Bispecifics in elderly myeloma patients

Does age change the risk-benefit balance?

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Disclosures

- **Speaker fees, advisory boards and other honoraria:**
  - Johnson and Johnson, BMS, Karyopharm/Arrotex, GSK, Gilead, Abbvie, Pfizer

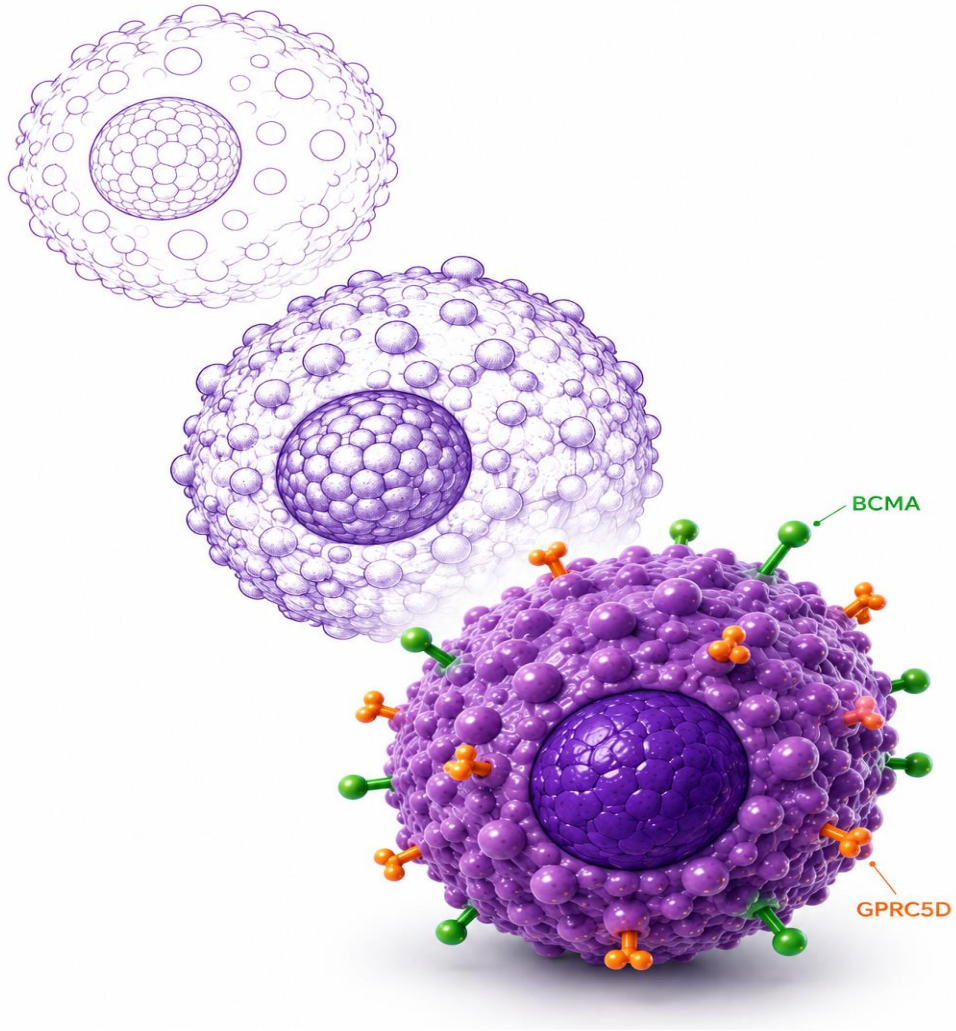
Outline of this session

1. **The older patient**
   Who is represented in the evidence?

2. **Efficacy in older adults**
   What is the data in older or frail patients?

3. **Toxicity and treatment burden**
   Is the risk of therapy actually greater?

4. **Delivering benefit in older patients**
   Choosing the treatment journey with the best risk-benefit trade



1. The older patient

Who is represented in the evidence?

Older adults are under-represented in pivotal bispecific trials

MajesTEC-1
Teclistamab (pivotal study)[1]

Adults ≥75 years

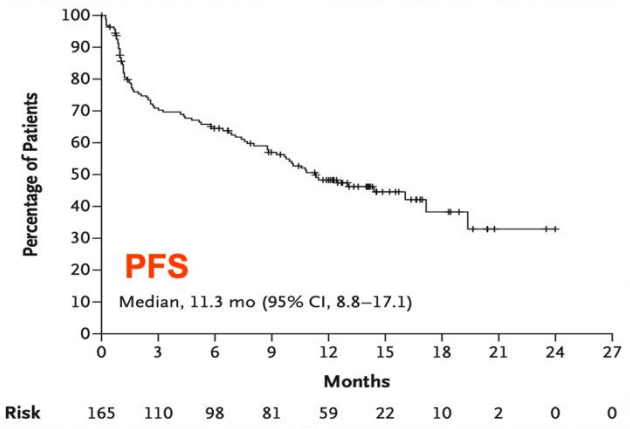
14.5%

24 / 165
of total trial population

Proportion ≥75 years

Overall Response Rate (ORR) at RP2D

63% (CR 45.5%)



[1]Moreau, P., et al., N Engl J Med, 2022

VS.

MagnetisMM-3
Elranatamab (pivotal study)[2]

Adults ≥75 years

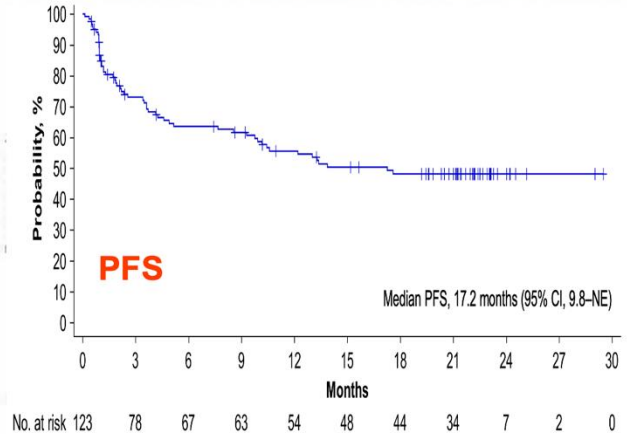
19.5%

24 / 123
of total trial population

Proportion ≥75 years

Overall Response Rate (ORR) at RP2D

61% (CR 35%)



[2]Tomasson MH, etal., Abstract: 3385.
Poster presented at: 2023 ASH Meeting, San Diego, CA.

SEER 2017–2021 (US)
Real-world myeloma population

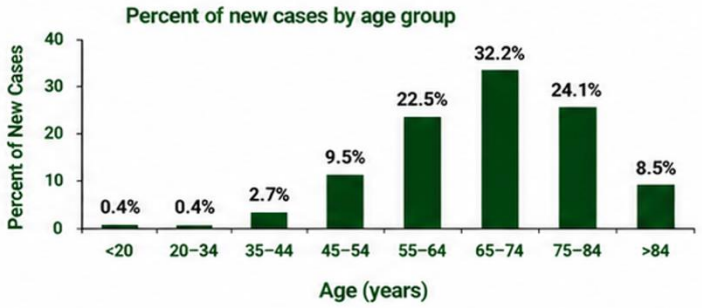
Adults ≥75 years

32.6%

of all new myeloma cases are ≥75 years

Proportion ≥75 years

Overall Response Rate not applicable



Median Age at Diagnosis
69
years

SEER 22 2017–2021, All Races, Both Sexes

And who are the older adults who actually make it into these trials?

Pivotal bispecific trials select beyond age

MajesTEC-1	MagnetisMM-3
• ECOG 0–1	• ECOG ≤2
• Adequate organ function	• Adequate organ function
• Active infection excluded	• Active uncontrolled infection excluded

Older patients entering trials have already passed a phyisological reserve filter

Even frontline 'transplant-ineligible' studies can exclude frailty

MajesTEC-7

NDMM
transplant-ineligible population

Up to 15%
transplant-deferred patients were permitted

Excluded
IMWG frailty index ≥2
except if score = 2 due to age alone

'Transplant-ineligible' does not equal 'frail-inclusive'

IMWG FRAILTY SCORE
(0–5 POINT COMPOSITE SCORE)

Palumbo A et al. Blood. 2015

AGE

≤75 years	0 points
76–80 years	+1 point
>80 years	+2 points

Age alone contributes points

COMORBIDITY

CHARLSON COMORBIDITY INDEX (CCI)

CCI ≥ 2 — +1 point

Examples of included conditions

- Congestive heart failure
- Myocardial infarction
- Peripheral vascular disease
- Cerebrovascular disease
- Chronic pulmonary disease
- Diabetes (with end-organ damage)
- Moderate–severe renal disease
- Liver disease (moderate–severe)
- Solid tumor / malignancy
- Other serious comorbidity

CCI ≥2 scores +1 point

FUNCTION

ADL
Activities of Daily Living
"Basic self-care"

ADL score ≤4 = +1 point

- Bathing
- Dressing
- Toileting
- Transferring / mobility
- Continence
- Feeding

IADL
Instrumental Activities of Daily Living
"Independent living skills"

IADL score ≤5 = +1 point

- Using telephone
- Shopping
- Preparing meals
- Housekeeping
- Transport
- Managing medications
- Handling finances

ADL score ≤4 or IADL score ≤5 adds 1 point

TOTAL SCORE

SCORE	CLASSIFICATION
0	FIT
1	INTERMEDIATE–FIT
≥2	FRAIL

≥2 POINTS = FRAIL

Age >75 years plus CCI ≥2 meets frailty criteria

Functional impairment is not required if age and comorbidity burden already reach ≥2 points.

BCMA

GPRC5D

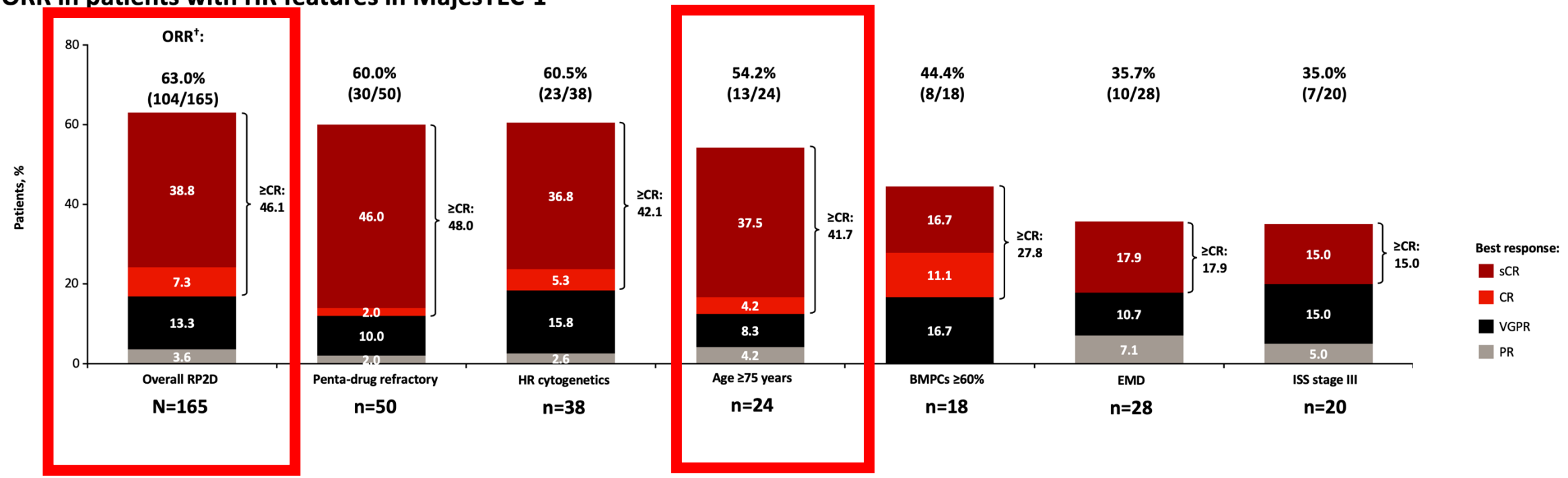
2. Efficacy in older adults

What is the data in older or frail patients?

In pivotal MajesTEC-1, patients aged ≥75 achieved meaningful responses

- Patients who were penta-drug refractory, had HR cytogenetics, or were aged ≥75 years had similar response rates to the overall RP2D population

ORR in patients with HR features in MajesTEC-1*

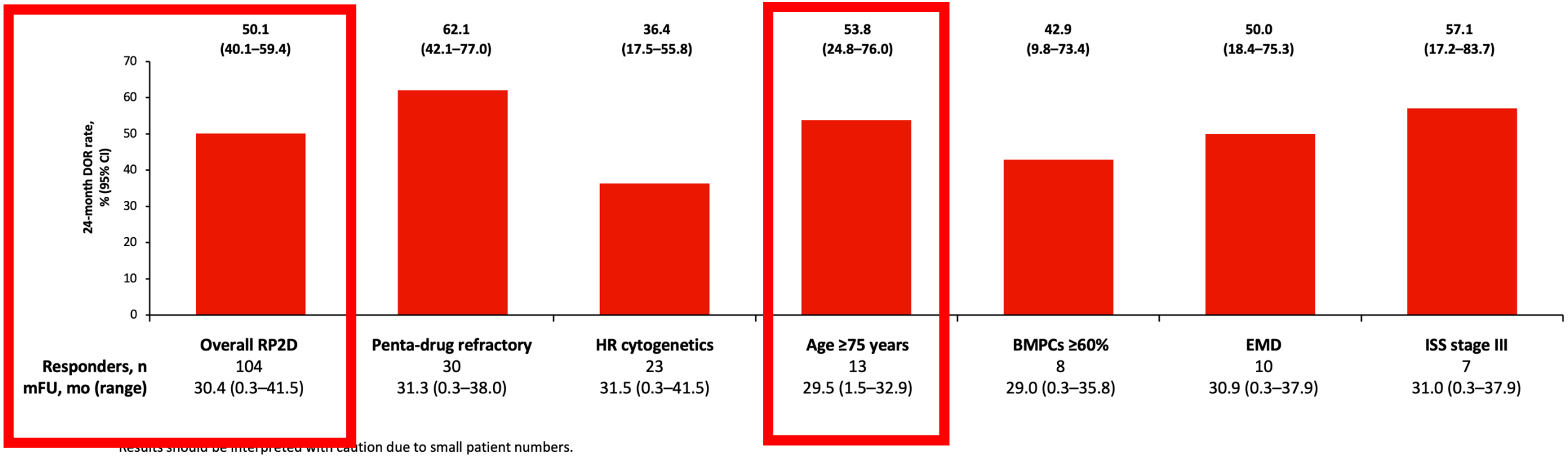


*This subgroup analysis included all 165 patients that were enrolled in the overall RP2D population of the MajesTEC-1 trial. †Response assessed by independent review committee.
BMPCs, bone marrow plasma cells; CR, complete response; EMD, extramedullary disease; HR, high-risk; ISS, International Staging System; ORR, overall response rate; PR, patrial response; RP2D, recommended phase 2 dose; sCR, stringent complete response; VGPR, very good partial response.
Costa LJ, et al. Presented at EHA; June 13-16, 2024; Madrid, Spain & Virtual. Poster #923.

Among responders aged ≥75, responses could be durable

- Duration of response (DOR) was generally comparable with the overall RP2D population across most subgroups

DOR to teclistamab in patients with HR features in MajesTEC-1*



Results should be interpreted with caution due to small patient numbers.
*This subgroup analysis included all 165 patients that were enrolled in the overall RP2D population of the MajesTEC-1 trial.
BMPCs, bone marrow plasma cells; CI, confidence interval; EMD, extramedullary disease; HR, high-risk; ISS, International Staging System; mo, months; mFU, median follow-up; RP2D, recommended phase 2 dose.
Costa LJ, et al. Presented at EHA; June 13-16, 2024; Madrid, Spain & Virtual. Poster #923.

Pivotal efficacy evidence extends beyond age to frailty

A Subgroup Analysis from MagnetisMM-3

Table 1: Baseline Demographics and Characteristics and Prior Treatments

	<65 y n=43	≥65 y n=80	Non-frail n=84	Frail n=39
Age, median (range), y	58.0 (36–64)	71.0 (65–89)	65.0 (36–79)	75.0 (47–89)
Male, n (%)	26 (60.5)	42 (52.5)	44 (52.4)	24 (61.5)
Race				
White	25 (58.1)	47 (58.8)	49 (58.3)	23 (59.0)
Asian	7 (16.3)	9 (11.3)	15 (17.9)	1 (2.6)
Black or African American	5 (11.6)	4 (5.0)	5 (6.0)	4 (10.3)
Not reported or unknown	6 (14.0)	20 (25.0)	15 (17.9)	11 (28.2)
ECOG performance status, n (%)				
0	23 (53.5)	22 (27.5)	41 (48.8)	4 (10.3)
1	19 (44.2)	52 (65.0)	43 (51.2)	28 (71.8)
2	1 (2.3)	6 (7.5)	0	7 (17.9)
R-ISS disease stage, n (%)				
I	11 (25.6)	17 (21.3)	24 (28.6)	4 (10.3)
II	24 (55.8)	44 (55.0)	47 (56.0)	21 (53.8)
III	6 (14.0)	13 (16.3)	8 (9.5)	11 (28.2)
Unknown	2 (4.7)	6 (7.5)	5 (6.0)	3 (7.7)
Extramedullary disease by BICR, n (%)*	14 (32.6)	25 (31.3)	26 (31.0)	13 (33.3)
Bone marrow plasma cells, n (%)				
<50%	30 (69.8)	59 (73.8)	60 (71.4)	29 (74.4)
≥50%	9 (20.9)	17 (21.3)	18 (21.4)	8 (20.5)
Missing	4 (9.3)	4 (5.0)	6 (7.1)	2 (5.1)
Prior lines of anti-myeloma therapy, median (range)	5.0 (2–22)	5.0 (2–12)	5.0 (2–22)	5.0 (2–12)
Refractory status, n (%)				
Triple-class†	41 (95.3)	78 (97.5)	84 (100.0)	35 (89.7)
Penta-drug‡	19 (44.2)	33 (41.3)	38 (45.2)	14 (35.9)
Refractory to last line of therapy	43 (100.0)	75 (93.8)	80 (95.2)	38 (97.4)

Table 2: Patient Disposition

	<65 y n=43	≥65 y n=80	Non-frail n=84	Frail n=39
Duration of treatment, median (range), mo	8.2 (0.1–19.4)	5.5 (0.0–24.4)	6.4 (0.0–23.5)	5.6 (0.1–24.4)
Discontinued	28 (65.1)	54 (67.5)	54 (64.3)	28 (71.8)
Adverse event	4 (9.3)	13 (16.3)	10 (11.9)	7 (17.9)
Death	1 (2.3)	8 (10.0)	5 (6.0)	4 (10.3)
Lack of efficacy	0	3 (3.8)	1 (1.2)	2 (5.1)
Progressive disease	22 (51.2)	26 (32.5)	36 (42.9)	12 (30.8)
Withdrawal by subject	0	4 (5.0)	1 (1.2)	3 (7.7)
Global deterioration of health status	1 (2.3)	0	1 (1.2)	0
Ongoing	15 (34.9)	26 (32.5)	30 (35.7)	11 (28.2)

Figure 1: Best Overall Response and Objective Response Rate*

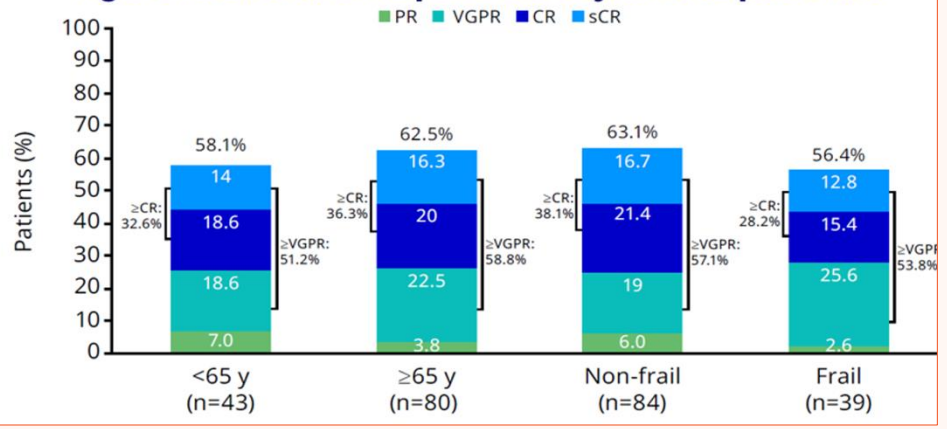
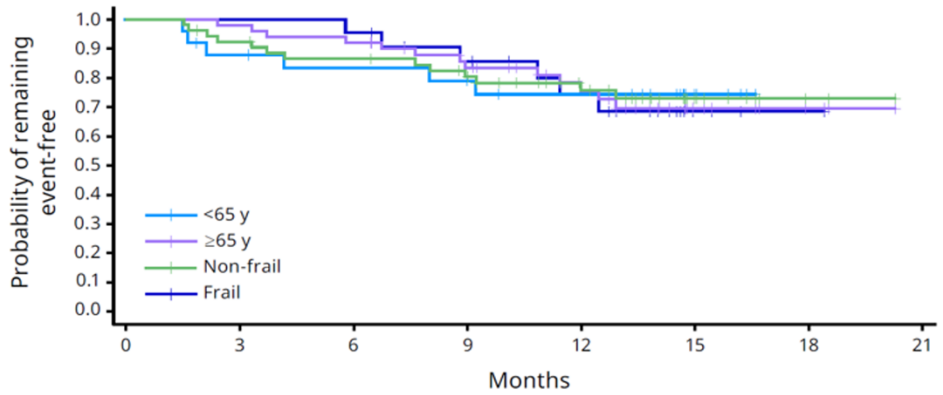


Figure 2: Duration of Response†



Raje N, et al. MagnetisMM-3 subgroup analysis by age and frailty. Presented at ASCO 2023; Abstract P8040.

From pivotal trials to real world data

CoMMitmenTT-Tec: pooled global evidence shows the efficacy signal is maintained in patients aged ≥75.

CoMMitmenTT-Tec

GLOBAL REAL-WORLD PLATFORM

n=356 | ≥75 years: n=59 | mean age 79.7

EMEA chart review + US panel + Canadian registry

ORR	≥VGPR
80%	**74%**

12-MONTH PFS	12-MONTH OS
59%	**62%**
Overall cohort: 57%	Overall cohort: 68%

Deep responses and meaningful disease control were maintained in the ≥75 subgroup.

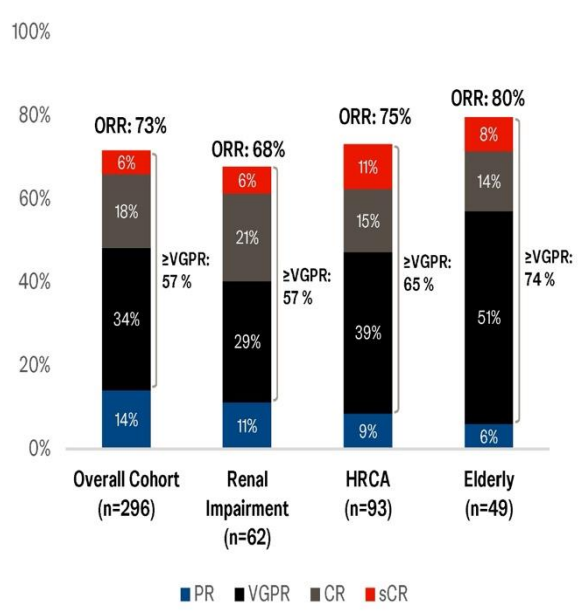
Descriptive subgroup; no formal comparison with the overall cohort.

Demographic data and response depth by subgroup

The ≥75 cohort retained high response depth in routine practice.

	Pooled Cohort (n=356)	Renal Impairment* (n=66)	HRCA† (n=104)	Elderly‡ (n=59)
Patient demographics				
Age, mean ± SD	66.5 ± 9.1	70.7 ± 8.6	66.4 ± 8.6	79.7 ± 3.9
Male, n (%)	195 (55%)	42 (64%)	49 (47%)	33 (56%)
Mean follow-up, months	10.6 ± 7.6	10.4 ± 7.5	11.0 ± 8.1	10.3 ± 7.7
Clinical characteristics, among those with available assessment				
ECOG ≥2, n (%)	18 (12%)	5 (15%)	10 (19%)	0 (0%)
HRCA, n (%)	104 (35%)	11 (23%)	104 (100%)	6 (13%)
EMD§, n (%)	34 (16%)	7 (14%)	10 (15%)	2 (8%)
Prior treatment history				
# prior LOTs, mean ± SD	5.2 ± 2.4	5.8 ± 2.9	5.0 ± 2.3	5.0 ± 2.5
Triple-class exposed, n (%)	336 (94%)	63 (96%)	99 (95%)	58 (98%)
Prior BCMA exposure, n (%)	54 (15%)	12 (18%)	18 (17%)	7 (12%)
Triple-refractory, n (%)	234 (66%)	44 (68%)	78 (75%)	42 (71%)
Penta-refractory, n (%)	104 (29%)	22 (34%)	35 (34%)	13 (22%)

Figure 1: Best response (%), overall and by subgroup



Waldschmidt J et al. CoMMitmenTT-Tec; presented at EHA 2026, Stockholm, Sweden.

Independent cohorts support the same real-world signal

US consortium real-world cohort

Teclistamab | n=385 (≥75: 83; <75: 302) | median 6 prior lines

MEDIAN PFS*	ORR	≥VGPR
≥75: 10.7 mo	≥75: 62%	≥75: 53%
<75: 5.2 mo	<75: 53%	<75: 44%
*unadjusted; no direct test	p=0.17	p=0.14

Adjusted PFS: age HR 1.15; p=0.55 (not significant)

Retrospective: ≥75 cohort had less HRCA (44.6% vs 57.9%), EMD (22% vs 40%) and prior BCMA therapy (33% vs 55%).

Pasvolsky O et al. Blood Cancer J. 2025;15:92. doi:10.1038/s41408-025-01297-7

French real-world teclistamab cohort

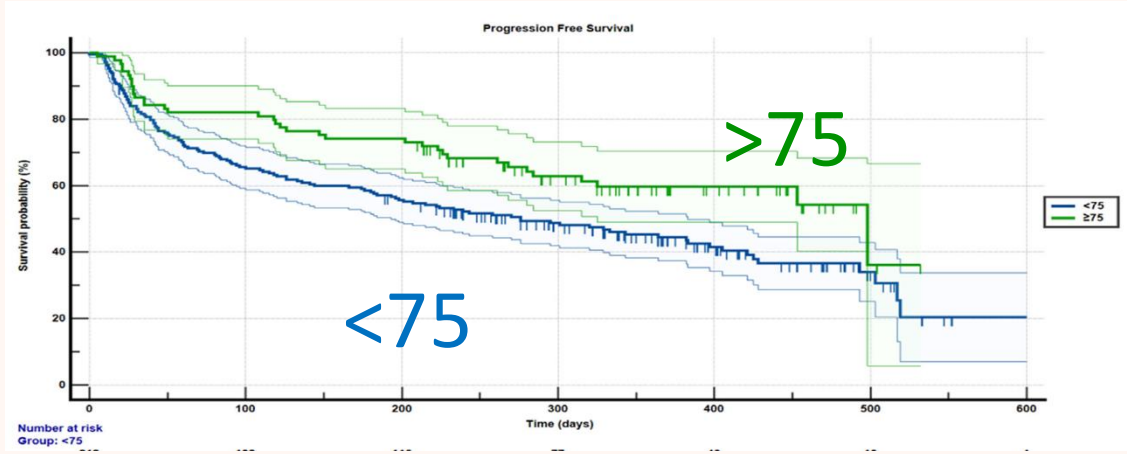
n=303 | ≥75 years: n=90 | <75 years: n=213

MEDIAN PFS	ORR	≥VGPR
≥75: 15.1 mo	≥75: 74%	≥75: 63%
<75: 12.4 mo	<75: 62%	<75: 57%
p=0.013		

Numerically favourable efficacy in selected patients aged ≥75

Retrospective comparison: ≥75 cohort had less high-risk cytogenetics (17% vs 42%) and penta-class exposure (37% vs 54%).

Coste A et al. eJHaem. 2026;7:e70233. doi:10.1002/jha2.70233



3. Toxicity and treatment burden

Is the risk of therapy actually greater?

Pivotal MagnetisMM-3: no signal of greater CRS or ICANS with age or frailty

Table: TEAEs of Special Interest*

	<65 y n=43			≥65 y n=80			Non-frail n=84			Frail n=39		
	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5
Infections	31 (72.1)	16 (37.2)	2 (4.7)	55 (68.8)	33 (41.3)	6 (7.5)						
CRS	25 (58.1)	0	0	46 (57.5)	0	0	48 (57.1)	0	0	23 (59.0)	0	0
ICANS	1 (2.3)	0	0	5 (6.3)	0	0	5 (6.0)	0	0	1 (2.6)	0	0

*TEAEs were graded according to MedDRA v25.1 and CTCAE V5 except for CRS and ICANS. Severity of CRS and ICANS was assessed according to the American Society for Transplantation and Cellular Therapy Criteria 2019.
CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell-associated neurotoxicity syndrome; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Raje N, et al. Poster presented at ASCO 2023 (Abstract P8040).

Raje N, et al. MagnetisMM-3 subgroup analysis by age and frailty. ASCO 2023; Abstract P8040.

Infection rates were similar, but fatal infection was higher in frail patients

Safety: TEAEs of Special Interest

- The incidences of TEAEs of special interest (infections, CRS, and ICANS) were consistent across subgroups (Table)
- Death due to TEAEs occurred in 7 (16.3%) patients aged <65 vs. 18 (22.5%) patients aged ≥65 years
  - Of these, 5 and 6, respectively, were due to progressive disease
- Death due to TEAE occurred in 14 (16.7%) patients in the non-frail subgroup and 11 (28.2%) patients in the frail subgroup
  - Of these, 7 and 4, respectively, were due to progressive disease

Table: TEAEs of Special Interest*

	<65 y n=43			≥65 y n=80			Non-frail n=84			Frail n=39		
	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5
Infections	31 (72.1)	16 (37.2)	2 (4.7)	55 (68.8)	33 (41.3)	6 (7.5)	59 (70.2)	35 (41.7)	4 (4.8)	27 (69.2)	14 (35.9)	4 (10.3)
CRS	25 (58.1)	0	0	46 (57.5)	0	0	48 (57.1)	0	0	23 (59.0)	0	0
ICANS	1 (2.3)	0	0	5 (6.3)	0	0	5 (6.0)	0	0	1 (2.6)	0	0

Raje N, et al. MagnetisMM-3 subgroup analysis by age and frailty. ASCO 2023; Abstract P8040.

Real-world safety broadly reproduces the pivotal pattern

Severe CRS and ICANS remain uncommon; ≥G3 infection is similar to the overall cohort but remains clinically important.

CoMMitmenTT-Tec

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EMEA chart review + US panel + Canadian registry

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Overall cohort: 57%	Overall cohort: 68%

Deep responses and meaningful disease control were maintained in the ≥75 subgroup.

Descriptive subgroup; no formal comparison with the overall cohort.

Real-world safety outcomes

Patients with at least one event, n (%)	OVERALL COHORT n=356	AGE ≥75 YEARS n=59
CRS Any grade	139 (39%)	25 (42%)
CRS Grade 3	3 (0.8%)	2 (3%)
ICANS Any grade	21 (6%)	6 (10%)
ICANS Grade 3	2 (0.6%)	0 (0%)
INFECTION Grade 3–4	46/214 (21%)	6/25 (24%)
INFECTION Grade 5	6/214 (3%)	1/25 (4%)

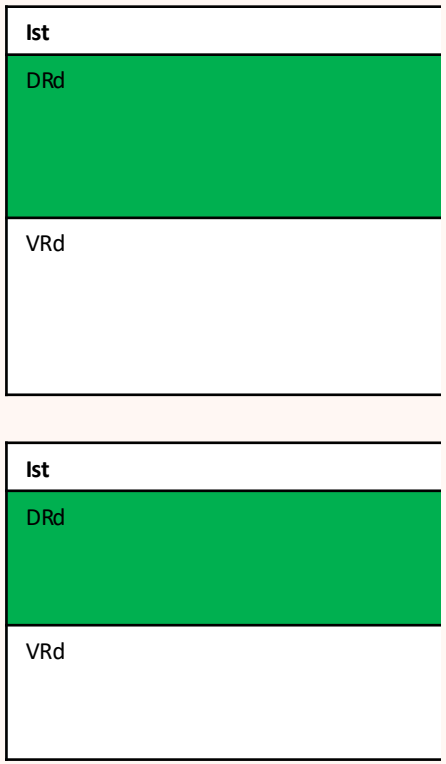
Infection data available for 214 overall and 25 age ≥75 patients.
Descriptive subgroup results; no formal comparison.

Presented by J. Waldschmidt at the European Hematology Association (EHA) 2026 Congress; June 11–14, 2026; Stockholm, Sweden

4. Delivering benefit in older patients

Choosing the treatment journey with the best risk-benefit trade

Planning a treatment journey for an older patient



FACTORS LIMITING CAR-T FEASIBILITY

- Poor ECOG performance status or frailty
- Limited reserve to withstand CRS or ICANS
- Organ dysfunction affecting lymphodepletion
- Rapidly progressive disease
- Caregiver, travel or treatment-centre barriers

A reasonable treatment now may close important options later

BelaVd may be a very reasonable choice, especially if our philosophy is to put our best foot forward early. But when CAR-T is not realistic, choosing BelaVd also closes the bispecific pathway. That downstream consequence needs explicit dialogue with the patient.

Either way, legacy options look quite unpalatable from 3rd line onwards

ASPIRE: grade ≥3 cardiac toxicity was higher with KRd in patients aged ≥70

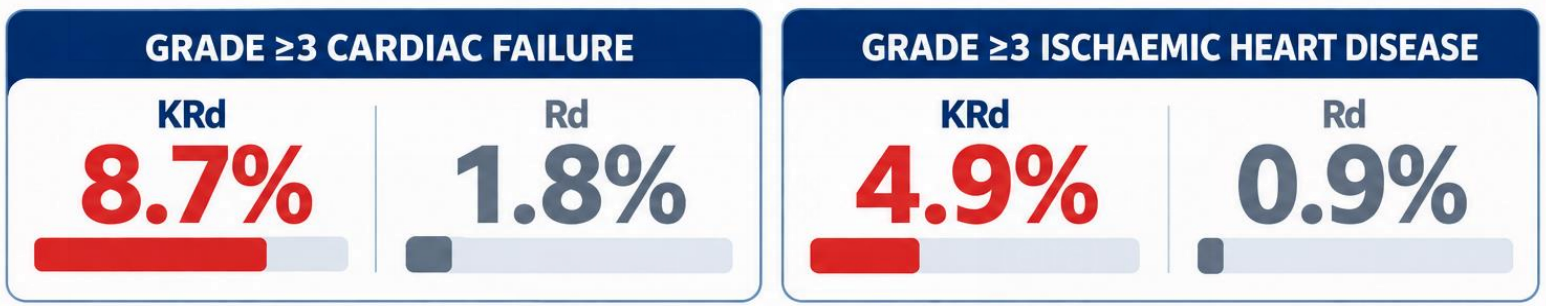
***Post hoc* age analysis of phase 3 ASPIRE in relapsed multiple myeloma**

792 patients randomized

218 aged ≥70 (27.5% of the trial population)

Randomized groups:
KRd: 103/396 aged ≥70 | **Rd:** 115/396 aged ≥70

Safety population: KRd n=103; Rd n=112



Interpretation: Cardiovascular toxicity was more prominent in older KRd-treated patients.

Selected trial population; patients with NYHA class III–IV heart failure were excluded.

Dimopoulos MA et al. *Br J Haamatol*. 2017.

KRd Rd

"INTENSIFY" OR RECYCLE

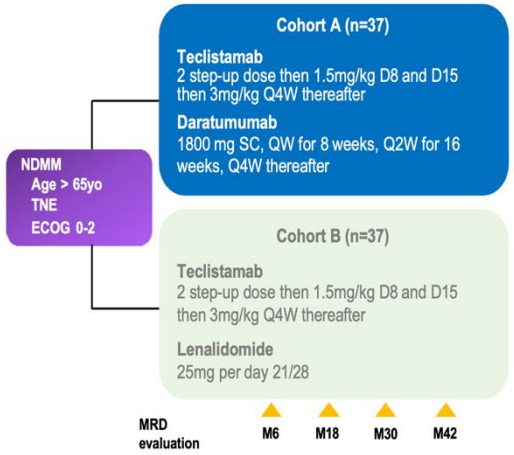
Kd, Seli+ or alternate bortezomib triplet

cardiac/renal vulnerability • emetogenic options • cumulative neuropathy • more steroids

Could an all-antibody bispecific regimen particularly suit older patients?

IFM 2021-01 TecLille - Study design

Phase 2 study of Tec-Dara and Tec-Len in TNE NDMM (n = 74)



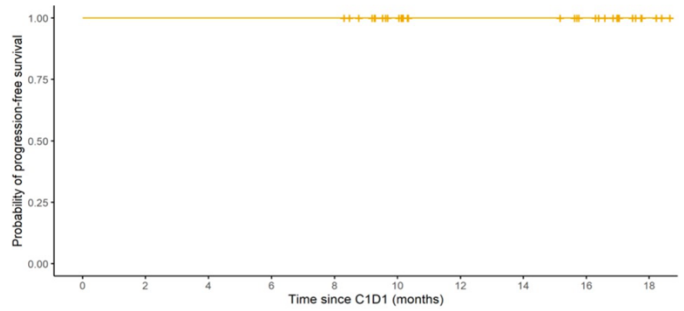
Hypothesises that doublets teclistamab-daratumumab (cohort A), an "all-antibody" regimen - will be effective and limit toxicity in elderly patients with NDMM

Patients characteristics	Tec-Dara (n=37)
Median age (range) - yr	73 (66-87)
Age category – no. (%)	
65 to < 70 yr	7 (19%)
70 to < 75 yr	18 (49%)
≥ 75 yr	12 (32%)
Sex - no. (%)	
Female	20 (54%)
Male	17 (46%)
ECOG – no. (%)	
0	9 (24%)
1	24 (65%)
2	4 (11%)
Frailty score (IMWG) – no. (%)	
Fit	16 (44%)
Intermediate	12 (33%)
Frail	8 (22%)
Creatinine clearance – no. (%)	
30 to < 60mL/min	14 (38%)
≥ 60 mL/min	23 (62%)

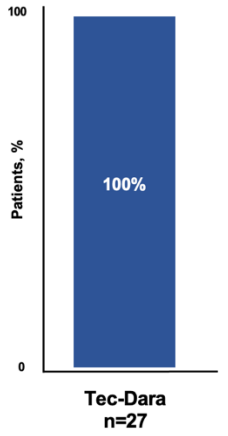
	Tec-Dara (n=37)
Median treatment duration, months (Q1-Q3*)	10.3 (9.3-16.6)
Median total number of cycles received (Q1-Q3)	12 (10-18)
Median relative dose intensity, % (Q1-Q3)	
Teclistamab	95 (89-100)
Daratumumab	96.6 (90.5-100)

Median follow up time = 10.3 months

PFS



MRD by NGS 10^{-6} at 6 months
Evaluable samples



All 37 patients had MRD evaluation by NGS (Clonoseq®) at 6 months. For technical reason, 27 patients were evaluable at 10^{-6}:

Missing causes	n
Calibration failure	4
Missing samples	3
Only evaluable at 10^{-5}	3

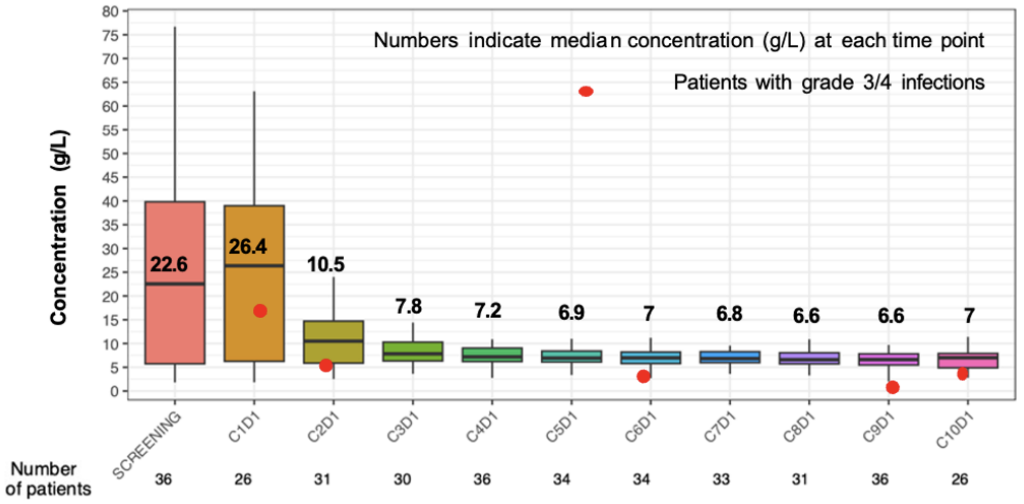
No patients had a positive MRD status.

Early safety appears manageable, but with intensive immune support

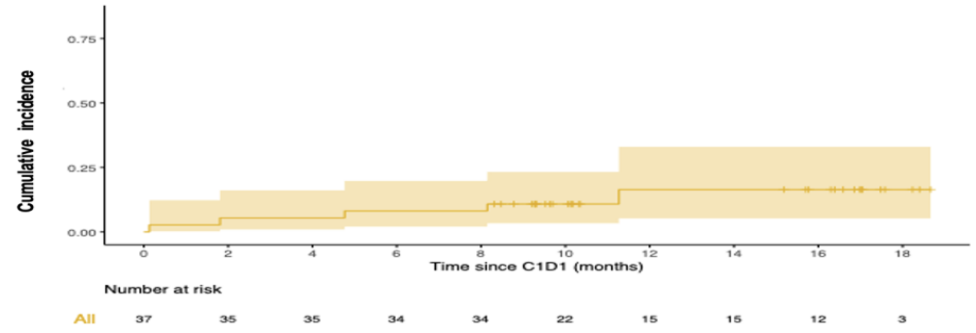
All grade AESI

AESI, n(%)	Tec-Dara (n=37) All grade	Grade 1-2	Grade ≥ 3
Infections	24 (65%)	19 (52%)	5 (14%)
Bronchitis	6 (16%)	6 (16%)	-
COVID-19	5 (14%)	4 (11%)	1 (3%)
Urinary tract infection	5 (14%)	5 (14%)	-
Sinusitis	4 (11%)	4 (11%)	-
Pneumonia	3 (8%)	2 (5%)	1 (3%)
GI salmonella	1 (3%)	-	1 (3%)
Peritonitis	1 (3%)	-	1 (3%)
HHV6 infection	1 (3%)	-	1 (3%)
CRS	22 (59%)	G1: 13 (35%) G2: 9 (24%)	-
ICANS	-	-	-
Injection site reaction	7 (19%)	7 (19%)	-
Second primary malignancy	1 (3%)	1 (3%)	-

IgG level evolution



Cumulative incidence of grade 3/4 infections



Immunoglobulin supplementation

	Tec-Dara (n=37)
Immunoglobulin supplementation – no. (%)	
Yes	35 (95%)
No	2 (5%)
Mediane cycle of initiation, n (Q1-Q3)	1 (1-2)

FACON etal Leukemia 2026

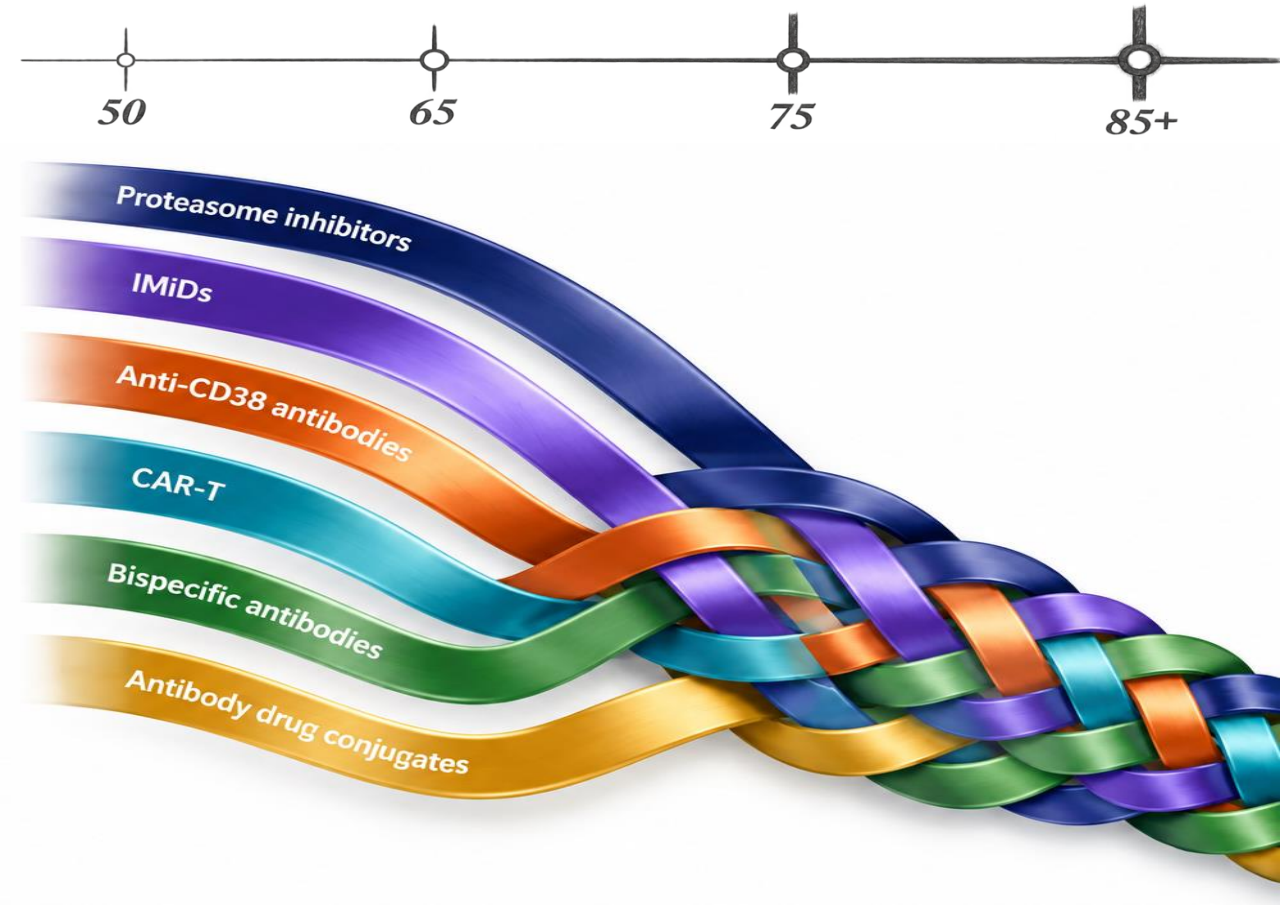
THE BAR IS SURVIVAL, NOT RESPONSE DEPTH

- MAIA sets an exceptionally high benchmark, with some older patients approaching normal life expectancy on a generally tolerable regimen. Even a small excess in treatment-related mortality could erase the benefit of greater disease control.

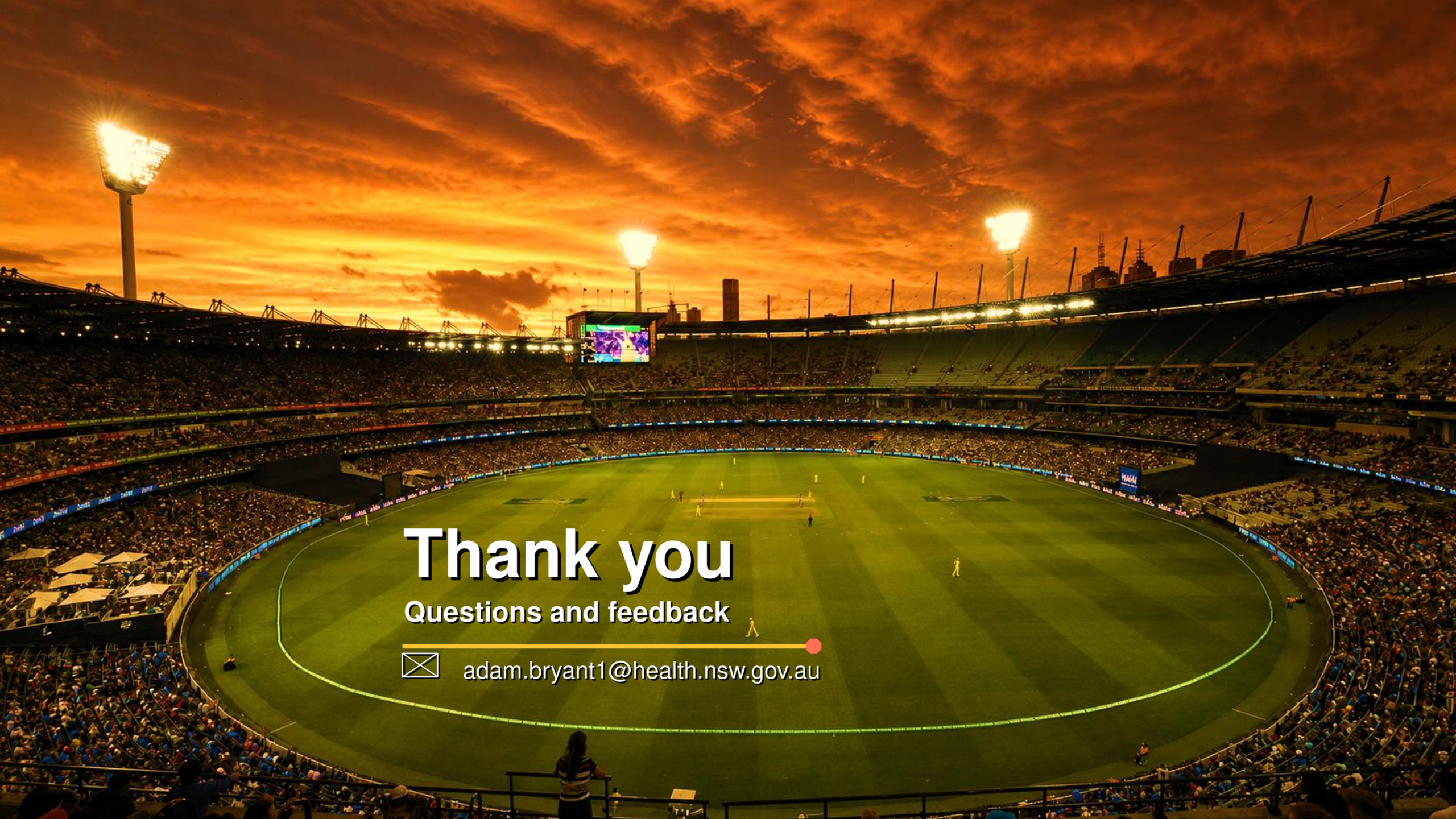
- Upfront bispecific strategies must therefore deliver both efficacy and tolerability, probably through planned fixed-duration treatment.

Summary

- Older and frail patients can achieve deep, durable responses with bispecifics, but they are not well represented in pivotal trials
- CRS and ICANS do not appear amplified; infection remains the central toxicity concern.
- From 3rd line, realistic alternatives are not completely benign.
- Patient selection, infection prevention and response-adapted dosing are central to delivery.



For many older patients, the question is not whether a bispecific carries risk, but whether that risk can be managed and justified by the prospect of substantially better disease control than realistic alternatives.


Thank you
Questions and feedback
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