ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Le vecchie e nuove immunoterapie per il management del mieloma multiplo nel 2024 ed oltre

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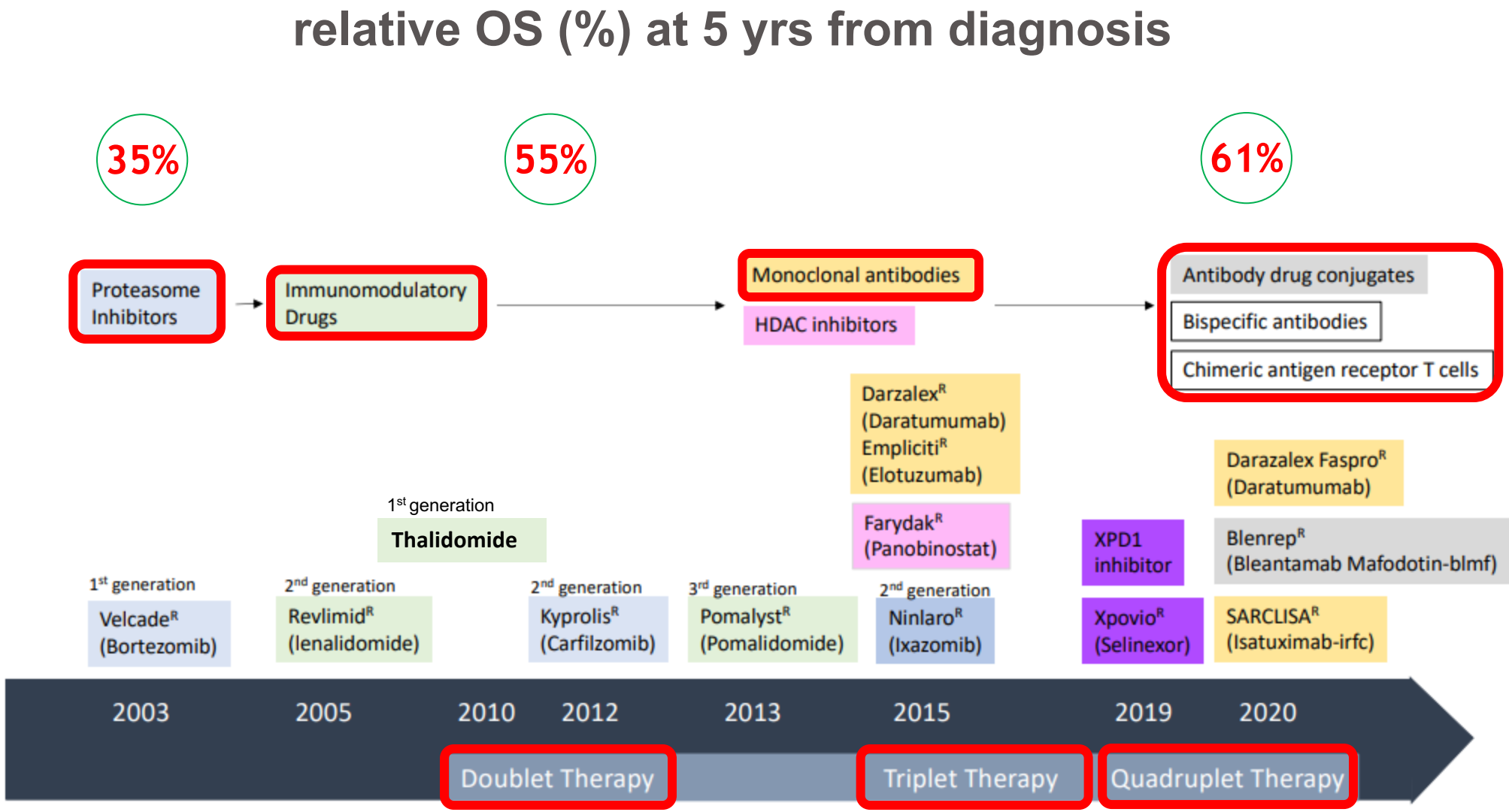
Treviso, 22-23 Novembre 2024

Disclosures - M Cavo

Research Support/P.I.	No relevant conflicts of interest to declare
Employee	No relevant conflicts of interest to declare
Consultant	Janssen, Celgene, Amgen, Bristol-Myers Squibb
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	Janssen, Celgene, Amgen, Sanofi
Honoraria	Janssen, Bristol-Myers Squibb, Amgen, Sanofi, GSK, Novartis, Pfizer, Takeda
Scientific Advisory Board	Janssen, Bristol-Myers Squibb, GSK, Amgen, Sanofi, Pfizer

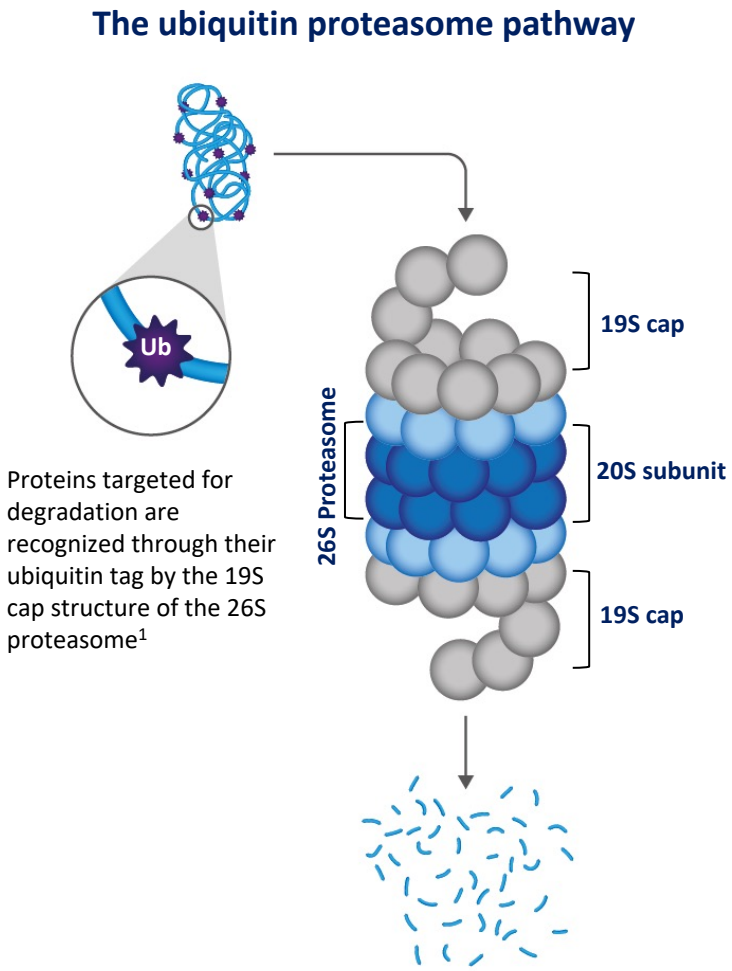
Presentation includes discussion of the off-label use of a drug or drugs

Improvements in MM therapies and OS over the 2000s



Hiroko Nishida, Cancers 2021, 13, 2712

The Role of the Proteasome in Protein Degradation



- The ubiquitin proteasome pathway maintains cellular homeostasis through degradation of misfolded and regulatory proteins[1]
- More than 80% of cellular proteins are degraded through this pathway, including those involved in processes such as cell cycle progression, apoptosis, and DNA repair[2]
- Disruption of proteasome activity interferes with normal protein elimination, thereby causing a buildup of unwanted proteins and eventual cell death[3]

The proteasome is critical for maintaining cellular homeostasis[1]

- Ub, ubiquitin.
- Image adapted from Hideshima T, et al. *Mol Cancer Ther*. 2011;10:2034-2042 and Chen D, et al. *Curr Cancer Drug Targets*. 2011;11:239-253. 1. Moreau P, et al. *Blood*. 2012;120:947-959. 2. Kubiczkova L, et al. *J Cell Mol Med*. 2014;18:947-961. 3. Chauhan, et al. *BMC Biochem.* 2008;9 Suppl 1:S1.

blood
Volume 106, Issue 1
July 1 2005

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS | JULY 1, 2005

Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma

Michele Cavo, Elena Zamagni, Patrizia Tosi, Paola Tacchetti, Claudia Cellini, Delia Cangini, Antonio de Vivo, Nicoletta Testoni, Chiara Nicci, Carolina Terragna, Tiziana Grafone, Giulia Perrone, Michela Ceccolini, Sante Tura, and Michele Baccarani, for the writing committee of the Bologna 2002 study

Table 2. Rates of response

	No. of patients		
	Thal-Dex, N = 100	VAD, N = 100	*P*
At least PR	76	52	< .001
CR	10	8	—
nCR	3	5	—
VGPR	6	1	—
PR	57	38	—
NR/PROGR	24	48	< .001

At least partial remission (PR) includes complete remission (CR), near complete remission (nCR), very good partial remission (VGPR), and partial remission (PR).
— indicates not applicable; NR/PROGR, no response/progression.

insideblood
1 JULY 2005 | VOLUME 106, NUMBER 1

CLINICAL OBSERVATIONS

Comment on Cavo et al, page 35

Multiple myeloma: the death of VAD as initial therapy

S. Vincent Rajkumar MAYO CLINIC

In a matched case-control study of 200 patients, Cavo and colleagues show that thalidomide plus dexamethasone (Thal-Dex) yields significantly higher response rates compared with VAD as pretransplant induction therapy for multiple myeloma.

VOLUME 27 · NUMBER 30 · OCTOBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Short-Term Thalidomide Incorporated Into Double Autologous Stem-Cell Transplantation Improves Outcomes in Comparison With Double Autotransplantation for Multiple Myeloma

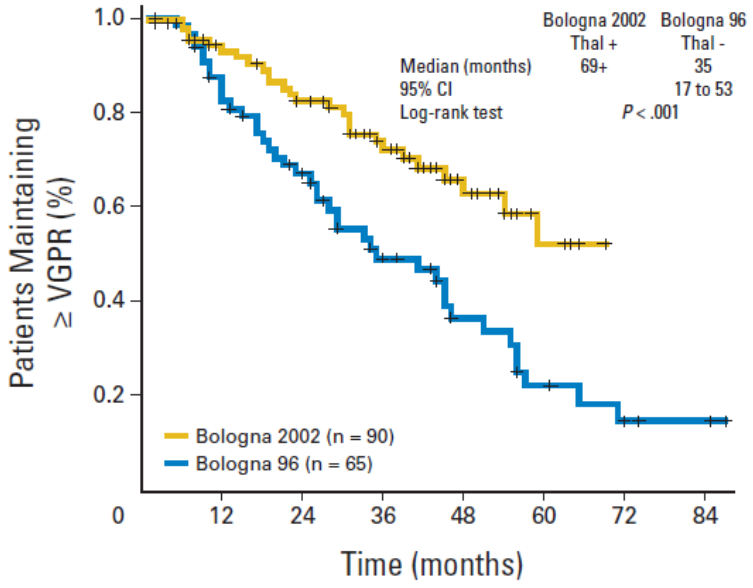
Michele Cavo, Francesco Di Raimondo, Elena Zamagni, Francesca Patriarca, Paola Tacchetti, Antonio Francesco Casulli, Silvestro Volpe, Giulia Perrone, Antonio Ledda, Michela Ceccolini, Catello Califano, Catia Bigazzi, Massimo Offidani, Piero Stefani, Filippo Ballerini, Mauro Fiacchini, Antonio de Vivo, Annamaria Brioli, Patrizia Tosi, and Michele Baccarani

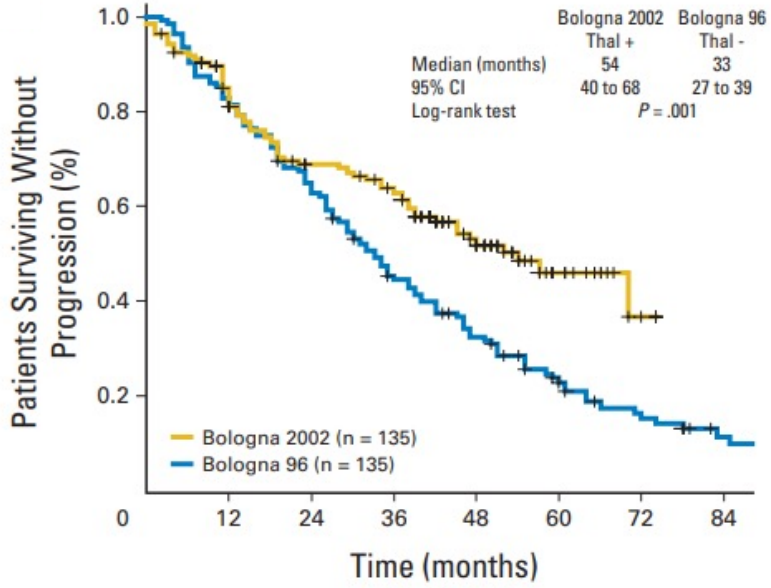
"Bologna 2002" study

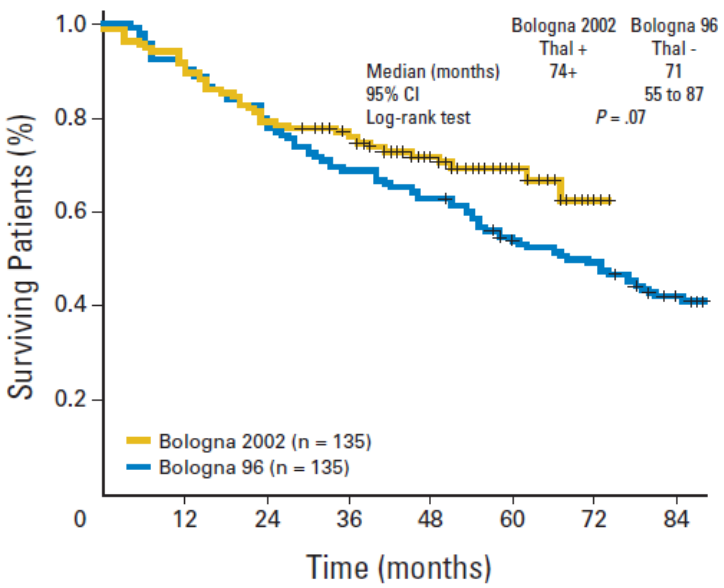
Aimed at exploring the incorporation of thal-dex into double ASCT as induction therapy and thereafter continuous treatment until the second ASCT

Table 3. Response to Therapy in Relationship to the Individual Treatment Phases in Bologna 2002 and Bologna 96 Studies

Treatment Phase	% With at Least VGPR		
	Bologna 2002 (n = 135)	Bologna 96 (n = 135)	*P*
Induction	30	15	.003
CTX	41	24	.002
First ASCT	60	35.5	< .001
Second ASCT	68	49	.001



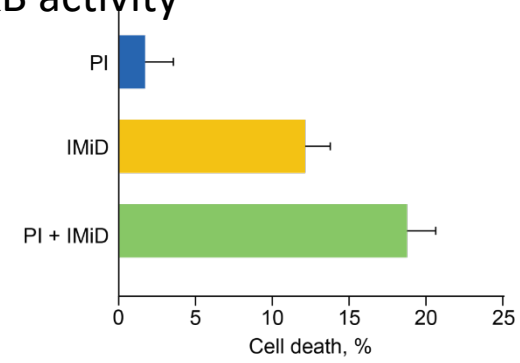




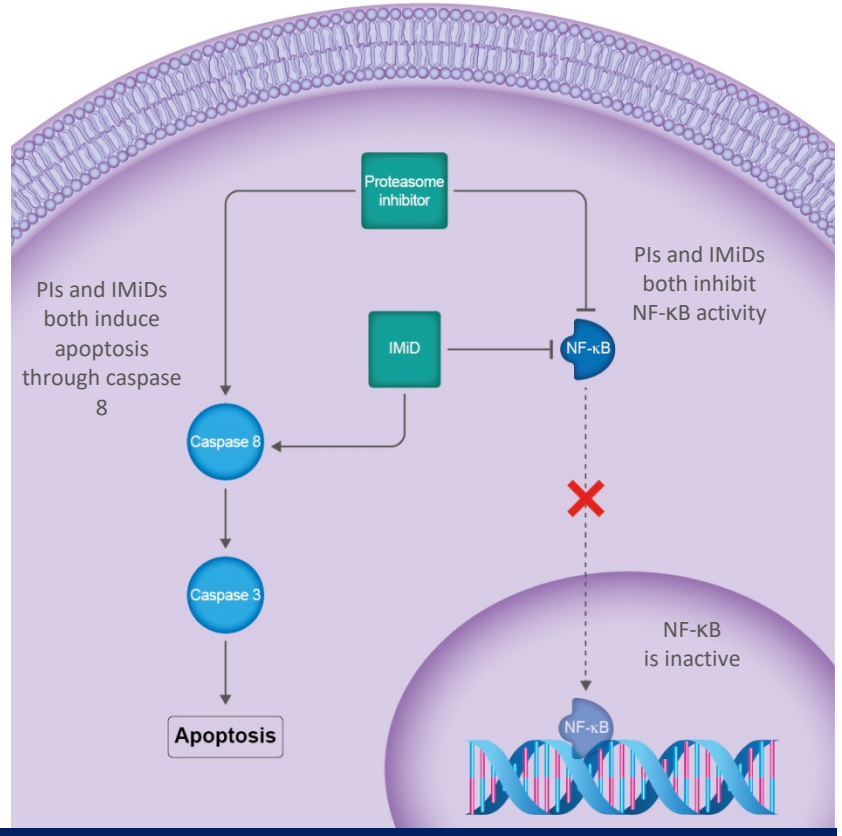
Synergistic anti-MM activity of PIs and IMiDs

- IMiDs exert potent anti-myeloma cell activity, including:
  - Stimulation of apoptosis[1]
  - Inhibition of angiogenesis, adhesion, and cytokine circuits within the bone marrow microenvironment[1]
  - Enhancement of antitumor immune response through T cells and natural killer cells[1]
- Preclinical studies demonstrate that IMiDs sensitize myeloma cells to PI-induced apoptosis through combined inhibition of prosurvival NF-κB activity[2]

Combination of PI and IMiD enhances proapoptotic effect on primary MM cells *in vitro*[2]



Anti-myeloma activity of PIs and IMiDs[2,3]



PIs and IMiDs work synergistically to induce myeloma cell death[2,3]

IMiD, immunomodulatory agent; NF-κB, nuclear factor κB; PI, proteasome inhibitor.

Image adapted from Hideshima T, Anderson K. *Nat Rev Cancer*. 2002;2:927-937. 1. Zhu YX, et al. *Leuk Lymphoma.* 2013;54:683-687. 2. Mitsiades N, et al. *Blood*. 2002;99:4525-4530. 3. Hideshima T, Anderson K. *Nat Rev Cancer*. 2002;2:927-937.

THE LANCET
Volume 376, Issue 9758, 18–31 December 2010, Pages 2075–2085

Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study

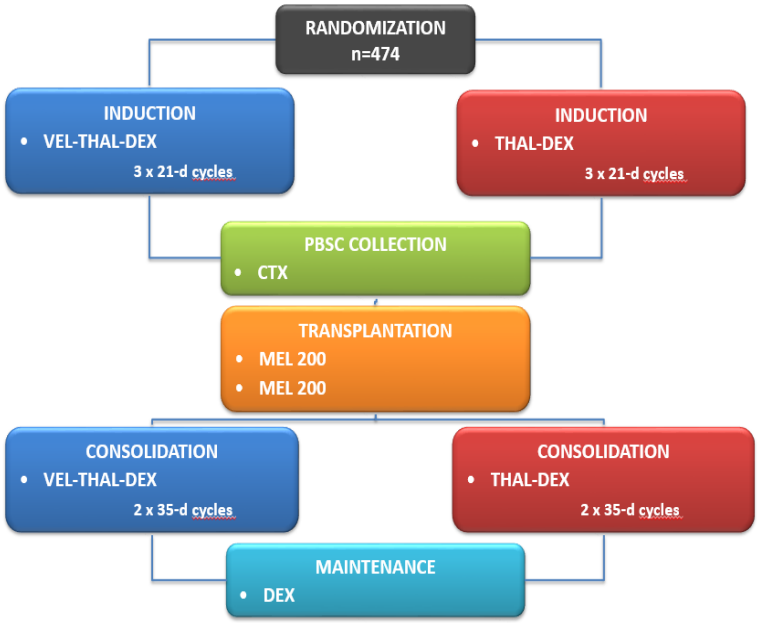
*Michele Cavo, Paola Tacchetti, Francesca Patriarca, Maria Teresa Petrucci, Lucia Pantani, Monica Galli, Francesco Di Raimondo, Claudia Crippa, Elena Zamagni, Antonio Palumbo, Massimo Offidani, Paolo Corradini, Franco Narni, Antonio Spadano, Norbert Pescosta, Giorgio Lambertenghi Deliliers, Antonio Ledda, Claudia Cellini, Tommaso Caravita, Patrizia Tosi, Michele Baccarani, for the GIMEMA Italian Myeloma Network**

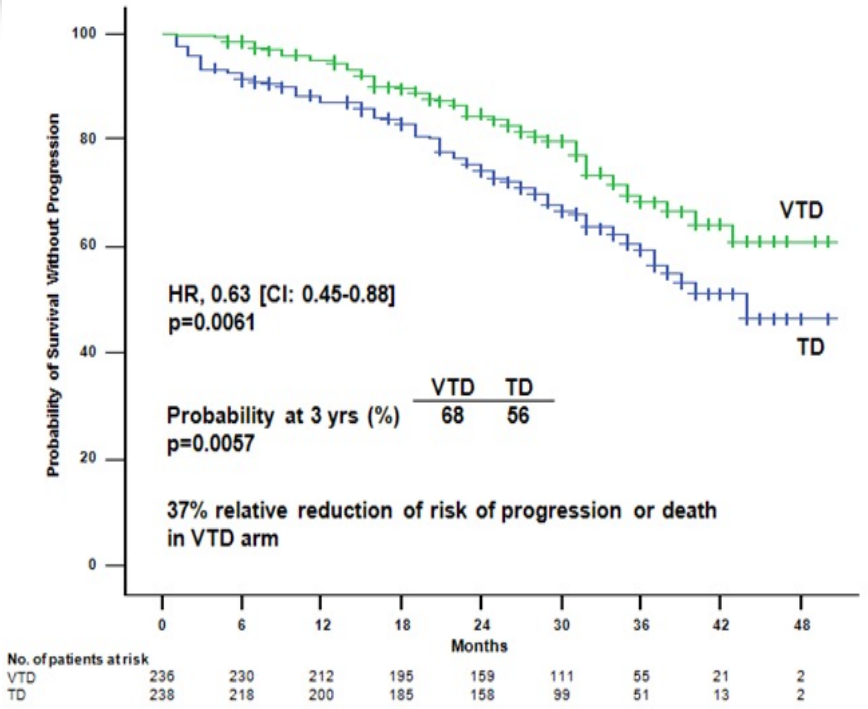
blood®
Plenary paper
BLOOD, 5 JULY 2012 • VOLUME 120, NUMBER 1

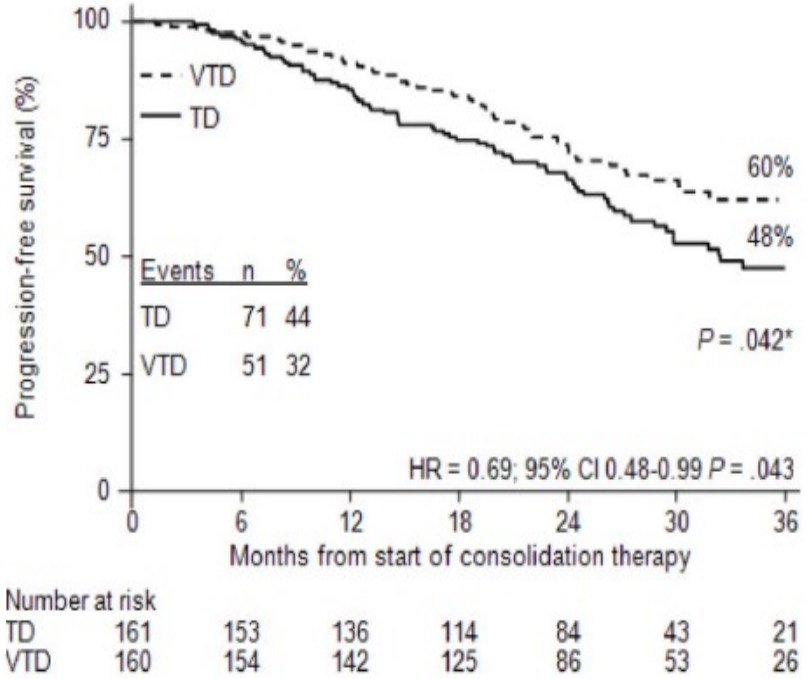
Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma

Michele Cavo,[1] Lucia Pantani,[1] Maria Teresa Petrucci,[2] Francesca Patriarca,[3] Elena Zamagni,[1] Daniela Donnarumma,[4] Claudia Crippa,[5] Mario Boccadoro,[6] Giulia Perrone,[1] Antonietta Falcone,[7] Chiara Nozzoli,[8] Renato Zambello,[9] Luciano Masini,[10] Anna Furlan,[11] Annamaria Brioli,[1] Daniele Derudas,[12] Stelvio Ballanti,[13] Maria Laura Dessanti,[14] Valerio De Stefano,[15] Angelo Michele Carella,[16] Magda Marcatti,[17] Andrea Nozza,[18] Felicetto Ferrara,[19] Vincenzo Callea,[20] Catello Califano,[21] Annalisa Pezzi,[1] Anna Baraldi,[22] Mariella Grasso,[23] Pellegrino Musto,[24] and Antonio Palumbo,[6] for the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network

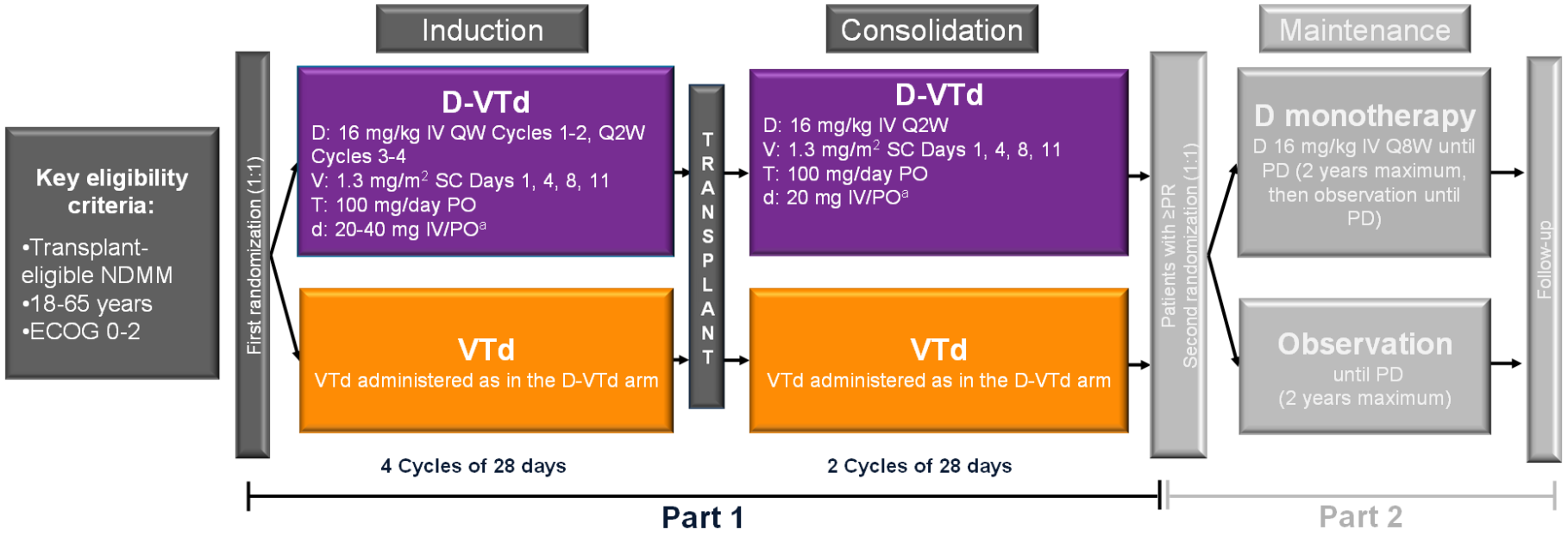
GIMEMA MMY-3006 STUDY DESIGN

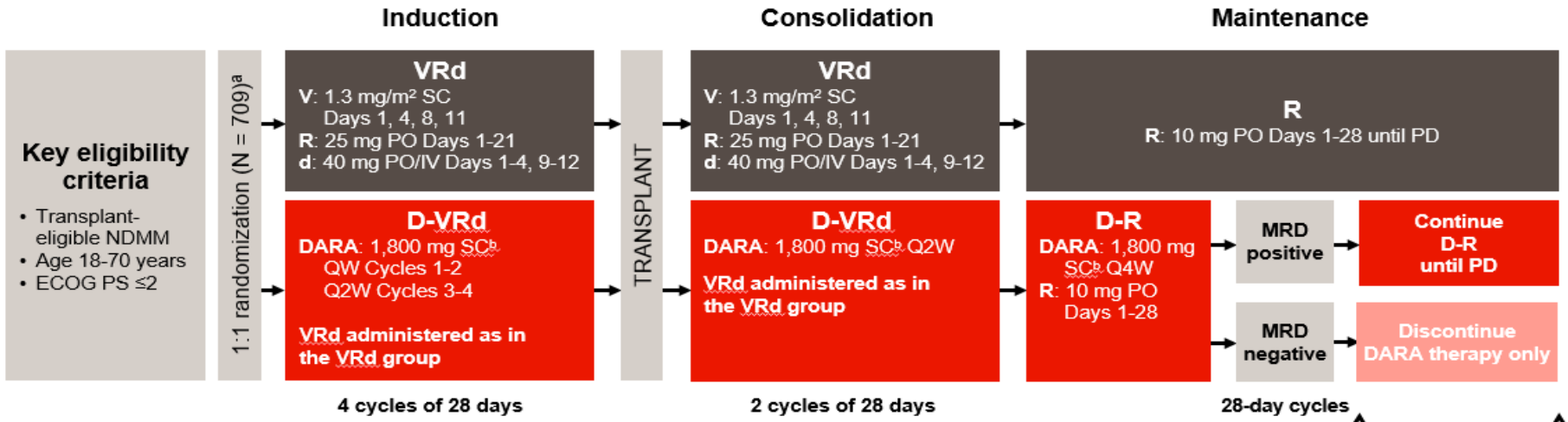






CASSIOPEIA and PERSEUS: Study Design





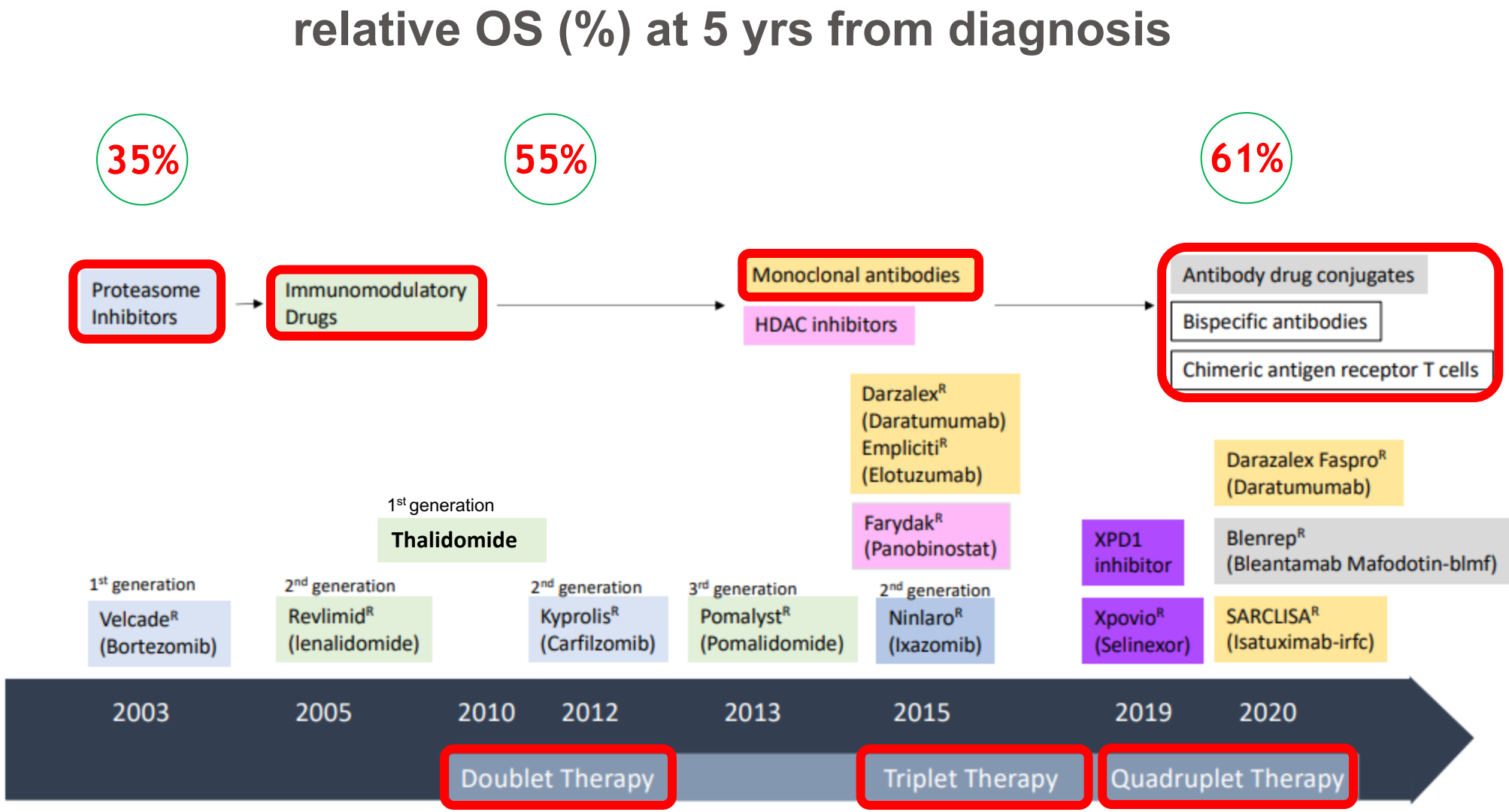
Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

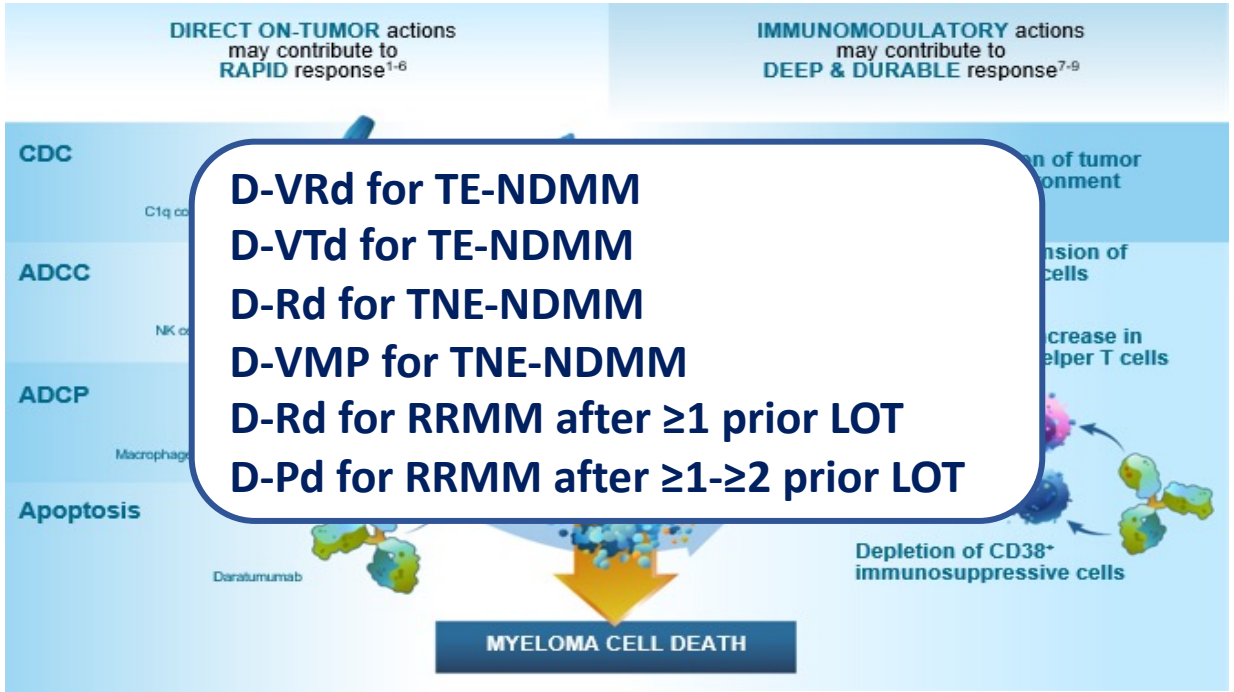
Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

Improvements in MM therapies and OS over the 2000s

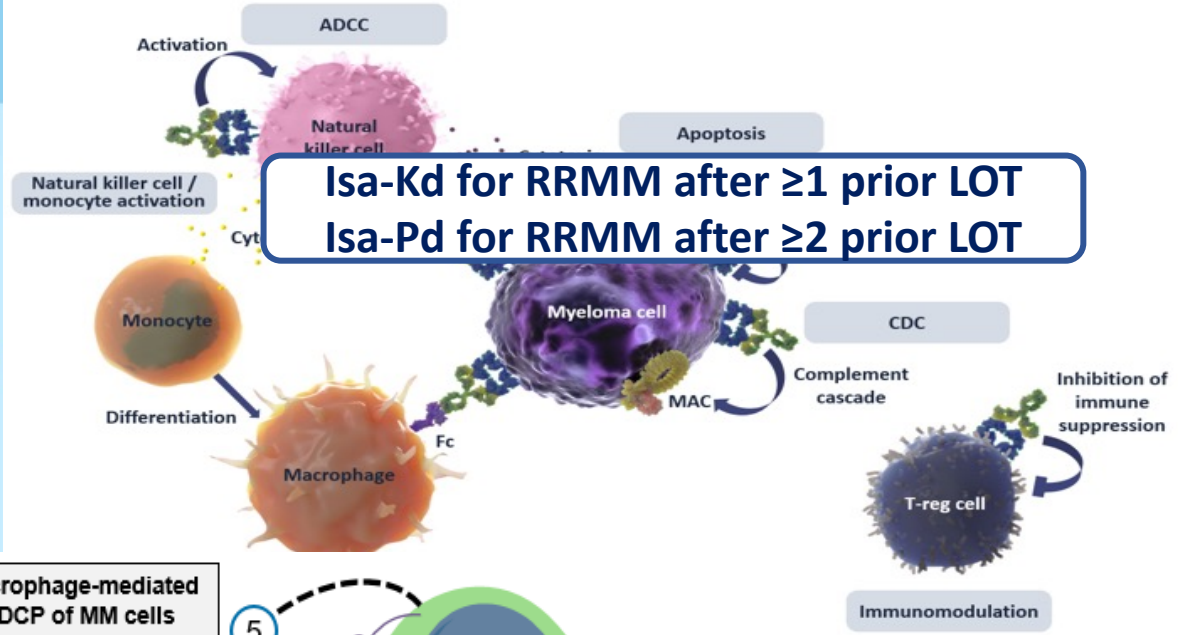


Hiroko Nishida, Cancers 2021, 13, 2712

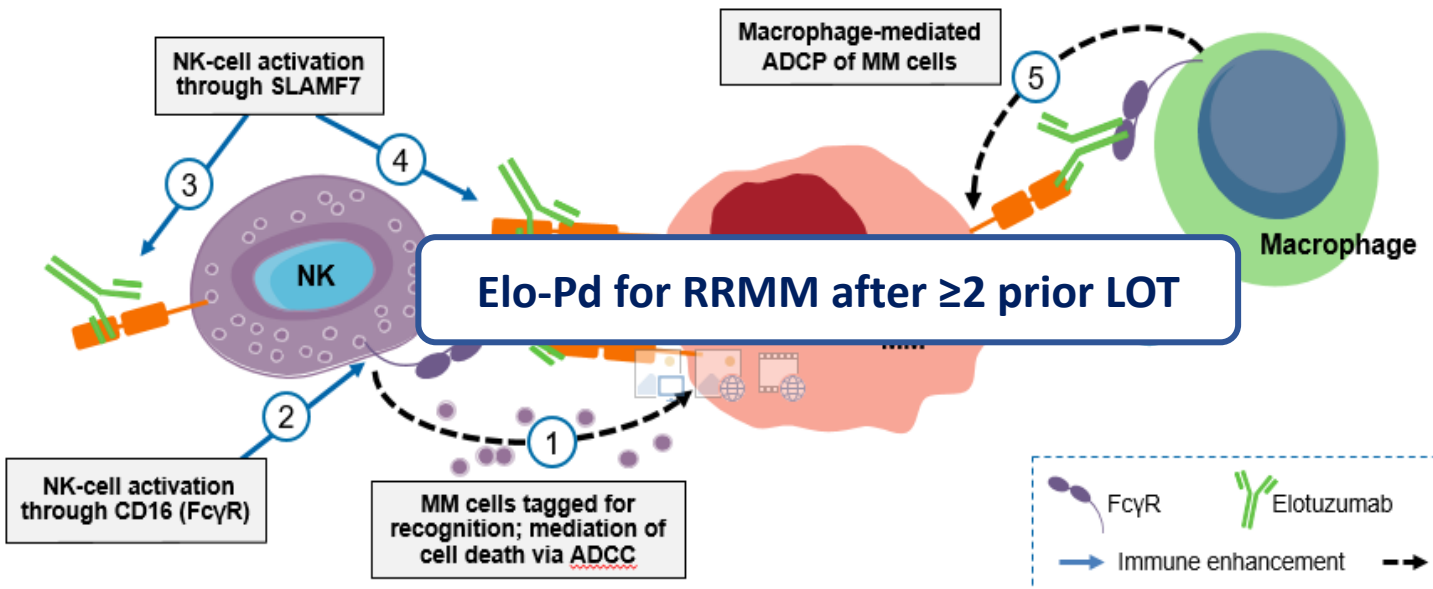
Multimodal mechanisms of action of anti-CD38 and SLAMF7 mAb



D-VRd for TE-NDMM
D-VTd for TE-NDMM
D-Rd for TNE-NDMM
D-VMP for TNE-NDMM
D-Rd for RRMM after ≥1 prior LOT
D-Pd for RRMM after ≥1-≥2 prior LOT



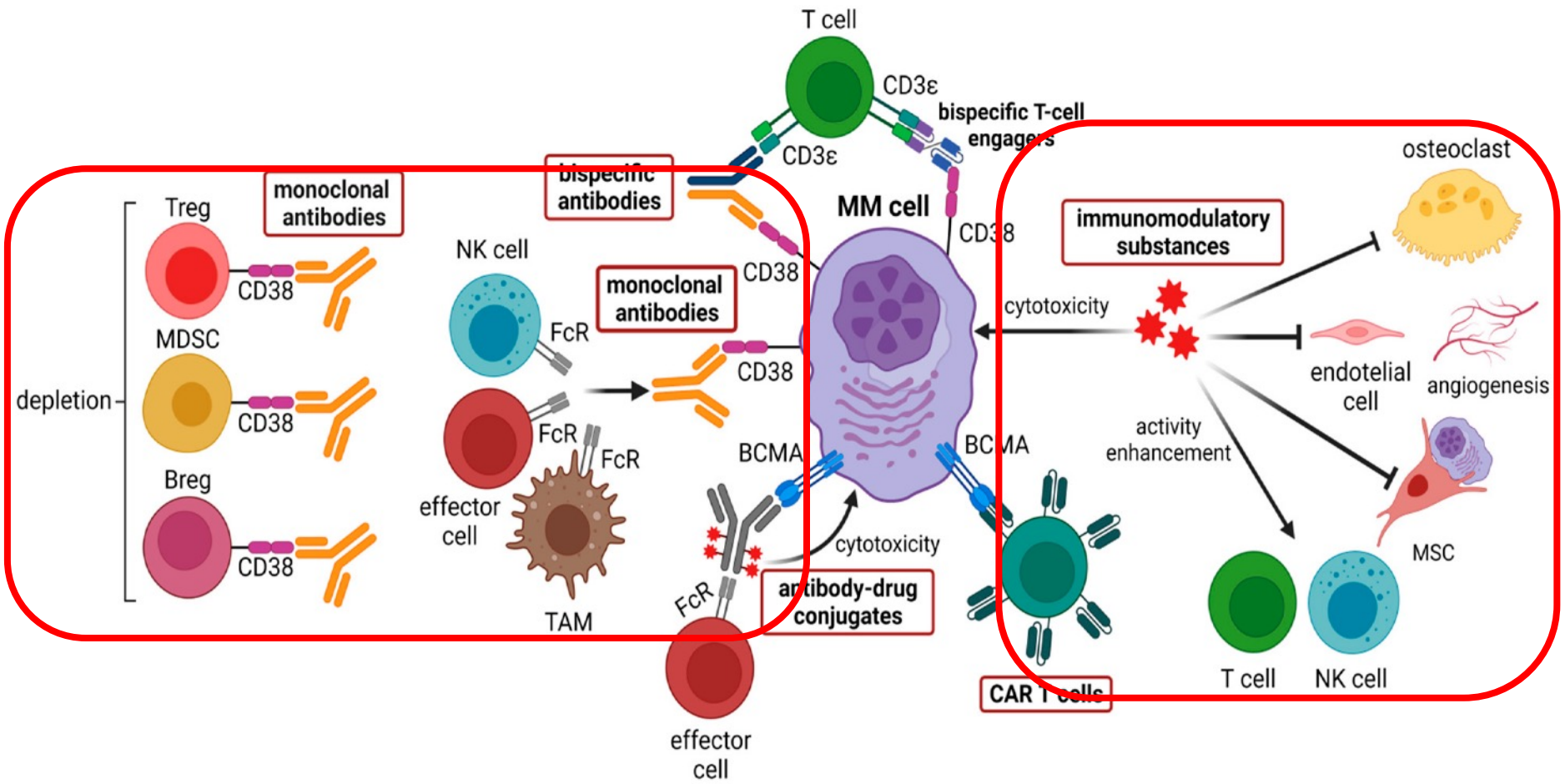
Isa-Kd for RRMM after ≥1 prior LOT
Isa-Pd for RRMM after ≥2 prior LOT



Elo-Pd for RRMM after ≥2 prior LOT

1. Lammerts van Bueren J, et al. Blood. 2014;124:Abstract 3474 2. Jansen JMH, et al. Blood. 2012;120:Abstract 2974 3. de Weers M, et al. J Immunol. 2011;186:1840-8 4. Overdijk MB, et al. MAbs. 2015;7:311-21 5. Krejcik J, et al. Blood. 2016. 128(3):384-94

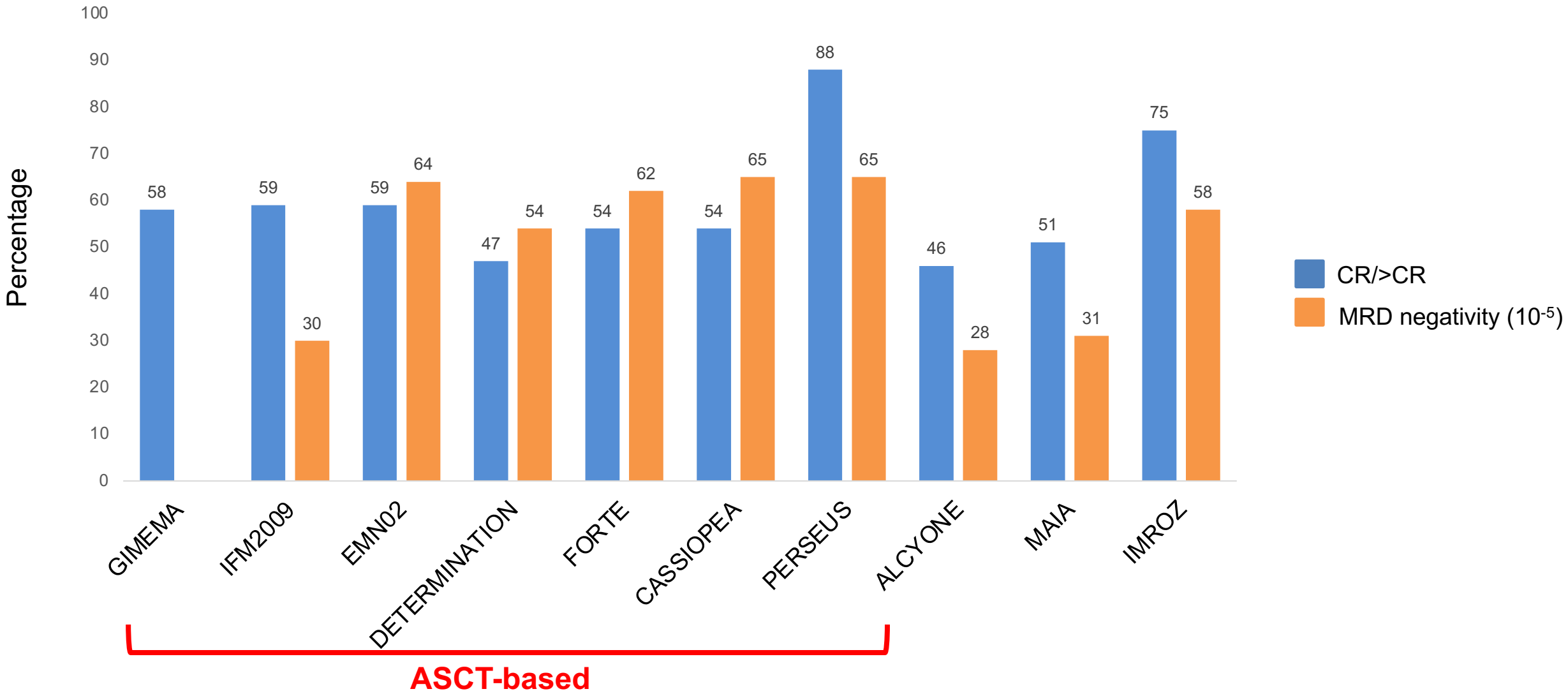
Rationale for IMiD + CD38 mAb Combinations



- Enhanced NK-cell mediated ADCC
- Increased antitumor activity of macrophages and enhanced ADCP
- Increased CD38 expression on T regs
- Enhanced cytotoxicity

Neumeister. Int J Mol Sci. 2022;23:7627. CC BY 4.0. No changes made. van de Donk. Blood. 2018;131:13.

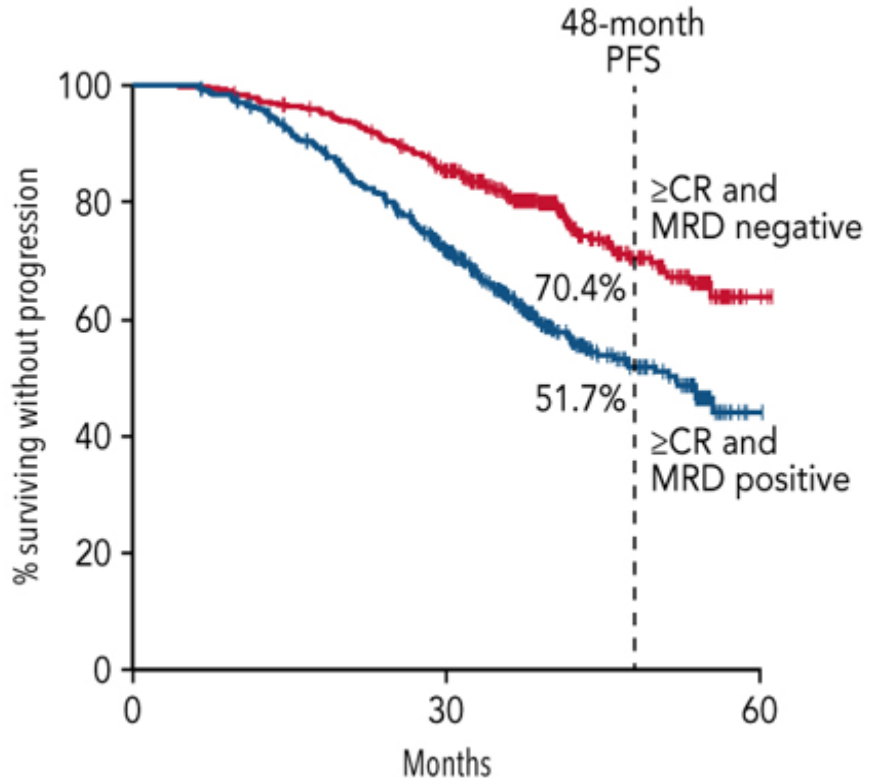
CR and MRD negativity rates with first-line 3 or 4 drug-based therapies w/wo ASCT



blood 10 FEBRUARY 2022 | VOLUME 139, NUMBER 6

Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA

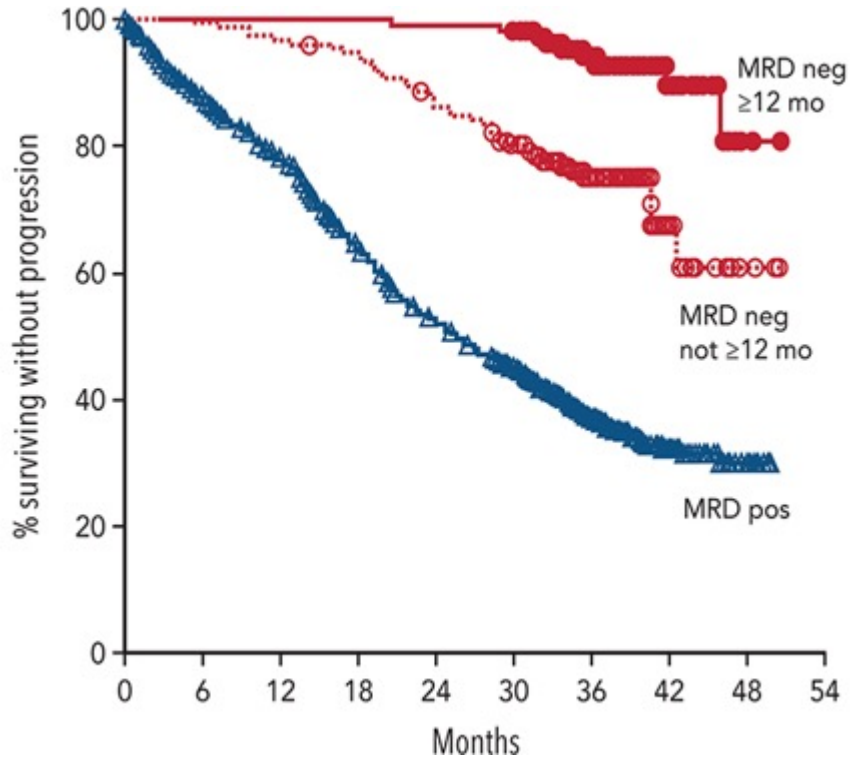
Michele Cavo,[1] Jesus San-Miguel,[2] Saad Z. Usmani,[3] Katja Weisel,[4] Meletios A. Dimopoulos,[5] Hervé Avet-Loiseau,[6] Bruno Paiva,[2] Nizar J. Bahlis,[7] Torben Plesner,[8] Vania Hungria,[9] Philippe Moreau,[10] Maria-Victoria Mateos,[11] Aurore Perrot,[12] Shinsuke Iida,[13] Thierry Facon,[14] Shaji Kumar,[15] Niels W. C. J. van de Donk,[16] Pieter Sonneveld,[17] Andrew Spencer,[18] Maria Krevvata,[19] Christoph Heuck,[19] Jianping Wang,[20] Jon Ukropec,[21] Rachel Kobos,[19] Steven Sun,[20] Mia Qi,[20] and Nikhil Munshi[22,23]



blood 27 JANUARY 2022 | VOLUME 139, NUMBER 4

Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE

Jesus San-Miguel,[1] Hervé Avet-Loiseau,[2] Bruno Paiva,[1] Shaji Kumar,[3] Meletios A. Dimopoulos,[4] Thierry Facon,[5] María-Victoria Mateos,[6] Cyrille Touzeau,[7] Andrzej Jakubowiak,[8] Saad Z. Usmani,[9] Gordon Cook,[10] Michele Cavo,[11] Hang Quach,[12] Jon Ukropec,[13] Priya Ramaswami,[14] Huiling Pei,[14] Mia Qi,[15] Steven Sun,[15] Jianping Wang,[15] Maria Krevvata,[16] Nikki DeAngelis,[16] Christoph Heuck,[16] Rian Van Rampelbergh,[17] Anupa Kudva,[15] Rachel Kobos,[15] Ming Qi,[16] and Nizar J. Bahlis[18]



1. Cavo M et al, Blood. 2022;139(6):835-844 2.San Miguel J, et al Blood. 2022 Jan 27;139(4):492-501.

FDA ODAC voted 12-0 to recommend MRD as a MM Endpoint

On April 12, 2024, FDA ODAC voted 12-0 in favor of using minimal residual disease (MRD) as an accelerated approval endpoint in multiple myeloma clinical trials

The EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical endpoint for MM
(Landgren O et al, Blood 2024,144(4):359-367)

Conclusion: The Applicants have worked with the broader MM community to develop a novel endpoint of MRD that has the potential to expedite drug development in MM. While there are still outstanding questions on how to best use MRD, the meta-analyses conducted **(University of Miami and IMF led i2TEAMM**) represent robust assessments of MRD that support its prognostic value, provide information regarding the appropriate timing of MRD assessment, and suggest that MRD may be appropriate to use as an intermediate clinical endpoint to support accelerated approval.

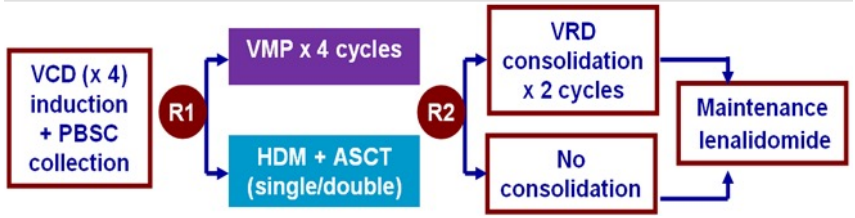
THE LANCET Haematology

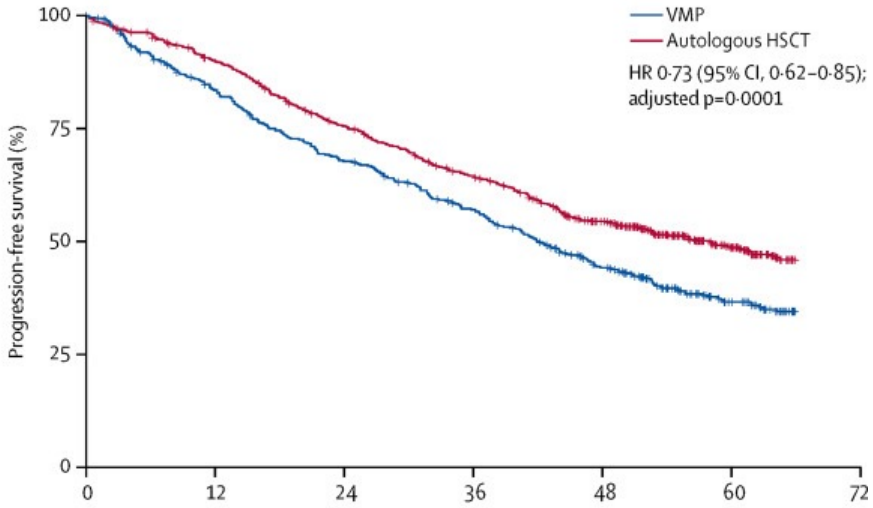
Lancet Haematol 2020; 7: e456–68

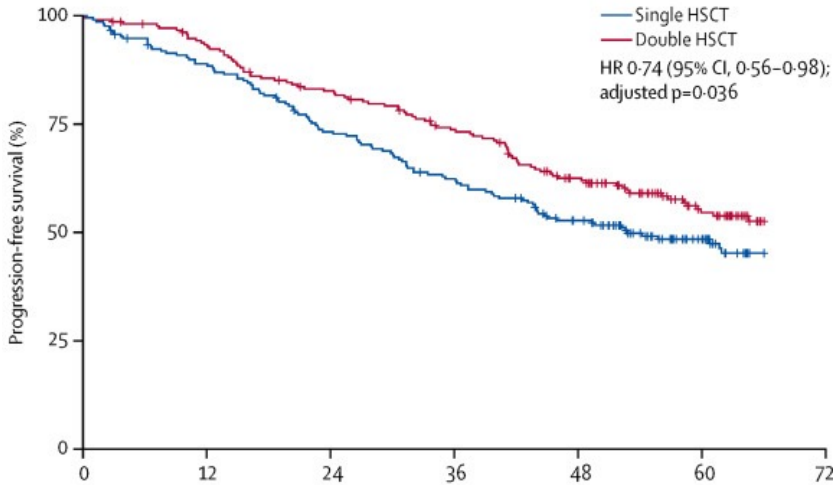
Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study

Michele Cavo, Francesca Gay, Meral Beksac, Lucia Pantani, Maria Teresa Petrucci, Meletios A Dimopoulos, Luca Dozza, Bronno van der Holt, Sonja Zweegman, Stefania Oliva, Vincent H J van der Velden, Elena Zamagni, Giuseppe A Palumbo, Francesca Patriarca, Vittorio Montefusco, Monica Galli, Vladimir Maisnar, Barbara Gamberi, Markus Hansson, Angelo Belotti, Ludek Pour, Paula Ypma, Mariella Grasso, Alexsandra Croockewit, Stelvio Ballanti, Massimo Offidani, Iolanda D Vincelli, Renato Zambello, Anna Marina Liberati, Niels Frost Andersen, Annemiek Broijl, Rossella Troia, Anna Pascarella, Giulia Benevolo, Mark-David Levin, Gerard Bos, Heinz Ludwig, Sara Aquino, Anna Maria Morelli, Ka Lung Wu, Rinske Boersma, Roman Hajek, Marc Durian, Peter A von dem Borne, Tommaso Caravita di Toritto, Thilo Zander, Christoph Driessen, Giorgina Specchia, Anders Waage, Peter Gimsing, Ulf-Henrik Mellqvist, Marinus van Marwijk Kooy, Monique Minnema, Caroline Mandigers, Anna Maria Cafro, Angelo Palmas, Susanna Carvalho, Andrew Spencer, Mario Boccadoro, Pieter Sonneveld

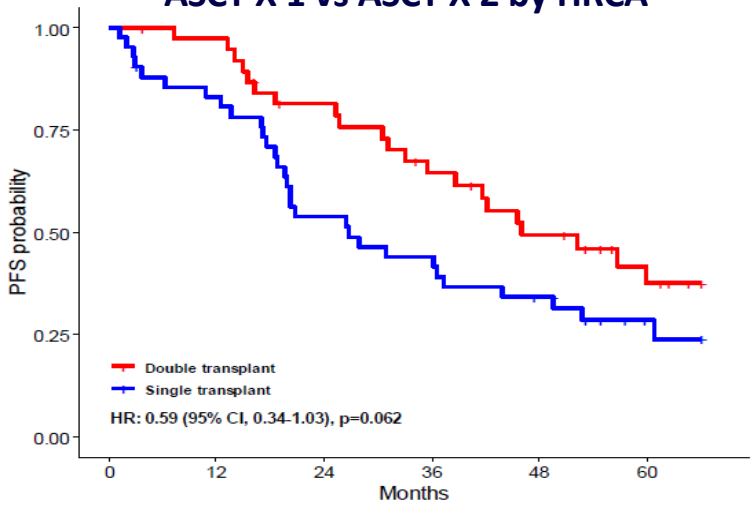
EMN02/HO95 phase 3 study







ASCT X 1 vs ASCT X 2 by HRCA



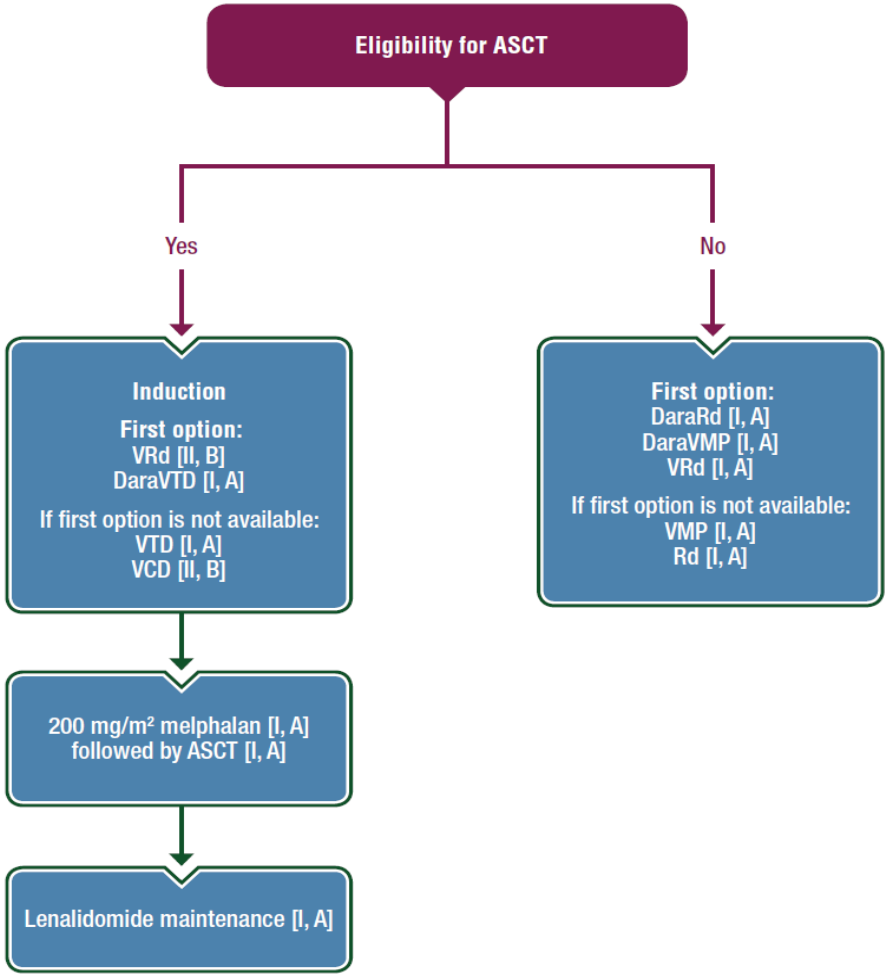
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

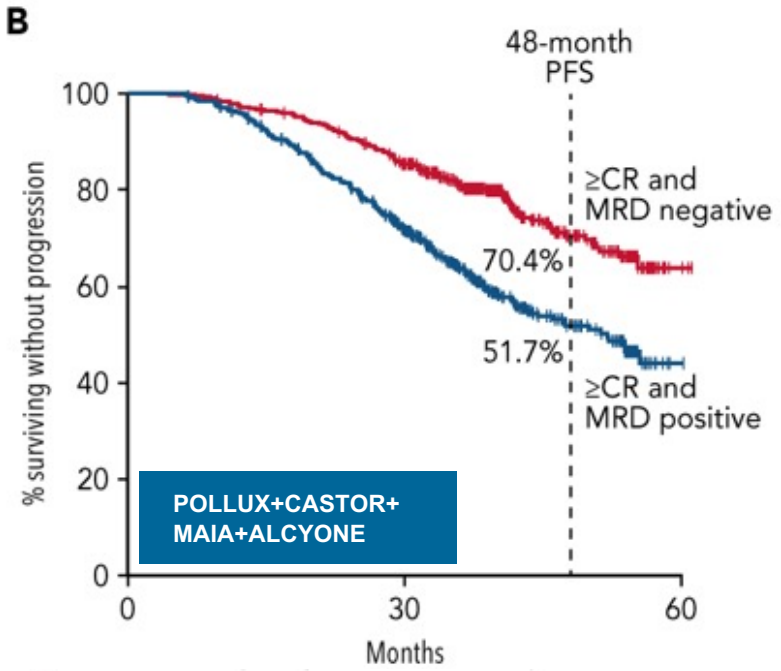
Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

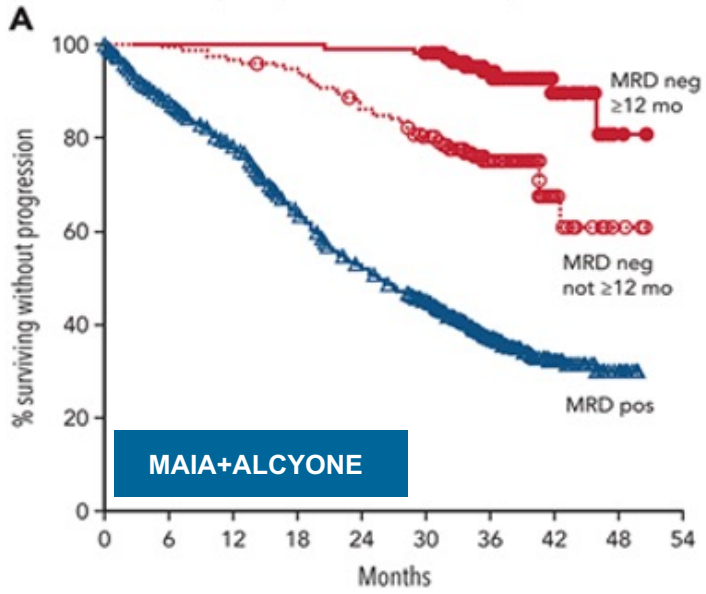
M. A. Dimopoulos[1], P. Moreau[2], E. Terpos[1], M. V. Mateos[3], S. Zweegman[4], G. Cook[5], M. Delforge[6], R. Hájek[7], F. Schjesvold[8,9], M. Cavo[10], H. Goldschmidt[11], T. Facon[12], H. Einsele[13], M. Boccadoro[14], J. San-Miguel[15], P. Sonneveld[16] & U. Mey[17], on behalf of the EHA Guidelines Committee* and ESMO Guidelines Committee*



Treatment endpoints

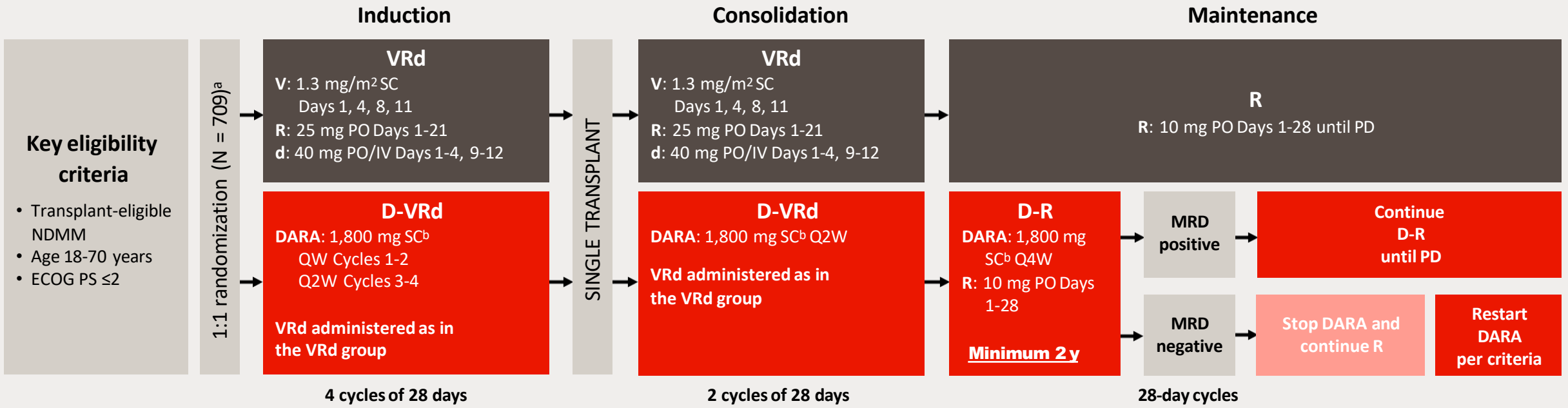
- **To maximize the rate of undetectable MRD**
- **To sustain MRD negativity**
- To prolong PFS/OS, offering a chance of cure (to a fraction of patients)
- To inform clinical decisions and tailor treatment





1. Cavo M et al, Blood 2022;139:835-44; 2. San Miguel J et al, Blood 2022;139:492-501

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

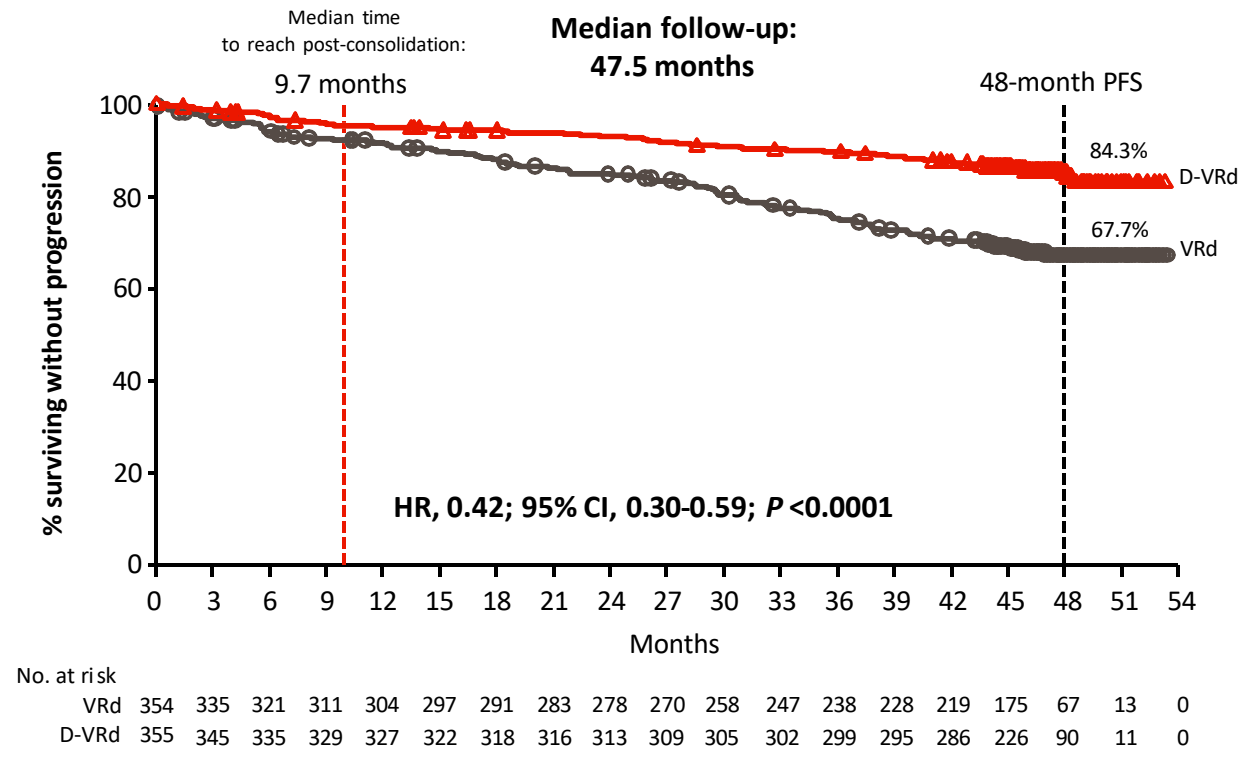
Stop DARA therapy after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity (10^{-5})

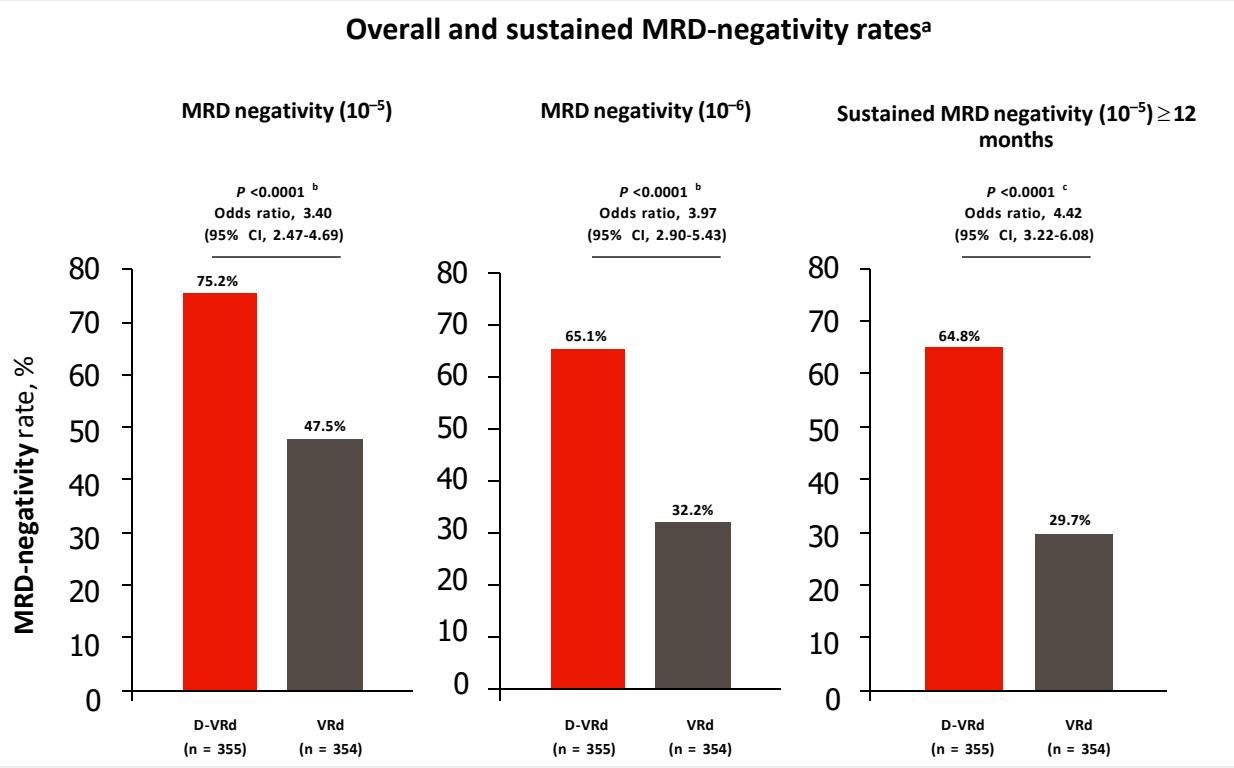
Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; . [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

PERSEUS study: improvement in PFS and MRD negativity with D-VRd followed by DR maintenance therapy





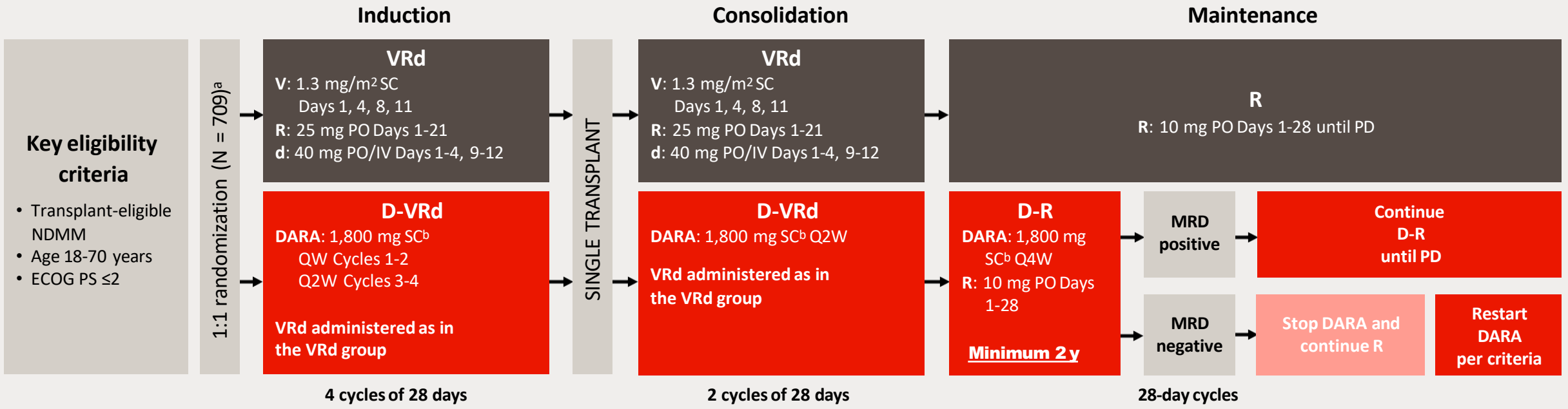
58% reduction in the risk of progression or death in patients receiving D-VRd

Deep and durable MRD negativity achieved with D-VRd

HR, hazard ratio; CI, confidence interval. [a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]*P* values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test.
[c]*P* value was calculated with the use of Fisher's exact test.

1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

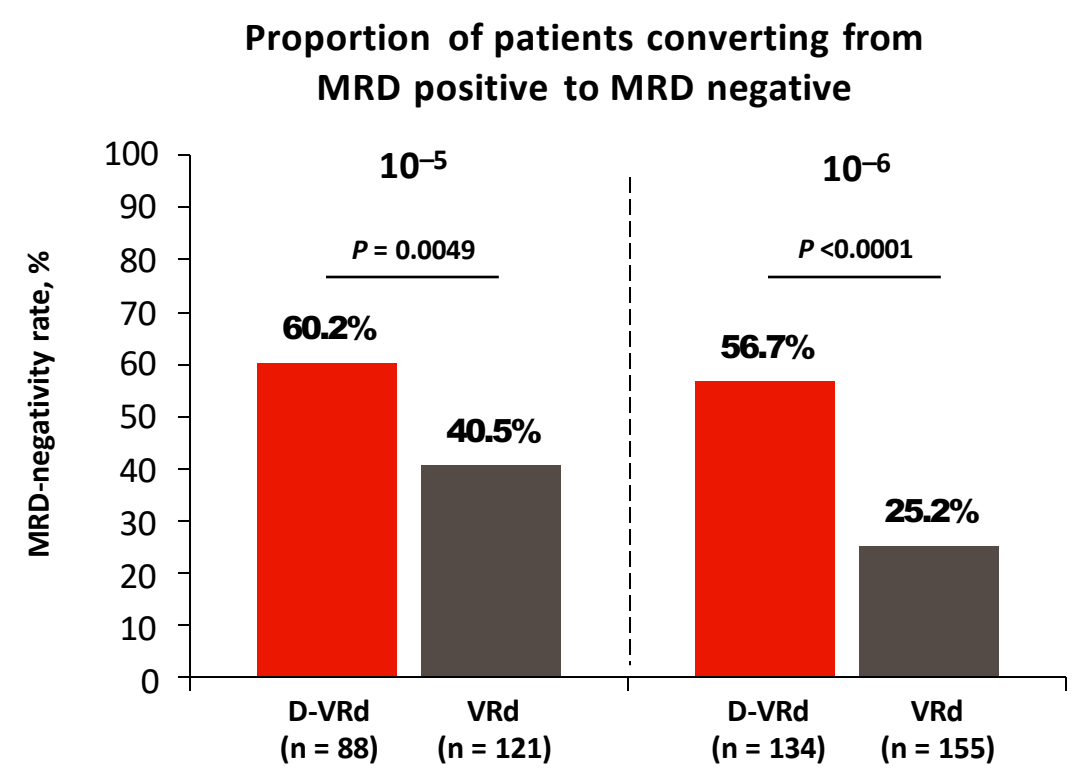
Stop DARA therapy after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity (10^{-5})

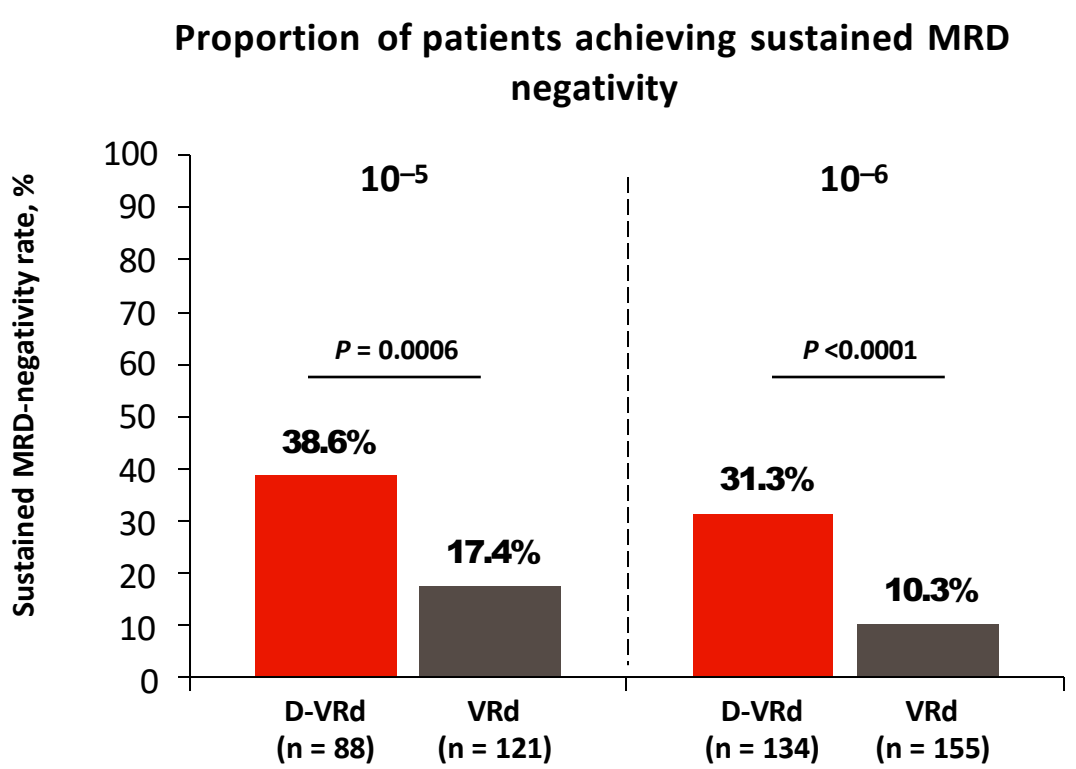
Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; . [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

PERSEUS study: MRD conversion rate during maintenance therapy for MRD positive patients after consolidation

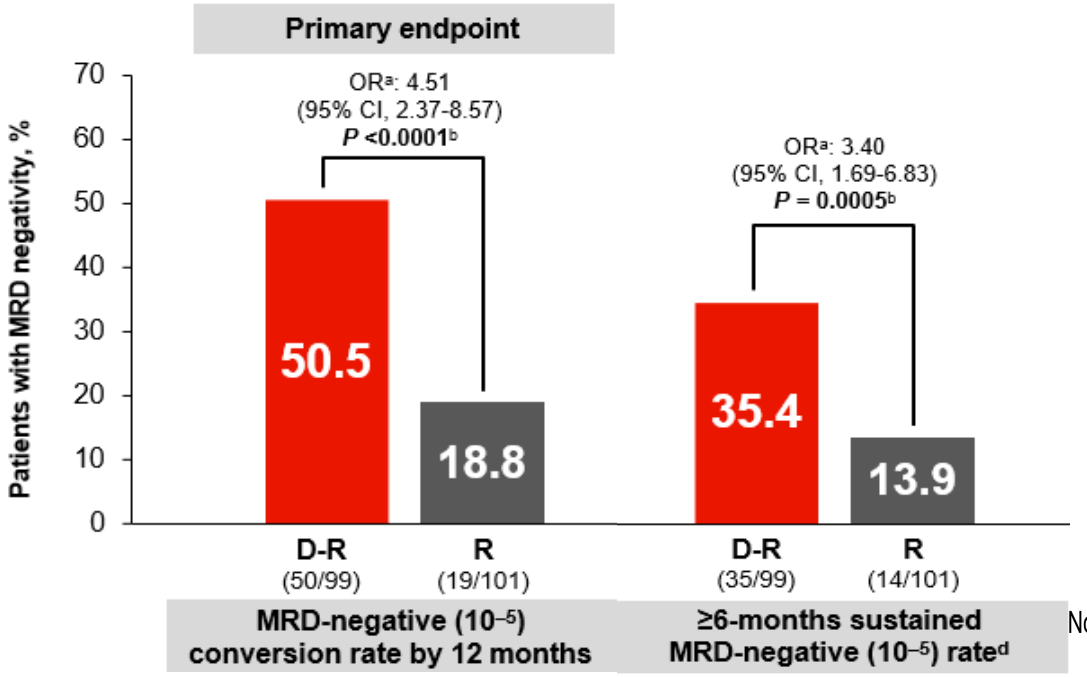


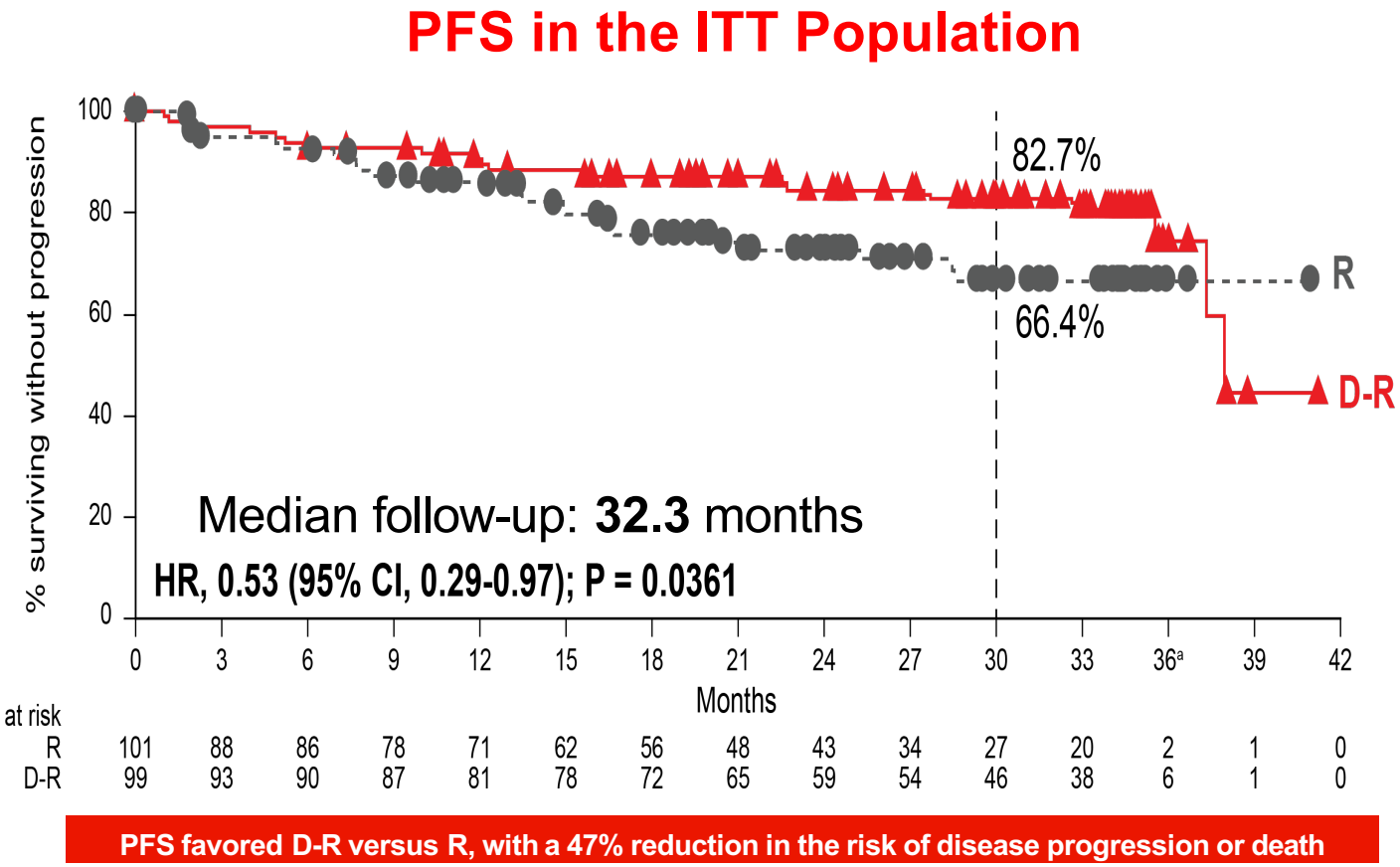


During maintenance, conversion to MRD negativity (10^{-6}) was doubled, and conversion to sustained MRD negativity was tripled, with D-R versus R

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. *P* values were calculated using the unstratified Cochran–Mantel–Haenszel chi-square test.

AURIGA study: increased MRD conversion rate and sustained MRD negativity during maintenance therapy

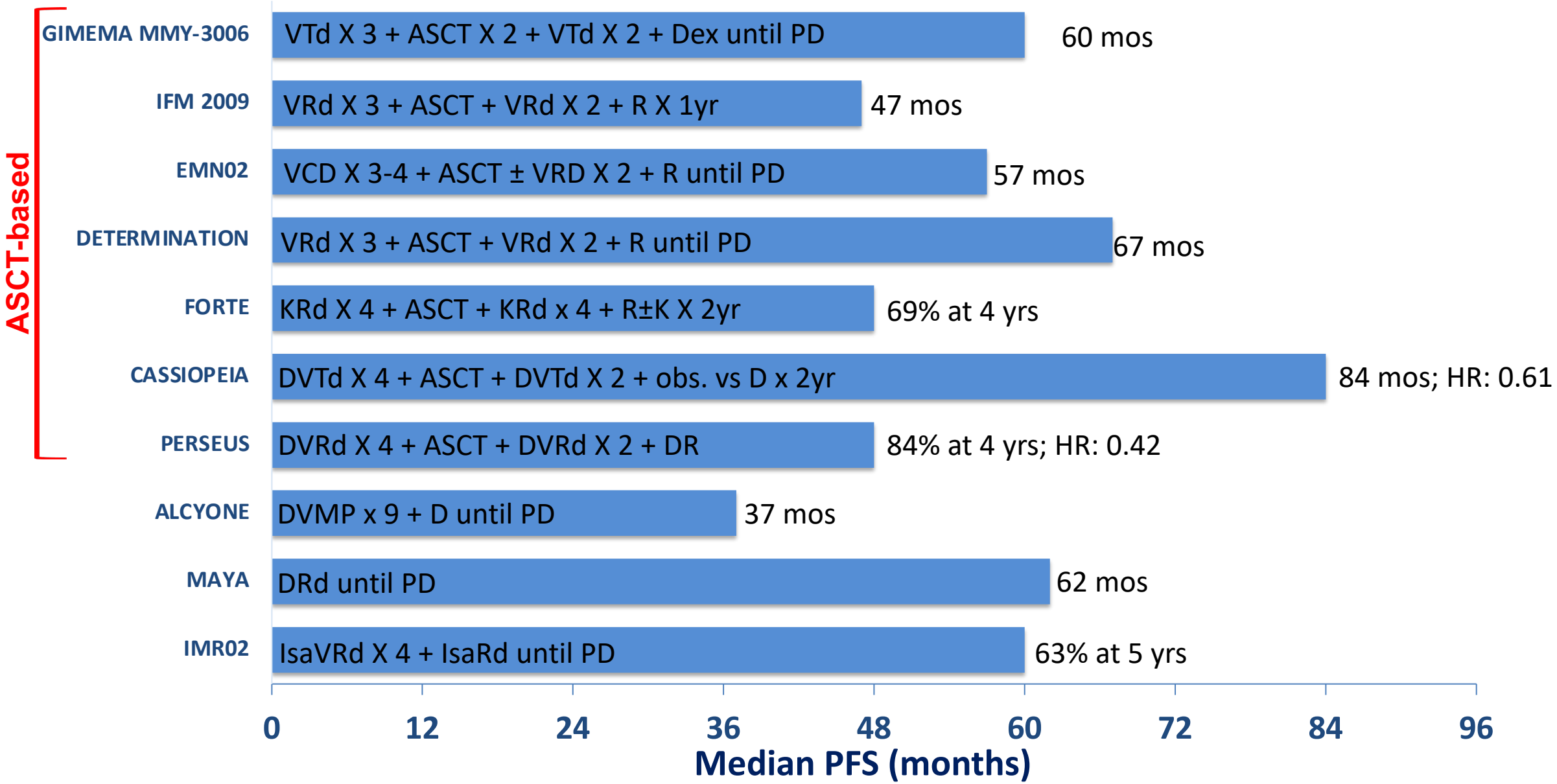




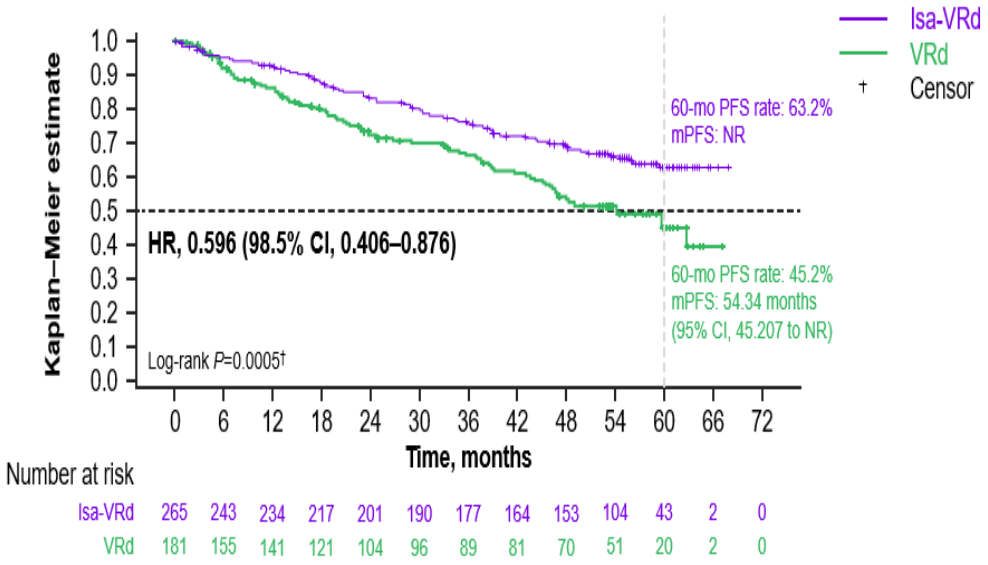
PFS favored D-R versus R, with a 47% reduction in the risk of disease progression or death

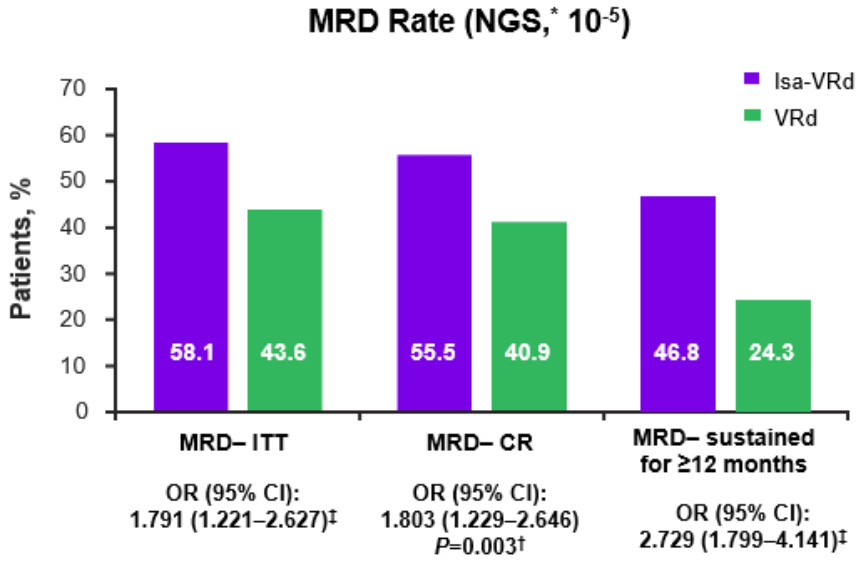
Badros A, IMS 2024

Progressive improvement in PFS with triplets or quadruplets w/wo ASCT for NDMM

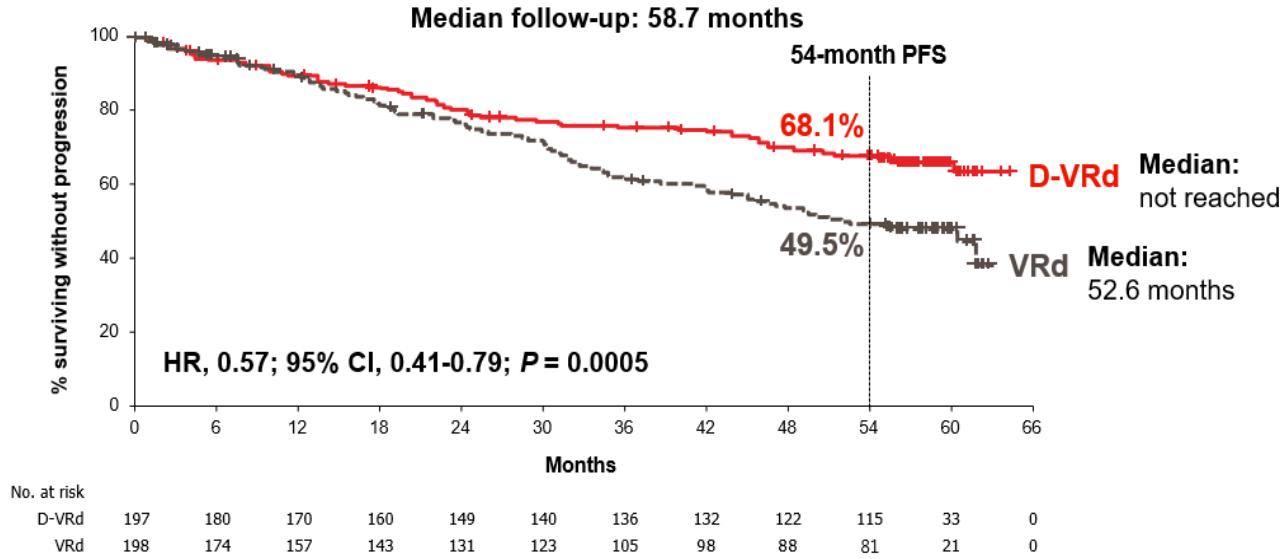


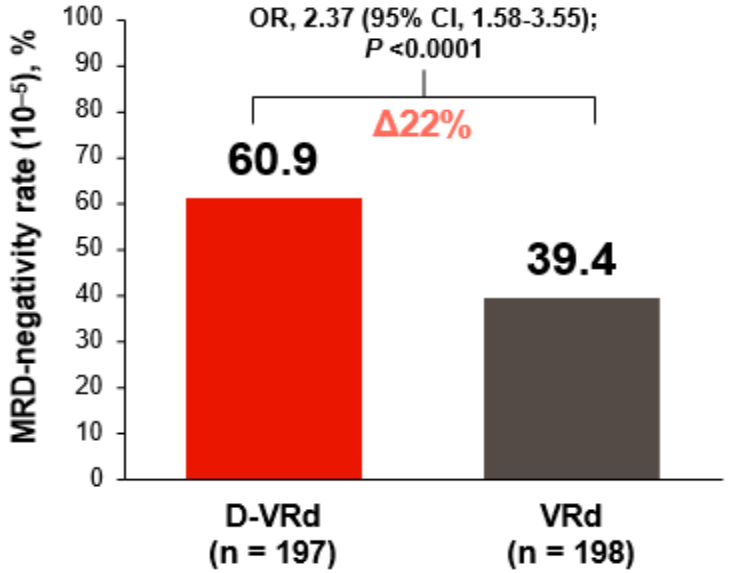
IMROZ: PFS with Isa-VRd vs VRd at a median follow-up of 5 years





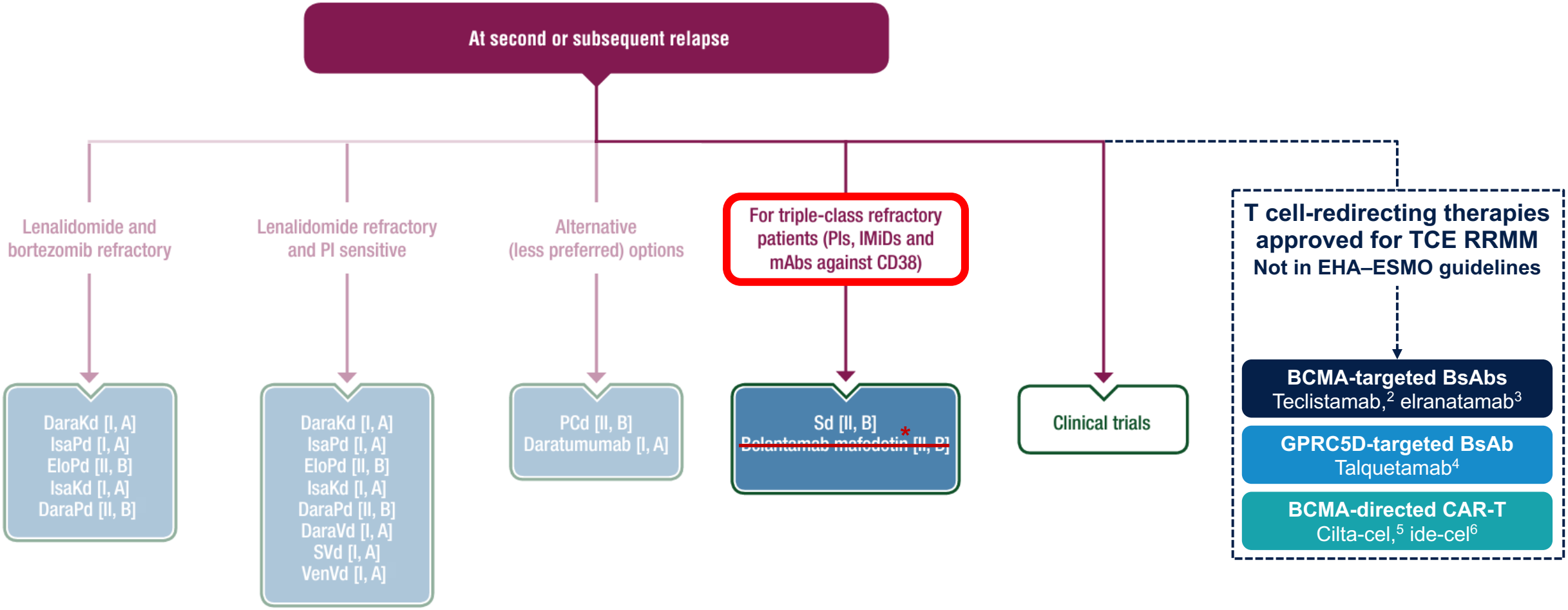
CEPHEUS: PFS with DVRd vs VRd at a median follow-up of ~ 5 years





1. Facon T et al. EHA 2024 P968 2. Usmani SZ, IMS 2024

Treatment options approved for TCE RRMM[1–6] after the EHA-ESMO guidelines

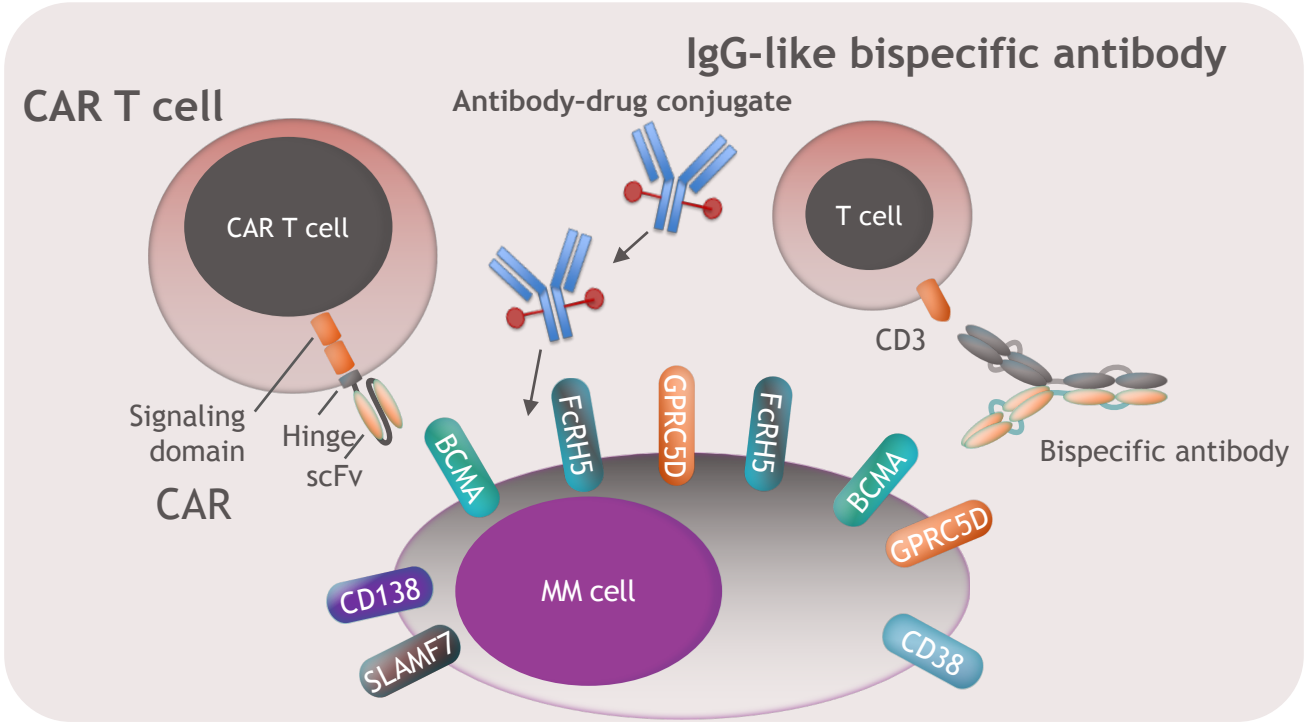


*Following a re-examination, the CHMP has confirmed its initial recommendation to not renew the conditional marketing authorisation for Blenrep (belantamab mafodotin), a medicine used to treat multiple myeloma.[7]

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; C, cyclophosphamide; CAR-T, chimeric antigen receptor T cell therapy; CD, cluster of differentiation; CHMP, Committee for Medicinal Products for Human Use; d, dexamethasone; Dara, daratumumab; EHA, European Hematology Association; Elo, elotuzumab; ESMO, European Society for Medical Oncology; GPRC5D, G protein–coupled receptor class C group 5 member D; IMiD, immunomodulatory drugs; Isa, isatuximab; K, carfilzomib; mAb, monoclonal antibody; P, pomalidomide; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; S, Selinexor; TCE, triple-class exposed; V, bortezomib; Ven, venetoclax.

1. Dimopoulos MA, et al. Ann Oncol 2021;32:309–322;
7. EMA. Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 11–14 December 2023. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-11-14-december-2023 (last accessed June 2024).

Targets for ADCs and T-cell redirecting therapies



BCMA

- TNF receptor superfamily member
- APRIL and BAFF are known ligands, leading to activation of the NF-κB pathway
- BCMA promotes plasma cell survival, growth, resistance to apoptosis, adhesion, and angiogenesis
- γ-secretase cleaving causes shedding of soluble BCMA
- Expressed on malignant PCs, at low levels on normal PCs, absent in non-hematological tissues

GPRC5D

- GPRC5D is a member of the G protein-coupled receptor family with an unknown function
- It is highly expressed on malignant PCs, as well as hard keratinized structures (hair shaft, nail, and central region of the tongue)

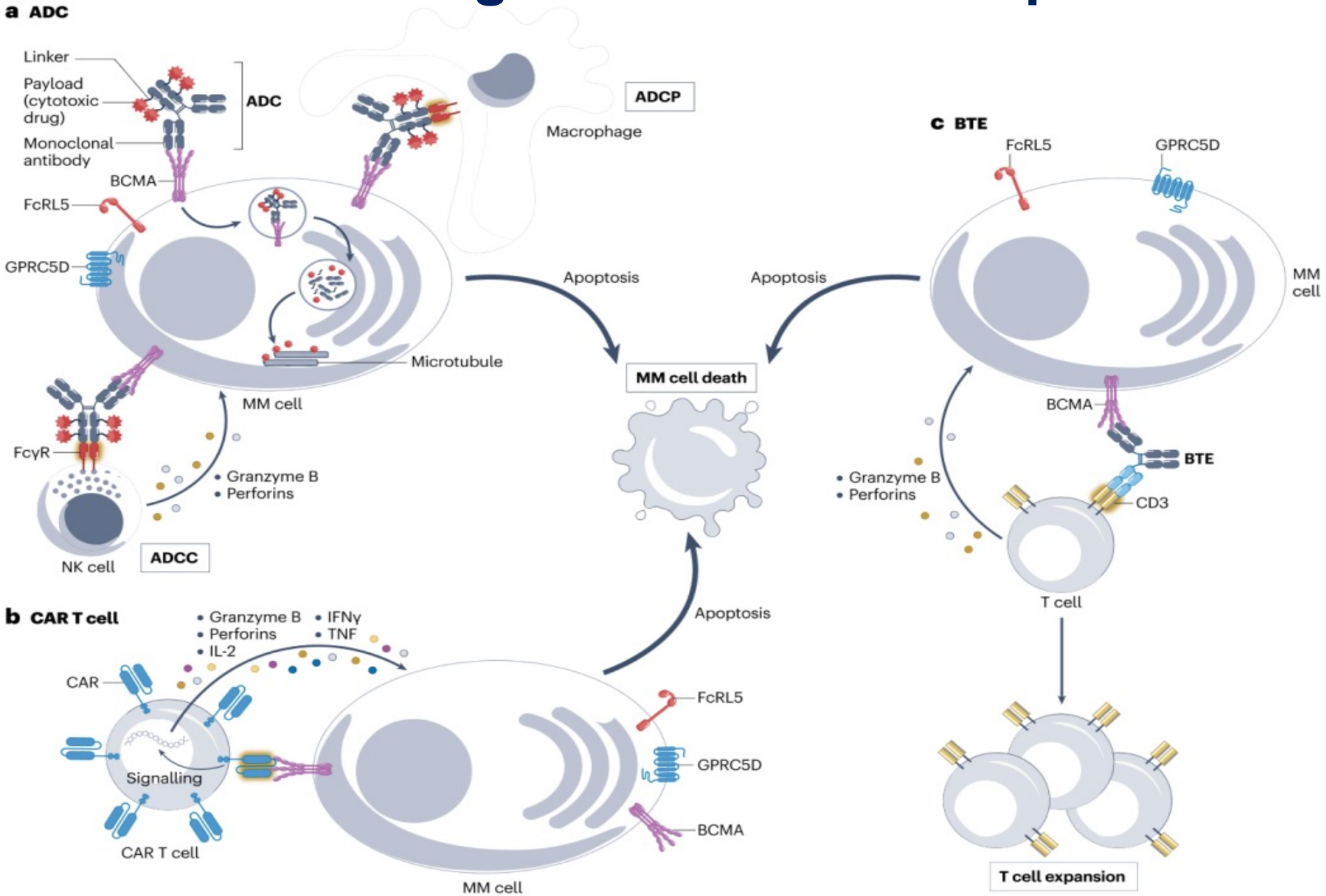
FcRH5

- FcRH5 is a surface protein in the Ig superfamily
- It is expressed only in B cells, with increasing expression in mature B cells and plasma cells
- FcRH5 is involved in proliferation and isotype expression

Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.
APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; MM, multiple myeloma; NF-κB, nuclear factor Bs; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor.

1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538-49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij CPM, et al. Blood Adv. 2020;5;2196-215. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-95. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155. 8. Lancman G, et al. Blood Cancer Discov. 2021;2:423-33.

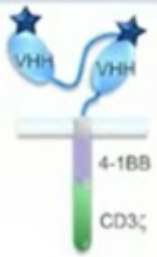
MoA of novel targeted immunotherapies in MM

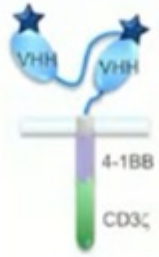


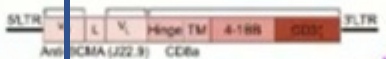
Neri P et al, Nat Rev Clin Oncol. 2024 Aug;21(8):590-609

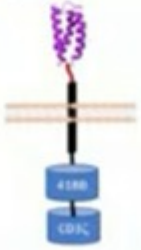
BCMA-targeting CAR-T cells

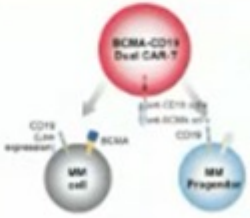
	EMA-approved				Academic	Alternative construct	Dual target	T-charge	Allo-CAR
	Ide-cel KarMMa[1] (n = 196)	Cilta-cel CARTITUDE-1[2] (n = 97)	Ide-cel KarMMa-3[3] (n = 254)	Cilta-cel CARTITUDE-4[4] (n =208)	ARI0002h[5] (n = 30)	CART-ddBCMA[6] (n = 31)	FasT CAR-T GC012F[7] (n=29)	PHE885[8] (n= 50)	ALLO-715 UNIVERSAL[9] (n = 43)
Phase	II	Ib/II	III	III	I/II	I/II	I	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA/CD19	BCMA	BCMA
scFv	Chimeric mouse	Chimeric llama	Chimeric mouse	Chimeric llama	Humanized	Synthetic protein	Not specified	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	NA	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Allogenic

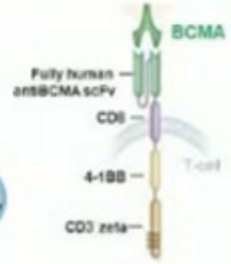


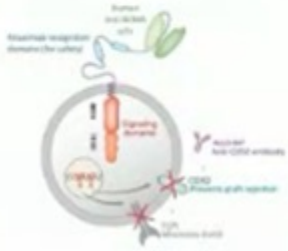












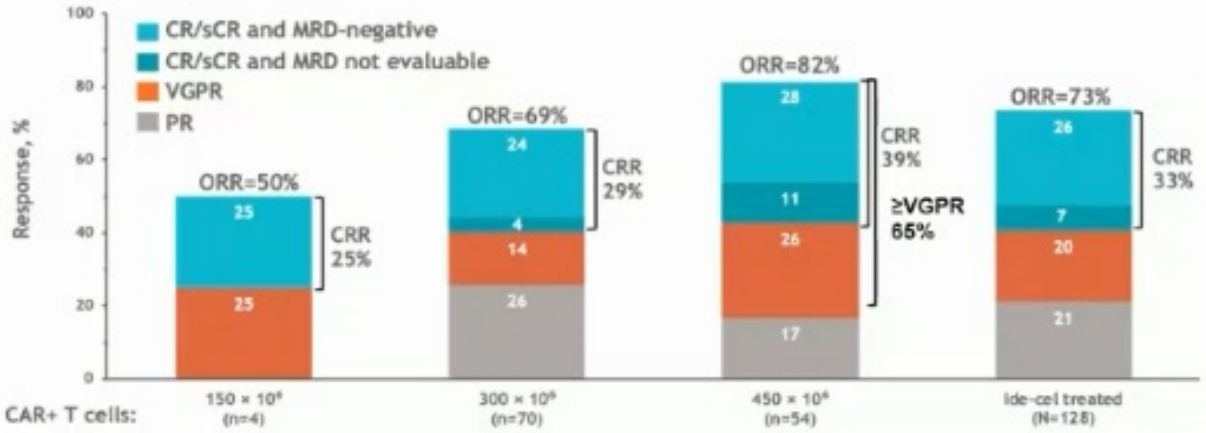
1. Munshi N, et al. ASCO 2020; 2. Usmani S, et al. ASCO 2022; 3. Rodrigues Otero, EBMT 2023; 4. Einsele H, et al. ASCO 2023; 5. Fernández de Larrea C, et al. EHA 2022; 6. Frigault MJ, et al. ASCO 2022; 7. Li C, et al. EHA 2022; 7. Du J, et al. ASCO 2022; 8. Sperling et al. ASCO 2023; 9. Huang H, et al. ASCO 2022;

Ide-cel approval: the KarMMa trial

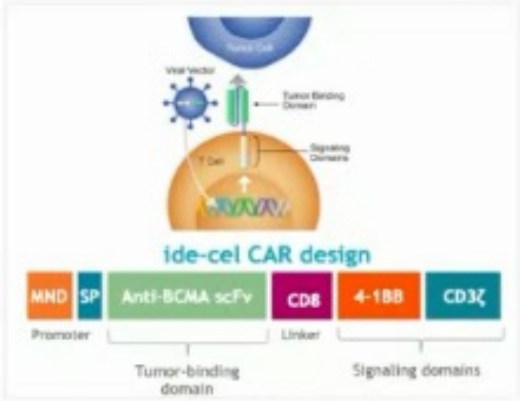
FDA approved in 2021
EMA approved in 2021

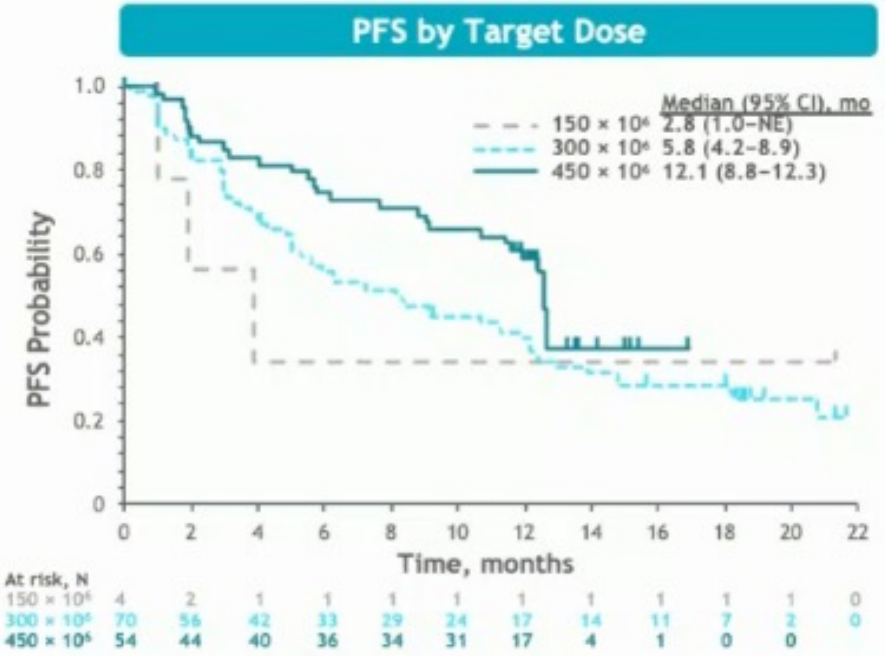
Second generation CAR-T cell, anti-BCMA murine scFv, 4-1BB costimulatory domain

KarMMa, phase 2 study (N = 128)		
Median prior lines: 6 (3–16)	84% of patients were triple-class refractory	Bridging possible Flu-Cy lymphodepletion



AE,* n (%)	Ide-Cel-Treated (N=128)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
CRS	107 (84)	7 (5)
Neurotoxicity	23 (18)	4 (3)

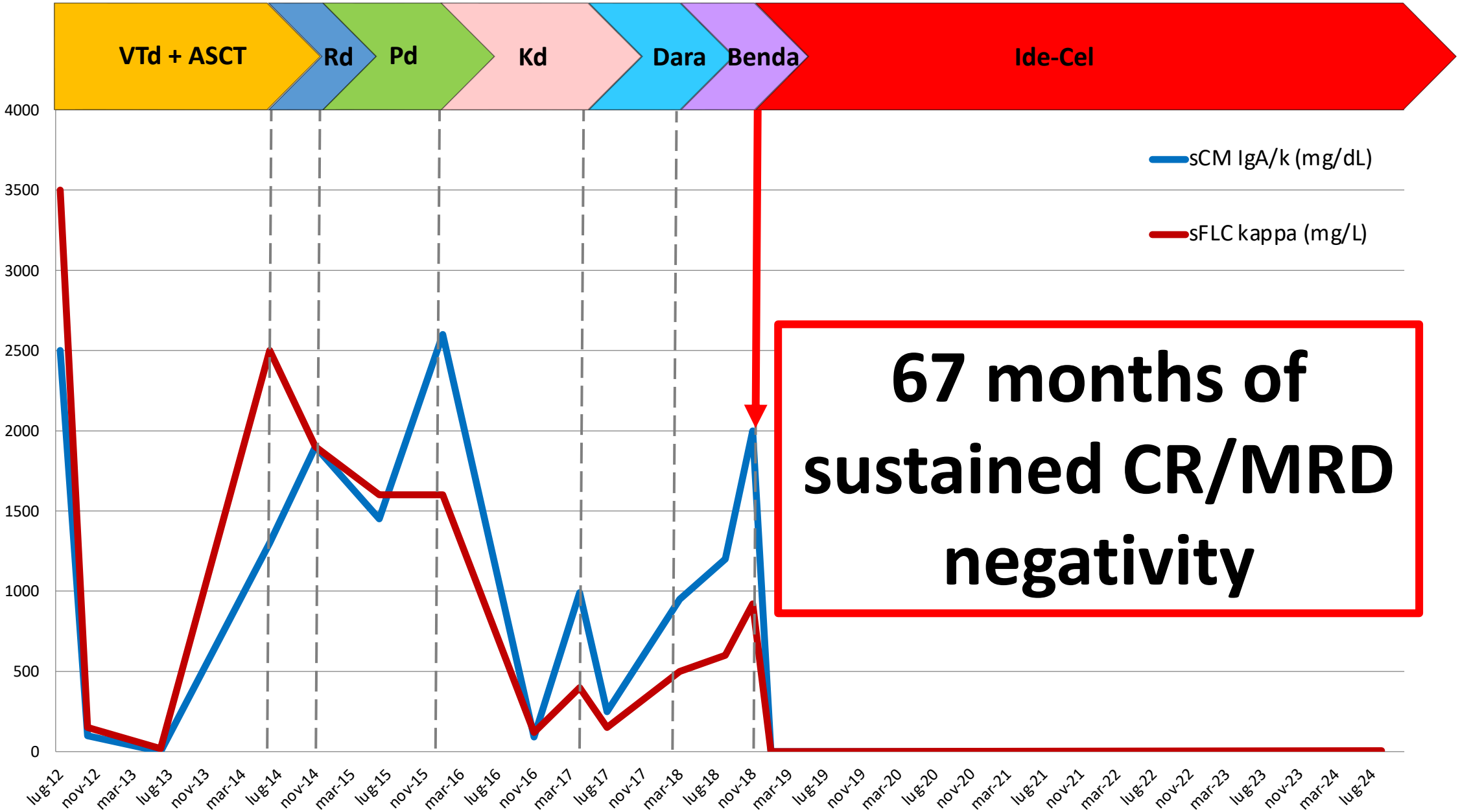




mOS = 24.8 mo

Munshi N, et al. *NEJM* 2021

First CAR-T cell therapy for RRMM in Italy (2019)

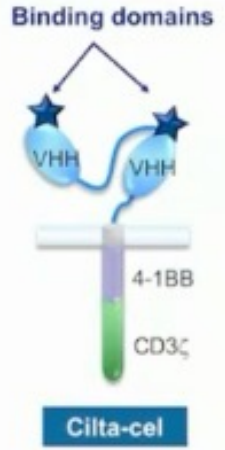


67 months of sustained CR/MRD negativity

Cilta-cel approval: the CARTITUDE-1 trial

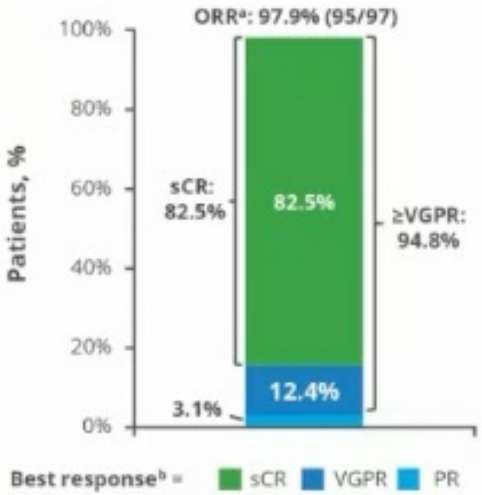
FDA approved in 2022
EMA approved in 2022

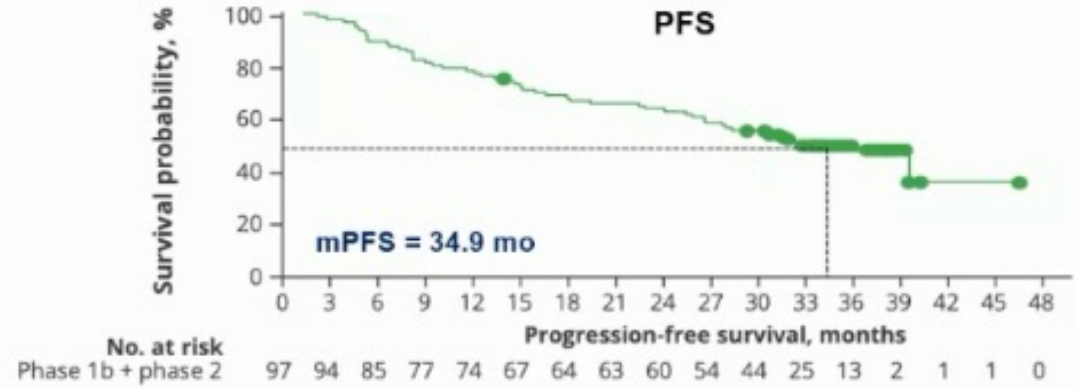
Second generation CAR-T cell, 2 anti-BCMA camelid VHH single domains, 4-1BB costimulatory domain

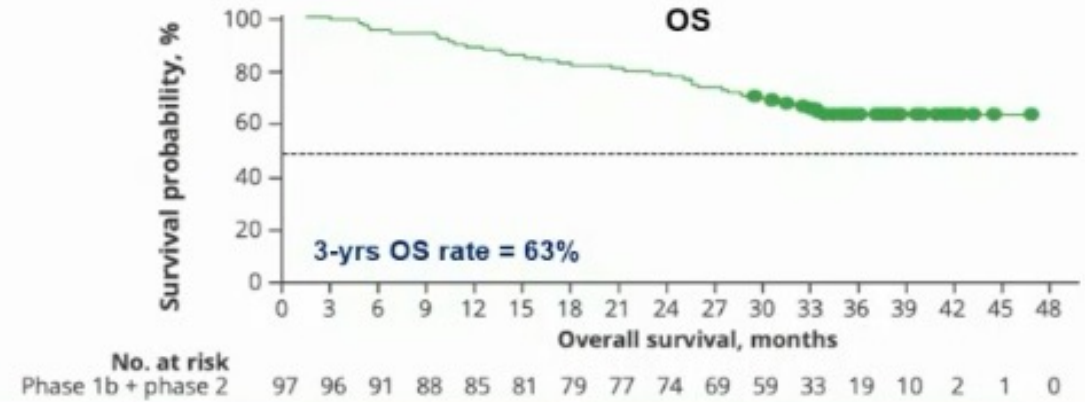


CARTITUDE-1, phase 2 study (N = 97)		
Median prior lines: 6 (3–18)	88% of patients were triple-class refractory	Bridging possible Flu-Cy lymphodepletion

12 mos-sustained MRD neg: 53%
PFS @ 30 mos: 75%



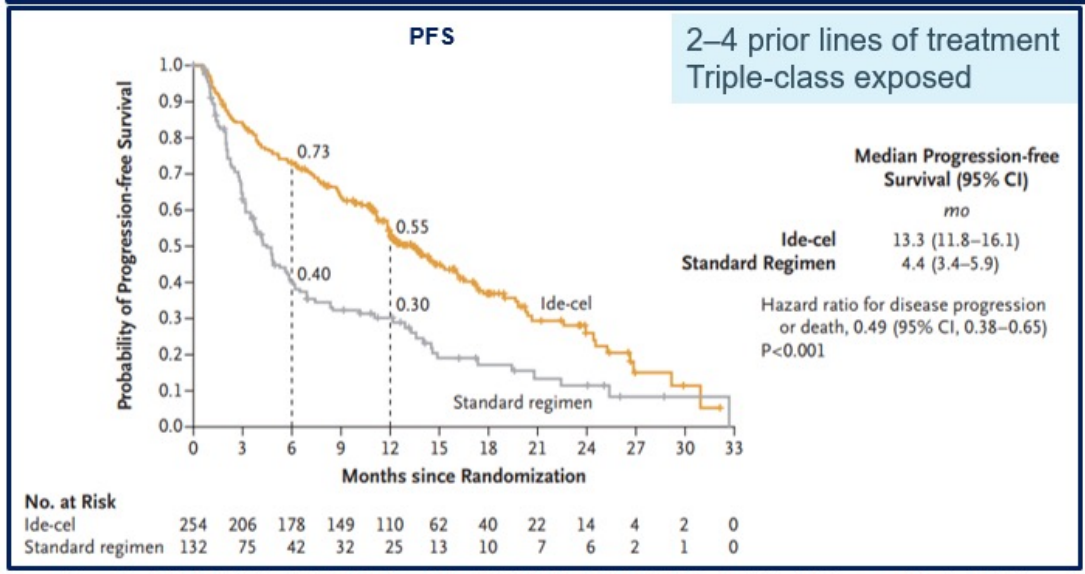


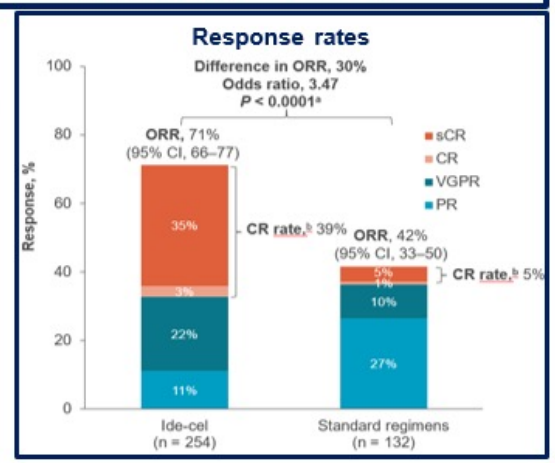


AE, n (%)	Cilta-cel-Treated (N=97)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	93 (96)	92 (95)
Anemia	79 (81)	66 (68)
Thrombocytopenia	77 (80)	58 (60)
CRS	92 (95)	6 (5)
Neurotoxicity	20 (21)	10 (10)

Berdeja J, et al. *Lancet* 2022;
Lin Y. et al. ASCO 2023

Ide-cel vs standard regimens (Dara-Vd/Dara-Pd/IRd/Kd/Elo-Pd)

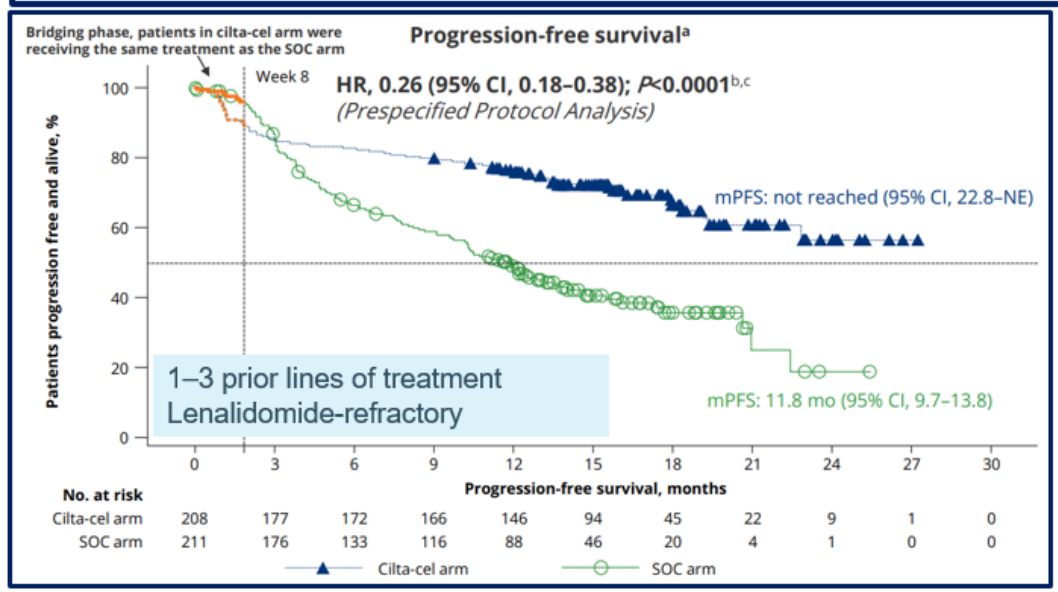


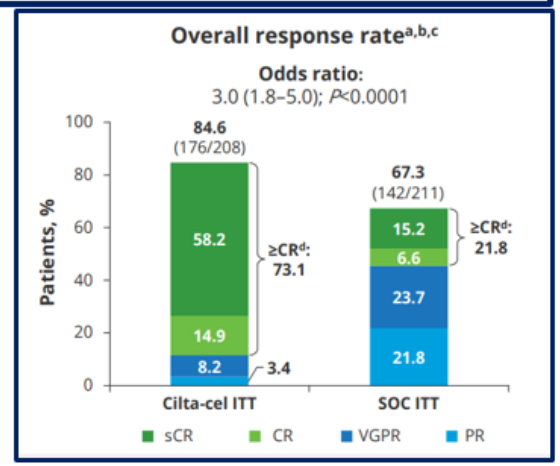


CR and MRD negative (10^{-5} by NGS)
Ide-cel: 20% (n=254; 95% CI, 15–25)
Standard regimens: 1% (n=132; 95% CI, 0–2)[3]

Rodriguez-Otero P, et al. N Engl J Med 2023:388;1002–1014; 2. Patel K, et al. EHA 2023 (Abstract No. S195 – presentation); 3. Rodriguez-Otero P, et al. N Engl J Med 2023:388;1002–1014 (Supplementary appendix).

Cilta-cel vs SoC regimens (PVd/Dara-Pd)

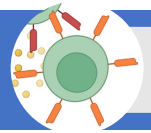




MRD negative (10^{-5} by NGS)
Cilta-cel: 87.5% (n=144)
SoC: 32.7% (n=101)

San-Miguel J, et al. N Engl J Med 2023:389;335–347; 2. Dhakal B, et al. ASCO 2023 (Abstract No. LBA106 – presentation).

EMA-approved CAR T and BsAbs for RRMM



CAR T cell therapy

Bispecific antibodies

Ide-cel[1,2]

- **Target: BCMA**

Cilta-cel[3,4]

- **Target: BCMA**

First approval (both, 2021 and 2022)

- Adult patients with RRMM who have received **≥ 3 prior LoT**, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

Expanded indication (both, 2024)

- Ide-cel: adult patients with RRMM who have received **≥ 2 prior LoT**, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
- Cilta-cel: adult patients with RRMM who have received **≥1 prior LoT** including an IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide

Teclistamab[5,6]

- Target: BCMA x CD3

Talquetamab[9,10]

- Target: GPRC5D x CD3

Elranatamab[7,8]

- Target: BCMA x CD3

Approval status (all)

- EU: adult patients with RRMM who have received ≥ 3 prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 384;8 NEJM.ORG FEBRUARY 25, 2021

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocca, M.D., Monica Massaro, M.P.H., Jamie N. Connarn, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 388;11 NEJM.ORG MARCH 16, 2023

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu, J. Piasecki, M. Cook, and S. Giralt

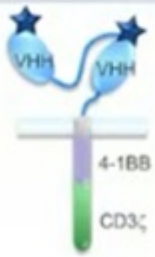
The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 389;4 NEJM.ORG JULY 27, 2023

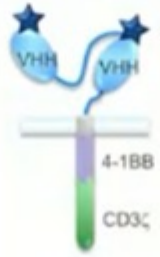
Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

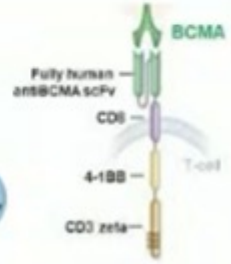
J. San-Miguel, B. Dhakal, K. Yong, A. Spencer, S. Anguille, M.-V. Mateos, C. Fernández de Larrea, J. Martínez-López, P. Moreau, C. Touzeau, X. Leleu, I. Avivi, M. Cavo, T. Ishida, S.J. Kim, W. Roeloffzen, N.W.C.J. van de Donk, D. Dytfeld, S. Sidana, L.J. Costa, A. Oriol, R. Popat, A.M. Khan, Y.C. Cohen, P.J. Ho, J. Griffin, N. Lendvai, C. Lonardi, A. Slaughter, J.M. Schecter, C.C. Jackson, K. Connors, K. Li, E. Zudaire, D. Chen, J. Gilbert, T. Yeh, S. Nagle, E. Florendo, L. Pacaud, N. Patel, S.J. Harrison, and H. Einsele

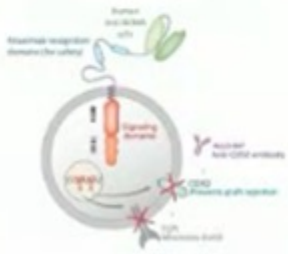
BCMA-targeting CAR-T cells

	EMA-approved				Academic	Alternative construct	Dual target	T-charge	Allo-CAR
	Ide-cel KarMMa[1] (n = 196)	Cilta-cel CARTITUDE-1[2] (n = 97)	Ide-cel KarMMa-3[3] (n = 254)	Cilta-cel CARTITUDE-4[4] (n =208)	ARI0002h[5] (n = 30)	CART-ddBCMA[6] (n = 31)	FasT CAR-T GC012F[7] (n=29)	PHE885[8] (n= 50)	ALLO-715 UNIVERSAL[9] (n = 43)
Phase	II	Ib/II	III	III	I/II	I/II	I	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA/CD19	BCMA	BCMA
scFv	Chimeric mouse	Chimeric llama	Chimeric mouse	Chimeric llama	Humanized	Synthetic protein	Not specified	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	NA	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Allogenic





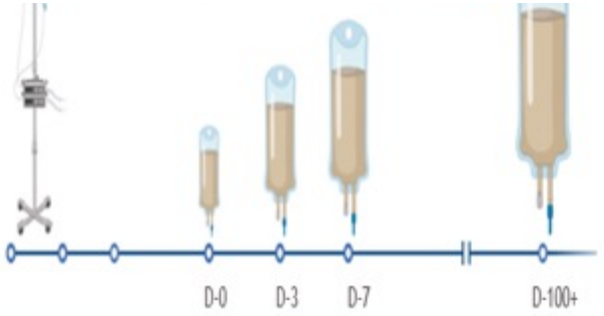




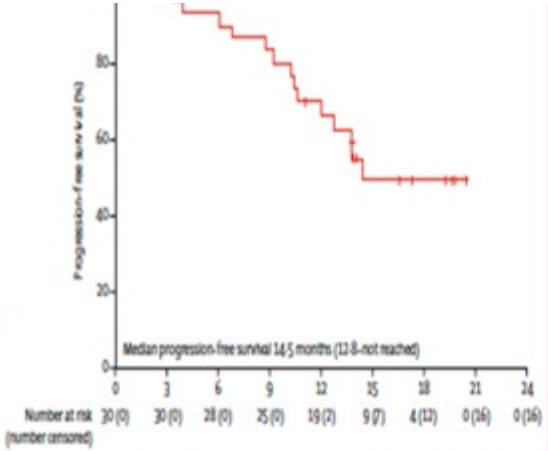
1. Munshi N, et al. ASCO 2020; 2. Usmani S, et al. ASCO 2022; 3. Rodrigues Otero, EBMT 2023; 4. Einsele H, et al. ASCO 2023; 5. Fernández de Larrea C, et al. EHA 2022; 6. Frigault MJ, et al. ASCO 2022; 7. Li C, et al. EHA 2022; 7. Du J, et al. ASCO 2022; 8. Sperling et al. ASCO 2023; 9. Huang H, et al. ASCO 2022;

Alternative constructs, manufacturing processes, and enginereed cells

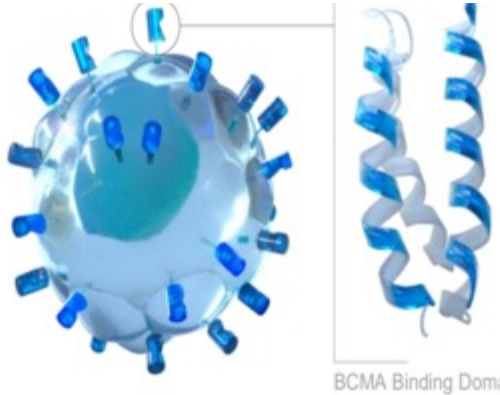
ARI0002h Cesni-cel

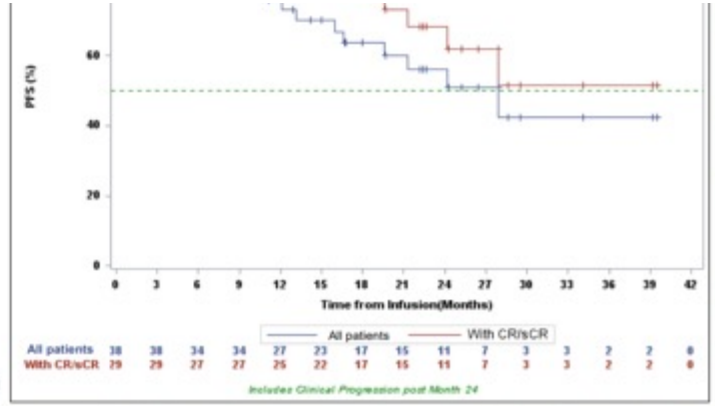


- Manufacturing process: 10 days.
- Median time from apheresis reception to product release: 30 d (range 19–45)



Anito-cel

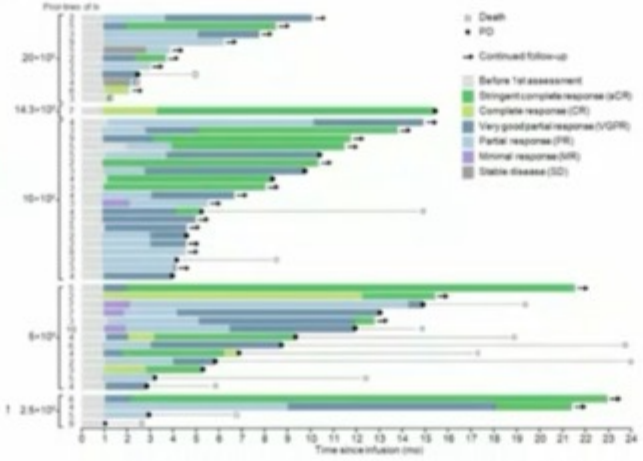




Friqault MJ, et al, ASH 2023

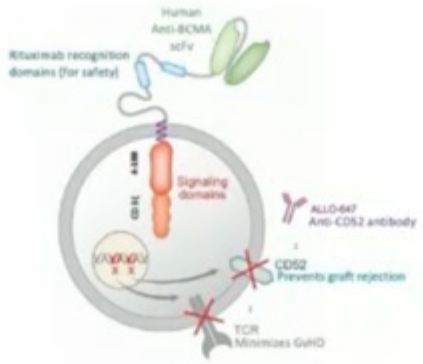
Short manufacturing: PHE885 Durca-cel

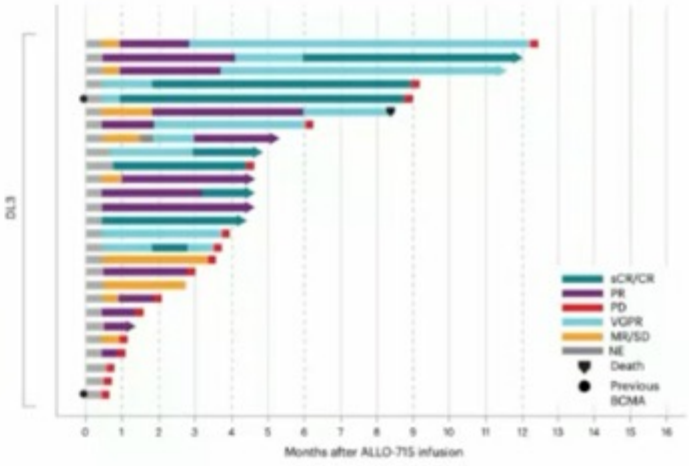
T-Charge platform
- <2 days manufacturing
- Preserves T stemness
- Enhances *in vivo* expansion



Sperling et al. ASCO 2023

Allo-CAR-T cells: ALLO-715





Mailankody et al. *Nat Med* 2022

Monovalent and bivalent IgG-like BsAbs

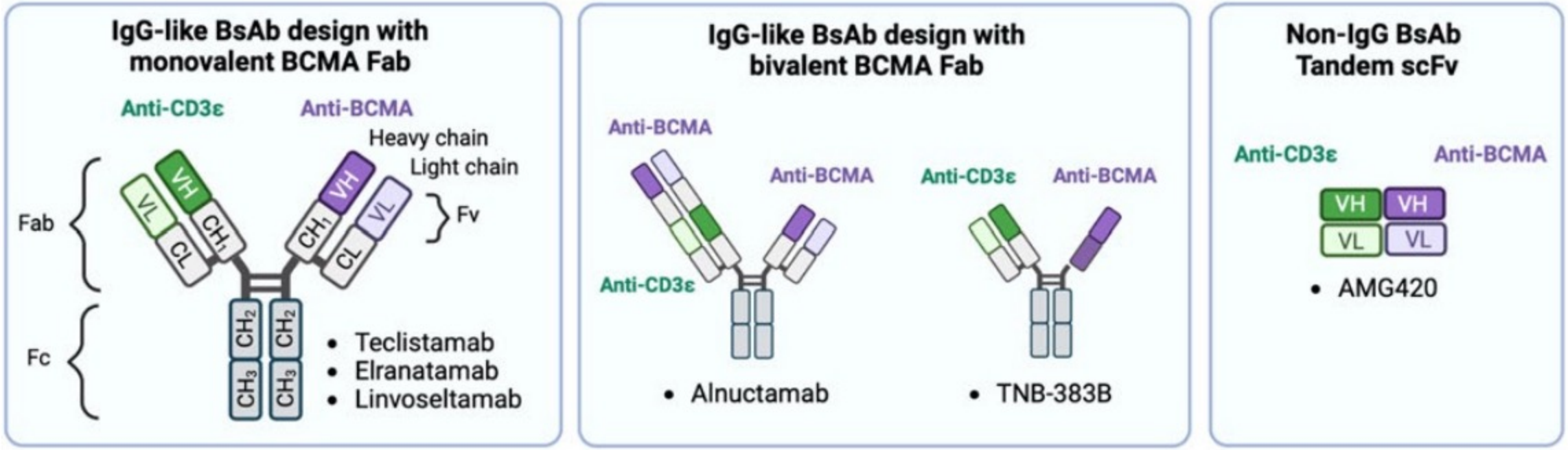


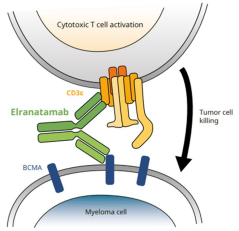
Figure 1. Structure of anti-BCMA bispecific antibodies. Anti-BCMA BsAb can be classified into immunoglobulin G (IgG)-like and non-IgG-like based on their structures. IgG-like BsAb consist of antibody binding fragments (Fab) which recognize target antigens, and a crystallizable fragment (Fc). In addition to having one Fab targeting CD3 (anti-CD3ε), BsAb with monovalent BCMA Fab consists of one Fab targeting BCMA (anti-BCMA). BsAb with bivalent BCMA Fabs are designed with either two anti-BCMA Fabs or two anti-BCMA variable domain of heavy chains (VH). Non-IgG BsAb, AMG420, is synthesized as tandem single chain Fvs and lacks Fc. CH, constant domain of heavy chain; CL, constant domain of light chain; Fv, variable fragment; VL, variable domain of light chain.

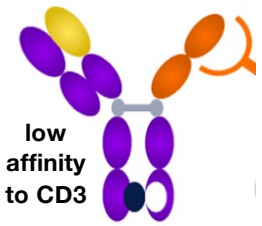
Lee H et al, Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):332-339

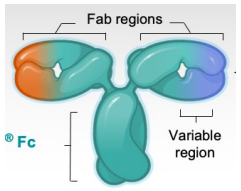
BCMA-targeting BsAbs

EMA approved | bivalent domain | IV infusion | CD3 low affinity

	Teclistamab MajesTEC-1[1] (n=165)	Elranatamab Magnetismm3[2] (n=123)	Alnuctamab[5] CC-93269 (n=68)	ABBV-383B[3] (n=118)	Linvoseltamab LINKER-MM1[4] (n=117)	REGN5459[6] (n=43)
Phase	I/II	I/II	I/II	I	II	I/II
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3
scFv	Humanized	Humanized	Humanized	Human	Human	Human
Ig	IgG4	IgG2a	IgG1-based	IgG4	IgG4	IgG4
Administration	SC	SC	SC	IV	IV	IV
# prior lines	5 (2-14)	5 (2-12)	4 (3-11)	5 (1-15)	5 (2-14)	5 (2-9)
Age	64 (33-84)	69 (44-89)	64 (36-79)	68 (35-88)	70 (37-91)	67 (26-85)





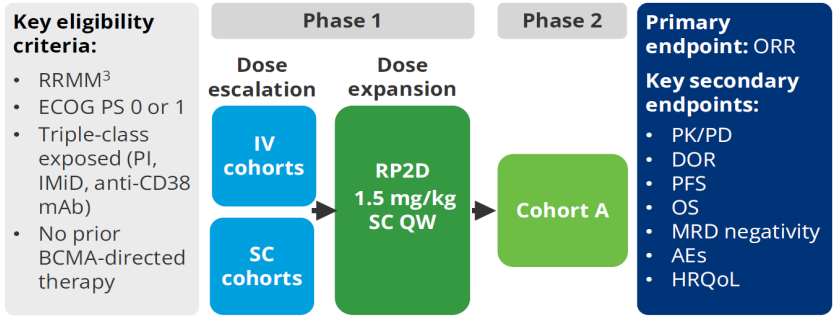


[1] Nooka et al. ASCO 2022; [2] Bahlis et al. ASH 2022; [3] Voorhees et al. IMS 2022; [4] Hans L. et al. ASCO 2023; [5] Wong et al. ASH 2019; [6] Suvannasankha et al. AACR 2023

BCMA × CD3 T-Cell bispecific antibody: Teclistamab MajesTEC-1, Phase Ib/II study[1]

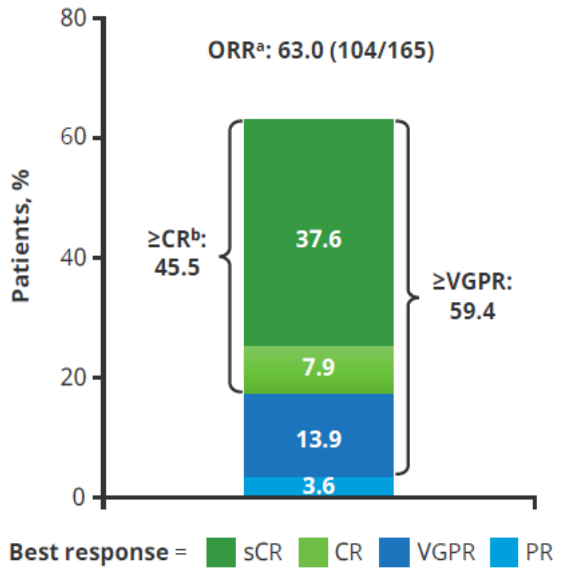
FDA/EMA approved

Trial design and dosing schedule[1]



Teclistamab dosing schedule: QW; option to **switch to Q2W*** after ≥4 cycles (Phase I) if ≥PR or **after ≥CR (Phase II) sustained for at least 6 months**[2]

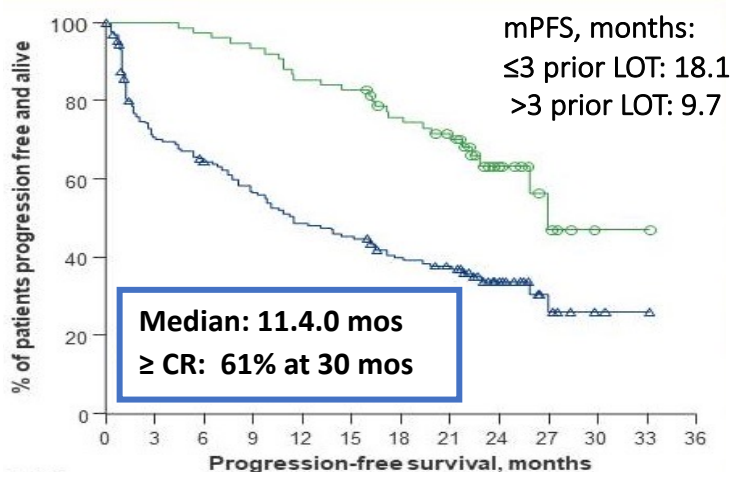
Response rates[1]



Median to first response: 1.2 mos[1]
Median to ≥CR: 4.6 mos[1]

MRD-neg. rate (10^{-5}): 27%[1]
MRD-evaluable/MRD neg: 85.7%

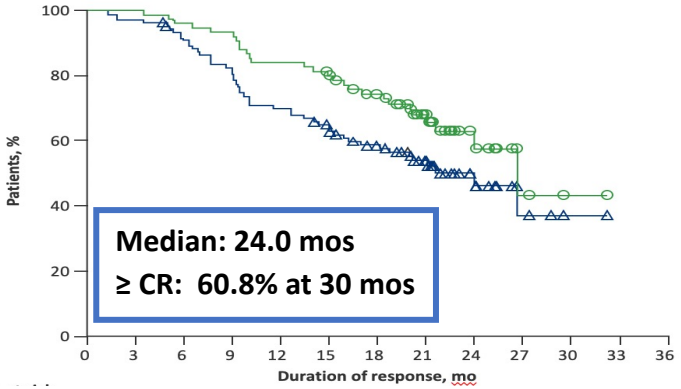
Progression-free survival[1]



Baseline characteristics, N=165[1]

Extramedullary disease,[†] n (%)	28 (17.0)
High-risk cytogenetics, n (%)	38 (25.7)
ISS stage III, n (%)	20 (12.3)
Prior lines of therapy, median (range)	**5 (2–14)**
Refractory status, n (%)	
Triple-class refractory	**128 (77.6)**
Penta-drug refractory	50 (30.3)

Duration of response[1]



*Patients could further switch to monthly dosing if they demonstrated continued response on the Q2W schedule; †Includes patients who had ≥1 soft tissue plasmacytoma not associated with bone; [a]ORR assessed by independent review committee; [b]For the Phase II efficacy population (patients enrolled in cohort A on or before March 18, 2021), ≥CR rate was 46.4% (51/110).

AE, adverse event; BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, heatlh-related quality of life; IMiD, immunomodulatory agent; IV, intravenous; LOT, line of therapy; (m)PFS, (median) progression-free survival; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhiitor; PK, pharmacokinetic; PR, partial response; PS, performance status; Q2W, every 2 weeks; QW, weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

1. Van de Donk NWCJ, et al. ASCO 2023 (Abstract No. 8011 – presentation); 2. Press release, August 2023. Available at: https://www.jnj.com/european-commission-approves-reduced-dosing-frequency-for-janssens-bispecific-antibody-tecvayli-teclistamab#:~:text=BEERSE%2C%20Belgium%2C%2018%20August%202023,kg%20every%20two%20weeks%20in (last accessed September 2023).

BCMA × CD3 T-cell bispecific antibody: Elranatamab MagnetisMM-3 phase 2 study[1]

FDA/EMA approved

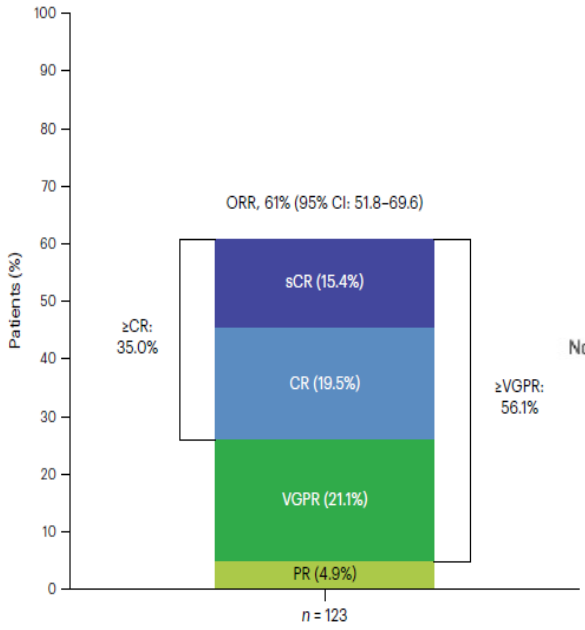
Elranatamab dosing schedule[1]

QW cycles 1–6; **Q2W cycles 7+ for patients with ≥PR**

Baseline characteristics, Cohort A (N=123)[1]

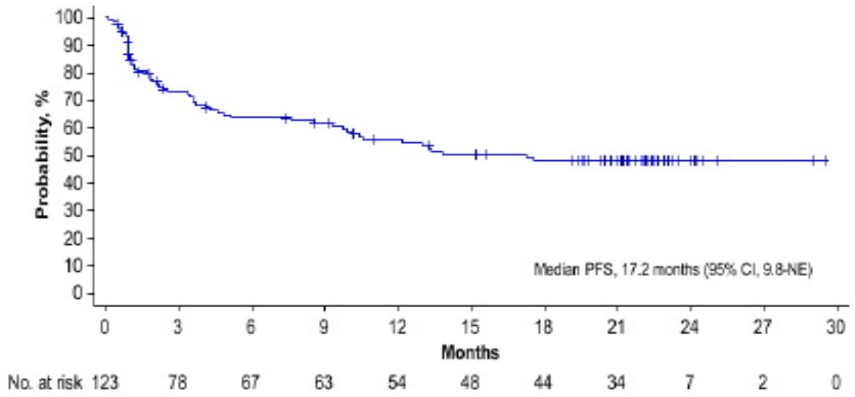
Extramedullary disease by BICR,[†] n (%)	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
Prior lines of therapy, median (range)	**5 (2–22)**
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class	123 (100.0)
Penta-drug	87 (70.7)
Refractory status, n (%)	
Triple-class refractory	**119 (96.7)**
Penta-drug refractory	52 (42.3)
Refractory to last line of therapy, n (%)	118 (95.9)

Response rates[1]

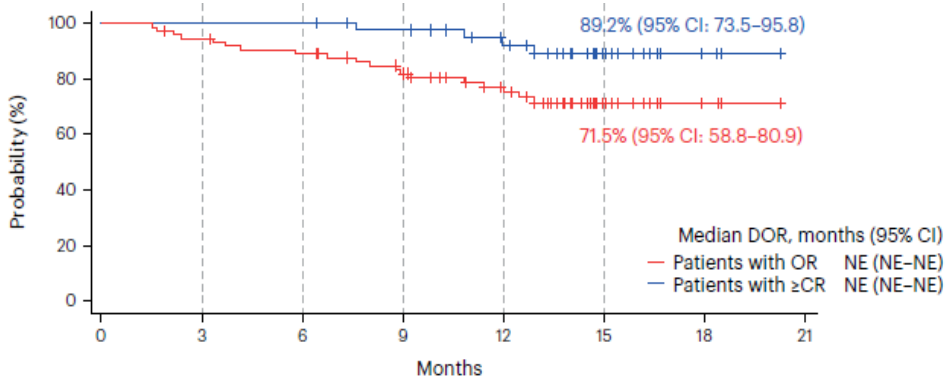


Median time to first response: 1.2 months[1]
Median time to ≥CR: 6.1 months[1]

Progression-free survival[1]



Duration of response[1]

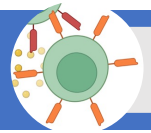


[d]Extramedullary disease was defined as presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component.

BCMA, B-cell maturation antigen; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; QW, weekly; VGPR, very good partial response.

1. Lesokhin AM, et al. Nat Med 2023; doi: 10.1038/s41591-023-02528-9. Online ahead of print. 2. 4th EMN Meeting, 2024

EMA-approved CAR T and BsAbs for RRMM



CAR T cell therapy

Bispecific antibodies

Ide-cel[1,2]

- Target: BCMA

Cilta-cel[3,4]

- Target: BCMA

First approval (ide-cel in 2021; cilta-cel in 2022)

- Adult patients with RRMM who have received ≥ 3 prior LoT, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

Expanded indication (both, 2024)

- Ide-cel: adult patients with RRMM who have received ≥ 2 prior LoT, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
- Cilta-cel: adult patients with RRMM who have received ≥1 prior LoT including an IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide

Teclistamab[5,6]

- **Target: BCMA x CD3**

Talquetamab[9,10]

- **Target: GPRC5D x CD3**

Elranatamab[7,8]

- **Target: BCMA x CD3**

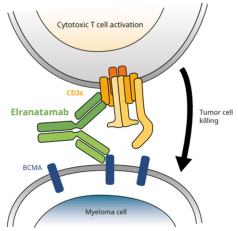
Approval status (all)

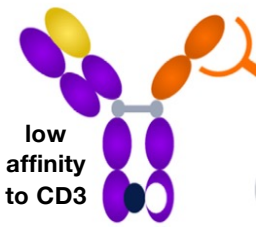
- EU: adult patients with RRMM who have received **≥ 3 prior therapies**, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

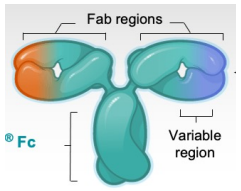
BCMA-targeting BsAbs

EMA approved | bivalent domain | IV infusion | CD3 low affinity

	Teclistamab MajesTEC-1[1] (n=165)	Elranatamab Magnetismm3[2] (n=123)	Alnuctamab[5] CC-93269 (n=68)	ABBV-383B[3] (n=118)	Linvoseltamab LINKER-MM1[4] (n=117)	REGN5459[6] (n=43)
Phase	I/II	I/II	I/II	I	II	I/II
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3
scFv	Humanized	Humanized	Humanized	Human	Human	Human
Ig	IgG4	IgG2a	IgG1-based	IgG4	IgG4	IgG4
Administration	SC	SC	SC	IV	IV	IV
# prior lines	5 (2-14)	5 (2-12)	4 (3-11)	5 (1-15)	5 (2-14)	5 (2-9)
Age	64 (33-84)	69 (44-89)	64 (36-79)	68 (35-88)	70 (37-91)	67 (26-85)







[1] Nooka et al. ASCO 2022; [2] Bahlis et al. ASH 2022; [3] Voorhees et al. IMS 2022; [4] Hans L. et al. ASCO 2023; [5] Wong et al. ASH 2019; [6] Suvannasankha et al. AACR 2023

BCMA-targeting BsAbs

Product	Schedule	n	PL/ TCR	Response RP2D	PFS/DoR/OS (m)
Teclistamab[1]	0.06–0.3–1.5 mg/kg QW SC; switch to **Q2W/Q4W dosing**	165	5PL/ **77.6%**	ORR 63% ≥CR: 45.4%	11.3/21.6 @23 months/21.9m
Elranatamab[2]	12–32–76 mg SC QW Option to switch to **Q2W** after ≥4 cycles (Phase I) if ≥PR or after 6 months (Phase II) if ≥CR	123	5PL/ **96.7%**	ORR 61% ≥CR: 35.0%	17.2m/69% at 12m/21.9m
ABBV-383[3]	60 mg IV **Q3W**	124	5PL/ **82%**	ORR 64% (27% ≥CR) @ 40mg ORR 60% (35% ≥CR) @ 60mg	10.4 months/NR in all patients @10.8 month follow-up
Linvoseltamab[4]	5–25–200 mg IV C1–C3 QW C4–C5 **Q2W Q4W** later if ≥VGPR	117 at 200mg	5–6PL/ **80%**	ORR 69% (39% ≥CR) (n=117)	70% at 12m/87% at 12m/NA
Alnuctamab[5]	Target dose: 30 mg SC C1–C2 QW; C3–C6 **Q2W**; **Q4W** from C7	73 30 at RP2D	4PL/ **63%**	ORR 69% (44% ≥CR) @ 30 mg (n=30)	11.4 m/NR (64% at 12m)

The data presented are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

BCMA, B-cell maturation antigen; bsAb, bispecific antibody; C, Cycle; CR, complete response; DoR, duration of response; IV, intravenous; mAb, monoclonal antibody; MM, multiple myeloma; MTD, maximum tolerated dose; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PL, prior lines; QW, every week; Q2W, every other week; Q3W, every three weeks; Q4W, every four weeks; RP2D, recommended phase II dose; SC, subcutaneous; sCR, stringent complete response; TCR, triple-class refractory; VGPR, very good partial response.

1. Van de Donk NWCJ, et al. ASCO 2023 (Abstract No. 8011 – presentation); 387:495-505; 2. Tomasson et al. ASH 2023: abstract 3385; 3. Vij R et al: ASH 2023: abstract 3378; 4. Lee HC. ASCO 2023 (Abstract No. 8006 – presentation); 5. Bar et al. ASH 2023: abstract 2011).

Mechanisms of resistance to T-cell based Therapies

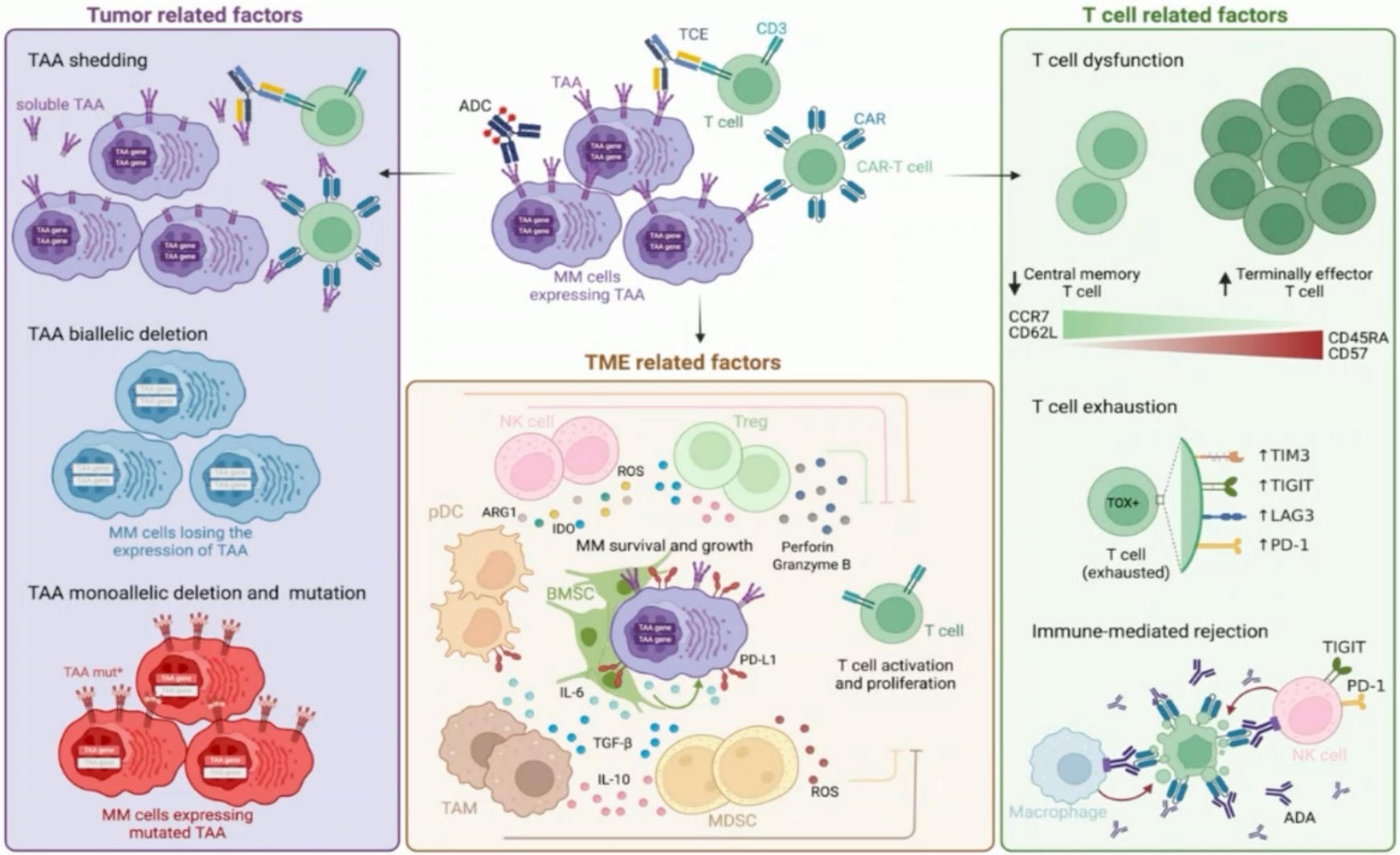


Figure produced by Dr Noemie Leblay with Biorender

Courtesy of P. Neri

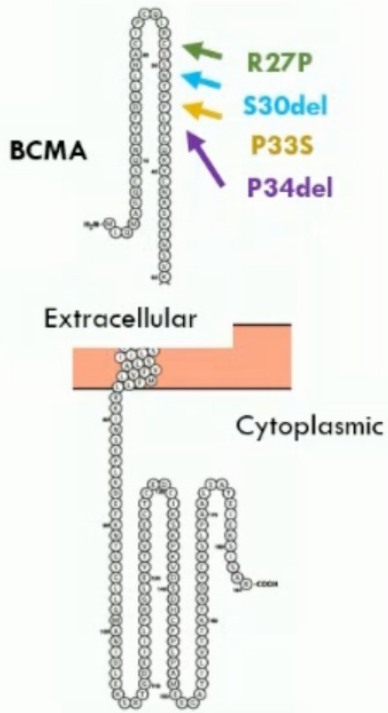
BCMA Antigen escape is a major mechanism of resistance post-TCE

We have analyzed a cohort of 40 MM patients treated with anti-BCMA and anti-GPRC5D CAR T and/or TCE.

We have observed biallelic loss or mutations in *TNFRSF17* (BCMA) in 6% of patients following anti-BCMA CAR T and more frequently (42%) post TCE therapies[1].

5 distinct genomic mechanisms leading to BCMA antigen escape including recurrent hotspot mutations in BCMA extracellular domain:

Diploid 16p	Focal biallelic loss of *TNFRSF17*
Subclone (<1%) with *TNFRSF17* biallelic loss ⟶	Clonal *TNFRSF17* biallelic loss
Diploid 16p	16p monoallelic loss + mut. *TNFRSF17* c.R27P point mutation
	16p monoallelic loss + mut. *TNFRSF17* in-frame deletion (p.Ser30del)
	16p monoallelic loss + mut. *TNFRSF17* in-frame deletion (p.Pro34del)



Lee H et al. Nat Med. 2023;29:2295-2306

GPRC5D- and FcRH5-targeting BsAbs

2:1 binding

	Anti-GPRC5D Talquetamab			Anti-GPRC5D Forimtamig		Anti-FCRH5 Cevostamab
Patients (n)	143	145	51	51	57	161
Prior TCE	Naïve (ADC allowed)	Naïve (ADC allowed)	Anti-BCMA CARs/BsAb allowed	Anti-BCMA CARs/BsAb allowed	Anti-BCMA CARs/BsAb allowed	
Schedule	405 µg/Kg SC QW	800 µg/Kg SC Q2W	5-1600 µg/Kg SC	18-10000µg/Kg IV Q2-3W	1200-7200 µg/Kg IV Q2-3W	20-198 mg IV Q3W
Prior LoT	5	5	6	5	4	6
TCR/Penta-ref (%)	**74**/29	**69**/23	84/41	**62**/36	**72**/42	**85**/68
ORR/≥CR (%)	74.1/33.6	71.7/38.7	64.7/35.3	71/35	64/25	56.7/8.9
ORR prior BCMA (%)			75% prior CAR-T 44.4% prior BsAbs	50	55	
PFS	7.5	14.2	5.1	NR	NR	NR
DoR	79% at 12m (≥CR)	90% at 12m (≥CR)	63% at 12m (≥CR)			11.5 m
OS	76% at 12m	76% at 12m	80% at 12m			NR

Schinke et al- ASCO 2023; Chari et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel et a ASH2021; Harrison et al . IMS 2023

GPRC5D × CD3 T-cell bispecific antibody: Talquetamab

MonumenTAL-1, Phase I/II study[1-3]

FDA/EMA approved

Trial design[2]

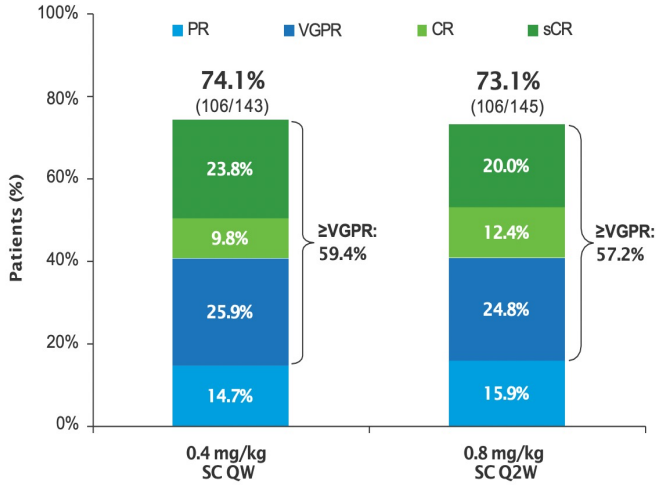
RP2D 0.4 mg/kg QW SC
- **Prior BCMA-targeting ADC treatment allowed**
- Prior T-cell redirecting therapy-naïve
  (n=143; n=21 Phase I and n=122 Phase II)

RP2D 0.8 mg/kg Q2W SC
- **Prior BCMA-targeting ADC treatment allowed**
- Prior T-cell redirecting therapy-naïve
  (n=145; n=36 Phase I and n=199 Phase II)

Prior T-cell redirection (QW and Q2W)
- Patients received either 0.4 mg/kg QW or 0.8 mg/kg talquetamab
  (n=51; n=17 Phase I and n=34 Phase II)

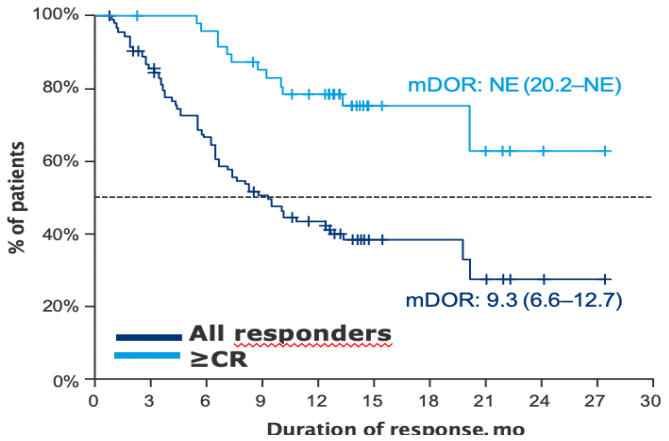
100% triple-class exposed
69–74% triple-class refractory

Response rates[2]



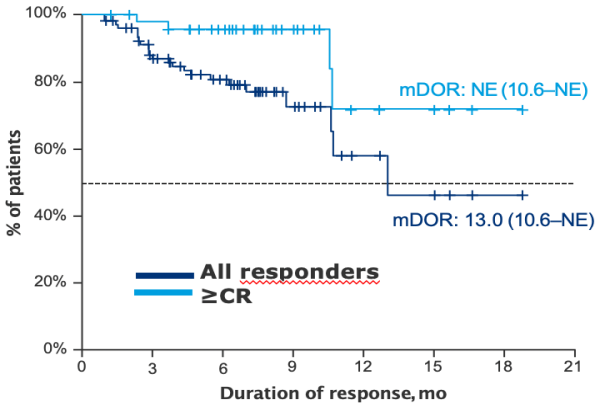
Duration of response[3]

DoR: 0.4 mg/kg SC QW



Overall mPFS: 7.5 months (95% CI, 5.7–9.4)

DoR: 0.8 mg/kg SC Q2W



Overall mPFS: 11.9 months (95% CI, 8.4–NE)

AE, adverse event; BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ICANS, immune cell effector cell-associated neurotoxicity syndrome; mPFS, median progression-free survival; PR, partial response; NA, not applicable; NR, not reported; Q2W, every 2 weeks; QW, weekly; RP2D, recommended Phase II dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

1. Chari A, et al. N Engl J Med 2022;387:2232-2244; 2. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – oral presentation); 3. Chari A, et al. ASH 2022 (Abstract No. 157 – presentation).

GPRC5D- and FcRH5-targeting BsAbs

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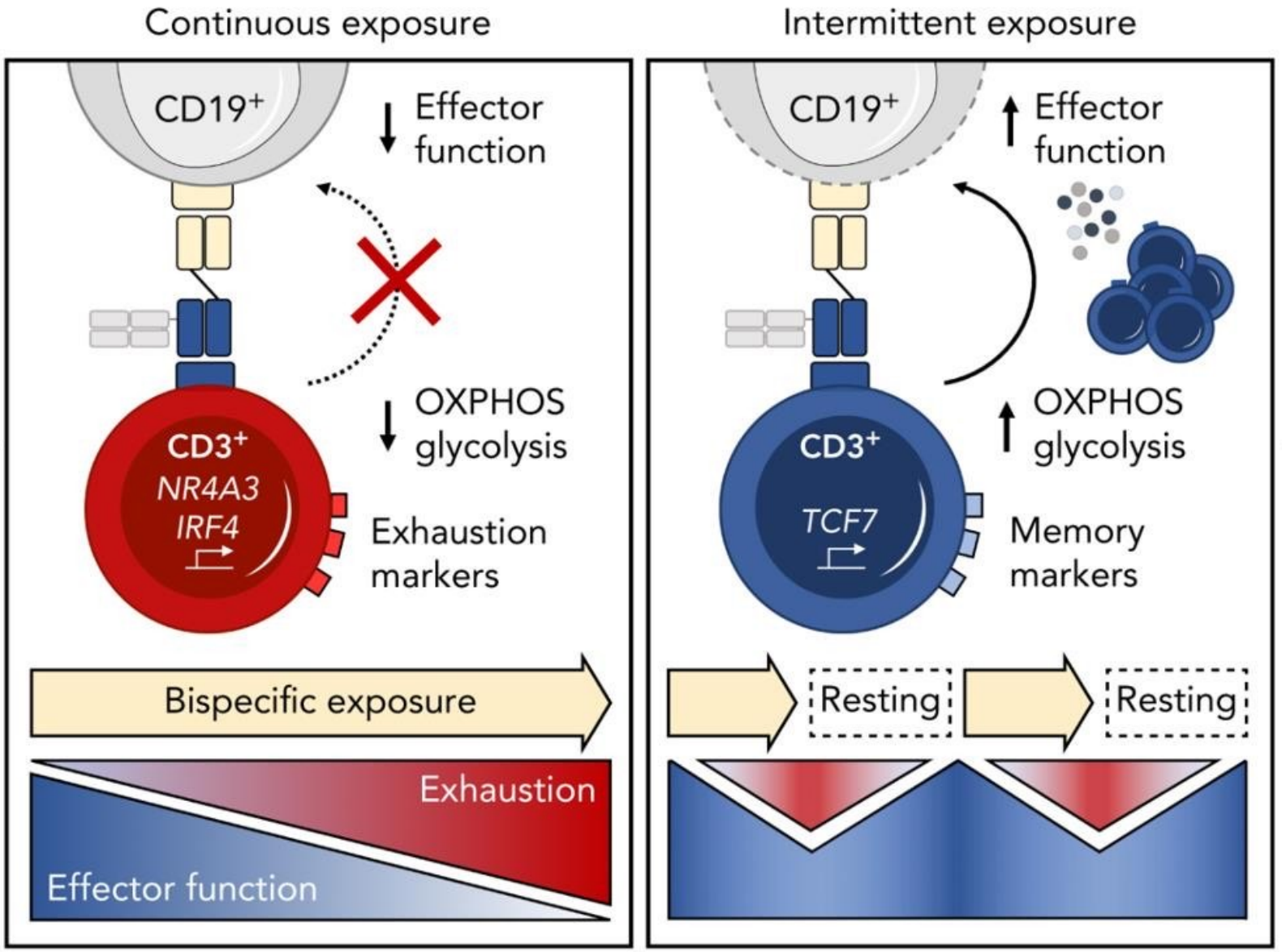
OS	76% at 12m	76% at 12m	80% at 12m			NR

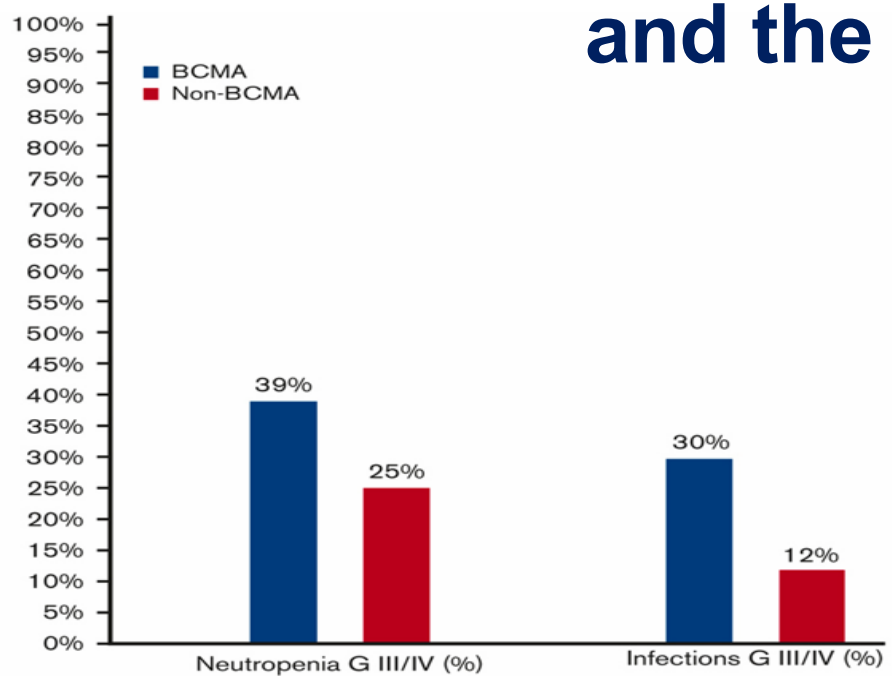
Schinke et al- ASCO 2023; Chari et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel et a ASH2021; Harrison et al . IMS 2023

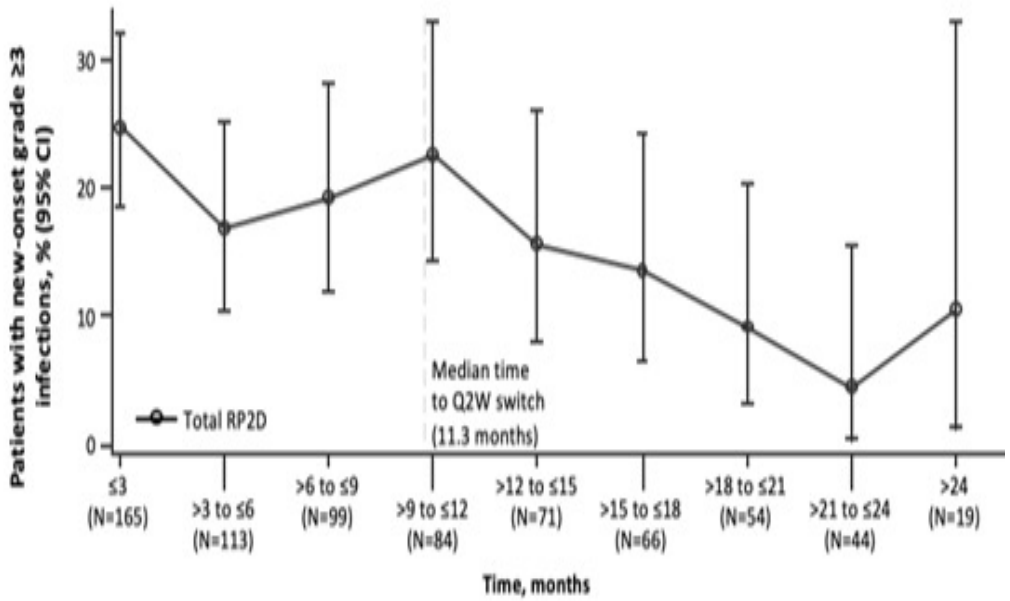
Resting improves/prevents T-cell exhaustion induced by continous exposure to BsAbs

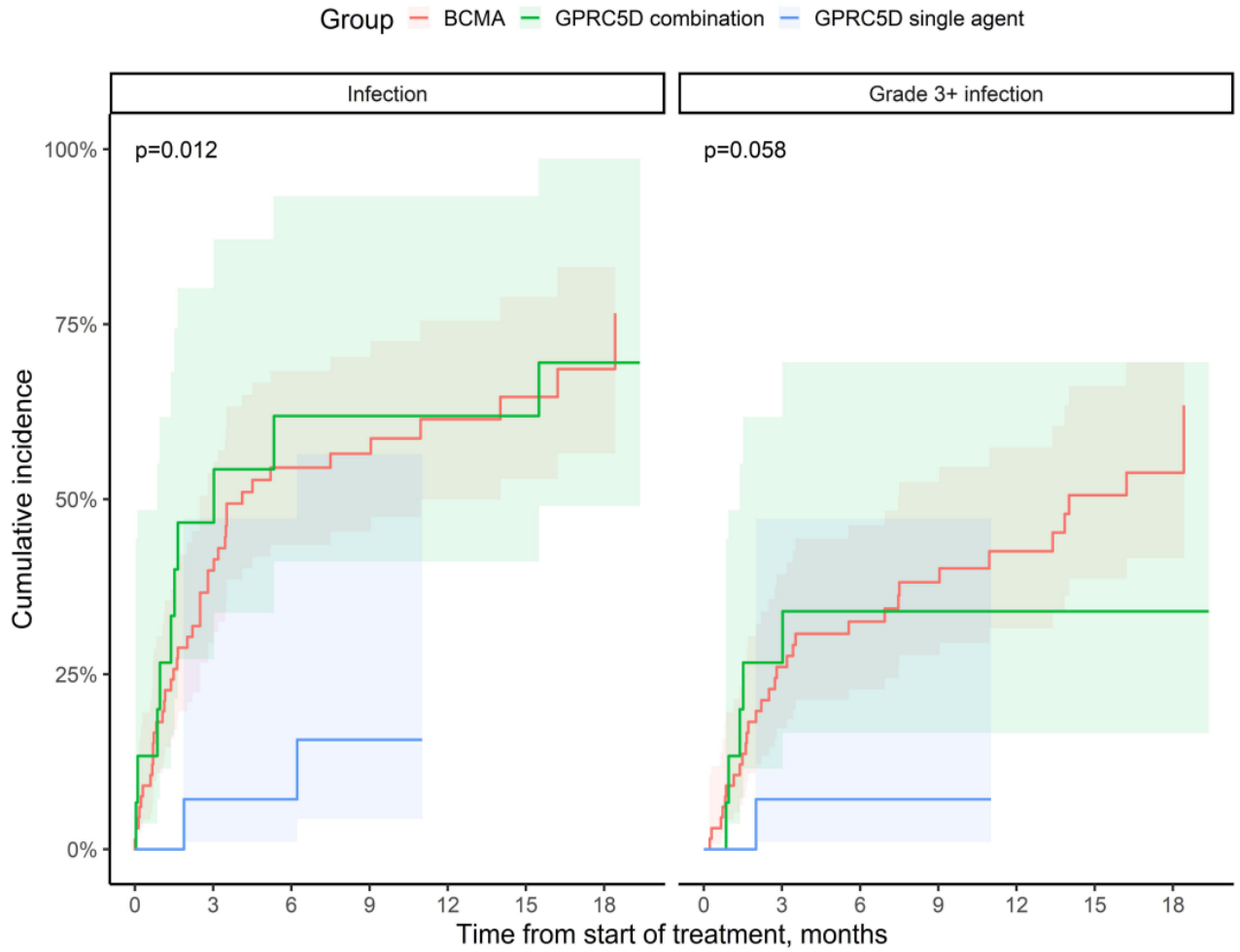


Philip et al., Blood, 8 September 2022

Mitigation of the infection risk according to the target of BsAbs and the administration schedule

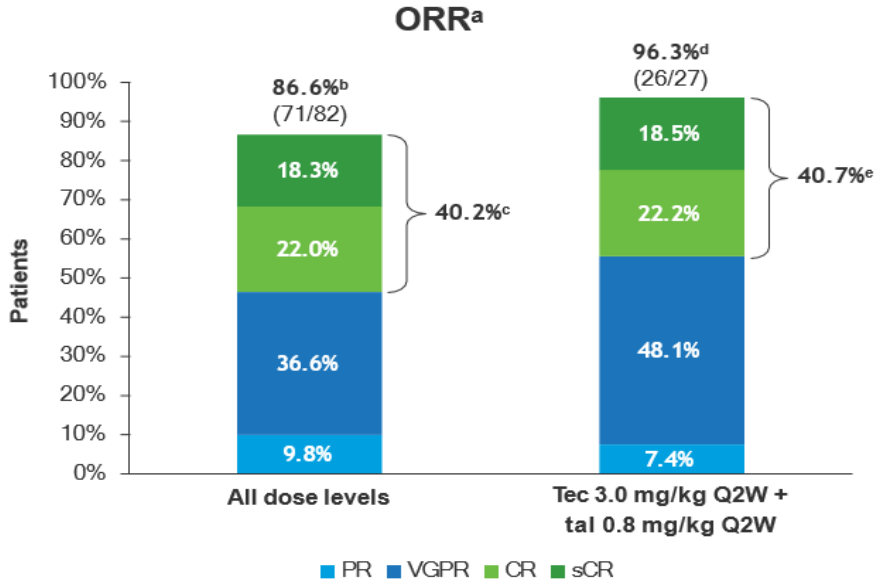




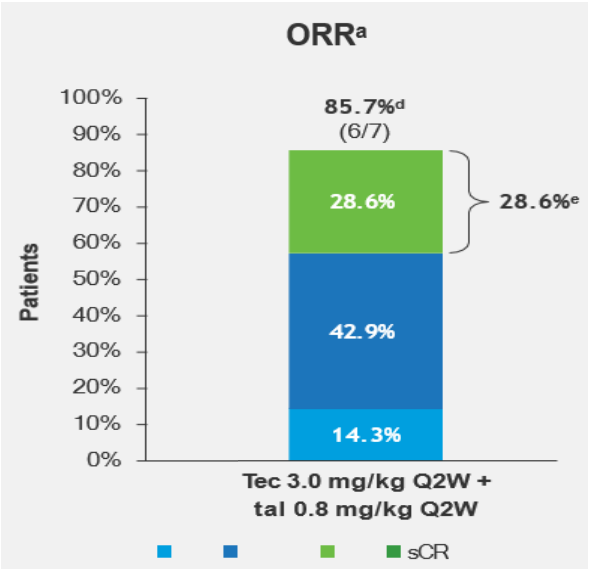


1. Lancman et al., Blood Cancer Discov (2023) 4 (6): 440–451. 2. Frerichs et al., Blood Advances, 8(1):194 3.Nooka et. Al., Cancer 2023 4. Mazahreh F, et al Blood Adv 2023; 7: 3069-3074 5. Frerichs K, et al. EHA 2023 (Abstract No. P1506 – poster

RedirecTT-1 study: teclistamab and talquetamab



EMD



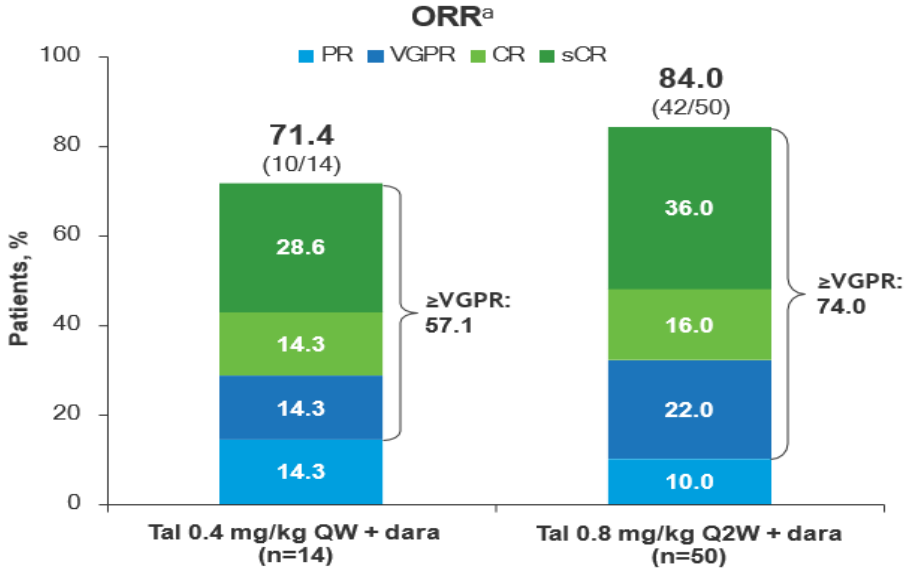
	All dose levels (N=93)	Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)
Median PFS,[g] months (95% CI)	20.9 (13.0-NE)	NE (9.9-NE)
9-month PFS rate[g] (95% CI)	70.1 (58.0-79.4)	77.1 (50.8-90.5)

	All dose levels (N=35)	Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (N=11)
Median DOR,[f] months (95% CI)	12.9 (4.17-NE)	NE (4.17-NE)
Median PFS,[g] months (95% CI)	6.1 (2.5-9.9)	9.9 (2.4-NE)

TEAE[a] (≥5% overall), n (%)	Total (N=93)		Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Infections	**78 (83.9)**	**49 (52.7)**	**27 (79.4)**	**13 (38.2)**
COVID-19	31 (33.3)	9 (9.7)	14 (41.2)	1 (2.9)
Pneumonia	25 (26.9)	10 (10.8)	4 (11.8)	2 (5.9)
Septic shock	7 (7.5)	6 (6.5)[b]	1 (2.9)	1 (2.9)
Urinary tract infection	7 (7.5)	1 (1.1)	5 (14.7)	1 (2.9)
COVID-19 pneumonia	6 (6.5)	5 (5.4)	4 (11.8)	3 (8.8)

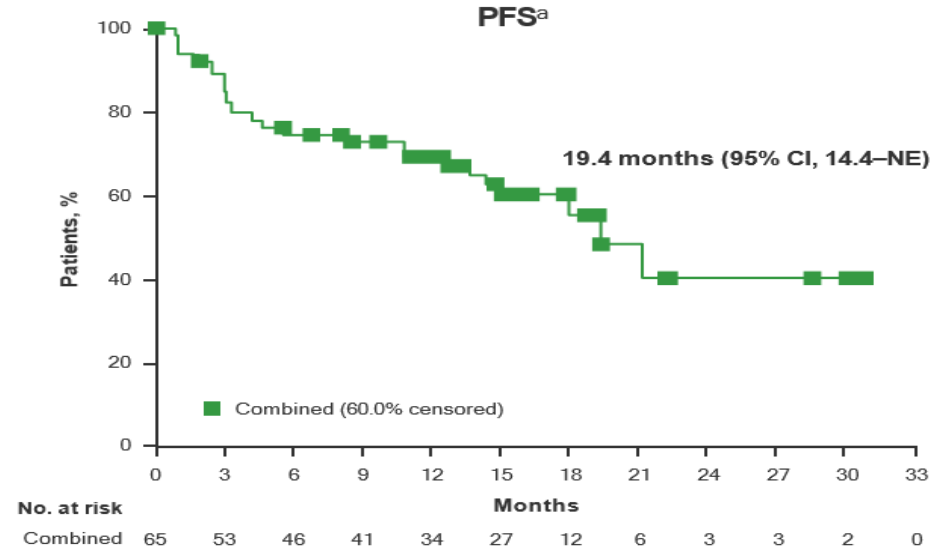
- Onset of the majority of high-grade infections occurred during the first 6 months (75.0%)
- Most high-grade infections were pneumonias
- 81.7% with ≥1 postbaseline IgG value <400 mg/dL or hypogammaglobulinemia TEAE (all grade 1 or 2)

TRIMM-2 study: talquetamab and daratumumab



Parameter	Tal 0.4 mg/kg QW + dara (n=14)	Tal 0.8 mg/kg Q2W + dara (n=51)
ORR in anti-CD38, n (%) Naïve Exposed	3/3 (100.0) 7/11 (63.6)	5/5 (100.0) 37/45 (82.2)
Refractory	7/11 (63.6)	32/40 (80.0)
ORR in T-cell redirection therapy[b] exposed, n (%)	4/6 (66.7)[c]	15/19 (78.9)
CAR-T BsAb	1/2 (50.0) 4/5 (80.0)	8/9 (88.9) 7/10 (70.0)

AE (≥5% overall), n (%)	Tal 0.4 mg/kg QW + dara (n=14)		Tal 0.8 mg/kg Q2W + dara (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Infections	8 (57.1)	3 (21.4)	37 (72.5)	13 (25.5)
COVID-19	4 (28.6)	0 (0)	12 (23.5)	2 (3.9)
Urinary tract infection	0 (0)	0 (0)	10 (19.6)	2 (3.9)
Pneumonia	2 (14.3)	1 (7.1)	7 (13.7)	7 (13.7)
Upper respiratory tract infection	3 (21.4)	0 (0)	4 (7.8)	0 (0)
Other respiratory tract infections	1 (7.1)	0 (0)	7 (13.7)	1 (2.0)



Parameter	Tal 0.4 mg/kg QW + dara (n=14)	Tal 0.8 mg/kg Q2W + dara (n=51)
Median PFS, mo (95% CI)	NR (2.73-NE)	19.4 (12.5-NE)
12-mo OS, % (95% CI)	92.3 (56.6-98.9)	91.5 (78.8-96.7)

- Onset of the majority of high-grade infections occurred during the first 6 months (75.0%)
- Most high-grade infections were pneumonias

How to improve upfront therapy w/wo TCR tx

1. Risk-adapted and MRD-driven approaches, including TCR therapies (if available) and treatment intensification or deintensification

2. Combination strategies

    + BsAbs (quintuplets?)

    doublet maintenance: lenalidomide + anti-CD38, or + PI, or + BsAb, or + CELMoDs)

How to improve TCR therapies

1. Earlier use (first line?)
2. Optimizing CAR-T constructs
    - binding and co-stimulatory domains
    - dual targeting (EMD)
3. Optimizing BsAb formats
    - high affinity binders to the target
    - dual targeting
    - low affinity binders to CD3

How to improve TCR therapies

4. Shortening CAR-T manufacturing process
5. Improving T-cell function, and/or
6. Preventing/reversing T-cell exhaustion, and/or
7. Inhibiting exhaustion related signals

    enriched with naive/stem cell memory T cells

    combination with anti-PD-1/PD-L1 inhibitors, or anti-CD38 mAbs, or IMiDs, or CELMoDs

    fixed treatment duration/extended treatment-free intervals (BsAbs)

How to improve TCR therapies

8. Overcoming the immunosuppressive microenvironment

    armored CAR-T

9. Optimal sequencing

10. Combination strategies

    BsAbs as a bridge to, or consolidation after, CAR-T

    IMiDs, CELMoDs, anti-CD38, anti-PD-1/PD-L1