EMORY
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Other investigational Agents

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t(11;14) Myeloma

Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients

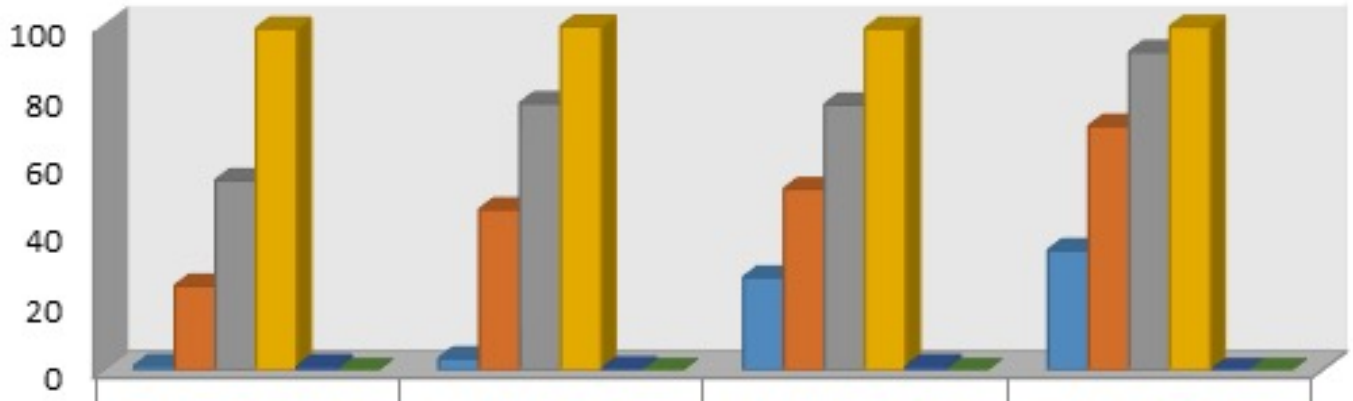
Rafael Fonseca, Emily A. Blood, Martin M. Oken, Robert A. Kyle, Gordon W. Dewald, Richard J. Bailey, Scott A. Van Wier, Kimberly J. Henderson, James D. Hoyer, David Harrington, Neil E. Kay, Brian Van Ness, and Philip R. Greipp

BLOOD, 15 MAY 2002 • VOLUME 99, NUMBER 10

TRANSLOCATION (11;14) MYELOMA

- Approximately 15% of myeloma
- Characteristic lymphoplasmacytoid morphology
- Most common abnormality in primary plasma cell leukemia
- Prevalent in AL amyloidosis
- More likely light chain myeloma
- More common in rare variants: IgM; IgD; non secretory
- Expression of CD20 more common

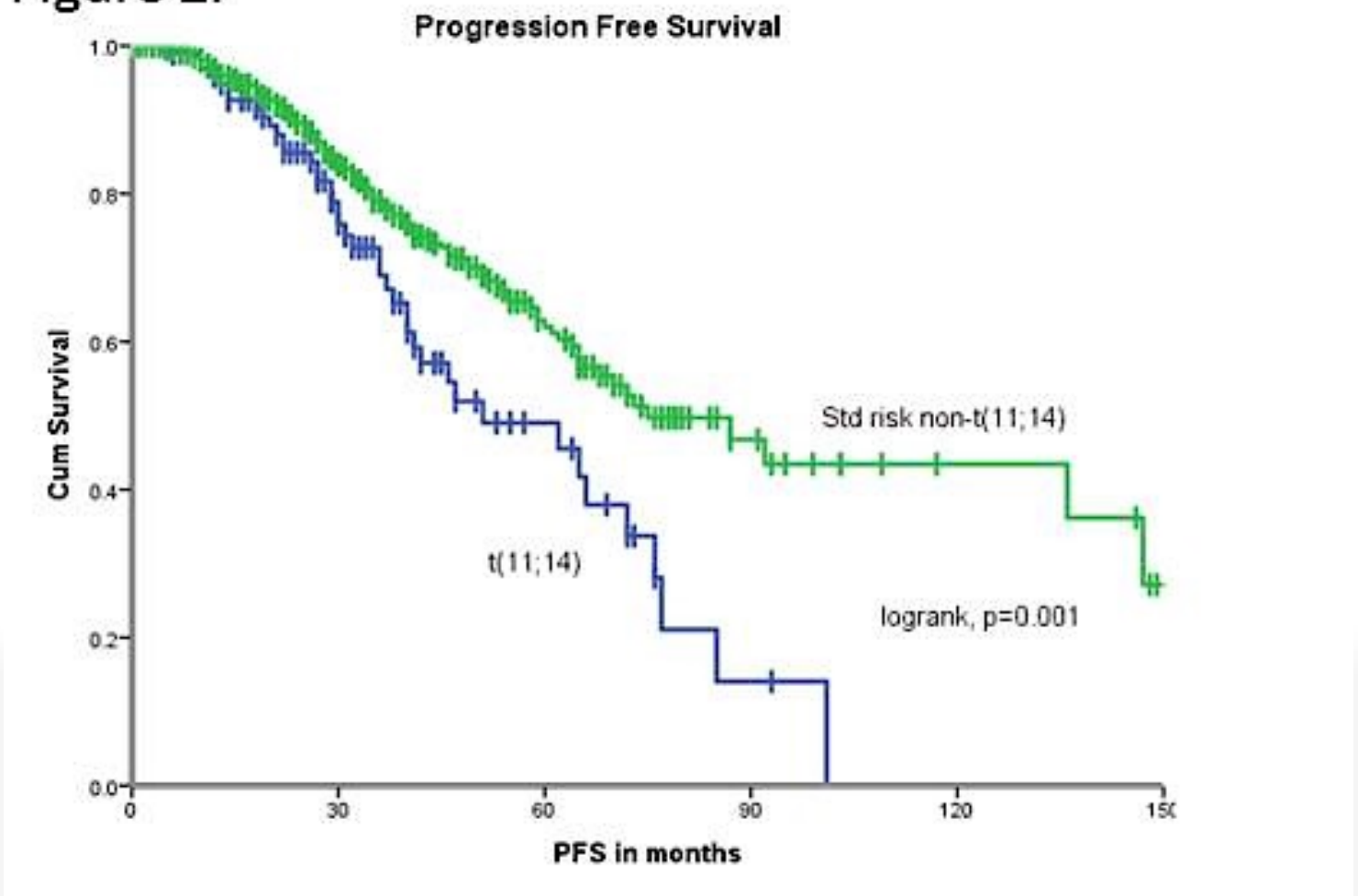
Emory experience in pts with t(11;14)



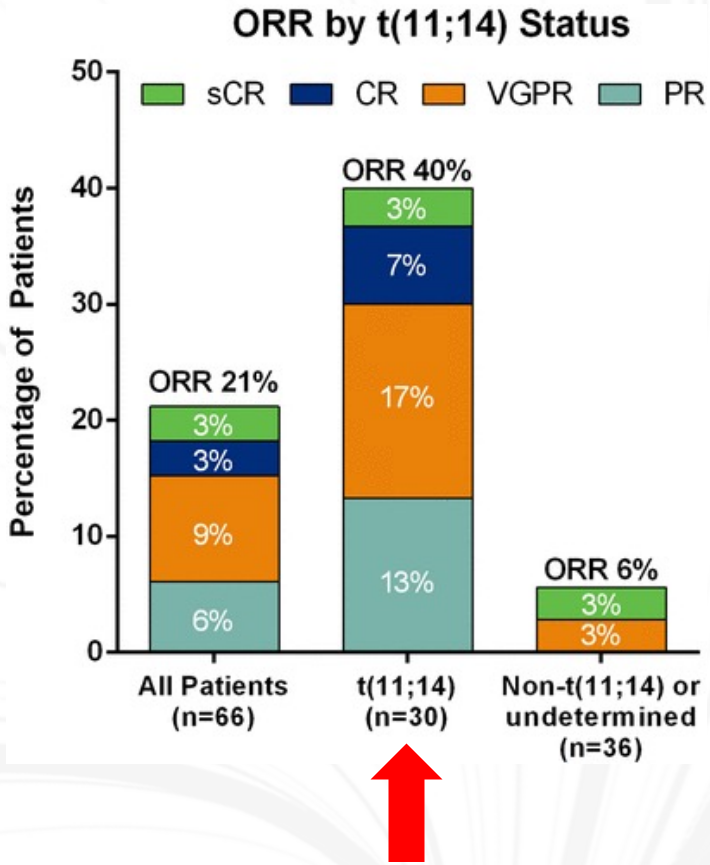
	Post-induction response t(11;14) (N=82)	Post-induction response non-t(11;14) (N=378)	Best response t(11;14) (N=82)	Best response non-t(11;14) (N=375)
sCR %	1.2	3.4	26.8	34.7
sCR + CR %	24.4	46.5	52.4	70.6
≥VGPR %	54.9	77.2	76.8	92
ORR %	98.8	99.4	98.8	99.3
SD %	1.2	0.5	1.2	0
PD %	0	0	0	0

Outcomes of t(11;14) myeloma patients treated with modern therapy are decreased compared to standard risk patients

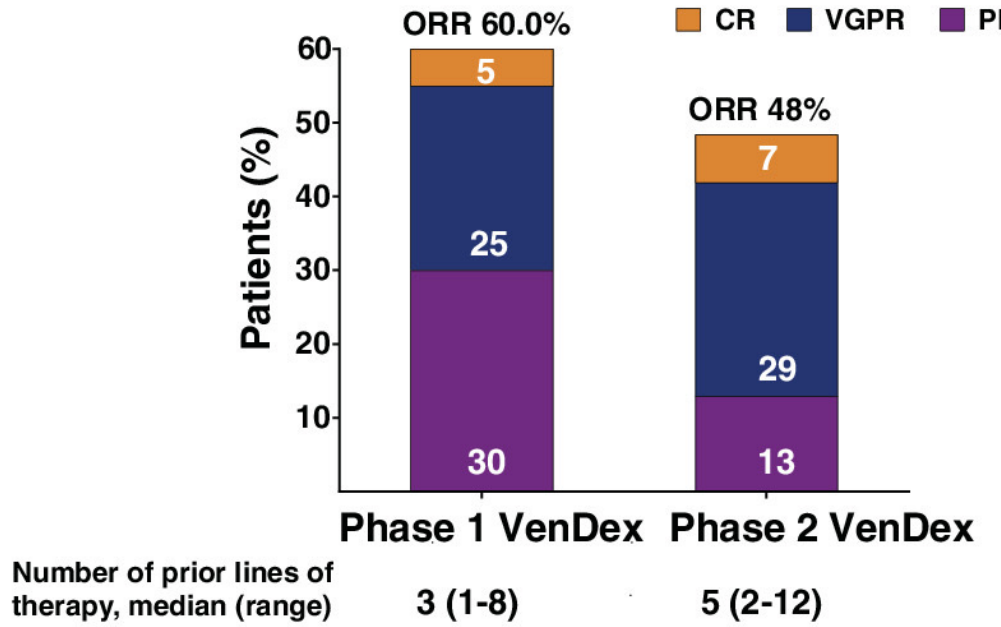
Figure 2.



TARGETING BCL2 IS EFFECTIVE IN PATIENTS WITH t(11;14) MYELOMA



Kumar *et al., Blood* , 2018

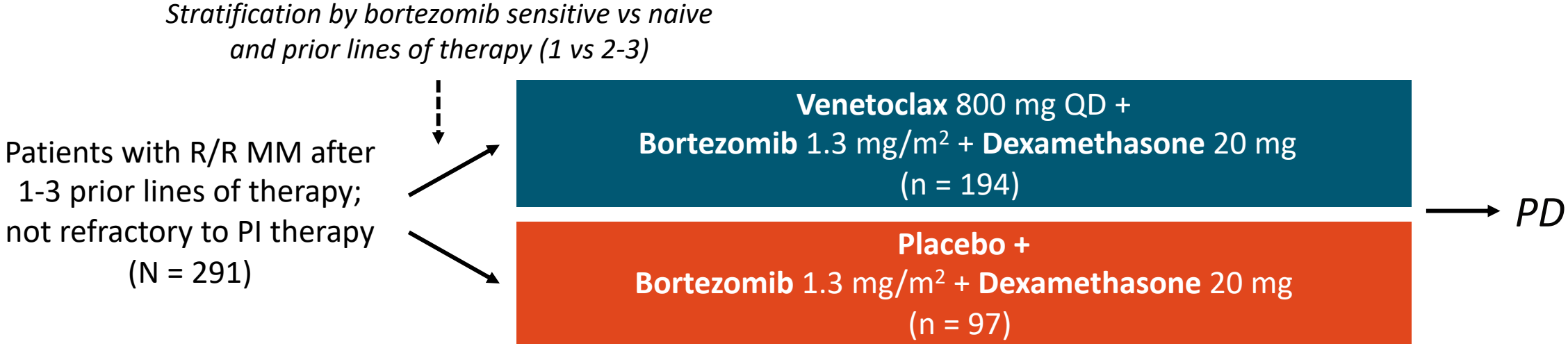


Kaufman *et al., Am. J. Hematol.*, 2021

Jonathan Kaufman
Shaji Kumar

BELLINI Final Survival Analysis: Study Design

- Double-blind, randomized 2:1, placebo-controlled phase III trial



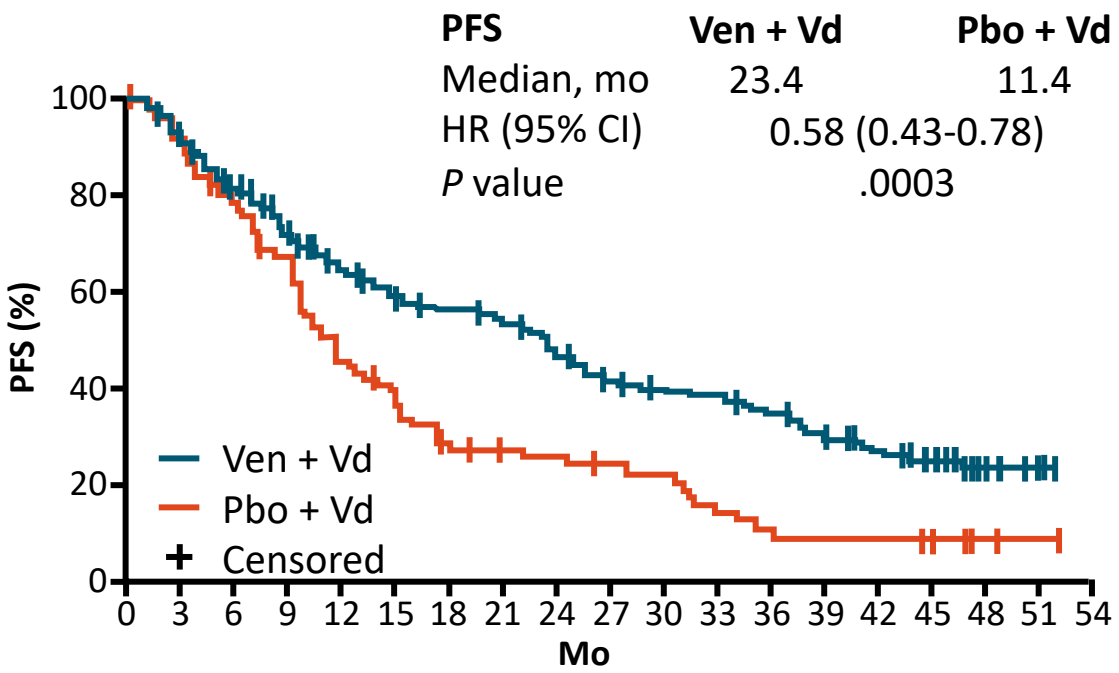
Cycles 1-8: 21-day cycles with bortezomib on Days 1, 4, 8, 11 and dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, 12; cycles 9+: 35-day cycles, bortezomib on Days 1, 8, 15, 22 and dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, 23

- **Primary endpoint:** PFS (per IRC)
- **Key secondary endpoints:** ORR, ≥VGPR, OS, QoL/PRO parameters (PFS was investigator-assessed in final OS analysis)

Kumar. ASH 2021. Abstr 84.

BELLINI Final Survival Analysis: PFS, OS in All Patients

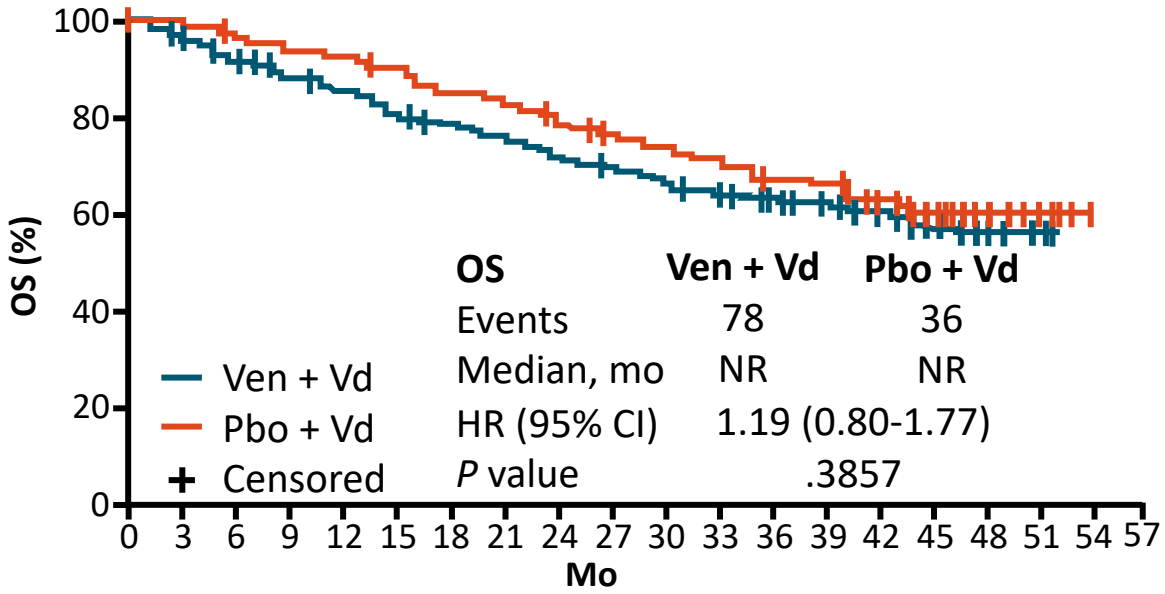
Investigator-Assessed PFS in All Patients



Patients at Risk, n

194	163	140	118	101	89	84	79	68	59	55	53	47	39	32	21	8	2	0
97	83	69	57	39	30	22	20	19	17	15	10	6	7	7	4	2	1	0

OS in All Patients



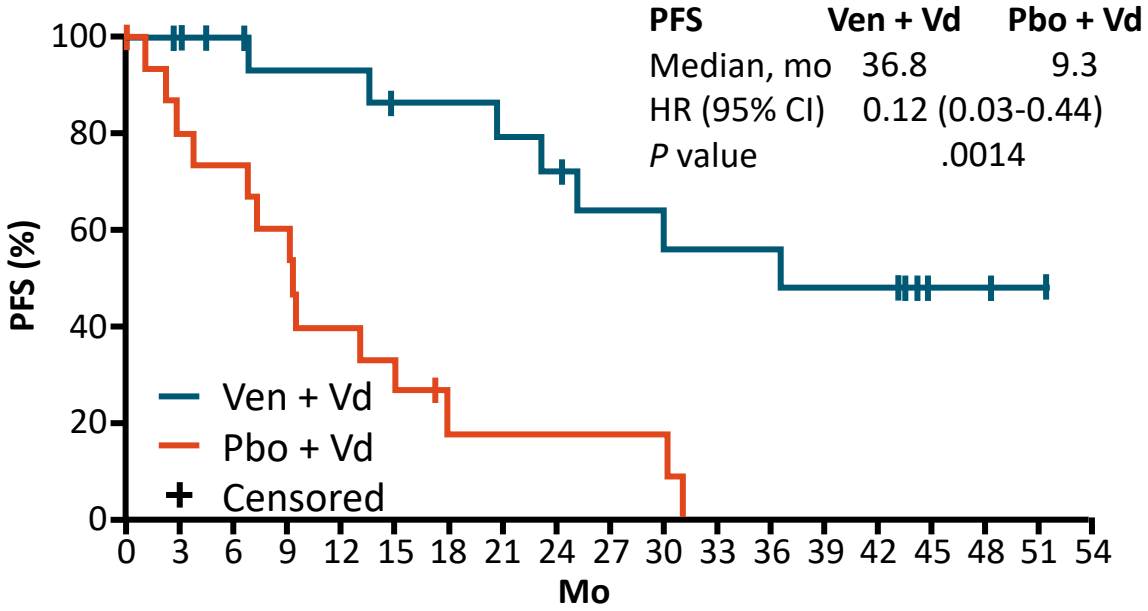
Patients at Risk, n

194	186	173	164	158	149	143	139	131	121	118	113	107	104	89	68	30	6	0	
97	95	91	88	87	84	79	78	73	67	65	63	58	57	50	37	20	6	1	0

Kumar. ASH 2021. Abstr 84. Reproduced with permission.

BELLINI Final Survival Analysis: PFS, OS in t(11;14) Subgroup

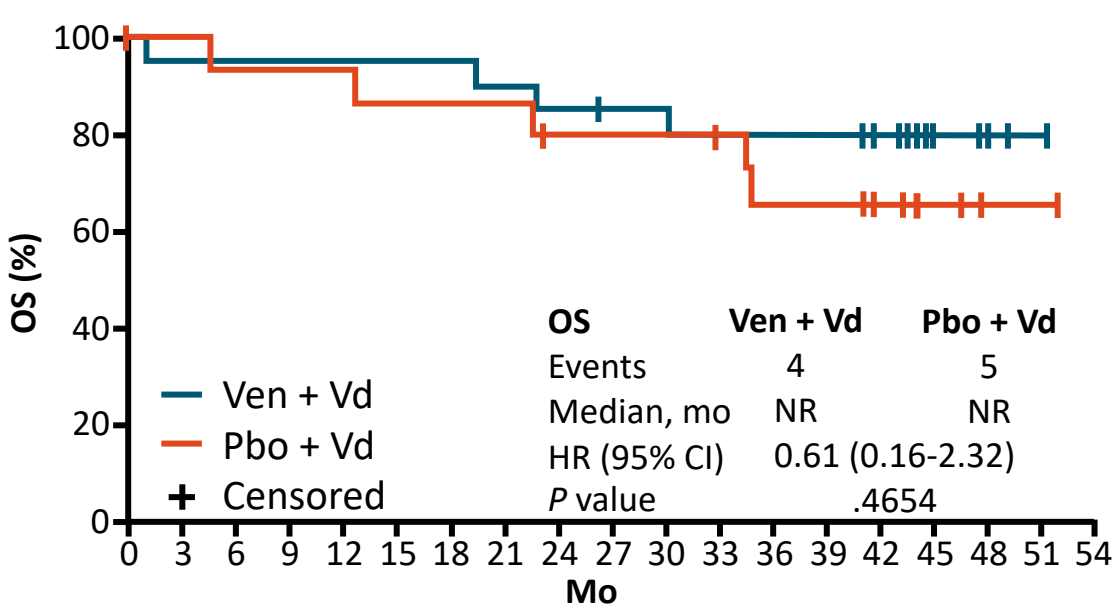
Investigator-Assessed PFS in Patients With t(11;14)



Patients at Risk, n

20	18	16	14	14	12	12	11	10	8	8	7	7	6	6	2	2	1	0
15	12	11	9	6	5	2	2	2	2	2	0							

OS in Patients With t(11;14)



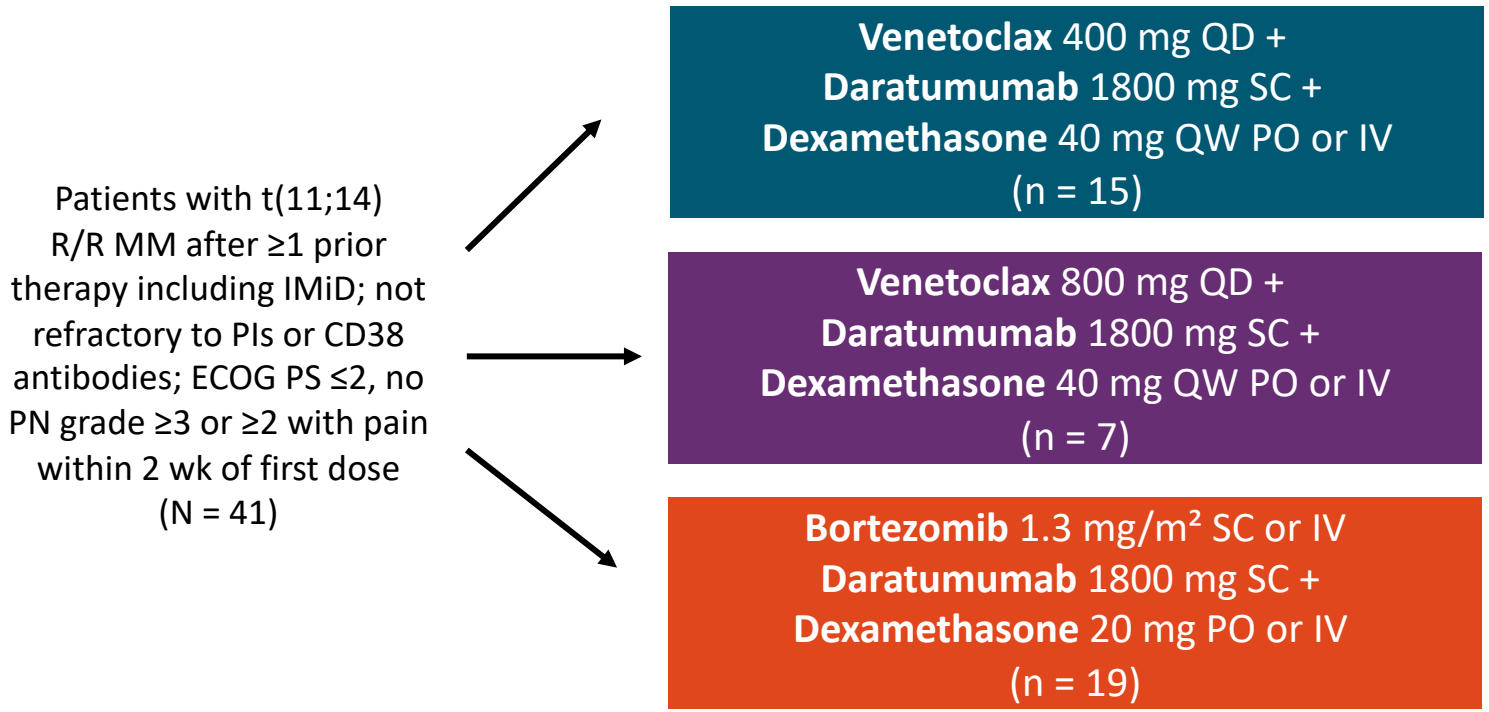
Patients at Risk, n

20	19	19	19	19	19	19	18	17	15	15	14	13	13	12	7	4	1	0
15	15	14	14	14	13	13	13	11	11	11	11	9	9	8	3	2	1	0

Kumar. ASH 2021. Abstr 84. Reproduced with permission.

Venetoclax/Dara/Dex vs Bortezomib/Dara/Dex in t(11;14) R/R MM: Part 3 Study Design

- Open-label, randomized phase I/II study (trial not fully accrued)



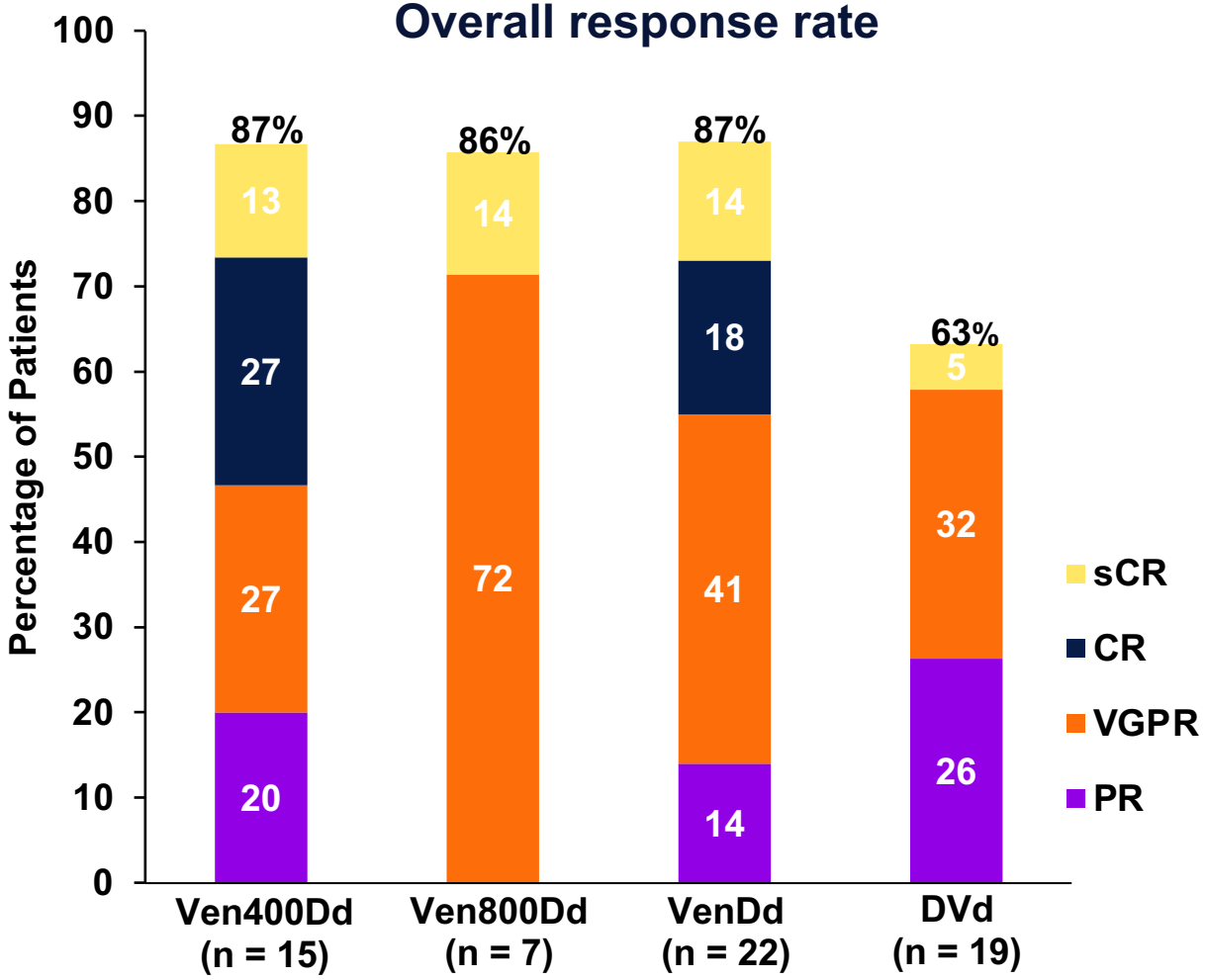
Cycle	Venetoclax	Dara	Dex
1-2 (28 days)	Once daily	D1, 8, 15, 22	Weekly
3-6 (28 days)	Once daily	D1, 15	Weekly
7+ (28 days)	Once daily	D1	Weekly
Cycle	**Bortez**	**Dara**	**Dex**
1-3 (21 days)	D1, 4, 8, 11	D1, 8, 15	D1, 2, 4, 5, 8, 9, 11, 12, 15
4-8 (21 days)	D1, 4, 8, 11	D1	D1, 2, 4, 5, 8, 9, 11, 12
9+ (28 days)	--	D1	D1

- Primary objective: safety and preliminary efficacy

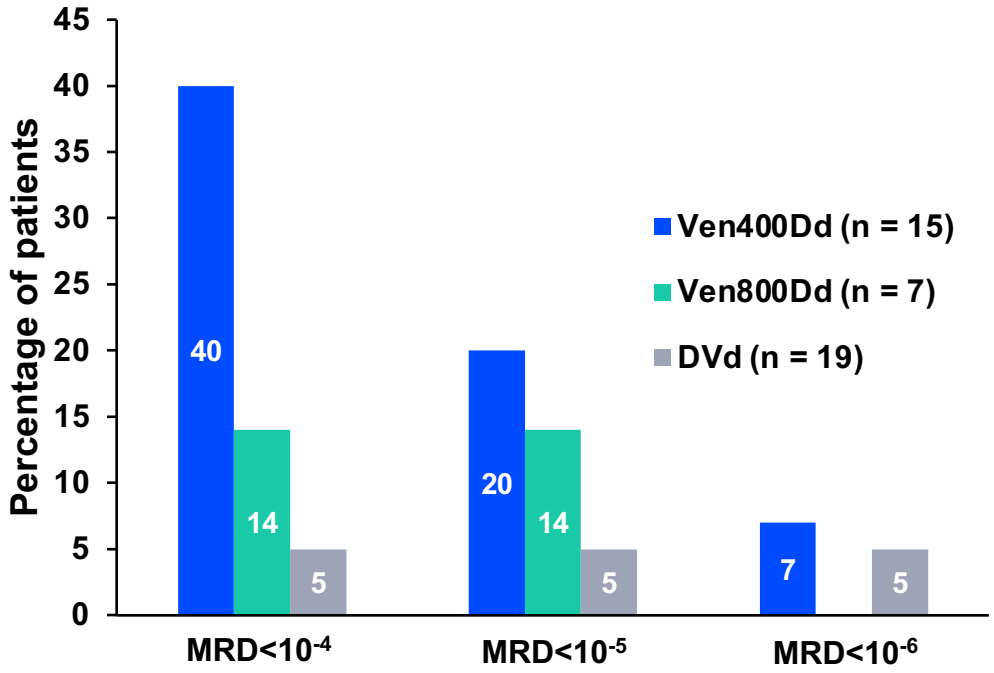
Kaufman. ASH 2021. Abstr 817.

VenDd arms achieved deep responses including MRD negativity

Overall response rate

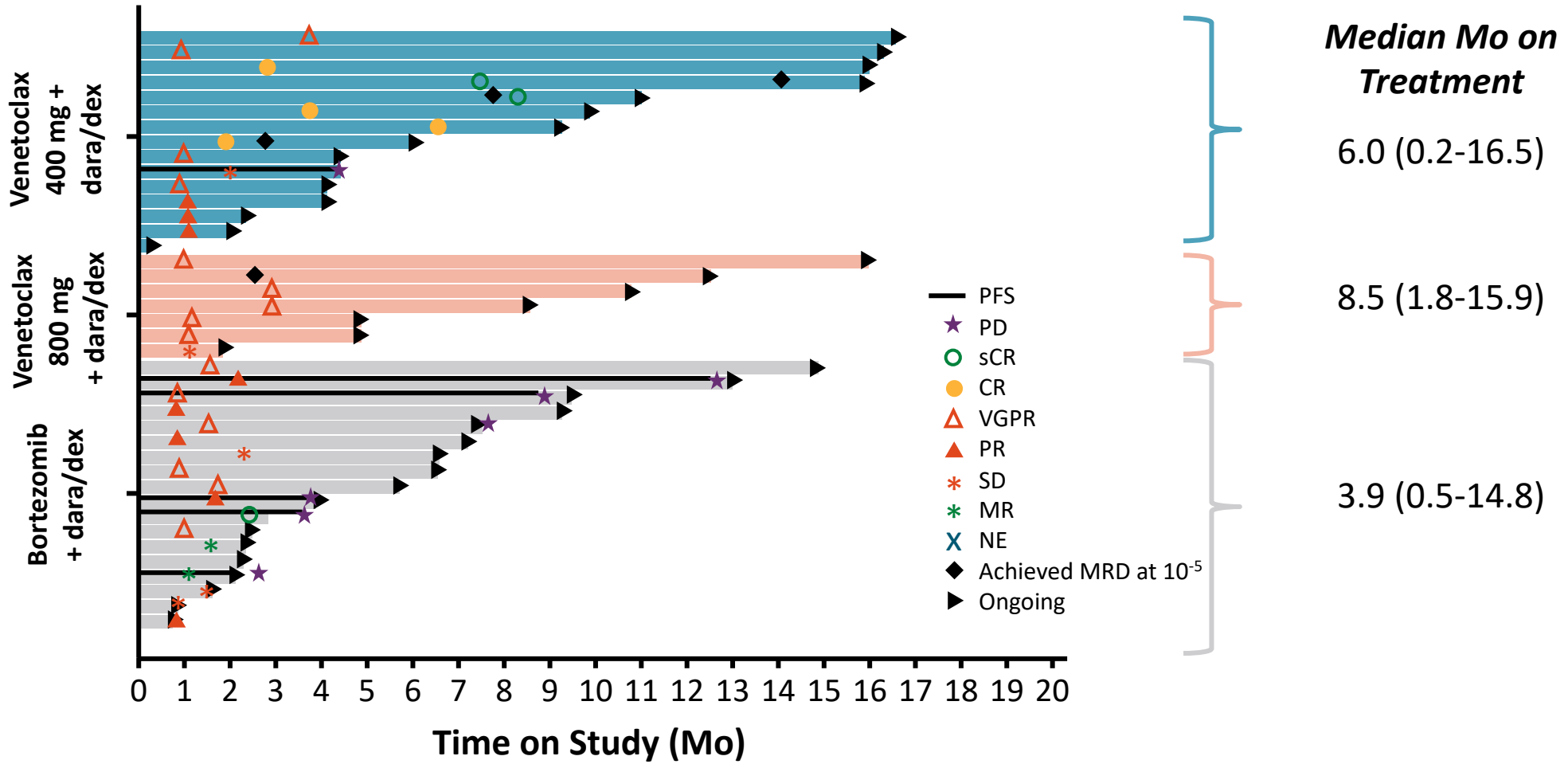


Minimal residual disease



sCR, stringent complete response, CR, complete response; ORR, overall response rate; VGPR, very good partial response; PR, partial response, MRD, minimal residual disease; Ven, venetoclax; Ven400, venetoclax 400 mg; Ven800, venetoclax 800 mg; D, daratumumab; d, dexamethasone; V, bortezomib

Venetoclax/Dara/Dex vs Bortezomib/Dara/Dex in t(11;14) R/R MM: Duration of Response

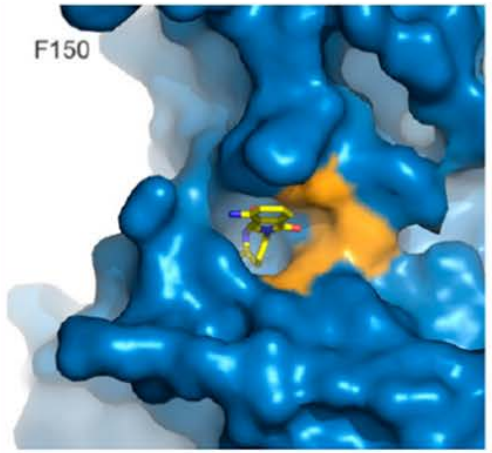


Kaufman. ASH 2021. Abstr 817. Reproduced with permission.

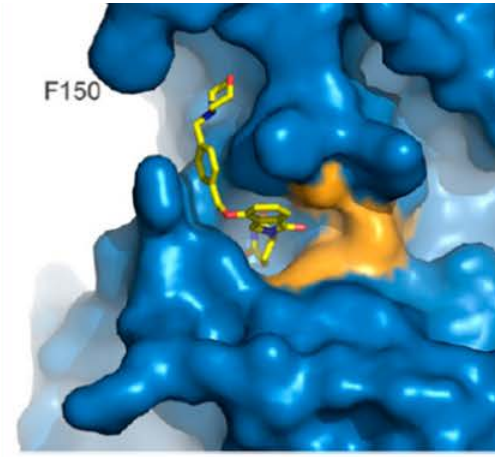
Iberdomide

- IBER binds to CRBN with higher affinity and degrades the target proteins Ikaros and Aiolos more potently compared with LEN and POM[1]

LEN[2]

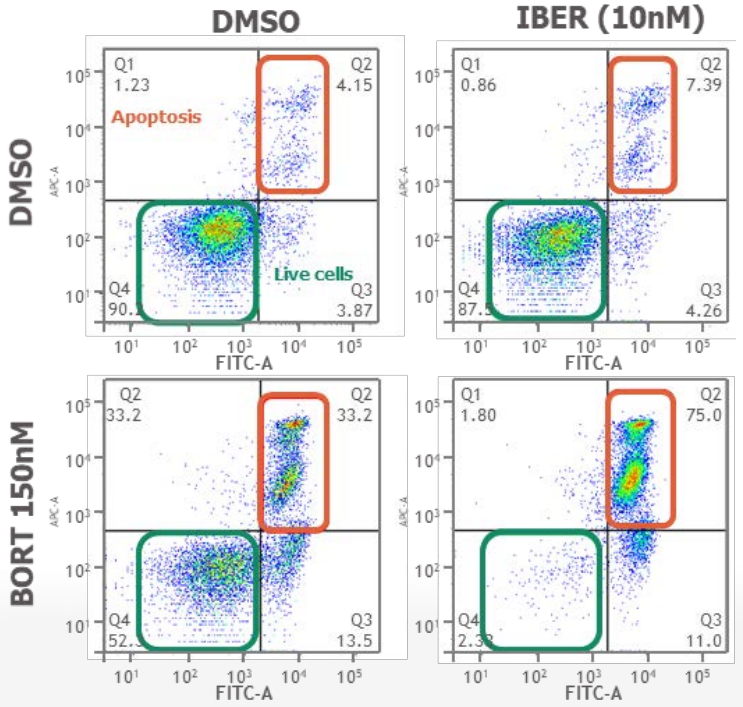


IBER[2]



EC_{50}, nM^2	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

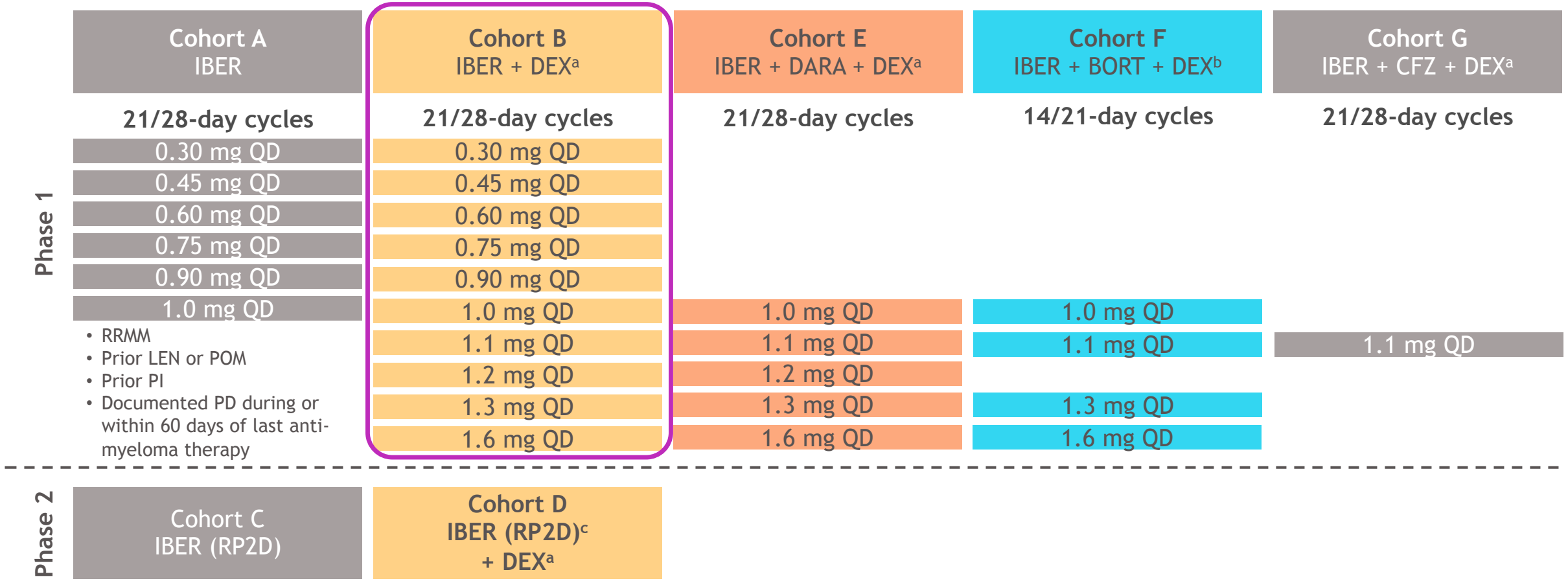
- IBER has marked synergistic tumoricidal and immune-stimulatory effects in combination with BORT or DARA in preclinical MM models[3-6]



- BORT, bortezomib; DARA, daratumumab; DSMO, dimethyl sulfoxide; EC50, half-maximal effective concentration; FITC, fluorescein isothiocyanate.
- 1. Bjorklund CC, et al. *Leukemia* 2020:34:1197–1201. 2. Adapted with permission from Matyskiela ME, et al. *J Med Chem* 2018;61:535-542 © 2018 American Chemical Society. 3. Amatangelo M, et al. *Blood* 2018; 132:1935; 4. Lonial S, et al. *Blood* 2019;134:3119. 5. Amatangelo M, et al. Presented at ASH 2020; December 5-8. Abstract 1358. 6. Amatangelo M, et al. Presented at ASH 2020; December 5-8. Abstract 1359.

van de Donk NWCJ, et al. ASH 2020. Abstract 724.

CC-220-MM-001: phase1/2 study design



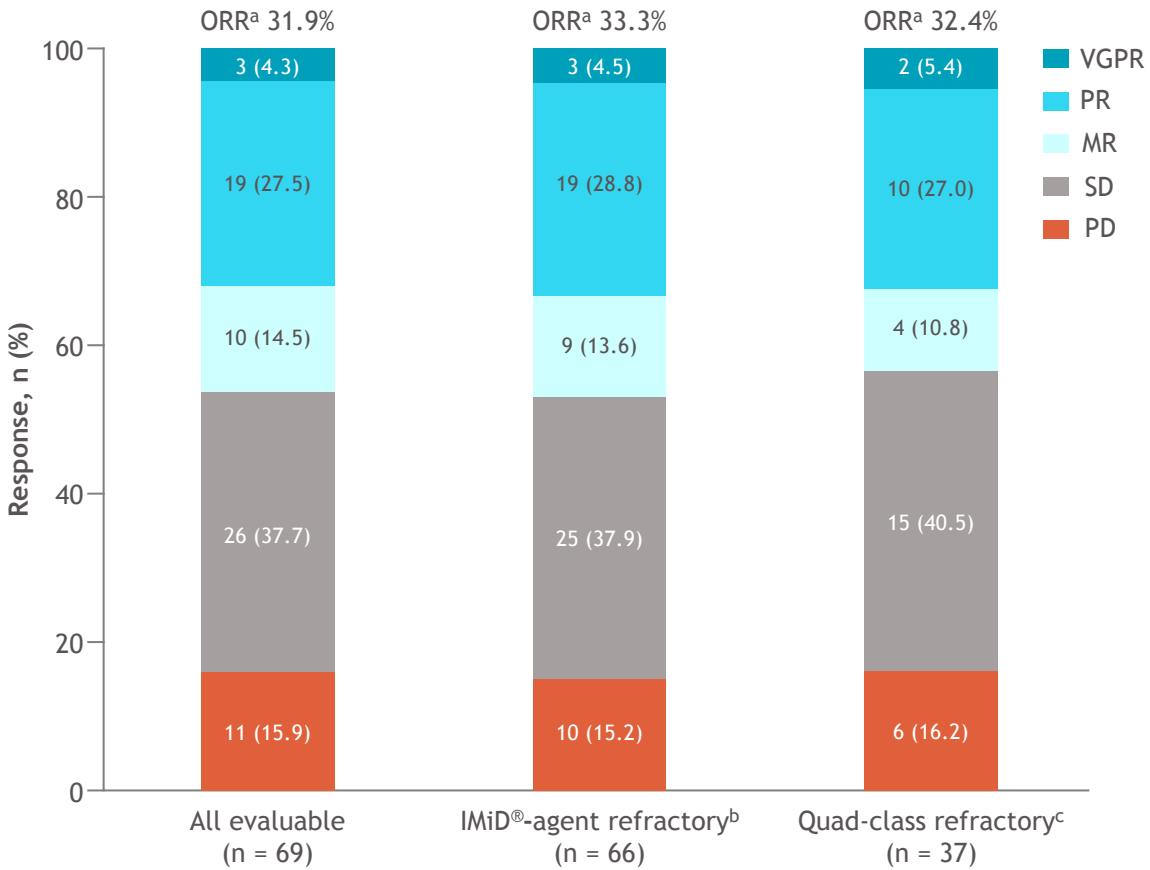
Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

[a] DEX given at a dose of 40 mg (20 mg in patients ≥ 75 years of age) on D1, 8, 15, and 22 of each 28-day cycle; [b] DEX given at a dose of 40 mg (20 mg in patients ≥ 75 years of age) on D1, 8, and 15 of each 21-day cycle. CFZ dosed once weekly (cohort G1) or twice weekly (cohort G2); [c] 1.6 mg QD.

PD, progressive disease; QD, once daily; RP2D, recommended phase 2 dose.

van de Donk NWCJ, et al. Oral presentation at ASH 2020; abstract 724.

CC-220-MM-001: response rates and safety



Common (> 20% all grade) TEAEs and events of interest, n (%)	Cohort B (IBER + DEX) (N = 75)		
	All grade	Grade 3	Grade 4
Anaemia	32 (42.7)	20 (26.7)	1 (1.3)
Neutropenia	30 (40.0)	13 (17.3)	12 (16.0)
Febrile neutropenia	4 (5.3)	4 (5.3)	0
Thrombocytopenia	13 (17.3)	3 (4.0)	5 (6.7)
Infection	38 (50.7)	16 (21.3)	1 (1.3)
Fatigue	26 (34.7)	0	1 (1.3)
Insomnia	23 (30.7)	0	0
Back pain	16 (21.3)	6 (8.0)	0
Muscle spasms	15 (20.0)	0	0
Diarrhoea	15 (20.0)	0	0
Constipation	11 (14.7)	1 (1.3)	0
Peripheral sensory neuropathy	4 (5.3)	1 (1.3)	0
Deep vein thrombosis	1 (1.3)	0	0
Pulmonary embolism	1 (1.3)	1 (1.3)	0

Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

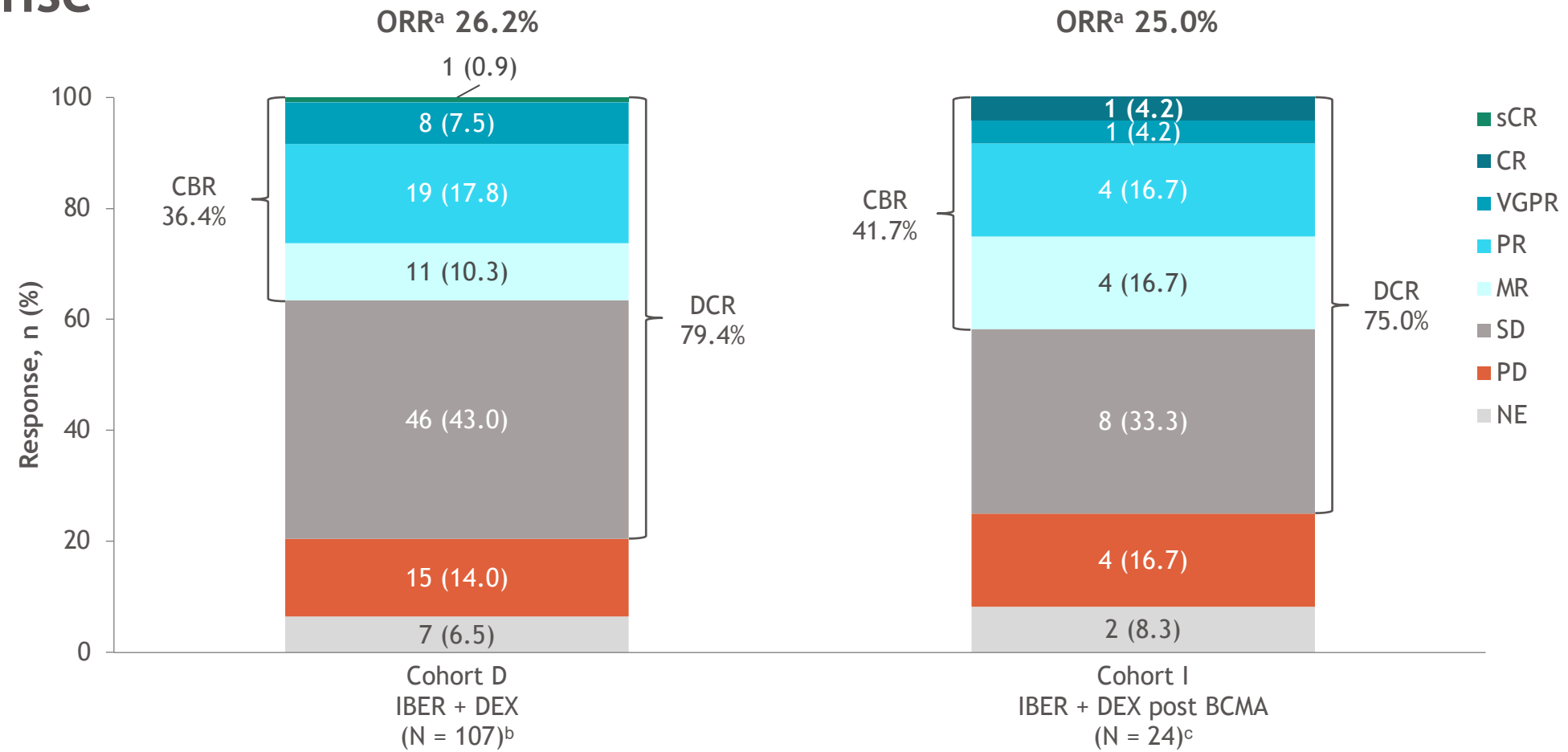
[a] PR or better. Evaluable patients include patients who have received ≥ 1 dose of IBER, had measurable disease at baseline, and ≥ 1 post-baseline response assessment; [b] Refractory to LEN or POM; [c] Refractory to ≥ 1 IMiD® agent, 1 PI, 1 anti-CD38 mAb, and 1 steroid.

mAb, monoclonal antibody; MR, minimal response; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

Lonial S, et al. Oral presentation at ASCO 2019; abstract 8006. Lonial S, et al. *Blood* 2019;134:abstract 3119.

CC-220-MM-001: cohort D and I (dose-expansion phase)

Response



Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

Numbers have been rounded-off to nearest integer.

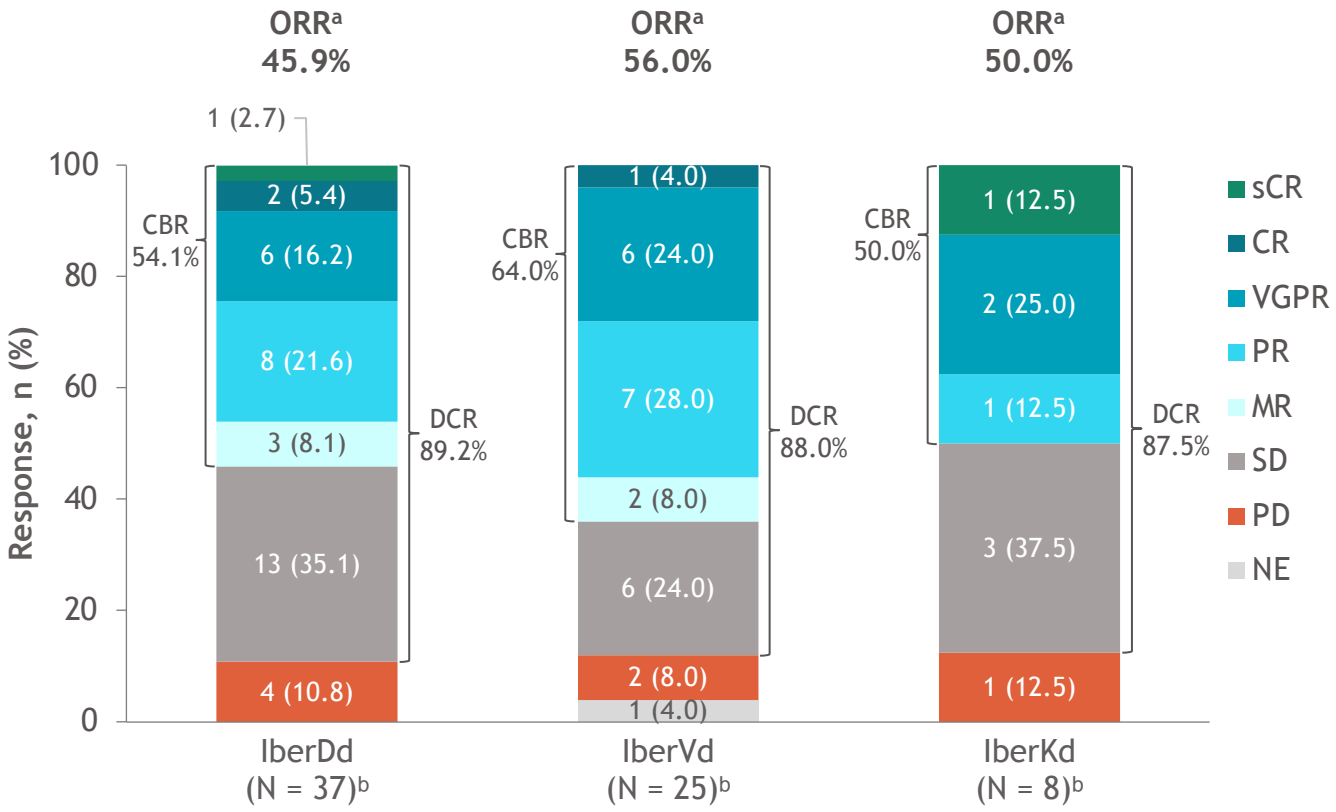
[a] PR or better; [b] 2 patients in SD and MR discontinued treatment because of death due to COVID-19; [c] Includes all treated patients who have post-baseline efficacy assessment or have discontinued treatment before any post-baseline efficacy assessment (2 patients were in C1 with no post-baseline efficacy assessments so were excluded from analysis).

CBR, clinical benefit rate; COVID, coronavirus disease; CR, complete response; DCR, disease control rate; NE, not evaluable; sCR, stringent complete response.

Lonial S, et al. Oral presentation at ASH 2021; abstract 162.

CC-220-MM-001: iberdomide in combination with DEX and DARA, BORT, or CFZ (Cohorts E, F and G) in patients with RRMM

- IBER + DEX in combination with DARA or BORT or CFZ showed a favourable safety profile in patients with heavily pretreated RRMM; TEAEs were mainly haematologic and well manageable
- The RP2D was determined at 1.6 mg in the IberDd cohort, while dose evaluation continues in the IberVd and IberKd cohorts
- Efficacy was observed even among patients refractory to IMiD® agents, DARA, and PIs



Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

Numbers have been rounded-off to nearest integer.

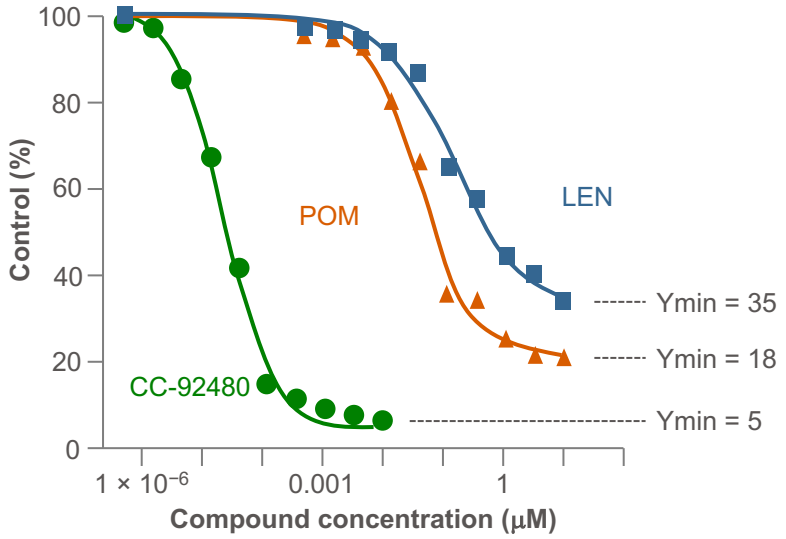
[a] PR or better; [b] Excludes treated patients who did not reach any post-baseline efficacy assessment and were still on treatment at time of data cut-off.

Lonial S, et al. Oral presentation at EHA 2021; abstract S187.

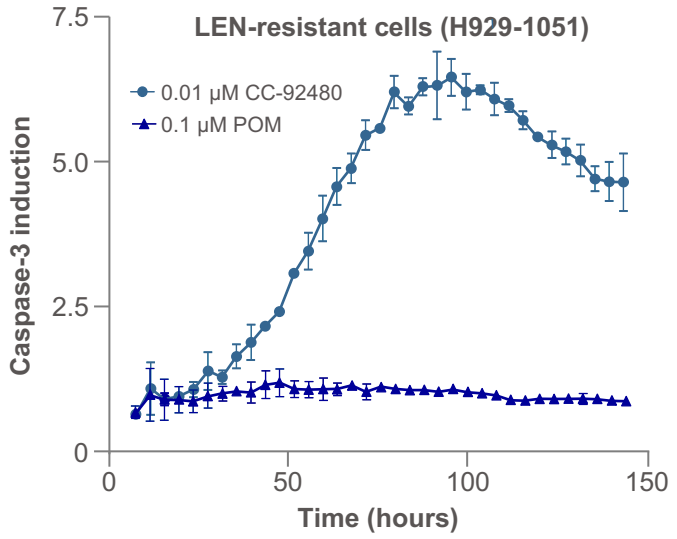
Mezigdomide (CC-92480) is a Novel CELMoD® Agent[1,2]

Efficient substrate degradation leading to apoptosis and potent antiproliferative activity in LEN and POM resistance[3]

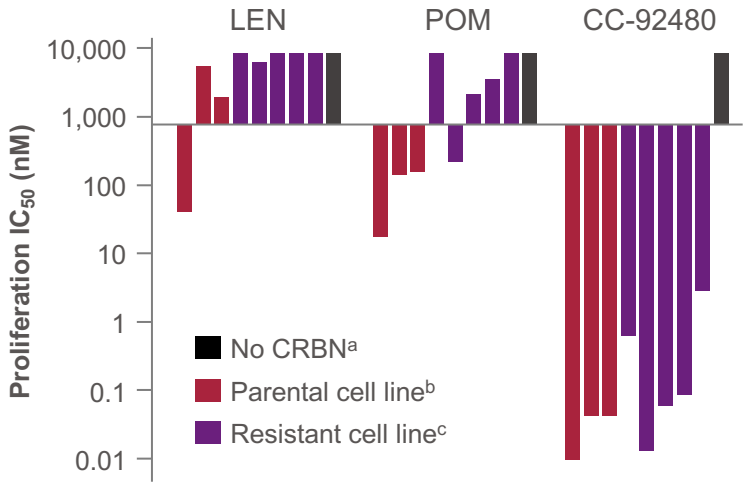
Aiolos degradation efficiency[1]

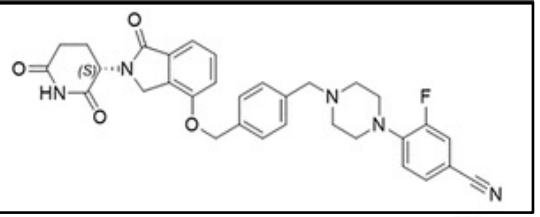
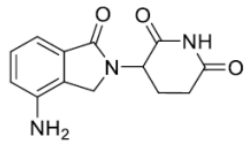
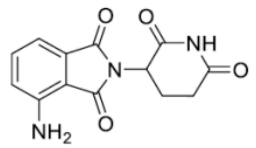


Apoptosis induction kinetics



Antiproliferative activity in LEN/POM resistance



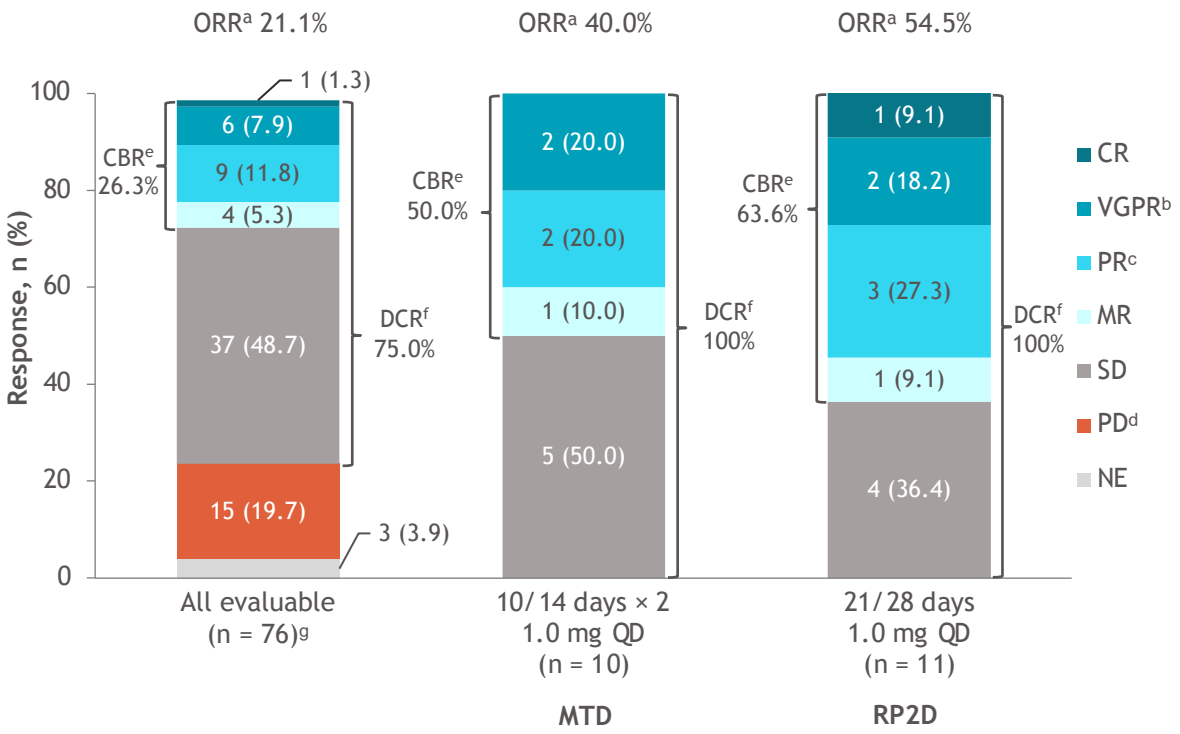
CC-92480, a potent CELMoD® agent[1]	LEN[1]	POM[1]
		

CC-92480 is an investigational product, currently not approved by any regulatory agency.

[a] DF15R; [b] DF15, H929, and OPM-2; [c] H929R1, H929R2, OPM-2R1, OPM-2R2, and OPM-2R3. IC_{50}, 50% inhibitory concentration; Ymin, maximum degradation point.

1. Hansen JD, et al. *J Med Chem* 2020;63:6648–6676; 2. Wong L, et al. *Blood* 2019;134(suppl 1). Abstract 1815; 3. Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

CC-92480-MM-001: efficacy and safety in patients with heavily pretreated RRMM



Common (> 20% all grade) TEAEs and events of interest, n (%)	All doses (N = 76)	
	Grade 3	Grade 4
Neutropenia	23 (30.3)	26 (34.2)
Febrile neutropenia	4 (5.3)	1 (1.3)
Anaemia	24 (31.6)	-
Thrombocytopenia	5 (6.6)	7 (9.2)
Fatigue	7 (9.2)	-
Pyrexia	3 (3.9)	-
Peripheral sensory neuropathy	-	-
Diarrhoea	1 (1.3)	-
Nausea	1 (1.3)	-
Deep vein thrombosis	-	-
Infections	25 (32.9)	2 (2.6)
Pneumonia[h]	11 (14.5)	-

- Prophylactic G-CSF was not permitted during C1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reduction of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

Mezigdomide (CC-92480) is an investigational product, currently not approved by any regulatory agency.

Numbers have been rounded-off to nearest integer.

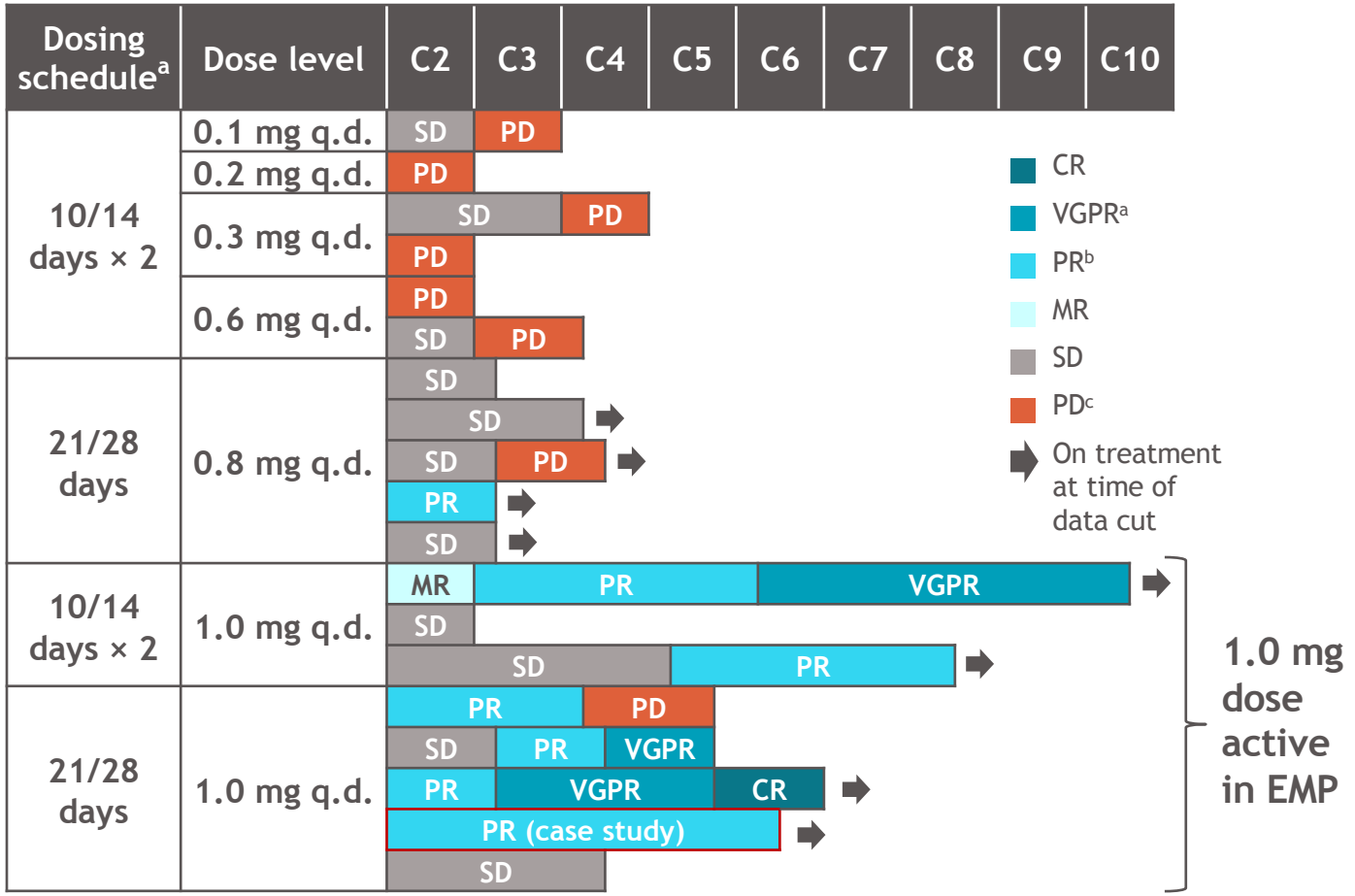
[a] PR or better; [b] 1 patient in the 21/28-day 1.0-mg QD cohort had an unconfirmed VGPR at time of data cut-off; [c] 2 patients in the 21/28-day 0.8-mg QD cohort had an unconfirmed PR at time of data cut-off; [d] 1 patient in the 21/28-day 0.8-mg QD cohort had an unconfirmed PD at time of data cut-off; [e] CBR defined as MR; [f] DCR defined as SD; [g] 1 patient had a pending response assessment at time of data cut-off; [h] Includes Medical Dictionary for Regulatory Activities Terminology version 22.0 preferred terms pneumonia, pneumocystis jirovecii pneumonia, respiratory syncytial viral pneumonia, and staphylococcal pneumonia.

AE, adverse event; G-CSF, granulocyte-colony stimulating factor.

Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

Responses in patients with EMP

- Only patients on continuous schedules are shown

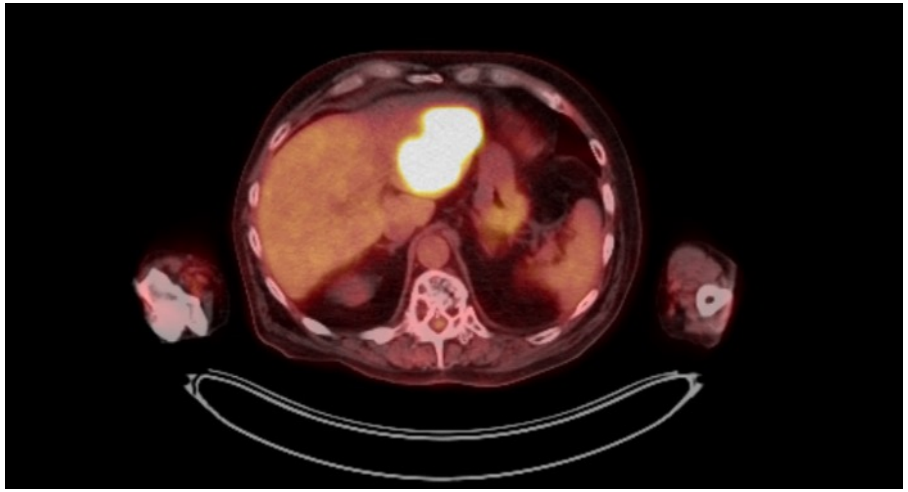


CC-92480 is an investigational product, currently not approved by any regulatory agency.

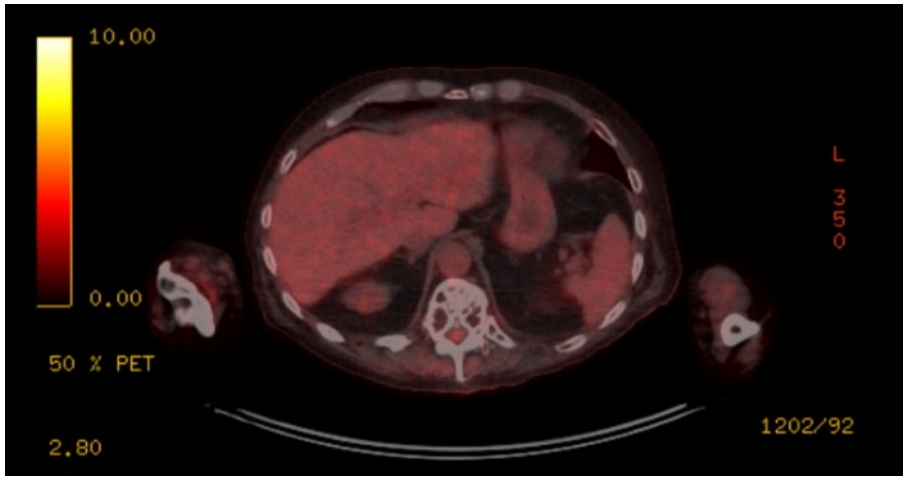
[a] 1 patient in the 21/28-day 1.0 mg q.d. cohort had an unconfirmed VGPR as of the data cut-off date. [b] 1 patient in the 21/28-day 0.8 mg q.d. cohort had an unconfirmed PR as of the data cut-off date. [c] 1 patient in the 21/28-day 0.8 mg q.d. cohort had an unconfirmed PD as of the data cut-off date. EMP, extramedullary plasmacytoma; PET, positron emission tomography.

Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

PET scan pretreatment



PET scan post CC-92480 C3D1



CFT 7455

CFT7455: A novel small molecule protein degrader, mechanism of action and pharmacologic characteristics

- Novel small molecule binds to Cereblon E3 ligase (CRBN)
- Creates a new surface on CRBN for interaction with the transcription factors IKZF1/3
- As a result, IKZF1/3 are ubiquitinated by the CRBN E3 ligase and degraded by the proteasome (Figure 2.)
- The high CRBN binding affinity (IC50=0.9nM) of CFT7455 enables rapid, deep, and durable degradation of IKZF1/3 resulting in apoptosis and potent activity in MM cell lines and multiple types of NHL cell lines in vitro
- In vivo, oral administration of CFT7455 in mice led to regression of MM and lymphoma in xenograft models
- CFT7455 promotes T-Cell activation[1,5]

Figure 1.

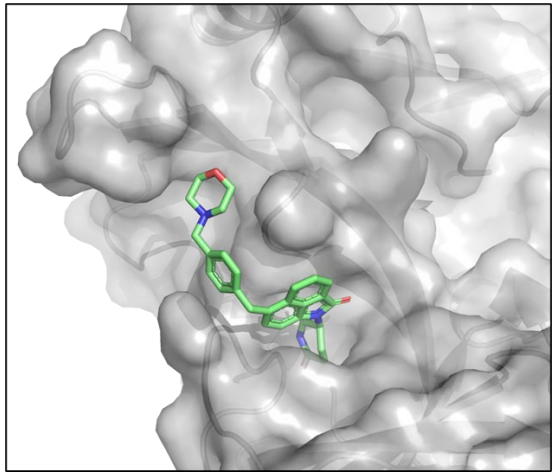


Figure 2: Mechanism of Action for CFT7455

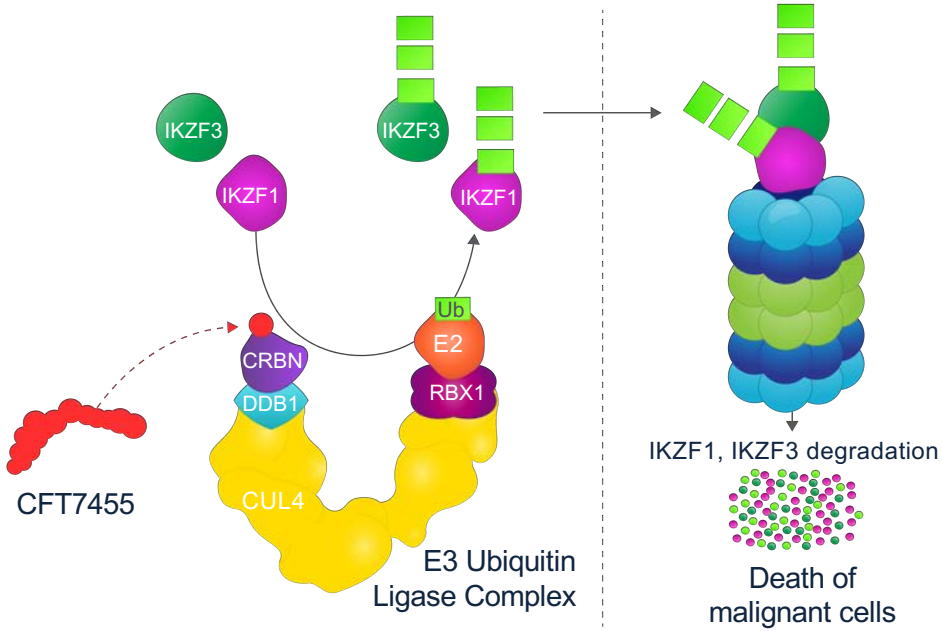
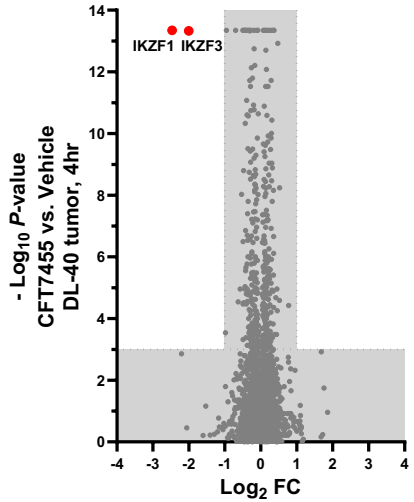


Figure 3: *In Vivo* Global Proteomics



Across ~8,000 proteins assessed in DL-40 xenograft, *in vivo*, the only proteins observed to be downregulated by CFT7455 are the intended targets IKZF1 and IKZF3

Other Precision Medicine options

- My DRUG trial presented by Kumar et al at ASCO demonstrated that mutation driven care could offer benefit in the right subsets
  - BRAF mutated
  - IDH mutated

Likely that Combination therapy will be needed for durable responses due to clonal escape

Conclusions

- Precision medicine is here, particularly for t(11;14) myeloma
- Venetoclax doesn’t need ramp up or caution used in CLL
- Combination therapy is often the way to go
- CELMoDs are here and not only have more potency, may have better AE profile
- Combinations here are the way as well
- Mutations may be important with the right agents and at the right time

Patients and Families

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International Myeloma Foundation
Education · Treatment · Research

Multiple Myeloma Research Foundation

Multiple Myeloma Research Consortium

The Leukemia & Lymphoma Society
Fighting Blood Cancers

Appendix

Editorial Review

- **Published data with venetoclax-based therapy for patients with MM, particularly those with t(11;14) or Bcl-2 overexpression**
  - **Slides 2-12**
- **Mechanism of action of cereblon E3 ligase modulators (CELMoDs); similarities and differences between CELMoDs and standard immunomodulatory drugs**
  - **Slides 13, 18**
- **Activity and safety observed with CELMoDs (eg, iberdomide, mezigdomide) in patients with heavily pretreated MM**
  - **Slides 14-17, 19-20**
- **Other promising novel strategies in development *(please refer to the topics assigned to the other faculty members to avoid significant overlap)***
  - **Slides 21-22**

Appendix Slides – None