Present Use & Future Directions of Bispecific Molecules in Relapsed or Refractory Multiple Myeloma

A presentation for HealthTrust Members
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Learning Objectives

1. Recall the current landscape of bispecific molecule treatment of relapsed or refractory multiple myeloma
2. Identify the differences between current FDA approved bispecific antibodies and bispecific T-cell engagers
3. Recognize treatment strategies currently being utilized in bispecific molecule clinical trials

Relapsed/Refractory Multiple Myeloma

An Introduction

Multiple Myeloma - Background

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure

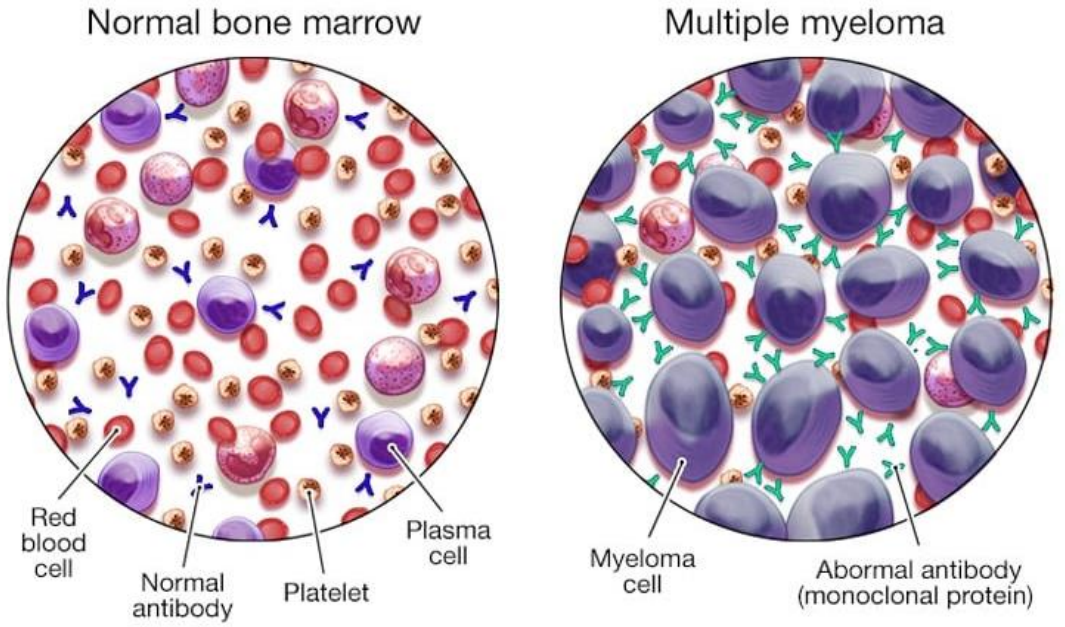
Clinical features

Calcium (hypercalcemia)
- Bone breakdown

Renal failure
- Light chain cast nephropathy
- Hypercalcemia

Anemia
- Bone marrow replacement
- Erythropoietin deficiency (secondary to kidney damage)

Bone lesions
- Increased osteoclast activity



www.mayoclinic.org/medical-professionals/cancer/news/msmart-a-clear-and-simple-guide-for-treating-patients-with-multiple-myeloma/mqc-20506750)

NCCN Multiple Myeloma Treatment Guidelines
Laubach, UpToDate

Multiple Myeloma - Background

Incidence

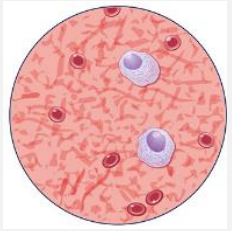
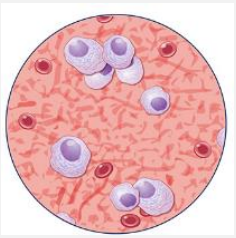
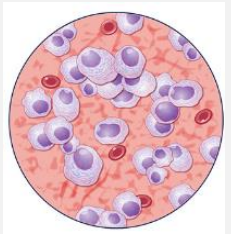
- Most frequently diagnosed among people aged 65 to 74 years
- In the United States in 2024 there will be about 35,780 new cases diagnosed and about 12,540 deaths
- 5-year survival rate is ~50%, lower in high-risk patients (frail elderly patients)
- Not considered curable, relapse is inevitable

Risk factors

- Age
- Gender
- Race
- Family history
- Obesity
- Diagnoses of other plasma cell disease

Multiple Myeloma - Background

Subtypes

	MGUS	Smoldering (Asymptomatic)	Active (Symptomatic)	Previously Treated (Relapsed/Refractory)
				
Description	No symptoms, fewer M proteins in blood "Precancerous state"	Stage of disease with no symptoms and no related organ or tissue impairment "Precursor state"	Patient has symptoms of multiple myeloma	Patient failed previous treatments/relapse of disease despite symptoms
Treatment	Historically managed with monitoring	Historically managed with close observation	Immunomodulatory drugs, proteasome inhibitors, and mABs Can be followed by autologous hematopoietic cell transplant	Depends prior treatment and duration of response Autologous HCT (if not previously received) or clinical trial

www.mskcc.org/cancer-care/types/multiple-myeloma

MGUS = monoclonal gammopathy of undetermined significance; **mABs** = monoclonal antibodies; **HCT** = hematopoietic cell transplantation

Introduction To Multiple Myeloma Treatment

	Mechanism of Action	Examples
Alkylating Agents	Targets highly proliferating malignant plasma cells, intercalates DNA causing cell death	Melphalan Cyclophosphamide
Proteasome Inhibitors	Reversibly inhibits chymotrypsin-like activity at 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis	Bortezomib, carfilzomib , ixazomib
Immunomodulatory Drugs	Inhibits secretion of proinflammatory cytokines, enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells, and induces cell cycle arrest and cell death	Thalidomide, lenalidomide, pomalidomide
Monoclonal Antibodies	Bind to antigens on malignant plasma cells (CD38, SLAMF7) inducing plasma cell death by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis	Daratumumab, isatuximab, elotuzumab

 Pinto et al. Multiple Myeloma: Available Therapies and Causes of Drug Resistance

NCCN Guideline-Recommended Therapy

Therapy for Previously Treated Multiple Myeloma

Relapsed/Refractory Disease After 1-3 Prior Therapies

Bortezomib-Refractory	Lenalidomide-Refractory
Carfilzomib/lenalidomide/dexamethasone Daratumumab/carfilzomib/dexamethasone Daratumumab/lenalidomide/dexamethasone Isatuximab-irfc/carfilzomib/dexamethasone Carfilzomib/pomalidomide/dexamethasone	Daratumumab/bortezomib/dexamethasone Daratumumab/carfilzomib/dexamethasone Isatuximab-irfc/carfilzomib/dexamethasone Pomalidomide/bortezomib/dexamethasone Selinexor/bortezomib/dexamethasone Carfilzomib/pomalidomide/dexamethasone Elotuzumab/pomalidomide/dexamethasone
After one prior therapy including lenalidomide and a PI Daratumumab/pomalidomide/dexamethasone	
After two prior therapies including lenalidomide and a PI Isatuximab-irfc/pomalidomide/dexamethasone	
	After two prior therapies including an IMiD and PI with disease progression w/in 60 days Ixazomib/pomalidomide/dexamethasone

PI = proteasome inhibitor; **IMiD** = immunomodulatory drug

NCCN Guideline-Recommended Therapy

Therapy for Previously Treated Multiple Myeloma

Relapsed/Refractory Disease After 4 Prior Therapies

Previous therapies must include an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory drug

CAR T-cell Therapy

Ciltacabtagene autoleucel (Carvykti)

Idecabtagene vicleucel (Abecma)

Bispecific Molecules

Elranatamab-bcmm (Elrexfio)

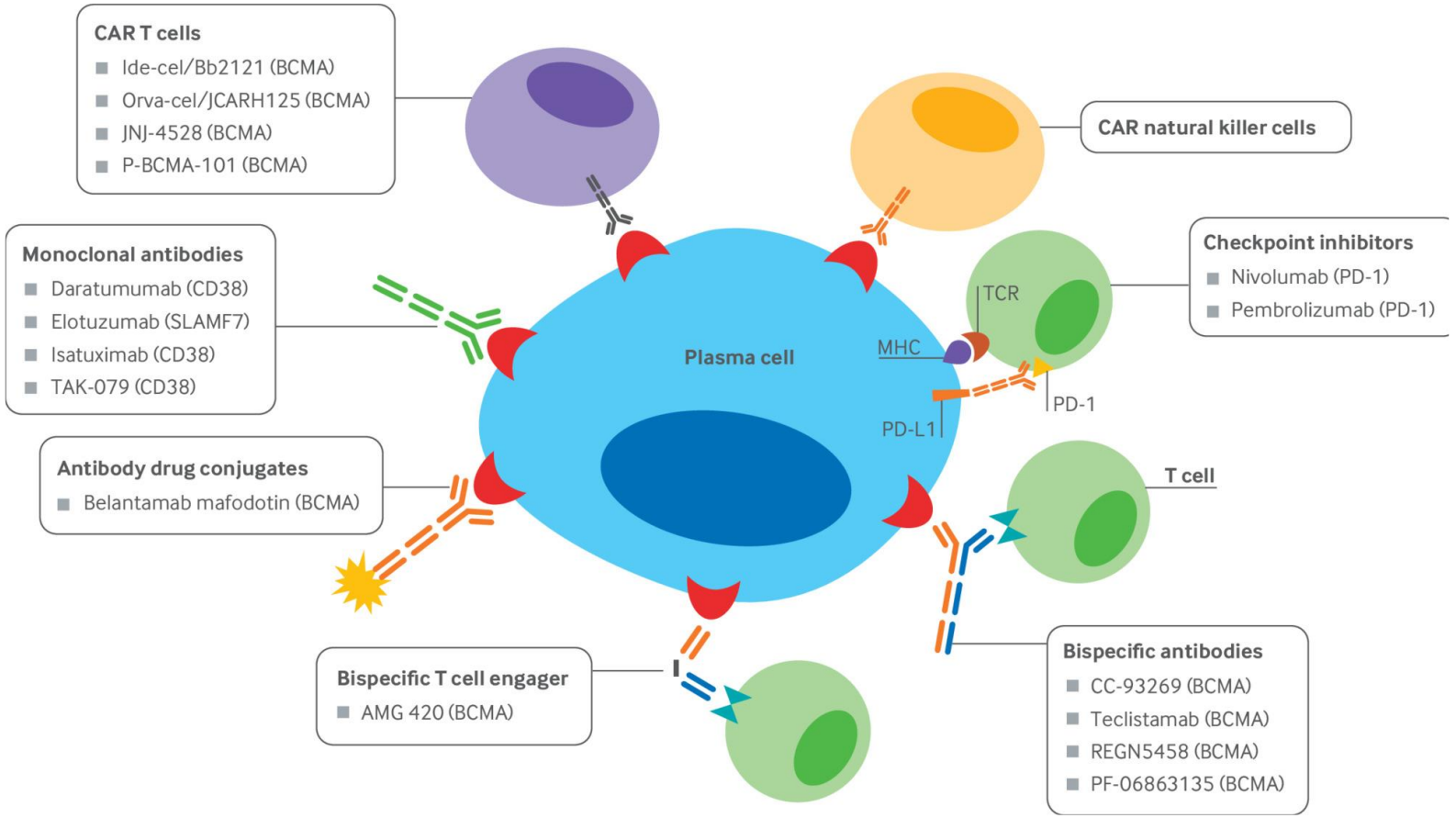
Talquetamab-tgvs (Talvey)

Teclistamab-cqyv (Tecvayli)

Bispecific Molecules

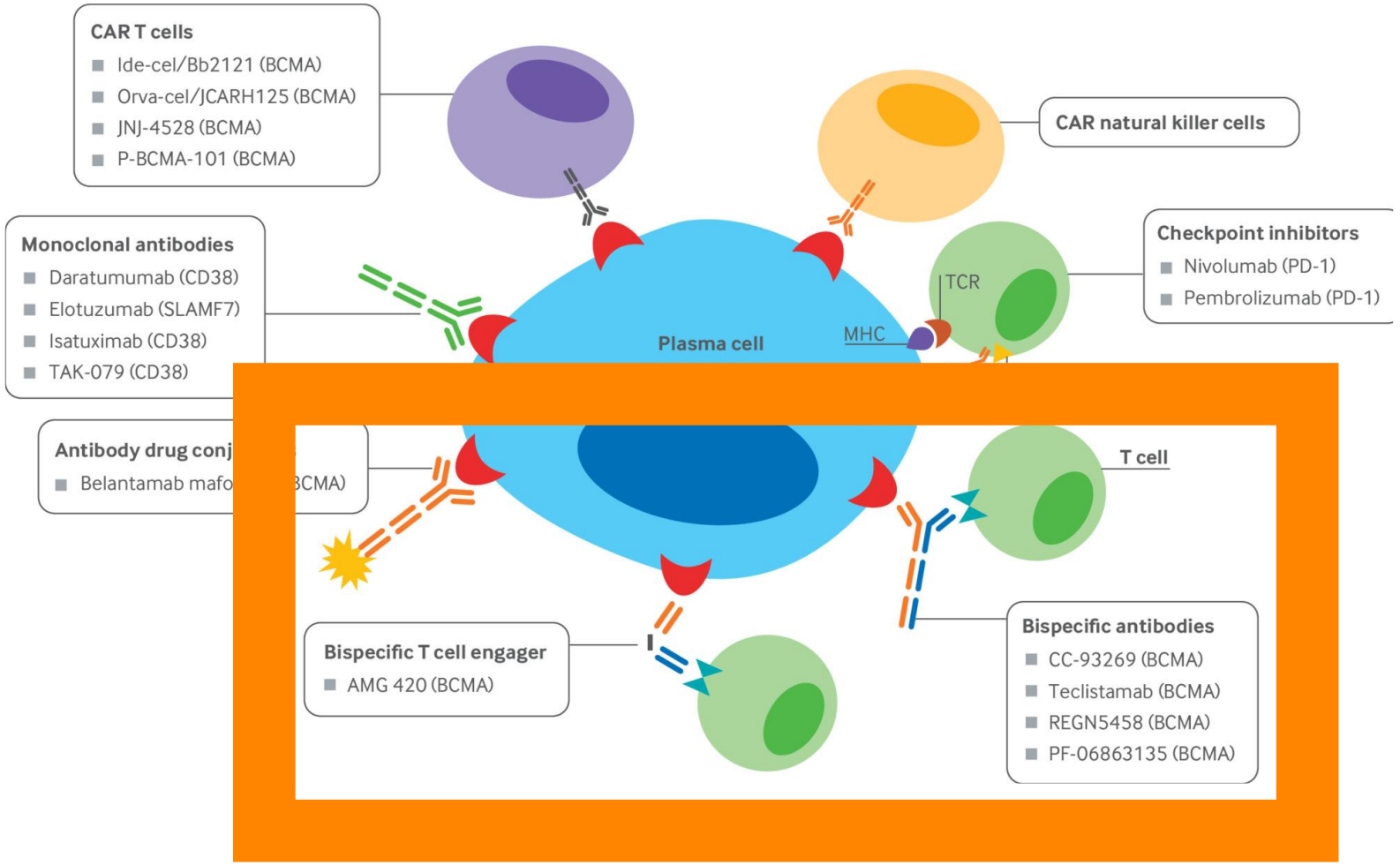
Bispecific Antibodies vs. Bispecific T-cell Engagers

Comparing Bispecific Molecules

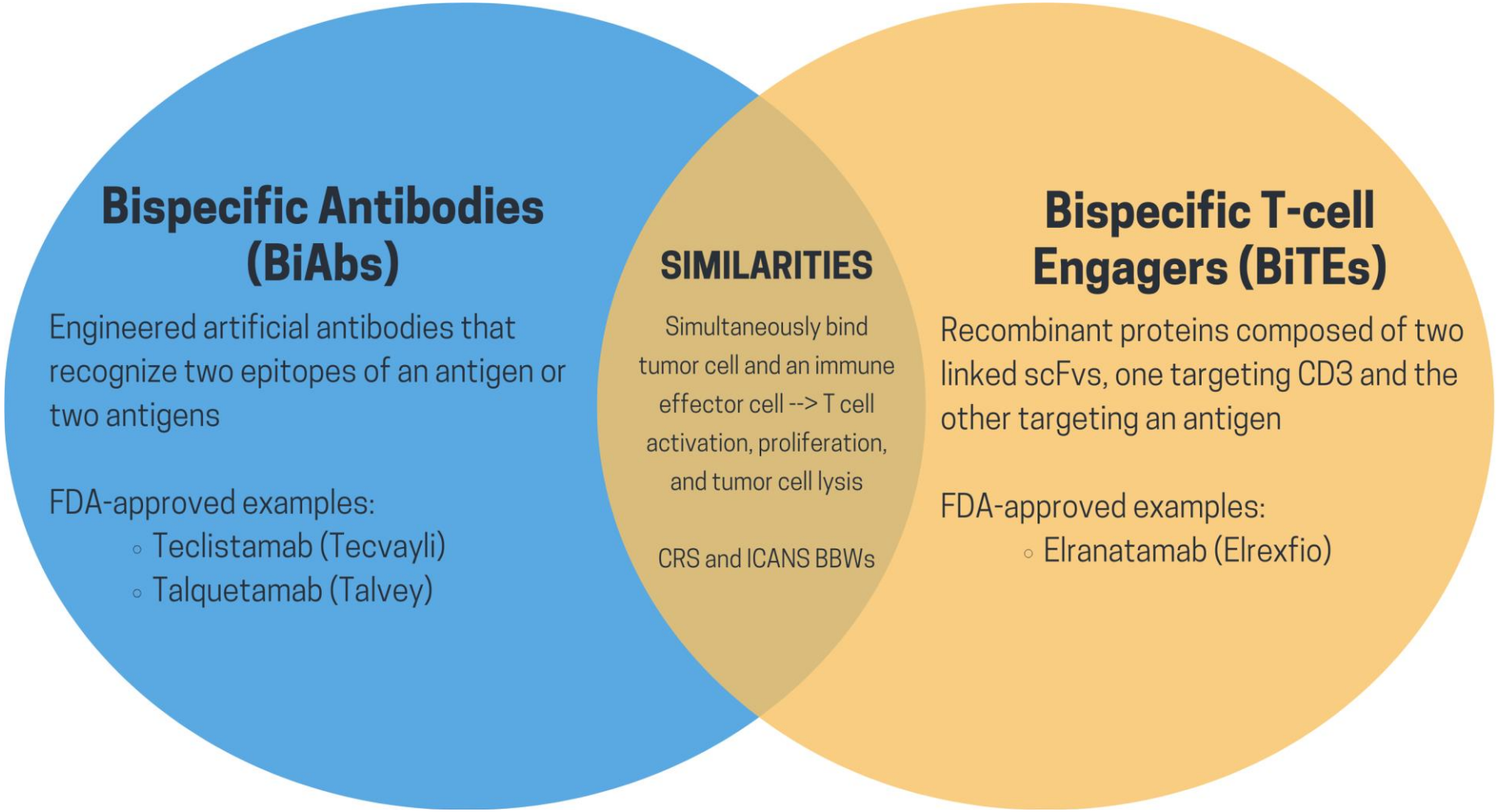


www.bmj.com/content/370/bmj.m3176

Comparing Bispecific Molecules



Comparing Bispecific Molecules



CRS = cytokine release syndrome; **ICANS** = immune effector cell-associated neurotoxicity syndrome; **BBW** = black box warning; **scFv** = single chain variable fragment

Cho SF et al. Bispecific Antibodies in Multiple Myeloma Treatment: A Journey in Progress

The Role of CD3

CD3

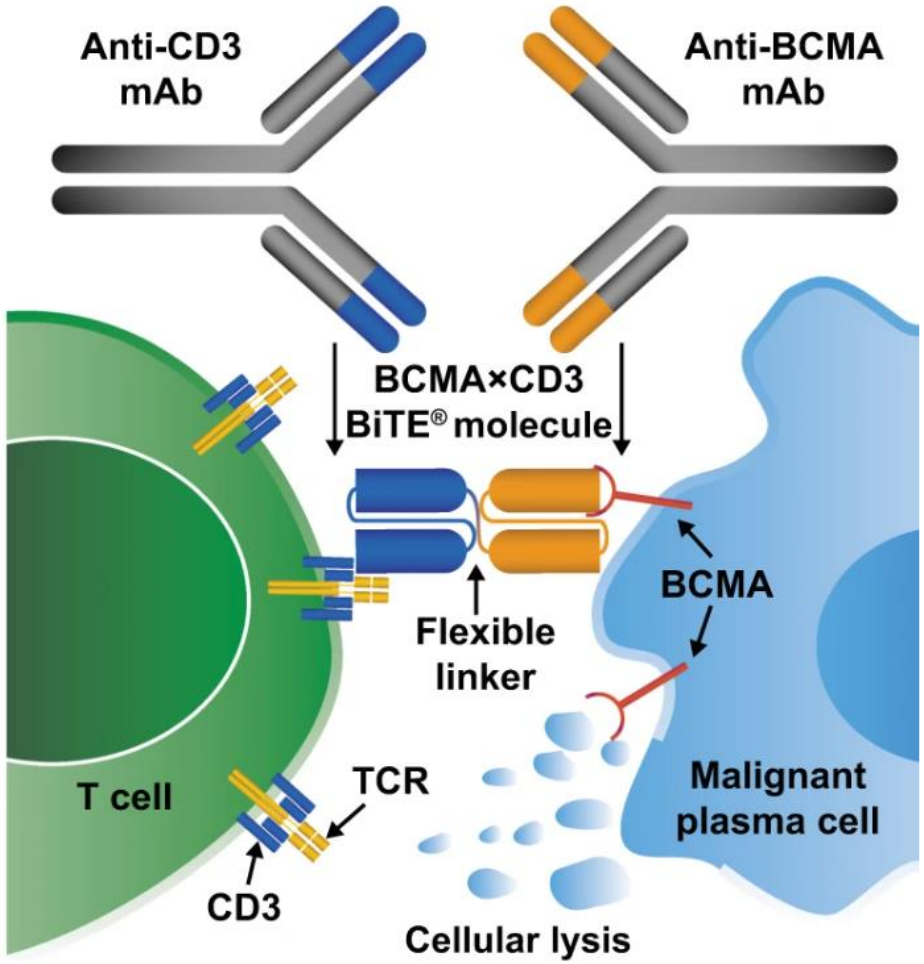
- The CD3 protein complex is the signaling subunit of the T cell
  - Provides the first signal that initiates T cell activation
- Immunotherapies targeting CD3 rescue and boost T cell effector function that is dysfunctional in many oncology disease states
  - Modify function and/or provide stimulatory signals directly to the T cells to rescue their activation potential, effector function, and memory formation ability

 Menon AP et al. Modulating T Cell Responses by Targeting CD3

Bispecific Molecule Multiple Myeloma Target Antigens

B-cell maturation antigen (BCMA)

- A member of the tumor necrosis factor superfamily, highly expressed on the surface of plasma cells and plasmacytoid dendritic cells
- Regulates plasma cell proliferation and long-term survival
- Regulates MM cell growth/survival
- Significantly higher serum BCMA levels in individuals with MM
  - Associated with increased disease burden and poorer overall and progression-free survival
- Current approved therapies targeting BCMA: teclistamab, elranatamab



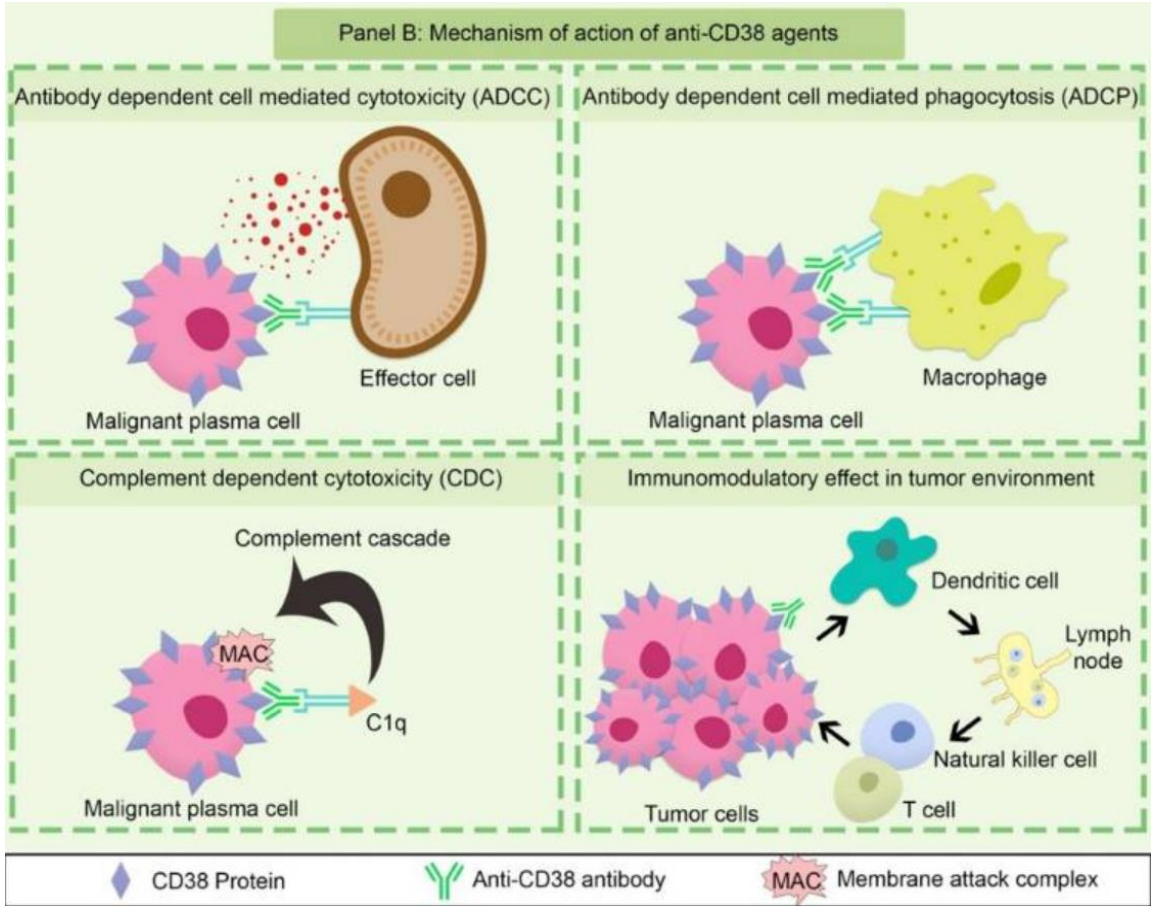
Shah et al. B-cell maturation antigen in multiple myeloma: rationale for targeting and current therapeutic approaches

MM = multiple myeloma

Bispecific Molecule Multiple Myeloma Target Antigens

CD38

- Transmembrane glycoprotein highly expressed on the surface of both normal and malignant plasma cells
- CD38 is expressed on regulatory T cells, regulatory B cells and myeloid derived suppressor cells
  - Associated with compromised immune surveillance for malignancies
- Current approved therapies targeting CD38: daratumumab, isatuximab



Hashmi, H, Husnain M, Khan A, et al. CD38-Directed Therapies for Management of Multiple Myeloma

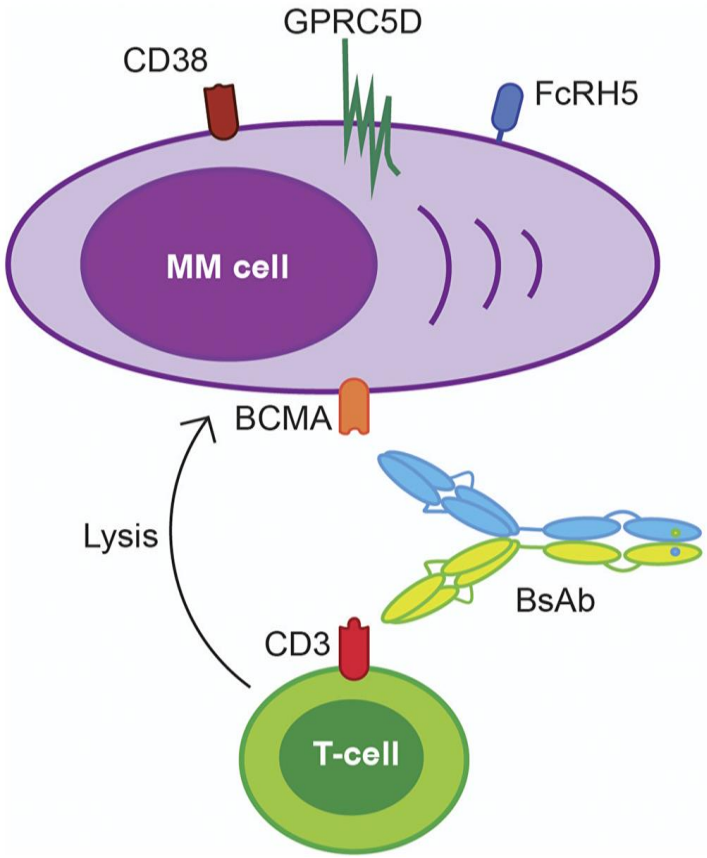
Bispecific Molecule Multiple Myeloma Target Antigens

G-protein coupled receptor family C group 5 member D (GPRC5D)

- Highly expressed on malignant MM plasma cells in the bone marrow, hair follicles, and testis
  - Potential for undesired on target/off-tumor effects is small
- Enriched expression in malignant plasma cells associated with markers of high-risk MM
- Current approved therapy targeting GPRC5D: talquetamab

Fc receptor homolog 5 (FcRH5)

- Type I membrane protein selectively expressed on B cells and plasma cells
- Promotes B-cell proliferation



www.oncotarget.com/article/27792/text/

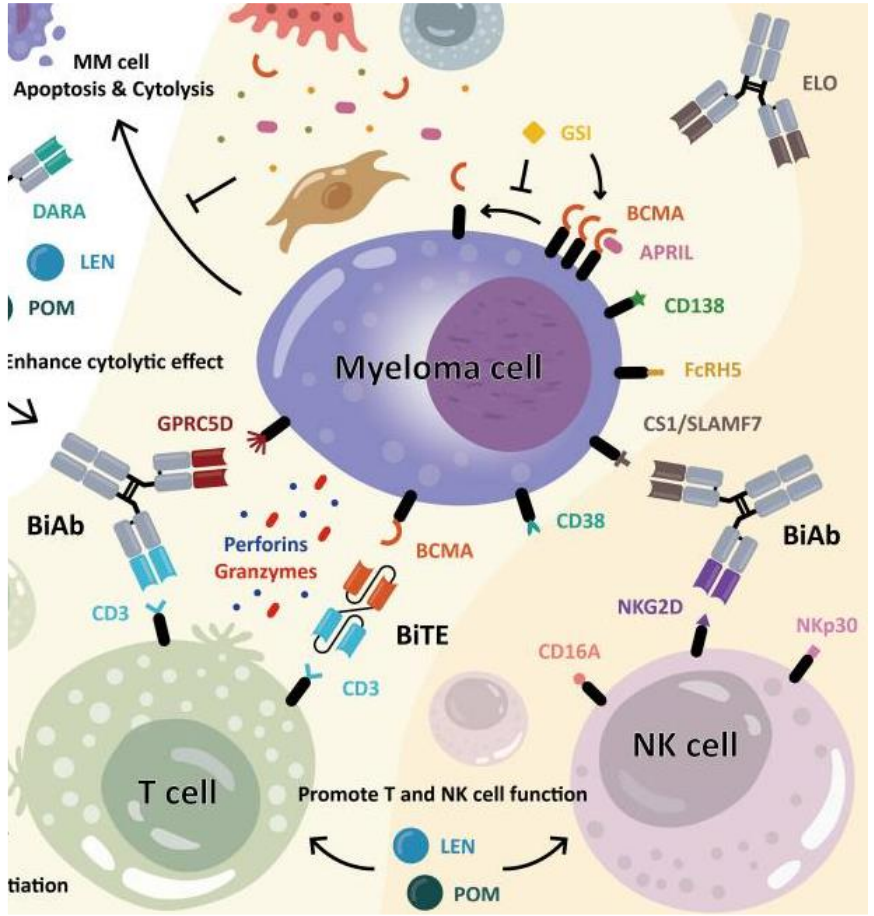
MM = multiple myeloma

Cho SF et al. Bispecific Antibodies in Multiple Myeloma Treatment: A Journey in Progress
Chari et al. Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Bispecific Molecule Multiple Myeloma Target Antigens

CD138 (Syndecan-1)

- Type I transmembrane proteoglycan on plasma cells
- Increased expression supports proliferation/survival as well as angiogenesis and IL-6 receptor sensitivity in MM cells



Cho et al. Bispecific Antibodies in Multiple Myeloma Treatment: a Journey in Progress

MM = multiple myeloma

Guideline-Recommended Therapy

Expanding on Current Bispecifics Recommended by NCCN Multiple Myeloma Guidelines

NCCN Guideline-Recommended Therapy

Therapy for Previously Treated Multiple Myeloma

Relapsed/Refractory Disease After 4 Prior Therapies

Generic Name	Brand Name	Molecular Target	Mechanism of Action	FDA Approval Date
Elranatamab-bcmm	Elrexfio	BCMA	Binds BCMA and CD3--> T-cell activation and release of proinflammatory cytokines--> lysis of BCMA-expressing malignant plasma cells	August 2023
Talquetamab-tgvs	Talvey	GPRC5D	Binds GPRC5D and CD3--> T-cell activation and release of proinflammatory cytokines--> lysis of malignant plasma cells	August 2023
Teclistamab-cqyv	Tecvayli	BCMA	Binds BCMA and CD3--> T-cell activation and release of proinflammatory cytokines--> lysis of BCMA-expressing malignant plasma cells	October 2022

BCMA = B-cell maturation antigen; **GPRC5D** = G-protein coupled receptor family C group 5 member D

NCCN Guideline-Recommended Therapy

Elranatamab

Generic Name	Brand Name	Molecular Target	Mechanism of Action	Administration	Warnings and Precautions	FDA Approval Date
Elranatamab	Elrexfio	BCMA	Binds BCMA and CD3 causing T-cell activation and release of proinflammatory cytokines leading to lysis of BCMA-expressing malignant plasma cells	Step-up dosing Patients should be hospitalized for 48H after administration of first dose and for 24H after administration of second dose SQ	**BBW**: Cytokine release syndrome **BBW**: ICANS Available only through REMS Infections, neutropenia, hepatotoxicity, embryo-fetal toxicity	August 2023

BCMA = B-cell maturation antigen; **SQ** = subcutaneous; **BBW** = black box warning; **REMS** = risk evaluation and mitigation strategy; **ICANS** = immune effector cell-associated neurotoxicity syndrome

NCCN Guideline-Recommended Therapy

Therapy for Previously Treated Multiple Myeloma

Clinical Trials

Trial	Design	Population	Intervention	Primary Endpoint	Results		Safety
					A	**B**	**A**
MagnetisMM-3	Open-label, single-arm, non-randomized, multicenter, phase 2	Adults with refractory, relapsed MM with ≥4 lines of prior therapy Cohort **A**: BCMA-naïve Cohort **B**: BCMA-exposed	Elranatamab monotherapy	ORR	ORR 61.0% (95% CI 51.8−69.6, P <0.001) Median time to first response 1.2 months (range 0.9-6.5) DOR at 9 months 82.3% (95% CI 67.1-90.9)	ORR 33.3% (95% CI 22.0-46.3) Median time to first response 1.9 months (range 0.9-6.7) DOR at 9 months 84.3% (95% CI 58.7-94.7)	Infections: 61.8 % (grade 3/4 31.7%) Peripheral neuropathy: 17.1% (grade 3/4 0.8%) CRS and ICANS: 56.3% and 3.4%

MM = multiple myeloma; **BCMA** = B-cell maturation antigen; **ORR** = objective response rate; **DOR** = duration of response; **CRS** = cytokine release syndrome; **ICANS** = immune effector cell-associated neurotoxicity syndrome

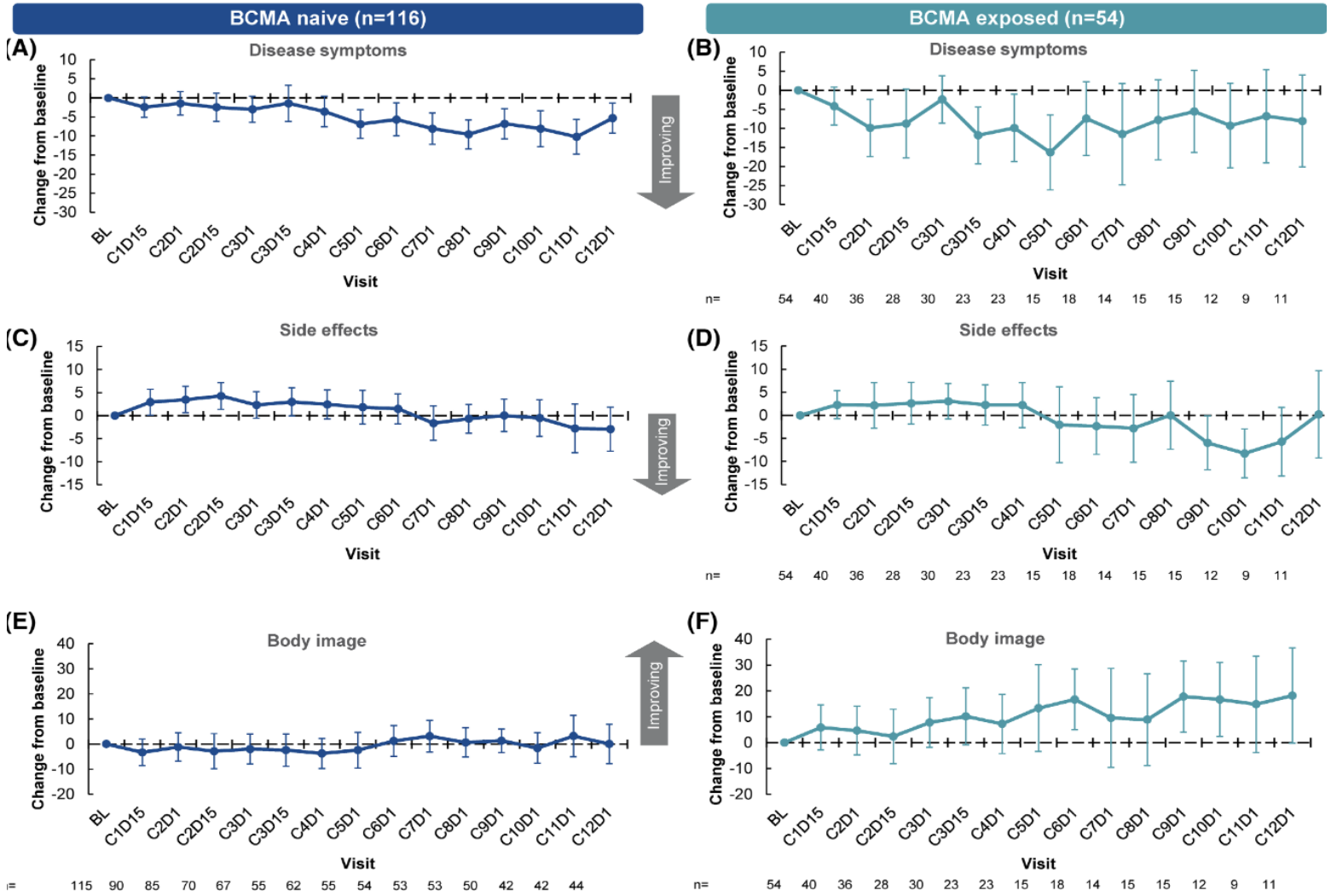
Harousseau J-L et al. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99-02 and 99-04 trials
ELREXFIO. Data on file. Pfizer Inc.

NCCN Guideline-Recommended Therapy

Patient Reported Outcomes from the MagnestisMM-3 Trial

Elranatamab monotherapy maintains or improves quality of life measures including pain, disease symptoms, side effects of treatment, body image and future perspectives.

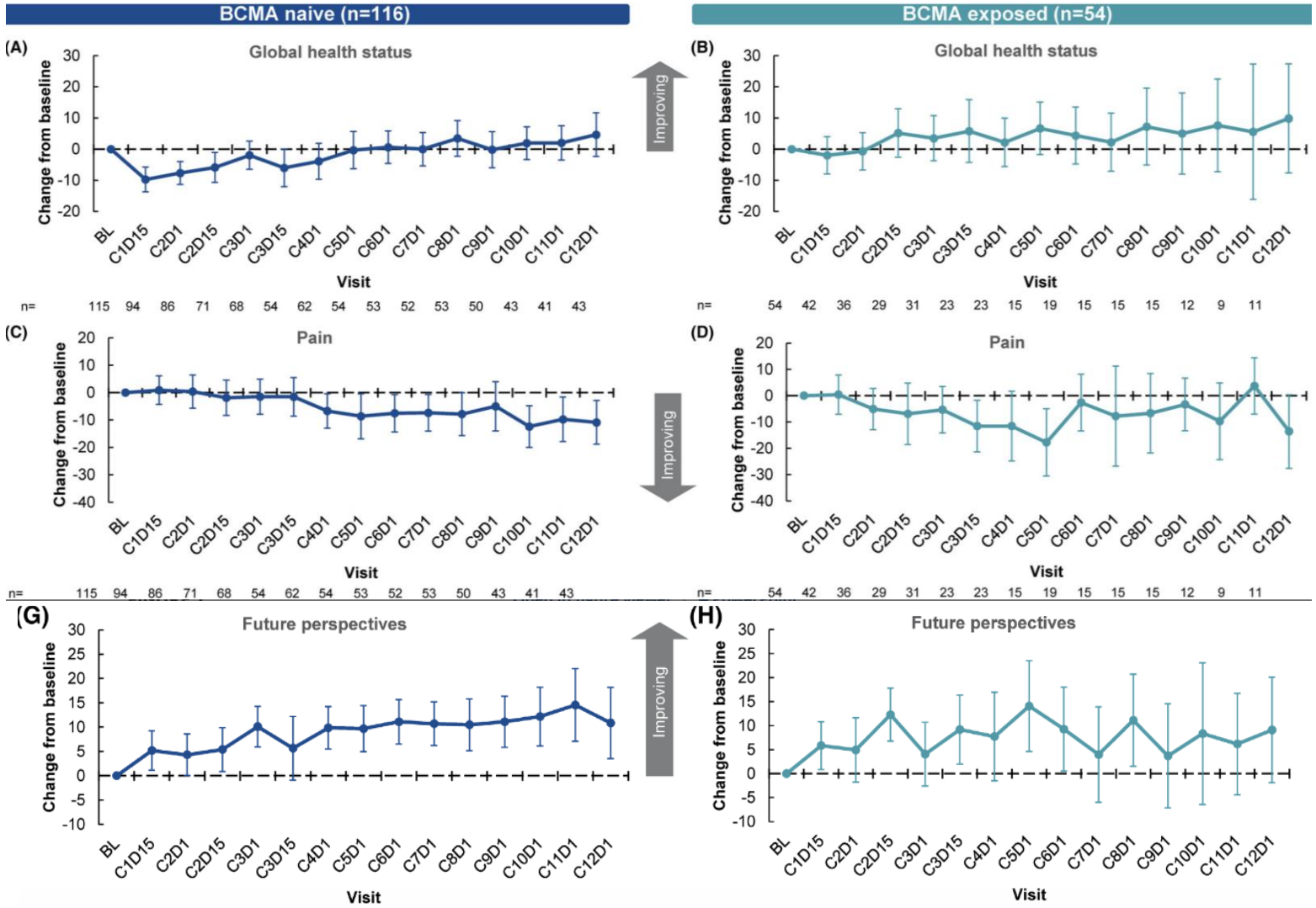
Only descriptive statistics were used, no conclusions can be drawn regarding statistical significance.



 Mohty at al. Impact of elranatamab on quality of life: Patient-reported outcomes from MagnetisMM-3

NCCN Guideline-Recommended Therapy

Patient Reported Outcomes from the MagnestisMM-3 Trial (cont.)



 Mohty at al. Impact of elranatamab on quality of life: Patient-reported outcomes from MagnetisMM-3

NCCN Guideline-Recommended Therapy

Talquetamab

Generic Name	Brand Name	Molecular Target	Mechanism of Action	Administration	Warnings and Precautions	FDA Approval Date
Talquetamab	Talvey	GPRC5D	Binds GPRC5D and CD3 causing T-cell activation and release of proinflammatory cytokines leading to lysis of malignant plasma cells	Step-up dosing Patients should be hospitalized for 48H after administration of first 3 doses SQ	**BBW**: Cytokine release syndrome **BBW**: ICANS Available only through REMS	August 2023

GPRC5D = G-protein coupled receptor family C group 5 member D; **SQ** = subcutaneous; **BBW** = black box warning; **REMS** = risk evaluation and mitigation strategy; **ICANS** = immune effector cell-associated neurotoxicity syndrome

NCCN Guideline-Recommended Therapy

Therapy for Previously Treated Multiple Myeloma

Clinical Trials

Trial	Design	Population	Intervention	Primary Endpoint	Results*		Safety*
MonumenTAL-1	Single-arm, open-label, multicenter, phase 1/2	Adults with relapsed, refractory MM with ≥3 lines of prior therapy	Talquetamab weekly or every 2 weeks	ORR	**QW** ORR 73% (95% CI 63.2-81.4) Median time to response 1.2 months (range 0.2-10.9) Median DOR 9.5 months (95% CI 6.5-NE)	**Q2W** ORR 73.6% (95% CI 63.0-82.4) Median time to response 1.3 months (range 0.2-9.2) Median DOR NE	AEs (≥20%): pyrexia, nail disorders, musculoskeletal pain, rash, fatigue, dry mouth CRS 76% (any grade), 18.5% (grade 3/4)

**In patients naïve to T-cell redirection therapy*

MM = multiple myeloma; **ORR** = objective response rate; **DOR** = duration of response; **NE** = not evaluable; **AEs** = adverse events; **CRS** = cytokine release syndrome

Chari A et al. Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma
TALVEY [Prescribing Information]

NCCN Guideline-Recommended Therapy

Teclistamab

Generic Name	Brand Name	Molecular Target	Mechanism of Action	Administration	Warnings and Precautions	FDA Approval Date
Teclistamab	Tecvayli	BCMA	Binds BCMA and CD3 causing T-cell activation and release of proinflammatory cytokines leading to lysis of BCMA-expressing malignant plasma cells	Step-up dosing Patients should be hospitalized for 48H after administration of first 3 doses SQ	**BBW**: Cytokine release syndrome **BBW**: ICANS Available only through REMS	October 2022

BCMA = B-cell maturation antigen; **SQ** = subcutaneous; **BBW** = black box warning; **REMS** = risk evaluation and mitigation strategy; **ICANS** = immune effector cell-associated neurotoxicity syndrome

NCCN Guideline-Recommended Therapy

Therapy for Previously Treated Multiple Myeloma

Clinical Trials

Trial	Design	Population	Intervention	Primary Endpoint	Results	Safety
MajesTEC-1 trial	Single-arm, open-label, multi-center, phase 1/2	Adults with relapsed, refractory MM with ≥3 lines of prior therapy	Teclistamab once weekly	ORR	ORR 61.8% (95% CI 52.1-70.9) Median time to first response 1.2 months (range 0.2-5.5) Median DOR NE 90.6% of patients continued to respond at 6 months (95% CI 80.3-95.7)	AEs (≥20%): pyrexia, injection site reactions, fatigue, musculoskeletal pain, upper respiratory tract infections CRS 72% (any grade), 0.6% (grade 3/4)

MM = multiple myeloma; **ORR** = objective response rate; **DOR** = duration of response; **NE** = not evaluable; **AEs** = adverse events; **CRS** = cytokine release syndrome

Moreau P, et al. Updated results from MajesTEC-1: phase 1/2 study of teclistamab, a B-cell maturation antigen x CD3 bispecific antibody, in relapsed/refractory multiple myeloma
TECVAYLI [Prescribing Information]

NCCN Guideline-Recommended Therapy

Durability of Responses With Biweekly Dosing of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma Achieving a Clinical Response in the MajesTEC-1 Study

Presented at the 2023 ASCO Annual Meeting

Trial	Intervention	Primary Endpoint	Results
MajesTEC-1 trial	Q2W dosing if patients achieved confirmed partial response after ≥4 cycles of treatment (phase 1) or CR for ≥6 months (phase 2)	DOR	Median time to switch from QW to Q2W dosing 11.1 months (range 3–20) Median DOR from date of switch 20.5 months (range 1–23), with 40/60 patients still in response and ongoing treatment 13/60 patients have progressed (median time from switch to progression NE), 2 discontinued due to AEs, 1 discontinued for other reason, and 4 died Overall, patients who transitioned from QW to Q2W dosing had sustained remission

CR = complete response; **DOR** = duration of response; **NE** = not evaluable; **AEs** = adverse events

Usmani S et al. Durability of Responses With Biweekly Dosing of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma Achieving a Clinical Response in the MajesTEC-1 Study

Bispecifics Supply and Preparation

	Elranatamab-bcmm	Talquetamab-tgvs	Teclistamab
Supplied	Vial sizes 44 mg/1.1 mL 76 mg/1.9 mL	Vial sizes 3 mg/1.5 mL 40 mg/mL	Vial sizes 30 mg/3 mL 153 mg/1.7 mL
Storage	2-8°C, do not freeze Store in original carton Do not shake vial or carton		
Preparation	Withdraw required volume using transfer needle, replace with injection needle Do not combine different vial concentrations		
Administration	SQ only Allow to come to room temperature Preferred site: abdomen Pre-medications (**corticosteroid**, **antihistamine**, **antipyretic**): prior to each step-up dose to reduce the risk of CRS		

SQ = subcutaneous

TECVAYLI [Prescribing Information]
ELREXFIO [Prescribing Information]
TALVEY [Prescribing Information]

Toxicities Associated with Bispecifics

Black Box Warnings

Cytokine Release Syndrome (CRS)

- Acute systemic inflammatory syndrome characterized by fever and organ dysfunction
- Onset
  - Typically within 2-3 days
- Duration
  - Resolves within 7-8 days
- Manifestations
  - Fever, fatigue, headache, rash, myalgia, diarrhea
  - Severe: hypotension, renal failure, cardiac dysfunction, pulmonary edema

Immune effector cell-associated neurotoxicity syndrome (ICANS)

- A neuropsychiatric syndrome
- Onset
  - Usually occurs in context of CRS
  - Within 4-10 days
- Duration
  - Resolves within 14-17 days
- Manifestations
  - Encephalopathy, hallucinations, headache, fatigue, tremors
  - Severe: seizures, cerebral edema

NCCN Management of Immunotherapy-Related Toxicities Guidelines
TECVAYLI [Prescribing Information]

Toxicities Associated with Bispecifics

CRS Treatment

Grade	Manifestations	Treatment Recommendations
1	Fever (≥ 38°C)	If prolonged CRS (> 3 days) or significant symptoms, comorbidities, or > 65 years of age: • Tocilizumab 8 mg/kg IV x 1 dose • Dexamethasone 10 mg IV q24H • Maintenance IV fluids
2	Fever with hypotension not requiring vasopressors Hypoxia requiring nasal cannula	Tocilizumab 8 mg/kg IV • Repeat in 8H if no improvement, limit 3 doses in 24H • Maximum of 4 doses total Dexamethasone 10 mg IV q6-24H IV fluids +/- boluses
3	Fever with hypotension requiring vasopressors +/- vasopressin Hypoxia requiring HFNC, face mask, or non-rebreather mask	
4	Fever with hypotension requiring multiple vasopressors Hypoxia requiring positive pressure, intubation, MV	

CRS = cytokine release syndrome; **HFNC** = high flow nasal cannula; **MV** = mechanical ventilation; **IV** = intravenous

NCCN Management of Immunotherapy-Related Toxicities Guidelines
TECVAYLI [Prescribing Information]

Toxicities Associated with Bispecifics

ICANs Treatment

Grade	Manifestations	Treatment Recommendations*
1	ICE** score 7-9; awakens spontaneously	Supportive care
2	ICE score 3-6; awakens to voice	Dexamethasone 10 mg IV x 1 dose, can repeat q6-12h if no improvement
3	ICE score 0-2; clinical seizures; focal edema on neuroimaging	Dexamethasone 10 mg IV q6H or methylprednisolone 1 mg/kg IV q12H
4	ICE score 0; unarousable or requires vigorous stimuli to arose/coma; prolonged seizure; deep focal motor weakness; diffuse cerebral edema on neuroimaging	High dose steroids • Example: methylprednisolone 1000 mg/day IV x 3 days, followed by rapid taper

*Tocilizumab 8 mg/kg x 1 recommended if concomitant CRS

**Immune Effector Cell-Associated Encephalopathy Assessment Tool, examines orientation, naming, following commands, writing, and attention abilities

ICANS = immune effector cell-associated neurotoxicity syndrome; **IV** = intravenous

NCCN Management of Immunotherapy-Related Toxicities Guidelines
TECVAYLI [Prescribing Information]

Bispecific Molecules in Clinical Trials

Current Clinical Trials Underway and Exploratory Targets

BCMA Targeting Clinical Trials

Trial Name	ClinicalTrials.gov Identifier	Intervention	Comparator	Population	Phase	Status
A Phase 1b/2a, Multicenter, Open-label Study to Determine the Recommended Dose and Schedule, and Evaluate the Safety and Preliminary Efficacy of **Alnuctamab** in Combination With Mezigdomide in Participants With Relapsed and/or Refractory Multiple Myeloma	NCT06163898	BCMA-CD3 bispecific antibody + Mezigdomide (cereblon E3 ubiquitin ligase modulator) + Dexamethasone	N/A	Relapsed/refractory MM	1, 2	Not yet recruiting
Phase 1/2 FIH Study of **REGN5458 (Linvoseltamab)** (Anti-BCMA x Anti-CD3 Bispecific Antibody) in Patients With Relapsed or Refractory Multiple Myeloma	NCT03761108	BCMA-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1, 2	Recruiting
An Open-label, Randomized, Phase 3 Study of **Linvoseltamab** Versus the Combination of Elotuzumab, Pomalidomide, and Dexamethasone, in Patients With Relapsed/Refractory Multiple Myeloma (LINKER-MM3)	NCT05730036	BCMA-CD3 bispecific antibody	Elotuzumab + pomalidomide + dexamethasone	Relapsed/refractory MM	3	Recruiting
A First-in-human, Phase I/II, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of **EMB-06** in Patients With Relapsed or Refractory Multiple Myeloma	NCT04735575	BCMA-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1, 2	Recruiting
A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of **TNB-383B**, a Bispecific Antibody Targeting BCMA in Subjects With Relapsed or Refractory Multiple Myeloma	NCT03933735	BCMA-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1, 2	Active, not recruiting

CD38 Targeting Clinical Trials

Trial Name	ClinicalTrials.gov Identifier	Intervention	Comparator	Population	Phase	Status
A Phase 1, First-in-Human, Multicenter, Open-Label, Two-Part Dose-Escalation and Cohort Expansion Study of Single-Agent **ISB 1342** in Subjects With Previously Treated Multiple Myeloma	NCT03309111	CD38-CD3 bispecific T cell engager	N/A	Relapsed/refractory MM	1	Recruiting
A Phase I Study to Evaluate the Safety, Tolerability, PK/PD and Immunogenicity Characteristics of Recombinant Anti-CD38 and Anti-CD3 Bispecific Antibodies **(Y150)** for Injection in Patients With Relapsed or Refractory Multiple Myeloma	NCT05011097	CD38-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1	Recruiting
An Open-Label, Multicenter, Phase 1 Study of **IGM-2644** in Participants With Relapsed and/or Refractory Multiple Myeloma	NCT05908396	CD38-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1	Recruiting

GPRC5D and FcRH5 Targeting Clinical Trials

Trial Name	ClinicalTrials.gov Identifier	Intervention	Comparator	Population	Phase	Status
A Phase 1 Study of **JNJ-64407564**, a Humanized GPRC5D*CD3 Bispecific Antibody in Japanese Subjects With Relapsed or Refractory Multiple Myeloma	NCT04773522	GPRC5D-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1	Active, not recruiting
Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity and Preliminary Effectiveness of **QLS32015** Injection in Patients With Relapsed or Refractory Multiple Myeloma	NCT05920876	GPRC5D-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1	Recruiting
An Open-Label, Multicenter, Phase I Study Evaluating the Safety and Pharmacokinetics of Escalating Doses of **Forimtamig (RO7425781)** in Participants With Relapsed or Refractory Multiple Myeloma	NCT04557150	GPRC5D-CD3 bispecific antibody	N/A	Relapsed/refractory MM	1	Recruiting
A Phase I/II, Open-Label, Multi-Cohort Study to Evaluate the Efficacy and Safety of **Cevostamab** in Prior B Cell Maturation Antigen-Exposed Patients With Relapsed/Refractory Multiple Myeloma	NCT05535244	FcRH5-CD3 bispecific antibody	N/A	Relapsed/refractory MM Prior BCMA Targeting Drug Exposure	1, 2	Recruiting

Combination Clinical Trials

Trial Name	ClinicalTrials.gov Identifier	Intervention	Comparator	Population	Phase	Status
A Phase 1b Study of Subcutaneous Daratumumab Regimens in Combination With Bispecific T Cell Redirection Antibodies for the Treatment of Subjects With Multiple Myeloma	NCT04108195	Daratumumab + **teclistamab**	1. Daratumumab + **talquetamab** 2. Daratumumab + **talquetamab** + pomalidomide 3. Daratumumab + **teclistamab** + pomalidomide	Relapsed Refractory Multiple Myeloma	1	Active, not recruiting
Elranatamab As Single Agent And In Combination With Immunomodulatory Agents In Relapse/Refractory Multiple Myeloma	NCT03269136	**Elranatamab**	1. Combination with dexamethasone 2. Combination with lenalidomide 3. Combination with pomalidomide	Relapsed Refractory Multiple Myeloma	1	Active, not recruiting
Phase 1b Study of Bispecific T Cell Redirection Antibodies in Combination With Checkpoint Inhibition for the Treatment of Participants With Relapsed or Refractory Multiple Myeloma	NCT05338775	**Teclistamab** + PD-1 inhibitor	**Talquetamab** + PD-1 inhibitor	Relapsed Refractory Multiple Myeloma	1	Recruiting
An Open-label, 3-arm, Multicenter, Randomized Phase 3 Study To Evaluate The Efficacy And Safety Of **Elranatamab** Monotherapy And **Elranatamab** + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone In Participants With Relapsed/Refractory Multiple Myeloma who Have Received At Least 1 Prior Line Of Therapy Including Lenalidomide And A Proteasome Inhibitor	NCT05020236	**Elranatamab**	1. Combination with daratumumab 2. Daratumumab + pomalidomide + dexamethasone	Relapsed Refractory Multiple Myeloma	3	Recruiting

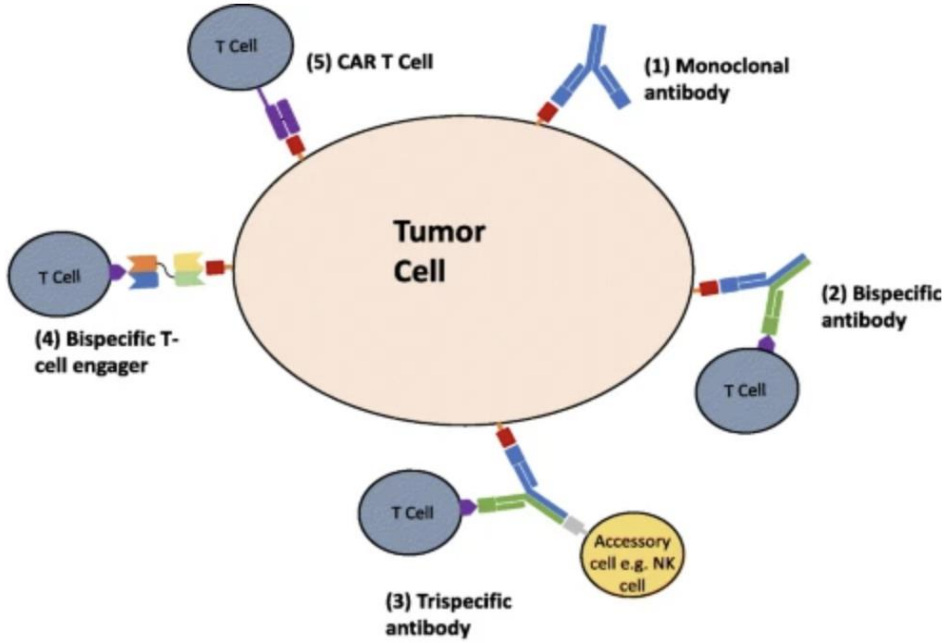
Beyond Bispecific Molecules

Trispecific antibodies and designed ankyrin repeat proteins

Trispecific Antibodies (TriAbs)

Currently undergoing preclinical development

- **Trispecific T-cell engagers**: 1 binding domain for myeloma antigen and 2 for T-cell antigens (CD3 and a costimulatory antigen)
- **Trispecific NK-cell engagers**: 2 myeloma antigen-binding domains and 1 NK-cell antigen domain
- Costimulatory antigen thought to provide a greater immune response and potency



molmed.biomedcentral.com/articles/10.1186/s10020-018-0051-4

aTriFlex Antibodies

- BCMA/CD200/CD16A specific antibody
  - Fusion protein bivalently engaged to CD16A on NK cells and two antibodies targeting BCMA and CD200 on MM cells

CD38 Trispecific Antibodies

- CD38/CD3/CD28 specific antibody
  - T-cell engager targeting CD38 and CD28 on MM cells

Wu L, et al. Trispecific antibodies enhance the therapeutic efficacy of tumor-directed T cells through T cell receptor co-stimulation
Gantke T et al. Trispecific antibodies for CD16A-directed NK cell engagement and dual-targeting of tumor cells
Lancman G et al. Bispecifics, trispecifics, and other novel immune treatments in myeloma

Question 1

Which of the following correctly describes the mechanism of action of elranatamab (Elrexfio)?

A. Binds BCMA and CD3, resulting in T-cell activation and the release of proinflammatory cytokines and ultimately lysis of BCMA-expressing plasma cells

B. Inhibits the growth of CD38-expressing tumor cells by inducing apoptosis through Fc-mediated cross linking

C. An antibody that binds GPRC5D and CD3, resulting in T-cell activation and the release of proinflammatory cytokines and ultimately lysis of GPRC5D-expressing plasma cells

D. Reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest and apoptosis

Question 1

Which of the following correctly describes the mechanism of action of elranatamab (Elrexfio)?

A. Binds BCMA and CD3, resulting in T-cell activation and the release of proinflammatory cytokines and ultimately lysis of BCMA-expressing plasma cells (Correct Answer)

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C. An antibody that binds GPRC5D and CD3, resulting in T-cell activation and the release of proinflammatory cytokines and ultimately lysis of GPRC5D-expressing plasma cells

D. Reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest and apoptosis

Question 2

Which of the following are common toxicities associated with the use of bispecific molecules?

A. Cytokine release syndrome

B. Neutropenia

C. Immune effector cell-associated neurotoxicity syndrome

D. All of the above

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D. All of the above (Correct Answer)

Question 3

After how many lines of therapy may a bispecific antibody be considered per NCCN guidelines?

A. One
B. Two
C. Three
D. Four

Question 3

After how many lines of therapy may a bispecific antibody be considered per NCCN guidelines?

A. One

B. Two

C. Three

D. Four (Correct Answer)

Question 4

What does the abbreviation ICANS stand for?

A) Immune cell and neurology system toxicity

B) Immunocompromised aggravated neurological system

C) Immune cancer neurological syndrome

D) Immune effector cell-associated neurotoxicity syndrome

Question 4

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Thank you!

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