Update and guidelines in myeloma

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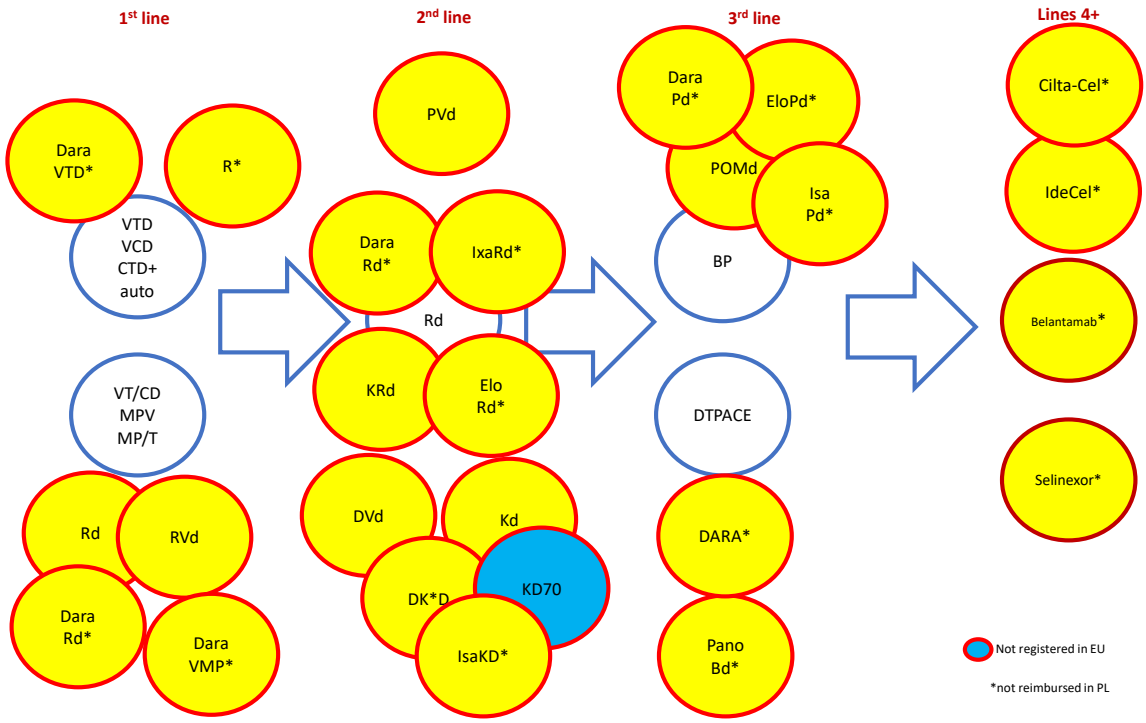
Hamburg
Online
2022

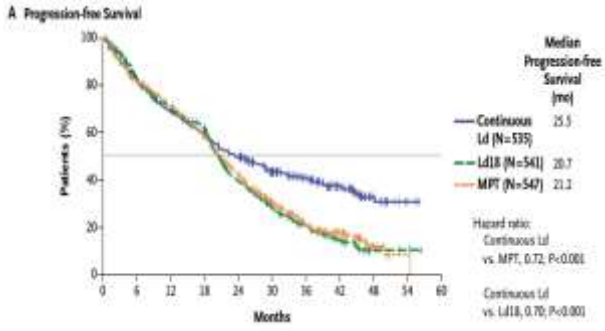
Disclosures for Dominik Dytfeld

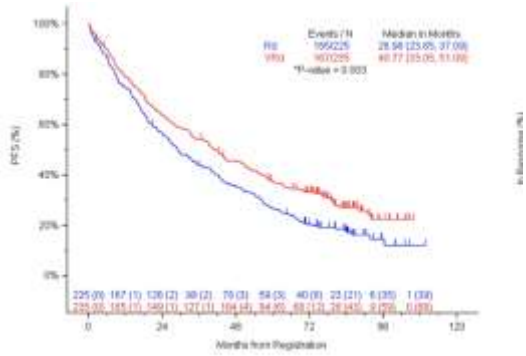
Research Support	Janssen, Celgene, Amgen
Employee	N/A
Consultant	Janssen
Major Stockholder	N/A
Speakers' Bureau/ Scientific Advisory Board	Janssen, Amgen, Celgene, Takeda, GSK, Sanofi



The best should be given upfront

Patients not eligible for transplantation





RD vs RD18 vs MPT → **RVD vs RD**

Benboubker, N Engl J Med 2014; 371:906-917
Durie, Blood Cancer Journal, 2020, 10

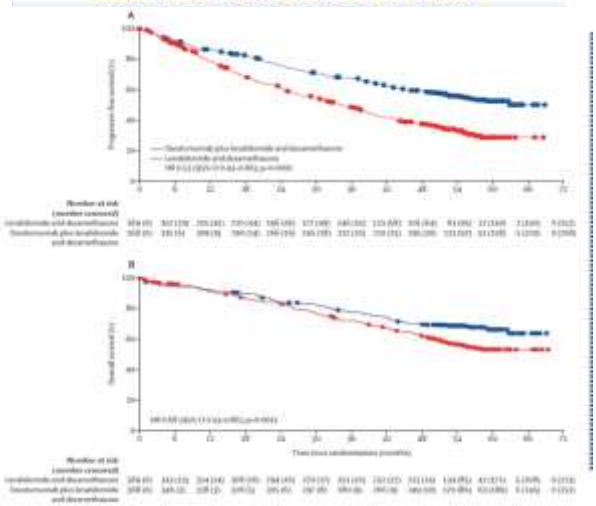
Daratumumab RD

Drug(s)	Study Name	Phase	Disease State	Patient Population	N
Daratumumab, lenalidomide, dexamethasone	MAIA	3	MM	Newly Diagnosed Ineligible for Transplant	737

Baseline Demographics

Median age, years (range)	73 (45-90)
≥75 years old	44%
Male	52%
ECOG Score, %	
0	34%
1	50%
2	17%
ISS Staging, %	
I	27%
II	43%
III	29%
FISH/karyotyping analysis, n	642
Standard risk	86%
High risk	14%

- Key baseline characteristics were well balanced between the 2 arms



Facon T, et :Lancet, 2021

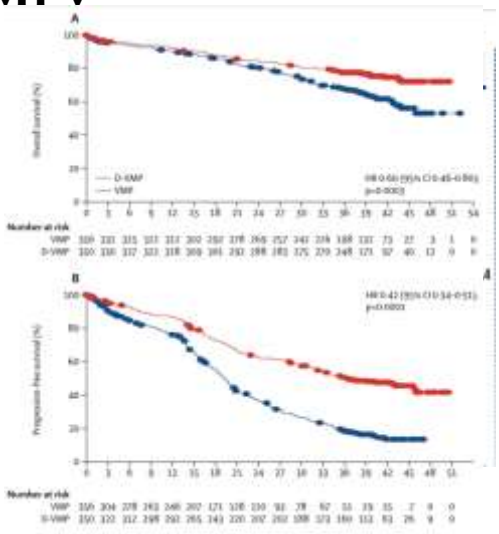
Bahlis N, et al. ASH 2019. Poster Presentation. Abstract 1875.

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; ISS, International Staging System.

Lenalidomide free induction is also an option

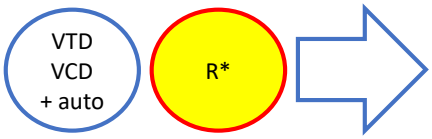
Daratumumab MPV

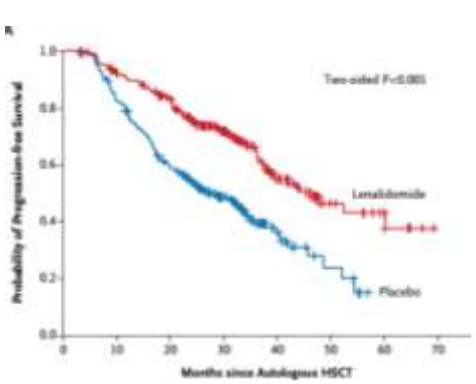
	VMP (N = 356)	D-VMP (N = 350)
Age		
Median (range), years	71.0 (50-91)	71.0 (40-93)
Distribution, n (%)		
<65 years	24 (6.7)	36 (10.3)
65-74 years	225 (63.2)	210 (60)
≥75 years	107 (30.1)	104 (29.7)
ECOG status[a], n (%)		
0	99 (27.8)	78 (22.3)
1	173 (48.6)	182 (52)
2	84 (23.6)	90 (25.7)

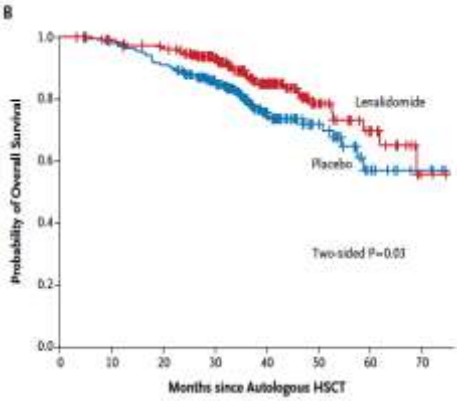


Mateos, Lancet, 2020

Patients not qualified for transplantation







*not reimbursed in PL

McCarthy, NEJM 2012; 366:1770-1781

The best induction is again ... daratumumab based

DVTD vs VTD +autoPBSCT
impact on MRD

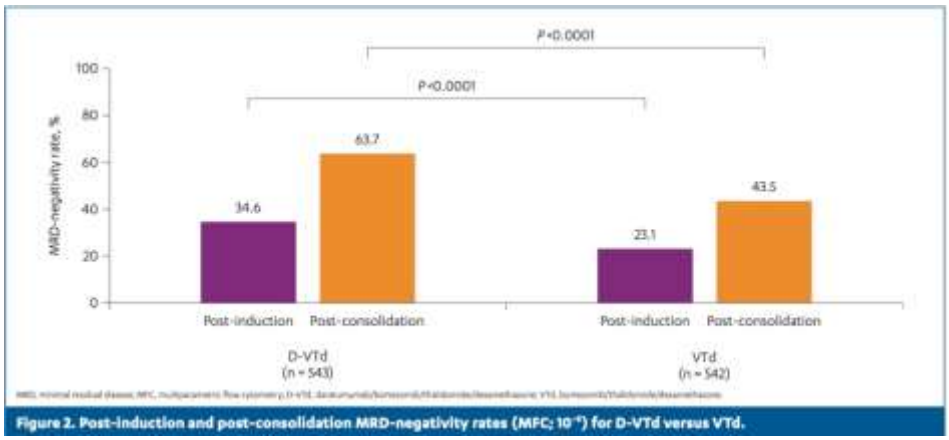
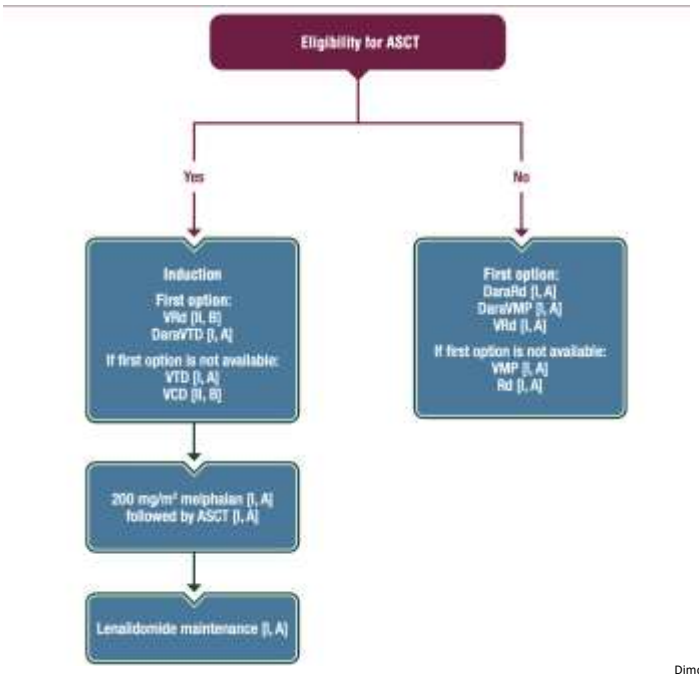


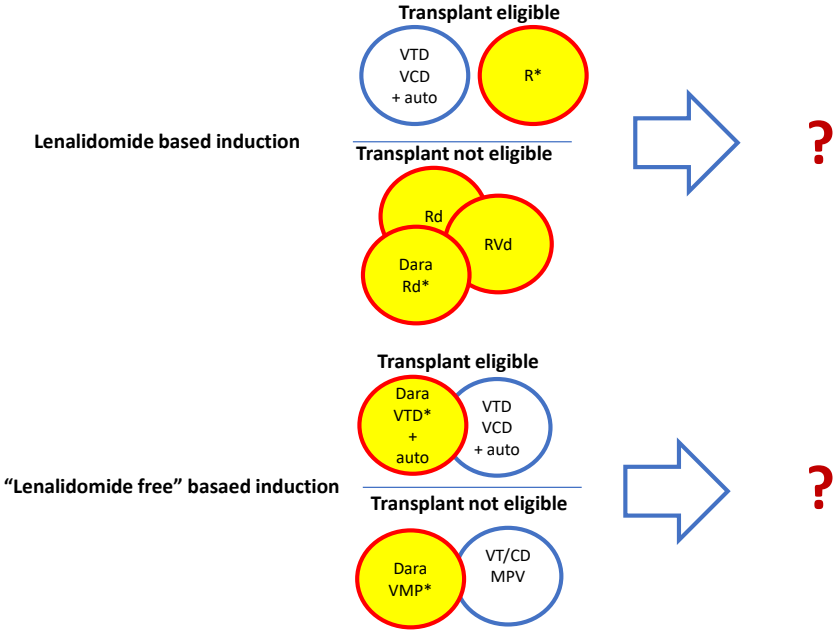
Figure 2. Post-induction and post-consolidation MRD-negativity rates (MFC; 10^{-5}) for D-VTd versus VTd.

Avet Loiseau ASCO, 2019



Dimopoulos, Annals of Oncology, 2020

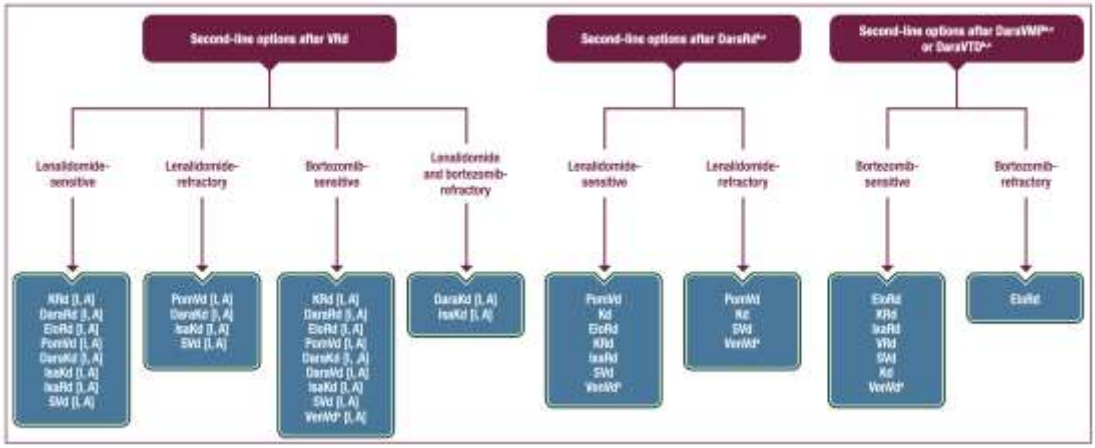
Treatment strategy in EU



*not reimbursed in PL

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

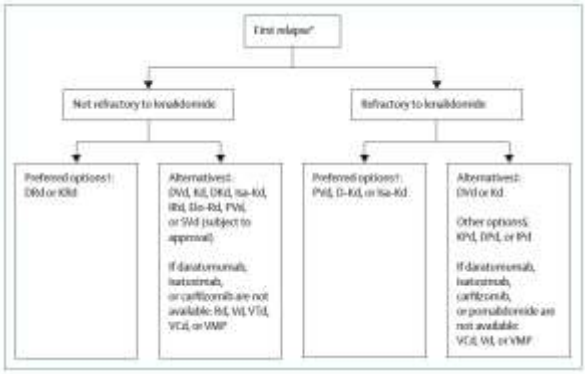
M. A. Dimopoulos[1], P. Moreau[2], E. Terpos[1], M. V. Mateos[3], S. Zweegman[4], G. Cook[5], M. Delforge[6], R. Hájek[7], F. Schjesvold[8,9], M. Cavo[10], H. Goldschmidt[11], T. Facon[12], H. Einsele[13], M. Boccadoro[14], J. San-Miguel[15], P. Sonneveld[16] & U. Mey[17], on behalf of the EHA Guidelines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

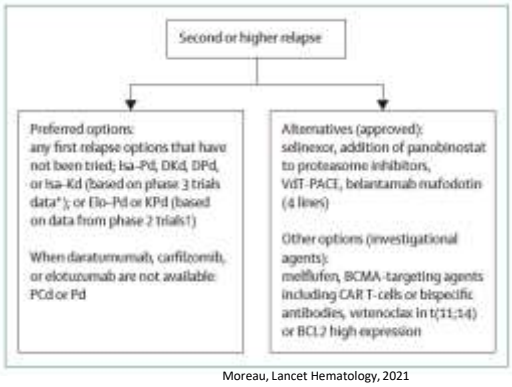


Dimopoulos, Annals of Oncology, 2020

Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group

Philippe Moreau, Shaji K Kumar, Jesús San Miguel, Faith Davies, Elena Zamagni, Nizar Bahlis, Heinz Ludwig, Joseph Mikhael, Evangelos Terpos, Fredrik Schjesvold, Thomas Martin, Kwee Yong, Brian G M Durie, Thierry Facon, Artur Jurczyszyn, Sushil Sahota, Noopur Raje, Mark van de Donk, Sagar Lonial, Michele Cavo, Sigurdur Y Kristinsson, Suzanne Lentzsch, Ruman Hajek, Kenneth C Anderson, Cristina João, Hermann Einsele, Pieter Sonneveld, Monika Engelhardt, Rafael Fonseca, Annette Vangsted, Katja Weisel, Rachid Baz, Vania Hungria, Jesus G Berdeja, Fernando Leal da Costa, Angelo Maiolino, Anders Waage, David H Vesole, Enrique M Ocio, Hang Quach, Christoph Driessen, Joan Blade, Xavier Leleu, Elvira Riva, Peter Leif Bergsagel, Jian Hou, Wee Joo Chng, Ulf-Henrik Mellqvist, Dominik Dytfeld, Jean-Luc Harousseau, Hartmut Goldschmidt, Jacob Laubach, Nikhil C Munshi, Francesca Gay, Meral Beksac, Luciano J Costa, Martin Kaiser, Paramaswaran Hari, Mario Boccadoro, Saad Z Usmani, Sonja Zweegman, Sarah Holstein, Orhan Sezer, Simon Harrison, Hareth Nahi, Gordon Cook, Maria-Victoria Mateos, S Vincent Rajkumar, Meletios A Dimopoulos, Paul G Richardson

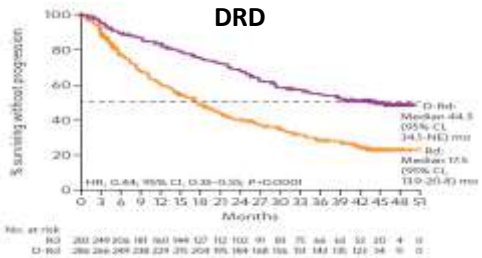




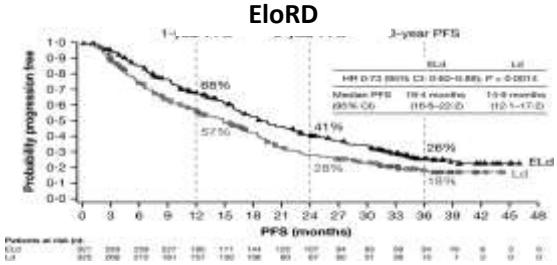
Moreau, Lancet Hematology, 2021

RRMM – lenalidomide based

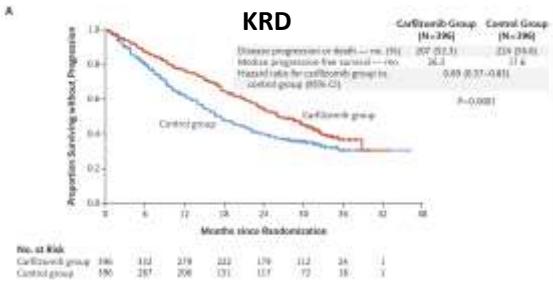
DRD



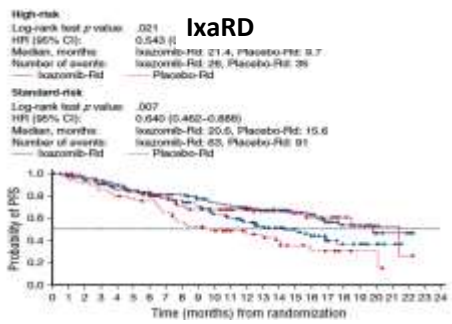
EloRD



KRD



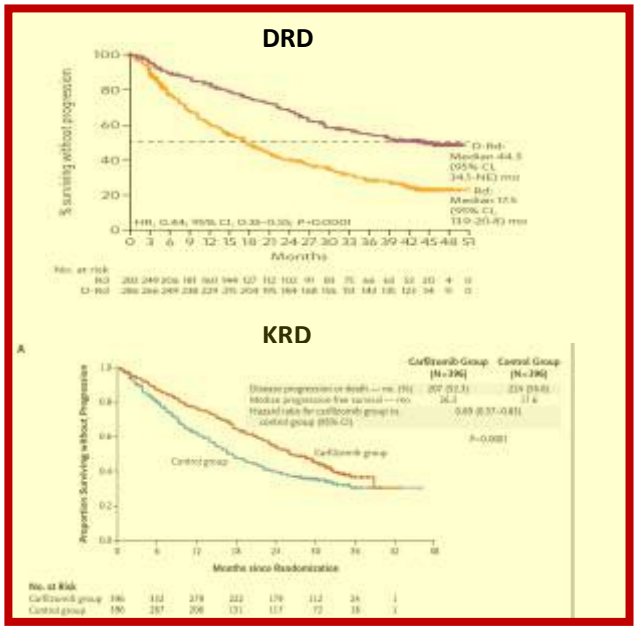
IxaRD



Bahlis, ASH, 2018, p1966
Dimopouols, BJH, 2017, 178, 896-905
Stewart, NEJM 2015; 372:142-152

FIRST CHOICE

DRD

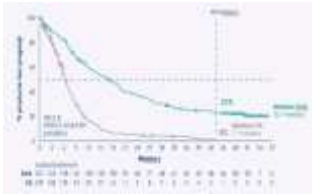


KRD

Bahlis, ASH, 2018, p1966
Dimopouols, BJH, 2017, 178, 896-905
Stewart, NEJM 2015; 372:142-152

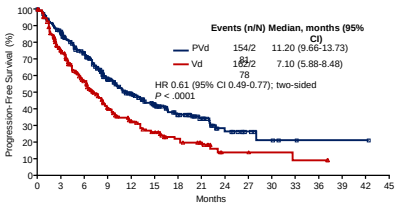
RRMM – lenalidomide free

DVD



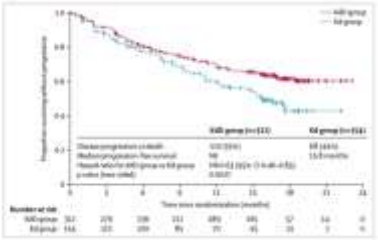
Dimopoulos, Lancet, 2020

PVd



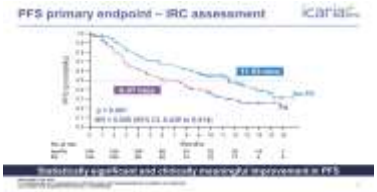
Richardson ASCO 2019
Richardson, Lancet Oncol 2019

DaraKD



Wiesel ASH 2019.

IsaPD



Moreau, Lancet Oncol, 2018

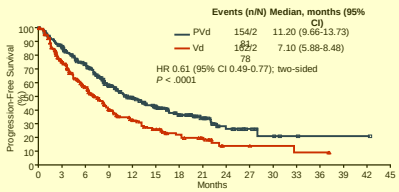
IsaKD

Dimopoulos, Lancet Oncol, 2016

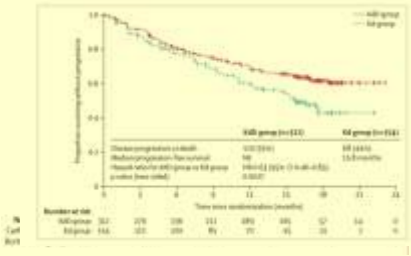
RRMM resistant to lenalidomide

FIRST CHOICE

PVd



DaraKD



IsaKD

Dimopoulos, Lancet, 2020

Richardson ASCO 2019

Richardson, Lancet Oncol 2019

Wiesel ASH 2019.

Moreau, Lancet Oncol, 2018

Dimopoulos, Lancet Oncol, 2016

RRMM treatment strategy

Lenalidomide based induction

Transplant eligible

VTD
VCD
CTD+
auto

R*

Transplant not eligible

Rd

RVd

Dara
Rd*

Dara/Isa
Kd*

Pd(X)

DVd

"Lenalidomide free" basaed induction

Transplant eligible

Dara
VTD*
+
auto

VTD
VCD
CTD+
auto

Transplant not eligible

Dara
VMP*

VT/CD
MPV

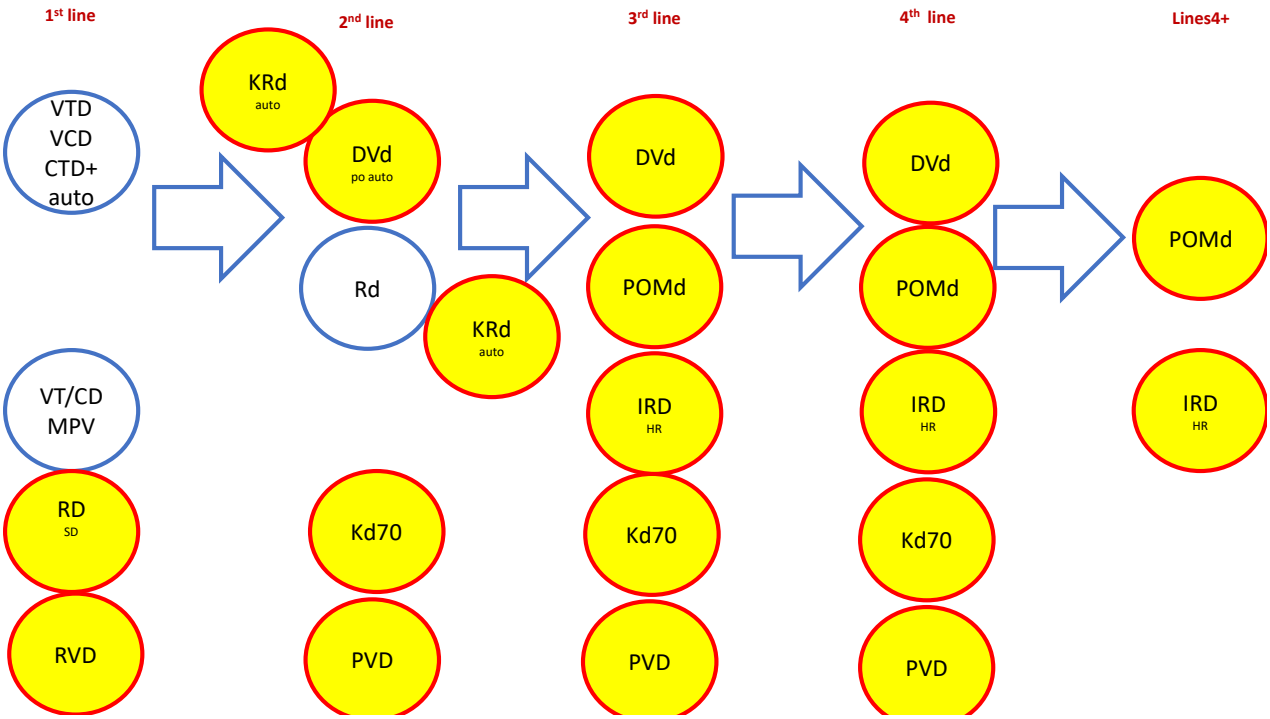
KRd

Dara
Rd*

Elo
Rd*

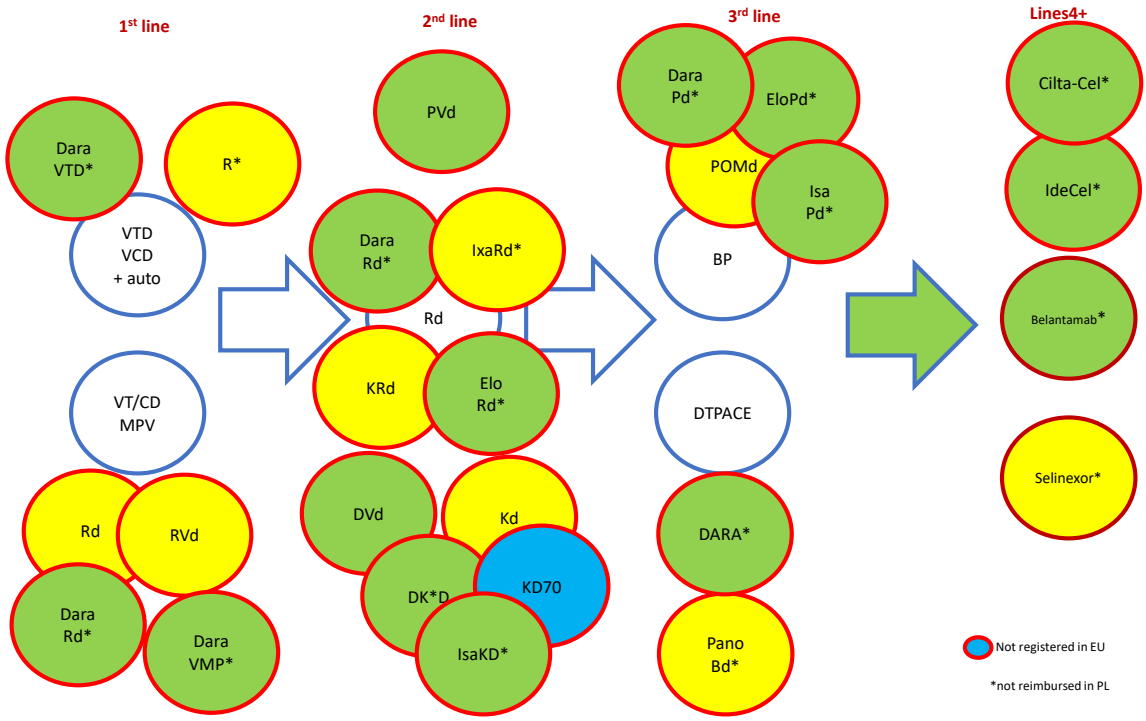
IxaRd*

*not reimbursed in PL



But the best about to come

IMMUNOTHERAPY


1st line
2nd line
3rd line
Lines4+
Dara VTD*
R*
VTD VCD + auto
VT/CD MPV
Rd
RVd
Dara Rd*
Dara VMP*
PVd
Dara Rd*
IxaRd*
Rd
KRd
Elo Rd*
DVd
Kd
DK*D
KD70
IsaKD*
Dara Pd*
EloPd*
POMd
Isa Pd*
BP
DTPACE
DARA*
Pano Bd*
Cilta-Cel*
IdeCel*
Belantamab*
Selinexor*
Not registered in EU
*not reimbursed in PL

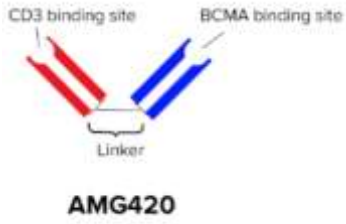
BITE's

AMG 420, an Anti-BCMA BiTE®, Induces MRD-Negative CRs in Relapsed/Refractory MM Patients: Results of a Dose Escalation FIH Phase 1 Study

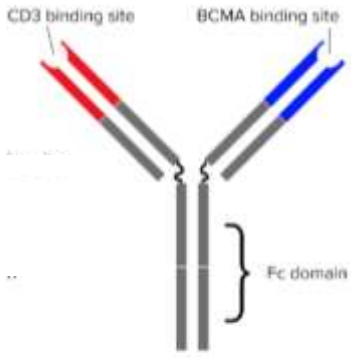
Max S Topp,[1] Johannes Duell,[1] Gerhard Zugmaier,[2] Michel Attal,[3] Philippe Moreau,[4] Christian Langer,[5] Jan Krönke,[6] Thierry Facon,[7] Hermann Einsele,[1*] Gerd Munzert[8*]

[1]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany, [2]Amgen Research (Munich), Munich, Germany, [3]University of Toulouse, Toulouse, France, [4]Hematology Department Chair, University Hospital Center of Nantes, Nantes, France, [5]Kempten Clinic, Kempten, Germany, [6]Ulm University, Ulm, Germany, [7]Regional University Hospital of Lille, Lille, France, [8]Boehringer Ingelheim, Ingelheim am Rhein, Germany
*Contributed equally

Teclistamab



AMG420



MajesTEC-1: Patient Characteristics

Characteristic	Safety Analysis N=165
Age (years), median (range)	64.0 (33–84)
Age ≥75 years, n (%)	24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%)	
White	134 (81.2)
African-American/Black	21 (12.7)
Other[a]	10 (6.1)
Bone marrow plasma cells ≥60%[b], n (%)	18 (11.3)
Extramedullary plasmacytomas ≥1[c], n (%)	28 (17.0)
High-risk cytogenetics[d], n (%)	38 (25.9)
ISS stage[e], n (%)	
I	85 (52.5)
II	57 (35.2)
III	20 (12.3)

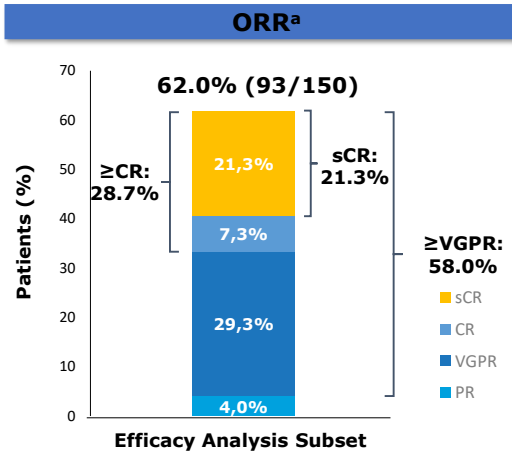
Characteristic	Safety Analysis N=165
Baseline renal function, n (%)	
<60 mL/min/1.73m^2	44 (26.7)
≥60 mL/min/1.73m^2	121 (73.3)
Time since diagnosis (years), median (range)	6.0 (0.8–22.7)
Prior lines of therapy, median (r	5.0 (2–14)
Prior stem cell transplantation, n (%)	135 (81.8)
Exposure status, n (%)	
Triple-class exposed[f]	165 (100)
Penta-drug exposed[g]	116 (70.3)
Selinexor	6 (3.6)
Refractory status, n (%)	
Triple-class refractory[f]	128 (77.6)
Penta-drug refractory[g]	50 (30.3)
Refractory to last line of therapy	148 (89.7)

[a]Reported as Asian, other, multiple, or not reported; [b]Percentages calculated from n=160, includes bone marrow biopsy and aspirate; [c]Soft-tissue plasmacytomas not associated with the bone were included; [d]del(17p), t(4:14), and/or t(14;16) (n=147); [e]At baseline, percentages calculated from n=162; [f]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb; [g]≥2 PI, ≥2 IMiD, and ≥1 anti-CD38 mAb. IMiD, immunomodulatory drug; ISS, international Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor.

ASH 2021

Moreau P, et al. ASH 2021. Oral Presentation 896.

MajesTEC-1: Overall Response Rate for Teclistamab



- At a median follow-up of 7.8 months (range: 0.5+–18):
  - ORR of 62.0% (95% CI: 53.7–69.8) represents a substantial benefit for patients with triple-class exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate[b]
  - 24.7% (37/150; 95% CI: 18.0–32.4) at a threshold of 10^{-5}
  - 16.7% (25/150; 95% CI: 11.1–23.6) at a threshold of 10^{-6}[,c]
- In patients who achieved ≥CR, the MRD-negativity rate was 41.9%

[a]PR or better, IRC assessed; ORR was assessed in efficacy analysis population, which includes all patients who received their first dose on or before March 18, 2021 (n=150); [b]Baseline clones were obtained for all patients All MRD assessments were done by next-generation sequencing ; [c]Patients who were not negative at the 10-6 threshold were indeterminate.

CR, complete response; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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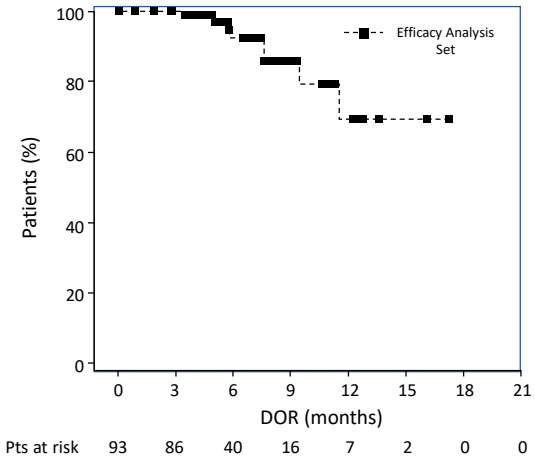
MajesTEC-1: Duration of Response



- At the clinical cutoff, the median follow-up for responders (n=93) was 8.0 months (range: 2.4+–18.0)
  - 91.4% of responders had ≥6 months of follow-up
- Median DOR not reached
- Event-free rate for responders
  - 6 month: 92.5% (95% CI: 80.6–97.2)
  - 9 month: 85.9% (95% CI: 70.0–93.7)
- PFS rates
  - 6 month: 64.4% (95% CI: 56.0–71.7)
  - 9 month: 58.5% (95% CI: 48.8–67.0)
- Median OS has not been reached

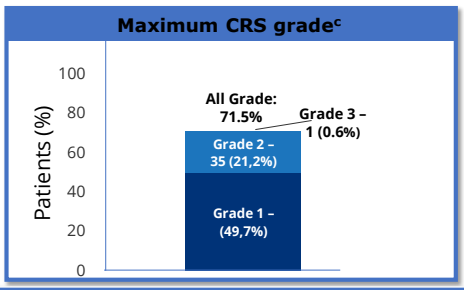
CI, confidence interval; DOR, duration of response; PFS, progression-free survival; Pt, patient; OS, overall survival; RP2D, recommended phase 2 dose.

ASH 2021

Moreau P, et al. ASH 2021. Oral Presentation 896.

MajesTEC-1: Cytokine Release Syndrome

Parameter	Safety Analysis Set N=165
Patients with CRS, n (%)	118 (71.5)
Patients with ≥2 CRS events	54 (32.7)
Time to onset (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Patients who received supportive measures[a], n (%)	
Tocilizumab	109 (66.1)
Low-flow oxygen by nasal cannula[b]	60 (36.4)
Steroids	21 (12.7)
Single vasopressor	13 (7.9)
	1 (0.6)



- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that fully resolved, and 97% of events were confined to step-up and cycle 1
- All CRS events resolved, with no treatment discontinuations due to CRS
- Over the course of their treatment, 2.4% of patients received >1 dose of tocilizumab for a single CRS event

[a]A patient could receive >1 supportive therapy; [b]≤6 L/min; [c]CRS was graded using Lee et al *Blood* 2014 in the phase 1 portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al *Blood* 2014 criteria were mapped to ASTCT criteria for patients in the phase 1 portion.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome.

ASH2021

Moreau P, et al. ASH 2021. Oral Presentation 896.

MajesTEC-1: Neurotoxicity

Parameter	Safety Analysis Set N=165
Patients with neurotoxicity, n (%)	21 (12.7)
Headache	14 (8.5)
ICANS[a]	5 (3.0)
Encephalopathy	2 (1.2)
Tremor	2 (1.2)
Patients with grade ≥3 events	0
Time to onset, median (range) days	2.5 (1–7)
Duration, median (range) days	3.0 (1–37)
Patients requiring supportive measures for neurotoxicity, n (%)	12 (7.3)
Tocilizumab	3 (1.8)
Dexamethasone	3 (1.8)
Levetiracetam	1 (0.6)

- The overall incidence of neurotoxicity was low
- The most commonly reported neurotoxicity event was headache (14 patients [8.5%])
- All events were grade 1/2
- There were no treatment discontinuations or dose reductions due to neurotoxicity[b]
- 12 patients (7.3%) required supportive measures for neurotoxicity
- There were 5 patients with ICANS events at the RP2D
  - All were grade1/2
  - Most (7/9) ICANS events were concurrent with CRS; all resolved

[a]1 of the events of confusional state reported in a patient treated at RP2D in phase 1 was considered by the sponsor to be consistent with ICANS and presented as such in summaries of ICANS events; [b]TEAEs under the "nervous system disorder" or "psychiatric disorder" SOC that were judged by the investigator to be related to study drug; including ICANS events. CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; RP2D, recommended phase 2 dose; SOC, system organ class.

Moreau P, et al. ASH 2021. Oral Presentation 896.

Teclistamab
Daratumumab

TRIMM-2: Study Design

Aim: to present updated data from RRMM patients who received tec in combination with dara in a phase 1b, open-label, multicenter, multicohort trial[1]

The data cut-off date for these analyses was September 7, 2021

Eligibility Criteria:
- Adults with documented diagnosis of MM per IMWG criteria
- ≥3 prior lines of therapy[a] or double refractory to a PI and an IMiD
- Treatment with anti-CD38 therapy >90 days prior allowed, including patients who were refractory to anti-CD38 therapy

Key objectives:
- Part 1: Identify RP2D(s) for each treatment combination
- Part 2: Characterize safety of each treatment combination at the selected RP2D(s)
- Antitumor activity, PK/PD

Tec + Dara Dosing Cohorts (n=37)

Tec	Dara SC	Patients enrolled to date (n)
1.5 mg/kg SC QW	1800 mg SC Cycles 1-2: QW Cycles 3-6: Q2W Cycles 7+: monthly	21
3 mg/kg SC Q2W		11
3 mg/kg SC QW		5

- Step-up dosing was used for tec[b]; dara was administered according to the approved SC schedule[2]
- 9 patients switched from 1.5 mg/kg SC QW to 3mg/kg SC Q2W (cycles 4–9)
- Premedications[c] were limited to step-up doses and first full dose
- No steroid requirement after first full dose

[a]Including a PI and IMiD; [b]1–3 step-up doses given within 1 week before a full dose; [c]Glucocorticoid, antihistamine, and antipyretic.
Dara, daratumumab; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, pharmacodynamic; PI, proteasome inhibitor; PK, pharmacokinetic; QW, weekly; Q2W, every other week; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; Tec, teclistamab
1. NCT04108195 2.DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use [package insert].

Rodriguez-Otero P, et al. ASH 2021. Poster Presentation 1647.

ASH 2021

TRIMM-2: Safety Overview

Tec + Dara SC[a] (n=37)		
AE (≥20%), n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (51.4)	17 (45.9)
Anemia	17 (45.9)	11 (29.7)
Thrombocytopenia	12 (32.4)	12 (32.4)
Nonhematologic		
CRS	24 (64.9)	0 (0)
Diarrhea	13 (35.1)	1 (2.7)
Nausea	11 (29.7)	0 (0)
Asthenia	11 (29.7)	1 (2.7)
Fatigue	10 (27.0)	2 (5.4)
Pyrexia	9 (24.3)	0 (0)
Headache	9 (24.3)	0 (0)

Tec + dara was well-tolerated, with no new AEs observed compared to single agents

- No overlapping toxicities were observed
- There were no treatment discontinuations due to AEs
- All CRS events were limited to grade 1/2
- 1 (2.7%) patient had a grade 2 ICANS event; event fully resolved in 5 days
- Infections occurred in 22 (59.5%) patients (grade ≥3: 29.7%)

[a]Dara SC 1800 mg + Tec (1.5 mg/kg QW or 3 mg/kg QW or 3 mg/kg Q2W).

AE, adverse event; CRS, cytokine release syndrome; Dara, daratumumab; ICANS, immune effector cell–associated neurotoxicity syndrome; SC, subcutaneous; Q2W, every other week; QW, weekly; Tec, teclistamab

Rodriguez-Otero P, et al. ASH 2021. Poster Presentation 1647.

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TRIMM-2: Overall Response Rate

Response categories	Evaluable patients[a], n (%)		
	Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly		
	Tec SC Q2W 3 mg/kg (n=10)	Tec SC QW 1.5 mg/kg (n=19)	Tec SC QW 3 mg/kg (n=4)
ORR[b]	**7 (70.0)**	**16 (84.0)**	**4 (100.0)**
CR	0 (0)	6 (31.6)	3 (75.0)
VGPR	6 (60.0)	7 (36.8)	1 (25.0)
PR	1 (10.0)	3 (15.8)	0 (0)
SD	3 (30.0)	1 (5.3)	0 (0)
PD	0 (0)	2 (10.5)	0 (0)

- Median follow-up was 5.1 months (range: 0.3–12.9)
- Median time to first confirmed response: 1.0 month (range: 1.0–2.8)
- ORR was improved compared to the RP2D for teclistamab monotherapy

[a]Patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator; includes unconfirmed responses; [b]PR or better in response-evaluable patients.

CR, complete response; Dara, daratumumab; ORR, overall response rate; PR, partial response; QW, weekly; Q2W, every other week; SC, subcutaneous; SD, stable disease; PD, progressive disease; RP2D, recommended phase 2 dose; tec, teclistamab; VGPR, very good partial response

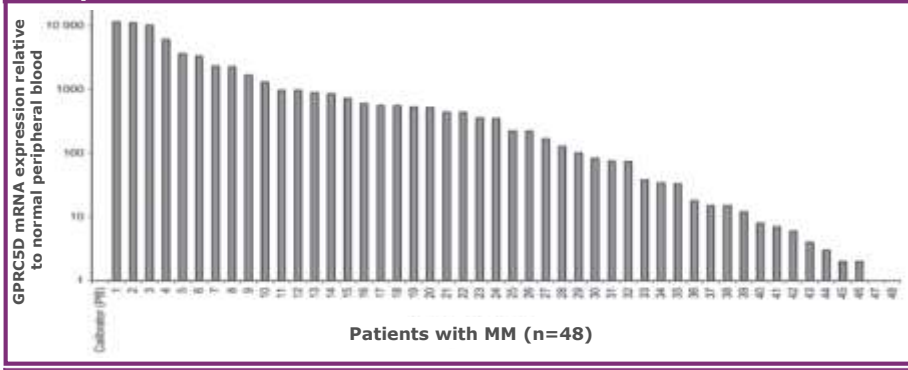
Rodriguez-Otero P, et al. ASH 2021. Poster Presentation 1647.

ASH 2021

Talquetamab

G Protein-Coupled Receptor 5D (GPRC5D)

Expression of GPRC5D in the Bone Marrow of Patients with MM



Rationale for GPRC5D as a Potential Novel Cancer Antigen

- Overexpression in poor-risk myeloma
- Limited low expression in normal tissues
- Association with clinical outcome (OS)
- Cell membrane expression with signaling capabilities
- Potential presence of T-helper and CTL epitopes

CTL, cytotoxic T lymphocytes; OS, overall survival.

Atamaniuk J, et al. *Eur J Clin Invest*. 2012;42(9):953-960.

MonumenTAL-1: Patient Characteristics

Characteristic	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=25
Age, years		
Median (range)	61.5 (46–80)	64.0 (47–84)
≥70, n (%)	7 (23)	9 (36)
Male, n (%)	19 (63)	11 (44)
Bone marrow plasma cells ≥60%[b], n (%)	6 (21)	2 (8)
Extramedullary plasmacytomas ≥1[c], n (%)	10 (33)	9 (36)
High-risk cytogenetics[d], n (%)	3 (11)	3 (13)
ISS stage[e], n (%)		
I	12 (43)	7 (29)
II	13 (46)	12 (50)
III	3 (11)	5 (21)
Time since diagnosis (years), median (range)	5.6 (1.7–19.6)	5.9 (0.8–14.9)
Prior lines of therapy, median (range)	6.0 (2–14)	5.0 (2–17)

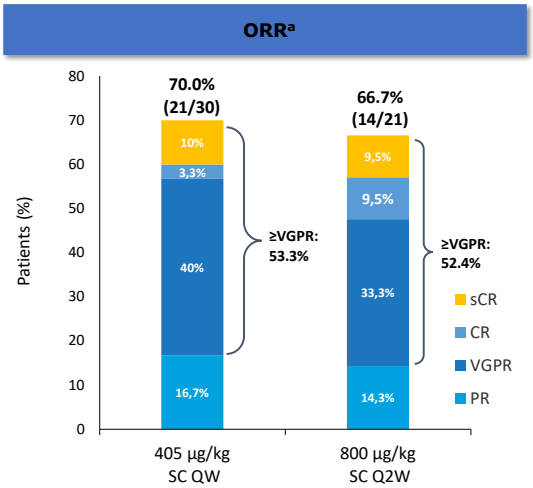
Characteristic	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=25
Prior stem cell transplantation, n (%)	27 (90)	18 (72)
Exposure status, n (%)		
Prior BCMA therapy[f]	8 (27)	4 (16)
Triple-class[g]	30 (100)	23 (92)
Penta-drug[h]	24 (80)	17 (68)
Refractory status, n (%)		
PI[i]	25 (83)	20 (80_
Carfilzomib	19 (63)	16 (64)
IMiD[j]	28 (93)	21 (84)
Pomalidomide	26 (87)	18 (72)
Anti-CD38 mAb[k]	30 (100)	21 (84)
Triple-class[g]	23 (77)	19 (76)
-drug[h]	6 (20)	6 (24)

[a]With 2–3 step-up doses; [b]Percentages calculated from n=29 for 405 µg/kg SC QW and n=24 for 800 µg/kg SC Q2W; [c]Soft tissue plasmacytomas not associated with the bone were included; [d]del(17p), t(4:14), and/or t(14;16); calculated from n=27 for 405 µg/kg SC QW and n=23 for 800 µg/kg SC Q2W; [e]At baseline, percentages calculated from n=28 for 405 µg/kg SC QW and n=24 for 800 µg/kg SC Q2W; [f]BCMA CAR-T therapy or BCMA non–CAR-T therapy; [g]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb; [h]≥2 PI, ≥2 IMiD, and ≥1 anti-CD38 mAb; [i]Bortezomib, carfilzomib, and/or ixazomib; [j]Thalidomide, lenalidomide, and/or pomalidomide; [k]Daratumumab and/or isatuximab.BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; Q2W, every other week; QW, weekly; SC, subcutaneous.

Krishnan AY, et al. ASH 2021. Oral Presentation 158.

ASH2021

MonumenTAL-1: Overall Response Rate



Response	405 µg/kg SC QW[b] n=30	800 µg/kg SC Q2W[b] n=25
Median follow-up, months, median (range)	9.0 (0.9–17.1)	4.8 (0.4–11.1)
Response-evaluable patients[c], n	30	21
ORR, n (%)	21 (70.0)	14 (66.7)
ORR in triple-class–refractory patients, n/N (%)	15/23 (65.2)	12/18 (66.7)
ORR in penta-drug–refractory patients, n/N (%)	5/6 (83.3)	5/6 (83.3)
Median time to first confirmed response, months, median (range)	0.9 (0.2–3.8)	1.2 (0.2–6.8)

- ORR appears to be comparable across both RP2Ds

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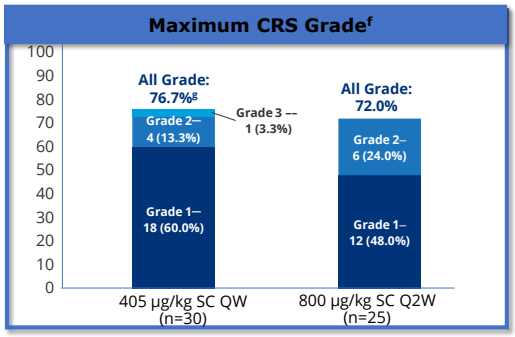
[a]Investigator assessment of evaluable patients-per 2011 IMWG response criteria; includes unconfirmed responses; [b]With 2–3 step-up doses; [c]Patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation. CR, complete response; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; Q2W, every other week; QW, weekly; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

Krishnan AY, et al. ASH 2021. Oral Presentation 158.

MonumenTAL-1: Cytokine Release Syndrome

Parameter	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=25
Patients with CRS, n (%)	23 (76.7)	18 (72.0)
Time to onset (days),[b] median (range)	2 (1–22)	2 (1–4)
Duration (days), median (range)	2 (1–3)	2 (1–5)
Patients who received supportive measures,[c] n (%)	23 (76.7)	18 (72.0)
Tocilizumab[d]	19 (63.3)	15 (60.0)
Steroids	1 (3.3)	1 (4.0)
Low-flow oxygen by nasal cannula	0 (0)	1 (4.0)
High-flow oxygen by face mask[e]	1 (3.3)	0 (0)
Single vasopressor[e]	1 (3.3)	0 (0)



- CRS was mostly grade 1/2 and limited to step-up dosing and Cycle 1 Day 1 dose
  - Only 1 patient with grade 3 CRS
  - CRS events after Cycle 1 Day 1 were limited to grade 1
  - 2 (3.6%) patients received >1 dose of tocilizumab for a single CRS event[h]

[a]With 2–3 step-up doses; [b]Relative to the most recent dose; [c]A patient could receive >1 supportive therapy; [d]Tocilizumab was allowed for all CRS events; [e]1 patient in the 405µg/kg SC QW cohort received a single vasopressor and high flow oxygen by face mask as supportive measures for CRS; [f]Graded according to Lee, et al. *Blood* 2014; 124:188; [g]Due to rounding; [h]Both patients received the 405 µg/kg SC QW dose level CRS, cytokine release syndrome; Q2W, every other week; QW, weekly; SC, subcutaneous.

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Krishnan AY, et al. ASH 2021. Oral Presentation 158.

MonumenTAL-1: Nonhematologic Safety Profile

AEs (≥20 of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=25	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nonhematologic				
CRS	23 (77)	1 (3)	18 (72)	0 (0)
Dysgeusia	18 (60)	N/A	9 (36)	N/A
Dysphagia	11(37)	0 (0)	4 (16)	0 (0)
Skin exfoliation	11(37)	0 (0)	9 (36)	0 (0)
Fatigue	9 (30)	1 (3)	7 (28)	0 (0)
Weight decreased	9 (30)	0 (0)	6 (24)	0 (0)
Nail disorder[b]	9 (30)	N/A	5 (20)	N/A
Pyrexia	6 (20)	0 (0)	4 (16)	0 (0)
Dry mouth	8 (27)	0 (0)	10 (40)	0 (0)
Diarrhea	8 (27)	0 (0)	3 (12)	0 (0)
Nausea	7 (23)	0 (0)	3 (12)	0 (0)
ALT increased	6 (20)	1 (3)	8 (32)	1 (4)

- Infections occurred in 33% (18/55) of patients
  - 3 (5%) patients had grade 3/4 infections
- Dysgeusia generally mild with few dose adjustments required
- Skin-related and nail disorder AEs[c] occurred in 75% of patients
  - Most commonly reported was exfoliation (all grade 1/2)
  - Rashes were mostly grade 1/2
    - Grade 3 rashes reported in 7.5% (4/55) of patients[d]; all patients successfully rechallenged (3 at the same dose level)
- Injection-site reactions in 16% (9/55) of patients (all grade 1/2)
- No AE deaths related to talquetamab
  - One AE death due to basilar artery thrombosis, in a patient with significant history of vascular disease

[a]With 2–3 step-up doses; [b]Includes nail disorders, onychomadesis, and nail dystrophy; [c]SOC for skin and subcutaneous disorders including nail disorders; [d]1 grade 3 rash was considered a DLT; Study protocol was amended and the other 3 rashes were not considered DLTs. AE, adverse event; ALT, alanine aminotransferase; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; N/A, not applicable; Pt, patient; RP2D, recommended phase 2 dose; SOC, system organ class; Q2W, every other week; QW, every week; SC, subcutaneous.

Krishnan AY, et al. ASH 2021. Oral Presentation 158.

ASH2021

Talquetamab
Daratumumab

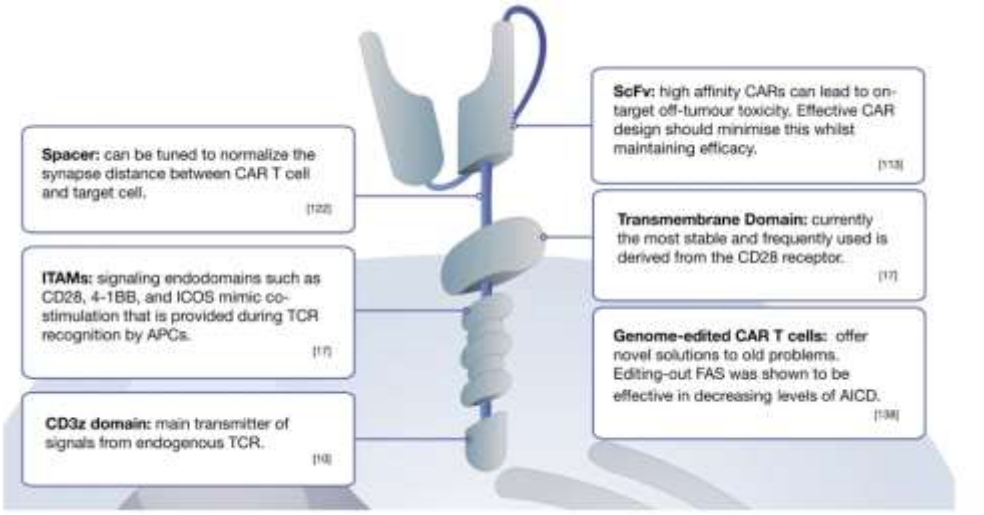
TRIMM-2: Overall Response Rate

Response Categories	Evaluable patients[a], n (%)		
	Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly		
	Tal 400 µg/kg SC Q2W (n=5)	Tal 400 µg/kg SC QW (n=7)	Tal 800 µg/kg SC Q2W (n=9)
ORR[b]	**4 (80.0)**	**6 (85.7)**	**7 (77.8)**
sCR/CR	1 (20.0)	2 (28.6)	1 (11.1)
VGPR	2 (40.0)	3 (42.9)	5 (55.6)
PR	1 (20.0)	1 (14.3)	1 (11.1)
MR	0 (0)	0 (0)	0 (0)
SD	0 (0)	1 (14.3)	2 (22.2)
PD	1 (20.0)	0 (0)	0 (0)

- Median follow-up was 4.2 months
- Median time to first confirmed response: 1.0 month (range 0.9-2.4)
- ORR across all dose levels was improved compared to RP2Ds for tal monotherapy

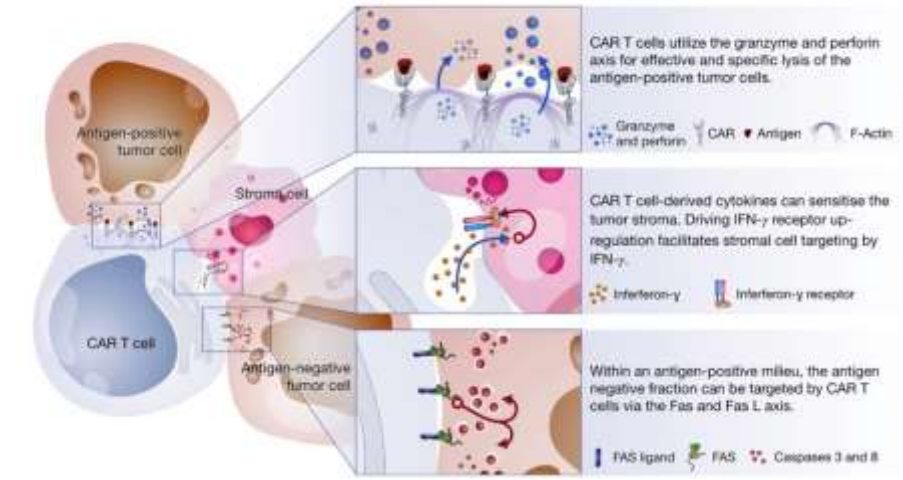
[a]Patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. Includes unconfirmed responses;
[b]PR or better in response-evaluable patients; includes unconfirmed responses.
CR, complete response; Dara, daratumumab; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; QW, weekly; Q2W, every other week; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; Tal, talquetamab; VGPR, very good partial response
Chari A, et al. ASH 2021. Oral Presentation 161.

CAR-T second generation

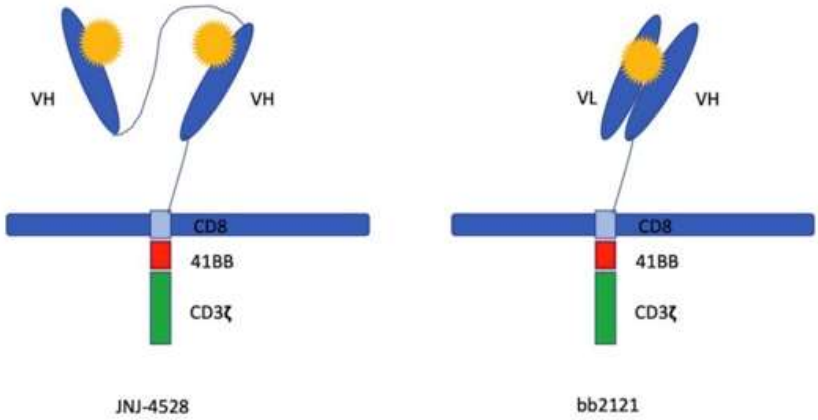


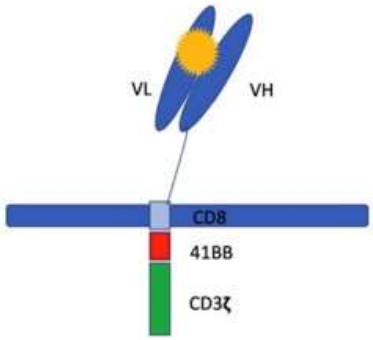
Benmebarek, Int J Mol Sci, 2019

The way of action of CART



CAR-T





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Ide- cel

KarMMA ide-cel faza 2

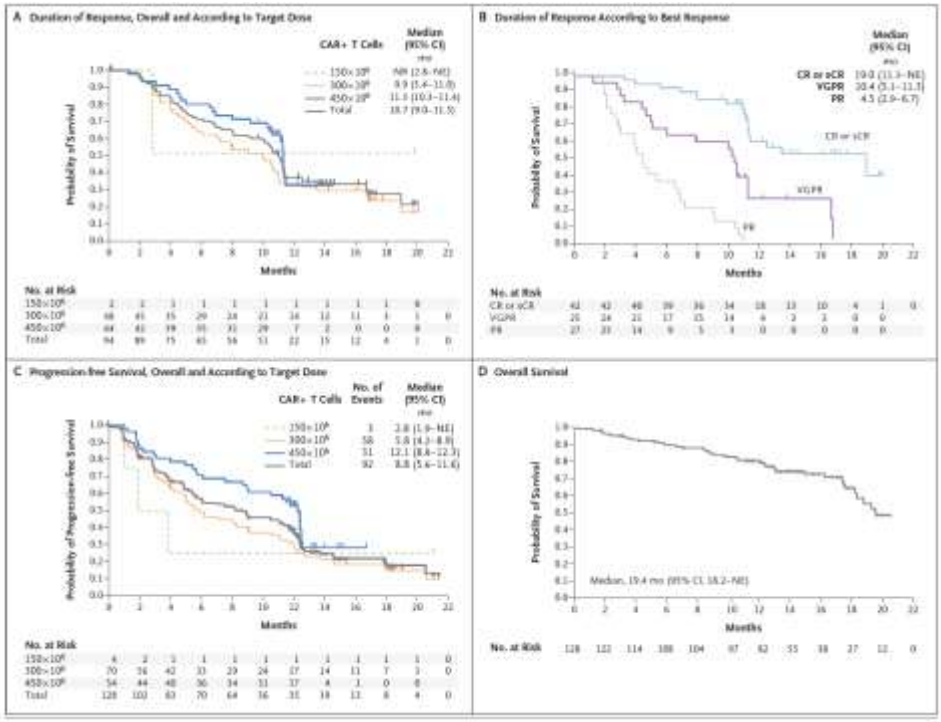
≥3 prior regimens (including IMiD, PI, and CD38 mAb) and refractory to their last regimen

Lymphodepletion: cyclophosphamide 300 mg/m²+ fludarabine 30 mg/m² x 3

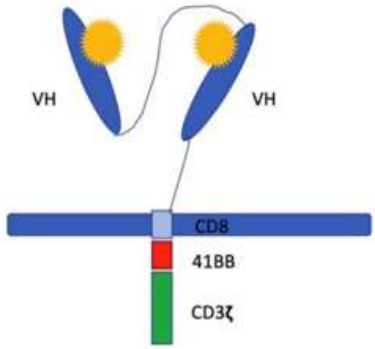
Dose: 150–450 × 10^6 CAR+ T cells (target dose range).

Characteristic	Ide-cel Target Dose of CAR+ T Cells			Total (N=128)
	150×10^6 (N=4)	300×10^6 (N=70)	450×10^6 (N=54)	
Median age (range) — yr	54 (49–69)	61 (33–76)	62 (43–78)	61 (33–78)
Male sex — no. (%)	4 (100)	38 (54)	34 (63)	76 (59)
Median time from initial diagnosis to screening (range) — yr	10 (6–12)	7 (2–38)	6 (1–17)	6 (1–18)
Extramedullary disease — no. (%)†	0	34 (49)	16 (30)	50 (39)
High tumor burden — no. (%)‡	3 (75)	34 (49)	28 (52)	65 (51)
Tumor BCMA expression ≥50% at screening — no. (%)	4 (100)	60 (86)	45 (83)	109 (85)
Median no. of previous antimyeloma regimens (range) — no. (%)	9 (4–12)	6 (3–16)		6 (3–16)
>1 Previous antimyeloma regimen per year — no. (%)	2 (50)	36 (51)	22 (41)	60 (47)
Previous autologous HSCT — no. (%)	4 (100)	67 (96)	49 (91)	120 (94)
>1 transplantation	3 (75)	23 (33)	18 (33)	44 (34)
Refractory status — no. (%)††				
Immunomodulatory agent	4 (100)	70 (100)	52 (96)	126 (98)
Proteasome inhibitor	4 (100)	63 (90)	49 (91)	116 (91)
Anti-CD38 monoclonal antibody	4 (100)	66 (94)		120 (94)
Daratumumab	3 (75)	61 (87)	45 (83)	109 (85)
Double-refractory disease‡‡	4 (100)	63 (90)		114 (89)
Triple-refractory disease§§	4 (100)	60 (86)		108 (84)
Penta-refractory disease¶¶	1 (25)	24 (34)	8 (15)	33 (26)

Munshi, ASCO, 2020, abstract 8503
Munshi, NEJM 2021



Munshi, NEJM, 2021



JNJ-4528

Cilta-cel

CARTITUDE-1: Baseline Characteristics

Characteristic	N=97
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Extramedullary plasmacytomas ≥1, n (%)	13 (13.4)[a]
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

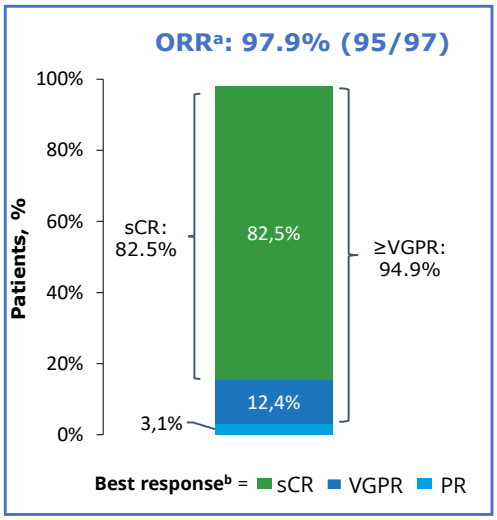
Characteristic	N=97
Prior lines of therapy, median (range)	6.0 (3–18)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogenic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PI, proteasome inhibitor
[a]Additional 6 patients had a soft-tissue component of a bone-based plasmacytoma (total plasmacytomas, 19.6%). [b]Denominator n=62, the number of evaluable samples; BCMA expression detected in all evaluable samples.
[c]At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody.

15

62nd ASH Annual Meeting 2020, Maddali D et al. PRESENTATION #177

CARTITUDE-1: Efficacy Response



Responses deepened over time from the 1-year follow-up

Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

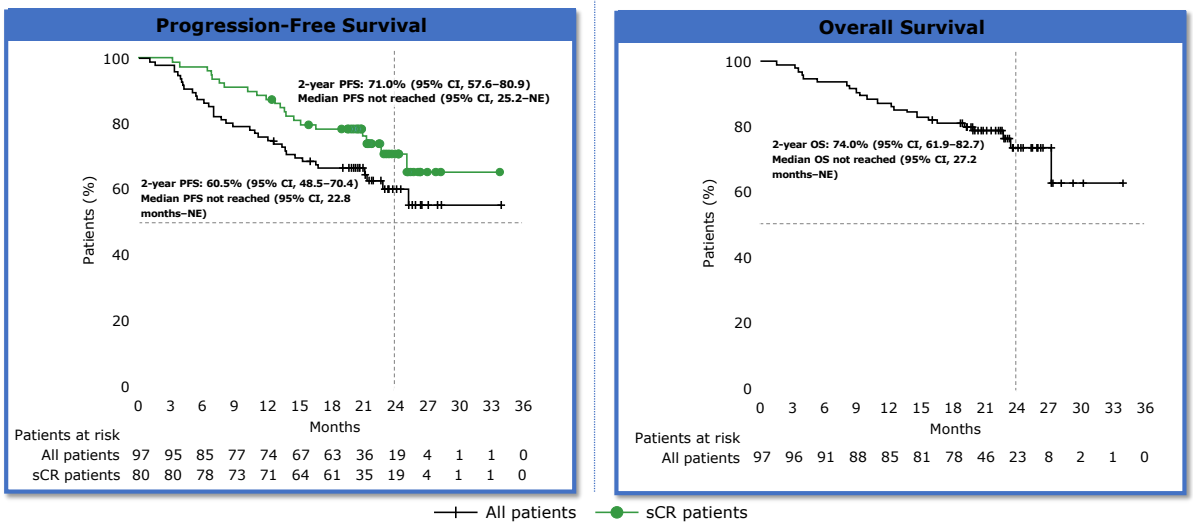
- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)
- 60.5% of patients are still progression-free at 2 years

CR, complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response.
[a]ORR assessed by independent review committee; [b]No patient had CR or stable disease as best response.

ASH2021

Martin T, et al. ASH 2021. Oral Presentation 549.

CARTITUDE-1:
Progression-Free Survival and Overall Survival



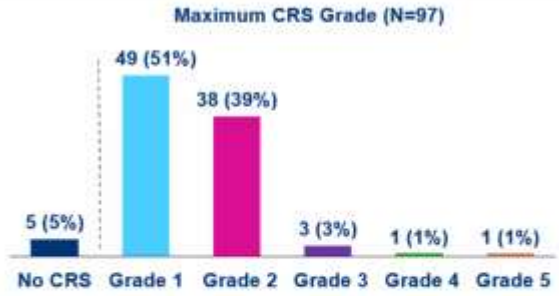
MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; sCR, stringent complete responsez

Martin T, et al. ASH 2021. Oral Presentation 549.

CARTITUDE-1: CRS

	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]
Supportive measures, n (%)	88 (90.7)
Tocilizumab	67 (69.1)
Corticosteroids	21 (21.6)
Anakinra	18 (18.6)
Vasopressor used	4 (4.1)
Intubation/mechanical ventilation	1 (1.0)
Other	
Cyclophosphamide	1 (1.0)
Etanercept	1 (1.0)

- Cilta-cel CAR+ T cells showed maximum peripheral expansion at a median of 13 days (range, 9–55)



- Of 92 patients with CRS, majority (94.6%) were grades 1/2
- CRS onset
  - Day 4 or later: 89.1% (n=82)
  - Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset

ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis.
[a]CRS was graded using Lee et al. (Blood 2014) in the phase 1b portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion. [b]The patient with 97-day duration died due to CRS/HLH

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CARTITUDE-1: Neurotoxicity

Total CAR-T cell neurotoxicities
- Any grade: 20 (20.6%)
- Grade ≥3: 10 (10.3%)

ICANS
- Any grade: 16 (16.5%)
- Grade ≥3: 2 (2.1%)

Other neurotoxicities[a]
- Any grade: 12 (12.4%)
- Grade ≥3: 9 (9.3%)

	ICANS	Other neurotoxicities[a]
Time to onset, median (range) days	8 (3–12)	27 (11–108)
Time to recovery, median (range) days	4 (1–12)	75 (2–160)

Other neurotoxicities[a]

- **Occurring after resolution of CRS and/or ICANS**
- Among 12 patients
  - 5 had AEs including movement and/or neurocognitive changes
  - 7 had AEs including nerve palsy, peripheral motor neuropathy

Outcomes for CAR-T cell neurotoxicities

- ICANS resolved in all patients
- Other neurotoxicities resolved in 6 patients, and did not resolve in 6 patients:
  - 1 patient has ongoing neurotoxicity
  - 1 patient died from complications of neurotoxicity
  - 4 patients died due to other causes
- No additional movement and neurocognitive AEs were seen in the CARTITUDE development program

AE, adverse event; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.
[a]Events not reported as ICANS (ie, onset after a period of recovery from CRS and/or ICANS)).

19

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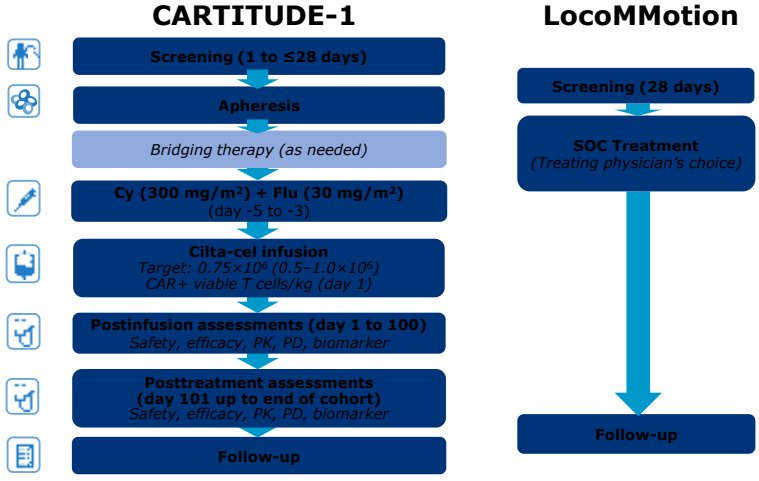
Phase 1b/2 CARTITUDE-1 and Real-world LocoMMotion Study Designs Were Aligned to Create Best Possible External Control

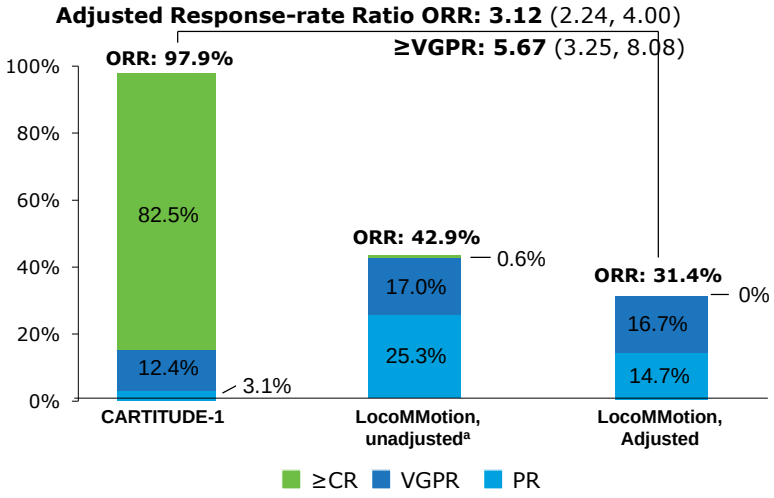
Key inclusion criteria are aligned for CARTITUDE-1 and LocoMMotion
- Progressive MM per IMWG criteria
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, and anti-CD38 antibody therapy
- Measurable disease
- ECOG PS ≤1



Populations aligned to the largest extent possible and individual patient data available for both studies

Mateos MV, et al. ASH 2021. Oral Presentation 550.

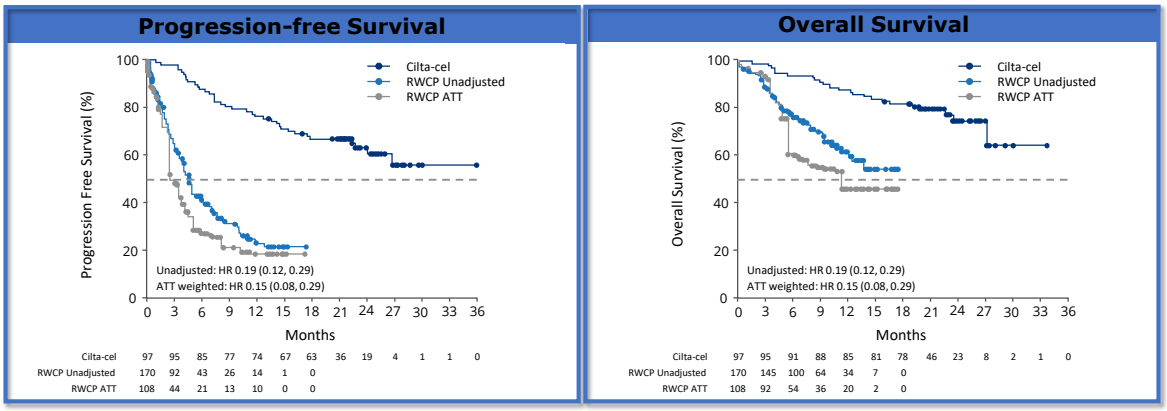
CARTITUDE-1 vs. LocoMMotion: Comparison of Response Rates



- Observed rates of ORR, ≥VGPR and ≥CR were all significantly higher in cilta-cel cohort
- Patients treated with cilta-cel are 3.12 times more likely to achieve a response (ORR) vs. RWCP and 5.67 times more likely to achieve ≥VGPR
- 82.5% of cilta-cel patients reached ≥CR vs. only one patient (0.6%) with RWCP

Mateos MV, et al. ASH 2021. Oral Presentation 550.

Cilta-cel Reduces Death and Risk of Progression Significantly Compared to RWCP



Cilta-cel significantly reduced the risk of progression or death (PFS) by 85% (HR 0.15, 95% CI: 0.08-0.29, p<0.0001) and risk of death (OS) by 80% (HR=0.20, 95% CI: 0.09-0.41, p<0.0001)

Mateos MV, et al. ASH 2021. Oral Presentation 550.

CARTITUDE-5 Randomized, Phase 3, Open-Label, Global, Multicenter Study

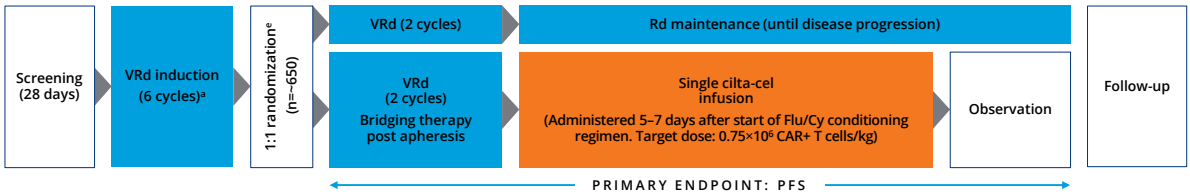
Aim: To describe the design of the CARTITUDE-5 (NCT04923893), which will compare the efficacy of VRd followed by cilta-cel versus VRd followed by Rd maintenance in patients with NDMM for whom ASCT is not planned as initial therapy

Key inclusion criteria
- ≥18 years of age with NDMM per IMWG criteria
- Measurable disease
- ECOG performance status score of 0 or 1
- Not candidates for high-dose chemotherapy with ASCT due to advanced age, comorbidities, or deferment of ASCT

All patients will complete 6[a] cycles (21 days each) of VRd induction therapy[b] prior to randomization (1:1)

VRd + cilta-cel arm
- Apheresis and 2 more cycles of VRd as bridging therapy
- Lymphodepletion daily for 3 days[c]
- Cilta-cel as a single infusion

VRd + Rd arm (SOC)
- Two more cycles of VRd
- Rd maintenance therapy[d] continues until progressive disease or unacceptable toxicity



[a]Participants who received 1 cycle of VRd prior to screening will only receive 5 cycles of VRd between screening and randomization; [b]Bortezomib 1.3 mg/m² subcutaneously on days 1, 4, 8, and 11, lenalidomide 25 mg orally on days 1–14, dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12; [c]Cyclophosphamide 300 mg/m² and fludarabine 30 mg/m²; [d]28-day cycle: lenalidomide 25 mg orally on days 1–21 and dexamethasone 40 mg orally on days 1, 8, 15, and 22; [e]At randomization, patients will be stratified by the following factors: R-ISS (I,II,III); age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); response to VRd induction (≥VGPR, ≤PR).
Dytfeld D, et al. ASH 2021. Poster Presentation 1835.

Update and guidelines in myeloma

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