Daratumumab Monotherapy Versus Active Monitoring in Patients With High-Risk Smoldering Multiple Myeloma: AQUILA Outcomes Based on Mayo 2018/IMWG 2020 Risk Stratification, IMWG Scoring, and Age

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AQUILA Subgroups: Introduction

- Daratumumab is approved for adults with high-risk SMM, reflecting a new standard of care
- The criteria for defining high-risk SMM have evolved since the initiation of the phase 3 AQUILA trial
- *Post hoc* analyses of AQUILA were performed to aid patient identification in clinical practice:
  - Efficacy stratified by different risk models, to determine which AQUILA patients benefitted most from treatment with daratumumab monotherapy
  - Safety and efficacy outcomes according to age
  - Stem-cell collection yield outcomes

AQUILA (NCT03301220)[1]

Daratumumab monotherapy significantly reduced the risk of progression to active MM or death by 51% compared with active monitoring

OS was improved

No new safety concerns were observed

IMWG, International Myeloma Working Group; MM, multiple myeloma; OS, overall survival; SMM, smoldering multiple myeloma.

1. Dimopoulos MA, et al. *N Engl J Med* 2025;392(18):1777-88.

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AQUILA Subgroups: IMWG 2020 Risk Stratification of SMM

- The IMWG 2020 risk stratification is the current, standard validated system
- Also referred to as Mayo 2018, or 20-2-20 as it comprises three risk factors:
  - BMPC >20%, monoclonal spike >2 g/dL, serum I/U FLC ratio >20

IMWG 2020 risk stratification category	Number of risk factors	2-year progression risk,[1] %	5-year progression risk,[2] %
Low risk	0	6	23
Intermediate risk	1	18	47
High risk	≥2	44	82

BMPC, bone marrowplasma cells; I/U FLC, involved/uninvolved free light chain; IMWG, International Myeloma Working Group; M, monoclonal; SMM, smoldering multiple myeloma.
1. Mateos M, et al. *Blood Cancer J* 2020;10:102. 2. Visram A, et al. *Hematology Am Soc Hematol Educ Program* 2021;2021(1):673–81.

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AQUILA Subgroups: Additional Investigational SMM Risk-Scoring Methods

- Models such as the IMWG scoring system incorporating cytogenetics are not yet validated; this comprises:
  - Serum FLC ratio: 0–10, 0 points; 10–25, 2 points; 25–40, 3 points; >40, 5 points
  - Monoclonal spike g/dL: 0–1.5, 0 points; 1.5–3, 3 points; >3, 4 points
  - Percentage of BMPCs: 0–15, 0 points; 15–20, 2 points; 20–30, 3 points; 30–40, 5 points; >40, 6 points
  - FISH abnormalities[a]: No, 0 points; Yes, 2 points

IMWG scoring system category[1]	Score	Corresponding IMWG 2020 risk stratification category based on 2-year progression risk	2-year progression risk, %	5-year progression risk, %
Low risk	0–4	Low risk	4	20
Low-intermediate risk	5–8	Low-intermediate risk	26	55
Intermediate risk	9–12	**High risk**	51	70
High risk	>12	**High risk**	73	85

[A] Comprising t(4;14), t(14;16), +1q, and/or del13q/monosomy 13.
BMPC, bone marrowplasma cells; FISH, fluorescence in situ hybridization; FLC, free light chain; IMWG, International Myeloma Working Group; SMM, smoldering multiple myeloma.
1. Visram A, et al. *Hematology Am Soc Hematol Educ Program* 2021;2021(1):673-81.

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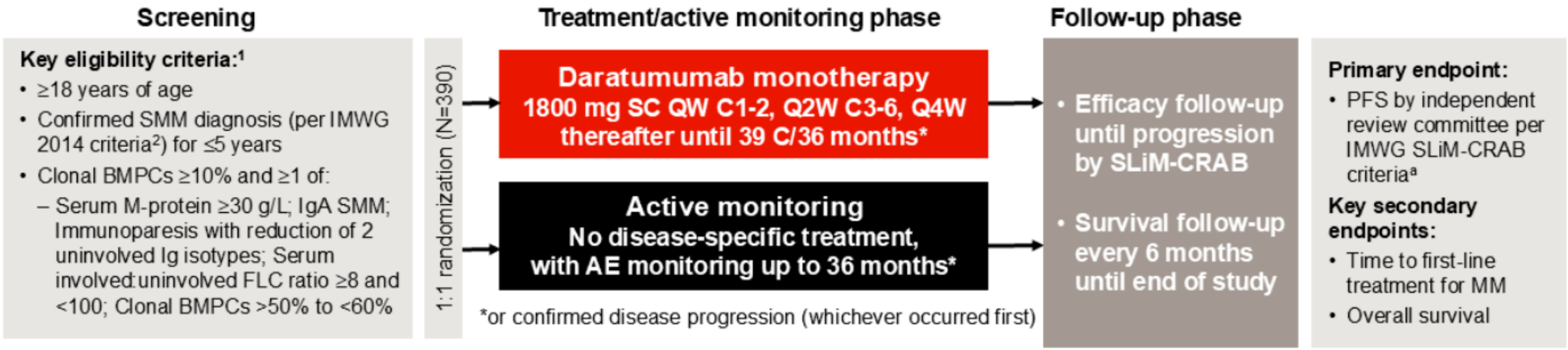
AQUILA: Study Design and Risk Stratification Methods



- For this *post hoc* analysis, outcomes were assessed by:

IMWG 2020 validated risk stratification:
BMPC >20%, M spike >2 g/dL, serum l/U FLC ratio >20
0 factors=low risk; 1 factor=intermediate risk; ≥2 factors=high risk

IMWG scoring system:
Points given based on values of serum FLC ratio, M spike g/dL, percentage of BMPCs, and FISH abnormalities
0–4 points=low risk; 5–8 points=low-intermediate risk; 9–12 points=intermediate; >12 points=high risk

Age:
<65 years
65 to <75 years
≥75 years

[a] SLiM-CRAB, ≥60% clonal plasma cells in bone marrow, involved/uninvolved free light chain ratio ≥100 or more with the involved free light chain ≥100 mg/L, magnetic resonance imagine with >1 focal marrow lesion, hypercalcemia, renal insufficiency, anemia, bone lesions. BMPC, bone marrow plasma cell; C, cycle; FLC, free light chain; IMWG, International Myeloma Working Group; M, monoclonal; PFS, progression-free survival; SC, subcutaneous; SMM, smoldering multiple myeloma; QW, once weekly. 1. Dimopoulos MA, et al. *N Engl J Med* 2025;392(18):1777-88. 2. Rajkumar SV, et al. *Lancet Oncol* 2014;15(12):e538-48.

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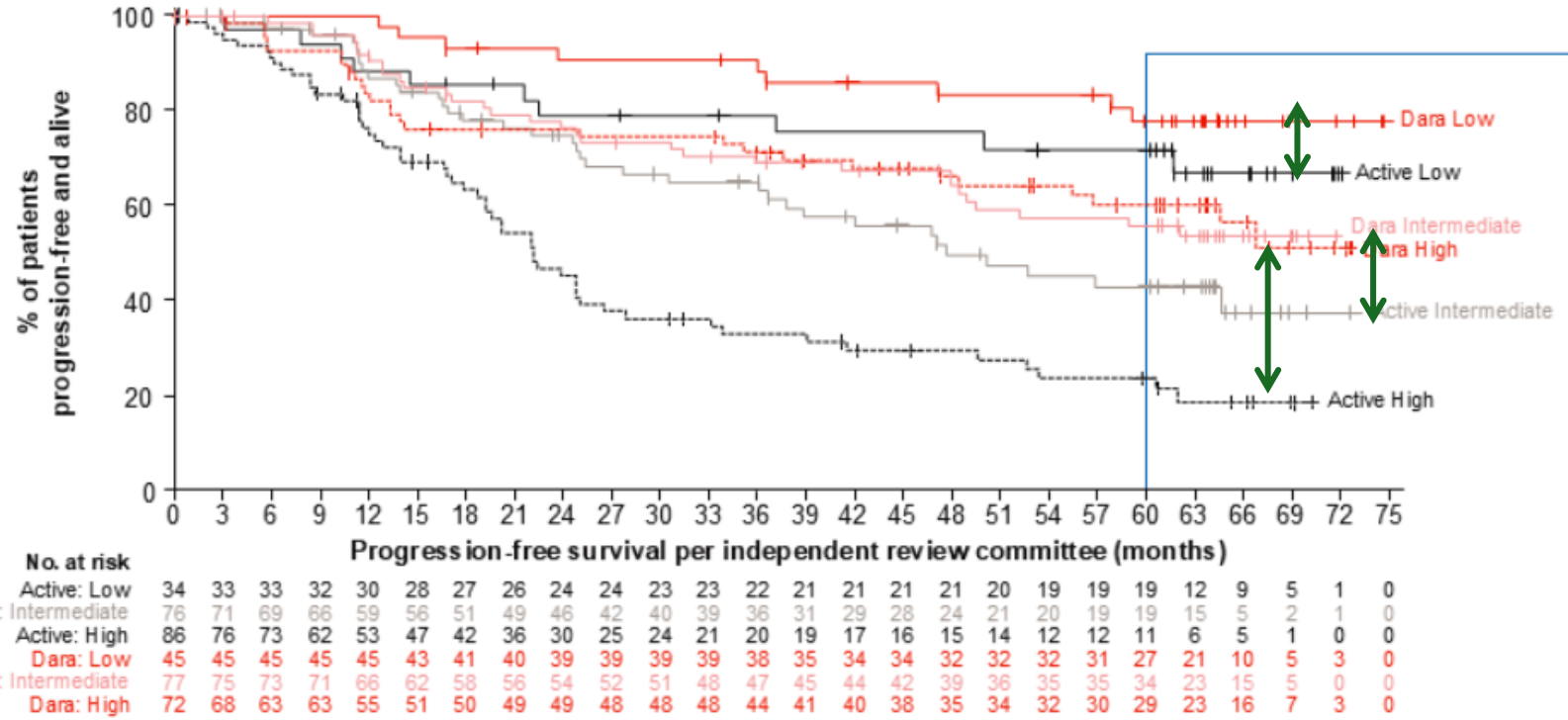
AQUILA: IMWG 2020 Subgroups: PFS



60-month PFS rates, %:

IMWG 2020 Risk group	Daratumumab	Active monitoring
Low	78.2	71.6
Intermediate	56.2	42.9
High	60.4	23.6

PFS active monitoring vs daratumumab monotherapy, high-risk group:
62.8% vs 37.5% events
HR 0.36 (95% CI: 0.23, 0.58)

Daratumumab monotherapy showed a PFS benefit vs active monitoring across IMWG 2020 risk subgroups, with the largest benefit observed in the high-risk subgroup

IMWG 2020 (aka Mayo 2018 or 20-2-20) risk stratification: BMPC >20%, monoclonal spike >2 g/dL, serum l/U FLC ratio >20.
0 factors=low risk; 1 factor=intermediate risk; ≥2 factors=high risk

BMPC, bone marrowplasma cells; FLC, free light chain; IMWG, International Myeloma Working Group; PFS, progression-free survival; SC, subcutaneous; SMM smoldering multiple myeloma.

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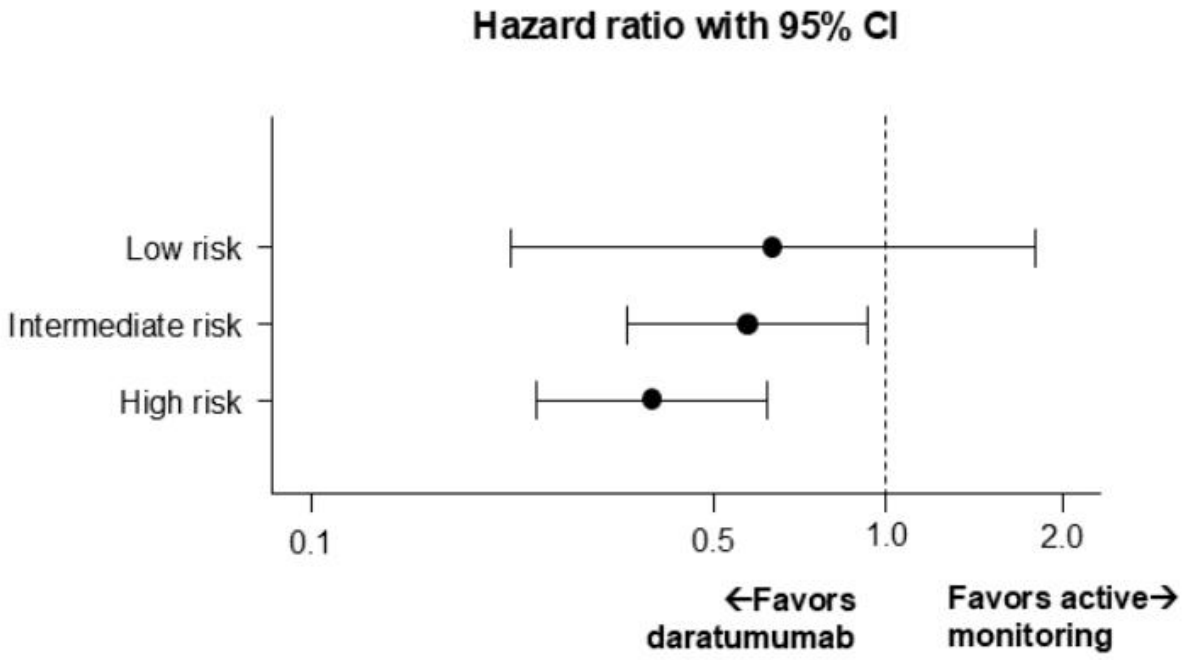
AQUILA: IMWG 2020 Subgroups: Time to Initial MM Treatment



	Daratumumab		Active monitoring		
	Event/N	Median (95% CI)	Event/N	Median (95% CI)	Hazard ratio 95% CI[a]
Low risk	7/45	NE (NE, NE)	7/34	NE (NE, NE)	0.63 (0.22, 1.80)
Intermediate risk	29/77	NE (60.6, NE)	40/76	51.8 (37.8, NE)	0.57 (0.35, 0.92)
High risk	28/72	NE (63.1, NE)	55/86	28.0 (21.1, 44.0)	0.39 (0.25, 0.62)

There was a positive trend favoring daratumumab monotherapy for time to initial MM treatment across all IMWG 2020 risk groups, with the strongest trend in the high-risk subgroup

IMWG 2020 (aka Mayo 2018 or 20-2-20) risk stratification: BMPC >20%, monoclonal spike >2 g/dL, serum I/U FLC ratio >20.
0 factors=low risk; 1 factor=intermediate risk; ≥2 factors=high risk

[a] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory.
IMWG, International Myeloma Working Group; MM, multiple myeloma; NE, not estimated.

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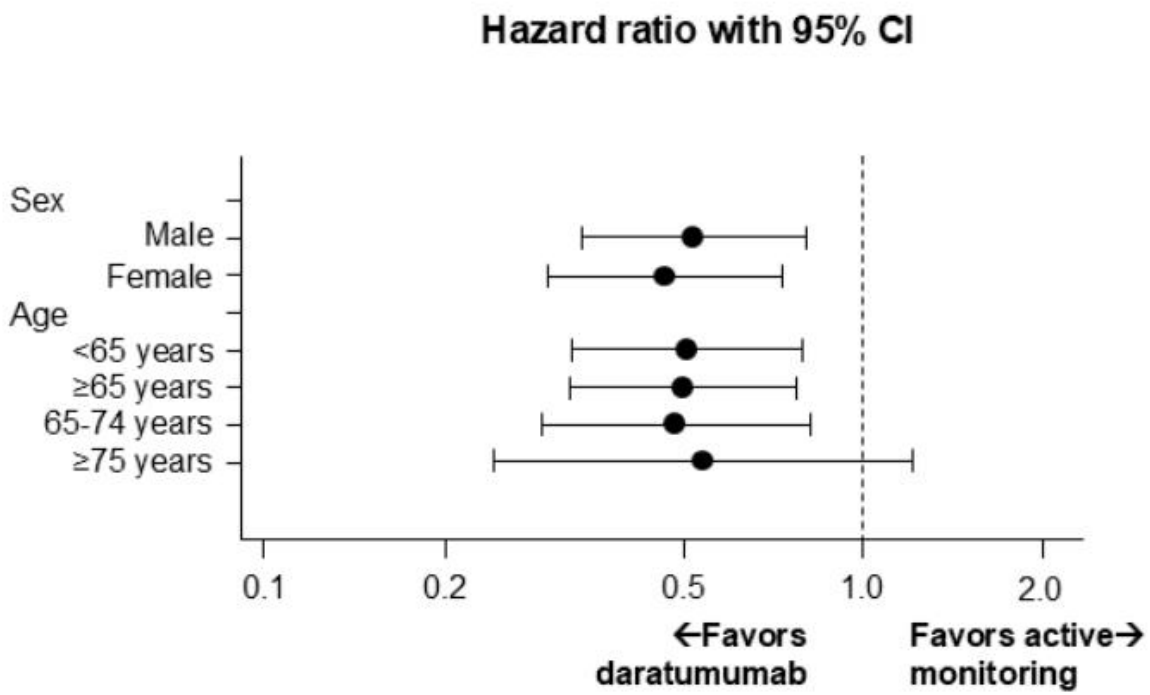
AQUILA: Age Subgroups: PFS



	Daratumumab		Active monitoring		
	Event/N	Median (95% CI)	Event/N	Median (95% CI)	Hazard ratio 95% CI[a]
Male	37/95	NE (57.8, NE)	48/93	41.5 (23.8, 53.3)	0.52 (0.34, 0.80)
Female	30/99	NE (66.7, NE)	51/103	38.9 (25, 61.9)	0.47 (0.30, 0.74)
<65 years	34/106	NE (66.7, NE)	45/98	42 (25, NE)	0.51 (0.32, 0.79)
≥65 years	33/88	NE (57.8, NE)	54/98	38.8 (22, 52.7)	0.50 (0.32, 0.77)
65-74 years	23/67	NE (62, NE)	38/74	50.2 (22, 64.7)	0.49 (0.29, 0.82)
≥75 years	10/21	49.5 (14.2, NE)	16/24	22.4 (17.8, 47)	0.54 (0.24, 1.21)

Daratumumab monotherapy improved PFS regardless of age

[a] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory.
NE, not estimated; PFS, progression-free survival.

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AQUILA: Age Subgroups: Safety Summary

n (%)	Daratumumab			Active monitoring		
	<65 yrs n=105	65 to <75 yrs n=67	≥75 yrs n=21	<65 yrs n=98	65 to <75 yrs n=74	≥75 yrs n=24
Any TEAE	101 (96.2)	66 (98.5)	20 (95.2)	81 (82.7)	60 (81.1)	21 (87.5)
Infections and infestations SOC, any grade	86 (81.9)	57 (85.1)	11 (52.4)	49 (50.0)	29 (39.2)	10 (41.7)
Infections and infestations SOC, grade ≥3	10 (9.5)	18 (26.9)	3 (14.3)	3 (3.1)	3 (4.1)	3 (12.5)
Any serious TEAE	26 (24.8)	24 (35.8)	6 (28.6)	12 (12.2)	14 (18.9)	12 (50.0)
Serious TEAEs occurring in ≥5% of any group:						
Pneumonia	1 (1.0)	6 (9.0)	0	0	1 (1.4)	0
TEAE leading to discontinuation	2 (1.9)	6 (9.0)	3 (14.3)	-	-	-
TEAE leading to dose modification[a]	35 (33.3)	44 (65.7)	11 (52.4)	-	-	-

The rates of TEAEs and serious TEAEs in the daratumumab group were similar across age groups

[a]Dose modification includes dose delay within cycle, cycle delay, and dose skipped.
SOC, system organ class; TEAE, treatment-emergent adverse event; yrs, years.

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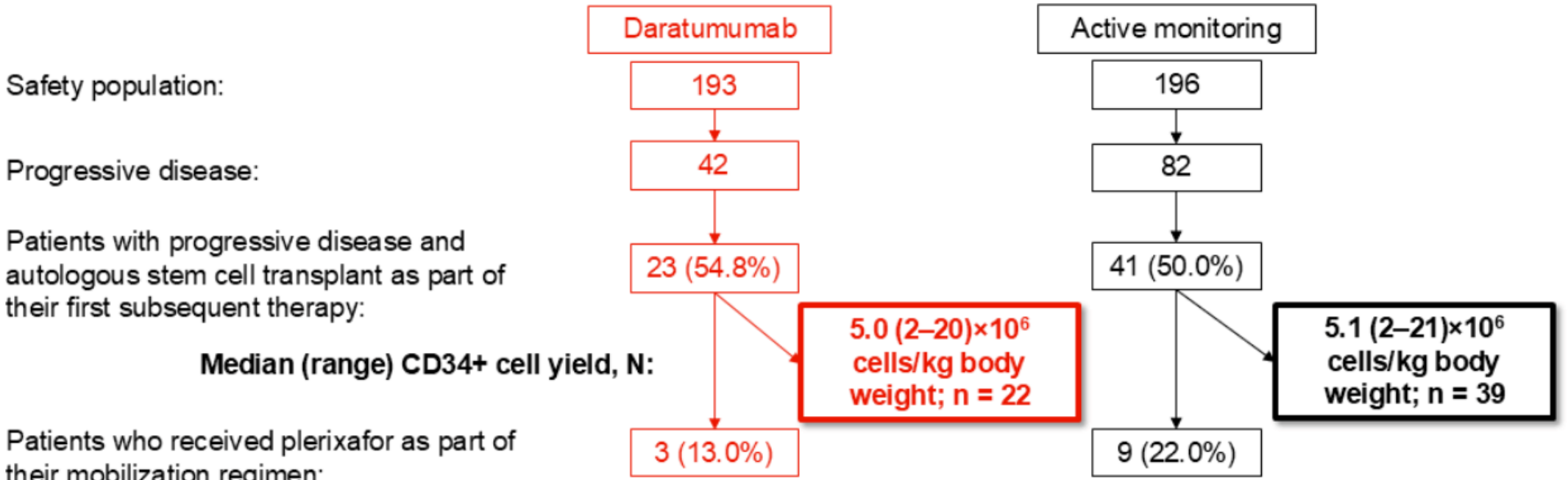
AQUILA: Peripheral Blood Stem Cell Collection for Subsequent Transplant



Median CD34+ cell yield was similar among patients in the daratumumab monotherapy arm and those in the active monitoring arm

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AQUILA: Conclusions

- Daratumumab is the first treatment approved to treat high-risk SMM, based on a significant improvement in PFS, and a trend toward improved overall survival
- In these *post hoc* subgroup analyses of AQUILA, up to 3 years of daratumumab monotherapy:
  - Delivered greater PFS benefit across IMWG 2020 intermediate and high-risk subgroups
    - The greatest benefits were observed in the IMWG 2020 high-risk subgroup
  - Prolonged time to initial MM therapy across intermediate and high-risk subgroups
  - Provided a PFS benefit across age subgroups; safety outcomes were similar in patients receiving daratumumab regardless of age
- Daratumumab treatment did not impair stem-cell yield
- The upcoming final analysis of AQUILA will formally evaluate overall survival

Treatment with daratumumab monotherapy in patients with high-risk SMM provides long-term PFS benefits across most subgroups regardless of risk stratification criteria, further supporting early intervention

FLC, free light chain; IMWG, International Myeloma Working Group; HR, hazard ratio; PFS, progression-free survival; SMM, smoldering multiple myeloma.

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נושאים לדיון

כמה התקדמו לדיאליזה או שהייתה להם אי ספיקת כליות בלתי הפיכה? שברים ולא "מחלה גרמית"?
היפרקלצמיה תסמינית? אנמיה זה פחות מעניין!

מה לגבי PFS2?

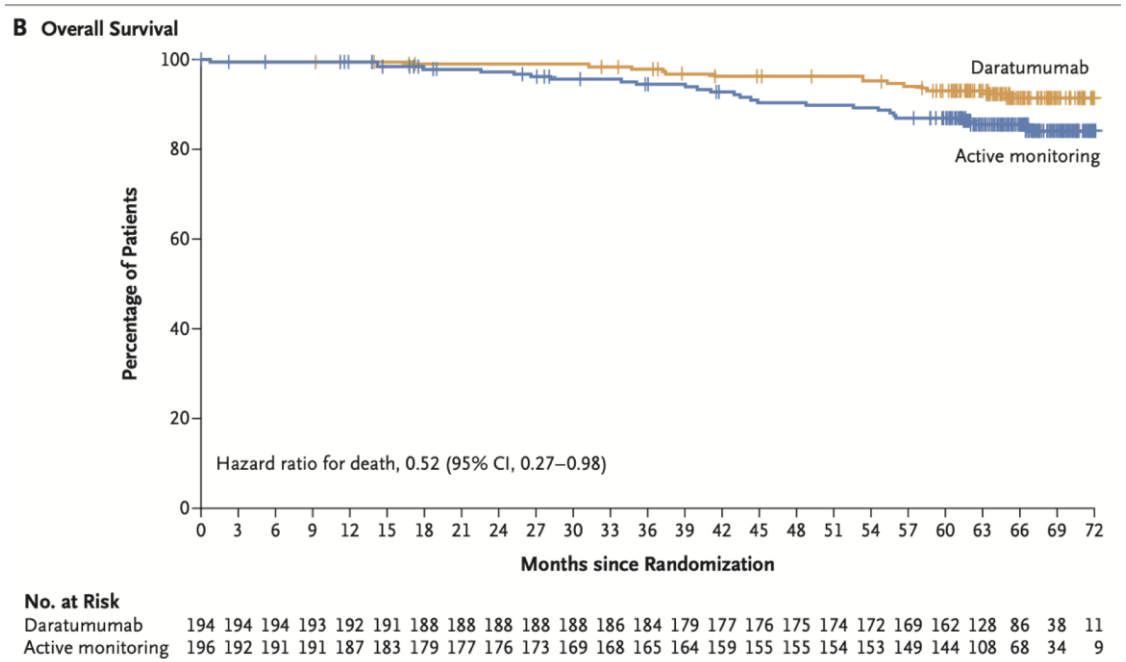
אין יתרון משמעותי סטטיסטית ב- OS

Characteristic	Daratumumab (N=194)	Active Monitoring (N=196)
Median time from diagnosis of smoldering multiple myeloma to randomization (range) — yr	0.80 (0–4.7)	0.67 (0–5.0)

Table 2. Summary of Progression Events (Intention-to-Treat Population).

Event	Daratumumab (N=194)	Active Monitoring (N=196)
Disease progression or death — no. (%)	67 (34.5)	99 (50.5)
Disease progression — no./total no. (%)*	62/67 (92.5)	94/99 (94.9)
CRAB criteria		
Calcium level elevation	0/62	2/94 (2.1)
Renal insufficiency	0/62	0/94
Anemia	2/62 (3.2)	14/94 (14.9)
Bone disease	10/62 (16.1)	18/94 (19.1)
SLiM criteria		
≥60% Clonal plasma cells in bone marrow	5/62 (8.1)	16/94 (17.0)
Serum FLC ratio ≥100	33/62 (53.2)	33/94 (35.1)
>1 Focal lesion on magnetic resonance imaging	12/62 (19.4)	16/94 (17.0)
Death without disease progression — no./total no. (%)	5/67 (7.5)	5/99 (5.1)

* Disease progression was assessed by an independent review committee in accordance with the International Myeloma Working Group SLiM–CRAB diagnostic criteria for multiple myeloma.[6] A patient could meet more than one criterion for disease progression.



Phase 1/2 Dose Escalation and Expansion Study of Etentamig in Patients With Relapsed or Refractory Light Chain Amyloidosis

Rajshekhar Chakraborty[1], Efstathios Kastritis[2], Antoine Huart[3], Arnaud Jaccard[4], Heather J Landau[5], Shinsuke Iida[6], Olga Motorna[7], Peter Mollee[8], Tadao Ishida[9], Yawara Kawano[10], Manisha Bhutani[11], Anita D'Souza[12], Andrew J Cowan[13], James E Hoffman[14], Chetasi Talati[15], Tanya S Rosenberg[15], Ross La Motte-Mohs[15], Fan Wang[15], David M Hoffman[15], Mingwei Fei[15], Emma L Arriola[15], Jovian Yu[15], Shaji Kumar[16], Angela Dispenzieri[17], Giovanni Palladini[18,19], Vaishali Sanchorawala[20]

[1]Multiple Myeloma and Amyloidosis Program, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY, USA; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [3]Department of Nephrology and Organ Transplantation, University Hospital Toulouse, Toulouse, France; [4]Hematology Department, French Reference Center for AL Amyloidosis (Limoges-Poitiers), CHU Limoges, Limoges, France; [5]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [7]Department of Haematology, Eastern Health, and Eastern Clinical School, Monash University; [8]Princess Alexandra Hospital and University of Queensland, Brisbane, Queensland, Australia; [9]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [10]Department of Hematology, Rheumatology, and Infectious Disease, Kumamoto University Graduate School of Medicine, Kumamoto, Japan; [11]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Advocate Health Wake Forest University School of Medicine, Charlotte, NC, USA; [12]Division of Hematology/Oncology, Department of Medicine, Froedtert & Medical College of Wisconsin Cancer Center, Milwaukee, WI, USA; [13]University of Washington and Fred Hutchinson Cancer Center, Seattle, WA, USA; [14]University of Miami Health System, Miami, FL, USA; [15]AbbVie Inc., North Chicago, IL, USA; [16]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [17]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [18]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [19]Amyloidosis Research and Treatment Center, Foundation "Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo," Pavia, Italy; [20]Amyloidosis Center, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA

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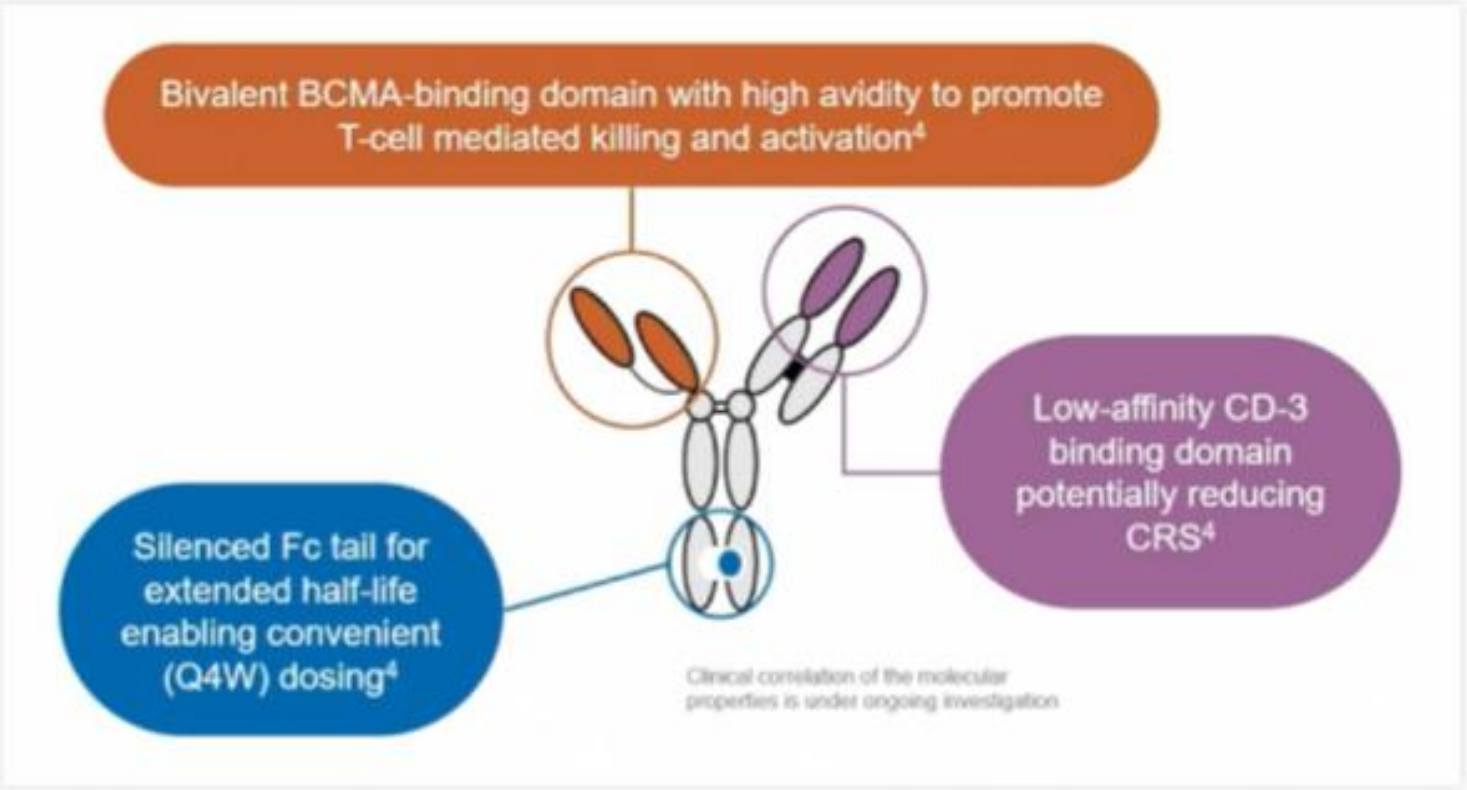
Etentamig is being developed as a next-generation BCMA bispecific

- BCMA is highly expressed on abnormal plasma cells[1,2]
- BCMA-targeting immunotherapies represent a promising class of treatment for AL amyloidosis, a clonal plasma cell-related disease[3]
- CERVINO (NCT06158841) is the ongoing Phase 3 study of etentamig monotherapy vs SoC in RRMM



Here, we report the first safety and efficacy results from M24-209 (NCT06158854), an open-label Phase 1/2 study evaluating etentamig monotherapy in patients with RR AL amyloidosis

1.Shah N, et al. *Leukemia*. 2020;34(4):985–1005. 2.Susan B, et al. *Blood*. 2019;134 (Supplement_1):5452. 3.Lewis E, et al. *Curr Oncol*. 2025;32(8):418. 4.D'Souza A, et al. *J Clin Oncol*. 2022;40(31):3576–3586.

AL, amyloid light-chain; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; MM, multiple myeloma; Q4W, every 4 weeks; RR, relapsed/refractory; SoC, standard of care.

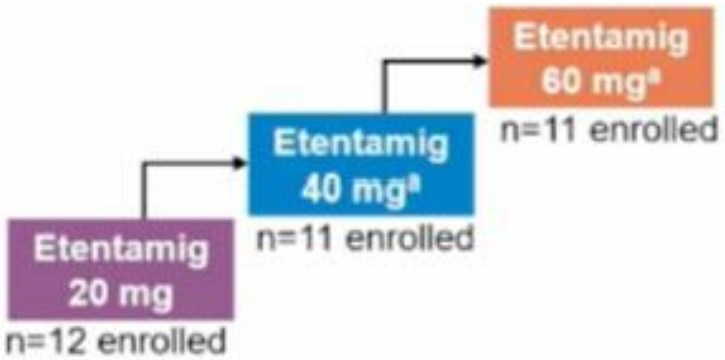
M24-209: Open-label, Phase 1/2 study evaluating safety and efficacy of etentamig monotherapy in patients with RR AL amyloidosis

Phase 1 dose escalation

Key eligibility

- RR after ≥1 prior therapy (including PI and anti-CD38 mAb), requiring further treatment
- ≥1 baseline organ involved
- Stage 1–3a
- Measurable hematologic disease: dFLC ≥50 mg/L

Dose Escalation (N=34; fully enrolled)



Dosing

- Etentamig IV QW4
- SUD incorporated from 40 mg onward
- Fixed 24 cycles of etentamig
- Premedication including dexamethasone, acetaminophen, and diphenhydramine

Endpoints

Primary endpoints

- Safety/tolerability, PK, and RP2D

Secondary endpoints

- Efficacy as measured by organ and hematologic response[b]

[a]Cohort with SUD incorporated. [b]Responses are investigator assessed per consensus guidelines (Comenzo, et al. *Leukemia*. 2012; 26(11):2317–2325; Palladini G, et al. *Amyloid*. 2021[Epub];28(1):1–2).
AL, amyloid light-chain; dFLC, difference between the involved and uninvolved free light chains; IV, intravenous; mAb, monoclonal antibody; PI, protease inhibitors; PK, pharmacokinetic; Q4W, every 4 weeks; RP2D, recommended Phase 2 dose; RR, relapsed/refractory; SUD, step-up dosing.

Baseline and clinical characteristics were generally well-balanced

	20 mg Q4W (n=12)	40 mg Q4W (n=11)	60 mg Q4W (n=11)	Total (N=34)
Age, median years (range)	72 (56–85)	74 (49–82)	66 (54–84)	70 (49–85)
Sex, Male	5 (41.7)	9 (81.8)	4 (36.4)	18 (52.9)
Race				
White	6 (54.5)	10 (90.9)	9 (81.8)	25 (75.8)
Black	1 (9.1)	0	1 (9.1)	2 (6.1)
Asian	4 (36.4)	1 (9.1)	1 (9.1)	6 (18.2)
Number of prior LoT, median (range)	2 (1–6)	2 (1–8)	2 (1–4)	2 (1–8)
Time from initial diagnosis, median years (range)	3.6 (0–12)	5.2 (0–13)	4.8 (0–21)	4.5 (0–21)
Had prior SCT (yes)	4 (33.3)	2 (18.2)	1 (9.1)	7 (20.6)
Prior anti-CD38 exposure	12 (100.0)	11 (100.0)	11 (100.0)	34 (100.0)
dFLC, median mg/L (range)	110.5 (56.6–617.5)	91.4 (55.8–345.3)	118.8 (49.0–862.5)	108.9 (49.0–862.5)
NT-proBNP, median ng/L (range)	548.1 (158.0–6827.2)	665.0 (118.4–1658.2)	414.5 (101.5–4982.9)	595.6 (101.5–6827.2)
eGFR, median mL/min/1.73m^2 (range)	60.3 (42.9–105.3)	66.7 (38.1–107.8)	75.3 (31.8–102.2)	62.4 (31.8–107.8)
Organ involvement at enrollment				
Cardiac	10 (83.3)	9 (81.8)	9 (90.0)	28 (84.8)
Renal	3 (25.0)	6 (54.5)	4 (40.0)	13 (39.4)
Hepatic	1 (8.3)	2 (18.2)	0	3 (9.1)
Other	0	0	1	1
Light chain type, lambda light chain	10 (83.3)	8 (72.7)	8 (72.7)	26 (76.5)

Data are displayed as n (%) unless stated otherwise. **(Data cut 20 Aug 2025)**

dFLC, difference between the involved and uninvolved free light chains; eGFR, estimated glomerular filtration rate; LoT, line of therapy; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q4W, every 4 weeks; SCT, stem cell transplant.

More than 90% of patients remain on etentamig treatment after a median follow up of 7 months

	20 mg Q4W (n=12)	40 mg Q4W (n=11)	60 mg Q4W (n=11)	Total (N=34)
Duration of follow up, median months (range)	11.6 (9.5–15.1)	6.5 (3.8–9.5)	3.7 (2.8–4.1)	6.9 (2.8–15.1)
Duration of exposure, median months (range)	12.3 (9–16)	7.4 (4–10)	4.1 (4–5)	7.8 (4–16)
Study treatment discontinuation	2 (16.7)	1 (9.1)	0	3 (8.8)
Due to AE[a]	1 (8.3)	0	0	1 (2.9)
Due to withdrawal from treatment by subject	1 (8.3)	1 (9.1)	0	2 (5.9)

Treatment discontinuation due to AE has only been observed in 1 patient

Data are displayed as n (%) unless stated otherwise. [a]1 patient discontinued treatment due to Grade 2 treatment-emergent AE of bronchiectasis.
AE, adverse event; Q4W, every 4 weeks.

(Data cut 20 Aug 2025)

Safety profile is consistent with existing etentamig safety data

	20 mg Q4W (n=12)		40 mg Q4W (n=11)		60 mg Q4W (n=11)		Total (N=34)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TEAE (≥15%)	12 (100.0)	6 (50.0)	10 (90.9)	4 (36.4)	10 (90.9)	5 (45.5)	32 (94.1)	15 (44.1)
Upper respiratory tract infection	4 (33.3)	1 (8.3)	2 (18.2)	0	3 (27.3)	0	9 (26.5)	1 (2.9)
Hypogammaglobulinemia	4 (33.3)	0	2 (18.2)	0	2 (18.2)	0	8 (23.5)	0
Blood creatinine increased	2 (16.7)	0	1 (9.1)	0	3 (27.3)	0	6 (17.6)	0
Cough	3 (25.0)	0	3 (27.3)	0	0	0	6 (17.6)	0
Diarrhea	1 (8.3)	0	3 (27.3)	0	2 (18.2)	0	6 (17.6)	0
Edema	2 (16.7)	0	3 (27.3)	0	1 (9.1)	0	6 (17.6)	0
Hematologic TEAE (≥2%)								
Anemia	0	0	0	0	3 (27.3)	1 (9.1)	3 (8.8)	1 (2.9)
Lymphopenia[a]	1 (8.3)	1 (8.3)	0	0	2 (18.2)	2 (18.2)	3 (8.8)	3 (8.8)
Neutropenia[b]	1 (8.3)	1 (8.3)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	3 (8.8)	3 (8.8)
Thrombocytopenia[c]	1 (8.3)	0	0	0	0	0	1 (2.9)	0

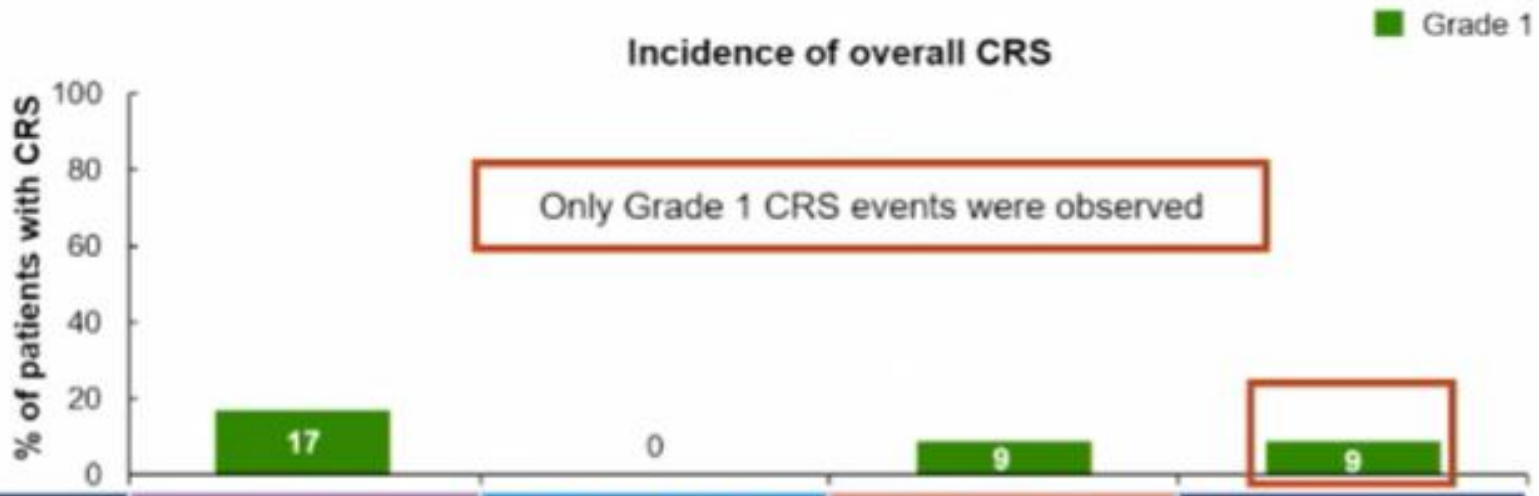
- Dose limiting toxicity occurred in 1 patient (left popliteal arterial thrombus in the 40 mg cohort)
- No patient experienced a Grade 5 TEAE across any cohort during dose escalation

Early data suggest encouraging tolerability in a highly debilitated patient population

Data are displayed as n (%) unless stated otherwise. [a]Combined lymphopenia and lymphocyte count reduced. [b]Combined neutropenia and neutrophil count reduced. [c]Combined thrombocytopenia and platelet count reduced.
Q4W, every 4 weeks; TEAE, treatment emergent adverse event.

(Data cut 20 Aug 2025)

Overall CRS incidence <10% without any ICANS observed



	20 mg Q4W (n=12)	40 mg Q4W[a] (n=11)	60 mg Q4W[a] (n=11)	Total (N=34)
Time to CRS onset, median hours (range)	6.8 (6.7–6.9)	0	NA	6.9 (6.7–12.4)
Time to CRS resolution, median hours (range)	79.4 (8.8–150.0)	0	NA	48.0 (8.8–150.0)
Tocilizumab for management of CRS	1 (8.3)	0	0	1 (2.9)
Rate of CRS recurrence	0	0	0	0

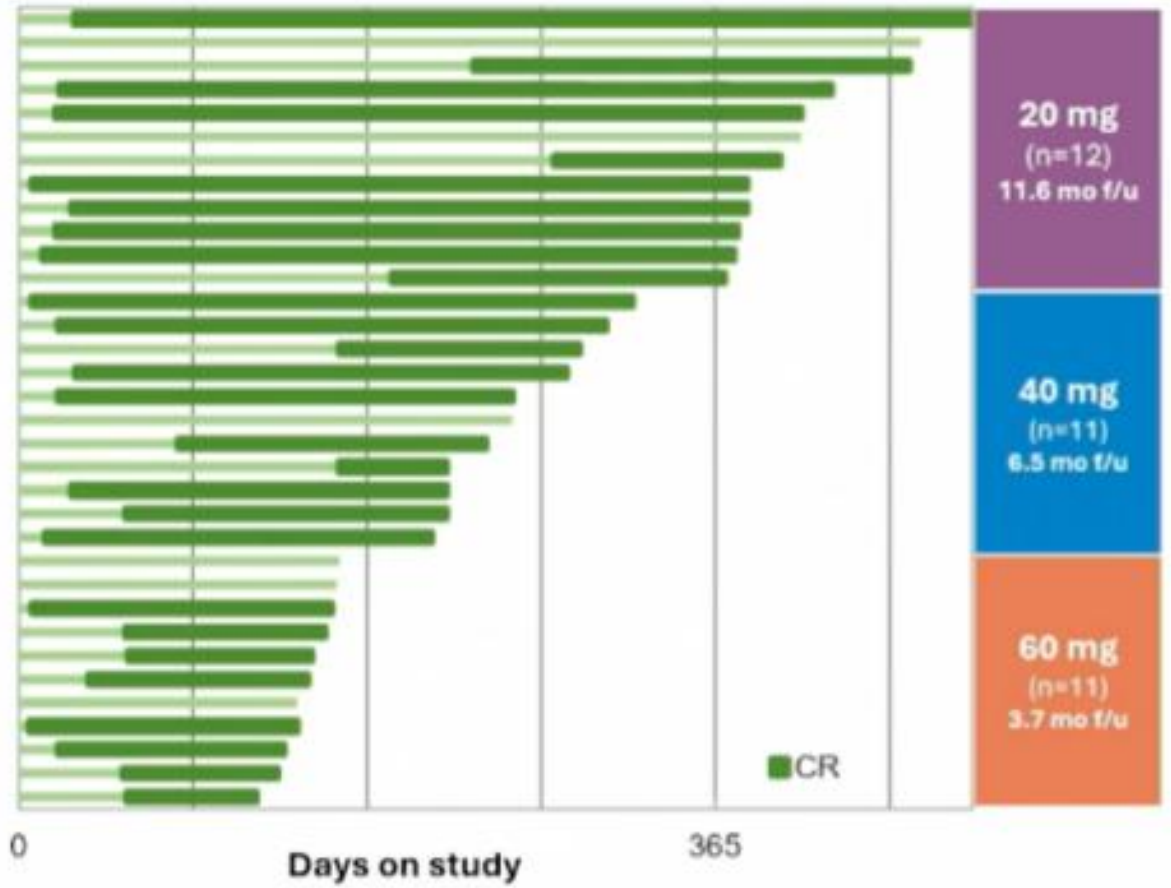
Very low CRS rates are observed with regular bispecific antibody premedication and without any tocilizumab prophylaxis

Data are displayed as n (%) unless stated otherwise. [a]Step-up dosing was implemented for 40 mg and 60 mg cohorts during cycle 1.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NA, not applicable; Q4W, every 4 weeks.

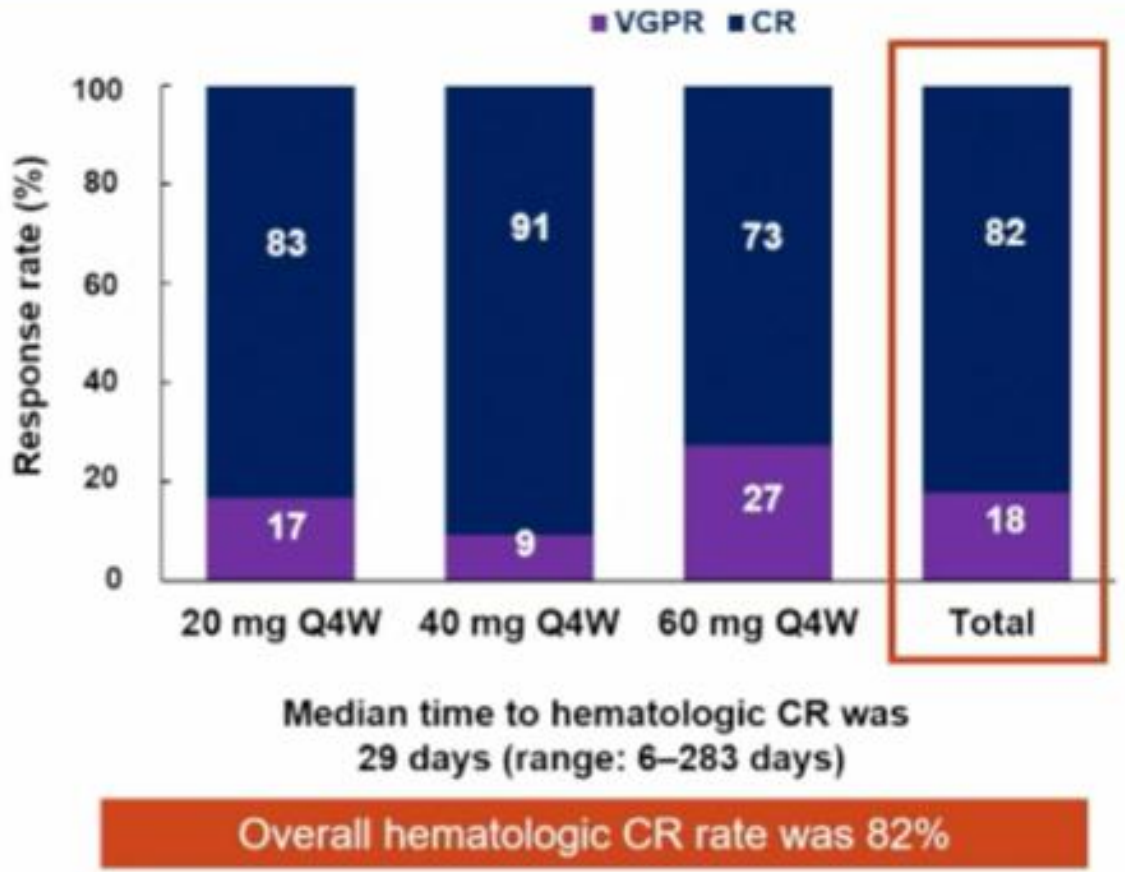
(Data cut 20 Aug 2025)

Treatment with etentamig led to 100% ≥VGPR rate across dose levels

Overall Hematologic Responses



Overall Hematologic Responses



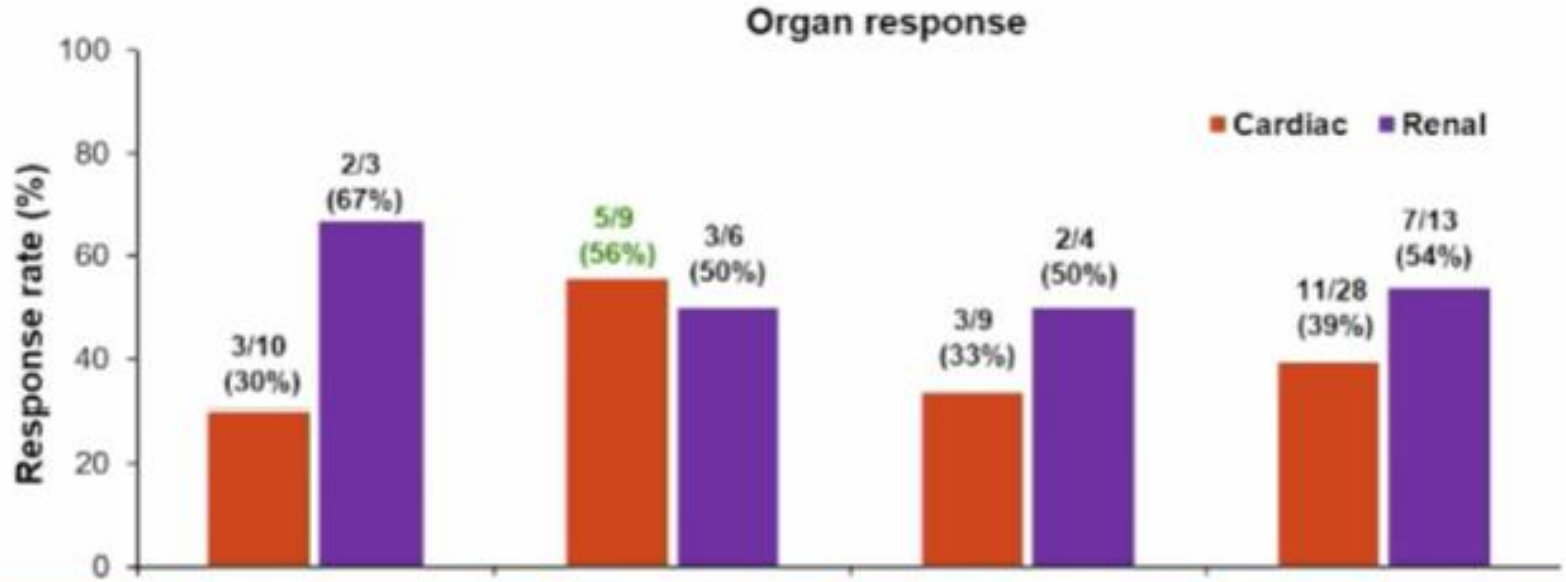
Median time to hematologic CR was
29 days (range: 6–283 days)

Overall hematologic CR rate was 82%

CR, complete response; f/u, follow up; mo, month; Q4W, every 4 weeks; VGPR, very good partial response.

(Data cut 20 Aug 2025)

Promising and rapid organ response rates observed during dose escalation



Response Outcomes	20 mg Q4W (n=12)	40 mg Q4W (n=11)	60 mg Q4W (n=11)	Total (N=34)
Time to cardiac response, median months (range)	4.7 (3.7–6.5)	1.0 (0.9–5.3)	2.10 (1.0–2.8)	2.10 (0.9–6.5)
Time to renal response, median months (range)	1.4 (0.9–1.9)	1.9 (1.0–2.9)	1.4 (1.0–1.8)	1.8 (0.9–2.9)

Q4W, every 4 weeks.

(Data cut 20 Aug 2025)

Conclusions

Etentamig monotherapy has a promising and manageable safety profile in RR AL amyloidosis, consistent with existing etentamig safety data, demonstrated by:

- <10% overall CRS rate
- No ICANS
- Limited Grade ≥3 cytopenias with low infection rates

Deep and rapid hematologic responses were observed with 100% ≥VGPR rate and 82% hematologic CR rate

The 40 mg dose will be further investigated in the dose expansion portion of the study

Etentamig monotherapy safety and efficacy data in RR AL amyloidosis supports further investigation in the newly diagnosed setting

(Data cut 20 Aug 2025)

AL, amyloid light-chain; CR, complete response, CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; RR, relapsed/refractory; VGPR, very good partial response.

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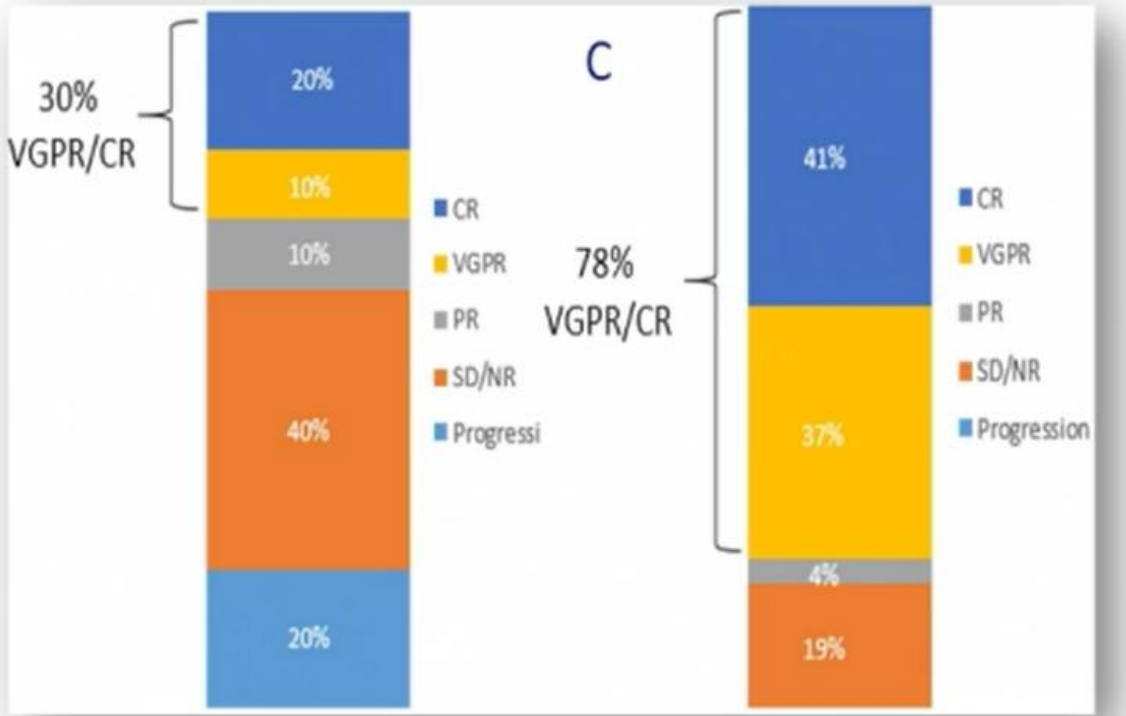
ABSTRACT #694

An Open-Label Multicenter Phase 1/2 Trial of Venetoclax-Dexamethasone in Relapsed/Refractory t(11;14)-positive Systemic AL Amyloidosis

Rajshekhar Chakraborty, Anita D'Souza, Prashant Kapoor, Shikun Wang, Divaya Bhutani, Susan Bal, Keith Stockerl-Goldstein, Sherin Selvan, Othman Akhtar, Vaishali Sanchorawala, Suzanne Lentzsch

Background

- Second-line therapies and beyond in AL amyloidosis remain a **critical unmet need** in the era of Dara-CyBorD in frontline setting
- t(11;14) is the most common cytogenetic abnormality in AL amyloidosis → **50-60%** of patients!
- Preclinical studies show **increased Bcl-2 dependence** in t(11;14)-positive myeloma cell lines
- Promising preliminary data of venetoclax (orally available Bcl-2 inhibitor) in patients with relapsed/refractory AL amyloidosis, especially in the t(11;14) subgroup



Bodet *et al.* Blood. 2011 Oct 6;118(14):3901-10.
Muchtar *et al.* Leukemia. 2017;31(7):1562-1569.
Premkumar *et al.* Blood Cancer J. 2021 Jan 11;11(1):10.

Hypothesis

We hypothesized that **Venetoclax-Dexamethasone** therapy administered for a fixed duration will be safe and achieve deep hematologic responses in patients with **relapsed**, **primary refractory**, and **relapsed-refractory** t(11;14) AL amyloidosis

Trial Design

Completed

Ongoing Accrual

H_0: ≥VGPR rate 30%
H_{alt}: ≥VGPR rate 60%
Two-sided alpha: 0.05
90% power
Sample Size: 28

Phase 1 Dose Escalation
(BOIN Accelerated Titration Design)

Single-Arm Phase 2

DLT definition for Phase 1

- G4 neutropenia >5 days
- Any grade febrile neutropenia
- G4 thrombocytopenia/G3 thrombocytopenia with bleeding
- Treatment-related ≥grade 2 non-heme toxicities leading to discontinuation
- Clinical TLS/Lab TLS if metabolic abnormalities deemed clinically significant by investigator
- All other grade≥3 AE except for above and a) G 3/4 lymphopenia and leukopenia; b) G 3 nausea/vomiting/diarrhea responsive to supportive care

Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Confirmed AL amyloidosis (Congo red+ along with mass spec/IHC/IF confirmation of AL) in ≥1 tissue biopsy	• Prior exposure to Bcl2 inhibitors
• **t(11;14)-positive** on FISH [**cut-off: 5%** in CD-138 enriched cells] performed centrally at CUIMC	• Concurrent multiple myeloma defined by SLiM-CRAB
• Measurable disease: - **dFLC ≥20 mg/L** or - M-protein ≥0.5 g/dL (or both)	• Advanced cardiac disease: - **NT-proBNP >8500 pg/mL** - **NYHA class IIIb/IV**
• ECOG ≤2	• Active uncontrolled infection
• CrCl ≥20 mL/min by Cockroft-Gault equation	• Patients on renal replacement therapy
• **≥1 prior line of therapy, including an anti-CD38 monoclonal antibody**	• Phase 1 only: Moderate or strong CYP3A inhibitors/inducers or P-glycoprotein inhibitors during the DLT period [cycle 1]

Baseline Characteristics (n=12; Phase 1)

Variable	Median (range), unless otherwise specified
Age, years; % males	64 (51-82); 75%
Race	White-75%; Black-16.7%; Other-8.3%
Number of prior lines of therapy	1 (1-5) [***8/12 patients got frontline Dara-VCd/Dara-Vd***]
Prior Anti-CD38mAb exposure; Prior PI exposure	100%; 91.7%
Time between diagnosis and enrollment (mo.)	**6.3 (0.3-112.9)**
dFLC [mg/dL]	13.86 (2.13-186.28)
NT-proBNP [pg/mL]	858 (54-8831)
eGFR, mL/min/1.73 m^2 [CKD-EPI]	83.5 (22.5-105.0)
24-hour urine protein [mg]	1274 (85-5018)

Safety [Primary endpoint of Phase 1]

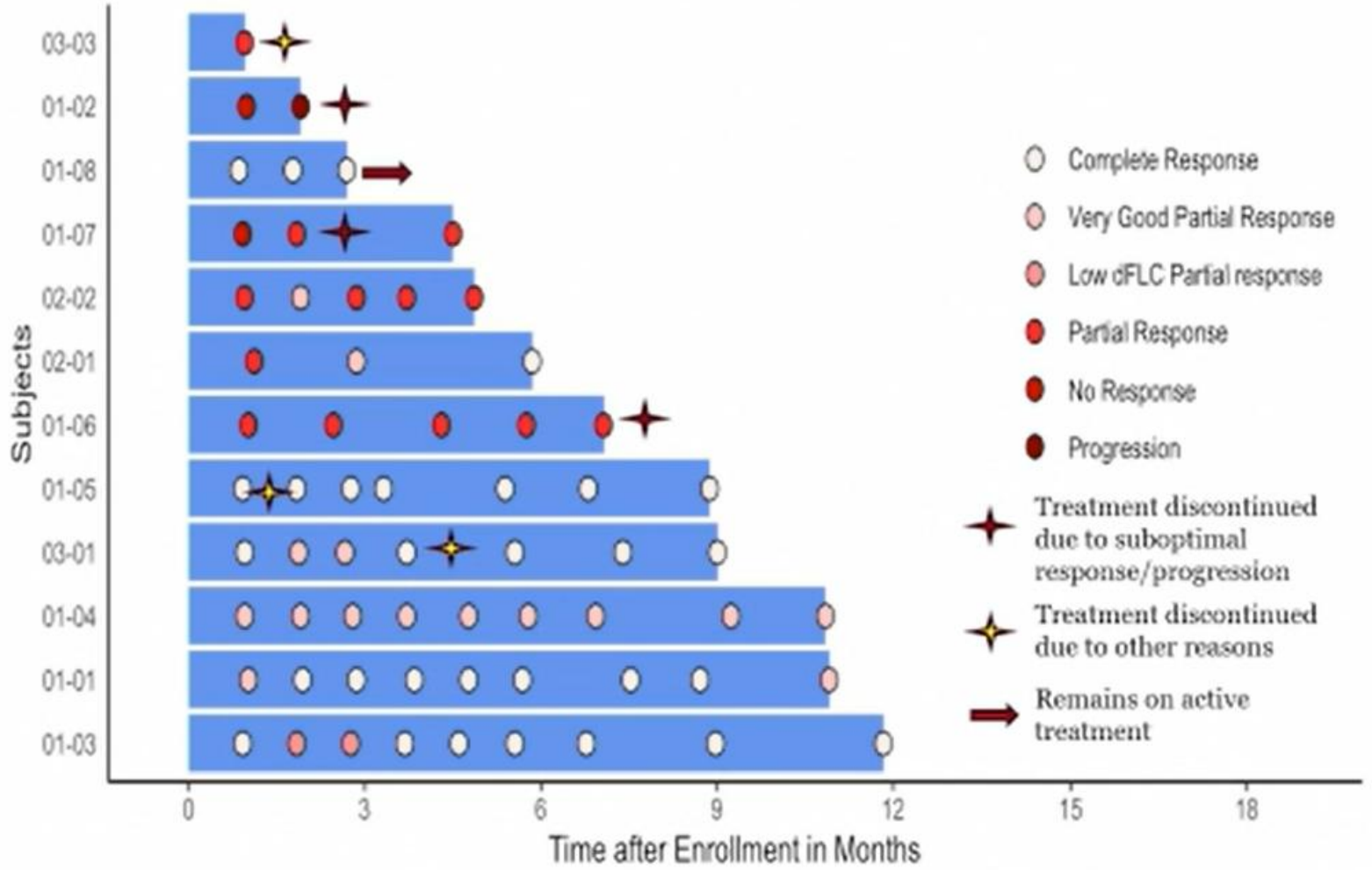
DLTs and Patient Disposition:

- **No DLTs** encountered during the time-frame [Cycle 1]
- One patient each received DLs 1, 2, and 3 , with the remaining on DL4 [Venetoclax 400 mg daily + Dexamethasone 20 mg weekly], which was the **RP2D**
- 5/12 patients completed 6 treatment cycles, with 6/12 discontinuing early due to: *hematologic progression (n=1), suboptimal hematologic response (n=2), patient preference (n=2), and heart transplantation (n=1)*

Adverse Events:

- Median duration of follow-up ~ 9 months
- Grade 3 infection: 1/12 patient (8.3%) [*COVID-19 lung infection*]
- No tumor lysis syndrome
- No grade 3 or higher cytopenias
- No treatment-emergent deaths
- No grade ≥3 non-hematologic adverse event related to study drugs except for one patients with grade 3 insomnia probably related to dexamethasone

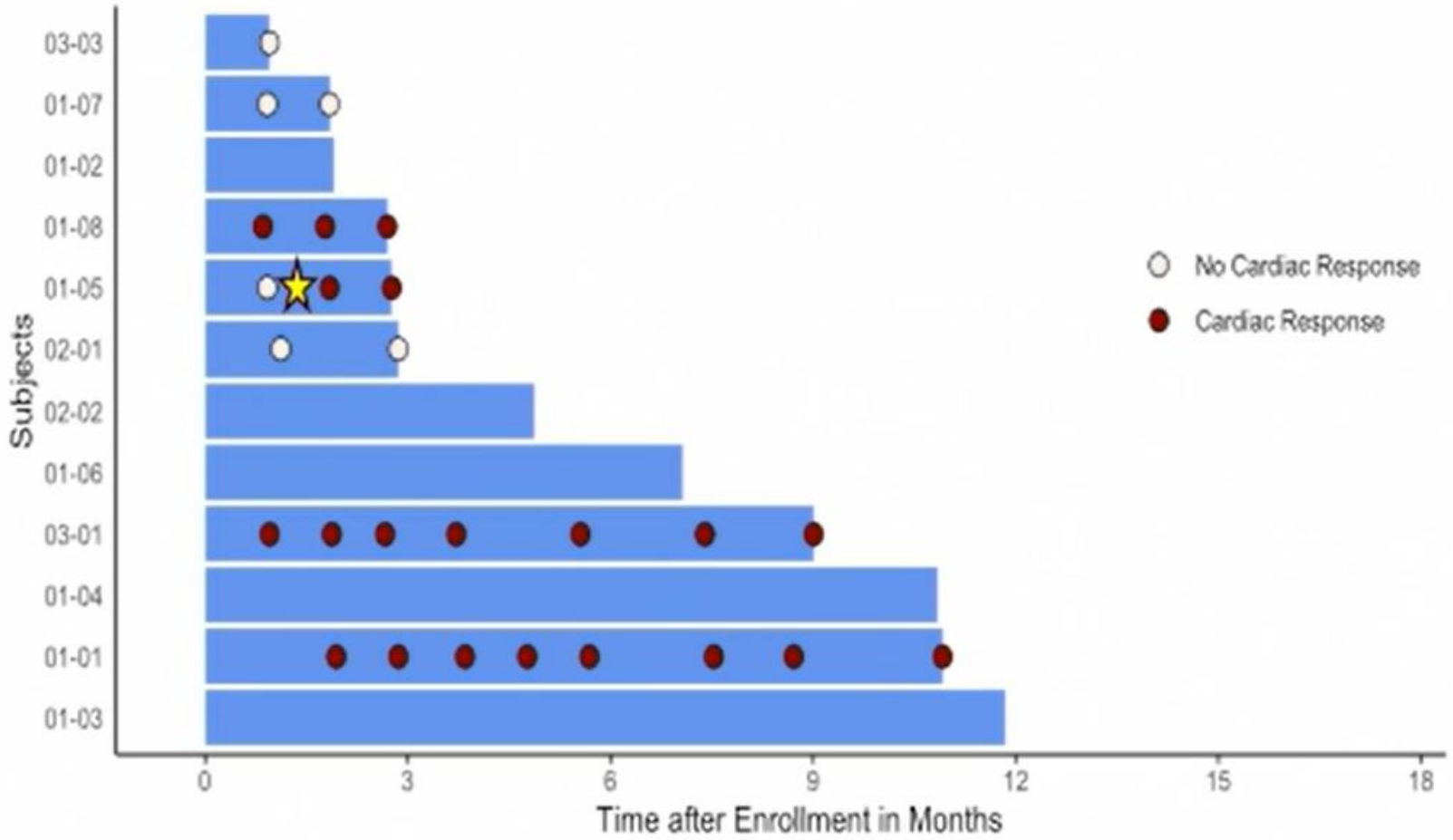
Hematologic Response



Hematologic Response:

- ORR (≥PR): 11/12 (91.7%)
- ≥VGPR at any time-point: 8/12 (66.7%)
- Heme-CR at any time-point: 6/12 (50%)
- Median time to best response: 0.9 months
- dFLC<1 mg/dL at C2D1: 3/12 patients
- iFLC<2 mg/dL at C2D1: 3/12 patients

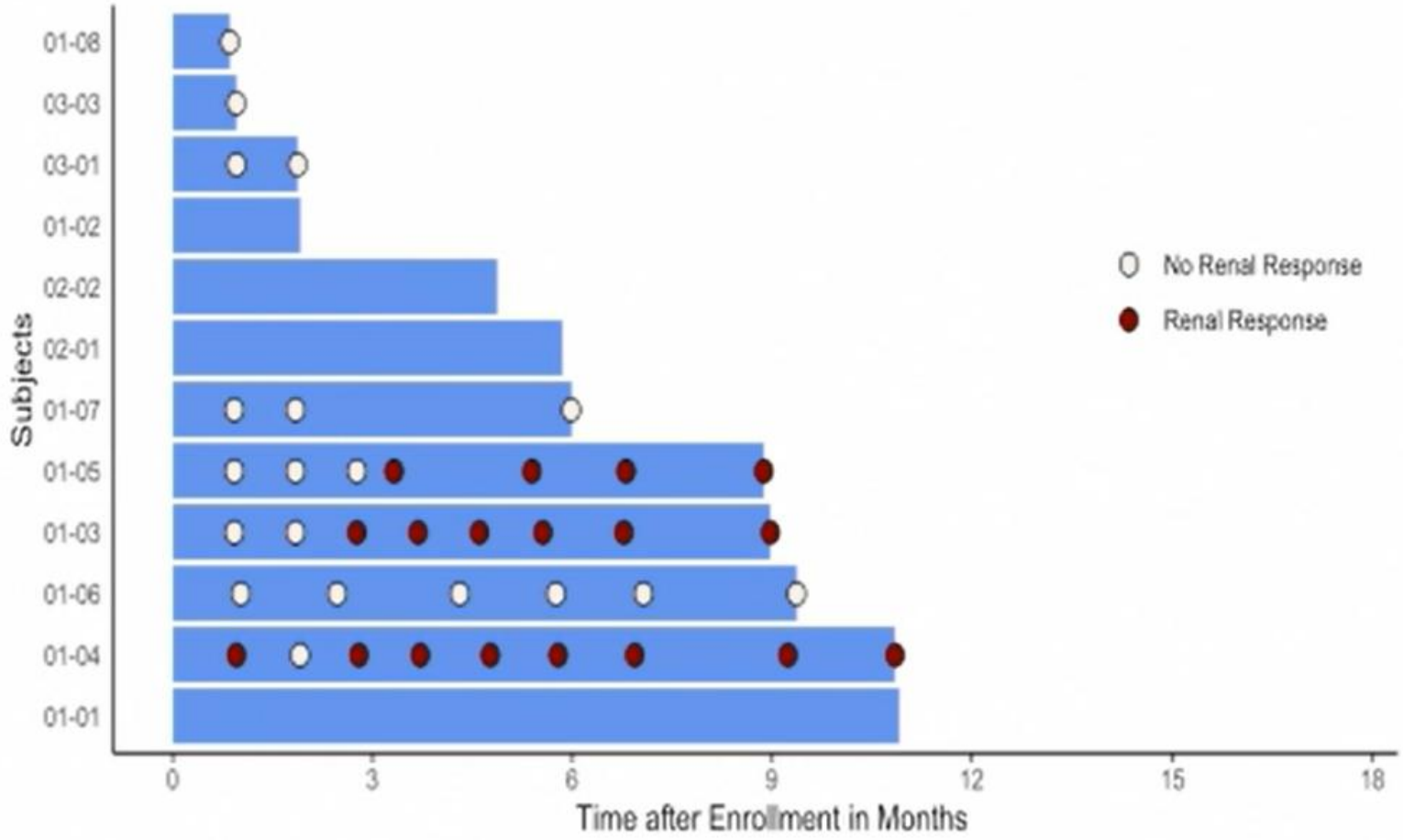
Cardiac Organ Response



Cardiac Organ Response: 3/6 evaluable patients

★ *Patient underwent heart transplantation after achieving heme-CR*

Renal Organ Response



Renal Organ Response: 3/7 evaluable patients

Summary/Conclusions

- Venetoclax-dexamethasone demonstrated excellent safety in relapsed/refractory t(11;14)-positive AL amyloidosis with no DLTs, no tumor lysis syndrome, and no treatment-emergent deaths
- MTD not reached; Venetoclax 400 mg daily/Dexamethasone 20 mg weekly was established as the recommended Phase 2 dose
- High hematologic response rates were achieved with ORR of 91.7%, including 66.7% ≥VGPR and 50% complete responses, with rapid onset of deep hematologic responses
- Meaningful organ responses were observed in evaluable patients, including cardiac (50%) and renal (43%) responses, suggesting potential for clinical benefit
- These results support further investigation of venetoclax-based therapy as a promising treatment option for t(11;14)-positive relapsed/refractory AL amyloidosis patients