La nuova era della immunoterapia. Gli anticorpi bispecifici: cosa sono, indicazione e meccanismo d'azione

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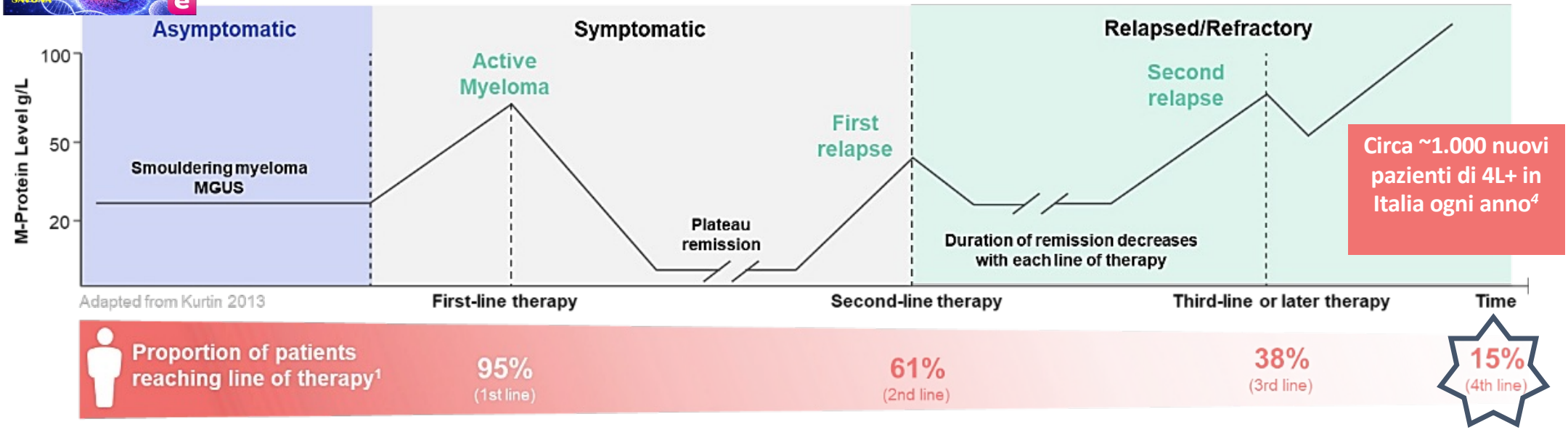
Multiple myeloma is a largely incurable disease characterized by periods of response followed by relapse and/or refractoriness to therapy



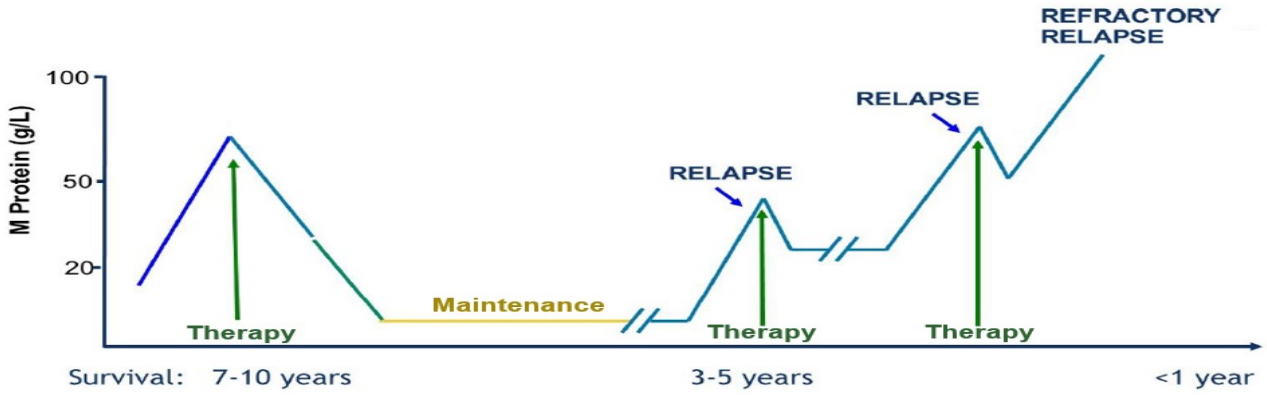
Circa ~1.000 nuovi pazienti di 4L+ in Italia ogni anno[4]

Il susseguirsi delle recidive aumenta ulteriormente l'impatto emotivo e fisico sui pazienti con MM, evidenziando un peggioramento significativo della QoL a seguito della ricaduta

L'ampio utilizzo nelle linee più precoci di trattamenti a base di IMID, PI e anti-CD38 ha generato e sta generando una popolazione di pazienti *triplo esposti* con un importante *unmet clinical need*

1) Fonseca et al. 2020 2)Kurtin et al, 2013 3) C. Hulin e al. 2017. 4) Yong et al.2016

Disease Progress



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Borrello I. *Leuk Res.* 2012;236:S3–12;
Gulla A, Anderson KC. *Haematologica*. 2020;105:2358–2367; Goldman-Mazur S, et al. *Blood Cancer J.* 2022;12:164.

Patients often have a **sustained response to front-line therapy** for several years, followed by **loss of response and disease progression***[1,2]

Treatment of disease progression is not standardized, but historically relies on **cycling through agents from three main drug classes** based on prior treatments and patterns of refractoriness†[2]

Response to subsequent therapy is often **not as deep or as sustained** as the response to front-line therapy, as **therapy-resistant clones** emerge over time[2–5]

•*Relapsed myeloma is previously treated disease that progresses and requires initiation of salvage therapy but is not primary refractory nor relapsed and refractory.[6]
•†Relapsed and refractory myeloma is disease that is nonresponsive on salvage therapy or progresses within 60 days of the last therapy in patients who achieved response at some point before progressing. Primary refractory myeloma is a disease that is nonresponsive in patients who have never achieved a response with any therapy.[6]
•M, monoclonal.

•1. Moreau P, et al. *Am Soc Clin Oncol Educ Book*. 2020;40:1–15. 2. Rajkumar SV, Kumar S. *Blood Cancer J.* 2020;10:94. 3. Borrello I. *Leuk Res.* 2012;236:S3–S12.
4. Kumar SK, et al. *Nat Rev Disease Primers* 2017;3:17046 (abstract). 5. Furukawa Y, Kikuchi J. *Int J Hematol.* 2020;111:496–511. 6. Rajkumar SV, et al. *Blood*. 2011;117:4695–4695.

Genetic mutations, along with immune evasion techniques, contribute to the development of refractory disease

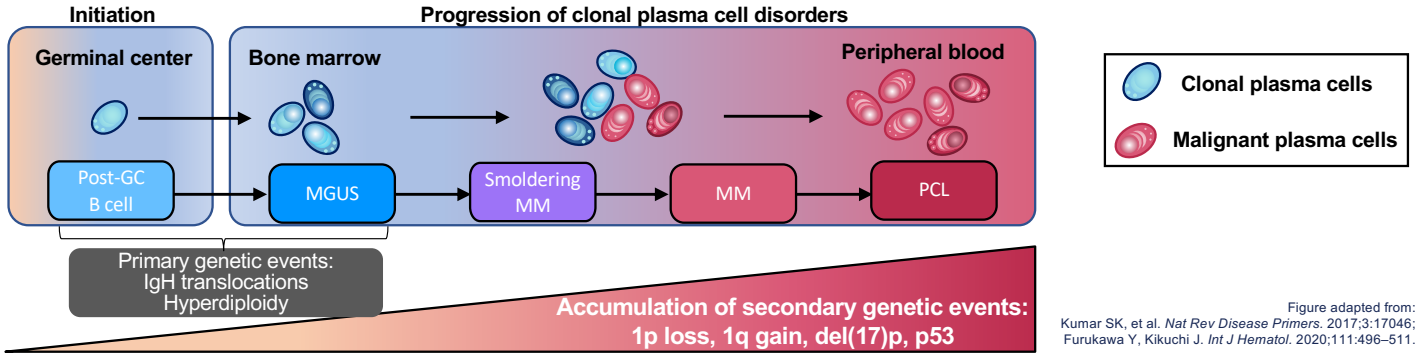


Figure adapted from:
Kumar SK, et al. *Nat Rev Disease Primers.* 2017;3:17046;
Furukawa Y, Kikuchi J. *Int J Hematol.* 2020;111:496–511.

Two primary genetic events account for nearly all cases of clonal plasma cell disorders: **Hyperdiploidy*** (40–50%) and ***IgH* (14q32) translocations**† (50–60%)[1]

High-risk cytogenetic abnormalities such as del(17p)/p53 and chromosome 1 abnormalities are rare in NDMM and **become increasingly prevalent** in RRMM, EMD, and PCL[1]

Plasma cells exhibit **more mechanisms of immune evasion as they progress** from healthy to MGUS to myeloma to RRMM[2]

Survival decreases and duration of **response becomes progressively shorter** with each line of therapy[3,4]

•*Hyperdiploidy is the presence of >46 chromosomes; in MM, it commonly involves additional copies of odd-numbered chromosomes 3, 5, 7, 9, 11, 15, 19, and 21.[3,5] †The *IgH* gene encodes the immunoglobulin heavy chains; the juxtaposition of *IgH* to various oncogenes enhances oncogene expression, resulting in impaired cell cycle progression and cell growth advantage.[3,5] del, deletion; EMD, extramedullary disease; GC, germinal center; *IgH*, immunoglobulin heavy chain gene; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; NDMM, newly diagnosed MM; p, short arm; PCL, plasma cell leukemia; q, long arm; RRMM, relapsed or refractory MM. References and definition of high-risk cytogenetics in MagnetisMM-3 in speaker notes.

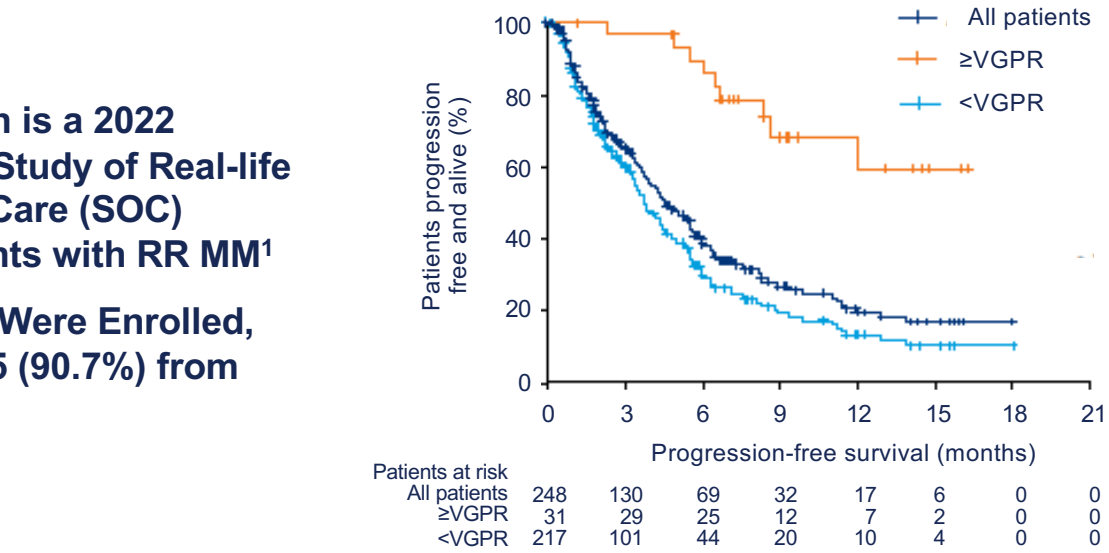
•Kumar SK et al. Nat Rev Dis Primers 2017;3:17046 (abstract) ; 2. Barwick BG, et al. Front Immunol.2019;10:1121.

RRMM Patients Who Are TCE Have Poor Prognosis (~30% ORR) and Survival Expectations of Approximately One Year Despite Recent Advances in Treatments

LocoMMotion is a 2022 Prospective Study of Real-life Standard of Care (SOC) in TCE Patients with RR MM[1]

248 Patients Were Enrolled, Including 225 (90.7%) from Europe[1]

LocoMMotion study (PFS; VGPR status)



92 unique treatment regimens were used in the enrolled population, including PIs, IMiDs, and anti-CD38 mAbs and various combinations demonstrating **the lack of a defined SOC**

29.8%
Overall Response Rate

4.6 months
Median PFS

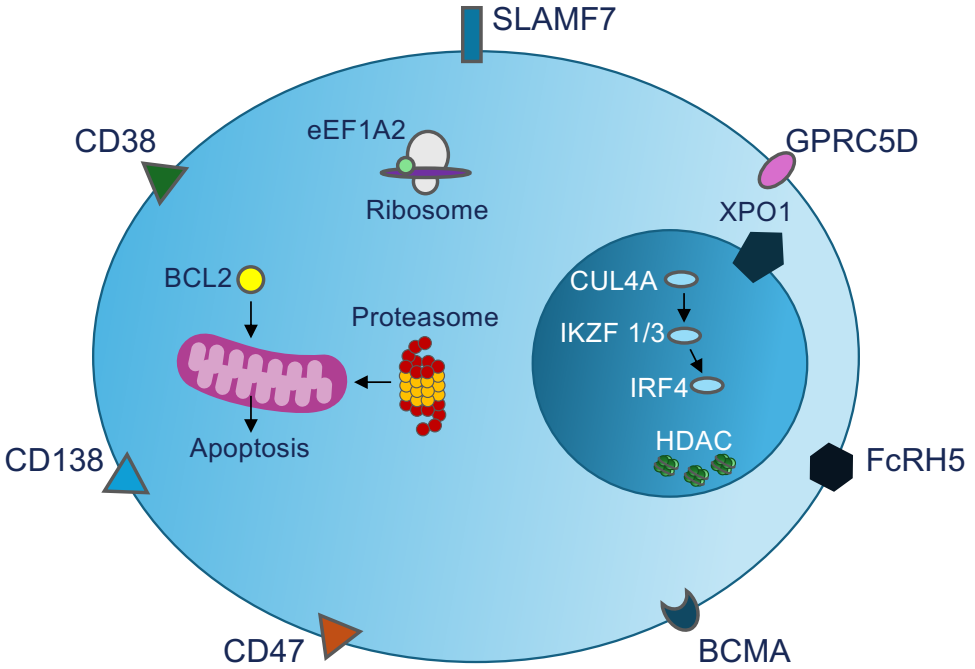
12.4 months
Median OS

- Mateos MV, et al. Leukemia. 2022;36(5):1371-1376.

Potential antigen targets for MM treatment

Characteristic antigens that are highly expressed on the surface of myeloma cells represent new and potential targets[1]

Antigen	Function
BCMA	Long-term survival of plasma cells[2]
CD138	Adhesion, proliferation, angiogenesis, suppression of apoptosis, and metastasis[2]
CD38	Regulation of calcium homeostasis, signaling, and adhesion[2]
FcRH5	Regulates BCR signaling and binds to IgG[2]
GPRC5D	Possible role in cell proliferation[2]
SLAMF7	Possible role in cell survival[2]
CD47	Role in cell survival, inhibition of macrophage phagocytic activity



- BCMA, B-cell maturation antigen; BCR, B-cell receptor; CD, cluster of differentiation; Fc, fragment crystallizable; FcRH5, FC receptor homologue 5; GPRC5D, G protein-coupled receptor class C group 5 member D; HDAC, Histone deacetylase; IgG, immunoglobulin G; IRF4, interferon regulatory factor 4; SLAMF7, signaling lymphocyte activation molecule family member 7.

1. Leow CC, Low MSY. J Pers Med. 2021;11:334; 2. Swan D, et al. Br J Haematol. 2022;196(3):488-506.

T-cell engagers: Redirecting T cells against myeloma cells

Bispecifics

BCMA	GPRC5D	FcRH5
Teclistamab	Talquetamab	Cevostamab
Elranatamab		
Linvoseltamab (REGN5458)		
ABBV-383 (TNB-383B)		
Alnuctamab (CC-93269)		

EMA has recommended a conditional marketing authorisation in the European Union (EU) for Teclistamb for the treatment of RRMM pts who have received at least 3 prior LOT, including an IMiD, a PI and an anti-CD38 antibody, and have demontrated PD on the last therapy.

The FDA has granted breakthrough therapy designation to talquetamab for the treatment of RRMM, who have previously received at least 4 prior LOT, including a PI, an IMiD, and an anti-CD38 antibody

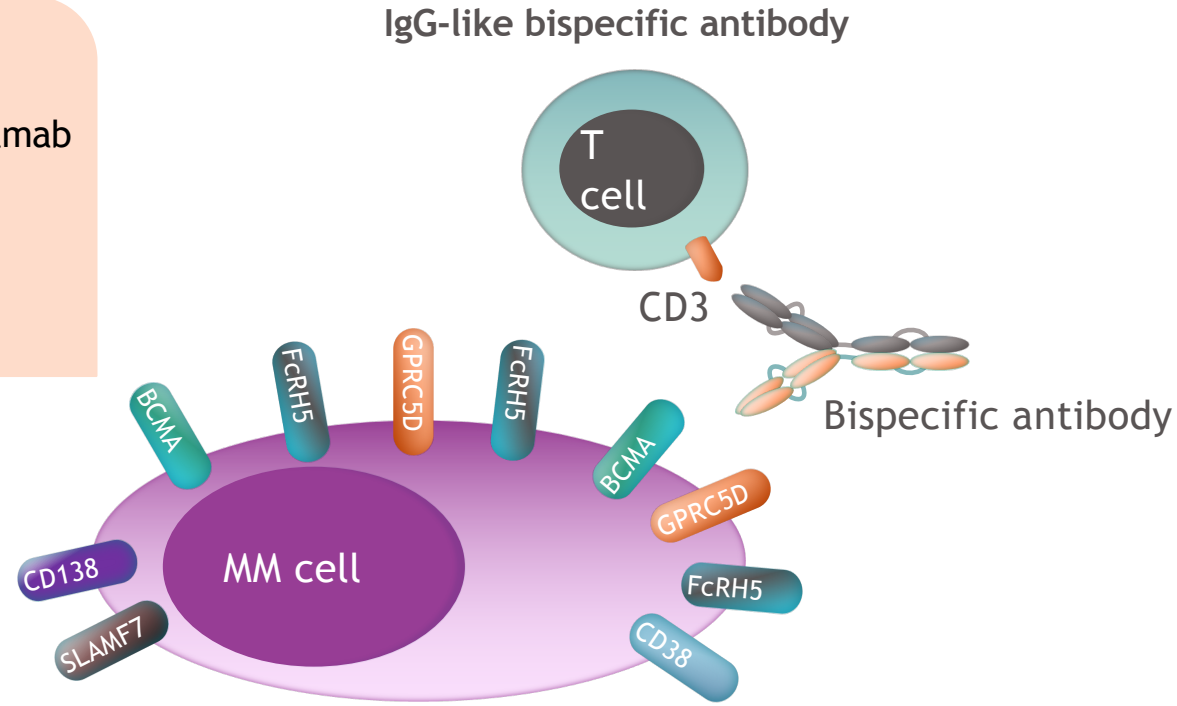


Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71; Rodriguez-Lobato LG, et al. Front Oncol. 2020;10:1243; and van de Donk NWCJ, et al. Lancet Haematol. 2021;8:e446-61.

Teclistamab è il primo anticorpo monoclonale bispecifico BCMA x CD3 off-the-shelf[1]

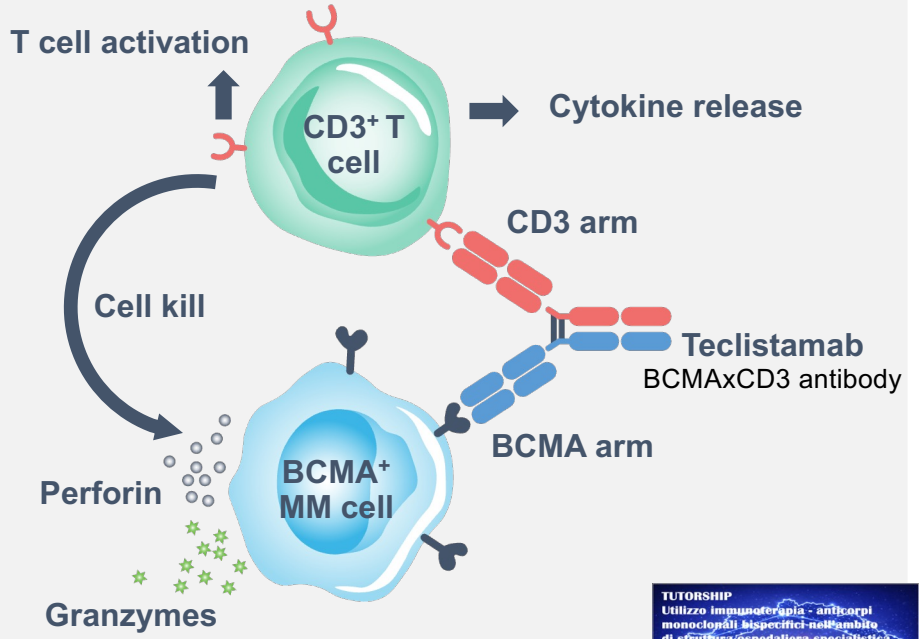
TECVAYLI **in monoterapia** è indicato per il trattamento di pazienti adulti affetti da mieloma multiplo recidivato e refrattario che abbiano ricevuto **almeno tre precedenti terapie**, compresi **un agente immunomodulatore, un inibitore del proteasoma e un anticorpo anti-CD38**, e che abbiano evidenziato **progressione della malattia durante l'ultima terapia**

Teclistamab è un **mAb bispecifico** che ha come bersaglio due diversi antigeni (BCMA e CD3) per aiutare il sistema immunitario a combattere il cancro

Teclistamab è stato rimborsato con Registro di monitoraggio che prevede la prescrivibilità **dopo 3 linee precedenti di terapia**

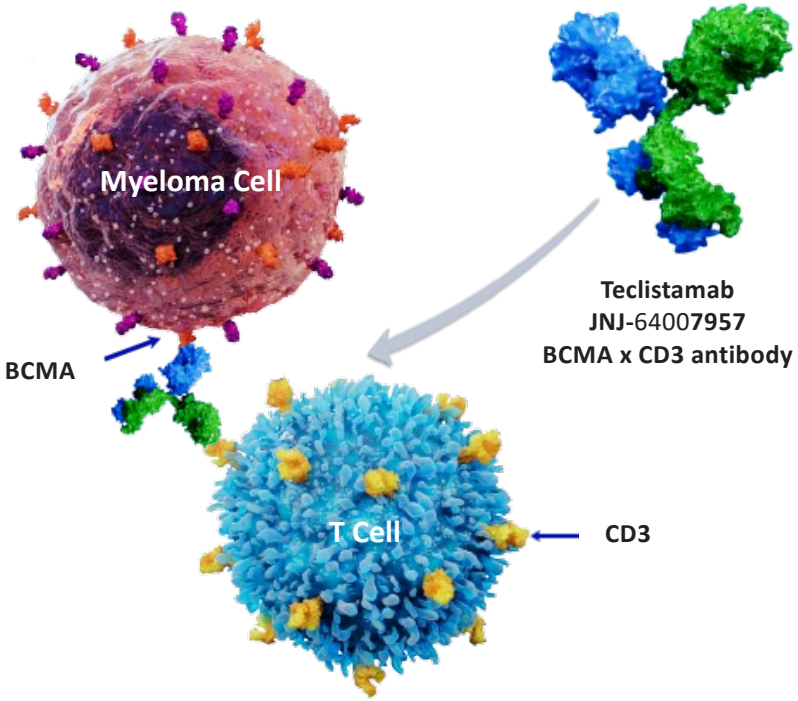
I pazienti riceveranno teclistamab sotto forma di **iniezione sottocutanea (SC)**

Meccanismo d'azione



1) Pilarisetti et al. 2020 2) SmPC TECVAYLI 2) Oriol et al. 2021 3) Lejeune et al. 2020 4) Novak et al.2004
5) Tai et al. 2006 6) Cho et al. 2020

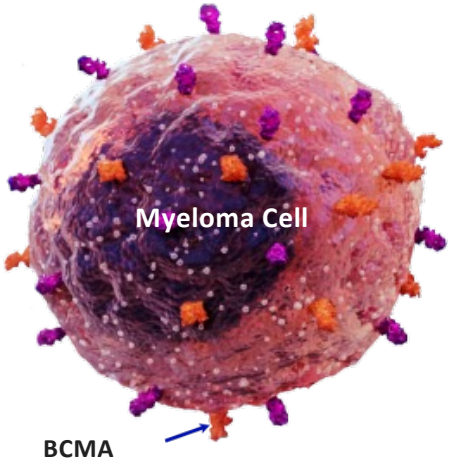
Teclistamab: A novel BCMA × CD3 T-cell redirecting bispecific antibody

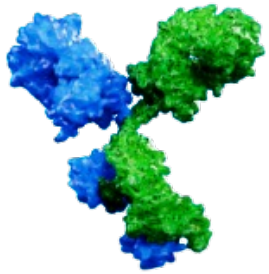


- Teclistamab (**JNJ-64007957**) is an off-the-shelf, personalised, weight-based, T-cell redirecting, bispecific antibody that **binds to CD3 on T cells** and **BCMA on plasma cells** to mediate T-cell activation and subsequent lysis of BCMA-expressing MM cells
- In August 2022, the European Commission approved teclistamab as **monotherapy** for adults with **R/R MM** who have received **≥3 prior therapies** and have demonstrated PD on the last therapy, marking teclistamab's **first worldwide approval**[1]
- In October 2022, the US FDA approved teclistamab as **monotherapy** for adult patients with **R/R MM** who have received **≥4 prior lines of therapies**[2]

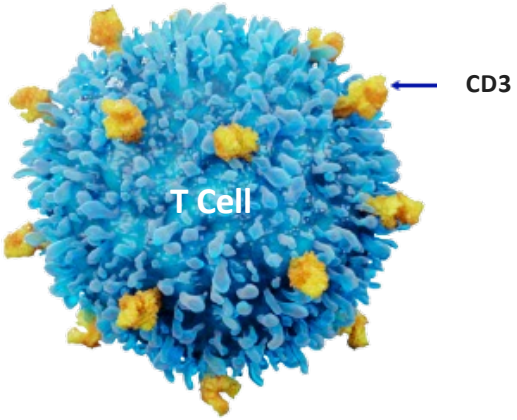
BCMA, B-cell maturation antigen; CD, cluster of differentiation; FDA, Food and Drug Administration; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PD, disease progression; QW, once weekly; RP2D, recommended Phase II dose; R/R, relapsed/refractory; SC, subcutaneous; SOC, standard of care.
Remaining footnotes have been extended to the slide notes.

Teclistamab: Mode of action





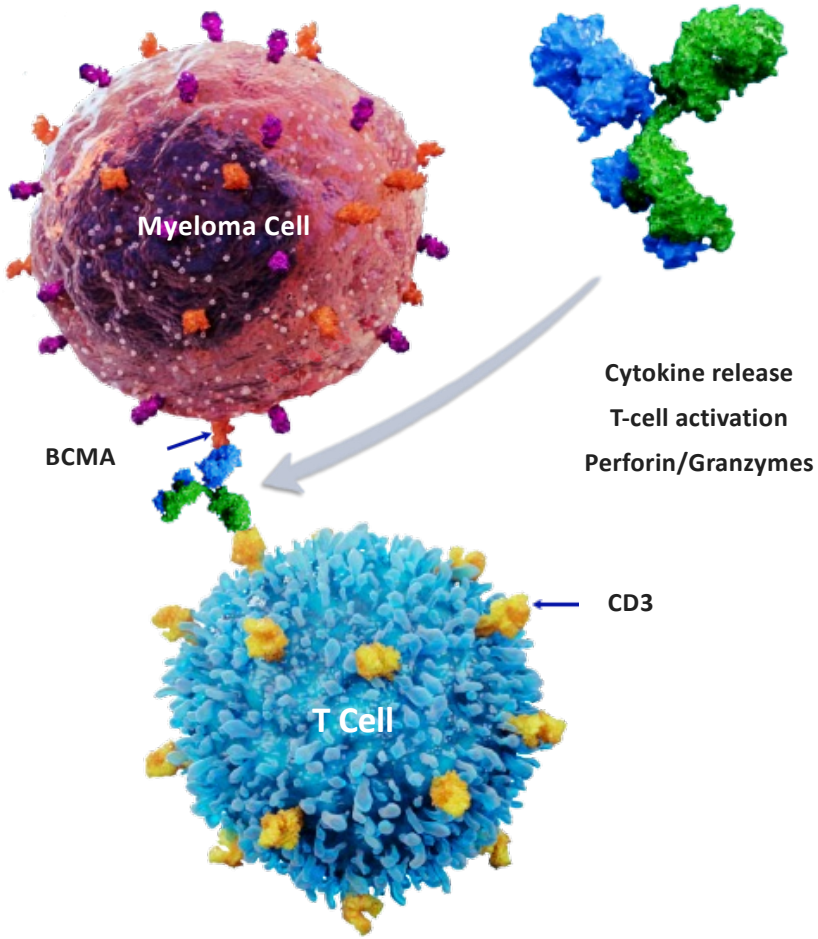
Teclistamab
JNJ-64007957
BCMA x CD3 antibody



Please refer to disclaimer slide.

Pillarisetti K, et al. Blood Adv 2020;4:4538–4549.

Teclistamab: Mode of action



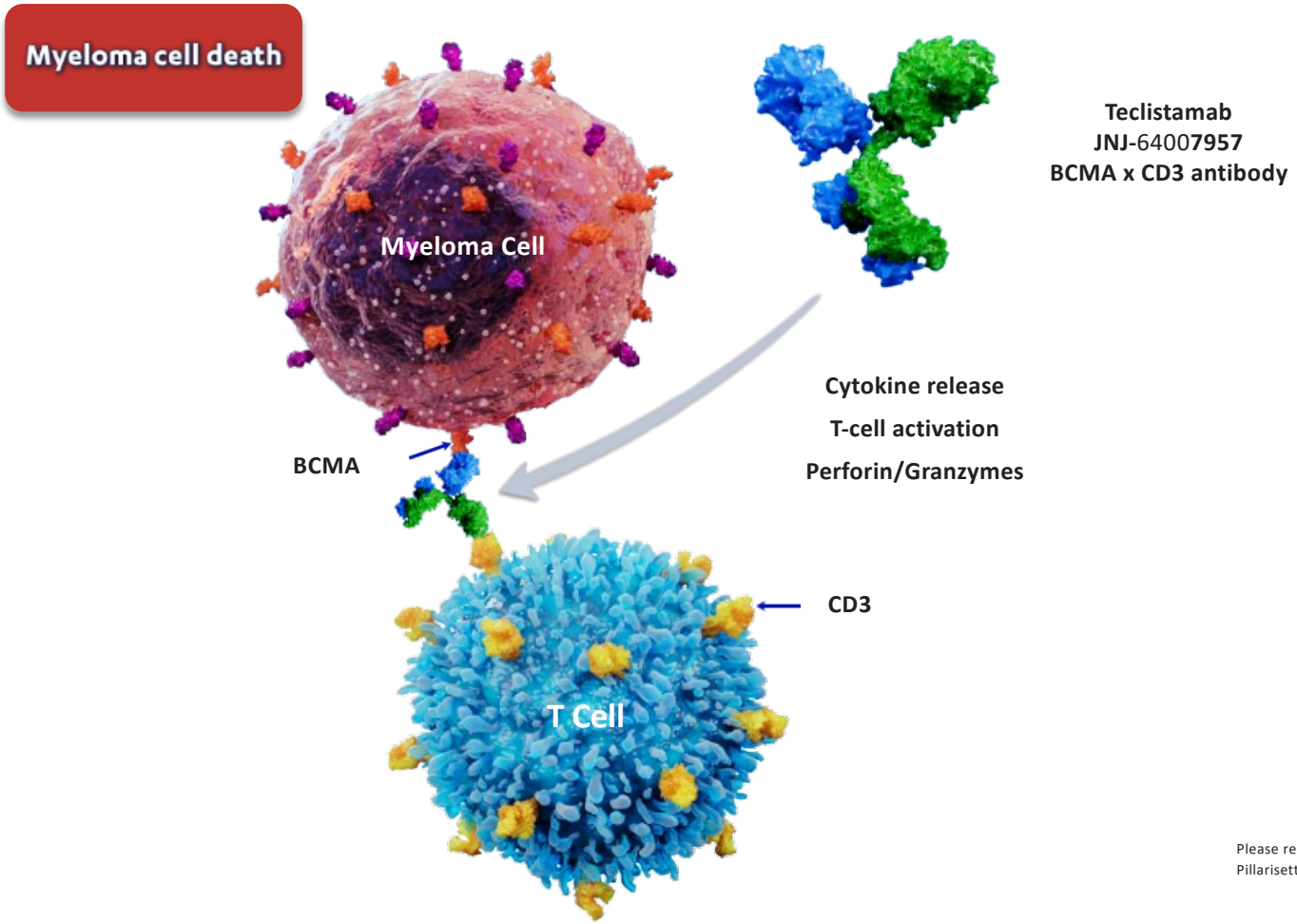
Teclistamab
JNJ-64007957
BCMA x CD3 antibody

Cytokine release
T-cell activation
Perforin/Granzymes

Please refer to disclaimer slide.

Pillarisetti K, et al. Blood Adv 2020;4:4538–4549.

Teclistamab: Mode of action



Teclistamab
JNJ-64007957
BCMA x CD3 antibody

Please refer to disclaimer slide.
Pillarisetti K, et al. Blood Adv 2020;4:4538–4549.

SAFETY

mFU 14.1 mo

AEs ≥20%, n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Nonhematologic		
CRS	119 (72.1)	1 (0.6)
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Pyrexia	45 (27.3)	1 (0.6)
Injection site erythema	43 (26.1)	0 (0)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0 (0)
Cough	33 (20.0)	0 (0)

Teclistamab was well tolerated; discontinuations and dose reductions were infrequent

- 2 patients (1.2%) discontinued due to AEs (grade 3 adenoviral pneumonia; grade 4 PML)
- The most common AEs were CRS and cytopenias
- **Infections** occurred in 126 (76.4%) patients (grade 3/4: 44.8%)
- There were 19 deaths due to AEs, including 12 COVID-19 deaths
- 5 deaths due to teclistamab-related AEs:
  - COVID-19 (n=2)
  - Pneumonia(n=1)
  - Hepatic failure (n=1)
  - PML (n=1)

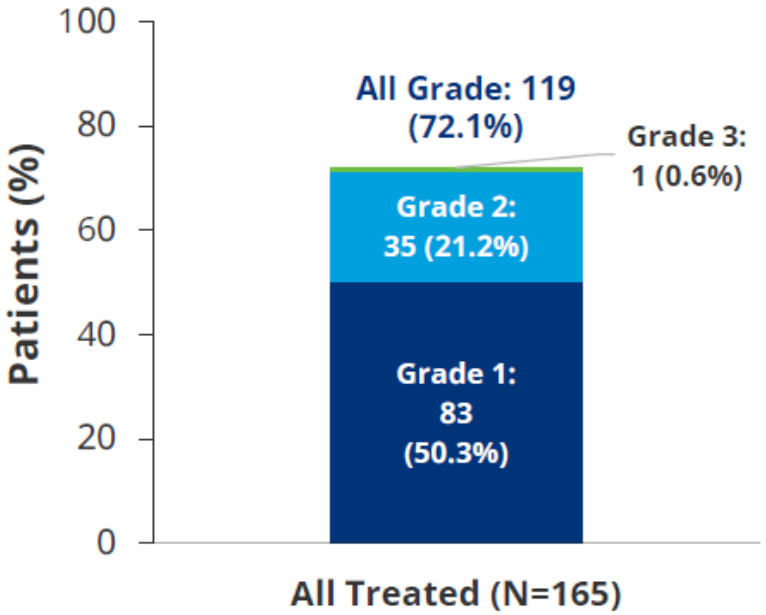
Nooka et al, Abs 8007 and Oral Presentation ASCO 2022

TECLISTAMAB: Cytokine Release Syndrome

mFU 14.1 mo

Parameter	N=165
Patients with CRS, n (%)	119 (72.1)
Patients with ≥2 CRS events	55 (33.3)
Time to onset[a] (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Received supportive measures[a] for CRS, n (%)	110 (66.7)
Tocilizumab[b]	60 (36.4)
Low-flow oxygen by nasal cannula[c]	21 (12.7)
Corticosteroids	14 (8.5)
Single vasopressor	1 (0.6)

Maximum CRS grade[d]



- Most CRS events were confined to step-up and first full treatment doses
- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that occurred in the context of concurrent pneumonia (resolved in 2 days)
- All CRS events fully resolved without treatment discontinuation or dose reduction

Nooka et al, Abs 8007 and Oral Presentation ASCO 2022

NEUROTOXIC EVENTS

Parameter	N=165
Neurotoxic event[a], n (%)	24 (14.5)
Headache	14 (8.5)
ICANS[b]	5 (3.0)
Dysgeusia	2 (1.2)
Lethargy	2 (1.2)
Tremor	2 (1.2)
Grade ≥3 events, n (%)	1 (0.6)
Time to onset, median (range) days	3.0 (1–13)
Duration, median (range) days	7.0 (1–291)
Received supportive measures for neurotoxic events[c], n (%)	14 (8.5)
Tocilizumab	3 (1.8)
Dexamethasone	3 (1.8)
Levetiracetam	2 (1.2)
Gabapentin	1 (0.6)

mFU 14.1 mo

- The overall incidence of neurotoxic events was low
- All neurotoxic events were grade 1/2, except for 1 grade 4 seizure (in the context of bacterial meningitis during cycle 7)
- 5 patients (3.0%) had a total of 9 ICANS events
- 7 events were concurrent with CRS
- All ICANS events were grade 1/2 and fully resolved
- There were no treatment discontinuations or dose reductions due to neurotoxic events, including ICAN

Nooka et al, Abs 8007 and Oral Presentation ASCO 2022

Hypogammaglobulinemia Prophylaxis, Management, and Recommendations

- Overall incidence: 71.5%[a]
- Incidence as an AE: 21.2%
- Deaths: 0%
- Discontinuations: 0%

Prophylaxis & management in MajesTEC-1	Recommendations per Nooka AK, et al. Cancer.2024
IgG replacement use: • Overall: 46.1% (≥1 dose of IgG replacement) – IV only: 35.2% – SC only: 3.6% – IM only: 0.6% – ≥1 route of administration: 6.7% • 6.1% started IgG replacement before receiving teclistamab-cqyv (including 5.5% who started before teclistamab-cqyv and continued throughout treatment)	• IgG levels should be monitored Q4W–Q6W and IgG replacement (IV or SC) should be used to maintain serum IgG levels ≥400 mg/dL. It is recommended to administer IgG replacement (0.4 g/kg) Q3W–Q6W. After reaching a steady state, IgG levels should be measured every 3 mo • IgG replacement should be administered per institutional guidelines for life-threatening infections (especially due to encapsulated bacteria), for serious or recurrent/chronic infections, and prophylactically based on physician-assessed clinical benefit • Note that IgG replacement may alter results of serum IgG testing and/or serum protein electrophoresis during assessment of disease status

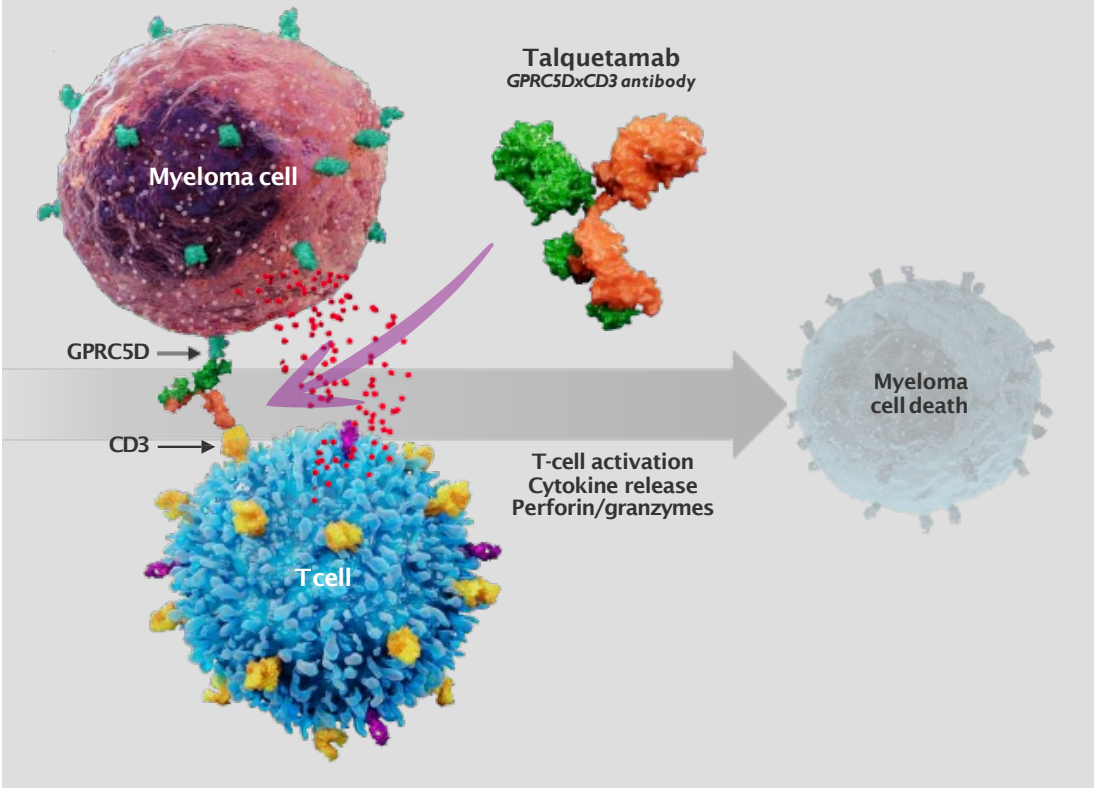
[a]Hypogammaglobulinemia defined as an AE, a laboratory IgG value <400 mg/dL, or both.

AE, adverse event; IgG, immunoglobulin G; IM, intramuscular; IV, intravenous; MM, multiple myeloma; mo, months; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; SC, subcutaneous.

Nooka AK, et al. *Cancer*. 2024;130(6):886–900.

Talquetamab: T-Cell Bispecific Antibody Targeting the Novel Antigen Target GPRC5D

- **Talquetamab is a novelfirst-in-class, off-the-shelf, T-cell redirecting bispecific antibody** directed against a new antigen target called GPRC5D[1,2]
- **GPRC5D is a novel antigen target in myeloma** that is highly expressed on malignant plasma cells with limited expression in normal human tissues,[3-6] including hematopoietic stem cells[7]
- **Talquetamab has shown an ORR of 64–70%** with QW and Q2W dosing in the MonumenTAL-1 study (NCT03399799/NCT04634552)[8]
- **Updated results** from the **MonumenTAL-1 study** are presented, including all patients treated at each RP2D for the first time, as well as a cohort of patients with prior CAR-T cell or bispecific antibody treatment

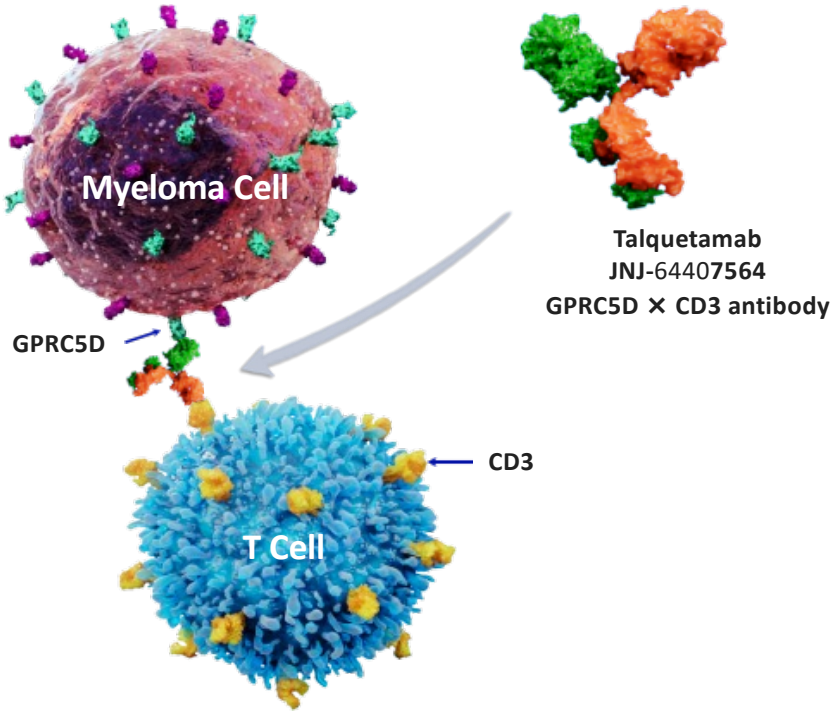


CAR-T, chimeric antigen receptor T cell; GPRC5D, G protein-coupled receptor family C group 5 member D; ORR, overall response rate; RP2D, recommended phase 2 dose; Q2W, every other week; QW, weekly.

1. Verkleij CPM, et al. *Blood Adv* 2021; 5(8):2196. 2. Pillarisetti K, et al. *Blood* 2020; 135:123. 3. Atamaniuk J, et al. *Eur J Clin Invest* 2012; 42:953. 4. Inoue S, et al. *J Invest Dermatol* 2004; 122:565. 5. Smith EL, et al. *Sci Transl Med* 2019; 11. 6. Goldsmith R, et al. Presented at IMW; September 8–11, 2021; Vienna, Austria. Poster P095. 7. Kodema T, et al. *Mol Cancer Ther* 2019; 18:15555. 8. Minnema M, et al. Presented at ASCO; June 3–7, 2022; Chicago, IL. Poster 8015.

Ajai Chari et al. - Oral Presentation #157 - ASH 2022

Talquetamab: A novel GPRC5D x CD3 T-Cell redirecting bispecific antibody



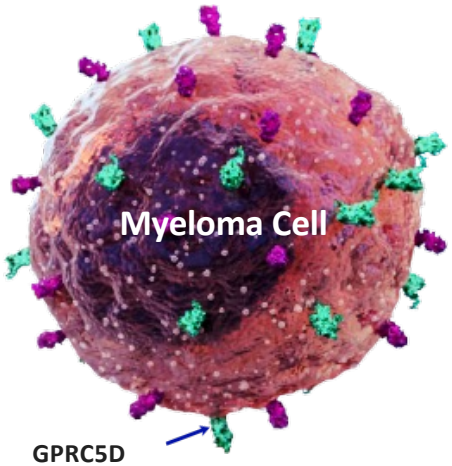
- Talquetamab (**JNJ-64407564**) is an off-the-shelf, T-cell redirecting bispecific antibody
- Talquetamab engages T cells via CD3 and targets **GPRC5D**, which is overexpressed on **myeloma cells**; this mediates T-cell activation and subsequent lysis of GPRC5D-expressing MM cells
- The **MonumenTAL-1 Phase I/II** study identified two RP2Ds for talquetamab monotherapy:[1]
  - **405 µg/kg SC QW**
  - **800 µg/kg SC Q2W**
- In August 2023, the EMA approved talquetamab for the treatment of patients with R/R MM who had received **≥3 LOT, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody**[2]
- In August 2023, talquetamab received FDA approval for the treatment of patients with R/R MM who have received **≥4 LOT, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody**[3]

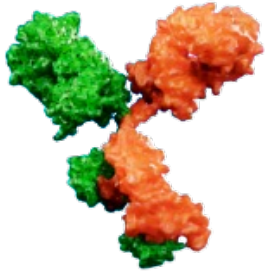
Please refer to disclaimer slide

CD, cluster of differentiation; EMA, European Medicines Agency; FDA, Food and Drug Administration; GPRC5D, G protein-coupled receptor class C group 5 member D; LOT, lines of therapy; MAA, marketing authorization application; MM, multiple myeloma; Q2W, every other week; QW, weekly; RP2D, recommended Phase II dose; R/R, relapsed/refractory; SC, subcutaneous.

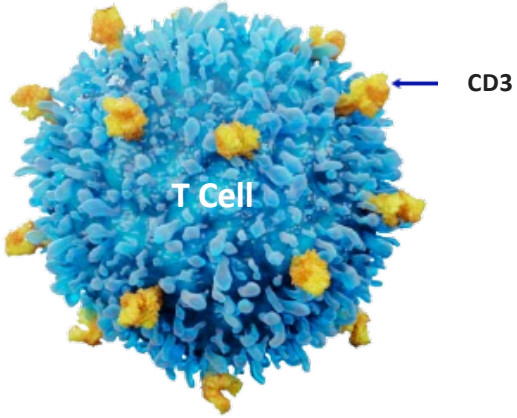
1. Chari A, et al. N Engl J Med. 2022;387(24):2232–2244; 2. https://www.jnj.com/european-commission-approves-talvey-talquetamab-janssens-novel-bispecific-therapy-for-the-treatment-of-patients-with-relapsed-and-refractory-multiple-myeloma.html (Accessed 19 January 2024);
3. https://www.prnewswire.com/news-releases/us-fda-approves-talvey-talquetamab-tgvs-a-first-in-class-bispecific-therapy-for-the-treatment-of-patients-with-heavily-pretreated-multiple-myeloma-301897786.html (Accessed 10 August 2023).

Talquetamab: Mode of action



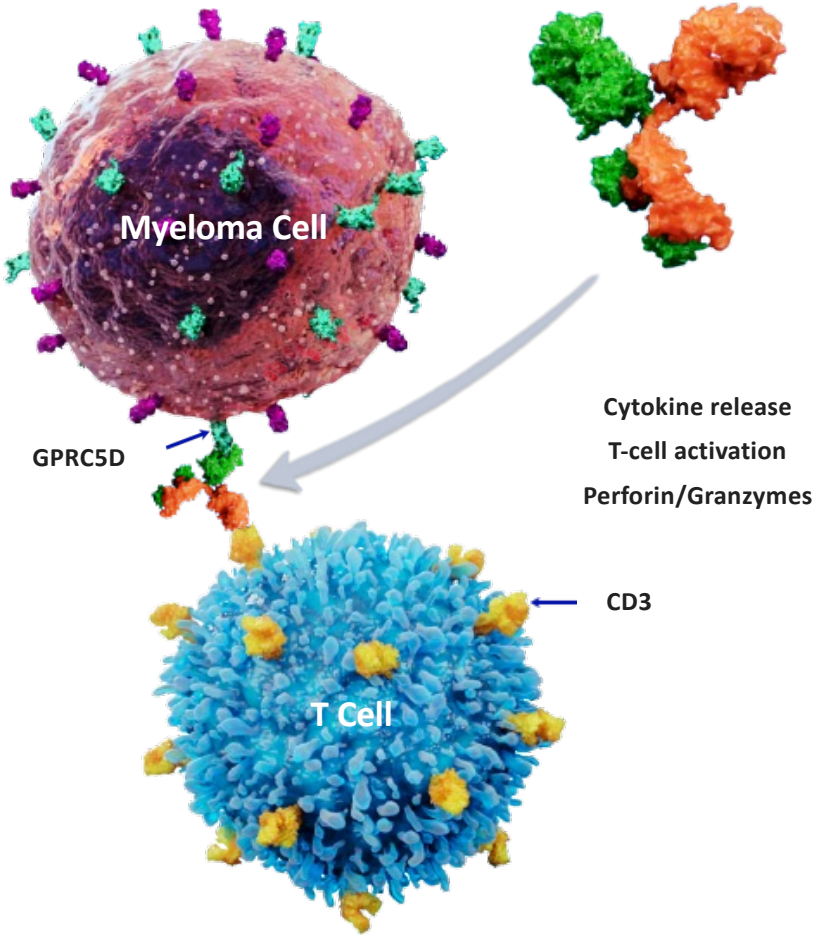


Talquetamab
JNJ-64407564
GPRC5D x CD3 antibody



Please refer to disclaimer slide.
Verkleij CPM, et al. Blood Adv. 2021;5:2196–2215.

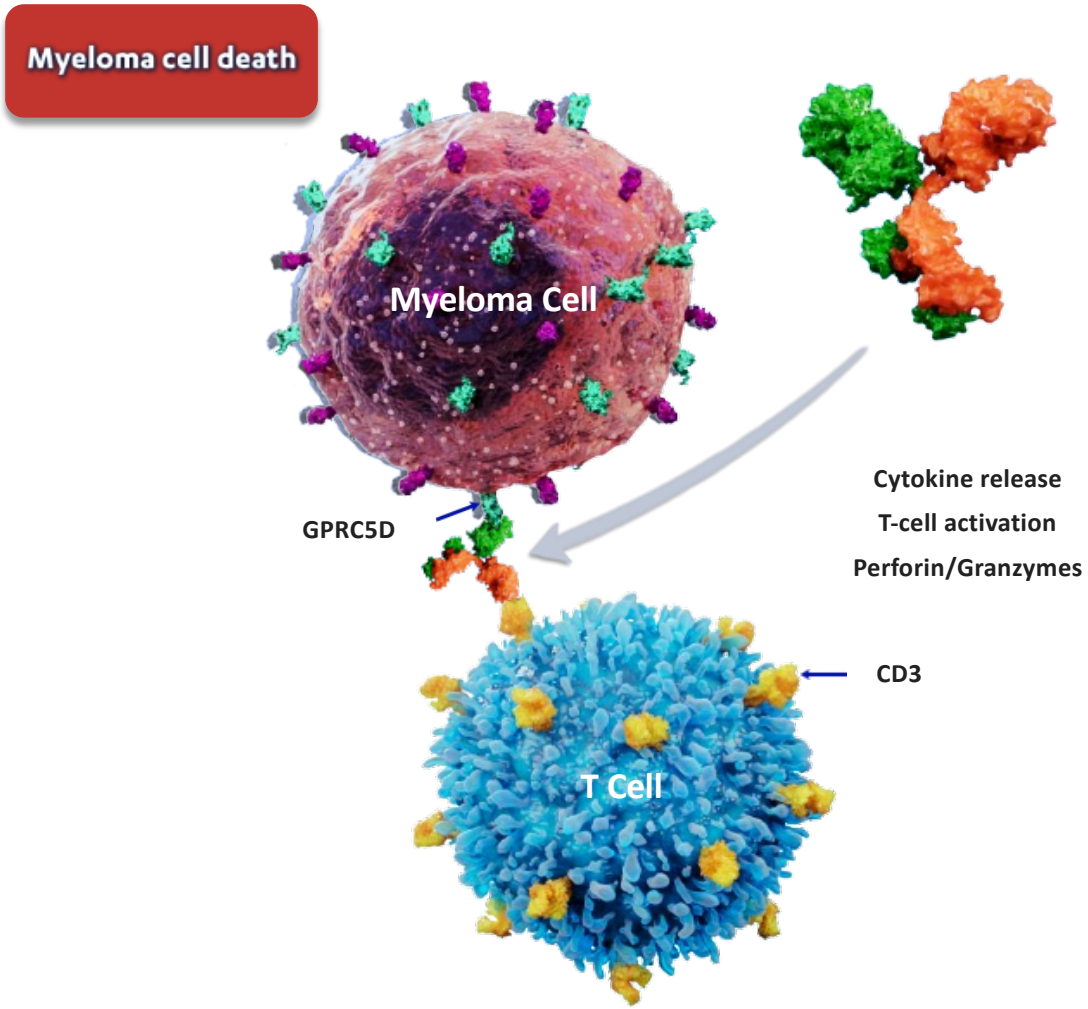
Talquetamab: Mode of action



Talquetamab
JNJ-64407564
GPRC5D x CD3 antibody

Please refer to disclaimer slide.
Verkleij CPM, et al. Blood Adv. 2021;5:2196–2215.

Talquetamab: Mode of action



Talquetamab
JNJ-64407564
GPRC5D x CD3 antibody

Please refer to disclaimer slide.
Verkleij CPM, et al. Blood Adv. 2021;5:2196–2215.

MonumenTAL-1: Nonhematologic Safety

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
CRS	113 (79.0)	3 (2.1)	105 (72.4)	1 (0.7)
Skin-related AEs[d]	80 (55.9)	0	98 (67.6)	1 (0.7)
Nail-related AEs[e]	74 (51.7)	0	63 (43.4)	0
Dysgeusia[f]	69 (48.3)	NA	67 (46.2)	NA
Rash-related AEs[g]	56 (39.2)	2 (1.4)	39 (26.9)	8 (5.5)
Weight decreased	57 (39.9)	3 (2.1)	47 (32.4)	2 (1.4)
Pyrexia	53 (37.1)	4 (2.8)	35 (24.1)	1 (0.7)
Asthenia	37 (25.9)	3 (2.1)	13 (9.0)	2 (1.4)
Dry mouth	36 (25.2)	0	53 (36.6)	0
Diarrhea	34 (23.8)	3 (2.1)	32 (22.1)	0
Dysphagia	34 (23.8)	0	33 (22.8)	3 (2.1)
Fatigue	32 (22.4)	5 (3.5)	29 (20.0)	1 (0.7)
Decreased appetite	25 (17.5)	2 (1.4)	29 (20.0)	2 (1.4)

Median follow-up 14.9

- **Low rates of grade 3/4 nonhematologic AEs** were observed
- **Low rates of discontinuation due to AEs** were observed with QW (4.9%) and Q2W (6.2%) schedules
  - **Most common AEs were CRS, skin-related events, nail-related events, and dysgeusia**
  - Rates of high-grade skin, nail, and rash-related events were low
  - Dysgeusia was managed with supportive care, and at times with dose reduction
- At 0.4 mg/kg QW and at 0.8 mg/kg Q2W,
  - 8.4% and 13.8% had dose delays due to AEs
  - 14.7% and 6.2% had dose reductions due to AEs
- At time of data cut-off, no patients in these cohorts died due to drug-related AEs

AEs were graded by CTCAE v4.03 with CRS events graded per Lee et al 2014 criteria. [a]With 2–3 step-up doses. [b]Range, 0.5–26.1, with lower range denoting patients who died. [c]Range, 0.2–17.9, with lower range denoting patients who died. [d]Includes skin exfoliation, dry skin, pruritus, palmar-plantar erythrodysesthesia syndrome. [e]Includes nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging. [f]Per CTCAE, the maximum grade of dysgeusia is 2. [g]Includes rash, maculopapular rash, erythematous rash, erythema. AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for AEs; mFU, median follow-up; NA, not applicable; RP2D, recommended phase 2 dose; Q2W, every other week; QW, weekly; SC, subcutaneous.

MonumenTAL-1: Safety

Hematologic adverse events

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	64 (44.8)	45 (31.5)	57 (39.3)	36 (24.8)
Neutropenia	49 (34.3)	44 (30.8)	41 (28.3)	32 (22.1)
Lymphopenia	40 (28.0)	37 (25.9)	38 (26.2)	37 (25.5)
Thrombocytopenia	39 (27.3)	29 (20.3)	39 (26.9)	24 (16.6)

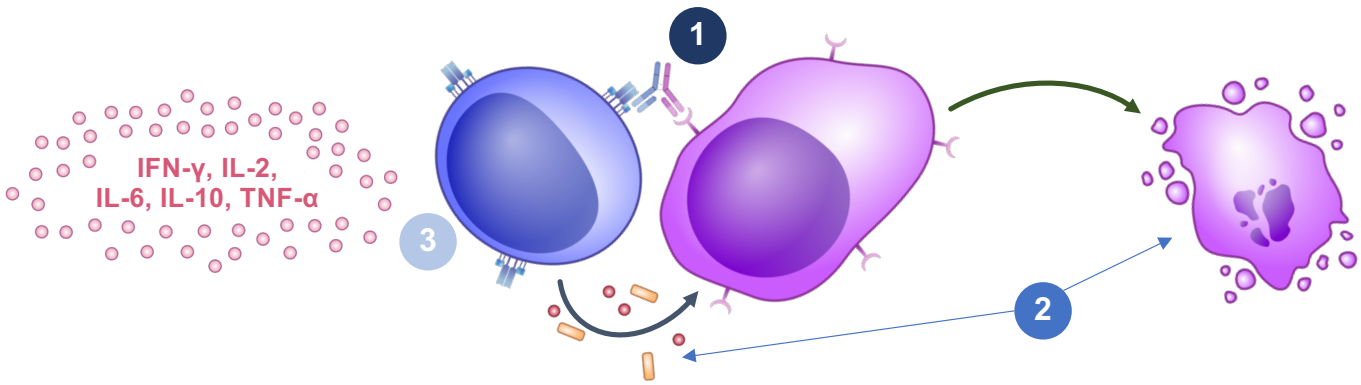
- Most high-grade AEs were cytopenias
- Cytopenias were generally limited to the first few cycles

Infections

- At 0.4 mg/kg QW and 0.8 mg/kg Q2W:
  - Infections occurred in 57.3% and 50.3%
    - Grade 3/4 in 16.8% and 11.7%
  - 5 (3.5%)[d] and 4 (2.8%)[e] patients had opportunistic infections
  - 13 (9.1%) and 16 (11.0%) patients had COVID-19
    - Grade 3/4 in 0.7% and 2.1%
    - 2 patients died from COVID-19
- 13.3% and 9.7% of patients received IVIg, respectively

Data cut-off date: May 16, 2022.
AEs were graded by CTCAE v4.03 [a]With 2–3 step-up doses. [b]Range, 0.5–26.1, with lower range denoting patients who died. [c]Range, 0.2–17.9, with lower range denoting patients who died. [d]Includes 2 cases of oesophageal candidiasis, and 1 case each of adenovirus infection, fungal sepsis, and retinitis viral. [e]Includes 1 case each of cytomegalovirus infection, cytomegalovirus viraemia, herpes ophthalmic, and esophageal candidiasis.
AE, adverse event; CTCAE, Common Terminology Criteria for AEs; IVIg, intravenous immunoglobulin; mFU, median follow-up; Q2W, every other week; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

Elranatamab is a BsAb that binds BCMA on myeloma cells and engages CD3 on T cells, activating T cells independent of the MHC I



Elranatamab bypasses the need to engage the whole **TCR** by engaging **CD3ε**, a specific subunit of CD3 that is part of the TCR, allowing for direct activation of **T cells** in the presence of **myeloma cells**

T-cell stimulation via **CD3ε** leads to the release of **perforin** (creating pores within the plasma cell membrane) + **granzyme B** (entering the plasma cell through those pores), and subsequent **myeloma cell apoptosis and cytolysis**

Elranatamab-mediated **T-cell activation** is associated with the release of **cytokines** that may further enhance the anti-tumor response

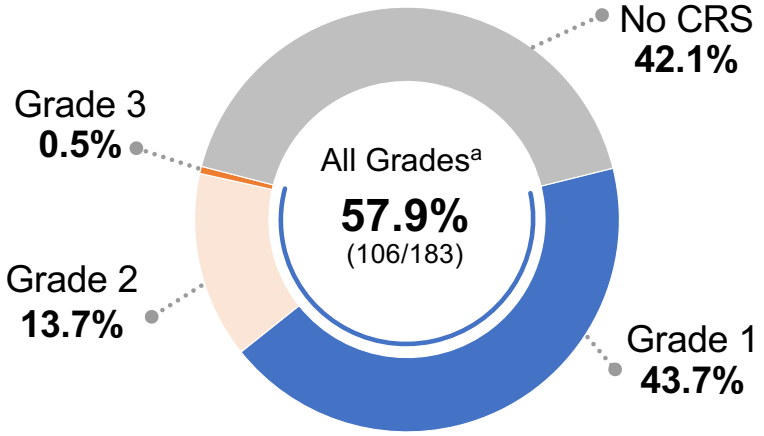
- BCMA, B-cell maturation antigen; CD, cluster of differentiation; IFN, interferon; IL, interleukin; MHC I, major histocompatibility complex class I; TCR, T-cell receptor; TNF, tumor necrosis factor.

- 1. Abramson HN. *Int J Mol Sci.* 2020;21:5192. 2. Shah N, et al. *Leukemia*. 2020;34:985–1005.
4. Tai Y-T, Anderson KC. *Expert Opinion Biol Ther*. 2019;19:1143–1156.

On Elranatamab, CRS Events Were Mostly Low Grade and Manageable with Appropriate Intervention, Majority Occurring with Early Onset

Total Safety population (n=183)
Including prior BCMA-directed therapy cohort

Incidence of CRS in Patients Receiving the Recommended Step-up Dose Regimen for *Elranatamab* (N=183)[1,c,d]



CRS Parameter[2]	Grade 1	Grade 2	Grade 3
Fever	≥38˚C	≥38˚C	≥38˚C
Hypotension	none	No vasopressor	One vasopressor with or without vasopressin
Hypoxia	none	Requires low-flow nasal cannula or blow-by	Requires low-flow nasal cannula, facemask, nonrebreather or Venturi

75.4% (79/106) of CRS Events Associated with *Elranatamab* Were Grade 1[1,2,3]

- The single Grade 3 CRS event occurred on the day following the first dose in a patient with prior BCMA-directed ADC or CAR T-cell therapy
- ***No Grade 4/5 CRS*** events were observed

Permanent Discontinuation Rates Due to CRS Events Were Low (0.5%)[1,2,3]

- CRS resolved in most patients with supportive care
  - 33% (35/106) received anti IL-6 inhibitor to manage CRS
  - 15,1% (16/106) patients received steroids to manage CRS

Time to Onset of CRS[1]

2 days median
(Range: 1–9 days)

Duration of CRS[1]

2 days median
(Range: 1–19 days)

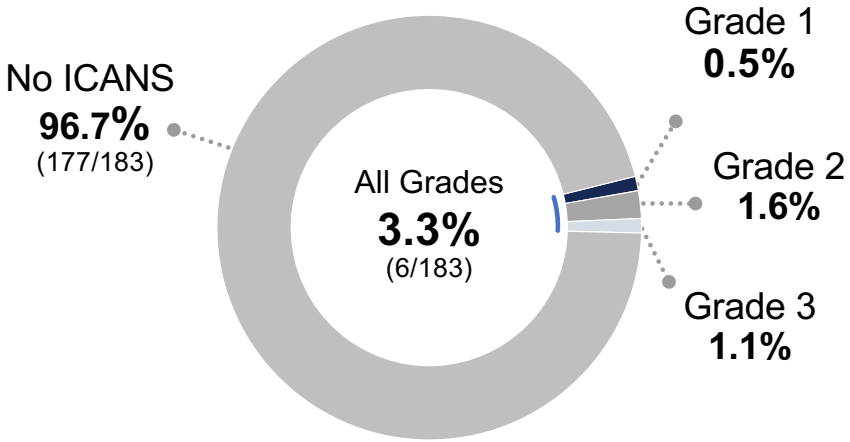
a. Short duration defined as 2 days. **b.** Supportive therapy (including antipyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) was administered and laboratory testing performed as appropriate.[2]
c. CRS was graded using ASTCT criteria.[2]
ASTCT, American Society for Transplantation and Cell Therapy; ADC, antibody drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome.

1. Elrexfio. SmPC 2. Lesokhin A, et al. *Nat Med.* 2023. 3.Lee et al. *Biol Blood Marrow Transplant*, 2019

On Elranatamab, 5 of 6 ICANS Cases Occurred with the First Dose, Were Mostly Low Grade (Grades 1/2) and Infrequent (3.3%); the Majority of Cases Were Reversible

Total Safety population (n=183)
Including prior BCMA-directed therapy cohort

Incidence of ICANS in Patients Receiving Recommended Step-up Dose Regimen for Elranatamab[1,2,3,a] (N=183)



Neurotoxicity Domain[2]	Grade 1	Grade 2	Grade 3
ICE Score	7–9	3–6	0–2
Depressed Level of Consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or non-convulsive seizures on EEG that resolve with intervention
Motor Findings	N/A	N/A	N/A
Raised Intracranial Pressure / Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging

96.7% of Patients Did Not Experience an ICANS Event[1,2,3]

- Grade 3 events occurred in 2 patients who had received prior BCMA-directed ADC or CAR T-cell therapy
- **No Grade 4/5 ICANS** events were observed

Onset of ICANS events occurred with the first dose in 5 patients; the majority of events were reversible[1]

Permanent Discontinuation Rates Due to ICANS in the Overall Population Were Low (1.1%)[1,2]

- 2 patients discontinued treatment permanently due to Grade 3 ICANS[1] – Both had received prior BCMA-directed ADC or CAR T-cell therapy[1]

Time to Onset of ICANS[1]

3 days median
(Range: 1–4 days)

Duration of ICANS[1]

2 days median
(Range: 1–18 days)

‡ICAN grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.
a. ICANS was graded by ASTCT criteria.[2]
ADC, antibody-drug conjugate; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ICANS, immune cell-associated neurotoxicity syndrome.
1. Elrexfio. SmPC, 2. Lesokhin A, et al. *Nat Med.* 2023. 2.Lee et al. *Biol Blood Marrow Transplant*, 2019

Infection TEAEs in patients receiving elranatamab

Cohort A (n=123)
No prior BCMA-directed therapy cohort

Infection TEAEs in ≥5% of patients, n (%)[1]	Any grade	Maximum Grade 3/4	Grade 5[a]
COVID-19 related[b]	36 (29.3)[c]	19 (15.4)	2 (1.6)
Pneumonia	20 (16.3)	10 (8.1)	0
Upper respiratory tract infection	20 (16.3)	0	0
Sinusitis	13 (10.6)	2 (1.6)	0
Urinary tract infection	12 (9.8)	4 (3.3)	0
Sepsis	8 (6.5)	8 (6.5)	0
Bacteremia	7 (5.7)	2 (1.6)	0
Cytomegalovirus infection reactivation	7 (5.7)	2 (1.6)	0

Opportunistic infections in <5% of patients, n (%)[1,d]	Any grade	Maximum Grade 3/4	Grade 5[a]
Pneumocystis jirovecii pneumonia	6 (4.9)	5 (4.1)	0
Cytomegalovirus infection	4 (3.3)	0	0
Adenoviral hepatitis	1 (0.8)	0	1 (0.8)
Adenovirus infection	1 (0.8)[e]	0	1 (0.8)
Pneumonia adenoviral	1 (0.8)[e]	0	1 (0.8)
Pneumonia cytomegaloviral	1 (0.8)	1 (0.8)	0

- **Infections occurred in 69.9% of patients; 39.8%** of patients had **Grade 3 or 4** events and infections were fatal in 6.5% of patients[1]

The most frequently reported infectious disease was COVID-19, coinciding with the ongoing pandemic during the study period[1]

- Among patients with quantitative Ig data (n=72 at baseline, n=102 post-baseline), **almost all (98.6%) had immune paresis[f] at baseline and 75.5% of patients had IgG <400mg/dL while on treatment[1]**
  - Ig replacement was received by 43.1% of patients during the study

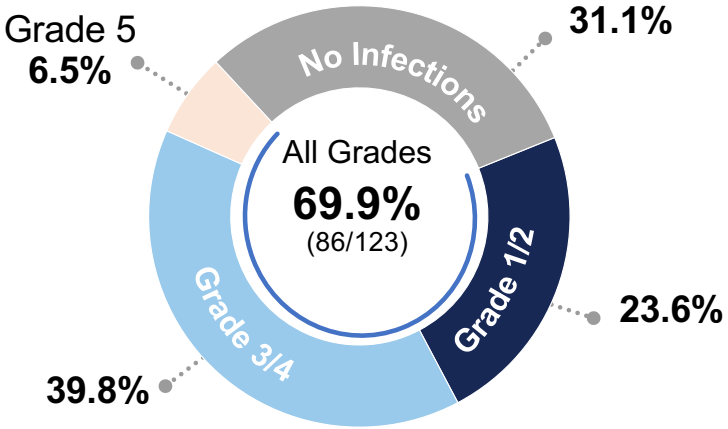
[a]Three (2.4%) patients had G5 septic shock. [b]Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries. [c]25/36 (69.4%) patients developed COVID-19 or COVID-19 pneumonia and 10/36 (30.6%) only had a positive SARS-CoV-2 test without developing the disease. [d]Opportunistic infection TEAEs includes preferred terms: Adenoviral hepatitis, Adenovirus infection, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Cytomegalovirus viremia, Pneumonia adenoviral, Pneumonia cytomegaloviral, *Pneumocystis jirovecii* pneumonia. [e]Preferred terms both reported in the same patient. [f]Defined as at least two uninvolved immunoglobulin isotypes below the lower limit of normal.
IgG, immunoglobulin G; TEAE, treatment-emergent adverse event.

1. Lesokhin A, et al. *Nat Med*. 2023.

Cohort A is Associated with 39.8% Grade 3/4 Infections; 7.3% of Patients Discontinued Due to Infections

COHORT A (n=123)
No Prior *BCMA-directed therapy*

Cohort A: Incidence of Infection with *Elranatamab* [a] (N=123)



Time to First Onset of Infections

15 days median
(Q1 and Q3: 7 and 28 days)

Duration of Infections

15 days median
(Q1 and Q3: 7 and 31 days)

Permanent Discontinuations Due to Infections Were 7.3%

Infections Occurring in ≥5% of Patients (N=123)

	All Grades n (%)
Upper Respiratory Tract Infection	20 (16.3)
Pneumonia	20 (16.3)
COVID-19 Pneumonia	18 (14.6)
Sinusitis	13 (10.6)
Urinary Tract Infection	12 (9.8)
Sepsis	8 (6.5)
Bacteremia	7 (5.7)
Covid-19	7 (5.7)
Cytomegalovirus Infection Reactivation	7 (5.7)

a. Infection was graded by NCI CTCAE v4.03. b. IVIg should be administered for Ig levels ≤400 mg/dL until resolution of hypogammaglobulinemia.[2]

COVID, coronavirus disease; IVIg, intravenous immunoglobulin; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Lesokhin A, et al. *Nat Med.* 2023..

Orientarsi tra diversi BsAbs (1/2)

	Elranatamab	Vs	Teclistamab
Patient Population	MagnetisMM-3 Cohort A BCMA-naïve[1] HR Cytogenetics 25.2% | R-ISS III 15.4 | EMD 31.7% TCR 96.7% | PDR 42.3% Median prior LoT: 5		MajesTEC-1 BCMA-naïve[6-8] HR Cytogenetics 26% | ISS III 12% | EMD 17% TCR 78% | PDR 30.3% Median prior LoT: 5
Admin/ convenience	Fixed dose, SC[2] Monitor ~5 days during SUD (48 h / 48 h)[2]; US inpatient doses FoC Flexibility for restart after dose delay[2] Dose frequency reduced to Q2W for ≥PR at W25+[2], Q4W after ≥6 cycles of Q2W [3]		Weight-based dose, SC[7] Monitor ~7 days during SUD (48 h d1 / 48 h d3 / 48 h d5 per SmPC) Janssen reviewing FoC SUD Less flexibility with restart after dose delays Dose frequency reduced to Q2W if ≥CR for ≥6 mo

	BCMA-naïve MagnetisMM-3[3] n=123	SmPC BCMA-naïve[2] n=123	Prior BCMA pooled analysis[4] N=87		BCMA-naïve MajesTEC-1[6] N=165	SmPC BCMA-naïve[7] N=165	Prior BCMA Cohort C[9] N=38
Efficacy							
mFU, mo	33.9	15.2*	11.3	**mFU, mo**	30.4	NR	6.9
ORR (≥CR), %	61.0 (37.4)	61.0 (35.7)	46.0 (18.4)	**ORR (≥CR), %**	63.0 (46.1)	63.0 (39.4)	ADC: 38 (NR) CAR T: 45 (NR)
MRD, %	90.3 of evaluable ≥CR	89.7 of evaluable ≥CR	NR	**MRD, %**	85.7 of evaluable	46.2 of evaluable ≥CR	NR
mDOR, mo	NE 30-mo rate 61.0%	NE 15-mo rate 70.8%	17.1	**mDOR, mo**	24.0	18.4	NE
mPFS, mo	17.2	NR	5.5	**mPFS, mo**	11.4	NR	NR
mOS, mo	24.6	NR	12.1	**mOS, mo**	22.2	NR	NR
Safety	**SmPC N=183**	**MM-3 *Nat Med.* 14.7 mo mFU**	**MM-3 33.9 mo mFU**		**SmPC[7]**	**MajesTEC-1 30.4mo mFU6**	
CRS, % (Gr3)	57.9 (0.5)	56.3 (all Gr 1–2) 90.6% *during* SUD	57.7†	**CRS, % (Gr3)**	72 (0.6) 24% *after* first full dose	72.1 (0.6)	
ICANS, % (Gr3)	3.3 (1.1)	3.4 (all Gr 1–2)	4.9†	**ICANS, % (Gr3)**	3.0 (0)	NR	
PN, % (Gr3)	15.8 (1.1)	Motor dysfunction 17.1 Sensory neuropathy 13.8	NR	**PN, % (Gr3)**	16 (0.6)	NR	
Infections, % ***COVID-19***	NR *NR*	69.9 (39.8 Gr3–4, 6.5 Gr5) *29.3 (15.4 Gr3–4, 1.6 Gr5)*	70.7 (41.5 Gr3–4, 7.3 Gr5) *NR*	**Infections, %** ***COVID-19***	NR 18 (12 Gr3–4)	78.8 (55.2 Gr3–4, 13.3 Gr5) 29.1 [(21.2 Gr3–4),18/22 Gr5)	
Cytopenias, % All Gr (Gr3–4)	Neutropenia 44.8 (43.2) Anaemia 54.1 (42.6) Thrombocytopenia 36.1 (27.9)	Neutropenia 48.8 (48.8) Anaemia 48.8 (37.4) Thrombocytopenia 30.9 (23.6)	Neutropenia 49.6 (49.6) Anaemia 48.8 (37.4) Thrombocytopenia 32.5 (23.6)	**Cytopenias, % All Gr (Gr3–4)**	Neutropenia 71 (64) Anaemia 55 (37) Thrombocytopenia 40 (21)	Neutropenia 71.5 (65.5) Anaemia 55.2 (37.6) Thrombocytopenia 41.8 (23.0)	
	Permanent discontinuation rate due to AEs 17% per USPI[5] dose interruption 73% per USPI[5]				**Permanent discontinuation rate due to AEs 4.8%[6]** dose interruption 73% per USPI[10]		

Non esistono studi di confronto head-to-head tra questi farmaci. I dati sono riportati per facilità espositiva e non intendono rappresentare un confronto diretto fra farmaci e studi

*Responders only. †Includes pts who did not receive recommended SUD. Abbreviations in slide notes.

1. Lesokhin AM, et al. Nat Med. 2023;29:2259–67. 2. ELREXFIO® RCP. 3. Prince HM, et al. Abstract 4738. Poster presented at: 2024 ASH Annual Meeting; San Diego, CA. 4. Nooka AK, et al. Abstract 8008. Oral presentation at: 2023 ASCO Annual Meeting, Chicago, IL.5. Tommasson 20224; teclistamab RCP; Moreau 2022 Majestec 1

Orientarsi tra diversi BsAbs (1/2)

	Elranatamab	Vs	Talquetemab
Patient Population	HR Cytogenetics 25.2% | R-ISS III 15.4 | EMD 31.7% TCR 96.7% | PDR 42.3% Median prior LoT: 5		HR Cytogenetics 16% | ISS III 19%‡ | EMD 32% TCR 75% | PDR 25% Median prior LoT: 6
Admin/ convenience	Fixed dose, SC[2] Monitor ~5 days during SUD (48 h / 48 h)[2]; US inpatient doses FoC Flexibility for restart after dose delay[2] Dose frequency reduced to Q2W for ≥PR at W25+[2], Q4W after ≥6 cycles of Q2W [3]		Weight-based dose; 2 dose levels depending on QW or Q2W, SC[8] Monitor ~9–11 days for SUD (48 h after each) Option for Q2W or QW dosing; no reduction in dose frequency for either dosing schedule

	BCMA-naïve MagnetisMM-3[3] n=123	SmPC BCMA-naïve[2] n=123	Prior BCMA pooled analysis[4] N=87		0.4 mg/kg QW (n = 143)[6]	0.8 mg/kg Q2W (n = 154)[6]	Prior TCRA (n = 78)[6]
mFU, mo	33.9	15.2*	11.3	**mFU, mo**	29.8	23.4	20.5
ORR (≥CR), %	61.0 (37.4)	61.0 (35.7)	46.0 (18.4)	**ORR (≥CR), %**	74.1 (32.8)	69.5 (40.3)	66.7 (42.4)
MRD, %	90.3 of evaluable ≥CR	89.7 of evaluable ≥CR	NR	**MRD, %**	NR	NR	NR
mDOR, mo	NE 30-mo rate 61.0%	NE 15-mo rate 70.8%	17.1	**mDOR, mo**	9.5	17.5	NA§
mPFS, mo	17.2	NR	5.5	**mPFS, mo**	7.5	11.2	7.7
mOS, mo	24.6	NR	12.1	**24-mo OS, %**	60.6	67.1	57.3
	SmPC N=183	**MM-3 *Nat Med.* 14.7 mo mFU**	**MM-3 33.9 mo mFU**		**SmPC[7]**	**QW *NEJM*[6]**	**Q2W *NEJM*[6]**
CRS, % (Gr3)	57.9 (0.5)	56.3 (all Gr 1–2) 90.6% *during* SUD	57.7†	**CRS, % (Gr3)**	77 (1.5)	77 (3)	80 (0)
ICANS, % (Gr3)	3.3 (1.1)	3.4 (all Gr 1–2)	4.9†	**NT, % (Gr3)**	9.8 (2.3)	10 (0)	5 (0)
PN, % (Gr3)	15.8 (1.1)	Motor dysfunction 17.1 Sensory neuropathy 13.8	NR	**Infections, %**	NR	47 (7 Gr3–4)	34 (7 Gr3–4)
Infections, % ***COVID-19***	NR *NR*	69.9 (39.8 Gr3–4, 6.5 Gr5) *29.3 (15.4 Gr3–4, 1.6 Gr5)*	70.7 (41.5 Gr3–4, 7.3 Gr5) *NR*	**Cytopenias, All Gr (3–4)** Neutropenia Anaemia Thrombocytopenia	35 (30) 47 (29) 30 (21)	67 (60) 60 (30) 37 (23)	36 (32) 43 (23) 23 (11)
Cytopenias, % **All Gr (Gr3–4)**	Neutropenia 44.8 (43.2) Anaemia 54.1 (42.6) Thrombocytopenia 36.1 (27.9)	Neutropenia 48.8 (48.8) Anaemia 48.8 (37.4) Thrombocytopenia 30.9 (23.6)	Neutropenia 49.6 (49.6) Anaemia 48.8 (37.4) Thrombocytopenia 32.5 (23.6)	**Skin / dysgeusia** **All gr (≥Gr3)**	Very common / 72 (0)	67 (0) / 63 (NA)	70 (2) / 57 (NA)
Permanent discontinuation rate due to AEs 17% per USPI[5] dose interruption 73% per USPI[5]				**Permanent discontinuation rate due to AEs 15%, 10% and 12%[6]** dose interruption 56% per USPI[9]			

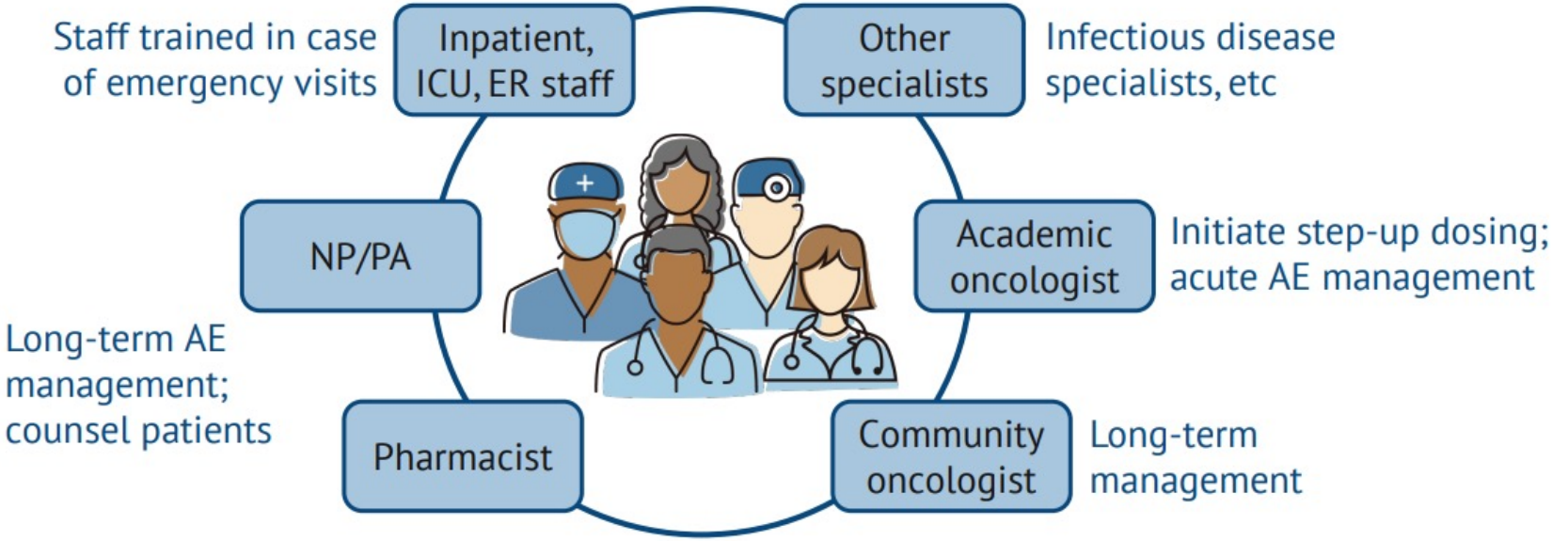
Non esistono studi di confronto head-to-head tra questi farmaci. I dati sono riportati per facilità espositiva e non intendono rappresentare un confronto diretto fra farmaci e studi

*Responders only. †Includes pts who did not receive recommended SUD. ‡SC only, n=130. §Not reported due to heavy censoring from 12 to 20 mo; the estimate may not be reliable at this time point. Abbreviations in slide notes

1. Lesokhin AM, et al. Nat Med. 2023;29:2259–67. 2. ELREXFIO® RCP. 3. Prince HM, et al. Abstract 4738. Poster presented at: 2024 ASH Annual Meeting; San Diego, CA. 4. Nooka AK, et al. Abstract 8008. Oral presentation at: 2023 ASCO Annual Meeting, Chicago, IL.5. Tommasson 20224; talquetamab RCP; Chari 2022 Monumental 1.

TAKE HOME MESSAGES

Comprehensive Multidisciplinary Safety Management: It Takes a V...age[1,2]



Educate patients/caregivers and provide tools to monitor AEs in outpatient settings

Abbreviation(s): ER: emergency room; ICU: intensive care unit; NP: nurse practitioner; PA: physician assistant.
Reference(s): 1. Braun A et al. *Am Soc Clin Oncol Educ Book*. 2024;44:e433516. doi:10.1200/EDBK_433516; 2. Association of Community Cancer Centers. https://www.accc-cancer.org/docs/projects/bispecific-antibodies/bispecific-antibodies-brief.pdf?sfvrsn=1331b35b_2&

U.O. Ematologia e Terapie Cellulari

S.S. Diagnosi e terapia delle malattie del sangue e dei linfatici

Dr. E. Angelucci
Dr.ssa G. Beltrami
Dr.ssa G. Bartalucci
Dr.ssa E. Coviello
Dr.ssa C. Ghiggi
Dr. A. Ibatici
Dr.ssa M. Laurino
Dr.ssa V. Pinto
Dr.ssa G. Rivoli
Dr.ssa L. Kratochwila

S.S. Trapianto cellule staminali e terapie cellulari

S.S. Laboratorio cellule staminali e terapie cellulari

Grazie per l'attenzione!