Monoclonal Antibodies: Isatuximab and MOR202

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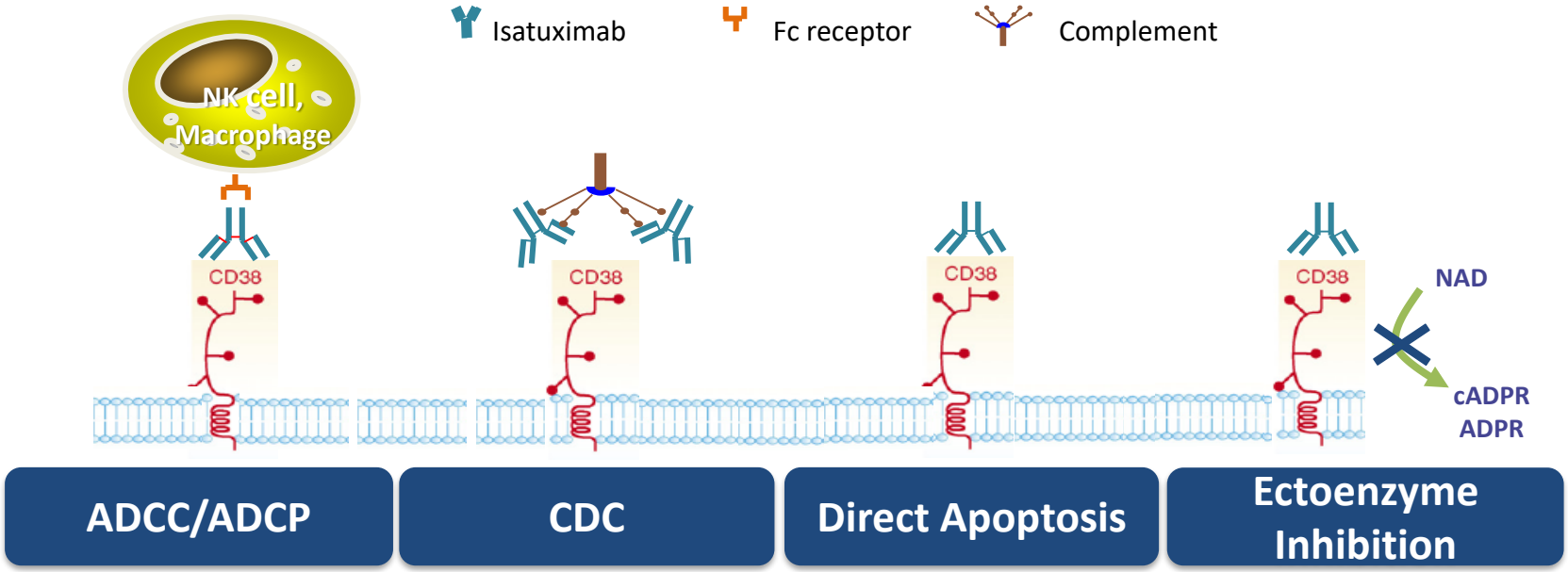
DISCLOSURES

- Advisory Board Participation:
  - Celgene, Takeda, Janssen, KITE, Merck, Abbvie, Medimmune,Genentech, Oncopeptides, Amgen, Adaptive
- Clinical Trial Support to the institution:
  - Celgene, Takeda, Janssen, BMS, Sanofi, KITE, Merck, Abbvie, Medimmune, Novartis, Roche-Genentech, Amgen
- Honorarium: Reddys Lab

Monoclonal Antibodies

- Next wave of therapeutics in myeloma
- Daratumumab (anti-CD38) and Elotuzumab (anti-SLAMF7) are approved and in the clinic
- Several others are in the clinic
  - Newer anti-CD38
  - BCMA
  - CD56
- Many are conjugated with toxins

Isatuximab: Multiple Modes of Action



Preclinical data demonstrated anti-MM activity of isatuximab was enhanced by combining with IMiDs, providing rationale for testing isatuximab plus Len/Dex and with Pom/Dex

Martin T, et al. Blood 2014;124:83

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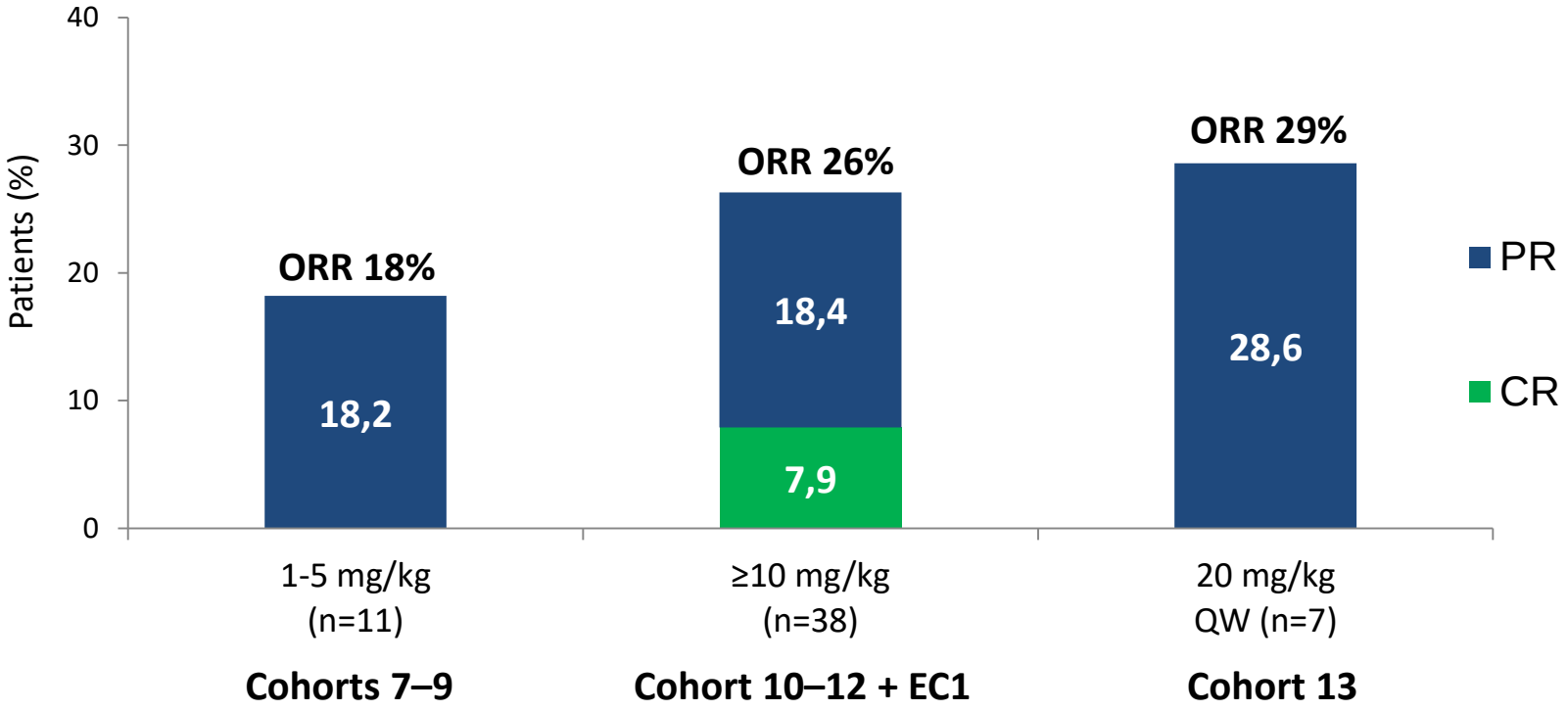
TED10893 Phase 1 monotherapy



Martin et al, ASH 2015

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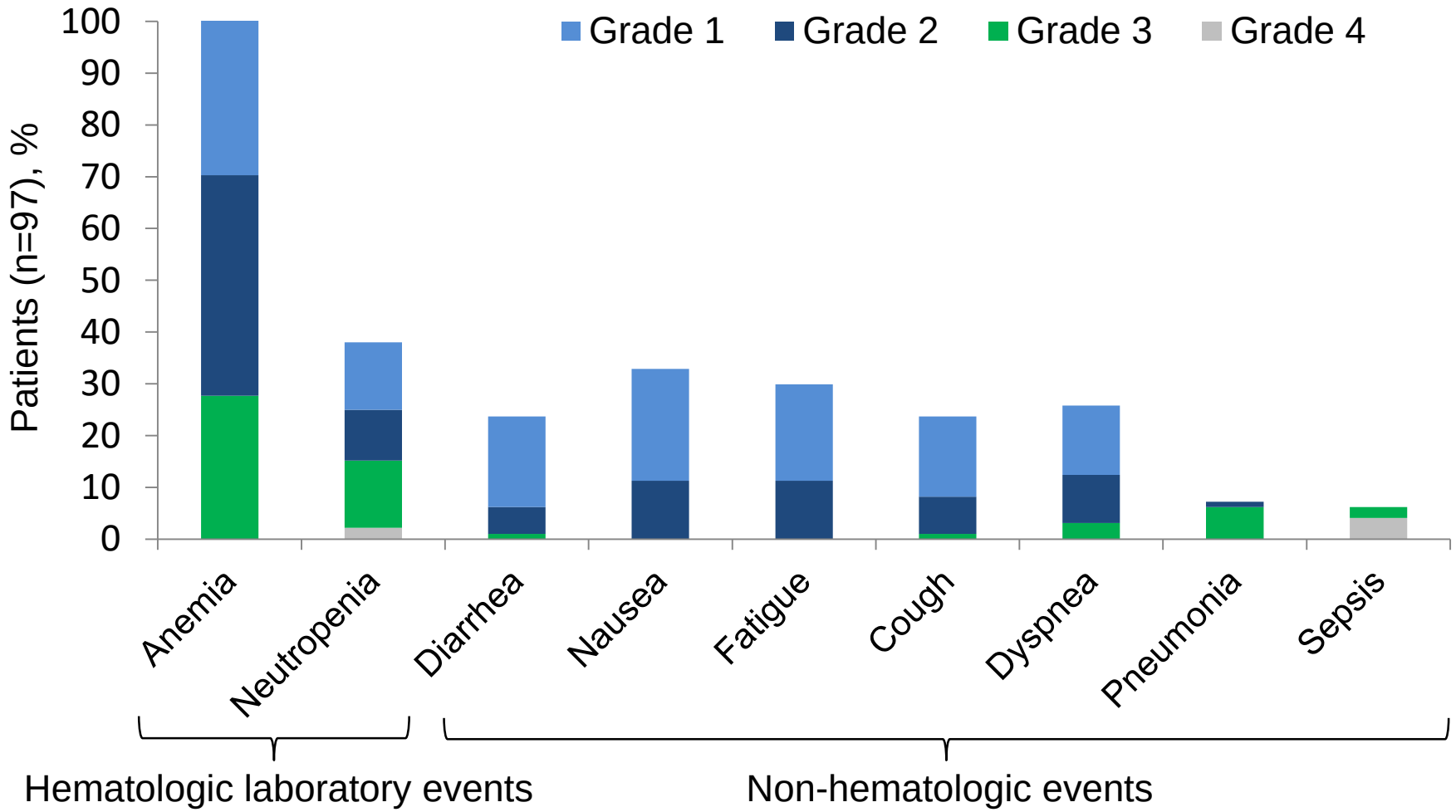
Isatuximab: Safety



Martin et al, ASH 2015

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Isatuximab Phase II Dose Finding Study

Eligibility

- RRMM; double refractory to an IMiD and PI OR have received ≥3 prior lines of therapy
- MR or better to at least one prior line of therapy

Primary Objective

- Evaluation of single agent-activity at different doses/schedules

Secondary Objectives

- Safety and tolerability; duration of response; PFS, OS; pharmacokinetics of different doses/schedules

Phase II Dose Finding	Interim Response Data[1]
Randomization (1:1:1)	
Arm 1: 3 mg/kg Q2W	ORR: 9%
Arm 2: 10 mg/kg Q2W Cycle 1, then Q4W	ORR: 20%
Arm 3: 10 mg/kg Q2W	ORR: 29%
Arm 4: 20 mg/kg QW Cycle 1, then Q2W	ORR: 24%
1 cycle=28 days	

IMiD, immunomodulatory drug; MR, minimal response; OS, overall survival;
ORR, overall response rate; PFS, progression-free survival;
PI, proteasome inhibitor; QnW, dosing once every n weeks;

Richter et al, ASCO 2016

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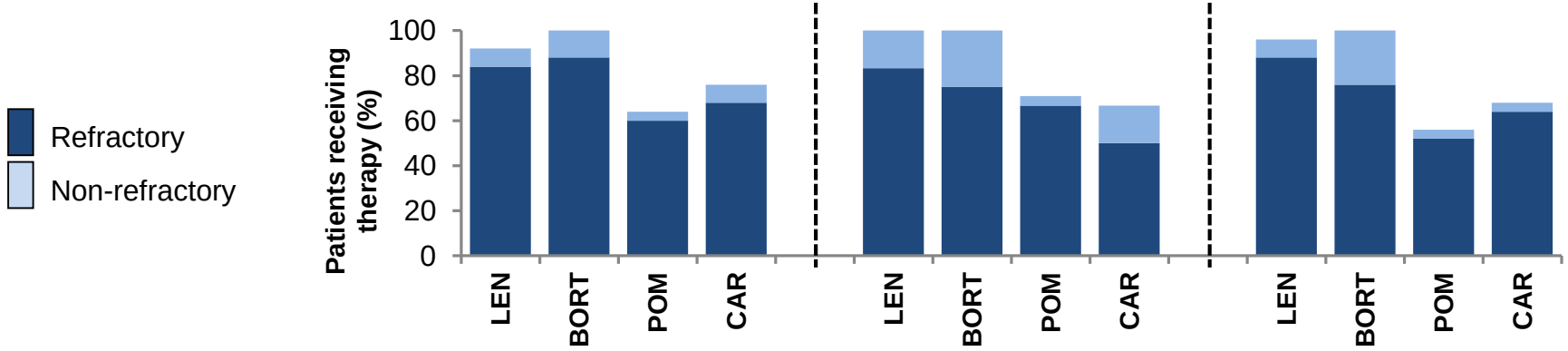
Patient characteristics

	Isatuximab dose, mg/kg and schedule		
	10 Q2W/Q4W (n=25)	10 Q2W (n=24)	20 QW/Q2W (n=25)
Median prior lines of therapy, n (range)	5 (3–14)	5.5 (2–13)	5 (2–10)
≥1 prior stem cell transplant, n (%)	23 (92)	21 (88)	22 (88)
Double refractory, n (%)	24 (96)	20 (83)	22 (88)
Quadruple refractory, n (%)	12 (48)	10 (42)	8 (32)



Richter et al, ASCO 2016

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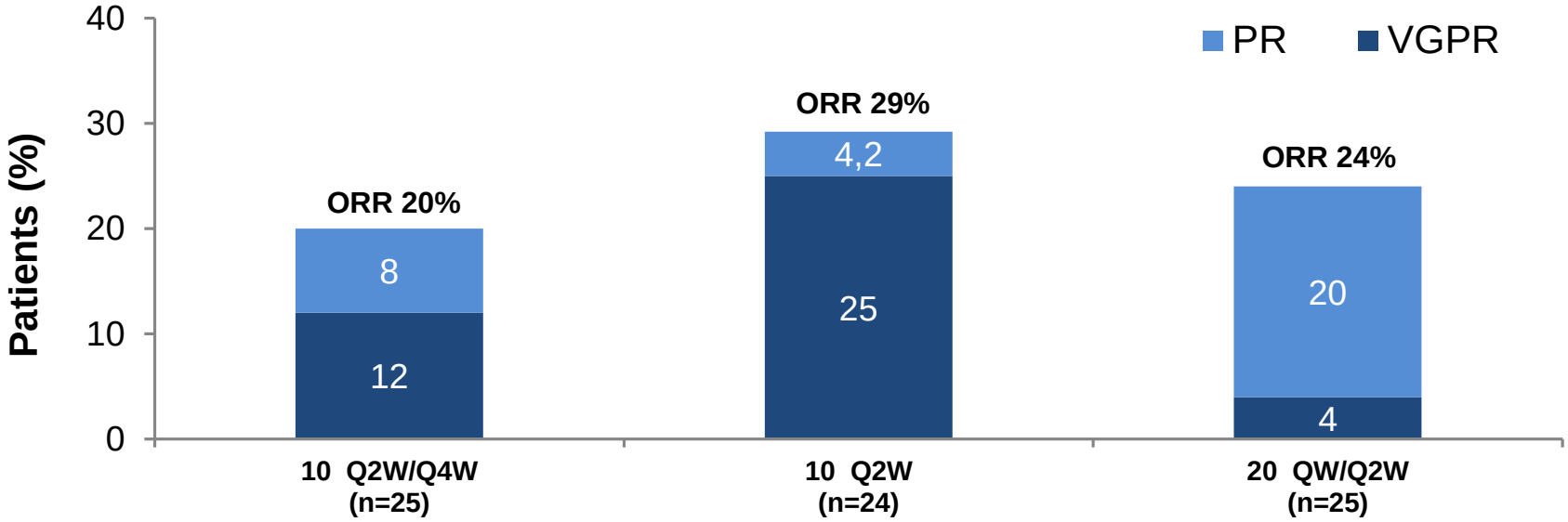
Isatuximab: Efficacy



Median time to first response, mo	2 (0.8–2.1)	0.9 (0.9–1)	1.35 (0.9–2.8)
Median time to best response, mo	3 (0.9–12.9)	4.6 (0.9–12.9)	1.35 (0.9–2.8)

Data cut-off: Feb 29, 2016
***Response defined according to IMWG criteria for all treated patients. Responses were confirmed**
PR, partial response; VGPR, very good partial response

Isatuximab: TED10893

Richter et al, ASCO 2016

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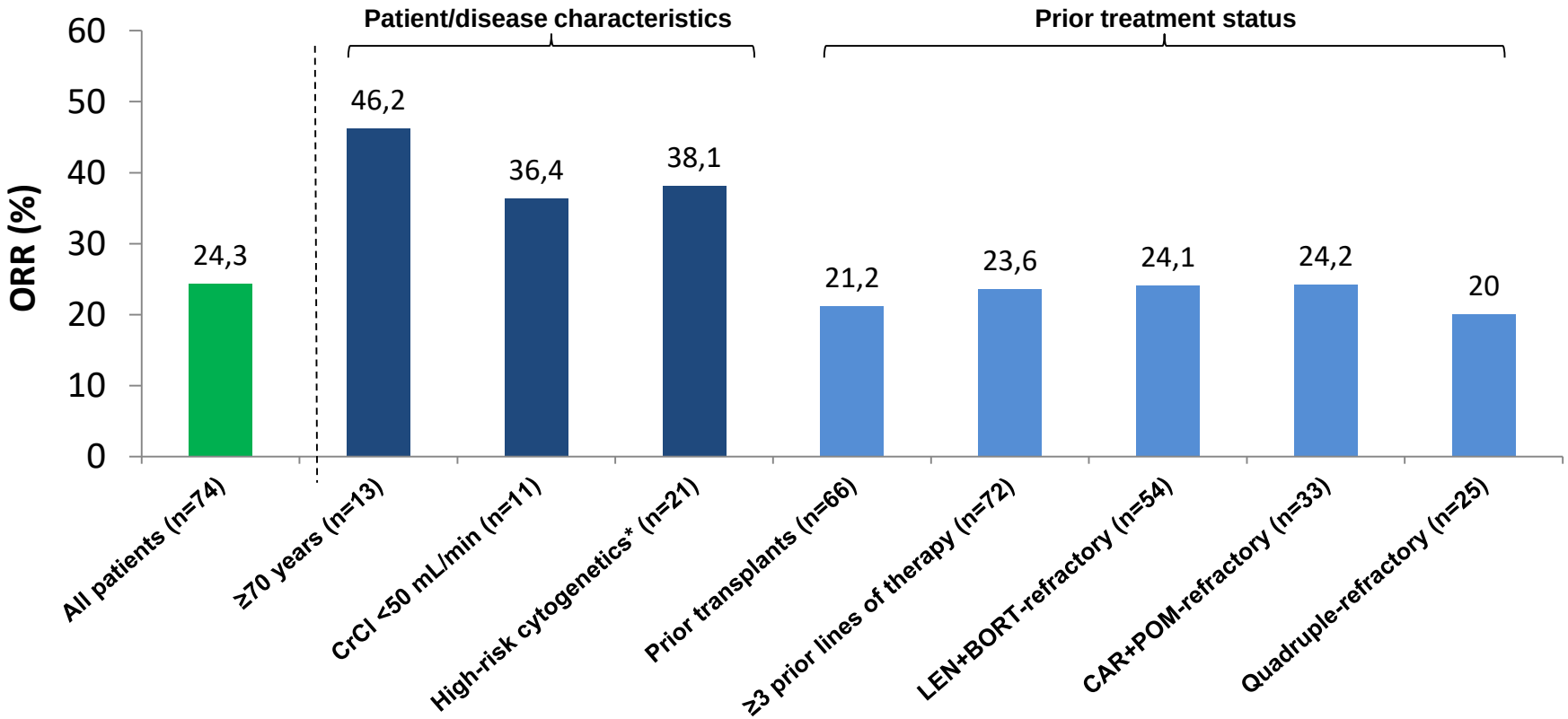
Response by Subgroups



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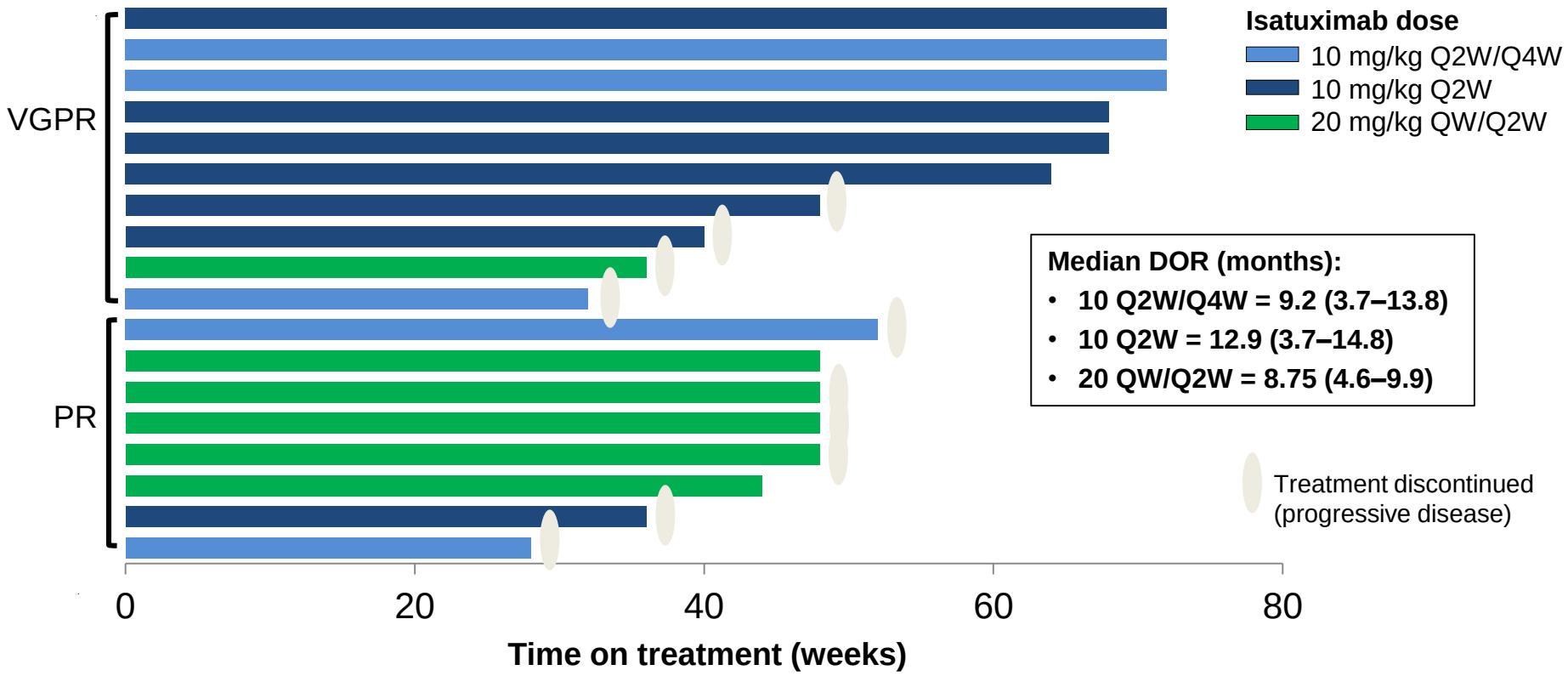
Time on Treatment by Best Response



Richter et al, ASCO 2016

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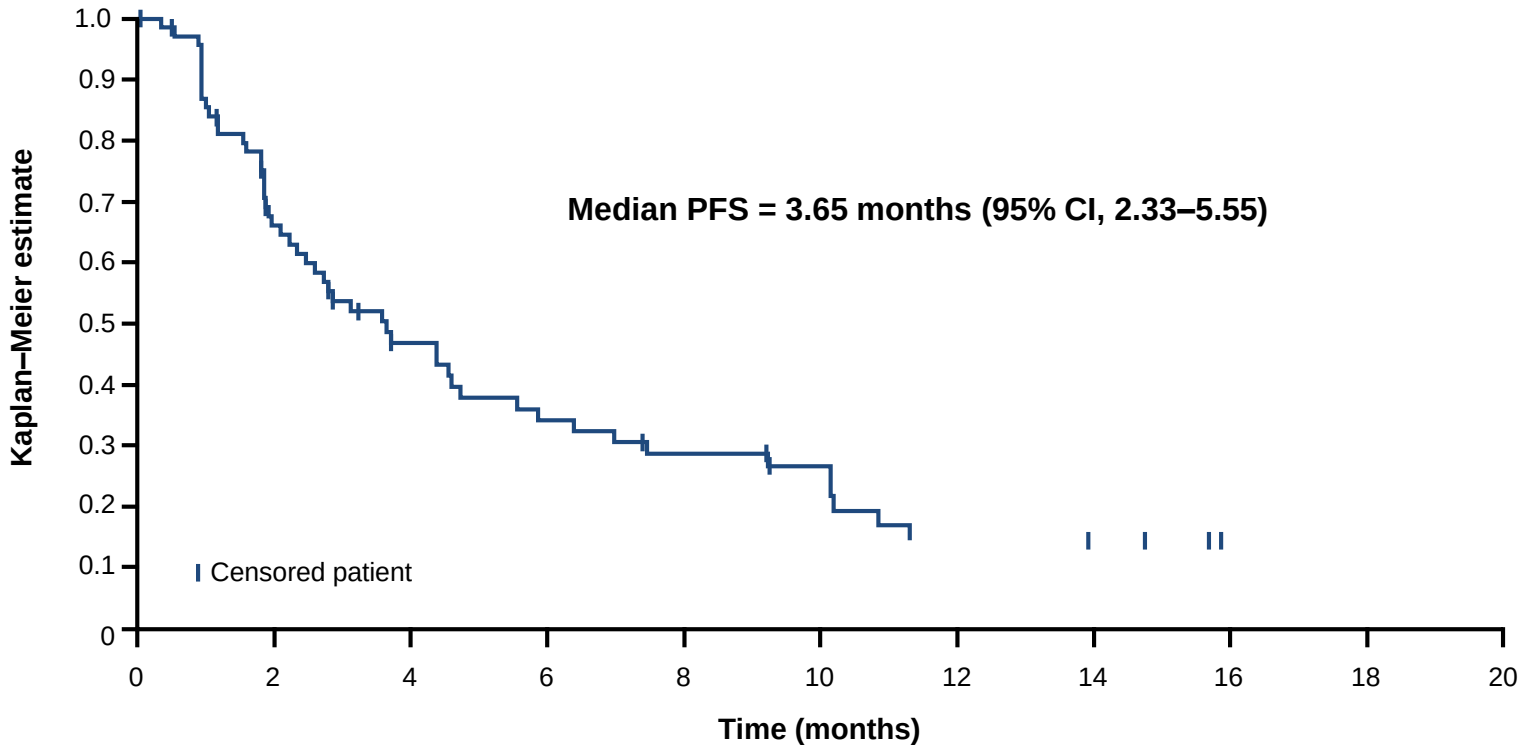
Progression-free Survival



Data cut-off: Feb 29, 2016

Isatuximab: TED10893

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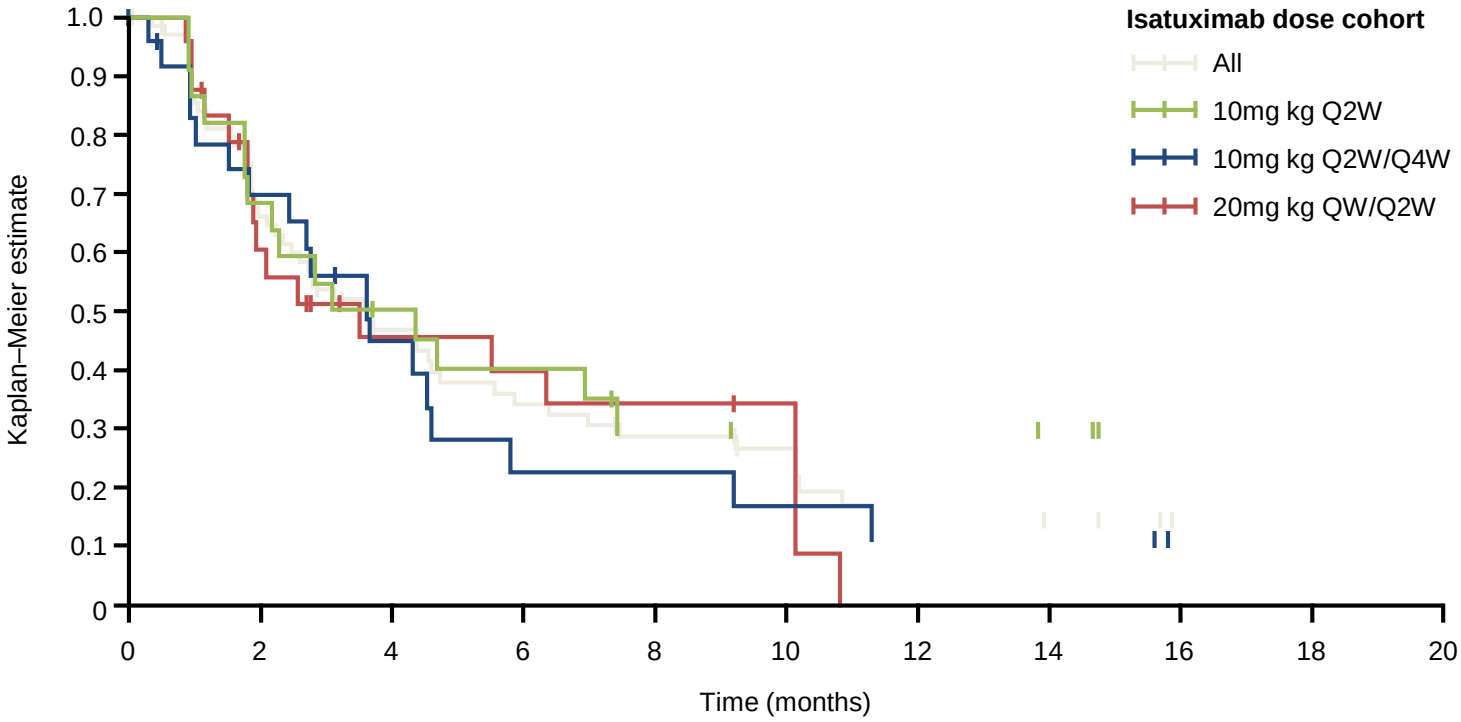
Progression-free Survival



Data cut-off: Feb 29, 2016

Isatuximab: TED10893

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Adverse events

n (%)	Isatuximab ≥10 mg/kg (n=74)	
	All grades	Grade 3/4
TEAEs*		
Nausea	27 (36)	0
Fatigue	25 (34)	0
Cough	25 (34)	0
Pneumonia	7 (9)	7 (9)
Hematologic laboratory abnormalities†		
Anemia	70 (97)	17 (24)
Thrombocytopenia	41 (57)	12 (17)
Neutropenia	30 (42)	11 (15)

- IARs occurred in 55% (41/74) of patients receiving ≥10 mg/kg‡
- Grade 3/4 IARs in only 2/74 patients (3%), both leading to discontinuation (10 mg/kg Q2W)
  - Grade 4 anaphylactic reaction & bronchospasm
  - Grade 3 dyspnea, Grade 3 hypertension
- The vast majority of IARs occurred with the first infusion; no IARs after 4th infusion

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Isatuximab, lenalidomide: Phase 1

ELIGIBILITY

RRMM; At least 2 prior therapies

- ≥2 prior lines and Len-exposed for QW/Q2W cohorts

No limit on maximum number of prior therapies

PRIMARY OBJECTIVE

Determine the MTD of isatuximab in combination with Len/Dex

SECONDARY OBJECTIVES

Safety and tolerability; Efficacy; PK; Dose-response relationship

Isatuximab IV, mg/kg and schedule per 28 day cycle†

- Len 25 mg (Days 1–21 per 28-day cycle)
- Dex 40 mg QW (Days 1, 8, 15, and 22)

Previous cohorts[1] (MTD not reached at 10 mg/kg Q2W)			New cohorts (Added based on PK/PD modeling data)	
3 Q2W (n=4)	5 Q2W (n=3)	10 Q2W (n=24)	10 QW/Q2W (n=12)	20 QW/Q2W (n=14)

† Prophylaxis against infusion reactions: diphenhydramine 50 mg iv, ranitidine 50 mg iv, and acetaminophen 650–1000 mg po (or equivalents)
PD, pharmacodynamics; PK, pharmacokinetics

Vij et al, ASCO 2016

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Patient characteristics

	Isatuximab, mg/kg and schedule		
	10 Q2W (n=24)	10 QW/Q2W (n=12)	20 QW/Q2W (n=10)
Median lines of therapy, n (range)	4 (1–9)	4 (1–8)	6.5 (3–9)
Median number of regimens, n (range)	6 (2–12)	6.5 (3–15)	8.5 (5–12)
Previous stem cell transplant, n (%)	23 (96)	10 (83)	9 (90)
Refractory to last regimen with, n (%)			
Bortezomib (Bort)	14 (58)	5 (42)	8 (57)
Lenalidomide (Len)	20 (83)	6 (50)	12 (86)
Carfilzomib (Car)	12 (50)	4 (33)	10 (71)
Pomalidomide (Pom)	7 (29)	3 (25)	10 (71)
Car + Pom refractory, n (%)	6 (25)	3 (25)	10 (71)
IMiD refractory, n (%)	21 (88)	8 (67)	10 (100)
IMiD + PI refractory, n (%)	17 (71)	6 (50)	12 (86)
Len + Bort + Car + Pom refractory, n (%)	4 (17)	1 (8)	5 (36)

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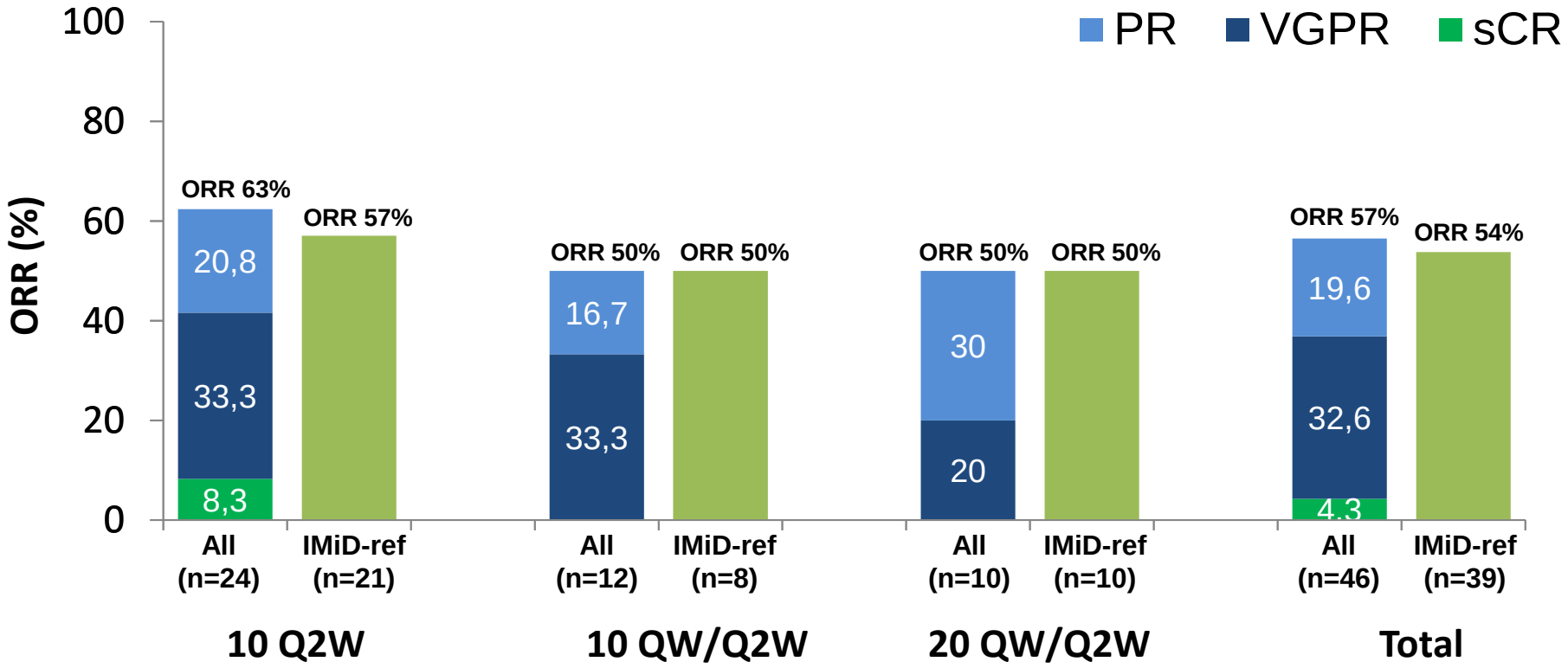
Efficacy: Isa + Len



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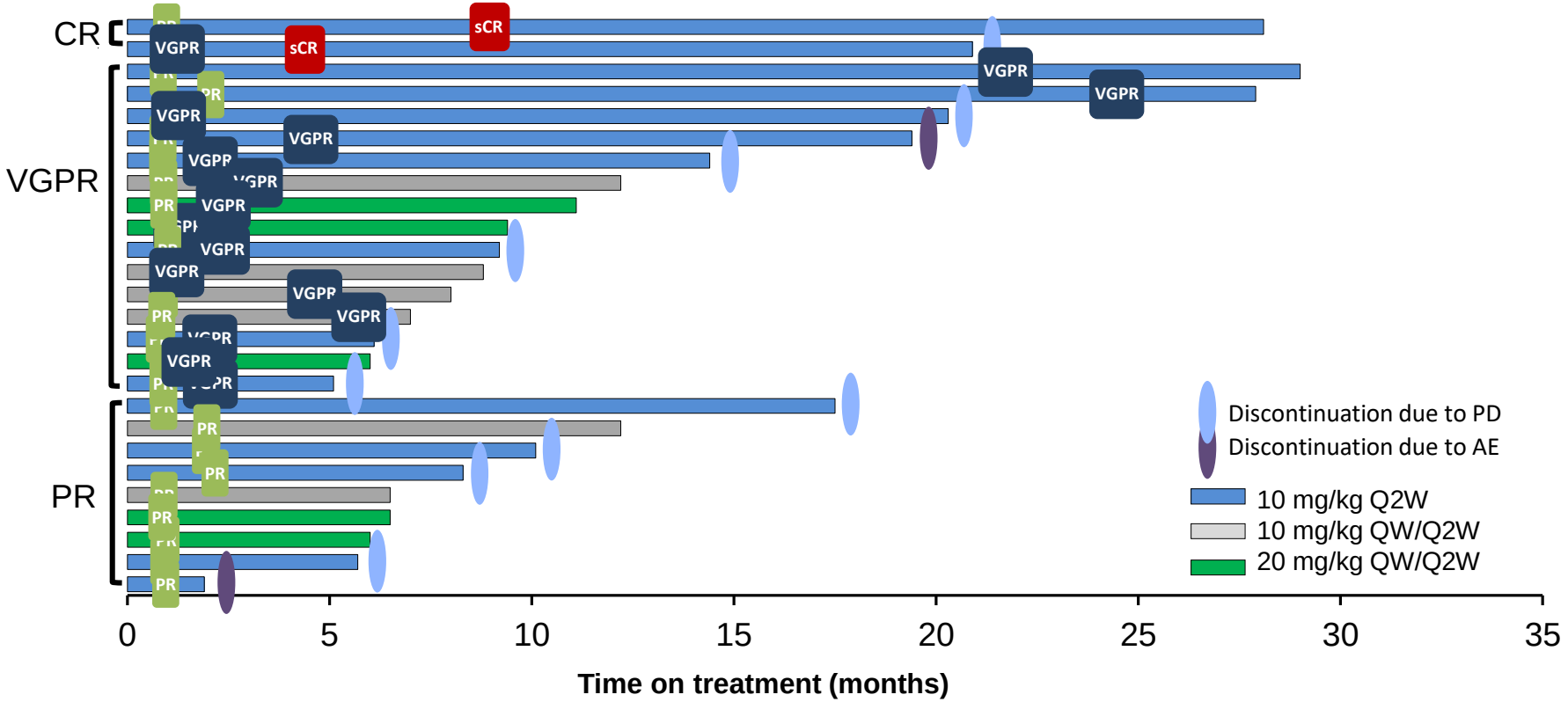
Time on Treatment by Response



Median duration of response = 7.6 (1.4–27.7) mo
Median time to first response = 0.95 (0.9–2.1) mo
Median time to best response = 1.9 (0.9–22.1) mo

Vij et al, ASCO 2016

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Adverse Events

N (%)	10 mg/kg Q2W (n=24)		10 mg/kg QW/Q2W (n=12)		20 mg/kg QW/Q2W (n=14)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any TEAE	24 (100)	21 (88)	12 (100)	10 (83)	14 (100)	12 (86)
Diarrhea	15 (63)	0	4 (33)	0	6 (43)	0
Fatigue	12 (50)	1 (4)	4 (33)	0	6 (43)	0
Pyrexia	10 (42)	0	5 (42)	0	4 (29)	0
Upper respiratory tract infection	10 (42)	0	5 (42)	0	3 (21)	0
Dyspnea	9 (38)	0	2 (17)	0	5 (36)	2 (14)
Nausea	11 (46)	0	1 (8)	0	4 (29)	0
Pneumonia	1 (4)	1 (4)	1 (8)	1 (8)	2 (14)	2 (14)
Febrile neutropenia	4 (17)	4 (17)	0	0	0	0
Hematologic laboratory abnormalities†						
Anemia	23 (96)	10 (42)	12 (100)	2 (17)	12 (100)	4 (33)
Thrombocytopenia	23 (96)	12 (50)	11 (92)	1 (8)	9 (75)	5 (42)
Neutropenia	22 (92)	11 (46)	11 (92)	8 (67)	10 (83)	8 (67)

Data cut-off Feb 10, 2016

*TEAEs in ≥25% of patients (all grades) or ≥5% (Grade 3/4)

† n=12 for hematologic laboratory abnormalities in the 20 mg/kg QW/Q2W cohort as 2 patients were not evaluable due to early withdrawal

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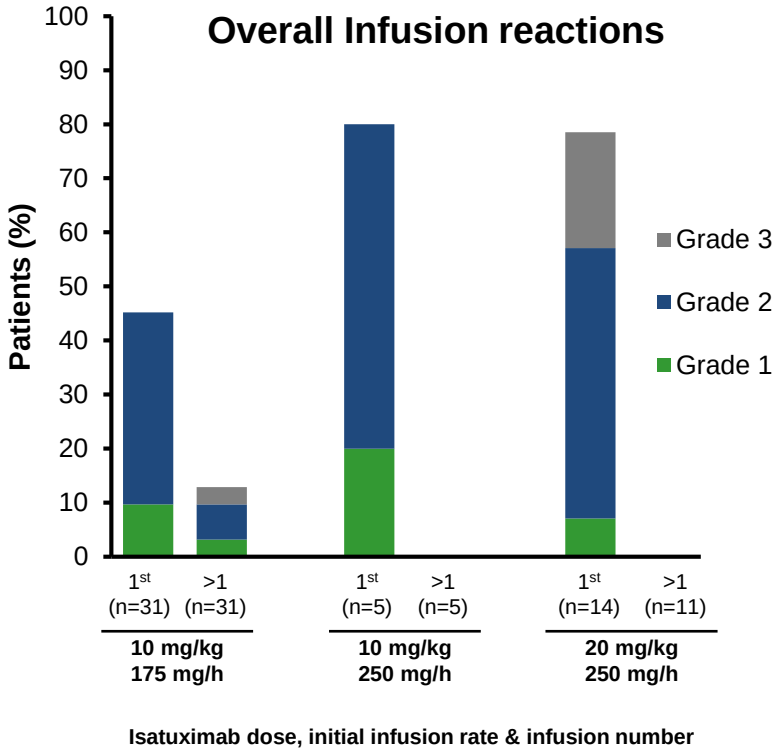
Infusion Associated Reactions (IARs)

- IARs reported in 31/50 (62%) patients; mostly Gr 1/2 (no Gr 4) and 88% during the first infusion
  - No IARs after 4th infusion
- 4 patients discontinued treatment due to Gr 3 IARs
  - 3 patients at 20 mg/kg QW/Q2W (initial rate, 250 mg/h)
  - 1 patient at 10 mg/kg Q2W
- Median infusion duration, h
  - 1st infusion: 3.2 (10 mg/kg); 4.9 (20 mg/kg)
  - Subsequent: 2.3 (10 mg/kg); 4.4 (20 mg/kg)



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Isatuximab + Pomalidomide

Eligibility

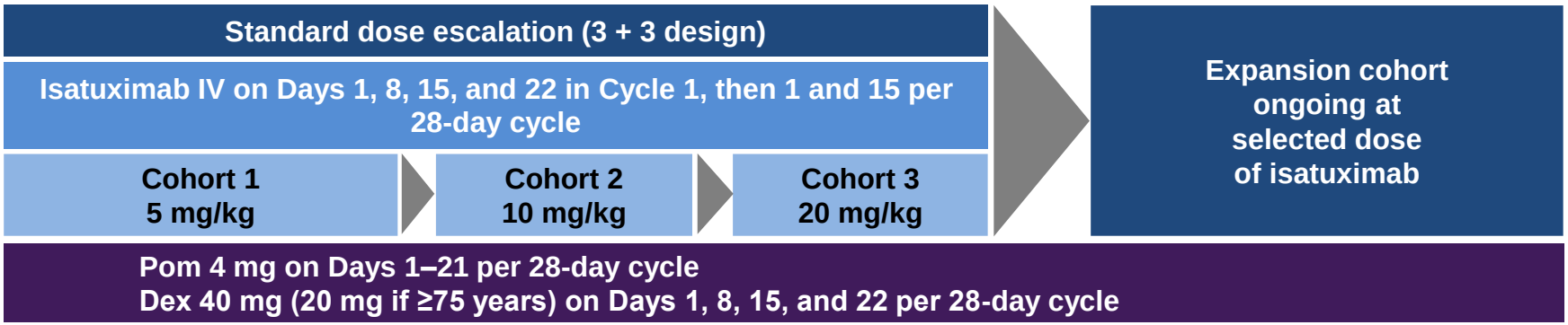
RRMM; At least 2 prior anti-MM therapies, including Len and a PI

Primary objective

Determine the recommended dose of isatuximab in combination with Pom/Dex

Secondary objectives

Safety and tolerability; PK,Efficacy



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Patient Characteristics

	Isatuximab, QW/Q2W			
	5 mg/kg (n=8)	10 mg/kg[a] (n=12)	20 mg/kg (n=6)	All patients (n=26)
Median prior regimens, n (range)	5.0 (3–7)	4.0 (3–11)	4.0 (4–5)	4.0 (3–11)
Prior stem cell transplant, n (%)				
1	4 (50)	9 (75)	3 (50)	16 (62)
>1	2 (25)	0	2 (33)	4 (15)
Refractory to, n (%)				
Bortezomib	5 (63)	5 (42)	2 (33)	12 (46)
Lenalidomide	6 (75)	10 (83)	4 (67)	20 (77)
Carfilzomib	3 (38)	6 (50)	2 (33)	11 (42)
Pomalidomide	0	0	1 (17)	1 (4)
IMiD + PI refractory, n (%)	4 (50)	7 (58)	4 (67)	15 (58)
Refractory to last regimen, n (%)	8 (100)	11 (92)	4 (67)	23 (89)

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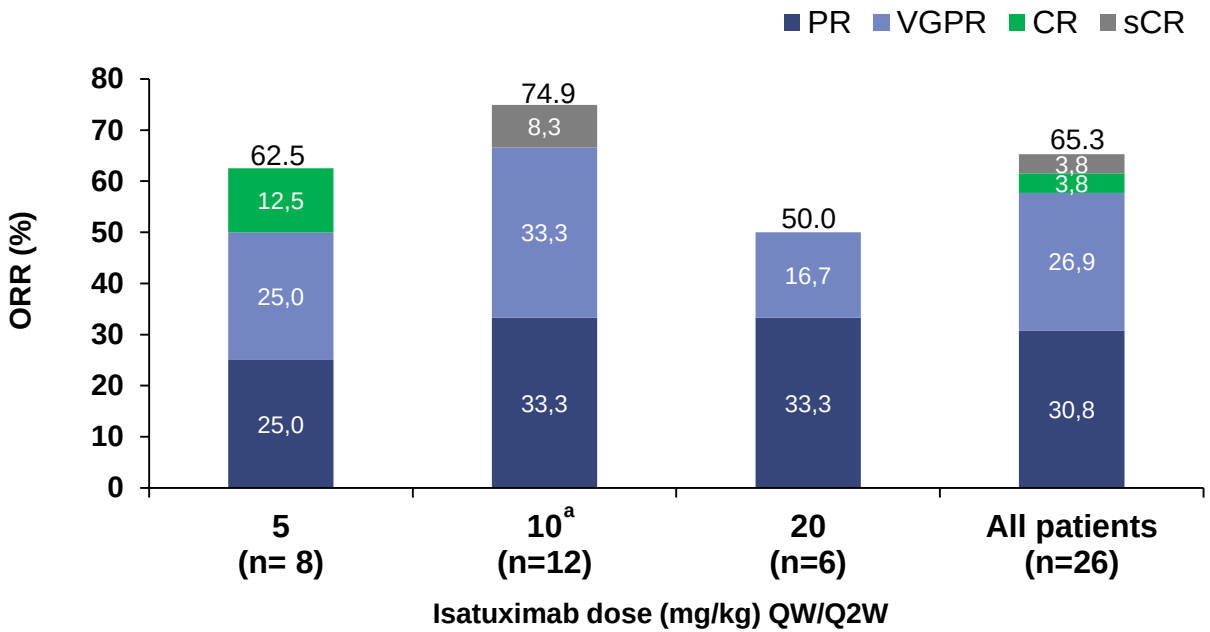
Efficacy: Isa Pom



Five patients with high-risk cytogenetics (del17p or t[4:14]): 1 attained VGPR, 1 PR, and 1 minimal response

Patients who were Len, PI, or IMiD and PI refractory had an ORR of 60%, 50%, and 47%, respectively

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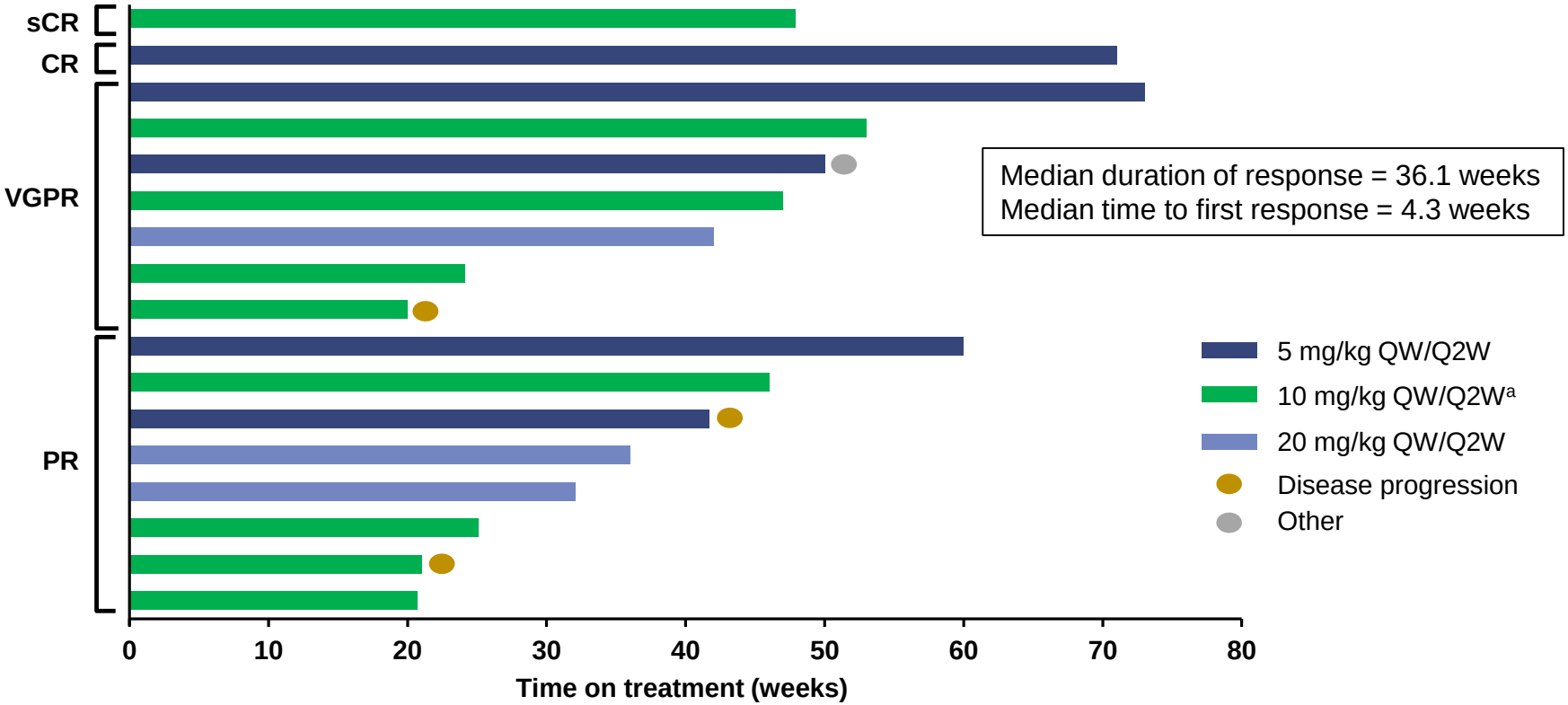
Time on Treatment by Response



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Treatment Emergent Adverse Events

	Isatuximab, QW/Q2W Number of patients, all grades/Gr ≥3			All patients, n (%) (n=26)	
	5 mg/kg (n=8)	10 mg/kg[a] (n=12)	20 mg/kg (n=6)	All grades	Gr ≥3
Any TEAE[b], n	8/8	12/8	6/5	26 (100)	21 (81)
Fatigue	5/1	8/1	4/0	17 (65)	2 (8)
Dyspnea	5/0	4/0	3/1	12 (46)	1 (4)
IARs	4/0	7/1	1/0	12 (46)	1 (4)
Diarrhea	2/0	5/0	3/0	10 (38)	0
URTI	4/0	3/0	3/0	10 (38)	0
Constipation	4/0	3/0	2/0	9 (35)	0
Acute kidney injury	1/1	1/1	0	2 (8)	2 (8)
Pneumonia	0	1/1	1/1	2 (8)	2 (8)

Dose omission of isatuximab or reduction/omission of Pom due to AEs in 9/26 (35%) and 17/26 (65%) patients, respectively

One patient died due to an AE (perforated bowel due to light-chain deposition disease [10 mg/kg])

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Hematologic Adverse Events

	Isatuximab, QW/Q2W Number of patients, all grades/Gr ≥3			All patients, n (%) (n=25)	
	5 mg/kg (n=8)	10 mg/kg[a] (n=11)	20 mg/kg (n=6)	All grades	Gr ≥3
Hematologic laboratory abnormalities, n					
Anemia	8/0	11/1	6/2	25 (100)	3 (12)
Leukopenia	8/7	11/9	6/5	25 (100)	21 (84)
Lymphopenia	8/7	11/9	6/4	25 (100)	20 (80)
Neutropenia	8/7	10/10	6/6	24 (96)	23 (92)
Thrombocytopenia	7/2	11/2	5/4	23 (92)	8 (32)

Neutropenia led to isatuximab dose omission in 3 patients and pomalidomide dose reduction in 9 patients

Three DLTs were reported: prolonged Gr 4 neutropenia (5 mg/kg), Gr 4 neutropenic infection (10 mg/kg), and Gr 3 confusional state (20 mg/kg); all resulted in study treatment dose omission/reduction

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IARs and Infusion Duration

Patients received prophylaxis against infusion reactions prior to isatuximab administration[a]

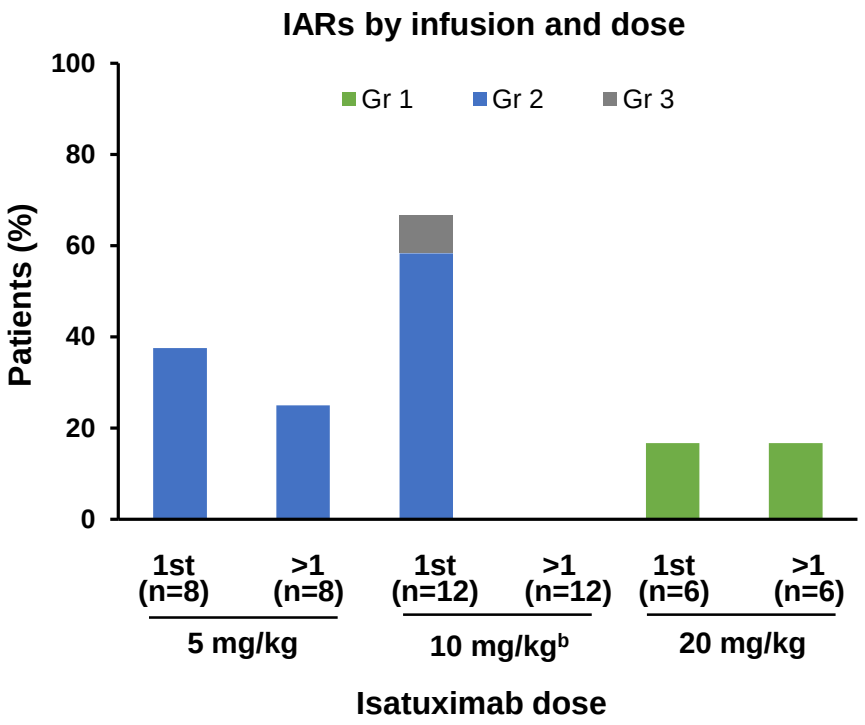
IARs reported in 13/26 patients (50%); Gr 3 in 1 patient (10 mg/kg); all others Gr 1/2 severity

IARs occurred predominantly during the first infusion

One treatment discontinuation due to Gr 3 IAR

Median infusion duration, 10 mg/kg

- First infusion: 3.9 hours
- Subsequent infusions: 2.8 hours



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On-going Trials for Isatuximab

- Phase III trial comparing **isatuximab plus Pom/dex** with Pom/dex in **refractory or relapsed and refractory multiple myeloma** (ICARIA-MM; NCT02990338)
- Phase I trial of isatuximab in **combination with VCD/VRD** in **newly diagnosed multiple myeloma ineligible for stem cell transplant** (CyBorDSAR; NCT02513186)
- Phase II stage II trial of isatuximab as a **single agent or in combination with dex in relapsed and refractory multiple myeloma** (NCT01084252)
- Phase I/II **single-agent** study in **Japanese relapsed and refractory multiple myeloma** patients (ISLANDS; NCT02812706)

MOR202

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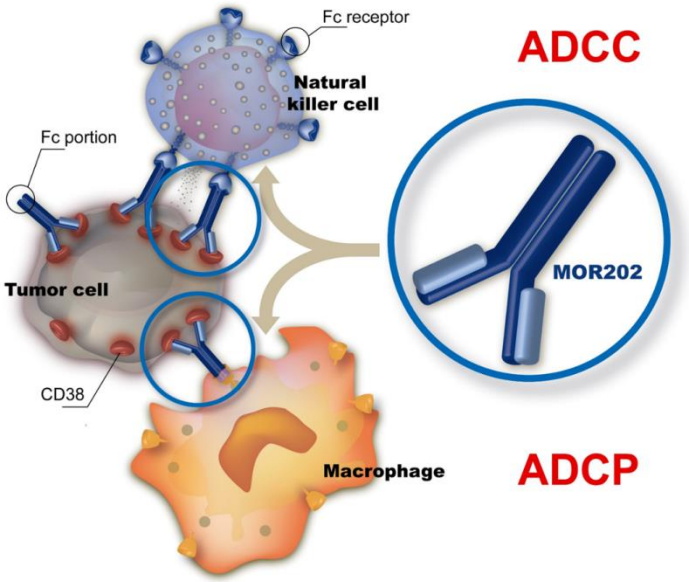
MOR202: Mechanisms of Action

MOR202

- Fully human monoclonal IgG1 antibody directed against CD38
- MOR202 induces potent immune effector mechanisms: **ADCC and ADCP**



ADCC, antigen-dependent cell-mediated cytotoxicity; ADCP, antigen-dependent cell-mediated phagocytosis

Raab et al, ASH 2016

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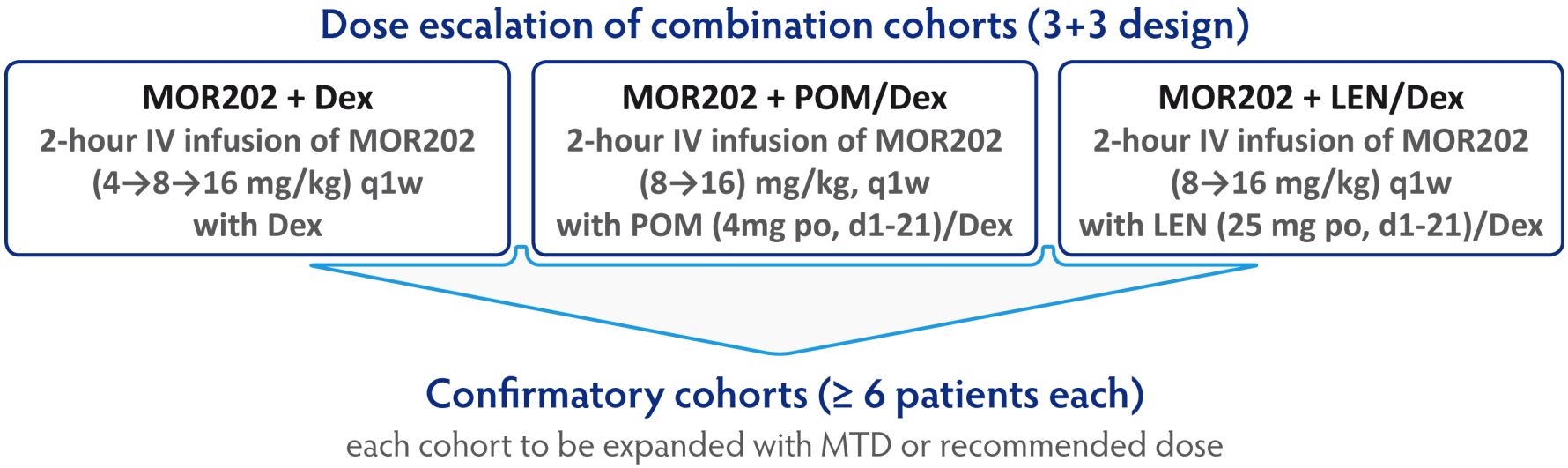
MOR202 combinations: cohorts and treatment



- Patients treated until progressive disease or a maximum of 2 years
- treatment cycle is 28 days
- During cycle 1, patients in all cohorts receiveda MOR202 loading dose on day 4
- Low dose Dex was orally administered: 40 mg (≤ 75 years old) or 20 mg (> 75 years old) q1w.

Raab et al, ASH 2016

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Patient characteristics

Schedule MOR202 dose Patient number	MOR202+Dex 4–16 mg/kg q1w n=18	MOR202+PomDex 8,16 mg/kg q1w n=9	MOR202+LenDex 8,16 mg/kg q1w n=14
Media age, years	67	64	66
Lines of prior therapy, n (Median)	3	3	2
Prior ASCT, %	78	56	79
Prior therapies, %			
Immunomodulatory drugs			
Lenalidomide	94	100	43
Thalidomide	39	11	14
Pomalidomide	11	11	0
Proteosome Inhibitors			
Bortezomib	100	100	86
Carfilzomib	6	11	0
Alkylating agents			
Melphalan	100	100	93
Cyclophosphamide	94	67	79
Other agents			
Doxorubicin	61	33	50
Panobinostat	0	11	7
Refractory to*, n (%)			
Last prior therapy	10 (56)	9 (100)	7 (50)
Any prior therapy	11 (61)	9 (100)	9 (64)

* Refractory is defined as resistance to treatment due to PD during treatment or within 2 months of last therapy; ASCT, autologous stem cell transplant

Raab et al, ASH 2016

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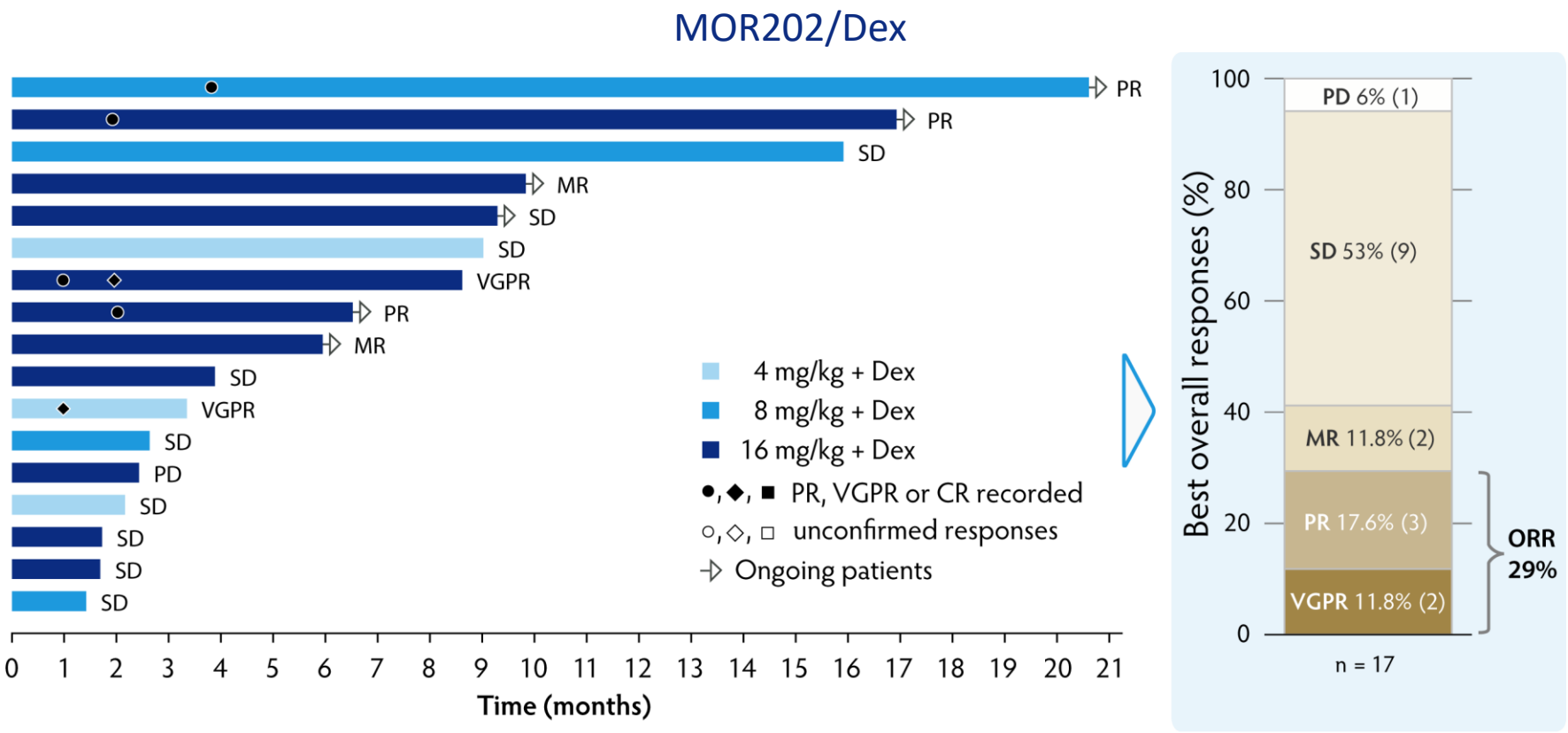
Efficacy: Time on Study by Best Response



Data from response-evaluable patients treated with clinically relevant dose regimens who received > 1 treatment cycle

CR, complete response; MR, marginal response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response

Raab et al, ASH 2016

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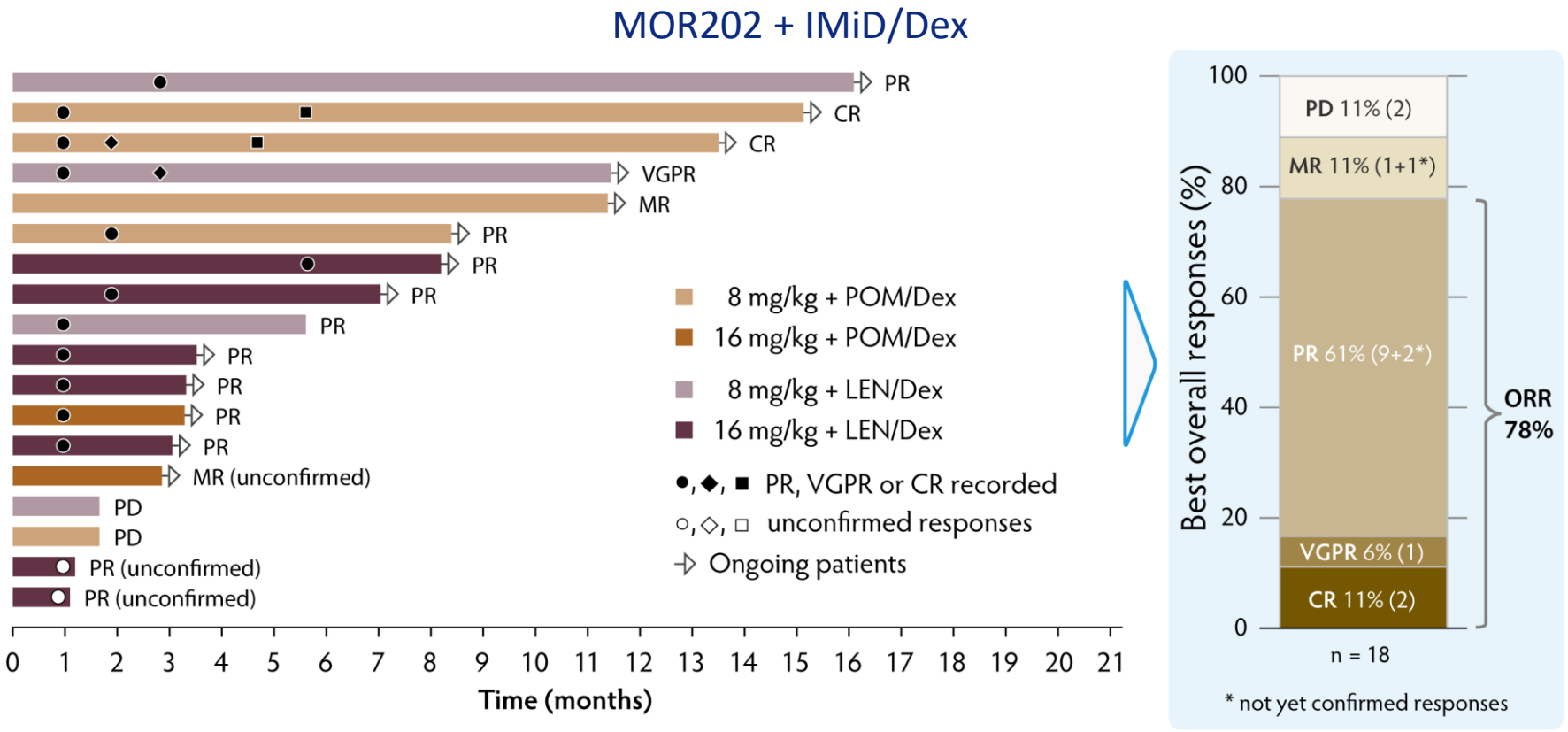
Efficacy: Time on Study by Best Response



Data from response-evaluable patients treated with clinically relevant dose regimens who received > 1 treatment cycle

Raab et al, ASH 2016

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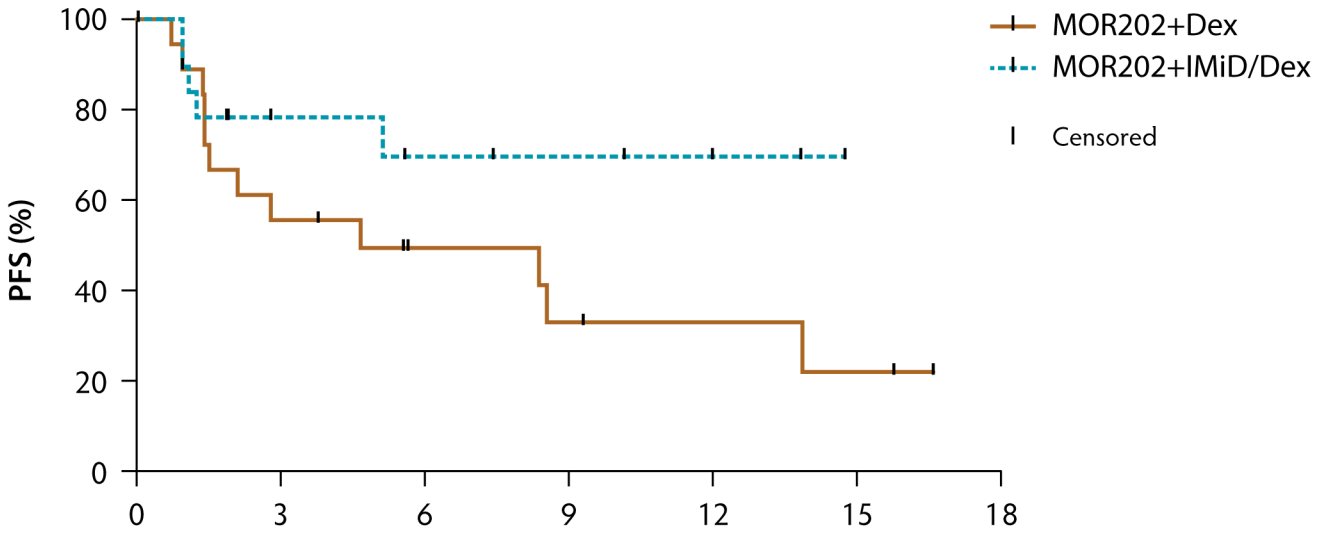
Efficacy: Progression Free Survival



Number of patients at risk							Median PFS	Median Follow-up
MOR202+Dex	18	10	6	4	3	2	4.7 months	15.8 months
MOR202+IMiD/Dex	23	9	7	5	2		not reached	5.6 months

PFS, progression-free survival

Raab et al, ASH 2016

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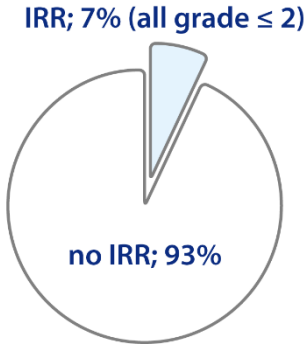
Safety: Adverse Events CTC Grade ≥3

- defined as ≥10% in at least one MOR202 combination treatment cohort

AEs, n (%)	MOR202+Dex n=18	MOR202+PomDex n=9	MOR202+LenDex n=14
Any	15 (83)	8 (89)	12 (86)
Hematological			
Leukopenia	2 (11)	5 (56)	4 (29)
Lymphopenia	7 (39)	2 (22)	7 (50)
Neutropenia	4 (22)	6 (67)	5 (36)
Thrombocytopenia	3 (17)	3 (33)	1 (7)
Anemia	3 (17)	1 (11)	2 (14)
CD4 lymphocyte decrease	0	1 (11)	2 (14)
CRP increase	0	1 (11)	0
Febrile neutropenia	0	1 (11)	0
Non-hematological			
Pneumonia	1 (6)	3 (33)	1 (7)
Hypokalemia	0	2 (22)	0
Hypertension	2 (11)	2 (22)	1 (7)
Hyperglycemia	1 (6)	0	2 (14)
Diarrhea	0	1 (11)	0
Hypophosphatemia	0	1 (11)	0
Atrial flutter	0	1 (11)	0
Skin infection	0	1 (11)	1 (7)

AE, adverse event; CRP, C-reactive protein;



- Only two patients (G4 thrombocytopenia and serious G3 bacterial infection) discontinued in these cohorts due to AEs with a suspected causal relationship to MOR202
- No treatment-related deaths

Raab et al, ASH 2016

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Conclusions

- Both Isatuximab and MOR2902 appear to be active alone and in combination with IMiDs
- Isatuximab activity appear to be comparable to that seen with dara so far
- No unique characteristics stand out, though IRRs may vary a bit
- Shorter infusions and possible SQ administration may dictate which gets used as well as cost

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THANK YOU