La terapia con anti bcl-2: «un target trasversale» Nel mieloma multiplo

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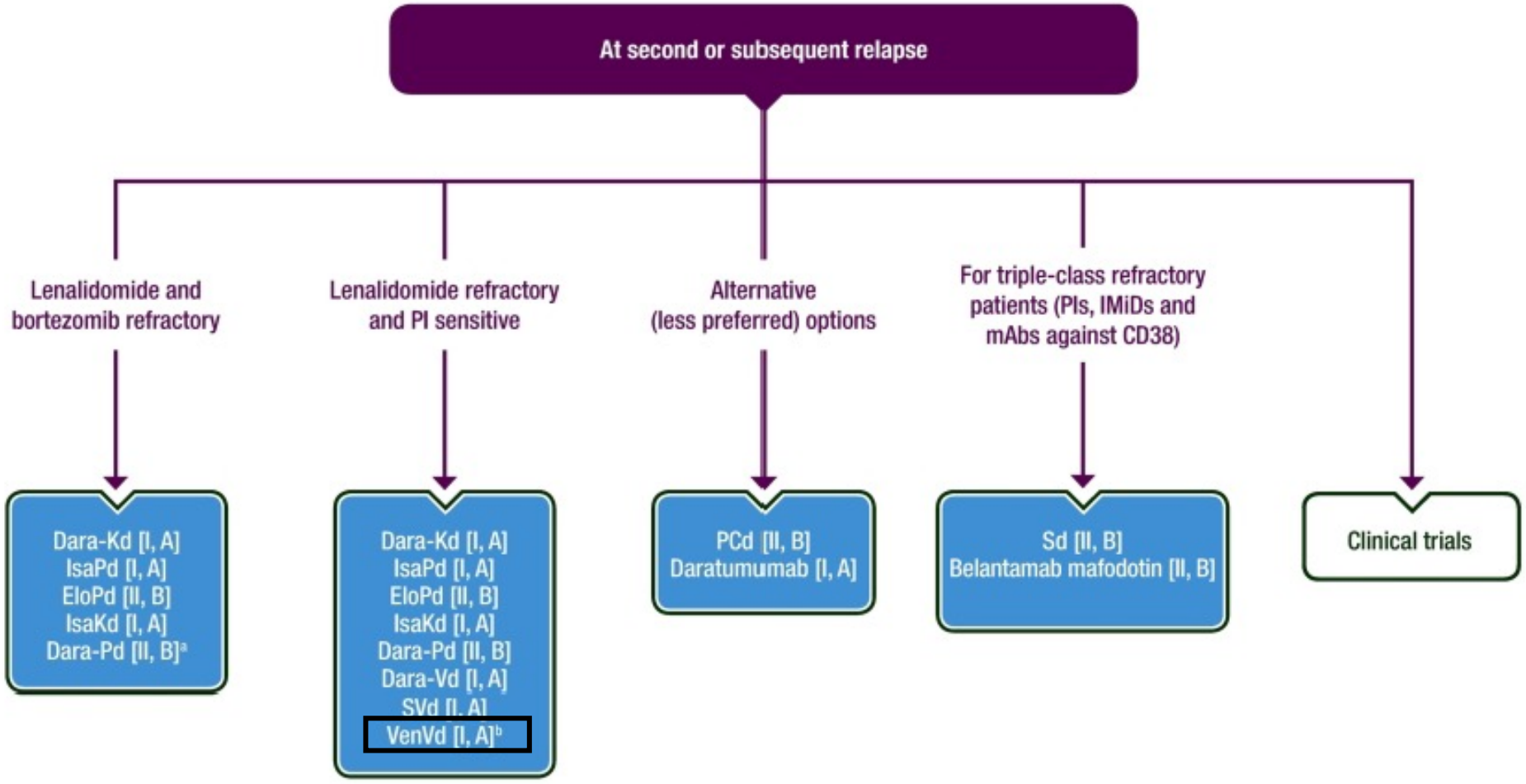
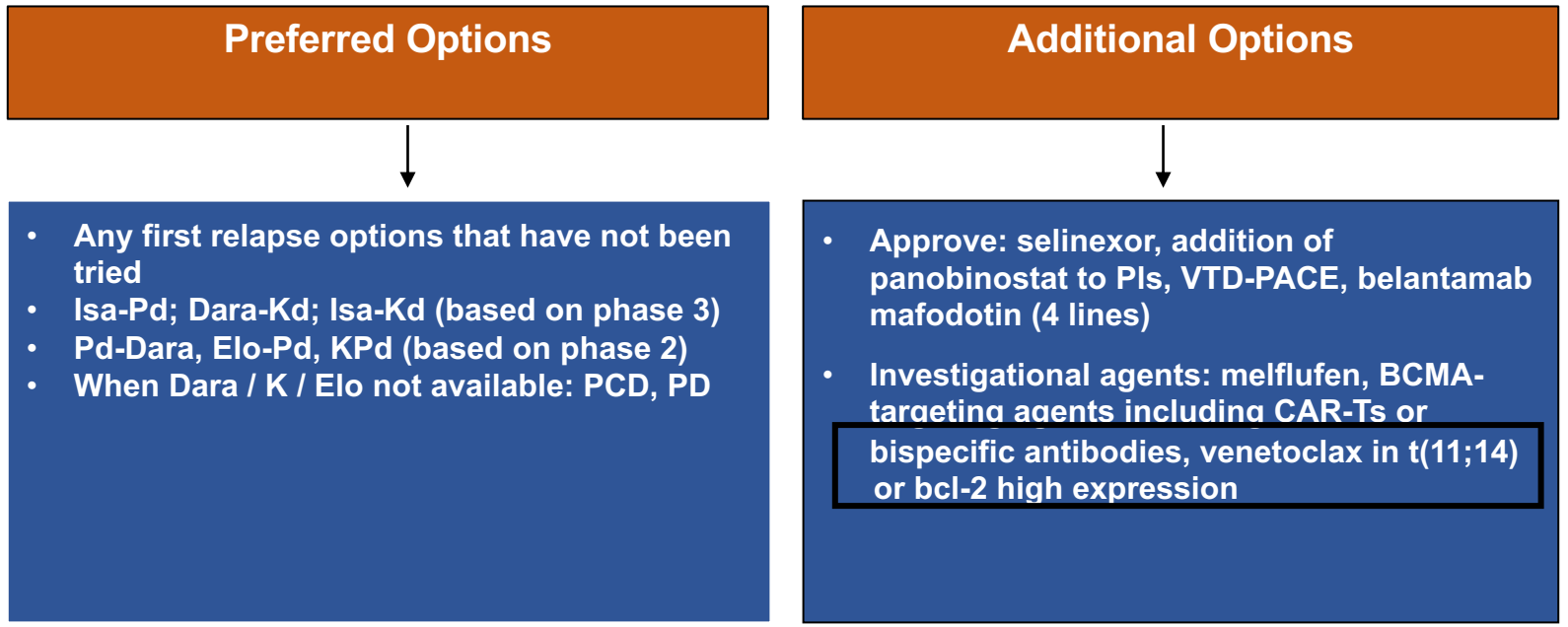
ESMO guidelines 2021



Dimopoulos MA et al. Ann Oncol 2021

IMWG guidelines 2021: second or higher relapse



Moreau P et al, Lancet Oncol 2021

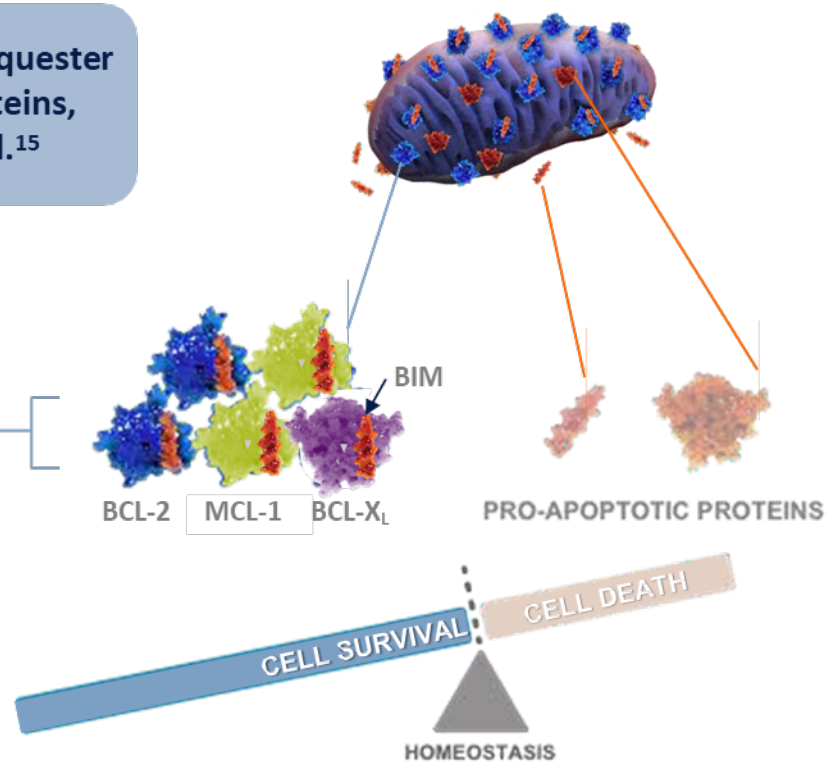
Venetoclax MOA:

B-cell Lymphoma 2 (BCL-2) Family Proteins – Cell Survival

The overexpression of pro-survival proteins (BCL-2, BCL-X_L, MCL-1) can promote survival of MM cells.[15]

Pro-survival proteins bind and sequester a surplus of pro-apoptotic proteins, thereby favoring cell survival.[15]

Implicated in tumorigenesis,[1,3-5] and increased resistance to chemotherapy[11-14]

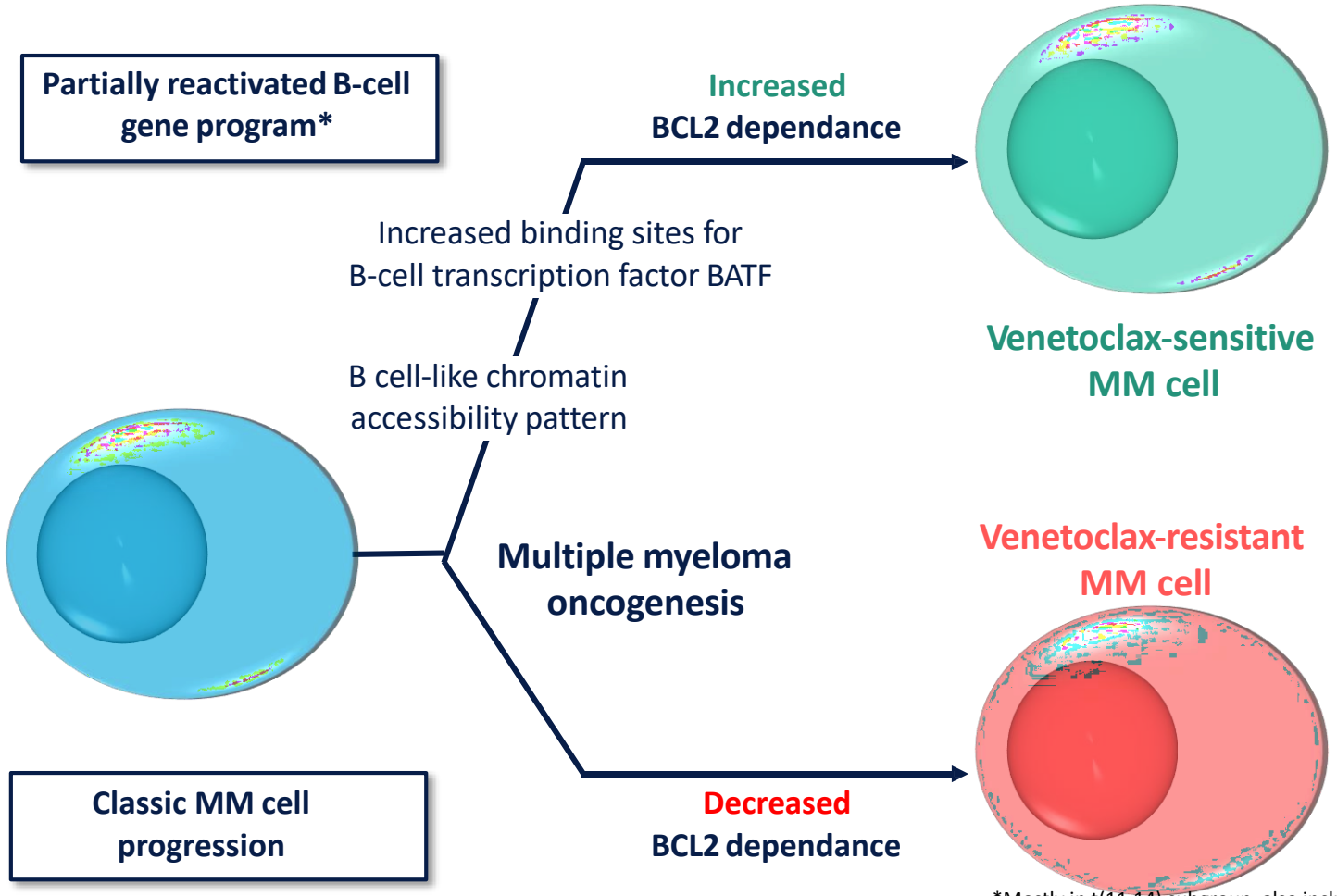


Elevated expression of anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1) play a critical role in MM tumorigenesis and response to treatment.[16]

1. Cory S, et al. Oncogene. 2003;22:8590-8607. 2. Rajan AM, et al. Blood Cancer J. 2016;6(7):e451.
3. Plati J, et al Integr Biol (Camb). 2011;3:279-296. 4. Adams JM, et al. Oncogene. 2007;26:1324-1337. 5. Reed JC. Blood. 2008;111:3322-3330.
6. Choi J, et al. Cancer Res. 2005;65:5554-5560. 7. Takaoka A, et al. Oncogene. 1997;14:2971-2977. 8. Biroccio A, et al. FASEB J. 2000;14:652-660.
9. Warner KA, et al. Neoplasia 2008;10:131-139. 10. Vanasse GJ, et al. Mol Cancer Res 2004;2:620-631. 11. Schmitt CA, et al Nat Med. 2000;6:1029-1035.
12. Wacheck V, et al. Oligonucleotides. 2003;13:393-400. 13. Mohammad RM, et al. Clin Cancer Res. 2007;13:2226-2235. 14. O'Brien S, et al. J Clin Oncol. 2007;25:1114-1120.
15. Punnoose, EA, et al. Mol Cancer Ther. 2016;15(5):1132-1144. 16. Trudel S, et al. Clin Cancer Res. 2007;13(2):621-629. 17. Souers AJ, et al. Nat Med. 2013;19(2):202-208.

Venetoclax MOA:
Plasma cell sensitivity to venetoclax in MM

BCL-2 dependency varies across MM; MM cells with the t(11;14) translocation are primarily dependent on BCL-2 for survival[3]



Venetoclax Sensitivity

- MM cells sensitive to venetoclax are **enriched for specific B-cell genes**, including **CD20 and CD79A**[1]
- Presence of CD20 and CD79A on MM plasma cells **predict sensitivity to venetoclax**[1]
- **CD20 expression** in MM is **mostly observed in patients with t(11;14)**[1]
- However, venetoclax sensitivity can be present **even in the absence of t(11;14)[1] (high bcl-2 without translocation)**
- Venetoclax-sensitive plasma cells have a more B cell-like phenotype[2]

*Mostly in t(11;14) subgroup, also includes patients from other subgroups (ie. MAF, hyperdiploid). MM=Multiple Myeloma.

1. Touzeau C, et al. *Blood* 2021; 137(26):3582-3. 2. Gupta VA, et al. Blood 2021; 132:1248–1264. 3. Touzeau C, et al. Leukemia 2018;32:1899–1907.

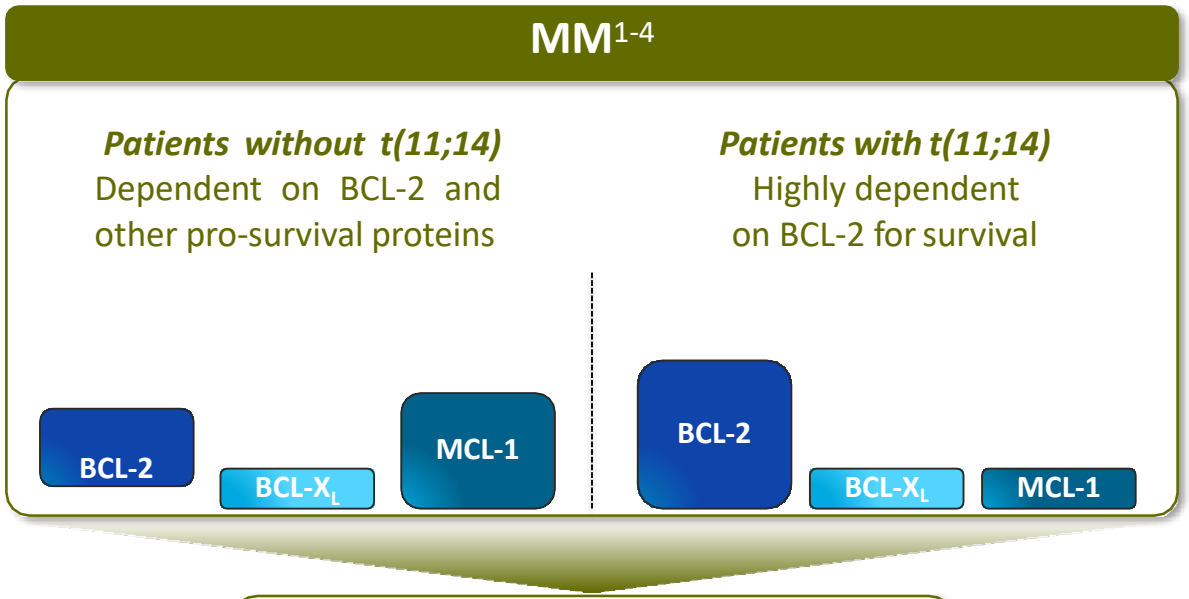
Primary and secondary genetic events that can be identified by FISH

Primary genetic events			Secondary genetic events		
IgH translocation	Gene(s)	Frequency (%)	Deletion	Gene(s)	Frequency (%)
t(4;14)	*FGFR3/MMSET*	15	1p	*CDKN2C, FAF1, FAM46C*	30
t(6;14)	*CCND3*	4	6q		33
t(11;14)	*CCND1*	20	8p		25
t(14;16)	*MAF*	4	13	*RB1, DIS3*	44
t(14;20)	*MAFB*	1	11q	*BIRC2/BIRC3*	7
			14q	*TRAF3*	38
			16q	*WWOX, CYLD*	35
			17p	*TP53*	7
Hyperdiploidy			Gain		
Trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21	NA	50	1q	*CKS1B, ANP32E*	40

	High-risk	Standard-risk
Cytogenetic abnormality	FISH: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q) Nonhyperdiploid Karyotipe Karyotype del(13) GEP: high-risk signature	All others including: FISH: t(11;14), t(6;14)

Sonneveld P, et al. Blood 2016; 127:2955-2962

Venetoclax MOA:
Rationale for Venetoclax Combinations in MM



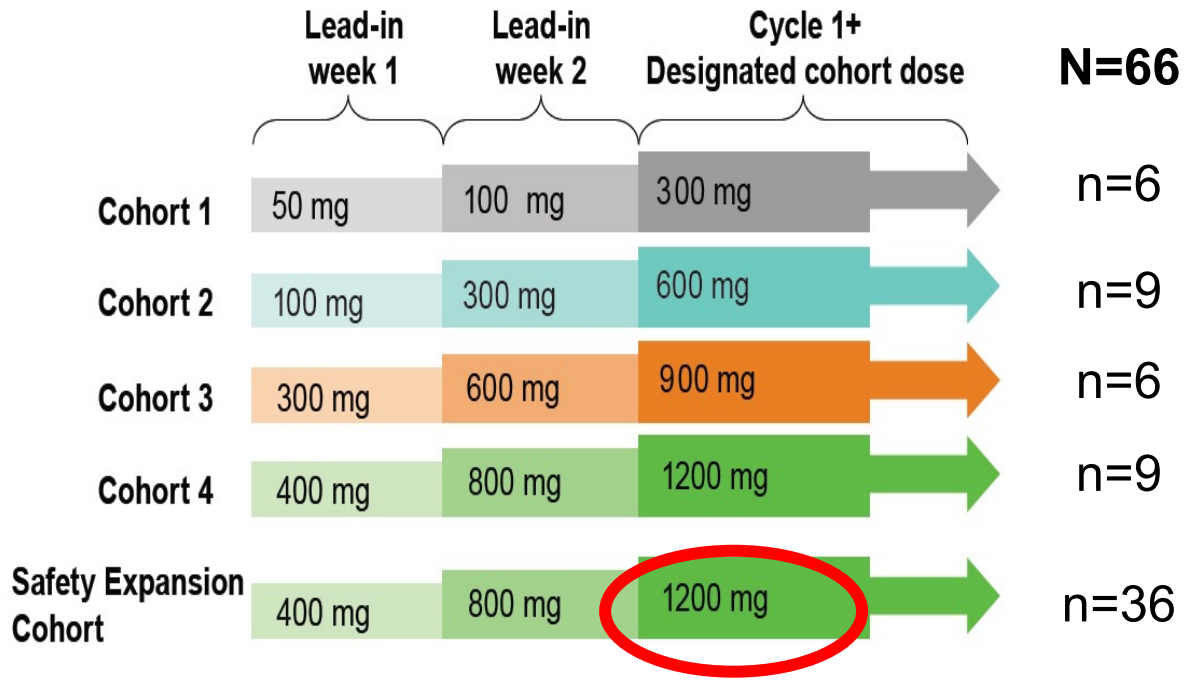
Patients with the t(11;14) translocation, which is present in 15% to 20% of all MM patients, express high BCL-2 and low MCL-1 and BCL-X_L levels.

DEX=Dexamethasone. MM=Multiple Myeloma. PI=Proteasome Inhibitor. VEN=Venetoclax.

1. Leverson JD, et al. Cancer Discov 2017; 7:1376–1393. 2. Valentin R, et al. Blood 2018; 132:1248–1264. 3. Touzeau C, et al. Leukemia 2018; 32:1899–1907. 4. Gomez-Bougie P, et al. Blood 2018; 132:2656–2669.

Venetoclax phase I study in RRMM

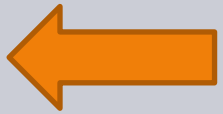
- Following a 2-week lead-in period, patients were treated on a 21-day cycle with daily venetoclax (300 to 1200 mg)
- Patients who progressed while receiving monotherapy could have dexamethasone added to venetoclax and continue on study



Kumar S et al, Blood 2017

Patient Characteristics

	N=66
Age, median (range), years	63 (31–79)
ISS stage, n (%)	
Stage I	24 (38)
Stage II/III	39 (62)
Unknown	3
Cytogenetic abnormalities, n (%)	
t(11;14)	30 (46)
t(4;14)	6 (9)
del(17p)	12 (18)
del(13q)	32 (48)
Hyperdiploid	27 (41)
No. of prior lines of therapy,[a] median (range)	5 (1–15)
Autologous stem cell transplant, n (%)	50 (76)
Bortezomib/refractory, n (%)	62 (94)/46 (70)
Lenalidomide/refractory, n (%)	62 (94)/51 (77)
Bortezomib and lenalidomide refractory, n (%)	40 (61)
Refractory to last prior therapy, n (%)	52 (79)

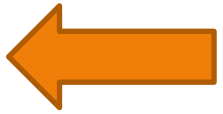


Summary of Adverse Events (AEs)

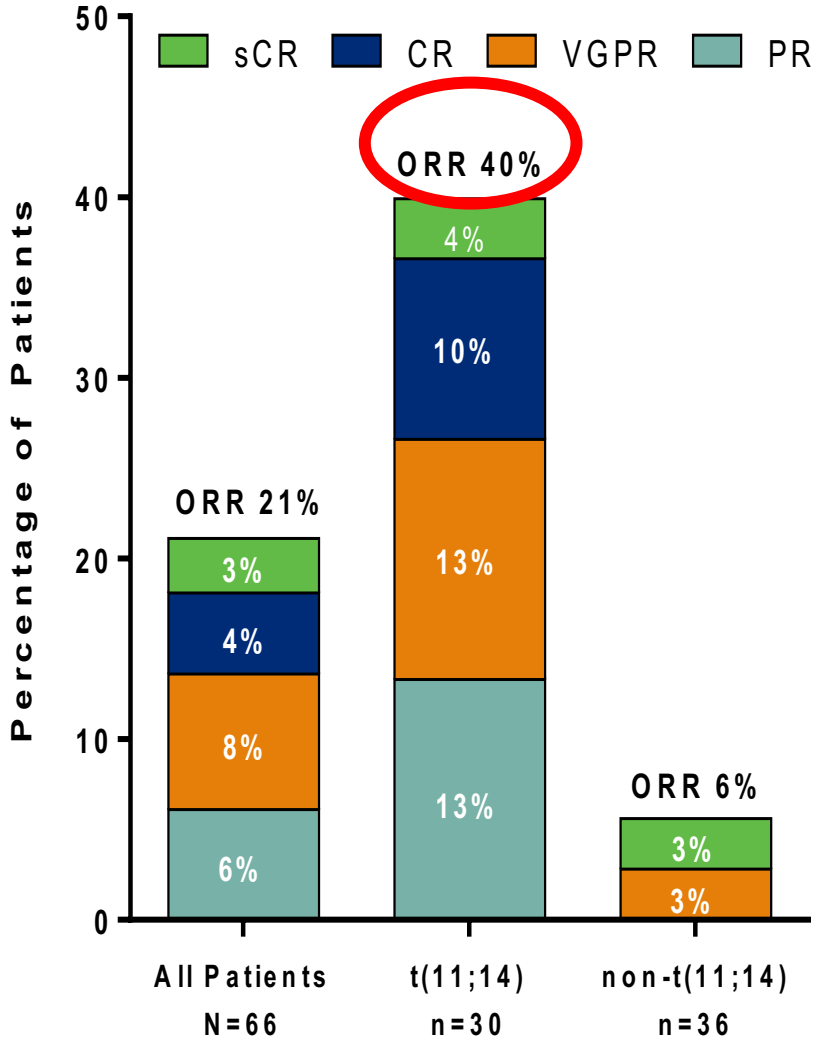
n (%)	Any Grade	Grade 3/4
Total	**66 (100)**	**45 (68)**
Hematologic		
Thrombocytopenia	21 (32)	17 (26)
Neutropenia	18 (27)	14 (21)
Anemia	15 (23)	9 (14)
Leukopenia	15 (23)	9 (14)
Lymphopenia	12 (18)	10 (15)
Non-hematologic		
Nausea	31 (47)	2 (3)
Diarrhea	24 (36)	2 (3)
Fatigue	18 (27)	3 (5)
Back pain	14 (21)	5 (8)
Vomiting	13 (20)	2 (3)

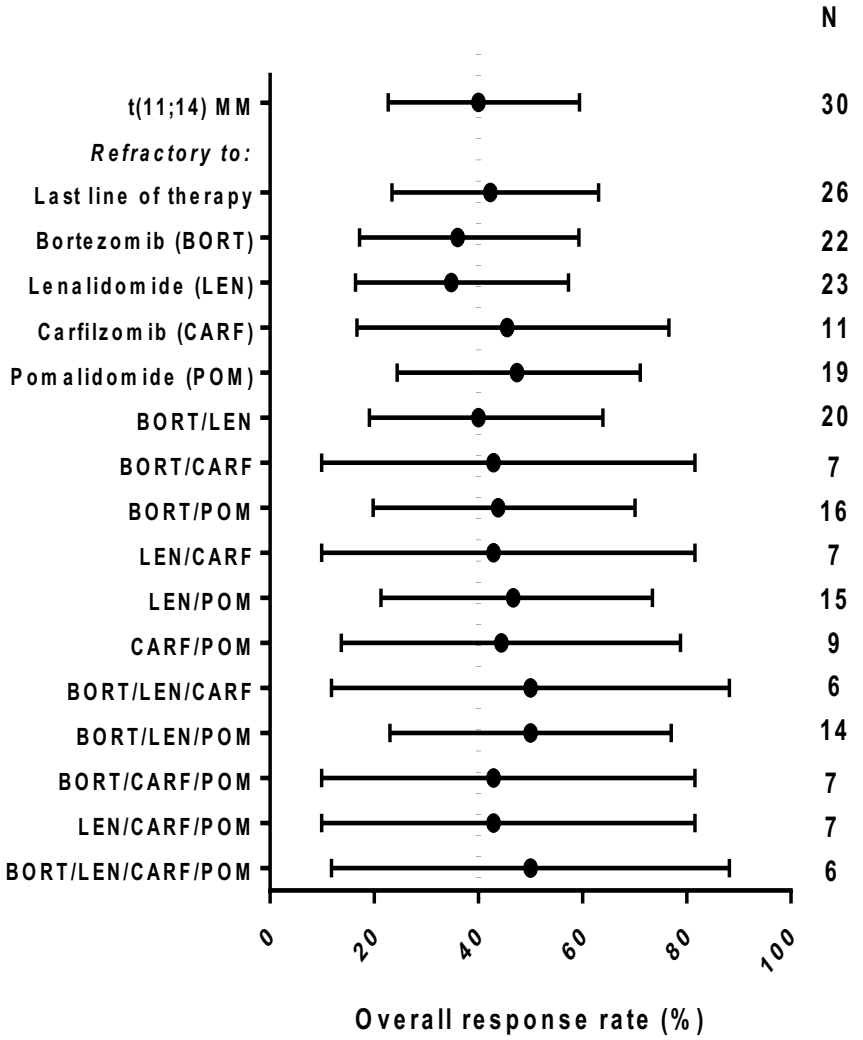
AEs for ≥20% of patients for any grade AE or for ≥10% with grade 3 or 4 AEs.

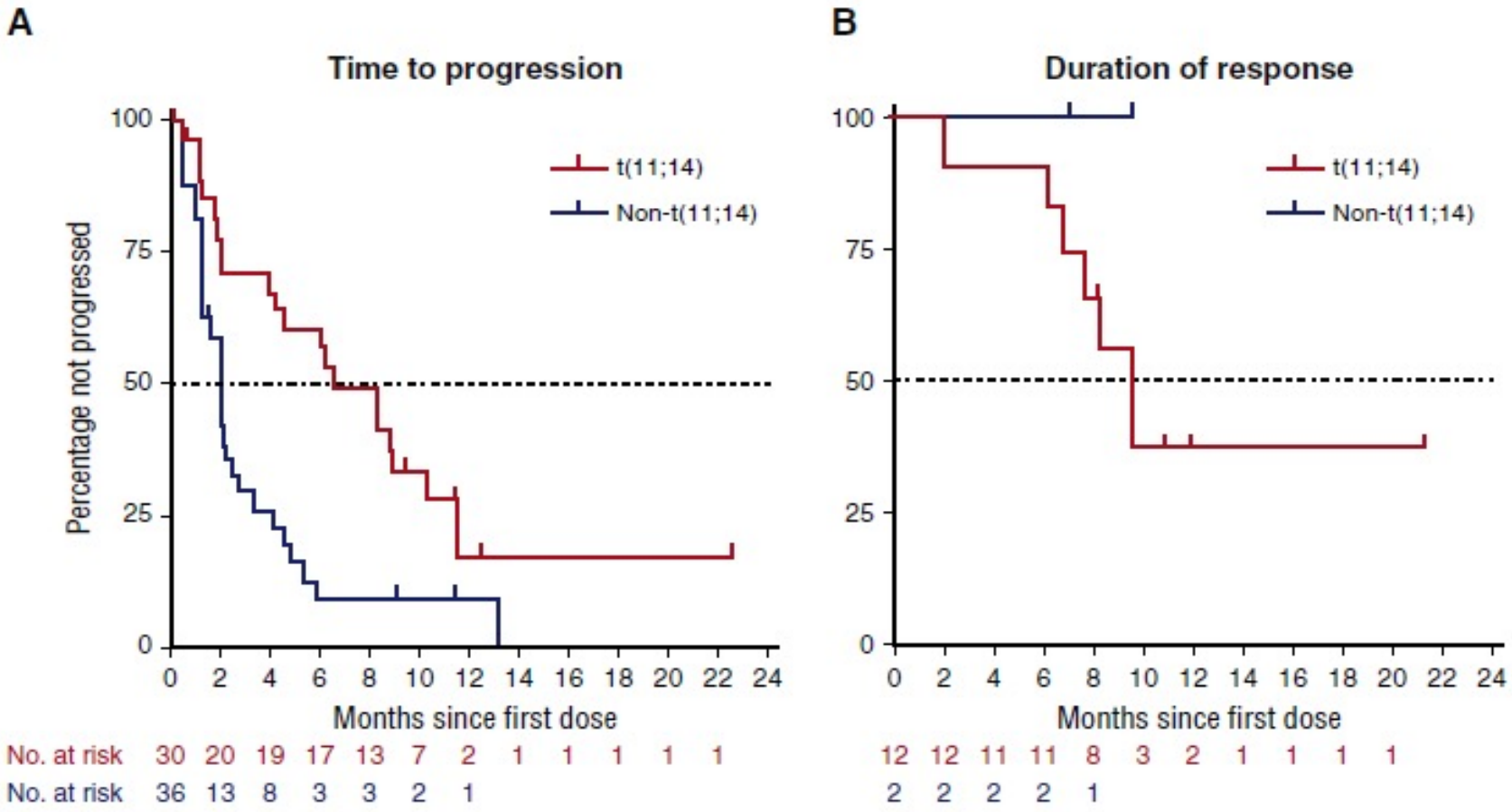
- Two patients had dose-limiting toxicities at 600 mg of abdominal pain and nausea
- Serious AEs (≥2% of patients): pneumonia (8%), sepsis (5%), pain, pyrexia, cough, and hypotension (3% each)
- No events of TLS were reported
- MTD was not reached



Objective Response Rates in All Patients and by t(11;14) Status



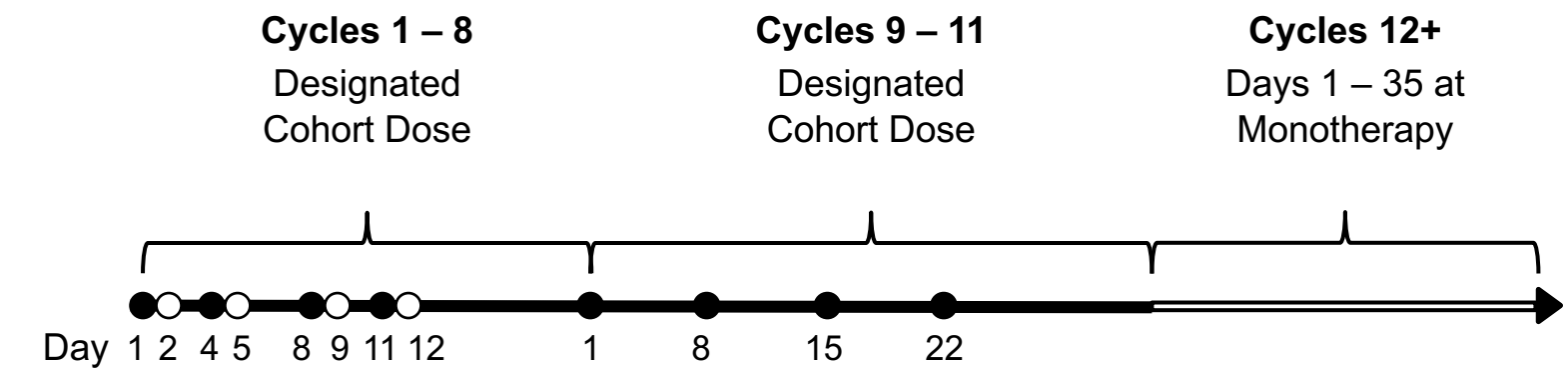




Group	Median TTP (95% CI)	Median DOR (95% CI)
t(11;14)	6.6 (3.9, 10.2)	9.7 (6.3, –)
Non-t(11;14)	1.9 (1.2, 2.3)	NE

Venetoclax + Bortezomib phase I study in RRMM

- Patients received 50–1200 mg venetoclax per designated dose escalation cohorts



Enrollment by Dose Cohort													
Dose (mg)	50	100	200	300	400	500	600	800	1000	1200	Total DE	SE	Total DE + SE
n	3	6	5	7	6	7	5	3	3	9	**54**	12	**66**

Moreau P et al, Blood 2017

Patient Characteristics

	N = 66
Age, median (range), years	64 (38–79)
ISS stage, n (%)	
Stage I	21 (35)
Stage II/III	39 (65)
Unknown	6
Cytogenetic abnormalities, n (%)	
t(11;14)	9 (14)
t(4;14)	5 (8)
del(17p)	15 (23)
del(13q)	30 (45)
Hyperdiploid	30 (45)
No. of prior lines of therapy, median (range)	3 (1–13)
Stem cell transplant, n (%)	39 (59)
Prior bortezomib/refractory, n (%)	53 (80)/26 (39)
Prior lenalidomide/refractory, n (%)	48 (73)/35 (53)
Refractory to last prior therapy	40 (61)

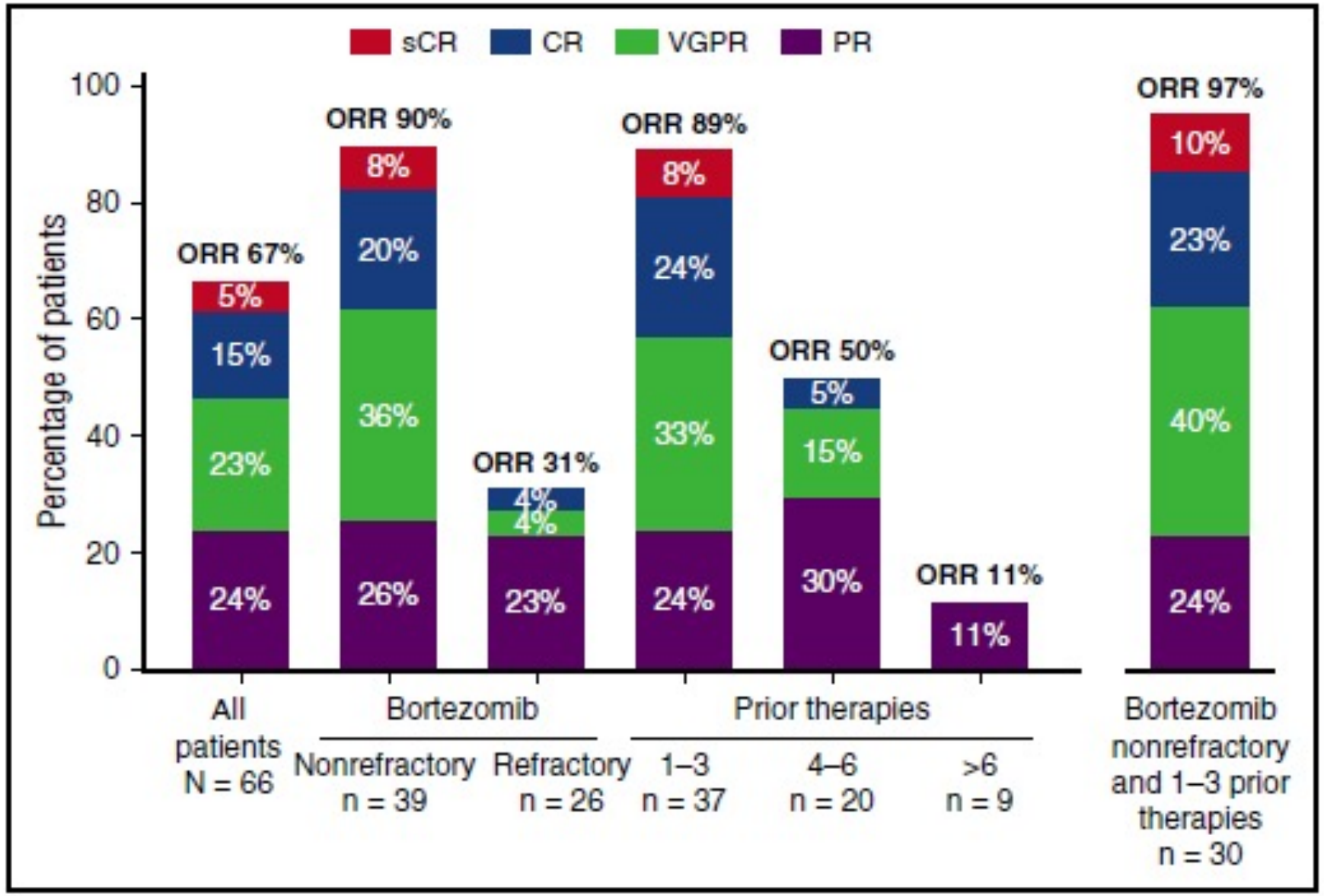
Adverse events

Adverse event, n (%)	Any Grade	Grade 3/4
Total	65 (99)	**55 (83)**
Diarrhea	30 (46)	4 (6)
Constipation	27 (41)	0
Thrombocytopenia	**26 (39)**	**19 (29)**
Nausea	25 (38)	3 (5)
Peripheral neuropathy	22 (33)	2 (3)
Insomnia	21 (32)	3 (5)
Peripheral edema	19 (29)	0
Anemia	**18 (27)**	**10 (15)**
Peripheral sensory neuropathy	18 (27)	0
Asthenia	16 (24)	1 (2)
Dyspnea	16 (24)	4 (6)
Fatigue	16 (24)	0
Upper respiratory tract infection	14 (21)	1 (2)
Neutropenia	**10 (15)**	**9 (14)**

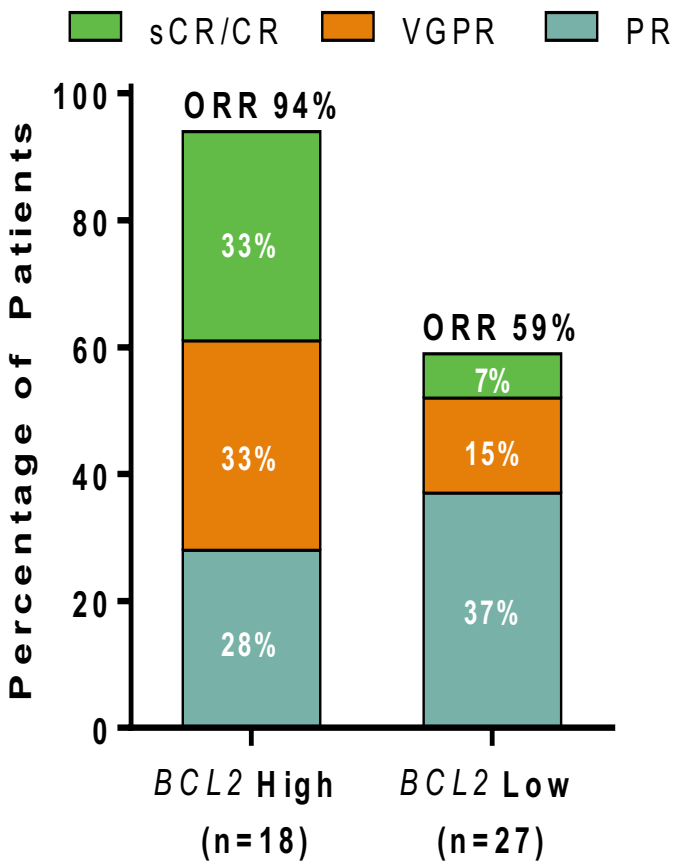
AEs for ≥ 20% of patients for any grade AE or for ≥ 10% with grade 3 or 4 AEs

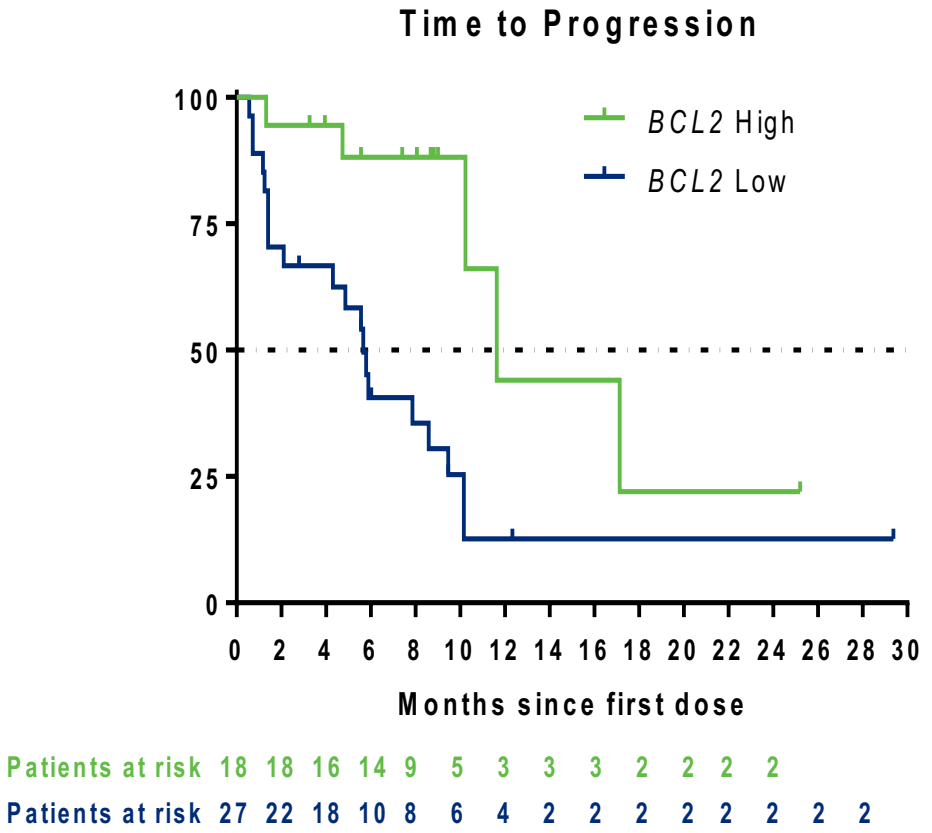
Serious adverse event, n (%)	Total
Any serious event	**35 (53)**
Pneumonia	5 (8)
Sepsis	3 (5)
Pyrexia	3 (5)
Influenza	3 (5)
Febrile neutropenia	3 (5)
Thrombocytopenia	2 (3)
Cardiac failure	2 (3)
Lower respiratory tract infection	2 (3)
Acute kidney injury	2 (3)
Embolism	2 (3)
Hypotension	2 (3)
Respiratory failure	2 (3)

Serious adverse events in ≥2 patients


sCR
CR
VGPR
PR
Percentage of patients
100
80
60
40
20
0
ORR 67%
5%
15%
23%
24%
ORR 90%
8%
20%
36%
26%
ORR 31%
4%
4%
23%
ORR 89%
8%
24%
33%
24%
ORR 50%
5%
15%
30%
ORR 11%
11%
ORR 97%
10%
23%
40%
24%
All patients N = 66
Bortezomib
Nonrefractory n = 39
Refractory n = 26
Prior therapies
1–3 n = 37
4–6 n = 20
>6 n = 9
Bortezomib nonrefractory and 1–3 prior therapies n = 30

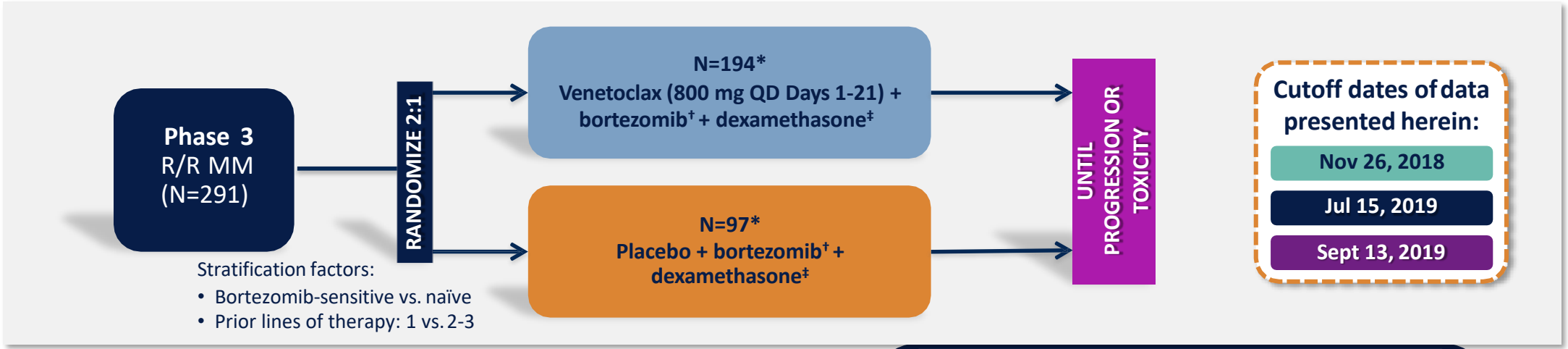
BCL2 Gene Expression and Clinical Response





BCL2 quantitation using ddPCR performed on CD138-selected bone marrow mononuclear cells collected at baseline. BATTing was used to estimate a threshold of *BCL2* to provide optimum selection of patients likely to have a response.

BELLINI (M14-031) – Study Design and Endpoints



INCLUSION CRITERIA
- 1-3 prior therapies
- ECOGPS≤2
- Measurable disease
- Proteasome inhibitor nonrefractory

EXCLUSION CRITERIA
- Disease refractory to any proteasome inhibitor
- Prior proteasome inhibitor treatment within 60 days of first dose

OBJECTIVES

Primary: ***PFS (per IRC)***

Secondary: ≥***VGPR, PFS in patients with high BCL-2 Expression, Efficacy (DOR, OS, TTP, ORR, MRD), QoL/PRO parameters***

†Bortezomib dosing=1.3 mg/m² Days 1, 4, 8, 11. ‡dexamethasone dosing=20 mg Days 1, 2, 4, 5, 8, 9, 11, 12 cycles 1-8
*** For cycles 9 and beyond, a 35-day dosing schedule is used: Venetoclax (800mg QD Days 1-35) + bortezomib (1.3 mg/m² Days 1, 8, 15, 22) + dexamethasone (20 mg Days 1, 2, 8, 9, 15, 16, 22, 23).**

1. ClinicalTrials.gov. NCT02755597. https://clinicaltrials.gov/ct2/show/NCT02755597. Accessed Jan 2021.
2. Harrison SJ, et al. Oral #142. 61st ASH Annual Meeting. December 7-10, 2019; Orlando, FL. 3. Spencer A, et al. Poster #3236. 62nd Annual ASH Meeting and Exposition. December 5-8, 2020. Virtual Format.

Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642

BELLINI (M14-031) – Patient Characteristics

Characteristic, n (%) unless otherwise stated		VEN + Bd (N=194)	Placebo + Bd (N=97)
Age in years, median (IQR)		66 (59-73)	65 (61-71)
≥65 years		108 (56)	52 (54)
Sex, male		97 (50)	55 (57)
MM ISS stage	Stage I	81 (42)	48 (49)
	Stage II	69 (36)	32 (33)
	Stage III	39 (20)	13 (13)
	NE/Missing	5 (3)	4 (4)
ECOG performance score	0	101 (52)	47 (48)
	1 or 2	92 (47)	49 (51)
	Missing	1 (1)	1 (1)
Median time since diagnosis, years (IQR)		3.5 (2.1-5.8)	4.0 (2.1-5.7)
Number of prior lines of therapy	1	**91 (47)**	**44 (45)**
	2 or 3	**103 (53)**	**53 (55)**
Prior stem cell transplant		116 (60)	57 (59)
Prior exposure to PI	Naïve	59 (30)	29 (30)
	Sensitive	135 (70)	68 (70)
Previous stem-cell transplant		116 (60)	57 (59)
Prior exposure to IMiD		131 (68)	65 (67)
Refractory to IMiD		64 (33)	36 (37)
Refractory to lenalidomide		38 (20)	27 (28)

Characteristic, n (%) unless otherwise stated		VEN + Bd (N=194)	Placebo + Bd (N=97)
Previous exposure to PI and IMiD drugs		78 (40)	42 (43)
Refractory to last line of therapy		158 (81)	81 (84)
Type of measurable disease	IgG	115 (59)	47 (48)
	IgA	40 (21)	25 (26)
	Free light chain	39 (20)	25 (26)
Cytogenetic risk	High-risk*	31 (16)	18 (19)
	Standard-risk†	141 (73)	72 (74)
	Unknown#/missing	22 (11)	7 (7)
t(11;14) status	Positive	**20 (10)**	**15 (15)**
	Negative	152 (78)	74 (76)
	Unknown/missing	22 (11)	8 (8)
BCL-2 protein expression (IHC),‡ n/N (%)	High	**93/119 (78)**	**47/58 (81)**
	Low	26/119 (22)	11/58 (19)
***BCL-2* gene expression[2] (qPCR)**§	High	66 (34)	32 (33)
	Low	104 (54)	55 (57)
	Unknown#/missing	24 (12)	10 (10)

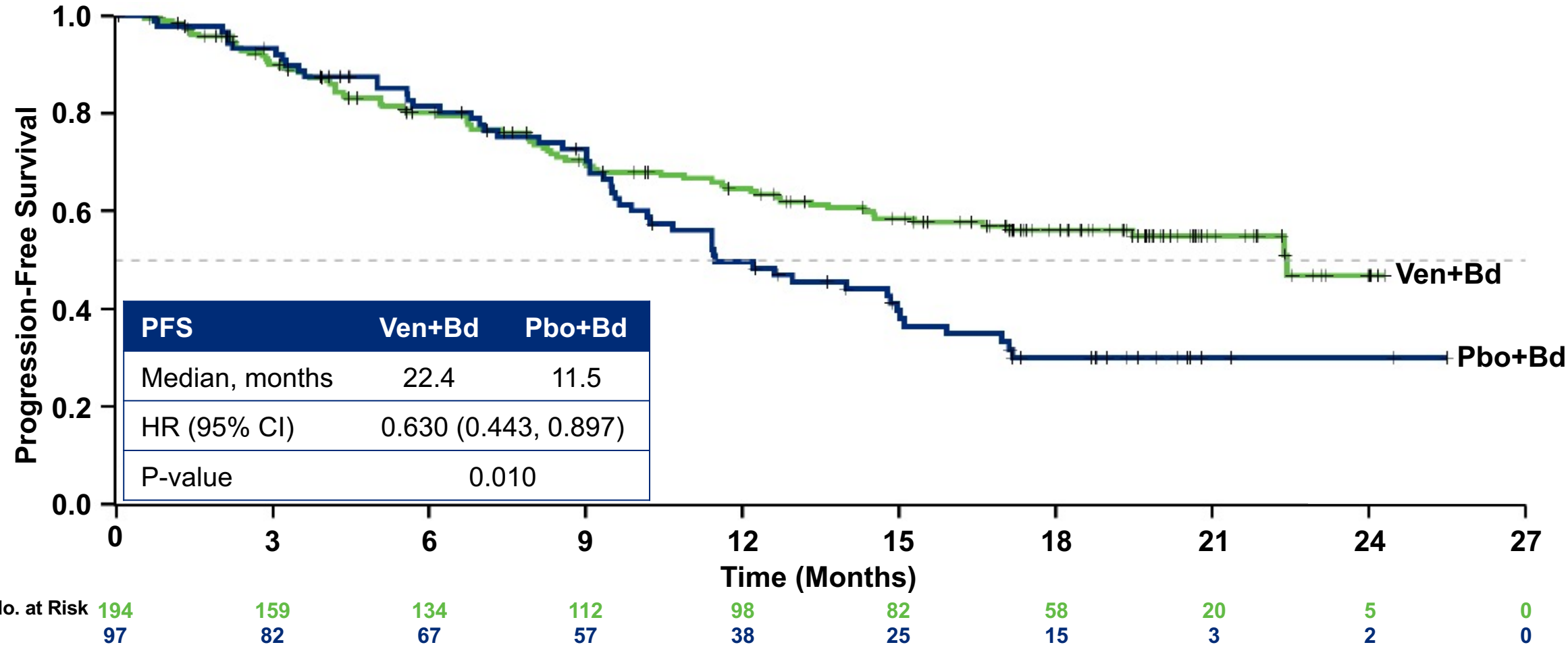
*t(4;14) or t(14;16) or del(17p). †No high-risk cytogenetics present. ‡Percentage calculated by excluding patients with missing data. §Retrospective BATTing analysis was used to determine optimum threshold of BCL2 gene expression to identify patients with maximum improvement in PFS when treated with VEN+Bd

Bd=Bortezomib+Dexamethasone. ECOG=Eastern Cooperative Oncology Group. IHC=Immunohistochemistry. IMiD=Immunomodulatory Drug. IQR=Interquartile Range. ISS=International Staging System. MM=Multiple Myeloma. NE=Not Evaluable. PI=Proteasome Inhibitor. qPCR=Quantitative Polymerase Chain Reaction. VEN=Venetoclax.

1. Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642. 2. Spencer A, et al. Poster #3236. 62nd Annual ASH Meeting and Exposition. December 5-8, 2020. Virtual Format.

Primary Endpoint Analysis: Progression-Free Survival

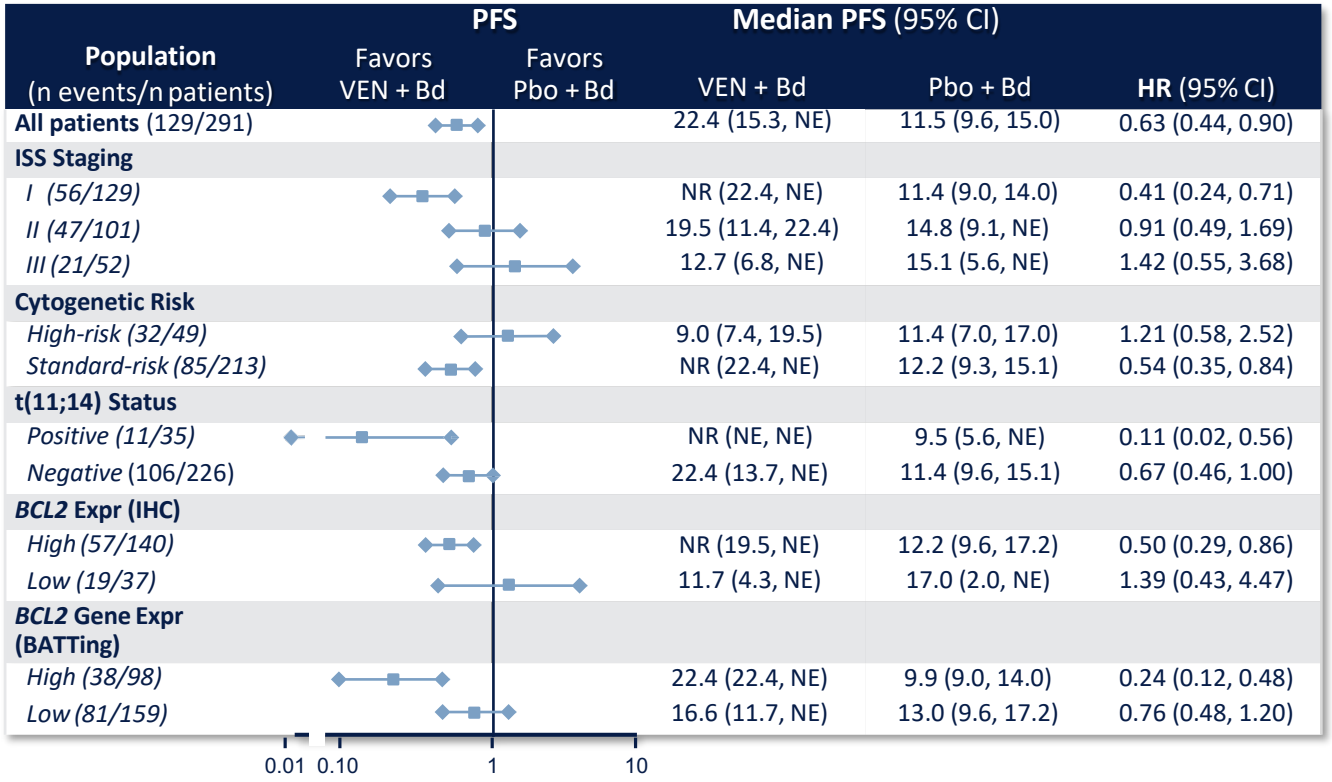
All Patients (ITT) (initial data cut-off: November 2018)



PFS	Ven+Bd	Pbo+Bd
Median, months	22.4	11.5
HR (95% CI)	0.630 (0.443, 0.897)	
P-value	0.010	

The BELLINI study met its primary endpoint with superior median PFS in the Ven+Bd arm versus Pbo+Bd

BELLINI (M14-031) – PFS Analysis in Key Subgroups



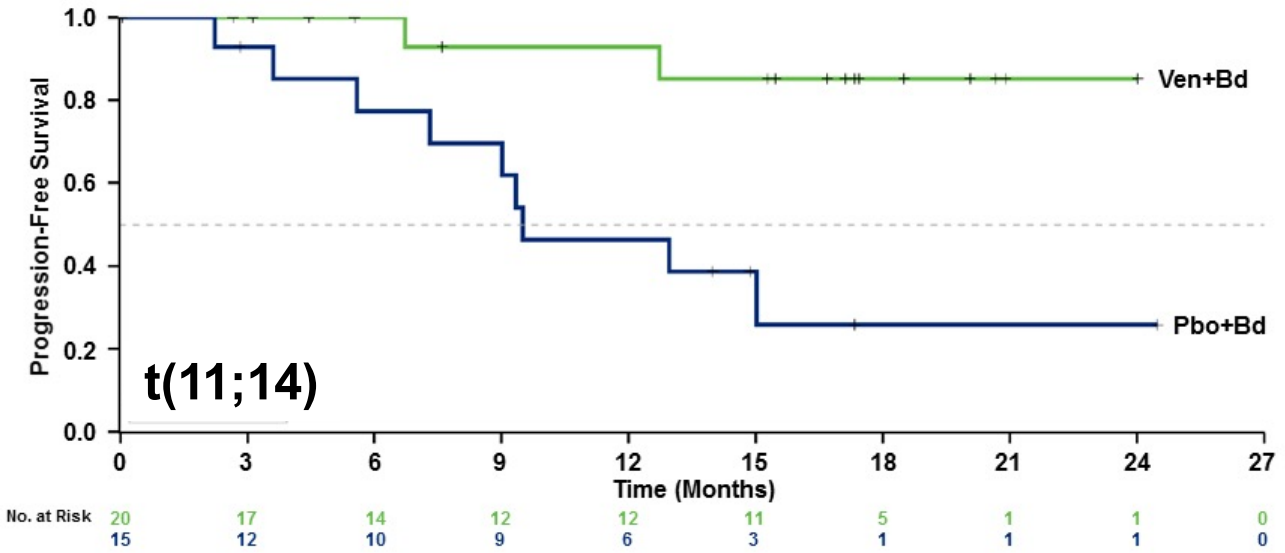
PFS was significantly prolonged in the VEN arm vs the Pbo arm in patients with t(11;14) or BCL2-high.

BATTing=Bootstrapping and Aggregating Thresholds from Trees. Bd=Bortezomib+Dexamethasone. CI=Confidence Interval.

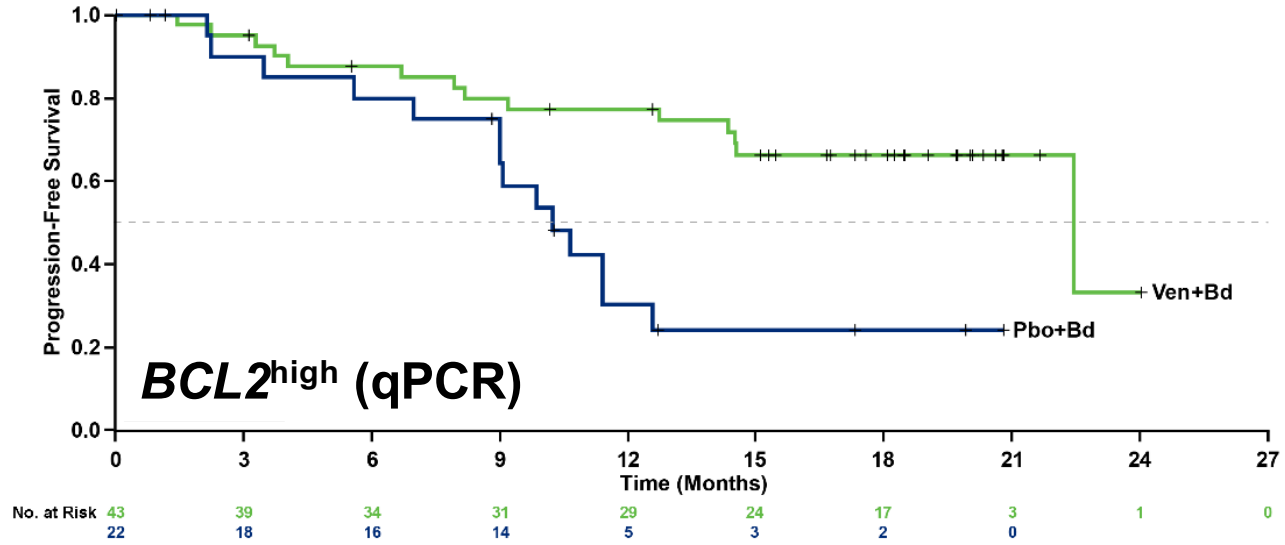
Expr=Expression. HR=Hazard Ratio. IHC=Immunohistochemistry. ISS=International Staging System. OS=Overall Survival. Pbo=Placebo. PFS=Progression-Free Survival. VEN=Venetoclax.

Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642.

Progression-Free Survival in Patients with t(11;14) or *BCL2*^{high} Expression



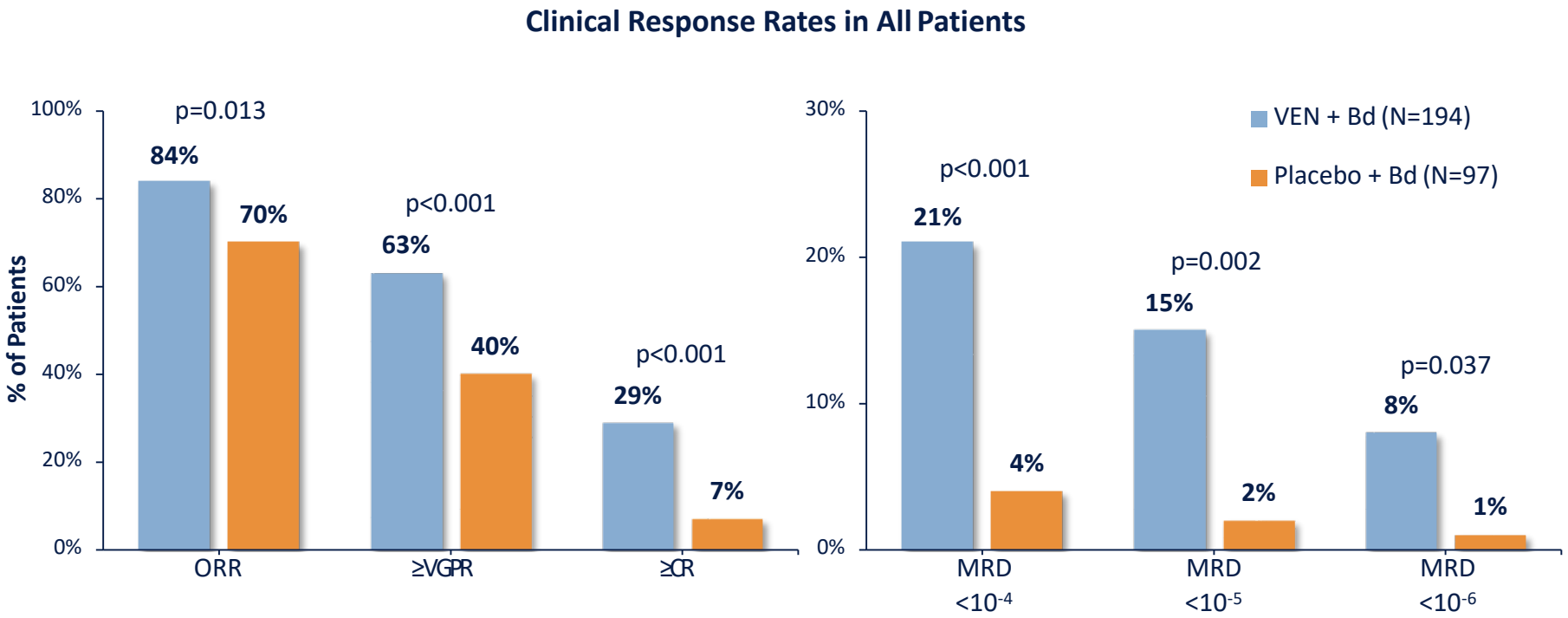
PFS: t(11;14)	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.5
HR (95% CI)	0.110 (0.022, 0.560)	
P-value	0.002	



PFS: *BCL2*^{high} (Upper quartile)	Ven+Bd	Pbo+Bd
Median, months	22.4	10.2
HR (95% CI)	0.341 (0.146, 0.560)	
P-value	0.011	

BELLINI (M14-031) – Clinical Response Rates

Data Cut-off: Sept 13, 2019

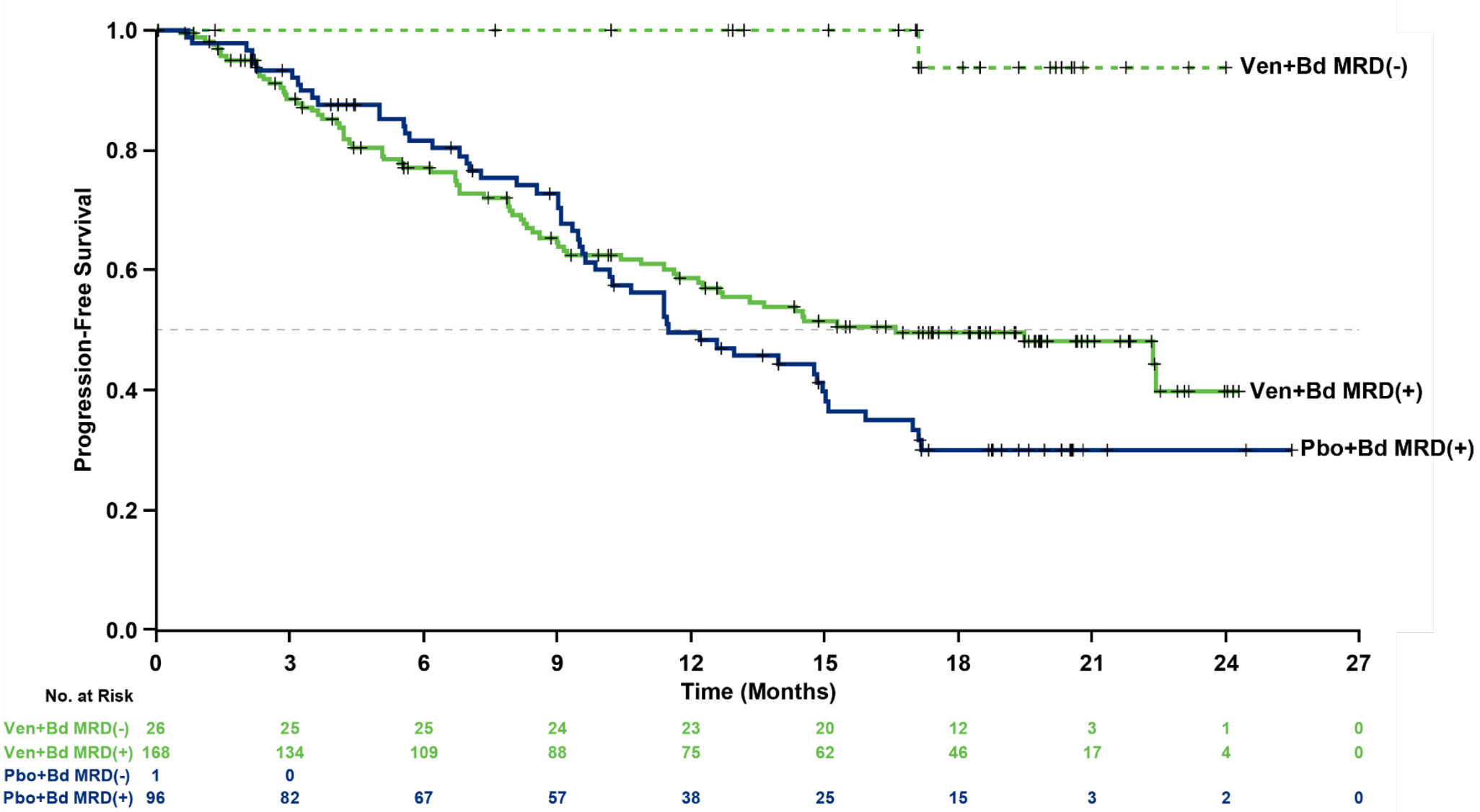


Overall response, ≥VGPR, ≥CR and MRD negativity rates were significantly higher with VEN + Bd.

Bd=Bortezomib+Dexamethasone. CR=Complete Response. MRD=Minimal Residual Disease. ORR=Overall Response Rate. VEN=Venetoclax. VGPR=Very Good Partial Response.

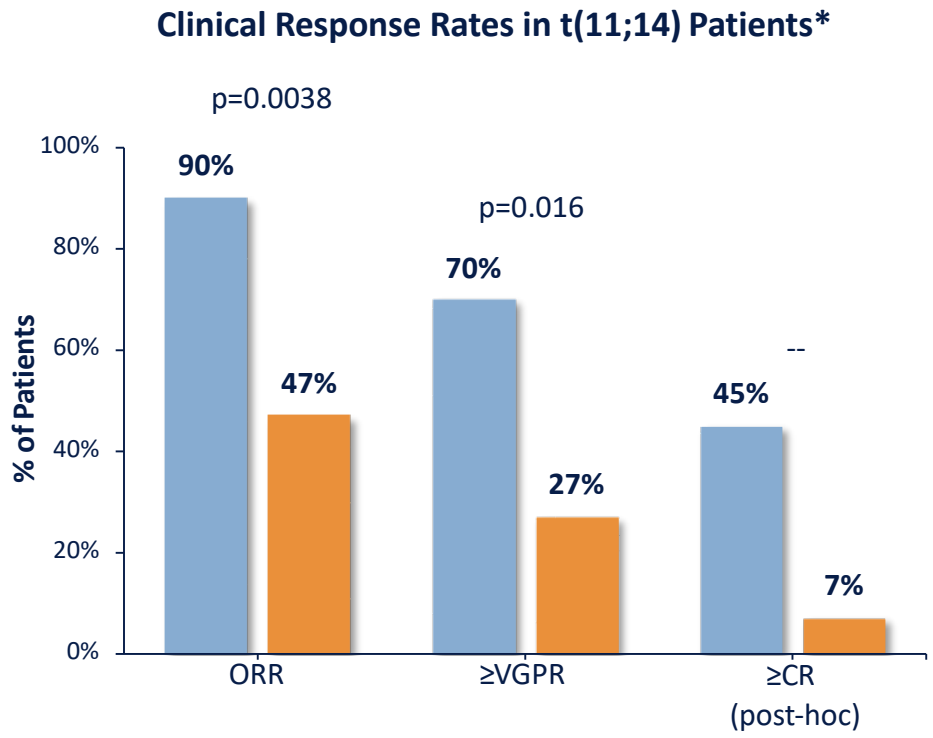
1. Kumar SK, et al. Poster #8509. ASCO20 Virtual Scientific Program. May 29-31, 2020. 2. Moreau P, et al. Poster #8547. ASCO20 Virtual Scientific Program. May 29-31, 2020.

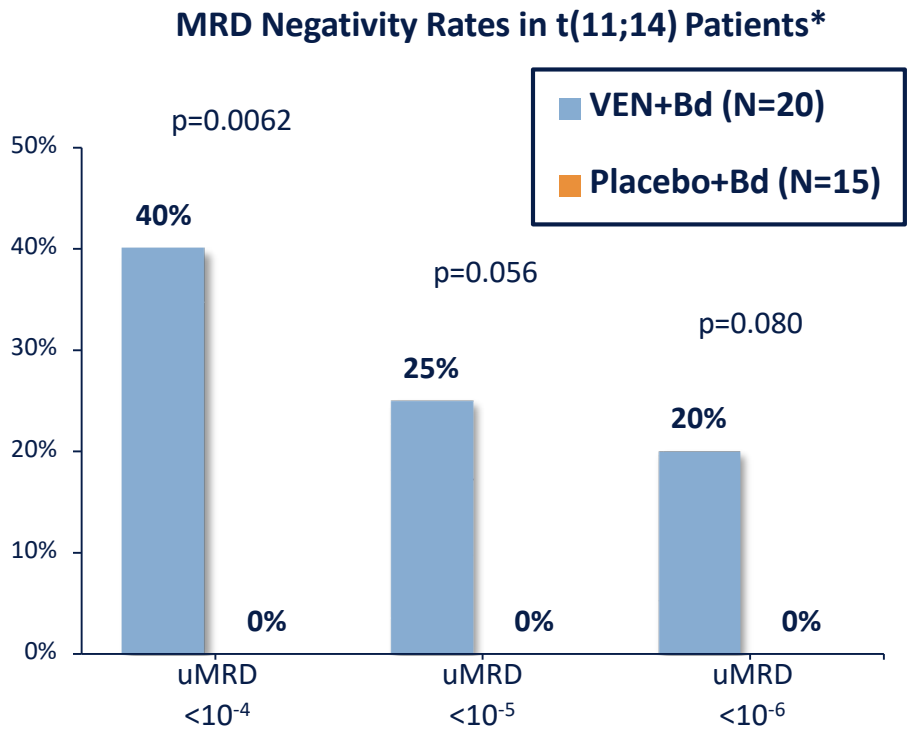
Progression-Free Survival by MRD (10^{-5}) Status



BELLINI (M14-031) – Clinical Response Rates in t(11;14) Patients

Data Cut-off: Nov 26, 2018





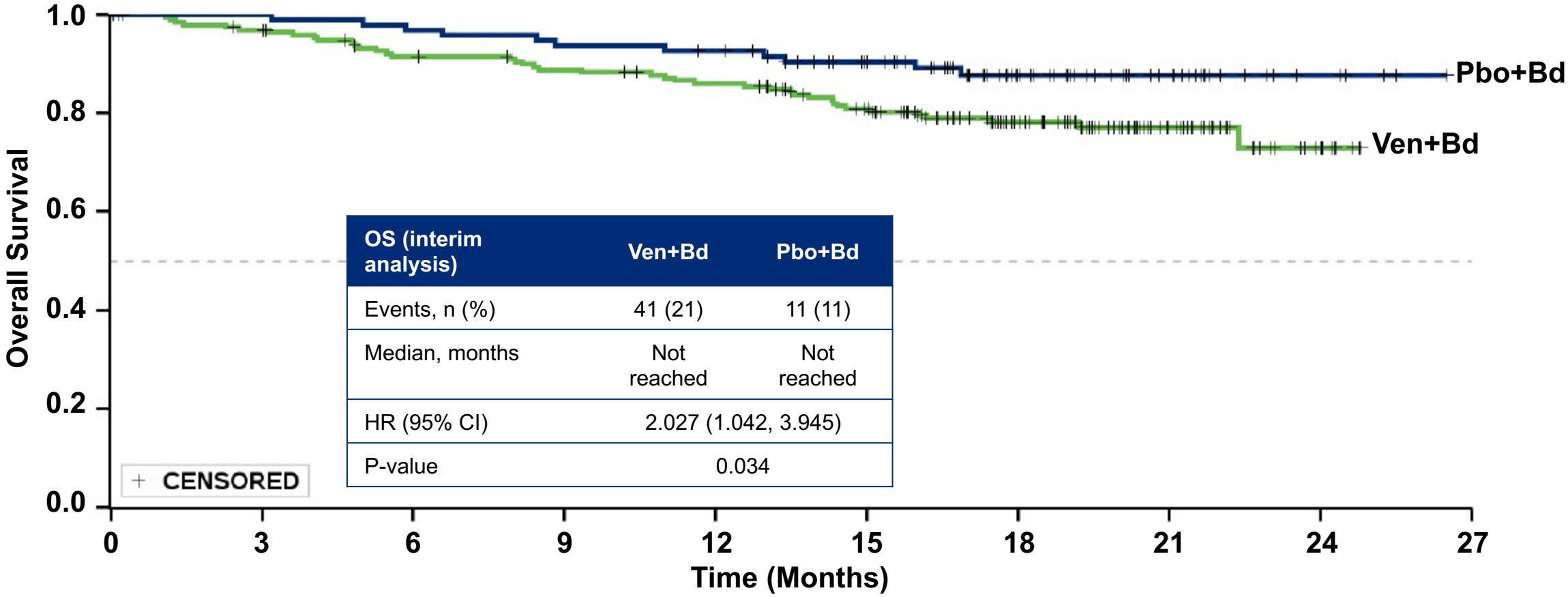
Patients with t(11;14) achieved higher rates of response, including MRD negativity with VEN compared with placebo

*Nominal p value without any adjustment for multiplicity. Not intended for statistical conclusions.
MRD assessment was performed by next-generation sequencing on bone marrow aspirate at time of CR/sCR and 6- and 12-months post-confirmation of CR/sCR. Bd=Bortezomib+Dexamethasone. CR=Complete Response. MRD=Minimal Residual Disease. ORR=Overall Response Rate. sCR=Stringent Complete Response. uMRD=Undetectable MRD. VEN=Venetoclax. VGPR=Very Good Partial Response.

Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642.

Overall Survival

All Patients (ITT)

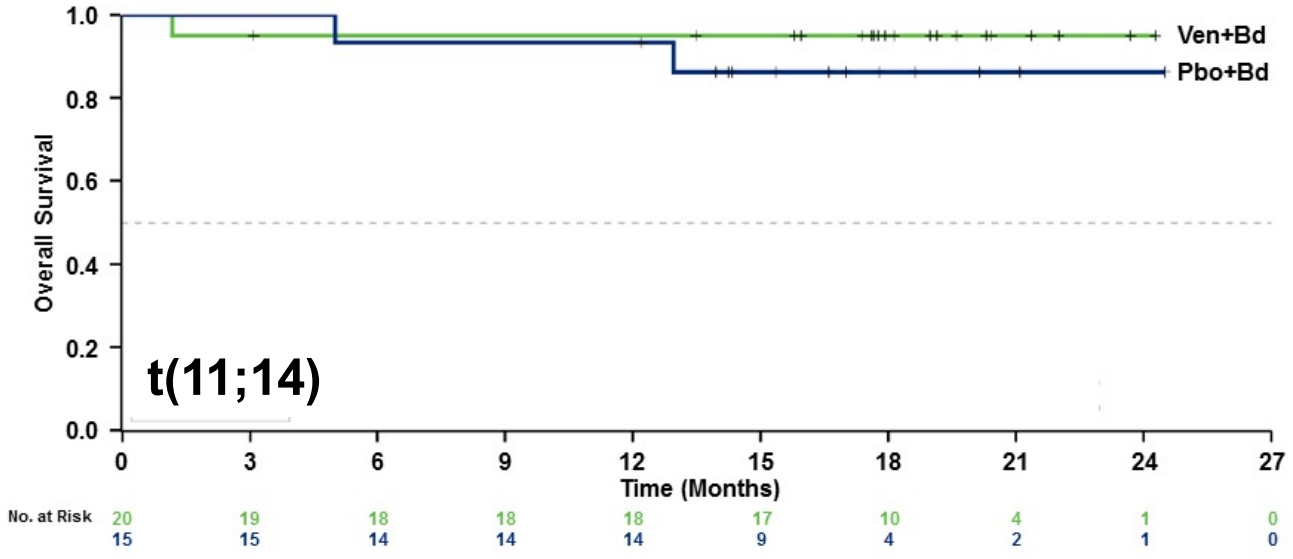


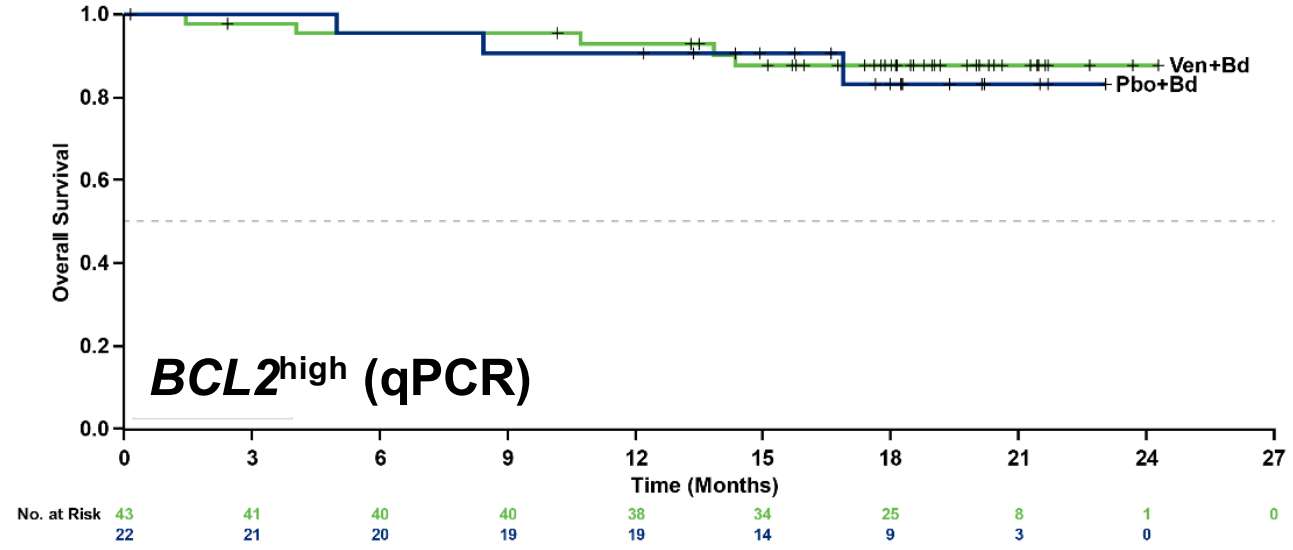
OS (interim analysis)	Ven+Bd	Pbo+Bd
Events, n (%)	41 (21)	11 (11)
Median, months	Not reached	Not reached
HR (95% CI)	2.027 (1.042, 3.945)	
P-value	0.034	

No. at Risk									
Ven+Bd	194	185	170	162	155	136	91	36	9	0
Pbo+Bd	97	95	92	89	87	74	44	20	5	0

A higher risk of death was observed in the Ven+Bd arm compared to Pbo+Bd at interim OS analysis

Overall Survival in Patients with t(11;14) or *BCL2*^{high} Expression



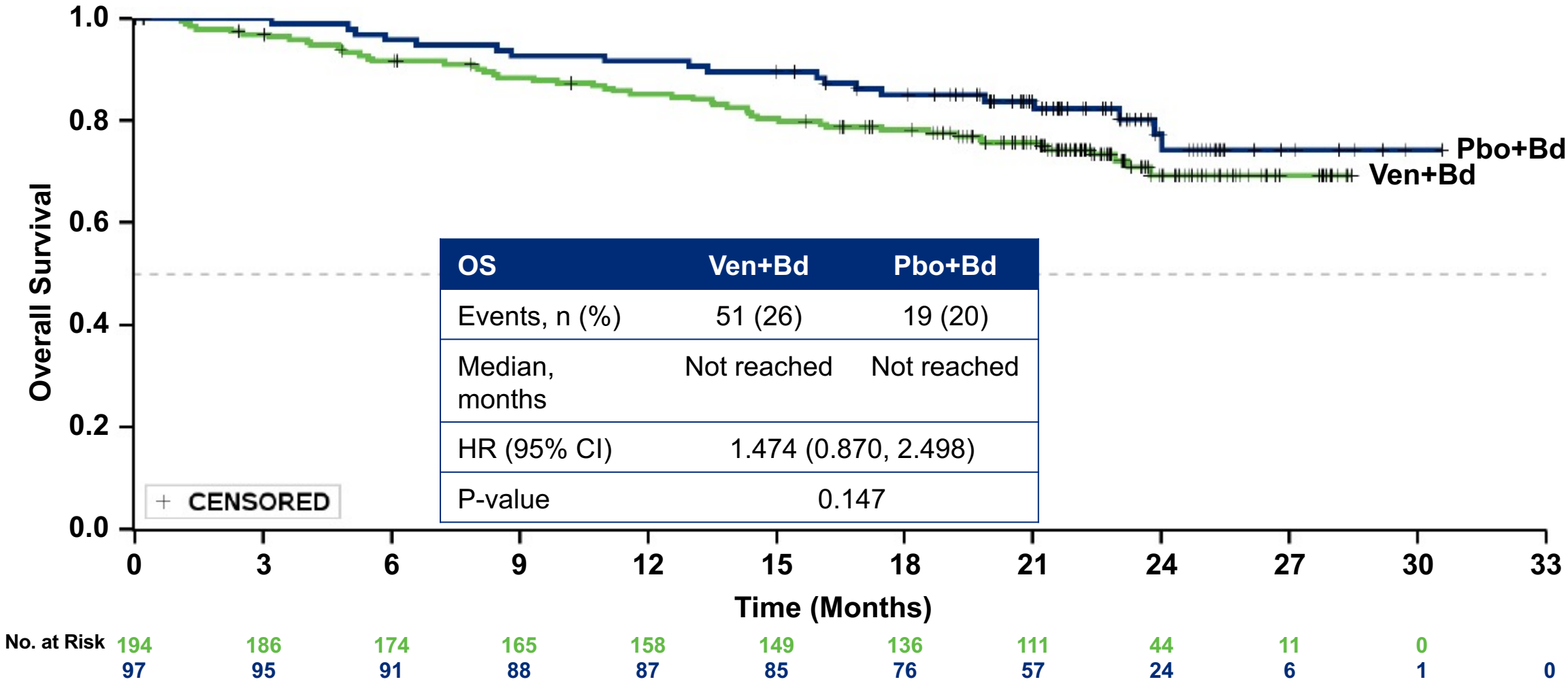


OS: t(11;14)	Ven+Bd	Pbo+Bd
Events, n (%)	1 (5)	2 (13)
Median, months	Not reached	Not reached
HR (95% CI)	0.343 (0.031, 3.842)	
P-value	0.363	

OS: *BCL2*^{high} (Upper quartile)	Ven+Bd	Pbo+Bd
Events, n (%)	5 (12)	3 (14)
Median, months	Not reached	Not reached
HR (95% CI)	1.114 (0.240, 5.179)	
P-value	0.890	

Overall Survival

All Patients (ITT), Updated 18 Mar 2019



OS	Ven+Bd	Pbo+Bd
Events, n (%)	51 (26)	19 (20)
Median, months	Not reached	Not reached
HR (95% CI)	1.474 (0.870, 2.498)	
P-value	0.147	

Summary of Cause of Death

Safety Population (Only patients who received treatment)	Ven+Bd (N = 193) n (%)	Pbo+Bd (N = 96) n (%)
All deaths	**40 (21)**	**11 (11)**
Infection	14 (7)	2 (2)
Progressive disease	17 (9)	8 (8)
Other*	9 (5)	1 (1)
Deaths occurring within 30 days of last dose	**13 (7)**	**1 (1)**
Infection	8 (4)	0
Progressive disease	2 (1)	1 (1)
Other	3 (2)	0
Deaths occurring after 30 days of last dose	**27 (14)**	**10 (10)**
Infection	6 (3)	2 (2)
Progressive disease	15 (8)	7 (7)
Other	6 (3)	1 (1)

*Includes: cardiac/cardiopulmonary arrest (n = 4), congestive heart failure (n = 1), pancreatic cancer (n = 1), and unknown cause (n = 4).

More deaths were observed in the Ven+Bd arm, with a more prominent imbalance in the treatment-emergent deaths attributed to infectious causes

BELLINI (M14-031) – Serious Adverse Events

Serious TEAEs, n (%)	VEN+Bd (N=193)	Placebo+Bd (N=96)
Any serious TEAE	93 (48)	48 (50)
Pneumonia	27 (14)	12 (13)
Sepsis	6 (3)	0 (0)
Orthostatic hypotension	5 (3)	2 (2)
Anemia	4 (2)	1 (1)
Lung infection	4 (2)	1 (1)
Syncope	4 (2)	0 (0)
Acute kidney failure	3 (2)	3 (3)
Diarrhea	2 (1)	2 (2)
Femur fracture	2 (1)	3 (3)
Urinary tract infection	2 (1)	2 (2)
Chronic obstructive pulmonary disease	1 (1)	2 (2)
Ileus	1 (1)	2 (2)
Influenza	3 (2)	4 (4)
Ankle fracture	0 (0)	2 (2)
Back pain	0 (0)	2 (2)
Cataract	0 (0)	3 (3)

Serious treatment-emergent adverse events with a suspected relationship to venetoclax or placebo occurred in:

32 (17%) patients in the venetoclax group and

10 (10%) patients in the placebo group,

with the most common in both groups being pneumonia (10 [5%] and 4 [4%]).

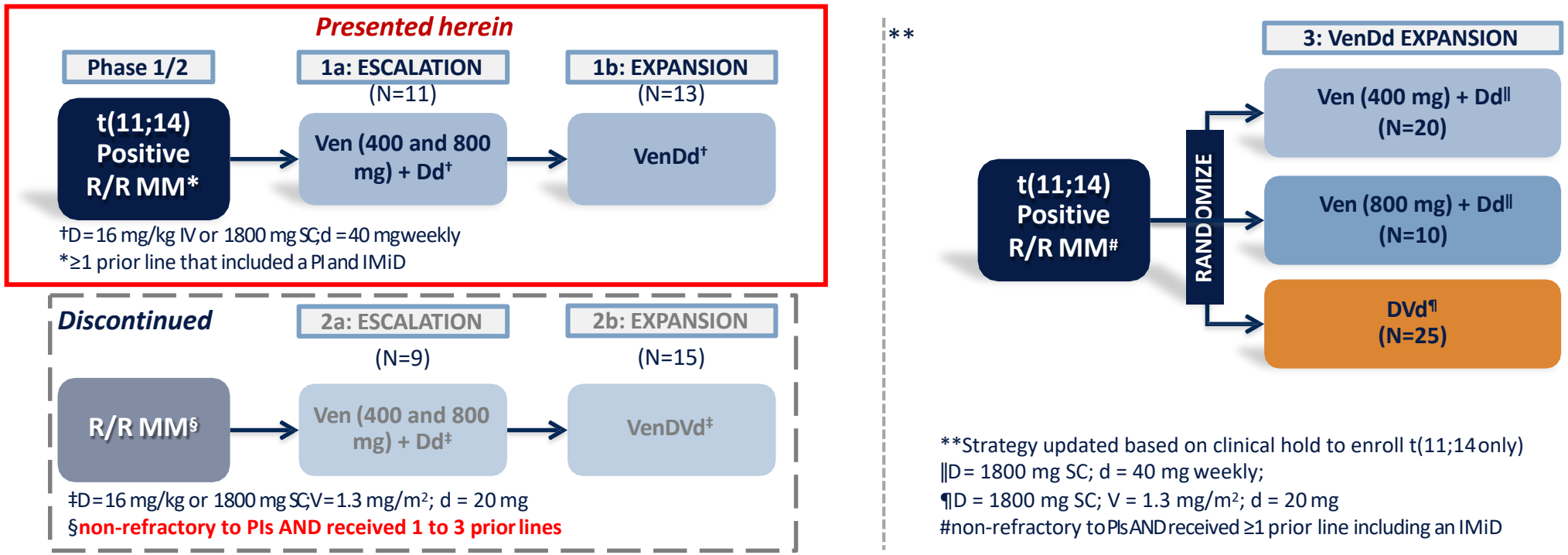
Bd=Bortezomib+Dexamethasone. TEAE=Treatment-Emergent Adverse Event. VEN=Venetoclax. Kumar SK, et al. Lancet Oncol. 2020;21(12):1630-1642.

Final OS results (cut-off: March 2021) (Kumar S et al, ASH 2021, oral presentation)

- Median f up: 45.6 months
- **Median PFS** Ven vs Pbo(all patients): 23.4 mos vs 11.4 mos, **HR 0.58**; in pts with t(11;14): 36.8 mos vs 9.3 mos, **HR 0.12**
- **Median OS** NR in either arms, **HR** Ven vs Pbo in all patients **1.19**, in pts with t(11;14) **0.61**
- SAE unchanged with respect to previous analysis

Venetoclax further clinical development in RRMM

M15-654 – Study Design and Endpoints



KEY INCLUSION CRITERIA

- ECOG PS≤2
- R/R MM as described in schema above

KEY EXCLUSION CRITERIA

- Prior venetoclax or other BCL-2 inhibitor (Parts 1, 2, 3)
- Prior daratumumab or other anti-CD38 therapy (Parts 1, 2)

OBJECTIVES

Primary: ***Cohort 1 and 2 - Safety and preliminary efficacy***

Cohort 3 - Safety and preliminary efficacy (response rates, PFS, TTP, TTR, DOR, OS)

Secondary: ***MRD in BM by NGS, PK***

BM=Bone Marrow. d=dexamethasone. D=Daratumumab. DOR=Duration of Response. ECOG PS=Eastern Cooperative Oncology Group Performance Score. IMiD=Immunomodulatory Agent. IV=Intravenous. MM=Multiple Myeloma. MRD=Minimal Residual Disease. NGS=Next Generation Sequencing. OS=Overall Survival. PFS=Progression-Free Survival. PI=Proteasome Inhibitor. PK=Pharmacokinetics. R/R=Relapsed/Refractory. SC=Subcutaneous. TTP=Time to Progression. TTR=Time to Response. V=Bortezomib. Ven=Venetoclax.

ClinicalTrials.gov. NCT03314181. https://clinicaltrials.gov/ct2/show/NCT03314181. Accessed October 2019.

Updated at ASH 2021, oral presentation, Kaufman et al

M15-654 – Patient Characteristics

Characteristic	Part 1 t(11;14) VenDd (N=24)	Part 2 VenDVd (N=24)
Median age, years (range)	63 (51–76)	64 (41–80)
ISS stage, n (%)		
I	7 (29)	9 (38)
II/III	14 (58)	14 (58)
Not evaluable/unknown	3 (13)	1 (4)
Cytogenetic abnormalities*, n (%)		
t(11;14)	24 (100)	6 (25)
t(4;14)	0	0
t(14;16)	0	1 (4)
del(17p)	1 (4)	3 (13)
1q gain (≥3 copoies)	9 (38)	1 (4)
Hyperdiploid†	3 (13)	2 (8)
High-risk‡	1 (4)	4 (17)
No. of prior lines of therapy, median (range)	**2.5 (1–8)**	1 (1–3)
Stem cell transplant, n (%)	15 (63)	12 (50)
Prior PI/refractory, n (%)	24 (100) / 11 (46)	22 (92) / 0
Prior IMiD/refractory, n (%)	24 (100) / 17 (71)	17 (71) / 8 (33)
Prior PI + IMiD/refractory, n (%)	24 (100) / 10 (42)	15 (63) / 0

Data cutoff: February 14, 2020.

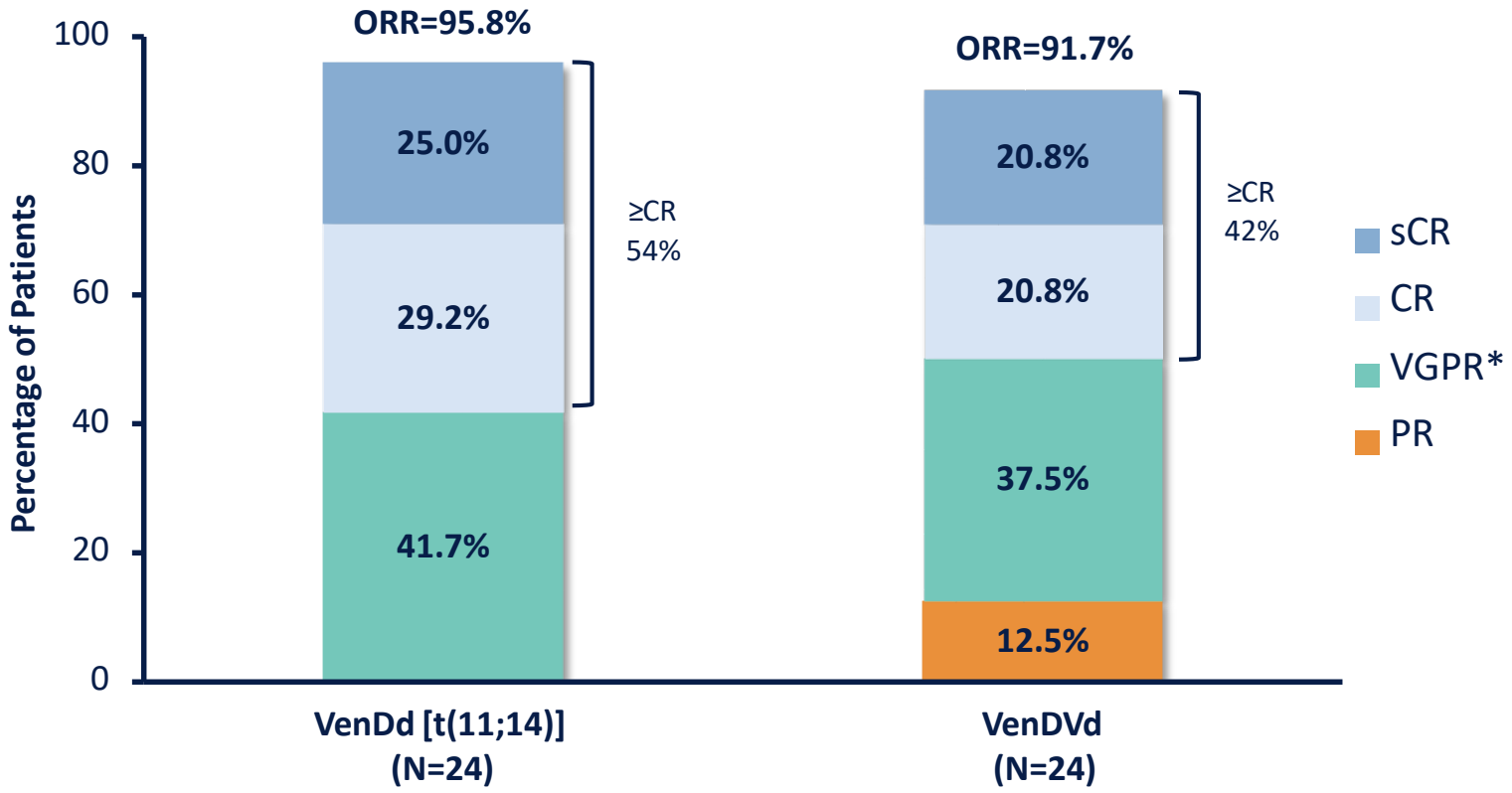
*Cytogenetic assessments were performed centrally by FISH. †Gain in chromosome 5, 9, or 15.

‡High-risk cytogenetics was defined as the presence of t(4;14), t(14;16), or del(17p).

d=dexamethasone. D=Daratumumab. FISH=Fluorescence In Situ Hybridization. IMiD=Immunomodulatory Drug. ISS=International Staging System. PI=Proteasome Inhibitor. V=Bortezomib. Ven=Venetoclax.

Kaufman JL, et al. Poster #8511. ASCO20 Virtual Scientific Program. May 29-31, 2020.

M15-654 – Overall Confirmed Responses



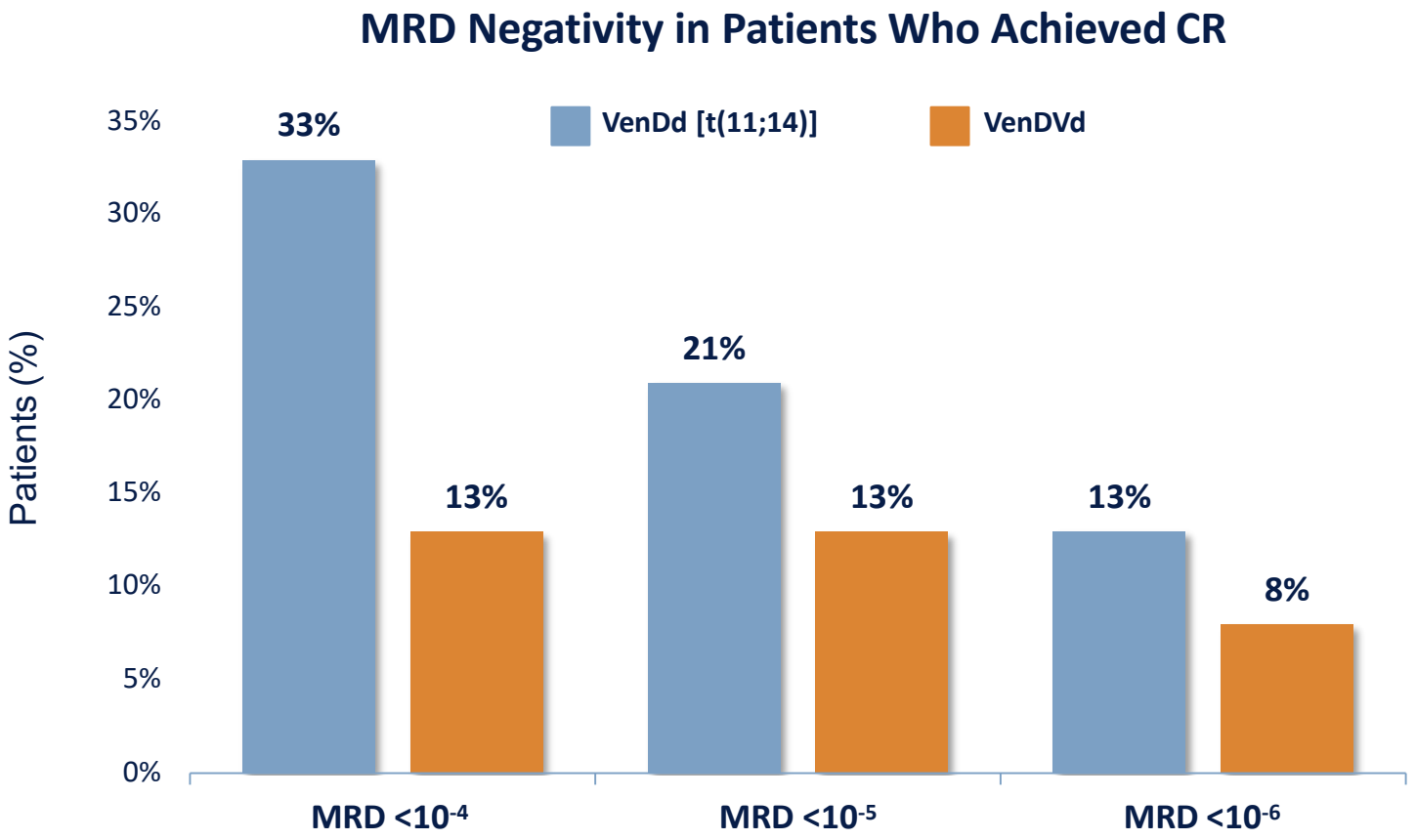
Data cutoff: February 14, 2020.

*One patient discontinued after 2 cycles of therapy prior to disease assessment and is counted as non-responder (unconfirmed VGPR).

CR=Complete Response. d=dexamethasone. D=Daratumumab. ORR=Objective Response Rate. PR=Partial Response. sCR=Stringent Complete Response. V=Bortezomib. Ven=Venetoclax. VGPR=Very Good Partial Response.

Kaufman JL, et al. Poster #8511. ASCO20 Virtual Scientific Program. May 29-31, 2020.

M15-654 – MRD Negativity



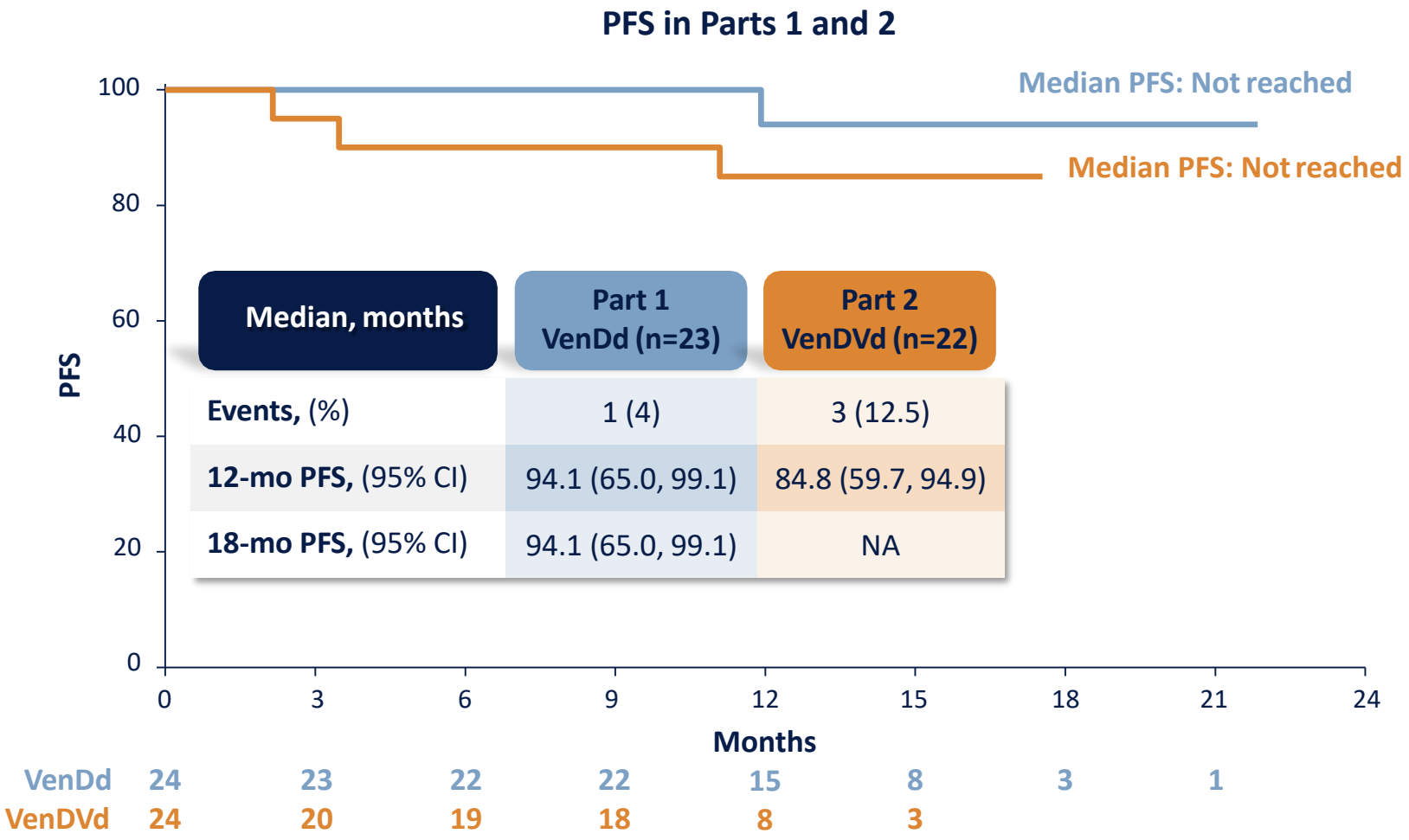
- 11 of 13 patients who achieved ≥CR in the VenDd arm, and 4 of 10 patients who achieved ≥CR in the VenDVd arm were evaluated for MRD

Data cutoff: February 14, 2020.

CR=Complete Response. d=dexamethasone. D=Daratumumab. MRD=Minimal Residual Disease. V=Bortezomib. Ven=Venetoclax.

Kaufman JL, et al. Poster #8511. ASCO20 Virtual Scientific Program. May 29-31, 2020.

M15-654 – PFS in Parts 1 and 2

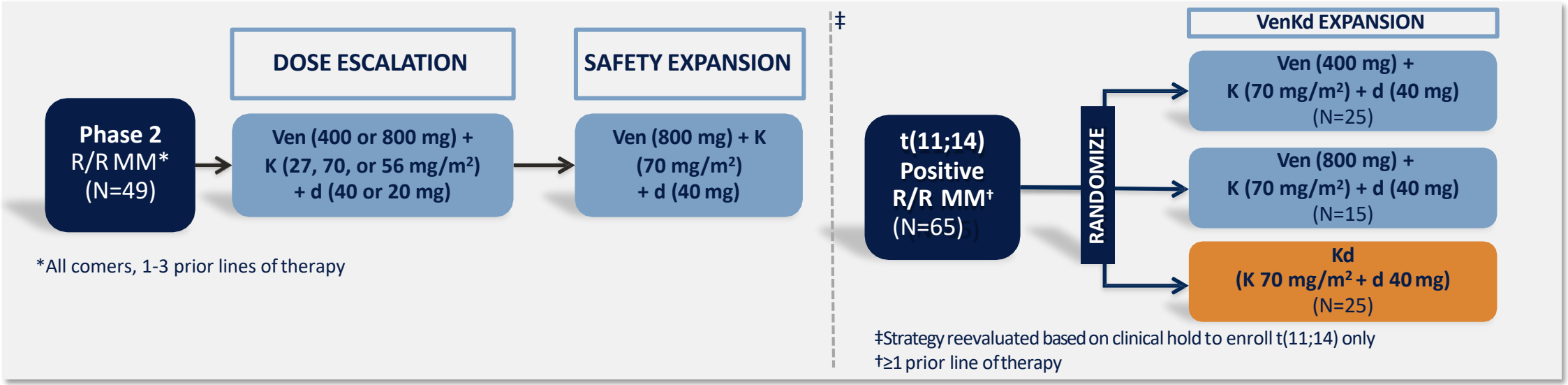


Data cutoff: February 14, 2020.

d=dexamethasone. D=Daratumumab. NA=Not Applicable. NE=Not Estimable. NR=Not Reached. PFS=Progression-Free Survival. V=Bortezomib. Ven=Venetoclax.

Kaufman JL, et al. Poster #8511. ASCO20 Virtual Scientific Program. May 29-31, 2020.

M15-538 – Study Design and Endpoints



INCLUSION CRITERIA

- R/R MM
- ECOG PS ≤2
- Measurable disease
- Adequate organ function

EXCLUSION CRITERIA

- Prior treatment with carfilzomib
- Grade 3 or 4 peripheral neuropathy
- Significant cardiovascular disease

OBJECTIVES

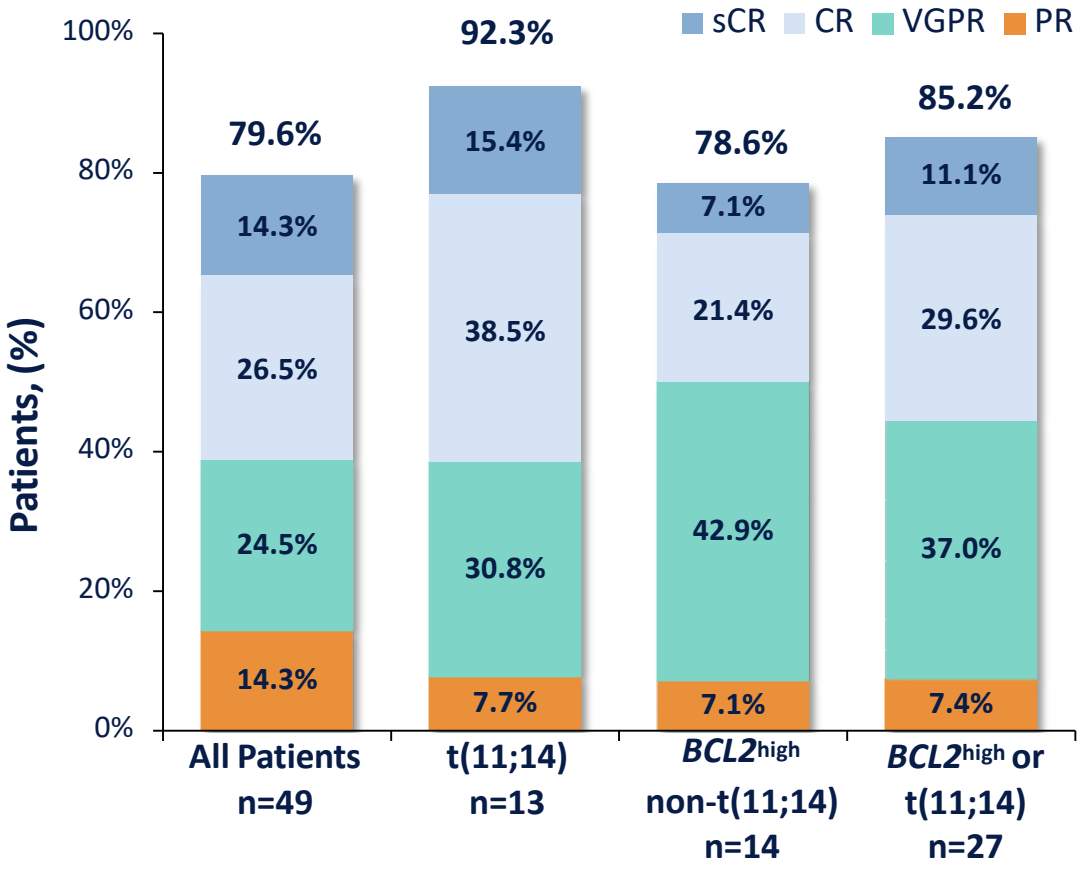
Primary: ***Safety***

Secondary: ***Efficacy (ORR, ≥VGPR, PFS, TTP, DOR, MRD in BM by NGS), PK, correlative biomarkers (BCL-2)***

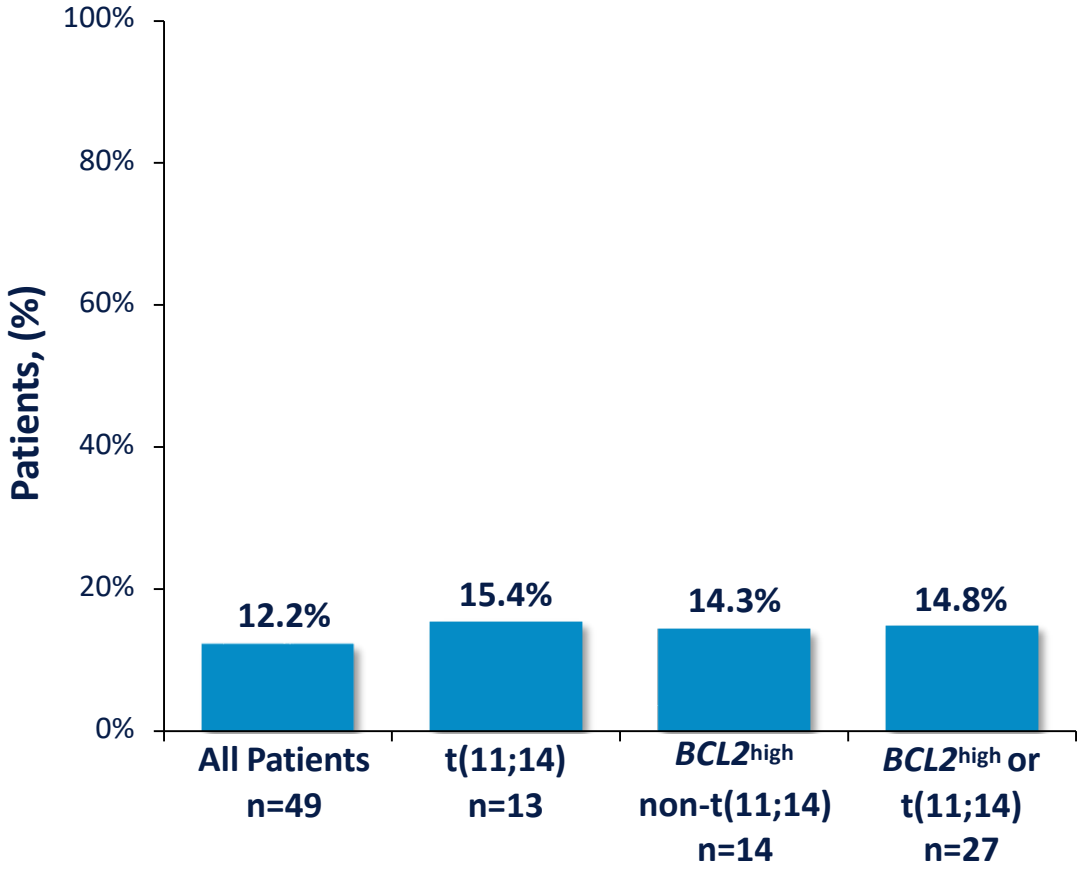
BM=Bone Marrow. d=Dexamethasone. DOR=Duration of Response. ECOG PS=Eastern Cooperative Oncology Group Performance Score. K=Carfilzomib. MM=Multiple Myeloma. MRD=Minimal Residual Disease. NGS=Next Generation Sequencing. ORR=Overall Response Rate. PK=Pharmacokinetics. PFS=Progression Free Survival. R/R=Relapsed/Refractory. TTP=Time to Progression. Ven=Venetoclax. VGPR=Very Good Partial Response. 1. Costa LJ, et al. Poster #PS1375. 24th EHA Congress; June 13-16, 2019; Amsterdam. 2. Clinicaltrials.gov. NCT02899052. https://clinicaltrials.gov/ct2/show/NCT02899052. Accessed Jan 2021.

Venetoclax Evidence Generation: M15-538 – Response Rates in Overall Population/ Biomarker Sub-Groups

Response rates



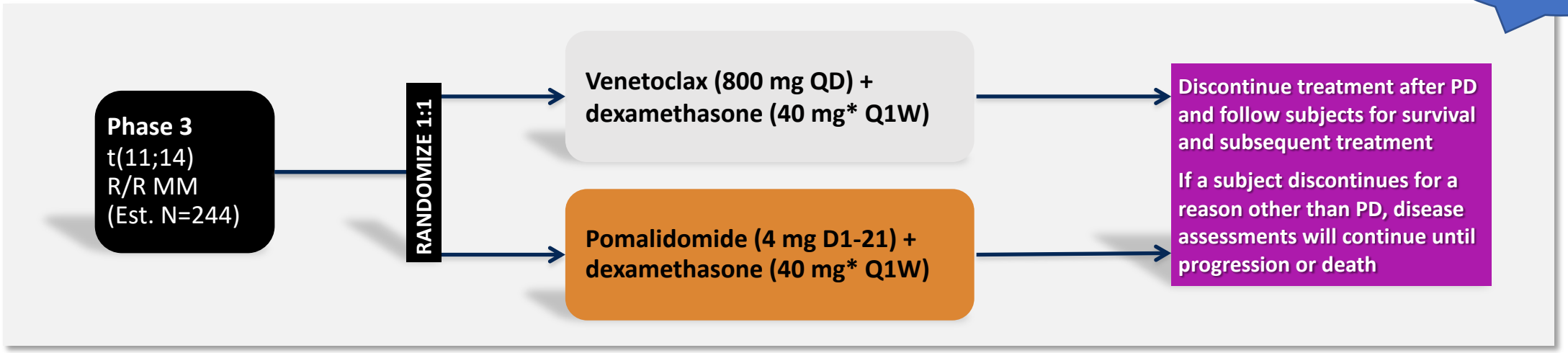
MRD negative (<10^{-5}) rates



Responses assessed by International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (Kumar et al. *Lancet*, 2016).
High *BCL2* gene expression status defined by qPCR(2^{-DCt}≥.0.323) based on the BELLINI study (Kumar et al. *Lancet Oncology, 2020*).
CR=Complete Response. MRD=Minimal Residual Disease. ORR=Overall Response Rate. sCR=Stringent CR. PR=Partial Response. VGPR=Very good or better Partial Response.
Costa JL, et al. Poster #2251. ASH 62nd Annual Meeting; Dec 5-8, 2020; Virtual.

CANOVA (M13-494) – Study Design and Endpoints

Enrollment on going



INCLUSION CRITERIA

- t(11;14)-positive multiple myeloma
- ≥ 2 prior lines of therapy
- ECOG PS ≤2
- Documented disease progression on or within 60 days after completion of their last therapy
- Received at least 2 cycles of both lenalidomide and a proteasome inhibitor, alone or together
- Refractory to lenalidomide

EXCLUSION CRITERIA

- Prior venetoclax or pomalidomide

OBJECTIVES

Primary: ***PFS***

Secondary: ***Response rates (ORR, VGPR or better), OS, DOR, TTP, TTR, MRD, PK, Safety, PROs***

*20mg if patient age≥75.

DOR=Duration of Response. ECOG PS=Eastern Cooperative Oncology Group Performance Score. MM=Multiple Myeloma. MRD=Minimal Residual Disease. ORR=Overall Response Rate. OS=Overall Survival. PD=Progressive Disease. PFS=Progression-Free Survival. PK=Pharmacokinetics. PRO=Patient Reported Outcome. Q1W=Once Weekly. QD=Daily. R/R=Relapsed/Refractory. TTP=Time to Progression. TTR=Time To Response. VGPR=Very Good Partial Response.

1. ClinicalTrials.gov. NCT03539744. https://clinicaltrials.gov/ct2/show/NCT03539744. Accessed Jan 2021. 2. Mateos M, et al. Poster #2319. ASH 62nd Annual Meeting; Dec 5-8, 2020; Virtual.

Global treatment patterns and outcomes among patients with t(4;14) in MM

- **IMWG retrospective study** aimed at identifying the outcomes of MM patients carrying t(11;14) diagnosed between 2005-2018 who received at least 1 LOT
- **1048 patients** collected from US, Japan/Pacific Asia, Canada and Western Europe
- The choice of therapies mirrors the treatment pattern for the general population
- I line PFS and OS mirrors what is seen for general MM population (US: NR and 123 months)
- II and III line PFS and OS (US): 62 and 92 mos, 22 and 59 mos, respectively
- These estimates provide important benchmark for comparison of targeted therapies

Kumar S et al, ASH 2021, poster presentation

Conclusion

- The addition of Venetoclax to one of the standard backbones, bortezomib-dex, significantly improved PFS, ORR, ≥VGPR, and MRD negativity rates in patients with RRMM; other combinations seem possible
- An increase in deaths was observed with Ven+Bd, occurring early on during treatment, commonly due to infection and in the context of PD
- Patients with t(11;14) or *BCL2*^{high} are those with the more consistent clinical benefit when treated with Venetoclax alone or in combination, and the benefit-risk profile appears to be favorable in these MM subsets
- The current development of venetoclax is to focus on t(11;14) and *BCL2*^{high} MM patients; several combinations are tested
- Venetoclax plays a role in PCL and AL amyloidosis, were the incidence of t(11;14) is higher; studies are on-going
- Venetoclax is currently one of the few “targeted” therapies for MM