Breakfast with the Investigators: Multiple Myeloma

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Tuesday, June 7, 2022

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Ajai Chari, MD

Elizabeth O'Donnell, MD

Robert Z Orlowski, MD, PhD

Moderator

Neil Love, MD

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Faculty

Ajai Chari, MD
Professor of Medicine (Hematology and Medical Oncology)
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Division of Cancer Medicine
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Elizabeth O'Donnell, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Friday June 3	**Acute Myeloid Leukemia and Myelodysplastic Syndromes** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 4	**Prostate Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Gastrointestinal Cancers 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Sunday June 5	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 6	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 7	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Spencer H Bachow, MD
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Boca Raton, Florida

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Brewer, Maine

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Advocate Aurora Health
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Boston, Massachusetts

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West Reading, Pennsylvania

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Commercial Support

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Love — Disclosures

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Dr Chari — Disclosures

Advisory Committee	Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Karyopharm Therapeutics, Sanofi Genzyme, Seagen Inc, Takeda Pharmaceuticals USA Inc
Consulting Agreements	Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Karyopharm Therapeutics, Takeda Pharmaceuticals USA Inc
Contracted Research	Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Novartis, Oncoceutics Inc, Pharmacyclics LLC, an AbbVie Company, Seagen Inc, Takeda Pharmaceuticals USA Inc

Dr O’Donnell — Disclosures

Advisory Committee	Bristol-Myers Squibb Company
Consulting Agreements	Bristol-Myers Squibb Company, Janssen Biotech Inc, Pfizer Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	Amgen Inc, Bristol-Myers Squibb Company, Janssen Biotech Inc, Takeda Pharmaceuticals USA Inc

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Dr Orlowski — Disclosures

Advisory Committee	Amgen Inc, BioTheryX Inc, Bristol-Myers Squibb Company, GlaxoSmithKline, Janssen Biotech Inc, Karyopharm Therapeutics, Meridian Therapeutics, Monte Rosa Therapeutics, Neoleukin Therapeutics, Oncopeptides, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Takeda Pharmaceuticals USA Inc
Clinical Research Funding	CARsgen Therapeutics, Celgene Corporation, Exelixis Inc, Janssen Biotech Inc, Sanofi Genzyme, Takeda Pharmaceuticals USA Inc
Laboratory Research Funding	Asylia Therapeutics Inc, BioTheryX Inc, Heidelberg Pharma

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Moderator

Neil Love, MD

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Agenda

Module 1 – Front-Line and Maintenance Treatment Options for Patients with Multiple Myeloma (MM)

Module 2 – Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) MM

Module 3 – Future Directions in the Management of MM

N Engl J Med 2022 Jun 5; Epub ahead of print

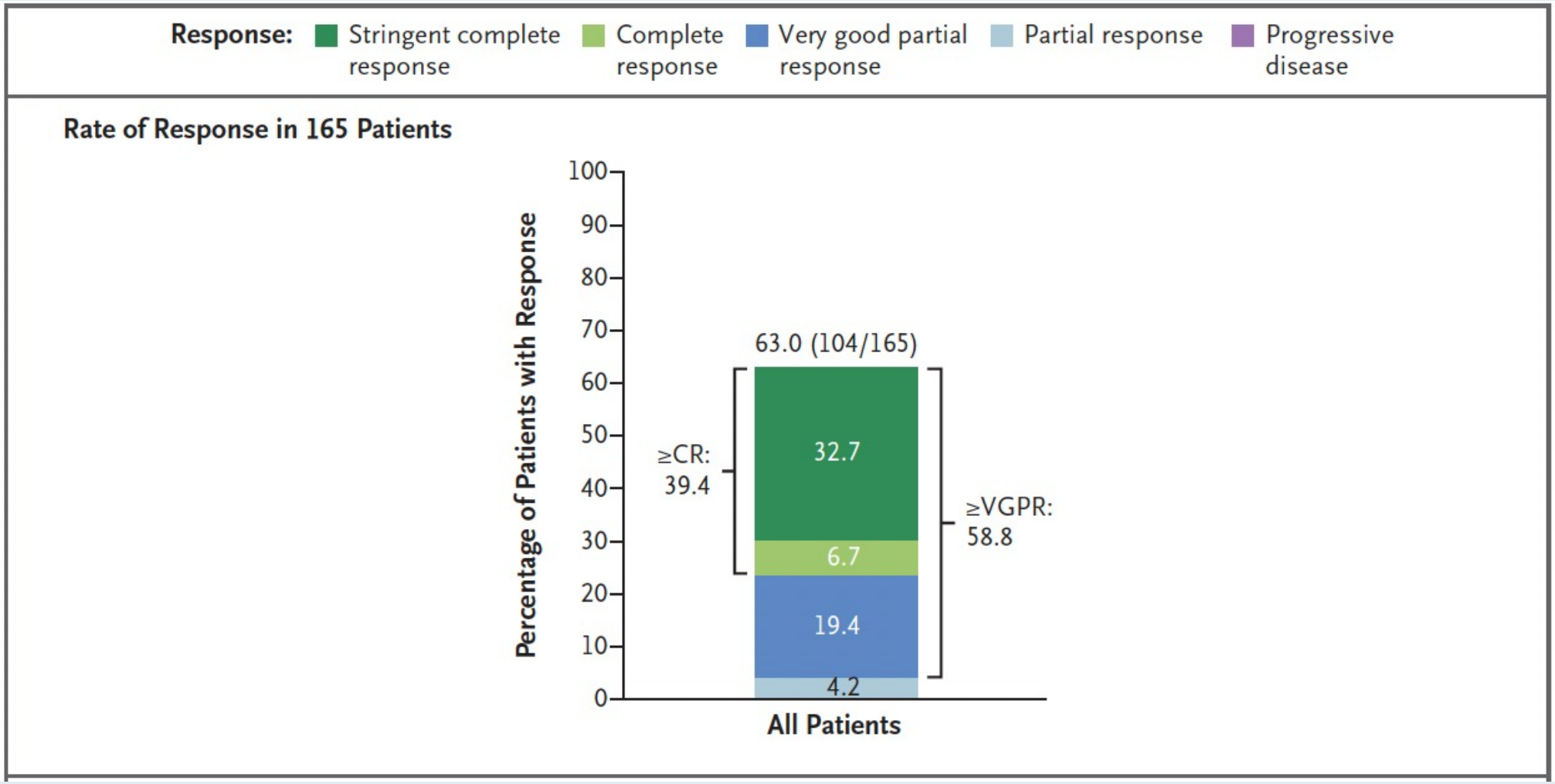
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

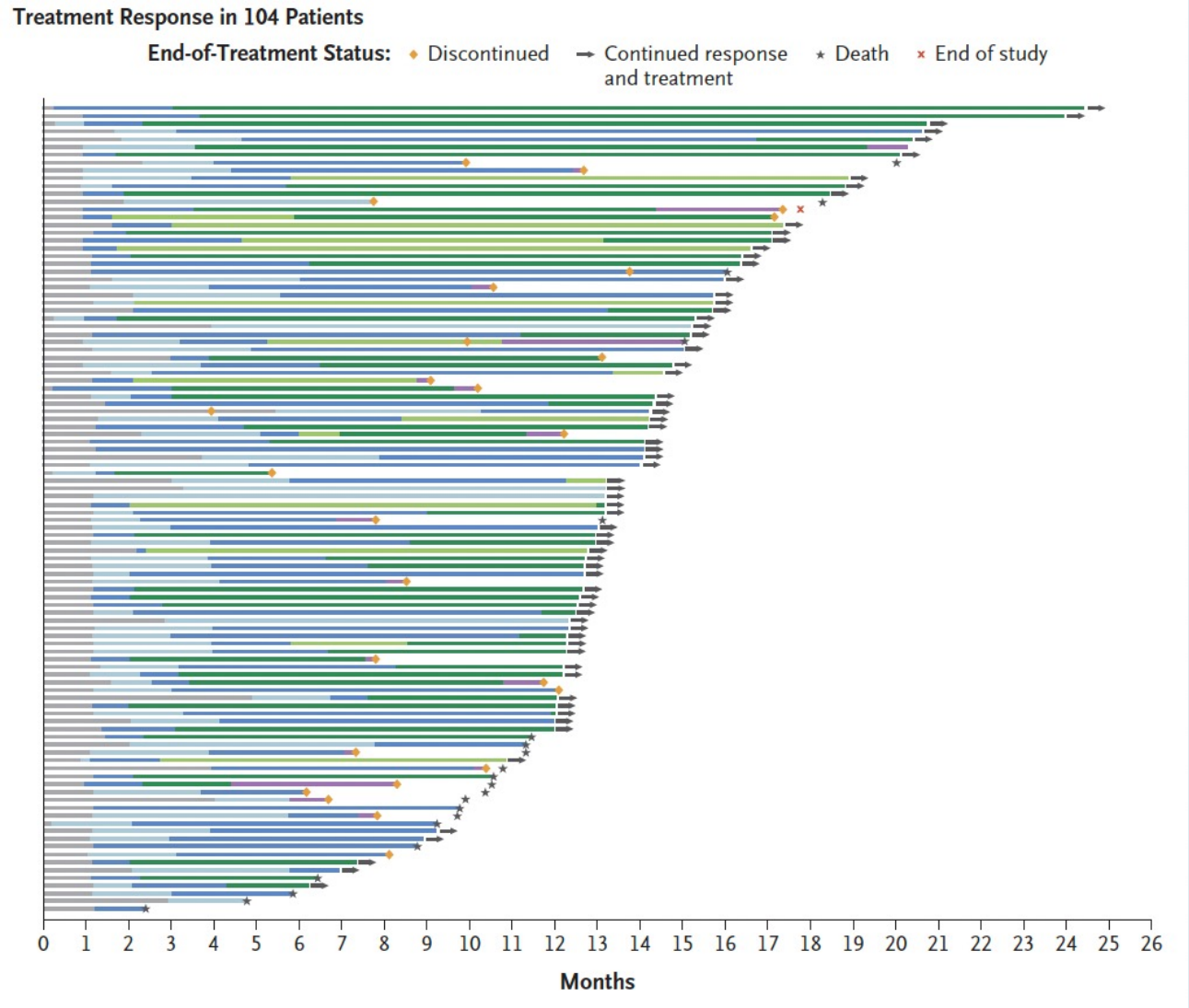
P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

Response to Teclistamab in Patients with Relapsed or Refractory Multiple Myeloma



Moreau P et al. N Engl J Med 2022 Jun 5; Epub ahead of print.

Response to Teclistamab Over Time in the 104 Patients Who had a Partial Response or Better



Moreau P et al. N Engl J Med 2022 Jun 5; Epub ahead of print.

Agenda

Module 1 – Front-Line and Maintenance Treatment Options for Patients with Multiple Myeloma (MM)

Module 2 – Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) MM

Module 3 – Future Directions in the Management of MM

Case 1 — Robert Z Orlowski, MD, PhD

- **A now 76 yo female who originally presented in 07/2018 with anemia (Hgb 10.5)**
- **Lab work-up showed lambda light chain on SPEP/IFE (sFLLC 498, sFKLC 14.3, ratio 35)**
- **Marrow showed 10% lambda-restricted plasma cells and normal CG/FISH**
- **Imaging showed no lesions**
- **Conclusion: SMM and started watchful waiting**

Case 1 — Robert Z Orlowski, MD, PhD

Follow-up and treatment initiation

- **Experienced progressively worsening anemia through 12/2020 that was at first asymptomatic**
- **Later, developed fatigue & DOE; lambda increased to 822.37, with λ/κ ratio of 51**
- **Decision made to begin treatment**
- **Patient was not interested in an ASCT**
- **Induction therapy started with daratumumab/lenalidomide/dexamethasone**

Case 1 — Robert Z Orlowski, MD, PhD

Treatment results

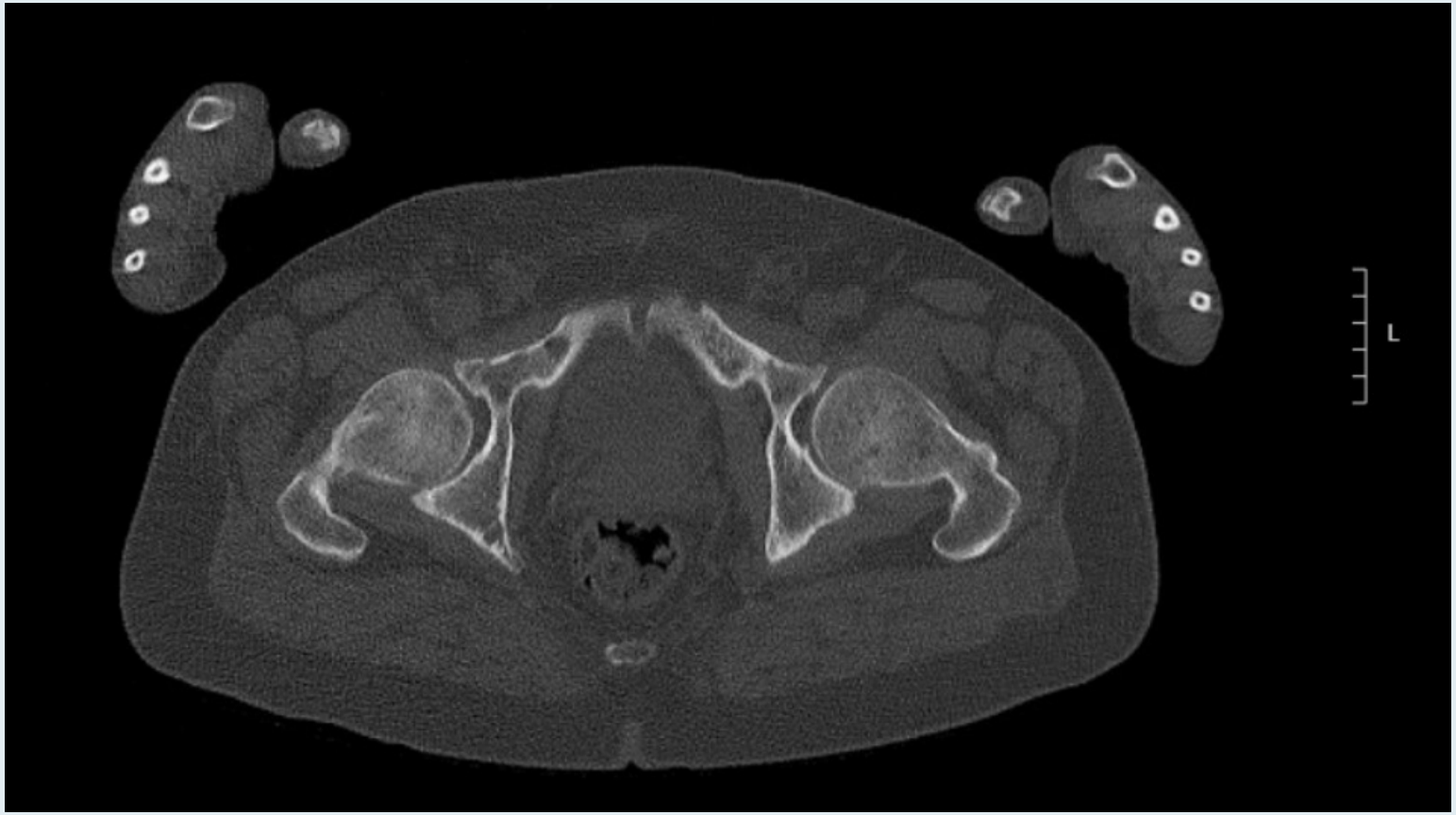
- **Rapid reduction in involved free light chain, which has since remained in the range of 63.84 to 98.10**
- **Lenalidomide dose has been adjusted progressively downward due to cytopenias (mostly anemia)**
- **Current dose at 2.5 mg and tolerating this well**

Case 2 — Elizabeth O'Donnell, MD

- **61M presented to an outside hospital with dyspnea on exertion and fatigue. He was found to have a hemoglobin of 5 requiring 4 units of packed red blood cell. An endoscopy and colonoscopy were performed and unremarkable. Hematology was consulted for his anemia. He was also noted to be mildly hypercalcemic.**
- **A PET scan was performed that showed multifocal hypermetabolic osseous uptake involving the T-spine, ribs, lumbar spine, pelvis, pubic symphysis, sacrum, right femoral shaft, and right iliac wing and crest.**
- **He had an elevated creatinine to 2.6. His lambda free light chain was elevated at 9,410.7 mg/L. SPEP detected a small IgG lambda monoclonal protein measuring 0.86 g/dL. He received denosumab on 7/20/2021 for hypercalcemia (Ca 10.8). Albumin 4.2 g/dL.**

Case 2 — Elizabeth O'Donnell, MD

CT myeloma at diagnosis:



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Case 2 — Elizabeth O'Donnell, MD

- **Bone marrow biopsy 70% hypercellular bone marrow showing high level involvement by a plasma cell neoplasm. Neoplastic plasma cells accounted for approximately 80% of the overall bone marrow cellularity. The aspirate showed 42% plasma cells and 17% by flow cytometry.**
- **Cytogenetics were significant for deletion 13q.**
- **Treatment with RVD was recommended.**
- **The patient is originally from Boston and has returned here for second opinion and initiation of treatment.**

Case 2 — Elizabeth O'Donnell, MD

On arrival to Boston:

- **Cr 2.19 mg/dL**
- **GFR 32**
- **WBC 4.75 K/uL**
- **Hgb 7.9 g/dL**
- **HCT 24.5%**
- **PLT 141**
- **Ca 8.0 mg/dL**

Case 2 — Elizabeth O'Donnell, MD

Past medical history:

- VSD (ventricular septal defect)
- Acute bacterial endocarditis
- T2DM (type 2 diabetes mellitus)
- Infection by streptococcus, viridans group
- Dental decay

Social history:

- Patient is employed and a father to 2 children. Currently engaged. He is a never cigarette smoker but smokes an occasional cigar. Historically he drinks several alcoholic beverages per day. Since his diagnosis he has limited self to a couple per week.

Family history:

- No family history of hematologic cancers

Case 2 — Elizabeth O'Donnell, MD

Treatment history:

7/27/21: C1 Dara-Vd on 21-day cycle

8/16/21: C2 Dara-Vd on 21-day cycle

9/10/21: C3 Dara-RVd on 21-day cycle - Lenalidomide 10 mg added (Cr 1.5, GFR 50)

9/29/21-10/6/21: Admission for septic arthritis/salmonella bacteremia and new DVT left lower extremity, rivaroxaban started

10/13/21: C4 D1 Dara-RVd

11/12/21: Stem cells collected, transplant deferred per patient preference

11/17/21: Restart treatment Cycle 5 Day 1 of Dara-RVD

12/27/21: C6 D1 Dara-RVD in Florida

1/25/22: C7 D1 Dara-RVD in Florida

2/22/22: C8 D1 Dara-RVD in Florida

3/22/22: Begin Dara-R maintenance

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Case 2 — Elizabeth O'Donnell, MD

Current SPEP:

- **IgG 391 mg/dL**
- **IgA 83**
- **IgM 45**
- **KFLC <0.9000**
- **LFLC <0.7000**
- **K/L 0.71**

BM Biopsy: No evidence of residual plasma cell neoplasm.

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2022 ASCO® ANNUAL MEETING

RVd ± ASCT and Lenalidomide Maintenance to Progression for NDMM

The Phase 3 DETERMINATION Trial

Paul G. Richardson, MD, RJ Corman Professor of Medicine, Harvard Medical School
Clinical Program Leader, Director of Clinical Research,
Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA

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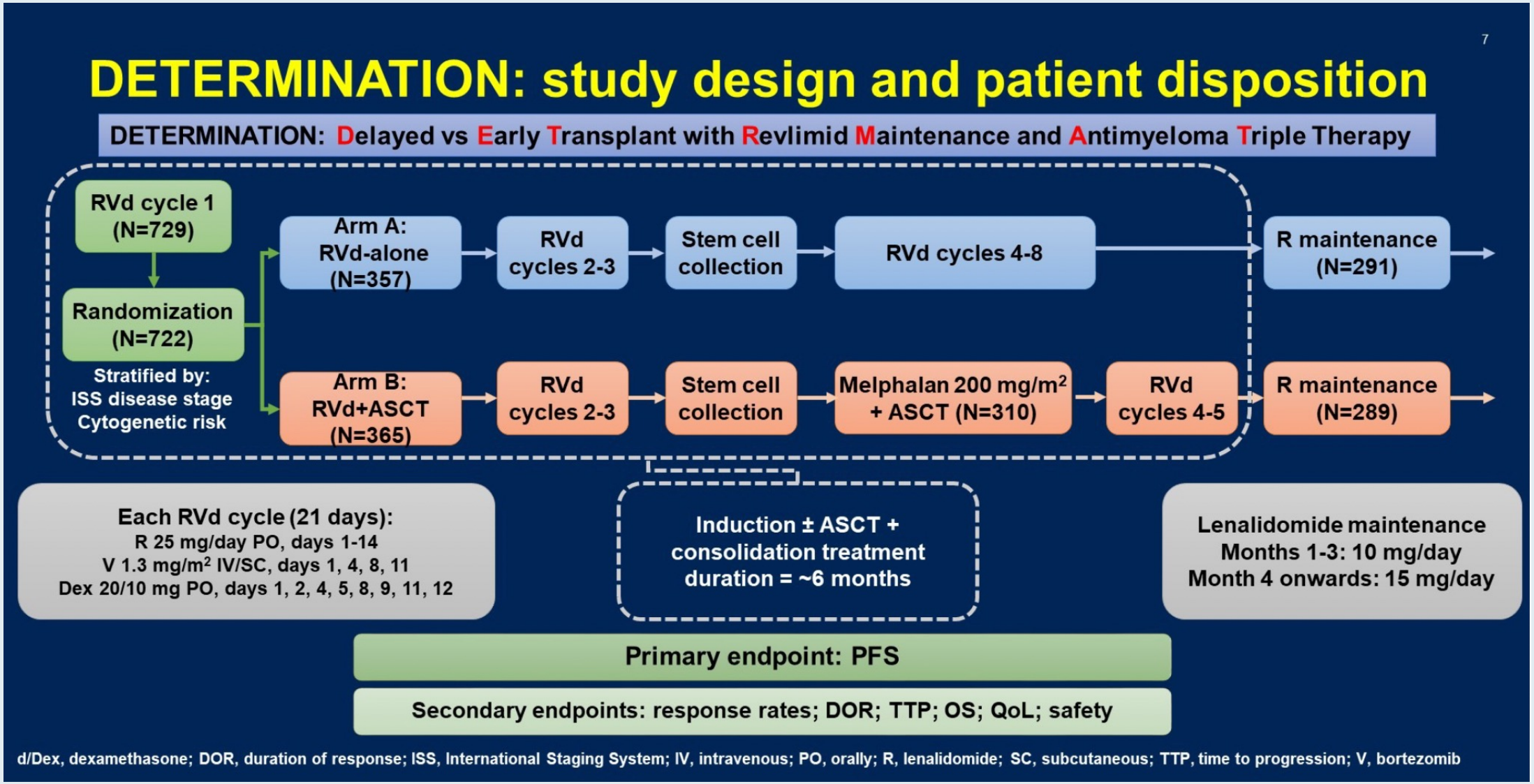
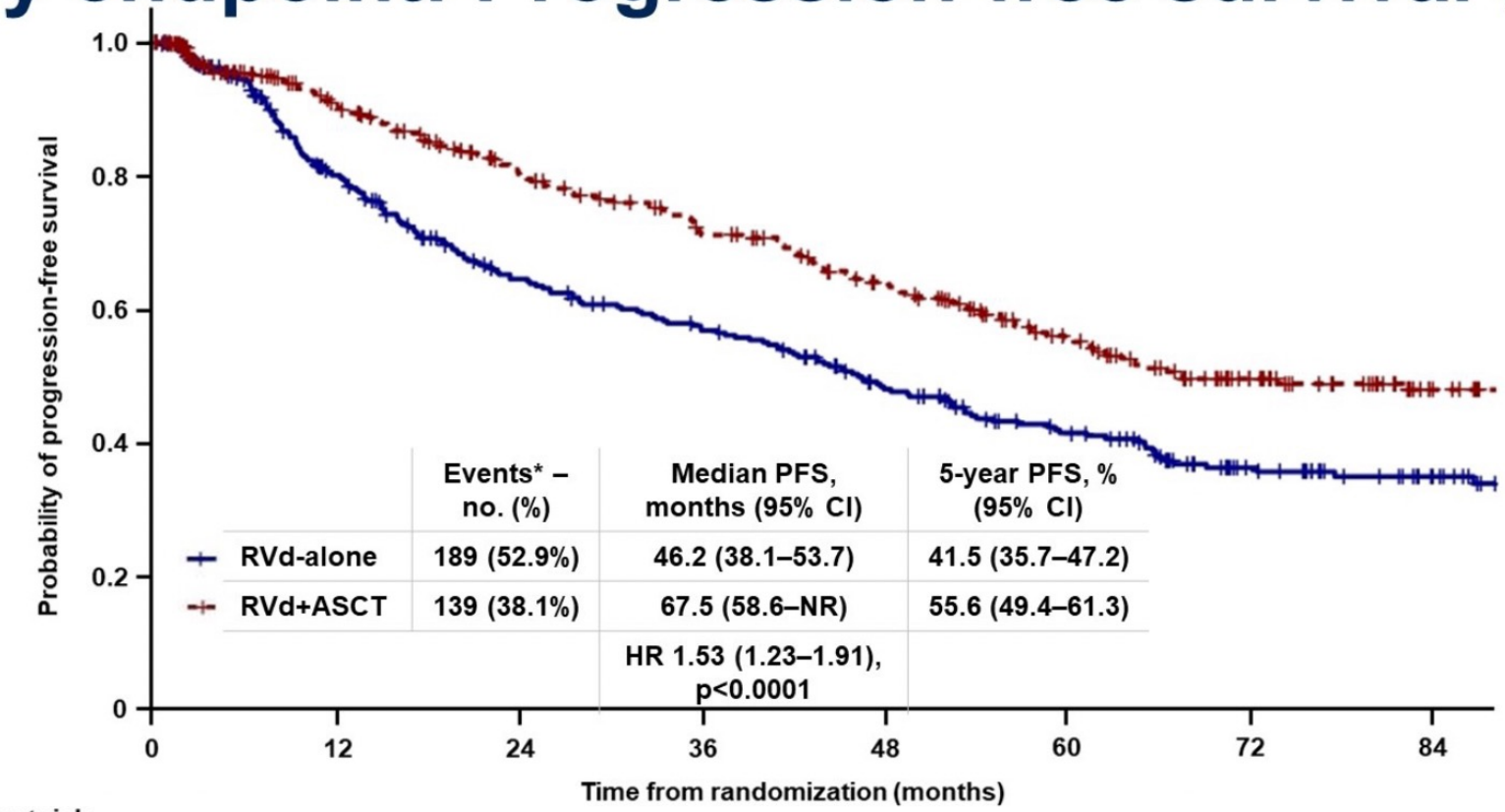
DETERMINATION: study design and patient disposition



d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

Richardson PG et al. ASCO 2022;Abstract LBA4 (Plenary).

Primary endpoint: Progression-free survival (PFS)



	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

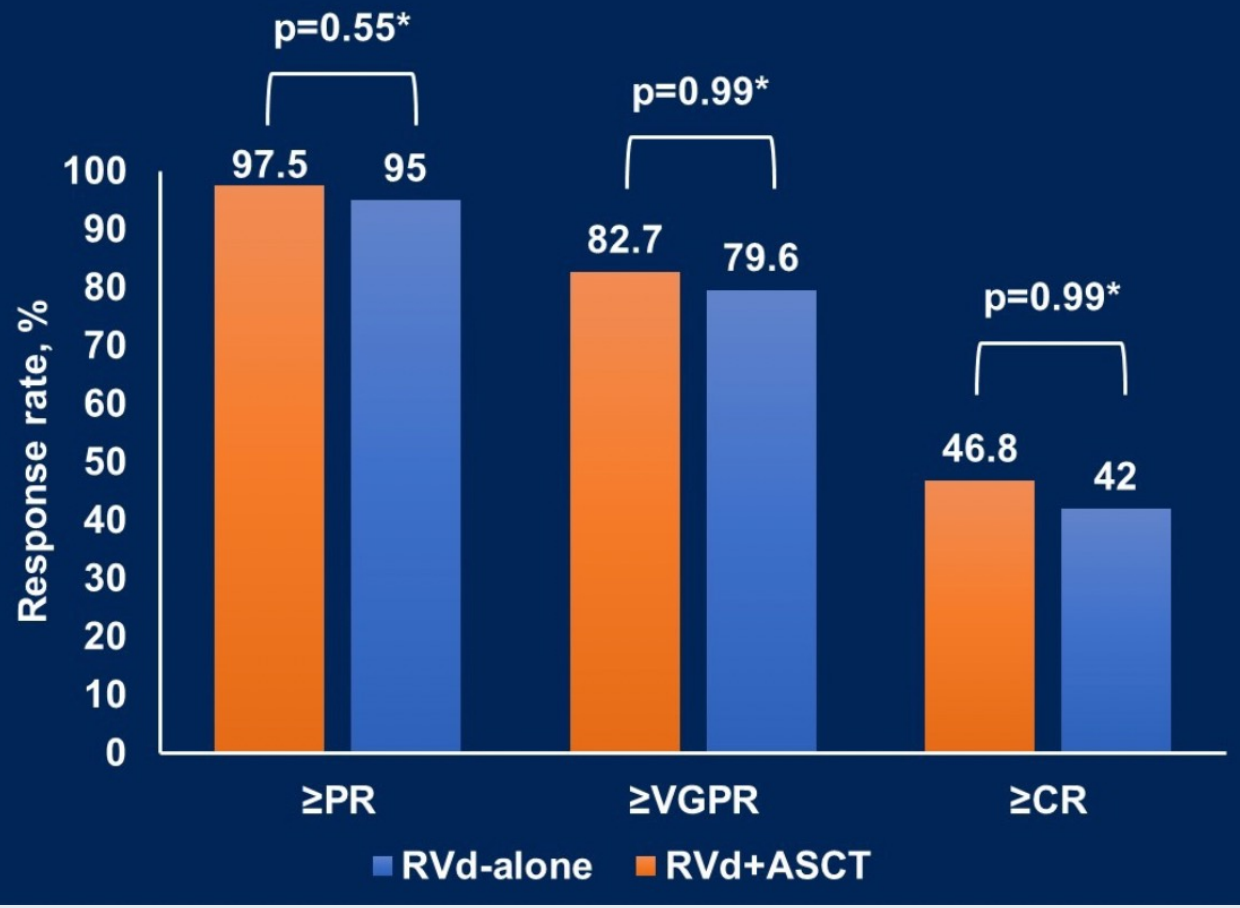
Patients at risk

RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

Richardson PG et al. ASCO 2022;Abstract LBA4 (Plenary).

Best response to treatment and duration of response

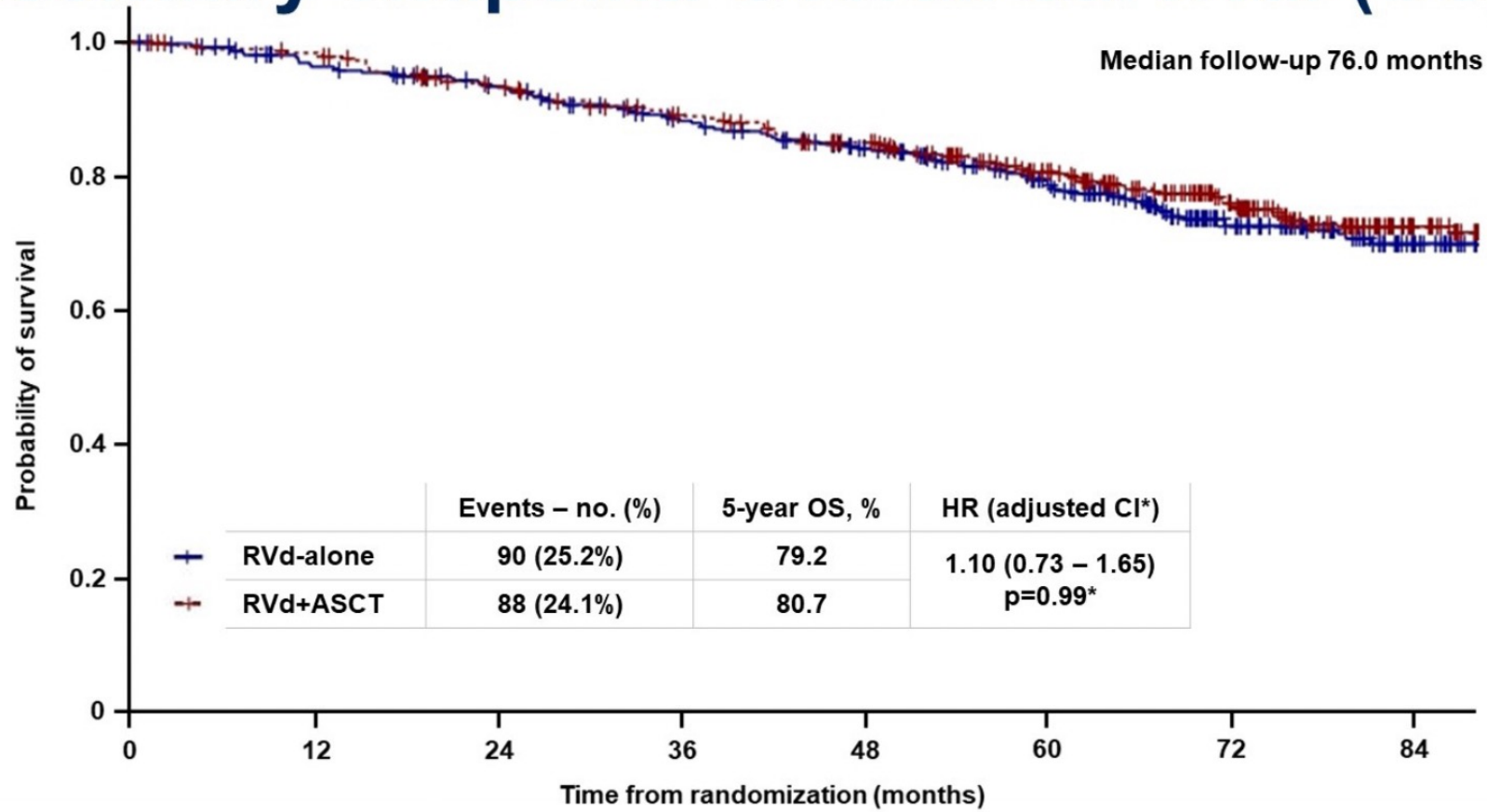


Duration of response	RVd-alone	RVd+ASCT
Median duration of ≥PR, months	38.9	56.4
	HR 1.45 (Adjusted CI* 1.09–1.93), p=0.003*	
5-year duration of ≥CR, %	52.9	60.6
	HR 1.35 (Adjusted CI* 0.83–2.22), p=0.698*	

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Richardson PG et al. ASCO 2022;Abstract LBA4 (Plenary).

Key secondary endpoint: Overall survival (OS)



	Events – no. (%)	5-year OS, %	HR (adjusted CI*)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

Patients at risk									
Data cutoff:12/10/21	RVd-alone	357	332	313	285	258	214	143	88
	RVd+ASCT	365	353	324	300	275	228	165	95

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Richardson PG et al. ASCO 2022;Abstract LBA4 (Plenary).

Grade ≥3 treatment-related AEs (all treatment)

AE, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	78.2	94.2
Any hematologic	60.5	89.9
Any grade 5 (fatal) AE	0.3	1.6 *
Neutropenia	42.6	86.3
Thrombocytopenia	19.9	82.7
Leukopenia	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Febrile neutropenia	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mucositis oral	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Hypophosphatemia	9.5	8.2
Neuropathy	5.6	7.1

(S)AE, (serious) adverse event

- Rates of all grade ≥3 and of hematologic grade ≥3 treatment-related AEs during all treatment significantly higher with RVd + ASCT (both p<0.001)
  - Rates hematologic grade ≥3 treatment-related AEs during maintenance: 26.1% vs 41.9%
- Related SAEs:
  - Prior to maintenance: 40.3% vs 47.1%
  - During maintenance: 11.3% vs 16.6%

* Includes 1 death related to ASCT on Arm B identified after data cutoff; p=0.12

Richardson PG et al. ASCO 2022;Abstract LBA4 (Plenary).

Daratumumab Carfilzomib Lenalidomide and Dexamethasone as Induction Therapy in High-Risk, Transplant-Eligible Patients with Newly Diagnosed Myeloma: Results of the Phase 2 Study IFM 2018-04

Touzeau C et al.

ASCO 2022;Abstract 8002 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

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IFM 2018-04 phase 2 study design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p del, t(14;16)
- ECOG 0-2

Objectives:

- **Primary Objective :**
  Feasibility (endpoint : >70% patients completed 2nd transplant)
- **Secondary Objectives:**
  Safety, ORR, PFS, OS, stem-cell collection

Induction Dara-KRd x 6	Stem cell collection	ASCT #1	Consolidation Dara KRd x 4	ASCT #2	Maintenance Dara Len 2 years
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 - 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex : 20 mg** D1-2,8-9,15-16,22-23 **28-day cycles**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara : 16 mg/kg IV** D1 D15 **K : 56 mg/m2 IV** D1, 8, 15 **Len : 15 mg** D1-21 **Dex : 40 mg** D1, 8, 15, 22 **28-day cycles**	**Mel 200**	**Dara** : 16 mg/kg IV every 8 weeks **Len** : 10 mg 21/28

Touzeau C et al. ASCO 2022;Abstract 8000.

Dara-KRd induction : Safety

Hematologic treatment related AE:

	Any grade N (%)	Grade 3/4 N (%)
Neutropenia	22 (44%)	20 (40%)
Anemia	14 (28%)	7 (14%)
Thrombocytopenia	13 (26%)	4 (8%)

AE leading to treatment discontinuation (n=2)
- COVID-19 infection (n=1)
- tumor lysis syndrome (n=1)

Grade 3/4 infection (n=3)
- COVID 19 infection (n=1)
- CMV infection (n=1)
- Pseudomonas aeruginosa bacteriemia (n=1)

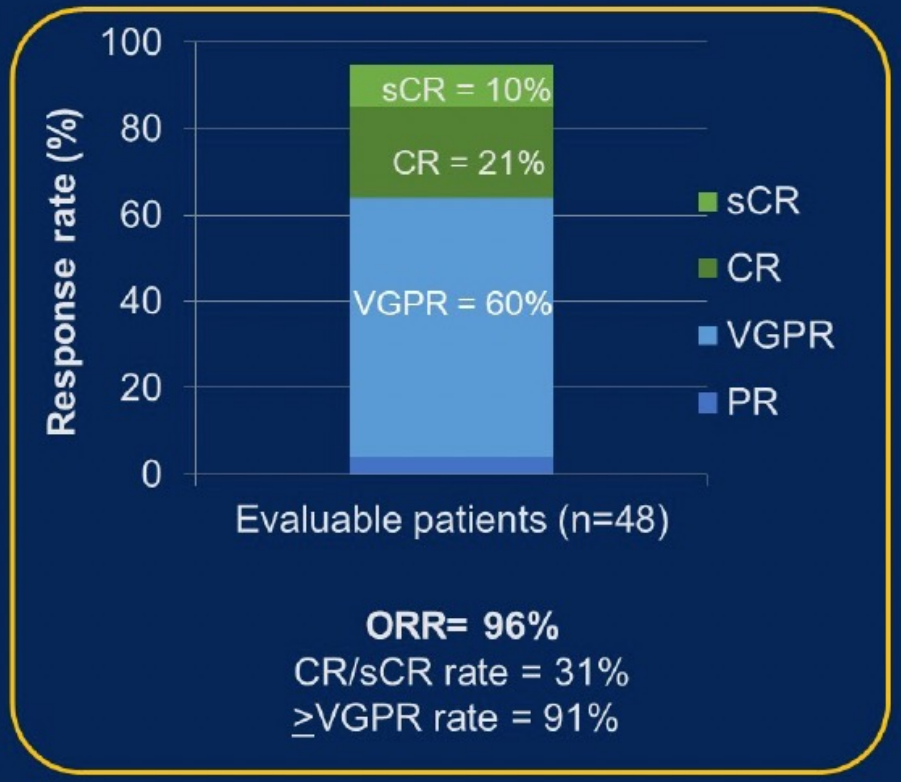
Most common non hematologic treatment related AE:

	Any grade N (%)	Grade 3/4 N (%)
GI disorders	23 (46%)	2(4%)
Infection	20 (40%)	3 (6%)
Skin rash	8 (16%)	0
Deep-vein thrombosis	7 (14%)	3 (6%)
Peripheral neuropathy	6 (12%)	0
Hepatic cytolysis	4 (8%)	2 (4%)
Renal failure	3 (6%)	3 (6%)
Cardiac event	1 (2%)	0

Touzeau C et al. ASCO 2022;Abstract 8000.

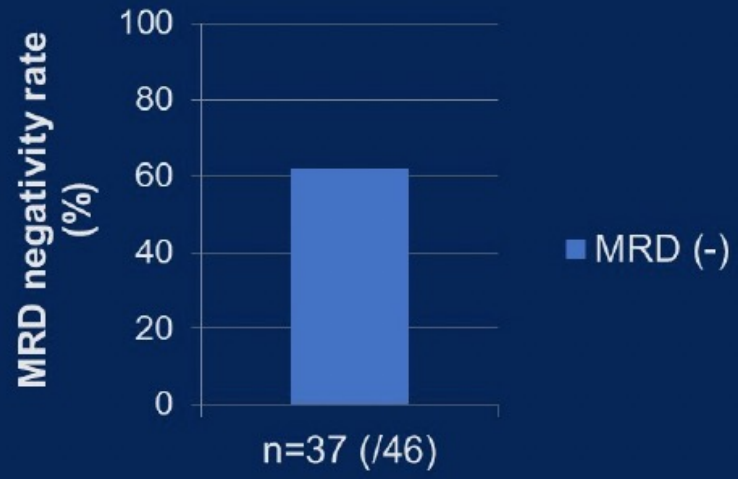
Dara-KRd induction : Response rates and MRD

Response Rate



ORR= 96%
CR/sCR rate = 31%
≥VGPR rate = 91%

MRD negativity (NGS, 10-5)



MRD negativity rate (NGS, 10-5) : 62%

Touzeau C et al. ASCO 2022;Abstract 8000.

Ixazomib and Daratumumab without Dexamethasone (I-Dara) in Elderly Frail RRMM Patients: A Multicenter Phase 2 Study (IFM 2018-02) of the Intergroupe Francophone du Myélome (IFM)

Macro M et al.

ASCO 2022;Abstract 8000 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

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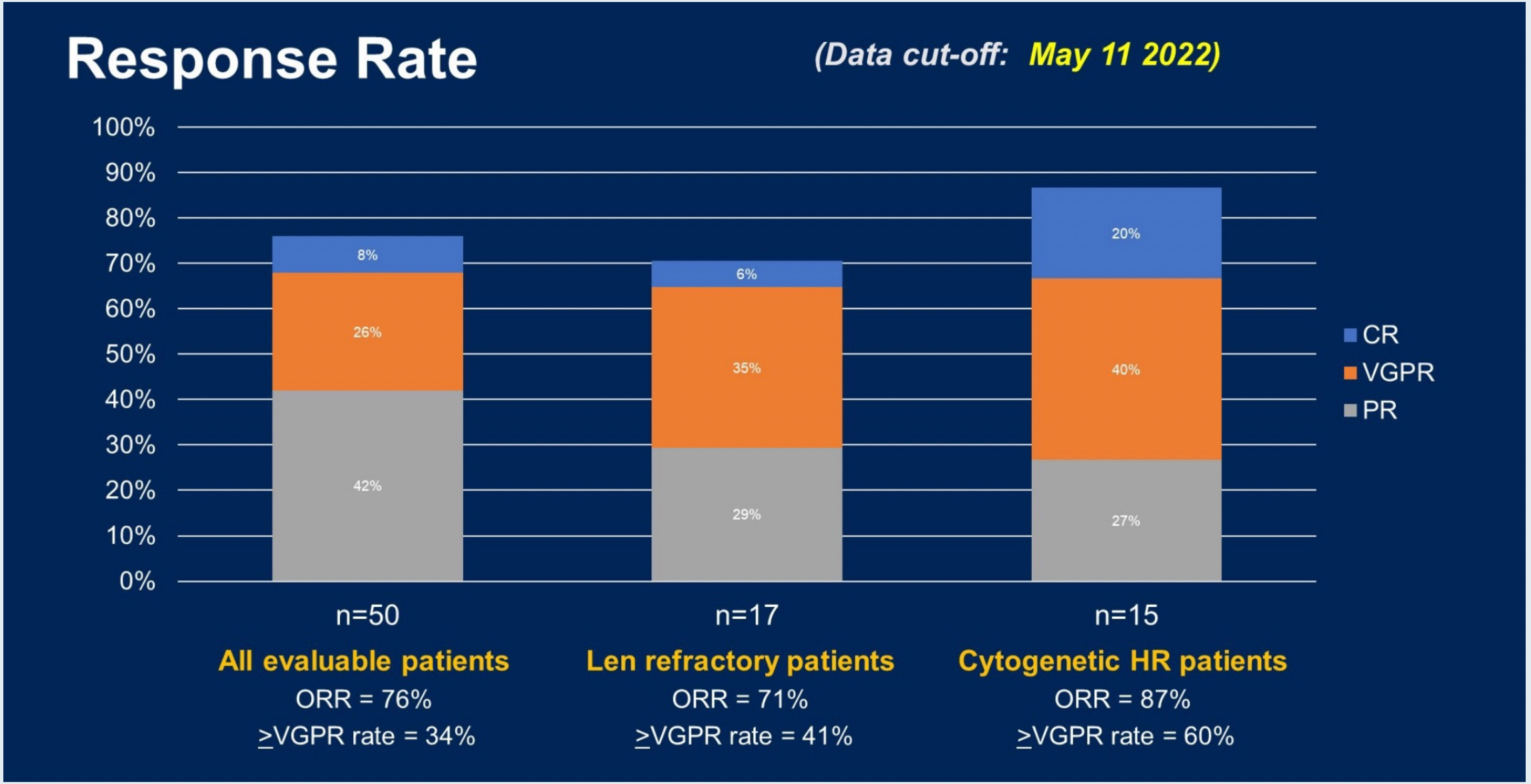


Macro M et al. ASCO 2022;Abstract 8000 (Oral).

Safety

Deaths : n (%)	9 (16)
Treatment related	2 (4)
Disease progression	4 (7)
Infection	3 (5)
At least 1 Grade ≥3 Adverse Ev	**31 (56)**
Thrombocytopenia	9 (16)
Other cytopenias	4 (7)
Infection	8 (14)
Hypertension	3 (5)
G.I. disorder	3 (5)
Infusion Related Reaction	2 (4)

➡ **2 treament related deaths:**

- Daratumumab related bronchospasm (n=1)
- Ixazomib overdose (n=1)

Most Common AE (≥10 %)	N (all grades)	N (Grade ≥ 3)
Diarrhea	20 (36)	2 (4)
Daratumumab IRR	18 (32)	2 (4)
Asthenia	18 (32)	0
Nausea/vomiting	15 (27)	1 (2)
Constipation	13 (23)	0
Thrombocytopenia	13 (23)	9 (16)

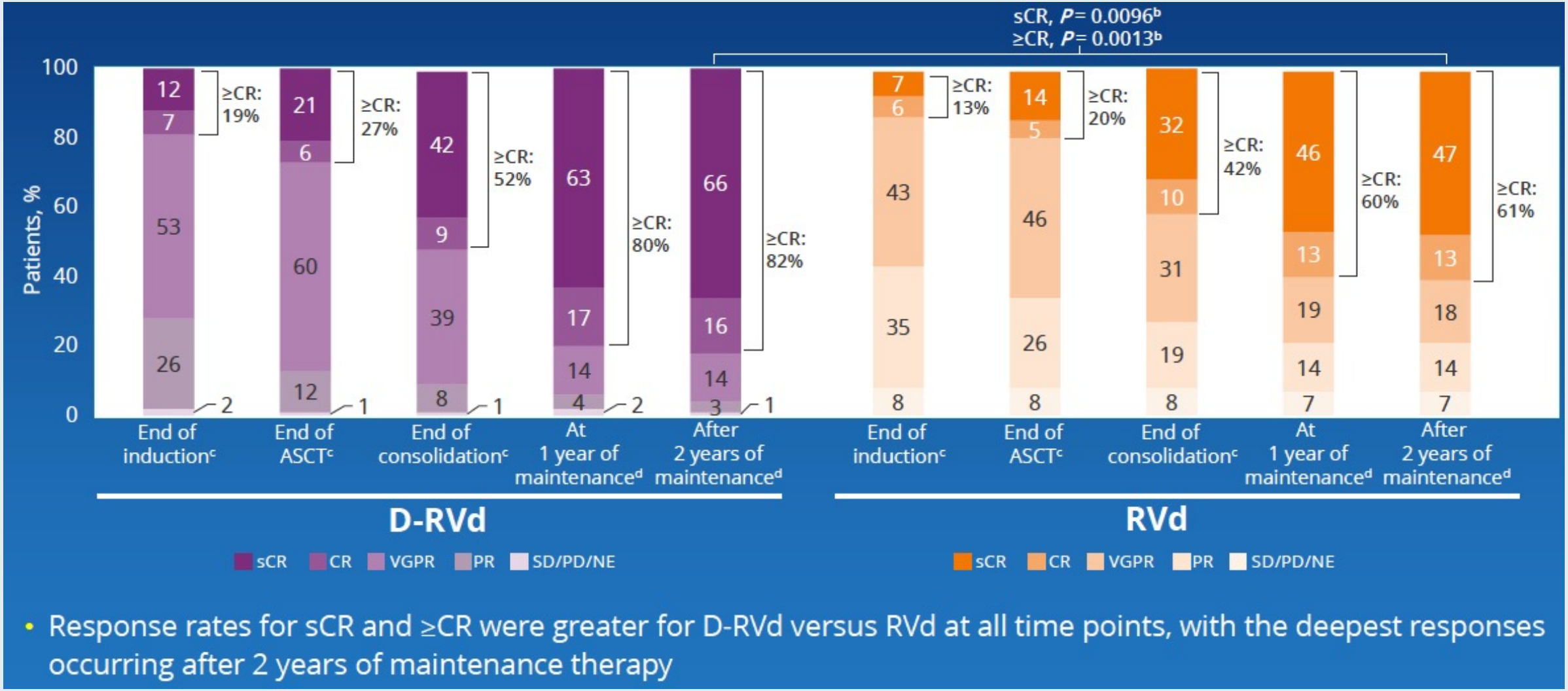
Macro M et al. ASCO 2022;Abstract 8000 (Oral).

Daratumumab (DARA) plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients (Pts) with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin After 24 Months of Maintenance

Laubach JP et al.

ASH 2021;Abstract 79.

GRIFFIN: Updated Analysis After 24 Months of Maintenance Therapy



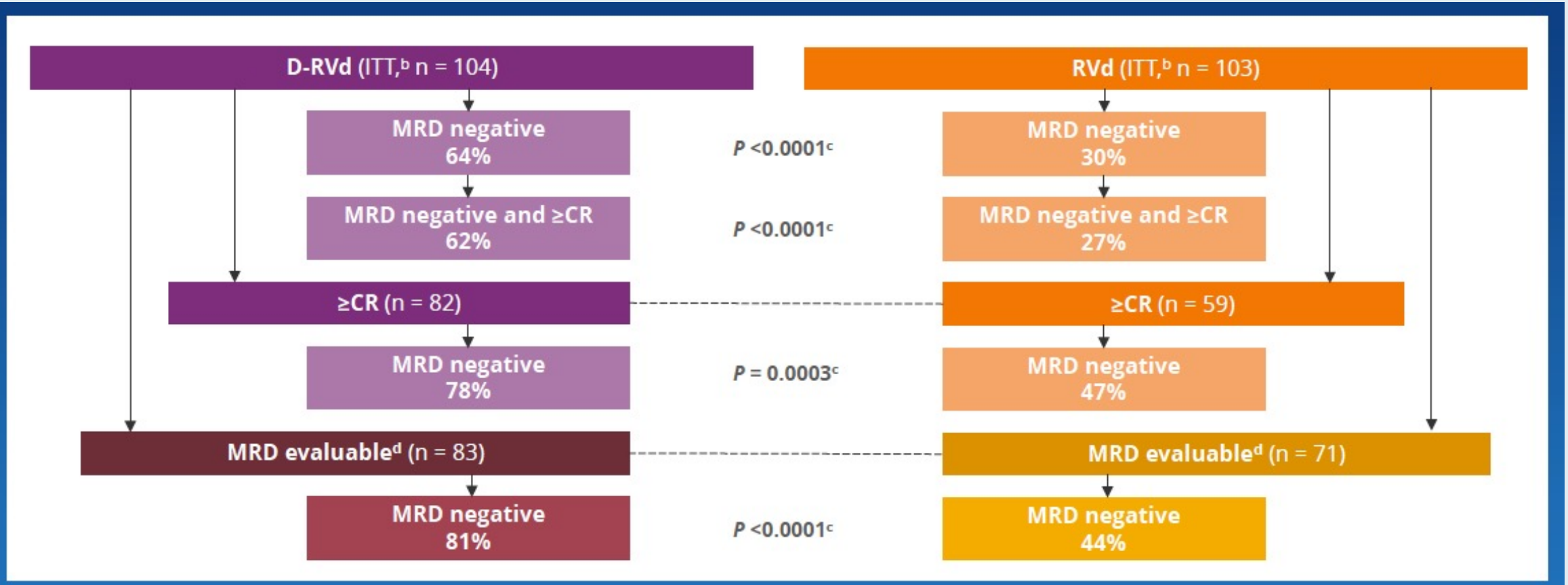
- Response rates for sCR and ≥CR were greater for D-RVd versus RVd at all time points, with the deepest responses occurring after 2 years of maintenance therapy

sCR = stringent complete response (CR); VGPR = very good partial response; PR = partial response; SD/PD/NE = stable disease/progressive disease/not evaluable

Laubach JP et al. ASH 2021;Abstract 79.

RTP RESEARCH TO PRACTICE

GRIFFIN: MRD Negativity (10^{-5}) After 2 Years of Maintenance Therapy

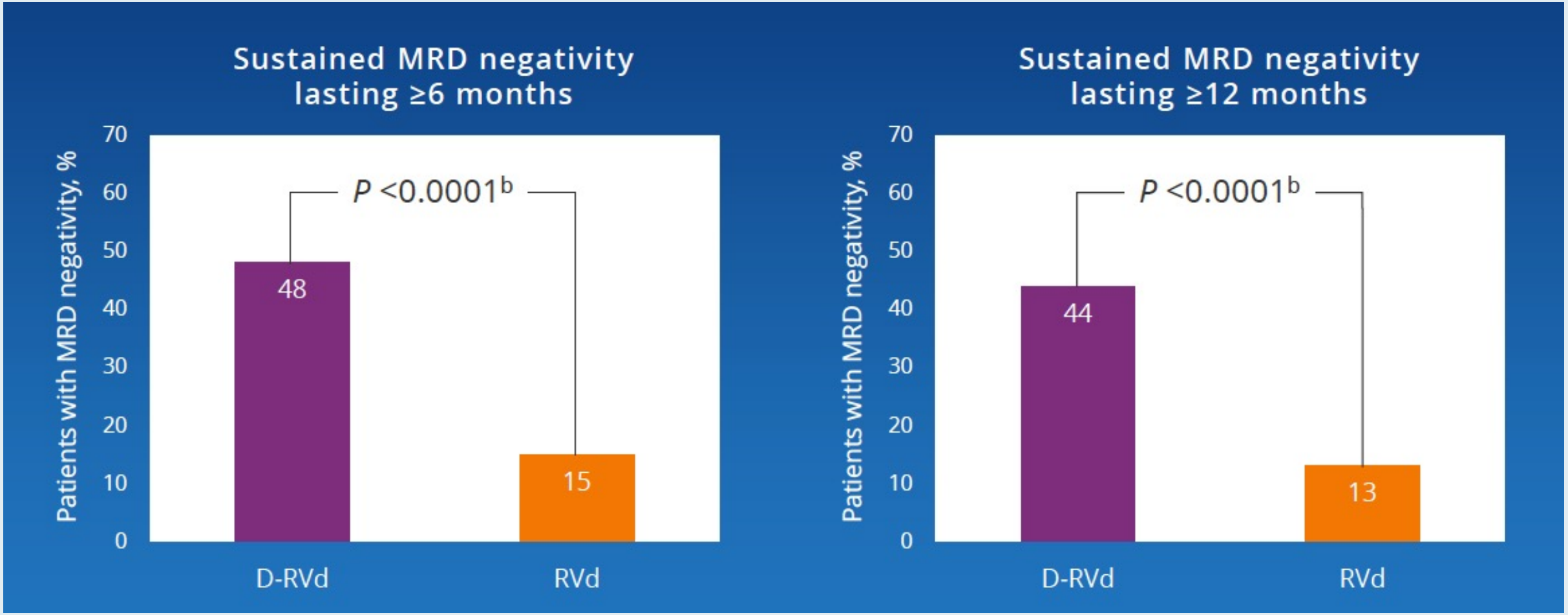


- Similarly, MRD-negativity (10^{-6}) rates favored D-RVd versus RVd in the ITT population (36% vs 15%, respectively; *P* = 0.0007), as well as among patients who achieved ≥CR (43% vs 22%; *P* = 0.0121)

MRD = minimal residual disease

Laubach JP et al. ASH 2021;Abstract 79.

GRIFFIN: D-RVd Improved Rates of Durable MRD Negativity (10^{-5}) Lasting ≥6 Months or ≥12 Months versus RVd



Laubach JP et al. ASH 2021;Abstract 79.

RTP RESEARCH TO PRACTICE

GRIFFIN: Infections and SPMs with First Onset During Maintenance Therapy (Cycles 7+)

Patients with ≥1 infections in maintenance, n (%)	D-RVd (DR maintenance, n = 89)		RVd (R maintenance, n = 71)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Overall infections in maintenance	32 (36)	16 (18)	23 (32)	15 (21)
Most common (≥5%) infections[a]				
Upper respiratory tract infection	47 (53)	2 (2)	29 (41)	2 (3)
Pneumonia	14 (16)	6 (7)	11 (15)	9 (13)
Urinary tract infection	10 (11)	0	2 (3)	0
Sinusitis	9 (10)	0	7 (10)	0
Influenza	9 (10)	0	5 (7)	0
Nasopharyngitis	9 (10)	0	2 (3)	0
Bronchitis	7 (8)	1 (1)	5 (7)	1 (1)
Cellulitis	7 (8)	1 (1)	2 (3)	1 (1)

Patients with ≥1 SPM in maintenance, n (%)	D-RVd (DR maintenance, n = 89)	RVd (R maintenance, n = 71)
Total number of patients with SPMs in maintenance	4 (4)	3 (4)
Squamous cell carcinoma of skin	3 (3)	0
Basal cell carcinoma	2 (2)	0
Nasal cavity cancer	1 (1)	0
Squamous cell carcinoma	1 (1)	0
Breast cancer	1 (1)	0
Malignant melanoma in situ	0	1 (1)
Nodular melanoma	0	1 (1)
Uterine cancer	0	1 (1)

- Similar rates of any grade and grade 3/4 infections occurred for the D-RVd and RVd groups

SPM = second primary malignancy

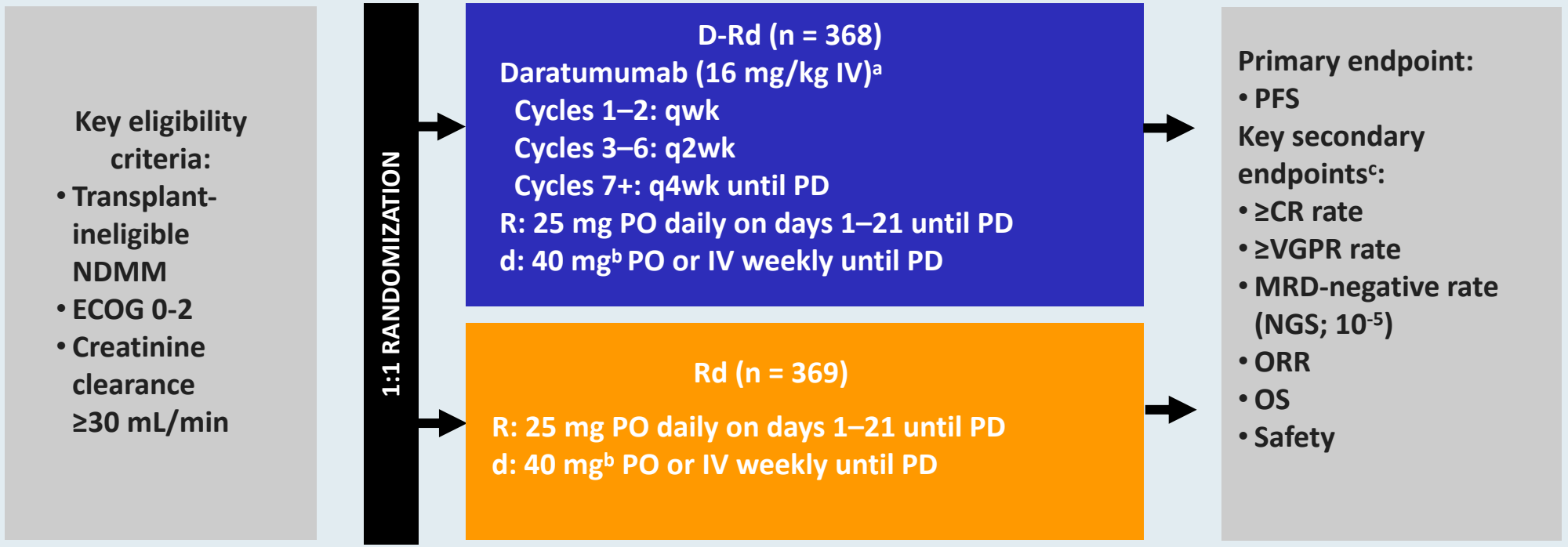
Laubach JP et al. ASH 2021;Abstract 79.

Overall Survival Results with Daratumumab, Lenalidomide and Dexamethasone versus Lenalidomide and Dexamethasone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): Phase 3 MAIA Study

Facon T et al.

EHA 2021;Abstract LB1901.

MAIA: Phase III Trial Design



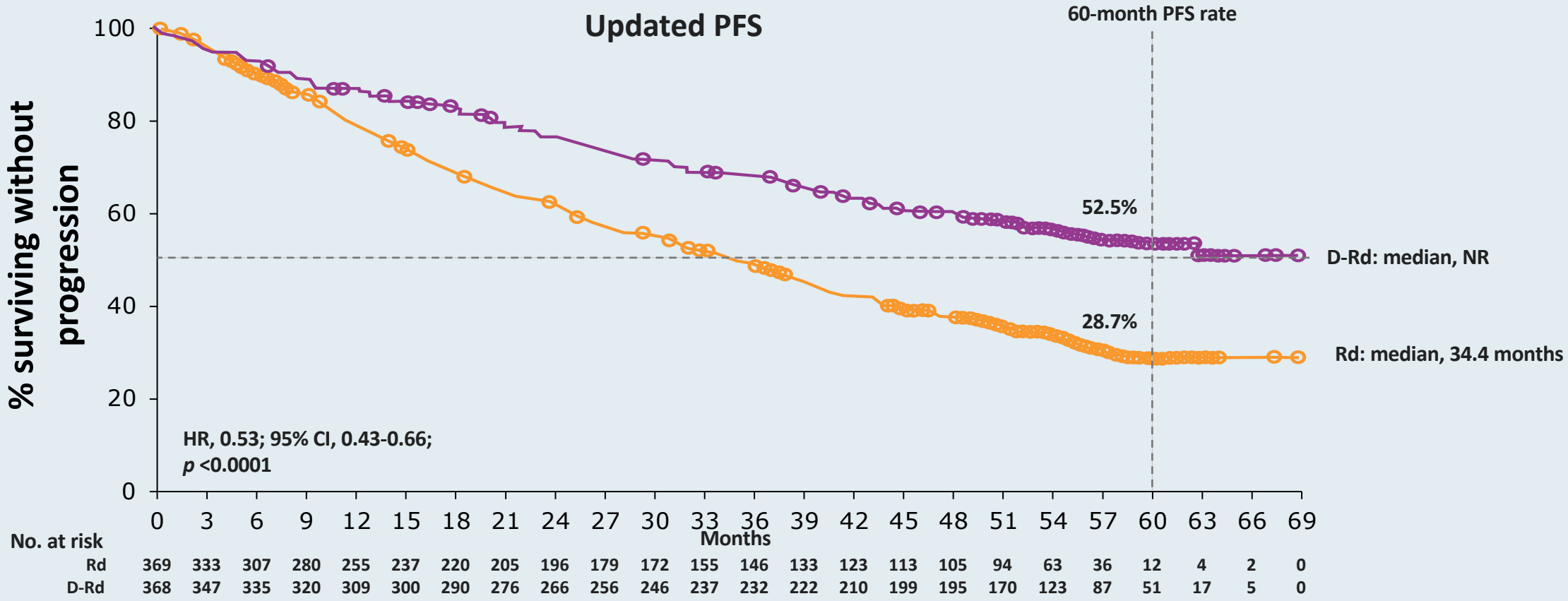
Stratification factors:
- **ISS (I vs II vs III)**
- **Region (NA vs other)**
- **Age (<75 vs ≥75 years)**

Cycle: 28 days

[a] On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required preinfusion medication.
[b] For patients older than 75 years or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c] Efficacy endpoints were sequentially tested in the order shown.

Facon T et al. EHA 2021;Abstract LB1901.

MAIA: Progression-Free Survival
New 60-Month Data

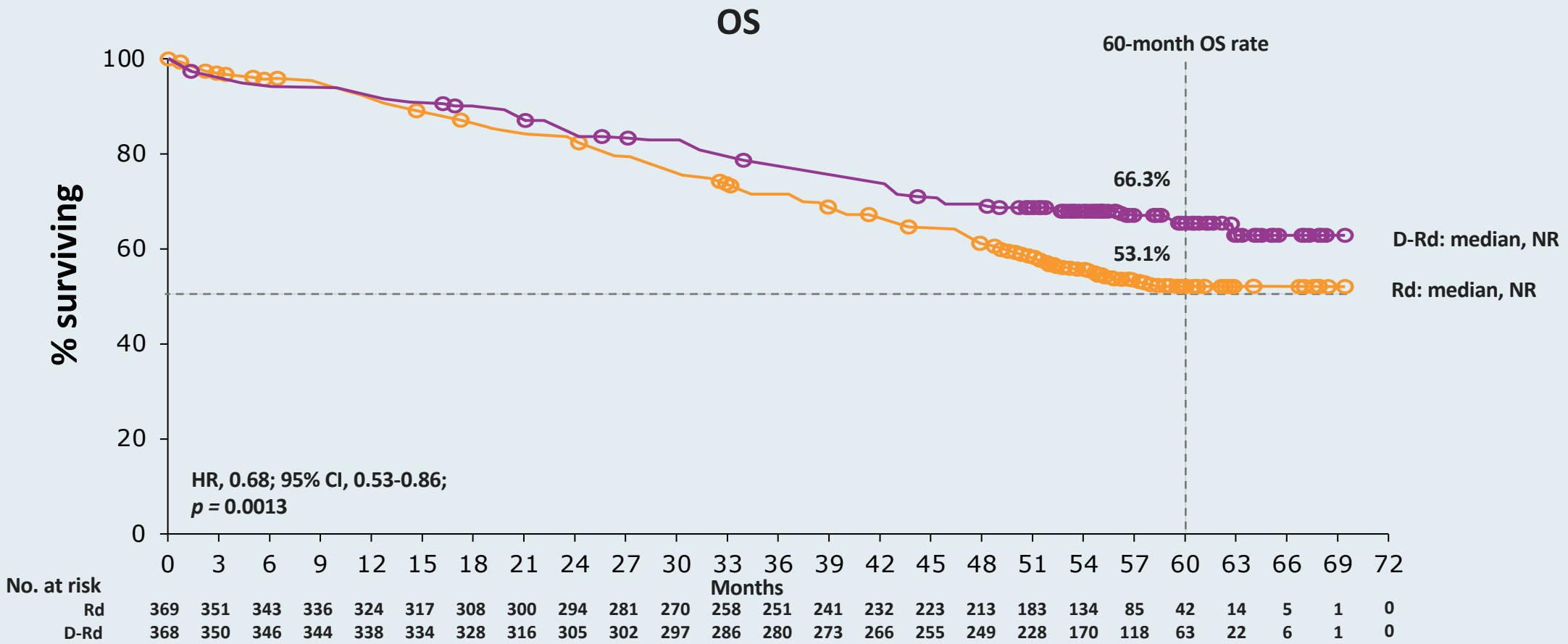


- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
  - These data provide a new PFS benchmark for patients with NDMM who are transplant ineligible

NR = not reached; HR = hazard ratio

Facon T et al. EHA 2021;Abstract LB1901.

MAIA: Overall Survival

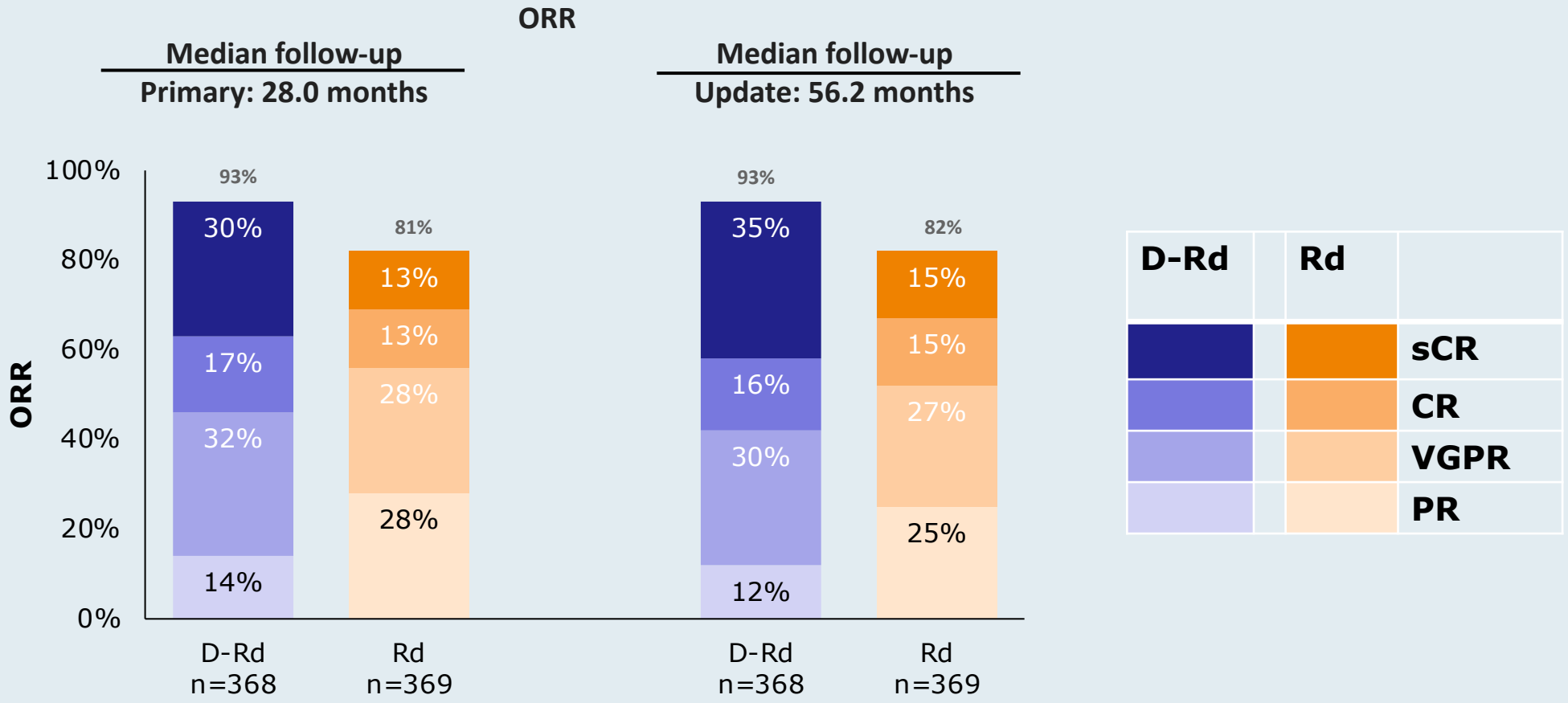


D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, for patients with NDMM who are transplant ineligible

Facon T et al. EHA 2021;Abstract LB1901.

RTP RESEARCH TO PRACTICE

MAIA: Updated Overall Response Rate (ITT Population)



- D-Rd induced deeper responses with significantly higher rates of ≥CR and ≥VGPR, compared with Rd
  - With >28 months of additional follow-up, responses deepened with continued DARA therapy

sCR = stringent complete response; VGPR = very good partial response

Falcon T et al. *N Engl J Med* 2019:380(22):2104-15; EHA 2021;Abstract LB1901.

ATLAS: A Phase 3 Randomized Trial of Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide Alone After Stem-Cell Transplant for Multiple Myeloma

Dytfeld D et al.

ASCO 2022;Abstract 8001 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

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TO PRACTICE

Agenda

Module 1 – Front-Line and Maintenance Treatment Options for Patients with Multiple Myeloma (MM)

Module 2 – Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) MM

Module 3 – Future Directions in the Management of MM

Case 3 — Ajai Chari, MD

XPO1 inhibition for triple-class and penta drug-refractory MM

53 yo male p/w Ca 14.1, Cr 7.3, anemia, T11 comp fx & MRI T6 with posterior epidural component/T7 lesion and 8th rib (with soft tissue component) lesions, serum Lambda FLC 16210. BM Bx 11/8/13 80% PC t(4;14) 95%, + 1q21 (77% 3 copies, 22% 4 copies). Lambda LC MM 11/8/13, ISS and RISS 3.

1. PE *3, pam, VCD *3 with BM Bx 2/18/14 10-15% PC. Mel 140 mg/m^2 ASCT #1 3/27/14 and BM Bx 7/1/14 5-10% PC, mel 140 mg/m^2 ASCT #2 8/11/14 (no cells remaining) then with BM Bx 10/21/14 1%. Started V maintenance qwk (3/4) 11/5/14 with PD.

2. EloR10D EAP 12/10/15 with PD after C2.

3. C1 KCD 2/10/16 s/p 6 cycles then KD maintenance, PD. BM Bx 5/24/17 50-60% PC +1q, -13, and t(4;14).

4. Dara-CF SQ 5/31/17 x 1 cycle. PD by C2D15. Transition to SOC Dara/Pom with PD.

5. C1 VDACE 9/25/17 c/b PNA with PD, C2 VDPACE 10/24/17.

6. BCNU 100 mg/m^2 and mel 100 mg/m^2 with ASCT 11/24/17 (2.97 x 10^6 CD34/kg remaining). PD with BM PC 70-80% cyto nl, FISH pending.

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Case 3 — Ajai Chari, MD

XPO1 inhibition for triple-class and penta drug-refractory MM

7. Selinexor x 3 cycles 1/30/18 best response VGPR, PD by 5/8/18.

8. Clinical trial C1D1 5/29/18 x 1 cycle, PD. C1 GCO #17-2680 + addition of ixa 6/28/18, x 1 cycle, PD.

9. Metro28 8/7/18.

10. Clinical trial C1D1 10/3/18 x 1 cycle, PD. OFF STUDY.

11. Metro28 11/6/18 with PD.

12. C1 DaraKTd 12/14/18 with PD.

13. C1 DaraKTd + pano 1/2/19.

14. Selinexor Bort/Dex CUP, consent signed 4/2/19. C1D1 4/4/19 x 3 cycles. PD.

15. Bispecific 7/19/19. C1D1 7/24/19 x 40 weeks (27 cycles) with PD; Consented to increased dose level re-treatment w/ sponsor approval - C1D1 6/1/20 x 4 weeks; PD.

16. Bispecific 9/1/20 in CR.

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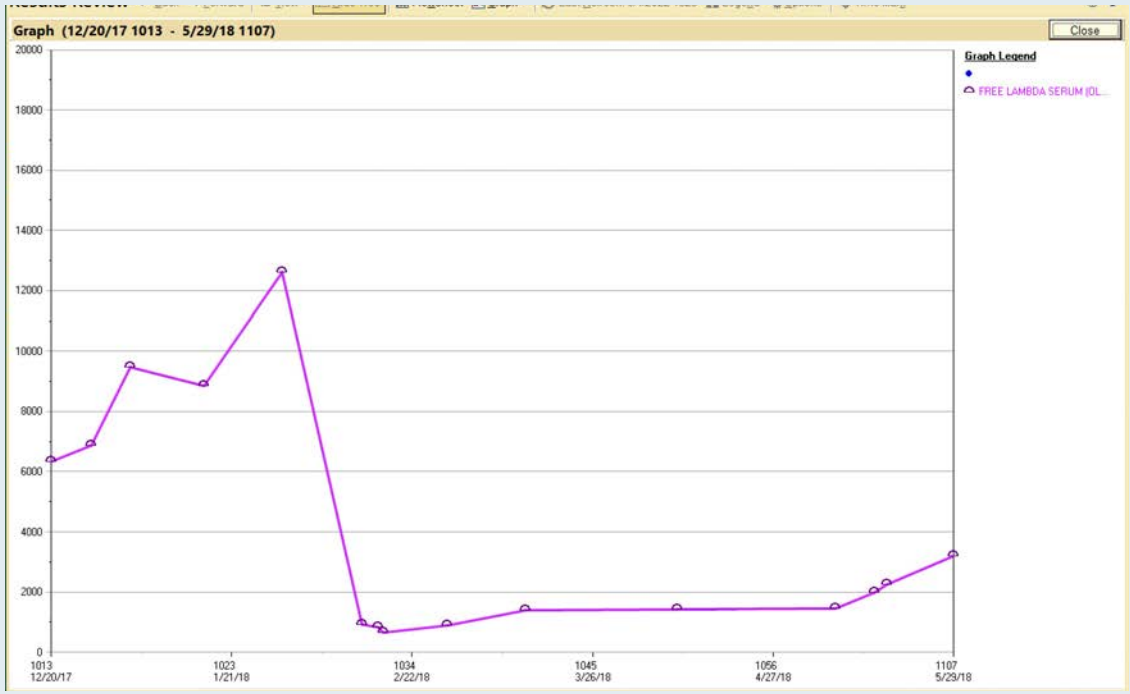
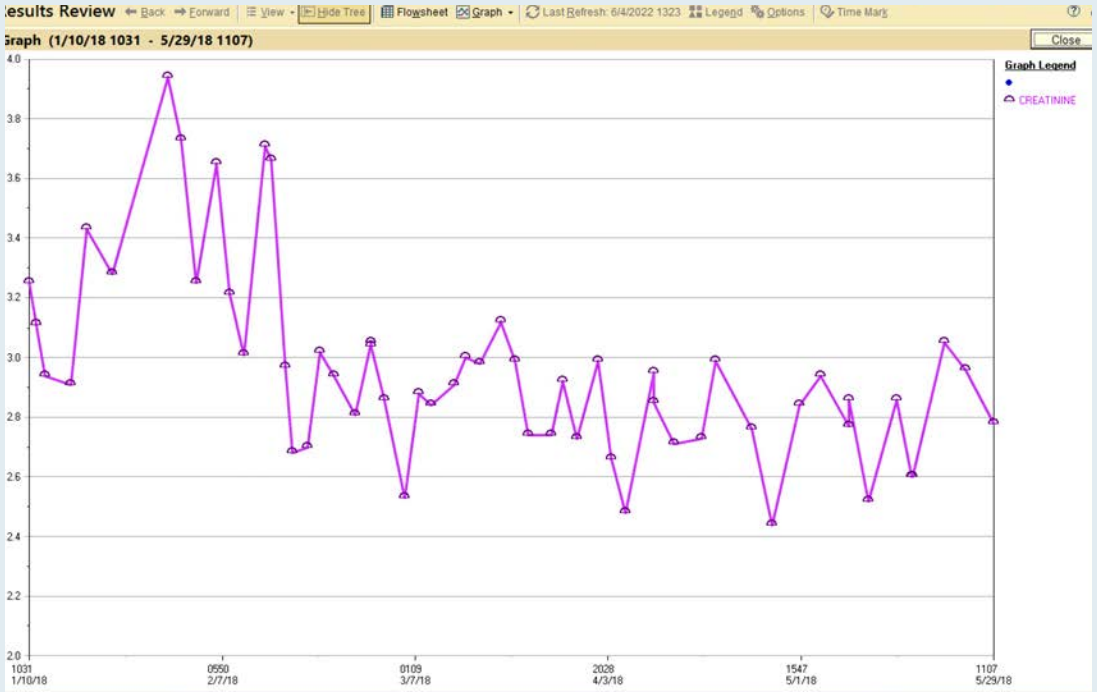
Case 3 — Ajai Chari, MD

Selinexor x 3 cycles 1/30/18 best response VGPR, PD by 5/8/18



Free kappa 12k mg/L prior to selinexor

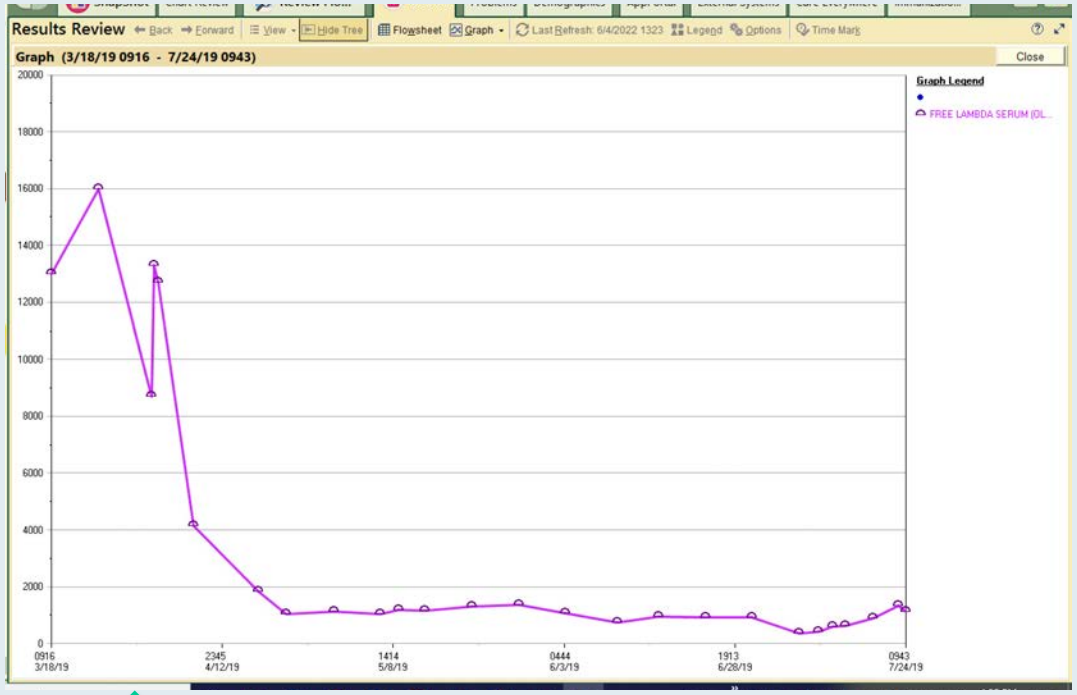


Cr 3.94 mg/dL prior to selinexor

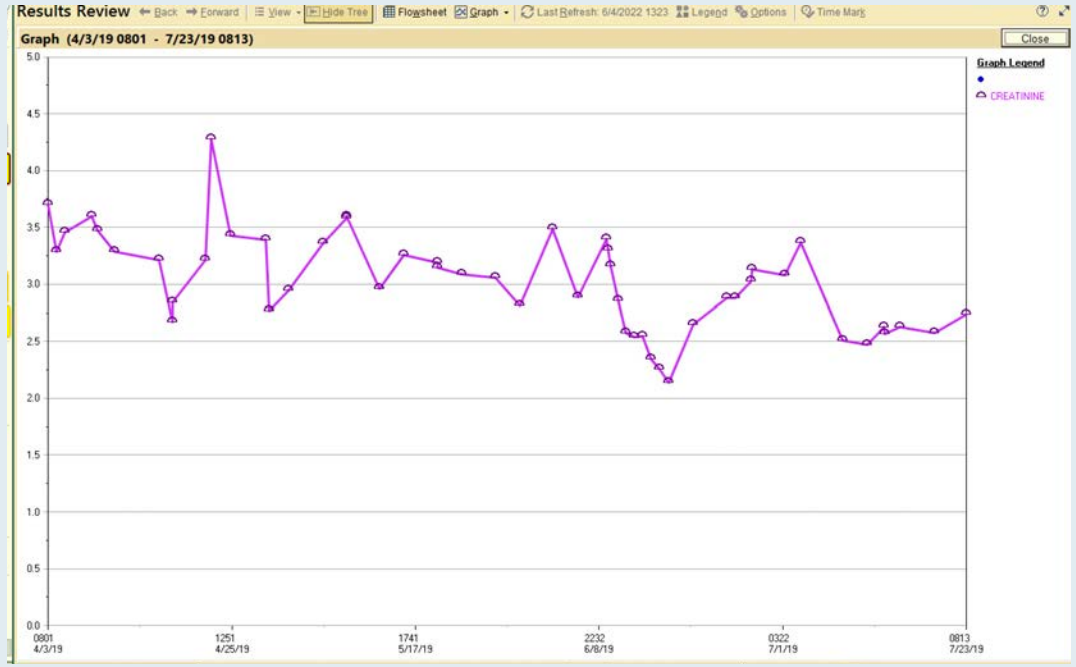
RTP RESEARCH TO PRACTICE

Case 3 — Ajai Chari, MD

Selinexor Bortezomib Dex CUP, consent signed 4/2/19. C1D1 4/4/19 x 3 cycles. PD

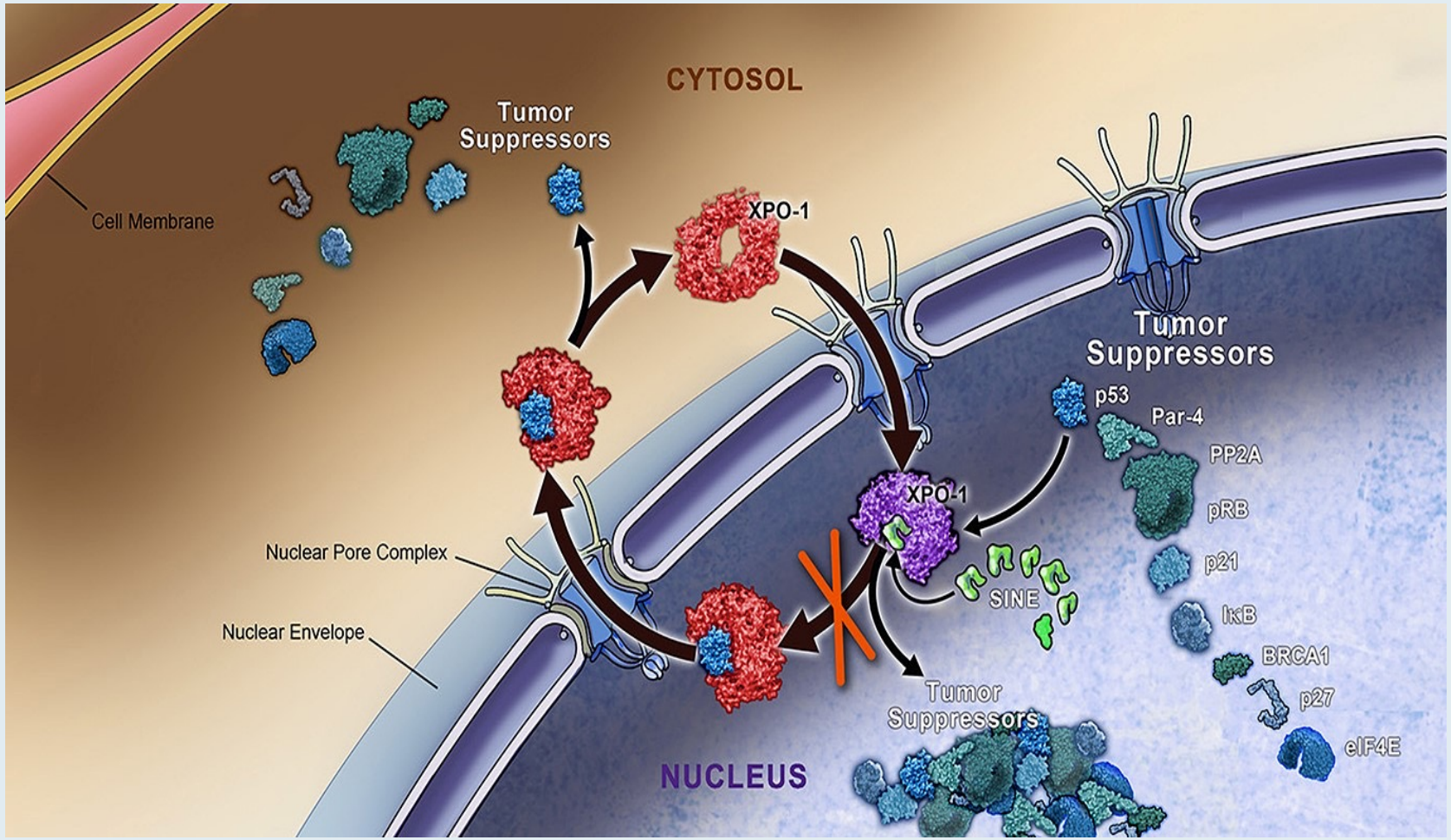


Free kappa 13k mg/L prior to selinexor



Cr 3.3 mg/dL prior to selinexor-bortezomib-dex

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR) and eIF4E-bound oncoprotein mRNAs (c-myc, Bcl-2, Bcl-xL and cyclins)
- XPO1 is overexpressed in MM and its levels often correlate with poor prognosis
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

Bahlis N et al. EHA 2016;Abstract P277.

RTP RESEARCH TO PRACTICE

Efficacy and Tolerability of Once-Weekly Selinexor, Bortezomib, and Dexamethasone in Comparison with Standard Twice-Weekly Bortezomib and Dexamethasone in Previously Treated Multiple Myeloma with Renal Impairment: Subgroup Analysis from the BOSTON Study

Delimpasi S et al.

Am J Hematol 2022;97(3):E83-6.

BOSTON: Subgroup Analysis of Patients with Renal Impairment

Outcome	<40 mL/min			40-60 mL/min			>60 mL/min		
	XVd ($n = 21$)	Vd ($n = 26$)	*p* value	XVd ($n = 35$)	Vd ($n = 44$)	*p* value	XVd ($n = 139$)	Vd ($n = 137$)	*p* value
Median PFS, months	7.62	4.30	.129	16.62	7.62	.028	13.24	9.66	.019
HR	0.62				0.49			0.71	
ORR, %	81.0	53.8	.027	80.0	59.1	.024	74.8	65.0	.037
OR		3.64			2.77			1.60	
≥VGPR, %	38.1	26.9	.210	48.6	27.3	.053	44.6	35.0	.053
OR		1.67			2.52			1.49	
Median DOR, months, (95% CI)	20.27	NR	.660	NR	12.58	.211	15.34	12.68	.053
HR		1.32			0.69			0.71	
Median OS, months (95% CI)	NR	19.06	.264	NR	21.22	.080	NR	24.97	.446
HR		0.74			0.55			0.97	
Median TTNT, months, (95% CI)	NR	19.06	.137	NR	20.93	.040	15.34	10.97	.007
HR		0.65			0.56			0.67	

XVd = selinexor/bortezomib/dexamethasone; Vd = bortezomib/dexamethasone; PFS = progression-free survival; HR = hazard ratio; ORR = overall response rate; OR = odds ratio; VGPR = very good partial response; DOR = duration of response; NR = not reached; TTNT = time to next treatment

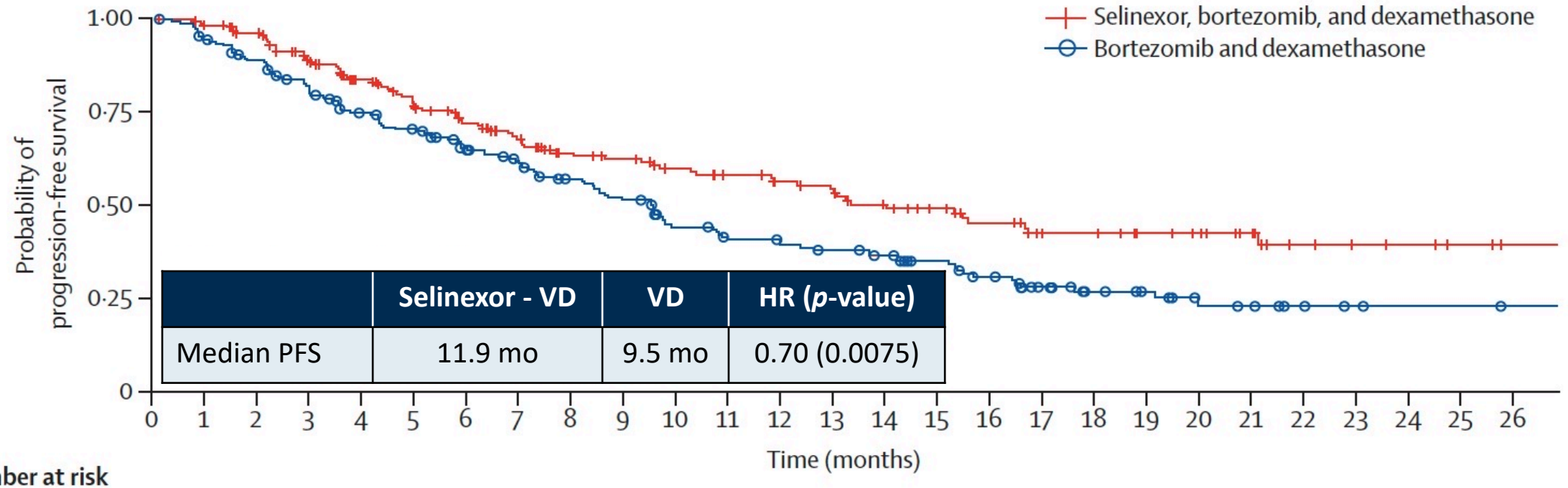
Delimpasi S et al. *Am J Hematol* 2022;97(3):E83-6.

Lancet 2020;396(10262):1563-73.

Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial

Sebastian Grosicki, Maryana Simonova, Ivan Spicka, Ludek Pour, Iryrna Kriachok, Maria Gavriatopoulou, Halyna Pylypenko, Holger W Auner, Xavier Leleu, Vadim Doronin, Ganna Usenko, Nizar J Bahlis, Roman Hajek, Reuben Benjamin, Tuphan K Dolai, Dinesh K Sinha, Christopher P Venner, Mamta Garg, Mercedes Gironella, Artur Jurczyszyn, Pawel Robak, Monica Galli, Craig Wallington-Beddoe, Atanas Radinoff, Galina Salogub, Don A Stevens, Supratik Basu, Anna M Liberati, Hang Quach, Vesselina S Goranova-Marinova, Jelena Bila, Eirini Katodritou, Hanna Oliynyk, Sybiryna Korenkova, Jeevan Kumar, Sundar Jagannath, Phillipe Moreau, Moshe Levy, Darrell White, Moshe E Gatt, Thierry Facon, Maria V Mateos, Michele Cavo, Donna Reece, Larry D Anderson Jr, Jean-Richard Saint-Martin, Jacqueline Jeha, Anita A Joshi, Yi Chai, Lingling Li, Vishnuvardhan Peddagali, Melina Arazy, Jatin Shah, Sharon Shacham, Michael G Kauffman, Meletios A Dimopoulos, Paul G Richardson, Sosana Delimpasi**

BOSTON: Progression-Free Survival (ITT)



	Selinexor - VD	VD	HR (*p*-value)
Median PFS	11.9 mo	9.5 mo	0.70 (0.0075)

Number at risk (number censored)

Selinexor, bortezomib, and dexamethasone	195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)
Bortezomib and dexamethasone	207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

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BOSTON: Select Adverse Events

Adverse event	Selinexor + bort/dex (n = 195)		Bort/dex (n = 204)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	60%	39%	27%	17%
Fatigue	42%	13%	18%	1%
Anemia	36%	16%	23%	10%
Peripheral neuropathy	32%	5%	47%	9%
Neutropenia	15%	9%	6%	3%

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

Case 4 — Elizabeth O'Donnell, MD

- **58M whose history dates back to May 2013 when he injured his back climbing through a vent at work.**
- **He had an MRI of his lumbar spine that showed an enlarged Schmorl's node at L2-L3 but also discovered multiple metastatic appearing lesions at T12, L2, L3, L4 and S1.**
- **On 05/24/13, he had a chest x-ray that also showed lytic lesion at his left seventh rib and second rib. These discoveries prompted a workup for multiple myeloma.**
- **His SPEP was significant for an IgG kappa M protein of 3.3 g/dL and his kappa free light chain was measured at 75.6 mg/L. UPEP performed did show kappa light chain and was positive for Bence Jones protein.**

Case 4 — Elizabeth O'Donnell, MD

- **On 06/17/13, the patient had a bone marrow biopsy that showed 65% plasma cells. Flow cytometry was also positive for monoclonal plasma cell population that was kappa-restricted.**
- **Beta-2-microglobulin was 2.5 and albumin was within normal limits making this patient Stage I myeloma by ISS.**
- **Standard-risk cytogenetics.**
- **The patient was seen by a local oncologist who recommended RVD therapy.**
- **The patient then came down to Boston for second opinion.**

Case 4 — Elizabeth O'Donnell, MD

Past medical history:

- **Hypothyroidism**
- **Disseminated herpes zoster**
- **Dermatofibrosis**
- **Compression fracture of spine 2/2 MM s/p kyphoplasty**
- **Vitamin D deficiency**

Social history:

- **Patient is married and father to 1 child. Never smoker. Drinks 3 beers on the weekends. Exposure to asbestos in his workplace**

Family history:

- **No cancer history**

Case 4 — Elizabeth O'Donnell, MD

Treatment summary:

7/13: Initiated RVD

10/24/13: Completed 4 cycles RVD

11/13: Stem cells collected

12/13: Began bortezomib maintenance at discretion of local provider

1/5/16: Has e/o progressive disease — Began oral lenalidomide, ixazomib, dex with good response in anticipation of autologous SCT

4/8-4/22/16: Melphalan ASCT

9/8/16: Lenalidomide and ixazomib maintenance

9/4/18: Progression. Begin daratumumab, pomalidomide, dex

9/5/19: Progressive disease on dara, pom, dex

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Case 4 — Elizabeth O'Donnell, MD

Pre-CAR T-cell labs:

11/11/19:

- **M-protein: 3.61 g/dL IgG kappa**
- **KFLC: 947.2**
- **LFLC: 1.4**
- **K/L: 676**

BM biopsy: 50-60% plasma cells, aspirate 60% plasma cells

Case 4 — Elizabeth O'Donnell, MD

Treatment summary (continued):

9/18/19: Screen and consent for BCMA CAR T cells — CARTITUDE study (ciltacabtagene autoleucel)

10/28/19: Hypercalcemic and has worsening creatinine

10/29/19: Cyclophosphamide 2g IV salvage

11/13/19: LDC chemo

11/18/19: Received CAR T cells

12/1/19: Discharged from hospital

12/16/19: 1 month post CAR T cells

5/19/22: Month 30 post CAR T cells sCR

RTP RESEARCH TO PRACTICE

Case 4 — Elizabeth O'Donnell, MD

CAR T-cell course:

- **Admitted for anti-BCMA CAR-T cells on protocol 19-156 s/p lymphodepleting fludarabine and cyclophosphamide x3 days. PICC placed 11/17, CAR-T cells infused 11/18. Overnight 11/18-19 experienced fevers, sweats, and chills with unremarkable UA and CXR. He was started on cefepime 2gm q8H for febrile neutropenia. Fevers continued and SpO2 downtrended to 91% on RA, and in this setting was treated for Grade 2 CRS with tocilizumab. Fever and hypoxia resolved.**
- **On 11/26 was noted to have new tachycardia, fatigue, anorexia, nausea/vomiting with Tmax 101.5 concerning for CRS v sepsis and vancomycin was added. He was additionally started on levetiracetam for neurotoxicity prophylaxis. These symptoms resolved on 11/27 and he has been afebrile without complaint thereafter with blood, urine and sputum Cx negative.**
- **His neuro exam remained unchanged and nonfocal throughout the hospitalization. Filgrastim was restarted on 11/28 and ANC subsequently increased from 0.02 to 0.91 on day of discharge. Vancomycin was discontinued on 11/29 and he received his last dose of cefepime on 11/30. Acyclovir prophylaxis was continued throughout hospitalization.**

Case 4 — Elizabeth O'Donnell, MD

Most recent labs:

- **No M-protein**
- **KFLC: <0.06**
- **LFLC: <1.3**
- **K/L: N/A**
- **BM biopsy: No morphologic evidence of myeloma; 0 plasma cells on aspirate or by flow**

FDA Approves Cilta-Cel for Relapsed/Refractory Multiple Myeloma

Press Release – February 28, 2022

The FDA has approved the use of ciltacabtagene autoleucel (cilta-cel) for the treatment of patients with relapsed/refractory multiple myeloma after 4 or more lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The approval was based on findings from the phase 1b/2 CARTITUDE-1 trial (NCT03548207) during which one-time treatment with cilta-cel resulted in an overall response rate of 98% (95% CI, 92.7%-99.7%). Additionally, investigators reported a stringent complete response rate of 78% (95% CI, 68.8%-86.1%). The median duration of response was 21.8 months after a median follow-up of 18 months.

Updated results were previously presented at the 2021 American Society of Clinical Oncology Annual Meeting. The CARTITUDE trial enrolled 97 patients, with a median turnaround time for cilta-cel therapy was 29 days. Additionally, patients had underwent a median of 6.0 lines of prior therapy. Moreover, 87.6% (n = 85) pf patients were triple-class refractory, and 42.3% (n = 41) were penta-drug refractory. Nearly all patients (99%; n = 96) were refractory to their last line of therapy.

www.cancernetwork.com/view/fda-approves-cilta-cel-for-relapsed-refractory-multiple-myeloma?utm_source=sfmc&utm_medium=email&utm_campaign=3.01.22_CN_Breaking_A&eKey=cmthZGVybWFuQHJlc2VhcmNodG9wcmFjdGljZS5jb20=

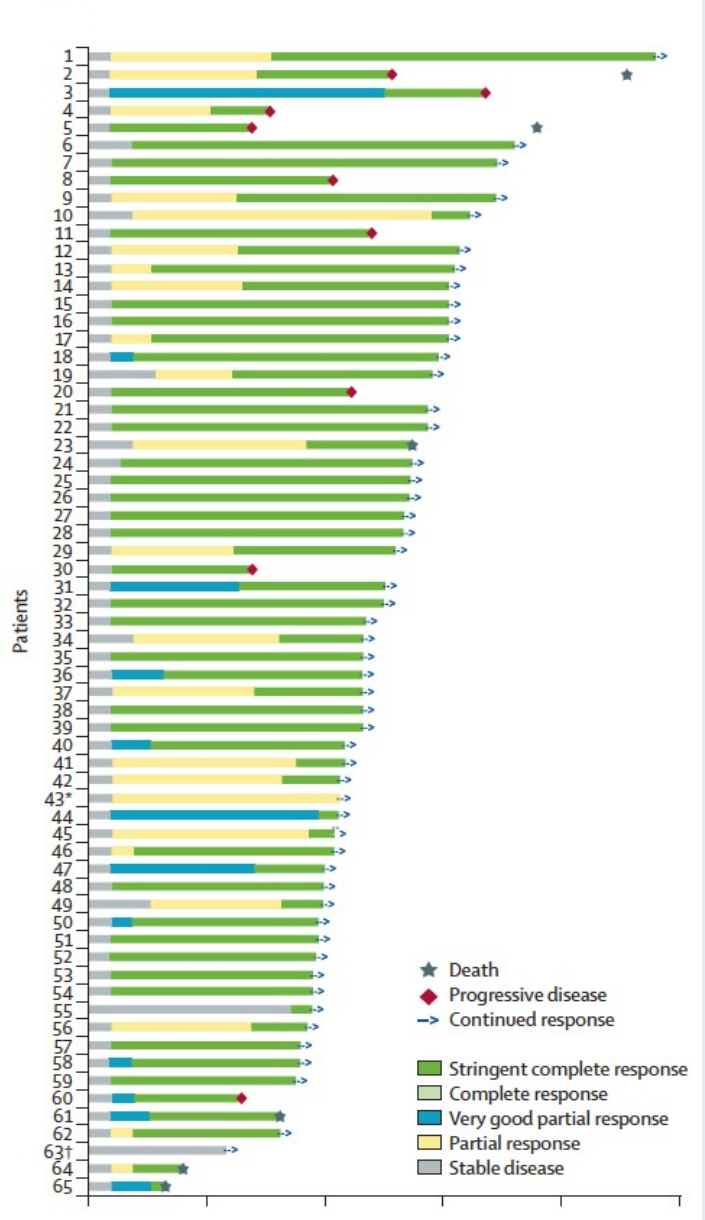
Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study

Jesus G Berdeja, Deepu Madduri*, Saad Z Usmani, Andrzej Jakubowiak, Mounzer Agha, Adam D Cohen, A Keith Stewart, Parameswaran Hari, Myo Htut, Alexander Lesokhin, Abhinav Deol, Nikhil C Munshi, Elizabeth O'Donnell, David Avigan, Indrajeet Singh, Enrique Zudaire, Tzu-Min Yeh, Alicia J Allred, Yunsi Olyslager, Arnob Banerjee, Carolyn C Jackson, Jenna D Goldberg, Jordan M Schecter, William Deraedt, Sen Hong Zhuang, Jeffrey Infante, Dong Geng, Xiaoling Wu, Marlene J Carrasco-Alfonso, Muhammad Akram, Farah Hossain, Syed Rizvi, Frank Fan, Yi Lin†, Thomas Martin†, Sundar Jagannath†*

Lancet 2021; 398: 314–24

CARTITUDE-1: Overall Response and Duration of Response

	Patients (n=97)
Overall response	
Number of patients with a response†	94
Proportion of patients with a response, % (95% CI)	96·9% (91·2–99·4)
Best overall response	
Stringent complete response	65 (67%)
MRD-negative complete response or stringent complete response	33 (34%)‡
Complete response	0
Very good partial response	25 (26%)
Partial response	4 (4%)
Minimal response	0
Stable disease	0
Progressive disease	1 (1%)
Not evaluable	2 (2%)
Median time to first response, months	1·0 (0·9–1·0)
Median time to best response, months	2·6 (1·0–6·1)
Median time to complete response or better, months	1·9 (1·0–6·5)
Median duration of response, months (95% CI)	NE (15·9–NE)
MRD negativity	
Number of patients evaluable for MRD at 10^{-5}	57
MRD negativity rate at 10^{-5}	53/57 (93%)



Berdeja JG et al. *Lancet* 2021;398(10297):314-24.

CARTITUDE-2: Efficacy and Safety of Ciltacabtagene Autoleucel (Cilta-Cel), a BCMA-Directed CAR T-Cell Therapy, in Patients with Progressive Multiple Myeloma (MM) After One to Three Prior Lines of Therapy

Agha ME et al.

ASCO 2021;Abstract 8013.

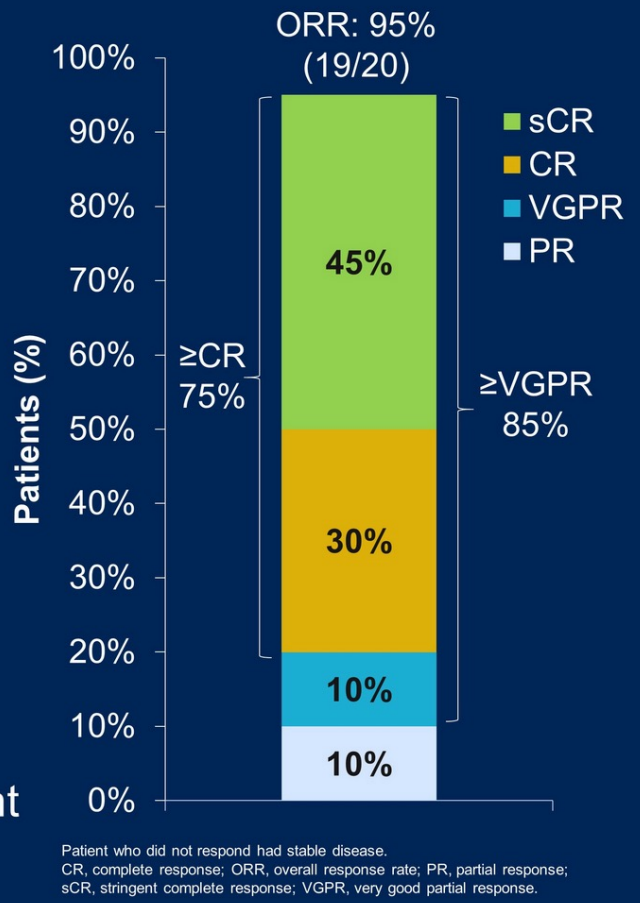
CARTITUDE-2: Ciltacabtagene Autoleucel After 1 to 3 Prior Lines of Therapy

Efficacy

- Median time to first response: 1.0 month
- Median time to best response: 1.9 months
- Median duration of response: not reached
- All patients (n=4) with MRD-evaluable samples at the 10^{-5} threshold were MRD negative at data cut-off

Safety

- Cilta-cel safety profile was manageable, including in the patient treated in an outpatient setting
- No movement and neurocognitive treatment-emergent AEs were observed in patients of Cohort A



Patient who did not respond had stable disease.
CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

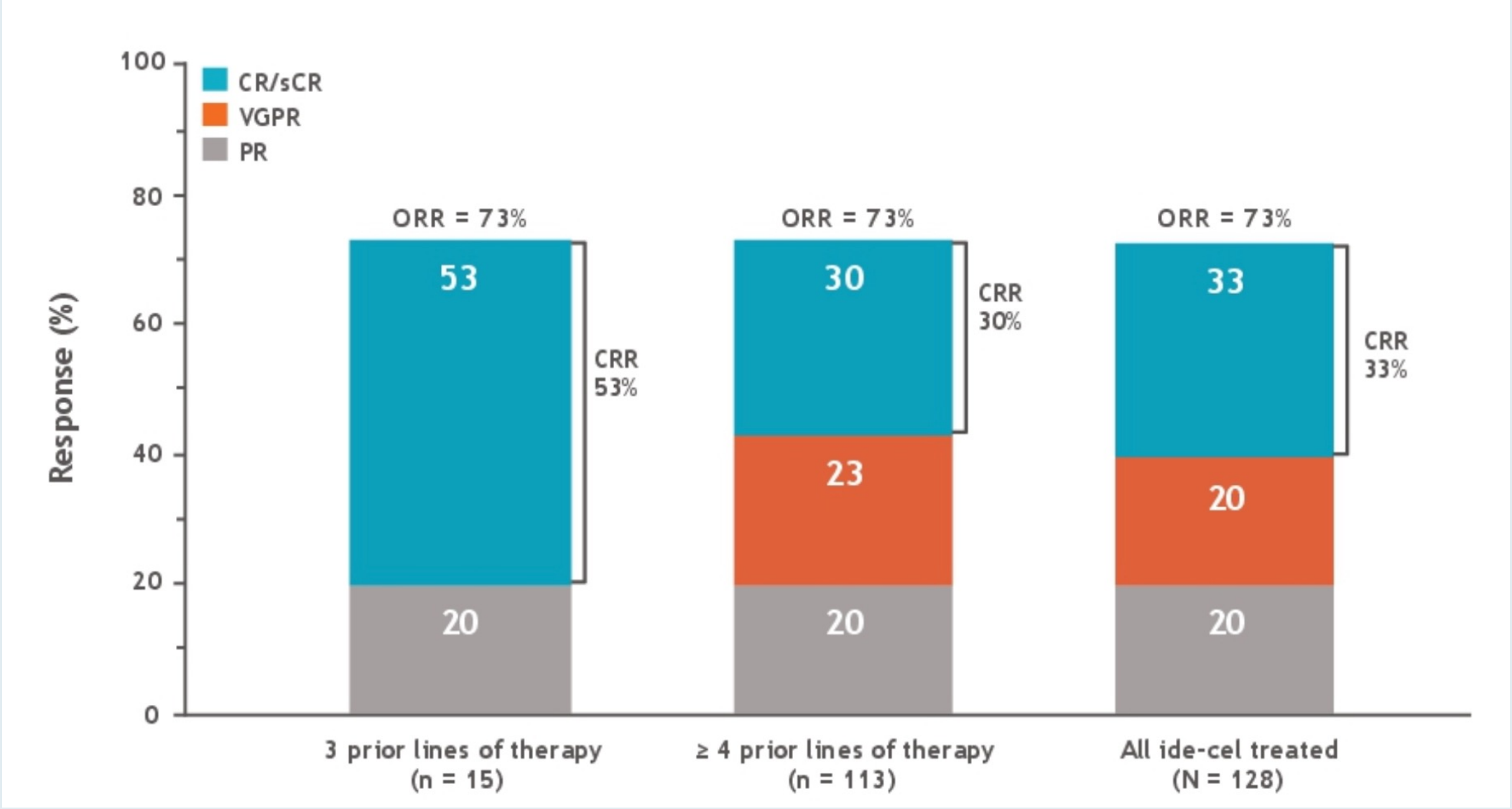
Agha M et al. ASCO 2021;Abstract 8013.

Idecabtagene Vicleucel (Ide-Cel, bb2121), a BCMA CAR T Cell Therapy, in Relapsed and Refractory Multiple Myeloma: Updated KarMMa Results

Anderson LD et al.

ASCO 2021;Abstract 8016.

KarMMa: Best Overall Response



Anderson LD et al. ASCO 2021;Abstract 8016.

KarMMa: Incidence of Cytokine Release Syndrome (CRS) and Neurotoxicity

	Prior line of therapy		All ide-cel treated (N = 128)
	3 (n = 15)	≥ 4 (n = 113)	
≥ 1 CRS event, n (%)	13 (87)	94 (83)	107 (84)
Max. grade (Lee criteria), n (%)[a]			
1/2	12 (80)	88 (78)	100 (78)
3	1 (7)	4 (4)	5 (4)
4	0	1 (< 1)	1 (< 1)
5	0	1 (< 1)	1 (< 1)
Median onset (range), d	1 (1-2)	1 (1-12)	1 (1-12)
Median duration (range), d	4 (1-63)	6 (2-28)	5 (1-63)
≥1 NT event, n (%)	2 (13)	21 (19)	23 (18)
Max. grade (CTCAE), n (%)[b]			
1	1 (7)	10 (9)	11 (9)
2	0	7 (6)	7 (5)
3	1 (7)	4 (4)	5 (4)[c]
Median onset (range), d	3 (1-5)	2 (1-10)	2 (1-10)
Median duration (range), d	3 (2-5)	3 (1-26)	3 (1-26)

Anderson LD et al. ASCO 2021;Abstract 8016.

Phase 1 Study of CART-ddBCMA in Relapsed or Refractory Multiple Myeloma

Frigault MJ et al.
ASCO 2022;Abstract 8003 (Oral).

June 5, 2022
9:00 AM – 12:00 PM EDT

RTP
RESEARCH
TO PRACTICE

Updated Results of a Multicenter First-in-Human Study of BCMA/CD19 Dual-Targeting Fast CAR-T GC012F for Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Du J et al.

ASCO 2022;Abstract 8005 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

Phase I Open-Label Single Arm Study of GPRC5D CAR T-Cells (OriCAR-017) in Patients with Relapsed/Refractory Multiple Myeloma (POLARIS)

Huang H et al.

ASCO 2022;Abstract 8004 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

Agenda

Module 1 – Front-Line and Maintenance Treatment Options for Patients with Multiple Myeloma (MM)

Module 2 – Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) MM

Module 3 – Future Directions in the Management of MM

Case 5 — Ajai Chari, MD

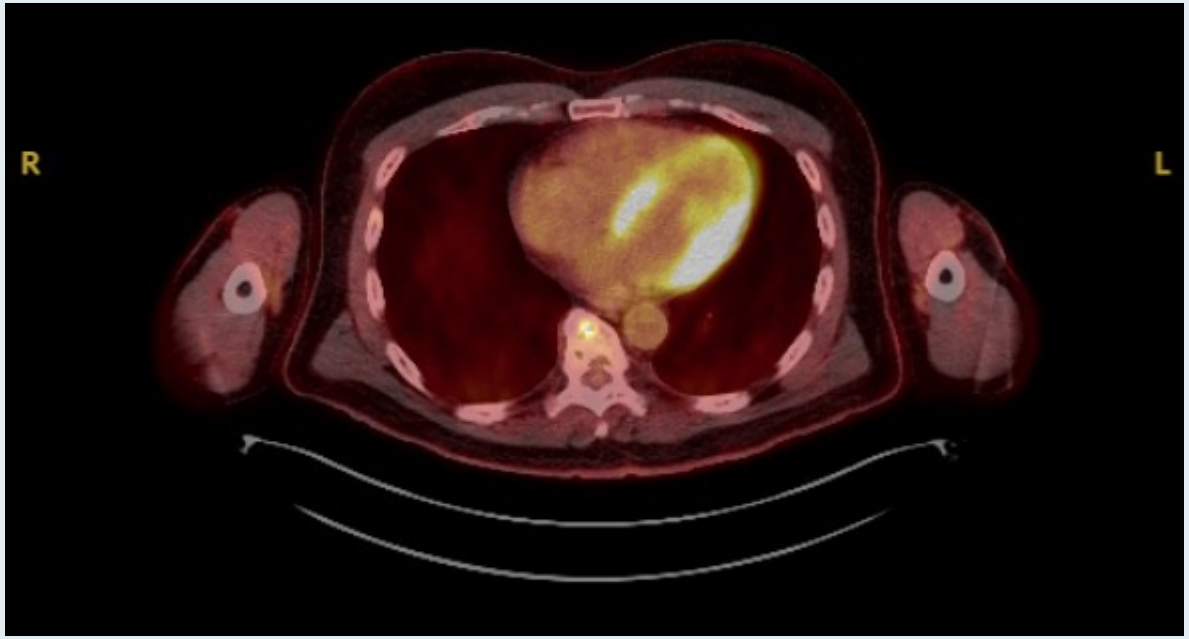
Anti-BCMA bispecific for triple-class and penta drug-refractory MM

IgG lambda MM (3/3/16) DS3. RISS: II FISH t(11;14).
Presented with R hip pain with anemia and lytic lesions, had further work up showing m-spike 6.56 g/dL; free lambda 924, IgG 8.2 g/dL. BMBx 3/6/16 >90% of PC. B2M: 2.04, alb: 3.41, LDH: 196 on 7/5/17, FISH t(11;14) on 6/22/17. Bone surv 7/26/17: lucencies proximal humeri, L proximal femur & pelvis.

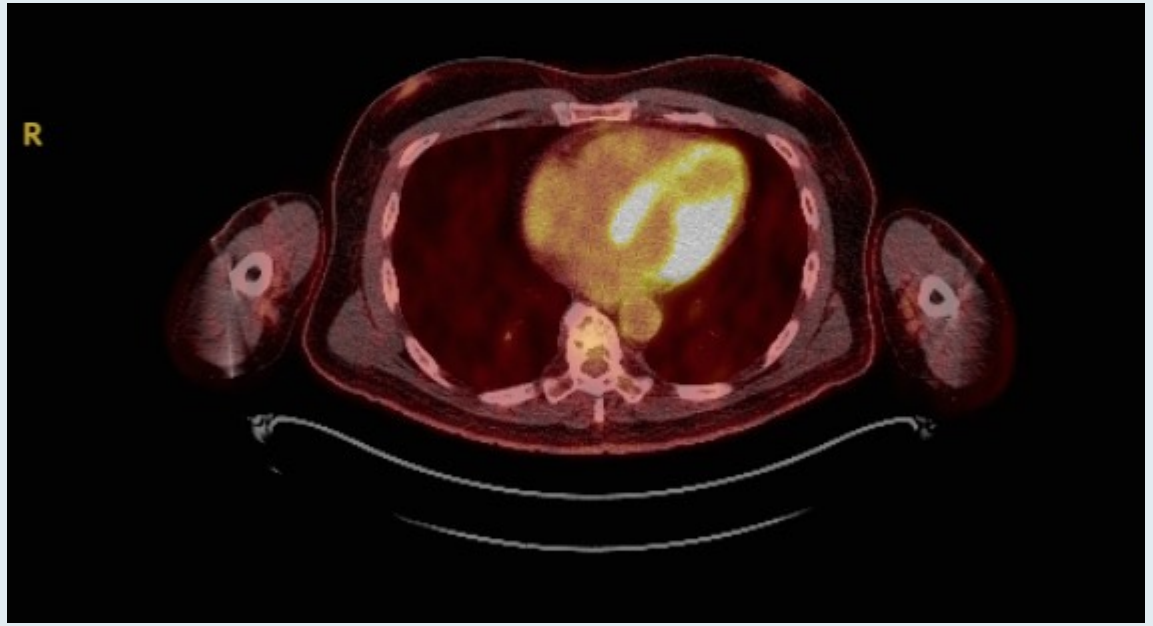
1. C1D1 VCD 3/22/16 *10 cycles with PR (m-spike 6.3 to nadir 2.1 g) then VRD 1/18 with 7 cycles with PR to 0.9 then PD to 1.4 and FLC 255 6/2/17.
2. Melphalan 200 mg/m^2 ASCT 8/23/17 with PR then rising FLC (PD). BM Bx 1/29/18 10-12% PC, nl cyto, FISH t(11;14) dup 1q. High risk GEP (52.8), CD2, t(11;14).
3. Clinical trial: IsaCar C1D1 2/20/18 x 10 cycles, PD by PET. OFF STUDY, EOT 12/11/18.
4. C1 PCD 2/8/19; Dara/pom started 5/17/19 - pom d/c'd 8/19 d/t neutropenia. PD.
5. Clinical trial: Novel ADC C1D1 11/14/19 x 2 cycles with PD with cauda equina syndrome s/p XRT 12/27-31/19 2000 cGy.
6. C1 Dar Bort Dex 1/14/20 + venetoclax 2/10/20, COVID+ and changed to Ixa/venetoclax/dex 3/20/20.
7. Teclistamab priming dose 1 12/11/20 x 15 cycles. Switched to biweekly dosing at C7.

Case 5 — Ajai Chari, MD (Cont)

PET CT Nov 2020

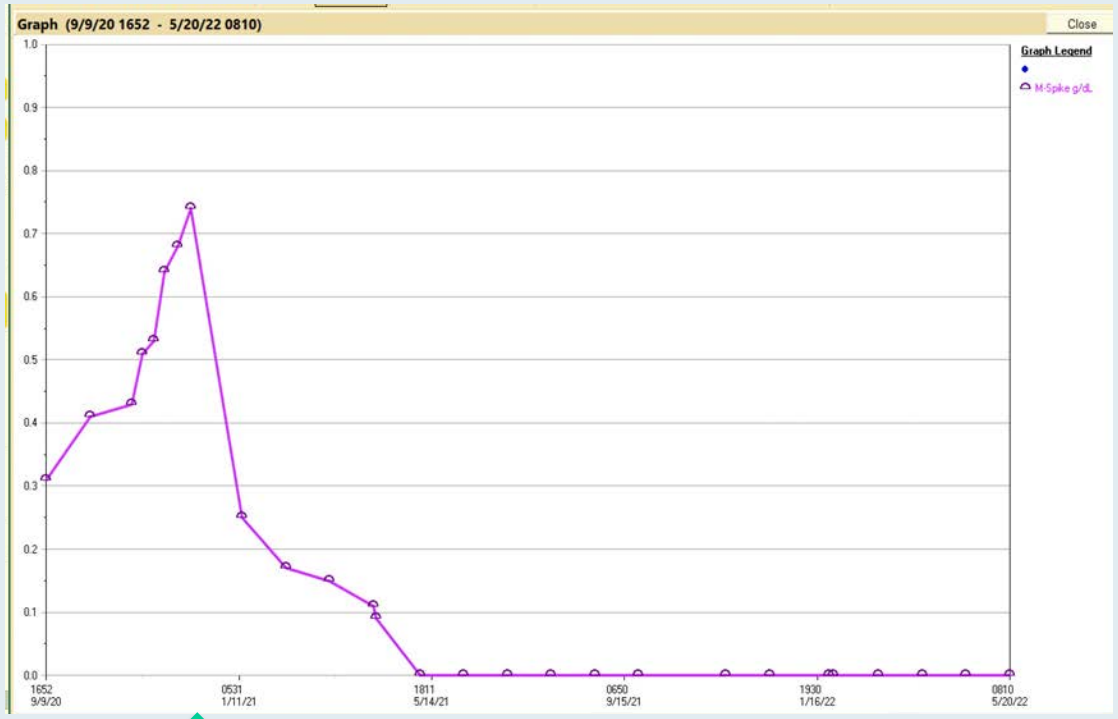


PET CT May 2022

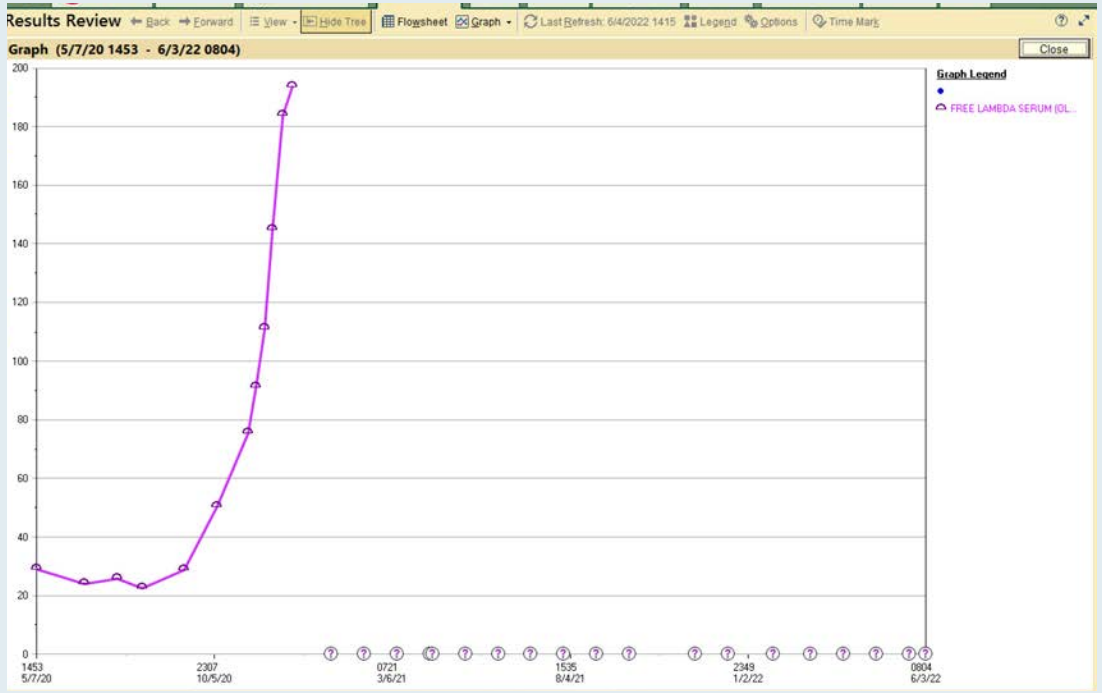


Case 5 — Ajai Chari, MD (Cont)

Teclistamab MRD-negative stringent complete remission



M-spike 0.74 mg/dL prior to teclistamab



Free lambda 193 mg/L prior to teclistamab

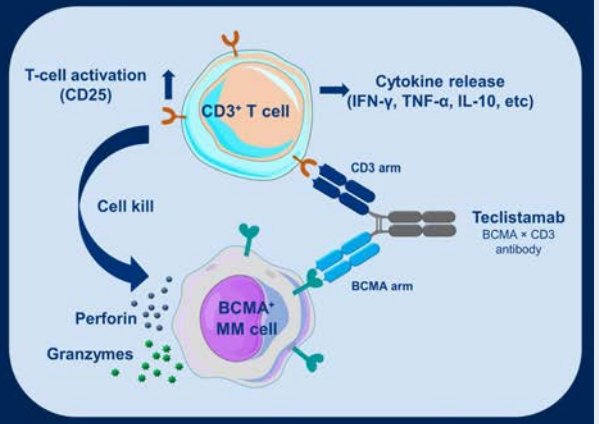
RTP RESEARCH TO PRACTICE

Bispecific Antibodies for R/R MM

TECLISTAMAB

BCMA × CD3 Bispecific Antibody

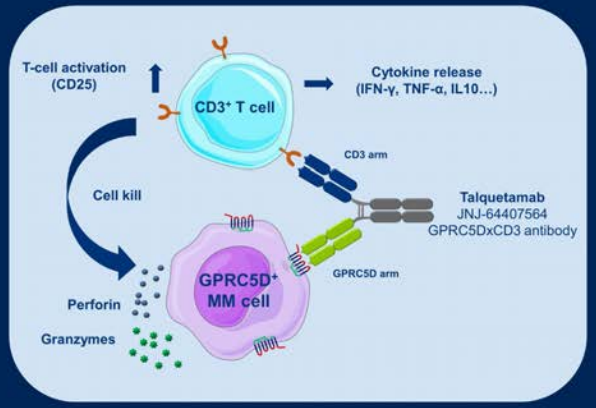
- Standard treatments and newly approved therapies for RRMM have limitations[1-3]
- Agents with new MOAs, including BCMA-targeted immunotherapies, offer considerable promise for RRMM
- Teclistamab (JNJ-64007957) is an off-the-shelf, full-size, BCMA × CD3, T-cell redirecting, bispecific antibody
- In the phase 1, first-in-human study in patients with RRMM (MajesTEC-1; NCT03145181), teclistamab was administered IV or SC in different dosing cohorts[4]
  - The RP2D was identified as a QW SC dose of teclistamab 1500 µg/kg with step-up doses of 60 µg/kg and 300 µg/kg
  - We present updated RP2D results with additional patients and longer follow-up



TALQUETAMAB

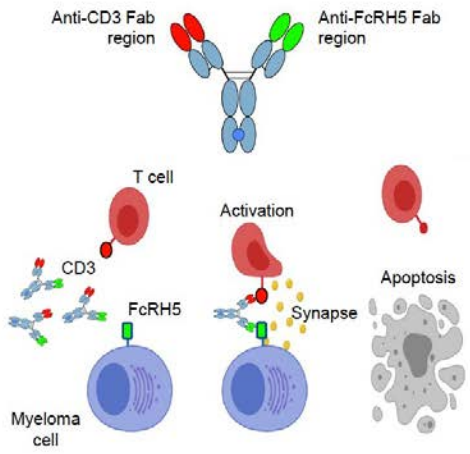
GPRC5D × CD3 Bispecific Antibody

- GPRC5D is a highly expressed receptor in MM, with limited expression in healthy human tissue[1-2]
- Talquetamab is a first-in-class antibody that binds to CD3 and GPRC5D to redirect T cells to kill MM cells[2-3]
- In the ongoing, phase 1, first-in-human study of talquetamab in patients with RRMM, the RP2D was identified as a QW SC dose of 400 µg/kg[a] (MonumenTAL-1; NCT03399799)[4]
- Here we present updated results of safety and efficacy of talquetamab at the RP2D, with additional patients and longer follow-up



Cevostamab: FcRH5xCD3 bispecific antibody

- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence[1]
  - Expression on myeloma and plasma cells > normal B cells[1]
- Cevostamab
  - Humanized IgG-based T-cell-engaging bispecific antibody[1]
  - Targets FcRH5 on myeloma cells and CD3 on T cells[1]
- Ongoing Phase I dose-escalation and expansion trial (NCT03275103) is evaluating the safety and activity of cevostamab monotherapy in patients with RRMM[2]



Krishnan AY et al. ASCO 2021;Abstract 8007;
Berdeja JG et al. ASCO 2021;Abstract 8008;
Cohen AD et al. ASH 2020;Abstract 292.

RTP RESEARCH TO PRACTICE

Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study

Saad Z Usmani, Alfred L Garfall, Niels W C J van de Donk, Hareth Nahi, Jesus F San-Miguel, Albert Oriol, Laura Rosinol, Ajai Chari, Manisha Bhutani, Lionel Karlin, Lotfi Benboubker, Lixia Pei, Raluca Verona, Suzette Girgis, Tara Stephenson, Yusri Elsayed, Jeffrey Infante, Jenna D Goldberg, Arnob Banerjee, María-Victoria Mateos, Amrita Krishnan

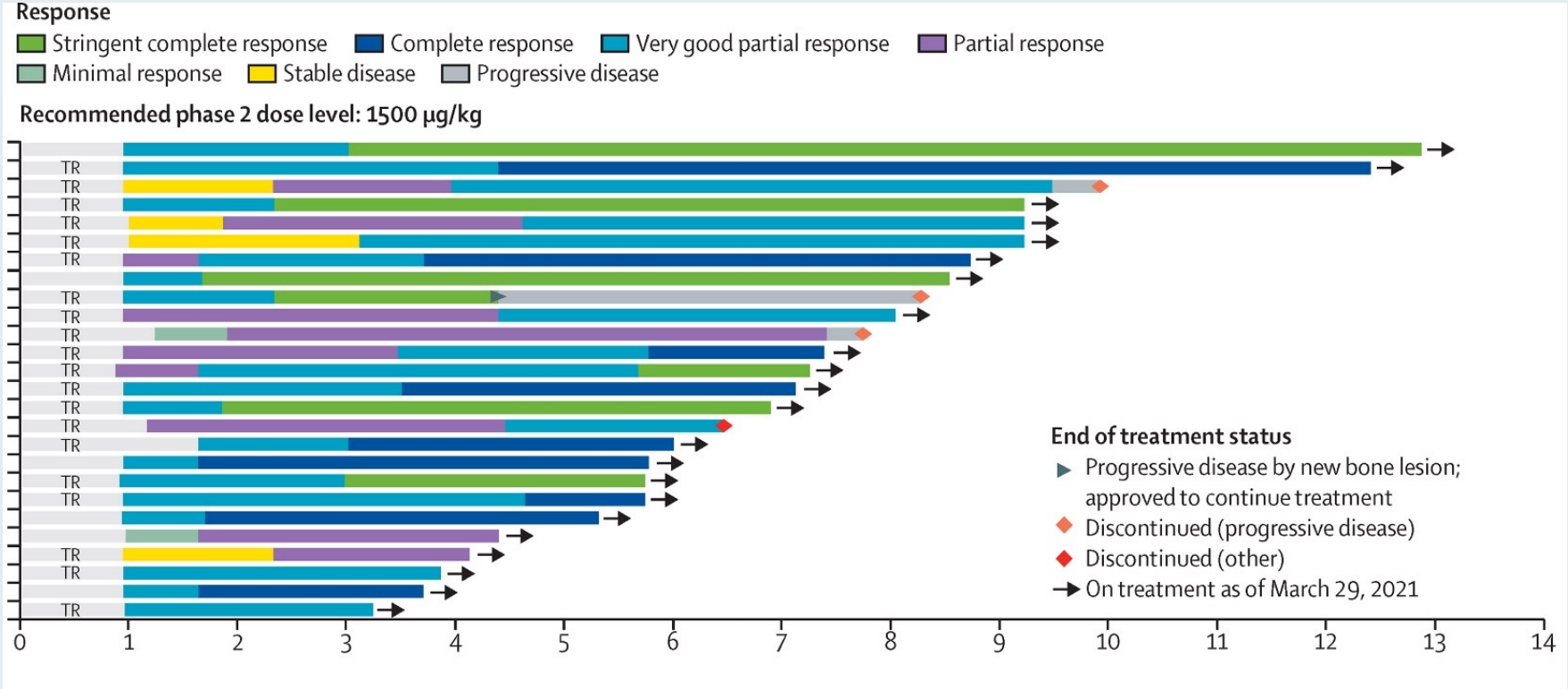
Lancet 2021; 398: 665–74

MajesTEC-1: A Phase I Study of Teclistamab for R/R MM

Teclistamab: A BCMA-targeted bispecific IgG4 mAb
Baseline characteristics: Median prior regimens, 5 (4-6); high-risk cytogenetics, 37%; extramedullary disease, 20%; triple refractory, 83%.

Response at RP2D (%)	N = 40
ORR	65%
sCR	18%
CR	23%
VGPR	18%
PR	8%

69% of CR/sCR patients MRD-



- CRS at RP2D (recommended Phase II dose): 70% (0% Grade ≥3)
- 1 patient with Grade 1 neurotoxicity at the RP2D

Usmani S et al. *Lancet* 2021;398(10301):665-74.

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

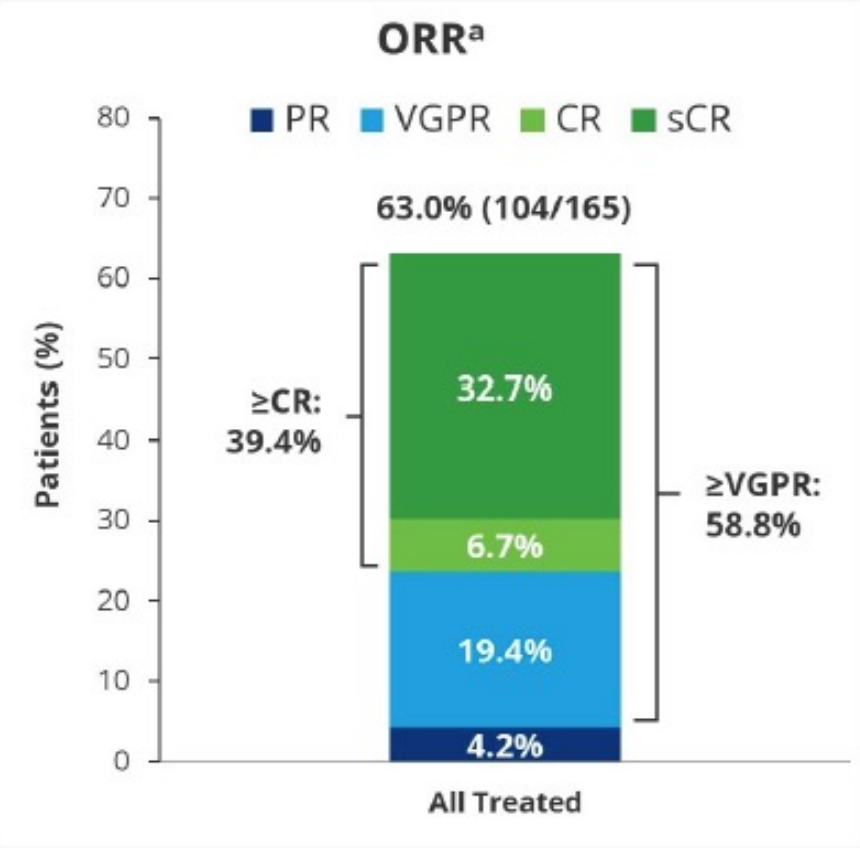
ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

N Engl J Med 2022; Jun 5 [epub ahead of print].

MajesTEC-1: Overall Response to Teclistamab



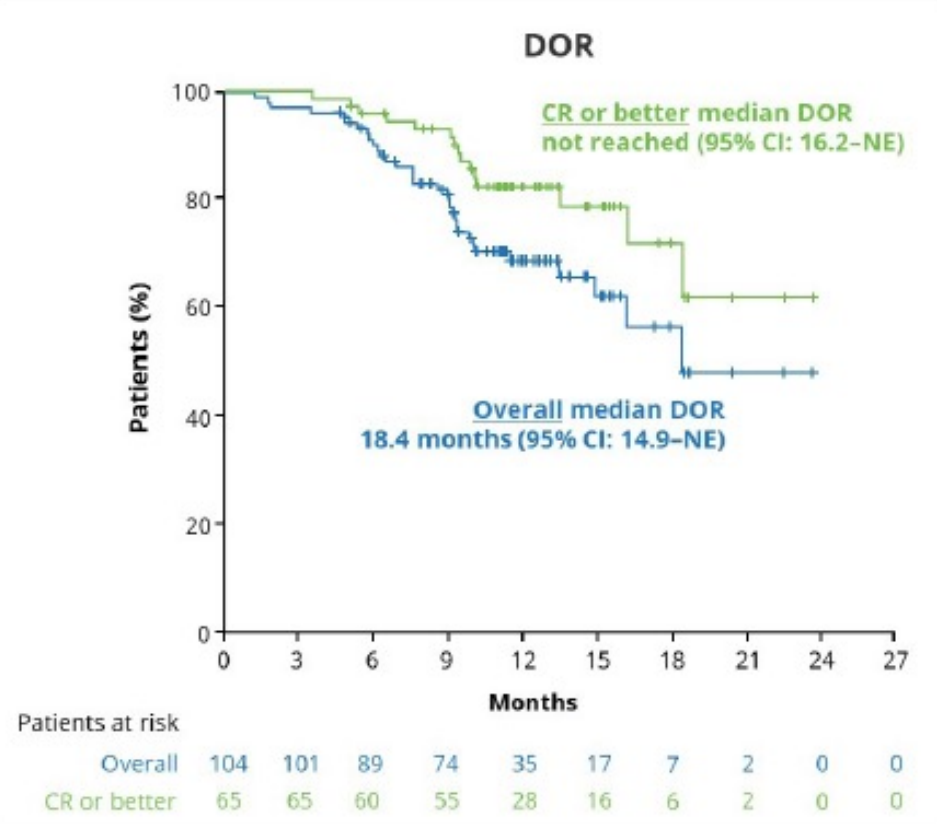
ORR of 63.0% (95% CI: 55.2–70.4) represents a substantial benefit for patients with triple-class exposed disease

- Median time to response (n=104)
  - First response: 1.2 months (range: 0.2–5.5)
  - Best response: 3.8 months (range: 1.1–16.8)
- MRD negativity rate at 10^{-5}[b]
  - 26.7% in the all-treated (N=165) patient population
    - 81.5% of MRD-evaluable patients (44 of 54) were MRD negative
  - Almost half (46.2%) of patients with ≥CR were MRD negative

Analysis cutoff date: March 16, 2022. [a]PR or better, IRC assessed, per IMWG 2016 criteria. [b]All MRD assessments were done by next-generation sequencing.
CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Nooka AK et al. ASCO 2022;Abstract 8007.

MajesTEC-1: Duration of Response



Overall median DOR of **18.4 months (95% CI: 14.9–NE),** and was not yet mature with data from 71 patients (68.3%) censored

12-month event-free rate:

- **Overall:** 68.5% (95% CI: 57.7–77.1)
- **Patients with CR or better:** 80.1% (95% CI: 67.6–88.2)

Analysis cutoff date: March 16, 2022.
CR, complete response; DOR, duration of response; NE, not estimable

Nooka AK et al. ASCO 2022;Abstract 8007.

MajesTEC-1: Overall Safety Profile

AEs ≥20%, n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Nonhematologic		
CRS	119 (72.1)	1 (0.6)
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Pyrexia	45 (27.3)	1 (0.6)
Injection site erythema	43 (26.1)	0 (0)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0 (0)
Cough	33 (20.0)	0 (0)

Teclistamab was well tolerated; discontinuations and dose reductions were infrequent

- 2 patients (1.2%) discontinued due to AEs (grade 3 adenoviral pneumonia; grade 4 PML)
- 1 patient had dose reduction at cycle 21
- The most common AEs were CRS and cytopenias
- Infections occurred in 126 (76.4%) patients (grade 3/4: 44.8%)
- 123 patients (74.5%) had evidence of hypogammaglobulinemia[a]
- There were 19 deaths due to AEs, including 12 COVID-19 deaths
  - 5 deaths due to teclistamab-related AEs:
    - COVID-19 (n=2)
    - Pneumonia (n=1)
    - Hepatic failure (n=1)
    - PML (n=1)

Analysis cutoff date: March 16, 2022. [a]Assessed by AE or lab values (postbaseline IgG level below 500 mg/dL).
AE, adverse event; CRS, cytokine release syndrome; IgG, immunoglobulin G; PML, progressive multifocal leukoencephalopathy

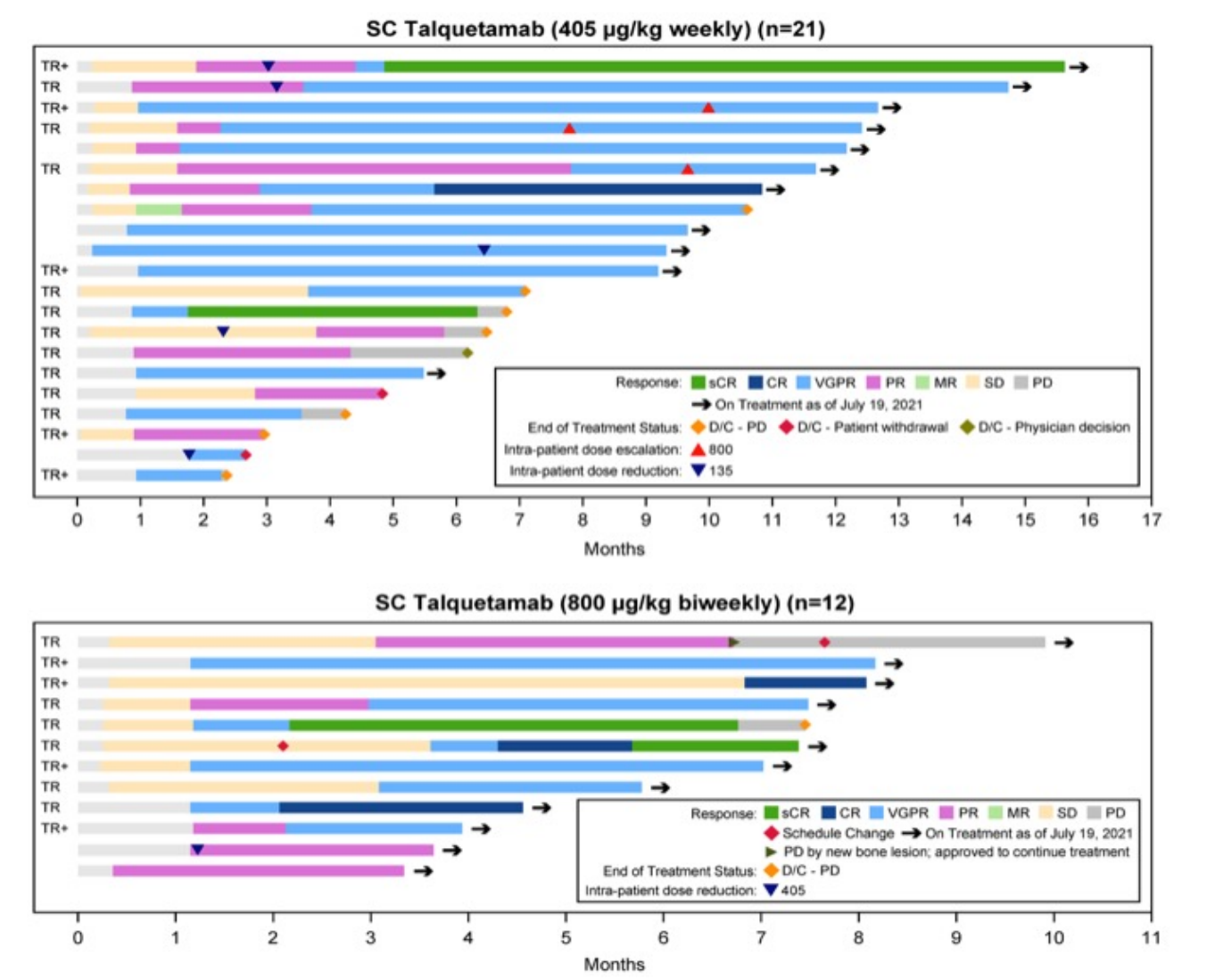
Nooka AK et al. ASCO 2022;Abstract 8007.

Updated Phase 1 Results from MonumenTAL-1: First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma

Krishnan AY et al.

ASH 2021;Abstract 158.

MonumenTAL-1: Duration of Response with Talquetamab for R/R MM



Krishnan AY et al. ASH 2021;Abstract 158.

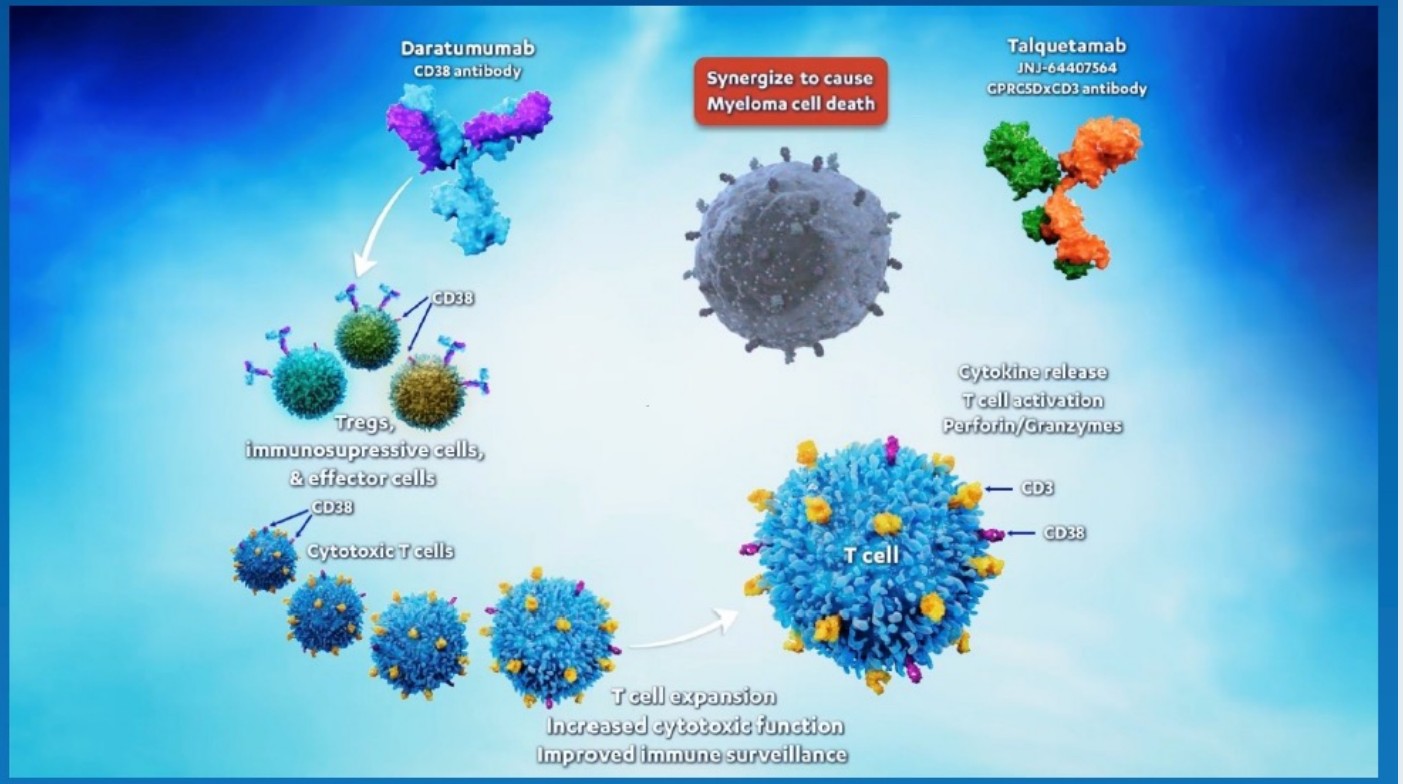
ASH 2021;Abstract 161

Phase 1b Results for Subcutaneous Talquetamab Plus Daratumumab in Patients With Relapsed/Refractory Multiple Myeloma

Ajai Chari[1*], Parameswaran Hari[2], Nizar Bahlis[3], Maria-Victoria Mateos[4], Niels WCJ van de Donk[5], Bhagirathbhai Dholaria[6], Alfred L Garfall[7], Hartmut Goldschmidt[8], K Martin Kortüm[9], Amrita Krishnan[10], Thomas Martin[11], Daniel Morillo[12], Albert Oriol[13], Donna Reece[14], Cesar Rodriguez[15], Paula Rodríguez-Otero[16], Jesús F San-Miguel[16], Saad Z Usmani[17], Raluca Verona[18], Shun Xin Wang Lin[18], Thomas J Prior[18], Mark Wade[18], Brendan Weiss[18], Jenna D Goldberg[19], Elham Askari[12]

Rationale for Combining Talquetamab and Daratumumab

- Daratumumab (dara) is a human IgG1κ mAb targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[1]
  - Dara monotherapy leads to T cell expansion and enhanced T cell cytotoxic potential[2]
  - Talquetamab (tal; JNJ-64407564) is a novel, first-in-class antibody that binds to GPRC5D and CD3 receptors, mediating T cell recruitment, activation, and subsequent lysis of GPRC5D+ MM cells[3]
- The combination of tal and dara has the potential to yield synergistic clinical efficacy
  - Preclinical studies showed the addition of dara enhanced tal-mediated lysis of MM cells[4]



Chari A et al. ASH 2021;Abstract 161.

RTP RESEARCH TO PRACTICE

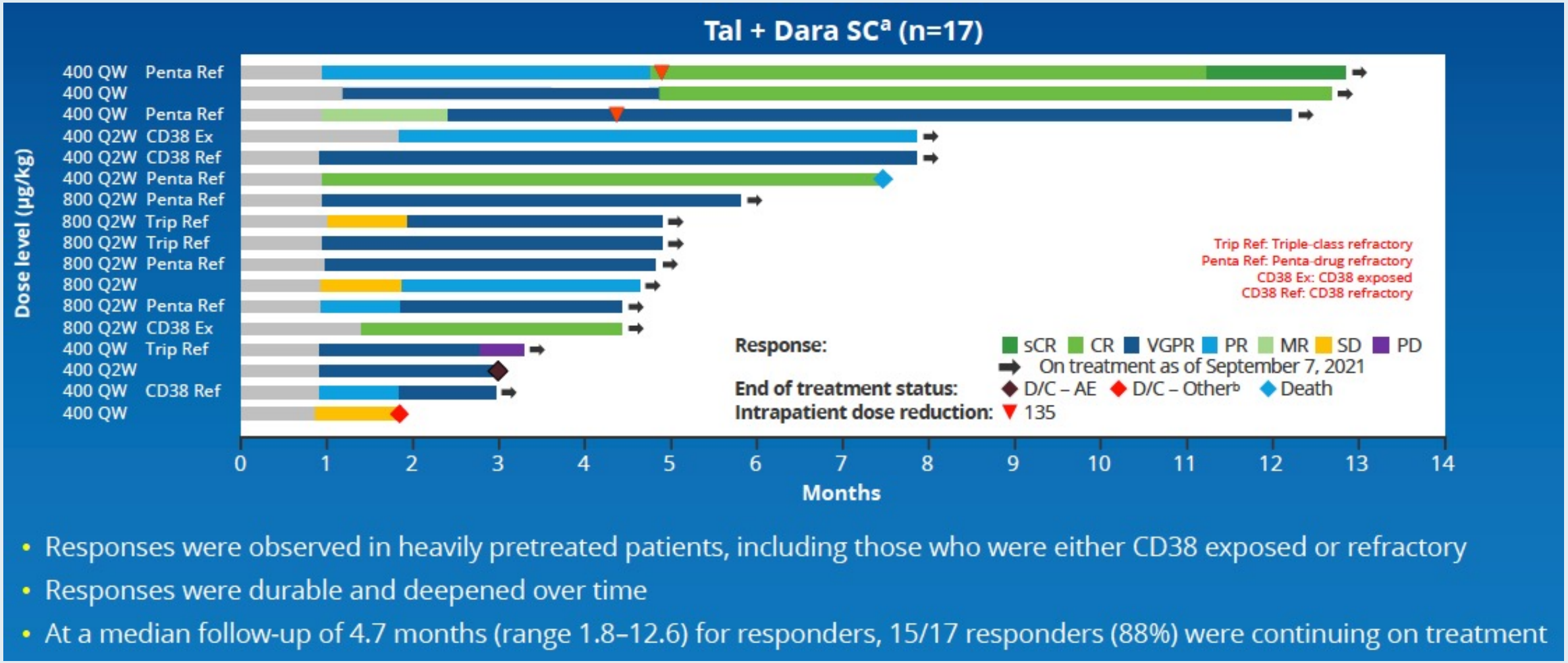
TRIMM-2: Overall Response

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

Chari A et al. ASH 2021;Abstract 161.

TRIMM-2: Duration of Response



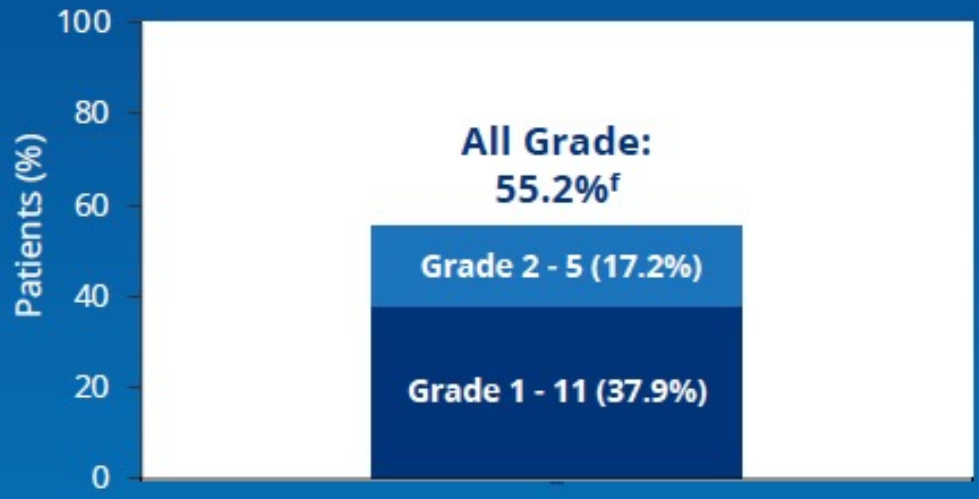
- Responses were observed in heavily pretreated patients, including those who were either CD38 exposed or refractory
- Responses were durable and deepened over time
- At a median follow-up of 4.7 months (range 1.8–12.6) for responders, 15/17 responders (88%) were continuing on treatment

Chari A et al. ASH 2021;Abstract 161.

TRIMM-2: Cytokine Release Syndrome (CRS)

Parameter	Tal + Dara SC[a] n=29
Patients with CRS, n (%)	16 (55.2)
Time to onset (days)[b], median (range)	2 (1–4)
Duration (days), median (range)	2 (1–6)
Patients who received supportive measures[c], n (%)	15 (51.7)
Tocilizumab[d]	10 (34.5)
Steroids	1 (3.4)
Oxygen	0

Maximum CRS Grade[e]



- **No grade 3/4 CRS events were observed**
  - All but 1 event of CRS occurred with step-up doses
- **CRS resolved in all patients, with no d/c due to CRS**
  - Only 1 patient received 2 doses of tocilizumab for a single CRS event[g]

Chari A et al. ASH 2021;Abstract 161.

Initial Safety Results for MagnetisMM-3: A Phase 2 Trial of Elranatamab, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients (pts) with Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Lesokhin AM et al.

ASCO 2022;Abstract 8006 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

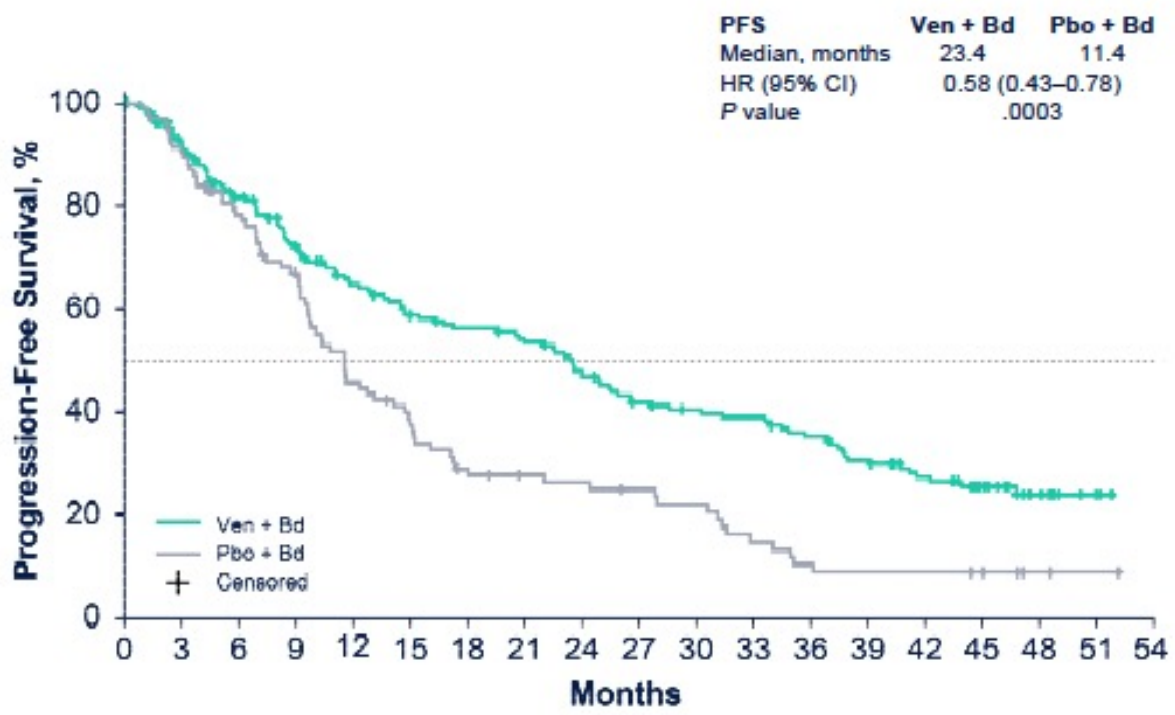
ASH 2021;Abstract 84.

Final Overall Survival Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination With Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma

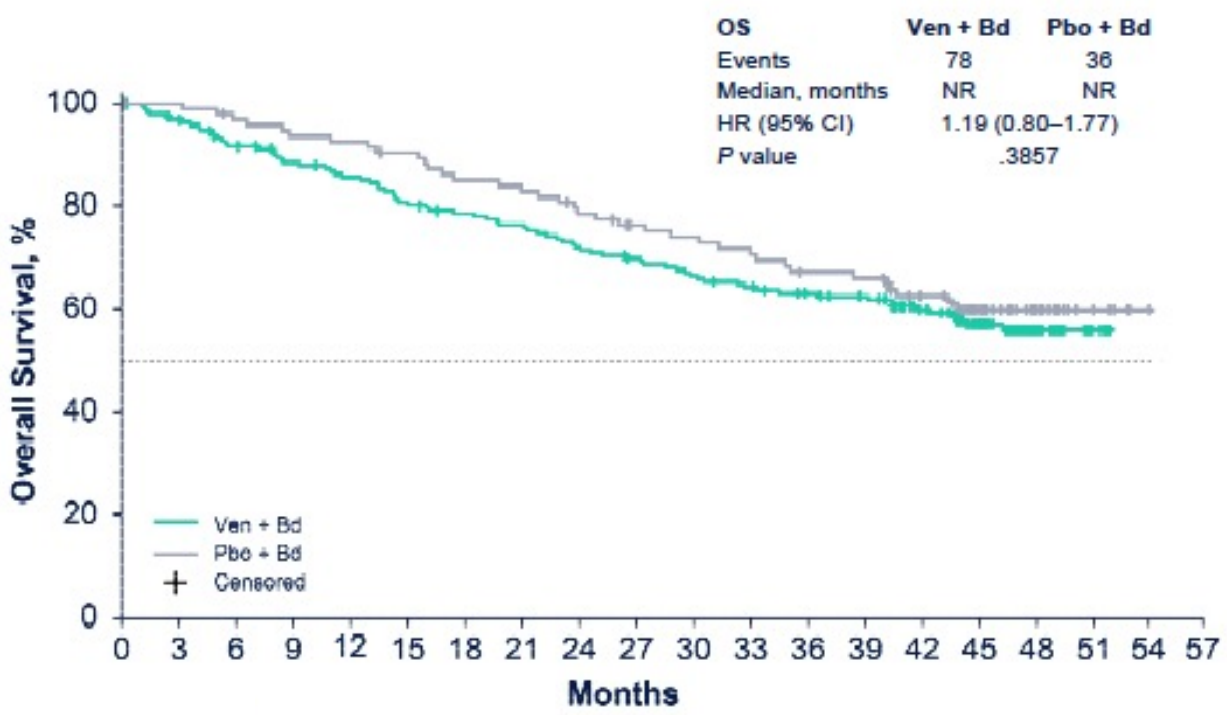
Shaji K. Kumar,[1] Simon J. Harrison,[2] Michele Cavo,[3] Javier de la Rubia,[4] Rakesh Popat,[5] Cristina Gasparetto,[6] Vania Hungria,[7] Hans Salwender,[8] Kenshi Suzuki,[9] Inho Kim,[10] Maika Onishi,[11] Grace Ku,[11] Rajvineeth Pothacamury,[12] Vasudha Sehgal,[12] Abdullah Masud,[12] Jeremy A. Ross,[12] Edyta Dobkowska,[13] and Philippe Moreau[14]

BELLINI: Updated Survival Results

Investigator-Assessed PFS in All Patients



OS in All Patients

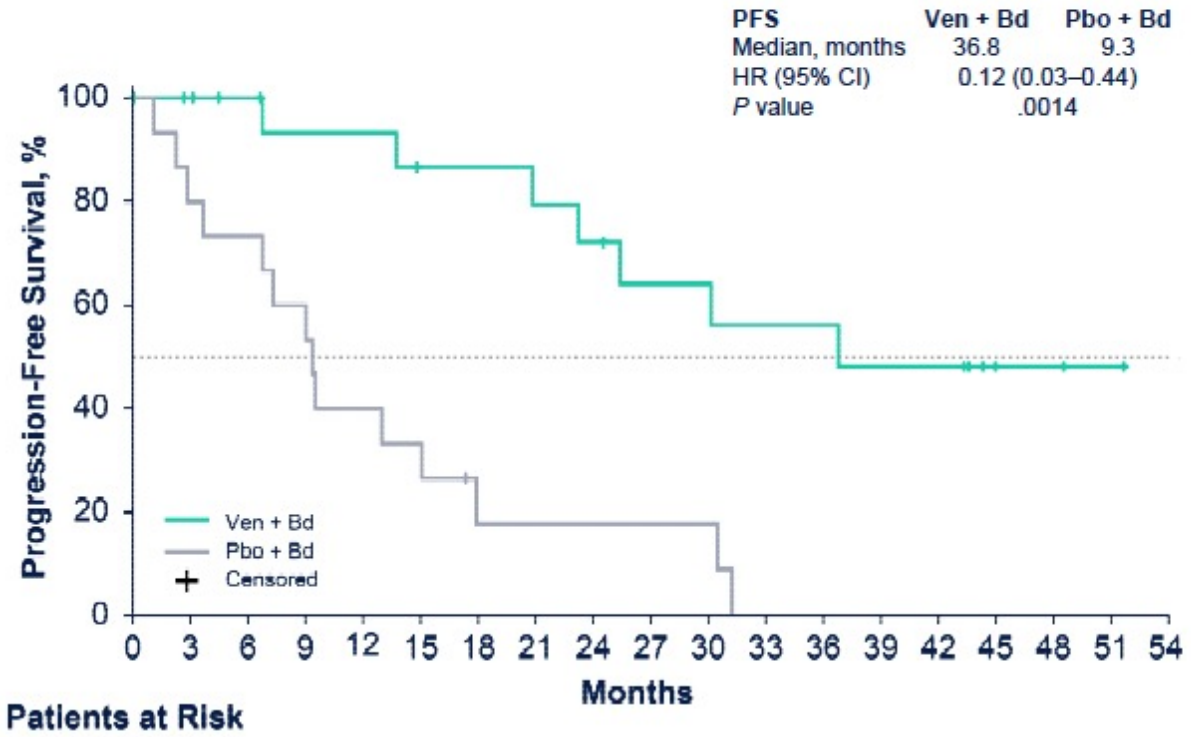


Kumar SK et al. ASH 2021;Abstract 84.

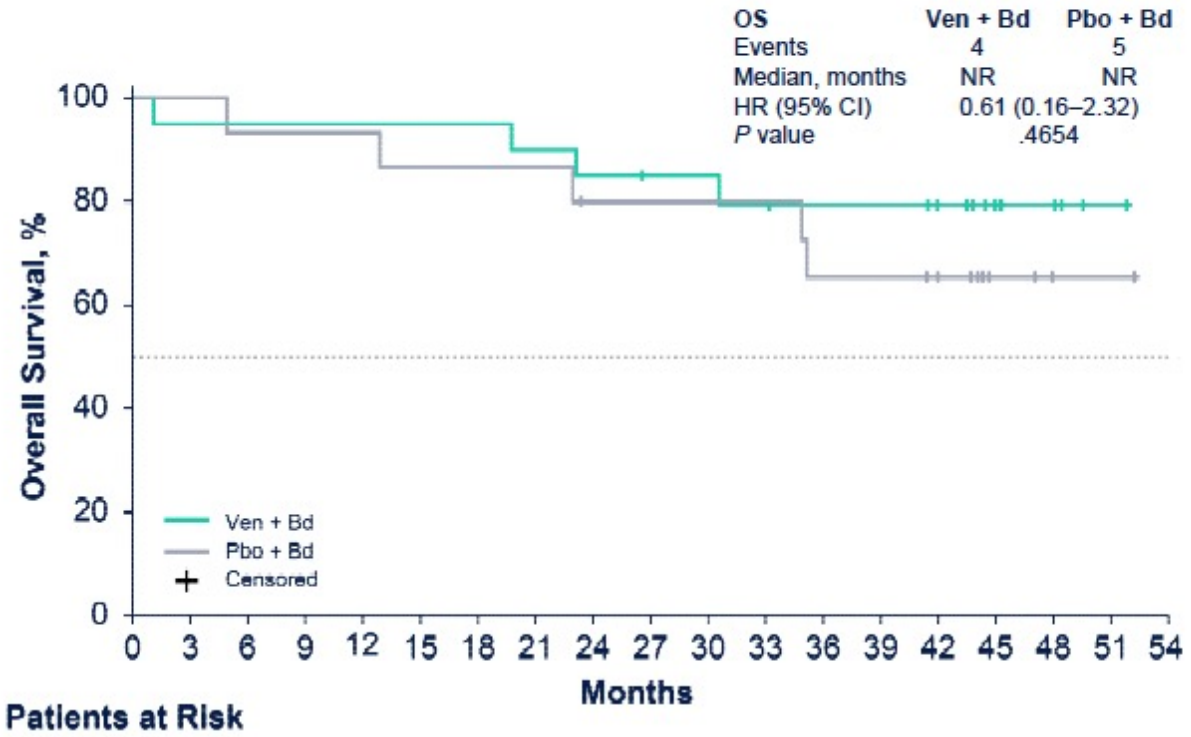
RTP RESEARCH TO PRACTICE

BELLINI: Updated Survival Results for Patients with t(11;14)

Investigator-Assessed PFS in Patients With t(11;14)



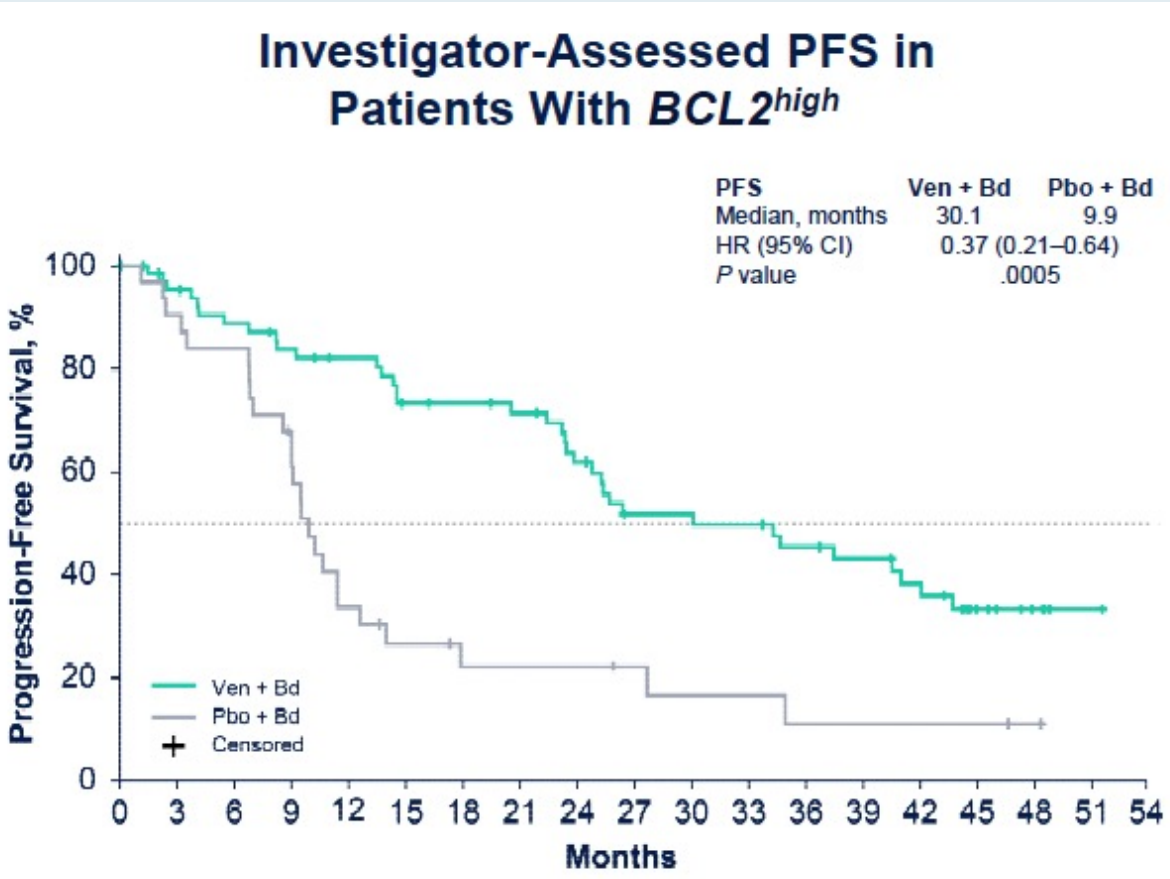
OS in Patients With t(11;14)

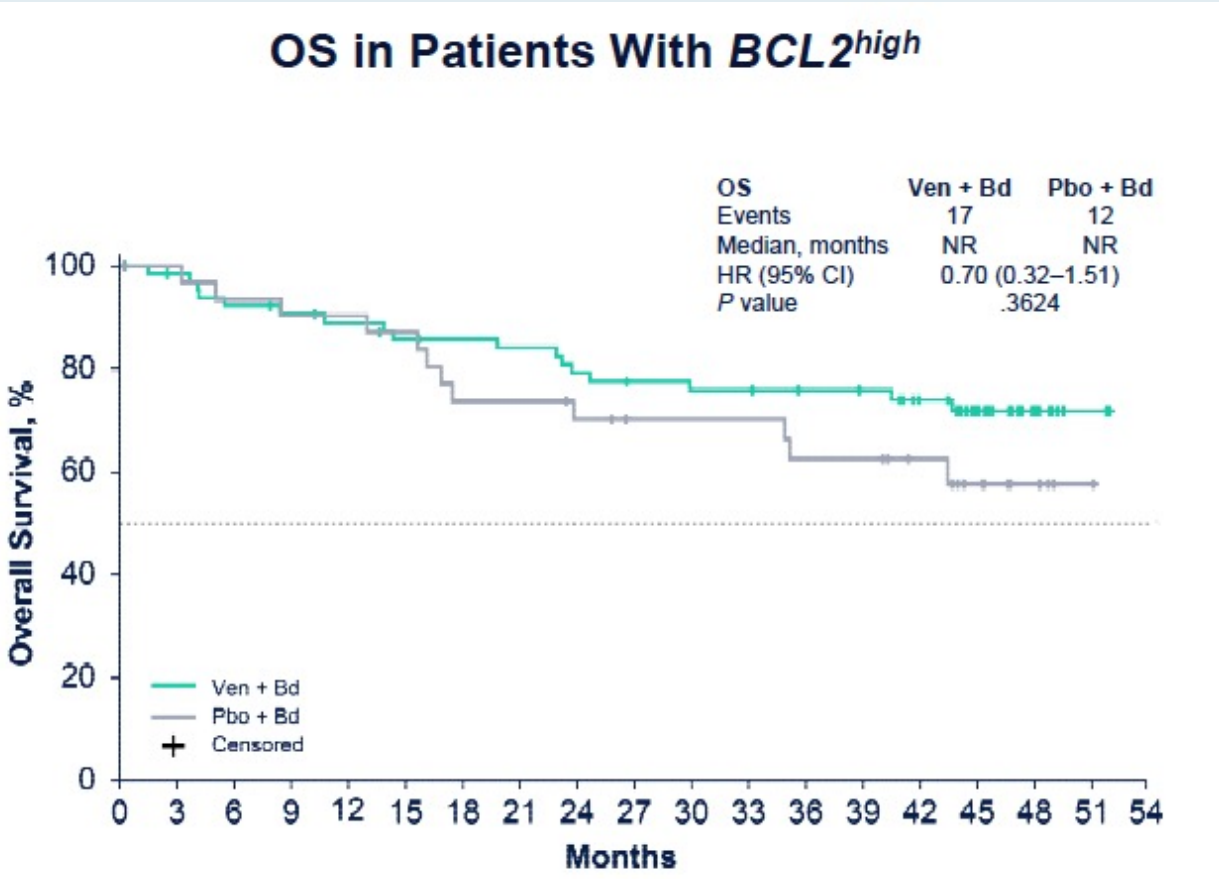


Kumar SK et al. ASH 2021;Abstract 84.

RTP RESEARCH TO PRACTICE

BELLINI: Updated Survival Results for Patients with High Bcl-2 Expression





Kumar SK et al. ASH 2021;Abstract 84.

RTP RESEARCH TO PRACTICE

Case 6 — Robert Z Orlowski, MD, PhD

- **A now 79-year-old M who presented initially in 06/2016 with symptomatic anemia and generalized osteopenia**
- **Outside work-up showed R-ISS Stage II IgG kappa myeloma with normal cytogenetics and hyperdiploidy by FISH**
- **Felt to be symptomatic due to anemia and osteopenia that was out of proportion to age**

Case 6 — Robert Z Orlowski, MD, PhD

Initial therapies

- **Induction therapy with RVd lite x 5 cycles producing a PR**
- **Followed by stem cell collection, and then adjusted dose Mel + ASCT**
- **Maintenance on study of elotuzumab/lenalidomide, which was later held/discontinued due to imbalance in favor of watchful waiting**

Case 6 — Robert Z Orlowski, MD, PhD

Subsequent therapies

- **At PD, started on ixazomib/dexamethasone with later addition of daratumumab, but combo stopped due to PD**
- **Carfilzomib/dexamethasone tried but was poorly tolerated**
- **Repeat BM was performed which showed t(11;14) in 96% of cells, 38% of cells with +CKS1B (3 copies)**

Case 6 — Robert Z Orlowski, MD, PhD

Switch to venetoclax

- **Venetoclax/dexamethasone started with escalation of ven dose up to 1,200 mg**
- **Produced a rapid decline in the M-protein from 3.1 to 1.3 within 4 months**
- **Venetoclax/dexamethasone tolerated well and then continued with maintenance of PR**

Appendix of Key Data Sets

FDA Approves Daratumumab and Hyaluronidase-fihj with Carfilzomib and Dexamethasone for R/R MM

Press Release – November 30, 2021

"The Food and Drug Administration approved daratumumab + hyaluronidase-fihj and carfilzomib plus dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

Efficacy was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. This cohort enrolled 66 patients with relapsed or refractory multiple myeloma who received at least one prior line of therapy. Patients received daratumumab + hyaluronidase-fihj 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously in combination with carfilzomib (20/70 mg/m^2 once weekly regimen) and dexamethasone.

The main efficacy outcome measure was overall response rate (ORR). The ORR was 84.8%. At a median follow-up of 9.2 months, the median duration of response had not been reached and an estimated 85.2% maintained response for at least 6 months and 82.5% maintained response for at least 9 months."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-darzalex-faspro-kyprolis-and-dexamethasone-multiple-myeloma

RTP RESEARCH TO PRACTICE

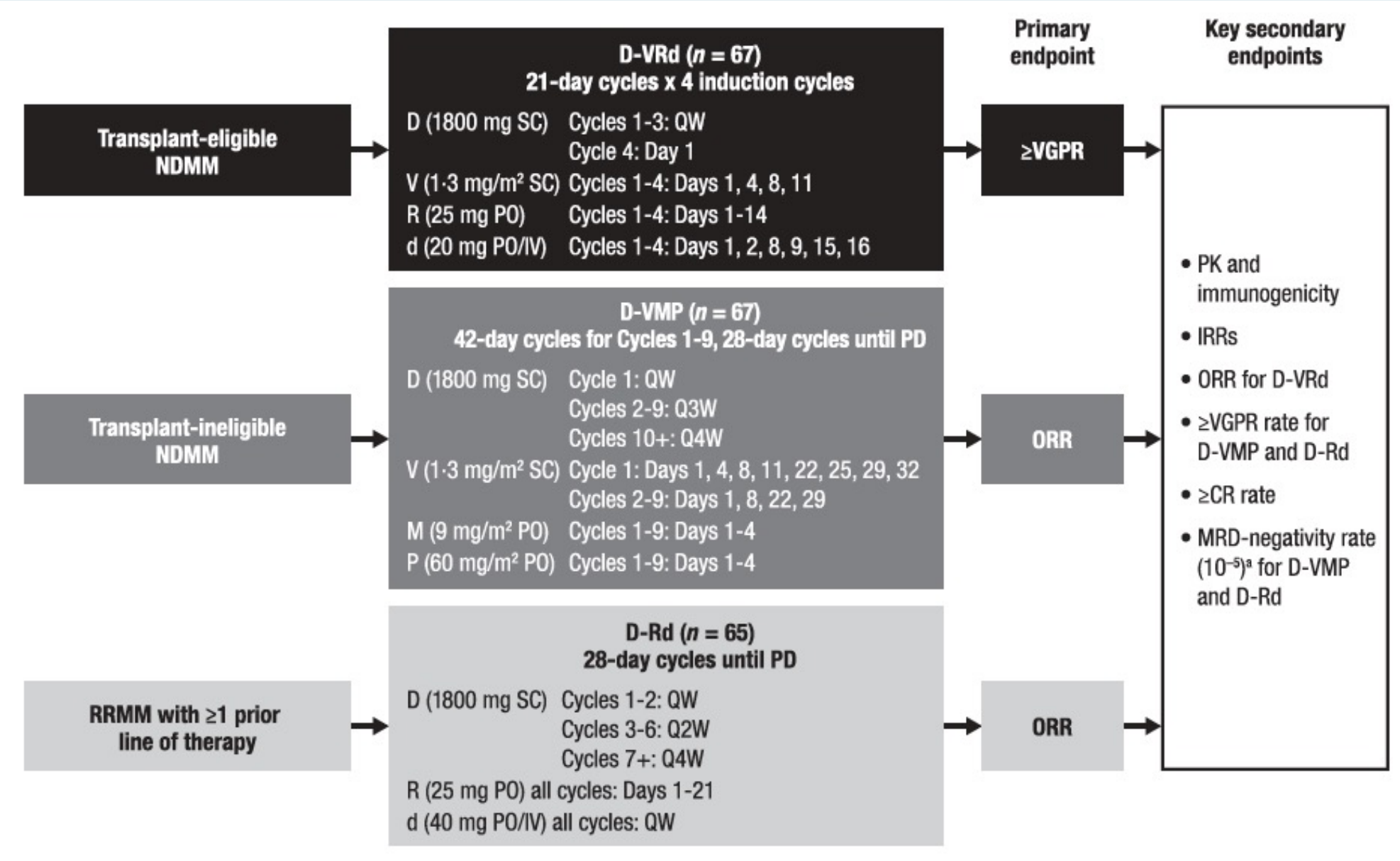
bjh research paper

Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label Phase II study

Ajai Chari,[1] Paula Rodriguez-Otero,[2] Helen McCarthy,[3] Kenshi Suzuki,[4] Vania Hungria,[5] Anna Sureda Balari,[6] Aurore Perrot,[7] Cyrille Hulin,[8] Hila Magen,[9] Shinsuke Iida,[10] Vladimir Maisnar,[11] Lionel Karlin,[12] Ludek Pour,[13] Dolly A. Parasrampuria,[14] Tara Masterson,[14] Michele Kosh,[14] Shiyi Yang,[14] Maria Delioukina,[14] Ming Qi,[14] Robin Carson[14] and Cyrille Touzeau[15]

Br J Haematol 2021;192(5):869-78.

PLEIADES: Phase II Trial Design



Chari A et al. *Br J Haematol* 2021;192(5):869-78.

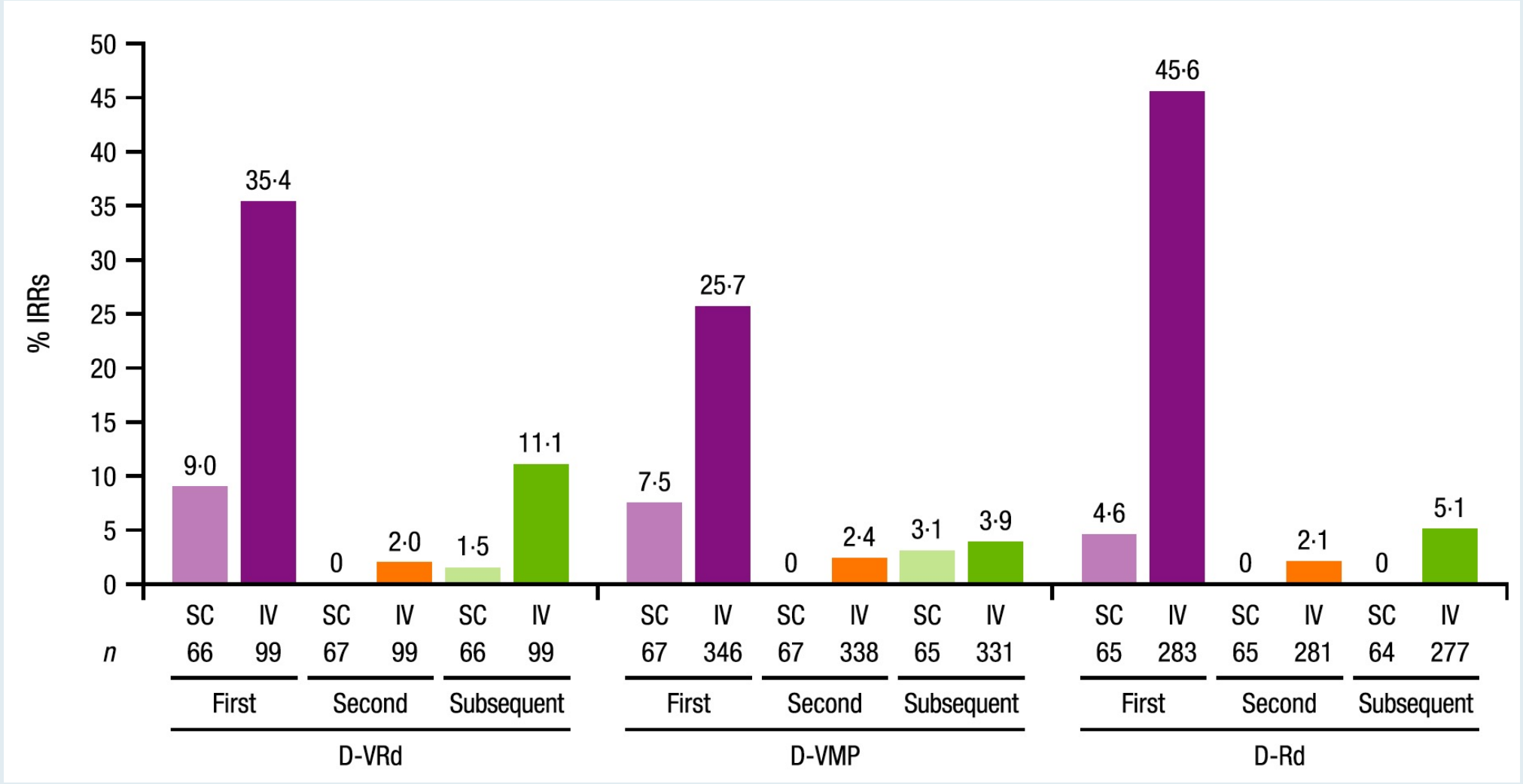
PLEIADES: Response Summary

	D-VRd (n = 67)		D-VMP (n = 67)		D-Rd (n = 65)	
	Transplant-eligible NDMM		Transplant-ineligible NDMM		RRMM with ≥1 prior line of therapy	
	Primary analysis Median follow-up, 3·9 months		Clinical cut-off Median follow-up, 14·3 months		Clinical cut-off Median follow-up, 14·7 months	
Response	n (%)	90% CI	n (%)	90% CI	n (%)	90% CI
Overall response	65 (97·0)	90·9–99·5	60 (89·6)	81·3–95·0	61 (93·8)	86·5–97·9
Stringent CR	6 (9·0)	4·0–16·9	13 (19·4)	11·9–29·1	12 (18·5)	11·0–28·2
CR	5 (7·5)	3·0–15·1	19 (28·4)	19·4–38·8	13 (20·0)	12·3–29·9
VGPR	37 (55·2)	44·5–65·6	20 (29·9)	20·7–40·4	26 (40·0)	29·8–51·0
PR	17 (25·4)	16·9–35·6	8 (11·9)	6·1–20·5	10 (15·4)	8·6–24·7
MR‡	–	–	–	–	1 (1·5)	0·1–7·1
Stable disease	1 (1·5)	0·1–6·9	5 (7·5)	3·0–15·1	1 (1·5)	0·1–7·1
Response could not be evaluated	1 (1·5)	0·1–6·9	2 (3·0)	0·5–9·1	2 (3·1)	0·5–9·4
≥CR	11 (16·4)	9·5–25·7	32 (47·8)	37·2–58·5	25 (38·5)	28·3–49·4
≥VGPR	48 (71·6)	61·2–80·6	52 (77·6)	67·6–85·7	51 (78·5)	68·4–86·5

Chari A et al. *Br J Haematol* 2021;192(5):869-78.

RTP RESEARCH TO PRACTICE

Infusion-Related Reactions with Subcutaneous versus Intravenous Daratumumab: Cross-Study Comparison



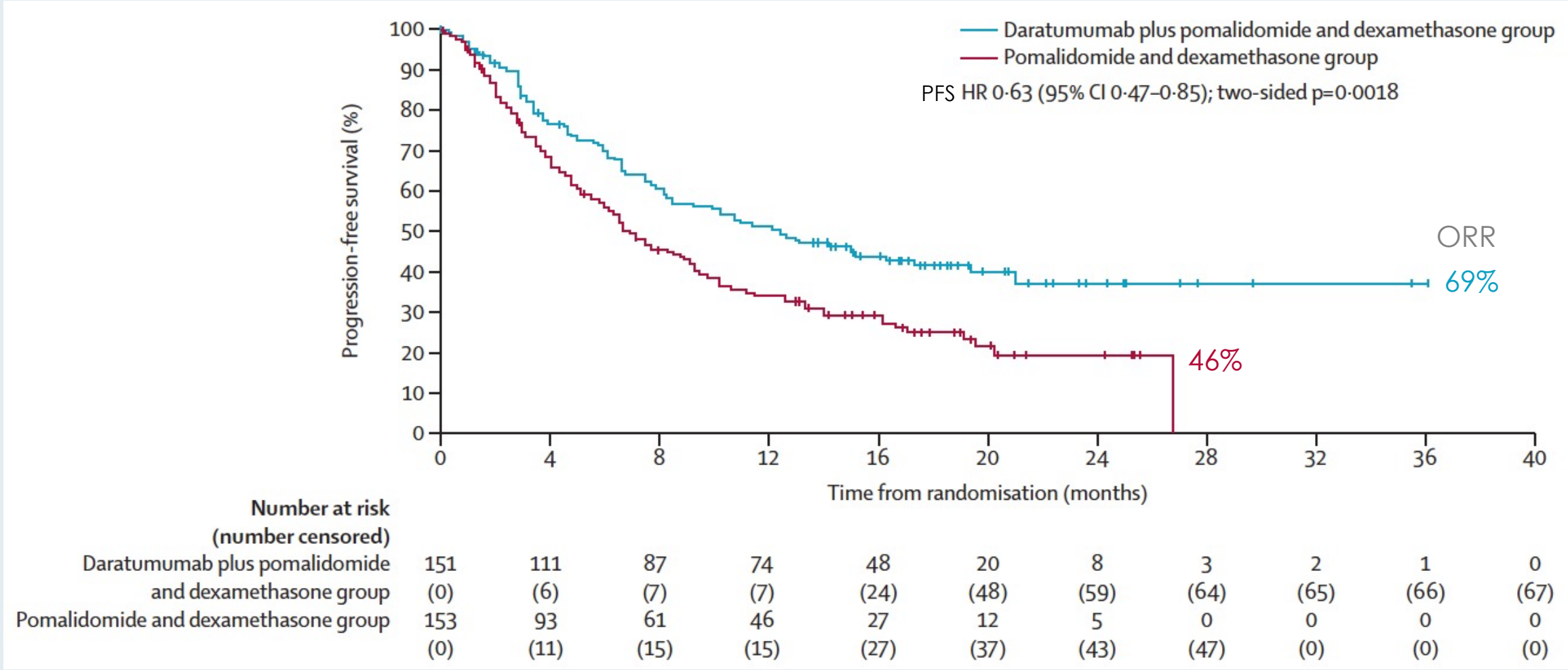
Chari A et al. *Br J Haematol* 2021;192(5):869-78.

Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial

*Meletios A Dimopoulos, Evangelos Terpos, Mario Boccadoro, Sosana Delimpasi, Meral Beksac, Eirini Katodritou, Philippe Moreau, Luca Baldini, Argiris Symeonidis, Jelena Bila, Albert Oriol, Maria-Victoria Mateos, Hermann Einsele, Ioannis Orfanidis, Tahamtan Ahmadi, Jon Ukropec, Tobias Kampfenkel, Jordan M Schecter, Yanping Qiu, Himal Amin, Jessica Vermeulen, Robin Carson, Pieter Sonneveld, for the APOLLO Trial Investigators**

Lancet Oncol 2021; 22: 801–12

APOLLO: PFS in the ITT Population and Response

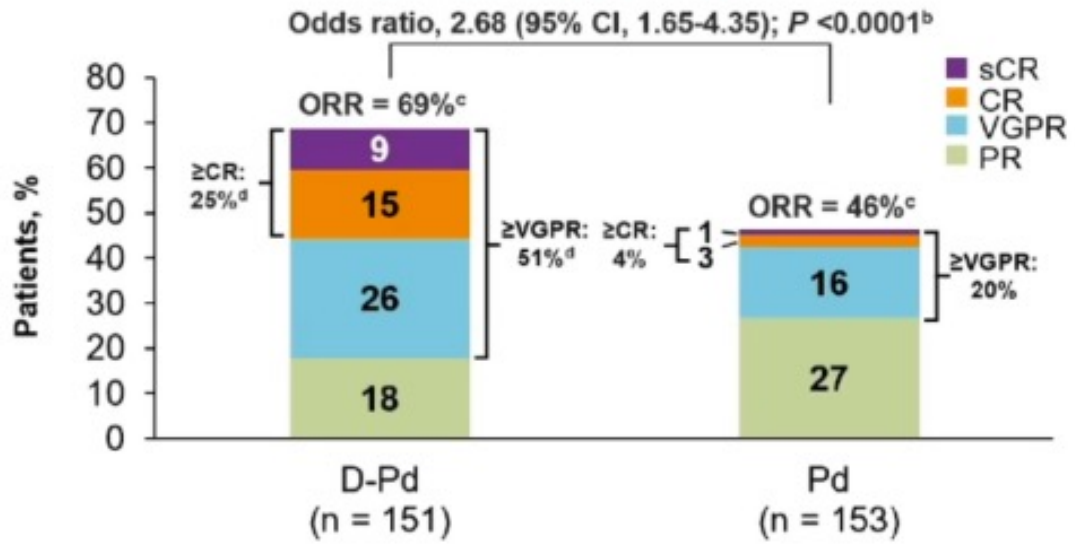


Number at risk (number censored)											
Daratumumab plus pomalidomide and dexamethasone group	151 (0)	111 (6)	87 (7)	74 (7)	48 (24)	20 (48)	8 (59)	3 (64)	2 (65)	1 (66)	0 (67)
Pomalidomide and dexamethasone group	153 (0)	93 (11)	61 (15)	46 (15)	27 (27)	12 (37)	5 (43)	0 (47)	0 (0)	0 (0)	0 (0)

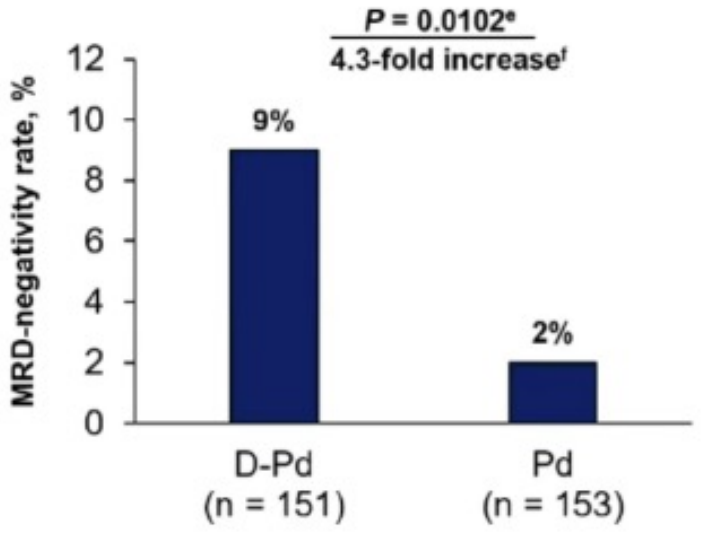
Dimopoulos MA et al. *Lancet Oncol* 2021;22(6):801-12.

Depth of Response[a]

Hematologic response



MRD negativity



ORR, ≥VGPR rate, ≥CR rate, and MRD-negativity rate were significantly higher with D-Pd versus Pd

PR, partial response; IMWG, International Myeloma Working Group; ITT, intent-to-treat. [a]Responses were assessed by computer algorithm in accordance with IMWG recommendations and included patients in the ITT population. [b]*P* value was calculated from the 2-sided Cochran–Mantel–Haenszel chi-square test, stratified for ISS stage (I, II, III) and number of lines of prior therapy (1, 2-3, ≥4). [c]Values may not add to total due to rounding. [d]*P* <0.0001. [e]*P* value (2-sided) was calculated using the Fisher's exact test. [f]Non-rounded values are 8.6% and 2.0%.

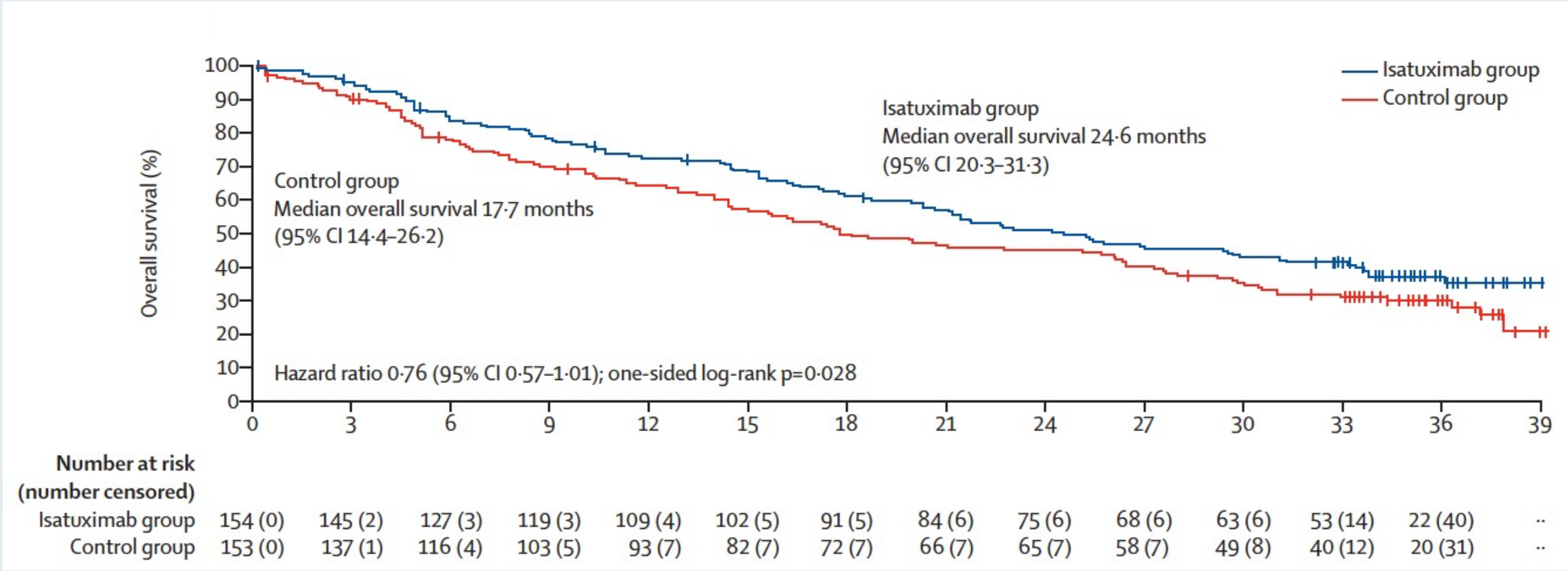
Dimopoulos MA et al. ASH 2020;Abstract 412.

Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study

Paul G Richardson, Aurore Perrot, Jesus San-Miguel, Meral Beksac, Ivan Spicka, Xavier Leleu, Fredrik Schjesvold, Philippe Moreau, Meletios A Dimopoulos, Jeffrey Shang-Yi Huang, Jiri Minarik, Michele Cavo, H Miles Prince, Laure Malinge, Franck Dubin, Helgi van de Velde, Kenneth C Anderson

Lancet Oncol 2022; 23: 416–27

ICARIA-MM: Overall Survival

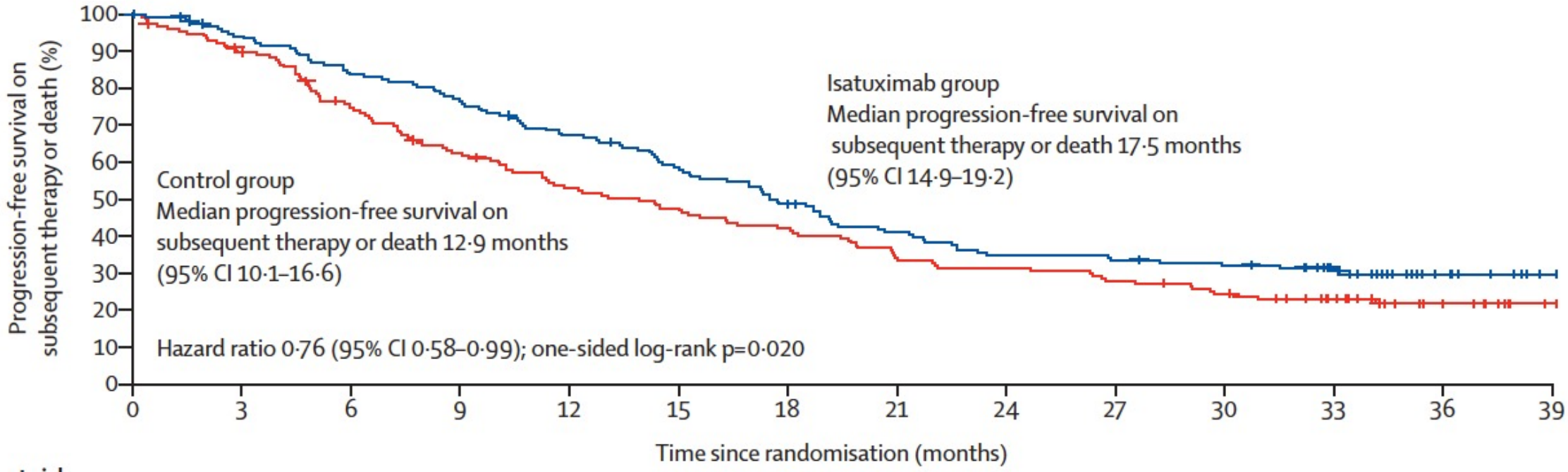


Number at risk (number censored)														
Isatuximab group	154 (0)	145 (2)	127 (3)	119 (3)	109 (4)	102 (5)	91 (5)	84 (6)	75 (6)	68 (6)	63 (6)	53 (14)	22 (40)	..
Control group	153 (0)	137 (1)	116 (4)	103 (5)	93 (7)	82 (7)	72 (7)	66 (7)	65 (7)	58 (7)	49 (8)	40 (12)	20 (31)	..

Richardson PD et al. *Lancet Oncol* 2022;23(3):416-27.

RTP RESEARCH TO PRACTICE

ICARIA-MM: Median PFS on Subsequent Therapy or Death



Number at risk (number censored)													
Isatuximab group	154 (0)	141 (4)	125 (4)	114 (4)	99 (5)	85 (6)	70 (6)	57 (8)	48 (8)	46 (8)	43 (9)	32 (18)	13 (36)	..
Control group	153 (0)	135 (2)	109 (5)	90 (6)	75 (7)	66 (7)	59 (7)	46 (7)	43 (7)	38 (7)	32 (8)	23 (15)	11 (26)	..

Richardson PD et al. *Lancet Oncol* 2022;23(3):416-27.

ATLAS: A Phase 3 Randomized Trial of Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide Alone After Stem-Cell Transplant for Multiple Myeloma

Dytfeld D et al.

ASCO 2022;Abstract 8001 (Oral).

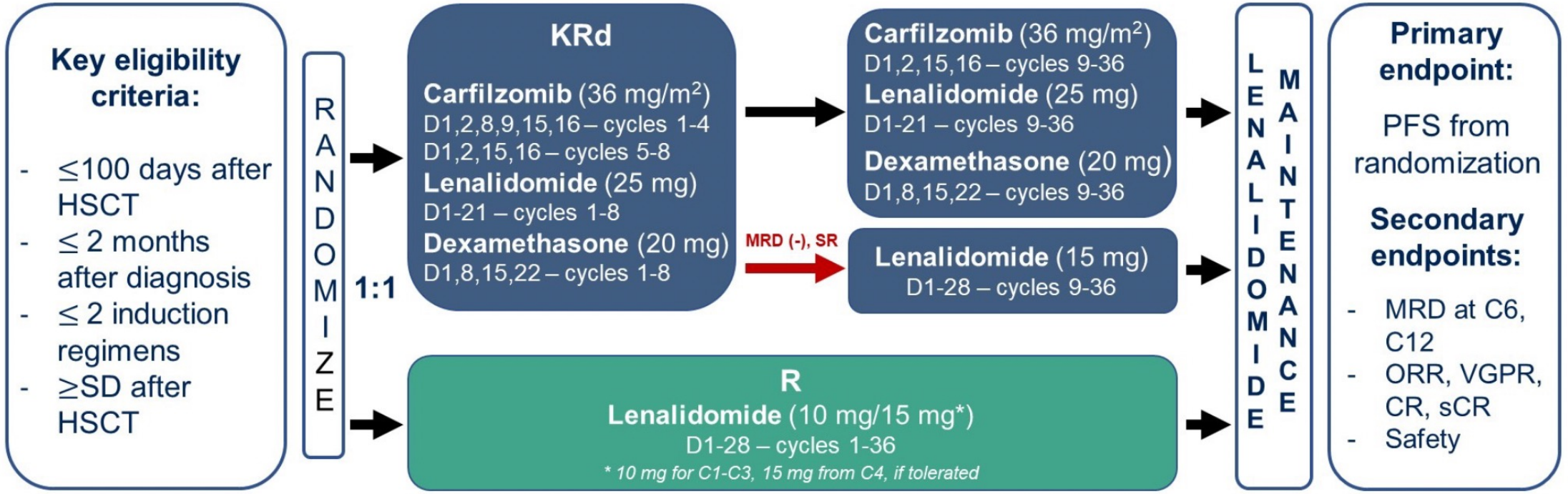
June 5, 2022

9:00 AM – 12:00 PM EDT

RTP
RESEARCH
TO PRACTICE

Study Design

Multicenter, randomized, open-label, phase 3 study



Stratification factors:

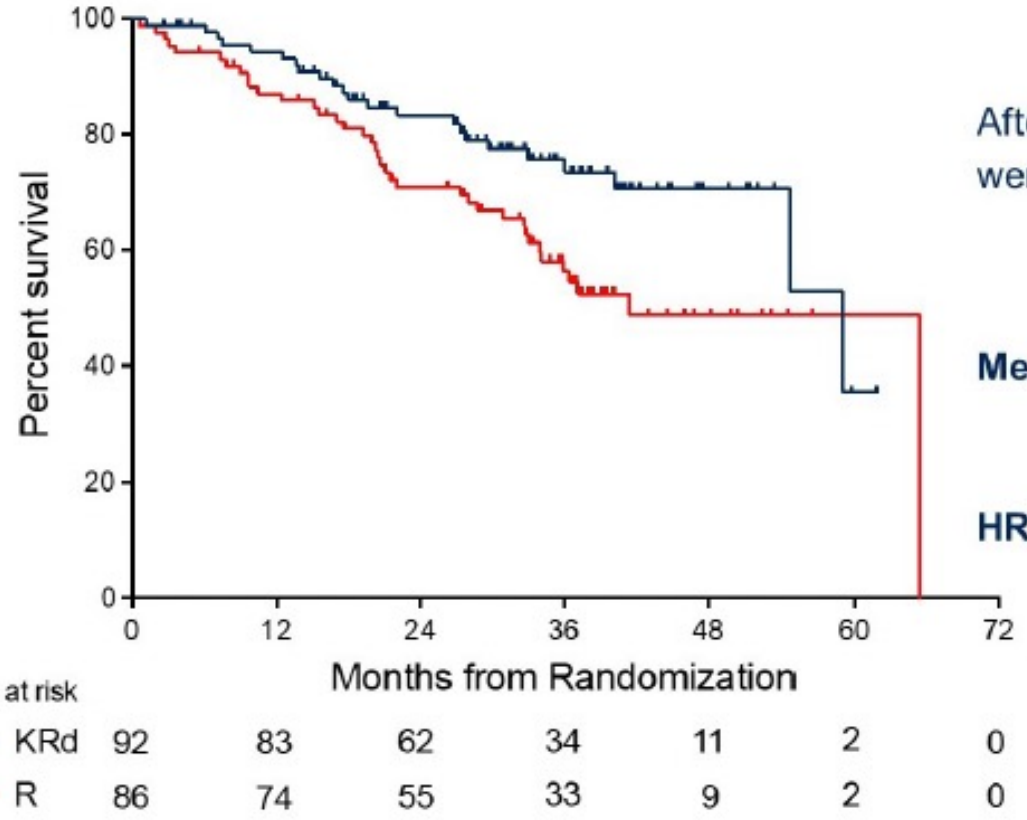
- post-transplant response (≥VGPR vs <VGPR)
- standard (SR) vs high risk (HR) cytogenetics

KRd pts with SR cytogenetics having reached IMWG MRD negativity[1] after C6 converted to R alone after C8

[1]*Kumar et al, Lancet Oncol 2016; 17:e328-46*

Dytfeld D et al. ASCO 2022;Abstract 8001 (Oral).

Progression Free Survival



After median follow-up of 33.8 months there were **61 PFS events:**

- **23 in the KRd arm**
- **38 in the R arm**

Median PFS:

KRd 59.0 months (95% CI 52.5-NR)

R 41.1 months (95% CI 33.4-65.4)

HR 0.56 (95% CI 0.34-0.93); **p=0.026**

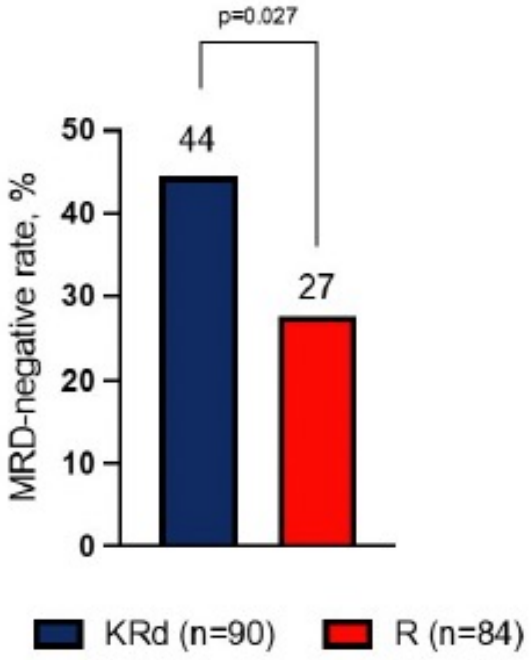
HR – hazard ratio (log rank)

This early analysis was at 60% of expected 105 events for primary analysis, for which the p-value criterion for significance (p=0.05) was not adjusted for the interim nature of the comparison. Patients will be followed up until the primary analysis which will be adjusted accordingly.

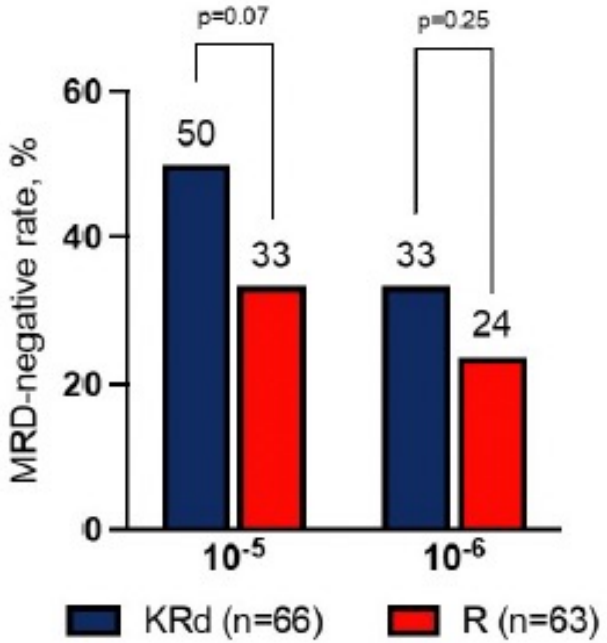
Dytfeld D et al. ASCO 2022;Abstract 8001 (Oral).

Minimal Residual Disease

MRD by IMWG* at cycle 6



MRD by NGS** at cycle 6



***MRD negativity as per IMWG definition[1]:** Minimum sensitivity 10^{-5} or higher by NGS and if not available by MFC, at least complete response

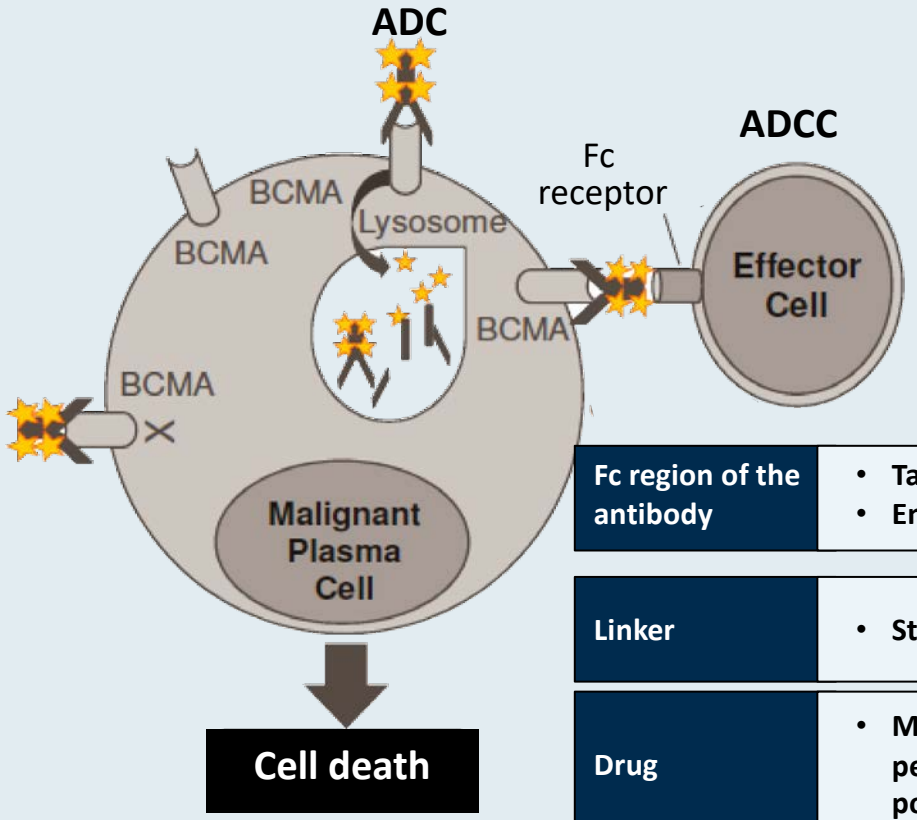
****MRD by NGS:** Using clonoSEQ (LoD 6.8 x 10^{-7} with input of 20 micrograms DNA)

[1]*Kumar et al, Lancet Oncol 2016; 17:e328-46*

Dytfeld D et al. ASCO 2022;Abstract 8001 (Oral).

Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

- B-cell maturation antigen (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent monomethyl auristatin-F (MMAF) via a stable, protease-resistant maleimidocaproyl linker



Fc region of the antibody	• **Target specific** • **Enhanced ADCC**
Linker	• **Stable in circulation**
Drug	• **MMAF (non cell permeable, highly potent auristatin)**

Mechanisms of action:

- Antibody-drug conjugate (ADC) mechanism
- Antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism
- Immunogenic cell death
- BCMA receptor signaling inhibition

Tai YT et al. *Blood* 2014;123(20):3128-38.

RTP RESEARCH TO PRACTICE

Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study

Sagar Lonial, MD [1]; Hans C. Lee, MD[2]; Ashraf Badros, MD [3]; Suzanne Trudel, MD[4]; Ajay K. Nooka, MD [1]; Ajai Chari, MD [5]; Al-Ola Abdallah, MD[6]; Natalie Callander, MD[7]; Douglas Sborov, MD[8]; Attaya Suvannasankha, MD[9]; Katja Weisel, MD[10]; Peter M. Voorhees, MD[11]; Lynsey Womersley, MSc[12]; January Baron, MS[13]; Trisha Piontek, BSN[13]; Eric Lewis, MD[14]; Joanna Opalinska, MD[13]; Ira Gupta, MD[13]; and Adam D. Cohen, MD[15]

Cancer 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

DREAMM-2: Single-Agent Belantamab Mafodotin Efficacy Outcomes

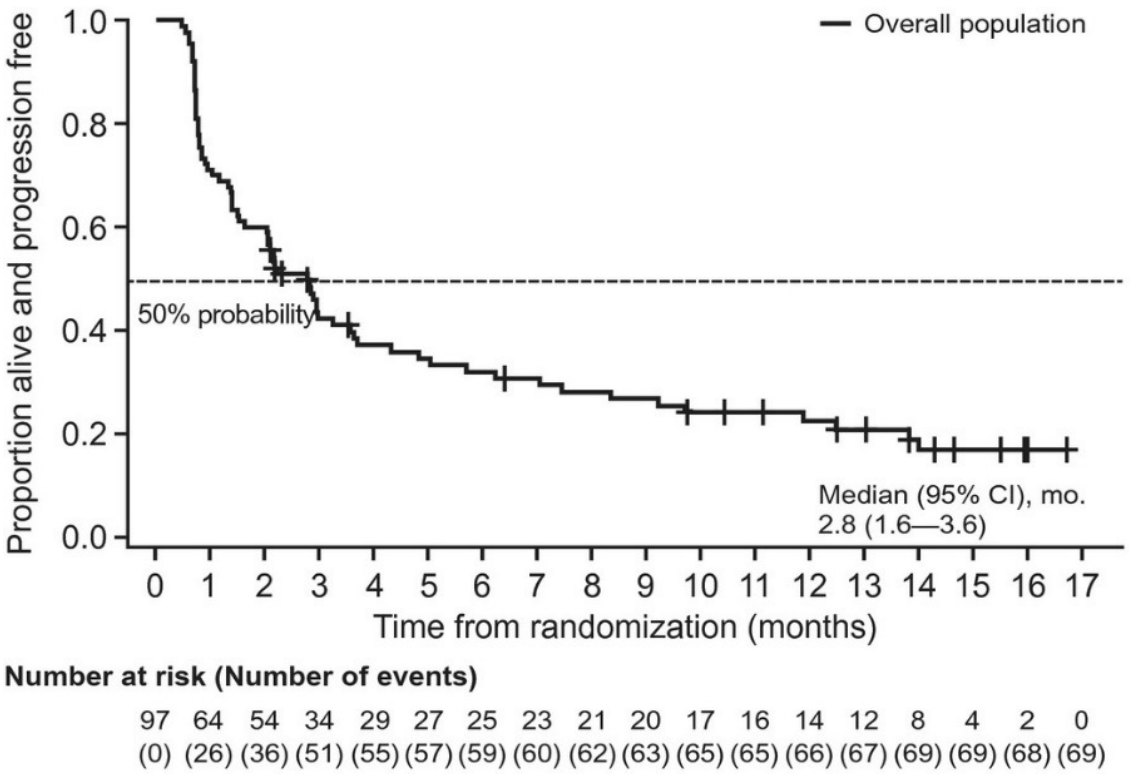
	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	32 (21.7-43.6)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.8 (1.6-3.6)	2.2 (1.2-3.6)
Probability of PFS at 6 months, % (95% CI estimates)	35 (20-50)	30 (17-43)

ORR = overall response rate; CI = confidence interval; DoR = duration of response; NR = not reached; PFS = progression-free survival

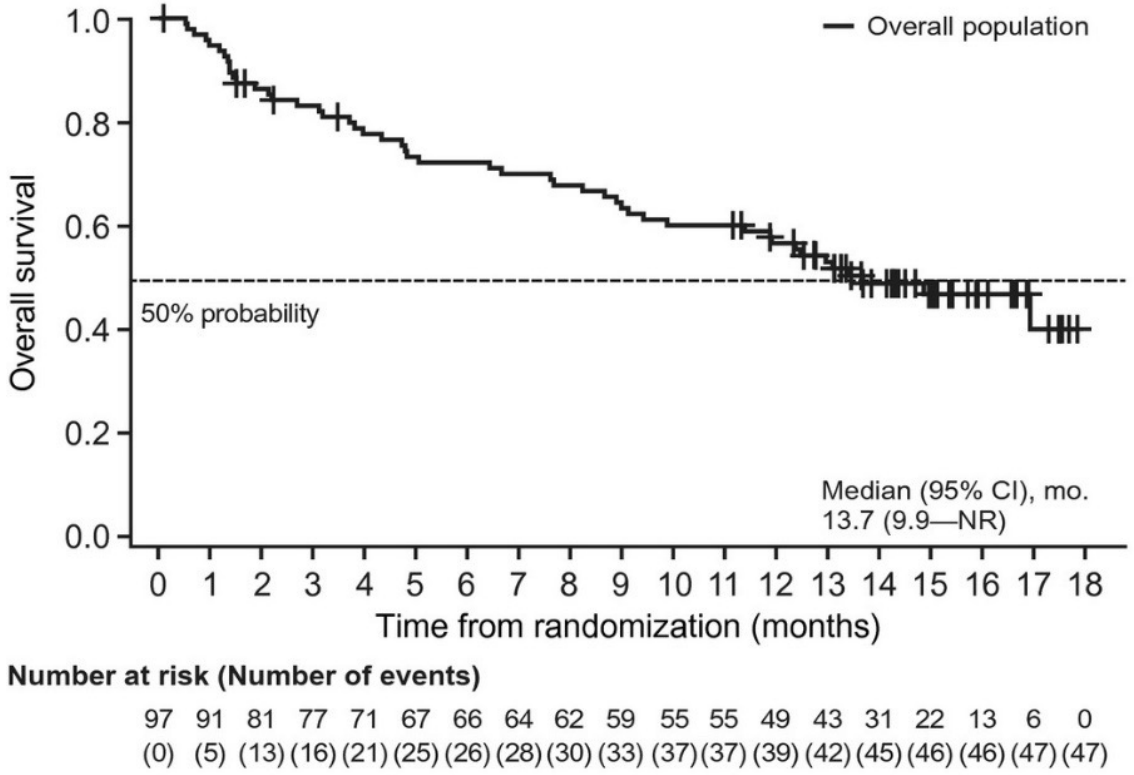
Lonial S et al. *Cancer* 2021;127(22):4198-212; ASH 2020;Abstract 1417.

DREAMM-2: Longitudinal Outcomes

Progression-free survival



Overall survival



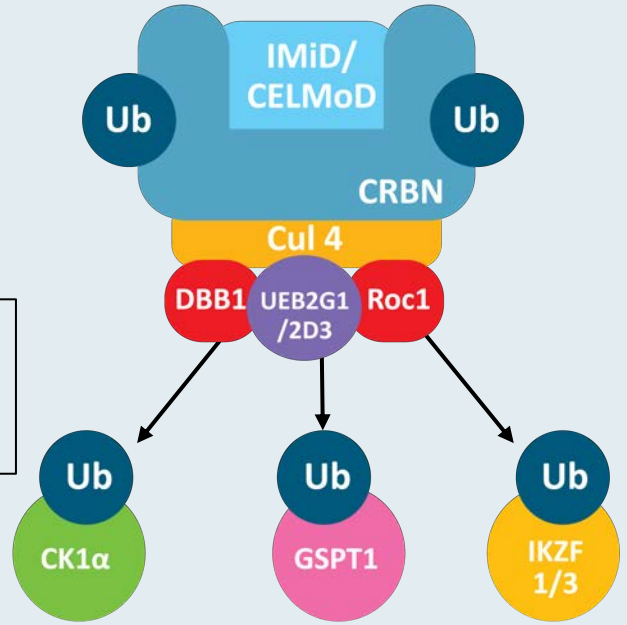
Expected median OS in triple-class refractory myeloma: 8.6 months

Lonial S et al. *Cancer* 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

CC-92480/Dexamethasone Combined with Bortezomib or Daratumumab or Carfilzomib

IMiD®	Indication
Thalidomide	Erythema Nodosum Erythema Leprosum Multiple Myeloma
Lenalidomide	Mantle Cell Lymphoma Multiple Myeloma Myelodysplastic Syndrome (5q-)
Pomalidomide	Multiple Myeloma Kaposi Sarcoma



Clinical trials	CELMoDs®
Multiple Myeloma Diffuse Large B-Cell Lymphoma CNS Lymphoma Glioblastoma Hepatocellular Carcinoma Chronic Lymphocytic Leukemia	CC-122
Multiple Myeloma Systemic Lupus Erythematosus	CC-220
Acute Myeloid Leukemia	CC-90009
Multiple Myeloma	CC-92480 Indisulam
Acute Myeloid Leukemia? (in vitro)	CC-885

Abbreviation: CK1a: casein kinase 1a;
CELMods: Cereblon E3 Ligase Modulation Drugs;
CRL4: cullin-4 RING E3 ligase;
CRBN: Cereblon; CNS: Central Nervous System;
CUL4: Cullin-4; DDB1: DNA damage-binding protein 1;
GSPT1: G1 To S Phase Transition 1;
IKZF1: Ikaros zinc-finger protein 1;
IKZF3: Aiolos zonc-finger protein 3;
IMiDs: Immunomodulatory Drugs;
MDS: Myelodysplastic Syndrome;
Roc1: Ring finger protein;
UB: Ubiquitination
UBE2G1/2D3: Ubiquitin-conjugating enzymes

Holstein et al, Next-Generation Drugs. Targeting the Cereblon Ubiquitin Ligase. JCO 2018.
Lu G et al eLife 2018
Gandhi AK et al Br Haem 2014
Krönke J et al Science 2014
Hansen JD et al J Med Chem 2020
Uehara T et al Nat Chem Biol 2017

McCarthy P. ASCO 2020 Discussant.

RTP RESEARCH TO PRACTICE

CC-92480, a Potent, Novel Cereblon E3 Ligase Modulator (CELMoD) Agent, in Combination with Dexamethasone (DEX) and Bortezomib (BORT) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Preliminary Results from the Phase 1/2 Study CC-92480-MM-002

Richardson PG et al.

ASH 2021;Abstract 2731.

Author Conclusions: *CC-92480 in combination with BORT and DEX appears to be safe and well tolerated with encouraging preliminary efficacy in pts with RRMM. These results support further development of CC-92480 in combination regimens in RRMM. In the CC-92480-MM-002 study, a CC-92480 + BORT + DEX expansion cohort is ongoing at the RP2D, as well as a CC-92480 + CFZ + DEX cohort.*

Iberdomide (IBER) in Combination with Dexamethasone (DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Results from the Dose-Expansion Phase of the CC-220-MM-001 Trial

Lonial S et al.

ASH 2021;Abstract 162.

CC-220-MM-001: Responses with Iberdomide and Dexamethasone for R/R MM

	IBER + DEX (N = 107)	IBER + DEX post anti-BCMA therapy (N = 24)
Response, n (%)		
ORR[a]	28 (26.2)	6 (25.0)
sCR	1 (0.9)	0
CR	0	1 (4.2)
VGPR	8 (7.5)	1 (4.2)
PR	19 (17.8)	4 (16.7)
MR	11 (10.3)	4 (16.7)
SD	46 (43.0)	8 (33.3)
PD	15 (14.0)	4 (16.7)
NE	7 (6.5)	2 (8.3)
Median DoR (95% CI), months	7.0 (4.5–11.3)	NA

[a]Defined as PR or better.

BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; DEX, dexamethasone; DoR, duration of response; IBER, iberdomide; MR, minimal response; NA not available; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Lonial S et al. ASH 2021;Abstract 162.

Phase 1 Study of CART-ddBCMA in Relapsed or Refractory Multiple Myeloma

Frigault MJ et al.
ASCO 2022;Abstract 8003 (Oral).

June 5, 2022
9:00 AM – 12:00 PM EDT

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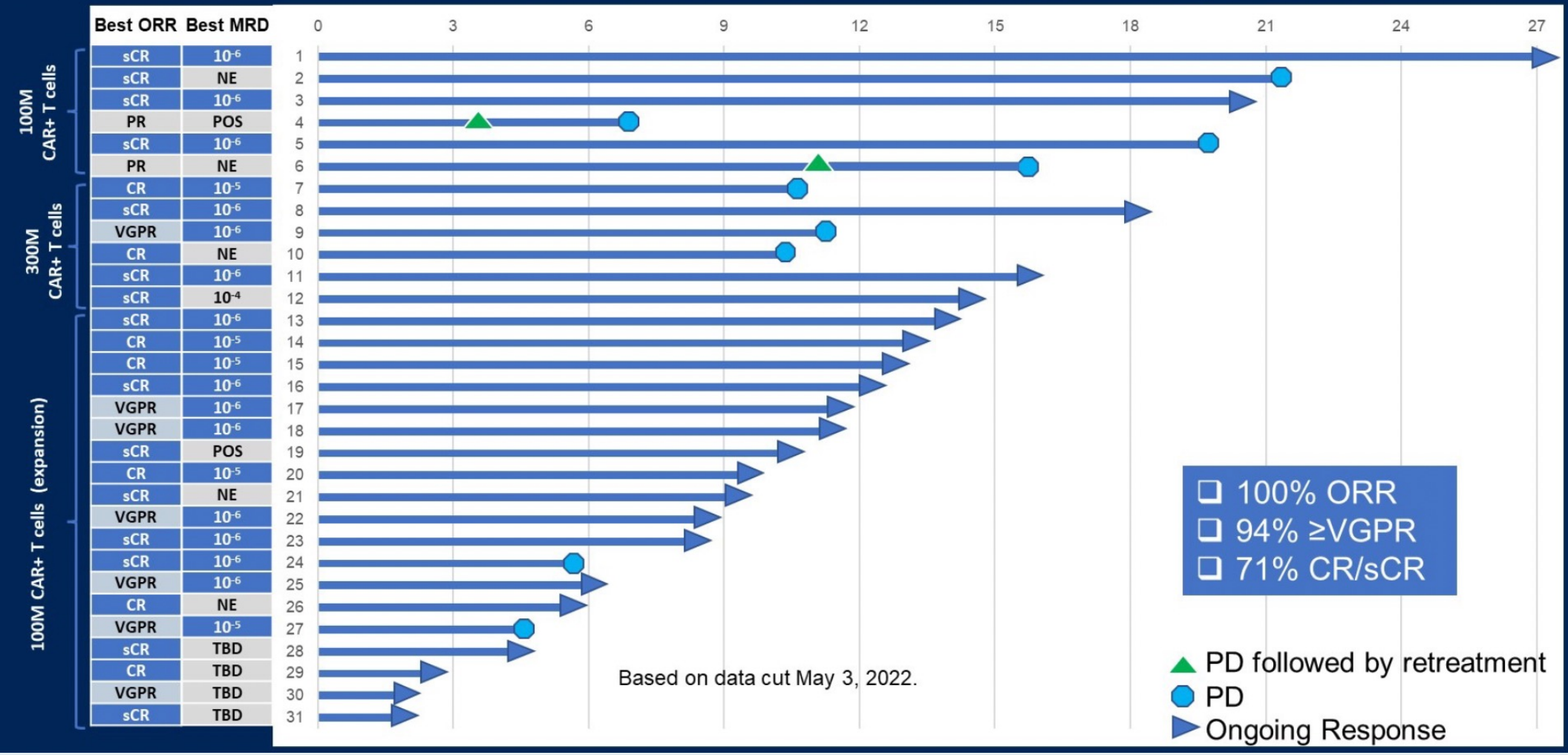
CART-ddBCMA: 100% ORR and Durable Responses



Frigault MJ et al. ASCO 2022;Abstract 8003 (Oral).

CART-ddBCMA Responses Deepen Over Time

	CART-ddBCMA		
Minimum follow-up (mo)	**1**	**6**	**12**
Sample Size (n)	31	24	16
Median Follow-up (mo)	12.1	13.3	17.7
EMD # (%)	12 (39%)	12 (50%)	8 (50%)
ORR	100%	100%	100%
CR rate	22 (71%)	19 (79%)	13 (81%)
% of patients in ongoing response:			
@ 6 months	-	92% (22/24)	94% (15/16)
@ 12 months	-	-	69% (11/16)

Based on data cut May 3, 2022.

Frigault MJ et al. ASCO 2022;Abstract 8003 (Oral).

Phase I Open-Label Single Arm Study of GPRC5D CAR T-Cells (OriCAR-017) in Patients with Relapsed/Refractory Multiple Myeloma (POLARIS)

Huang H et al.

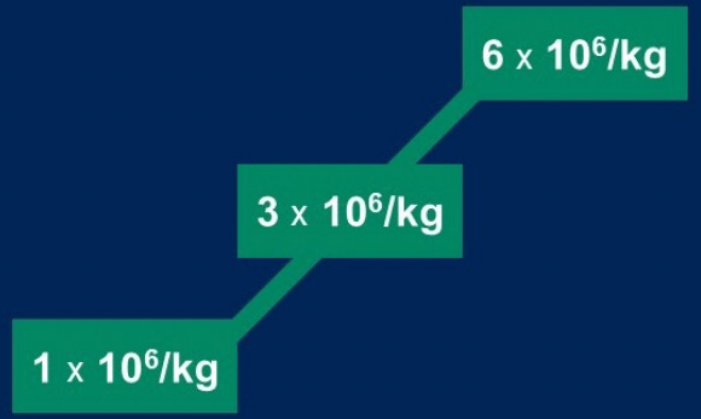
ASCO 2022;Abstract 8004 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

Study Design

- Key eligibility criteria：
  - RRMM
  - Measurable disease per IMWG criteria
  - Refractory to 3 or more lines of therapy
  - GPRC5D expression more than 20% on myeloma cells
  - Prior BCMA-targeted therapy allowed
  - Bridging treatments allowed
- Primary endpoint: Safety and tolerability
- Secondary endpoints: PK, PD, and efficacy
- Data cutoff was April 30, 2022



Dosing: a single IV infusion (CAR+ T cell) After fludarabine 30mg/m²/day and cyclophosphamide 300mg/m²/day for 3 days (from D-5 to D-3)

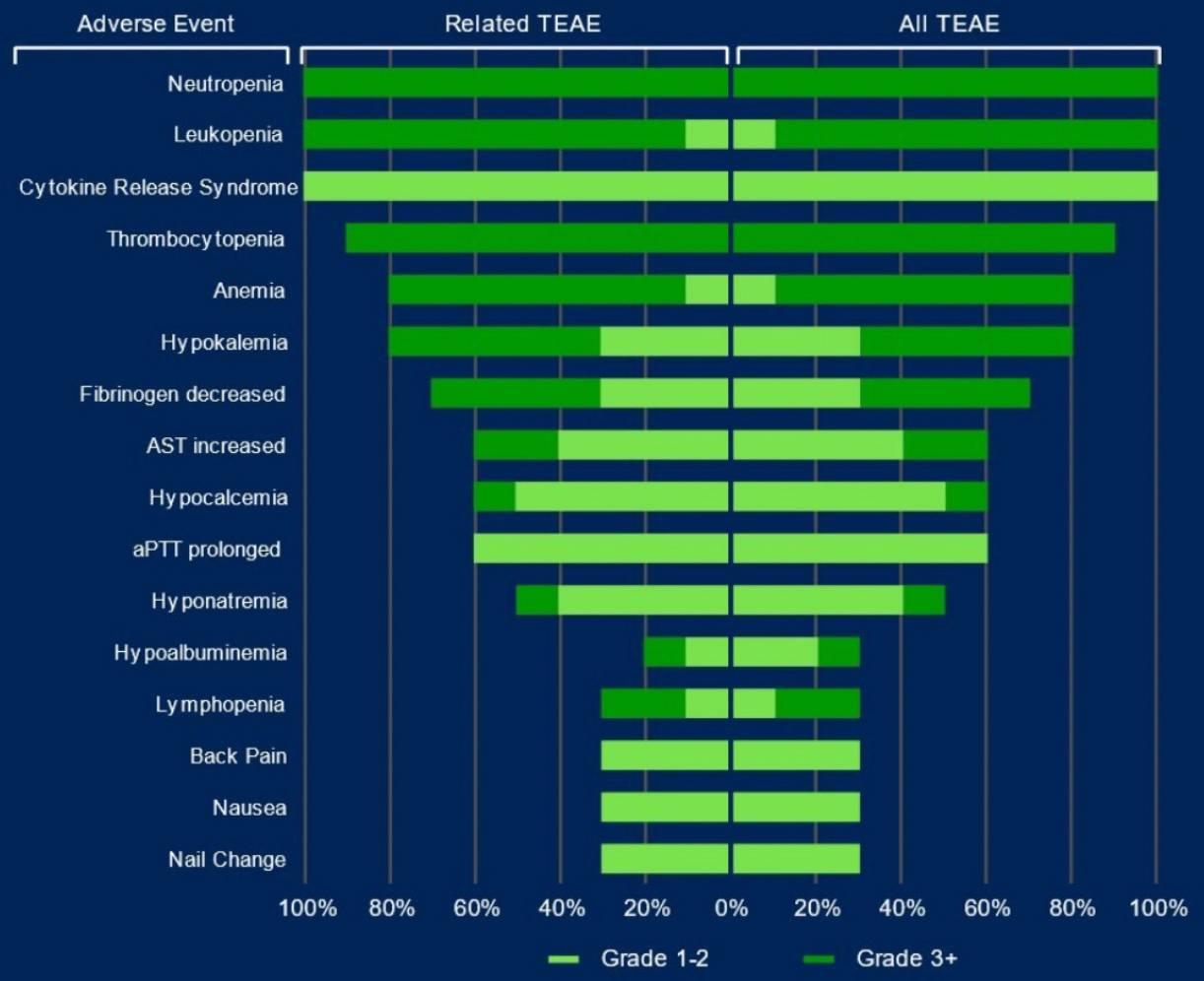
BCMA=B-cell maturation antigen; CRS=cytokine release syndrome; IMWG: International Myeloma Working Group; IMiD: immunomodulatory drugs; PI: proteasome inhibitor.

Huang H et al. ASCO 2022;Abstract 8004 (Oral).

OriCAR-017: Safety

- No DLTs were observed during dose-escalation phase
- No ICANS was observed
- No Grade 3 or higher CRS
- No death due to AEs

OriCAR-017 has a tolerable safety profile at all dose levels



Huang H et al. ASCO 2022;Abstract 8004 (Oral).

Updated Results of a Multicenter First-in-Human Study of BCMA/CD19 Dual-Targeting Fast CAR-T GC012F for Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Du J et al.

ASCO 2022;Abstract 8005 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

GC012F DUAL CAR-T for MM : Study Design

Multicenter, open label, single-arm IIT[1] study (N=28)

FPI October 2019, LPI November 2021

Pts continued to be assessed for response

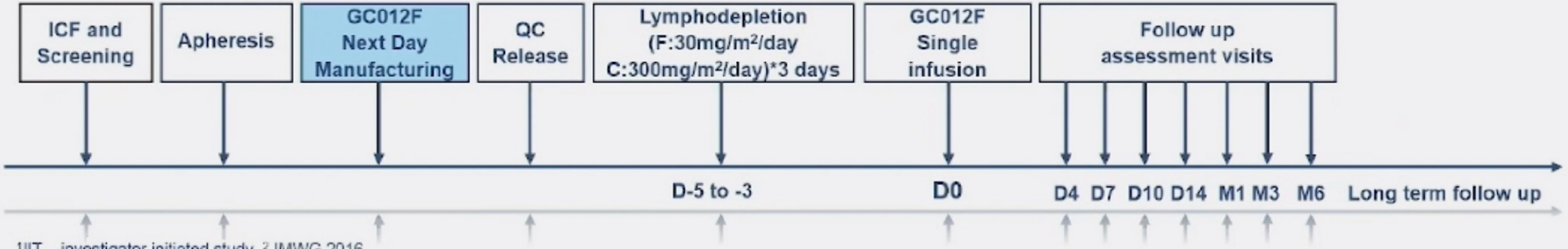
The data cut off January 26th 2022

Key Eligibility Criteria

- Relapsed/Refractory Multiple Myeloma[2]
- 3+prior lines of therapy and/or refractory to PI and IMiDs, primary refractory
- Expected survival ≥ 3 months

- **Primary endpoint:**
  - Adverse Events
- **Secondary endpoints:**
  - ORR, BOR
  - MRD assessment at pre-specified timepoints post CAR-T infusion
  - PK/PD

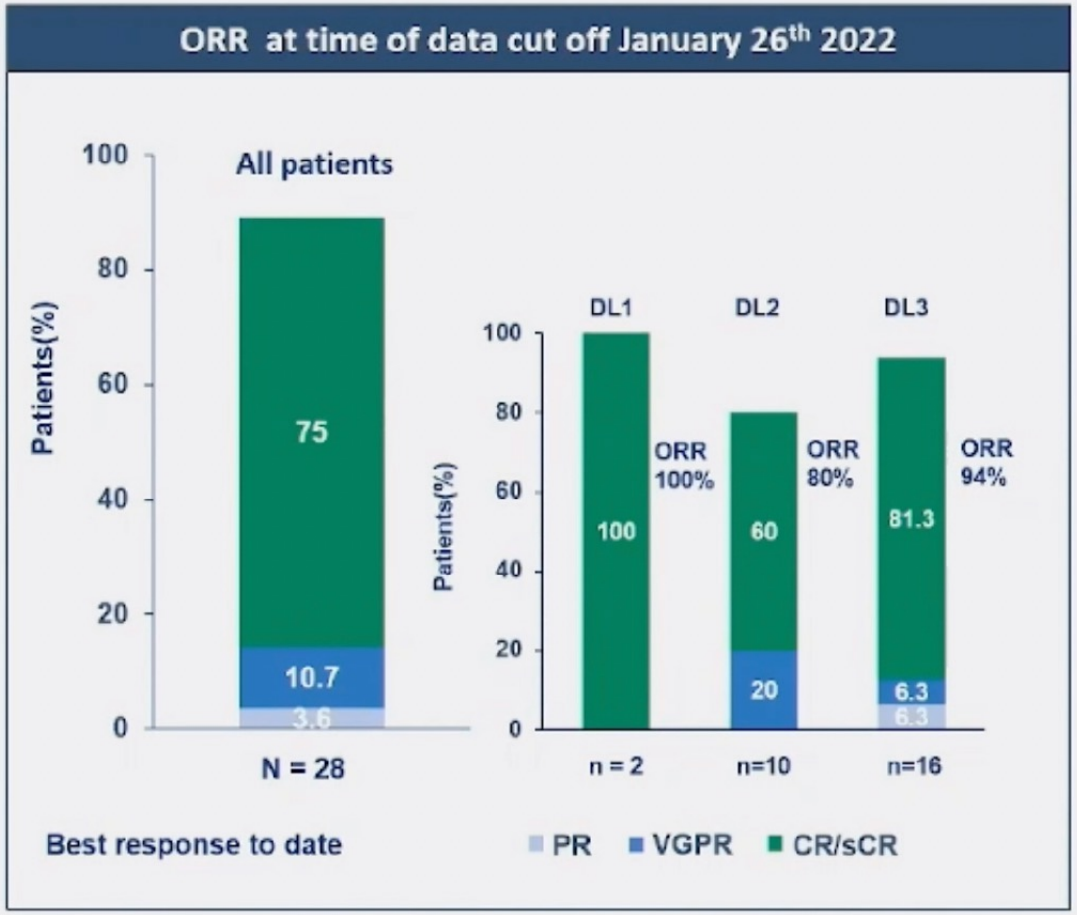
Dose Levels
DL1: $1x10^5$ cells/kg
DL2: $2x10^5$ cells/kg
DL3: $3x10^5$ cells/kg



[1]IIT – investigator initiated study, [2] IMWG 2016

Du J et al. ASCO 2022;Abstract 8005 (Oral).

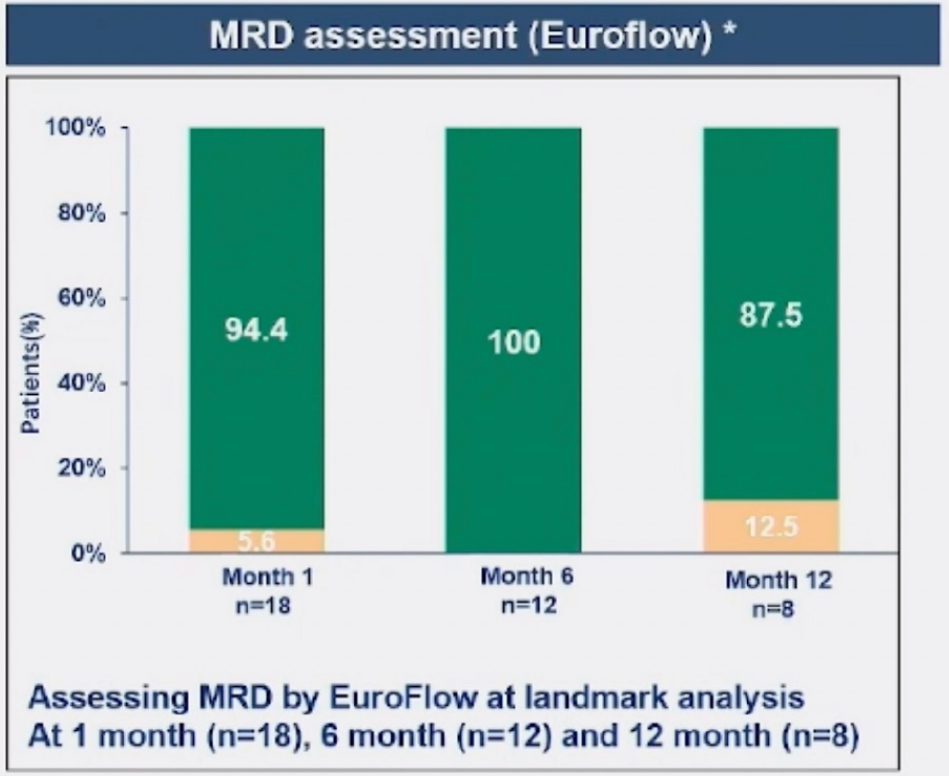
GC012F DUAL CAR-T for MM : Response Assessment



- Time to earliest response: 28 days (first assessment timepoint)
- ORR = 89.3% (25/28) patients
  - Best response achieved to date
  - 75% (21/28) MRD-CR/sCR
  - 86% (24/28) VGPR or better
- Median duration of response (DOR) not yet reached
- Median duration of follow up 6.3 months (range 1.8 months to 29.9 months)

Du J et al. ASCO 2022;Abstract 8005 (Oral).

GC012F DUAL CAR-T for MM : Minimal Residual Disease Landm



- 100% of evaluable pts with BM samples available were MRD negative at Month 6 (n=12)
  - Some pts with shorter duration of follow up could not get assessed at time of data cut of Jan 26th 2022
  - This analysis only includes pts assessed by Euroflow
- 87.5% of evaluable patients were MRD negative by Euroflow at Month 12 (n=8)

Du J et al. ASCO 2022;Abstract 8005 (Oral).

GC012F DUAL CAR-T for MM : Safety Profile

N=28	All Grades, n (%)	Grade ≥3, n (%)
Hematologic TEAEs* (≥ 25% All Grades)		
Neutropenia	23 (82)	23 (82)
Lymphopenia	18 (64)	18 (64)
Leukopenia	23 (82)	22 (79)
Thrombocytopenia	22 (79)	16 (57)
Anemia	13 (46)	10 (36)
Non-Hematologic TEAEs* (≥ 25% All Grades)		
LDH increased	17 (61)	0 (0)
Hypoalbuminemia	13 (46)	0 (0)
AST increased	12 (43)	8 (29)
Hypokalemia	18 (64)	4 (14)
Hypophosphatemia	9 (32)	0 (0)
Hypocalcemia	7 (25)	1 (4)

N=28	CRS[1], n (%)	ICANS[2], n (%)
Grade 0	3 (11)	0 (0)
Grade 1-2	23 (82)	0 (0)
Grade 3	2 (7)	0 (0)
Grade 4-5	0 (0)	0 (0)

[1]CRS treated with Tocilizumab, vasopressors and dexamethasone

CRS any grade	Median (days)	Range (days)
Time to onset	6	2-10
Duration	3	1-8

*AE were graded according to CTCAE v5.0, TEAE- treatment emergent adverse event, AST Aspartate Aminotransferase, LDH Lactase dehydrogenase, CRS – [1]Cytokine Release Syndrome - ASBMT consensus grading, [2] ICANS – Immune Effector Cell-Associated Neurotoxicity Syndrome

Du J et al. ASCO 2022;Abstract 8005 (Oral).

Initial Safety Results for MagnetisMM-3: A Phase 2 Trial of Elranatamab, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients (pts) with Relapsed/Refractory (R/R) Multiple Myeloma (MM)

Lesokhin AM et al.

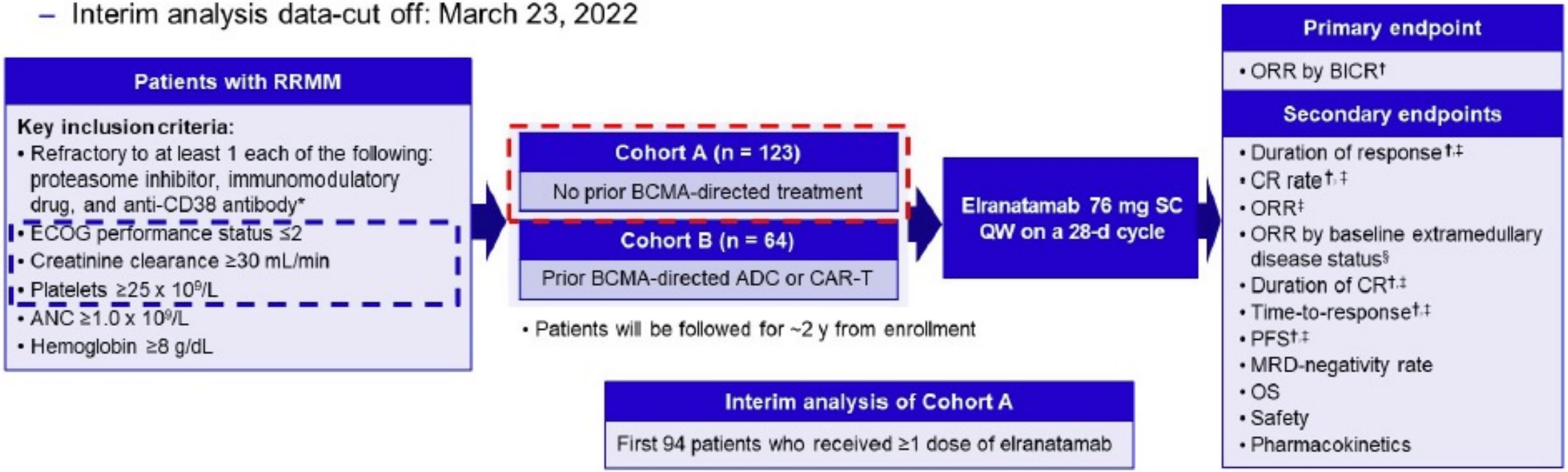
ASCO 2022;Abstract 8006 (Oral).

June 5, 2022

9:00 AM – 12:00 PM EDT

MagnetisMM-3 Study

- MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study
  - Interim analysis data-cut off: March 23, 2022

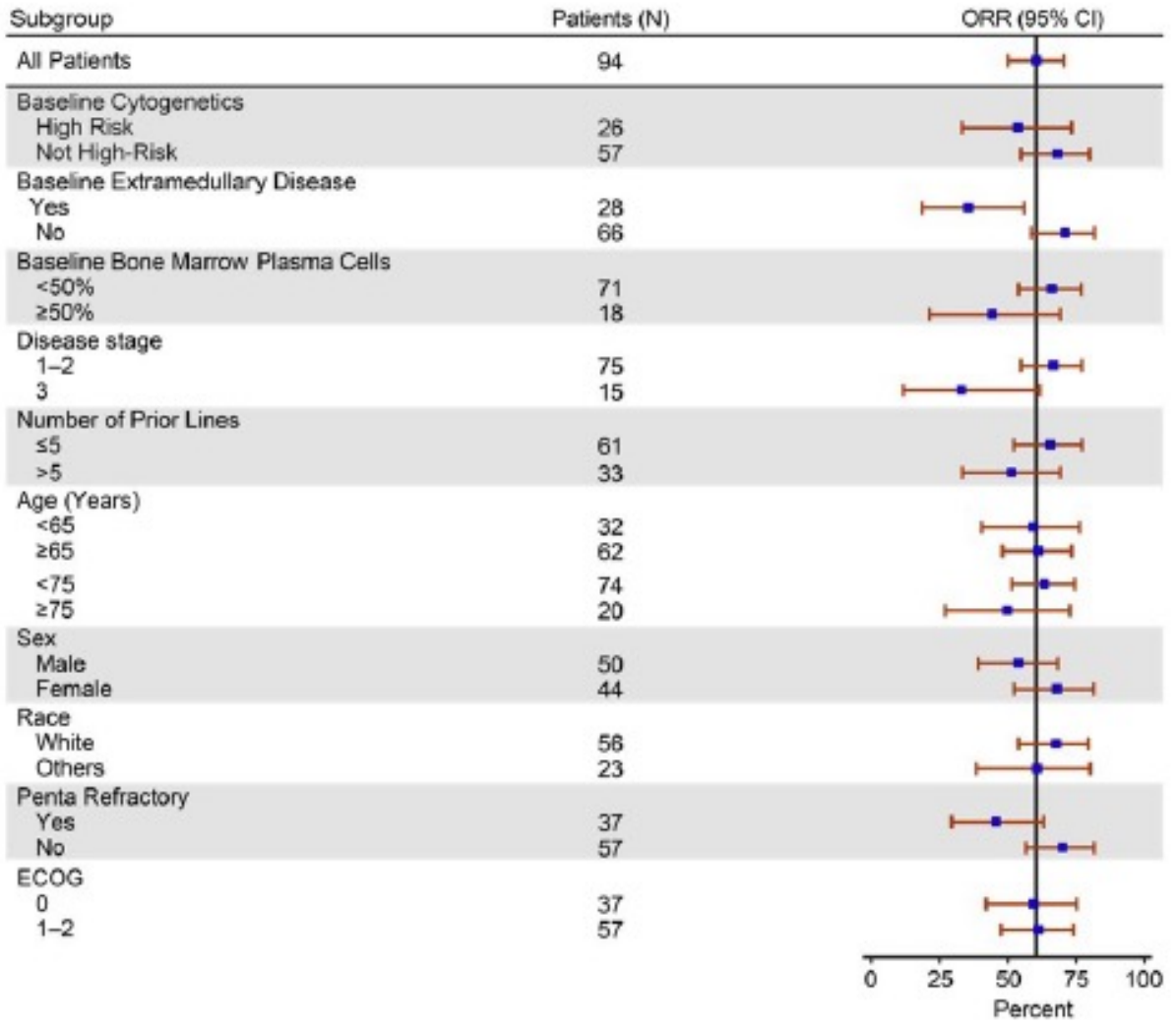


*Refractory was defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response. †By BICR assessment per IMWG response criteria (Kumar S, et al. Lancet Oncol 2016;17(8):e328-e346). ‡By investigator assessment per IMWG response criteria. §Includes patients in Cohort A initially dosed at least 4 months prior to the March 23, 2022, data cutoff date.
ADC=antibody drug conjugate; ANC=absolute neutrophil count; BICR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete remission; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; OS=overall survival; PFS=progression-free survival; QW=once weekly; SC=subcutaneous

Lesokhin AM et al. ASCO 2022;Abstract 8006.

Overall Response

- After a median follow-up of 3.71 (range, 0.03−12.91) months, the ORR was 60.6% (95% CI, 50.0−70.6)
- As of the data cut-off, 89.5% of objective responders were ongoing without confirmed progression or death



ORR was defined as confirmed stringent complete response, complete response, very good partial response, or partial response.

Lesokhin AM et al. ASCO 2022;Abstract 8006.

AE of Special Interest: Infections

- Infections were reported in 52.1% (grade 3/4, 22.3%) of patients; 24.5% (grade 3/4, 8.5%) were assessed as treatment-related by the investigator
- One (1.1%) patient had an infection that led to permanent discontinuation of elranatamab

n (%)	Cohort A n = 94	
	Any grade	Grade 3/4
Infection TEAEs in ≥5% of patients		
COVID-related AE	14 (14.9)	8 (8.5)
Upper respiratory tract infection	10 (10.6)	0
Pneumonia	8 (8.5)	4 (4.3)
Urinary tract infection	5 (5.3)	2 (2.1)
TEAEs of interest		
Pneumocystis jirovecii pneumonia	4 (4.3)	3 (3.2)
CMV infection	4 (4.3)	0
CMV infection reactivation	1 (1.1)	0

AE of Special Interest: Peripheral Neuropathy

Peripheral neuropathy, n (%)	Cohort A n = 94	
	Any grade	Grade 3/4
All causality	15 (16.0)	1 (1.1)
Treatment-related	5 (6.4)	1 (1.1)

- Most common events (≥2% of patients) were peripheral sensory neuropathy (5.3%) and paresthesia (3.2%). All were grade 1/2, except for 1 patient with grade 3 motor neuropathy
- Two (2.1%) patients had peripheral neuropathy events that led to permanent discontinuation of elranatamab
- A medical history of peripheral neuropathy was reported by 7/15 (46.7%) patients with peripheral neuropathy events

Lesokhin AM et al. ASCO 2022;Abstract 8006.

Major Risk Factors Associated with Severe COVID-19 Outcomes in Patients with Multiple Myeloma: Report from the National COVID-19 Cohort Collaborative (N3C)

Mitra AK et al.

ASCO 2022;Abstract 8008 (Oral).

June 5, 2022

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CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.

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