TCE due to faster access.

**8** Both BCMA-targeted and GPRC5D-targeted immunotherapy are safe and active in patients with prior BCMA-targeted CAR T-cell therapy. Post BCMA-targeted CAR T-cell therapy, responses to BCMA-targeting therapies are likely less frequent and durable than in patients not previously treated with BCMA-targeted CAR T-cell therapy.

**9** There are limited data on the feasibility and efficacy of BCMA-targeted therapy of a different modality upon progression on BCMA-targeted TCE at the approved dose intensities until progression.

- Outcomes after lower-dose intensity or fixed duration of therapy are unknown
- The IMWG Immunotherapy Committee recommends therapy with different mechanism of action or immunotherapy targeting a different antigen for patients progressing while receiving or shortly after receiving BCMA-targeting TCE

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; GPRC5D, G protein–coupled receptor, class C, group 5, member D; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; TCE, T-cell engager; TCRT, T-cell redirecting therapy.