Novel Strategies Under Investigation for Treatment of Myeloma

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Disclosures

Consulting Agreements	Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Takeda Oncology

Case Presentation: Dr Brenner

88-year-old man

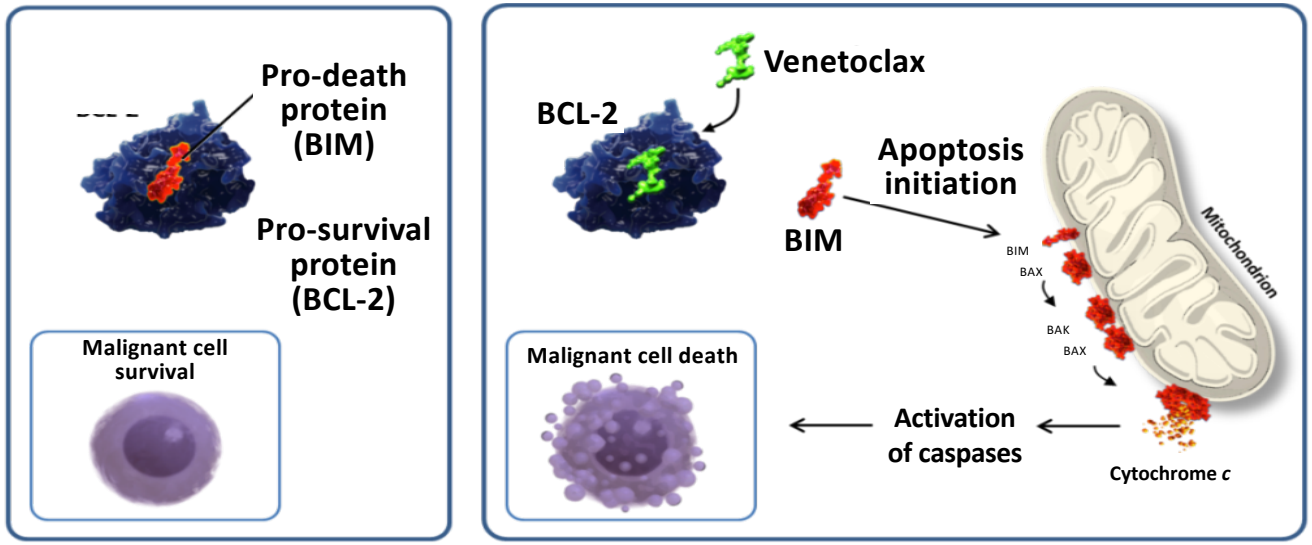
- Chronic renal insufficiency, decreased ejection fraction
- Diagnosis: t(11;14) multiple myeloma
- RVD → progressive disease (PD)
- Pomalidomide/daratumumab/dexamethasone x 18 months → PD

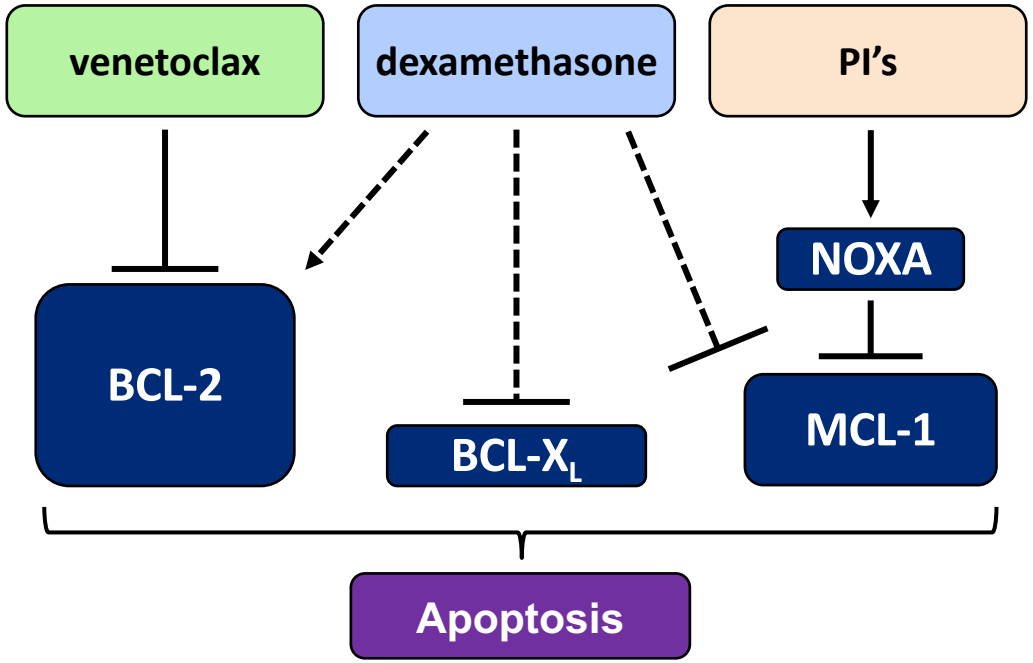
New Approaches in Late relapse

- Most patients have cycled through common agents
- Chemotherapy based approaches while resulting in short term response, don’t result in long term control
- Need new MOA or targets
  - Bcl-2/MCL-1
  - New CD38 MOAB
  - New IMIDs

Background

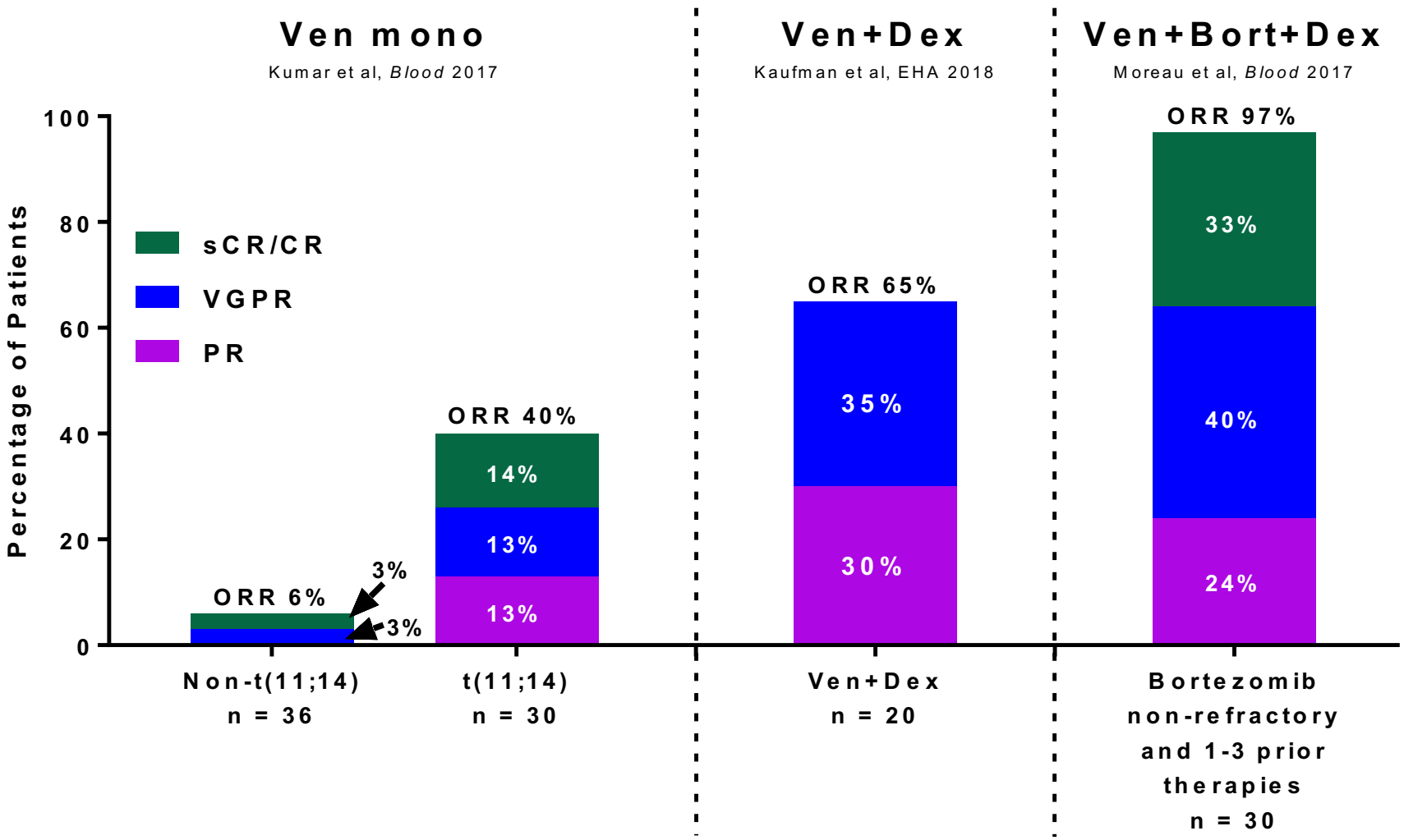
- Pro-survival proteins BCL-2, MCL-1, and BCL-X_L promote multiple myeloma (MM) cell survival[1]
- Venetoclax is a highly selective, potent, oral BCL-2 inhibitor[2]
- Dexamethasone (d) is a glucocorticoid that can indirectly promote BCL-2 dependency in MM cells[4]





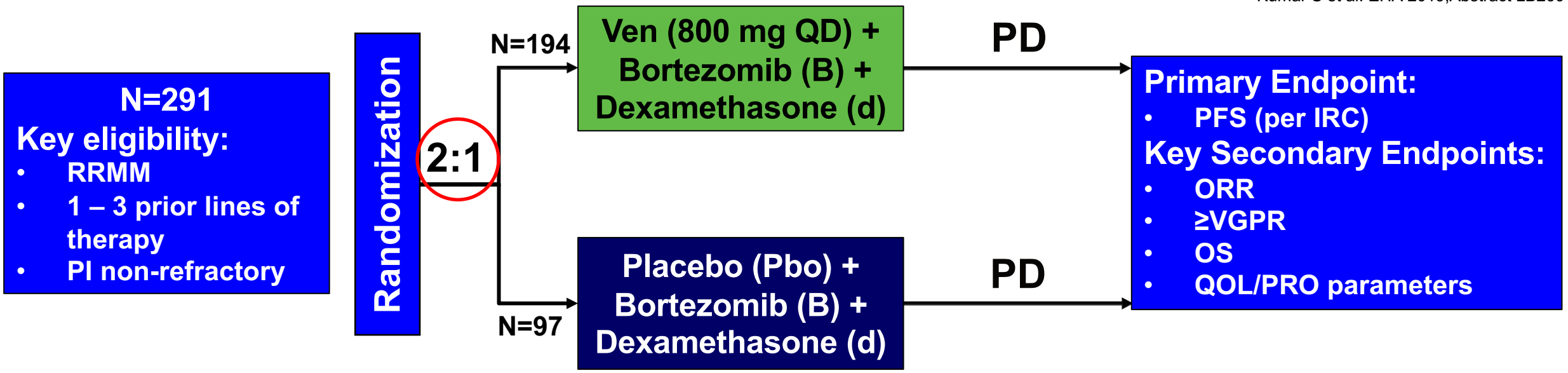
1. Touzeau C et al. Leukemia. 2018 Sep;32(9):1899-1907.
2. Souers AJ et al. *Nat Med.* 2013 Feb; 19(2): 202-8.
3. Ponder K et al. *Cancer Bio & Ther.* 2016 Jul; 17(7):769-777.
4. Matulis SM et al. *Leukemia*. 2016 May;30(5):1086-93.

Venetoclax activity in MM: Early studies



BELLINI Study Design

Kumar S et al. EHA 2019;Abstract LB2601.



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

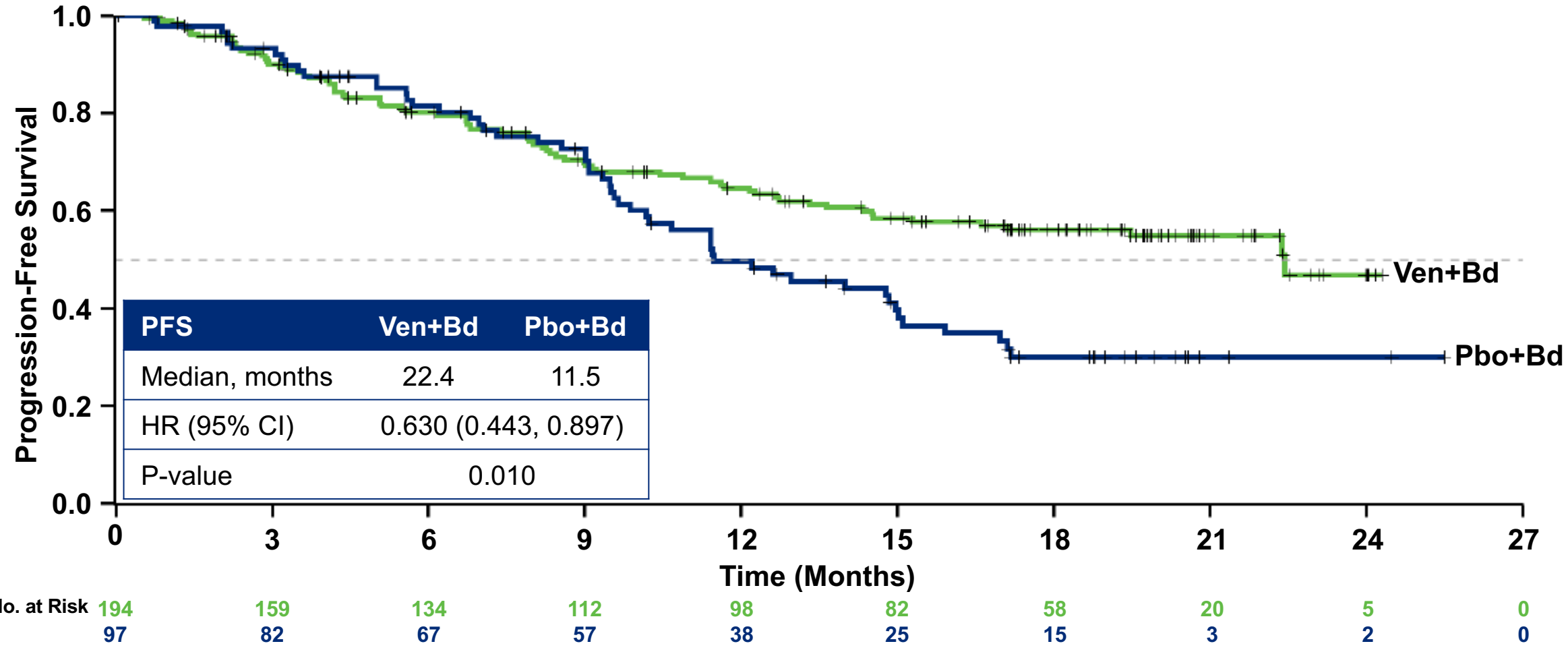
Cycles 9+: 35-day, Bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

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.

Primary Endpoint Analysis: Progression-Free Survival

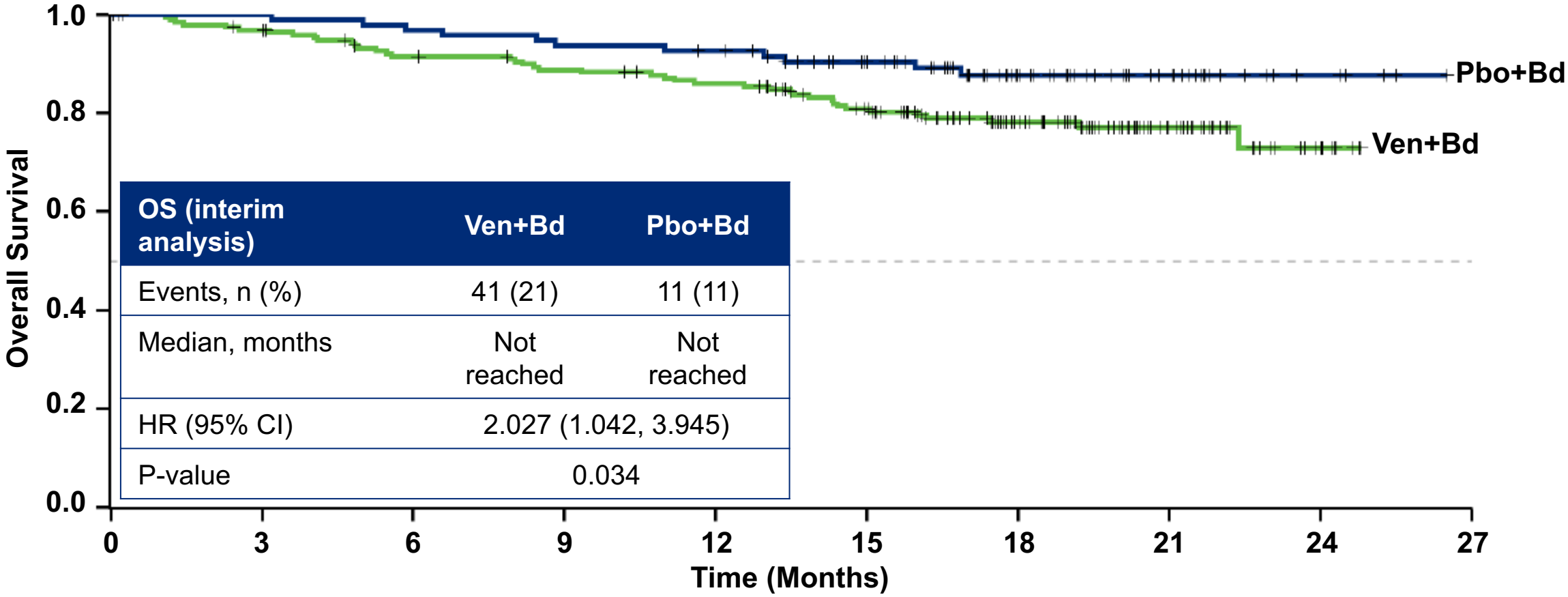
All Patients (ITT), 26 Nov 2018



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

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

Summary of Cause of Death

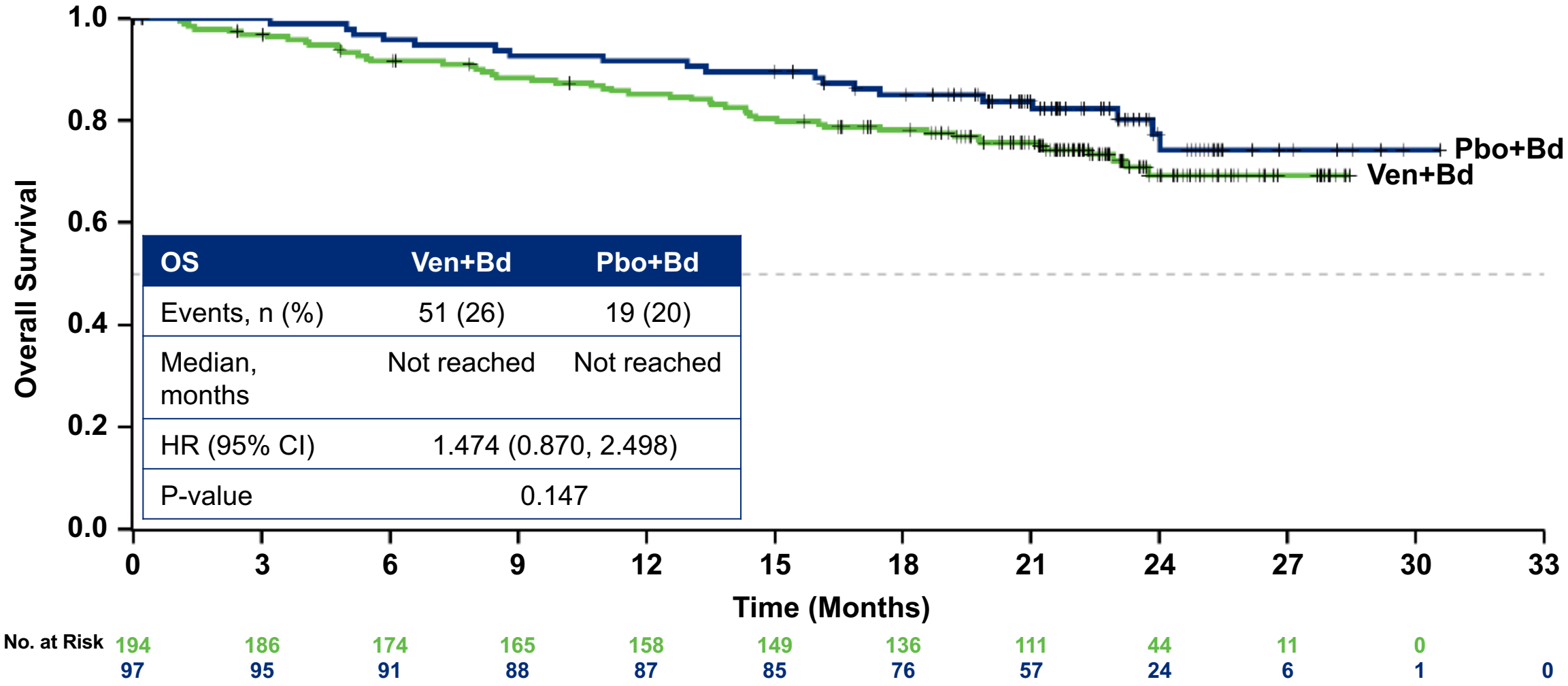
Safety Population (Only patients who received treatment)	Ven+Bd (N = 193) n (%)	Pbo+Bd (N = 96) n (%)
All deaths	**40 (21)**	**11 (11)**
Infection	14 (7)	2 (2)
Progressive disease	17 (9)	8 (8)
Other*	9 (5)	1 (1)
Deaths occurring within 30 days of last dose	**13 (7)**	**1 (1)**
Infection	8 (4)	0
Progressive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

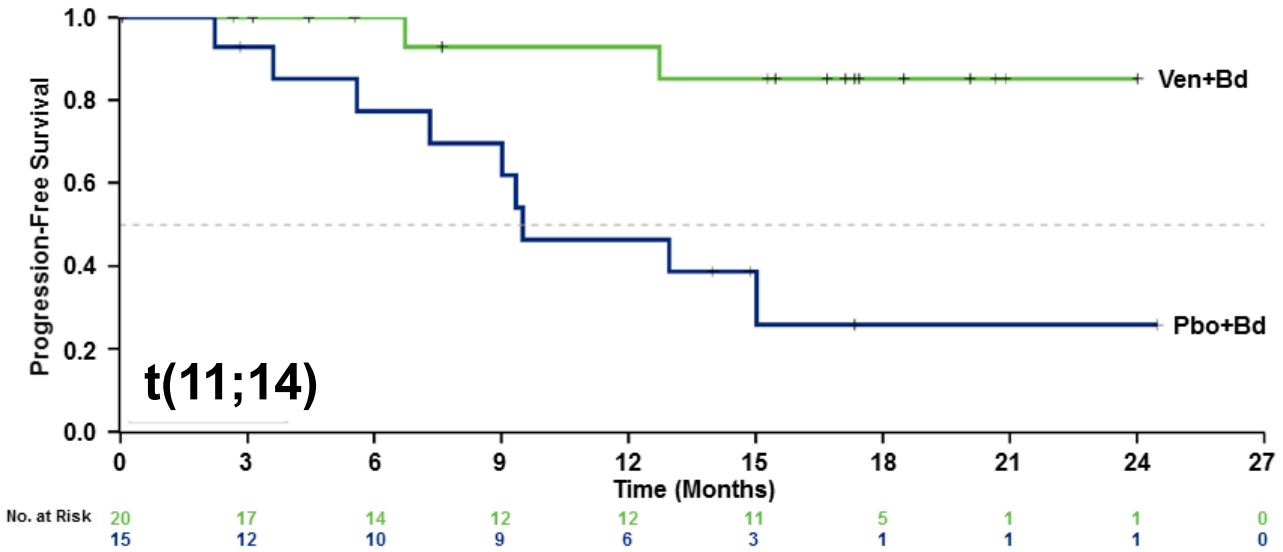
Overall Survival

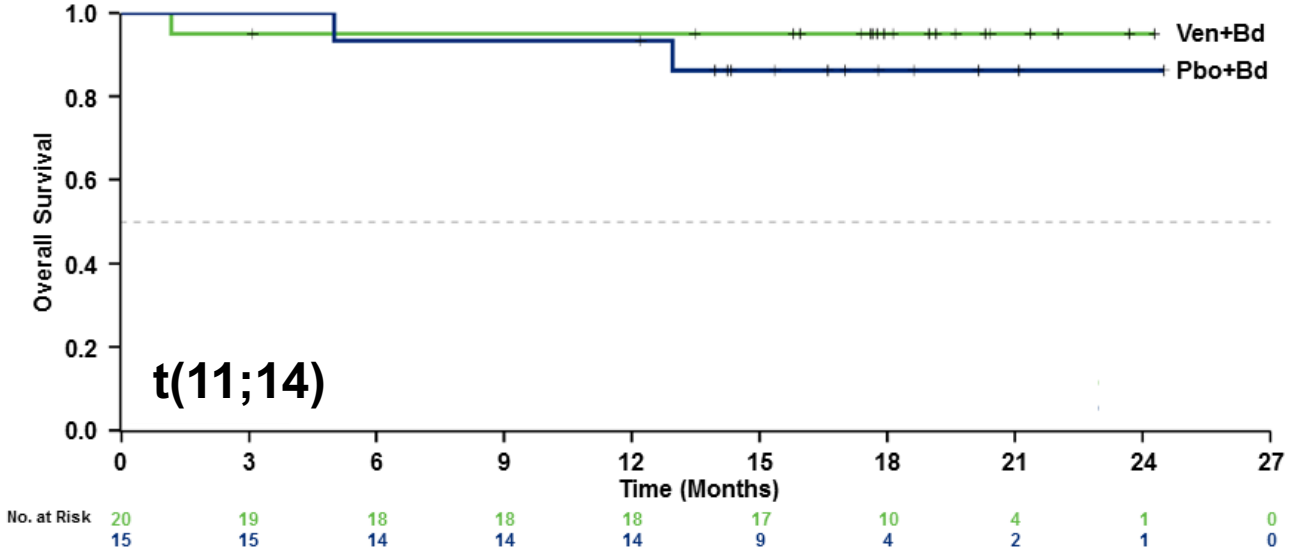
All Patients (ITT), Updated 18 Mar 2019



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	

PFS and OS in Patients with t(11;14)

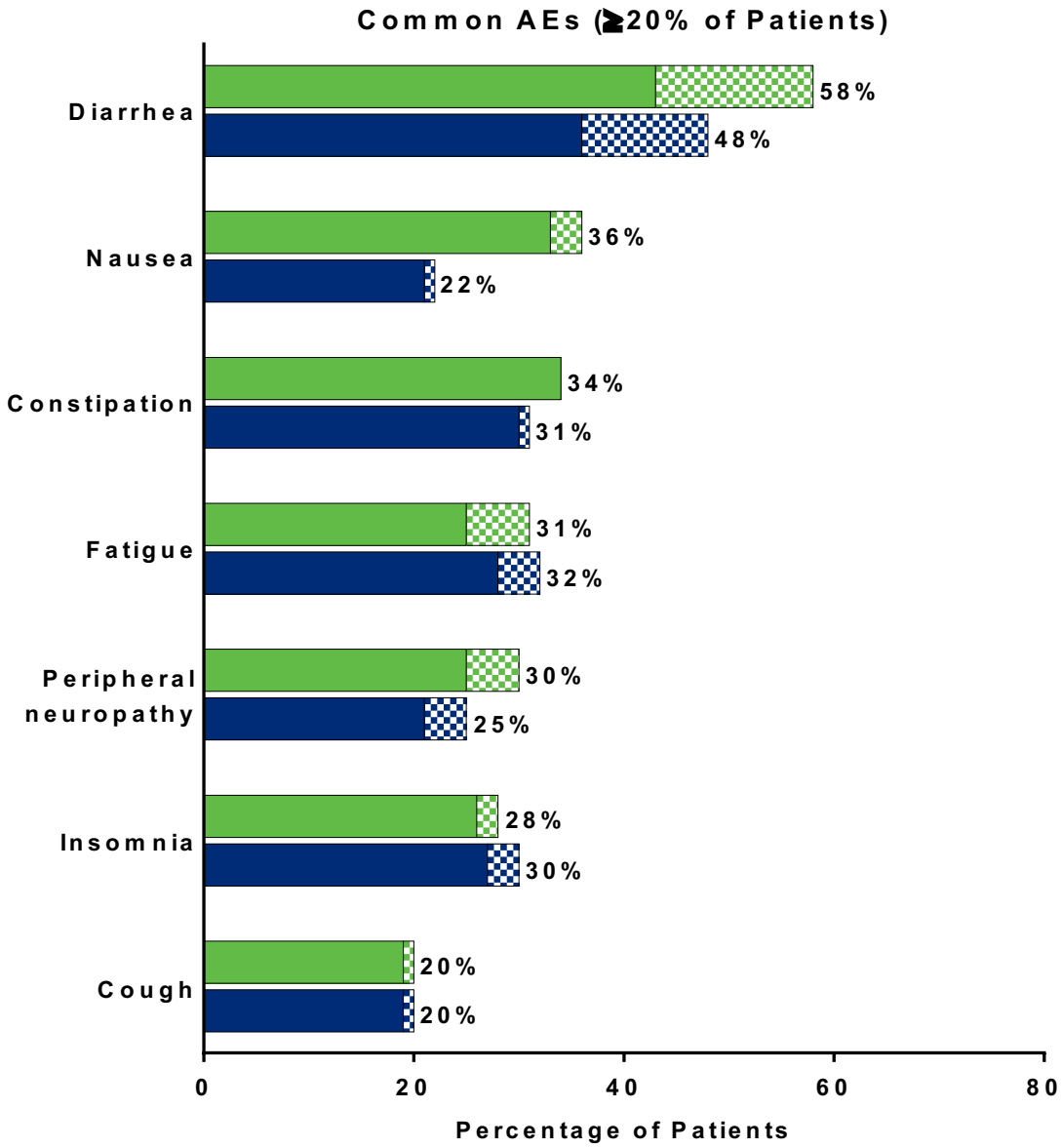


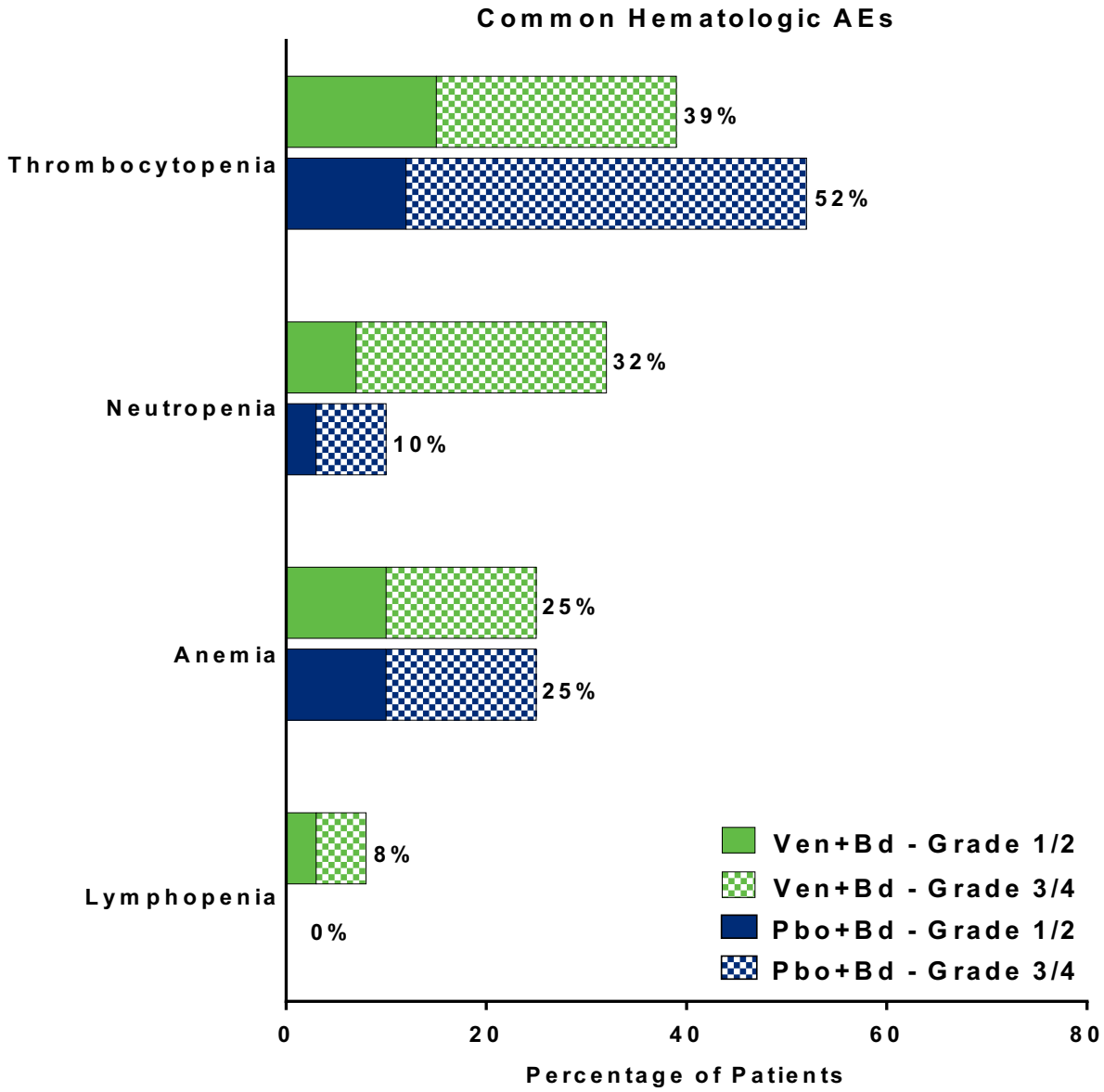


PFS: t(11;14)	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.5
HR (95% CI)	0.110 (0.022, 0.560)	
P-value	0.002	

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	

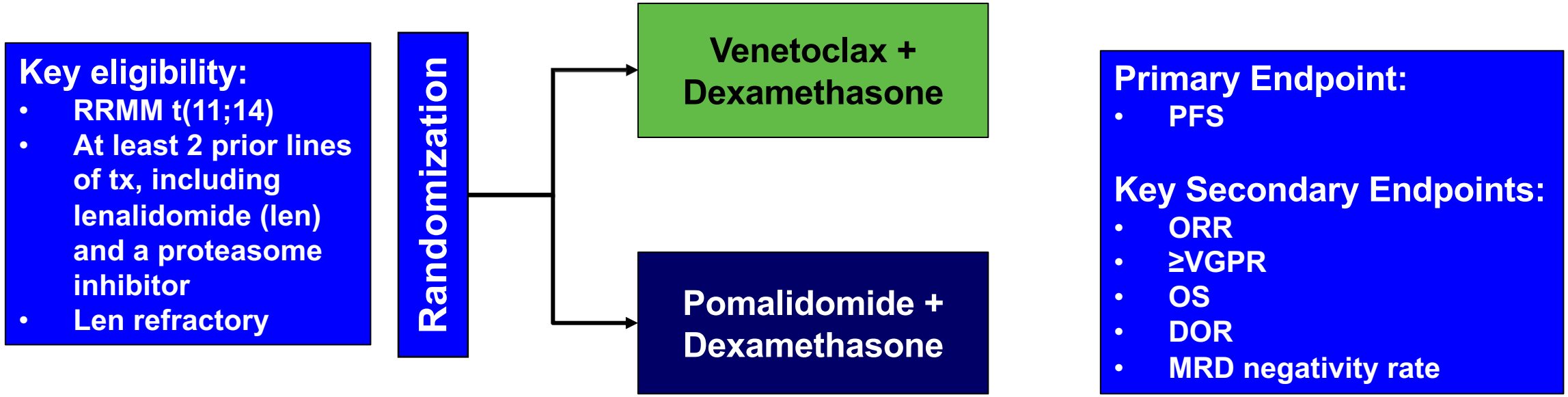
Most Common Adverse Events





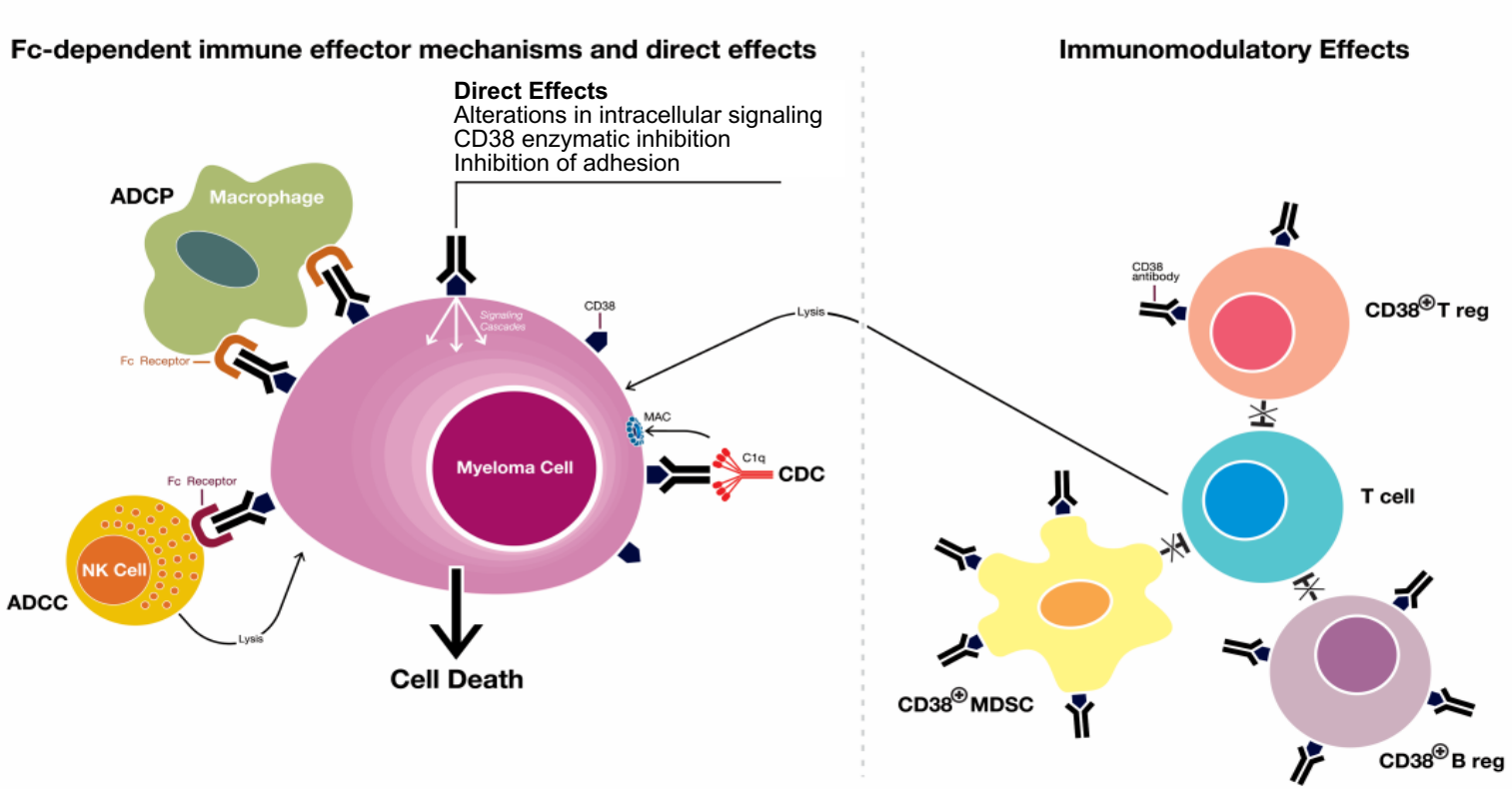
CANOVA Phase III Study Design

NCT03539744
Estimated Enrollment: 244



www.clinicaltrials.gov (Accessed December 2019)

A

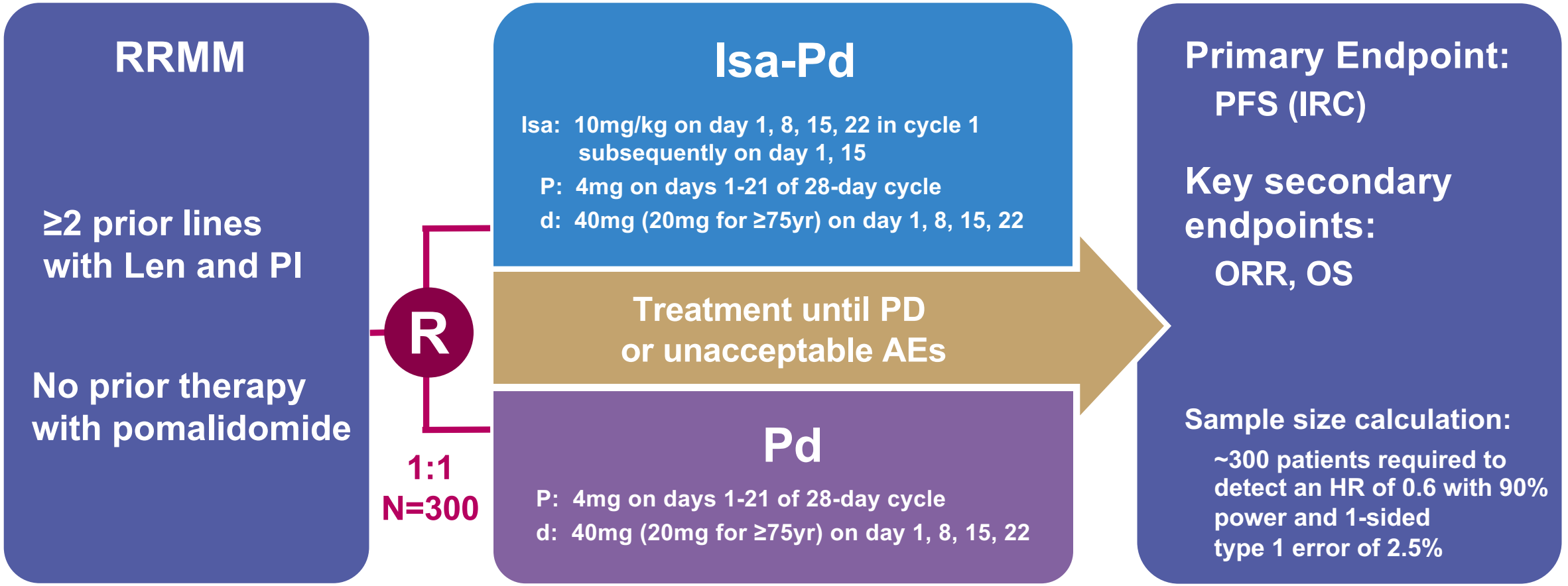


B

MoA	DARATUMUMAB	ISATUXIMAB	MOR202
Origin, isotype	Human IgG-kappa	Chimeric IgG1-kappa	Human IgG1-lambda
CDC	+++	+	+
ADCC	++	++	++
ADCP	+++	nd	++
PCD direct	-	++	-
PCD cross linking	+++	+++	+++
Modulation ectoenzyme function	+	+++	-

N. van de Donk, P. G. Richardson and F. Malavasi (*Blood* 131: 13-29, 2018)

Global phase 3 pivotal study of isatuximab with Pd in RRMM - Study design



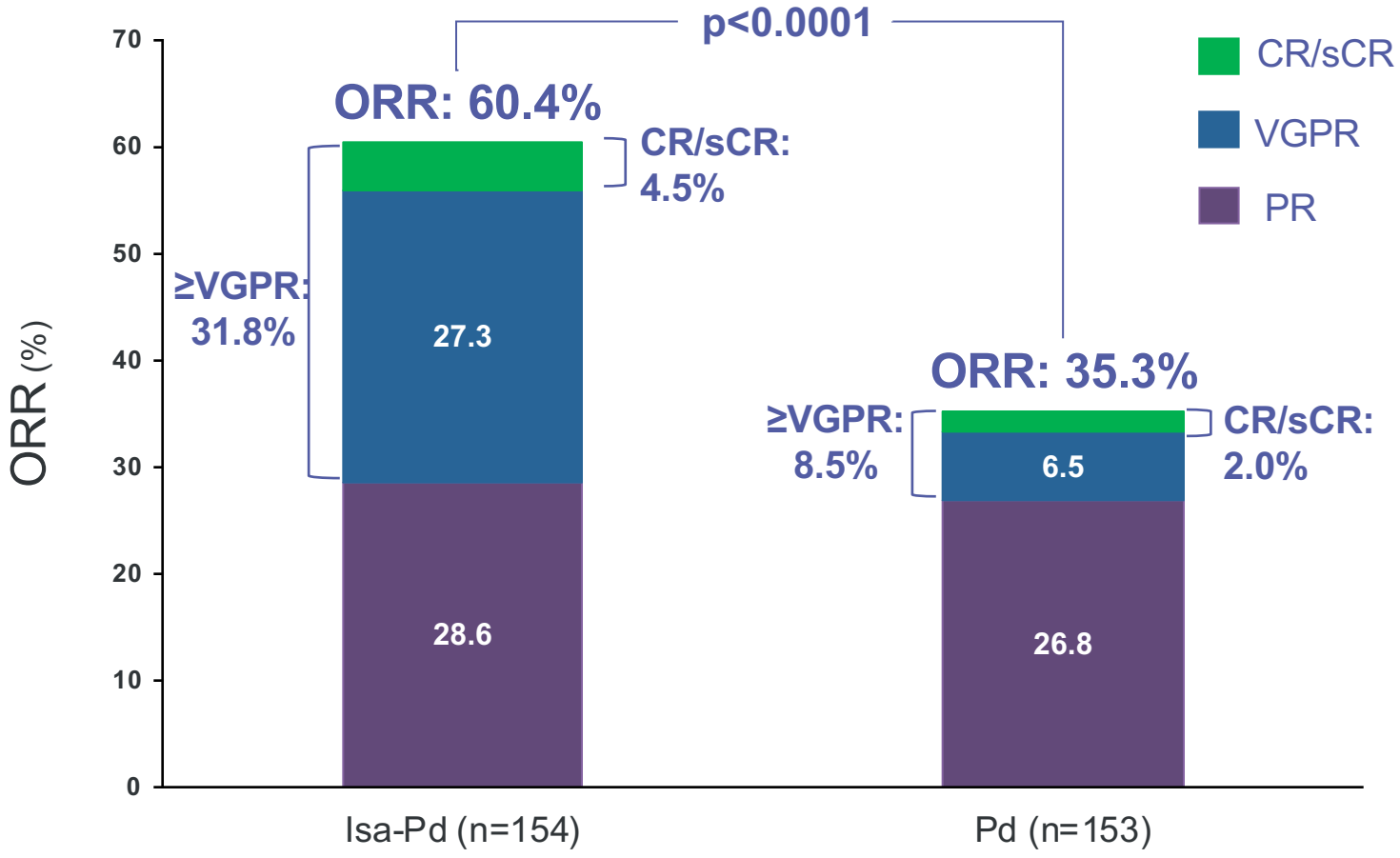
ICARIA-MM is the 1st randomized phase 3 trial adding a CD38 antibody to the Pd backbone

ICARIA-MM study: EFC14335; NCT02990338

AE, adverse event; d, dexamethasone; HR, hazard ratio; IRC, independent review committee; Isa, isatuximab; ORR, overall response rate; OS, overall survival; P, pomalidomide; PD, progressive disease; PFS , progression-free survival; R, randomization

Richardson PG, et al. *Future Oncol* 2018;14:1035–47

Response summary – IRC assessment



Median time to 1st response: Isa-Pd 35 days vs Pd 58 days

True CR rate in Isa-Pd underestimated because of isatuximab interference with M-protein measurement

	Isa-Pd (n=154)	Pd (n=153)
nCR*, %	15.6	3.3

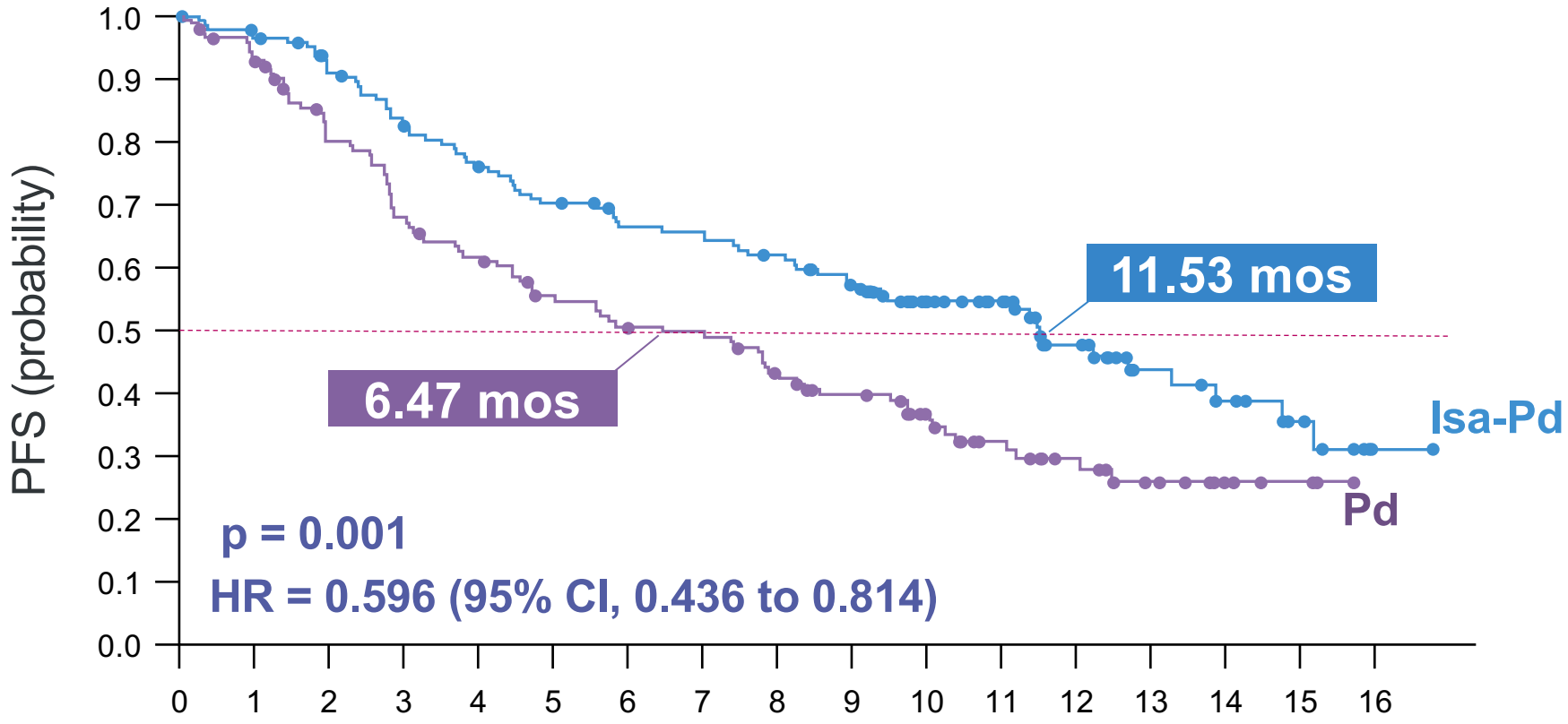
MRD negativity at 10^{-5} (ITT): 5.2% for Isa-Pd vs 0% for Pd

Addition of Isa to Pd resulted in significant improvement in overall and depth of response

Data cut-off 11 Oct, 2018
CR complete response; d, dexamethasone; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent-to-treat; MRD, minimal residual disease; nCR, near complete response; ORR, overall response rate; P, pomalidomide; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
*All criteria for a complete response were met except that immunofixation remained positive [Richardson PG, et al. *N Engl J Med.* 2003;348(26):2609-2617]

Richardson *ASCO 2019;Abstract 8004; Attal Lancet 2019*

PFS primary endpoint – IRC assessment



No. at risk									
Isa-Pd	154	129	106	89	81	52	30	14	1
Pd	153	105	80	63	51	33	17	5	0

Statistically significant and clinically meaningful improvement in PFS

Data cut-off 11 Oct, 2018
CI, confidence interval; d, dexamethasone; HR, Hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; mos, months; PFS, progression-free survival; P, pomalidomide

Richardson *ASCO 2019;Abstract 8004; Attal Lancet 2019*

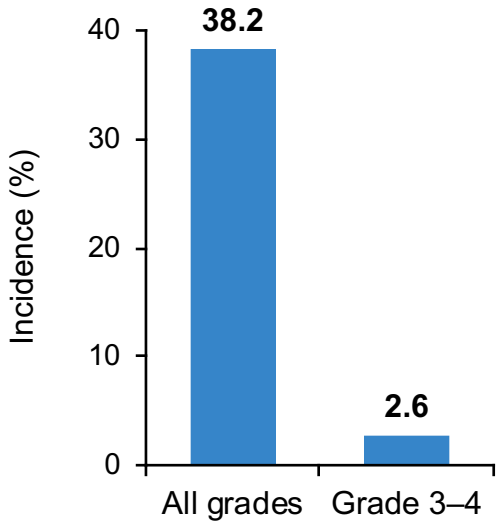
Treatment-emergent adverse events

TEAE (≥15% of Isa-Pd)	Isa-Pd (n=152)			Pd (n=149)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
URTI	28.3	3.3	0	17.4	0.7	0
Diarrhea	25.7	2.0	0	19.5	0.7	0
Bronchitis	23.7	3.3	0	8.7	0.7	0
Pneumonia	20.4	15.1	1.3	17.4	13.4	1.3
Fatigue	17.1	3.9	0	21.5	0	0
Back pain	16.4	2.0	0	14.8	1.3	0
Constipation	15.8	0	0	17.4	0	0
Asthenia	15.1	3.3	0	18.1	2.7	0
Dyspnea	15.1	3.9	0	10.1	1.3	0
Nausea	15.1	0	0	9.4	0	0

Isa-Pd infusion reactions

No delayed reactions

Vast majority during 1st infusion

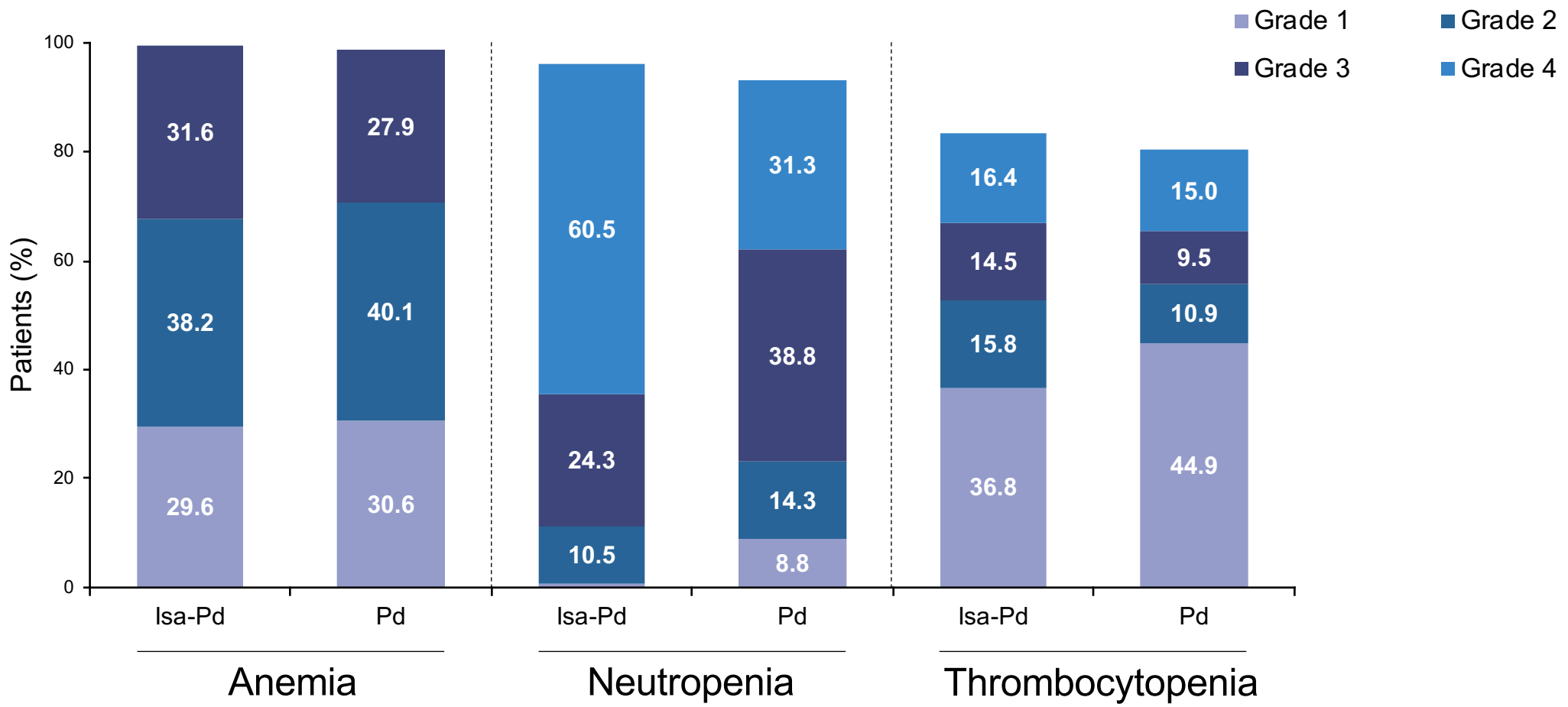


Isa-Pd had a manageable safety profile

Data cut-off 22 Nov., 2018
d, dexamethasone; Isa, isatuximab; P, pomalidomide; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

Richardson *ASCO 2019;Abstract 8004; Attal Lancet 2019*

Hematologic abnormalities



Anemia and thrombocytopenia were similar in both arms
Grade 4 neutropenia was more frequent with Isa-Pd

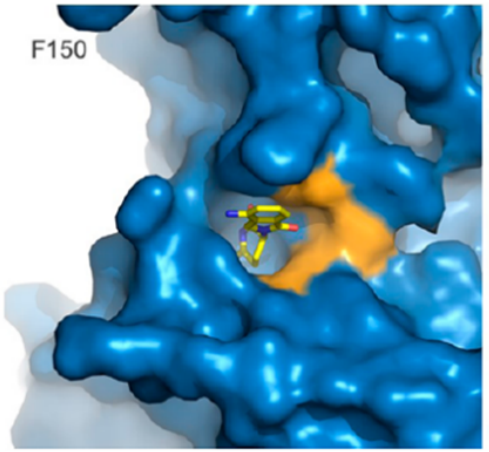
d, dexamethasone; Isa, isatuximab; P, pomalidomide

Richardson *ASCO 2019;Abstract 8004; Attal Lancet 2019*

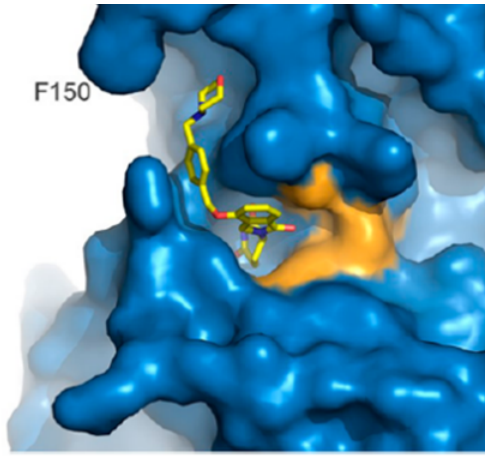
IBERDOMIDE MECHANISM OF ACTION

- IBER enhances in vitro immune stimulatory activity versus LEN and POM[1]

LEN[2]

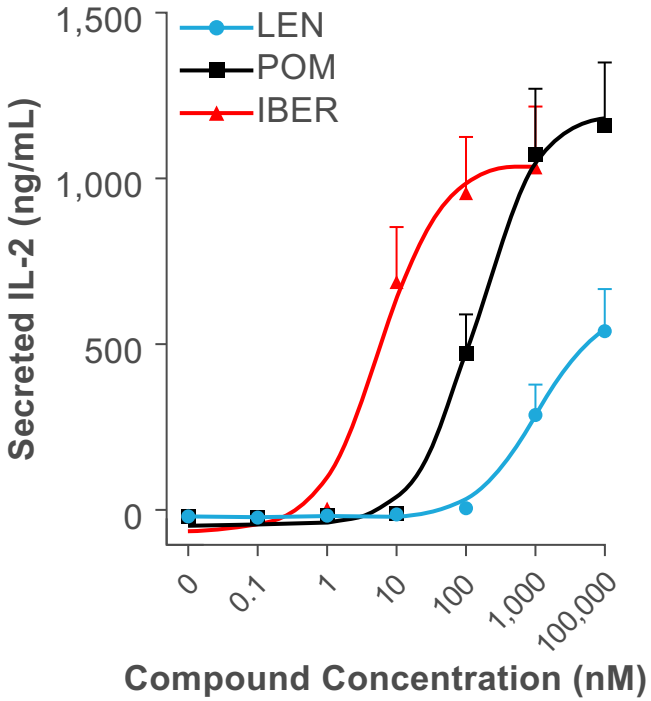


IBER[2]

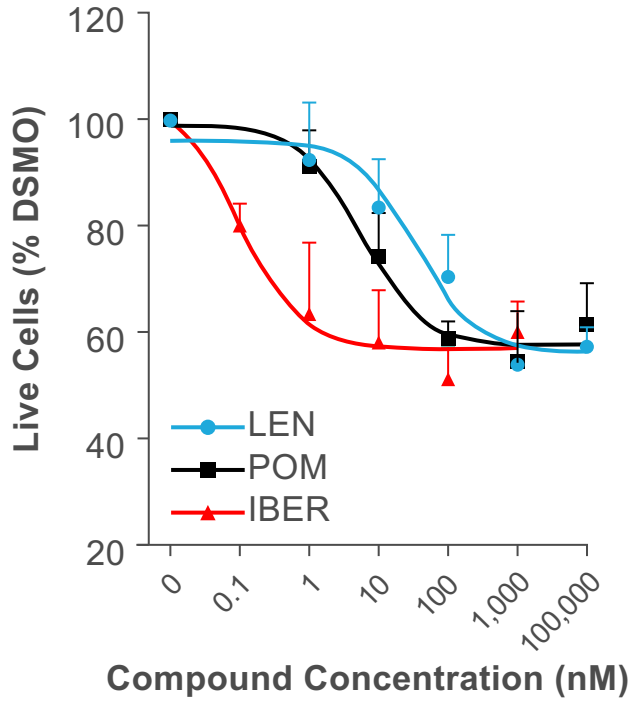


EC_{50}, nM[2]	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

IL-2 Secretion by Treated PBMCs[1]



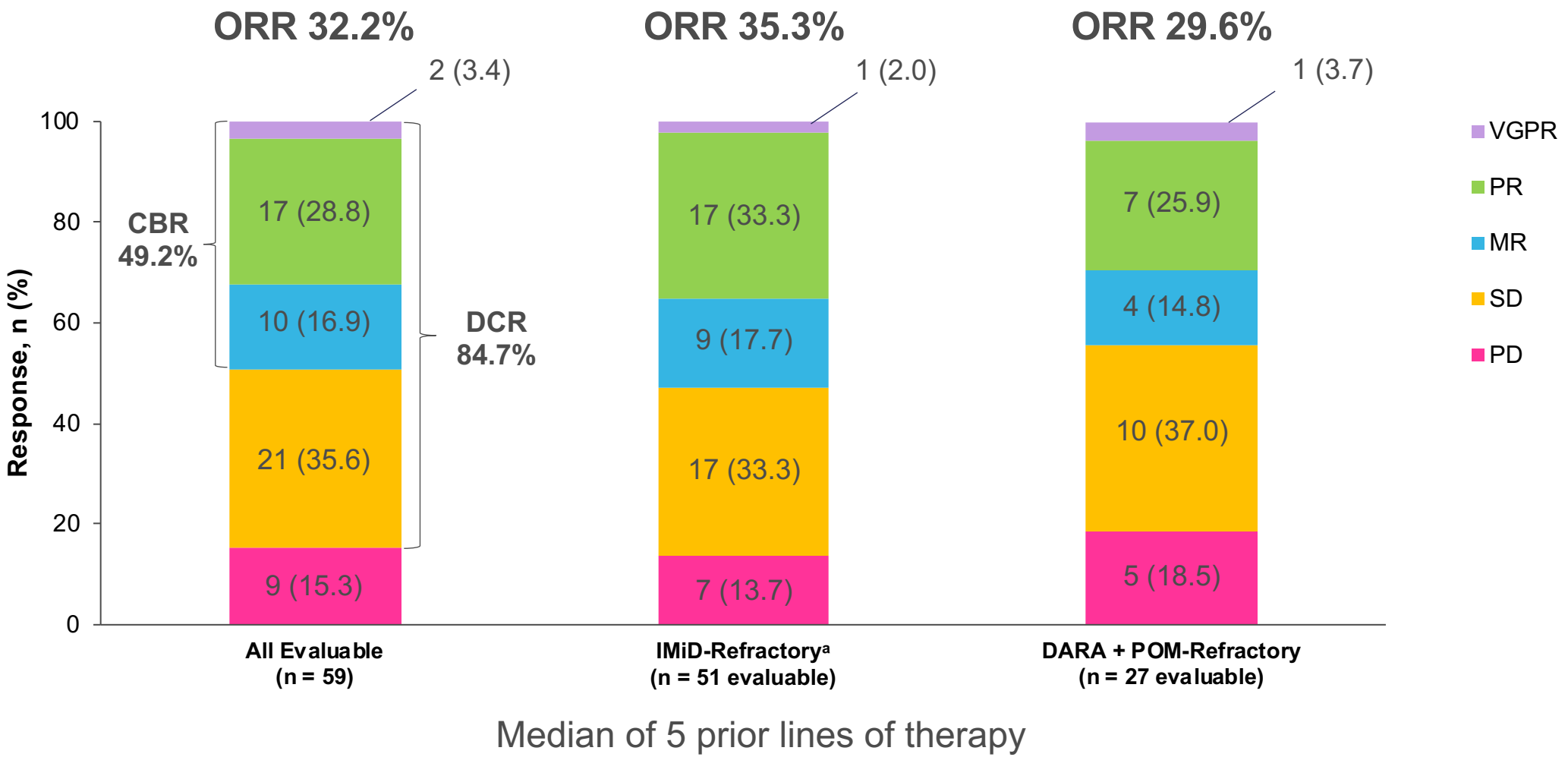
MM Cell Survival in Co-Culture With Treated PBMCs[1]



BORT, bortezomib; DARA, daratumumab; DSMO, dimethylsulfoxide; EC_{50}, half maximal effective concentration; IL, interleukin; NK, natural killer; PBMC, peripheral blood mononuclear cell.

1. Bjorklund CC, et al. Unpublished data. 2. Adapted with permission from Matyskiela ME, et al. J Med Chem. 2018;61:535-542 © 2018 American Chemical Society.

RESPONSE



Evaluable patients include patients who have received ≥ 1 dose of IBER, had measurable disease at baseline, and ≥ 1 post-baseline response assessment.

[a] Includes LEN and POM.
CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.

Lonial ASCO 2019;Abstract 8006.