Terapia del paziente refrattario a IMiDs e PIs

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Unmet medical need in MM: MAMMOTH study

Most patients with MM receive PIs, IMiD® agents, and anti-CD38 mAbs

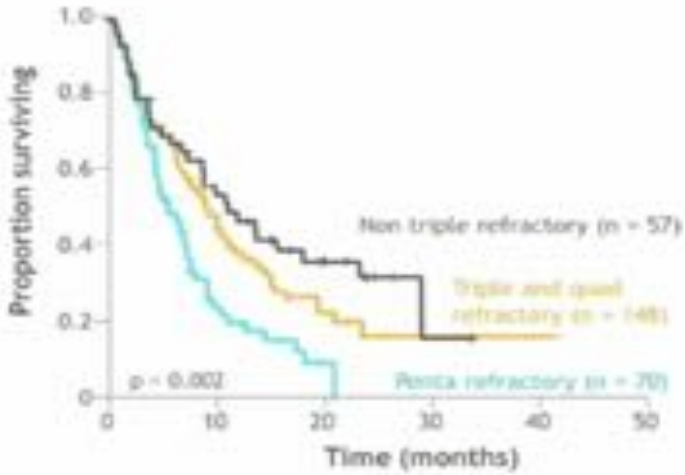
Suboptimal outcomes in patients refractory to anti-CD38 mAbs

	Median OS, months	
Non-triple-refractory MM	11.2	Refractory to 1 anti-CD38 mAb, and PI or IMiD® agents (but not both)
Triple- and quad-refractory MM	9.2	Refractory to 1 anti-CD38 mAb + one PI + one or two IMiD® agents
Penta-refractory MM	5.6	Refractory to one anti-CD38 mAb + two PIs + two IMiD® agents
Overall cohort	8.6	

275 patients were refractory to anti-CD38 mAbs.

ORR: 31%
Median PFS: 3.4 months
Median OS: 9.3 months

OS according to refractory status

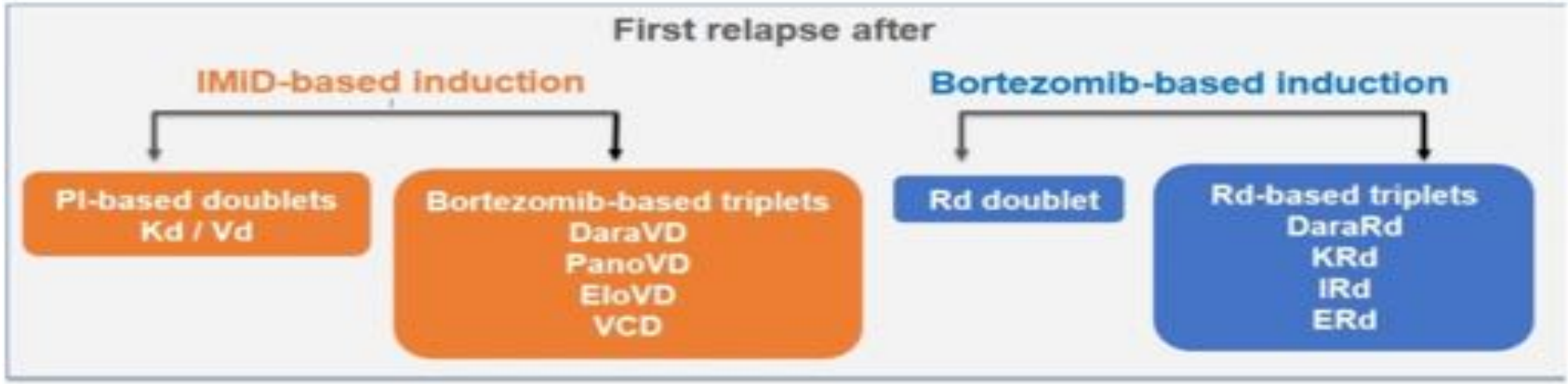


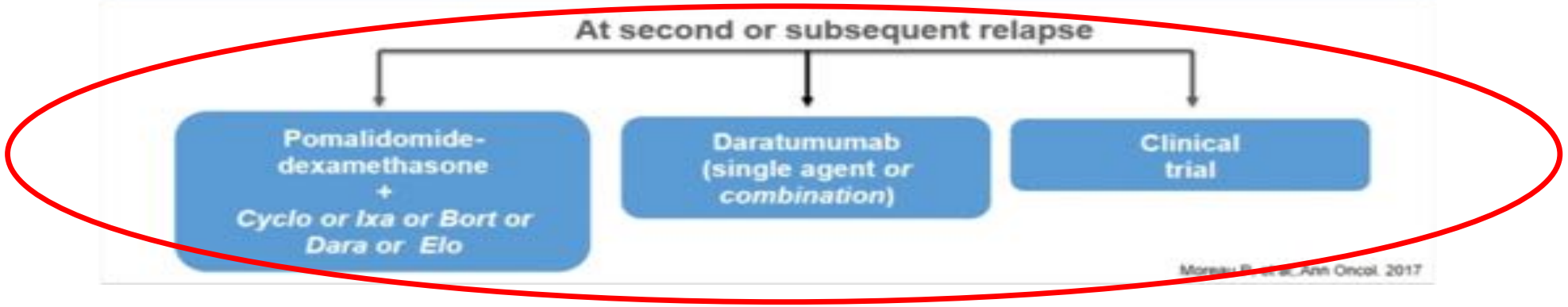
CD, cluster of differentiation; IMiD®, immunomodulatory drug; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor.

Gandhi UH, et al. Leukemia. 2019;33:2266-75.

18th International Myeloma Workshop, 2021

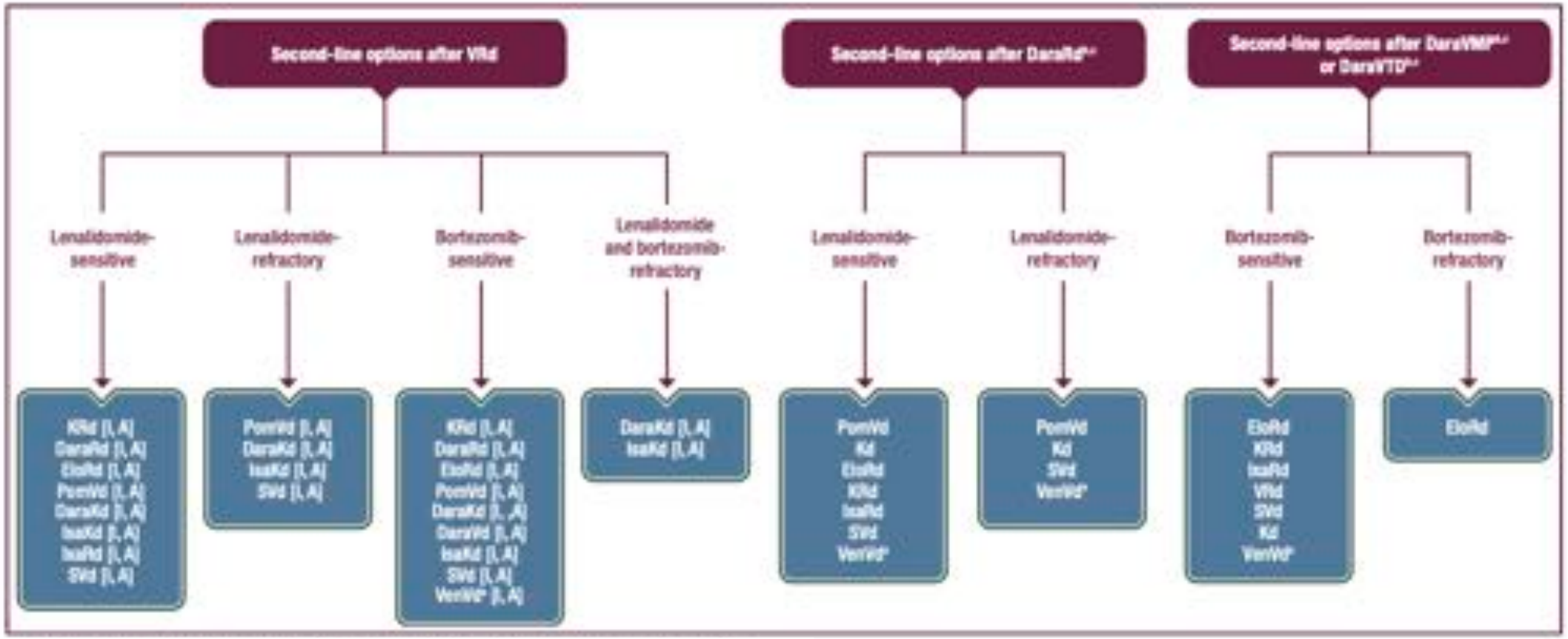
ESMO Guidelines 2017: RRMM



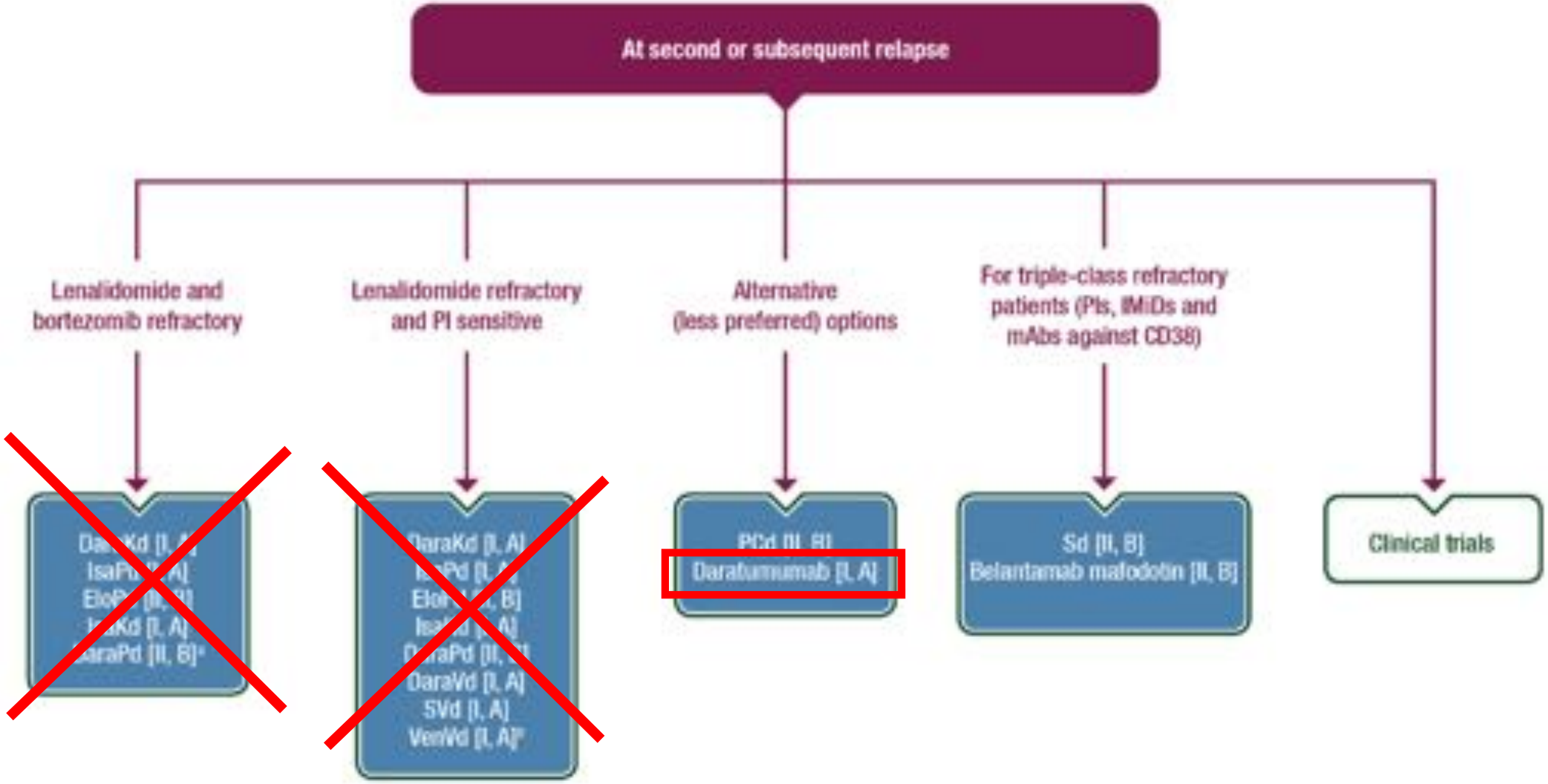


Moreau P. et al. Ann Oncol. 2017

Terapia di seconda linea per pazienti con MM che hanno ricevuto VRD o terapia Dara –based di prima linea

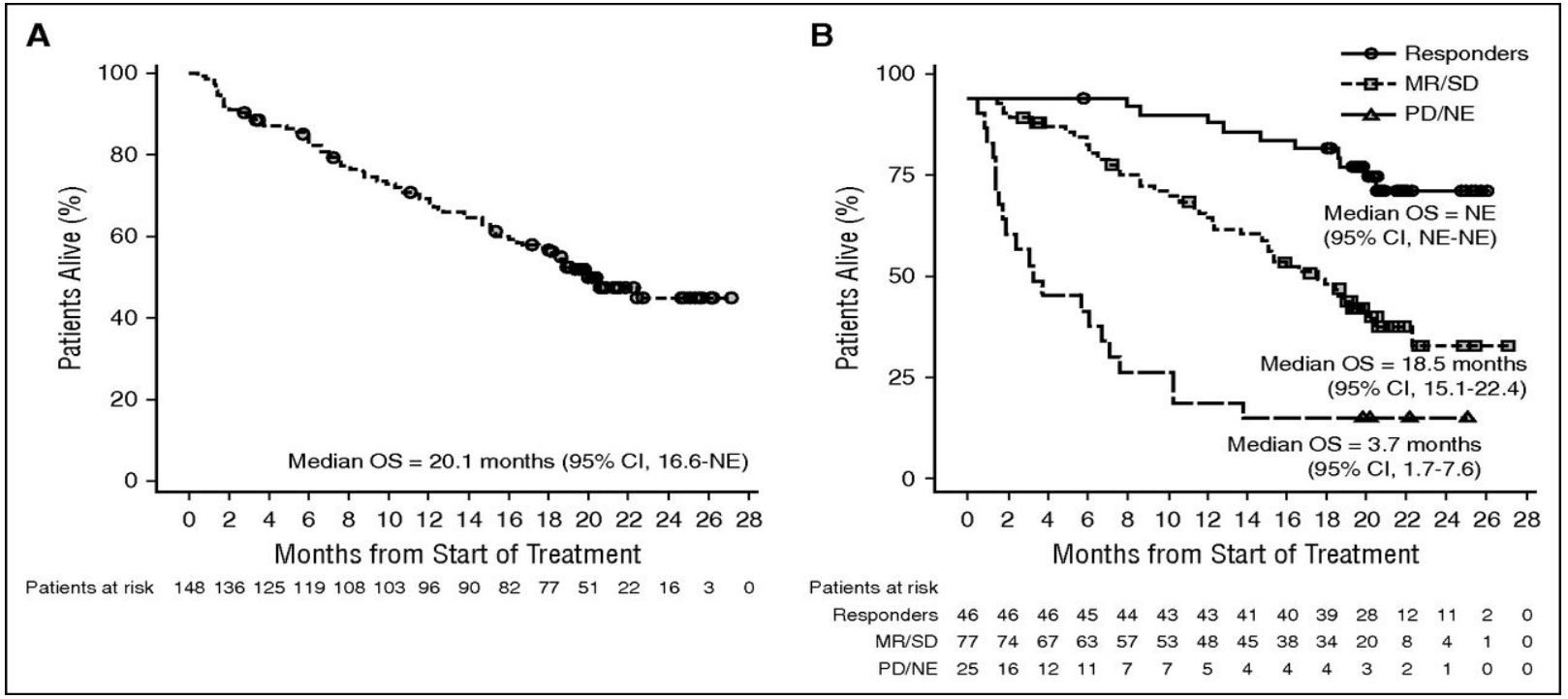


Dimopoulos et al, Annals of Oncology 2021



Dimopoulos et al, Annals of Oncology 2021

Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma (Sirius and GEN501)



Saad Z. Usmani,Brendan M. Weiss,Torben Plesner,Nizar J. Bahlis,Andrew Belch,Sagar Lonial,Henk M. Lokhorst,Peter M. Voorhees,Paul G. Richardson,Ajai Chari,A. Kate Sasser,Amy Axel,Huaibao Feng,Clarissa M. Uhlar,Jianping Wang,Imran Khan,Tahamtan Ahmadi,Hareth Nahi, Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma, Blood, 2016, Figure 4

Recent New FDA Approvals for Novel Agents in R/R MM

Selinexor +D

FDA approved July 3, 2019

In combination with dex for patients with R/R MM who have received ≥ 4 previous therapies and whose disease is refractory ≥2 PI, ≥2 IMiD and 1 anti-CD38 mAb.

Belantamab Mafodotin

FDA approved Aug 5, 2020

For patients with R/R MM who have received ≥ 4 previous therapies including an anti–CD-38 mAb, a PI, and an IMiD

[illegible]

FDA approved Dec 18, 2020

In combination with bortezomib/dex for patients with R/R MM who have received ≥ 1 previous of therapy

Selinexor is also approved in combination with dex for patients with R/R MM who have received ≥ 4 previous therapies and whose disease is refractory to ≥ 2 PI, ≥ 2 IMiD, and an anti–CD-38 mAb

Melphalan Flufenamide (Melflufen)

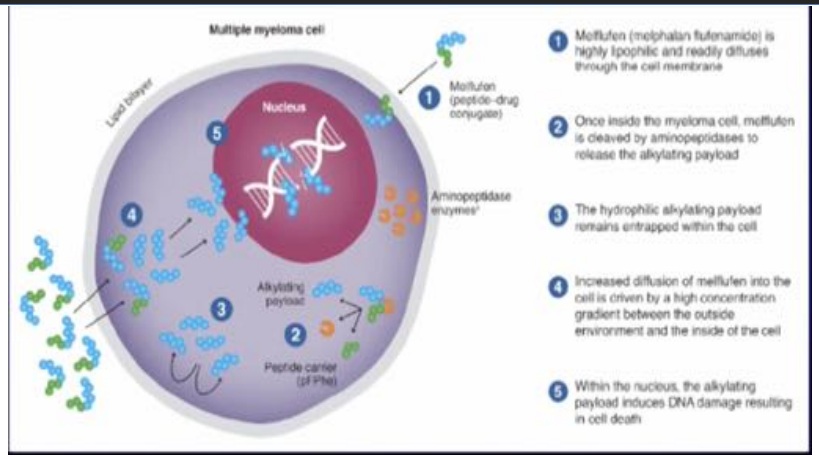
FDA approved Feb 26, 2021

In combination with dex for patients with R/R MM who have received ≥ 4 previous lines of therapy and whose disease is refractory to ≥ 1 PI, 1 IMiD, and 1 anti–CD-38 mAb

Management of Patients > 3 line - Novel Drugs Under Development

Novel Alkylators: Melflufen

- **Melflufen is a highly lipophilic alkylating peptide, belonging to the novel class of Peptidase Enhanced Compounds**
- **Intracellular amino-peptidases that are overexpressed in most malignant cells, will rapidly cleave melflufen releasing the hydrophilic, active alkylating metabolite**
- **In vitro, treatment of tumor cells with melflufen results in 50-fold higher intracellular concentration of alkylating metabolite than those treated with equimolar melphalan alone. In vivo, human xenograft mouse models treated with melflufen showed prolonged survival.**



Melflufen 40 mg iv every 28 days + Dex 40 mg weekly

Phase II O-12-M1 trial

RR MM pts ≥ 2 lines and refr. to last line.

N = **45 in combination cohort.**

Median 4 (2-14) lines; 64% double refr.; 53% Alkylator refr.

ORR 31% ..... 5 VGPR & 9 PR patients
PFS: 5.7m .....DOR 8.4m; OS: 20.7m

G3/4 AEs: Thromboc. (62%), Neutrop. (58%), Anemia: 42%

Richardson. Lancet Haematology. 2020;7:E395.

Phase II Horizon trial

- **125 RRMM pts. Median 5 (2-12) prior lines;** 38% patients had high-risk cytogenetics; 88% double refr ; 71% triple refractory (PI + IMiD + anti-CD38)

ORR 29% .
PFS: 4.2 mos. OS: 11.6 mos

G3/4AEs: Neutropenia (66%), Thromboc. (69%), Anemia: (37%)

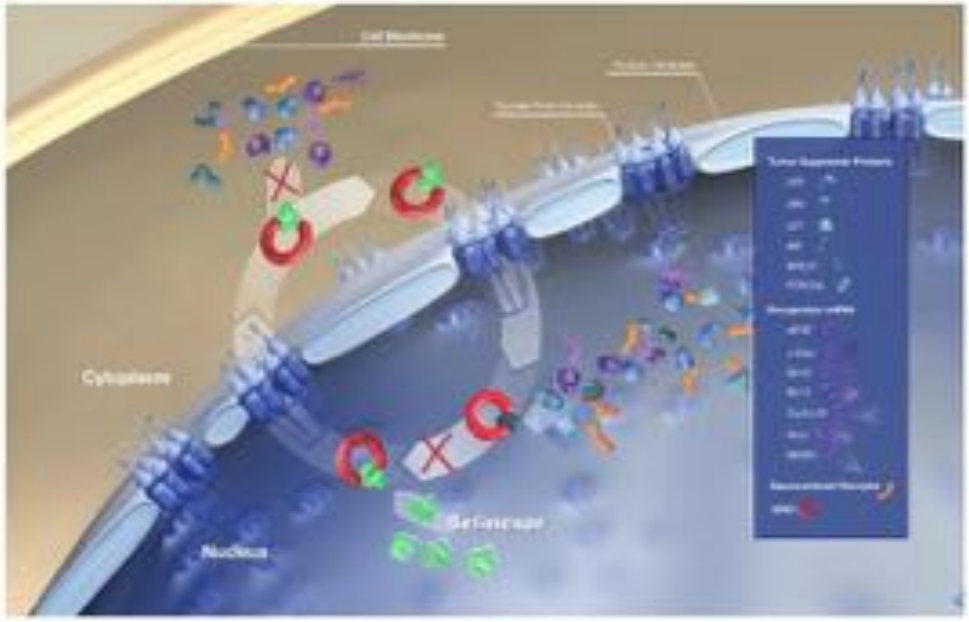
Ocio. ASH 2020. Abstr 417. ***Richardson.*** J Clin Oncol 2021 39:757-767 .

Anchor Trial…ORR for (Melf-Dex) + Dara: 70%; PFS: 11.5 mos…….+ Btz: 60%

SELINEXOR

Selinexor:

First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]



Exportin 1 (XPO1) is the major nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g., p53, IκB, and FOXO)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
- Glucocorticoid receptor (GR)

XPO1 is overexpressed in MM:

- High **XPO1** levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis
- **XPO1** levels correlate with poor prognosis and drug resistance

Selinexor is an oral selective **XPO1 inhibitor**; preclinical data supports that selinexor:

- Reactivates multiple TSPs by preventing nuclear export
- Inhibits oncoprotein translation
- Reactivates GR signaling in presence of dexamethasone

[1]Schmidt et al., Leukemia, 2013. [2]Tai et al., Leukemia, 2018. [3]Argueta et al., Oncotarget, 2018 [4]Turner et al. 2017 unpublished

STORM: Selinexor + Dexamethasone in R/R Myeloma

- Multicenter, pivotal phase II trial

Treatment-experienced patients with penta-refractory MM* and adequate organ function† (N = 122) → **Selinexor** 80 mg PO + **Dexamethasone** 20 mg QW2 on Days 1, 3 of 28-day cycle → *Until PD*

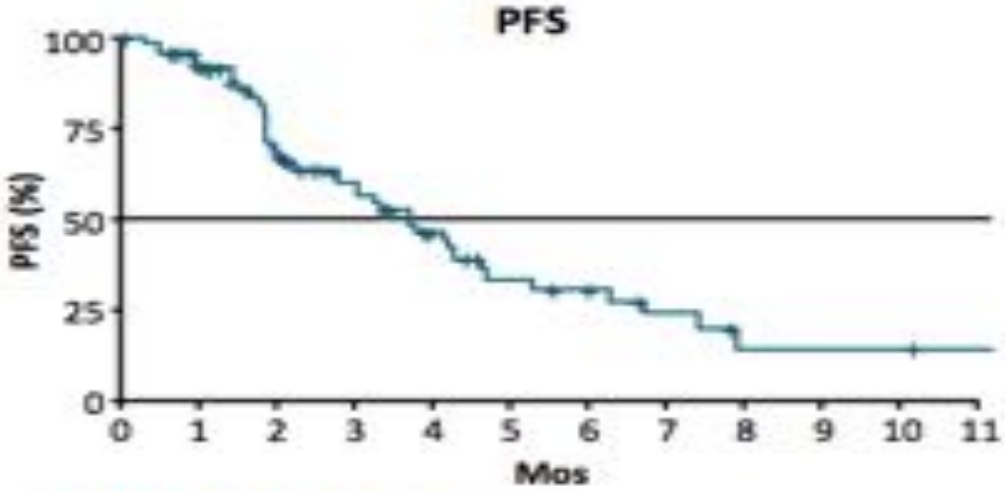
*Previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, an alkylating agent, and glucocorticoid, with disease documented to be refractory to ≥ 1 PI, ≥ 1 IMiD, daratumumab, a glucocorticoid, and last therapy.
†Creatinine clearance ≥ 20 mL/min; ANC ≥ 1000/mm^3; platelets ≥ 75,000/mm^3 or ≥ 50,000/mm^3 if BM plasma cells ≥ 50%; Hb ≥ 8.5 g/dL.

- Median age: 65 years (range: 40-86)
- Median prior regimens: 7 (range: 3-18)
- Refractory
  - PI, IMiD, Dara: 100%
  - Car/Pom/Dara: 96%
  - Bort/Car/Len/Pom/Dara: 68%

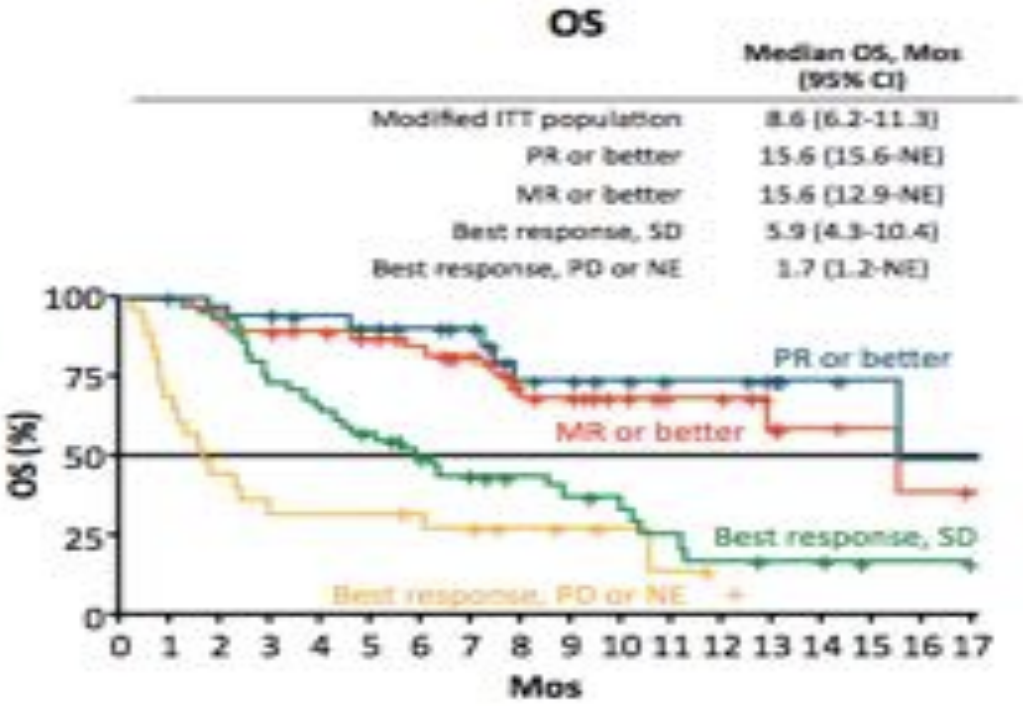
- Supportive care: IV hydration, antiemetics, NaCl tablets, cytokine transfusions
- Primary endpoint: ORR
- Secondary endpoints: DoR, CBR, OS, PFS, safety

Chari. N Engl J Med. 2019;381:727.

STORM: Responses and Survival



- ORR: 26.2%
  - Penta-refractory: 25.3%



Chari. N Engl J Med. 2015;381:727.

STORM: Treatment-Related Nonhematologic AEs

TRAEs in ≥ 15% of patients, n (%)	Total (N = 123)	Grade 1	Grade 2	Grade 3
Fatigue	90 (73)	16 (13)	43 (35)	31 (25)
Nausea	88 (72)	34 (28)	42 (34)	12 (10)
Anorexia/ decreased appetite	69 (56)	22 (18)	41 (33)	6 (5)
Weight loss	62 (50)	34 (28)	27 (22)	1 (1)
Diarrhea	56 (46)	32 (26)	15 (12)	9 (7)
Vomiting	47 (38)	22 (18)	21 (17)	4 (3)
Hyponatremia	45 (37)	18 (15)	0	26 (21)
Upper respiratory tract infection	28 (23)	3 (2)	23 (19)	2 (2)

TRAEs in ≥ 15% of patients, n (%)	Total (N = 123)	Grade 1	Grade 2	Grade 3
Constipation	27 (22)	16 (13)	9 (7)	2 (2)
Dyspnea	27 (22)	11 (9)	11 (9)	5 (4)
Cough	21 (17)	14 (11)	7 (6)	0
Hypokalemia	21 (17)	10 (8)	3 (2)	8 (7)
Insomnia	21 (17)	13 (11)	6 (5)	2 (2)
Mental status changes	21 (17)	7 (6)	7 (6)	7 (6)
Pneumonia	21 (17)	0	8 (7)	10 (8)
Dizziness	19 (15)	14 (11)	5 (4)	0
Pyrexia	19 (15)	11 (9)	8 (7)	0

- n = 1 (0.8%) each: grade 4 pneumonia, grade 4 hyponatremia; n = 2 (1.6%): grade 5 pneumonia

Chari. N Engl J Med. 2019;381:727.

STORM: Treatment-Related Hematologic AEs

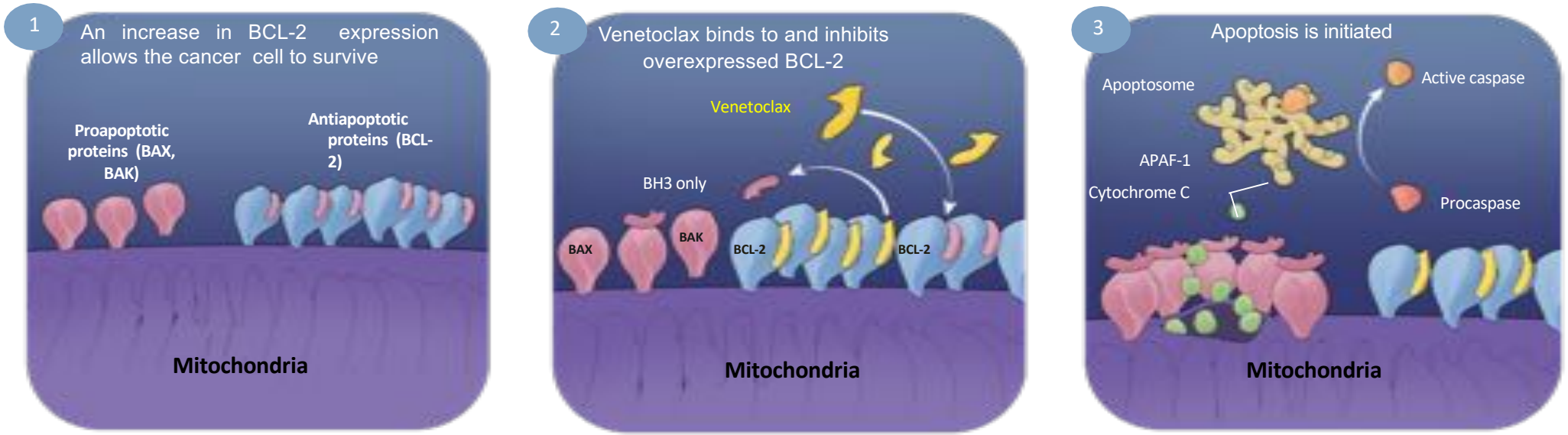
TRAEs in ≥ 10% of Patients, n (%)	Total (N = 123*)	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	90 (73)	12 (10)	6 (5)	31 (25)	41 (33)
Anemia	83 (67)	7 (6)	22 (18)	53 (43)	1 (1)
Neutropenia	49(40)	7 (6)	16 (13)	22 (18)	4 (3)
• Febrile neutropenia	2 (2)	--	--	2 (2)	--
Leukopenia	41 (33)	8 (7)	16 (13)	17 (14)	--
Lymphopenia	20 (16)	2 (2)	4 (3)	10 (8)	4 (3)

*22 discontinuations due to TRAEs.

- Low platelet count at baseline associated with risk of developing grade 3/4 thrombocytopenia

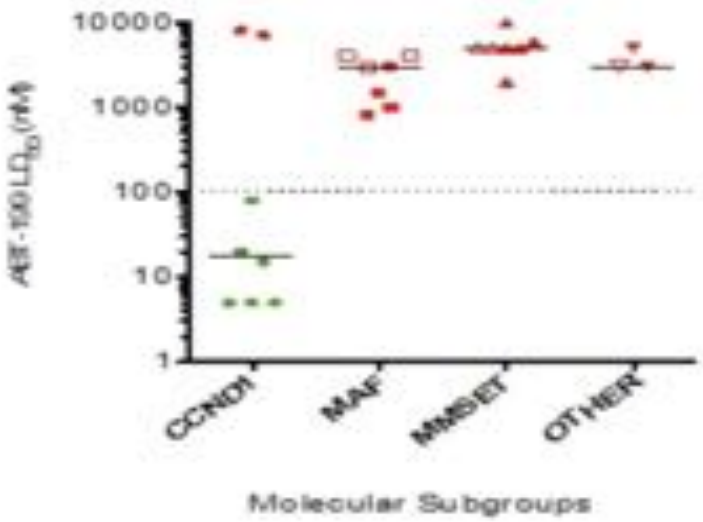
Chari. N Engl J Med. 2019;381:727.

Venetoclax: Mechanism of Action



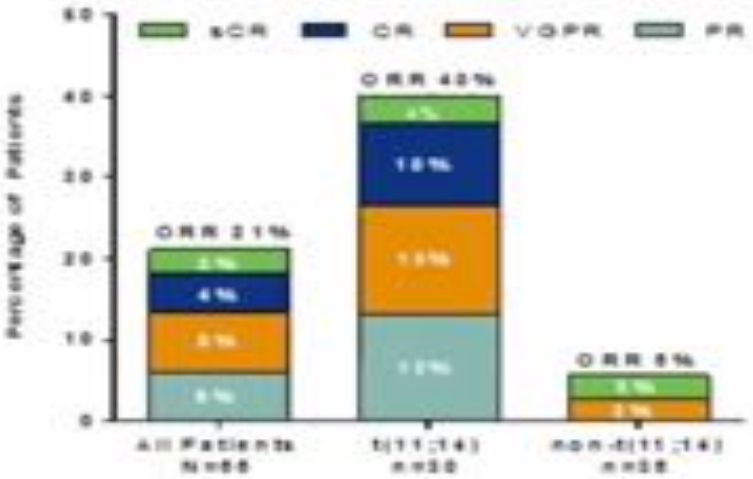
Kumar S, et al. ASCO 2015. Abstract 8576.

Efficacy of venetoclax in t(11;14) myeloma



Sensitivity to venetoclax is mostly restricted to MM cells harboring the t(11;14) translocation

Touzeau et al. Leukemia 2015



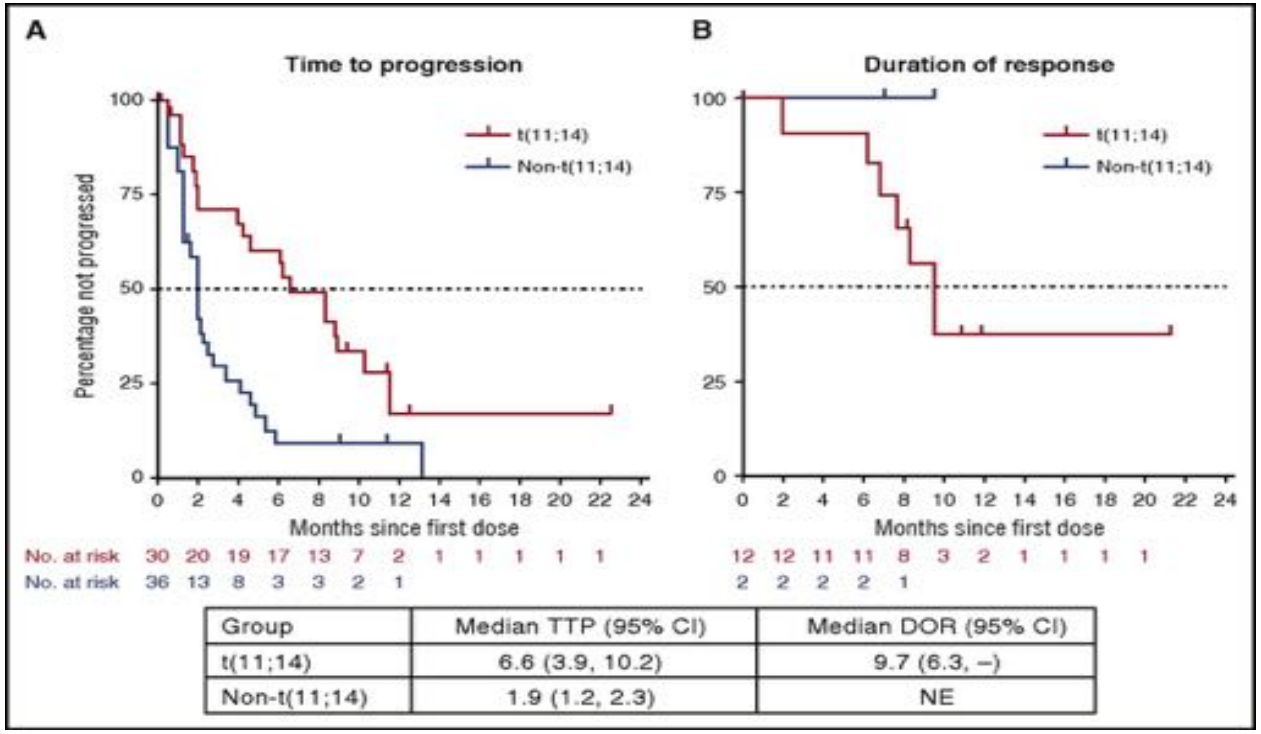
Phase 1 study confirmed the efficacy of Ven single agent in advanced RRMM patients with t(11;14)

Kumar Blood 2017;130(22):2401-2409)

Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma

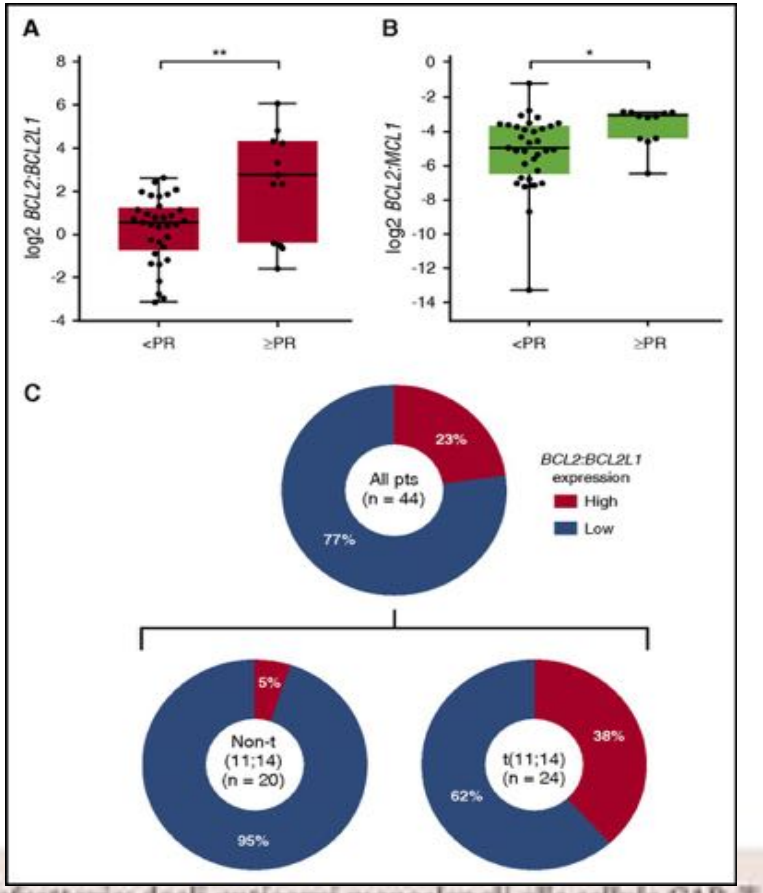
Shaji Kumar,[1] Jonathan L. Kaufman,[2] Cristina Gasparetto,[3] Joseph Mikhael,[4] Ravi Vij,[5] Brigitte Pegourie,[6] Lofti Benboubker,[7] Thierry Facon,[8] Martine Amiot,[9] Philippe Moreau,[9] Elizabeth A. Punnoose,[10] Stefanie Alzate,[11] Martin Dunbar,[11] Tu Xu,[11] Suresh K. Agarwal,[11] Sari Heitner Enschede,[11] Joel D. Leverson,[11] Jeremy A. Ross,[11] Paulo C. Maciag,[11] Maria Verdugo,[11] and Cyrille Touzeau[9]

Time to progression and duration of response by t(11;14) status.



Group	Median TTP (95% CI)	Median DOR (95% CI)
t(11;14)	6.6 (3.9, 10.2)	9.7 (6.3, –)
Non-t(11;14)	1.9 (1.2, 2.3)	NE

Baseline BCL2:BCL2L1 and BCL2:MCL1 gene expression levels by best response

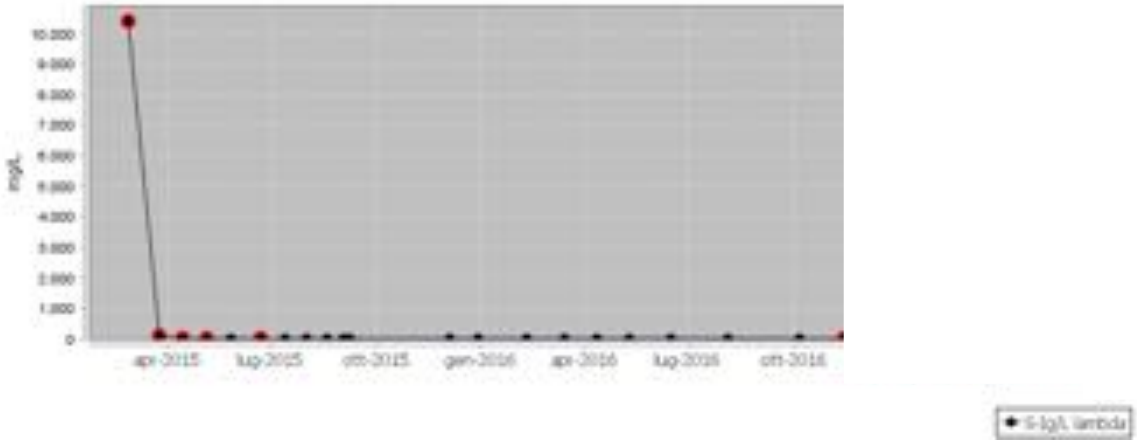


Blood 2017;130(22):2401-2409),

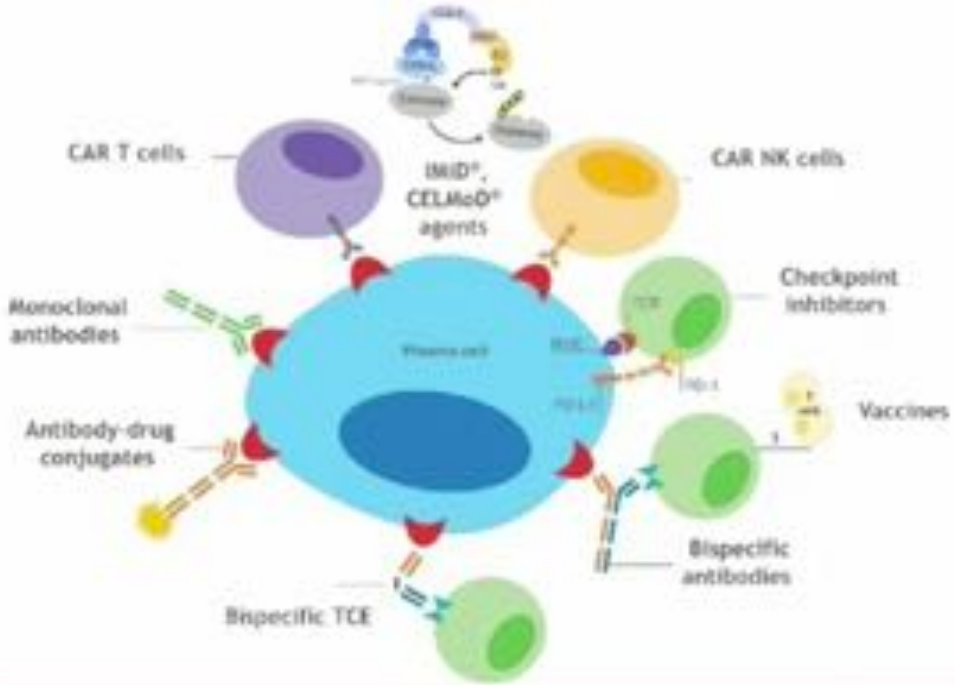
Caso clinico

P.V, 68 anni, viene ricoverato nel 2015 per leucemia plasmacellulare (51 x10^9/L GB, popolazione clonale lambda ic CD138+CD38+CD56+CD19-), a cui concomita anemia e piastrinopenia, ipercalcemia e IRA. Agli esami ematochimici CM IgD (14.200 mg/l) , sFLCkappa<0.35; sFLCLambda 104000 mg/L. BOM: infiltrazione totale di PC. Citogenetica: trisomia 1, FISH t(11;14)(q13;q32), monosomia Cr13. TAC TB low dose: Numerose lesioni litiche a livello di scheletro assile, non fratture patologiche. MRI DWI: diffusa sostituzione del midollo con numerosi focolai patologici a pattern misto focale e diffuso.

VTDx4 Auto mel 200
RC



Current and novel immunotherapies in MM



Optimal combination of targeted and various immune-based strategies may effectively restore host immunosurveillance

APC, antigen presenting cell; CELMoD®, cereblon E3 ligase modulator; DC, dendritic cell; CTL, cytotoxic T cell; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TCE, T cell engager; TCR, T cell receptor.
Gulla A, Anderson KC. Haematologica. 2020;105:2258-67. Mikhael J. Clin Lymphoma Myeloma Leuk. 2020;20:1-7. Image adapted from Shah UA, Mailankody S. BMJ. 2020;370:m3176.

18th International Myeloma Workshop, 2021

Emerging immunotherapies may help overcome poor outcomes seen in treatment-refractory patients

Clinical trials for emerging immunotherapies focus mainly on patients exposed to around 3 lines of therapy, including ≥ 1 IMiD® agent, ≥ 1 PI, and an anti-CD38 mAb[1]

CELMoD® agents	ADCs	CAR T cell therapies	T cell engagers
• Iberdomide (CC-220)[2] • CC-92480[3]	• Belantamab mafodotin[4] • CC-99712[5] • MEDI2228[6]	• Ide-cel (bb2121)[7] • Cilta-cel (JNJ-68284528)[8] • P-BCMA-101[9] • CT053[10] • Bb21217[11] • BCMA-CD19 GC012F[12] • ALLO-715[13]	• CC-93269[14] • Cevostamab (BFCR4350A)[15] • Teclistamab (JNJ-64007957)[16] • Talquetamab (JNJ-64407564)[17] • Elranatamab (PF-06863135)[18] • REGN5458[19] • AMG701[20] • TNB-383B[21]

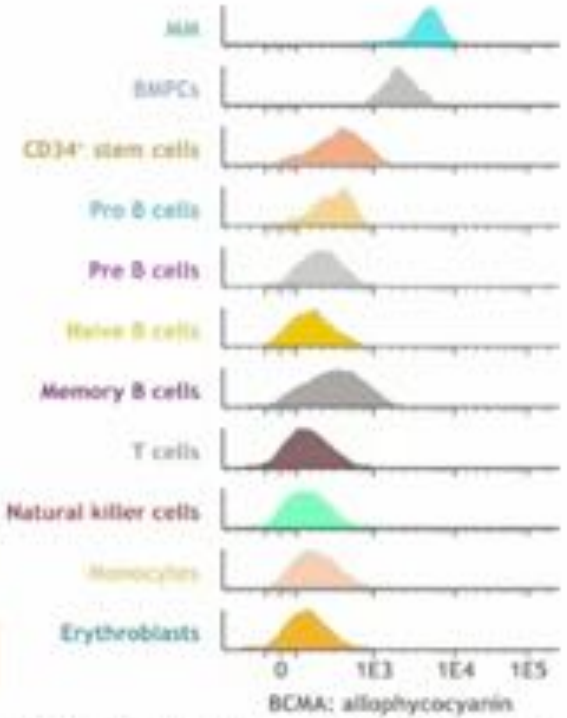
The treatment modalities and products listed are subject to individual country approval. The table does not cover every immunotherapy being studied in MM, but only a summarized selection of products/therapies.

ADC, antibody drug conjugate.

1. Mikhael J. Clin Lymphoma Myeloma Leuk. 2020;20:1-7. 2. NCT02773030. 3. NCT03374085. 4. NCT03525678. 5. NCT04036461. 6. NCT03489525. 7. NCT03601897. 8. NCT03548207. 9. NCT03338649. NCT03915184. 11. NCT03274219. 12. NCT04236011. 13. NCT04093596. 14. NCT03480067. 15. NCT03275103. 16. NCT03145181. 17. NCT03399799. 18. NCT03269136. 19. NCT03761108. 20. NCT03. NCT03910725. All available from: https://clinicaltrials.gov/ct2/home. Accessed August 2021.

Targeting BCMA in MM

- Several surface antigens are being targeted for CAR T cell therapy in MM:
  - BCMA, CD19, CD138, SLAMF7, immunoglobulin light chain
- BCMA: member of the TNFR superfamily (TNFRS17)
  - Regulate B-cell proliferation, survival, and maturation to plasma cells
  - Expression and activation associated with myeloma cell growth and survival
  - Expressed on the surface of plasmablasts and differentiated plasma cells
  - Soluble BCMA (mediated via gamma-secretase cleavage) in circulation serves as a biomarker for tumour burden in patients with MM



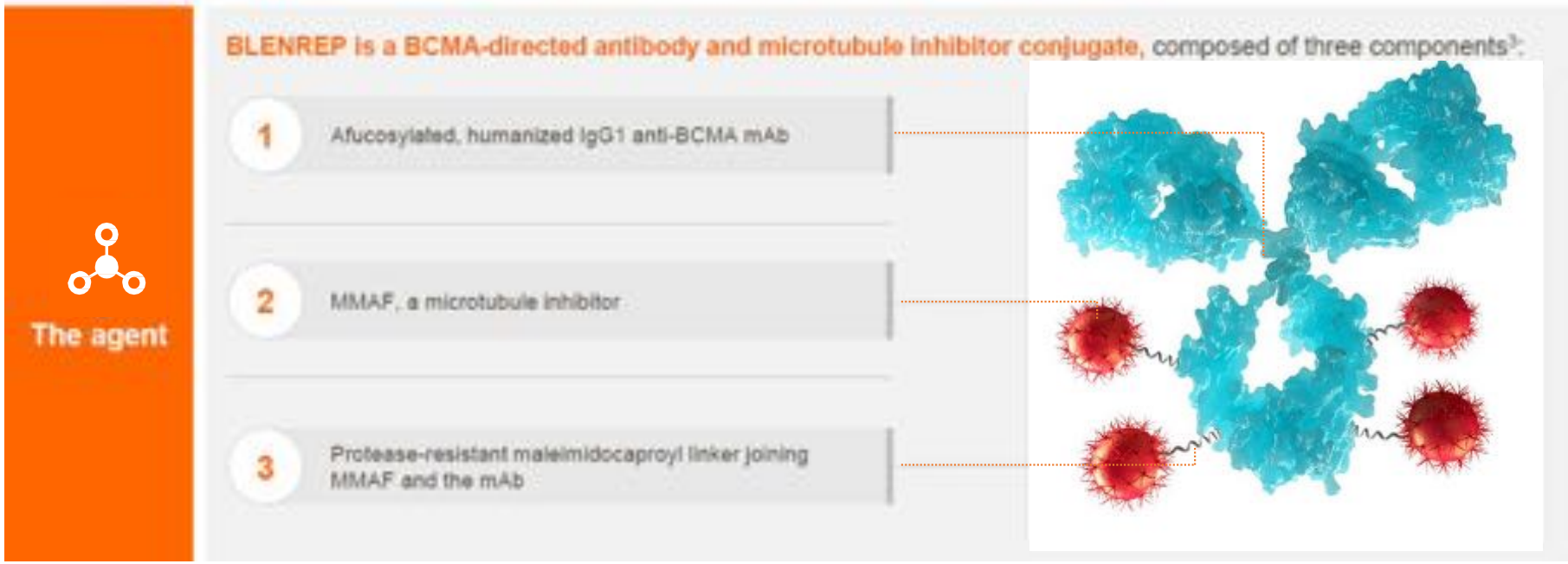
Flow cytometry demonstrated BCMA expression on MM cells and normal plasma cells, but not on other normal BM cell subsets

BCMA, B-cell maturation antigen; BM, bone marrow; BMPC, bone marrow plasma cell; MM, multiple myeloma; Pre B cell, progenitor B cell stage; Pro B cell, progenitor B cell stage preceding pre B cell; SLAMF7, signalling lymphocytic activation molecule F7; TNFR, tumour necrosis factor receptor.

Laurent SA, et al. Nat Commun. 2015;6:7333. Lin Q, et al. Mol Cancer. 2019;18:154. Sanchez E, et al. Br J Haematol. 2012;158:727-38. Reproduced from Seckinger A, et al. Cancer Cell. 2017;31:396-410 © 2017, Elsevier Inc.

nali alle cellule CAR-T

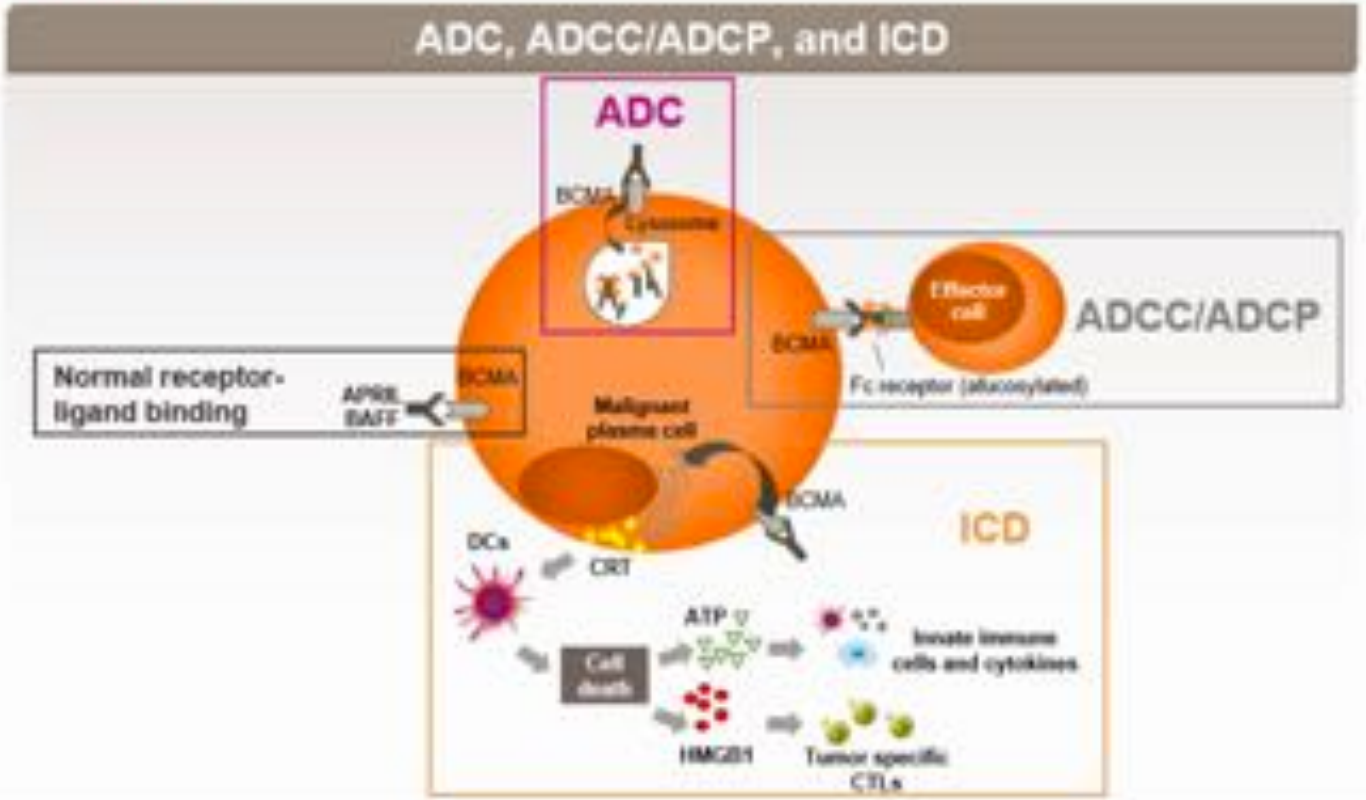
Belantamab mafodotin is an Antibody-Drug Conjugate Targeting BCMA



IgG1: immunoglobulin G1; mAb, monoclonal antibody; MMAF: monomethyl auristatin-F

1. O'Connor BP, et al. J Exp Med 2004;199:91-8; 2. Lee L, et al. Br J Haematology2016; 174:911-22; 3. Tai Y-T, et al. Blood 2014; 123:3128-38

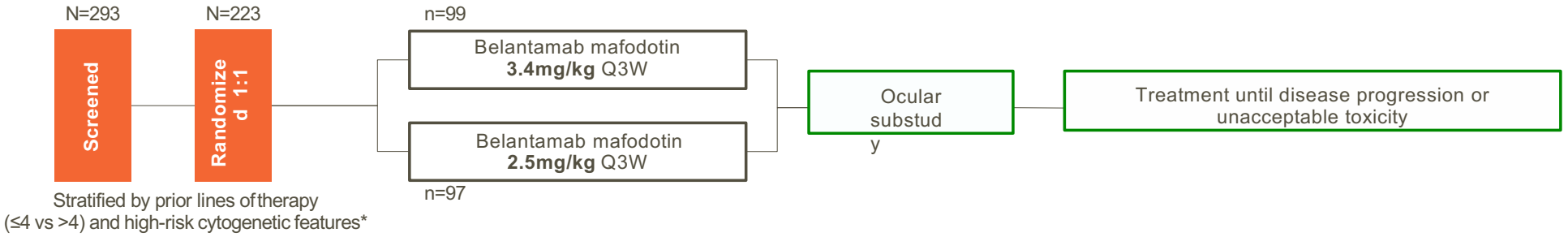
Mechanisms of Action of Belantamab Mafodotin: Summary



ADC = antibody–drug conjugate; ADCC/ADCP = antibody-dependent cell-mediated cytotoxicity and phagocytosis; APRIL = A proliferation-inducing ligand; BAFF = B-cell activating factor; BCMA = B-cell maturation antigen; ICD = immunogenic cell death.

DREAMM-2: study design

A phase II, open-label, randomized, 2-dose study in patients with RRMM who were refractory to an immunomodulatory drug and a PI and refractory and/or intolerant to an anti-CD38 mAb



Inclusion criteria

- ≥3 prior lines of MM therapy
- Refractory to prior immunomodulatory agents, proteasome inhibitors, and refractory and/or intolerant to an anti-CD38 monoclonal antibody
- BCMA-targeted therapy naïve
- Prior ASCT allowed
- ECOG PS 0-2

Primary endpoint

- ORR (IRC)

Secondary endpoints

- DOR, PFS, OS, CBR
- Safety
- ORR assessed by investigator,† TTR,† TTP†
- ADA activities†
- PK profiles†
- PROs†
- HRQOL†

Screening occurred between June 18, 2018, and January 2, 2019.
*Presence or absence of t(4;14), t(14;16), 17p13del, or 1q21+. †Will be reported separately.
ADA, anti-drug antibody; ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CBR, clinical benefit rate; CD, cluster of differentiation; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQOL, health-related quality of life; IRC, independent review committee; mAb, monoclonal antibody; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PI, proteasome inhibitor; PRO, patient-reported outcome; Q3W, every 3 weeks; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

Lonial S et al. *Lancet Oncol.* 2020;21(2):207-221.

DREAMM-2 Results: Efficacy from 13-month Follow-up

Single Agent Belantamab Mafodotin Demonstrated Deep Activity

Independent Review Committee-assessed Response*	Belantamab Mafodotin 2.5 mg/kg (N = 97)
Overall response rate,† n (%) (97.5% CI)	31 (32) (21.7-43.6)
Best response, n (%)	
Stringent complete response	2 (2)
Complete response	5 (5)
Very good partial response	11 (11)
Partial response	13 (13)
Minimal response	4 (4)
Stable disease	27 (28)
Clinical benefit rate‡ (95% CI)	35 (36)

58% [18/31] of responders **achieved a very good partial response or better**

Among patients with ≥ VGPR 5 of 13 evaluated (38%) achieved MRD negativity

*Best response as assessed in the intention-to-treat population (including all randomly assigned patients) by an independent review committee using 2016 IMWG criteria. Six patients were not evaluable for response and were treated as non-responders.

†ORR = sCR+CR+VGPR+PR

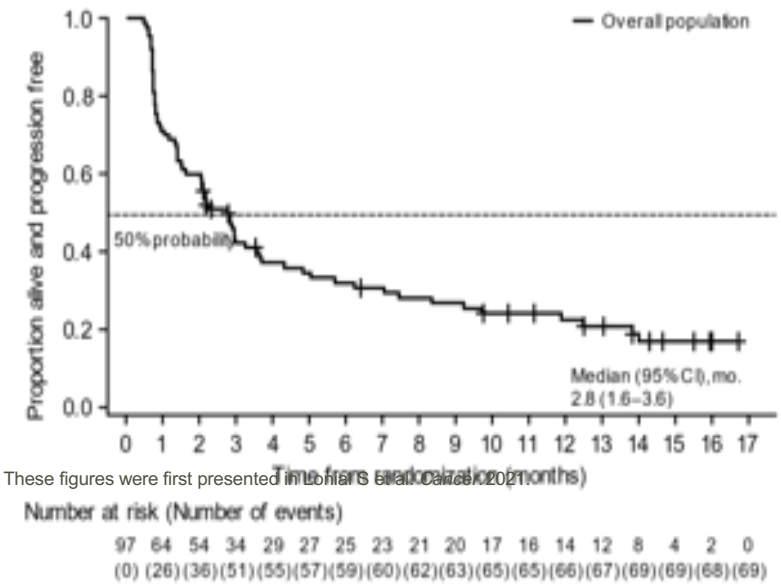
‡CBR = sCR+CR+VGPR+PR+MR

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; IIMWG= International Myeloma Working Group; MR = minimal response; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

DREAMM-2 Results: Efficacy from 13-month Follow-up

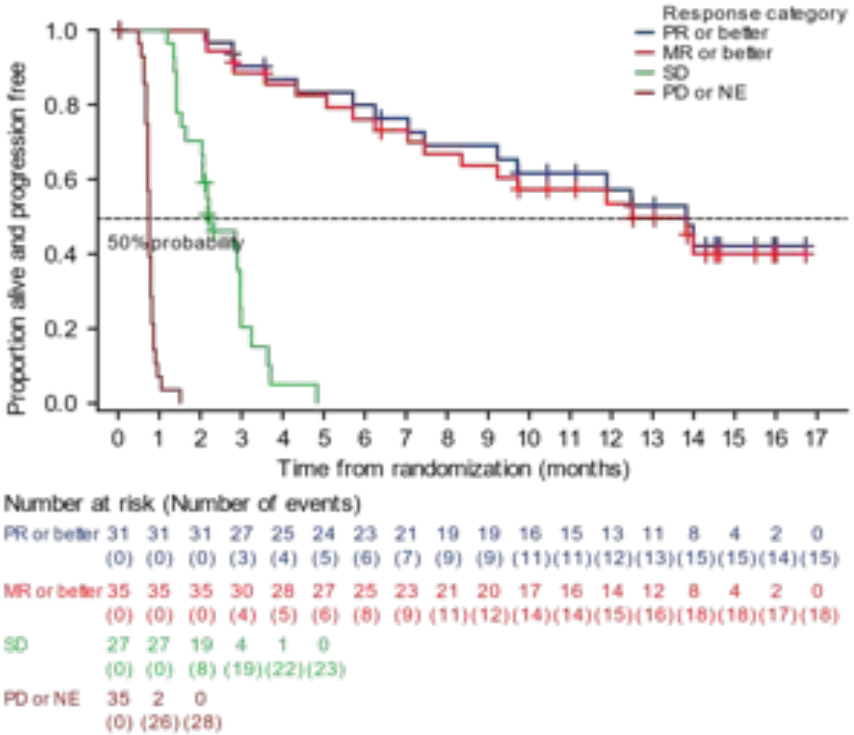
Median Estimated Progression-free Survival

Progression-free Survival



These figures were first presented in Lonial S et al. *Cancer*. 2021.

Progression-free Survival by Response Category



CI = confidence interval; CR = complete response; NE = not evaluable; NR = not reached; PD = progressive disease; PR = patrial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response

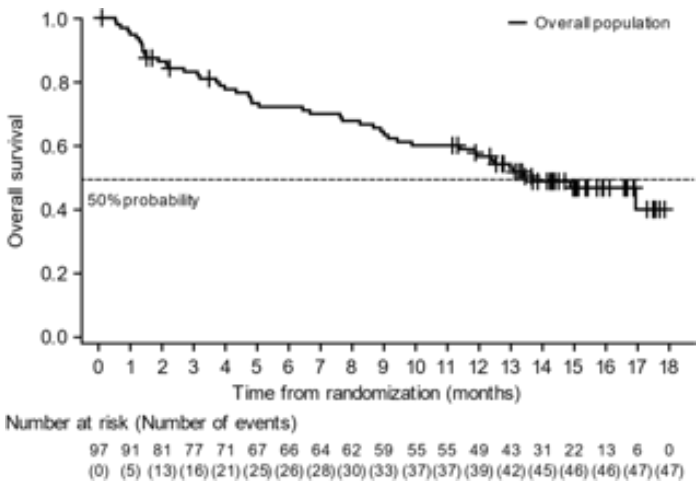
Lonial S, et al. Cancer 2021;

The chart has been independently created by GSK from original data first presented in Lonial S et al. *Cancer*. 2021.

DREAMM-2 Results: Efficacy from 13-month Follow-up

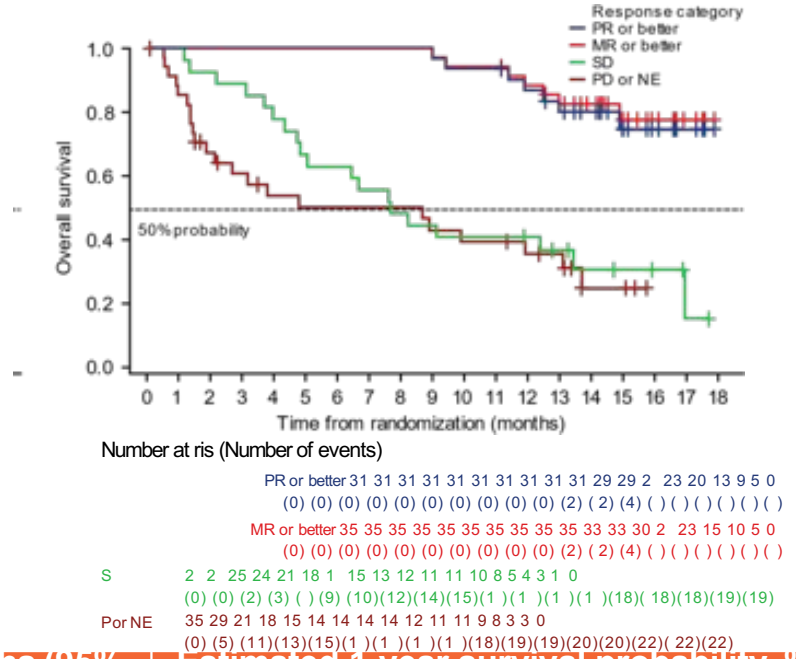
Median Estimated Overall Survival

Overall Survival



These figures were first presented in Lonial S et al. *Cancer.* 2021.

Overall Survival by Response Category



	Median Overall Survival, months (95% CI)	Estimated 1-year survival probability, % (95% CI)
Overall	13.7 (9.9-NR)	58 (47-67)
MR or better	NR	88 (72-95)
PR or better	NR	87 (69-95)

CI = confidence interval;
CR = complete response;
MR = minimal response;
NE = not evaluable;
NR = not reached;
PD = progressive disease;
PR = patrial response;
SD = stable disease

Lonial S et al. *Cancer.* 2021.

DREAMM-2 Results: Efficacy from 13-month Follow-up

Belantamab Mafodotin Demonstrated Durable Activity

	Belantamab Mafodotin 2.5 mg/kg (N = 97)
Median Estimated DoR, months (95% CI)[1]	11 (4.2-NR)
Median PFS, months (95% CI)[1]	2.8 (1.6-3.6)
Median Estimated OS, months (95% CI)[1]	13.7 (9.9-NR)

This overall survival has not been observed to date in a similar heavily pretreated RRMM population

Previous studies show a median OS of only 9.31 months in similar patient populations across all regimens[1,2]

CI = confidence interval; DoR = duration of response; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RRMM = relapsed/refractory multiple myeloma.

Overview of DREAMM-2: Safety from 13-month Follow-up

Adverse Events of Special Interest

Adverse Events of Special Interest*	Belantamab Mafodotin 2.5 mg/kg (N = 95)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
Thrombocytopenia	36 (38)	56 (57)**
IRRs	20 (21)	16 (16)
Keratopathy (MECs)	68 (72)	76 (77)
Median time to onset of first MEC, days	37.0	22.5
Percent recovered from first event	77	73
Percent recovered from last event	48	47
Other Corneal Events		
Blurred vision†	24 (25)	33 (33)
Dry eye†	14 (15)	25 (25)
BCVA decline to 20/50 or worse in better-seeing eye	17 (18)	20 (20)

*Values expressed as n (%) unless otherwise noted. **Events include 2 Grade 5 events in the 3.4 mg/kg cohort only.
†All events of any grade

BCVA = best corrected visual acuity; IRR = infusion-related reaction; MEC = microcyst-like epithelial change

The most common AE was keratopathy (MECs), defined as changes to the superficial corneal epithelium.

Patients may experience symptoms of dry eye blurred vision and changes in visual acuity.

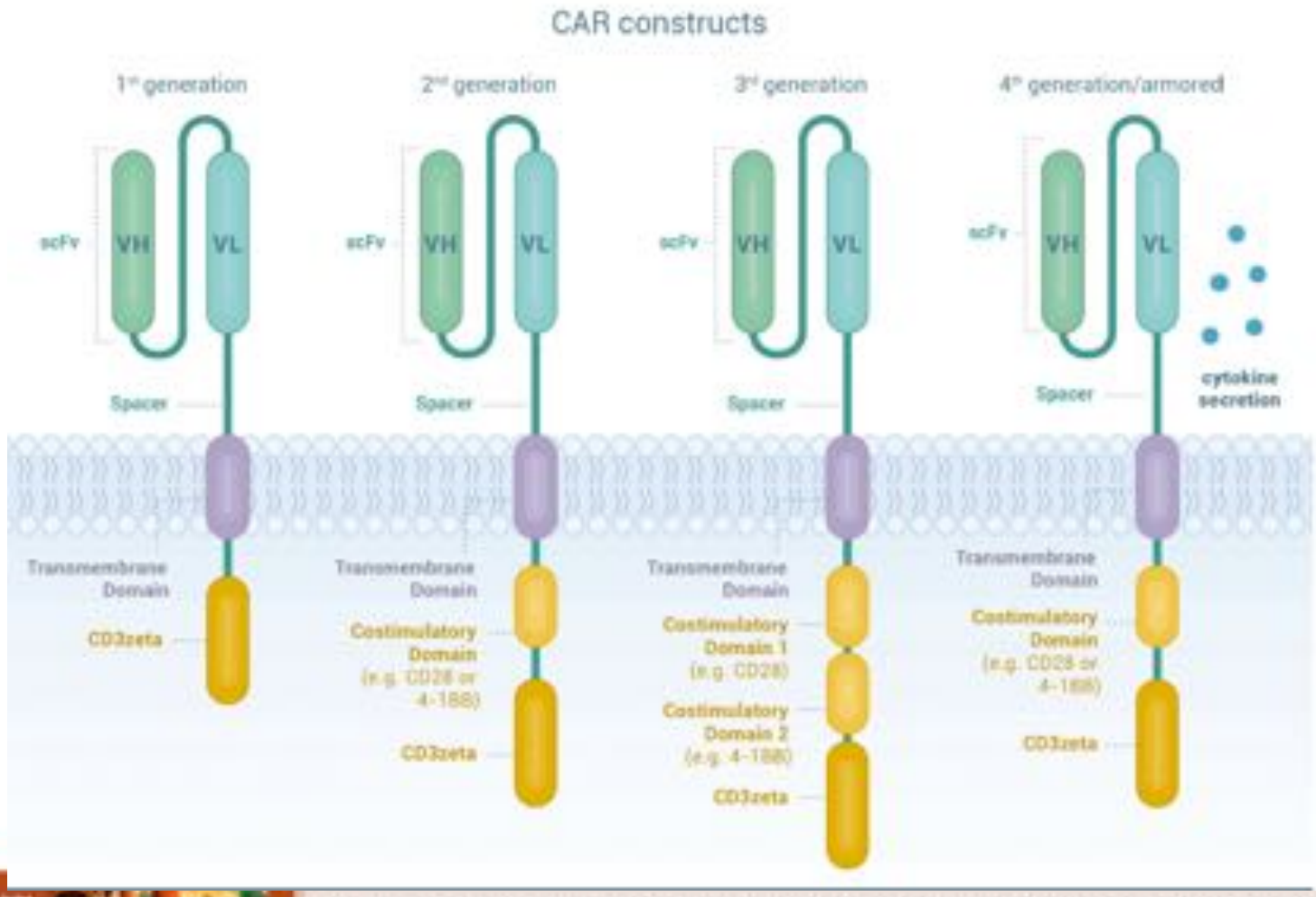
Grade 3/4 symptoms were less common: dry eye (1% and 0% in the 2.5 and 3.4-mg/kg groups) and blurred vision (4% in both groups).

18% (17/95) and 20% (20/99) in the 2.5 mg/kg and 3.4 mg/kg groups, respectively, had a BCVA decline to 20/50 or worse in their better-seeing eye at least once during or after the treatment period.
The median time to onset of first BCVA change was 66.0 and 83.5 days in the 2.5 mg/kg and 3.4 mg/kg groups, respectively.
First events resolved in 82% and 100% patients in a median of 21.5 or 23.5 days in 2.5 mg/kg and 3.4 mg/kg groups, respectively; dose delays/reductions were used in 41% and 60% respectively.
As of the last follow-up, 82% (14/17) and 90% (18/20) of patients recovered from any BCVA change (BCVA better than 20/50).

No permanent loss of vision has been reported to date.

Lonial S, Lee HC, Badros A, et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2020; Virtual.

CAR-T CELLS



Bruno, Haematologica, 2021

BCMA CAR T-cell therapy clinical data summary

	Ide-cel (KarMMa)[1,2]		Cilta-cel[3] CARTITUDE-1 (N = 97)
	All (N=128)	450 x 10^6 (n=54)	
Median follow-up (range)	13.3 mos (0.2-21)	13.3 mos (0.2-21)	12.4 mos (10.6-15.2)
Median prior LoT (range)	9 (4-11)	5 (3-13)	6 (4-8)
Refractory to last LoT	Not reported	Not reported	99%
Triple refractory	100%	81%	88%
Extramedullary disease	0%	49%	13%
High-risk cytogenetics	25%	44%	24%
Received bridging therapy	100%	87%	75%
ORR	73%	81%	97%
≥CR	33%	39%	67% sCR
MRD negative (10^{-5})	33/42 CR (79%)	15/21 CR (71%)	53/57 (93%) in eval pts (≥CR)
Median DoR, months	10.7	11.3	Not reached
Median PFS, months	8.8	12.1	NR (12-mo: 77.0%)
Median OS, months	19.4	Not reported	12-mo: 89.0%

1. Munshi N et al. N Eng J Med 2021;384:705-16; 2. Munshi N et al. ASCO 2020;abstract 8503 (oral presentation); 3. Berdeja J et al. Lancet 2021; 398: 314–24

BCMA, B-cell maturation antigen; CR, complete response; DoR, duration of response; Lot, lines of treatment; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

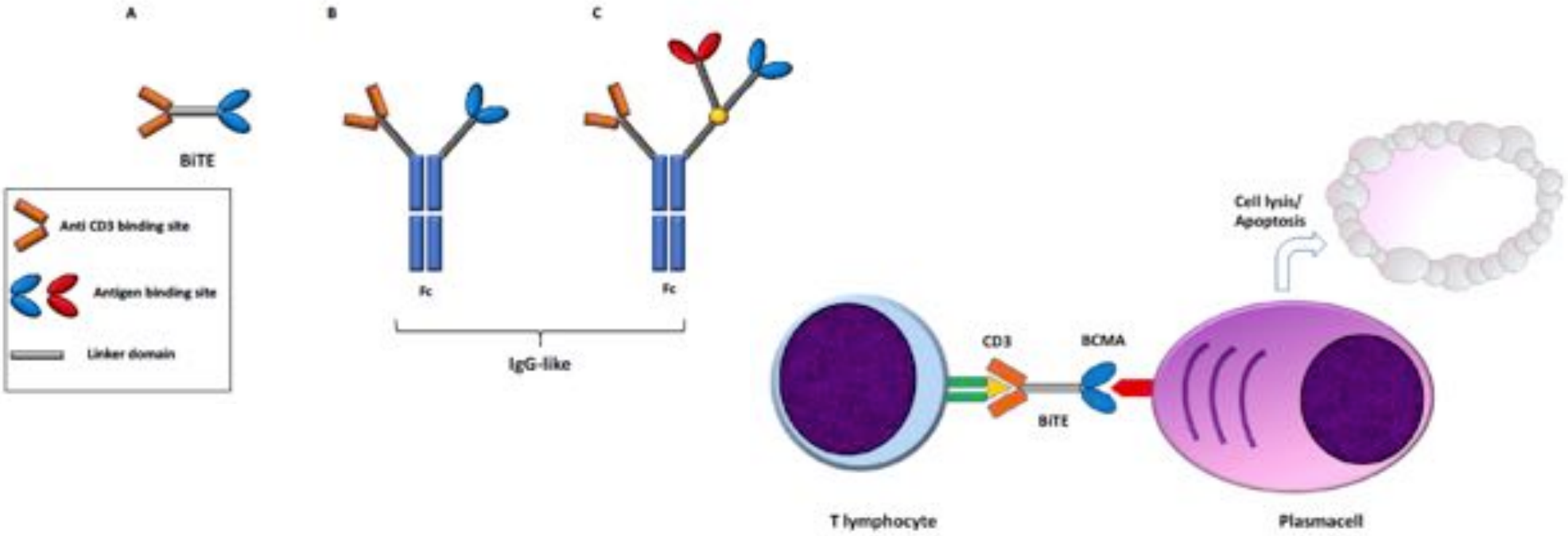
Anti-BCMA CAR T cell therapies in RRMM presented in 2020

Data from products that are either investigational only and subject to individual country/region approval.

PFS, progression free survival; RRMM, relapsed and refractory multiple myeloma.

Alsina M, et al. Blood. 2020;136 Suppl 1:25-6. Costello CL, et al. Presented at ASH 2020; abstract 134. Frigault MJ, et al. J Clin Oncol. 2021;39 Suppl 15:8015. Kumar SK, et al. Blood. 2020;136 Suppl 1:28-9. Lin Y, et al. Blood. 2020;136 Suppl 1:26-7. Madduri D, et al. Presented at ASH 2020; abstract 177. Munshi NC, et al. N Engl J Med. 2021;384:705-16.

ANTICORPI BISPECIFICI E BITE



T-Cell engagers with data in RRMM

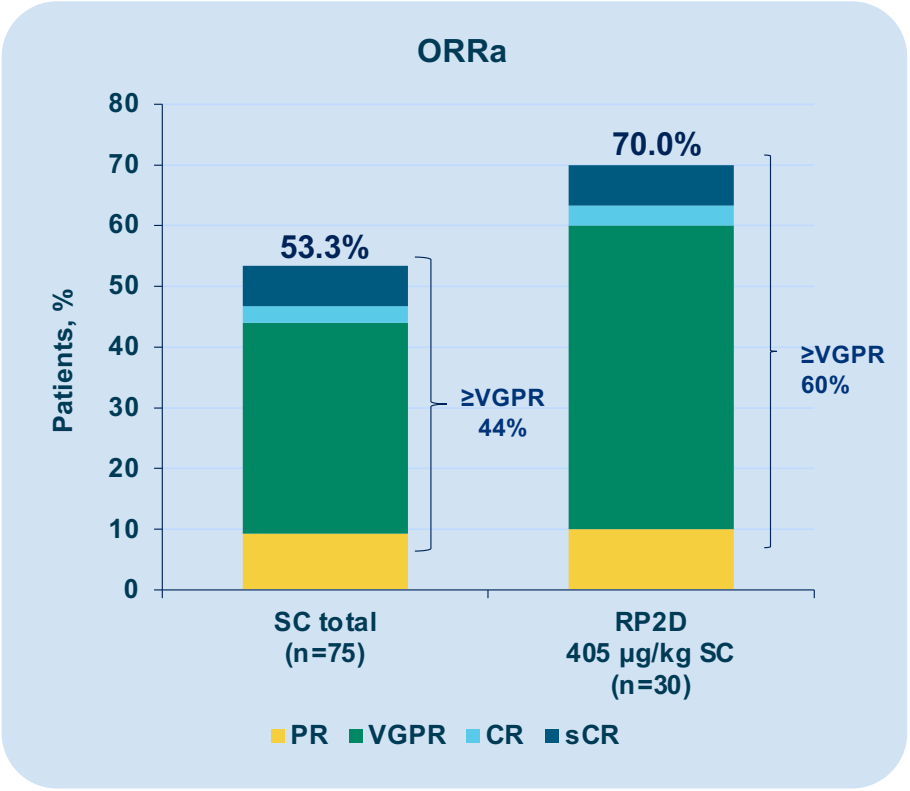
	Elranatamab[1,2]	Teclistamab[3,4]	AMG-701[5,6]	TNB-383B[7]	REGN-5458[8,9]	Talquetamab[10]	Cevostamab[11]
Antibody Format	IgG2 monovalent to BCMA	IgG1 monovalent to BCMA	scFVs-based monovalent to BCMA	IgG4 bivalent VH to BCMA	IgG monovalent to BCMA	IgG4 monovalent to GPRC5D	IgG1 monovalent to FcRH5
TCE Technology	Symmetric 1+1	DuoBody® (symmetric 1+1)	BiTE® tech (1+1 $(scFVs)_2$) with fusion to Fc domain	UniRat® (monovalent to CD3, bivalent to BCMA)	Symmetric 1+1	DuoBody® (symmetric 1+1)	BiTE® (Fab against FCRH4 and Fab CD3)
Fc	Wt Fc, not engineered	Silenced Fc	No Fc, but conjugated for half-life	Silenced human IgG4 Fc	Silenced IgG4 Fc	Silenced Fc	IgG1, not engineered
Antibody Half Life	4-6 days	10 days	4-5 days	15-18 days	5 days	NA	NA
ORR	83% @ RP2D	65% @ RP2D	26%	80%	95% (≥VGPR)	70% @ RP2D	61%
CR	16.7% @ RP2D	40.0%	17% ≥VGPR	30%	42% CR/sCR	3.3%/6.7% CR/sCR	11/6% CR/sCR

1. Carraccio C et al. Front Immunol 2020;11:501; 2. Costello C et al. EHA 2021; abstract S192 (oral presentation); 3. Pilarisetti K et al. Blood Adv 2020;4(18):4538-45497; 4. van de Donk N et al. EHA 2021; abstract S193 (oral presentation); 5. Goldstein RL et al. Blood Adv 2020;4(17):4180-4194; 6. Harrison S et al. ASH 2020; abstract 181 (oral presentation); 7. Rodriguez C et al. ASH 2020; abstract 293 (oral presentation); 8. Madduri D et al. ASH 2020; abstract 291 (oral presentation); 9. REGN-5458. https://investor.regeneron.com/static-files/2bdbbbac-f2bb-4c1f-b3be-55fac15eafca (accessed August 2021); 10. Krishnan A et al. EHA 2021; abstract S191 (oral presentation); 11. Cohen A et al. ASH 2020; abstract 292 (oral presentation)

Five anti-BCMA bispecific antibodies presented at ASH 2020

Data from products that are either investigational only or subject to individual country/region approval.
Nearly all patients had prior anti-CD38 mAb across these trials. Responses shown for: CC-93269: 10 mg dosing, i.v. weekly; teclistamab: RP2D, s.c. weekly; AMG 701: most recent evaluable cohort, i.v. weekly; REGN5458: D16, i.v. weekly; TNB-383B: 40-60 mg i.v. q3w; elranatamab (PF-06863135): 215-1,000 µg/kg s.c.
CD, cluster of differentiation; CR, complete response; DL, dose level; mAb, monoclonal antibody; ORR, overall response rate; RP2D, recommended phase 2 dose.
Garfall AL, et al. Blood. 2020;136 Suppl 1:28. Harrison, SJ, et al. Blood. 2020;136 Suppl 1:28-9. Lesokhin AM, et al. Blood. 2020;136 Suppl 1:8-9. Madduri D, et al. Blood. 2020;136 Suppl 1:41-2. Rodriguez C, et al. Blood. 2020;136 Suppl 1:43-4.

TALQUETAMAB targeting GPRC5B



- The RP2D of 405 µg/kg SC QW has been administered to 30 patients with a median follow-up of 6.3 months (range: 1.4–12.0) for responders
- At the RP2D:
  - 70.0% ORR (21/30)
  - Median time to first confirmed response was 1 month (range: 0.2–3.8)
  - 65.2% (15/23) of triple-refractory patients responded
  - 83.3% (5/6) of penta-refractory patients responded
- Of 6 evaluable patients across IV and SC cohorts, 4 had MRD-negative CR/sCR at 10^{-6}, including 1 patient in RP2D cohort
  - MRD negativity was sustained 7 months post CR in 1 evaluable patient

[a]Investigator assessment of evaluable patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation per 2011 International Myeloma Working Group response criteria; includes unconfirmed response.
CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

Comparison of immunotherapy strategies for multiple myeloma.

	Antibody-Drug Conjugate(s)	Bispecific Antibodies	CAR-T
Pros	"Off the shelf" product	"Off the shelf" product	High response in the relapsed refractory setting
	Independent from host immune function	High response in the relapsed refractory setting	Only one treatment required
	No delay in administration	No delay in administration	
	Can be given in the community setting	Can be given in the community setting?	
Cons	High cost	High cost	High cost
	Continuous therapy	Continuous therapy	Long production time (4–6 weeks)
	Higher doses may be required for antigen downmodulation	CRS and ICANs toxicity	CRS and ICANs toxicity
	Payload mediated toxicity		Requires conditioning therapy
	Potential lower response rate		Require adequate lymphocyte count and function

CRS: Cytokine release syndrome. ICANs: immune effector cell associated neurotoxicity syndrome.

Barilà G et al Pharmaceuticals 2021

Conclusioni

- L’orizzonte delle nuove terapie continua ad evolversi ad una velocità esponenziale
- L’utilizzo di farmaci con meccanismo d’azione nuovo può in parte superare la resistenza delle cellule mielomatose
- La vera sfida per il clinico oggi è con che sequenza procedere con le varie terapie, chi beneficia di una specifica terapia/ o sequenza di farmaci, in uno scenario di costi sempre in aumento.
- Un importante obiettivo sarà colmare il divario tra i dati di efficacia e tossicità dei trials clinici e il dato di real word