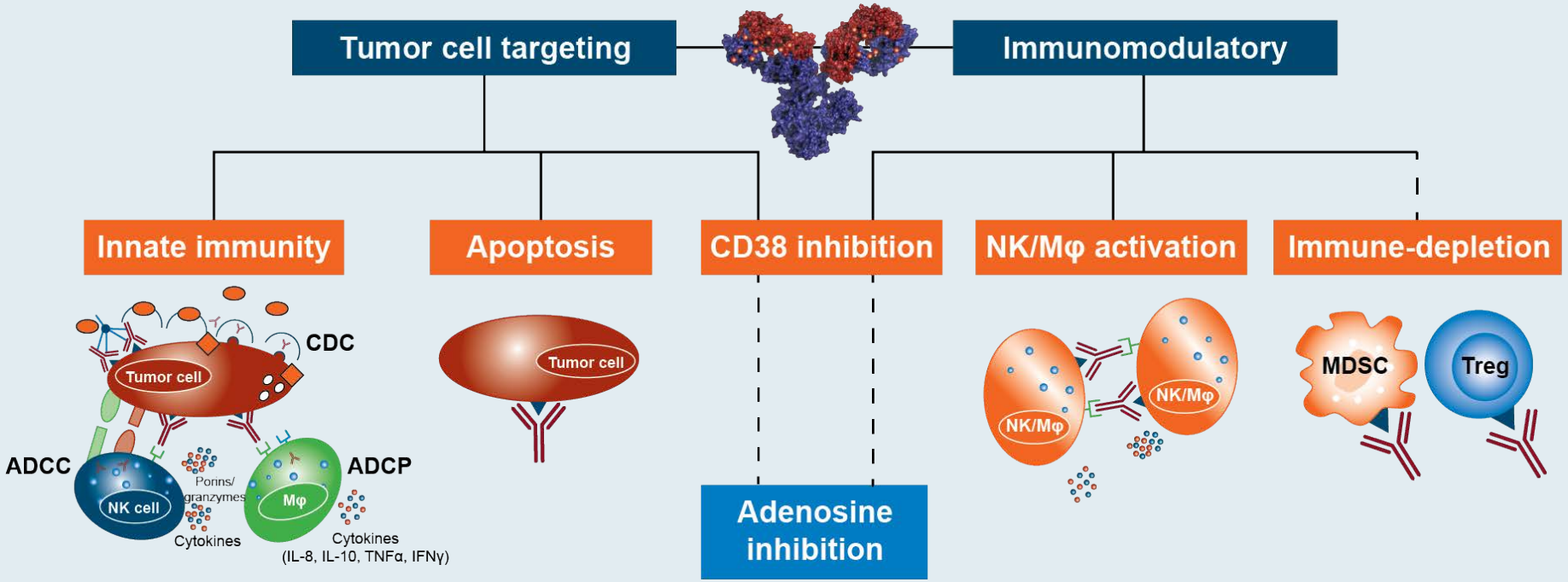
Year in Review 2020
Multiple Myeloma

Dr Jonathan Kaufman

Isatuximab: Mechanism of Action

- **Active in combination studies in R/R MM**



- **Effective combinations**
  - **ICARIA-MM – Isa Pd**
  - **IKEMA – Isa Kd**

Courtesy of Jonathan L Kaufman, MD

Isatuximab plus pomalidomide and dexamethasone in elderly patients with relapsed/refractory multiple myeloma: ICARIA-MM subgroup analysis[1]

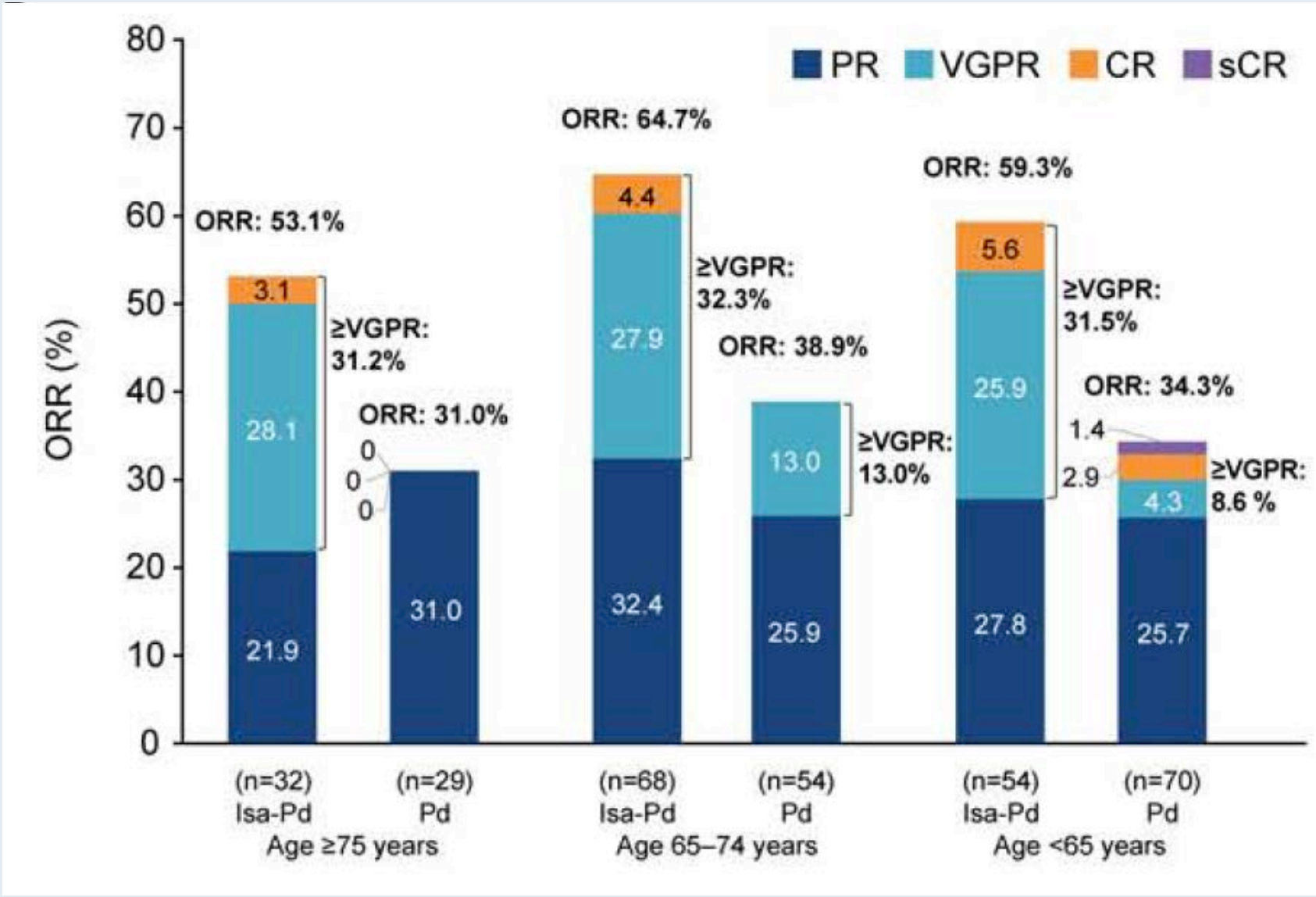
Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis[2]

[1] Schjesvold FH et al. *Haematologica* 2020 [Epub ahead of print].

[2] Dimopoulos MA et al. *Leukemia* 2020 [Epub ahead of print].

Courtesy of Jonathan L Kaufman, MD

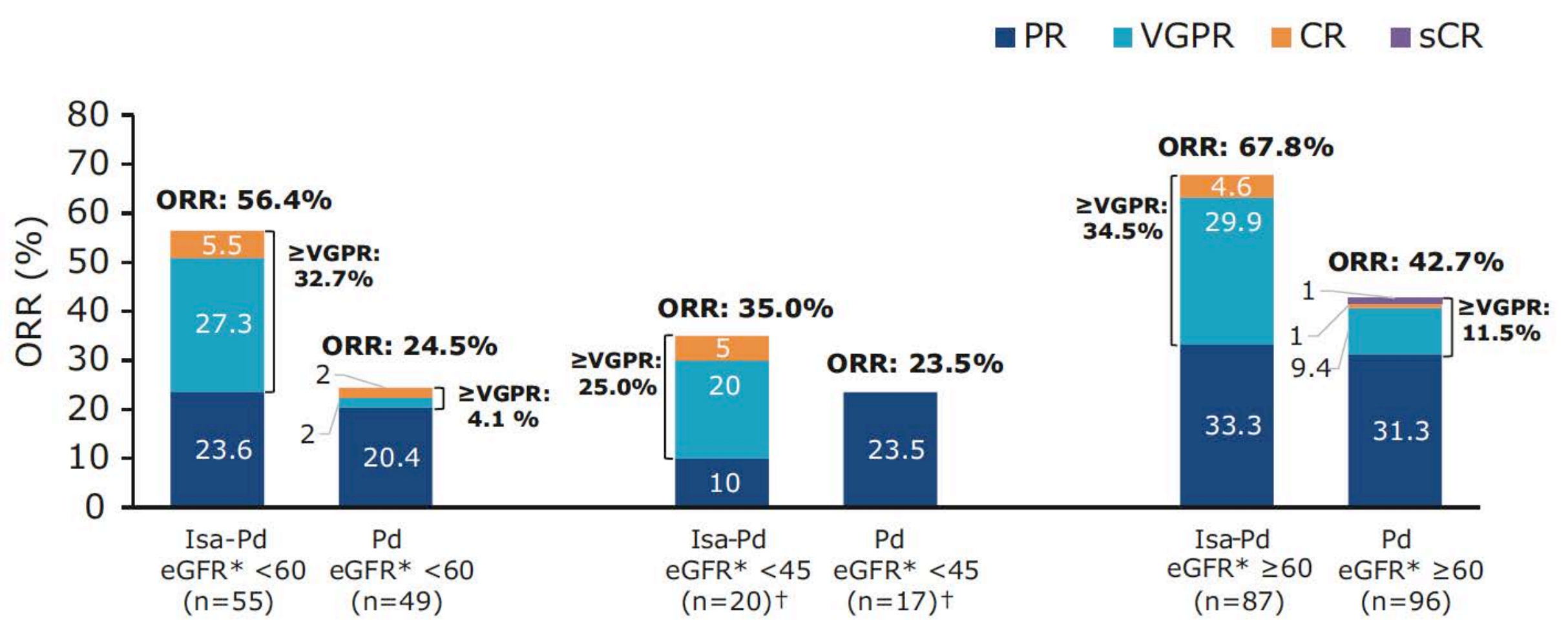
ICARIA-MM: Response to Therapy by Patient Age Group



Schjesvold FH et al. *Haematologica* 2020 [Epub ahead of print].

Courtesy of Jonathan L Kaufman, MD

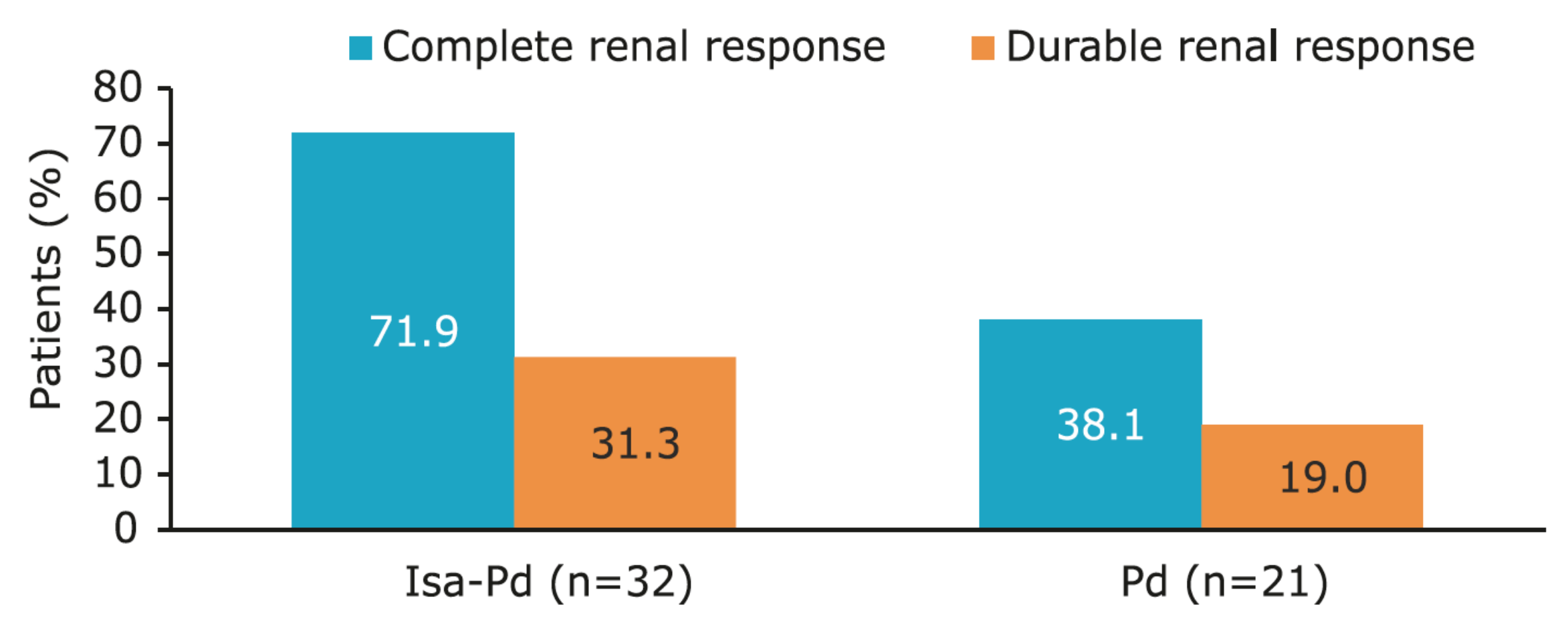
ICARIA-MM: ORR and Depth of Response According to Renal Function



Dimopoulos MA et al. *Leukemia* 2020 [Epub ahead of print].

Courtesy of Jonathan L Kaufman, MD

ICARIA-MM: Renal Response



Dimopoulos MA et al. *Leukemia* 2020 [Epub ahead of print].

Courtesy of Jonathan L Kaufman, MD

3.5 – Schjesvold FH, et al. Isatuximab plus pomalidomide and dexamethasone in elderly patients with relapsed/refractory multiple myeloma: ICARIA-MM subgroup analysis. Haematologica. 2020 Jun 25 Epub ahead of print

- Dimopoulos MA, et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. Leukemia. 2020 May 23. Epub ahead of print.

- ICARIA demonstrated that the combination of isatuximab with pom/dex (IsaPd) was superior to pom/dex (Pd) alone in RRMM
- These two studies are follow up studies that looked at subsets of interest.
- IsaPd was superior to Pd in all age groups including patients > 75 y/o
- IsaPd was superior to Pd at all levels of renal function from normal to > 30 mL/min.
- Complete and durable renal responses were doubled with IsaPd.

Courtesy of Jonathan L Kaufman, MD

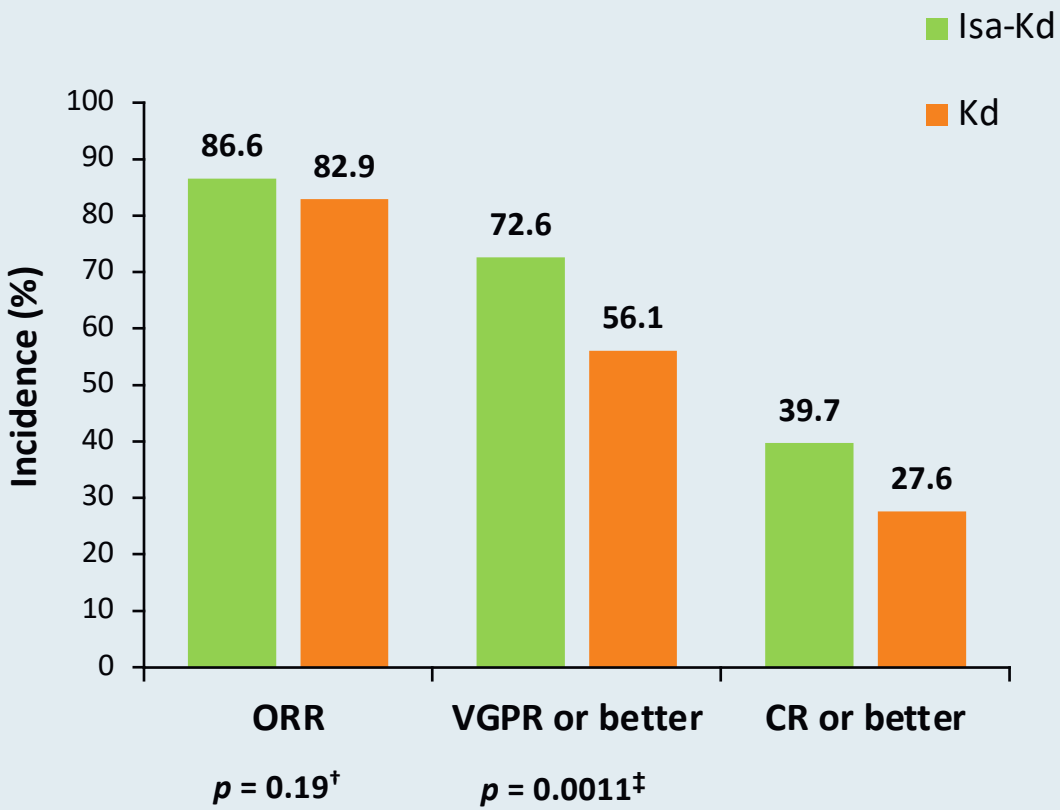
Isatuximab plus carfilzomib and dexamethasone vs carfilzomib and dexamethasone in relapsed/refractory multiple myeloma (IKEMA): Interim analysis of a phase 3, randomized, open-label study

Moreau P et al.
EHA 2020;Abstract LBA2603.

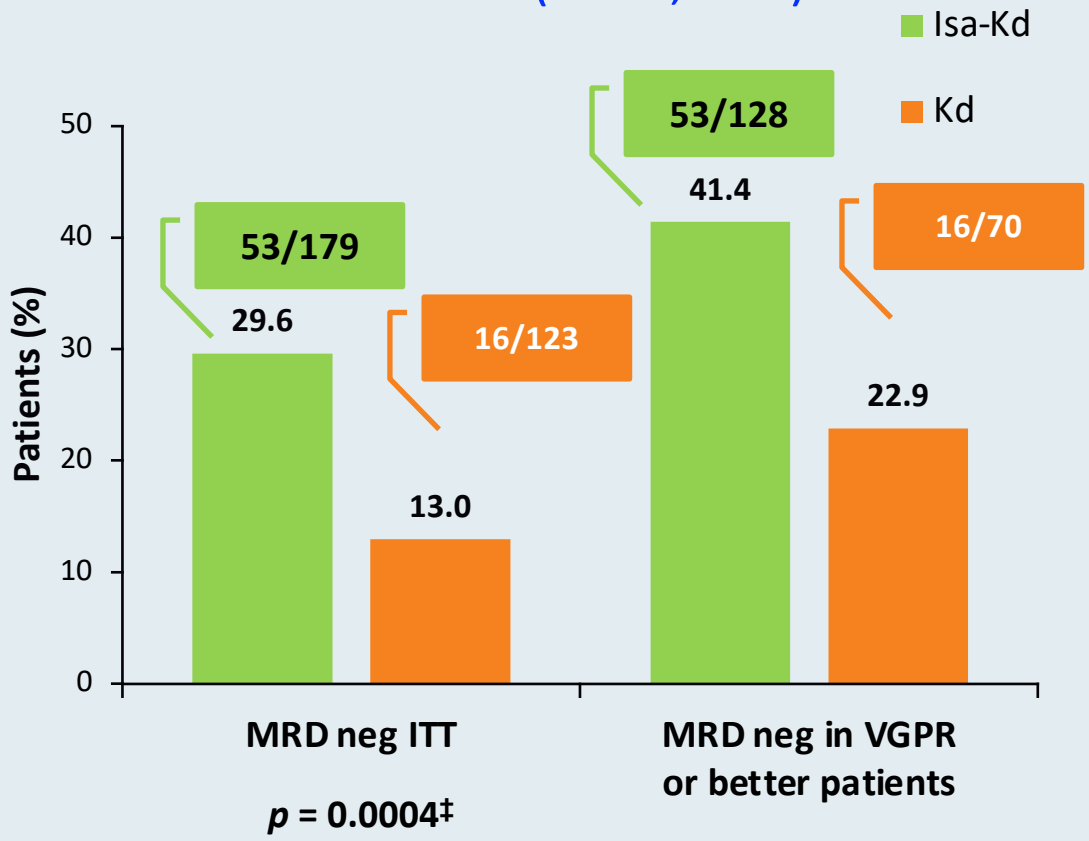
Courtesy of Jonathan L Kaufman, MD

IKEMA: Depth of response

Best overall response



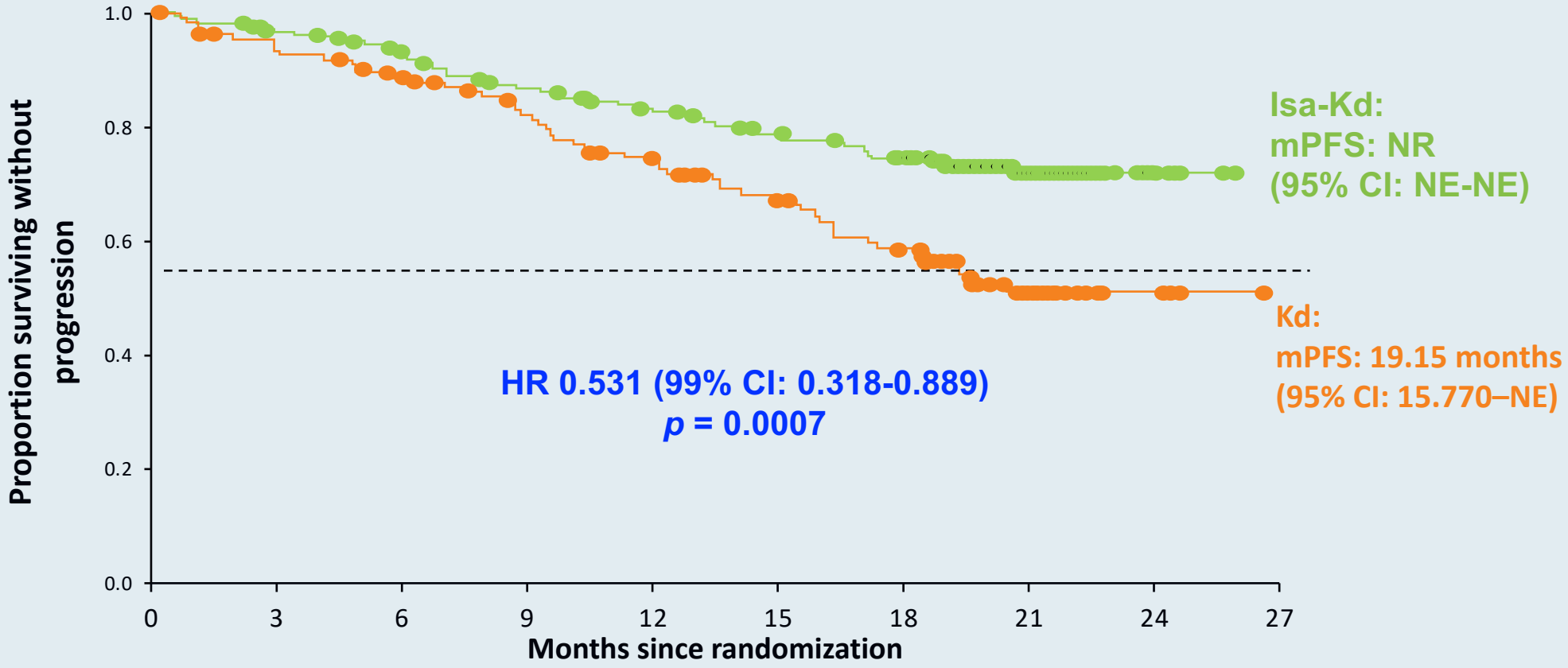
MRD rate (NGS*, 10^{-5})



Moreau P et al. EHA 2020;Abstract LBA2603.

Courtesy of Jonathan L Kaufman, MD

IKEMA: PFS



No. at risk										
Isa-Kd	179	164	151	136	124	110	100	36	5	0
Kd	123	108	99	85	72	61	50	19	6	0

One-sided *p* value, level of significance <0.005

Moreau P et al. EHA 2020;Abstract LBA2603.

Courtesy of Jonathan L Kaufman, MD

Depth of Response and Response Kinetics of Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Interim Analysis

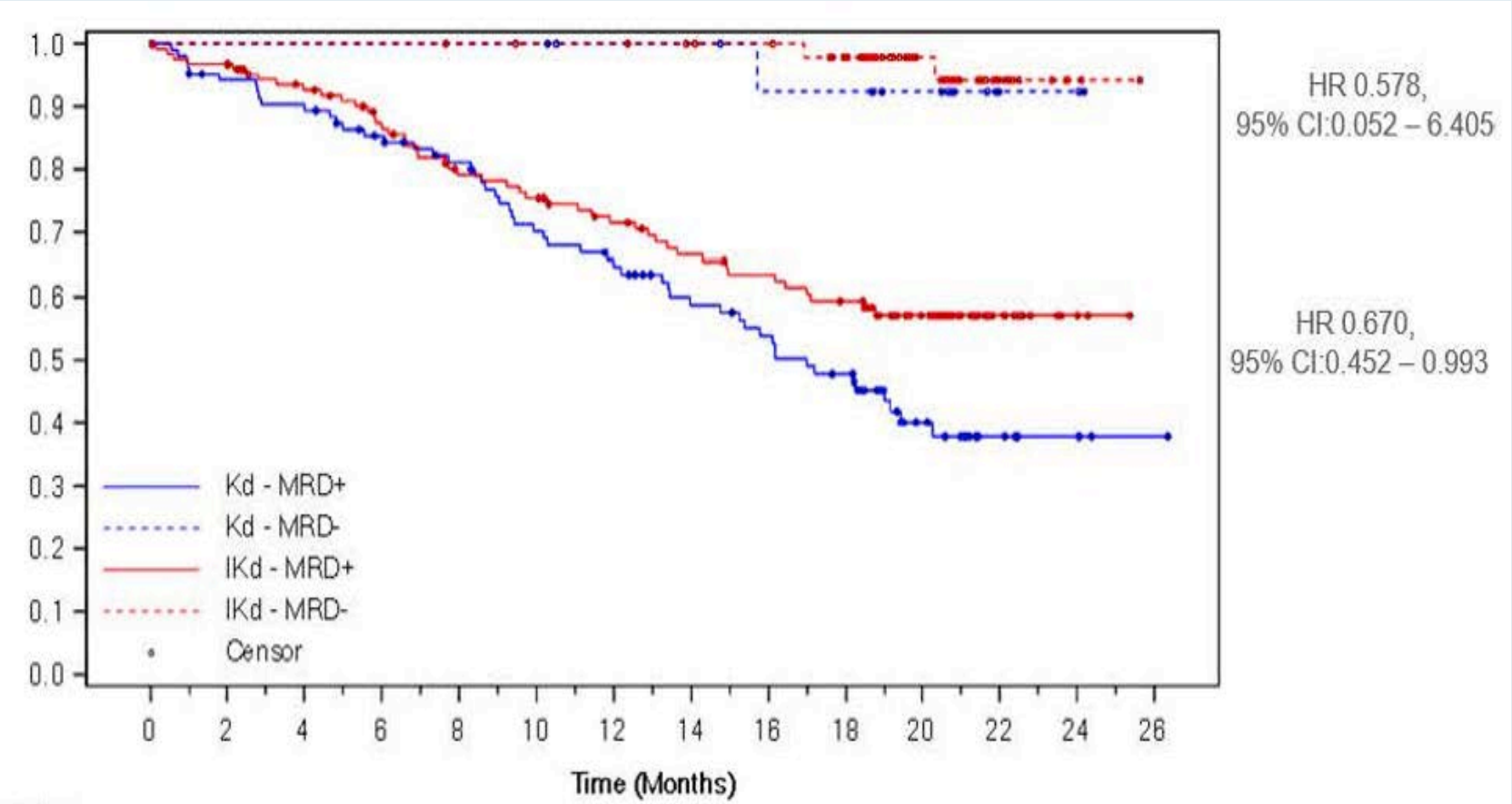
Martin T et al.

ASH 2020;Abstract 414.

Courtesy of Jonathan L Kaufman, MD

IKEMA: Summary of Response Rates and PFS by MRD Status

PFS by MRD status



Isa-Kd vs Kd

- **≥CR** = 39.7% vs 27.6%
- **≥VGPR** = 72.6% vs 56.1%
- **MRD (-)** = 30% vs 13%

Martin T et al. *ASH* 2020;Abstract 414.

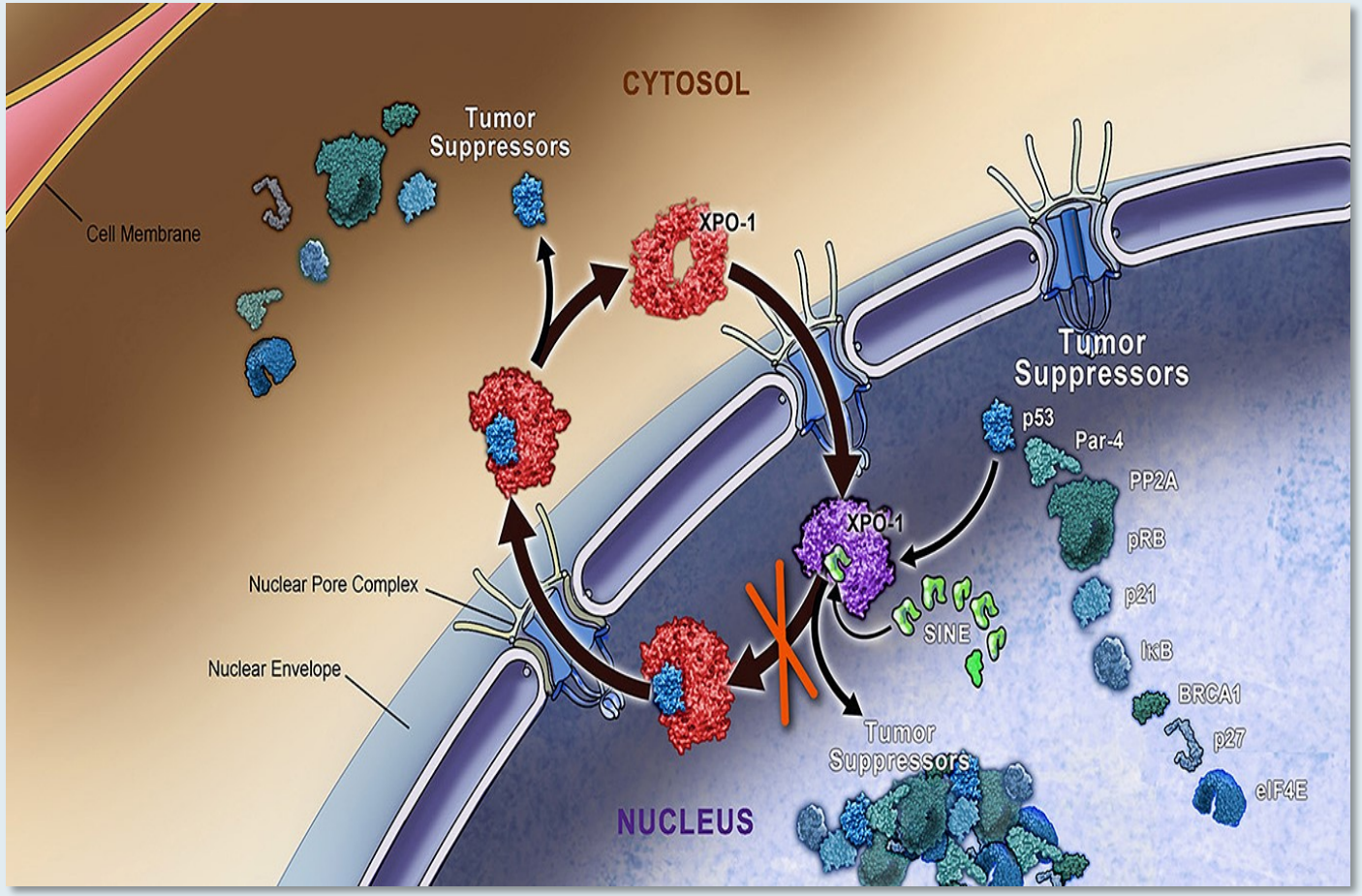
Courtesy of Jonathan L Kaufman, MD

3.6 – Martin T et al. Depth of Response and Response Kinetics of Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Interim Analysis. ASH 2020;Abstract 414.

- Isatuximab with carfilzomib (IsaKd) is superior to Kd in patients with RRMM
- Increased ORR, VGPR and MRD negativity rate.
- Final PFS analysis is pending.
- No increased safety issues reported with the combination

Courtesy of Jonathan L Kaufman, MD

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, BCL2, 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.

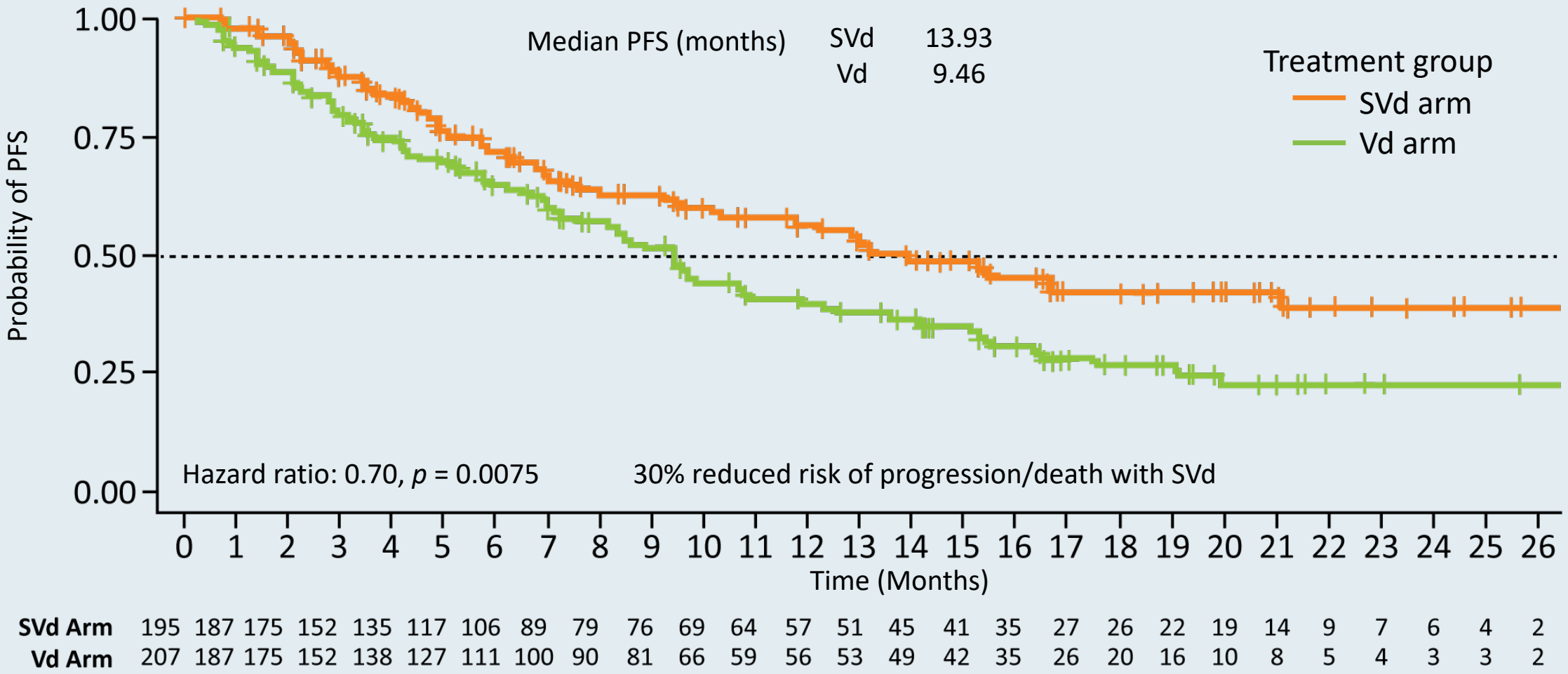
Courtesy of Jonathan L Kaufman, MD

Weekly Selinexor, Bortezomib, and Dexamethasone (SVd) versus Twice Weekly Bortezomib and Dexamethasone (Vd) in Patients with Multiple Myeloma (MM) After One to Three Prior Therapies: Initial Results of the Phase III BOSTON Study

Dimopoulos MA et al.
ASCO 2020;Abstract 8501.

Courtesy of Jonathan L Kaufman, MD

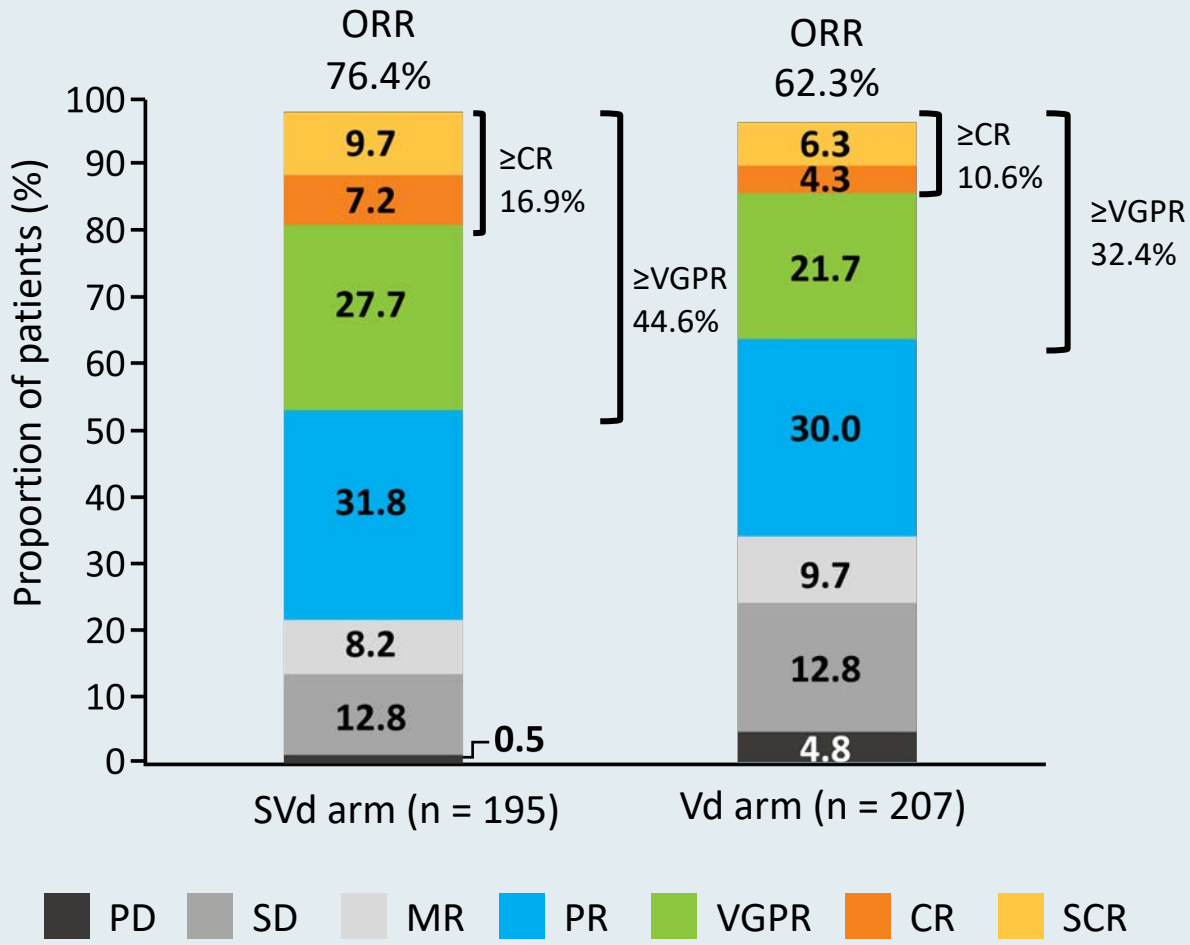
BOSTON Trial: PFS



Dimopoulos M et al. ASCO 2020;Abstract 8501.

Courtesy of Jonathan L Kaufman, MD

BOSTON Trial: Response



Longer duration of response with SVd

	SVd arm (n = 149)	Vd arm (n = 129)
Median time to response (months)	1.1	1.4
Median duration of response (months)	20.3	12.9

Fewer patients with progressive disease:
SVd (n = 1, 0.5%) vs Vd (n = 10, 4.8%)

Dimopoulos M et al. ASCO 2020;Abstract 8501.

Courtesy of Jonathan L Kaufman, MD

3.7 – Dimopoulos MA et al. Weekly selinexor, bortezomib, and dexamethasone (SVd) versus twice weekly bortezomib and dexamethasone (Vd) in patients with multiple myeloma (MM) after one to three prior therapies: Initial results of the phase III BOSTON study. ASCO 2020; Abstract 8501. Oral, HoD

- Selinexor, a first in class XPO1 inhibitor is approved with dex in RRMM. Selinexor/bortezomib/dex (SVd) was compared to bortezomib/dex (Vd)
- This was studied in 1-3 prior lines of therapy.
- Once weekly bortezomib in the SVd arm vs twice weekly in Vd
- Increased ORR and PFS. No new safety signals
- SVd is approved by the FDA for patients with 1-3 prior lines of therapy with RRMM

Courtesy of Jonathan L Kaufman, MD

Selinexor in Combination with Pomalidomide and Dexamethasone (SPd) for Treatment of Patients with Relapsed Refractory Multiple Myeloma (RRMM)

Chen CI et al.
ASH 2020;Abstract 726.

Courtesy of Jonathan L Kaufman, MD

3.8 – Chen CI et al. Selinexor in Combination with Pomalidomide and Dexamethasone (SPd) for Treatment of Patients with Relapsed Refractory Multiple Myeloma (RRMM). ASH 2020;Abstract 726.

- Selinexor with pom/dex (SPd) is safe at the following dose level:

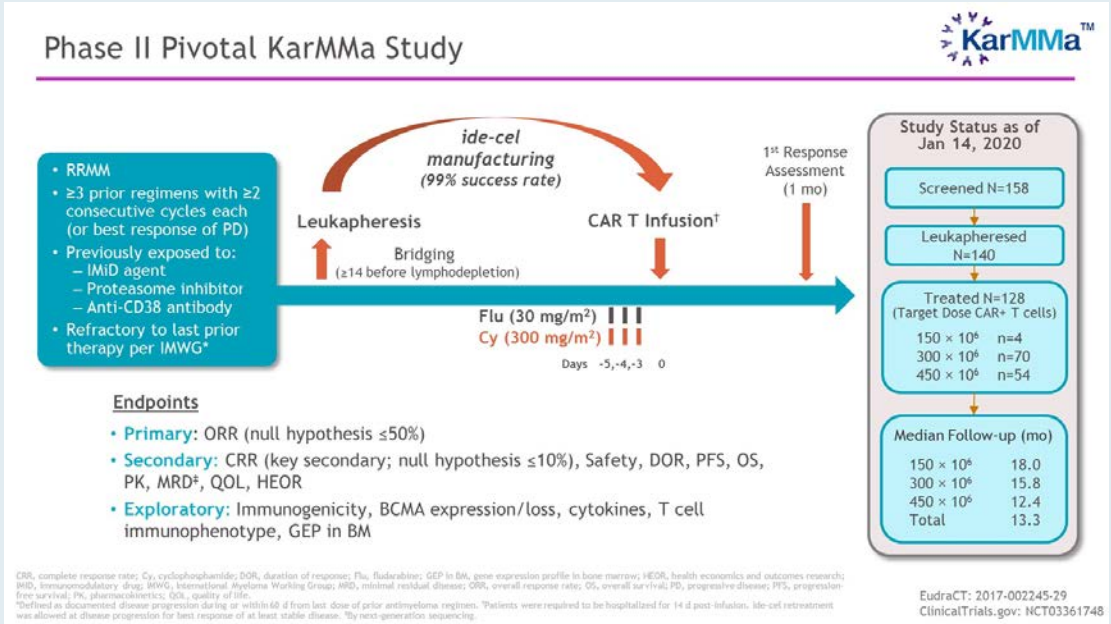
  Selinexor 60 mg per week; pom 4 mg 1-21 every 28 days; dex 40 mg q week

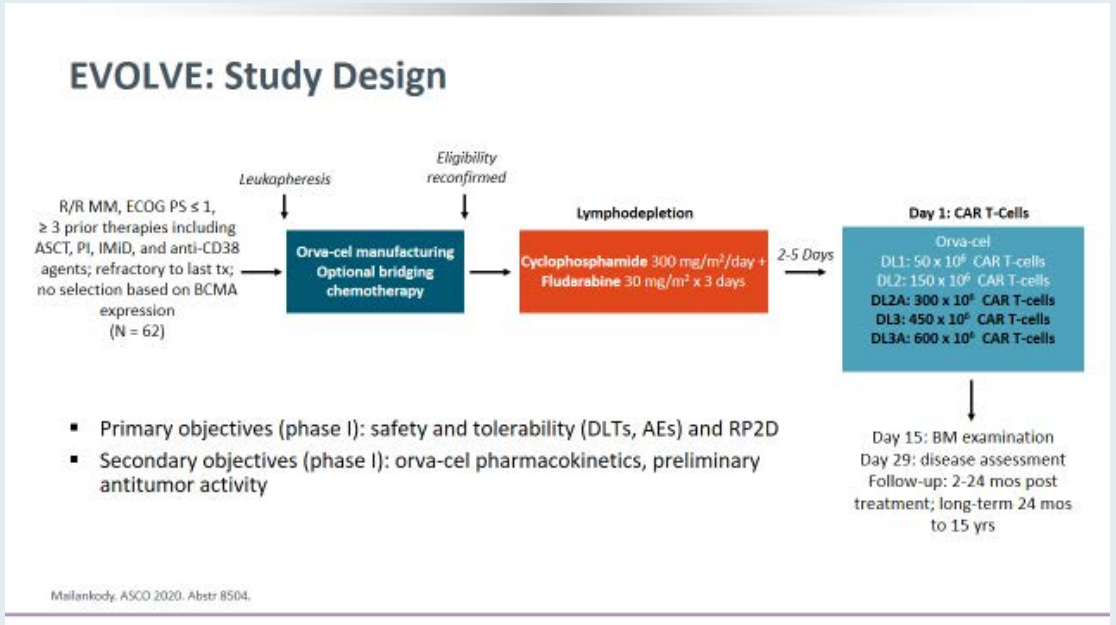
  ORR was 58% which is approximately double of what is expected with Pd alone

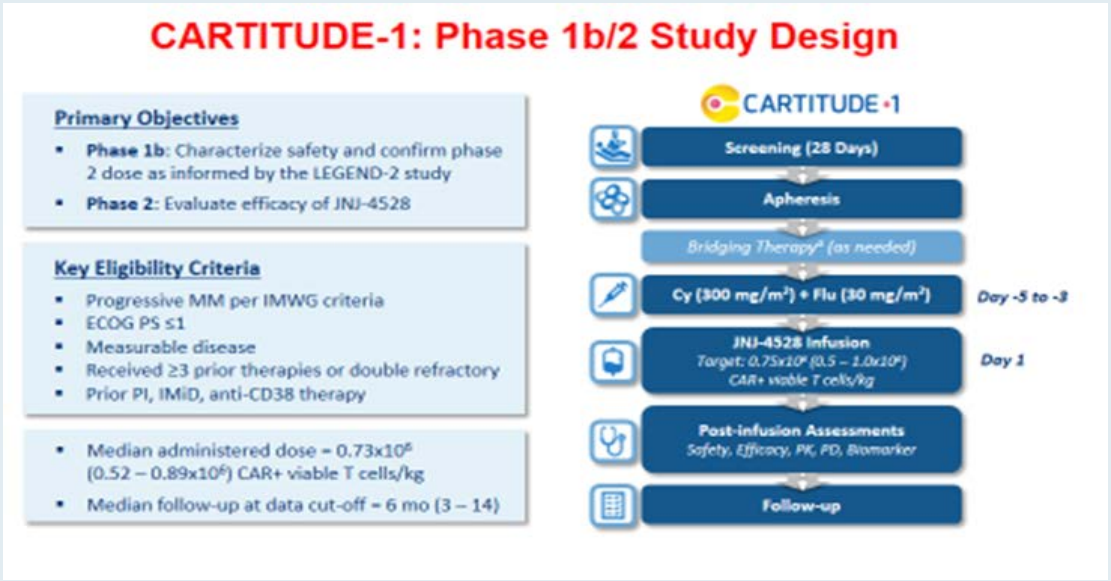
  PFS was 12.3 months which is much higher than expected with Pd alone (4-6 months)

Courtesy of Jonathan L Kaufman, MD

Key BCMA Directed CAR T Study Designs







Similar approach in 3 studies:

R/R MM
Steady state T cell collection
CY/FLU lymphodepletion
Single infusion

Courtesy of Jonathan L Kaufman, MD

Efficacy and Safety of Idecabtagene Vicleucel (ide-cel, bb2121) in Elderly Patients With Relapsed and Refractory Multiple Myeloma: KarMMa Subgroup Analysis

Berdeja J et al.

ASH 2020;Abstract 1367.

Courtesy of Jonathan L Kaufman, MD

KarMMa: Subgroup Analysis by Age

		Age ≥65 Years (n=45)	Age ≥70 Years (n=20)	All ide-cel Treated (N=128)
Efficacy Outcomes				
ORR, n (%) [95% CI]		38 (84) [70.5–93.5]	18 (90) [76.9–100]	94 (73) [65.8–81.1]
CR rate, n (%) [95% CI]		14 (31) [18.2–46.6]	7 (35) [14.1–55.9]	42 (33) [24.7–40.9]
PFS, median (95% CI), mo		8.6 (4.9–12.2)	10.2 (3.1–12.3)	8.8 (5.6–11.6)
DOR,[a] median (95% CI), mo		10.9 (4.5–11.4)	11.0 (3.9–11.4)	10.7 (9.0–11.3)
Adverse Events of Interest[b]				
CRS, n (%)	Overall Grade ≥3	40 (89) 2 (4)	20 (100) 2 (10)	107 (84) 7 (5)
NT, n (%)	Overall Grade ≥3	11 (24) 4 (9)	6 (30) 1 (5)	23 (18) 4 (3)

CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NT, investigator-identified neurotoxicity; ORR, overall response rate; PFS, progression-free survival.
[a]Duration of response among responders.
[b]NT was graded according to NCI CTCAE v4.03. CRS was graded according to Lee et al. criteria (*Blood* 2014; 124:188-95).

Berdeja J et al. ASH 2020;Abstract 1367.

Courtesy of Jonathan L Kaufman, MD

4.1 – Berdeja J et al. Efficacy and Safety of Idecabtagene Vicleucel (ide-cel, bb2121) in Elderly Patients With Relapsed and Refractory Multiple Myeloma: KarMMa Subgroup Analysis. ASH 2020;Abstract 1367.

- Ide-cel in elderly patients 65 – 78 years old
- Similar ORR and CR rates
- No difference in PFS
- No difference in toxicity

- All with good PS at baseline

Courtesy of Jonathan L Kaufman, MD

Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma: Updated Results from Phase 1 CRB-401 Study

Lin Y et al.

ASH 2020;Abstract 131.

Courtesy of Jonathan L Kaufman, MD

4.2 – Lin Y et al. Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma: Updated Results from Phase 1 CRB-401 Study. ASH 2020;Abstract 131.

- Ide-cel has deep and durable responses in RRMM
- Response appears dose related
- ORR 73%; DOR 10.7 months; PFS 8.8; OS 19.4
- CRS common but typically not severe
- Neurologic toxicity: uncommon and rarely severe

Courtesy of Jonathan L Kaufman, MD

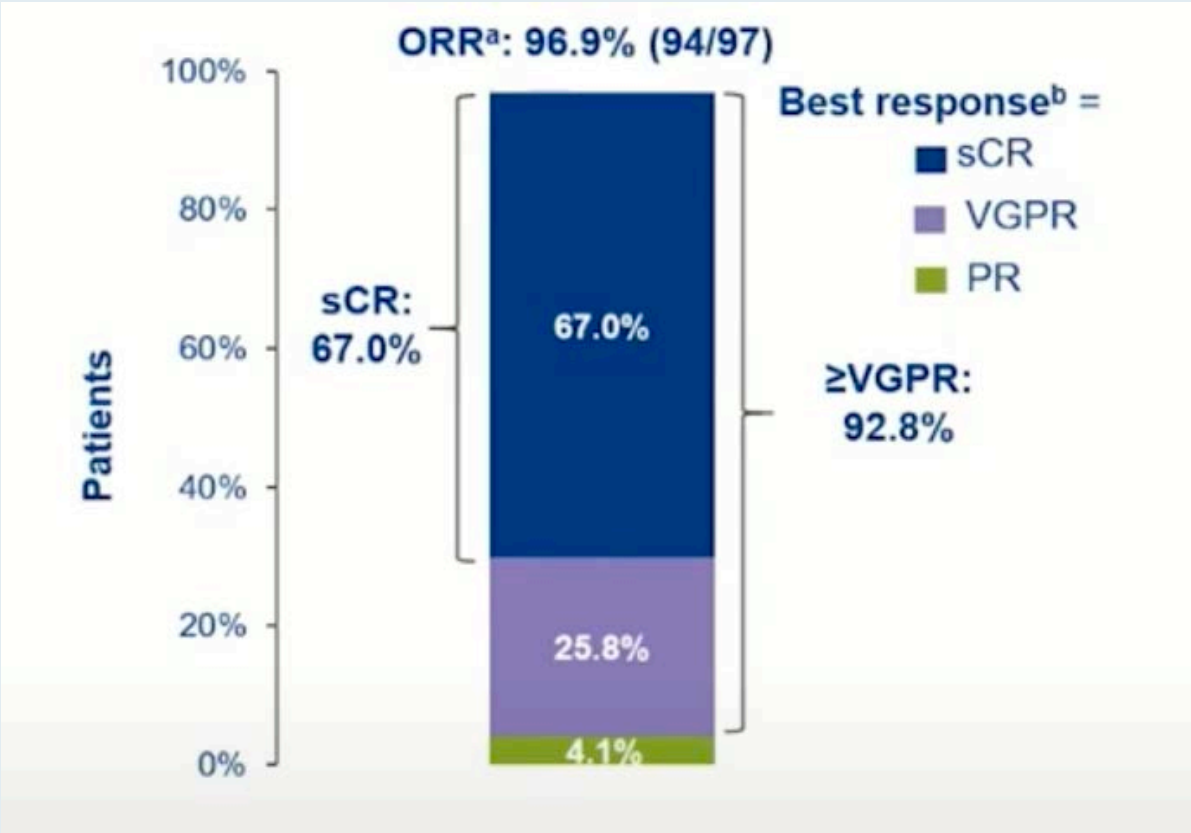
CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma

Madduri D et al.

ASH 2020;Abstract 177.

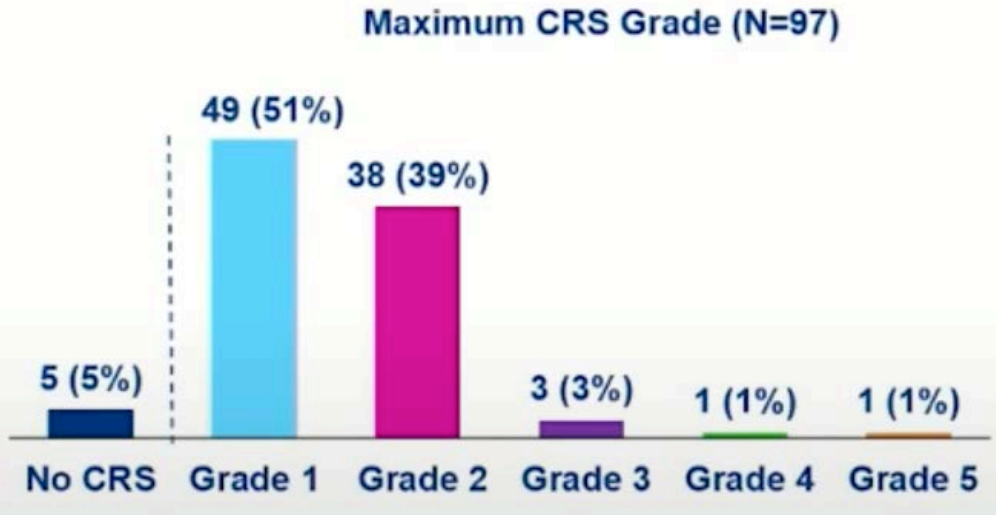
Courtesy of Jonathan L Kaufman, MD

CARTITUDE-1: Response and Rates of CRS



- Median time to first response: 1 month (0.9–8.5)
- Responses ongoing in 70 (72.2%) patients
- 93.0% (evaluable patients) achieved MRD 10^{-5} negativity in median 1 month[c]
- In patients with 6 months follow-up, most had cilta-cel CAR+ T cells below the level of quantification in peripheral blood

	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]



- CRS onset
  - Day 4 or later: 89.1% (n=82)
  - Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset

Madduri D et al. ASH 2020;Abstract 177.

Courtesy of Jonathan L Kaufman, MD

4.3 – Madduri D et al. CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma. ASH 2020;Abstract 177.

- Ciltacabtagene Autoleucel is a novel CAR T cell with 2 BCMA single domain antibodies
- High ORR, CR and MRD negativity rate
- Durable responses
- CRS and NT expected. CRS onset later than other CAR T cells. Median time to onset is 7 days.

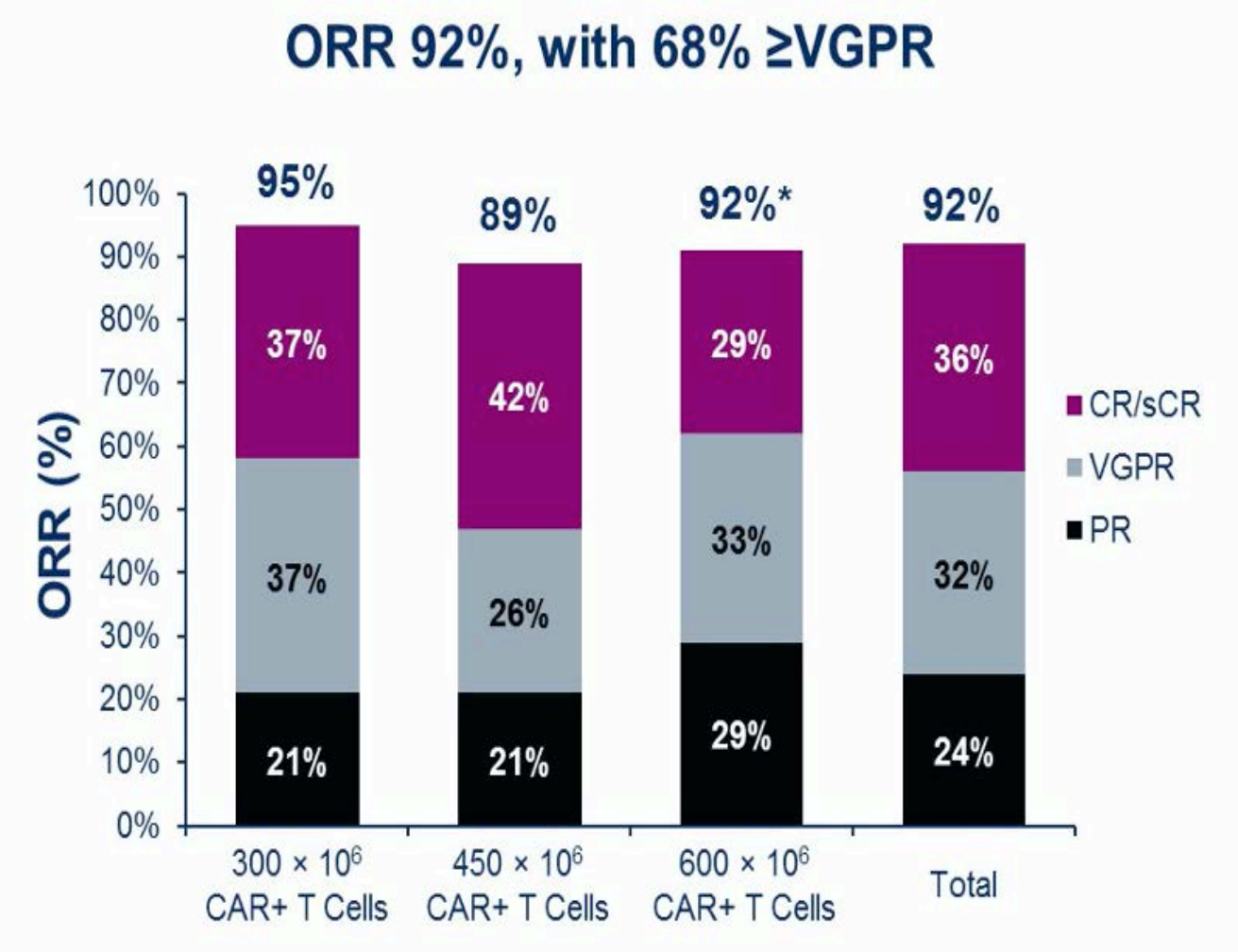
Courtesy of Jonathan L Kaufman, MD

Orvacabtagene Autoleucel (Orva-cel), a B-Cell Maturation Antigen (BCMA)-Directed CAR T Cell Therapy for Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Update of the Phase 1/2 EVOLVE Study (NCT03430011)

Mailankody S et al.
ASCO 2020;Abstract 8504.

Courtesy of Jonathan L Kaufman, MD

EVOLVE: Response, Rates of CRS and NE



Cytokine release syndrome (CRS), n (%)	**55 (89)**
Grade ≥3 CRS	2 (3)
Median time to onset, days (range)	2 (1–4)
Median time to resolution, days (range)	4 (1–10)
Neurological events (NE), n (%)	**8 (13)**
Grade ≥3 NE	2 (3)
Median time to onset, days (range)	4 (1–6)
Median time to resolution, days (range)	4 (1–10)

Mailankody S et al. ASCO 2020; Abstract 8504.

Courtesy of Jonathan L Kaufman, MD

4.4 – Mailankody S et al. Orvacabtagene autoleucel (orva-cel), a B-cell maturation antigen (BCMA)-directed CAR T cell therapy for patients (pts) with relapsed/refractory multiple myeloma (RRMM): update of the phase 1/2 EVOLVE study (NCT03430011). ASCO 2020; Abstract 8504. Oral

- Orva-cel, BCMA CAR T
- High ORR and CR rates
- Expected CRS and neurologic toxicity (rare)

Courtesy of Jonathan L Kaufman, MD

Updated Results from the Phase I CRB-402 Study of Anti-Bcma CAR-T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma: Correlation of Expansion and Duration of Response with T Cell Phenotypes

Alsina M et al.

ASH 2020;Abstract 130.

Courtesy of Jonathan L Kaufman, MD

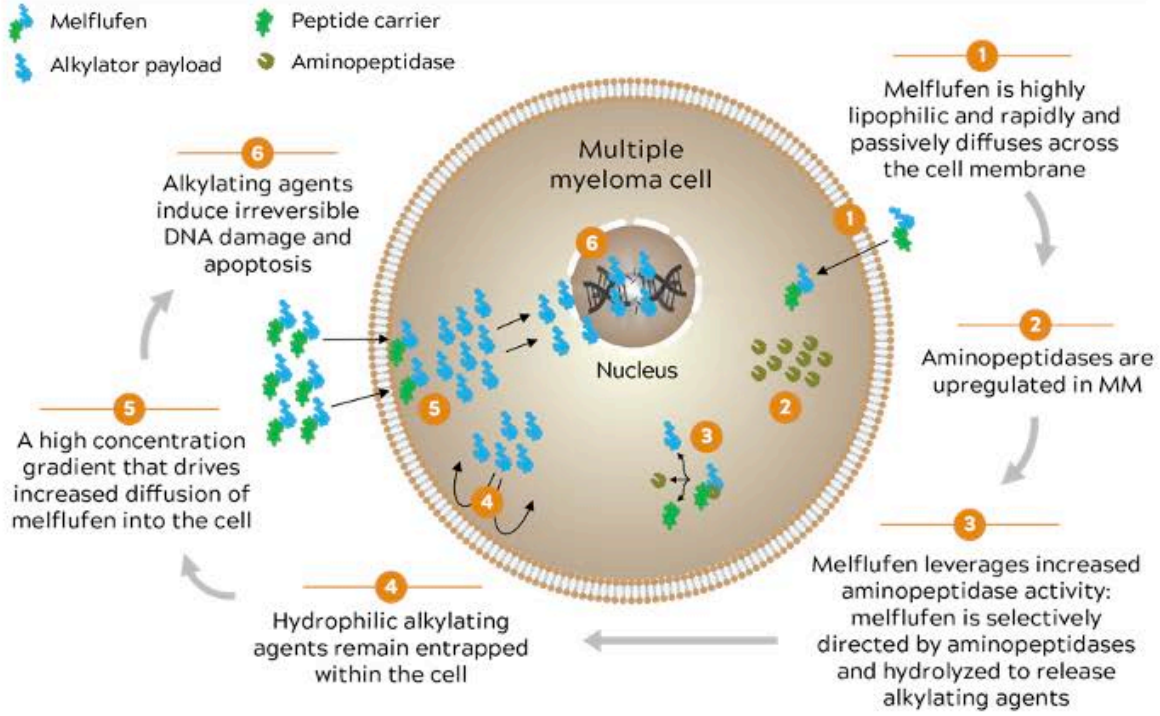
4.5 – Alsina M et al. Updated Results from the Phase I CRB-402 Study of Anti-Bcma CAR-T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma: Correlation of Expansion and Duration of Response with T Cell Phenotypes. ASH 2020;Abstract 130.

- Unique BCMA CAR T; BB2121 with PI3K inhibitor to skew t cells to memory phenotype
- High ORR and CR rates
- Possible increase in ORR at RP2D of 450
- DOR was 17 months; possibly supports hypothesis of long-term CAR T persistence

Courtesy of Jonathan L Kaufman, MD

Melphalan Flufenamide (Melflufen): Mechanism of Action

Melflufen is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**[1-5]



- In the pivotal phase 2 HORIZON study (OP-106), the activity of melflufen plus dexamethasone was further shown in heavily pretreated RRMM patients refractory to pomalidomide and/or anti-CD38 mAb therapy, with acceptable safety[6]
  - ORR was 29%; median PFS was 4.2 months, and median OS was 11.6 months
  - Grade 3/4 hematologic AEs were common (mainly neutropenia [79%], thrombocytopenia [76%], and anemia [71%]) but clinically manageable; nonhematologic AEs were infrequent

AE, adverse event; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-rate survival; RRMM, relapsed/refractory multiple myeloma.

Ocio E et al. ASH 2020;Abstract 417.

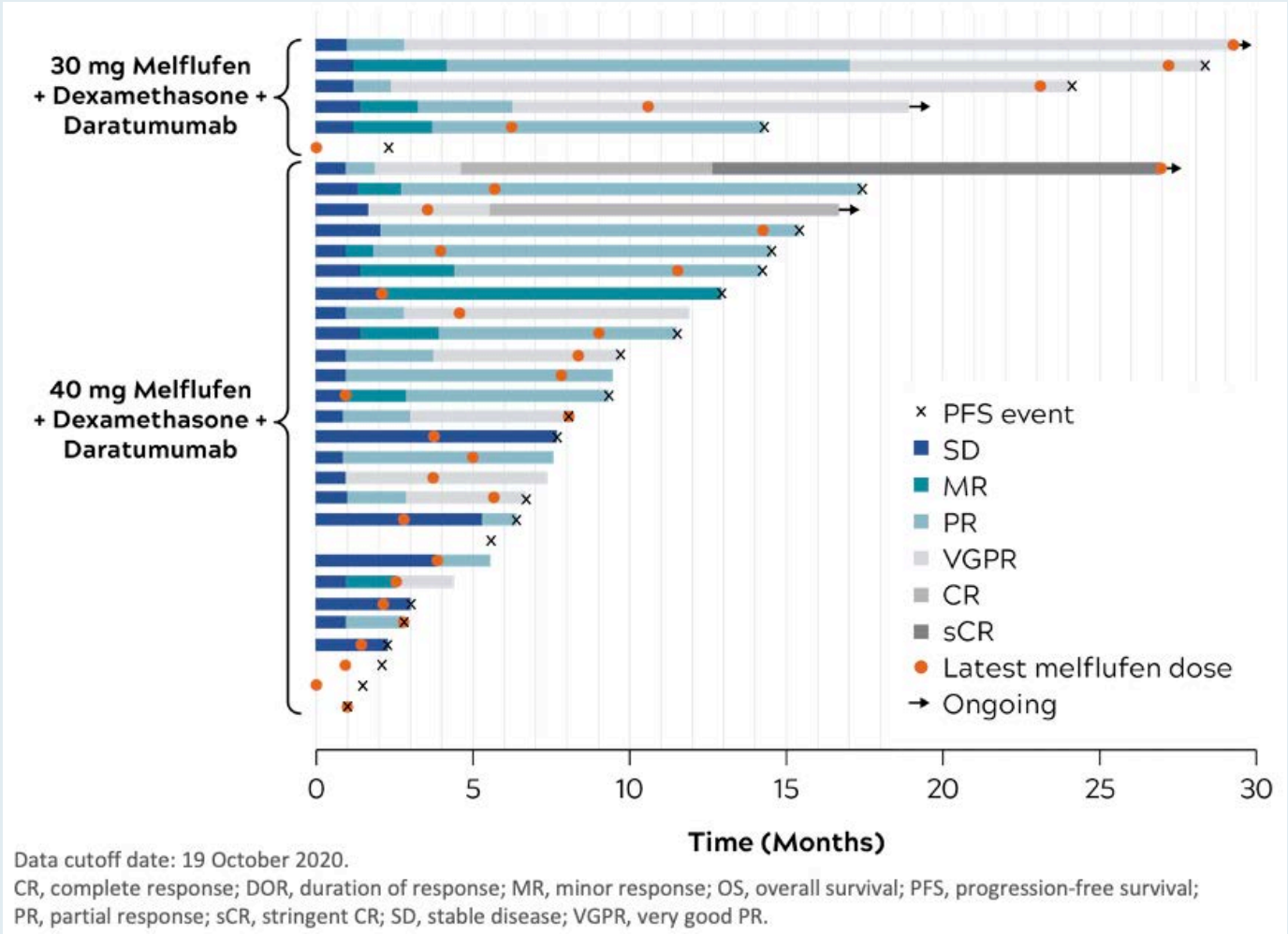
Courtesy of Jonathan L Kaufman, MD

ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) - Updated Efficacy and Safety

Ocio E et al.
ASH 2020;Abstract 417.

Courtesy of Jonathan L Kaufman, MD

ANCHOR: Melflufen Plus Dexamethasone and Daratumumab



Data cutoff date: 19 October 2020.
CR, complete response; DOR, duration of response; MR, minor response; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

- No DLTs were observed at any dose
- 15 patients (45%) experienced SAEs, most commonly pneumonia (12%); influenza (9%); and parainfluenza virus infection, sepsis, urinary tract infection, and febrile neutropenia (6% each)[a]
  - 30 mg: 4 patients (67%)
  - 40 mg: 11 patients (41%)
- Four AEs with fatal outcomes
  - 30 mg: sepsis (unrelated to study treatment)
  - 40 mg: sepsis (possibly related to melflufen), and cardiac failure chronic and and general physical health deterioration (unrelated to study treatment)[b]

Ocio E et al. ASH 2020;Abstract 417.

Courtesy of Jonathan L Kaufman, MD

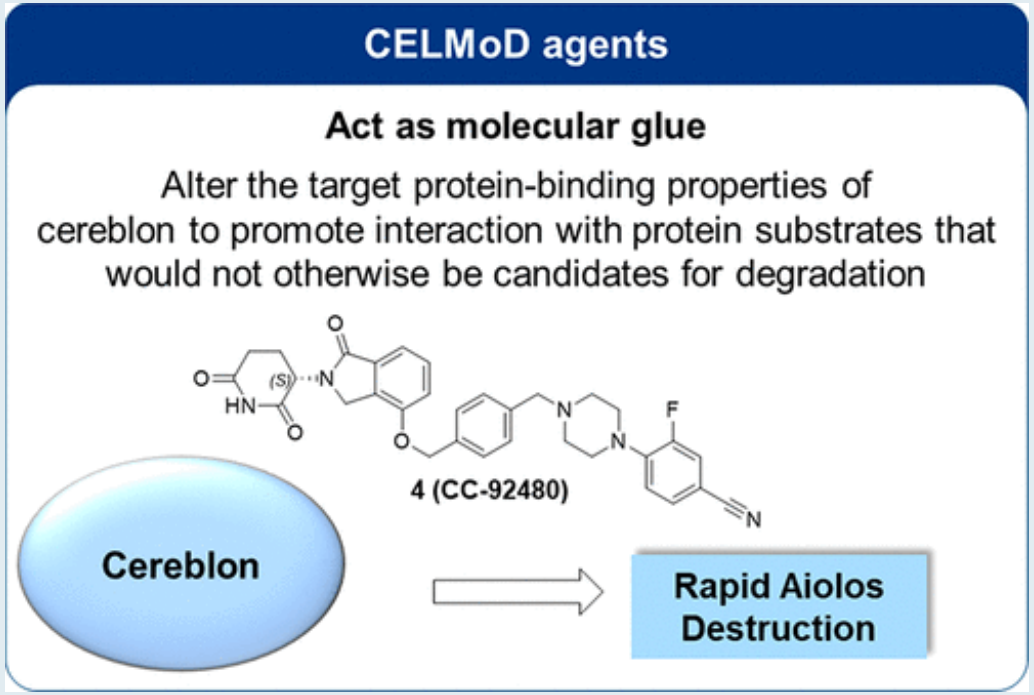
5.1 – Ocio E et al. ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) - Updated Efficacy and Safety. ASH 2020;Abstract 417.

- Melflufen is a new alkylating agent with unique properties as an aminopeptidase targeted peptide drug conjugate
- Single agent activity in the 20-25% range
- Combines here with dara or bortezomib
- No new safety signals
- Moving forward to find optimal dose and combinations

Courtesy of Jonathan L Kaufman, MD

Cereblon E3 ligase modulators (CELMoDs): Mechanism of Action

- CC-92480 binds to cereblon, thereby affecting the ubiquitin E3 ligase activity, and targeting certain substrate proteins for ubiquitination…
- … this induces proteasome-mediated degradation of certain transcription factors, some of which are transcriptional repressors in T cells…
- … this leads to modulation of the immune system, including activation of T lymphocytes; and antiproliferative effects and induction of apoptosis in myeloma cells



Hansen JD, et al. *J Med Chem*. 2020 Jul 9;63(13):6648-76.

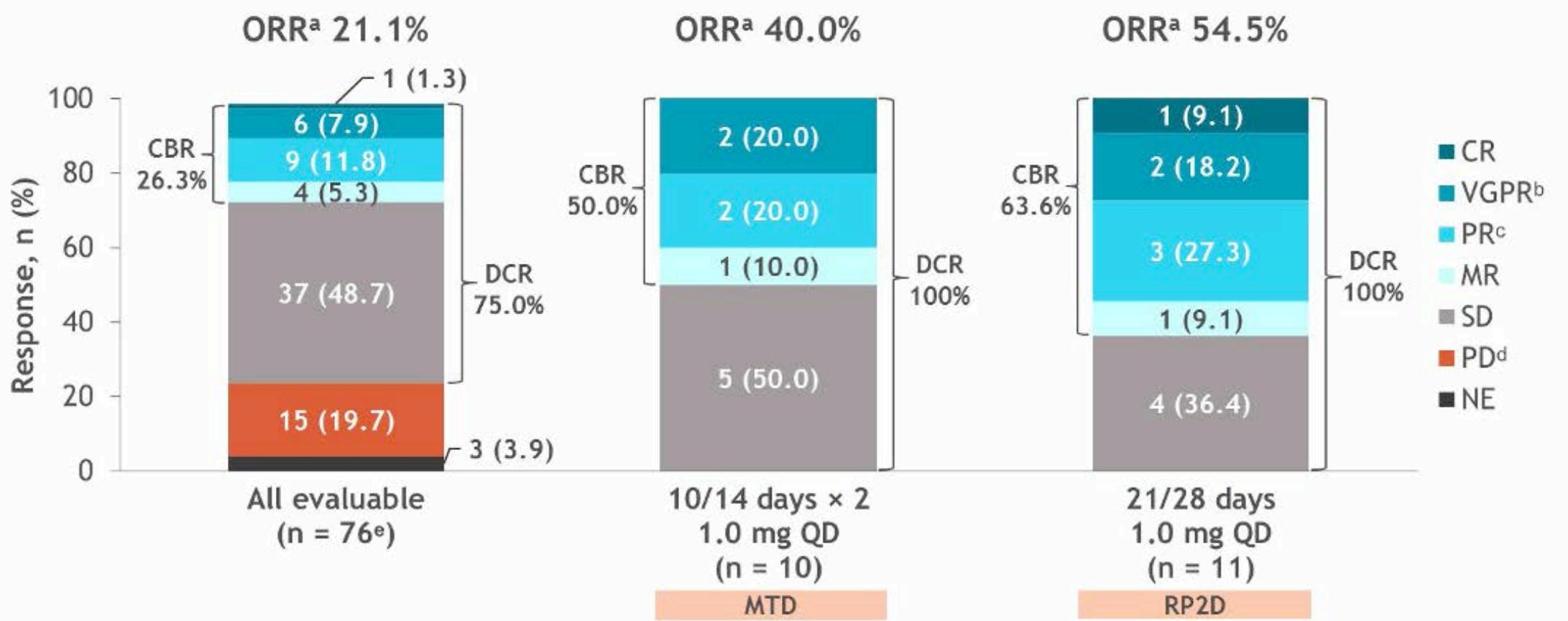
Courtesy of Jonathan L Kaufman, MD

First-in-human phase I study of the novel CELMoD agent CC-92480 combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM)

Richardson PG et al.
ASCO 2020;Abstract 8500.

Courtesy of Jonathan L Kaufman, MD

CC-92480 plus Dexamethasone for R/R MM: Response



- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple-class-refractory[f]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

Richardson PG et al. ASCO 2020;Abstract 8500.

Courtesy of Jonathan L Kaufman, MD

CC-92480 plus Dexamethasone for R/R MM: Adverse Events

Common (> 20 % all grade) TEAEs and events of interest, n (%)	All doses (N = 76)		
	All grade	Grade 3	Grade 4
Neutropenia	56 (73.7)	23 (30.3)	26 (34.2)
Febrile neutropenia	6 (7.9)	4 (5.3)	1 (1.3)
Anemia	42 (55.3)	24 (31.6)	-
Thrombocytopenia	33 (43.4)	5 (6.6)	7 (9.2)
Infections	54 (71.1)	25 (32.9)	2 (2.6)
Pneumonia[a]	13 (17.1)	11 (14.5)	-
Fatigue	29 (38.2)	7 (9.2)	-
Pyrexia	17 (22.4)	3 (3.9)	-
Peripheral sensory neuropathy	4 (5.3)	-	-
Diarrhea	18 (23.7)	1 (1.3)	-
Nausea	17 (22.4)	1 (1.3)	-
Deep vein thrombosis	1 (1.3)	-	-

- Prophylactic G-CSF was not permitted during Cycle 1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reductions of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

Richardson PG et al. ASCO 2020;Abstract 8500.

Courtesy of Jonathan L Kaufman, MD

5.2 – Richardson PG et al. First-in-human phase I study of the novel CELMoD agent CC-92480 combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). ASCO 2020; Abstract 8500.

- New CELMoD (used to be called IMiDs)
- Phase 1 study in RRMM with dex
- Toxicity primarily myelosuppression
- Responses in heavily refractory patients
- RR at 48% at “therapeutic” doses

Courtesy of Jonathan L Kaufman, MD