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Bispecific antibody therapy

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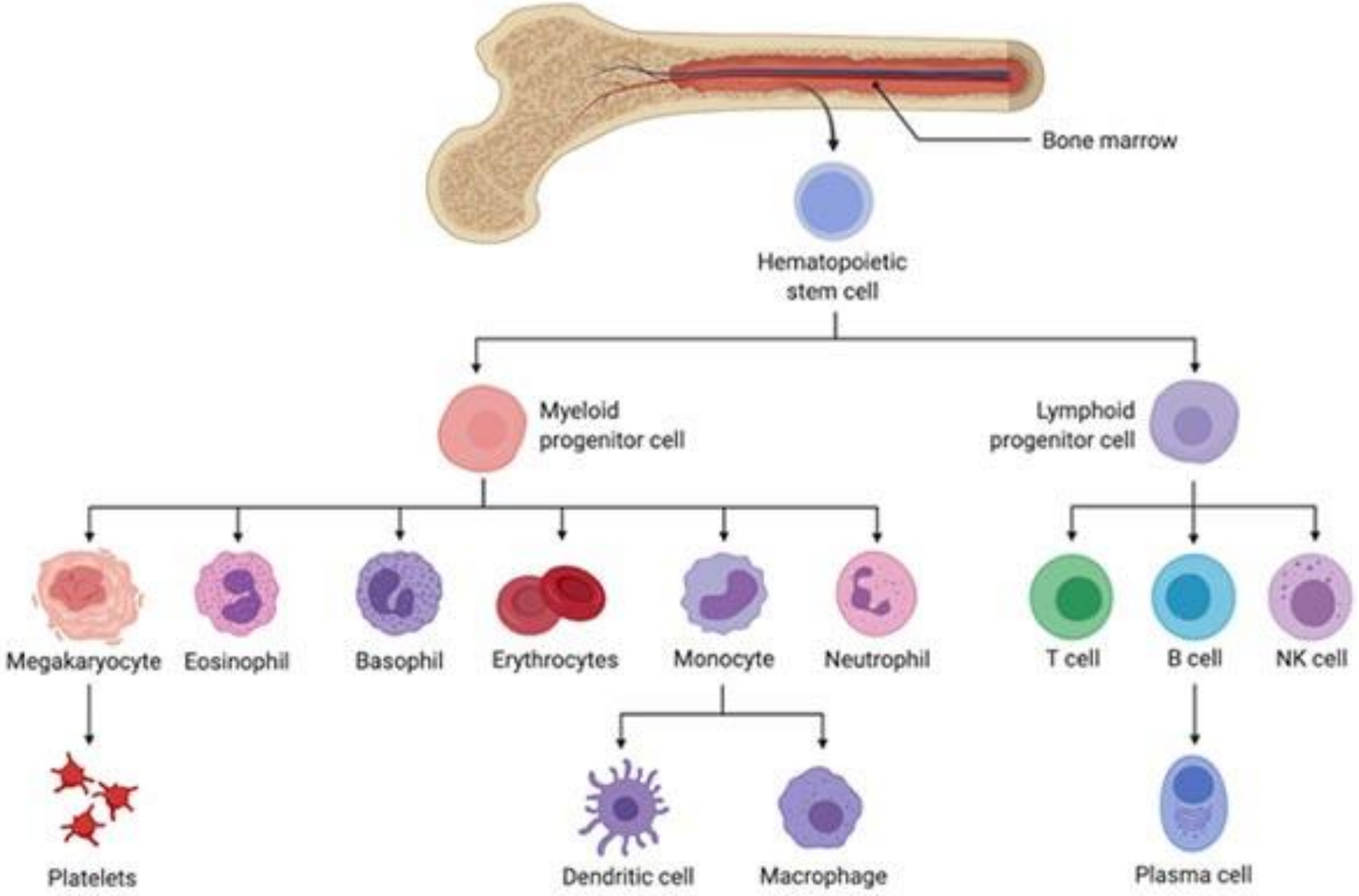
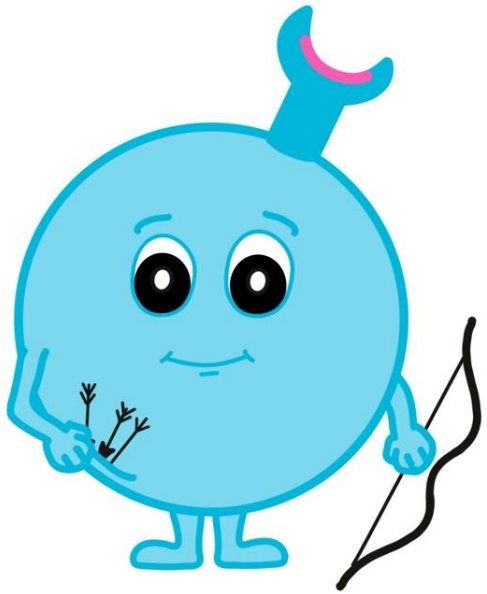
Agenda

1. What are bispecific antibodies?
2. BCMA targeting bispecific antibodies
3. GPRC5D targeting bispecific antibodies
4. Clinical trials with currently available medications
5. Bispecifics → evolution to Trispecifics?!

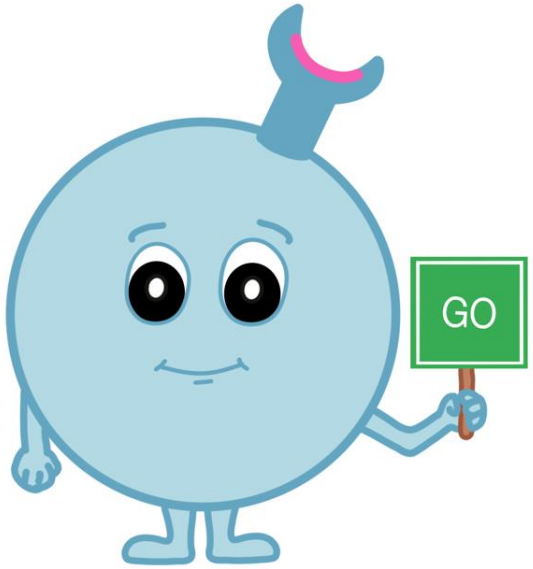

Bone marrow
Hematopoietic stem cell
Myeloid progenitor cell
Lymphoid progenitor cell
Megakaryocyte
Eosinophil
Basophil
Erythrocytes
Monocyte
Neutrophil
T cell
B cell
NK cell
Platelets
Dendritic cell
Macrophage
Plasma cell

cytotoxic T cells



produce toxic agents to kill their targets

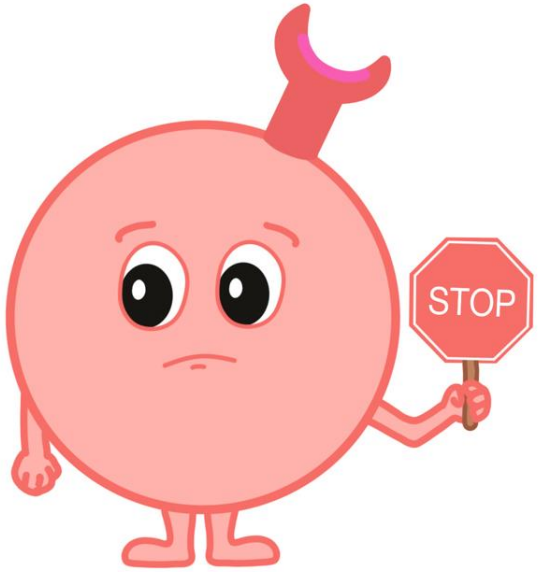
helper T cells



stimulate B cells to make antibodies

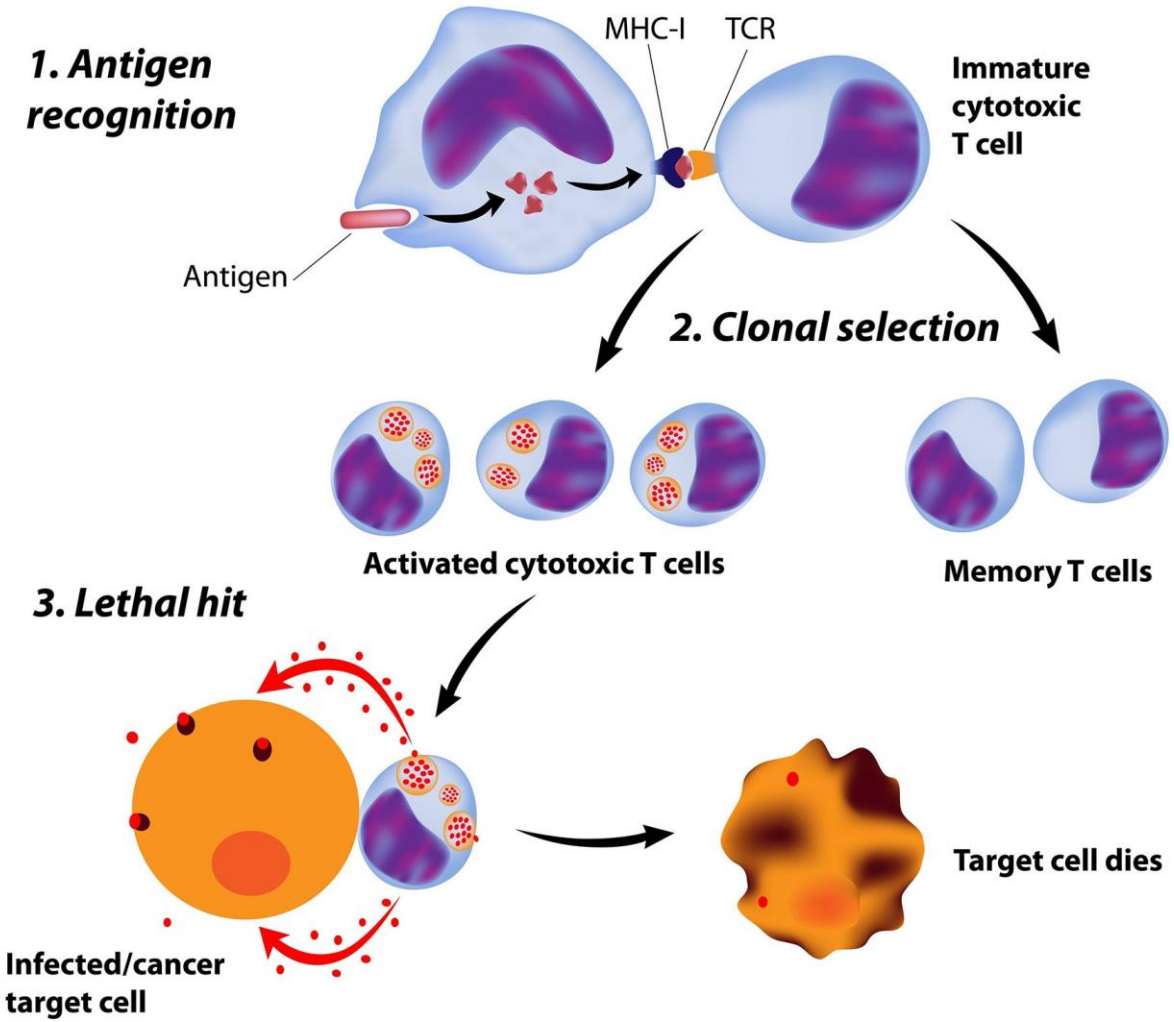
stimulate T cells to become active

regulatory T cells



suppress immune responses

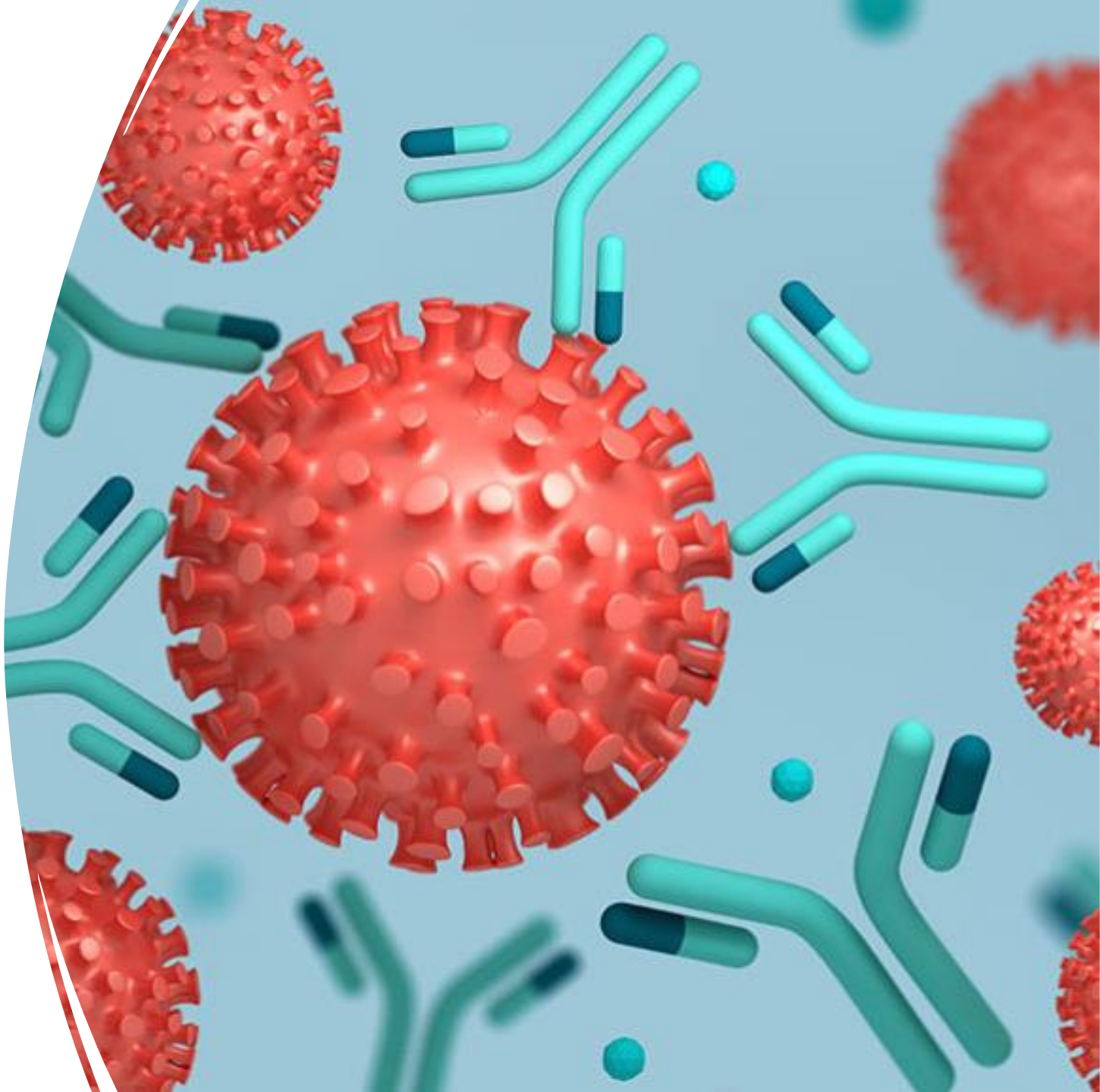
Cytotoxic T cell Activation and Action



Beckman.com

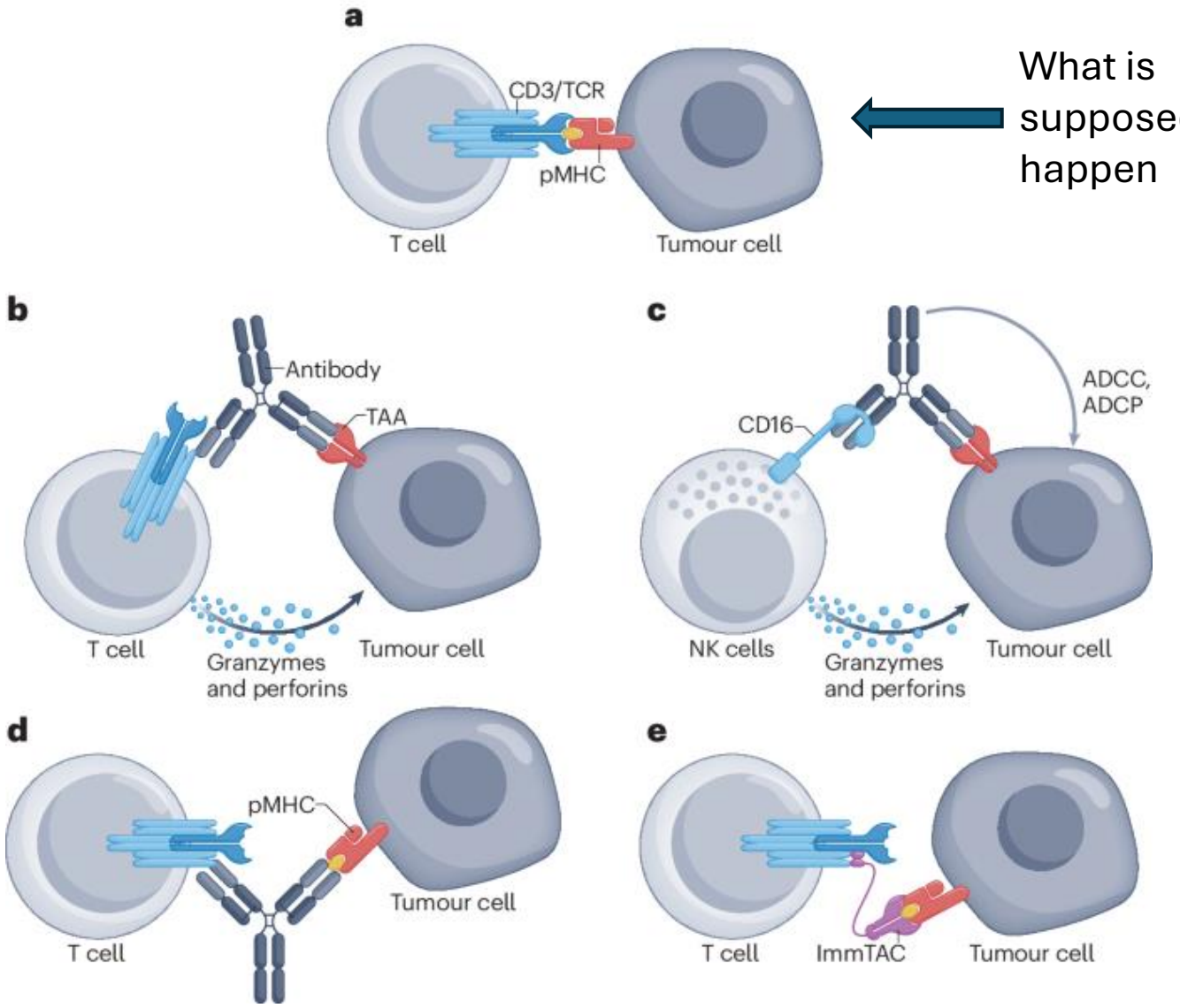
What is an antibody?

- You probably know a lot about the CLONAL antibodies that their cancerous plasma cells produce
- BUT antibodies can also be made to target cells and lead to cell death.
- Daratumumab and Elotuzumab are therapeutic antibodies routinely used to treat myeloma



What is different about a bispecific antibody?

Designed to promote interactions between myeloma cells and T cells independently from specific TCR recognition, via the CD3 signaling complex



Currently approved bispecific antibodies world wide across multiple different cancers

AGENT	TARGET	INDICATION AND ACTIVITY	COMMON SIDE EFFECTS	YEAR OF APPROVAL
Blinatumomab[77,78,79,80]	CD3 × CD19	RR B-ALL: CR/CRh in 43–44%, mRFS 5.9 months, mOS 6.1–6.9 months	Neutropenia (37.8–41%), infection (34.1%), elevated circulating liver enzymes (6–12.7%), neurological events (9.4–11%), CRS (4.9%)	2014[a], 2017 (FDA); 2015[a], 2018 (EMA), 2020 (NMPA) Subsequently, expanded to include patients with MRD$^+$ B-ALL
Mosunetuzumab[88]	CD3 × CD20	RR FL: CRR 60%, ORR 80%, mPFS 17.9 months, mOS NR	Neutropenia or reduced neutrophil count (26%), hypophosphataemia (17%), anaemia (8%), increased serum ALT (5%), CRS (2%)	2022[a] (EMA), 2022[a] (FDA)
Tebentafusp[240,247]	CD3 × gp100–HLA-A*02:01	HLA-A*02:01-positive uveal melanoma: ORR 11%, mPFS 3.4 months, mOS 21.6 months	Rash (19%), elevated circulating liver enzymes (10%), pyrexia (5%), pruritus (5%), CRS (1%)	2022 (FDA), 2022 (EMA)
Teclistamab[115,117]	CD3 × BCMA	RR MM: CRR 39.4%, ORR 63%, mPFS 11.3 months, mOS 18.3 months	Neutropenia (64.2%), anaemia (37.0%), lymphopenia (32.7%), thrombocytopenia (21.2%), CRS (0.6%)	2022[a] (FDA), 2022[a] (EMA)
Glofitamab[91]	CD3 × CD20	RR DLBCL: CRR 39%, ORR 52%, mPFS 4.9 months, mOS 12 months	Neutropenia (27%), thrombocytopenia (8%), anaemia (6%), CRS (4%)	2023[a] (FDA), 2023[a] (EMA), 2023[a] (NMPA)
Amivantamab[198,199,200]	EGFR × MET	Advanced-stage NSCLC harbouring *EGFR* exon 20 insertion mutations (in combination with chemotherapy): ORR 73%, mPFS 11.4 months, mOS NR	Neutropenia (33%), rash (11%), leukopenia (11%), anaemia (11%), thrombocytopenia (10%)	2021[a] (FDA)
Epcoritamab[94]	CD3 × CD20	RR DLBCL: CRR 38.9%, mPFS 4.4 months, mOS NR	Neutropenia (14.6%), anaemia (10.2%), thrombocytopenia (5.7%), CRS (2.5%)	2023[a] (FDA) 2023[a] (EMA)
Elranatamab[118,119,120]	CD3 × BCMA	RR MM: ORR 61%, estimated 15-month PFS 50.9%, estimated 15-month OS 56.7%	Neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), thrombocytopenia (23.6%)	2023[a] (FDA), 2024[a] (EMA)
Cadonilimab[168]	PD-1 × CTLA4	Advanced-stage cervical cancer: ORR 32.3%, mPFS 3.7 months, mOS NR	Anaemia (5%), reduced appetite (4%), dyspnoea (2%)	2022 (NMPA)
Talquetamab[130]	GPRC5D × CD3	RR MM: ORR 72%, mDOR 9.5 months, mPFS NR	Lymphopenia (47%), anaemia (33%), neutropenia (26%), leukopenia (16%)	2023[a] (FDA)
Tarlatamab[141,142]	CD3 x DLL3	RR SCLC: ORR 40%, mDOR 9.7 months, mPFS 4.9 months	CRS (26%), neutropenia (8%)	2024[a] (FDA)

The current 3 approved bispecific antibodies

- Teclistamab (Tecvayli)
- Elranatamab (Elrexfio)
- Talquetamab (Talvey)

How ELREXFIO works

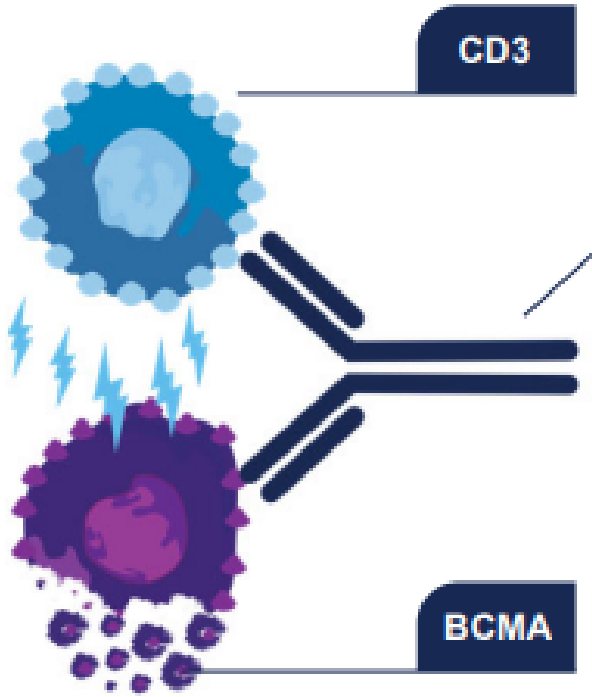
ELREXFIO binds to myeloma cells and T cells. ELREXFIO activates those T cells to help destroy myeloma cells

T cell
Fighter cell

ELREXFIO binds to the CD3 protein found on the surface of **T cells**. This is a type of white blood cell that can act as a weapon against myeloma cells and other cells.

Myeloma cell
Cancer cell

ELREXFIO is designed to bind to BCMA, a protein that is overexpressed on the surface of myeloma cells. BCMA can be found on other B cells, too.



ELREXFIO

This dual-binding process activates T cells to target and destroy myeloma cells with BCMA on their surface. It may also harm a type of normal antibody-producing cell.

Basic principles of treatment

- Patients receive “off-the-shelf” treatment, drug is orderable just like any other antibody treatment
- Can be Intravenous or subcutaneous. Currently subcutaneous for approved drugs.
- Dose is ramped up slowly until full dose. Usually pre-medications are given
- Usually 2-3 “ramp up” doses
- Cytokine release syndrome or neuro toxicity typically occurs in the first month only
- Works fast. Typically know within 4-6 weeks whether it is working or not.

How different are the toxicities between CAR-T and Bispecifics?

- CRS management
  - Typically grade 1-2.
  - Mostly low grade fevers
  - Self-limited
  - Next dose administration
  - Can still use tocilizumab and steroids
  - Use of pre-medications in bispecifics

- Neurotoxicity management
  - Lower grade
  - Reversible
  - Steroids
  - Quite low risk for seizures, no prophylaxis

Dosing examples:

TECVAYLI Recommended Dosing Schedule (2.1)			
Dosing Schedule	**Day**	**Dose**	
Step-up Dosing Schedule	Day 1	Step-up dose 1	0.06 mg/kg
	Day 4	Step-up dose 2	0.3 mg/kg
	Day 7	First treatment dose	1.5 mg/kg
Weekly Dosing Schedule	One week after first treatment dose and weekly thereafter	Subsequent treatment doses	1.5 mg/kg once weekly

- For subcutaneous injection only. (2.1)

Generally similar guidelines for management of CRS

Grade[a]	Presenting Symptoms	Actions
Grade 1	Temperature ≥100.4°F (38°C)[b]	• Withhold TECVAYLI until CRS resolves. • Administer pretreatment medications prior to next dose of TECVAYLI.[c]
Grade 2	Temperature ≥100.4°F (38°C)[b] with: Hypotension responsive to fluids and not requiring vasopressors, and/or, Oxygen requirement of low-flow nasal cannula[d] or blow-by.	• Withhold TECVAYLI until CRS resolves. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Patients should be hospitalized for 48 hours following the next dose of TECVAYLI *[see Dosage and Administration (2.1)]*.[c]
Grade 3	Temperature ≥100.4°F (38°C)[b] with: Hypotension requiring one vasopressor with or without vasopressin, and/or, Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask.	First Occurrence of Grade 3 CRS with Duration Less than 48 Hours: • Withhold TECVAYLI until CRS resolves. • Provide supportive therapy, which may include intensive care. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Patients should be hospitalized for 48 hours following the next dose of TECVAYLI *[see Dosage and Administration (2.1)]*.[c]
		Recurrent Grade 3 CRS or Grade 3 CRS with Duration 48 Hours or Longer: • Permanently discontinue TECVAYLI. • Provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥100.4°F (38°C)[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Oxygen requirement of positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Permanently discontinue TECVAYLI. • Provide supportive therapy, which may include intensive care.

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Dosing frequency can change!

- Time limited dosing
- Continue until progression
- Adjustments due to toxicity
- Physician discretion based on patient care

Rapidly evolving landscape - How different can a new target be?

- Teclistamab
  - Infection risk quite high

Talquetamab

- Skin reactions occurred in 62% of patients (Gr 1-2)
- Dysgeusia (70%)
- Nail disorder (50%)

Published clinical trials of BCMA BsAbs in RRMM.

Bispecific Antibody	Clinical Trials Identifier	Antibody Structure	Administration	Safety	CRS/ICANS	Responses	Ongoing Studies
Teclistamab	MajesTEC-1 NCT03145181	humanized, IgG Fc	Teclistamab 1.5 mg/kg weekly S/C with a 2-step-up priming dose regimen (0.06 mg/kg and 0.3 mg/kg)	Anaemia 52%, neutropenia 71%, thrombocytopenia 40%, infections 76% (grade 3–4 45%), neurotoxicity 15%	CRS 72% (all but one case grade 1–2), ICANS 3% (all grade 1–2)	ORR 63%, 39% CR or better, median DOR 18.4 months	Several MagesTEC studies ongoing using teclistamab in RRMM and NDMM in combination therapies
Elranatamab	MagnetisMM-3 NCT04649359 Cohort A	full length, humanized, IgG2a	Elranatamab 76 mg weekly S/C on a 28 day cycles with a 2-step-up priming dose regimen (12 mg and 32 mg)	Anaemia 56%, neutropenia 53%, thrombocytopenia 27%, infection 62% (grade 3–4 32%), %, peripheral neuropathy 17%, nausea 30%, diarrhoea 45%	CRS 56% (all grade 1–2), ICANS 3% (all grade 1–2)	ORR 61%, median DOR not reached	Several MagnetisMM studies ongoing using elranatamab in RRMM and NDMM in combination therapies
AMG 420	NCT02514239	BiTE	Continuous 28 day IV infusion followed by 2 week break. Dose-escalation from 0.2–800 µg/day	Infection 33%, polyneuropathy 5%, 12% deranged liver enzymes	CRS 38% (94% Grade 1–2)	ORR 31% across all doses, 70% for the 400 ug/day cohort	Development discontinued by Amgen
AMG 701	NCT03287908	extended half-life, scFvs plus Fc region	Weekly IV. Dose-escalation from 5 µg–12 mg	Anaemia 43%, neutropenia 23%, thrombocytopenia 20%, diarrhoea 31%, fatigue 25%, infection 17%, elevated pancreatic enzymes 3%.	CRS 61% (90% Grade 1–2)	ORR 36% for 3–12 mg doses	Development discontinued by Amgen
Linvoseltamab (REGN5458)	NCT03761108	Fc Fab arms	IV weekly, then every 2 weeks. Dose escalation over 9 dose levels.	Anaemia 37%, neutropenia 29%, thrombocytopenia 21%, fatigue 34%	CRS 48% (all but one case Grade 1–2)	ORR 41% for doses <200 mg and 75% ≥200 mg, median DOR not reached	Phase 2 study of 200 mg REGN5458 is recruiting
Alnuctamab (CC-93269)	NCT03486067	2 arm humanized IgG1 Fc	Dose escalation of IV alnuctamab from 0.15–10 mg. S/C alnuctamab given on D1, 4, 8, 15 and 22 of C1, weekly in C2–3, every other week in C4–6 and every 28 days thereafter. Dose escalation from 10–60 mg	Anaemia 34%, neutropenia 34%	CRS 53% (all grade 1–2), 1 grade 1 ICANS	IV alnuctamab ORR 39%, median PFS 13 weeks, median DOR in responding patients 146 weeks. S/C alnuctamab ORR 51% across all doses, 77% for doses ≥30 mg	Ongoing recruitment to the phase 1 study
Abbv-383	NCT03933735	IgG4 Fc. 2 heavy chain only anti-BCMA moieties	Dose escalation and expansion cohorts (n = 6 in 40 mg cohort, n = 60 in 60 mg cohort)	Infections in 50% of 40 mg cohort and 43% of 60 mg cohort, neutropenia in 67%/40%, anaemia in 33%/32%, thrombocytopenia 33%/25%	CRS 83% (all grade 1–2) in 40 mg cohort and 72% (2% grade 3–4) in 60 mg cohort	ORR 57% across all groups, 83% at 40 mg and 60% at 60 mg. ≥CR 67% at 40 mg and 29% at 60 mg	Phase 1b study planned NCT05650632

Cancers (Basel). 2023 Mar; 15(6): 1819.

Other Side effects

- Low blood counts
  - Increased risk for infections
  - Injection site reactions
  - Fatigue / Muscle pain
  - Nausea / vomiting / diarrhea

Talquetamab – GPRC5D toxicity

ORAL : what do we track?

- Change in taste
- Burning or tongue pain
- Dry mouth
- Suggestions about food
- Artificial saliva
- Hydration
- Weight measurements
- Nutritionist evaluation

SKIN/NAIL: what do we track?

- Lukewarm or cool showers
- Intensive lubrication advice
- Advanced skin care
- Attention to shoes/socks
- Apply cuticle cream
- Apply nail hardener polish
- Treat rash early
- Itchy skin prevention interventions

Will the treatment work?

Generally around 62-73% chance of response.

Responses can be for 6 months- 3+ years.

We have had patients respond for 5+ years on clinical trial.

Ongoing treatment may not be needed for response.

Treatment maybe able to be spaced apart over time.

Take home messages

Less toxic, off the shelf immune effector cell based therapy

- Expect some manageable CRS and low chance for neurotoxicity
  - Physical administration aspect will be very similar to other antibody drugs
  - There will be a lot of different drugs - but we use the same tools to assess and manage
  - Step-up and hospitalization requirements may change
  - There will be combinations coming

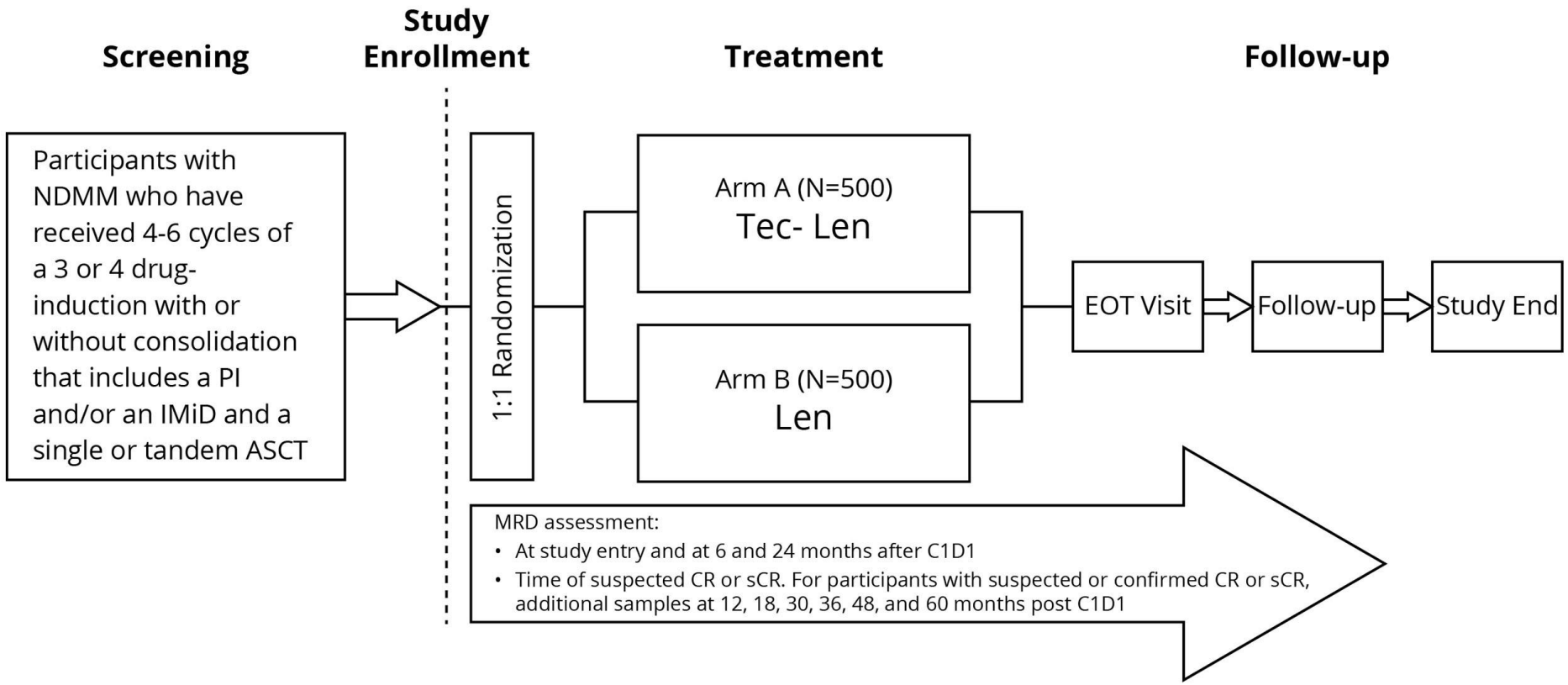
Clinical trials with Bispecifics: open now

Randomized
World-wide 800 patients
1-4 prior lines of treatment

- Talquetamab+ Pomalidomide
- Talquetamab + Teclistamab
- Elotuzumab-pom-dex
  Velcade-pom-dex

Likely to open in spring 2025. EMN 30 (European Myeloma Network)

Figure: MajesTEC-4 study design



ASCT, autologous stem cell transplant; C, cycle; CR, complete response; D, day; EOT, end of treatment; IMiD, immunomodulatory agent; len, lenalidomide; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; sCR, stringent complete response; Tec, teclistamab

= cellular therapy
= required hospitalization
= open at network sites

Myeloma and Amyloidosis Research Portfolio

Open – no enrollment restrictions | **Check with RC – slot-based availability** | **Temporarily Closed to Enrollment** | **In Startup, Post-RSC/PEC**

Multiple Myeloma

- Newly Diagnosed
  - NCORP SWOG S2209
- R/R to 3+ lines (**no** prior BCMA)
  - BB2121-MM-002
- R/R to 3+ lines (**allows** prior BCMA)
  - BMS CA119-0002
- R/R to 1-3 lines
  - Janssen MonumenTAL-6
  - Kite iMMagine-3
- Post Ide-cel
  - NCORP A062102

AL Amyloidosis

- R/R to 1-3 lines
  - Nexcella NXC-201-AL-001

PRIOR Bispecific antibodies: now closed

Celgene 93269: CD3 x BCMA (Alnuctumab)

Regeneron LINKER-MM1 (Linvoseltamab)

BMS CA119-0002: BCMA x GPRC5D CAR-T

NCORP S22009: VRd-R or DRd-R or DRd-DR

Janssen TAL-6: Tal-P vs. Tal-Tec vs. EPd or PVd

NCORP A062102: Iberdomide after Ide-Cel

Kite: Anito-cel (BCMA CAR-T) vs Standard of care.

Nexcella: BCMA CAR-T

Hopeful holiday presents:

EMN-30 / TEC-4

GC012F-CD19/BCMA-001

Questions / Discussion