Multiple Myeloma Updates from ASH 2024

Timothy Schmidt, MD

Assistant Professor

Division of Hematology, Oncology & Palliative Care, Department of Medicine

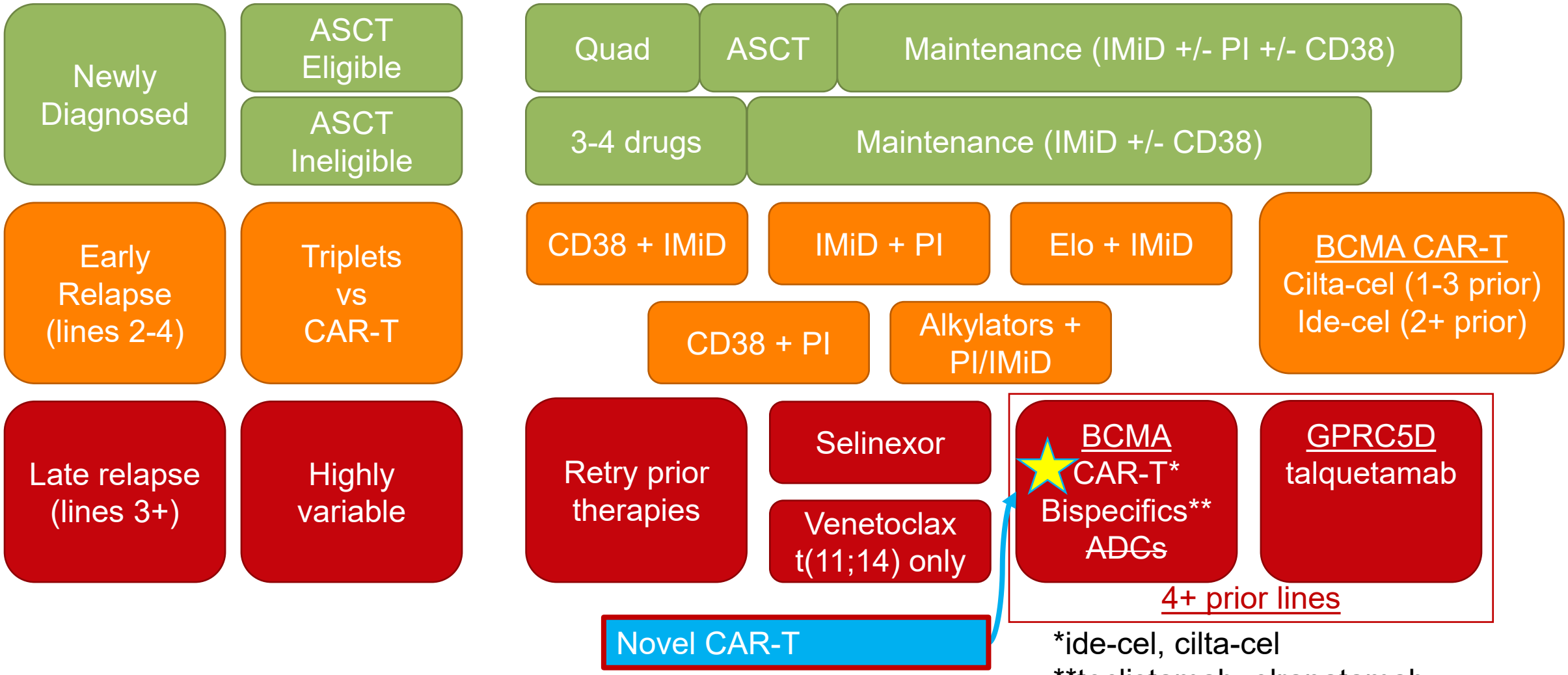
University of Wisconsin - Carbone Cancer Center

Disclosures

- I will discuss off-label/investigational use of pharmaceuticals in this presentation

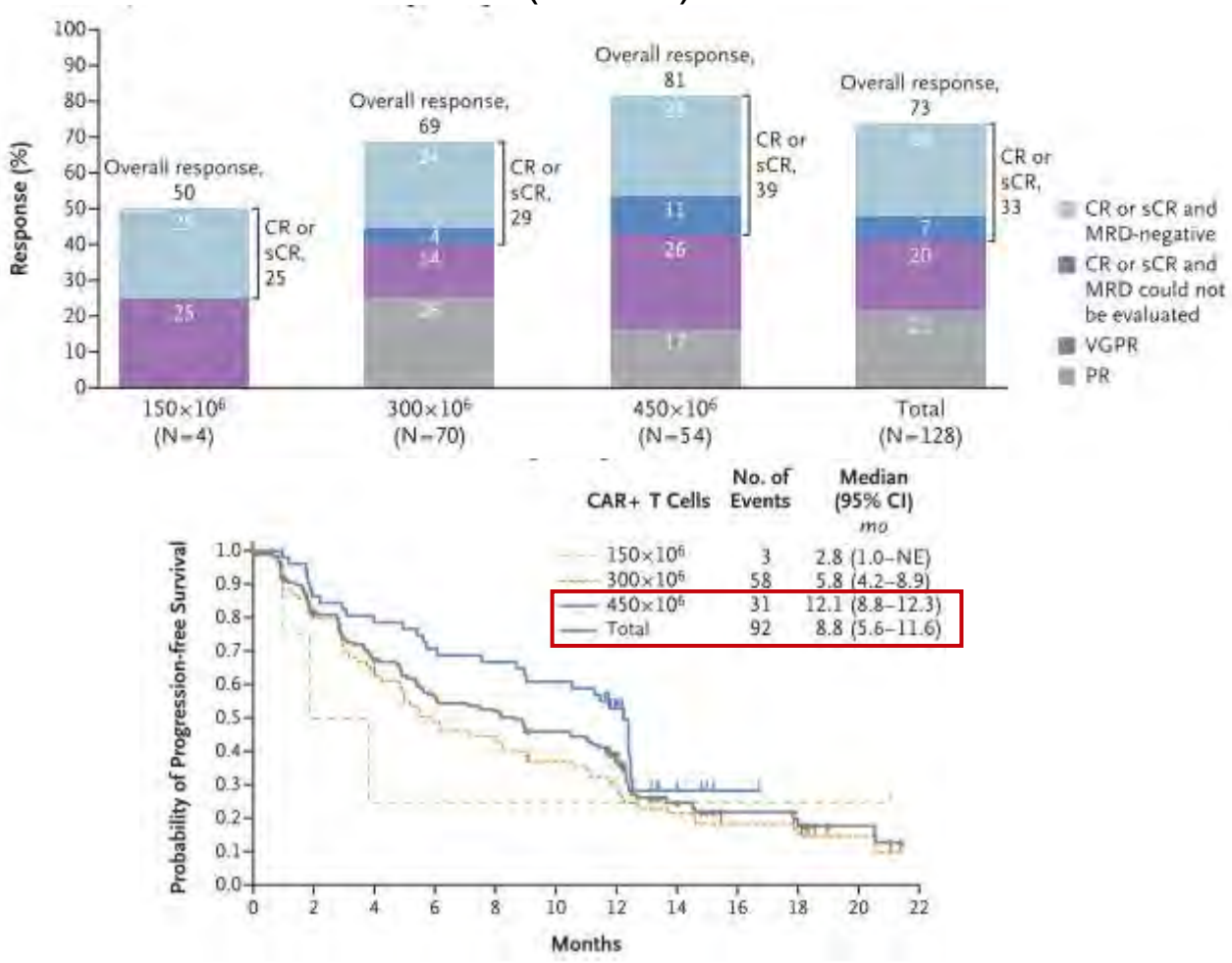
Affiliation/Financial Interest	Name of Corporate Organization(s)
Grant/Research Support	Alexion Pharmaceuticals, Bristol-Meyers Squibb, Janssen
Consultant	BiolineRx, Janssen, Pfizer, Sanofi
Speaker's Bureau	
Major Stock Shareholder	
Other Financial or Material Support	

Multiple Myeloma Therapeutic Landscape in 2025



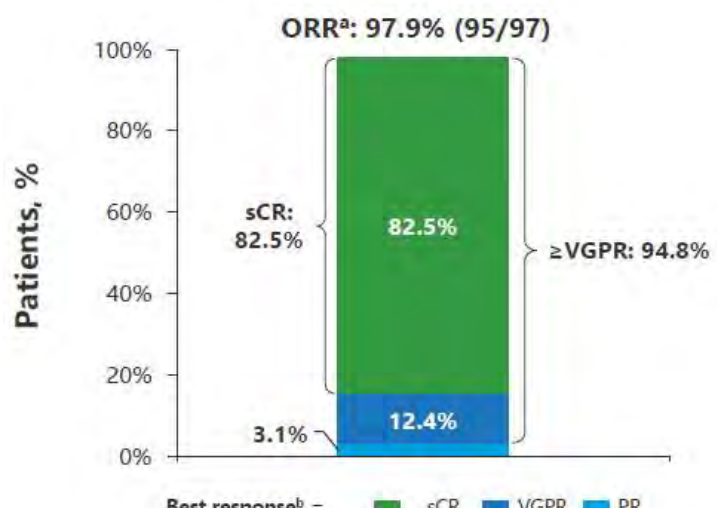
Approved CAR-T therapies in multiple myeloma

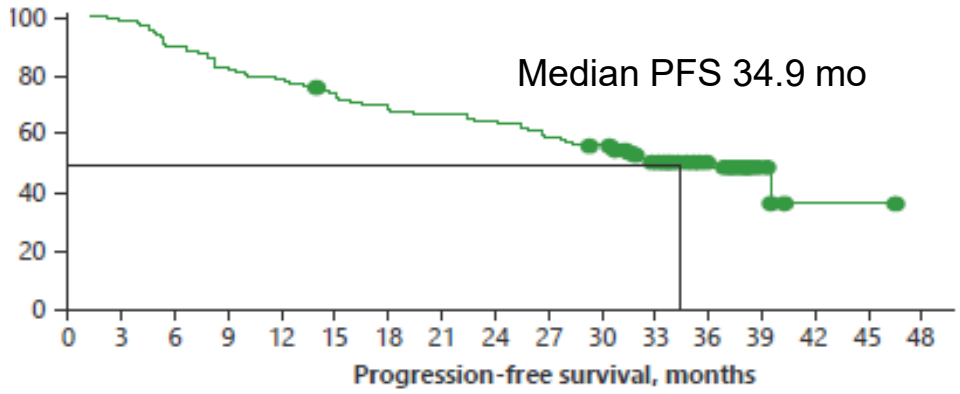
Idecabtagene vicleucel (ide-cel)



Munshi, N. C. *et al. New England Journal of Medicine* **384**, 705-716, doi:10.1056/NEJMoa2024850 (2021).

Ciltacabtagene autoleucel (cilta-cel)





Lin, Y. *et al. Journal of Clinical Oncology* **41**, 8009-8009, doi:10.1200/JCO.2023.41.16_suppl.8009 (2023).

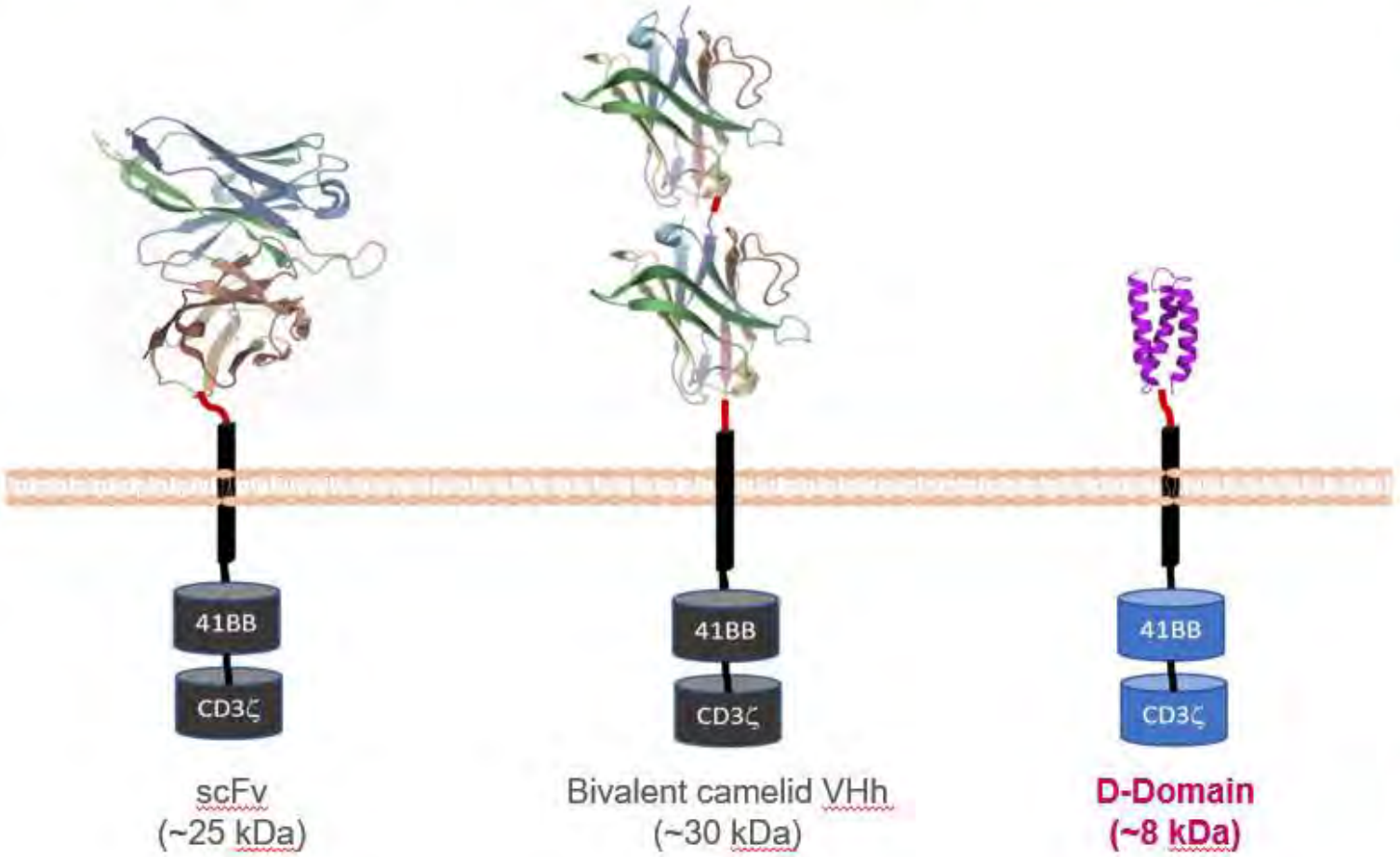
Abstract 1031
Phase 2 Registrational Study of Anitocabtagene Autoleucel for the Treatment of Patients with Relapsed and/or Refractory Multiple Myeloma: Preliminary Results From the iMMagine-1 Trial

Ciara Freeman, MD, PhD[1]; Binod Dhakal, MD, MS[2]; Gurbakhash Kaur, MD[3]; Richard T. Maziarz, MD[4]; Natalie S. Callander, MD[5]; Adam S. Sperling, MD, PhD[6]; Carolina Schinke, MD[7]; Andrzej J. Jakubowiak, MD, PhD[8]; Noa Biran, MD[9]; Douglas W. Sborov, MD, MS[10]; Cindy Varga, MD[11]; Abhinav Deol, MD[12]; Abraham S. Kanate, MD[13]; Mehmet Hakan Kocoglu, MD[14]; Melhem Solh, MD[15]; Kamalika C. Banerjee, MS, MA[16]; Rebecca Chan, MD, PhD[16]; Myrna Nahas, MD[17]; Ana Kostic, MD[16]; Enrique Granados, MD[17]; Carolyn C. Jackson, MD, MPH[17]; Christopher R. Heery, MD[16]; Tim Welliver, MD, PhD[16]; Krina Patel, MD, MSc[18]; and Matthew J. Frigault, MD, MS[19]

1. H. Lee Moffitt Cancer Center, Tampa, FL, USA; 2. Medical College of Wisconsin, Milwaukee, WI, USA; 3. University of Texas Southwestern Medical Center, Dallas, TX, USA; 4. Oregon Health & Science University, Portland, OR, USA; 5. University of Wisconsin Carbone Cancer Center, Madison, WI, USA; 6. Dana-Farber Cancer Institute, Boston, MA, USA; 7. University of Arkansas for Medical Sciences, Little Rock, AR, USA; 8. University of Chicago, Chicago, IL, USA; 9. HMH Hackensack University Medical Center, Hackensack, NJ, USA; 10. University of Utah-Huntsman Cancer Institute, Salt Lake City, UT, USA; 11. Atrium Health Levine Cancer Center, Charlotte, NC, USA; 12. Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; 13. HonorHealth Cancer Transplant Institute, Scottsdale, AZ, USA; 14. University of Maryland School of Medicine, Baltimore, MD, USA; 15. Northside Hospital, Atlanta, GA, USA; 16. Arcellx, Inc., Redwood City, CA, USA; 17. Kite, a Gilead Company, Santa Monica, CA, USA; 18. MD Anderson Cancer Center, Houston, TX, USA; and 19. Massachusetts General Hospital Cancer Center, Boston, MA, USA

Anitocabtagene autoleucel (anito-cel/CART-ddBCMA)

Autologous BCMA-directed CAR T-cell therapy using a novel, D-Domain binder[1,2]



scFv
(~25 kDa)

Bivalent camelid VHh
(~30 kDa)

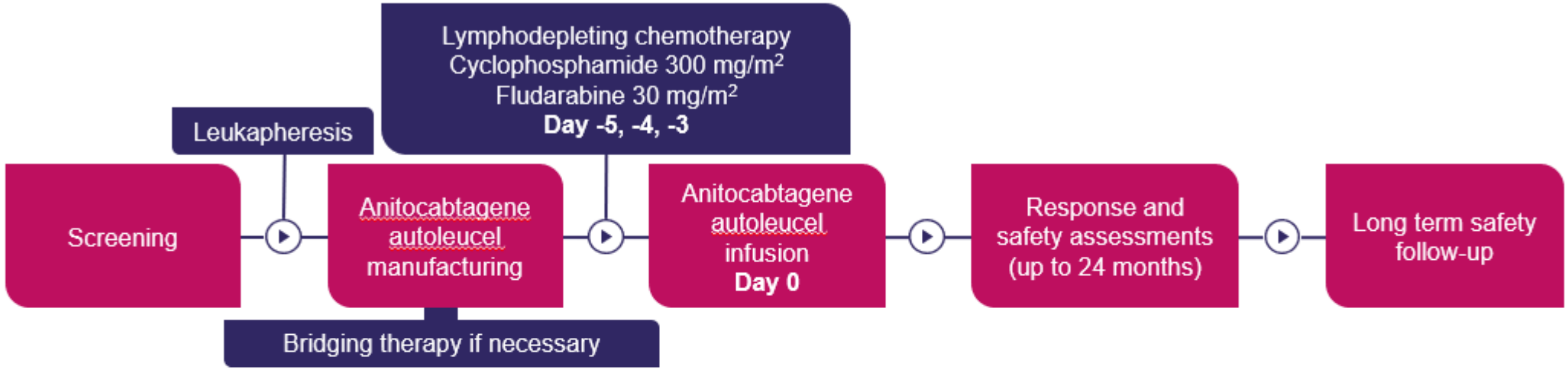
D-Domain
(~8 kDa)

D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size	Small D-Domain construct facilitates high transduction efficiency, CAR positivity, and CAR density on the T-cell surface[3,4]
Structure & Stability	Rapid D-Domain folding, lack of disulfide bonds, and a hydrophobic core enables D-Domain CAR stability[5,6]
Binding	The D-Domain binder lacks tonic signaling[6] and has a fast off-rate[4] that may allow optimal tumor cell killing without prolonged inflammation

[1]Rotte, et al. Immuno-Oncology Insights 2022; 3(1), 13–24; [2]Frigault, et al. Blood Adv. 2023; 7(5):768-777; [3]Cante-Barrett, et al. BMC Res. Notes 2016; 9:13; [4]Buonato, et al. Mol. Cancer Ther. 2022; 21(7):1171-1183; [5]Zhu, et al. Proc. Nat. Acad. Sci. 2003; 100(26); 15486-15491; [6]Qin, et al. Mol. Ther. 2019; 27(7): 1262-1274.

iMMagine-1: Phase 2 Study Design



Key Eligibility Criteria

- Prior IMiD, PI, and CD38-targeted therapy
- Received ≥3 prior lines of therapy
- Refractory to the last line of therapy
- ECOG PS of 0 or 1
- Evidence of measurable disease

Target Dose of 115 x 10^6 CAR+ T cells

Primary Endpoint:

- ORR, per 2016 IMWG criteria

Key Secondary Endpoints:

- CR/sCR rate, per 2016 IMWG criteria
- ORR in patients limited to 3 prior LOT, per 2016 IMWG criteria

Freeman et al, American Society of Hematology 2024, Abstract 1031

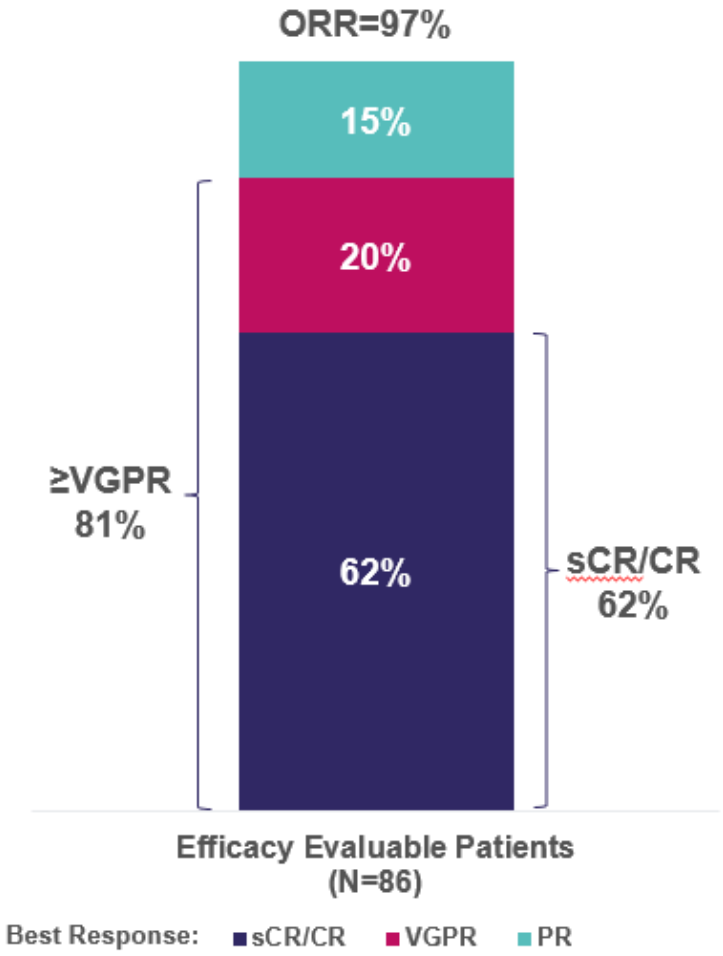
iMMagine-1: Patient and Disease Characteristics

Characteristics	Safety Evaluable (n=98)	Efficacy Evaluable (n=86)
Age, median (min - max)	65 (38 – 78)	65 (38 – 78)
Age ≥ 65	51 (52%)	47 (55%)
Age ≥ 75	10 (10%)	10 (12%)
Gender (male / female)	55 (56%) / 43 (44%)	48 (56%) / 38 (44%)
Race		
White	79 (81%)	70 (81%)
Black / African American	9 (9%)	8 (9%)
Asian / Other	10 (10%)	8 (9%)
ECOG PS[a] 0 / 1	45 (46%) / 53 (54%)	39 (45%) / 47 (55%)
High Risk Prognostic Feature	52 (53%)	45 (52%)
BMPC ≥60%	7 (7%)	5 (6%)
ISS Stage III (B2M ≥ 5.5)	4 (4%)	3 (4%)
Extramedullary disease	16 (16%)	13 (15%)
High Risk Cytogenetics[c]	39 (40%)	33 (38%)
Refractory to last line of therapy	**98 (100%)**	**86 (100%)**
Triple refractory	**85 (87%)**	**74 (86%)**
Penta refractory	**41 (42%)**	**37 (43%)**
Prior Lines of Therapy, median (min - max)	**4 (3 – 8)**	**4 (3 – 8)**
3 Prior LOT	**45 (46%)**	**37 (43%)**
Time since diagnosis, median (min-max)	7.2 (1.0 – 23.1)	7.5 (1.0 – 23.1)
Prior ASCT	73 (75%)	64 (74%)
Bridging therapy[d]	65 (66%)	61 (71%)
Outpatient administration	8 (8%)	5 (6%)

a) Eastern Cooperative Oncology Group Performance Status Scale; b) EMD is a form of Multiple Myeloma characterized by the presence of a non-bone based plasmacytoma; c) Defined as the presence of Del 17p, t(14;16), or t(4;14); d) Bridging agents were limited only to those previously received.

iMMagine-1: Overall Response Rate and MRD Negativity

Efficacy Evaluable Patients (N=86)

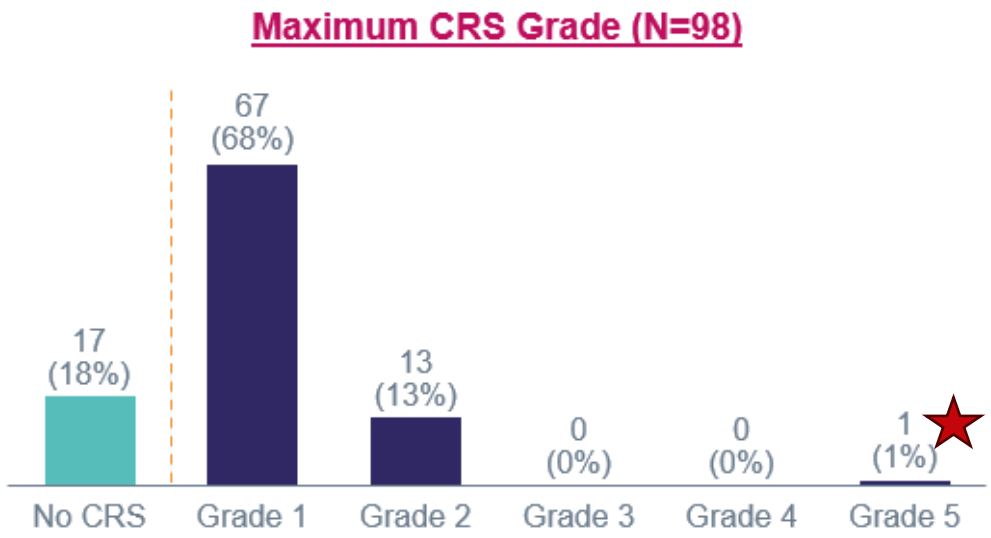


- At a median follow-up of 9.5 months, responses were ongoing in 80.2% of 86 patients
- 93.1% (n=54/58) of evaluable* patients MRD negative at minimum of 10^{-5} sensitivity

	Evaluable Patients	Months (min - max)
Median time to first response	84	1 (0.9 - 7.3)
Median time to MRD negativity of 10^{-5} or lower	58	1.0 (0.9 - 6.4)

Freeman et al, American Society of Hematology 2024, Abstract 1031

iMMagine-1: Cytokine Release Syndrome



- In the 82% (81/98) of patients with CRS, the median onset was 4 days
- 86% (84/98) of patients had CRS Grade 1 or less, including 18% (17/98) with no CRS
- % of patients with either no CRS or CRS that resolved by:
  - ≤7 days of anito-cel infusion: 63% (62/98)
  - ≤10 days of anito-cel infusion: 93% (91/98)
  - ≤14 days of anito-cel infusion: 98% (96/98)

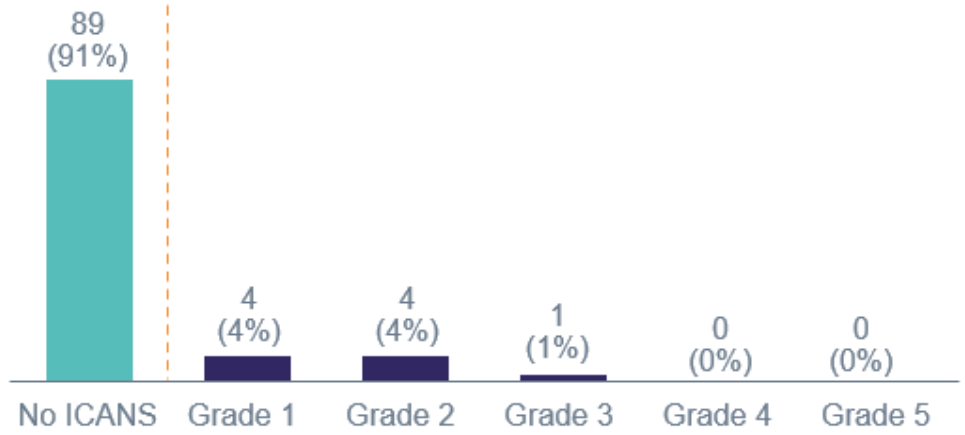
Cytokine Release Syndrome (CRS) Per ASTCT criteria	Safety Evaluable Patients N=98
Median onset (min-max)	4 days (1-17 days)
Median duration (min-max)	3 days (1-9 days)
Supportive Measures	
Tocilizumab	70% (69/98)
Dexamethasone	63% (62/98)
Anakinra	7% (7/98)
Vasopressor used	1% (1/98)
Intubation/mechanical ventilation	1% (1/98)

- CRS management per protocol was in line with standard medical practice with no prophylactic administration of tocilizumab or dexamethasone
  - For CRS onset in the first 48 hours, tocilizumab and dexamethasone were protocol recommended
  - For CRS onset after the first 48 hours, if tocilizumab was administered at investigator discretion, dexamethasone was also recommended

Freeman et al, American Society of Hematology 2024, Abstract 1031

iMMagine-1: Immune-effector Cell-associated Neurotoxicity Syndrome (ICANS)

Maximum ICANS Grade (N=98)



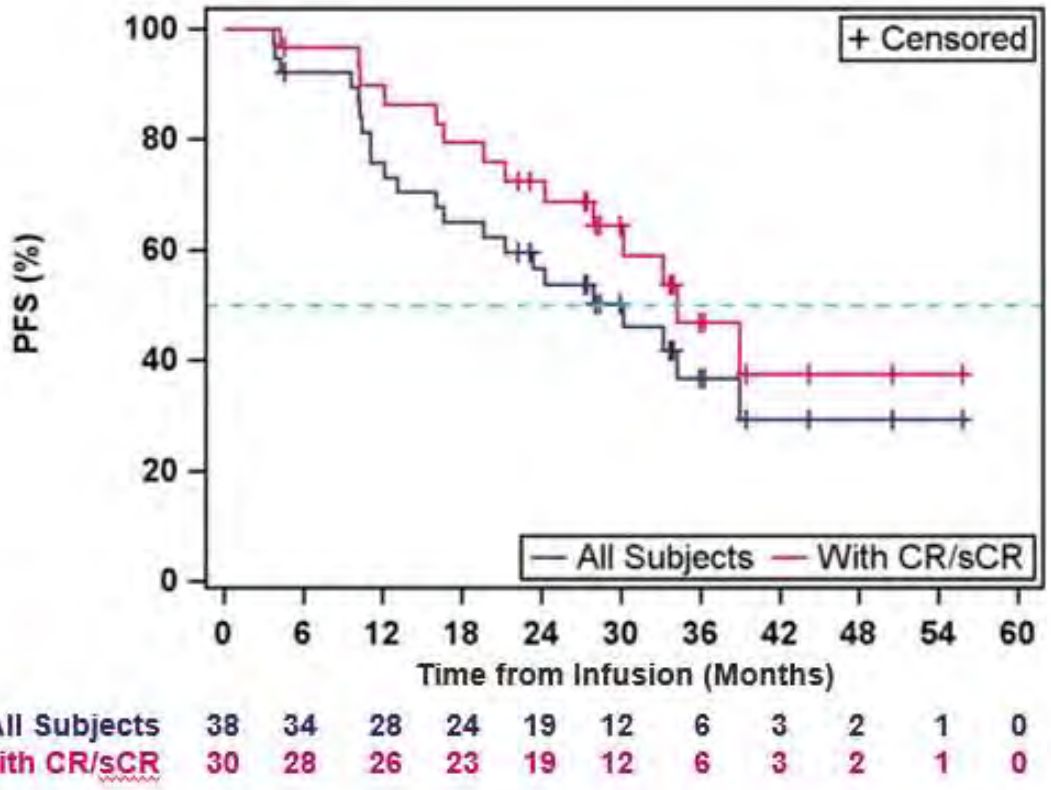
- 9% (9/98) of patients had ICANS of any grade; all cases resolved
- No delayed or non-ICANS neurotoxicities were observed, including no incidence of Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome (n=98)
- Similarly, no delayed or non-ICANS neurotoxicities have been observed in the Phase 1 study[1] (n=38, median follow-up of 38.1 months with minimum follow-up of 25 months)

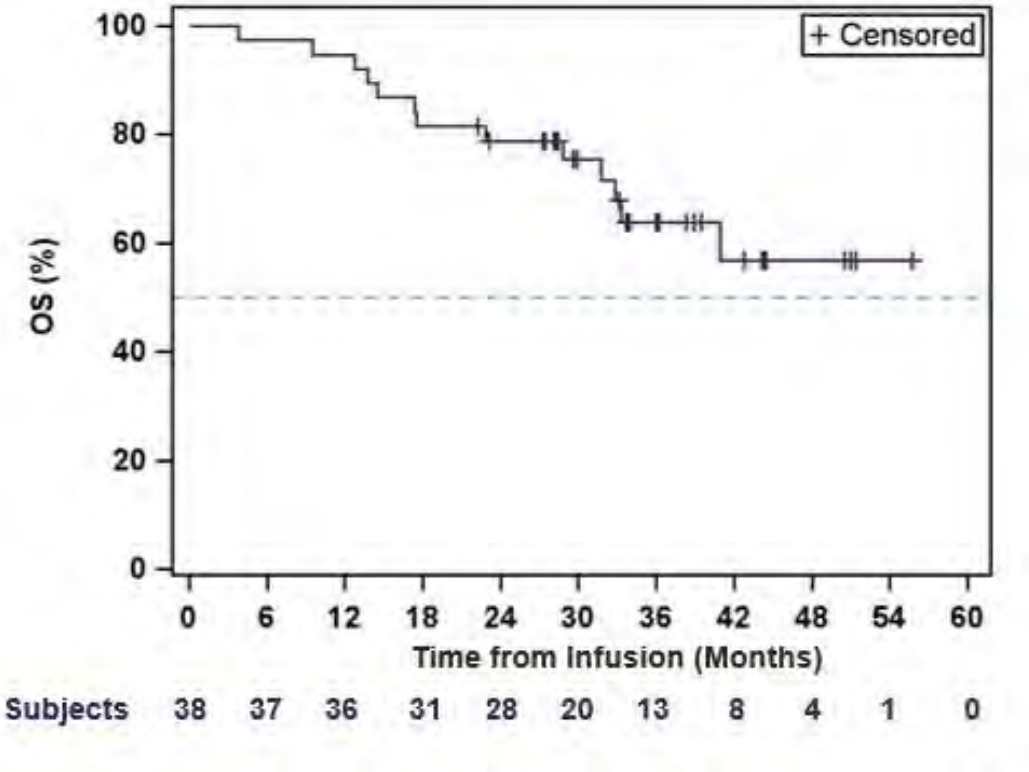
ICANS Per ASTCT criteria	Safety Evaluable Patients N=98
Median onset (min-max)	7 days (2 - 10[a] days)
Median duration (min-max)	4 days (1 - 10[b] days)
Toxicity Management	
Tocilizumab	3% (3/98)
Dexamethasone	5% (5/98)
Anakinra	1% (1/98)
Siltuximab	1% (1/98)

[a] With the exception of n=1 Grade 1 ICANS (Grade 1 confusion), onset 34 days post infusion, 1 day duration to resolution
[b] With the exception of n=1 max Grade 2 ICANS with 29-day duration to resolution

Freeman et al, American Society of Hematology 2024, Abstract 1031

Background (ASH Poster 4825): Anito-cel Phase 1 demonstrated mPFS of 30.2 months in a 4L+ RRMM population, of whom 68% had high-risk features

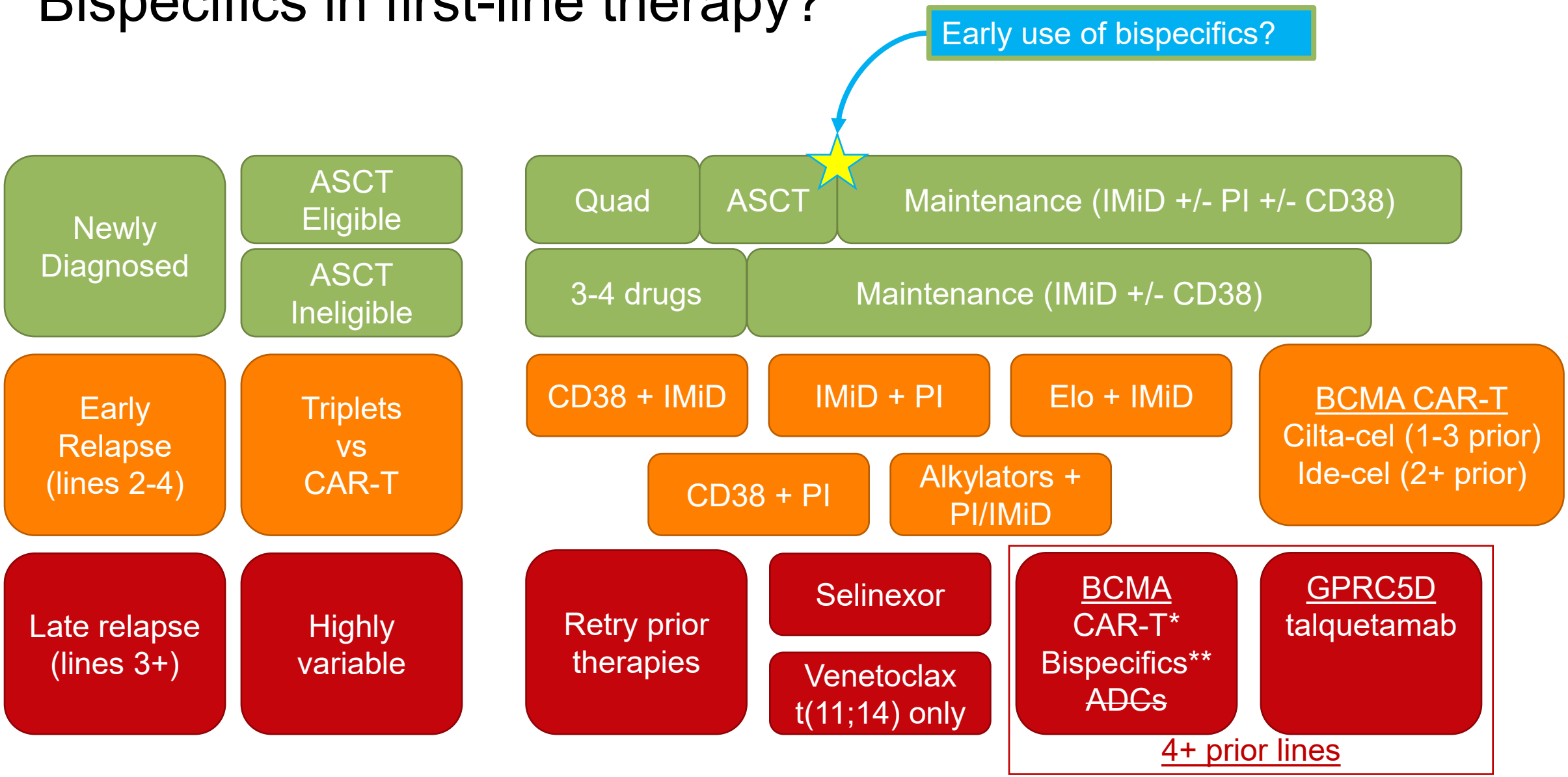




My take

- Appears to be similarly efficacious to cilta-cel, probably not more toxic
- Effective bridging therapy prior to infusion is key
- Need more data before saying for certain whether there is a significantly lower risk of delayed neurotoxicity, but encouraging that it hasn’t been seen yet
- Likely to gain regulatory approval in late relapse

Bispecifics in first-line therapy?



*ide-cel, cilta-cel
**teclistamab, elranatamab

Rationale for earlier use

- Better T-cell profile, potentially more effective
- CRS tends to be milder if there is a lower disease burden
- Potent therapy with high toxicity profile, perhaps can optimize efficacy and safety by using earlier

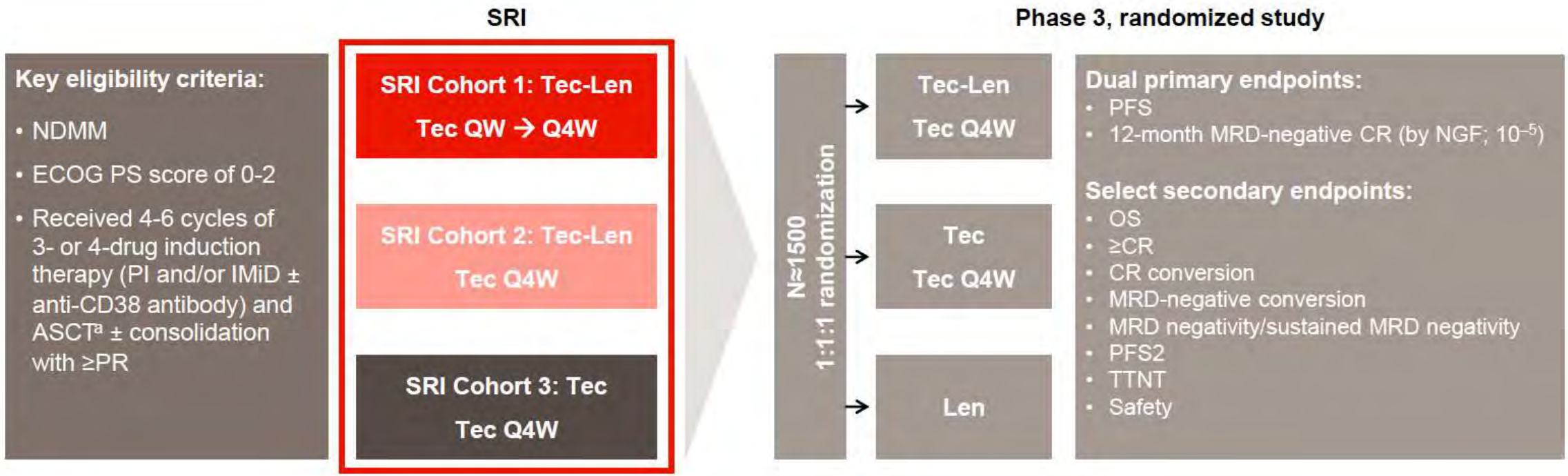
Phase 3 Study of Teclistamab in Combination With Lenalidomide and Teclistamab Alone vs Lenalidomide Alone in Newly Diagnosed Multiple Myeloma as Maintenance Therapy Following Autologous Stem Cell Transplantation: Safety Run-in Results From the EMN30/MajesTEC-4 Trial*

*ClinicalTrials.gov Identifier: NCT05243797; sponsored by EMN in collaboration with Janssen Research & Development, LLC

Elena Zamagni[1], Tobias Silzle[2], Ivan Špička[3], Sabrin Tahri[4], Sarah Lonergan[4], Inger Nijhof[5], Antonietta Pia Falcone[6], Evangelos Terpos[7], Jakub Radocha[8], Roberto Mina[9], Guldane Cengiz Seval[10], Meral Beksac[10], Cesar Rodriguez[11], Marcelo C Pasquini[12], Michel Delforge[13], Vania Hungria[14], Donna Reece[15], Philippe Moreau[16], Yael C Cohen[17], Kihyun Kim[18], Dominik Dytfeld[19], Jiří Minařik[20], Irene Strassl[21], Jelena Bila[22], Martin Schreder[23], Janusz Krawczyk[24], Fredrik Schjesvold[25], Caroline Cicin-Sain[26], Christoph Driessen[26], Gordon Cook[27], Lugui Qiu[28], Gonzalo M Garate[29], Agoston Gyula Szabo[30], Roman Hájek[31], Marc S Raab[32], Silvia Mangiacavalli[33], Hermann Einsele[34], Andrew Spencer[35], Mario Boccadoro[36], Helen Vassalou[37], Lixia Pei[38], Yingqi Shi[38], Maria Krevvata[39], Ryan Gruber[39], Caline Sakabedoyan[40], Margaret Cobb[41], Jagoda Jasielec[38], Himal Amin[38], Rachel Kobos[38], Pieter Sonneveld[4,42], Niels WCJ van de Donk[43]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", and Università di Bologna, Bologna, Italy; [2]Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [3]Charles University and General Hospital, Prague, Czech Republic; [4]Stichting European Myeloma Network, Rotterdam, The Netherlands; [5]St. Antonius Hospital Nieuwegein, Nieuwegein, The Netherlands; [6]IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [7]University of Athens, School of Medicine, Athens, Greece; [8]University Hospital Hradec Kralove and Charles University, Hradec Kralove, Czech Republic; [9]AOU Città della Salute e della Scienza di Torino and University of Torino, Torino, Italy; [10]Ankara University, Ankara, Türkiye; [11]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [12]Medical College of Wisconsin, Milwaukee, WI, USA; [13]University of Leuven, Leuven, Belgium; [14]Clínica Médica São Germano, São Paulo, Brazil; [15]Princess Margaret Cancer Centre, Toronto, ON, Canada; [16]University Hospital Hôtel-Dieu, Nantes, France; [17]Tel Aviv Sourasky (Ichilov) Medical Center and Tel Aviv University, Tel Aviv, Israel; [18]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea; [19]Poznan University of Medical Sciences, Poznań, Poland; [20]University Hospital and Palacký University Olomouc, Olomouc, Czech Republic; [21]Ordensklinikum Linz Hospital, Linz, Austria; [22]University of Belgrade, University Clinical Centre of Serbia, Belgrade, Serbia; [23]Klinik Ottakring, Vienna, Austria; [24]University Hospital Galway, Galway, Ireland and National University of Ireland, Galway, Ireland; [25]Oslo Myeloma Center and University of Oslo, Oslo, Norway; [26]Kantonsspital St. Gallen, St. Gallen, Switzerland; [27]University of Leeds, Leeds, UK; [28]Chinese Academy of Medical Sciences, Blood Diseases Hospital (Institute of Hematology), Tianjin, China; [29]Hospital Alemán, Buenos Aires, Argentina; [30]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [31]University Hospital Ostrava and University of Ostrava, Ostrava, Czech Republic; [32]University Hospital Heidelberg, Heidelberg, Germany; [33]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [34]University Hospital Würzburg, Würzburg, Germany; [35]The Alfred Hospital, Monash University, Melbourne, Australia; [36]European Myeloma Network, Torino, Italy; [37]Health Data Specialists, Dublin, Ireland; [38]Janssen Research & Development, LLC, Raritan, NJ, USA; [39]Janssen Research & Development, LLC, Spring House, PA, USA; [40]Janssen Research & Development, LLC, Paris, France; [41]Janssen Research & Development, LLC, High Wycombe, UK; [42]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [43]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

EMN30/MajesTEC-4: Study Design



Zamagni E, et al. ASH 2024 #205608

EMN30/MajesTEC-4 SRI: Dosing

	Cycle 1	Cycle 2	Cycles 3-6	Cycles 7-26
Cohort 1: Tec-Len Tec QW → Q4W	Tec step up[a] + Tec 1.5 mg/kg on D8, D15, and D22	Tec 1.5 mg/kg QW + Len	Tec 3.0 mg/kg Q2W + Len	Tec 3.0 mg/kg Q4W + Len
Cohort 2: Tec-Len Tec Q4W	Tec step up[a] + Tec 1.5 mg/kg on D8 and D15	Tec 3.0 mg/kg Q4W + Len		
Cohort 3: Tec Tec Q4W	Tec step up[a] + Tec 1.5 mg/kg on D8 and D15	Tec 3.0 mg/kg Q4W		

- Len was initiated at 10 mg/day[b] from Cycles 2 to 4, followed by 15 mg/day in Cycles 5 to 26, if tolerated

★ 2-year fixed-duration maintenance regimen[c]

EMN30/MajesTEC-4 SRI: Nonhematologic TEAEs

	Cohort 1: Tec-Len (QW → Q4W) (N=32)		Cohort 2: Tec-Len (Q4W) (N=32)		Cohort 3: Tec (Q4W) (N=30)	
Median follow-up, mo	21.1		9.2		9.2	
TEAEs,[a] n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Nonhematologic AEs[b]						
CRS	16 (50.0)	0	13 (40.6)	0	13 (43.3)	0
URTI	20 (62.5)	1 (3.1)	13 (40.6)	0	8 (26.7)	0
Cough	15 (46.9)	0	6 (18.8)	0	8 (26.7)	0
Diarrhea	13 (40.6)	3 (9.4)	9 (28.1)	1 (3.1)	6 (20.0)	0
Injection-site erythema	7 (21.9)	0	12 (37.5)	0	8 (26.7)	0
COVID-19	12 (37.5)	1 (3.1)	5 (15.6)	0	9 (30.0)	1 (3.3)
Fatigue	10 (31.3)	1 (3.1)	8 (25.0)	1 (3.1)	5 (16.7)	0
Pneumonia	9 (28.1)	4 (12.5)	3 (9.4)	0	2 (6.7)	1 (3.3)

- Among the most common nonhematologic TEAEs, rates of grade 3/4 events were low
- All CRS events were grade 1/2, mostly occurring during Tec step-up dosing
  - 37.2% after Step-up Dose 1
  - 8.5% after Step-up Dose 2
  - 5.3% after Treatment Dose 1
  - No discontinuations due to CRS
- No ICANS

EMN30/MajesTEC-4 SRI: Hematologic TEAEs

	Cohort 1: Tec-Len (QW → Q4W) (N=32)		Cohort 2: Tec-Len (Q4W) (N=32)		Cohort 3: Tec (Q4W) (N=30)	
Median follow-up, mo	21.1		9.2		9.2	
TEAEs,[a] n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any TEAE	32 (100)	32 (100)	32 (100)	27 (84.4)	30 (100)	17 (56.7)
Hematologic Aes						
Neutropenia	30 (93.8)	30 (93.8)	21 (65.6)	20 (62.5)	17 (56.7)	14 (46.7)
Leukopenia	9 (28.1)	3 (9.4)	1 (3.1)	0	1 (3.3)	1 (3.3)
Lymphopenia	2 (6.3)	1 (3.1)	4 (12.5)	4 (12.5)	4 (13.3)	4 (13.3)
Thrombocytopenia	6 (18.8)	2 (6.2)	0	0	2 (6.7)	0
Febrile neutropenia	3 (9.4)	3 (9.4)	3 (9.4)	3 (9.4)	0	0
Anemia	3 (9.4)	0	1 (3.1)	1 (3.1)	1 (3.3)	0
Eosinophilia	1 (3.1)	1 (3.1)	1 (3.1)	1 (3.1)	0	0

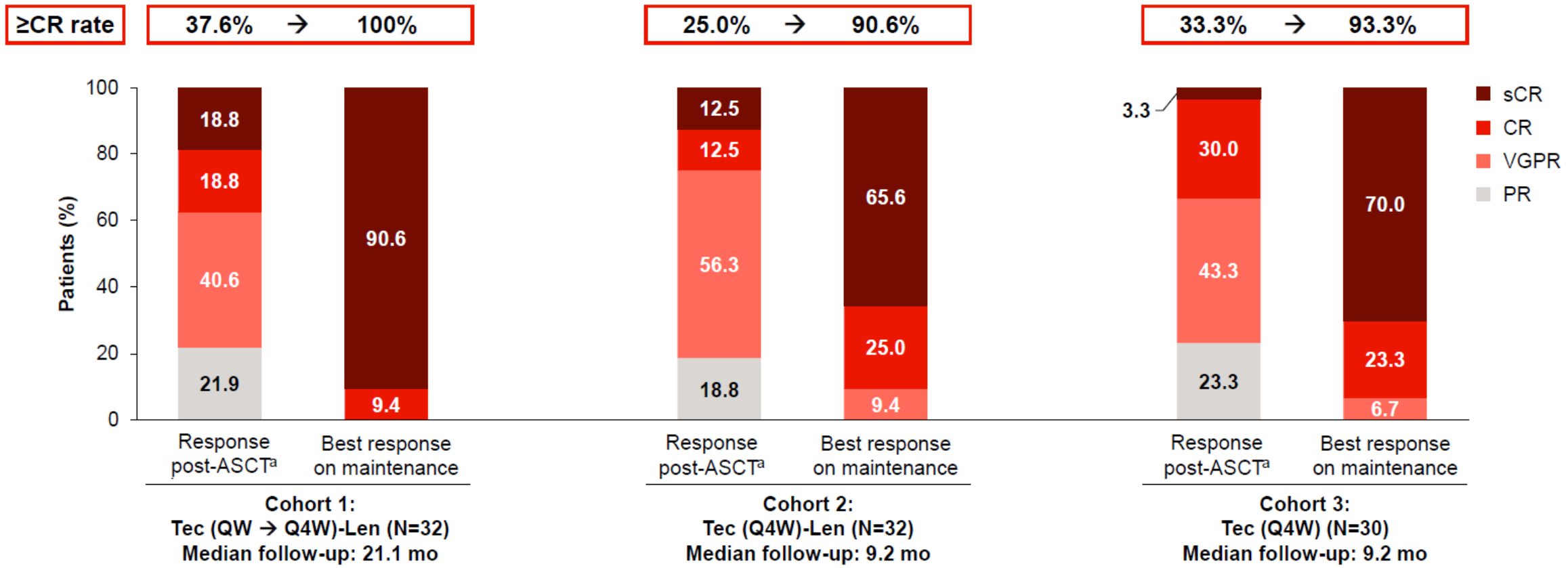
- Cumulative incidence of grade 3/4 neutropenia at 6 months:
  - Cohort 1: 81.3%
  - Cohort 2: 56.3%
  - Cohort 3: 40.0%
- Median relative dose intensity:
  - 95.5% to 99.7% for Tec
  - 58.4% to 61.5% for Len
- Low rates of treatment discontinuation due to TEAEs (5.3% overall)

EMN30/MajesTEC-4 SRI: Infections and Hypogammaglobulinemia

	Cohort 1: Tec-Len (QW → Q4W) (N=32)		Cohort 2: Tec-Len (Q4W) (N=32)		Cohort 3: Tec (Q4W) (N=30)	
Median follow-up, mo	21.1		9.2		9.2	
TEAEs,[a] n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any infection	30 (93.8)	12 (37.5)	25 (78.1)	9 (28.1)	23 (76.7)	6 (20.0)
Most common infections[b]						
URTI	20 (62.5)	1 (3.1)	13 (40.6)	0	8 (26.7)	0
COVID-19	12 (37.5)	1 (3.1)	5 (15.6)	0	9 (30.0)	1 (3.3)
Pneumonia	9 (28.1)	4 (12.5)	3 (9.4)	0	2 (6.7)	1 (3.3)
Nasopharyngitis	6 (18.8)	0	0	0	3 (10.0)	0

- Hypogammaglobulinemia[c] reported in:
  - Cohort 1: 31 (96.9%) patients
  - Cohort 2: 25 (78.1%) patients
  - Cohort 3: 28 (93.3%) patients
  - All received ≥1 dose of IVIg or SCIg
- One grade 5 COVID-19 TEAE occurred in Cohort 2
- Infection prophylaxis, including Ig replacement, was strongly recommended[d]

EMN30/MajesTEC-4 SRI: Response Rates Post-ASCT and During Maintenance



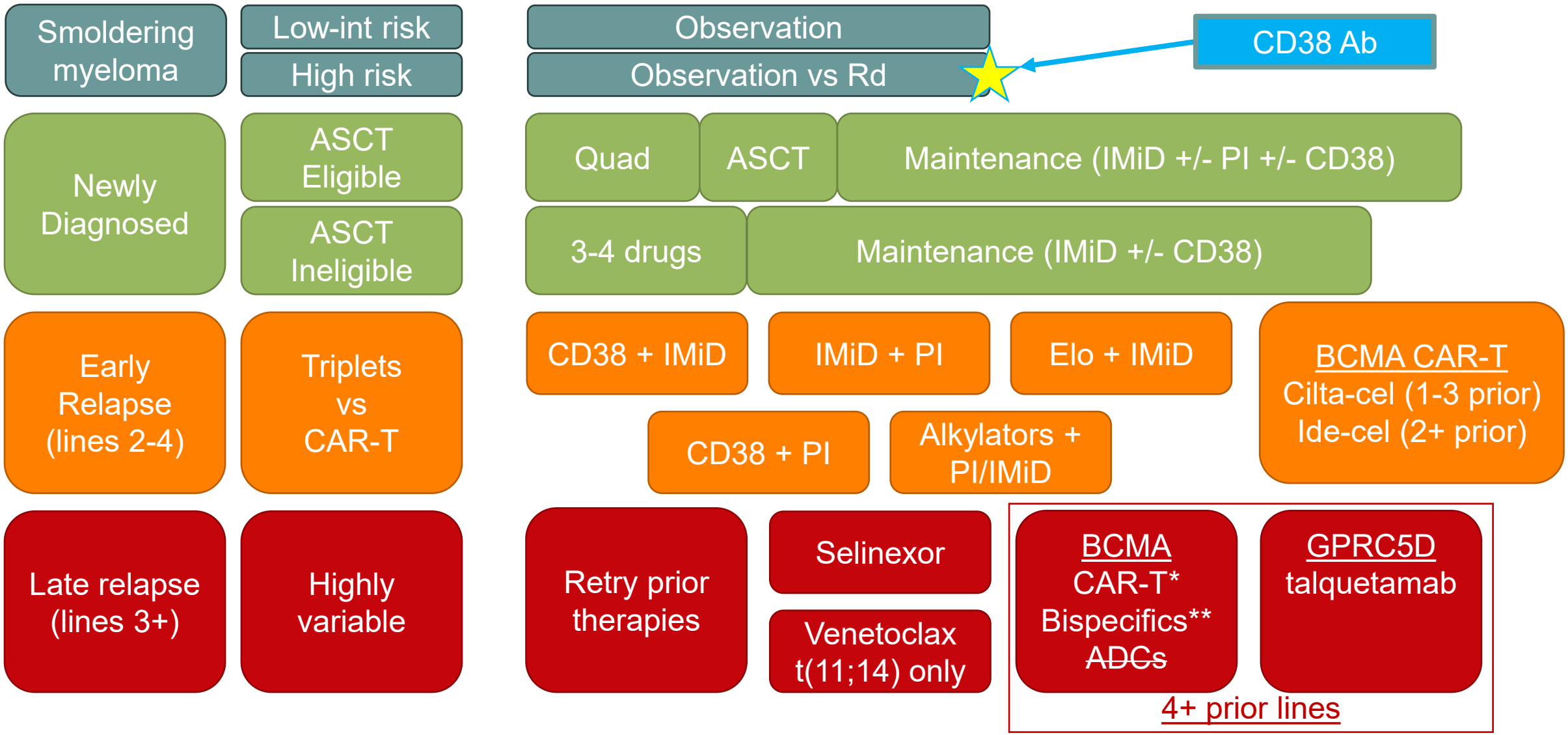
EMN30/MajesTEC-4 SRI: MRD Negativity (10^{-5}) in Evaluable Patients Post-ASCT and During Maintenance

100% of evaluable patients were MRD negative during maintenance

My take

- Remarkable efficacy…but need more data and longer follow up
- Not sure that the IMiD adds much to BCMA BsAb in this setting aside from toxicity
- Will infectious complications negate the benefit from deeper response?
- Optimal duration of therapy?
- Will it be helpful for all patients, or best utilized in certain populations?
  - High risk
  - Standard risk with high MRD burden
- Perhaps this is the best way to implement risk and response-adapted therapy and limit duration of maintenance

Should we treat high-risk smoldering myeloma?

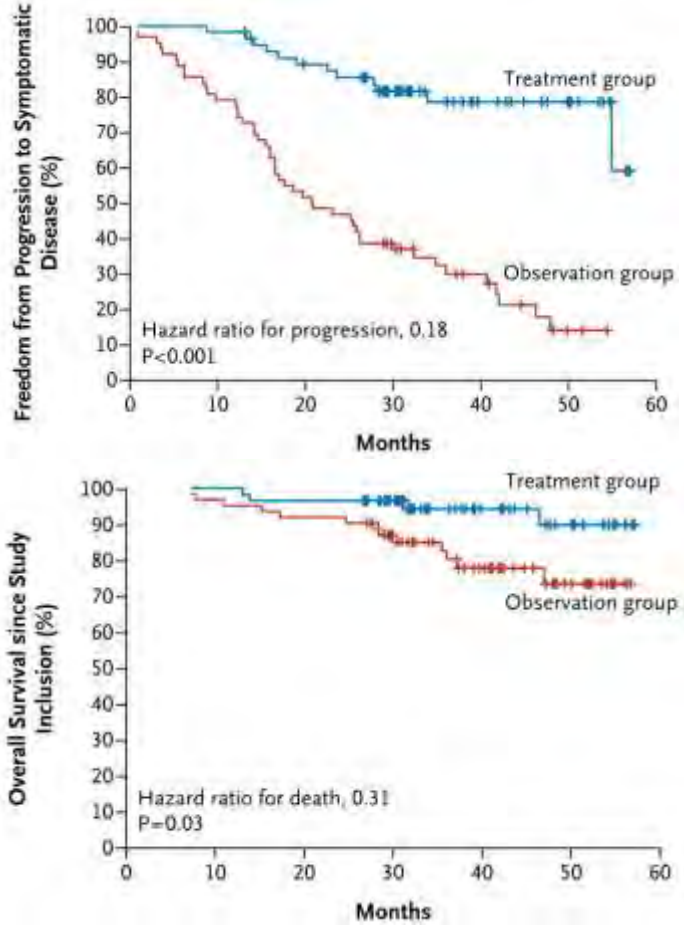


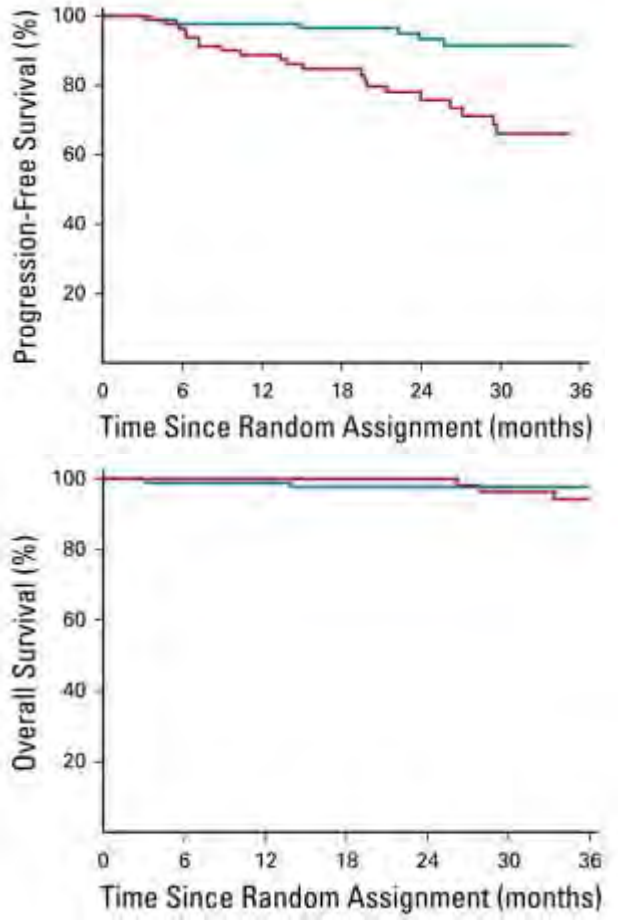
*ide-cel, cilta-cel

**teclistamab, elranatamab

Low intensity therapy in SMM

- Early treatment with len +/- dex prolongs time to developing active myeloma
- But impact on overall survival remains unclear



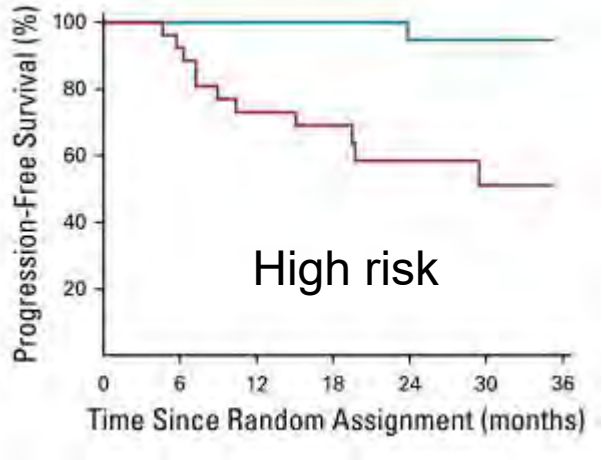


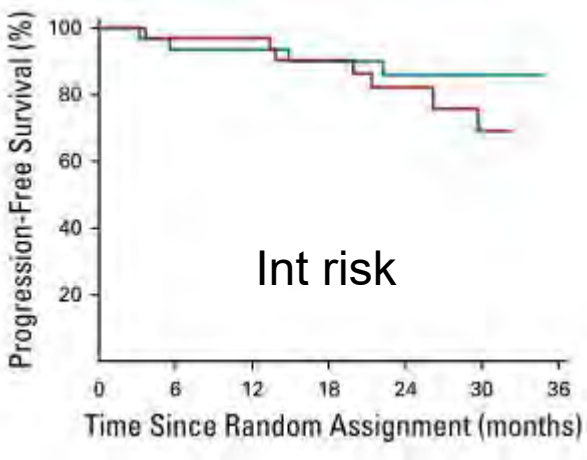
Mateos, et al, NEJM 2013
Lonial, et al, JCO 2020

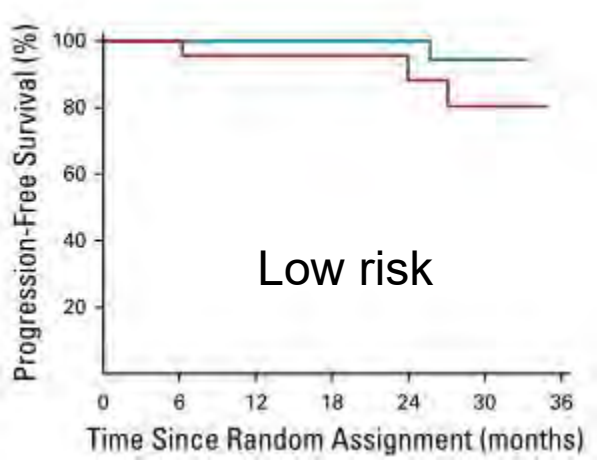
Smoldering myeloma

- Patients at the highest risk of progression to multiple myeloma seem to derive the most benefit from early intervention
- 20/2/20 system
  - BMPC ≥ 20%
  - M-spike ≥ 2 g/dL
  - FLCr ≥ 20:1

Risk status	# of risk factors	2-year risk PD
Low	0	10%
Intermediate	1	26%
High	2-3	47%







Lakshman, et al, BCJ 2018
Lonial, et al, JCO 2020

Many questions remain

- Best type of therapy?
- Duration of therapy?
- How to define disease progression?
- Does early treatment impact efficacy of subsequent myeloma therapy?
- What is the best way to define high risk SMM?

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

Meletios A Dimopoulos[1], Peter M Voorhees[2], Fredrik Schjesvold[3], Yael C Cohen[4], Vania Hungria[5], Irwindeep Sandhu[6], Jindriska Lindsay[7], Ross I Baker[8], Kenshi Suzuki[9], Hiroshi Kosugi[10], Mark-David Levin[11], Meral Beksac[12], Keith Stockerl-Goldstein[13], Albert Oriol[14], Gabor Mikala[15], Gonzalo Garate[16], Koen Theunissen[17], Ivan Spicka[18], Anne K Mylin[19], Sara Bringhen[20], Katarina Uttervall[21], Bartosz Pula[22], Eva Medvedova[23], Andrew J Cowan[24], Philippe Moreau[25], Maria-Victoria Mateos[26], Hartmut Goldschmidt[27], Tahamtan Ahmadi[28], Linlin Sha[29], Els Rousseau[30], Liang Li[29], Robyn M Dennis[31], Robin Carson[32], S Vincent Rajkumar[33]

[1]National and Kapodistrian University of Athens, Alexandra General Hospital, Athens, Greece; [2]Levine Cancer Institute, Atrium Health Wake Forest University School of Medicine, Charlotte, NC, USA; [3]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital, Oslo, Norway; [4]Tel-Aviv Sourasky (Ichilov) Medical Center and Tel Aviv University, Tel Aviv, Israel; [5]Clínica Medica São Germano, São Paulo, Brazil; [6]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [7]Kent and Canterbury Hospital, Kent, UK; [8]Perth Blood Institute, Murdoch University, Perth, Australia; [9]Japanese Red Cross Medical Center, Tokyo, Japan; [10]Ogaki Municipal Hospital, Ogaki City, Japan; [11]Albert Schweitzer Hospital, Dordrecht, The Netherlands; [12]Ankara University, Ankara, Turkey; [13]Washington University School of Medicine, St. Louis, MO, USA; [14]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias I Pujol, Barcelona, Spain; [15]South-Pest Central Hospital, National Institute for Hematology and Infectious Diseases, Budapest, Hungary; [16]Hospital Alemán, Buenos Aires, Argentina; [17]Jessa Hospital, Hasselt, Belgium; [18]Charles University and General Hospital, Prague, Czech Republic; [19]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [20]SSD Clinical Trials in Oncol-ematologia e Mieloma Multiplo, AOU Città della Salute e della Scienza di Torino, Torino, Italy; [21]Medical Unit Hematology, Karolinska University Hospital, Stockholm, Sweden; [22]Institute of Hematology and Transfusion Medicine, Warszawa, Poland; [23]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [24]University of Washington and Fred Hutchinson Cancer Center, Seattle, WA, USA; [25]University Hospital Hôtel-Dieu, Nantes, France; [26]University Hospital of Salamanca/IBSAL/Cancer Research Center-IBMCC (USAL-CSIC), Salamanca, Spain; [27]GMMG Study Group at University Hospital Heidelberg, Internal Medicine V, Heidelberg, Germany; [28]Genmab US Inc., Plainsboro, NJ, USA; [29]Janssen Research & Development, LLC, Shanghai, China; [30]Janssen Research & Development, Beerse, Belgium; [31]Janssen Research & Development, LLC, Raritan, NJ, USA; [32]Janssen Research & Development, LLC, Spring House, PA, USA; [33]Mayo Clinic, Rochester, MN, USA.

Presented by M A Dimopoulos at the 66th American Society of Hematology (ASH) Annual Meeting; December 7–10, 2024; San Diego, CA, USA

AQUILA: Study Design

AQUILA enrollment period: December 2017 and May 2019, at 124 sites in 23 countries

Screening

Key eligibility criteria:

- ≥18 years of age
- Confirmed SMM diagnosis (per IMWG criteria) for ≤5 years
- ECOG PS score of 0 or 1
- Clonal BMPCs ≥10% and ≥1 of the following risk factors:
  - Serum M-protein ≥30 g/L
  - IgA SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes
  - Serum involved:uninvolved FLC ratio ≥8 and <100
  - Clonal BMPCs >50% to <60%

All patients were required to have CT/PET-CT and MRI imaging during screening

1:1 randomization (N = 390)

Stratified by number of risk factors[a] for progression to MM (<3 vs ≥3)

Treatment/active monitoring phase

DARA monotherapy

1800 mg SC[b] QW Cycles 1-2, Q2W Cycles 3-6, Q4W thereafter in 28-day cycles until 39 cycles/36 months*

Active monitoring

No disease-specific treatment, with AE monitoring up to 36 months*

*or confirmed disease progression (whichever occurred first)

Disease evaluation schedule

- Laboratory efficacy – Every 12 weeks by central lab until disease progression
- Imaging (CT/PET-CT, MRI) – Yearly (central review)
- Bone marrow – At least every 2 years

Follow-up phase

- **Efficacy follow-up until progression by SLiM-CRAB**
- **Survival follow-up every 6 months until end of study**

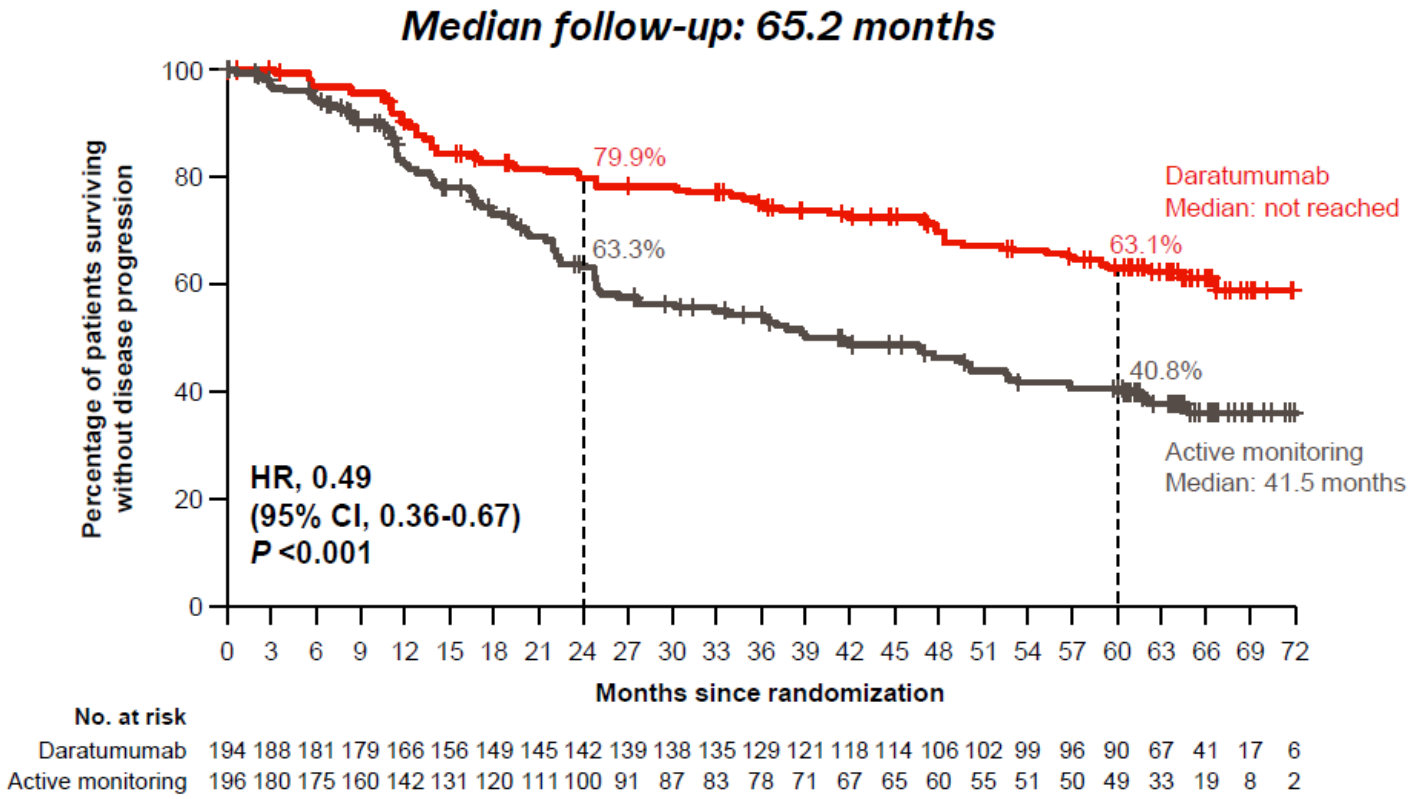
Primary endpoint:

- PFS by IRC per IMWG SLiM-CRAB criteria[c]

Key secondary endpoints:

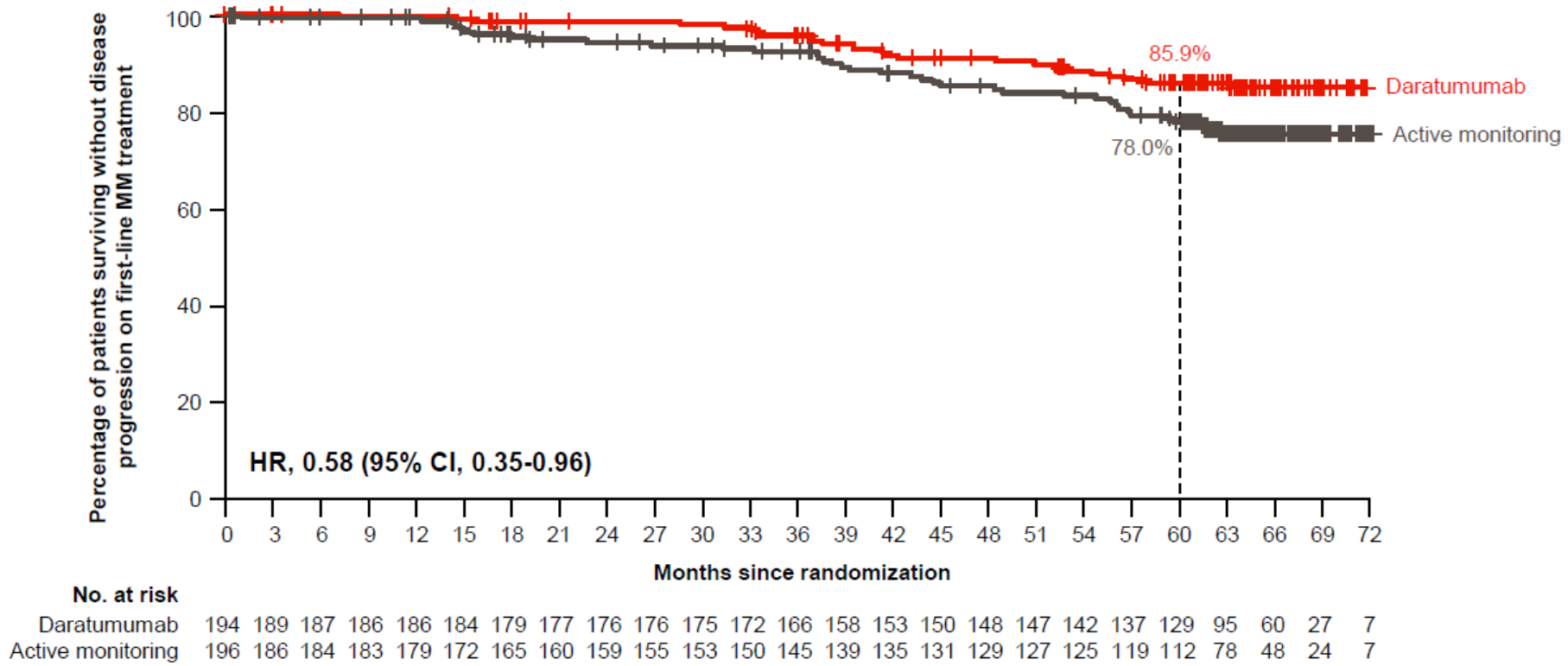
- ORR
- Time to first-line treatment for MM
- PFS on first-line treatment for MM
- Overall survival

AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria (IRC Assessment)



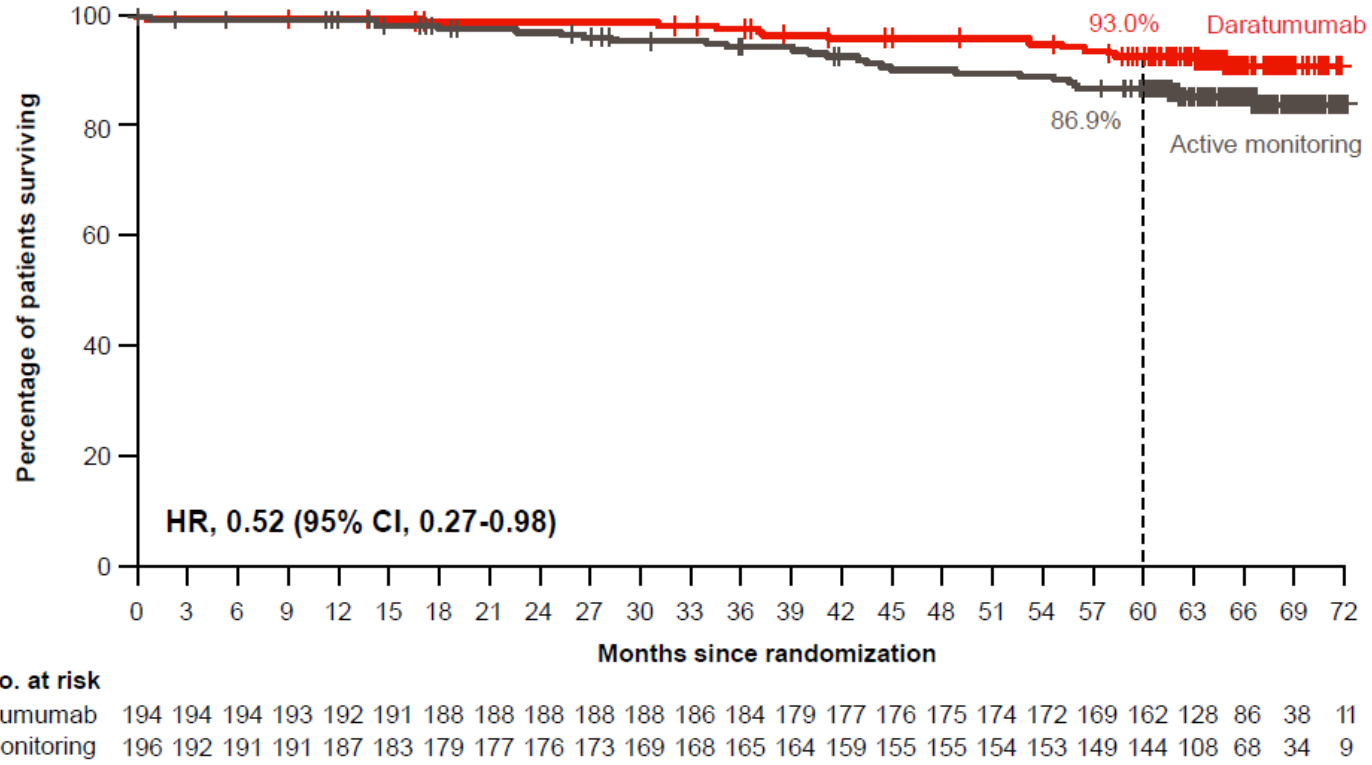
	DARA (n = 194)	Active monitoring (n = 196)
PFS event, n (%)	67 (34.5)	99 (50.5)
Death without disease progression	5 (7.5)	5 (5.1)
Disease progression[a,b]	62 (92.5)	94 (94.9)
CRAB criteria[c]	12 (19.4)	34 (36.2)
Calcium elevation	0	2 (2.1)
Renal insufficiency[d]	0	0
Anemia	2 (3.2)	14 (14.9)
Bone disease	10 (16.1)	18 (19.1)
SLiM criteria[c]	50 (80.6)	65 (69.1)
Clonal BMPCs	5 (8.1)	16 (17.0)
Serum FLC	33 (53.2)	33 (35.1)
Focal lesion by MRI	12 (19.4)	16 (17.0)

AQUILA: PFS on First-line Treatment for MM (PFS2)[a]



- VRd was the most common first-line treatment for MM (DARA, 9.8%; active monitoring, 14.8%)
- 25.0% (16/64) in the DARA group and 33.3% (35/105) in the active monitoring group received anti-CD38 regimens

AQUILA: Overall Survival



	DARA (n = 194)	Active monitoring (n = 196)
Deaths, n (%)	15 (7.7)	26 (13.3)
Primary cause, n		
Disease progression	3	9
AE	2	4
Other*	10	13

*Deaths due to an event occurring after the AE reporting window (ie, events that happened after patient started subsequent therapy or >30 days after last dose) or deaths with unknown reason.

AQUILA: AEs of Special Interest

Event, n (%)	DARA (n = 193)	Active monitoring (n = 196)
Systemic infusion-related reactions	32 (16.6)	–
Grade 3 or 4	2 (1.0)	–
Local injection-site reactions	53 (27.5)	–
Grade 3 or 4	0	–
Second primary malignancies	18 (9.3)	20 (10.2)
Noncutaneous	9 (4.7)	11 (5.6)
Cutaneous	7 (3.6)	3 (1.5)
Hematologic	3 (1.6)	6 (3.1)

Event, n (%)	DARA (n = 193)	Active monitoring (n = 196)
Cytopenias (all grades)	23 (11.9)	24 (12.2)
Neutropenia	13 (6.7)	5 (2.6)
Anemia	9 (4.7)	19 (9.7)
Thrombocytopenia	4 (2.1)	3 (1.5)
Lymphopenia	3 (1.6)	1 (0.5)
Grade 3 or 4 infections	31 (16.1)	9 (4.6)
Number of grade 3 or 4 infections	37	11
Recovered or resolved	35 (94.6)	8 (72.7)
Median duration of infection	9 days	5 days

My take

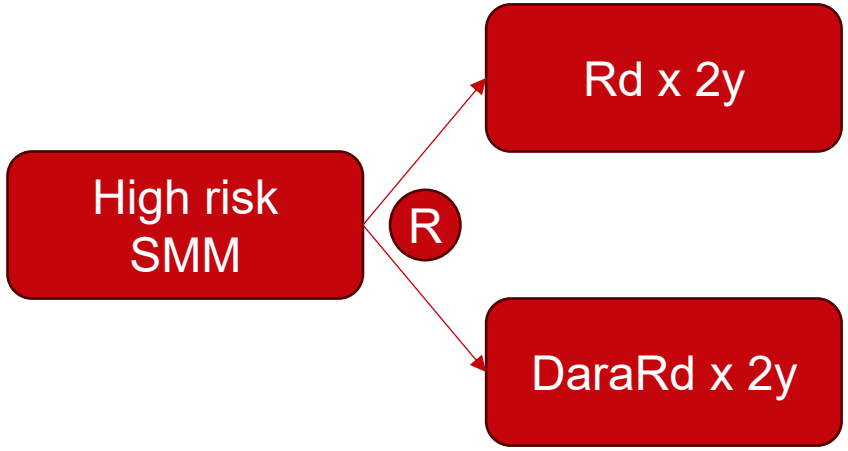
- Likely to generate regulatory approval for dara in SMM

- Early intervention with dara probably doesn't harm most patients.
- Better tolerated than lenalidomide

- Statistical benefit is clear. Meaningful clinical benefit is modest

- We still need a better system to identify which patients are best suited for early therapy

- Added rationale for the ongoing EAA173 trial



Thank you!

Email: tschmidt@medicine.wisc.edu

Cell phone: (314) 413-3434

Twitter/X: @TMSchmidtMD