DREAMM-7 update: subgroup analyses from a phase 3 trial of belantamab mafodotin + bortezomib and dexamethasone vs daratumumab, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma

Key takeaways

In the phase 3 DREAMM-7 trial, BVd led to a statistically significant and clinically meaningful improvement in PFS vs DVd (HR, 0.41; *P*<.00001) and showed a strong, early trend toward improved OS (HR, 0.57)

- In poor prognostic subgroups, which included patients with disease refractory to lenalidomide and those with high-risk cytogenetic abnormalities, BVd was associated with more pronounced benefits vs DVd, including:
  - Clinically meaningful risk reduction in PFS
  - Greater between-arm differences in ORR, depth of response, and MRD-negative status
  - Increased response durability
- The safety profile of BVd in these subgroups was consistent with that in the overall trial population and with the known safety profile of belamaf and the constituent therapies

Background

Triplet and quadruplet therapies incorporating PIs, immunomodulatory drugs, and anti-CD38 antibodies are the SOC in NDMM, leading to an increased number of patients exposed/refractory to these agents at first relapse[1-4]

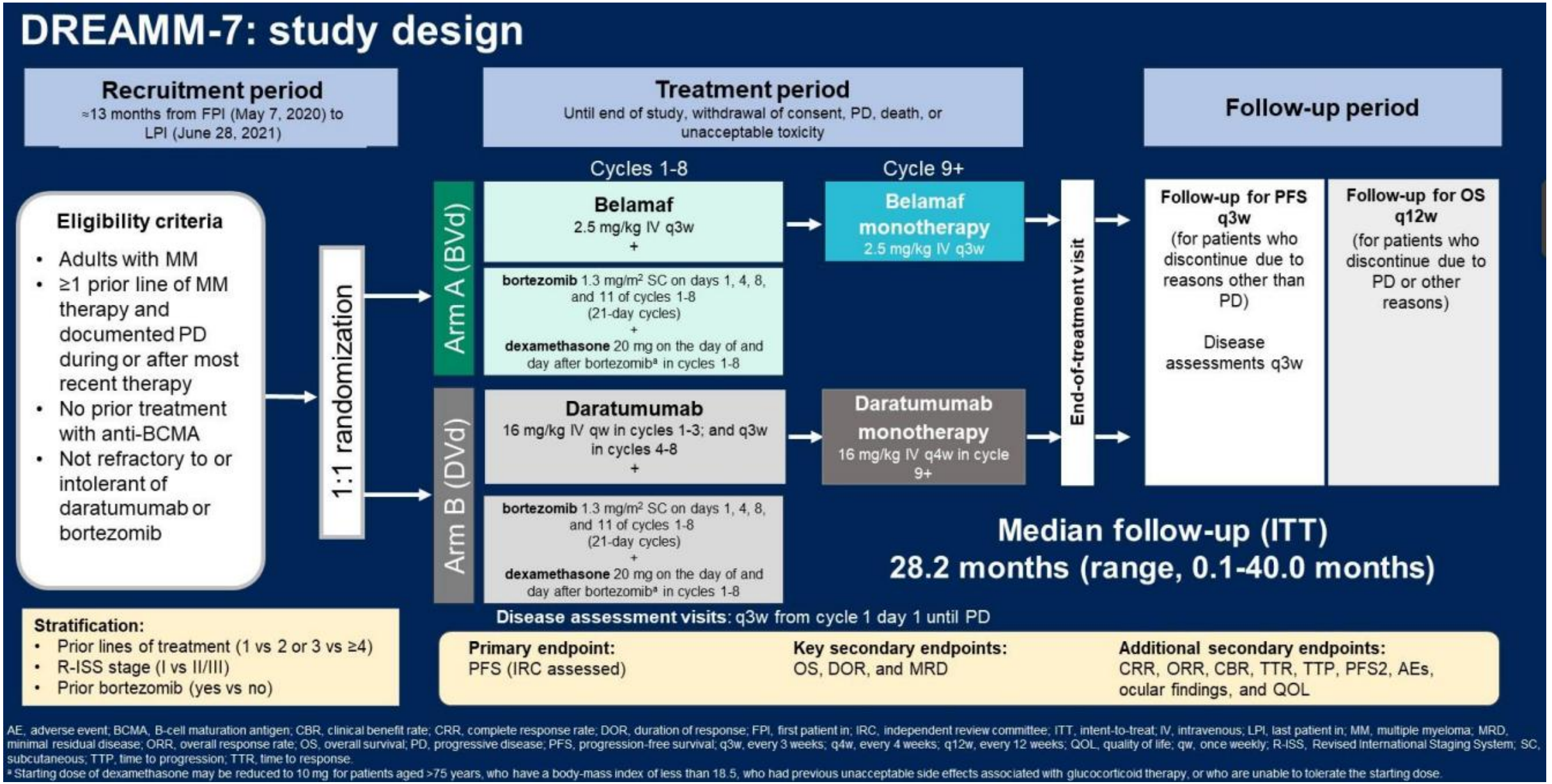
- Hence the need for combinations incorporating novel MOAs for patients with RRMM at the first and subsequent relapse

Belantamab mafodotin (belamaf) is a humanized, afucosylated, anti-BCMA ADC that induces immune-independent ADC-mediated apoptosis, immune-dependent enhancement of ADCC and ADCP, and release of markers characteristic of ICD leading to an adaptive immune response[5-7]

The presence of certain features, including disease refractory to prior lenalidomide and the presence of ≥1 high-risk cytogenetic abnormality, is associated with worse prognosis and response to treatment in patients with RRMM; this underscores the high medical need in these patients[4,8,9]

Here, we evaluated the efficacy and safety of BVd and DVd in patient subgroups from the DREAMM-7 trial based on lenalidomide refractory status and cytogenetic risk

DREAMM-7: study design

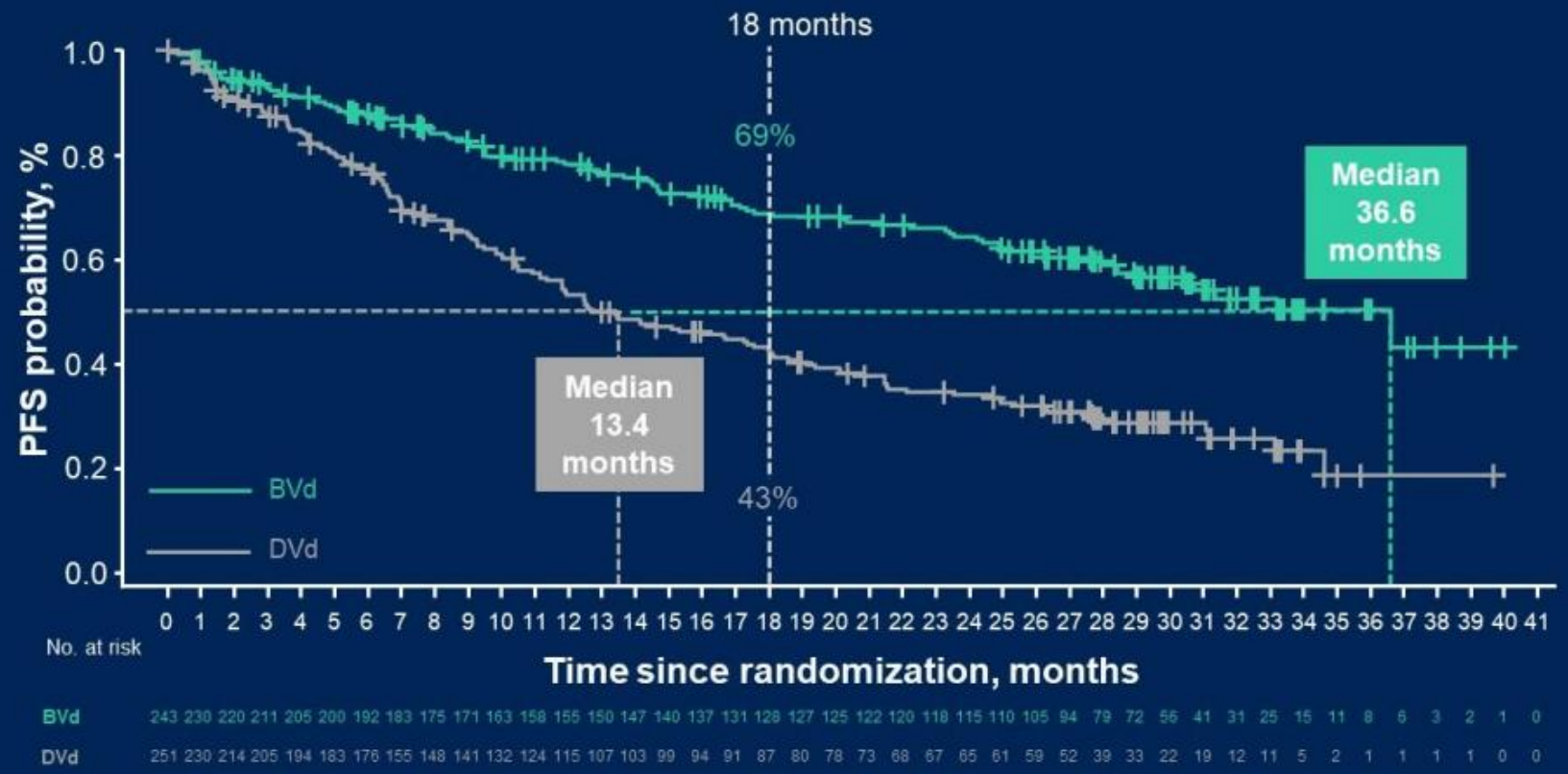


AE, adverse event; BCMA, B-cell maturation antigen; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; FPI, first patient in; IRC, independent review committee; ITT, intent-to-treat; IV, intravenous; LPI, last patient in; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; q4w, every 4 weeks; q12w, every 12 weeks; QOL, quality of life; qw, once weekly; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.

[a] Starting dose of dexamethasone may be reduced to 10 mg for patients aged >75 years, who have a body-mass index of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose.

DREAMM-7: ITT population

BVd led to a significant increase in PFS vs DVd



PFS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	91 (37)	158 (63)
PFS, median (95% CI), mo[b]	36.6 (28.4-NR)	13.4 (11.1-17.5)
HR (95% CI)[c]	0.41 (0.31-0.53)	
P value[d]	<.00001	

BVd demonstrated a statistically significant and clinically meaningful PFS benefit, with a median PFS that was 23 months longer than that with DVd (36.6 vs 13.4 months)

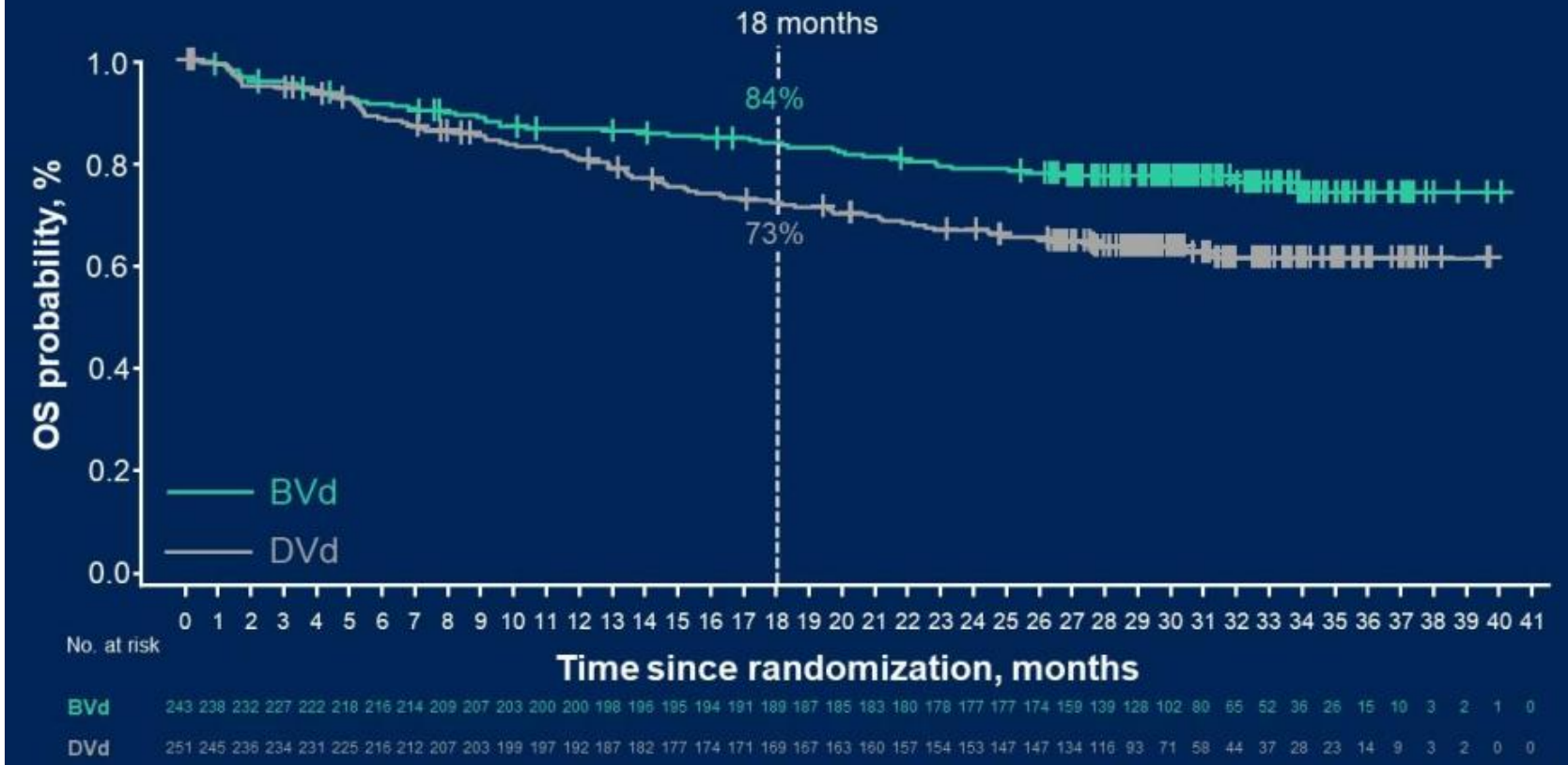
Median follow-up: 28.2 months (range, 0.1-40.0 months)

HR, hazard ratio; ITT, intent to treat; NR, not reached; PFS, progression-free survival; R-ISS, Revised International Staging System.

[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III), with a covariate of treatment. [d] *P* value from 1-sided stratified log-rank test.

DREAMM-7: ITT population

Early OS trend favoring BVd vs DVd



OS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	54 (22)	87 (35)
OS, median (95% CI), mo[b]	NR	NR
HR (95% CI)[c]	0.57 (0.4-0.8)	
P value[d]	.00049[e]	

OS showed an early, strong, and clinically meaningful trend favoring the BVd arm; additional OS follow-up is ongoing

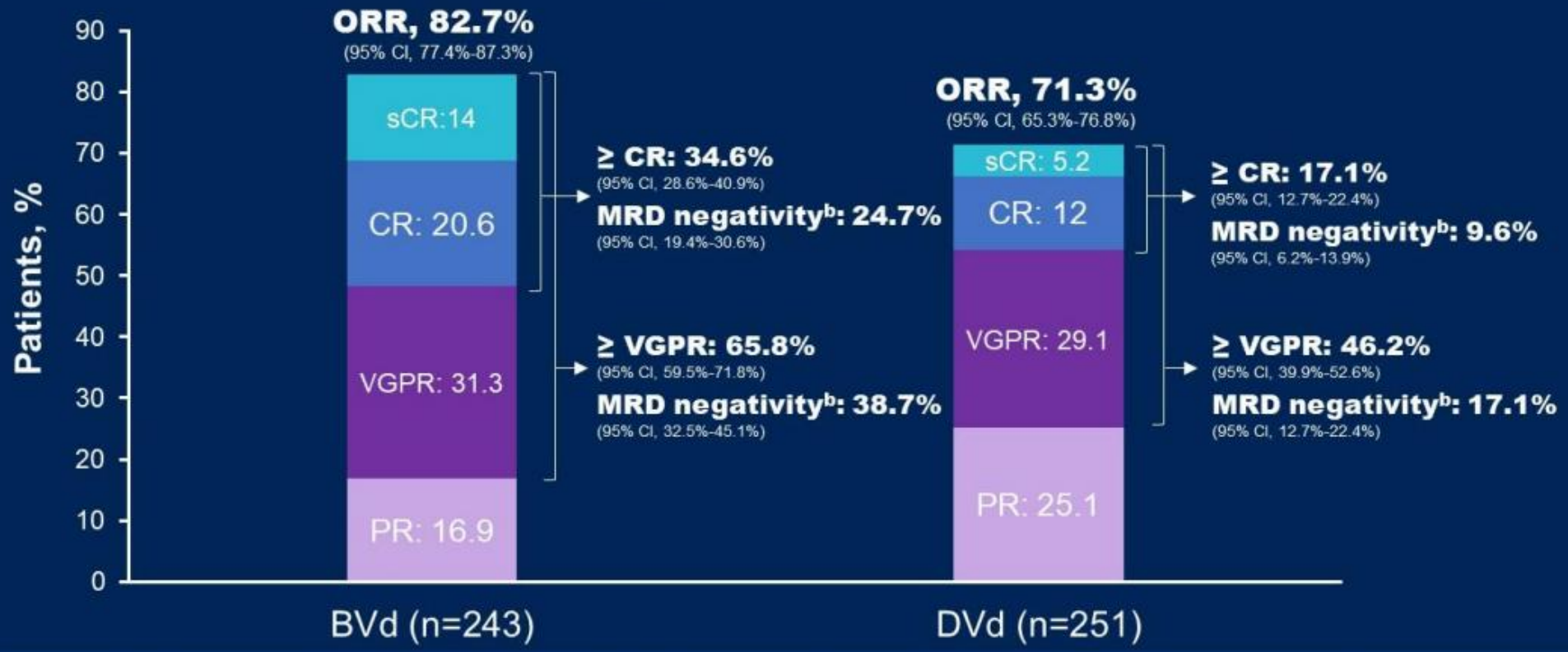
Median follow-up: 28.2 months (range, 0.1-40.0 months)

HR, hazard ratio; ITT, intent to treat; NR, not reached; OS, overall survival; R-ISS, Revised International Staging System.

[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III), with a covariate of treatment. [d] *P* value is from 1-sided stratified log-rank test. [e] The *P* value has not yet reached criteria for statistical significance ($P \leq .00037$) at this interim analysis. Follow-up for OS is ongoing.

DREAMM-7: ITT population

Deeper responses and increased MRD negativity rate with BVd vs DVd[a]



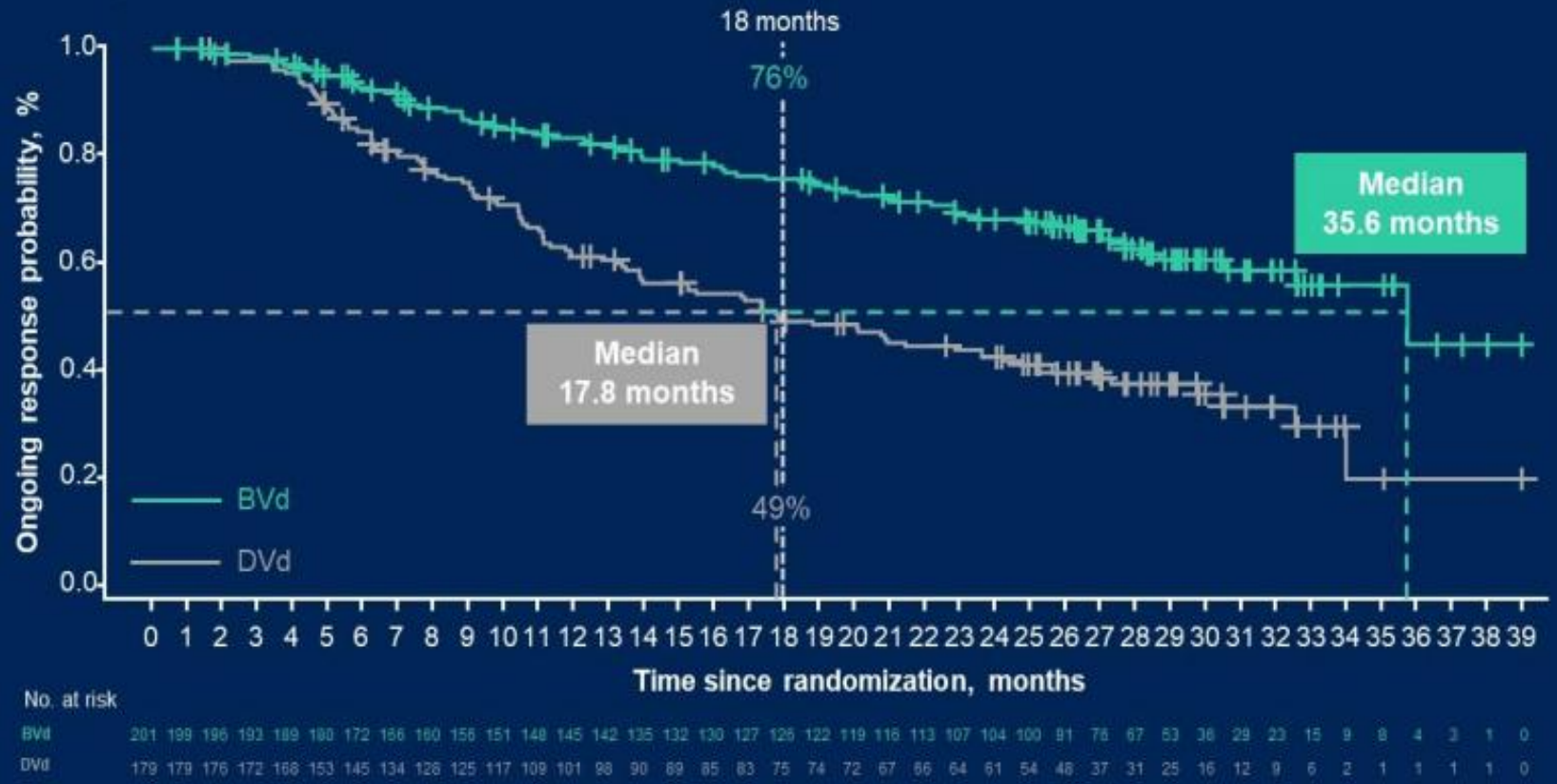
- BVd was associated with greater depth of response, with a ≥ CR rate that was double that with DVd
- MRD negativity rate (sensitivity of 10^{-5}) in patients treated with BVd was more than double that in patients treated with DVd (*P*<.00001)[c]

CR, complete response; ITT, intent to treat; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; PR, partial response; R-ISS, Revised International Staging System; sCR, stringent complete response; VGPR, very good partial response.

[a] CIs were based on the exact method. Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] MRD negativity rate was defined as the percentage of patients who were MRD negative by NGS based on a sensitivity of 10^{-5}. [c] Nominal *P* value. Cochran–Mantel–Haenszel test was used and adjusted for stratification factors, including number of prior lines of therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III).

DREAMM-7: ITT population (responders only)

Longer DOR with BVd vs DVd



DOR[a]	BVd (n=201)	DVd (n=179)
Events, n (%)	68 (34)	105 (59)
Patients with ongoing response, n (%)	106 (53)	52 (29)
DOR, median (95% CI), months[b]	35.6 (30.5-NR)	17.8 (13.8-23.6)

A separate analysis of restricted mean DOR using the ITT population comparing DOR between arms showed a statistically significant benefit in favor of BVd ($P<.00001$).[1,c]

BVd led to greater response durability, with a longer median DOR vs DVd (35.6 vs 17.8 months)

DREAMM-7: ITT population
Prior treatments

Prior treatments, n (%)	ITT population			
	BVd (N=243)		DVd (N=251)	
Prior LOT				
1	125 (51)		125 (50)	
2 or 3	88 (36)		99 (39)	
4+	30 (12)		27 (11)	
Prior ASCT	164 (67)		173 (69)	
Prior proteasome inhibitor	218 (90)		216 (86)	
Prior bortezomib	210 (86)		211 (84)	
Prior carfilzomib	31 (13)		35 (14)	
Prior daratumumab	3 (1)		4 (2)	
Prior immunomodulatory drugs	198 (81)		216 (86)	
Prior thalidomide	121 (50)		144 (57)	
Prior pomalidomide	25 (10)		19 (8)	
Prior lenalidomide	127 (52)		130 (52)	
Refractory to lenalidomide	**79 (33)**		**87 (35)**	
Refractory status by number of prior LOT[a]	Refractory (n=79)	Not refractory (n=164)	Refractory (n=87)	Not refractory (n=164)
1 prior LOT	22 (28)	103 (63)	27 (31)	98 (60)
2 prior LOT	24 (30)	30 (18)	21 (24)	42 (26)
3+ prior LOT	33 (42)	31 (19)	39 (45)	24 (15)

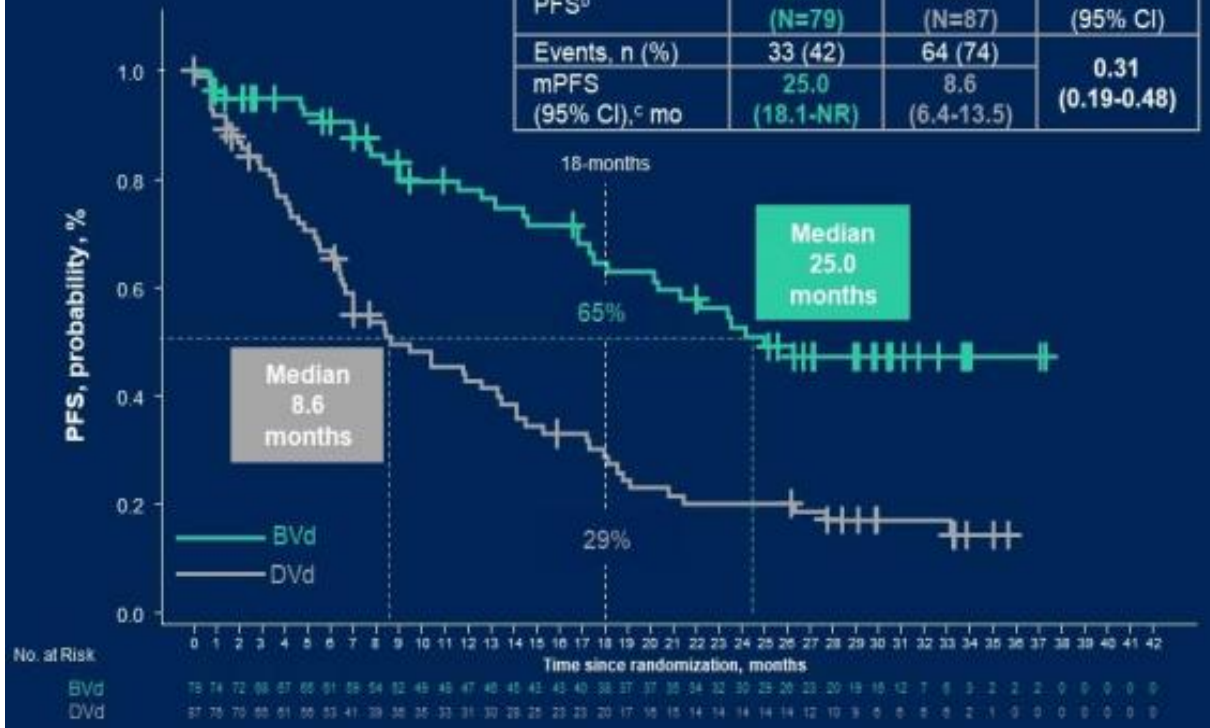
In both arms, approximately one-third of patients had disease that was refractory to prior lenalidomide; refractoriness to lenalidomide has been previously associated with a poor prognosis[1]

DREAMM-7: subgroup by lenalidomide refractory status

Progression-free survival (lenalidomide refractory and not refractory)

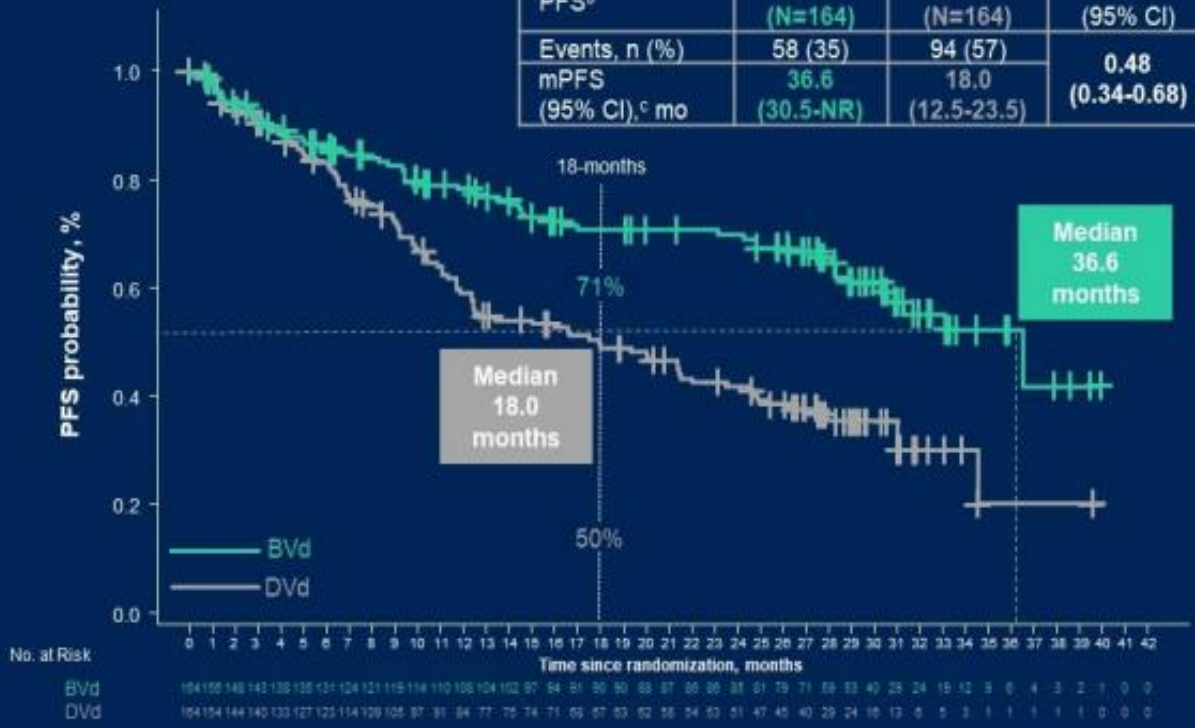
Lenalidomide Refractory

PFS[b]	BVd (N=79)	DVd (N=87)	HR[d] (95% CI)
Events, n (%)	33 (42)	64 (74)	0.31 (0.19-0.48)
mPFS (95% CI),[c] mo	25.0 (18.1-NR)	8.6 (6.4-13.5)	



Not Lenalidomide Refractory[a]

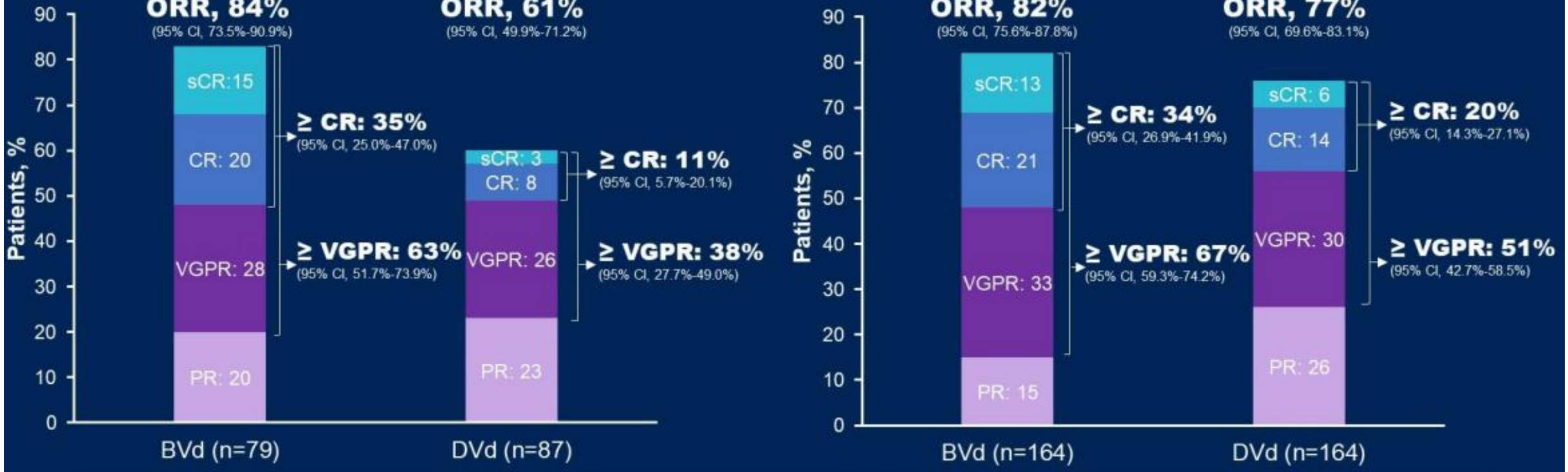
PFS[b]	BVd (N=164)	DVd (N=164)	HR[d] (95% CI)
Events, n (%)	58 (35)	94 (57)	0.48 (0.34-0.68)
mPFS (95% CI),[c] mo	36.6 (30.5-NR)	18.0 (12.5-23.5)	



BVd was associated with clinically meaningful PFS benefit in both lenalidomide refractory and non-lenalidomide refractory patients

DREAMM-7: subgroup by lenalidomide refractory status

Response

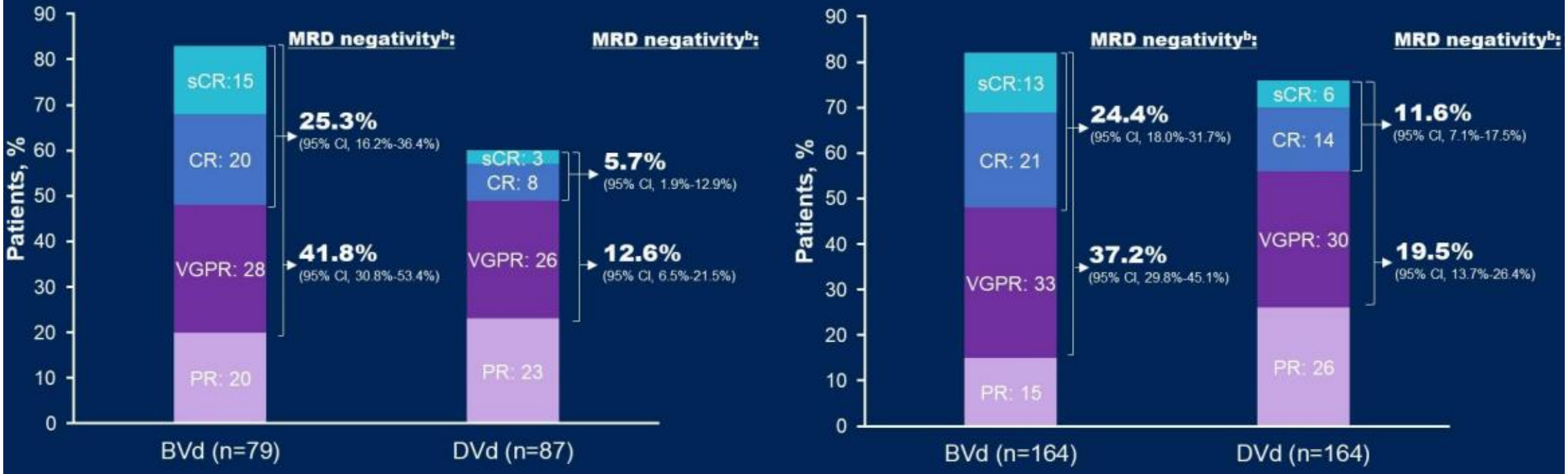


- Response was consistent in patients treated with BVd regardless of lenalidomide refractory status
- In patients refractory to lenalidomide, BVd led to greater depth of response vs DVd

Post hoc analyses.
CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
[a] Includes patients who are lenalidomide exposed but not refractory and patients who have not been exposed to lenalidomide.

DREAMM-7: subgroup by lenalidomide refractory status

MRD negativity rates



In patients with positive lenalidomide refractory status, BVd led to a nearly 5-fold increase in MRD negativity in those with ≥ CR

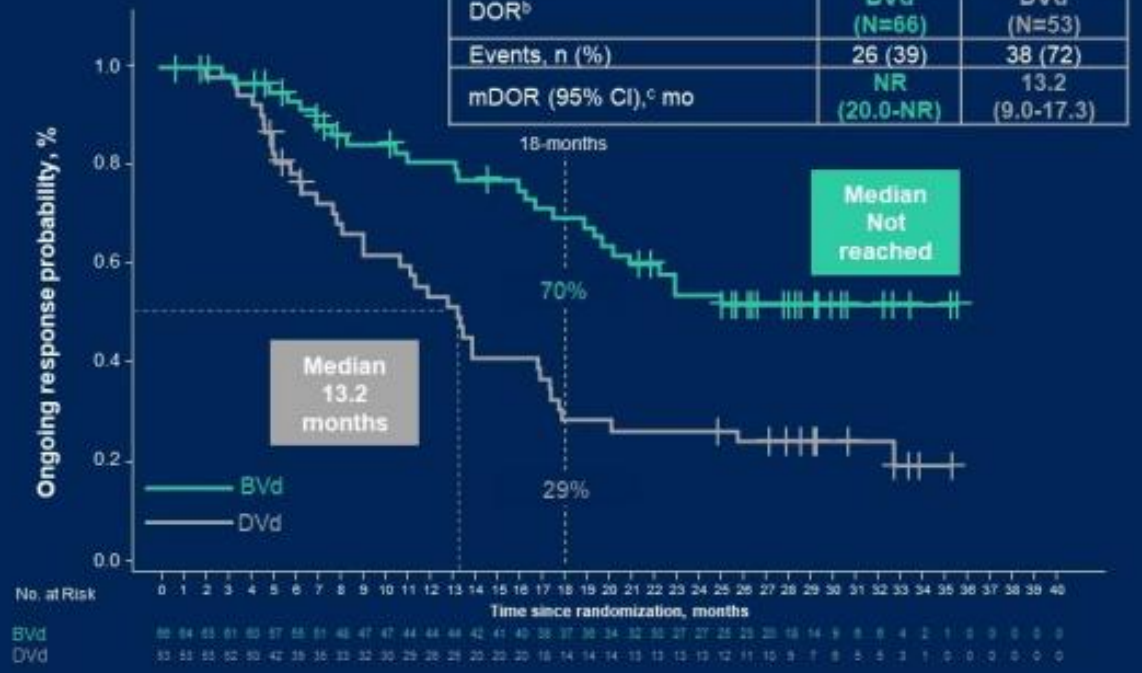
Post hoc analyses.
CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
[a] Includes patients who are lenalidomide exposed but not refractory and patients who have not been exposed to lenalidomide. [b] MRD negativity rate was defined as percentage of patients who were MRD negative by NGS based on sensitivity of 10^{-5}

DREAMM-7: subgroup by lenalidomide refractory status

Duration of response

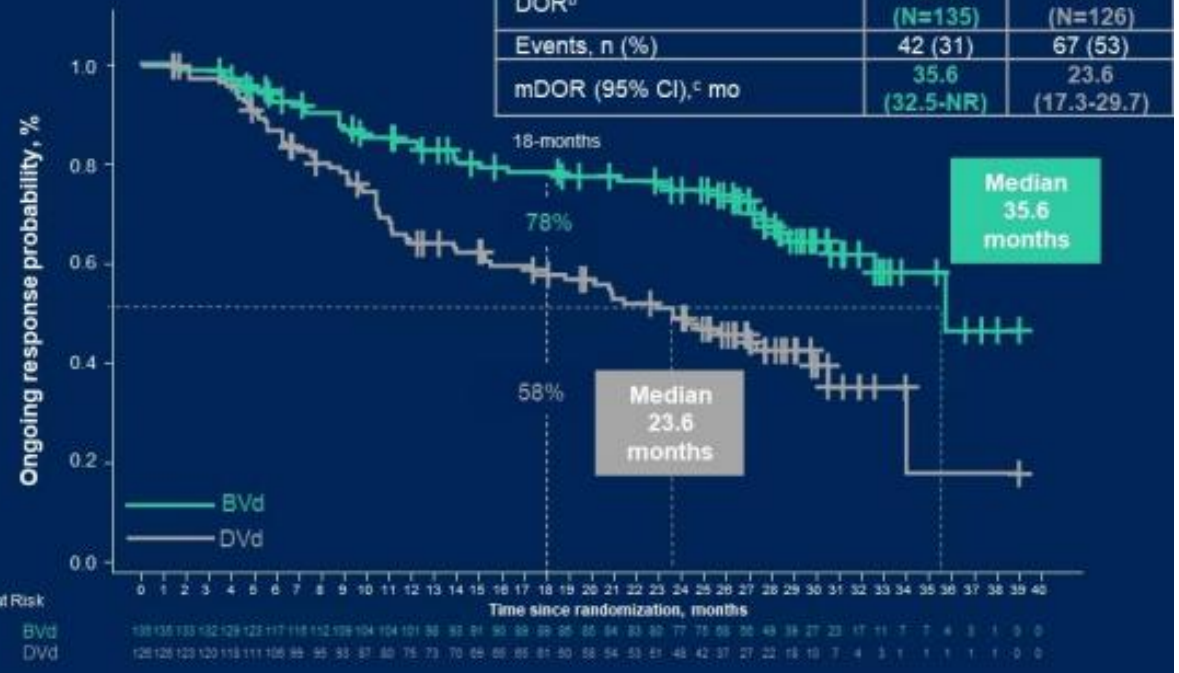
Refractory to Lenalidomide

DOR[b]	BVd (N=66)	DVd (N=53)
Events, n (%)	26 (39)	38 (72)
mDOR (95% CI),[c] mo	NR (20.0-NR)	13.2 (9.0-17.3)



Not Refractory to Lenalidomide[a]

DOR[b]	BVd (N=135)	DVd (N=126)
Events, n (%)	42 (31)	67 (53)
mDOR (95% CI),[c] mo	35.6 (32.5-NR)	23.6 (17.3-29.7)



BVd led to greater response duration vs DVd, with early and sustained separation of K-M curves regardless of lenalidomide refractory status

Post hoc analyses.

[a] Includes patients who are lenalidomide exposed but not refractory and patients who have not been exposed to lenalidomide. [b] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [c] CIs were estimated using the Brookmeyer-Crowley method. 95% CIs were not adjusted for multiplicity and cannot be used for hypothesis testing.

DREAMM-7: grade ≥3 AEs of special interest by lenalidomide refractory status

Occurring in ≥5% of patients in any subgroup

Preferred term, n (%)	BVd (N=242)			DVd (N=246)		
	Lenalidomide refractory		Total	Lenalidomide refractory		Total
	Yes (n=79)	No (n=163)	N=242	Yes (n=87)	No (n=159)	N=246
Any	65 (82)	133 (82)	198 (82)	55 (63)	65 (41)	120 (49)
Thrombocytopenia	41 (52)	93 (57)	134 (55)	40 (46)	47 (30)	87 (35)
Platelet count decreased	19 (24)	25 (15)	44 (18)	13 (15)	13 (8)	26 (11)
Vision blurred	18 (23)	35 (21)	53 (22)	1 (1)	1 (<1)	2 (1)
Visual impairment	6 (8)	7 (4)	13 (5)	0	1 (<1)	1 (<1)
Dry eye	4 (5)	13 (8)	17 (7)	0	0	0
Eye irritation	4 (5)	8 (5)	12 (5)	0	0	0

The rates of grade ≥3 AEs of special interest in the BVd arm were similar regardless of lenalidomide refractory status and consistent with those reported in the overall population

Post hoc analyses. AEs were graded according to NCI-CTCAE version 5.0.
AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

DREAMM-7: subgroup by cytogenetic risk[a]

Patient and disease characteristics

Overall, 67 (28%) patients in the BVd arm and 69 (27%) patients in the DVd arm had high-risk cytogenetic features.

	High risk[b]		Standard risk[c]	
	BVd (n=67)	DVd (n=69)	BVd (n=175)	DVd (n=175)
Age, median (range), years	65.0 (40-84)	61.0 (39-85)	64.0 (34-86)	66.0 (32-89)
<65 years, n (%)	33 (49)	44 (64)	88 (50)	78 (45)
65 to <75 years, n (%)	23 (34)	20 (29)	61 (35)	73 (42)
≥75 years, n (%)	11 (16)	5 (7)	26 (15)	24 (14)
Male, n (%)	38 (57)	40 (58)	89 (51)	101 (58)
White/Black or African American/other, n (%)[d]	56 (84)/1 (1)/9 (13)	58 (84)/1 (1)/9 (13)	149 (85)/7 (4)/19 (11)	139 (79)/11 (6)/25 (14)
R-ISS stage at screening, n (%)				
I	2 (3)	2 (3)	100 (57)	96 (55)
II	58 (87)	57 (83)	71 (41)	73 (42)
III	7 (10)	9 (13)	2 (1)	5 (3)
Unknown	0	1 (1)	2 (1)	1 (<1)
High-risk cytogenetic abnormalities, n (%)				
t(4;14)	41 (61)	42 (61)	–	–
t(14;16)	8 (12)	6 (9)	–	–
17p13del	30 (45)	35 (51)	–	–
Extramedullary disease, n (%)	4 (6)	10 (14)	9 (5)	15 (9)
No. of prior lines of therapy, median (range)	2.0 (1-7)	1.0 (1-7)	1.0 (1-7)	2.0 (1-7)
Prior ASCT, n (%)	43 (64)	48 (70)	120 (69)	122 (70)

Post hoc analyses. ASCT, autologous stem cell transplant; R-ISS, Revised International Staging System.

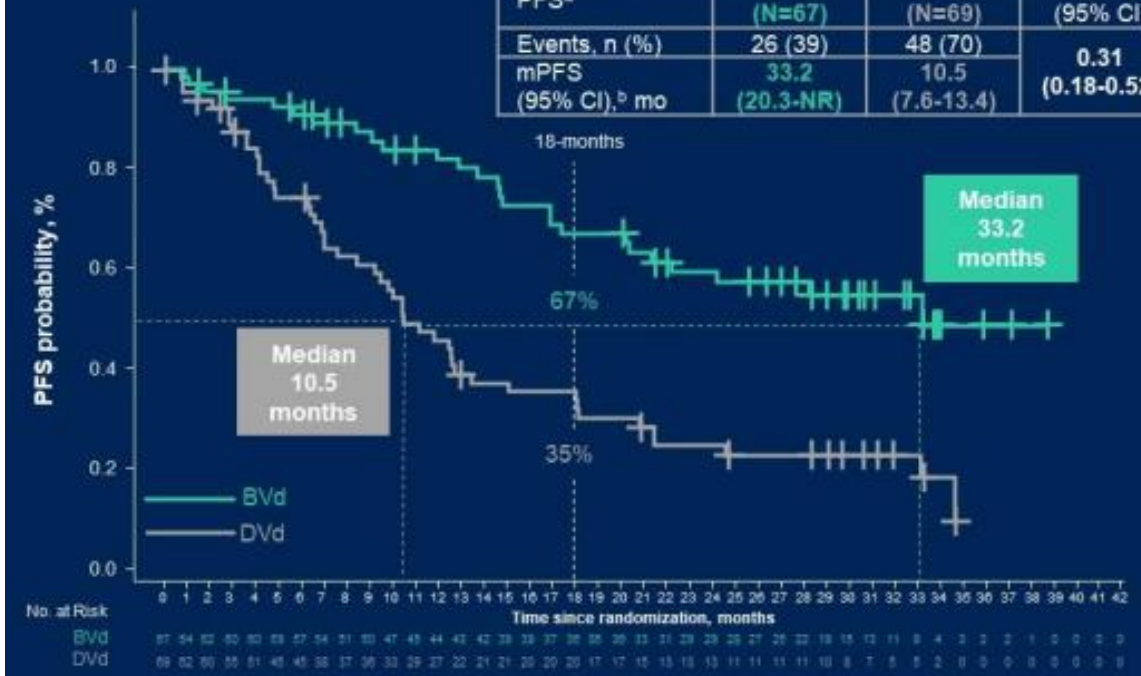
[a] Cytogenetic abnormalities were assessed by interphase fluorescent in situ hybridization with the following central laboratory thresholds: t(4;14) cut off at 2%, t(14;16) cut off at 2%, and 17p13del cut off at 5%. Local laboratory thresholds were based on local standards. [b] Patient had ≥1 high-risk abnormality: t(4;14), t(14;16), or 17p13del. [c] Patient had tested negative for all the following: t(4;14), t(14;16), and 17p13del. [d] Other includes patients of Asian or mixed race. One patient in each arm in the high-risk subgroup had missing data for race.

DREAMM-7: subgroup by cytogenetic risk

Progression-free survival (high risk and standard risk)

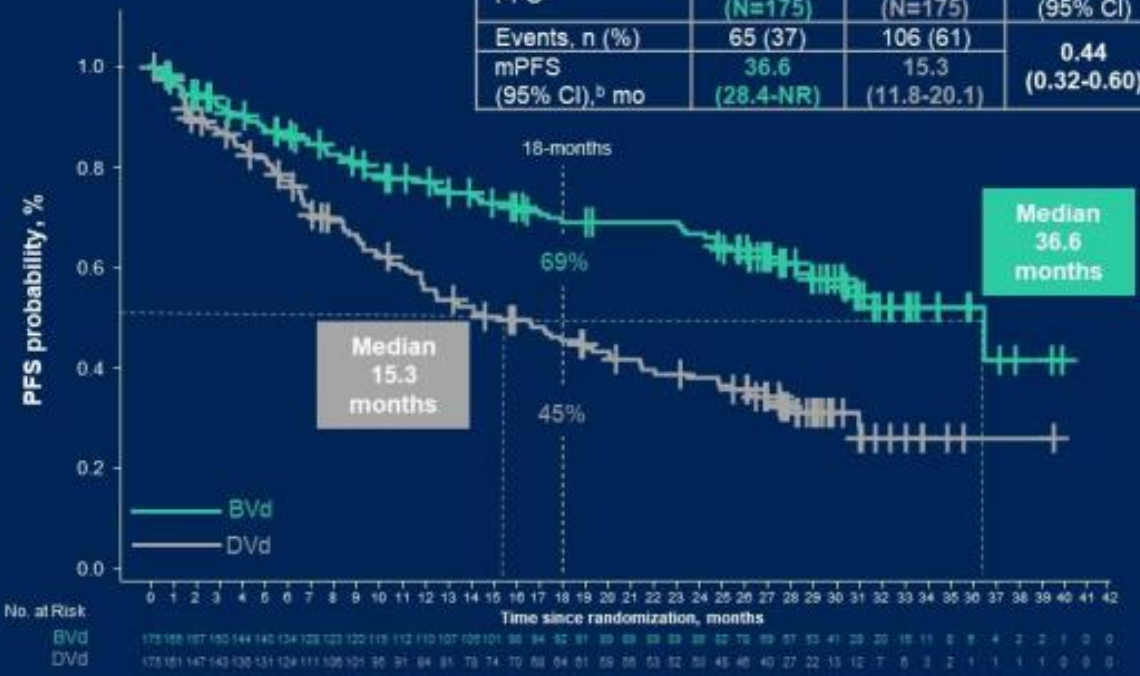
High Risk

PFS[a]	BVd (N=67)	DVd (N=69)	HR[c] (95% CI)
Events, n (%)	26 (39)	48 (70)	0.31 (0.18-0.52)
mPFS (95% CI),[b] mo	33.2 (20.3-NR)	10.5 (7.6-13.4)	



Standard Risk

PFS[a]	BVd (N=175)	DVd (N=175)	HR[c] (95% CI)
Events, n (%)	65 (37)	106 (61)	0.44 (0.32-0.60)
mPFS (95% CI),[b] mo	36.6 (28.4-NR)	15.3 (11.8-20.1)	

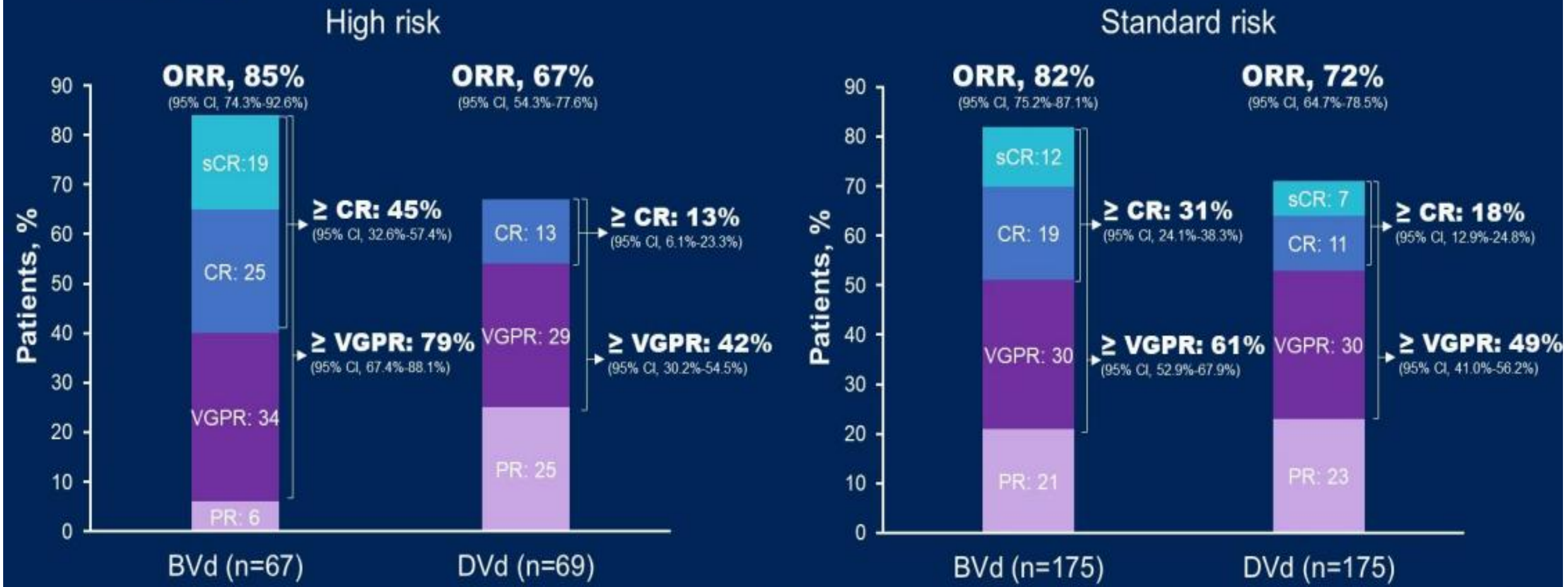


BVd led to strong PFS benefit (more than double to triple the median PFS) regardless of cytogenetic risk status compared with DVd

[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. 95% CIs were not adjusted for multiplicity and cannot be used for hypothesis testing. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III), with a covariate of treatment

DREAMM-7: subgroup by cytogenetic risk

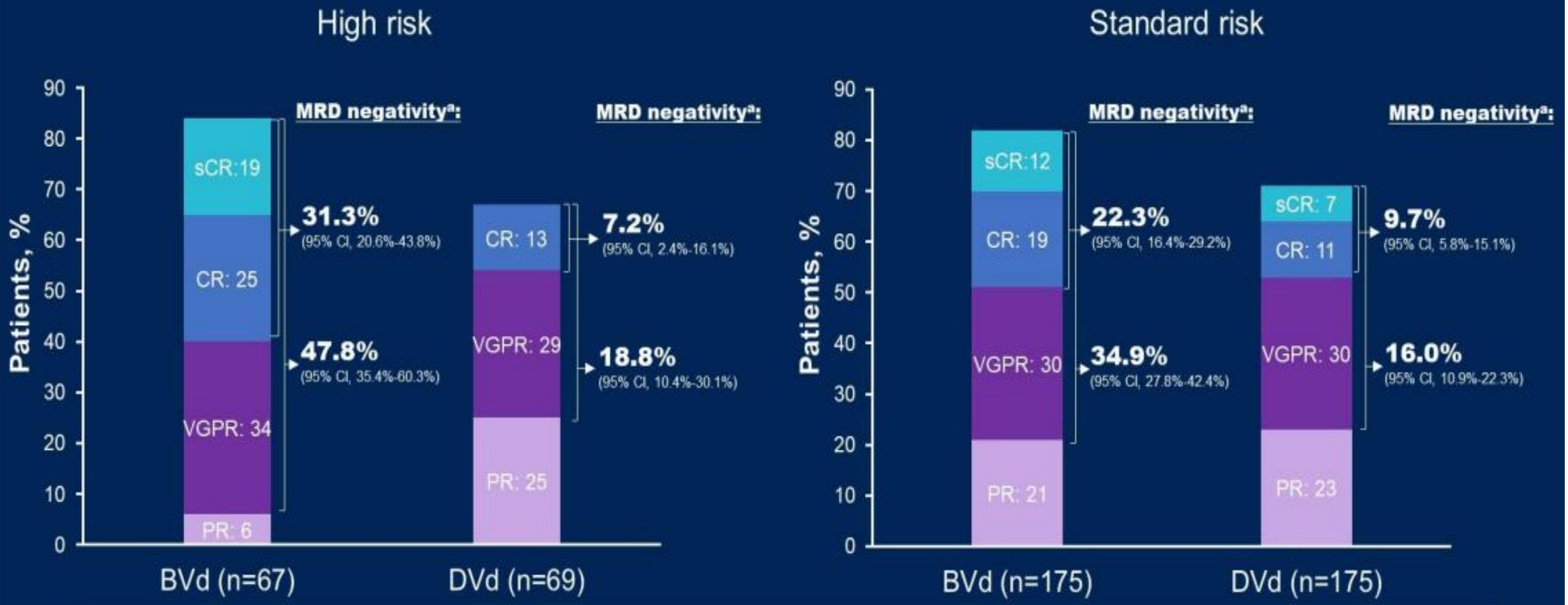
Response



Regardless of cytogenetic risk status, BVd was associated with a higher ORR and substantially greater response depth compared with DVd

DREAMM-7: subgroup by cytogenetic risk

MRD negativity rates



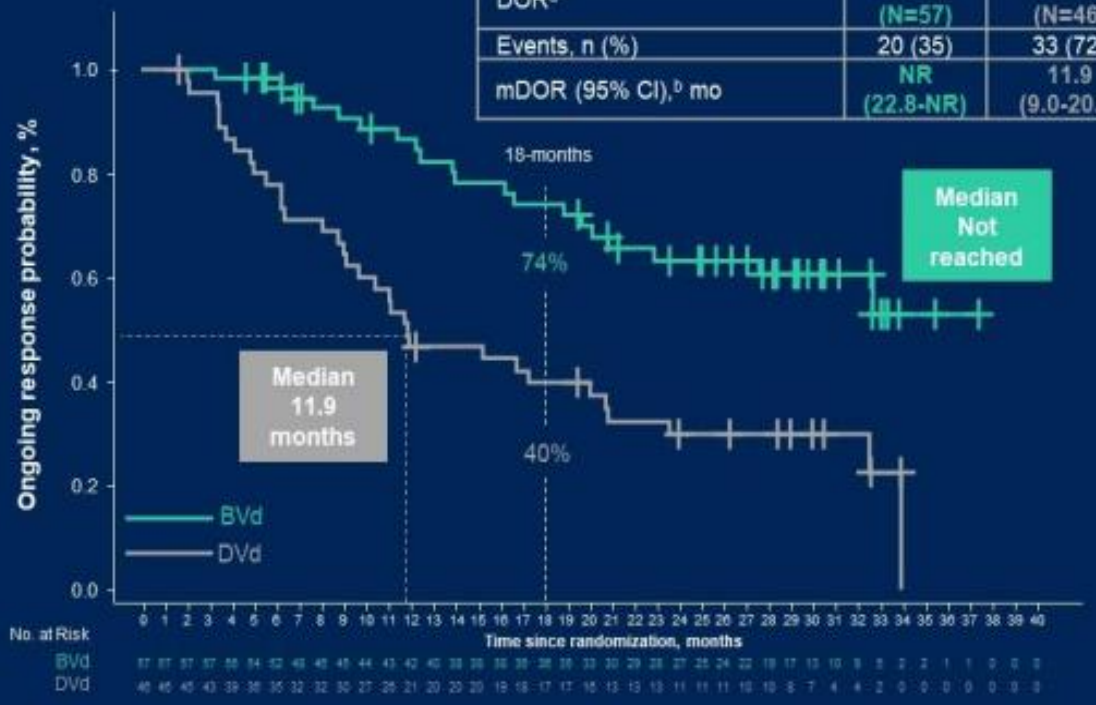
Treatment with BVd was associated with higher MRD negativity rates vs DVd regardless of cytogenetic risk status

DREAMM-7: subgroup by cytogenetic risk

Duration of response

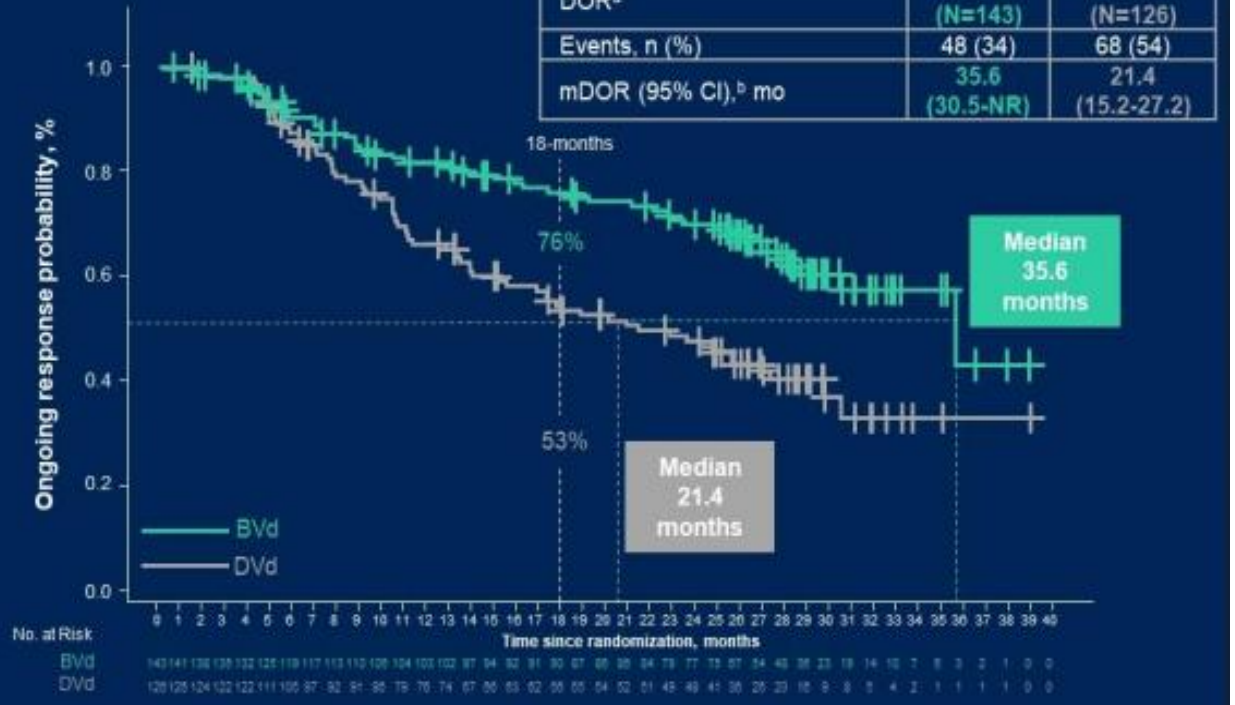
High Risk

DOR[a]	BVd (N=57)	DVd (N=46)
Events, n (%)	20 (35)	33 (72)
mDOR (95% CI),[b] mo	NR (22.8-NR)	11.9 (9.0-20.7)



Standard Risk

DOR[a]	BVd (N=143)	DVd (N=126)
Events, n (%)	48 (34)	68 (54)
mDOR (95% CI),[b] mo	35.6 (30.5-NR)	21.4 (15.2-27.2)



Regardless of cytogenetic risk, patients treated with BVd had greater response durability than those receiving DVd

Post hoc analyses.
[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method.

DREAMM-7: grade ≥3 AEs of special interest by cytogenetic risk status

Occurring in ≥5% of patients in any subgroup

Preferred term, n (%)	BVd (N=242)			DVd (N=246)		
	Cytogenetic risk[a]		Total	Cytogenetic risk[a]		Total
	High (n=66)	Standard (n=175)	N=242	High (n=68)	Standard (n=171)	N=246
Any	53 (80)	144 (82)	198 (82)	35 (51)	82 (48)	120 (49)
Thrombocytopenia	34 (52)	99 (57)	134 (55)	26 (38)	58 (34)	87 (35)
Platelet count decreased	14 (21)	30 (17)	44 (18)	9 (13)	17 (10)	26 (11)
Vision blurred	16 (24)	37 (21)	53 (22)	1 (1)	1 (<1)	2 (1)
Visual impairment	2 (3)	11 (6)	13 (5)	0	1 (<1)	1 (<1)
Dry eye	3 (5)	14 (8)	17 (7)	0	0	0
Eye irritation	1 (2)	11 (6)	12 (5)	0	0	0

The rates of grade ≥3 AEs of special interest in the BVd arm were consistent with those reported in the overall population regardless of cytogenetic risk status

Post hoc analyses.
[a] One patient in the BVd arm and 7 patients in the DVd arm had missing or nonevaluable cytogenetic risk.
AEs were graded according to NCI-CTCAE version 5.0.
AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Conclusions

- In the ITT population, BVd led to a statistically significant and clinically meaningful improvement in PFS vs DVd (HR, 0.41; 95% CI, 0.31-0.53; *P*<.00001) and showed a strong and clinically meaningful OS benefit (HR, 0.57; *P*=.00049[a])
- Analysis of key subgroups associated with poor prognosis, including patients with disease refractory to lenalidomide and those with high-risk cytogenetic abnormalities, showed that:
  - In patients with poor prognostic features, BVd was associated with more pronounced benefit vs DVd
    - Clinically meaningful risk reduction in PFS
    - Larger between-arm differences in ORR, depth of response (≥ CR and ≥ VGPR), and MRD-negative status
    - Greater increase in response durability
- The safety profile of BVd in these subgroups was consistent with that in the overall trial population and with the known safety profile of belamaf and the constituent therapies

These results demonstrate efficacy benefit and a consistent safety profile in key subgroups with a high unmet need and support BVd as a potential new standard of care in patients with RRMM at first relapse or later

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