ASH 2021 Update: Multiple Myeloma

Rebecca Silbermann, MD
silbermr@ohsu.edu

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Disease Biology – Screening

Quads vs Triplets

BCMA Targets

Non-BCMA Targets

Updates in AL Amyloidosis

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Disease Biology

- iStopMM (Iceland Screens, Treats or Prevents MM)
  - Overall results (#156)
  - High prevalence of SMM (#156)
  - No increased COVID with MGUS (#154)
  - New FreeLite reference levels (#542)

- PROMISE
  - Screening data for 2,960 subjects (#152)

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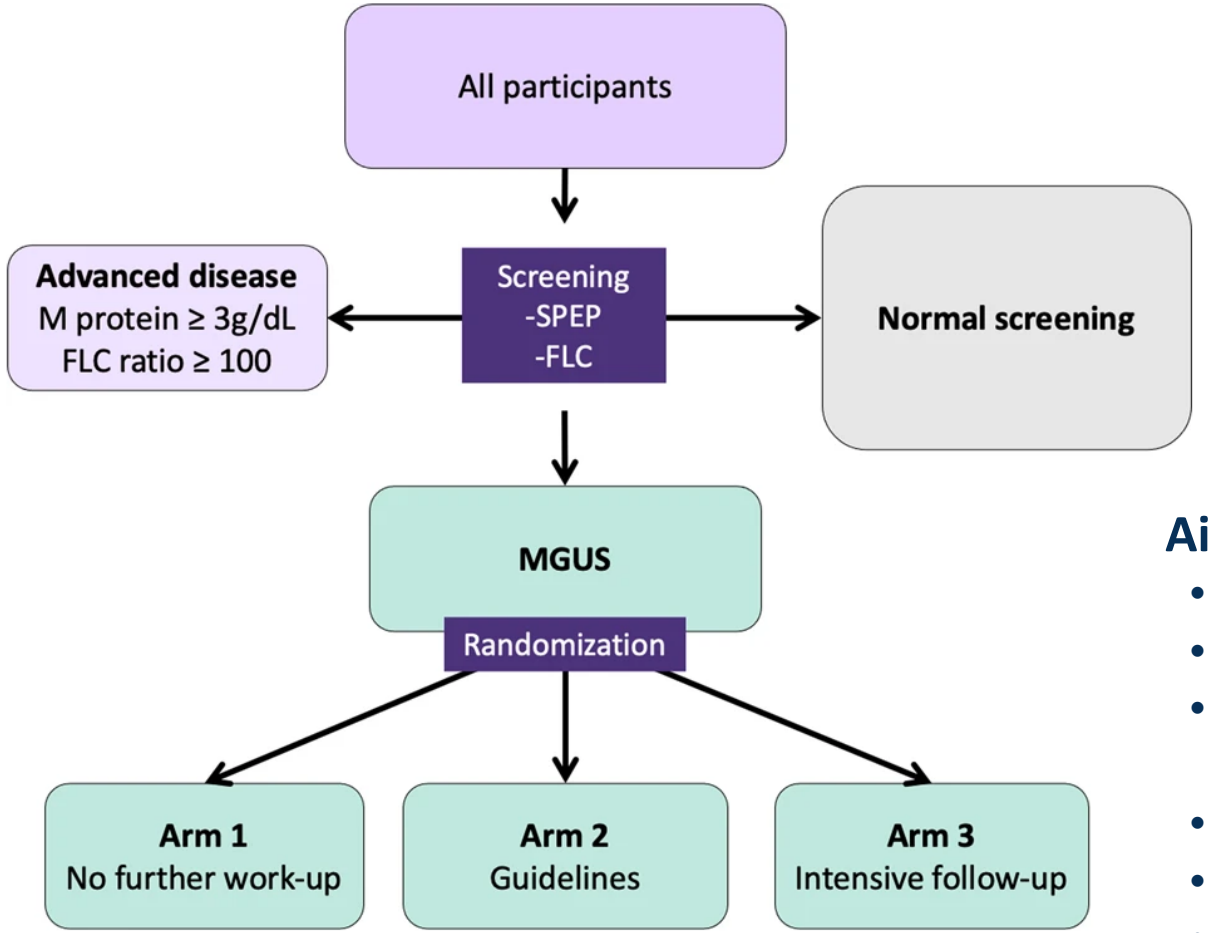
Disease Biology: iStopMM

- All Iceland residents born before 1976



(IMWG recommendations)

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

Aims:

- Evaluate the impact of MGUS screening
- Obtain evidence for optimal work-up and follow-up
- Integrate biological, imaging, and germline genetic markers in risk models for progression
- Evaluate the impact of screening on quality of life
- Biobanking
- Evaluate the effect of early detection and early treatment

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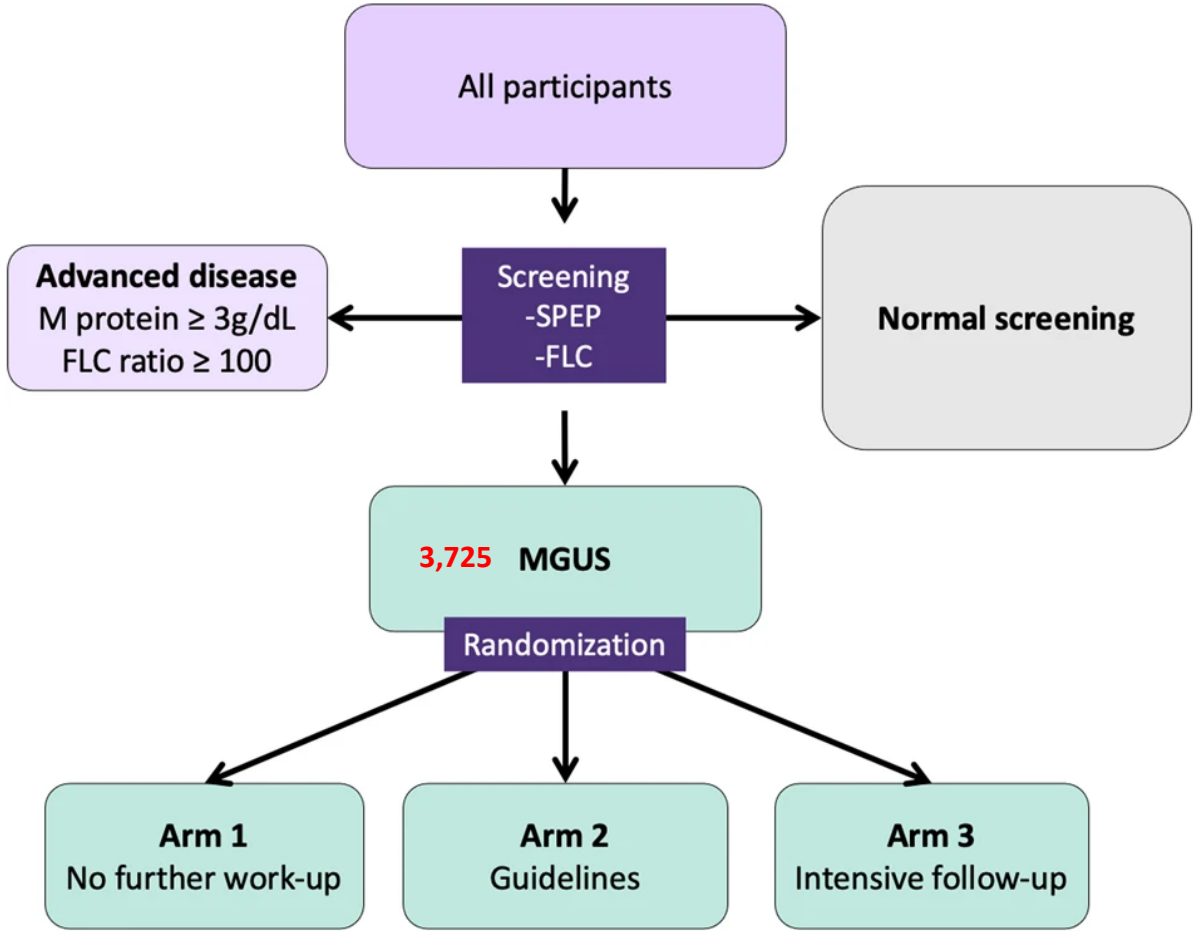
Disease Biology: iStopMM



(IMWG recommendations)

- All Iceland residents born before 1976
- 54% (80,759) agreed to participate
- 93% (75,422) screened
- 4.9% (3,725) overall prevalence of MGUS
  - 2.3% ages 40-59
  - 6.2% ages 60 – 79
  - 12.9% ages 80 - 103

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

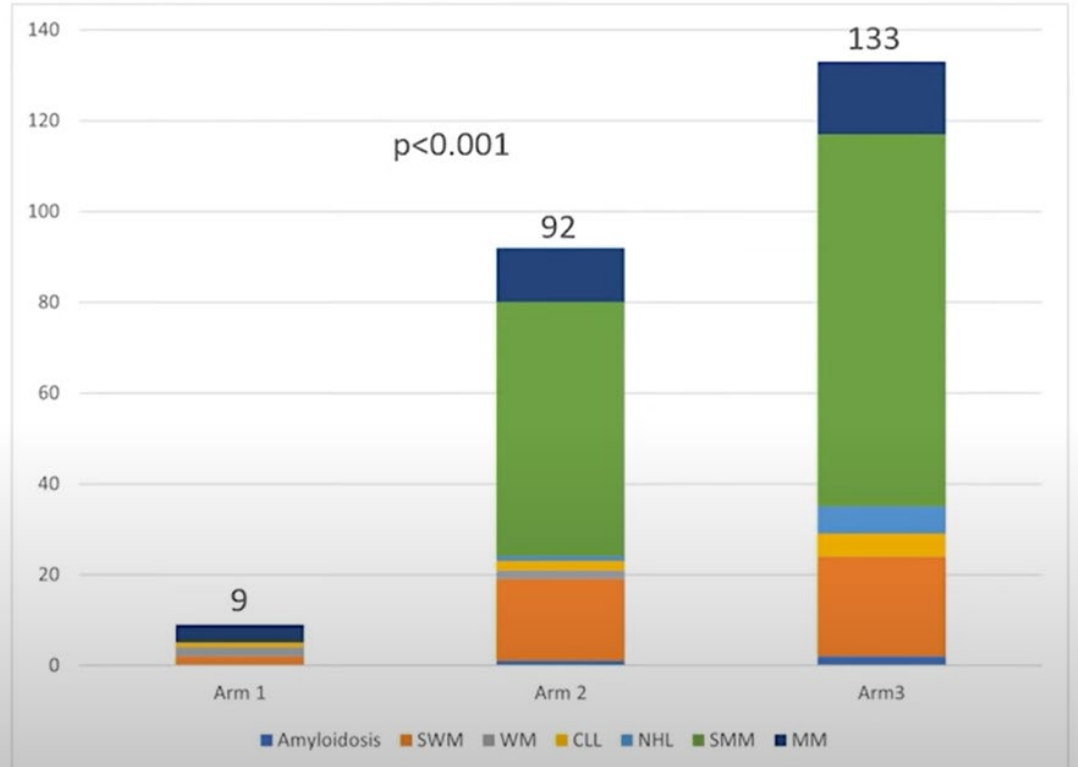
Characteristics	Arm 1	Arm 2	Arm 3	
Number of participants	1164	1159	1164	
Female sex	527 (45%)	534 (46%)	531 (46%)	
Median Age years	69	69	69	
Isotype				
IgG	586 (50%)	580 (50%)	586 (50%)	
IgA	130 (11%)	104 (9%)	137 (11%)	
IgM	214 (18%)	226 (20%)	208 (18%)	
Biclonal	91 (8%)	106 (9%)	91 (8%)	
Mean M-protein conc (g/dL)	0.34	0.32	0.34	
LC-MGUS	143	143	142	
Outcome				**p-value**
Any LP disorder	9	92	133	p<0.001
Amyloidosis	0	1	2	NS
SWM	2	18	22	p<0.001
WM	2	2	0	p=0.48
CLL	1	2	5	p=0.21
NHL	0	1	6	p=0.06
SMM	0	56	82	p<0.001
MM	4	12	16	p<0.001

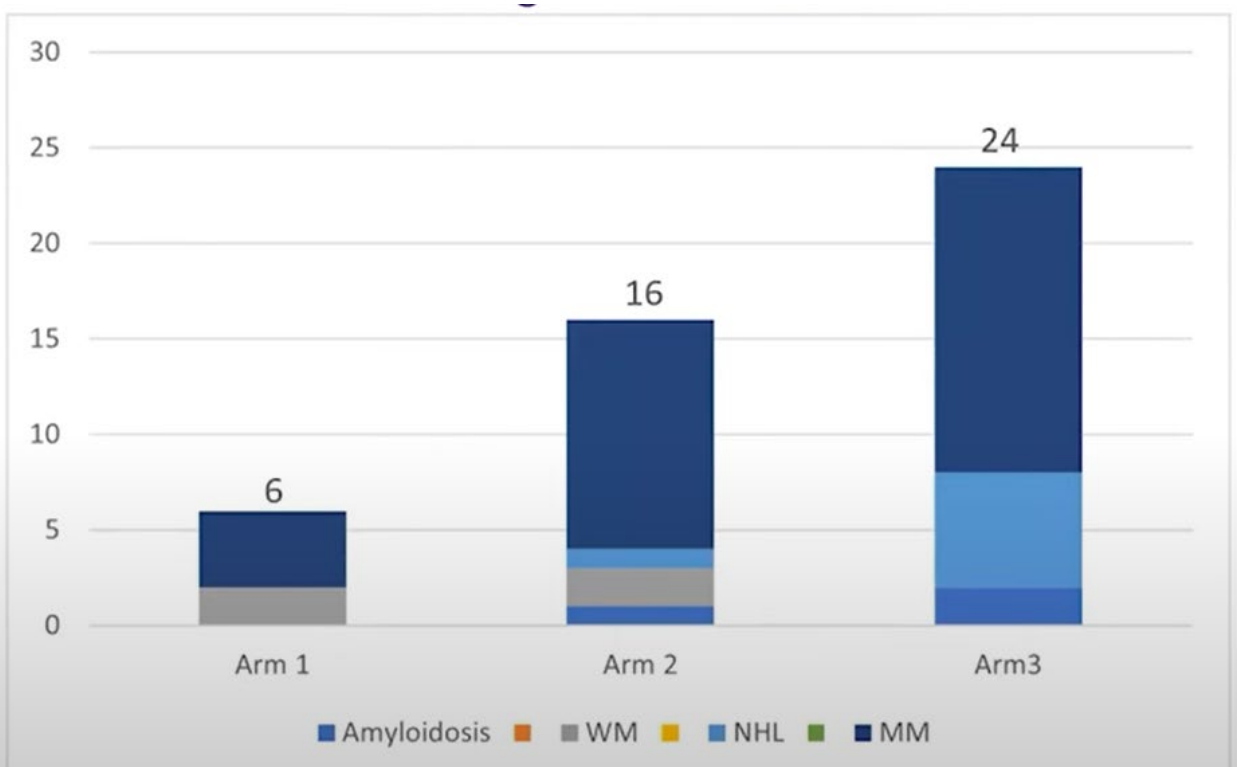
Abbreviations: LC-MGUS=Light-chain MGUS; LP=Lymphoproliferative; SWM=Smoldering Waldenström´s macroglobulinemia; WM= Waldenström´s macroglobulinemia; CLL=Chronic lymphocytic leukemia; NHL=non-Hodgkin lymphoma; SMM=Smoldering multiple myeloma; MM=Multiple myeloma; and NS=Not significant.

Disease Biology: iStopMM

At 3y follow-up

- Active screening identifies a significantly higher number of individuals with full blown malignancies and smoldering disease
- The authors advise against systematic screening in healthy individuals





Disease Biology: iStopMM
SMM Prevalence

Of the total 75,422 patients screened (51% of target population)

- 3,725 were randomized
- BMBx completed in 1,503
- 180 diagnosed with SMM

Study Arm 3 (1,279 individuals) used to estimate prevalence of SMM

- 10.8% had SMM (prevalence of 0.53%: 95% CI 0.49 - 0.57%))
- 1/3 of patients had intermediate or high risk SMM (based on the 2/20/20 Mayo risk stratification model)

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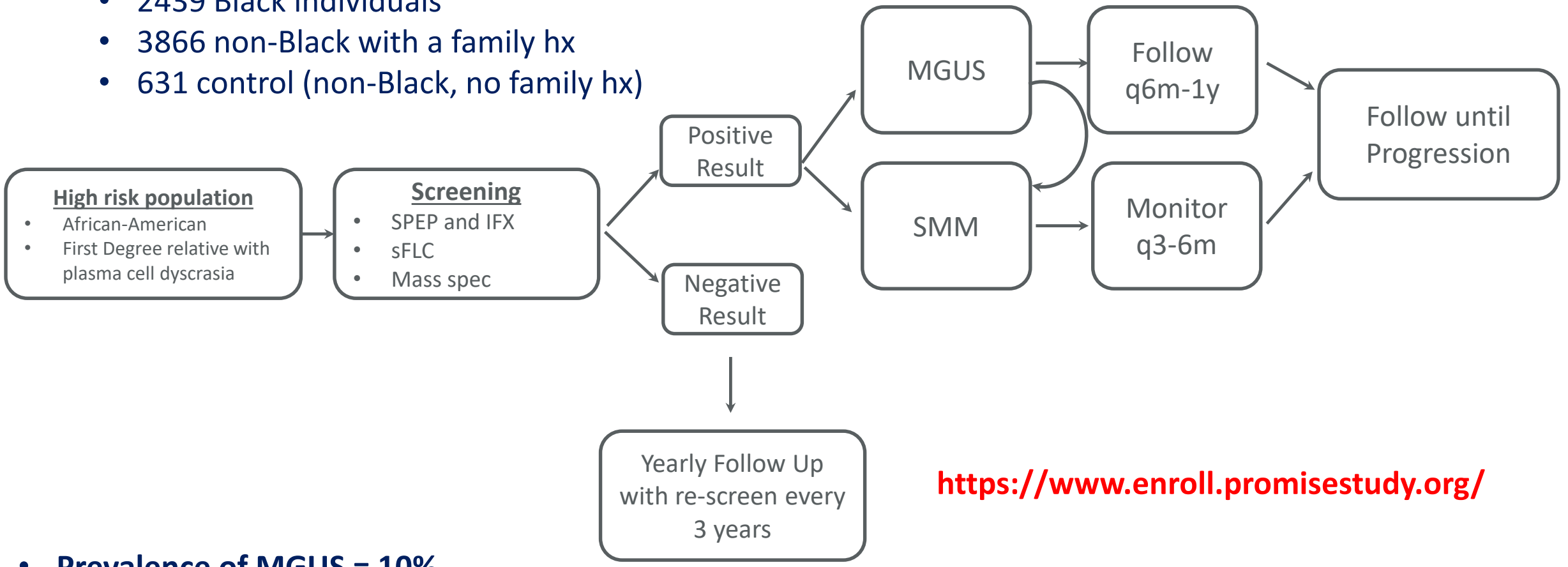
Disease Biology: PROMISE

Screened 2211 individuals from PROMISE and 5411 from MGH biobank

- 2439 Black individuals
- 3866 non-Black with a family hx
- 631 control (non-Black, no family hx)



https://www.enroll.promisestudy.org/

- **Prevalence of MGUS = 10%**
  - **Among individuals ≥ 50, MGUS incidence: 10% in controls, 17% among Black individuals, 13% among non-Black with a family hx**

- **Higher rate of MGUS detection by mass spec**

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Quadruplet Therapy for NDMM

	Induction	ASCT	Consolidation	Maintenance	Primary End Point(s)	Abstract #
GRIFFIN (phase 2)	Dara-RVd vs RVd	Yes	Dara-RVd vs RVd	Dara-R vs R	sCR rate at end of post-ASCT consolidation	79
GMMG-HD7 (phase 3)	Isa-RVd vs RVd	Yes	-	Isa-R vs R	Rate of MRD negativity after induction	463
IFM 2018-01 (phase 2)	Dara-Ird	Yes	Dara-Ird	R	Rate of MRD negativity after consolidation and before maintenance	464
MASTER (phase 2)	Dara-KRd	Yes	Dara-KRd (by MRD status)*	* Based on MRD status or R	Rate of MRD negativity in intent-to-treat population	481
GMMG-HD6 (phase 3)	Elo-RVd vs RVd	Yes	Elo-RVD vs RVd	Elo-R vs R	PFS from randomization	486

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Quadruplet Therapy for NDMM

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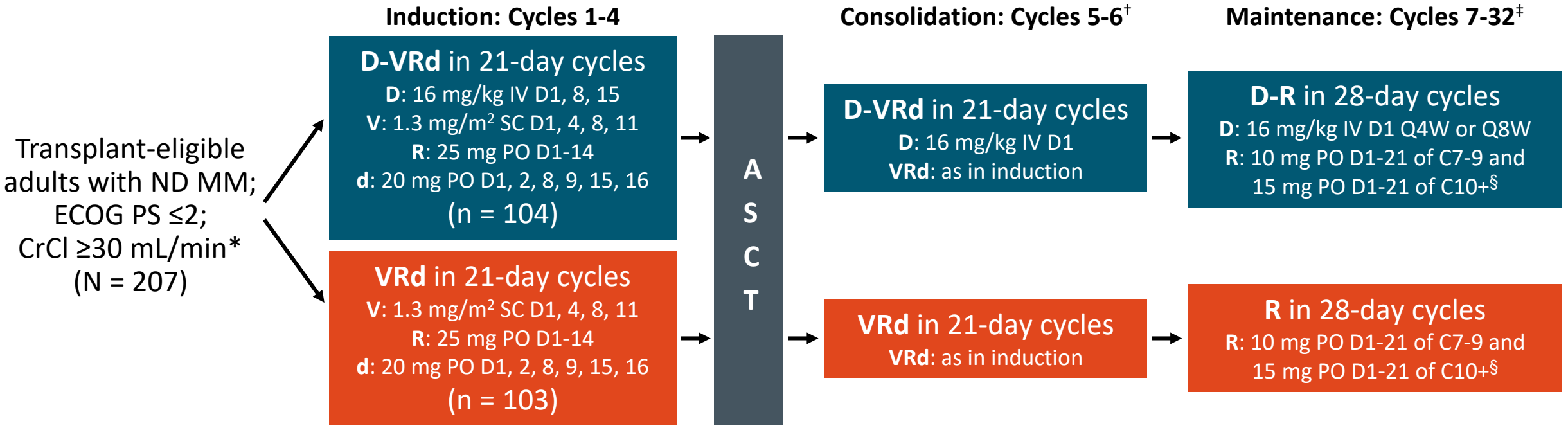
Quad Therapy for NDMM: GRIFFIN UPDATE



*Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

After 24 mo of maintenance therapy D-VRd followed by D-R maintenance continued to show significant improvement in sCR and depth of response vs VRd followed by R maintenance[1]

- **Patients with sCR after 24-mo maintenance: 66.0% vs 47.4% (*P* = .0096)**
- **Patients with MRD negativity after 24-mo maintenance at 10^{-5} threshold: 64.4% vs 30.1% (*P* <.0001); at 10^{-6} threshold: 35.6% vs 14.6% (*P* = .0007)**
- **MRD negativity rates for D-VRd treated patients were consistent in all subgroups of patients, including those with high risk features.**

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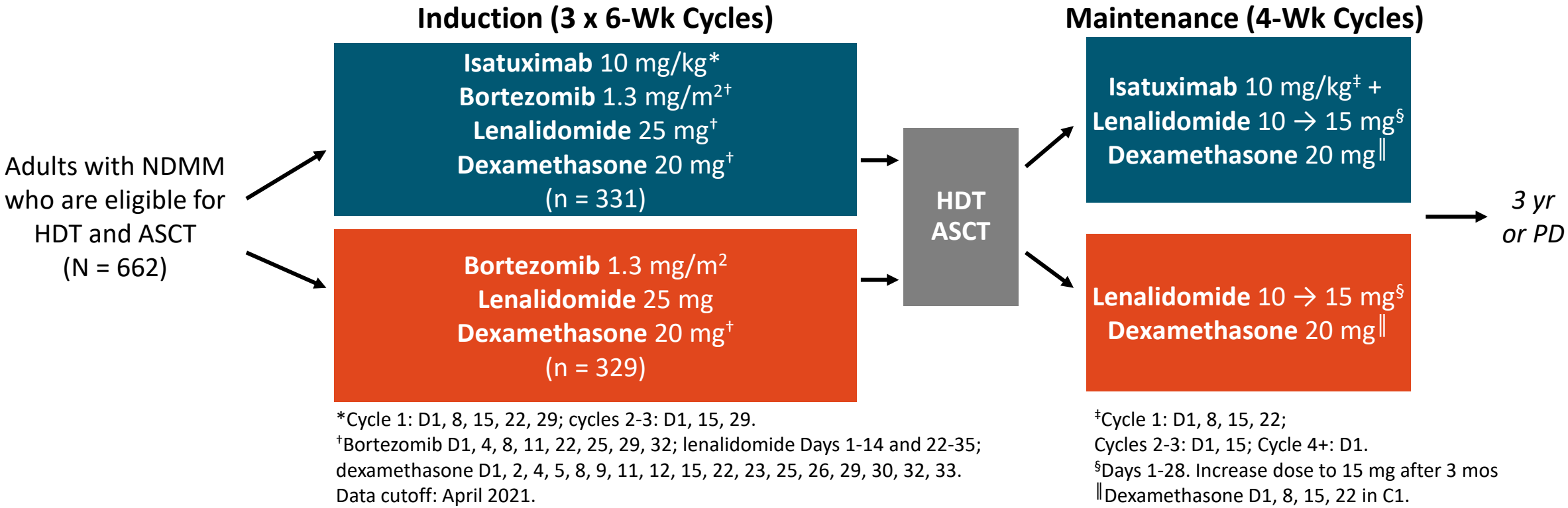
Laubach. ASH 2021. Abstr 79.

Quad Therapy for NDMM: GMMG-HD7



*Cycle 1: D1, 8, 15, 22, 29; cycles 2-3: D1, 15, 29.
†Bortezomib D1, 4, 8, 11, 22, 25, 29, 32; lenalidomide Days 1-14 and 22-35; dexamethasone D1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33.
Data cutoff: April 2021.

‡Cycle 1: D1, 8, 15, 22;
Cycles 2-3: D1, 15; Cycle 4+: D1.
§Days 1-28. Increase dose to 15 mg after 3 mos
‖Dexamethasone D1, 8, 15, 22 in C1.

- **Addition of isatuximab to VRd produced superior rates of MRD negativity vs VRd alone**
  - **MRD-negative rate at end of 18-wk induction: 50.1% vs 35.6%**
- **The benefit of adding isatuximab was seen across all patient subgroups**
- **Trial ongoing, including analyses of second randomization after ASCT of isatuximab + lenalidomide vs lenalidomide alone as maintenance therapy**

Goldschmidt. ASH 2021. Abstr 463.

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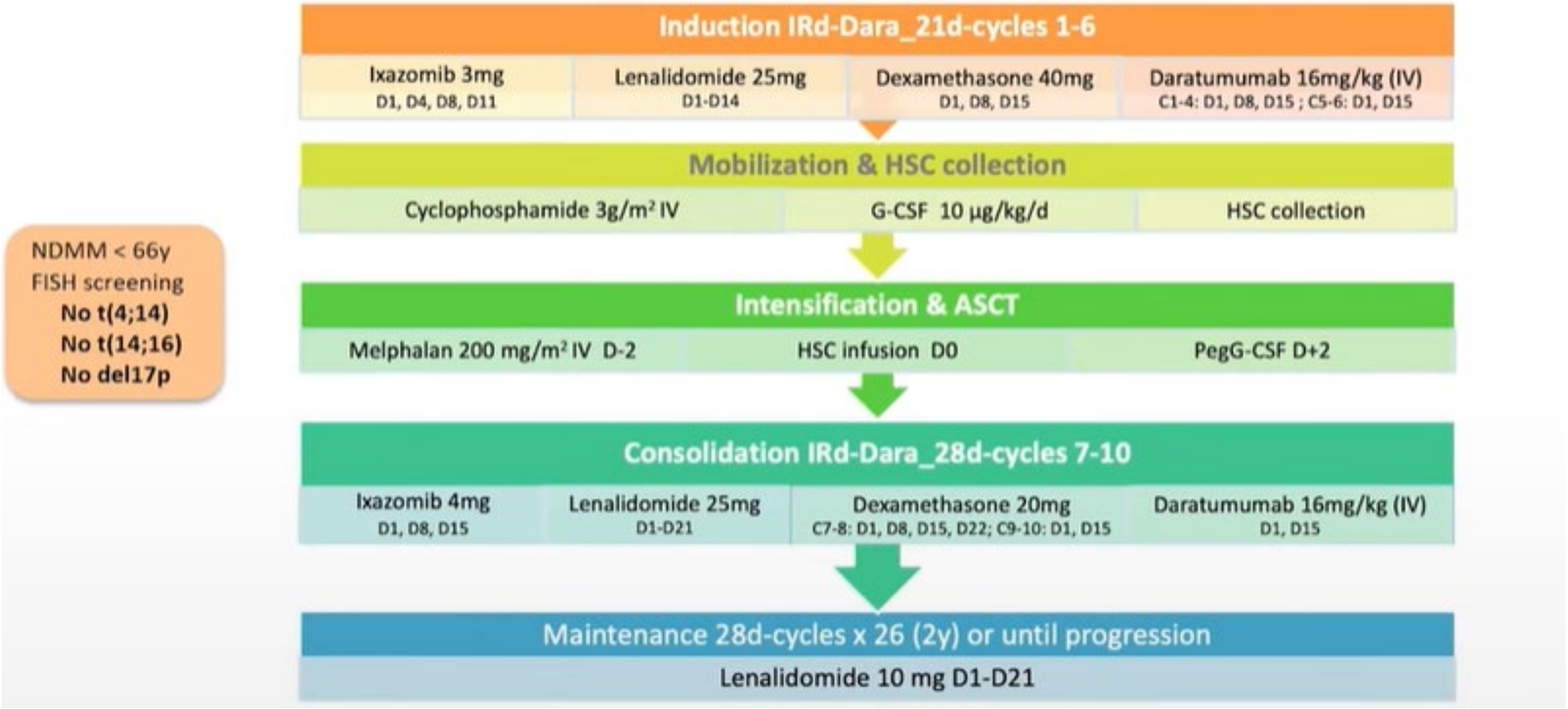
Quad Therapy for NDMM: IFM 2018-01



- 95.2% of patients responded (measured after 1y of maintenance therapy), Over half of patients achieved CR or sCR
- 39.5% of patients achieved MRD negativity to 10x^-6, 51.4% at 10x^-5
- Responses (including MRD negativity) deepened over time

Perrot. ASH 2021. Abstr 464.

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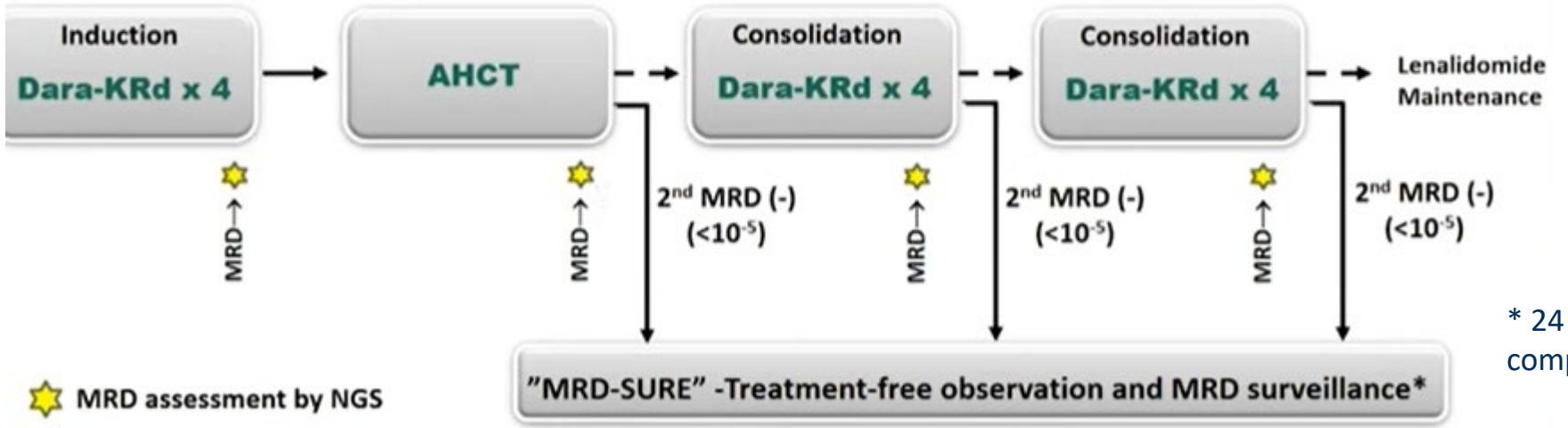
Quad Therapy for NDMM: MASTER UPDATE

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



* 24 and 72 weeks after completing therapy

- **86% of patients achieved a CR or better**
- **80% of patients achieved MRD negativity (10x^-5), 66% achieved MRD negativity at 10x^-6**
- **Responses deepened with each phase of treatment and were similar in patients with 0, 1, or 2+ high-risk genetic abnormalities**
- **ASCT increased the rates of MRD negativity following induction therapy, benefitting patients with highest-risk disease features**
- **Nearly all patients with no or only 1 high-risk genetic abnormality and confirmed MRD negativity had no disease progression or MRD resurgence since stopping therapy**

Costa. ASH 2021. Abstr 481.

BCMA Targets for Relapsed Disease

Current FDA Approved Therapies

Belantamab mafodotin (DREAMM-2 trial) [FDA approval 8/5/20]

- ORR 32% (7% with CR/sCR, 11% with VGPR), median DoR 11mo

  Common AE of keratopathy, generally reversible

  - ASH 2021 Updates DREAMM-5: Belantamab + Feladilimab (Inducible T-cell Co-Stimulator Agonist): ORR 52%

    ALGONQUIN: Bela + Pd

    DREAMM-9: Bela + RVd in transplant-ineligible, NDMM – alternative dosing schedules

Idecabtagene vicleucel (KarMMa) [FDA approval 3/26/21]

- ORR 73%, ORR 81% in patients who received the highest target dose

Ciltacabtagene autoleucel (JNJ-4528, CARTITUDE-1) [FDA approval 2/28/22]

- 1y follow-up: ORR 97% (sCR 67%), PFS 77%, OS 89%
  - ASH 2021 Update 2y follow-up: ORR 98% (sCR 83%), PFS 60.5%, OS 74%

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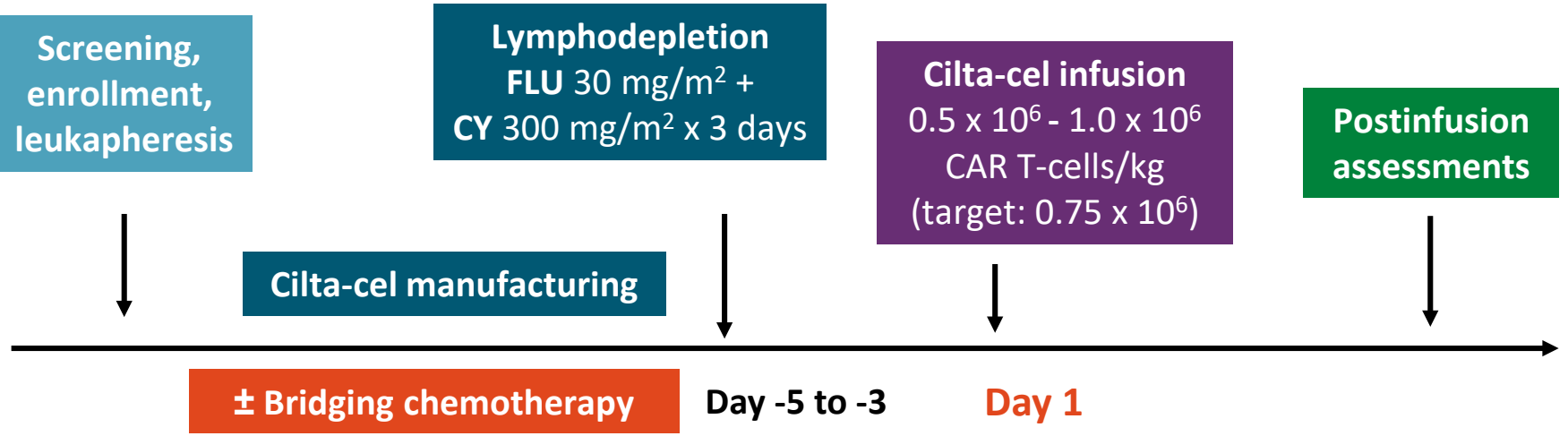
BCMA Targets: CARTITUDE-1

Ciltacabtagene autoleucel: 2 BCMA-targeting single-domain antibodies intended to boost avidity plus a 4-1BB costimulatory domain

≥3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD
(N = 113)



- Of 113 patients enrolled, 97 received cilta-cel; median administered dose: 0.71 x 10^6 (0.51-0.95 x 10^6) CAR+ viable T-cells/kg
- **Primary endpoint:** safety and RP2D (phase Ib), efficacy (phase II)

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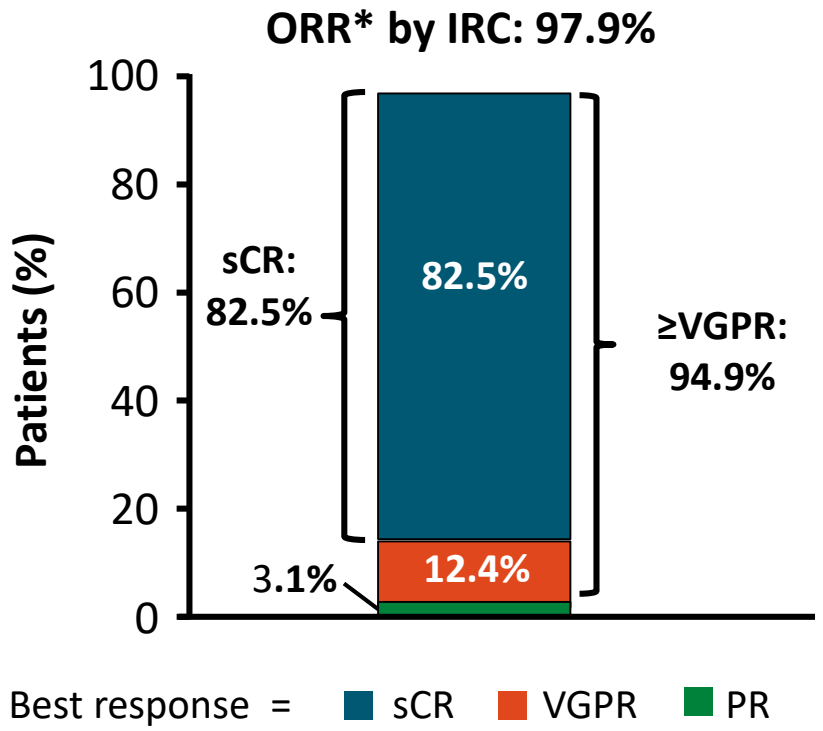
1. Berdeja. Lancet. 2021;398:314. 2. Martin. ASH 2021. Abstr 549.

BCMA Targets: CARTITUDE-1, 2y follow-up



*ORR assessed by independent review committee.

- sCR rates deepened over time
  - 67% at median 1-yr follow-up
  - 83% at median 2-yr follow-up
- Median time to first response: 1 mo (range: 0.9-10.7)
- Median time to best response: 2.6 mo (range: 0.9-17.8)
- Median time to ≥CR: 2.9 mo (range: 0.9-17.8)
- Median DoR: NE (range: 21.8-NE)
- Percentage of patients remaining progression-free at 2 yr was 60.5%

Martin. ASH 2021. Abstr 549. Reproduced with permission.

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Bispecific Antibodies for RRMM

	MagnetisMM-1 (Ph 1)	MajesTEC-1 (Ph 1/2)	Ph1	Ph1	MonumenTAL-1 (Ph 1)
Agent	**Elranatamab**	**Teclistamab**	**REGN5458**	**Cevostamab**	**Talquetemab**
Target	BCMA x CD3	BCMA x CD3	BCMA x CD3	FcRH5 x CD3	GPRC5D x CD3
Dosing	sc weekly	sc weekly	iv q2w	iv q3w	sc weekly
# patients*	55	169	73	161*	55 at 2 RP2D*
Median # prior rx	6 (2-15)	5 (2-14)	5 (2-17)	6 (2-18)	6 (2-17)
ORR, %	69	65	75	56.7	69
CR or better, %	30	29	16	5	16
Med DoR	Not reported	Not reached	Not reported	11.5	Not reached
CRS, all grades (G3/4), %	87 (0)	72 (1)	36 (0)	80 (1.2)	75 (5)
Neurotox, all grades (G3/4), %	Not reported	13 (0)	4 (0)	14 (1)	Not reported
Abstract #	895	896	160	157	158

*included patients with prior BCMA tx

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BCMA x CD3: REGN5458

Patients with MM who are R/R to ≥3 lines of prior therapy including an IMiD, a PI, and an anti-CD38 Ab, or double refractory to an IMiD and PI with PD on/after anti-CD38 Ab; nonsecretory MM allowed (N = 73)

Part 1: REGN5458 IV Dose Escalation (4+3 design)

DL1: 3 mg (n = 4)*	DL2: 6 mg (n = 10)*	DL3: 12 mg (n = 10)*	DL4: 24 mg (n = 10)*	DL5: 48 mg (n = 7)*	DL6: 96 mg (n = 8)*†	DL7: 200 mg (n = 12)†	DL8: 400 mg (n = 8)†	DL9: 800 mg (n = 4)†

RP2D → Part 2: Dose Expansion

*1 dose-level specific step-up dose. †5-mg and 25-mg step-up doses.

- **Primary objectives:** safety, tolerability, DLTs, RP2D
- **Secondary objectives:** ORR, DoR, PFS, MRD status, and OS

Zonder. ASH 2021. Abstr 160. NCT03761108.

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BCMA x CD3: REGN5458

- 51% ORR for all enrolled patients
- 86% ≥VGPR and 43% ≥CR among all responders
- For patients achieving CR/sCR (with available data), 4/10 negative at MRD 10^{-5}

Response, n (%)	DL 1-3 (n = 24)	DL 4-6 (n = 25)	DL 7-9 (n = 24)
ORR	29	48	75*
▪ sCR	13	20	8
▪ CR	13	4	8
▪ VGPR	0	24	42
▪ PR	7	0	17

*Includes all patients who were evaluable for response assessment at 4 wk.

- Median time to response < 1mo, 70% response within first 2 mo
- Estimated median DoR not reached
  - Probability of EFS in responders at 8 mo: 90.2% (95% CI: 72.6-96.7)
- Longest responses ongoing for >19 mo at latest data cutoff (September 30, 2021)
- MTD was not reached
- CRS: 38%; no grade ≥3 CRS or neurotoxicity; grade 2 CRS in 3 patients; grade 1 CRS within first 2 wk and resolved within a day; dose level did not correlate with CRS

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FcRH5 x CD3: Cevostamab

- FcRH5 surface receptor is ubiquitously and highly expressed on myeloma cells
- Cevostamab is a novel, humanized T-cell–engaging bispecific IgG antibody
  - Targets CD3 on T-cells and FcRH5 on myeloma cells to encourage immunologic synapse formation, leading to myeloma cell death

Patients with R/R MM for which there is no available, appropriate, or tolerable tx

- ECOG PS 0-1
- Prior CAR T-cells, ADCs, and bispecific antibodies allowed

Cevostamab treatment schedule

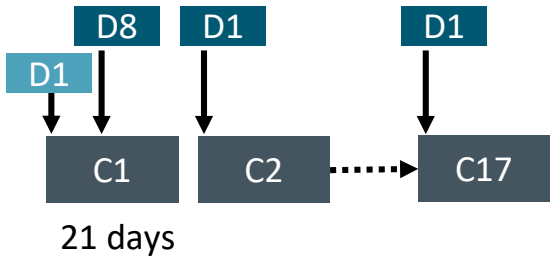
- Q3W (IV) for 17 cycles (~12 mo) or until PD or unacceptable AE
- Prophylaxis for mitigation of CRS/infusion-related reaction
  - C1 step-up dosing
  - C1-2 corticosteroid premedication*; C1–17 acetaminophen/diphenhydramine premedication
- Hospitalization (≥72 hr) after each C1 infusion

C1 single step-up escalation†

C1D1	C1D8	
3.6	198	n = 9
3.6	160	n = 8
3.6	132	n = 7
3.6	90	n = 12
3.6	60	n = 7
3.6	40	n = 6
3.6	20	n = 3
0.05-3.6	0.15-10.8	n = 17

C1 single step-up expansion†

C1D1	C1D8	
3.6	90	n = 31

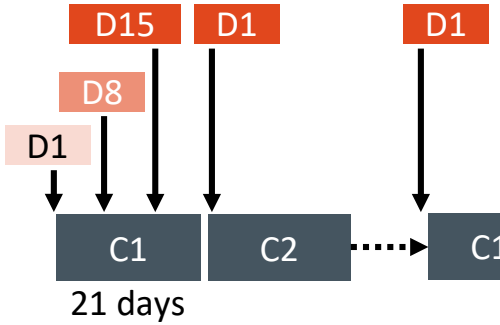


C1 double step-up escalation†

C1D1	C1D8	C1D15	
0.3	3.6	160	n = 5
0.6	3.6	90	n = 8
0.3	3.6	90	n = 8
1.2	3.6	90	n = 3
1.2	3.6	60	n = 6

C1 double step-up expansion†

C1D1	C1D8	C1D15	
0.3	3.6	160	n = 31



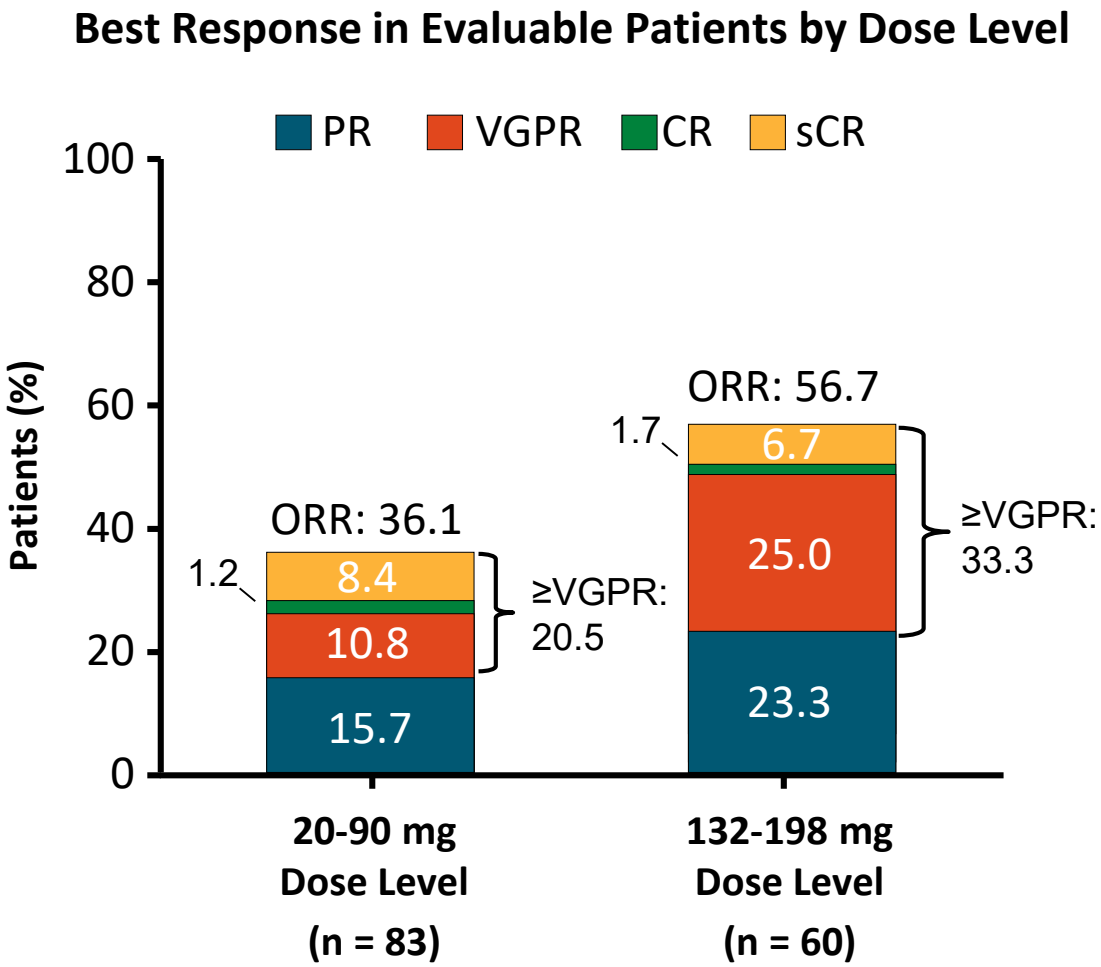
*Corticosteroid premedication optional from C3 onward. †All doses in mg.

1. Li. Cancer Cell. 2017;31:383. 2. Cohen. ASH 2020. Abstr 292. 3. Trudel. ASH 2021. Abstr 157.

FcRH5 x CD3: Cevostamab

- Responses occurred at and above 20-mg target dose level (n = 143)
- ORR increased with target dose
  - ORR in C1 single step-up expansion (3.6 mg/90 mg): 29.0%
  - ORR in C1 double step-up expansion (0.3 mg/3.6 mg/160 mg): 54.8%

Outcome	Cevostamab (N = 161)
Median time to response among responders, mo (range)	1.0 (0.7-5.9)
Median time to best response, mo (range)	2.1 (0.7-11.4)
MRD negativity at $<10^{-5}$ in patients with ≥VGPR, n/N (%)	7/10 (70)

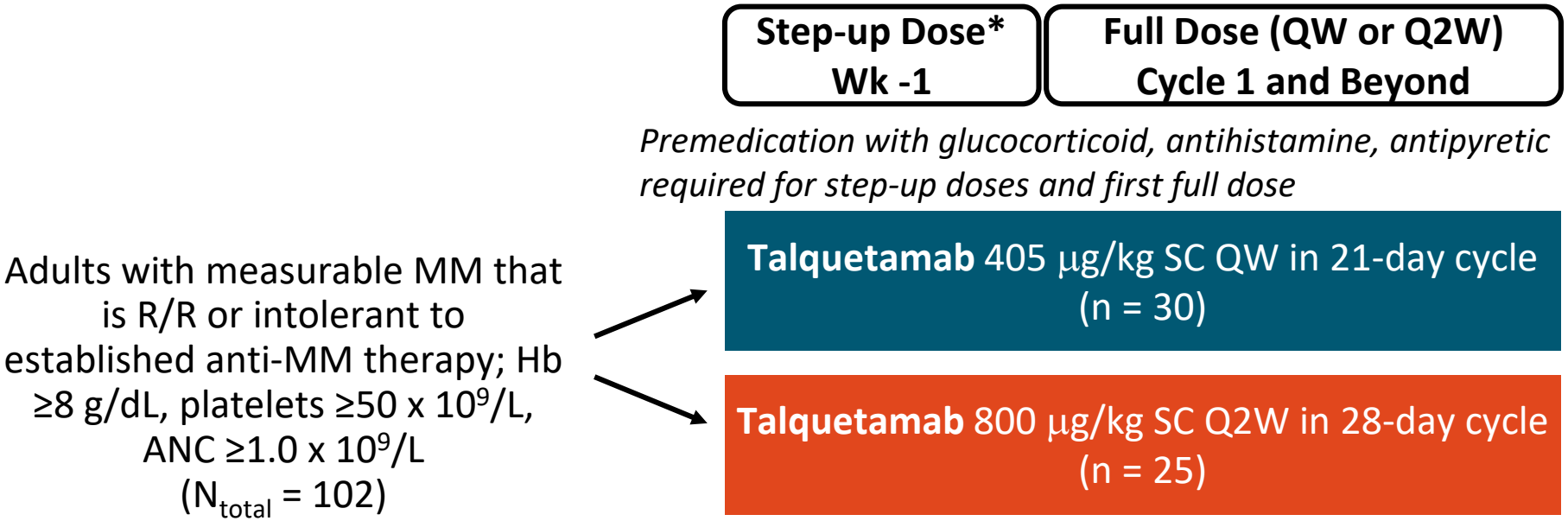


- **Median duration of response:** 11.5 mo (95% CI: 6.0-18.4)

Trudel. ASH 2021. Abstr 157. Reproduced with permission.

GPRC5D x CD3: Talquetemab (MonumenTAL-1)

- GPCR5D: orphan receptor highly expressed on MM cells relative to normal cells[1]
- Talquetamab: first-in-class bispecific IgG4 antibody binding GPCR5D and CD3 receptors
  - Recruits CD3+ cells to GPCR5D+ myeloma cells and induces tumor cell death in preclinical cell and xenograft models[2]



- Key objectives: assess safety and tolerability of RP2D(s), antitumor activity, PK, PD

1. Verkleij. Blood Adv. 2021;5:2196. 2. Pillarisetti. Blood. 2020;135:1232.

Krishnan. ASH 2021. Abstr 158.

GPRC5D x CD3: Talquetemab (MonumenTAL-1)

Hematologic AEs in ≥20% of Total SC Population, n (%)	405 µg/kg SC QW* (n = 30)		800 µg/kg SC Q2W* (n = 25)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	20 (67)	18 (60)	11 (44)	9 (36)
Anemia	18 (60)	8 (27)	9 (36)	2 (8)
Lymphopenia	12 (40)	12 (40)	6 (24)	6 (24)
Thrombocytopenia	11 (37)	7 (23)	5 (20)	2 (8)
Leukopenia	12 (40)	9 (30)	4 (16)	4 (16)

*With 2-3 step-up doses.

- Infections: 18/55 (33%) [3 (5%) with grade 3/4]
- Skin and nail AEs: 75% [7.5% with grade 3 rashes]
- ISR: 9/55 (16%); all grade 1/2
- No toxicity-related deaths

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GPRC5D x CD3: Talquetemab (MonumenTAL-1)

Response, %	405 µg/kg SC QW*	800 µg/kg SC Q2W*
ORR, n/N (%)	21/30 (70.0)	14/21 (66.7)
sCR	10	9.5
CR	3.3	9.5
VGPR	40	33.3
≥VGPR (sCR + CR + VGPR)	53.3	52.4
PR	16.7	14.3

- Median DoR not reached in either arm
- QW arm: 11/21 (52%) responders still receiving treatment at median 10.1-mo follow-up
- Q2W arm: 12/14 (86%) responders still receiving treatment at median 7.9-mo follow-up

Response	405 µg/kg SC QW* (n = 30)	800 µg/kg SC Q2W* (n = 25)
Median follow-up, mo (range)	9.0 (0.9-17.1)	4.8 (0.4-11.1)
Response-evaluable patients, n	30	21
ORR, n (%)	21 (70.0)	14 (66.7)
▪ Triple-class-refractory patients, n/N (%)	15/23 (65.2)	12/18 (66.7)
▪ Penta-drug refractory patients, n/N (%)	5/6 (83.3)	5/6 (83.3)
Median time to first confirmed response, mo (range)	0.9 (0.2-3.8)	1.2 (0.2-6.8)

*With 2-3 step-up doses.

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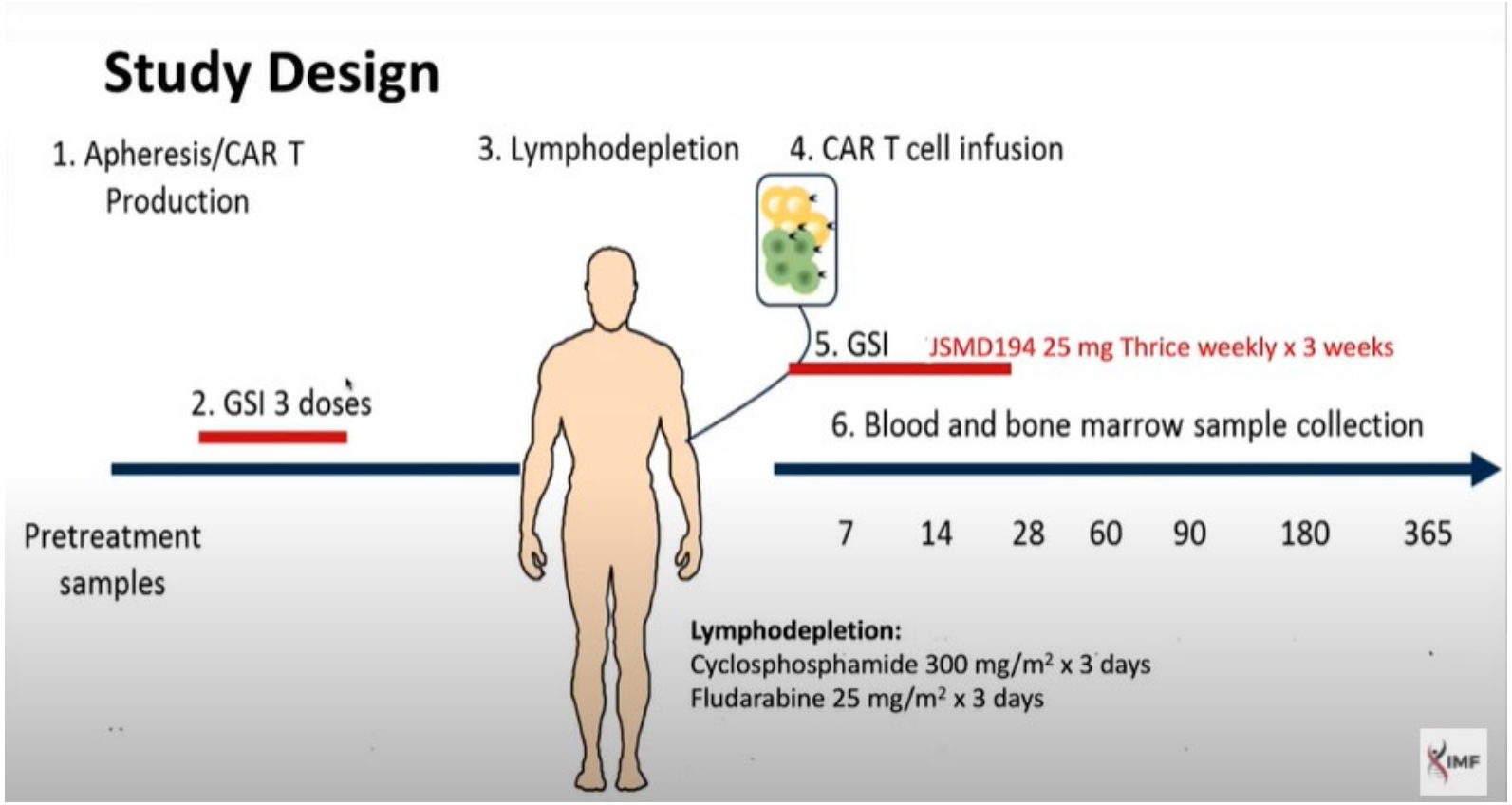
Other New Treatment Mechanisms (glimpses of the future?)

- **Gamma secretase inhibitors**
- **CelMoDs: small-molecule inhibitor of cereblon E3 ligase (fancy IMIDs) – Iberdomide**
- **Immunocytokines: TAK573**

OHSU

Gamma Secretase Inhibitors to increase BCMA Expression: Abstract 551

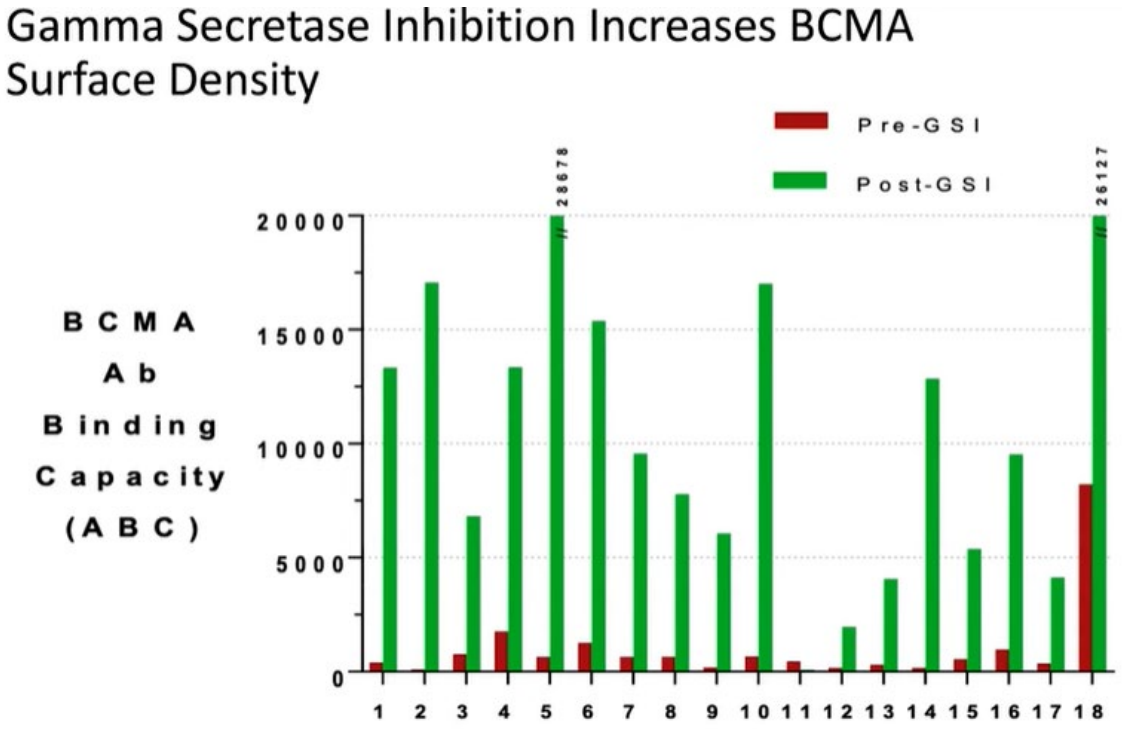
- Gamma secretase cleaves BCMA from the plasma cell surface
- Gamma secretase inhibitors can be used to increase BCMA expression on plasma cells

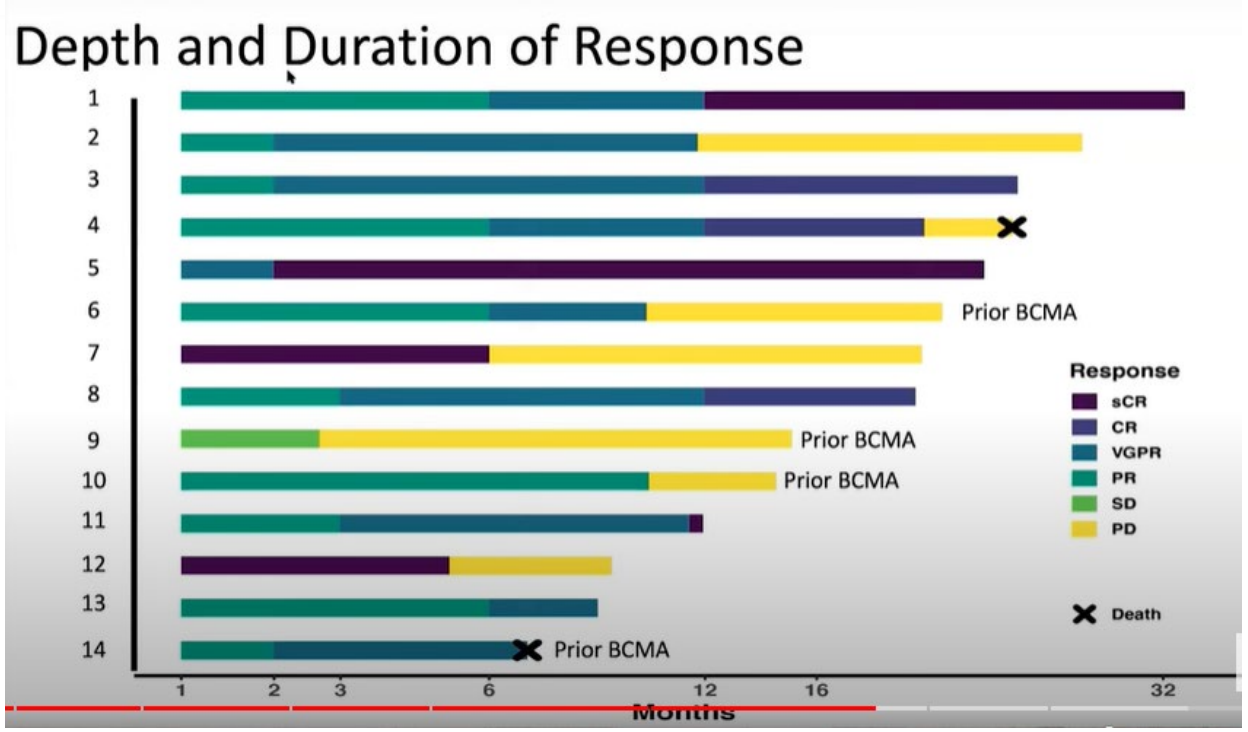


- **GSI held at discretion of clinical team, typically in setting of CRS or neurotox**
- **Most patients received all preplanned doses of GSI.**

OHSU

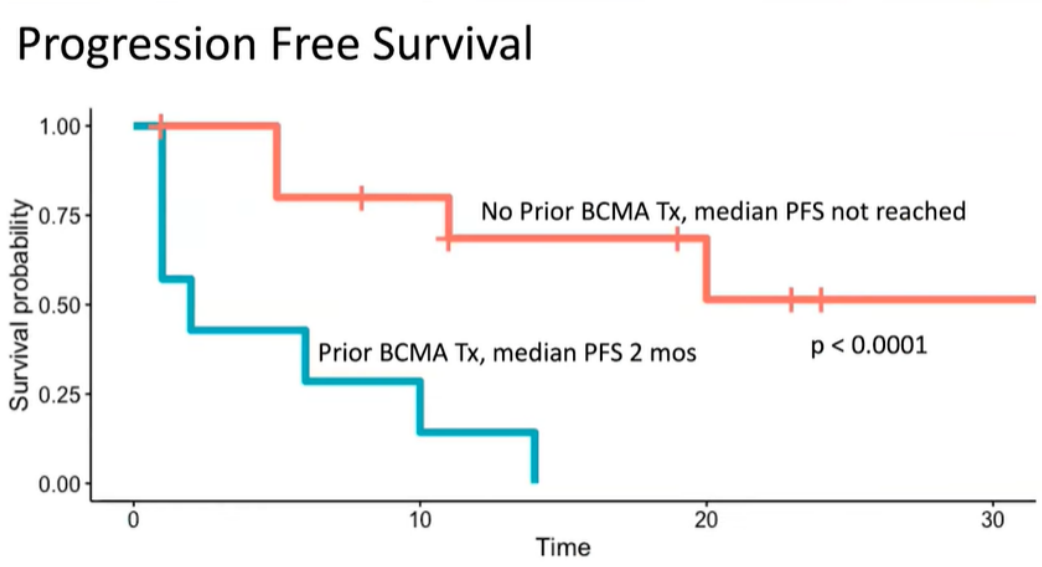
Gamma Secretase Inhibitors to increase BCMA Expression: Abstract 551

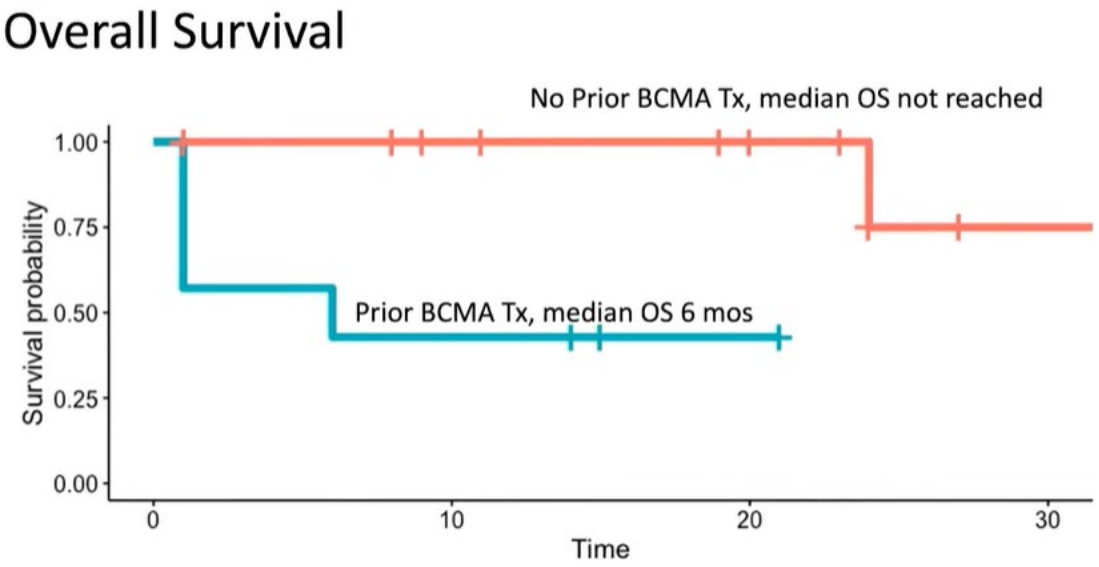




OHSU

Gamma Secretase Inhibitors to increase BCMA Expression: Abstract 551





OHSU

CELMoDs (Iberdomide): Abstract 162

CC-220-MM-001 Iberdomide + Dexamethasone

- Iberdomide (CC-220): novel small-molecule inhibitor of cereblon E3 ligase modulator under development as a next-generation IMiD in MM[1,2]
  - Binding to cereblon induces degradation of target proteins, including Ikaros and Aiolos[1]
  - Shows enhanced tumoricidal and immune-stimulatory effects compared with other IMiDs and remains active in lenalidomide- and pomalidomide-resistant MM cell lines[1,2]
  - In preclinical models, demonstrated synergistic activity with dexamethasone, anti-CD38 mAbs, and PIs[3-6]
  - Administered as a single enantiomer (S isomer), which may mitigate sedative adverse events (sleepiness, fatigue)[1,7]
- CC-220-MM-001 phase Ib/IIa study designed to identify MTD/RP2D of iberdomide alone or in combination with chemotherapy in patients with R/R MM
  - Current analysis reports results from the dose-expansion phase for patients with R/R MM treated with iberdomide + dexamethasone[8]

1. Matyskiela. J Med Chem. 2018;61:535. 2. Bjorklund. ASH 2016. Abstr 1591. 3. Amatangelo. Blood. 2018;132. Abstr 1935. 4. Lonial. Blood. 2019;134. Abstr 3119. 5. Amatangelo. Blood. 2020;136. Abstr 1358. 6. Amatangelo. Blood. 2020;136. Abstr 1359. 7. Hansen. J Med Chem. 2020;63:6648. 8. Lonial. ASH 2021. Abstr 162.

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CELMoDs (Iberdomide): Abstract 162

Phase II (at RP2D)

≥3 prior therapies, refractory to an IMiD, PI, glucocorticoid, and anti-CD38 mAb (N = 107)

→ Cohort D **Iberdomide*** 1.6 mg + **Dexamethasone†** →

- **Primary:** efficacy (ORR)
- **Secondary:** safety, additional efficacy (DoR, PFS, OS)

≥3 prior therapies, including BCMA-targeted therapy, LEN, POM, PI, glucocorticoid, and anti-CD38 mAb; documented disease progression within 60 days of last therapy (or PD if CAR T-cell therapy was last therapy) (N = 26)

→ Cohort I (post BCMA) **Iberdomide*** 1.6 mg + **Dexamethasone†** →

- **Primary: preliminary efficacy and safety**

***Iberdomide (oral): Days 1-21 of each 28-day cycle.**
†Dexamethasone (oral): 40 mg (20 mg if >75 yr) on Days 1, 8, 15, and 22 of each 28-day cycle.

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CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Baseline Characteristics and Prior Therapy

Characteristic	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 26)
Median age, yr (range)	64 (44-83)	65 (50-78)
Male, n (%)	60 (56.1)	15 (57.7)
Median time since diagnosis, yr (range)	6.90 (1.6-24.5)	7.75 (0.6-24.8)
ECOG PS, n (%) ▪ 0 ▪ 1 ▪ 2	 42 (39.3) 55 (51.4) 10 (9.3)	 6 (23.1) 20 (76.9) 0
ISS at entry, n (%) ▪ Stage I ▪ Stage II ▪ Stage III	 46 (43.0) 45 (42.1) 16 (15.0)	 15 (57.7) 6 (23.1) 5 (19.2)
Extramedullary plasmacytoma, n (%)	27 (25.2)	8 (30.8)
High-risk cytogenetics, n (%)	(n = 57) 32 (29.9)	(n = 18) 6 (23.1)

Prior Therapy	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 26)
Median prior lines of therapy, n (range)	6 (3-23)	7 (4-15)
ASCT, n (%)	84 (78.5)	23 (88.5)
IMiD refractory, n (%) ▪ Pomalidomide ▪ Lenalidomide	107 (100) 102 (95.3) 91 (85.0)	26 (100) 23 (88.5) 22 (84.6)
PI refractory, n (%) ▪ Bortezomib ▪ Carfilzomib	104 (97.2) 62 (57.9) 66 (61.7)	25 (96.2) 14 (53.8) 21 (80.8)
Anti-CD38 mAb refractory, n (%)	107 (100)	22 (84.6)
Triple-class refractory, n (%)	104 (97.2)	21 (80.8)
BCMA exposed, n (%) ▪ CAR T-cell therapy ▪ ADC ▪ T-cell engager	1 (0.9) 0 1 (0.9) 0	26 (100) 6 (23.1) 13 (50.0) 8 (30.8)

Data cutoff: June 2, 2021

Lonial. ASH 2021. Abstr 162.

Slide credit: clinicaloptions.com

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: TEAEs

TEAEs of Interest, n (%)	Cohort D (N = 107)			Cohort I (Post BCMA) (N = 26)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Hematologic						
▪ Neutropenia	64 (59.8)	27 (25.2)	21 (19.6)	11 (42.3)	8 (30.8)	3 (11.5)
▪ Febrile neutropenia	5 (4.7)	4 (3.7)	1 (0.9)	1 (3.8)	1 (3.8)	0
▪ Anemia	44 (41.1)	30 (28.0)	0	9 (34.6)	4 (15.4)	0
▪ Thrombocytopenia	38 (35.5)	7 (6.5)	16 (15.0)	8 (30.8)	3 (11.5)	3 (11.5)
▪ Leukopenia	30 (28.0)	11 (10.3)	11 (10.3)	4 (15.4)	2 (7.7)	1 (3.8)
Nonhematologic						
▪ Fatigue	25 (23.4)	2 (1.9)	1 (0.9)	6 (23.1)	1 (3.8)	0
▪ Diarrhea	25 (23.4)	1 (0.9)	0	4 (15.4)	0	0
▪ Constipation	23 (21.5)	0	0	3 (11.5)	0	0
▪ Rash	21 (19.6)	3 (2.8)	0	2 (7.7)	1 (3.8)	0
Infections	62 (57.9)	26 (24.3)	3 (2.8)	13 (50.0)	6 (23.1)	0
▪ Pneumonia	13 (12.1)	9 (8.4)	0	5 (19.2)	4 (15.4)	0
▪ COVID-19	10 (9.3)	5 (4.7)	2 (1.9)	1 (3.8)	1 (3.8)	0

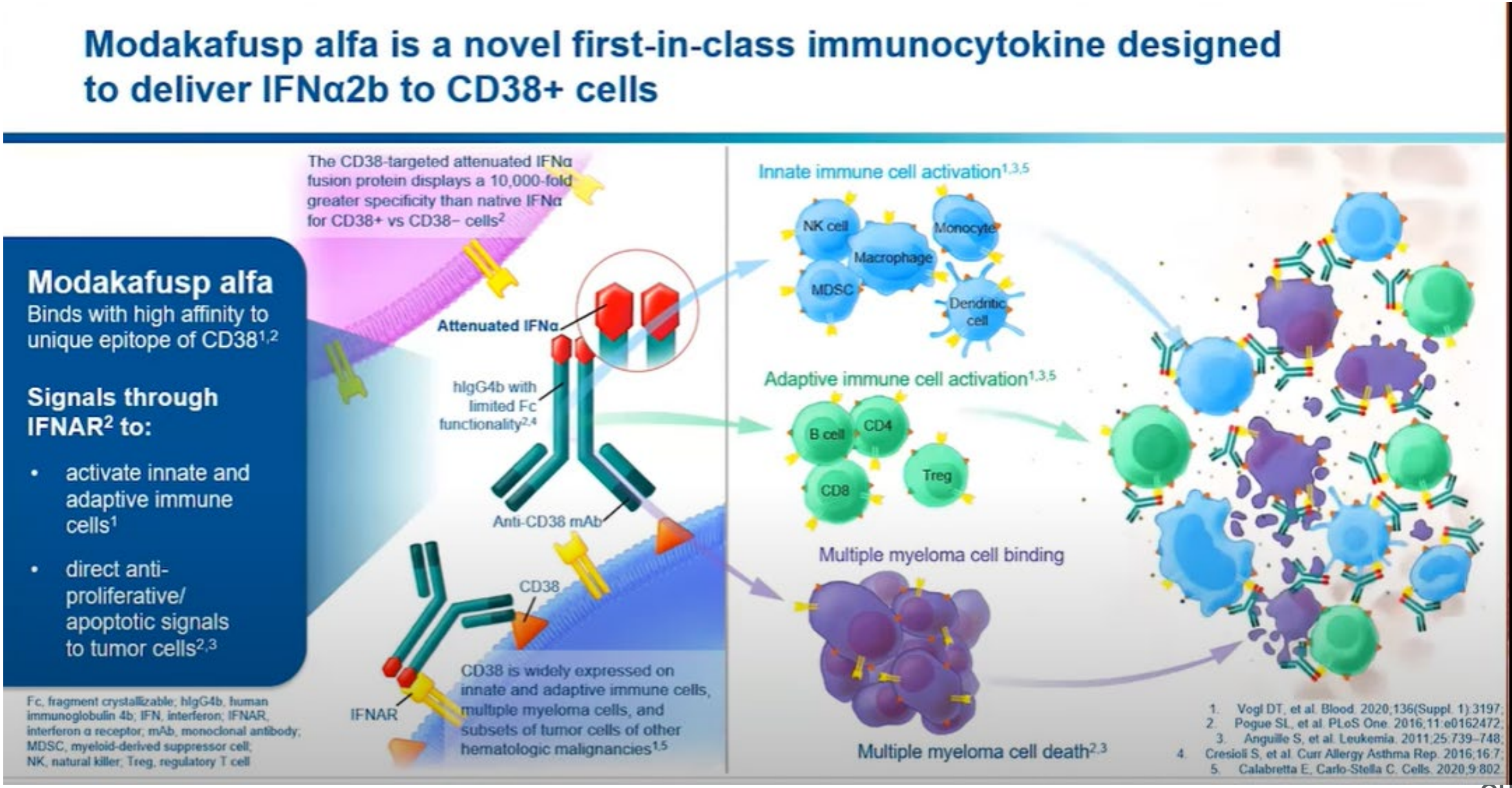
Lonial. ASH 2021. Abstr 162.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: ORR

Response, n (%)	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 24)
ORR	28 (26.2)	6 (25.0)
▪ sCR	1 (0.9)	0
▪ CR	0	1 (4.2)
▪ VGPR	8 (7.5)	1 (4.2)
▪ PR	19 (17.8)	4 (16.7)
MR	11 (10.3)	4 (16.7)
SD	46 (43.0)	8 (33.3)
PD	15 (14.0)	4 (16.7)
NE	7 (6.5)	2 (8.3)
CBR (sCR + CR + VGPR + PR + MR)	39 (36.4)	10 (41.7)
DCR (sCR + CR + VGPR + PR + MR + SD)	85 (79.4)	18 (75.0)

Lonial. ASH 2021. Abstr 162.

Immunocytokines: Modakafusp Alfa (TAK573) Abstract 898



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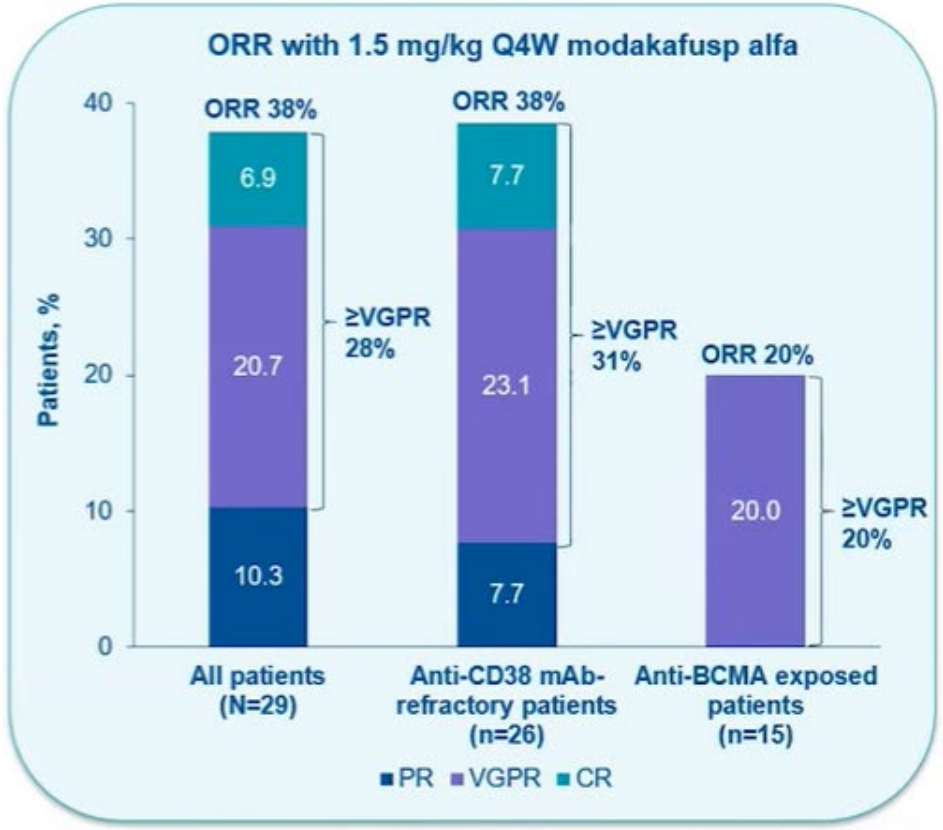
Modakafusp Alfa (TAK573): Abstract 898

Overall response rate

- **Among 29 patients who received modakafusp alfa 1.5 mg/kg Q4W (5 in dose escalation and 24 in ongoing dose expansion):**
  - 11 patients had ≥PR (ORR 38%), including 6 with VGPR and 2 with CR (28% ≥VGPR)
- **Among 26 anti-CD38 mAb-refractory patients, ORR was also 38% (31% ≥VGPR):**
  - Among the 4 patients who received an anti-CD38 mAb in their most recent line of therapy, 1 achieved a CR, and 2 achieved a VGPR (ORR 75%)
- **Of the 15 patients with prior anti-BCMA therapy, 3 (20%) had a VGPR**



CR, complete response; PR, partial response; VGPR, very good partial response

Among patients with ≥ PR

- **Median time to response was 1m, median time to best response was 2 m**

Among all patients in the 1.5mg/kg cohort, median PFS was 5.7 mo

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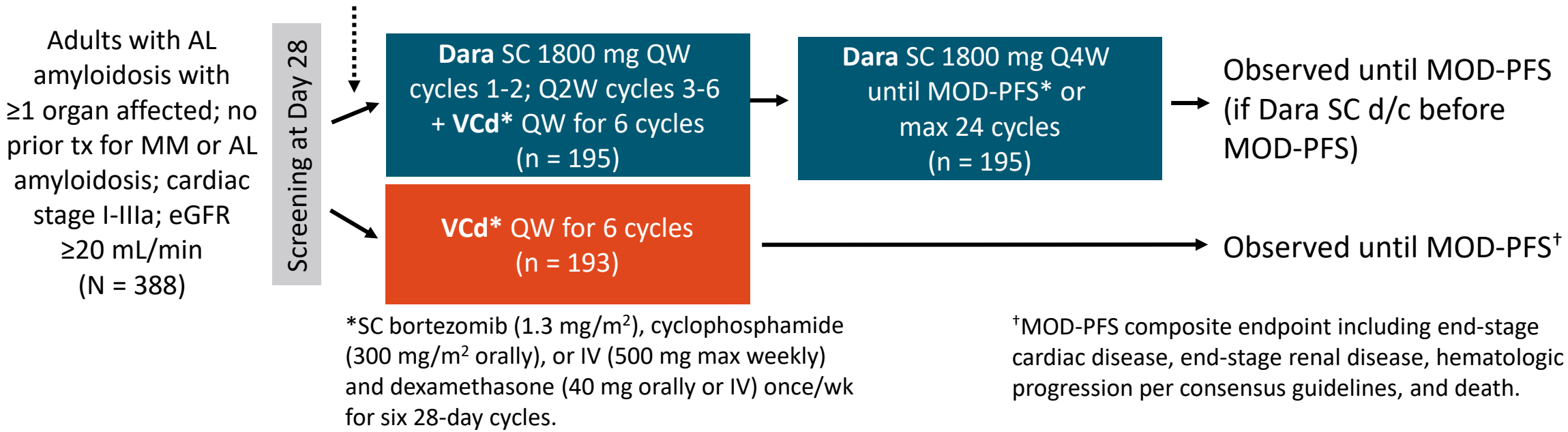
Updates in AL Amyloidosis

- **ANDROMEDA**
- **CAEL-101**

OHSU

ANDROMEDA: Subcutaneous Daratumumab + VCd vs VCd Alone in Newly Diagnosed AL Amyloidosis

- Randomized, open-label phase III trial of Dara-VCd vs VCd alone in patients with newly diagnosed AL amyloidosis



*SC bortezomib (1.3 mg/m^2), cyclophosphamide (300 mg/m^2 orally), or IV (500 mg max weekly) and dexamethasone (40 mg orally or IV) once/wk for six 28-day cycles.

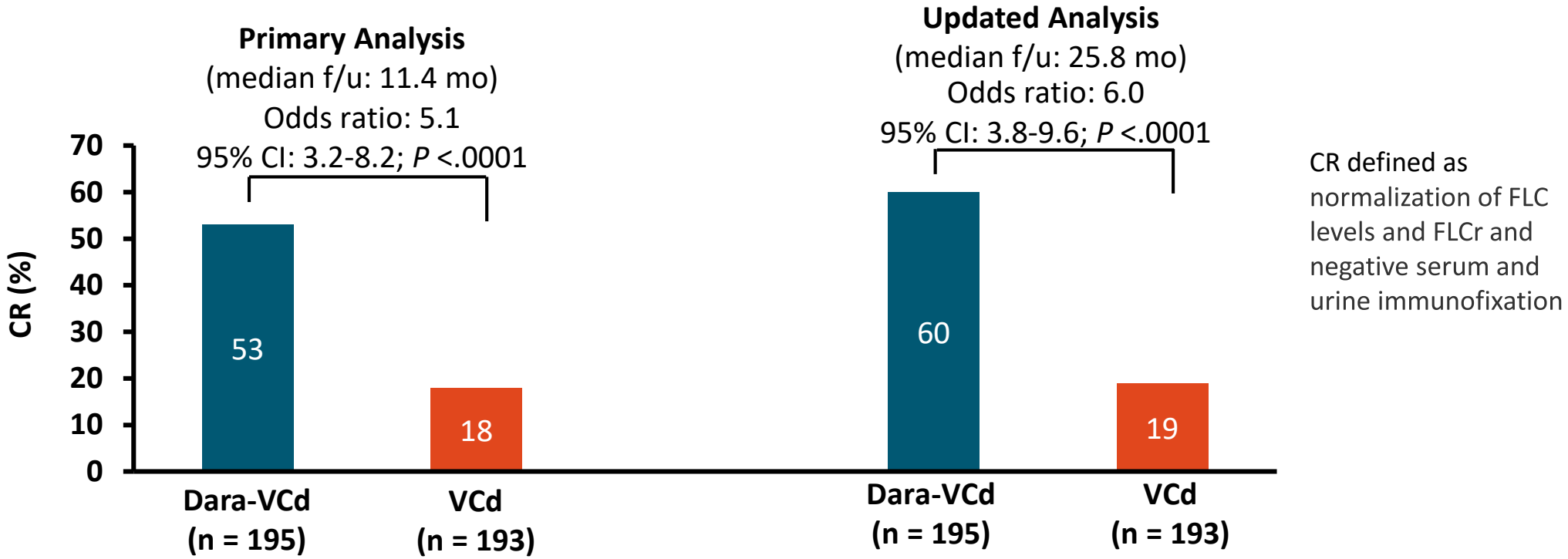
†MOD-PFS composite endpoint including end-stage cardiac disease, end-stage renal disease, hematologic progression per consensus guidelines, and death.

- **Primary endpoint:** hematologic CR in ITT population
- **Secondary endpoints:** MOD-PFS, organ response rate, time to hematologic response, OS, safety

Kastritis. NEJM. 2021;385:46. Kastritis. ASCO 2021. Abstr 8003. Comenzo. ASH 2021. Abstr 159.

Over 2 Yr of Follow-up, Hematologic Response Rates Deepened Over Time With Dara-VCd vs VCd

- Longer follow-up confirmed the increasingly higher rate of CR with Dara-VCd vs VCd (60% vs 19%)
  - Within the Dara-VCd arm the CR rate deepened over time (53% vs 60% with 14.4 mo longer follow-up)
  - ≥VGPR* within the Dara-VCd arm increased from 77% to 79%



CR defined as normalization of FLC levels and FLCr and negative serum and urine immunofixation

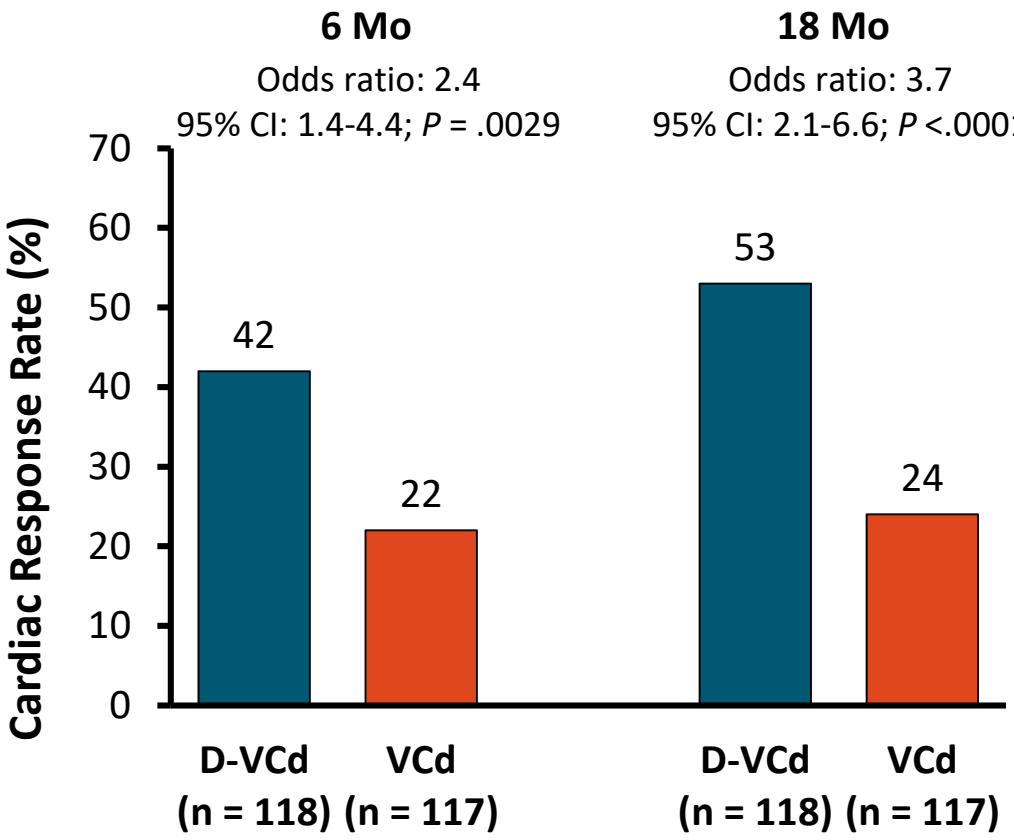
*Among ≥VGPR responders (D-VCd, n = 154; VCd, n = 97).

Kastritis. ASCO 2021. Abstr 8003. NCT03201965. Comenzo. ASH 2021. Abstr 159.

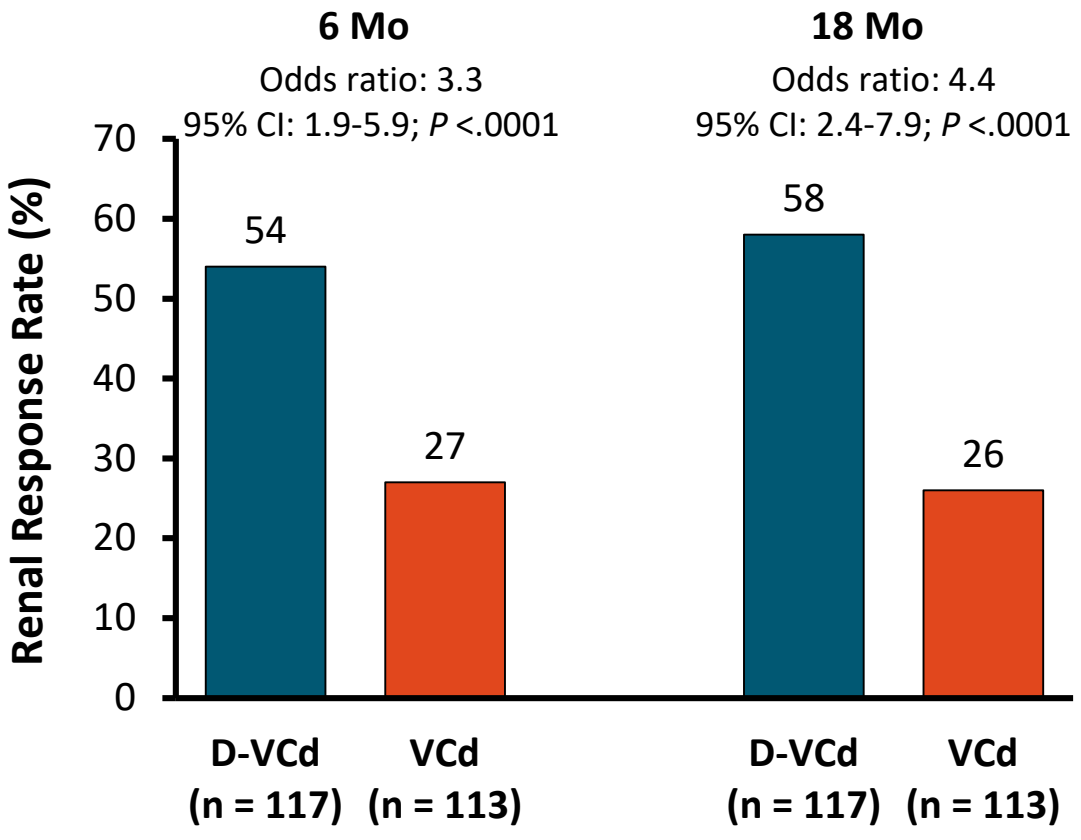
Slide credit: clinicaloptions.com

Higher Organ Response Rates With D-VCd vs VCd

Cardiac Response Rates



Renal Response Rates

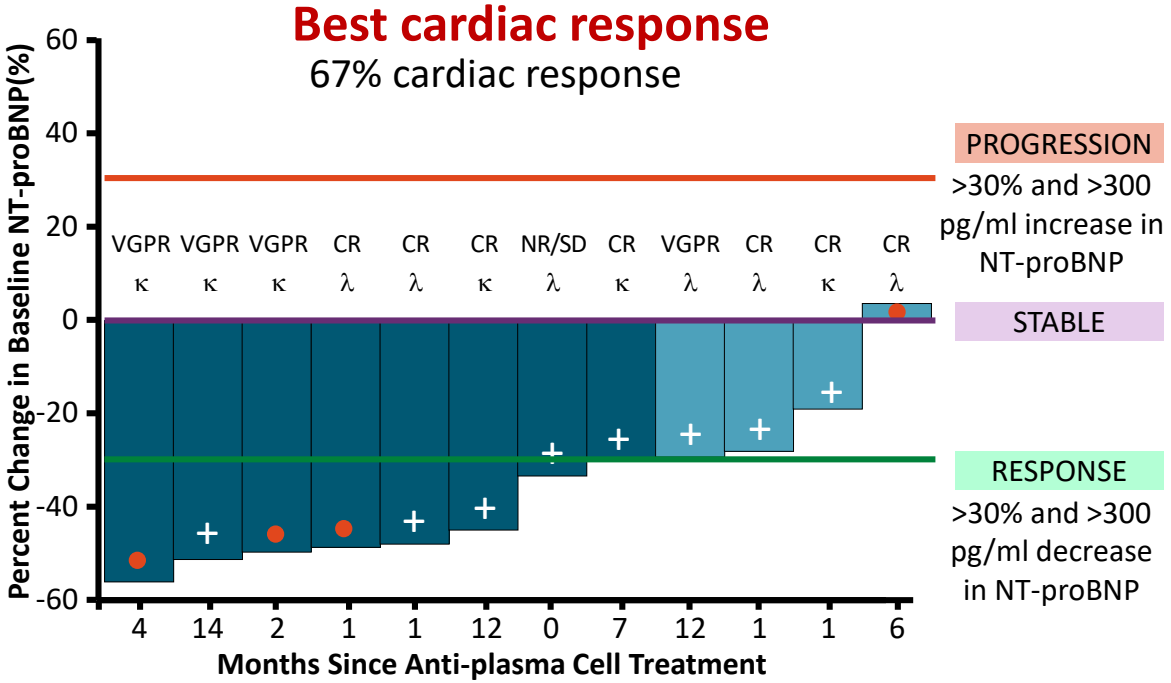


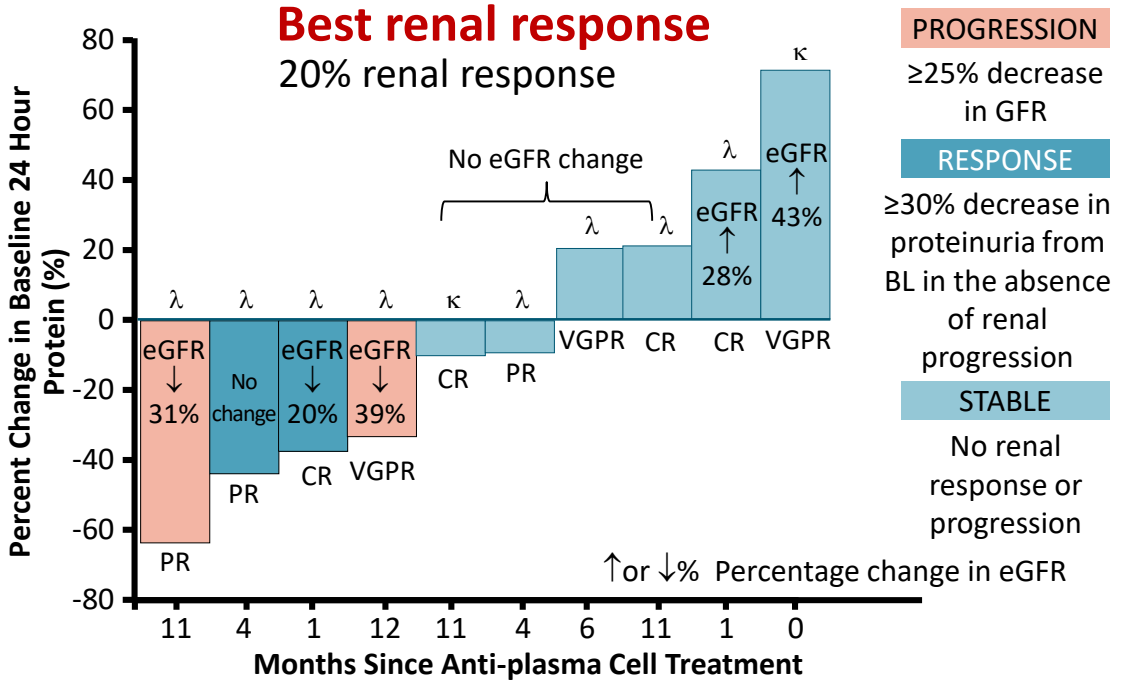
Kastritis. ASCO 2021. Abstr 8003. NCT03201965. Comenzo. ASH 2021. Abstr 159.

Slide credit: clinicaloptions.com

Monoclonal Antibody CAEL-101 in Patients With R/R AL Amyloidosis

- CAEL101 is a monoclonal antibody that binds to a neoepitope on κ and λ light chain fibrils, resulting in the clearance of amyloid from tissues and organs
- An open-label phase Ia/b study enrolling patients (N = 27) with established the safety of CAEL-101 up to 500 mg/m^2 in patients with R/R AL amyloidosis





4 patients with cardiac involvement were not evaluable due to BL NT-proBNP being too low (≤650 pg/mL) for a meaningful evaluation.

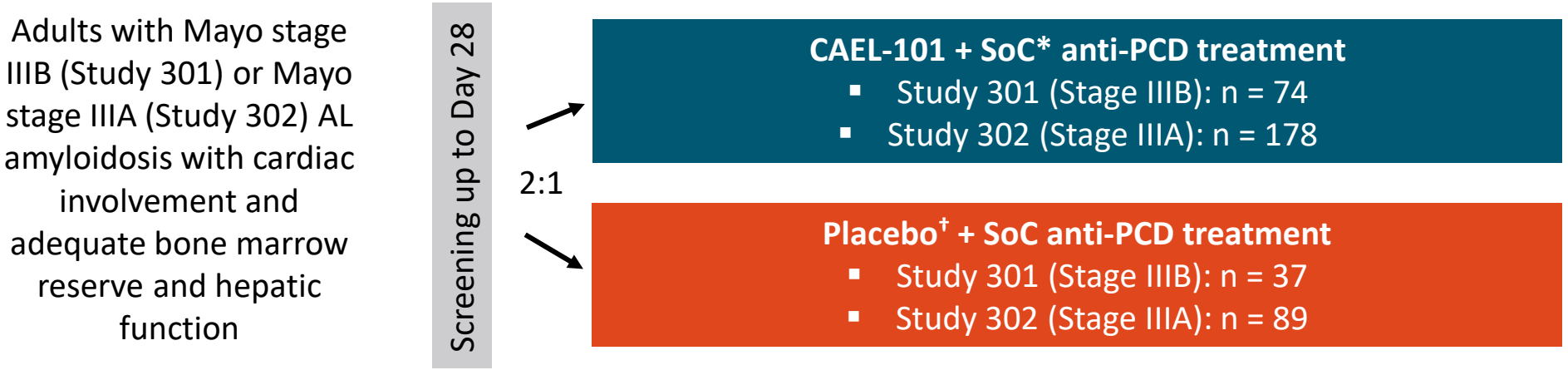
4 patients with renal involvement were not evaluable due to BL proteinuria being too low (≤500 mg/24 hr) for a meaningful evaluation.

Edwards. Blood. 2021;138:2632.

Slide credit: clinicaloptions.com

Caelum CARES Program

- Evaluating the safety of CAEL-101 in patients with Mayo Stage IIIA/B AL amyloidosis in 2 parallel phase III trials (Study 301: NCT04504825 and Study 302: NCT04512235)



*CyBorD. †CAEL-101/matching placebo 1000 mg/m2 Q1 wk x 4, then every other wk until required number of deaths observed.

- **Primary endpoint:** OS
- **Secondary endpoints:** change from BL to wk 50 (6MWT distance, QoL per KCCQ-OS and SF-36 v2 PCS, GLS %), safety

Valent. ASH 2021. Abstr 468. NCT04504825. NCT04512235.

Slide credit: clinicaloptions.com

MM / AL Amyloid Trials at OHSU

OHSU Myeloma Clinical Research Team:
myelomaRT@ohsu.edu

Smoldering

- ECOG EAA173: Daratumumab / Len / Dex vs Len / Dex

Newly Diagnosed

- ECOG EAA181 (Transplant ineligible): Daratumumab / Len / Dex x9, then Dara / Len / Dex vs Dara / Len / Dex + Velcade consolidation

Relapsed / Refractory

- OHSU IIT: Isatuximab / Carfilzomib / Pomalidomide (1st relapse)
- HPN217 (Harpoon): T-cell activating construct (BCMA target)
- CC-99712 (Celgene): IV CC-99712 (BCMA ADC)
- DREAMM 12: Belantamab in renal failure

Maintenance

- MMY3021 (Janssen): MRD+ patients only: SC Dara + Len vs Len
- SWOG S1803: MRD+ or MRD- patients: SC Dara + Len vs Len

AL Amyloidosis

- CAEL 101-301/302: Newly dx AL amyloid, Mayo Stage IIIa and IIIb cardiac disease

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Thank You