Highlights from IMS 20th meeting 2023

Patrizia Tosi

Anticorpi bispecifici anti-BCMA con approvazione FDA/EMA

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

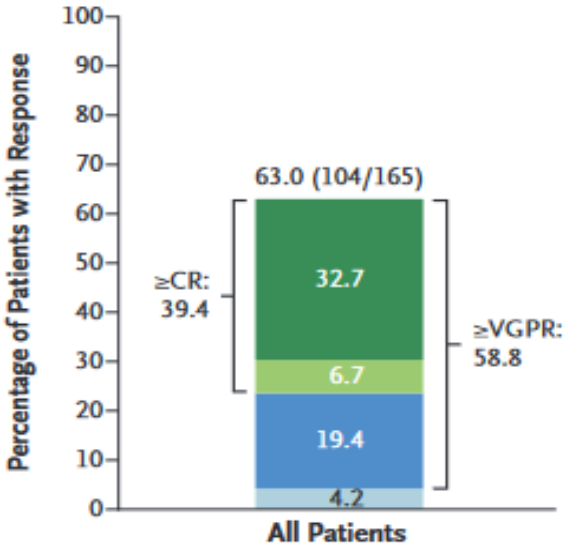
Anticorpi bispecifici anti BCMA con approvazione FDA/EMA

• Teclistamab	IgG4	Ottobre 2022
• Elranatamab	IgG2a	Agosto 2023

Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

- Patients with R/R MM after ≥3 lines of therapy, including exposure to IMiD, PI, and anti-CD38 mAb
  - 26% high-risk cytogenetics
  - Median 5 prior lines of therapy (range: 2-14)
  - 77.6% triple-class refractory; 30.3% penta-drug refractory
  - 89.7% refractory to last therapy line
- **Teclistamab**: 1.5 mg/kg SC weekly, after step-up



Patient Subgroup	ORR, % (n/N)
≤3 prior lines of treatment	74.4 (32/43)
>3 prior lines of treatment	59.0 (72/122)
High-risk cytogenetics and/or EMD	53.3 (32/60)

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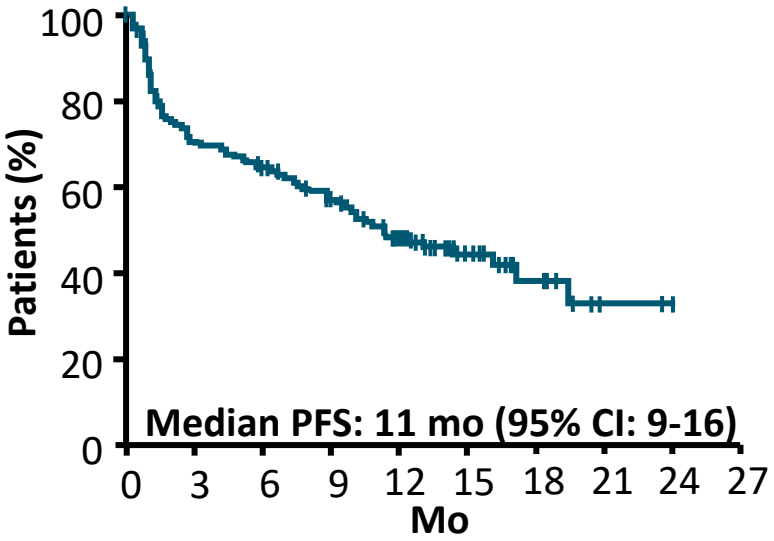
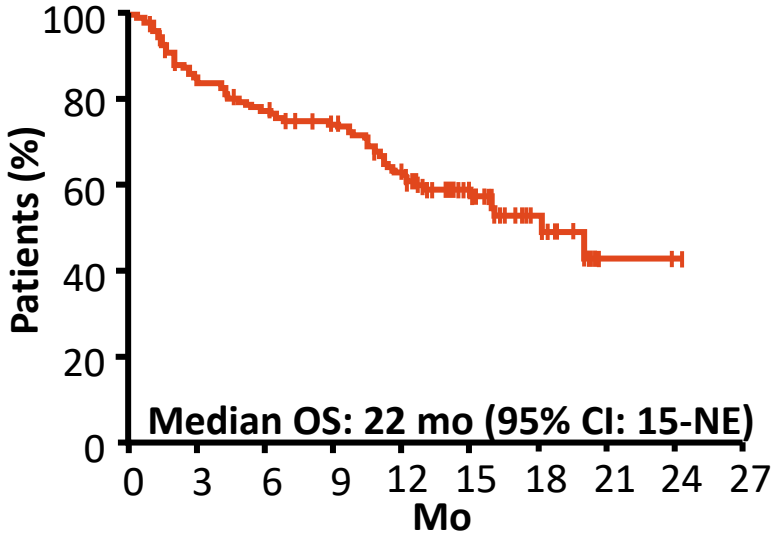
Progression-Free Survival



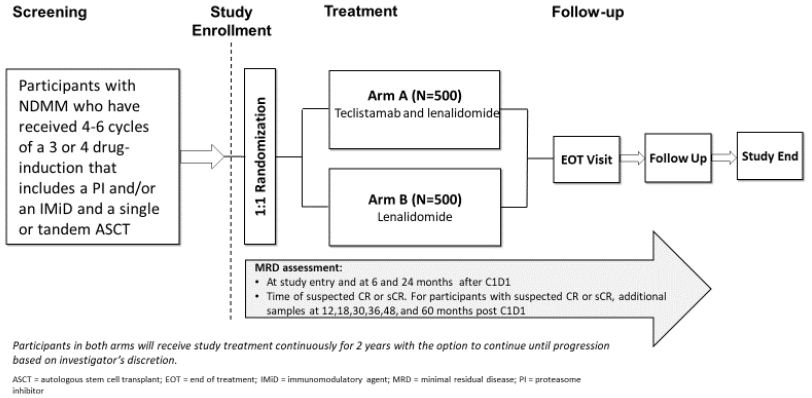
Overall Survival



Teclistamab in Combination With subcutaneous Daratumumab and Lenalidomide in relapsed/refractory MM (1-3 lines of therapy) (MajesTEC-2)

MajesTEC-3: Randomized, phase 3 study of teclistamab plus daratumumab versus investigator's choice of daratumumab, pomalidomide, and dexamethasone or daratumumab, bortezomib, and dexamethasone in patients with relapsed/refractory multiple myeloma.

Phase 3 Study of Teclistamab in Combination With Lenalidomide and Teclistamab Alone Versus Lenalidomide Alone in Participants With Newly Diagnosed Multiple Myeloma as Maintenance Therapy Following Autologous Stem Cell Transplantation (MajesTEC-4)



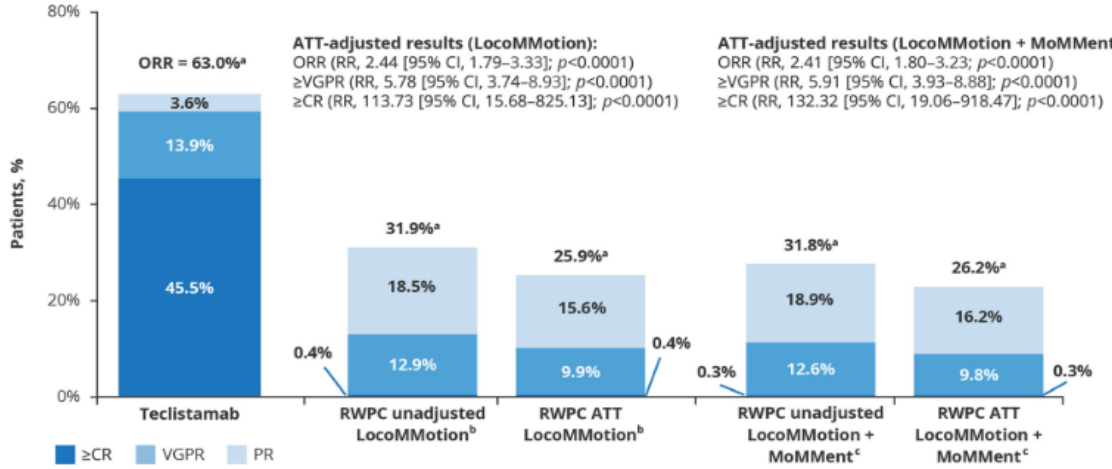
Phase 2 Study to Evaluate Safety and Efficacy of Teclistamab in Combination With Daratumumab, Lenalidomide, and Dexamethasone With or Without Bortezomib as Induction Therapy and Teclistamab in Combination With Daratumumab and Lenalidomide as Maintenance Therapy in Participants With Newly Diagnosed Transplant Eligible Multiple Myeloma (GMMG-HD10 / DSMM-XX / 64007957MMY2003) MajesTEC-5

A Study of Teclistamab in Combination With Daratumumab and Lenalidomide (Tec-DR) and Talquetamab in Combination With Daratumumab and Lenalidomide (Tal-DR) in Participants With Newly Diagnosed Multiple Myeloma (MajesTEC-7)

A Study of the Combination of Talquetamab and Teclistamab in Participants With Relapsed or Refractory Multiple Myeloma (RedirecTT-1)

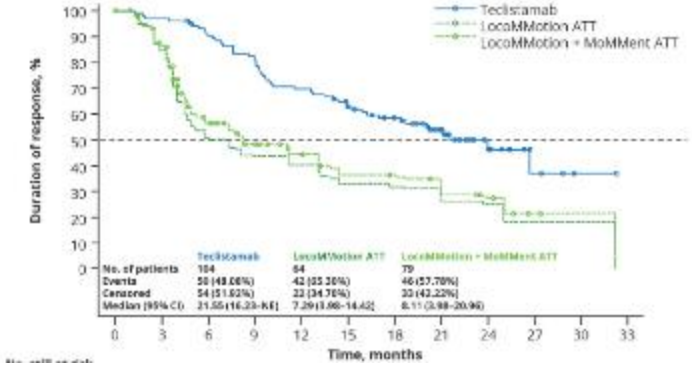
Comparative Effectiveness of Teclistamab Versus Real-World Physician's Choice of Therapy in LocoMMotion and MoMMent in Triple-Class Exposed Relapsed/Refractory Multiple Myeloma

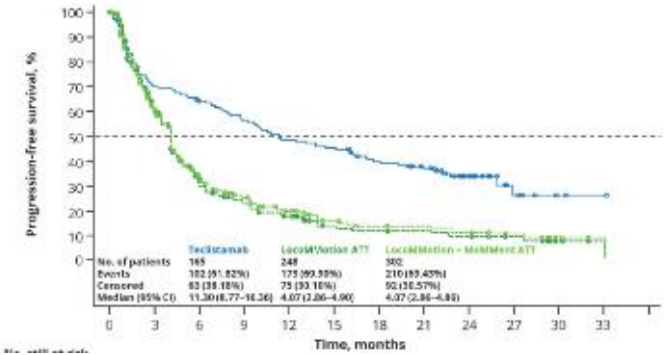
	MajesTEC-1 (*N* = 165)	LocoMMotion[a] (*N* = 248)	LocoMMotion[a] + MoMMent[b] (*N* = 302)
Treatment	Teclistamab (1.5 mg/kg)[c]	RWPC	RWPC
Median follow-up, months (CCO)	22.8 (January 4, 2023)	26.4 (October 27, 2022)	24.2 (March 13, 2023

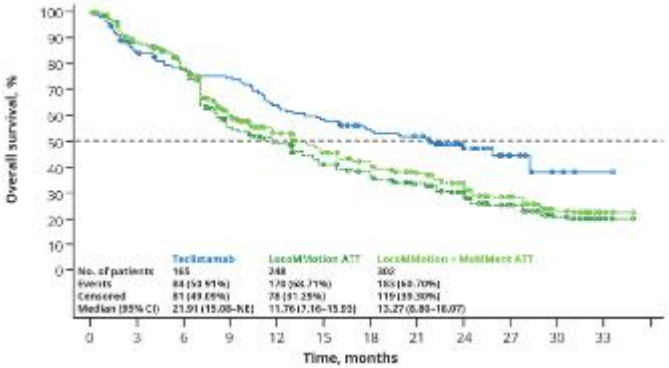


Moreau 2023

Comparative Effectiveness of Teclistamab Versus Real-World Physician's Choice of Therapy in LocoMMotion and MoMMent in Triple-Class Exposed Relapsed/ Refractory Multiple Myeloma





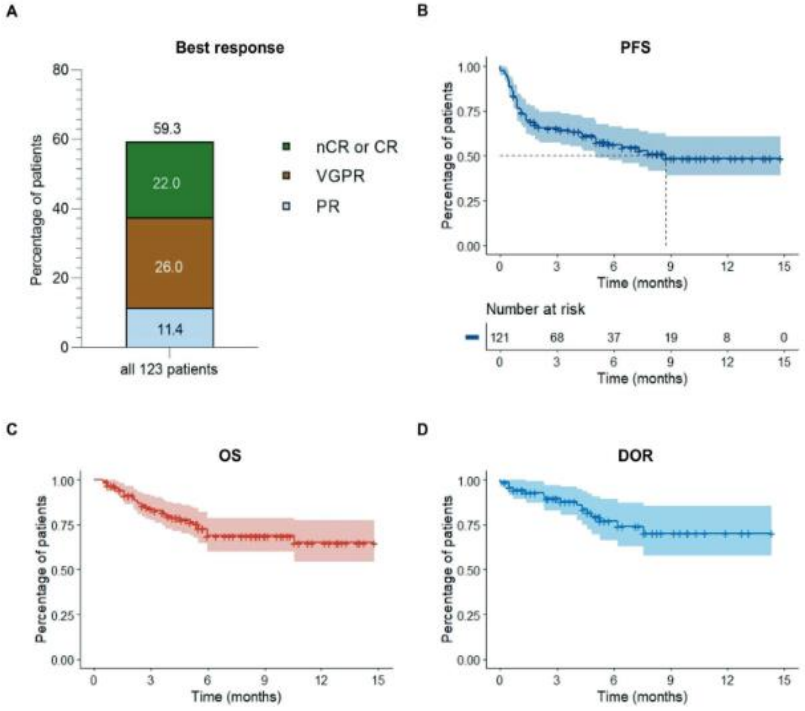


Moreau 2023

Real-world analysis of teclistamab in 123 RRMM patients from Germany

C. Riedhammer[1], F. Bassermann[2], B. Besemer[3], M. Bewarder[4], F. Brunner[5], A. Carpinteiro[6], H. Einsele[1], J. Faltin[7], J. Frenking[8], D. Gezer[9,10], S. Goldman-Mazur[11], M. Hänel[12], M. Hoegner[2], K. M. Kortuem[1], J. Krönke[13], M. Kull[14], T. Leitner[15], C. Mann[16], R. Mecklenbrauck[17], M. Merz[11], A. Morgner[12], A. Nogai[13], M. S. Raab[8], R. Teipel[18], R. Wäsch[19] and L. Rasche[1]✉

Characteristic	MAJESTEC-1	Real-world
Median age (range) - yr	64.0 (33.0–84.0)	67.0 (35.0–87.0)
Gender: male/female - %	58.2/41.8	56.9/43.1
Median time since diagnosis - yr (range)	6.0 (0.8–22.7)	6.5 (0.5–18.7)
Median no. of lines of previous therapy (range)	5 (2–14)	6 (3–14)
Extramedullary disease - no./ total no. (%)	28/165 (17.0)	43/119 (36.1)
≥60% plasma cells in bone marrow no./total no. (%)	18/160 (11.2)	21/59 (35.6)
ISS no./total no. (%)		
I	85/162 (52.5)	25/92 (27.1)
II	57/162 (35.2)	35/92 (38.0)
III	20/162 (12.3)	31/92 (33.7)
High risk cytogenetic profile no./total no. (%)	38/148 (25.7)	39/106 (36.8)
Refractory status no./total no. (%)		
triple-class	128/162 (77.6)	113/123 (92.6)
penta-drug	50/162 (30.3	74/123 (60.2)

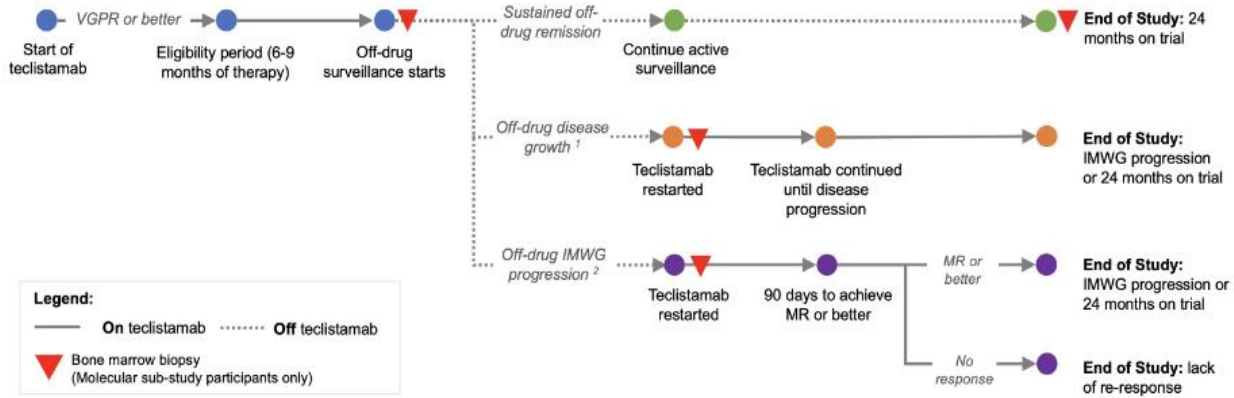


Leukemia 2024

Further hints

- **Limited duration for responding patients**
- **Elderly patients**
- **Outpatient step up**
- **Patients with renal failure**
- **Tocilizumab prophylaxis**

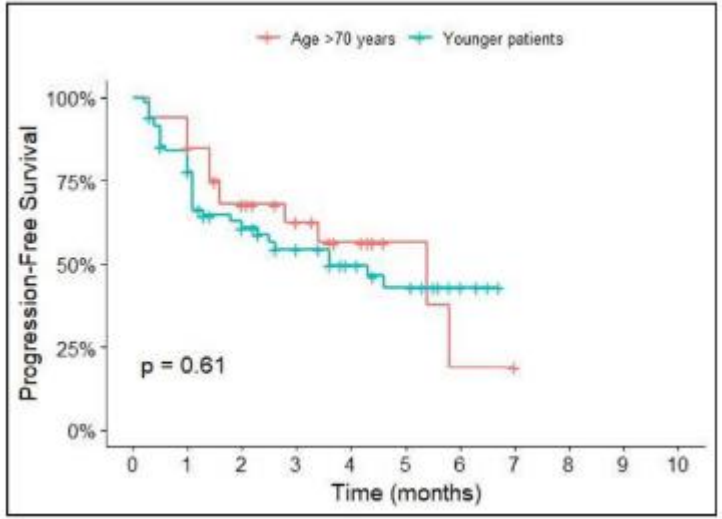
3394 A Phase 2, Single-Arm, Non-Inferiority Study of Limited-Duration Teclistamab for Relapsed and Refractory Multiple Myeloma (LimiTec)



Razzo et al ASH 2023

3330 Toxicity and Efficacy Outcomes of Teclistamab in Patients with Relapsed-Refractory Multiple Myeloma (RRMM) Above the Age of 70 Years: A Multicenter Study

Baseline Characteristics	Older pts (age >70 yrs) n=33	Younger pts (Age ≤70 yrs) n=69	p value
Age, years, median (range)	75 (71-87)	62(35-70)	
ECOG PS ≥2	15 (45%)	18 (26%)	
IgG subtype	18 (55%)	36 (52%)	
Revised International Staging System	6 (18%)	19 (27%)	
High risk cytogenetics (defined above)	19 (58%)	36 (52%)	
Extramedullary disease	13 (39%)	31 (45%)	
Prior LOT (median, range)	6 (4-17)	6(4-14)	
Prior Autologous stem cell transplant	19 (58%)	41 (59%)	
Triple Refractory disease	32 (97%)	62 (90%)	
Penta refractory disease	19 (58%)	49 (71%)	
BDT refractory disease	19 (58%)	37 (54%)	
Efficacy and Safety Outcomes			
Overall response rate	23 (70%)	42 (61%)	0.37
Complete response of better (≥CR)	10 (30%)	19 (28%)	0.8
PFS (median) – months	5.4 (95% CI, 2.8–NA)	3.6 (95% CI, 2.0–NA)	0.61
CRS (any grade)	22 (67%)	44 (64%)	0.7
CRS ≥3 grade	1 (3%)	0 (0%)	0.2
ICANS	7 (21%)	8 (11%)	0.17
ICANS ≥3 grade	0 (0%)	3 (4%)	0.2
Neutropenia grade 3-4	8 (24%)	15 (22%)	0.82
Anemia grade 3-4	7 (21%)	11 (16%)	0.53
Thrombocytopenia grade 3-4	9 (27%)	8 (12%)	**0.05**
Infection	11 (33%)	18 (26%)	0.46
Hospital readmission	12 (36%)	16 (23%)	0.16



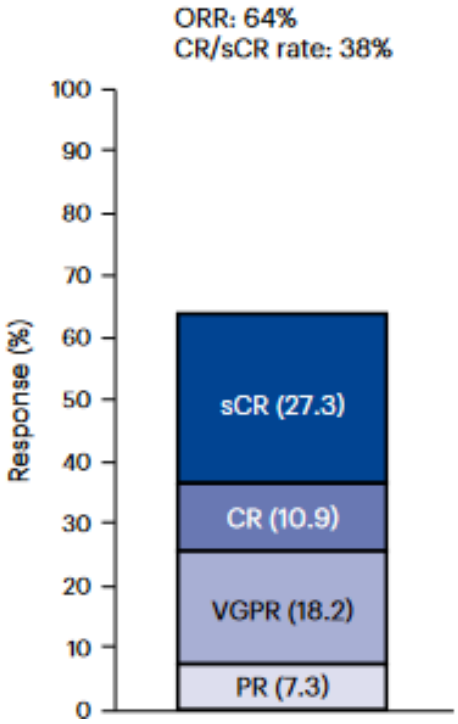
Dima et al ASH 2023

Further hints

- Limited duration for responding patients
- Elderly patients
- Outpatient step up
- Patients with renal failure
- Tocilizumab prophylaxis

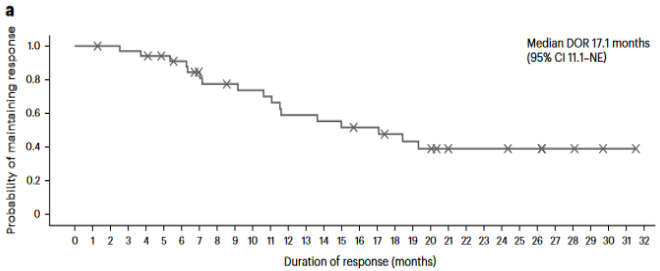
Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial

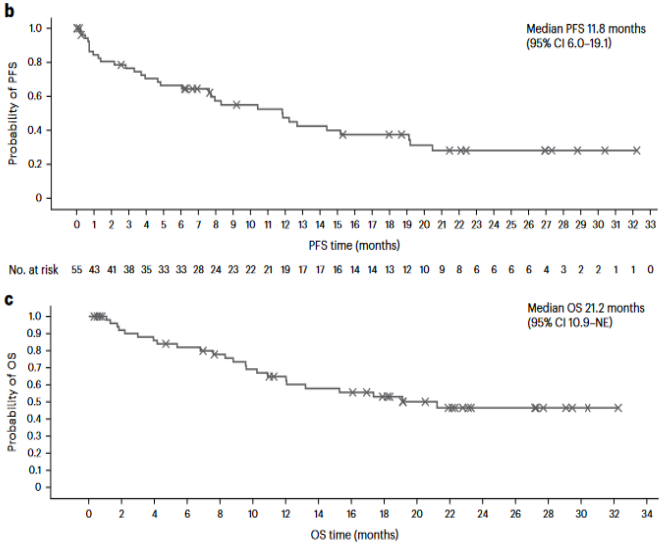
- Patients with R/R MM after ≥3 lines of therapy, including exposure to IMiD, PI, and anti-CD38 mAb
  - Prior BCMC-targeted therapy allowed (7.3%)
  - Median 5 prior lines of therapy (range: 2-14)
  - 90% triple-class refractory
  - 89.1% refractory to last therapy line
- **Erlanatamab** step up



Usmani Nat Med 2023

Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial

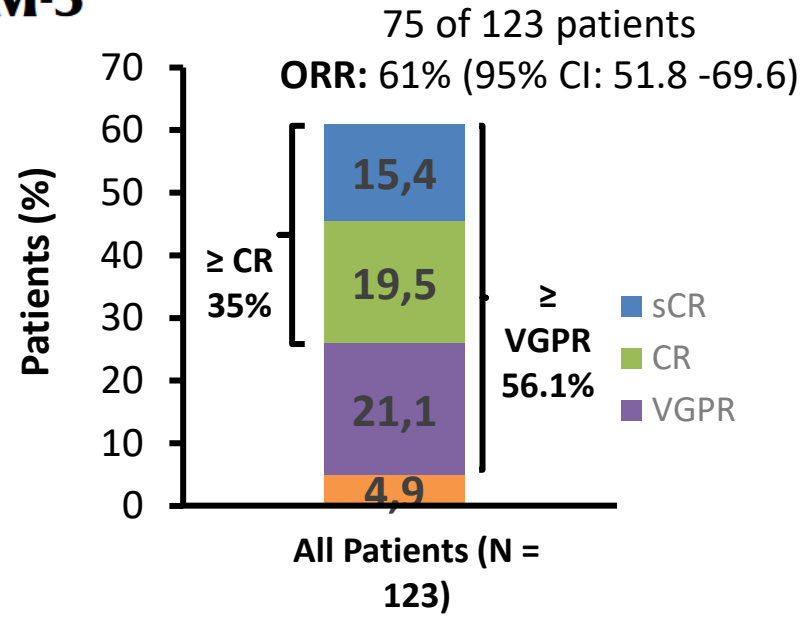




Usmani Nat Med 2023

Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results

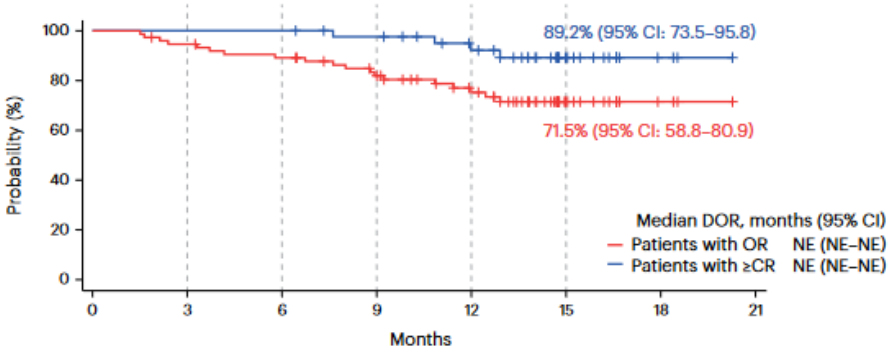
- Patients with MM refractory to ≥1 IMiD, PI, anti-CD38 mAb
  - 96.7% triple-class refractory
  - 25.2% with high-risk cytogenetics
- **Elranatamab**: 76 mg SC weekly with priming and/or premedication to reduce CRS
  - If weekly dosing received for ≥6 cycles with achievement of ≥PR for ≥2 mo, then dosing interval changed to every 2 weeks

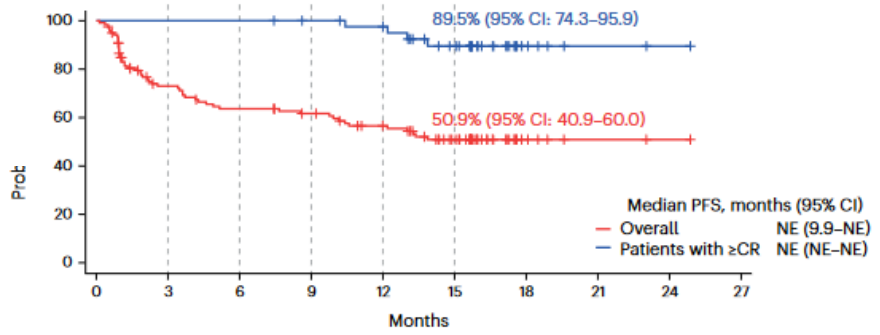


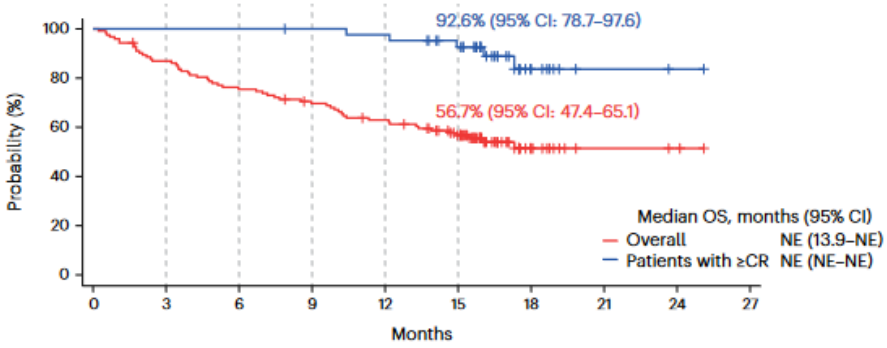
- Median follow-up: 14.7 mo (range: 0.2-25.1)

Lesokhin Nat Med 2023

Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results







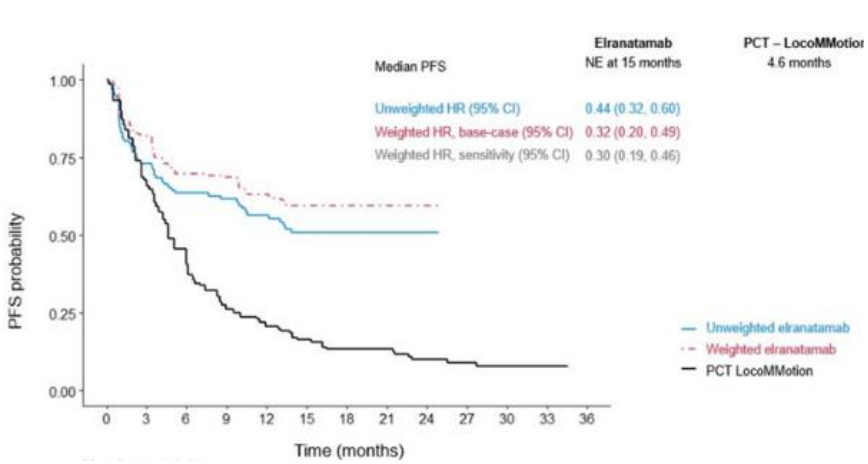
Lesokhin Nat Med 2023

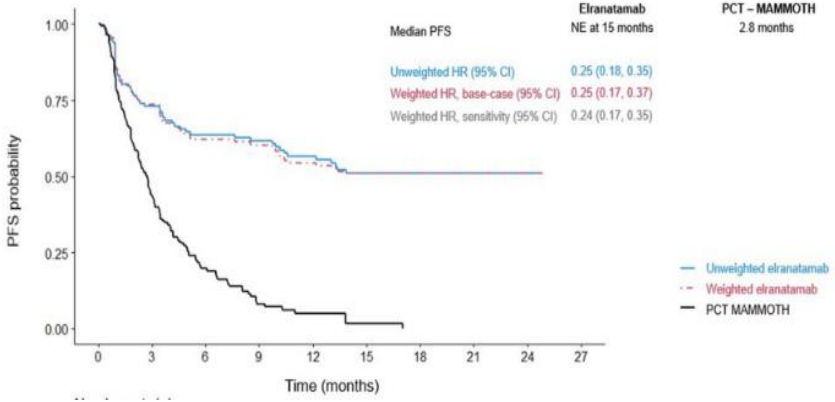
A matching-adjusted indirect comparison of the efficacy of elranatamab versus physician's choice of treatment in patients with triple-class exposed/refractory multiple myeloma

	MagnestisMM-3 (cohort A; $n = 123$)	LocoMMotion ($n = 248$)	MAMMOTH ($n = 177$)
Age, median, years	68	68	65
Sex, male	55%	54%	53%
Median time since diagnosis, years	6.1	6.3	4.8
High-risk cytogenetics	25%	—	29%
ISS risk stage			
Stage I	28%	28%	—
Stage II	38%	28%	—
Stage III	20%	31%	28%
ECOG status			
0	37%	25%	—
1	58%	73%	—
≥2	6%	2%	—
Extramedullary disease	32%	13%	—
Number of prior lines, median	5	4	5
2	4%	6%	—
3	17%	19%	—
4	27%	25%	—
≥5	52%	49%	—
Creatinine clearance			
≤60	30%	38%	—
Refractory/exposure status			—
Triple-class refractory[a]	97%	74%	—
Penta-drug refractory	42%	18%	30%
Penta-drug exposed	71%	—	58%

Mol Curr Med Res 2023

A matching-adjusted indirect comparison of the efficacy of elranatamab versus physician's choice of treatment in patients with triple-class exposed/refractory multiple myeloma





Mol Curr Med Res 2023

Elranatamab After Previous BCMA Therapy

Pooled analysis of single-agent elranatamab in 87 patients with R/R MM who received ≥1 PI, ≥1 IMiD, ≥1 anti-CD38 antibody, and ≥1 BCMA-directed tx (ADC or CAR-T) across 4 studies

Efficacy endpoints per IMWG criteria

Safety outcomes per CTCAE: TEAEs, CRS, and ICANS

Median follow-up: 11.3 mo (range: 0.3-32.3)

Nooka 2023

Elranatamab After Previous BCMA Therapy

	MagnetisMM-1	MagnetisMM-2	MagnetisMM-3	MagnetisMM-9
Study Phase	I	I	II	I/II
Elranatamab dosage • Dose frequency • Step-up dosing	215-1000 µg/kg SC QW or Q2W None	1000 µg/kg SC QW 600 µg/kg	76 mg SC QW 12 mg and 32 mg	76 mg SC QW 4 mg and 20 mg
N included in pooled analysis	13	1	64	9

Nooka 2023

Response	Any Prior BCMA (n = 87)	Prior ADC (n = 59)	Prior CAR-T (n = 36)
ORR, % ▪ sCR ▪ CR ▪ VGPR ▪ PR	46.0 4.6 13.8 24.1 3.4	42.4 5.1 13.6 20.3 3.4	52.8 2.8 16.7 27.8 5.6
Median DoR, mo (95% CI)*	17.1 (9.8-NE)	13.6 (6.8-NE)	NE (9.8-NE)
Median PFS, mo (95% CI)	5.5 (2.2-10.0)	3.9 (1.9-6.6)	10.0 (1.9-NE)
Median OS, mo (95%CI)	12.1 (7.5-NE)	12.1 (6.4-NE)	12.1 (6.5-NE)

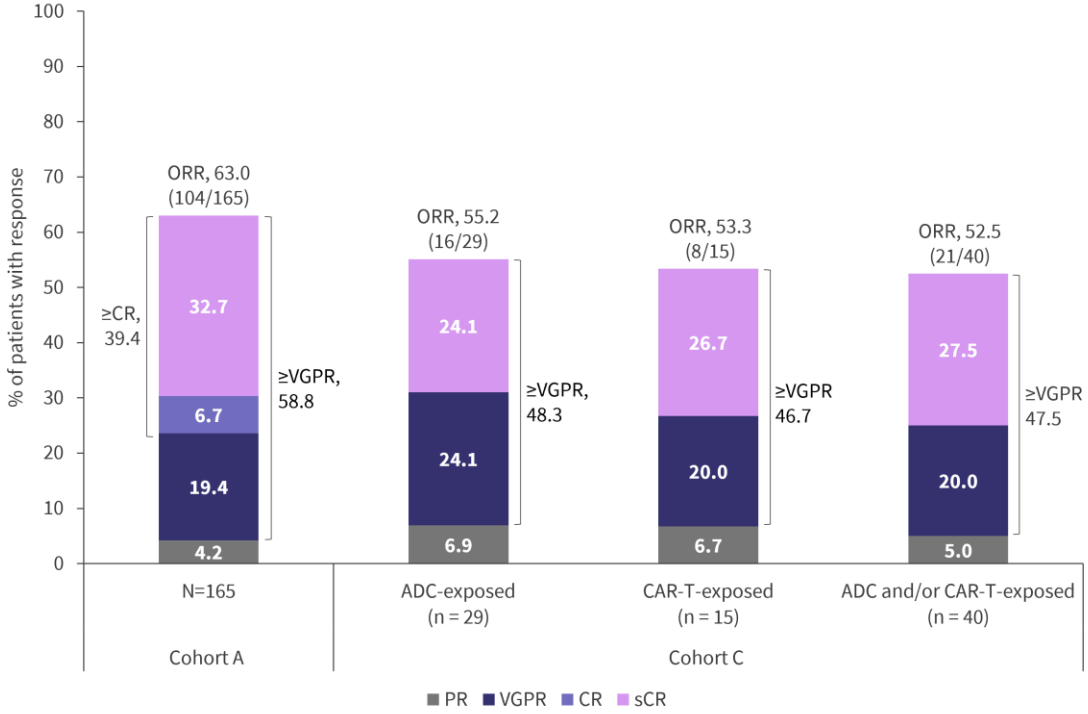
Nooka 2023

Teclistamab Induces Favorable Responses in Patients with Relapsed and Refractory Multiple Myeloma after Prior BCMA-Directed Therapy

	Intended SOC, N=22	MajesTEC-1, N=165
Median age, yrs	66 (48-81)	64 (33-84)
ECOG PS 0 or 1	20 (91%)	165 (100%)
Extramedullary disease	3 (14%)	28 (17%)
High marrow burden	6 (27%)	18 (11%)
High-risk cytogenetics	11 (50%)	38 (26%)
Median prior regimens (range)	8 (5-13)	5 (2-14)
Penta-refractory disease	11 (50%)	50 (30%)
Grade ≥ 3 CRS and ICANS	0%/5%	0.6%/3%
Prior BCMA-TT		
CAR-T	15 (68%)	0%
ADC	2 (9%)	0%
Both CAR-T and ADC	5 (23%)	0%
Best ORR/≥CR	63%/36%	63%/39%

Grajales 2023

Teclistamab Induces Favorable Responses in Patients with Relapsed and Refractory Multiple Myeloma after Prior BCMA-Directed Therapy



Grajales 2023

Magnetismm – 3

Safety

Treatment-emergent adverse events, *n* (%)	*n*=123	
	Any grade	Grade 3 or 4
Any treatment-emergent adverse event	123 (100)	87 (70.7)
Hematologic[a]		
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)
Nonhematologic		
Cytokine release syndrome	71 (57.7)	0
Diarrhea	52 (42.3)	2 (1.6)
Fatigue	45 (36.6)	4 (3.3)
Decreased appetite	41 (33.3)	1 (0.8)
Pyrexia	37 (30.1)	5 (4.1)
COVID-19 related[b]	36 (29.3)[c]	19 (15.4)
Injection site reaction	33 (26.8)	0
Nausea	33 (26.8)	0
Hypokalemia	32 (26.0)	13 (10.6)
Cough	31 (25.2)	0
Headache	29 (23.6)	0

MajesTEC– 1 Safety

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
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)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

Conclusions

- Efficacy in heavily pretreated patients
- Schedules could be further improved
- Patients selection and sequencing will be major issues for the future