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Newly approved therapies in multiple myeloma

Clinical and translational perspectives

October 30, 2021. Miami, FL

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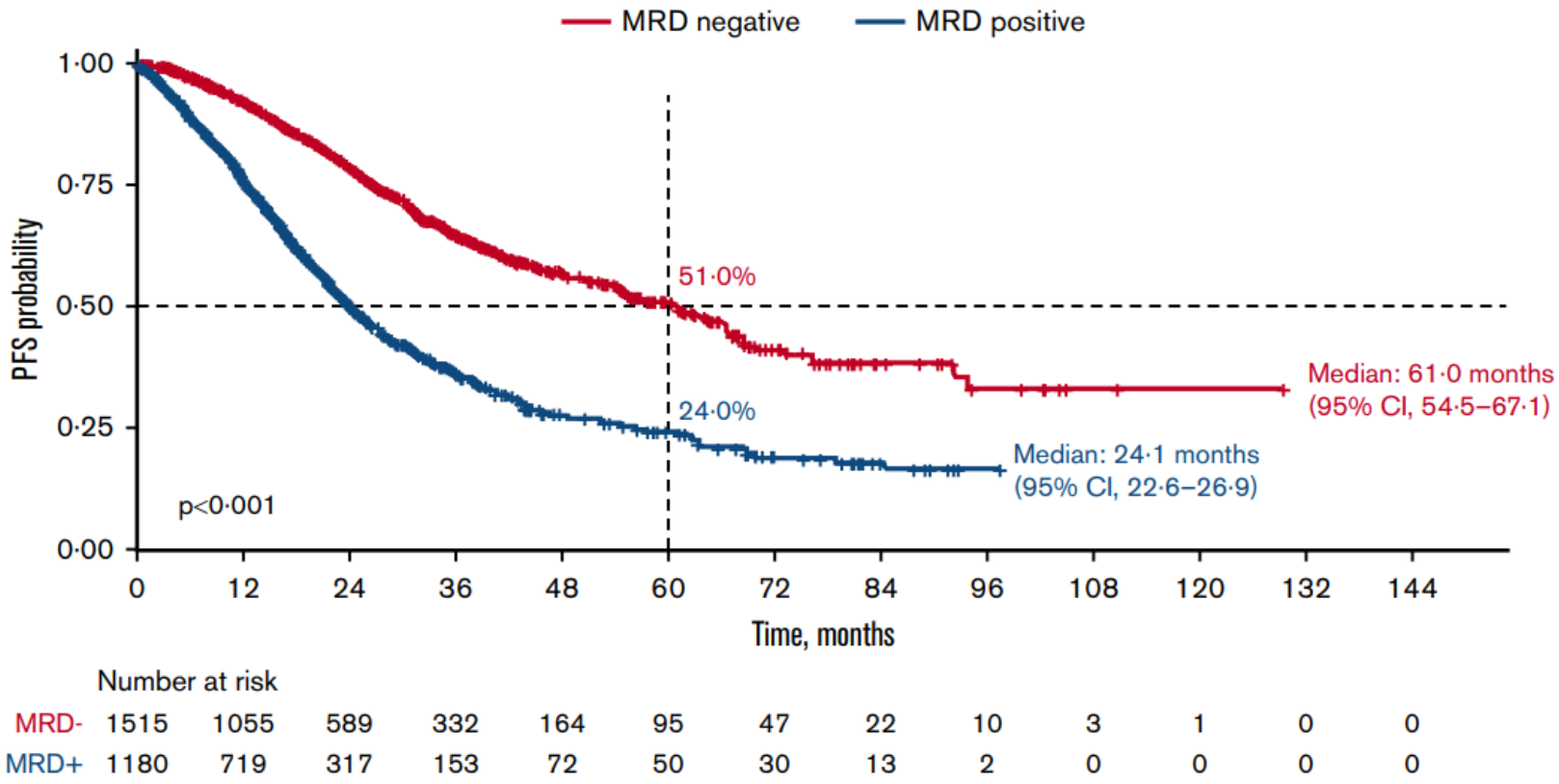
Is MRD important in myeloma?

Role of MRD-negativity in newly diagnosed multiple myeloma

Progression-free survival in transplant eligible patients



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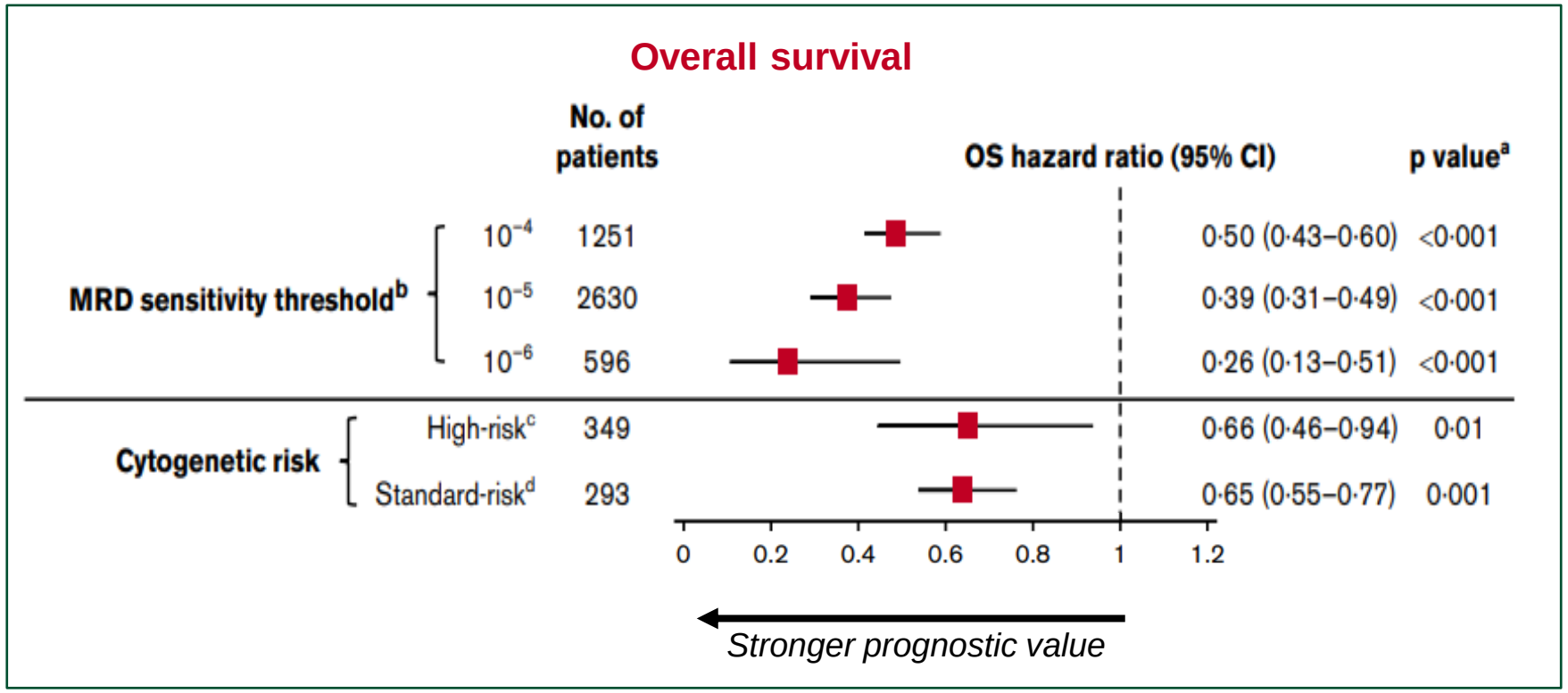
Munshi NC, et al. *Blood Advances*. 2020 Dec 8;4(23):5988-5999

Role of MRD-negativity in newly diagnosed multiple myeloma



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Munshi NC, et al. *Blood Advances*. 2020 Dec 8;4(23):5988-5999

Beginning of a new treatment era for newly diagnosed myeloma

Plenary paper

Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma

Paul G. Richardson,[1] Edie Weller,[1] Sagar Lonial,[2] Andrzej J. Jakubowiak,[3] Sundar Jagannath,[4] Noopur S. Raje,[5] David E. Avigan,[6] Wanling Xie,[1] Irene M. Ghobrial,[1] Robert L. Schlossman,[1] Amitabha Mazumder,[4] Nikhil C. Munshi,[1] David H. Vesole,[4] Robin Joyce,[6] Jonathan L. Kaufman,[2] Deborah Doss,[1] Diane L. Warren,[1] Laura E. Lunde,[1] Sarah Kaster,[5] Carol DeLaney,[6] Teru Hideshima,[1] Constantine S. Mitsiades,[1] Robert Knight,[7] Dixie-Lee Esseltine,[8] and Kenneth C. Anderson[1]

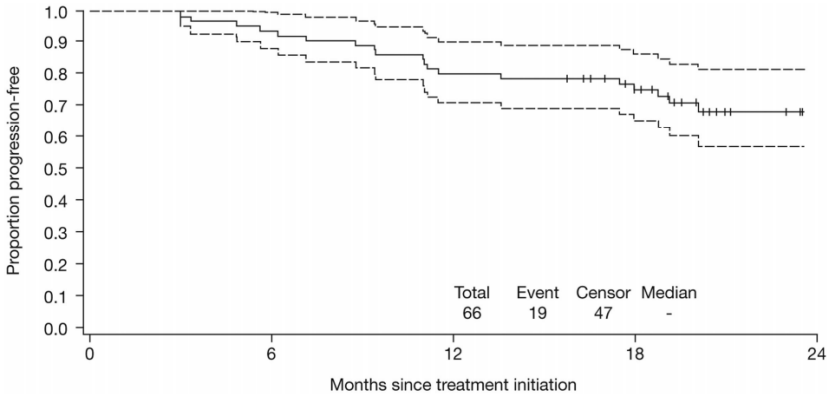
[1]Dana-Farber Cancer Institute, Boston, MA; [2]Emory Winship Cancer Institute, Atlanta, GA; [3]University of Michigan Comprehensive Cancer Center, Ann Arbor; [4]St Vincent's Comprehensive Cancer Center, New York, NY; [5]Massachusetts General Hospital, Boston; [6]Beth Israel Deaconess Medical Center, Boston, MA; [7]Celgene Inc, Summit, NJ; and [8]Millennium Pharmaceuticals Inc, Cambridge, MA

This phase 1/2 study is the first prospective evaluation of lenalidomide-bortezomib-dexamethasone in front-line myeloma. Patients (N = 66) received 3-week cycles (n = 8) of bortezomib 1.0 or 1.3 mg/m² (days 1, 4, 8, 11), lenalidomide 15 to 25 mg (days 1-14), and dexamethasone 40 or 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12). Responding patients proceeded to maintenance or transplantation. Phase 2 dosing was determined to be bortezomib 1.3 mg/m², lenalidomide 25 mg, and dexamethasone 20 mg. Most common toxicities included sensory neuropathy (80%) and fatigue (64%), with only 27%/2% and 32%/3% grade 2/3, respectively. In addition, 32% reported neuropathic pain (11%/3%, grade 2/3). Grade 3/4 hematologic toxicities included lymphopenia (14%), neutropenia (9%), and thrombocytopenia (6%). Thrombosis was rare (6% overall), and no treatment-related mortality was observed. Rate of partial response was 100% in both the phase 2 population and overall, with 74% and 67% each achieving very good partial response or better. Twenty-eight patients (42%) proceeded to undergo transplantation. With median follow-up of 21 months, estimated 18-month progression-free and overall survival for the combination treatment with/without transplantation were 75% and 97%, respectively. Lenalidomide-bortezomib-dexamethasone demonstrates favorable tolerability and is highly effective in the treatment of newly diagnosed myeloma. This study is registered at http://clinicaltrials.gov as NCT00378105. (*Blood.* 2010;116(5):679-686)

Best response

	All patients (N = 66)			Phase 2 population (n = 35)		
Response*	**n**	**%**	**90% CI**	**n**	**%**	**90% CI**
CR	19	29	20-39	13	37	24-52
nCR	7	11	5-19	7	20	10-34
VGPR	18	27	18-38	6	17	8-31
PR	22	33	24-44	9	26	14-41
CR + nCR	26	39	29-50	20	57	42-71
CR + nCR + VGPR	44	67	56-76	26	74	59-86
At least PR	66	100	96-100	35	100	92-100

Progression-free survival



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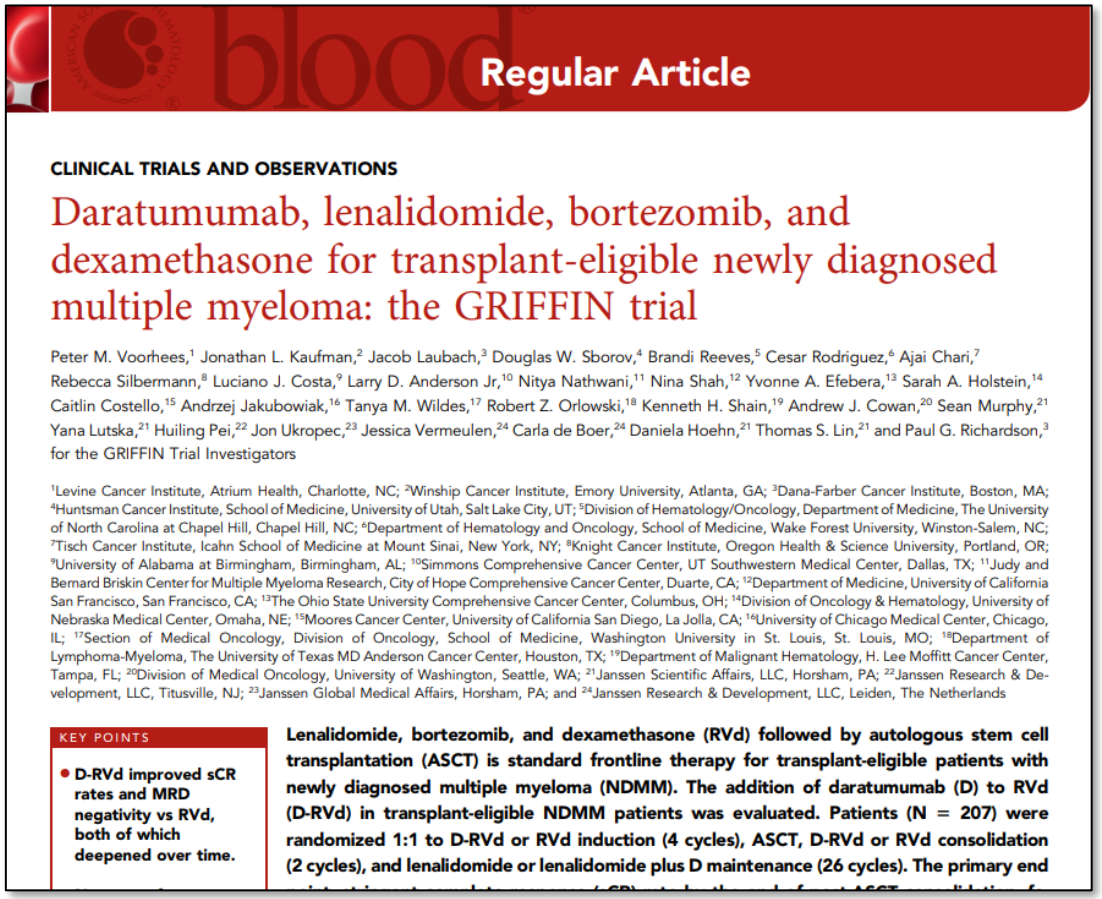
Richardson P, et al. *Blood.* 2010 Aug 5;116(5):679-86

GRIFFIN study



blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial

Peter M. Voorhees,[1] Jonathan L. Kaufman,[2] Jacob Laubach,[3] Douglas W. Sborov,[4] Brandi Reeves,[5] Cesar Rodriguez,[6] Ajai Chari,[7] Rebecca Silbermann,[8] Luciano J. Costa,[9] Larry D. Anderson Jr,[10] Nitya Nathwani,[11] Nina Shah,[12] Yvonne A. Efebera,[13] Sarah A. Holstein,[14] Caitlin Costello,[15] Andrzej Jakubowiak,[16] Tanya M. Wildes,[17] Robert Z. Orlowski,[18] Kenneth H. Shain,[19] Andrew J. Cowan,[20] Sean Murphy,[21] Yana Lutska,[21] Huiling Pei,[22] Jon Ukropec,[23] Jessica Vermeulen,[24] Carla de Boer,[24] Daniela Hoehn,[21] Thomas S. Lin,[21] and Paul G. Richardson,[3] for the GRIFFIN Trial Investigators

[1]Levine Cancer Institute, Atrium Health, Charlotte, NC; [2]Winship Cancer Institute, Emory University, Atlanta, GA; [3]Dana-Farber Cancer Institute, Boston, MA; [4]Huntsman Cancer Institute, School of Medicine, University of Utah, Salt Lake City, UT; [5]Division of Hematology/Oncology, Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Department of Hematology and Oncology, School of Medicine, Wake Forest University, Winston-Salem, NC; [7]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [8]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [9]University of Alabama at Birmingham, Birmingham, AL; [10]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [11]Judy and Bernard Briskin Center for Multiple Myeloma Research, City of Hope Comprehensive Cancer Center, Duarte, CA; [12]Department of Medicine, University of California San Francisco, San Francisco, CA; [13]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [14]Division of Oncology & Hematology, University of Nebraska Medical Center, Omaha, NE; [15]Moores Cancer Center, University of California San Diego, La Jolla, CA; [16]University of Chicago Medical Center, Chicago, IL; [17]Section of Medical Oncology, Division of Oncology, School of Medicine, Washington University in St. Louis, St. Louis, MO; [18]Department of Lymphoma-Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [19]Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL; [20]Division of Medical Oncology, University of Washington, Seattle, WA; [21]Janssen Scientific Affairs, LLC, Horsham, PA; [22]Janssen Research & Development, LLC, Titusville, NJ; [23]Janssen Global Medical Affairs, Horsham, PA; and [24]Janssen Research & Development, LLC, Leiden, The Netherlands

KEY POINTS

- D-RVd improved sCR rates and MRD negativity vs RVd, both of which deepened over time.

Lenalidomide, bortezomib, and dexamethasone (RVd) followed by autologous stem cell transplantation (ASCT) is standard frontline therapy for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). The addition of daratumumab (D) to RVd (D-RVd) in transplant-eligible NDMM patients was evaluated. Patients (N = 207) were randomized 1:1 to D-RVd or RVd induction (4 cycles), ASCT, D-RVd or RVd consolidation (2 cycles), and lenalidomide or lenalidomide plus D maintenance (26 cycles). The primary end

- Addition of daratumumab (Dara) to RVd (Dara-RVd*) in transplant-eligible newly diagnosed multiple myeloma patients
- Patients (N = 207) were randomized 1:1 to Dara-RVd or RVd induction (4 cycles), ASCT, Dara-RVd or RVd consolidation (2 cycles), followed by maintenance (26 cycles)
- Primary end-point, stringent complete response (sCR) rate by the end of post-ASCT consolidation, favored Dara-RVd vs RVd (42.4% vs 32.0%; odds ratio=1.57; 95% confidence interval, 0.87-2.82; P=0.068)

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**Not an approved combination outside the U.S.*

Voorhees PM, et al. *Blood*. 2020 Aug 20;136(8):936-945

GRIFFIN: depth of response, over time

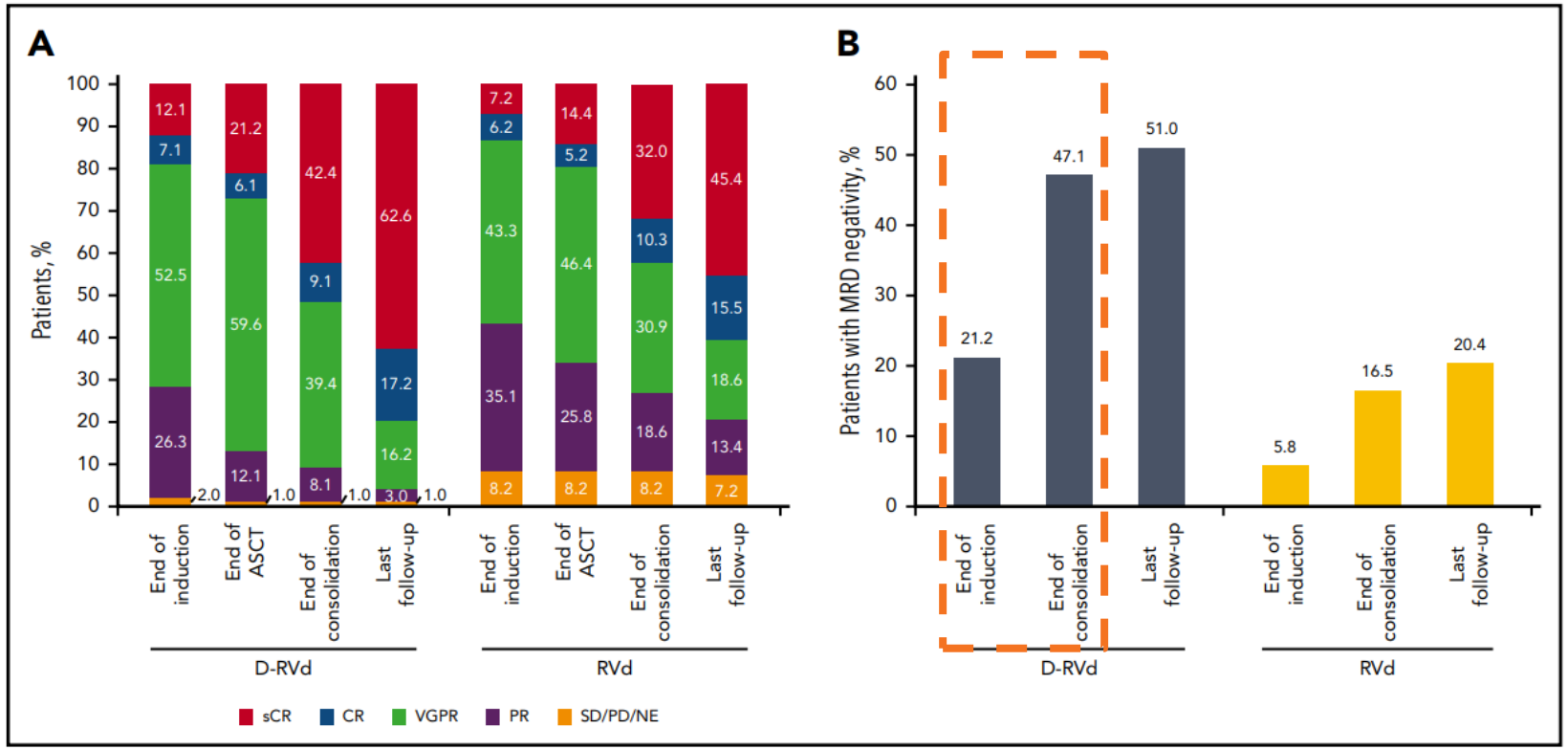

Figure 1. Summary of response rates and MRD-negativity (10^{-5}) rates over time. (A) Response rates over time are shown. Data for the end of induction, end of ASCT, and end of consolidation are from the primary analysis. Response data with longer median follow-up of 22.1 months are also shown (last follow-up). (B) MRD-negativity (10^{-5}) rates in the intent-to-treat population by the end of induction therapy, end of consolidation, and last follow-up. All MRD data are from the analysis with a median follow-up of 22.1 months. MRD was evaluated at baseline, first evidence of suspected CR or sCR, at the end of induction and consolidation, and after 12 and 24 months of maintenance, regardless of response (per protocol amendment 2).

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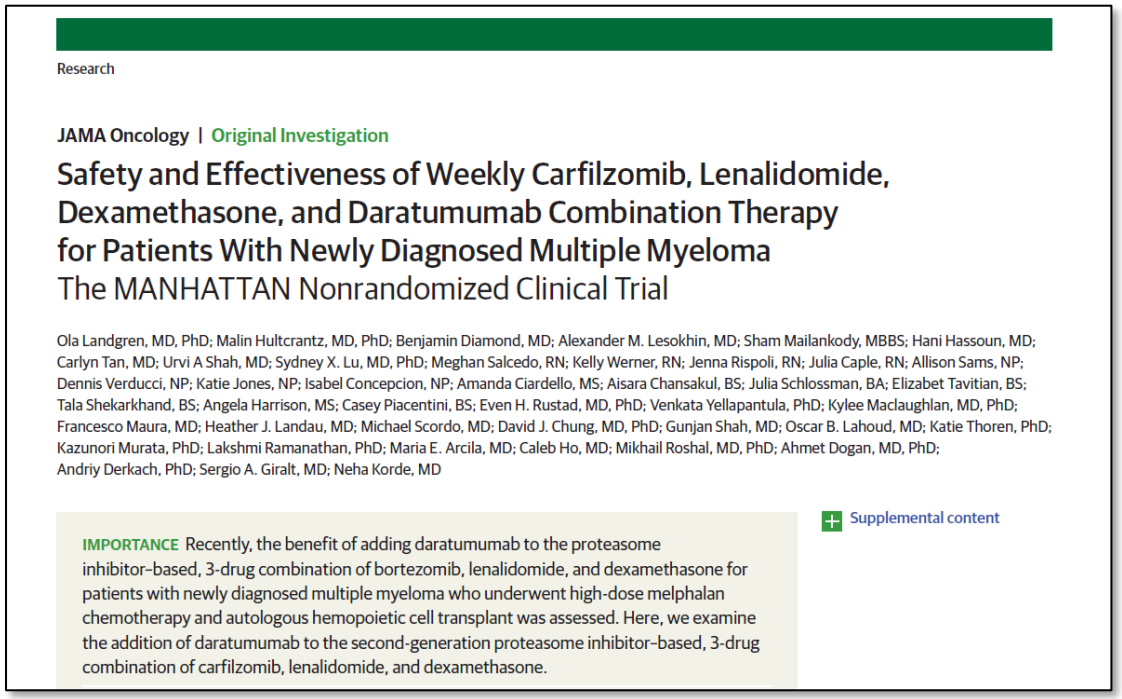
Voorhees PM, et al. *Blood*. 2020 Aug 20;136(8):936-945

MANHATTAN study



Research

JAMA Oncology | Original Investigation

Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma
The MANHATTAN Nonrandomized Clinical Trial

Ola Landgren, MD, PhD; Malin Hultcrantz, MD, PhD; Benjamin Diamond, MD; Alexander M. Lesokhin, MD; Sham Mailankody, MBBS; Hani Hassoun, MD; Carlyn Tan, MD; Urvi A Shah, MD; Sydney X. Lu, MD, PhD; Meghan Salcedo, RN; Kelly Werner, RN; Jenna Rispoli, RN; Julia Caple, RN; Allison Sams, NP; Dennis Verducci, NP; Katie Jones, NP; Isabel Concepcion, NP; Amanda Ciardello, MS; Aisara Chansakul, BS; Julia Schlossman, BA; Elizabet Tavitian, BS; Tala Shekarkhand, BS; Angela Harrison, MS; Casey Piacentini, BS; Even H. Rustad, MD, PhD; Venkata Yellapantula, PhD; Kylee Maclaughlan, MD, PhD; Francesco Maura, MD; Heather J. Landau, MD; Michael Scordo, MD; David J. Chung, MD, PhD; Gunjan Shah, MD; Oscar B. Lahoud, MD; Katie Thoren, PhD; Kazunori Murata, PhD; Lakshmi Ramanathan, PhD; Maria E. Arcila, MD; Caleb Ho, MD; Mikhail Roshal, MD, PhD; Ahmet Dogan, MD, PhD; Andriy Derkach, PhD; Sergio A. Giralt, MD; Neha Korde, MD

Supplemental content

IMPORTANCE Recently, the benefit of adding daratumumab to the proteasome inhibitor–based, 3-drug combination of bortezomib, lenalidomide, and dexamethasone for patients with newly diagnosed multiple myeloma who underwent high-dose melphalan chemotherapy and autologous hemopoietic cell transplant was assessed. Here, we examine the addition of daratumumab to the second-generation proteasome inhibitor–based, 3-drug combination of carfilzomib, lenalidomide, and dexamethasone.

- Addition of daratumumab (Dara) to weekly KRd (Dara-wKRd*) in newly diagnosed multiple myeloma patients, independent of transplant eligibility
- Single-arm, phase 2 study; all patients (N = 41) planned to receive 8 cycles Dara-wKRd
- Primary end-point: MRD-negativity after up to 8 cycles of Dara-wKRd, in the absence of HDM-ASCT
- Patients who were potential future candidates for high-dose melphalan followed by autologous stem cell transplant (HDM-ASCT) were offered collection of stem cells after 4-6 cycles of Dara-wKRd

**Not an approved combination outside the U.S.*

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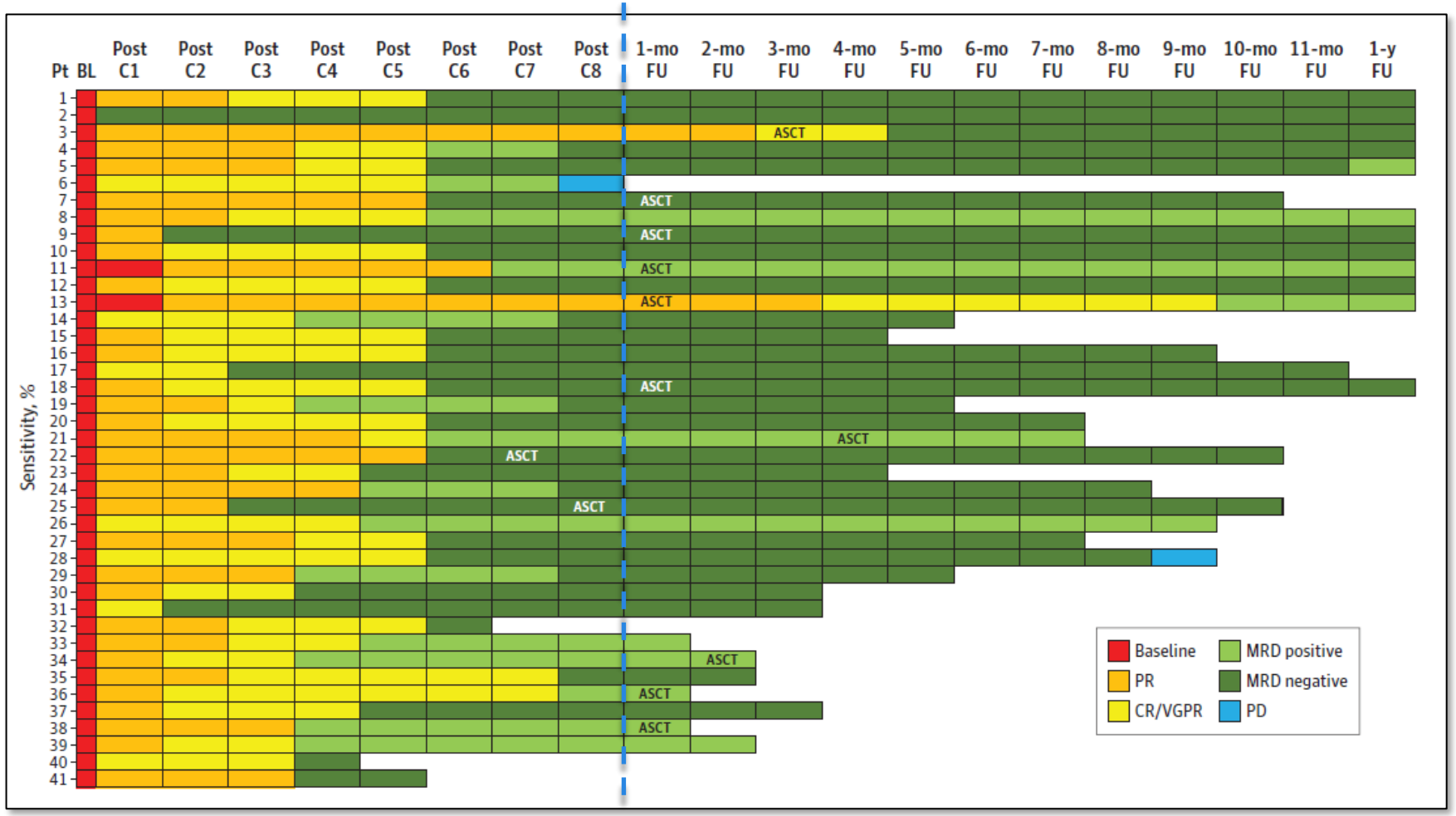
Landgren O, et al. *JAMA Oncol* 2021; 2021 Jun 1;7(6):862-868

Dara-wKRd: 71% MRD negativity, as best response after ≤8 cycles



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Landgren O, et al. *JAMA Oncol* 2021; 2021 Jun 1;7(6):862-868

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Multiple Myeloma

NCCN Guidelines Index
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Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[f] • Ixazomib/cyclophosphamide/dexamethasone[f] • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab/carfilzomib/lenalidomide/dexamethasone[g] • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Daratumumab/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[g] (VTD-PACE)

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[h] (category 1)
Other Recommended Regimens • Ixazomib (category 1) • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide ± dexamethasone[i]

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See General Considerations for Myeloma Therapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-J).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[f] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[g] Generally reserved for the treatment of aggressive MM.
[h] There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.
[i] Dual maintenance recommended for high-risk MM.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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www.nccn.org (version 1.2022. posted on 081621)

MRD negativity in relapsed/refractory and newly diagnosed non-transplant eligible myeloma patients receiving modern therapies

	POLLUX			CASTOR		
MRD negativity (10^{-5}) in RRMM	**D-Rd**	**Rd**	**p value***	**D-Vd**	**Vd**	***P* value***
ITT						
Number evaluable	286	283		251	247	
Rate	93 (32.5%)	19 (6.7%)	<0.0001	38 (15.1%)	4 (1.6%)	< .0001
≥CR						
Number evaluable	162	65		72	23	
Rate	93 (57.4%)	19 (29.2%)	0.0001	38 (52.8%)	4 (17.4%)	.0035
≤2PL, ITT						
Number evaluable	234	226		192	187	
Rate	77 (32.9%)	19 (8.4%)	<0.0001	35 (18.2%)	3 (1.6%)	< .0001
≤2PL, ≥CR						
Number evaluable	135	56		67	22	
Rate	77 (57.0%)	19 (33.9%)	0.0042	35 (52.2%)	3 (13.6%)	.0023
	ALCYONE			**MAIA**		
MRD negativity (10^{-5}) in TIE NDMM	**D-VMP**	**VMP**	**p value***	**D-Rd**	**Rd**	***P* value***
ITT						
Number evaluable	350	356		368	369	
Rate	99 (28.3%)	25 (7.0%)	<0.0001	106 (28.8%)	34 (9.2%)	< .0001
≥CR						
Number evaluable	160	90		182	100	
Rate	94 (58.8%)	25 (27.8%)	<0.0001	106 (58.2%)	34 (34.0%)	.0001

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Cavo M, et al. *Blood* 2021; [Epub ahead of print]

MRD negativity in relapsed/refractory and newly diagnosed non-transplant eligible myeloma patients receiving modern therapies

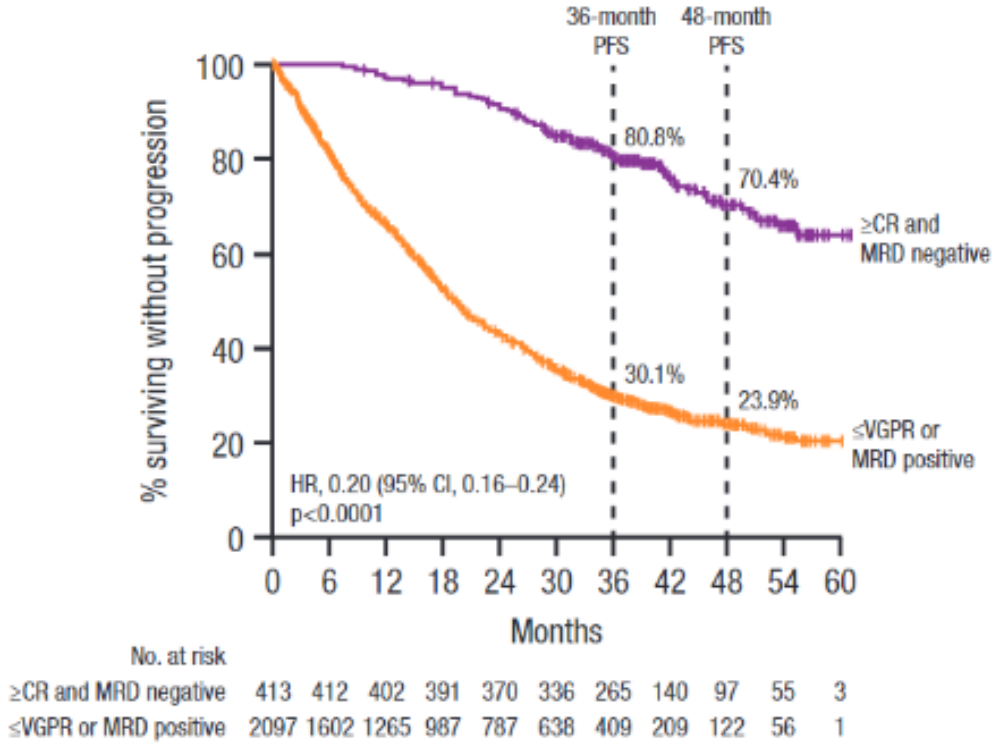


Table 2. Time-varying Cox proportional hazard model for PFS*

Variable	HR (95% CI)	*P* value
RRMM and TIE NDMM		
Univariate analysis		
Response group (≥CR + MRD⁻ vs ≤VGPR or MRD⁺)	0.17 (0.12-0.24)	< .0001
Multivariate analysis		
Response group (≥CR + MRD⁻ vs ≤VGPR or MRD⁺)	0.20 (0.14-0.29)	< .0001
Disease setting (NDMM vs RRMM)	0.45 (0.39-0.52)	< .0001
Treatment (daratumumab-containing regimen vs SoC)	0.48 (0.43-0.54)	< .0001
Age	1.00 (0.99-1.01)	.9619
ISS disease stage (II vs I)	1.76 (1.52-2.03)	< .0001
ISS disease stage (III vs I)	1.94 (1.64-2.30)	< .0001
Baseline renal function (>60 mL/min vs ≤60 mL/min)	1.00 (0.87-1.14)	.9449
Cytogenetic risk (high vs standard)	1.53 (1.30-1.79)	< .0001

Cavo M, et al. *Blood* 2021; [Epub ahead of print]

At this time, MRD testing is a prognostic tool in newly diagnosed multiple myeloma

- Currently, MRD-negativity is a prognostic marker of long PFS/OS
- Modern combination therapies deliver high rates of MRD-negativity
- Validated and sensitive methods for MRD tracking should be standard

Relapsed/refractory myeloma

How and when should response assessment be performed in multiple myeloma?

- Relapsed/refractory myeloma is defined as relapse in patients who must have achieved at least minimal response (MR), which either becomes non-responsive while on salvage therapy or progresses within 60 days of last treatment

- Biochemical *versus* clinical relapse
  - Current IMWG criteria defines relapse as a 25% increased from nadir (absolute M spike increase by 0.5 g/dL)

- MRD assessments are becoming gradually more common; will that trigger relapse therapy in the future?

Recent FDA approved agents/combinations for myeloma

Treatment	Number of lines of prior therapy
Belantamab mafodotin-blmf (DREAMM-2[15])	≥4
Carfilzomib monotherapy (PX-171–003[11]; FOCUS[12])	≥ 1
Carfilzomib + lenalidomide + dexamethasone (ASPIRE trial[1])	1-3
Carfilzomib(56), dexamethasone (Endeavor trial[8])	1-3
Daratumumab + either lenalidomide or bortezomib + dex (Pollux[5] & Castor[6] trials)	≥1
Daratumumab + pomalidomide + dexamethasone[7]	≥2
Daratumumab monotherapy (Sirius trial[9])	≥3
Elotuzumab + lenalidomide + dexamethasone (ELOQUENT- 2 trial[2])	1-3
Elotuzumab + pomalidomide + dexamethasone (ELOQUENT-3[13])	≥ 2
Idecabtagene vicleucel (KarMMA[16])	≥4
Isatuximab-irfc + pomalidomide + dexamethasone (ICARIA-MM[14])	≥ 1
Isatuximab-irfc + carfilzomib + dexamethasone (IKEMA[17])	1-3
Ixazomib + lenalidomide + dexamethasone (Tourmaline-MM1 trial[3])	≥ 2
Melphalan flufenamide (melflufen) + dexamethasone (HORIZON[19])	≥4
Panobinostat + bortezomib + dexamethasone (Panorama-1[4])	≥2
Pomalidomide + dexamethasone	≥2
Selinexor + dexamethasone (STORM[10])	≥4
Selinexor + bortezomib + dexamethasone (BOSTON[18])	≥ 1

Isatuximab in Combination with Kd or Pd for RRMM: Phase III IKEMA and ICARIA study designs

IKEMA

N=302
- Patients with relapsed MM
- 1-3 prior therapy lines
- No prior carfilzomib
- Not refractory to prior anti-CD38

Stratified by:
- *No. of prior lines of therapy (1 vs <1)*
- *R-ISS (I or II vs III vs not classified)*

Isa-Kd
Isatuximab + Carfilzomib/dex

Kd
Carfilzomib/dex

Primary endpoint: PFS by IRC

Key secondary endpoints: ORR, ≥VGPR, MRD negativity, CR, OS, safety

- *Isatuximab: 10 mg/kg on Days 1, 8, 15, 22 in cycle 1, then Q2W.*
- *Carfilzomib: 20 mg/m^2 on Days 1, 2; 56 mg/m^2 on Days 8, 9, Days 15, 16 in cycle 1; 56 mg/m^2 on Days 1, 2, 8, 9, 15, 16 in subsequent cycles.*
- *Dexamethasone: 20 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of each cycle of 28-day cycles.*

ICARIA

N=307
- Patients with R/R MM after ≥2 lines (including len and a PI)
- PD on last line
- Pomalidomide naïve
- CD38 antibody naive/sensitive

Stratified by:
- *No. of prior lines of therapy (1 vs <1)*
- *Age*

Isa-Pd
Isatuximab + Pom/Dex

Pd
Pom/Dex

Primary endpoint: PFS by IRC

Key secondary endpoints: ORR, OS, DoR, QoL, safety

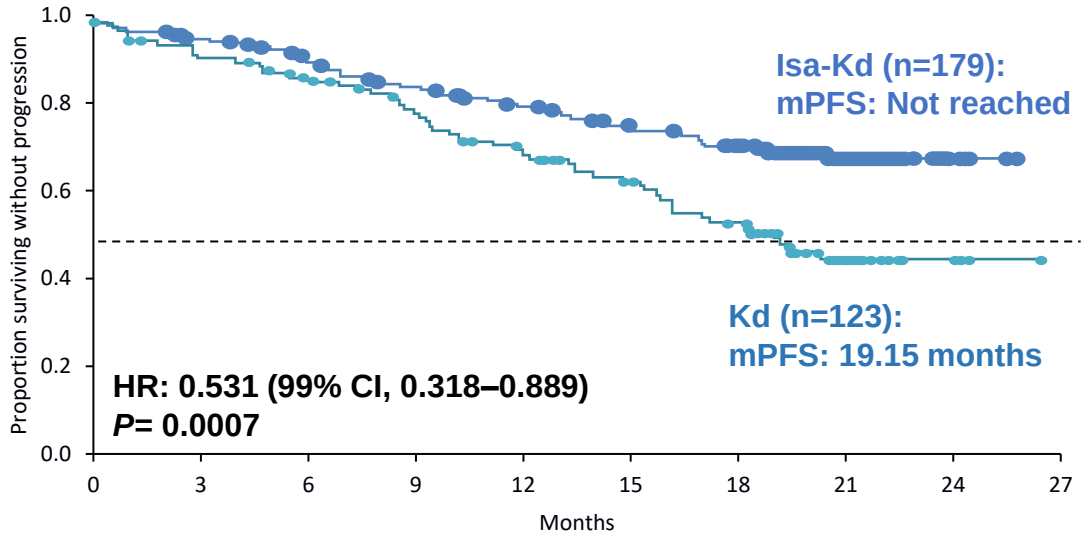
- *Isatuximab 10 mg/kg IV, D1,8,15,22 (C1); D1,15 until PD*
- *Pomalidomide 4 mg PO, D1-21 until PD*
- *Dexamethasone 40 mg PO (20 mg ≥75 yr of age.), D1,8,15,22 until PD 28-day cycles*

Moreau P, et al. Lancet. 2021;397(10292):2361-2371; Richardson. ASCO 2021. Abstr 8017

Isatuximab in Combination with Kd or Pd for RRMM: Phase III IKEMA and ICARIA PFS results

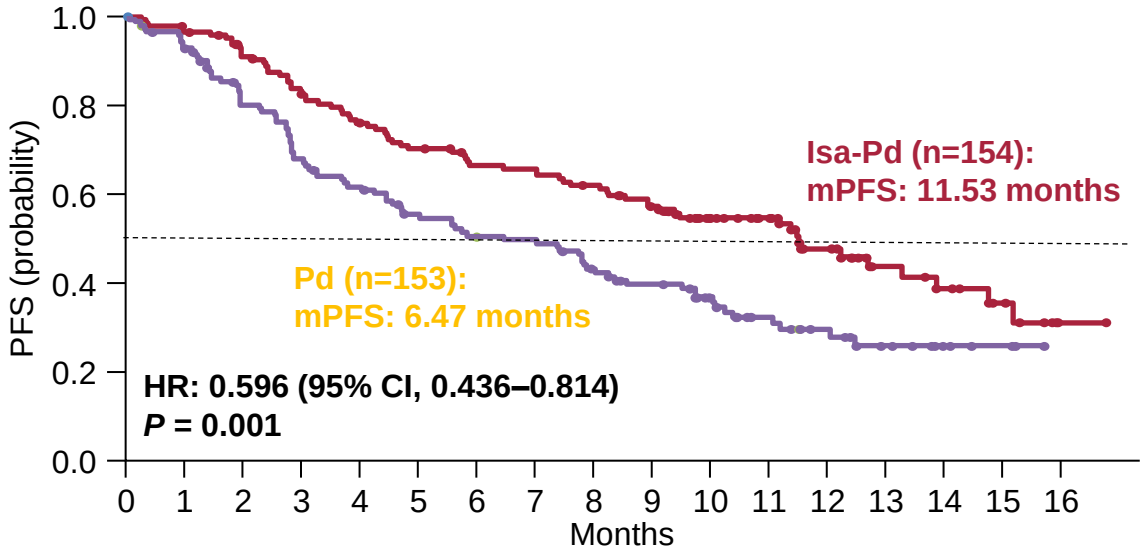
IKEMA PFS

Isa-Kd vs Kd
Patients with 1–3 prior lines of therapy



ICARIA PFS

Isa-Pd vs Pd
Patients with ≥2 prior lines of therapy



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Moreau P, et al. Lancet. 2021;397(10292):2361-2371; Richardson. ASCO 2021. Abstr 8017

Isatuximab in Combination with Kd or Pd for RRMM: Phase III IKEMA and ICARIA results

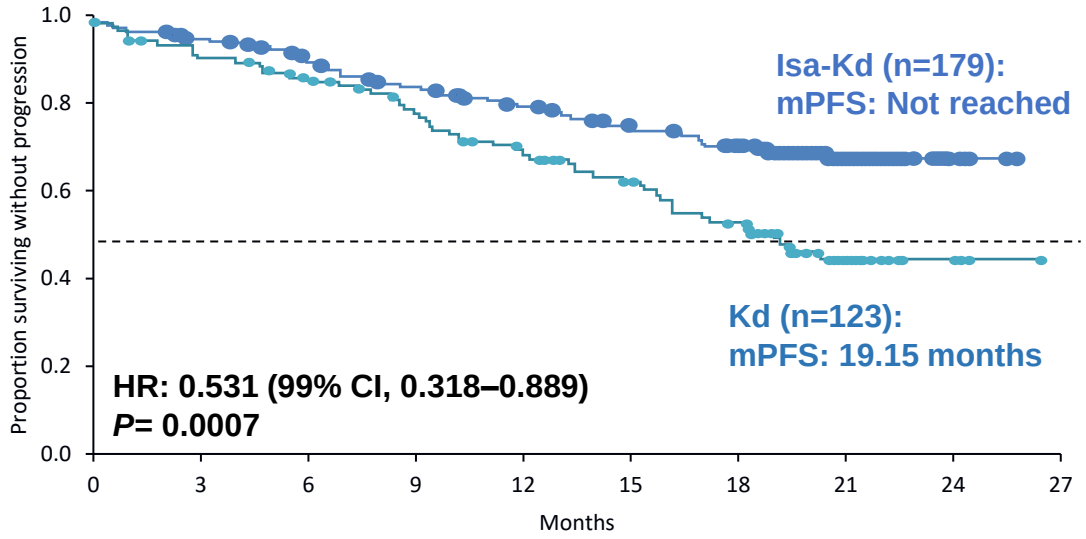
	IKEMA (Isa-Kd vs Kd)	ICARIA (Isa-Pd vs Pd)
Median prior lines, n (range)	2 (1–4)	3 (2–11)
% Len refractory	31.8 vs 34.1	93.5 vs 91.5
Median follow-up, months	20.7	11.6
ORR, % (≥VGPR, %)	86.6 vs 82.9 (72.6 vs 56.1)	60.4 vs 35.3 (31.8 vs 8.5)
MRD–ve (10^{-5}), %	29.6 vs 13.0	5.2 vs 0
TEAEs Grade ≥3, % (Fatal TEAEs, %)	76.8 vs 67.2 (3.4 vs 3.3)	86.8 vs 70.5 (7.9 vs 9.4)
Discontinuation due to TEAEs, %	8.5 vs 13.9	7.2 vs 12.8

Moreau P, et al. Lancet. 2021;397(10292):2361-2371; Richardson. ASCO 2021. Abstr 8017

Isatuximab in Combination with Kd or Pd for RRMM: Phase III IKEMA and ICARIA PFS results

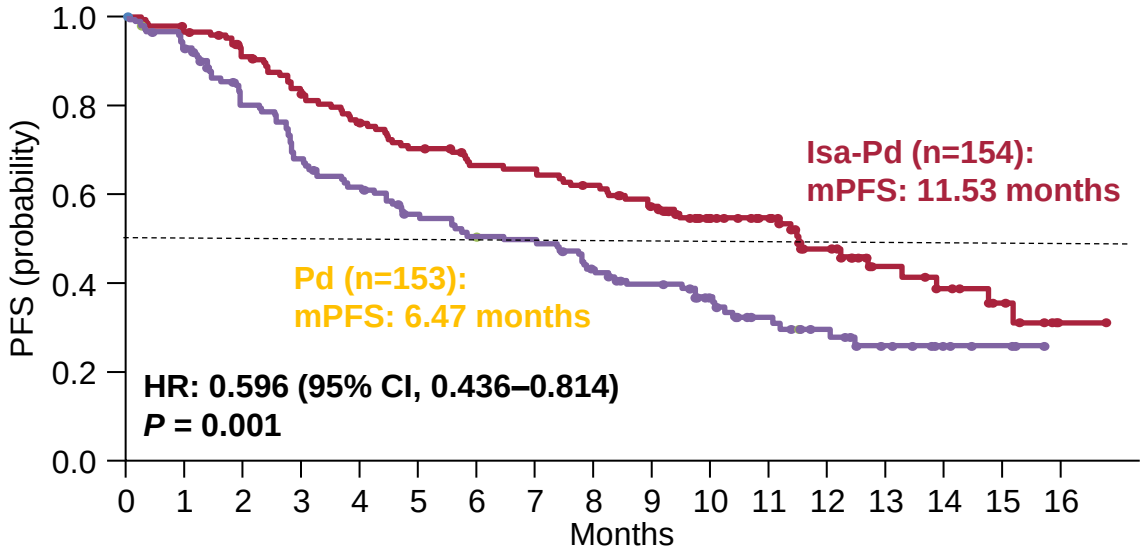
IKEMA PFS

Isa-Kd vs Kd
Patients with 1–3 prior lines of therapy



ICARIA PFS

Isa-Pd vs Pd
Patients with ≥2 prior lines of therapy



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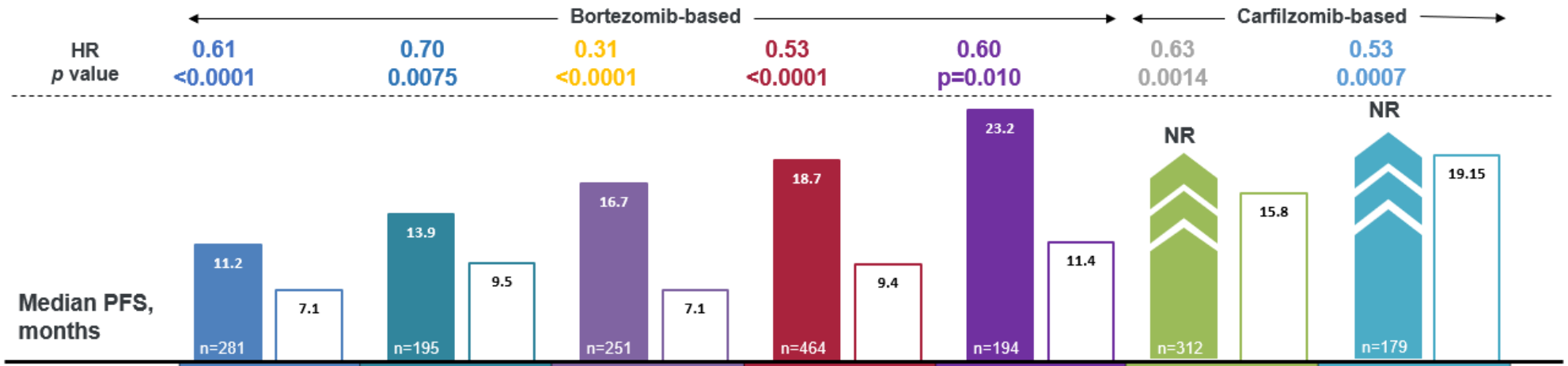
Moreau P, et al. Lancet. 2021;397(10292):2361-2371; Richardson. ASCO 2021. Abstr 8017

Phase III, lenalidomide-free backbones: key efficacy data



	OPTIMISMM[1] PVd vs Vd	BOSTON[2] SVd vs Vd	CASTOR[3] DVd vs Vd	ENDEAVOR[4] Kd vs Vd	BELLINI[5] VenVd vs Vd	CANDOR[6] DKd vs Kd	IKEMA[7] Isa-Kd vs Kd
m prior lines, n (range)	2 (1–2)*	NA	2 (1–10)**	2 (1–2)*	NA	NA	2 (1–4)
Len refractory, %	71.2 vs 68.7	NA	23.9 vs 32.8	24.4 vs 26.2	NA	31.7 vs 35.7	31.8 vs 34.1
mFU, months	15.9	13.2 vs 16.5	50.2	11.9 vs 11.1	28.6	16.9 vs 16.3	20.7
≥CR, %	15.6 vs 4.0	16.9 vs 10.6	30.0 vs 9.8	12.5 vs 6.2	29 vs 7	28.5 vs 10.4	39.7§ vs 27.6
MRD–ve (10^{-5}), %	NA	NA	15.1 vs 1.6	NA	15 vs 2	17.6 vs 3.9†	29.6 vs 13.0

*Interquartile range; **Eligibility was ≥1 prior therapies; †MRD at 12 months;
‡99% confidence interval; §May be an underestimate due to M-protein interference

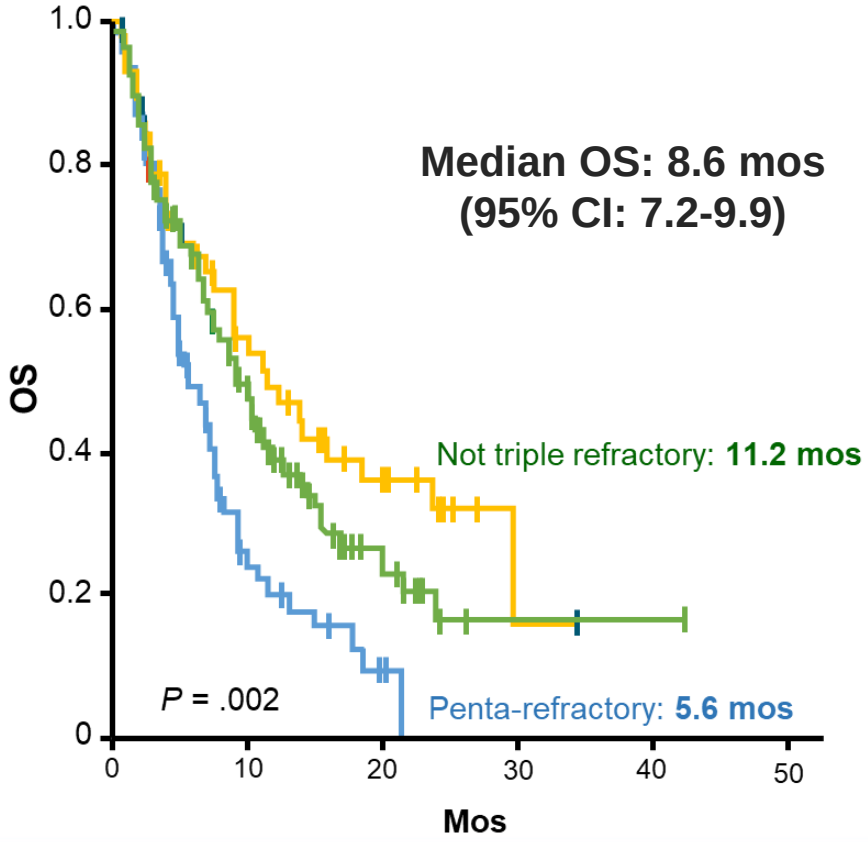
Treatment considerations: a few clinical perspectives

- Doublet *versus* triplet (vs quadruplets)?
- When to consider SCT – upfront *versus* delayed?
- Optimal sequencing of therapies?
- Real-world data *versus* clinical trial data?

Survival outcomes of penta-refractory myeloma patients

Retrospective study of patients with myeloma refractory to CD38 antibodies from 14 academic institutions (N=275)

	Refractory, %
Triple refractory (CD38 antibody + 1 PI + 1 IMiD) Quad refractory (CD38 antibody + 1 PI + 2 IMiDs OR 2 PIs and 1 IMID)	54
Penta-refractory (CD38 antibody + 2 PIs + 2 IMiDs)	25
Bortezomib	68.4
Carfilzomib	47.3
Lenalidomide	76.7
Pomalidomide	65.1



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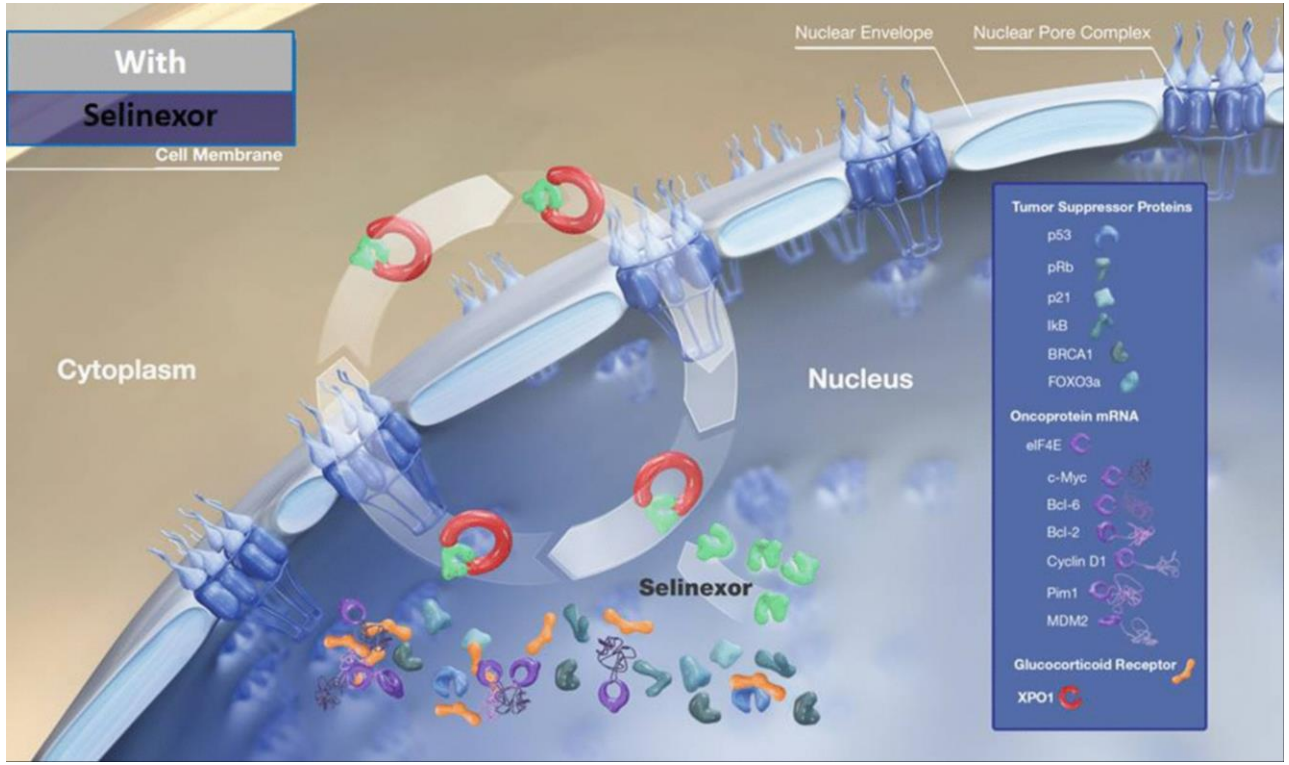
Gandhi UH, et al. *Leukemia*. 2019;33(9):2266-2275

New and emerging treatment options for patients with relapsed/refractory multiple myeloma

- Selinexor
- Venetoclax
- BCMA-targeted agents
  - ADCs: Belantamab mafodotin
  - CAR T-cells: Ide-cel, Orva-cel, Cilta-cel
  - BiTEs: Talquetamab, Teclistamab (and many other…)

Selinexor is a first in class, oral selective inhibitor of nuclear export: mechanism of action



- Selinexor
  - Inhibits XPO1 through reversible covalent modification
  - ➢ **Currently FDA approved in combination with dexamethasone based on the STORM study**
  - ➢ **Currently FDA approved in combination with bortezomib and dexamethasone based on the BOSTON study**
  - Ongoing STOMP study looking into combinations of Selinexor with other anti-myeloma agents

- XPO1 in myeloma
  - Transports >200 proteins from the nucleus to cytoplasm
  - Expression increased in MM vs normal PC/MGUS/SMM
  - Correlates with shorter survival and increased bone disease

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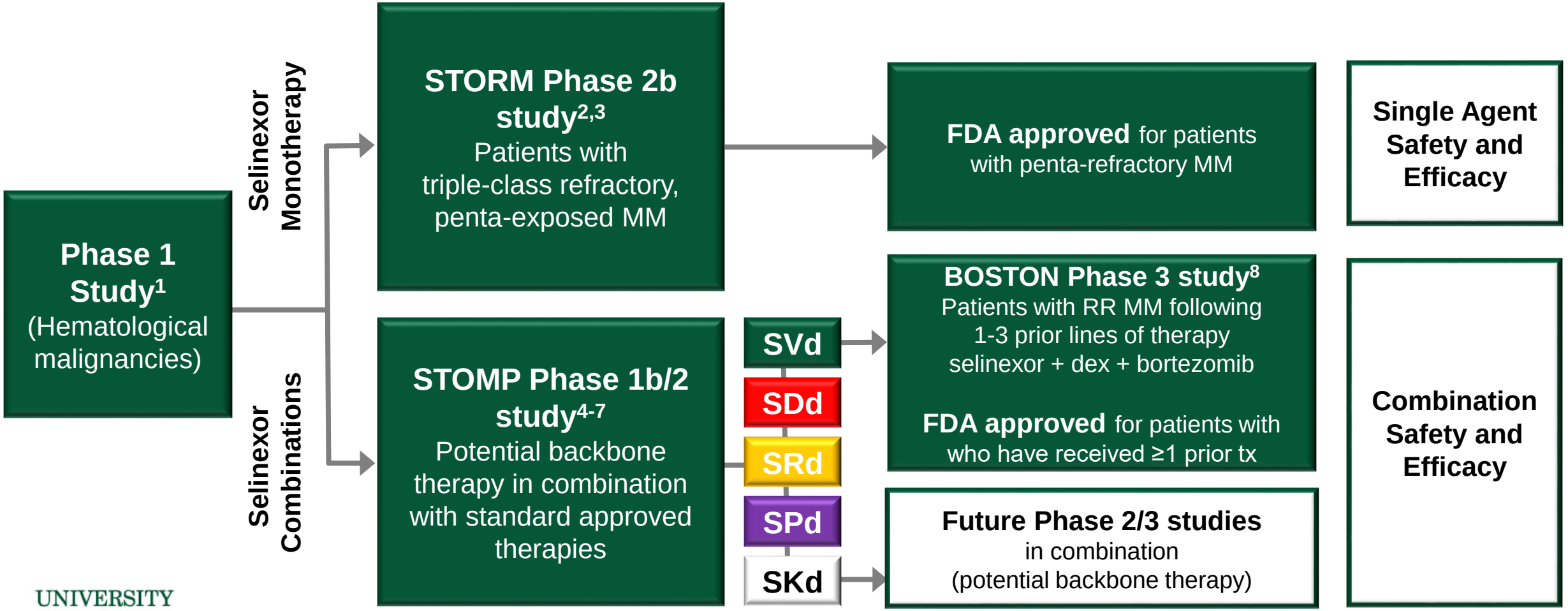
Theodoropoulos, N. et al. Targ Oncol. 2020;15, 697-708

Selinexor in relapsed/refractory multiple myeloma



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1. Chen C, et al. *Blood*. 2018;131(8):855-863. 2. Vogl DT, et al. *J Clin Oncol*. 2018;36(9):859-866. 3. Chari A, et al. Presented at ASH Annual Meeting, 2018. 4. Chen C, et al. Presented at ASH Annual Meeting, 2018. 5. Bahlis N, et al. *Blood*. Oct 23 2018 [Epub ahead of print]. 6. White D, et al. Presented at ASH Annual Meeting, 2017. 7. Gasparetto C, et al. Presented at ASH Annual Meeting, 2018. 8. Clinicaltrials.gov. NCT03110562

STORM part 2: expansion in penta-refractory myeloma

Patient Population

Penta-Refractory MM (N=122)

- MM documented refractory to ≥1 PI, ≥1 IMiD, D, a glucocorticoid and last therapy

Key Inclusion Criteria

- **Creatinine clearance ≥ 20 mL/min**
- **ANC ≥ 1,000/mm^3**
- **Platelets ≥ 75,000/mm^3 (if bone marrow plasma cell > 50%; plt > 50,000/mm^3)**
- **Hemoglobin ≥ 8.5 g/dL**

Selinexor (80 mg) **+ dexamethasone** (20 mg)
Twice Weekly (Day 1 and 3)

Until PD or intolerability

Primary Endpoint

- **ORR**

Secondary Endpoints:

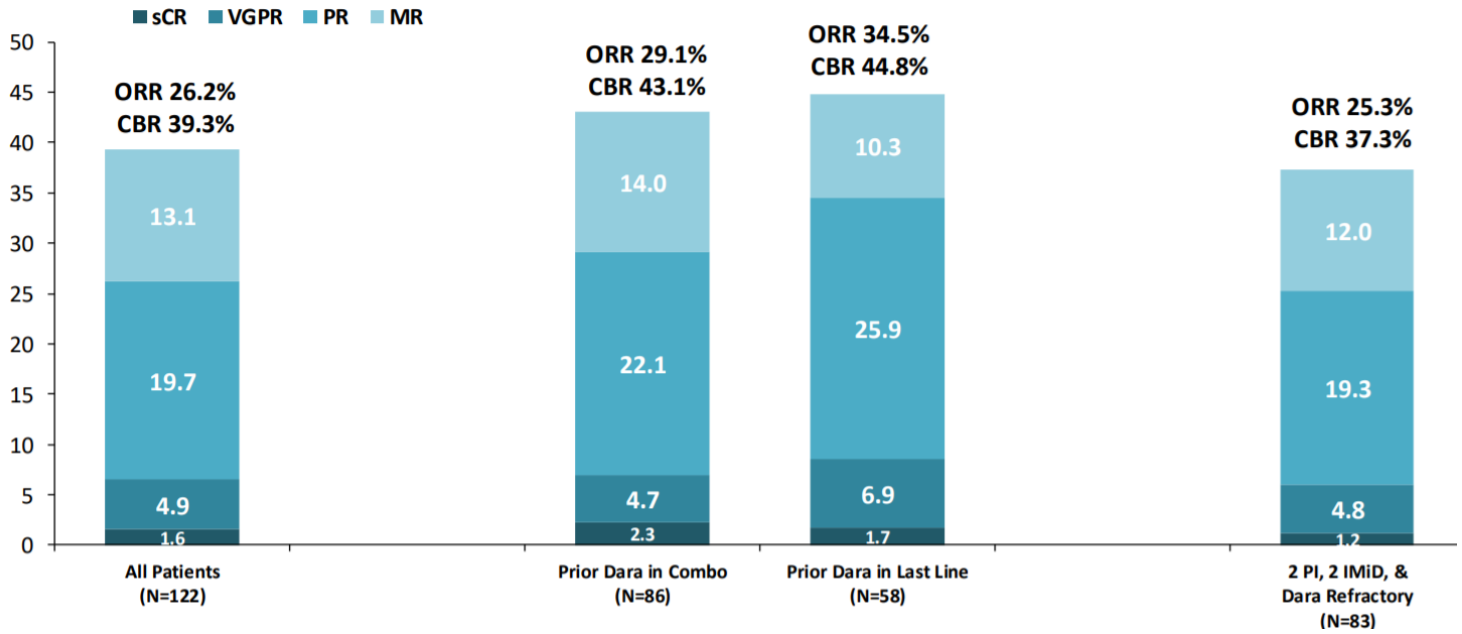
- **DOR**
- **CBR**
- **OS**
- **PFS**
- **Safety**

Median Prior LOT: 7

ANC, absolute neutrophil count; B, bortezomib; C, carfilzomib; CBR, clinical benefit rate; D, daratumumab; DOR, duration of response; IMiD, immunomodulatory drug; L, lenalidomide; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression free survival; PI, proteasome inhibitor

Jagannath S, et al. Presented at SOHO annual meeting, 2018.

Selinexor in heavily pretreated, penta-exposed, triple-class refractory myeloma: STORM Phase II Trial



- In heavily pretreated penta-exposed, triple-class refractory MM, oral selinexor + low-dose dex produced deep, durable responses with an ORR of 26.2% and DoR of 4.4 mos

➢ **FDA approved in combination with dexamethasone based on the STORM study**

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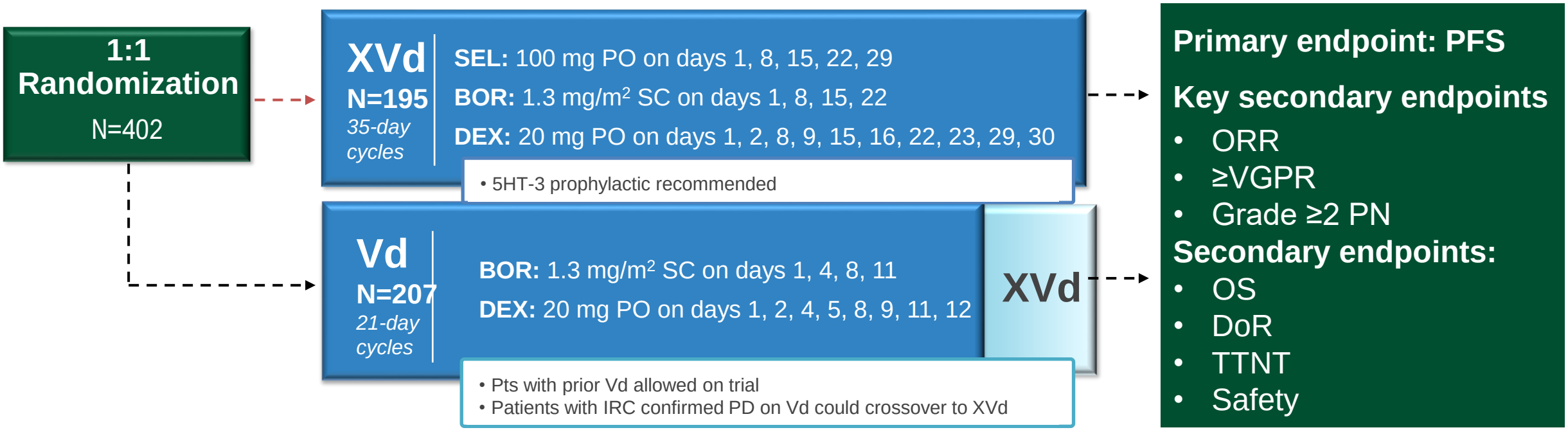
Figures from Chari. ASH 2018. Abstr 598. Chari, et al. N Engl J Med 2019; 381:727-738

Selinexor in patients who had received 1-3 prior therapies: Phase III BOSTON



The XVd regimen requires approximately 40% less bortezomib than Vd which entails 37% fewer clinic visits over the first 6 months of treatment

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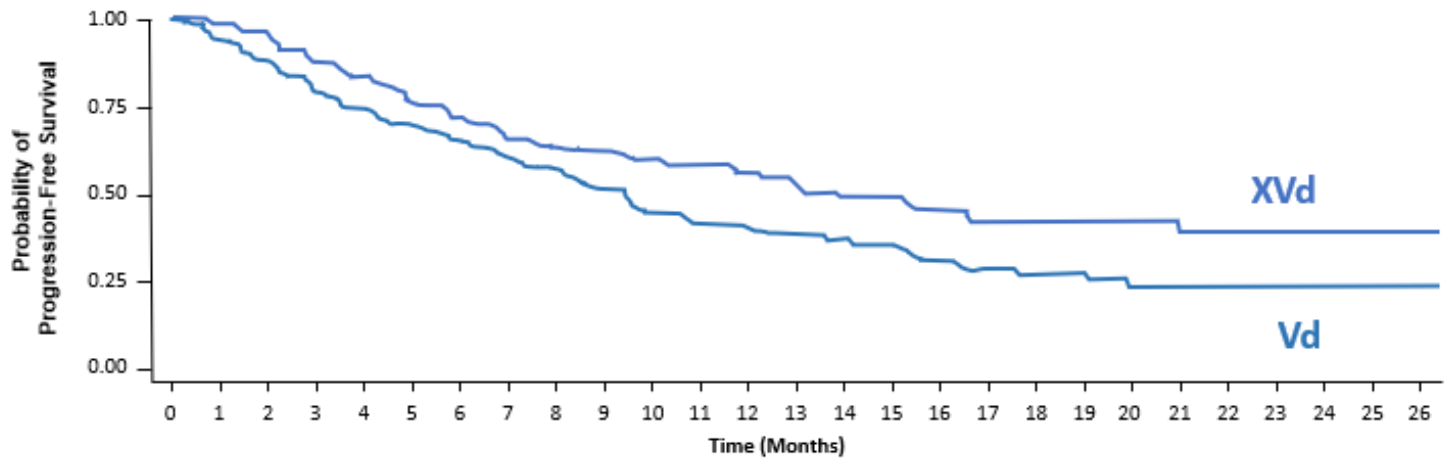
Grosicki S, et al. Lancet. 2020;396:1563-1573

Selinexor in patients who had received 1-3 prior therapies: Phase III BOSTON

	XVd (n=195)	Vd (n=207)
Median PFS, mos (95% CI)	**13.93 (11.73, NE)**	**9.46 (8.11, 10.78)**

HR=0.7020 (95% CI: 0.5279, 0.9335); one-sided *P*=0.0075



- An increase of 4.5 months in median PFS
- 30% reduction in the risk of disease progression or death

Selinexor is FDA approved in combination with bortezomib and dexamethasone after 1 or more prior therapies based on the BOSTON study

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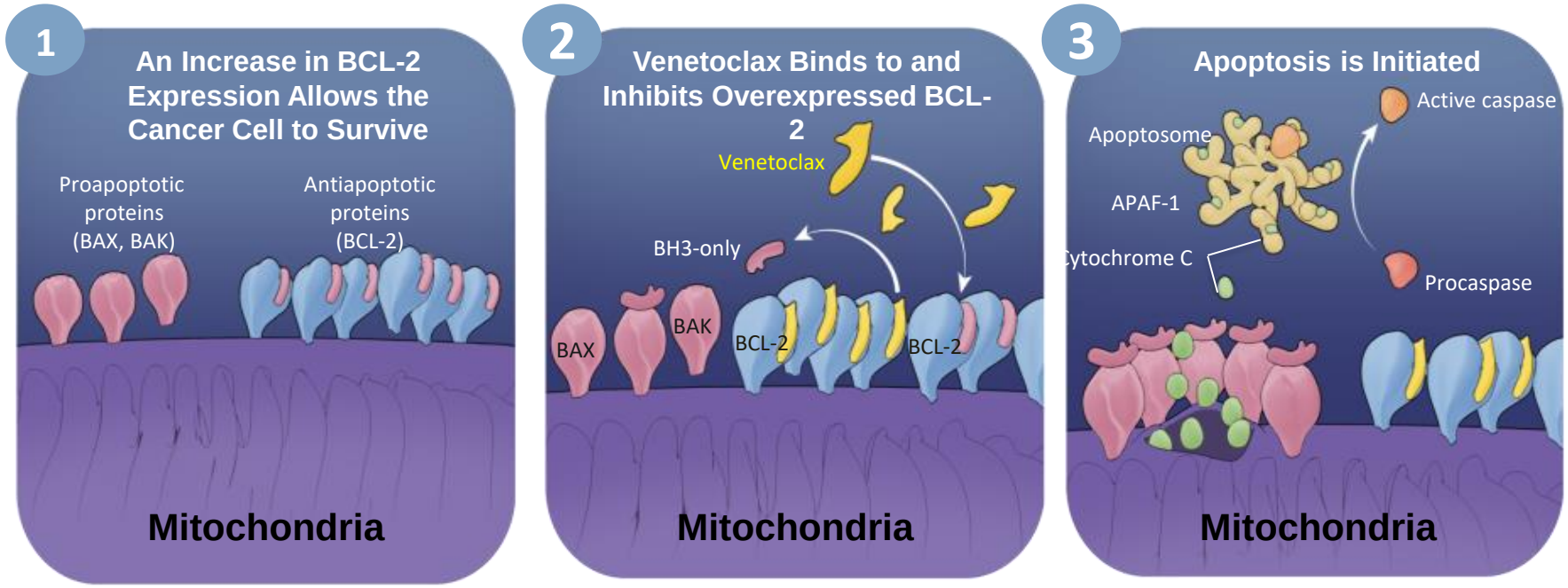
Grosicki S, et al. Lancet. 2020;396:1563-1573

Selinexor: applications to clinical practice

- Currently FDA approved in combination with dexamethasone based on the STORM study and in combination with bortezomib and dexamethasone based on the BOSTON study
- Effective for triple class refractory myeloma
- Works in earlier line disease, too
- Encouraging data for other combos (pomalidomide, carfilzomib)
- Careful prophylaxis with antiemetics and correct dosing make the regimen manageable in most patients

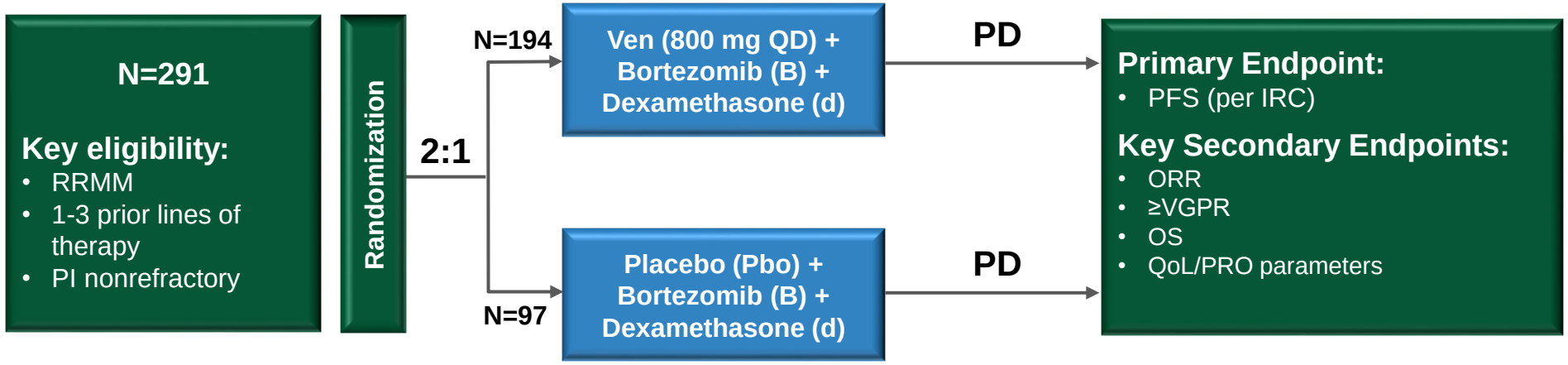
Venetoclax: mechanism of action



- Venetoclax is a small, and highly selective orally bioavailable molecule designed to target specifically the BH3 domain of BCL2
- Venetoclax triggers and restores apoptosis in tumor cells by releasing pro-apoptotic proteins from BCL2

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

Venetoclax or placebo with bortezomib/dexamethasone in RRMM, Phase III BELLINI study design



Cycles 1-8: 21-day, bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 and dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 9+: 35-day, bortezomib 1.3 mg/m^2 days 1, 8, 11, 15, 22 and dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, 23

Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2–3
Nonranked secondary endpoints	PFS in BCL-2^{high} (IHC), DOR, TTP, MRD, negatively rate, other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and BCL2 gene expression

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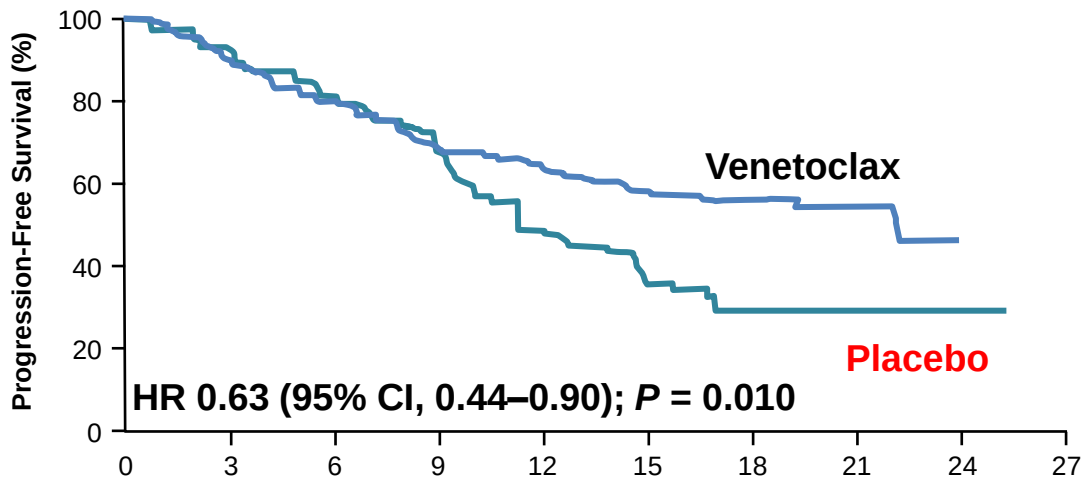
Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642

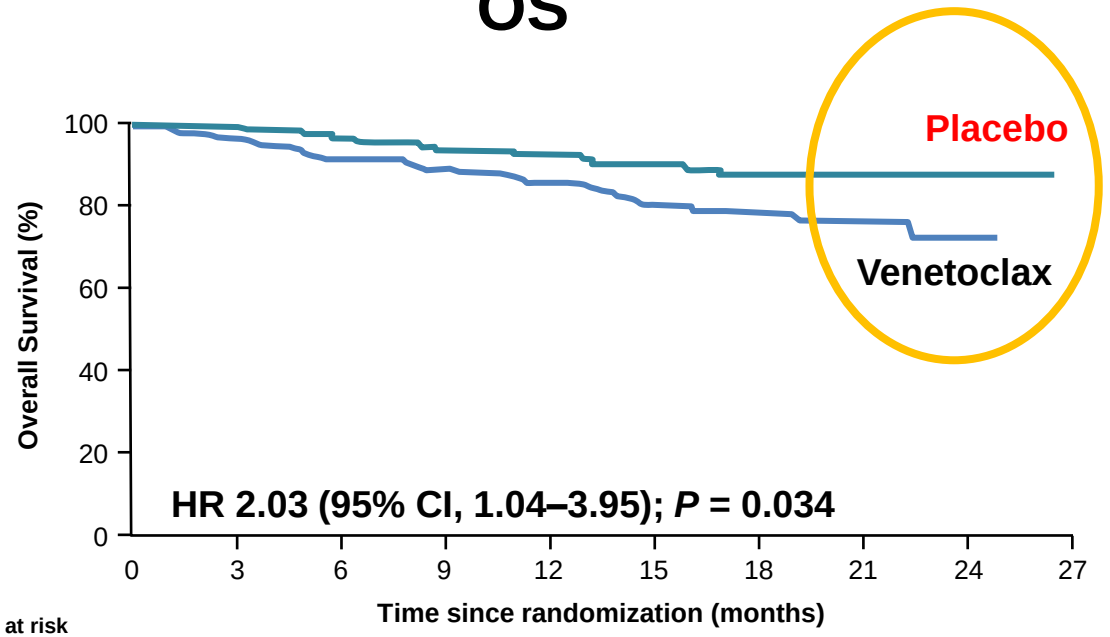
Venetoclax or placebo with bortezomib/dexamethasone in RRMM, Phase III BELLINI study: PFS and OS

PFS



No. at risk (no. censored)										
Venetoclax	194 (0)	159 (35)	134 (60)	112 (82)	98 (96)	82 (112)	58 (136)	20 (174)	5 (189)	0 (194)
Placebo	97 (0)	82 (15)	67 (30)	57 (40)	38 (59)	25 (72)	15 (82)	3 (94)	2 (95)	0 (97)

OS



No. at risk (no. censored)										
Venetoclax	194 (0)	185 (9)	170 (24)	162 (32)	155 (39)	136 (58)	91 (103)	36 (158)	9 (185)	0 (194)
Placebo	97 (0)	95 (2)	92 (5)	89 (8)	87 (10)	74 (23)	44 (53)	20 (77)	5 (92)	0 (97)

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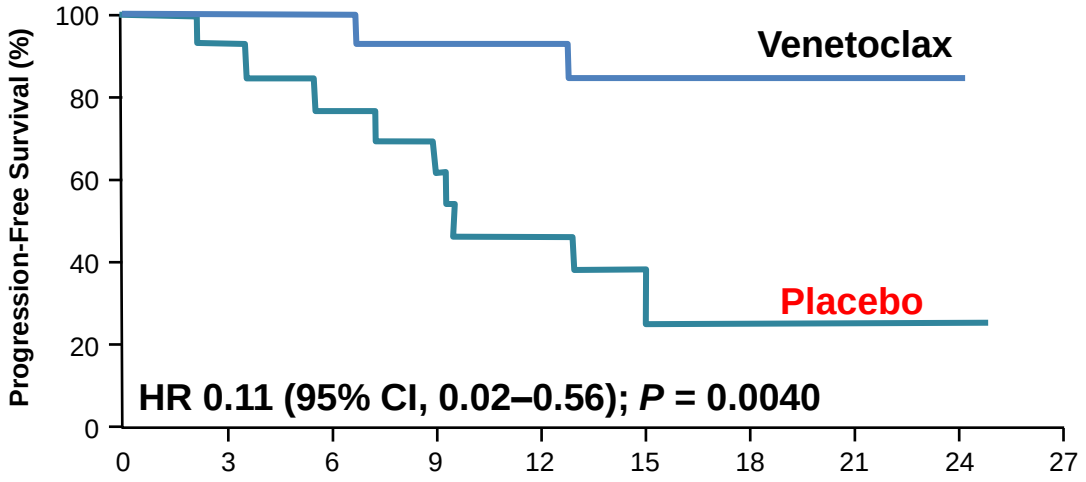
Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642

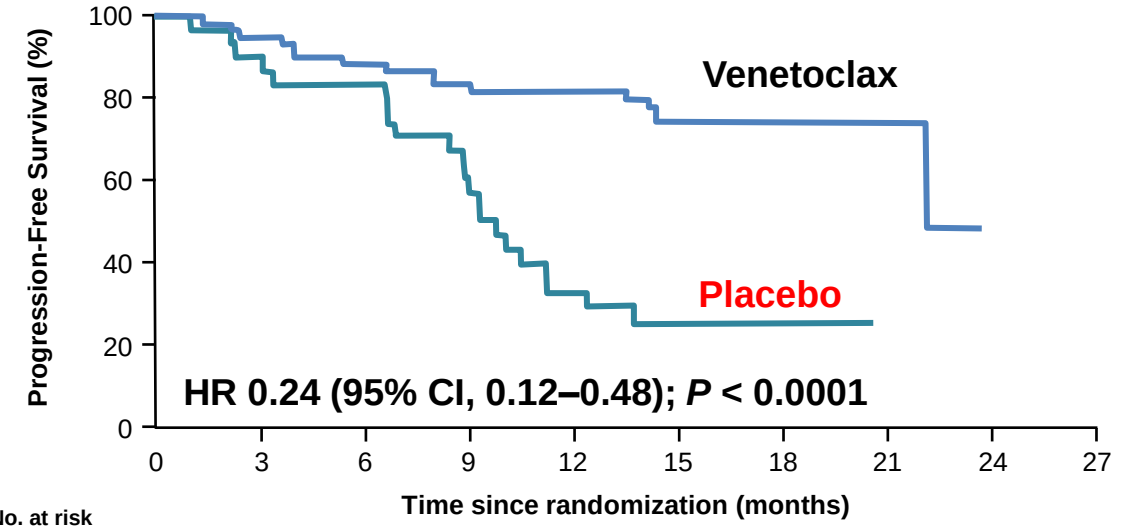
Venetoclax or placebo with bortezomib/dexamethasone in RRMM, Phase III BELLINI study: PFS by t(11;14) and high BCL2

t(11;14)



No. at risk (no. censored)										
Venetoclax	20 (0)	17 (3)	14 (6)	12 (8)	12 (8)	11 (9)	5 (15)	1 (19)	1 (19)	0 (20)
Placebo	15 (0)	12 (3)	10 (5)	9 (6)	6 (9)	3 (12)	1 (14)	1 (114)	1 (14)	0 (15)

High BCL2



No. at risk (no. censored)										
Venetoclax	66 (0)	59 (7)	54 (12)	50 (16)	47 (19)	40 (26)	27 (39)	4 (62)	1 (65)	0 (66)
Placebo	32 (0)	28 (4)	26 (6)	20 (12)	10 (22)	5 (27)	3 (29)	0 (32)		

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Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642

Venetoclax ongoing trials

Trial name	Description	NCT number
M15-538	This phase II, open-label, dose-escalation study evaluates the safety and efficacy of venetoclax in combination with carfilzomib + dexamethasone in patients with R/R MM who have received 1–3 prior lines of therapy	NCT02899052
CANOVA	A phase III study designed to evaluate the safety and efficacy of venetoclax plus dexamethasone compared with pomalidomide plus dexamethasone in patients with t(11;14) R/R MM	NCT03539744
M15-654	Phase II study of venetoclax, daratumumab, and dexamethasone with and without bortezomib in participants with R/R MM. Select parts of the trial include only patients with t(11;14)	NCT03314181
MyDRUG	Precision medicine trial to treat patients with drugs targeted to affect specific genes that are mutated as part of the disease. Patients with a > 30% mutation in several genes including t(11;14) can be enrolled in the treatment arm evaluating venetoclax combined with ixazomib + pomalidomide + dexamethasone.	NCT03732703

Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642

Venetoclax: applications to clinical practice

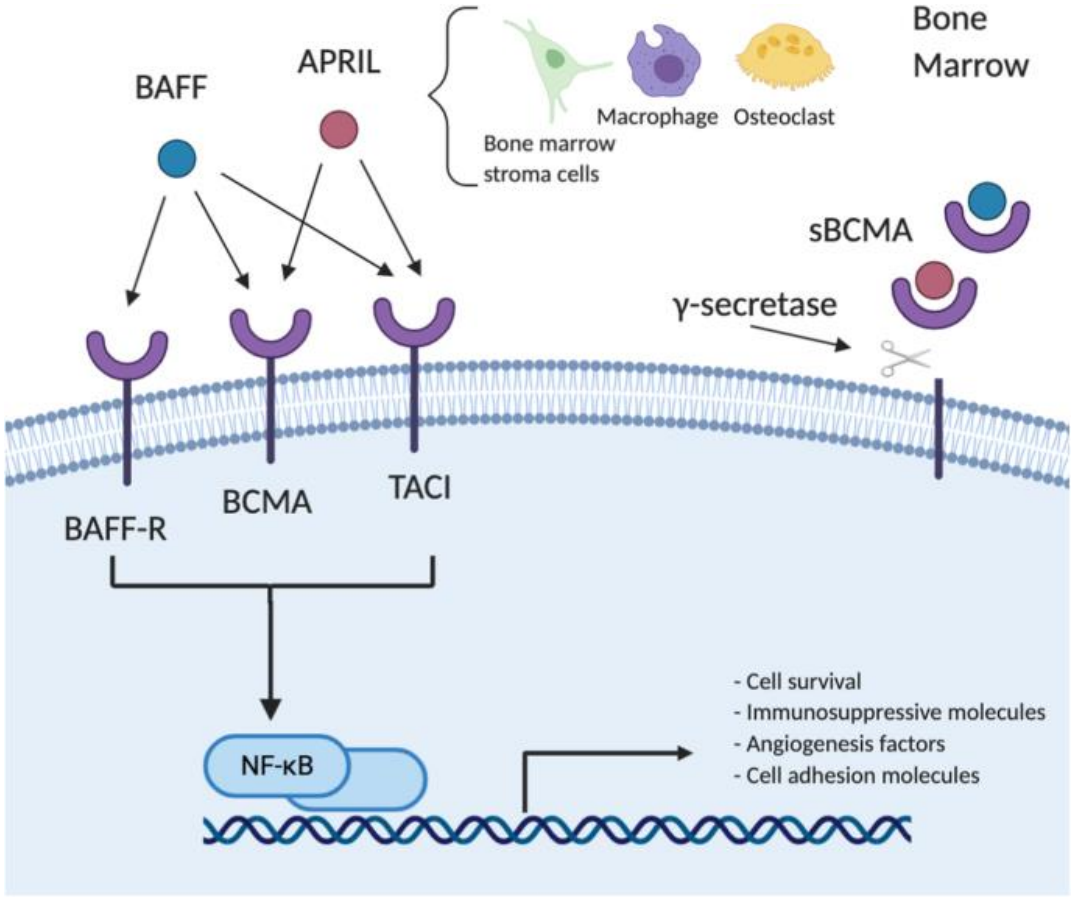
- Not currently FDA-approved for myeloma
- ORR is high in t(11:14) multiple myeloma patients
- Inferior OS for all comers has been a cause for concern; careful patient selection is needed
- Preclinical biomarkers of Bcl-2 activation; in clinical practice FISH markers of t(11;14) are only available option
- Synergistic combination with proteasome inhibitors

Rationale for targeting BCMA

- Expression of B cell maturation antigen (BCMA) is nearly universal on MM cells, and largely restricted to plasma cells and some mature B cells

- Expression of BCMA has two agonist ligands: APRIL and BAFF
  - In MM patients, the serum levels of APRIL and BAFF are elevated about 5-fold over those in the healthy controls, and the more advanced the stage of MM is, the higher concentration of ligands is detected

- Upon binding of the ligands to BCMA, multiple growth and survival signaling cascades activates in MM cells



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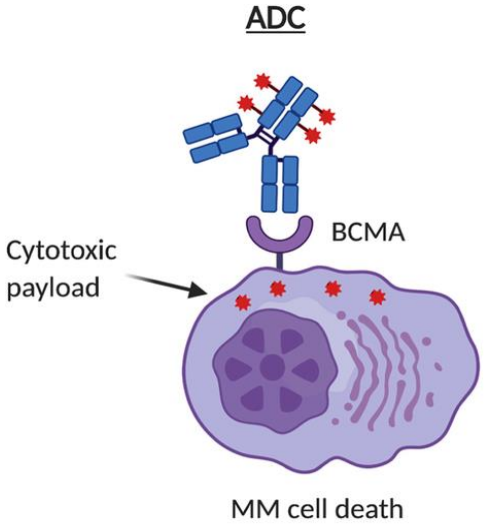
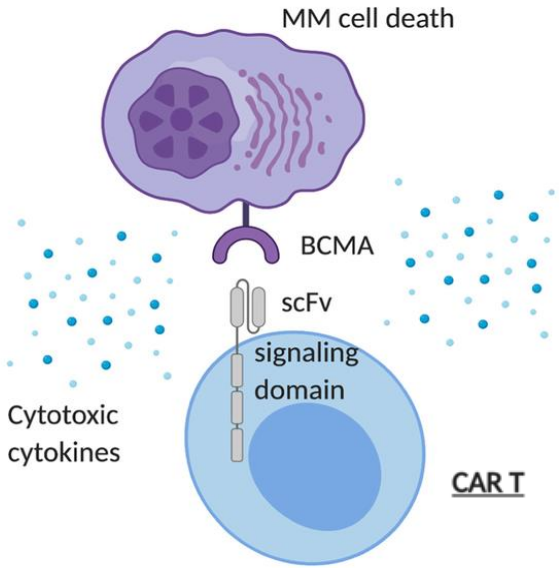
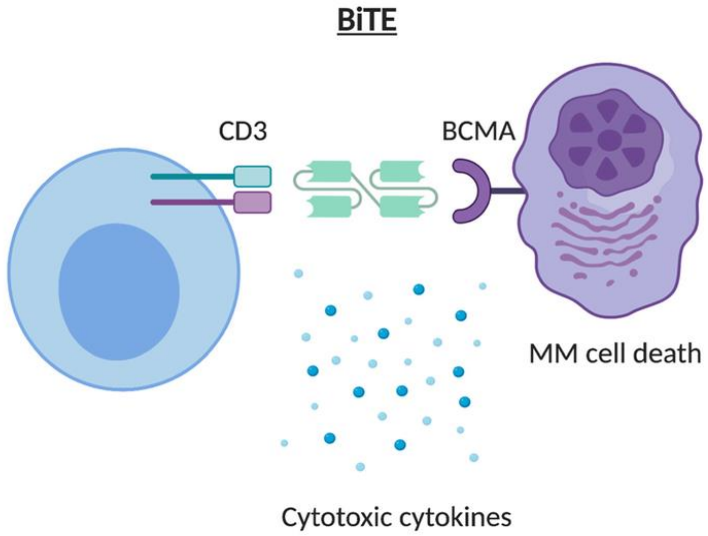
Yu, B., et al. J Hematol Oncol. 2020;13:125; Moreaux J, et al. Blood. 2004;103(8):3148–57;
Pan J, et al. Oncol Lett. 2017;14(3):2657–62

BCMA-Targeted Therapies for Multiple Myeloma







Antibody–Drug Conjugates (ADCs)
Belantamab mafodotin
MEDI2228
CC-99712

CAR T-Cell Therapies
Idecabtagene vicleucel
Ciltacabtagene autoleucel
Orvacabtagene autoleucel
P-BCMA-101
bb21217
ALLO-715

Bispecific T-Cell Engagers
AMG 420
AMG 701
CC-93269
REGN5458
JNJ-64007957
PF-06863135

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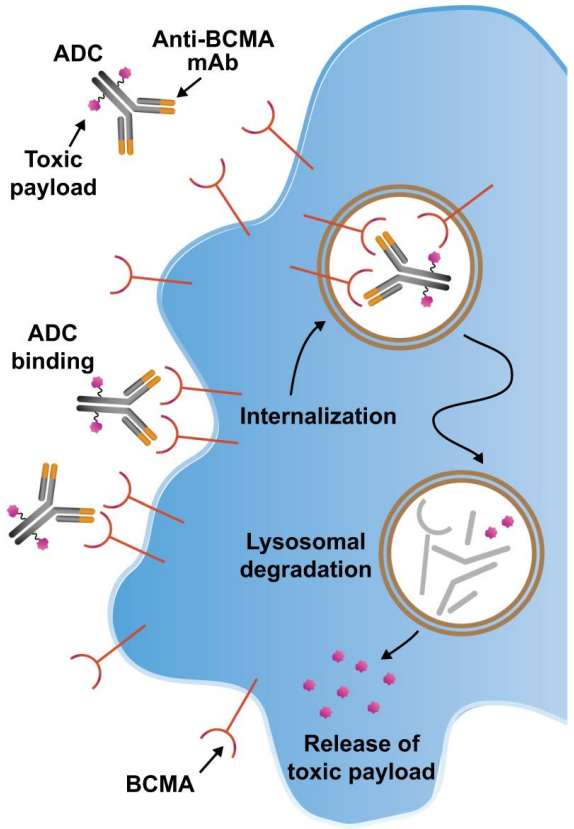
Figure from: Yu, B., et al. J Hematol Oncol. 2020;13:125

Anti-BCMA antibody-drug conjugate (ADC): belantamab mafodotin



- Belantamab mafodotin (GSK2857916): Humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA

- Four mechanisms of action:
  - ADC
  - ADCC
  - Immunogenic cell death
  - BCMA receptor signaling inhibition

➢ **Belantamab mafodotin was granted accelerated FDA approval in August 2020 as therapy for patients with R/R MM who have received ≥ 4 therapies, including a PI, and IMiD, and an anti-CD38 monoclonal antibody**

Figure from: Yu, B., et al. J Hematol Oncol. 2020;13:125

Belantamab mafodotin: Phase II DREAMM-2: Study Design

N=196

- Patients with R/R MM after ≥ 3 prior lines of therapy
- Refractory or intolerant to IMiDs, PIs, and CD38 antibodies

Stratification by:

- *High-risk cytogenetic features*
- *Prior lines of therapy (≤ 4 vs > 4)*

Belantamab mafodotin 2.5 mg/kg IV Q3W (n = 97)

Belantamab mafodotin 3.4 mg/kg IV Q3W (n = 99)

- Primary endpoint: ORR
- Key secondary endpoints: DoR, CBR, PFS, OS, TTBR, TTR, safety

Ocular Toxicity Monitoring

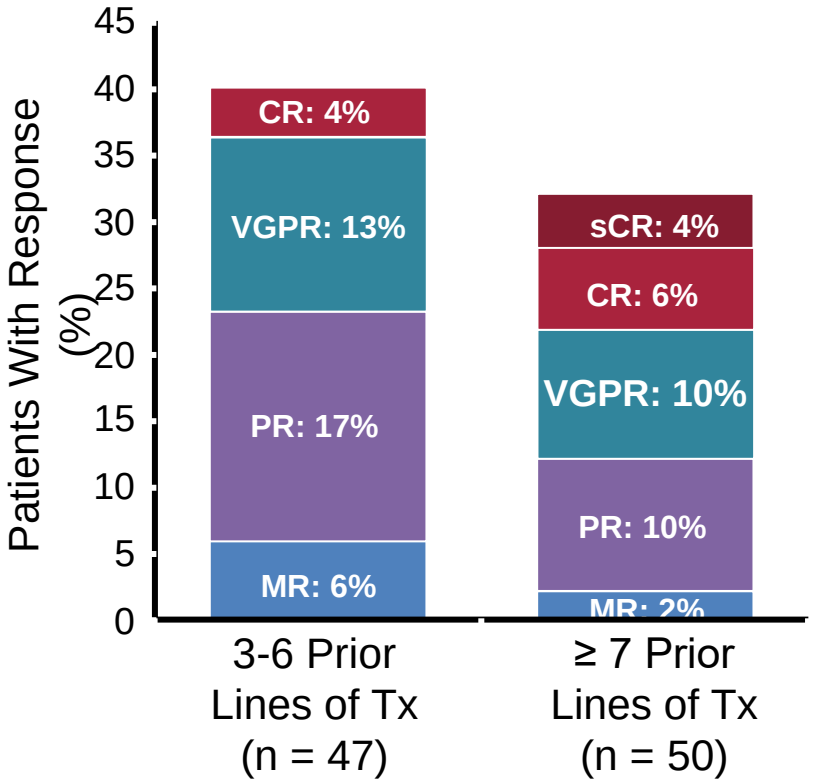
Patients had ocular exams by an eye care professional at baseline and prior to each treatment cycle or every 3 weeks.

Ocular events characterized by protocol-specified KVA scale (slit lamp exam) and changes in visual acuity measured by Snellen Test. Eye-related AEs (eg, blurred vision and dry eye) assessed by CTCAE criteria (v4.03)

Lonial. Lancet Oncol. 2020;21:207. Lonial. ASH 2020. Abstr 1417.

Belantamab mafodotin: Phase II DREAMM-2: responses

Efficacy Endpoints	3-6 Prior Lines of Tx (n = 47)	≥ 7 Prior Lines of Tx (n = 50)	All Patients (n = 97)
ORR, % (97.5% CI)	34 (19.3-51.4)	30 (16.5-46.6)	31 (21.7-43.6)
OS, mos (95% CI)	13.7 (9.1-NR)	13.4 (8.7-NR)	13.7 (9.9-NR)
Median DoR, mos (95% CI)	11.0 (4.2-NR)	13.1 (4.0-NR)	11.0 (4.2-NR)
Probability of DoR ≥ 6 mos, % (95% CI)	63 (31-83)	73 (44-89)	68 (48-82)
Median PFS, mos (95% CI)	2.9 (1.5-5.7)	2.2 (1.2-3.6)	2.8 (1.6-3.6)
Probability of PFS at 6 mos, % (95% CI)	35 (20-50)	30 (17-43)	32 (22-42)



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Lonial. Lancet Oncol. 2020;21:207. Lonial. ASH 2020. Abstr 1417.

Belantamab mafodotin + Vd: DREAMM-6

- All patients had evaluable responses
- ORR: 78% (95% CI: 52.4-93.6)[1]
  - Higher than previously reported ORRs for Vd in patients with ≥ 1 prior therapy (50% to 63%)[2-4]
- Median duration of response not yet reached

Best Confirmed Response, n (%)	Belantamab mafodotin + Vd (N = 18)
Clinical benefit rate*	15 (83)
ORR	14 (78)
• VGPR	9 (50)
• PR	5 (28)
MR	1 (6)
SD	3 (17)

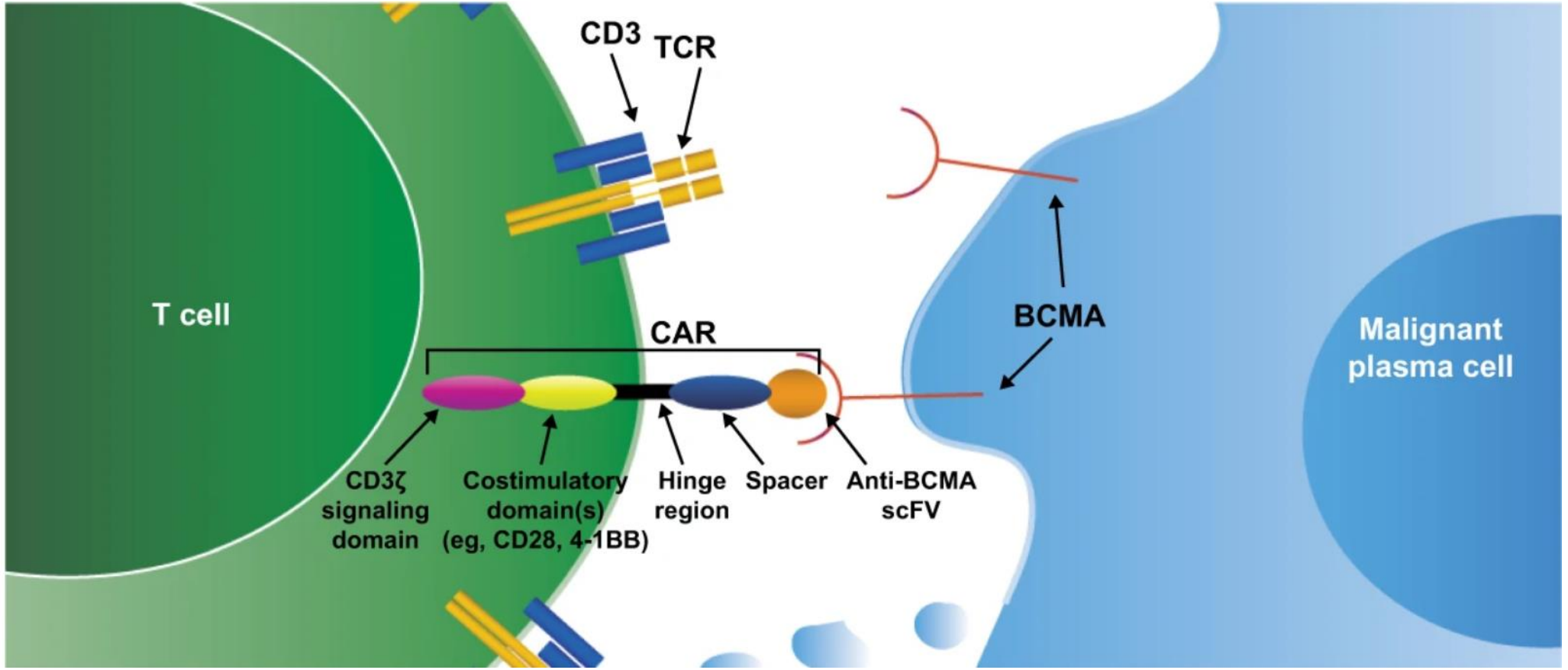
*Single: Day 1 of 21; Split: 1.25 mg/kg on Days 1, 8 of 21.
†Bortezomib 1.3 mg/m^2 on Days 1,4,8,11 + dex 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12.
‡No DLTs at either dose

Nooka, et al. J Clin Oncol. 2020;38(15_suppl):Abstract 8502

Belantamab: applications to clinical practice

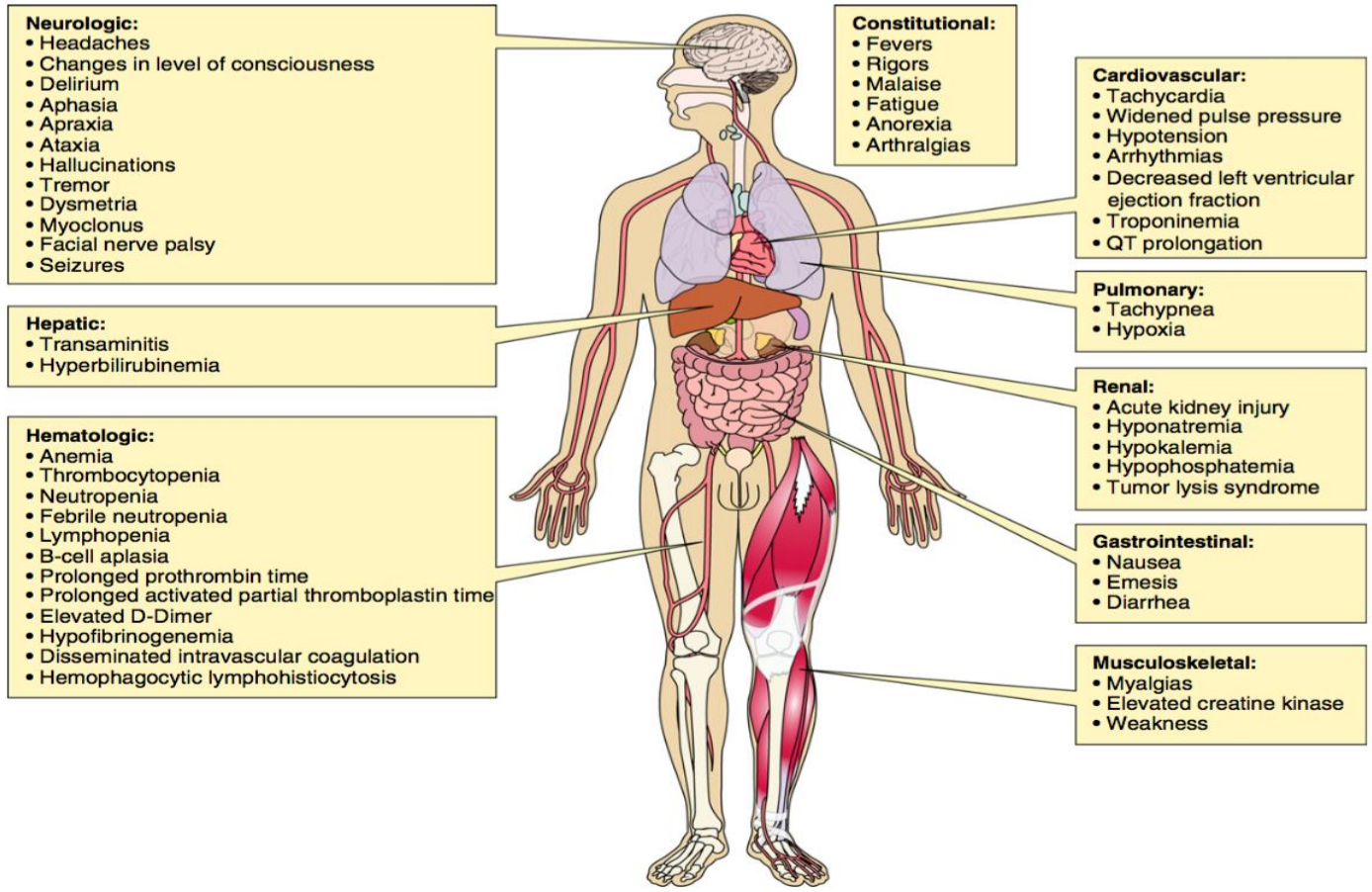
- Currently approved as a therapy for patients with R/R MM who have received ≥ 4 therapies, including a PI, and IMiD, and an anti-CD38 monoclonal antibody
- 1st approved off the shelf anti-BCMA targeted agent in MM
- Modest activity as single agent; more exciting in combination. More data needed.
- Keratopathy monitoring is necessary / REMS

Anti-BCMA CAR-T



Shah, et al. Leukemia. 2020; 34: 985-1005

CAR T-cell therapy: toxicities



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Shah, et al. Leukemia. 2020; 34: 985-1005

Characteristics of RRMM patients enrolled in CAR T-cell studies

	KarMMa[1,2] Ide-cel (n=128)	CRB-402[6] Bb21217 (n=69)	EVOLVE[3] Orva-cel (n=62)	CARTITUDE-1[4,5] Cilta-cel (n=29)
Age (range)	61 (33-78)	62 (33-76)	61 (33-77)	60 (50-75)
High-risk Cytogenetics, %	35	33	41*	27
Tumor Burden in BM, %	>50% PC=51	—	—	≥ 60% PC=24
Extramedullary PCs, %	39	—	23	10
Median prior lines of therapy	6 (3-16)	6 (3-17)	6 (3-18)	5 (3-18)
Triple refractory, %	84	64	94	86
Bridging therapy, %	88		63	79
Unique properties	Human BCMA, 4-1BB, CD3z	bb2121 cultured with PI3K inhibitor to enrich for T-cells with memory-like phenotype	Modified spacer, CD4:CD8 enriched for CM	Median cell dose 0.72x10^6 cells/kg, 2 BCMA single chain Abs

*Includes +1q21

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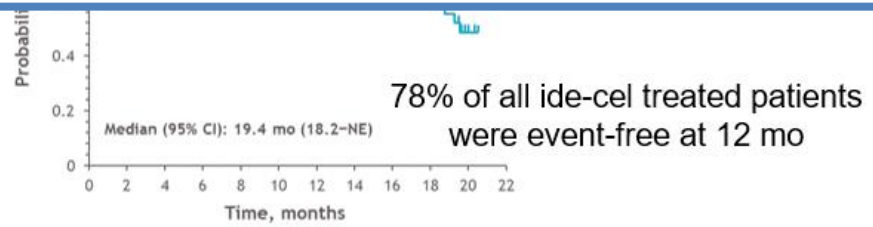
1. Munshi, et al. J Clin Oncol. 2020; 8(no. 15_suppl):8503. 2. Munshi, et al. *N Engl J Med.* 2021; 384:705-716. 3. Mailankody, et al. *J Clin Oncol*. 2020;38(15_suppl.): Abstract 8504. 4. Madduri, et al. *Blood.* 2020;136 (Supplement 1): 22–25. 5. Madduri, et al. *Blood.* 2020;136 (Supplement 1): 22–25. 6. Alsina, et al. *Blood.* 2020;136 (Supplement 1): 130

Table adapted from Patel, K. Presented at ASCO 2020

KarMMa: Phase II pivotal trial of Idecabtagene Vicleucel (Ide-Cel) in RRMM (N=128)

- **March 2021: The FDA has approved idecabtagene vicleucel** as the first BCMA-directed CAR T-cell therapy for patients with R/R MM after ≥ 4 prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody.
- **Phase III trial is now underway**: The multicenter, randomized, open-label, phase 3 study, KarMMa-3, is comparing ide-cel vs standard regimens in patients whose disease is refractory to the last line of therapy (ClinicalTrials.gov: NCT03651128)

MRD-negative and ≥CR, n (%)	15 (28)	33 (26)
MRD-negative and ≥VGPR, n (%)	26 (48)	50 (39)



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Munshi, et al. J Clin Oncol. 2020; 8 (no.15 suppl):8503; Munshi, et al. N Engl J Med. 2021; 384:705-716

BCMA CAR T-cells for RRMM: results of pivotal trials

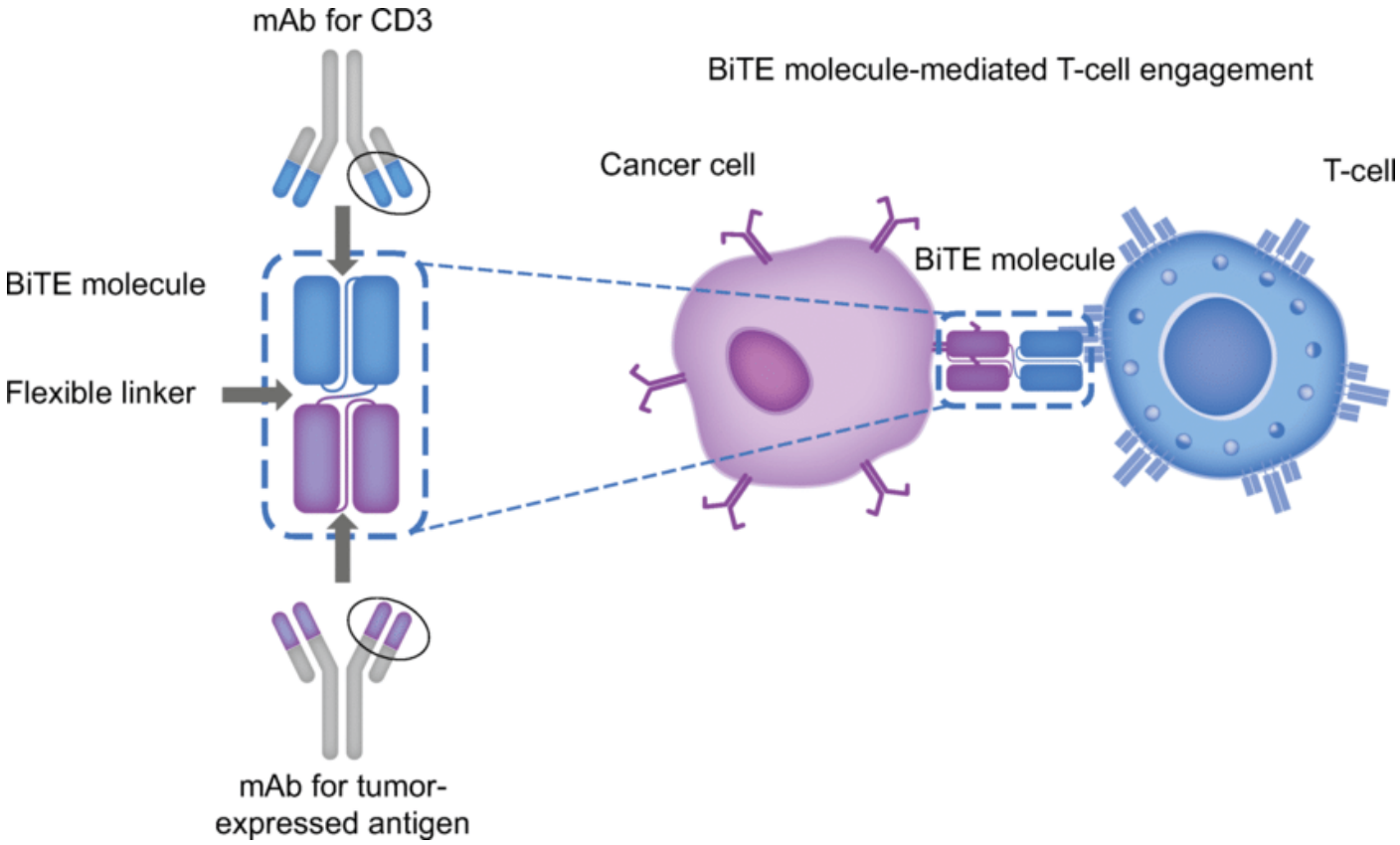
	KarMMA[1,2]	CRB-402[6]	EVOLVE[3]	CARTITUDE-1[4,5]
Product	**Ide-cel**	**bb21217**	**Orva-cel**	**Cilta-cel**
# pheresed	140	—	—	113
# treated	128	69	62	97
ORR (%)	73	68	92	98
sCR/CR (%)	33	29	36	80
MRD neg (%), of evaluable	48% (target dose)	89% (≥ PR) 100% (≥ CR)	84% (total) 100% (target dose)	92%
mDOR	10.7 months	17 months	—	21.8 months
mPFS	8.8 months	—	NR	22.8m; 18-months: 66%
mOS	19.4 months	—	NR	18-months: 81%

1. Munshi, et al. J Clin Oncol. 2020; 8(no. 15_suppl):8503. 2. Munshi, et al. N Engl J Med. 2021; 384:705-716. 3. Mailankody, et al. J Clin Oncol. 2020;38(15_suppl.): Abstract 8504.
4. Madduri, et al. Blood. 2020;136 (Supplement 1): 22–25. 5. Usmani et al. Oral Presentation at ASCO 2021. Abstract 8005.

CAR T-cell therapies: applications to clinical practice

- In 1Q 2021, first FDA approved CAR T cell therapy (Ide-Cel) for myeloma, autologous BCMA targeted cells
- Additional CAR T cells in development; Cilta-Cel has 95% ORR and at 18 months not yet reached median PFS (ASCO 2021)
- Dual-targeted autologous CAR T cells, allogeneic CAR T cells, and NK CAR T cells in development for myeloma
- Optimal use is unknown for cell therapies; first line? Second line? Later lines?
- Other clinical questions include: Can it replace high-dose melphalan? Sequence in relation of bispecific antibody therapies?

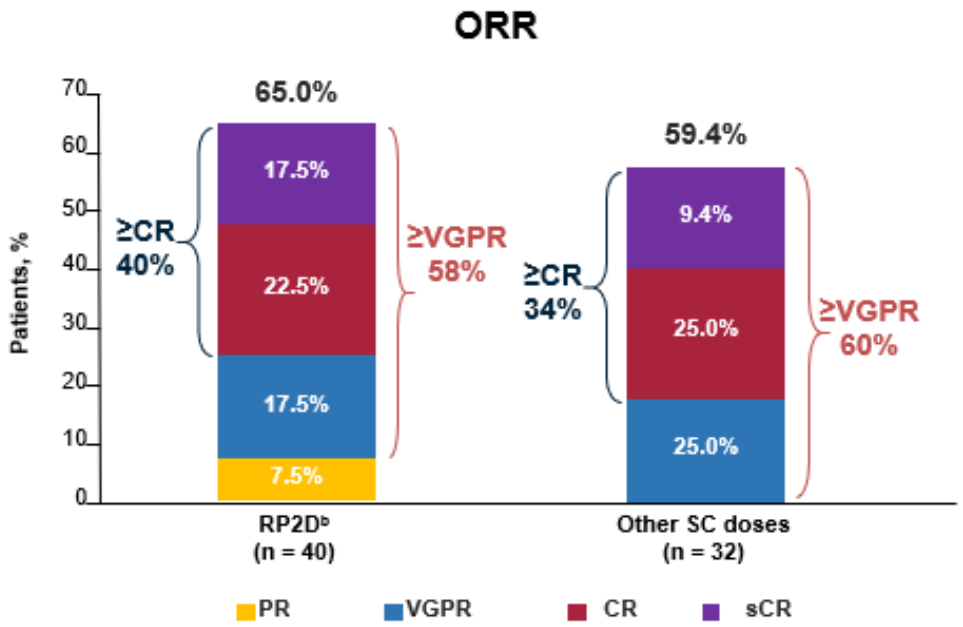
Bispecific antibodies (BiTEs)



Viardot A, et al. Ann Hematol. 2020;99(10):2215-2229

Updated Phase I results of 2 bispecific antibodies: Teclistamab (BCMA × CD3)

Characteristic	SC Total n=73	RP2D (1500 µg/kg SC QW)[a] n=40
Prior number of lines of therapy, median (range)	5.0 (2–14)	5.0 (2–11)
Prior transplantation ,n (%)	63 (86)	34 (85)
Exposure status, n (%)		
Triple-class	71 (97)	40 (100)
Penta-drug	50 (68)	26 (65)
Refractory status, n (%)		
PI	65 (89)	35 (88)
Carfilzomib	49 (67)	27 (68)
IMiD	70 (96)	38 (95)
Pomalidomide	55 (75)	28 (70)
Anti-CD38 mAb	68 (93)	39 (98)
Triple-class	58 (79)	33 (83)
Penta-drug	28 (38)	15 (38)
Refractory to last line of therapy	64 (88)	33 (83)



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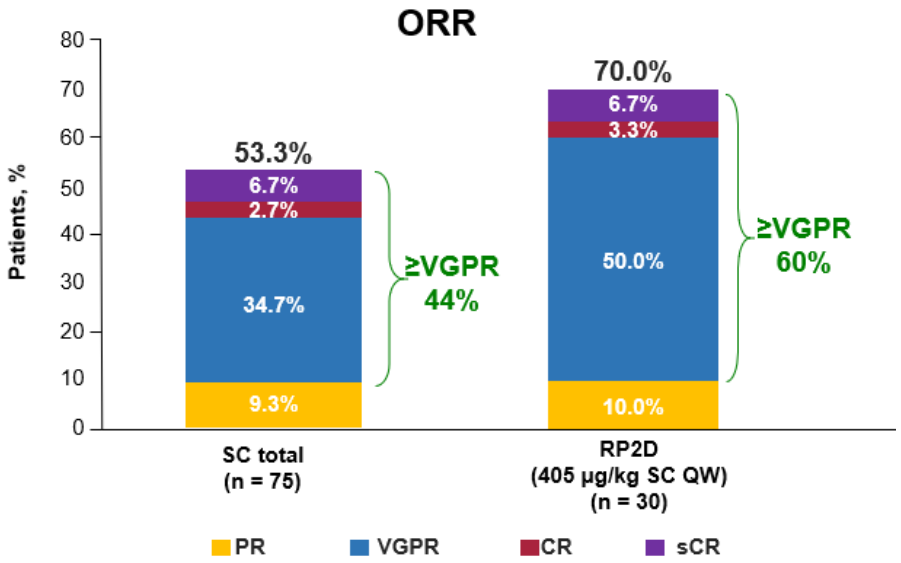
RP2D = recommended Phase II dose

van de Donk et al. Presented at EHA 2021

Updated Phase I results of 2 bispecific antibodies: Talquetamab (GPRC5D x CD3)

Characteristic	SC Total n=82	RP2D (450 µg/kg SC QW)[a] n=30
Prior number of lines of therapy, median (range)	6.0 (2–17)	6.0 (2–14)
Exposure status, n (%)		
Prior BCMA therapy	20 (24)	8 (27)
Triple-class	81 (99)	30 (100)
Penta-drug	64 (78)	24 (80)
Refractory status, n (%)		
PI	69 (84)	25 (83)
Carfilzomib	54 (66)	19 (63)
IMiD	76 (93)	28 (93)
Pomalidomide	67 (82)	26 (87)
Anti-CD38 mAb	77 (94)	30 (100)
BCMA	14 (17)	5 (16)
Triple-class	62 (76)	23 (77)
Penta-drug	23 (28)	6 (20)
To last line of therapy	69 (84)	26 (87)



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RP2D = recommended Phase II dose

Krishnan et al. Presented at EHA 2021

BiTEs: applications to clinical practice

- Several targets in development: Teclistamab, Talquetamab, Cevostamab, AMG-701, REGN-5458, Teneobio TNB-383B, etc
- Already several in SC formulation
- Preliminary data show high rates of ORR (~60-80% across the board) with single drug in heavily pretreated myeloma patients
- Ongoing trials with combinations
- How will these drugs be implemented in the clinic? Sequence in relation to other effective combinations and CAR T cells?

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INTERNATIONAL MYELOMA SOCIETY IMS
THE SOCIETY of MEMORIAL SLOAN KETTERING CANCER CENTER
NEW YORK GENOME CENTER

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Thank you for your attention!

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