Anticorpi monoclonali: benefici clinici nella terapia di combinazione

Anticorpi monoclonali + Immunomodulanti

Sara Bringhen, MD, PhD
Ematologia U
AOU Città della Salute e della Scienza
University of Torino, Italy, EU

Elotuzumab

ELOQUENT-2: Study Design

- **ELOQUENT-2 is an open-label, randomized, multicenter, phase 3 trial**

Patients

- RRMM
- 1–3 prior lines of therapy
- Prior Len permitted in 10% of patients (if sensitive)

Elotuzumab plus Ld (E-Ld): n=321

- Elo: Cycles 1 and 2 weekly, then every other week, 10 mg/kg IV
- Len: D1–21, 25 mg PO
- Dex: weekly equivalent, 40 mg

Len/Dex (Ld): n=325

- Len: D1–21, 25 mg PO
- Dex: weekly, 40 mg PO

Premedication administered prior to elotuzumab infusion to mitigate infusion reactions

Endpoints

Co-primary
- PFS
- ORR

Others
- OS
- Safety
- Duration of response
- Quality of life

June 2011 start

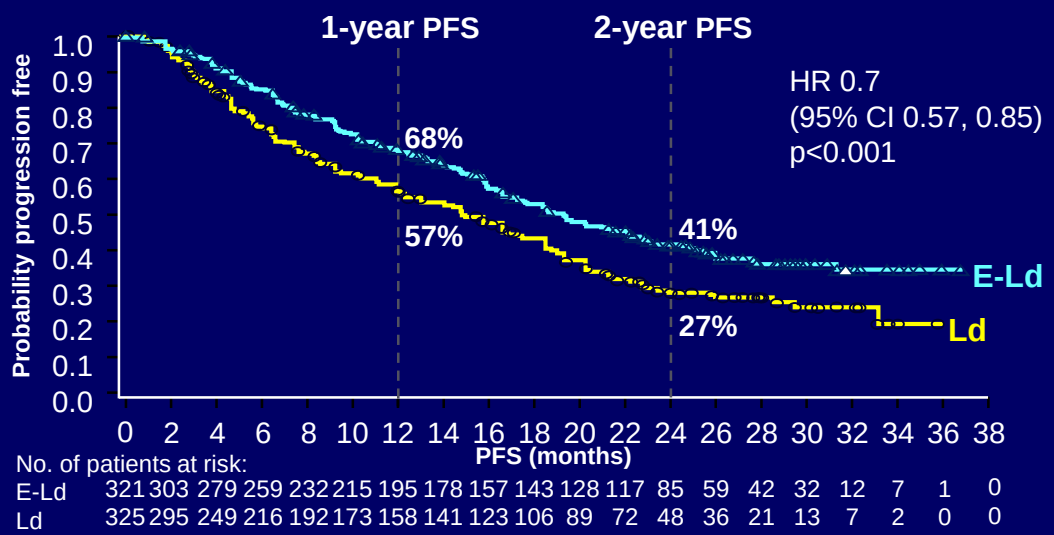
Database lock: November 2014 (ASCO/EHA 2015) Primary analysis

Database lock: August 2015 (ASH 2015) Extended follow-up

- **Statistical analysis**
  - **Threshold for interim OS significance was 0.014 based on 295/427 events required for final analysis**

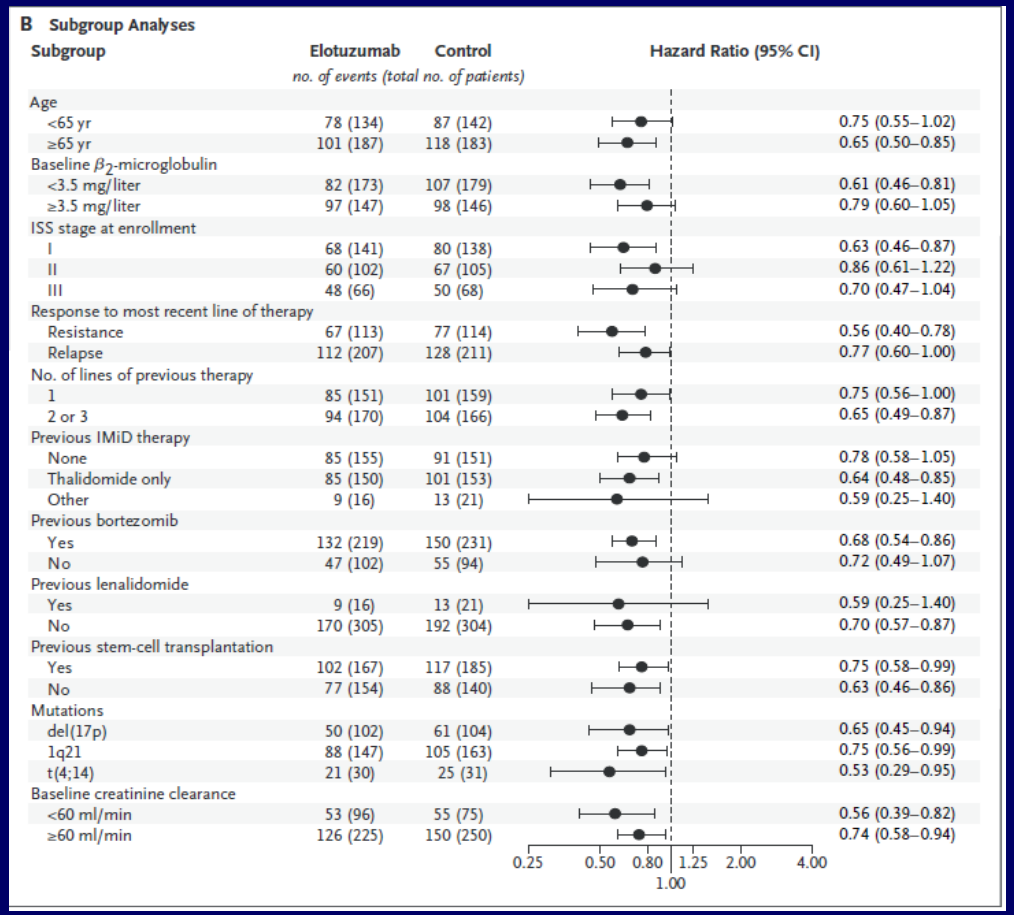
ELOQUENT-2: Primary Analysis

Co-primary endpoint: PFS



From *N Engl J Med*, Lonial S et al, Elotuzumab therapy for relapsed or refractory multiple myeloma, 373, 621–31.

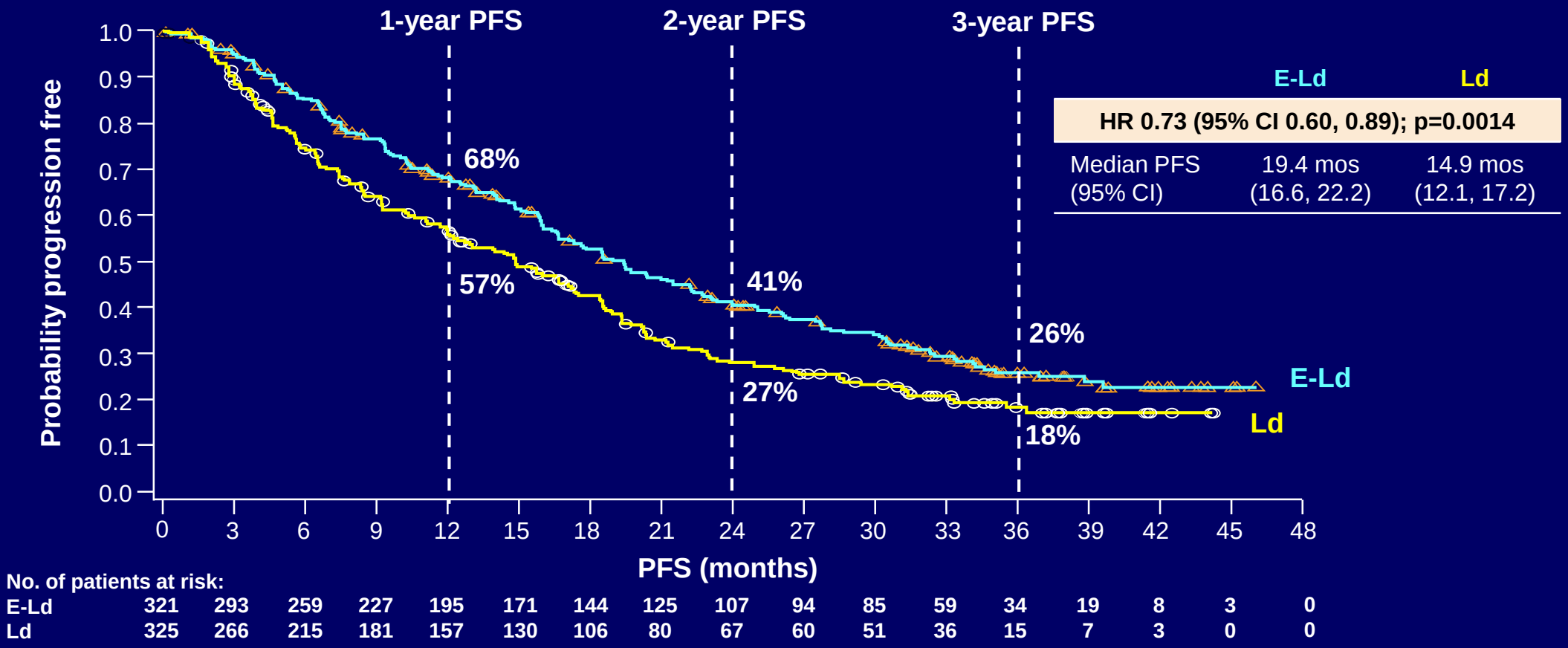
Co-primary endpoint: ORR	E-Ld	Ld
%	79	66
95% CI	74, 83	60, 71



ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone[1]

1. Lonial S et al. *N Engl J Med* 2015;373:621–31.

Extended Progression-Free Survival

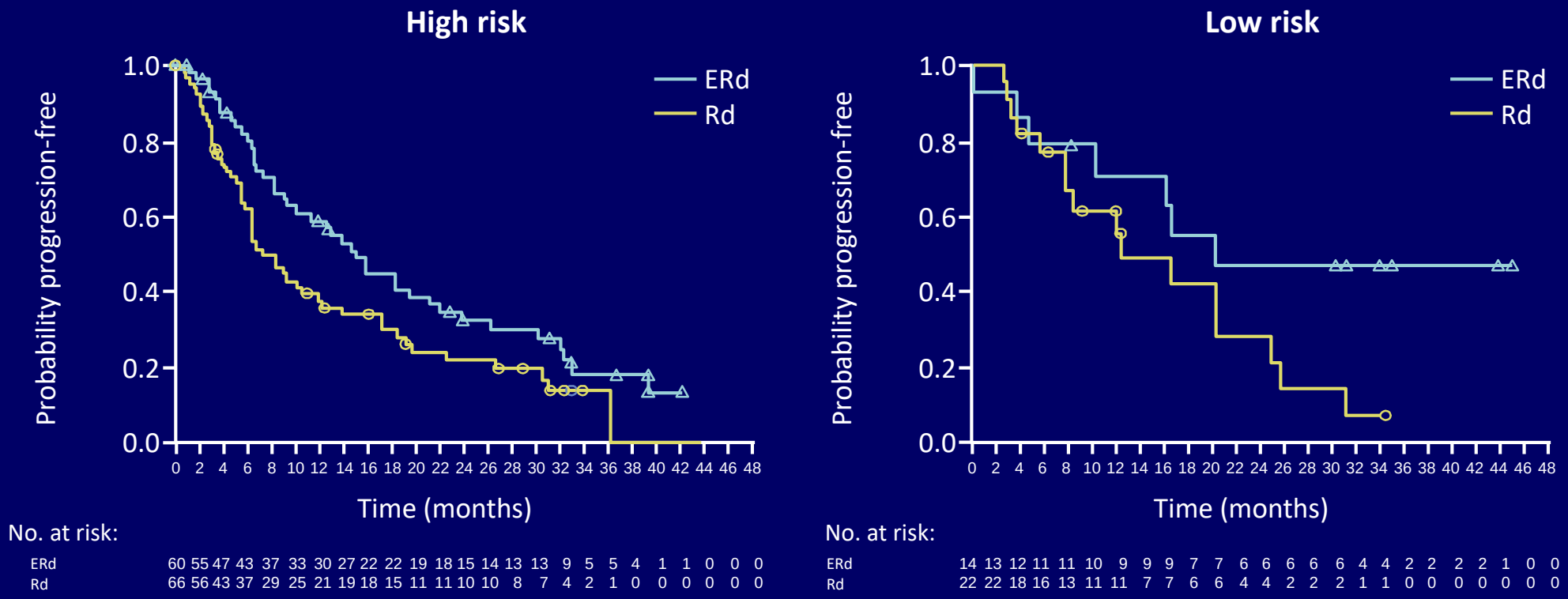


	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

PFS benefit with E-Ld was maintained over time (vs Ld):

- **Overall 27% reduction in the risk of disease progression or death**
- **Relative improvement in PFS of 44% at 3 years**

PFS by baseline risk status



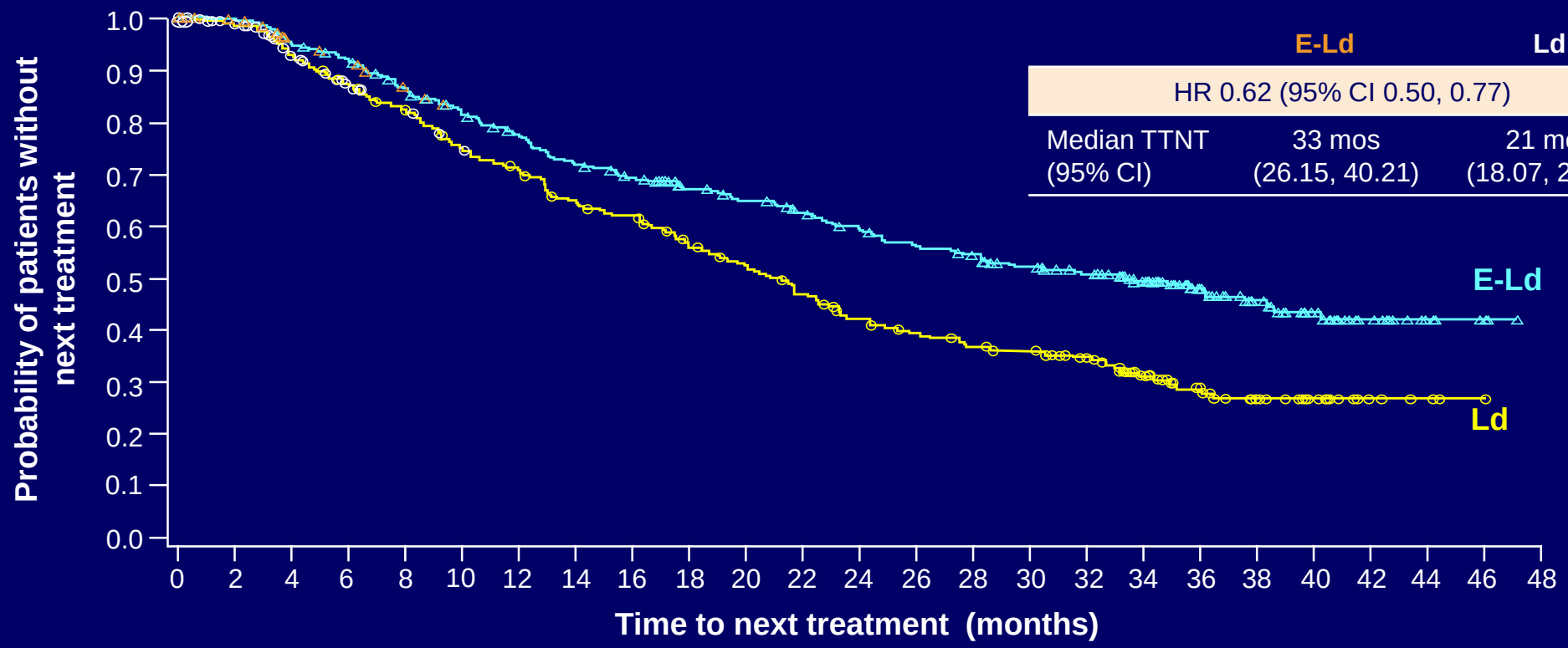
Adapted from Lonial S et al. 2016.[1]

- High-risk patients had a 37% reduction in the risk of progression or death with ERd versus Rd (HR 0.63)
  - Relative improvement in median PFS of 105% with ERd versus Rd
- The PFS benefit of ERd over Rd was also maintained regardless of whether patients had the high-risk cytogenetic abnormality del(17p) at baseline (HR 0.70)

ERd, elotuzumab, lenalidomide/dexamethasone; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

1. Lonial S et al. Poster presentation at ASCO 2016. Abstract 8037.

Time to Next Treatment

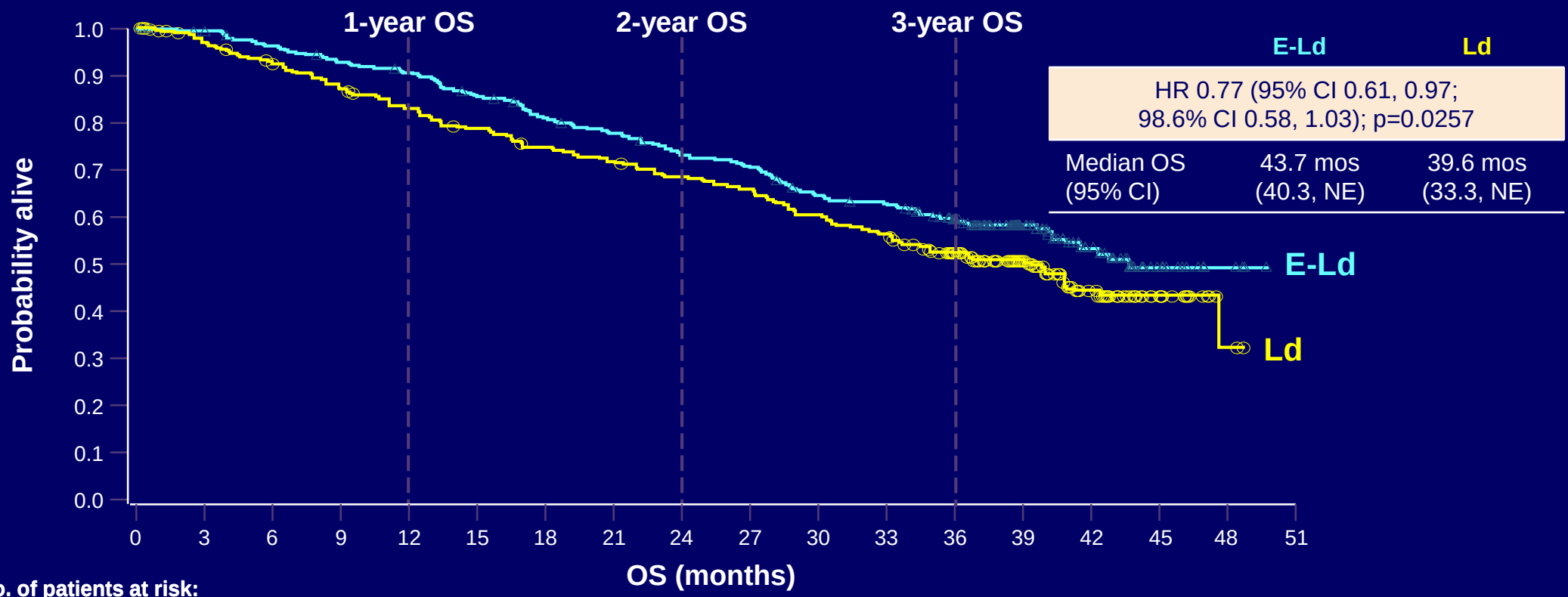


No. of patients at risk:

E-Ld	321	315	294	282	259	239	225	208	198	182	174	165	153	144	138	126	118	94	65	46	32	14	6	3	0
Ld	325	305	276	251	232	206	193	174	166	148	135	120	105	96	89	85	76	46	30	20	13	5	3	1	0

E-Ld-treated patients had a median delay of 1 year in the time to next treatment vs Ld-treated patients

Interim Overall Survival



No. of patients at risk:

E-Ld	321	314	303	291	283	266	250	239	224	217	196	190	152	95	48	15	5	0
Ld	325	305	287	269	255	241	228	218	208	200	184	171	134	88	41	17	3	0

Prespecified interim analysis for overall survival indicates a strong trend (p=0.0257) with early separation sustained over time for E-Ld vs Ld

ELOQUENT-2: Elotuzumab-Ld vs Ld

Safety

Event	Elotuzumab Group (N=318)		Control Group (N=317)	
	Any Grade	Grade 3 to 4	Any Grade	Grade 3 to 4
Common hematologic toxic effect — no. (%)†				
Lymphocytopenia	316 (99)	244 (77)	311 (98)	154 (49)
Anemia	306 (96)	60 (19)	301 (95)	67 (21)
Thrombocytopenia	266 (84)	61 (19)	246 (78)	64 (20)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Common nonhematologic adverse event — no. (%)				
General disorder				
Fatigue	149 (47)	27 (8)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Peripheral edema	82 (26)	4 (1)	70 (22)	1 (<1)
Nasopharyngitis	78 (25)	0	61 (19)	0
Gastrointestinal disorder				
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (<1)
Musculoskeletal or connective-tissue disorder				
Muscle spasms	95 (30)	1 (<1)	84 (26)	3 (1)
Back pain	90 (28)	16 (5)	89 (28)	14 (4)
Other disorder				
Cough	100 (31)	1 (<1)	57 (18)	0
Insomnia	73 (23)	6 (2)	82 (26)	8 (3)

- **No Grade 4–5 infusion reactions**
- **33 patients (10%) infusion reaction , 29/33 grade 1-2**
- **2 (1%) discontinued because of an infusion reaction**

Ld: lenalidomide-dexamethasone

Lonial S et al N Engl J Med, 2015: 1-11

Anti-CD38 monoclonal antibodies

Chimeric:

Isatuximab (SAR650984)

Fully human:

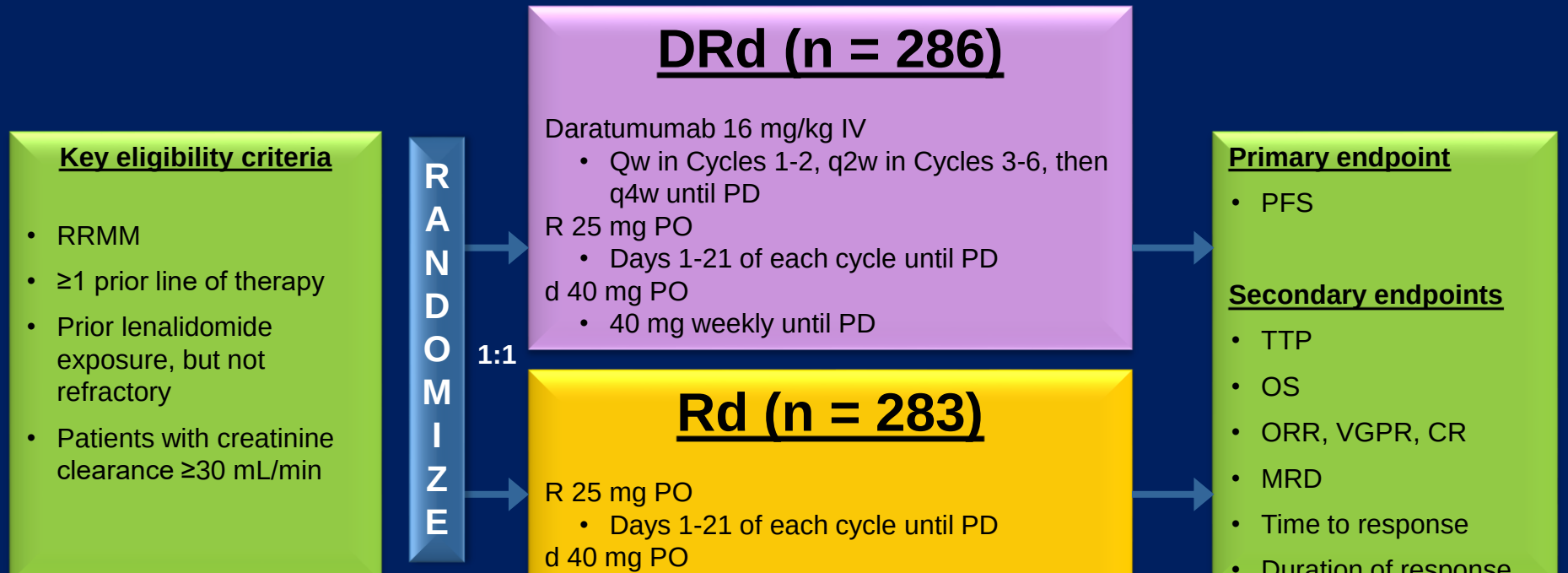
Daratumumab (DARA)

MOR202 (MOR)

https://download.ama-assn.org/resources/doc/usan/x-pub/isatuximab.pdf
de Weers et al. J Immunol 2011;186: 1840–1848
http://www.morphosys.com/pipeline/proprietary-product-portfolio/mor202

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study



Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

Statistical analyses

- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

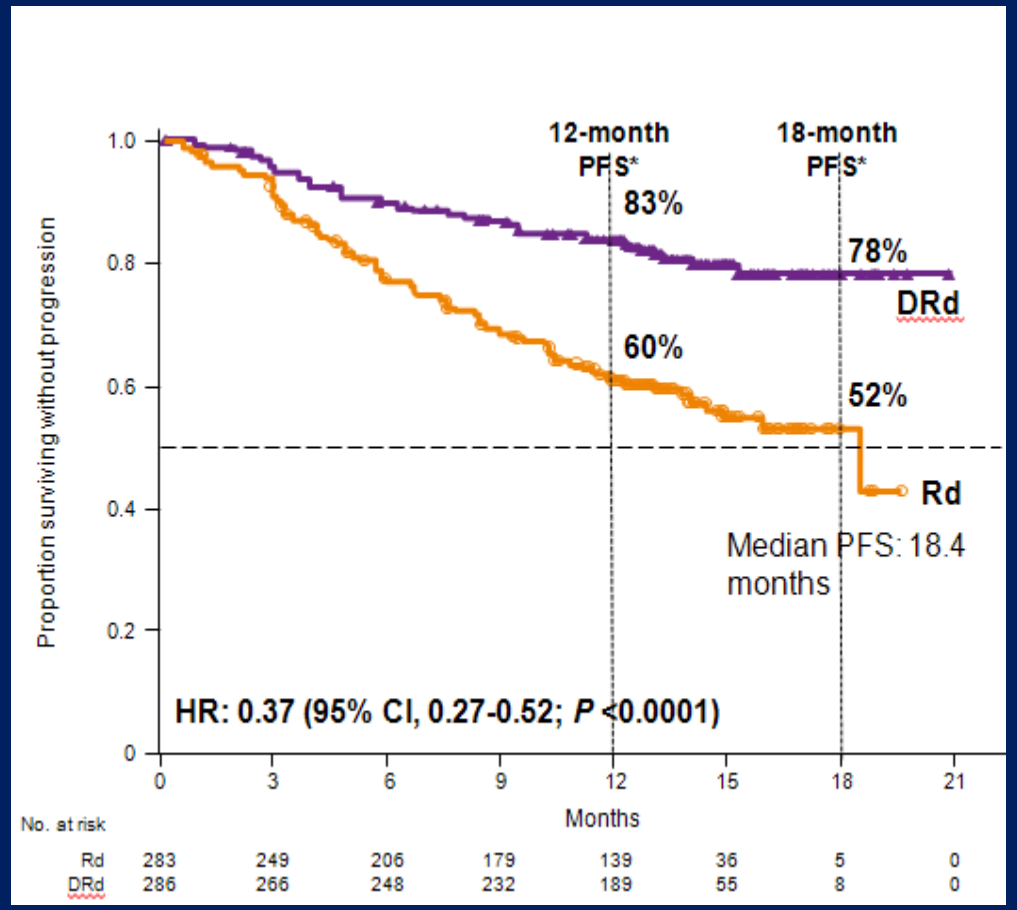
Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

Dimopoulus et al. EHA 2016

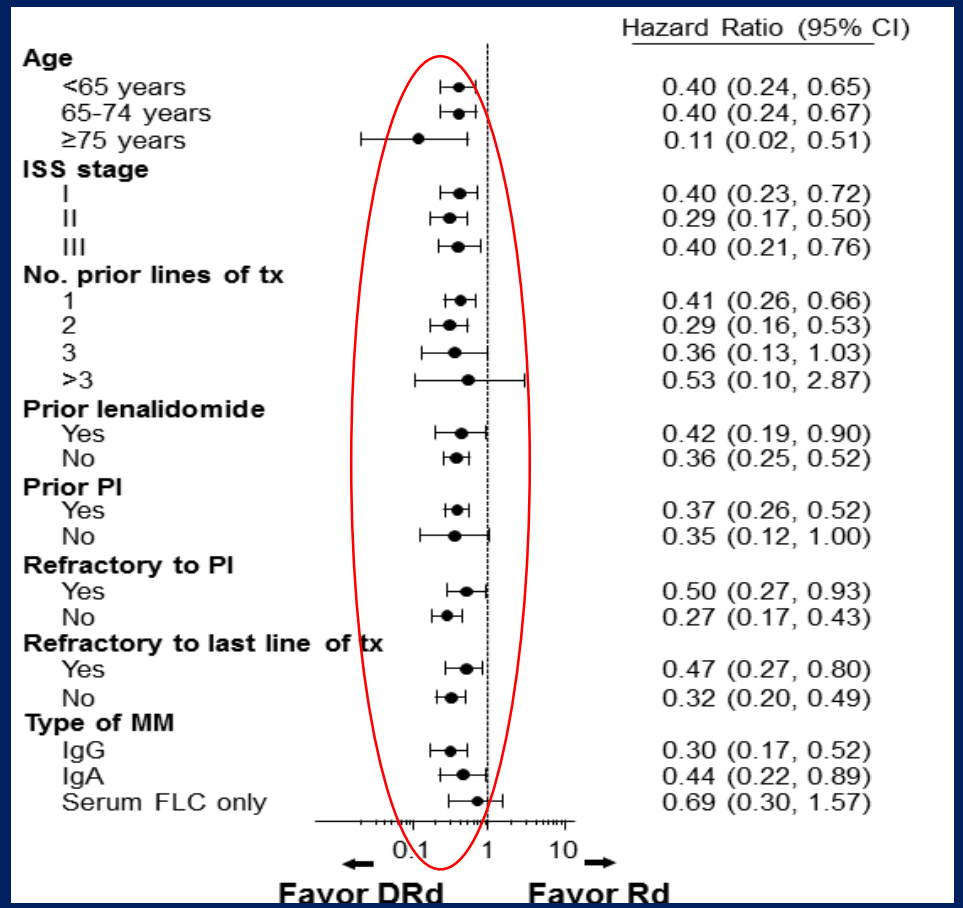
POLLUX: Study Design

Progression-free Survival (PFS)



63% reduction in the risk of disease progression or death for DRd vs Rd

PFS: Subgroup analysis



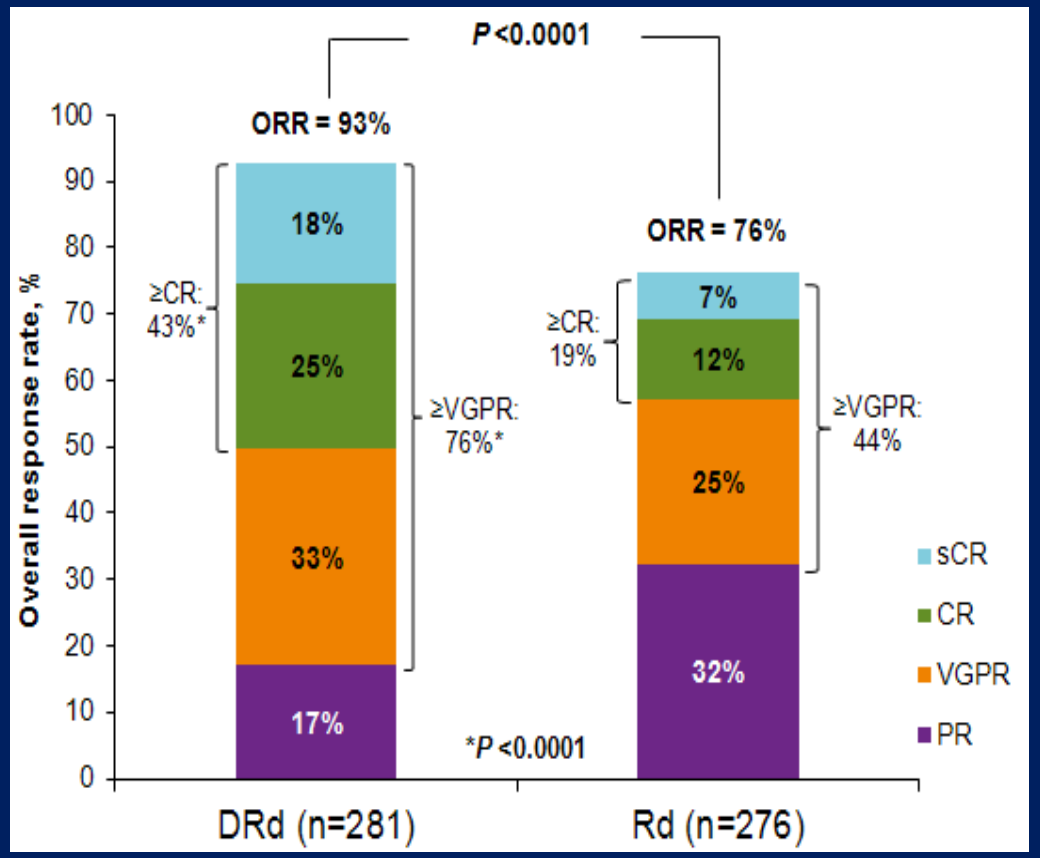
Higher efficacy was observed for DRd versus Rd across all subgroups

DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

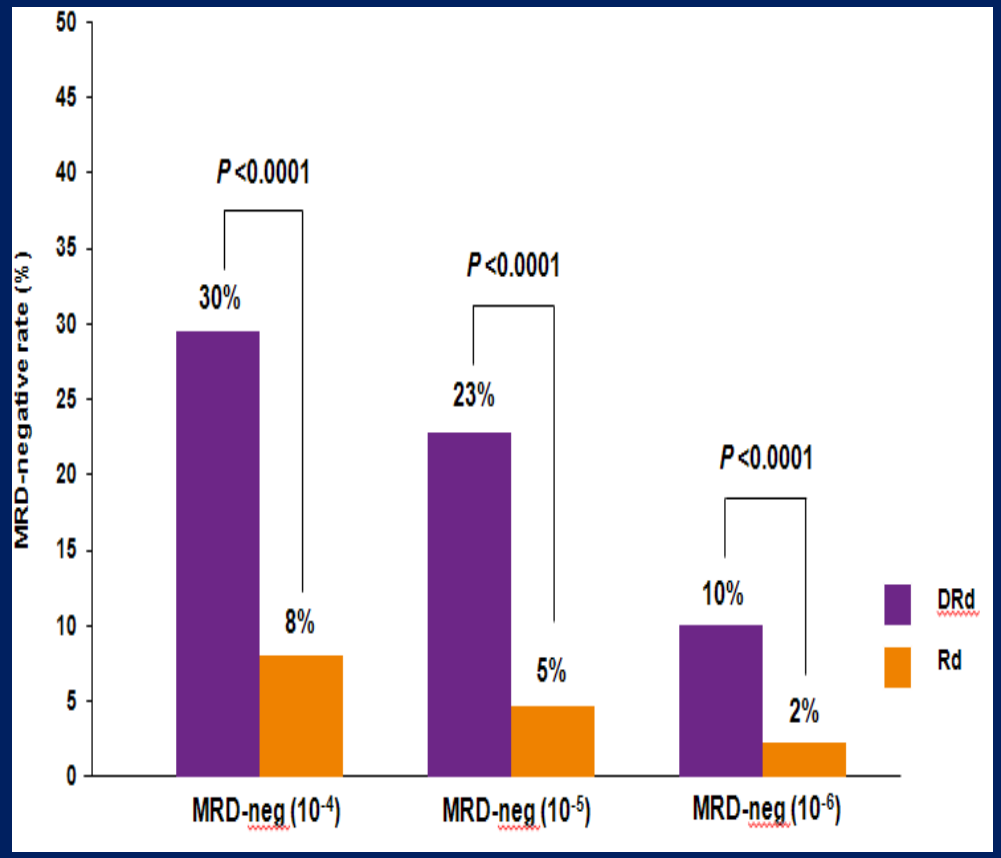
Dimopoulus et al. EHA 2016

POLLUX: Study Design

Overall response rate



MRD negative rate



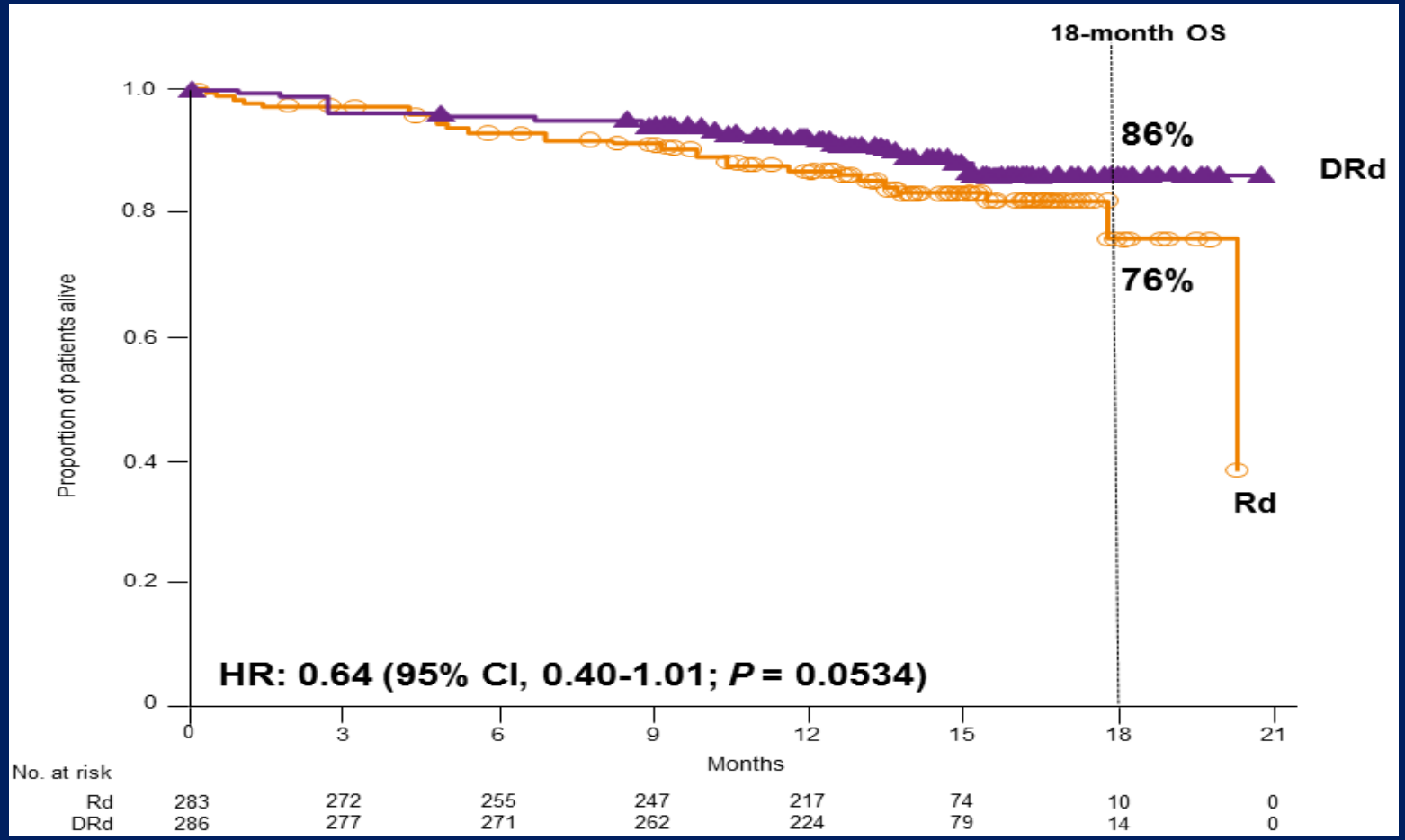
- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

Significantly higher MRD-negative rates for DRd vs Rd

DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

Dimopoulus et al. EHA 2016

Overall Survival



18-month overall survival: 86% in DRd versus 76% in Rd

DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

Dimopoulus M et al. EHA 2016

Adverse Events (AEs)

Infusion-related Reactions (IRRs)

IRRs ≥2%	Safety Analysis Set (n = 283)	
	All grades (%)	Grade 3 (%)
Patients with IRRs	48	5
Cough	9	0
Dyspnea	9	0.7
Vomiting	6	0.4
Nausea	5	0
Chills	5	0.4
Bronchospasm	5	0.4
Pruritus	3	0.4
Throat irritation	3	0
Headache	3	0
Nasal congestion	3	0
Wheezing	2	0.7
Laryngeal edema	2	0.4
Rhinorrhea	2	0
Pyrexia	2	0

- No grade 4 or 5 IRRs were reported
- 92% of all IRRs occurred during the first infusion
- 1 patient discontinued daratumumab due to an IRR

Most common AEs

	DRd (n = 283)		Rd (n = 281)	
Hemat AEs	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%
Neutropenia	59	52	43	37
Febrile neutropenia	6	6	3	3
Anemia	31	12	35	20
Thrombocytopenia	27	13	27	14
Lymphopenia	6	5	5	4
Non-hemat AEs				
Diarrhea	43	5	25	3
Fatigue	35	6	28	3
Upper resp. tract infection	32	1	21	1
Constipation	29	1	25	0.7
Cough	29	0	13	0
Muscle spasms	26	0.7	19	2
Pneumonia	14	8	13	8

Infections and infestations:

- Grade 3 or 4: 28% patients in DRd vs 23% patients in Rd
- The most common grade 3 or 4 infections/infestations AE was pneumonia (8% vs 8%)

DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

Dimopoulus et al. EHA 2016

Lenalidomide-based Studies

	POLLUX DRd vs Rd[5]	ASPIRE KRd vs Rd[1]	ELOQUENT-2 ERd vs Rd[2,3]	TOURMALINE-MM1 NRd vs Rd[4]
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥VGPR	76%	70%	33%	48%
≥CR	43%	32%	4%	14%
Duration of response, mo	NE	28.6	20.7	20.5
OS HR (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

K, carfilzomib; E, elotuzumab; N, ixazomib.

DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

1. Stewart AK, et al. N Engl J Med. 2015;372(2):142-152.
2. Lonial S, et al. N Engl J Med. 2015;373(7):621-631.
3. Dimopoulos MA, et al. Blood. 2015;126(23):Abstract 28.
4. Moreau P, et al. N Engl J Med. 2016;374(17):1621-1634.
5. Dimopoulus EHA 2016

Phase I Dara + Pom-Dex (MMY-1001)

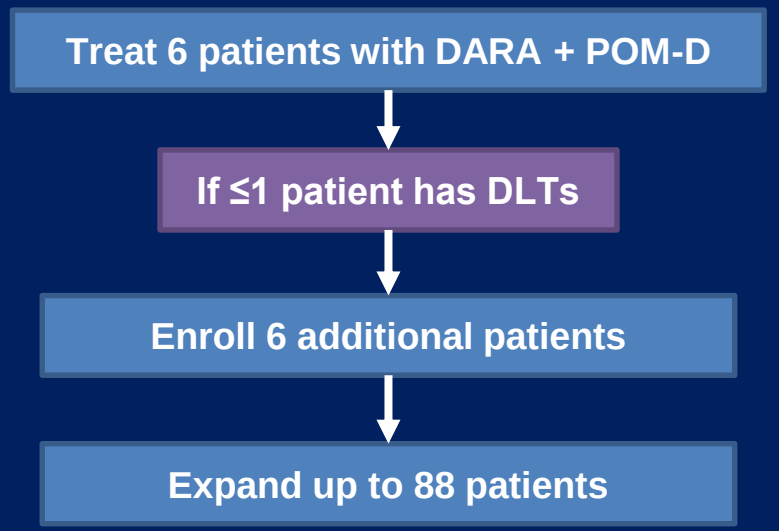
Eligibility criteria

- Refractory to last line of therapy
- ≥2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and bortezomib
- Pomalidomide naïve
- ECOG score ≤2
- Absolute neutrophil count ≥1.0×10^9/L, and platelet count ≥75×10^9/L for patients with <50% plasma cells (>50×10^9/L, otherwise)
- Calculated creatinine clearance ≥45 mL/min/1.73 m^2

Open-label, multicenter, six-arm, Phase 1b study (28-day cycles)

DARA* IV 16 mg/kg + Pomalidomide 4 mg (Days 1-21) + Dexamethasone 40 mg QW

*QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W beyond.



Dara-Pom-Dex: Daratumumab pomalidomide dexamethasone

Chari A, ASH 2015 Abst 508

Safety Dara + Pom-Dex (MMY-1001)

Treatment-emergent adverse events in >20% pts

	N = 98	
	Any grade	Grade ≥3
Any grade	97	91
Neutropenia	63	60
Anemia	42	25
Fatigue	41	8
Thrombocytopenia	34	15
Leukopenia	32	20
Cough	31	0
Diarrhea	30	1
Dyspnea	28	6
Nausea	25	0
Constipation	22	0

- **Rates of grade ≥3 AEs were similar to those observed with POM-D alone**
- **Serious AEs occurred in 42% of patients**
- **17 (17%) deaths occurred**
- **No new safety signals were identified**

Infusion-related Reactions (IRR) in >3 pts

	N = 98	
	Any grade	Grade 3
Any event	52 (53)	6 (6)
Chills	14 (14)	0
Cough	11 (11)	0
Dyspnea	11 (11)	0
Nasal congestion	7 (7)	0
Throat irritation	7 (7)	0
Nausea	7 (7)	0
Chest discomfort	6 (6)	0
Pyrexia	6 (6)	0

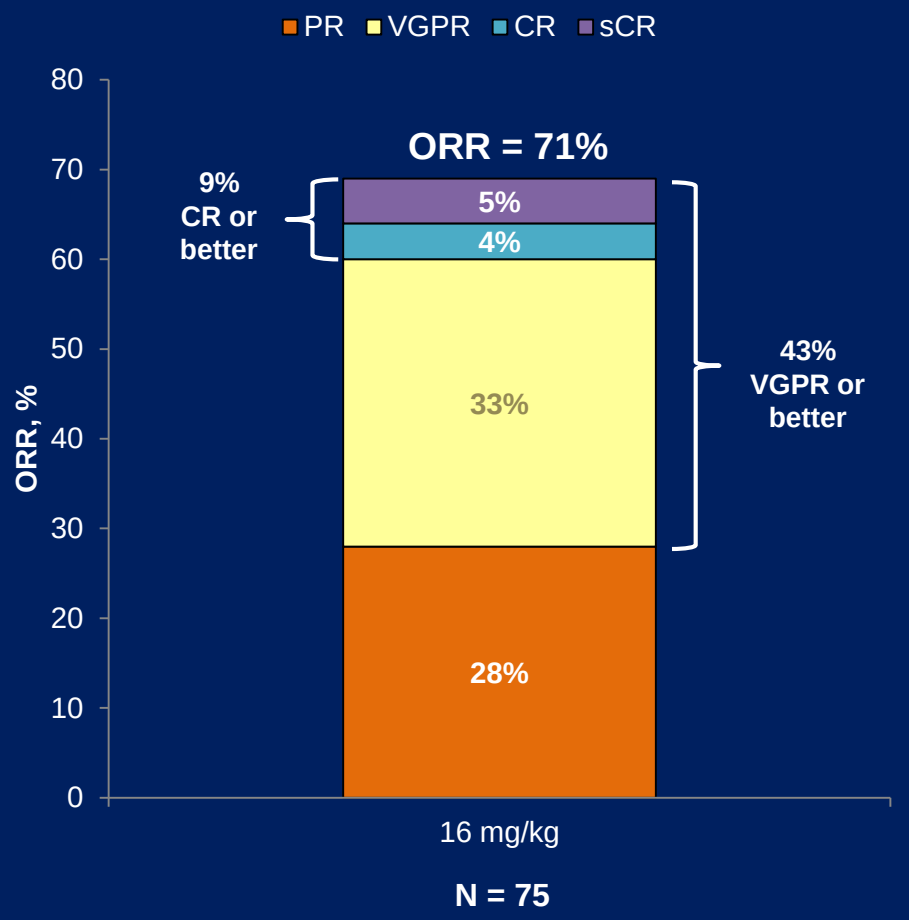
- **IRRs were predominantly grade ≤2**
  - **6 (6%) patients had grade 3 IRRs**
  - **Only 2 patients discontinued due to an IRR**
- **53%, 1%, and 0% of patients had IRRs during the 1st, 2nd, and subsequent inf., respectively**
- **IRRs were managed with premedication and reduced infusion rates**

Dara-Pom-Dex: Daratumumab pomalidomide dexamethasone

Chari A, ASH 2015 Abst 508

ORR to Dara + Pom-Dex (MMY-1001)

	DARA + POM-D (N = 75)	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	53 (71)	59.0-80.6
Best response		
sCR	4 (5)	1.5-13.1
CR	3 (4)	0.8-11.2
VGPR	25 (33)	22.9-45.2
PR	21 (28)	18.2-39.6
MR	2 (3)	0.3-9.3
SD	17 (23)	13.8-33.8
PD	3 (4)	0.8-11.2
VGPR or better (sCR+CR+VGPR)	32 (43)	31.3-54.6
CR or better (sCR+CR)	7 (9)	3.8-18.3

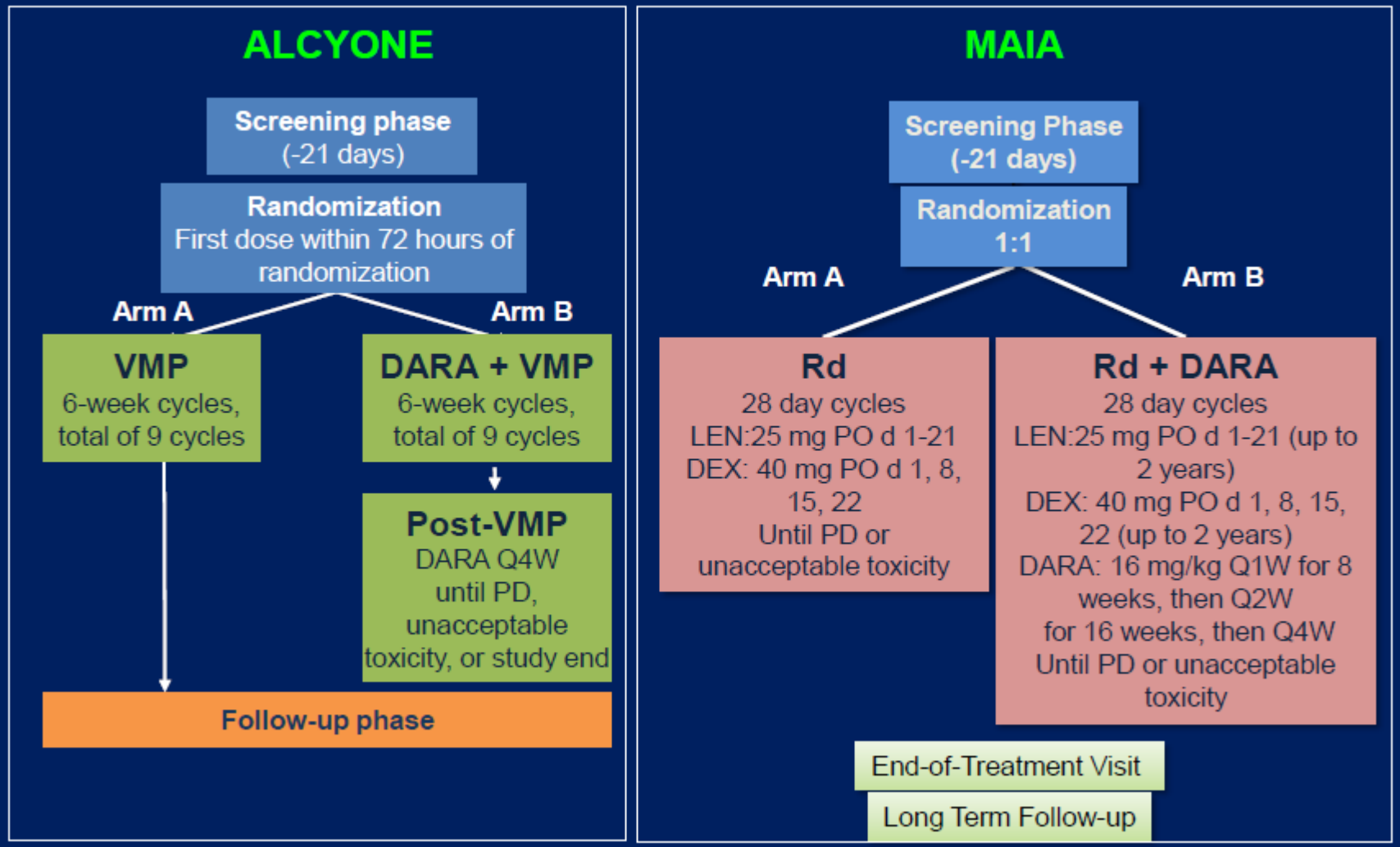


- **ORR = 71%**
- **ORR in double-refractory patients = 67%**
- **Clinical benefit rate (ORR + minimal response) = 73%**

Dara-Pom-Dex: Daratumumab pomalidomide dexamethasone

Chari A, ASH 2015 Abst 508

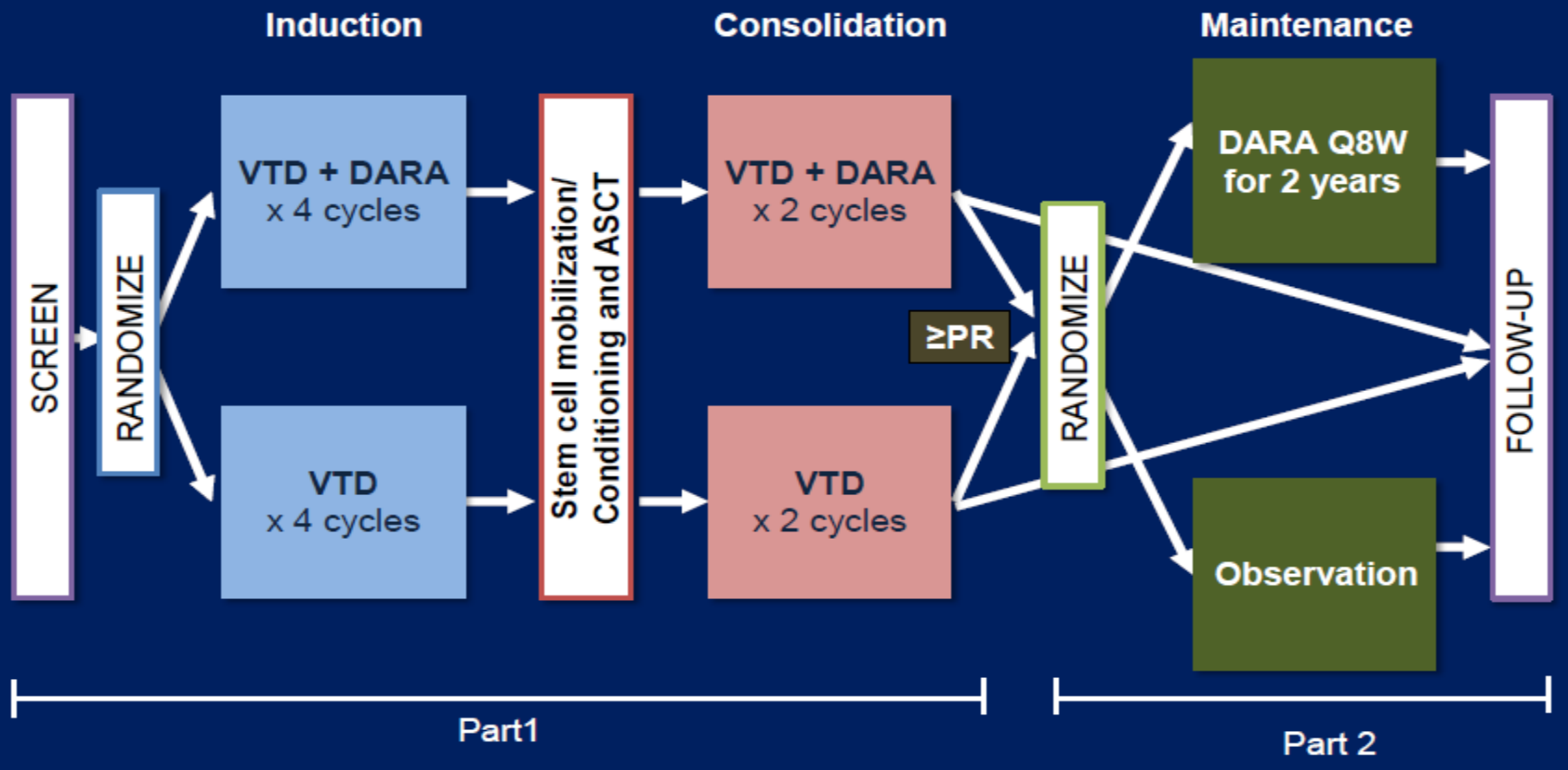
Ongoing studies in newly diagnosed MM



www.clinicaltrials.gov

Ongoing studies in newly diagnosed MM

CASSIOPEIA (IFM & HOVON)



www.clinicaltrials.gov

Isatuximab

- Isatuximab (ISA) is a novel monoclonal antibody that is effective and well tolerated as a monotherapy
- Like daratumumab, it targets CD38 molecules

1. Vij R et al. *J Clin Oncol* 2016;34(suppl):abstr 8009. NCT01749969

ISA + REV + DEX

- Phase 1 study of isatuximab (ISA) plus lenalidomide (REV) and dexamethasone (DEX)
- As a phase 1 study, the goal was to identify the maximum tolerated dose (MTD) and the optimal dose schedule, to determine how to prescribe it in future studies and eventually in practice
- Subjects had RRMM with at least 2 prior therapies (median 4–6 prior lines of therapy)

DEX, dexamethasone; ISA, isatuximab; REV, lenalidomide (Revlimid); RRMM, relapsed/refractory multiple myeloma

1. Vij R et al. *J Clin Oncol* 2016;34(suppl):abstr 8009. NCT01749969

ISA/REV/DEX Results

- The combination had an acceptable safety profile, with adverse events similar to those of the individual drugs
- No drug-drug interactions were seen between ISA and REV
- Overall response rate was 57%, and median duration of response was 7.6 months

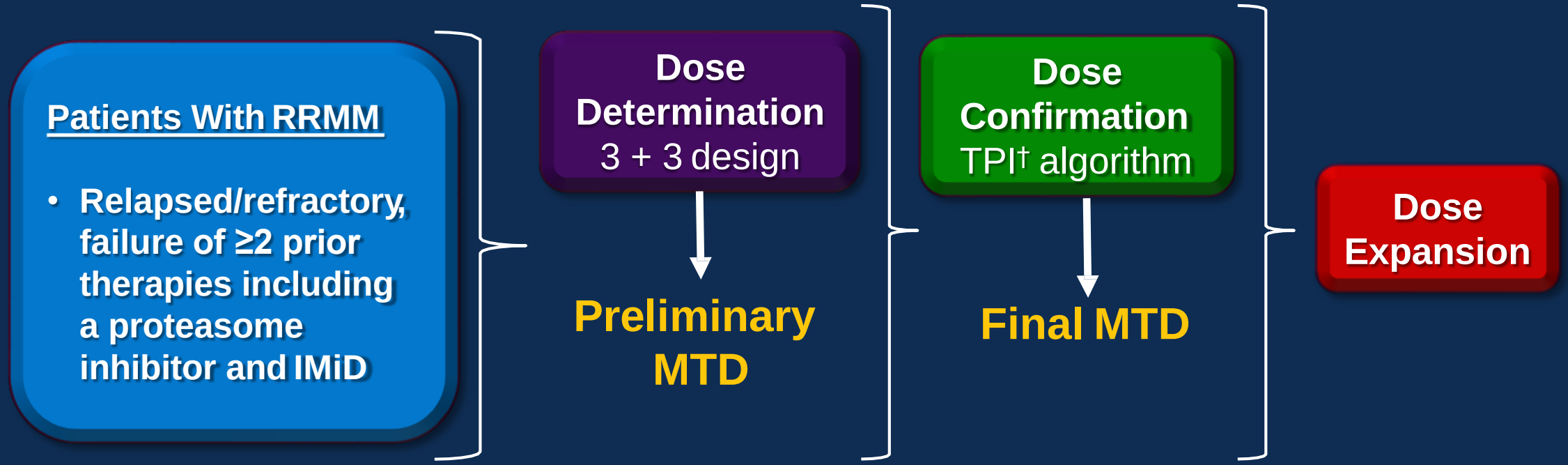
Conclusion: a phase 3 trial of ISA/REV/DEX at 10 mg/ kg once weekly/once every 2 weeks will begin soon

DEX, dexamethasone; ISA, isatuximab; REV, lenalidomide (Revlimid)

1. Vij R et al. *J Clin Oncol* 2016;34(suppl):abstr 8009. NCT01749969

Pembrolizumab

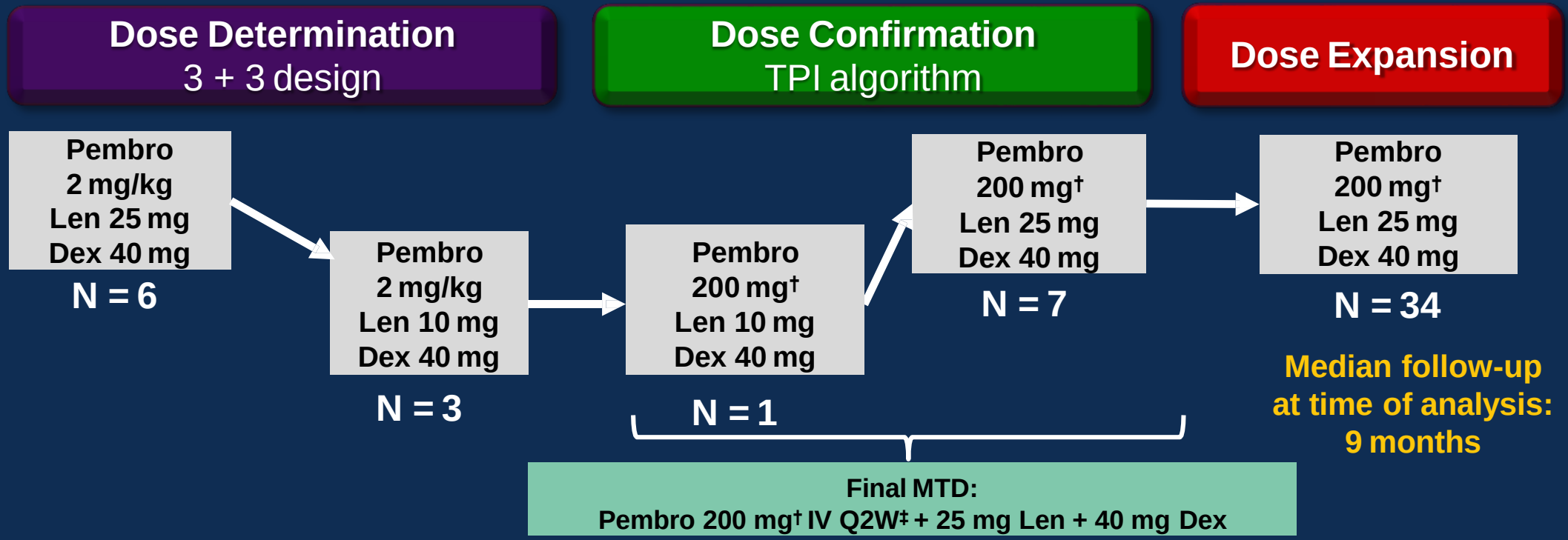
KEYNOTE-023: Phase 1 Trial of Pembrolizumab + Lenalidomide and Low-Dose Dexamethasone in RRMM



- Primary end points: Safety and tolerability
- Secondary end points: ORR, DOR, PFS, OS

†TPI = Toxicity Probability Interval
(Ji Y et al. *Clin Trials.* 2007;4:235-244)

KEYNOTE-023: Study Chronology



- **Safety analysis: all patients enrolled in the study (N = 51)**
- **Efficacy analysis: patients who completed 3 cycle of treatment or discontinued for PD (N = 40)**

†Pembrolizumab 2 mg/kg ≈ 200 mg fixed dose Q2W (based upon PK/PD studies)
‡Pembrolizumab IV 30 minutes (no premedication) Q2W, lenalidomide 1-21 day, dexamethasone weekly

Dose-Limiting Toxicities

- In the dose determination stage, 3/6 patients treated with pembrolizumab 2 mg/kg + Len 25 mg + Dex experienced DLTs
  - One patient experienced tumor lysis syndrome (Grade 3), hyperuricemia (Grade 4), and neutropenia (Grade 4)
  - One patient experienced neutropenia (Grade 3)
  - One patient experienced pneumonia (Grade 3)
- All patients recovered from the DLTs without treatment discontinuation
- In the dose confirmation stage, 7 additional patients were treated with pembro 200 mg + Len 25 mg + Dex with no DLTs observed

Treatment-Related Adverse Events

n (%)	All AEs	Grade 3-5
All AEs (N = 51)	48 (94)	33 (65)
AEs in ≥6 Patients		
Neutropenia	19 (37)	17 (33)
Thrombocytopenia	21 (41)	9 (18)
Diarrhea	14 (28)	0
Fatigue	13 (26)	1 (2)
Anemia	11 (22)	6 (12)
Pruritus	6 (12)	0
Hyperglycemia	9 (18)	4 (8)
Muscle spasms	7 (14)	0
Myalgia	8 (16)	0
Blurred vision	7 (14)	0
Dizziness	6 (12)	0
Dyspnea	6 (12)	0

- AEs consistent with individual drug safety profiles for approved indications
- AEs associated with pembrolizumab were similar to other indications
- There were 2 (4%) deaths due to treatment-related AEs
  - Hepatic failure related to venoocclusive disease, related to treatment combination
  - Ischemic stroke related to lenalidomide
- 3 (6%) patients discontinued due to treatment-related AEs

Immune-Mediated Adverse Events

n (%)	Pembro + Len + Dex (N = 51)
Hyperthyroidism	
Grade 1	1 (2)
Hypothyroidism	
Grade 1	2 (4)
Thyroiditis	
Grade 1	1 (2)
Increased transaminases	
Grade 3	1 (2)
Renal failure	
Grade 3	1 (2)

- No dose modification or treatment discontinuation required for management of the reported immune related AEs
- No infusion reactions were reported

In Summary – Immune Related Toxicity (%)

Toxicity	IB (n=2799) All Patients	KN183* (n=104) RRMM	KN185* (n=69) TNMM
Pneumonitis	3.4	1	0
Colitis	1.7	0	0
Hyperthyroid	3.4	0	0
Hypothyroid	8.5	0	1.4
Hepatitis	0.7	0	0
Nephritis / Renal Dys	0.3	0	0
Infusional	0.2	0	0
Hypophysitis	0.6	0	0
T1DM	0.2	0	0

Other immune related toxicities (<1% unless otherwise indicated) from IB Oct 2016: arthritis (1.5%), exfoliative dermatitis, bullous pemphigoid, rash 1.4%, uveitis, myositis, Guillain-Barré, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in the brain parenchyma.

* Aggregate data from both arms as of July 2016

Antitumor Activity
Central Review (IMWG 2006)

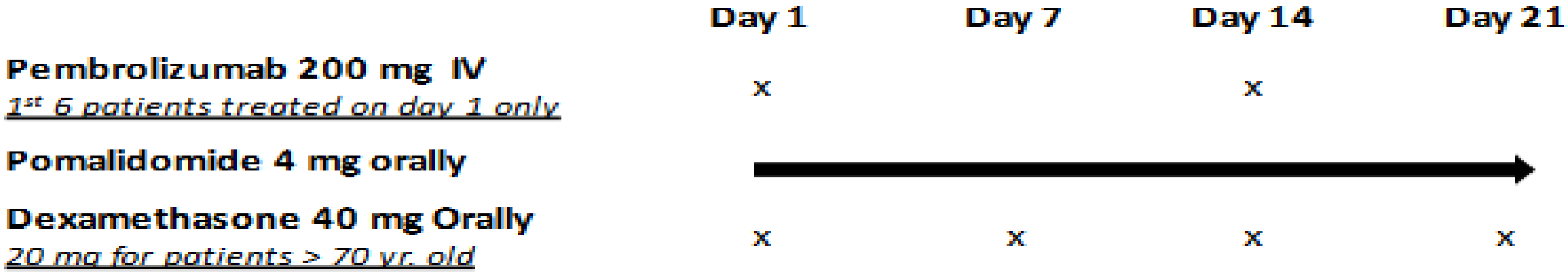
Best Overall Response n (%)	Efficacy Population† (n = 40)	Len-Refractory (n = 29)
Overall response rate	**20 (50)**	**11 (38)**
Stringent complete response (sCR)	1 (3)	1 (3)
Very good partial response (VGPR)	5 (13)	3 (10)
Partial response (PR)	14 (35)	7 (24)
Stable disease (SD)	19 (48)	17 (59)
Disease control rate (CR+PR+SD)	39 (98)	28 (97)
Progressive disease (PD)	1 (3)	1 (3)

†11 patients NE by central review
3 discontinued within cycle 1 for reasons other than PD (2 no treatment assessments and 1 SD by investigator)
8 inadequate myeloma data for response assessment (5 PD and 3 SD by investigator)

Conclusions

- MTD/MAD was defined as pembrolizumab 200 mg in combination with lenalidomide 25 mg and low-dose dexamethasone 40 mg
- These data suggest that this treatment combination has an acceptable safety and tolerability profile, and is consistent with AEs reported for pembrolizumab in solid tumors
- Initial efficacy results show promising activity in heavily pretreated patients with RRMM and support the continued development of pembrolizumab in patients with multiple myeloma
- Phase 3 studies of pembrolizumab in MM patients have been initiated (KEYNOTE-185 [NCT02579863] and KEYNOTE-183 [NCT02576977])

Pembrolizumab + Pom/Dex
ASH abstract 506



- Cycles are repeated every 28 days for responding/stable pts
- After 24 months; responding patients can continue pomalidomide and dexamethasone alone until progression.

ASH Abstract 506, Badros et al
Slide Courtesy of Dr. Badros

Prior Therapy

Characteristic	N=33
No. of prior lines of therapy	
Median (Range)	3 (2-5)
Time from Diagnosis to Study – yr	
Median (Range)	3.7 (1.2-16.8)
Prior Therapy – no. (%)	
ASCT	22 (67%)
Proteosome Inhibitors	33 (100%)
Bortezomib	33 (100%)
Carfilzomib	16 (48%)
Oprozomib	4 (12%)
IMiDs	33 (100%)
Lenalidomide	32 (97%)
Thalidomide	1 (3%)
Refractory	
Proteosome Inhibitors	27 (82%)
Bortezomib	9 (33%)
Carfilzomib	14 (52%)
Oprozomib	4 (15%)
Lenalidomide	29 (89%)
Double Refractory to IMiDs & PI	23 (70%)

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Best Response to Treatment (IMWG Criteria)

Evaluable Pts (n=27)

	All N=27	Double refractory N=20	High risk cytogenetics N=12
ORR (≥ PR), %			
sCR	1	0	0
CR	0	0	0
VGPR	4	2	1
PR	11	9	5
	60%	55%	50%
Stable Disease	8 (30%)	6 (30%)	5 (42%)
Progressive disease	3 (10%)	3 (15%)	1 (8%)

ASH Abstract 506, Badros et al, Slide Courtesy of Dr. Badros

What do these results with monoclonal antibodies mean?

- **Confirmed Remarkable activity**
  - Anti- SLAMF7 in combo with Rd and Vd
  - Anti-CD38 as single agent in heavily pretreated pts (unmeat medical need) and in combo with Rd, Vd, Pom-dex

- **Good tolerability overall**
  - →**No increase** toxicity of combo
  - →**Infusion reactions** as major Monoclonal Antibody-related toxicity

Rd: lenalidomide-dexamethasone; Vd: bortezomib-dexamethasone; Pom-Dex: pomalidomide dexamethasone

What do these results with checkpoint blockade mean?

- Immuno-oncology with checkpoint blockade is one strategy that
  - can overcome the immunosuppressive effect of the tumor
  - does not rely on the identification of specific tumor antigens
- Immuno-oncology in the myeloma field opens the door to an entirely new and promising strategy