Updates in Multiple Myeloma Advances In Oncology 2019

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Disclosures

- Research: Amgen
- Speakers Bureau: Janssen, Millenium-Takeda
- Ad-boards: Karyopharm, Celgene

- Discussion of off label use: will discuss investigational treatments not yet approved by the FDA

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Updates on Multiple Myeloma: 2019 was an active year

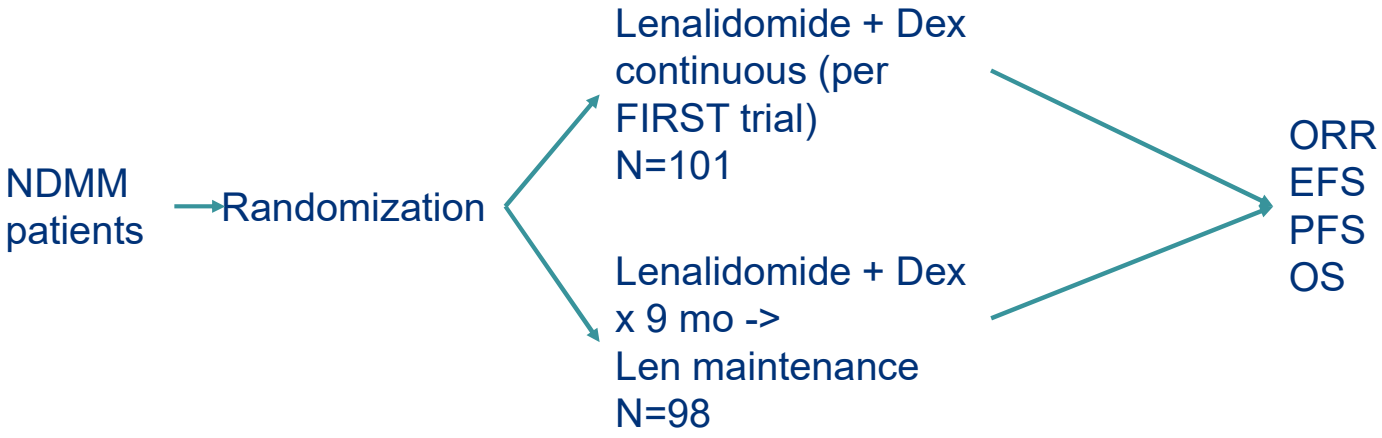
- Carfilzomib + Daratumumab (Chari et al Blood 2019)
- Approval of Selinexor (Chari et al, NEJM 2019)
- Phase III ADMYRE study: Plitidepsin + Dex (Spika et al, Ann of Hematol 2019)
  - Now approved in Australia
- Bortez + Thal + Dex +/- Dara (CASSIOPEIA) (Attal, Lancet 2019)
- Len + Dex +/- Dara (MAIA) (Facon et al, NEJM 2019)
- Anti-BCMA CAR-T cells show efficacy (Raje et al NEJM 2019)
- Maintenance Ixazomib: TOURMALINE-MM3 (Dimopoulos et al, Lancet 2019)
- Isatuximab (CD38 antibody) +Pom + Dex presented at ASCO 2019

Outline

- Sparing dexamethasone in older and intermediate frailty patients (ASH18, EHA19)
- GRIFFIN trial: Dara+VRd vs VRd in newly diagnosed myeloma (IMW2019)
- What to do with venetoclax?
  - Quick look at the BELLINI trial (IMW2019)
- If there's time:
  - Balantamab Mafodotin

Dex-sparing in older/frail patients

- IMWG frailty index includes age, ADL and IADL and charlson comorbity index
  - Predicts toxicity, treatment interruptions and mortality
  - http://www.myelomafrailtyscorecalculator.net/
- Patients with a score of 1 or more were included



LaRocca et al HemaSphere 2019

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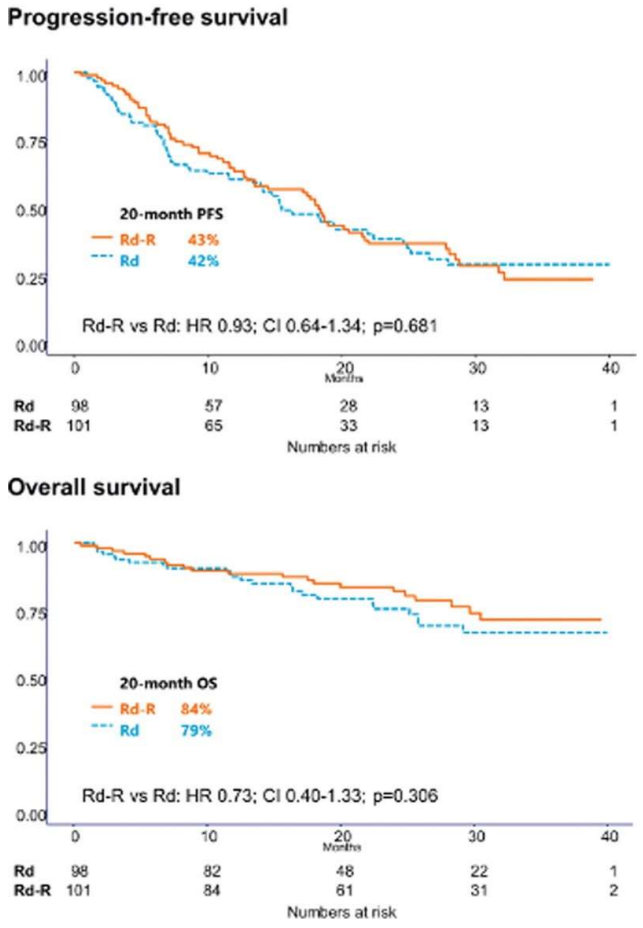
Dex-sparing in older/frail patients

- Median follow up 25 mo
- ≥ VGPR rates comparable
  - 35% Len-dex continuous
  - 43% Len-dex -> len maintenance
- At least 1 non-hematologic grade 3-4 tox seen in:
  - 39% len-dex continuous
  - 31% len-dex -> len maintenance
- Len discontinued more frequently in continuous arm

LaRocca et al HemaSphere 2019

Dex-sparing in older/frail patients

- 20 month PFS:
  - Len-dex cont: 42%
  - Len-dex-> maint: 43%
- 20 month OS:
  - Len-dex cont: 79%
  - Len-dex-> maint: 84%
- Median EFS:
  - Len-dex cont: 6.6 mo
  - Len-dex-> maint: 9.3 mo



LaRocca et al HemaSphere 2019

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Dex-sparing in older/frail patients

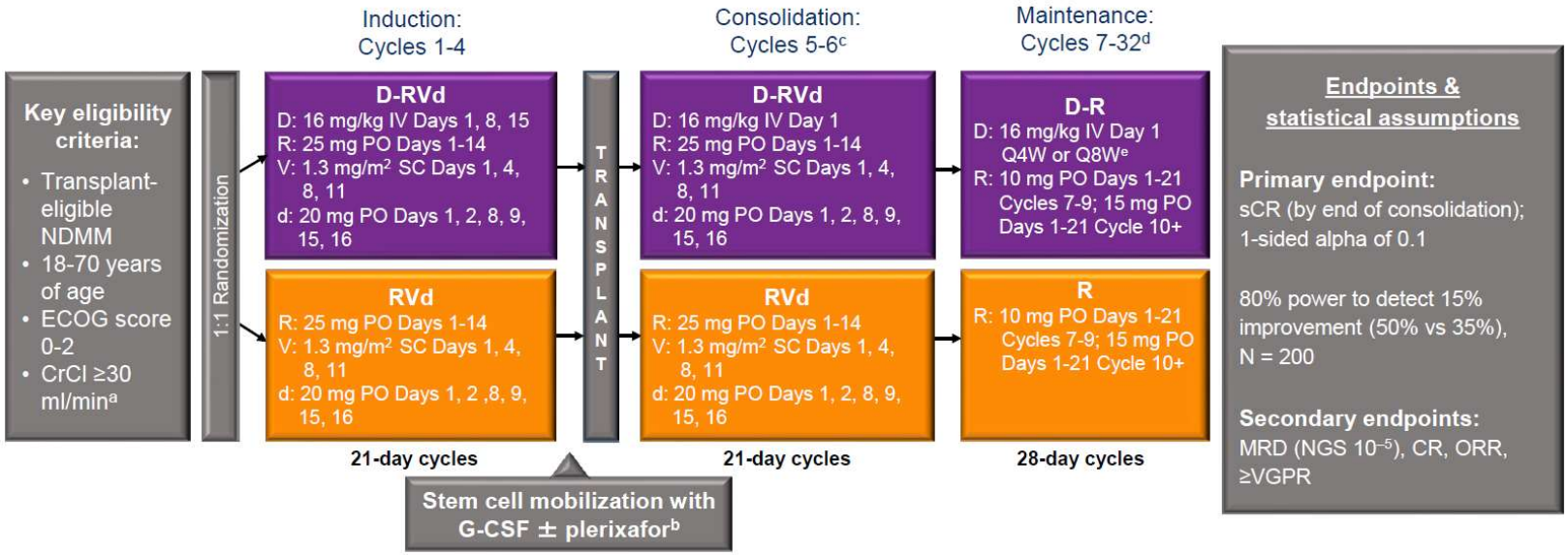
- Conclusions:
  - At least in older patients there does not appear to be an advantage to continued doublet therapy
  - The strategy of starting with a more intensive regimen and the proceeding to maintenance is in line with current practice
  - Need long term follow up to ensure that OS is comparable (or better?) in the dex-sparing arm
- Have I implemented this?
  - Yes – and I have extrapolated this data to other regimens
  - Dex sparing, anecdotally, associated with improved patient morale

LaRocca et al HemaSphere 2019

GRIFFIN (Voorhees et al)

GRIFFIN (NCT02874742): Randomized Phase

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018



D-RVd, daratumumab-lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.
[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post transplant. [d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

GRIFFIN (Voorhees et al)

Baseline Demographic and Clinical Characteristics (ITT)

	D-RVd (n = 104)	RVd (n = 103)
Age		
Median (range), years	59 (29-70)	61 (40-70)
≥65 years	28 (27)	28 (27)
Male, n (%)	58 (56)	60 (58)
ECOG status,[a] n (%)	n = 101	n = 102
0	39 (39)	40 (39)
1	51 (51)	52 (51)
2	11 (11)	10 (10)
Baseline creatinine clearance, n (%)		
30-50 mL/min	9 (9)	9 (9)
>50 mL/min	95 (91)	94 (91)

	D-RVd (n = 104)	RVd (n = 103)
ISS stage,[b] n (%)		
I	49 (47)	50 (49)
II	40 (39)	37 (36)
III	14 (14)	14 (14)
Missing	1 (1)	2 (2)
Cytogenetic profile,[c] n (%)	n = 98	n = 97
Standard risk	82 (84)	83 (86)
High risk	16 (16)	14 (14)
Time since diagnosis of MM	n = 103	n = 102
Median, months	0.7	0.9

Treatment arms were well balanced

ITT, intent-to-treat; ISS, International Staging System; MM, multiple myeloma.
[a]ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
[b]The ISS disease stage is based on the combination of serum β_2-microglobulin and albumin levels. Higher stages indicate more advanced disease.
[c]Cytogenetic risk was assessed by fluorescence in situ hybridization (locally tested) among patients with available cytogenetic risk data; high risk was defined as the presence of del(17p), t(4;14), or t(14;16).

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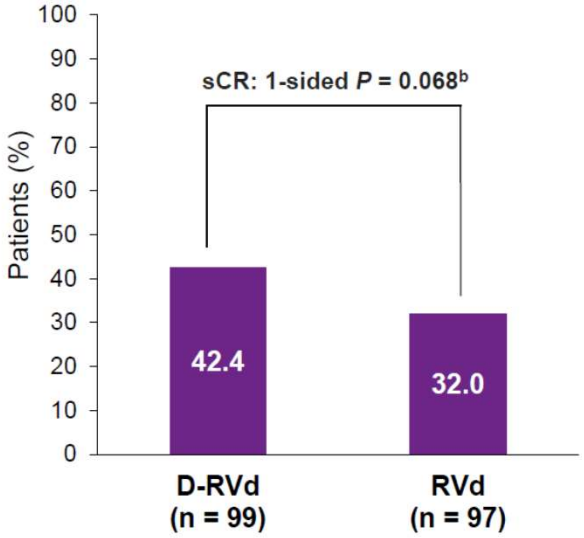
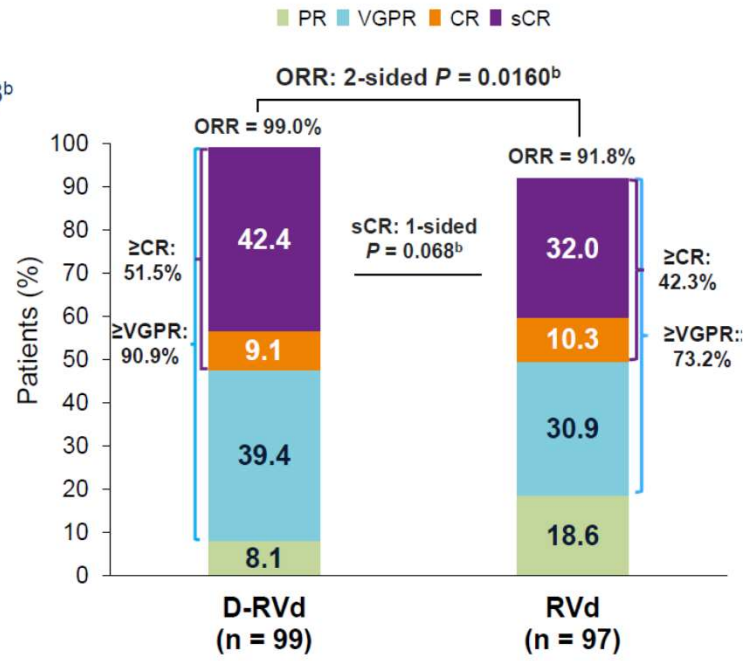
GRIFFIN (Vorhees et al)

Primary Endpoint: sCR by the End of Consolidation[a]

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]



Post-consolidation depth of response[a]



PR, partial response.
[a]Included patients in the response-evaluable population (all randomized patients with a confirmed diagnoses of MM, measurable disease at baseline, received ≥1 dose of study treatment, and had ≥1 post-baseline disease assessment).
[b]*P* values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A 1-sided *P* value is reported for sCR; for all other responses, 2-sided *P* values not adjusted for multiplicity are reported.

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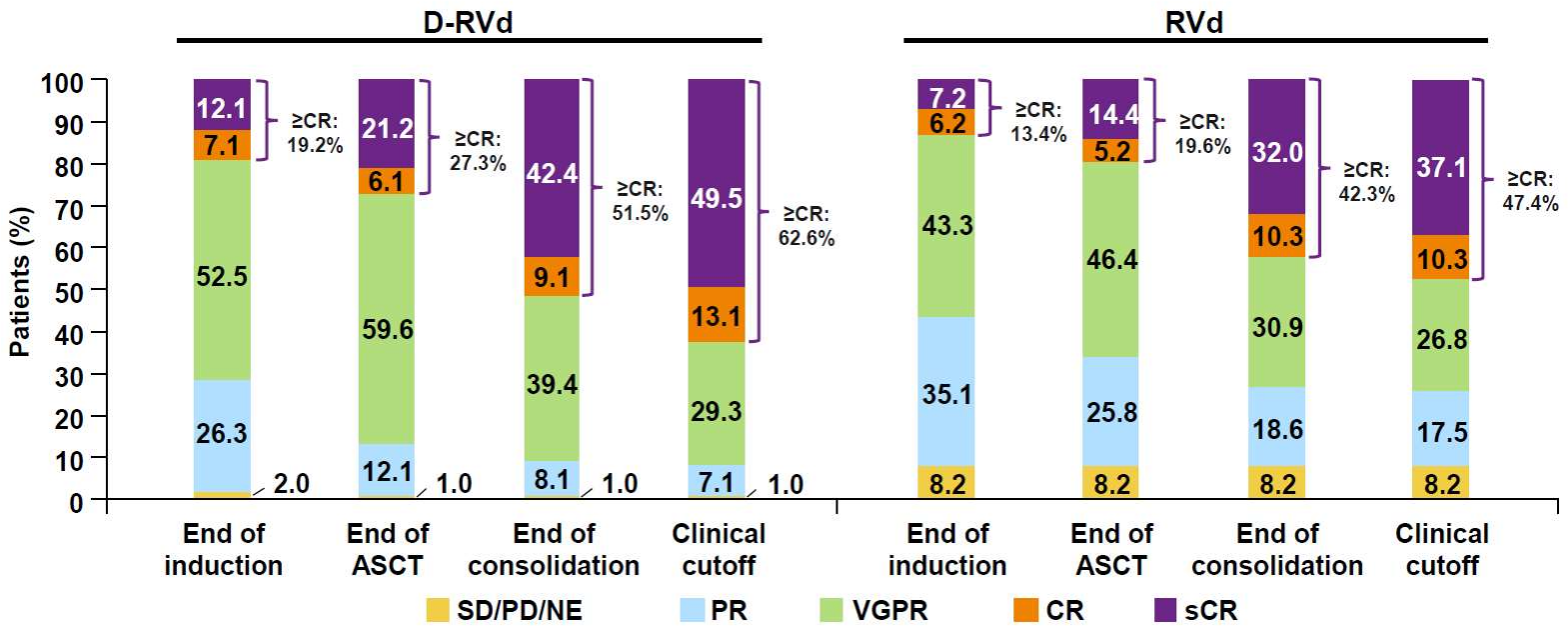
GRIFFIN (Vorhees et al)

Responses Deepened Over Time



Response rates and depths were greater for D-RVd at all time points

SD, stable disease; PD, progressive disease; NE, not evaluable.

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GRIFFIN (Vorhees et al)

Stem Cell Collection and Transplantation

	D-RVd	RVd
CD34+ cell yield,[a,b] median (10^6 cells/kg)	8.1	9.4
CD34+ cells transplanted,[c] median (10^6 cells/kg)	4.2	4.8
Patients receiving plerixafor for mobilization,[d] n (%)	66 (70)	44 (55)
Patients receiving cyclophosphamide,[d] n (%)	5 (5)	4 (5)
Days to neutrophil (0.5×10^9/L) engraftment, median	12	12
Days to platelet (20×10^9/L) engraftment, median	13	12

DARA did not impact time to engraftment

[a]Among patients who underwent peripheral blood stem cell apheresis (D-RVd, n = 94; RVd, n = 80). [b]One patient in the D-RVd group had a stem cell yield <$3x10^6$ cells/kg; no patients in either group had a stem cell yield <$2x10^6$ cells/kg. [c]Among patients receiving transplant (D-RVd, n = 94; RVd, n = 78). [d]Among patients who underwent mobilization (D-RVd, n = 95; RVd, n = 80). Patients underwent stem cell mobilization with G-CSF with or without plerixafor, according to institutional standards; if unsuccessful, cyclophosphamide-based mobilization was permitted.

GRIFFIN (Vorhees et al)

Most Common TEAEs[a]

	D-RVd (n = 99)		RVd (n = 102)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	48 (49)	32 (32)	32 (31)	15 (15)
Thrombocytopenia	43 (43)	16 (16)	31 (30)	8 (8)
Leukopenia	34 (34)	15 (15)	27 (27)	7 (7)
Anemia	32 (32)	8 (8)	32 (31)	6 (6)
Lymphopenia	30 (30)	23 (23)	29 (28)	23 (23)
Non-hematologic, n (%)				
Fatigue	61 (62)	5 (5)	56 (55)	4 (4)
Peripheral neuropathy[b]	58 (59)	7 (7)	74 (73)	7 (7)
Diarrhea	53 (54)	6 (6)	43 (42)	4 (4)
Constipation	46 (47)	2 (2)	41 (40)	1 (1)
Nausea	46 (47)	1 (1)	47 (46)	1 (1)
Upper respiratory tract infection	46 (47)	1 (1)	37 (36)	1 (1)
Pyrexia	39 (39)	2 (2)	25 (25)	3 (3)
Insomnia	39 (39)	2 (2)	30 (29)	1 (1)
Cough	38 (38)	0	25 (25)	0
Edema peripheral	32 (32)	2 (2)	35 (34)	3 (3)
Back pain	32 (32)	1 (1)	28 (28)	4 (4)
Infusion-related reactions	41 (41)	5 (5)	–	–

- Any-grade infections occurred in 81 (82%) patients in the D-RVd arm and 56 (55%) patients in the RVd arm; grade 3/4 infections were similar between groups (17 [17%] patients each)
  - Pneumonia occurred in 10 (10%) patients in the D-RVd arm and 9 (9%) patients in the RVd arm

TEAE, treatment-emergent adverse event.
[a]Any-grade TEAEs are listed that occurred in ≥30% of patients in either group. The safety analysis population included all randomized patients who received ≥1 dose of study treatment; analysis was according to treatment received.
[b]Includes patients with neuropathy peripheral and peripheral sensory neuropathy.

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GRIFFIN: Rosenberg's Hot Takes

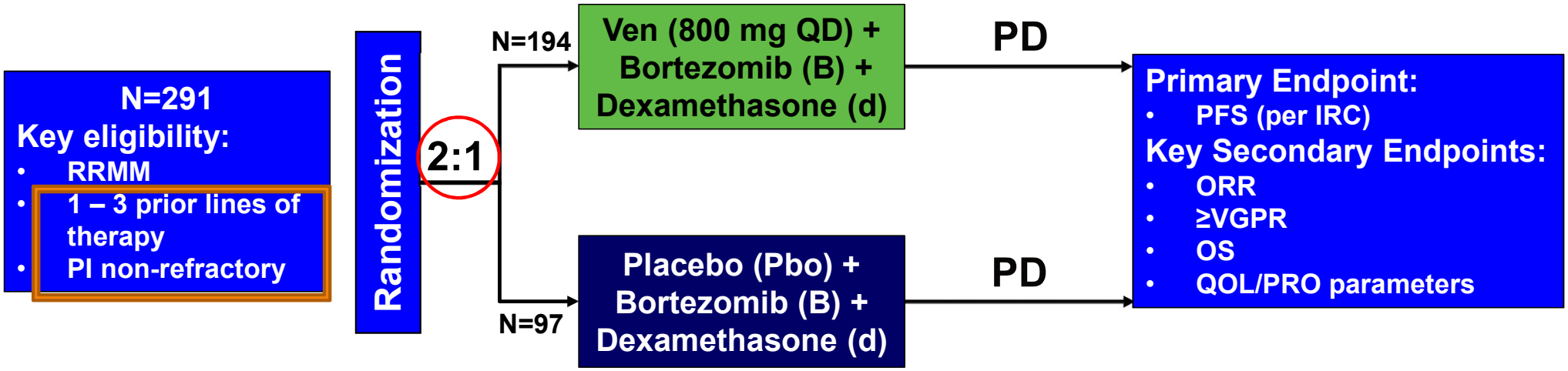
- Between MAIA, CASSIOPEIA and GRIFFIN, we're likely moving into an era of antibody based inductions
- Is it ready for prime time?
  - No PFS or OS data, so I don't think we necessarily need this in all patients
  - No data on daratumumab re-treatment, thus I worry about the strategy of continuous dara in newly diagnosed patients as opposed to an induction strategy
  - This is a costly strategy and we need some answers on who needs intensive vs lower intensity strategies

BELLINI: Ven+Bor+Dex vs Bor+Dex

- Slides curtusy of Dr. Shaji Kumar
- IMW 2019 update

Kumar et al, IMW 2019

BELLINI Study Design



Cycles 1 – 8: 21-day, Bortezomib 1.3 mg/m^2 Days 1, 4, 8, 11 and dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 9+: 35-day, Bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2–3
Non-ranked secondary endpoints	PFS in BCL-2^{high} (IHC), DOR, TTP, MRD negativity rate, other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and *BCL2* expression (gene expression)

DOR, duration of response; GHS, global health status; IHC, immunohistochemistry; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient reported outcome; QD, daily; QOL, quality of life; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; VGPR, very good partial response.

Demographics and Baseline Characteristics

	Ven+Bd (N=194)	Pbo+Bd (N=97)
Median age, years (range)	66 (36, 87)	65 (44, 83)
≥ 65 years, n (%)	108 (56)	52 (54)
Multiple myeloma ISS, n (%)		
Stage 1	81 (42)	48 (50)
Stage 2	69 (36)	32 (33)
Stage 3	39 (20)	13 (14)
ECOG performance score, n (%)		
0	101 (52)	47 (49)
1 or 2	92 (48)	49 (51)
No. of prior lines of therapy, n (%)		
1	91 (47)	44 (45)
2 or 3	103 (53)	53 (55)
Prior stem cell transplant, n (%)	116 (59)	57 (59)
Prior exposure to PI, n (%)	135 (70)	68 (70)
Prior exposure to IMiD, n (%)	131 (68)	65 (67)
Prior exposure to PI + IMiD, n (%)	78 (40)	42 (44)

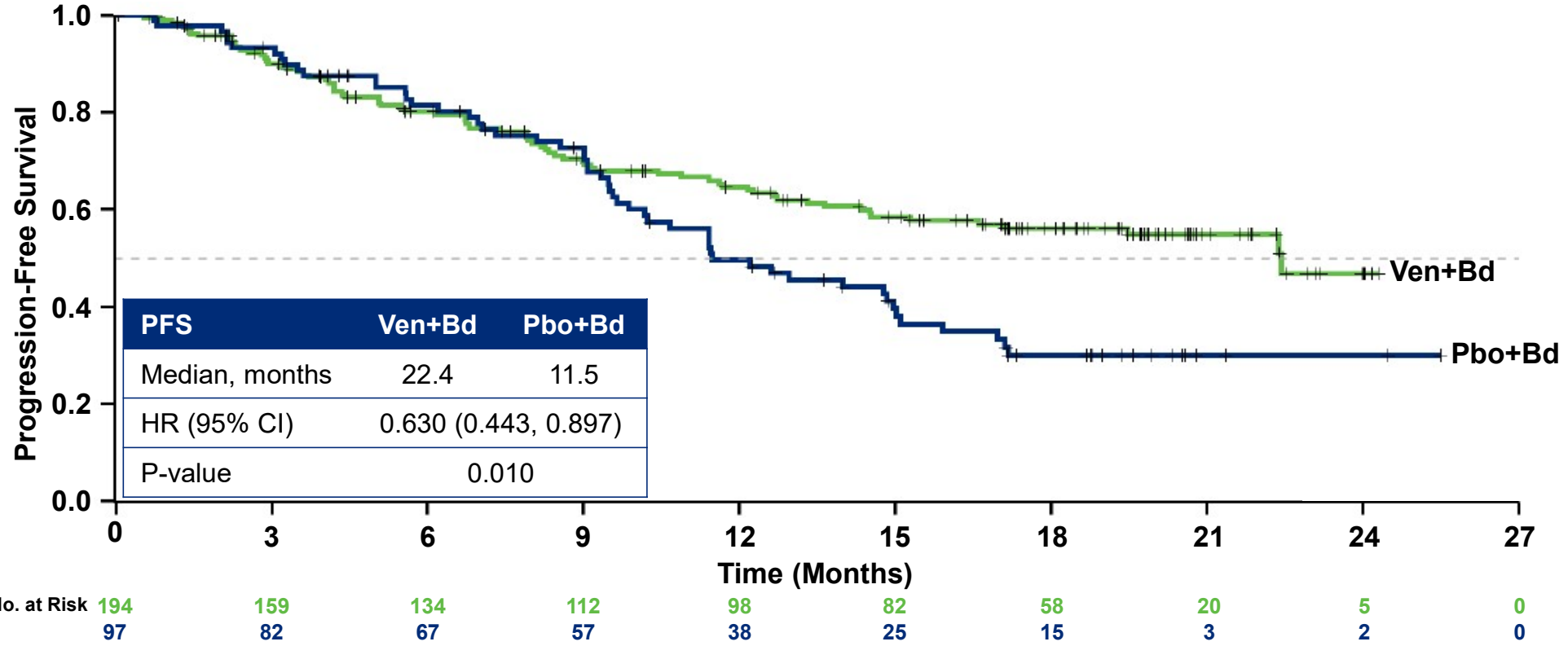
ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor.

	Ven+Bd (N=194)	Pbo+Bd (N=97)
Type of measurable disease, n (%)		
IgG	115 (59)	47 (49)
IgA	40 (21)	25 (26)
FLC / Other	39 (20)	25 (26)
Cytogenetics, n (%)*		
High-risk†	31 (17)	18 (19)
Standard-risk‡	141 (78)	72 (77)
Unknown§	9 (5)	4 (4)
t(11;14) status, n (%)*		
Positive	20 (11)	15 (16)
Negative	152 (84)	74 (79)
Unknown§	9 (5)	5 (5)
BCL-2 expression (IHC), n (%)*		
High	93 (78)	47 (81)
Low	26 (22)	11 (19)

FLC, serum free light chain; IHC, immunohistochemistry.
* Percentage calculated by excluding patients with missing data
† t(4;14) or t(14;16) or del(17p)
‡ No high-risk cytogenetics
§ Sample was tested but results were inconclusive

Primary Endpoint Analysis: Progression-Free Survival

All Patients (ITT), 26 Nov 2018

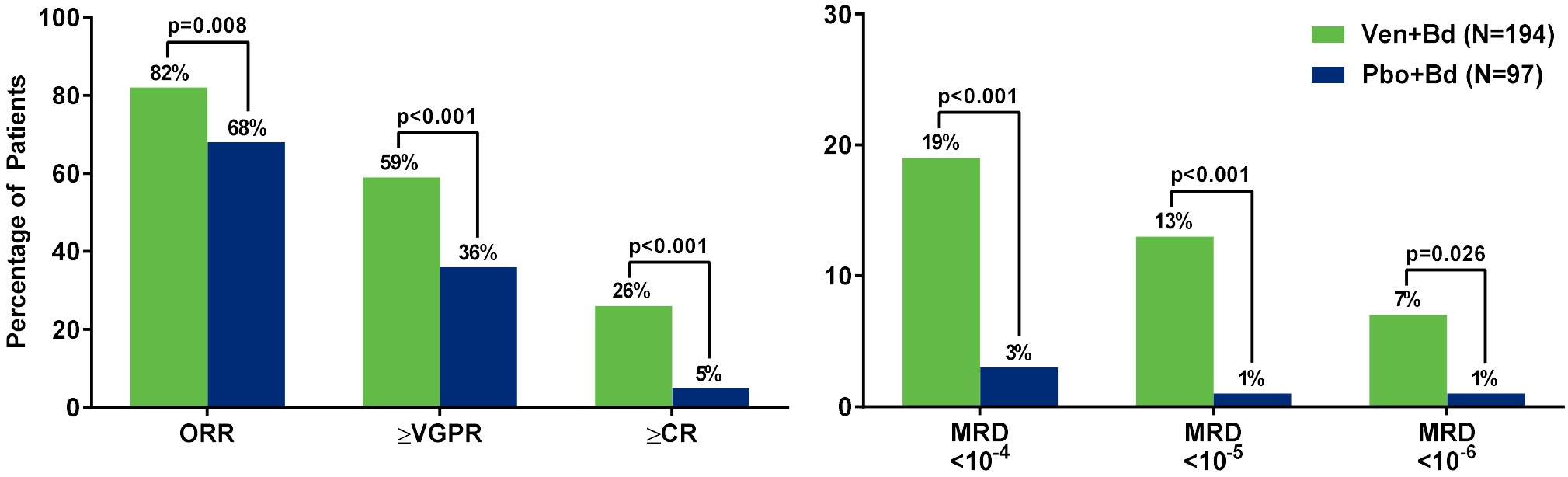


PFS	Ven+Bd	Pbo+Bd
Median, months	22.4	11.5
HR (95% CI)	0.630 (0.443, 0.897)	
P-value	0.010	

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

Clinical Response Rates in All Patients

26 Nov 2018

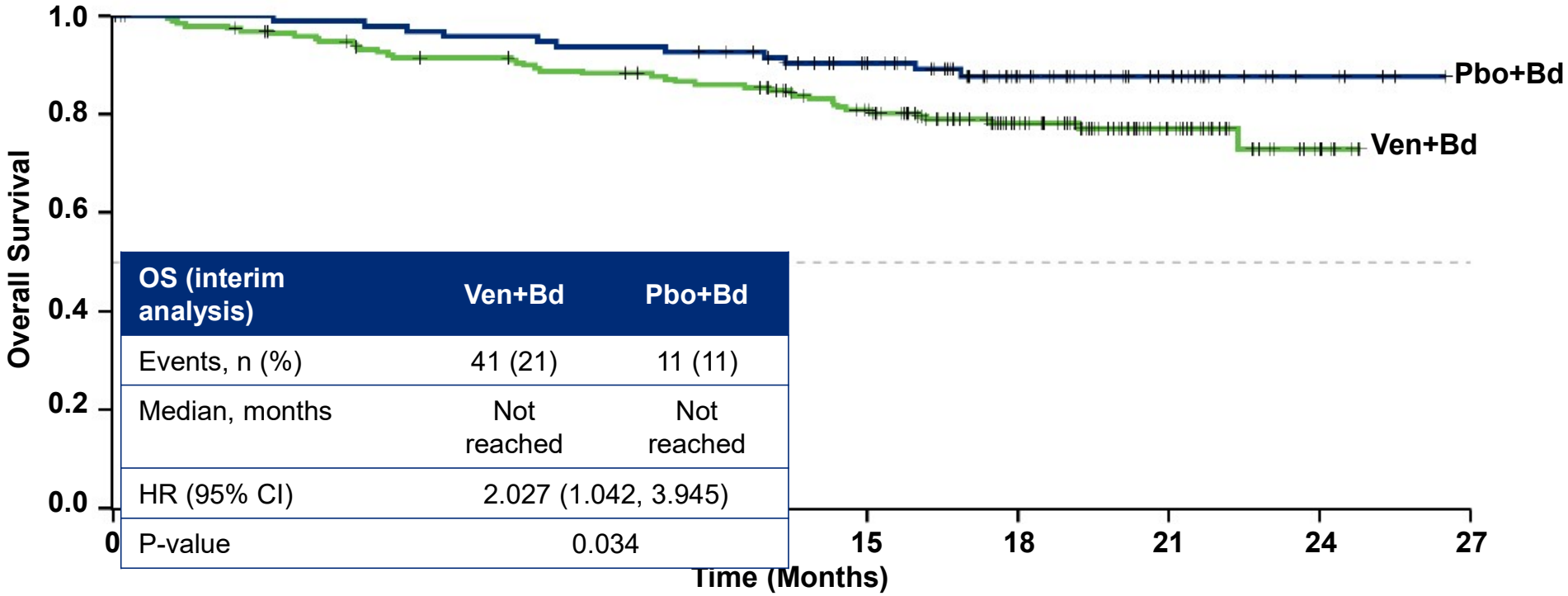


Overall response, ≥VGPR, ≥CR and MRD negativity rates were significantly higher with Ven+Bd

MRD assessment was performed by next-generation sequencing on bone marrow aspirate at time of CR/sCR

Overall Survival

All Patients (ITT), 26 Nov 2018

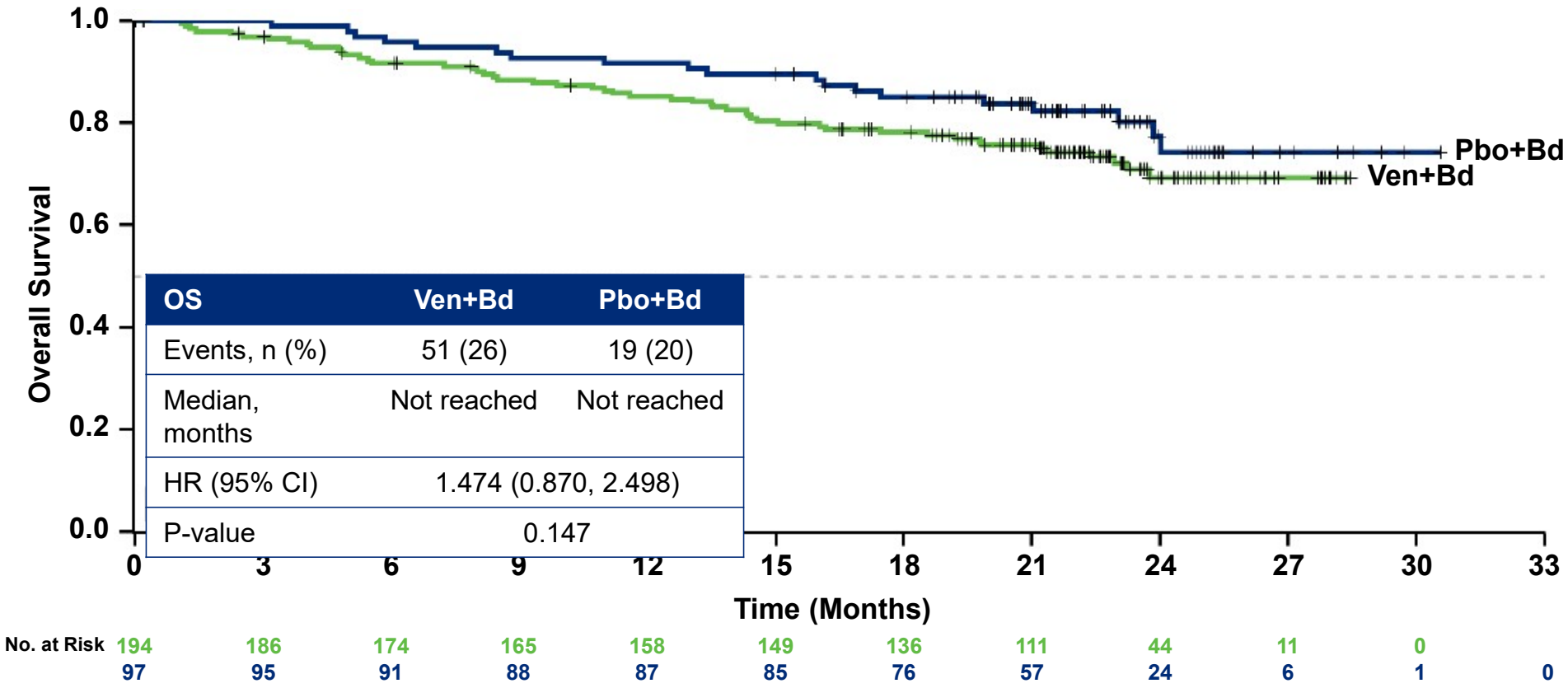


OS (interim analysis)	Ven+Bd	Pbo+Bd
Events, n (%)	41 (21)	11 (11)
Median, months	Not reached	Not reached
HR (95% CI)	2.027 (1.042, 3.945)	
P-value	0.034	

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

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	

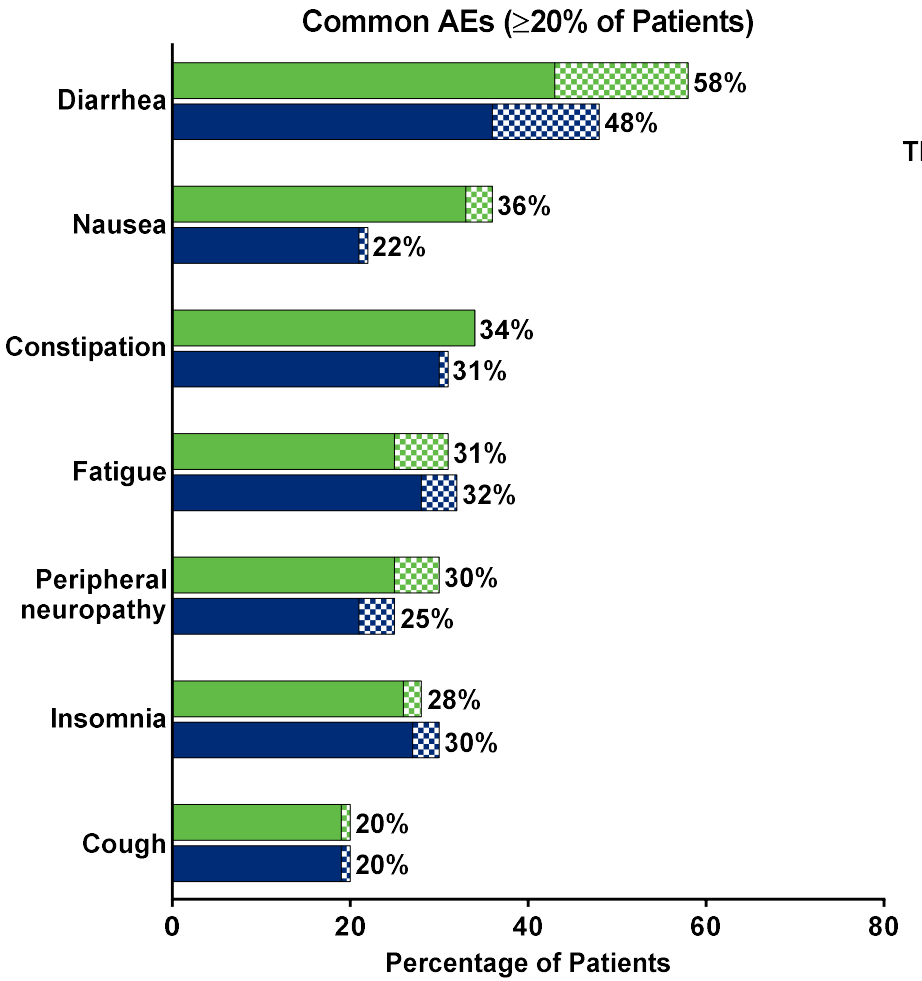
Summary of Cause of Death

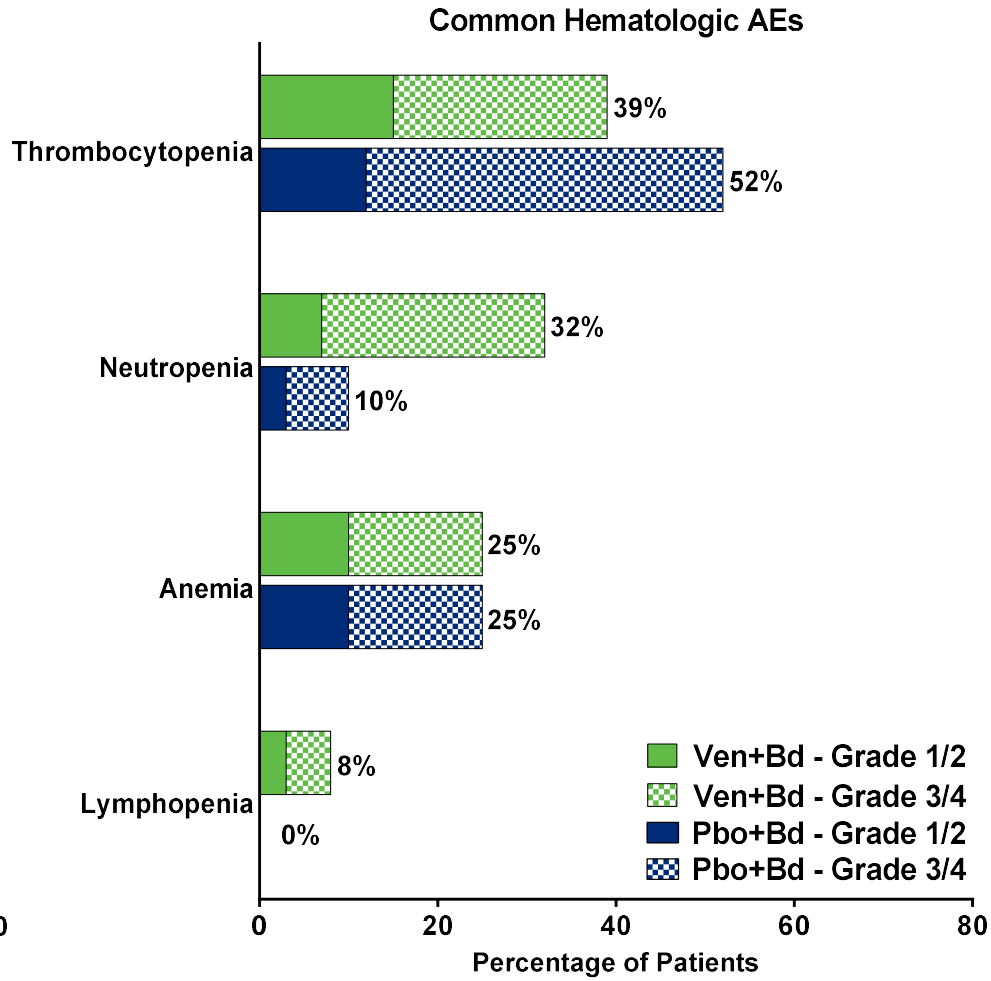
Safety Population (Only patients who received treatment)	Ven+Bd (N = 193) n (%)	Pbo+Bd (N = 96) n (%)
All deaths	**40 (21)**	**11 (11)**
Infection	14 (7)	2 (2)
Progressive disease	17 (9)	8 (8)
Other*	9 (5)	1 (1)
Deaths occurring within 30 days of last dose	**13 (7)**	**1 (1)**
Infection	8 (4)	0
Progressive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

Most Common Adverse Events





BELLINI: Ven+Bor+Dex vs Bor+Dex

- Conclusions:
  - Venetoclax is clearly active, with a pronounced increase in efficacy in the t(11;14) and BLC2high population
  - Increased risk of infection lead to early deaths, with the flipping of the PFS and OS signals
    - This has lead to consternation at the FDA about using PFS as an endpoint in MM – hopefully we won't see a chilling effect on drug development
  - Would have differences in prophylaxis have made a difference?
    - Unknown how many were immunoparetic
    - Prior studies on primary prophy with fluroquinolones in MM have been positive

Kumar et al, IMW 2019