REGIONAL COMMUNITY WORKSHOP

Welcome and Announcements

Kelly Cox

IMF Senior Director, Regional Community Workshops

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Workshop Video Replay & Slides

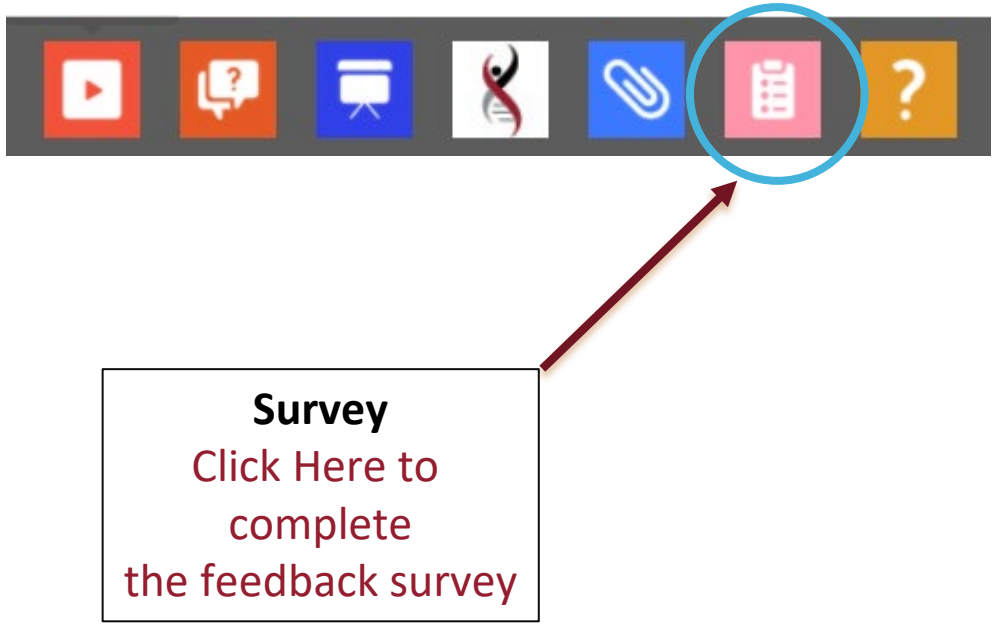
As follow up to today's workshop, we will have the speaker slides and a video replay available.

These will be provided to you shortly after the workshop concludes.

We want to hear from you!

Feedback Survey

Please take a moment to complete the survey.
It will also be emailed to you shortly after the workshop.



REGIONAL COMMUNITY WORKSHOP

SOUTHWEST
REGIONAL COMMUNITY WORKSHOP
Saturday June 26, 2021 ~ Agenda

Welcome and Announcements

Kelly Cox, Senior Director Regional Community Workshops

Myeloma 101 and Frontline Therapy

Joseph Mikhael, MD, Med, FRCPC, FACP, Translational Genomics Research Institute, Phoenix, AZ

Q & A with Panelist

Stretch Break

Relapsed Therapy and Clinical Trials

Amrita Krishnan, MD, City of Hope Medical Center, Duarte, CA

Q & A with Panelist

How to Manage Myeloma Symptoms and Side Effects

Deb Doss, RN, OCN, Dana-Farber Cancer Institute, Boston, MA

Q&A with Panel

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Myeloma 101 and Frontline Therapy

Joseph Mikhael MD, Med, FRCPC, TGen, Pheonix, AZ

Multiple Myeloma 101 and Frontline Therapy

IMF Regional Community Workshop

November 2020

Joseph Mikhael, MD, MEd, FRCPC
Chief Medical Officer, International Myeloma Foundation
Professor, Translational Genomics Research Institute (TGen)
City of Hope Cancer Center

Objectives

- Review the basics of blood and cancer
- Define multiple myeloma and its key features
- Highlight the approach to initial therapy for myeloma

The Basics of Blood

- The blood is an “organ” made up of both cells and liquid “plasma”
- Think of wine (red/white/rose)

1. Red Cells – carry Oxygen…trucks
2. White Cells – immune system…army
3. Platelets – help with clotting…ambulance

All produced in the blood factory = Bone Marrow

What is Cancer?

- Simple definition:
  - Identical, uncontrolled growth

- The body usually has a balance to allow cells to grow in the right place for the right period of time
  - When that system is unbalanced, cancers grow
  - Ie, solid tissue (breast, colon…) or blood cells

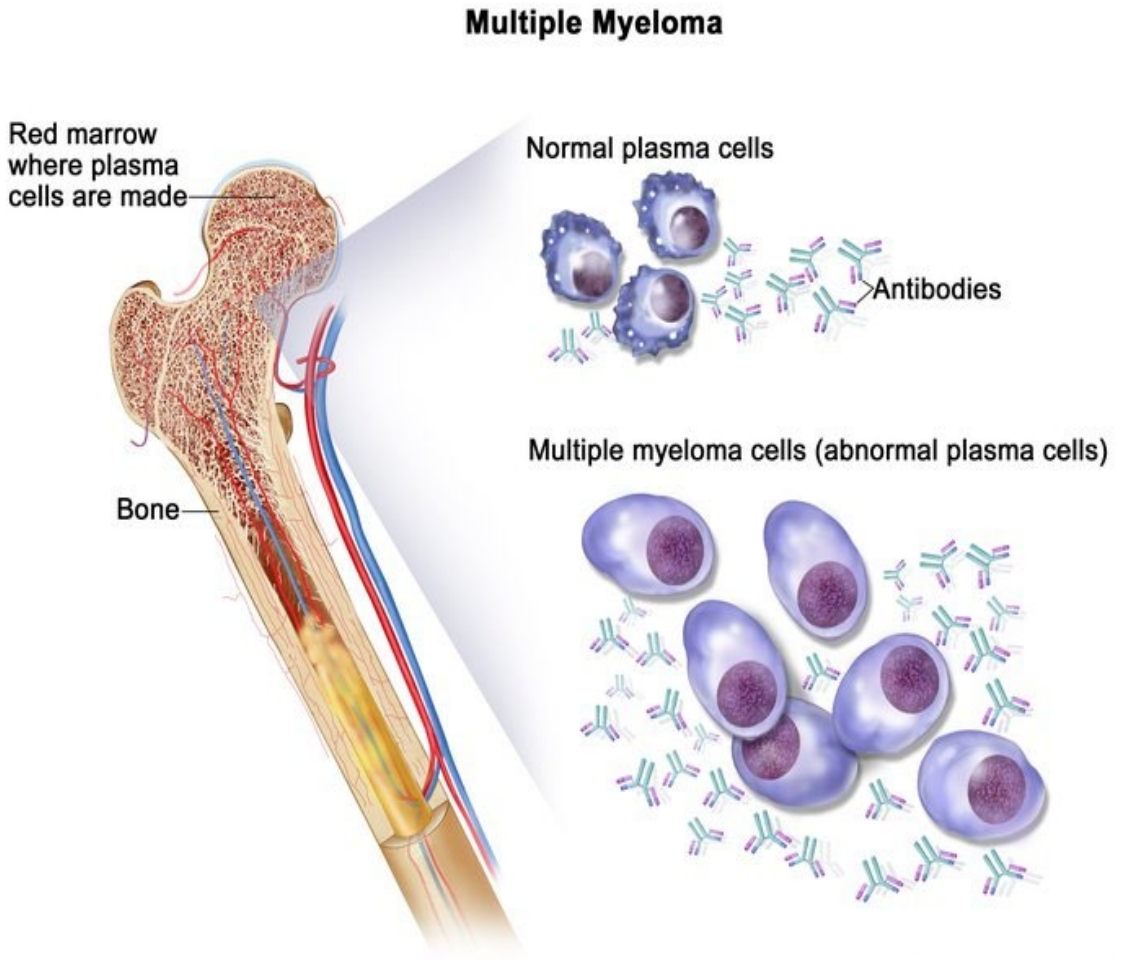
- The “double whammy” of blood cancers is that they are the cells meant to protect you
    - *citizen crime vs police crime*

What is Multiple Myeloma?

Multiple Myeloma* is a blood cancer that starts in plasma cells of the spongy center of bones (bone marrow).

- This is where stem cells mature into red blood cells, white blood cells, and platelets.
- Myeloma cells are abnormal plasma cells that make an abnormal antibody called “M protein”.

** Myeloma is **NOT** a bone cancer or skin cancer (melanoma), it is a type of blood cancer.*



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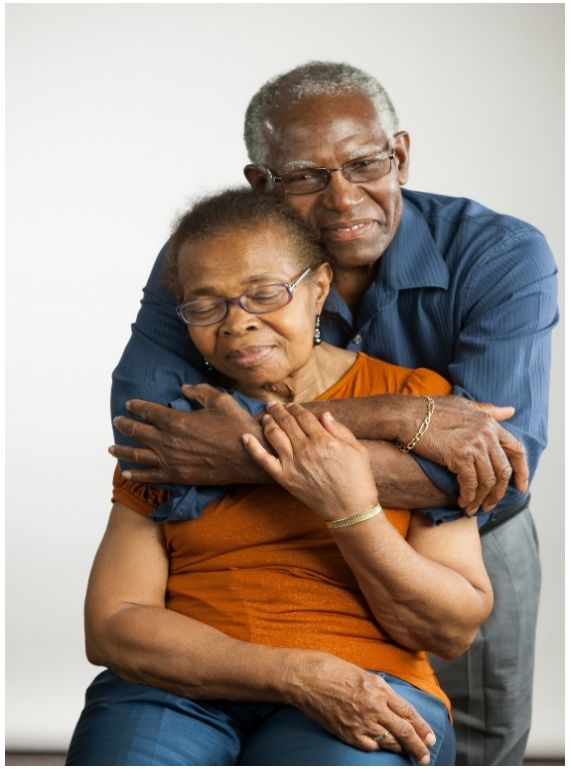
Who's at Risk for Multiple Myeloma

About 1 in 132 people are diagnosed each year
(MM is the second most common blood cancer diagnosed)



Your risk of myeloma increases if you are:

- Older than age 60
- African American (with a 2x greater risk than whites)
- Closely related to someone with MM
- A man (diagnosed more than women)
- Very overweight or obese
- Diagnosed with other plasma cell diseases, like MGUS (monoclonal gammopathy of undetermined significance).

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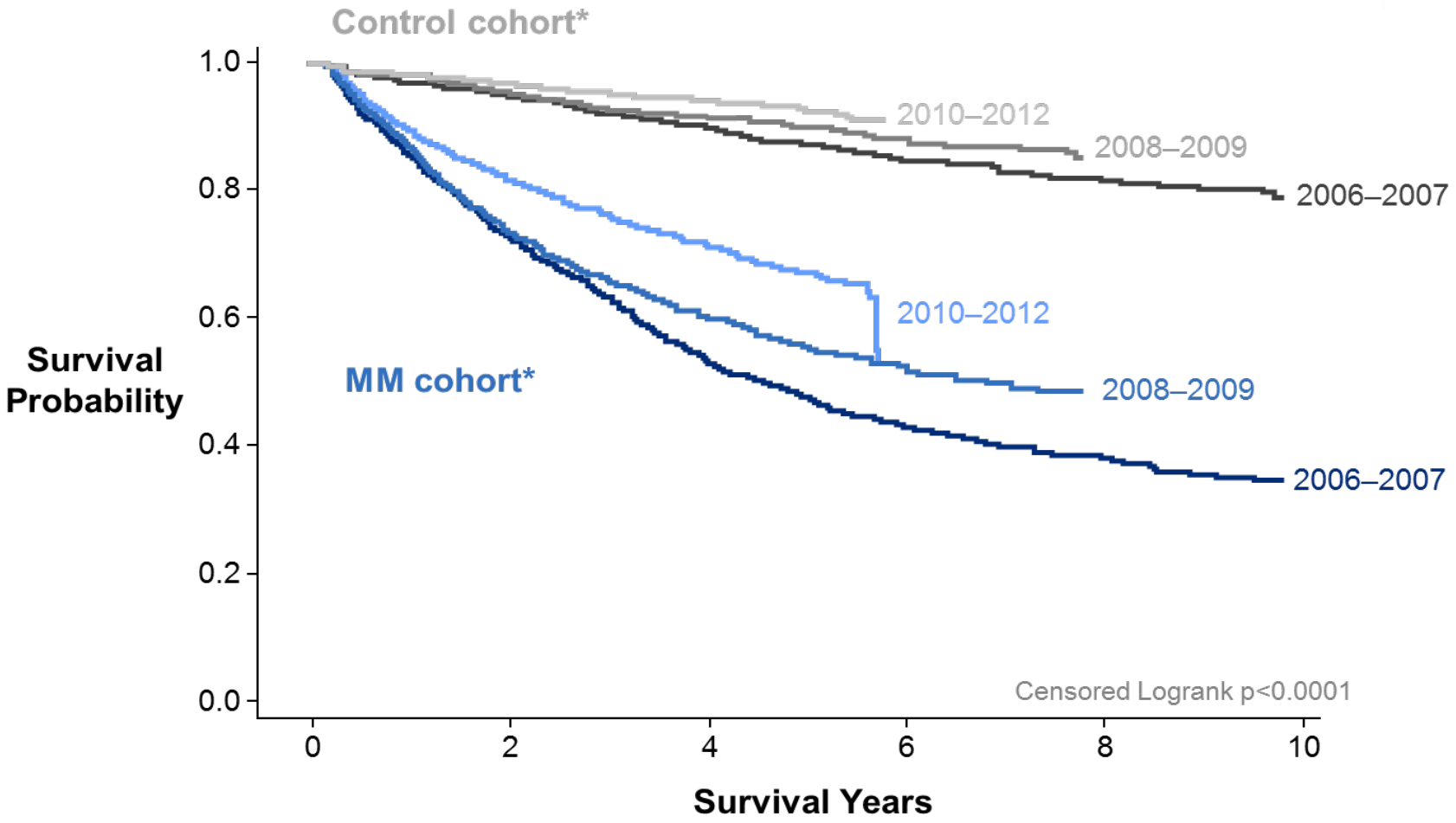
A Call to Action: Facts About African Americans & Myeloma

1. **There is a longer time from symptoms to diagnosis among African Americans**
2. **African Americans are younger by about 5 years on average at diagnosis**
3. **MM and MGUS are more than 2x as common in African Americans**
4. **African Americans are less likely to receive the three T's: Transplant, Triplets and Trials**
5. **Survival improvements have not been equal across race – for every 1.3 years of life gained in whites, it was only 0.8 in blacks**
6. **African Americans have** biologic differences **and** achieve equal or better outcomes **when they receive therapy**

Improving Survival in MM

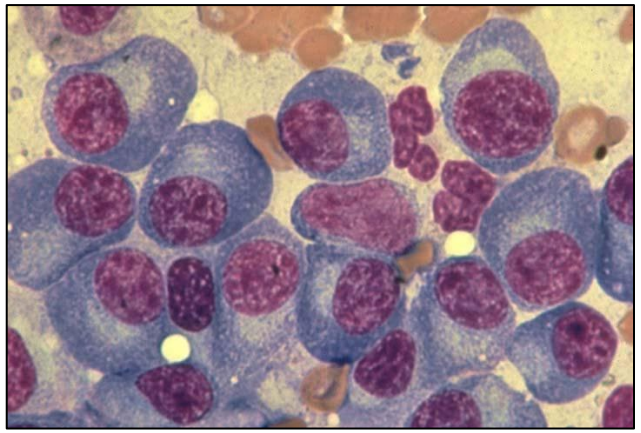


*Year ranges represent the year of diagnosis.
Note: By linking to the SSA Master Death File, survival was measured as time from diagnosis date to the date of death obtained from the SSA, time from diagnosis date to the date of inpatient death, or time from diagnosis date to September 30, 2015; Survival estimates were presented for multiple myeloma patients diagnosed and treated during 2006-2012 (n=9,521).

Fonseca B et al. Leukemia 2017;31:1915-1921.

Myeloma Is a Cancer of Plasma Cells

- Cancer of plasma cells
- Healthy plasma cells produce immunoglobulins G, A, M, D, and E
- Myeloma cells produce abnormal immunoglobulin "paraprotein" or monoclonal protein



Bone marrow of patient with multiple myeloma

Image courtesy of American Society of Hematology
Kyle et al. *Mayo Clin Proc.* 2003;78:21-33;

FAST STATS

1.8% of all cancers;
17% of hematologic malignancies
in the United States

Most frequently diagnosed in ages
65 to 74 years
(median, 69 years)

In 2020:
32,000 estimated new cases;
13,000 estimated deaths

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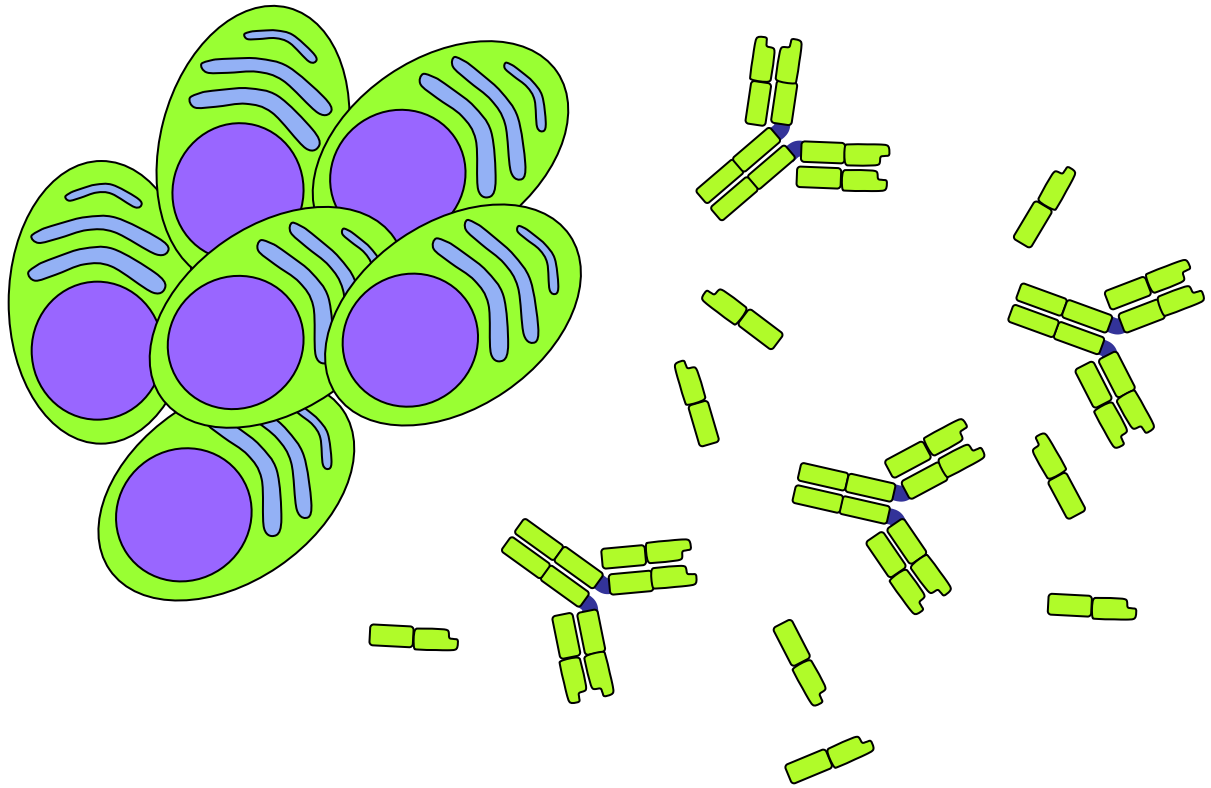
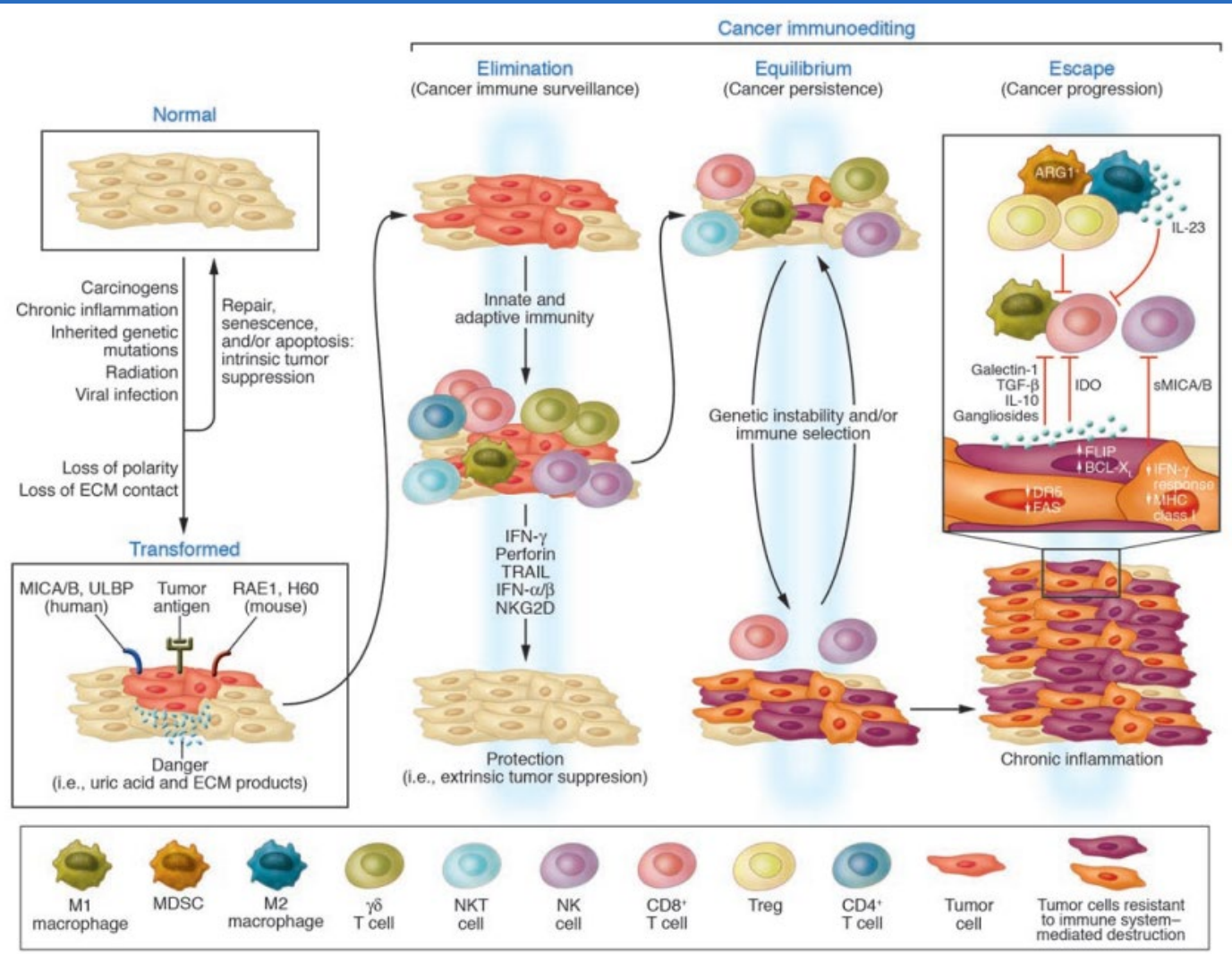
Diagnosis of multiple myeloma: Monoclonal immunoglobulin



The Immune System and Cancer – Myeloma is Classic



Swann JB & Smyth MJ. J Clin Invest. 2007 May 1; 117(5): 1137–1146.

Multiple Myeloma Typically Preceded by Premalignant Conditions

	Premalignant		Malignant
Condition	**MGUS[1-4] (Monoclonal Gammopathy of Undetermined Significance)**	**SMM[1-5,8] (Smoldering Multiple Myeloma)**	**Active Multiple Myeloma[6-8]**
Clonal plasma cells in bone marrow	<10%	10%-60%	≥10%
Presence of Myeloma Defining Events	None	None	Yes
Likelihood of progression	~1% per year	~10% per year	Not Applicable
Treatment	No; observation	Yes for high risk*; No for others	Yes

* In clinical trial (preferred) or offer treatment for those likely to progress within 2 years

1. Kyle RA, et al. *N Engl J Med.* 2007;356:2582-90.
2. International Myeloma Working Group. *Br J Haematol.* 2003;121:749-57.
3. Jagannath S, et al. *Clin Lymphoma Myeloma Leuk*. 2010;10(1):28-43.
4. Kyle RA, et al. *Curr Hematol Malig Rep*. 2010;5(2):62-69.
5. Mateos M-V, et al. *Blood.* 2009;114:Abstract 614.
6. Durie BG, Salmon SE. *Cancer*. 1975;36:842-854.
7. Durie BG, et al. *Leukemia*. 2006;20(9):1467-1473.
8. Rajkumar SV, et al. Lancet *Oncology* 2014; 15:e538-e548.

2014 IMWG Active Myeloma Criteria: Myeloma-Defining Events

Clonal bone marrow ≥10% or bony/extramedullary plasmacytoma

AND any one or more **M**yeloma-**D**efining **E**vents

Calcium elevation

Renal complications

Anemia

Bone disease

BM	Clonal bone marrow ≥60%
FLC	sFLC ratio >100
MRI	1 focal lesion by MRI

BM, bone marrow; FLC, free light chain; MRI, magnetic resonance imaging; sFLC, serum free light chain.
Rajkumar et al. *Lancet Oncol.* 2014;15:e538-e548. Kyle et al. *Leukemia* 2010;24:1121-1127.

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Active Myeloma

Not CRAB but now SLiM CRAB

- S (60% Plasmacytosis)
- Li (Light chains I/U >100)
- M (MRI 1 or more focal lesion)
- C (calcium elevation)
- R (renal insufficiency)
- A (anemia)
- B (bone disease)

Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-e548.

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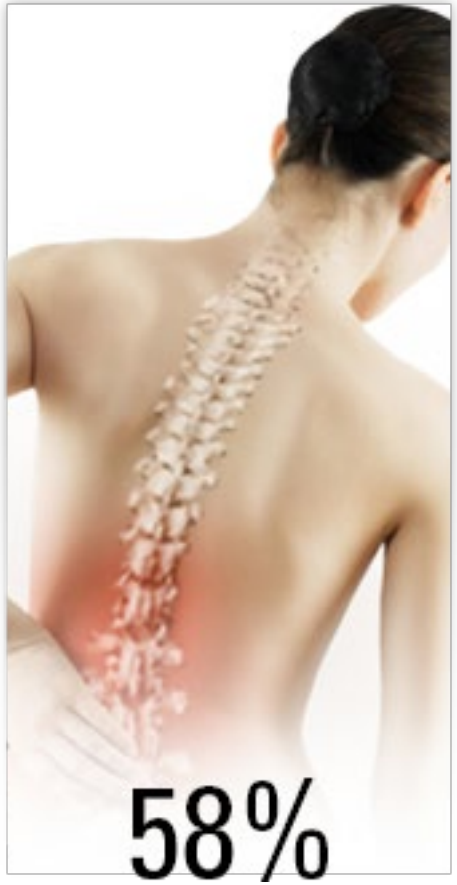
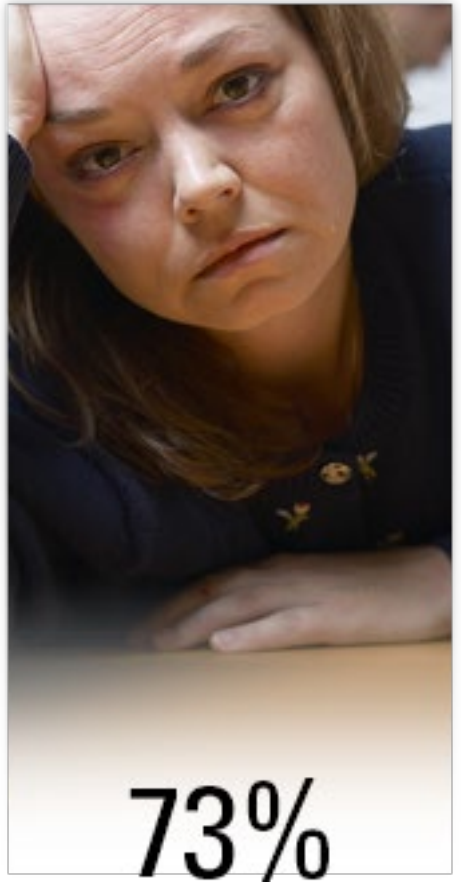
Multiple Myeloma diagnosis can be challenging

Fatigue



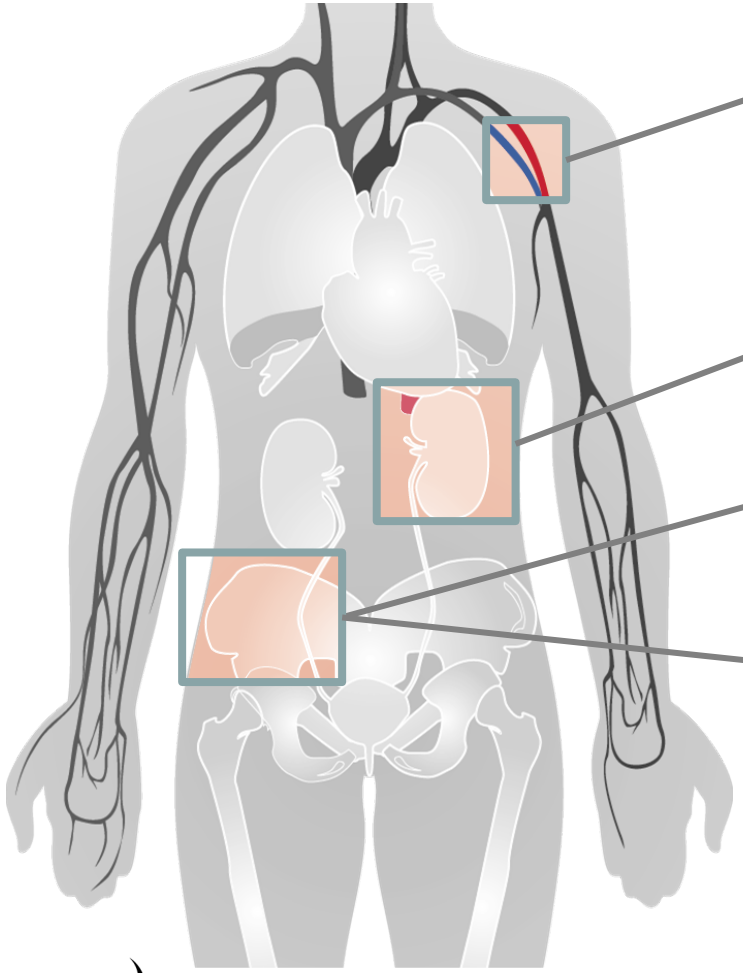
Bone Pain



Anemia

Kyle RA. Mayo Clin Proc. 2003;78:21-33.

More About the Common "CRAB" Symptoms



Low Blood Counts
- May lead to **anemia** and infection
- **Anemia** is present in 60% at diagnosis

→ **Weakness Fatigue Infection**

Decreased Kidney Function
- Occurs in over half of myeloma patients

→ **Weakness**

Bone Damage
- Affects 85% of patients
- Leads to fractures

→ **Bone pain**

Bone Turnover
- Leads to high levels of **calcium** in blood (hypercalcemia)

→ **Loss of Appetite & Weight loss**

About 10% to 20% of patients with newly diagnosed myeloma will not have any symptoms.

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Multiple Myeloma - Types

- Subtypes of MM are determined based on the kind of abnormal protein
  - IgG – 55%
  - IgA – 25%
  - IgD – 1-2%
  - IgM – 1%
  - Light Chain Disease only – 20%
  - Non Secretors 1-2 %

Learn Your Labs

Counts the number of red blood cells, white blood cells, and platelets

Measures levels of albumin, calcium, and creatinine to assess kidney and liver functions, bone status ,and the extent of disease

Determines the level of a protein linked to MM and kidney function: **USED FOR STAGE**

Determines the level of myeloma cell production and extent of MM : **USED FOR STAGE**

Detects the presence and level of M protein = ***how much myeloma***

Identifies the ***type*** of abnormal antibody proteins: IgG, IgA, IgM

Measures myeloma free light chains (kappa or lambda) in blood = ***how much myeloma***

Detects Bence-Jones proteins (otherwise known as myeloma light chains) in urine **(**to determine if it's ***present or not present*****)**

24 hours of urine collected to test the presence and levels of Bence Jones protein in the urine = ***how much myeloma***

Myeloma Stage:
Staging refers to the degree to which the cancer has progressed

Stage 1

β2-microglobulin under 3.6 mg/L

+

Normal Lactate Dehydrogenase (LDH)

AND

NO High Risk Cytogenetics (FISH)

Stage 2

β2-microglobulin Between 3.5 & 5.4mg/L

+

NO High Risk Cytogenetics (FISH)

Stage 3

β2-microglobulin over 5.5 mg/L

+

HIGH Lactate Dehydrogenase (LDH)

AND/OR

High Risk Cytogenetics (FISH)

Deletion 17th chromosome
Translocation 4th and 14th
Translocation 14th and 16th
Translocation 14th and 20th

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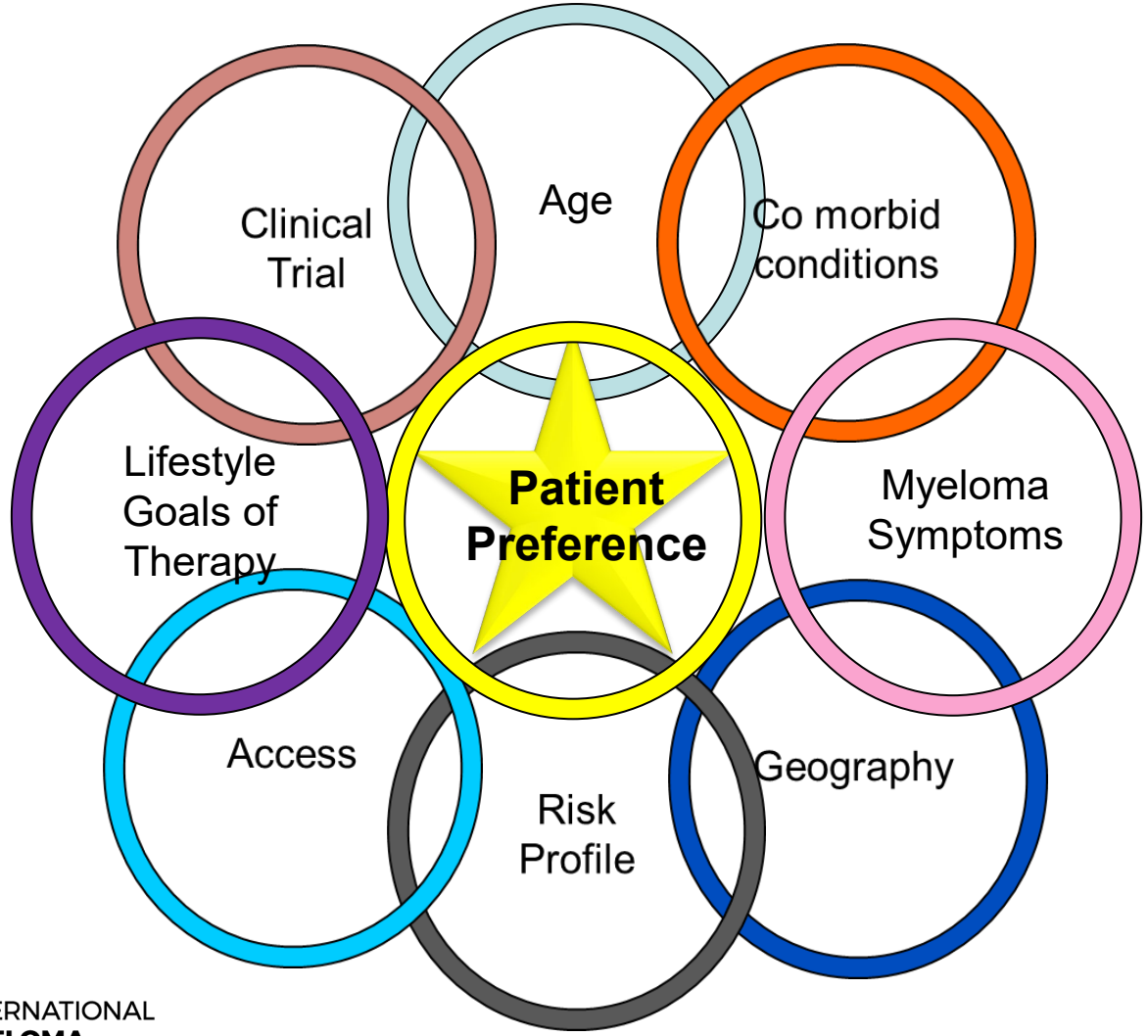
Treatment Planning

Treatment Planning is the process of thinking about the treatment steps you can take with your doctor, based on your goals and preferences. Treatment decisions are based on:

- The results of biomarker tests, cytogenetic (FISH) test, and the stage of multiple myeloma
- Your values, goals, and preferences
- Your age
- Your health and symptoms (if you have kidney disease, heart disease, anemia, or other issues)
- Your medical history and past treatments for multiple myeloma

How to Choose a Treatment Plan



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Tools of the Trade for Frontline Therapy

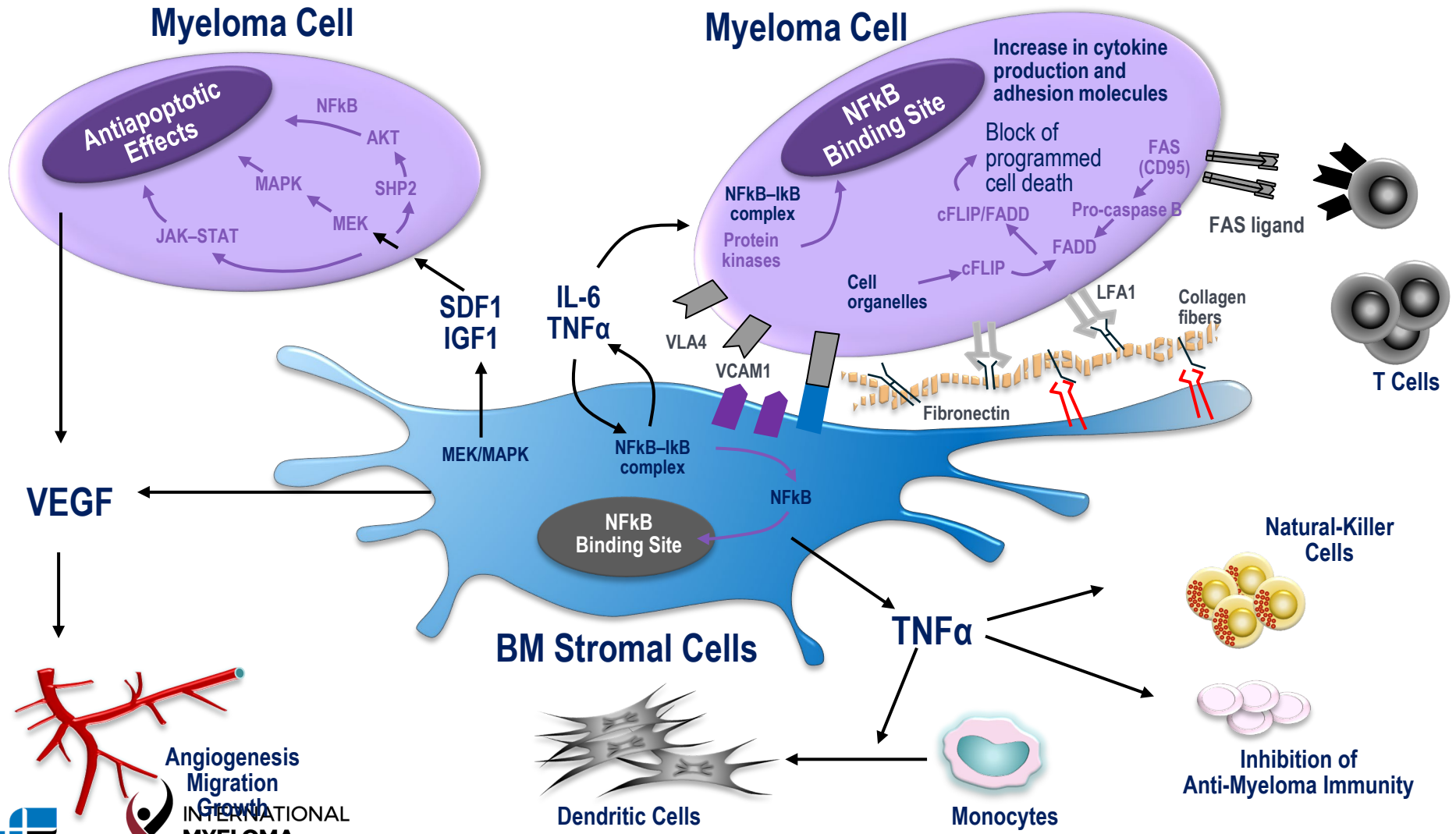
Standard Drug Overview

Class	Drug Name	Abbreviation	Administration
IMiD immunomodulatory drug	Revlimid (lenalidomide)	R or Rev	Oral
	Thalomid (thalidomide)	T or Thal	
Proteasome inhibitor	Velcade (bortezomib)	V or Vel or B	Intravenous (IV) or subcutaneous injection (under the skin)
	Kyprolis (carfilzomib)	C or K or Car	
	Ninlaro (ixazomib)	N or I	Oral
Chemotherapy	Cytoxan (cyclophosphamide)	C	Oral or intravenous
	Alkeran or Evomela (melphalan)	M or Mel	
Steroids	Decadron (dexamethasone)	Dex or D or d	Oral or intravenous
	Prednisone	P	
Monoclonal Antibodies	Daratumumab (Darzalex)	Dara	Intravenous (IV)

Second/Expert Opinion

- **You have the right** to get a second opinion. Insurance providers may require second opinions.
- A second opinion can help you:
  - Confirm your diagnosis
  - Give you more information about options
  - Talk to other experts
  - Introduce you to clinical trials
  - Help you learn which health care team you'd like to work with, and which facility

The Myeloma Microenvironment is Key To Disease Pathophysiology



Bruno B et al. Lancet Oncol. 2004;5:430-442.

Options of Therapy for Myeloma – Current

	ASCT eligible	non-ASCT eligible
Induction therapy	Bortezomib-Lenalidomide-Dex OR Carfilzomib-Lenalidomide-Dex ASCT (melphalan) ↓ Lenalidomide Maintenance	Bortezomib-Lenalidomide-Dex OR Daratumumab-Lenalidomide-dexamethasone OR Doublets (rarely) ↓ Lenalidomide Maintenance
First relapse	Daratumumab-Pomalidomide-Dex Daratumumab-Carfilzomib-Dex Daratumumab-Lenalidomide-Dex Daratumumab-Bortezomib-Dex Isatuximab-Pomalidomide-Dex Selinexor-Bortezomib-Dex Isatuximab-Carfilzomib-Dex	
Second Relapse	Carfilzomib Based Combination – Pomalidomide or Cyclophosphamide Pomalidomide Based Combination – Isatuximab or Elotuzumab	
Third+ Relapse	Selinexor-Dex Belantamab mafodotin Melphalan-Flufenamide CAR T Cell Therapy	

ASCT, autologous stem cell transplant;
CAR, chimeric antigen receptor

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Transplant Eligible

Key Questions:

1. Is Transplant still necessary?

2. What is the triplet combination? (VRD or KRD)

3. Should we switch to quadruplet combinations? (D-VRD, D-KRD or I-VRD, I-KRD)

IFM 2009 Study design

700 patients randomized stratified on ISS and FISH

Arm A – RVD alone	Arm B - Transplantation
3 RVD	3 RVD

PBSC collection (cyclophosphamide 3g/m^2 and GCSF 10 µg/kg/d)

5 RVD	HD Melphalan 200 mg/m^2 + ASCT
	2 RVD

Lenalidomide maintenance 13 cycles (10-15 mg/d)

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RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m^2 D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

M Attal et al, N Engl J Med 2017

Updated PFS (primary endpoint)

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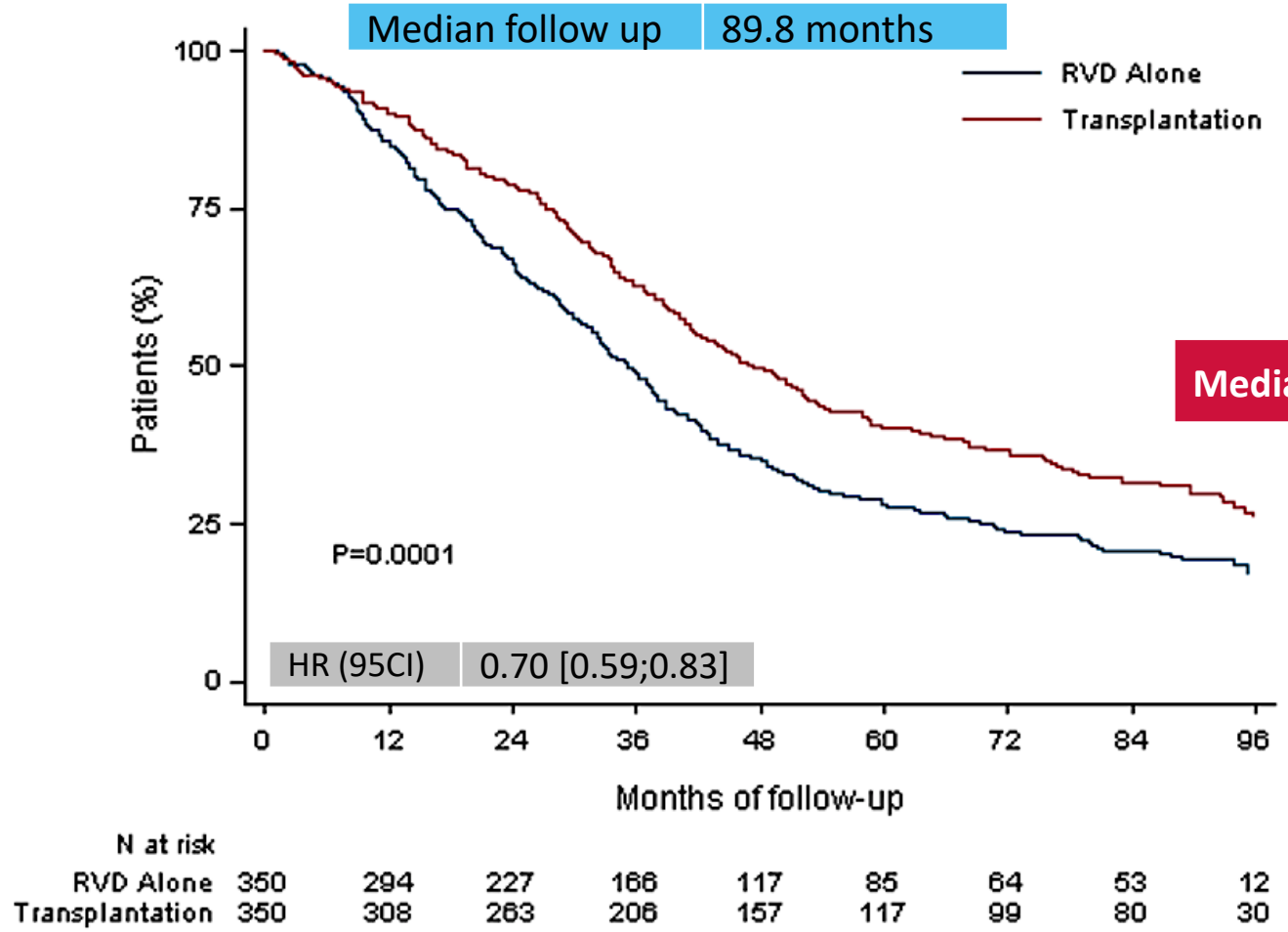


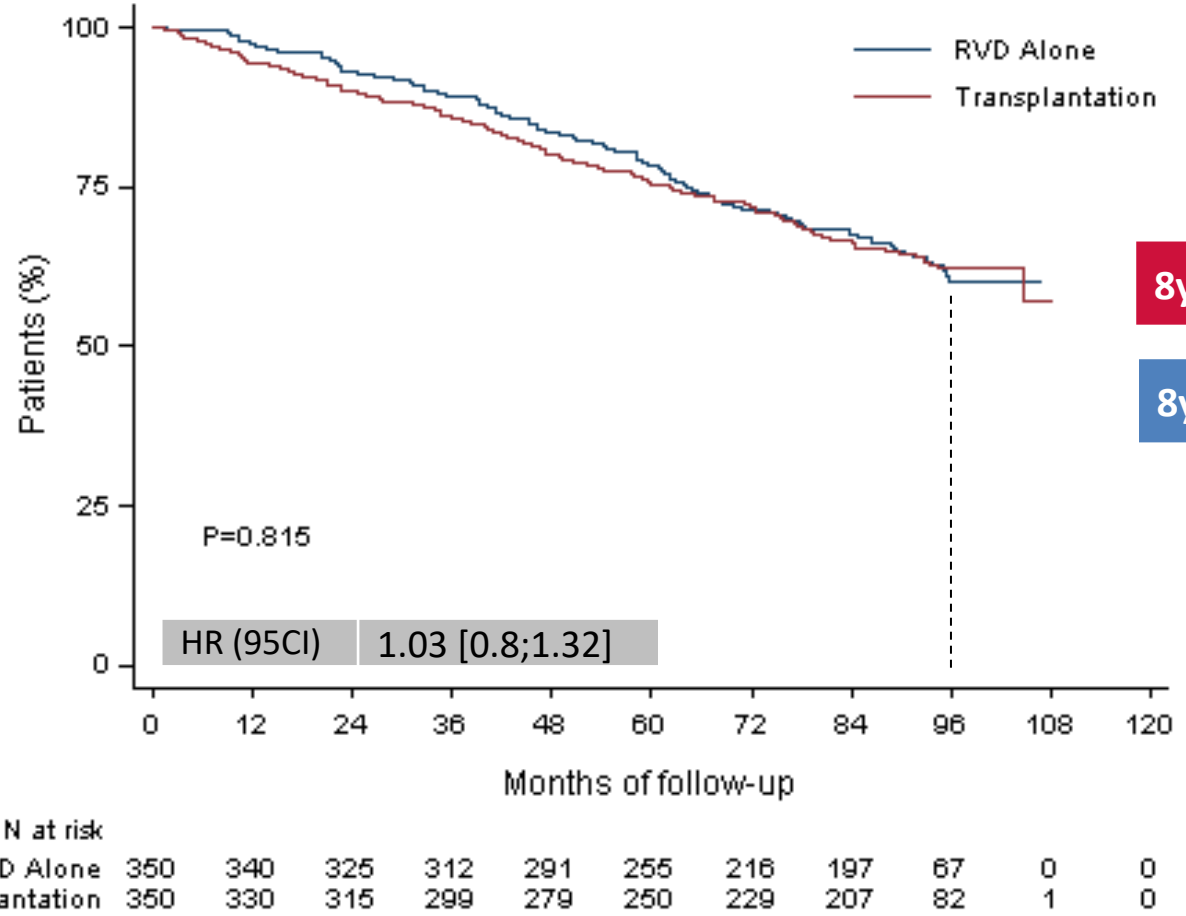
Median PFS 47.3 months (Transplantation, arm B)

Median PFS 35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant

OS

Median follow up	89.8 months



N at risk											
RVD Alone	350	340	325	312	291	255	216	197	67	0	0
Transplantation	350	330	315	299	279	250	229	207	82	1	0

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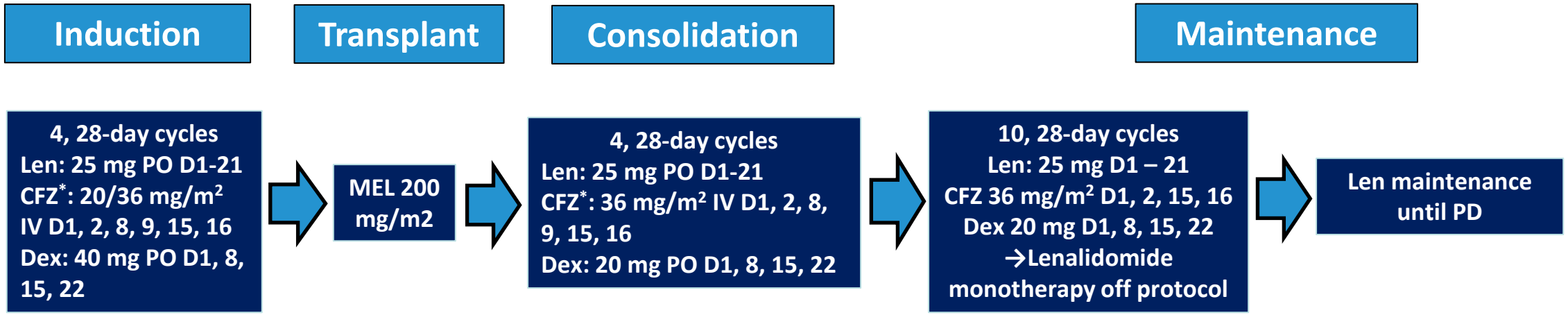
8y-OS 62.2% (Transplantation, arm B)

8y-OS 60.2% (RVD alone, arm A)

More than 60% of the patients in the two arms are alive after 8 years of follow-up

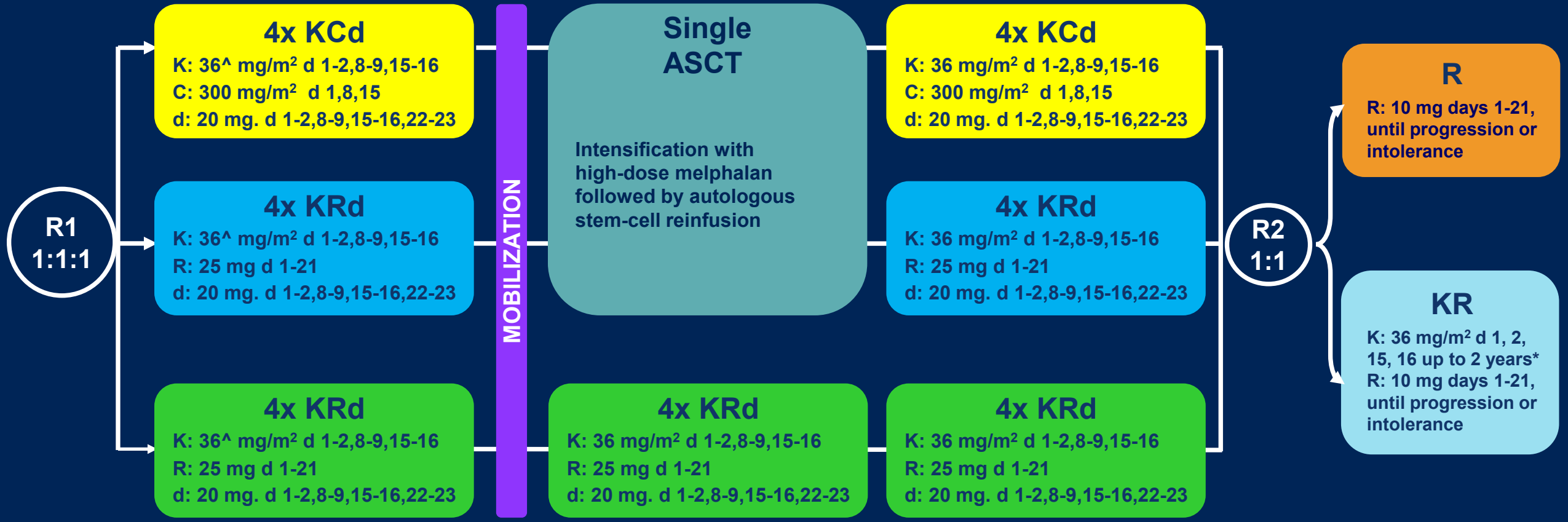
Carfilzomib, Lenalidomide and Dexamethasone (KRD) for Newly-Diagnosed, Transplant-Eligible Multiple Myeloma



Jasielec, J, et al. *Blood* 2020; Epub ahead of print.

Trial design

474 NDMM patients, transplant-eligible and younger than 65 years

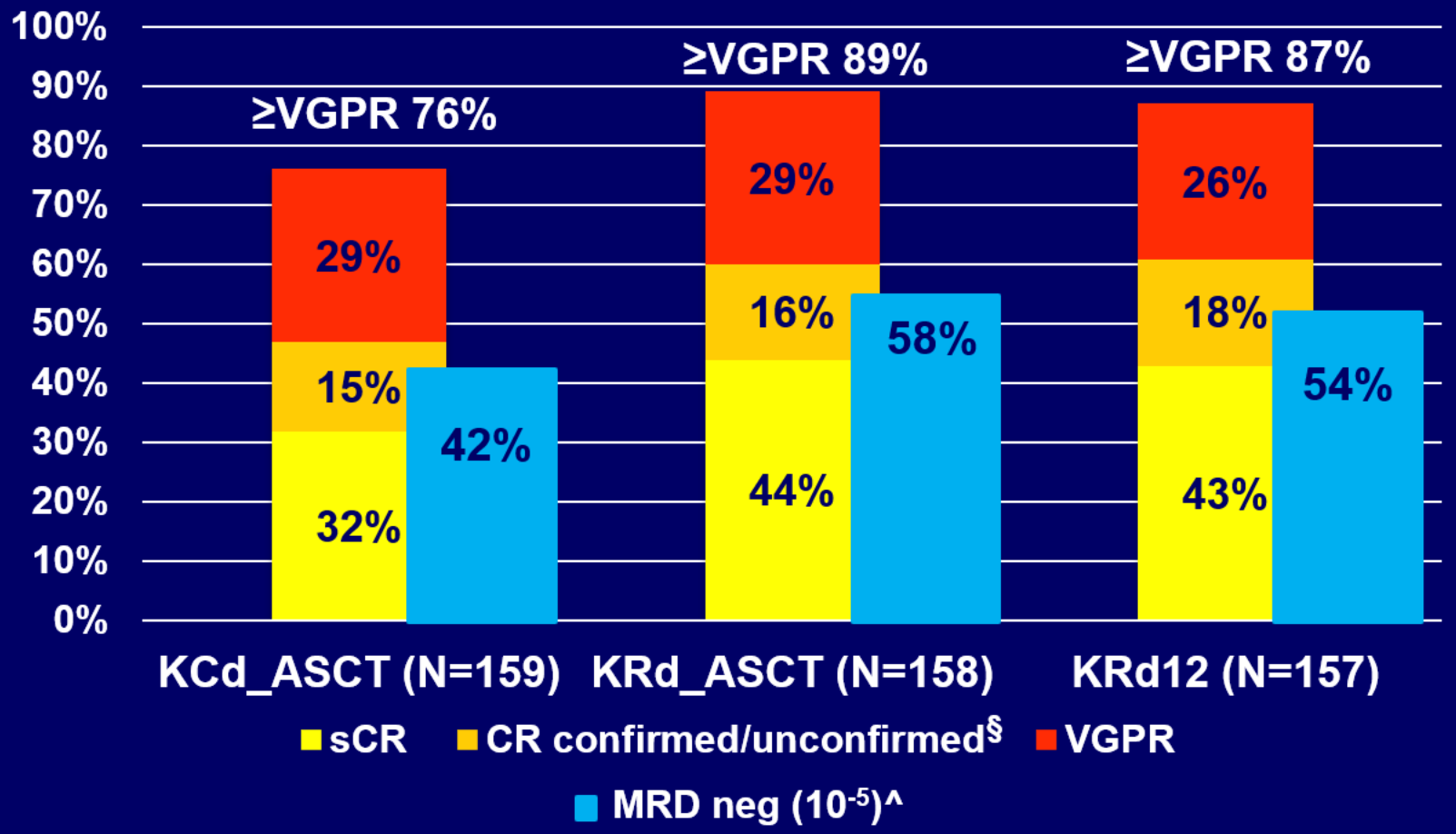


^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd.

KRd_ASCT vs. KRd12 vs. KCd_ASCT: Efficacy

Pre-maintenance response rate and MRD negativity
ITT analysis



	OR	p-value*
≥VGPR		
KRd_ASCT vs KCd_ASCT	2.53	0.004
KRd12 vs KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT vs KCd_ASCT	1.65	0.035
KRd12 vs KCd_ASCT	1.60	0.048

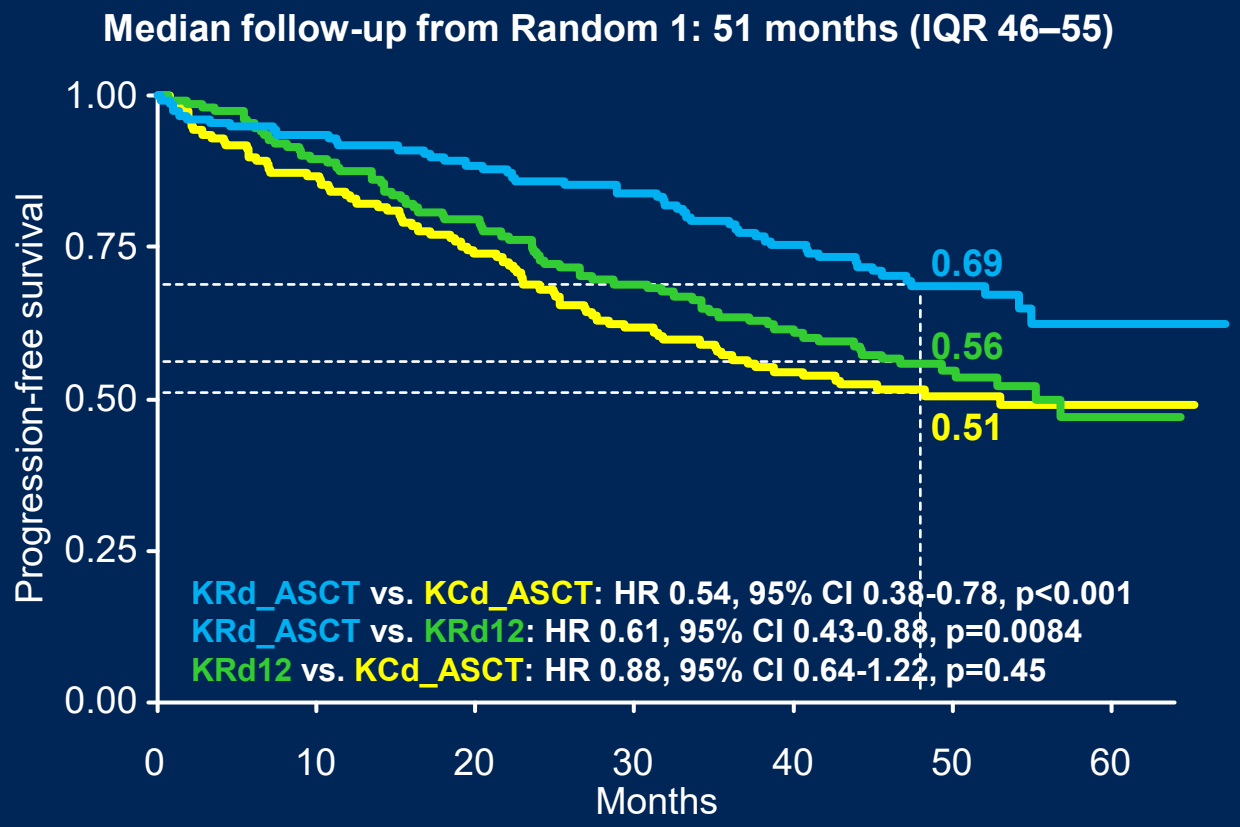
MRD neg (10^{-5})	OR	p-value*
KRd_ASCT vs KCd_ASCT	2.02	0.009
KRd12 vs KCd_ASCT	1.73	0.042

^Patients whose samples were not available (~10%) were considered as positive. *Adjusted for ISS, Age, FISH, LDH.
§ Unconfirmed CR/sCR: patients missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT_KCd; 8% in KRd_ASCT_KRd; 6% KRd_12).
ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; neg, negativity; ITT, intention to treat; sCR, stringent complete response; CR: complete response; VGPR: very good partial response; OR: odds ratio; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; FLC, free light chain, ISS, International Staging System.

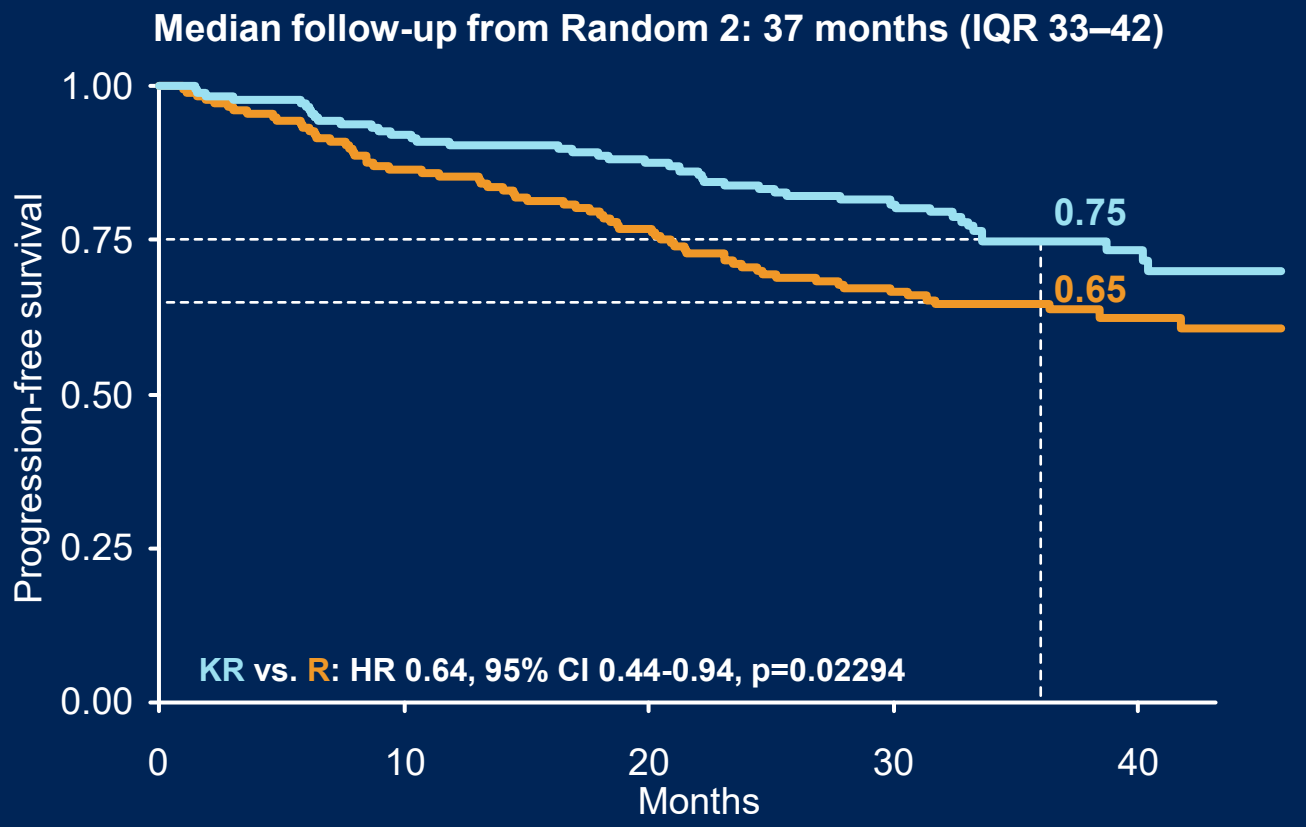
Gay F et al. Blood. 2018;132(Supplement 1):Abstract #121 [ASH 2018 60th Meeting]. doi:10.1182/blood-2018-99-112093.

Progression-free survival

KRd_ASCT vs. KRd12 vs. KCd_ASCT



KR vs. R

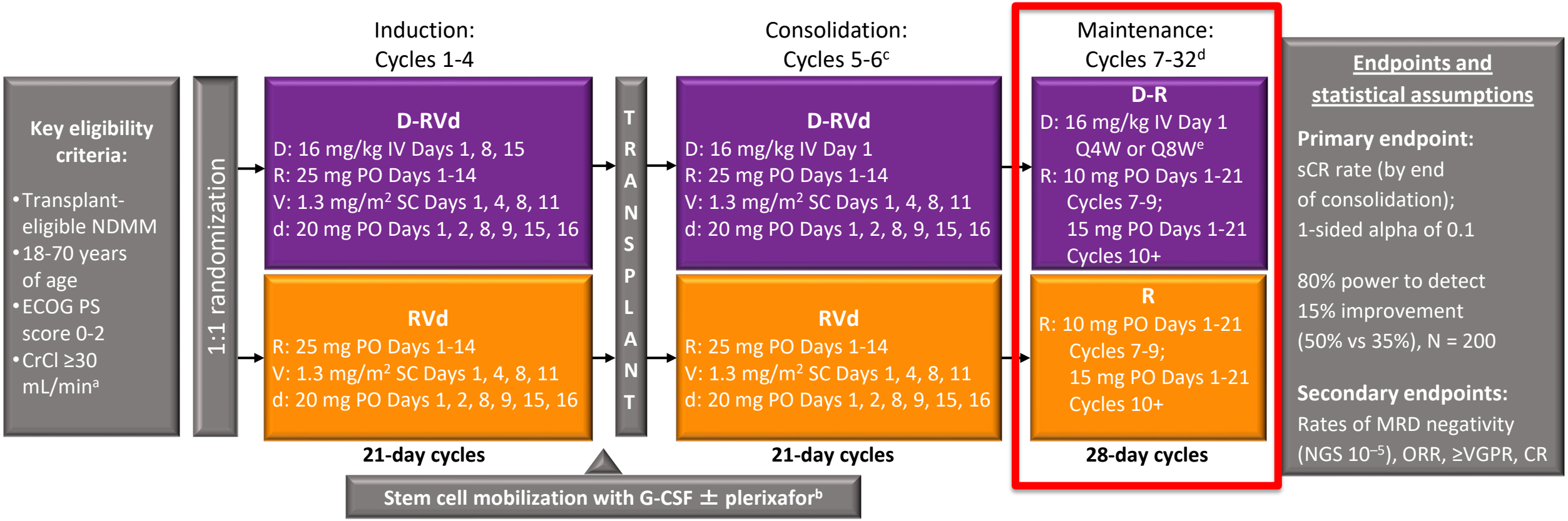


3-year PFS reported in the figure. Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; Random 2, second randomization (maintenance treatment); p, p-value; HR, hazard ratio; CI, confidence interval.

Number at risk
KR vs R: HR 0.64, 95% CI 0.44 - 0.94, p-value=0.02294

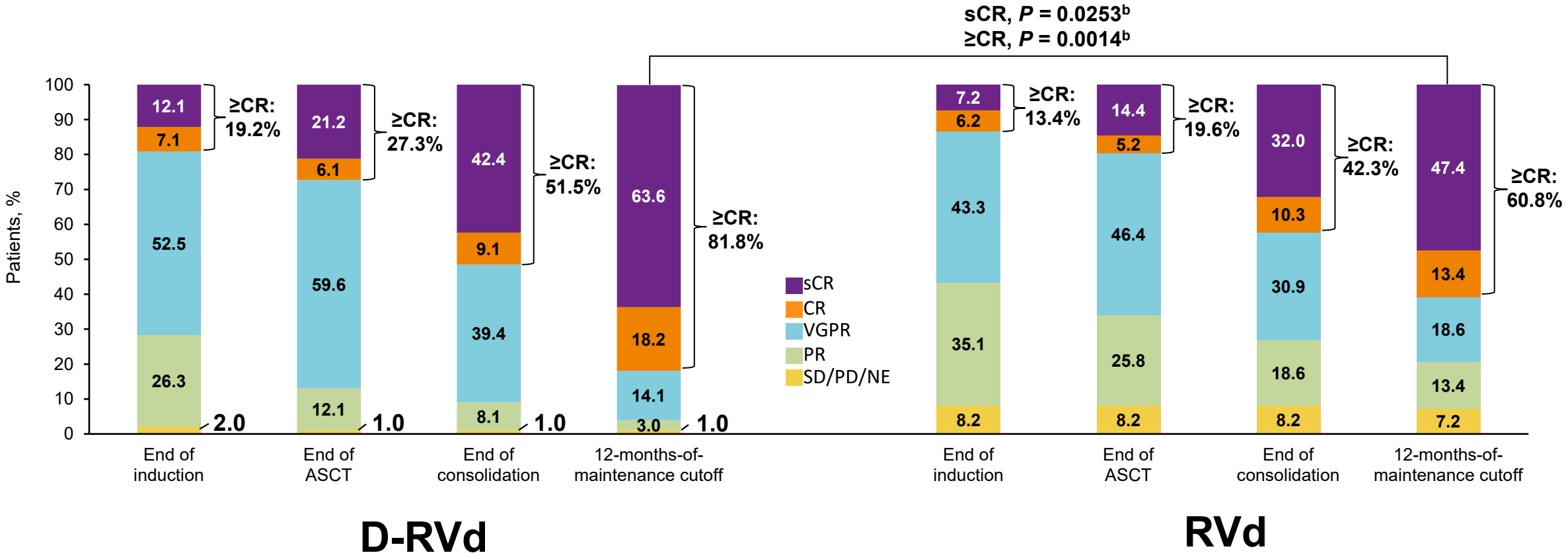
GRIFFIN: Randomized Phase

- Phase 2 study of D-RVd versus RVd in transplant-eligible NDMM, 35 sites in the United States with enrollment between December 2016 and April 2018



ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; G-CSF, granulocyte colony-stimulating factor; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response. [a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60 to 100 days post transplant. [d]Patients who complete maintenance cycles 7 to 32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

Responses Deepened over Time[a]



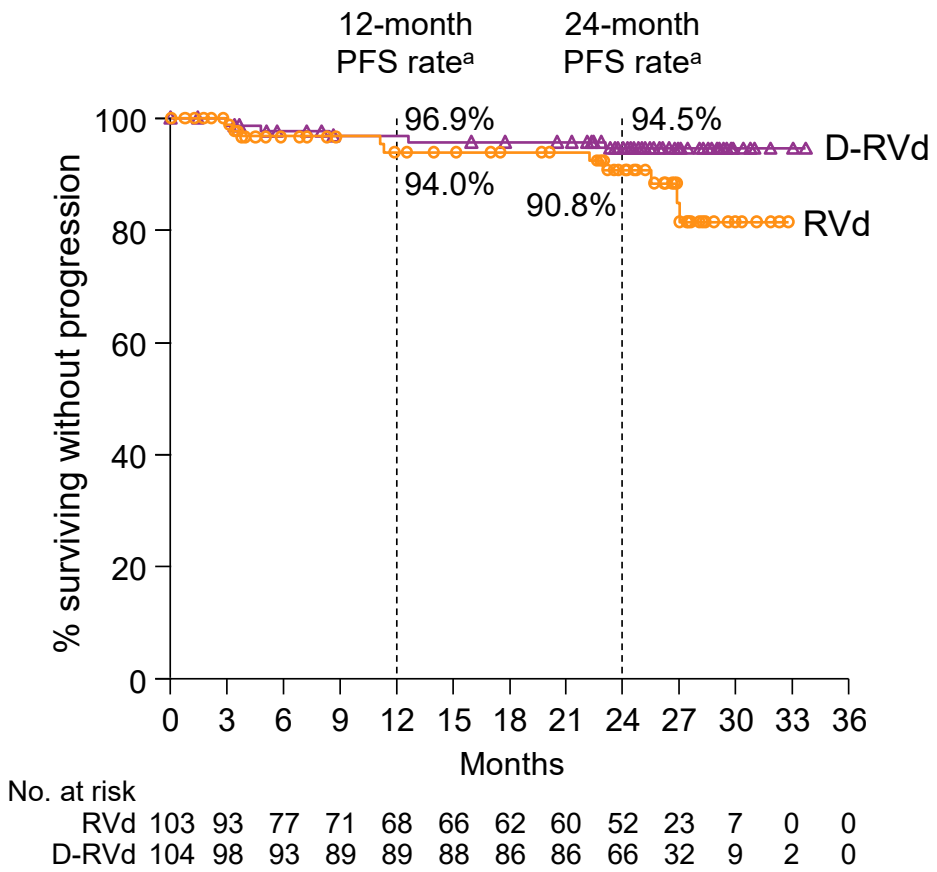
- *Results for end of induction, ASCT, and consolidation are based on a median follow up of 13.5 months at the primary analysis*
- *Median follow up at 12-months-of-maintenance therapy cutoff was 27.4 months*

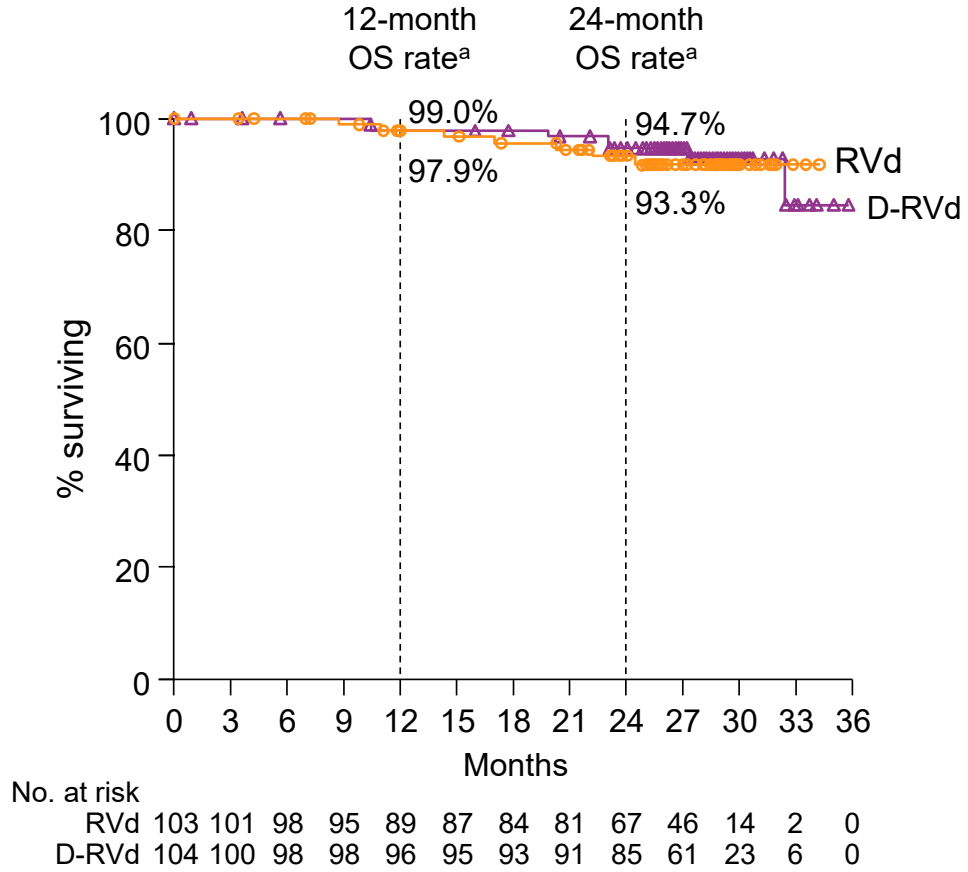
Response rates and depths were greater for D-RVd at all time points

PR, partial response. SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test.

PFS and OS in the ITT Population

- Median follow-up = 27.4 months

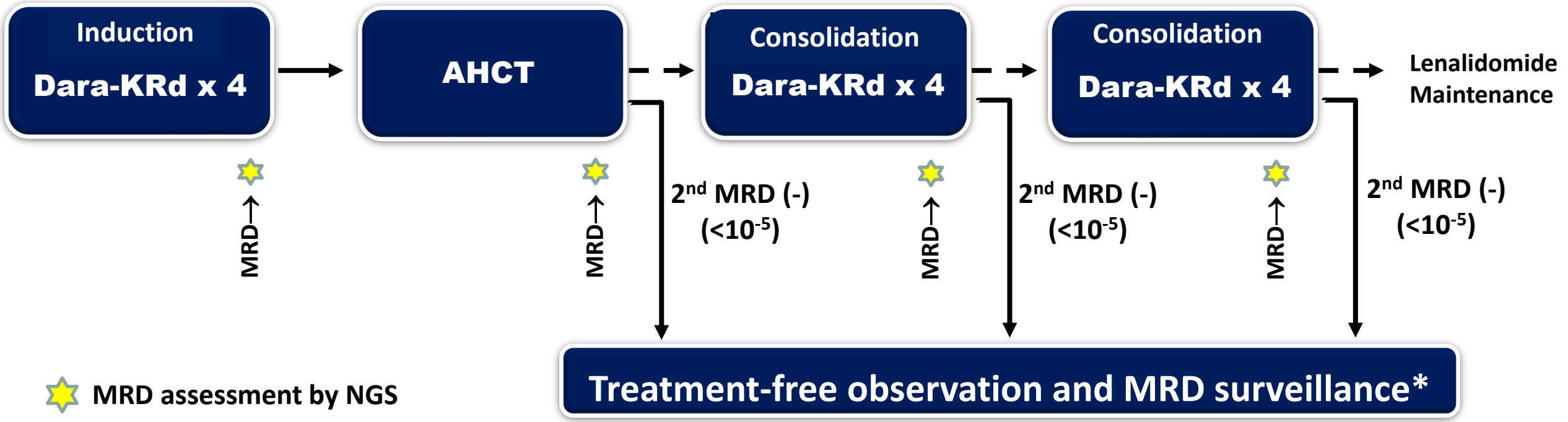




Median PFS and OS were not reached for D-RVd and RVd

OS, overall survival. [a]Kaplan–Meier estimate.

MASTER: Phase 2 Study of Dara-KRd in TEMM



Dara-Based Quads: Depth of Response

	N	Post-Induction		Post-ASCT		Post-Consolidation		
		sCR	≥VGPR	sCR	≥VGPR	sCR	≥VGPR	MRD-
VTd	542	6.5%	56.1%	9.4%	67.4%	20.3%	78.0%	43%
D-VTd	542	7.4%	64.9%	13.4%	76.7%	28.9%	83.4%	62%
RVd	103	7.2%	56.7%	14.4%	66.0%	32.0%	72.9%	20.4%
D-RVd	104	12.1%	71.7%	21.2%	86.9%	42.4%	90.9%	51.0%
D-KRd	81	39%	91%	81%	100%	95%	100%	82%

Costa L, et al. ASH 2019.

Moreau, P et al. *Lancet* 2019;394:29-38.

Voorhees P, et al. ASH 2019.

Transplant Eligible

Key Questions:

1. Is Transplant still necessary?

   YES, it seems that it still helps with DEPTH and DURATION of response

2. What is the triplet combination? (VRD or KRD)

   Both are legitimate, we tend to use VRD more but KRD in certain patients

3. Should we switch to quadruplet combinations? (D-VRD, D-KRD or I-VRD, I-KRD)

   It is still early, but is clearly promising and will come soon…

Transplant Ineligible

- Key Questions:

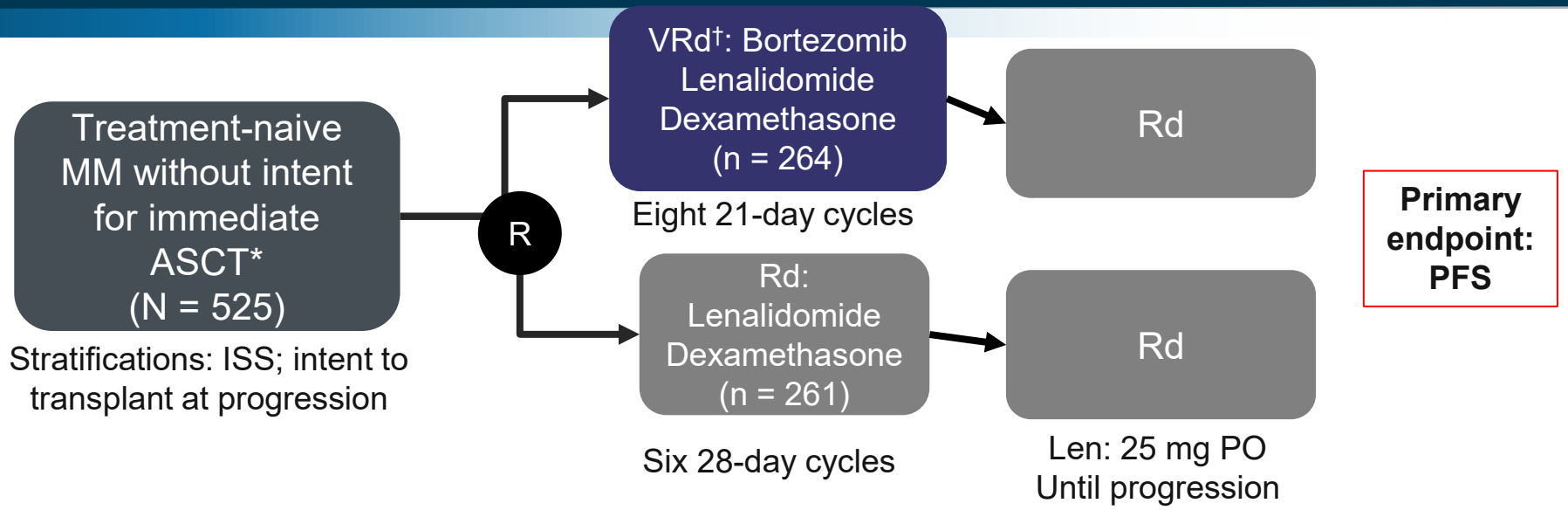
1. Are triplets better than Doublets? (VRD vs RD and DRD vs RD)

2. How long should patients be treated?

3. How can we make these combinations more tolerable?

VRd vs Rd: SWOG S0777 Data

3-Drug Regimen as Initial Induction



	VRd	Rd	HR; *P* Value
Median PFS, mo	43	30	0.712; .0018 (1-sided)
Median OS, mo	75	64	0.709; .025 (2-sided)

VRd showed better PFS in patients with high- or standard-risk vs Rd‡

*All patients received aspirin (325 mg/d). †Patients received HSV prophylaxis.
‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

Durie BG, et al. *Lancet.* 2017;389:519-527.

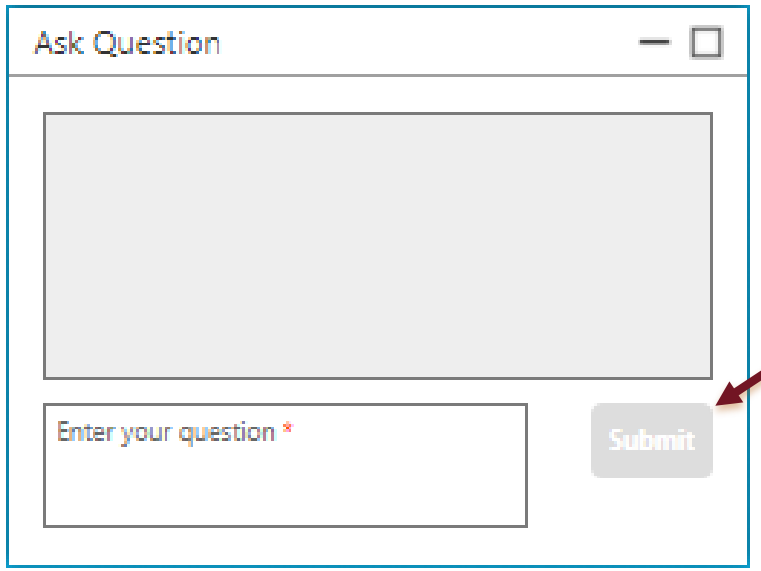
Audience Q&A with Panel

Kelly Cox
International Myeloma Foundation
Los Angeles, CA

Joseph Mikhael, MD
TGen
Phoenix, AZ

Amrita Krishnan, MD
City of Hope Medical Center
Duarte, CA

Deb Doss, RN, OCN
Dana-Farber Cancer Institute
Boston, MA



Type and submit your questions here. Click the Q&A icon circled below if you have minimized the Ask Question window.

REGIONAL COMMUNITY WORKSHOP

BREAK

10 minutes

Agenda After the Break

Relapsed Therapy and Clinical Trials

Amrita Krishnan, MD, City of Hope Medical Center, Duarte, CA

Q & A with Panelist

How to Manage Myeloma Symptoms and Side Effects

Deb Doss, RN, OCN, Dana-Farber Cancer Institute, Boston, MA

Q&A with Panel

Relapsed Therapy and Clinical Trials

Amrita Krishnan, MD, City of Hope Medical Center, CA

RELAPSED MYELOMA

AMRITA KRISHNAN, M.D.
Director of Judy and Bernard Briskin Multiple Myeloma Center
Professor of Hematology and Hematopoietic Cell Transplantation

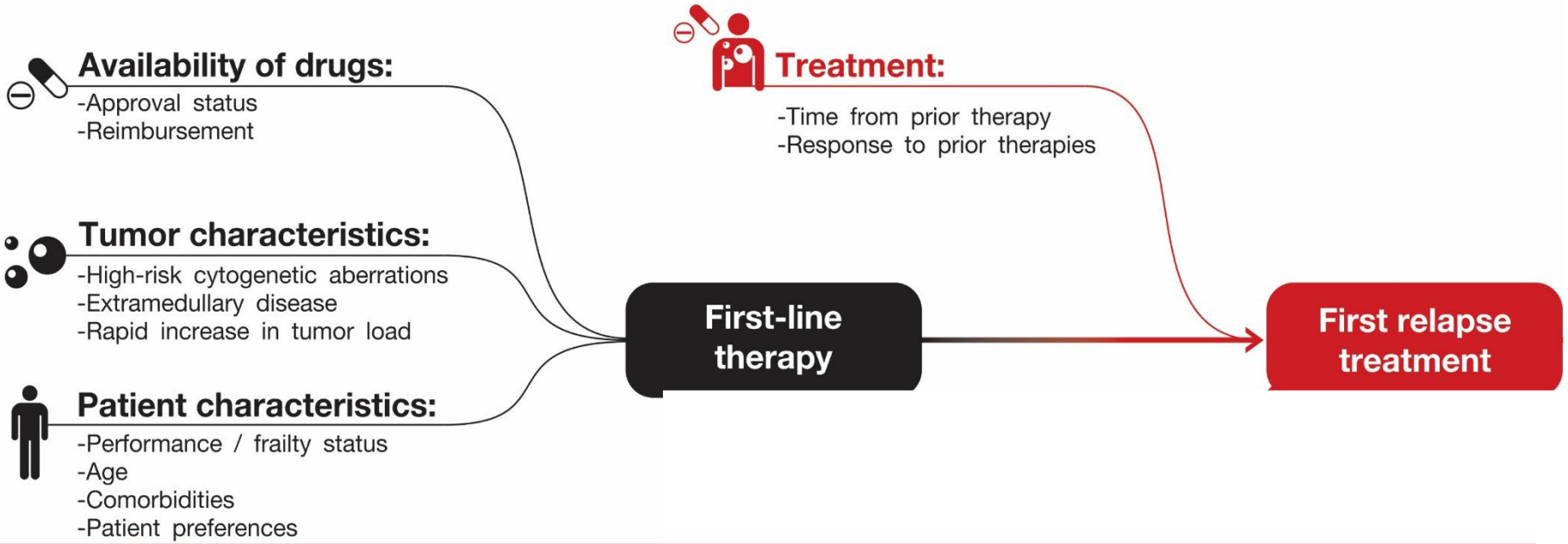
Newport Beach on a hot day on Saturday, April 25, 2020, during the COVID pandemic

(Telephoto lens Photo by Mindy Schauer, Orange County Register/SCNG)

Newport Beach on the same day (still of aerial video from helicopter)

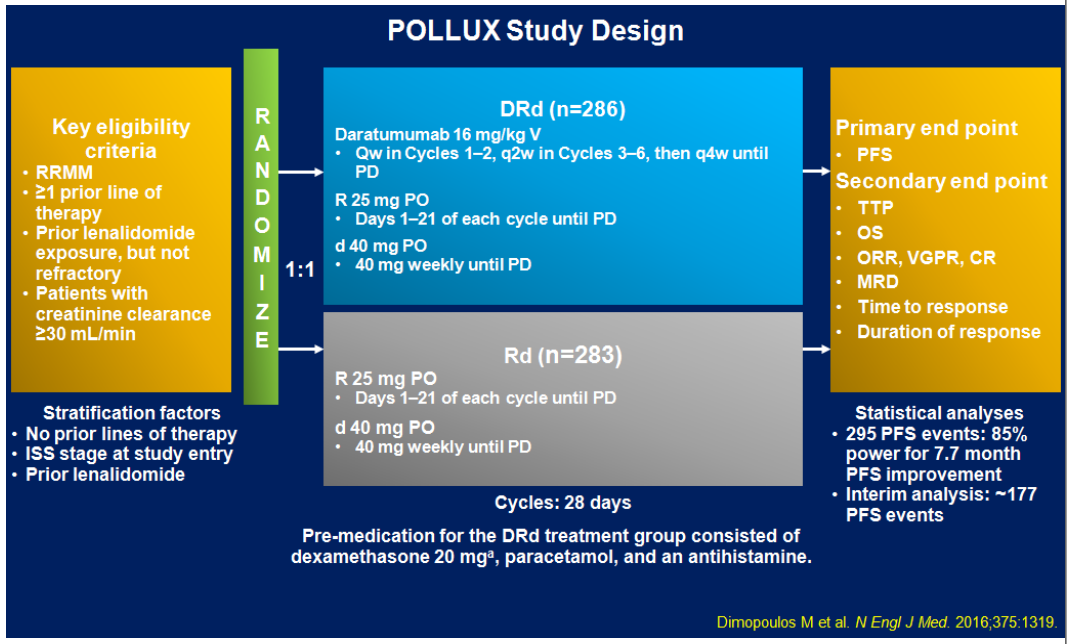
First relapse

- Treatment selection dependent on patient-, tumor-, and treatment-related factors

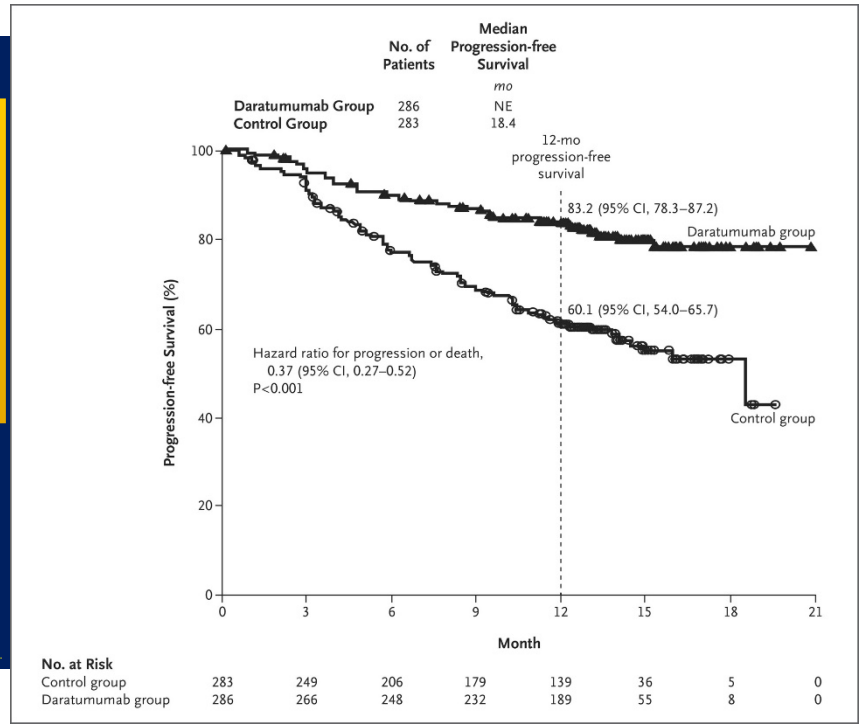


- Sequencing of drugs with different modes of action
- Triplet regimens are superior to doublet regimens (response rate and PFS, and in some studies also OS)
- (Dose-adjusted) doublet can be the best option for frail patients
- Reusing a drug can be considered based on prior response and treatment-free interval

In 2021: CASTOR and POLLUX are emblematic of active combinatorial regimens



POLLUX



Dimopoulos et al, NEJM 2016;375:1319-1331.

Randomized studies with lenalidomide-dexamethasone control arms

	Carfilzomib*		Elotuzumab		Daratumumab		Ixazomib	
N	KRd vs Rd 792		ERd vs Rd 646		DRd vs Rd 569		IRd vs Rd 722	
Efficacy	Tx	Control	Tx	Control	Tx	Control	Tx	Control
Median follow up, mos	67		Min 48 mos		32.9		23	
ORR	87.1%	66.7%	79%	66%	93%	76%	78.3%	71.5%
CR	32%	9.3%	5%	9%	55%	23%	12%	7%
Median PFS, mos	26	16.6	19	14.9	NR	17.5	21	14.7
PFS HR (95% CI)	0.69 (0.57–0.83)		0.71 (0.59–0.86)		0.44 (0.34–0.55)		0.74 (0.59–0.94)	
Median OS, mos	48.3	40.4	48.3	39.6	NR	NR	NR	NR
OS HR (95% CI)	0.79 (0.67–0.95)		0.78 (0.63–0.96)		NR		NR	

*PFS HR 0.58 @ 18 mos

Dimopoulos MA et al. *N Engl J Med*. 2016;375:1319; Dimopoulos MA et al. *Br J Haematol*. 2017;178:896; Stewart AK et al. *N Engl J Med*. 2015;372:142; Stewart AK et al. *Blood*. 2017;130: Abstract 743.; Dimopoulos M et al. *J Hematol Oncol*. 2018;11:49; Moreau P et al. *N Engl J Med*. 2016;374:1621.

The good news: Many regimens are improving outcomes for patients with relapsed myeloma (DVd vs Vd; DRd vs Rd; KRd vs Rd)

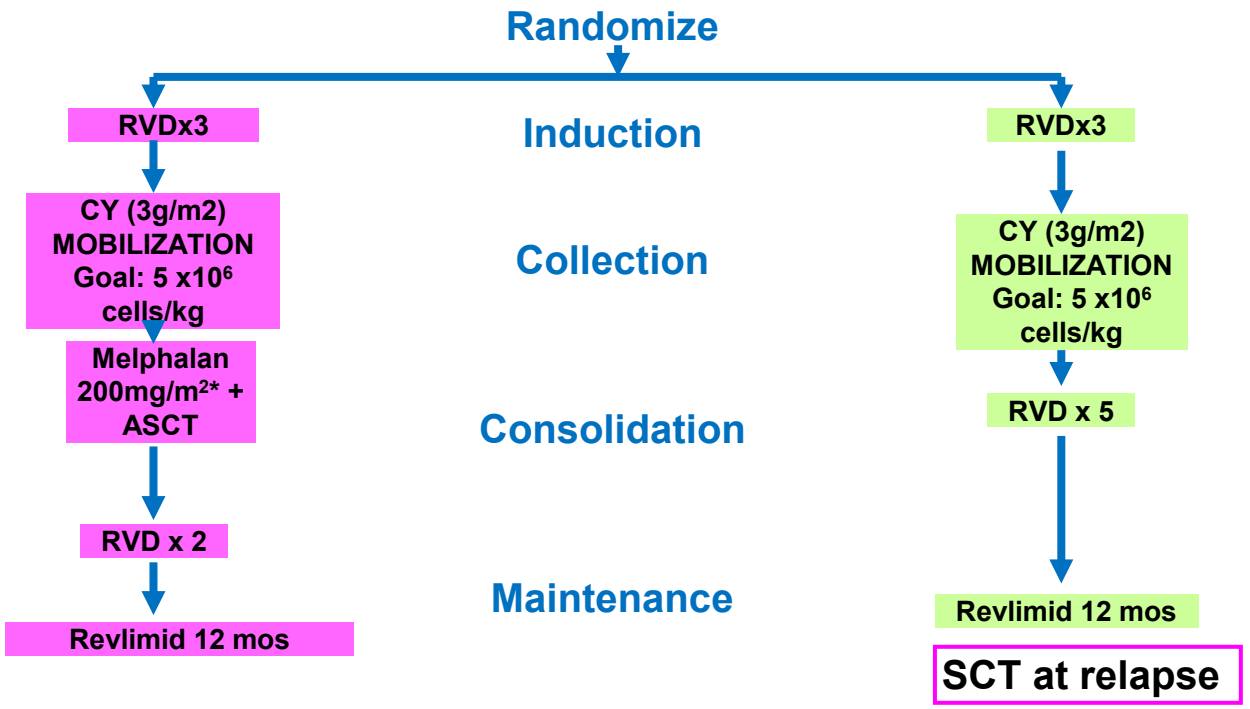
Japan to stage Tokyo Olympics without overseas spectators

Mar 9, 2021 | KYODO NEWS

The reality bringing us back to earth: Most patients are relapsing on lenalidomide maintenance.

Don’t forget about transplantation

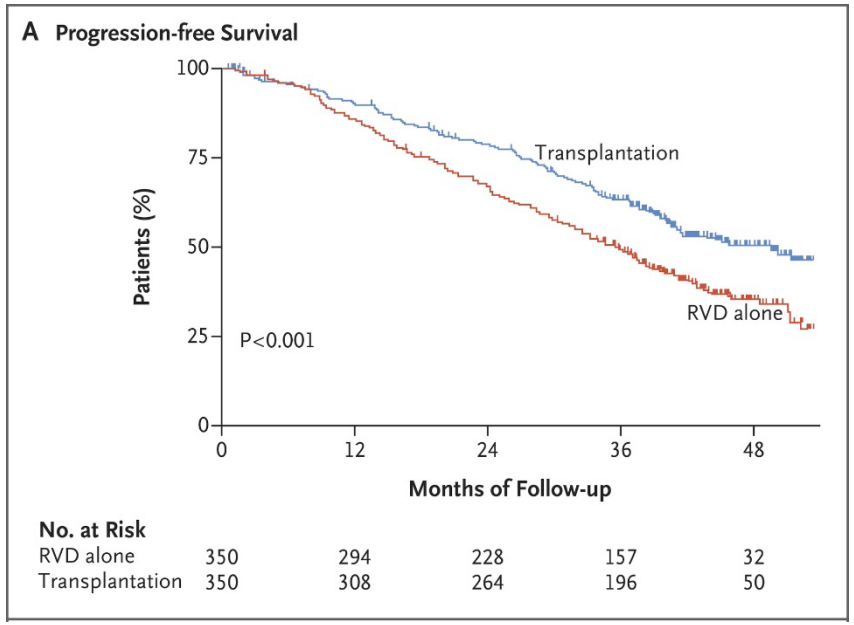
IFM/DFCI 2009 study

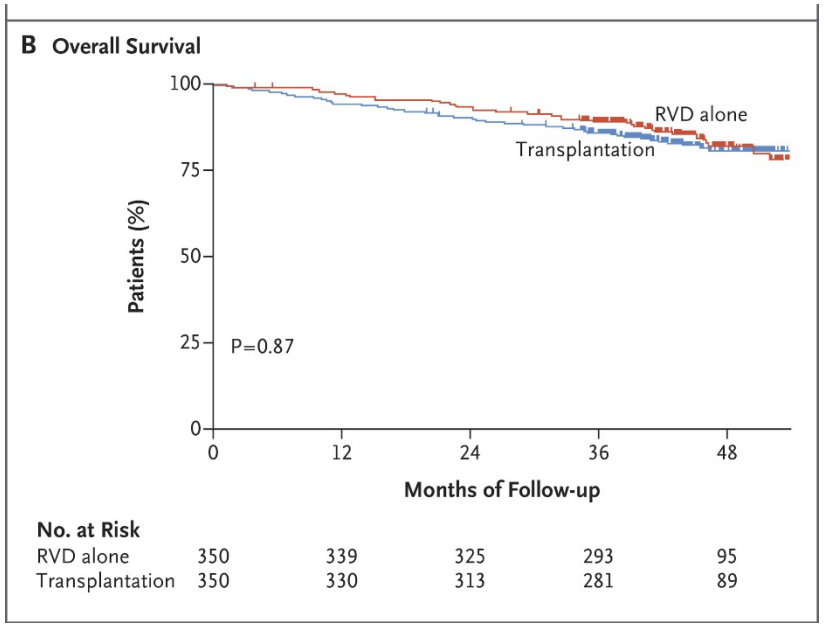


Attal et al., NEJM 2017;376:1311-20

Don’t forget about transplantation

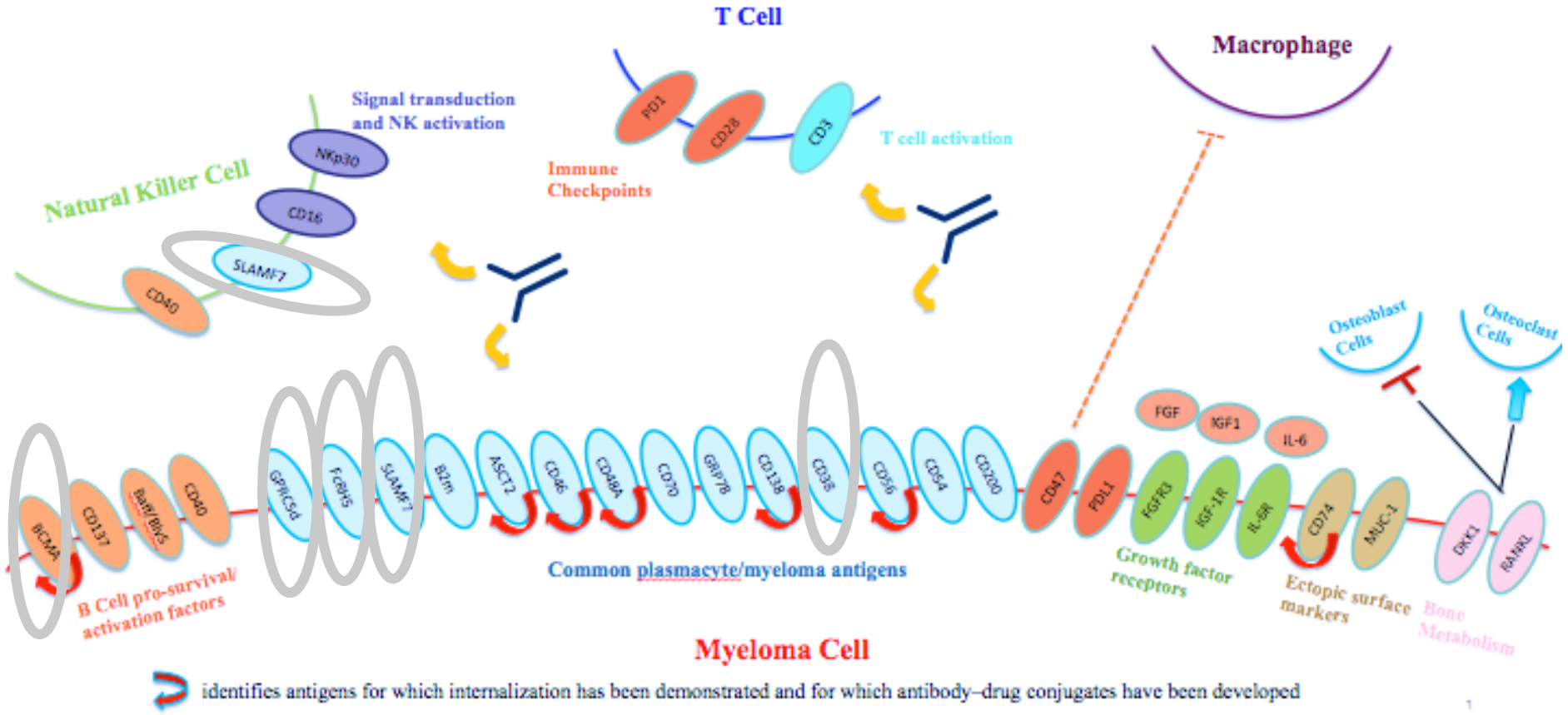
Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma





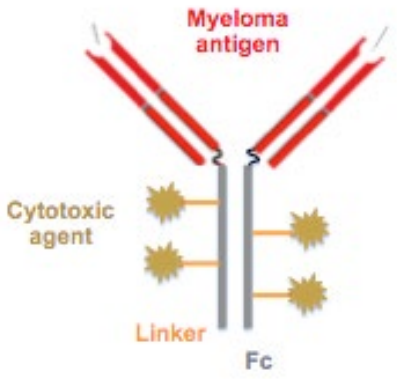
Attal et al., NEJM 2017;376:1311-20

Immunotherapeutic Targets in Multiple Myeloma

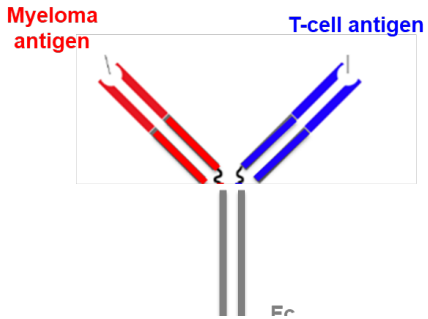


Anti-Multiple Myeloma Immunotherapeutic Agent Structures

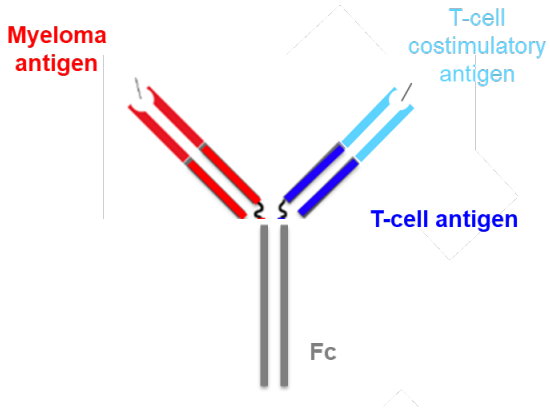
Antibody Drug Conjugate



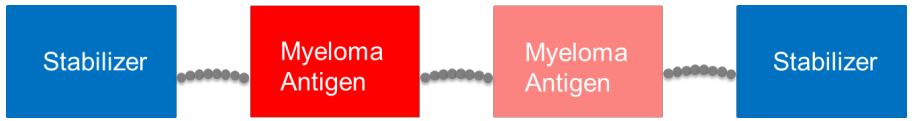
T-Cell Bispecific Antibody



T-Cell Trispecific Antibody

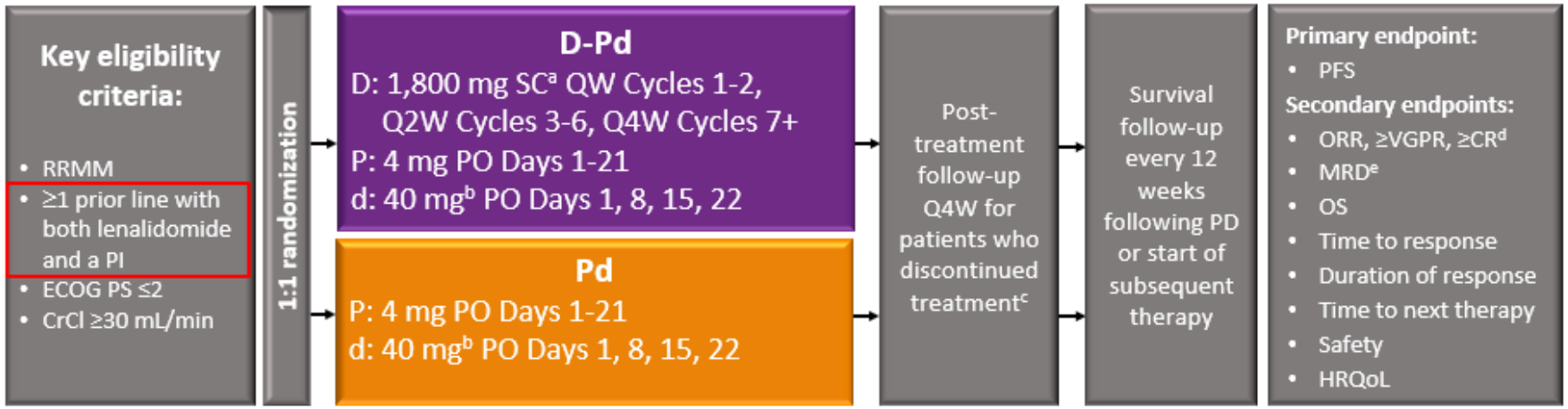


Designed ankyrin repeat proteins (DARPins)

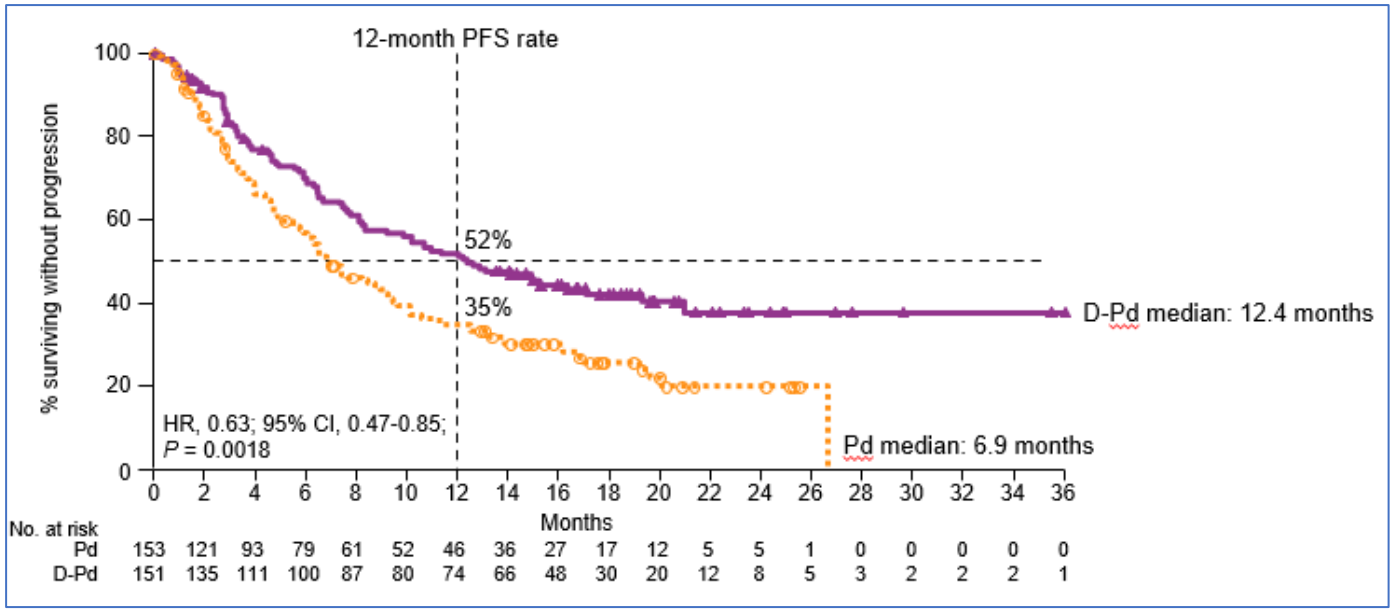


Lancman, et al. ASH 2020.

APOLLO: Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Vs Pomalidomide and Dexamethasone (Pd) Alone

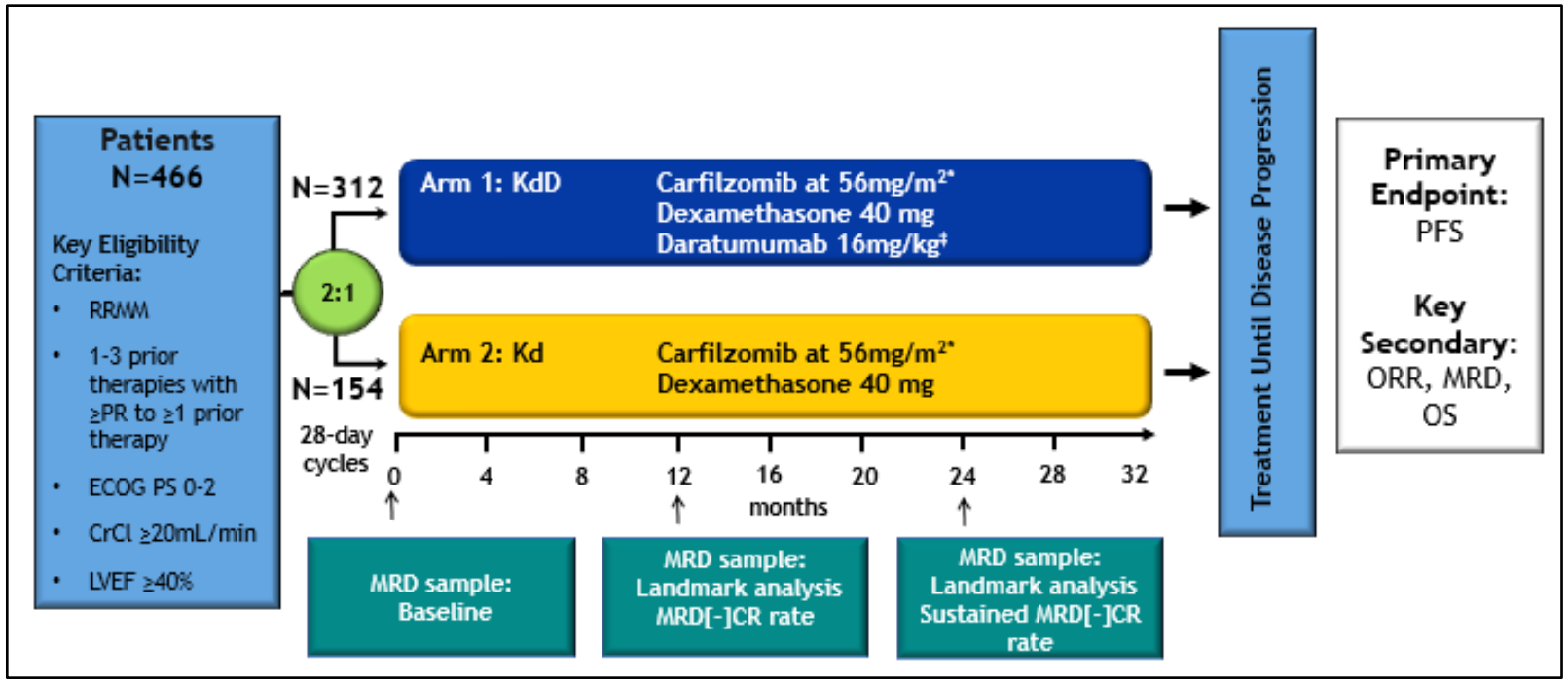


APOLLO: Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Vs Pomalidomide and Dexamethasone (Pd) Alone

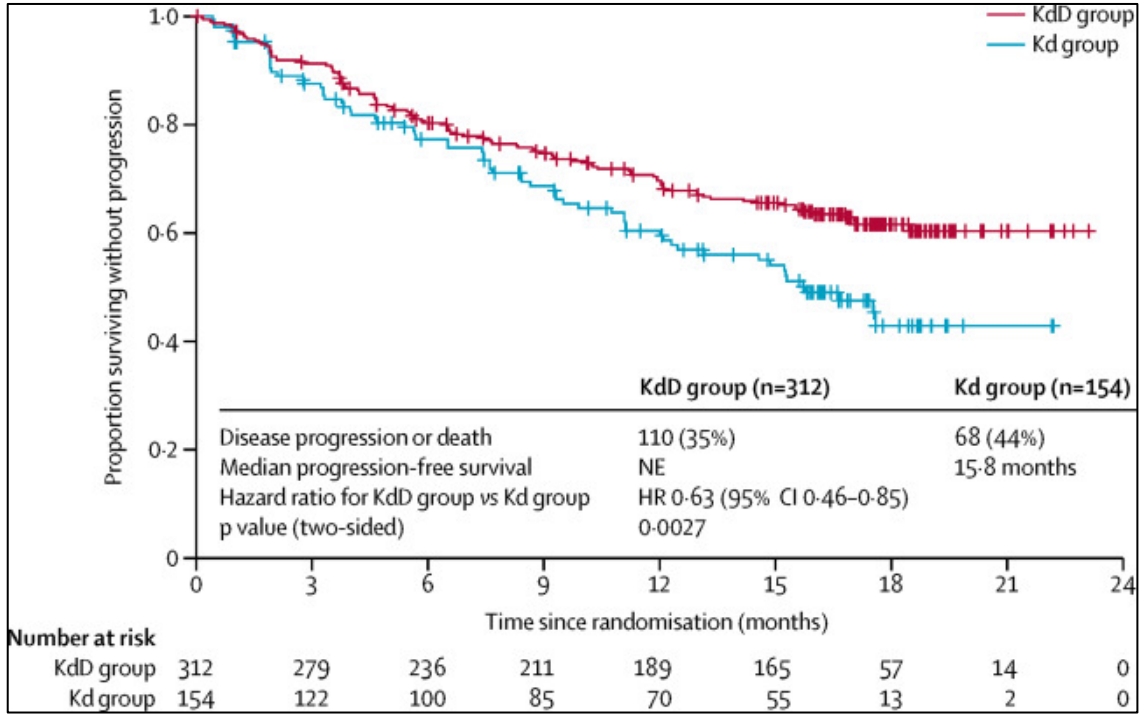


Dimopolous et al., 2020; 136(Supplement 1): 5-6

CANDOR: Carfilzomib, Dexamethasone, and Daratumumab Vs Carfilzomib and Dexamethasone alone



CANDOR: Carfilzomib, Dexamethasone, and Daratumumab Vs Carfilzomib and Dexamethasone alone



Dimopoulos et al., Lancet 2020;396:186-97.

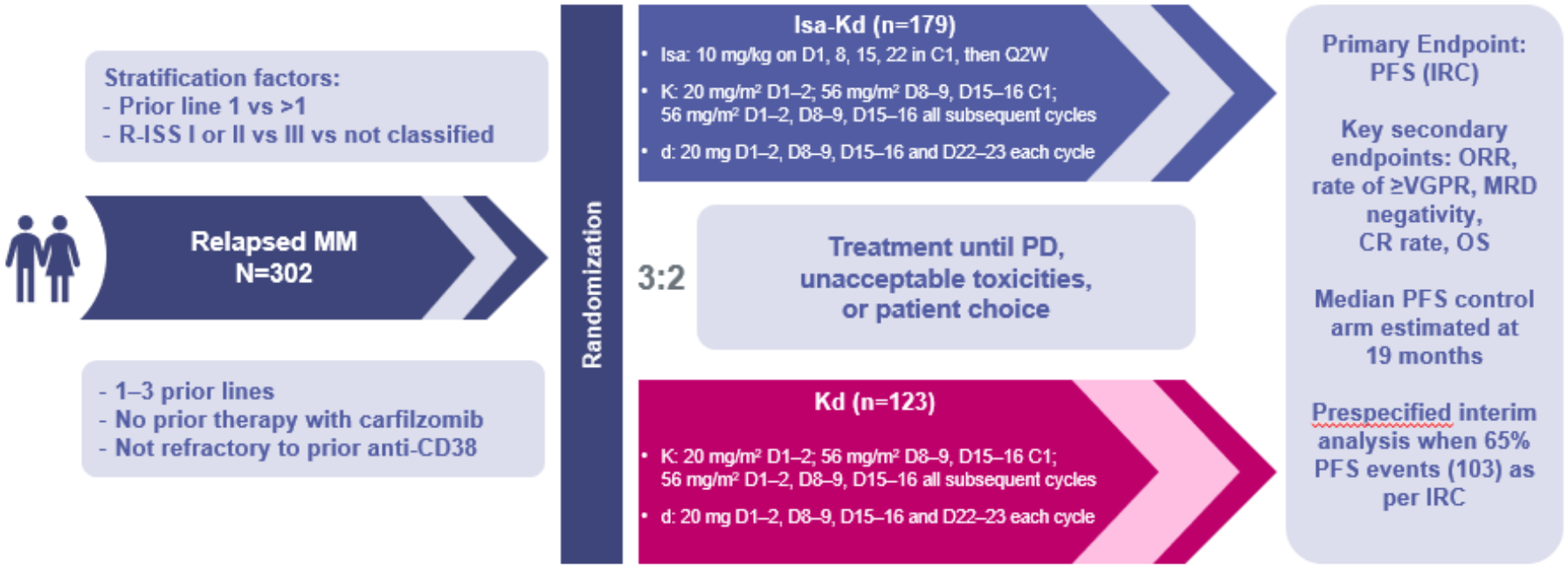
CANDOR: Carfilzomib, Dexamethasone, and Daratumumab Vs Carfilzomib and Dexamethasone alone

	Carfilzomib, dexamethasone, and daratumumab group (n=308)					Carfilzomib and dexamethasone group (n=153)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological adverse events										
Thrombocytopenia	115 (37%)	40 (13%)	49 (16%)	26 (8%)	0	45 (29%)	20 (13%)	19 (12%)	6 (4%)	0
Anaemia	101 (33%)	50 (16%)	48 (16%)	3 (1%)	0	48 (31%)	26 (17%)	21 (14%)	1 (1%)	0
Neutropenia	43 (14%)	17 (6%)	24 (8%)	2 (1%)	0	15 (10%)	6 (4%)	7 (5%)	2 (1%)	0
Lymphopenia	27 (9%)	6 (2%)	9 (3%)	12 (4%)	0	12 (8%)	1 (1%)	9 (6%)	2 (1%)	0
Non-haematological adverse events										
Hypertension	94 (31%)	40 (13%)	54 (18%)	0	0	42 (27%)	22 (14%)	20 (13%)	0	0
Upper respiratory tract infection	90 (29%)	82 (27%)	7 (2%)	1 (<1%)	0	35 (23%)	33 (22%)	2 (1%)	0	0
Diarrhoea	97 (31%)	85 (28%)	12 (4%)	0	0	22 (14%)	21 (14%)	1 (1%)	0	0
Fatigue	75 (24%)	51 (17%)	23 (7%)	1 (<1%)	0	28 (18%)	21 (14%)	7 (5%)	0	0
Dyspnoea	61 (20%)	49 (16%)	12 (4%)	0	0	34 (22%)	30 (20%)	4 (3%)	0	0
Pneumonia	55 (18%)	14 (5%)	32 (10%)	5 (2%)	4 (1%)	19 (12%)	6 (4%)	12 (8%)	1 (1%)	0
Adverse events of interest										
Respiratory tract infections (HLGT)	225 (73%)	136 (44%)	77 (25%)	7 (2%)	5 (2%)	84 (55%)	60 (39%)	22 (14%)	1 (1%)	1 (1%)
Viral infection (JMQ)	63 (20%)	44 (14%)	19 (6%)	0	0	22 (14%)	19 (12%)	2 (1%)	0	1 (1%)
Peripheral neuropathy (SMQN)	53 (17%)	50 (16%)	3 (1%)	0	0	13 (8%)	13 (8%)	0	0	0
Daratumumab-related infusion reaction (AMQN)†	56 (18%)	49 (16%)	7 (2%)	0	0	0	0	0	0	0
Cardiac failure (SMQN)	23 (7%)	11 (4%)	9 (3%)	1 (<1%)	2 (1%)	16 (10%)	3 (2%)	10 (7%)	3 (2%)	0
Acute renal failure (SMQN)	18 (6%)	9 (3%)	5 (2%)	4 (1%)	0	12 (8%)	2 (1%)	6 (4%)	4 (3%)	0
Ischaemic heart disease (SMQN)	13 (4%)	4 (1%)	7 (2%)	2 (1%)	0	5 (3%)	1 (1%)	4 (3%)	0	0

Data are n (%). Haematological and non-haematological all-grade adverse events (preferred terms) occurring in ≥20% of patients and grade ≥3 adverse events (preferred terms) occurring in >5% of patients in either treatment group are shown; no percentage cutoff was applied to adverse events of interest. AMQN=Amgen MedDRA query—narrow. HLGT=high level group terms. JMQ=Janssen MedDRA query. MedDRA=Medical Dictionary of Regulatory Activities. SMQN=Standardised MedDRA query—narrow. *The safety population included all patients who received at least 1 dose of trial treatment. †Event on same date or next date of any daratumumab dosing.

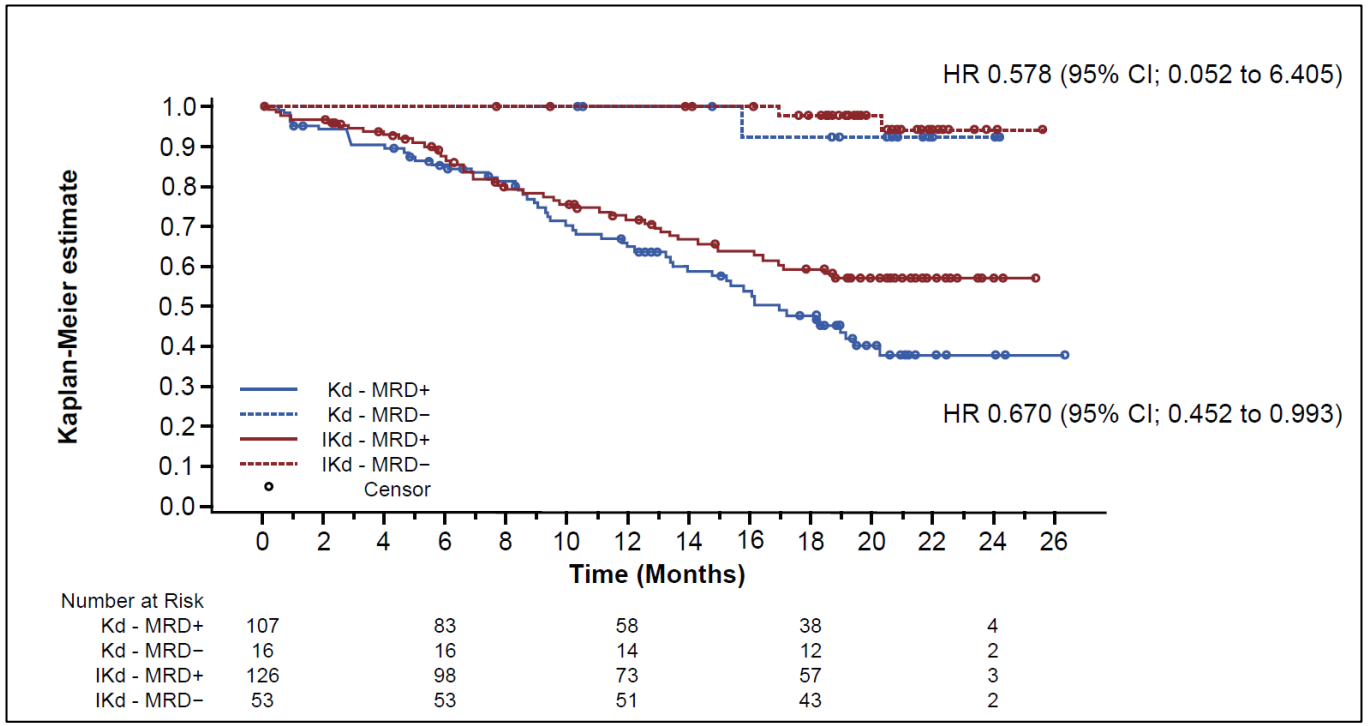
Dimopoulos et al., Lancet 2020;396:186-97.

IKEMA: Isatuximab/Carfilzomib/Dexamethasone (Isa-Kd) vs Carfilzomib/Dexamethasone (Kd) alone

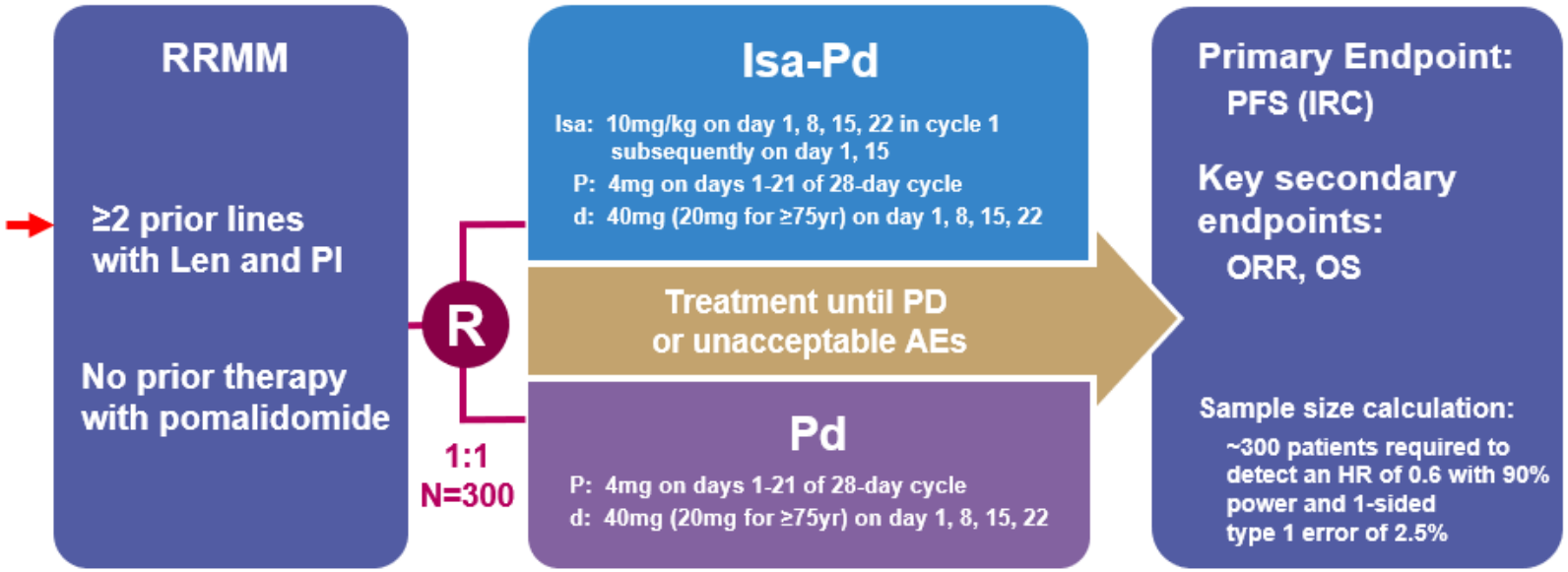


Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

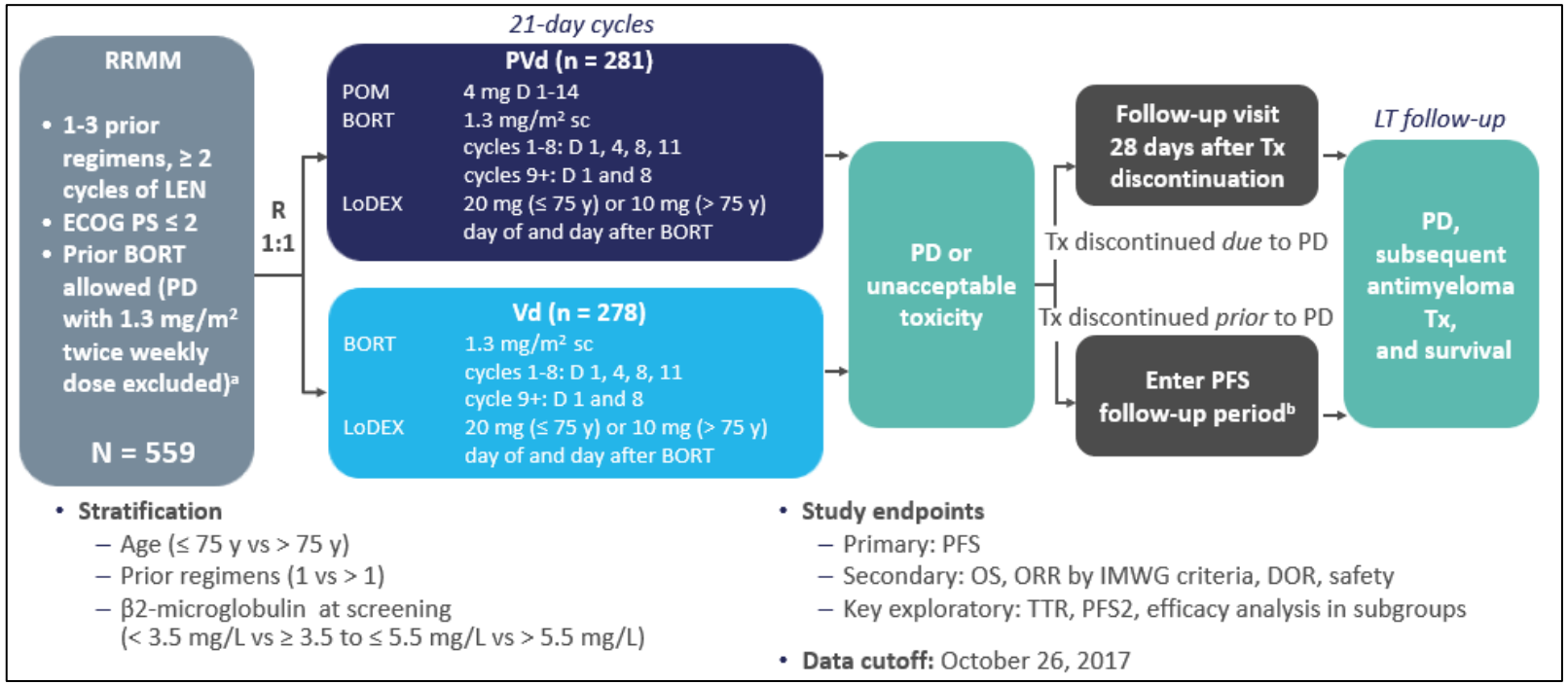
IKEMA: Isatuximab/Carfilzomib/Dexamethasone (Isa-Kd) vs Carfilzomib/Dexamethasone (Kd) alone



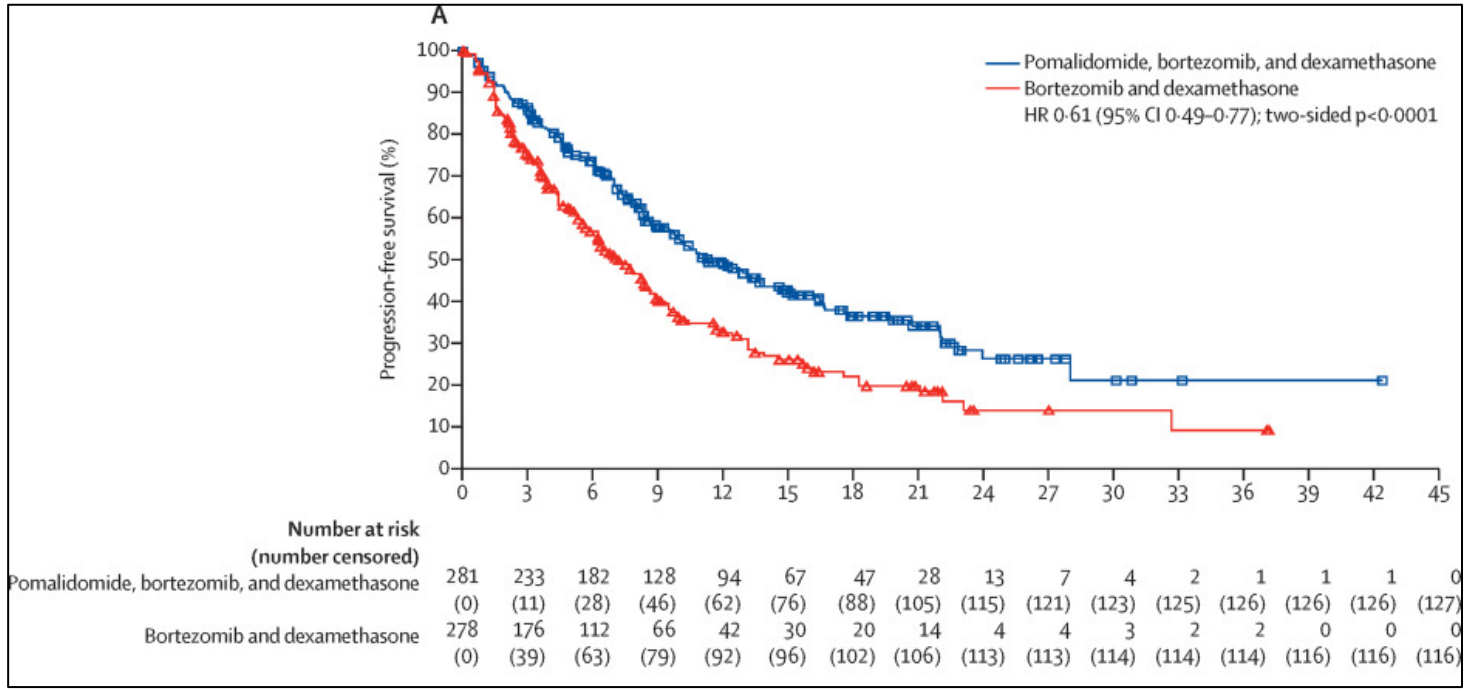
ICARIA: Isatuximab/Pomalidomide/Dexamethasone (Isa-Pd) vs Pomalidomide/Dexamethasone (Pd) alone



OPTIMISMM: Pomalidomide, Bortezomib, and Dexamethasone vs Bortezomib and Dexamethasone alone, in Lenalidomide-exposed patients



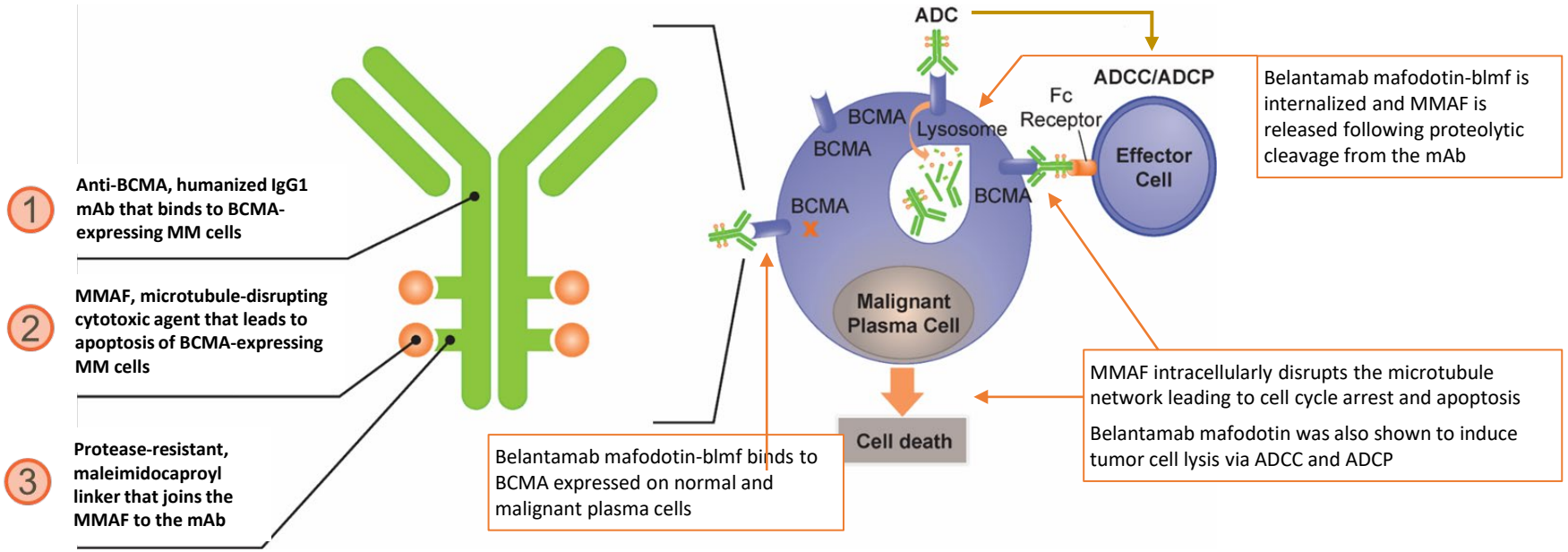
OPTIMISMM: Pomalidomide, Bortezomib, and Dexamethasone vs Bortezomib and Dexamethasone alone, in Lenalidomide-exposed patients



Richardson et al. Lancet Oncol 2019; 20:781-94.

Belantamab Mafodotin Overview

Belantamab mafodotin-blmf is a BCMA-directed antibody and microtubule inhibitor conjugate, composed of 3 components[1,2]



Tai Y-T, et al. Blood. 2014;123(20):3128–3138. 2. Farooq A, et al. Ophthalmol Ther. 2020 July 25. doi:

BCMA Antibody Drug Conjugates

Study	DREAMM-1	DREAMM-2	DREAMM-4	DREAMM-6	MEDI2228
Phase	I	II	I/II	I/II	I
Treatment (All are IV q 3wk)	Belamaf dose escalation, expansion 3.4 mg/kg	Belamaf 2.5 or 3.4 mg/kg	Belamaf 2.5 or 3.4 mg/kg + pembro	Belamaf 2.5 mg/kg + bortezomib-dex	MEDI2228
Patients	n=35	n=196	n=13	n=18	n= 82
Median prior lines	5	6-7	8/ 5	3	range 2-11
Triple-class refractory	37%	100%	NR	NR	NR (100% exposed)
ORR %	60% (38.5% if prior dara exposure)	31% / 34%	67% / 14%	78%	61% (25/41) (0.14 mg /kg)
PFS	12 months (6.8 months if prior dara)	2.9 / 4.9 months	NR	NR	NR
AEs- all grade (gr3+) Keratopathy Thrombocytopenia Anemia Infusion reaction Other	 52% (3%) 63% (35%) 28% (17%) 12% (3%)	 70% (27%)/ 75% (21%) 35% (20%)/ 58% (34%) 24% (20) / 37% (25%) 21% (3%) / 16% (1%)	 67% (33%) / 57% (0%) 50% (0%) / 14% (0%)	 100% (56%) 67% (61%) 17% (0%)	 0% 32% (NR) Photophobia 54% Dry eye 20% Rash (29%) Pleural eff (20%)

Phase 3 DREAMM studies recruiting: 3: Blmf vs Pd, 7: BlmfVd vs DVd, 8: BlmfPd vs VPd

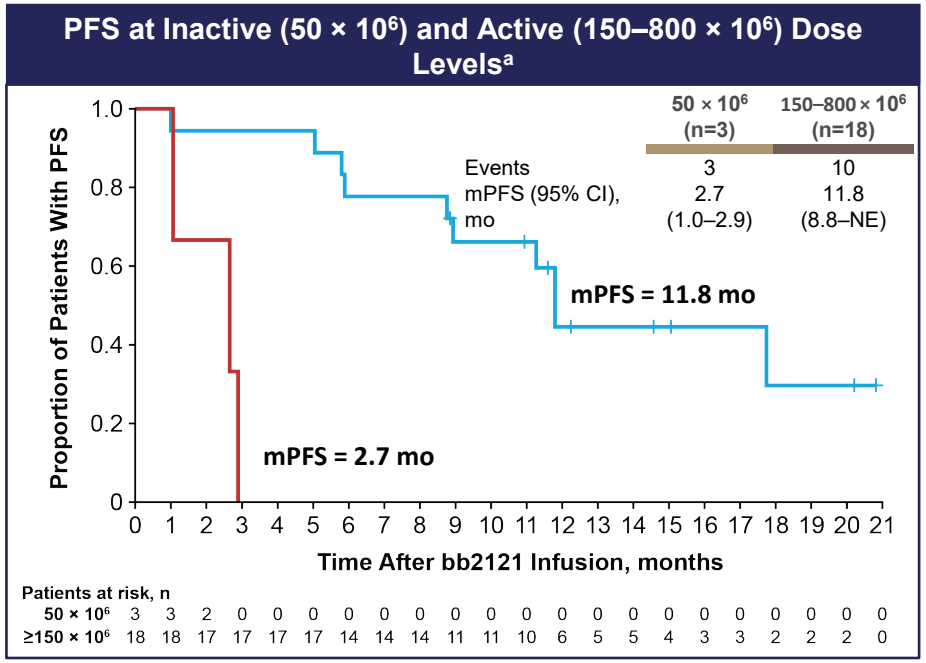
Trudel, et al. *Blood Cancer J* 2019; Lonial, et al. *Lancet Oncol* 2019; Nooka, et al. *Hematology Reports* 2020;; Popat, et al. ASH 2020; Kumar, et al. ASH 2020

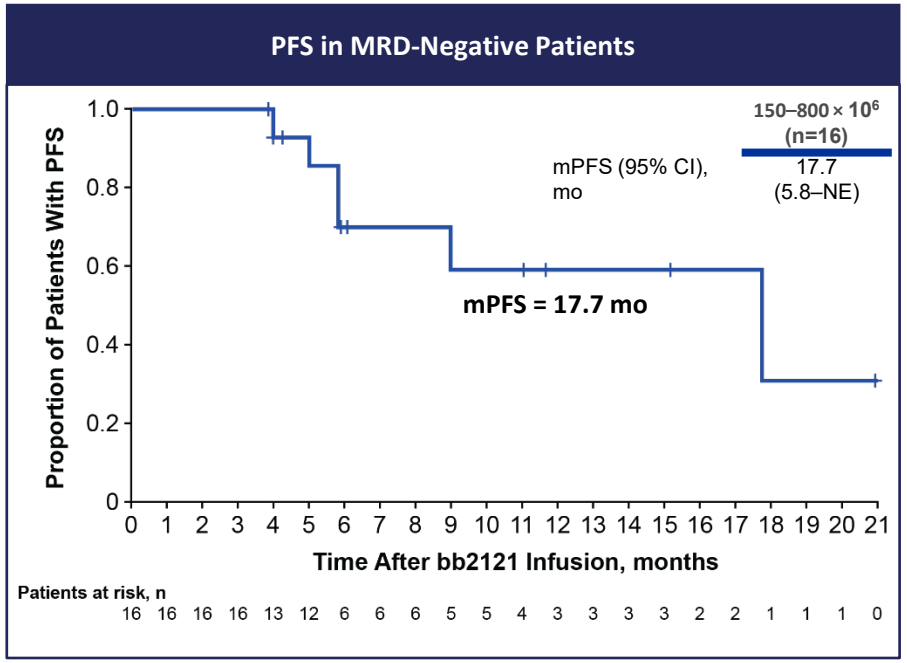
ABECMA

- Triple Class exposed (received an IMID, PI, and anti CD38 monoclonal antibody) and have received at least four prior lines of therapy

BB2121 ANTI-BCMA CAR-T PHASE I RESULTS

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

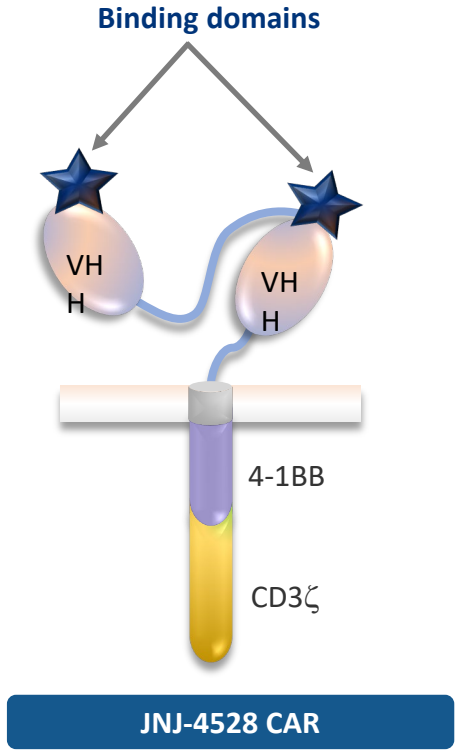




Raje et al, ASCO 2019, NEJM 2019

JNJ-4528: BCMA-targeted CAR-T Cell Therapy

- **JNJ-68284528 (JNJ-4528) is a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy**
  - Contains a CD3ζ signaling domain and 4-1BB costimulatory domain
  - 2 BCMA-targeting single domain antibodies designed to confer avidity
  - Identical to the CAR construct used in the LEGEND-2 study
- **LEGEND-2 (N = 74): Phase 1 investigator-initiated study conducted in China**
  - High, deep, and durable overall response and manageable safety in R/R MM[a,b]

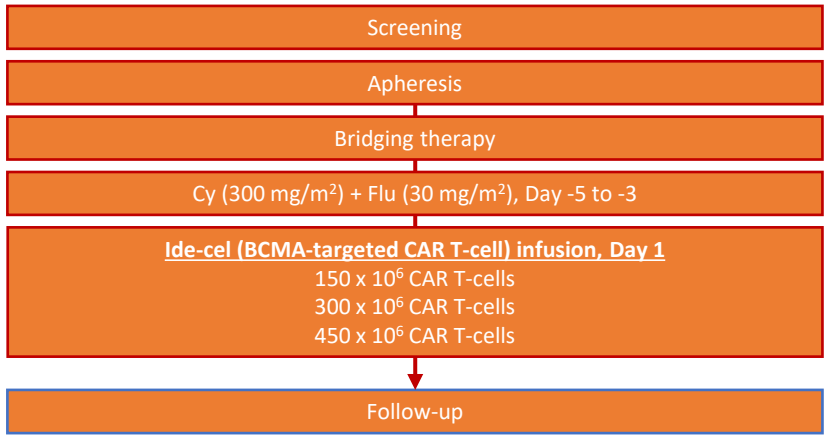


[a]Zhao et al. *JHO* 2018;11(1):141; [b]Xu et al. *PNAS* 2019;116(19):9543; BCMA=B-cell maturation antigen; MM=multiple myeloma; R/R=relapsed/refractory; VHH=single variable domain on a heavy chain

KarMMa Phase 2 Study of Idecabtagene Vicleucel (Ide-cel) in Patients With RRMM: Study Design and Patients

Ide-cel is a CAR T-cell therapy targeting BCMA

Key eligibility criteria
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- RRMM after ≥3 prior tx, including PI, IMiD, and anti-CD38 mAb



Patient Characteristics	(N=128)
Median age, y (range)	69 (33-78)
ISS stage (I/II/III), %	11/70/16
High-risk cytogenetics[a], %	35
High tumor burden (≥50% BMPCs), %	51
Tumor BCMA expression (≥50% BCMA+), %	85
Extramedullary disease, %	39
Median prior tx, n (range)	6 (3-16)
Received 1 or >1 prior ASCT, %	94/34
Received bridging tx for MM, %	88
Refractory to anti-CD38 mAb/ triple-refractory to PI, IMiD, and anti-CD38 mAb	94/84

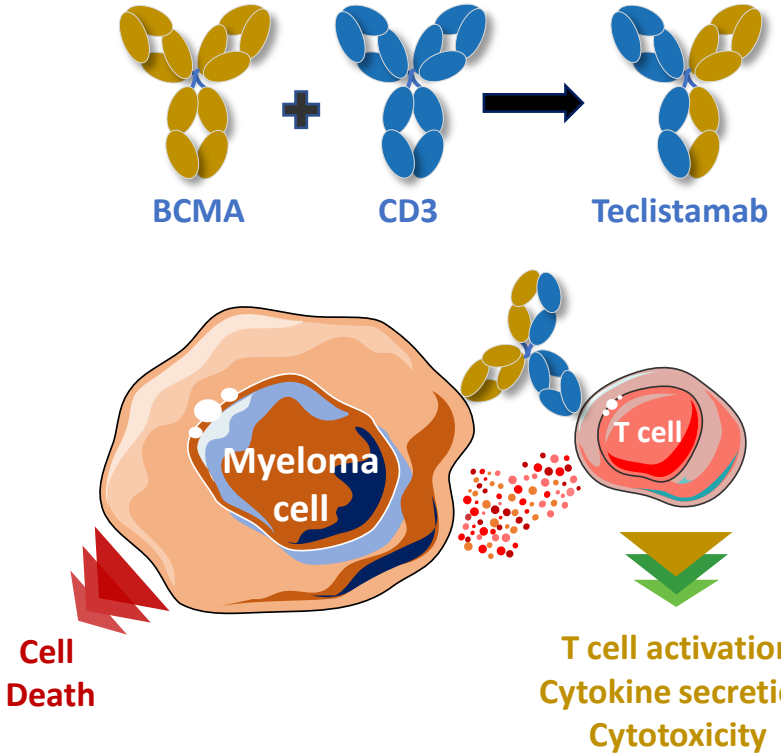
Primary endpoint: ORR
Secondary endpoints: CRR (key), safety, DoR, PFS, OS, PK, MRD, QoL, HEOR
Exploratory endpoints: immunogenicity, BCMA expression/loss, cytokines, T-cell immunophenotype, GEP in BM

[a]Defined as del(17p), t(4;14), or t(14;16). Baseline cytogenetics NE/missing for 17 patients; 45 (35%) had 1q amp abnormality.
Munshi NC, et al. ASCO 2020. Abstract 8503.

autoSCT, autologous stem cell transplantation; CRR, complete response ratio; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory imide drug; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life; R-ISS, Revised International Staging System.

Teclistamab: BCMA × CD3 DuoBody® Antibody

- Prognosis is poor for patients who progress on available classes of therapies, with ORR ~30%, mPFS of ~3 months, and mOS between 6–11 months[1]
- Teclistamab (JNJ-64007957)[a] is a humanized BCMA × CD3 bispecific IgG-4 antibody that redirects $CD3^+$ T cells to BCMA-expressing myeloma cells
- Teclistamab induces T cell-mediated killing of myeloma cells from heavily-treated patients and in xenograft models[2-4]
- Updated results from an ongoing phase 1 study of teclistamab administered IV or SC in patients with RRMM (NCT03145181) are presented here[5]



1. Ghandi *Leukemia* 2019;33:2266. 2. Labrijn AF *PNAS*. 2013;110:5145. 3. Frerichs KA *Clin Cancer Res*. 2020;26:2203. 4. Pillarisetti K *Blood Adv.* 2020;4:4538. 5. Usmani SZ. *JCO* 2020:38 (Suppl) Abstract 100. BCMA, B-cell maturation antigen; IV, intravenously; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; RRMM, relapsed and/or refractory multiple myeloma; SC, subcutaneously. [a]Includes technology licensed from GenMab.

Bispecific Antibodies- BCMAxCD3

Bispecific Antibody	AMG-420	AMG-701	CC-93269	PF-06863135	REGN5458	JNJ-64007957 (Teclistamab)	TNB-383B
Treatment	Continuous IV 4/6 weeks	Weekly IV	Weekly IV	Weekly SC	Weekly IV	Weekly IV or SC	IV q3w
Patients	n=42	n= 75	n= 19	n=18	n=45	n= 84 (IV), 44 (SC)	n= 38
Median prior lines	3.5	6	6	7	5	6	7
Triple-class refractory	IMiD + PI 36% Dara 21%	68%	IMiD 84%, PI 90%, Dara 89%	NR; 22% prior BCMA-directed	93%	79%	NR
ORR at therapeutic dose	7/10 (70%); 5 MRD- (400 µg/d)	16/45 (36%) (3-12mg)	10/12 (83%) 9 MRD – (≥ 6mg)	6/8 (75%) (215 and 260 µg/kg)	60% (96mg)	30/47 (64%) 6 MRD-; (IV 270 & 720 µg/kg SC 720 & 1500	12/23 (52%) (≥ 5.4mg)
Duration of Response	9 months	3.8 mos (14/17 ongoing)	NR	NR	≥ 4 months- 44%	NR (up to 21 months +)	
AEs, (All/(Gr 3+) CRS Infections Neutropenia Anemia Thrombocytopenia Deaths Other	38% (2%) 33% (24%) NR NR NR 4 (10%) Polyneuropathy (5%)	61% (7%) (17%) 23% 40% 20% 4 (5%) Neurotoxicity 8% (0%)	90% (5%) NR (26%) NR (53%) NR (42%) NR (21%) 1 (5%)	61% (0%) NR NR (22%) 50% (44%) 39% (28%) 3 (17%) ISR 33% (0%)	38% (0%) 47% (20%) NR NR (9%) NR 3 (7%) IRR 7% (0%)	53% (0%) NR (15%) 55% (23%) 55% (9%) 41% (NR) 4 (3%) ISR 25% (0%) IRR 5% (0%)	21% (0%) NR NR NR (16%) NR (13%) 5 (13%)

Topp, et al. *Journal of Clinical Oncology* 2020; Harrison, et al. ASH 2020; Costa, et al. ASH 2019; Lesokhin, et al. ASH 2020; Madduri, et al. ASH 2020; Garfall, et al. ASH 2020; Rodriguez, et al. ASH 2020

Updated Phase 1 Results of Teclistamab, a B-cell Maturation Antigen (BCMA) × CD3 Bispecific Antibody, in Relapsed and/or Refractory Multiple Myeloma (RRMM)

Alfred L. Garfall[1], Saad Z. Usmani[2], María-Victoria Mateos[3], Hareth Nahi[4], Niels W.C.J. van de Donk[5], Jesus F. San-Miguel[6], Albert Oriol[7], Laura Rosinol[8], Ajai Chari[9], Manisha Bhutani[2], Lixia Pei[10], Raluca Verona[10], Suzette Girgis[10], Tara Stephenson[10], Jenna D. Goldberg[10], Arnob Banerjee[10], Amrita Krishnan[11]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [2]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [3]Hospital Clinico Universitario de Salamanca, Salamanca, Spain; [4]Karolinska University Hospital at Huddinge, Stockholm, Sweden; [5]Amsterdam University Medical Center, Location VU University Medical Center, Amsterdam, The Netherlands; [6]Clínica Universidad de Navarra, Navarra, Spain; [7]Institut Català d'Oncologia and Institut Josep Carreras. Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [8]Hospital Clínic, Barcelona, Spain; [9]Mt. Sinai School of Medicine, New York, NY, USA; [10]Janssen R&D, Spring House, PA, USA; [11]City of Hope, Duarte, CA, USA

Additional information can be viewed by scanning the QR code or accessing this link: https://oncologysciencehub.com/ASH2020/bispecifics/Garfall.
The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way

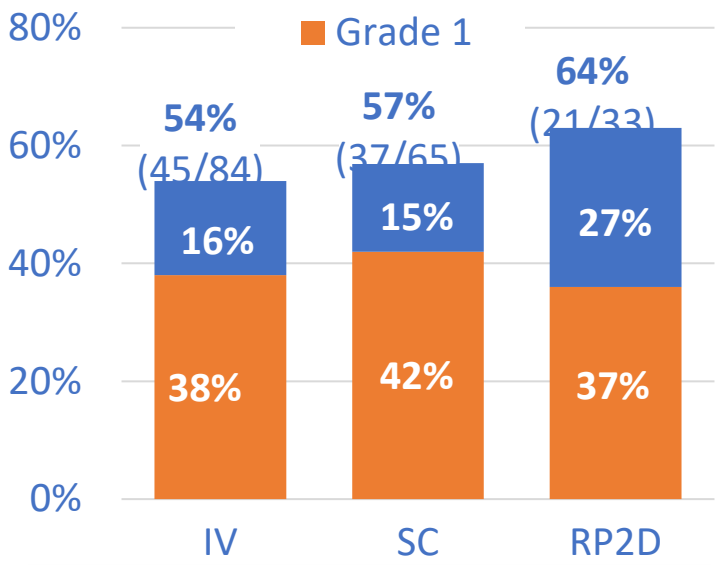
City of Hope.

Teclistamab: BCMA × CD3 DuoBody® Antibody

Parameter, n (%)	Total (N=149)	IV (n=84)	SC (n=65)
Patients with CRS	82 (55)	45 (54)	37 (57)
Median time to CRS onset[a] (range), days	2 (1–5)	1 (1–3)	2 (1–5)
Median duration of CRS (range), days	2 (1–8)	1 (1–7)	2 (1–8)
Patients with supportive measures to treat CRS[b]	76 (51)	43 (51)	33 (51)
Tocilizumab	35 (23)	22 (26)	13 (20)
Steroids	19 (13)	15 (18)	4 (6)
Low flow oxygen	9 (6)	6 (7)	3 (5)
Single low-dose vasopressor	1 (1)	1 (1)	0

- No treatment discontinuations due to CRS
- CRS was generally confined to step-up and first full doses

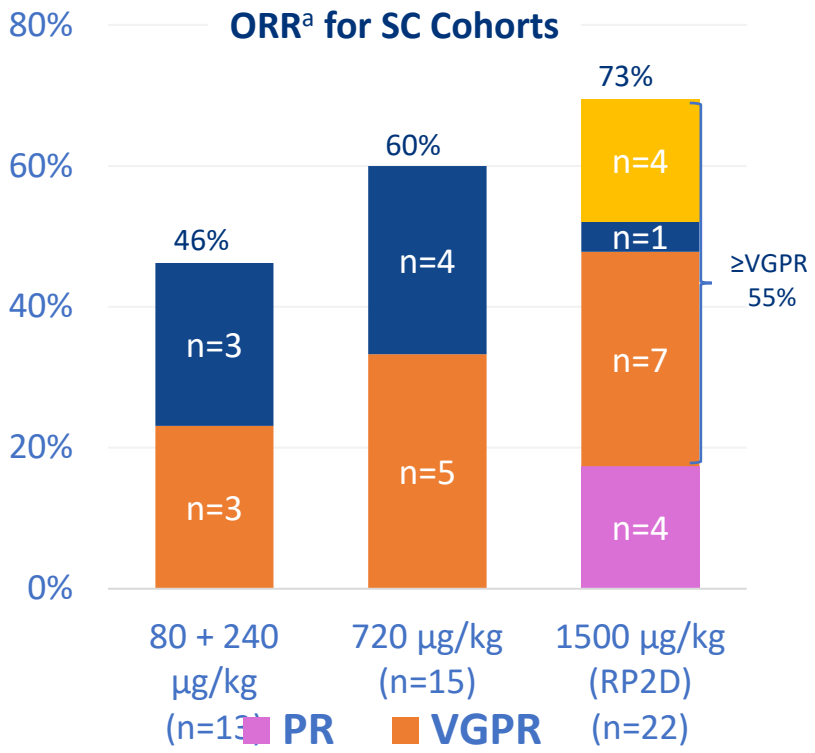
Maximum CRS Grade by Dose Groups[c]



- Step-up dosing to mitigate risk of severe CRS
- No grade ≥3 CRS events

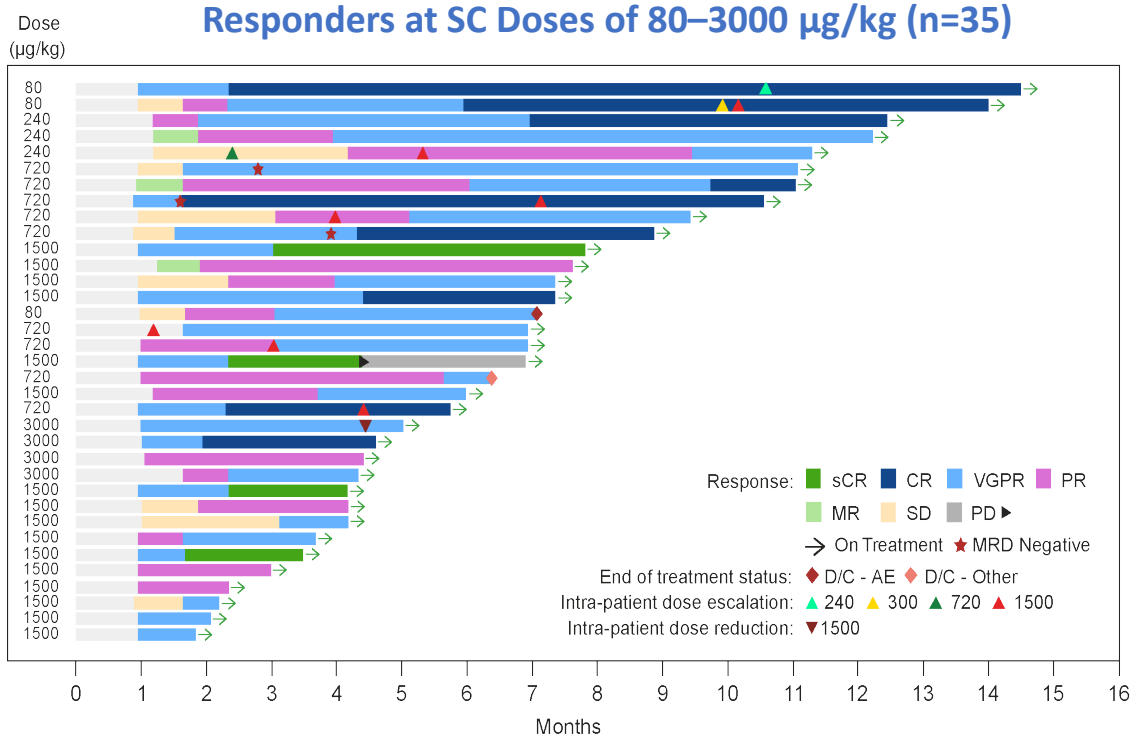
[a]Day 1 was day of most recent dose. [b]A patient could receive >1 supportive therapies. [c]Graded according to Lee et al. *Blood* 2014;124:188.

Teclistamab: Overall Response Rate



- At the RP2D of 1500 µg/kg SC:
  - Median time to first confirmed response was 1 month (0.3–3)
  - 14/20 (70%) triple-class refractory patients responded
  - 6/8 (75%) penta-drug refractory patients responded
- Most active doses were 270–720 µg/kg IV and 720–3000[b] µg/kg SC
  - ORR[a] at these doses was 69% (47/68)
  - ≥VGPR was 59%; ≥CR was 26%
  - 67% (18/27) ORR in IV cohorts and 71% (29/41) ORR in SC cohorts
- Of 11 evaluable patients across all IV and SC doses so far, 8 had MRD-neg CR at 10^{-6} and 1 at 10^{-5} sensitivity[c]

Teclistamab: Duration of Response



- Responses were durable and deepened over time
- Among responders treated at the RP2D, 15/16 (94%) are alive and progression-free after mF/U of 3.9 months (1.7–7.4)
- Among responders in SC cohorts, 32/35 (91%) remain on treatment with ongoing responses after mF/U of 6.5 months (1.7–14)
- Among responders treated at the most active IV and SC doses, 44/47 (94%) remain on treatment with ongoing responses after mF/U of 6.5 months (1.7–14)
- 5/5 evaluable patients across IV and SC cohorts showed sustained MRD negativity

BCMA CAR-T Cells ASCO 2020

Characteristics Summary

	KarMMA: Idecabtagene vicleucel (n = 128)	EVOLVE: orvacabtagene autoleucel (n = 62)	CARTITUDE-1: JNJ-4528 (n = 29)
Age	61 (33-78)	61 (33-77)	60 (50-75)
High Risk Cytogenetics, %	35	41	27
Tumor Burden in BM, %	>50% PC = 51	--	≥60% PC = 24
Extramedullary PCs, %	39	23	10
Median prior lines of therapy	6 (3-16)	6 (3-18)	5 (3-18)
Triple refractory, %	84	94	86
Bridging therapy, %	88	63	79
Unique properties	Human BCMA, 4-1BB, CD3z	Modified spacer, CD4:CD8 enriched for CM	Median cell dose 0.72 x10^6 cells/kg 2 BCMA single chain antibodies

BCMA CAR-T Cells ASCO 2020

Safety

	KarMMa	EVOLVE	CARTITUDE-1
↓ ANC ≥G3, %	89	90	100
↓ Plts ≥G3, %	52	47	69
CRS: all, ≥G3, %	84, 6	89, 3	93, 7
Med. Time to CRS, duration, days	1 (1-12) 5 (1-63)	2 (1-4) 4 (1—10)	7 (2-12) 4 (2-64)
ICANS: all, ≥G3, %	17, 3	13, 3	10, 3
HLH/MAS, %	--	5	? 7 (lfts)
Infections: all, ≥G3 %	69, --	40, 13	--, 19
Toci / steroid / anakinra use, %	52/15/0	76/52/23	79/21/21

Efficacy

	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-81)	92	100
sCR/CR, %	33	36	86
MRD neg ≥10^{-5}, % evaluable	94	84	81
PFS/DoR, months	8.8/10.7	NR	NR
Screened Apheresed Treated	150 140 128	--	35 35 29

Emerging Data on BMCA-Targeting Agents in R/R MM

Class	Agent	Trial	Prior Tx	N	Efficacy	Safety
CAR T-cell therapy	Idecabtagene vicleucel	Phase II KarMMa[1]	≥ 3 prior tx; prior IMiD, PI, anti-CD38	158	▪ ORR: 73%; CR: 33% ▪ mTTR: 1.0 mo ▪ PFS: 8.8 mos	▪ CRS: 84% (gr 3/4/5: 4%/< 1%/< 1%) ▪ NT: 18% (gr 3: 3%)
	JNJ-4528	Phase Ib/II CARTITUDE-1[2]	≥ 3 prior tx; prior IMiD, PI, anti-CD38 or double refractory to PI and IMiD	29	▪ ORR: 100%; sCR: 86% ▪ mTTR: 1 mo	▪ CRS: 93% (gr ≥ 3: 7%) ▪ ICANS: 10% (gr ≥ 3: 3%)
	Orvacabtagene autoleucel	Phase I/II EVOLVE[3]	≥ 3 prior tx; prior autoSCT, IMiD, PI, anti-CD38	62	▪ ORR: 92%; sCR/CR: 36%	▪ CRS: 3% (gr ≥ 3: 3%) ▪ Neurologic events: 3% (gr ≥ 3: 3%)
	Bb21217	Phase I CRB-402[4]	≥ 3 prior tx; prior PI and IMiD or double refractory to PI and IMiD	38	• ORR: 43% to 83% • mTTR: 1.0 mo	CRS: 66% (gr ≥ 3: 5%) NT: 24% (gr ≥ 3: 8%)
Bispecific T-cell engagers	CC-93269 (CD3ε x BCMA)	Phase I (NCT03486067)[5]	≥ 3 prior tx; no prior anti-BCMA	30	▪ ORR: 43.3%; sCR/CR: 16.7% ▪ mTTR: 4.1 wks	▪ CRS: 76.7% (gr ≥ 3: 3.3%) ▪ No encephalopathy
	Teclistamab	Phase I[6]	Refractory to std therapies with prior PI and IMiD	78	▪ ORR: 67% ▪ ≥ VGR: 50%	▪ CRS: 56% (no gr ≥ 3) ▪ Neurologic events: 8% (gr ≥ 3: 5%)

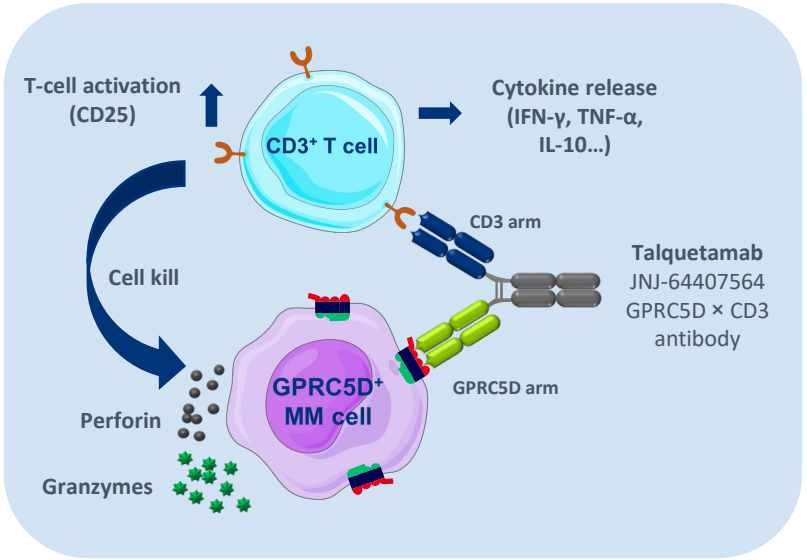
1. Munshi. ASCO 2020. Abstr 8503. 2. Berdeja. ASCO 2020. Abstr 8505. 3. Mailankody. ASCO 2020. Abstr 8504.
4. Berdeja. ASH 2019. Abstr 927. 5. Cortes. ASH 2019. Abstr 143. 6. Zafar. ASCO 2020. Abstr 100.

Slide credit: clinicaloptions.com

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

TALQUETAMAB



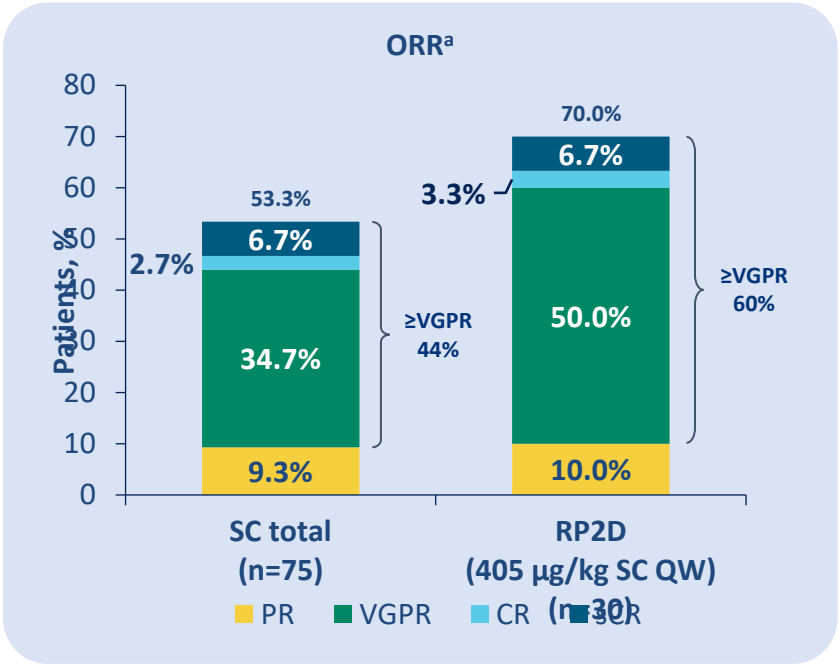
[a]400 µg/kg was selected as final dosing concentration in phase 2 for operational convenience; in phase 1, 405 µg/kg was the RP2D.

GPRC5D, G protein–coupled receptor family C group 5 member D; IFN, interferon; IL, interleukin; MM, multiple myeloma; QW, once weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; TNF, tumour necrosis factor.

1. Smith EL, et al. *Sci Transl Med* 2019;11:eaau7746. 2. Pillarisetti K, et al. *Blood* 2020;135:1232-43. 3. Verkleij CPM, et al. *Blood Adv* 2021;5:2196-215. 4. Chari A, et al. 62nd ASH Annual Meeting and Exposition 2020, Abstract 290.

Overall Response Rate

TALQUETAMAB

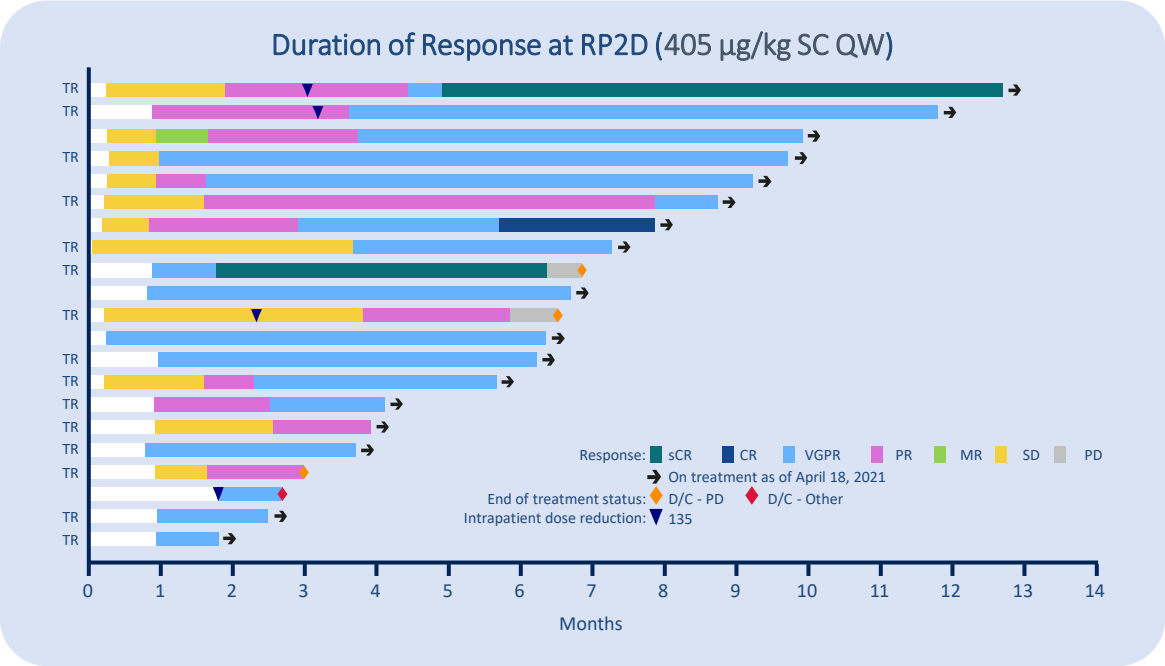


- The RP2D of 405 µg/kg SC QW has been administered to 30 patients with a median follow-up of 6.3 months (range: 1.4–12.0) for responders
- At the RP2D:
  - 70.0% ORR (21/30)
  - Median time to first confirmed response was 1 month (range: 0.2–3.8)
  - 65.2% (15/23) of triple-refractory patients responded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

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

Duration of Response

TALQUETAMAB



- Responses were durable and deepened over time
- At the RP2D of 405 µg/kg SC QW:
  - Median duration of response was not reached
  - 17/21 responders (81%) were continuing on treatment, after median follow-up of 6.3 months (range: 1.4–12.2)
- Data in IV cohorts (not shown) were more mature
  - Even at subtherapeutic doses, responses are ongoing at 22+ months in patients with longer follow-up

CR, complete response; D/C, discontinued; IV, intravenous; MR, minimal response; PD, progressive disease; PR, partial response; QW, once weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; TR, triple-class refractory; VGPR, very good partial response.

Summary :Comparison of Novel Immunotherapeutic Approaches

	Chimeric antigen receptor T cells (CAR-T)	Bispecific antibodies	Antibody-drug conjugates
Pros	Unprecedented ORR including MRD neg in heavily pre-treated patients One time intervention; long chemo holiday resulting in median PFS ~1 year	Off the shelf Deep responses Limited severe CRS - ? Safety in frail elderly Can be given in community settings after 1st cycle	Off the shelf Encouraging response rates 1 hour infusion every 3 weeks No CRS, can be given in community settings
Cons	Manufacturing time makes impractical for patients with aggressive/rapidly progressing disease Requires complex infrastructure – stem cell lab, RN/ ICU/ER training – thus restricted to accredited centers CRS ? role in frail elderly Impact of bridging chemo on remission duration Low WBC and plts post CAR-T Cost given relapses even in MRD neg patients; mgmt. challenging especially if soon after flu/cy given impact on T cells	? Need for admissions with initial doses until CRS risk low Dosing/schedule to be determined Need for continuous treatment until progression Toxicities require further study – infections, neurotoxicty	Ocular toxicity – requires close collaboration with opthamology & impact on pt quality of life Thrombocytopenia Need for continuous treatment until progression Modest ORR and PFS in triple class/penta refractory

Lancman, et al. ASH 2020.

Conclusions

- Future therapies for myeloma
- New targets
- High response rates

Audience Q&A with Panel

Kelly Cox
International Myeloma Foundation
Los Angeles, CA

Joseph Mikhael, MD
TGen
Phoenix, AZ

Amrita Krishnan, MD
City of Hope Medical Center
Duarte, CA

Deb Doss, RN, OCN
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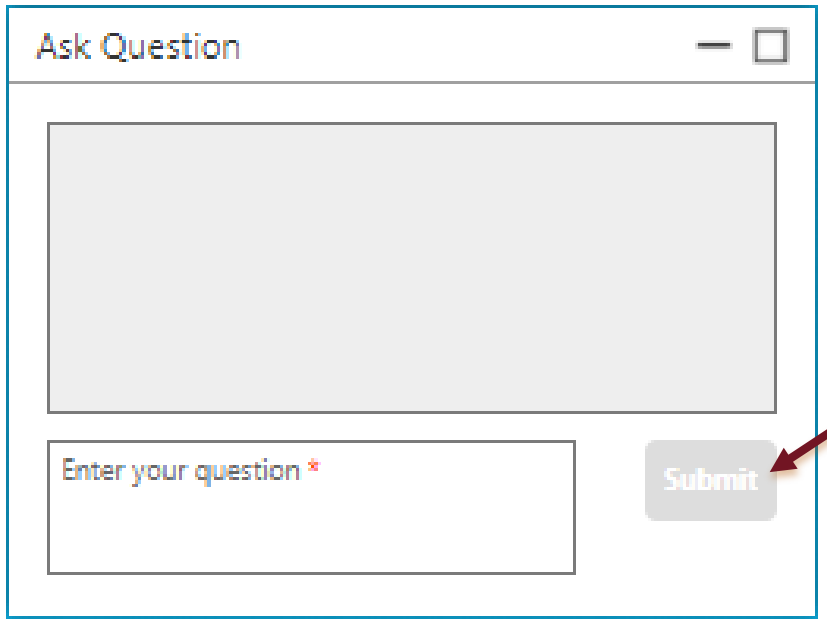


Type and submit your questions here. Click the Q&A icon circled below if you have minimized the Ask Question window.

REGIONAL COMMUNITY WORKSHOP

How to Manage Myeloma Symptoms and Side Effects

Deborah Doss, RN OCN, Dana-Farber Cancer Institute

NURSE LEADERSHIP BOARD
A Division of International Myeloma Foundation

Be the Commander of Your Galactic Journey: Navigating the Journey

Deborah Doss, RN, OCN
Dana-Farber Cancer Institute

Southwest Regional Community Workshop

June 26, 2021

You are in the Commander's Chair

All Crew Members are Needed for a Successful Journey

Subspecialists

General Hem/Onc

Primary Care Provider (PCP)

You and Your Caregiver(s)

Myeloma Specialist

Family/Support Network

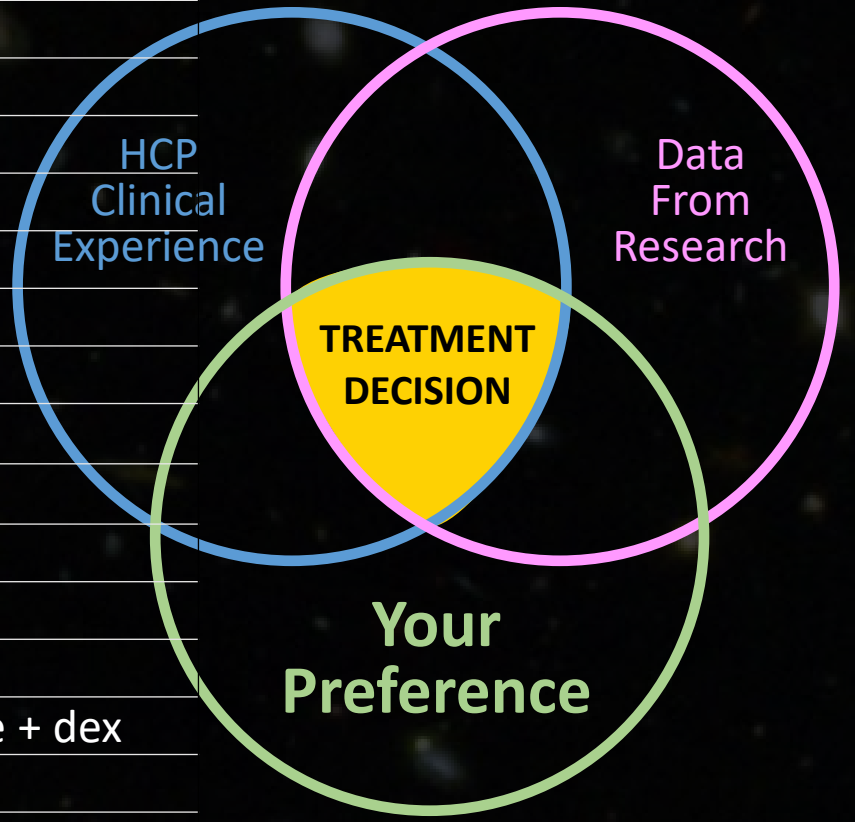
Allied Health Staff

- You and your caregiver are the center
- Understand the different roles of your health care team
- Understand how they can help you

Explore Treatment Options & Plan Your Course

Navigating the Journey

Drug class	Myeloma therapies	Common combinations
Proteosome inhibitor	Bortezomib (SQ)	VRD, Vd
	Carfilzomib	KRd, Kd, K
	Ixazomib	IxRd
Immuno-modulatory agent	Pomalidomide	Pd, DPd, EPd
	Lenalidomide	VRD, Rd
	Thalidomide	Dara + VTd
Monoclonal antibody	Daratumumab	DRd, DVd, DPd, D-VMP
	Elotuzumab	ERd, EPd
	Isatuximab-irfc	IsaPd
Antibody-drug conjugate	Belantamab mafodotin	Bela montherapy
Nuclear export inhibitor	Selinexor	Sel + d, Sel + Vd
Anthracycline	Liposomal doxorubicin	BRd, BVd
Alkylating agents	Cyclophosphamide	PCd, VTD-PACE
	Melphalan	MVP, MPT
Alkylator conjugate	Melphalan flufenamide	Melphalan flufenamide + dex
HDACi	Panobinostat	Panobinostat + Vd
CAR T	Abecma	
Many	Clinical trials are always an option	



Philippe Moreau. ASH 2015.

Bela = belantamab C = cyclophosphamide; D = daratumumab; d = dexamethasone; E = elotuzumab; HDACi = histone deacytlase inhibitor; Isa = Isatuximab; Ix = ixazomib; K = carfilzomib; P = pomalidomide; R = lenalidomide; Sel = Selinexor; SQ = subcutaneous; V = bortezomib

Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29. Philippe Moreau. ASH 2015; Prescribing information.

Be an Empowered Patient
"Scotty, We Need More Power!"

Navigating the Journey

- Participate in decisions
- Ask for time to consider options
  (if needed/appropriate)
- Understand options
  - Use reliable sources of information
  - Use caution considering stories of personal experiences
- Create a dialogue
- Express your goals/values/preferences
- Arrive at a treatment decision together

Major Tom to Ground Control… Communicating Effectively with Your Crew

Navigating the Journey

Prepare for Your Away Mission	Achieve Your Appointment	Navigate Home
• Write down your questions and concerns • Bring current medications and supplements or a list • Any medical or life changes since your last visit? • Current symptoms - how have they changed?	• Speak up! • Ask your most important questions first • Understand your treatment plan and next steps • Have a list of who to contact and when • Bring a Caregiver for another “set of ears”	• Communicate with other members of your health care crew (pharmacist, others) • Take your medications as directed • Follow up with members of your heath care crew

A Tool to Help You Discuss Your Treatment With Your Healthcare Team

Take Time to Consider Your Preferences Before an Appointment

Ask Important Questions at Your Appointments

- ***What Can I Expect Now?***
- ***What Can I Expect In the Future?***

Have these conversations…

- Whenever your treatment stops working
- Whenever you start a new treatment
- Whenever there is a change in your life priorities
- Whenever you have a question or concern

Available in the IMF Resources or at myeloma.org

Myeloma and Treatments Both Contribute to How You Feel

Constellation of Symptoms

Myeloma cells in excess can cause symptoms

- Calcium elevation
- Renal dysfunction
- Anemia
- Bone pain
- Fatigue
- Infection
- Other symptoms

Treatments for myeloma kill myeloma cells but can cause symptoms

- Myelosuppression
- Peripheral neuropathy
- Diarrhea
- Fatigue
- Deep vein thrombosis
- Infection (eg, shingles)
- Other symptoms

How You Feel

What Happens if Symptoms Are Not Managed Effectively?

Constellation of Symptoms

Poorly managed symptoms can lead to...

- Anxiety
- Depression
- Social isolation
- Missed doses
- Reduced treatment efficacy
- Reduced quality of life

Discuss how you feel with your team...

- Keep a symptom diary; discuss with team
- Many options but your team cannot help if they don't know
- Express your priorities
  - Fatigue is common concern but making the right treatment decision is higher priority for most

Faiman, B. *CJON.* 2017, 21(5)suppl 3-6. Faiman, B. et al 2017. Patient Reported Symptoms, Concerns and Provider Intervention in Patients with Multiple Myeloma

Steroid Side Effects and Management

Constellation of Symptoms

Steroid Side Effects

- Irritability, mood swings, depression
- Difficulty sleeping (insomnia), fatigue
- Increased risk of infections, heart disease
- Muscle weakness, cramping
- Increase in blood pressure, water retention
- Blurred vision, cataracts
- Flushing/sweating
- Stomach bloating, hiccups, heartburn, ulcers, or gas
- Weight gain, hair thinning/loss, skin rashes
- Increase in blood sugar levels, diabetes

Managing Steroid Side Effects

- Consistent schedule (AM vs. PM)
- Take with food
- Stomach discomfort: Over-the-counter or prescription medications
- Medications to prevent shingles, thrush, or other infections

Steroids help kill myeloma cells.
Do not stop or adjust steroid doses without discussing it with your health care provider.

King T, Faiman B. *CJON.* 2017; 21(5)suppl:240-249. Faiman B, et al. *CJON.* 2008;12(3)suppl:53-63.

Fatigue, Depression, and Anxiety

Constellation of Symptoms

- All can effect quality of life and relationships
- Sources include anemia, pain, reduced activity, insomnia, treatment toxicity, bone marrow suppression

Management

- Exercise (walking, yoga, etc)
- Proper rest
- Support (social network, support group, professional counseling, etc)
- Prayer, meditation, spiritual support
- Mindfulness-based stress reduction
- Medications
- Massage, aroma therapy
- Supplements: ginseng
- Transfusion, if indicated
- Effective management of other symptoms

At least 70% of patients experience fatigue, but only 20% tell their provider. Let your provider know about symptoms that are not well controlled or thoughts of self harm.

Catamero D et al. *CJON.* 2017; 21(5)suppl:7-18. Faiman, B. et al 2017.
Patient Reported Symptoms, Concerns and Provider Intervention in Patients with Multiple Myeloma.

Infection Prevention & Treatment

Constellation of Symptoms

- Compromised immune function comes from multiple myeloma and from treatment
- Good personal hygiene (skin, oral)
- Environmental control (wash hands, avoid crowds and sick people, etc)
- Growth factor (Neupogen [filgrastim])
- Immunizations (NO live vaccines)
- Medications (antibacterial, antiviral)
  - New research: for patients receiving active myeloma therapy, levofloxacin 500 mg once daily for 12 weeks reduced infection (fevers, death) (ASH 2017 #903)

Report fever of more than 100.4°F, shaking chills even without fever, dizziness, shortness of breath, low blood pressure to HCP as directed.
Infection is serious for myeloma patients!

Brigle K, et al. *CJON.* 2017; 21(5)suppl:60-76.

Pain Prevention and Management

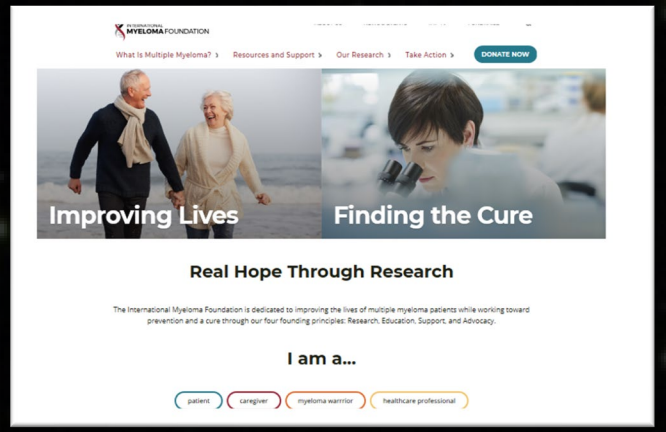
Constellation of Symptoms

- Pain can significantly compromise quality of life
- Sources of pain include bone disease, neuropathy and medical procedures
- Management
  - Prevent pain when possible
    - Bone strengtheners to decrease fracture risk; antiviral to prevent shingles; sedation before procedures
  - Intervention depends on source of pain
  - May include medications, activity, surgical intervention, radiation therapy, etc
  - Complementary and alternative medicine (supplements, acupuncture, etc)

Tell your health care provider about any new bone pain or chronic pain that is not adequately controlled

Faiman B, et al. *CJON.* 2017;21(5)suppl:19-36.

Knowledge is Power
IMF has many resources to help you learn more



Website: http://myeloma.org

Using the Immune System to Fight Multiple Myeloma

Videos

eNewsletter: Myeloma Minute

IMF TV Teleconferences

Download or order at myeloma.org

You are Not Alone

Questions?

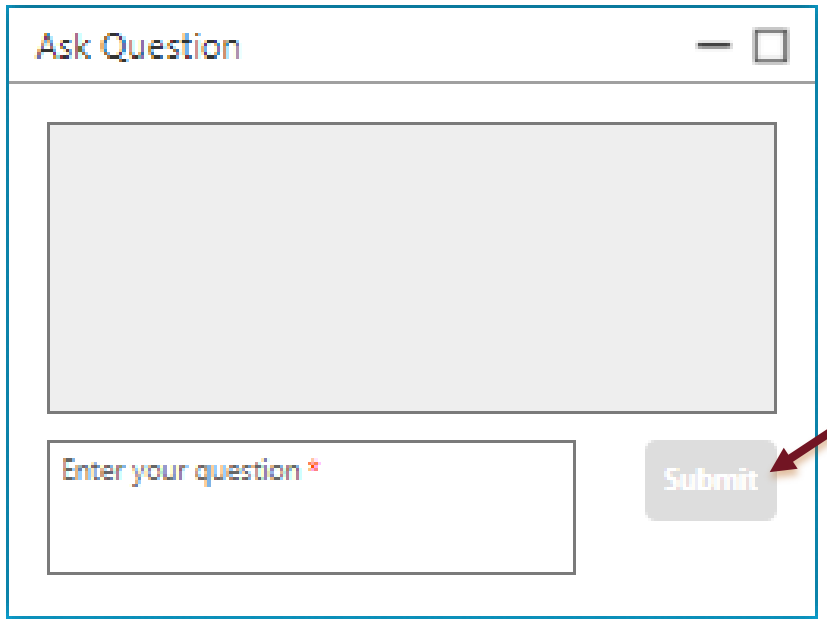
Audience Q&A with Panel

Kelly Cox
International Myeloma Foundation
Los Angeles, CA

Joseph Mikhael, MD
TGen
Phoenix, AZ

Amrita Krishnan, MD
City of Hope Medical Center
Duarte, CA

Deb Doss, RN, OCN
Dana-Farber Cancer Institute
Boston, MA



Type and submit your questions here. Click the Q&A icon circled below if you have minimized the Ask Question window.

REGIONAL COMMUNITY WORKSHOP

Workshop Video Replay & Slides

As follow up to today's workshop, we will have the speaker slides and a video replay available.

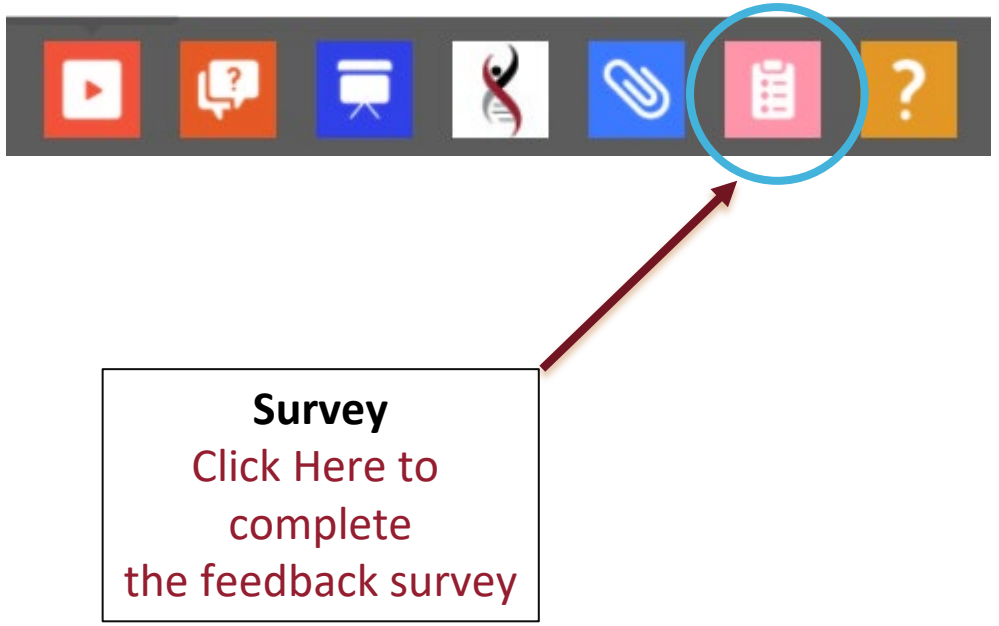
These will be provided to you shortly after the workshop concludes.

REGIONAL COMMUNITY WORKSHOP

We want to hear from you!

Feedback Survey

Please take a moment to complete the survey.
It will also be emailed to you shortly after the workshop.



REGIONAL COMMUNITY WORKSHOP

Thank you to our sponsors!

REGIONAL COMMUNITY WORKSHOP